Ciclaciones radicalarias con transferencia de átomo a partir de di- y tricloroacetamidas. Aplicaciones a la síntesis de alcaloides: FR901483, daphniphyllum y madangaminas

Agustín Martínez Laporta

UNIVERSITAT DE BARCELONA

Ciclaciones radicalarias con transferencia de átomo a partir de di- y tricloroacetamidas. Aplicaciones a la síntesis de alcaloides: FR901483, daphniphyllum y madangaminas

AGUSTÍN MARTÍNEZ LAPORTA

UNIVERSITAT DE BARCELONA

FACULTAT DE FARMÀCIA

DEPARTAMENT DE FARMACOLOGIA I QUÍMICA TERAPÈUTICA

Programa de Doctorado: Química Orgánica Experimental e Industrial

Ciclaciones radicalarias con transferencia de átomo a partir de di- y tricloroacetamidas. Aplicaciones a la síntesis de alcaloides: FR901483, daphniphyllum y madangaminas

Memoria presentada por Agustín Martínez Laporta
para optar al título de Doctor por la Universitat de Barcelona

Dirigida por:

Dr. Josep Bonjoch Sesé

Dra. Faïza Diaba

Agustín Martínez Laporta

Barcelona, octubre de 2014

El trabajo experimental recogido en esta memoria se llevó a cabo en el Laboratorio de Química Orgánica de la Facultat de Farmàcia de la Universitat de Barcelona bajo la dirección del Dr. Josep Bonjoch y de la Dra. Faïza Diaba en el periodo comprendido entre abril del 2011 y julio del 2014.

Este trabajo ha sido financiado por MICINN (España, CTQ2010-14846/BQU)

Indice

AGRADECIMIENTOS

La época de estudiante puede ser una de las mejores etapas de la vida de una persona. Al terminar una etapa de estudios uno siente lo que ha aprendido y madurado en esos años que ha dedicado buena parte de su vida a un objetivo concreto, en el caso que nos ocupa estamos hablando de conseguir el título de doctor.

Estos valiosos años en el departamento de Farmacia junto con las condiciones personales que me han rodeado, me han marcado un cambio sustancial en la forma de ver la vida, me ha ayudado a entender el mundo que nos rodea y a entenderme a mí mismo, en definitiva a madurar los valores personales y a entender que no todos somos iguales y, aunque todos usemos los mismos operadores, no todos los usamos de la misma manera.

Esta Tesis, con todo lo que ello conlleva, es fruto del trabajo distribuido, en su debida forma, por el director de la orquestra, Dr. Josep Bonjoch, y por la pulidora de diamantes en bruto, Dra. Faïza Diaba, que han depositado en mí la responsabilidad de afrontar los objetivos marcados en el día a día de estos años de intensa investigación. En este aspecto, y debido a las consecuencias de la crisis de sobreproducción, tanto el grupo de investigación como mi condición personal se han visto afectados a distintos niveles y ha sido más duro de llevar para todos nosotros, pero aquí seguimos.

PUBLICACIONES

1. **Cu(I)-catalyzed atom transfer radical cyclization of trichloroacetamides tethered to electron-deficient, -neutral, and –rich alkenes: syntheseis of polyfunctionalized 2-azabicyclo[3.3.1]nonanes.** Diaba, F.; Martínez-Laporta, A.; Bonjoch, J.; Pereira, A.; Muñoz-Molina, J.; Pérez, J.; Belderrain, T. *Chem. Commun.* **2012**, *48*, 8799-8801.

2. **Chlorine Atom Transfer Radical 6-*exo* Cyclizations of Carbamoiyldichloroacetate-Tethered Alkenes, Enol Acetates and α,β-Unsatured Nitriles Leading to Morphans.** Diaba, F.; Martínez-Laporta, A.; Bonjoch, J. *Eur. J. Org. Chem.* **2014**, 2371–2378.

3. **Dearomative radical spirocyclization from *N*-benzyltrichloroacetamides revisited using a copper(I)-mediated atom transfer reaction leading to 2-azaspiro[4.5]decanes.** Diaba, F.; Montiel, J.; Martínez-Laporta, A.; Bonjoch, J. *Tetrahedron Lett.* **2013**, *54*¸ 2619-2622.

4. **Atom Transfer Radical Cyclization of Trichloroacetamides to Electron-rich Acceptors Using Grubbs' Catalysts: Synthesis of the Tricyclic Framework of FR901483.** Diaba, F.; Martínez-Laporta, A.; Bonjoch, J. *J. Org. Chem.* **2014**, *79*, 9365-9772.

5. **Synthesis of the ABC Fragment of Calyciphylline A-type Daphniphyllum Alkaloids.** Diaba, F.; Martínez-Laporta A.; Coussanes, G.; Fernández, I.; Bonjoch, J. *Tetrahedron* **2015**, *71*, 0000 *(Tetrahedron Symposium-in-print: Ang. Li (editor) Synthesis of indole/pyrrole-containing natural products).*

6. **Synthesis of Tetracyclic ABCD Fragments of Madangamines D, E, and F,** Diaba, F.; Pujol-Grau, C.; Martínez-Laporta, A.; Fernandez, I.; Bonjoch, J. *Org. Lett. (en proceso de redacción).*

ABBREVIATIONS AND ACRONYMS

AIBN	2,2’-azobis(iso-butyronitrile)
Ac	acetyl group
AcOH	acetic acid
aq.	aqueous
Ar	aryl group
ATRA	atom transfer radical adittion
ATRC	atom transfer radical cyclization
ATRP	atom transfer radical polymerization
ax	axial
bipy/bpy	2,2'-bipyridine
Bn	benzyl group
Boc	*tert*-butoxycarbonyl
Boc_2O	di-*tert*-butyl carbonate
bp	boiling point
bpy	2,2´-bipyridine
br	broad
Bu	butyl group
c	concentration
/C	supported on activated carbon
calcd	calculated
cat.	catalytic
Celite®	filtration agent
COSY	correlation spectroscopy
Cy	cyclohexyl group
d	day(s), doublet (spectra)
δ	chemical shift
DCE	1,2-dichloroethane
DEAD	diethyl azodicarboxylate
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
DCM	dichloromethane
dd	doublet of doublets

dm	doublet of multiplets
DMAP	4-dimethylaminopyridine
DMEDA	*N*,*N'*-dimethylethylenediamine
DMF	*N*,*N*-dimethylformamide
DMP	Dess-Martin periodinane
1,4-DMP	1,4-dimetilpiperazine
DMSO	dimethyl sulfoxide
dr	diastereomeric ratio
dt	doublet of triplets
epi	epimer
equiv.	equivalent
eq	equatorial
Et	ethyl group
EWG	electron withdrawing groups
Grubbs II	Grubbs second-generation metathesis catalyst
HMPA	hexamethylphosphoramide
HOMO	highest occupied molecular orbital
HRMS	high resolution mass spectrum
HSQC	heteronuclear single quantum correlation spectroscopy
IBX	*o*-iodoxybenzoic acid
IR	infrared spectroscopy
J	coupling constant
KHMDS	potassium bis(trimethylsilyl)azide
LAH	lithium aluminum hydride
LDA	lithium diisopropylamide
LHMDS	lithium bis(trimethylsilyl)azide
Lit.	literature
LUMO	lowest unoccupied molecular orbital
M	molar
m	meta
m	multiplet
M	metal or molar
M^+	molecular ion
m/z	mass to charge ratio

m-CPBA	meta-chloroperbenzoic acid
Me	methyl group
mol	mol(es)
mp	melting point
MS	mass spectrometry
Ms	mesyl group (methylsulfonyl)
μW	microwave
NBS	*N*-bromosuccinimide
NOE	nuclear Overhauser effect
NOESY	2D nuclear Overhauser effect spectroscopy
NR	no reaction
Ns	nosyl Group
o	ortho
OTMS	trimethylsilyl enol ether
p	para
p. or pp.	page
PCC	pyridinium chlorochromate
PDC	pyridinium dichromate
Ph	phenyl Group
Py, py or Pyr	pyridine group
ppm	parts per million
q	quartet
R	generalized alkyl group or substituent
R_f	retention factor
RCM	ring closing metathesis
ref.	reference
rt	room temperature
rfx.	reflux
s	singlet
sat.	saturated
SOMO	singly occupied molecular orbital
t	triplet
t	tertiary
TBAF	tetra-*n*-butylammonium fluoride

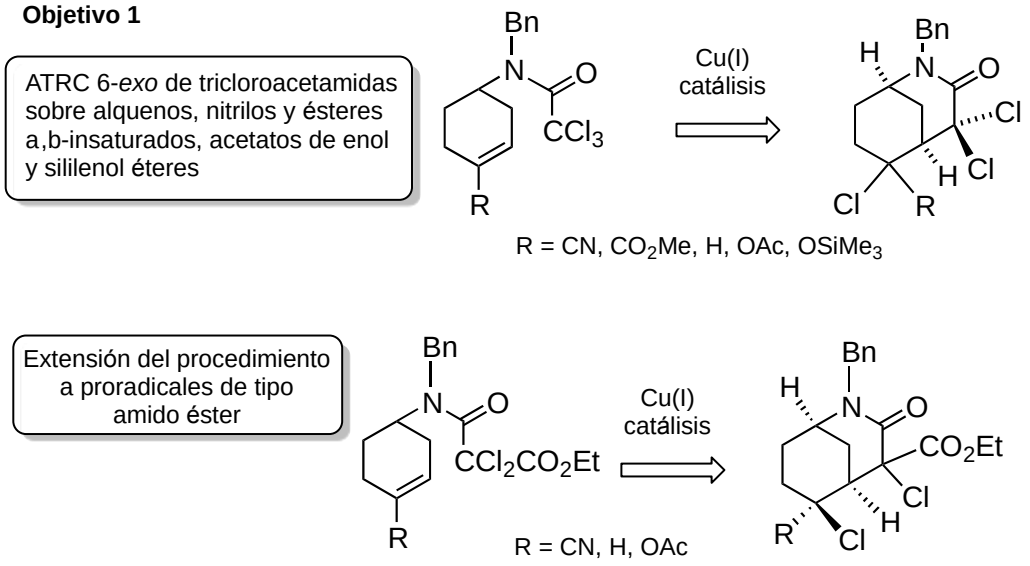
TBHP	*tert*-butyl hydroperoxide
td	triplet of doublets
TEA	triethylamine
TEMPO	2,2,6,6-tetramethylpiperidin-1-yl)oxidanyl
Tf	trifluoromethanesulfonyl group
TFA	trifluoroacetic acid
THF	tetrahydrofurane
TLC	thin layer chromatography
TMS	trimethylsilyl group
TPMA	tris(2-pyridylmethyl)amine
Ts	*p*-toluenesulfonyl or *p*-toluenesulfonic
TsOH	*p*-toluenesulfonic acid
TTMSS	tris(trimethylsilyl)silane
UV	ultraviolet
wt	weight

1. Introducción y Objetivos

1.1 Objetivos

La presente Memoria, que se presenta como compendio de publicaciones resultantes del trabajo desarrollado a lo largo de la Tesis Doctoral, refleja los dos ejes sobre los que se articularon los objetivos de la Tesis: a) desarrollo de metodología de síntesis basada en química radicalaria[1] y b) aplicación de los métodos en estudio a procesos encaminados a la síntesis total de productos naturales,[2] específicamente alcaloides.

En el capítulo 2 se introducen los resultados en la ciclación de tricloroacetamidas sobre alquenos neutros, con grupos electrón-atrayentes y grupos electrón-donadores, como aceptores radicalarios, utilizando Cu(I) como promotor del proceso de ciclación radicalaria con transferencia de átomo (ATRC), que establecen un método de síntesis de morfanos (2-azabiciclo[3.3.1]nonanos) funcionalizados. En el capítulo 3 se estudia el alcance de la metodología, examinando su aplicación a la ciclación de dicloroetoxicarbonilacetamidas para generar morfanos de mayor complejidad estructural (Esquema 1.1).



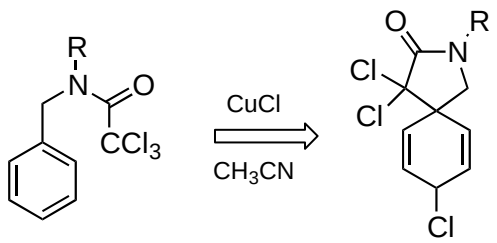
1.1 Objetivos metodológicos en química radicalaria

[1] Renaud, P.; Sibi, M.P. editors. Radicals in organic synthesis. Vols. 1 and 2. Weinheim: Wiley-VCH; **2001**.

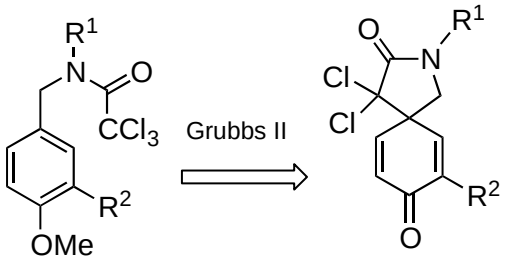
[2] Bonjoch, J.; Bradshaw, B.; Diaba, F. *Radicals in stereoselective C-C bond formation* In Stereoselective Synthesis of Drugs and Natural Products; Andrushko, V.; Andrushhko, N. Eds.; Wiley-VCH: New York 2013; pp 733-768.

Objetivo 2

Procesos de desaromatización mediante ATRC catalizados por Cu(I) a partir de *N*-benciltricloroacetamidas: Síntesis de 2-azaespiro[4.5]decanos



Procesos de desaromatización mediante ATRC promovidas por el catalizador de Grubbs II a partir de *N*-(p-metoxibencil)tricloroacetamidas: Síntesis de 2-azaespiro[4.5]decan-8-onas



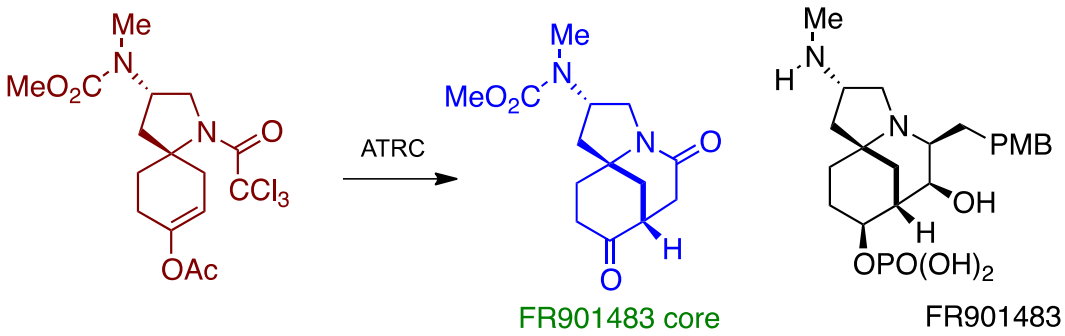
R^1 = *t*-Bu, Cy, Bn; R^2 = H, Me, F

1.1 (cont) Objetivos metodológicos en química radicalaria

En el capítulo 4 se describen los estudios encaminados a procesos de desaromatización mediante ciclaciones radicalarias de tricloroacetamidas sobre núcleos bencénicos, para generar 2-azaespiro[4.5]decanos, utilizando como agentes promotores de los procesos de ATRC tanto Cu(I) como el catalizador de Grubbs II (Esquema 1.1 cont). Así pues, los estudios compilados en los capítulos 2-4 son metodológicos para ampliar el alcance del uso de radicales en síntesis orgánica

Por otra parte, los capítulos 5 a 7 describen la preparación de "building-blocks" nitrogenados tri- y tetracíclicos de interés para la síntesis total del inmunosupresor FR901483 (cap. 5), alcaloides *Daphniphyllum* (cap. 6) y alcaloides marinos madangaminas (cap. 7) (Esquema 1.2). Todos ellos presentan en común el núcleo de 2-azabiciclo[3.3.1]nonano[3] y en su preparación se hará uso de la metodología sintética radicalaria reflejada en la primera parte de la Tesis.

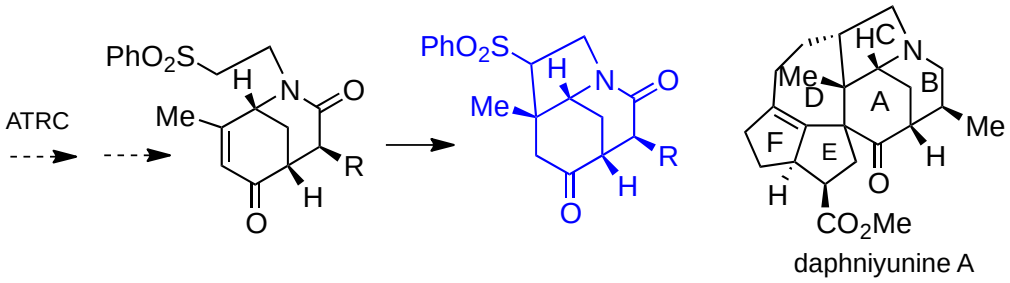
Objetivo 3 Síntesis del esqueleto azatricíclico del inmunosupresor FR901483



1.2 Objetivos en síntesis total de alcaloides

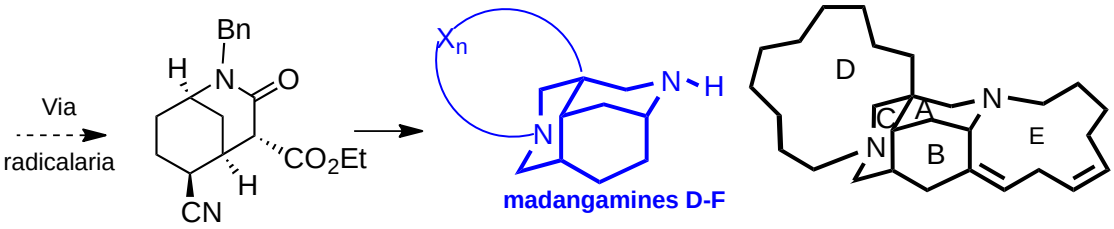
[3] Para una revisión en la síntesis de 2-azabiciclo[3.3.1]nonanos. Véase: Bonjoch, J.; Diaba, F.; Bradshaw, B. *Synthesis* **2011**, 993-1018.

Objetivo 4 Síntesis del fragmento azatricíclico ABC de los alcaloides de tipo calicifilina A



daphniyunine A

Objetivo 5 Síntesis del fragmento diazatetracíclico ABCD de las madangaminas



macrociclo 13-15 eslabones
n = 10-12 átomos de C

madangamina E

Esquema 1.2 (cont) Objetivos en síntesis total de alcaloides

A continuación, se introduce el estado del arte en los temas metodológicos y sintéticos que son objetivos de esta Tesis Doctoral.

1.2 Ciclaciones radicalarias con transferencia de átomo (ATRC). Síntesis de lactamas bicíclicas a partir de tricloroacetamidas y proradicales relacionados en procesos 6-exo (Cap 2 y 3)

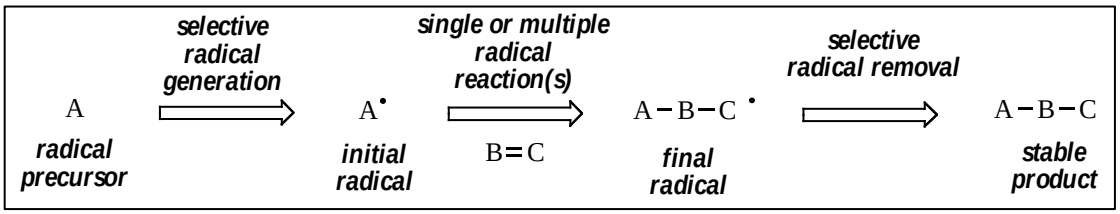
1.2.1 Ciclaciones radicalarias

La formación de enlaces carbono-carbono es un proceso fundamental en la construcción del esqueleto molecular y por tanto es uno de los temas de permanente interés en síntesis orgánica. Las estrategias que implican reacciones radicalarias se han convertido en herramientas importantes en la síntesis orgánica[4]. Las ventajas de los procesos radicalarios incluyen una alta tolerancia a grupos funcionales (quimioselectividad), condiciones de reacción suaves y altos niveles de regio- y estereoselectividad. En particular, la ciclación mediada por radicales se ha implementado como un método poderoso para la preparación de una gran variedad de tipos de compuestos cíclicos a través de procesos de formación de enlaces carbono-

[4] (a) Rowlands, G. J. *Tetrahedron* **2009**, *65*, 8603-8655; (b) Rowlands, G. J. *Tetrahedron* **2010**, *66*,1593-1636.

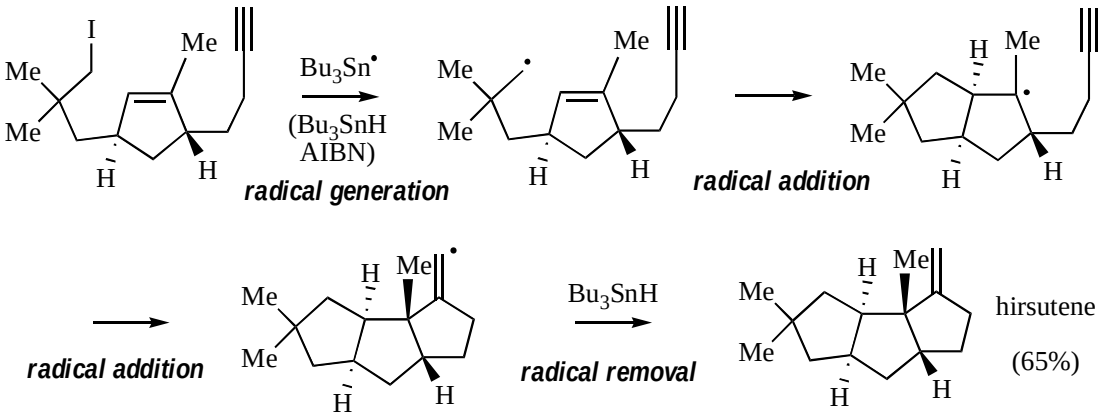
carbono[5]. La química radicalaria es muy adecuada para el diseño de procesos en cascada y se encuentran numerosos ejemplos en la síntesis de productos naturales[6].

Las reacciones radicalarias de ciclación (o adición) comprenden tres pasos básicos: la generación selectiva del radical, ciclación radicalaria/ adición y, después de la formación de uno o más enlaces carbono-carbono, conversión del nuevo radical formado en el producto final estable (Esquema 1.3).



1.3 Esquema general de reacción para los procesos radicalarios (ref. 2)

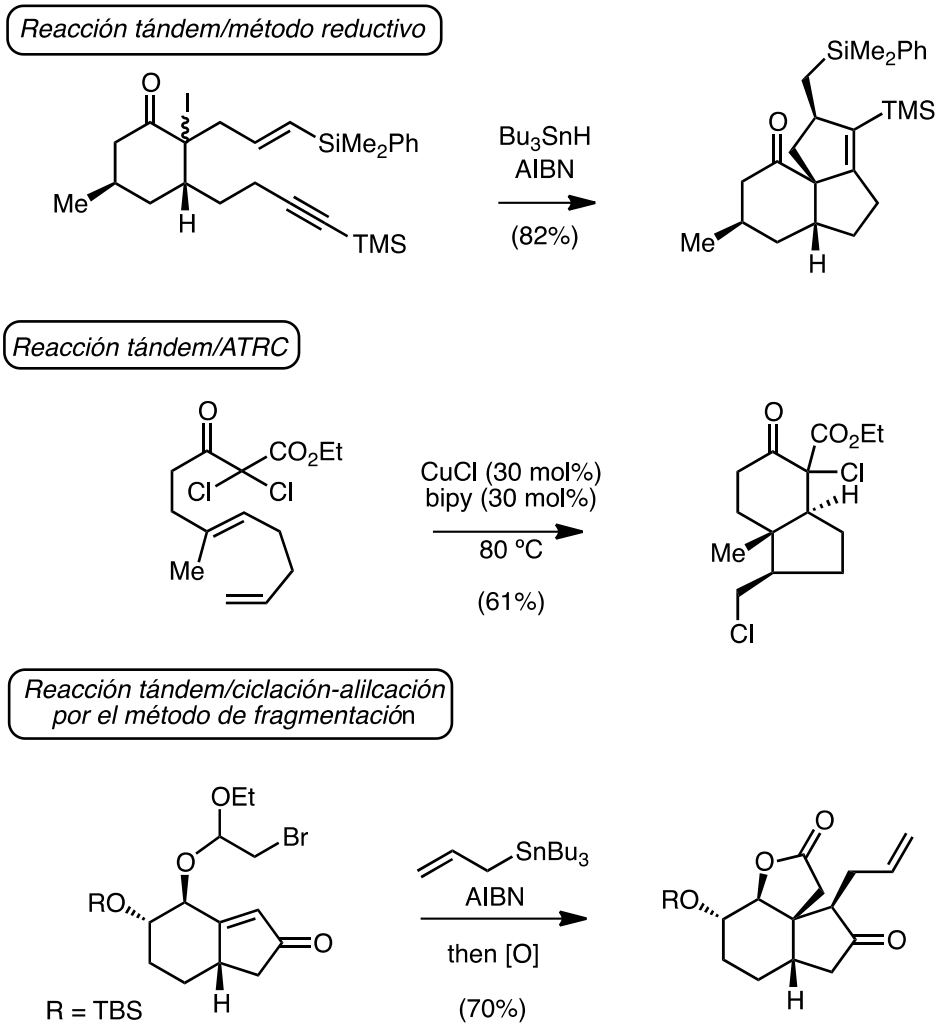
El proceso general se ilustra mediante la clásica síntesis de Curran del hirsuteno (Esquema 1.4) [7]. En la década de 1980, Stork y Curran contribuyeron a una rápida expansión de las aplicaciones sintéticas que involucran procesos radicalarios, que tuvieron como precedentes el trabajo de Barton, Giese y Hart, que habían abierto una nueva era para la química radicalaria mediante la introducción de métodos novedosos de síntesis mediante radicales intermedios. Estudios posteriores sobre las reacciones de radicales estereoselectivas fueron desarrollados, entre otros por Giese, Curran y Porter[8], y al final del siglo pasado, Sibi llevó a cabo notables progresos en las reacciones de radicales enantioselectivas[9].



1.4 Síntesis del hirsuteno (Curran)

[5] McCarroll, A. J.; Walton, J. C. *Angew. Chem. Int. Ed.* **2001**, *40*, 2224-2248.
[6] (a) Jasperse, C. P.; Curran, D. P.; Flevig, T. L. *Chem. Rev.* **1991**, *91*, 1237-1286. (b) Justicia, J.; Alvarez de Cienfuegos, L.; Campaña, A. G.; Miguel, D.; Kakoby, V.; Gansäuer, A.; Cuerva, J. M. *Chem. Soc. Rev.* **2011**, *40*, 3525-3537.
[7] Curran, D. P.; Rakiewicz. *J. Am. Chem. Soc.* **1985**, *107*, 1448-1449.
[8] (a) Curran, D. P.; Porter, N. A.; Giese, B. editors. Stereochemistry of radical reactions: concepts, guidelines, and synthetic applications. Weinheim: VCH; **1996**. (b) Bar, G.; Parsons, A. F. *Chem. Soc. Rev.* **2003**, *32*, 251-263.
[9] Sibi, M. P., Manyem, S.; Zimmerman, J. *Chem. Rev.* **2003**, *103*, 3263-3295. (b) Miyabe H, Takemoto Y. *Chem. Eur. J.* **2007**, *13*, 7280-7286.

Las reacciones radicalarias pueden llevarse a cabo en procesos en cadena [(i) método reductivo,[10] (ii) con transferencia de átomo,[11] (iii) de fragmentación[12]], veánse ejemplos representativos en el Esquema 1.5 o en procesos no en cadena.

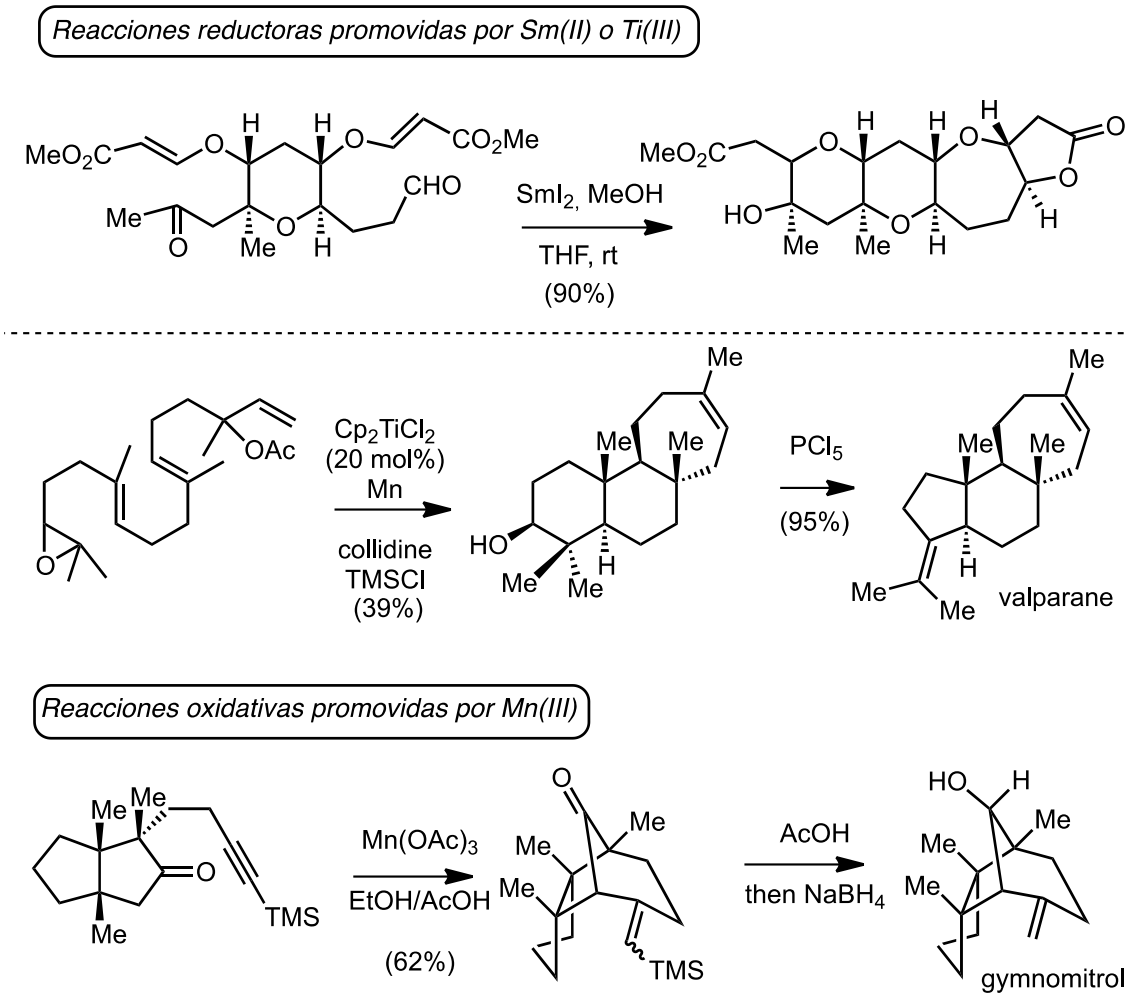


Esquema 1.5

Este segundo supuesto implica el uso de reactivos reductores (SmI_2[13], Cp_2TiCl[14]) para generar el radical inicial a partir de cetonas o epóxidos, respectivamente, y reducción final del radical generado después de la etapa de formación del enlace C-C, o reactivos oxidantes como derivados de Mn(III) para promover radicales a partir de enlaces C-H activados (β-dicarbonílicos o cetonas) y una oxidación de una especie radicalaria para terminar el proceso sintético. Así pues, en los procesos no en cadena

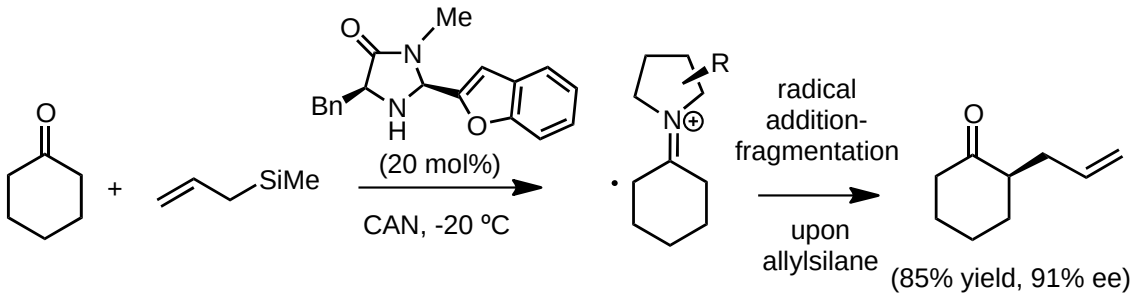
[10] Giese B, Kopping B, Göbel T, Dickhaut J, Thoma G, Kulicke KJ, Trach F. Radical cyclization reactions. *Org. React.* **1998**, *48*, 301-856.
[11] Clark, A. *Chem. Soc. Rev.* **2002**, *31*, 1-11.
[12] (a) Keck, G. E.; Tafesh, A. M. *J. Org. Chem.* **1989**, *54*, 5845-5846. (b) Smith, M. W.; Snyder, S. A. *J. Am. Chem. Soc*. **2013**, *135*, 12964-12967.
[13] Szostak, M.; Fazakerley, N. J.; Parmar, D.; Procter, D. J. *Chem. Rev.* **2014**, *114*, 5959-6039.
[14] Morcillo, S. P.; Miguel, D.; Resa, S.; Martin-Lasanta, A.; Millán, A.; Choquesillo-Lazarte, D.; García-Ruiz, J. M.; Mota, A. J.; Justicia, J.; Cuerva, J. M. *J. Am. Chem. Soc.* **2014**, *136*, 6943-6951.

se genera tanto el radical inicial como se elimina el radical final por reducción o bien por oxidación, según el sustrato de partida (Esquema 1.6).



Esquema 1.6

Recientemente, MacMillan ha introducido un nueva metodología de activación mediante radicales, la activación SOMO-enamina[15] (Esquema 1.7). El intermedio radicalario se obtiene por oxidación con CAN de una enamina, obtenida de manera organocatalítica.



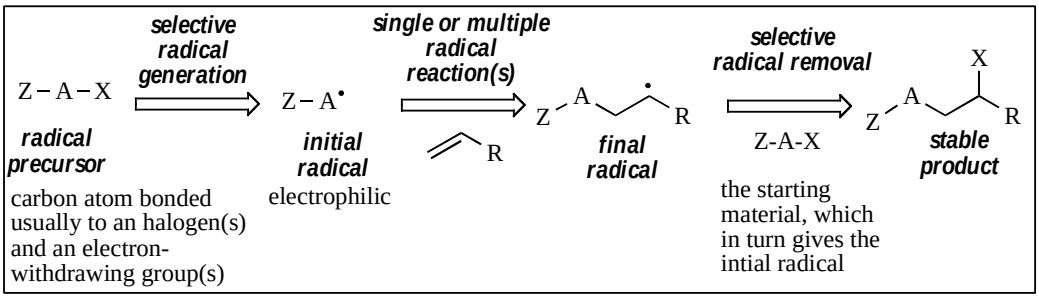
Esquema 1.7

[15] Devery III, J.J.; Conrad, J. C.; MacMillan, D. W. C.; Flowers II, R. A. *Angew. Chem. Int. Ed.* **2010**, *49*, 6106–6110.

1.2.2 Reacciones de ciclación radicalaria con transferencia de átomo (ATRC)

Entre las reacciones de radicales más importantes para la formación de enlaces carbono-carbono están las que implican transferencia de átomo. Las reacciones radicalarias de transferencia de átomo y de grupo se pueden clasificar en dos categorías básicas: adición de radicales intermolecular con transferencia de átomo (ATRA) y ciclación radicalaria con transferencia de átomo (ATRC). Como estos procesos son inherentemente no reductores, no se pierde la funcionalidad del material de partida. Los productos obtenidos de este modo facilitan posteriores transformaciones via radicales y no radicales. La primera reacción ATRA con transferencia de halógeno fue reportada por Kharasch[16], que utilizó peróxidos en la etapa de iniciación. Posteriormente, el proceso fue desarrollado por Curran[17], quien utilizó yoduros de alquilo, como pro-radicales electrofílicos y bis-tributilestaño en reacciones de ciclación. Un nuevo avance se derivó del hecho que el trietilborano en presencia de oxígeno produce radicales etilo[18], que pueden abstraer un átomo de yodo de iodoalcanos, y por lo tanto se puede utilizar como un iniciador para las reacciones de ATR (Esquema 1.8).

Para facilitar la etapa de iniciación se requiere un enlace C-X débil, pero el éxito de la reacción depende de que el enlace C-heteroátomo formado posteriormente sea más fuerte que el roto en el reactivo inicial En otras palabras, para garantizar el proceso en cadena, el radical generado inicialmente debe ser más estable que el formado después de la adición. También es fundamental que la etapa de transferencia de átomo de halógeno sea suficientemente rápida para propagar la cadena. Procesos habituales en reacciones ATRC implican radicales α-carbonilo que conducen a la formación de lactonas, lactamas o cicloalcanonas, que contienen un nuevo enlace carbono-halógeno después de la etapa de transferencia.



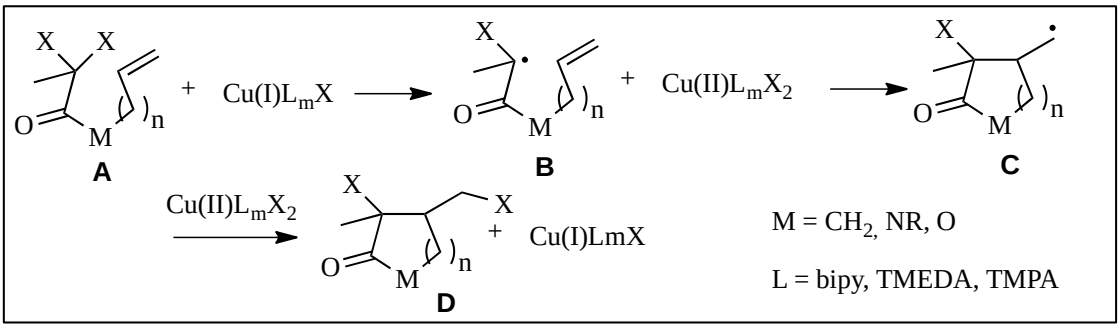
1.8 Mecanismo de reacción para la adición radicalaria con transferencia de átomo (ATRA)

[16] Kharasch, M.S.; Jenson, E.V.; Urry, W.H. *Science* **1945**, *102*, 128-129.
[17] Curran, D.P.; Chen, M.H.; Spletzer,E.; Seong, C.M.; Chang, C.T. *J. Am. Chem. Soc.* **1989**, *111*, 8872-8878.
[18] Ollivier, C.; Renaud, P. *Chem. Rev.* **2001**,*101*, 3415-3434.

1.2.3. Procedimientos catalizados por metales de transición

Es bien conocido que una serie de metales de transición pueden catalizar reacciones de transferencia de átomo y durante el ultimo medio siglo se han invertido considerable esfuerzos en el desarrollo de procesos económicamente baratos y de química sostenible. La introducción del sistema catalítico CuCl y diaminas bidentadas[19] permite llevar a cabo la reacción a baja temperatura y sobre este sistema diversas modificaciones adicionando una serie de aditivos se han introducido de manera constante en el último decenio. En el esquema 1.9 se representa el proceso de reacción con transferencia de átomo catalizado por Cu(I) (ATRA / ATRC) en el que la abstracción de un átomo de halógeno, por ejemplo, por parte del CuCl es seguida por la generación de un enlace C-C.

En la etapa inicial, la ruptura homolítica del enlace en el haloalcano **A** por el complejo de cobre (I) genera un radical alquilo estabilizado **B**, aumentando el estado de oxidación del cobre a Cu (II). El radical **B** se adiciona a un doble enlace de un alqueno, por lo general intramolecularmente, para generar **C**. Por último, el nuevo radical formado, menos estable es atrapado mediante la transferencia de halógeno del complejo de metal en su estado oxidado, regenerándose la forma activa del catalizador y generando el producto de reacción **D**. Para que se produzca la abstracción de átomo inicial, el enlace C-X debe ser activado y esto requiere, invariablemente, la presencia de varios grupos aceptores de electrones para debilitar el enlace. El metal debe tener un potencial redox adecuado para facilitar el ciclo catalítico.



1.9 Mecanismo general para la ciclación radicalaria con transferencia de átomo (ATRC) catalizada por Cu(I)

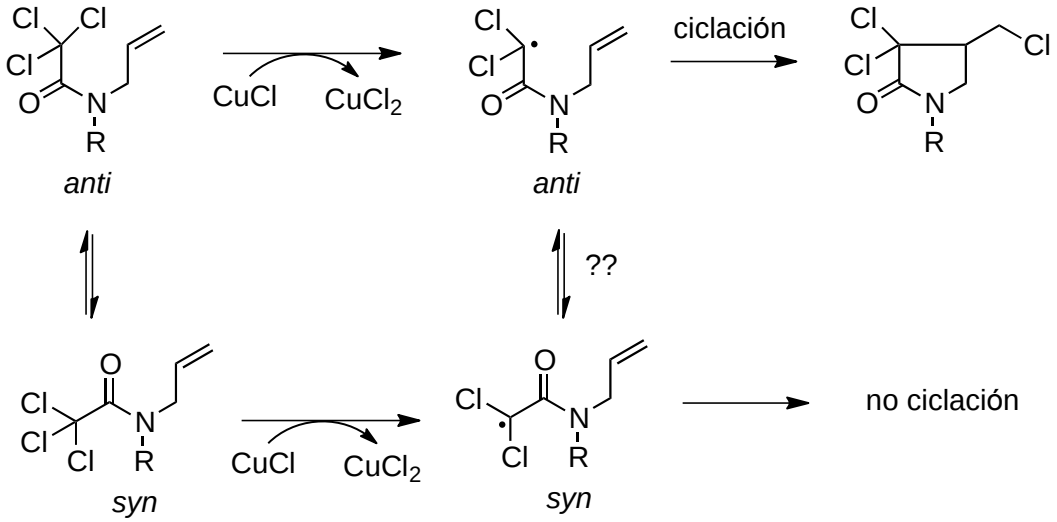
La ATRC 5-exo trig promovida por cobre (I) es el modo de ciclación radicalario más fácil y más ampliamente estudiado. Diversos factores influyen en la velocidad y el resultado de la ATRC catalizada por cobre (I). En primer lugar, la ciclación se inicia por homólisis del enlace C-X (halógeno); la velocidad de la misma depende de la energía de disociación de enlace en cuestión[20,21]. Los enlaces más fuertes son más renuentes

[19] Nagashima, H.; Ozaki, N.; Ishii, M.; Seki, K.; Washiyama, M.; Itoh, K. *J. Org. Chem.* **1993**, *58*, 464-470.
[20] Kropp, P. *Acc. Chem. Res*. **1984**, *17*, 131-137.
[21] (a) Lin, L. J.; Bent. B. E. *J. Phys. Chem.* **1992**, *96*, 8529-8538. (b) Zhang, X. M. *J. Chem. Soc. Perkin Trans 2*, **1993**, 2275-2279.

a experimentar la ruptura homolítica que los más débiles y como resultado, la facilidad de homólisis del enlace CX sigue el orden C-F<C-Cl<C-Br<C-I. Además, los sustituyentes halógeno adyacentes debilitan la energía de disociación de enlace y por tanto el orden de homolisis es CCl_3 > $CHCl_2$ > CH_2Cl.

Una vez que el radical se ha formado, la velocidad y el resultado de la ciclación está determinada por la estabilidad del radical, los efectos estereoelectrónicos en la formación del anillo y la conformación del radical. Al igual que sus análogos iónicos (carbocationes R_3C^+), los carboradicales se estabilizan por sustituyentes dadores de electrones adyacentes. Por lo tanto, los radicales muestran el siguiente orden de estabilidad: $R_3C^\cdot$ > $R_2HC^\cdot$ > $RH_2C^\cdot$. Además, y a diferencia de carbocationes, los radicales pueden también ser estabilizados por grupos electrón-atrayentes tales como halógenos y grupos carbonilo.

En el campo de la síntesis de compuestos nitrogenados debe tenerse en cuenta que algunos precursores de radicales no están predispuestos para la ciclación ya que se encuentran en conformaciones que impiden el solapamiento requerido entre el radical y el carbono insaturado, aceptor radicalario. Las tricloroacetamidas y los radicales derivados de ellas pueden existir como dos confórmeros de amida debido a la rotación lenta alrededor del enlace N-CO. Utilizando amidas secundarias (R = H), el confórmero *syn*, menos impedido estéricamente, es el preferido, pero no es adecuado para la ciclación. Sin embargo la adición de grupos R voluminosos o aceptores de electrones desplaza el equilibrio conformacional hacia el confórmero anti que puede experimentar la ciclación (Esquema 1.10)[22].



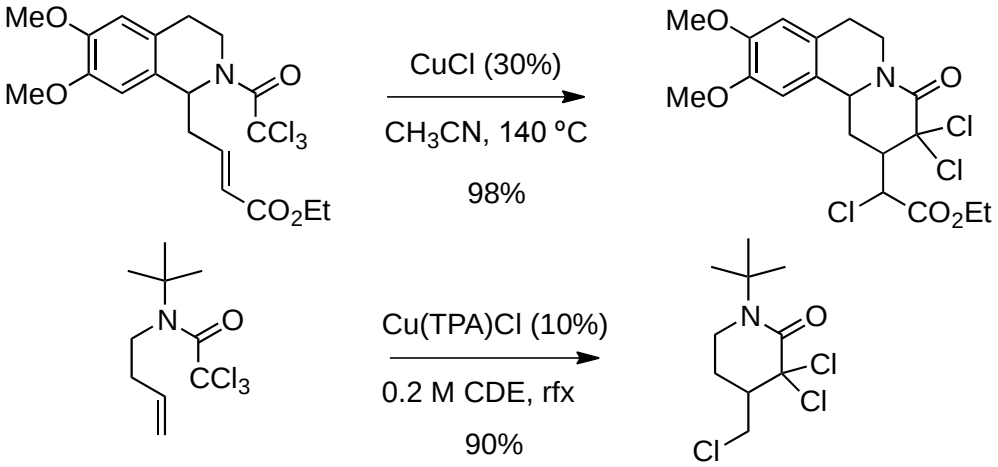
1.10 La rotación del enlace amida genera los rotámeros syn/anti

Otros dos factores que afectan el resultado de la ciclación radicalaria son la naturaleza del disolvente de reacción y la adición de aditivos. Disolventes dadores de hidrógeno, como el THF[23], pueden interceptar los radicales intermedios (por ejemplo,

[22] Stork, G.; Mash, R. *Heterocycles* **1989**, *28*, 723-727. (b) Iwamatsu, K.; Matsubara, K.; Nagashima. H; *J. Org. Chem.* **1999**, *64*, 9625-9631.
[23] Clark, A. J.; Battle, G. M.; Bridge, A. Tetrahedron Lett. **2001**, *42*, 1999-2001.

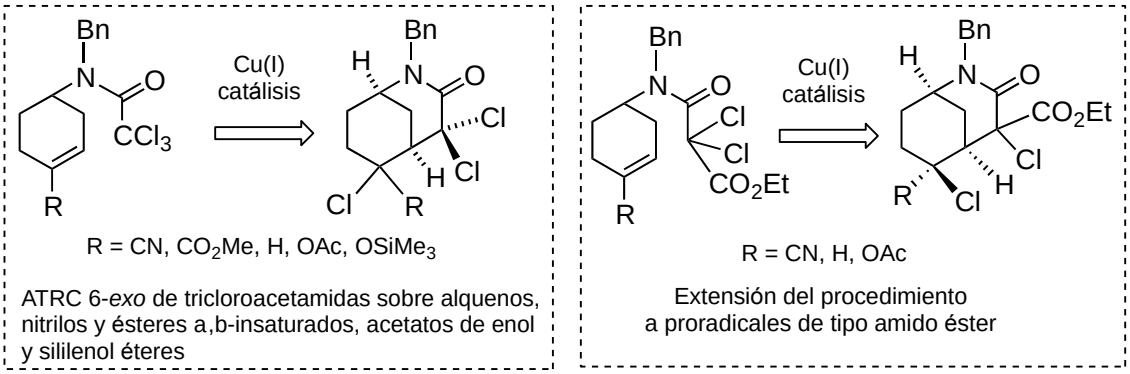
B o **C**, Esquema 1.9) conduciendo a la reducción y, consecuentemente disolventes pobres como dadores son más utilizados en ATRC (tolueno, DCM). La adición de ligandos basados en grupos amina y piridina acelera significativamente la velocidad de ciclación mediante la mejora de la solubilidad de las sales de cobre y / o alteración el potencial redox del sistema catalítico[24].

En condiciones de ATRC (Cu(L)X, 30 mol%) la síntesis de lactamas con un tamaño de anillo de seis miembros o mayor, a partir de acetamidas y enamidas ha tenido un éxito limitado, aparte de nuestros estudios en el campo de la síntesis de 2-azabiciclo[3.3.1]nonanos. En el Esquema 1.11 se ejemplifican los dos únicos ejemplos previos de ATRC[25] 6-exo trig conducentes a δ-lactamas utilizando complejos de Cu(I) .



1.11 6-*Exo* Trig ATRC de tricloroacetamidas

Esta revisión permite enmarcar el contexto de los objetivos de la primera parte de la Tesis, acerca de la síntesis de morfanos funcionalizados mediante ATRC (cap. 2 y 3).



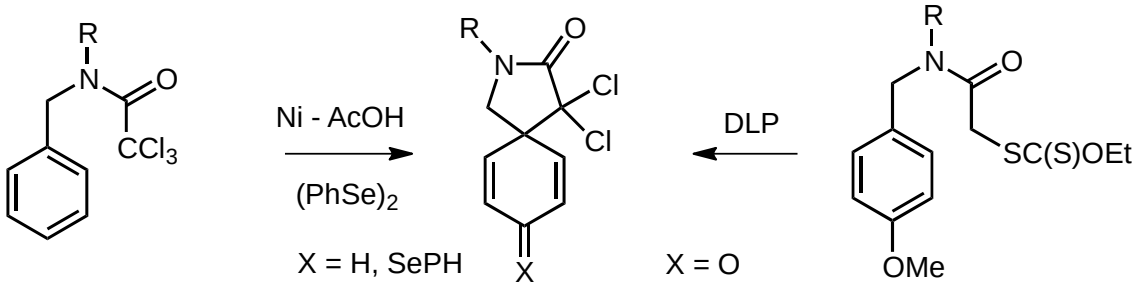
[24] (a) Nagashima, H.; Seji, K.; Ozaki, N.; Wakamatsu, H.; Itoh, K.; Tomo, Y.; Tsuji, J. *J. Org. Chem.* **1990**, *55*, 985-990. (b) Nagashima, H.; Ozaki, N.; Ishii, M.; Seki, K.; Washiyama, M.; Itoh, K. *J. Org. Chem.* **1993**, *58*, 646-470.

[25] (a) Hirai, Y.; Hagiwara, A.; Terada, T.; Yamazaki, T. *Chem. Lett*. 1987, 2417-2418; (b) Clark, A. J.; De Campo, F.; Deeth, R. J.; Filik.; R. P.; Gatard, S.; Hunt, N. A.; Lastecoueres, D.; Thomas, G. H.; Verhlac, J. B.; Wongtap, H. *J. Chem. Soc., Perkin Trans. 1* **2000**, 671-680.

1.3. Procesos de dearomatización a partir de N-benciltricloroacetamidas: síntesis de 2-azaespiro[4.5]decanos funcionalizados (Cap. 4)

El segundo objetivo de la presente tesis (Esquema 1.1, pag 4) fue estudiar el proceso de desaromatización de *N*-bencil- y *N*-(4-metoxibencil)tricloroacetamidas mediante reacciones de transferencia de átomo catalizadas por Cu(I) y Ru(II), respectivamente.

Las reacciones de desaromatización son un motivo de interés permanente en el campo de la síntesis orgánica, con un valor añadido cuando se promueve simultáneamente la formación de un enlace C-C.[26] Es remarcable que la versión radicalaria utilizando tricloroacetamidas tenía unos precedentes exiguos. Sobre anillos de benceno sólo existía el trabajo de Zard utilizando Ni[27] y sobre anillos activados (fenoles o anisoles) habían dos trabajos de Miranda.[28] En estos últimos se utilizan xantatos como productos de partida (esquema 1.12). Adicionalmente, se halla descrita una síntesis de espiroindolinas, mediante ciclación radicalaria de tricloroacetamidas sobre un anillo de indol[29].



Esquema 1.12

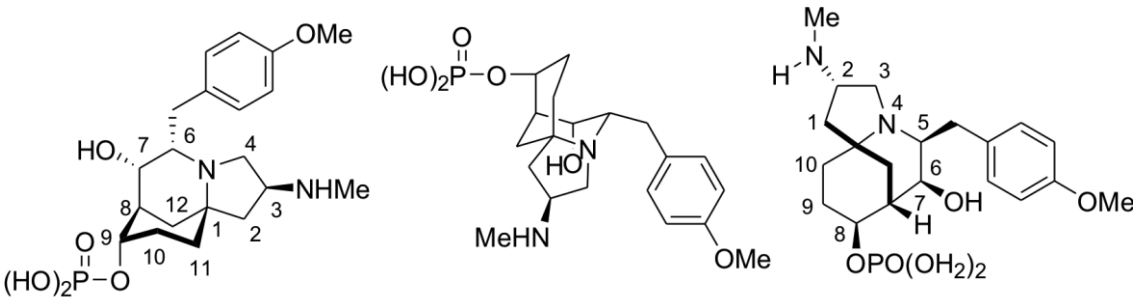
[26] Roche, S.P.; Porco Jr., J. A. *Angew. Chem. Int. Ed.* **20111**, *50*, 4068-4903.
[27] Boivin, J.; Yousfi, M.; Zard, S. *Tetrahedron Lett.* **1997**, *38*, 5985-5988.
[28] (a) Ibarra-Rivera, T. R.; Gámez-Montaño, R.; Miranda, L. D. *Chem. Comm.* **2007**, 3485-3487. (b) Gámez-Montaño, R.; Ibarra-Rivera, T.; El Kaïm, L.; Miranda, L. D. *Synthesis* **2010**, 1285-1290.
[29] Van der Jeught, S.; De Vos, N.; Masschelein, K.; Ghiviriga, I.; Stevens, C. V. *Eur. J. Org. Chem.* 2010, 544-5453. See also, Kyei, A. S.; Tchabaneko, K.; Baldwin, J. E.; Adlington, R. M. *Tetrahedron Lett.* **2004**, *45*, 8931-8934.

1.4. Estudios encaminados a la síntesis del inmunosupresor FR901483 (Cap. 5)

La segunda parte de esta Tesis Doctoral (capítulos 5 a 7) tiene como objetivo la preparación de compuestos azapolicíclicos mediante el uso de ciclaciones radicalarias, que puedan ser utilizados como building-blocks para la síntesis de productos naturales. En este sentido en este apartado y los dos siguientes (1.5 y 1.6) se introducen los precedentes sintéticos de los tres tipos de compuestos objeto de estudio (el compuesto FR901483, los alcaloides Daphniphyllum con el esqueleto de tipo calicifilina A y las madangaminas)

El inmunosupresor FR901483 (Figura 2) fue aislado en 1996 por investigadores de la compañía farmacéutica Fujisawa[30]. Su estructura se determinó por cristalografía de rayos X, y la configuración absoluta no se estableció hasta que Snider alcanzó la primera síntesis total enantioselectiva en 1999[31]. Desde un punto de vista estructural, la característica más destacada del FR901483 es un sistema anular azatricíclico de 7,10a-metanopirrolo[1,2-*a*]azocina, que es la combinación de un núcleo de morfano y uno de indolizidina que comparten el anillo de piperidina. Además, destaca la presencia de un éster fosfórico que es esencial para la actividad del FR901483.

En nuestro grupo de investigación se despertó inmediatamente un gran interés en la síntesis de compuestos análogos de este inmunosupresor debido a su novedad estructural así como por su potencial valor terapéutico. Así, ya en 1999 se describió en nuestro grupo de investigación la síntesis de un seco-análogo del FR901483 y su evaluación farmacológica, en un proyecto en colaboración con la empresa farmacéutica Almirall.[32]



FR901483

1.13. Representaciones del FR901483 y las numeraciones según sea la nomenclatura. A la derecha la utilizada en esta tesis (octahidro-1*H*-7,10a-metanopirrolo[1,2-*a*]azocina)

[30] Sakamoto, K.; Tsuji, E.; Abe, F.; Nakanishi, T.; Yamashita, M.; Shigematsu, N.; Izumi, S.; Okuhara, M. *J. Antibiot.* **1996**, 49, 37-44.
[31] Snider, B. B.; Lin, H. *J. Am. Chem. Soc.* **1999**, 121, 7778-7786.
[32] Bonjoch, J.; Diaba, F.; Puigbó, G.; Solé, D.; Segarra, V.; Santamaria, L.; Beleta, J.; Ryder, H.; Palacios, J.-M. *Bioorg. Med. Chem.* **1999**, 7, 2891–2897.

Nueve síntesis totales del FR901483 se han descrito en los últimos quince años: ocho de ellas enantioselectivas de Snider[31], Sorensen[33], Ciufolini[34] , Brummond[35], Fukuyama[36], Kerr[37], Tu[38] y Huang[39]. Además Funk[40] ha reportado una síntesis de la forma racémica. En las Tablas 1 se muestra un resumen de todos los estudios sintéticos acerca del FR901483.

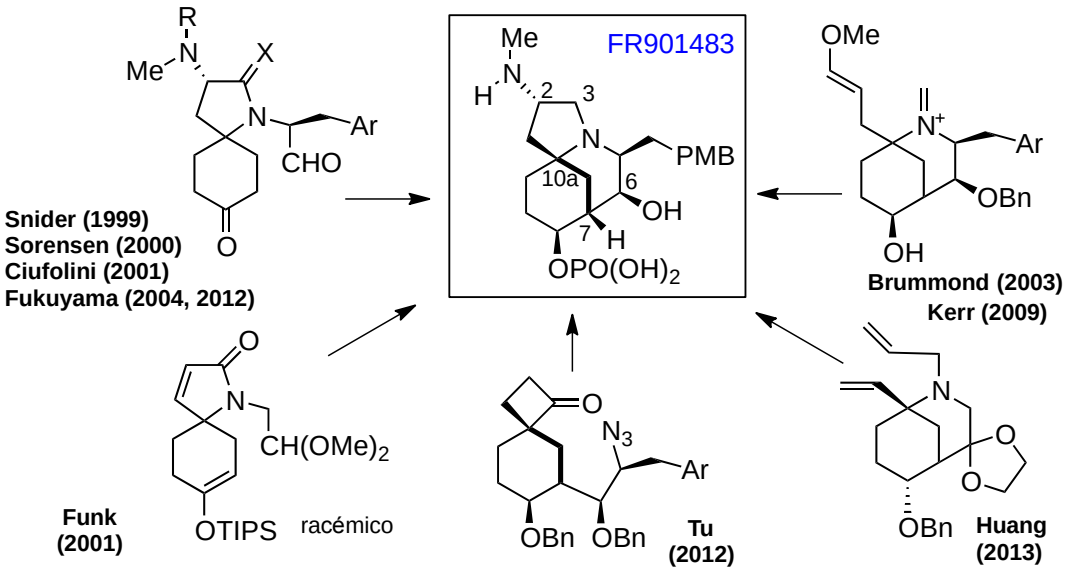
Autor principal (Año)	**Ref**	**Precursor de núcleo azatricíclico**	**Enlace formado**	**Tipo Proceso**
Snider (1999)	30	azaespirodecanona	C(6)-C(7)	reacción aldólica
Sorensen (2000)	33	azaespirodecanona	C(6)-C(7)	reacción aldólica
Ciufolini (2001)	34	azaespirodecanona	C(6)-C(7)	reacción aldólica
Funk (2001)*	40	ciclohexanona	C(6)-C(7)	reacción aldólica
Brummond (2003)	35	ciclohexanona	C(2)-C(3)	reacción Manich
Fukuyama (2004)	36	azaespirodecanona	C(6)-C(7)	reacción aldòlica
Kerr (2009)	37	ciclohexanona	C(2)-C(3)	reacción Mannich
Tu (2012)	38	espirodecanona	N(4)-C(10a)	Inserción Schmidt
Huang (2013)	39	azabiciclononano	C(1)-C(2)	RCM

* síntesis racémica

Tabla 1.1 Síntesis totales enantioselectivas del FR9014883

Las estrategias sintéticas desarrolladas para la síntesis del FR901483 merecen un breve comentario general. Los mayores obstáculos en su síntesis son la generación del espirocentro en C-1 y el cierre anular para formar el fragmento con puente. Las diferentes aproximaciones para la construcción del esqueleto azatricíclico se muestran en el esquema 1.14, en el que se han omitido los sustituyentes del sistema tricíclico para una mayor claridad. Cinco de las síntesis totales utilizan una reacción aldólica a partir de una 1-azaspiro[4.5]decanona funcionalizada para construir el núcleo azatricíclico. En las síntesis de Brummond y Kerr la última etapa para la génesis del núcleo tricíclico es una reacció de Mannich, consecuencia de un proceso *domino* que parte de una ciclohexanona polisustituïda.

[33] Scheffler, G.; Seike, H.; Sorensen, E. J. *Angew. Chem. Int. Ed.* **2000**, 39, 4593-4596.
[34] (a) Ousmer, M.; Braun, N. A.; Ciufolini, M. A. *Org. Lett.* **2001**, 3, 765-767. (b) Ousmer, M.; Braun, N. A.; Bavoux, C.; Perrin, M.; Ciufolini, M. A. *J. Am. Chem. Soc.* **2001**, 123, 7534-7538.
[35] Brummond, K. M.; Hong, S.-P. *J. Org.Chem.* **2005**, 70, 907-916.
[36] Kan, T.; Fujimoto, T.; Ieda, S.; Asoh, Y.; Kitaoka, H.; Fukuyama, T. *Org. Lett*. **2004**, 6, 2729-2731.
[37] Carson, C. A.; Kerr, M. A. *Org. Lett.* **2009**, *11*, 777-779.
[38] Ma, A.-J.; Tu, Y.-Q.; Peng, J.-B.; Dou, Q.-Y.; Hou, S.- H.; Zhang, F.-M.; Wang, S.-H. *Org. Lett.* **2012**, *14*, 3604-3607.
[39] Huo, H.-H.; Xia, X.-E.; Zhang, H.-K.; Huang, P.-Q. *J. Org. Chem.* **2013**, *78*, 455-465.
[40] Maeng, J.-H.; Funk, R. L. *Org. Lett.* **2001**, 3, 1125-1128.



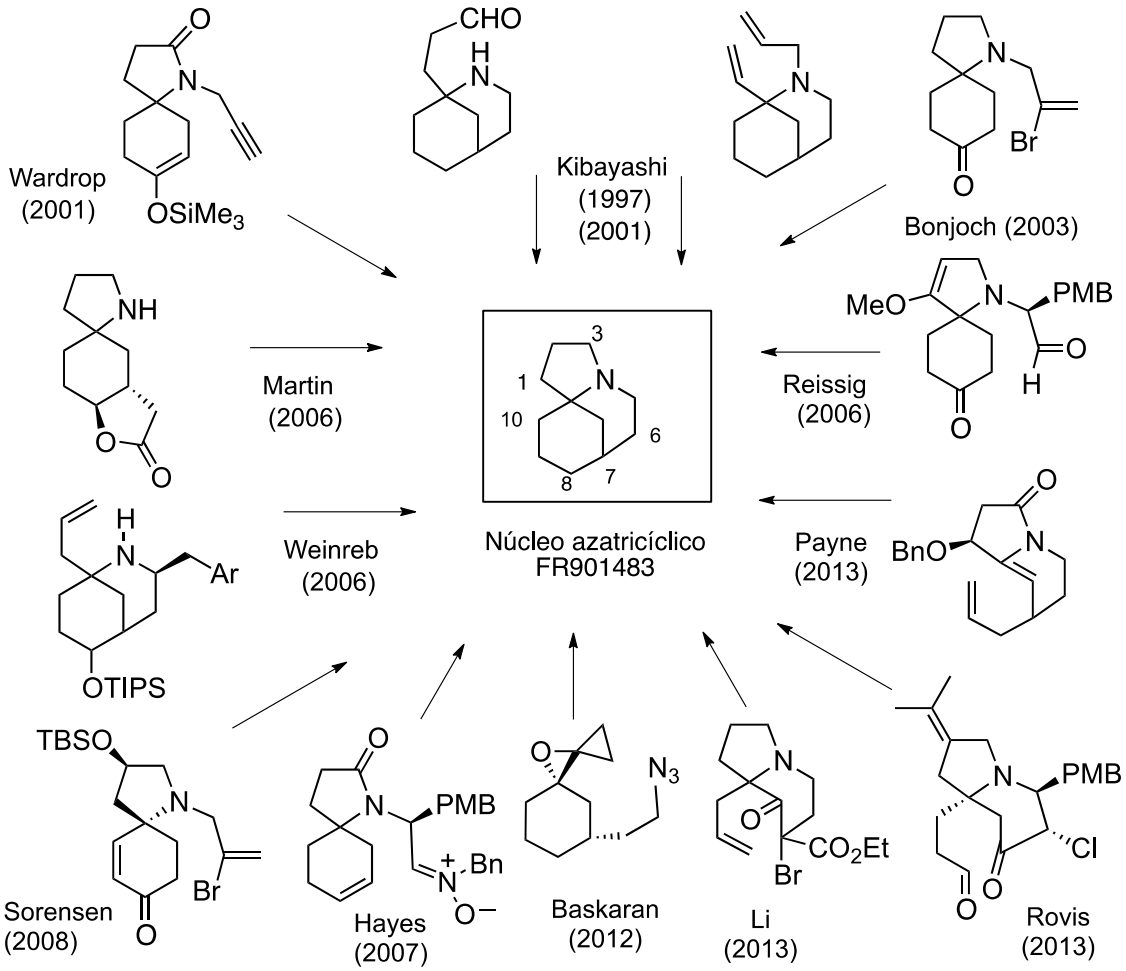
1.14. Construcción del esqueleto en las síntesis totales del FR901483

Aparte de las aproximaciones sintéticas descritas en las síntesis totales del FR901483, se han publicado numerosas metodologías para obtener el esqueleto azatricíclico (Esquema 1.15). El núcleo azatricíclico del FR901483 con mayor o menor grado de funcionalización ha sido objeto de trabajos por parte de Kibayashi[41], Wardrop[42], nuestro grupo de investigación[43], Martin[44], Weinreb[45],Reissig,[46] Hayes,[47] Sorensen,[48] Baskaran,[49] Rovis[50], Li[51] y Pyne[52].

En cuatro de estas aproximaciones, el sistema con puente se elabora por cierre anular a partir de una azaespiro[4.5]decanona ya sea por ciclación radicalaria (Wardrop)[15] o por un acoplamiento catalizado por paladio de haluros de vinilo con enolatos de cetona (Bonjoch)[16]. Martin[17] utilizó un proceso de lactamitzación para generar el sistema con puente, mientras que Reissig[19] optó por la clásica ciclación aldólica, pero utilizando organocatálisis. En las dos aproximacionse de Kibayashi[14] el anillo de pirrolidina es el último en formarse a partir de 2-azabiciclo[3.3.1]nonanos substituidos en C-1 ya sea por una *N*-alquilación intramolecular o por una reacción de

[41] (a)Yamazaki, N.; Suzuki, H.; Kibayashi, C. *J. Org. Chem.* **1997**, 62, 8280-8281. (b) Suzuki, H.; Yamazaki, N.; Kibayashi, C. *Tet. Lett.* **2001**, 42, 3013-3015.
[42] Wardrop, D. J.; Zhang, W. *Org. Lett.* **2001**, 3, 2353-2356.
[43] (a) Bonjoch, J.; Diaba, F.; Puigbó, G.; Peidró, E.; Solé, D. *Tet. Lett.* **2003**, 44, 8387-8390. (b) (c) Diaba, F.; Ricou, E.; Solé, D.; Teixido, E.; Valls, N.; Bonjoch, J. *ARKIVOC* **2007**, 320-330.
[44] Simila, S. T. M.; Reichelt, A.; Martin, S. F. *Tet. Lett*. **2006**, 47, 2933-2936.
[45] Kropf, J. E.; Meigh, I. C.; Bebbington, M. W. P.; Weinreb, S. M. *J. Org. Chem.* **2006**, 2046-2055.
[46] Kaden, S.; Reissig, H-U. *Org. Lett*. **2006**, 8, 4763-4766.
[47] Asari, A.; Angelov, P.; Auty, J. M.; Hayes, C. *Tetrahedron Lett.* **2007**, *48*, 2631-2634.
[48] Seike, H.; Sorensen, E. J. *Synlett* **2008**, 695-701.
[49] Puppala, M.; Murali, A.; Baskaran, S. *Chem. Commun.* **2012**, *48*, 5778-5780.
[50] Perreault, S.; Rovis, T. *Synthesis* **2013**, *45*, 719-728.
[51] Zhang, J.; Wang, Y.-Q.; Wang, X.-W.; Li, W.-D. Z. *J. Org. Chem.* **2013**, *78*, 6154-6162.
[52] Yazici, A.; Pyne, S. G. *Org. Lett.* **2013**, *15*, 5878-5881.

RCM. Weinreb[18] utilizó una reacción promovida por cloruro de fenilsulfenilo para realizar una aminociclación.

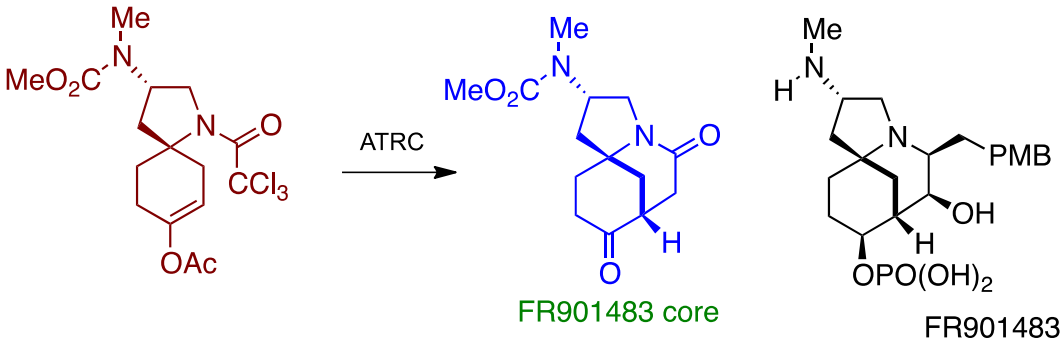


1.15. Aproximaciones sintéticas para el esqueleto del FR901483

Autor (Año)	Ref	Precursor	Enlace formado	Tipo Proceso
Kibayashi (1997)	41a	2-azabiciclononano	C(3)-N(4)	aminación reductiva
Wardrop (2001)	42	azaespirodecanona	C(6)-C(7)	radicalaria
Kibayashi (2001)	41b	2-azabiciclononano	C(1)-C(2)	metátesis (RCM)
Bonjoch (2003)	43	azasepirodecanona	C(6)-C(7)	acop. enolatos (Pd)
Martin (2006)	44	azaespirodecanol	N(4)-C(5)	lactamitzación
Weinreb (2006)	45	2-azabiciclononano	C(3)-N(4)	tioaminociclación
Reissig (2006)	46	azaespirodecanona	C(6)-C(7)	reacción aldólica
Hayes (2007)	47	azaespirodecenona	C(6)-C(7)	acop. de enolatos (Pd)
Sorensen (2008)	48	azaespirodeceno	C(6)-C(7)	cicload. Nitro-alqueno
Baskaran (2012)	49	ciclohexano	N(5)-C(10a)	semipinacol-Schmidt
Rovis (2013)	50	indolizidina	C(7)-C(8)	condens. benzoínica
Li (2013)	51	indolizidina	C(7)-C(8)	radicalaria
Pyne (2013)	52	indolizidinona	C(10)-C(10a)	sal de aciliiminio

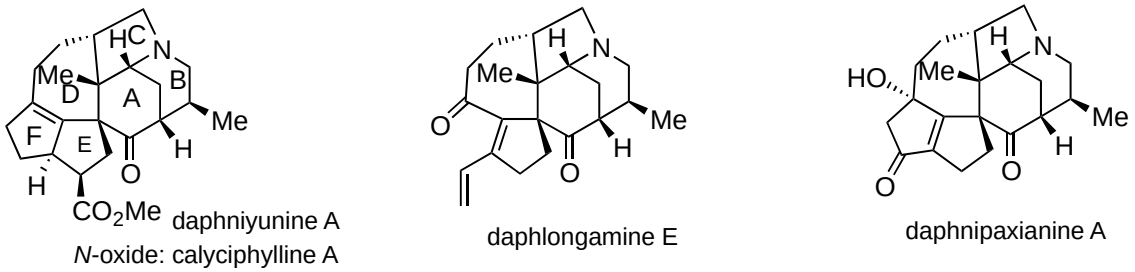
Tabla 1.2 Síntesis del esqueleto azatricíclico del FR9014883

El objetivo que nos planteamos en el campo de la síntesis del FR901483 fue investigar la factibilidad de la síntesis de su núcleo azabicíclico a partir de sistemas de 1-azaespiro[4.5]decano funcionalizados mediante una ciclación con transferencia de átomo, como primera aplicación de la metodología radicalaria que se ha estudiado y expuesta en la primera parte de la Tesis.



***1.5 Estudios para una via de acceso a perhidro-1,6-etanoindoles: alcaloides Daphniphyllum de tipo calicifilina-A* (Cap. 6)**

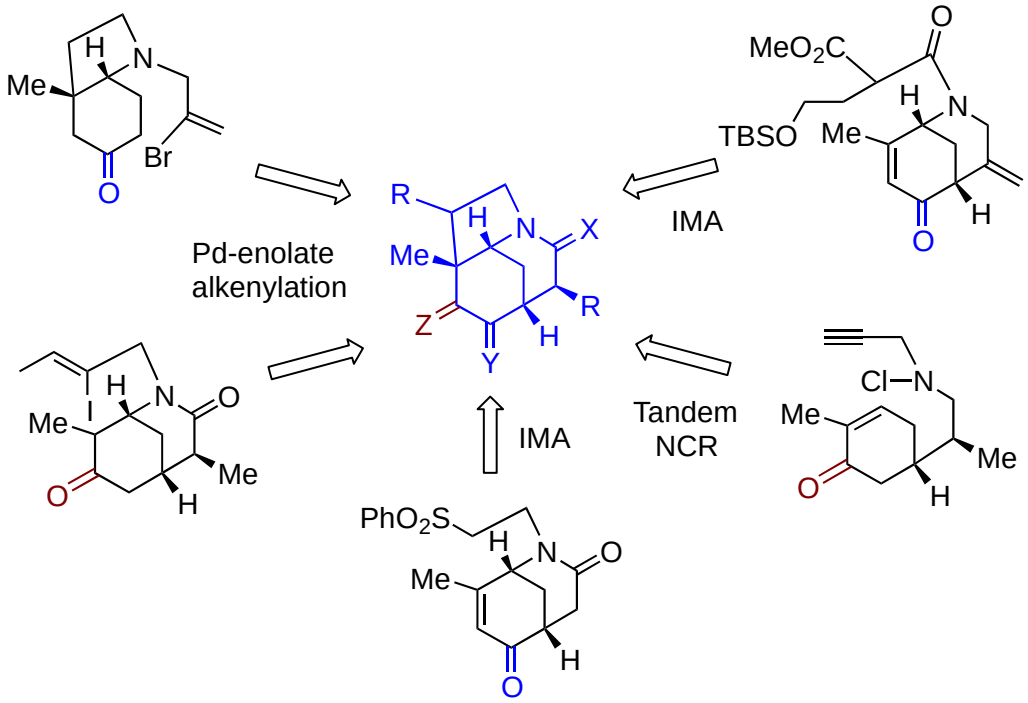
Los alcaloides Daphniphyllum son una familia diversa de productos naturales ricos en número y diversidad estructural que se conocen desde hace muchas décadas[53]. Sin embargo, la subclase estructuralmente única de alcaloides del tipo calicifilna A, que fue descubierto en forma tardía,[54] ha sido relativamente inexplorada (Esquema 1.15).



1.16 Alcaloides *daphniphyllum* del grupo de la calicifilina A

Se han descrito varias síntesis del núcleo ABC de perhidro-1,6-etanoindol, característico de esta subclase, mediante el desarrollo de una gama de estrategias sintéticas basadas en la alquenilación de enolatos catalizada por Pd, adición de Michael intramolecular, y procesos radicalarios (Esquema 1.16).

[53] Kobayashi, J.; Kubota, T. *Nat. Prod. Rep.* **2009**, *26*, 936-962.
[54] Kang, B.; Jakubec, P.; Dixon, D. J. *Nat. Prod. Rep.* **2014**, *31*, 550-562,



1.17 Aproximaciones al núcleo azatricíclico de los alcaloides calicifilina A

El primer trabajo en este campo fue realizado por nuestro grupo en 2005[55] y sólo cinco años después empezaron a aparecer trabajos ya continuados de diversos grupos con interés en esta área de síntesis total de productos naturales. Ang Li[56] describió su aproximación mediante una reacción de Michael intramolecular a partir de un morfano funcionalizado preparado mediante acoplamiento intramolecular de un alquino con una cetona catalizado por Au(I). Posteriormente, Liang[57] a partir del "Chiral pool" elaboró el núcleo AB y el cierre de anillo C de pirrolidina se llevó a cabo mediante la reacción alquenilación promovida por acoplamineto de enolatos. Finalmente, Stockdill[58] alcanzó el sistema azatricíclico mediante una doble ciclación tandem a partir de una *N*-cloroamina.

El conjunto de aproximaciones a otras subunidades de alcaloides del grupo de la calicifilina A pueden encontrarse en el reciente trabajo de revision de Dixon.[54]

En este contexto, el segundo objetivo sintético de esta Tesis que se expondrá en el capítulo 6 será una nueva aproximación al sistema azatricíclico de los alcaloides calicifilina, utilizando la química de ATRC para la elaboración del sistema morfánico y un proceso de Michael intramolecular basado en enolatos de sulfona.

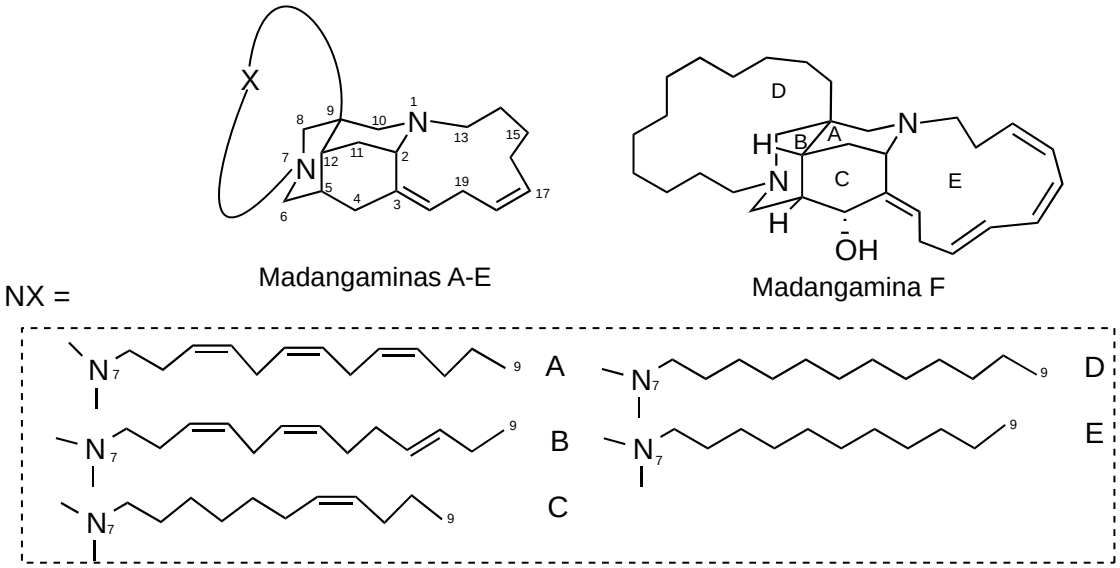
[55] Solé, D.; Urbaneja, X.; Bonjoch, J. *Org. Lett.* **2005**, *7*, 5461-5464.
[56] (a) Lu, Z.; Li, Y.; Deng, J.; Li, A. *Nature Chem.* **2013**, *5*, 679-684. (b) Xiong, X.; Li, Y.; Lu, Z.; Wan, M.; Deng, J.; Wu, S.; Shao, H.; Li, A. *Chem. Commun.* **2014**, *50*, 5294-5297.
[57] Yao, Y.; Liang, G. *Org. Lett.* **2012**, *14*, 5499-5501.
[58] Ibrahim, A. A.; Golonka, A. N.; Lopez, A. M.; Stockdill, J. L. *Org. Lett.* **2014**, *16*, 1072-1075.

1.6. Síntesis de los sistemas tetracíclicos ABCD de las madangaminas (Cap. 7)

Finalmente, nuestra atención se centró en la posible extensión de un procedimiento de síntesis radicalario a la síntesis de un morfano polifuncionalizado que pudiese dar acceso al sistema diazatetracíclico ABCD de los alcaloides marinos madangamina.

Las madangaminas son alcaloides marinos con una biogénesis específica que comporta una estructura esqueletal única entre el gran número de metabolitos, genéricamente agrupados como alcaloides del grupo 3-alquilpiperidinas, generados por las esponjas del orden Haplosclerida.[59]

Las madangaminas A-E fueron aisladas de esponjas *Xestospongia ingens* recolectadas en Madang en Nova Guinea Papua (A,[60] B-E[61]) en la década de los 90. La madangamina F fue aislada posteriormente de la esponja *Pachychalina alcaloidifera* en aguas del Brasil. [62]



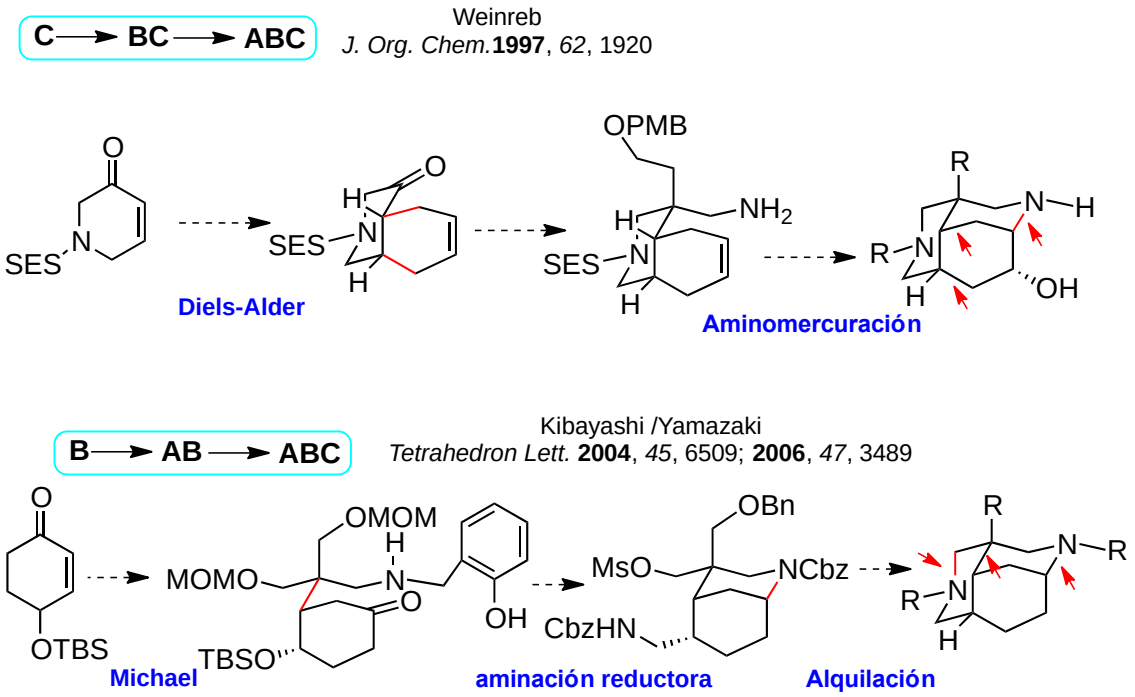
1.18 Estructuras de las madangaminas

El esqueleto pentacíclico de las seis madangaminas aisladas consiste en un núcleo diazatricíclico de perhidro-6,4-(iminometano)isoquinolina con dos puentes lineales que generen dos macrociclos. Uno de los hemisferios macrocíclicos es común en las madangaminas A-E, mientras que el macrociclo que implica al centro cuaternario varia en el número de insaturaciones, la localización de las mismas, y en su tamaño (13-15 átomos). La madangamina F presenta modificaciones estructurales más remarcables: un macrociclo E de 13 eslabones con cuatro insaturaciones, un

[59] Andersen, R. J.; van Soest, R. W. M.; Kong, F. *Alkaloids: Chemical and Biological Perspectives*; Pelletier, S. W. Ed.; Pergamon: New York, 1996; Vol. 10, pp 301-355.
[60] Kong, F.; Andersen, R. J.; Allen, T. M. *J. Am. Chem. Soc.* **1994**, *116*, 6007-6008.
[61] Kong, F.; Graziani, E. I.; Andersen, R. J. *J. Nat. Prod.* **1998**, *61*, 267-271.
[62] Oliveira, J. H. H. L.; Nascimento, A. M.; Kossuga, M. H.; Cavalcanti, B. C.; Pessoa, C. O.; Moraes, M. O.; Macedo, M. L.; Ferreira, A. G.; Hajdu, E.; Pinheiro, U. S.; Berlinck, R. G. S. *J. Nat. Prod.* **2007**, *70*, 538-543.

macrociclo D de 15 eslabones completamente saturado y la presencia de un grupo hidroxilo en C(4) (Figura 1.18).

En el curso del último sesquidecenio, se han desarrollado cinco diversos procedimientos[63] para acceder al núcleo diazatricíclico de las madangaminas (Esquema 1.19)[64] y muy recientemente la síntesis total de la madangamina D[65] (esquema 1.20), que constituye el único ejemplo de síntesis de un miembro de esta familia de alcaloides marinos.



1.19 Aproximaciones al núcleo azatricíclico de las madangaminas

La primera aproximación al sistema ABC de las madangaminas fue descrita en 1997 por Weinreb[59a]. En esta síntesis de 12 etapas la formación de la *cis*-hidroisoquinolina (BC) se consigue mediante una reacción de Diels-Alder entre una dihidropiridona, preparada según un protocolo descrito por Hiemstra,[66] y el butadieno. La homologació de la cetona proporciona un aldehído que mediante un

[63] (a) Matzanke, N.; Gregg, R. J.; Weinreb, S. M.; Parvez, M. *J. Org. Chem.* **1997**, *62*, 1920-1921; (b) Yamazaki, N.; Kusanagi, T.; Kibayashi, C. *Tetrahedron Lett.* **2004**, *45*, 6509-6512; (c) Tong, H. M.; Martin, M.-T.; Chiaroni, A.; Be´ne´chie, M.; Marazano, C. *Org. Lett.* **2005**, *7*, 2437-2440; (d) Quirante, J.; Paloma, L.; Diaba, F.; Vila, X.; Bonjoch, J. *J. Org. Chem.* **2008**, *73*, 768-771; (e) Amat, M.; Ballette, R.; Proto, S.; Pérez, M.; Bosch, J. *Chem. Commun.* **2013**, *49*, 3149-3151. Véase también: Amat, M.; Pérez, M.; Proto, S.; Gatti, T.; Bosch, J. *Chem. Eur. J.* **2010**, *16*, 9438-9441.

[64] Para la síntesis del fragmento azatricíclico ACE, véase: Proto, S.; Amat, M.; Pérez, M.; Ballette, R.; Romagnoli, F.; Mancinelli, A.; Bosch, J. *Org. Lett.* **2012**, *14*, 3916-3919.

[65] Ballette, R.; Pérez, M.; Proto, S.; Amat, M.; Bosch, J. *Angew. Chem. Int. Ed.* **2014**, 53, 6202-6205.

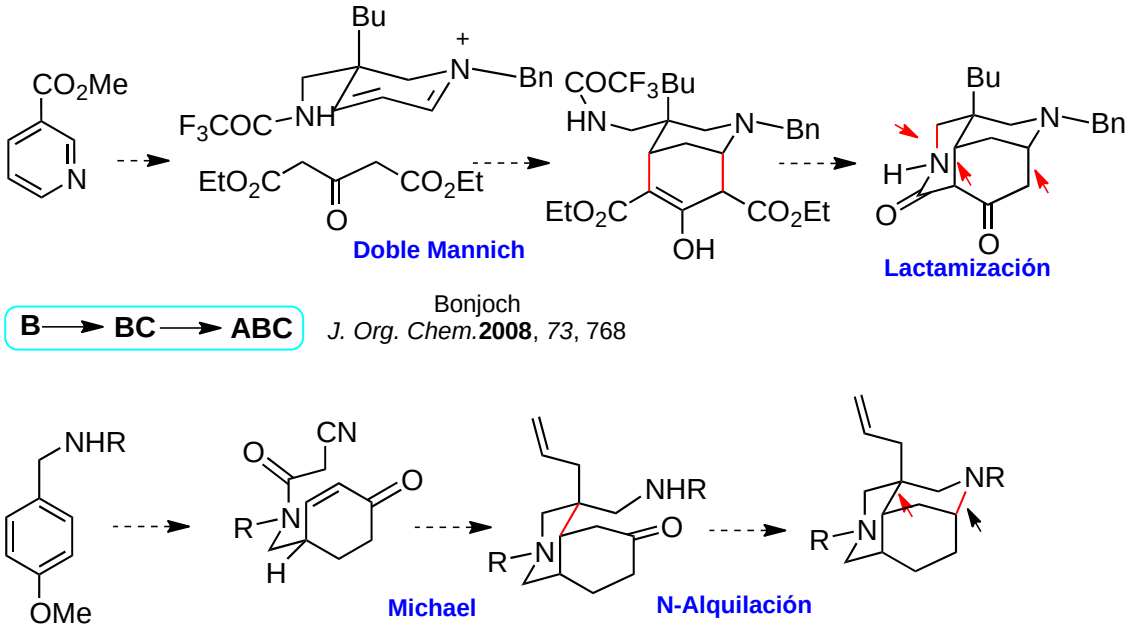
[66] Hopman, J. C. P.; van der Berg, E.; Ollero, L. O.; Hiemstra, H.; Speckamp, W. N. *Tetrahedron Lett*. **1995**, *36*, 4315-4318.

aliliminoderivado y transposición de tipo aza-Claisen[67] permite la formación del centro cuaternario requerido. Finalmente una aminomercuración conduce al diazatriciclo ABC con las funciones adecuadas para seguir con la síntesis.

La segunda síntesis del núcleo azatricíclico, publicada 7 años más tarde por Yamazaki y Kibayashi,[59b] implica más etapas que la anterior pero los estudios llevados a cabo en este trabajo generaron otros que permitieron la elaboración del macrociclo E característico de las madangaminas A-E.[68] En esta ruta sintética se parte de un anillo carbocíclico[69] que mediante una reacción de Michael intermolecular con cianoacetato de etilo y una serie de transformaciones incluyendo una reducción del nitrilo y una aminación reductora proporciona el intermedio polihidroxilado precursor del núcleo del morfano. Finalmente el cierre del tercer anillo se consigue mediante una alquilación intramolecular de la amina primaria protegida en presencia de *t*-BuOK.

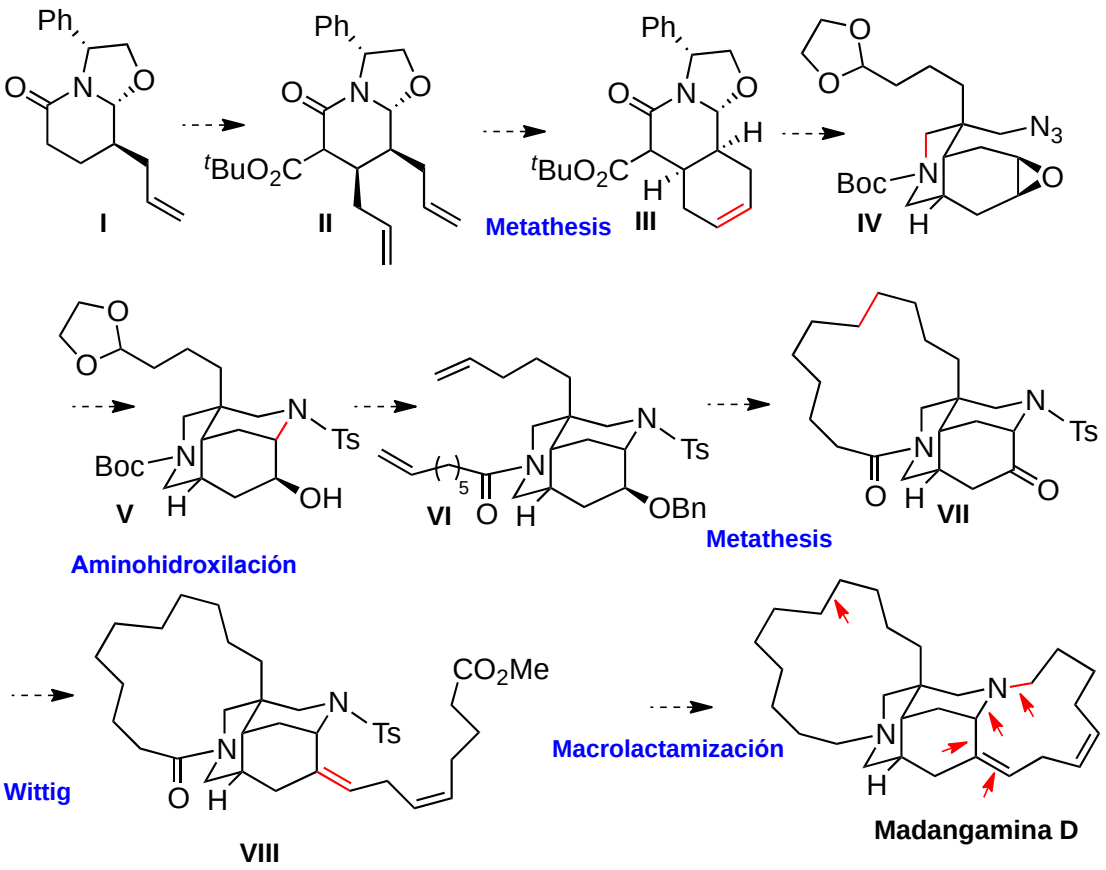
La tercera aproximación al núcleo diazatricíclico de las madangaminas fue publicada el año 2005 por el grupo de Marazano.[59c] En este caso el sistema de 2-azabiciclo[3.3.1]nonano se obtiene por una vía biomimética. A partir del éster metílico del ácido nicotínico se prepara la sal de dihidropiridinio que reacciona con la sal sódica de la acetonadicarboxilato de dietilo y posterior tratamiento con una base proporciona el sistema tricíclico como mezcla de productos. Finalmente la aproximación desarrollada en nuestro grupo de investigación se emplea una 4-metoxibenzilamina como producto de partida que al someterla a la reducción de Birch, posterior acoplamiento con un ácido y una reacción de Michael conduce de manera diastereoselectiva a la *cis*-perhidroisoquinolona que presenta la funcionalización requerida para el cierre final del tercer anillo piperidinico mediante una reacción de Mitsunobu.

[67] Murahashi, S. I.; Makabe, Y.; Kunita, K. *J. Org. Chem*. **1988**, *53*, 4489-4495.
[68] Yoshimura, Y.; Inoue, J.; Yamazaki, N.; Aoyagi, S.; Kibayashi, C. *Tetrahedron Lett.* **2006**, *47*, 3489-3492.
[69] Danishefsky, S. J.; Simoneau, B. *J. Am. Chem. Soc*. **1989**, *111*, 2599-2604.



1.19 (cont) Aproximaciones al núcleo azatricíclico de las madangaminas

Como se ha mencionado anteriormente, en el año 2014 se publicó la primera síntesis total de la madangamina D[61] que fue precedida por unos estudios en los cuales se logró la síntesis del esqueleto tetracíclico ABCD de la misma.[59e] La síntesis parte de la piperidina **I** enantiopura, a partir de la cual y mediante una serie de transformaciones se accedió al dieno **II** precursor del anillo C de la isoquinolina **III** por RCM. La apertura del epóxido **IV** por el grupo amino generado in situ condujo al núcleo diazatricíclico de las madangaminas. La síntesis del compuesto tetracíclico **VII**, que implica la formación del anillo D se basa en la instalación de dos cadenas laterales con dobles enlaces terminales y ulterior RCM para generar el sistema anular de 14 eslabones (Esquema 1.17). La macrociclación se indujo con el catalizador de Grubbs I que proporcionó una mezcla (2:1) de isómeros Z/E, irrelevante desde el punto de vista sintético, por el proceso de hidrogenación posterior.

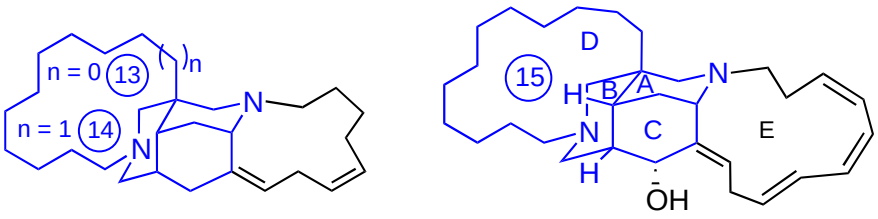


1. 20 Síntesis total de la madangamina D

El fragmento de 8 carbonos (*Z*,*Z*)-insaturado requerido para completar la síntesis de la madangamina D, fue incorporado de manera directa por reacción de Wittig en condiciones estrictamente anhidras. La eliminación del grupo tosilo en la resultante mezcla diastereomérica de alquenos (Z/E = 2.2:1)[70] seguido de la hidrólisis del éster y macrolactamización proporcionó una dilactama pentacíclica que por reducción con $LiAlH_4$ rindió la madangamina D.

El último objetivo de esta tesis doctoral fue la síntesis del esqueleto tetracíclico de las madangaminas E, D y F (Figura 1.21). Estas últimas presentan un macrociclo D completamente saturado de 13, 14 y 15 eslabones respectivamente y una oxigenación inusual en el anillo C en el caso de la madangamina F.

[70] Para estudios modelo, véase: ref. 64.



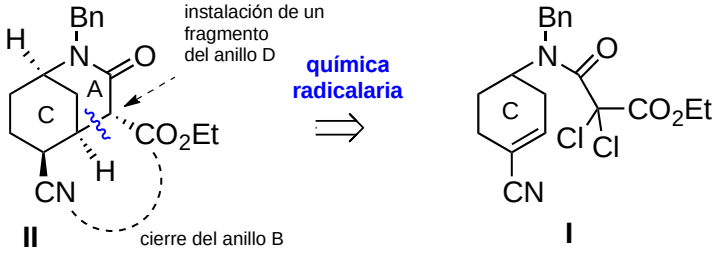
Madangaminas D y E Madangamina F

1.21 Madangaminas D, E y F

La síntesis se iniciaría con la construcción del biciclo morfánico a partir de la dicloromalonamida **I** utilizando la química radicalaria que constituye la parte metodológica de la presente Tesis (esquema 1.19).

El morfano propuesto **II** tendría todas las funciones necesarias y debría presentar la estereoquímica adecuada para

- La construcción del tercer anillo piperidínico B.
- La instalación de una cadena adecuada en el carbono 4 para el cierre del macrociclo D mediante una RCM.

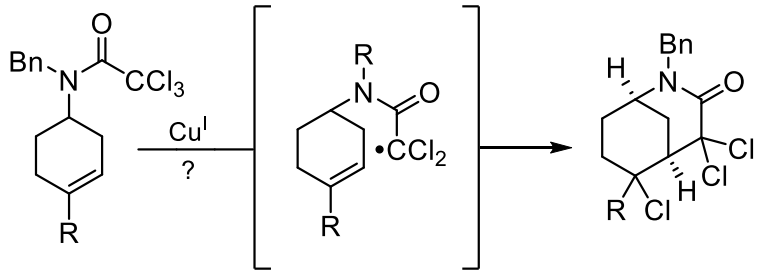


Esquema 1.22

2. Ciclación radicalaria con transferencia de átomo (ATRC) catalizada por Cu(I) de tricloroacetamidas en alquenos deficientes, neutros y ricos electrónicamente: síntesis de 2-azabiciclo[3.3.1]nonanos polifuncionalizados

2.1 Introducción y Objetivos

El primer objetivo de la Tesis es el estudio sistemático de las condiciones de reacción para llevar a cabo ciclaciones radicalarias con transferencia de átomo para la síntesis de 2-azabiciclo[3.3.1]nonanos utilizando Cu(I) como catalizador y diversos tricloroacetamidociclohexenos como sustratos (esquema 2.1). Estos pueden prepararse a partir de la 4-(bencilamino)ciclohexanona y muestran un amplio espectro de densidad electrónica como aceptor radicalario así como una gama de grupos funcionales de interés para el acceso a intermedios avanzados para la síntesis total de productos naturales[1].



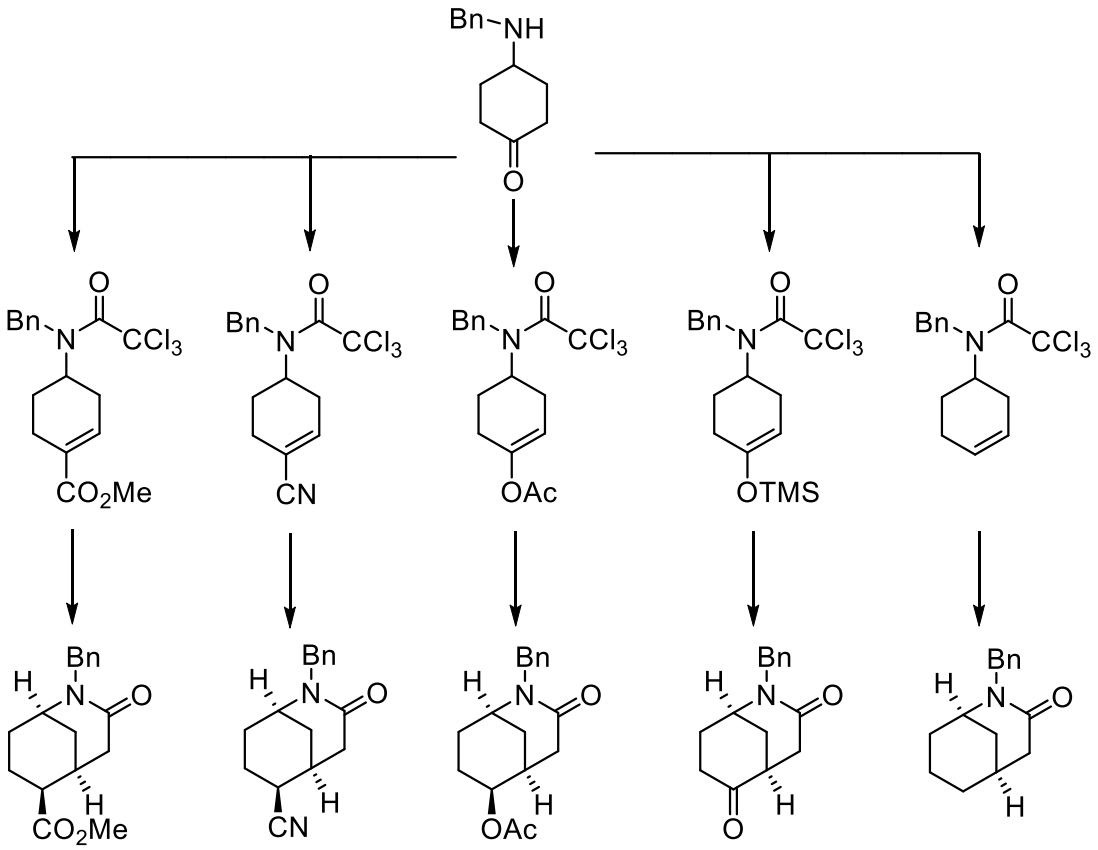
R = CO_2Me, CN, H, OAc, $OSiMe_3$

2.1 Primer objetivo de la Tesis: Síntesis de azabiciclos

Para el uso de tricloroacetamidas en la síntesis de anillos nitrogenados hay dos métodos esenciales: el método reductivo (p.ej. con hidruros de estaño) y el método de transferencia de átomo.

El método reductivo ha sido ampliamente estudiado en nuestro grupo de investigación con distintos agentes reductores (Bu_3SnH, $(Me_3Si_3)_3SiH$) para la síntesis de 2-azabiciclo[3.3.1]nonanos. Como se puede observar (esquema 2.2), la ciclación radicalaria tiene lugar sobre alquenos no activados, ricos electrónicamente (OAc, OTMS) o pobres (CN, CO_2Me).

[1] Para métodos previos de síntesis de 2-azabiciclo[3.3.1]nonanos desarrollados en el grupo de investigación, véase: (a) Bonjoch, J.; Casamitjana, N.; Bosch, J.*Tetrahedron*, **1988**, *44*, 1735; (b) Quirante, J.; Escolano, C.; Merino, A.; Bonjoch, J. *J. Org. Chem*., **1998**, *63*, 968; (c) D. Solé, D.; Urbaneja, X.; Bonjoch, J.; *Org. Lett*. **2005**, *7*, 5461; (d) Diaba, F.; Bonjoch, J. *Org. Biomol. Chem*. **2009**, *7*, 2517; (e) Bradshaw, B.; Parra, C.; Bonjoch, J. *Org. Lett.* **2013**, *15*, 2458.



2.2 Precedentes en nuestro grupo de investigación (método reductivo)

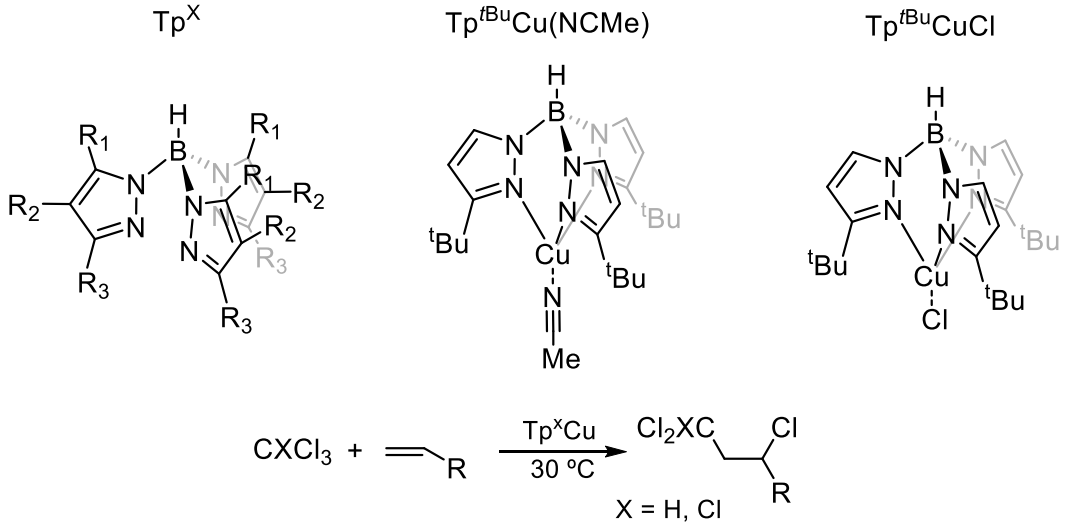
El método de transferencia de átomo introduce una química más sostenible ya que se trata de un método catalítico y no requiere el uso de derivados de estaño. Además, el método permite una mayor funcionalización en el producto final que posibilita ulteriores transformaciones. La utilización de derivados de Cu(I) para la transferencia de átomo presenta ventajas adicionales por el bajo coste del cobre y la facilidad operativa en su manejo.

Enmarcados en este contexto, el cual dio lugar a los objetivos iniciales de la presente Tesis, en la fase inicial de la Tesis se estableció una colaboración con el grupo de los Prof. Pedro J. Pérez y Tomás R. Belderraín de la Universidad de Huelva, para el estudio de reacciones radicalarias con transferencia de átomo catalizadas por Cu (I) con ligandos tipo homoescorpionato, que habían estado desarrollados en su grupo, aplicadas a nuestros sustratos de interés para generar 2-azabiciclo[3.3.1]nonanos[2].

En 1966 había aparecido una nueva clase de ligandos versátiles llamados polipirazolboratos[3], para los que en 2008 ya se habían reportado complejos con 70

[2] Parte de los resultados obtenidos fueron llevados a cabo durante una estancia de A.M.L. en la Universidad de Huelva
[3] Trofimenko, S. *J. Am. Chem. Soc.* **1966**, *88*, 1842.

elementos de la tabla periódica[4]. Los complejos más utilizados son los de tipo hidrotrispirazolboratos, abreviados como Tp^x y conocidos como homoescorpionatos (esquema 2.3).



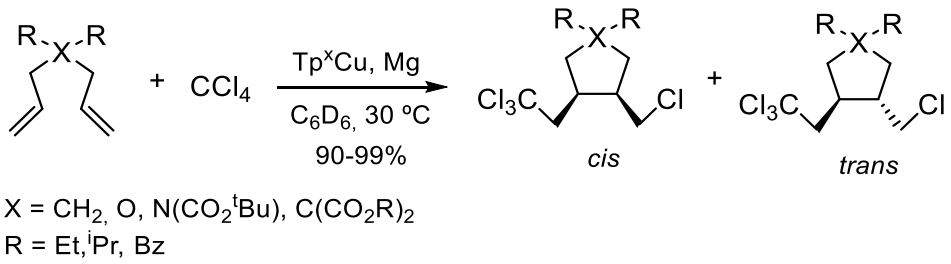
2.3 Precedentes grupo de colaboración en Huelva

Los complejos de Cu(I) con ligandos hidrotrispirazolilborato de tipo $Tp^xCu(NCMe)$ han sido empleados de manera eficiente como catalizadores en las reacciones de ATRA de CCl_4 o $CHCl_3$ a olefinas bajo condiciones de reacción suaves (30 ºC). Se ha descrito que los efectos electrónicos y estéricos de los ligandos Tp^x ejercen una clara influencia sobre la actividad catalítica del centro metálico, de manera que los catalizadores más activos resultan ser los que poseen ligandos Tp^x voluminosos y con un marcado carácter donador de densidad electrónica.[5] Se ha demostrado que los complejos $Tp^{tBu}Cu(NCMe)$ tienen una actividad en reacciones radicalarias con transferencia de átomo que supera los otros catalizadores basados en Cu(I) descritos hasta la fecha.[6]

[4] (a) Trofimenko, S. Scorpionates: *The Coordination Chemistry of Polypyrazolylborate Ligands*; Imperial College Press: London, **1999**. (b) Pettinari, C. Scorpionates II. *Chelating Borate Ligands*; Imperial College Press: London **2008**.

[5] Muñoz-Molina, J. M.; Caballero, A.; Díaz-Requejo, M.; Trofimenko, S.; Belderraín T. R.; Pérez, P. J. *Inorg. Chem*. **2007**, *46*, 7725.

[6] (a) Carrier, S. M.; Ruggiero, C. E.; Houser, R. P.; Tolman, W. B. *Inorg. Chem.* **1993**, *32*, 4889. (b) Muñoz-Molina, J. M.; Belderrain, T. R.; Pérez, P. J. *Inorg. Chem*. **2010**, *49*, 642. (c) Muñoz-Molina, J. M.; Belderrain T. R.; Pérez, P. J. *Eur. J. Inorg. Chem*. **2011**, 3155.



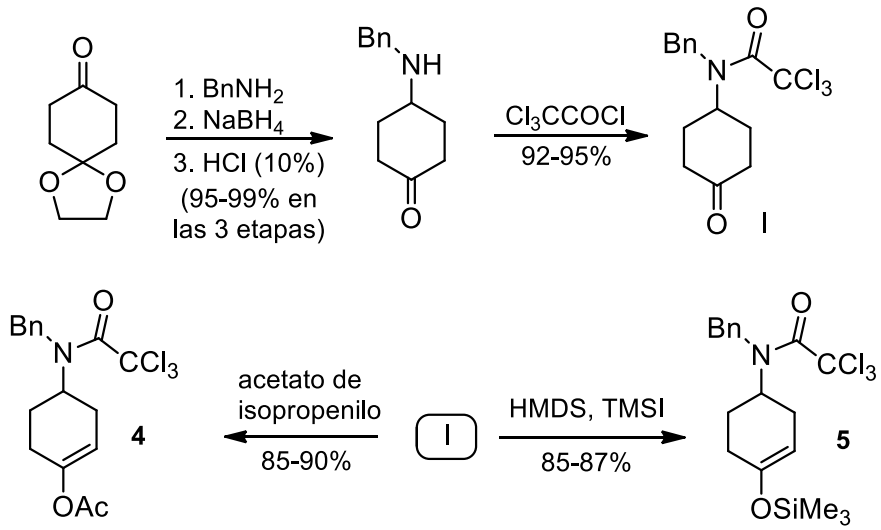
2.3 (cont) Precedentes grupo de colaboración en Huelva

Los complejos de tipo $Tp^xCu(NCMe)$ se han empleado con éxito como catalizadores para la síntesis de hetero- y carbociclos de 5 miembros 1,2-disustituidos vía ATRAC (adición-ciclación) de 1,6-dienos en condiciones suaves de reacción (30 ºC).[7]

2.2 Discusión y resultados

*2.2.1 Preparación de las tricloroacetamidas **1-5**.*

Nuestros primeros esfuerzos fueron encaminados a la preparación de los sustratos de tipo tricloroacetamida requeridas para el estudio, utilizando los protocolos desarrollados en nuestro grupo de investigación[8] con dos propósitos: a) mejorar los rendimientos y b) acortar las etapas de su obtención.

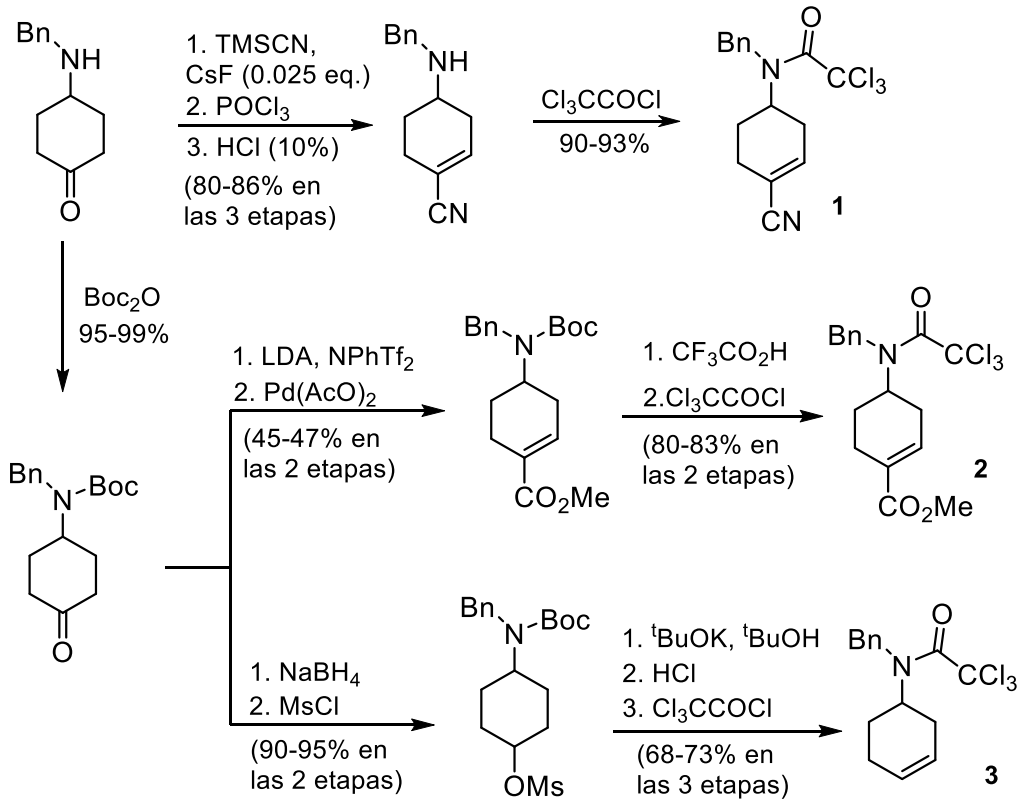


2.4 Preparación de los alquenos **4** y **5**

Partiendo de la 1,4-ciclohexandiona monoetilenacetal (esquema 2.4), la tricloroacetamida **I** se sintetizó mediante una aminación reductiva con bencilamina,

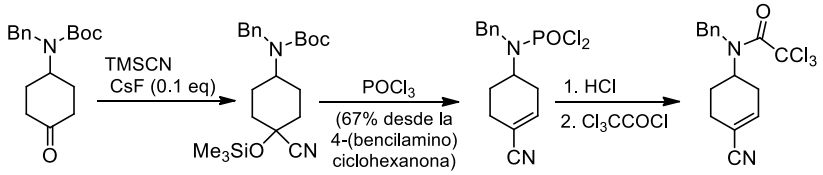
[7] Muñoz-Molina, J. M.; Belderraín, T. R.; Pérez, P. J. *Adv. Synth. Catal.,* **2008**, *350*, 2365.
[8] (a) Quirante, J.; Escolano, C.; Massot, M.; Bonjoch, J. *Tetrahedron*, **1997**, *53*, 1391; (b) Quirante, J.; Escolano, C.; Diaba, F.; Bonjoch, J. *Heterocycles*, **1999**, *50*, 731; (c) Quirante, J.; Escolano, C.; Diaba, F.; Bonjoch, J. *J. Chem. Soc*., Perkin Trans. *1*, **1999**, 1157.

seguida de hidrólisis y tricloroacetilación. Este intermedio fue común para la preparación de los alquenos ricos electrónicamente, mediante tratamiento con acetato de isopropenilo para obtener el acetato de enol **4** y utilizando iodotrimetilsilano para rendir el sililenol éter **5**. La preparación de los alquenos pobres electrónicamente **1** y **2**, así como la del alqueno **3** se consiguió siguiendo la ruta sintética del esquema 2.5.[9,10]



2.5 Preparación de las tricloroacetamidas **1-3**

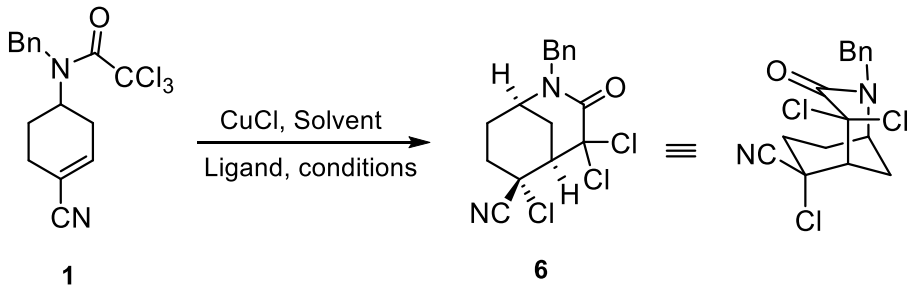
[9] En trabajos anteriores (ref 8a) la preparación del nitrilo **1** pasaba por la protección de la 4-(bencilamino)ciclohexanona en forma de carbamato y, o bien formar su triflato, desde la correspondiente cetona, para entonces con $Pd(Ph_3P)_4$ y éter corona promover la formación del nitrilo α,β-insaturado, que debía ser desprotegido y acilado, o bien formar la cianohidrina, desde la amina libre, con Me_3SiCN y ZnI_2, para entonces acilar y promover la eliminación con $POCl_3$. Sin embargo ambos protocólos proporcionaban el nitrilo **1** desde la amina libre con rendimientos globales pobres. En el inicio de la presente tesis (abril de 2011), ya se había optimizado la ruta aunque utilizaba una etapa de protección innecesaria:



[10] La metodología descrita (ref 8b) proporcionaba la tricloroacetamida deseada desde el mesilato, ahorrando la protección y desprotección del carbamato, no obstante la eliminación del mesilato se realizaba mediante una pirolisis que requería de temperaturas elevadas y presiones bajas.

2.2.2 Ciclaciones radicalarias utilizando Tp^{tBu}Cu(NCMe)

El estudio metodológico se centró en el nitrilo α,β-insaturado **1** al ser uno de los más interesantes para acceder a intermedios avanzados de síntesis funcionalizados.



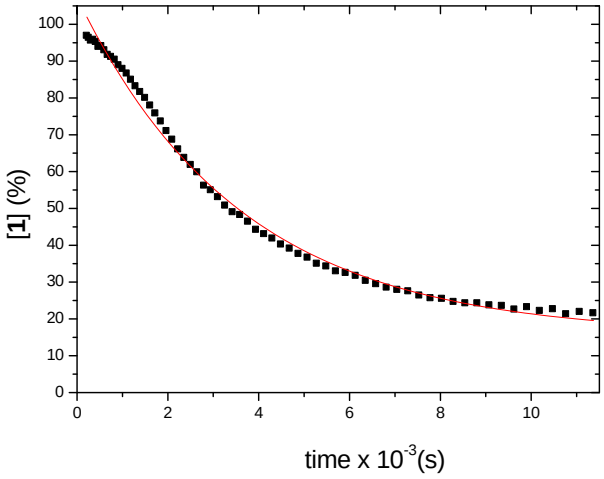
1 **6**

2.6 Estudios de ATRC a partir de **1** (realizados en Huelva)

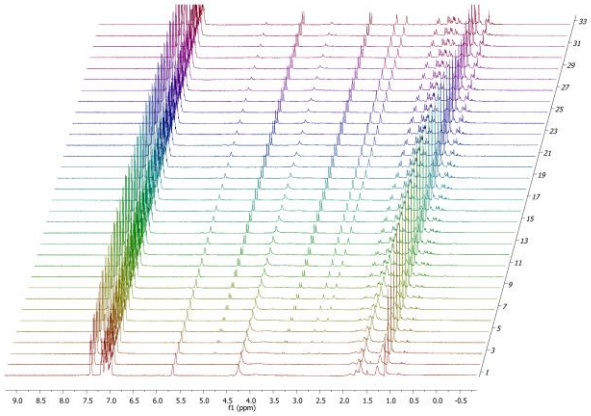
a) 2% Tp^{tBu}Cu(NCMe), 10% AIBN, C_6D_6, 15 h, 60 ºC (**6**, 90%); b) 1% Tp^{tBu}CuCl, 10% AIBN, C_6D_6, 6 h, 60 ºC (**6**, 78%); c) 10% Tp^{tBu}Cu(NCMe), 20% AIBN, Tolueno, 24 h, 60 ºC (**6**, 79%).[11]

Los estudios iniciales fueron realizados en la universidad de Huelva a escalas de tubo de RMN, del orden de 10 a 40 mg, utilizando un 2% de catalizador Tp^{tBu}Cu(NCMe), 10% de AIBN en benceno deuterado a 60 ºC durante 6 h. La tricloroacetamida **1** procedió de forma satisfactoria al proceso ATRC para rendir **6** con excelentes rendimientos (esquema 2.6, a). Al utilizar el complejo Tp^{tBu}CuCl (1%), 10% AIBN en C_6D_6 a 60 ºC durante 6 h se obtuvo el morfano deseado **6** en un 78% de rendimiento (esquema 2.6, b).[12] Además, fueron realizados una serie de estudios del seguimiento de la reacción, en la figura 2.8 se muestra la monitorización cinética de la consumición de **1** por el complejo Tp^{tBu}CuCl (1%) y en la figura 2.9 se muestra la monitorización de la reacción de **1** mediante resonancia magnética nuclear del protón para el complejo Tp^{tBu}Cu(NCMe) (0.5%).

[11] Los experimentos a) y b) están realizados a escala de RMN (10-40 mg), el experimento c) a escala preparativa (100-200 mg).
[12] Los rendimientos de todos los ensayos a escalas de RMN, 10 a 40 mg, están calculados en base a los crudos de reacción analizados directamente mediante 1H RMN.



2.7 Monitorización cinética de la consumición de **1** (^{1}H NMR, 60 ºC, C_6D_6) en la reacción de formación de **6**, utilizando Tp^{tBu}CuCl [Cu]/[AIBN]/[**1**] = 1:2:10. Rate constant, k_{obs} = 2.78x10^{-4} s^{-1}.



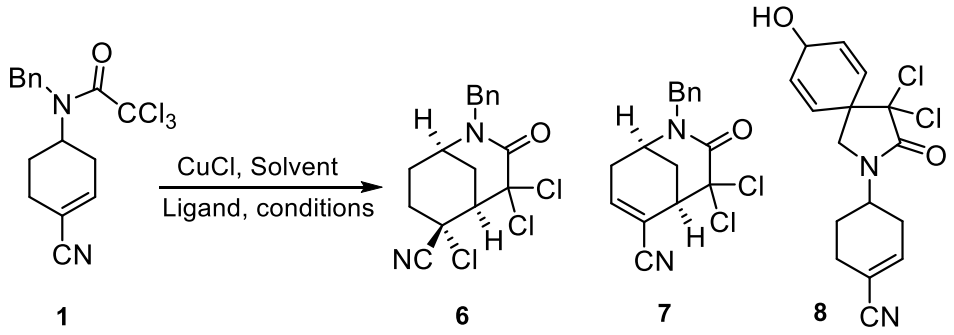
2.8 Monitorización de la reacción mediante espectro ^{1}H de Tp^{tBu}Cu(NCMe):AIBN:**1** (ratio1:20:200) en C_6D_6 a 60 ºC. Un espectro de protón se registró cada 3.6 min.

El grupo de colaboración también ensayó con las demás tricloroacetamidas **2-5**, a escalas de 10 a 40 mg, obteniendo resultados prometedores.

Esperanzados por estos resultados se realizó una breve estancia a fin de comprobar la reproducibilidad en nuestras instalaciones así como comprobar su escalado. Desafortunadamente para conseguir conversiones completas a escalas preparativas, 100-200 mg, fue necesario el aumento al 10% Tp^{tBu}Cu(NCMe) y tras su purificación se aisló **6** en rendimientos inferiores a lo esperado (esquema 2.6, entrada 3). Peor aún, los complejos de Cu con ligandos hidrotrispirazolilborato necesitan de unas instalaciones aisladas del medio ambiente de tipo caja seca “Dry Box”, de las que no disponíamos en nuestro laboratorio.

*2.2.3 Estudios metodológicos de las tricloroacetamidas **1** a **5***

A fin de seguir con nuestros objetivos el trabajo se orientó a la búsqueda de unas condiciones de reacción más robustas y que permitieran un escalado del proceso. Los estudios se llevaron a cabo utilizando **1** como substrato.



1 **6** **7** **8**

Entrada	Catalizador CuCl	Ligando TPMA	Aditivo AIBN	Disolvente	Tiempo	Temp.	Rendimiento
1	10-30%	-	-	EtOH	4-24 h	t.a. - rfx.	-
2	10-30%	0-30%	-	CH_2Cl_2	4 -24 h	t.a. - rfx.	-
3	30%	30%	-	1,2-DCE	4 h	80 ºC	**6** (83%)
4	30%	30%	-	1,2-DCE	60 h	60 ºC	**6** (57%), **7** (12%)
5	10%	10%	50%	1,2-DCE	48 h	60 ºC	**6** (87%)
6	30%	-	-	DMF	16 h	80 ºC	**6** (70%)
7	30%	30%	-	DMF	16 h	80 ºC	**7** (60%)
8	30%	-	-	CH_3CN	16 h	80 ºC	**6** (50%), **8** (10%)

2.9 ,Optimización de la reacción de ciclación a partir de **1**

El estudio empezó explorando las condiciones de reacción que se encuentran en la literatura para las ATRC y así se utilizaron los disolventes más típicos. Como se puede observar (Tabla 2.9) disolventes como el EtOH conducían a la recuperación del material de partida incluso con altas cargas de CuCl y a temperatura de reflujo (entrada 1). Los distintos ensayos que se realizaron con CH_2Cl_2 tampoco fueron fructíferos (entrada 2). Estos resultados se deben en gran parte a la insolubilidad del sustrato o el cloruro de cobre en estos disolventes.

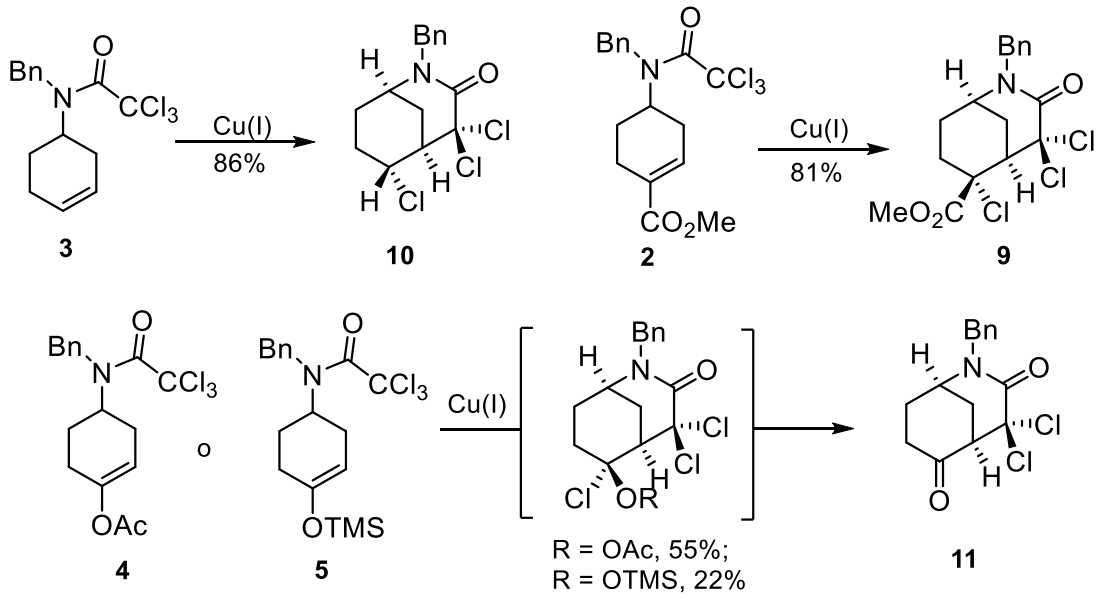
Afortunadamente, cuando la reacción se realizó en 1,2-dicloroetano (1,2-DCE) proporcionó el morfano **6** con muy buen rendimiento. Para ello fue necesario cargas del 30% de CuCl combinado con el uso de tris[(2-piridil)metil]amina (TPMA) como ligando y temperaturas de 80 ºC durante un mínimo de 4 h de reacción (entrada 3).[13] El uso de otros ligandos como el 2,2-bipiridilo o temperaturas superiores no llevaron a resultados dignos de mención y los intentos por conseguir bajar la carga de catalizador pasaron por la inclusión de AIBN, como agente regenerador, consiguiendo así las que serían las condiciones optimizadas: 10% CuCl-TPMA, 50% AIBN, 60 ºC, 48 h (entrada

[13] En la escala de 100 mg a 1 g los rendimientos oscilan del 79-84%

5). Adicionalmente se ha utilizado $CuCl_2$/TPMA/AIBN en 1,2-DCE esperando que según lo expuesto por Pintauer[14] se formase el complejo y fuera reducido por el AIBN, no obstante las los diferentes ensayos condujeron a conversiones no superiores al 10%.

Con el uso de DMF como disolvente no fue necesaria la adición de ligandos, así con el 30% de carga a 80 ºC y 16 h de reacción se conseguía obtener el morfano **6** con buenos rendimientos (entrada 6). Con la inclusión de TPMA como ligando en las mismas condiciones el morfano formado fue **7** en un 60% (entrada 7).

Utilizando CH_3CN como disolvente con el 30% de CuCl a 80 ºC y 16 h de reacción condujo a un 50% del morfano **6** junto a un 10% de **8** como mezcla de epímeros (entrada 8). Los 2-azaespiro[4.5]decanos **8** se formarían mediante una ciclación radicalaria del radical diclorocarbamoilo sobre el anillo aromático. Las limitaciones y el alcance de este proceso de desaromatización se encuentran desarrollados en el capítulo 4 de la presente Tesis.



2.10 Extensión de la ATRC a las tricloroacetamidas **2-5**:
(10% CuCl-TPMA, 50% AIBN, DCE, 48 h, 60 ºC)

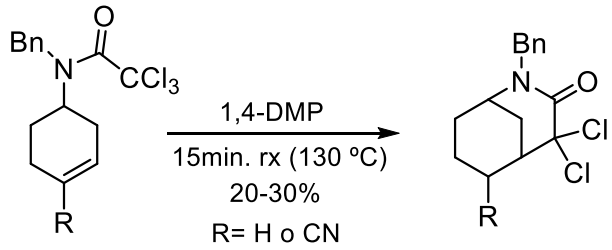
Las condiciones de ciclación optimizadas se aplicaron al resto de tricloroacetamidas (CuCl-TPMA-AIBN 0.1/0.1/0.5). De esta forma se obtuvieron **9** y **10** con 81% y 86% de rendimiento respectivamente. Además de los excelentes resultados cabe destacar que todas las ciclaciones, tanto para los alquenos pobres electrónicamente como para el alqueno desactivado, son procesos diastereoselectivos y la configuración del nuevo estereocentro donde se ha transferido el átomo de cloro se encuentra en disposición axial.

Por último se examinaron los alquenos ricos electrónicamente el acetato de enol **4** y el sililenol éter **5**. Ambos condujeron a la cetona **11** con bajos rendimientos (55 y 22%

[14] Pintauer, T.; Matyjaszewski, K. *Chem. Soc. Rev*. **2008**, *37*, 1087.

respectivamente), formada cuando el producto de anulación inicial evoluciona a la cetona más estable ya sea en el sí de la reacción o durante la purificación.

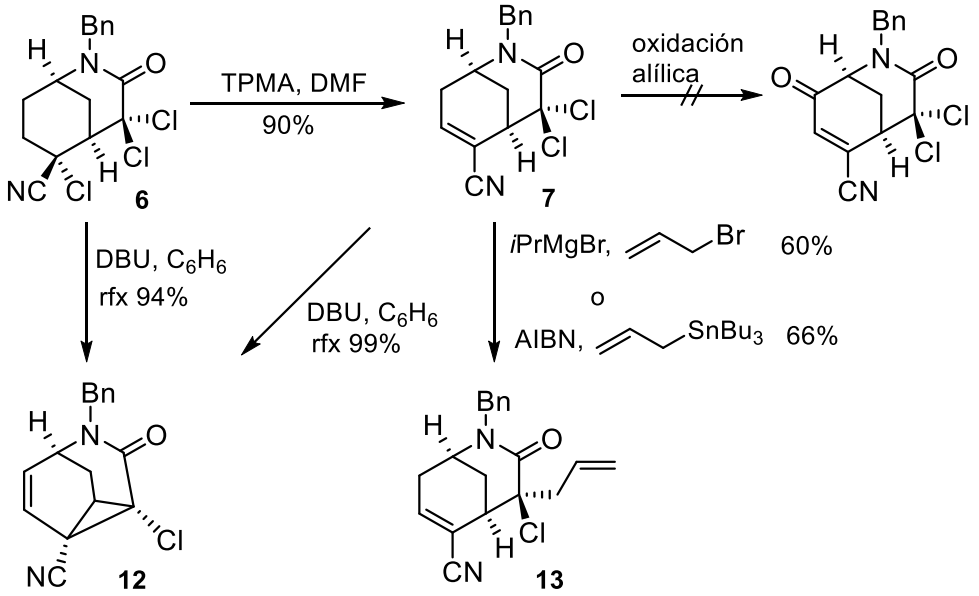
Adicionalment, en el transcurso del estudio metodológico se realizaron ensayos con 1,4-dimetilpiperazina (esquema 2.11)[15]. Los resultados fueron pobres, si bien no sería descartable un ulterior intento de optimización.



2.11 Ensayos realizados con 1,4-dimetilpiperazina

2.2.4 Estudios preliminares en la serie nitrilo

En estudios preliminares con el morfano **6** (esquema 2.12) la unidad α-cloronitrilo demostró ser un precursor sintético versátil en virtud de disponer de dos funciones ortogonales en el mismo carbono.

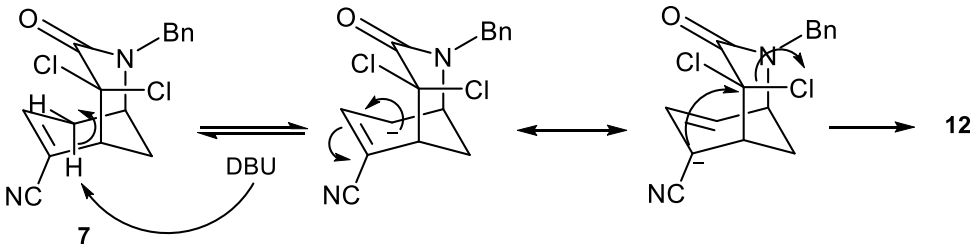


2.12 Transformaciones sintéticas del nitrilo insaturado **6**

Los primeros intentos de transformar el morfano **6** bien a su derivado de eliminación **7** (DBU, Et_3N) o bien a su hidrólisis para obtener la cetona **11** (KOH)[16] condujeron de

[15] Ishibashi, H.; Sasaki, M.; Taniguchi, T. *Tetrahedron* **2008**, *64*, 7771-7773.
[16] Luo, Y. and Carnell, J. A. *J. Org. Chem.* **2010**, *75*, 2057.

forma inesperada a un producto tricíclico **12**, con un ciclopropano incrustado en el sistema de morfano.



2.13. Mecanismo propuesto para la formación de **12** desde **7**

Aprovechando los conocimientos obtenidos en el estudio metodológico se pudo transformar con excelentes rendimientos el morfano **6** a su producto de eliminación **7**, usando las condiciones de TPMA en DMF a 80 ºC. Asimismo, se observó que en condiciones de reacción más drásticas (DBU a reflujo), el producto de eliminación evolucionaba con excelentes rendimientos al ciclopropano **12**.

En base a los datos obtenidos lo más probable es que este compuesto inesperado **12** (esquema 2.13) se forme a través de una γ-desprotonación del producto de eliminación **7** seguida por un ataque nucleófilo del anión nitrilo al C(4) teniendo como grupo saliente a un átomo de cloro, generando así el ciclopropano con el esqueleto morfano. Cabe destacar que este tipo de compuestos contiene la estructura básica del 4-azabarbaraleno[17], que tiene solamente un único precedente sintético.[18]

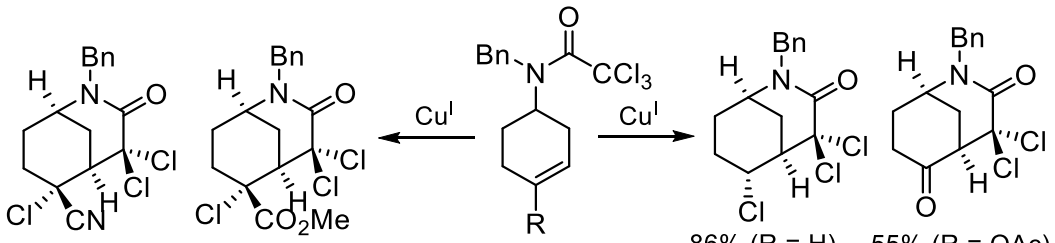
Los intentos de conseguir una oxidación alílica (IBX, $Mn(OAc)_3$) en el compuesto de eliminación **7** sólo condujo a la recuperación del material de partida.[19]

Por otro lado, al someter **7** a un proceso de alilación, ya sea aniónica o radicalaria, se pudo obtener estereoselectivamente **13** con unos rendimientos, sin optimizar, del 60 y del 66% respectivamente.

[17] Hrovat, D. A.; Brown, E. C.; Williams, R. V.; Quast, H.; Borden, W. T. *J. Org. Chem*. **2005**, *70*, 2627.
[18] Neidlein, R.; Wesch, K. F. *Chem. Ber.* **1983**, *116*, 2466.
[19] Shing, T. K. M.; Yeung, Y.-Y.; Su, P. L. *Org. Lett.* **2006**, *8*, 3149.

2.3 Resumen

- Se ha descrito la aplicación de la metodología ATRC para la síntesis de 2-azabiciclo[3.3.1]nonanos utilizando Cu(I) como catalizador y diversos tricloroacetamidociclohexenos como sustratos. Los resultados obtenidos con los distintos alquenos: con alta densidad electrónica (R=OAc, R=OTMS), con baja densidad electrónica (R=CN, R=CO_2Me) y neutro (R=H) amplían el espectro de la utilización de los procesos ATRC en síntesis orgánica.



Condiciones de reacción: CuCl (10%), TPMA (10%), AIBN (50%), DCE 60 ºC, 48 h

2.14 Resultados optimizados de las tricloroacetamidas **1-5**

- Los resultados obtenidos indujeron una extensión de los estudios metodológicos a sustratos más complejos (véase cap. 3) así como la ulterior aplicación a procesos encaminados a la síntesis de productos naturales (véase cap. 5-7). La posibilidad de nuevos estudios se basa en: a) la optimización en la preparación de los precursores de ciclación radicalaria, mediante etapas robustas, de fácil manipulación y purificación, y altos rendimientos globales, y b) el proceso ATRC permite acceder a 2-azabiciclo[3.3.1]nonanos con excelentes rendimientos hasta escalas de 1-2 g.

- En el transcurso del estudio metodológico de la serie nitrilo se observó que al emplear acetonitrilo como disolvente parte del sustrato experimentaba una desaromatización del anillo benceno mediante un proceso ATRC. Las limitaciones y el alcance de este proceso de desaromatización se encuentran desarrollados en el capítulo 4 de la presente Tesis.

2.4 Cu(I)-catalyzed atom transfer radical cyclization of trichloroacetamides tethered to electron-deficient, -neutral, and –rich alkenes: syntheseis of polyfunctionalized 2-azabicyclo[3.3.1]nonanes.

Diaba, F.; Martínez-Laporta, A.; Bonjoch, J.; Pereira, A.; Muñoz-Molina, J.; Pérez, J.; Belderrain, T.

Chem. Commun, **2012**, *48*, 8799-8801.

ChemComm

Dynamic Article Links

Cite this: *Chem. Commun.*, 2012, **48**, 8799–8801

www.rsc.org/chemcomm

COMMUNICATION

Cu(I)-catalyzed atom transfer radical cyclization of trichloroacetamides tethered to electron-deficient, -neutral, and -rich alkenes: synthesis of polyfunctionalized 2-azabicyclo[3.3.1]nonanes†

Faïza Diaba,[a] Agustín Martínez-Laporta,[a] Josep Bonjoch,*[a] Ana Pereira,[b] José María Muñoz-Molina,[b] Pedro J. Pérez[b] and Tomás R. Belderrain*[b]

Received 7th May 2012, Accepted 13th July 2012
DOI: 10.1039/c2cc34133f

A novel synthetic entry to 2-azabicyclo[3.3.1]nonanes based on a copper(I)-catalyzed intramolecular coupling of amino-tethered trichloroacetamides and unsaturated nitriles, esters and alkenes, as well as enol acetates, is described. A study of the reaction conditions and the scope of the process is reported.

The 2-azabicyclo[3.3.1]nonane framework is found in over 300 natural products of several biogenetic types[1] (Fig. 1). As part of our ongoing interest in developing synthetic procedures to obtain this azabicyclic ring,[2] we considered that Cu(I)-catalyzed atom transfer radical cyclization (ATRC, Scheme 1),[3] using trichloroacetamide-tethered cyclohexenes as substrates,‡ could be a suitable methodology to achieve polyfunctionalized 2-azabicyclononanes, which would serve as valuable building blocks for alkaloid synthesis. Although Cu(I)-promoted radical reactions are recognized as a useful method for the formation of C–C bonds in carbocyclization processes,[4] they have been largely ignored for the synthesis of nitrogen-containing six-membered rings.[5]

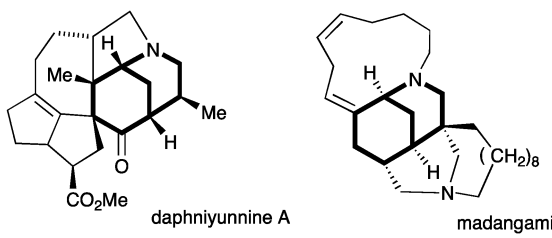


Fig. 1 Natural products embodying a 2-azabicyclo[3.3.1]nonane framework.

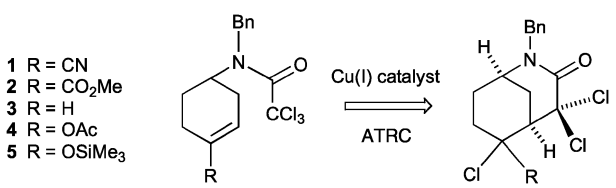
[a] *Laboratori de Química Orgànica, Facultat de Farmàcia, IBUB, Universitat de Barcelona, Av. Joan XXIII s/n, 08028-Barcelona, Spain. E-mail: josep.bonjoch@ub.edu; Tel: +34 934024540*
[b] *Laboratorio de Catálisis Homogénea, Departamento de Química y Ciencia de los Materiales, Unidad Asociada al CSIC, CIQSO, Universidad de Huelva, Campus de El Carmen, 21007 Huelva, Spain. E-mail: trodri@uhu.es; Tel: +34 959219955*

† Electronic supplementary information (ESI) available: Experimental procedures for all new compounds, and NMR data and copies of ^{1}H and ^{13}C NMR. Kinetic and ^{1}H NMR spectra reaction monitoring for the transformation of **1** into **6** using $Tp^{tBu}CuCl$. See DOI: 10.1039/c2cc34133f

Since the classical studies by Nagashima *et al.* using Cu(I) as a sole catalyst,[6] ATRC has been improved by the implementation of nitrogen-based ligands to stabilize Cu(I).[7] Furthermore, based on Matyjaszewski's studies of atom transfer radical polymerization processes (ATRP),[8] new reaction conditions involving initiators for continuous activator regeneration (ICAR) have successfully overcome the accumulation of the persistent radical Cu(II), which deactivates the radical chain propagation. However, in spite of these substantial advances in the ATRC field,[9] when applied to azacycles this methodology has been almost entirely focused on studies leading to the formation of five-membered lactams. Moreover, when starting from trichloroacetamides, using either Cu or Ru catalysts, the radical acceptor has usually been limited to a simple alkene.[10]

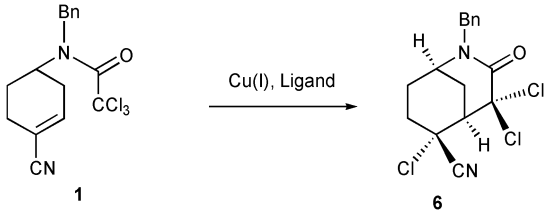
In this contribution, we report the application of the ATRC methodology to the synthesis of 2-azabicyclo[3.3.1]nonanes using Cu(I) as the catalyst and several trichloroacetamide-tethered cyclohexenes as reactants (**1–5**, Scheme 1). The latter are readily available from 4-(benzylamino)cyclohexanone[11] and show a broad spectrum of electron densities in the radical acceptor site as well as a wide portfolio of functional groups, which is of interest for gaining access to advanced intermediates in natural product synthesis.

Our efforts were initially focused on the cyclization of trichloroacetamide **1**[11a] (Table 1), which embodied an α,β-unsaturated nitrile as the radical acceptor. In the initial screening process, homoscorpionate ligands [hydrotris(3-*t*-butylpyrazolyl)borate, Tp^{tBu}][12] were used. Using a 2% catalyst loading of $Tp^{tBu}Cu(NCMe)$[13] at 60 °C in C_6D_6, and AIBN as a reducing agent,§ trichloroacetamide **1** underwent cyclization to **6** (90% yield, entry 1). Fig. 2 shows the monitoring of the reaction in which the amount of catalyst has been reduced by up to 0.5 mol% without any significant effect on the cyclization yield.

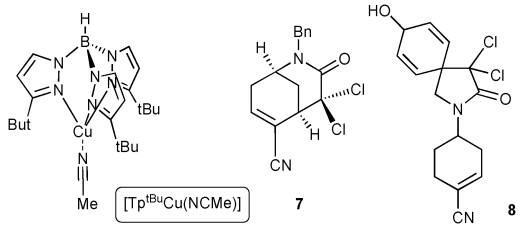


Scheme 1

Table 1 Cu(I)-catalyzed cyclization of **1**[a]



Entry	Cu(I)/ligand (equiv.)	Additive (equiv.)	Solvent (time, temp)	Products (%)[a]
1	[Tp^{tBu}Cu(NCMe)] (2%)	AIBN (10%)	C_6D_6 (15 h, 60 °C)	**6** (90)[b]
2	Tp^{tBu}CuCl (1%)	AIBN (10%)	C_6D_6 (6 h, 60 °C)[c]	**6** (78)[b]
3	[Tp^{tBu}Cu(NCMe)] (10%)	AIBN (20%)	Toluene (24 h, 60 °C)	**6** (79)[c]
4	CuCl (30%) TPMA (30%)	—	DCE (4 h, 80 °C)	**6** (83)[d]
5	*CuCl (10%) TPMA (10%)*	*AIBN (50%)*	*DCE (48 h, 60 °C)*	***6** (81)*[e]
6	CuCl (30%)	—	DMF (16 h, 80 °C)	**6** (70)[f]
7	CuCl (30%) TPMA (30%)	—	DMF (16 h, 80 °C)	**7** (60)[d]
8	CuCl (30%)	—	CH_3CN (16 h, 80 °C)	**6** (50)[c] **8** (10)



[a] Unless noted otherwise, yields refer to pure isolated products. [b] Yield calculated by ^{1}H NMR spectroscopy of a crude reaction mixture using an internal standard. [c] 100 mg scale. [d] 250 mg scale. [e] 500 mg scale. [f] 1.0 g scale.

A similar result was found when Tp^{tBu}CuCl was used as the catalyst precursor (entry 2), as expected from the already proposed involvement of such species during the catalytic cycle.[13] The use of tris[(2-pyridyl)methyl]amine (TPMA) as the ligand and DCE as the solvent (entry 4) gave good results at the expense of using a catalyst loading of 30%. To improve the results, AIBN was employed again as an initiator for continuous activator regeneration[14] and hence the reaction with a catalyst loading of 10% (entry 5) afforded the cyclized compound **6** in 81% yield. This procedure becomes the method of choice when gram scale reactions are needed due to the commercial availability of TPMA. Interestingly, the cyclization process also took place without standard ligands when using DMF as the solvent[15] and 30% catalyst loading (70% yield, entry 6). When TPMA was added to the reaction in DMF (entry 7), the isolated compound was identified as **7**, which resulted from the elimination of the transferred chlorine atom in **6** (see below). Using CH_3CN as the solvent and ligand[15] (entry 8), together with **6** (50%), a radical cyclization upon benzene gave compound **8** as a mixture of epimers. The scope of this process, which results in the relatively rare dearomatization of a benzene ring,[16] is under consideration.

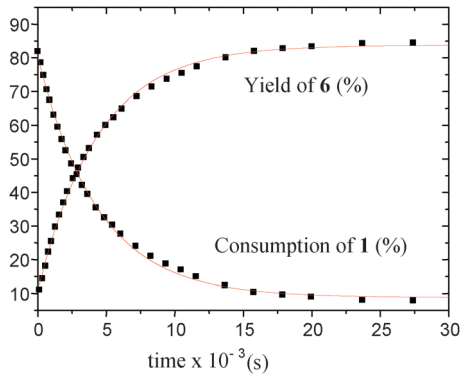
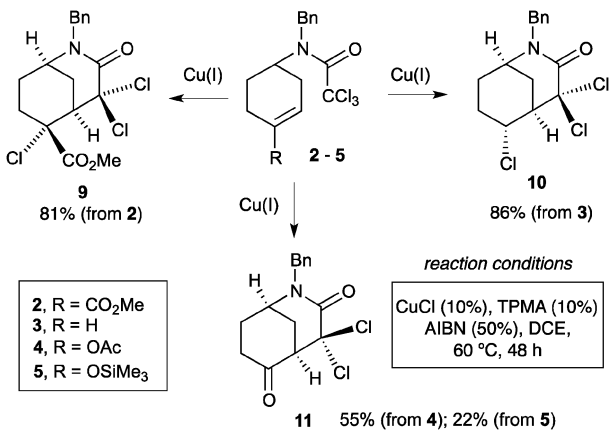


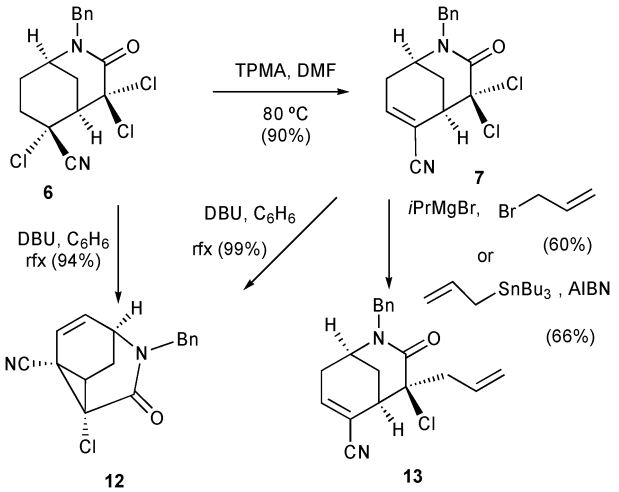
Fig. 2 Kinetic monitoring (^{1}H NMR, 60 °C, C_6D_6) of the consumption of **1** in the reaction forming **6** using Tp^{tBu}Cu(NCMe) as the catalyst. [Cu]/[AIBN]/[**1**] = 1 : 20 : 200. Initial rate constant, $k_{obs} = 2.29 \times 10^{-4}$ s^{-1}.

The Cu(I)-catalyzed ATRC was extended to other trichloroacetamide substrates (**2–5**, Scheme 2) in which the substituent attached to the alkene moiety modulates the electron-density in the alkene radical acceptor from electron-poor (*e.g.* **2**) to electron-rich (*e.g.* **5**). Results from α,β-unsaturated ester **2** were similar to those obtained from nitrile **1**, the azabicyclo **9** being isolated in 81% yield under the best reaction conditions using CuCl–TMPA–AIBN in a ratio of 0.1/0.1/0.5 with respect to trichloroacetamide **2**. The results were also very good from unactivated alkene **3**, which underwent cyclization to afford azabicycle **10** in 85% yield. All cyclization processes from **1–3** were diastereoselective, and the configuration of the new stereogenic center bearing the transferred chlorine atom was in an axial disposition in the rigid azabicyclic ring formed.

Finally, we examined the Cu(I)-catalyzed annulation of enol acetate **4** and silylenol ether **5** (Scheme 2), both with an electron-donating group, upon the alkene radical acceptor. Interestingly, treatment of either **4** or **5** under the standard cyclization conditions afforded a reaction mixture in which the only product isolated was 2-azabicyclo[3.3.1]nonanedione **11**[11c] formed when the initial annulation product (*e.g.* α-chloro acetoxy from **4**) evolved into the more stable ketone under the reaction conditions or during work-up. In preliminary studies with morphan **6** (Scheme 3), the α-chloronitrile unit proved to be a versatile synthetic precursor by virtue of having



Scheme 2 Cu(I)-catalyzed cyclization of **4** and **5**. (For other reaction-conditions in ARTC from **2–5** with several ligand-types like those used in Table 1, see the ESI.†)



Scheme 3 Synthetic transformations from **6**.

two orthogonal functionalities substituting the same carbon.[17] As expected, **6** was transformed into the unsaturated nitrile **7** when subjected to the same reaction conditions that furnished **7** from **1**. Under more drastic basic reaction conditions using DBU as a base, both **6** and **7** afforded **12** in excellent yields (90–99%). This compound was formed *via* γ-deprotonation of **7**, followed by a nucleophilic attack of the α-nitrile anion on C-4 with a chlorine atom as the leaving group, which generated a cyclopropane embedded in the morphan skeleton.¶ Interestingly, compound **12** has a 4-azabarbaralene-like[18] structure for which there is only one synthetic precedent.[19] Finally, the anionic or radical allylation of **7** stereoselectively gave compound **13** with a non-optimized yield of 60 and 66%, respectively.

In summary, the application of the Cu(I)-catalyzed ATRC methodology to the synthesis of 2-azabicyclo[3.3.1]nonanes[20] from trichloroacetamides tethered with cyclohexenes has been described. The polyfunctionalized compounds obtained could be chemoselectively converted to other value-added compounds by transforming the chlorine atoms of the initial azabicyclic compound. Further studies directed towards the application of this methodology to the synthesis of natural products embodying the 2-azabicyclo[3.3.1]nonane framework are in progress.

This work was funded by the MINECO of Spain through projects CTQ2010-14846/BQU and CTQ2011-28942-CO2-1 and Junta de Andalucía (Grants P07-FQM-02794 and P10-FQM-6292). AP thanks the MEC for a research fellowship.

Notes and references

‡ A metal-free ATRC of trichloroacetamides upon alkenes with electron-withdrawing groups would be inappropriate since for a successful reaction the final radical has to be less stable than the initial radical.

§ Radicals formed from the decomposition of the free radical initiator 2,2′-azobisisobutyronitrile (AIBN) at 60 °C continuously regenerate the catalytically active lower oxidation state transition metal complex (activator) by the abstraction of a halogen atom from the higher oxidation state complex (deactivator), see ref. 3*b*.

¶ Another possible pathway suggested by a reviewer could be a nucleophilic addition of DBU onto the unsaturated nitrile, followed by the three-membered ring-closure and β-elimination of the ammonium salt.

1 For a review on the synthesis of 2-azabicyclo[3.3.1]nonanes, see: J. Bonjoch, F. Diaba and B. Bradshaw, *Synthesis*, 2011, 993.
2 (*a*) J. Bonjoch, N. Casamitjana and J. Bosch, *Tetrahedron*, 1988, **44**, 1735; (*b*) J. Quirante, C. Escolano, A. Merino and J. Bonjoch, *J. Org. Chem.*, 1998, **63**, 968; (*c*) D. Solé, X. Urbaneja and J. Bonjoch, *Org. Lett.*, 2005, **7**, 5461; (*d*) F. Diaba and J. Bonjoch, *Org. Biomol. Chem.*, 2009, **7**, 2517.
3 (*a*) A. J. Clark, *Chem. Soc. Rev.*, 2002, **31**, 1; (*b*) W. T Eckenhoff and T. Pintauer, *Catal. Rev. Sci. Eng.*, 2010, **52**, 1; (*c*) For the use of other metal-based catalysts in ATRC, see: J. M. Muñoz-Molina, T. R. Belderrain and P. J. Pérez, *Eur. J. Inorg. Chem.*, 2011, 3155.
4 For some recent examples, see: (*a*) J. M. Muñoz-Molina, T. R. Belderraín and P. J. Pérez, *Adv. Synth. Catal.*, 2008, **350**, 2365; (*b*) S. Van der Jeught, N. De Vos, K. Masschelein, I. Ghiviriga and C. V. Stevens, *Eur. J. Org. Chem.*, 2010, 5444; (*c*) V. X. Chen, F.-D. Boyer, C. Rameau, P. Retailleau, J.-P. Vors and J.-M. Beau, *Chem.–Eur. J.*, 2010, **16**, 13941.
5 To our knowledge there are only two old examples: (*a*) Y. Hirai, A. Hagiwara, T. Terada and T. Yamazaki, *Chem. Lett.*, 1987, 2417; (*b*) A. J. Clark, F. De Campo, R. J. Deeth, R. P. Filik, S. Gatard, N. A. Hunt, D. Lastécouères, G. H. Thomas, J.-B. Verlhac and H. Wongtap, *J. Chem. Soc., Perkin Trans. 1*, 2000, 671.
6 H. Nagashima, H. Wakamatsu and K. Itoh, *J. Chem. Soc., Chem. Commun.*, 1984, 652.
7 (*a*) H. Nagashima, N. Ozaki, M. Ishii, K. Seki, M. Washiyama and K. Itoh, *J. Org. Chem.*, 1993, **58**, 646; (*b*) S. Iwamatsu, H. Kondo, K. Matsubara and H. Nagashima, *Tetrahedron*, 1999, **55**, 1687; (*c*) Y. Motoyama, K. Kamo, A. Yuasa and H. Nagashima, *Chem. Commun.*, 2010, **46**, 2256.
8 (*a*) K. Matyjaszewski, W. Jakubowski, K. Min, J. Huang, W. A. Braunecker and N. V. Tsarevsky, *Proc. Natl. Acad. Sci. U. S. A.*, 2006, **103**, 15309; (*b*) T. Pintauer and K. Matyjaszewski, *Chem. Soc. Rev.*, 2008, **37**, 1087.
9 T. Pintauer, *Eur. J. Inorg. Chem.*, 2010, 2449.
10 (*a*) A. J. Clark, R. J. Filik, D. M. Haddleton, A. Radigue and C. J. Sanders, *J. Org. Chem.*, 1999, **64**, 8954; (*b*) B. A. Seigal, C. Fajardo and M. L. Snapper, *J. Am. Chem. Soc.*, 2005, **127**, 16329; (*c*) C. D. Edlin, J. Faulkner and P. Quayle, *Tetrahedron Lett.*, 2006, **47**, 1145; (*d*) J. Wolf, K. Thommes, O. Briel, R. Scopelliti and K. Severin, *Organometallics*, 2008, **27**, 4464; (*e*) F. I. McGonagle, L. Brown, A. Cooke and A. Sutherland, *Org. Biomol. Chem.*, 2010, **8**, 3418.
11 (*a*) J. Quirante, C. Escolano, M. Massot and J. Bonjoch, *Tetrahedron*, 1997, **53**, 1391; (*b*) J. Quirante, C. Escolano, F. Diaba and J. Bonjoch, *Heterocycles*, 1999, **50**, 731; (*c*) J. Quirante, C. Escolano, F. Diaba and J. Bonjoch, *J. Chem. Soc., Perkin Trans. 1*, 1999, 1157.
12 J. M. Muñoz-Molina, A. Caballero, M. Díaz-Requejo, S. Trofimenko, T. R. Belderraín and P. J. Pérez, *Inorg. Chem.*, 2007, **46**, 7725.
13 J. M. Muñoz-Molina, W. M. C. Sameera, E. Álvarez, F. Maseras, T. R. Belderrain and P. J. Pérez, *Inorg. Chem.*, 2011, **50**, 2458.
14 The only example of this methodology applied to nitrogen heterocycle synthesis leading to five-membered lactam derivatives uses bromoacetamides as proradicals: A. J. Clark and P. Wilson, *Tetrahedron Lett.*, 2008, **49**, 4848.
15 M. Pattarozzi, F. Roncaglia, V. Giangiordano, P. Davoli, F. Prati and F. Ghelfi, *Synthesis*, 2010, 694.
16 J. Boivin, M. Yousfi and S. Z. Zard, *Tetrahedron Lett.*, 1997, **38**, 5985.
17 B. R. Pitta and F. F. Fleming, *Org. Lett.*, 2010, **12**, 2810.
18 D. A. Hrovat, E. C. Brown, R. V. Williams, H. Quast and W. T. Borden, *J. Org. Chem.*, 2005, **70**, 2627.
19 R. Neidlein and K. F. Wesch, *Chem. Ber.*, 1983, **116**, 2466.
20 For other recent synthetic methods to build up this azabicyclic system, see: (*a*) Y.-F. Wang, K. K. Toh, E. P. J. Ng and S. Chiba, *J. Am. Chem. Soc.*, 2011, **62**, 7418; (*b*) L. Zu, B. W. Boal and N. K. Garg, *J. Am. Chem. Soc.*, 2011, **62**, 7418.

Electronic Supplementary Material (ESI) for Chemical Communications

Supporting information

for

Cu(I)-Catalyzed Atom Transfer Radical Cyclization of Trichloroacetamides Tethered to Electron-deficient, -neutral, and -rich Alkenes: Synthesis of 2-Azabicyclo[3.3.1]nonanes

Faïza Diaba, Agustín Martínez-Laporta, Josep Bonjoch*

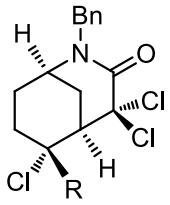
Laboratori de Química Orgànica, Facultat de Farmàcia, IBUB, Universitat de Barcelona, Av. Joan XXIII s/n, 08028-Barcelona, Spain

Ana Pereira, José-María Muñoz-Molina, Pedro J. Pérez, Tomás R. Belderrain*

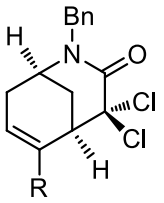
Laboratorio de Catálisis Homogénea, Departamento de Química y Ciencia de los Materiales, Unidad Asociada al CSIC, Centro de Investigación en Química Sostenible (CIQSO), Universidad de Huelva,Campus de El Carmen s/n, 21007-Huelva, Spain

Table of contents

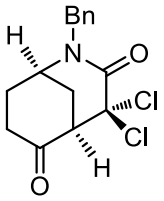
Table 1. ^{13}C NMR chemical shifts of 2-azabicyclo[3.3.1]nonanes **6**,**7**, **9**-**11, 14**[a]



R = CN **6**
CO_2Me **9**
H **10**



R = CN **7**
CO_2Me **14**



11

	6	**7**	**9**	**10**	**11**	**14**
C-1	49.6	48.6	50.3	51.5	51.1	49.3
C-3	163.3	162.9	163.7	164.2	163.9	162.9
C-4	83.0	83.6	84.4	85.4	81.2	85.0
C-5	53.4	45.8	53.0	51.8	63.0	43.1
C-6	59.5	113.4	69.8	57.6	203.5	137.0
C-7	29.7	144.7	26.1	24.4	35.0	131.2
C-8	23.6	31.7	24.2	22.5	30.2	31.2
C-9	26.0	25.9	26.7	24.5	31.1	26.3
Other	118.7	118.4	52.9	-	-	52.3
	(CN)	(CN)	(CH_3)	-	-	(CH_3)
	-	-	170.0	-	-	166.8
	-	-	(CO)	-	-	(CO)
CH_2Ar	49.6	49.7	49.5	49.3	49.7	49.6
Ar(C)	127.9	127.7	127.8	127.8	127.9	127.7
	128.2	128.1	128.0	127.9	128.2	127.9
	129.1	129.0	128.9	128.9	129.1	128.9
	135.6	135.7	136.0	136.1	135.9	136.1

[a] Values were assigned on the basis of gCOSY and gHSQC spectra in $CDCl_3$ (100 MHz).

General. ^{1}H and ^{13}C NMR spectra were recorded in $CDCl_3$ solution. Chemical shifts are reported as δ values (ppm) relative to internal Me_4Si. All NMR data assignments are supported by COSY and HSQC experiments. Infrared spectra were recorded on a Nicolet 320 FT-IR spectrophotometer. TLC was performed on SiO_2 (silica gel 60 F_{254}, Merck). The spots were located by UV light or a 1% $KMnO_4$ aqueous solution. Chromatography refers to flash chromatography and was carried out on SiO_2 (silica gel 60, SDS, 230–400 mesh). CuCl (99.99%) was purchased from Sigma-Aldrich and was used as received. All reactions were carried out under an argon atmosphere with dry, freshly distilled solvents and under anhydrous conditions. The reactions were heated using a dry-syn single position heating block and the temperature indicated refers to external temperature. Drying of the organic extracts during reaction work-up was performed over anhydrous Na_2SO_4. Compounds **1**-**5** were synthesized according to our previous published procedures.[1]

General procedures for Atom Transfer Radical Cyclization of trichloroacetamides 1-5.

a) Representative procedure for the $Tp^{x}Cu$ complex radical cyclization. A solution of trichloroacetamide **2** (100 mg, 0.282 mmol), and the corresponding $Tp^{tBu}Cu(NCMe)$ complex (1.25 mg from 0.5 mL of a stock solution,[2] $2.82x10^{-3}$ mmol from a stock solution, 0.01 equiv) and AIBN (4.2 mg, 0.1 equiv) were dissolved in toluene (0.75 mL, 1.25 mL as total volume of solvent). The flask was sealed with a Teflon screw cap and removed from the globe box. The reaction mixture was stirred at 60 ºC for 14 h, worked up, and purified by chromatography (hexane/CH_2Cl_2) to give **9** (80 mg, 80%).

b) Representative procedure for the CuCl radical cyclization in DCE. To a suspension of CuCl (20 mg, 0.2 mmol) in 1,2-dichloroethane (6.5 mL) were successively added TPMA (58 mg, 0.2 mmol) and nitrile **1** (240 mg, 0.67 mmol), and the mixture was heated at 80 °C for 4 h in a sealed tube. The solution was then allowed to reach rt, concentrated and purified by chromatography (hexane/CH_2Cl_2 1:9 to CH_2Cl_2) to yield morphan **6** as a white solid (200 mg, 83%).

c) Representative procedure for the CuCl radical cyclization in DCE and in the presence of AIBN. To a suspension of CuCl (13.3 mg, 0.13 mmol 10%) in 1,2-dichloroethane (8 mL) were successively added TPMA (38.7 mg, 0.13 mmol), nitrile **1**

[1] a) Quirante, J.; Escolano, C.; Massot, M.; Bonjoch, J. *Tetrahedron* **1997**, *53*, 1391-1402. (b) Quirante, J.; Escolano, C.; Diaba, F.; Bonjoch, J. *Heterocycles* **1999**, *50*, 731-738. (c) Quirante, J.; Escolano, C.; Diaba, F.; Bonjoch, J. *J. Chem. Soc. Perkin Trans 1* **1999**, 1157-1162.

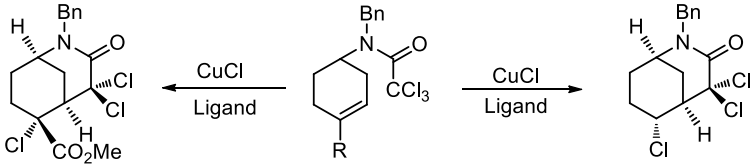
[2] Stock solution was prepared from 5.0 mg of $Tp^{tBu}Cu(NCMe)$ in 2 mL of toluene. (a) Muñoz-Molina, J.M.; Caballero, A.; Díaz-Requejo, M.M.; Trofimenko, S.; Belderraín, T. R.; Pérez, P. J. *Inorg. Chem.* **2007**, *46*, 7725-7730. (b) Muñoz-Molina, J. M.; Belderrain, T. R.; Pérez, P. J. *Inorg. Chem.* **2010**, *49*, 642 –645.

(475 mg, 1.33 mmol), AIBN (109 mg, 0.66 mmol 50%) and the mixture was heated at 60 °C for 2 days in a sealed tube. The solution was then allowed to reach rt, concentrated and purified by chromatography (hexane/CH_2Cl_2 1:9 to CH_2Cl_2) to yield morphan **6** (385 mg, 81%).

d) Representative procedure for the CuCl radical cyclization in DMF. A mixture of CuCl (84 mg, 0.85 mmol, 30%) and nitrile **1** (1 g, 2.80 mmol) in DMF (10 mL) was heated at 80 °C overnight in a sealed tube. The solution was then allowed to reach rt, and water (30 mL), 10 % HCl aqueous solution (10 mL) and AcOEt (50 mL) were successively added. The layers were separated and the aqueous layer was extracted with AcOEt. The combined organic layers were washed with brine, dried and concentrated. After chromatography (hexane/CH_2Cl_2 1:9 to CH_2Cl_2) morphan **6** was isolated (705 mg, 71%).

e) Representative procedure for the CuCl radical cyclization in DMF and in the presence of TPMA. A mixture of CuCl (43 mg, 0.43 mmol, 30%), nitrile **1** (0.5 g, 1.40 mmol) and TPMA (119.3 mg, 0.41 mmol, 30%) in DMF (5 mL) was heated at 80 °C overnight in a sealed tube. The solution was then allowed to reach rt, and water (30 mL), 10 % HCl aqueous solution (10 mL) and AcOEt (50 mL) were successively added. The layers were separated and the aqueous layer was extracted with AcOEt. The combined organic layers were washed with brine dried and concentrated. After chromatography (hexane/CH_2Cl_2 1:9 to CH_2Cl_2) morphan **7** was isolated (270 mg, 60%).

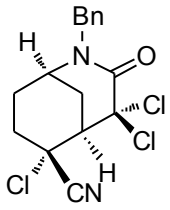
Table 2. Cu(I)-Catalyzed Cyclization of **2** and **3**



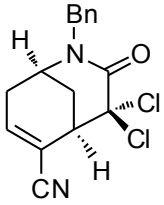
9 **2**, R = CO_2Me; **3**, R = H **10**

Entry Compd	Ligand (equiv)	Additive (equiv)	Solvent (time, Temp)	Products (%)[a]
From **2**				
1	$Tp^{t\,Bu}CuCl$ (0.01)	AIBN (0.1)	Toluene (14 h, 60 ºC)	**9** (70)
2	[$Tp^{tBu}Cu$(NCMe)] (0.01)	AIBN (0.1)	Toluene (14 h, 60 ºC)	**9** (80)
3	CuCl (0.3) TPMA (0.3)	----	DCE (4 h, 80 ºC)	**9** (74)
4	CuCl (0.1) TPMA (0.1)	AIBN (0.5)	DCE (16 h, 60ºC)	**9** (81) **2** (15)
5	CuCl (0.3)	-----	DMF (22 h, 80 ºC)	**9** (67)
6	CuCl (0.3) TPMA (0.3)		DMF (22 h, 80 ºC)	**9** (46) **14**[b] (21)
From **3**				
7	$Tp^{tBu}CuCl$ (0.01)	AIBN (0.1)	Toluene (14 h, 60 ºC)	**10** (60)[c]
8	[$Tp^{tBu}Cu$(NCMe)] (0.1)	AIBN (0.2)	Toluene (24 h, 60 ºC)	**10** (66)
9	CuCl (0.003) TPMA (0.003)	AIBN (0.2)	Toluene (18 h, 60 ºC)	**10** (90)[d]
10	CuCl (0.3) TPMA (0.3)	-----	DCE (4 h, 80 ºC)	**10** (70)
11	CuCl (0.1) TPMA (0.1)	AIBN (0.5)	DCE (48 h 60ºC)	**10** (85)[e]
12	CuCl (0.3)	-------	DMF (16 h, 80 ºC)	**10** (57)

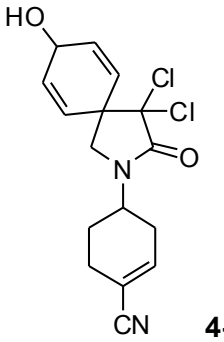
[a]Yields refer to pure isolated products. Unless noted otherwise, reactions were on a 100 mg scale.[b] See S9 of this ESI for the structure of **14.**[c] 200 mg scale.[d] 33 mg scale.[e] 1 g scale.



(1*RS*,5*RS*,6*RS*)-2-Benzyl-4,4,6-trichloro-3-oxo-2-azabicyclo[3.3.1]nonane-6-carbonitrile (6): White solid, mp 139-141 °C; IR (NaCl, neat): 3055, 3034, 2996, 2975, 2949, 2248, 1682, 1492, 1450, 1427, 1366, 1249, 1202, 1188, 1095, 946, 827, 737, 702, 687, 626, 596, 575, 520 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 1.86 (dm, 1H, *J* = 14.8 Hz, H-8eq), 2.00 (dddd, 1H, *J* = 14.8, 12, 4.8, 2.4 Hz, H-8ax), 2.22 (ddd, 1H, *J* = 15.6, 11.2, 4.4 Hz, H-7ax), 2.29 (dm, 1H, *J* = 15.6 Hz, H-7eq), 2.60 (m, 2H, CH_2-9), 3.38 (m, 1H, H-5), 3.54 (m, 1H, H-1), 4.00 (d, 1H, *J* = 14.8 Hz, CH_2Ar), 5.26 (d, 1H, *J* = 14.8 Hz, CH_2Ar), 7.24-7.40 (m, 5H, ArH); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 23.6 (C-8), 26.0 (C-9), 29.7 (C-7), 49.6 (C-1 and CH_2Ar), 53.4 (C-5), 59.5 (C-6), 83.0 (C-4), 118.7 (CN), 127.9, 128.2, 129.1 (Ar-CH), 135.6 (*ipso*-C), 163.3 (C-3). HRMS (ESI-TOF): Calcd for $C_{16}H_{16}Cl_3N_2O$ 357.0323 (M^++1). Found 357.0330.



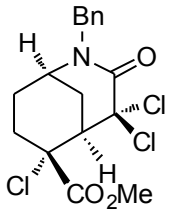
(1*RS*,5*RS*)-2-Benzyl-4,4-dichloro-3oxo-2-azabicyclo[3.3.1]non-6-ene-6-carbonitrile (7): White solid, mp 168-170 °C; IR (NaCl, neat): 3036, 2978, 2953, 2928, 2219, 1658, 1493, 1452, 1435, 1415, 1365, 1323, 1261, 1226, 1203, 1066, 1029, 981, 953, 877, 841, 832, 747, 702, 690, 670, 614, 578 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 1.95 (ddd, 1H, *J* = 14, 4, 2 Hz, H-9), 2.41 (dddd, 1H, *J* = 20.4, 4.4, 2.8, 1.6 Hz, H-8ax), 2.57 (dd, 1H, *J* = 20.4, 4.4 Hz, H-8eq), 2.80 (dm, 1H, *J* = 14 Hz, H-9), 3.48 (m, 1H, H-5), 3.75 (m, 1H, H-1), 3.92 (d, 1H, *J* = 14.8 Hz, CH_2Ar), 5.35 (d, 1H, *J* = 14.8 Hz, CH_2Ar), 6.75 (ddd, 1H, *J* = 4.4, 2.8, 1.2 Hz, H-7), 7.22-7.39 (m, 5H, ArH); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 25.9 (C-9), 31.7 (C-8), 45.8 (C-5), 48.6 (C-1), 49.7 (CH_2Ar), 83.6 (C-4), 113.4 (C-6), 118.4 (CN), 127.7, 128.1, 129.0 (Ar-CH), 135.7 (*ipso*-C), 144.7 (C-7), 162.9 (C-3). HRMS (ESI-TOF): Calcd for $C_{16}H_{15}Cl_2N_2O$ 321.0556 (M^++1). Found 321.0552.



4-(4,4-Dichloro-8-hydroxy-3-oxo-2-azaspiro[4.5]deca-6,9-dien-2-yl) cyclohex-1-ene-1-carbonitrile (8): A mixture of CuCl (21 mg, 0.21 mmol, 30%) and nitrile **1** (250 mg, 0.7 mmol) in acetonitrile (5 mL) was heated at 80 °C overnight in a sealed tube. The solution was allowed to reach rt, and water (10 mL), 10 % HCl aqueous solution (3 mL) and AcOEt (30 mL) were successively added. The layers were separated and the aqueous layer was extracted with AcOEt. The combined organic layers were washed with brine, dried and concentrated. After chromatography (hexane/CH_2Cl_2 1:9 to CH_2Cl_2), besides morphan **6** (121 mg, 48%) **8** was isolated as a mixture of two epimers (23 mg, 10%), which were separated by chromatography (CH_2Cl_2/ AcOEt 8:2).

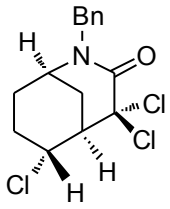
The less polar isomer: IR (NaCl, neat): 3458, 3044, 2930, 2854, 2215, 1722, 1670, 1634, 1477, 1433, 1421, 1307, 1245, 1189, 1027, 858, 735, 681 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz): δ 1.77 (m, 1H), 1.92 (m, 1H), 2.27 (m, 1H), 2.46 (m, 3H), 3.23 (d, 1H, *J* = 10 Hz), 3.27 (d, 1H, *J* = 10 Hz), 4.25 (m, 1H), 4.53 (brs, 1H), 5.94 (m, 2H), 6.26 (m, 2H), 6.58 (m, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 25.0 (CH_2), 26.5 (CH_2), 28.1 (CH_2), 47.2 (CH), 49.4 (C), 50.9 (CH_2), 62.0 (CH), 88.4 (C), 112.6 (C), 118.4 (CN), 126.2 (2 CH), 132.9 (CH), 133.0 (CH), 141.6 (CH), 165.7 (CO). HRMS (ESI-TOF): Calcd for $C_{16}H_{17}Cl_2N_2O_2$ 339.0662 (M^++1). Found 339.0648.

The more polar isomer: IR (NaCl, neat): 3429, 3041, 2938, 2851, 2215, 1715, 1643, 1477, 1433, 1418, 1306, 1244, 1188, 1023, 887, 861, 826, 736, 796 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz): δ 1.78 (m, 1H), 1.93 (m, 1H), 2.28 (m, 1H), 2.46 (m, 3H), 3.28 (d, 1H, *J* = 10 Hz), 3.31 (d, 1H, *J* = 10 Hz), 4.26 (m, 1H), 4.67 (brs, 1H), 5.85 (m, 2H), 6.25 (m, 2H), 6.58 (m, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 25.0 (CH_2), 26.5 (CH_2), 28.2 (CH_2), 47.2 (CH), 49.8 (C), 50.4 (CH_2), 62.3 (CH), 89.2 (C), 112.6 (C), 118.5 (CN), 125.3 (2 CH), 133.8 (2 CH), 141.7 (CH), 165.6 (CO). HRMS (ESI-TOF): Calcd for $C_{16}H_{17}Cl_2N_2O_2$ 339.0662 (M^++1). Found 339.0665.



(1*RS*,5*RS*,6*RS*) Methyl 2-Benzyl-4,4,6-trichloro-3-oxo-2-azabicyclo [3.3.1]nonane-6-carboxylate (9): To a suspension of CuCl (2.5 mg, 0.025 mmol 10%) in 1,2-dichloroethane (2.7 mL) were successively added TPMA (7.4 mg, 0.025 mmol), **2** (100 mg, 0.25 mmol), and AIBN (20.9 mg, 0.125 mmol 50%), and the mixture was heated at 60 °C for 16 h in a sealed tube. The solution was then allowed to reach rt, concentrated and purified by chromatography (CH_2Cl_2) yielding morphan **9** (81 mg, 81%) and **2** (15 mg, 15%).

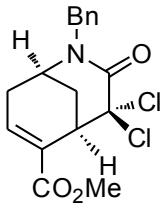
White solid, mp 130-131 °C; IR (NaCl, neat): 3086, 3062, 3030, 2950, 2861, 1745, 1678, 1447, 1360, 1289, 1244, 1203, 1187, 1066, 915, 824, 731, 700, 683 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz): δ 1.72-2.24 (m, 3H, CH_2-8 and H-7ax), 2.17 (m, 1H, H-7eq), 2.44 (brd, 1H, *J* = 14.4 Hz, H-9), 2.57 (brd, 1H, *J* = 14.4 Hz, H-9), 3.46 (m, 1H, H-1), 3.59 (brs, 1H, H-5), 3.78 (s, 3H, CH_3), 3.92 (d, 1H, *J* = 14.8 Hz, CH_2Ar), 5.18 (d, 1H, *J* = 14.8 Hz, CH_2Ar), 7.18-7.32 (m, 5H, ArH); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 24.2 (C-8), 26.1 (C-7), 26.7 (C-9), 49.5 (CH_2Ar), 50.3 (C-1), 52.9 (CH_3), 53.0 (C-5), 69.8 (C-6), 84.4 (C-4), 127.8, 128.0, 128.9 (Ar-CH), 136.0 (*ipso*-C), 163.7 (C-3), 170.0 (CO). HRMS (ESI-TOF): Calcd for $C_{17}H_{19}Cl_3NO_3$ 390.0425 (M^++1). Found 390.0426.



(1*RS*,5*RS*,6*RS*)-2-Benzyl-4,4,6-trichloro-2-azabicyclo[3.3.1]nonan-3-one (10): To a suspension of CuCl (30 mg, 0.3 mmol 10%) in 1,2-dichloroethane (15 mL) were successively added TPMA (87.2 mg, 0.3 mmol), **3** (1 g, 3 mmol), and AIBN (246 mg, 1.50 mmol 50%), and the mixture was heated at 60 °C for 2 days in a sealed tube. The solution was then allowed to reach rt, concentrated and purified by chromatography (hexane/CH_2Cl_2 1:9 to CH_2Cl_2) to yield morphan **10** (850 mg, 85%).

White solid, mp 116-118 °C; IR (NaCl, neat): 3109, 3089, 3063, 3032, 2960, 2946, 2933, 2859 1659, 1496, 1452, 1423, 1348, 1306, 1241, 1213, 1185, 1149, 1078, 1045, 999, 948, 867, 825, 808, 741, 699, 671, 613, 565 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz): δ 1.70 (m, 1H, H-8eq), 1.84-1.97 (m, 3H,CH_2-7 and H-8ax), 2.41 (m, 2H, CH_2-9), 3.04 (brd, 1H, *J* = 3.2 Hz, H-5), 3.54 (brd, 1H, H-1), 3.91 (d, 1H, *J* = 15.2 Hz, CH_2Ar), 4.96 (brs, 1H, H-6), 5.31 (d, 1H, *J* = 15.2 Hz, CH_2Ar), 7.24-7.40 (m, 5H, ArH); ^{13}C NMR

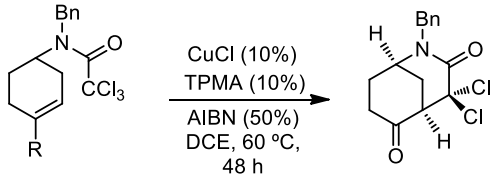
($CDCl_3$, 100 MHz): δ 22.5 (C-8), 24.4 (C-7), 24.5 (C-9), 49.3 (CH_2Ar), 51.5 (C-1), 51.8 (C-5), 57.6 (C-6), 85.4 (C-4), 127.8, 127.9, 128.9 (Ar-CH), 136.1 (*ipso*-C), 164.2 (C-3). HRMS (ESI-TOF): Calcd for $C_{15}H_{17}Cl_3NO$ 332.0370 (M^++1). Found 332.0371.



Methyl 2-Benzyl-4,4,6-trichloro-3-oxo-2-azabicyclo[3.3.1]non-6-ene-6-carboxylate (14): A mixture of CuCl (6.7 mg, 0.07 mmol, 30%) and nitrile **2** (80 mg, 0.22 mmol) in DMF (0.8 mL) was heated at 80 °C overnight in a sealed tube. The solution was then allowed to reach rt, concentrated and purified by chromatography (hexane/CH_2Cl_2 1:9 to CH_2Cl_2) to yield **9** (36.5 mg, 46%) and **14** (16.5 mg, 21%).

IR (NaCl, neat): 3082, 3042, 2950, 2926, 2850, 1719, 1670, 1449, 1332, 1258, 1206, 1088, 1060, 759, 732, 698, 672 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz): δ 1.86 (ddd, 1H, *J* = 14, 4, 2.4 Hz, H-9), 2.37 (dddd, 1H, *J* = 20, 3.6, 2.8, 1.6 Hz, H-8ax), 2.55 (dd, 1H, *J* = 20, 4 Hz, H-8eq), 2.77 (dm, 1H, *J* = 14 Hz, H-9), 3.71 (brs, 1H, H-1), 3.81 (s, 3H, CH_3), 3.89 (d, 1H, *J* = 14.8 Hz, CH_2Ar), 4.04 (m, 1H, H-5), 5.84 (d, 1H, *J* = 14.8 Hz, CH_2Ar), 6.92 (t, 1H, *J* = 4, Hz, H-7), 7.24-7.39 (m, 5H, ArH); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 26.3 (C-9), 31.2 (C-8), 43.1 (C-5), 49.3 (C-1), 49.6 (CH_2Ar), 52.3 (CH_3), 85.0 (C-4), 127.7, 127.9, 128.9 (Ar-CH), 131.2 (C-7), 136.1 (*ipso*-C), 137.0 (C-6), 162.9 (C-3), 166.8 (CO). HRMS (ESI-TOF): Calcd for $C_{17}H_{18}Cl_2NO_3$ 354.0658 (M^++1). Found 354.0655.

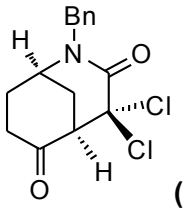
Scheme 1. Cu(I)-Catalyzed Cyclization of **4** and **5**



4, R = OAc
5, R = $OSiMe_3$

11 55% (from 4)[a,b]
22% (from 5)[c]

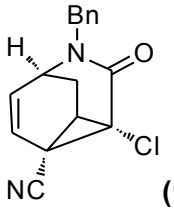
[a] 500 mg scale. [b] No AIBN, and 30 % catalyst and ligand loadings led to **11** in 42% yield from **4**. Using CuCl (30%) in DMF (80 ºC, 16 h), **11** was isolated in 51% yield from **4**, these runs were carried out using 100 mg of starting material. [c] *N*-benzyl-2,2,2-trichloro-*N*-(4-oxocyclohexyl) acetamide (25%) was recovered.



(1*RS*,5*RS*)-2-Benzyl-4,4-dichloro-2-azabicyclo[3.3.1]nonane-3,6-dione (11): To a suspension of CuCl (11 mg, 0.11 mmol 10%) in 1,2-dichloroethane (4 mL) were successively added TPMA (32 mg, 0.11 mmol), **4** (500 mg, 1.1 mmol), AIBN (89 mg, 0.55 mmol 50%) and the mixture was heated at 60 °C for 2 days in a sealed tube. The solution was then allowed to reach rt, concentrated and purified by chromatography (hexane/AcOEt 8:2) to yield morphan **11** (187 mg, 55%).

IR (NaCl, neat): 2924, 2853, 1732, 1668, 1450, 1423, 1275, 1243, 1202, 1108, 1033, 956, 860, 813, 733, 662, 565 cm^{-1}; **^{1}H NMR** ($CDCl_3$, 400 MHz): δ 1.70 (dddd, 1H, *J* = 16, 10.4, 6, 2.4 H-8ax), 2.07 (ddd, 1H, J = 14.4, 3.6. 2.8 Hz, H-9), 2.24 (m, 1H, H-8eq), 2.51 (m, 2H, CH_2-7), 2.77 (dq, 1H, *J* = 14.4, 3.2 Hz, H-9), 3.59 (m, 1H, H-5), 3.70 (brs, 1H, H-1), 4.10 (d, 1H, *J* = 15.4 Hz, CH_2Ar), 5.38 (d, 1H, *J* = 15.4 Hz, CH_2Ar), 7.29-7.41 (m, 5H, ArH); **^{13}C NMR** ($CDCl_3$, 100 MHz): δ 30.2 (C-8), 31.1 (C-9), 35.0 (C-7), 49.7 (CH_2Ar), 51.1 (C-1), 63.0 (C-5), 81.2 (C-4), 127.9, 128.2, 129.1 (Ar-CH), 135.9 (*ipso*-C), 163.9 (C-3), 203.5 (C-6). **HRMS** (ESI-TOF): Calcd for $C_{15}H_{16}Cl_2NO_2$ 312.0553 (M^++1). Found 312.0555.

Reaction of 6 with DBU. To a solution of **6** (100 mg, 0.28 mmol) in benzene (4.5 mL) was added DBU (0.083 mL, 0.56 mmol) and the mixture was heated to reflux for 3 h. The mixture was then diluted in ether and washed with 1M HCl solution and brine, dried and concentrated to yield **12** (75 mg, 94%).

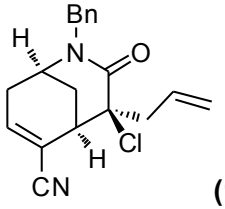


(1*RS*,2*SR*,5*SR*,8*SR*)-4-benzyl-2-chloro-3-oxo-4-azatricyclo[3.3.1.0^{2,8}] non-6-ene-8-carbonitrile (12): Colorless oil; IR (NaCl, neat): 3059, 3033, 2966, 2930, 2243, 1667, 1495, 1450, 1428, 1357, 1333, 1268, 1180, 1106, 1075, 973, 936, 844, 790, 735, 702, 679, 614, 578, 526 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 1.50 (dt, 1H, *J* = 14, 2.8 Hz, H-9), 2.13 (ddd, 1H, *J* = 14, 3.6, 2.4 Hz, H-9), 2.92 (dt, 1H, *J* =2.8, 1.6 Hz, H-1), 3.82 (m, 1H, H-5), 4.55 (d, 1H, *J* = 14.4 Hz, CH_2Ar), 4.71 (d, 1H, *J* = 14.4 Hz, CH_2Ar), 5.95 (dd, 1H, *J* = 9.2, 6.4 Hz, H-6), 6.11 (dd, 1H, *J* = 9.2, 1.2 Hz, H-7), 7.22-7.38 (m, 5H, ArH); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 19.7 (C-9), 26.2 (C-8), 32.6 (C-1), 47.3 (C-5), 50.8 (CH_2Ar), 50.9 (C-2), 117.4 (CN), 122.9 (C-7), 128.2, 128.6, 128.9, 136.5 (*ipso*-C), 136.5 (C-6), 160.4 (C-3). HRMS (ESI-TOF): Calcd for $C_{16}H_{14}ClN_2O$ 285.0789 (M^++1). Found 285.0788.

Allylation of 7

Method A: To a solution of **7** (74 mg, 0.23 mmol) and allylbromide (0.35 mL, 4.66 mmol) in THF (2 mL) was added a 2-methyltetrahydrofuran solution of *i*-PrMgBr (1.52, 1.5 mmol) dropwise at -78 ºC. The mixture was then stirred at this temperature for 1 h and at rt for 3 h. The reaction was quenched with satd. aqueous NH_4Cl solution, extracted with CH_2Cl_2 and the organic layers were dried and concentrated. Flash chromatography (hexane/AcOEt 8:2 to 7:3) afforded **13** as a white solid (46 mg, 60%).

Method B: A solution of **7** (75 mg, 0.23 mmol), allyl tributyltin (0.14 mL, 0.53 mmol) and AIBN (3.8 mg, 0.023 mmol) in benzene (2 mL) was heated to reflux for 4 h then 0.02 mL of allyl tributyltin and 3.8 mg of AIBN were added and the mixture was heated to reflux for 3 h. The reaction mixture was concentrated and the residue purified by chromatography (hexane/AcOEt 8:2 to 7:3) to yield **13** (49 mg, 63%).



(1*RS*,4*SR*,5*RS*)-4-Allyl-2-Benzyl-4-chloro-6-cyano-2-azabicyclo [3.3.1]non-6-en-3-one (13): White solid, mp 136-138 °C; IR (NaCl, neat): 3062, 3031, 2928, 2217, 1652, 1494, 1450, 1415, 1204, 1069, 927, 760, 730, 696 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 1.83 (ddd, 1H, *J* = 14, 4, 2 Hz, H-9), 2.24 (dm, 1H, *J* = 14 Hz, H-9), 2.37 (dm, 1H, *J* = 20.4, H-8ax), 2.56 (dd, 1H, *J* = 20.4, 4.4 Hz, H-8eq), 2.74 (dd, 1H,

J = 14.8, 8.8 Hz, CH_2C=), 3.08 (brs, 1H, H-5), 3.11 (dd, 1H, *J* = 14.8, 4.8 Hz, CH_2C=), 3.70 (brs, 1H, H-1), 3.90 (d, 1H, *J* = 14.8 Hz, CH_2Ar), 5.28 (m, 2H, =CH_2), 5.35 (d, 1H, *J* = 14.8 Hz, CH_2Ar), 6.06 (m, 1H, =CH), 6.69 (t, 1H, *J* = 3.2 Hz, H-7), 7.20-7.39 (m, 5H, ArH); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 25.7 (C-9), 31.4 (C-8), 38.1 (C-5), 45.2 (CH_2C=), 48.3 (C-1), 49.3 (CH_2Ar), 71.9 (C-4), 115.8 (C-6), 119.2 (CN), 120.6 (=CH_2), 127.8, 127.9, 128.9 (Ar-CH), 131.4 (=CH), 136.5 (*ipso*-C),142.9 (C-7), 168.0 (C-3). HRMS (ESI-TOF): Calcd for $C_{19}H_{20}ClN_2O$ 327.1259 (M^++1). Found 327.12

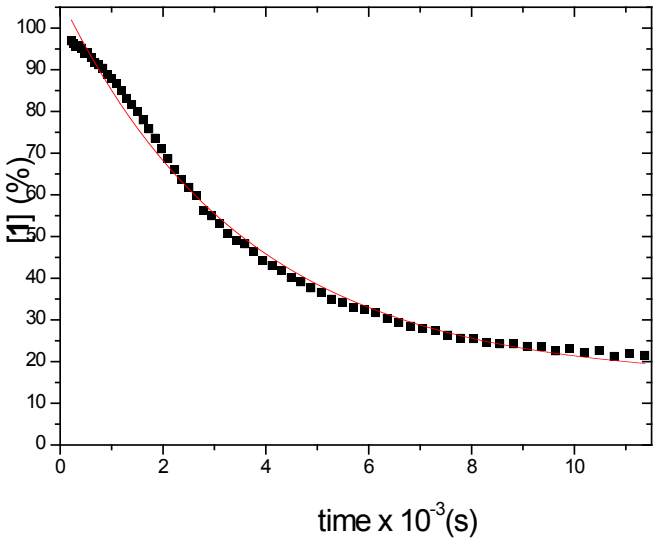


Figure S-1. Kinetic monitoring of **1** consumption (^{1}H NMR, 60 ºC, C_6D_6) in the reaction of the formation of **6,** using Tp^{tBu}CuCl. [Cu]/[AIBN]/[**1**] = 1:2:10. Rate constant, k_{obs} = 2.78x10^{-4} s^{-1}.

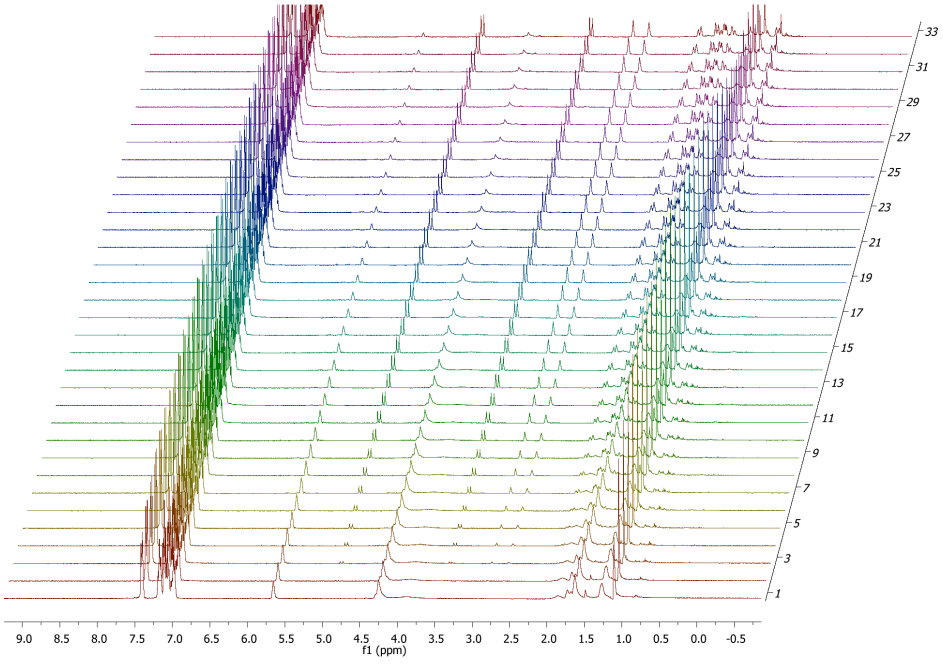
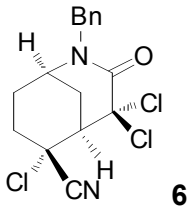
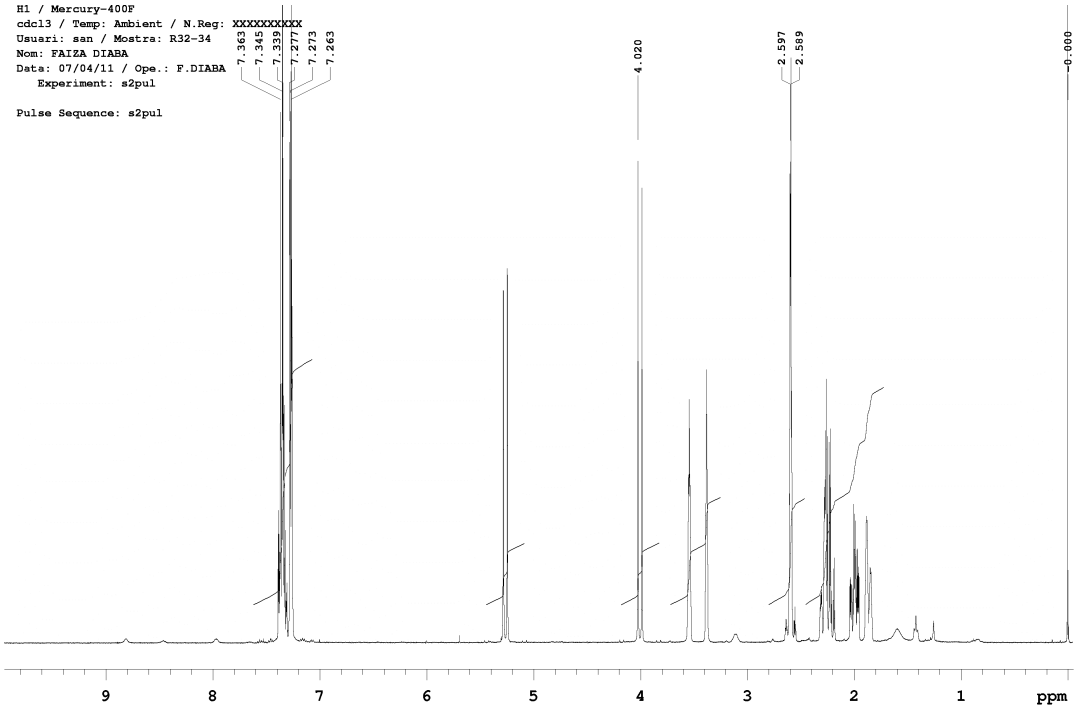
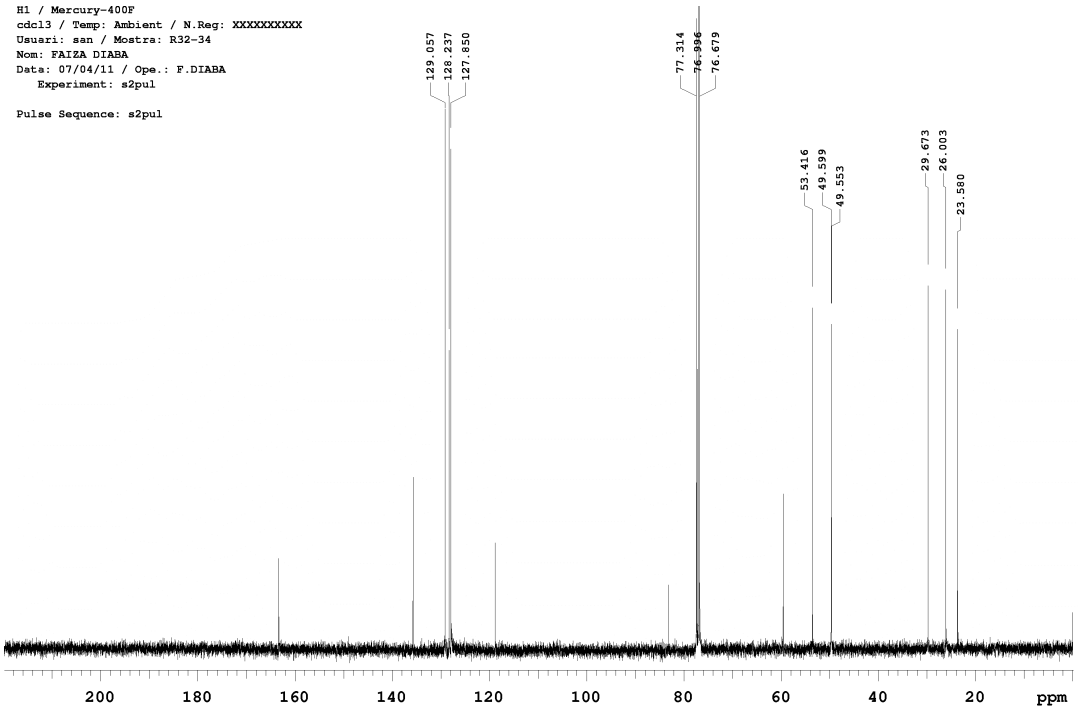


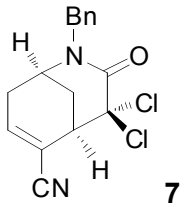
Figure S-2. ^{1}H spectra reaction monitoring of Tp^{tBu}Cu(NCMe):AIBN:**1** (ratio1:20:200) in C_6D_6 at 60ºC. A proton spectrum was registered every 3.6 min.


Bn
H
N
O
Cl
Cl
Cl
CN
H

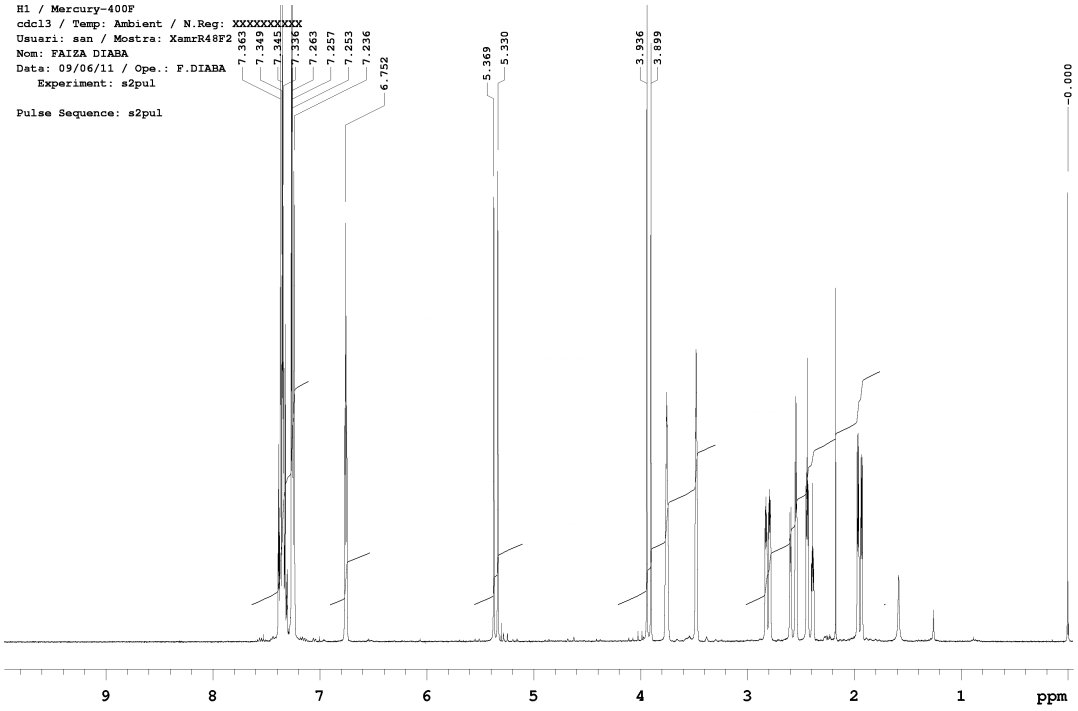
6

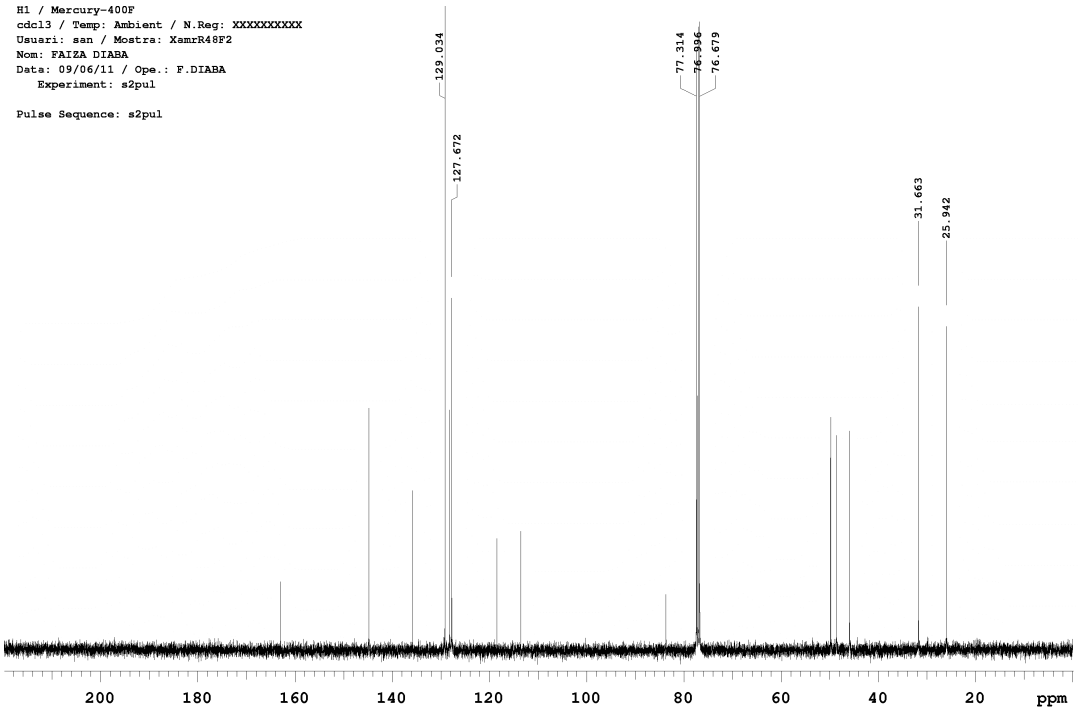

H1 / Mercury-400F
cdcl3 / Temp: Ambient / N.Reg: XXXXXXXXX
Usuari: san / Mostra: R32-34
Nom: FAIZA DIABA
Data: 07/04/11 / Ope.: F.DIABA
Experiment: s2pul
Pulse Sequence: s2pul
7.363
7.345
7.339
7.277
7.273
7.263
4.020
2.597
2.589
0.000
9
8
7
6
5
4
3
2
1
ppm

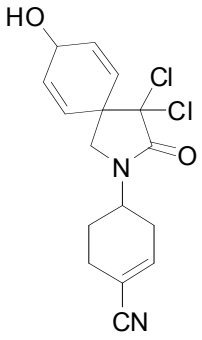

H1 / Mercury-400F
cdcl3 / Temp: Ambient / N.Reg: XXXXXXXXX
Usuari: san / Mostra: R32-34
Nom: FAIZA DIABA
Data: 07/04/11 / Ope.: F.DIABA
Experiment: s2pul
Pulse Sequence: s2pul
129.057
128.237
127.850
77.314
76.996
76.679
53.416
49.599
49.553
29.673
26.003
23.580
200
180
160
140
120
100
80
60
40
20
ppm


Bn
H
N
O
Cl
Cl
H
CN

7

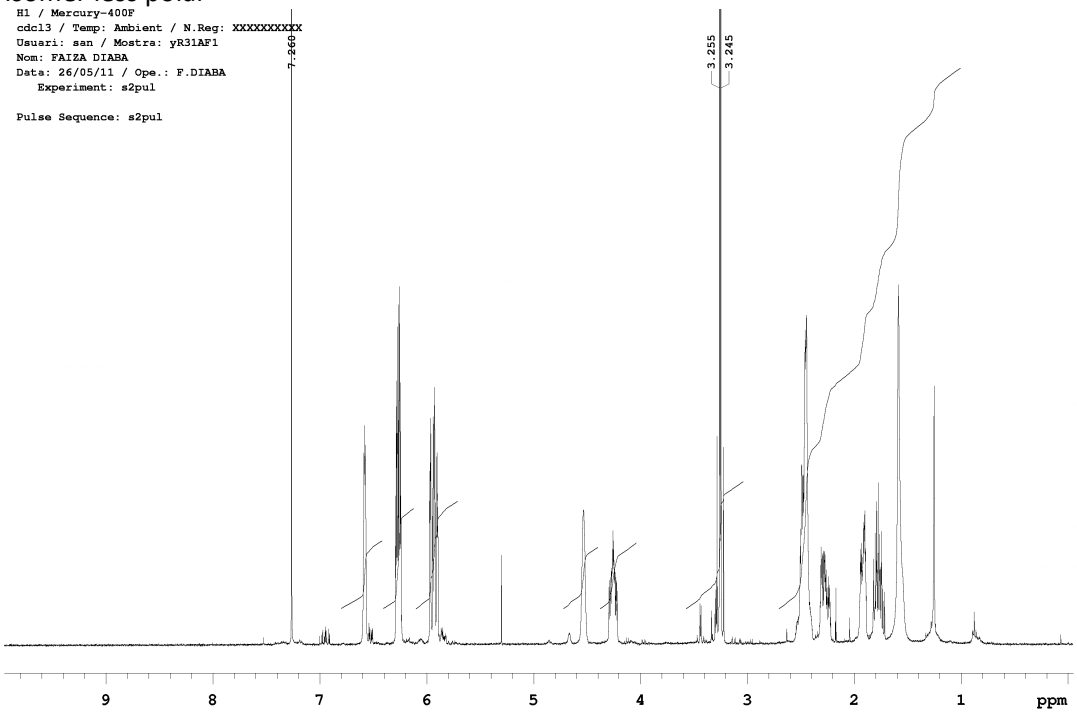

H1 / Mercury-400F
cdcl3 / Temp: Ambient / N.Reg: XXXXXXXXXX
Usuari: san / Mostra: XamrR48F2
Nom: FAIZA DIABA
Data: 09/06/11 / Ope.: F.DIABA
Experiment: s2pul
Pulse Sequence: s2pul
7.363
7.349
7.345
7.336
7.263
7.257
7.253
7.236
6.752
5.369
5.330
3.936
3.899
0.000
9
8
7
6
5
4
3
2
1
ppm

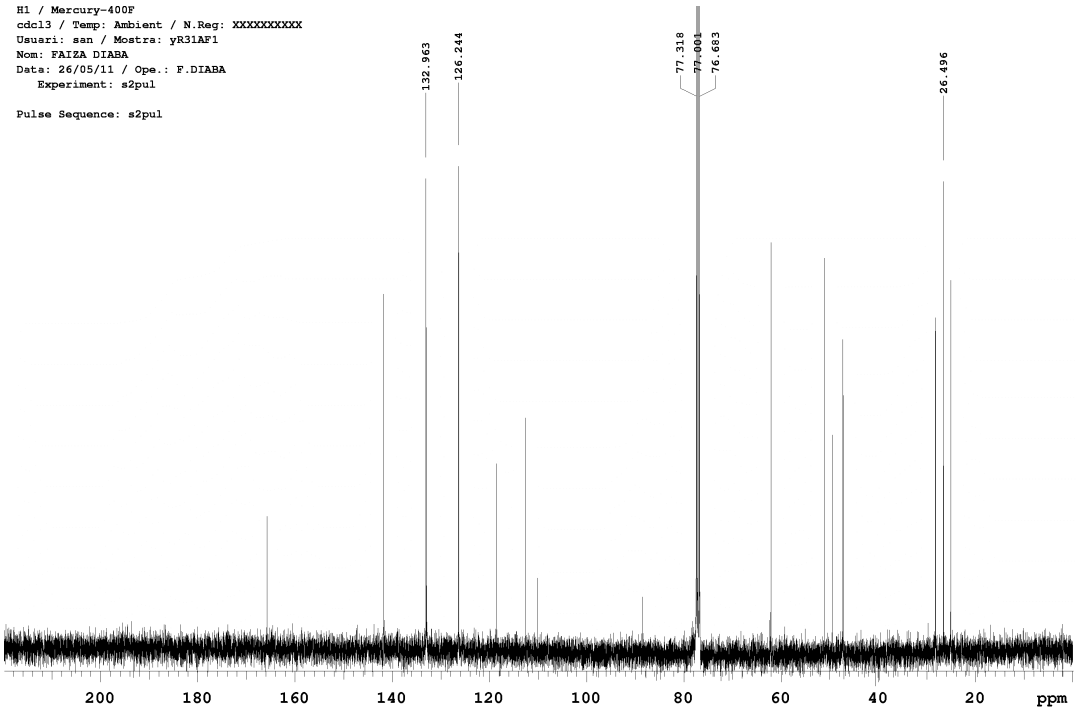

H1 / Mercury-400F
cdcl3 / Temp: Ambient / N.Reg: XXXXXXXXXX
Usuari: san / Mostra: XamrR48F2
Nom: FAIZA DIABA
Data: 09/06/11 / Ope.: F.DIABA
Experiment: s2pul
Pulse Sequence: s2pul
129.034
127.672
77.314
76.996
76.679
31.663
25.942
200
180
160
140
120
100
80
60
40
20
ppm

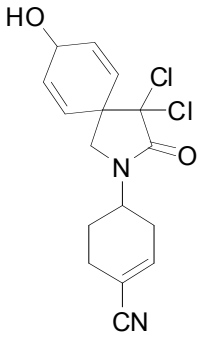


8 (epimer less polar)

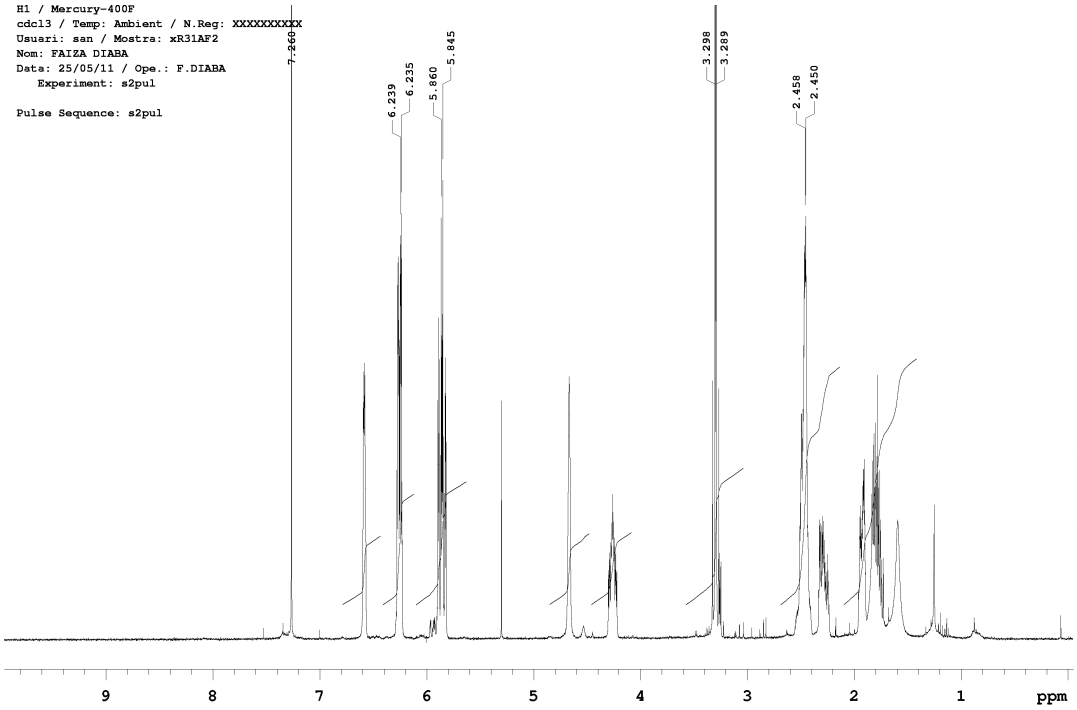
Isomer less polar

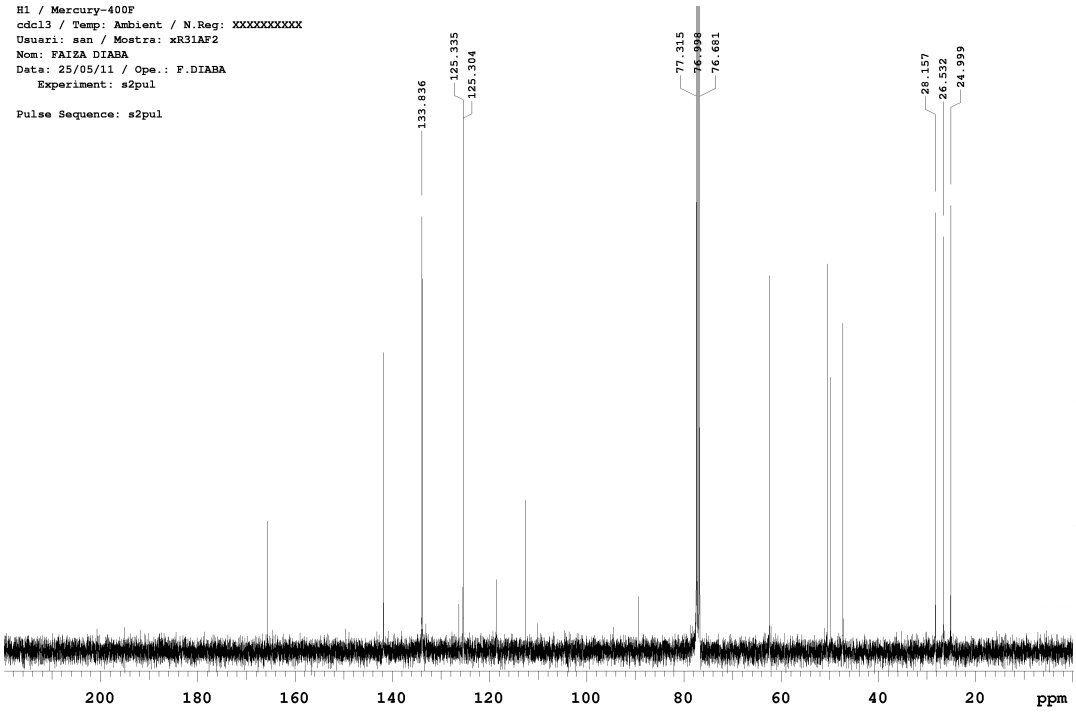


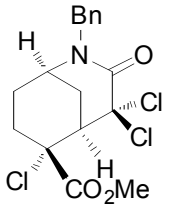




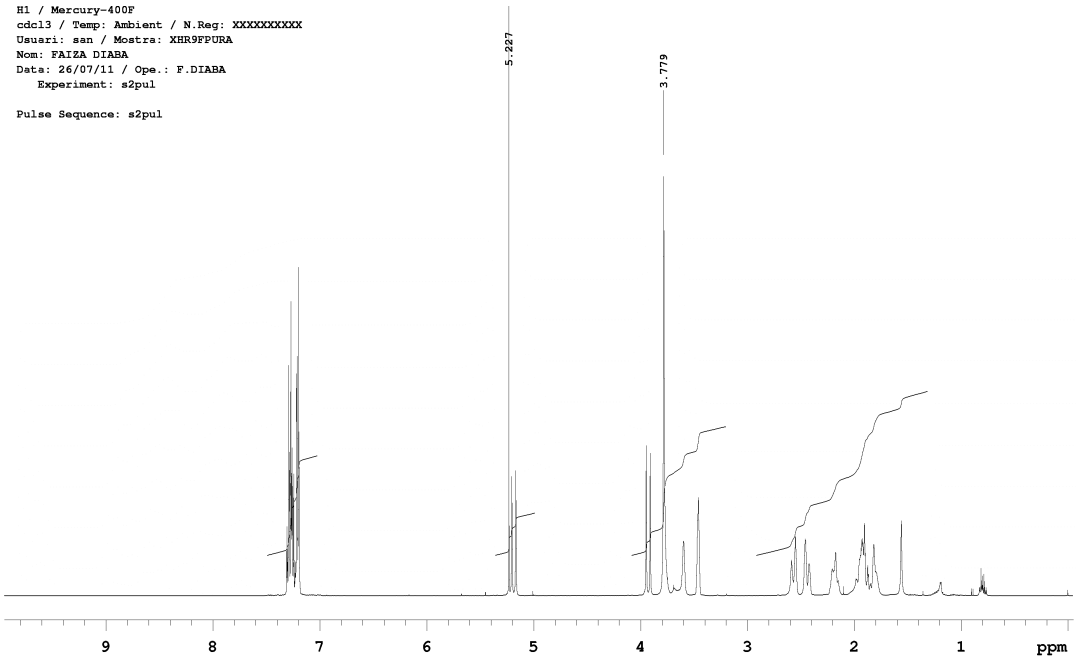
8 (epimer more polar)

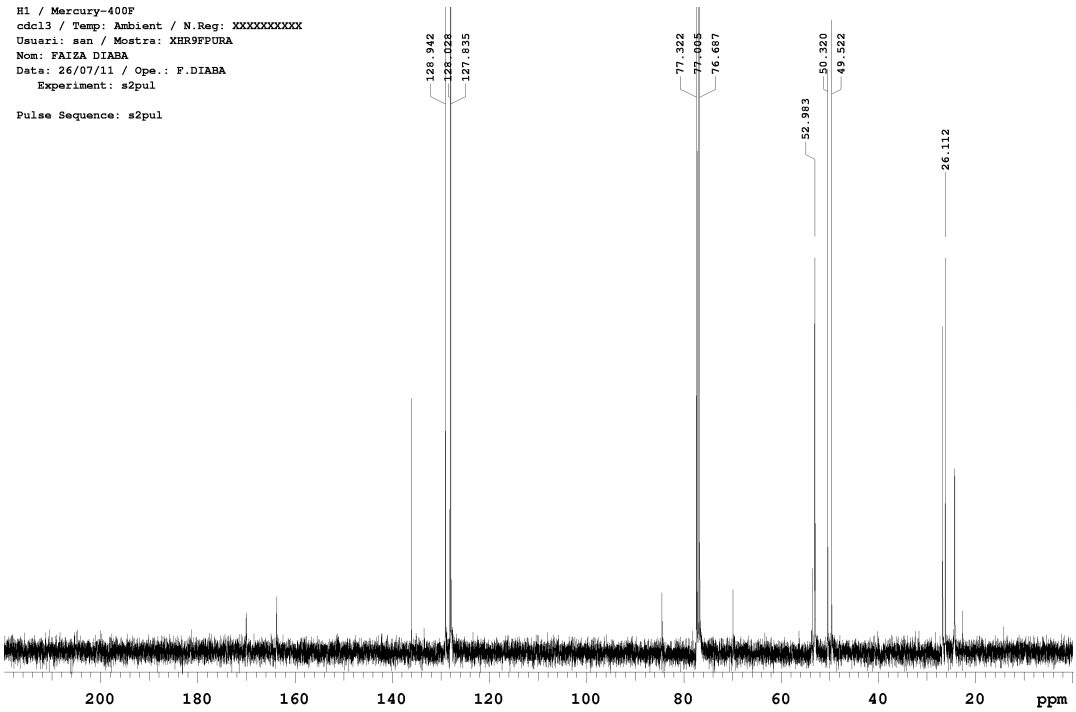


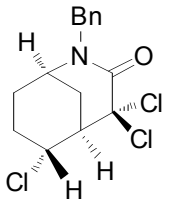



Bn
H
N
O
Cl
Cl
Cl
H
CO2Me

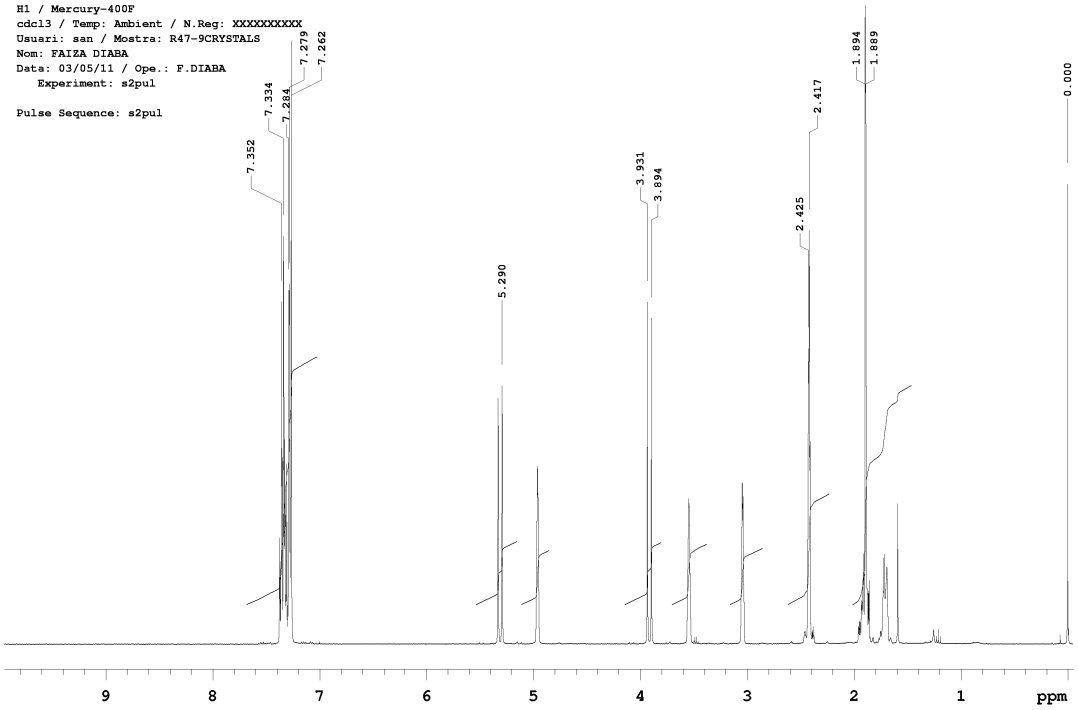
9

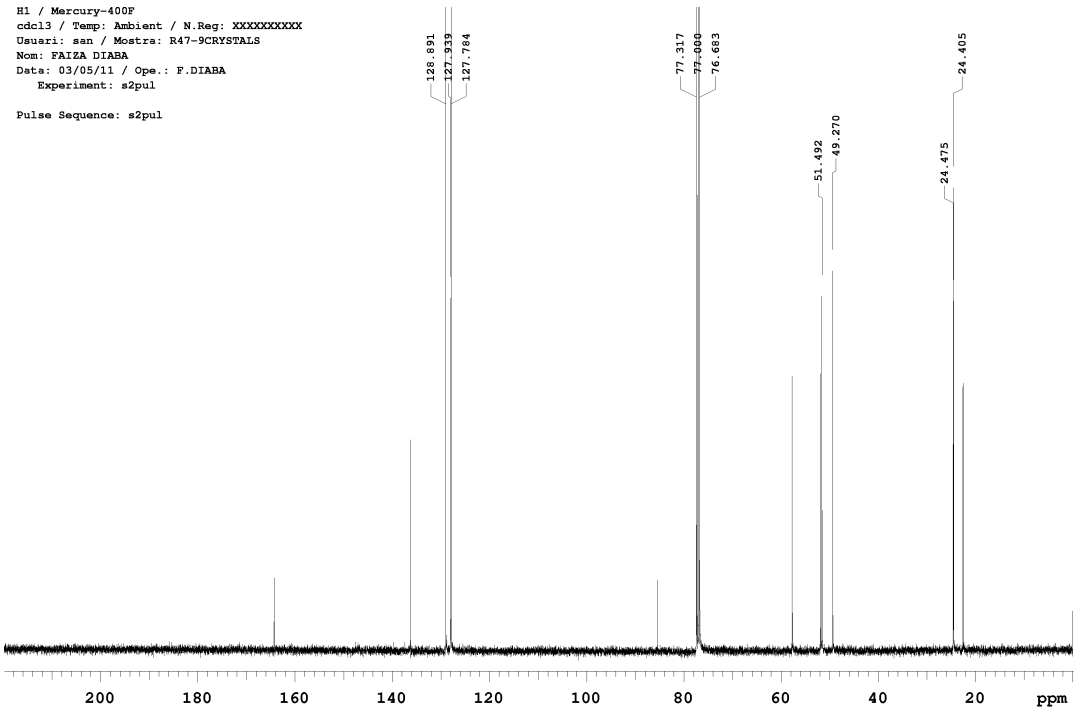

H1 / Mercury-400F
cdcl3 / Temp: Ambient / N.Reg: XXXXXXXXXX
Usuari: san / Mostra: XHR9FPURA
Nom: FAIZA DIABA
Data: 26/07/11 / Ope.: F.DIABA
Experiment: s2pul
Pulse Sequence: s2pul
5.227
3.779
9
8
7
6
5
4
3
2
1
ppm

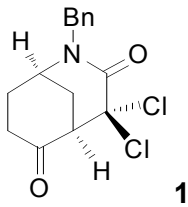

H1 / Mercury-400F
cdcl3 / Temp: Ambient / N.Reg: XXXXXXXXXX
Usuari: san / Mostra: XHR9FPURA
Nom: FAIZA DIABA
Data: 26/07/11 / Ope.: F.DIABA
Experiment: s2pul
Pulse Sequence: s2pul
128.942
128.028
127.835
77.322
77.005
76.687
52.983
50.320
49.522
26.112
200
180
160
140
120
100
80
60
40
20
ppm


Bn
H
N
O
Cl
Cl
Cl
H
H

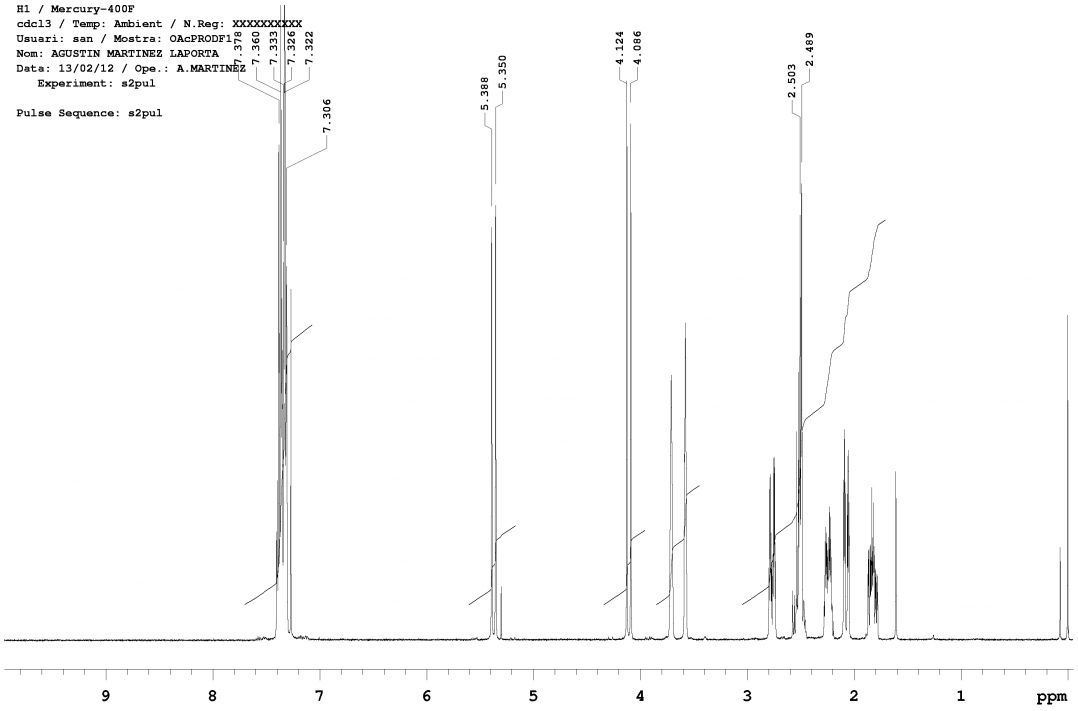
10

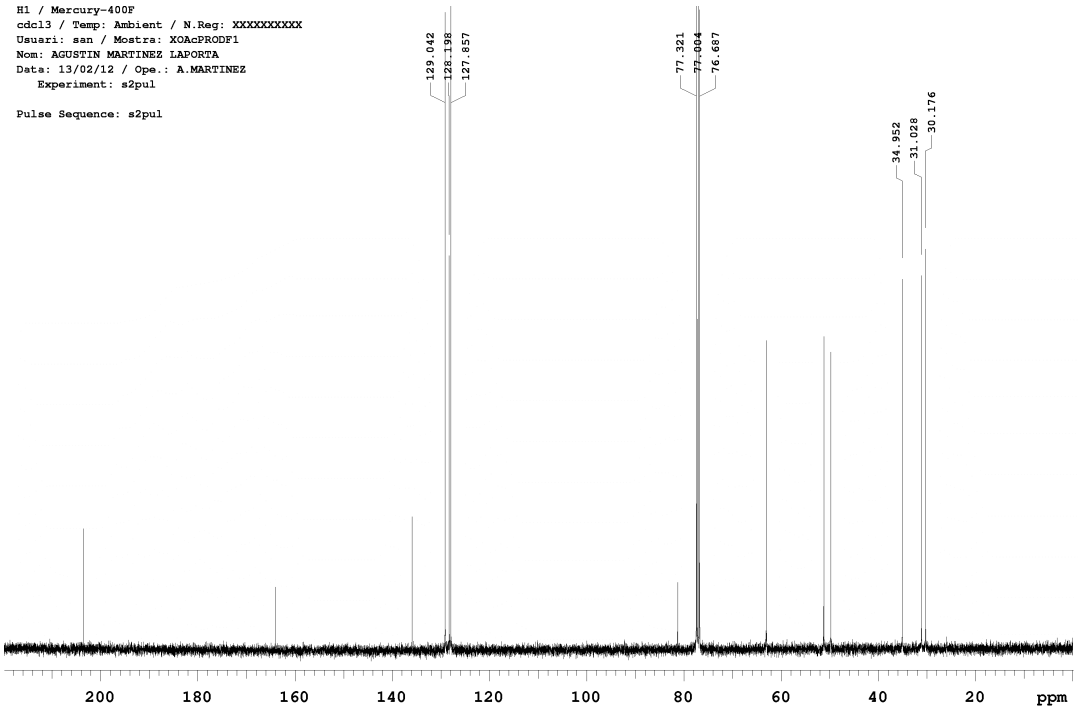

H1 / Mercury-400F
cdcl3 / Temp: Ambient / N.Reg: XXXXXXXXXX
Usuari: san / Mostra: R47-9CRYSTALS
Nom: FAIZA DIABA
Data: 03/05/11 / Ope.: F.DIABA
Experiment: s2pul
Pulse Sequence: s2pul
7.352
7.334
7.284
7.279
7.262
5.290
3.931
3.894
2.425
2.417
1.894
1.889
0.000
9
8
7
6
5
4
3
2
1
ppm

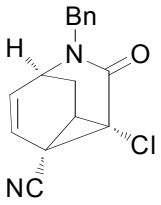

H1 / Mercury-400F
cdcl3 / Temp: Ambient / N.Reg: XXXXXXXXXX
Usuari: san / Mostra: R47-9CRYSTALS
Nom: FAIZA DIABA
Data: 03/05/11 / Ope.: F.DIABA
Experiment: s2pul
Pulse Sequence: s2pul
128.891
127.939
127.784
77.317
77.000
76.683
51.492
49.270
24.475
24.405
200
180
160
140
120
100
80
60
40
20
ppm


Bn
H
N
O
Cl
Cl
H
O

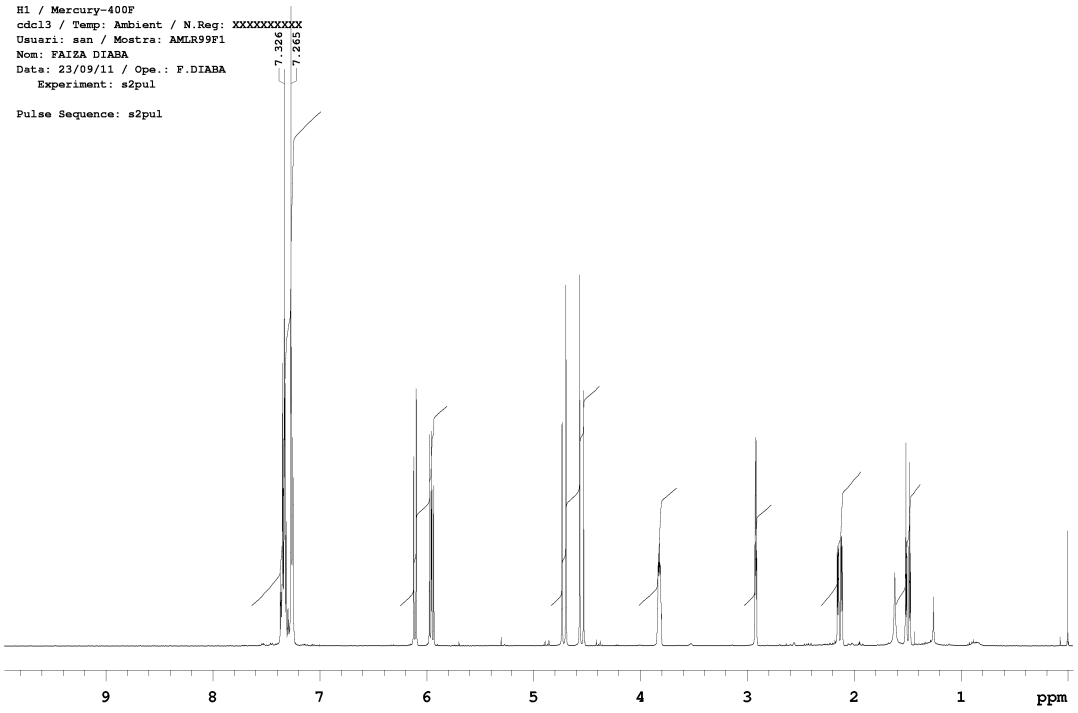
11

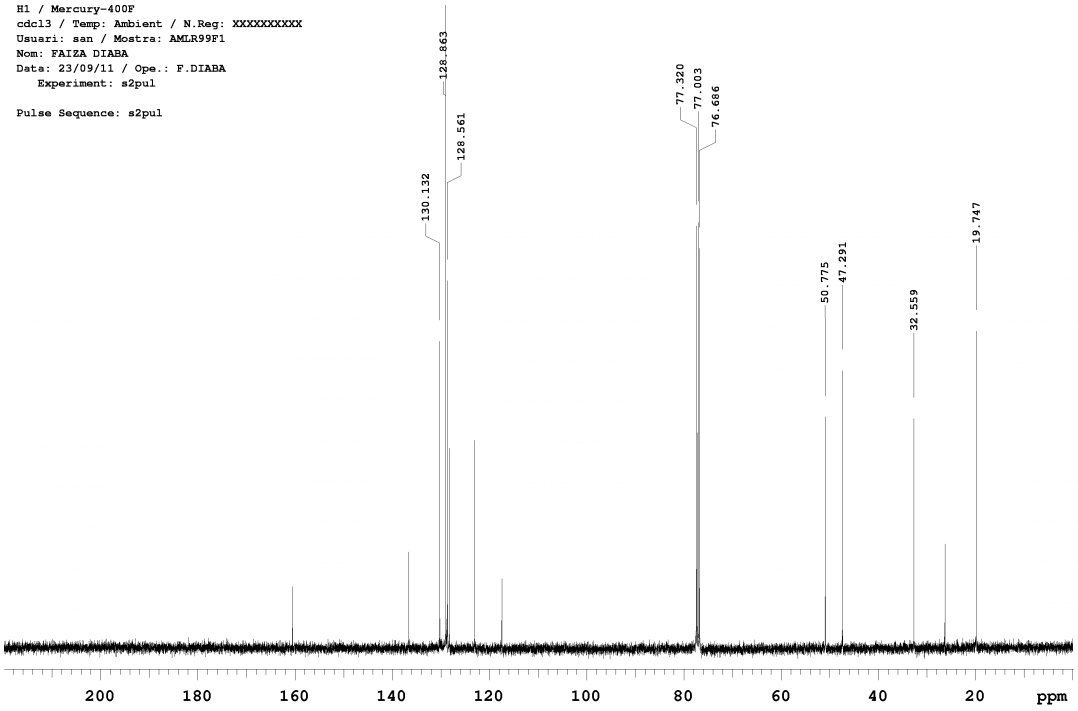

H1 / Mercury-400F
cdcl3 / Temp: Ambient / N.Reg: XXXXXXXXXX
Usuari: san / Mostra: OAcPRODF1
Nom: AGUSTIN MARTINEZ LAPORTA
Data: 13/02/12 / Ope.: A.MARTINEZ
Experiment: s2pul
Pulse Sequence: s2pul
7.378
7.360
7.333
7.326
7.322
7.306
5.388
5.350
4.124
4.086
2.503
2.489
9
8
7
6
5
4
3
2
1
ppm

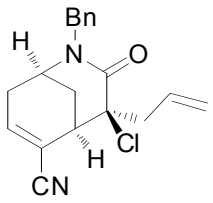

H1 / Mercury-400F
cdcl3 / Temp: Ambient / N.Reg: XXXXXXXXXX
Usuari: san / Mostra: XOAcPRODF1
Nom: AGUSTIN MARTINEZ LAPORTA
Data: 13/02/12 / Ope.: A.MARTINEZ
Experiment: s2pul
Pulse Sequence: s2pul
129.042
128.198
127.857
77.321
77.004
76.687
34.952
31.028
30.176
200
180
160
140
120
100
80
60
40
20
ppm


Bn
H
N
O
Cl
NC

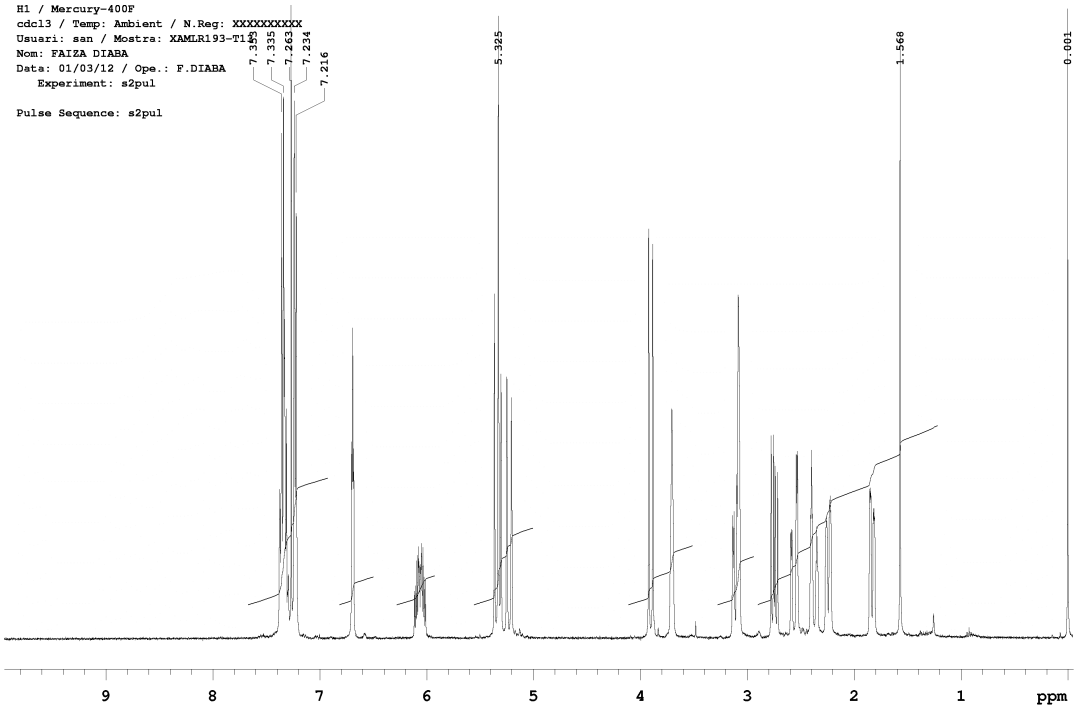
12

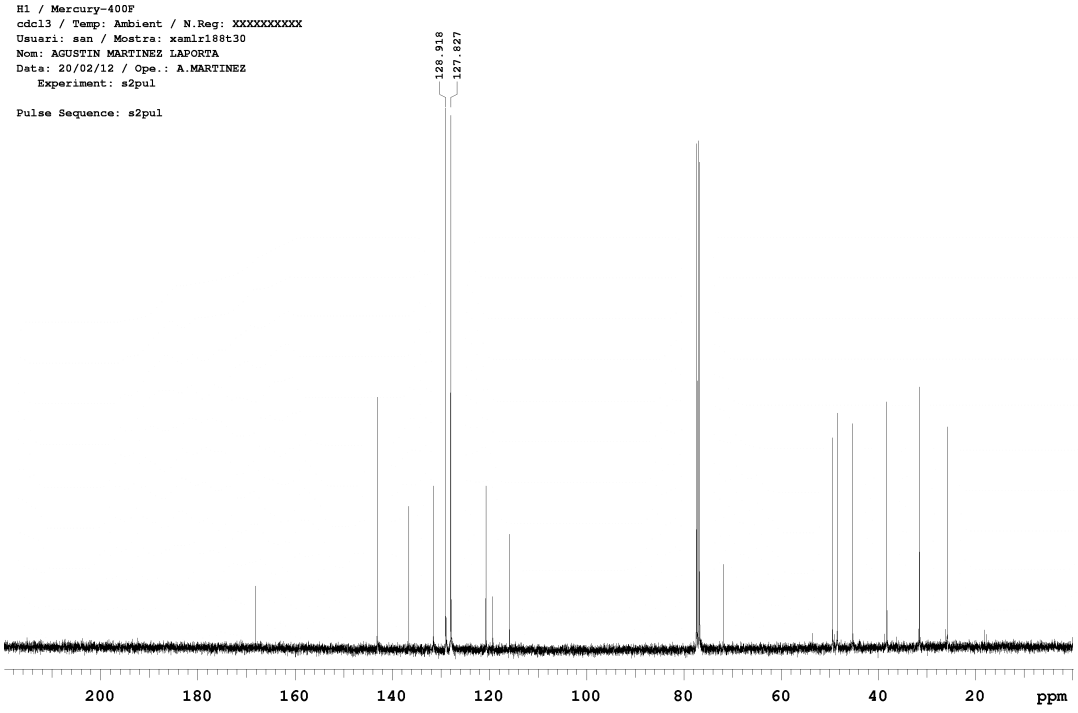

H1 / Mercury-400F
cdcl3 / Temp: Ambient / N.Reg: XXXXXXXXXX
Usuari: san / Mostra: AMLR99F1
Nom: FAIZA DIABA
Data: 23/09/11 / Ope.: F.DIABA
Experiment: s2pul
Pulse Sequence: s2pul
7.326
7.265
9
8
7
6
5
4
3
2
1
ppm

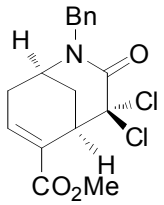

H1 / Mercury-400F
cdcl3 / Temp: Ambient / N.Reg: XXXXXXXXXX
Usuari: san / Mostra: AMLR99F1
Nom: FAIZA DIABA
Data: 23/09/11 / Ope.: F.DIABA
Experiment: s2pul
Pulse Sequence: s2pul
128.863
128.561
130.132
77.320
77.003
76.686
50.775
47.291
32.559
19.747
200
180
160
140
120
100
80
60
40
20
ppm


Bn
H
N
O
Cl
H
CN

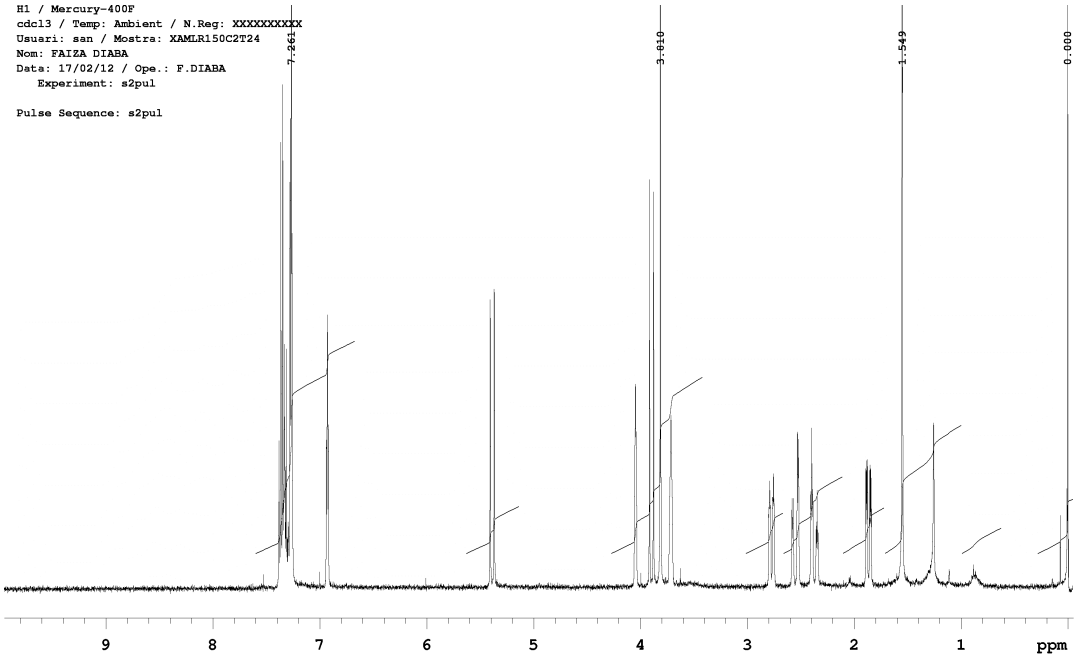
13

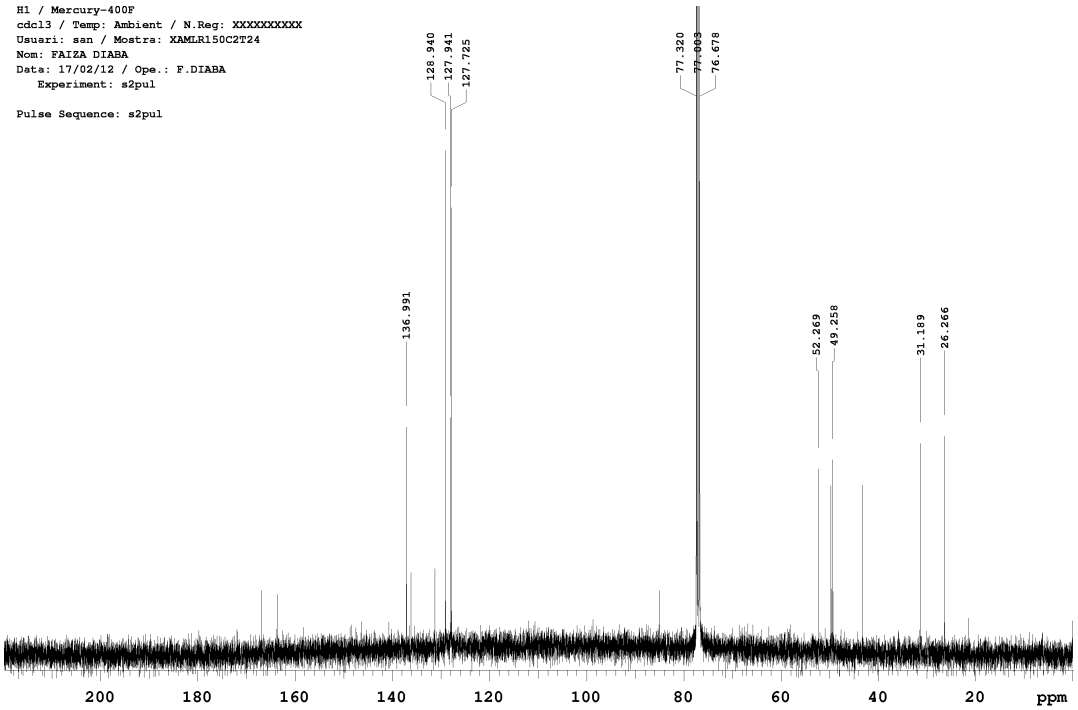

H1 / Mercury-400F
cdcl3 / Temp: Ambient / N.Reg: XXXXXXXXXX
Usuari: san / Mostra: XAMLR193-T13
Nom: FAIZA DIABA
Data: 01/03/12 / Ope.: F.DIABA
Experiment: s2pul
Pulse Sequence: s2pul
7.355
7.335
7.263
7.234
7.216
5.325
1.568
0.001
9
8
7
6
5
4
3
2
1
ppm


H1 / Mercury-400F
cdcl3 / Temp: Ambient / N.Reg: XXXXXXXXXX
Usuari: san / Mostra: xamlr188t30
Nom: AGUSTIN MARTINEZ LAPORTA
Data: 20/02/12 / Ope.: A.MARTINEZ
Experiment: s2pul
Pulse Sequence: s2pul
128.918
127.827
200
180
160
140
120
100
80
60
40
20
ppm


Bn
H
N
O
Cl
Cl
H
CO2Me

14


H1 / Mercury-400F
cdcl3 / Temp: Ambient / N.Reg: XXXXXXXXXX
Usuari: san / Mostra: XAMLR150C2T24
Nom: FAIZA DIABA
Data: 17/02/12 / Ope.: F.DIABA
Experiment: s2pul
Pulse Sequence: s2pul
7.261
3.810
1.549
0.000
9
8
7
6
5
4
3
2
1
ppm

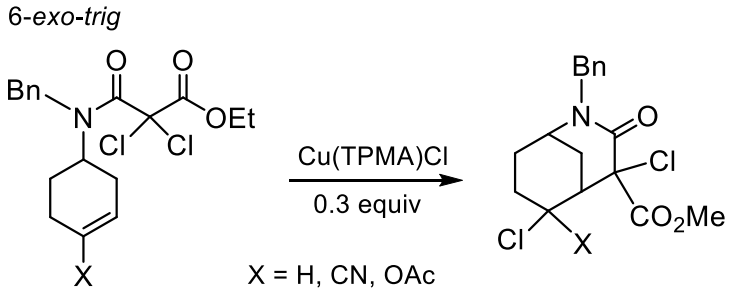

H1 / Mercury-400F
cdcl3 / Temp: Ambient / N.Reg: XXXXXXXXXX
Usuari: san / Mostra: XAMLR150C2T24
Nom: FAIZA DIABA
Data: 17/02/12 / Ope.: F.DIABA
Experiment: s2pul
Pulse Sequence: s2pul
128.940
127.941
127.725
77.320
77.003
76.678
136.991
52.269
49.258
31.189
26.266
200
180
160
140
120
100
80
60
40
20
ppm

3. Ciclación radicalaria con transferencia de átomo (ATRC) catalizada por Cu(I) de carbamoil-dicloroacetamidas en alquenos, acetatos de enol y nitrilos α,β-insaturados: síntesis de morfanos

3.1 Introducción y Objetivos

A fin de estudiar el alcance de la metodología ATRC con Cu (I) en la síntesis de morfanos, decidimos examinar su aplicación utilizando dicloromalonamidas como proradicales para el proceso de ciclación. La presencia del grupo éster tiene un carácter dual: a) facilitar la etapa de abstracción del átomo de cloro y b) su presencia en el producto de ciclación sería útil para la preparación de intermedios de síntesis avanzados para la síntesis total de productos naturales.

El estudio metodológico del proceso se llevó a cabo utilizando diversos tipos de aceptores radicalarios según su densidad electrónica: alqueno (neutro); nitrilo α,β-insaturado (pobre) y acetato de enol (rico).

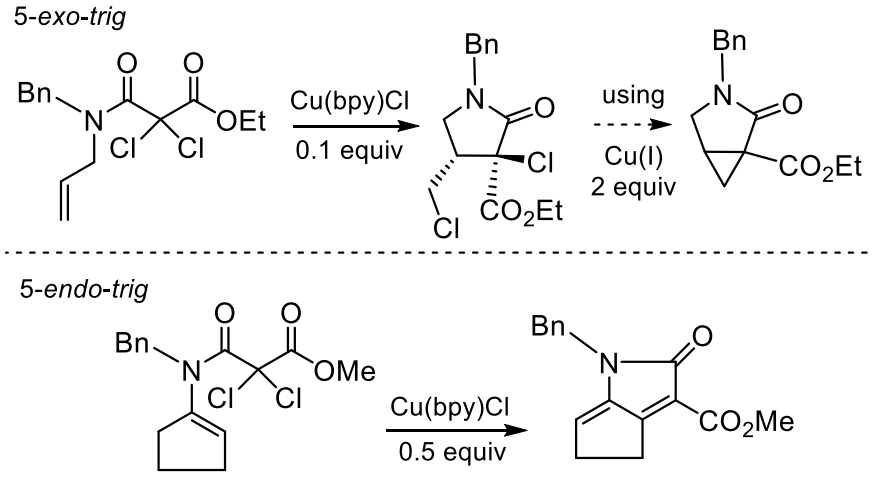


3.1 Extensión de la ATRC a la síntesis de *morfanos* a partir de compuestos 1,3-dicarbonílicos

Los precedentes en el uso de sustratos α,α-dicloro-β-dicarbonílicos[1] como pro-radicales para la síntesis de heterociclos nitrogenados son escasos. Sólo se han descrito dos ejemplos encaminados, en ambos casos, a γ-lactamas.[2]

[1] Para el uso de compuestos α-halodicarbonílicos en la síntesis de heterociclos oxigenados mediante procesos de ATRC, véase: (a) Hayes T. K.; Vil-lani R.; Weinreb S. M. *J. Am. Chem. Soc*. **1988**, *110*, 5533–5543; (b) Yang D.; Yan Y.-L.; Zheng B.-F.; Gao Q.; Zhu N.-Y. *Org.Lett*. **2013**, *15*, 5757–5760.

[2] Para el uso de compuestos α-halodicarbonílicos en la síntesis de heterociclos nitrogenados mediante procesos de ATRC véase: (a) Baldovini N.; Bertrand M.-P.; Carrière A.; Nouguier R.; Plancher J.-M. *J. Org. Chem*. **1996**, *61*, 3205–3208; (b) Davies D. T.; Kapur N.; Parsons A. F. *Tetrahedron Lett.* **1999**, *40*, 8615–8618; Davies D. T.; Kapur N.; Parsons A. F. *Tetrahedron,* **2000**, *56*, 3941–3949.

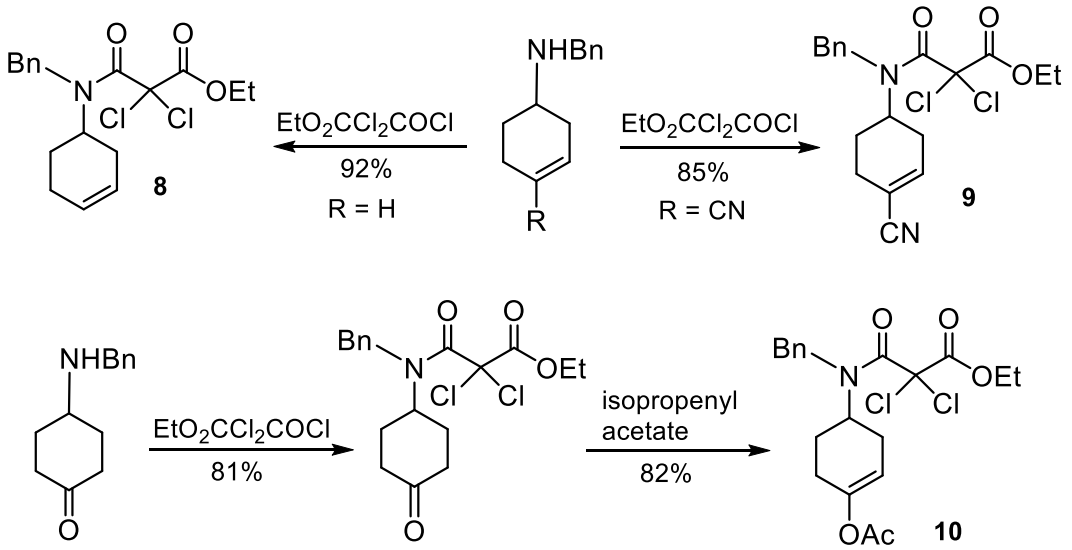


3.2 Precedentes en el uso de sustratos α,α-dicloro-β-dicarbonílicos en procesos ATRC

3.2 Resultados y discusión

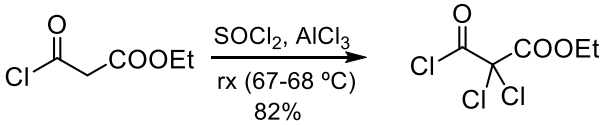
3.2.1 Preparación de las dicloromalonamidas

La preparación de los materiales de partida es análoga al capítulo anterior utilizando como agente acilante en este caso el cloruro de 2,2-dicloro-2-(etoxicarbonil)acetilo, preparado según el procedimiento[3] de Perrotti con la variante de utilizar el éster etílico en lugar de metílico.



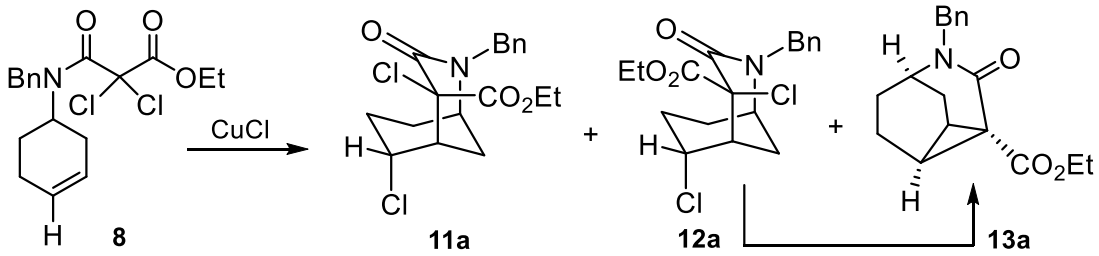
3.3 Preparación de los proradicales **9** y **10**

[3] Castelfranchi G.; Perrotti E. *Ann. Chim*. **1957**, *47*, 1201–1224:



*3.2.2 Estudios metodológicos de las dicloromalonamidas **8-10***

Los estudios de la reacción ATRC se iniciaron con el alqueno **8** obteniendo unos resultados distintos a los previamente reportados en el capítulo anterior (tricloroacetamidas). Así, se requirió una mayor carga de catalizador y la reacción era mucho más compleja, no sólo por la formación de epímeros por la génesis de un centro estereogénico en C-4, sino también por la aparición de productos de evolución de los mismos en el medio de reacción.

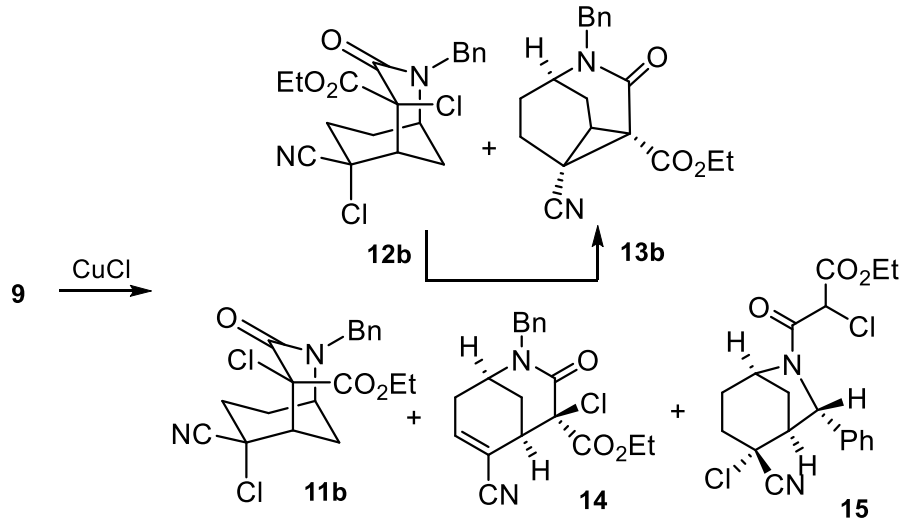


3.4 Procesos ATRC sobre el alqueno **8**:
1) 30% CuCl-TPMA, 50% AIBN, 1,2-DCE, 60 ºC, 48 h; 2) 30% CuCl-TPMA, 1,2-DCE, 80 ºC, 16 h; 3) 30% CuCl, DMF, 80 ºC, 16 h

El tratamiento del dicloroderivado **8** en las condiciones descritas en el esquema 3.4 (entrada 1)[4] condujo a la formación del morfano **11a** (29%) y del compuesto azatricíclico **13a** (42%), con un anillo ciclopropánico incrustado. El compuesto **13a** proviene del epímero **12a**, probablemente mediante una secuencia de rotura homolítica del enlace C-Cl axial en C-4 promovida por el CuCl, reducción del radical formado, generándose un enolato de Cu (II), que induce la formación intramolecular del anillo de ciclopropano debida al desplazamiento del átomo de cloro dispuesto en forma axial en C-6. Este tipo de S_N2 intramoleculares ya se había observado en compuestos 1,3-diclorados,[2a] aunque sin mención a una disposición antiperiplanar como favorita para la inducción de la ciclopropanación.

Curiosamente, en ausencia de AIBN (entrada 2) sí que se aisló además de **11a** (29%), su epímero **12a** (25%) y el producto ciclopropánico **13a** en bajo rendimiento (~10%). El proceso de ciclación también tuvo lugar en la ausencia de ligandos, al usar la DMF como propio disolvente-ligando (entrada 3) obteniéndose un rendimiento moderado de ambos morfanos **11a** (18%) y **12a** (24%).

[4] Las condiciones optimizadas en la serie tricloroacetamida (10% CuCl-TPMA, 50% AIBN, 1,2-DCE, 60 ºC, 48 h) daban bajas conversiones.

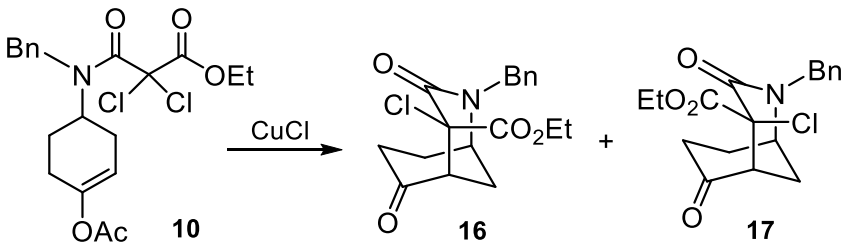


3.5 Procesos ATRC sobre el alqueno **9**: **1)** 30% CuCl-TPMA, 50% AIBN, 1,2-DCE, 60 ºC, 48 h; **2)** 30% CuCl-TPMA, 1,2-DCE, 80 ºC, 16 h; **3)** 30% CuCl, DMF, 80 ºC, 16 h

A continuación, se examinó el proceso de ciclación radicalaria del nitrilo α,β-insaturado **9** (esquema 3.5). En las mismas condiciones utilizadas a partir de **8** (entrada 1) se obtuvo el morfano **11b** (28%), el ciclopropano **13b** (49%), el producto de deshidrohalogenación **14** (9%) y el normorfano **15** (15%).[5] Como en la serie anterior, operando en ausencia de AIBN y a 80 ºC (entrada 2), sí que se aisló el morfano precursor del compuesto ciclopropánico, es decir **12b** (19%), junto con el morfano **11b** (22%), el ciclopropano **13b** (11%), el producto de eliminación **14** (8%) y el normorfano **15** (<5%). Es de resaltar que en estas condiciones la reacción no fue completa, recuperándose material de partida **9** (25%). Este hecho es indicativo para interpretar porque **12b** se aísla en estas condiciones. Si la reacción se detiene nos indica que la regeneración de Cu(I) a partir de Cu(II) se ha estancado y consecuentemente la evolución de **12b** a **13b** tampoco es factible en ausencia de Cu(I).

En esta serie con el uso de DMF como disolvente-ligando (entrada 3) no se observó el morfano **12b**, salvo algún caso puntual, y los rendimientos que se obtuvieron fueron para el morfano **11b** del 35% y del producto de ciclopropanación **13b** del 36%. Un estudio por rayos X de la estructura cristalina de **11b** confirmó la configuración relativa del centro cuaternario en C-4,[6] así como un estudio por RMN de los distintos compuestos fue clave para elucidar las configuraciones relativas de cada compuesto.

[5] Para una discusión acerca de la formación de normorfanos en la ciclación radicalaria de dicloroamido ésteres, véase capítulo 7.
[6] Para el estudio configuracional mediante análisis de los espectros de RMN (^{1}H y ^{13}C), véase la discusión en el artículo asociado a este capítulo.

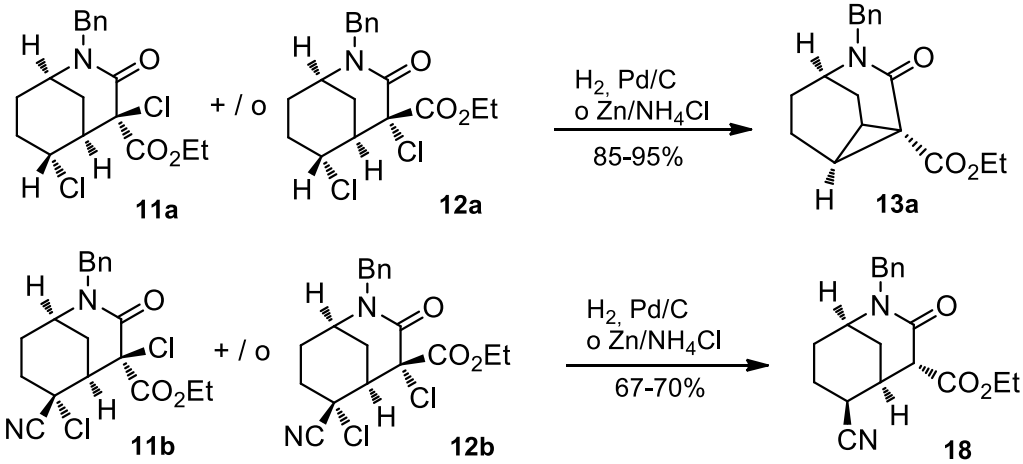


3.6 Procesos ATRC sobre el alqueno **10**:
1) 30% CuCl-TPMA, 50% AIBN, 1,2-DCE, 60 ºC, 48 h; **2)** 30% CuCl, DMF, 80 ºC, 16 h

Por último se examinó el comportamiento del acetato de enol **10** (esquema 3.6). Su tratamineto tanto en las condiciones de referencia (30% CuCl-TPMA, 50% AIBN, 1,2-DCE, 60 ºC, 48 h) como sin ligando (30% CuCl, DMF, 80 ºC, 16 h) condujo a una mezcla epimérica (1:1) de los morfanos **16** y **17** (55%).

3.2.3 Procesos de reducción de los morfanos obtenidos

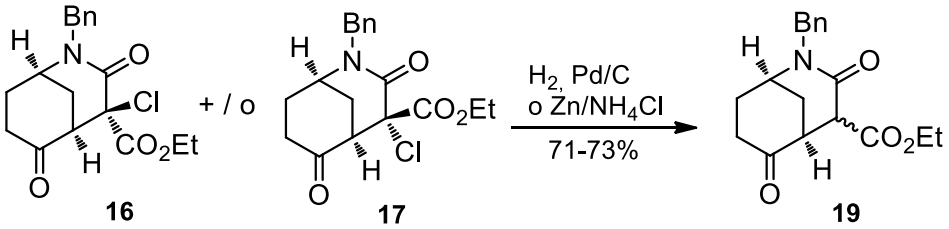
Finalmente, se examinó el proceso de reducción en los morfanos obtenidos (**11**, **12** y **16/17**), ya sea mediante reacciones de hidrogenación o tratamiento con Zn (esquemas 3.7 y 3.8). Los resultados fueron equiparables según el agente reductor, pero diferentes según el sustrato. Así, el tratamiento de **11a**, de **12a** o de la combinación en forma epimérica de ambos en condiciones de reducción nos llevaron siempre a aislar de forma *cuantitativa* el ciclopropano **13a**. En la literatura se encuentra ejemplos usando metales que intervienen en la formación de ciclopropanos desde compuestos 1,3-diclorados,[7] no obstante no se encuentra ningún reporte utilizando un proceso de hidrogenación promovido por Pd.



3.7 Proceso de reducción de los morfanos **11** y **12**

[7] Para un acoplamiento reductivo 1,3-dihalo derivados promovido por especies de titanoceno (II), véase: Takeda T.; Shimane K.; Fujiwara T.; Tsubouchi A. *Chem. Lett*. **2002**, 290–291.

En contraste, el tratamiento de **11b** y/o **12b** (esquema 3.7) en condiciones de reducción condujo con rendimientos del 67-70% al producto de reducción **18** sin detectar trazas de **13b** en ningún caso. Cabe mencionar que el epímero **12b** evoluciona fácilmente al producto reducido mientras que **11b** necesita de largos tiempos de reacción para su completa transformación (mayores a 48 horas). Esto se debe a que en el reajuste estereoquímico, el grupo etoxicarbonilo se encuentra en disposición axial causando interacciones 1,3-diaxiales, con el átomo de cloro en C-6, que desfavorecen el proceso de reducción.



3.8 Proceso de reducción de los morfanos **16**-**17**

Finalmente la reducción de **16** y/o **17** (esquema 3.8) proporcionó el producto reducido **19** en forma de epímeros 1:1 inseparable. Posiblemente esta diferencia respecto al éster **18** sea debida a la ausencia de interacción 1,3-diaxial entre el grupo etoxicarbonilo y el sustituyente en C(6) con hibridación sp^2. Así pues, ambos epímeros en **19** tendrían una estabilidad termodinámica similar.

3.3. Resumen

- Los estudios sintéticos han revelado la habilidad de las distintas especies radicalarias con sustituyentes carbamoilo y éster, electroatrayentes, para inducir procesos de ATRC, independientemente de la naturaleza del aceptor radicalario (pobre, neutro o rico electrónicamente), para generar morfanos.

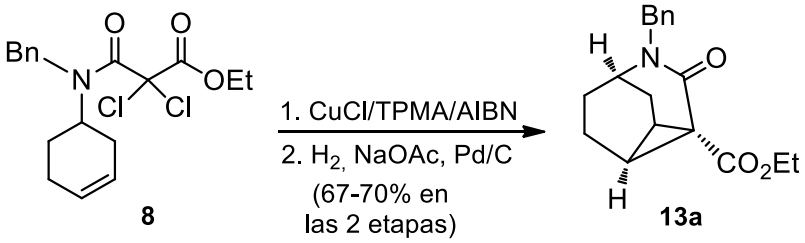
- A diferencia de los productos análogos resultantes de la ATRC a partir de tricloroacetamidas, en algunos casos se observa, después de la formación del núcleo de morfano, una etapa adicional de ciclopropananción *in situ*. La presencia del grupo éster favorece la ruptura del enlace C-Cl axial que es el elemento desencadenante del proceso de deshalogenación en los sustratos 1,3-diclorados dispuestos axialmente.

- El comportamiento frente a la reducción de los compuestos mono- y disustituídos en C-6 es diferente. La reducción de los cloroderivados **11a** y **12a** conduce al producto de

ciclopropanación **13a**, mientras que la reducción en la serie **11b**/**12b**, con un carbono cuaternario en C-6 conduce exclusivamente en ambos compuestos al azabiclo **18**.

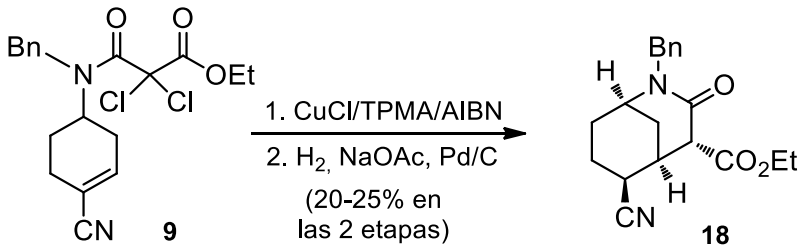
- Desde el punto de vista sintético los procesos más relevantes son:

a) Síntesis del azatriciclo **13**



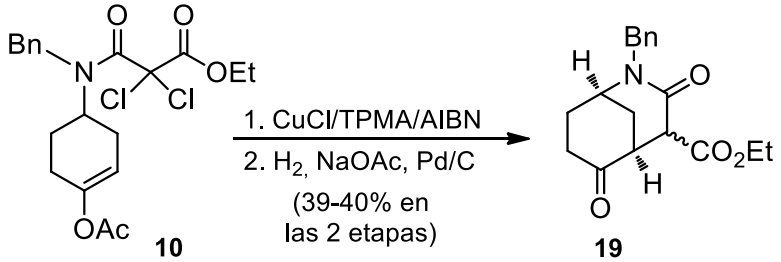
3.9 Conversión total de **8** a **13a**

b) Síntesis del morfano polifuncionalizado **18**



3.10 Conversión total de **9** a **18**

c) Síntesis de los morfanos dicarbonílicos **19**



3.11 Conversión total de **10** a **19**

3.4 Chlorine Atom Transfer Radical 6-exo Cyclizations of Carbamoiyldichloroacetate-Tethered Alkenes, Enol Acetates and α,β-Unsatured Nitriles Leading to Morphans.

Diaba, F.; Martínez-Laporta, A.;
Bonjoch *J.*
Eur. J. Org. Chem. **2014,** 2371–2378

EurJOC European Journal of Organic Chemistry

FULL PAPER

DOI: 10.1002/ejoc.201301590

Chlorine Atom Transfer Radical 6-*exo* Cyclizations of Carbamoyldichloroacetate-Tethered Alkenes, Enol Acetates and α,β-Unsaturated Nitriles Leading to Morphans

Faïza Diaba,*[a] Agustín Martínez-Laporta,[a] and Josep Bonjoch*[a]

Keywords: Synthetic methods / Radicals / Cyclization / Nitrogen heterocycles / Lactams

The Cu^I-mediated atom transfer radical cyclization of amino-tethered dichloromalonamides and electron-rich, electron-poor, and nonactivated double bonds is a useful methodology for the synthesis of 2-azabicyclo[3.3.1]nonanes. A study of the reaction conditions and the scope of the process is reported. Cyclopropane ring formation was observed from the resulting 1,3-dichlorides in some morphan substrates using either Cu^I, Pd, or Zn.

Introduction

The morphan nucleus (2-azabicyclo[3.3.1]nonane ring) is found in many alkaloids[1] belonging to highly diverse biogenetic families (Figure 1). In earlier work, we developed a synthetic entry to morphan derivatives based on the reductive cyclization of trichloroacetamides, using tributyltin hydride as well as tris(trimethylsilyl)silane.[2] Recently, based on the well-known ability of copper(I) complexes to catalyze atom transfer radical cyclization (ATRC) reactions of olefins with polyhalogenated compounds,[3] we reported a new synthetic route to polyfunctionalized morphan compounds.[4] The procedure was based on the use of a Cu^I complex with TPMA [tris(2-pyridylmethyl)amine] in conjunction with the additive AIBN,[5] which regenerates the catalytically active copper(I) species by reduction of the Cu^{II} complex.

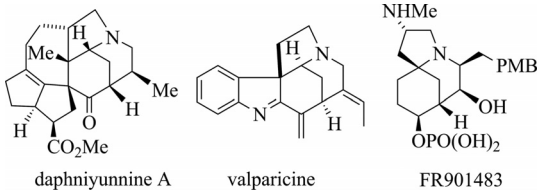
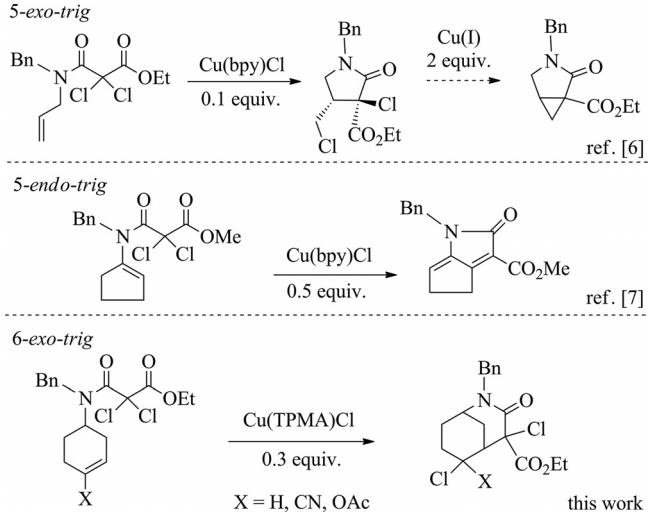


Figure 1. Alkaloids embodying the azabicyclic morphan framework.

In the synthesis of nitrogen-containing heterocycles,[6,7] the use of α,α-dichloro β-dicarbonylated substrates as pro-radicals[8] has been far less studied (Scheme 1) than the use of trichloro- or dichloroacetamides.[9] We report herein the first 6-*exo-trig* radical cyclization of α,α-dichloroamido esters (Scheme 1). The purpose of this work is to examine the scope and limitations of this radical methodology in the search for nitrogen-containing building blocks that might be useful in alkaloid synthesis. The process was studied with three types of radical acceptors: α,β-unsaturated nitriles, alkenes, and enol acetate moieties, each with different electron density. The stereochemical course of the reactions as well as the chemical behavior of the resulting azabicyclic compounds is also reported.



Scheme 1. Atom transfer radical cyclization (ATRC) of dichloromalonamides.

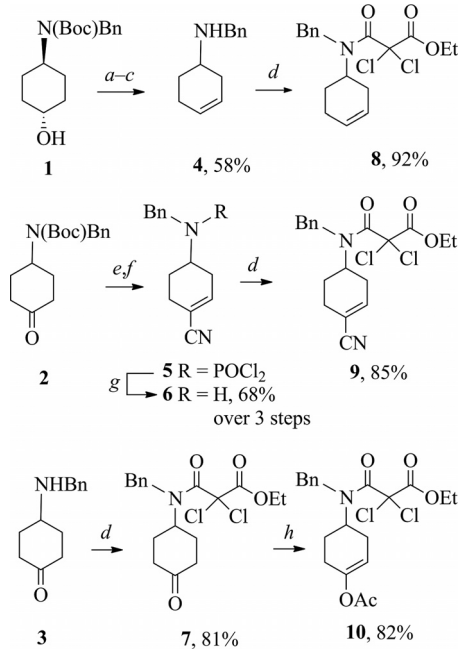
Results and Discussion

The dichlorocarbamoylacetates (α,α-dichloro-β-amido esters) required for this study were prepared from the

[a] Laboratori de Química Orgànica, Facultat de Farmàcia, IBUB, University of Barcelona,
Av. Joan XXIII s/n, 08028 Barcelona, Spain
E-mail: faiza.diaba@ub.edu
josep.bonjoch@ub.edu
http://www.ub.edu/farmaco/en/quimica/llistat_recerca/

Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/ejoc.201301590

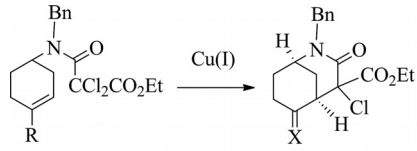
known aminocyclohexane derivatives **1**[10] and **2**–**3**,[2a] by following the synthetic sequences depicted in Scheme 2.



Scheme 2. Preparation of the starting dichloromalonamides **8**–**10**. Reagents and conditions: (a) MsCl, iPr_2EtN, CH_2Cl_2, room temp., 3 h; (b) *t*BuOK, *t*BuOH, 90 °C, 24 h; (c) 10% HCl, THF, reflux, 2 h; (d) EtO_2CCl_2COCl, Et_3N, CH_2Cl_2, room temp., overnight; (e) TMSCN, CsF, CH_3CN, room temp., overnight; (f) $POCl_3$, pyridine, benzene, reflux, 5 h; (g) 10% HCl, THF, reflux, 5 h; (h) isopropenyl acetate, TsOH, reflux, 5 h.

took place without standard ligands when *N*,*N*-dimethylformamide (DMF) was used as the solvent[11] with 30% catalyst loading (42% combined yield, diastereomeric mixture: entry 2).

Table 1. ATRC from α-carbamoyl-α,α-dichloro esters **8**–**10** using CuCl.[a]



8 X = H
9 X = CN
10 X = O

11a/12a X = Cl, H
11b/12b X = Cl, CN
16/17 X = O

Entry	Compd.	Ligand (%)	Additive (%)	Solvent	Yield (%)[c] 11	12	13
1	**8**	TPMA (30)	AIBN (50)	DCE	29	–[b]	42
2	**8**	none	none	DMF	18	24	–
3[c]	**9**	TPMA (30)	AIBN (50)	DCE	28	–[d]	49
4	**9**	none	none	DMF	35	–	36
5	**10**	TPMA (30)	AIBN (50)	DCE		55[e]	
6	**10**	none	none	DMF		56[e]	

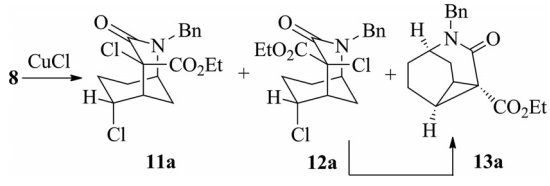
[a] Reaction conditions (unless noted otherwise): CuCl (30%) and either 60 °C, 48 h, DCE or 80 °C overnight DMF. [b] When AIBN was omitted, **12a** was isolated (ca. 25%) and the yield of **13a** decreased. [c] In this series, **14** (9%) and **15** (15%) were isolated under these reaction conditions (Figure 3). [d] When AIBN was omitted, **12b** was isolated (ca. 22%) and the yield of **13b** decreased. [e] Mixture of compounds **16** and **17** (1:1).

Cyclization of Alkene 8

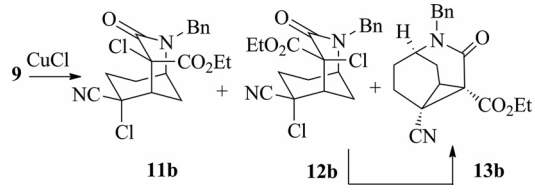
Representative results of the studies carried out with amido ester **8**, which bears an alkene as the radical acceptor (Scheme 3), are summarized in Table 1.Thus, in the presence of 0.3 equiv. of CuCl and TPMA and 0.5 equiv. of AIBN at 60 °C in 1,2-dichloroethane (DCE) (entry 1), dichloride **8** underwent the desired cyclization reaction to give the expected atom transfer product **11a** (29%) and the azatricyclic compound **13a** (42%). The latter presumably arose from the epimer **12a** by a sequence of homolytic cleavage of the axial C–Cl bond at C-4 promoted by CuCl, reduction of the intermediate radical into the Cu^{II} enolate, and intramolecular cyclopropane ring formation by displacement of the axial chlorine atom at C-6. This intramolecular S_N2 reaction has been previously observed in dichlorides with a 1,3-relationship.[6] Interestingly, the cyclization process also

Cyclization of α,β-Unsaturated Nitrile 9

The cyclization process using dichloroamido ester **9**, in which the radical acceptor shows a lower electron density than in **8**, proceeded in a similar manner (Table 1, entry 3; Scheme 4). Of the two isomeric morphans, **11b** was stable in the reaction medium whereas the epimer **12b**, with the axial chlorine at C-4, quickly evolved to the cyclopropane **13b**. In this series, using the reaction conditions of CuCl/DMF, the cyclopropanation process from **12b** was also observed[12] (Table 1, entry 4). The relative configuration of **11b** was determined by X-ray crystal structure analysis (Figure 2). For a detailed NMR analysis of morphans **11**–**12**, see below. The structure of **11b** unambiguously showed that the radical cyclization leading to the compound with the chlorine atom equatorially located at C-4 gave a stable



Scheme 3. ATRC from dichloroamido ester **8**.



Scheme 4. ATRC from dichloroamido ester **9**.

epimer in the reaction medium and did not undergo the cyclopropanation process observed from the epimer **12b**, in which the chlorine atom at C-4 was axially located.

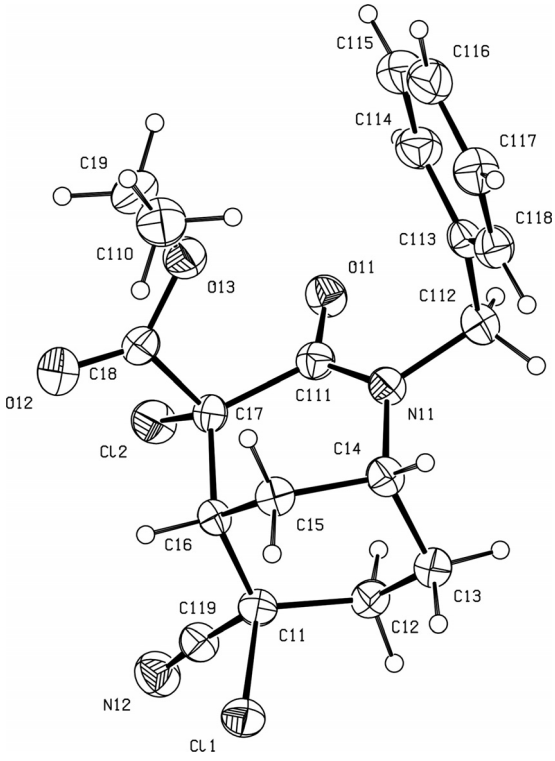


Figure 2. ORTEP drawing of morphan **11b**. Elipsoid plots drawn with 50% probability.

The minor compounds morphan **14**, arising from a dehydrohalogenation process from **11a**, and normorphan **15**, generated directly from the carbocyclic starting material **9**, were also isolated (Figure 3). The unexpected normorphan **15** came from the initial α-dicarbonylic radical after a 1,4-hydrogen transfer, which generated a benzylic radical that reacted with the unsaturated nitrile leading to the normorphan derivative. It is notable that, to the best of our knowledge, this reaction pathway has never been observed in radical reactions using *N*-benzylacetamides other than in our previous studies on related *N*-(1-phenylethyl)trichloroacetamides.[13] The stereochemistry of **15** was initially only tentative due to the formation of a mixture of epimers, each with two rotamers, at the stereogenic carbon atom in the side chain, which gave a complex NMR spectrum. After the reduction of both C–Cl bonds, the NMR spectroscopic data allowed the unequivocal assignment of the relative configuration of both normorphans (see below).

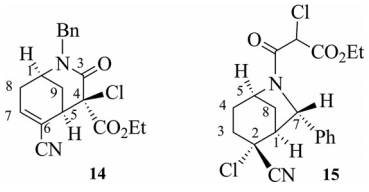
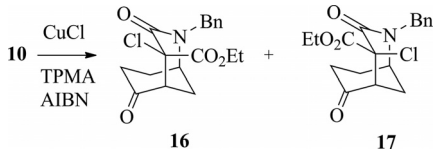


Figure 3. Compounds **14** and **15** and numbering of morphan and normorphan derivatives.

Cyclization of Enol Acetate 10

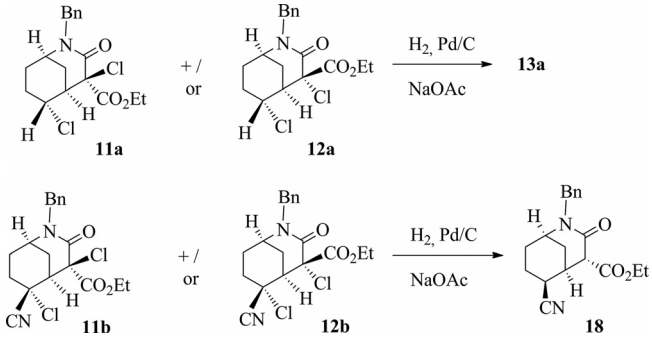
Finally, we examined the Cu^{I}-catalyzed annulation of enol acetate **10** (Scheme 5), with an electron-donating group upon the alkene radical acceptor. Interestingly, treatment of **10** either under the standard cyclization conditions using TPMA and AIBN or without additives (Table 1, entries 5 and 6) afforded ketone derivatives **16** and **17** as a 1:1 mixture of epimers in 55% yield. They were formed when the initial annulation products (i.e., α-chloro acetoxy intermediates, see Scheme 1) evolved into the more stable ketone either under the reaction conditions or during workup.



Scheme 5. ATRC from dichloroamido ester **10**.

Reduction Processes from Dihalides 11 and 12

We examined the behavior of the synthesized dichloromorphans in reduction processes by using either a hydrogenation reaction or treatment by zinc metal. Catalytic hydrogenation of either **11a** or **12a**, as well as the epimeric mixture of both, quantitatively gave rise to the cyclopropane derivative **13a** (Scheme 6). The formation of cyclopropane compounds from 1,3-dichlorides by using metals has been reported,[14] but to the best of our knowledge there are no examples of the use of Pd as a promoter in a hydrogenation process.

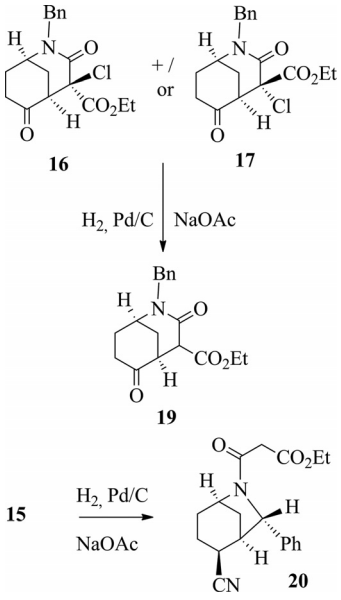


Scheme 6. Hydrogenation processes from morphans **11** and **12** (series **a**–**b**).

In contrast, epimeric dichloro derivatives with an equatorial cyano group at C-6 (**11b** and **12b**) instead of a hydrogen atom, as in **11a** and **12a**, behaved differently in the hydrogenation process.[15] In this case, both dichlorides gave the same morphan compound **18** without any detectable cyclopropanation. The epimer **12b** evolved easily to morphan **18**, whereas catalytic hydrogenation of **11b** was slow. It is noteworthy that the stereochemical result at C-4 was the same regardless of the configuration of this carbon atom in the starting material. In the stereochemical arrangement of **18**, in which the ethoxycarbonyl group was in an axial disposi-

tion, the 1,3-diaxial interaction with the equatorial substituent at C-6 was avoided.

Interestingly, when the hydrogenation was carried out from the chloro compounds **16** and **17**, irrespective of which epimer was used, a mixture of amido esters **19**, epimers at C-4, was isolated. (Scheme 7). This probably reflects the fact that when C-6 has an sp^2 hybridization both epimers of **19** show similar stability, since the 1,3-diaxial interaction between the equatorial substituents at C-4 and C-6 in morphan compounds does not take place.



Scheme 7. Hydrogenation processes from morphans **16**–**17** and normorphan **15**.

The minor normorphan product **15** was also submitted to the hydrogenation process to ascertain the configuration at the benzylic methine at C-7 (see below for NMR studies); in this case, normorphan **20** was isolated (Scheme 7).

The reduction of chlorinated morphans by using Zn afforded similar results. Whereas the reduction of the epimeric mixture of morphans **11a** and **12a** again gave the cyclopropane derivative **13a** (now as a methyl ester, due to a transesterification process in the reaction medium),[16] the reduction of nitrile **12b** gave **18** together with small quantities of its epimer at C-6 and cyclopropane **13b** (as a methyl ester). The reduction of chloro ketones **16** and **17** afforded the same epimeric mixture as in the hydrogenation process (i.e., **19**).

NMR Studies

The stereochemistry of all synthesized morphans was established on the basis of their ^1H and ^{13}C NMR spectroscopic data by considering the electronic, anisotropic, and steric effects of the chlorine[17] and ester substituents. The relative configuration at C-6 for the 6-monosubstituted morphans **11a** and **12a** (for numbering of these compounds, see Figure 3) was easily established by the coupling constant pattern arising from H-6, which appears as a broad singlet, indicating its equatorial location. The stereochemistry at C-6 in **11b** and **12b**, in which C-6 is quaternary, was established by X-ray analysis of the former (Figure 2). This stereochemical assignment is consistent with mechanistic considerations, since the configuration at C-6 arose from the transfer of the chlorine atom from the less hindered face of the cyclohexane ring generated after the radical cyclization, which locates the chlorine in an axial disposition.

On the other hand, the configuration at the quaternary C-4 position (disubstituted with chloro and ethoxycarbonyl groups) in **11**, **12** (both series a/b), **16** and **17** was deduced from the chemical shift of the axial H-9 in the piperidone ring, which always appears upfield (δ = 1.95–2.05 ppm) when it has a 1,3-diaxial relationship with the ester at C-4, compared with the chemical shift observed (δ = 2.55–2.8 ppm) in the epimeric counterparts. A greater deshielding effect of the chlorine atom with respect to the ethoxycarbonyl group on hydrogen atoms with a 1,3-diaxial relationship was also observed in the chemical shift of H-6_{eq} when comparing the values in **11a** (δ = 5.0 ppm) and **11b** (δ = 4.3 ppm). It is also noteworthy that, in compounds with the chlorine atom equatorial with respect to the piperidone ring, the chemical shift of H-5 was always more deshielded than in the corresponding epimer in which the chlorine atom was axial. In the ^{13}C NMR spectra of compounds with the ester group located axially (**11a**, **11b**, and **16**) the ester carbonyl group resonated at lower field (ca. 1.5 ppm) than in the corresponding epimers in which the ester groups were located equatorially.

The stereostructure of normorphan **20**, and hence of its precursor normorphan **15**, was ascertained on the basis of the NMR spectroscopic data by comparison with a normorphan analogue lacking the phenyl group at C-7.[10] The ^{13}C NMR chemical shift of C-8 (δ = 31.9 ppm) in **20** was shifted upfield with respect to that found in the compound unsubstituted at C-7 (δ = 35.5 ppm). This result indicates a compression upon H-8_{eq}, which is only possible with the stereochemistry assigned to **20**, considering that the cyano group at C-2 is located equatorially.

Conclusions

The synthetic studies have revealed the ability of radical species with electron-withdrawing groups to undergo cyclization processes leading to morphan compounds, irrespective of the nature of the radical acceptor. Because the intramolecular addition products are 1,3-dichlorides, under some conditions we observed an additional dehalogenation step leading to cyclopropanes embedded in the morphan nucleus.

Experimental Section

General Methods: ^1H and ^{13}C NMR spectra were recorded in $CDCl_3$ solution. ^1H chemical shifts are reported as δ values (ppm) relative to internal Me_4Si, and ^{13}C NMR spectra are referenced to the deuterated solvent signal ($CDCl_3$: δ = 77.00 ppm). All NMR

spectroscopic data assignments are supported by COSY and HSQC experiments. Infrared spectra were recorded with a Nicolet 320 FTIR spectrophotometer. TLC was performed on SiO_2 (silica gel 60 F_{254}, Merck). The spots were located under UV light or by staining with a 1% $KMnO_4$ aqueous solution. Chromatography refers to flash chromatography and was carried out on SiO_2 (silica gel 60, SDS, 230–400 mesh). CuCl (99.99%) was purchased from Sigma–Aldrich and was used as received. All reactions were carried out under an argon atmosphere with anhydrous, freshly distilled solvents, under anhydrous conditions. Drying of the organic extracts during reaction workup was performed over anhydrous Na_2SO_4.

***N*-Benzyl-*N*-(3-cyclohexenyl)amine (4):** A solution of alcohol **1**[10] (3.85 g, 12.6 mmol) and *i*Pr_2EtN (6.5 mL, 37.9 mmol) in CH_2Cl_2 (50 mL) was cooled in an ice bath, then $MeSO_2Cl$ (1.5 mL, 18.95 mmol) was added dropwise. After stirring at 0 °C for 1 h and at room temp. for 3 h, the reaction mixture was washed with brine and the aqueous phase was extracted with CH_2Cl_2. The organics were dried, concentrated, dissolved in *t*BuOH, and treated with *t*BuOK (1 M in *t*BuOH, 63 mL, 63 mmol) in *t*BuOH (200 mL) at 90 °C for 24 h. The reaction mixture was concentrated and the residue was diluted with CH_2Cl_2 and washed with brine. The organics were dried, concentrated, and purified by chromatography (hexane/EtOAc, 80:20) to give the corresponding alkene (2.43 g, 67%). A mixture of the above alkene (4.06 g, 14.13 mmol), hydrochloric acid (10%, 70 mL), and THF (50 mL) was heated to reflux for 2 h. The reaction was allowed to reach room temp., then NaOH aqueous solution (2.5 M) was added until pH 11, and the mixture was extracted with CH_2Cl_2. The organics were dried and concentrated to yield the corresponding secondary amine **4** (2.30 g, 87%). For NMR spectroscopic data see Quirante et al.[10]

4-(Benzylamino)cyclohex-1-encarbonitrile (6): To a solution of ketone **2** (4.1 g, 12.53 mmol) in CH_3CN (15 mL) at room temp., were added successively CsF[18] (0.19 g, 1.25 mmol) and TMSCN (1.78 mL, 13.79 mmol) and the mixture was stirred overnight. The mixture was then filtered through a Celite pad and concentrated to yield the corresponding cyanohydrin (not shown), which was used in the next step without further purification. To a solution of the above cyanohydrin in benzene (4 mL), were added pyridine (21 mL, 26.1 mmol) and $POCl_3$ (3.73 mL, 40.75 mmol). The mixture was heated to reflux for 5 h, concentrated, diluted in CH_2Cl_2, and washed with HCl (1 N) and then brine. The organics were dried and concentrated to give **5**, which was redissolved in THF (50 mL) and HCl (10%, 70 mL), and heated at reflux for 5 h. The mixture was then basified with NaOH (2 N) and extracted with CH_2Cl_2. The organics were dried and concentrated, giving **6** (1.8 g, 68%, yield over three steps). For NMR spectroscopic data see ref.[2a]

Ethyl 3-[Benzyl(cyclohex-3-en-1-yl)amino]-2,2-dichloro-3-oxopropanoate (8): To a solution of secondary amine **4** (0.42 g, 2.35 mmol) and Et_3N (0.65 mL, 4.7 mmol) in CH_2Cl_2 (5 mL) cooled in an ice bath, ethyl 2,2,3-trichloro-3-oxopropanoate[19] (0.62 g, 2.82 mmol) was added dropwise. The reaction mixture was warmed to room temp. while stirring overnight. The mixture was diluted with CH_2Cl_2, washed with brine, dried, concentrated, and purified by chromatography (hexane/EtOAc, 80:20) to give **8** (765 mg, 92%) as a waxy solid. IR (NaCl): $\tilde{\nu}$ = 3088, 3063, 3029, 2983, 2935, 2840, 1761, 1740, 1680, 1655 cm^{-1}. ^1H NMR ($CDCl_3$, 400 MHz): δ = 1.37 (t, J = 7.2 Hz, 3 H, CH_3), 1.74 and 1.86 (2m, 2 H), 2.19 (m, 4 H), 4.33 (m, 1 H), 4.38 (q, J = 7.2 Hz, 2 H, CH_2O), 4.52 (d, J = 15.6 Hz, 1 H, CH_2Ph), 4.67 (d, J = 15.6 Hz, 1 H, CH_2Ph), 5.56 (br. d, J = 10.0 Hz, 1 H, =CH), 5.63 (br. d, J = 10.0 Hz, 1 H, =CH), 7.18–7.35 (m, 5 H, PhH) ppm. ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 13.8 (CH_3), 25.5 (CH_2), 27.4 (CH_2), 29.3 (CH_2), 46.6 (CH_2Ar), 55.3 (CH), 64.7 (OCH_2), 80.3 (CCl_2), 124.5 (=CH), 126.6 (=CH), 126.2, 126.9, 128.5 (Ph), 137.6 (*ipso*-C), 162.4 (CO), 163.7 (CO) ppm. HRMS (ESI-TOF): calcd. for $C_{18}H_{22}Cl_2NO_3$ [M^+ + 1] 370.0971; found 370.0968.

Ethyl 3-[Benzyl(4-cyanocyclohex-3-en-1-yl)amino]-2,2-dichloro-3-oxopropanoate (9): Operating as above, starting from **6** (0.77 g), after chromatography, **9** (1.21 g, 85%) was obtained (*Z*/*E* rotamers, 4:1 ratio, estimated by ^1H NMR) as an amorphous white solid; m.p. 133–134 °C. IR (NaCl): $\tilde{\nu}$ = 3062, 3031, 2981, 2937, 2873, 2215, 1759, 1739, 1679, 1655 cm^{-1}. ^1H NMR ($CDCl_3$, 400 MHz): δ (Z rotamer) = 1.36 (t, J = 7.2 Hz, 3 H, CH_3), 1.81 and 1.96 (2m, 2 H), 2.34 (m, 4 H), 4.37 (m, 2 H, OCH_2), 4.46 (m, 1 H), 4.49 (d, J = 16.4 Hz, 1 H, CH_2Ph), 4.46 (m, 1 H), 4.66 (d, J = 16.4 Hz, 1 H, CH_2Ph), 6.48 (br. s, 1 H, =CH), 7.25 (m, 5 H, PhH) ppm. δ (*E* rotamer; main different signals) = 2.87 (br. s, 1 H), 3.44 (m, 1 H), 4.70 and 4.80 (2d, J = 16.4 Hz, 1 H each, CH_2Ph), 6.43 (br. s, 1 H, =CH) ppm. ^{13}C NMR ($CDCl_3$, 100 MHz): δ (*Z* rotamer) = 13.7 (CH_3), 26.2 (CH_2), 27.1 (CH_2), 29.6 (CH_2), 46.3 (CH_2Ar), 53.3 (CH), 64.8 (OCH_2), 79.9 (CCl_2), 112.1 (C=), 118.3 (CN), 136.9 (*ipso*-C), 142.1 (CH=), 162.4 (CO), 163.2 (CO) ppm. δ (*E* rotamer; main different signals) = 24.0 (CH_2), 27.6 (CH_2), 52.5 (CH_2Ph), 55.9 (CH), 118.7 (CN), 126.0, 127.1, 128.6 (Ar-CH), 111.6 (=C), 127.3, 128.1, 128.6 (Ph), 135.2 (*ipso*-C), 143.0 (=CH) ppm. HRMS (ESI-TOF): calcd. for $C_{19}H_{21}Cl_2N_2O_3$ [M^+ + 1] 395.0924; found 395.0926.

Ethyl 3-{[4-(Acetyloxy)cyclohex-3-en-1-yl]benzylamino}-2,2-dichloro-3-oxopropanoate (10): Operating as above, starting from **3** (0.8 g), after chromatography, **7** (1.22 g, 81%) was obtained as a yellowish viscous oil. IR (NaCl): $\tilde{\nu}$ = 3061, 3029, 1758, 1718, 1677, 1654 cm^{-1}. ^1H NMR ($CDCl_3$, 400 MHz): δ = 1.39 (t, J = 7.2 Hz, 3 H, CH_3), 1.86–2.28 (m, 4 H), 2.42 (m, 4 H), 4.41 (q, J = 7.2 Hz, 2 H, CH_2O), 4.60 (s, 2 H, CH_2Ph), 4.74 (m, 1 H), 7.15–7.40 (m, 5 H, PhH) ppm. ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 13.8 (CH_3), 29.8 (CH_2), 39.7 (CH_2), 46.5 (CH_2Ph), 56.5 (CH), 64.9 (CH_2O), 80.2 (CCl_2), 126.3, 127.2, 128.6 (Ph), 137.2 (*ipso*-C), 162.4 (CO), 163.4 (CO), 207.7 (CO) ppm. HRMS (ESI-TOF): calcd. for $C_{18}H_{22}Cl_2NO_4$ [M^+ + 1] 386.0920; found 386.0917.

A solution of ketone **7** (0.5 g, 1.29 mmol) and *p*TsOH (0.295 g, 1.55 mmol) in isopropenyl acetate (17 mL) was heated to reflux for 5 h. The mixture was then concentrated and purified by chromatography to give enol acetate **10** (0.453 mg, 82%). IR (NaCl, neat): $\tilde{\nu}$ = 3062, 3029, 2984, 2935, 2852, 1758, 1679, 1655 cm^{-1}. ^1H NMR ($CDCl_3$, 400 MHz): δ = 1.38 (t, J = 7.2 Hz, 3 H, CH_3), 1.94 (m, 2 H), 2.10 (s, 3 H, CH_3CO), 2.14–2.46 (m, 4 H), 4.39 (q, J = 7.2 Hz, 2 H, CH_2O), 4.42 (m, 1 H), 4.52 (d, J = 16.0 Hz, 1 H, CH_2Ph), 4.67 (d, J = 16 Hz, 1 H, CH_2Ph), 5.26 (br. s, CH=), 7.16–7.34 (m, 5 H, PhH) ppm. ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 13.8 (CH_3), 20.9 (CH_3CO), 26.7 (CH_2), 26.9 (CH_2), 27.1 (CH_2), 46.6 (CH_2Ph), 54.5 (CH), 64.8 (OCH_2), 80.1 (CCl_2), 111.8 (CH=), 126.1, 127.0, 128.5 (Ph), 137.3 (*ipso*-C), 147.3 (C=), 162.6 (CO), 163.5 (CO), 169.2 (CO) ppm. HRMS (ESI-TOF): calcd. for $C_{20}H_{24}Cl_2NO_5$ [M^+ + 1] 428.1026; found 428.1021.

General Procedures for Atom Transfer Radical Cyclization of Dichloroacetamides 8–10

Procedure A (Cu^I, TPMA, AIBN): To a suspension of CuCl (15.2 mg, 0.15 mmol, 30%) in 1,2-dichloroethane (4 mL) were successively added TPMA (44 mg, 0.15 mmol), AIBN (41.6 mg, 0.25 mmol, 50%), and nitrile **9** (200 mg, 0.51 mmol) and the mixture was heated at 60 °C for 48 h in a sealed tube. The solution was then allowed to reach room temp., concentrated, and purified by chromatography (hexane/EtOAc, 8:2 to hexane/EtOAc, 3:7).

Procedure B (Cu^I, DMF): A mixture of CuCl (7.6 mg, 0.07 mmol, 30%) and nitrile **9** (100 mg, 0.26 mmol) in DMF (1 mL) was heated at 80 °C overnight in a sealed tube. The solution was then concentrated and purified by chromatography by using the same conditions as in procedure A.

For the overall results, see Table 1.

Ethyl (1*RS*,4*SR*,5*RS*,6*RS*)-2-Benzyl-4,6-dichloro-3-oxo-2-azabicyclo[3.3.1]nonane-4-carboxylate (11a): Colorless oil. IR (NaCl): $\tilde{\nu}$ = 3063, 3029, 2943, 2860, 1739, 1667 cm^{-1}. ^1H NMR ($CDCl_3$, 400 MHz): δ = 1.32 (t, J = 7.2 Hz, 3 H, CH_3), 1.77 (br. d, J = 14.8 Hz, 1 H, 8-H_{eq}), 1.85–2.07 (m, 4 H, 7-CH_2, 8-H_{ax} and 9-H), 2.39 (dt, J = 14.0, 3.2 Hz, 1 H, 9-H), 2.87 (br. d, J = 3.2 Hz, 1 H, 5-H), 3.52 (br. s, 1 H, 1-H), 3.82 (d, J = 15.2 Hz, 1 H, CH_2Ph), 4.31 (m, 2 H, OCH_2), 4.99 (br. s, 1 H, 6-H), 5.49 (d, J = 15.2 Hz, 1 H, CH_2Ph), 7.26–7.37 (m, 5 H, PhH) ppm. ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 13.9 (CH_3), 22.2 (C-8), 24.6 (C-7), 25.0 (C-9), 44.1 (C-5), 48.8 (CH_2Ph), 50.9 (C-1), 57.7 (C-6), 63.7 (OCH_2), 71.6 (C-4), 127.7, 127.9, 128.7 (Ph), 136.5 (*ipso*-C), 164.6 (C-3), 168.2 (CO) ppm. HRMS (ESI-TOF): calcd. for $C_{18}H_{22}Cl_2NO_3$ [M^+ + 1] 370.0971; found 370.0968.

Ethyl (1*RS*,4*SR*,5*RS*,6*RS*)-2-Benzyl-4,6-dichloro-6-cyano-3-oxo-2-azabicyclo[3.3.1]nonane-4-carboxylate (11b): White solid; m.p. 124–125 °C (Et_2O/CH_2Cl_2, 9:1). IR (NaCl): $\tilde{\nu}$ = 3062, 3030, 2981, 2960, 2940, 2214, 1741, 1670 cm^{-1}. ^1H NMR ($CDCl_3$, 400 MHz): δ = 1.34 (t, J = 7.2 Hz, 3 H, CH_3), 1.95 (m, 2 H, 8-CH_2), 2.04 (br. d, J = 15.2 Hz, 1 H, 9-H), 2.33 (m, 2 H, 7-CH_2), 2.54 (dt, J = 15.2, 3.2 Hz, 1 H, 9-H), 3.29 (br. s, 1 H, 5-H), 3.50 (br. s, 1 H, 1-H), 3.88 (d, J = 14.8 Hz, 1 H, CH_2Ph), 4.34 (m, 2 H, OCH_2), 5.45 (d, J = 14.8 Hz, 1 H, CH_2Ph), 7.27–7.38 (m, 5 H, PhH) ppm. ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 13.8 (CH_3), 23.3 (C-8), 26.6 (C-9), 30.1 (C-7), 46.0 (C-5), 49.0 (CH_2Ph), 49.2 (C-1), 59.6 (C-6), 64.2 (OCH_2), 69.8 (C-4), 118.9 (CN), 128.0, 128.1, 128.8 (Ph), 136.1 (*ipso*-C), 163.6 (C-3), 167.2 (CO) ppm. HRMS (ESI-TOF): calcd. for $C_{19}H_{21}Cl_2N_2O_3$ [M^+ + 1] 395.0924; found 395.0916.

Ethyl (1*RS*,4*RS*,5*RS*,6*RS*)-2-Benzyl-4,6-dichloro-3-oxo-2-azabicyclo[3.3.1]nonane-4-carboxylate (12a): Colorless oil. IR (NaCl): $\tilde{\nu}$ = 3089, 3061, 3029, 2953, 2938, 2867, 1736, 1658 cm^{-1}. ^1H NMR ($CDCl_3$, 400 MHz): δ = 1.40 (t, J = 7.2 Hz, 3 H, CH_3), 1.71 (br. d, J = 14.8 Hz, 1 H, 8-H_{eq}), 1.84 (m, 1 H, 7-H_{eq}), 1.87 (tdd, J = 14, 4.4, 2.4 Hz, 1 H, 8-H_{ax}), 2.33 (ddt, J = 16, 12.4, 3.2 Hz, 1 H, 7-H_{ax}), 2.38 (t, J = 3.2 Hz, 2 H, 9-CH_2), 2.77 (m, 1 H, 5-H), 3.58 (br. s, 1 H, 1-H), 3.87 (d, J = 14.8 Hz, 1 H, CH_2Ph), 4.31 (m, 1 H, 6-H), 4.39 (m, 2 H, OCH_2), 5.28 (d, J = 14.8 Hz, 1 H, CH_2Ph), 7.26–7.37 (m, 5 H, PhH) ppm. ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 14.0 (CH_3), 22.5 (C-8), 23.5 (C-7), 25.0 (C-9), 47.2 (C-5), 48.7 (CH_2Ar), 51.3 (C-1), 57.8 (C-6), 63.4 (OCH_2), 69.1 (C-4), 127.8, 128.8 (Ph), 136.5 (*ipso*-C), 164.6 (C-3), 166.7 (CO) ppm. HRMS (ESI-TOF): calcd. for $C_{18}H_{22}Cl_2NO_3$ [M^+ + 1] 370.0971; found 370.0971.

Ethyl (1*RS*,4*RS*,5*RS*,6*RS*)-2-Benzyl-4,6-dichloro-6-cyano-3-oxo-2-azabicyclo[3.3.1]nonane-4-carboxylate (12b): IR (NaCl): $\tilde{\nu}$ = 3087, 3062, 3029, 2982, 2962, 2939, 2870, 2243, 1762, 1736, 1664 cm^{-1}. ^1H NMR ($CDCl_3$, 400 MHz): δ = 1.40 (t, J = 7.2 Hz, 3 H, CH_3), 1.82 (br. d, J = 14.4 Hz, 1 H, 8-H_{eq}), 1.93 (tdd, J = 14.4, 4.4, 2.4 Hz, 1 H, 8-H_{ax}), 2.13 (dm, J = 15.2 Hz, 1 H, 7-H_{eq}), 2.53 (t, J = 3.2 Hz, 2 H, 9-CH_2), 2.78 (ddd, J = 15.2, 12.4, 5.2 Hz, 1 H, 7-H_{ax}), 3.08 (br. s, 1 H, 5-H), 3.59 (br. s, 1 H, 1-H), 4.19 (d, J = 14.8 Hz, 1 H, CH_2Ph), 4.45 (q, J = 7.2 Hz, 2 H, OCH_2), 5.10 (d, J = 14.8 Hz, 1 H, CH_2Ph), 7.25–7.38 (m, 5 H, PhH) ppm. ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 13.5 (CH_3), 23.4 (C-8), 25.1 (C-9), 29.1 (C-7), 49.3 (CH_2Ar), 49.8 (C-1), 49.9 (C-5), 59.1 (C-6), 64.0 (CH_2O), 68.9 (C-4), 117.7 (CN), 127.8, 128.0, 128.9 (Ph), 136.2 (*ipso*-C), 164.1 (C-3), 165.7 (CO) ppm. HRMS (ESI-TOF): calcd. for $C_{19}H_{21}Cl_2N_2O_3$ [M^+ + 1] 395.0924; found 395.0924.

Ethyl (1*RS*,2*RS*,5*RS*,8*SR*)-4-Benzyl-3-oxo-4-azatricyclo[3.3.1.$0^{2,8}$]-nonane-2-carboxylate (13a): Yellowish oil. IR (NaCl): $\tilde{\nu}$ = 3061, 3028, 2935, 2868, 1729, 1642 cm^{-1}. ^1H NMR ($CDCl_3$, 400 MHz): δ = 1.26 (dm, J = 12 Hz, 1 H, 6-H_{eq}), 1.32 (t, J = 7.2 Hz, 3 H, CH_3), 1.50 (ddd, J = 12, 8, 4 Hz, 1 H, 6-H_{ax}), 1.86 (m, 1 H, 7-H_{eq}), 1.88 (dt, J = 13.2, 2.4 Hz, 1 H, 9-H), 1.96 (dm, J = 13.2 Hz, 1 H, 9-H), 2.08 (m, 1 H, 1-H), 2.10 (m, 1 H, 7-H_{ax}), 2.13 (m, 1 H, 8-H), 3.40 (br. s, 1 H, 5-H), 4.25 (q, J = 7.2 Hz, 2 H, OCH_2), 4.37 and 4.89 (2d, J = 14.8 Hz, 1 H each, CH_2Ph), 7.23–7.32 (m, 5 H, PhH) ppm. ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 14.2 (CH_3), 16.9 (C-7), 22.7 (C-8), 24.6 (C-6), 25.5 (C-9), 26.2 (C-1), 35.4 (C-2), 49.3 (CH_2Ph), 50.7 (C-5), 61.3 (OCH_2), 127.4, 128.2, 128.5 (Ph), 137.8 (*ipso*-C), 166.5 (C-3), 170.0 (CO) ppm. HRMS (ESI-TOF): calcd. for $C_{18}H_{22}NO_3$ [M^+ + 1] 300.1600; found 300.1597.

Ethyl (1*RS*,2*SR*,5*RS*,8*RS*)-4-Benzyl-8-cyano-3-oxo-4-azatricyclo-[3.3.1.$0^{2,8}$]nonane-2-carboxylate (13b): White solid; m.p. 79–80 °C. IR (NaCl): $\tilde{\nu}$ = 3061, 3030, 2938, 2871, 2235, 1735, 1652 cm^{-1}. ^1H NMR ($CDCl_3$, 400 MHz): δ = 1.37 (m, 1 H, 6-H_{eq}), 1.39 (t, J = 7.2 Hz, 3 H, CH_3), 1.58 (ddd, J = 13.6, 8.8, 4.8 Hz, 1 H, 6-H_{ax}), 1.95 (br. s, 2 H, 9-CH_2), 2.64 (br. s, 1 H, 1-H), 3.48 (br. s, 1 H, 5-H), 4.34 (d, J = 14.0 Hz, 1 H, CH_2Ph), 4.36 (m, 2 H, OCH_2), 4.85 (d, J = 14.0 Hz, 1 H, CH_2Ph), 7.24–7.35 (m, 5 H, PhH) ppm. ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 14.0 (CH_3), 17.5 (C-8), 21.2 (C-7), 24.2 (C-6), 24.2 (C-9), 28.5 (C-1), 41.3 (C-2), 49.5 (C-5), 49.9 (CH_2Ph), 62.7 (OCH_2), 119.6 (CN), 128.0, 128.2, 128.8 (Ph), 136.7 (*ipso*-C), 162.7 (C-3), 165.7 (CO) ppm. HRMS (ESI-TOF): calcd. for $C_{19}H_{21}N_2O_3$ [M^+ + 1] 325.1547; found 325.1555.

Ethyl (1*RS*,4*SR*,5*RS*)-2-Benzyl-4-chloro-6-cyano-3-oxo-2-azabicyclo[3.3.1]non-6-ene-4-carboxylate (14): Yellow solid; m.p. 148–149 °C. IR (NaCl): $\tilde{\nu}$ = 3060, 3028, 2935, 2218, 1739, 1664 cm^{-1}. ^1H NMR ($CDCl_3$, 400 MHz): δ = 1.34 (t, J = 7.2 Hz, 3 H, CH_3), 1.95 (ddd, J = 14.4, 4.4, 1.6 Hz, 1 H, 9-H), 2.22 (dm, J = 14.4 Hz, 1 H, 9-H), 2.38 (dm, J = 20.6 Hz, 1 H, 8-H), 2.61 (dd, J = 20.6, 4.4 Hz, 1 H, 8-H), 3.45 (br. s, 1 H, 5-H), 3.72 (br. s, 1 H, 1-H), 3.82 (d, J = 15.2 Hz, 1 H, CH_2Ph), 4.34 (m, 2 H, OCH_2), 5.54 (d, J = 15.2 Hz, 1 H, CH_2Ph), 6.77 (t, J = 3.6 Hz, 1 H, 7-H), 7.28–7.38 (m, 5 H, PhH) ppm. ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 13.9 (CH_3), 26.7 (C-9), 31.2 (C-8), 38.9 (C-5), 48.1 (C-1), 49.2 (CH_2Ph), 63.8 (OCH_2), 70.5 (C-4), 113.5 (C-6), 118.8 (CN), 127.9, 128.0, 128.8 (Ph), 136.2 (*ipso*-C), 144.3 (C-7), 163.2 (C-3), 167.4 (CO) ppm. HRMS (ESI-TOF): calcd. for $C_{19}H_{20}ClN_2O_3$ [M^+ + 1] 359.1157; found 359.1157.

Ethyl 2-Chloro-3-(2-chloro-2-cyano-7-phenyl-6-azabicyclo[3.2.1]oct-6-yl)-3-oxopropanoate (15): IR (NaCl): $\tilde{\nu}$ = 1768, 1668 cm^{-1}. ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 13.9 and 14.1 (CH_3), 23.8 and 24.0 (C-3), 27.2 and 27.4 (C-4), 31.3, 33.1, 35.0 (C-2 and C-8), 54.3 and 55.4 (CHClCO), 54.2 and 54.3 (C-5), 56.1, 56.3 (C-1), 63.0 and 63.6 (OCH_2), 62.1 and 64.6 (C-7), 118.5, 119.0 (CN), 125.6, 125.7, 128.7, 128.8, 129.4, 129.5 (Ph), 138.1, 138.5 (*ipso*-C), 163.0, 163.8, 163.9, 164.9 (CO) ppm. Minor signals for rotamer of each epimer were also observed. HRMS (ESI-TOF): calcd. for $C_{19}H_{21}Cl_2N_2O_3$ [M^+ + 1] 395.0924; found 395.0923.

Ethyl (1*RS*,4*SR*,5*RS*)-2-Benzyl-4-chloro-3,6-dioxo-2-azabicyclo-[3.3.1]nonane-4-carboxylate (16): White solid. IR (NaCl): $\tilde{\nu}$ = 3063, 3029, 2931, 2853, 1754, 1720, 1662 cm^{-1}. ^1H NMR ($CDCl_3$, 400 MHz): δ = 1.34 (t, J = 7.2 Hz, 3 H, CH_3), 1.82 (tdd, J = 14, 5.2, 2.4 Hz, 1 H, 8-H_{ax}), 2.01 (dt, J = 14.4, 3.2 Hz, 1 H, 9-H), 2.30 (dm, J = 14.0 Hz, 1 H, 8-H_{eq}), 2.50 (dd, J = 15.6, 5.2 Hz, 1 H, 7-H_{eq}), 2.58 (dq, J = 14.4, 3.2 Hz, 1 H, 9-H), 2.72 (ddd, J = 15.6, 14.0, 7.2 Hz, 1 H, 7-H_{ax}), 3.31 (br. s, 1 H, 5-H), 3.70 (br. s, 1 H, 1-

H), 4.03 (d, J = 15.2 Hz, 1 H, CH_2Ph), 4.36 (m, 2 H, OCH_2), 5.54 (d, J = 15.2 Hz, 1 H, CH_2Ph), 7.28–7.39 (m, 5 H, PhH) ppm. ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 13.9 (CH_3), 29.9 (C-8), 31.0 (C-9), 35.0 (C-7), 49.2 (CH_2Ph), 50.6 (C-1), 55.1 (C-5), 63.9 (OCH_2), 67.1 (C-4), 127.9, 128.0, 128.9 (Ph), 136.2 (*ipso*-C), 164.3 (C-3), 167.2 (CO), 204.3 (CO) ppm. HRMS (ESI-TOF): calcd. for $C_{18}H_{21}ClNO_4$ [M^+ + 1] 350.1154; found 350.1152.

Ethyl (1*RS*,4*RS*,5*RS*)-2-Benzyl-4-chloro-3,6-dioxo-2-azabicyclo-[3.3.1]nonane-4-carboxylate (17): White solid. IR (NaCl): $\tilde{\nu}$ = 3062, 3028, 2938, 1760, 1715, 1659 cm^{-1}. ^1H NMR ($CDCl_3$, 400 MHz): δ = 1.31 (t, J = 7.2 Hz, 3 H, CH_3), 1.79 (tdd, J = 13.6, 5.2, 2.4 Hz, 1 H, 8-H_{ax}), 2.03 (dt, J = 14.4, 2.8 Hz, 1 H, 9-H), 2.25 (m, 1 H, 8-H_{eq}), 2.50 (dd, J = 15.6, 5.2 Hz, 1 H, 7-H_{eq}), 2.87 (m, 1 H, 9-H), 2.91 (ddd, J = 15.6, 13.6, 7.2 Hz, 1 H, 7-H_{ax}), 3.12 (br. s, 1 H, 5-H), 3.73 (br. s, 1 H, 1-H), 4.09 (d, J = 15.2 Hz, 1 H, CH_2Ph), 4.29 (q, J = 7.2 Hz, 2 H, OCH_2), 5.36 (d, J = 15.2 Hz, 1 H, CH_2Ph), 7.28–7.37 (m, 5 H, PhH) ppm. ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 13.7 (CH_3), 29.5 (C-9), 29.6 (C-8), 35.3 (C-7), 48.9 (CH_2Ph), 50.9 (C-1), 56.9 (C-5), 63.9 (OCH_2), 68.2 (C-4), 127.8, 128.0, 129.0 (Ph), 136.2 (*ipso*-C), 164.5 (C-3), 166.1 (CO), 205.6 (CO) ppm. HRMS (ESI-TOF): calcd. for $C_{18}H_{21}ClNO_4$ [M^+ + 1] 350.1154; found 350.1152.

Ethyl (1*RS*,4*RS*,5*RS*,6*SR*)-2-Benzyl-6-cyano-3-oxo-2-azabicyclo-[3.3.1]nonane-4-carboxylate (18): A mixture of morphans **11b** and **12b** (25 mg, 0.06 mmol) was hydrogenated using Pd-C (3 mg) and NaOAc (15 mg, 0.18 mmol) in ethanol (2.5 mL). After purification, morphan **18** (14 mg, 70%) was isolated as a white solid; m.p. 114–115 °C. IR (NaCl): $\tilde{\nu}$ = 3063, 3028, 2872, 2237, 1734, 1645, 1734, 1651 cm^{-1}. ^1H NMR ($CDCl_3$, 400 MHz): δ = 1.33 (t, J = 7.2 Hz, 3 H, CH_3), 1.42 (tdd, J = 14.4, 4.4, 2.4 Hz, 1 H, 8-H_{ax}), 1.60 (dm, J = 13.6 Hz, 1 H, 9-H), 1.72 (qd, J = 14, 4.4 Hz, 1 H, 7-H_{ax}), 1.89 (dm, J = 14.0 Hz, 1 H, 8-H_{eq}), 2.00 (dm, J = 14.0 Hz, 1 H, 7-H_{eq}), 2.39 (ddt, J = 13.6, 3.6, 2.4 Hz, 1 H, 9-H), 2.65 (br. s, 1 H, 5-H), 2.82 (dt, J = 13.2, 4.0 Hz, 1 H, 6-H), 3.52 (br. s, 1 H, 1-H), 3.74 (br. s, 1 H, 4-H), 3.90 (d, J = 14.8 Hz, 1 H, CH_2Ph), 4.26 (m, 2 H, OCH_2), 5.39 (d, J = 15.2 Hz, 1 H, CH_2Ph), 7.24–7.37 (m, 5 H, PhH) ppm. ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 14.1 (CH_3), 20.8 (C-7), 27.1 (C-8), 28.6 (C-9), 32.7 (C-6), 34.0 (C-5), 48.3 (CH_2Ph), 49.6 (C-1), 49.9 (C-4), 62.0 (CH_2O), 120.0 (CN), 127.6, 128.7 (Ph), 136.6 (*ipso*-C), 165.8 (CO), 170.4 (CO) ppm. HRMS (ESI-TOF): calcd. for $C_{19}H_{23}N_2O_3$ [M^+ + 1] 327.1703; found 327.1700.

Ethyl 2-Benzyl-3,6-dioxo-2-azabicyclo[3.3.1]nonane-4-carboxylate (19): A 1:1 mixture of morphans **16** and **17** (40 mg, 0.11 mmol), NaOAc (26.7 mg, 0.33 mmol), and a catalytic amount of Pd-C (4 mg, 10%) in ethanol (3 mL) was stirred under a hydrogen atmosphere overnight. The catalyst was removed by filtration through Celite and the filtrate was concentrated and purified by chromatography (hexane/EtOAc, 9:1 to 6:4) to give **19** (27 mg, 73%) as a 1:1 epimeric mixture. IR (NaCl): $\tilde{\nu}$ = 2928, 2871, 1737, 1715, 1644 cm^{-1}. ^1H NMR ($CDCl_3$, 400 MHz): δ = 1.28 (t, J = 7.2 Hz, 3 H, CH_3), 1.32 (t, J = 7.2 Hz, 3 H, CH_3), 1.70–1.86 (m, 2 H, 8-H_{ax} of both), 1.96 (dm, J = 14.0 Hz, 1 H, 9-H), 2.10 (dt, J = 13.6, 3.2 Hz, 1 H, 9-H), 2.18 (dt, J = 13.6, 3.2 Hz, 1 H, 9-H), 2.22 (m, 2 H, 8-H_{eq} of both), 2.45 (m, 3 H, 7-H_{eq}, 7-CH_2), 2.59 (dq, J = 14.0, 3.2 Hz, 1 H, 9-H), 2.88 (ddd, J = 15.2, 14, 7.2 Hz, 1 H, 7-H_{ax}), 2.98 (br. s, 1 H, 5-H), 3.04 (br. s, 1 H, 5-H), 3.49 (s, 1 H, 4-H), 3.69 (br. s, 2 H, 1-H of both), 3.76 (d, J = 6 Hz, 1 H, 4-H), 4.03 and 4.13 (d, J = 15.2 Hz, 1 H, CH_2Ph), 4.13 (d, J = 15.2 Hz, 1 H, CH_2Ph), 4.15–4.30 (m, 4 H, OCH_2 of both), 5.32 (d, J = 15.2 Hz, 1 H, CH_2Ph), 5.49 (d, J = 15.2 Hz, 1 H, CH_2Ph), 7.29–7.38 (m, 10 H, PhH of both) ppm. ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 13.9 (CH_3), 14.0 (CH_3), 29.2 (C-9), 29.5 (C-8), 29.6 (C-8), 32.7 (C-9), 34.3 (C-7), 35.0 (C-7), 47.6 (C-5), 48.4 (CH_2Ph), 48.6 (CH_2Ph), 50.0 (C-1), 50.2 (C-4), 50.5 (C-1), 52.6 (C-4), 61.9 (OCH_2), 62.1 (OCH_2), 127.7, 127.9, 128.1, 128.8, 128.9 (Ph), 136.5 (*ipso*-C), 136.8 (*ipso*-C), 165.0 (C-3), 165.4 (C-3), 168.6 (CO), 169.4 (CO), 208.2 (CO), 208.9 (CO) ppm. HRMS (ESI-TOF): calcd. for $C_{18}H_{22}NO_4$ [M^+ + 1] 316.1543; found 316.1551.

The same stereochemical result was observed when the hydrogenation reaction was performed from **16** or **17** (20 mg in each case).

Ethyl (1*RS*,2*SR*,5*RS*,7*SR*)-3-(2-Cyano-7-phenyl-6-azabicyclo[3.2.1]-oct-6-yl)-3-oxopropanoate (20): IR (NaCl): $\tilde{\nu}$ = 3026, 2955, 2925, 2855, 2235, 1734, 1651 cm^{-1}. ^1H NMR ($CDCl_3$, 400 MHz): δ (*E*-rotamer) = 1.28 (t, J = 7.6 Hz, 3 H, CH_3), 1.39 (d, J = 12.0 Hz, 1 H, 8-H_{ax}), 1.46 (m, 1 H, 4-H), 2.12 (m, 2 H, 3-CH_2), 2.17 (m, 1 H, 8-H_{eq}), 2.41 (m, 1 H, 4-H), 2.54 (br. s, 1 H, 1-H), 2.86 (ddd, J = 9.0, 7.2, 2.4 Hz, 1 H, 2-H), 3.07 and 3.18 (2d, J = 15.6 Hz, 1 H each, $NCOCH_2$), 4.19 (q, J = 7.6 Hz, 2 H, OCH_2), 4.66 (t, J = 5.2 Hz, 1 H, 5-H), 5.07 (s, 1 H, 7-H_{eq}), 7.20–7.42 (m, 5 H, PhH) ppm; minor signals for *Z* rotamer were also observed at δ = 3.43 and 3.53 (2d, J = 15.0 Hz, $NCOCH_2$), 4.39 (t, J = 5.2 Hz, 5-H) ppm. ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 14.1 (CH_3), 22.6 (C-3), 27.3 (C-4), 31.9 (two peaks, C-2 and C-8), 42.4 (CH_2CO), 47.8 (C-1), 54.3 (C-5), 61.6 (OCH_2), 63.9 (C-7), 121.3 (CN), 125.7, 128.1, 129.1 (Ph), 140.2 (*ipso*-C), 165.3 (CO), 167.4 (CO) ppm. HRMS (ESI-TOF): calcd. for $C_{19}H_{23}N_2O_3$ [M^+ + 1] 317.1703; found 327.1702.

Single-Crystal X-ray Analysis of 11b: The structures were solved by direct methods by using the SHELXS computer program and refined by full-matrix least-squares method with SHELX97.[20] CCDC-967928 (for **11b**) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

Crystal Data, X-ray Data Collection and Refinement Results of Morphan 11b: $C_{19}H_{20}Cl_2N_2O_3$; M = 395.27; monoclinic; space group $P2_1/c$; a = 10.688(6) Å, b = 32.756(15) Å, c = 12.276(8) Å, α = 90°, β = 117.00(4)°, γ = 90°; V = 3829(4) $Å^3$; Z = 8; D = 1.371 $Mg\,m^{-3}$; λ(Mo-K_α) = 0.71073 Å; F(000) = 1648; T = 293(2) K. The sample (0.12 × 0.09 × 0.08 mm) was studied with a diffractometer with an image plate detector. The data collection (θ_{max} = 32.33°, range of *hkl*: *h* –12→11, *k* –44→47, *l* –15→18) gave 16555 reflections with 6288 unique reflections from which 4408 with $I > 2.0\sigma(I)$.

Supporting Information (see footnote on the first page of this article): Copies of ^1H and ^{13}C NMR spectra of all compounds, three dimensional drawings of morphans **11**, **12**, **16**–**18** with the NMR spectroscopic data embedded, and additional X-ray crystallographic data and ORTEP plots of **11b**.

Acknowledgments

Support of this research was provided by the Spanish Ministry of Economy and Competitiveness (project number CTQ2010-14846/BQU). M. Font-Bardia (University of Barcelona) and T. Calvet (CCiTUB) are thanked for performing the X-ray analysis.

[1] For a review, see: J. Bonjoch, F. Diaba, B. Bradshaw, *Synthesis* **2011**, 993–1018.

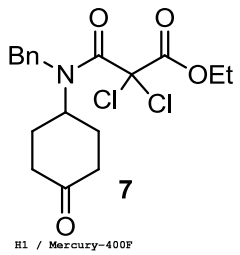
[2] a) J. Quirante, C. Escolano, M. Massot, J. Bonjoch, *Tetrahedron* **1997**, *53*, 1391–1402; b) J. Quirante, C. Escolano, A. Merino, J. Bonjoch, *J. Org. Chem.* **1998**, *63*, 968–976; c) J. Quir-

ante, C. Escolano, F. Diaba, J. Bonjoch, *J. Chem. Soc. Perkin Trans. 1* **1999**, 1157–1162.
[3] For reviews, see: a) A. J. Clark, *Chem. Soc. Rev.* **2002**, *31*, 1–11; b) W. T. Eckenhoff, T. Pintauer, *Catal. Rev. Sci. Eng.* **2010**, *52*, 1–59.
[4] F. Diaba, A. Martínez-Laporta, J. Bonjoch, A. Pereira, J. M. Muñoz-Molina, P. J. Pérez, T. R. Belderrain, *Chem. Commun.* **2012**, *48*, 8799–8801.
[5] Radicals formed from decomposition of the free radical initiator 2,2′-azobis(isobutyronitrile) (AIBN) at 60 °C continuously regenerate the catalytically active lower oxidation state transition metal complex (activator) by abstraction of a halogen atom from the higher oxidation state complex (deactivator), see: C. Ricardo, T. Pintauer, *Chem. Commun.* **2009**, 3029–3031.
[6] Using stoichiometric Cu^{I} reaction conditions from acyclic starting materials, see: N. Baldovini, M.-P. Bertrand, A. Carrière, R. Nouguier, J.-M. Plancher, *J. Org. Chem.* **1996**, *61*, 3205–3208.
[7] By using CuCl/bipyridine (0.5 equiv.) at 110 °C, toluene from *N*-cyclohex-1-enyl derivatives, see: a) D. T. Davies, N. Kapur, A. F. Parsons, *Tetrahedron Lett.* **1999**, *40*, 8615–8618; b) D. T. Davies, N. Kapur, A. F. Parsons, *Tetrahedron* **2000**, *56*, 3941–3949.
[8] For other examples of chlorine transfer cyclization of unsaturated α-dicarbonylated compounds, see: a) T. K. Hayes, R. Villani, S. M. Weinreb, *J. Am. Chem. Soc.* **1988**, *110*, 5533–5543; b) D. Yang, Y.-L. Yan, B.-F. Zheng, Q. Gao, N.-Y. Zhu, *Org. Lett.* **2013**, *15*, 5757–5760.
[9] For some recent atom transfer radical cyclizations from dichloro- or trichloroacetamides leading to nitrogen-containing ring formation, see: a) Y. Motoyama, K. Kamo, A. Yuasa, H. Nagashima, *Chem. Commun.* **2010**, *46*, 2256–2258; b) F. I. McGonagle, L. Brown, A. Cooke, A. Sutherland, *Org. Biomol. Chem.* **2010**, *8*, 3418–3425; c) F. Bellesia, A. J. Clark, F. Felluga, A. Gennaro, A. A. Isse, F. Roncaglia, F. Ghelfi, *Adv. Synth. Catal.* **2013**, *355*, 1649–1660; d) Q. Li, G. Li, S. Ma, P. Feng, Y. Shi, *Org. Lett.* **2013**, *15*, 2601–2603.
[10] J. Quirante, X. Vila, C. Escolano, J. Bonjoch, *J. Org. Chem.* **2002**, *67*, 2323–2328.
[11] M. Pattarozzi, F. Roncaglia, V. Giangiordano, P. Davoli, F. Prati, F. Ghelfi, *Synthesis* **2010**, 694–700.
[12] For a sequential Ru/Mg ATRA/dechlorination reaction providing cyclopropanes, see: a) M. A. Fernández-Zúmel, C. Buron, K. Sseverin, *Eur. J. Org. Chem.* **2011**, 2272–2277; b) J. Risse, M. Fernández-Zúmel, Y. Cudré, K. Severin, *Org. Lett.* **2012**, *14*, 3060–3063.
[13] a) J. Quirante, M. Torra, F. Diaba, C. Escolano, J. Bonjoch, *Tetrahedron: Asymmetry* **1999**, *10*, 2339–2410; b) J. Quirante, F. Diaba, X. Vila, J. Bonjoch, E. Lago, E. Molins, *C. R. Acad. Sci., Ser. IIc* **2001**, *4*, 513–521; c) F. Diaba, J. A. Montiel, J. Bonjoch, *Tetrahedron* **2013**, *69*, 4883–4889.
[14] For reductive coupling of 1,3-dihalides promoted by titanocene(II) species, see: T. Takeda, K. Shimane, T. Fujiwara, A. Tsubouchi, *Chem. Lett.* **2002**, 290–291.
[15] J. A. Seijas, M. P. Vázquez-Tato, L. Castedo, R. J. Estévez, G. Ónega, M. Ruíz, *Tetrahedron* **1992**, *48*, 1637–1642.
[16] For the preparation of cyclopropanes from 1,3-diiodoalkanes with zinc powder, see: a) D. Sakuma, H. Togo, *Tetrahedron* **2005**, *61*, 10138–10145. To the best of our knowledge, only one low-yielding example using a 1,3-dichloroalkane has been reported, see also: b) M. Heliwell, D. Fengas, C. K. Knight, J. Parker, P. Quayle, J. Raftery, S. N. Richards, *Tetrahedron Lett.* **2005**, *46*, 7129–7134.
[17] R. J. Abraham, M. A. Warne, L. Griffiths, *J. Chem. Soc. Perkin Trans. 2* **1997**, 881–886.
[18] S. S. Kim, G. Rajagopal, D. H. Song, *J. Organomet. Chem.* **2004**, *689*, 1734–1738.
[19] EtO_2CCCl_2COCl was prepared by chlorination (SO_2Cl_2) of ethyl malonyl chloride on a 3 g scale by following a reported procedure, see: G. Castelfranchi, E. Perrotti, *Ann. Chim.* **1957**, *47*, 1201–1224.
[20] G. M. Sheldrick, *Acta Crystallogr., Sect. A* **2008**, *64*, 112–122.
Received: October 23, 2013
Published Online: February 6, 2014

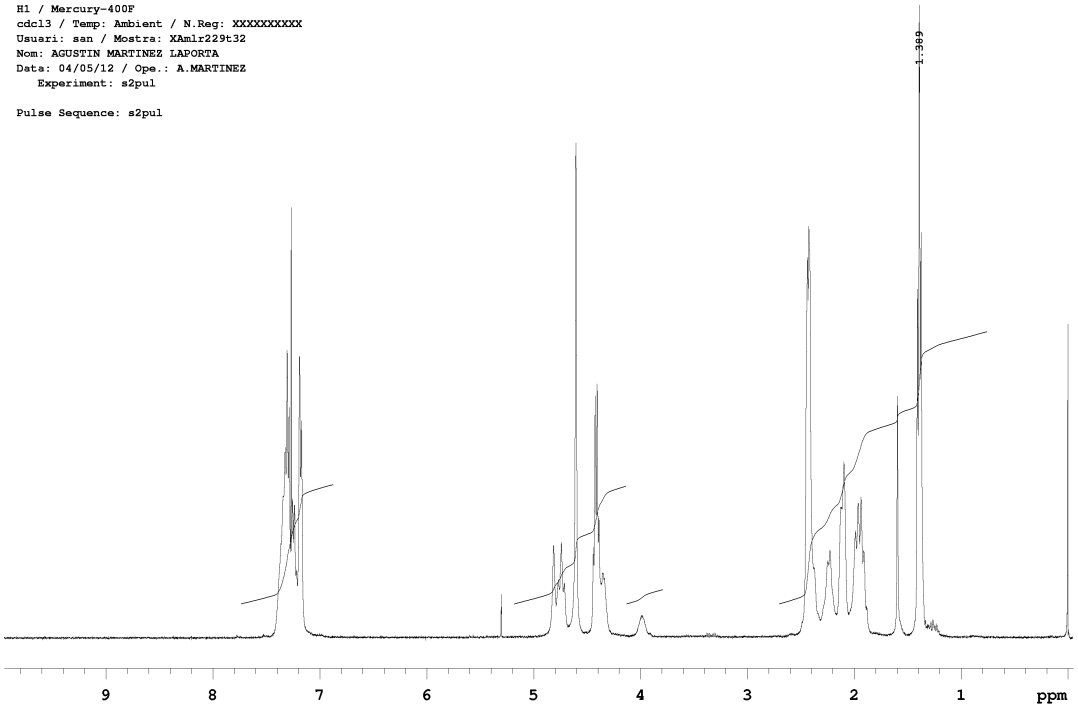
Eur. J. Org. Chem. **2014** · © WILEY-VCH Verlag GmbH & Co. KGaA, 69451 Weinheim, 2014 · ISSN 1099–0690

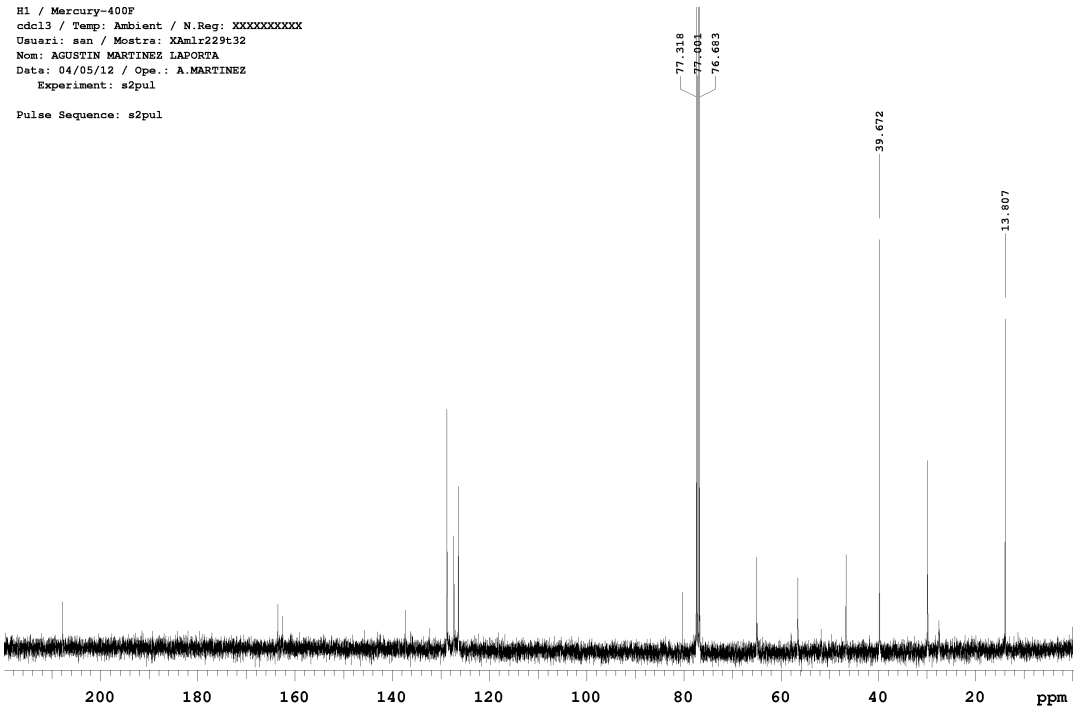
SUPPORTING INFORMATION

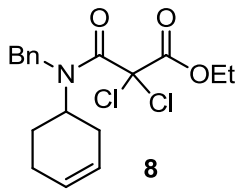
DOI: 10.1002/ejoc.201301590
Title: Chlorine Atom Transfer Radical 6-*exo* Cyclizations of Carbamoyldichloroacetate-Tethered Alkenes, Enol Acetates and α,β-Unsaturated Nitriles Leading to Morphans
Author(s): Faïza Diaba,* Agustín Martínez-Laporta, Josep Bonjoch*


O
O
Bn
N
OEt
Cl
Cl
O

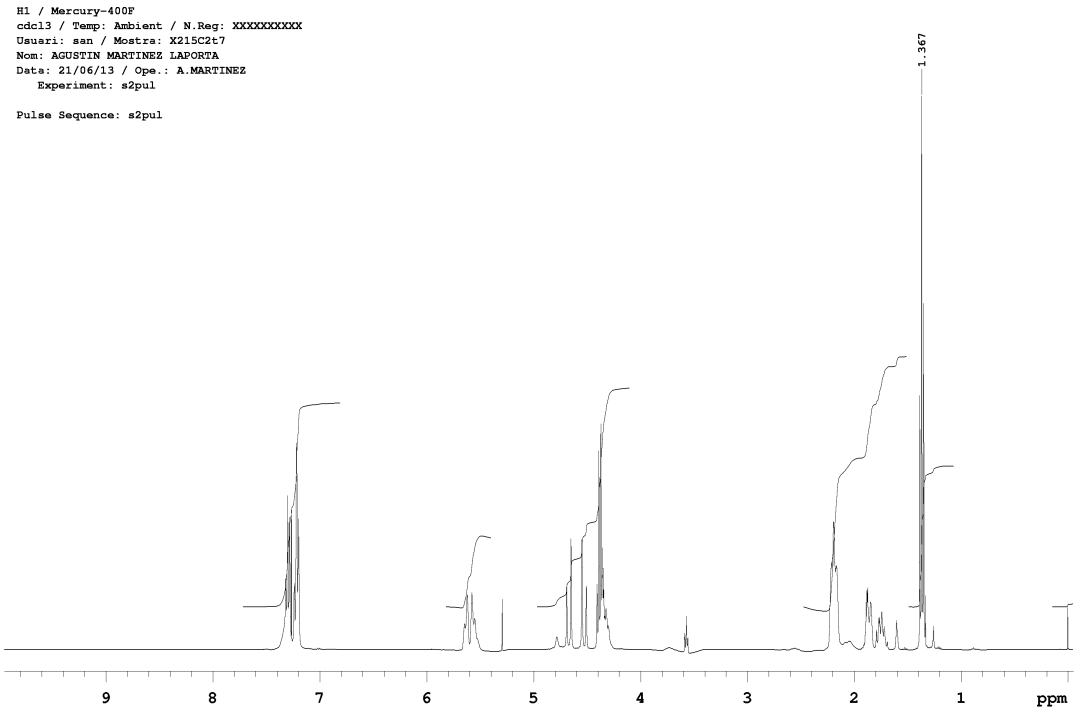
7

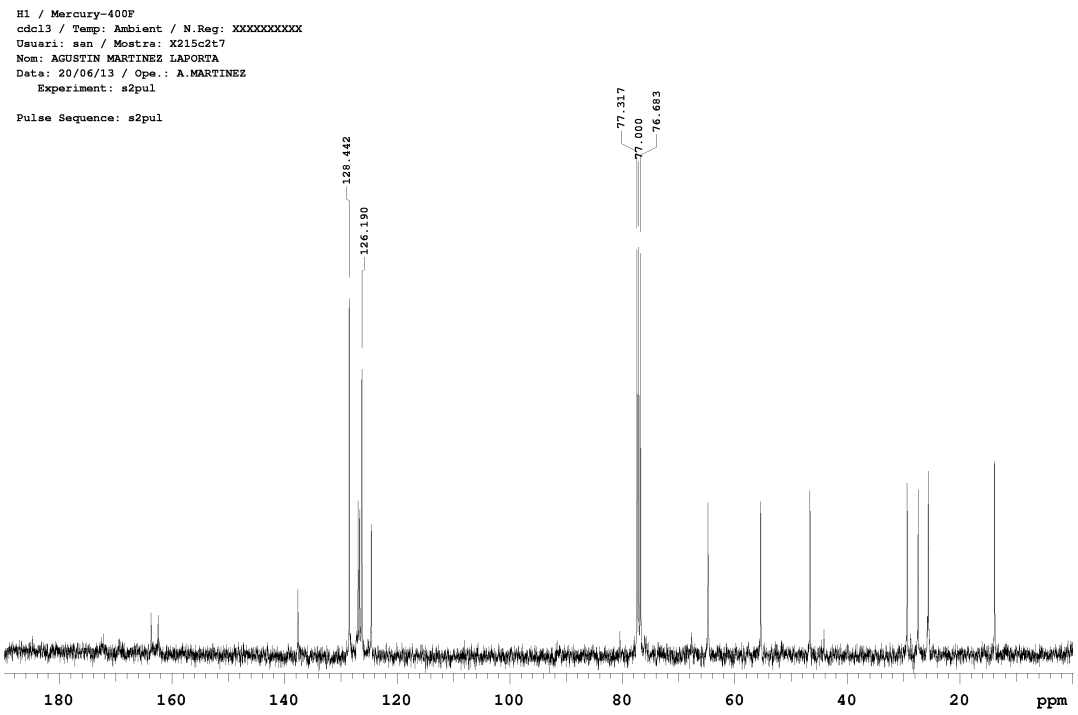

H1 / Mercury-400F
cdcl3 / Temp: Ambient / N.Reg: XXXXXXXXXX
Usuari: san / Mostra: XAmlr229t32
Nom: AGUSTIN MARTINEZ LAPORTA
Data: 04/05/12 / Ope.: A.MARTINEZ
Experiment: s2pul
Pulse Sequence: s2pul
1.389
9
8
7
6
5
4
3
2
1
ppm

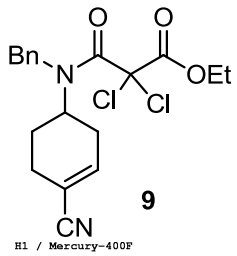

H1 / Mercury-400F
cdcl3 / Temp: Ambient / N.Reg: XXXXXXXXXX
Usuari: san / Mostra: XAmlr229t32
Nom: AGUSTIN MARTINEZ LAPORTA
Data: 04/05/12 / Ope.: A.MARTINEZ
Experiment: s2pul
Pulse Sequence: s2pul
77.318
77.001
76.683
39.672
13.807
200
180
160
140
120
100
80
60
40
20
ppm


O
O
Bn
N
OEt
Cl
Cl

8


H1 / Mercury-400F
cdcl3 / Temp: Ambient / N.Reg: XXXXXXXXXX
Usuari: san / Mostra: X215C2t7
Nom: AGUSTIN MARTINEZ LAPORTA
Data: 21/06/13 / Ope.: A.MARTINEZ
Experiment: s2pul
Pulse Sequence: s2pul
1.367
9
8
7
6
5
4
3
2
1
ppm

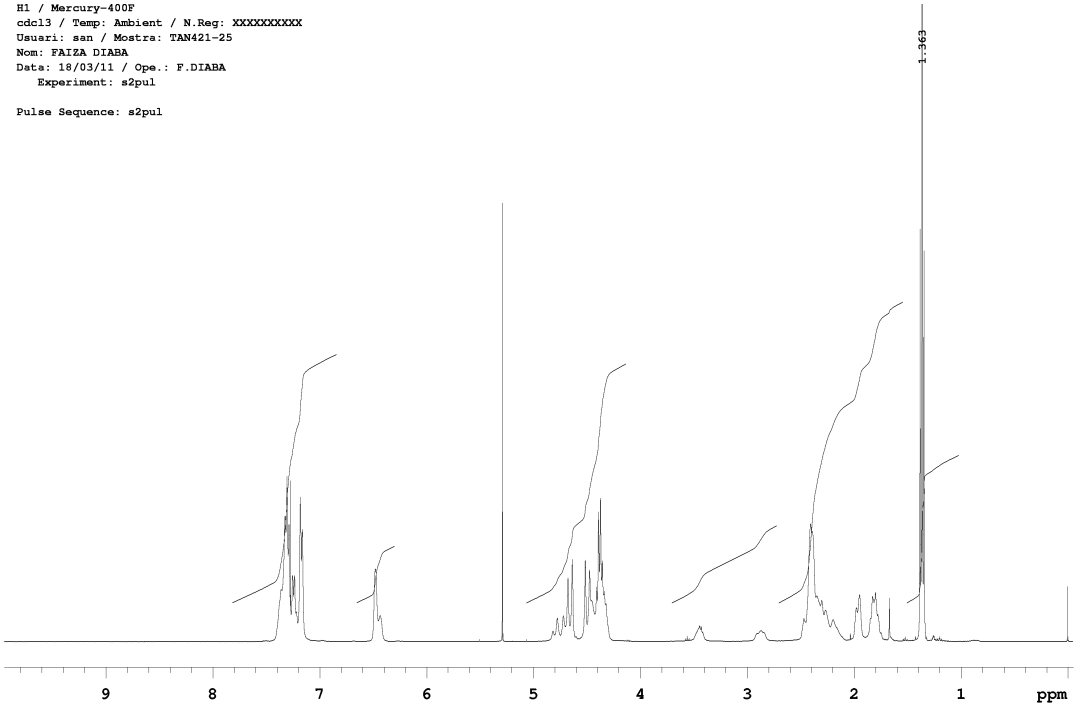

H1 / Mercury-400F
cdcl3 / Temp: Ambient / N.Reg: XXXXXXXXXX
Usuari: san / Mostra: X215c2t7
Nom: AGUSTIN MARTINEZ LAPORTA
Data: 20/06/13 / Ope.: A.MARTINEZ
Experiment: s2pul
Pulse Sequence: s2pul
128.442
126.190
77.317
77.000
76.683
180
160
140
120
100
80
60
40
20
ppm



9

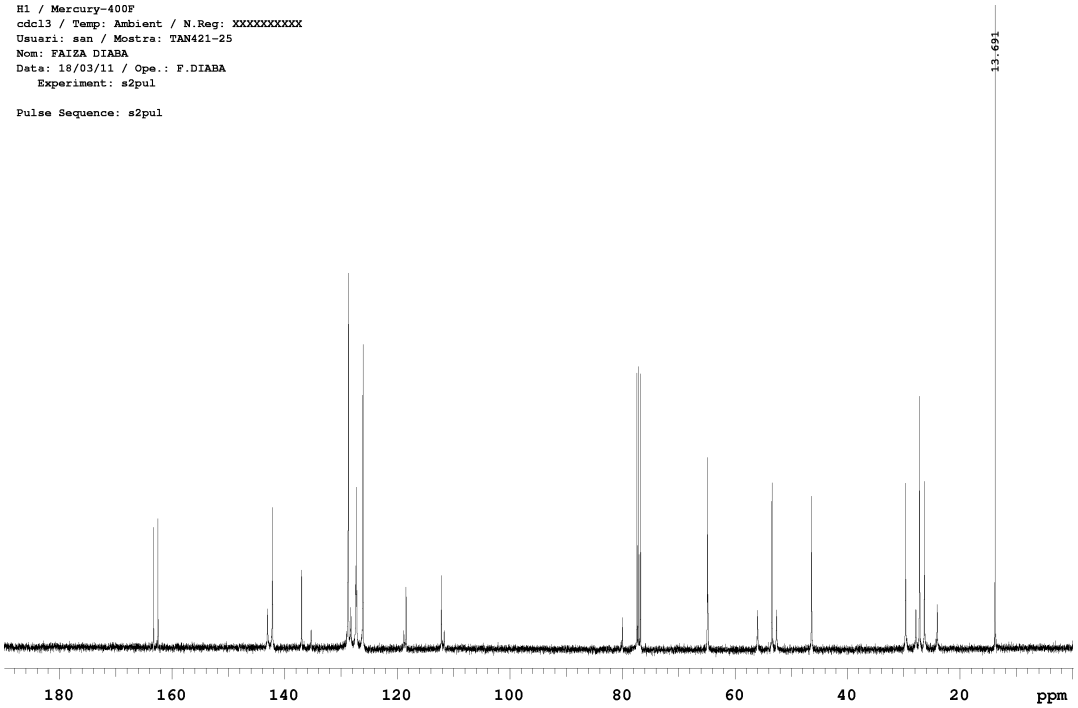
H1 / Mercury-400F
cdcl3 / Temp: Ambient / N.Reg: XXXXXXXXXX
Usuari: san / Mostra: TAN421-25
Nom: FAIZA DIABA
Data: 18/03/11 / Ope.: F.DIABA
Experiment: s2pul

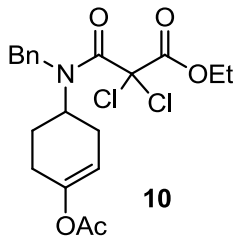
Pulse Sequence: s2pul



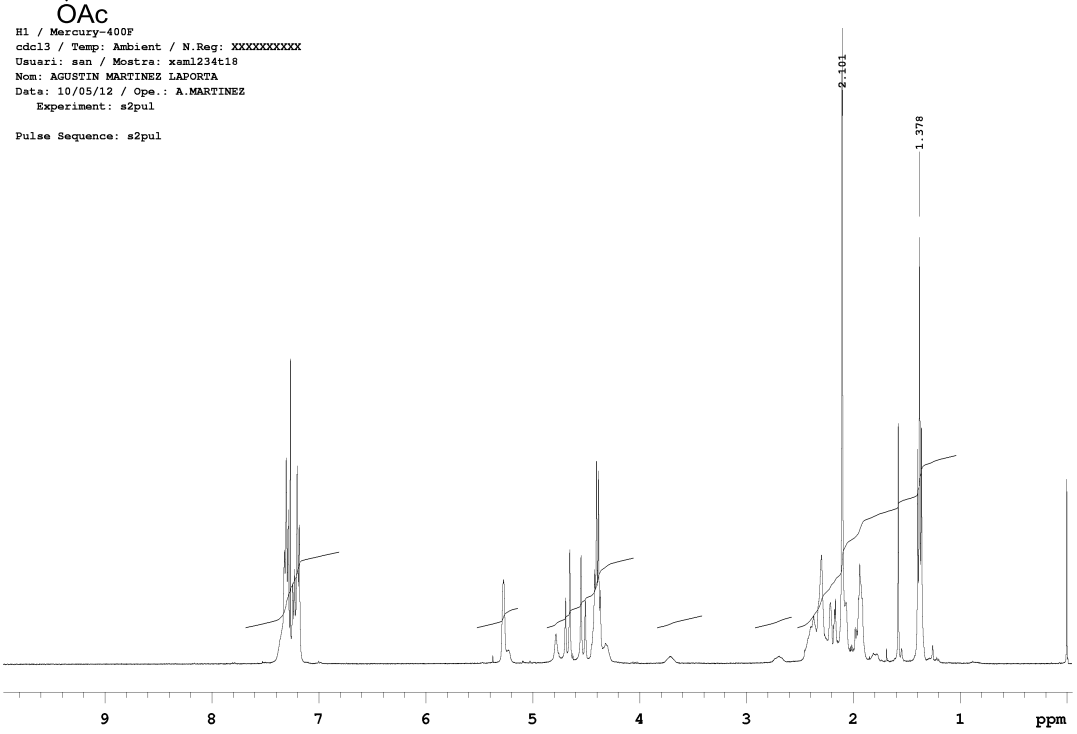
H1 / Mercury-400F
cdcl3 / Temp: Ambient / N.Reg: XXXXXXXXXX
Usuari: san / Mostra: TAN421-25
Nom: FAIZA DIABA
Data: 18/03/11 / Ope.: F.DIABA
Experiment: s2pul

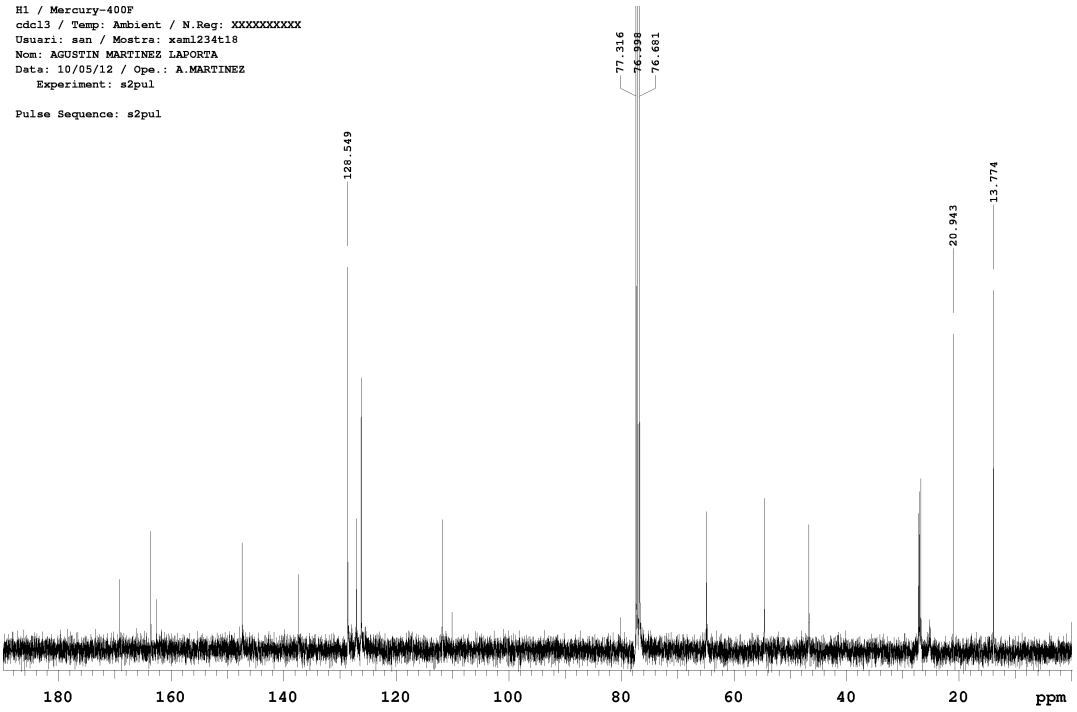
Pulse Sequence: s2pul

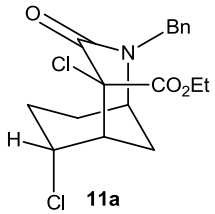



O
O
Bn
N
OEt
Cl
Cl
OAc

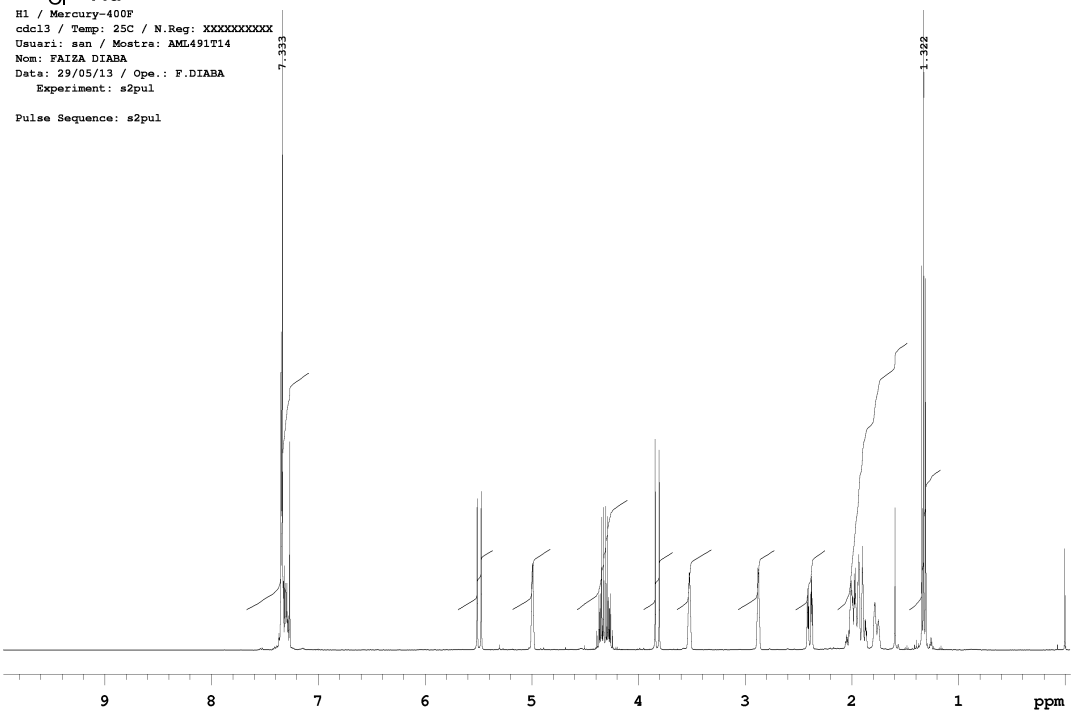
10

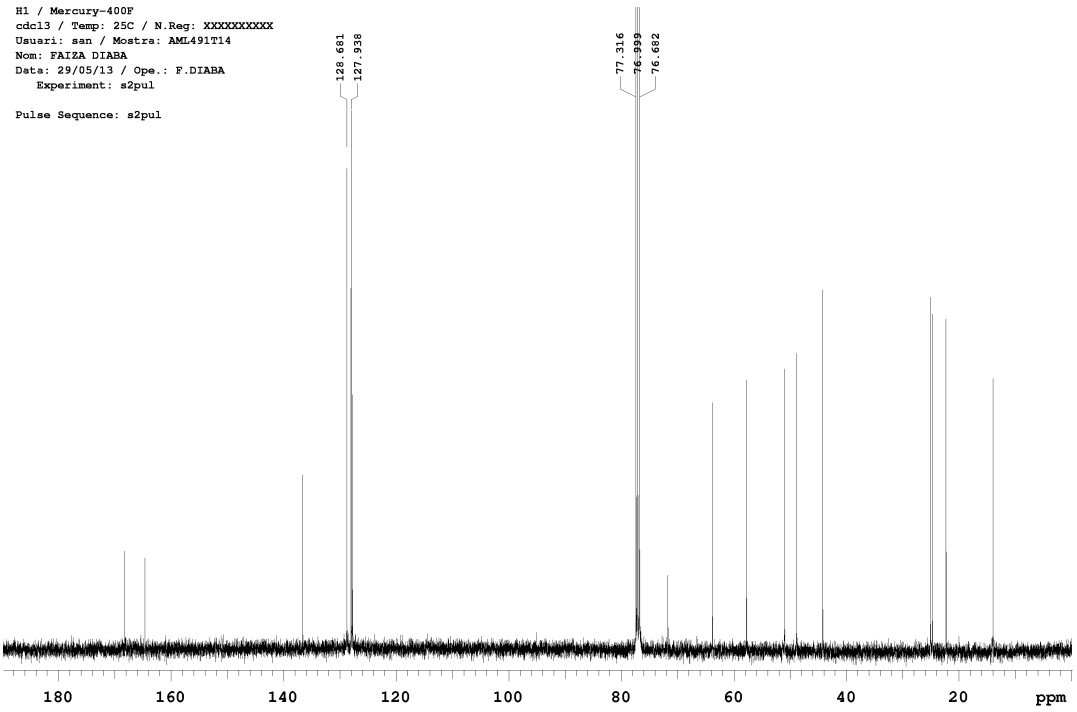

H1 / Mercury-400F
cdcl3 / Temp: Ambient / N.Reg: XXXXXXXXXX
Usuari: san / Mostra: xaml234t18
Nom: AGUSTIN MARTINEZ LAPORTA
Data: 10/05/12 / Ope.: A.MARTINEZ
Experiment: s2pul
Pulse Sequence: s2pul
2.101
1.378
9
8
7
6
5
4
3
2
1
ppm

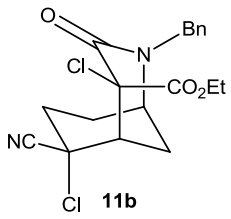

H1 / Mercury-400F
cdcl3 / Temp: Ambient / N.Reg: XXXXXXXXXX
Usuari: san / Mostra: xaml234t18
Nom: AGUSTIN MARTINEZ LAPORTA
Data: 10/05/12 / Ope.: A.MARTINEZ
Experiment: s2pul
Pulse Sequence: s2pul
77.316
76.998
76.681
128.549
20.943
13.774
180
160
140
120
100
80
60
40
20
ppm


O
Bn
N
Cl
CO2Et
H
Cl

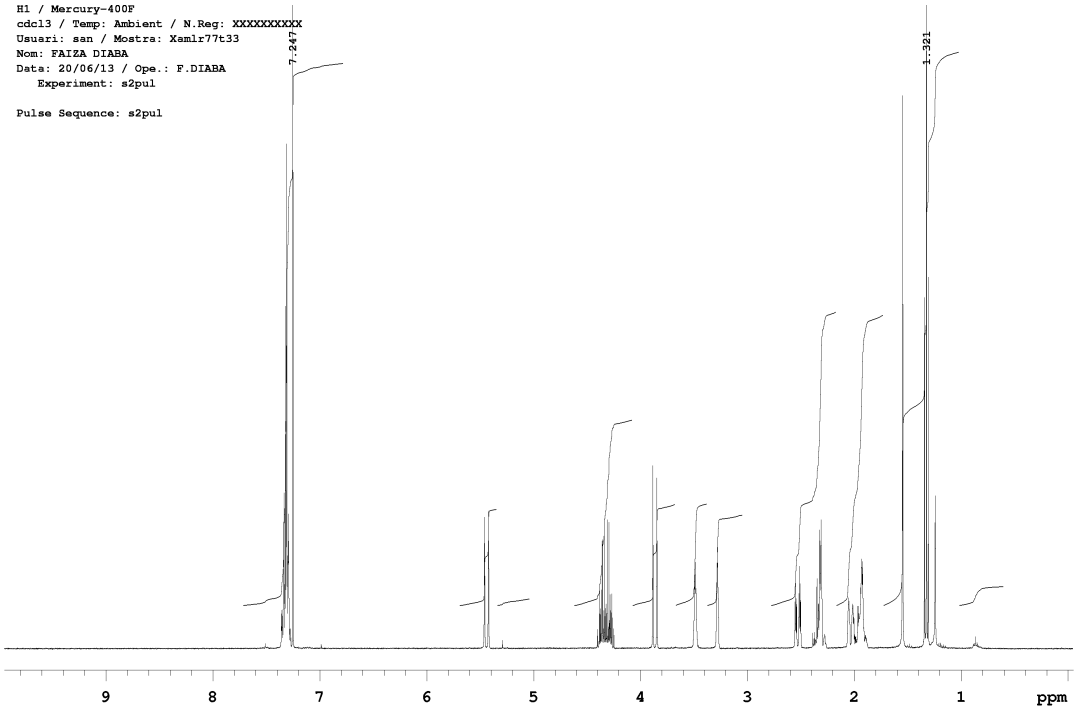
11a

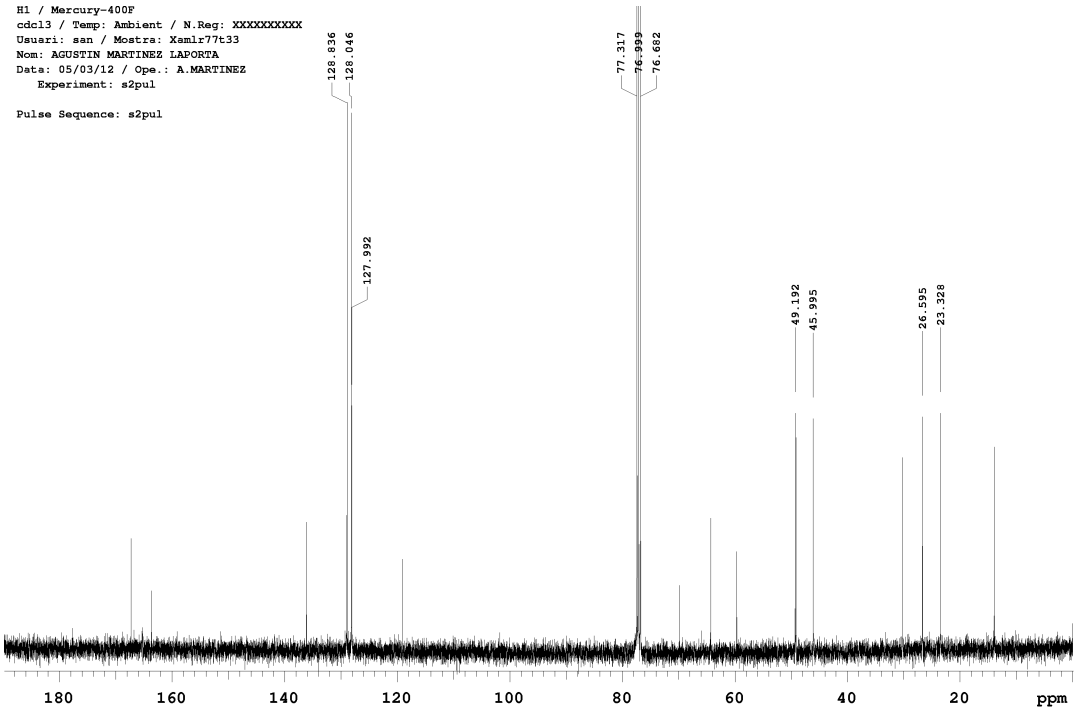

H1 / Mercury-400F
cdcl3 / Temp: 25C / N.Reg: XXXXXXXXXX
Usuari: san / Mostra: AML491T14
Nom: FAIZA DIABA
Data: 29/05/13 / Ope.: F.DIABA
Experiment: s2pul
Pulse Sequence: s2pul
7.333
1.322
9
8
7
6
5
4
3
2
1
ppm

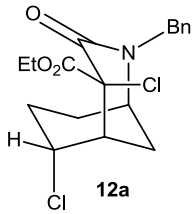

H1 / Mercury-400F
cdcl3 / Temp: 25C / N.Reg: XXXXXXXXXX
Usuari: san / Mostra: AML491T14
Nom: FAIZA DIABA
Data: 29/05/13 / Ope.: F.DIABA
Experiment: s2pul
Pulse Sequence: s2pul
128.681
127.938
77.316
76.999
76.682
180
160
140
120
100
80
60
40
20
ppm


O
Bn
N
Cl
CO2Et
NC
Cl

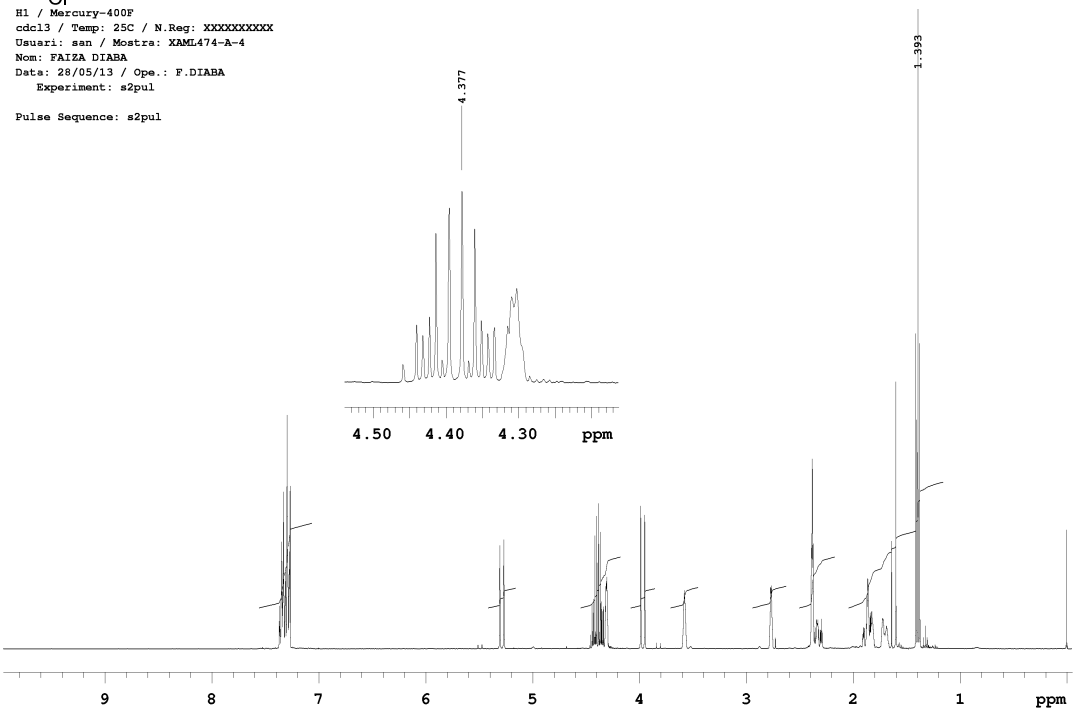
11b

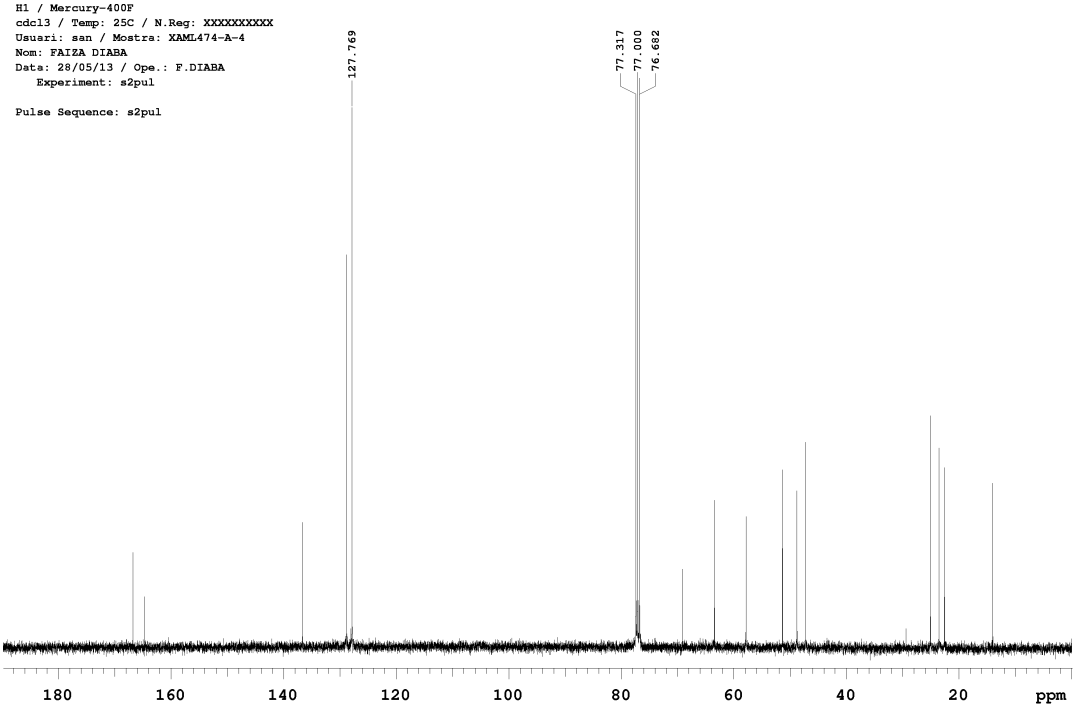

H1 / Mercury-400F
cdcl3 / Temp: Ambient / N.Reg: XXXXXXXXXX
Usuari: san / Mostra: Xamlr77t33
Nom: FAIZA DIABA
Data: 20/06/13 / Ope.: F.DIABA
Experiment: s2pul
Pulse Sequence: s2pul
7.247
1.321
9
8
7
6
5
4
3
2
1
ppm

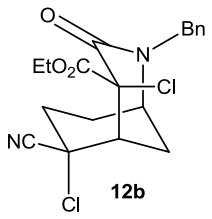

H1 / Mercury-400F
cdcl3 / Temp: Ambient / N.Reg: XXXXXXXXXX
Usuari: san / Mostra: Xamlr77t33
Nom: AGUSTIN MARTINEZ LAPORTA
Data: 05/03/12 / Ope.: A.MARTINEZ
Experiment: s2pul
Pulse Sequence: s2pul
128.836
128.046
127.992
77.317
76.999
76.682
49.192
45.995
26.595
23.328
180
160
140
120
100
80
60
40
20
ppm


O
Bn
N
EtO2C
Cl
H
Cl

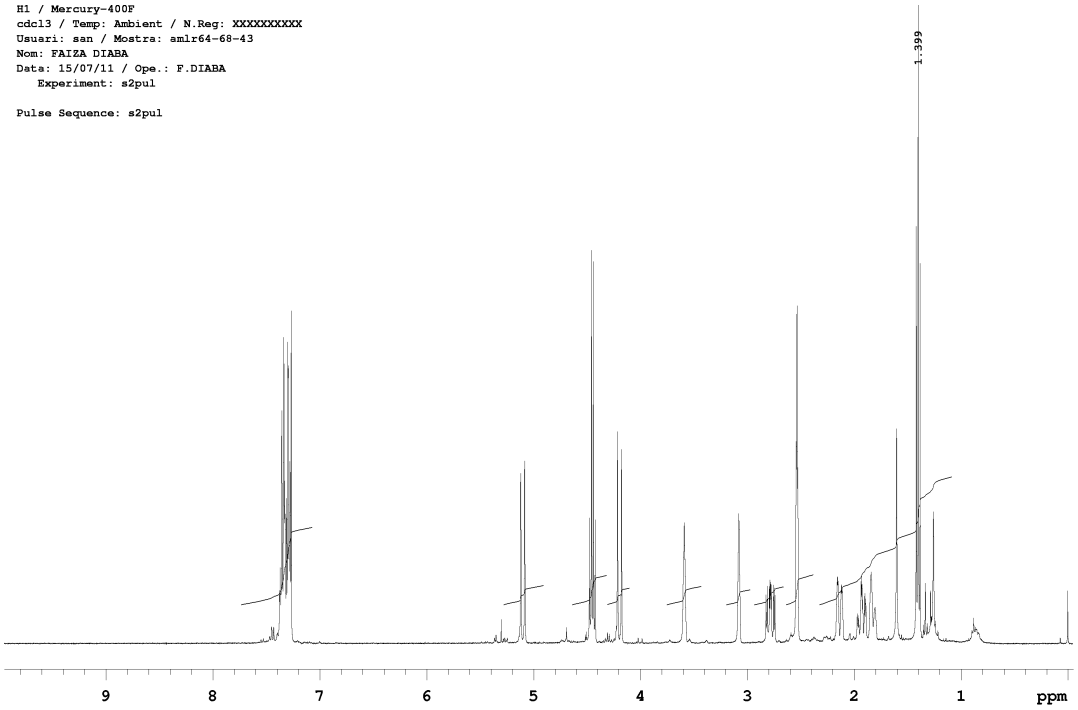
12a

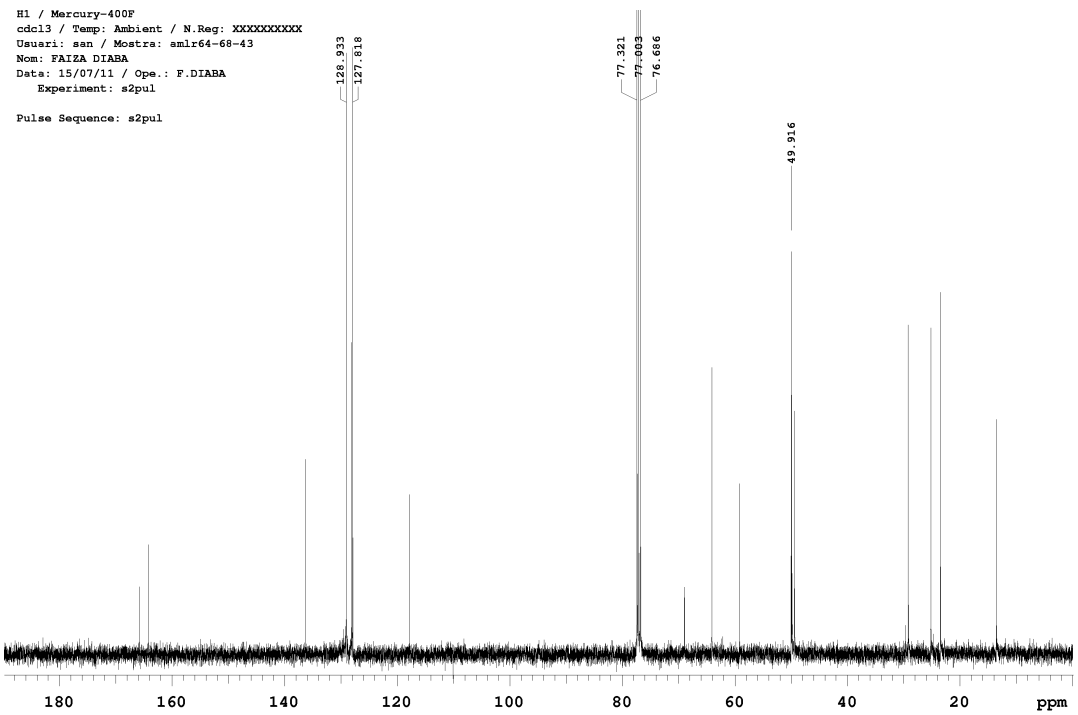

H1 / Mercury-400F
cdcl3 / Temp: 25C / N.Reg: XXXXXXXXXX
Usuari: san / Mostra: XAML474-A-4
Nom: FAIZA DIABA
Data: 28/05/13 / Ope.: F.DIABA
Experiment: s2pul
Pulse Sequence: s2pul
4.377
1.393
4.50
4.40
4.30
ppm
9
8
7
6
5
4
3
2
1
ppm

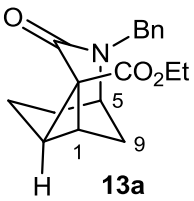

H1 / Mercury-400F
cdcl3 / Temp: 25C / N.Reg: XXXXXXXXXX
Usuari: san / Mostra: XAML474-A-4
Nom: FAIZA DIABA
Data: 28/05/13 / Ope.: F.DIABA
Experiment: s2pul
Pulse Sequence: s2pul
127.769
77.317
77.000
76.682
180
160
140
120
100
80
60
40
20
ppm


O
Bn
N
EtO2C
Cl
NC
Cl

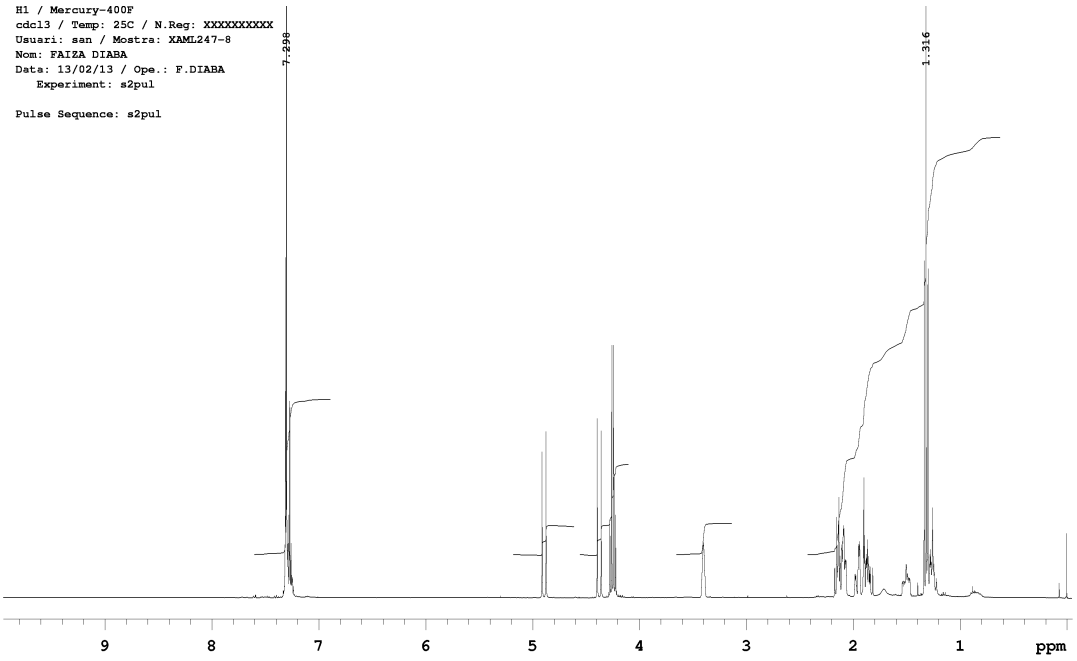
12b

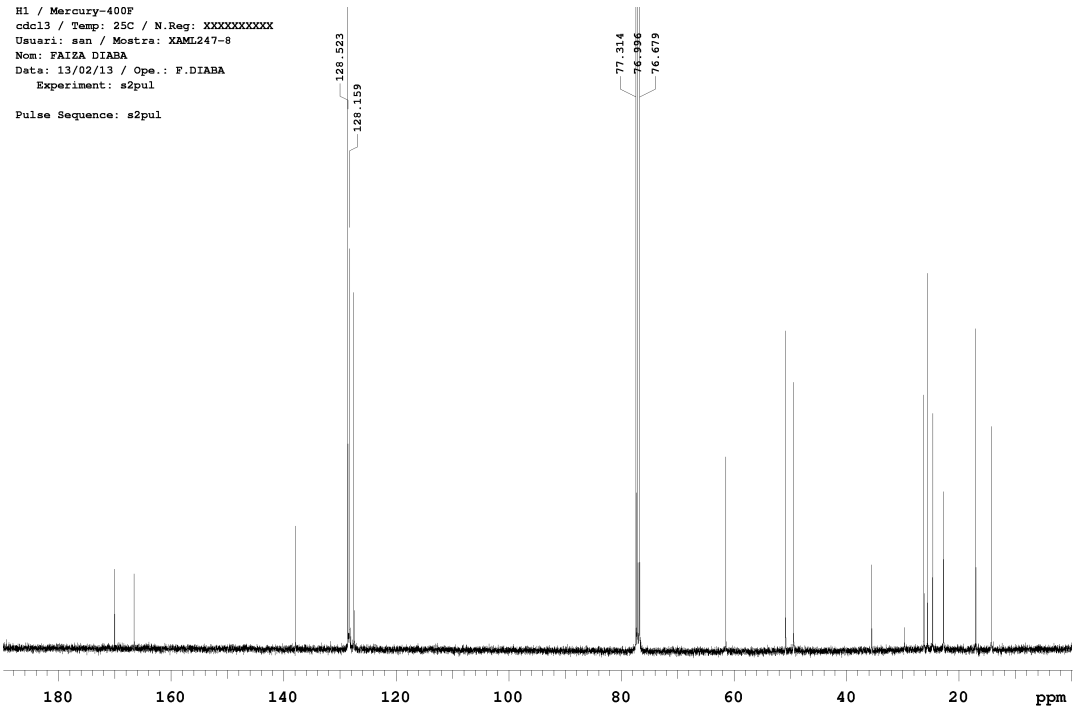

H1 / Mercury-400F
cdcl3 / Temp: Ambient / N.Reg: XXXXXXXXXX
Ususari: san / Mostra: amlr64-68-43
Nom: FAIZA DIABA
Data: 15/07/11 / Ope.: F.DIABA
Experiment: s2pul
Pulse Sequence: s2pul
1.399
9
8
7
6
5
4
3
2
1
ppm

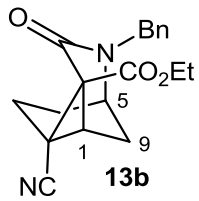

H1 / Mercury-400F
cdcl3 / Temp: Ambient / N.Reg: XXXXXXXXXX
Ususari: san / Mostra: amlr64-68-43
Nom: FAIZA DIABA
Data: 15/07/11 / Ope.: F.DIABA
Experiment: s2pul
Pulse Sequence: s2pul
128.933
127.818
77.321
77.003
76.686
49.916
180
160
140
120
100
80
60
40
20
ppm


O
N
Bn
CO2Et
5
9
1
H

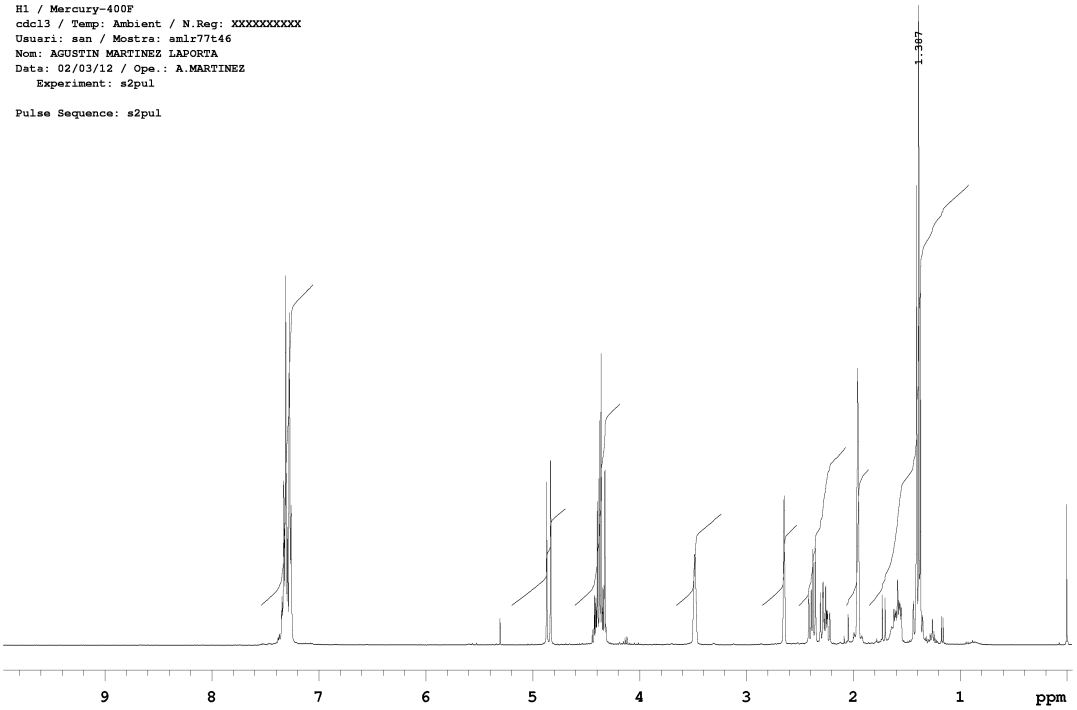
13a

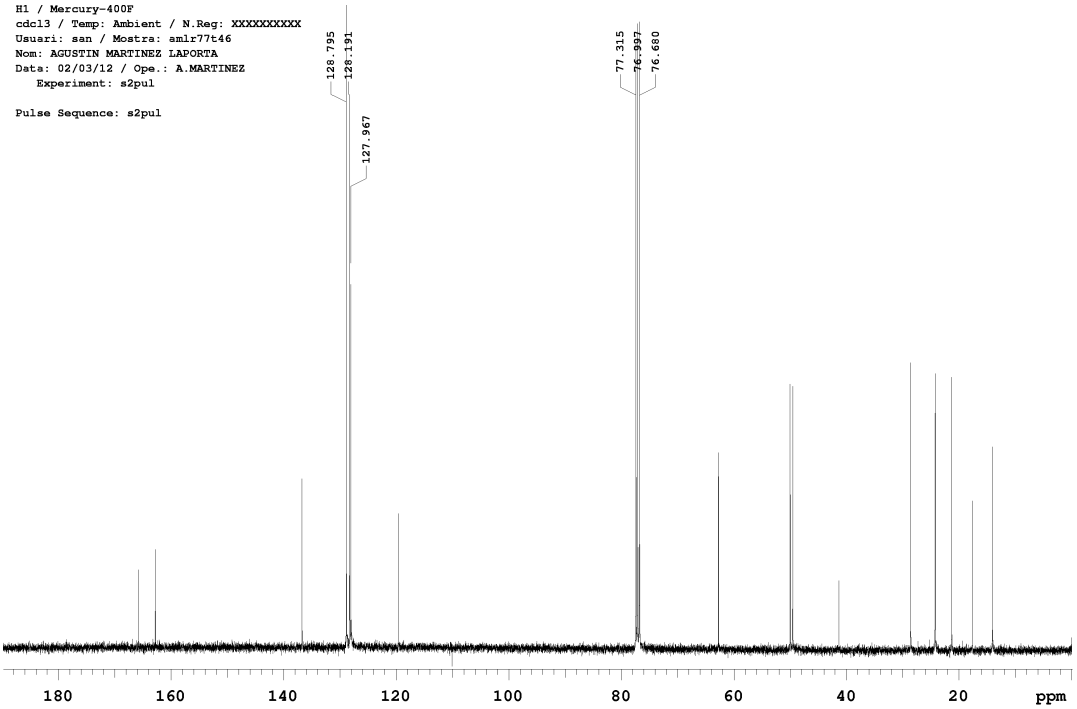

H1 / Mercury-400F
cdcl3 / Temp: 25C / N.Reg: XXXXXXXXXX
Usuari: san / Mostra: XAML247-8
Nom: FAIZA DIABA
Data: 13/02/13 / Ope.: F.DIABA
Experiment: s2pul
Pulse Sequence: s2pul
7.298
1.316
9
8
7
6
5
4
3
2
1
ppm

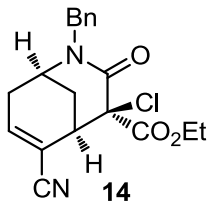

H1 / Mercury-400F
cdcl3 / Temp: 25C / N.Reg: XXXXXXXXXX
Usuari: san / Mostra: XAML247-8
Nom: FAIZA DIABA
Data: 13/02/13 / Ope.: F.DIABA
Experiment: s2pul
Pulse Sequence: s2pul
128.523
128.159
77.314
76.996
76.679
180
160
140
120
100
80
60
40
20
ppm


O
N
Bn
CO2Et
5
9
1
NC

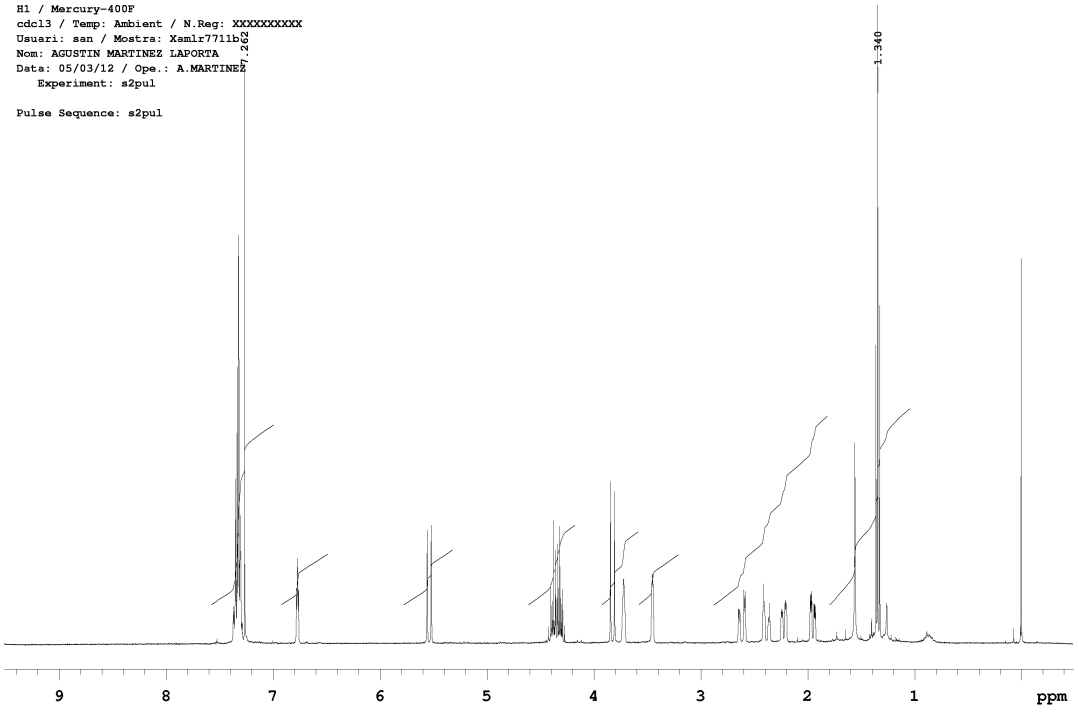
13b

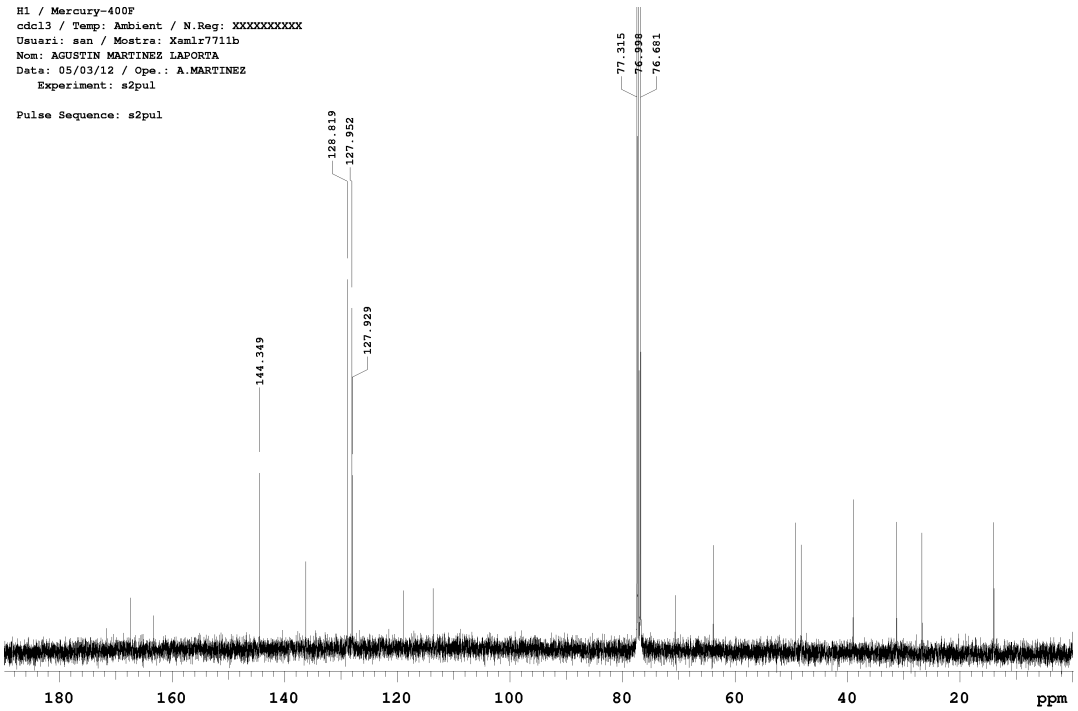

H1 / Mercury-400F
cdcl3 / Temp: Ambient / N.Reg: XXXXXXXXXX
Usuari: san / Mostra: amlr77t46
Nom: AGUSTIN MARTINEZ LAPORTA
Data: 02/03/12 / Ope.: A.MARTINEZ
Experiment: s2pul
Pulse Sequence: s2pul
1.387
9
8
7
6
5
4
3
2
1
ppm

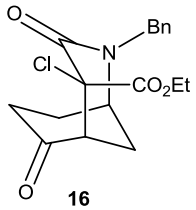

H1 / Mercury-400F
cdcl3 / Temp: Ambient / N.Reg: XXXXXXXXXX
Usuari: san / Mostra: amlr77t46
Nom: AGUSTIN MARTINEZ LAPORTA
Data: 02/03/12 / Ope.: A.MARTINEZ
Experiment: s2pul
Pulse Sequence: s2pul
128.795
128.191
127.967
77.315
76.997
76.680
180
160
140
120
100
80
60
40
20
ppm


Bn
H
N
O
Cl
CO2Et
H
CN

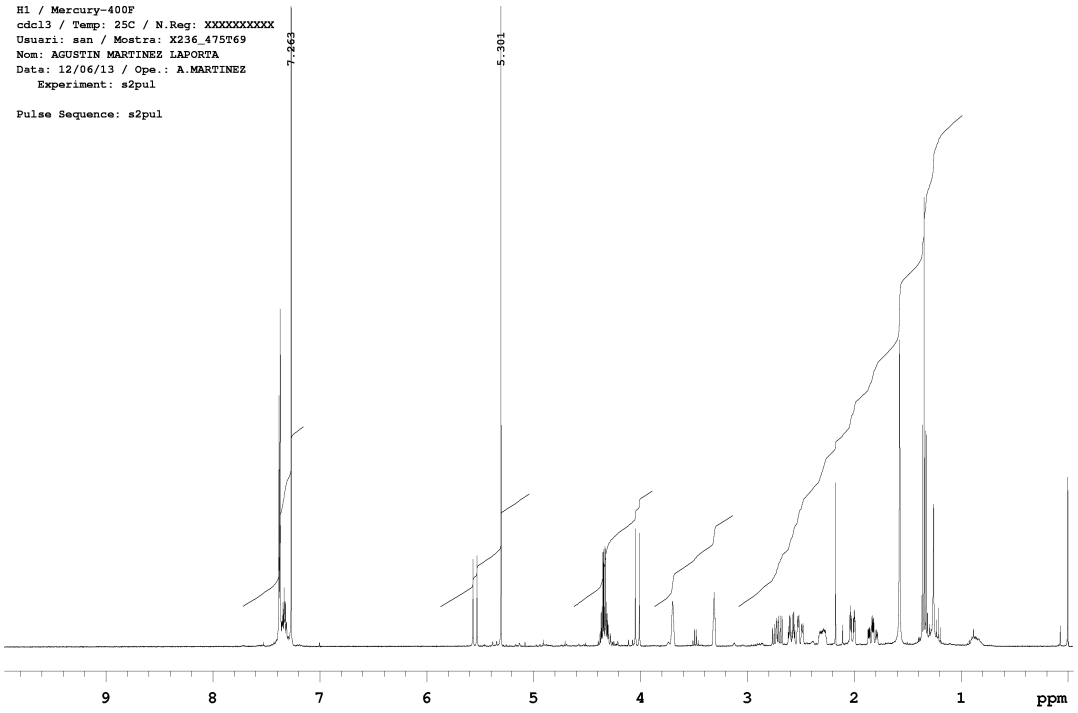
14

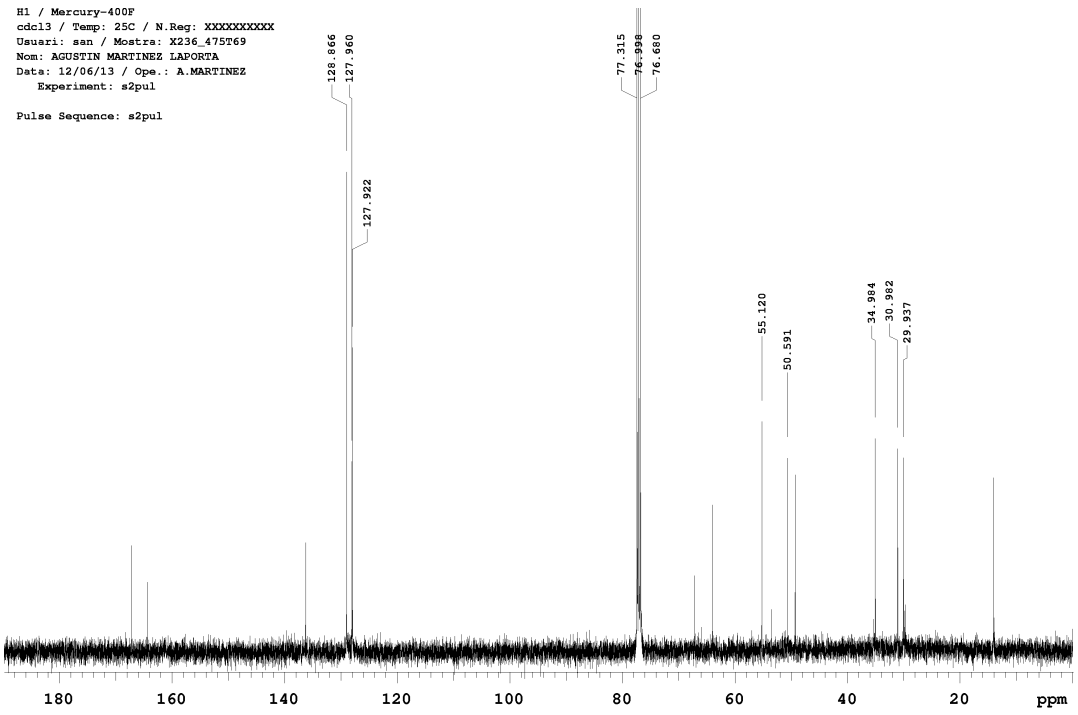

H1 / Mercury-400F
cdcl3 / Temp: Ambient / N.Reg: XXXXXXXXXX
Usuari: san / Mostra: Xamlr7711b
Nom: AGUSTIN MARTINEZ LAPORTA
Data: 05/03/12 / Ope.: A.MARTINEZ
Experiment: s2pul
Pulse Sequence: s2pul
7.262
1.340
9
8
7
6
5
4
3
2
1
ppm

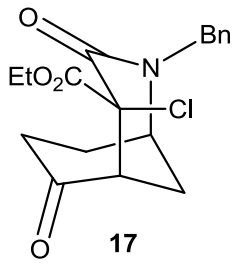

H1 / Mercury-400F
cdcl3 / Temp: Ambient / N.Reg: XXXXXXXXXX
Usuari: san / Mostra: Xamlr7711b
Nom: AGUSTIN MARTINEZ LAPORTA
Data: 05/03/12 / Ope.: A.MARTINEZ
Experiment: s2pul
Pulse Sequence: s2pul
77.315
76.998
76.681
128.819
127.952
127.929
144.349
180
160
140
120
100
80
60
40
20
ppm


O
Bn
N
Cl
CO2Et
O

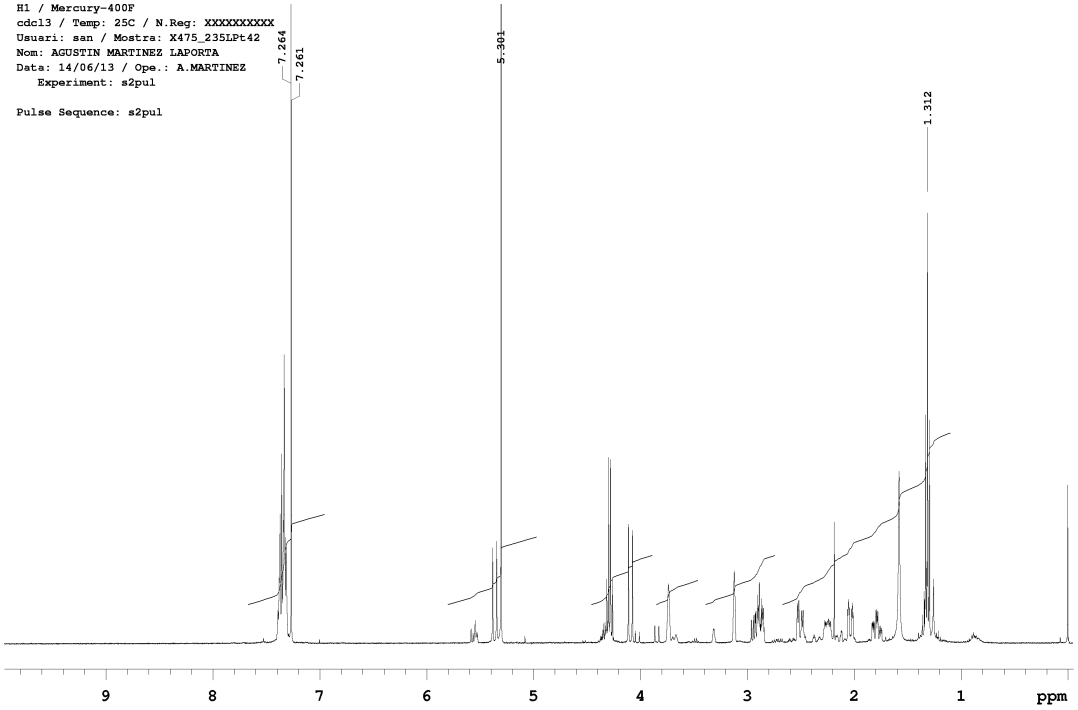
16

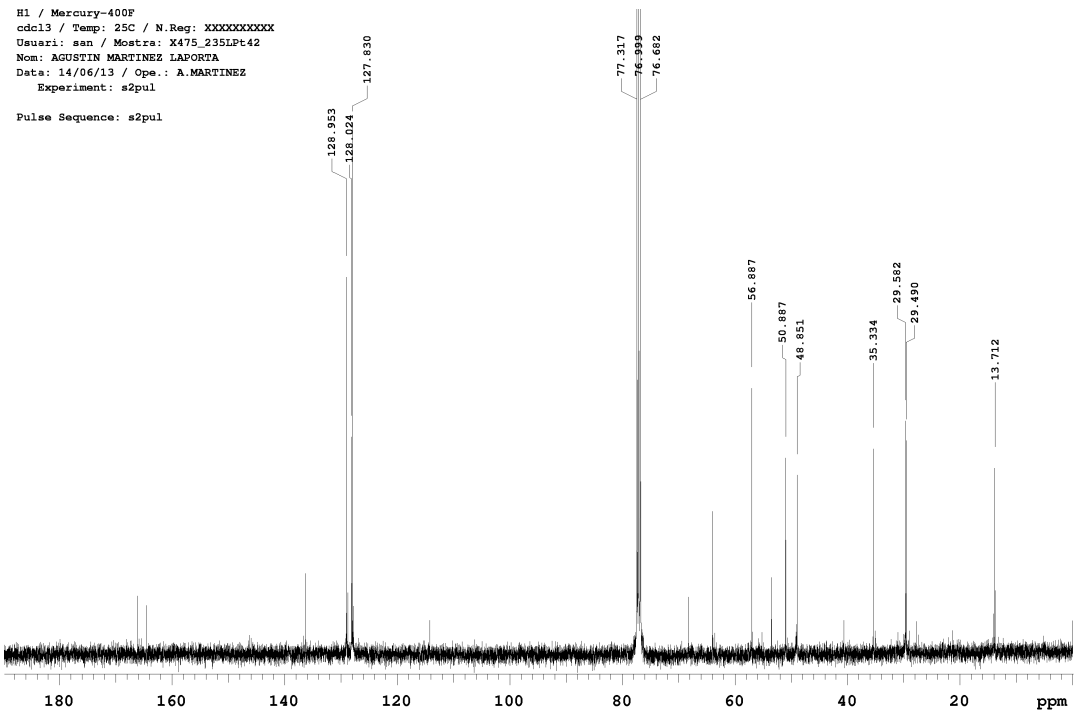

H1 / Mercury-400F
cdcl3 / Temp: 25C / N.Reg: XXXXXXXXXX
Usuari: san / Mostra: X236_475T69
Nom: AGUSTIN MARTINEZ LAPORTA
Data: 12/06/13 / Ope.: A.MARTINEZ
Experiment: s2pul
Pulse Sequence: s2pul
7.263
5.301
9
8
7
6
5
4
3
2
1
ppm

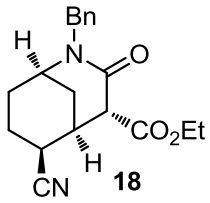

H1 / Mercury-400F
cdcl3 / Temp: 25C / N.Reg: XXXXXXXXXX
Usuari: san / Mostra: X236_475T69
Nom: AGUSTIN MARTINEZ LAPORTA
Data: 12/06/13 / Ope.: A.MARTINEZ
Experiment: s2pul
Pulse Sequence: s2pul
128.866
127.960
127.922
77.315
76.998
76.680
55.120
50.591
34.984
30.982
29.937
180
160
140
120
100
80
60
40
20
ppm


O
Bn
N
EtO2C
Cl
O

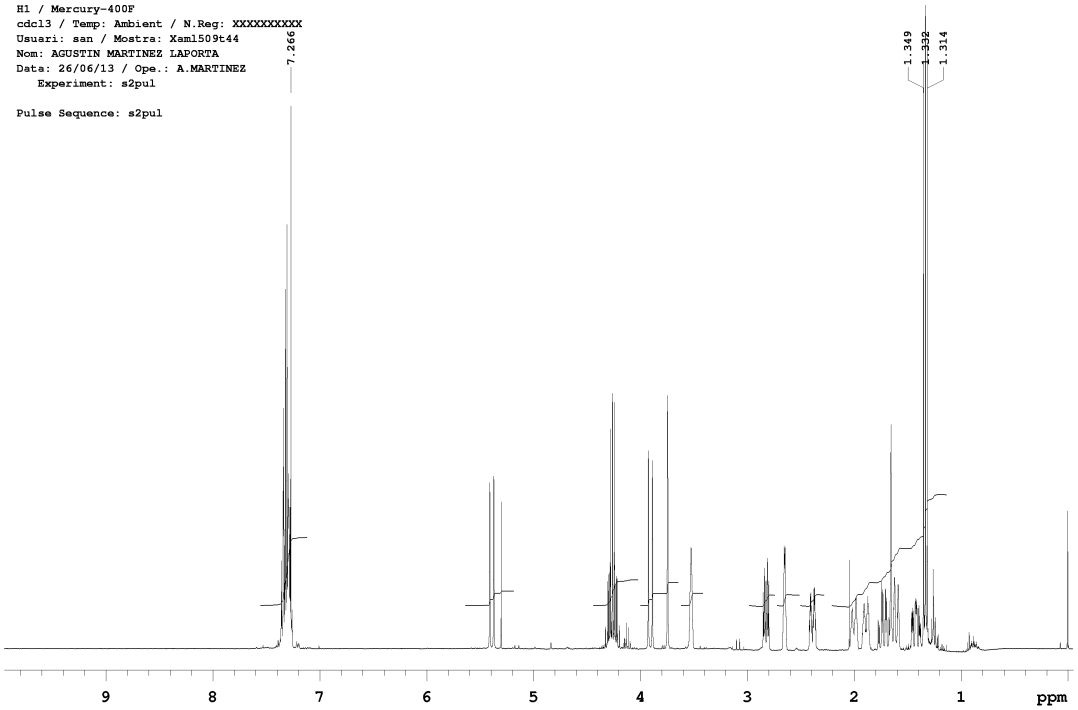
17

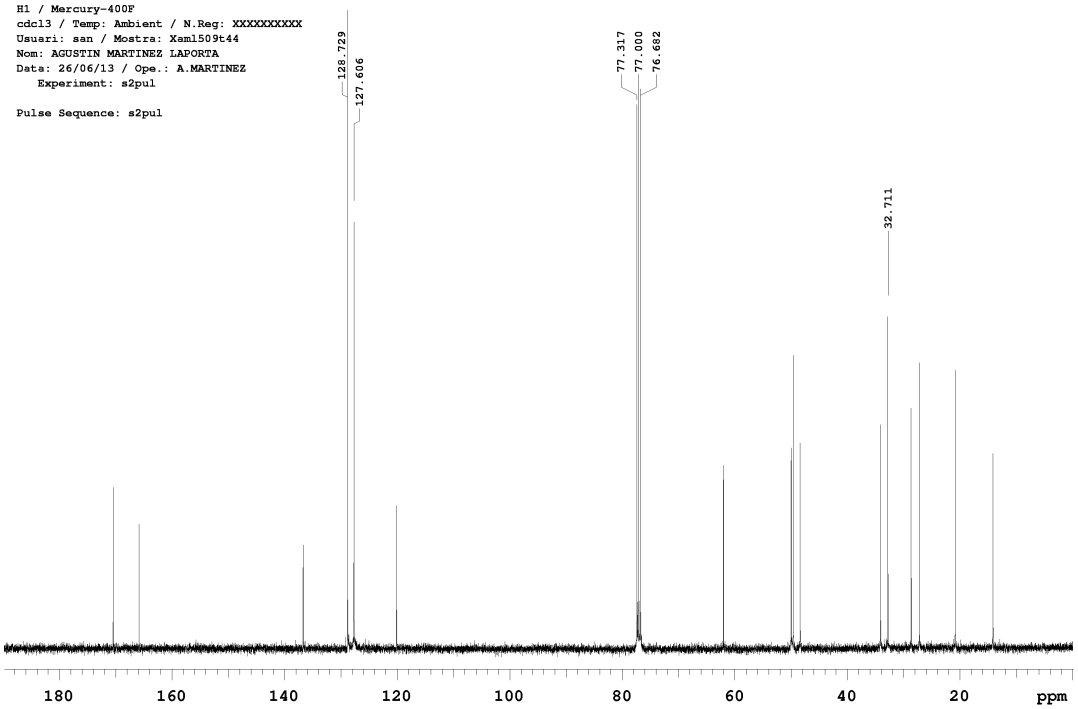

H1 / Mercury-400F
cdcl3 / Temp: 25C / N.Reg: XXXXXXXXX
Ususari: san / Mostra: X475_235LPt42
Nom: AGUSTIN MARTINEZ LAPORTA
Data: 14/06/13 / Ope.: A.MARTINEZ
Experiment: s2pul
Pulse Sequence: s2pul
7.264
7.261
5.301
1.312
9
8
7
6
5
4
3
2
1
ppm

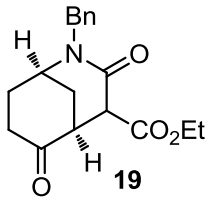

H1 / Mercury-400F
cdcl3 / Temp: 25C / N.Reg: XXXXXXXXX
Ususari: san / Mostra: X475_235LPt42
Nom: AGUSTIN MARTINEZ LAPORTA
Data: 14/06/13 / Ope.: A.MARTINEZ
Experiment: s2pul
Pulse Sequence: s2pul
128.953
128.024
127.830
77.317
76.999
76.682
56.887
50.887
48.851
35.334
29.582
29.490
13.712
180
160
140
120
100
80
60
40
20
ppm


Bn
H
N
O
CO2Et
H
CN

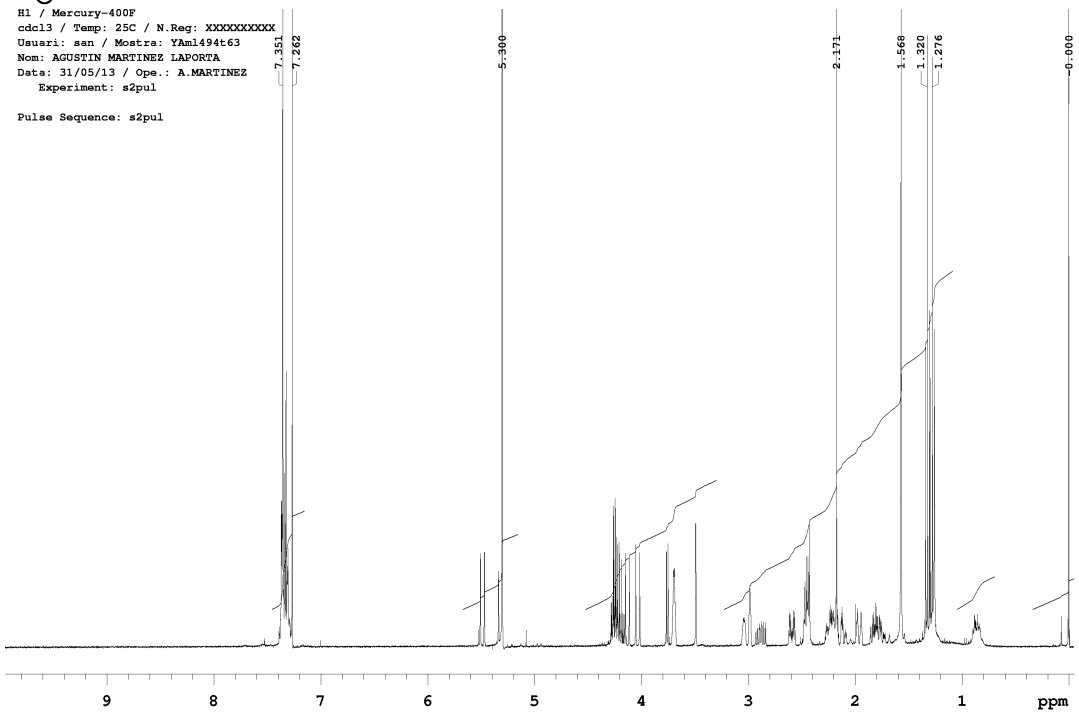
18

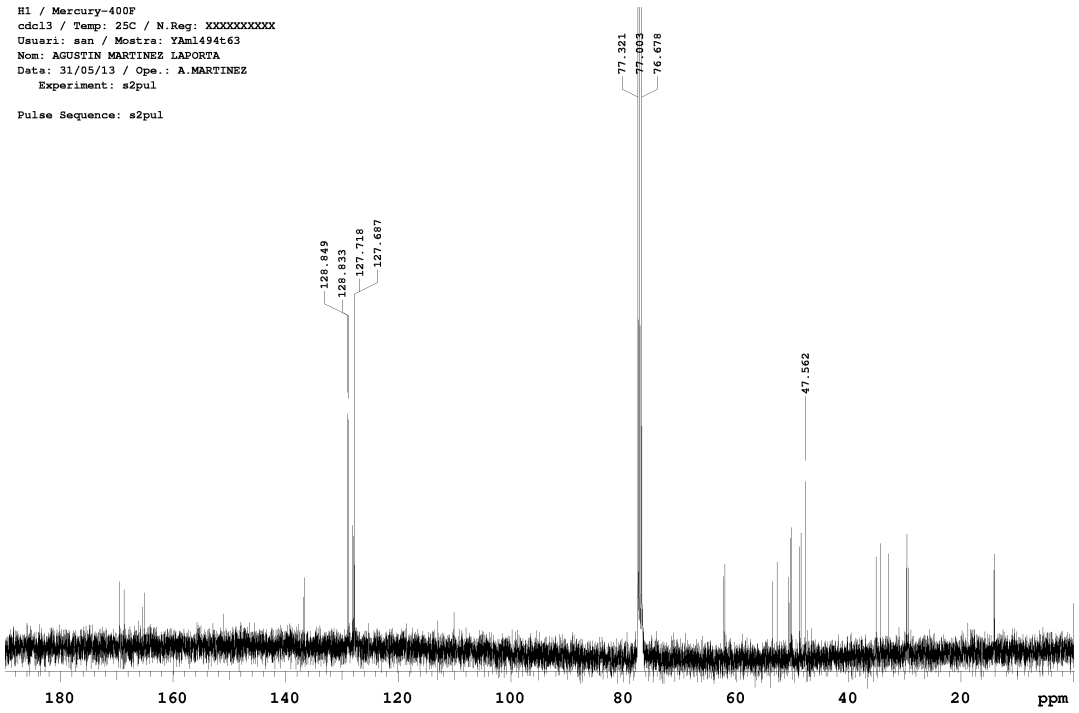

H1 / Mercury-400F
cdcl3 / Temp: Ambient / N.Reg: XXXXXXXXXX
Usuari: san / Mostra: Xaml509t44
Nom: AGUSTIN MARTINEZ LAPORTA
Data: 26/06/13 / Ope.: A.MARTINEZ
Experiment: s2pul
Pulse Sequence: s2pul
7.266
1.349
1.332
1.314
9
8
7
6
5
4
3
2
1
ppm

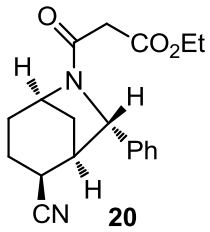

H1 / Mercury-400F
cdcl3 / Temp: Ambient / N.Reg: XXXXXXXXXX
Usuari: san / Mostra: Xaml509t44
Nom: AGUSTIN MARTINEZ LAPORTA
Data: 26/06/13 / Ope.: A.MARTINEZ
Experiment: s2pul
Pulse Sequence: s2pul
128.729
127.606
77.317
77.000
76.682
32.711
180
160
140
120
100
80
60
40
20
ppm


Bn
H
N
O
CO2Et
H
O

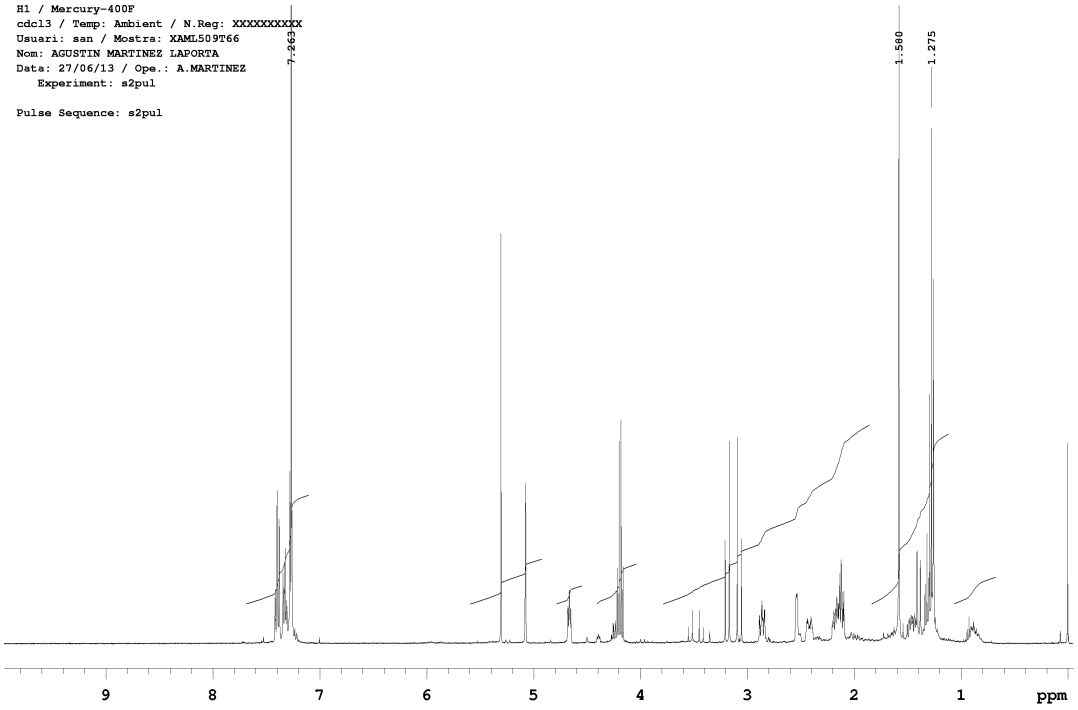
19

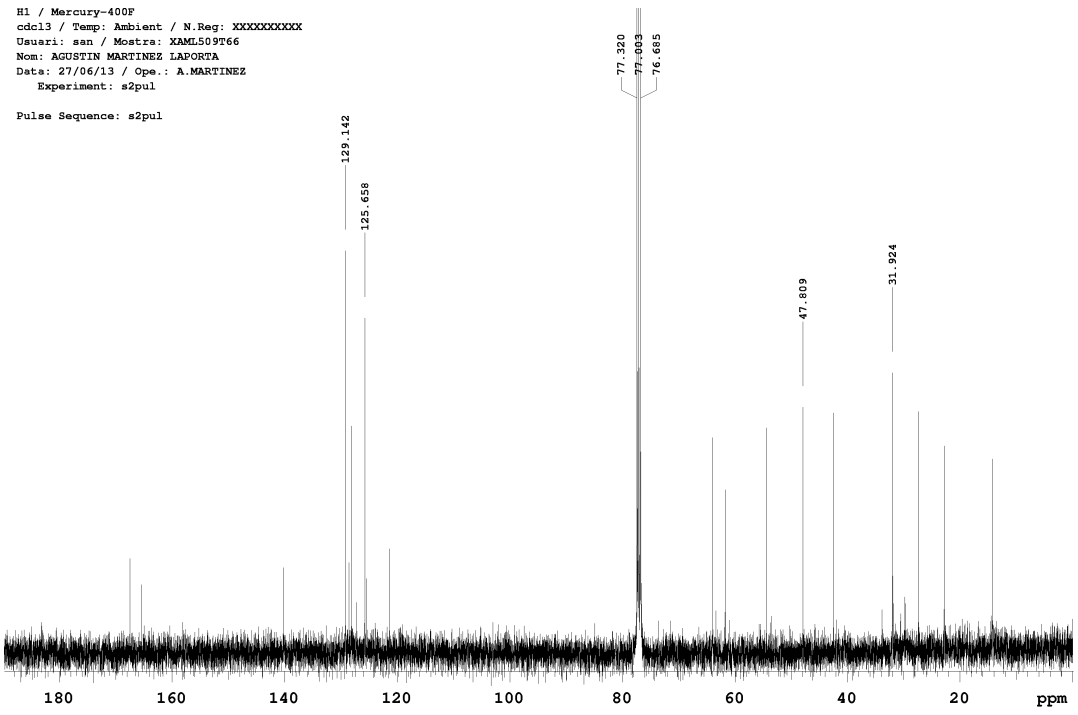

H1 / Mercury-400F
cdcl3 / Temp: 25C / N.Reg: XXXXXXXXXX
Usuari: san / Mostra: YAml494t63
Nom: AGUSTIN MARTINEZ LAPORTA
Data: 31/05/13 / Ope.: A.MARTINEZ
Experiment: s2pul
Pulse Sequence: s2pul
7.351
7.262
5.300
2.171
1.568
1.320
1.276
0.000
9
8
7
6
5
4
3
2
1
ppm

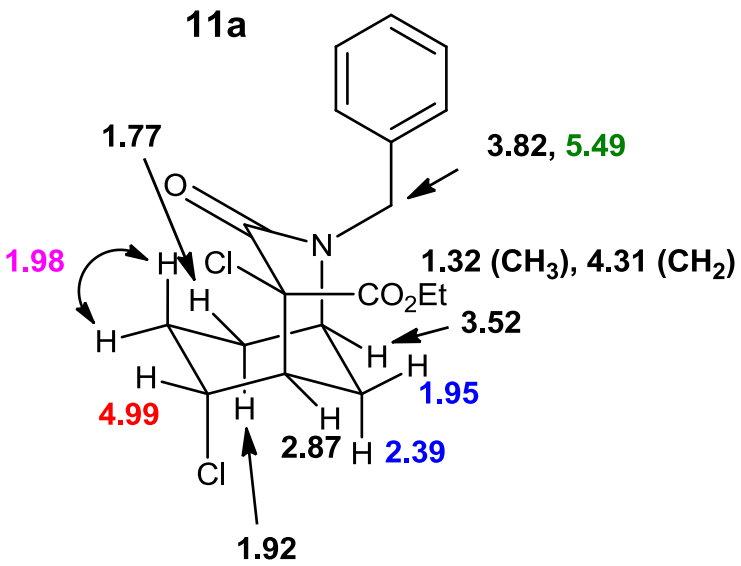

H1 / Mercury-400F
cdcl3 / Temp: 25C / N.Reg: XXXXXXXXXX
Usuari: san / Mostra: YAml494t63
Nom: AGUSTIN MARTINEZ LAPORTA
Data: 31/05/13 / Ope.: A.MARTINEZ
Experiment: s2pul
Pulse Sequence: s2pul
77.321
77.003
76.678
128.849
128.833
127.718
127.687
47.562
180
160
140
120
100
80
60
40
20
ppm

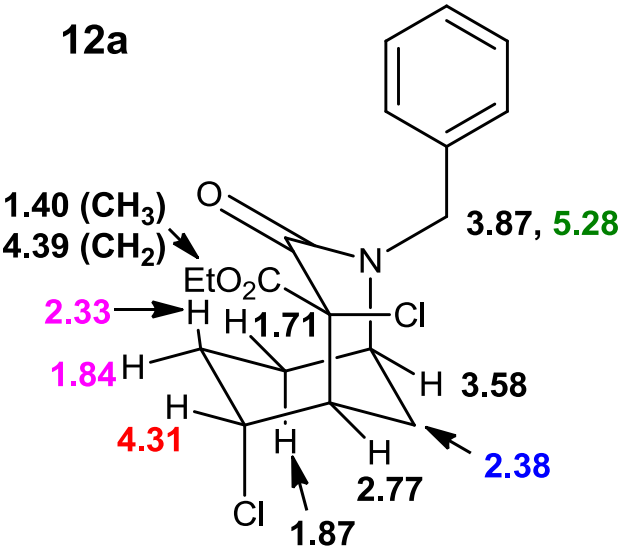

O
CO2Et
H
N
H
Ph
H
CN

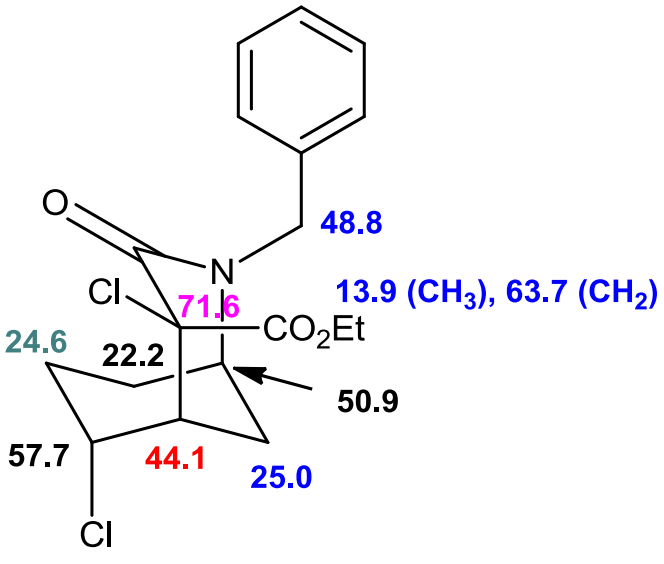
20

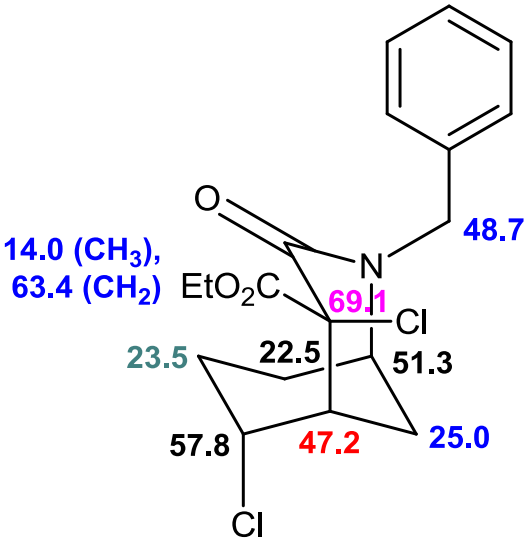

H1 / Mercury-400F
cdcl3 / Temp: Ambient / N.Reg: XXXXXXXXXX
Usuari: san / Mostra: XAML509T66
Nom: AGUSTIN MARTINEZ LAPORTA
Data: 27/06/13 / Ope.: A.MARTINEZ
Experiment: s2pul
Pulse Sequence: s2pul
7.263
1.580
1.275
9
8
7
6
5
4
3
2
1
ppm


H1 / Mercury-400F
cdcl3 / Temp: Ambient / N.Reg: XXXXXXXXXX
Usuari: san / Mostra: XAML509T66
Nom: AGUSTIN MARTINEZ LAPORTA
Data: 27/06/13 / Ope.: A.MARTINEZ
Experiment: s2pul
Pulse Sequence: s2pul
77.320
77.003
76.685
129.142
125.658
47.809
31.924
180
160
140
120
100
80
60
40
20
ppm

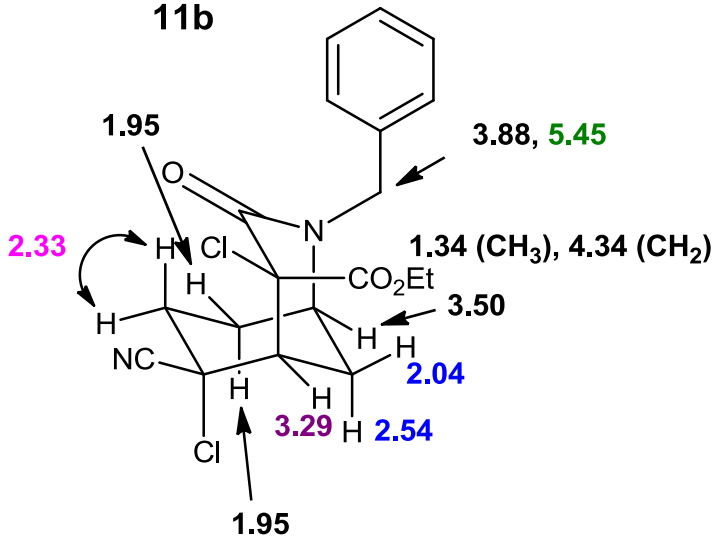

11a
1.77
3.82, 5.49
1.98
1.32 (CH3), 4.31 (CH2)
3.52
1.95
4.99
2.87
2.39
1.92


12a
1.40 (CH3)
4.39 (CH2)
3.87, 5.28
2.33
1.71
1.84
3.58
4.31
2.38
2.77
1.87

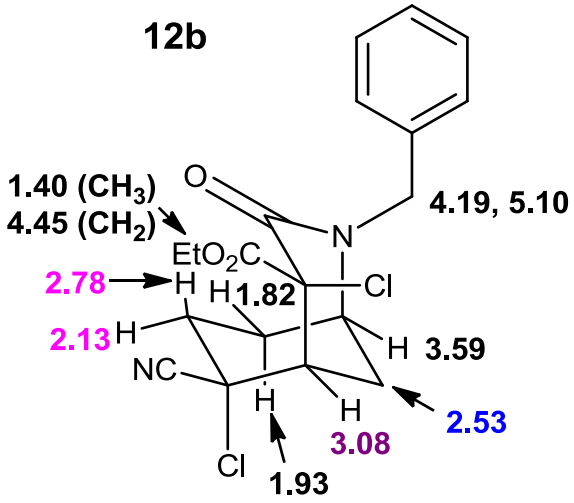

48.8
13.9 (CH3), 63.7 (CH2)
71.6
24.6
22.2
50.9
57.7
44.1
25.0

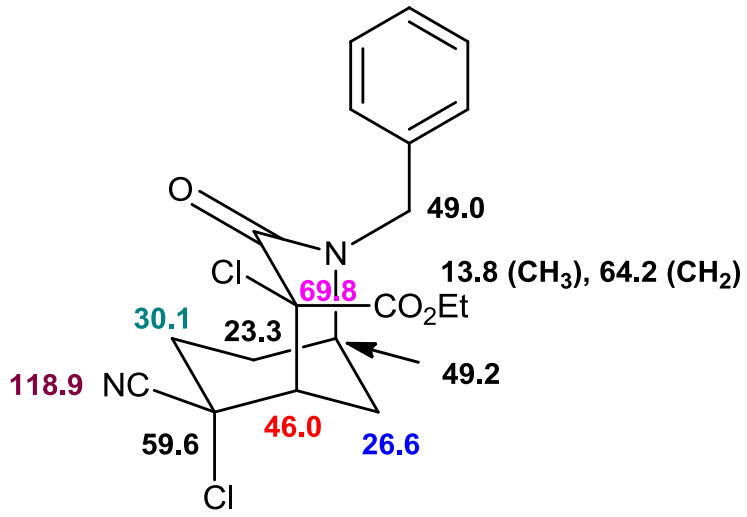

48.7
14.0 (CH3),
63.4 (CH2)
69.1
23.5
22.5
51.3
57.8
47.2
25.0

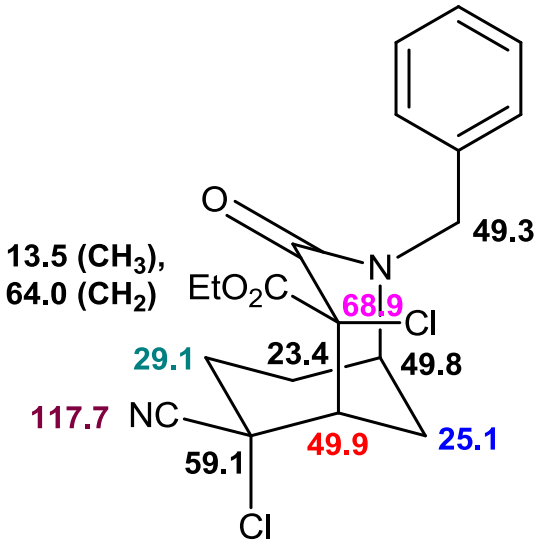
11b

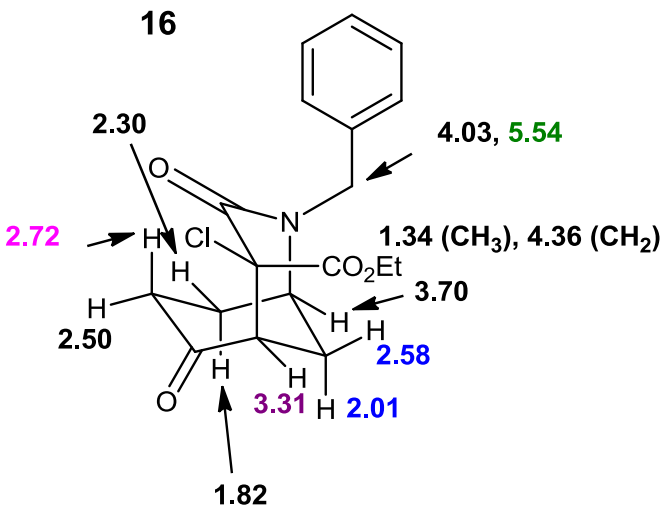

1.95
3.88, 5.45
O
N
2.33
H
Cl
1.34 (CH3), 4.34 (CH2)
H
CO2Et
H
3.50
H
H
NC
2.04
H
H
3.29
H
2.54
Cl
1.95

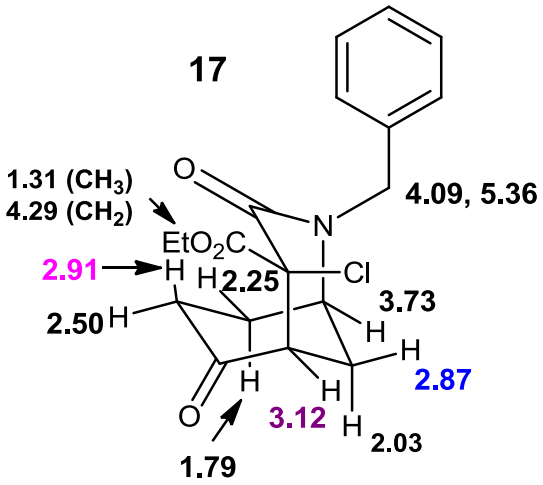
12b

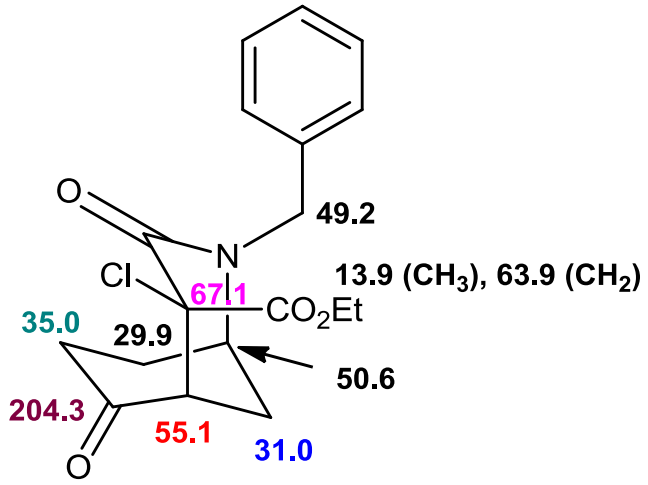

1.40 (CH3)
4.45 (CH2)
O
4.19, 5.10
N
EtO2C
2.78
H
H
1.82
Cl
2.13
H
H
3.59
NC
H
H
2.53
3.08
Cl
1.93

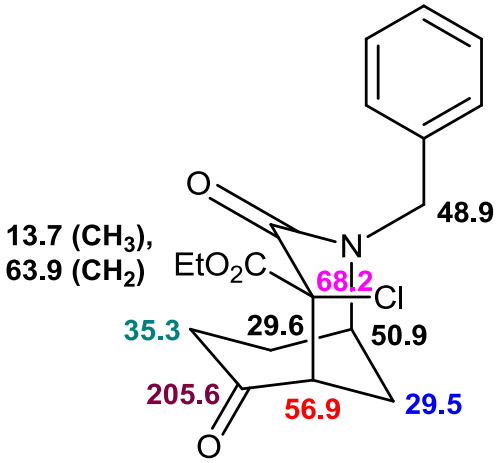

O
49.0
N
Cl
13.8 (CH3), 64.2 (CH2)
69.8
CO2Et
30.1
23.3
49.2
118.9
NC
46.0
59.6
26.6
Cl

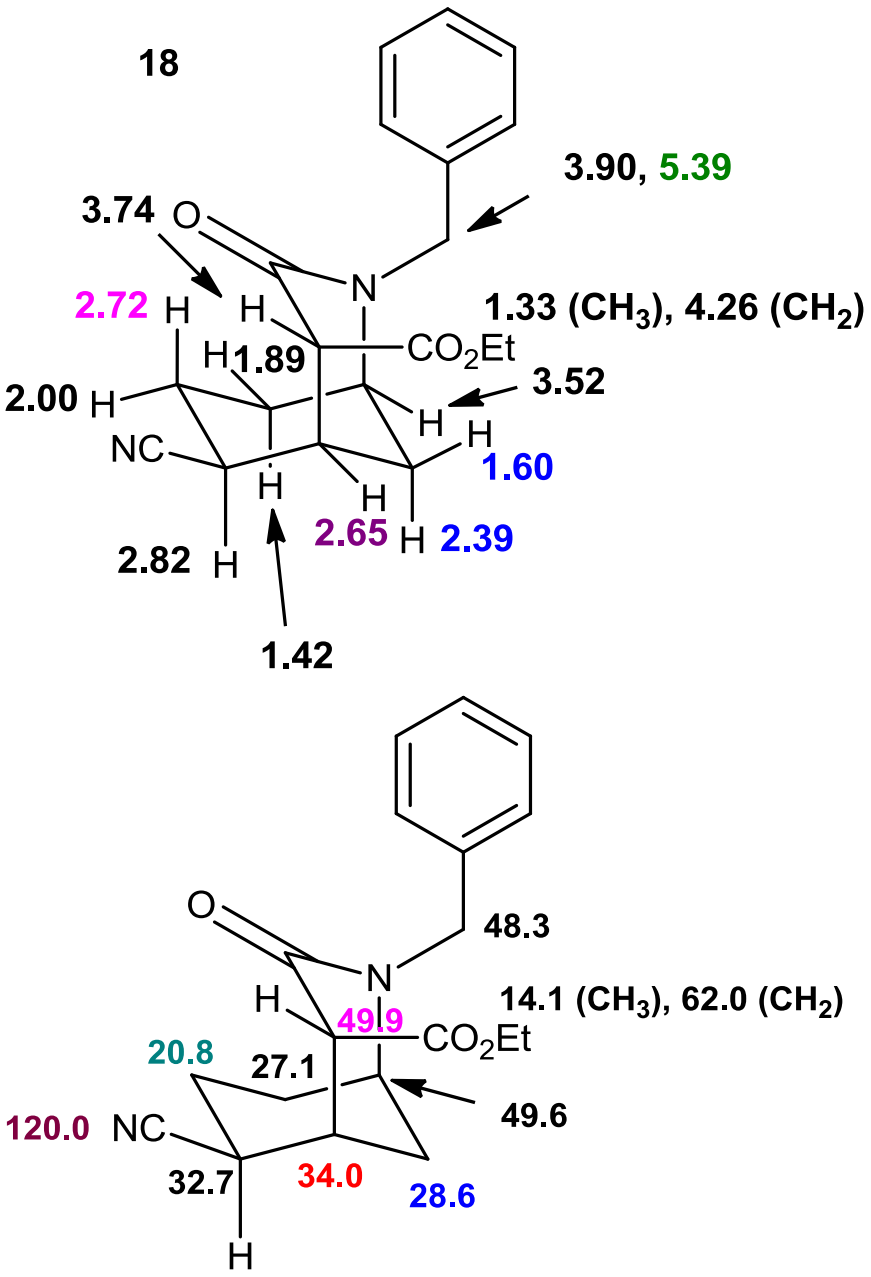

13.5 (CH3),
64.0 (CH2)
O
49.3
N
EtO2C
68.9
Cl
29.1
23.4
49.8
117.7
NC
49.9
25.1
59.1
Cl


16
2.30
4.03, 5.54
2.72
1.34 (CH3), 4.36 (CH2)
CO2Et
3.70
2.50
2.58
3.31
2.01
1.82

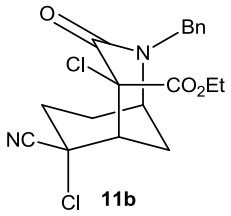

17
1.31 (CH3)
4.29 (CH2)
4.09, 5.36
EtO2C
2.91
2.25
3.73
2.50
2.87
3.12
2.03
1.79


49.2
13.9 (CH3), 63.9 (CH2)
67.1
CO2Et
35.0
29.9
50.6
204.3
55.1
31.0


48.9
13.7 (CH3),
63.9 (CH2)
EtO2C
68.2
35.3
29.6
50.9
205.6
56.9
29.5

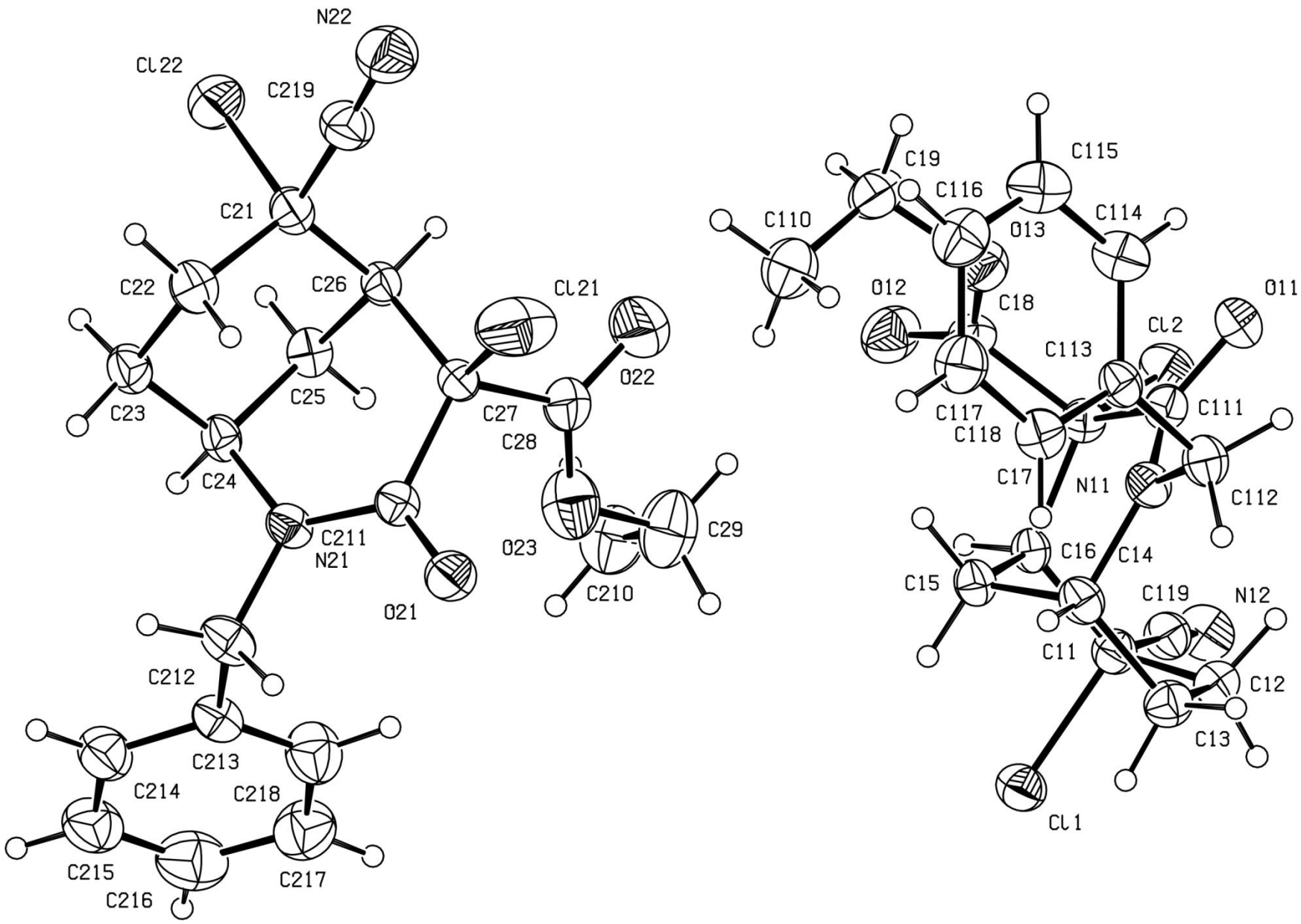

18
3.90, 5.39
3.74
O
N
2.72
H
H
1.33 (CH3), 4.26 (CH2)
H
1.89
CO2Et
2.00
H
3.52
H
H
NC
1.60
H
H
2.65
H
2.39
2.82
H
1.42
O
48.3
N
H
14.1 (CH3), 62.0 (CH2)
49.9
CO2Et
20.8
27.1
49.6
120.0
NC
32.7
34.0
28.6
H

Crystal data and structure refinement for compound 11b



11b

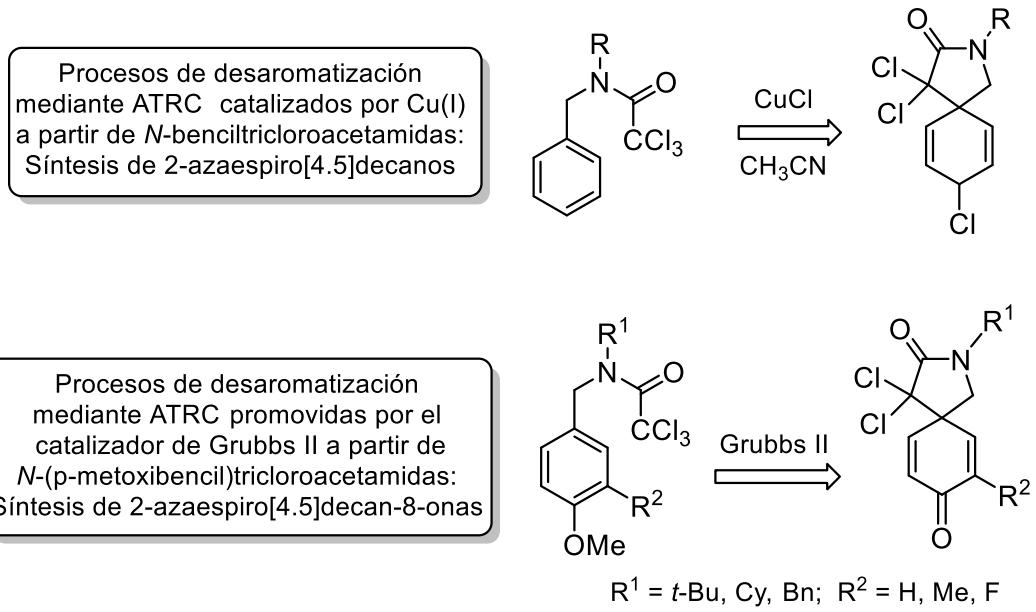
Identification code	**bonqm45a**
Empirical formula	**C_{19} H_{20} Cl_2 N_2 O_3**
Formula weight	**395.27**
Temperature	**293(2) K**
Wavelength	**0.71073 Å**
Crystal system, space group	**Monoclinic, $P2_1/c$**
Unit cell dimensions	**a = 10.688(6) Å α= 90º.** **b = 32.756(15) Å β= 117.00(4)º.** **c = 12.276(8) Å γ= 90º.**
Volume	**3829(4) $Å^3$**
Z, Calculated density	**8, 1.371 Mg/m^3**
Absorption coefficient	**0.360 mm^{-1}**
F(000)	**1648**
Crystal size	**0.12 x 0.09 x 0.08 mm**
Theta range for data collection	**1.96 to 32.33º.**
Limiting indices	**-12<=h<=11, -44<=k<=47, -15<=l<=18**
Reflections collected / unique	**16555 / 6288 [R(int) = 0.0571]**
Completeness to theta = 25.00	**60.8 %**
Absorption correction	**Empirical**
Max. and min. transmission	**0.97 and 0.96**
Refinement method	**Full-matrix least-squares on F^2**
Data / restraints / parameters	**6288 / 5 / 469**
Goodness-of-fit on F^2	**1.136**
Final R indices [I>2σ(I)]	**R1 = 0.0692, wR2 = 0.1376**
R indices (all data)	**R1 = 0.1090, wR2 = 0.1530**
Largest diff. peak and hole	**0.728 and -0.450 e.$Å^{-3}$**


N22
Cl22
C219
C21
C22
C26
Cl21
O22
C23
C25
C27
C28
C24
C211
N21
O23
C29
O21
C210
C212
C213
C214
C218
C215
C217
C216
C19
C115
C116
C110
O13
C114
O12
C18
O11
Cl2
C113
C111
C117
C118
C17
N11
C112
C16
C14
C15
C119
N12
C11
C12
C13
Cl1

4. Desaromatización mediante ciclación radicalaria con transferencia de átomo de *N*-benciltricloroacetamidas: Síntesis de 2-azaespiro[4.5]decanos

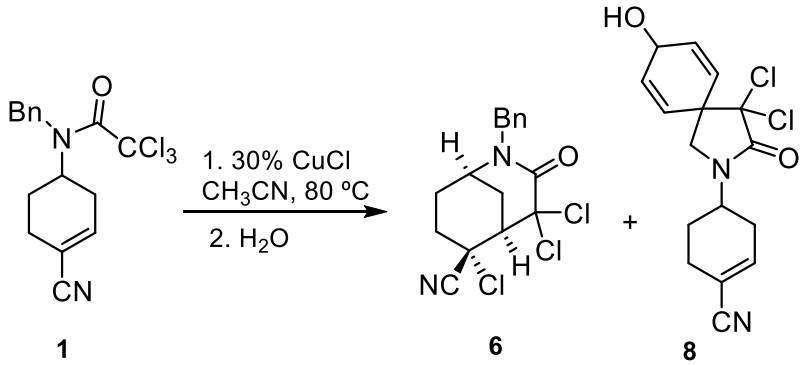
4.1 Introducción y Objetivos

En este capítulo se describen los estudios encaminados a procesos de desaromatización mediante ciclaciones radicalarias de tricloroacetamidas sobre núcleos bencénicos, para generar 2-azaespiro[4.5]decanos, utilizando como agentes promotores de los procesos de ATRC tanto Cu(I) como el catalizador de Grubbs II.



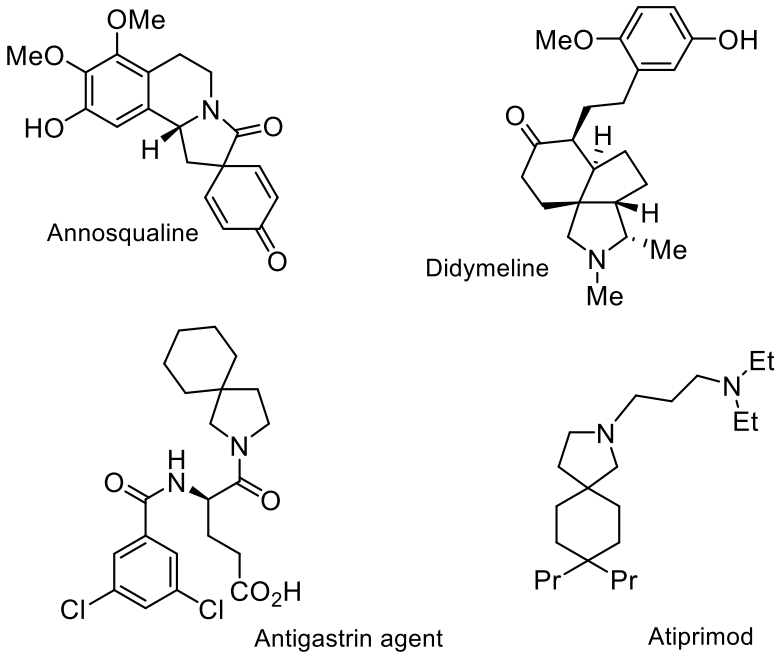
4.1 Segundo objetivo de la presente Tesis

El estudio se llevó a cabo en base a la observación, en el transcurso de los estudios metodológicos de procesos ATRC (esquema 4.2), de la formación como producto minoritario de un compuesto de *ipso*-ciclación, que implicaba una desaromatización.



4.2 Ciclación Radicalaria de la tricloroacetamida **1** (cap. 2)

El interés de la investigación era tanto metodológica como por el hecho que las estructuras espirocíclicas se encuentran en numerosos productos naturales.[1] En concreto, el sistema de 2-azaespiro[4.5]decano es presente en productos naturales con alta diversidad en su origen biogenético[2], así como en diversos compuestos sintéticos de interés farmacológico[3].



4.3 Estructuras con 2-azaespiro[4.5]decanos de productos naturales y no naturales

Usualmente, los 2-azaespiro[4.5]decanos son preparados a partir de ciclohexilaminas[4] o a través de procesos de desaromatización como etapa clave desde derivados del benceno. En este caso, el método estándar para construir el esqueleto

[1] Roche, S. P.; Porco, J. A. Jr. *Angew. Chem*. **2011**, *50*, 4068–4093.

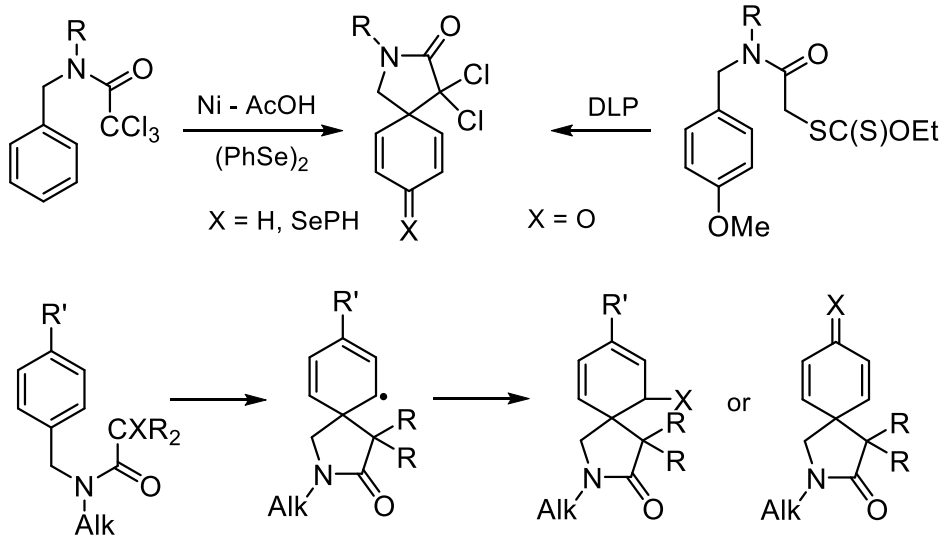
[2] (a) Yang, Y.-L.; Chang, F.-R.; Wu, Y.-C. *Helv. Chim. Acta*, **2004**, *87*, 1392–1399; (b) Shigehisa, H.; Takayama, J.; Honda, T. *Tetrahedron Lett*. **2006**, *47*, 7301–7306. (c) Hallock, Y. F.; Lu, H. S. M.; Clardy, J.; Strobel, G. A.; Sugawara, F.; Samsoedin, R.; Yoshida, S. J. *Nat. Prod*. **1993**, *56*, 747–754. (d) Sandmeier, P.; Tamm, C. *Helv. Chim. Acta* **1990**, *73*, 975–984. (e) Sánchez, V.; Ahond, A.; Guilhem, J.; Poupat, C.; Poitier, P. Bull. *Soc. Chim. Fr*. **1987**, 877–884; (f) Bhutani, K. K.; Ali, M.; Sharma, S. R. R.; Vaid, M.; Gupta, D. K. *Phytochemistry,* **1988**, *27*, 925–928; (g) Siddiqui, B. S.; Usmani, S. B.; Begum, S.; Siddiqui, S. *Phytochemistry,* **1993**, *33*, 925–928.

[3] (a) Rice, L. M.; Sheth, B. S.; Wheeler, J. W. J. *Heterocycl. Chem*. **1973**, *10*, 731–735; (b) Amit-Vazina, M.; Shishodia, S.; Harris, D.; Van, Q.; Wang, M.; Weber, D.; Alexanian, R.; Talpaz, M.; Aggarwal, B. B.; Estrov, Z. Br. *J. Cancer,* **2005**, *93*, 70–80; (c) Makovec, F.; Peris, W.; Revel, L.; Giovanetti, R.; Mennuni, L.; Rovati, L. C. *J. Med. Chem*. **1992**, *35*, 28–38. (d) Badger, A. M.; Schwartz, D. A.; Picker, D. H.; Dorman, J. W.; Bradley, F. C.; Cheeseman, E. N.; Dimartino, M. J.; Hanna, N.; Mirabelli, C. K. *J. Med. Chem*. **1990**, *33*, 2963–2970. (e) Kazmierski, W. M.; Furfine, E.; Spaltenstein, A.; Wright, L. L. *Bioorg. Med. Chem. Lett*. **2002**, *12*, 3431–3433

[4] Para procedimientos de aminociclación asistido por metales: (a) Solé, D.; Cancho, Y.; Llebaria, A.; Moretó, J. M.; Delgado, A. *J. Org. Chem*. **1996**, *61*, 5895–5904; (b) Zhou, C.-Y.; Che, C.-M. *J. Am. Chem. Soc*. **2007**, *129*, 5828–5829; (c) Rosewall, C. F.; Sibbald, P. A.; Liskin, D. V.; Michael, F. E. *J. Am. Chem. Soc*. **2009**, *131*, 9488–9489.

espiránico implica un proceso oxidativo de espirociclación de derivados fenólicos,[5] mientras que hay un número limitado de ejemplos a partir de bencenos no activados que experimenten una desaromatización.[6]

Los únicos precedentes para espirociclaciones con desaromatización que conducen a 2-azaespirodecadienos vía proceso radicalario son: a) a partir de *N*-benciltricloroacetamidas por tratamiento con Ni–AcOH, que conduce a 1,2-ciclohexadienos, mientras que la adición de $(PhSe)_2$ al medio de reacción para atrapar el intermedio radicalario ciclohexandienilo proporciona 1,4-ciclohexadienos[6]; b) A partir de derivados del fenol como sustratos, utilizando xantatos como grupos proradicales.[5c,d]



4.4 Precedentes en la literatura de espirociclaciones con desaromatización vía radicalaria

Inspirados por la espirociclación catalizada por Cu(I) sin precedentes en los procesos ATRC, nos interesamos por explorar alternativas para la construcción de espirociclos. En un primer estudio nos centramos en los procesos de desaromatización mediante ATRC catalizados por Cu(I) a partir de *N*-benciltricloroacetamidas para la síntesis de 2-azaespiro[4.5]decanos y en un segundo estudio se extendió a procesos de desaromatización mediante ATRC promovidos por el catalizador de Grubbs II a partir de *N*-(p-metoxibencil)tricloroacetamidas para la síntesis de 2-azaespiro[4.5] decan-8-onas.

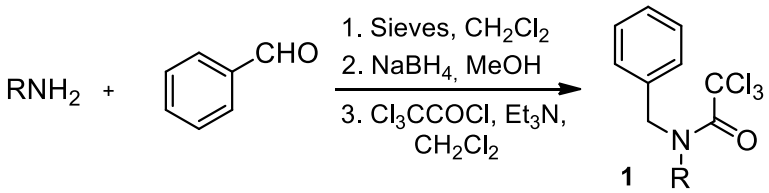
[5] (a) Rishton, G. M.; Schwartz, M. A. *Tetrahedron Lett*. **1988**, *29*, 2643–2646; (b) Santra, S.; Andreana, P. R. *Org. Lett*. **2007**, *9*, 5035–5038; (c) Pigge, F. C.; Dhanya, R.; Hoefgen, E. R. *Angew. Chem.* **2007**, *46*, 2887–2890; (d) Ibarra-Rivera, T. R.; Gámez-Montaño, R.; Miranda, L. D. *Chem. Commun*. **2007**, 3485–3487; (e) Gámez-Montaño, R.; Ibarra-Rivera, T.; El Kaïm, L.; Miranda, L. D. *Synthesis,* **2010**, 1285–129.

[6] Boivin, J.; Yousfi, M.; Zard, S. Z. *Tetrahedron Lett*. **1997**, *38*, 5985–5988.

4.2 Estudios ATRC promovidas por Cu(I)[7]

*4.2.1 Preparación de las tricloroacetamidas **1**(a-e)*

Las tricloroacetamidas **1**(a-e)[8] requeridas fueron fácilmente disponibles mediante aminación reductiva de la correspondiente alquilamina con benzaldehído y acilación de la amina secundaria resultante utilizando cloruro de tricloroacetilo.

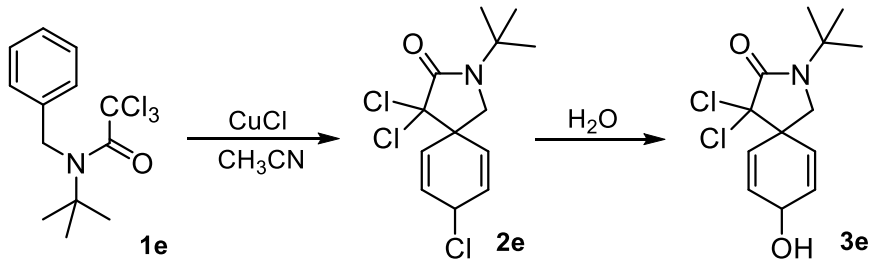


4.5 Síntesis de las tricloroacetamidas

1a (R = Bn, 78%); **1b** (R = Bu, 96%); **1c** (R = *i*Pr, 98%); **1d** (R = cHex, 96%); **1e** (R = *t*Bu, 85%)

*4.2.2 Ciclaciones radicalarias con transferencia de átomo en **1**(a-e)*

Nuestro estudio metodológico se centró en la tricloroacetamida **1e** como sustrato de preferencia puesto que el sustituyente voluminoso *tert*-butilo en el átomo de nitrógeno acelera las reacciones radicalarias que conducen a anillos de 5 miembros. El origen de este fenómeno es que por motivos estéricos el rotámero Z es preferente y el radical que se genera a partir del mismo está en la disposicón adecuada para la ciclación[9].



Entrada	Catalizador CuCl	Tiempo	Temp.	Activación Microondas	Rendimiento **3e** (menos/más polar)
1	30%	16 h	80 ºC	No	65% (1.4:1)
2	30%	15 min	80 ºC	Si	49% (3:2)
3	60%	15 min	80 ºC	Si	74% (3:2)
4	60%	30 min	80 ºC	Si	68% (3:2)

4.6 Optimización del proceso ATRC en **1e**

[7] La numeración de los compuestos del apartado 4.2 corresponde a la reportada en *Tetrahedron Lett.*

[8] El compuesto **1d** se preparó mediante aminación reductiva de la ciclohexanona utilizando bencilamina, seguido por la reacción con cloruro de tricloroacetilo.

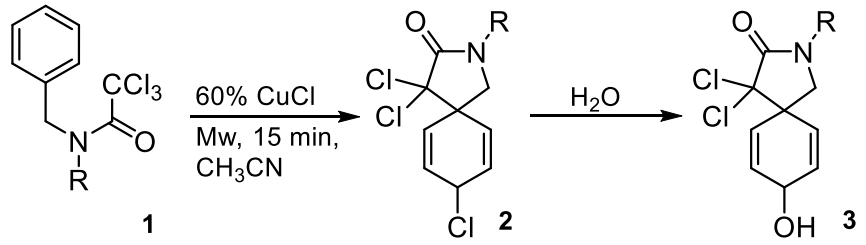
[9] (a) Stork, G.; Mah, R. *Heterocycles,* **1989**, *28*, 723–727; (b) Yu, J.-D.; Ding, W.; Lian, G.-Y.; Song, K.-S.; Zhang, D.-W.; Gao, X.; Yang, D. *J. Org. Chem*. **2010**, *75*, 3232–3239.

Utilizando CuCl (30%) y después de 16 h a 80 ºC se observó de forma satisfactoria, en el espectro de RMN ^{1}H del crudo, las señales principales que caracterizan al compuesto **2e**. Sin embargo, la purificación de **2** en gel de sílice dio una mezcla de compuestos, mostrando la inestabilidad de los cloro derivados.

Afortunadamente, una vez terminada la reacción, un simple tratamiento con H_2O de la mezcla de reacción generó el correspondiente alcohol **3**, el cual es suficiente estable para ser purificado mediante cromatografía en gel de sílice, obteniendo **3e** en un 65% como una mezcla 1.4:1 de epímeros (tabla 4.6, entrada 1).

Así, al contrario que Zard, que obtenía 1,2-dihidrobencenos mediante Ni–AcOH en la espirocilación,[10] nosotros obtuvimos 1,4-dihidrobencenos después de la ATRC utilizando Cu(I). La secuencia implica la generación de un radical carbamoildiclorometilo, un ataque *ipso* intramolecular al anillo del benceno, seguido consecutivamente de la formación regioselectiva del enlace C-Cl en el radical ciclohexadienilo inicialmente formado.[11] Mediante hidrólisis, el lábil cloruro alílico condujo al correspondiente alcohol **3**. Por lo tanto, el proceso general es una 1,4-carbooxigenación del anillo bencénico presente en **1**.

A fin de optimizar el proceso se decidió utilizar la activación mediante microondas. Como se puede observar (entradas 2, 3 y 4) las mejores condiciones pasaron por aumentar al 60% el CuCl con tiempos no superiores a 15 min[12], obteniendo **3e** en un 74% en una mezcla 3:2 de epímeros.

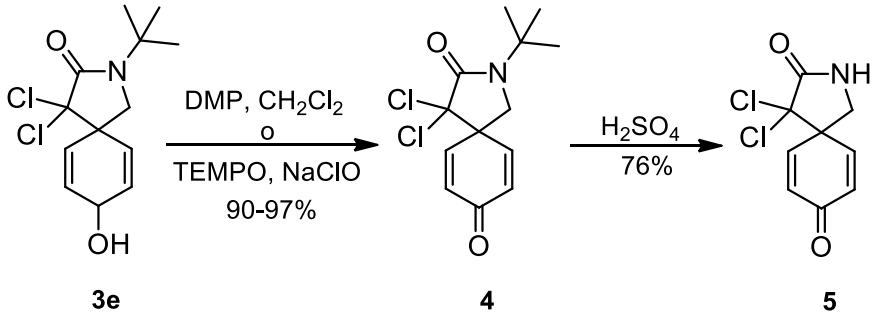


4.7 Aplicación de las condiciones optimizadas a las tricloroacetamidas **1a**-**1d**:
3a (R = Bn, 24%); **3b** (R = Bu, 17%); **3c** (R = *i*Pr, 42%); **3d** (R = *c*Hex, 29%)

Las condiciones optimizadas fueron aplicadas a las demás tricloroacetamidas (esquema 4.7) obteniendo en todos los casos el correspondiente alcohol, en forma de mezcla epimérica, con rendimientos incluidos entre 17 y 42%. Como se esperaba, los sustratos **1a** y **1b**, con grupos no voluminosos, dieron los peores resultados, mientras que el isopropilo o el ciclohexilo proporcionaron los alcoholes **3** con rendimientos moderados.

[10] Cuando no se utiliza ningún agente radicalario, la captura del radical ciclohexandienilo probablemente tiene lugar mediante una oxidación y posterior ataque nucleófilo.
[11] La formación de 1,4-dienos refleja la conocida propensión de los radicales ciclohexandienilos para un *trapping* cinético: (a) Beckwith, A. L. J.; O'Shea, D. M.; Roberts, D. H. *J. Am. Chem. Soc*. **1986**, *108*, 6408–6409; (b) Crich, D.; Krishnamurthy, V. *Tetrahedron* **2006**, *62*, 6830–6840.
[12] Los tiempos para la conversión completa del material de partida oscila entre los 13-17 min, tiempos de exposición superiores solo conducen a la degradación del producto.

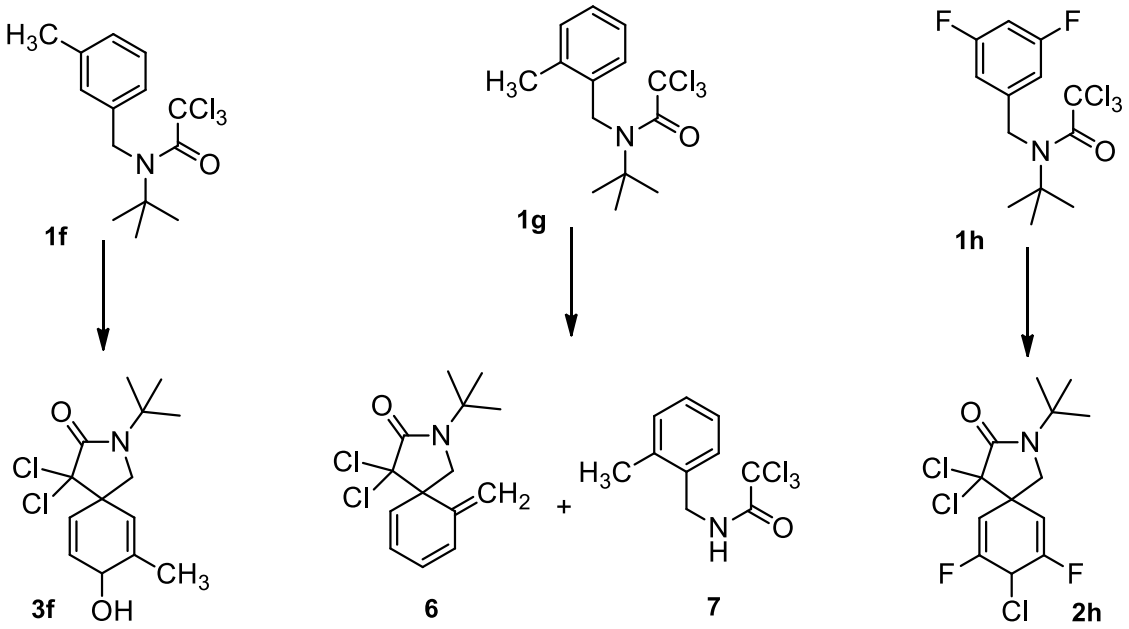
*4.2.3 Transformaciones sintéticas de la azaespirolactama **3e***



4.8 Transformaciones de **3e** a **5**

La mezcla de alcoholes **3e** fue fácilmente convertida a la correspondiente cetona **4** con excelentes rendimientos ya sea con Dess-Martin o TEMPO. La posterior desprotección del grupo *tert*-butilo en medio ácido[13] proporcionó la amina secundaria **5** con un 76% de rendimiento.

4.2.4 Extensión de la metodología a arenos sustituidos



4.9 Extensión de la metodología a arenos sustituidos. Condiciones de reacción: 60% CuCl, CH_3CN, mW, 80 ºC, 15 min. **3f** (54%); **6** (21%); **2h** (42%)

Adicionalmente se estudió la aplicación de la metodología sobre bencenos sustituidos (esquema 4.9). Las tricloroacetamidas requeridas se preparon de manera

[13] (a) Rosenberg, S. H.; Rapoport, H. *J. Org. Chem*. **1985**, *50*, 3979–3982; (b) Albrecht, D.; Basler, B.; Bach, T. *J. Org. Chem*. **2008**, *73*, 2345–2356.

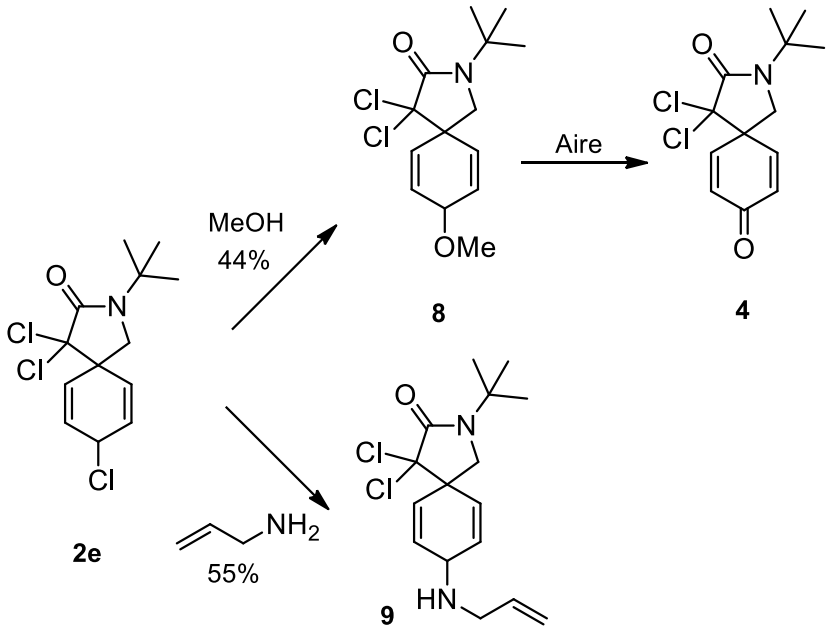
análoga a la descrita en el apartado 4.2.1 (esquema 4.5)[14]. El tratamiento de **1f** con CuCl dio resultados similares a su análogo **1e**, aislándose una mezcla epimérica de **3f**.

En contraste, en el benceno con el sustituyente 2-metilo **1g**, la captura del radical ciclohexildienilo parece que tiene lugar en el C-2 y el cloro derivado evoluciona al metileno derivado **6** a través de un proceso de eliminación. Más aún, por motivos estéricos la espirociclación está desfavorecida respecto a los derivados **1e** y **1f**, recuperándose material de partida dealquilado **7** (25%).

Por último el derivado 3,5-difluorobencilo **1h** tiene un comportamiento particular pues el producto con el cloro derivado **2h** mostró prácticamente una nula reactividad en medio acuoso, pudiendo ser aislado después de su purificación en gel de sílice.

*4.2.5 Reactividad de **2e** frente a distintos nucleófilos*

Por último, se examinó la introducción de otros nucleófilos distintos al H_2O como aminas o alcoholes. Así, al tratar la mezcla de cloroderivados al final de la reacción con MeOH o alilamina se accedió al éter **8** (44%) y la amina **9** (55%) respectivamente. Cabe destacar la sensibilidad de **8** al oxígeno de la atmósfera puesto que cantidades sustanciales de la cetona **4** se formaron al dejarlo en contacto con el aire.



4.10 Distintos Nucleófilos, MeOH o alilamina, para atrapar **2e**

[14] Los rendimientos para las 3 etapas son: **1f** (56%), **1g** (41%) y **1h** (51%)

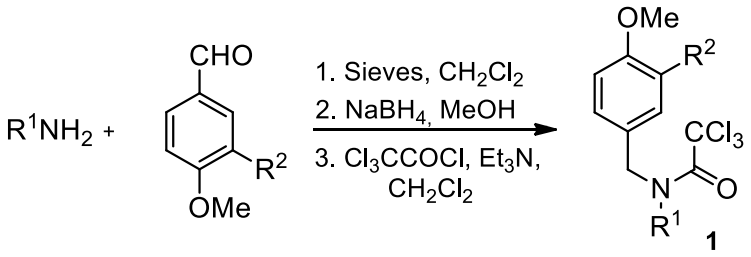
4.3 Estudios ATRC promovidas por Grubbs(II)[15]

4.3.1 Antecedentes

Los procesos de ATRC[16] promovidos por el catalizador de Grubbs que se encuentran en la literatura están limitados a sustratos que contienen simples alquenos como radicales aceptores. Esto nos alentó a investigar sobre sustratos que contienen dobles enlaces ricos electrónicamente que actúan como aceptores radicalarios (esquema 4.1).

4.3.2 Preparación de los materiales de partida

La preparación de las tricloroacetamidas **1** (a-f) fue homóloga a la previamente descrita en este capítulo: aminación reductiva seguida de acilación .[17]



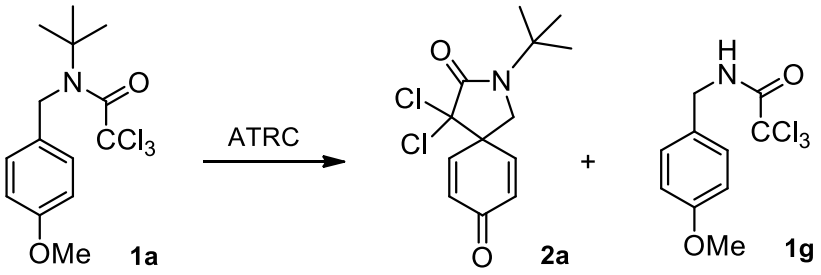
4.11 Síntesis de las tricloroacetamidas **1**

1a (R^1 = *t*Bu, R^2 = H, 85%); **1b** (R^1 = Cy, R^2 = H, 91%); **1c** (R^1 = *t*Bu, R^2 = Me, 40%); **1d** (R^1 = *t*Bu, R^2 = F, 63%); **1e** (R^1 = Bn, R^2 = H, 89%); **1f** (R^1 = Bn, R^2 = F, 93%)

*4.3.3 Estudios metodológicos de las tricloroacetamidas **1**(a-f)*

En base a los resultados obtenidos en espirociclaciones con desaromatización radicalarias sobre bencenos inactivados promovidos por Cu(I), nuestros esfuerzos metodológicos se concentraron en el derivado *tert*-butilo **1a** como sustrato de preferencia.

[15] La numeración del apartado 4.3 refleja la de la publicación en *J. Org. Chem.* (Capítulo 5).
[16] (a) Eckenhoff, W. T.; Pintauer, T. *Catal. Rev. Sci. Eng*. **2010**, *52*, 1−59. (b) Muñoz-Molina, J. M.; Belderrain, T. R.; Perez, P. J. *Eur. J. Inorg. Chem*. **2011**, 3155−3164.
[17] En la preparación de **1c** y **1f** los bajos rendimientos son debidos a una primera etapa incompleta de la formación de la imina, recuperando material de partida.

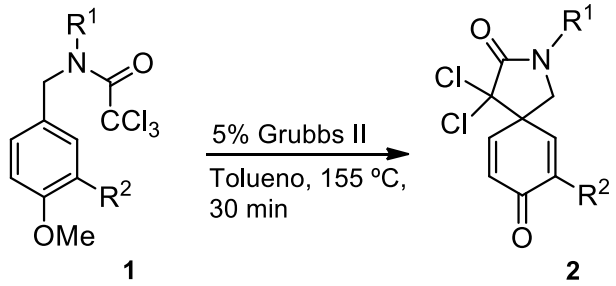


Entrada	Catalizador	Disolvente	Tiempo	Temp.	Rendimiento
1	5% Grubbs I	Tolueno	30 min	155 ºC	**2a** (58%), **1g** (36%)
2	5% Grubbs II	Tolueno	30 min	155 ºC	**2a** (81%)
3	5% Hov-Grubbs II	Tolueno	30 min	155 ºC	**2a** (35%), **1g** (21%)
4	5% Grubbs II	Tolueno	1 h Mw	120 ºC	**2a** (32%), **1g** (20%)
5	30% CuCl	CH_3CN	16 h	80 ºC	**2a** (61%), **1g** (35%)

4.12 Optimización del proceso ATRC en **1a**

Como se puede observar (tabla 4.12) los mejores resultados pasaron por el uso del catalizador de Grubbs II (entrada 2) obteniendo excelentes rendimientos. En los demás catalizadores los rendimientos son inferiores debido a la rotura del grupo *tert*-butilo de **1a**, llevando a la correspondiente amida secundaria **1g**, el cual muestra la incapacidad para llevar a cabo el proceso ATRC.

Los intentos para mejorar el proceso mediante activación de microondas fueron infructuosos (entrada 4).



4.13 Extensión de las condiciones optimizadas: **2b** (R^1 = Cy, R^2 = H, 17%); **2c** (R^1 = *t*Bu, R^2 = Me, 72%); **2d** (R^1 = *t*Bu, R^2 = F, 54%); **2e** (R^1 = Bn, R^2 = Me, 52%); **2f** (R^1 = Bn, R^2 = F, 37%)

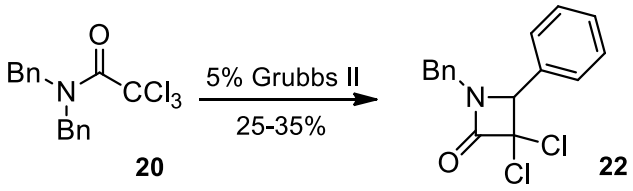
Las condiciones optimizadas fueron aplicadas a las demás tricloroacetamidas (esquema 4.13) obteniéndose la correspondiente cetona en cada caso. El bajo rendimiento observado para **2b** pone de manifiesto, una vez más, la importancia del sustituyente en el nitrógeno, como el *tert*-butilo, que favorezca la conformación correcta para la ciclación.

Adicionalmente, partiendo de **1d,** que presenta un grupo electroatrayente en el anillo aromático, la espirociclación procede en rendimientos inferiores al anisol **1c**.

Finalmente, también se exploró las espirociclaciones utilizando sustratos, **1e** y **1f**, que contienen dos grupos aromáticos con diferentes propiedades electrónicas. En ambos casos la ciclación tuvo lugar en el anillo de anisol y una vez más el sustrato con mayor densidad electrónica en el anillo aromático, en este caso **1e**, procedió con mejores rendimientos.

Los rendimientos inferiores en la serie *N*-bencilo (**1e**, **1f**) comparado con las series con sustituyente *N*-*tert*-butilo (**1a**, **1c**, **1d**) pueden ser atribuidas a la mezcla de rotámeros (1:1 ratio) en la serie bencilo.

Por último, cabe destacar que la aplicación de las condiciones en un sustrato que presenta 2 anillos aromáticos inactivados procedió de forma inesperada al compuesto **22** (esquema 4.14). Este proceso probablemente implica la formación de un diradical que aclopa entre sí debido a la particularidad espacial de los CH_2 del bencilo.



20 **22**

4.14 Reactividad anómala de **20** en la ATRC promovida por Grubbs(II)

4.4 Resumen

- Se ha descrito la primera metodología sobre procesos de desaromatización mediante ciclaciones radicalarias de tricloroacetamidas sobre núcleos bencénicos, para generar 2-azaespiro[4,5]decanos, utilizando como agentes promotores de los procesos de ATRC tanto Cu(I) como el catalizador de Grubbs II.

- Los resultados obtenidos con las distintas tricloroacetamidas muestran la importancia de disponer de un sustituyente voluminoso en el átomo de nitrógeno a fin de conseguir el proceso de ciclación con buen rendimiento.

- Se dispone de cierta versatilidad sintética para conseguir 2-azaespiro[4.5]decanos diversamente funcionalizados de interés para la síntesis de productos que contengan dicho esqueleto molecular.

4.5 Dearomative radical spirocyclization from *N*-benzyltrichloroacetamides revisited using a copper(I)-mediated atom transfer reaction leading to 2-azaspiro[4.5]decanes.

Diaba, F.; Montiel, J.; Martínez-Laporta, A.; Bonjoch, J.

Tetrahedron Lett. **2013**, *54*, 2619-2622.

Tetrahedron Letters 54 (2013) 2619–2622

Contents lists available at SciVerse ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

Dearomative radical spirocyclization from *N*-benzyltrichloroacetamides revisited using a copper(I)-mediated atom transfer reaction leading to 2-azaspiro[4.5]decanes

Faïza Diaba *, Juan A. Montiel, Agustín Martínez-Laporta, Josep Bonjoch *

Laboratori de Química Orgànica, Facultat de Farmàcia, Institut de Biomedicina (IBUB), Universitat de Barcelona, Av. Joan XXIII s/n, 08028 Barcelona, Spain

ARTICLE INFO

Article history:
Received 7 January 2013
Revised 5 March 2013
Accepted 6 March 2013
Available online 15 March 2013

Keywords:
Atom transfer radical cyclization
Azaspirodecanes
Copper
Dearomatization
Heterocycles

ABSTRACT

An atom transfer radical dearomatizing spirocyclization from N-benzyltrichloroacetamides using CuCl regioselectively leads to 2-azaspiro[4.5]decadienes, in which the labile allylic chlorine atom is easily replaced by a hydroxyl group in aqueous medium or by quenching with methanol or allylamine. After oxidation of the target compound, the N-tert-butyl group can be removed from the resulting spirocyclohexanedienone.

Spirocyclic structures are prevalent in a variety of natural products.[1] Among them, the 2-azaspiro[4.5]decane ring system is found embedded in a small number of compounds of diverse biogenetic origin, such as annosqualine,[2] the fungal metabolites triticones[3] and spirostaphylotricins,[4] and some stereoidal alkaloids.[5] Additionally, several synthetic compounds embodying this framework exhibit a wide range of biological activities, including antiangiogenic (e.g. atiprimod),[6] antigastrin,[7] and antiarthritic,[8] as well as HIV-1 protease inhibiton[9] (Fig. 1).

2-Azaspiro[4.5]decanes are generally prepared from cyclohexylmethylamine starting materials[10,11] or through a dearomatizing process as the key step from benzene derivatives. In the latter approach, the typical method to construct the spirocyclic core involves oxidative spirocyclization of phenol derivatives,[12,13] while there are limited examples of the use of non-activated benzene substrates that could deliver spirocyclohexadienes through a dearomatization.[14]

We have recently been interested in copper(I)-mediated atom transfer radical cyclisation (ATRC)[15] of trichloroacetamides leading to six-membered ring formation.[16] During the course of these studies, we disclosed a copper-catalyzed ATRC leading to an azaspirocyclohexadienol as a by-product (less than 10%) from trichloroacetamide **I** (Scheme 1).

Inspired by this unprecedented Cu(I)-catalysed spirocyclization, we went on to explore other ways of constructing spirocycles. In this paper we report the first dearomative spirocyclization of ben-

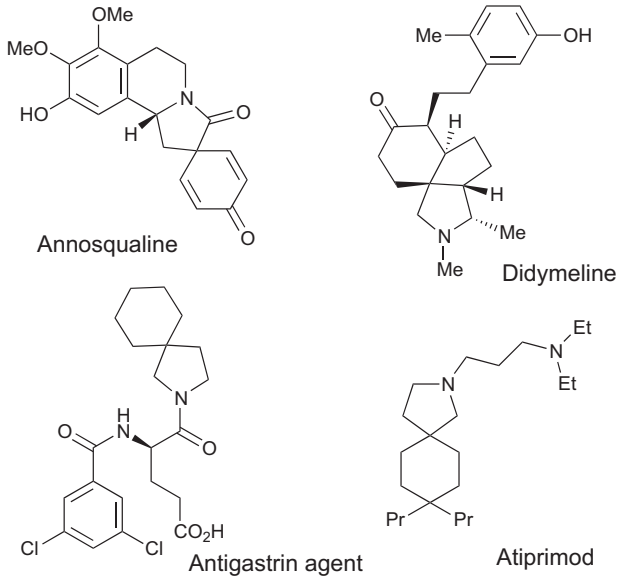
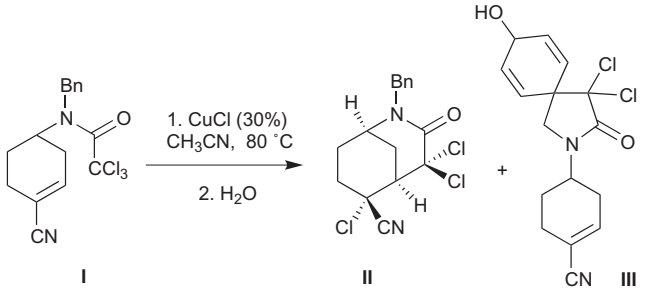


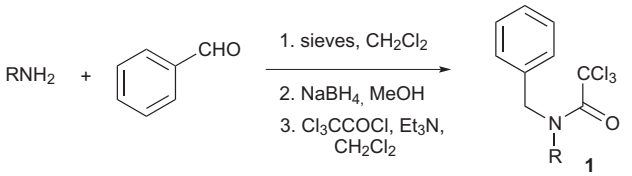
Fig. 1. Structures of 2-azaspiro[4.5]decane natural and unnatural products.

* Corresponding authors. Tel.: +34 934024540; fax: +34 934024539.
E-mail addresses: faiza.diaba@ub.edu (F. Diaba), josep.bonjoch@ub.edu (J. Bonjoch).

0040-4039/$ - see front matter © 2013 Elsevier Ltd. All rights reserved.
http://dx.doi.org/10.1016/j.tetlet.2013.03.019

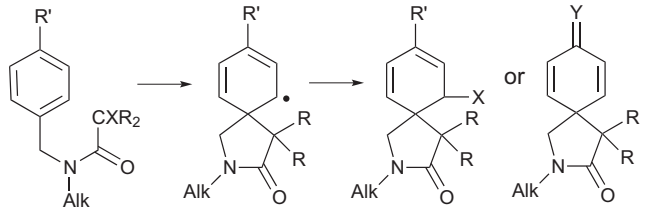


Scheme 1. Radical cyclization of trichloroacetamide **I**.



Scheme 2. Synthesis of trichloroacetamides: **1a** (*R* = Bn, 78%); **1b** (*R* = Bu, 96%); **1c** (*R* = *i*Pr (98%); **1d** (*R* = *c*Hex, 96%); **1e** (*R* = *t*Bu, 85%).

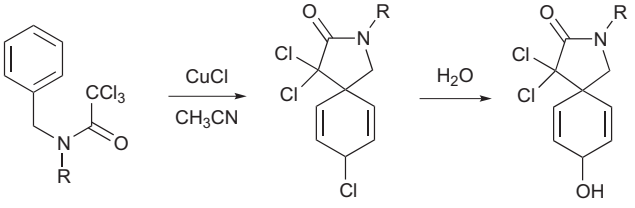
Table 1
Dearomative radical spirocyclization



Promoter	Ref.	X	R	R′	X/R′ or	Y
Ni-AcOH	14	Cl	Cl	H	Cl/H	H, SePh[a]
$(RO)_2$	13	SC(S)OEt	H	OMe	—	O
CuCl	This work	Cl	Cl	H	—	H, Cl

[a] If $(PhSe)_2$ was added to the reaction mixture.

Table 2
CuCl-promoted spirocyclization of trichloroacetamides **1**[a]



Entry	R	CuCl [%]	Time	Yield[b] [%]	Ratio[c]
1	*t*Bu (**1e**)	30	16 h[d]	65	1.4:1
2	1e	30	15 min	49	3:2
3[e]	1e	60	15 min	74	3:2
4	1e	60	30 min	68	3:2
5	*c*Hex (**1d**)	60	15 min	29	3:2
6	*i*Pr (**1c**)	60	15 min	42	2:3
7	Bu (**1b**)	60	15 min	17	3:2
8	Bn (**1a**)	60	15 min	24	2:3

[a] Unless otherwise noted, all reactions were carried out from 200 mg of trichloroacetamide **1** at 80 °C and using microwave activation.
[b] Isolated yield of alcohols **3**.
[c] Diastereoisomeric ratio of less and more polar alcohols.
[d] Reaction carried out at 80 °C in a sealed tube.
[e] Reaction carried out on a 100 mg scale.

zyltrichloroacetamides mediated by Cu(I) leading to 2-azaspiro[4.5]decane compounds through an ATRC process.[17]

The only precedents for dearomative spirocyclization leading to 2-azaspirodecadienes via a radical process are the following: (i) When working with benzyl derivatives as starting material, the use of Ni-AcOH leads to 1,2-cyclohexadienes, *p*-tolyl compounds lead to a mixture of cyclohexadienes, while adding $(PhSe)_2$ to the reaction medium to trap the cyclohexadienyl radical intermediate regioselectivity provides 1,4-cyclohexadienes.[14] (ii) Using phenol derivatives as substrates in an oxidative process from xanthates, which is initiated and terminated by dilauryl peroxide, provides spirocyclohexanedienones[13] (Table 1).

The trichloroacetamides **1**(a-e)[18] required for our studies were easily available by reductive amination of the corresponding alkylamine with benzaldehyde and acylation of the resulting secondary amines using trichroacetyl chloride (Scheme 2).

Initially, we chose trichloroacetamide **1e** as the preferred substrate to develop the methodology, since the bulky *tert*-butyl substituent on the nitrogen atom accelerates radical reactions leading to five-membered rings. This well-established helpful effect is due to the favoring of the productive *Z* rotamer in the proradical haloacetamide.[19]

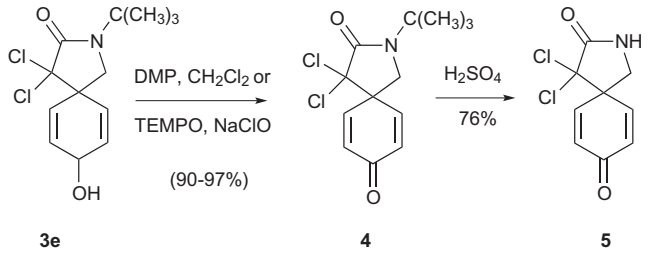
Using 30% of CuCl and after 16 h of heating at 80 °C, we were pleased to see that the main signals in the ^{1}H NMR spectrum of the crude product belonged to a mixture of epimers of spirolactam **2**. However, purification of **2** on silica gel gave a mixture of compounds, showing the instability of the chloro derivatives. Luckily, a simple treatment of the reaction mixture with water at the end of the reaction generated the corresponding alcohols **3**, which were stable enough to be easily separated by chromatography in 65% yield and as a 1.4:1 mixture of epimers (Table 2, entry 1).

Thus, unlike Zard,[14] who achieved 1,2-dihydrobenzenes by a Ni-AcOH-promoted spirocyclisation,[20] we obtained 1,4-dihydrobenzenes after cyclisation and atom transfer using Cu(I) (Table 1). The sequence involved the generation of the carbamoyldichloromethyl radical, an intramolecular ipso attack on the benzene ring, followed by consecutive regioselective C–Cl bond formation on the initially formed cyclohexadienyl radical.[21] Upon hydrolysis, the lability of the allylic chloride gave the corresponding alcohol **3**. Thus, the overall process constitutes a 1,4-carbooxygenation of the benzene ring present in **1**.

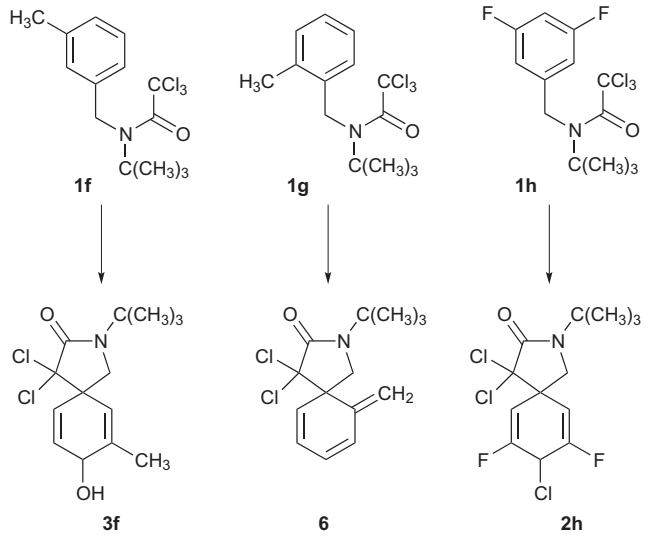
To optimize the process we decided to use microwave activation, but the same catalyst loading, a 15-minute reaction time and further treatment with water gave the same mixture of alcohols with a lower yield of 49% (entry 2). The best results were obtained with 60% of CuCl, which gave **3e** in 74% yield (entry 3).[22] Prolonging the reaction time to 30 min did not improve the yield (entry 4).[23] The optimum conditions were then applied to the other trichloroacetamides, and in all cases the corresponding alcohols were obtained in low to moderate yields. As expected, substrates **1a** and **1b**, with non-hindering groups, gave the worst results, whereas isopropyl and cyclohexyl substrates provided alcohols **3** with slightly better yields (Table 2).

The mixture of alcohols **3e** was readily converted to the corresponding ketone **4** in excellent yields using Dess–Martin periodinane or TEMPO. Further cleavage of the *tert*-butyl group in acid medium[24] provided secondary amide **5** in 76% yield (Scheme 3).

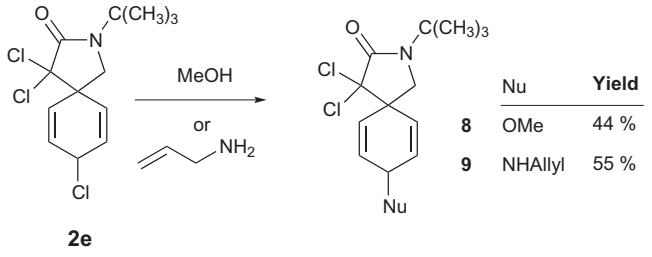
We next sought to explore the scope of the reaction and examined a number of substituted benzene derivatives (Scheme 4). Starting materials were prepared following the same reaction



Scheme 3. Synthetic transformations from azaspirolactam **3e**.



Scheme 4. Substrate scope of the ATRC. Reagents and conditions: CuCl (60%), CH_3CN, μW, 80 °C, 15 min. Compounds **3f** (54%); **6** (21%); **2h** (42%).



Scheme 5. Trapping of chloride **2e** with MeOH or allylamine.

sequence of reductive amination and trichloroacetylation as depicted above in Scheme 2. Treatment of 3-methylsubstituted benzene **1f** with CuCl gave a result similar to that observed in the unsubstituted series **1e**, the allylic alcohol **3f** being isolated as a diastereomeric mixture. In contrast, in the 2-methyl substituted benzene **1g**, the trapping of the cyclohexadienyl radical seems to have occurred at C-2, and the chloride derivative evolved to exocyclic methylene derivative **6** through an elimination process. Moreover, for steric reasons the spirocyclization was disfavoured with respect to the ortho-unsubstituted derivatives (**1e**, **1f**), and a remarkable increase in the de-*tert*-butylation reaction from **1g** occurred leading to secondary amide **7** in 25% yield (not shown; see Supplementary material). The 3,5-difluorobenzyl derivative **1h** behaved in a particular way, since after the ATRC cyclization the allyl chloride showed a low reactivity in the aqueous medium, and the initially formed chloride **2h,** remaining unchanged, was isolated.

Finally, we used trapping reagents other than water for the allylic chlorides formed after the ATRC, starting from **1e** as the radical precursor (Scheme 5). Thus, when MeOH was added to the reaction in the work-up, a mixture of ethers **8** was isolated. These were noted to be sensitive to the oxygen atmosphere since substantial amounts of ketone **4** were formed on standing in air. Otherwise, when the reaction mixture containing **2e** was treated with allylamine, an epimeric mixture of dienylallylamine epimers **9** was isolated.

In summary, we have described the first dearomative spirocyclization promoted by CuCl upon a benzene ring. The results obtained with the different trichloroacetamides used in this work again showed the importance of having a bulky group on the nitrogen to achieve the cyclization process. Oxidation of the epimeric alcohol mixture **3e** to the corresponding ketone and further cleavage of the *tert*-butyl group provided polyfunctionalized 2-azaspiro[4.5]decadienone **5**, which is now under study for use as a building block in the synthesis of natural and unnatural compounds.[25]

Acknowledgments

Support of this research was provided by the Spanish Ministry of Economy and Competitiveness (Project CTQ2010-14846/BQU).

Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2013.03.019.

References and notes

1. Roche, S. P.; Porco, J. A., Jr. *Angew. Chem., Int. Ed.* **2011**, *50*, 4068–4093.
2. (a) Yang, Y.-L.; Chang, F.-R.; Wu, Y.-C. *Helv. Chim. Acta* **2004**, *87*, 1392–1399; (b) Shigehisa, H.; Takayama, J.; Honda, T. *Tetrahedron Lett.* **2006**, *47*, 7301–7306.
3. Hallock, Y. F.; Lu, H. S. M.; Clardy, J.; Strobel, G. A.; Sugawara, F.; Samsoedin, R.; Yoshida, S. *J. Nat. Prod.* **1993**, *56*, 747–754.
4. Sandmeier, P.; Tamm, C. *Helv. Chim. Acta* **1990**, *73*, 975–984.
5. (a) Sánchez, V.; Ahond, A.; Guilhem, J.; Poupat, C.; Poitier, P. *Bull. Soc. Chim. Fr.* **1987**, 877–884; (b) Bhutani, K. K.; Ali, M.; Sharma, S. R. R.; Vaid, M.; Gupta, D. K. *Phytochemistry* **1988**, *27*, 925–928; (c) Siddiqui, B. S.; Usmani, S. B.; Begum, S.; Siddiqui, S. *Phytochemistry* **1993**, *33*, 925–928.
6. (a) Rice, L. M.; Sheth, B. S.; Wheeler, J. W. *J. Heterocycl. Chem.* **1973**, *10*, 731–735; (b) Amit-Vazina, M.; Shishodia, S.; Harris, D.; Van, Q.; Wang, M.; Weber, D.; Alexanian, R.; Talpaz, M.; Aggarwal, B. B.; Estrov, Z. *Br. J. Cancer* **2005**, *93*, 70–80.
7. Makovec, F.; Peris, W.; Revel, L.; Giovanetti, R.; Mennuni, L.; Rovati, L. C. *J. Med. Chem.* **1992**, *35*, 28–38.
8. Badger, A. M.; Schwartz, D. A.; Picker, D. H.; Dorman, J. W.; Bradley, F. C.; Cheeseman, E. N.; Dimartino, M. J.; Hanna, N.; Mirabelli, C. K. *J. Med. Chem.* **1990**, *33*, 2963–2970.
9. Kazmierski, W. M.; Furfine, E.; Spaltenstein, A.; Wright, L. L. *Bioorg. Med. Chem. Lett.* **2002**, *12*, 3431–3433.
10. For metal-assisted aminocyclization procedures, see: (a) Solé, D.; Cancho, Y.; Llebaria, A.; Moretó, J. M.; Delgado, A. *J. Org. Chem.* **1996**, *61*, 5895–5904; (b) Zhou, C.-Y.; Che, C.-M. *J. Am. Chem. Soc.* **2007**, *129*, 5828–5829; (c) Rosewall, C. F.; Sibbald, P. A.; Liskin, D. V.; Michael, F. E. *J. Am. Chem. Soc.* **2009**, *131*, 9488–9489; (d) Reznichenko, A. L.; Hultzch, K. C. *Organometallics* **2010**, *29*, 24–27; (e) Yeh, M.-C. P.; Pai, H.-F.; Hsiow, C.-Y.; Wang, Y.-R. *Organometallics* **2010**, *29*, 160–166; (f) Rosen, B. R.; Ney, J. E.; Wolfe, P. P. *J. Org. Chem.* **2010**, *75*, 2756–2759; (g) Hesp, K. D.; Tobisch, S.; Stradiotto, M. *J. Am. Chem. Soc.* **2010**, *132*, 413–426; (h) Yeh, M.-C. P.; Fang, C.-W.; Lin, H.-H. *Org. Lett.* **2012**, *14*, 1830–1833.
11. For other synthetic approaches, see: (a) Cossy, J.; Bouzide, A.; Pfau, M. *J. Org. Chem.* **1997**, *62*, 7106–7113; (b) Bryans, J. S.; Davies, N.; Gee, N. S.; Dissanayake, V. U. K.; Ratcliffe, G. S.; Horwell, D. C.; Kneen, C. O.; Morrell, A. I.; Oles, R. J.; O'Toole, J. C.; Perkins, G. M.; Singh, L.; Suman-Chauahan, N.; O'Neill, J. A. *J. Med. Chem.* **1998**, *41*, 1838–1845; (c) Cossy, J.; Bouzide, A.; Leblanc, C. *J. Org. Chem.* **2000**, *65*, 7257–7265; (d) Kitagawa, O.; Miyaji, S.; Yamada, Y.; Fujiwara, H.; Taguchi, T. *J. Org. Chem.* **2003**, *68*, 3184–3189; (e) Iwasaki, H.; Tsutsui, N.; Eguchi, T.; Ohno, H.; Yamashita, M.; Tanaka, T. *Tetrahedron Lett.* **2011**, *52*, 1770–1772; (f) Moriyama, K.; Izumisawa, Y.; Togo, H. *J. Org. Chem.* **2011**, *76*, 7249–7255.

12. (a) Rishton, G. M.; Schwartz, M. A. *Tetrahedron Lett.* **1988**, *29*, 2643–2646; (b) Santra, S.; Andreana, P. R. *Org. Lett.* **2007**, *9*, 5035–5038; (c) Pigge, F. C.; Dhanya, R.; Hoefgen, E. R. *Angew. Chem., Int. Ed.* **2007**, *46*, 2887–2890; (d) Ovens, C.; Martin, N. G.; Procter, D. *J. Org. Lett.* **2008**, *10*, 1441–1444; (e) Rozhkova, Y. S.; Khmelevskaya, K. A.; Shklyaev, Y. V.; Ezhikova, M. A.; Kodess, M. I. *Russ. J. Org. Chem.* **2012**, *48*, 69–77.
13. (a) Ibarra-Rivera, T. R.; Gámez-Montaño, R.; Miranda, L. D. *Chem. Commun.* **2007**, 3485–3487; (b) Gámez-Montaño, R.; Ibarra-Rivera, T.; El Kaïm, L.; Miranda, L. D. *Synthesis* **2010**, 1285–1290.
14. Boivin, J.; Yousfi, M.; Zard, S. Z. *Tetrahedron Lett.* **1997**, *38*, 5985–5988.
15. For a review, see: Eckenhoff, W. T.; Pintauer, T. *Catal. Rev. Sci. Eng.* **2010**, *52*, 1–59.
16. Diaba, F.; Martínez-Laporta, A.; Bonjoch, J.; Pereira, A.; Muñoz-Molina, J. M.; Pérez, J. P.; Belderrain, T. R. *Chem. Commun.* **2012**, 8799–8801.
17. For a related reaction upon an indole ring leading to spiroindolines, see: a Van der Jeught, S.; De Vos, N.; Masschelein, K.; Ghiviriga, I.; Stevens, C. V. *Eur. J. Org. Chem.* **2010**, 5444–5453; See also: b Kyei, A. S.; Tchabaneko, K.; Baldwin, J. E.; Adlington, R. M.; Stevens, C. V. *Tetrahedron Lett.* **2004**, *45*, 8931–8934.
18. Compound **1d** was prepared by reductive amination of cyclohexanone using benzylamine, followed by reaction with trichloroacetyl chloride.
19. (a) Stork, G.; Mah, R. *Heterocycles* **1989**, *28*, 723–727; (b) Yu, J.-D.; Ding, W.; Lian, G.-Y.; Song, K.-S.; Zhang, D.-W.; Gao, X.; Yang, D. *J. Org. Chem.* **2010**, *75*, 3232–3239.
20. When no radical trapping reagent was used, the capture of the cyclohexanedienyl radical probably occurred by an oxidation and later nucleophilic addition.
21. The formation of 1,4-dienes reflects the known propensity of cyclohexanedienyl radicals for kinetic trapping at the internal position: (a) Beckwith, A. L. J.; O'Shea, D. M.; Roberts, D. H. *J. Am. Chem. Soc.* **1986**, *108*, 6408–6409; (b) Crich, D.; Krishnamurthy, V. *Tetrahedron* **2006**, *62*, 6830–6840.
22. Reaction procedure: In a 10 mL vessel were placed trichloroacetamide **1e** (100 mg, 0.32 mmol), CuCl (19 mg, 0.19 mmol, 60%), and acetonitrile (1 mL). The stirred reaction mixture was heated at 80 °C using microwave irradiation for 15 min. After reaching rt, water (1 mL) was added, the mixture was stirred for an additional 1 h, and then extracted with CH_2Cl_2. The organics were dried, concentrated, and purified by chromatography (CH_2Cl_2 to CH_2Cl_2/AcOEt 98:2) to give separable alcohols **3e** (70 mg, 74%) in a 3:2 proportion. Less polar: IR (NaCl, neat): 3529, 3399, 3284, 3039, 2977, 2934, 2870, 1720, 1478, 1399, 1365, 1305, 1246, 1222, 1032, 1010, 895, 872, 829, 775, 739, 681, 582, 525 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz, COSY): δ 1.43 (9H, s, CH_3), 1.97 (1H, br s, OH), 3.39 (2H, s, 1-H), 4.66 (1H, br s, 8-H), 5.88 (2H, dq, J = 10.4, 2 Hz, 6-H and 10-H), 6.23 (2H, ddt, J = 10.4, 3, 2 Hz, 7-H and 9-H); ^{13}C NMR ($CDCl_3$, 100 MHz, HSQC): 27.1 (CH_3-^{t}Bu), 48.9 (C-5), 52.3 (C-1), 55.4 (C), 62.3 (C-8), 90.5 (C-4), 125.9 (C-6 and C-10), 133.3 (C-7 and C-9), 165.3 (C-3). HRMS (ESI-TOF): Calcd for $C_{13}H_{18}Cl_2NO_2$ 290.0709 (M^++1). Found: 290.0719. More polar: IR (NaCl, neat): 3254, 3034, 2972, 2871, 1713, 1474, 1400, 1367, 1306, 1245, 1216, 1015, 923, 885, 777, 741, 694, 682, 563, 516 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz): 1.43 (9H, s, CH_3), 1.58 (1H, br s, OH), 3.34 (2H, s, 1-H), 4.52 (1H, br s, 8-H), 5.96 (2H, dq, J = 10.4, 1.6 Hz, 6-H and 10-H), 6.24 (2H, ddt, J = 10.4, 3.6, 2 Hz, 7-H and 9-H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 27.1 (CH_3-^{t}Bu), 48.6 (C-5), 52.7 (C-1), 55.4 (C), 62.1 (C-8), 89.7 (C-4), 126.9 (C-6 and C-10), 132.4 (C-7 and C-9), 165.3 (C-3). HRMS (ESI-TOF): Calcd for $C_{13}H_{18}Cl_2NO_2$ 290.0709 (M^++1). Found: 290.0698.
23. Almost of the reactions from **1e** provided also a variable amount of secondary amide resulting from the cleavage of the *tert*-butyl group.
24. (a) Rosenberg, S. H.; Rapoport, H. *J. Org. Chem.* **1985**, *50*, 3979–3982; (b) Albrecht, D.; Basler, B.; Bach, T. *J. Org. Chem.* **2008**, *73*, 2345–2356.
25. As suggested by the reviewers, an extension of the ATRC process reported here to different aromatic rings[25a,b] and tethers[25c,d] could be of interest: (a) Kaoudi, T.; Quiclet-Sire, B.; Seguin, S.; Zard, S. Z. *Angew. Chem., Int. Ed.* **2000**, *39*, 31–733; (b) Guindeuil, S.; Zard, S. Z. *Chem. Commun.* **2006**, 665–667; (c) Quiclet-Sire, B.; Zard, S. Z. *Chem. Commun.* **2002**, 2306–2307; (d) Bacqué, E.; El Qacemi, M.; Zard, S. Z. *Org. Lett.* **2005**, *7*, 3817–3820.

Dearomative radical spirocyclization from *N*-benzyltrichloroacetamides revisited using a copper(I)-mediated atom transfer reaction leading to 2-azaspiro[4.5]decanes

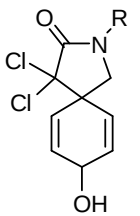
Faïza Diaba*, Juan A. Montiel, Agustín Martinez-Laporta and Josep Bonjoch*

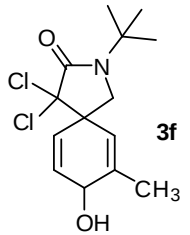
Laboratori de Química Orgànica, Facultat de Farmàcia, IBUB, Universitat de Barcelona, Av. Joan XXIII s/n, 08028-Barcelona, Spain

faiza.diaba@ub.edu; josep.bonjoch@ub.edu

Table of contents

Table 1. ^{13}C NMR chemical shifts of 2-azaspiro[4.5]decanes **3**[a]





3f

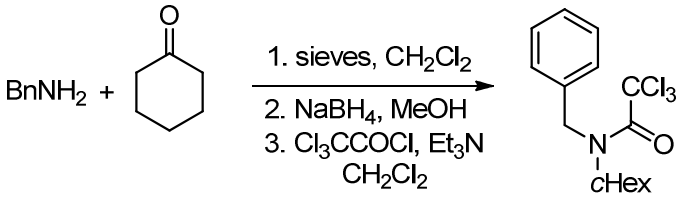
	3a R = Bn		**3b** R = Bu		**3c** R = *i*Pr		**3d** **R** = *c*Hex		**3e** R = *t*Bu		**3f**	
	LP	**MP**	**LP**	**MP**	**LP**	**MP**	**LP**	**MP**	**LP**	**MP**	**LP**	**MP**
C-1	53.8	53.3	54.5	54.0	49.6	49.1	50.2	50.6	52.3	52.7	52.5	52.8
C-3	165.8	165.8	165.2	165.7	165.0	165.0	165.1	165.1	165.3	165.3	165.5	165.5
C-4	88.2	88.5	90.6	89.5	89.0	89.8	89.9	89.0	90.5	89.7	90.9	90.0
C-5	49.3	49.7	49.5	49.9	49.2	49.6	49.8	49.4	48.9	48.6	49.9	49.6
C-6, C-10	126.7	125.7	126.9	126.0	126.8	125.8	125.9	126.9	125.9	126.9	121.2	121.9
											126.2	127.2
C-7, C-9	132.4	133.4	132.4	133.3	132.5	133.4	133.3	132.4	133.3	132.4	140.1	140.3
											132.9	132.2
C-8	62.0	62.3	62.0	62.3	62.0	62.4	62.4	62.1	62.3	62.1	65.5	65.6
Other	47.9	47.9	13.7	13.7	19.2	19.2	25.1	25.1	27.1	27.1	20.0	20.4
	128.3	128.3	19.9	19.9	44.2	44.2	25.2	25.2	55.4	55.4	27.1	27.1
	128.4	128.4	28.9	28.9			29.7	29.6			55.4	55.4
	129.0	129.0	43.6	43.7			52.0	52.0				
	134.5	134.5										

[a] Values were assigned on the basis of gCOSY and gHSQC spectra in $CDCl_3$ (100 MHz). **LP** and **MP** refer to the diastereomer less polar and the diastereomer more polar respectively.

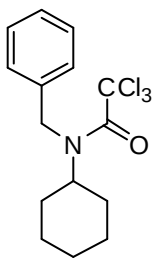
General. ^{1}H and ^{13}C NMR spectra were recorded in $CDCl_3$ solution. Chemical shifts are reported as δ values (ppm) relative to internal Me_4Si. All NMR data assignments are supported by COSY and HSQC experiments. Infrared spectra were recorded on a Nicolet 320 FT-IR spectrophotometer. TLC was performed on SiO_2 (silica gel 60 F_{254}, Merck). The spots were located by UV light or a 1% $KMnO_4$ aqueous solution. Chromatography refers to flash chromatography and was carried out on SiO_2 (silica gel 60, SDS, 230–400 mesh). CuCl (99.99%) was purchased from Sigma-Aldrich and was used as received. All reactions were carried out under an argon atmosphere with dry, freshly distilled solvents and under anhydrous conditions. Drying of the organic extracts during reaction work-up was performed over anhydrous Na_2SO_4. Microwave irradiation experiments were performed using a single-mode Discover System from CEM Corporation using standard Pyrex vessel (capacity 10 mL).

- **Preparation of trichloroacetamides 1**

a. Preparation of trichloroacetamide 1d



Cyclohexanone (3 g, 30.4 mmol), benzylamine (4.36 mL, 39.5 mmol) and sieves (4 Å, 6 g) in CH_2Cl_2 (30 mL) were stirred at rt for 4 h. The mixture was then filtered on a celite pad, concentrated and treated with $NaBH_4$ (1.73 g, 45.7 mmol) in MeOH (40 mL) at 0 ºC then at rt for 2 h. After elimination of methanol, brine was added and the mixture was extracted with CH_2Cl_2. The organics were dried and the solvent removed to yield a viscous oil which was treated with trichloroacetylchloride (5.11 mL, 45.5 mmol) and triethylamine (8.52 mL, 61.1 mmol) at rt overnight. Water was then added and the mixture extracted with CH_2Cl_2. The organics were dried, concentrated and purified by chromatography (hexane/CH_2Cl_2 50:50 to CH_2Cl_2) to yield **1d** (9.8 g, 96%).

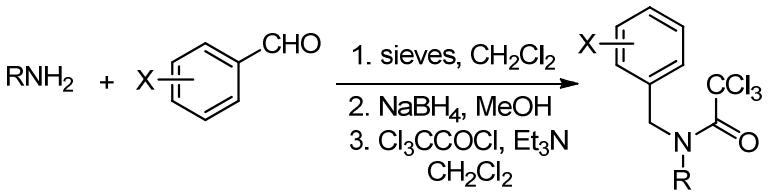


***N*-Benzyl-2,2,2-trichloro-*N*-cyclohexylacetamide (1d)**

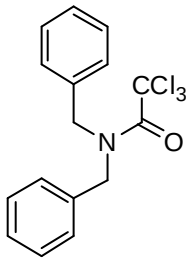
IR (NaCl, neat): 3086, 3063, 3030, 2936, 2859, 1971, 1951, 1873, 1854, 1806, 1775, 1667, 1495, 1453, 1418, 1362, 1325, 1284, 1243, 1161, 1141, 1029, 997, 891, 840, 823, 811, 736, 700, 670, 605, 531 cm^{-1}; ^{1}H

NMR ($CDCl_3$, 400 MHz): δ 1.07 (qt, 1H, *J* = 13.2, 3.6 Hz, H-4ax), 1.32 (dt, 2H, *J* = 13.2, 12.8 Hz, H-3ax and H-5ax), 1.49 (q, 2H, *J* = 12.4 Hz, H-2ax and H-6ax), 1.66 (d, 1H, *J* = 13.2 Hz, H-4eq), 1.80 (d, 2H, *J* = 12.8 Hz, H-3eq and H-5eq), 1.92 (d, 2H, *J* = 11.2 Hz, H-2eq and H-6eq), 4.47 (brt, 1H, *J* = 12.0 Hz, H-1), 4.60 (s, 2H, CH_2Ar),7.17-7.34 (m, 5H, ArH); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 25.1 (C-4), 25.6 (C3 and C-5), 30.9 (C-2 and C-6), 47.8 (CH_2Ar), 59.3 (C-1), 93.7 (CCl_3), 126.3, 126.8, 128.4 (Ar-CH), 137.6 (*ipso*-C), 160.6 (CO). HRMS (ESI-TOF): Calcd for $C_{15}H_{19}Cl_3NO$ 334.0527 (M^++1). Found 334.0530.

b. General procedure for the preparation of trichloroacetamides 1a-c, 1e-h



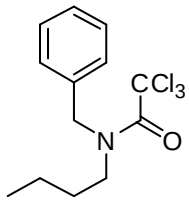
	X	R	
1a	H	Bn	78%
1b	H	Bu	96%
1c	H	*i*Pr	98%
1e	H	*t*Bu	85%
1f	3-Me	*t*Bu	56%
1g	2-Me	*t*Bu	41%
1h	3,5-diF	*t*Bu	51%



***N*,*N*-Dibenzyl-2,2,2-trichloroacetamide (1a)**[1]

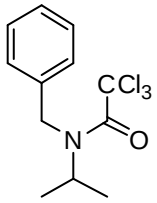
IR (NaCl, neat): 3063, 3027, 2919, 2870, 1954, 1863, 1812, 1679, 1494, 1452, 1420, 1361, 1304, 1282, 1225, 1198, 1160, 1077, 1030, 947, 848, 813, 739, 698, 665, 506 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz): δ 4.58 (s, 2H, CH_2Ar), 4.91 (s, 2H, CH_2Ar), 7.12-7.46 (m, 10H, ArH); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 50.2 (CH_2Ar), 52.0 (CH_2Ar), 93.2 (CCl_3), 127.2, 127.8, 127.9, 128.0, 128.8 (Ar-CH), 135.0 (*ipso*-C), 135.6 (*ipso*-C), 161.3 (CO). HRMS (ESI-TOF): Calcd for $C_{16}H_{15}Cl_3NO$ 342.0214 (M^++1). Found 342.0213.

[1] A. R. Surrey, M. K. Rukwid, *J. Am. Chem. Soc.* 1955, **77**, 3798-3801.



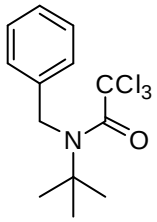
***N*-Benzyl-*N*-butyl-2,2,2-trichloroacetamide (1b)**

IR (NaCl, neat): 3083, 3027, 2958, 2934, 2875, 1975, 1955, 1875, 1810, 1661, 1492, 1453, 1421, 1375, 1306, 1282, 1255, 1217, 1168, 1125, 1080, 1003, 945, 928, 907, 844, 809, 740, 701, 667, 605, 510 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz): δ 0.90 (brs, 3H, CH_3), 1.29 (brs, 2H, CH_2), 1.57 and 1.71 (2 brs, 2H, CH_2), 3.31 and 3.61 (2 brs, 2H, CH_2), 4.70 and 4.97 (2 s, 2H, CH_2Ar), 7.22-7.40 (m, 5H, ArH); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 13.8 (CH_3), 19.9 (CH_2), 28.2 and 29.5 (CH_2), 48.1 and 48.7 (CH_2), 50.7 and 52.9 (CH_2Ar), 93.4 (CCl_3), 127.0, 127.6, 127.8, 128.8 (Ar-CH), 135.5 and 136.1 (*ipso*-C), 160.6 (CO). HRMS (ESI-TOF): Calcd for $C_{13}H_{17}Cl_3NO$ 308.0370 (M^++1). Found 308.0374.



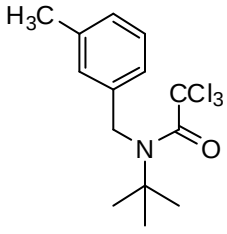
***N*-Benzyl-2,2,2-trichloro-*N*-isopropylacetamide (1c)**[1]

IR (NaCl, neat): 3087, 3065, 3033, 2973, 2933, 2877, 1951, 1861, 1810, 1669, 1495, 1451, 1415, 1373, 1344, 1291, 1202, 1180, 1128, 1068, 1030, 1013, 943, 882, 831, 810, 797, 725, 693, 668, 628, 535 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz): δ 1.28 (d, 6H, *J* = 6.4 Hz, 2 CH_3), 4.57 (s, 2H, CH_2Ar), 4.96 (m, 1H, CH), 7.18-7.38 (m, 5H, ArH); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 20.6 (CH_3), 46.7 (CH_2Ar), 51.0 (CH), 93.7 (CCl_3), 126.3, 126.9, 128.5 (Ar-CH), 137.6 (*ipso*-C), 160.5 (CO). HRMS (ESI-TOF): Calcd for $C_{12}H_{15}Cl_3NO$ 294.0214 (M^++1). Found 294.0204.



***N*-Benzyl-*N*-*tert*-butyl-2,2,2-trichloroacetamide (1e)**[2]

IR (NaCl, neat): 3062, 3031, 2966, 2919, 1977, 1961, 1900, 1882, 1820, 1677, 1486, 1449, 1383, 1365, 1354, 1256, 1226, 1185, 1145, 1074, 1026, 984, 912, 879, 838, 810, 739, 695, 665, 587, 502 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz): δ 1.42 (s, 9H, 3 CH_3), 5.04 (brs, 2H, CH_2Ar), 7.23-7.37 (m, 5H, ArH); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 28.1 (CH_3), 51.0 (CH_2Ar), 61.9 (C), 95.3 (CCl_3), 126.5, 127.2, 128.4 (Ar-CH), 138.6 (*ipso*-C), 160.8 (CO). HRMS (ESI-TOF): Calcd for $C_{13}H_{17}Cl_3NO$ 308.0370 (M^++1). Found 308.0384.

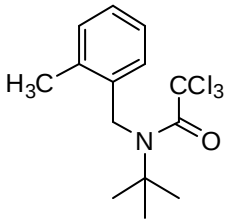


***N*-tert-Butyl-2,2,2-trichloro-*N*-(3-methylbenzyl)acetamide (1f)**[2]

IR (NaCl, neat): 3001, 2973, 2924, 2873, 1684, 1608, 1483, 1379, 1256, 1223, 1185, 1157, 1139, 1091, 1036, 983, 903, 885, 840, 812, 777, 742, 693, 666 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz): δ 1.43 (s, 9H, 3 CH_3), 2.34 (s, 3H, CH_3), 5.00 (brs, 2H, CH_2Ar), 7.07 (brs, 3H,

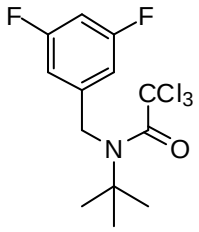
[2] J. Boivin, M. Yousfi, S. Z. Zard, *Tetrahedron lett.* 1997, **38**, 5985-5988

ArH), 7.22 (m, 1H, ArH); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 21.4 (CH_3), 28.1 (CH_3), 51.0 (CH_2Ar), 61.9 (C), 95.4 (CCl_3), 123.6, 127.1, 127.9, 128.3 (Ar-CH), 138.1 (C), 138.6 (*ipso*-C), 160.8 (CO). HRMS (ESI-TOF): Calcd for $C_{14}H_{19}Cl_3NO$ 322.0527 (M^++1). Found 322.0528.



***N*-tert-Butyl-2,2,2-trichloro-*N*-(2-methylbenzyl)acetamide (1g)**[2]

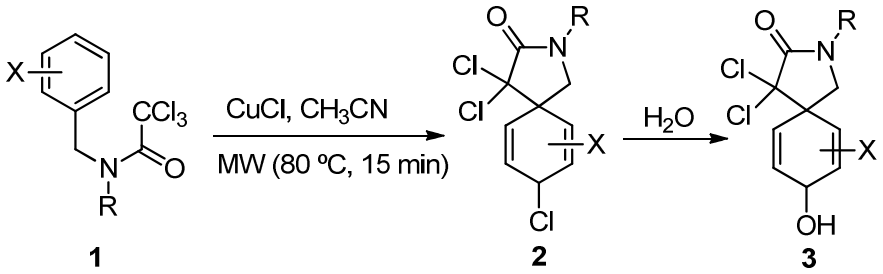
IR (NaCl, neat): 3067, 2969, 2930, 1679, 1606, 1476, 1460, 1382, 1365, 1350, 1254, 1226, 1183, 1145, 1101, 1050, 982, 885, 840, 823, 812, 768, 753, 696, 666, cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 1.45 (s, 9H, 3 CH_3), 2.28 (s, 3H, CH_3), 4.93 (brs, 2H, CH_2Ar), 7.12-7.24 (m, 3H, ArH), 7.34 (d, 1H, *J* = 7.6 Hz, ArH) ; ^{13}C NMR ($CDCl_3$, 100 MHz): δ 19.0 (CH_3), 27.8 (CH_3), 48.3 (CH_2Ar), 61.9 (C), 95.2 (CCl_3), 125.7, 126.7, 126.8, 130.3 (Ar-CH), 133.4 (C), 136.6 (*ipso*-C), 160.8 (CO). HRMS (ESI-TOF): Calcd for $C_{14}H_{19}Cl_3NO$ 322.0527 (M^++1). Found 322.0529.



***N*-tert-Butyl-2,2,2-trichloro-*N*-(3,5-difluorobenzyl)acetamide (1h)**

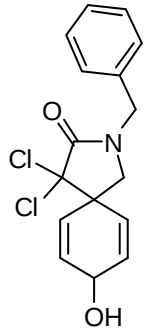
IR (NaCl, neat): 3078, 3064, 3018, 3000, 2976, 2931, 1668, 1625, 1598, 1475, 1451, 1384, 1365, 1351, 1319, 1304, 1256, 1219, 1181, 1153, 1120, 998, 983, 964, 887, 869, 849, 836, 814, 720, 669, 646 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 1.44 (s, 9H, 3 CH_3), 5.01 (brs, 2H, CH_2Ar), 6.72 (tt, 1H, *J* = 8.8, 2.4 Hz, ArH), 6.83 (m, 2H, ArH); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 28.1 (CH_3), 50.4 (CH_2Ar), 62.2 (C), 94.9 (CCl_3), 102.8 (t, 1C, *J* = 25 Hz, Ar-CH), 109.4 (d, 2C, *J* = 26.4 Hz, Ar-CH), 143.2 (t, 1C, *J* = 8.6 Hz, *ipso*-C), 160.6 (CO), 163.1 (dd, 2C, *J* = 247.7, 12.4 Hz, C-F). HRMS (ESI-TOF): Calcd for $C_{13}H_{15}Cl_3F_2NO$ 344.0182 (M^++1). Found 344.0185.

- **Representative procedure for the CuCl radical cyclization**



1 2 3

In a 10 mL vessel were placed acetamide **1e** (100 mg, 0.32 mmol), CuCl (19 mg, 0.19 mmol, 60%) and acetonitrile (1 mL).The mixture was heated with stirring to 80 ºC using microwave irradiation for 15 min. After reaching rt water[3] (1 mL) was added, the mixture was stirred for an additional hour and then extracted with CH_2Cl_2. The organics were dried, concentrated and purified by chromatography (CH_2Cl_2 to CH_2Cl_2/AcOEt 98:2) to give separable alcohols **3e** (70 mg, 74%) as a mixture of epimers in a 3:2 proportion.



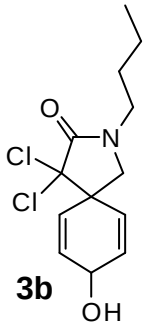
2-Benzyl-4,4-dichloro-8-hydroxy-2-azaspiro[4.5]deca-6,9-dien-3-one (3a)

Less polar: IR (NaCl, neat): 3422, 3223, 3029, 2925, 1717, 1480, 1428, 1307, 1249, 1073, 1028, 958, 917, 887, 846, 820, 743, 701, 677 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz): δ 1.43 (brs, 1H, OH), 3.15 (s, 2H, CH_2-1), 4.45 (brs, 1H, H-8), 4.54 (s, 2H, CH_2Ar), 5.88 (dq, 2H, *J* = 10.4, 1.6 Hz, H-6 and H-10), 6.19 (ddt, 2H, *J* = 10.4, 3.6, 2 Hz, H-7 and H-9) ; ^{13}C NMR ($CDCl_3$, 100 MHz): δ 47.9 (CH_2Ar), 49.3 (C-5), 53.8 (C-1), 62.0 (C-8), 88.2 (C-4), 126.7 (C-6 and C-10), 128.3, 128.4, 129.0 (Ar-CH), 132.4 (C-7 and C-9), 134.5 (*ipso*-C), 165.8 (C-3). HRMS (ESI-TOF): Calcd for $C_{16}H_{16}Cl_2NO_2$ 324.0553 (M^++1). Found 324.0558.

More polar: IR (NaCl, neat): 3393, 3063, 3032, 2923, 2883, 2855, 1717, 1479, 1430, 1360, 1306, 1246, 1075, 1026, 956, 883, 849, 825, 739, 701, 677 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz): δ 1.65 (brs, 1H, OH), 3.19 (s, 2H, CH_2-1), 4.55 (s, 2H, CH_2Ar), 4.62 (brs, 1H, H-8), 5.79 (dq, 2H, *J* = 10.4, 2 Hz, H-6 and H-10), 6.17 (ddt, 2H, *J* = 10.4, 3.6, 2 Hz, H-7 and H-9); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 47.9 (CH_2Ar), 49.7 (C-5), 53.3 (C-1), 62.3 (C-8), 88.5 (C-4), 125.7 (C-6 and C-10), 128.3, 128.4, 129.0 (Ar-CH), 133.4 (C-7 and C-9), 134.5 (*ipso*-C), 165.8 (C-3). HRMS (ESI-TOF): Calcd for $C_{16}H_{16}Cl_2NO_2$ 324.0553 (M^++1). Found 324.0556.

[3] In the case of **8** and **9**, 1 mL of methanol or allylamine were added respectively.

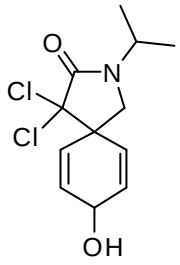
2-Butyl-4,4-dichloro-8-hydroxy-2-azaspiro[4.5]deca-6,9-dien-3-one (3b)



3b

Less polar. IR (NaCl, neat): 3428, 3038, 2959, 2931, 2871, 1716, 1479, 1429, 1370, 1306, 1248, 1213, 1188, 1130, 1073, 1032, 921, 888, 864, 845, 822, 761, 680 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz): δ 0.95 (t, 3H, *J* = 7.6 Hz, CH_3), 1.36 (m, 2H, CH_2), 1.54 (m, 2H, CH_2), 3.29 (s, 2H, CH_2-1), 3.37 (t, 2H, *J* = 7.6 Hz, CH_2), 4.53 (brs, 1H, H-8), 5.96 (dq, 2H, *J* = 10.4, 2 Hz, H-6 and H-10), 6.25 (ddt, 2H, *J* = 10.4, 3.6, 2 Hz, H-7 and H-9); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 13.7 (CH_3), 19.9 (CH_2), 28.9 (CH_2), 43.6 (CH_2), 49.5 (C-5), 54.5 (C-1), 62.0 (C-8), 90.6 (C-4), 126.9 (C-6 and C-10), 132.4 (C-7 and C-9), 165.2 (C-3). HRMS (ESI-TOF): Calcd for $C_{13}H_{18}Cl_2NO_2$ 290.0709 (M^++1). Found 290.0716.

More polar. IR (NaCl, neat): 3411, 3039, 2960, 2931, 2871, 1716, 1480, 1431, 1305, 1247, 1188, 1099, 1026, 949, 883, 826, 742 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz): δ 0.95 (t, 3H, *J* = 7.6 Hz, CH_3), 1.36 (m, 2H, CH_2), 1.54 (m, 2H, CH_2), 1.75 (brs, 1H, OH), 3.33 (s, 2H, CH_2-1), 3.39 (t, 2H, *J* = 7.6 Hz, CH_2), 4.66 (m, 1H, H-8), 5.89 (dq, 2H, *J* = 10.4, 2 Hz, H-6 and H-10), 6.24 (ddt, 2H, *J* = 10.4, 2.8, 2 Hz, H-7 and H-9); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 13.7 (CH_3), 19.9 (CH_2), 28.9 (CH_2), 43.7 (CH_2), 49.9 (C-5), 54.0 (C-1), 62.3 (C-8), 89.5 (C-4), 126.0 (C-6 and C-10), 133.3 (C-7 and C-9), 165.7 (C-3). HRMS (ESI-TOF): Calcd for $C_{13}H_{18}Cl_2NO_2$ 290.0709 (M^++1). Found 290.0711.

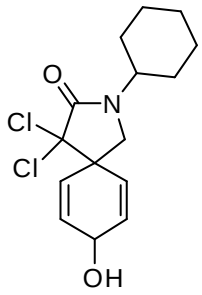


4,4-Dichloro-8-hydroxy-2-isopropyl-2-azaspiro[4.5]deca-6,9-dien-3-one (3c)

Less polar. IR (NaCl, neat): 3260, 3041, 2973, 2932, 2878, 2850, 1717, 1477, 1426, 1372, 1306, 1231, 1025, 918, 889, 858, 751, 694 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz): δ 1.17 (d, 6H, *J* = 7.2 Hz, 2 CH_3), 1.57 (d, 1H, *J* = 10.4 Hz, OH), 3.24 (s, 2H, CH_2-1), 4.40 (sept, 1H, *J* = 7.2 Hz, CH), 4.53 (dtt, 1H, *J* = 10.4, 4, 1.2 Hz, H-8), 5.95 (dq, 2H, *J* = 10.4, 1.6 Hz, H-6 and H-10), 6.25 (ddt, 2H, *J* = 10.4, 3.6, 2 Hz, H-7 and H-9); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 19.2 (CH_3), 44.2 (CH), 49.2 (C-5), 49.6 (C-1), 62.0 (C-8), 89.0 (C-4), 126.8 (C-6 and C-10), 132.5 (C-7 and C-9), 165.0 (C-3). HRMS (ESI-TOF): Calcd for $C_{12}H_{16}Cl_2NO_2$ 276.0553 (M^++1). Found 276.0557.

More polar. IR (NaCl, neat): 3403, 3038, 2975, 2933, 2878, 1717, 1477, 1426, 1369, 1306, 1231, 1194, 1130, 1018, 947, 889, 863, 826, 804, 744, 679 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz): δ 1.18 (d, 6H, *J* = 7.2 Hz, 2 CH_3), 1.84 (brd, 1H, *J* = 7.2 Hz, OH),

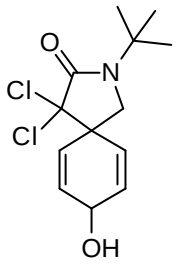
3.28 (s, 2H, CH_2-1), 4.41 (sept, 1H, *J* = 7.2 Hz, CH), 4.66 (brs, 1H, H-8), 5.87 (dq, 2H, *J* = 10.4, 2 Hz, H-6 and H-10), 6.24 (ddt, 2H, *J* = 10.4, 2.8, 2 Hz, H-7 and H-9); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 19.2 (CH_3), 44.2 (CH), 49.1 (C-1), 49.6 (C-5), 62.4 (C-8), 89.8 (C-4), 125.8 (C-6 and C-10), 133.4 (C-7 and C-9), 165.0 (C-3). HRMS (ESI-TOF): Calcd for $C_{12}H_{16}Cl_2NO_2$ 276.0553 (M^++1). Found 276.0554.



2-Cyclohexyl-4,4-dichloro-8-hydroxy-2-azaspiro[4.5]deca-6,9-dien-3-one (3d)

Less polar. IR (NaCl, neat): 3408, 3026, 2938, 2880, 2861, 1694, 1479, 1432, 1306, 1249, 1217, 1181, 1081, 1018, 954, 882, 856, 826, 759, 686, 612 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 1.09 (qt, 1H, *J* = 12.8, 3.6 Hz), 1.25-1.47 (m, 4H), 1.59 (brs, 1H, OH), 1.70 (dm, 1H, *J* = 12.8 Hz), 1.74-1.88 (m, 4H), 3.30 (s, 2H, CH_2-1), 3.99 (tt, 1H, *J* = 12, 4 Hz), 4.66 (brs, 1H, H-8), 5.87 (dq, 2H, *J* = 10.4, 2 Hz, H-6 and H-10), 6.23 (ddt, 2H, *J* = 10.4, 2.8, 2 Hz, H-7 and H-9); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 25.1 (CH_2), 25.2 (CH_2), 29.7 (CH_2), 49.8 (C-5), 50.2 (C-1), 52.0 (CH), 62.4 (C-8), 89.9 (C-4), 125.9 (C-6 and C-10), 133.3 (C-7 and C-9), 165.1 (C-3). HRMS (ESI-TOF): Calcd for $C_{15}H_{20}Cl_2NO_2$ 316.0866 (M^++1). Found 316.0870.

More polar. IR (NaCl, neat): 3244, 3031, 2930, 2854, 1715, 1477, 1449, 1425, 1338, 1306, 1247, 1215, 1191, 1143, 1080, 1030, 949, 919, 890, 853, 820, 759, 679, 632, 545 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 1.08 (qt, 1H, *J* = 12.8, 3.6 Hz), 1.24-1.46 (m, 4H), 1.56 (brs, 1H, OH), 1.69 (dm, 1H, *J* = 12.8 Hz), 1.74-1.88 (m, 4H), 3.26 (s, 2H, CH_2-1), 3.99 (tt, 1H, *J* = 12, 4 Hz), 4.52 (brs, 1H, H-8), 5.94 (dq, 2H, *J* = 10.4, 2 Hz, H-6 and H-10), 6.24 (ddt, 2H, *J* = 10.4, 4, 2 Hz, H-7 and H-9); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 25.1 (CH_2), 25.2 (CH_2), 29.6 (CH_2), 49.4 (C-5), 50.6 (C-1), 52.0 (CH), 62.1 (C-8), 89.0 (C-4), 126.9 (C-6 and C-10), 132.4 (C-7 and C-9), 165.1 (C-3). HRMS (ESI-TOF): Calcd for $C_{15}H_{20}Cl_2NO_2$ 316.0866 (M^++1). Found 316.0870.

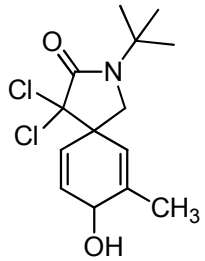


2-*tert*-Butyl-4,4-dichloro-8-hydroxy-2-azaspiro[4.5]deca-6,9-dien-3-one (3e)

Less polar: IR (NaCl, neat): 3529, 3399, 3284, 3039, 2977, 2934, 2870, 1720, 1478,1399, 1365, 1305, 1246, 1222, 1032, 1010, 895, 872, 829, 775, 739, 681, 582, 525 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 1.43 (s, 9H, 3 CH_3), 1.98 (brs, 1H, OH), 3.39 (s, 2H, CH_2-1), 4.66 (brs, 1H, H-8), 5.88 (dq, 2H, *J* = 10.4, 2 Hz, H-6 and H-10), 6.23 (ddt, 2H, *J* = 10.4, 3, 2 Hz, H-7 and H-9); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 27.1 (CH_3), 48.9 (C-5), 52.3 (C-1), 55.4 (C), 62.3 (C-8), 90.5

(C-4), 125.9 (C-6 and C-10), 133.3 (C-7 and C-9), 165.3 (C-3). HRMS (ESI-TOF): Calcd for $C_{13}H_{18}Cl_2NO_2$ 290.0709 (M^++1). Found 290.0719.

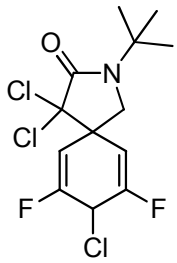
More polar: IR (NaCl, neat): 3254, 3034, 2972, 2871, 1713, 1474, 1400, 1367, 1306, 1245, 1216, 1015, 923, 885, 777, 741, 694, 682, 563, 516 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz): δ 1.43 (s, 9H, 3 CH_3), 1.58 (brs, 1H, OH), 3.34 (s, 2H, CH_2-1), 4.52 (brs, 1H, H-8), 5.96 (dq, 2H, *J* = 10.4, 1.6 Hz, H-6 and H-10), 6.24 (ddt, 2H, *J* = 10.4, 3.6, 2 Hz, H-7 and H-9); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 27.1 (CH_3), 48.6 (C-5), 52.7 (C-1), 55.4 (C), 62.1 (C-8), 89.7 (C-4), 126.9 (C-6 and C-10), 132.4 (C-7 and C-9), 165.3 (C-3). HRMS (ESI-TOF): Calcd for $C_{13}H_{18}Cl_2NO_2$ 290.0709 (M^++1). Found 290.0698.



2-*tert*-Butyl-4,4-dichloro-8-hydroxy-7-methyl-2-azaspiro[4.5]deca-6,9-dien-3-one (3f)

Less polar: IR (NaCl, neat): 3434, 3033, 2976, 2917, 2883, 1705, 1459, 1398, 1367, 1311, 1266, 1240, 1214, 1149, 1087, 1038, 1010, 946, 892, 857, 840, 792, 769, 730, 693, 676 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz): δ 1.43 (s, 9H, 3 CH_3), 1.67 (d, 1H, *J* = 8 Hz, OH), 1.96 (s, 3H, CH_3), 3.34 (d, 1H, *J* = 10 Hz, CH_2-1), 3.37 (d, 1H, *J* = 10 Hz, CH_2-1), 4.48 (brd, 1H, *J* = 6.8 Hz, H-8), 5.60 (m, 1H, H-6), 5.87 (dt, 1H, *J* = 10.4, 2 Hz, H-10), 6.19 (dd, H, *J* = 10.4, 3.2 Hz, H-9); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 20.0 (CH_3), 27.1 (CH_3), 49.9 (C-5), 52.5 (C-1), 55.4 (C), 65.5 (C-8), 90.9 (C-4), 121.2 (C-6), 126.2 (C-10), 132.9 (C-9), 140.1 (C-7), 165.5 (C-3). HRMS (ESI-TOF): Calcd for $C_{14}H_{20}Cl_2NO_2$ 304.0866 (M^++1). Found 304.0862.

More polar: IR (NaCl, neat): 3434, 2975, 2916, 2883, 1715, 1474, 1398, 1367, 1305, 1266, 1240, 1215, 1148, 1056, 1020, 894, 831, 768, 732, 695, 679, cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz): δ 1.30 (d, 1H, *J* = 10.8 Hz, OH), 1.43 (s, 9H, 3 CH_3), 1.96 (dd, 3H, *J* = 1.6, 0.4 Hz, CH_3), 3.32 (d, 1H, *J* = 10 Hz, CH_2-1), 3.34 (d, 1H, *J* = 10 Hz, CH_2-1), 4.30 (dd, 1H, *J* = 10.8, 4 Hz, H-8), 5.62 (m, 1H, H-6), 5.90 (ddd, 1H, *J* = 10.4, 2.4, 1.2 Hz, H-10), 6.22 (dd, H, *J* = 10.4, 3.6 Hz, H-9); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 20.4 (CH_3), 27.1 (CH_3), 49.6 (C-5), 52.8 (C-1), 55.4 (C), 65.6 (C-8), 90.0 (C-4), 121.9 (C-6), 127.2 (C-10), 132.2 (C-9), 140.3 (C-7), 165.5 (C-3). HRMS (ESI-TOF): Calcd for $C_{14}H_{20}Cl_2NO_2$ 304.0866 (M^++1). Found 304.0865.



2-*tert*-Butyl-4,4,8-trichloro-7,9-difluoro-2-azaspiro[4.5]deca-6,9-dien-3-one (2h)

Less polar: IR (NaCl, neat): 2977, 1716, 1464, 1390, 1369, 1346, 1311, 1258, 1226, 1130, 1010, 973, 953, 934, 904, 866, 838, 758, 745, 677 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 1.44 (s, 9H, 3 CH_3), 3.47 (s, 2H, CH_2-1), 5.09 (t, 1H, *J* = 2.4 Hz, H-8), 5.71 (dm, 2H, *J* = 14 Hz, H-6 and H-10); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 27.1 (CH_3), 47.3 (t, *J* = 30 Hz, C-8), 51.0 (t, *J* = 7.7 Hz, C-5), 51.8 (C-1), 55.9 (C), 89.2 (C-4), 106.2 (dd, 2C, J = 16.3, 2.3 Hz, C-6 and C-10), 155.5 (dd, 2C, J = 260.1, 11.7 Hz, C-7 and C-9), 164.4 (C-3). HRMS (ESI-TOF): Calcd for $C_{13}H_{15}F_2Cl_3NO$ 344.0181 (M^++1). Found 344.0180.

More polar: IR (NaCl, neat): 3055, 2983, 2940, 1720, 1462, 1390, 1369, 1265, 1226, 1130, 907, 868, 740, 705 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 1.44 (s, 9H,CH_3), 3.44 (s, 2H, CH_2-1), 5.02 (t, 1H, *J* = 23.6 Hz, H-8), 5.66 (dm, 2H, *J* = 13.6 Hz, H-6 and H-10); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 27.1 (CH_3), 47.1 (t, *J* = 30 Hz, C-8), 51.2 (t, 1C, *J* = 7.7 Hz, C-5), 52.5 (t, 1C, *J* = 3.1 Hz, C-1), 55.8 (C), 88.4 (C-4), 106.5 (dd, 2C, *J* = 16.3, 2.3 Hz, C-6 and C-10), 155.7 (dd, 2C, *J* = 260.1, 11.6 Hz, C-7 and C-9), 164.6 (C-3). HRMS (ESI-TOF): Calcd for $C_{13}H_{15}F_2Cl_3NO$ 344.0181 (M^++1). Found 344.0182.

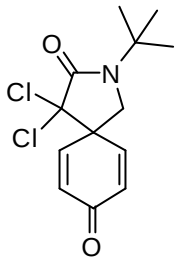
- **Oxidation of alcohols 3e**

Method A:

A suspension of alcohols **3e** (50 mg, 0.17 mmol) and Dess-Martin periodinane (146 mg, 0.34 mmol) in CH_2Cl_2 (2 mL) was stirred at rt for 2h. The mixture was then quenched with 1 N NaOH solution and extracted with CH_2Cl_2. The organic layers were washed with a saturated $Na_2S_2O_3$ solution, dried and concentrated to yield pure **4** (48 mg, 97%).

Method B:

To a solution of alcohols **3e** (65 mg, 0.22 mmol) in CH_2Cl_2 (1.5 mL) were added successively, at rt and under vigorous stirring TEMPO (2 mg, 0.011 mmol, 5%), NaBr (23 mg, 0.22 mmol), a solution of $NaHCO_3$ (47 mg, 0.55 mmol) and 10% NaClO in active chlorine (0.42 mL) and the mixture was stirred at rt for 1 h. After this time the mixture was treated with saturated $NaHCO_3$ solution, extracted with CH_2Cl_2 and the organics dried to yield **4** alone (58 mg, 90%).

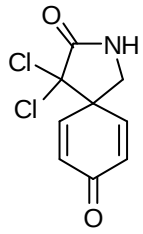


2-*t*ert-Butyl-4,4-dichloro-2-azaspiro[4.5]deca-6,9-diene-3,8-dione (4)

IR (NaCl, neat): 3054, 3024, 2938, 2915, 2882, 1713, 1669, 1632, 1609, 1513, 1462, 1403, 1368, 1322, 1244, 1183, 1154, 1096, 1072, 1032, 1008, 928, 870, 840, 826, 770 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 1.47 (s, 9H, 3 CH_3), 3.51 (s, 2H, CH_2-1), 6.51 (dm, 2H, *J* = 10 Hz, H-6 and H-10), 6.97 (dm, 2H, *J* = 10 Hz, H-7 and H-9); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 27.1 (CH_3), 50.0 (C-1), 51.3 (C-5), 56.0 (C), 88.0 (C-4), 132.4 (C-6 and C-10), 143.6 (C-7 and C-9), 164.5 (C-3), 184.1 (C-8). HRMS (ESI-TOF): Calcd for $C_{13}H_{16}Cl_2NO_2$ 288.0553 (M^++1). Found 288.0562.

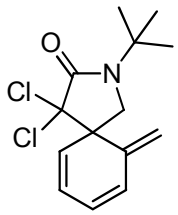
- ***tert*-Butyl group cleavage**

A mixture of **4** (56 mg, 0.19 mmol) and H_2SO_4 96% (0.5 mL) was heated at 55 ºC for 1 h. The reaction was then let to reach rt, diluted with cold water and extracted with CH_2Cl_2. The organic phase was concentrated and the residue purified by chromatography (CH_2Cl_2/AcOEt 75:25) to yield **5** (34 mg, 76%).



4,4-Dichloro-2-azaspiro[4.5]deca-6,9-diene-3,8-dione (5)

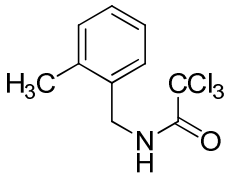
IR (NaCl, neat): 3214, 3154, 3047, 2986, 2873, 2798, 1739, 1668, 1627, 1408, 1366, 1322, 1272, 1252, 1215, 1187, 1093, 1062, 978, 866, 825, 726 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 3.57 (d, 2H, *J* = 1.2 Hz, CH_2-1), 6.53 (dm, 2H, *J* = 10 Hz, H-7 and H-9), 7.04 (dm, 2H, *J* = 10 Hz, H-6 and H-10), 7.23 (brs, 1H, NH); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 47.5 (C-1), 53.8 (C-5), 86.2 (C-4), 132.4 (C-7 and C-9), 143.1 (C-6 and C-10), 167.8 (C-3), 184.0 (C-8). HRMS (ESI-TOF): Calcd for $C_9H_8Cl_2NO_2$ 231.9927 (M^++1). Found 231.9918.



2-*tert*-Butyl-4,4-dichloro-10-methylene-2-azaspiro[4.5]deca-6,8-dien-3-one (6)

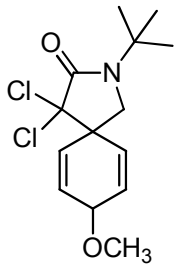
IR (NaCl, neat): 3042, 2959, 2920, 2872, 1712, 1596, 1563, 1476, 1403, 1369, 1296, 1284, 1274, 1258, 1214, 1151, 1121, 1097, 1011, 925, 896, 882, 867, 836, 766, 736, 697, 683, 653 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 1.45 (s, 9H, 3 CH_3), 3.39 (d, 1H, *J* = 10.4 Hz, CH_2-1), 3.56 (d, 1H, *J* = 10.4 Hz, CH_2-1), 5.48 (s, 1H, H_2C=), 5.50 (s, 1H, H_2C=), 5.79 (d, 1H, *J* = 9.6 Hz, HC=), 5.91 (ddm, 1H, *J* = 9.6, 5.6 Hz, HC=), 6.22 (d, 1H, *J* = 9.6 Hz, HC=), 6.30 (ddd, 1H, *J* = 9.6, 5.6, 1.2 Hz, HC=); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 27.1 (CH_3), 51.8 (C-5), 53.7 (C-1),

55.5 (C), 120.8 (H_2C=), 121.7 (HC=), 127.0 (HC=), 127.3 (HC=), 129.9 (HC=), 141.7 (C-10), 165.6 (C-3). HRMS (ESI-TOF): Calcd for $C_{14}H_{18}Cl_2NO$ 286.0759 (M^++1). Found 286.0762.



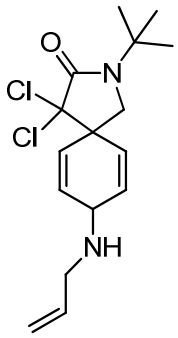
2,2,2-Trichloro-*N*-(2-methylbenzyl)acetamide (7)

IR (NaCl, neat): 3336, 3021, 2926, 1697, 1518, 1462, 1356, 1246, 1051, 820, 751, 736, 679, 640 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz): δ 2.36 (s, 3H, CH_3), 4.55 and 4.57 (2 s, 2H, CH_2Ar), 6.75 (brs, 1H, NH), 7.19-7.30 (m, 4H, ArH); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 19.0 (CH_3), 43.8 (CH_2Ar), 92.0 (CCl_3), 126.5, 128.5, 128.7, 130.9, (Ar-CH), 133.9 (C), 136.7 (*ipso*-C), 161.6 (CO). HRMS (ESI-TOF): Calcd for $C_{10}H_{11}Cl_3NO$ 265.9901 (M^++1). Found 265.9902.



2-*tert*-Butyl-4,4-dichloro-8-methoxy-2-azaspiro[4.5]deca-6,9-dien-3-one (8)

IR (NaCl, neat): 3037, 2976, 2934, 2821, 1722, 1464, 1396, 1367, 1304, 1266, 1239, 1217, 1151, 1089, 1011, 946, 919, 897, 870, 839, 825, 774, 735, 681 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz): mixture of diastereomers δ 1.42 and 1.43 (2 s, 9H each, 3 CH_3), 3.30 (s, 3H, CH_3O), 3.31 (s, 2H, CH_2-1), 3.38 (s, 2H, CH_2-1), 3.39 (s, 3H, CH_3O), 4.37 (m, 1H, H-8), 4.50 (m, 1H, H-8), 5.95 (dq, 2H, *J* = 10.8, 2 Hz, H-6 and H-10), 6.08 (dm, 2H, *J* = 10.8 Hz, H-6 and H-10), 6.13 (dm, 2H, *J* = 10.8 Hz, H-7 and H-9), 6.23 (dm, 2H, *J* = 10.8 Hz, H-7 and H-9); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 27.1 (2 CH_3), 48.5 and 49.2 (C-5), 52.3 and 53.1 (C-1), 53.3 and 55.1 (CH_3O), 55.4 (2 C), 69.0 and 70.1 (C-8), 90.6 (C-4), 127.1 and 128.5 (C-6 and C-10), 130.4 and 130.9 (C-7 and C-9), 165.3 and 165.5 (C-3). HRMS (ESI-TOF): Calcd for $C_{14}H_{20}Cl_2NO_2$ 304.0866 (M^++1). Found 304.0860.

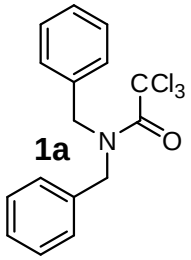


8-Allylamino-2-*tert*-butyl-4,4-dichloro-2-azaspiro[4.5]deca-6,9-dien-3-one (9)

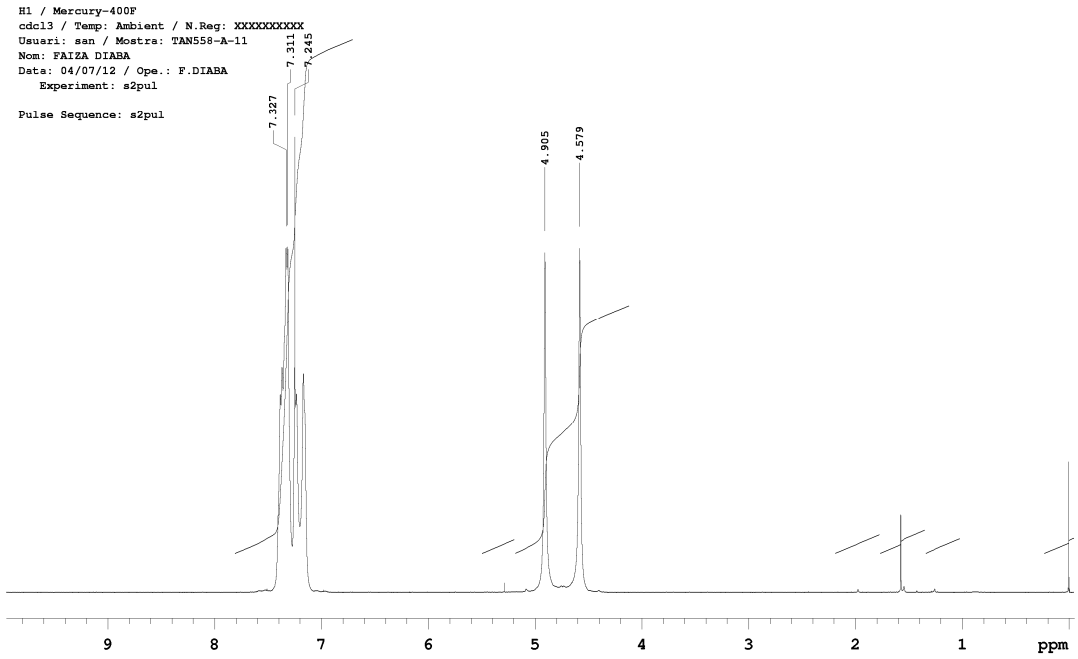
Less polar: IR (NaCl, neat): 3324, 3077, 3032, 2975, 2915, 2879, 1719, 1674, 1555, 1459, 1396, 1366, 1301, 1239, 1217, 1149, 1095, 1011, 917, 870, 826, 775, 739, 680 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 1.43 (s, 9H, 3 CH_3), 1.50 (brs, 1H, NH), 3.31 (d, 2H, *J* = 6 Hz, CH_2N), 3.35 (s, 2H, CH_2-1), 3.81 (m, 1H, H-8), 5.12 (ddd, 1H, *J* = 10, 1.6, 1.2 Hz, CH_2=), 5.22 (dq, 1H, *J* = 17.2, 1.6 Hz, CH_2=), 5. 85 (ddm, 2H, *J* = 10, 2 Hz, H-6 and H-10), 5.92 (ddt, 1H, *J* = 17.2, 10, 6 Hz, CH=), 6.17 (ddm, 2H, *J* = 10, 2.8 Hz, H-7 and H-9); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 27.2 (CH_3), 48.7 (CH_2N), 48.9 (C-5), 50.6 (C-8), 52.9 (C-1), 55.3 (C), 90.1 (C-4), 116.4 (CH_2=), 125.4 (C-6 and C-10), 133.1 (C-7 and C-9), 136.6 (CH=), 165.5 (C-3). HRMS (ESI-TOF): Calcd for $C_{16}H_{23}Cl_2N_2O$ 329.1182 (M^++1). Found 329.1179.

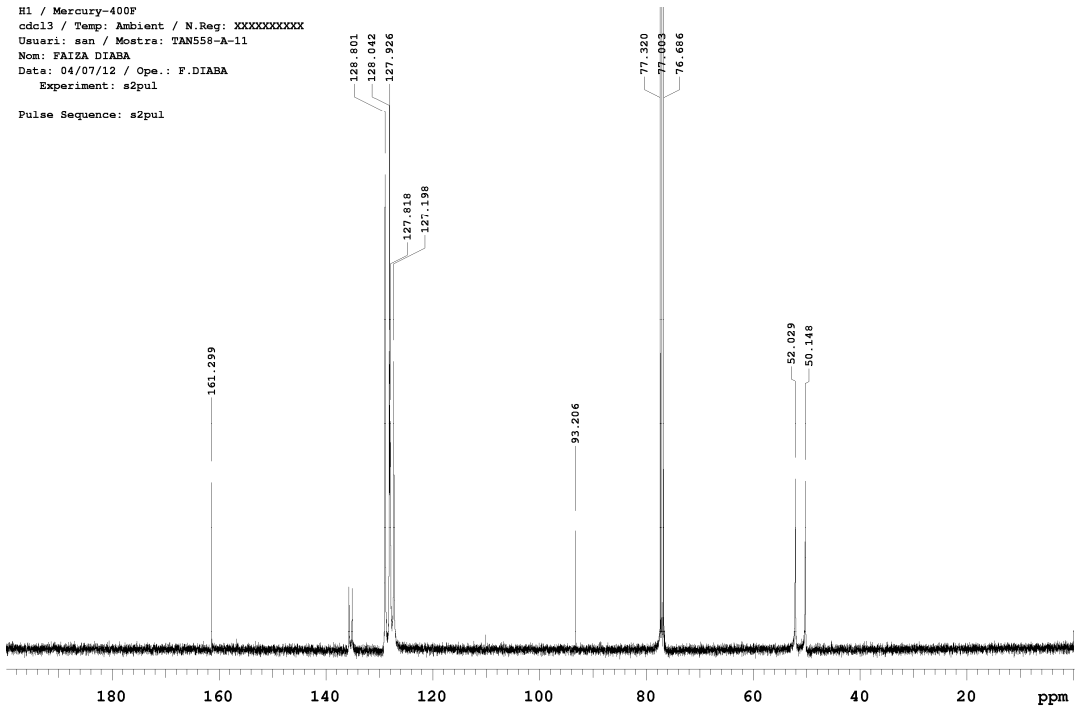
More polar: IR (NaCl, neat): 3324, 3077, 2975, 2929, 2879, 1721, 1461, 1395, 1366, 1302, 1218, 1150, 1094, 1011, 918, 870, 823, 778, 740, 682 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 1.42 (s, 9H, 3 CH_3), 1.55 (brs, 1H, NH), 3.33 (s, 2H, CH_2-1), 3.35 (s, 2H, CH_2N), 3.75 (brs, 1H, H-8), 5.11 (d, 1H, *J* = 9.6 Hz, CH_2=), 5.21 (d, 1H, *J* = 17.2 Hz, CH_2=), 5.90 (d, 2H, *J* = 10, 2 Hz, H-6 and H-10), 5.90 (m, 1H, CH=), 6.18 (dd, 2H, *J* = 10, 3.2 Hz, H-7 and H-9); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 27.1 (CH_3), 48.6 (CH_2N), 48.6 (C-5), 50.4 (C-8), 53.3 (C-1), 55.3 (C), 90.3 (C-4), 116.2 (CH_2=), 125.9 (C-6 and C-10), 132.6 (C-7 and C-9), 136.8 (CH=), 165.5 (C-3). HRMS (ESI-TOF): Calcd for $C_{16}H_{23}Cl_2N_2O$ 329.1182 (M^++1). Found 329.1179.

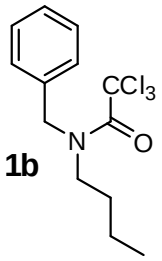
- **Copies of ^{1}H NMR and ^{13}C NMR spectra of compounds 1-5**



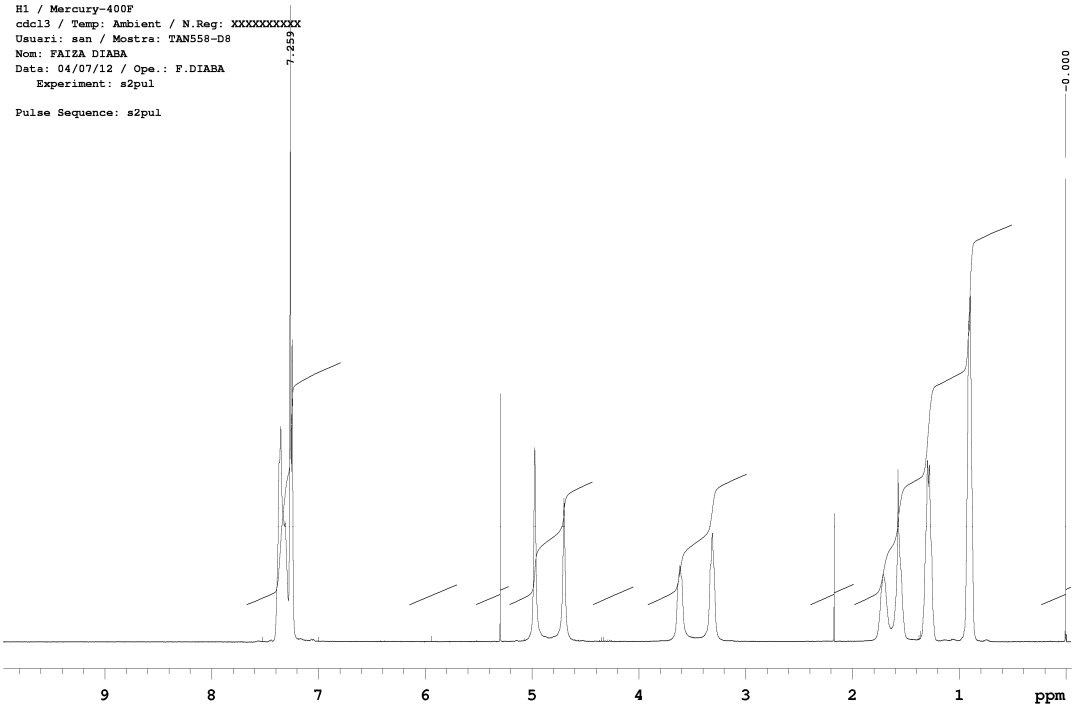
1a

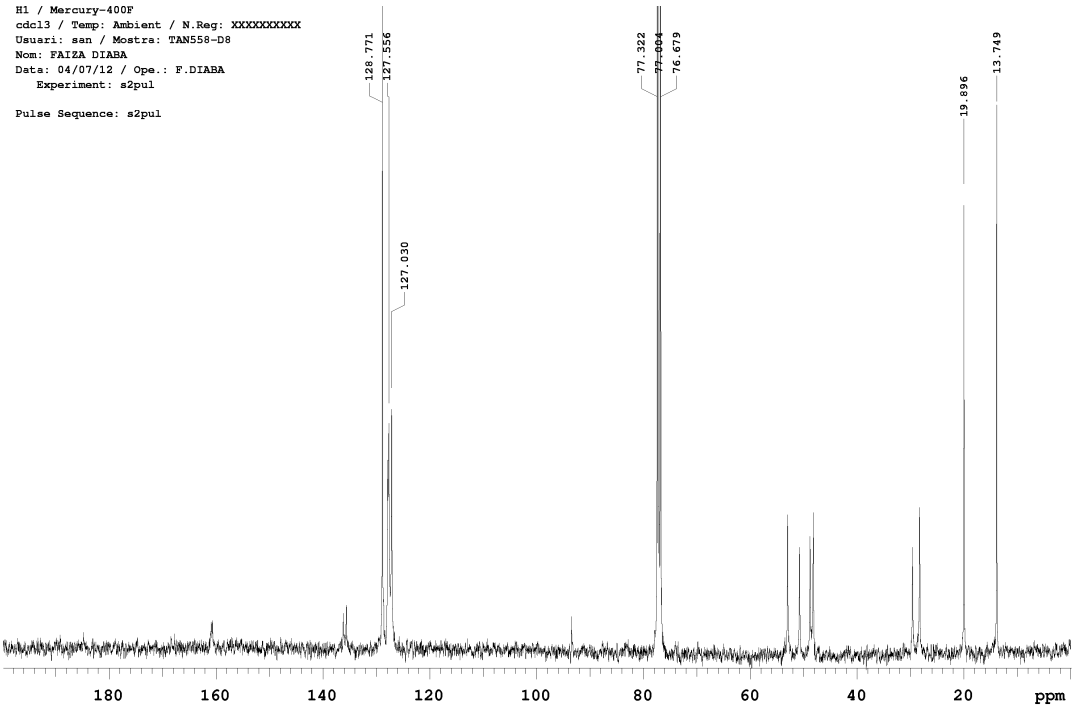


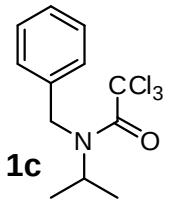



CCl3
N
O

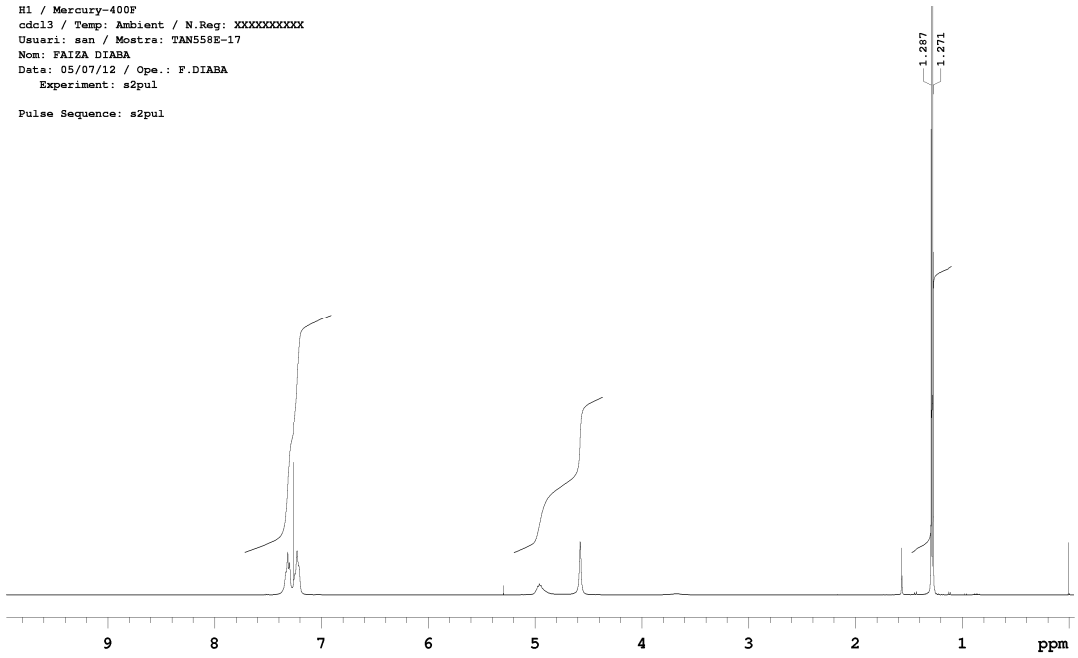
1b

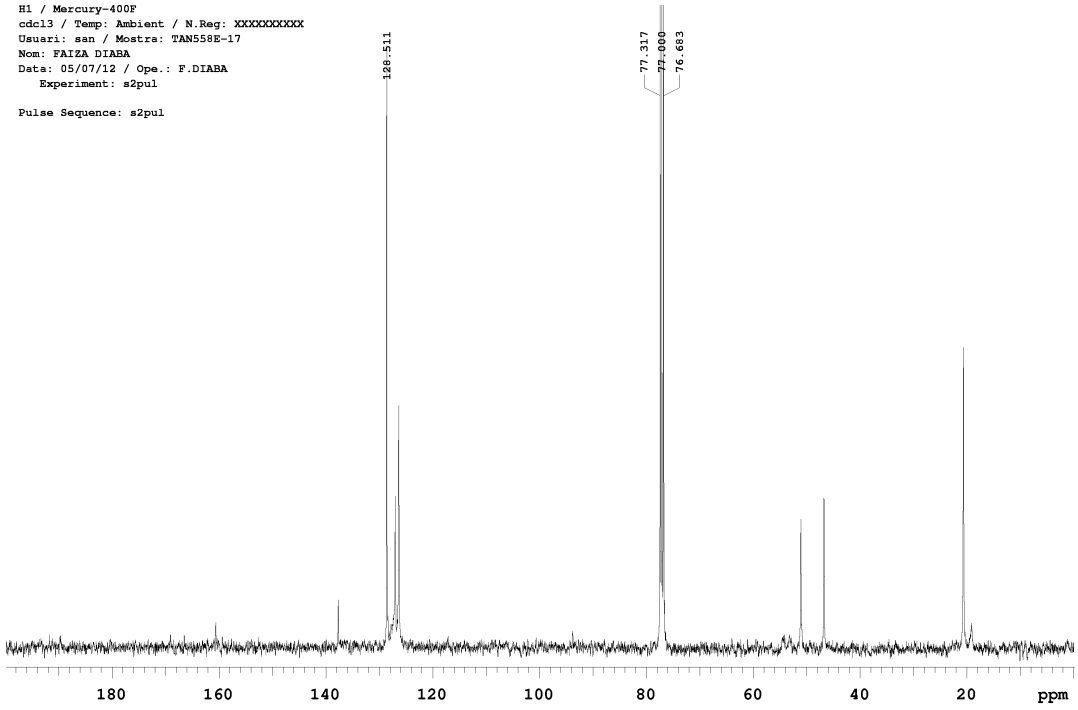

H1 / Mercury-400F
cdcl3 / Temp: Ambient / N.Reg: XXXXXXXXXX
Usuari: san / Mostra: TAN558-D8
Nom: FAIZA DIABA
Data: 04/07/12 / Ope.: F.DIABA
Experiment: s2pul
Pulse Sequence: s2pul
7.259
0.000
9
8
7
6
5
4
3
2
1
ppm

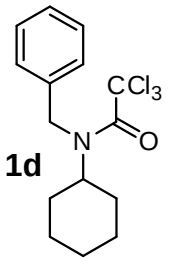

H1 / Mercury-400F
cdcl3 / Temp: Ambient / N.Reg: XXXXXXXXXX
Usuari: san / Mostra: TAN558-D8
Nom: FAIZA DIABA
Data: 04/07/12 / Ope.: F.DIABA
Experiment: s2pul
Pulse Sequence: s2pul
128.771
127.556
127.030
77.322
77.004
76.679
19.896
13.749
180
160
140
120
100
80
60
40
20
ppm


CCl3
N
O

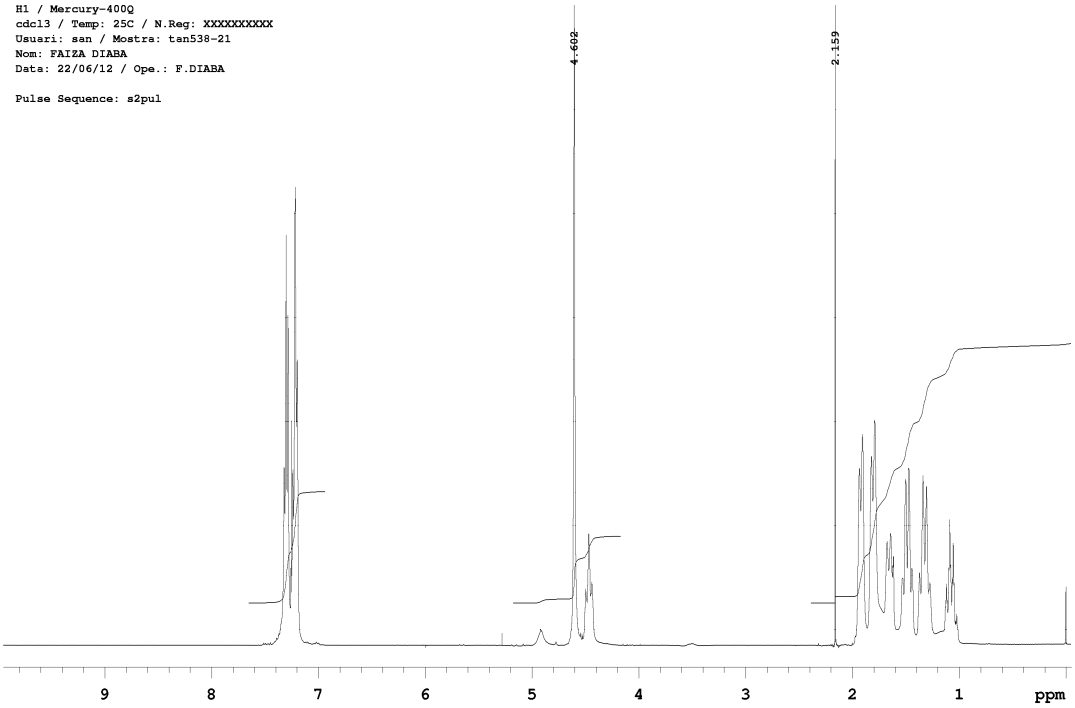
1c

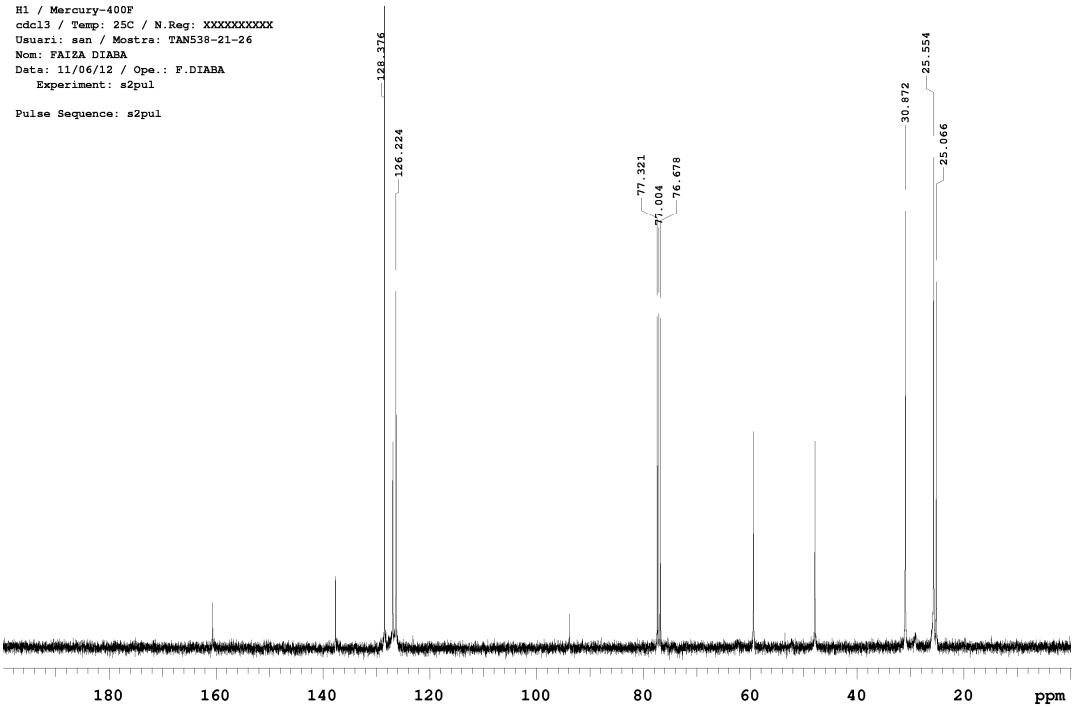

H1 / Mercury-400F
cdcl3 / Temp: Ambient / N.Reg: XXXXXXXXXX
Usuari: san / Mostra: TAN558E-17
Nom: FAIZA DIABA
Data: 05/07/12 / Ope.: F.DIABA
Experiment: s2pul
Pulse Sequence: s2pul
1.287
1.271
9
8
7
6
5
4
3
2
1
ppm

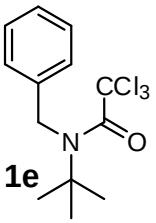

H1 / Mercury-400F
cdcl3 / Temp: Ambient / N.Reg: XXXXXXXXXX
Usuari: san / Mostra: TAN558E-17
Nom: FAIZA DIABA
Data: 05/07/12 / Ope.: F.DIABA
Experiment: s2pul
Pulse Sequence: s2pul
128.511
77.317
77.000
76.683
180
160
140
120
100
80
60
40
20
ppm


CCl3
O
N

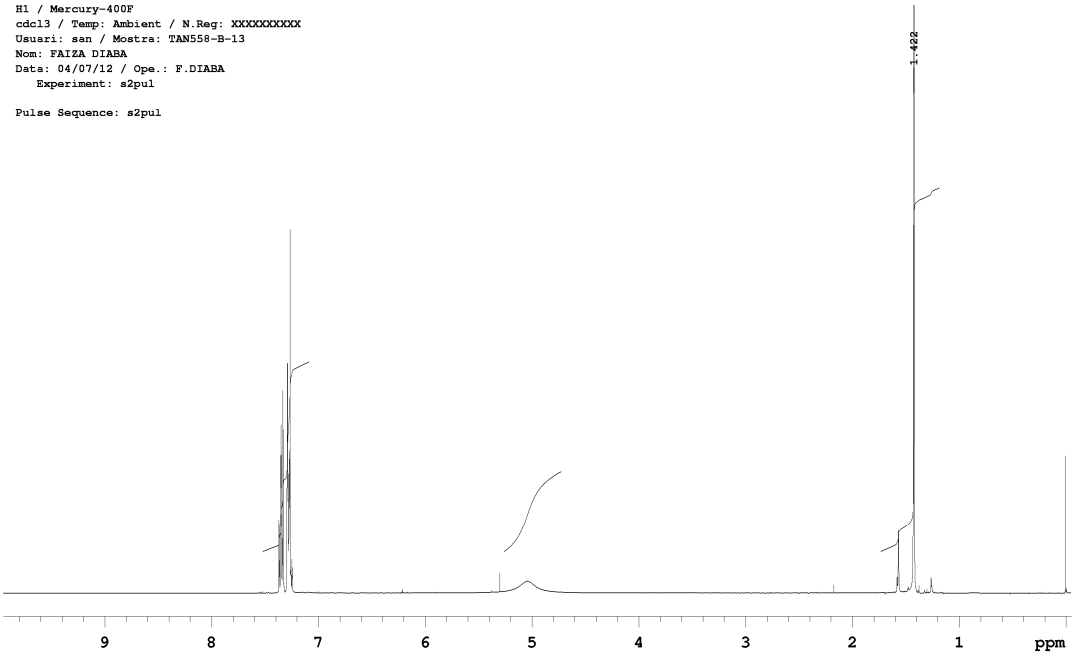
1d

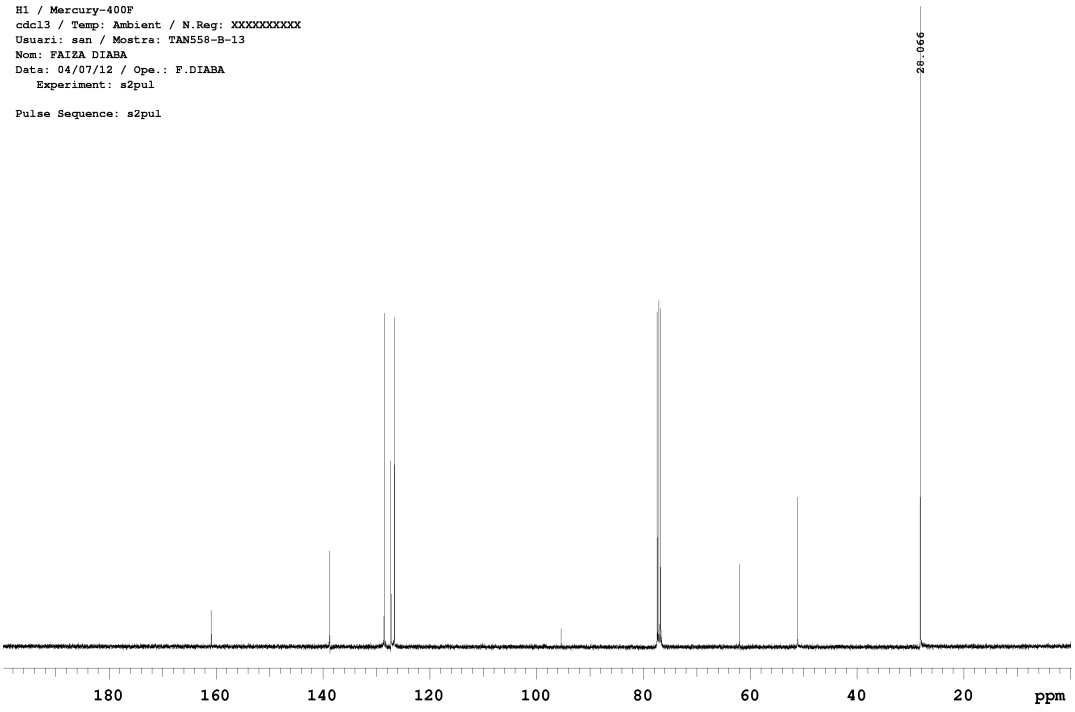

H1 / Mercury-400Q
cdcl3 / Temp: 25C / N.Reg: XXXXXXXXXX
Usuari: san / Mostra: tan538-21
Nom: FAIZA DIABA
Data: 22/06/12 / Ope.: F.DIABA
Pulse Sequence: s2pul
4.602
2.159
9
8
7
6
5
4
3
2
1
ppm

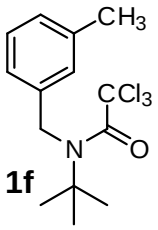

H1 / Mercury-400F
cdcl3 / Temp: 25C / N.Reg: XXXXXXXXXX
Usuari: san / Mostra: TAN538-21-26
Nom: FAIZA DIABA
Data: 11/06/12 / Ope.: F.DIABA
Experiment: s2pul
Pulse Sequence: s2pul
128.376
126.224
77.321
77.004
76.678
30.872
25.554
25.066
180
160
140
120
100
80
60
40
20
ppm


CCl3
N
O

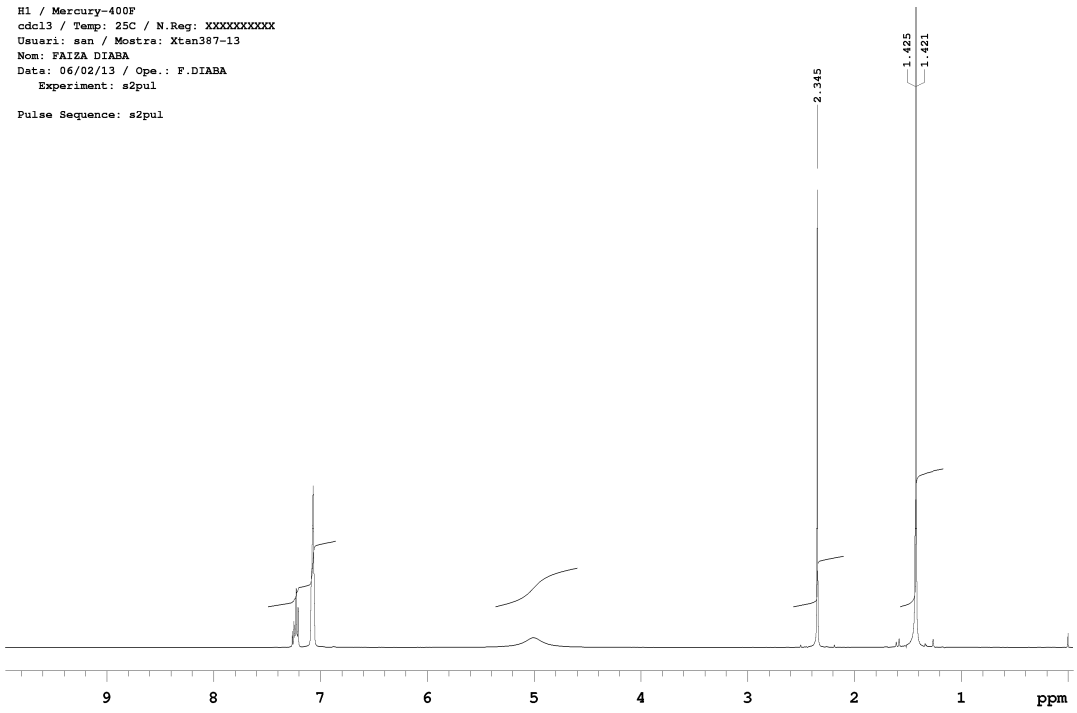
1e

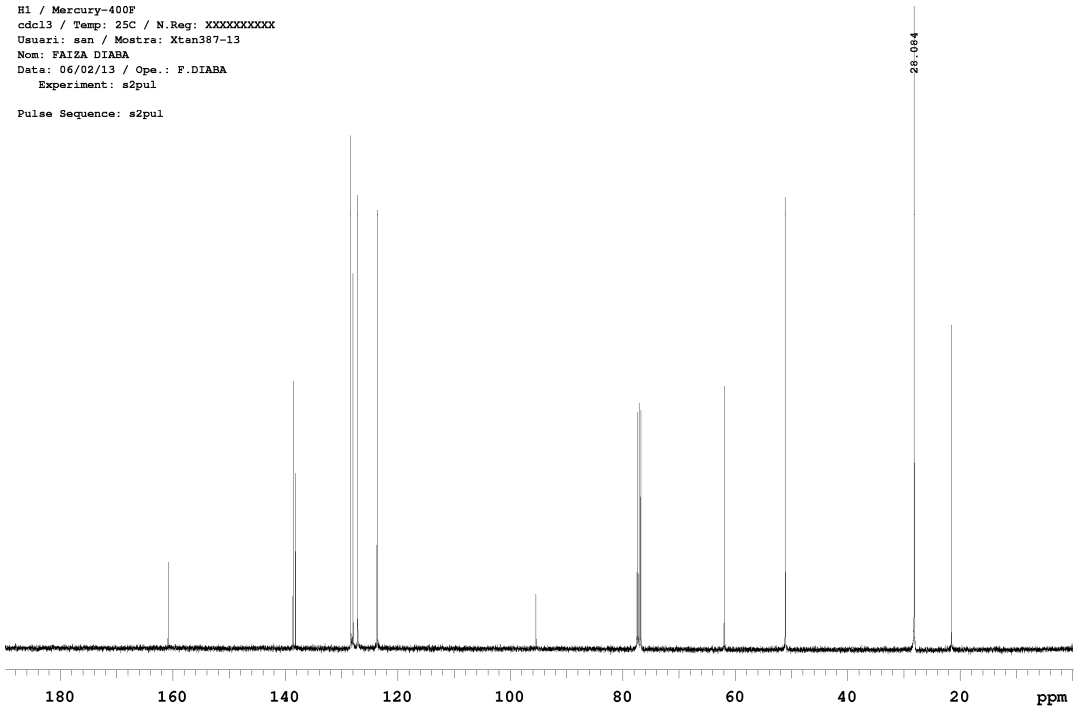

H1 / Mercury-400F
cdcl3 / Temp: Ambient / N.Reg: XXXXXXXXXX
Usuari: san / Mostra: TAN558-B-13
Nom: FAIZA DIABA
Data: 04/07/12 / Ope.: F.DIABA
Experiment: s2pul
Pulse Sequence: s2pul
1.422
9
8
7
6
5
4
3
2
1
ppm

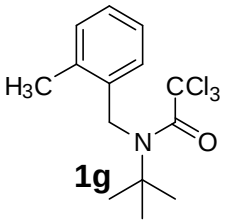

H1 / Mercury-400F
cdcl3 / Temp: Ambient / N.Reg: XXXXXXXXXX
Usuari: san / Mostra: TAN558-B-13
Nom: FAIZA DIABA
Data: 04/07/12 / Ope.: F.DIABA
Experiment: s2pul
Pulse Sequence: s2pul
28.066
180
160
140
120
100
80
60
40
20
ppm


CH3
CCl3
N
O

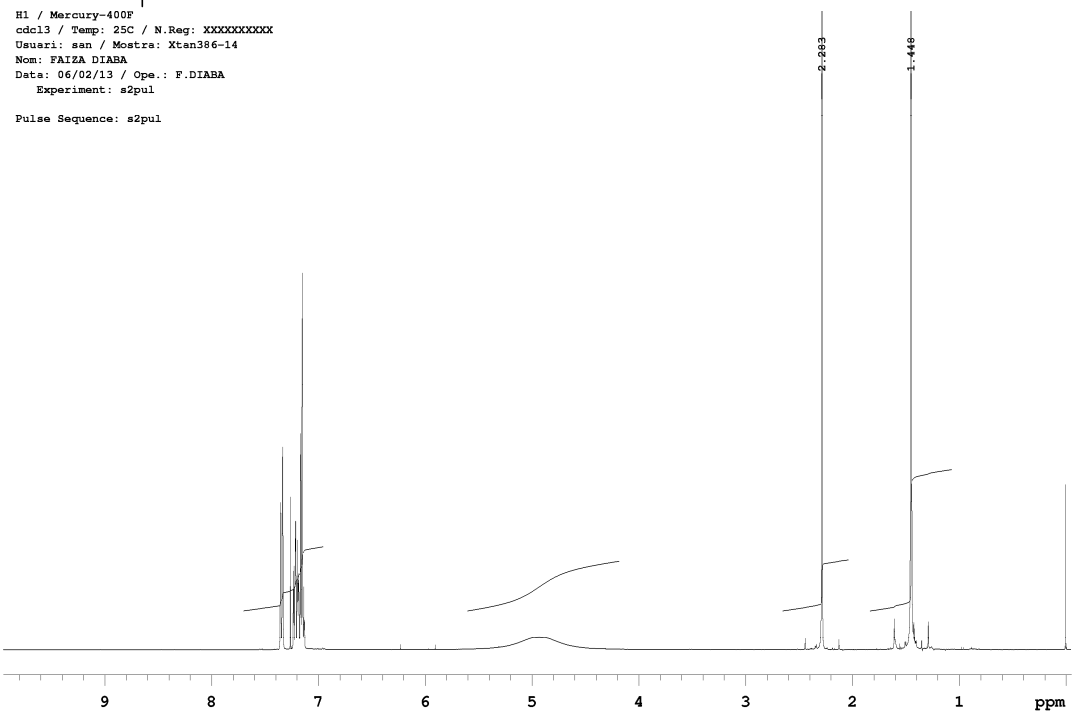
1f

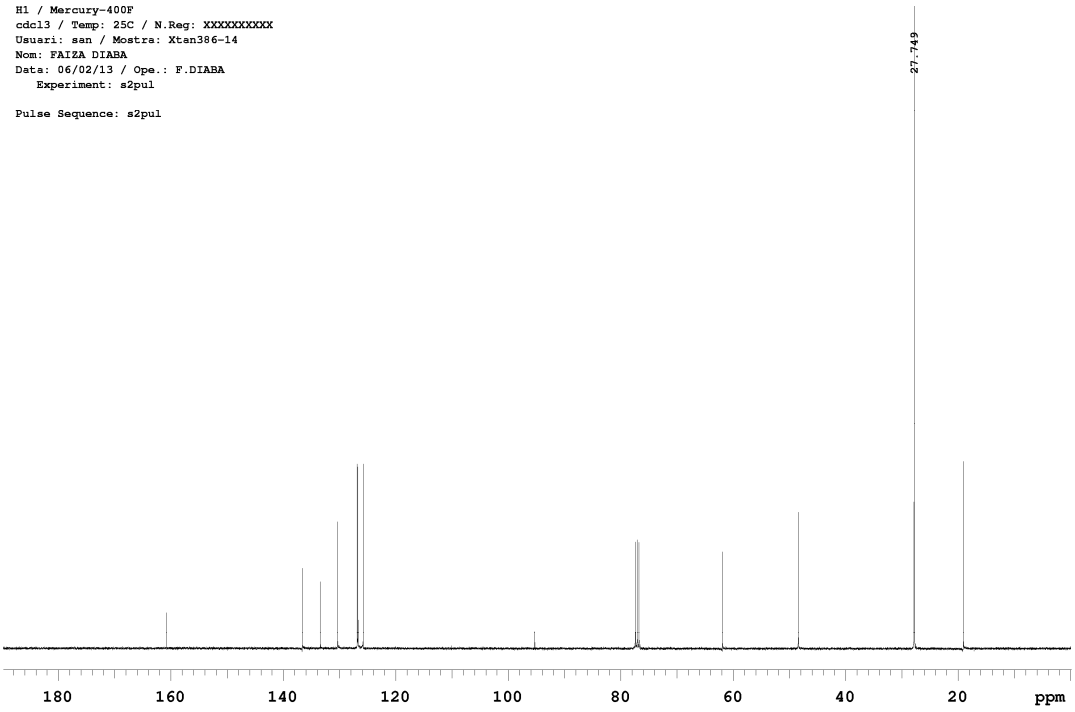

H1 / Mercury-400F
cdcl3 / Temp: 25C / N.Reg: XXXXXXXXXX
Usuari: san / Mostra: Xtan387-13
Nom: FAIZA DIABA
Data: 06/02/13 / Ope.: F.DIABA
Experiment: s2pul
Pulse Sequence: s2pul
2.345
1.425
1.421
9
8
7
6
5
4
3
2
1
ppm

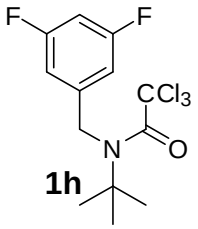

H1 / Mercury-400F
cdcl3 / Temp: 25C / N.Reg: XXXXXXXXXX
Usuari: san / Mostra: Xtan387-13
Nom: FAIZA DIABA
Data: 06/02/13 / Ope.: F.DIABA
Experiment: s2pul
Pulse Sequence: s2pul
28.084
180
160
140
120
100
80
60
40
20
ppm


H3C
CCl3
N
O

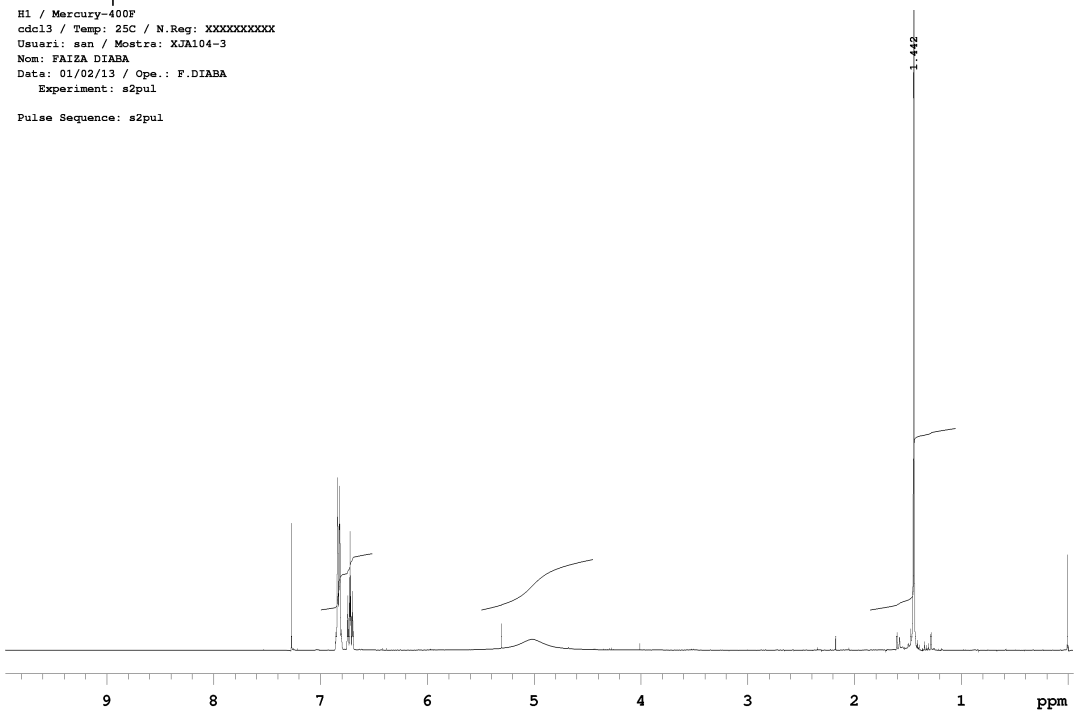
1g

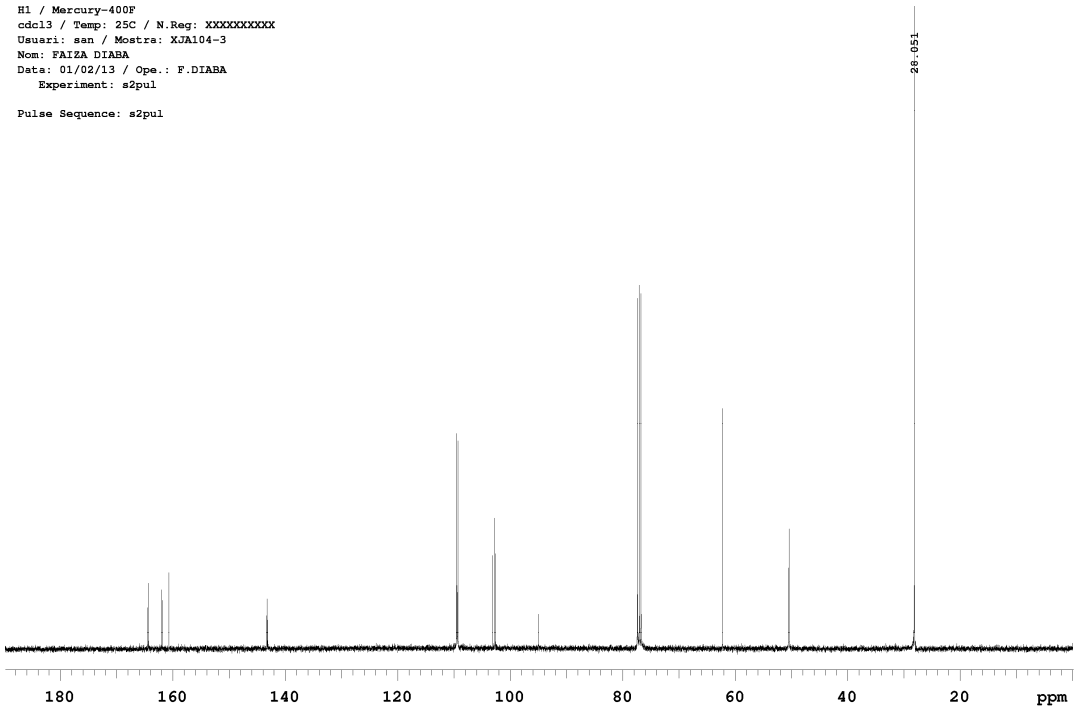

H1 / Mercury-400F
cdcl3 / Temp: 25C / N.Reg: XXXXXXXXXX
Usuari: san / Mostra: Xtan386-14
Nom: FAIZA DIABA
Data: 06/02/13 / Ope.: F.DIABA
Experiment: s2pul
Pulse Sequence: s2pul
2.283
1.448
9
8
7
6
5
4
3
2
1
ppm

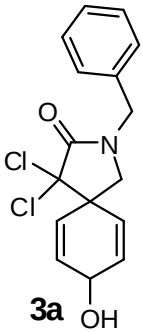

H1 / Mercury-400F
cdcl3 / Temp: 25C / N.Reg: XXXXXXXXXX
Usuari: san / Mostra: Xtan386-14
Nom: FAIZA DIABA
Data: 06/02/13 / Ope.: F.DIABA
Experiment: s2pul
Pulse Sequence: s2pul
27.749
180
160
140
120
100
80
60
40
20
ppm


F
F
CCl3
N
O

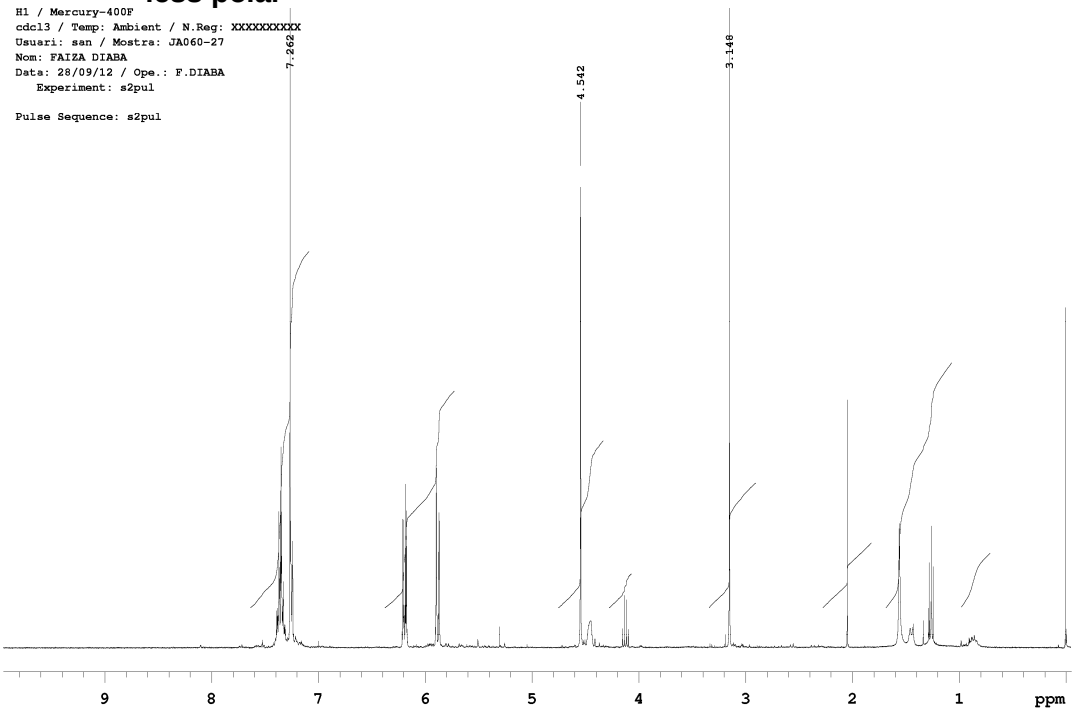
1h

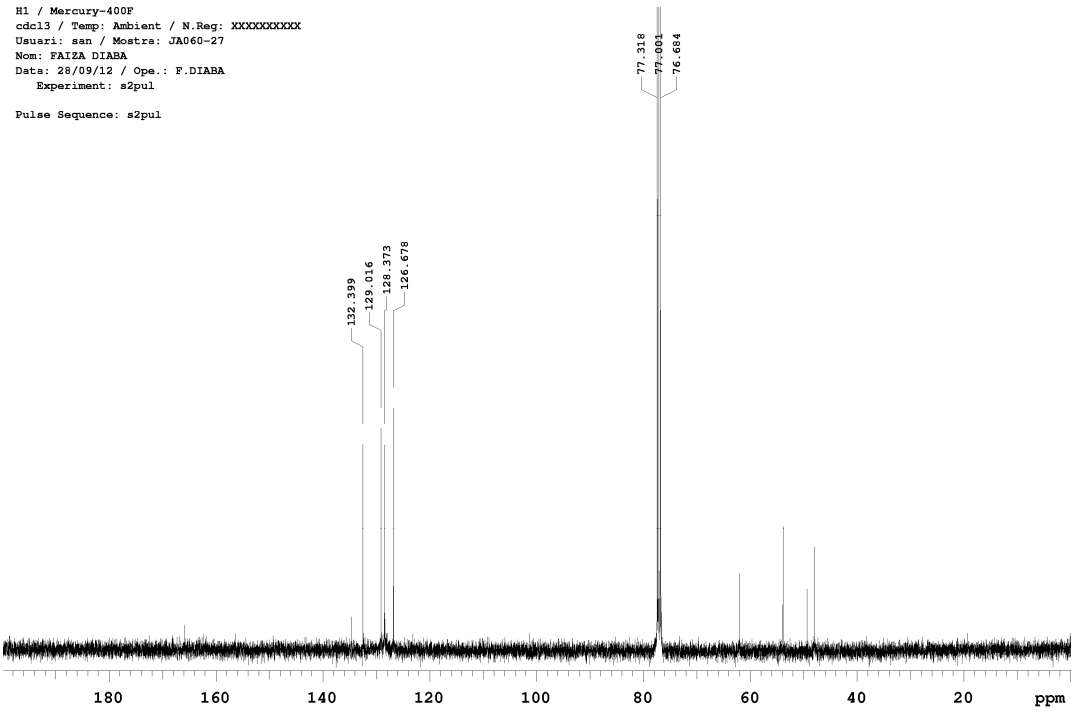

H1 / Mercury-400F
cdcl3 / Temp: 25C / N.Reg: XXXXXXXXXX
Usuari: san / Mostra: XJA104-3
Nom: FAIZA DIABA
Data: 01/02/13 / Ope.: F.DIABA
Experiment: s2pul
Pulse Sequence: s2pul
1.442
9
8
7
6
5
4
3
2
1
ppm

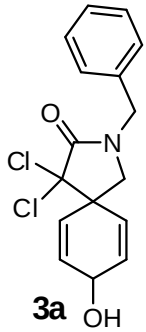

H1 / Mercury-400F
cdcl3 / Temp: 25C / N.Reg: XXXXXXXXXX
Usuari: san / Mostra: XJA104-3
Nom: FAIZA DIABA
Data: 01/02/13 / Ope.: F.DIABA
Experiment: s2pul
Pulse Sequence: s2pul
28.051
180
160
140
120
100
80
60
40
20
ppm



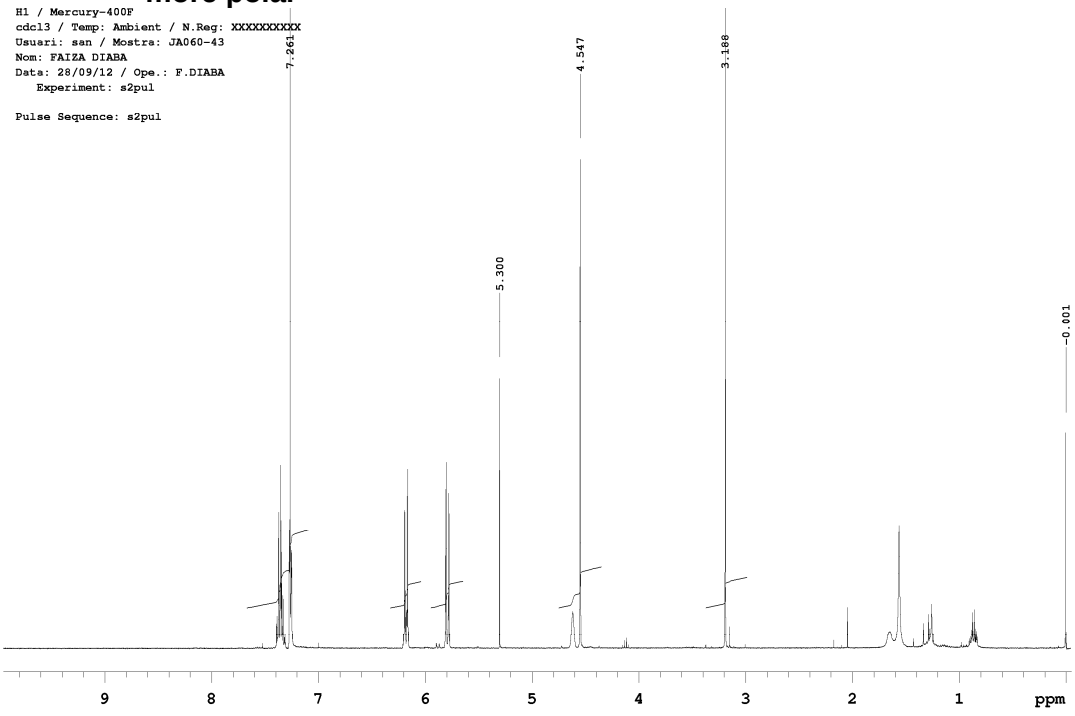
3a **less polar**

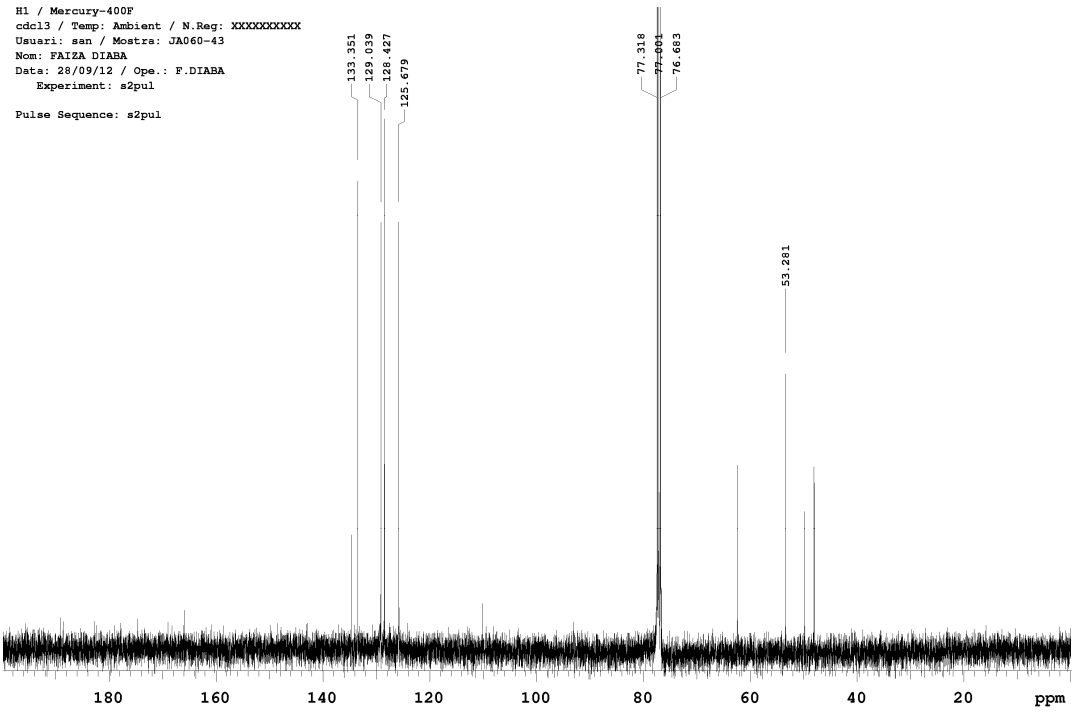


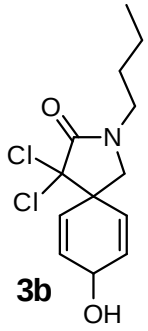




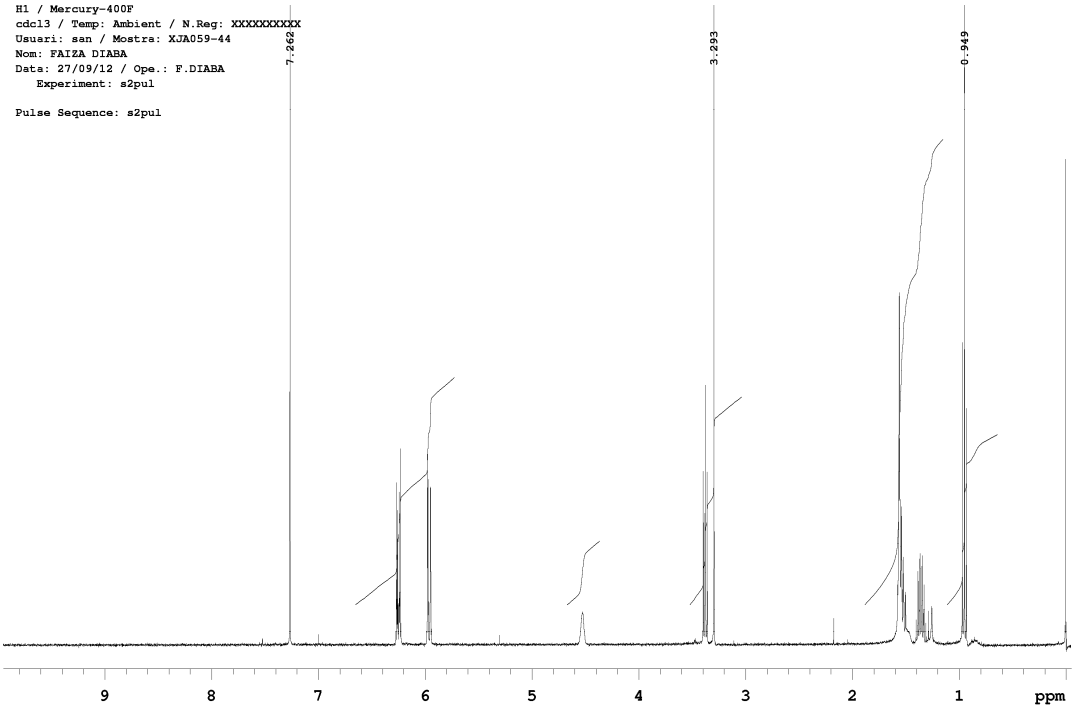
3a **more polar**

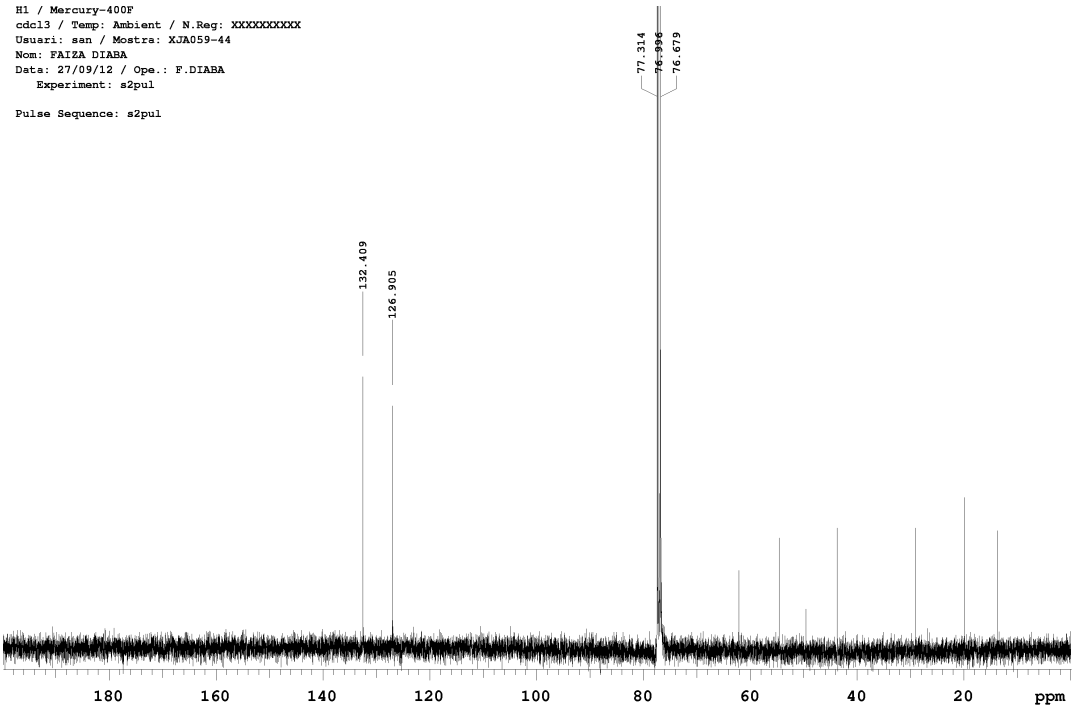


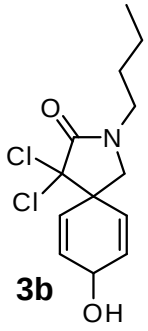




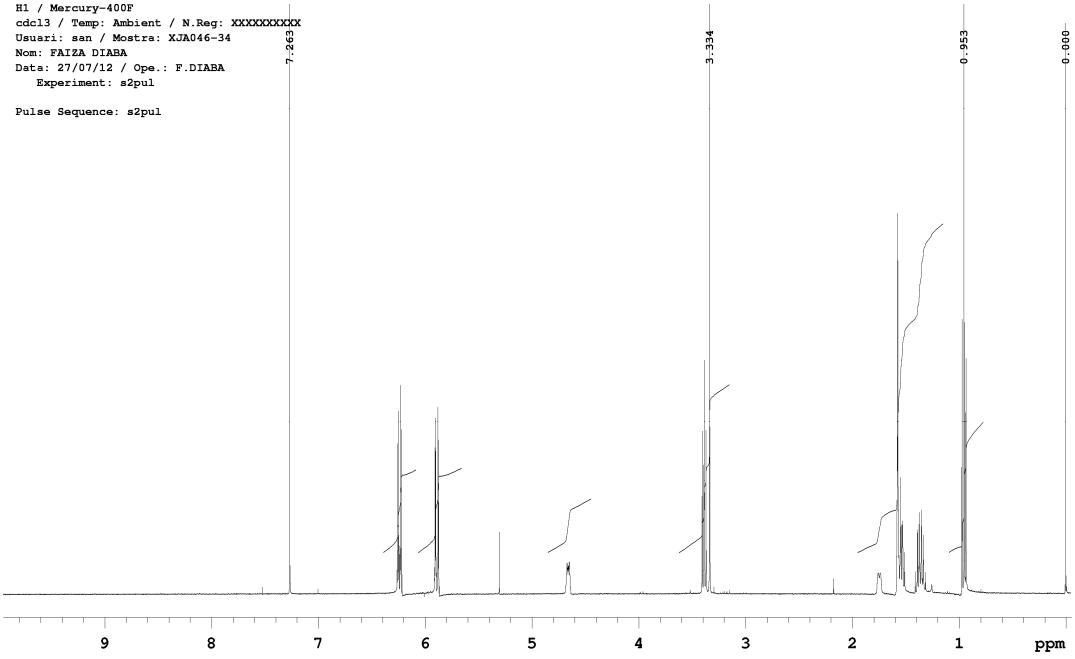
3b **Less polar**

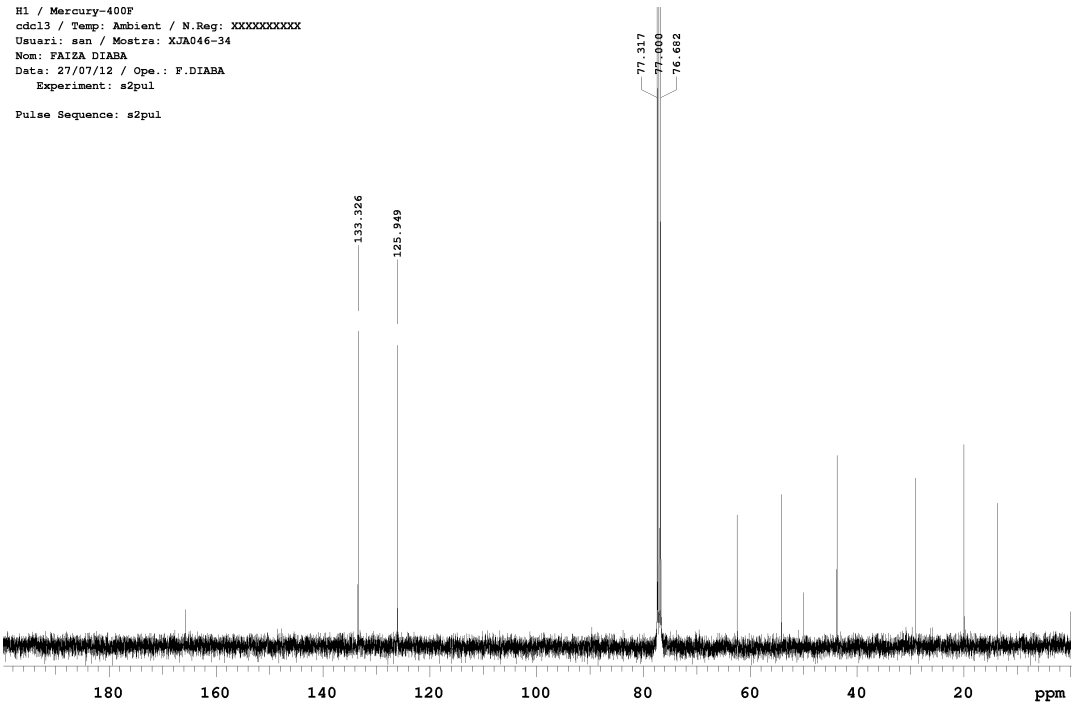


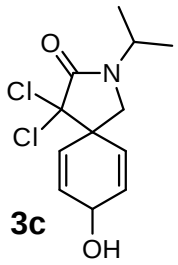




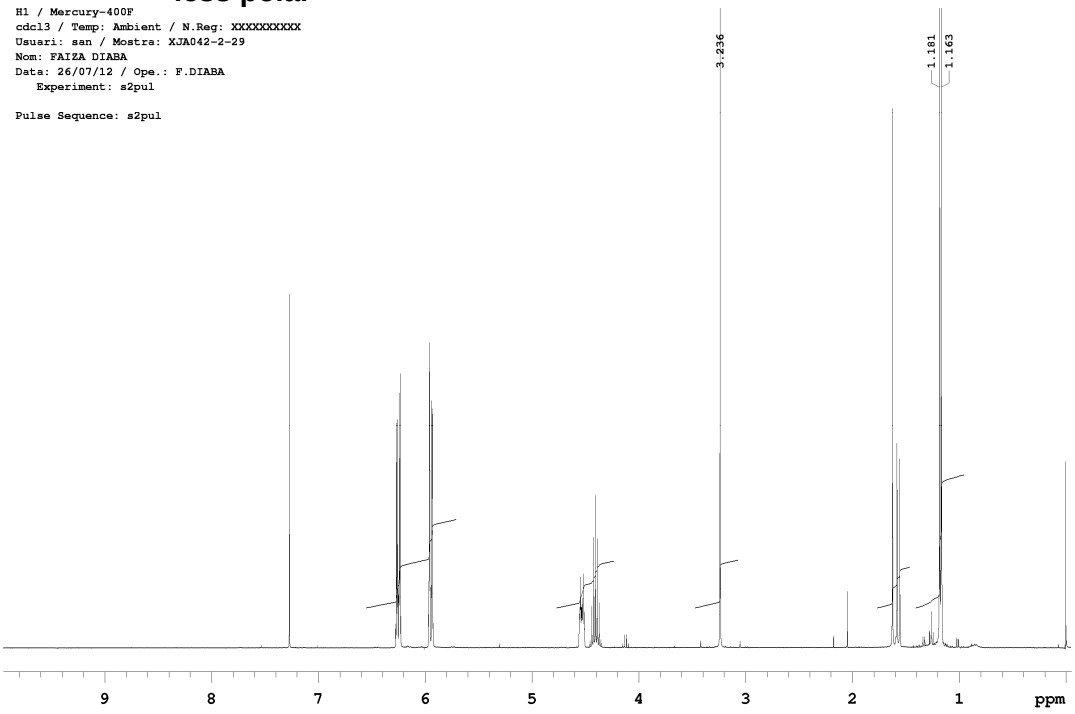
3b **More polar**

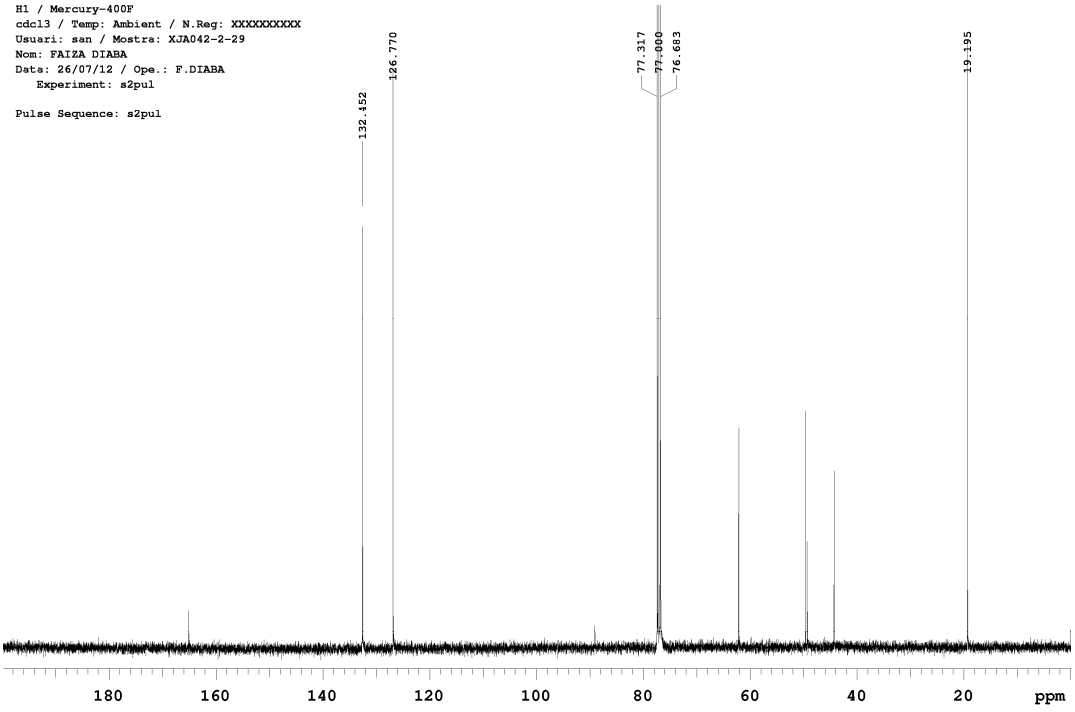


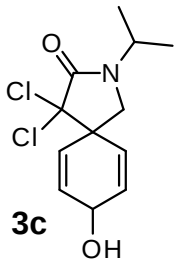




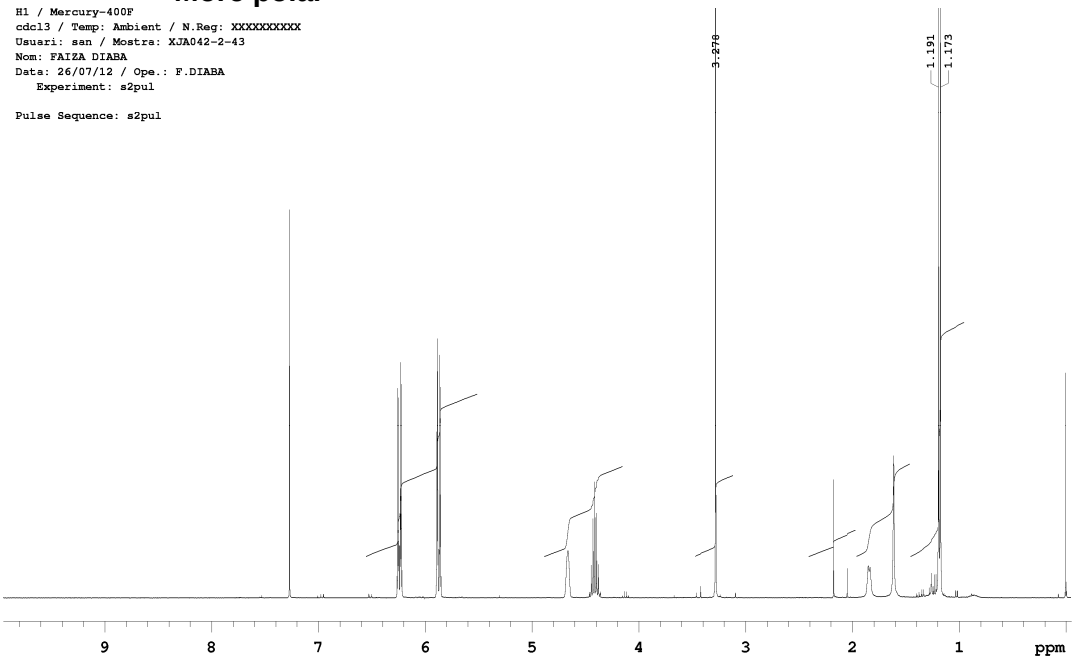
3c **less polar**

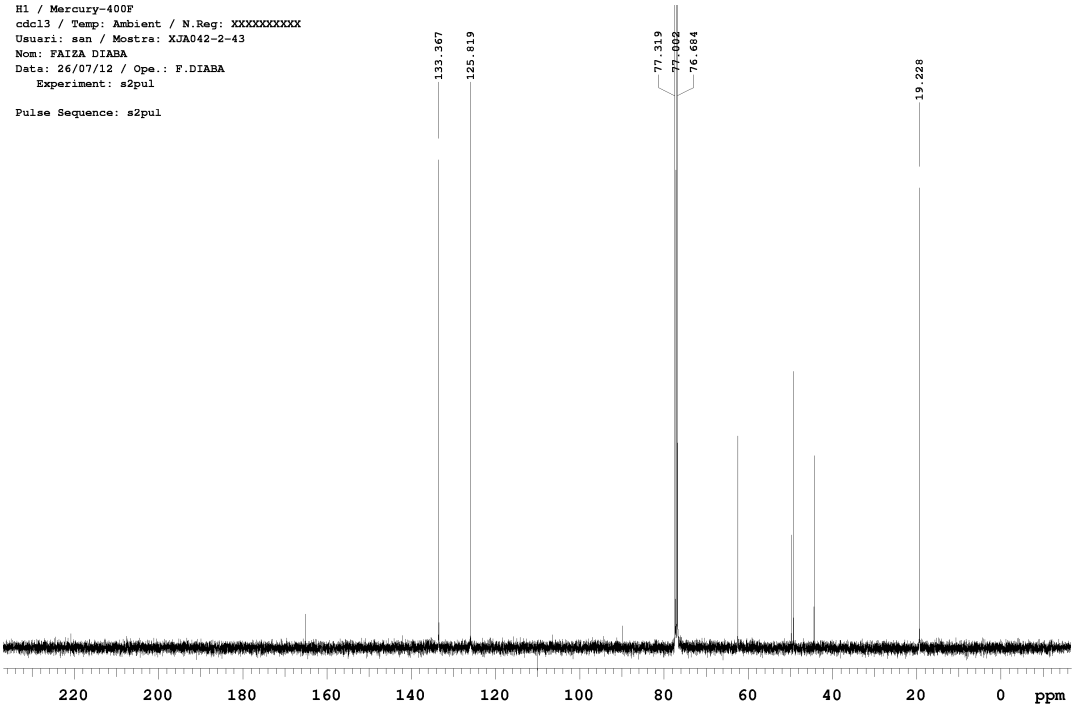


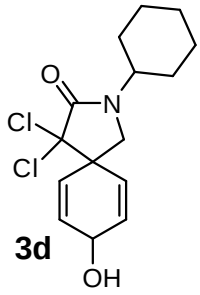




3c **More polar**

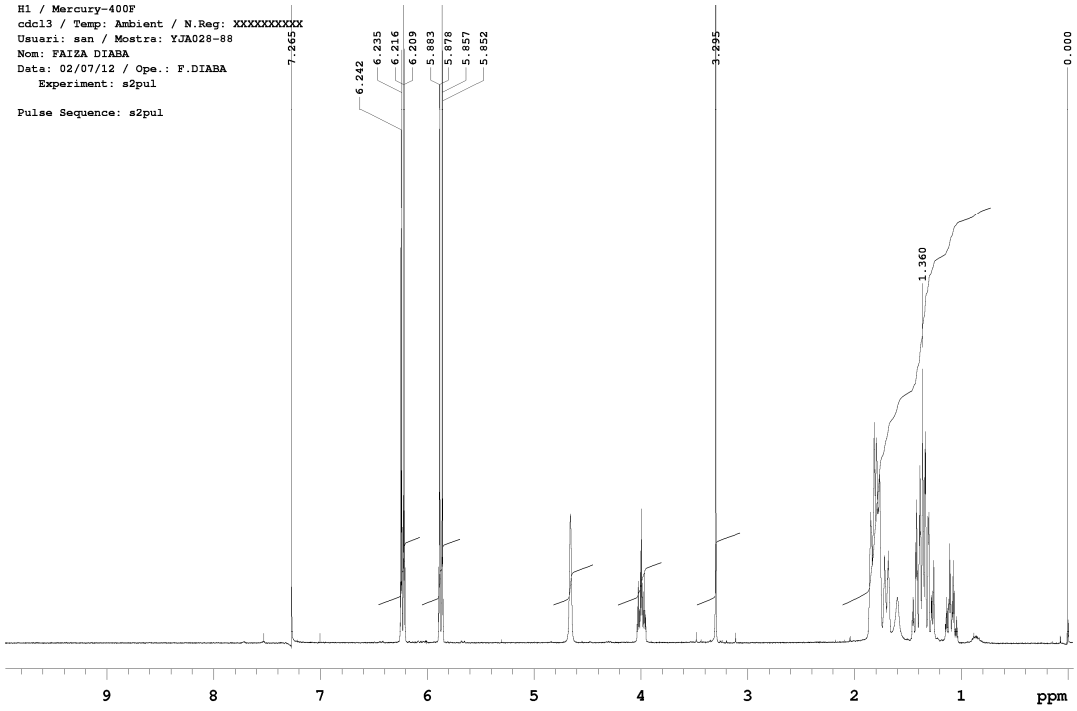


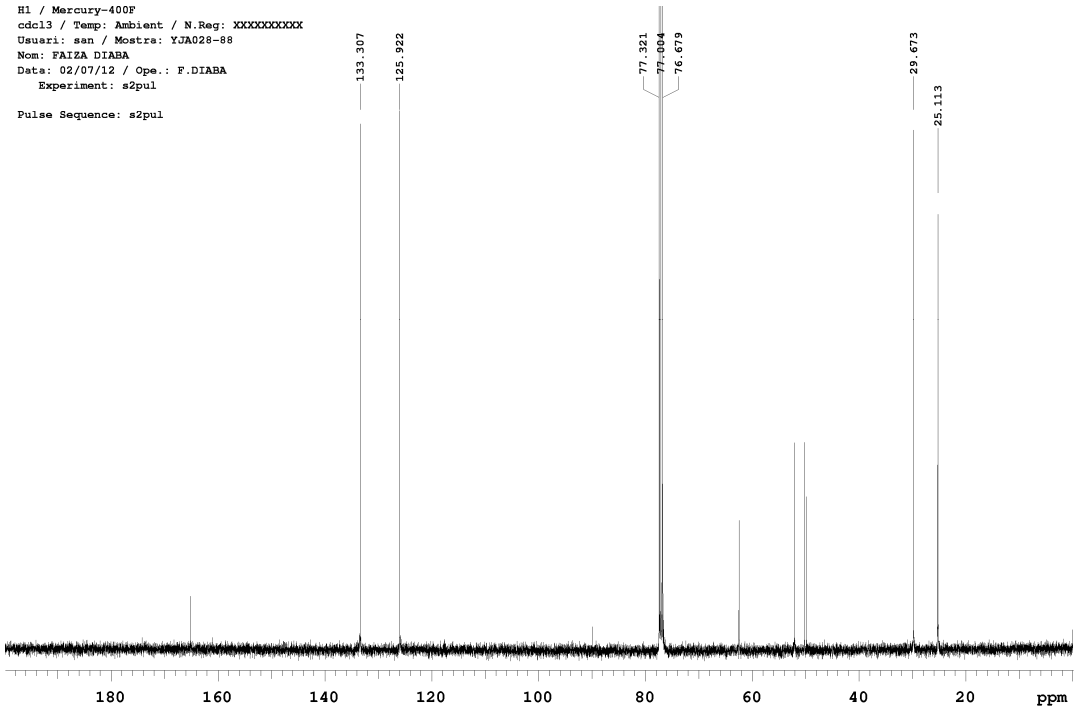


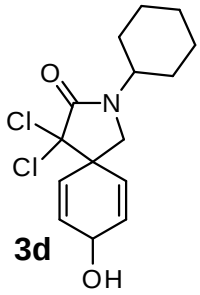


3d

Less polar

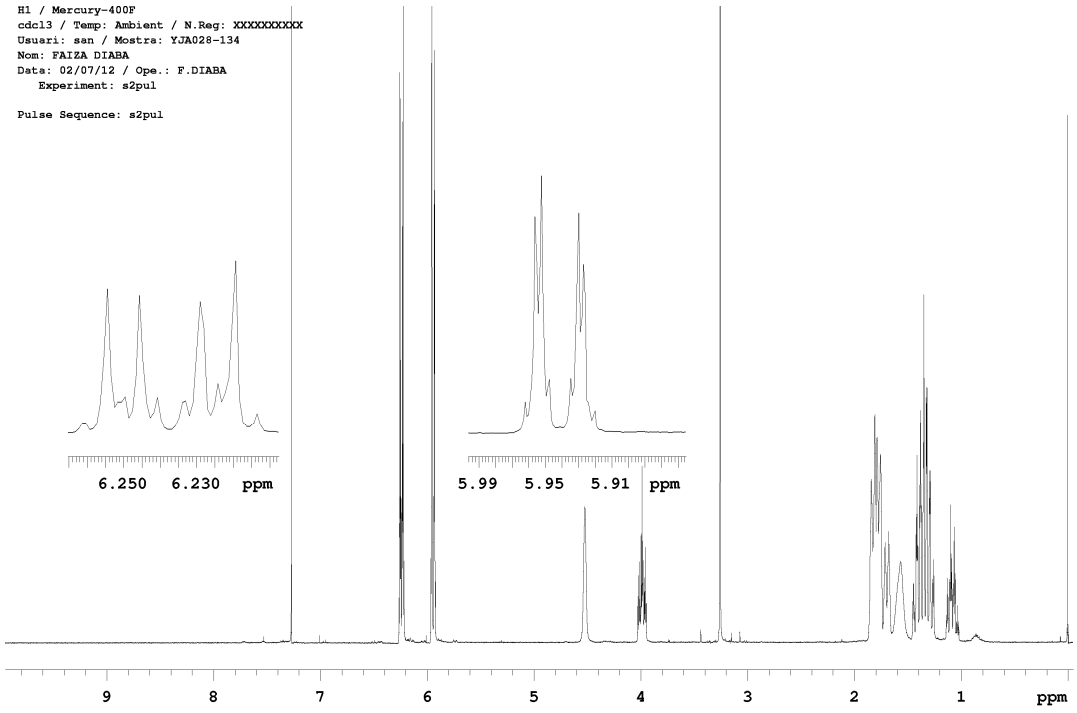


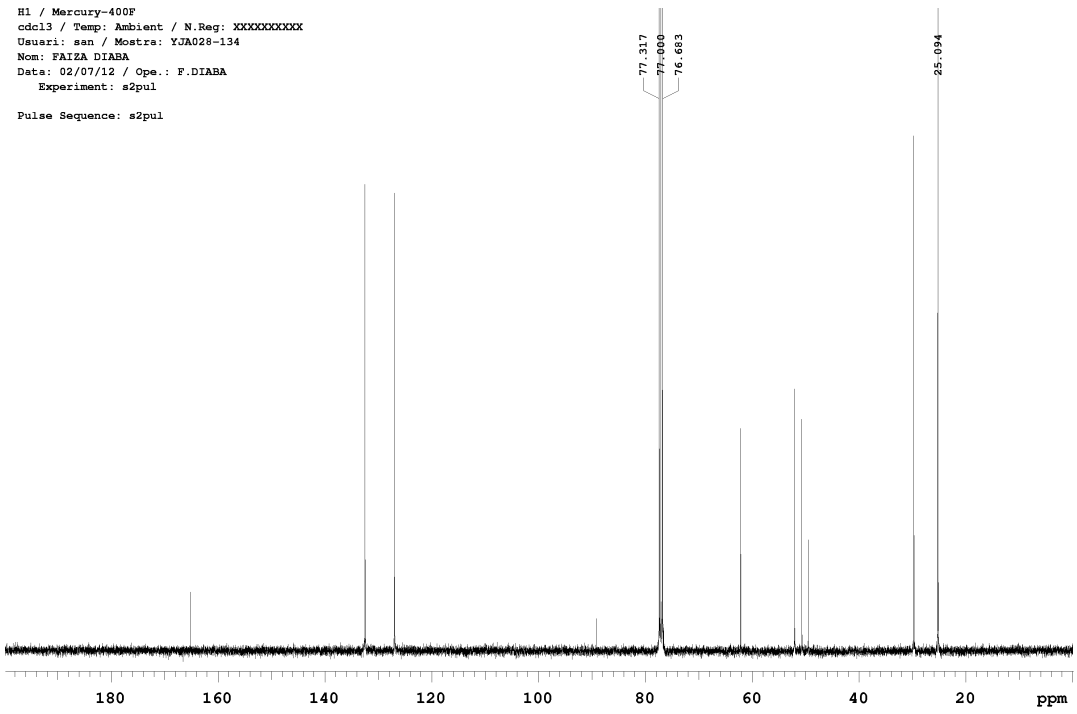


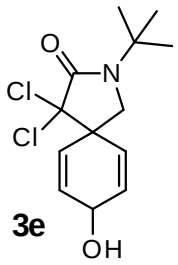


3d

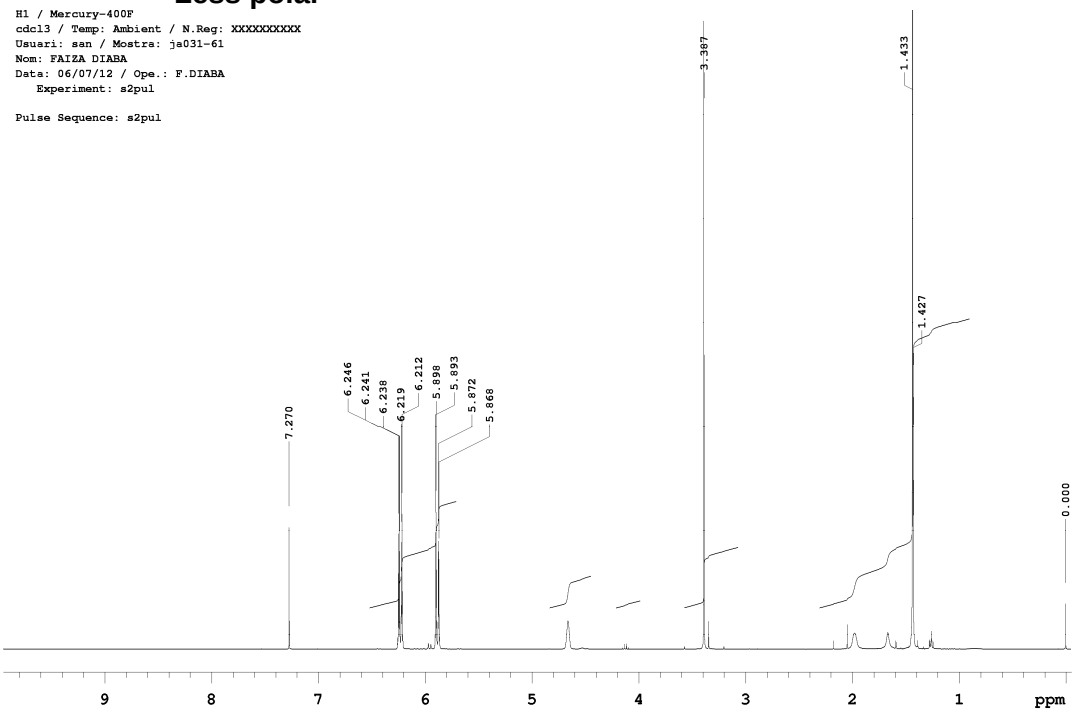
More polar

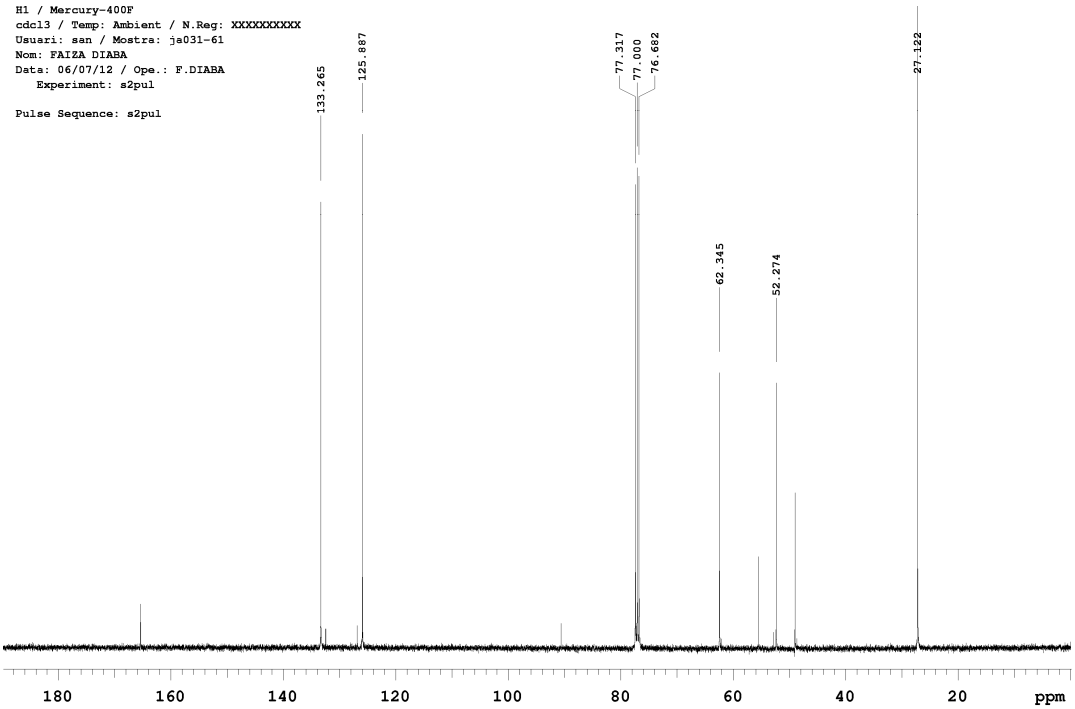


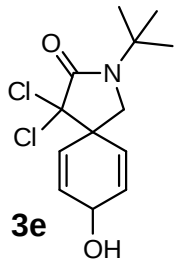




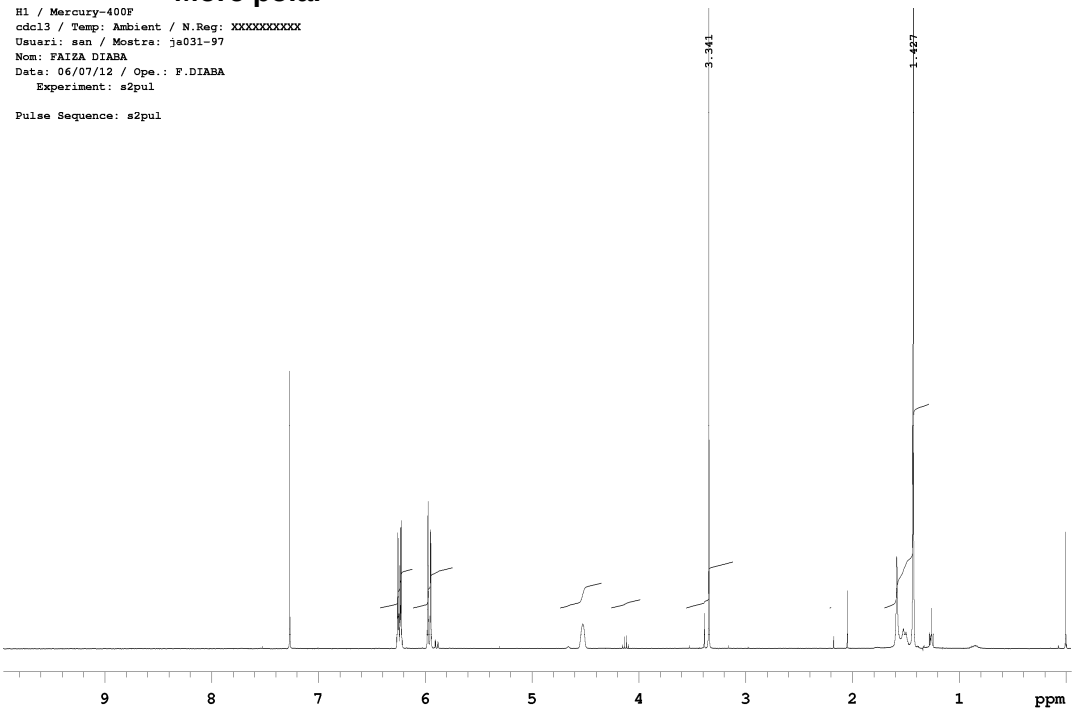
3e **Less polar**

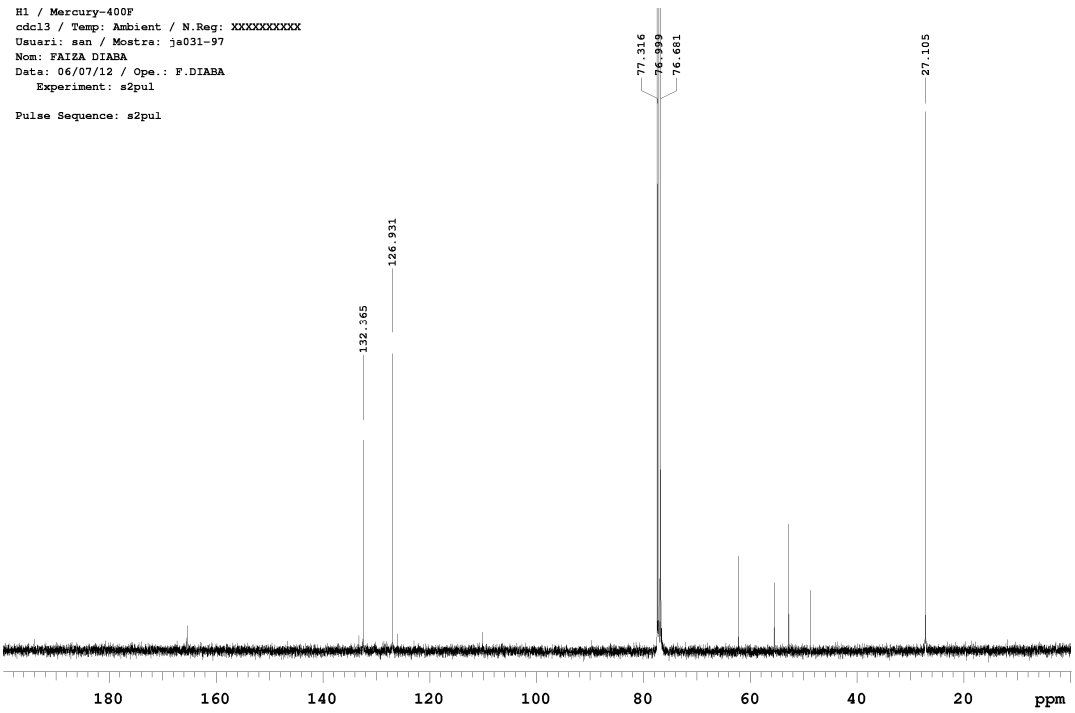


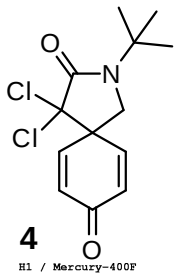




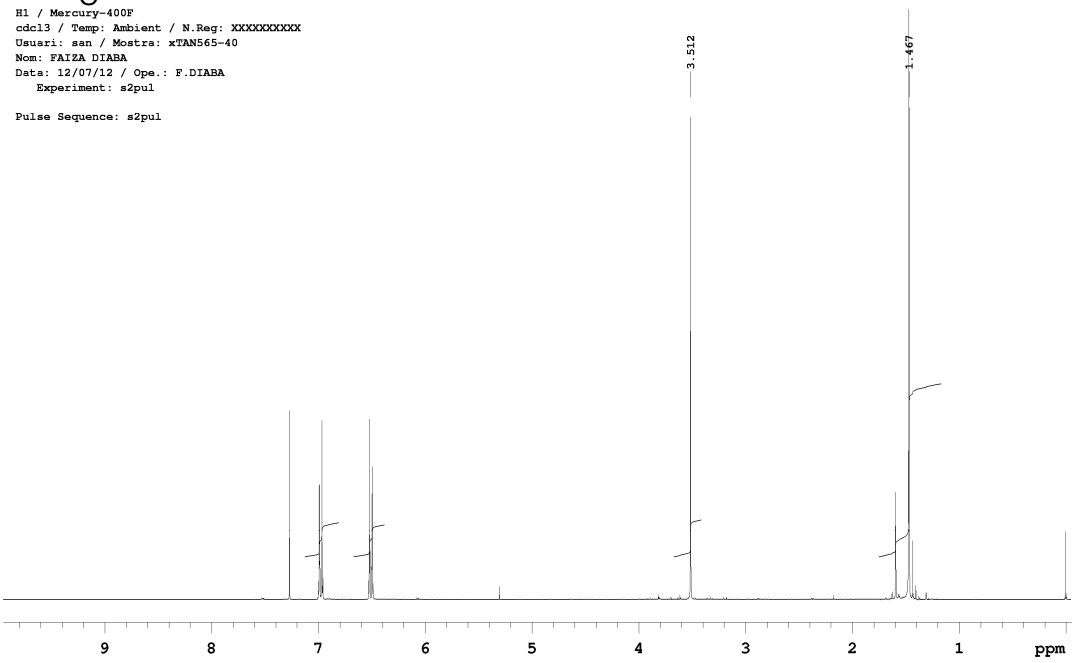
3e **More polar**

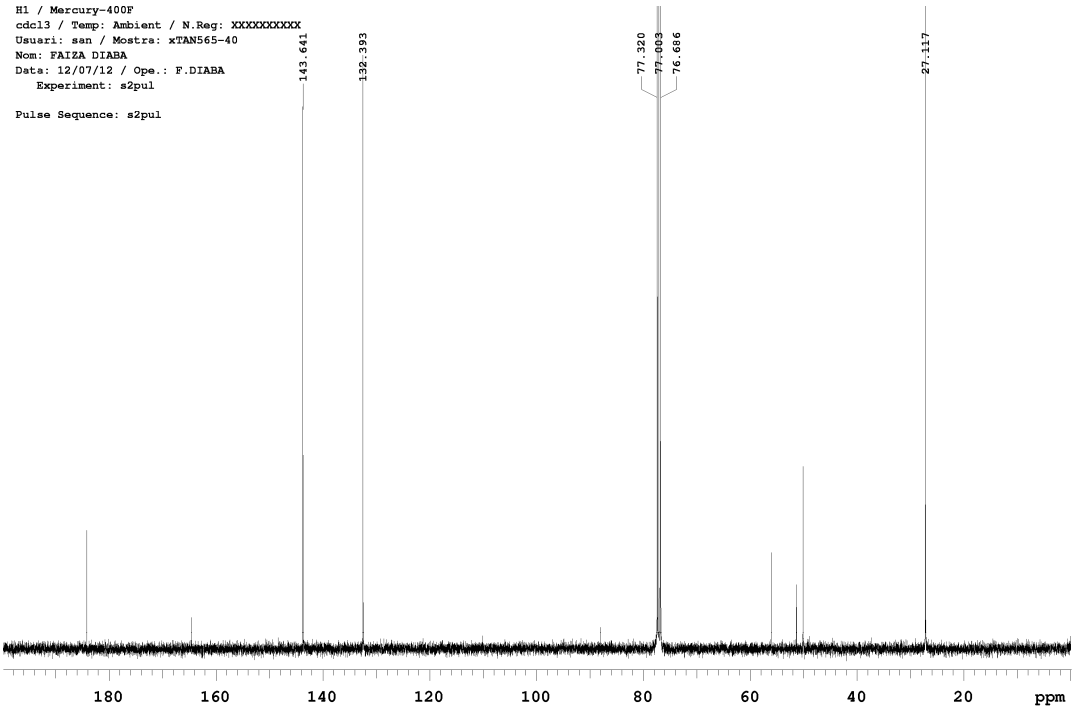


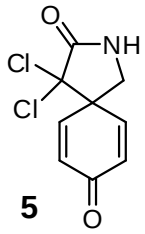



O
N
Cl
Cl
O

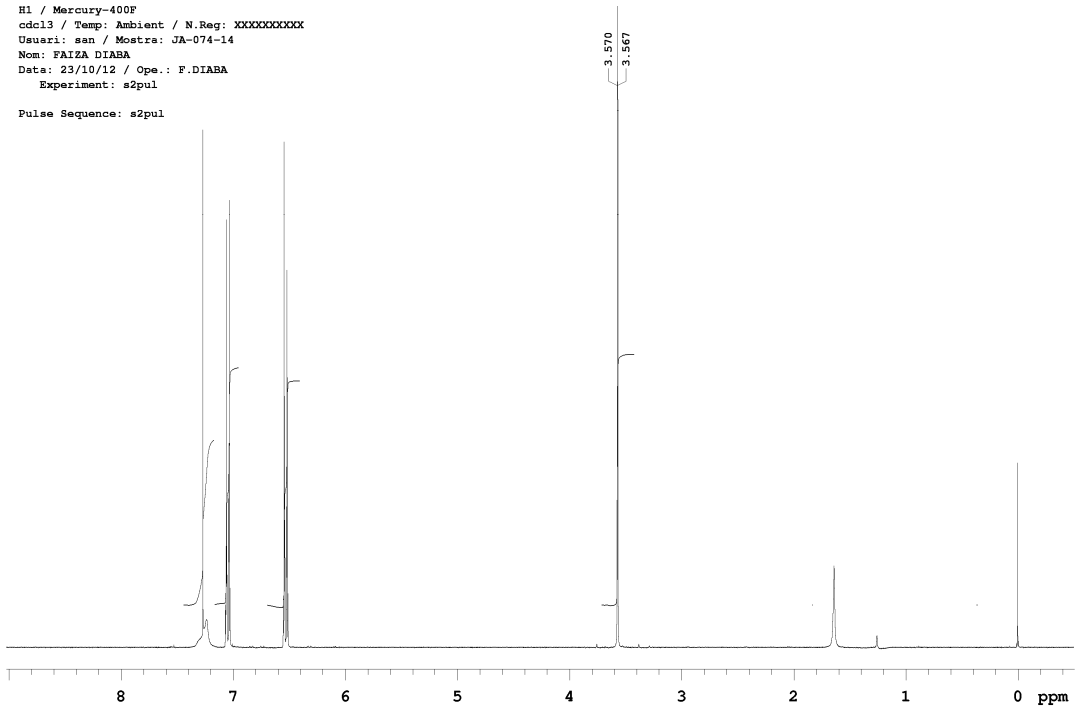
4

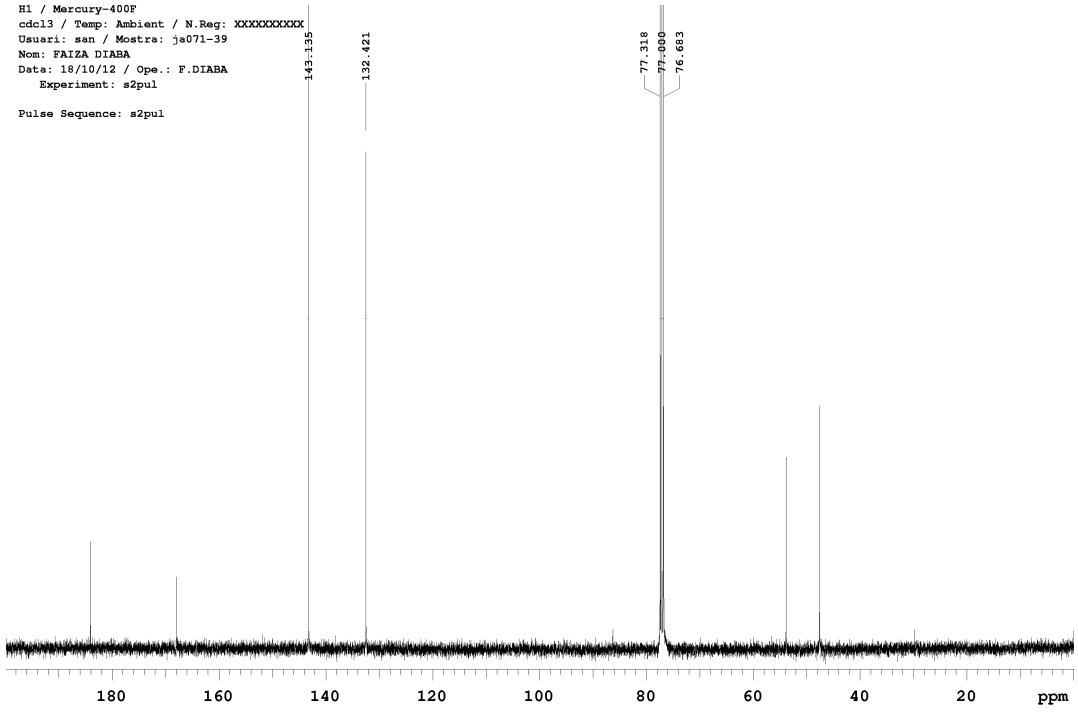

H1 / Mercury-400F
cdcl3 / Temp: Ambient / N.Reg: XXXXXXXXXX
Usuari: san / Mostra: xTAN565-40
Nom: FAIZA DIABA
Data: 12/07/12 / Ope.: F.DIABA
Experiment: s2pul
Pulse Sequence: s2pul
3.512
1.467
9
8
7
6
5
4
3
2
1
ppm

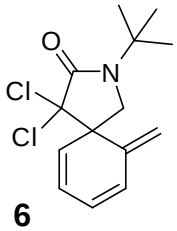

H1 / Mercury-400F
cdcl3 / Temp: Ambient / N.Reg: XXXXXXXXXX
Usuari: san / Mostra: xTAN565-40
Nom: FAIZA DIABA
Data: 12/07/12 / Ope.: F.DIABA
Experiment: s2pul
Pulse Sequence: s2pul
143.641
132.393
77.320
77.003
76.686
27.117
180
160
140
120
100
80
60
40
20
ppm


O
NH
Cl
Cl
O

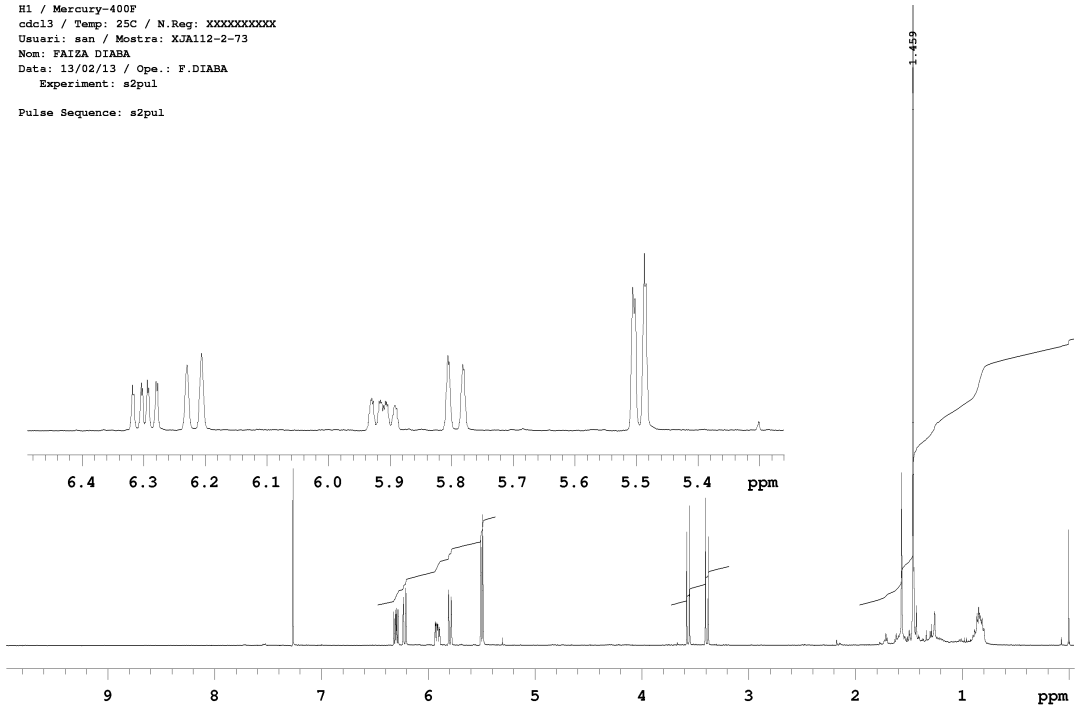
5

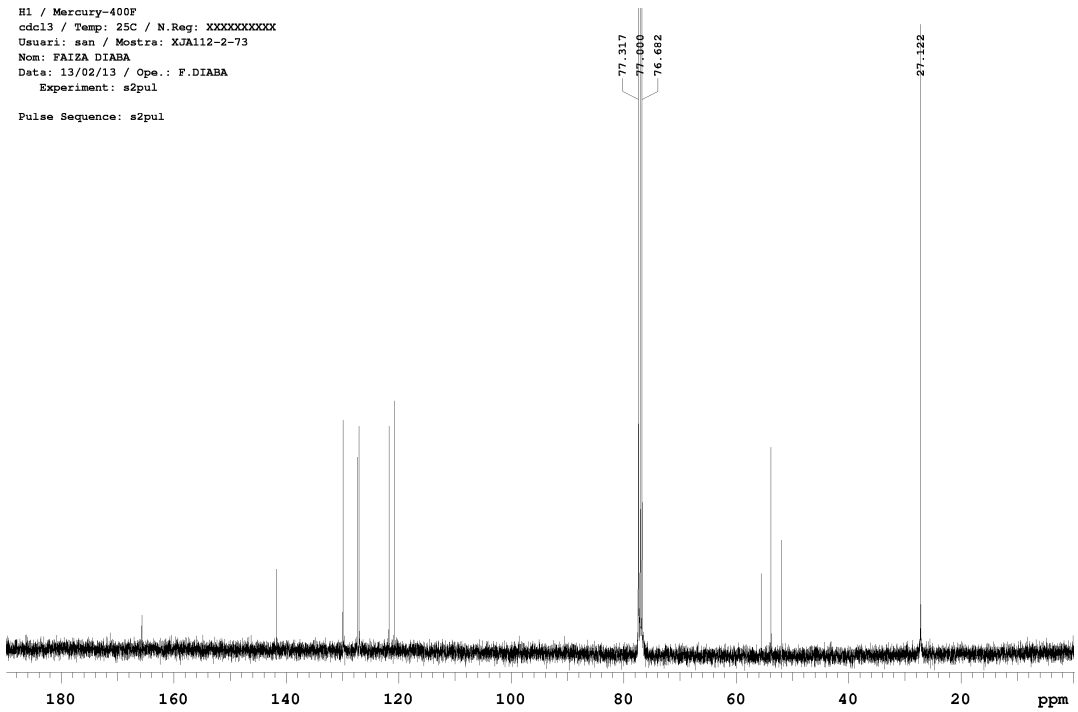

H1 / Mercury-400F
cdcl3 / Temp: Ambient / N.Reg: XXXXXXXXXX
Usuari: san / Mostra: JA-074-14
Nom: FAIZA DIABA
Data: 23/10/12 / Ope.: F.DIABA
Experiment: s2pul
Pulse Sequence: s2pul
3.570
3.567
8
7
6
5
4
3
2
1
0
ppm

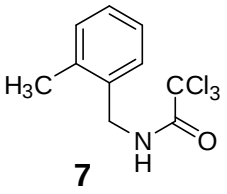

H1 / Mercury-400F
cdcl3 / Temp: Ambient / N.Reg: XXXXXXXXXX
Usuari: san / Mostra: js071-39
Nom: FAIZA DIABA
Data: 18/10/12 / Ope.: F.DIABA
Experiment: s2pul
Pulse Sequence: s2pul
143.135
132.421
77.318
77.000
76.683
180
160
140
120
100
80
60
40
20
ppm


O
N
Cl
Cl

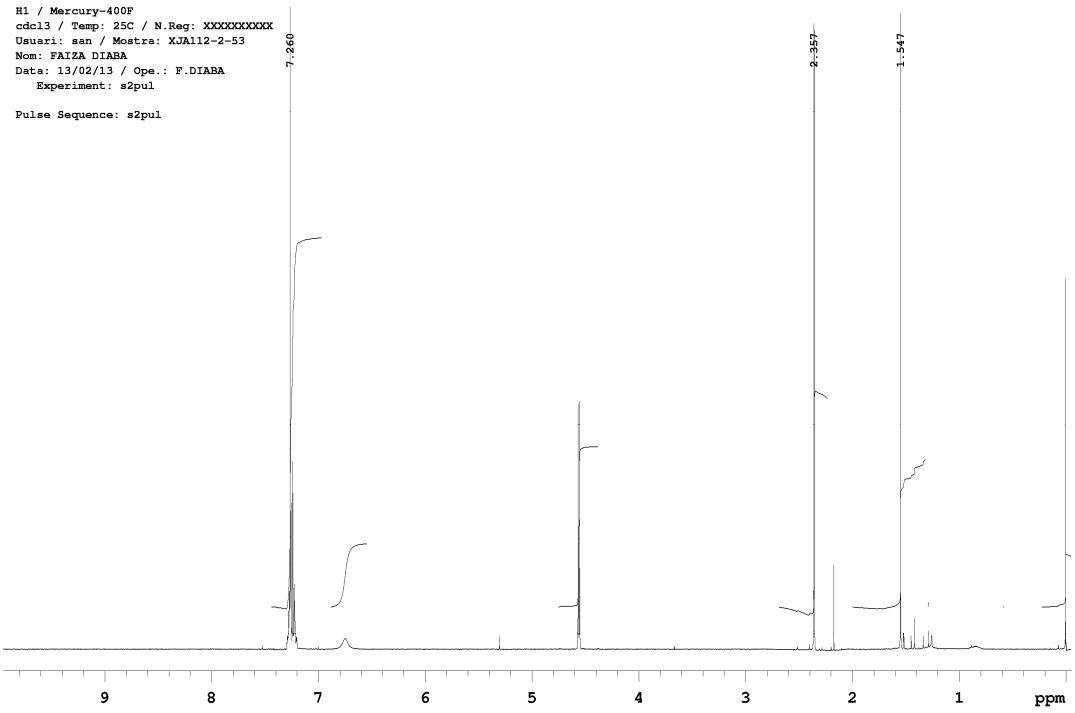
6

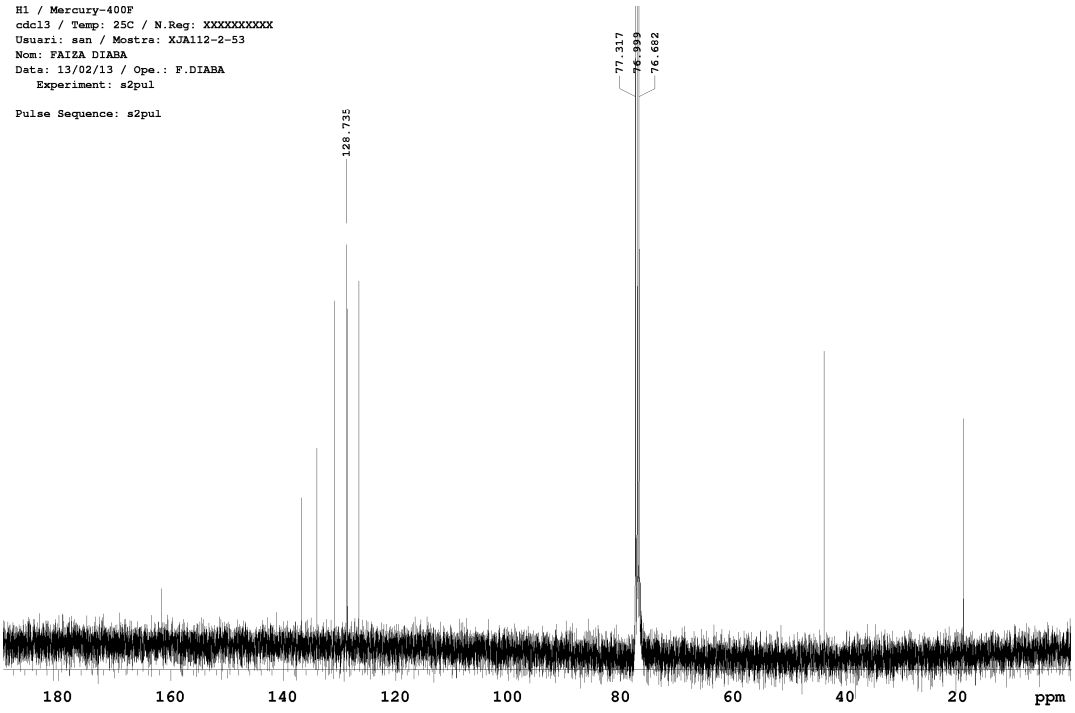

H1 / Mercury-400F
cdcl3 / Temp: 25C / N.Reg: XXXXXXXXXX
Usuari: san / Mostra: XJA112-2-73
Nom: FAIZA DIABA
Data: 13/02/13 / Ope.: F.DIABA
Experiment: s2pul
Pulse Sequence: s2pul
1.459
6.4 6.3 6.2 6.1 6.0 5.9 5.8 5.7 5.6 5.5 5.4 ppm
9 8 7 6 5 4 3 2 1 ppm

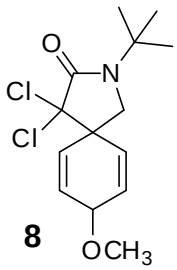

H1 / Mercury-400F
cdcl3 / Temp: 25C / N.Reg: XXXXXXXXXX
Usuari: san / Mostra: XJA112-2-73
Nom: FAIZA DIABA
Data: 13/02/13 / Ope.: F.DIABA
Experiment: s2pul
Pulse Sequence: s2pul
77.317
77.000
76.682
27.122
180 160 140 120 100 80 60 40 20 ppm


H3C
CCl3
N
H
O

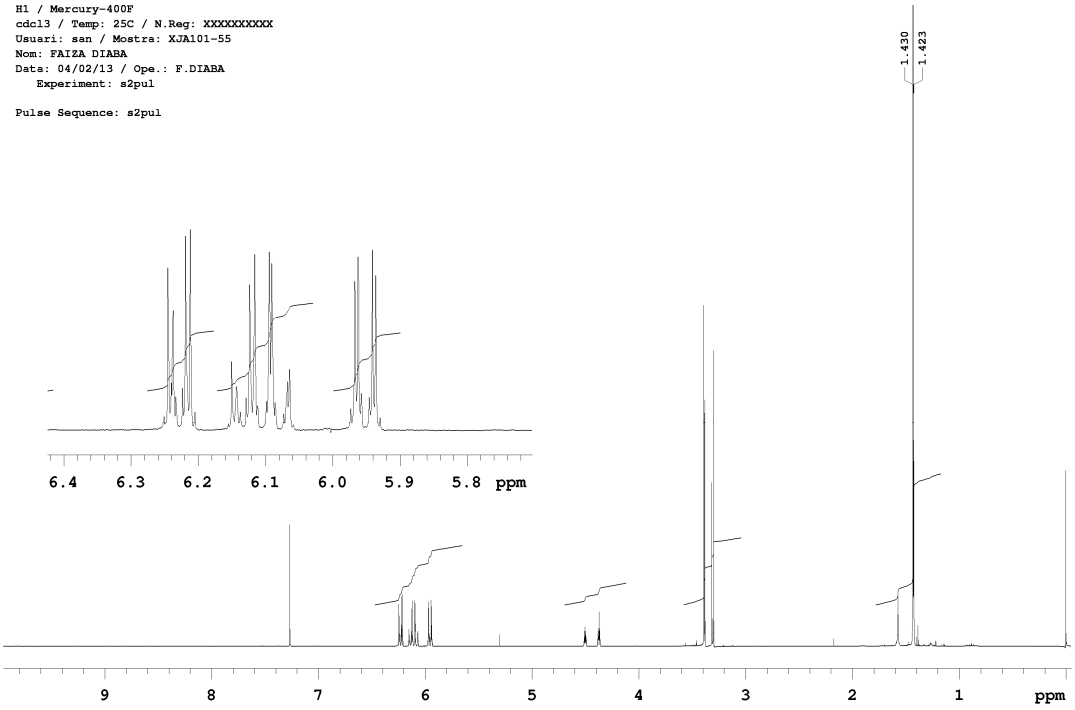
7

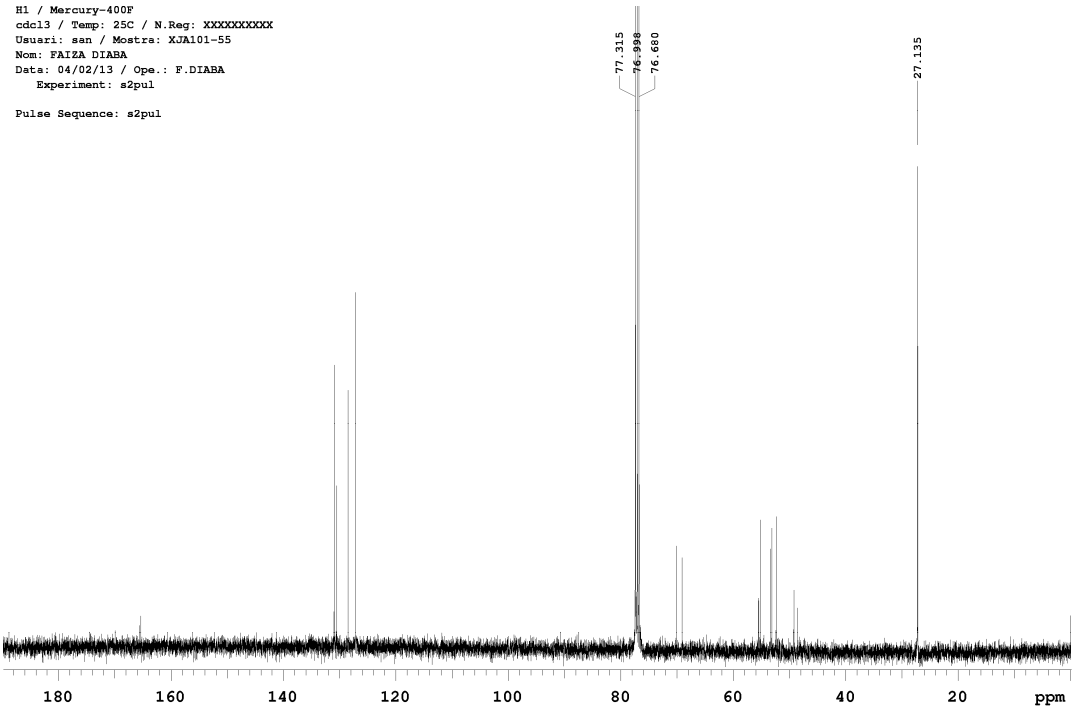

H1 / Mercury-400F
cdcl3 / Temp: 25C / N.Reg: XXXXXXXXXX
Usuari: san / Mostra: XJA112-2-53
Nom: FAIZA DIABA
Data: 13/02/13 / Ope.: F.DIABA
Experiment: s2pul
Pulse Sequence: s2pul
7.260
2.357
1.547
9
8
7
6
5
4
3
2
1
ppm

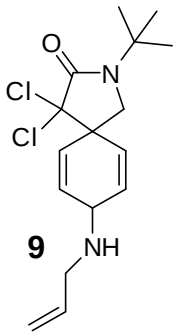

H1 / Mercury-400F
cdcl3 / Temp: 25C / N.Reg: XXXXXXXXXX
Usuari: san / Mostra: XJA112-2-53
Nom: FAIZA DIABA
Data: 13/02/13 / Ope.: F.DIABA
Experiment: s2pul
Pulse Sequence: s2pul
77.317
76.999
76.682
128.735
180
160
140
120
100
80
60
40
20
ppm


O
N
Cl
Cl
OCH3

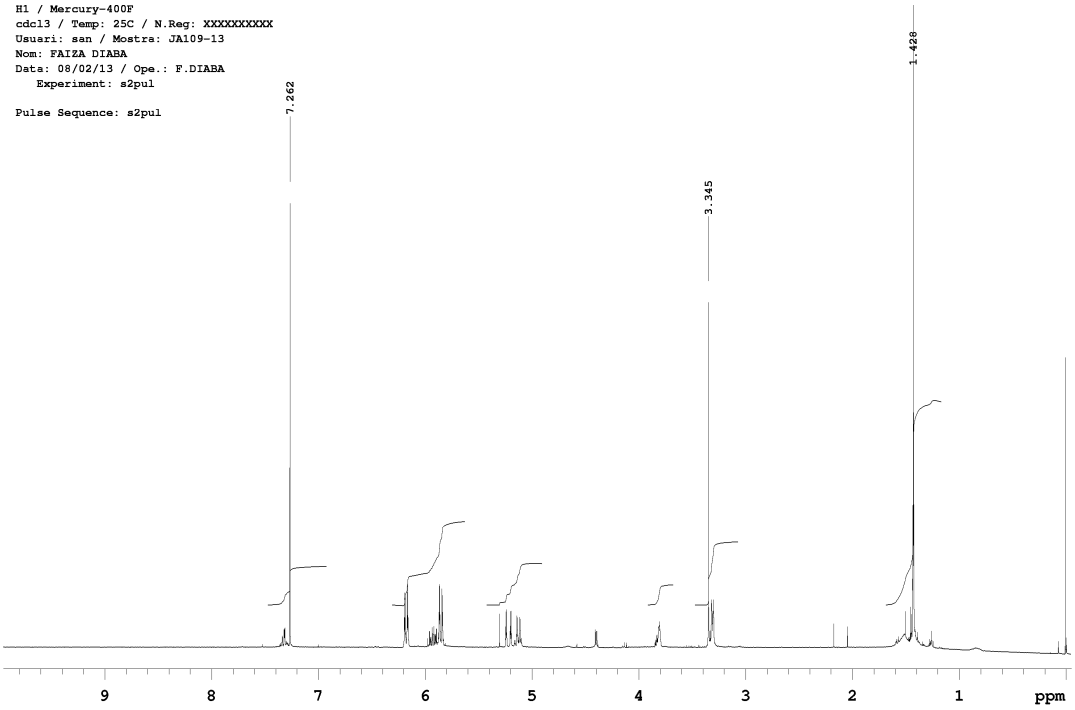
8

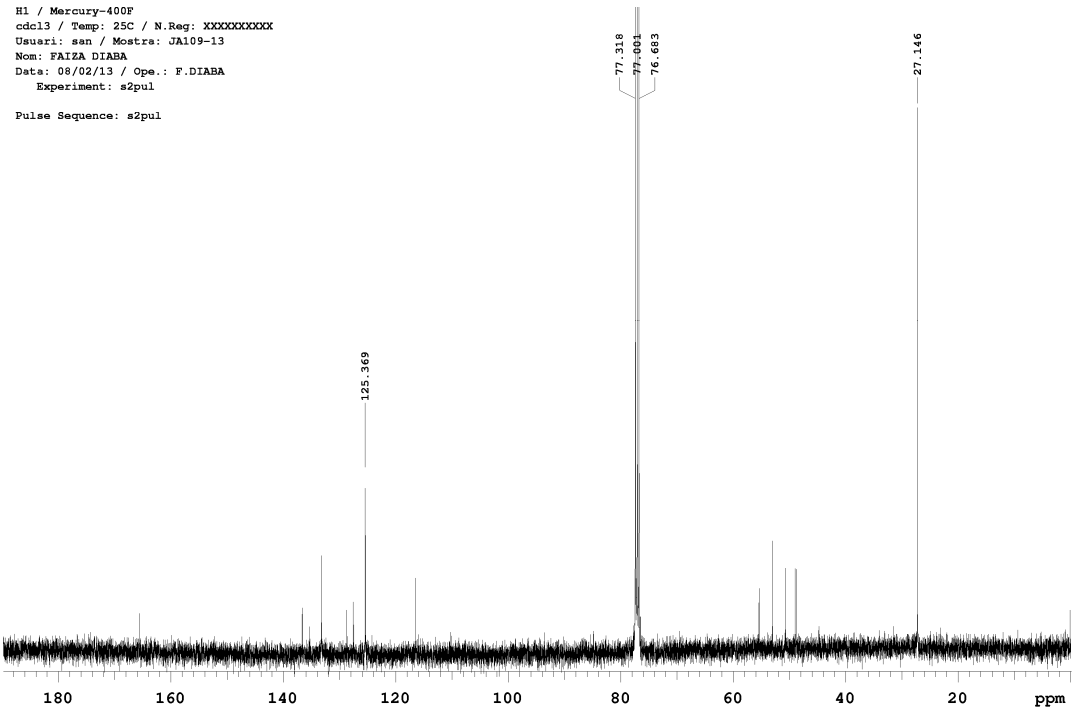

H1 / Mercury-400F
cdcl3 / Temp: 25C / N.Reg: XXXXXXXXXX
Usuari: san / Mostra: XJA101-55
Nom: FAIZA DIABA
Data: 04/02/13 / Ope.: F.DIABA
Experiment: s2pul
Pulse Sequence: s2pul
1.430
1.423
6.4 6.3 6.2 6.1 6.0 5.9 5.8 ppm
9 8 7 6 5 4 3 2 1 ppm

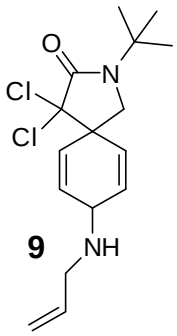

H1 / Mercury-400F
cdcl3 / Temp: 25C / N.Reg: XXXXXXXXXX
Usuari: san / Mostra: XJA101-55
Nom: FAIZA DIABA
Data: 04/02/13 / Ope.: F.DIABA
Experiment: s2pul
Pulse Sequence: s2pul
77.315
76.998
76.680
27.135
180 160 140 120 100 80 60 40 20 ppm


O
N
Cl
Cl
9
NH

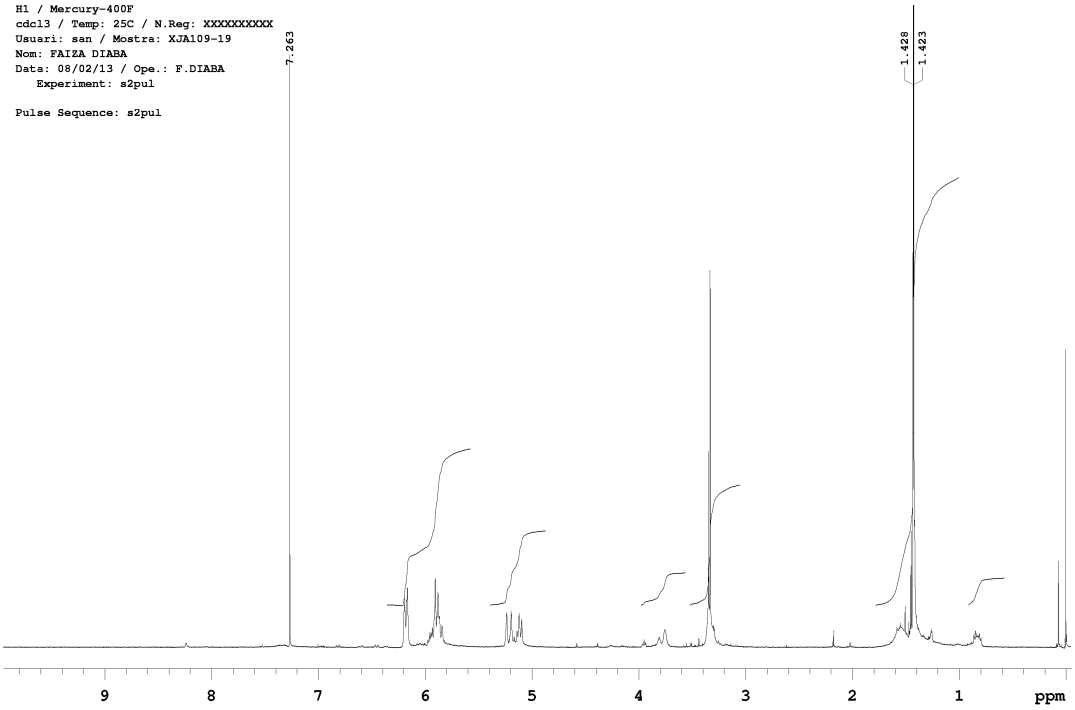
Less polar

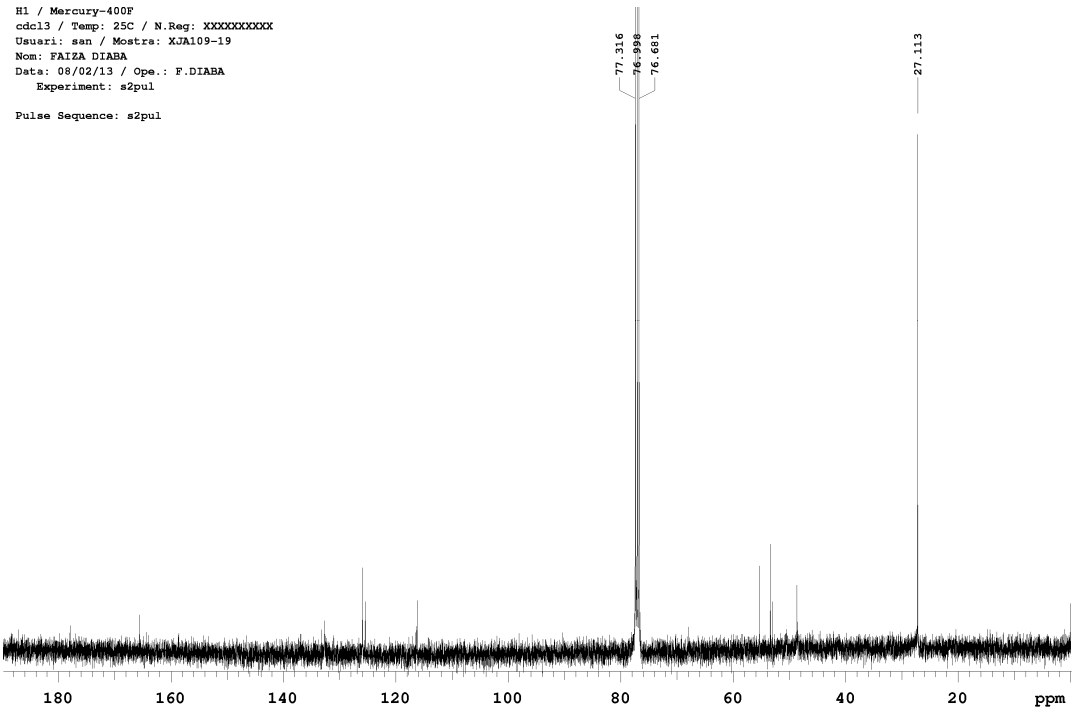

H1 / Mercury-400F
cdcl3 / Temp: 25C / N.Reg: XXXXXXXXXX
Usuari: san / Mostra: JA109-13
Nom: FAIZA DIABA
Data: 08/02/13 / Ope.: F.DIABA
Experiment: s2pul
Pulse Sequence: s2pul
7.262
3.345
1.428
9
8
7
6
5
4
3
2
1
ppm

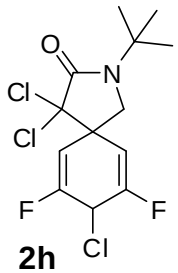

H1 / Mercury-400F
cdcl3 / Temp: 25C / N.Reg: XXXXXXXXXX
Usuari: san / Mostra: JA109-13
Nom: FAIZA DIABA
Data: 08/02/13 / Ope.: F.DIABA
Experiment: s2pul
Pulse Sequence: s2pul
77.318
77.001
76.683
27.146
125.369
180
160
140
120
100
80
60
40
20
ppm


O
N
Cl
Cl
9
NH

More polar

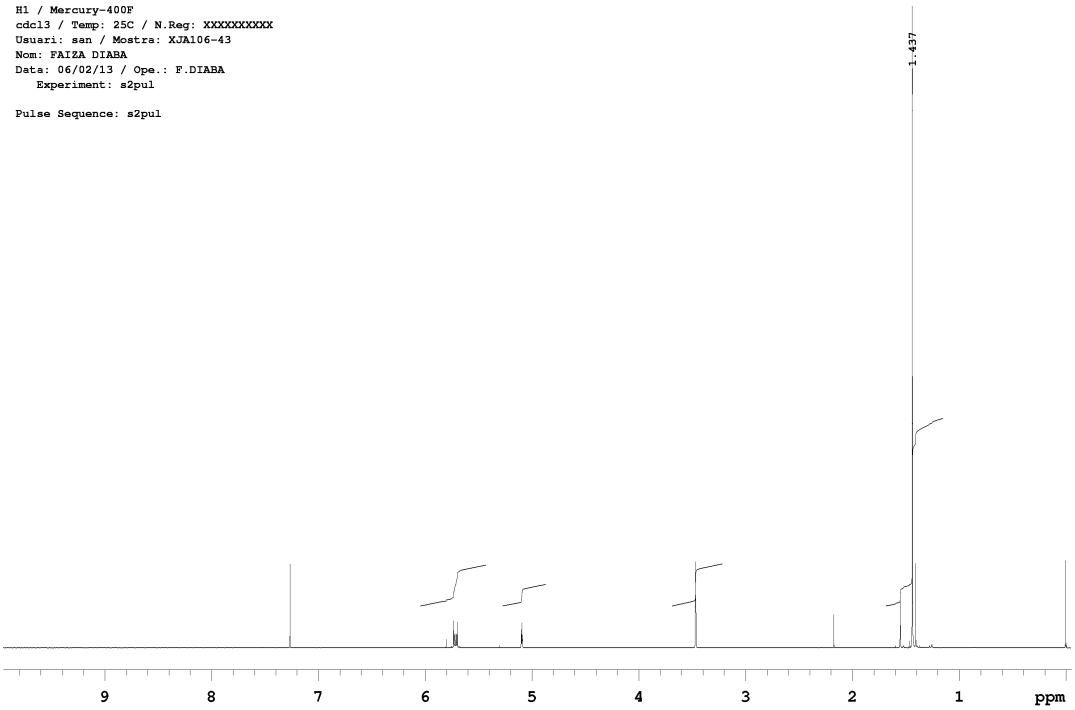

H1 / Mercury-400F
cdcl3 / Temp: 25C / N.Reg: XXXXXXXXXX
Usuari: san / Mostra: XJA109-19
Nom: FAIZA DIABA
Data: 08/02/13 / Ope.: F.DIABA
Experiment: s2pul
Pulse Sequence: s2pul
7.263
1.428
1.423
9
8
7
6
5
4
3
2
1
ppm

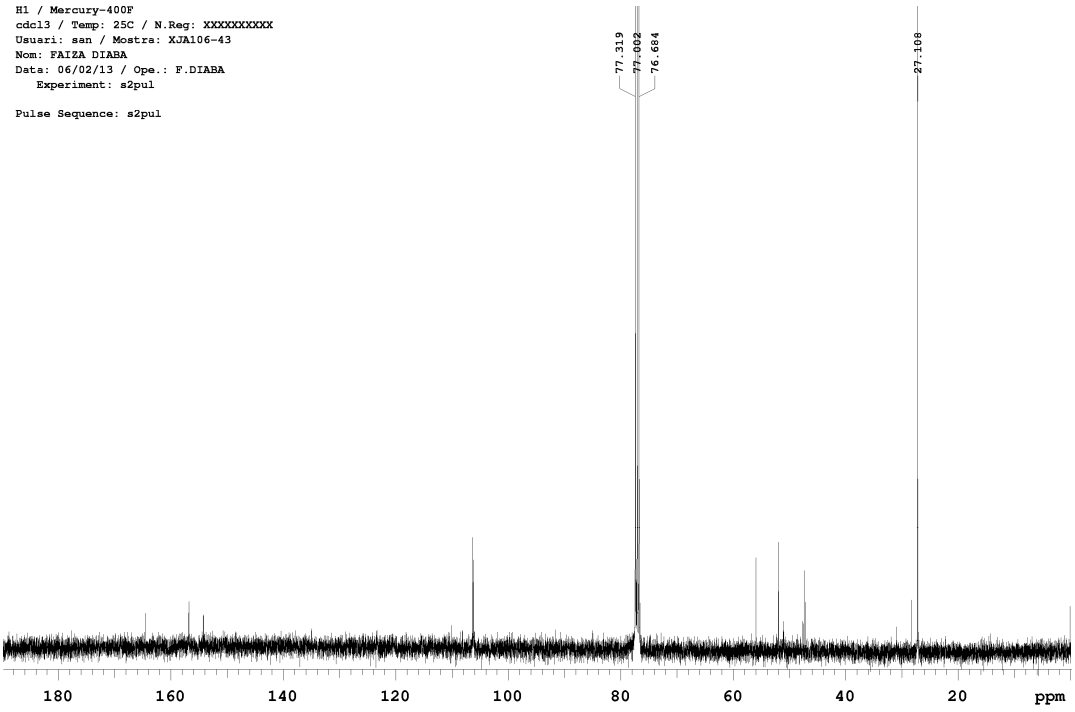

H1 / Mercury-400F
cdcl3 / Temp: 25C / N.Reg: XXXXXXXXXX
Usuari: san / Mostra: XJA109-19
Nom: FAIZA DIABA
Data: 08/02/13 / Ope.: F.DIABA
Experiment: s2pul
Pulse Sequence: s2pul
77.316
76.998
76.681
27.113
180
160
140
120
100
80
60
40
20
ppm

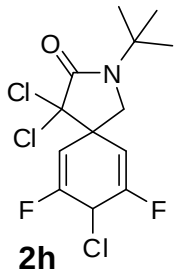


2h

Less polar

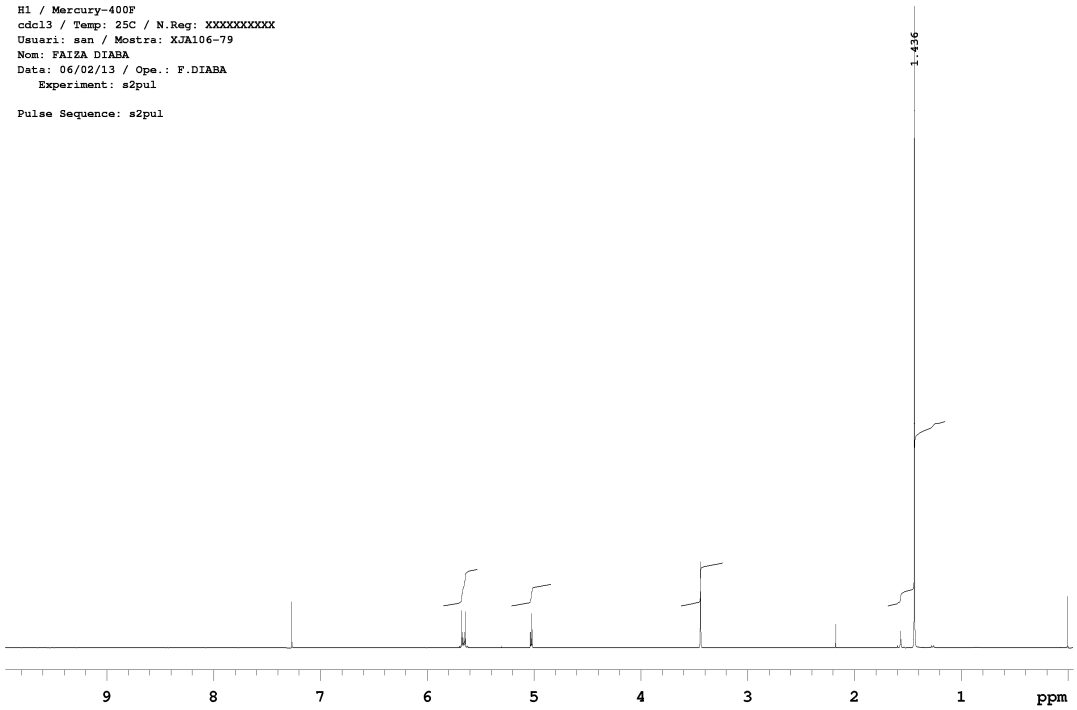


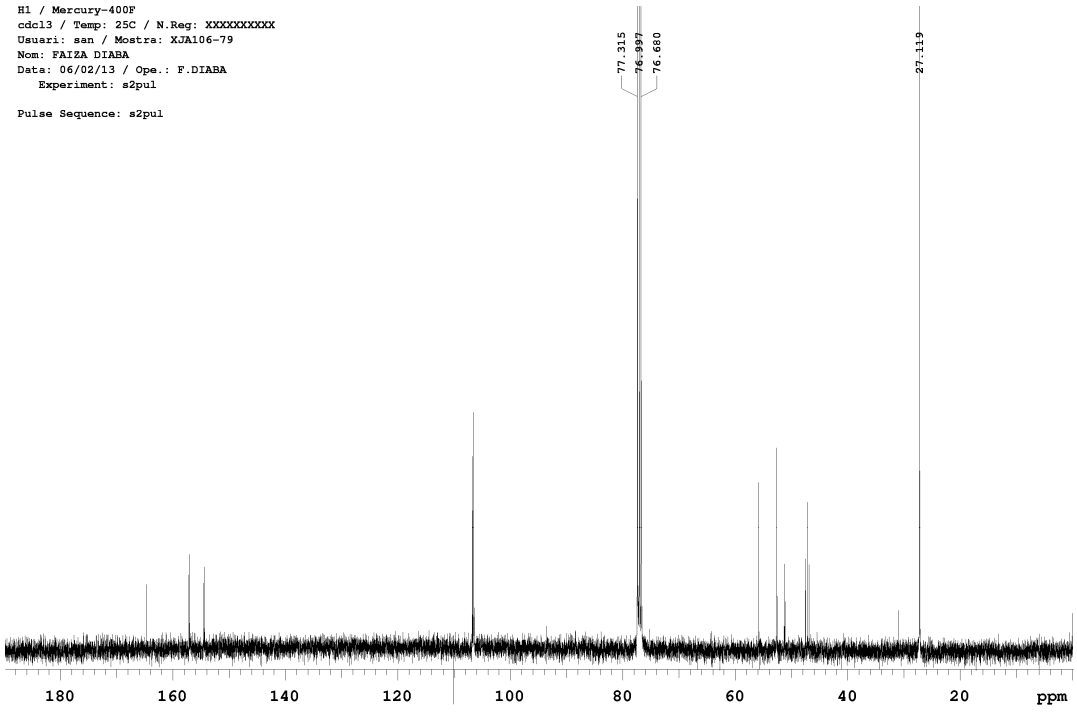




2h

More polar

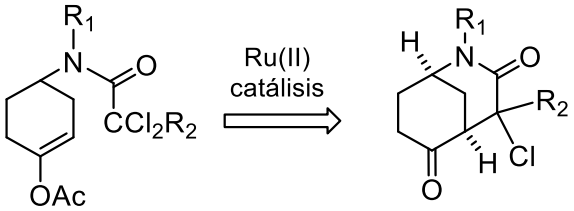




5. Ciclaciones de tricloroacetamidas con transferencia de átomo sobre acetatos de enol catalizadas por Grubbs II: Síntesis del esqueleto tricíclico del FR901483

5.1 Introducción y Objetivos

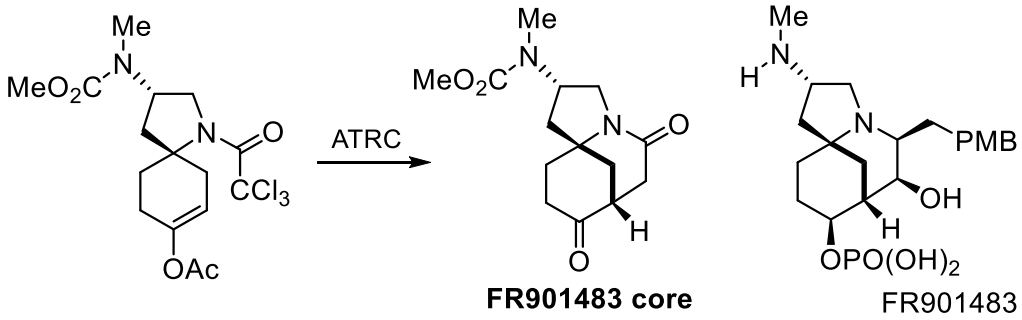
En el capítulo anterior se ha introducido el uso del catalizador de Grubbs-II para promover reacciones de espirociclación mediante un proceso radicalario a partir de tricloroacetamidas derivadas de *p*-metoxibencilaminas. En el último proceso metodológico estudiado en esta Tesis se evaluó si el proceso se podía aplicar a la ciclación radicalaria con transferencia de átomo de tricloroacetamidas sobre acetatos de enol para acceder a morfanos.



R_1 = Bn, SO_2Ph, $CH(CH_3)Ph$
R_2 = Cl, H, CO_2Et

5.1 Síntesis de morfanos mediante ATRC catalizada por Grubbs II

En base a los resultados positivos que se comentarán, posteriormente se planteó la aplicación del procedimiento a un sustrato mucho más exigente estructuralmente para acceder al sistema azatricíclico del inmunosupresor FR901483.[1]



5.2 Objetivo 3: Síntesis del esqueleto azatricíclico del inmunosupresor FR901483

[1] Para los precedentes de síntesis del FR901483, véase apartado 1.4 (pp 14-18).

5.2 Síntesis de morfanos mediante ATRC catalizadas por Grubbs II

Desde 1999, cuando Snapper reportó el uso del catalizador de Grubbs de primera generación como promotor de reacciones radicalarias de tipo Kharasch en procesos intermoleculares entre cloroformo y alquenos,[2] el número de ejemplos de reacciones con transferencia de átomo catalizadas por los distintos complejos de Grubbs ha ido en aumento. Una extensión del proceso ha sido la aplicación a la versión intramolecular para la síntesis de γ-lactonas y γ-lactamas,[3] así como en procesos tándem tanto intra- como intermoleculares involucrando una metátesis de olefinas por cierre de anillo (RCM) seguida de un proceso radicalario con transferencia de átomo (ATRC).[4] Estas etapas de formaciones de enlaces C-C también se han descrito utilizando el catalizador de Grubbs II en escalas preparativas.[5]

5.2.1 Estudios ATRC para la síntesis de morfanos.

Nuestro estudio metodológico se inició con el acetato de enol **3a** (cap 2), como sustrato de referencia, y en base a los resultados previamente obtenidos en el capítulo 4 se llevaron a cabo los estudios de optimización del proceso. Posteriormente se estudió brevemente la aplicación a otros sustratos tales como **3b** (cap. 3), la dicloroacetamida **16**[6] y el producto enantiopuro **17**[6].

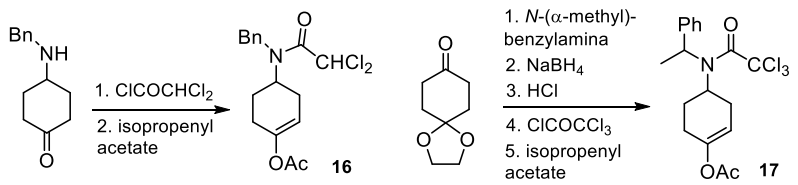
[2] (a) Tallarico, J. A.; Malnick, L. M.; Snapper, M. L. *J. Org. Chem.* **1999**, *64*, 344-345. (b) Simal, F.; Demonceau, A.; Noels, A. F.*Tetrahedron Lett.* **1999**, *40*, 5689-5693.

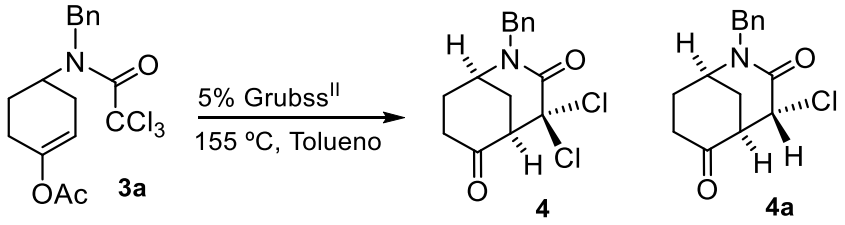
[3] (a) Quayle, P.; Fengas, D.; Richards, S. *Synlett* **2003**, 1797-1800. (b) Faulkner, J.; Edin, C. D.; Fengas, D.; Preece, I.; Quayle, P.; Richards, S. N. *Tetrahedron Lett.* **2005***, 46,* 2381-2385.

[4] (a) Seigal, B. A.; Fajardo, C.; Snapper, M. L. *J. Am. Chem. Soc.* **2005**, *127*, 16329-16332. (b) Edlin, C. D.; Faulkner, J.; Quayle, P. *Tetrahedron Lett.* **2006**, *47*, 1145-1151. (c) Edlin, C. D.; Faulkner, J.; Fengas, D.; Helliwell, M.; Knight, C. K.; House, D.; Parker, J.; Preece, I.; Quayle, P.; Taftery, J.; Richards, S. N. *J. Organometal. Chem.* **2006**, *691*, 5375-5382. (d) McGonagle F. I.; Brown, L.; Cooke, A.; Sutherland, A. *Org. Biomol. Chem.* **2010**, *8*, 3418-3425. (e) Para un proceso competitivo de RCM y ATRC, véase: Schmidt, B.; Pohler, M. Costisella, B. *J. Org. Chem.* **2004**, *69*, 1421-1424.

[5] (a) Schmidt, B.; Pohler, M. *J. Organomet. Chem.* **2005**, 690, 5552-5555. (b) Borguet, Y.; Sauvage, X.; Zaragoza, G.; Demonceau, A.; Delaude, L. *Beilstein J. Org. Chem.* **2010**, *6*, 1167-1173.

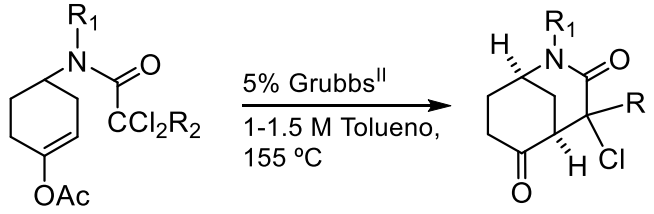
[6] En la figura adjunta se detalla la preparación de lo acetatos de enol **16** y **17**.





5.3 ATRC catalizada por Grubbs II.
a) 2 h, 0.64 M (**4**, 61%, **3a**, 12%); b) 4 h, 0.64 M (**4**, 67%); c) 30 min, 1.3 M (**4**, 68%); d) 15 min, μW, 0.26 M (**4**, 52%, **4a**, 13%).

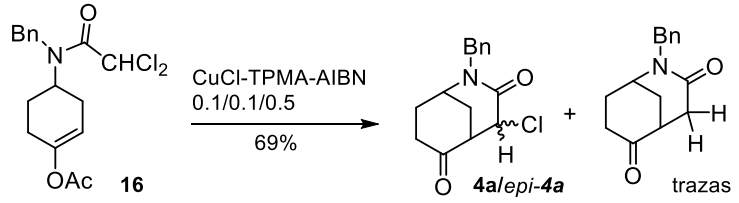
En el transcurso de los estudios (esquema 5.3) se observó la importancia de altas concentraciones para que la reacción ATRC tuviera lugar de manera satisfactoria[7]. Con el uso de activación por microondas también se consiguieron buenos resultados globales. Con los resultados obtenidos se procedió a la aplicación de las condiciones optimizadas a los demás acetatos de enol[8] (Esquema 5.4). Para la completa transformación de la dicloromalonamida **4** fueron necesarios tiempos mínimos de 6 h (1.2 M) obteniéndose una mezcla epimérica (1:1) de **5/*epi*-5**. La dicloroacetamida **16** condujo al morfano **4a** con bajos rendimientos y como mezcla epimérica.[9] El estudio prelimiar a partir de **17** condujo a una mezcla de productos.



4 (R_1 = Bn, R_2 = CO_2Et; **16** (R_1 = Bn, R_2 = H);
17 (R_1 = $CH(CH)_3Ph$, R_2 = Cl);

5.4 Otras síntesis de morfanos mediante ATRC con el catalitzador de Grubbs II.
a) **4** → **5/epi-5** (R_1 = Bn, R_2 = CO_2Et, 50%); b) **16** → **4a** (R_1 = Bn, R_2 = H, 30%); c) **17** → mezcla de diastereómeros (R_1 = $CH(CH)_3Ph$, R_2 = Cl, 30-40% en total).

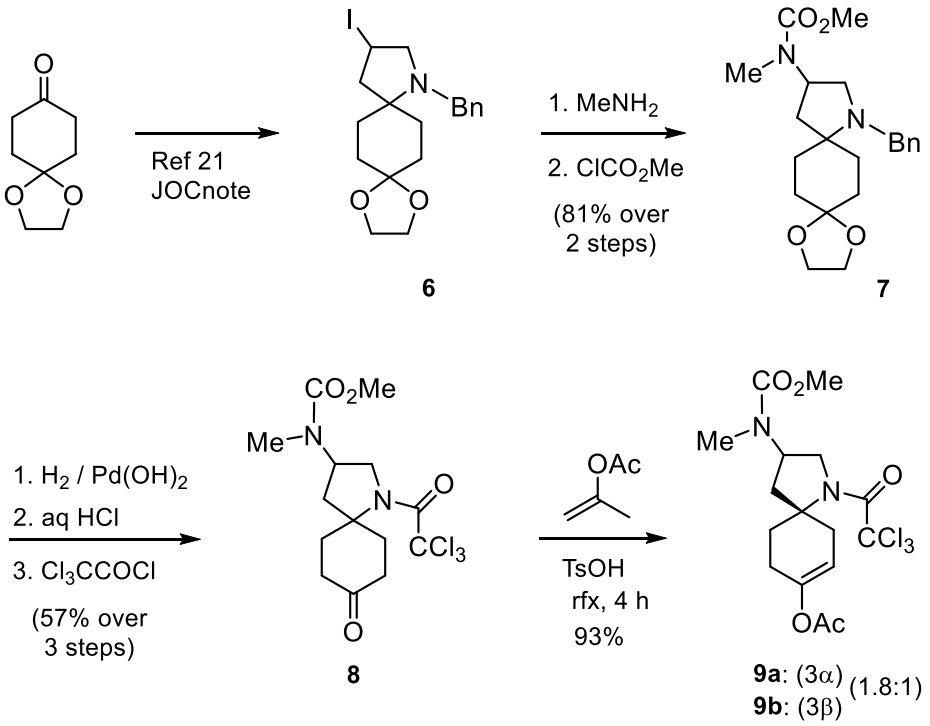
[7] Los ensayos realizados con Grubbs^I o Hoveyda-Grubbs^II dieron pobres resultados, temperaturas inferiores conducían a muy bajas conversiones con largos tiempos de reacción.
[8] El estudio metodológico usaba típicamente ensayos de 100 mg de sustrato en 0.2 mL de tolueno, así pues en realidad y como se observa la molaridad varía según el caso.
[9] El único ensayo realizado de **16** vía ATRC en Grubbs(II) generó asimismo una estructura de normorfano (20%). Un único ensayo realizado en condiciones optimizadas de Cu(I) proporcionó de manera más satisfactoria el morfano **4a**, sin detección de normorfano:



5.3 Síntesis del esqueleto azatricícliclo del inmunosupresor FR901483

5.3.1 Preparación del sustrato de partida

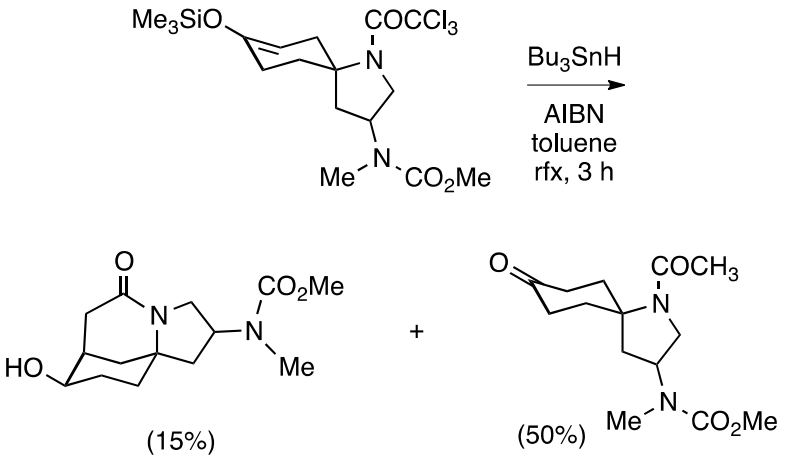
Con estos resultados en mano y los precedentes, tanto en la literatura como en nuestro grupo, nos propusimos explorar la síntesis del núcleo del FR901483 por cierre de anillo piperidínico vía ATRC promovido por Grubbs^{II}. En el esquema adjunto (5.5) se detalla la preparación del acetato de enol **9**, que se formó como una mezcla de regioisómeros 1.8:1, de difícil separación.



5.5 Preparación del sustrato requerido para la ciclación radicalaria

En el grupo de investigación se había observado que el uso de un proceso radicalario reductivo para formar el esqueleto FR901483,[10] proporcionaba bajos rendimientos del producto de ciclación. La ineficiencia del proceso era debida a que la tricloroacetamida de partida no experimentaba el cambio conformacional necesario (Esquema 5.6). La barrera energética requerida para disponer la unidad de tricloroacetamida en axial había sido evaluada aproximadamente en 3 Kcal/mol para sistemas análogos.[11] Puesto que el proceso era lento, la reducción del radical diclorocarbamoilmetilo compite favorablemente con el proceso de ciclación.

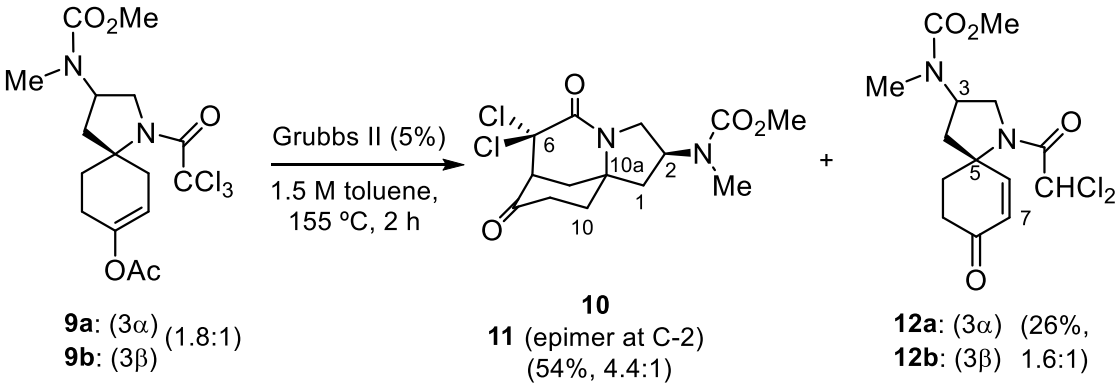
[10] Eva Ricou, Tesis Dotoral, Universidad de Barcelona, 2007.
[11] Bonjoch, J.; Diaba, F.; Puigbó, G.; Solé, D.; Segarra, V.; Santamaria, L.; Beleta, J.; Ryder, H.; Palacios, J.-M. *Bioorg. Med. Chem.* **1999**, *7*, 2891-2897.



5.6 Antecedentes grupo de investigación de química radicalaria reductiva en la síntesis del esqueleto del inmunosupresor FR901483

5.3.2 ATRC promovida por Grubbs(II) para el esqueleto FR901483

A la vista de estos resultados previos, un proceso no reductivo tal como la ATRC parecía una alternativa prometedora. Al operar con una mezcla 1.8:1 de los acetatos de enol **9,** en las condiciones optimizadas dio lugar al derivado azatricíclico **10** y su epímero **11** en una relación 4.4:1 y en un 54% de rendimiento global, así como la inesperada mezcla epimérica de enonas **12**.



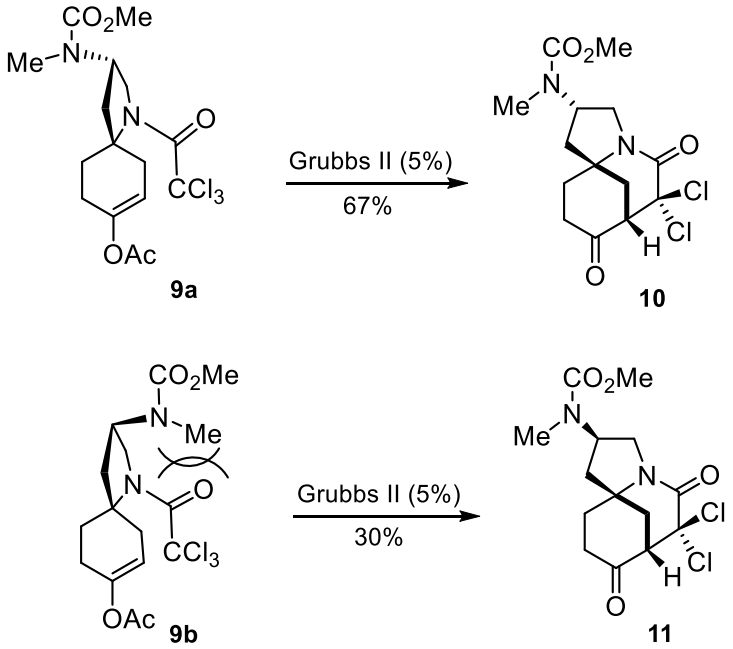
9a: (3α) (1.8:1)
9b: (3β)

10
11 (epimer at C-2)
(54%, 4.4:1)

12a: (3α) (26%,
12b: (3β) 1.6:1)

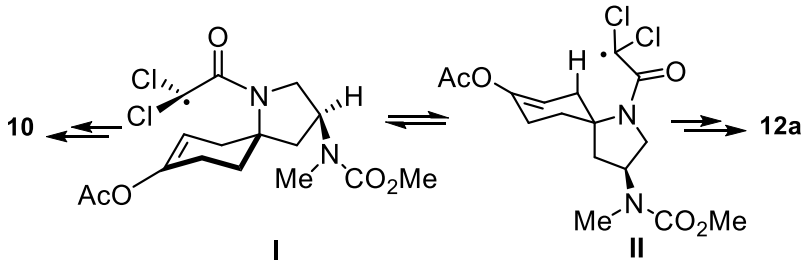
5.7 Condiciones optimizadas ATRC promovida por Grubbs(II) a la mezcla **9a** y **9b**

El rendimiento para la etapa de ciclación fue del 67% (esquema 5.8) en el caso de **9a** pero tan solo un 30% para **9b**. Parece verosímil relacionar el distinto comportamiento de ambos casos a motivos estéricos debido a la conformación necesaria para la ciclación, como se puede ver (esquema 5.8) la disposición del *N*-metilo del carbamato en **9b** dificulta su proceso en comparación a **9a**.



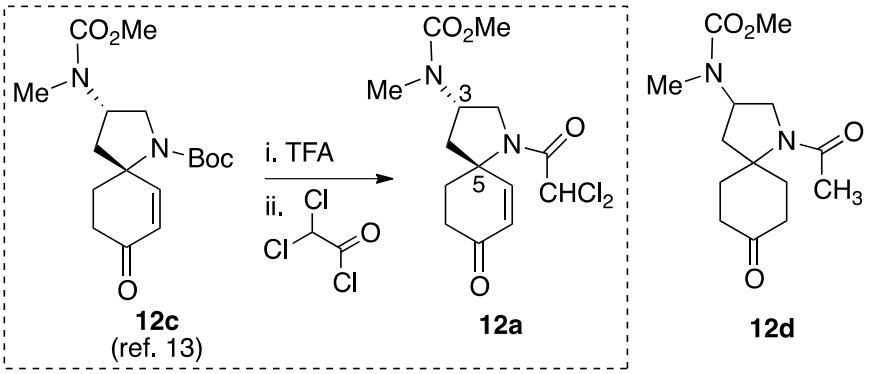
5.8 Efectos estéricos para la ATRC de **9**

Asimismo, el subproducto **12a** proviene de **9a**, el cual surge de una transferencia 1,5-hidrógeno del mismo radical diclorocarbamoilo que da **10** y **12a** desde **9a**. Una vez más se pone de manifiesto que la activación necesaria para la ciclación permite competir en los caminos de reacción. En base a estas observaciones se ha argumentado (esquema 5.9) en términos de confórmeros **I** y **II**. Así, mientras **I** se encuentra en la geometría necesaria para la ciclación 6-*exo*, **II** no puede experimentar una ciclación.[12] Sin embargo, **II** cumple con los requisitos estereoelectrónicos para realizar una transferencia 1,5 con el átomo de hidrógeno alílico adyacente. Este radical alílico generado procede a una transferencia de átomo para acabar formando **12a**. Lo mismo ocurre para **12b** proveniente de **9b**.



5.9 Caminos radicalarios competitivos: Ciclación vs transferencia de átomo 1,5-hidrógeno

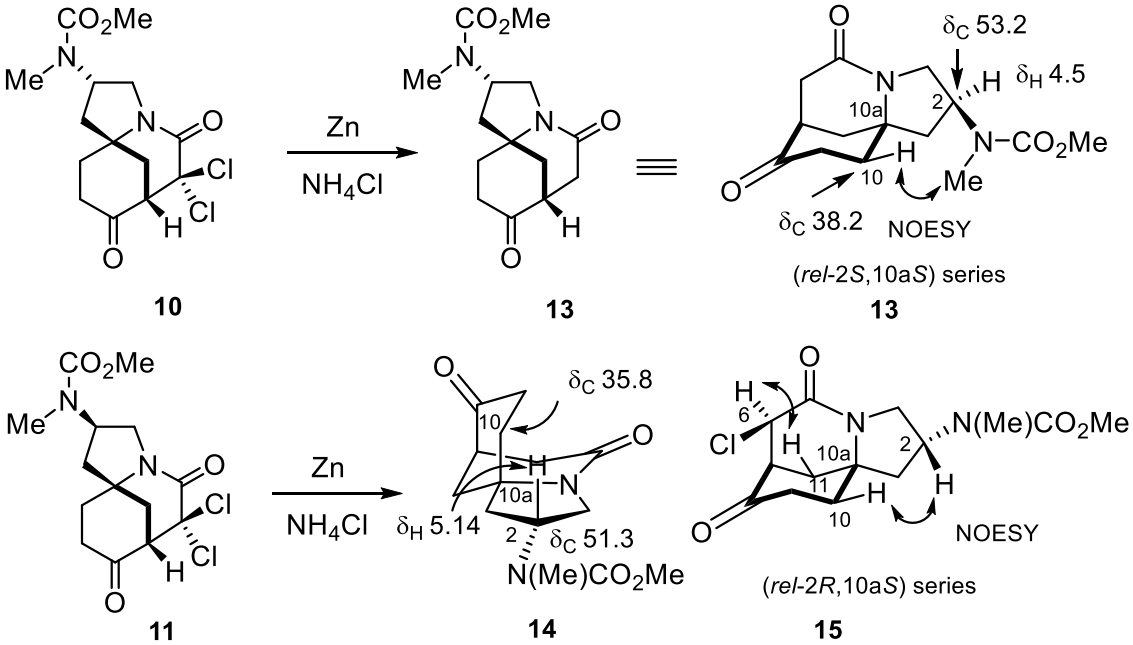
[12] Wardrop, D. J.; Zhang, W. *Org. Lett*. **2001**, *3*, 2353-2356.



5.10 Elucidación estructural de **12a** por correlación química

A fin de establecer la estructura de **12a**, se llevó a cabo una correlación química con el azaespiro **12c**[13], el cual tiene un sustituyente *N*-Boc y una configuración conocida (3*S*, 5*R*). La desprotección de **12c** seguida por dicloroacetilación proveyó un compuesto, cuyos datos de RMN ^{1}H eran totalemnte coincidentes con el isómero mayoritario **12a**.

Como se esperaba, la reducción de la mezcla de epímeros **12a**/**12b** mediante hidrogenación proveyó como único compuesto el azaespiro **12d**. El tratamiento de **10** y de **11** con Zinc proporcionó los correspondientes compuestos **13** y **14**, respectivamente, así como el compuesto parcialmente reducido **15** proveniente de **11**.



5.11 Procesos de reducción de **10** y **11** con sus datos representativos de RMN

La estereoquímica de los compuestos azatricíclicos sintetizados se elucidó mediante espectros bidimensionales de RMN (COSY, HSQC, NOESY). Para una discusión de la elucidación estructural, véase el artículo en el apartado 5.5.

[13] Diaba, F.; Ricou, E.; Bonjoch, J. *Tetrahedron Asymmetry* **2006**, *17*, 1437-1443.

5.4 Resumen

Se ha descrito la primera ATRC intramolecular entre tricloroacetamidas y acetatos de enol utilizando el catalizador de Grubbs(II) aplicado a la síntesis de morfanos[14], expandiendo los alcances de estos catalizadores más allá de las reacciones de metátesis.[15]

Los resultados de los estudios metodológicos permitieron construir el esqueleto azatricíclico del inmunosupresor FR901483. Aunque el rendimiento de la etapa clave de ciclación es moderado, está en consonancia con lo descrito en la literatura para esta etapa conflictiva de generación del sistema azatricíclico a partir de 2-azaespiro[4.5]decan-8-onas debido a problemas en la regioselectividad del proceso.

[14] Recientemente, en una aproximación a la aspidofilina A, el núcleo morfano se formó mediante $(Ph_3P)_3RuCl_2$ como catalitzador promotor de la ciclación de una tricloroacetamida en un alqueno simple: Li, Q.; Li, G.; Ma, S.; Feng, P.; Shi, Y. *Org. Lett*. **2013**, *15*, 2601-2603.
[15] Alcaide, B.; Almendros, P.; Luna, A. *Chem. Rev.* **2009**, *109*, 3817-3858.

5.5 Atom transfer radical cyclization of trichloroacetamides to electron-rich acceptors using Grubbs´catalysts: Synthesis of the tricyclic framework of FR901483

Faïza Diaba, Agustín Martínez-Laporta,
Josep Bonjoch
J. Org. Chem. **2014**, *79*, 9365-9772

JOC The Journal of Organic Chemistry

Note

pubs.acs.org/joc

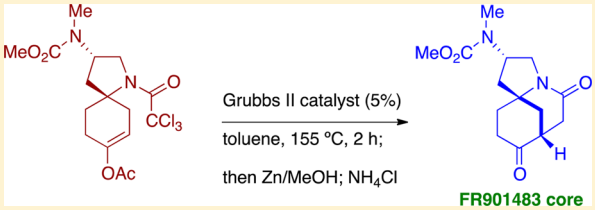
Atom Transfer Radical Cyclization of Trichloroacetamides to Electron-Rich Acceptors Using Grubbs' Catalysts: Synthesis of the Tricyclic Framework of FR901483

Faïza Diaba,* Agustín Martínez-Laporta, and Josep Bonjoch*

Laboratori de Química Orgànica, Facultat de Farmàcia, IBUB, Universitat de Barcelona, Av. Joan XXIII s/n, 08028-Barcelona, Spain

Supporting Information

ABSTRACT: Intramolecular Kharasch-type additions of trichloroacetamides on anisole and enol acetates catalyzed by Grubbs' ruthenium carbenes are described. This protocol provides access to highly functionalized 2-azaspiro[4.5]decanes, morphan compounds, and the azatricyclic core of FR901483.



Since 1999, when Snapper reported the use of Grubbs' first generation catalyst (**G-1**) as a promoter in the Kharasch intermolecular reaction of chloroform and alkenes,[1] the number of reported atom transfer radical reactions catalyzed by Grubbs' ruthenium carbene complexes has been growing. An extended version of the process has been applied intramolecularly in the synthesis of γ-lactones and γ-lactams,[2] as well as in both intra- and intermolecular tandem processes involving olefin ring-closing metathesis (RCM) and atom transfer radical processes (ATRC).[3] These two C−C bond-forming steps were also mediated by Grubbs' second generation catalyst (**G-2**) in preparative yields.[4]

The intramolecular processes reported to date are limited to substrates embodying simple alkenes as radical acceptors. This encouraged us to investigate ATRC[5] promoted by Grubbs' catalysts using substrates in which electron-rich double bonds (e.g., anisole or enol acetate substrates) act as radical acceptors. We report herein the use of a Grubbs' catalyst (**G-2**) to promote reactions of trichloroacetamides upon anisoles to afford, through a dearomative cyclization, 2-azaspiro[4.5]decane derivatives (Figure 1), whose skeleton occurs in several natural compounds,[6] as well as upon cyclic enol acetates to give morphan compounds.[7] The latter procedure was also applied to synthesize the azatricyclic framework of the immunosuppressant FR901483[8,9] by the elaboration of the bridged nucleus.

We began by examining the feasibility of applying the **G-2**-mediated ATRC to anisole derivatives bearing a trichloroacetamide handle (i.e., **1**) to achieve 1-azaspiro[4.5]decane compounds.[10,11] On the basis of our previous results in dearomatizing radical spirocyclization upon inactivated benzene promoted by Cu(I),[11d] we used the *tert*-butyl derivative **1a** as the substrate. The required trichloroacetamide **1a** was prepared through imine formation from 4-methoxybenzaldehyde and *tert*-butylamine, followed by reduction and trichloroacetylation.

Treatment of **1a** with 5% of **G-2** at 155 °C for 30 min in 0.2 mL of toluene provided **2a** in very good yield (Table 1, entry 1). The importance of having a *tert*-butyl group on the nitrogen to lock the substrate in a conformation prone to cyclization was once again evident, since the reaction with **1b** in the same conditions provided the corresponding azaspirocycle **2b** in poor yield (entry 2). Microwave activation gave the azaspirodecane derivative with a lower yield (entry 3), and switching to **G-1** or Hoveyda−Grubbs' second generation catalyst (**G-3**) did not improve the results (entries 4 and 5). When **1a** was treated overnight with 30% of CuCl at 80 °C, **2a** was also isolated in an acceptable yield (61%), although accompanied by the secondary amide **1g** ($R^1 = R^2 = H$) arising from the cleavage of the *tert*-butyl group in **1a** (entry 6).

The results of optimization studies carried out with **1a** prompted us to apply the cyclization procedure to more substituted methoxybenzenes (Table 1, entries 7 and 8). It was

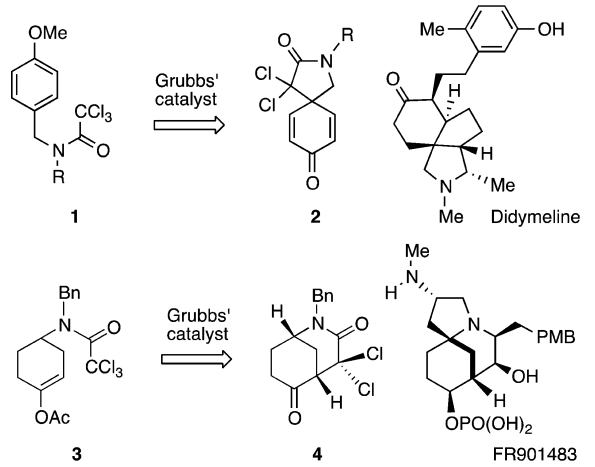
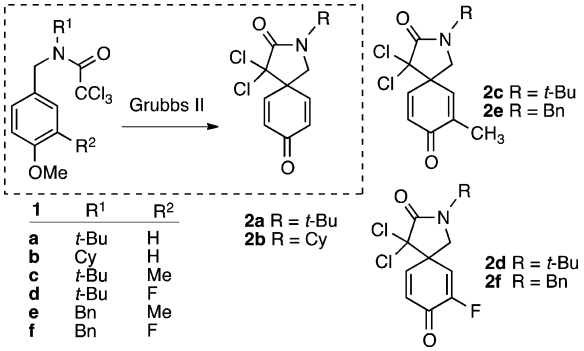


Figure 1. An approach to 2-azaspiro[4.5]decanes and 2-azabicyclo[3.3.1]nonanes by a radical cyclization using Grubbs' catalyst.

Received: May 20, 2014
Published: September 9, 2014

   dx.doi.org/10.1021/jo501110c | J. Org. Chem. 2014, 79, 9365−9372

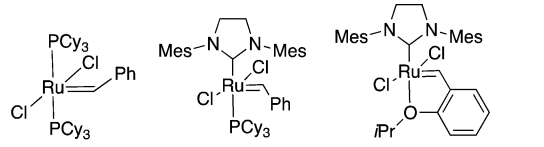
Table 1. Ruthenium(II)-Catalyzed ATRC in the Synthesis of 2-Azaspirodecanes



1	R^1	R^2
a	*t*-Bu	H
b	Cy	H
c	*t*-Bu	Me
d	*t*-Bu	F
e	Bn	Me
f	Bn	F

entry	compd	catalyst[a] (mol %)	method[b]	compd (yield %)[c]
1	**1a**	**G-2** (5)	A	**2a** (81)
2	**1b**	**G-2** (5)	A	**2b** (17)
3	**1a**	**G-2** (5)	B	**2a** (32)[d]
4	**1a**	**G-1**(5)	A	**2a** (58)[e]
5	**1a**	**G-3** (5)	A	**2a** (35)[e]
6	**1a**	CuCl (30)	C	**2a** (61)[e]
7	**1c**	**G-2** (5)	A	**2c** (72)
8	**1d**	**G-2** (5)	A	**2d** (54)
9	**1e**	**G-2** (5)	A	**2e** (52)
10	**1f**	**G-2** (5)	A	**2f** (37)

[a]



Grubbs I catalyst **G-1** | Grubbs II catalyst **G-2** | Hoveyda-Grubbs II catalyst **G-3**

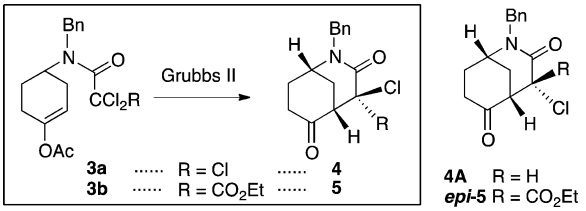
[b]A: 100 mg scale in 0.2 mL of toluene at 155 °C for 30 min. B: 200 mg scale in 1.5 mL of toluene at 120 °C for 1 h, μW. C: 200 mg scale in 2 mL of CH_3CN at 80 °C, overnight. [c]Yields refer to pure products isolated by flash chromatography. [d]**1a** was also recovered (20%). [e]The de-*tert*-butyl derivative **1g** ($R^1 = R^2 = H$) was also isolated (36%, entry 4, 21%, entry 5, 35%, entry 6).

found that the substrate **1d**, with an electron-withdrawing group (F) at the arene ring, underwent spirocyclization in lower yield than from the anisole **1c** bearing an electron-neutral group (Me). We also explored the spirocyclization using substrates embodying two aromatic rings with different electronic properties (Table 1, entries 9 and 10). In both cases the cyclization took place on the anisole ring, and once again the substrate with the higher electron density in the aromatic ring (i.e., **1e**) underwent the spirocyclization in better yield than compound **1f** bearing a fluorine atom in the aromatic ring. The lower yield in the series with a *N*-benzyl substituent (**1e**, **1f**) compared with the series with a *N*-*tert*-butyl substituent (**1a**, **1c**, **1d**) may be attributed to the mixture of rotamers (1:1 ratio) in the former.

To our knowledge, this 2-azaspiro[4.5]decadienone synthetic entry is the first reported Grubbs' catalyst-promoted dearomatizing cyclization of benzene compounds.

These promising results encouraged us to explore the Ru-catalyzed coupling of the amino-tethered trichloroacetamide and enol acetate **3a** to achieve morphan compounds.[12] Thus, **3a** was treated with **G-2** (5%) in 0.4 mL of toluene, and after 2 h of reaction at 155 °C, **4** was isolated in 61% yield, together with some starting material (Table 2, entry 1). A longer reaction time

Table 2. Ruthenium(II)-Catalyzed ATRC in Morphan Synthesis



entry	catalyst (%)	conditions[a]	yield (%)
1	**G-2** (5)	2 h, 155 °C, 0.64 M	61[b]
2	**G-2** (5)	4 h, 155 °C, 0.64 M	67
3	**G-2** (5)	30 min, 155 °C, 1.3 M	68
4	**G-2** (5)	15 min, 155 °C μW, 0.26 M	65[c]
5	**G-1** (5)	15 min, 155 °C μW, 0.26 M	52[d]
6[e]	**G-2** (5)	6 h, 155 °C, 0.23 M	50[e]

[a]Reactions on 100 mg scale in toluene. [b]12% of **3** was recovered. [c]Overall yield of a 4:1 mixture of **4** and **4A**, respectively. [d]10% of starting material was recovered. [e]Reaction from **3b** leading to a 1:1 mixture of **5** and *epi*-**5**.

was required to achieve a full conversion, providing **4** in 67% yield (entry 2), but the reaction time was shortened to 30 min by increasing the concentration in the reaction mixture to 1.5 M (entry 3). Microwave activation (entry 4) also reduced the reaction time, giving a similar result, although **4** was partially monodechlorinated to morphan **4A**,[13] and no improvement was obtained when using **G-1** (entry 5). The procedure was also applied to dichloroester **3b**, which furnished morphan **5** in 52% yield as a mixture of diastereomers at C-4 (entry 6).

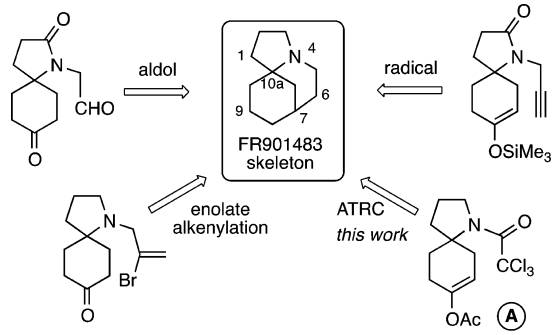
In summary, to our knowledge, using this protocol to obtain morphan compounds (**3** → **4**/**5**), we have described the first intramolecular C−C bond between a trichloroacetamide and an enol acetate promoted by Grubbs' ruthenium carbenes,[14] thus expanding the scope of these catalysts beyond the metathesis reaction.[15]

With these results in hand, we investigated the potential synthetic utility of the procedure to achieve the core structure of the immunosuppressant FR901483.[8,9] The major stumbling blocks in the synthesis of this alkaloid[16] are the generation of the spirocenter at C(10a) and the assembly of the bridged framework.[17] The synthetic strategies adopted to construct the bridged framework of FR901483 from a functionalized 1-azaspiro[4.5]decanone, involving the formation of C(6)−C(7), are outlined in Scheme 1, which for the sake of clarity omits the substituents in the tricyclic framework. Almost all of the strategies developed for the synthesis of the FR901483 skeleton based on a ring closure of a 1-azaspiro[4.5]decane derivative utilize aldol processes,[16a−e,h,17g] while the other procedures are based on a palladium-promoted coupling of a vinyl halide and ketone enolate[17d,e,i,j] or a Bu_3SnH-promoted radical closure from an alkyne tethered with a trimethylsilyl enol ether.[17b]

We observed some time ago that using reductive processes to form the FR901483 skeleton,[18] such as the radical cyclization of trichloroacetamides upon silyl enol ether analogues of **A** (TMS instead of Ac, Scheme 1), gave poor results,[19] probably because the starting trichloroacetamide was reluctant to undergo the required conformational change. The energy barrier required to axially locate the trichloroacetamide unit has been evaluated to

dx.doi.org/10.1021/jo501110c | J. Org. Chem. 2014, 79, 9365−9372

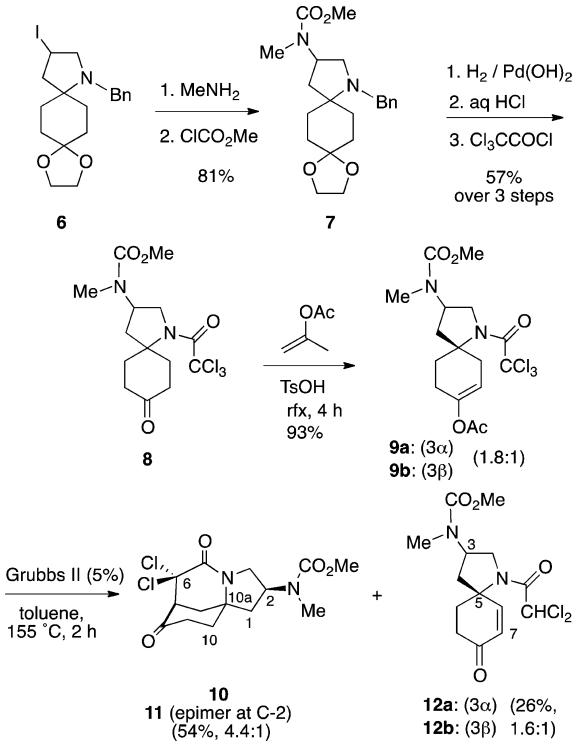
Scheme 1. Synthesis of the FR901483 Core by Piperidine Ring Closure



be approximately 3 kcal/mol in similar systems.[20] Since the process is slow, the reduction of the dichlorocarbamoylmethyl radical strongly competed with the cyclization process.

In the light of these previous results, a nonreductive process such as the ATRC studied here seemed a promising alternative to achieve the radical cyclization toward the diazatricyclic core of the natural product. The proradical trichloroacetamide required was prepared from azaspirodecane **6**,[21] via carbamate **7**,[17d] following the transformations depicted in Scheme 2, with a final

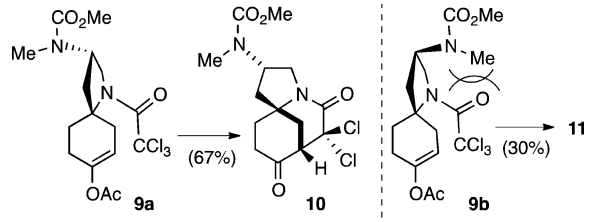
Scheme 2. Grubbs II Catalyst-Mediated ATRC Leading to the FR901483 Framework



treatment of ketone **8** with isopropenyl acetate to yield a regioisomeric mixture of enol acetates **9** in a 1.8:1 ratio. When the nonseparated mixture of **9** was treated with **G-2** at 155 °C for 2 h, the diazatricyclic derivative **10** and its epimer **11** were obtained in a 4.4:1 ratio and 54% overall yield,[22] in addition to the unexpected epimeric mixture of enones **12** (Scheme 2).

The yield for the cyclization step was 67% in the case of **9a**, but only 30% for **9b**. It is plausible that this different behavior could be due to the steric crowding of the *N*-methyl carbamate substituent with the trichloroacetyl group in the conformer required for the cyclization of **9b** to **11**. This steric effect was not present in the transition state of the cyclization leading to **10** from **9a** (Scheme 3).

Scheme 3. Steric Grounds for the ATRC of 9



The formation of enones **12** from **9** arises from a 1,5-H hydrogen transfer from the same dichlorocarbamoyl radical intermediate that gave **10** and **12a** from **9a**. The formation of **12a** again made evident that, for conformational reasons, the activation required for the radical cyclization allows competitive reaction pathways. As illustrated in Figure 2, we have

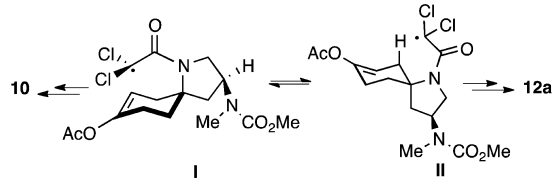


Figure 2. Competing radical pathways: cyclization versus 1,5-hydrogen atom transfer.

rationalized these observations in terms of conformers **I** and **II**. While **I** can adopt the geometry necessary for 6-*exo* cyclization to take place, **II** is unable to cyclize.[17b] However, **II** does meet the stereoelectronic requirements for a 1,5-transfer of the adjacent allylic hydrogen atom. The allylic radical thus generated undergoes an atom transfer with the pendant trichloroacetamide to form **12a**. The same pathway led to **12b** from **9b**.

The structure of **12a**, with relative configuration (3*S*,5*R*), was ascertained by chemical correlation with azaspiro **12c**,[23] which has a *N*-Boc substituent and known configuration.[24]

Treatment of **10** and **11** with zinc afforded the corresponding dechlorinated derivatives **13** and **14**, the partially reduced compound **15** also being isolated from **11**. The stereochemistry of the synthesized azatricyclic compounds was elucidated by 2D NMR spectra (COSY, HSQC, NOESY). The relative configuration (relationship between C-2 and C-10a) in both series of FR901483 skeletons was fixed by NOESY experiments. The NOESY correlation of the *N*-methyl group with the H-10eq in compound **13** indicated that this group is on the same side of the pyrrolidine ring as C-10, which occurs only when the relative configuration is (2*S*,10a*S*). This assignment for **13** established the relative configuration of its dichlorinated precursor **10**. The relative configuration (2*R*,10a*S*) for the epimeric series was confirmed in compound **15** (Figure 3), based on the correlation between H-2 and H-10eq observed in the NOESY NMR spectrum.[25] In turn, this assignment ensured the relative stereochemistry of the synthetically interrelated **11** and **14**. The ^{1}H and ^{13}C NMR spectra of azatricyclic compounds show two patterns, according to the relative configuration at C-2 versus C-10a. Hence, the isomers **10** and **13** with the chemical

dx.doi.org/10.1021/jo501110c | J. Org. Chem. 2014, 79, 9365−9372

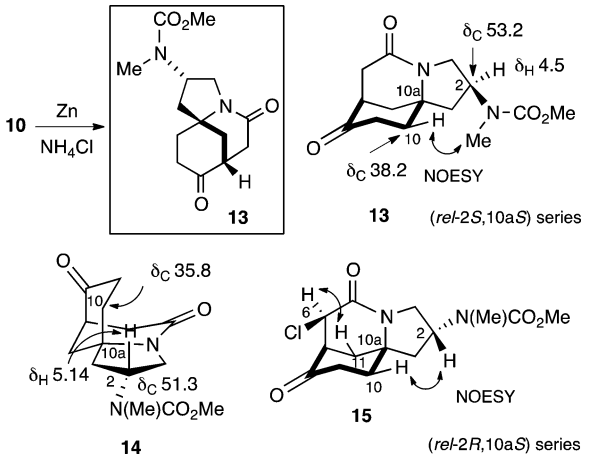


Figure 3. Representative NMR data of azatricyclic compounds **13**−**15**.

shift δ 4.55 for H-2 and δ ~53.5 for C-2 correspond to the FR901483 relative configuration, while the epimeric isomers **11**, **14**, and **15** showed a chemical shift δ ~5.15 for H-2 and δ ~51.5 for C-2. These downfield and upfield effects, compared with the data in the FR901483 stereochemistry series, are a consequence of the compression[26] of the C10−C10a bond with the H-2 in compounds with the relative configuration (2*R*,10a*S*) for the key stereogenic atoms in the azatricyclic ring.

In summary, we have reported here the first intramolecular ATRC between a trichloroacetamide and an enol acetate using Grubbs' second generation catalyst, which was applied to synthesize the morphan ring. The reaction then enabled us to build the tricyclic skeleton of the immunosuppressant FR901483. Moreover, the process was also used with electron-rich arenes for the preparation of 2-azaspirodecadienes. We have therefore described the first ATRC using Grubbs II catalyst on substituted electron-rich double bonds as radical acceptors.

EXPERIMENTAL SECTION

General. All product mixtures were analyzed by thin layer chromatography using TLC silica gel plates with a fluorescent indicator (λ = 254 nm). The spots were located by UV light or a 1% $KMnO_4$ aqueous solution. Unless otherwise noted, chromatography refers to flash chromatography and was carried out on SiO_2 (silica gel 60, 200−500 mesh). Drying of the organic extracts during the reaction workup was performed over anhydrous Na_2SO_4. A CEM Discover microwave reactor with an external sensor was used. Infrared spectra were recorded on a FT-IR spectrometer. Chemical shifts of ^1H and ^{13}C NMR spectra are reported in ppm downfield (δ) from Me_4Si. All NMR data assignments are supported by gCOSY and gHSQC experiments.

***N*-(*tert*-Butyl)-2,2,2-trichloro-*N*-(4-methoxybenzyl)acetamide (1a).** From 4-methoxybenzaldehyde (2 g, 14.7 mmol) and *tert*-butylamine (1.75 g, 23.9 mmol), following the three-step procedure previously described,[11d] **1a** was obtained as a white solid (4.43 g, 85%): mp 68−70 °C; IR (film) 2998, 2968, 2934, 2835, 1714, 1683, 1613 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 1.41 (s, 9H, CH_3), 3.81 (s, 3H, OCH_3), 4.98 (br s, 2H, CH_2Ar), 6.88 (d, J = 8.4 Hz, 2H, ArH), 7.19 (d, J = 8.8 Hz, 2H, ArH); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 28.1 (CH_3), 50.5 (CH_2Ar), 55.3 (OCH_3), 61.8 (C), 95.5 (CCl_3), 113.8 (*m*-C), 127.7 (*ipso*-C), 130.4 (*o*-C), 158.7 (*p*-C), 160.8 (CO). HRMS (ESI-TOF) *m*/*z*: $[M + H]^+$ calcd for $C_{14}H_{19}Cl_3NO_2$ 338.0476; found 338.0484.

2,2,2-Trichloro-*N*-cyclohexyl-*N*-(4-methoxybenzyl)acetamide (1b). Operating as above, **1b** was obtained from 4-methoxybenzaldehyde (4 g, 29.4 mmol) and cyclohexylamine (3.5 g, 35.29 mmol) as a white solid (9.73 g, 91% over three steps): mp 109−110 °C; IR (film) 3004, 2935, 2855, 1673, 1613 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 1.08 (m, 1H), 1.32 (m, 2H), 1.51 (m, 2H), 1.66 (d, J = 13.2 Hz, 1H), 1.81 (d, 2H), 1.90 (d, J = 11.2 Hz, 2H), 3.78 (s, 3H), 4.44 (t, J = 11.4 Hz, 1H), 4.53 (s, 2H), 6.84 (d, J = 8.4 Hz, 2H), 7.15 (d, J = 8 Hz, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 25.1 (CH_2), 25.6 (CH_2), 31.0 (CH_2), 47.3 (CH_2), 55.2 (CH_3), 59.3 (CH), 93.9 (C), 113.8 (CH), 127.8 (C), 129.7 (CH), 158.5 (CH), 160.6 (CO). HRMS (ESI-TOF) *m*/*z*: $[M + H]^+$ calcd for $C_{16}H_{21}Cl_3NO_2$ 364.0632; found 364.0642.

***N*-*tert*-Butyl-2,2,2-trichloro-*N*-(4-methoxy-3-methylbenzyl)-acetamide (1c).** Operating as above, from 4-methoxy-3-methylbenzaldehyde (2 g, 13.3 mmol) and *tert*-butylamine (1.85 mL, 17.3 mmol), **1c** was obtained (1.90 g, 40% over three steps) after chromatography (hexane/CH_2Cl_2 3:1 to CH_2Cl_2) as an amorphous solid: mp 113−114 °C; IR (KBr) 3014, 2955, 2926, 2837, 1678, 1611 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 1.42 (s, 9H), 2.21 (s, 3H), 3.82 (s, 3H), 4.95 (br s, 2H), 6.78 (d, J = 8.4 Hz, 1H), 7.01 (br s, 1H), 7.06 (dd, J = 8.4, 2 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 16.3 (CH_3), 28.0 (CH_3), 50.5 (CH_2), 55.3 (CH_3), 61.7 (C), 95.4 (C), 109.6 (CH), 124.9 (CH), 126.6 (C), 128.7 (CH), 129.8 (C), 156.8 (C), 160.7 (CO). HRMS (ESI-TOF) *m*/*z*: $[M + Na]^+$ calcd for $C_{15}H_{20}Cl_3NNaO_2$ 374.0452; found 374.0457.

***N*-*tert*-Butyl-2,2,2-trichloro-*N*-(3-fluoro-4-methoxybenzyl)-acetamide (1d).** Operating as above, from 3-fluoro-4-methoxybenzaldehyde (0.5 g, 3.24 mmol) and *tert*-butylamine (0.45 mL, 4.21 mmol), **1c** was obtained (0.72 g, 63%) after chromatography (hexane/CH_2Cl_2 3:1 to CH_2Cl_2) as an amorphous solid: mp 131−132 °C; IR (KBr) 3007, 2975, 2938, 2845, 1663, 1628 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 1.42 (s, 9H), 3.89 (s, 3H), 4.96 (br s, 2H), 6.91−7.04 (m, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 28.1 (CH_3), 50.1 (CH_2), 56.3 (CH_3), 61.9 (C), 95.2 (C), 113.3 (d, J = 2.3 Hz, CH), 114.4 (d, J = 19.3 Hz, CH), 122.11 (d, J = 3.9 Hz, CH), 131.5 (d, J = 5.4 Hz, C), 146.7 (d, J = 10.1 Hz, C), 152.3 (d, J = 245.4 Hz, CF), 160.7 (CO). HRMS (ESI-TOF) *m*/*z*: $[M + Na]^+$ calcd for $C_{14}H_{17}Cl_3FNNaO_2$ 378.0201; found 378.0205.

***N*-Benzyl-2,2,2-trichloro-*N*-(4-methoxy-3-methylbenzyl)-acetamide (1e).** Operating as above, from 4-methoxy-3-methylbenzaldehyde (2 g, 13.3 mmol) and benzylamine (1.9 mL, 17.3 mmol), **1e** was obtained (4.6 g, 89% over three steps) after chromatography (hexane/CH_2Cl_2 1:1 to CH_2Cl_2) as a yellow oil: IR (film) 3063, 3029, 3003, 2948, 2835, 1680, 1610 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz): 2 rotamers δ 2.18 and 2.21 (2s, 3H), 3.80 and 3.82 (2s, 3H), 4.49 and 4.55 (2s, 2H), 4.81 and 4.88 (2s, 2H), 6.70−7.42 (m, 8H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 16.2 (CH_3), 49.6 and 49.8 (CH_2), 51.6 (CH_2), 55.2 (CH_3), 93.3 (C), 109.9 (CH), 125.8 (CH), 126.2 (C), 126.8 (CH), 126.9 (C),127.1 (CH), 127.6 (CH), 127.8 (CH), 127.9 (CH), 128.7 (CH), 128.8 (CH), 129.5 (CH), 130.6 (CH), 135.1 and 135.7 (C), 157.4 (C), 161.1 (CO). HRMS (ESI-TOF) *m*/*z*: $[M + H]^+$ calcd for $C_{18}H_{19}Cl_3NO_2$ 386.0476; found 386.0475.

***N*-Benzyl-2,2,2-trichloro-*N*-(3-fluoro-4-methoxybenzyl)acetamide (1f).** Operating as above, from 3-fluoro-4-methoxybenzaldehyde (0.5 g, 3.24 mmol) and benzylamine (0.46 mL, 4.21 mmol), **1f** (1.18 g, 93%) was obtained after chromatography (hexane/CH_2Cl_2 1:1 to CH_2Cl_2) as a yellow oil: IR (film) 3065, 3031, 2935, 2839, 1678, 1624 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz): 2 rotamers δ 3.87 (s, 3H), 4.47 and 4.55 (2s, 2H), 4.81 and 4.90 (2s, 2H), 6.92 (m, 3H), 7.12−7.42 (m, 5H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 49.3 and 49.9 (CH_2), 51.0 and 52.0 (CH_2), 56.1 (CH_3), 93.0 (C), 113.4 (CH), 115.0 (d, J = 18.6 Hz, CH), 116.0 (d, J = 18.6 Hz, CH), 123.2 (CH), 124.2 (CH), 127.3 (CH), 128.1 (CH), 128.9 (CH), 134.7 (C), 135.3 (C), 147.2 (d, J = 10.1 Hz, C), 152.2 (d, J = 245.4 Hz, CF), 161.1 (CO). HRMS (ESI-TOF) *m*/*z*: $[M + H]^+$ calcd for $C_{17}H_{16}Cl_3FNO_2$ 390.0225; found 390.0226.

2-*tert*-Butyl-4,4-Dichloro-2-azaspiro[4.5]deca-6,9-diene-3,8-dione (2a). *Method A*: A mixture of Grubbs II catalyst (12.5 mg, 0.015 mmol, 5%) and **1a** (100 mg, 0.3 mmol) in toluene (0.2 mL) was heated at 155 °C for 30 min in a sealed tube. The dark solution was allowed to reach rt and purified by chromatography (hexane/CH_2Cl_2 1:1 to CH_2Cl_2) to yield **2a**[11d] (70 mg, 81%). *Method B*: In a 10 mL vessel were placed Grubbs II catalyst (25 mg, 0.03 mmol, 5%) and **1a** (200 mg, 0.59 mmol) in toluene (1.5 mL), and the mixture was heated to 120 °C while stirring using microwave irradiation for 1 h. After concentration,

dx.doi.org/10.1021/jo501110c | J. Org. Chem. 2014, 79, 9365−9372

the reaction mixture was purified by chromatography (hexane/CH_2Cl_2 4:6 to CH_2Cl_2) to yield **1a** (40 mg, 20%) and then **2a** (54 mg, 32%). *Method C*: To a suspension of CuCl (17.5 mg, 0.18 mmol, 30%) in acetonitrile (2 mL) was added **1a** (200 mg, 0.59 mmol), and the mixture was heated at 80 °C overnight in a sealed tube. The solution was then allowed to reach rt, concentrated, and purified by chromatography (hexane/CH_2Cl_2 1:1 to CH_2Cl_2) to yield **2a**[11d] (104 mg, 61%) and secondary amide **1g**[27] as a solid (58 mg, 35%). For **1g** (see Table 1): IR (film) 3316, 3044, 3002, 2955, 2838, 1693, 1659, 1615, 1583 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 3.81 (s, 3H), 4.48 (s, 2H), 6.90 (dm, J = 8.6 Hz, 2H), 7.24 (dm, J = 8.6 Hz, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 44.9 (CH_2), 55.3 (CH_3), 92.6 (CCl_3), 114.3, 129.2, 128.3, 159.5, 161.7 (NCO). HRMS (ESI-TOF) m/z: $[M + H]^+$ calcd for $C_{10}H_{11}Cl_3NO_2$ 281.9850; found 281.9835.

4,4-Dichloro-2-cyclohexyl-2-azaspiro[4.5]deca-6,9-diene-3,8-dione (2b). See Table 1. Yellow oil; IR (film) 2923, 2854, 1727, 1670 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 1.10 (m, 1H), 1.38 (m, 4H), 1.72 (br d, J = 13.6 Hz, 1H), 1.84 (m, 4H), 3.44 (s, 2H,), 4.03 (tt, J = 12, 3.6 Hz, 1H), 6.50 (dm, J = 10.4 Hz, 2H), 6.96 (dm, J = 10.4 Hz, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 25.1 (two signals, CH_2), 29.7 (CH_2), 48.1 (C-1), 52.0 (C-5), 52.5 (CH), 87.4 (C-4), 132.3 (C-7 and C-9), 143.5 (C-6 and C-10), 164.3 (C-3), 184.0 (C-8). HRMS (ESI-TOF) m/z: $[M + H]^+$ calcd for $C_{15}H_{18}Cl_2NO_2$ 314.0709; found 314.0708.

2-*tert*-Butyl-4,4-dichloro-7-methyl-2-azaspiro[4.5]deca-6,9-diene-3,8-dione (2c). A mixture of Grubbs II catalyst (12 mg, 0.014 mmol, 5%) and **1c** (100 mg, 0.28 mmol) in toluene (0.2 mL) was heated at 155 °C for 4 h in a sealed tube. Chromatography (hexane to hexane/CH_2Cl_2 1:9) afforded **2c** (62 mg, 72%) as a yellow oil: IR (film) 2953, 2923, 2854, 1724, 1668, 1644 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 1.47 (s, 9H, CH_3), 1.99 (d, J = 1.6 Hz, 3H, CH_3), 3.48 (d, J = 10.4 Hz, 1H, H-1), 3.51 (d, J = 10.4 Hz, 1H, H-1), 6.48 (d, J = 10 Hz, 1H, H-9), 6.75 (m, 1H, H-6), 6.92 (dd, J = 10, 3.2 Hz, 1H, H-10); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 16.2 (CH_3), 27.1 (CH_3), 50.1 (C-1), 51.3 (C-5), 55.9 (C), 88.4 (C-4), 131.9 (CH), 138.6 (CH), 139.5 (C-7), 143.5 (CH), 164.7 (C-3), 184.8 (C-8). HRMS (ESI-TOF) m/z: $[M + H]^+$ calcd for $C_{14}H_{18}Cl_2NO_2$ 302.0709; found 302.0721. $[M + Na]^+$ calcd for $C_{14}H_{17}Cl_2NNaO_2$ 324.0529; found 324.0531.

2-*tert*-Butyl-4,4-dichloro-7-fluoro-2-azaspiro[4.5]deca-6,9-diene-3,8-dione (2d). A mixture of Grubbs II catalyst (12 mg, 0.014 mmol, 5%) and **1d** (100 mg, 0.28 mmol) in toluene (0.2 mL) was heated at 155 °C for 4 h in a sealed tube. After chromatography (hexane/CH_2Cl_2 3:1 to CH_2Cl_2), **2d** (46 mg, 54%) was obtained as a yellow oil: IR (film) 2954, 2924, 2854, 1724, 1691, 1666 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 1.47 (s, 9H, CH_3), 3.54 (dd, J = 10.4, 1.2 Hz, 1H, H-1), 3.61 (d, J = 10.4 Hz, 1H, H-1), 6.52 (dd, J = 10.4, 6.8 Hz, 1H, H-9), 6.59 (dd, J = 12.4, 3.2 Hz, 1H, H-6), 6.96 (dd, J = 10, 3.2 Hz, 1H, H-10); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 27.1 (CH_3), 50.0 (d, J = 3.1 Hz, C-1), 53.3 (d, J = 7 Hz, C-5), 56.1 (C), 87.6 (C-4), 119.9 (d, J = 17.8 Hz, CH), 131.3 (d, J = 4.6 Hz, CH), 144.5 (d, J = 2.3 Hz, CH), 155.9 (d, J = 267.8 Hz, CF), 164.2 (C-3), 176.8 (d, J = 21.7 Hz, C-8). HRMS (ESI-TOF) m/z: $[M + H]^+$ calcd for $C_{13}H_{15}Cl_2FNO_2$ 306.0458; found 306.0469. $[M + Na]^+$ calcd for $C_{13}H_{14}Cl_2FNNaO_2$ 328.0278; found 328.0278.

2-Benzyl-4,4-dichloro-7-methyl-2-azaspiro[4.5]deca-6,9-diene-3,8-dione (2e). A mixture of Grubbs II catalyst (22 mg, 0.026 mmol, 5%) and **1e** (200 mg, 0.51 mmol) in toluene (0.4 mL) was heated at 155 °C for 4 h in a sealed tube. After chromatography (3:1 hexane/CH_2Cl_2 to CH_2Cl_2), **2e** (90 mg, 52%) was isolated as a yellow oil: IR (film) 3031, 2918, 2849, 1730, 1671, 1645 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 1.92 (d, J = 1.6 Hz, 3H, CH_3), 3.28 (d, J = 10.4 Hz, 1H, H-1), 3.32 (d, J = 10.4 Hz, 1H, H-1), 4.57 (d, J = 14.8 Hz, 1H), 4.61 (d, J = 14.8 Hz, 1H), 6.41 (d, J = 9.6 Hz, 1H, H-9), 6.66 (m, 1H, H-6), 6.83 (dd, J = 9.6, 3.2 Hz, 1H, H-10), 7.27 (m, 2H), 7.37 (m, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 16.1 (CH_3), 48.0 (CH_2), 51.1 (C-1), 51.9 (C-5), 87.3 (C-4), 128.3 (CH), 128.5 (CH), 129.1 (CH), 131.8 (CH), 134.0 (C), 138.3 (CH), 139.3 (C-7), 143.0 (CH), 165.1 (C-3), 184.6 (C-8). HRMS (ESI-TOF) m/z: $[M + H]^+$ calcd for $C_{17}H_{16}Cl_2NO_2$ 336.0553; found 336.0553.

2-Benzyl-4,4-dichloro-7-fluoro-2-azaspiro[4.5]deca-6,9-diene-3,8-dione (2f). A mixture of Grubbs II catalyst (11 mg, 0.013 mmol, 5%) and **1f** (100 mg, 0.26 mmol) in toluene (0.2 mL) was heated at 155 °C for 1.5 h in a sealed tube. Chromatography (3:1 hexane/CH_2Cl_2 to CH_2Cl_2) afforded **2f** (32 mg, 37%) as a yellow oil: IR (film) 2954, 2923, 2853, 1731, 1689, 1666 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 3.32 (d, J = 10 Hz, 1H, H-1), 3.43 (d, J = 10 Hz, 1H, H-1), 4.60 (s, 2H, CH_2), 6.44 (dd, J = 10, 6.8 Hz, 1H, H-9), 6.51 (dd, J = 12.4, 3.2 Hz, 1H, H-6), 6.84 (dd, J = 10, 3.2 Hz, 1H, H-10), 7.27 (m, 2H), 7.37 (m, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 48.1 (CH_2), 50.9 (d, J = 2.3 Hz, C-1), 53.9 (d, J = 7.2 Hz, C-5), 86.6 (C-4), 119.6 (d, J = 17.8 Hz, CH), 128.4 (CH), 128.7 (CH), 129.3 (CH), 131.2 (d, J = 4.6 Hz, CH), 133.8 (C), 144.0 (d, J = 2.4 Hz, CH), 155.8 (d, J = 268.7 Hz, CF), 164.6 (C-3), 176.7 (d, J = 22.4 Hz, C-8). HRMS (ESI-TOF) m/z: $[M + H]^+$ calcd for $C_{16}H_{13}Cl_2FNO_2$ 340.0302; found 340.0311. $[M + Na]^+$ calcd for $C_{16}H_{12}Cl_2FNNaO_2$ 362.0121; found 362.00128.

2-Benzyl-4,4-dichloro-2-azabicyclo[3.3.1]nonane-3,6-dione (4). *Method A*: A mixture of Grubbs II catalyst (11 mg, 0.013 mmol, 5%) and enol acetate **3a**[13] (100 mg, 0.26 mmol) in toluene (0.4 mL) was heated at 155 °C for 4 h in a sealed tube. The dark solution was allowed to reach rt and purified by chromatography (hexane/EtOAc 8:2 to 7:3) to yield morphan **4** (54 mg, 67%). NMR spectra matched those previously reported.[13] *Method B*: In a 10 mL vessel were placed Grubbs II catalyst (11 mg, 0.013 mmol, 5%) and **3a** (100 mg, 0.26 mmol) in toluene (1 mL), and the mixture was heated to 155 °C while stirring using microwave irradiation for 15 min. After concentration the reaction mixture was purified by chromatography (hexane/EtOAc 8:1 to 1:1) to yield successively **4**[13] (38 mg, 47%) and **4A**[13] (13 mg, 18%).

Ethyl (1*RS*,4*SR*,5*RS*)- and (1*RS*,4*RS*,5*RS*)-2-Benzyl-4-chloro-3,6-dioxo-2-azabicyclo[3.3.1]nonane-4-carboxylate (5a and *epi*-5). According to the above Method A, the reaction of **4b** (100 mg, 0.23 mmol), toluene (0.2 mL), and Grubbs II catalyst (10 mg, 5% catalyst loading) for 6 h at 155 °C afforded a 1:1 epimeric mixture of **5** and *epi*-**5** (41 mg, 50%). Spectroscopic properties matched those previously described.[28]

1-Benzyl-3-(*N*-methyl-*N*-methoxycarbonyl)amino-1-azaspiro[4.5]decan-8-one Ethylene Acetal (7). A solution of iodo derivative **6**[21] (4.51 g, 10.9 mmol) in an aqueous solution of methylamine at 40% (50 mL) was heated in a sealed tube at 100 °C overnight. The mixture was extracted with CH_2Cl_2, and the organic extracts were dried and concentrated to yield the corresponding amine, which was used in the next step without further purification (3.4 g): ^1H NMR (300 MHz, $CDCl_3$) δ 1.45 (m, 1H), 1.54 (dd, J = 12.9, 5.7 Hz, 1H), 1.55 (m, 1H), 1.61−1.82 (m, 5H), 1.91 (td, J = 13.2, 4.2 Hz, 1H), 2.17−2.25 (dd, J = 12.9, 8.4 Hz, 1H), 2.31 (s, 3H), 2.55 (dd, J = 9.5, 4.5 Hz, 1H), 2.80 (dd, J = 9.5, 6.6 Hz, 1H), 3.11 (m, 1H), 3.54 and 3.69 (2d, J = 13.2 Hz, 1H each), 3.94 (s, 4H), 7.30 (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 28.8 (CH_2), 30.9 (CH_2), 32.4 (CH_2), 32.5 (CH_2), 34.6 (CH_3), 41.7 (CH_2), 51.8 (CH_2), 56.4 (CH_2), 56.7 (CH), 61.9 (C), 64.1 (CH_2), 108.4 (C), 126.3 (CH), 127.9 (CH), 128.0 (CH), 140.6 (C). To a solution of the above amine (3.4 g, 10.7 mmol) in CH_3CN (180 mL) were added K_2CO_3 (3.02 g, 21.8 mmol) and methyl chloroformate (1.7 mL, 21.8 mmol), and the mixture was stirred at rt for 4 h. After concentration the residue was treated with a saturated aqueous sodium bicarbonate solution (100 mL) and extracted with CH_2Cl_2. The combined organic phases were dried, concentrated, and purified by chromatography (CH_2Cl_2 to 98:2 CH_2Cl_2/MeOH) to yield carbamate **7** (3.3 g, 81% over two steps) as a colorless oil: ^1H NMR (300 MHz, $CDCl_3$, COSY) δ 1.51−1.56 (m, 3H, H-4, H-7 and H-10), 1.65−1.73 (m, 3H, H-6, H-7 and H-10), 1.78−1.82 (m, 2H, H-6 and H-9eq), 2.06 (td, J = 12.2, 3.8 Hz, 1H, H-9ax), 2.35−2.48 (m, 1H, H-4), 2.68 (m, 2H, H-2), 2.77 (s, 3H, NCH_3), 3.24 (d, J = 13.2, 4.5 Hz, 1H, CH_2Ar), 3.64 (s, 3H, OCH_3), 3.92 (d, J = 13.2 Hz, 1H, CH_2Ar), 3.95 (s, 4H, CH_2O), 4.79 (m, 1H, H-3), 7.27 (m, 5H, ArH); ^{13}C NMR (75 MHz, $CDCl_3$, HSQC) δ 25.0 (br, C-10), 28.4 (br, NCH_3), 30.9 (C-6), 32.3 (C-7), 32.9 (C-9), 38.2 (C-4), 51.9 (C-3), 52.0 (CH_2Ar), 52.4 (OCH_3), 53.6 (C-2), 62.5 (C-5), 64.1 and 64.2 (OCH_2), 108.4 (C-8), 126.5 (*p*-Ar), 128.0 (*o*-, *m*-Ar), 140.4 (*ipso*-Ar), 156.8 (CO_2Me). HRMS (ESI-TOF) m/z: $[M + H]^+$ calcd for $C_{21}H_{31}N_2O_4$ 375.2278; found 375.2275.

dx.doi.org/10.1021/jo501110c | J. Org. Chem. 2014, 79, 9365−9372

1-Tricloroacetyl-3-(*N*-methyl-*N*-methoxycarbonyl)amino-1-azaspiro[4.5]decan-8-one (8). To a solution of carbamate **7** (1.04 g, 2.78 mmol) in MeOH (70 mL) was added 10% $Pd(OH)_2/C$ (0.23 g), and the mixture was stirred at 60 °C under 400 psi hydrogen atmosphere overnight. The mixture was filtered on a Celite pad, concentrated, and purified by chromatography (Al_2O_3, CH_2Cl_2 to CH_2Cl_2/MeOH 95:5) to yield the corresponding secondary amine (0.64 g, 81%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.65 (m, 2H), 1.81−2.38 (m, 8H), 2.95 (s, 3H), 3.38 (dd, J = 12.3, 7.8 Hz, 1H), 3.62 (dd, J = 12.3, 9.5 Hz, 1H), 3.72 (s, 3H), 3.94 (s, 4H), 4.99 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 30.6 (CH_3), 30.9 (CH_2), 31.6 (CH_2), 32.7 (2 CH_2), 36.6 (CH_2), 43.9 (CH_2), 52.9 (CH_3), 53.4 (CH), 64.2 (CH_2), 64.3 (CH_2), 65.8 (C), 106.7 (C), 156.5 (CO_2Me). To a solution of the above amine (1.58 g, 5.56 mmol) in THF (80 mL) was added a 10% HCl aqueous solution (160 mL), and the mixture was stirred at rt overnight. The solution was basified with K_2CO_3 and extracted with CH_2Cl_2. The organic extracts were dried and concentrated, and the residue was purified by chromatography (Al_2O_3, hexane/CH_2Cl_2 3:2 to CH_2Cl_2/MeOH 99:1) to yield the corresponding deprotected ketone (0.92 g, 73%), which was used directly in the next step: ^{1}H RMN (300 MHz, $CDCl_3$) δ 1.66−1.74 (m, 2H), 1.82−1.94 (m, 3H), 1.98 (dd, J = 7.5, 6.3 Hz, 1H), 2.07 (dd, J = 12.9, 9.0 Hz, 1H), 2.25−2.35 (m, 2H), 2.50−2.68 (m, 2H), 2.87 (s, 3H), 2.98 (dd, J = 12.0, 6.9 Hz, 1H), 3.20 (dd, J = 12.0, 7.9 Hz, 1H), 3.70 (s, 3H), 4.69 (dt, J = 15.6, 8.4 Hz, 1H); ^{13}C RMN (75 MHz, $CDCl_3$) δ 28.9 (CH_2), 29.7 (CH_2) 30.0 (CH_3), 37.4 (CH_2), 38.0 (CH_2), 39.1 (CH_2), 47.4 (CH_2), 52.3 (CH_3 and CH), 59.8 (C), 156.4 (NCO), 210.6 (CO). To a solution of the above ketone (0.55 g, 2.3 mmol) in CH_2Cl_2 (5 mL) were added successively Et_3N (0.63 mL, 0.45 mmol) and trichloroacetyl chloride (0.39 mL, 3.4 mmol) at 0 °C, and the mixture was stirred at rt overnight. The mixture was quenched with water, extracted with CH_2Cl_2, dried, and concentrated. After chromatography (CH_2Cl_2 to CH_2Cl_2/EtOAc 9:1) **8** was isolated (0.85 g, 96%) as a colorless viscous oil: IR (film) 2954, 2880, 1708, 1681 cm^{-1}; ^{1}H NMR (400 MHz) δ 1.80 (m, 2H, H-6eq and H-10eq), 2.04 (t, J = 12.4 Hz, 1H, H-4), 2.30−2.42 (m, 2H, H-7ax and H-9ax), 2.48 (dd, J = 12.4, 6.4 Hz, 1H, H-4), 2.54 (dm, J = 16.2 Hz, 1H, H-9eq), 2.68 (dtd, J = 16.2, 5.2, 1.6 Hz, 1H, H-7eq), 2.91 (s, 3H, NCH_3), 3.00 (td, J = 13.2, 6 Hz, 1H, H-10ax), 3.19 (td, J = 12.4, 5.2 Hz, 1H, H-6ax), 3.69 (t, J = 10.8 Hz, 1H, H-2), 3.75 (s, 3H, CH_3O), 4.39 (dd, J = 10.8, 7.2 Hz, 1H, H-2), 4.79 (br s, 1H, H-3); ^{13}C NMR (100 MHz) δ 29.0 (C-10), 29.4 (NCH_3), 32.9 (C-6), 37.7 (C-9), 38.1 (C-4 and C-7), 50.5 (C-2), 52.2 (C-3), 53.1 (OCH_3), 67.1 (C-5), 94.2 (CCl_3), 156.8 (CO_2Me), 158.6 (NCO), 209.5 (C-8). Anal. Calcd For $C_{14}H_{19}Cl_3N_2O_4$: C, 43.60; H, 4.97; N, 7.26. Found: C, 43.53; H, 5.00; N, 7.09. HRMS (ESI-TOF) m/z: $[M + H]^+$ calcd for $C_{14}H_{20}Cl_3N_2O_4$ 385.0483; found 385.0477.

8-Acetyloxy-1-tricloroacetyl-3-(*N*-methyl-*N*-methoxycarbonyl)amino-1-azaspiro[4.5]dec-7-ene (9). A mixture of **8** (0.64 g, 1.66 mmol) and *p*-toluenesulfonic acid monohydrate (0.32 g, 1.66 mmol) in isopropenyl acetate (5 mL) was heated to reflux for 4 h. The mixture was allowed to reach rt, treated with sodium hydrogen carbonate, filtered, concentrated, and purified by chromatography (CH_2Cl_2 to CH_2Cl_2/EtOAc 9:1) to yield **9**, a colorless viscous oil, as a 1.8:1mixture of epimers (0.76 g, 93%): IR (film) 2953, 2850, 1749, 1680 cm^{-1}; ^{1}H NMR (400 MHz) major epimer δ 1.55 (dm, J = 12.8 Hz, 1H, H-10eq), 1.87 (m, 1H, H-4), 1.98 (dm, J = 16.8 Hz, 1H, H-6), 2.12 (s, 3H, CH_3CO), 2.19 (m, 1H, H-9ax), 2.34 (dd, J = 12, 6,4 Hz, 1H, H-4), 2.44 (m, 1H, H-9eq), 2.87 (s, 3H, NCH_3), 3.17 (td, J = 12.8, 6.4 Hz, 1H, H-10ax), 3.30 (br d, J = 16.8 Hz, 1H, H-6), 3.64 (q, J = 10.8 Hz, 1H, H-2), 3.73 (s, 3H, OCH_3), 3.37 (dt, J = 10.8, 6.4 Hz, 1H, H-2), 4.74 (br s, 1H, H-3), 5.29 (dm, J = 5.2 Hz, 1H, H-7); minor epimer δ 1.60 (dm, J = 12.4 Hz, 1H, H-10eq), 1.93 (m, 1H, H-6), 2.11 (s, 3H, $COCH_3$), 2.87 (s, 3H, NCH_3), 3.02 (td, 1H, J = 12.4, 6.8 Hz, H-10ax), 3.74 (s, 3H, OCH_3), 5.36 (dm, 1H, J = 6 Hz, H-7). Only the different signals are mentioned: ^{13}C NMR (100 MHz) major epimer δ 20.9 (CH_3CO), 25.2 (C-9), 29.1 (NCH_3), 29.5 (C-6), 30.4 (C-10), 37.2 (C-4), 50.6 (C-2), 52.1 (C-3), 52.9 (OCH_3), 66.7 (C-5), 94.3 (CCl_3), 112.3 (C-7), 147.2 (C-8), 156.8 (NCO_2), 158.3 (NCO), 169.4 (CO); minor epimer δ 25.3 (C-9), 26.1 (C-10), 29.1 (NCH_3), 32.5 (C-6), 50.8 (C-2), 52.0 (C-3), 66.8 (C-5), 112.1 (C-7), 146.8 (C-8). Only the different signals are mentioned. HRMS (ESI-TOF) m/z: $[M + H]^+$ calcd for $C_{16}H_{22}Cl_3N_2O_5$ 427.0589; found 427.0581.

(2*RS*,7*RS*,10a*RS*)- and (2*RS*,7*SR*,10a*SR*)-6,6-Dichloro-2-[*N*-(methoxycarbonyl)-*N*-methylamino]hexahydro-1*H*-7,10a-methanopyrrolo[1,2-*a*]azocin-5,8-dione (10 and 11). A mixture of **9** (100 mg, 0.23 mmol) and Grubbs II catalyst (10 mg, 0.012 mmol) in toluene (0.15 mL) was heated in a sealed tube at 155 °C for 2 h. The mixture was concentrated and purified by chromatography (CH_2Cl_2 to CH_2Cl_2/EtOAc 1:1) to afford the following three products: **10** (32 mg, 39%) as a brown oil, a 2:1 ratio of **10** and **11** (12 mg, 15%), and a 1.6:1 epimeric mixture of azaspiro derivatives **12** (21 mg, 26%). A more enriched sample of **11** was obtained with an additional chromatography using the same conditions.

10: IR (film) 2954, 1723, 1678 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.96 (m, 1H, H-10ax), 2.12 (m, 1H, H-1), 2.30 (d, J = 14.4 Hz, 1H, H-11 *pro*-S), 2.33 (dd, J = 14, 10.4 Hz, 1H, H-1), 2.51 (m, 3H, H-9 and H-10eq), 2.63 (dt, J = 14, 3.2 Hz, 1H, H-11*pro*-R), 2.93 (s, 3H, NCH_3), 3.50 (brt, J = 11.6 Hz, 1H, H-3), 3.55 (m, 1H, H-7), 3.72 (s, 3H, OCH_3), 4.33 (dd, J = 12, 8 Hz, 1H, H-3), 4.53 (br s, 1H, H-2); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 32.3 (NCH_3), 35.9 (C-9), 36.9 (C-11), 37.9 (C-10), 39.7 (C-1), 45.2 (C-3), 52.9 (OCH_3), 53.9 (C-2), 60.8 (C-10a), 63.0 (C-7), 80.5 (C-6), 156.3 (CO_2), 161.4 (C-5), 203.4 (C-8). HRMS (ESI-TOF) m/z: $[M + H]^+$ calcd for $C_{14}H_{19}Cl_2N_2O_4$ 349.0716; found 349.0722.

11: IR (film) 2954, 2926, 1718, 1697, 1676 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.83 (ddd, J = 14, 12, 6 Hz, 1H, H-10ax), 2.06 (dd, J = 12.4, 10.4 Hz, 1H, H-1), 2.17 (dd, J = 12.4, 7.6 Hz, 1H, H-1), 2.22 (m, 1H, H-10eq), 2.38 (dd, J = 14.4, 3.6 Hz, 1H, H-11 *pro*-S), 2.49 (m, 2H, H-9), 2.61 (dt, J = 14.4, 3.6 Hz, 1H, H-11 *pro*-R), 2.84 (s, 3H, NCH_3), 3.59 (m, 1H, H-7), 3.73 (s, 3H, OCH_3), 3.75 (m, 2H, H-3), 5.17 (br s, 1H, H-2); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 29.0 (NCH_3), 35.4 (C-9), 35.7 (C-10), 36.6 (C-11), 40.7 (C-1), 46.7 (C-3), 51.7 (C-2), 53.1 (OCH_3), 61.5 (C-10a), 63.1 (C-7), 80.5 (C-6), 156.7 (CO_2), 161.7 (C-5), 203.1 (C-8). HRMS (ESI-TOF) m/z: $[M + H]^+$ calcd for $C_{14}H_{19}Cl_2N_2O_4$ 349.0716; found 349.0723.

1-Dicloroacetyl-3-[(*N*-methoxycarbonyl)-*N*-methyl]amino-1-azaspiro[4.5]dec-6-en-8-one (12a and 12b). Two isomers were observed in the NMR spectra in a 1.6:1 ratio. IR (film) 2955, 1680 cm^{-1}. For NMR data of the major epimer **12a**, see below (**12c** → **12a**). Minor epimer **12b**: ^{1}H NMR (400 MHz) δ 1.82 (ddd, J = 14.4, 12.4, 6.4 Hz, 1H, H-10ax), 2.00 (m, 1H, H-4), 2.21 (m, 1H, H-10eq), 2.32 (m, 1H, H-4), 2.49 (m, 2H, H-9), 2.90 (s, 3H, NCH_3), 3.65 (m, 1H, H-2), 3.74 (s, 3H, OCH_3), 4.03 (dd, J = 10, 8.4 Hz, 1H, H-2), 4.95 (m, 1H, H-3), 5.97 (d, J = 10 Hz, 1H, H-7), 6.06 (s, 1H, $CHCl_2$), 6.77 (dd, J = 10, 2 Hz, 1H, H-6); ^{13}C NMR (100 MHz) δ 30.0 (NCH_3), 34.6 (C-4), 34.9 (C-9), 35.7 (C-10), 47.3 (C-2), 53.1 (C-3), 53.1 (OCH_3), 64.0 (C-5), 66.0 ($CHCl_2$), 127.6 (C-7), 153.5 (C-6), 156.7 (CO_2), 161.7 (NCO), 196.8 (C-8). HRMS (ESI-TOF) m/z: $[M + H]^+$ calcd for $C_{14}H_{19}Cl_2N_2O_4$ 349.0716; found 349.0717.

Chemical Correlation of 12a from 12c. To a solution of enone **12c**[23] (30 mg, 0.09 mmol) in CH_2Cl_2 (1 mL) was added TFA (0.068 mL, 0.9 mmol), and the mixture was stirred at rt for 2 h. The reaction was concentrated, to the resulting residue dissolved in CH_2Cl_2 (1 mL) were added Et_3N (0.06 mL, 0.45 mmol) and dichloroacetyl chloride (0.026 mL, 0.27 mmol), and the mixture was stirred at rt for 2 h. Water was added, and the mixture was extracted with CH_2Cl_2. The organics were dried, concentrated, and purified by chromatography (from CH_2Cl_2 to 3:1 CH_2Cl_2/EtOAc) to yield **12a** (22 mg, 71%): ^{1}H NMR (400 MHz) δ 1.92 (dm, J = 12.8 Hz, 1H, H-10eq), 2.35 (dd, J = 12.4, 7.2 Hz, 1H, H-4), 2.43 (t, J = 12.4 Hz, 1H, H-4), 2.50 (ddd, J = 17.6, 14, 4.8 Hz, 1H, H-9ax), 2.66 (dm, J = 17.6, 1H, H-9eq), 2.91 (s, 3H, NCH_3), 3.23 (ddd, J = 14, 12.8, 4.8 Hz, 1H, H-10ax), 3.66 (t, J = 10.4 Hz, 1H, H-2), 3.75 (s, 3H, OCH_3), 4.18 (dd, J = 10.4, 7.2 Hz, 1H, H-2), 4.73 (tt, J = 10.8, 7.2 Hz, 1H, H-3), 5.96 (d, J = 10 Hz, 1H, H-7), 6.09 (s, 1H, $CHCl_2$), 6.90 (dd, J = 10, 2 Hz, 1H, H-6); ^{13}C NMR (100 MHz) δ 30.0 (NCH_3), 32.9 (C-10), 35.0 (C-9), 39.8 (C-4), 48.0 (C-2), 53.1 (C-3 and OCH_3), 64.1 (C-5), 66.4 ($CHCl_2$), 127.8 (C-7), 154.1 (C-6), 156.7 (CO_2), 161.8 (NCO), 196.8 (C-8)

1-Acetyl-3-[*N*-(methoxycarbonyl)-*N*-methyl]amino-1-azaspiro[4.5]decan-8-one (12d). Yellow oil; IR (film) 2955, 2924, 1853,

dx.doi.org/10.1021/jo501110c | J. Org. Chem. 2014, 79, 9365−9372

1698, 1644 cm^{-1}; ^1H NMR (400 MHz) δ 1.73 (m, 2H, H-6eq and H-10eq), 1.99 (t, J = 12.4 Hz, 1H, H-4), 2.04 (s, 3H, CH_3CO), 2.32 (m, 2H, H-7ax and H-9ax), 2.45 (dd, J = 12.4, 7.2 Hz, 1H, H-4), 2.45 (masked, 1H, H-9eq), 2.63 (dtd, J = 15.6, 4.8, 1.6 Hz, 1H, H-7eq), 2.89 (s, 3H, NCH_3), 2.97 (tdd, J = 13.6, 5.6, 1.2 Hz, 1H, H-10ax), 3.29 (td, J = 13.2, 5.2 Hz, 1H, H-6ax), 3.42 (t, J = 10.4 Hz, 1H, H-2), 3.70 (t, J = 8.8 Hz, 1H, H-2), 3.75 (s, 3H, OCH_3), 4.81 (br s, 1H, H-3); ^{13}C NMR (100 MHz) δ 24.9 (CH_3CO), 29.1 (NCH_3), 30.0 (C-10), 33.6 (C-6), 37.9 (C-7 and C-9), 38.5 (C-4), 49.4 (C-2), 51.5 (C-3), 53.0 (OCH_3), 63.2 (C-5), 157.0 (CO_2Me), 169.5 ($NCOCH_3$), 210.2 (C-8). HRMS (ESI-TOF) m/z: $[M + H]^+$ calcd for $C_{14}H_{23}N_2O_4$ 283.1652; found 283.1656.

(2*RS*,7*SR*,10a*RS*)-2-[*N*-(Methoxycarbonyl)-*N*-methylamino]-hexahydro-1*H*-7,10a-methanopyrrolo[1,2-*a*]azocine-5,8-dione (13). To a solution of **10** (36 mg, 0.10 mmol) in MeOH (2 mL) at 0 °C were added NH_4Cl (33 mg, 0.62 mmol) and then Zn (67.4 mg, 1.03 mmol) portionwise over 1 h. The mixture was allowed to reach rt, stirred overnight, filtered on a Celite pad, concentrated, and purified by chromatography (CH_2Cl_2 to CH_2Cl_2/MeOH 95:5) to yield **13** (16 mg, 58%) as a white solid: mp 152−154 °C; IR (film) 2953, 1697, 1636 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 1.95 (td, J = 14, 5.2 Hz, 1H, H-10ax), 2.01 (m, 1H, H-1), 2.05 (m, 1H, H-11 *pro*-R), 2.27 (m, 2H, H-1 and H-11 *pro*-S), 2.36 (m, 1H, H-10eq), 2.37 (dd, J = 16, 6 Hz, 1H, H-9eq), 2.44 (d, J = 19.2 Hz, 1H, H-6eq), 2.57 (ddd, J = 16, 13.2, 7.2 Hz, 1H, H-9ax), 2.67 (dd, J = 19.2, 7.2 Hz, 1H, H-6ax), 2.83 (br s, 1H, H-7), 2.90 (s, 3H, NCH_3), 3.29 (t, J = 10.8 Hz, 1H, H-3), 3.72 (s, 3H, OCH_3), 4.42 (dd, J = 11.6, 7.6 Hz, 1H, H-3), 4.55 (m, 1H, H-2); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 30.8 (NCH_3), 33.9 (C-6), 34.9 (C-9), 38.0 (C-1), 38.2 (C-10), 40.2 (C-11), 44.1 (C-7 and C-3), 52.8 (OCH_3), 53.2 (C-2), 59.2 (C-10a), 156.6 (NCO), 166.6 (C-5), 210.5 (C-8). HRMS (ESI-TOF) m/z: $[M + H]^+$ calcd for $C_{14}H_{21}N_2O_4$ 281.1496; found 281.1501.

(2*RS*,7*RS*,10a*SR*)-2-[*N*-(Methoxycarbonyl)-*N*-methylamino]-hexahydro-1*H*-7,10a-methanopyrrolo[1,2-*a*]azocin-5,8-dione (14). Operating as above, from an enriched sample of **11** (18 mg, 0.05 mmol), MeOH (1 mL), NH_4Cl (16.5 mg, 0.31 mmol), and Zn (33.7 mg, 0.52 mmol), **14** was isolated, slightly contaminated with **13**, after chromatography (9.4 mg, 65%): IR (film) 2952, 1698, 1638 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 1.81 (td, J = 13.2, 5.6 Hz, 1H, H-10ax), 1.93 (dt, J = 13.2, 3.6 Hz, 1H, H-11 *pro*-R), 1.99 (m, 1H, H-1), 2.11 (dd, J = 12.4, 7.6 Hz, 1H, H-1), 2.22 (m, 1H, H-10eq), 2.36 (m, 1H, H-11 *pro*-S), 2.39 (m, 2H, H-9), 2.45 (d, J = 19.6 Hz, 1H, H-6eq), 2.67 (dd, J = 18.8, 7.6 Hz, 1H, H-6ax), 2.82 (s, 3H, NCH_3), 2.87 (m, 1H, H-7), 3.71 (m, 2H, 4-CH_2), 3.73 (s, 3H, OCH_3), 5.14 (br s, 1H, H-2); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 28.6 (NCH_3), 34.2 (C-6), 34.4 (C-9), 35.8 (C-10), 37.9 (C-11), 40.8 (C-1), 44.4 (C-7), 45.5 (C-3), 51.3 (C-2), 53.0 (CH_3O), 59.9 (C-10a), 157.0 (CO_2), 167.2 (C-5), 210.3 (C-8). HRMS (ESI-TOF) m/z: $[M + H]^+$ calcd for $C_{14}H_{21}N_2O_4$ 281.14966; found 281.1497. In another run, the partially reduced azatricyclic lactam **15** was isolated as a waxy solid: IR (film) 2924, 2854, 1717, 1697, 1653 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 1.82 (td, J = 13.6, 5.6 Hz, 1H, H-10ax), 2.02 (t, J = 12 Hz, 1H, H-1), 2.12 (dd, J = 12.4, 7.6 Hz, 1H, H-1), 2.14 (m, 1H, H-11*pro*-R), 2.21 (m, 1H, H-10eq), 2.43 (dd, J = 14, 4 Hz, 1H, H-11 *pro*-S), 2.52 (m, 2H, H-9), 2.83 (s, 3H, NCH_3), 3.21 (br s, 1H, H-7), 3.72 (s, 3H, OCH_3), 3.75 (m, 2H, H-3), 4.61 (d, J = 7.2 Hz, 1H, H-6ax), 5.13 (br s, 1H, H-2); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 29.0 (CH_3N), 35.2 (C-9), 35.4 (C-10), 38.8 (C-11), 40.6 (C-1), 46.2 (C-3), 51.8 (C-2), 52.0 (C-7), 53.0 (CH_3O), 54.4 (C-6), 60.7 (C-10a), 156.7 (CO_2), 164.0 (C-5), 206.0 (C-8). HRMS (ESI-TOF) m/z: $[M + H]^+$ calcd for $C_{14}H_{20}ClN_2O_4$ 315.1106; found 315.1103.

■ ASSOCIATED CONTENT

Supporting Information

^1H and ^{13}C NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

■ AUTHOR INFORMATION

Corresponding Authors

*E-mail: faiza.diaba@ub.edu.

*E-mail: josep.bonjoch@ub.edu.

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

Financial support for this research was provided by Projects CTQ2010-14846/BQU and CTQ2013-41338-P from the Ministry of Economy and Competitiveness of Spain. The authors thank Dr. Gemma Puigbó and Dr. Eva Ricou for their experimental contributions.

■ REFERENCES

(1) (a) Tallarico, J. A.; Malnick, L. M.; Snapper, M. L. *J. Org. Chem.* **1999**, *64*, 344−345. (b) Simal, F.; Demonceau, A.; Noels, A. F. *Tetrahedron Lett.* **1999**, *40*, 5689−5693.

(2) (a) Quayle, P.; Fengas, D.; Richards, S. *Synlett* **2003**, 1797−1800. (b) Faulkner, J.; Edin, C. D.; Fengas, D.; Preece, I.; Quayle, P.; Richards, S. N. *Tetrahedron Lett.* **2005**, *46*, 2381−2385.

(3) (a) Seigal, B. A.; Fajardo, C.; Snapper, M. L. *J. Am. Chem. Soc.* **2005**, *127*, 16329−16332. (b) Edlin, C. D.; Faulkner, J.; Quayle, P. *Tetrahedron Lett.* **2006**, *47*, 1145−1151. (c) Edlin, C. D.; Faulkner, J.; Fengas, D.; Helliwell, M.; Knight, C. K.; House, D.; Parker, J.; Preece, I.; Quayle, P.; Taftery, J.; Richards, S. N. *J. Organomet. Chem.* **2006**, *691*, 5375−5382. (d) McGonagle, F. I.; Brown, L.; Cooke, A.; Sutherland, A. *Org. Biomol. Chem.* **2010**, *8*, 3418−3425. (e) For ring-closing olefin metathesis and radical cyclization as competing pathways, see: Schmidt, B.; Pohler, M.; Costisella, B. *J. Org. Chem.* **2004**, *69*, 1421−1424.

(4) (a) Schmidt, B.; Pohler, M. *J. Organomet. Chem.* **2005**, *690*, 5552−5555. (b) See also: Borguet, Y.; Sauvage, X.; Zaragoza, G.; Demonceau, A.; Delaude, L. *Beilstein J. Org. Chem.* **2010**, *6*, 1167−1173.

(5) (a) Eckenhoff, W. T.; Pintauer, T. *Catal. Rev. Sci. Eng.* **2010**, *52*, 1−59. (b) Muñoz-Molina, J. M.; Belderrain, T. R.; Pérez, P. J. *Eur. J. Inorg. Chem.* **2011**, 3155−3164. (c) Bonjoch, J.; Bradshaw, B.; Diaba, F. In *Stereoselective Synthesis of Drugs and Natural Products*; Andrushko, V., Andrushhko, N., Eds.; Wiley-VCH: New York, 2013; pp 733−768.

(6) (a) Sandmeier, P.; Tamm, C. *Helv. Chim. Acta* **1990**, *73*, 975−984. (b) Siddiqui, B. S.; Usmani, S. B.; Begum, S.; Siddiqui, S. *Phytochemistry* **1993**, *33*, 925−928. (c) Hallock, Y. F.; Lu, H. S. M.; Clardy, J.; Strobel, G. A.; Sugawara, F.; Samsoedin, R.; Yoshida, S. *J. Nat. Prod.* **1993**, *56*, 747−754. (d) Yang, Y.-L.; Chang, F.-R.; Wu, Y.-C. *Helv. Chim. Acta* **2004**, *87*, 1392−1399. (e) Shigehisa, H.; Takayama, J.; Honda, T. *Tetrahedron Lett.* **2006**, *47*, 7301−7306.

(7) For a review on the synthesis of 2-azabicyclo[3.3.1]nonanes, see: Bonjoch, J.; Diaba, F.; Bradshaw, B. *Synthesis* **2011**, 993−1018.

(8) Sakamoto, K.; Tsujii, E.; Abe, F.; Nakanishi, T.; Yamashita, M.; Shigematsu, N.; Izumi, S.; Okuhara, M. *J. Antibiot.* **1996**, *49*, 37−44.

(9) For a review on the biology and synthesis of FR901483, see: Bonjoch, J.; Diaba, F. In *Studies in Natural Products Chemistry, Bioactive Natural Products (Part L)*; Atta-ur-Rahman, Ed.; Elsevier: Amsterdam, 2005; Vol. *32*, pp 3−60.

(10) For some representative oxidative spirocyclizations upon phenols or anisoles, see: (a) Rishton, G. M.; Schwarts, M. A. *Tetrahedron Lett.* **1988**, *29*, 2643−2646. (b) Santra, S.; Andreana, P. R. *Org. Lett.* **2007**, *9*, 5035−5038. (c) Pigge, F. C.; Dhanya, R.; Hoefgen, E. R. *Angew. Chem., Int. Ed.* **2007**, *46*, 2887−2890. (d) Ovens, C.; Martin, N. G.; Procter, D. J. *Org. Lett.* **2008**, *10*, 1441−1444. (e) Liang, J.; Chen, J.; Du, F.; Zeng, X.; Li, L.; Zhang, H. *Org. Lett.* **2009**, *11*, 2820−2823. (f) Rozhkova, Y. S.; Khmelevskaya, K. A.; Shklyaev, Y. V.; Ezhikova, M. A.; Kodess, M. I. *Russ. J. Org. Chem.* **2012**, *48*, 69−77.

(11) For radical spirocyclization upon anisole compounds, using Ni/AcOH,[11a] lauryl peroxide,[11b,c] or Cu(I),[11d] see: (a) Boivin, J.; Yousfi, M.; Zard, S. Z. *Tetrahedron Lett.* **1997**, *38*, 5985−5988. (b) Ibarra-Rivera, T. R.; Gámez-Montaño, R.; Miranda, L. D. *Chem. Commun.* **2007**, 3485−3487. (c) Gámez-Montaño, R.; Ibarra- Rivera, T.; El Kaïm,

L.; Miranda, L. D. *Synthesis* **2010**, 1285−1290. (d) Diaba, F.; Montiel, J. A.; Martinez-Laporta, A.; Bonjoch, J. *Tetrahedron Lett.* **2013**, *54*, 2619−2622.

(12) For studies of cyclization using Cu(I) catalysts, see: Diaba, F.; Martínez-Laporta, A.; Bonjoch, J.; Pereira, A.; Muñoz-Molina, J. M.; Pérez, J. P.; Belderrain, T. R. *Chem. Commun.* **2012**, *48*, 8799−8801.

(13) Quirante, J.; Escolano, C.; Diaba, F.; Bonjoch, J. *J. Chem. Soc., Perkin Trans. 1* **1999**, 1157−1162.

(14) Recently, in an approach to aspidophylline A, the embedded morphan nucleus was formed using $(Ph_3P)_3RuCl_2$ as a catalyst to promote the cyclization of a trichloroacetamide upon a simple alkene: Li, Q.; Li, G.; Ma, S.; Feng, P.; Shi, Y. *Org. Lett.* **2013**, *15*, 2601−2603.

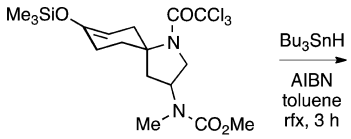
(15) Alcaide, B.; Almendros, P.; Luna, A. *Chem. Rev.* **2009**, *109*, 3817−3858.

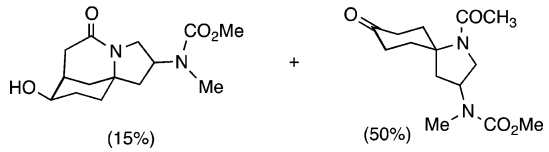
(16) (a) Snider, B. B.; Lin, H. *J. Am. Chem. Soc.* **1999**, *121*, 7778−7786. (b) Scheffer, G.; Seike, H.; Sorensen, E. J. *Angew. Chem., Int. Ed.* **2000**, *39*, 4593−4596. (c) Ousmer, M.; Braun, N. A.; Bavoux, C.; Perrin, M.; Ciufolini, M. A. *J. Am. Chem. Soc.* **2001**, *123*, 7534−7538. (d) Maeng, J.-H.; Funk, R. L. *Org. Lett.* **2001**, *3*, 1125−1128. (e) Kan, T.; Fujimoto, T.; Ieda, S.; Asoh, Y.; Kitaoka, H.; Fukuyama, T. *Org. Lett.* **2004**, *6*, 2729−2731. (f) Brummond, K. M.; Hong, S.-P. *J. Org. Chem.* **2005**, *70*, 907−916. (g) Carson, C. A.; Kerr, M. A. *Org. Lett.* **2009**, *11*, 777−779. (h) Ieda, S.; Masuda, A.; Kariyama, M.; Wakimoto, T.; Asakawa, T.; Fukuyama, T.; Kan, T. *Heterocycles* **2012**, *86*, 1071−1092. (i) Ma, A.-J.; Tu, Y.-Q.; Peng, J.-B.; Dou, Q.-Y.; Hou, S.- H.; Zhang, F.-M.; Wang, S.-H. *Org. Lett.* **2012**, *14*, 3604−3607. (j) Huo, H.-H.; Xia, X.-E.; Zhang, H.-K.; Huang, P.-Q. *J. Org. Chem.* **2013**, *78*, 455−465.

(17) For synthetic approaches towards the tricyclic framework of FR901483, see: (a) Yamazaki, N.; Suzuki, H.; Kibayashi, C. *J. Org. Chem.* **1997**, *62*, 8280−8281. (b) Wardrop, D. J.; Zhang, W. *Org. Lett.* **2001**, *3*, 2353−2356. (c) Suzuki, H.; Yamazaki, N.; Kibayashi, C. *Tetrahedron Lett.* **2001**, *42*, 3013−3015. (d) Bonjoch, J.; Diaba, F.; Puigbó, G.; Peidró, E.; Solé, D. *Tetrahedron Lett.* **2003**, *44*, 8387−8390. (e) Solé, D.; Urbaneja, X.; Bonjoch, J. *Adv. Synth. Catal.* **2004**, *346*, 1646−1650. (f) Kropf, J. E.; Meigh, I. C.; Bebbington, W. P.; Weinreb, S. M. *J. Org. Chem.* **2006**, *71*, 2046−2055. (g) Kaden, S.; Reissig, H.-U. *Org. Lett.* **2006**, *8*, 4763−4766. (h) Simila, S. T. M.; Martin, S. F. *J. Org. Chem.* **2007**, *72*, 5342−5349. (i) Diaba, F.; Ricou, E.; Solé, D.; Teixido, E.; Valls, N.; Bonjoch, J. *ARKIVOC* **2007**, 320−330. (j) Asari, A.; Angelov, P.; Auty, J. M.; Hayes, C. *Tetrahedron Lett.* **2007**, *48*, 2631−2634. (k) Seike, H.; Sorensen, E. J. *Synlett* **2008**, 695−701. (l) Puppala, M.; Murali, A.; Baskaran, S. *Chem. Commun.* **2012**, *48*, 5778−5780. (m) Perreault, S.; Rovis, T. *Synthesis* **2013**, *45*, 719−728. (n) Zhang, J.; Wang, Y.-Q.; Wang, X.-W.; Li, W.-D. Z. *J. Org. Chem.* **2013**, *78*, 6154−6162. (o) Yazici, A.; Pyne, S. G. *Org. Lett.* **2013**, *15*, 5878−5881.

(18) Ricou, E. Ph.D. Thesis, University of Barcelona, 2007.

(19)





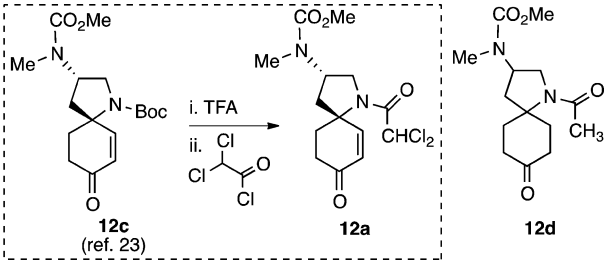
(20) Bonjoch, J.; Diaba, F.; Puigbó, G.; Solé, D.; Segarra, V.; Santamaria, L.; Beleta, J.; Ryder, H.; Palacios, J.-M. *Bioorg. Med. Chem.* **1999**, *7*, 2891−2897.

(21) Diaba, F.; Puigbó, G.; Bonjoch, J. *Eur. J. Org. Chem.* **2007**, 3038−3044.

(22) While the cyclization yield (40%) was moderate, it is in line (21−60%) with all of the cyclizations reported so far for this intriguing step giving access to the azatricyclic FR901483 framework from 1-azaspiro[4.5]decan-8-one substrates, whose substitution pattern allows regioisomeric products to be formed. See refs16a−c,h and 17b,d,g,i,j.

(23) Diaba, F.; Ricou, E.; Bonjoch, J. *Tetrahedron Asymmetry* **2006**, *17*, 1437−1443.

(24) Deprotection of **12c** followed by dichloroacetylation gave a compound with ^{1}H NMR data that matched those of the major isomer formed in the translocation process (i.e., **12a**). As expected, the reduction of the mixture of epimers **12a**/**12b** by hydrogenation provided the sole azaspirodecane **12d**.



(25) The configuration at C-6 in **15** was ascertained by the NOESY correlation of H-6_{ax} with the H-$11_{pro\text{-}R}$ as the coupling constant (J = 7.2 Hz) of H-6_{ax}/H-7. For this type of bridged compounds, the coupling constant of H6_{eq}/H7 is near zero; see, for example, NMR data for compounds **13** and **14**.

(26) For the influence of the steric compression effect on NMR chemical shifts, see: (a) Katakawa, K.; Kitajima, M.; Yamaguchi, K.; Takayama, H. *Heterocycles* **2006**, *69*, 223−229. (b) Kolocouris, A. *Tetrahedron Lett.* **2007**, *48*, 2117−2122.

(27) Atanasova, I.; Petrov, I.; Mollov, N. *Synth. Commun.* **1989**, *19*, 147−153.

(28) Diaba, F.; Martínez-Laporta, A.; Bonjoch, J. *Eur. J. Org. Chem.* **2014**, 2371−2378.

Atom Transfer Radical Cyclization of Trichloroacetamides to Electron-rich Acceptors Using Grubbs' Catalysts: Synthesis of the Tricyclic Framework of FR901483

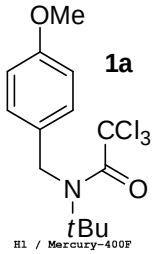
Faïza Diaba,* Agustín Martinez-Laporta, Josep Bonjoch*

Laboratori de Química Orgànica, Facultat de Farmàcia, IBUB,Universitat de Barcelona, Av. Joan XXIII s/n, 08028-Barcelona, Spain

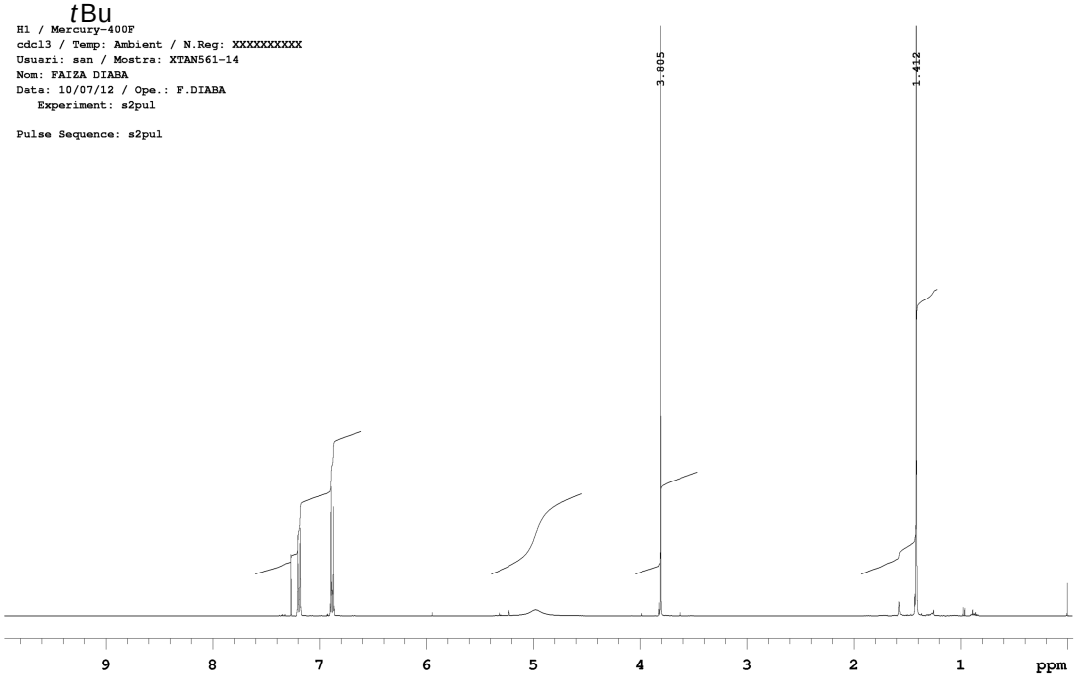
faiza.diaba@ub.edu; josep.bonjoch@ub.edu

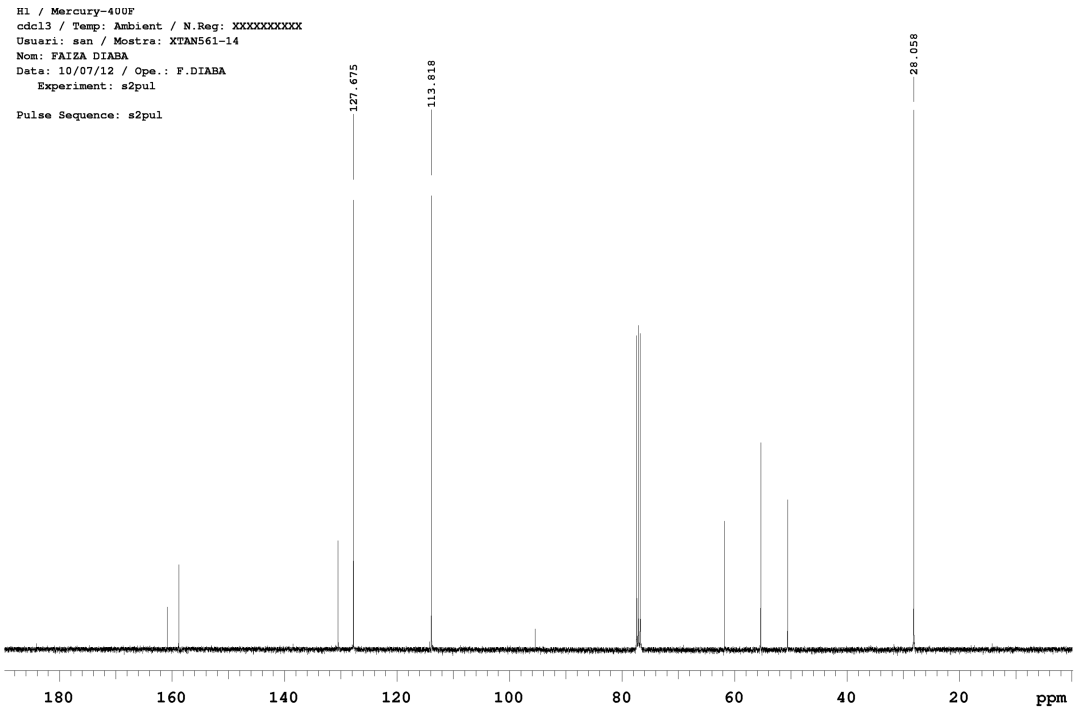
Supporting information

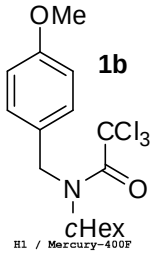
Contents **Page**


OMe
CCl3
N
O
tBu

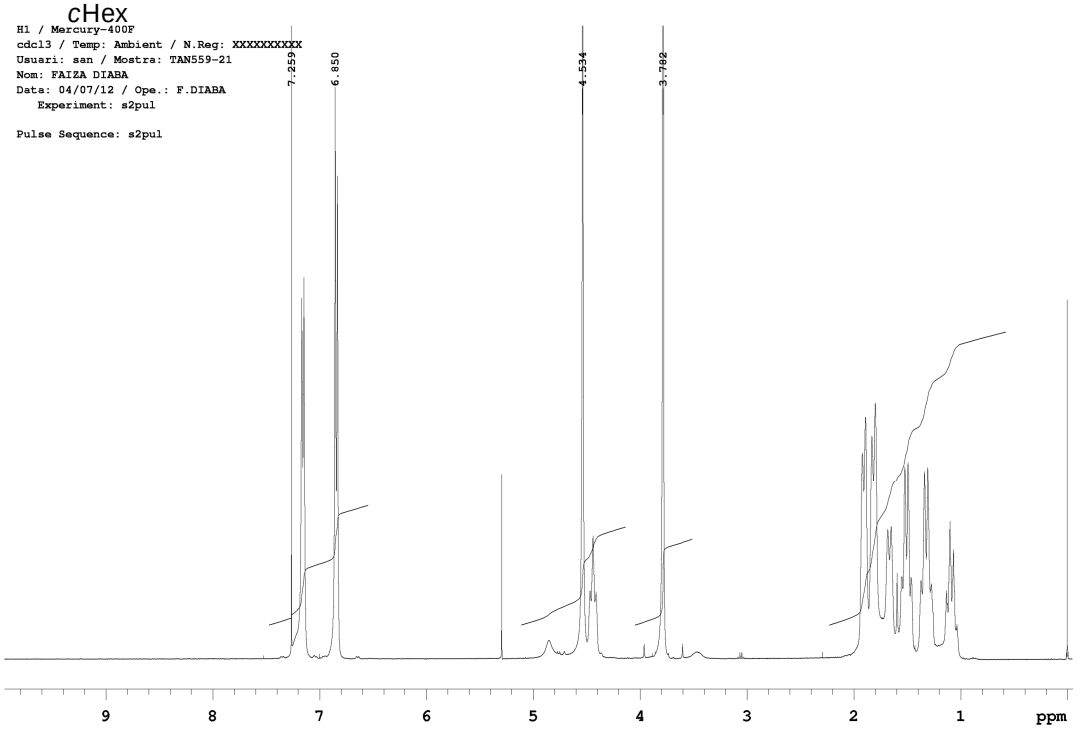
1a

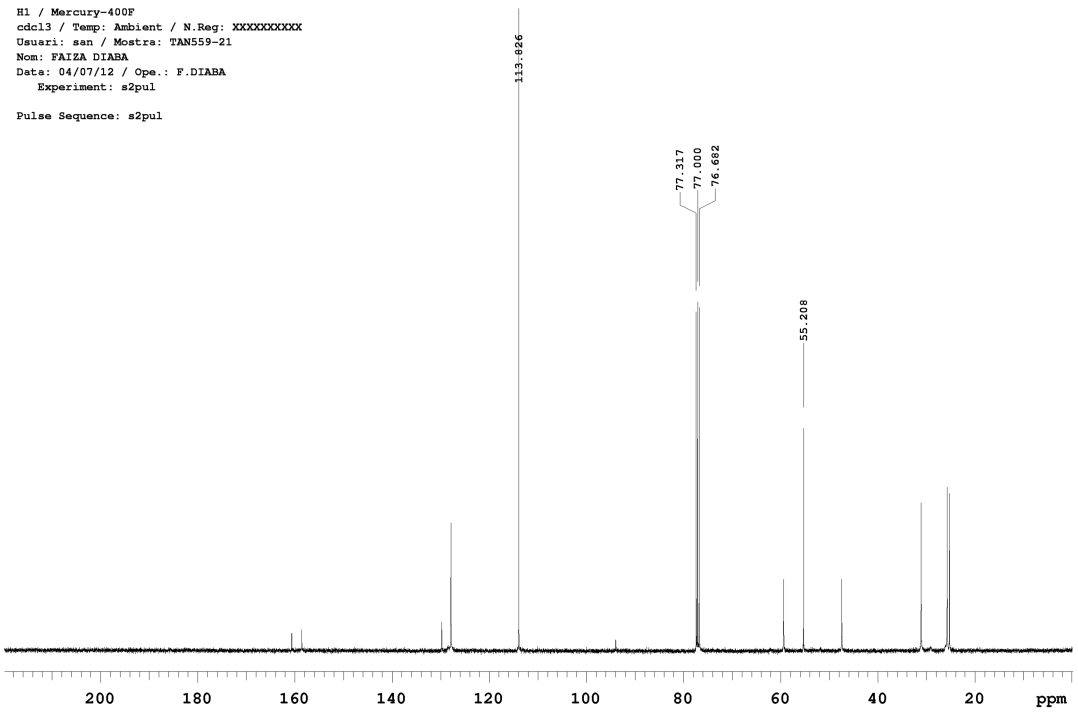

H1 / Mercury-400F
cdcl3 / Temp: Ambient / N.Reg: XXXXXXXXXX
Usuari: san / Mostra: XTAN561-14
Nom: FAIZA DIABA
Data: 10/07/12 / Ope.: F.DIABA
Experiment: s2pul
Pulse Sequence: s2pul
3.805
1.412
9
8
7
6
5
4
3
2
1
ppm

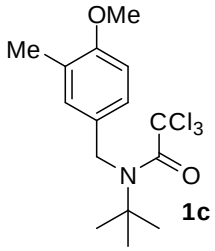

H1 / Mercury-400F
cdcl3 / Temp: Ambient / N.Reg: XXXXXXXXXX
Usuari: san / Mostra: XTAN561-14
Nom: FAIZA DIABA
Data: 10/07/12 / Ope.: F.DIABA
Experiment: s2pul
Pulse Sequence: s2pul
127.675
113.818
28.058
180
160
140
120
100
80
60
40
20
ppm


OMe
CCl3
N
O
cHex

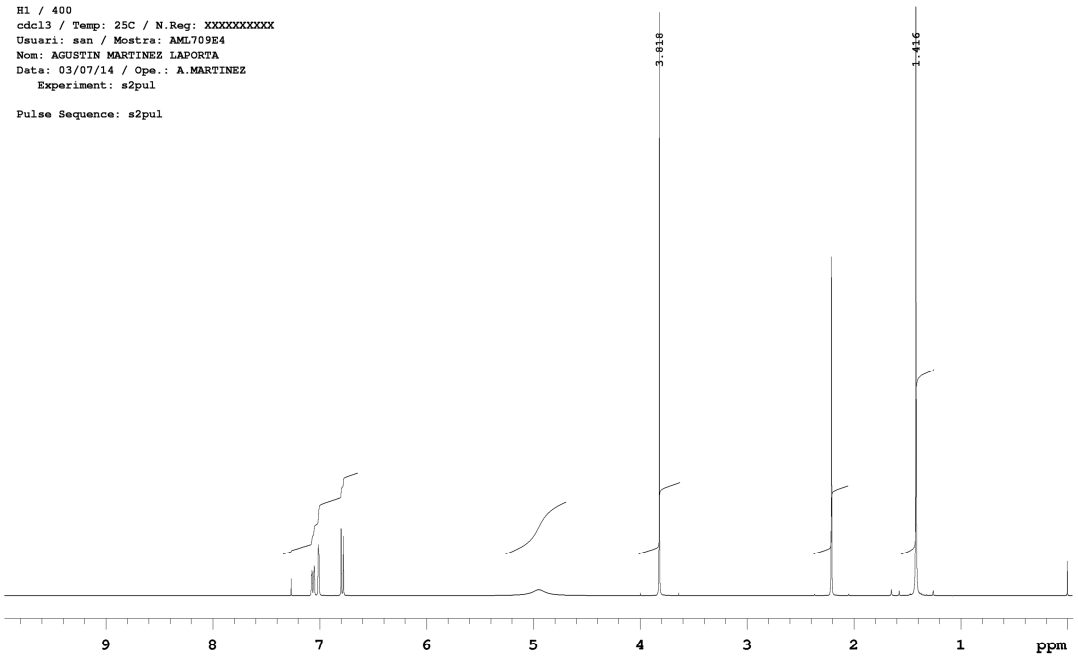
1b

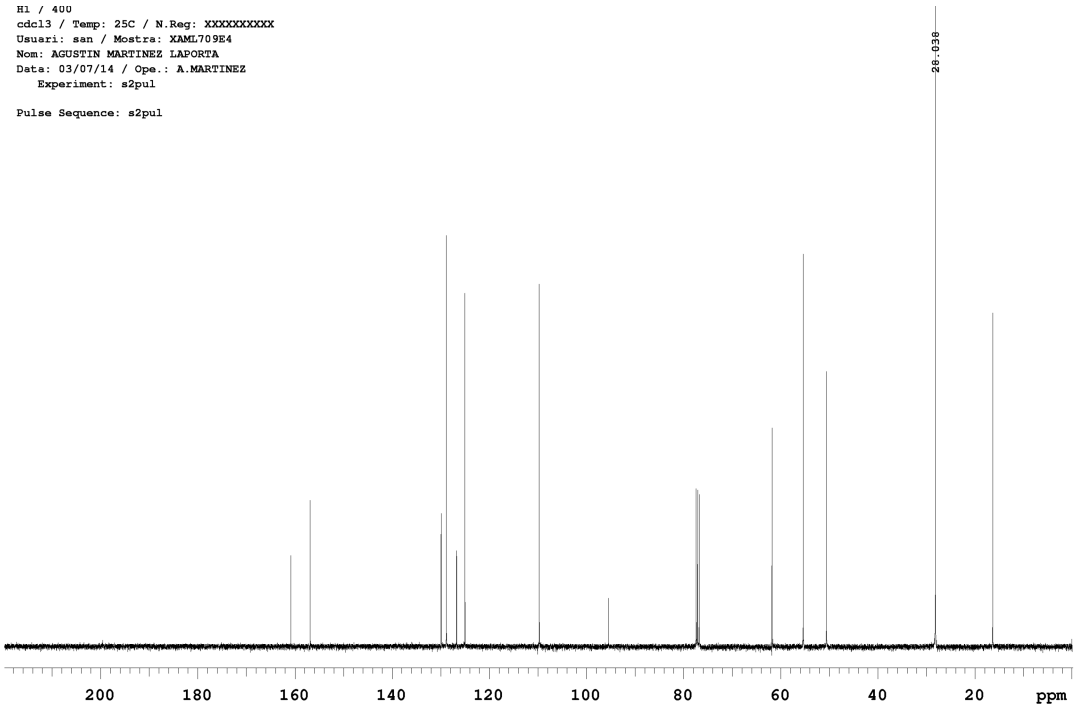

H1 / Mercury-400F
cdcl3 / Temp: Ambient / N.Reg: XXXXXXXXXX
Usuari: san / Mostra: TAN559-21
Nom: FAIZA DIABA
Data: 04/07/12 / Ope.: F.DIABA
Experiment: s2pul
Pulse Sequence: s2pul
7.259
6.850
4.534
3.782
9
8
7
6
5
4
3
2
1
ppm

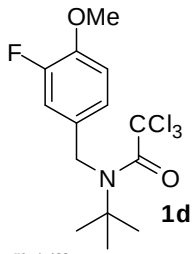

H1 / Mercury-400F
cdcl3 / Temp: Ambient / N.Reg: XXXXXXXXXX
Usuari: san / Mostra: TAN559-21
Nom: FAIZA DIABA
Data: 04/07/12 / Ope.: F.DIABA
Experiment: s2pul
Pulse Sequence: s2pul
113.826
77.317
77.000
76.682
55.208
200
180
160
140
120
100
80
60
40
20
ppm


OMe
Me
CCl3
N
O

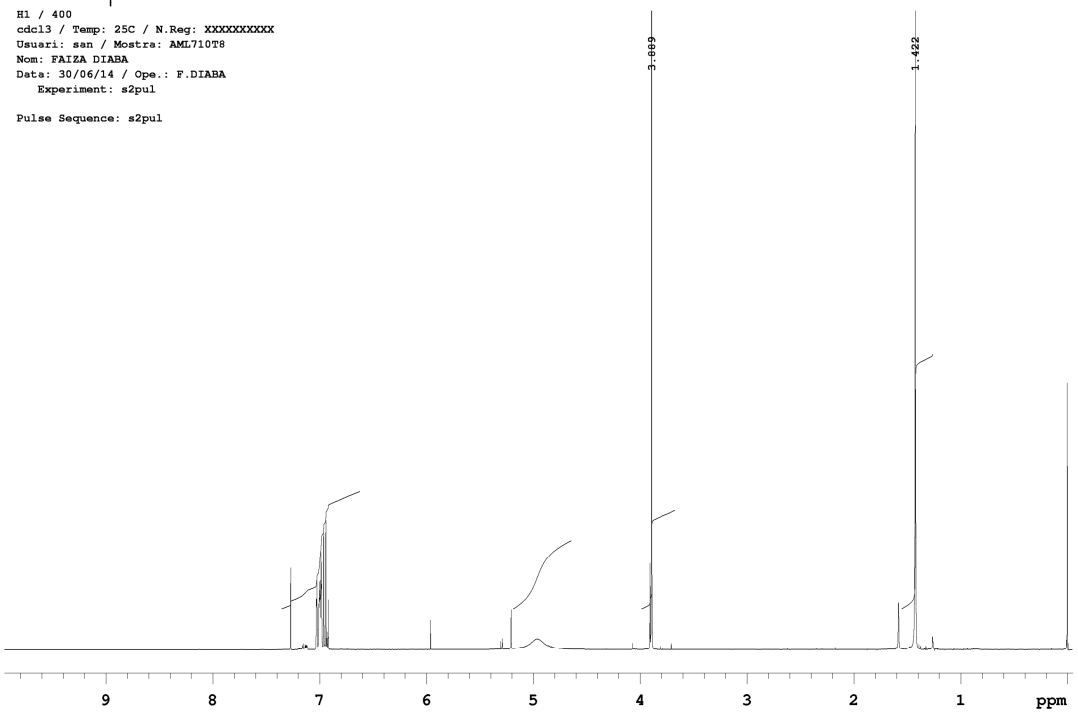
1c

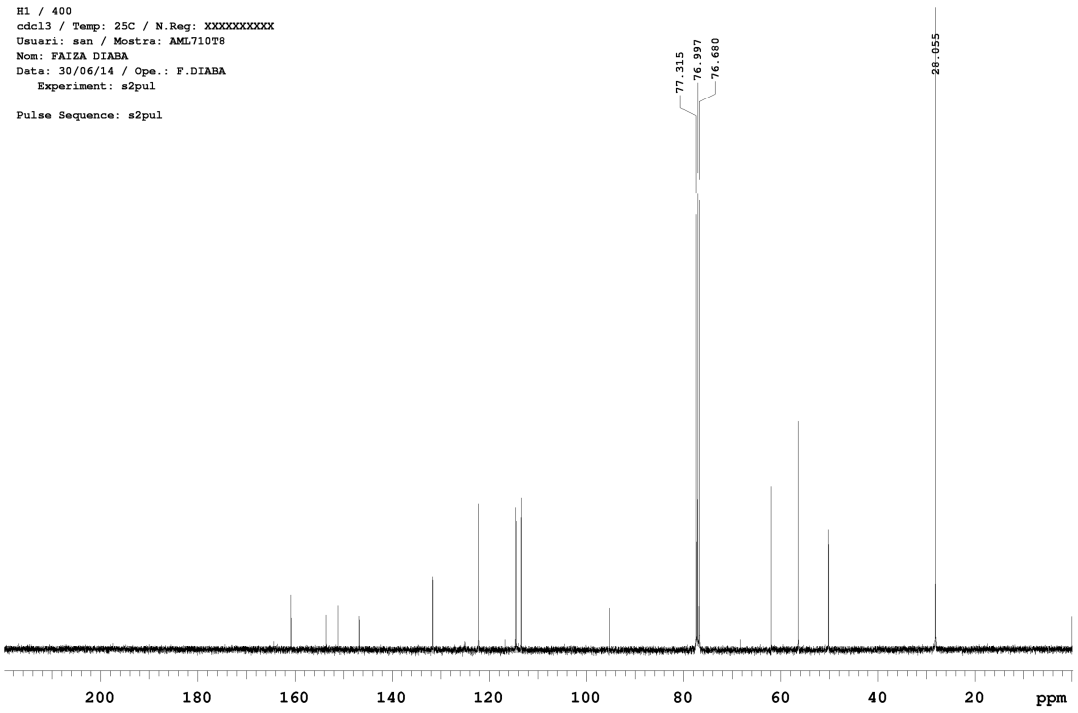

H1 / 400
cdcl3 / Temp: 25C / N.Reg: XXXXXXXXX
Usuari: san / Mostra: AML709E4
Nom: AGUSTIN MARTINEZ LAPORTA
Data: 03/07/14 / Ope.: A.MARTINEZ
Experiment: s2pul
Pulse Sequence: s2pul
3.018
1.416
9
8
7
6
5
4
3
2
1
ppm

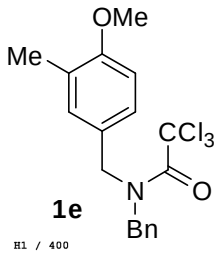

H1 / 400
cdcl3 / Temp: 25C / N.Reg: XXXXXXXXX
Usuari: san / Mostra: XAML709E4
Nom: AGUSTIN MARTINEZ LAPORTA
Data: 03/07/14 / Ope.: A.MARTINEZ
Experiment: s2pul
Pulse Sequence: s2pul
28.038
200
180
160
140
120
100
80
60
40
20
ppm


OMe
F
CCl3
N
O

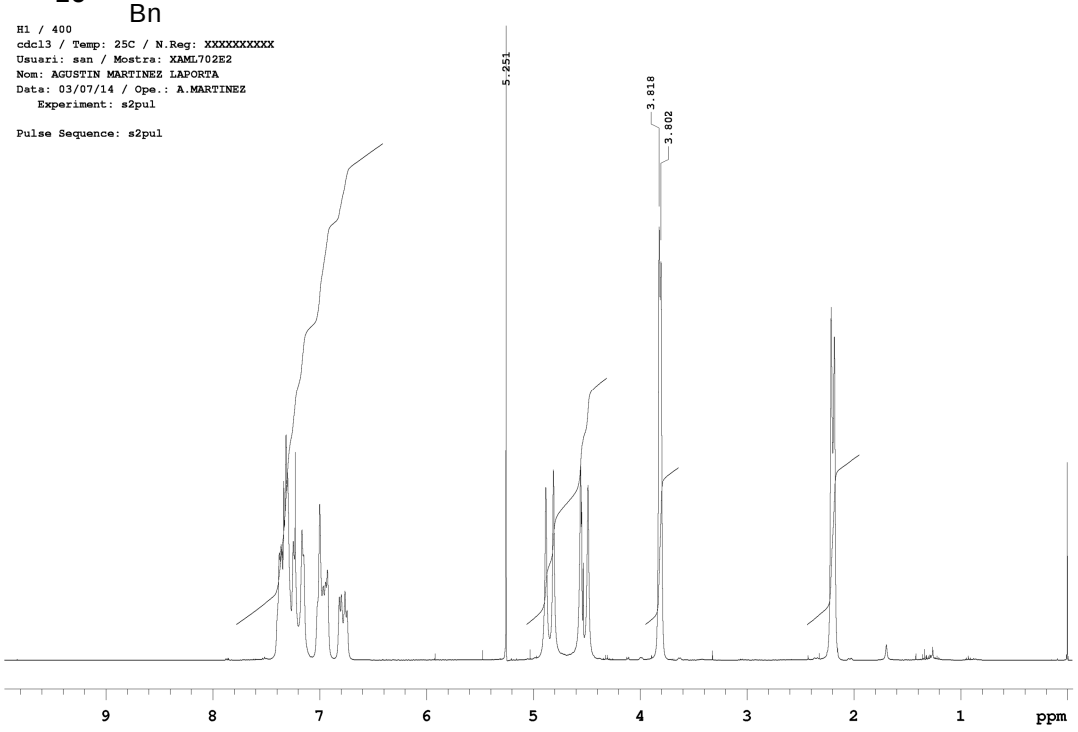
1d

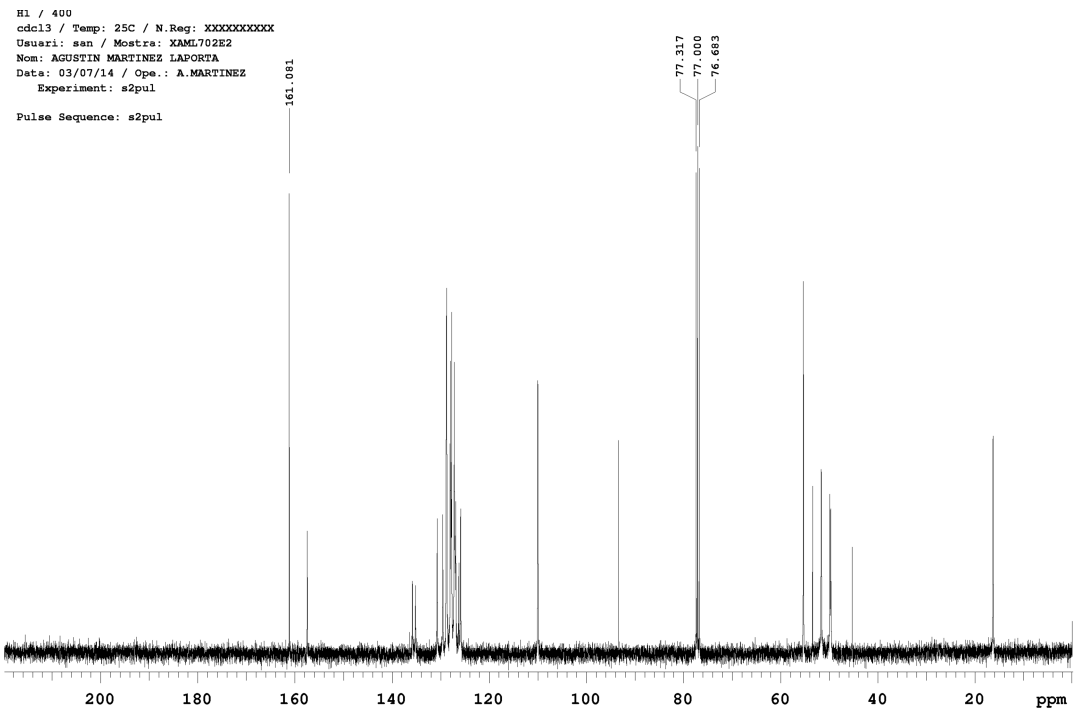

H1 / 400
cdcl3 / Temp: 25C / N.Reg: XXXXXXXXXX
Usuari: san / Mostra: AML710T8
Nom: FAIZA DIABA
Data: 30/06/14 / Ope.: F.DIABA
Experiment: s2pul
Pulse Sequence: s2pul
3.889
1.422
9
8
7
6
5
4
3
2
1
ppm

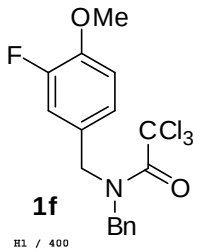

H1 / 400
cdcl3 / Temp: 25C / N.Reg: XXXXXXXXXX
Usuari: san / Mostra: AML710T8
Nom: FAIZA DIABA
Data: 30/06/14 / Ope.: F.DIABA
Experiment: s2pul
Pulse Sequence: s2pul
77.315
76.997
76.680
28.055
200
180
160
140
120
100
80
60
40
20
ppm


OMe
Me
CCl3
N
O
Bn

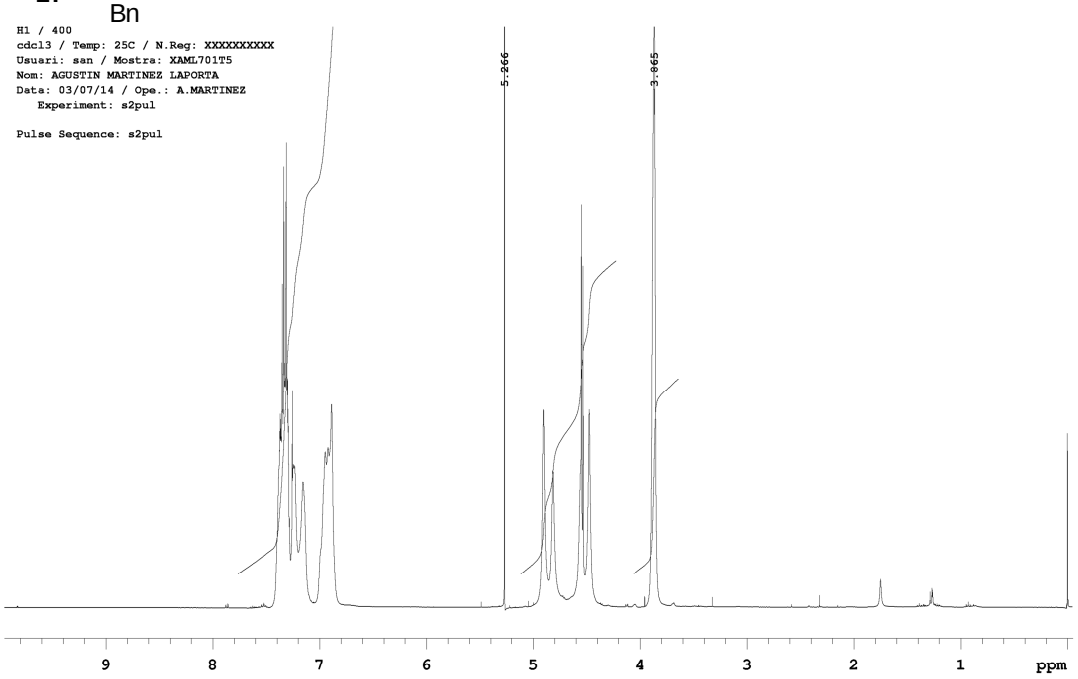
1e

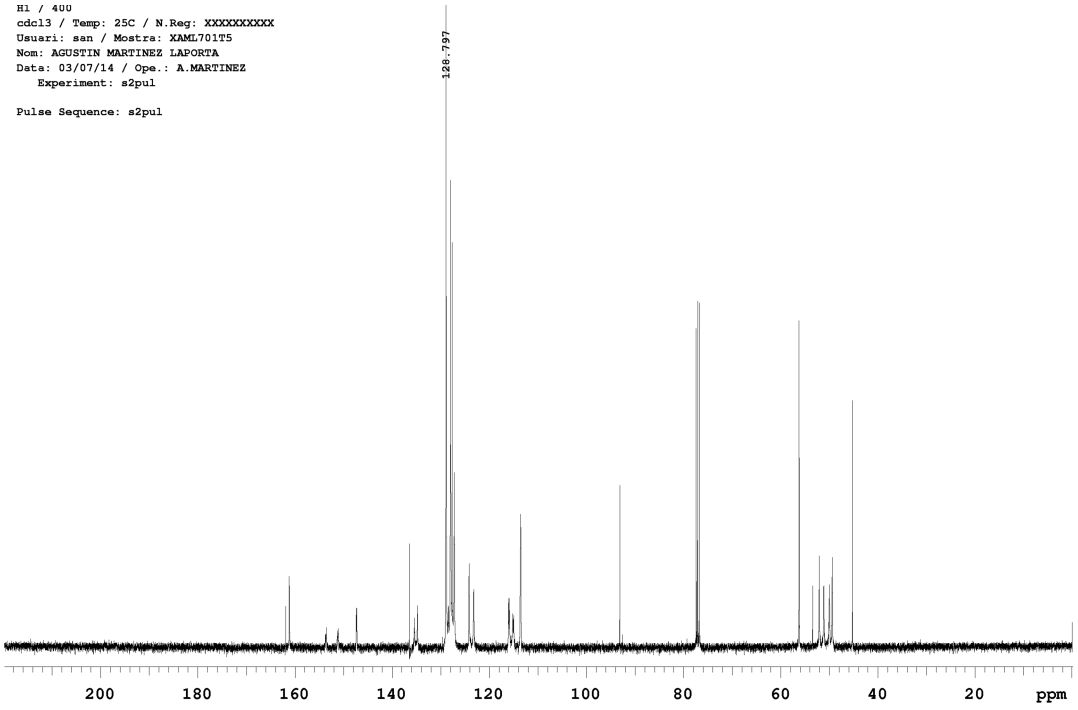

H1 / 400
cdcl3 / Temp: 25C / N.Reg: XXXXXXXXXX
Usuari: san / Mostra: XAML702E2
Nom: AGUSTIN MARTINEZ LAPORTA
Data: 03/07/14 / Ope.: A.MARTINEZ
Experiment: s2pul
Pulse Sequence: s2pul
5.251
3.818
3.802
9
8
7
6
5
4
3
2
1
ppm

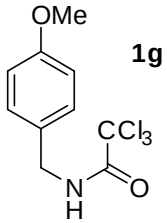

H1 / 400
cdcl3 / Temp: 25C / N.Reg: XXXXXXXXXX
Usuari: san / Mostra: XAML702E2
Nom: AGUSTIN MARTINEZ LAPORTA
Data: 03/07/14 / Ope.: A.MARTINEZ
Experiment: s2pul
Pulse Sequence: s2pul
161.081
77.317
77.000
76.683
200
180
160
140
120
100
80
60
40
20
ppm


OMe
F
CCl3
O
N
Bn

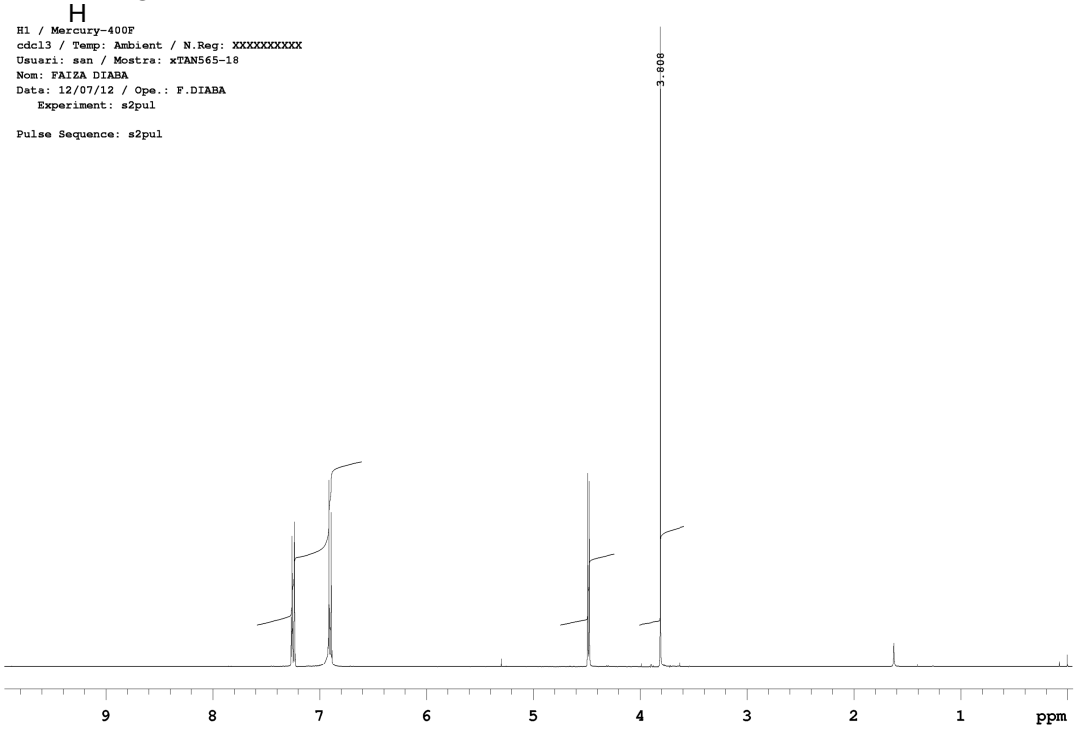
1f

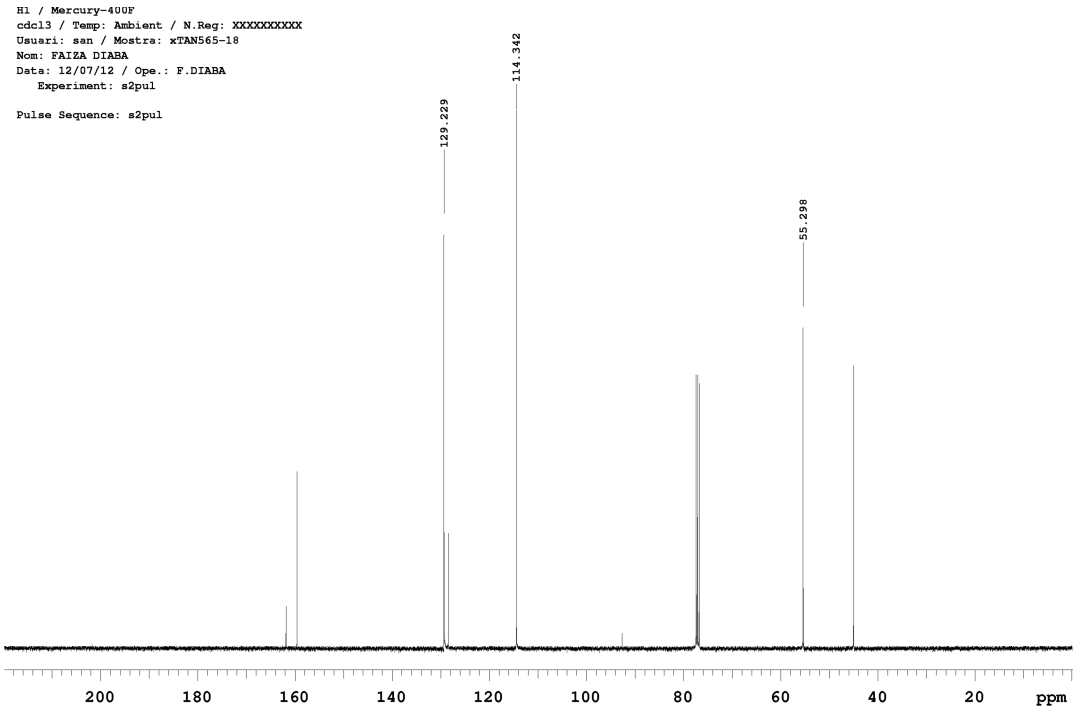

H1 / 400
cdcl3 / Temp: 25C / N.Reg: XXXXXXXXXX
Usuari: san / Mostra: XAML701T5
Nom: AGUSTIN MARTINEZ LAPORTA
Data: 03/07/14 / Ope.: A.MARTINEZ
Experiment: s2pul
Pulse Sequence: s2pul
5.266
3.865
9
8
7
6
5
4
3
2
1
ppm

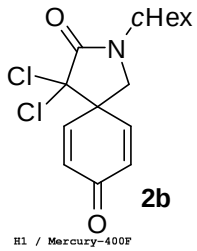

H1 / 400
cdcl3 / Temp: 25C / N.Reg: XXXXXXXXXX
Usuari: san / Mostra: XAML701T5
Nom: AGUSTIN MARTINEZ LAPORTA
Data: 03/07/14 / Ope.: A.MARTINEZ
Experiment: s2pul
Pulse Sequence: s2pul
128.797
200
180
160
140
120
100
80
60
40
20
ppm


OMe
CCl3
N
H
O

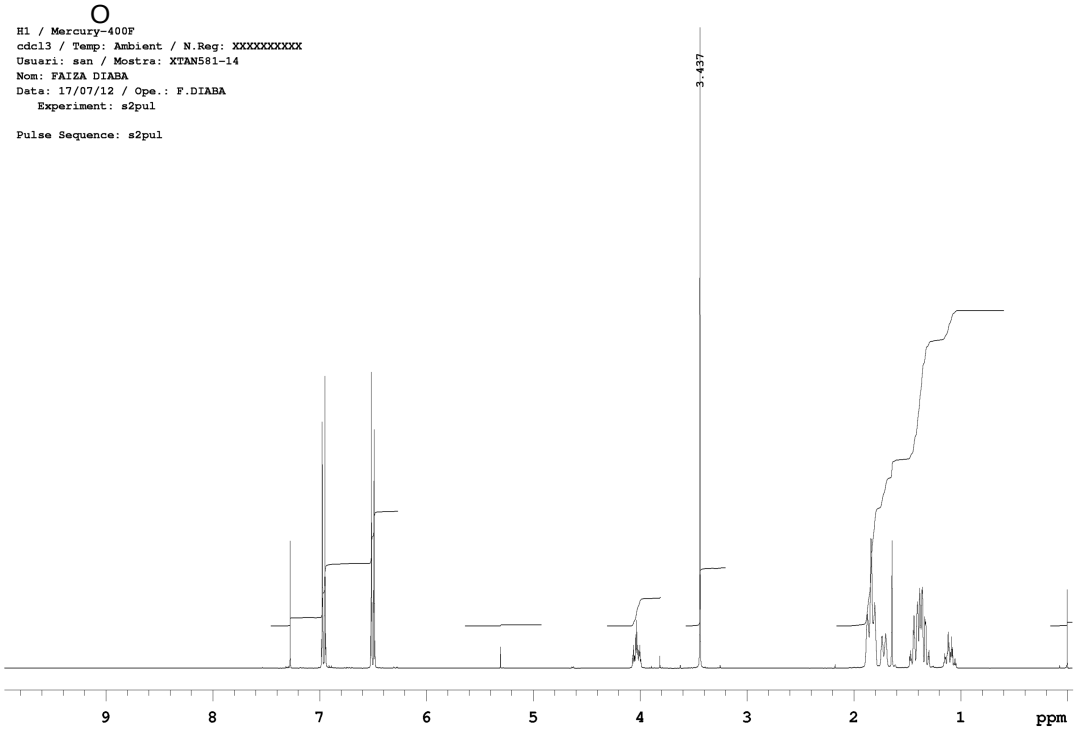
1g

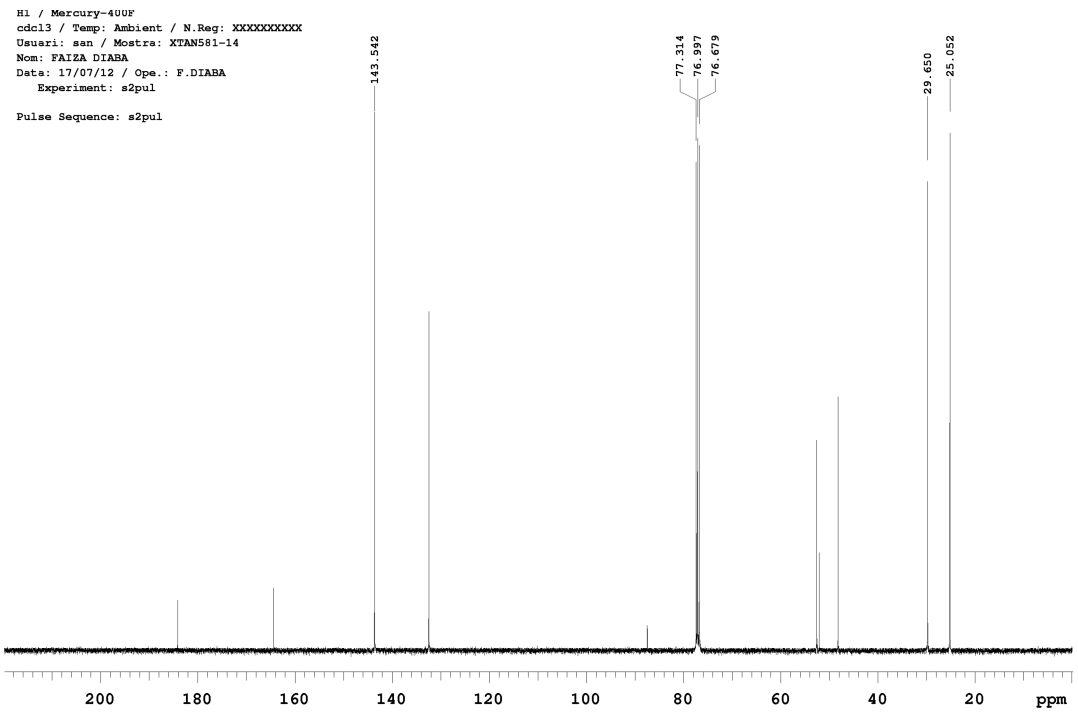

H1 / Mercury-400F
cdcl3 / Temp: Ambient / N.Reg: XXXXXXXXXX
Usuari: san / Mostra: xTAN565-18
Nom: FAIZA DIABA
Data: 12/07/12 / Ope.: F.DIABA
Experiment: s2pul
Pulse Sequence: s2pul
3.808
9
8
7
6
5
4
3
2
1
ppm

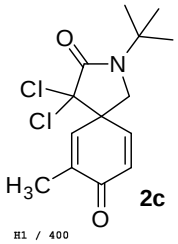

H1 / Mercury-400F
cdcl3 / Temp: Ambient / N.Reg: XXXXXXXXXX
Usuari: san / Mostra: xTAN565-18
Nom: FAIZA DIABA
Data: 12/07/12 / Ope.: F.DIABA
Experiment: s2pul
Pulse Sequence: s2pul
129.229
114.342
55.298
200
180
160
140
120
100
80
60
40
20
ppm


O
cHex
N
Cl
Cl
O

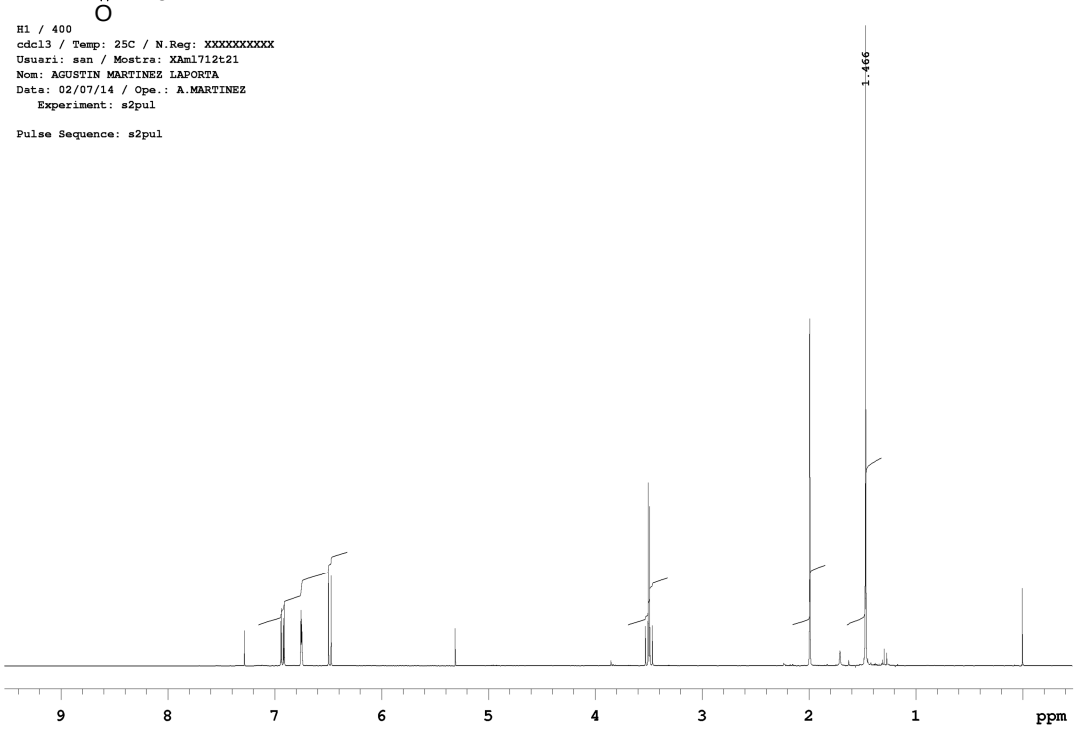
2b

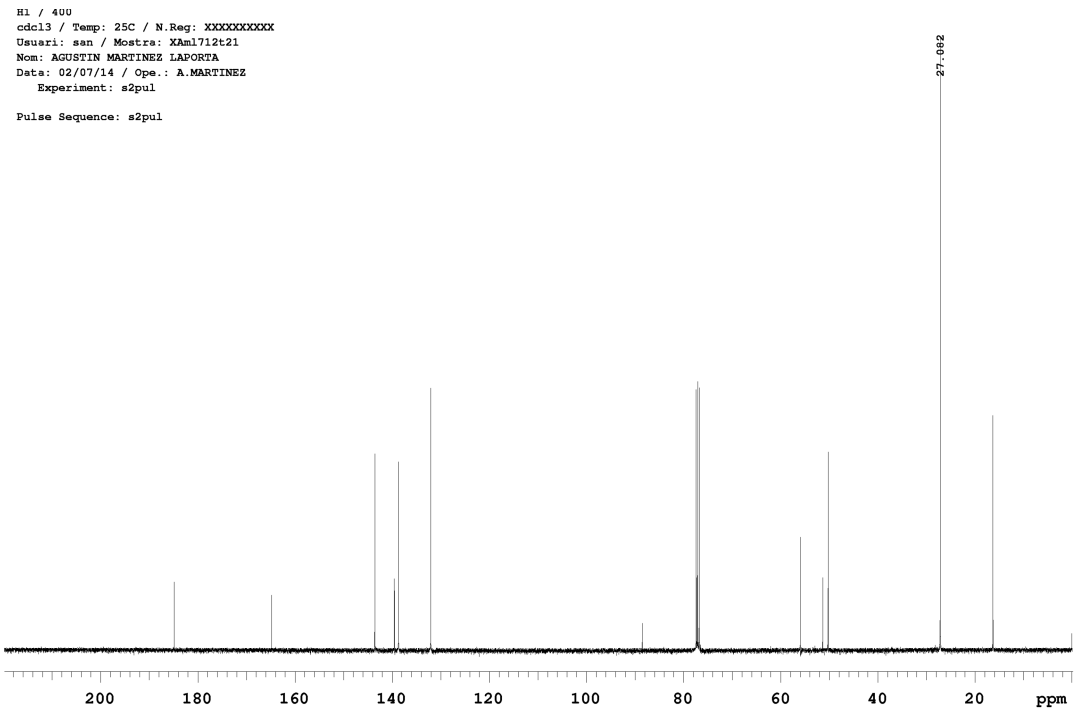

H1 / Mercury-400F
cdcl3 / Temp: Ambient / N.Reg: XXXXXXXXXX
Usuari: san / Mostra: XTAN581-14
Nom: FAIZA DIABA
Data: 17/07/12 / Ope.: F.DIABA
Experiment: s2pul
Pulse Sequence: s2pul
3.437
9
8
7
6
5
4
3
2
1
ppm

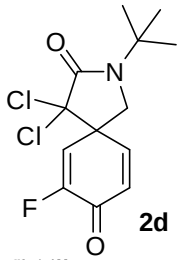

H1 / Mercury-400F
cdcl3 / Temp: Ambient / N.Reg: XXXXXXXXXX
Usuari: san / Mostra: XTAN581-14
Nom: FAIZA DIABA
Data: 17/07/12 / Ope.: F.DIABA
Experiment: s2pul
Pulse Sequence: s2pul
143.542
77.314
76.997
76.679
29.650
25.052
200
180
160
140
120
100
80
60
40
20
ppm


O
N
Cl
Cl
H3C
O

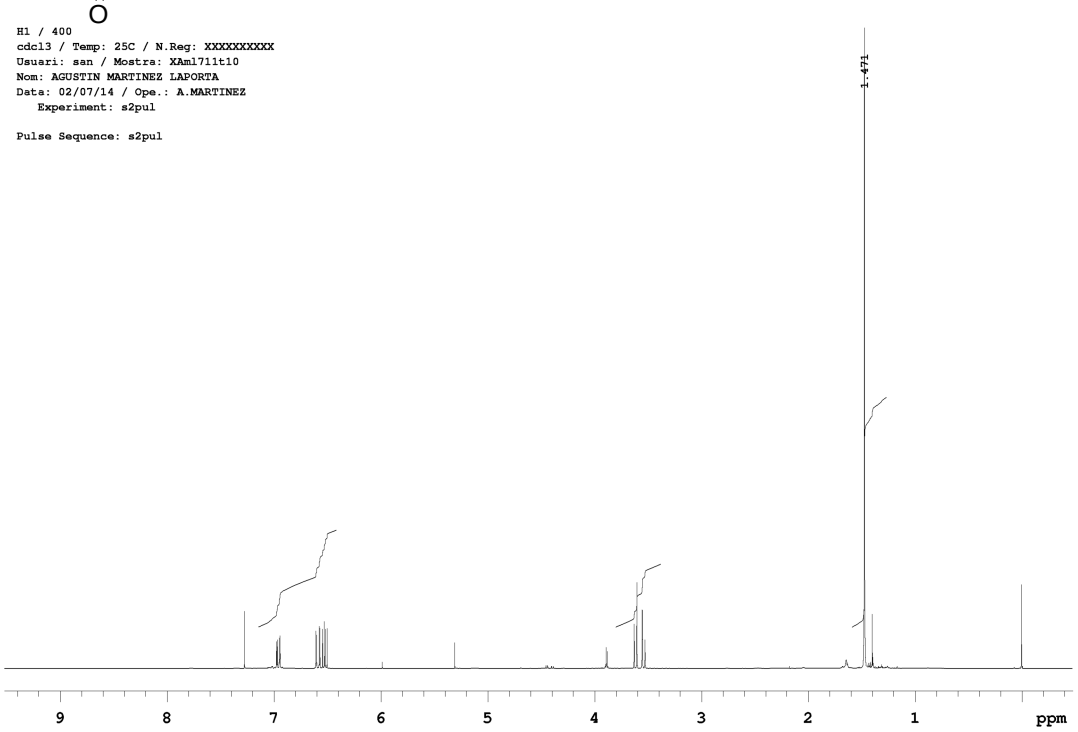
2c

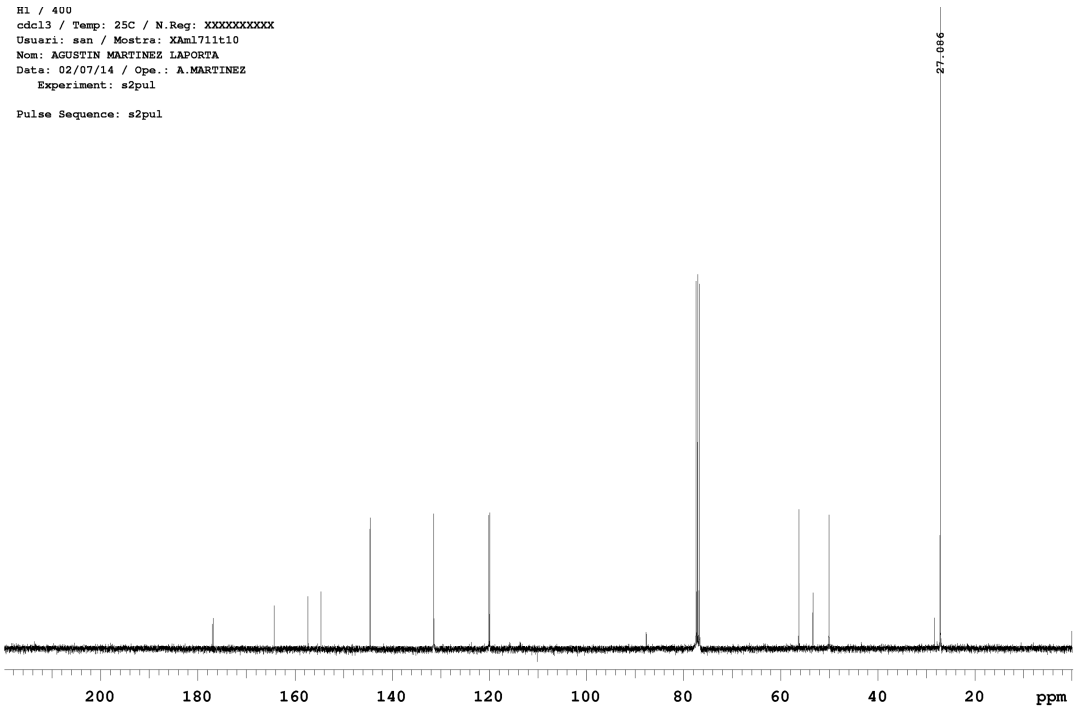

H1 / 400
cdcl3 / Temp: 25C / N.Reg: XXXXXXXXXX
Usuari: san / Mostra: XAml712t21
Nom: AGUSTIN MARTINEZ LAPORTA
Data: 02/07/14 / Ope.: A.MARTINEZ
Experiment: s2pul
Pulse Sequence: s2pul
1.466
9
8
7
6
5
4
3
2
1
ppm

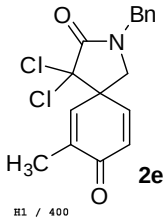

H1 / 400
cdcl3 / Temp: 25C / N.Reg: XXXXXXXXXX
Usuari: san / Mostra: XAml712t21
Nom: AGUSTIN MARTINEZ LAPORTA
Data: 02/07/14 / Ope.: A.MARTINEZ
Experiment: s2pul
Pulse Sequence: s2pul
27.082
200
180
160
140
120
100
80
60
40
20
ppm


O
N
Cl
Cl
F
O

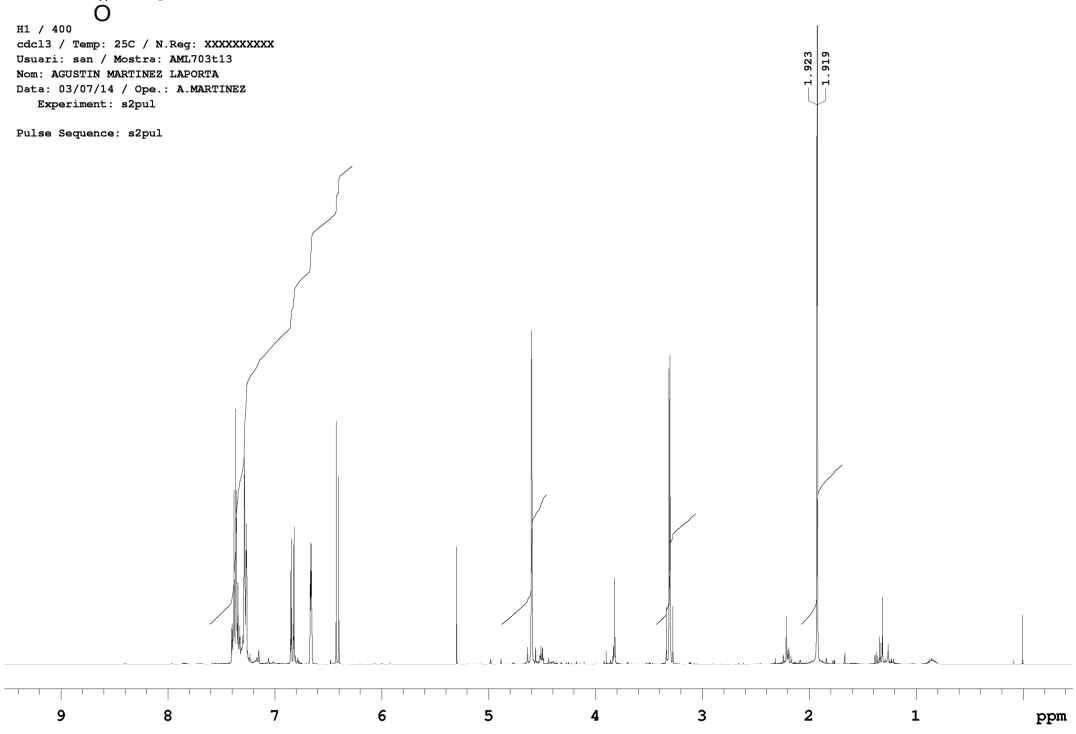
2d

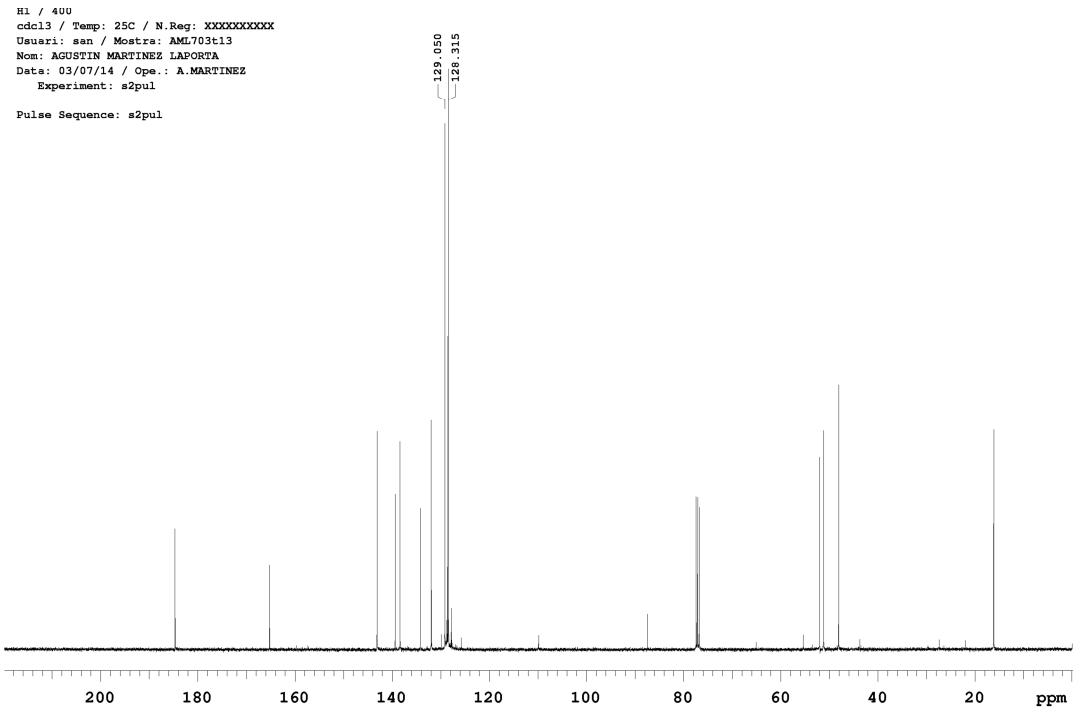

H1 / 400
cdcl3 / Temp: 25C / N.Reg: XXXXXXXXXX
Usuari: san / Mostra: XAml711t10
Nom: AGUSTIN MARTINEZ LAPORTA
Data: 02/07/14 / Ope.: A.MARTINEZ
Experiment: s2pul
Pulse Sequence: s2pul
1.471
9
8
7
6
5
4
3
2
1
ppm

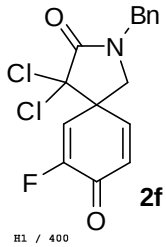

H1 / 400
cdcl3 / Temp: 25C / N.Reg: XXXXXXXXXX
Usuari: san / Mostra: XAml711t10
Nom: AGUSTIN MARTINEZ LAPORTA
Data: 02/07/14 / Ope.: A.MARTINEZ
Experiment: s2pul
Pulse Sequence: s2pul
27.086
200
180
160
140
120
100
80
60
40
20
ppm


O
Bn
N
Cl
Cl
H3C
O

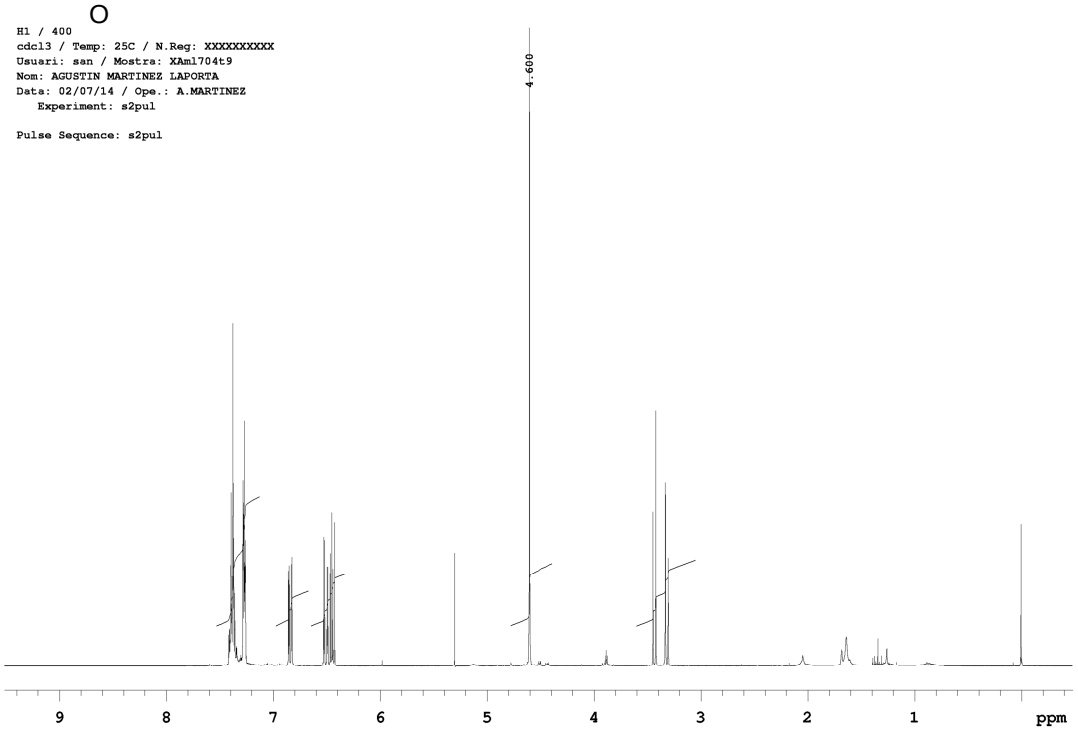
2e

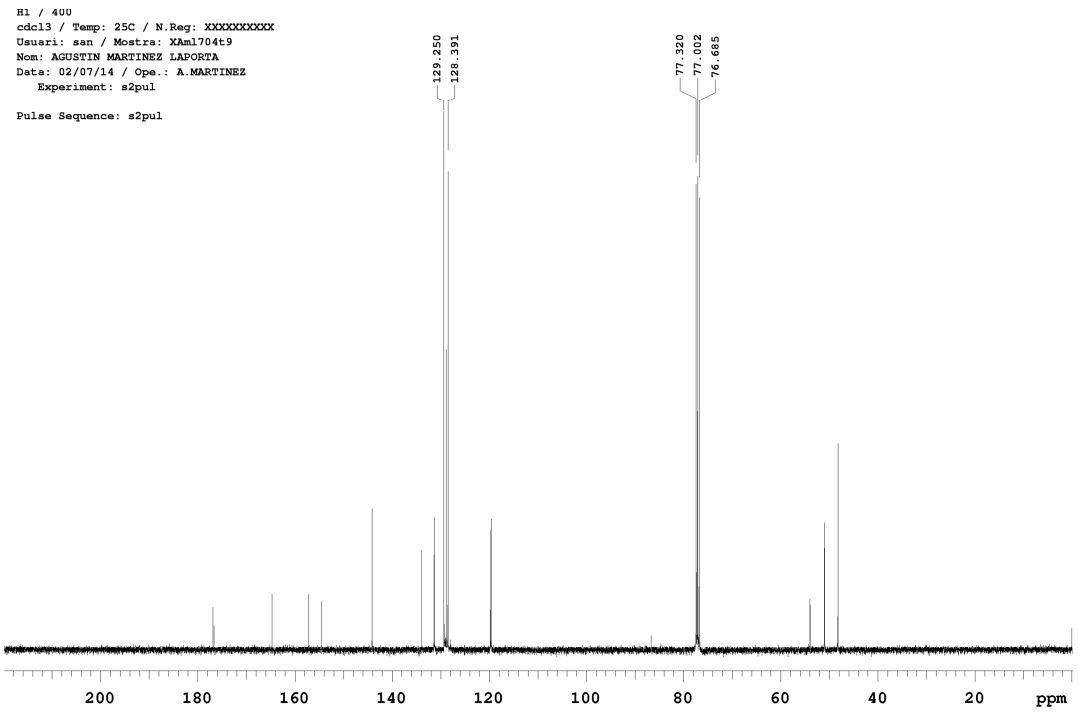

H1 / 400
cdcl3 / Temp: 25C / N.Reg: XXXXXXXXX
Usuari: san / Mostra: AML703t13
Nom: AGUSTIN MARTINEZ LAPORTA
Data: 03/07/14 / Ope.: A.MARTINEZ
Experiment: s2pul
Pulse Sequence: s2pul
1.923
1.919
9
8
7
6
5
4
3
2
1
ppm

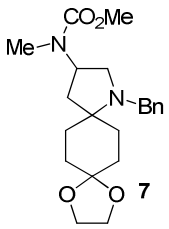

H1 / 400
cdcl3 / Temp: 25C / N.Reg: XXXXXXXXX
Usuari: san / Mostra: AML703t13
Nom: AGUSTIN MARTINEZ LAPORTA
Data: 03/07/14 / Ope.: A.MARTINEZ
Experiment: s2pul
Pulse Sequence: s2pul
129.050
128.315
200
180
160
140
120
100
80
60
40
20
ppm


O
Bn
N
Cl
Cl
F
O

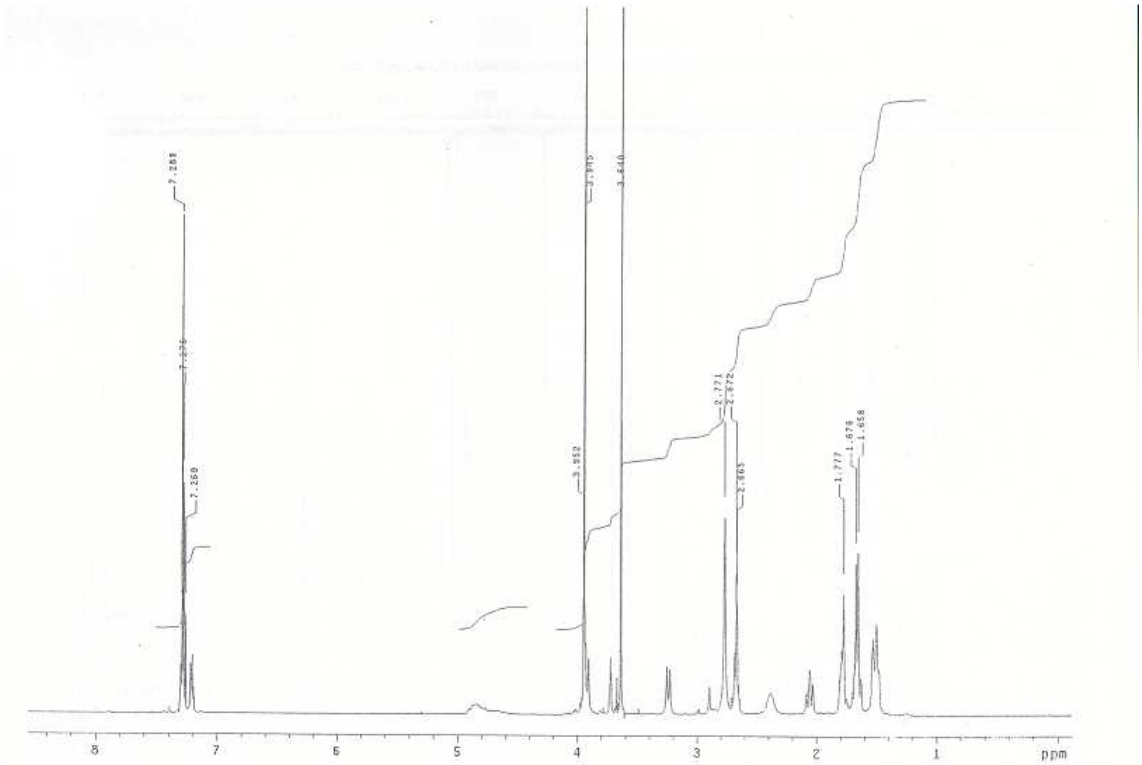
2f

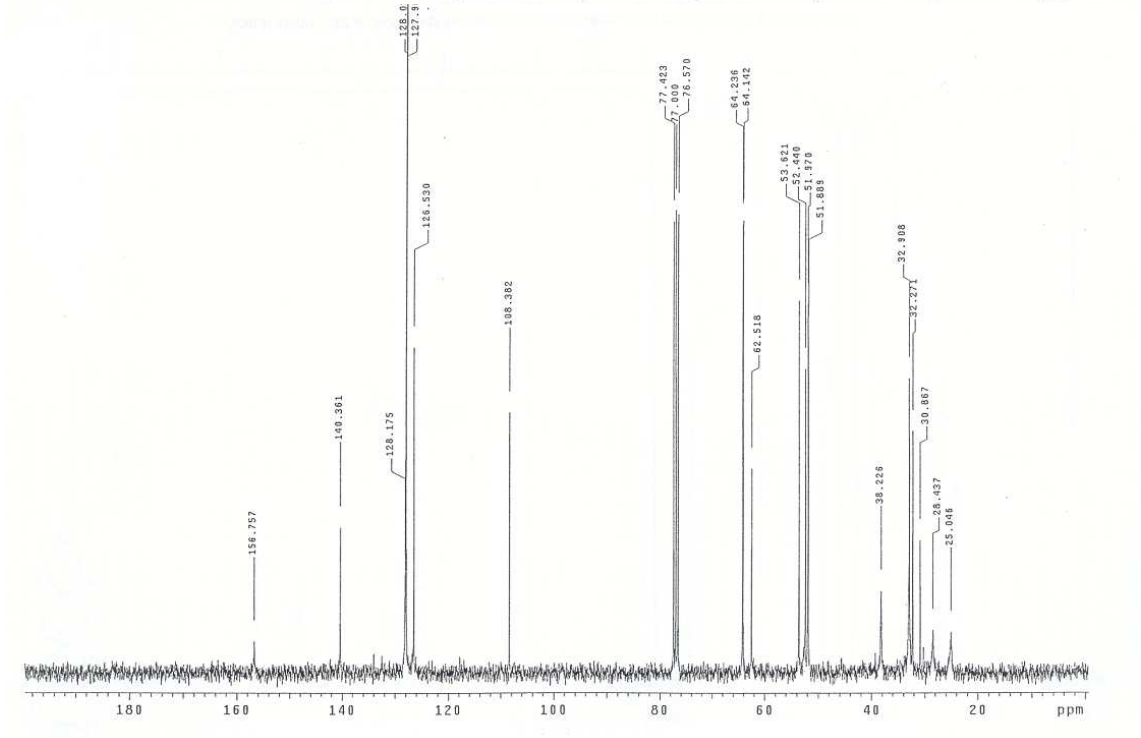

H1 / 400
cdcl3 / Temp: 25C / N.Reg: XXXXXXXXX
Usuari: san / Mostra: XAml704t9
Nom: AGUSTIN MARTINEZ LAPORTA
Data: 02/07/14 / Ope.: A.MARTINEZ
Experiment: s2pul
Pulse Sequence: s2pul
4.600
9
8
7
6
5
4
3
2
1
ppm

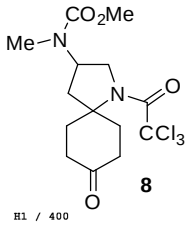

H1 / 400
cdcl3 / Temp: 25C / N.Reg: XXXXXXXXX
Usuari: san / Mostra: XAml704t9
Nom: AGUSTIN MARTINEZ LAPORTA
Data: 02/07/14 / Ope.: A.MARTINEZ
Experiment: s2pul
Pulse Sequence: s2pul
129.250
128.391
77.320
77.002
76.685
200
180
160
140
120
100
80
60
40
20
ppm


CO2Me
Me
N
N
Bn
O
O

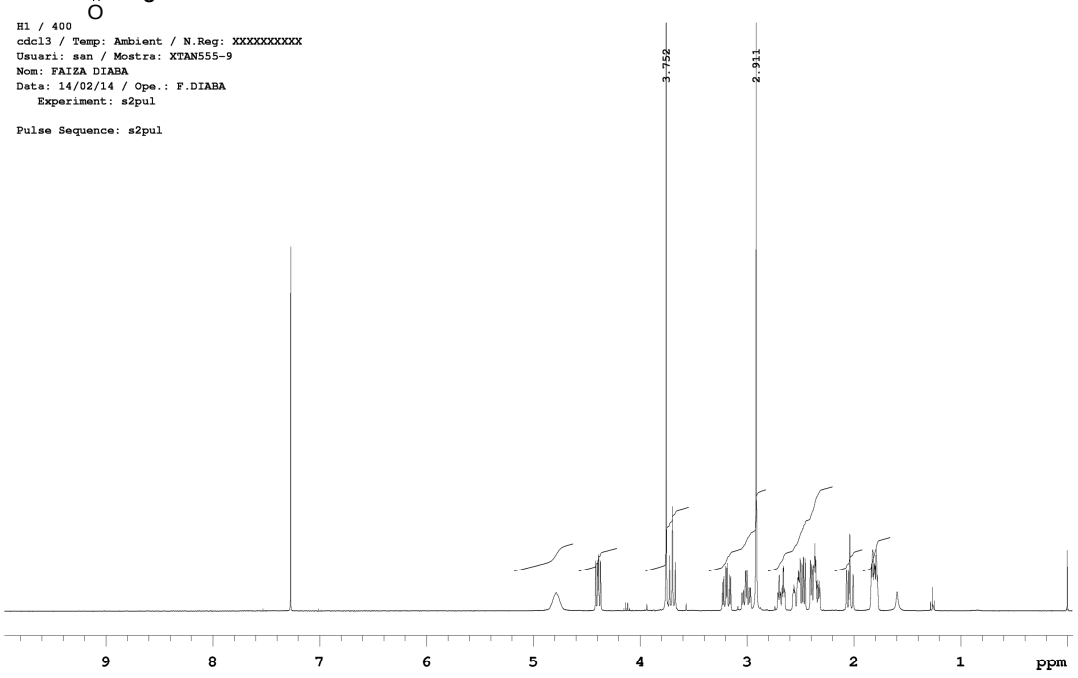
7

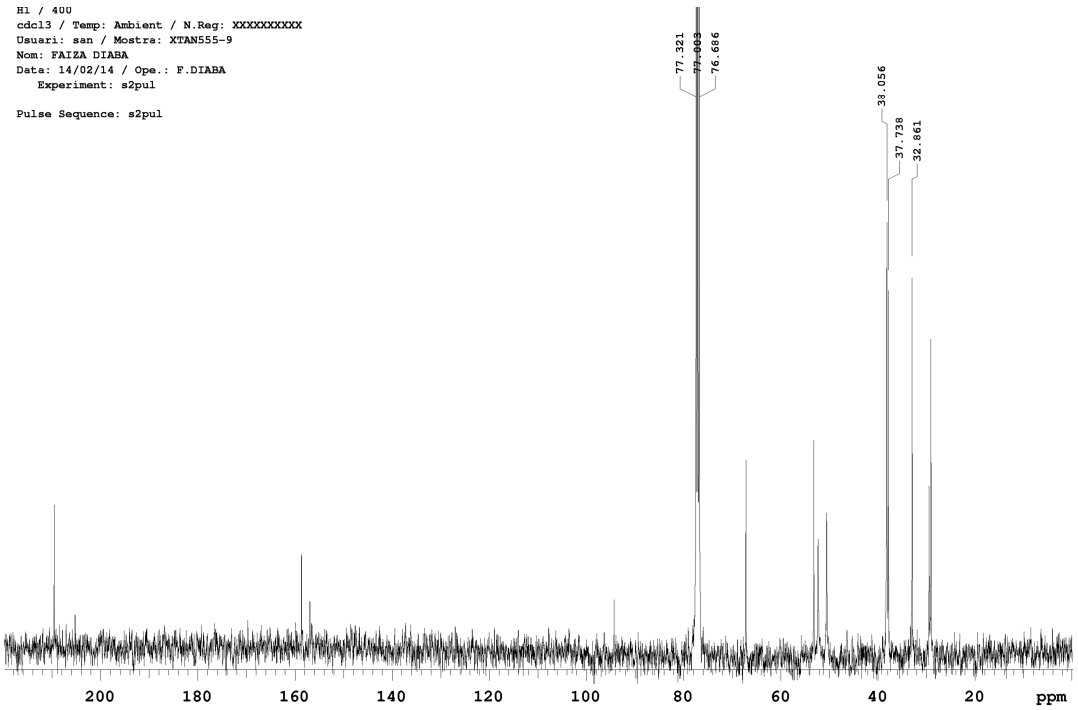

7.268
7.269
3.952
3.840
2.771
2.672
2.665
1.777
1.678
1.658
8
7
6
5
4
3
2
1
ppm

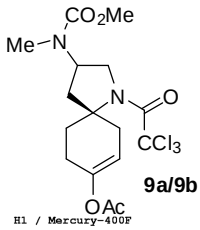

128.0
127.9
126.530
77.423
77.000
76.570
64.236
64.142
53.621
52.440
51.970
51.889
32.908
32.271
30.867
28.437
25.046
62.518
38.226
198.382
140.361
128.175
156.757
180
160
140
120
100
80
60
40
20
ppm


CO2Me
Me
N
N
O
CCl3
O

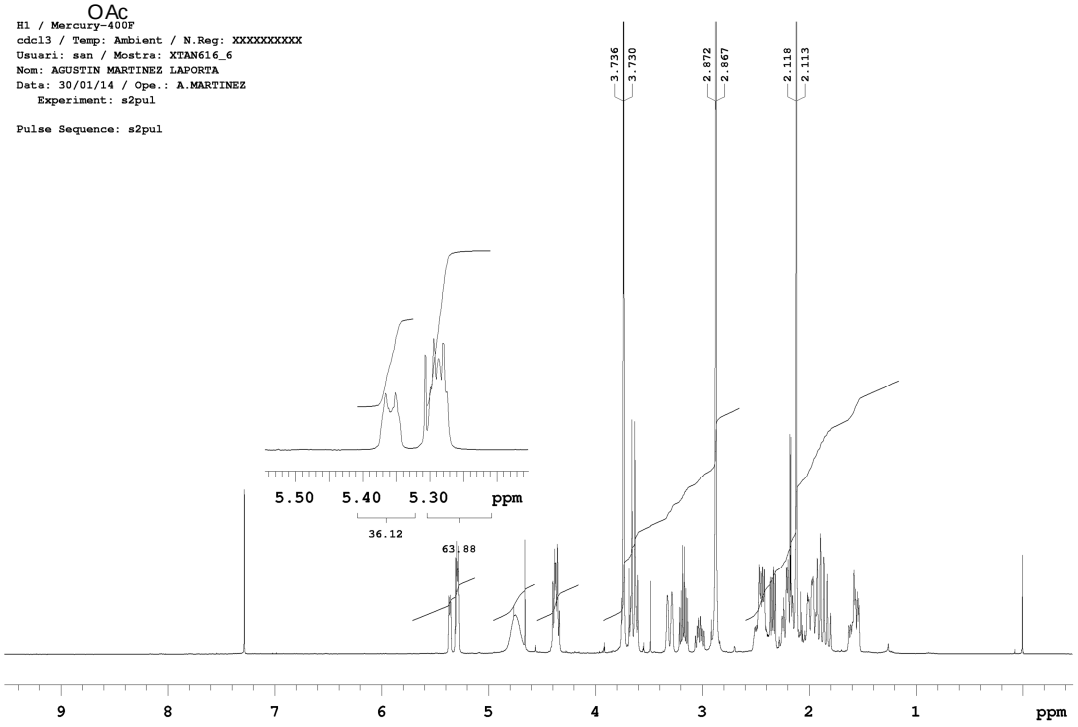
8

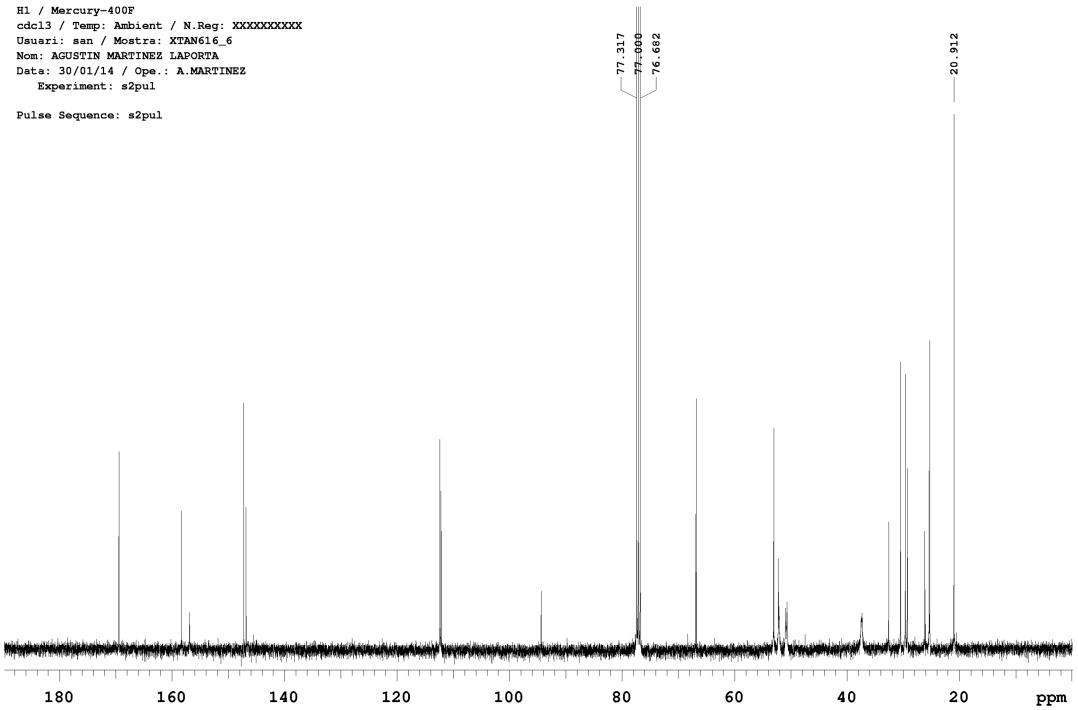

H1 / 400
cdcl3 / Temp: Ambient / N.Reg: XXXXXXXXXX
Usuari: san / Mostra: XTAN555-9
Nom: FAIZA DIABA
Data: 14/02/14 / Ope.: F.DIABA
Experiment: s2pul
Pulse Sequence: s2pul
3.752
2.911
9
8
7
6
5
4
3
2
1
ppm

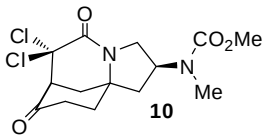

H1 / 400
cdcl3 / Temp: Ambient / N.Reg: XXXXXXXXXX
Usuari: san / Mostra: XTAN555-9
Nom: FAIZA DIABA
Data: 14/02/14 / Ope.: F.DIABA
Experiment: s2pul
Pulse Sequence: s2pul
77.321
77.003
76.686
38.056
37.738
32.861
200
180
160
140
120
100
80
60
40
20
ppm


CO2Me
Me
N
N
O
CCl3
OAc

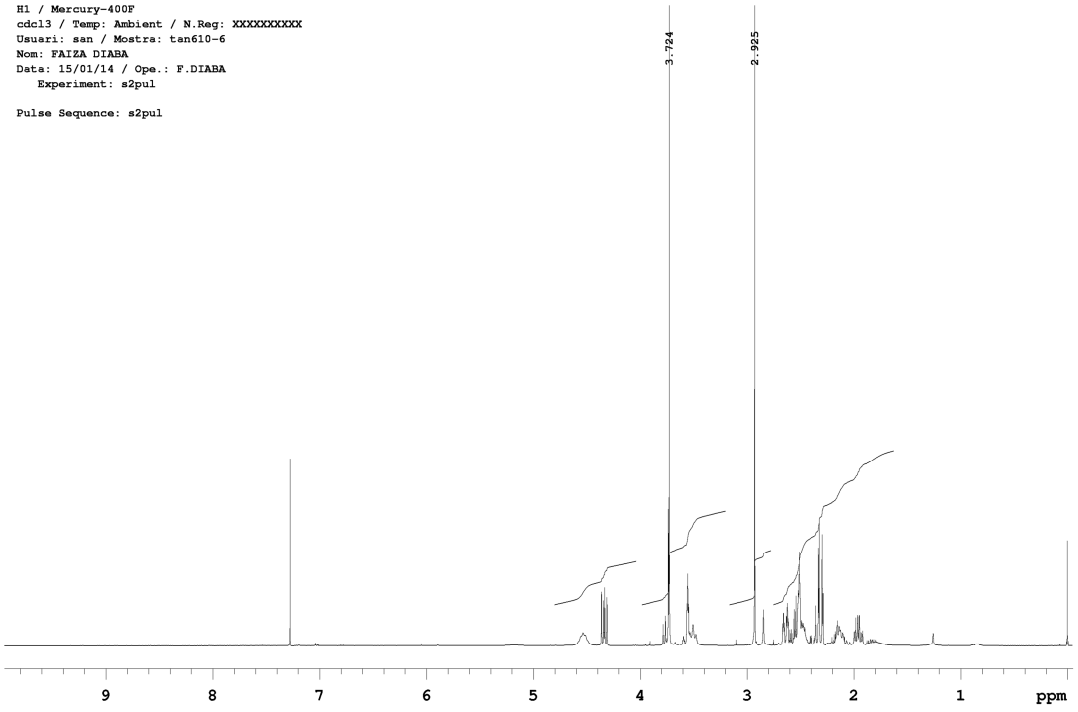
9a/9b

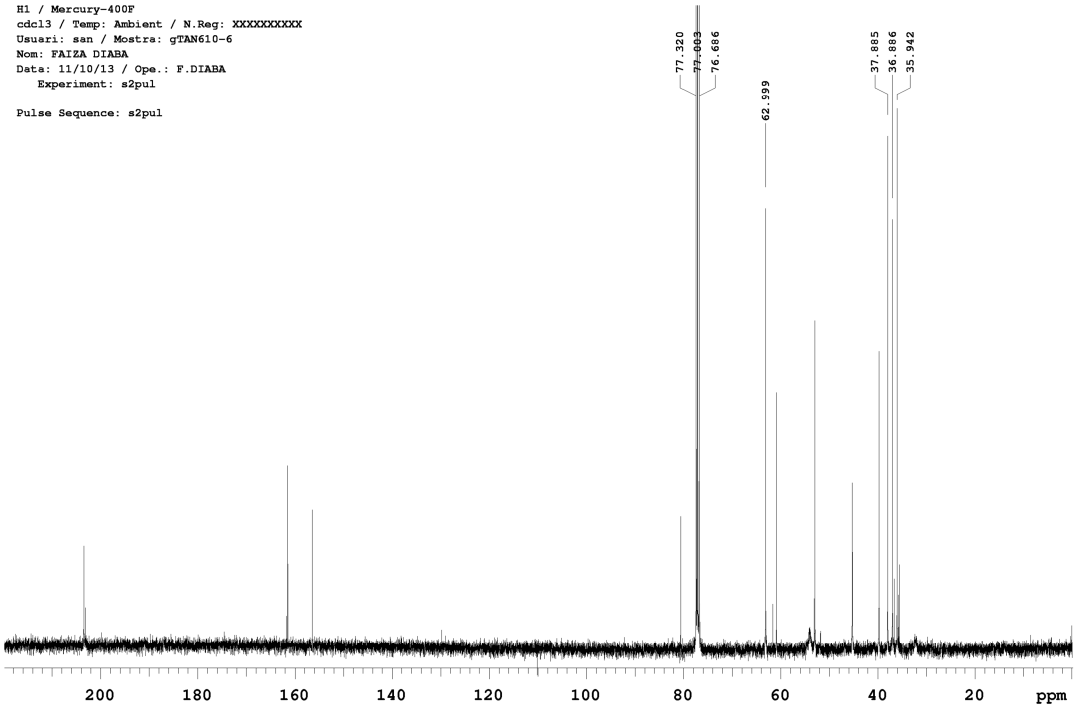

H1 / Mercury-400F
cdcl3 / Temp: Ambient / N.Reg: XXXXXXXXXX
Usuari: san / Mostra: XTAN616_6
Nom: AGUSTIN MARTINEZ LAPORTA
Data: 30/01/14 / Ope.: A.MARTINEZ
Experiment: s2pul
Pulse Sequence: s2pul
3.736
3.730
2.872
2.867
2.118
2.113
5.50
5.40
5.30
ppm
36.12
63.88
9
8
7
6
5
4
3
2
1
ppm

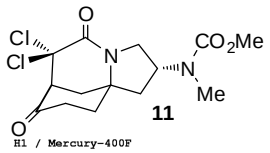

H1 / Mercury-400F
cdcl3 / Temp: Ambient / N.Reg: XXXXXXXXXX
Usuari: san / Mostra: XTAN616_6
Nom: AGUSTIN MARTINEZ LAPORTA
Data: 30/01/14 / Ope.: A.MARTINEZ
Experiment: s2pul
Pulse Sequence: s2pul
77.317
77.000
76.682
20.912
180
160
140
120
100
80
60
40
20
ppm


O
Cl
Cl
N
CO2Me
N
Me
O

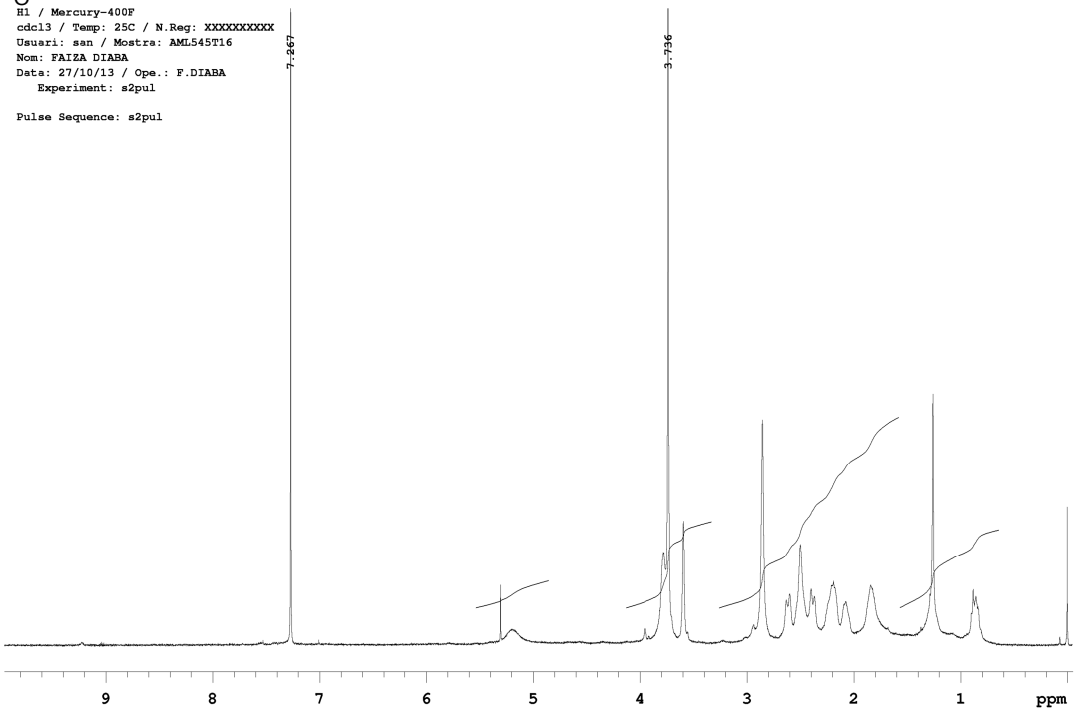
10

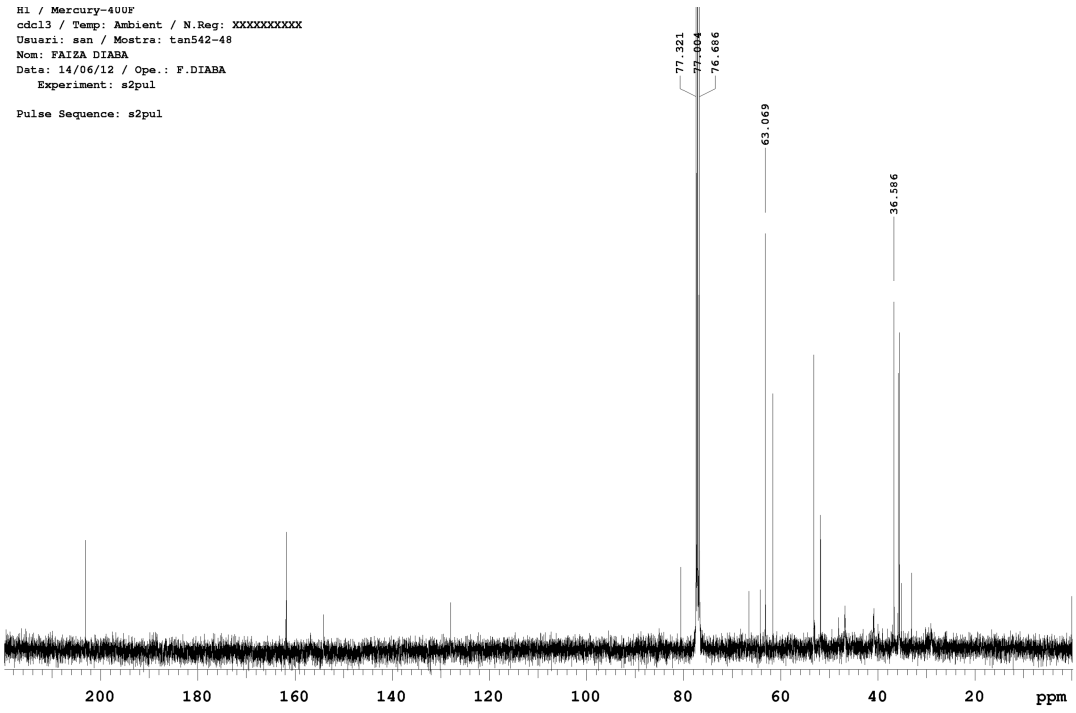

H1 / Mercury-400F
cdcl3 / Temp: Ambient / N.Reg: XXXXXXXXXX
Usuari: san / Mostra: tan610-6
Nom: FAIZA DIABA
Data: 15/01/14 / Ope.: F.DIABA
Experiment: s2pul
Pulse Sequence: s2pul
3.724
2.925
9
8
7
6
5
4
3
2
1
ppm

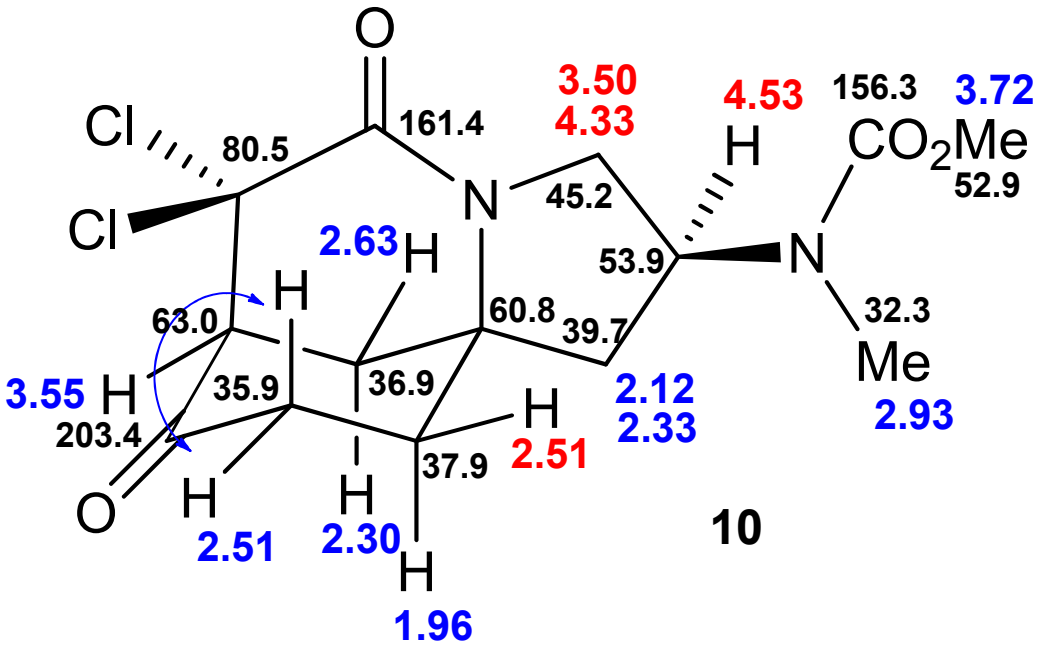

H1 / Mercury-400F
cdcl3 / Temp: Ambient / N.Reg: XXXXXXXXXX
Usuari: san / Mostra: gTAN610-6
Nom: FAIZA DIABA
Data: 11/10/13 / Ope.: F.DIABA
Experiment: s2pul
Pulse Sequence: s2pul
77.320
77.003
76.686
62.999
37.885
36.886
35.942
200
180
160
140
120
100
80
60
40
20
ppm

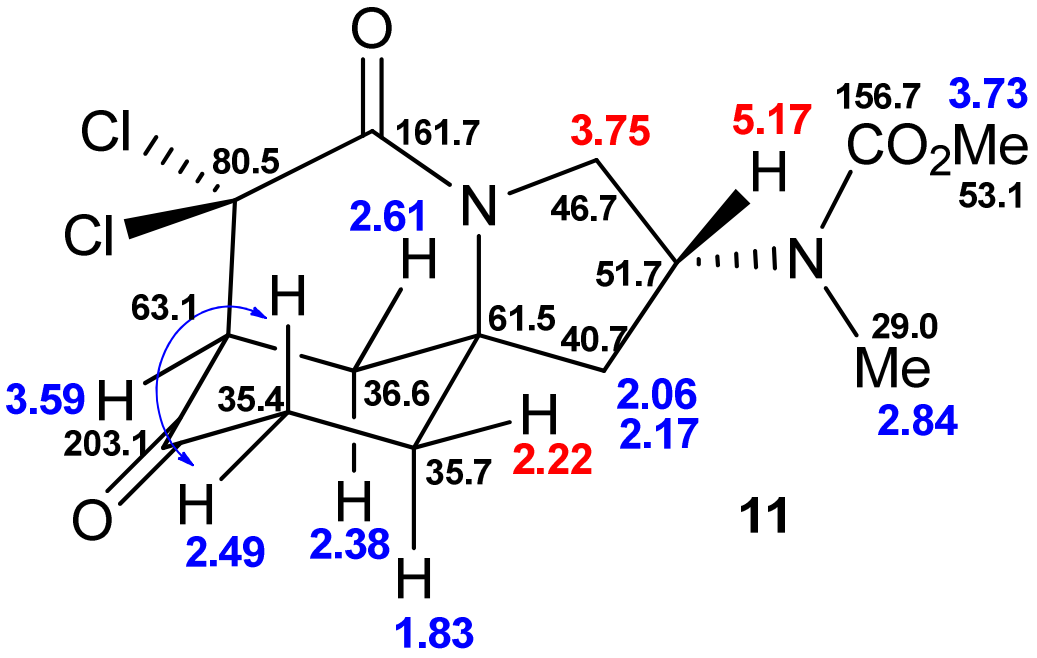

O
Cl
Cl
N
CO2Me
N
Me
O

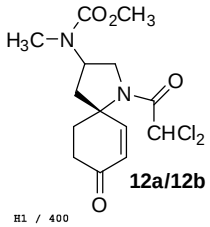
11


H1 / Mercury-400F
cdcl3 / Temp: 25C / N.Reg: XXXXXXXXX
Usuari: san / Mostra: AML545T16
Nom: FAIZA DIABA
Data: 27/10/13 / Ope.: F.DIABA
Experiment: s2pul
Pulse Sequence: s2pul
7.267
3.736
9
8
7
6
5
4
3
2
1
ppm

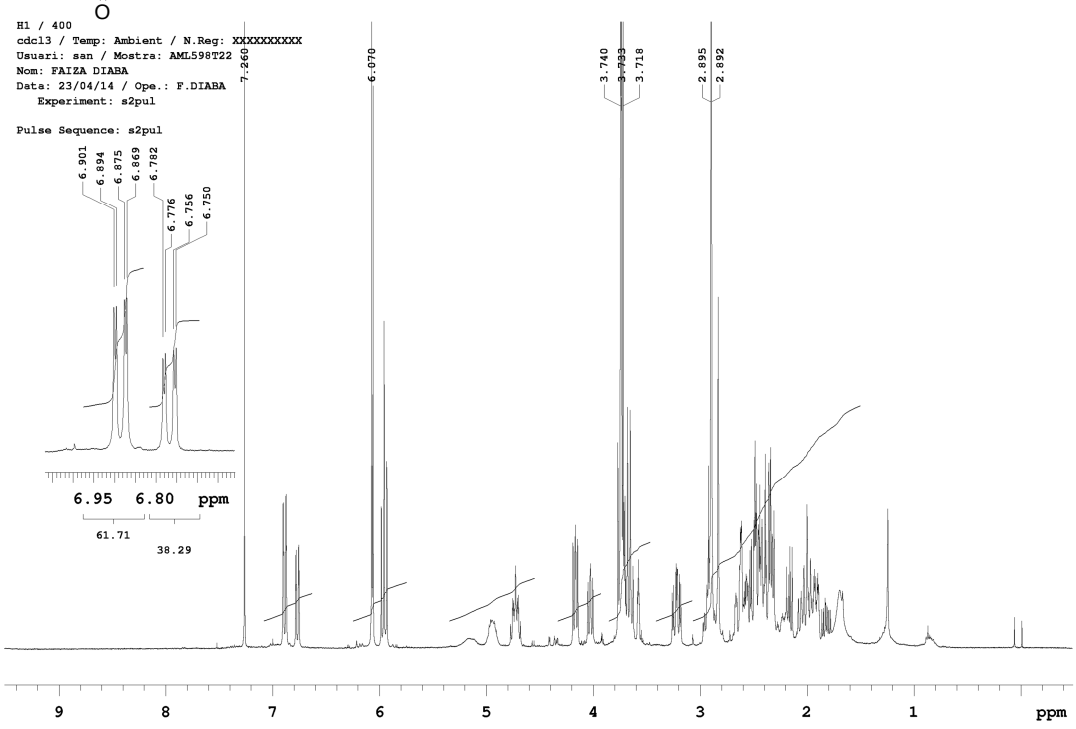

H1 / Mercury-400F
cdcl3 / Temp: Ambient / N.Reg: XXXXXXXXX
Usuari: san / Mostra: tan542-48
Nom: FAIZA DIABA
Data: 14/06/12 / Ope.: F.DIABA
Experiment: s2pul
Pulse Sequence: s2pul
77.321
77.004
76.686
63.069
36.586
200
180
160
140
120
100
80
60
40
20
ppm

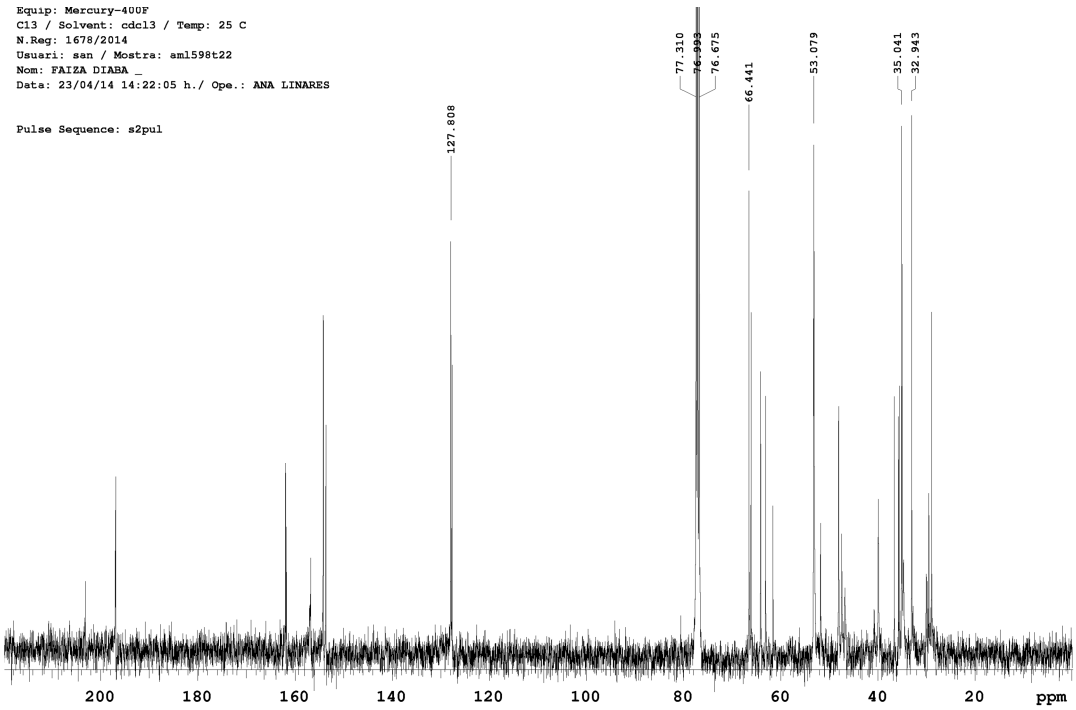

O
Cl
80.5
161.4
3.50
4.33
4.53
156.3
3.72
H
CO2Me
52.9
Cl
N
45.2
2.63
H
53.9
N
H
63.0
60.8
39.7
32.3
Me
3.55 H
35.9
36.9
2.12
2.33
2.93
203.4
H
2.51
37.9
O
H
H
2.51
2.30
H
1.96
10

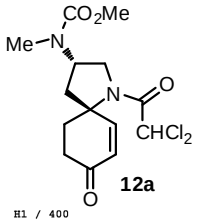

O
Cl
80.5
161.7
3.75
5.17
156.7
3.73
H
CO2Me
53.1
Cl
N
46.7
2.61
H
51.7
N
H
63.1
61.5
40.7
29.0
Me
3.59 H
35.4
36.6
2.06
2.17
2.84
203.1
H
2.22
35.7
O
H
H
2.49
2.38
H
1.83
11


CO2CH3
H3C–N
N
O
CHCl2
O

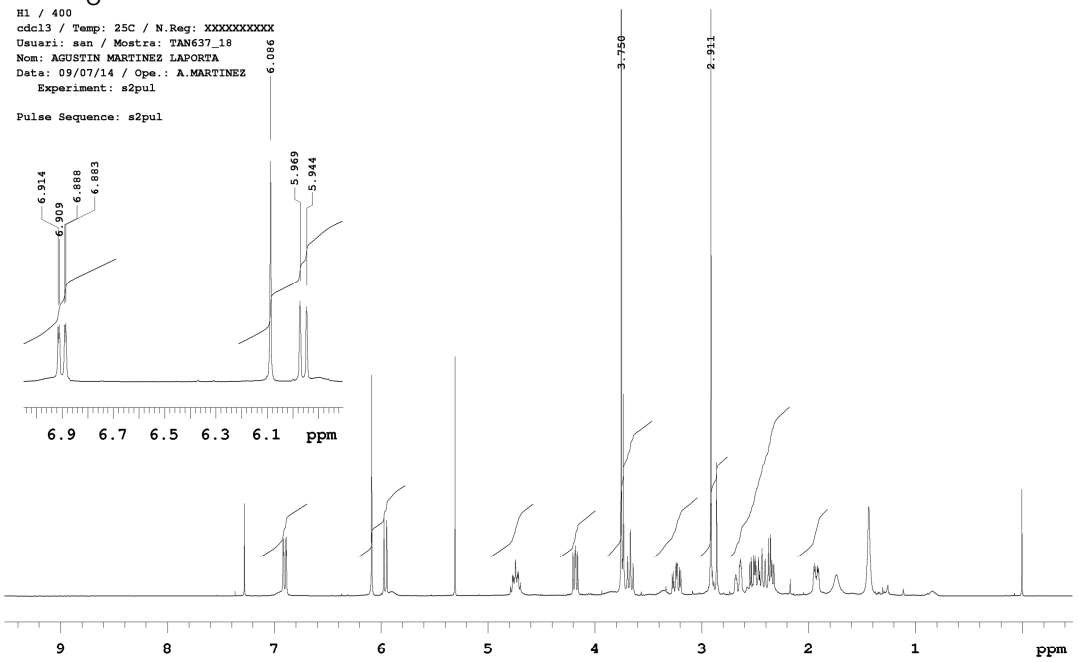
12a/12b

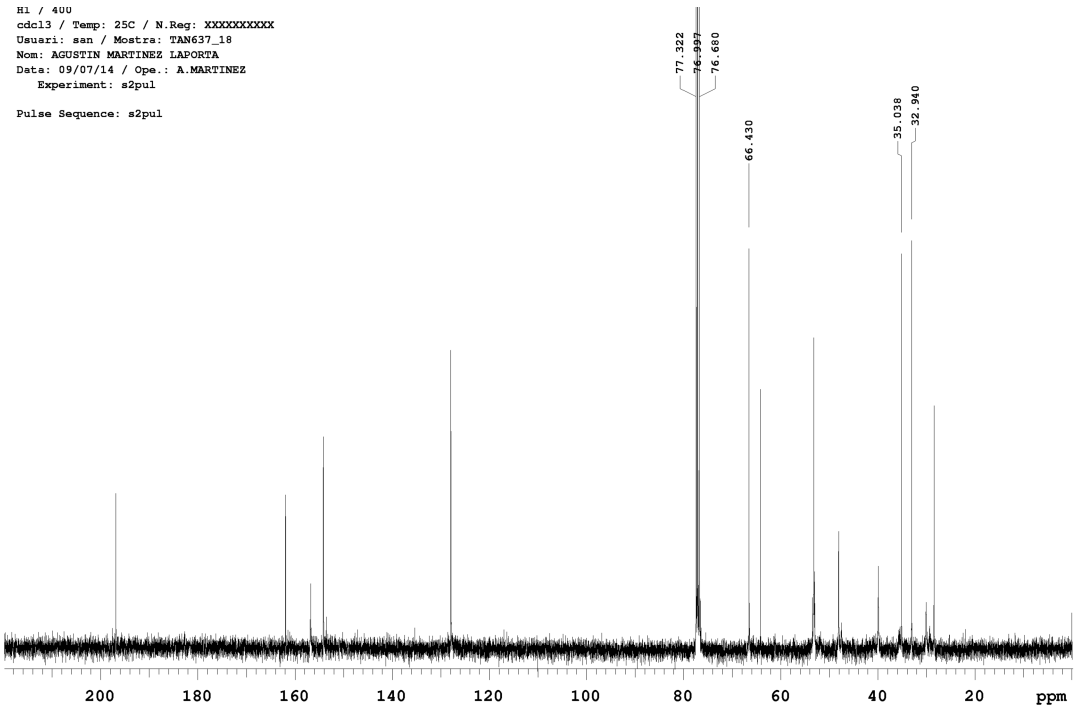

H1 / 400
cdcl3 / Temp: Ambient / N.Reg: XXXXXXXXXX
Usuari: san / Mostra: AML598T22
Nom: FAIZA DIABA
Data: 23/04/14 / Ope.: F.DIABA
Experiment: s2pul
Pulse Sequence: s2pul
7.260
6.070
3.740
3.733
3.718
2.895
2.892
6.901
6.894
6.875
6.869
6.782
6.776
6.756
6.750
6.95 6.80 ppm
61.71
38.29
9 8 7 6 5 4 3 2 1 ppm

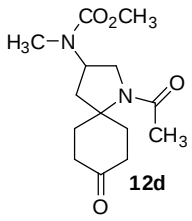

Equip: Mercury-400F
C13 / Solvent: cdcl3 / Temp: 25 C
N.Reg: 1678/2014
Usuari: san / Mostra: aml598t22
Nom: FAIZA DIABA _
Data: 23/04/14 14:22:05 h./ Ope.: ANA LINARES
Pulse Sequence: s2pul
127.808
77.310
76.993
76.675
66.441
53.079
35.041
32.943
200 180 160 140 120 100 80 60 40 20 ppm


CO2Me
Me
N
O
CHCl2
O

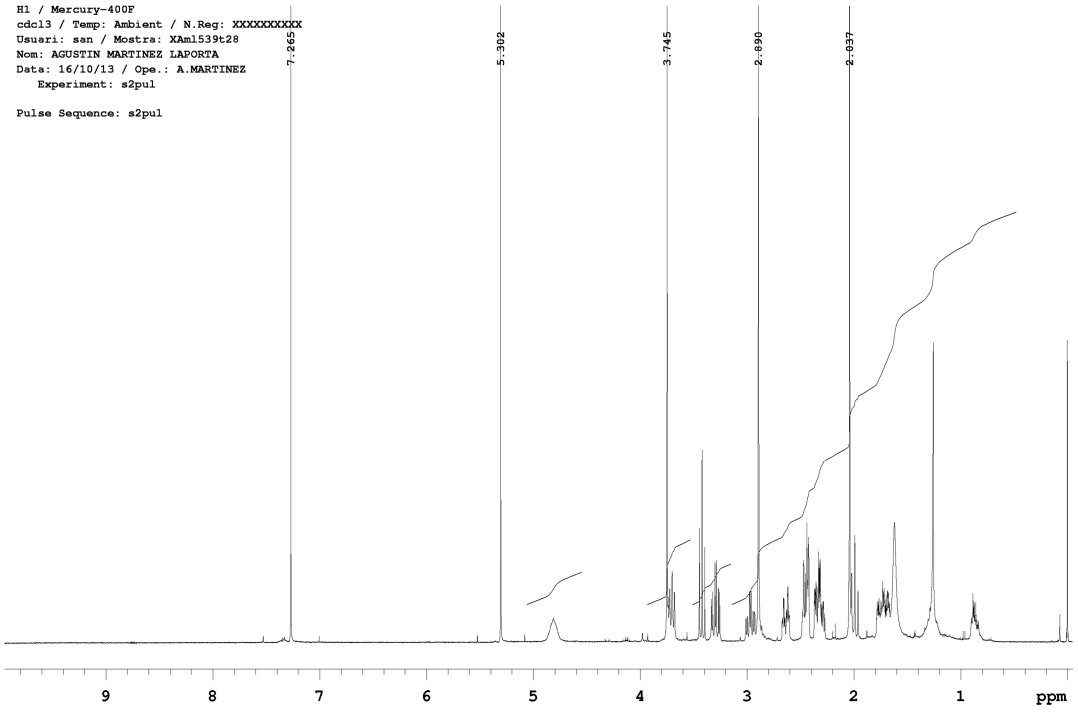
12a

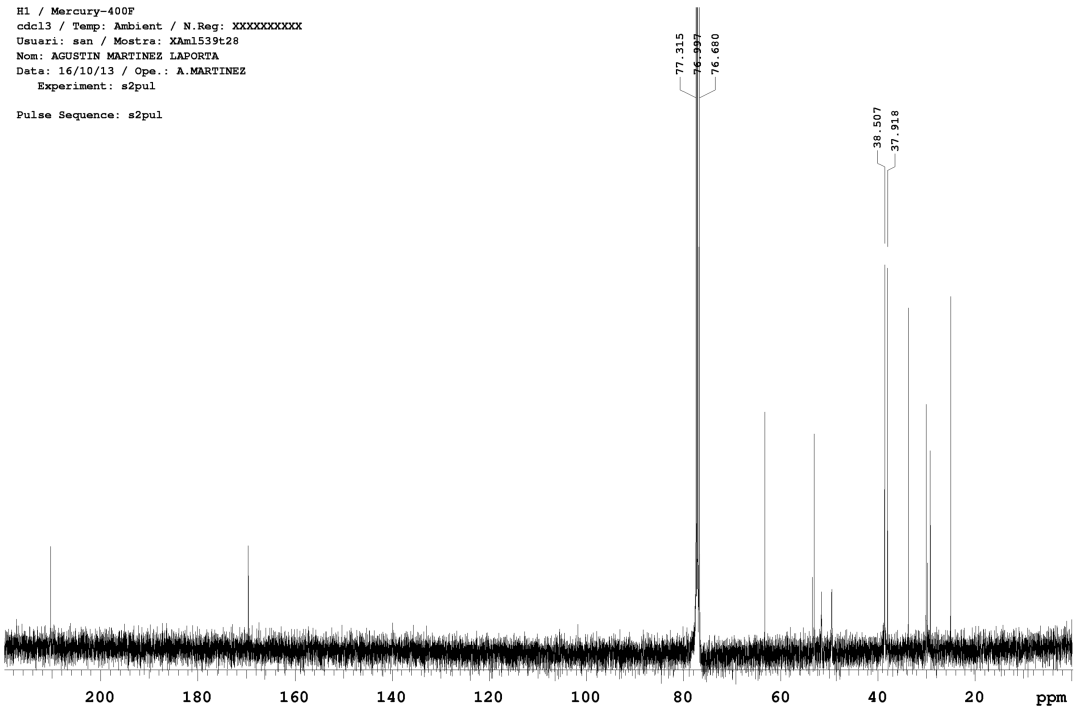

H1 / 400
cdcl3 / Temp: 25C / N.Reg: XXXXXXXXXX
Usuari: san / Mostra: TAN637_18
Nom: AGUSTIN MARTINEZ LAPORTA
Data: 09/07/14 / Ope.: A.MARTINEZ
Experiment: s2pul
Pulse Sequence: s2pul
6.086
3.750
2.911
6.914
6.909
6.888
6.883
5.969
5.944
6.9 6.7 6.5 6.3 6.1 ppm
9 8 7 6 5 4 3 2 1 ppm

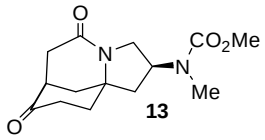

H1 / 400
cdcl3 / Temp: 25C / N.Reg: XXXXXXXXXX
Usuari: san / Mostra: TAN637_18
Nom: AGUSTIN MARTINEZ LAPORTA
Data: 09/07/14 / Ope.: A.MARTINEZ
Experiment: s2pul
Pulse Sequence: s2pul
77.322
76.997
76.680
66.430
35.038
32.940
200 180 160 140 120 100 80 60 40 20 ppm


CO2CH3
H3C–N
N
O
CH3
O

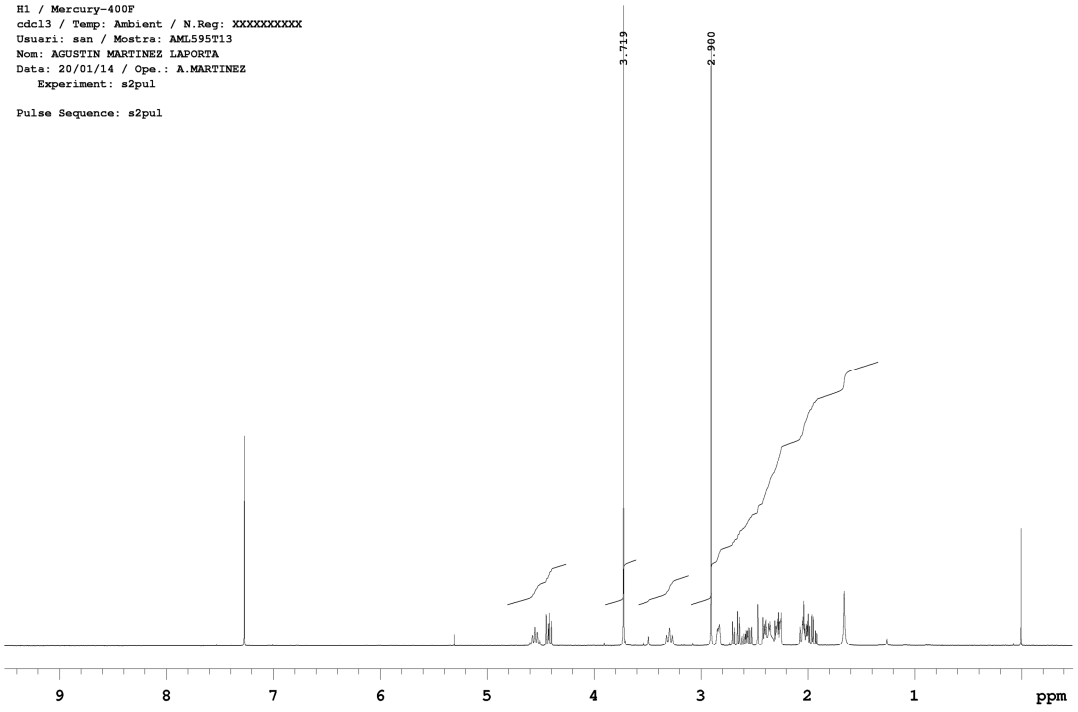
12d

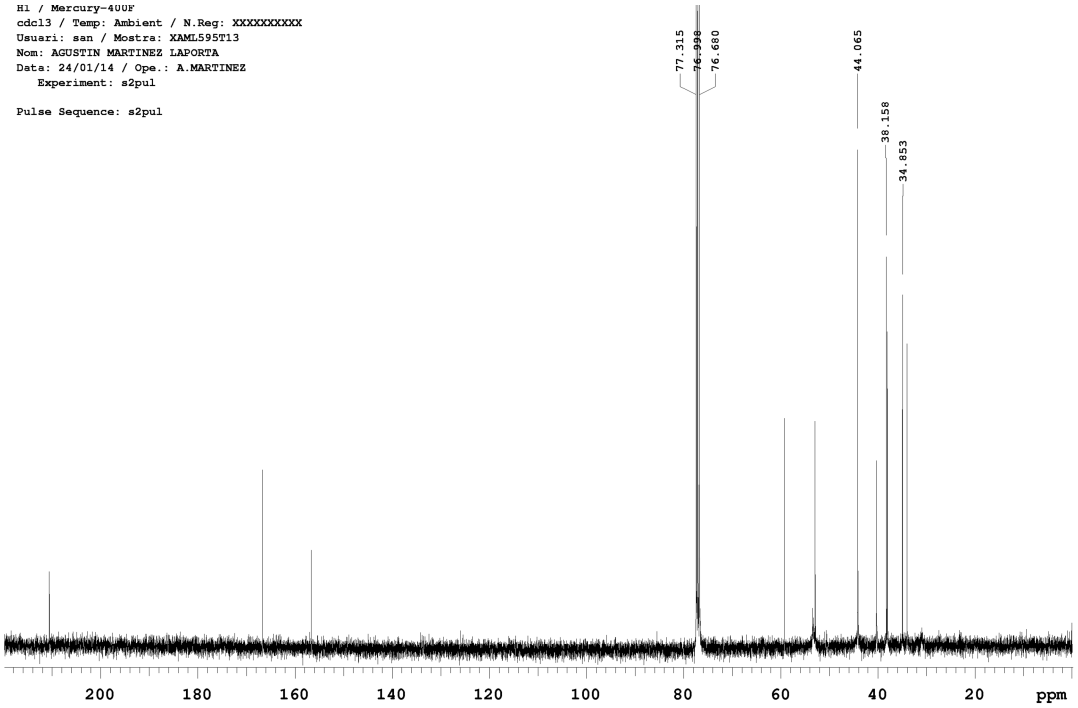

H1 / Mercury-400F
cdcl3 / Temp: Ambient / N.Reg: XXXXXXXXXX
Usuari: san / Mostra: XAml539t28
Nom: AGUSTIN MARTINEZ LAPORTA
Data: 16/10/13 / Ope.: A.MARTINEZ
Experiment: s2pul
Pulse Sequence: s2pul
7.265
5.302
3.745
2.890
2.037
9
8
7
6
5
4
3
2
1
ppm

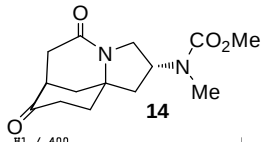

H1 / Mercury-400F
cdcl3 / Temp: Ambient / N.Reg: XXXXXXXXXX
Usuari: san / Mostra: XAml539t28
Nom: AGUSTIN MARTINEZ LAPORTA
Data: 16/10/13 / Ope.: A.MARTINEZ
Experiment: s2pul
Pulse Sequence: s2pul
77.315
76.997
76.680
38.507
37.918
200
180
160
140
120
100
80
60
40
20
ppm


O
N
CO2Me
N
Me
O

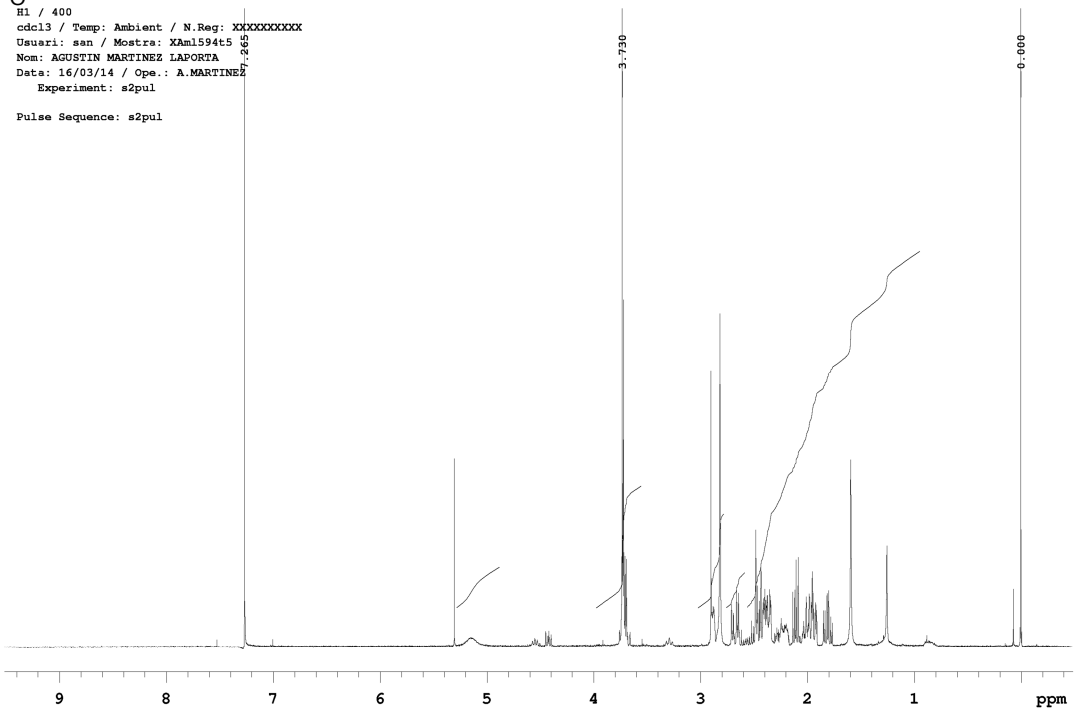
13

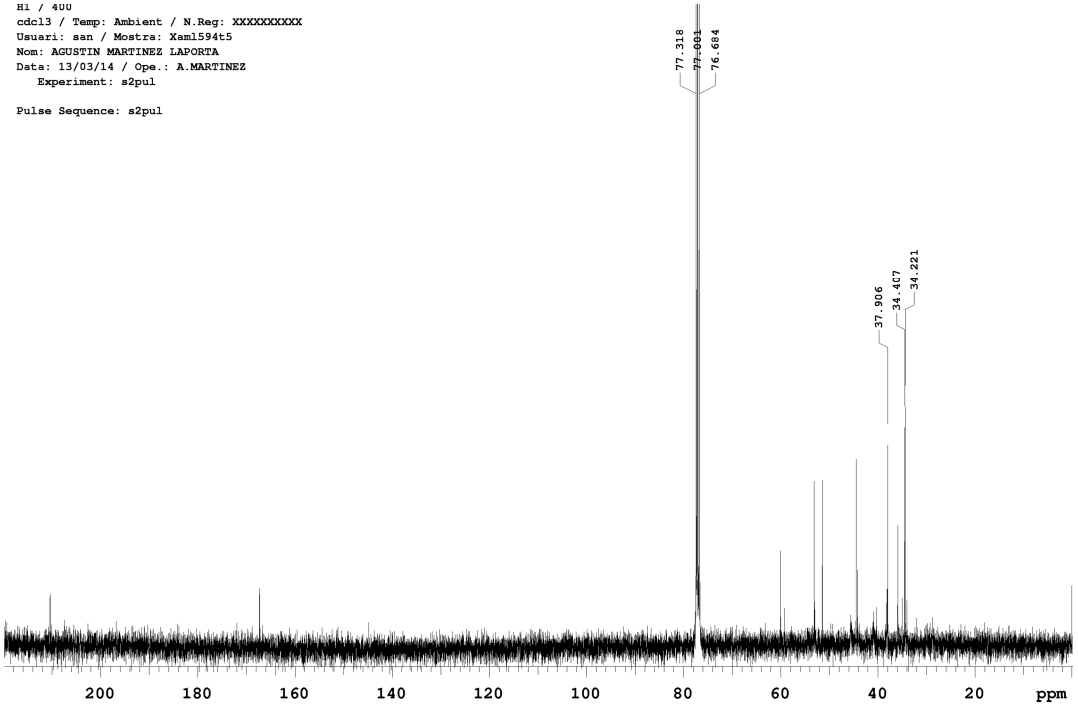

H1 / Mercury-400F
cdcl3 / Temp: Ambient / N.Reg: XXXXXXXXXX
Usuari: san / Mostra: AML595T13
Nom: AGUSTIN MARTINEZ LAPORTA
Data: 20/01/14 / Ope.: A.MARTINEZ
Experiment: s2pul
Pulse Sequence: s2pul
3.719
2.900
9
8
7
6
5
4
3
2
1
ppm

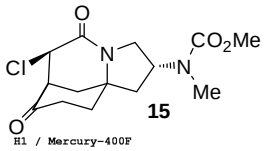

H1 / Mercury-400F
cdcl3 / Temp: Ambient / N.Reg: XXXXXXXXXX
Usuari: san / Mostra: XAML595T13
Nom: AGUSTIN MARTINEZ LAPORTA
Data: 24/01/14 / Ope.: A.MARTINEZ
Experiment: s2pul
Pulse Sequence: s2pul
77.315
76.998
76.680
44.065
38.158
34.853
200
180
160
140
120
100
80
60
40
20
ppm


O
N
CO2Me
N
Me
O

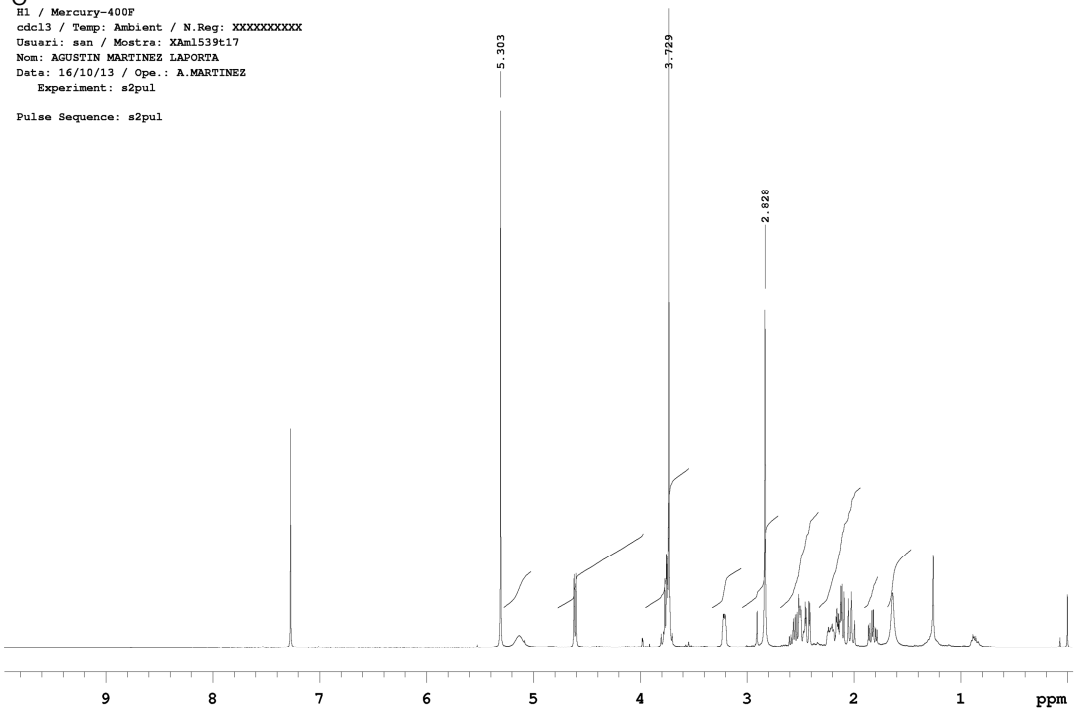
14

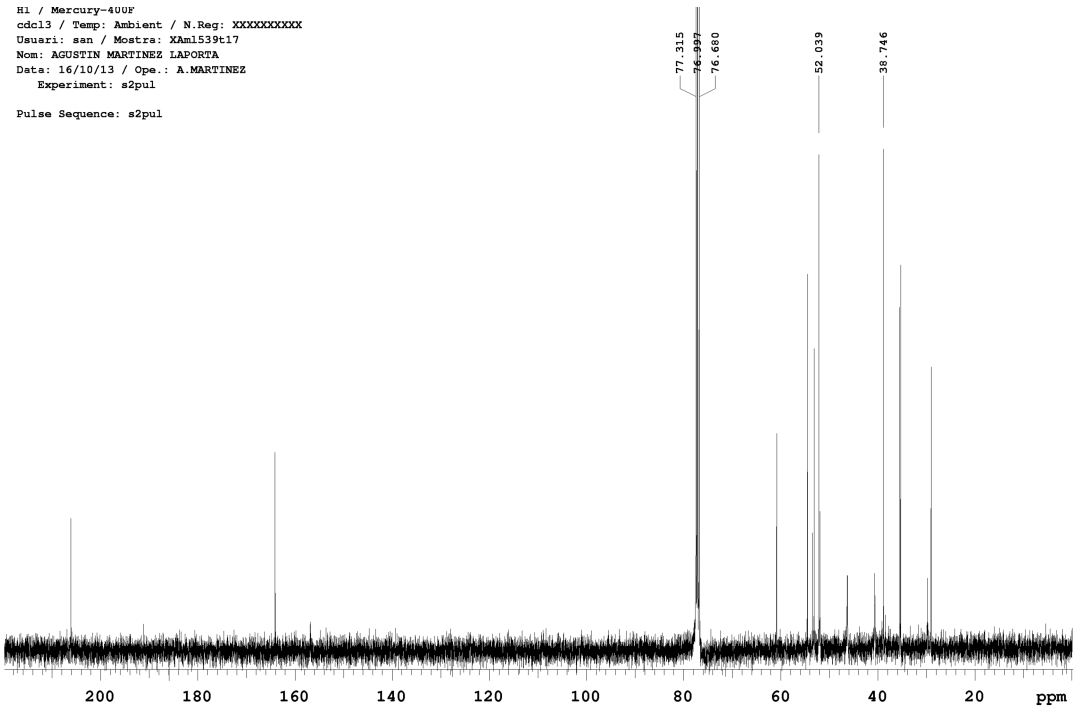

H1 / 400
cdcl3 / Temp: Ambient / N.Reg: XXXXXXXXX
Usuari: san / Mostra: XAml594t5
Nom: AGUSTIN MARTINEZ LAPORTA
Data: 16/03/14 / Ope.: A.MARTINEZ
Experiment: s2pul
Pulse Sequence: s2pul
7.265
3.730
0.000
9
8
7
6
5
4
3
2
1
ppm

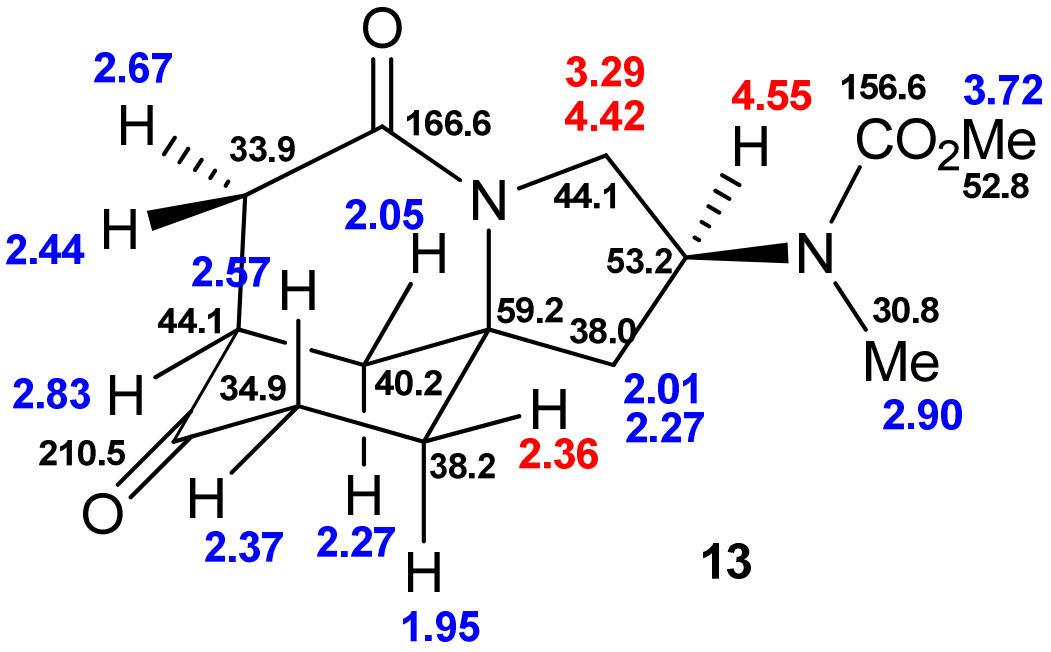

H1 / 400
cdcl3 / Temp: Ambient / N.Reg: XXXXXXXXX
Usuari: san / Mostra: Xaml594t5
Nom: AGUSTIN MARTINEZ LAPORTA
Data: 13/03/14 / Ope.: A.MARTINEZ
Experiment: s2pul
Pulse Sequence: s2pul
77.318
77.001
76.684
37.906
34.407
34.221
200
180
160
140
120
100
80
60
40
20
ppm


O
N
Cl
CO2Me
N
Me
O

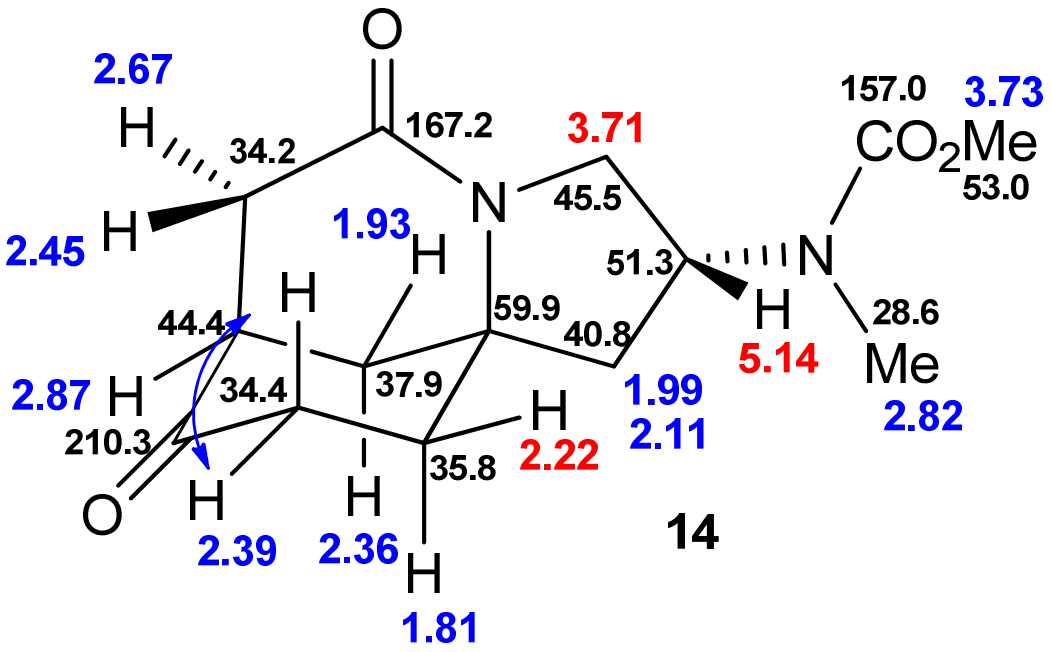
15


H1 / Mercury-400F
cdcl3 / Temp: Ambient / N.Reg: XXXXXXXXX
Usuari: san / Mostra: XAm1539t17
Nom: AGUSTIN MARTINEZ LAPORTA
Data: 16/10/13 / Ope.: A.MARTINEZ
Experiment: s2pul
Pulse Sequence: s2pul
5.303
3.729
2.828
9
8
7
6
5
4
3
2
1
ppm

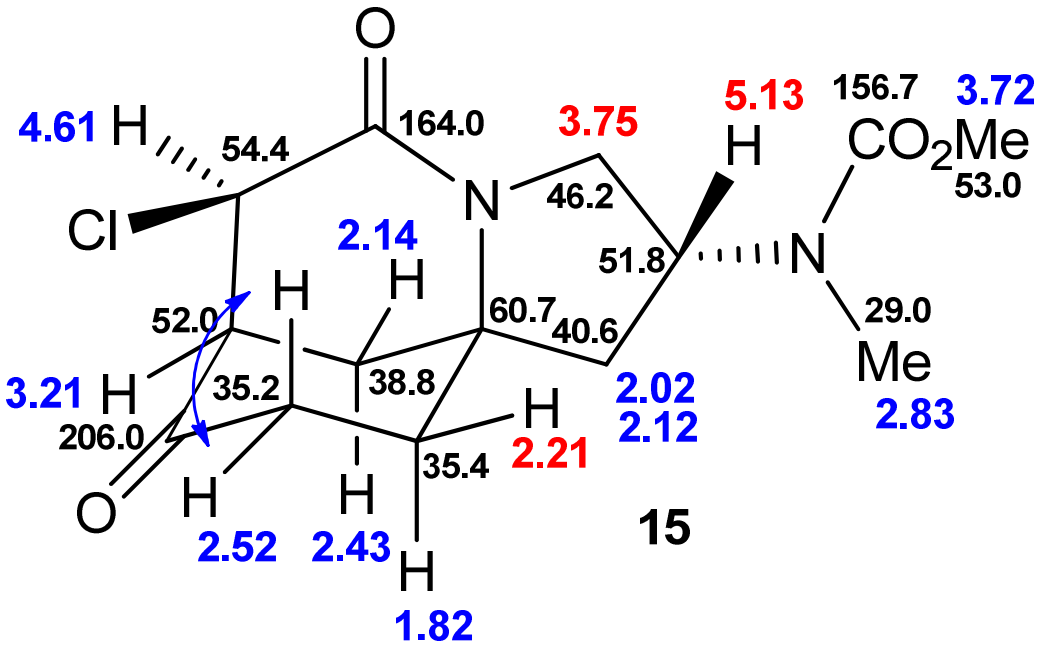

H1 / Mercury-400F
cdcl3 / Temp: Ambient / N.Reg: XXXXXXXXX
Usuari: san / Mostra: XAm1539t17
Nom: AGUSTIN MARTINEZ LAPORTA
Data: 16/10/13 / Ope.: A.MARTINEZ
Experiment: s2pul
Pulse Sequence: s2pul
77.315
76.997
76.680
52.039
38.746
200
180
160
140
120
100
80
60
40
20
ppm


O
2.67
H
33.9
166.6
3.29
4.42
4.55
156.6
3.72
CO2Me
52.8
H
N
44.1
H
2.44
2.05
H
2.57
H
53.2
N
44.1
59.2
38.0
30.8
Me
2.90
2.83 H
34.9
40.2
2.01
2.27
H
2.36
210.5
38.2
O
H
H
2.37
2.27
H
1.95

13


O
2.67
H
34.2
167.2
3.71
157.0
3.73
CO2Me
53.0
N
45.5
H
2.45
1.93
H
51.3
N
H
5.14
28.6
Me
2.82
44.4
H
59.9
40.8
2.87 H
34.4
37.9
1.99
2.11
H
2.22
210.3
35.8
O
H
H
2.39
2.36
H
1.81

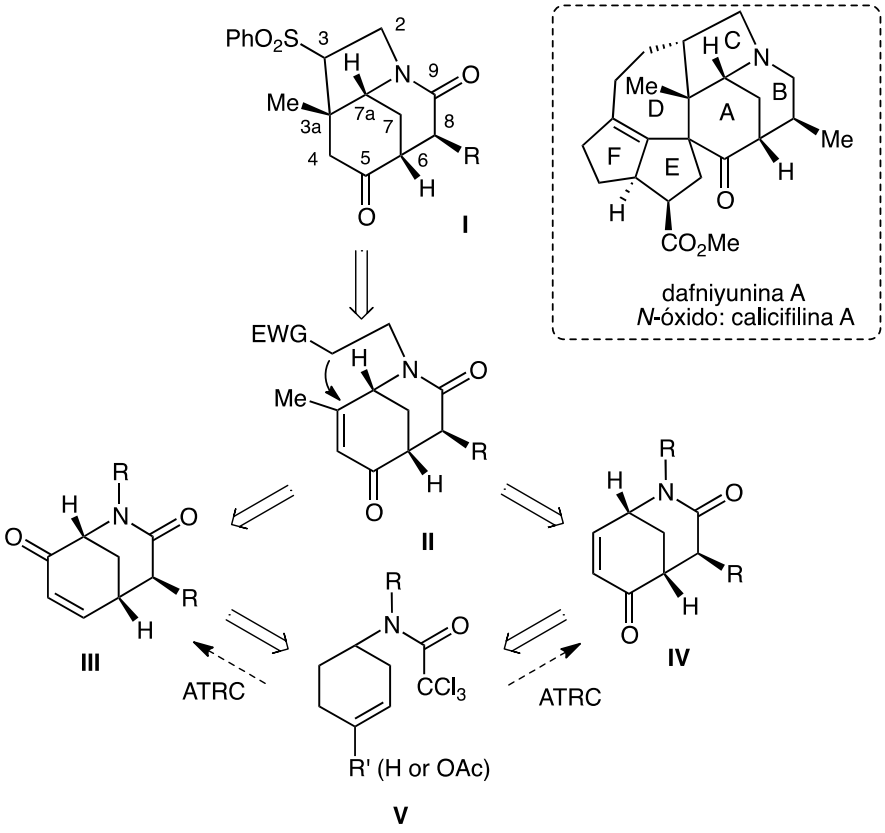
14


O
4.61 H
54.4
164.0
3.75
5.13
156.7
3.72
H
CO2Me
53.0
Cl
N
46.2
2.14
51.8
N
H
H
52.0
60.7
40.6
29.0
Me
3.21 H
35.2
38.8
2.02
2.12
2.83
206.0
H
2.21
35.4
O
H
H
2.52
2.43
H
1.82
15

6. Síntesis del fragmento ABC de los alcaloides *Daphniphyllum* del tipo calicifilina A

6.1 Introducción y Objetivos

El siguiente objetivo en el marco del estudio de síntesis de productos naturales, basado en la elaboración del núcleo azabicíclico de morfano mediante ciclación radicalaria, está encaminado a la síntesis de alcaloides *dapniphyllum*[1] y concretamente al subgrupo de alcaloides de tipo calicifilina A[2] (p. ej. dafniyunina A). en base a la disponibilidad de los compuestos azabicíclicos preparados mediante ATRC y que presentan una alta densidad de funcionalización.



6.1 Análisis retrosintético del azatriciclo **I** (anillos ABC de los alcaloides del grupo de la calicifilina A)

Nuestra estrategia sintética consiste en formar el azatricíclo **I** a partir de **II** mediante una reacción intramolecular de Michael utilizando un sustituyente adecuado, tal que permita proseguir hacia la síntesis del producto natural gracias a su funcionalización. A su vez, el compuesto **II** podría obtenerse ya fuera mediante la enona **III** o **IV**. En ambos casos, el 2-azabiciclo[3.3.1]nonano es accesible mediante una ciclación

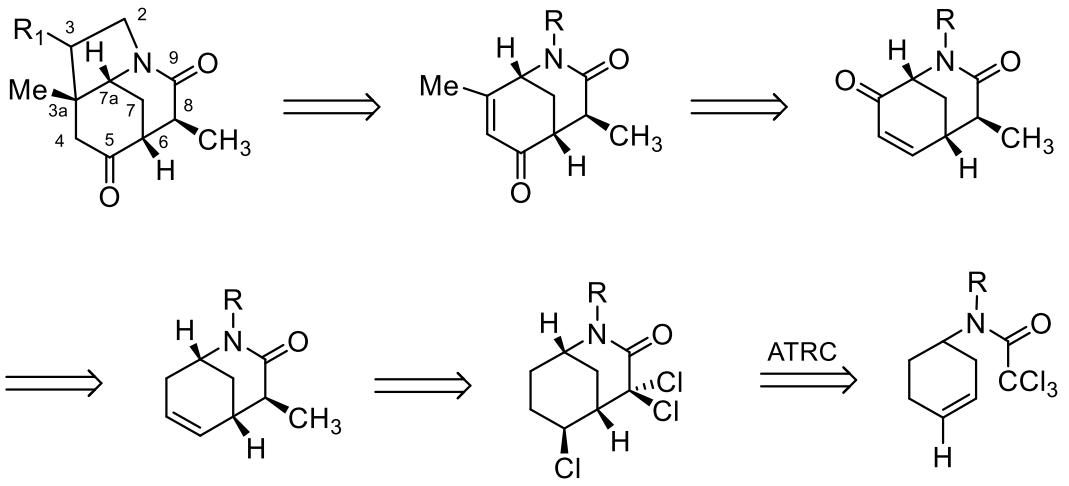
[1] Kobayashi, J.; Kubota, T. *Nat. Prod. Rep.* **2009**, *26*, 936-962.
[2] Para una revisión, véase: Kang, B.; Jakubec, P.; Dixon, D. J. *Nat. Prod. Rep*. **2014**, *31*, 550–562.

radicalaria de una tricloroacetamida seguida de los ajustes necesarios en su funcionalización.

En este capítulo se describe los resultados acerca de la síntesis del fragmento azatricíclico ABC común a este subconjuto de alcaloides *Daphniphyllum*, para el que ya existen diversas aproximaciones sintéticas, pero ni éstas ni otros trabajos publicados[3] conducentes a otros fragmentos del sistema hexacíclico[4] han fructificado en una síntesis total de ningún alcaloide de esta familia.

6.2 Aproximación sintética infructuosa

En una primera aproximación, que tendría como producto intermedio de síntesis el morfano resultante de la ciclación de la tricloroacetamida sobre un alqueno simple (**V**, R´= H, cap.2), se planteó la ruta retrosintética indicada en el Esquema 6.2.

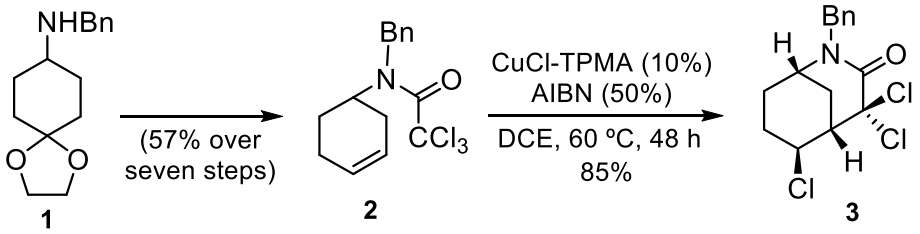


6.2 Estrategia sintética para el esqueleto azatriciclo ABC utilizando un morfano triclorado

Decidimos explorar la factibilidad de esta primera ruta operando a partir del morfano **3** con un sustituyente *N*-bencilo (Esquema 6.3). En caso de éxito, posteriormente deberíamos reproducir el procedimiento con un sustituyente adecuado para el cierre del anillo C de pirrolidina.

[3] (a) Solé, D.; Urbaneja, X.; Bonjoch, J. *Org.Lett.* **2005**, *7*, 5461–5464. (b) Yao, Y.; Liang, G. *Org. Lett.* **2012**, *14*, 5499–5501. (c) Lu, Z.; Li, Y.; Deng, J.; Li, A. *Nature Chem.* **2013**, *5*, 679–684. (d) Xiong, X.; Li, Y.; Lu, Z.; Wan, M.; Deng, J.; Wu, S.; Shao, H.; Li, A. *Chem. Commun.* **2014**, *50*, 5294–5297. (e) Ibrahim, A. A.; Golonka, A. N.; Lopez, A. M.; Stockdill, J. L. *Org. Lett.* **2014**, *16*, 1072–1075.

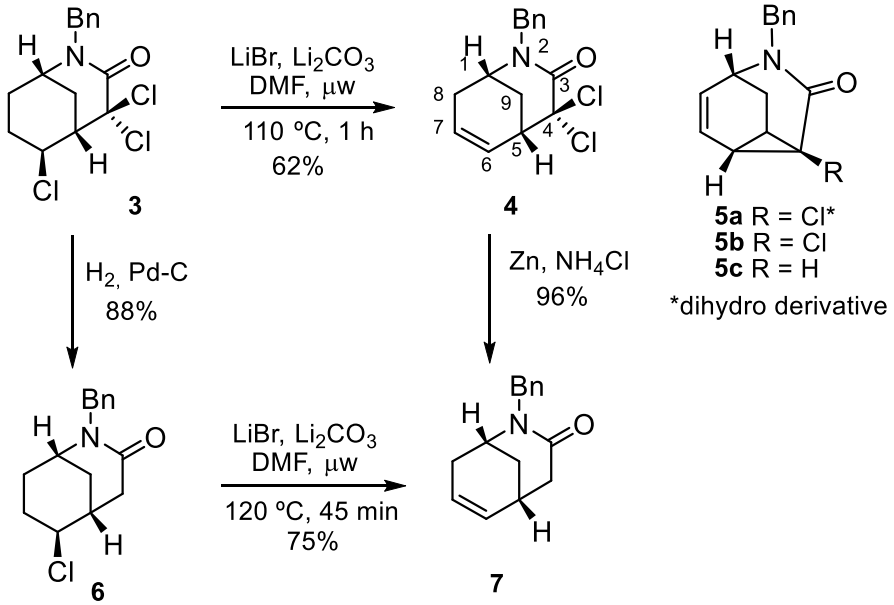
[4] Para estudios sintéticos hacia fragmentos tri- y tetracíclicos de alcaloides del grupo de la calicifilina A, véase: *ACD ring*: (a) Sladojevich, F.; Michaelides, I. N.; Darses, B.; Ward, J. W.; Dixon, D. J. *Org. Lett.* **2011**, *13*, 5132-5235. (b) Wang, L.; Xu, C.; Chen, Li, Hao, X.; Wang, D. Z. *Org. Lett.* **2014**, *16*, 1076-1079. *DEF ring*: (c) Darses, B.; Michaelides, I. N.; Sladojevich, F.; Ward, J. W.; Rzepa, P. R.; Dixon, D. *J. Org. Lett*. **2012**, *14*, 1684-1687. *ABCD ring*: (d) Xu, C.; Wang, L.; Hao, X.; Wang, D. Z. J. *Org. Chem*. **2012**, *77*, 6307-6313.



1 2 3

6.3 Síntesis del morfano **3**

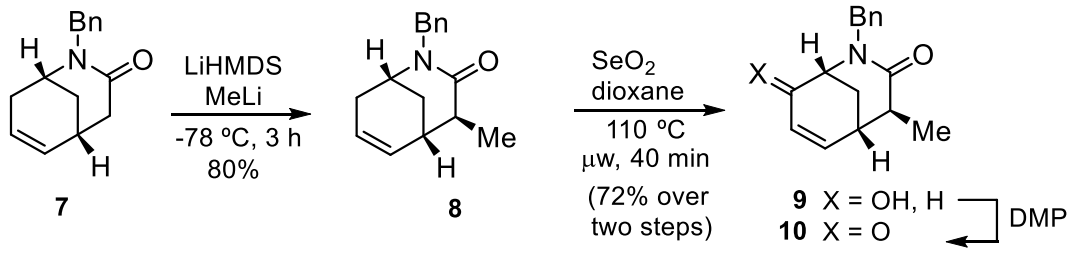
La ulterior génesis del alqueno **7** (Esquema 6.4) fue inicialmente problemática ya que la etapa de eliminación del cloro en C(6) no fue trivial. Así, mientras bases nitrogenadas (DBU, TPMA) conducían a la recuperación de **3**, bases fuertes (K*t*BuO, NaOEt, LDA) condujeron a procesos competitivos intramoleculares de ciclopropanación del tipo **5 (5a-5c)** como producto/s mayoritario/s o exclusivos de la reacción.[5] Después de un estudio de distintas bases (ej. AgOAc) se consiguió convertir **3** en **4** utilizando Li_2CO_3 y utilizando activación de microondas. Los rendimientos fueron moderados y aunque pudo obtenerse finalmente el alqueno **7** por reducción con Zn de los dos enlaces C-Cl geminales en **6**, la secuencia se descartó. El motivo fue que la inversión de la secuencia de reacciones (reducción quimioselectiva para generar **6** y su posterior reacción de β-eliminación para dar el alqueno 7) transcurrió con mejores rendimientos globales.



6.4 Transformaciones del morfano **3** a su derivado **7**

[5] Véase parte experimental para la descripción de las condiciones de formación de **5**(**a**-**c**).

A partir de la lactama **7**, se examinó la introducción del grupo metilo en C(4). Al operar en las condiciones expuestas en el esquema 6.5, se obtuvo de forma diastereoselectiva la lactama **8**, en la que el grupo metilo presenta la estereoquímica adecuada, fruto de la aproximación axial del agente alquilante al enolato.[6] Seguidamente nos concentramos en la génsis del grupo carbonilo en C(8). Los intentos de obtener la enona **10** de manera directa resultaron infructuosos.[7] La oxidación alílica utilizando SeO_2 con activación por microondas proporcionó el alcohol **9**, cuya posterior oxidación con el reactivo de Dess-Martin condujo satisfactoriamente a la enona **10**.



6.5 Conversión del alqueno **7** en la enona **10**

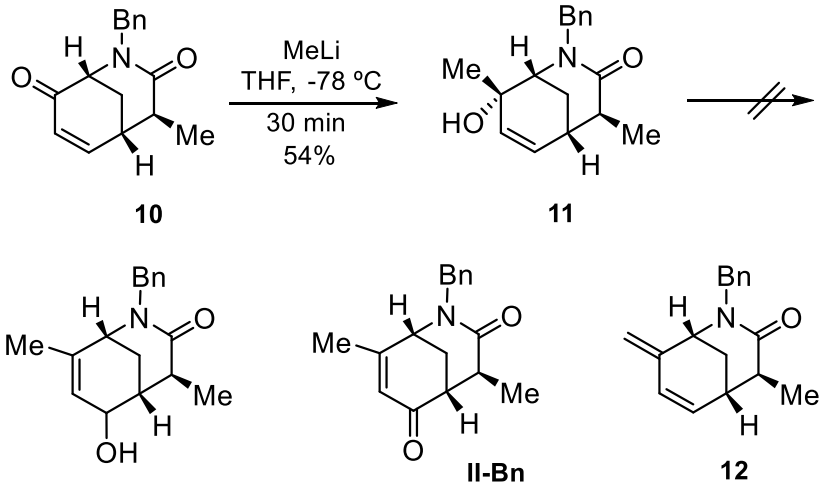
Una vez obtenido el producto **11** mediante adición-1,2 de metil-litio a la enona **10** (Esquema 6.6), debía procederse a la etapa de transposición de tipo Dauben[8] para generar la enona **II-Bn** o alternativamente a una transposición alílica, que requeriría una etapa de oxidación adicional. Sea como fuere, después de un amplio abanico de ensayos todo lo que se conseguía era la recuperación del material de partida.[9] El derivado con el metileno exocíclico **12** fue el único compuesto aislado al ser tratado con HCl y dioxano a 100 ºC con activación de microondas.

[6] Para la elucidación estructural de **8** véase el articulo de referencia (apartado 6.5)

[7] Oxidantes como PDC, PCC, CrO_3, $BiCl_3$/TBHP o $Mn(OAc)_3$/TBHP sólo indujeron a la recuperación parcial o total del sustrato con mayor o menor pérdida de materia.

[8] Dauben, W. G.; Michno, D. M. *J. Org. Chem.* **1977**, *42*, 682–685.

[9] Para las condiciones de reacción utilizadas a partir del alcohol **11**, véase: (a) PCC: Karol M.; Michal M.; Jerzy W. *J. Org. Chem*. **2010**, *75*, 8337-8350; (b) IBX: Masatoshi S.; Shinichiro I.; Michiyasu T.; Yoshiharu I.; *Org. Lett*. **2004**, *6*, 4303-4306; (c) SO_3.Py: Kimberly K. L.; Richmond S. *J. Am. Chem. Soc,*, **2009**, *131*, 13244-13245; (d) ReO_3CH_3: Josemon J.; James H. E.; Jan H. J.; Mark S. G. *Organometallics*, **1998**, *17*, 1835-1840; (e) TEMPO, $NaIO_4$: Masatoshi S.; Masaki T.; Yoshiharu I. *Org. Lett*. **2008**, *10*, 4715-4718; (f) HCl (6 M): Magnus, P.; Booth, J.; Donohoe, T.; Lynch, V.; Magnis, N.; Mendoza, J.; Pye, P.; Tarraut, J. *Tetrahedron* **1996**, *52*, 14103-14146; (g) $LiClO_4$: Grieco. A. P.; Collins J. L.; Kenneth J. H. Jr. *Tetrahedron Lett*. **1992**, *33*, 4735-4738; (h) H_2O, 80 ºC: Pei-Fang Li, Heng-Lu Wang, Jin Qu, *J. Org. Chem.* **2014**, *79*, 3955-3962.



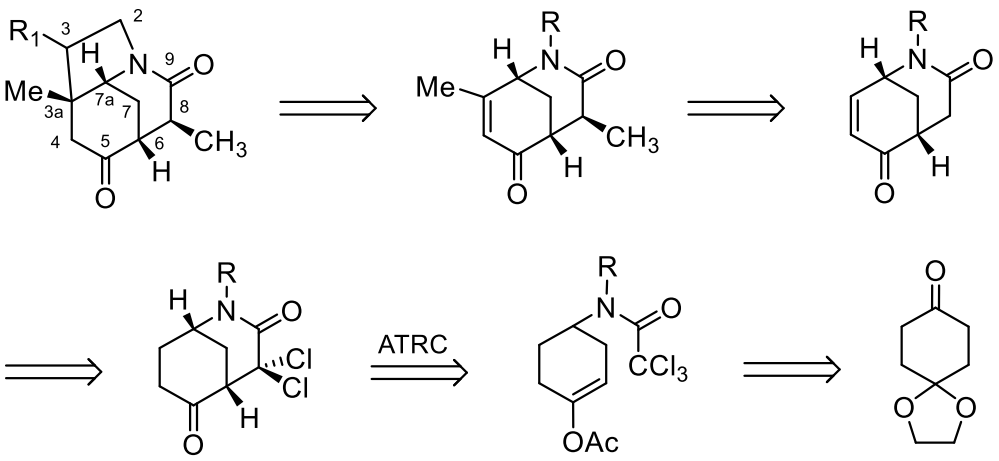
6.6 Introducción del metilo e intentos infructuosos de transposición alílica

A la vista de todos los problemas presentados en esta aproximación sintética, se decidió replantear el enfoque sintético utilizando un compuesto azabicicíclico con un grupo carbonilo cetónico y con un sustituyente en el nitrógeno lactámico que permitiese el acceso al azatriciclo **I**, tal como se comenta en el siguiente apartado 6.3.

6.3 Ruta sintética hacia el anillo azatricíclico

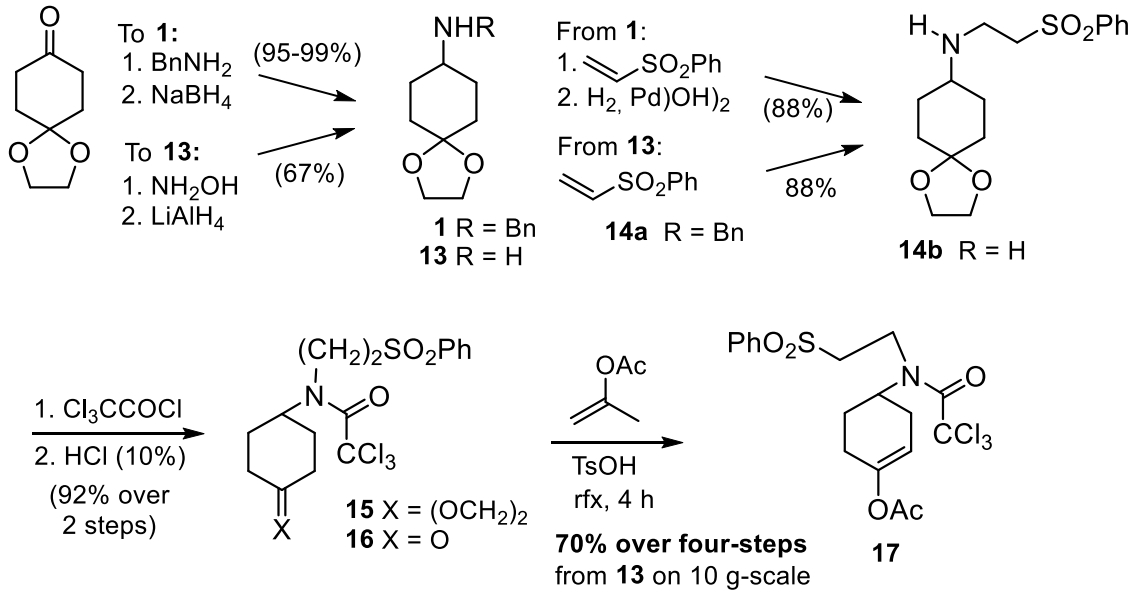
6.3.1 Preparación del sustrato de partida

En esta segunda aproximación se decidió afrontar la síntesis utilizando un núcleo de morfano en el que hubiese instalado un carbonilo de cetona en vez de un alqueno (Esquema 6.7).



6.7 Aproximación sintética al esqueleto azatriciclo utilizando el alqueno activado

Adicionalmente, el sustituyente incorporado en el átomo de nitrógeno permitiría el cierre de anillo pirrolidínico. El compuesto 17 necesario para la primera etapa clave de la síntesis , que sería la ATRC, se preparó según lo expuesto en el Esquema 6.8.

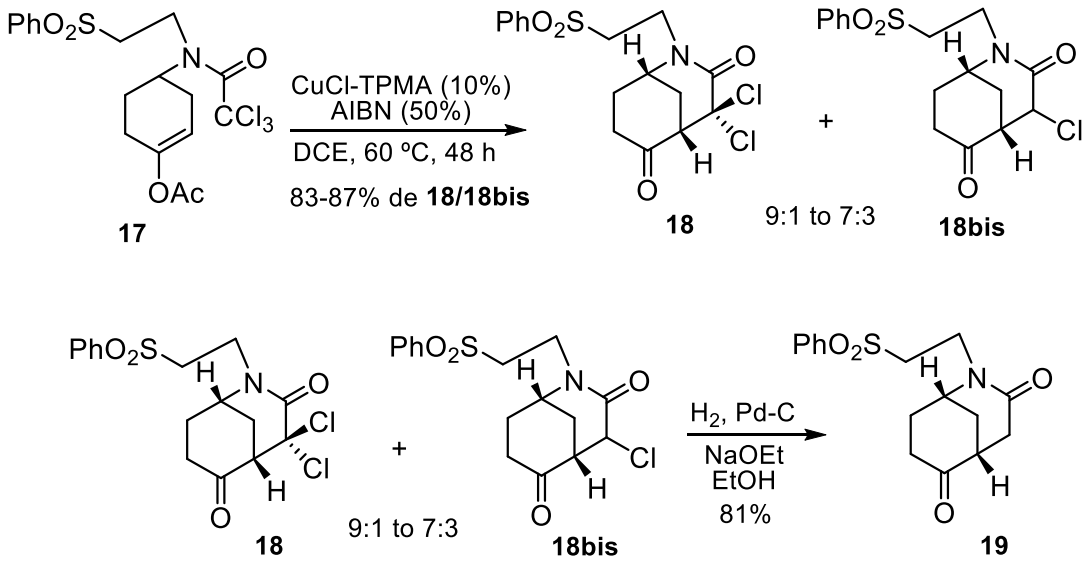


6.8 Preparación de la tricloroacetamida **17**, precursora del morfano necesario

6.3.2 Formación del azabicíclo y ulteriores transformaciones hacia el azatricíclo

La formación del morfano procedió con excelentes resultados (Esquema 6.9) utilizando las condiciones de reacción optimizadas para la ciclación de tricloroacetamidas *N*-benciladas sobre acetatos de enol, descritas en el capítulo 2. A partir de la tricloroacetamida **17** se obtuvo en la ATRC una mezcla de los productos diclorado (**18**) y monoclorado, (**18bis**) fácilmente separable, de **18** y **18bis**[10,11]. Desde el punto de vista sintético la separación es innecesaria ya que la posterior reducción de la mezcla mediante hidrogenación[12] proveyó exclusivamente la cetona bicíclica **19**.[13]

[10] En los diversos ensayos realizados se obtuvo un subproducto no identificado (8-10%).
[11] La ciclación radicalaria de **17** (escala de 100 mg) se ensayó también utilizando catalizadores de Ru(II). En condiciones análogas a las descritas en el capítulo 5 con el catalizador de Grubbs de segunda generación (5 mol%, tolueno, 155 ºC, 2 h) se obtuvieron resultados similares (80%), mientras que con $RuCl_2(PPh_3)_2$ (5 mol%, tolueno, 115 ºC, 3 h) el rendimiento fue inferior (55%), pero la recuperación parcial de producto partida presupone que podría optimizarse este proceso.
[12] Seijas, J. A.; Vázquez-Tato, M. P.; Castedo, L.; Estévez, R. J.; Onega, M. G.; Ruiz, M. *Tetrahedron* **1992**, *48*, 1637-1642.
[13] Los rendimientos con una simple filtración eran cuantitativos, aparentemente el aspecto y la caracterización eran concluyentes, sin embargo sino se purificaba la siguiente etapa tenía unos rendimientos más bajos de lo esperado.



6.9 Proceso ATRC de **17** y su proceso de reducción hacia **19**

Con un método de síntesis de **19** que permitía su acceso en escala de 1-2 g, nuestros siguientes esfuerzos se concentraron en transformarlo en un precursor del tipo **II** (Esquema 6.1), tal como **23**, para acceder al sistema azatricíclico

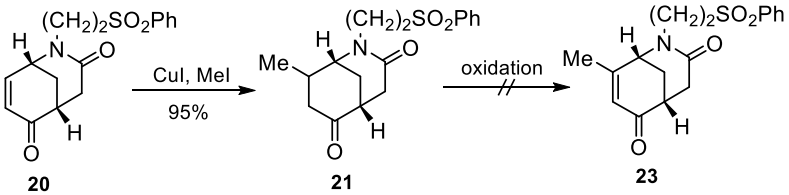
Después de un laborioso trabajo de experimentación, debido a la presencia de tres metilenos activos[14] en el substrato inicial **19**, la ruta optimizada para la obtención de la enona **23** es la que se refleja en el Esquema 6.10. La cetona α,β-insaturada **20** se obtuvo mediante una dehidrogenación aeróbica catalizada por paladio[15,16,17]. La introducción del grupo metilo en C(8) mediante adición conjugada mediante dimetilcuprato de litio funcionó muy bien, pero la cetona resultante **21** no permitió en ningún caso (p.ej. $Pd(OAc)_2$; IBX) el acceso a la enona requerida **23**.[18]

[14] Los átotmos de hidrógeno en a a un grupo carbonilo cetónico, CH_3COCH_3 (pK_a 26.5), son más ácidos que los vecinos a una sulfona, $CH_3SO_2CH_3$ (pKa 31.1). La diferencia de pKa es de 4-5 unidades: Bordwell, F. G. Acc. Chem. Res. **1988**, 456-463.

[15] Muzart, J. *Eur. J. Org. Chem.* **2010**, 3779-3790.

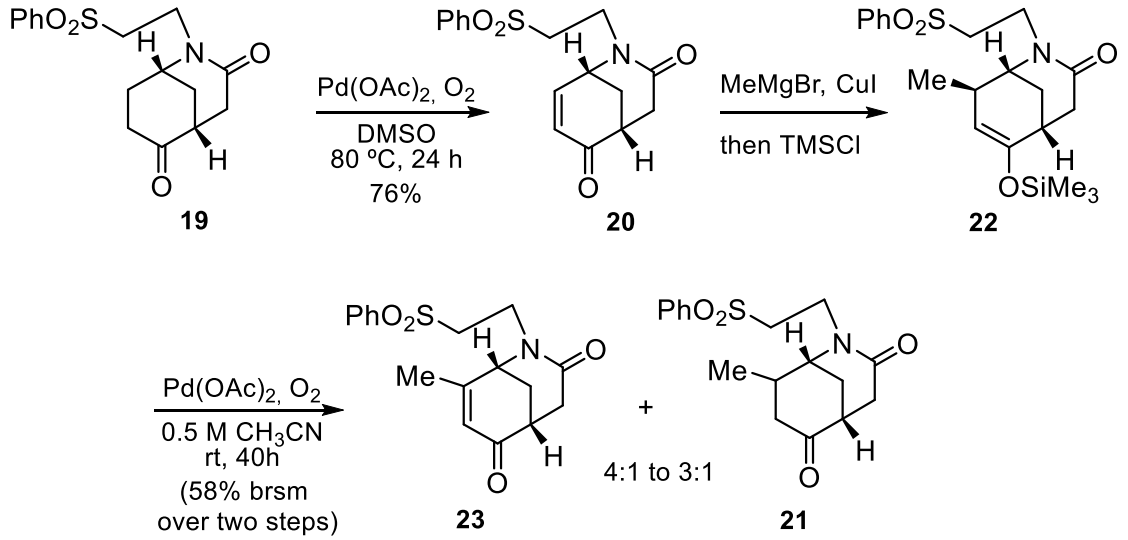
[16] El uso de $Pd(TFA)_2$ o $Pd(OAc)_2$ a temperatura ambiente proporcionaba bajas conversiones de **19** en **20**, incluso a largos tiempos de reacción. Los intentos de obtener la enona **20** con IBX, a distintas temperaturas con o sin catálisis ácida no proporcionaron en ningún caso un rendimiento superior al 45% y el proceso de purificación mostraba problemas.

[17] En esta etapa se estudió de manera somera la posibilidad de introducir el grupo metilo en α del carbonilo lactámico, pero el tratamiento de **20** con LHMDS y posterior adición de ioduro de metilo no condujo al aislamiento de producto alguno sino a la degradación del compuesto de partida.



[18]

Para obtener la enona **23** hubo que operar en un proceso one-pot en el que el enolato resultante de la adición conjugada a la enona 20, mediante cloruro de metilmagnesio/CuI, fue atrapado con TMSCl, para generar el trimetilsilienoléter de enol **22**. El tratamiento de 22 según el protocolo de Saegusa[19], pero requiriendo en nuestro caso cantidades estequiométricas de Pd[20], permitió la obtención de la enona **23** para el estudio del cierre del anillo de pirrolidina y así acceder al sistema de anillos ABC del compuesto objetivo.

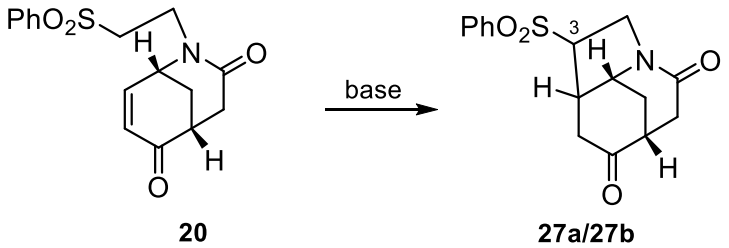


6.10 Transformaciones de **19** hacia el precursor azatricíclico **23**

*6.3.3 Formación del esqueleto azatricíclico del tipo **I** con sus respectivos estudios*

Debido a los problemas para obtener la enona **23** y en consecuencia a una disponibilidad limitada de la misma, así como su presumible menor reactividad por motivos estéricos que la enona **20**, inicialmente se decidió estudiar la reacción intramolecular de Michael a partir de **20**. El estudio preliminar permitió observar que el uso de bases fuertes conllevaba a la descomposición del material de partida[21], mientras que con el uso de K_2CO_3 se empezaron a detectar resultados prometedores para el proceso de ciclación (Esquema 6.11).

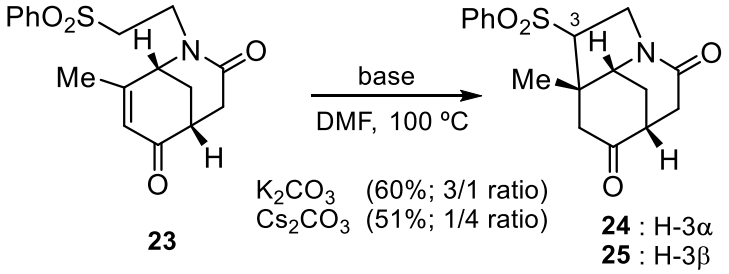
[19] Ito, Y.; Hirao, T.; Saegusa, T. *J. Org. Chem.* **1978**, *43*, 1011-1013.
[20] Aún así, en el mejor de los casos se obtenían rendimientos inferiores al 60%, desde **20**, para una mezcla inseparable de **23** y **21** que oscilaba de 80:20 a 75:25, respectivamente y la concentración de CH_3CN era crucial, así a concentraciones menores de 0.5 M la reacción apenas tenía lugar y se iba hidrolizando poco a poco el sustrato de partida.
[21] Sólo utilizando KHMDS (0.5 equiv, a -30 ºC) se observó la recuperación parcial del producto de partida **20** , siendo mayoritario, como con otras bases fuertes los productos de degradación.



20 **27a/27b**

6.11 Ciclaciones de **20**: **a)** LDA, THF, 1 h, -78 ºC (descomposición); **b)** KHMDS, THF, 30 min, -30 ºC (descomposición); **c)** NaH, THF, 5 h, t.a. (*no reacción*); **d)** 1 eq. K_2CO_3, DMF, 60 ºC (**27a**, 27%, **27b**, 17%, **20**, 10% y *subproductos*)

Cuando se aplicó a la enona **23** condiciones similares (Esquema 6.12), se encontró que el tratamiento con K_2CO_3, a temperaturas superiores que las empleadas para **20**, generó de forma mayoritaria la ceto sulfona **24**, y de forma minoritaria **25**, incorporando el núcleo azatricíclico de los alcaloides calcilifina del tipo A en forma de dos epímeros en C-3 en una relación 3:1. Al cambiar el contra catión K^+ por Cs^+,[22] el tiempo de reacción fue más cortó y la diastereoselectividad, aislándose **24** y **25** en una relación de 1:4.[23]

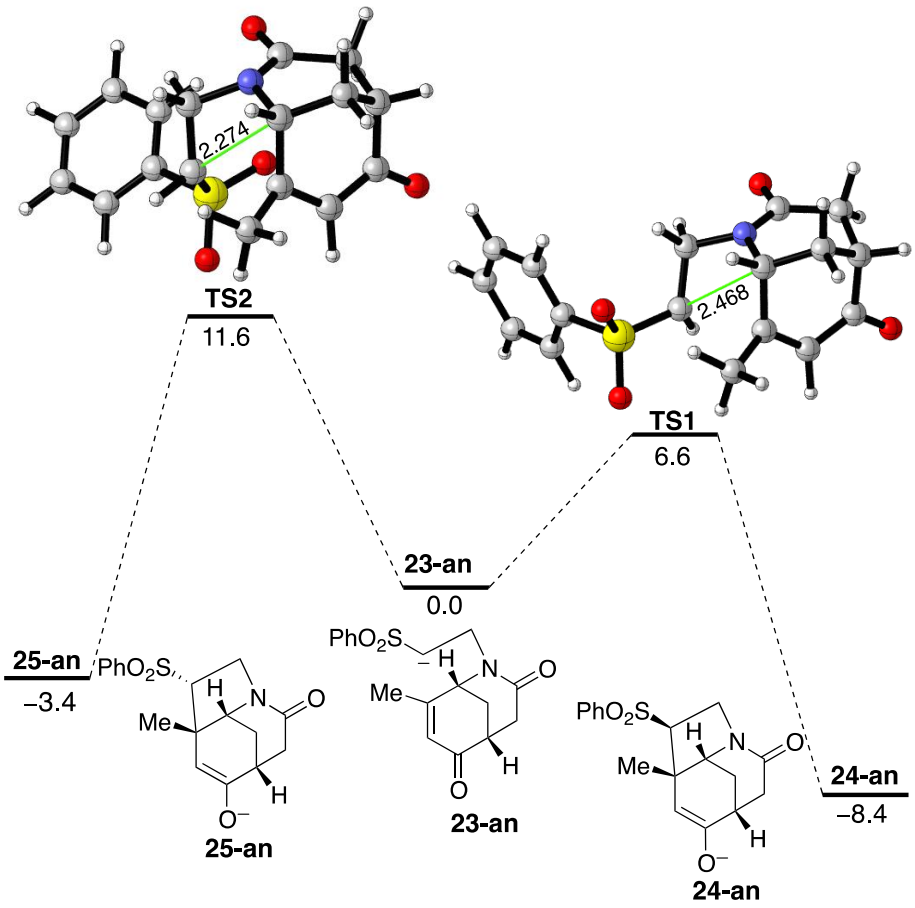


23

6.12 Adición de Michael para obtener el esqueleto azatricíclico

El cierre aniónico del anillo C que lleva hacia **24** se puede visionar (Figura 6.13) que tiene lugar en condiciones cinéticas. De esta forma al ser tratado con K_2CO_3, **23** brindaría un pequeño porcentaje de especie sulfonil carbaniónica, la cual puede proceder a una adición conjugada intramolecular a través de estados de transición del tipo **TS1** o **TS2**. La formación del compuesto azatricíclico **24** a través del estado de transición **TS1** debe ser la preferida puesto que el estado de transición **TS2**, que lleva al epímero **25**, padece de repulsiones estéricas entre el grupo sulfonilo y el enlace C(7)-C(8) con una relación 1,3-diaxial (se observa la congestión estérica en la Figura 6.13).

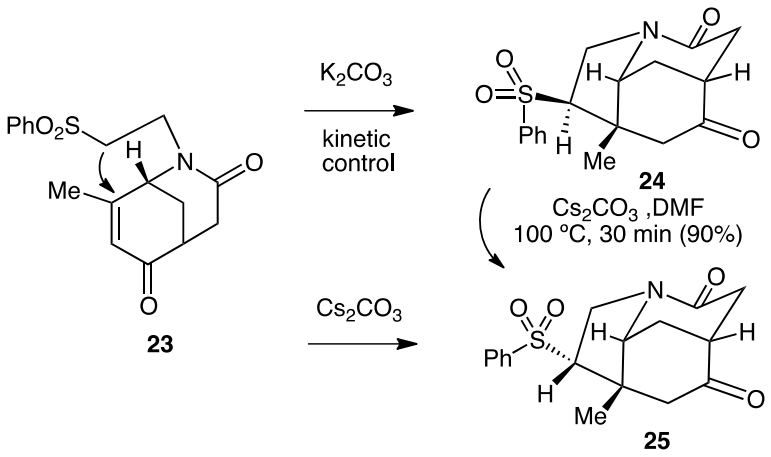
[22] El conocido como "efecto cesio" deriva de: (i) la mayor solubilidad de las bases de cesio y la generación de aniones "naked" altamente reactivos; (ii) el gran tamaño del Cs; y (iii) su fácil polarizabilidad: Musaev, D.G.; Figg, T.M.; Kaledin, A. L. *Chem. Soc. Rev.* **2014**, *43*, 5009-5031.
[23] Al utilizar Na_2CO_3 la reacción avanzaba aún más lenta que para el caso del potasio y más selectiva, sin embargo al necesitar tiempos tan prolongados a temperaturas elevadas los sustratos se iban degradando, consiguiendo unos rendimientos inferiores al 25%.



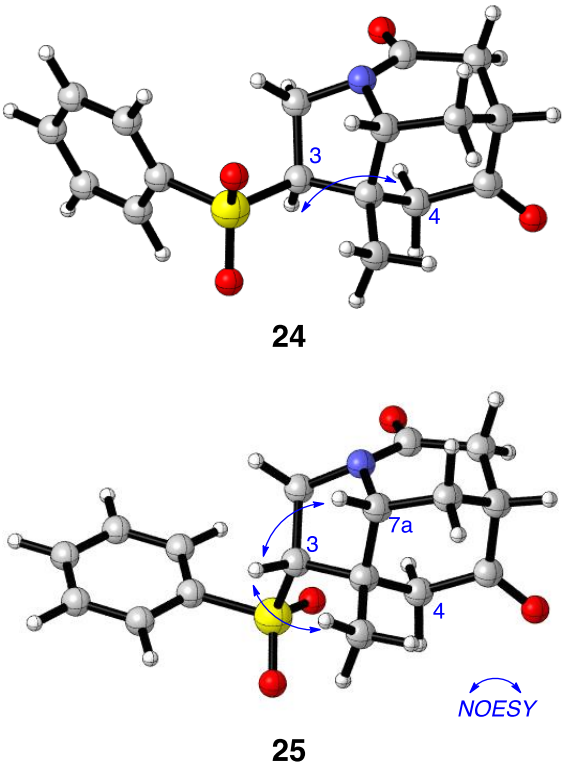
6.13 Estados de transición propuestos en la reacción de Michael intramolecular de **23**[24]

Para arrojar luz sobre la diastereoselectividad del proceso de Michael intramolecular, se llevaron a cabo cálculos computacionales para evaluar la estabilidad termodinámica relativa de ambos epímeros (24 y 25, véase la Figura 6.15). Curiosamente, se encontró que ambas especies eran prácticamente isoenergéticas[25], y por tanto, debería descartarse un posible control termodinámico en el proceso inducido por Cs_2CO_3. Por otra parte, **24**, cuando se trata con Cs_2CO_3 en las mismas condiciones de reacción que en el proceso de ciclación, se transforma en **25** (Esquema 6.14). Estos resultados indican que aparentemente el Cs_2CO_3 no induce una epimerización en el centro estereogénico en C(3), sino que muy probablemente promueve un proceso retro-Michael seguido por una reciclación que conduce a **25**.[26]

[24] Los cálculos DFT han sido llevados a cabo por el Dr. Israel Fernández (UCM).
[25] E_{rel} = **24** (0.0), **25** (0.6) at M06/6-31+G(d) level. E_{rel} = **24** (0.1), **25** (0.0) at B3LYP-D3/6-31+G(d) level.
[26] Para la elucidación de las estructuras mediante RMN, véase publicación adjunta (6.5).



6.14 Formación del compuesto azatricíclico de **25** utilizando Cs_2CO_3



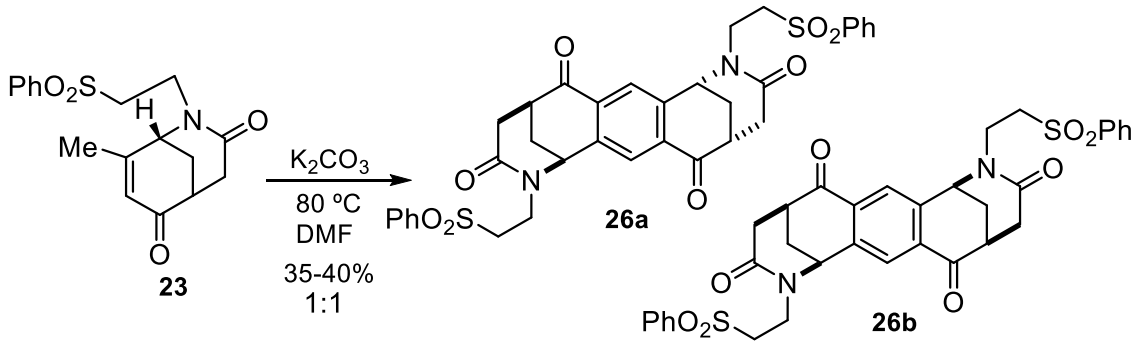
6.15 Conformación preferida para los azatriciclos **24** y **25** y datos NOESY

Por último, se observó (esquema 6.16) que una autocondensación del β-metilciclohexenona **23** tenía lugar a 80 ºC en una solución concentrada de DMF.[27] Estas estructuras aisladas, **26a** y **26b**, fueron elucidadas mediante HRMS y RMN. A pesar que un proceso de autocondensación que implique el γ-anión del 3-

[27] Las reacciones que conllevaron a estas estructuras anómalas del tipo **26** fueron a pequeña escala, 20-30 mg, en una concentración inicial de 0.5 M en DMF. Sin embargo, realmente estaba más concentrado al haber muy poco disolvente y parte ir refluyendo ligeramente por las paredes, esto es así desde el momento que su escalado a 100 mg proveyó a 80 ºC en K_2CO_3 con una cinética muy lenta el azatricíclo **24**.

metilciclohexen-2-enona ha sido observado,[28] hasta donde conocemos no se encuentran precedentes para una dimerización que conduce a la formación de un producto con un núcleo bencénico tetrasustituido.

Evidentemente, la formación de los compuestos **26a** y **26b** con estructuras inéditas abren el camino a un posible estudio de este procesos sin precedentes en la literatura.



6.16 Estructuras diméricas formadas desde **23** a altas concentraciones

6.4 Conclusiones

El alcance y limitaciones de la ruta sintética descrita se resumen en

- La metodología ATRC promovida por Cu(I) para la síntesis de 2-azabiciclo[3.3.1]nonanos es robusta y ha permitido su aplicación a una *N*-(2-fenilsulfoniletil)tricloroacetamida con un acetato de enol como aceptor radicalario para generar compuestos morfánicos altamente funcionalizados de interés como building blocks en la síntesis de alcaloides.

- La reacción de Michael intramolecular para generar el sistema azatricíclico de perhidro-1,6-etanoindol es muy sensible a la base utilizada. Así se obtienen resultados divergentes al utilizar K_2CO_3 y Cs_2CO_3. Considerando que los azatriciclos epiméricos **24** y **25** son isoenergéticos, el estudio del comportamiento diverso de las sales de potasio y cesio en el proceso merecerá un ulterior estudio computacional.

- La ruta sintética conducente a un azatriciclo de tipo **I** no está exenta de ciertas limitaciones, que no son otras que las derivadas de la introducción de los grupos metilos en las posiciones correspondientes mientras se mantiene los grupos funcionales necesarios (lactama, cetona y sulfona) para su posterior desarrollo del proceso global de síntesis.

[28] (a) Gurst, J. E.; Miller, R. W.; McPhail, A. T. *Tetrahedron Lett*. **1980**, *21*, 3223-3226. (b) Kasum, B.; Prager, R. H. Aust. *J. Chem*. **1990**, *43*, 63-68.

6.5 Synthesis of the ABC Fragment of Calyciphylline A-type Daphniphyllum Alkaloids

Faïza Diaba, Agustín Martínez-Laporta, Guilhem Coussanes, Israel Fernández, Josep Bonjoch

Tetrahedron Symposium-in-print (*accepted)*

Tetrahedron
journal homepage: www.elsevier.com

Synthesis of the ABC Fragment of Calyciphylline A-type *Daphniphyllum* Alkaloids

Faïza Diaba[a,*], Agustín Martínez-Laporta[a], Guilhem Coussanes[a], Israel Fernández[b], Josep Bonjoch [a,*]

[a] *Laboratori de Química Orgànica, Facultat de Farmàcia, IBUB, Universitat de Barcelona, Av. Joan XXIII s/n, 08028-Barcelona, Spain*
[b] *Departamento de Química Orgánica I, Facultad de Ciencias Químicas, Universidad Complutense Madrid, 28040-Madrid, Spain*

ARTICLE INFO

Article history:
Received
Received in revised form
Accepted
Available online

Keywords:alkaloids;
atom transfer radical cyclization;
cesium effect;
kinetic vs thermodynamic stereocontol;
natural product synthesis;
sulfone-based intramolecular Michael;

ABSTRACT

The ABC-ring system of calyciphylline A-type alkaloids has been synthesized. The key steps of the synthetic approach are an atom transfer radical cyclization of a trichloroacetamide upon an enol acetate to generate the B ring, and a sulfone-based conjugated addition upon a β-methyl-α,β-unsaturated ketone to give the target azatricyclic ketone. Selecting the cation (K^+ or Cs^+) of the carbonate in the C ring-forming intramolecular Michael addition gives stereodivergent access to both epimers of the cyclized product.

1. Introduction

The 3a,8-dimethylhexahydro-1,6-ethanoindol-5(6*H*)-one azatricyclic ring system constitutes the common ABC fragment of all members of the calyciphylline A-type *Daphniphyllum* alkaloids[1] (Figure 1). Despite becoming important targets in natural-product chemistry, no member of this subset of alkaloids has yet been achieved by total synthesis. In our initial studies toward this end, we obtained access, for the first time, to the azatricyclic ring decorated with the aforementioned substituents, using a reductive amination to build the octahydroindole fragment and a Pd-catalyzed enolate alkenylation to close the bridged ring.[2,3] Since then, three other approaches to the targeted ABC azatricyclic ring have been reported, and their key steps are summarized in Scheme 1. Li's strategy[4] was based on a gold-catalyzed alkyne-cyclization Toste-Conia-ene reaction to form the morphan nucleus, followed by an intramolecular Michael reaction of an α-substituted β-dicarbonyl group upon an enone, which led to the total synthesis of daphnenylline[4] and the tetracyclic core of daphnilongeranin B.[5] Liang's route used an enolate-alkenylation reaction to set the quaternary center at the BC junction, the morphan nucleus being prepared from the chiral pool.[6] Lastly, Stockdill achieved the azatricyclic ring using a

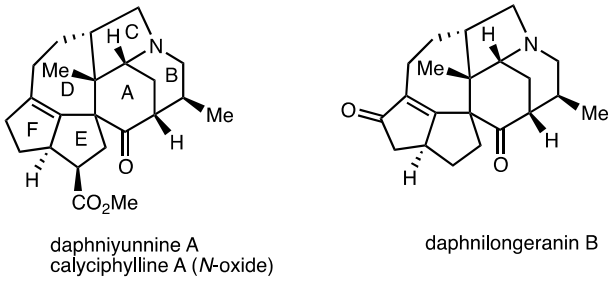
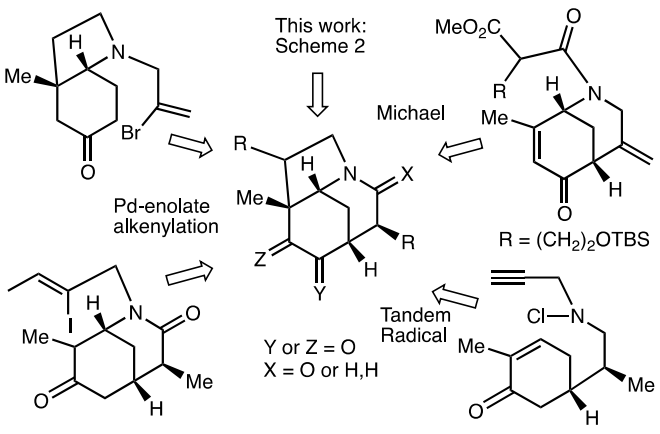
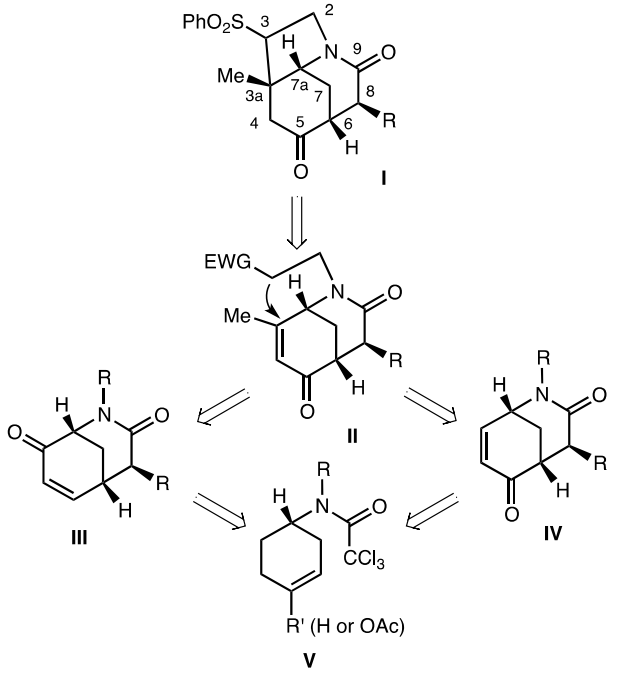


Figure 1. Some calyciphylline A-type *Daphniphyllum* alkaloids



Scheme 1. Previous syntheses of the ABC rIng

* Corresponding author. Tel.: +34-934 024 540; e-mail: faiza.diaba@ub.edu; e-mail: josep.bonjoch@ub.edu



Scheme 2. Retrosynthetic analysis of azatricyclo **I**

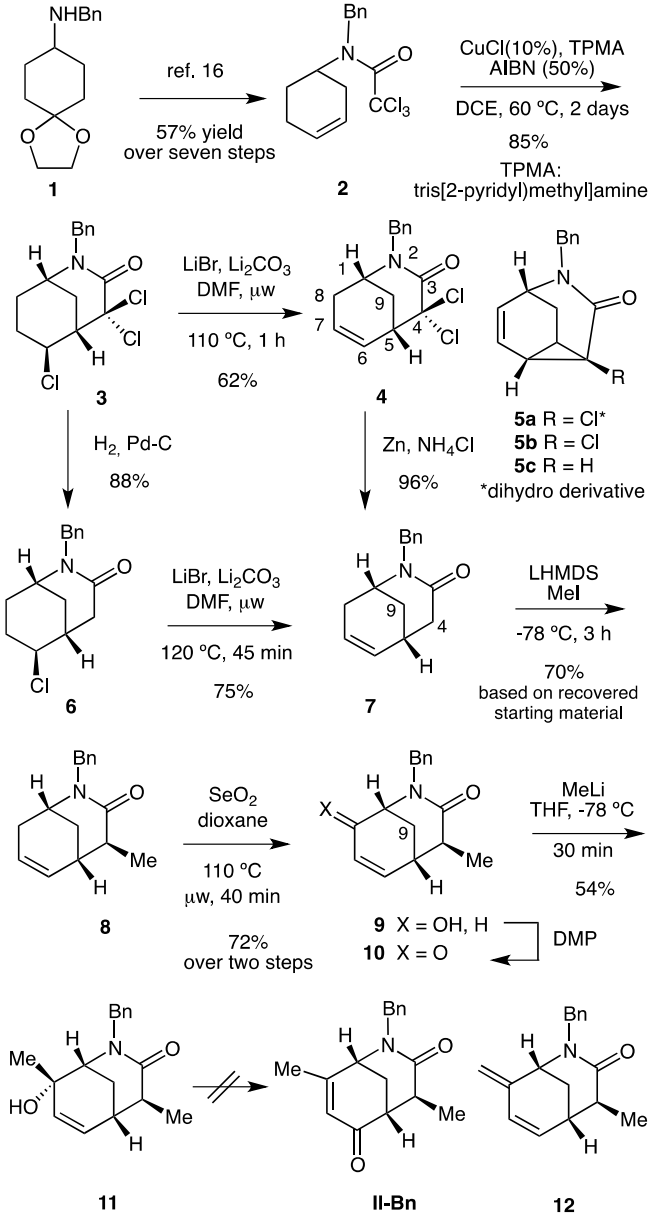
tandem radical cyclization starting from an enantiopure cyclohexenone with an *N*-chloroamine-bearing appendage.[7] Other members of this subfamily of alkaloids with different ring patterns have been successfully synthesized.[8]

In this paper, we describe our new approach to the azatricyclic core of calyciphylline A-type alkaloids, involving a sulfone-based intramolecular Michael reaction[9] to form azatricycloundecane **I** with a functionalization that could be applied in further studies toward more advanced intermediates in *Daphniphyllum* alkaloid synthesis (Scheme 2). In turn, we envisaged obtaining compound **II** from either enone **III** or **IV**, considering that in both cases, the 2-azabicyclo[3.3.1]nonane motif[10] may be accessible by a radical cyclization of a trichloroacetamide (e.g. **V**) and subsequently adjusting the functionalization. The usefulness of radical synthetic methods for constructing valuable intermediates in target-oriented natural product synthesis has been established in the last twenty years.[11] In particular, trichloroacetamides are able to generate radical species for the building of nitrogen-containing rings, both in reductive[12] and atom transfer radical cyclizations.[13]

2. Results and Discussion[14]

2.1. Initial unsuccessful approach

We commenced with the transformation of aminocyclohexanone **1**[15] to trichloroacetamide **2** (57% over seven steps),[16] which, following our recently reported protocol, underwent a Cu(I)-promoted atom transfer radical cyclization using AIBN as a reducing agent[17] to furnish the azabicyclic compound **3**.[18] The elimination of the chlorine atom to obtain alkene **4** was not straightforward, since under some reaction conditions (e.g. K*t*BuO, NaOEt) competing intramolecular cyclopropanation processes led to **5 (5a-5c)** as the major or exclusive compounds in the reaction mixture (Scheme 3 and experimental part, 4.2.3). The pathway to cyclopropane **5a** is unclear, since it involves a reductive process,[19] whereas the most likely mechanism in the formation of **5b** seems to be a γ-deprotonation of **4**, followed by a nucleophilic attack of the α-allylic anion upon C(4), with a chlorine atom as the leaving group, and concomitant embedding of a cyclopropane in the morphan skeleton. While trichlorolactam **3** gave **4** when using Li_2CO_3 and LiBr, the process was not exempt from minor by-products and the purification step was troublesome. For this reason, this pathway was discarded, even though the two remaining chlorine atoms in **4** readily underwent reduction by zinc in an acid medium.[20] To overcome this obstacle and successfully achieve alkene **7**, we reversed the order of the two reactions (base-elimination of the isolated chlorine at C(4) / reduction of *gem*-dichloride at C(8)). Thus, chemoselective removal of the two geminal chlorine atoms in lactam **3** was carried out by hydrogenolysis in a basic medium[21] to obtain the chloro derivative **6**, which under basic conditions and microwave irradiation underwent β-elimination to give the required alkene **7** in good overall yield.



Scheme 3. Synthesis of azabicyclic compound **11** (for numbering, see ref 14)

At this point, we examined the introduction of the methyl group at C-4. Treatment of lactam **7** with LHDMS followed by methylation of the enolate diastereoselectively gave morphan **8**, in which the methyl group is axially located (i.e. with the same relative stereochemistry as in the target *Daphniphyllum* alkaloids). In the reaction conditions, only monomethylation was observed.[22] The stereochemical outcome of the α-alkylation is due to the sterically favored axial approach of the alkylating

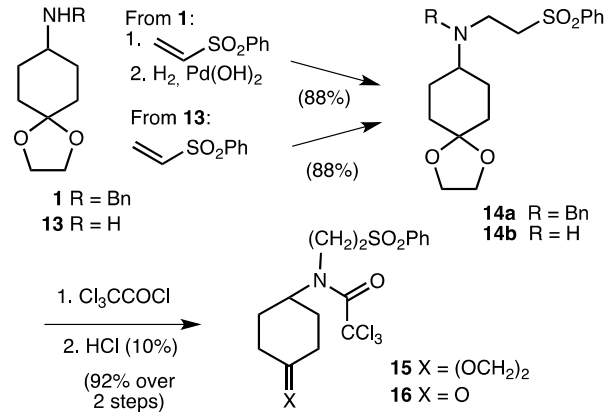
agent to the lactam enolate. The axial disposition of the methyl group at C(4) in **8** was revealed by comparing the ^{13}C NMR chemical shift of C(9) (δ 24.5) with the corresponding value for the unsubstituted precursor morphan **7** (δ 29.1). The shielding observed in the methylene bridge is due to the 1,3-diaxial interaction between the axially located methyl group at C(4) and a H-9 proton.[23,24]

With the methyl appendage stereoselectively in place at C(4), we turned our attention to introducing the methyl group at C(8), at the same time attempting the installation of the required enone functionality. After some experimentation,[25] we found that oxidation of alkene **8** with 3 equiv of SeO_2 in dioxane at 110 °C in a microwave reactor for 40 min afforded allylic alcohol **9** in 66% yield and enone **10** in 10% yield. Oxidation of alcohol **9** with Dess-Martin periodinane provided enone **10** in 95% yield. This two-step sequence converts alkene **8** into enone **10** in 72% yield. After the 1,2-addition upon the enone to give **11**, our intention was to perform an allylic hydroxyl group transposition or oxidative transposition[26] to establish the appropriate oxygenation pattern in the six-membered ring. The use of standard reagents (PCC, IBX, PDC, TEMPO) in the Dauben oxidation[27] only returned the starting material. Moreover, considerable experimentation with a variety of acids failed to promote the formation of any productive compound.[28] The exocyclic methylene **12** was the only compound identified when **11** was treated with aqueous HCl in dioxane at 100 ºC. Altogether, a variety of factors may contribute to the obstinacy of the allylic alcohol transposition, including the conformational rigidity of **11** and the steric encumbrance around the tertiary hydroxyl group.[29]

Although this approach toward the model bicyclic lactam **II-Bn** was unsuccessful, we were hopeful that an alternative strategy might circumvent the problem. So, to pursue our studies to the azatricyclic target **I**, a second route was designed to obtain a morphan derivative with a β-methyl-substituted enone embedded in the azabicyclic framework (*i.e.* **II**).

2.2. The synthetic route to the azatricyclic ring

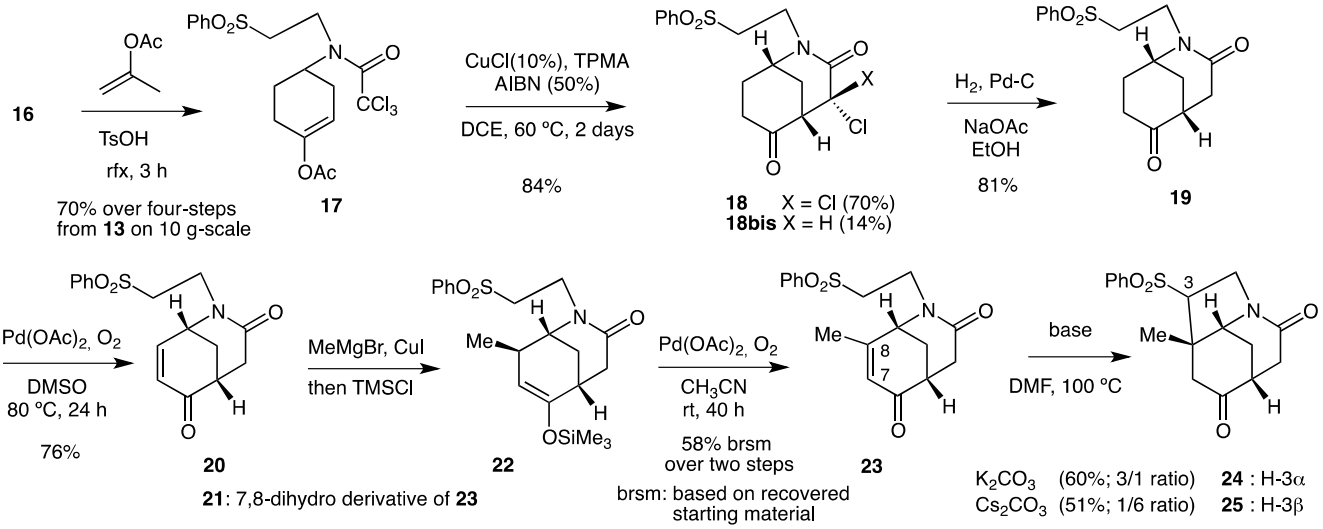
In the new approach, it was envisioned that the morphan nucleus would include a ketone instead of an alkene as a precursor of the key β-methyl-substituted α,β-unsaturated ketone **II**. Moreover, working with a substituent on the nitrogen atom that allows the pyrrolidine ring closure would give access to **I**



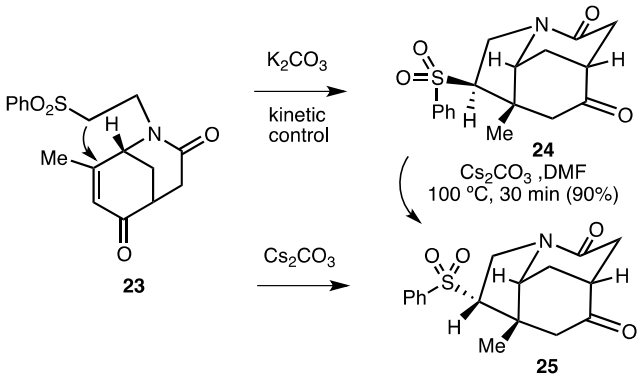
Scheme 4. Synthesis of trichloroacetamide **16**

(Scheme 2). The first stage of this strategy required the synthesis of the substrate trichloroacetamide **16** (Scheme 4), using the known amines **1** or **13**[30] as starting material. Reaction with phenyl vinyl sulfone, followed by debenzylation in the case of **1**, gave β-amino sulfone **14b**, which was pure enough to be treated directly with trichloroacetyl chloride to give **15.** Exposure of **15** to acid hydrolysis rendered the required **16** in good overall yield.

The first ring closure, to achieve ring B, was carried out using our Cu(I)-catalyzed radical cyclization of trichloroacetamides with an electron-donating group upon the alkene radical acceptor (Scheme 5). Thus, ketone **16** was converted into its enol acetate **17**, which underwent atom transfer radical cyclization in high yield (84%)[31] to give a mixture of the dichloro- and monochloroderivatives **18** and **18bis**. However, this turned out to be inconsequential, since reduction of the mixture through hydrogenation[21] afforded the same bicyclic ketone **19**. Although attempted IBX oxidation gave unsatisfactory results, palladium-catalyzed aerobic dehydrogenation of **19** using $Pd(OAc)_2$ in DMSO[32] under an atmosphere of oxygen directly furnished enone **20**. We next targeted the β-methyl-α,β-unsaturated ketone **23** (Scheme 5). Copper-catalyzed 1,4-addition of methylmagnesium chloride to cyclohexenone **20**, followed by trapping of the resulting enolate with cholorotrimethylsilane (TMSCl), gave trimethylsilyl enol ether **22**.[33,34] Finally, the precursor for the new ring-closure step, enone **23**, was successfully obtained using a Saegusa-type reaction[35] requiring a stoichiometric amount of palladium-reagent.



Scheme 5. Synthesis of the ABC ring system of calyciphylline A-type alkaloids.



Scheme 6. Formation of azatricyclic compound **25** using Cs_2CO_3.

Despite unsuccessful attempts to promote the sulfone-based ring closure from **23** with strong bases (general decomposition with LDA and NaHMDS),[36] we felt there was a chance the strategy would work under weak basic conditions. After considerable experimentation, it was found that treatment of sulfone **23** with K_2CO_3 in DMF induced the intramolecular Michael reaction to generate keto sulfone **24** embodying the azatricyclic core of calyciphylline A-type alkaloids (Scheme 6).

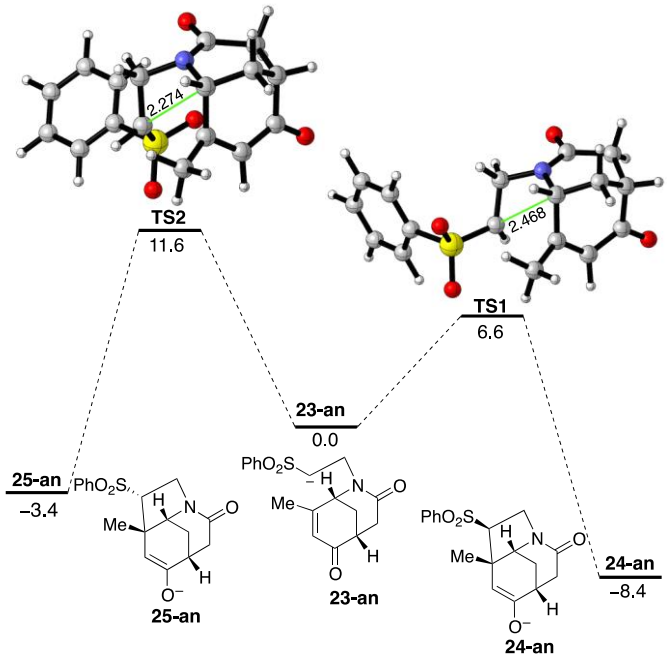


Figure 2. Computed reaction profile for the intermolecular conjugate addition of carbanion **23-an**. Relative energies (ZPVE included) and bond distances are given in kcal/mol and angstroms, respectively. All data have been computed at the M06-2X/6-31+G(d) level.

The sulfone anion closure of the C ring can be viewed as taking place under kinetic conditions. On treatment with K_2CO_3, **23** would afford a small percentage of a sulfonyl carbanionic species **23-an**, which may undergo intramolecular conjugate addition leading to the tricyclic species **24-an** (via the saddle point **TS1**) or, alternatively, to its epimer **25-an** (via **TS2**). Both compounds would afford the observed reaction products **24** and **25**, respectively, upon protonation. Our Density Functional Theory (DFT) calculations (see computational details below) suggest that formation of **24-an** takes place under both kinetic and thermodynamic control, in view of the higher activation barrier ($\Delta\Delta E^{\neq}$ = 5.0 kcal/mol) and less exothermic reaction energy ($\Delta\Delta E_R$ = –5.0 kcal/mol) computed for the formation of the epimer **25-an**. The kinetic control of this cyclization reaction is very likely due to the destabilizing steric repulsion between the phenylsulfonyl group and the C(7)-C(8) bond with a 1,3-diaxial relationship occurring in the transition structure **TS2**, which is not present in **TS1** (Figure 2). The stereochemical features observed in the cyclization reaction leading to **24** (see below for NMR data) agree with the configurational assignment.

Interestingly, when the cyclization process was induced by Cs_2CO_3,[37,38] its diastereoselectivity was reversed,[39] the epimeric compound at C(3), sulfone **25**, being the major diastereomer in the isolated coupled compounds (6:1). To shed light on the diastereoselectivity of the intramolecular Michael process, calculations were carried out to assess the relative thermodynamic stability of both epimers (**24** and **25**, see Figure 3). Interestingly, both species were found to be practically isoenergetic,[40] therefore ruling out a possible thermodynamic control of the process induced by Cs_2CO_3. Moreover, **24** is transformed into **25** when using Cs_2CO_3 under the same reaction conditions as in the cyclization step (Scheme 6). These results indicate that Cs_2CO_3 apparently does not just induce an epimerization at the stereogenic center at C(3), but very likely promotes a retro aza-Michael followed by a recyclization leading to **25**.

The assignment of the relative configuration at C(3) was elucidated by both NOESY spectra and analysis of the chemical shifts in ^{1}H and ^{13}C NMR spectra. In compound **24**, the cross peak between H-3 and H-4ax was only compatible with a pseudoaxial location for H-3. The assignment of the cis-relationship between H-3 and the methyl at C(3) in **25** follows from the NOESY cross peaks involving the methyl group at C(3a) and H-3, which in turn correlates with the bridgehead hydrogen H-7a (Scheme 6 or Figure 3). This assignment is also supported by the short- and long-range deshielding effects of the SO_2 functional group, with the γ-effect of the oxygen atom exhibiting an orientational dependence.[41] Thus, the sulfone group induced a strong deshielding of H-7a (δ 3.82) and methyl protons (δ 1.65) in **24** compared with these protons in epimer **25** (δ 3.16 and 1.32, respectively). Strong deshielding was also observed in sulfone **25** for H-4ax (δ 2.57 *vs* 1.98 in **24**), arising from the 1,3-diaxial relationship between the sulfone and H-4ax in **25**, which, in turn, induced a shielding in the δ_C of C(4) (δ 42.1) compared with epimer **24** (δ 49.9).

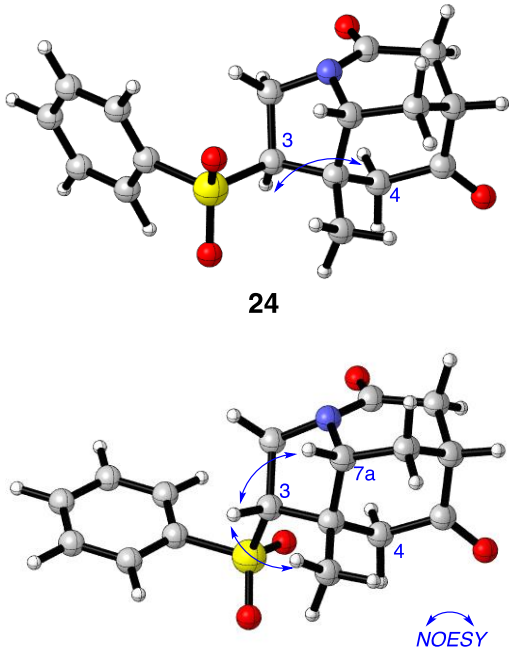


Figure 3. Fully optimized geometries (M06-2X/6-31+G(d) level) of azatricyclic compounds **24** and **25**.

Finally, we observed that self-condensation of the β-methylcyclohexenone **23** took place when heated at 80 ºC in a concentrated DMF solution. The structure of the two isolated compounds (**26**) depicted in Figure 4 was elucidated based on their HRMS and NMR (see Supplementary Material). Although self-condensation processes involving the γ-anion of the 3-methylcyclohex-2-enone have been noted,[42] to our knowledge there is no precedent for a dimerization leading to the formation of a product with a tetrasubstituted benzene core. Further studies to understand this unexpected process are underway.

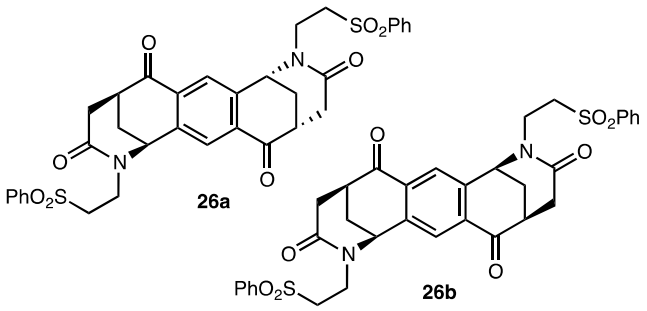


Figure 4. Structures of dimeric ketones **26**

3. Conclusion

In summary, the application of the Cu(I)-catalyzed ATRC methodology to the synthesis of 2-azabicyclo[3.3.1]nonanes from trichloroacetamides tethered with electron-rich cyclohexenes (i.e. cyclic enol acetates) gave access to a polyfunctionalized azabicyclic ketone. After adjustment of the oxidation level, the resulting sulphone compound enabled the assembly of the pyrrolidine ring. Subsequent–intramolecular Michael addition, either from K_2CO_3 or Cs_2CO_3, respectively, gave epimeric azatricyclic compounds embodying the ABC fragment of calyciphylline-A-type alkaloids. The functionalization of the three rings (ketone, lactam, and sulfone in rings A, B, and C) in the compounds reported here suggests these building blocks have potential for further application in the synthesis of natural products embodying this azatricyclic framework.

4. Experimental section

4.1 General

All the product mixtures were analyzed by thin-layer chromatography using TLC silica gel plates with a fluorescent indicator (λ = 254 nm). The spots were located by UV light or a 1% $KMnO_4$ aqueous solution. Unless otherwise noted, chromatography refers to flash chromatography and was carried out on SiO_2 (silica gel 60, 200–500 mesh). Drying of the organic extracts during the reaction work-up was performed over anhydrous Na_2SO_4. A CEM Discover™ microwave reactor with an external sensor was used. Infrared spectra were recorded on a FT-IR spectrometer. Chemical shifts of ^1H and ^{13}C NMR spectra are reported in ppm downfield (δ) from Me_4Si. All NMR data assignments were supported by gCOSY and gHSQC experiments.

4.2 Experimental procedures: first approach

*4.2.1. (1RS,5RS,6RS)-2-Benzyl-4,4,6-trichloro-2-azabicyclo [3.3.1]nonan-3-one (**3**).* To a suspension of CuCl (30 mg, 0.3 mmol 10%) in 1,2-dichloroethane (15 mL) were successively added TPMA (87.2 mg, 0.3 mmol), trichloroacetamide **2**[43] (1 g, 3 mmol), and AIBN (246 mg, 1.50 mmol 50%), and the mixture was heated at 60 °C for 2 days in a sealed tube. The solution was then allowed to reach rt, concentrated and purified by chromatography (1:9 hexane/CH_2Cl_2 to CH_2Cl_2) to yield morphan **3** (850 mg, 85%) as a white solid. For analytical and spectroscopic data, see reference 14.

*4.2.2 (1RS,5RS)-2-Benzyl-4,4-dichloro-2-azabicyclo[3.3.1] nonan-6-en-3-one (**4**).* In a 10 mL vessel a mixture of **3** (100 mg, 0.30 mmol), Li_2CO_3 (133 mg, 1.8 mmol), and LiBr (156 mg, 1.8 mmol) in DMF (2 mL) was heated with stirring at 110 ºC, using microwave irradiation for 1 h. The mixture was then diluted in EtOAc and washed with brine. The organics were dried, concentrated and purified by chromatography (Hexane/EtOAc 9:1) to yield recovered starting material **3** (15 mg, 15%) and then **4** (55 mg, 62%, 72% based on recovered starting material). IR (film): 3062, 3037, 2965, 2926, 1670 1603 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 1.95 (ddd, *J* = 13.6, 4.4, 1.6 Hz, 1H, H-9), 2.22 (dm, *J* = 18.8, 1H, H-8), 2.32 (dm, *J* = 18.8 Hz, 1H, H-8), 2.71 (dm, *J* = 13.6 Hz, 1H, H-9), 3.20 (br s, 1H, H-5), 3.69 (br s, 1H, H-1), 3.88 (d, *J* = 15.2 Hz, 1H, CH_2Ar), 5.38 (d, *J* = 15.2 Hz, 1H, CH_2Ar), 5.81 (dm, *J* = 10 Hz, 1H, H-7), 6.06-6.10 (m, 1H, H-6), 7.24-7.38 (m, 5H, ArH); ^{13}C NMR ($CDCl_3$, 100 MHz) δ□26.4 (C-9), 30.2 (C-8), 44.0 (C-5), 49.4 (CH_2Ar), 50.5 (C-1), 85.8 (C-4), 126.9 (C-7), 127.0 (C-6), 127.6, 127.7, 128.8 (ArH), 136.5 (*ipso*-C), 164.1 (C-3). HRMS (ESI-TOF) *m/z*: $[M+H]^+$ calculated for $C_{15}H_{16}Cl_2NO$ 296.0603; found 296.0598.

*4.2.3. Attempts at dehydrohalogenation of chloride **3** leading to cyclopropane derivatives **5***

Procedure 1: A mixture of **3** (50 mg, 0.15 mmol) and *t*BuOK solution (1 M in *t*BuOH, 0.75 mL, 0.75 mmol) in *t*BuOH (2 mL) was heated to reflux overnight. The mixture was concentrated, diluted in CH_2Cl_2 and washed with brine. The organic phase was dried, concentrated and purified by chromatography (8:2 CH_2Cl_2/Hexane to CH_2Cl_2) to yield **5b** (4 mg, 10%) and then **5a** (17 mg, 44%).

(1*RS*,2*RS*,5*RS*,8*SR*)-4-Benzyl-2-chloro-4-azatricyclo [3.3.1.$0^{2,8}$]nonan-3-one (**5a).** IR (film): 3029, 2928, 2865, 1651 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 1.24 (dddd, *J* = 15.2, 7.6, 1.0, 1.0 Hz, 1H, H-6), 1.51-1.59 (m, 1H, H-6), 1.81 (dt, *J* = 12.8, 2.8 Hz, 1H, H-9), 1.88 (t, *J* = 8 Hz, H-8), 1.95 (dt, *J* = 12.8, 2.8 Hz, 1H, H-9), 1.99 (ddd, *J* = 15.2, 8.4, 1.0 Hz, 1H, H-7)), 2.10 (dddd, *J* = 15.2, 7.6, 1.0, 1.0 Hz, 1H, H-7), 2.16 (dq, *J* = 8.4, 1.0 Hz, 1H, H-1), 3.42 (br s, 1H, H-5), 4.30 (d, *J* = 14.8 Hz, 1H, CH_2Ar), 4.97 (d, *J* = 14.8 Hz, 1H, CH_2Ar), 7.24-7.34 (m, 5H, ArH); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 17.3 (C-7), 24.0 (C-6), 25.3 (C-9), 26.8 (C-8), 28.1 (C-1), 45.5 (C-2), 50.3 (CH_2Ar), 51.5 (C-5), 127.6, 128.1, 128.6 (ArH), 137.6 (*ipso*-C), 166.7 (C-3). HRMS (ESI-TOF) *m/z*: $[M+H]^+$ calculated for $C_{15}H_{17}ClNO$ 262.0993; found 262.0990.

(1*RS*,2*SR*,5*SR*,8*SR*)-4-Benzyl-2-chloro-4-azatricyclo [3.3.1.$0^{2,8}$]non-6-en-3-one (**5b).** IR (film): 3050, 2925, 2854, 1650 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 1.34 (dt, *J* = 13.2, 2.4 Hz, 1H, H-9), 2.02 (dt, *J* = 13.2, 3.2 Hz, 1H, H-9), 2.50 (dq, *J* = 8, 2.4 Hz, 1H, H-1), 2.58 (brt, *J* = 8 Hz, 1H, H-8), 3.72 (m, 1H, H-5), 4.45 (d, *J* = 14.8 Hz, 1H, CH_2Ar), 4.84 (d, *J* = 14.8 Hz, 1H, CH_2Ar), 5.85 (ddd, *J* = 9.0, 7.2, 1.2 Hz, 1H, H-6), 6.12 (ddd, *J* = 9.0, 7.0, 1.2 Hz, 1H, H-7), 7.24-7.35 (m, 5H, ArH); ^{13}C NMR ($CDCl_3$, 100 MHz) δ□20.9 (C-9), 26.6 (C-1), 30.5 (C-8), 47.8 (C-2), 48.6 (C-5), 50.3 (CH_2Ar), 125.9 (C-7), 127.6 (ArH), 127.9 (C-6), 128.5, 128.6 (ArH), 137.4 (*ipso*-C), 164.0 (C-3). HRMS (ESI-TOF) *m/z*: $[M+H]^+$ calculated for $C_{15}H_{15}ClNO$ 260.0837; found 260.0836.

Procedure 2: In a similar way **3** (50 mg, 0.15 mmol) and NaOEt (1 M in EtOH, 0.45 mL, 0.45 mmol) in ethanol (2 mL) was heated to reflux overnight. The mixture was concentrated, diluted in CH_2Cl_2 and washed with brine. The organic phase was dried, and concentrated to provide **5a** in a quantitative yield.

Procedure 3: In a 10 mL vessel a mixture of **3** (50 mg, 0.15 mmol), Li_2CO_3 (66.5 mg, 0.9 mmol), and LiBr (78 mg, 0.9 mmol) in DMF (1 mL) was heated with stirring at 150 ºC using microwave irradiation for 15 min. The mixture was concentrated and purified by chromatography (Hexane/EtOAc 95:5 to 75:25) to yield **5b** (8 mg, 21%) and then **5c** (15 mg, 45%).

(1*RS*,2*RS*,5*SR*,8*SR*)-4-Benzyl-4-azatricyclo[3.3.1.$0^{2,8}$]non-6-en-3-one (**5c**). IR (film): 3049, 3031, 2920, 2854, 1635 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 1.37 (dt, *J* = 13.2, 2.4 Hz, 1H, H-9), 1.84 (br d, *J* = 13.2 Hz, 1H, H-9), 2.07 (dq, *J* = 7.2, 2 Hz, 1H, H-1), 2.13 (m, 1H, H-8), 2.34 (br t, *J* = 7.2 Hz, 1H, H-2), 3.65 (br s, 1H, H-5), 4.34 (d, *J* = 14.8 Hz, 1H, CH_2Ar), 4.87 (d, *J* = 14.8 Hz, 1H, CH_2Ar), 5.80 (dd, *J* = 9.2, 7.6 Hz, 1H, H-6), 6.11 (ddd, *J* = 9.2, 6.4, 0.8 Hz, 1H, H-7), 7.23-7.35 (m, 5H, ArH); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 15.4 (C-1), 19.4 (C-8), 22.0 (C-9), 25.4 (C-2), 48.0 (C-5), 49.2 (CH_2Ar), 126.2 (C-6), 127.3 (ArH), 127.5 (C-7), 128.3, 128.5 (ArH), 137.9 (*ipso*-C), 167.8 (C-3). HRMS (ESI-TOF) *m/z*: $[M+H]^+$ calculated for $C_{15}H_{16}NO$ 226.1226; found 226.1222.

4.2.4. *(1RS,5SR,6RS)-2-Benzyl-6-chloro-2-azabicyclo[3.3.1]nonan-3-one (**6**).* To a solution of **3** (2 g, 6.0 mmol) in ethanol (120 mL) were added NaOEt (1.48 g, 18.0 mmol) and Pd/C (200 mg, 10%) and the mixture was left stirring under a H_2 atmosphere at rt for 16 h. The mixture was then concentrated, diluted in CH_2Cl_2, filtered on a short celite pad and concentrated. After chromatography (CH_2Cl_2 to CH_2Cl_2/EtOAc 9:1) **6** was isolated (1.41 g, 88%). IR (film): 3061, 3028, 2938, 2857, 1641 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 1.66 (m, 2H, H-8eq and H-9), 1.80-2.00 (m, 3H, H-8ax and 7-CH_2), 2.30 (dq, *J* = 13.2, 2.8 Hz, 1H, H-9), 2.38 (br d, *J* = 18.4 Hz, 1H, H-4), 2.42 (br s, 1H, H-5), 2.83 (dd, *J* = 18.4, 7.6 Hz, 1H, H-4), 3.49 (br s, 1H, H-1), 3.93 (d, *J* = 15.2 Hz, 1H, CH_2Ar), 4.28 (br s, 1H, H-6), 5.27 (d, *J* = 15.2 Hz, 1H, CH_2Ar), 7.23-7.35 (m, 5H, ArH); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 22.9 (C-8), 25.1 (C-7), 26.3 (C-9), 35.0 (C-5), 37.1 (C-4), 48.2 (CH_2Ar), 50.6 (C-1), 61.9 (C-6), 127.4, 127.8, 128.6 (ArH), 137.4 (*ipso*-C), 169.3 (C-3). HRMS (ESI-TOF) m/z: $[M+H]^+$ calculated for $C_{15}H_{19}ClNO$ 264.1150; found 264.1145.

*4.2.5. 2-Benzyl-2-azabicyclo[3.3.1]nonan-6-en-3-one (**7**)*

From **4**: To a solution of **4** (50 mg, 0.17 mmol) in methanol (2 mL) at 0 ºC were added NH_4Cl (54 mg, 1 mmol) and Zn (110 mg, 1.7 mmol) and the mixture was stirred at this temperature for 1 h and at rt overnight. The mixture was filtered on a short celite pad, which was washed with MeOH. The resulting solution was concentrated to yield **7** (37 mg, 96%). For analytical data, see below.

From **6**: In a 10 mL vessel a mixture of **6** (200 mg, 0.75 mmol), Li_2CO_3 (335 mg, 4.5 mmol), and LiBr (395 mg, 4.5 mmol) in DMF (4 mL) was heated with stirring at 120 °C using microwave irradiation for 45 min. The mixture was then diluted in AcOEt and washed with brine. The organics were dried, concentrated and purified by chromatography (CH_2Cl_2 to CH_2Cl_2/EtOAc 9:1) to yield **7** (128 mg, 75%). IR (film): 3025, 2923, 2852, 1638 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 1.92 (m, 2H, 9-CH_2), 2.16 (dm, *J* = 18.4 Hz, 1H, H-8), 2.24 (dm, *J* = 18.4 Hz, 1H, H-8), 2.46 (dd, *J* = 16.2, 2 Hz, 1H, H-4), 2.56 (br s, 1H, H-5), 2.59 (dd, *J* = 16.2, 5.6 Hz, 1H, H-4), 3.66 (br s, 1H, H-1), 3.92 (d, *J* = 15.2 Hz, 1H, CH_2Ar), 5.35 (d, *J* = 15.2 Hz, 1H, CH_2Ar), 5.60 (dm, *J* = 10 Hz, 1H, H-7), 5.87 (m, 1H, H-6), 7.22-7.35 (m, 5H, ArH); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 27.3 (C-5), 29.1 (C-9), 29.9 (C-8), 38.2 (C-4), 48.2 (CH_2Ar), 50.0 (C-1), 123.6 (C-7), 127.2, 127.6, 128.5 (ArH), 131.0 (C-6), 137.7 (*ipso*-C), 169.6 (C-3). HRMS (ESI-TOF) *m/z*: $[M+H]^+$ calculated for $C_{15}H_{18}NO$ 228.1383; found 228.1376.

*4.2.6. (1RS,4RS,5RS)-2-Benzyl-4-methyl-2-azabicyclo[3.3.1]nonan-6-en-3-one (**8**).* To a solution of **7** (315 mg, 1.38 mmol) in THF (15 mL) at -78 ºC was added dropwise a 1 M solution of LHMDS in THF (2.8 mL, 1.4 mmol) and the mixture was stirred at this temperature for 1 h. MeI (0.26 mL, 4.12 mmol) was added and stirring continued for an additional 2 h at -78 ºC. The reaction was allowed to reach rt, quenched with brine (20 mL) and extracted with EtOAc. The organics were dried, concentrated and purified by chromatography (Hexane/EtOAc, 8:2 to 1:1) to yield **8** (205 mg, 61%, 70% based on recovered starting material) and recovered **7** (30 mg, 10%). IR (film): 3026, 2923, 2853, 1635 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 1.36 (d, *J* = 7.6 Hz, 3H, CH_3), 1.78 (ddt, *J* = 12.8, 4, 2 Hz, 1H, H-9 *pro*-R), 2.08 (dm, *J* = 12.8 Hz, 1H, H-9 *pro*-S), 2.15 (dm, *J* = 18 Hz, 1H, H-8), 2.19-2.27 (m, 2H, H-8 and H-5), 2.54 (br q, *J* = 7.6 Hz, 1H, H-4), 3.61 (br s, 1H, H-1), 3.85 (d, *J* = 14.8 Hz, 1H, CH_2Ar), 5.37 (d, *J* = 14.8 Hz, 1H, CH_2Ar), 5.58 (dm, *J* = 10 Hz, 1H, H-7), 5.88 (m, 1H, H-6), 7.19-7.34 (m, 5H, ArH); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 19.1 (CH_3), 24.5 (C-9), 29.9 (C-8), 33.7 (C-5), 41.7 (C-4), 48.1 (CH_2Ar), 50.2 (C-1), 123.2 (C-7), 127.1, 127.4, 128.5 (ArH), 131.5 (C-6), 137.9 (*ipso*-C), 173.4 (C-3). HRMS (ESI-TOF) *m/z*: $[M+H]^+$ calculated for $C_{16}H_{20}NO$ 242.1539; found 242.1533.

In a 200 mg-scale run, the epimer at C-4 (*epi*-**8**) was also isolated in 3% yield (6 mg).

(1*RS*,*4SR*,*5RS*)-2-Benzyl-4-methyl-2-azabicyclo[3.3.1]non-6-en-3-one (*epi*-**8**). IR (film): 3027, 2926, 2854, 1636 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 1.29 (d, *J* = 7.2 Hz, 3H, CH_3), 1.96 (m, 9-CH_2), 2.16 (dm, *J* = 18 Hz, 1H, H-8), 2.27 (dm, *J* = 18 Hz, 1H, H-8), 2.45 (br s, 1H, H-5), 2.62 (qd, *J* = 7.6, 5.2 Hz, 1H, H-4), 3.67 (br s, 1H, H-1), 3.88 (d, *J* = 15 Hz, 1H, CH_2Ar), 5.33 (d, *J* = 15 Hz, 1H, CH_2Ar), 5.65 (dm, *J* = 10.4 Hz, 1H, H-7), 5.92 (m, 1H, H-6), 7.22-7.34 (m, 5H, ArH); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 15.0 (CH_3), 30.1 (C-9), 30.7 (C-8), 32.6 (C-5), 42.4 (C-4), 48.3 (CH_2Ar), 50.6 (C-1), 124.5 (C-7), 127.1, 127.6, 128.5 (ArH), 128.7 (C-6), 138.1 (*ipso*-C), 173.1 (C-3). HRMS (ESI-TOF) *m/z*: $[M+H]^+$ calculated for $C_{16}H_{20}NO$ 242.1539; found 242.1539.

*4.2.7. (1RS,4SR,5SR,8RS)-2-Benzyl-8-hydroxy-4-methyl-2-azabicyclo[3.3.1]non-6-en-3-one (**9**).* In a 10 mL vessel a mixture of **8** (100 mg, 0.41 mmol) and SeO_2 (115 mg, 1.03 mmol) in dioxane (5 mL) was heated at 110 ºC using microwave irradiation for 40 min. The mixture was then filtered on a short celite pad, which was washed with CH_2Cl_2. Evaporation of the solvent followed by chromatography (Hexane/EtOAc 7:3 to 1:1) provided enone **10** (11 mg, 10%, see 4.2.8 for analytical data) and alcohol **9** (70 mg, 66%). IR (film): 3340, 3026, 2920, 2850, 1615 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 1.37 (d, *J* = 7.2 Hz, 3H, CH_3), 1.76 (br s, OH), 1.90 (dm, *J* = 13.6 Hz, 1H, H-9), 1.98 (dm, *J* = 13.6 Hz, 1H, H-9), 2.26 (m, 1H, H-5), 2.48 (q, *J* = 7.2 Hz, 1H, H-4), 3.50 (br s, 1H, H-1), 3.90 (d, *J* = 15.6 Hz, 1H, CH_2Ar), 4.00 (br s, 1H, H-8), 5.31 (d, *J* = 15.6 Hz, 1H, CH_2Ar), 5.75 (dd, *J* = 10, 4.4 Hz, 1H, H-7), 6.08 (dd, *J* = 10, 5.6 Hz, 1H,

H-6), 7.18-7.34 (m, 5H, ArH); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 19.2 (CH_3), 19.8 (C-9), 34.1 (C-5), 40.7 (C-4), 48.7 (CH_2Ar), 56.2 (C-1), 64.0 (C-8), 125.2 (C-7), 127.3, 127.4, 128.6 (ArH), 135.1 (C-6), 137.5 (*ipso*-C), 172.7 (C-3). HRMS (ESI-TOF) *m/z*: $[M+H]^+$ calculated for $C_{16}H_{20}NO_2$ 258.1489; found 258.1483.

*4.2.8. (1RS,4SR,5SR)-2-Benzyl-4-methyl-2-azabicyclo[3.3.1] non-6-ene-3,8-dione **(10)***. A mixture of **9** (120 mg, 0.46 mmol) and Dess-Martin reagent (396 mg, 0.93 mmol) in CH_2Cl_2 (8 mL) was stirred at rt for 30 min and then a 1 M NaOH solution (5 mL) was added. The mixture was extracted with CH_2Cl_2, and the organics were washed with a saturated $Na_2S_2O_3$ solution, dried and concentrated to yield **10** in quantitative yield sufficiently pure to be used in the next step without further purification. An analytical sample was prepared by chromatography (7:3 Hexane/EtOAc). IR (film): 3051, 3034, 2923, 2852, 1684, 1645 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.51 (d, *J* = 7.2 Hz, 3H, CH_3), 2.19 (dm, *J* = 13.6 Hz, 1H, H-9), 2.28 (dm, *J* = 13.6 Hz, 1H, H-9), 2.58 (m, 1H, H-5), 2.68 (q, *J* = 7.2 Hz, 1H, H-4), 3.65 (m, 1H, H-1), 3.68 (d, *J* = 15.2 Hz, 1H, CH_2Ar), 5.49 (d, *J* = 15.2 Hz, 1H, CH_2Ar), 5.99 (dm, *J* = 10.4 Hz, 1H, H-7), 7.11 (ddd, *J* = 10.4, 6, 2 Hz, 1H, H-6), 7.24-7.37 (m, 5H, ArH); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 19.8 (CH_3), 26.5 (C-9), 35.2 (C-5), 40.0 (C-4), 47.6 (CH_2Ar), 58.9 (C-1), 125.8 (C-7), 127.5, 128.3, 128.7 (ArH), 136.7 (*ipso*-C), 152.2 (C-6), 171.1 (C-3), 194.2 (C-8). HRMS (ESI-TOF) m/z: $[M+H]^+$ calculated for $C_{16}H_{18}NO_2$ 256.1332; found 256.1327.

The oxidation step was also carried out on a small scale as follows: to a solution of **9** (25 mg, 0.1 mmol) in CH_2Cl_2 (0.5 mL) were successively added NaBr (10 mg, 0.10 mmol), TEMPO (0.75 mg, 0.005 mmol), a 10% NaClO solution in H_2O (0.2 mL), and $NaHCO_3$ (21 mg, 0.25 mmol), and the mixture was stirred at rt for 1 h. A 5% aqueous $NaHCO_3$ solution (5 mL) was added and the mixture was extracted with CH_2Cl_2. The organics were dried and concentrated to yield **10** (25 mg, 99%) sufficiently pure to be used in the next step without further purification.

*4.2.9. (1RS,4SR,5SR,8SR)-2-Benzyl-8-hydroxy-4,8-dimethyl-2-azabicyclo[3.3.1]non-6-en-3-one **(11)***. To a solution of **10** (35 mg, 0.14 mmol) in THF (1.5 mL) at -78 ºC was added dropwise a 1.6 M MeLi solution in ether (0.21 mL, 0.34 mmol), and the mixture was stirred for 30 min. The reaction was allowed to reach rt, quenched with a saturated aqueous NH_4Cl solution (5 mL) and extracted with EtOAc. The organics were washed with brine, dried, concentrated and purified by chromatography (1:1 Hexane/EtOAc) to yield **11** (20 mg, 54%). IR (film): 3340, 3025, 2971, 2925, 2853, 1623 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.31 (s, 3H, CH_3), 1.36 (d, *J* = 7.6 Hz, 3H, CH_3), 1.91 (dm, *J* = 13.6 Hz, 1H, H-9), 1.97 (dm, *J* = 13.6 Hz, 1H, H-9), 2.20 (m, 1H, H-5), 2.49 (q, *J* = 7.6 Hz, 1H, H-4), 3.14 (br s, OH), 3.38 (m, 1H, H-1), 4.22 (d, *J* = 15.2 Hz, 1H, CH_2Ar), 5.53 (dm, *J* = 10 Hz, 1H, H-7), 5.63 (d, *J* = 15.2 Hz, 1H, CH_2Ar), 5.84 (ddd, *J* = 10, 6, 1.6 Hz, 1H, H-6), 7.19-7.34 (m, 5H, ArH); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 20.0 (4-CH_3), 25.0 (C-9), 27.3 (8-CH_3), 34.2 (C-5), 41.6 (C-4), 51.1 (CH_2Ar), 59.6 (C-1), 73.2 (C-8), 127.1, 127.6, 128.6 (ArH), 131.1 (C-6), 132.0 (C-7), 138.0 (*ipso*-C), 173.8 (C-3). HRMS (ESI-TOF) *m/z*: $[M+H]^+$ calculated for $C_{17}H_{22}NO_2$ 272.1645; found 272.1638.

*4.2.10. (1RS,4SR,5SR)-2-Benzyl-4-methyl-8-methylene-2-azabicyclo[3.3.1]non-6-en-3-one **(12)***. In a 10 mL vessel a mixture of **11** (6 mg, 0.02 mmol), 6 M HCl aqueous solution (0.25 mL) and dioxane (0.45 mL) was heated at 100 ºC using 15 min microwave irradiation. A saturated $NaHCO_3$ solution was added and the mixture extracted with CH_2Cl_2. After chromatography (8:2 Hexane/ EtOAc) **12** was isolated (3 mg, 54%). IR (film): 3056, 2925, 2854, 1633 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.42 (d, *J* = 7.6 Hz, 3H, CH_3), 1.87 (dm, *J* = 12.8 Hz, 1H, H-9), 2.16 (dm, *J* = 12.8 Hz, 1H, H-9), 2.35 (br s, 1H, H-5), 2.58 (q, *J* = 7.6 Hz, 1H, H-4), 3.68 (d, *J* = 15.2 Hz, 1H, CH_2Ar), 3.80 (br s, 1H, H-1), 4.88 (s, 1H, =CH_2), 4.50 (s, 1H, =CH_2), 5.51 (d, *J* = 15.2 Hz, 1H, CH_2Ar), 6.00 (dd, *J* = 9.6, 6 Hz, 1H, H-6), 6.09 (d, *J* = 9.6 Hz, 1H, H-7), 7.20-7.37 (m, 5H, ArH); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 19.4 (CH_3), 25.8 (C-9), 34.5 (C-5), 41.5 (C-4), 46.5 (CH_2Ar), 55.6 (C-1), 113.7 (=CH_2), 126.1 (C-7), 127.2, 127.8, 128.7 (ArH), 133.5 (C-6), 137.7 (*ipso*-C), 141.2 (C-8), 171.5 (C-3). HRMS (ESI-TOF) *m/z*: $[M+H]^+$ calculated for $C_{17}H_{20}NO$ 254.11539; found 254.1541.

4.3 Experimental procedures: second approach

*4.3.1. 4-[(2-(phenylsulfonyl)ethylamino]cyclohexanone ethylene acetal (**14b**).*

Method A. To a solution of **1** (5 g, 20.2 mmol) in EtOH (75 mL) was added phenyl vinyl sulfone (3.4 g, 20.2 mmol) and the mixture was heated to reflux for 20 h. The mixture was concentrated and purified by chromatography (7:3 Hexane/EtOAc) to yield **14a** (7.4 g, 88%): IR (film): 3060, 3026, 2939, 2883, 1602, 1585 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.41-1.62 (m, 4H), 1.66-1.79 (m, 4H), 2.49 (tt, *J* = 10.8, 3.2 Hz, 1H), 2.91 (m, 2H), 3.07 (m, 2H), 3.55 (s, 2H), 3.91 (s, 4H), 7.10-7.25 (m, 5H), 7.50 (t, *J* = 7.6 Hz, 2H), 7.62 (t, *J* = 7.2 Hz, 1H), 7.79 (d, *J* =7.6 Hz, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 25.7 (CH_2), 33.8 (CH_2), 44.6 (CH_2), 55.1 (CH_2), 55.5 (CH_2), 59.6 (CH), 64.2 (CH_2), 64.3 (CH_2), 108.2 (C), 126.9, 127.8, 128.2, 128.3, 129.2, 133.5 (ArH), 139.4, 139.9 (*ipso*-C). HRMS (ESI-TOF) *m/z*: $[M+H]^+$ calculated for $C_{23}H_3NO_4S$ 416.1890; found 416.1895.

A mixture of amine **14a** (3.6 g, 8.7 mmol) and $Pd(OH)_2$ on carbon 20% wt. (0.36 g, 10%) in MeOH (70 mL) was stirred at rt and under a H_2 atmosphere for 16 h. The mixture was then filtered on a celite pad and concentrated to yield secondary amine **14b** (2.8 g, 99%), which was sufficiently pure to be used in the next step without further purification. An analytical sample was obtained by chromatography (95:5 CH_2Cl_2/MeOH). IR (film): 3326, 3063, 2932, 2883, 1585 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.35-1.44 (m, 2H), 1.52 (td, *J* = 12, 3.6 Hz, 2H), 1.67 (br s, 1H, NH), 1.70-1.84 (m, 4H), 2.50 (tt, *J* = 10, 3.6 Hz, 1H), 3.03 (t, *J* = 6.4 Hz, 2H), 3.29 (t, *J* = 6.4 Hz, 2H), 3.92 (s, 4H), 7.55-7.61 (m, 2H), 7.67 (tt, *J* = 7.2, 1.2 Hz, 1H), 7.90-7.94 (m, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 29.9 (CH_2), 32.7 (CH_2), 40.4 (CH_2), 54.6 (CH), 56.4 (CH_2), 64.2 (CH_2), 64.3 (CH_2), 108.4 (C), 127.9, 129.3, 133.8 (ArH), 139.3 (*ipso*-C). HRMS (ESI-TOF) *m/z*: $[M+H]^+$ calculated for $C_{16}H_{24}NO_4S$ 326.1420; found 326.1422.

Method B. A mixture of ethylene acetal 4-aminocyclohexanone (**13**)[49] (4.65 g, 29.4 mmol) and phenyl vinyl sulfone (5 g, 29.4 mmol) in EtOH (120 mL) was heated to reflux for 20 h. The mixture was then allowed to reach rt and concentrated to yield **14b** sufficiently pure to be used in the next step without further purification.

*4.3.2. 2,2,2-Trichloro-N-(4-oxocyclohexyl)-N-[2-(phenylsulfonyl)ethyl]acetamide ethyelene acetal (**15**).* To a mixture of **14b** (29.4 mmol), Et_3N (8.3 mL, 60 mmol) in CH_2Cl_2

(70 mL) at 0 ºC was added dropwise trichloroacetyl chloride (4 mL, 36 mmol) and the mixture was stirred at 0 ºC for 10 min and at rt for 3 h. Water was added and the mixture was extracted with CH_2Cl_2. The organic layers were washed with brine, dried and concentrated to yield trichloroacetamide **15** (15 g), which was sufficiently pure to be used in the next step without further purification. An analytical sample of **15** was obtained by chromatography (Hexane/EtOAc 7:3 to 1:1). IR (film): 3063, 2943, 2884, 1672, 1584 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 1.60 (td, *J* = 13.6, 4.0 Hz, 2H), 1.76-1.95 (m, 6H), 3.40-3.48 (m, 2H), 3.60-3.68 (m, 2H), 3.95 (s, 4H), 4.38 (tt, *J* = 11.6, 3.6 Hz, 1H), 7.57-7.64 (m, 2H), 7.69 (tt, *J* = 7.6, 1.2 Hz, 1H), 7.93-7.97 (m, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 26.9 (CH_2), 33.7 (CH_2), 38.9 (CH_2), 53.3 (CH_2), 58.1 (CH), 64.3 (CH_2), 64.6 (CH_2), 92.9 (CCl_3), 106.7 (C), 127.9, 129.5, 134.0 (ArH), 138.7 (*ipso*-C), 160.3 (CO). HRMS (ESI-TOF) *m/z*: $[M+NH_4]^+$ calculated for $C_{18}H_{26}Cl_3N_2O_5S$ 487.0622; found 487.0629.

*4.3.3. 2,2,2-Trichloro-N-(4-oxocyclohexyl)-N-(2-(phenylsulfonyl)ethyl)acetamide (**16**).* A mixture of the above trichloroacetamide **15** (29.4 mmol), THF (60 mL**)** and 10% HCl (150 mL) was heated to reflux for 3 h. The mixture was extracted with CH_2Cl_2, and the organic layers were dried and concentrated to yield ketone **16** (14.5 g), which was used in the next step without further purification. An analytical sample was obtained by chromatography (Hexane/EtOAc 7:3 to 1:1). IR (film): 3061, 2952, 1716, 1673, 1584 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz): δ 1.98-2.24 (m, 4H), 2.38-2.57 (m, 4H), 3.41-3.49 (m, 2H), 3.61-3.69 (m, 2H), 4.88 (br t, *J* = 12 Hz, 1H), 7.61 (t, *J* = 7.6 Hz, 2H), 7.71 (t, *J* = 7.2 Hz, 1H), 7.93 (d, *J* = 7.2 Hz, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 28.7 (CH_2), 38.8 (CH_2), 39.3 (CH_2), 53.5 (CH_2), 57.2 (CH), 92.7 (CCl_3), 127.9, 129.5, 134.2 (ArH), 138.6 (*ipso*-C), 160.3 (CO), 206.8 (CO). HRMS (ESI-TOF) *m/z*: $[M+H]^+$ calculated for $C_{16}H_{19}Cl_3NO_4S$ 426.0095; found 426.0086.

4.3.4. N-(4-Acetoxycyclohex-3-enyl)-*N*-[(2-phenylsulfonyl) ethyl]-2,2,2-trichloroacetamide (**17**). A mixture of the above ketone **16** (29.4 mmol) and TsOH (6.8 g, 36 mmol) in isopropenyl acetate 250 mL) was heated to reflux for 3 h. The mixture was then concentrated and purified by chromatography (Hexane/EtOAc 7:3 to 1:1) to yield enol acetate **17** (9.6 g, 70%, over 4 steps from **14b**). IR (film): 2939, 1754, 1673 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 2.02 (m, 2H), 2.13 (s, 3H, CH_3), 2.20-2.53 (m, 4H), 3.46 (m, 2H), 3.64 (m, 2H), 4.65 (br s, 1H), 5.34 (m, 1H), 7.60 (m, 2H), 7.70 (t, *J* = 7.6 Hz, 1H), 7.94 (m, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 21.0 (CH_3), 26.2 (CH_2), 26.4 (CH_2), 26.5 (CH_2), 39.0 (CH_2), 53.5 (CH_2), 55.4 (CH), 92.7 (CCl_3), 111.3 (CH), 127.9, 129.6, 134.2 (ArH), 138.7 (*ipso*-C), 147.3 (C), 160.7 (CO), 169.1 (CO). HRMS (ESI-TOF) *m/z*: $[M+NH_4]^+$ calculated for $C_{18}H_{24}Cl_3N_2O_5S$ 485.0466; found 485.0469.

*4.3.5. 4,4-Dichloro-2-(2-(phenylsulfonyl)ethyl)-2-azabicyclo [3.3.1]nonane-3,6-dione (**18**).* To a suspension of CuCl (32 mg, 0.32 mmol 10%) in 1,2-dichloroethane (30 mL) were added successively TPMA (93 mg, 0.32 mmol 10%), AIBN (263 mg, 1.6 mmol 50%) and enol acetate **17** (1.5 g, 3.2 mmol) and the mixture was heated at 60 °C for 48 h in a sealed tube. The solution was allowed to reach rt, concentrated and purified by chromatography (hexane/EtOAc 7:3 to 3:7) to yield **18** (870 mg, 70%) then **18bis** (162 mg, 14%). Compound **18**: IR (NaCl, neat): 3059, 2944, 1720, 1673, 1584 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 1.96 (dddd, *J* = 14.4, 13.2, 5.6, 2.4 Hz, 1H, H-8ax), 2.12 (ddd, *J* = 14.4, 3.6, 2.4 Hz, 1H, H-9), 2.31 (dm, *J* = 14.4 Hz, 1H, H-8eq), 2.42 (ddd, *J* = 15.6, 13.2, 7.2 Hz, 1H, H-7ax), 2.53 (dd, *J* = 15.6, 5.6 Hz, 1H, H-7eq), 2.91 (dq, *J* = 14.4, 3.6 Hz, 1H, H-9), 3.34 (dt, *J* = 14, 4.8 Hz, 1H), 3.53 (br s, 1H, H-5), 3.56 (dt, *J* = 14, 4.8 Hz, 1H), 3.71 (ddd, *J* = 14, 8.8, 5.2 Hz, 1H), 4.12 (br s, 1H, H-1), 4.21 (dt, *J* = 14, 5.2 Hz, 1H), 7.61 (tm, *J* = 7.2 Hz, 2H), 7.70 (tt, *J* = 7.2, 1.6 Hz, 1H), 7.90-7.96 (m, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 30.7 (C-8 and C-9), 34.6 (C-7), 42.4 (CH_2), 53.3 (CH_2), 54.5 (C-1), 62.6 (C-5), 80.4 (C-4), 127.7, 129.6, 134.2 (ArH), 139.2 (*ipso*-C), 163.9 (C-3), 203.1 (C-6). HRMS (ESI-TOF) *m/z*: $[M+NH_4]^+$ calculated for $C_{16}H_{21}Cl_2N_2O_4S$ 407.0594; found 407.0595.

*(1RS,4SR,5RS)-4-Chloro-2-(2-(phenylsulfonyl)ethyl)-2-azabicyclo[3.3.1]nonane-3,6-dione (**18bis**).* IR (film): 2939, 1721, 1659, 1584 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 1.94 (dddd, *J* = 14.4, 12.4, 6.4, 2.4 Hz, 1H, H-8ax), 2.18 (dt, *J* = 14.4, 3.2 Hz, 1H, H-9), 2.28 (dm, *J* = 14.4 Hz, 1H, H-8eq), 2.40-2.55 (m, 3H, 7-CH_2 and H-9), 3.16 (br s, 1H, H-5), 3.25 (dt, *J* = 14, 4.8 Hz, 1H), 3.53 (ddd, *J* = 14, 9.2, 4.4 Hz, 1H), 3.80 (ddd, *J* = 14, 9.2, 4.8 Hz, 1H), 4.07 (br s, 1H, H-1), 4.23 (dt, *J* = 14, 4.8 Hz, 1H), 4.58 (d, *J* = 6.8 Hz, H-4), 7.61 (t, *J* = 7.2 Hz, 2H), 7.70 (t, *J* = 7.2 Hz, 1H), 7.92 (d, *J* = 7.2 Hz, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ□30.3 (C-8), 32.6 (C-9), 34.4 (C-7), 42.1 (CH_2), 51.9 (C-5), 53.3 (CH_2), 54.0 (C-1), 54.9 (C-4), 127.6, 129.6, 134.2 (ArH), 139.4 (*ipso*-C), 166.2 (C-3), 206.1 (C-6). HRMS (ESI-TOF) *m/z*: $[M+NH_4]^+$ calculated for $C_{16}H_{22}ClN_2O_4S$ 373.0983; found 373.0985.

4.3.6 *2-[2-(Phenylsulfonyl)ethyl]-2-azabicyclo[3.3.1] nonane-3,6-dione (**19**).* To a 7:2 mixture of **18** and **18bis** (3.26 g, 8.40 mmol) in ethanol (160 mL) were added NaOAc (2.1 g, 25 mmol) and Pd/C (0.33 g, 10%) and the mixture was left stirring under a H_2 atmosphere at rt overnight. The mixture was then filtered on a celite pad and concentrated. After chromatography (CH_2Cl_2/EtOAc 9:1 to 1:1) **19** was obtained (2.17 g, 81%). IR (film): 3060, 2940, 1710, 1638, 1584 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 1.92 (dddd, *J* = 14, 12, 7.6, 2 Hz, 1H, H-8ax), 2.10 (dm, *J* = 13.6 Hz, 1H, H-9), 2.22 (dq, *J* = 13.6, 3.2 Hz, 1H, H-9), 2.27 (dm, *J* = 14 Hz, 1H, H-8eq), 2.35-2.45 (m, 3H, 7-CH_2 and H-4), 2.65 (dd, *J* = 18.8, 7.2 Hz,1H, H-4), 2.79 (br s, 1H, H-5), 3.32 (dt, *J* = 14.4, 5.2 Hz, 1H), 3.46 (ddd, *J* = 14, 8, 5.6 Hz, 1H), 3.73 (ddd, *J* = 14.4, 8, 6 Hz, 1H), 4.00 (br s, 1H, H-1), 4.18 (dt, *J* = 14, 5.6 Hz, 1H), 7.60 (tm, *J* = 7.2 Hz, 2H), 7.69 (tt, *J* = 7.2, 1.6 Hz, 1H), 7.93 (dm, *J* = 7.2 Hz, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ□30.5 (C-8), 31.8 (C-9), 33.8 (C-7), 35.0 (C-4), 41.3 (CH_2), 43.8 (C-5), 53.1(C-1), 53.7 (CH_2), 127.6, 129.5, 134.0 (ArH), 139.4 (*ipso*-C), 169.2 (C-3), 210.4 (C-6). HRMS (ESI-TOF) m/z: $[M+H]^+$ calculated for $C_{16}H_{20}NO_4S$ 322.1108; found 322.1098.

*4.3.7. 2-[2-(Phenylsulfonyl)ethyl]-2-azabicyclo[3.3.1] non-7-ene-3,6-dione (**20**).* A mixture of **19** (2 g, 6.3 mmol), and $Pd(OAc)_2$ (0.28 g, 1.24 mmol) in DMSO (35 mL) was stirred under oxygen atmosphere and at 80 ºC for 24 h. The mixture was then concentrated and purified by chromatography (CH_2Cl_2/EtOAc 8:2) to yield enone **20** as a white solid (1.52 g, 76%). IR (film): 3059, 2940, 1681, 1645, 1584 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 2.27 (dm, *J* = 13.2 Hz, 1H, H-9), 2.40 (dm, *J* = 13.2 Hz, 1H, H-9), 2.45 (d, *J* = 18.8 Hz, 1H, H-4), 2.78 (dd, *J* = 18.8, 8 Hz, 1H, H-4), 2.95 (m, 1H, H-5), 3.24 (dt, *J* = 14, 5.2 Hz, 1H), 3.54 (ddd, *J* = 14, 8.8, 5.2 Hz, 1H), 3.66 (ddd, *J* = 14, 8.8, 5.6 Hz, 1H), 4.10 (dt, *J* = 14, 5.2 Hz, 1H), 4.26 (dtd, *J* = 5.6, 3.2, 1.2 Hz, 1H, H-1), 6.07 (dd, *J* = 10, 1.2 Hz, 1H, H-7), 7.32 (ddd, *J* = 10, 5.6, 1.6 Hz, 1H, H-8), 7.60 (tm, *J* = 7.2 Hz, 2H),

7.69 (tt, *J* = 7.2, 1.6 Hz, 1H), 7.92 (dm, *J* = 7.2 Hz, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 31.2 (C-9), 35.0 (C-4), 40.9 (C-5), 41.9 (CH_2), 51.4 (C-1), 54.2 (CH_2), 127.6, 129.5 (Ar-CH), 129.6 (C-7), 134.0 (ArH), 139.3 (*ipso*-C), 147.7 (C-8), 168.6 (C-3), 200.0 (C-6). HRMS (ESI-TOF) *m/z*: $[M+H]^+$ calculated for $C_{16}H_{18}NO_4S$ 320.0952; found 320.0953.

*4.3.8. (1RS,5RS,8RS)-8-Methyl-2-[2-(phenylsulfonyl)ethyl]-2-azabicyclo[3.3.1]nonane-3,6-dione (**21**).* To a suspension of CuI (71 mg, 0.37 mmol) in THF (1.5 mL) at 0 ºC was added dropwise a 1.6 M solution of MeLi in ether (0.47 mL, 0.75 mmol) and the mixture was stirred for 50 min. A solution of **20** (100 mg, 0.31 mmol) in THF (1.8 mL) was added and the resulting mixture was stirred for 30 min at 0 ºC. An NH_4Cl saturated solution (2 mL) was added and the mixture was extracted with EtOAc. The organics were washed with brine, dried, concentrated and purified by chromatography (CH_2Cl_2/EtOAc 8:2) to yield **21** (99 mg, 95%). IR (film) 2958, 1709, 1641 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.06 (d, *J* = 7.2 Hz, 3H, CH_3), 2.05 (dm, *J* = 14 Hz, 1H, H-9), 2.14 (dm, *J* = 13.6 Hz, 1H, H-7), 2.29 (dm, *J* = 14, 1H, H-9), 2.39 (d, *J* = 18.4 Hz, 1H, H-4), 2.53-2.55 (m, 1H, H-8), 2.55-2.58 (m, 1H, H-7), 2.63 (dd, *J* = 18.4, 6.8 Hz, 1H, H-4), 2.73 (br s, 1H, H-5), 3.34 (dt, *J* = 14, 5.2 Hz, 1H), 3.47 (ddd, *J* = 14, 8.4, 6 Hz, 1H), 3.64 (br s, 1H, H-1), 3.72 (ddd, *J* = 14, 8, 6 Hz, 1H), 4.19 (dt, *J* = 14, 5.2 Hz, 1H), 7.60 (tm, *J* = 7.6 Hz, 2H), 7.69 (tt, *J* = 7.6, 1.2 Hz, 1H), 7.93 (dm, *J* = 7.6 Hz, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 18.1 (CH_3), 27.0 (C-9), 34.9 (C-4), 35.4 (C-8), 40.6 (C-7), 41.5 (CH_2), 43.9 (C-5), 53.7 (CH_2), 58.5 (C-1), 127.6, 129.4, 134.0 (ArH), 139.4 (*ipso*-C), 168.9 (C-3), 210.7 (C-6). HRMS (ESI-TOF) *m/z*: $[M+H]^+$ calculated for $C_{17}H_{22}NO_4S$ 336.1264; found 336.1266.

*4.3.9. (1RS,5RS,8RS)-8-Methyl-2-[2-(phenylsulfonyl)ethyl]-6-[(trimethylsilyl)oxy]-2-azabicyclo[3.3.1]non-6-en-3-one (**22**).* A mixture of CuI (60 mg, 0.31 mmol) and 3 M solution of MeMgBr in diethyl ether (1.15 mL, 3.44 mmol) was cooled to -30 ºC and the mixture was stirred for 10 min. A solution of **20** (1 g, 3.1 mmol) in THF (8 mL, followed by a 2 mL rinse) was added via cannula. The mixture was cooled to -50 ºC and then were successively added HMPA (0.6 mL, 3.44 mmol), Et_3N (0.88 mL, 6.25 mmol) and TMSCl (0.8 mL, 6.25 mmol). The mixture was stirred at this temperature for 30 min then at -78 ºC for 1 h. The reaction was allowed to reach rt, diluted with ether, and washed with a saturated $NaHCO_3$ solution, and the aqueous layer was extracted with diethyl ether. The organics were washed with brine, dried and concentrated to yield **22** (1.25 g, 98%) sufficiently pure to be used in the next step without further purification. IR (film): 3061, 2958, 2928, 2872, 1639, 1585 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 0.16 (s, 9H, $(CH_3)_3Si$), 1.04 (d, *J* = 6.8 Hz, 3H, CH_3), 2.70 (dm, *J* = 12.8 Hz, 1H, H-9), 2.01 (dtd, *J* = 12.8, 4.0, 2.4 Hz, 1H, H-9), 2.23 (br s, 1H, H-5), 2.30 (dd, *J* = 17.6, 5.6 Hz, 1H, H-4), 2.31-2.40 (m, 1H, H-8), 2.44 (dm, *J* = 17.6 Hz, 1H, H-4), 3.30-3.40 (m, 2H), 3.45 (br s, 1H, H-1), 3.64-3.73 (m, 1H), 3.91-4.01 (m, 1H), 4.57 (dd, *J* = 5.2, 1.2 Hz, 1H, H-7), 7.55-7.61 (m, 2H), 7.67 (tt, *J* = 7.6, 1.2 Hz, 1H), 7.89-7.95 (m, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 0.3 ($(CH_3)_3Si$), 20.4 (CH_3), 24.9 (C-9), 32.8 (C-5), 34.4 (C-8), 36.7 (C-4), 41.6 (CH_2), 53.7 (CH_2), 58.4 (C-1), 104.1 (C-7), 127.7, 129.4, 133.8 (ArH), 139.5 (*ipso*-C), 152.0 (C-6), 169.8 (C-3). HRMS (ESI-TOF) *m/z*: $[M+H]^+$ calculated for $C_{20}H_{30}NO_4SSi$ 408.1659; found 408.1660.

*4.3.10. 8-Methyl-2-[2-(phenylsulfonyl)ethyl]-2-azabicyclo [3.3.1]non-7-ene-3,6-dione (**23**).* A mixture of **22** (1.25 g, 3.1 mmol), $Pd(OAc)_2$ (0.79 g, 3.5 mmol) in CH_3CN (5 mL**)** was stirred under an oxygen atmosphere at rt for 40 h. The mixture was concentrated and purified by chromatography using alumina (CH_2Cl_2/EtOAc 9:1) to yield a 4:1 mixture of enone **23** (0.48 g, 47% over two steps, from **20**) and the recovered ketone **21** (0.12 g, 11%). IR (film): 3058, 2944, 2849, 1709, 1655 1584 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.18 (d, *J* = 1.6 Hz, 3H, CH_3), 2.26-2.40 (m, 2H, 9-CH_2), 2.43 (d, *J* = 18.4 Hz, 1H, H-4), 2.76 (dd, *J* = 18.4, 8 Hz, 1H, H-4), 2.86 (br s, 1H, H-5), 3.21 (dt, *J* = 13.6, 4.8 Hz, 1H), 3.57 (ddd, *J* = 13.6, 9.2, 4.8 Hz, 1H), 3.74 (ddd, *J* = 14.0, 8.8, 5.2 Hz, 1H), 4.12 (br s, 1H, H-1), 4.26 (dt, *J* = 13.6, 4.8 Hz, 1H), 5.83 (br s, 1H, H-7), 7.60 (t, *J* = 7.2 Hz, 2H), 7.69 (t, *J* = 7.2 Hz, 1H), 7.92 (d, *J* = 7.2 Hz, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 23.7 (CH_3), 31.4 (C-9), 35.0 (C-4), 39.6 (C-5), 43.1 (CH_2), 53.8 (CH_2), 56.9 (C-1), 125.6 (C-7), 127.5, 129.4, 134.0 (ArH), 139.3 (*ipso*-C), 161.1 (C-8), 168.7 (C-3), 200.1 (C-6). HRMS (ESI-TOF) m/z: $[M+H]^+$ calculated for $C_{17}H_{20}NO_4S$ 334.1107; found 334.1100.

*4.3.11. (3RS,3aSR,6RS,7aRS)-3a-Methyl-3-(phenylsulfonyl) hexahydro-1,6-ethanoindole-5,9(4H)-dione (**24**).* A 3:1 mixture of enone **23** and ketone **21** (200 mg, 0.6 mmol) and K_2CO_3 (62 mg, 0.45 mmol) in DMF (3 mL) was heated at 100 ºC for 7 h. The mixture was then concentrated and purified by chromatography (CH_2Cl_2/EtOAc 9:1 to 1:1) to yield **24** (67 mg, 45%), **25** (15 mg, 10%; for analytical data, see below 4.3.12) and recovered **21** (43 mg). For **24**: m.p. 240 ºC. IR (film): 3058, 2944, 2918, 2849, 1709, 1655 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.65 (s, 3H, CH_3), 1.98 (d, *J* = 15.6 Hz, 1H, H-4), 2.30 (ddt, *J* = 14.4, 4, 2 Hz, 1H, H-7), 2.39 (ddd, *J* = 14.4, 4.4, 2.4 Hz, 1H, H-7), 2.42 (d, *J* = 15.6 Hz, 1H, H-4), 2.54 (dt, *J* = 17.6, 2.4 Hz, 1H, H-8), 2.66 (dd, *J* = 17.6, 4.8 Hz, 1H, H-8), 2.76 (br s, 1H, H-6), 3.21 (dd, *J* = 12.4, 6.8 Hz, 1H, H-2), 3.28 (dd, *J* = 8.4, 6.8 Hz, 1H, H-3), 3.82 (br s, 1H, H-7a), 4.31 (dd, *J* = 12.4, 8.4 Hz, 1H, H-2), 7.61 (t, *J* = 7.6 Hz, 2H), 7.70 (tt, *J* = 7.6, 1.6 Hz, 1H), 7.87 (dm, *J* = 7.6 Hz, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 19.3 (CH_3), 24.5 (C-7), 36.9 (C-8), 42.9 (C-6), 45.4 (C-2), 49.0 (C-3a), 49.9 (C-4), 60.9 (C-7a), 68.6 (C-3), 128.2, 129.7, 134.3 (ArH), 138.9 (*ipso*-C), 171.2 (C-9), 208.0 (C-5). HRMS (ESI-TOF) *m/z*: $[M+H]^+$ calculated for $C_{17}H_{20}NO_4S$ 334.1108; found 334.1114.

4.3.12. (3RS,3aRS,6SR,7aSR)-3a-Methyl-3-(phenylsulfonyl) hexahydro-1,6-ethanoindole-5,9(4H)-dione (**25**). A 3:1 mixture of enone **23** and ketone **21** (200 mg, 0.6 mmol) and Cs_2CO_3 (148 mg, 0.45 mmol) in DMF (3 mL) was heated at 100 ºC for 30 min. The mixture was then concentrated and purified by chromatography (CH_2Cl_2/EtOAc 9:1 to 1:1) to yield **24** (11 mg, 7%), **25** (66 mg, 44%) and recovered **21** (20 mg). For **25**: m.p. 207-208 ºC. IR (film): 3064, 2958, 1709, 1652, 1583 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.32 (s, 3H, CH_3), 2.21 (ddt, *J* = 14.8, 3.2, 2.4 Hz, 1H, H-7), 2.34 (ddd, *J* = 14.8, 4.4, 2.4 Hz, 1H, H-7), 2.57 (d, *J* = 17.2 Hz, 1H, H-4), 2.60 (dm, *J* = 17.2 Hz, 1H, H-8), 2.73 (dd, *J* = 17.2, 5.2 Hz, 1H, H-8), 2.76 (br s, 1H, H-6), 2.87 (d, *J* = 17.2, 1H, H-4), 3.16 (br s, 1H, H-7a), 3.19 (dd, *J* = 12.8, 10 Hz, 1H, H-2), 3.45 (dd, *J* = 10, 6.6 Hz, 1H, H-3), 4.72 (dd, *J* = 12.8, 6.6 Hz, 1H, H-2), 7.61 (t, *J* = 7.6 Hz, 2H), 7.70 (tt, *J* = 7.6, 1.2 Hz, 1H), 7.93 (d, *J* = 7.6 Hz, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 22.0 (CH_3), 24.2 (C-7), 36.5 (C-8), 42.1 (C-4), 42.9 (C-6), 44.8 (C-2), 48.8 (C-3a), 63.0 (C-7a), 70.8 (C-3), 128.1, 129.7, 134.3 (ArH), 139.9 (*ipso*-C), 171.2 (C-9), 208.0 (C-5). HRMS (ESI-TOF) *m/z*: $[M+H]^+$ calculated for $C_{17}H_{20}NO_4S$ 334.1108; found 334.1116.

*4.3.13. Epimerization of azatricyclic sulfone **24** to **25**.* A mixture of sulfone **24** (15 mg, 0.045 mmol) and Cs_2CO_3 (14 mg, 0.045 mmol) in DMF (0.4 mL) was heated at 100 ºC for 30 min. The mixture was then concentrated and purified by chromatography (CH_2Cl_2/EtOAc 9:1 to 3:1) to yield **25** (10 mg, 67%).

*4.3.14. (1RS,5RS,8SR,12SR)- and (1RS,5RS,8RS,12RS)-2,9-bis(2-(phenylsulfonyl)ethyl)-1,2,4,5,8,9,11,12-octahydro-1,5:8,12-dimethanobenzo[1,2-c:4,5-c']bis(azocine)-3,6,10,13-tetraone (**26a** and **26b**).* A 4:1 mixture of enone **23** and methylketone **21** (30 mg, 0.09 mmol) and K_2CO_3 (10 mg, 0.07 mmols) in DMF (0.2 mL) was heated at 80 ºC for 4 h. The mixture was then concentrated and purified by chromatography (CH_2Cl_2/MeOH 99:1) to yield **21** (7 mg) unchanged together with a 1:1 mixture of dimers **26a** and **26b** (9 mg, 39%), which were separated by precipitation in ether (**26a** as a solid, **26b** in the mother liquor).

26a. IR (film): 3063, 3029, 2853, 1686, 1644 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 2.54-2.57 (m, 4H), 2.62 (d, *J* = 18.4 Hz, 2H), 2.90 (dd, *J* = 18.4, 8 Hz, 2H), 3.15-3.2 (m, 4H), 3.50 (ddd, *J* = 14.4, 9.2, 4.4 Hz, 2H), 3.73 (ddd, *J* = 14.4, 9.2, 5.2 Hz, 2H), 3.98 (dt, *J* = 14.4, 4.8 Hz, 2H), 4.90 (br s, 2H), 7.60-7.66 (m, 4H), 7.72 (tt, *J* = 7.6, 1.6 Hz, 2H), 7.93-7.98 (m, 4H), 8.14 (s, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 30.6 (CH_2), 35.9 (CH_2), 40.5 (CH), 41.2 (CH_2), 53.6 (CH_2), 56.0 (CH), 127.5 (CH), 127.7 (CH), 129.6 (CH), 133.6 (C), 134.1 (CH), 139.4 (C), 143.9 (C), 167.6 (CO), 197.9 (CO). HRMS (ESI-TOF) *m*/*z*: $[M+H]^+$ calculated for $C_{34}H_{33}N_2O_8S_2$ 661.1672; found 661.1699. $[M+NH_4]^+$ calculated for $C_{34}H_{36}N_3O_8S_2$ 678.1938; found 678.1934.

26b. IR (film): 2927, 2854, 1683, 1644 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 2.53 (br d, *J* = 14 Hz, 2H), 2.59 (dt, *J* = 14, 2.8 Hz, 2H), 2.63 (d, *J* = 18.4 Hz, 2H), 2.92 (dd, *J* = 18.4, 8 Hz, 2H), 3.17-3.25 (m, 4H), 3.46 (ddd, *J* = 14.4, 9.6, 4 Hz, 2H), 3.75 (ddd, *J* = 14.4, 9.6, 4.4 Hz, 2H), 4.04 (dt, *J* = 14.4, 4.8 Hz, 2H), 4.96 (br s, 2H), 7.60-7.66 (m, 4H), 7.71 (tt, *J* = 7.6, 1.2 Hz, 2H), 7.94-7.98 (m, 4H), 8.15 (s, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 30.7 (CH_2), 35.9 (CH_2), 40.6 (CH), 41.0 (CH_2), 53.8 (CH_2), 56.1 (CH), 127.5 (CH), 127.7 (CH), 129.6 (CH), 133.5 (C), 134.1 (CH), 139.5 (C), 144.0 (C), 167.6 (CO), 198.0 (CO) . HRMS (ESI-TOF) *m*/*z*: $[M+H]^+$ calculated for $C_{34}H_{33}N_2O_8S_2$ 661.1672; found 661.1678. $[M+NH_4]^+$ calculated for $C_{34}H_{36}N_3O_8S_2$ 678.1938; found 678.1940.

4.4 Computational Details

All the calculations reported in this paper were obtained with the GAUSSIAN 09 suite of programs[46] using the dispersion corrected M06-2X[47] functional in conjuction with the standard double-ζ quality plus polarization and diffuse functions 6-31+G(d) basis set.[48] Reactants and products were characterized by frequency calculations,[49] and have positive definite Hessian matrices. Transition structures (TS's) show only one negative eigenvalue in their diagonalized force constant matrices, and their associated eigenvectors were confirmed to correspond to the motion along the reaction coordinate under consideration using the Intrinsic Reaction Coordinate (IRC) method.[50]

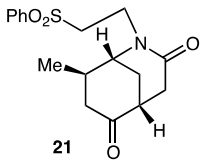
Acknowledgments

Financial support for this research was provided by Projects CTQ2010-14846/BQU, CTQ2013-41338-P, and CTQ2013-44303-P from the Ministry of Economy and Competitiveness of Spain and the FP7 Marie Curie Actions of the European Commission via the ITN ECHONET Network (MCITN-2012–316379).

References and notes

1. For a review, see: Kang, B.; Jakubec, P.; Dixon, D. J. *Nat. Prod. Rep.* **2014**, *31*, 550–562.
2. Solé, D.; Urbaneja, X.; Bonjoch, J. *Org.Lett.* **2005**, *7*, 5461–5464.
3. For our studies on 3-substituted *cis*-3a-methyloctahydroindole compounds (AC ring), see: (a) Cordero-Vargas, A.; Urbaneja, X.; Bonjoch, J. *Synlett.* **2007**, 2379–2382. (b) Cordero-Vargas, A.; Bradshaw, B.; Bonjoch, J. *Tetrahedron* **2008**, *64*, 8134–8140.
4. Lu, Z.; Li, Y.; Deng, J.; Li, A. *Nature Chem.* **2013**, *5*, 679–684.
5. Xiong, X.; Li, Y.; Lu, Z.; Wan, M.; Deng, J.; Wu, S.; Shao, H.; Li, A. *Chem. Commun.* **2014**, *50*, 5294–5297.
6. Yao, Y.; Liang, G. *Org. Lett.* **2012**, *14*, 5499–5501.
7. Ibrahim, A. A.; Golonka, A. N.; Lopez, A. M.; Stockdill, J. L. *Org. Lett.* **2014**, *16*, 1072–1075.
8. For other synthetic studies leading to tri- and tetracyclic fragments of calyciphylline A-type alkaloids, see: ACD ring: (a) Xu, C.; Liu, Z.; Wang, H.; Zhang, B.; Xiang, Z.; Hao, X.; Wang, D. Z. *Org. Lett.* **2011**, *13*, 1812-1815. (b) Sladojevich, F.; Michaelides, I. N.; Darses, B.; Ward, J. W.; Dixon, D. J. *Org. Lett.* **2011**, *13*, 5132–5235. (c) Wang, L.; Xu, C.; Chen, Li, Hao, X.; Wang, D. Z. *Org. Lett.* **2014**, *16*, 1076–1079. BCD ring: (d) Ikeda, S.; Shibuya, M.; Kanoh, N.; Iwabuchi, Y. *Org. Lett.* **2009**, *11*, 1833-1836. DEF ring: (e) Darses, B.; Michaelides, I. N.; Sladojevich, F.; Ward, J. W.; Rzepa, P. R.; Dixon, D. J. *Org. Lett.* **2012**, *14*, 1684–1687. ABCD ring: (f) Xu, C.; Wang, L.; Hao, X.; Wang, D. Z. *J. Org. Chem.* **2012**, *77*, 6307–6313.
9. For Dixon's pioneering use of the intramolecular Michael reaction to build ring B in studies towards calychiphille A-type alkaloids, see reference 8b.
10. For a review on the synthesis of 2-azabicyclo[3.3.1]nonanes, see: Bonjoch, J.; Diaba, F.; Bradshaw, B. *Synthesis* **2011**, 993–1018.
11. (a) For a classical review, see: Jasperse C.P.; Curran D.P.; Flevig T.L. Chem. Rev. **1991**,91, 1237–1286; (b) Bonjoch, J.; Bradshaw, B.; Diaba, F. In Stereoselective Synthesis of Drugs and Natural Products; Andrushko, V.; Andrushhko, N. Eds.; Wiley-VCH: New York 2013; pp 733–768.
12. (a) Quirante, J.; Escolano, C.; Merino, A.; Bonjoch, J. *J. Org. Chem.* **1998**, *63*, 968–976; (b) Cassayre, J.; Quiclet-Sire, B.; Saunier, J.-B.; Zard, S. Z. *Tetrahedron Lett.* **1998**, *39*, 8995–8998; (c) J. Cassayre, S. Z. Zard, *Synlett* **1999**, 501–503.
13. (a) Seijas, J. A.; Vázquez-Tato, M. P.; Castedo, L.; Estévez, R. J.; Onega, M. G.; Ruiz, M. *Tetrahedron* **1992**, *48*, 1637–1642; (b) Li, Q.; Li, G.; Ma, S.; Feng, P.; Shi, Y. *Org. Lett*. **2013**, *15*, 2601–2603; (c) Diaba, F.; Martínez-Laporta, A.; Bonjoch, J. *J. Org. Chem.* **2014**, *79*, 9365–9372.
14. Throughout the discussion, the systematic numbering for each compound is used. Thus, the numbering depicted in Scheme 1 is only applicable to azatriyclic compounds and not to 2-azabicyclo[3.3.1]nonane derivatives (see compound **4** in Scheme 2).
15. Quirante, J.; Escolano, C.; Massot, M.; Bonjoch, J. *Tetrahedron* **1997**, *53*, 1391–1402.
16. Diaba, F.; Martínez-Laporta, A.; Bonjoch, J. *Eur. J. Org. Chem.* **2014**, 2371–2378.
17. Radicals formed from the decomposition of the free radical initiator 2,2'-azobisisobutyronitrile (AIBN) at 60 ºC continuously regenerate the catalytically active lower oxidation state transition metal complex (activator) by the abstraction of a halogen atom from the higher oxidation state complex (deactivator). See: Eckenhoff, W. T.; Pintauer, T. *Catal. Rev. Sci. Eng.* 2010, **52**, 1–59.
18. Diaba, F.; Martínez-Laporta, A.; Bonjoch, J.; Pereira, A.; Muñoz-Molina, J. M.; Pérez, P. J.; Belderrain, T. R. *Chem. Commun.* **2012**, *48*, 8799–8801.
19. For the synthesis of cyclopropanes from 1,3-dihalides, see: (a) Fernández-Zúmel, M. A.; Buron, C.; Severin, K. *Eur. J. Org. Chem.* **2011**, 2272–2277; (b) Risse, J.; Fernández-Zúmel, M. A.; Cudré, Y.; Severin, K. *Org. Lett.* **2012**, *14*, 3060–3063.

20. Cid, M. M.; Pombo-Villar, E. *Helv. Chim. Acta* **1993**, 76, 1591–1607.
21. Seijas, J. A.; Vázquez-Tato, M. P.; Castedo, L.; Estévez, R. J.; Onega, M. G.; Ruiz, M. *Tetrahedron* **1992**, *48*, 1637–1642.
22. For a seminal study, see: Trost, B.; Kunz, R. A. *J. Org. Chem.* **1974**, *39*, 2475–2476.
23. The chemical shift of C-4 (δ 41.7) and C-9 (δ 24.5) of a sample of *epi*-**8** (see experimental part) is also in agreement with the stereochemical elucidation.
24. For a review on ^{13}C NMR data for substituted 2-azabicyclo[3.3.1nonan-3-ones, see: Quirante, J.; Escolano, C.; Diaba, F.; Torra, M.; Bonjoch, J. *Magn. Reson. Chem.* **2000**, *38*, 891–893.
25. The use of standard reagents (PDC, PCC, CrO_3) mainly returned the starting material.
26. For a review on 1,3-oxidative transpositions of allylic alcohols in organic synthesis, see: Luzzio, F. A. *Tetrahedron* **2012**, *68*, 5323–5339.
27. Dauben, W. G.; Michno, D. M. *J. Org. Chem.* **1977**, *42*, 682–685.
28. Treatment of **11** with hot water returned only the starting material. For this procedure promoting 1,3-rearrangement of allylic alcohols, as well as examples mediated by Bronsted acids, see: Li, P.-F.; Wang, H.-L.; Qu, J. *J. Org. Chem.* **2014**, *79*, 3955-3962.
29. For related problems in the Dauben oxidation in structurally demanding allylic tertiary alcohols, see: (a) Jiménez-Núñez, E.; Molawi, K.; Echavarren, A. M. *Chem. Commun.* **2009**, 7327–7329; (b) Larson, K. K.; Sarpong, R. *J. Am. Chem. Soc.* **2009**, *131*, 13244–13245.
30. Nirogi, R. V. S.; Konda, J. B.; Kambhampati, R.; Shinde, A.; Bandyala, T. R.; Gudla, P.; Kandukuri, K. K.; Jayarajan, P.; Kandikere, V.; Dubey, P. K. *Bioorganic Med. Chem. Lett.* **2012**, *22*, 6980–6985.
31. Radical cyclization of **17** was also checked on a 100 mg scale, although under non optimized conditions, using Ru(II) catalysts, such as Grubbs 2nd generation catalyst (5 mol%, toluene, 155 ºC, 2 h, 80%) and $RuCl_2(PPh_3)_2$ (5 mol%, toluene, 115 ºC, 3 h, 55% yield, 68% based on recovered starting material).
32. Diao, T.; Stahl, S. S. *J. Am. Chem. Som.* **2011**, *133*, 14566–14569.
33. Woo, C. M.; Gholap, S. L.; Lu, L.; Kaneko, M.; Li, Z.; Ravikumar, P. C.; Herzon, S. B. *J. Am. Chem. Soc.* **2012**, *134*, 17262–17273.
34. In preliminary studies, avoiding the trapping step, the β-methyl ketone **21** was stereoselectively obtained (see experimental part). Attempts to oxidize **21** directly to **23** ($Pd(OAc)_2$, DMSO, O_2; IBX, TsOH, DMSO) were unsuccessful.



21

35. Larock, R. C.; Hightower, T. R.; Kraus, G. A.; Hahn, P.; Zheng, D. *Tetrahedron Lett.* **1995**, *36*, 2423–2426 and references therein.
36. For an intramolecular Michael addition of sulfonyl carbanions upon enones using strong bases such as $KN(TMS)_2$, see: Fujishima, H.; Takeshita, H.; Suzuki, S.; Toyota, M.; Ihara, M. *J. Chem. Soc. Perkin Trans1*, **1999**, 2609–2616.
37. Dijkstra, G.; Kruizinga, W. H.; Kellogg, R. M. *J. Org. Chem.* **1987**, *52*, 4230–4234.
38. It is believed that the cesium effect stems from: (i) better solubility of cesium bases and the generation of highly reactive "naked" anions; (ii) the large size of Cs; and (iii) its facile polarizability: Musaev, D. G.; Figg, T. M.; Kaledin, A. L. *Chem. Soc. Rev.* **2014**, *43*, 5009-5031.
39. For the importance of alkali metal counterions as stereocontrol elements in cyclization processes, see for example: Hu, Y.; Bishop, R. L.; Luxenburger, A.; Dong, S.; Paquette, L. A. *Org. Lett.* **2006**, *8*, 2735–2737.
40. E_{rel} = **24** (0.0), **25** (0.6) at M06/6-31+G(d) level. E_{rel} = **24** (0.1), **25** (0.0) at B3LYP-D3/6-31+G(d) level.
41. For the influence of the SO bond on the ^1H chemical shifts in the NMR of sulphones, see: Abraham, R.J.; Byrne, J. J.; Griffiths, L. *Magn. Reson. Chem.* **2008**, *46*, 667–675.
42. (a) Gurst, J. E.; Miller, R. W.; McPhail, A. T. *Tetrahedron Lett.* **1980**, *21*, 3223–3226; (b) Kasum, B.; Prager, R. H. *Aust. J. Chem.* **1990**, *43*, 63–68.
43. Compound **2** was synthesized following our previously reported procedure (ref 16), using trichloroacetyl chloride as the acylating agent.
44. Compound **13** was prepared according to the previously reported procedures for oxime formation[45] and the reduction step.[30] To a solution of $NH_2OH{\cdot}HCl$ (6.36 g, 91.5 mmol) and NaOAc (7.5 g, 91.5 mmol) in H_2O (37.5 mL) was added a solution of cyclohexanedione monoethylene acetal (13 g, 83.2 mmol) in MeOH (155 mL) and the mixture was heated to reflux for 2 h. After elimination of the methanol, water (10 mL) was added and the resulting mixture was extracted with EtOAc. The organic layers were washed with a 10% $NaHCO_3$ solution and brine, dried and concentrated to yield the corresponding oxime (12.9 g, 92%), which was sufficiently pure to be used in the next step without further purification. To a suspension of $LiAlH_4$ (5.5 g, 146 mmol) in THF (75 mL) at 0 ºC was added dropwise over 25 min a solution of the above oxime (12.5 g, 73 mmol) in THF (75 mL) and the mixture was heated to reflux for 1 h. The mixture was cooled to 5-10 ºC and then a 1 M NaOH aqueous solution (7 mL) was added dropwise. After filtration on a celite pad, the primary amine **13** was obtained as a yellowish oil (7.5 g, 65%).
45. Tarkin-Tas, E.; Mathias, L. J. *Macromolecules* **2010**, 43, 968–974.
46. Gaussian 09, Revision D.01, Frisch, M. J.; Trucks, G. W.; Schlegel, H. B.; Scuseria, G. E.; Robb, M. A.; Cheeseman, J. R.; Scalmani, G.; Barone, V.; Mennucci, B.; Petersson, G. A.; Nakatsuji, H.; Caricato, M.; Li, X.; Hratchian, H. P.; Izmaylov, A. F.; Bloino, J.; Zheng, G.; Sonnenberg, J. L.; Hada, M.; Ehara, M.; Toyota, K.; Fukuda, R.; Hasegawa, J.; Ishida, M.; Nakajima, T.; Honda, Y.; Kitao, O.; Nakai, H.; Vreven, T.; Montgomery, J. A., Jr.; Peralta, J. E.; Ogliaro, F.; Bearpark, M.; Heyd, J. J.; Brothers, E.; Kudin, K. N.; Staroverov, V. N.; Kobayashi, R.; Normand, J.; Raghavachari, K.; Rendell, A.; Burant, J. C.; Iyengar, S. S.; Tomasi, J.; Cossi, M.; Rega, N.; Millam, M. J.; Klene, M.; Knox, J. E.; Cross, J. B.; Bakken, V.; Adamo, C.; Jaramillo, J.; Gomperts, R.; Stratmann, R. E.; Yazyev, O.; Austin, A. J.; Cammi, R.; Pomelli, C.; Ochterski, J. W.; Martin, R. L.; Morokuma, K.; Zakrzewski, V. G.; Voth, G. A.; Salvador, P.; Dannenberg, J. J.; Dapprich, S.; Daniels, A. D.; Farkas, Ö.; Foresman, J. B.; Ortiz, J. V.; Cioslowski, J.; Fox, D. J. Gaussian, Inc., Wallingford CT, 2009.
47. Zhao, Y.; Truhlar, D. G. *Theor. Chem. Acc.*, 2008, **120**, 215.
48. Hehre, W. J.; Radom, L.; Scheleyer, P. v. R.; Pople, J. A. *Ab Initio Molecular Orbital Theory*; Wiley: New York, 1986; p 76, and references therein.
49. McIver, J. W.; Komornicki, A. K. *J. Am. Chem. Soc.* **1972**, *94*, 2625.
50. C. González, H. B. Schlegel, *J. Phys. Chem*. **1990**, *94*, 5523.

Supplementary Material

Supplementary data associated with this article (copies of NMR spectra of all compounds and Cartesian coordinates and potential energies for all the species studied in Figures 2 and 3) can be found in the online version, at http://dx.doi.org/ .

Synthesis of the ABC Fragment of Calyciphylline A-type *Daphniphyllum* Alkaloids

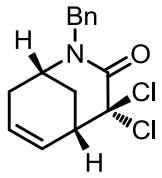
Faïza Diaba, Agustín Martínez-Laporta, and Josep Bonjoch

Laboratori de Química Orgànica, Facultat de Farmàcia, IBUB, Universitat de Barcelona, Av. Joan XXIII s/n, 08028-Barcelona, Spain

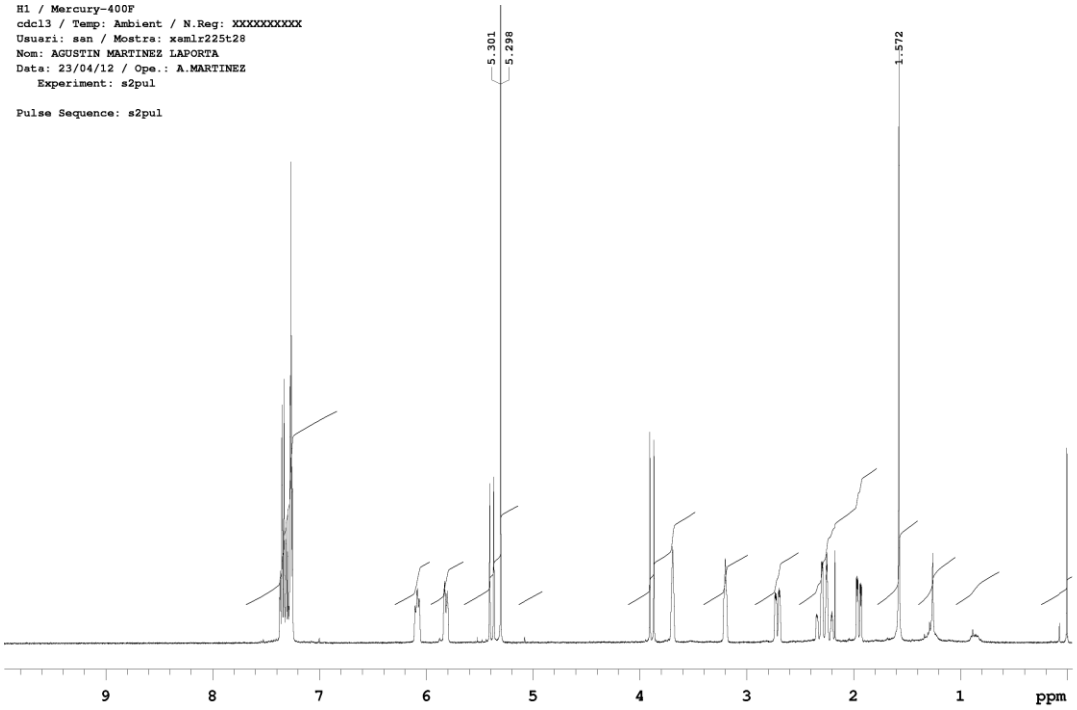
faiza.diaba@ub.edu; josep.bonjoch@ub.edu

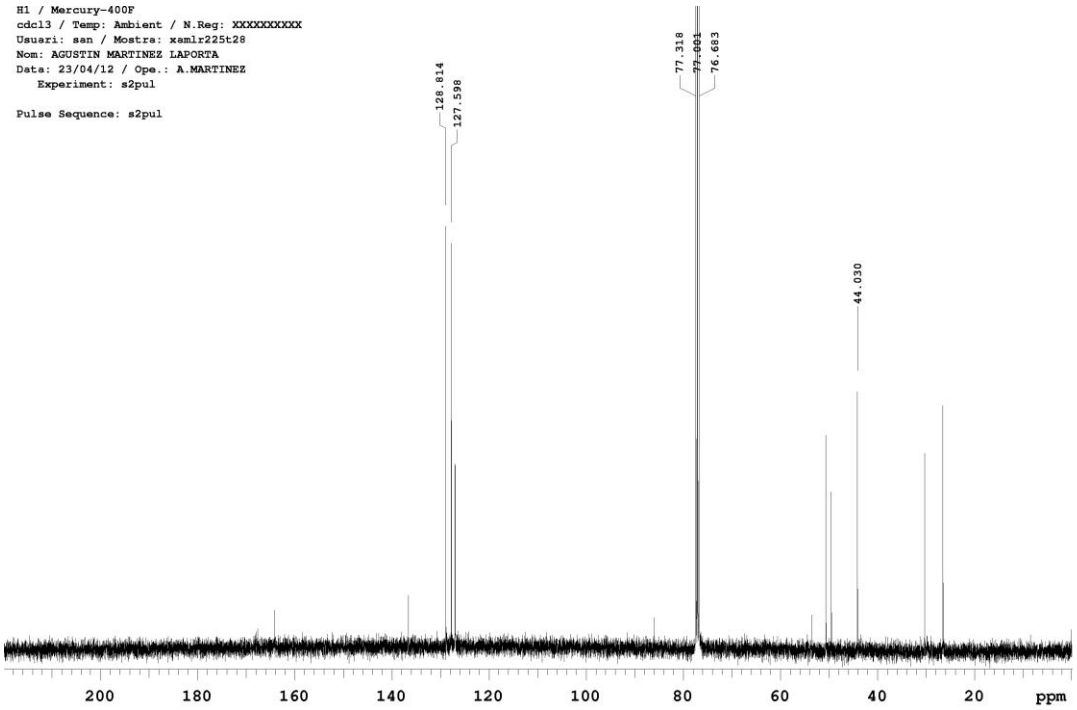
Supporting information

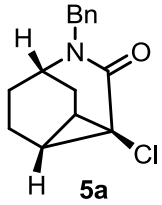
Contents ***Page***


Bn
H
N
O
Cl
Cl
H

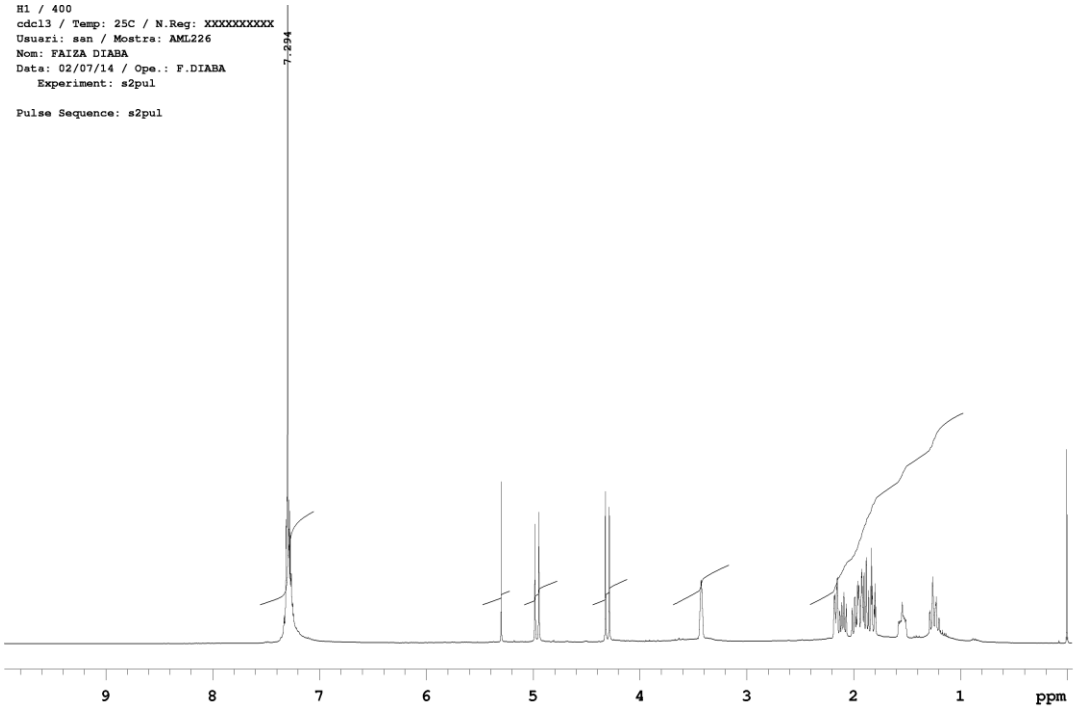
4

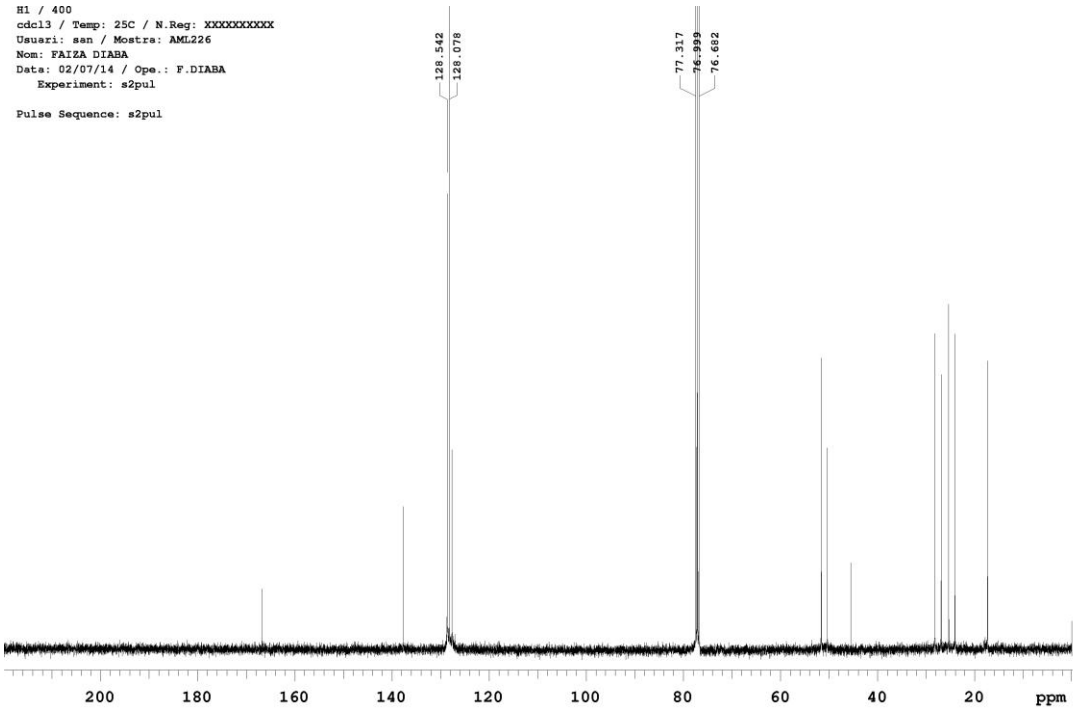

H1 / Mercury-400F
cdcl3 / Temp: Ambient / N.Reg: XXXXXXXXXX
Usuari: san / Mostra: xamlr225t28
Nom: AGUSTIN MARTINEZ LAPORTA
Data: 23/04/12 / Ope.: A.MARTINEZ
Experiment: s2pul
Pulse Sequence: s2pul
5.301
5.298
1.572
9
8
7
6
5
4
3
2
1
ppm

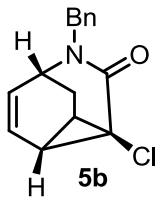

H1 / Mercury-400F
cdcl3 / Temp: Ambient / N.Reg: XXXXXXXXXX
Usuari: san / Mostra: xamlr225t28
Nom: AGUSTIN MARTINEZ LAPORTA
Data: 23/04/12 / Ope.: A.MARTINEZ
Experiment: s2pul
Pulse Sequence: s2pul
128.814
127.598
77.318
77.001
76.683
44.030
200
180
160
140
120
100
80
60
40
20
ppm


Bn
H
N
O
Cl
H

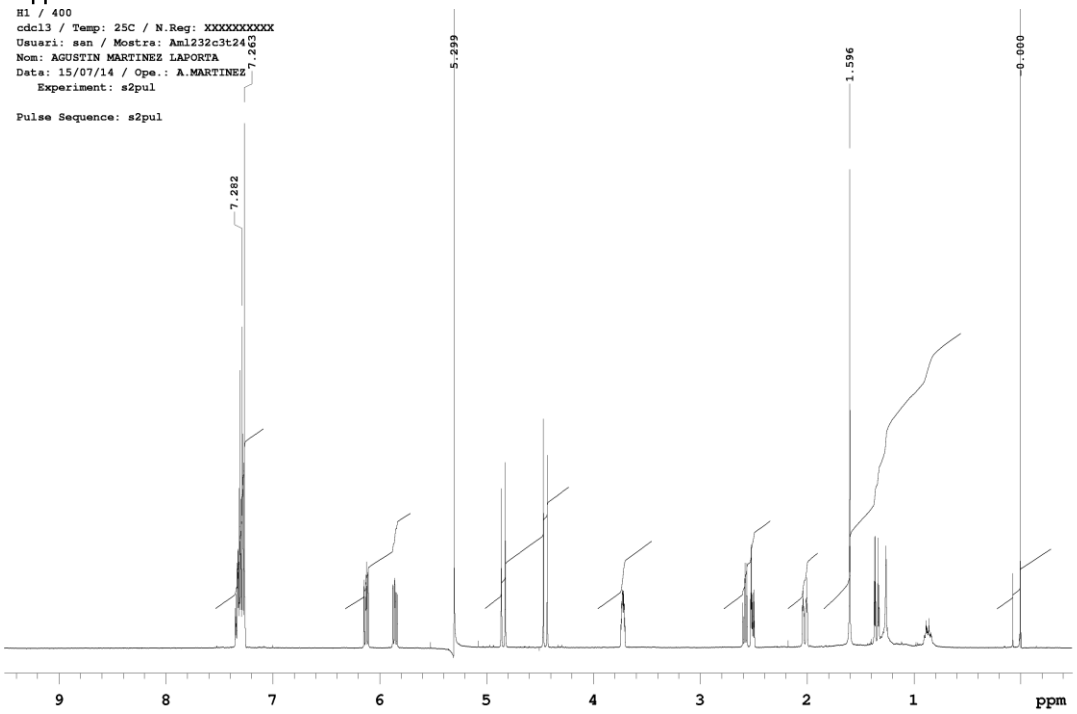
5a

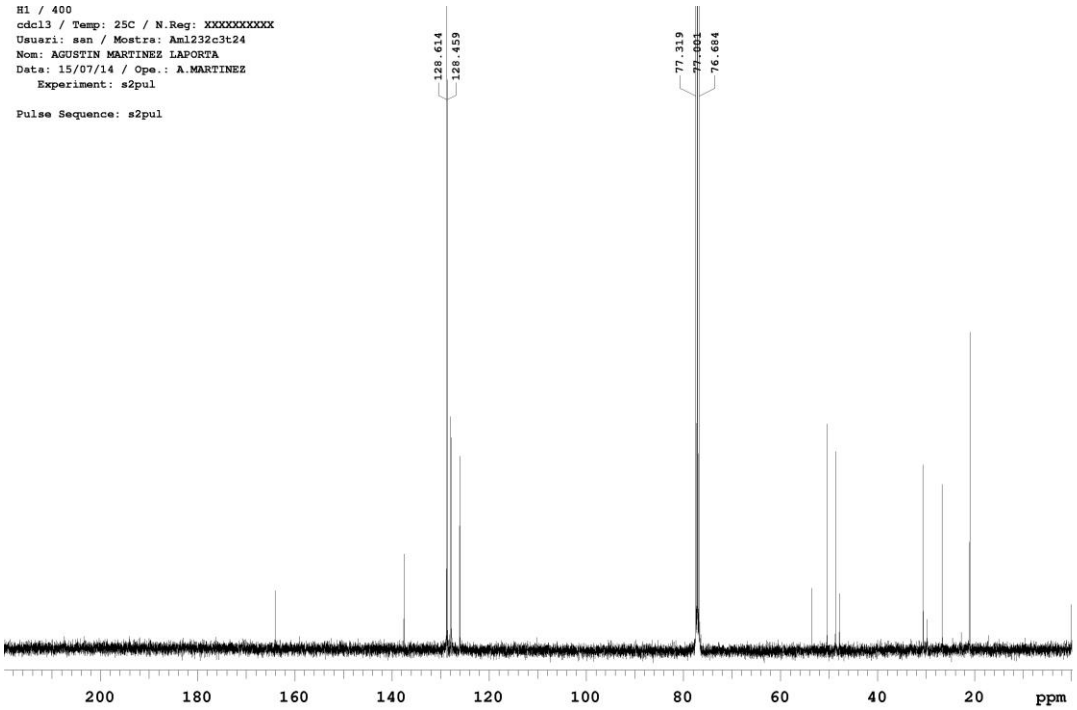

H1 / 400
cdcl3 / Temp: 25C / N.Reg: XXXXXXXXXX
Usuari: san / Mostra: AML226
Nom: FAIZA DIABA
Data: 02/07/14 / Ope.: F.DIABA
Experiment: s2pul
Pulse Sequence: s2pul
7.294
9
8
7
6
5
4
3
2
1
ppm

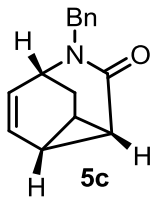

H1 / 400
cdcl3 / Temp: 25C / N.Reg: XXXXXXXXXX
Usuari: san / Mostra: AML226
Nom: FAIZA DIABA
Data: 02/07/14 / Ope.: F.DIABA
Experiment: s2pul
Pulse Sequence: s2pul
128.542
128.078
77.317
76.999
76.682
200
180
160
140
120
100
80
60
40
20
ppm


Bn
H
N
O
Cl
H

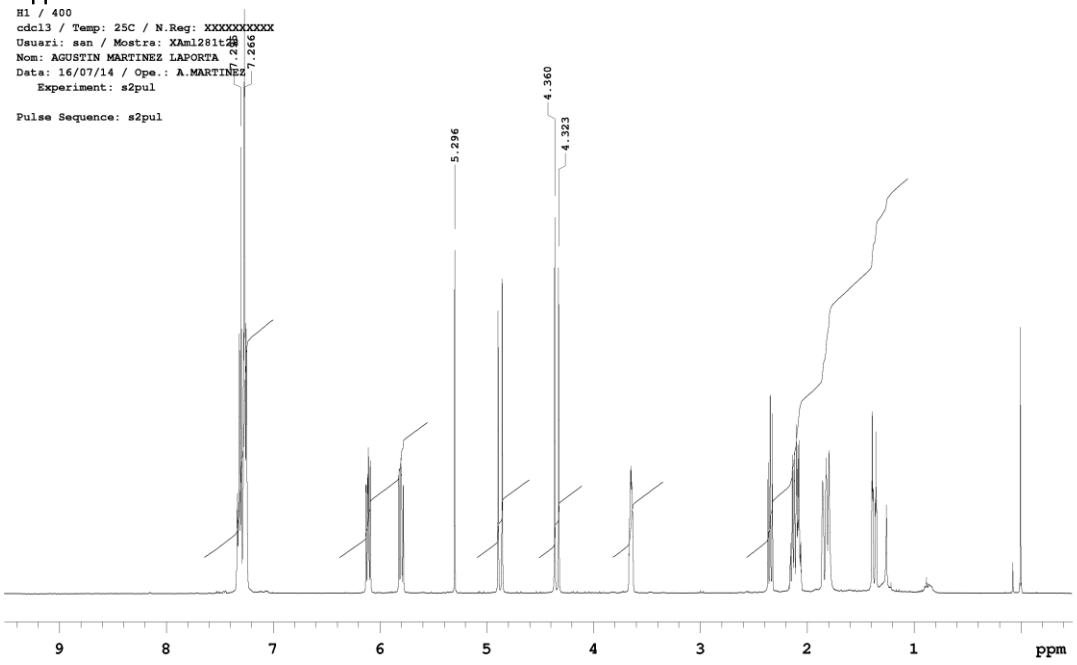
5b

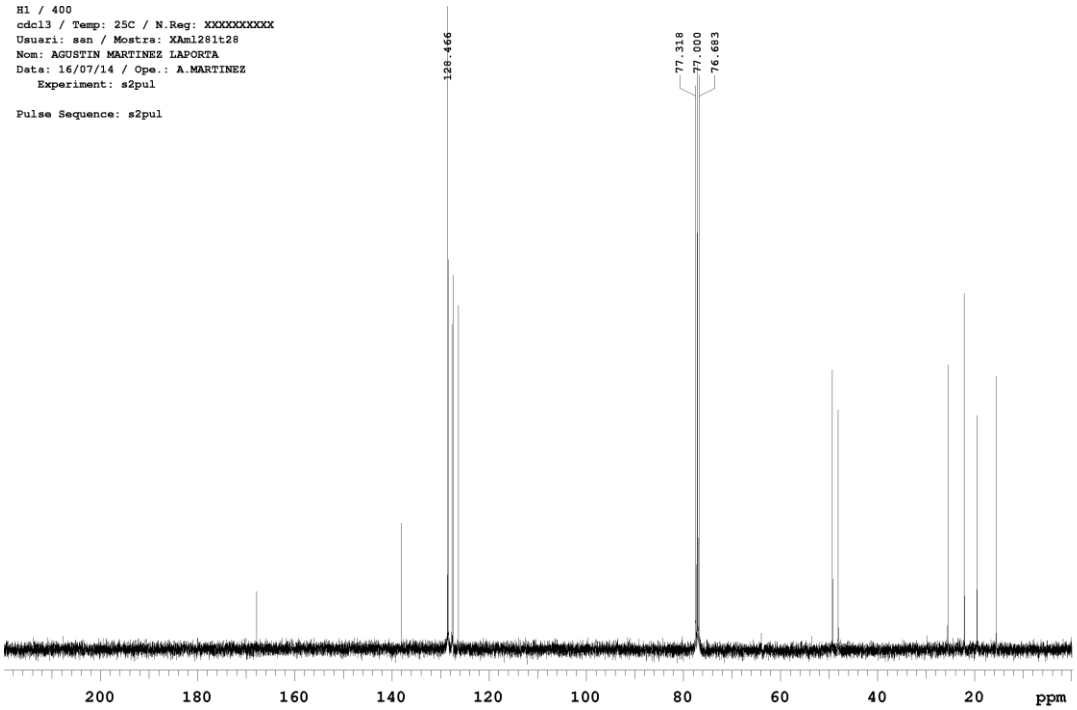

H1 / 400
cdcl3 / Temp: 25C / N.Reg: XXXXXXXXXX
Usuari: san / Mostra: Aml232c3t24
Nom: AGUSTIN MARTINEZ LAPORTA
Data: 15/07/14 / Ope.: A.MARTINEZ
Experiment: s2pul
Pulse Sequence: s2pul
7.282
7.263
5.299
1.596
0.000
9
8
7
6
5
4
3
2
1
ppm

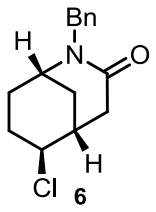

H1 / 400
cdcl3 / Temp: 25C / N.Reg: XXXXXXXXXX
Usuari: san / Mostra: Aml232c3t24
Nom: AGUSTIN MARTINEZ LAPORTA
Data: 15/07/14 / Ope.: A.MARTINEZ
Experiment: s2pul
Pulse Sequence: s2pul
128.614
128.459
77.319
77.001
76.684
200
180
160
140
120
100
80
60
40
20
ppm


Bn
H
N
O
H
H

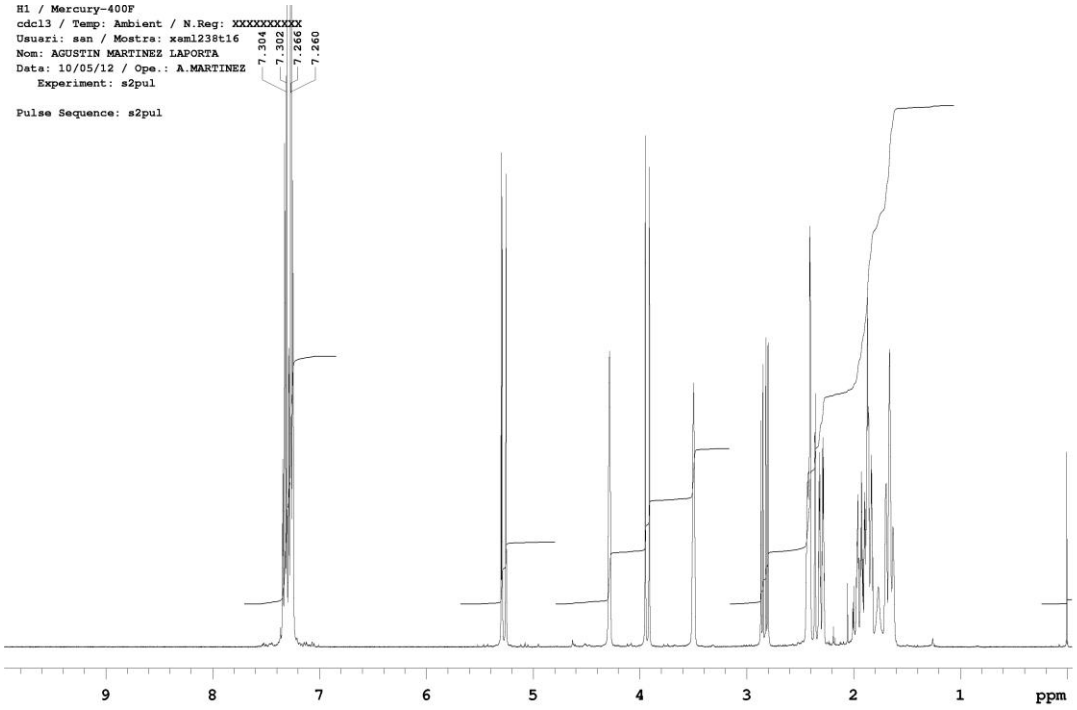
5c

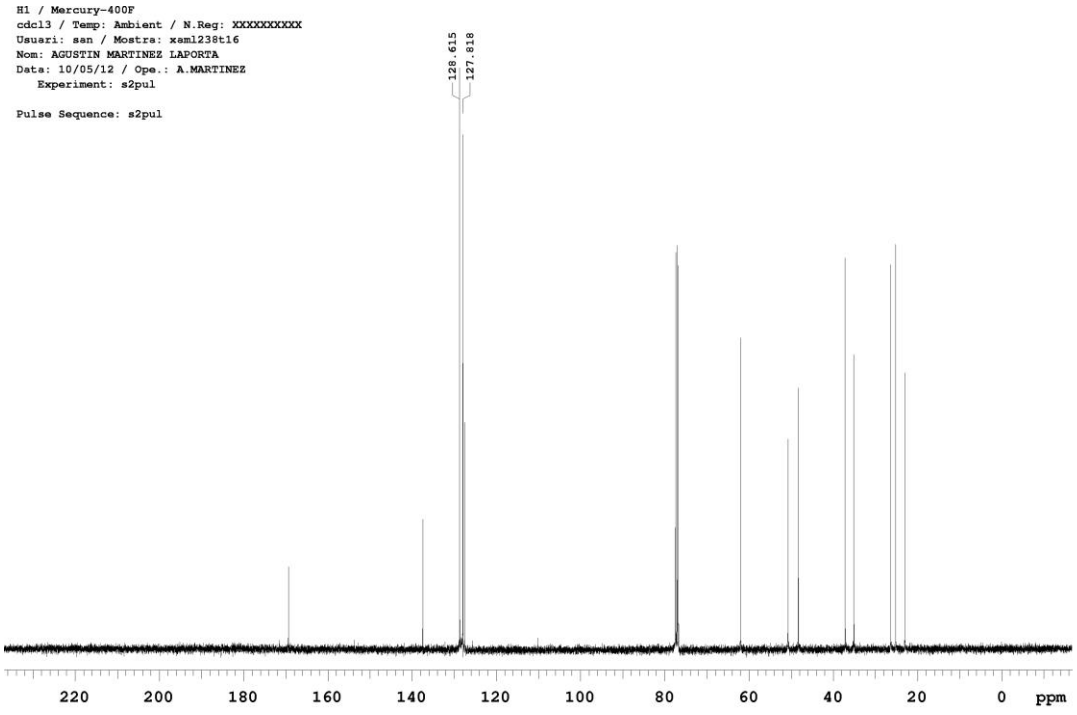

H1 / 400
cdcl3 / Temp: 25C / N.Reg: XXXXXXXXXX
Usuari: san / Mostra: XAml281t28
Nom: AGUSTIN MARTINEZ LAPORTA
Data: 16/07/14 / Ope.: A.MARTINEZ
Experiment: s2pul
Pulse Sequence: s2pul
7.266
5.296
4.360
4.323
9
8
7
6
5
4
3
2
1
ppm

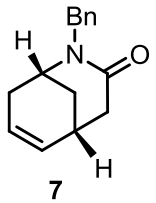

H1 / 400
cdcl3 / Temp: 25C / N.Reg: XXXXXXXXXX
Usuari: san / Mostra: XAml281t28
Nom: AGUSTIN MARTINEZ LAPORTA
Data: 16/07/14 / Ope.: A.MARTINEZ
Experiment: s2pul
Pulse Sequence: s2pul
128.466
77.318
77.000
76.683
200
180
160
140
120
100
80
60
40
20
ppm


Bn
H
N
O
H
Cl

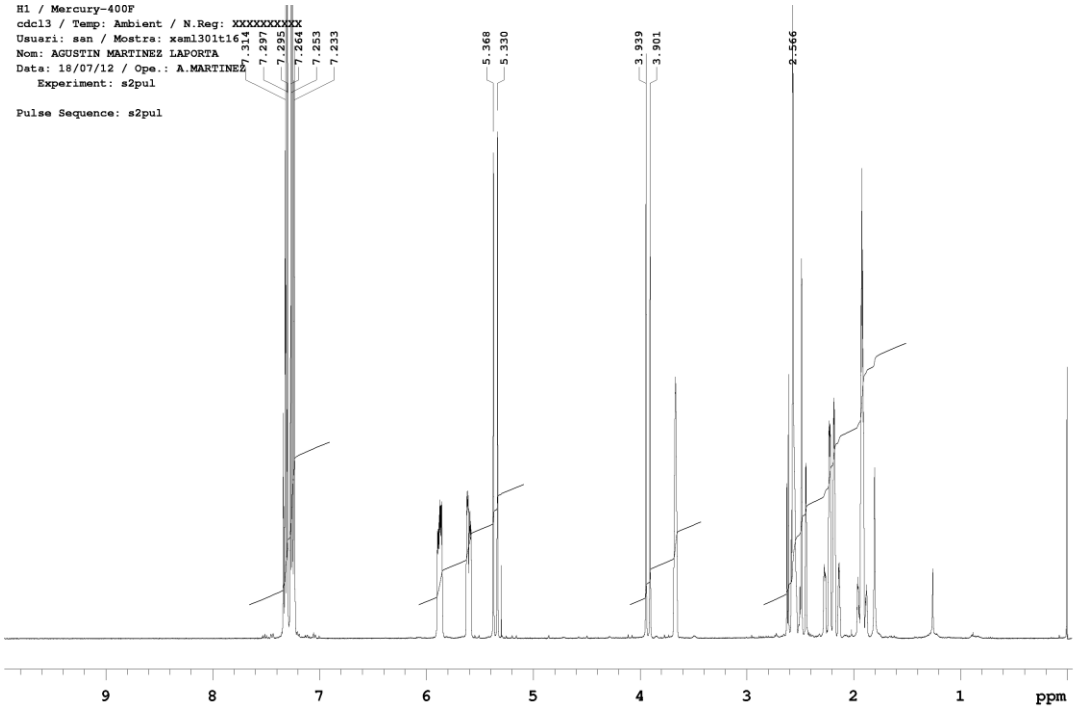
6

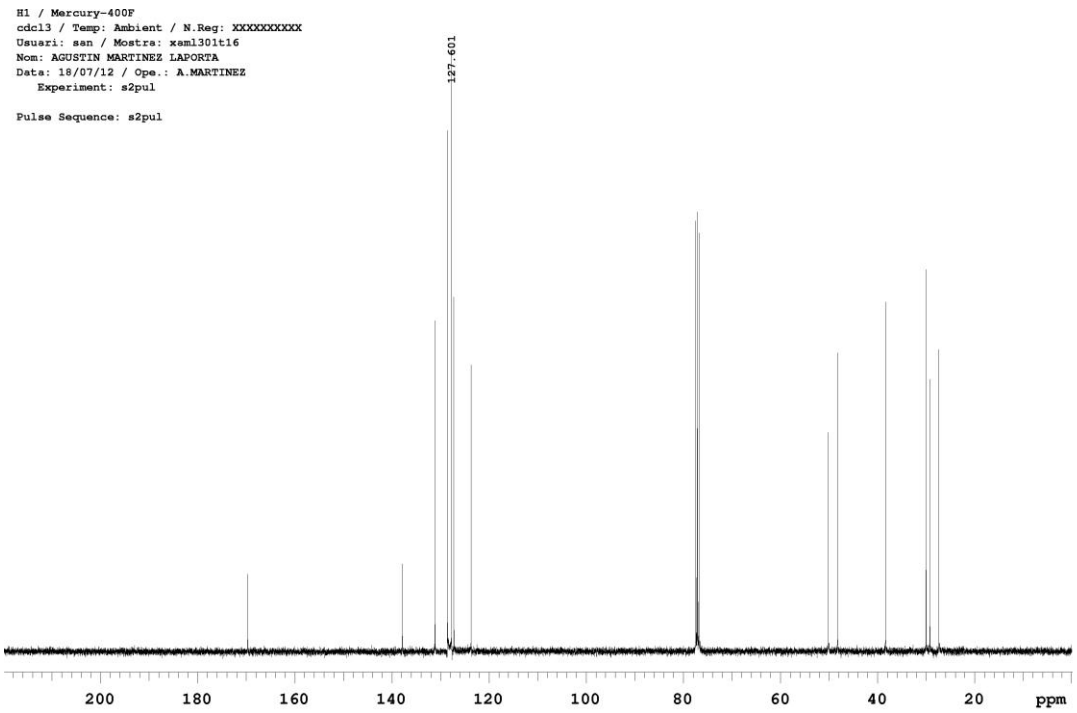

H1 / Mercury-400F
cdcl3 / Temp: Ambient / N.Reg: XXXXXXXXXX
Usuari: san / Mostra: xaml238t16
Nom: AGUSTIN MARTINEZ LAPORTA
Data: 10/05/12 / Ope.: A.MARTINEZ
Experiment: s2pul
Pulse Sequence: s2pul
7.304
7.302
7.266
7.260
9
8
7
6
5
4
3
2
1
ppm

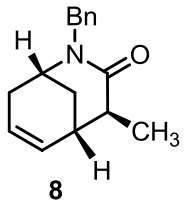

H1 / Mercury-400F
cdcl3 / Temp: Ambient / N.Reg: XXXXXXXXXX
Usuari: san / Mostra: xaml238t16
Nom: AGUSTIN MARTINEZ LAPORTA
Data: 10/05/12 / Ope.: A.MARTINEZ
Experiment: s2pul
Pulse Sequence: s2pul
128.615
127.818
220
200
180
160
140
120
100
80
60
40
20
0
ppm


Bn
H
N
O
H

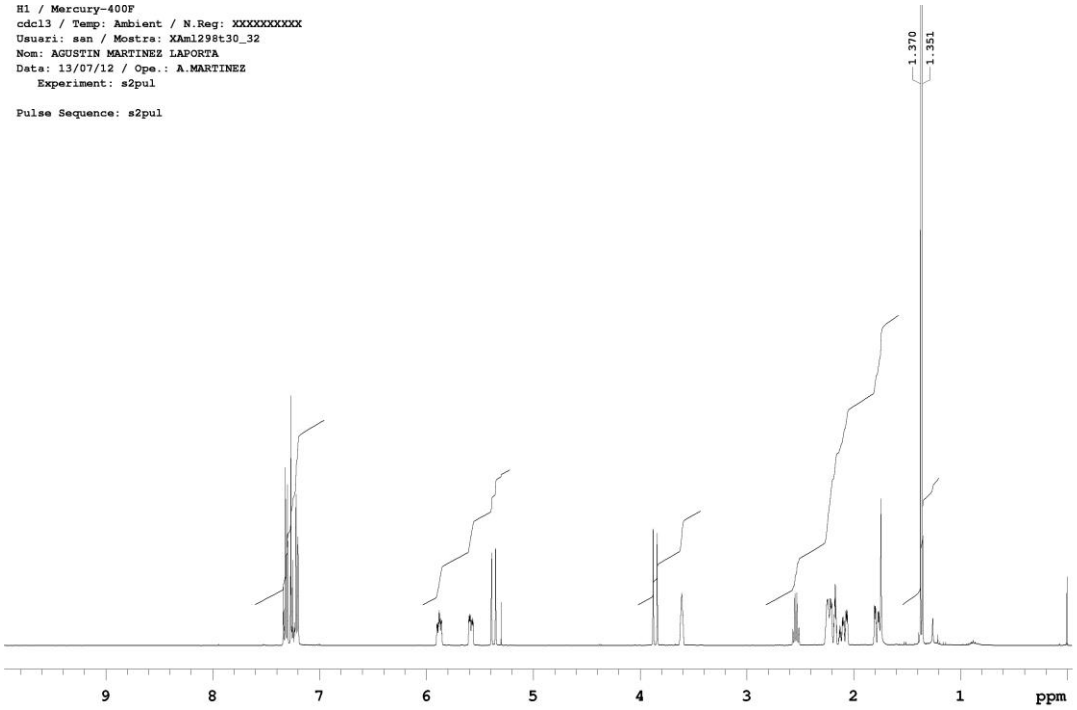
7

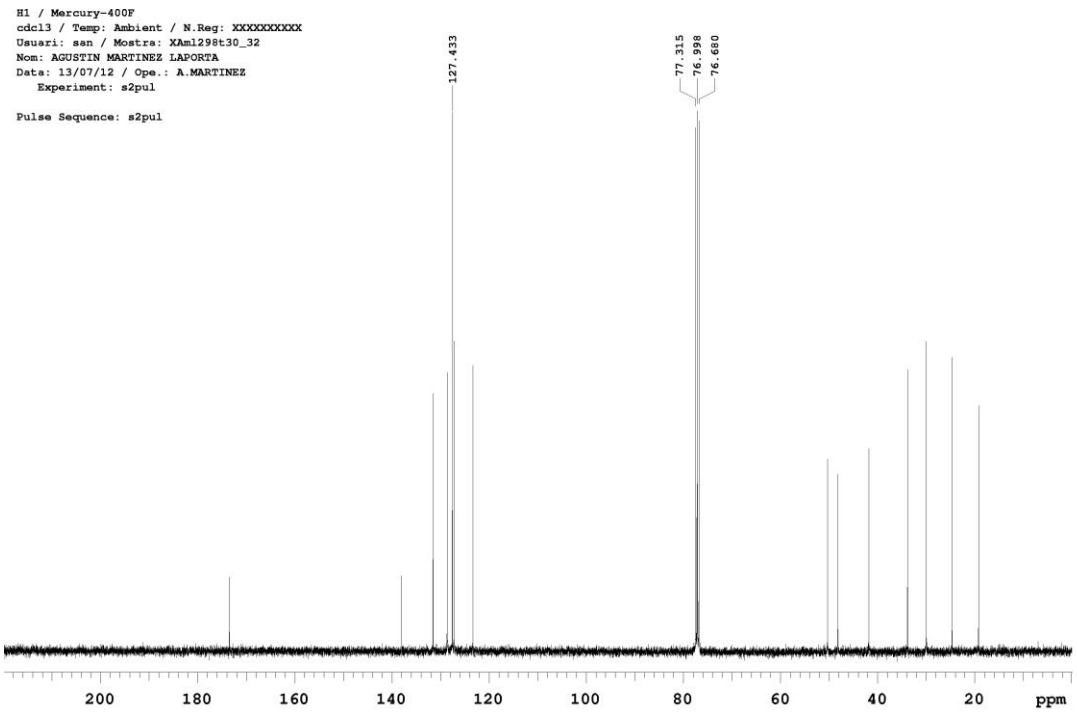

H1 / Mercury-400F
cdcl3 / Temp: Ambient / N.Reg: XXXXXXXXXX
Usuari: san / Mostra: xaml301t16
Nom: AGUSTIN MARTINEZ LAPORTA
Data: 18/07/12 / Ope.: A.MARTINEZ
Experiment: s2pul
Pulse Sequence: s2pul
7.314
7.297
7.295
7.264
7.253
7.233
5.368
5.330
3.939
3.901
2.566
9
8
7
6
5
4
3
2
1
ppm

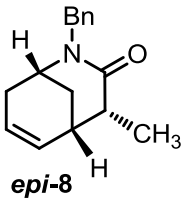

H1 / Mercury-400F
cdcl3 / Temp: Ambient / N.Reg: XXXXXXXXXX
Usuari: san / Mostra: xaml301t16
Nom: AGUSTIN MARTINEZ LAPORTA
Data: 18/07/12 / Ope.: A.MARTINEZ
Experiment: s2pul
Pulse Sequence: s2pul
127.601
200
180
160
140
120
100
80
60
40
20
ppm


Bn
H
N
O
CH3
H

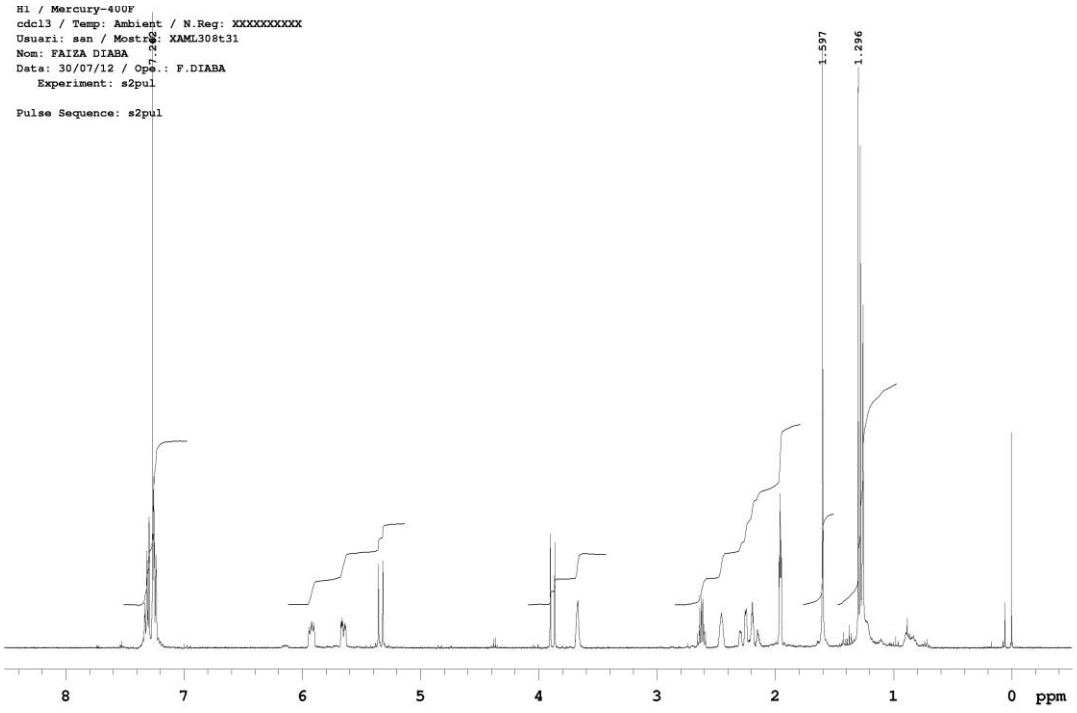
8

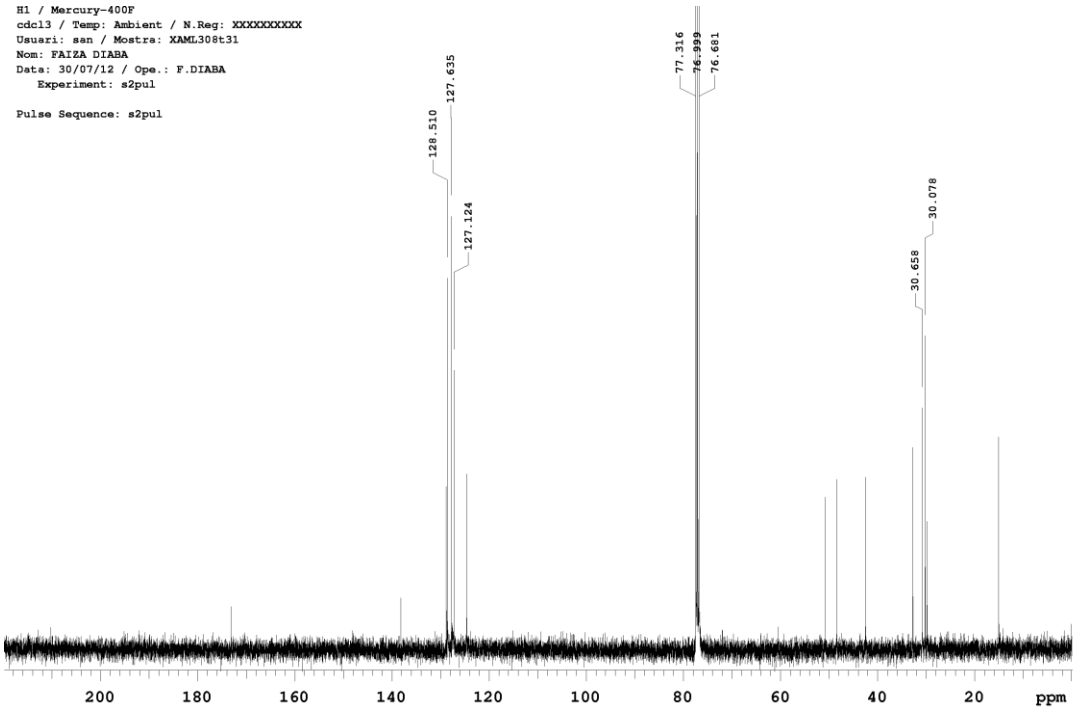

H1 / Mercury-400F
cdcl3 / Temp: Ambient / N.Reg: XXXXXXXXXX
Usuari: san / Mostra: XAml298t30_32
Nom: AGUSTIN MARTINEZ LAPORTA
Data: 13/07/12 / Ope.: A.MARTINEZ
Experiment: s2pul
Pulse Sequence: s2pul
1.370
1.351
9
8
7
6
5
4
3
2
1
ppm

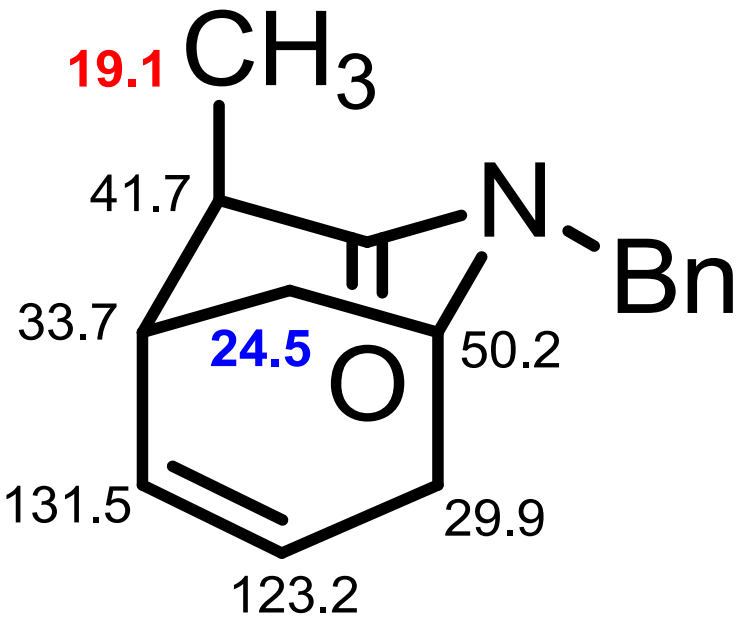

H1 / Mercury-400F
cdcl3 / Temp: Ambient / N.Reg: XXXXXXXXXX
Usuari: san / Mostra: XAml298t30_32
Nom: AGUSTIN MARTINEZ LAPORTA
Data: 13/07/12 / Ope.: A.MARTINEZ
Experiment: s2pul
Pulse Sequence: s2pul
127.433
77.315
76.998
76.680
200
180
160
140
120
100
80
60
40
20
ppm


Bn
H
N
O
CH3
H

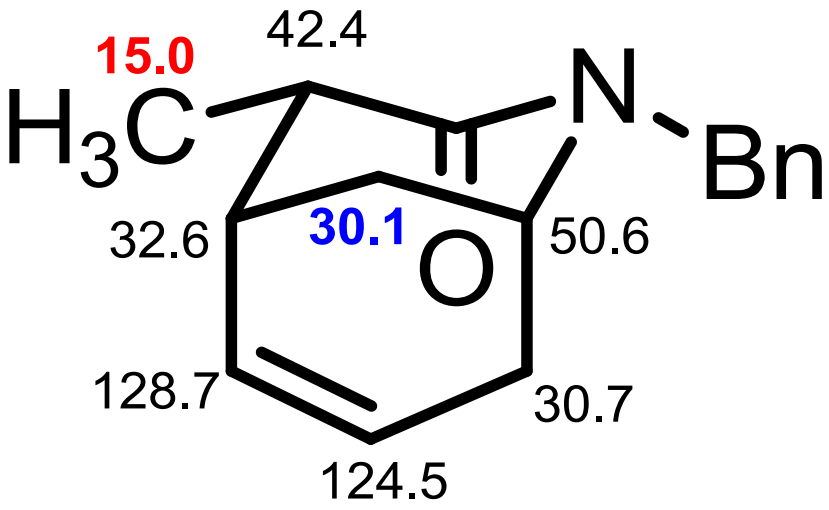
***epi*-8**


H1 / Mercury-400F
cdcl3 / Temp: Ambient / N.Reg: XXXXXXXXXX
Usuari: san / Mostra: XAML308t31
Nom: FAIZA DIABA
Data: 30/07/12 / Ope.: F.DIABA
Experiment: s2pul
Pulse Sequence: s2pul
7.296
1.597
1.296
8
7
6
5
4
3
2
1
0
ppm


H1 / Mercury-400F
cdcl3 / Temp: Ambient / N.Reg: XXXXXXXXXX
Usuari: san / Mostra: XAML308t31
Nom: FAIZA DIABA
Data: 30/07/12 / Ope.: F.DIABA
Experiment: s2pul
Pulse Sequence: s2pul
128.510
127.635
127.124
77.316
76.999
76.681
30.658
30.078
200
180
160
140
120
100
80
60
40
20
ppm

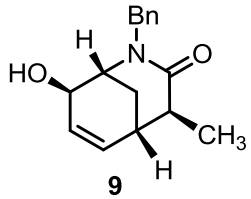


8

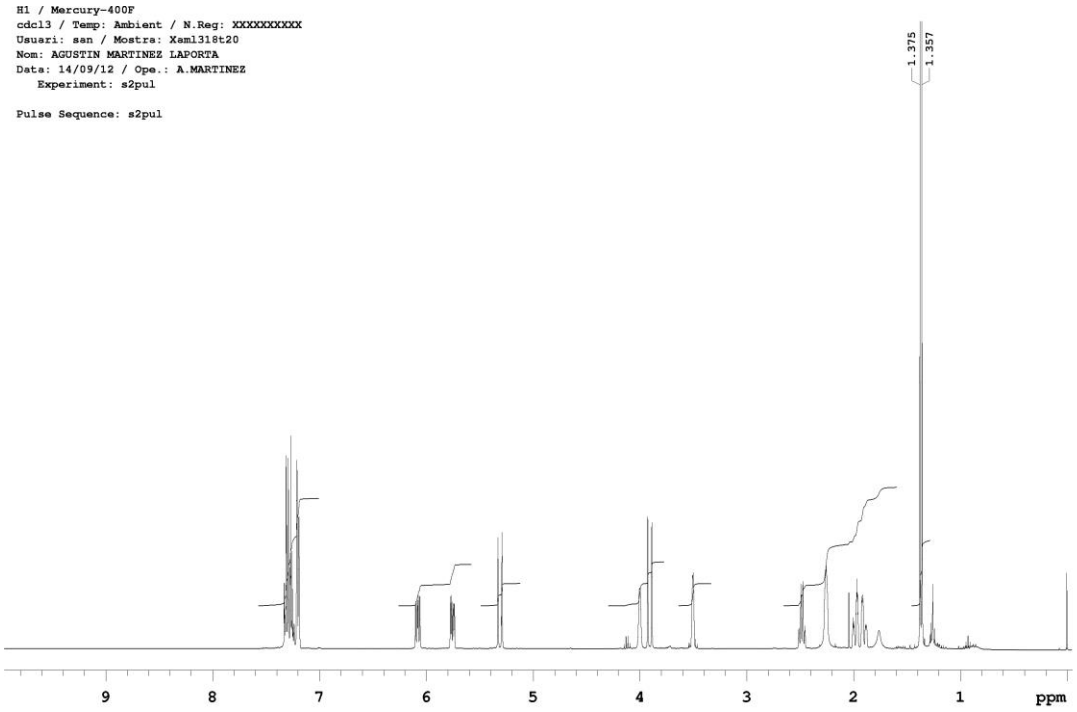


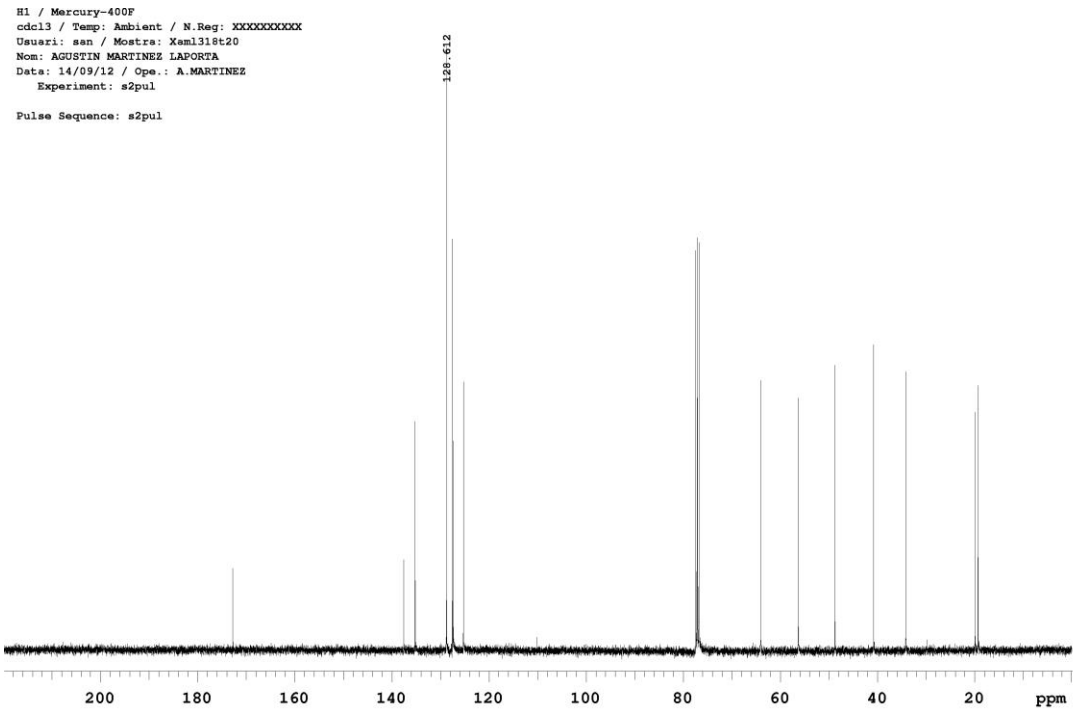
***epi*-8**

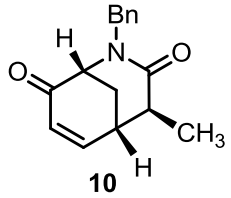
^{13}C chemical shifts of 8 and *epi*-8


Bn
H
N
O
HO
CH3
H

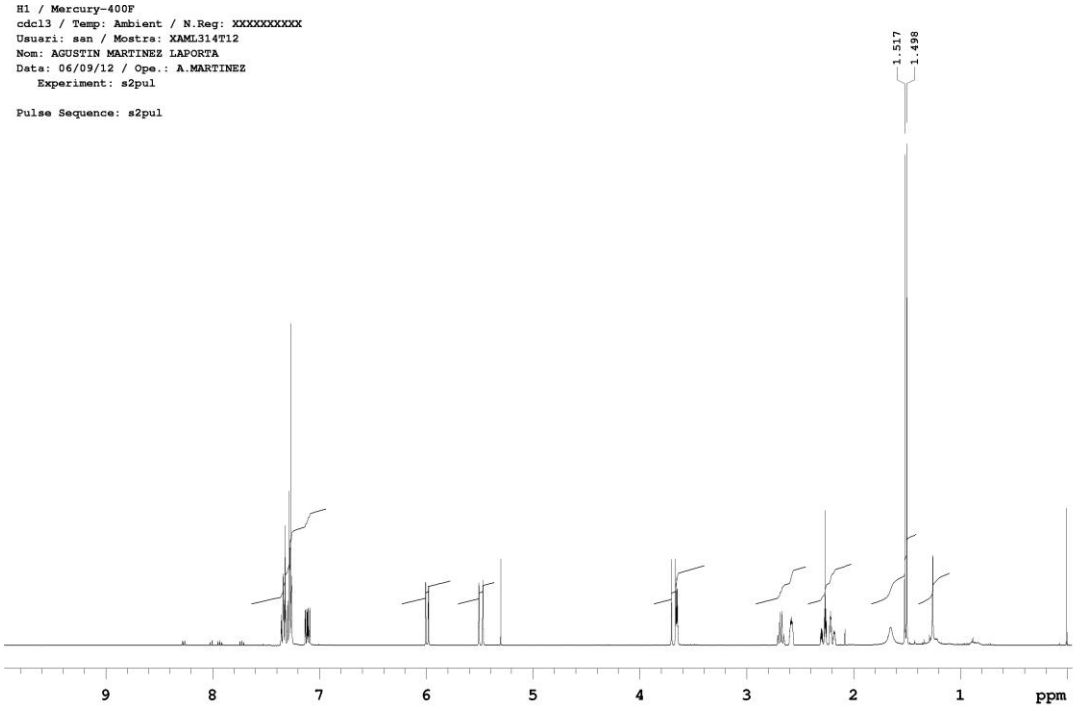
9

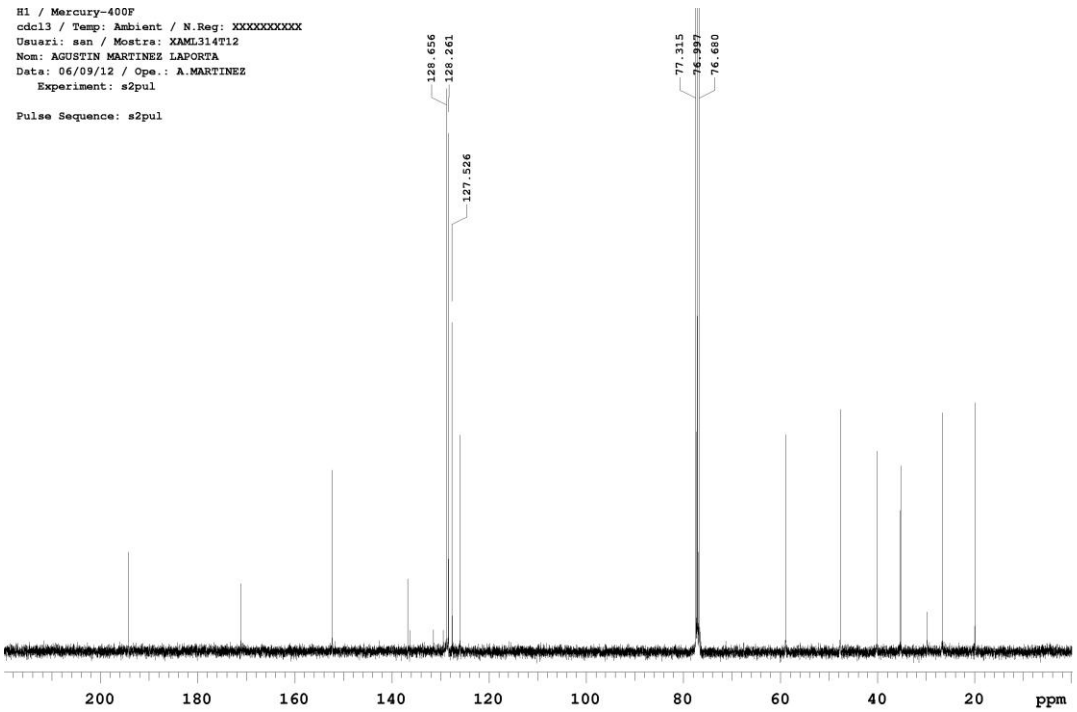

H1 / Mercury-400F
cdcl3 / Temp: Ambient / N.Reg: XXXXXXXXX
Usuari: san / Mostra: Xaml318t20
Nom: AGUSTIN MARTINEZ LAPORTA
Data: 14/09/12 / Ope.: A.MARTINEZ
Experiment: s2pul
Pulse Sequence: s2pul
1.375
1.357
9
8
7
6
5
4
3
2
1
ppm

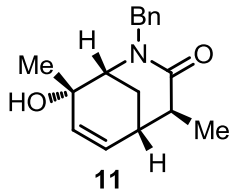

H1 / Mercury-400F
cdcl3 / Temp: Ambient / N.Reg: XXXXXXXXX
Usuari: san / Mostra: Xaml318t20
Nom: AGUSTIN MARTINEZ LAPORTA
Data: 14/09/12 / Ope.: A.MARTINEZ
Experiment: s2pul
Pulse Sequence: s2pul
128.612
200
180
160
140
120
100
80
60
40
20
ppm


Bn
H
N
O
O
CH3
H

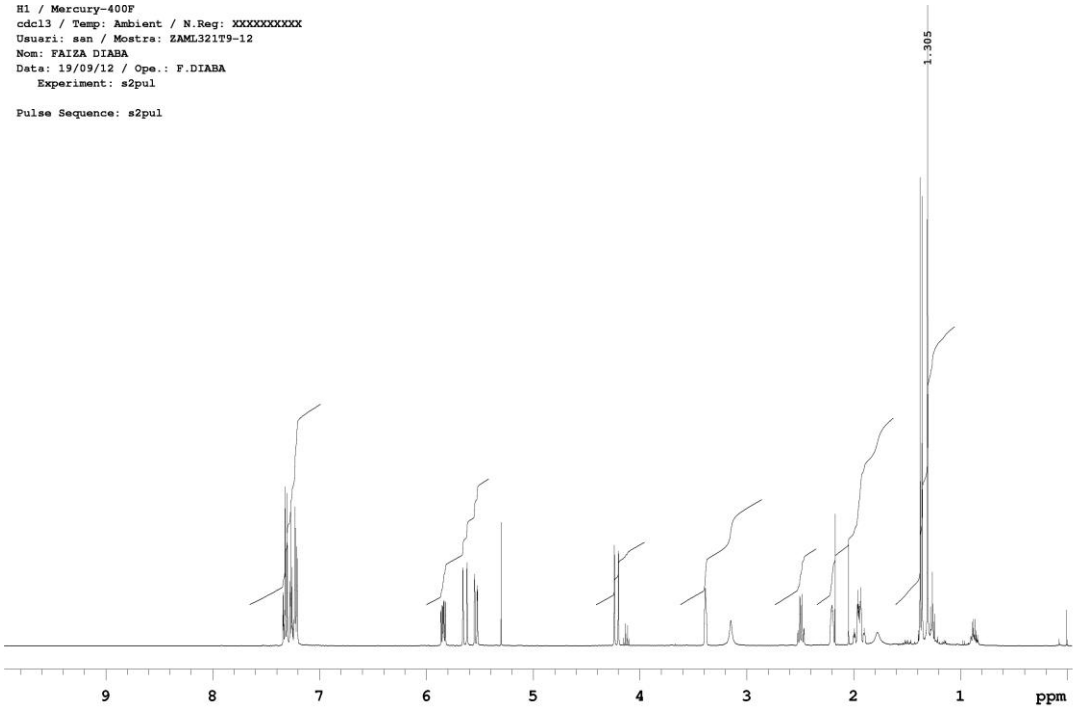
10

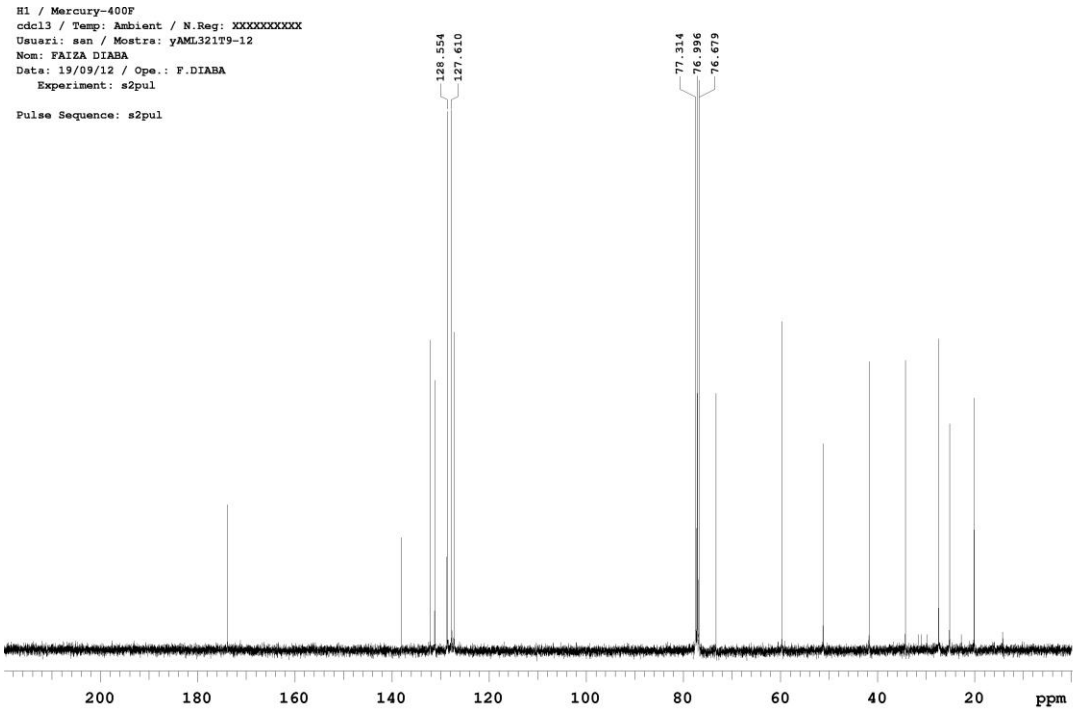

H1 / Mercury-400F
cdcl3 / Temp: Ambient / N.Reg: XXXXXXXXXX
Usuari: san / Mostra: XAML314T12
Nom: AGUSTIN MARTINEZ LAPORTA
Data: 06/09/12 / Ope.: A.MARTINEZ
Experiment: s2pul
Pulse Sequence: s2pul
1.517
1.498
9
8
7
6
5
4
3
2
1
ppm

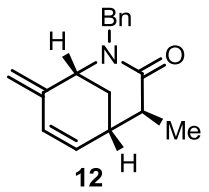

H1 / Mercury-400F
cdcl3 / Temp: Ambient / N.Reg: XXXXXXXXXX
Usuari: san / Mostra: XAML314T12
Nom: AGUSTIN MARTINEZ LAPORTA
Data: 06/09/12 / Ope.: A.MARTINEZ
Experiment: s2pul
Pulse Sequence: s2pul
128.656
128.261
127.526
77.315
76.997
76.680
200
180
160
140
120
100
80
60
40
20
ppm


Bn
H
N
O
Me
HO
Me
H

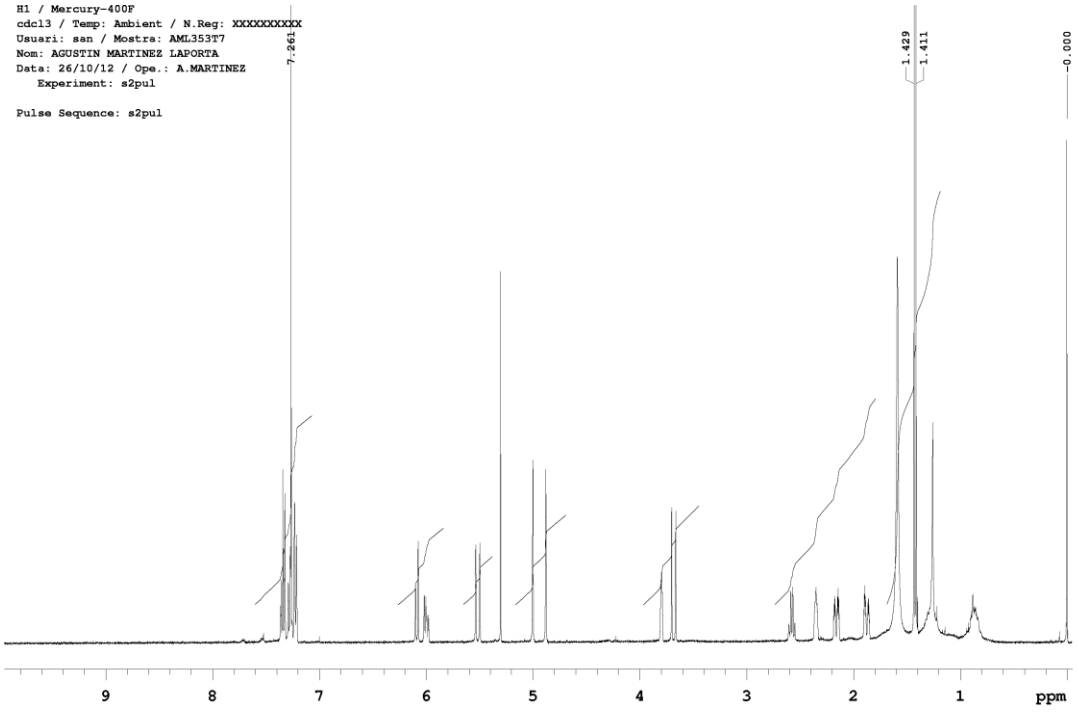
11

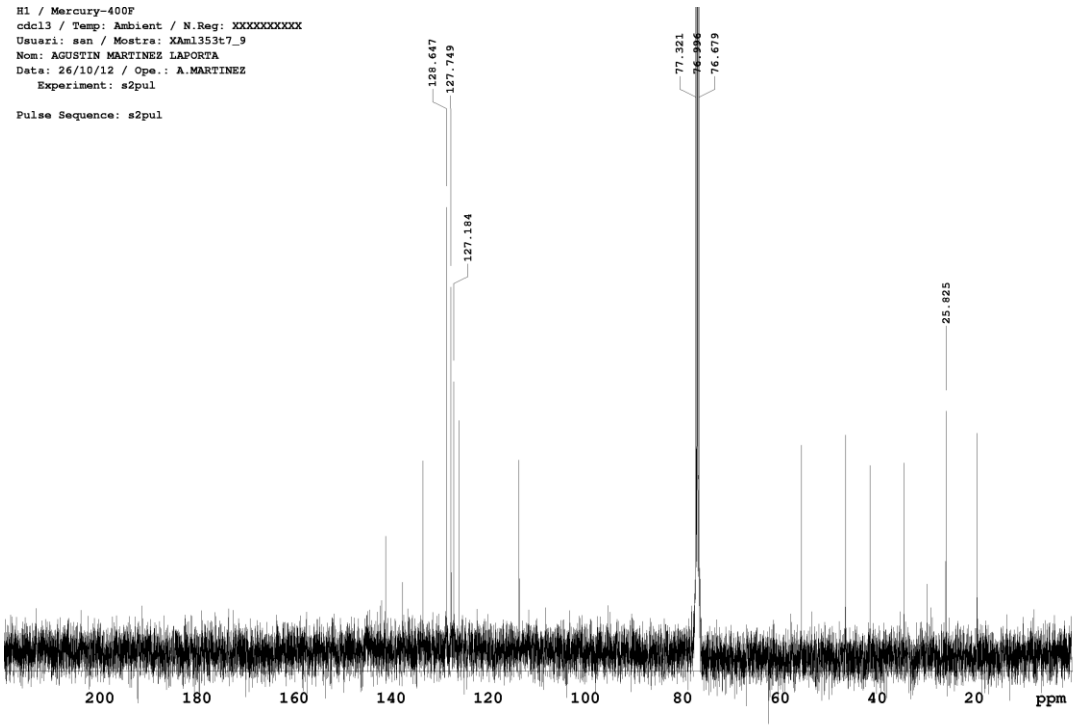

H1 / Mercury-400F
cdcl3 / Temp: Ambient / N.Reg: XXXXXXXXXX
Usuari: san / Mostra: ZAML321T9-12
Nom: FAIZA DIABA
Data: 19/09/12 / Ope.: F.DIABA
Experiment: s2pul
Pulse Sequence: s2pul
1.305
9
8
7
6
5
4
3
2
1
ppm

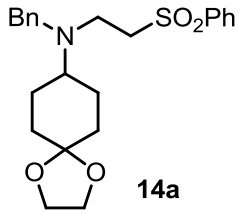

H1 / Mercury-400F
cdcl3 / Temp: Ambient / N.Reg: XXXXXXXXXX
Usuari: san / Mostra: yAML321T9-12
Nom: FAIZA DIABA
Data: 19/09/12 / Ope.: F.DIABA
Experiment: s2pul
Pulse Sequence: s2pul
128.554
127.610
77.314
76.996
76.679
200
180
160
140
120
100
80
60
40
20
ppm


Bn
H
N
O
Me
H

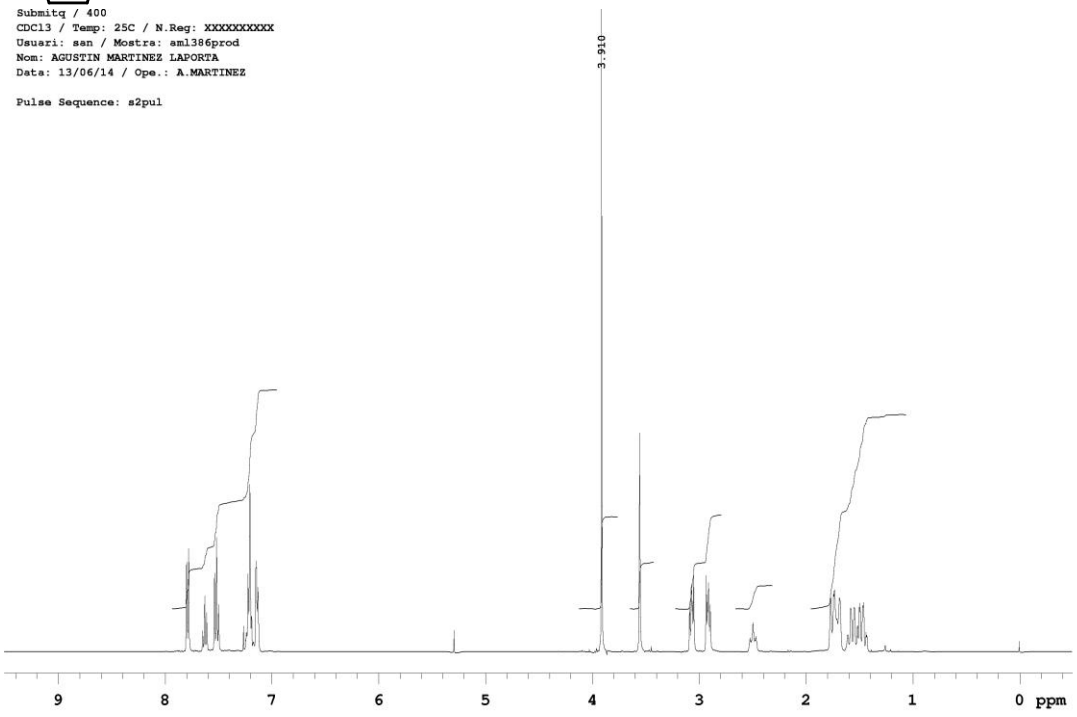
12

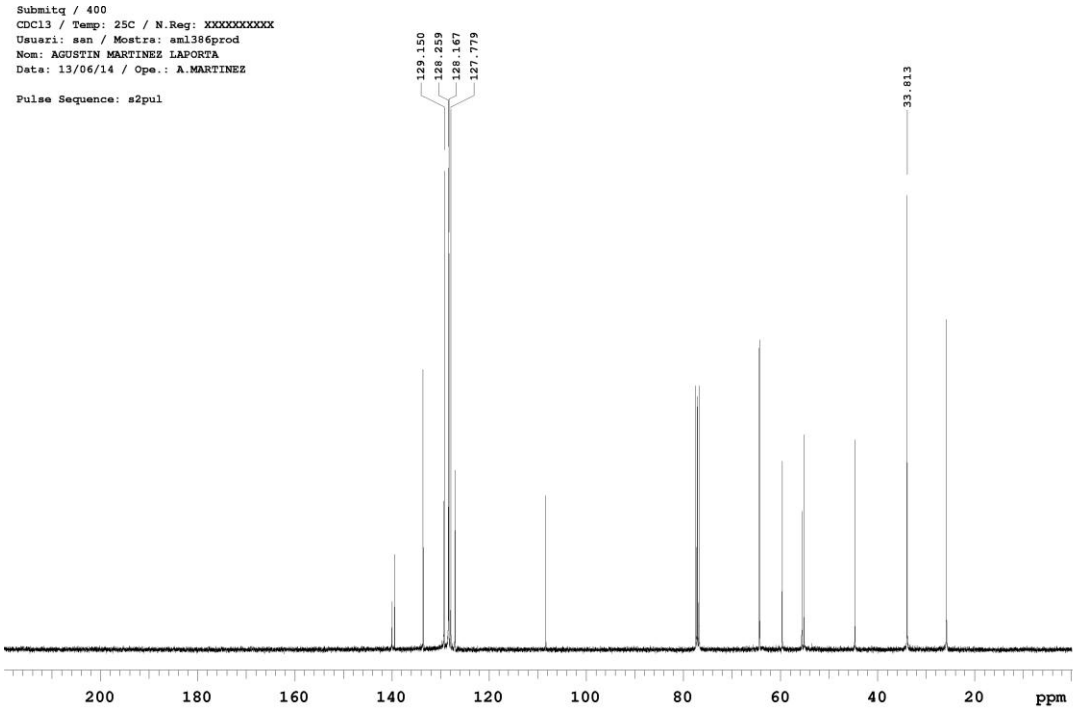

H1 / Mercury-400F
cdcl3 / Temp: Ambient / N.Reg: XXXXXXXXXX
Usuari: san / Mostra: AML353T7
Nom: AGUSTIN MARTINEZ LAPORTA
Data: 26/10/12 / Ope.: A.MARTINEZ
Experiment: s2pul
Pulse Sequence: s2pul
7.261
1.429
1.411
0.000
9
8
7
6
5
4
3
2
1
ppm

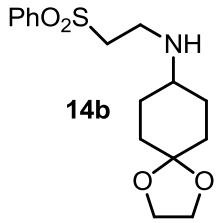

H1 / Mercury-400F
cdcl3 / Temp: Ambient / N.Reg: XXXXXXXXXX
Usuari: san / Mostra: XAml353t7_9
Nom: AGUSTIN MARTINEZ LAPORTA
Data: 26/10/12 / Ope.: A.MARTINEZ
Experiment: s2pul
Pulse Sequence: s2pul
128.647
127.749
127.184
77.321
76.996
76.679
25.825
200
180
160
140
120
100
80
60
40
20
ppm


Bn
N
SO2Ph
O
O

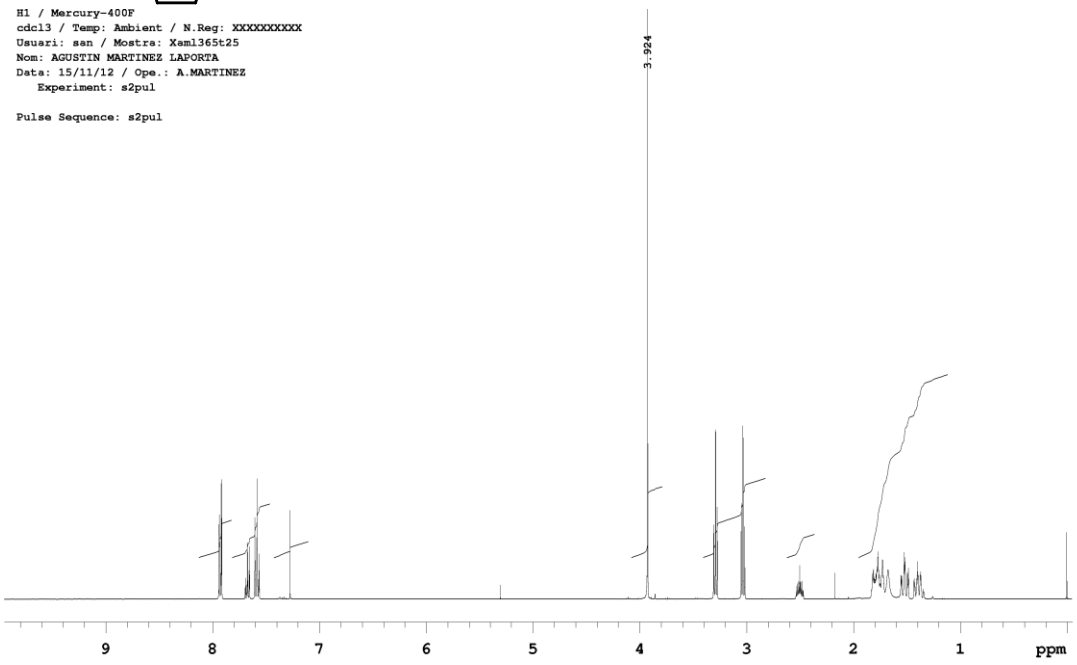
14a

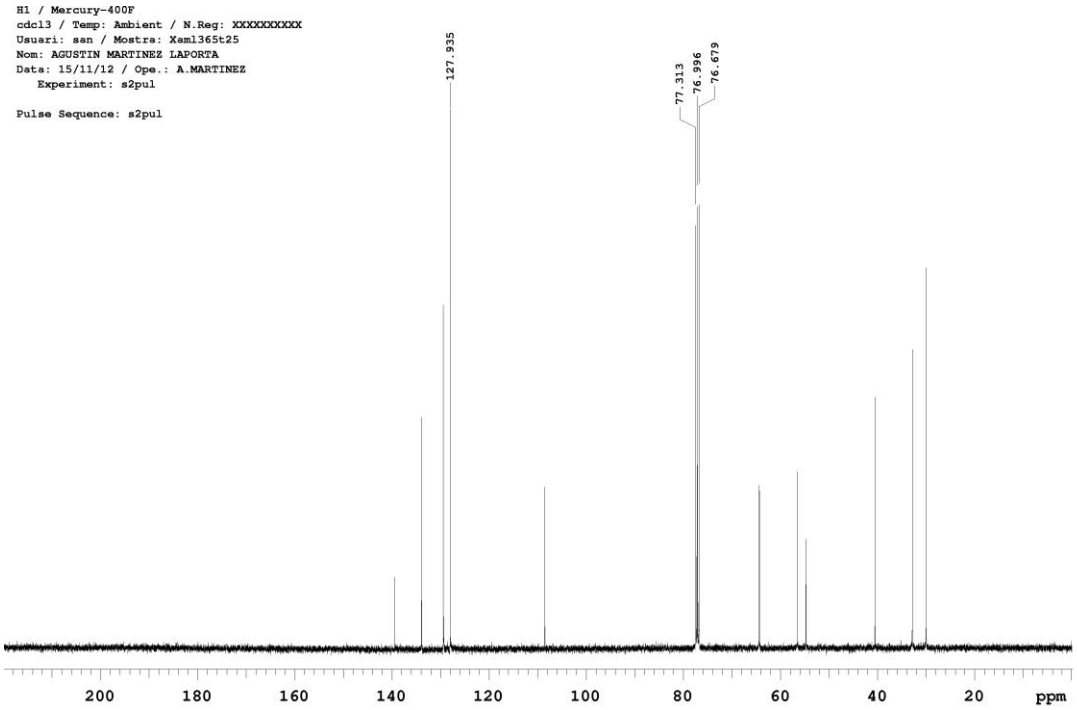

Submitq / 400
CDCl3 / Temp: 25C / N.Reg: XXXXXXXXXX
Usuari: san / Mostra: aml386prod
Nom: AGUSTIN MARTINEZ LAPORTA
Data: 13/06/14 / Ope.: A.MARTINEZ
Pulse Sequence: s2pul
3.910
9
8
7
6
5
4
3
2
1
0 ppm

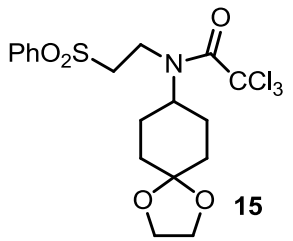

Submitq / 400
CDCl3 / Temp: 25C / N.Reg: XXXXXXXXXX
Usuari: san / Mostra: aml386prod
Nom: AGUSTIN MARTINEZ LAPORTA
Data: 13/06/14 / Ope.: A.MARTINEZ
Pulse Sequence: s2pul
129.150
128.259
128.167
127.779
33.813
200
180
160
140
120
100
80
60
40
20
ppm


PhO2S
NH
O
O

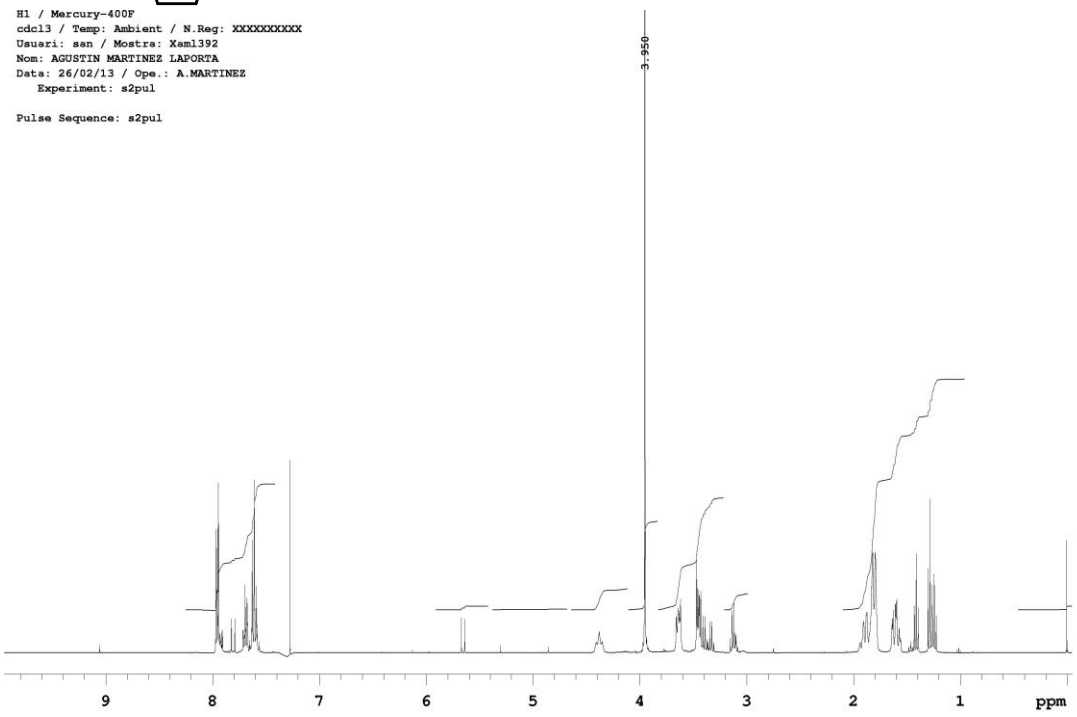
14b

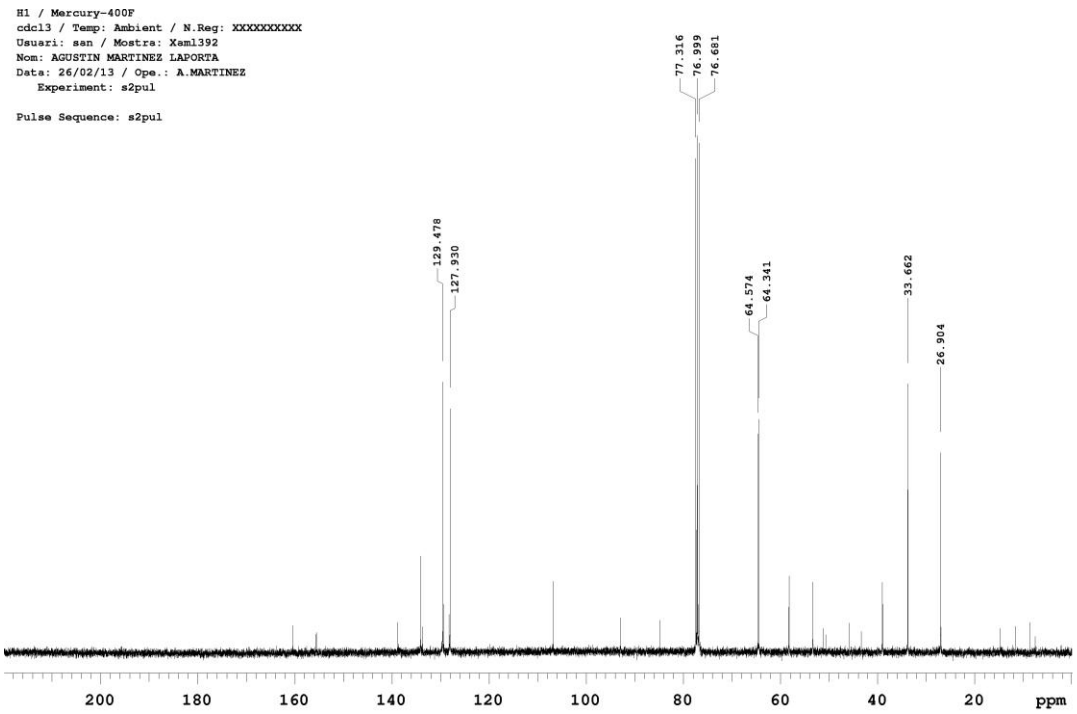

H1 / Mercury-400F
cdcl3 / Temp: Ambient / N.Reg: XXXXXXXXXX
Usuari: san / Mostra: Xaml365t25
Nom: AGUSTIN MARTINEZ LAPORTA
Data: 15/11/12 / Ope.: A.MARTINEZ
Experiment: s2pul
Pulse Sequence: s2pul
3.924
9
8
7
6
5
4
3
2
1
ppm

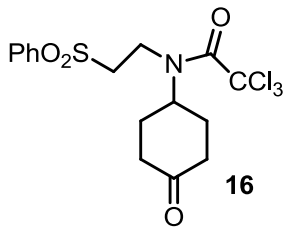

H1 / Mercury-400F
cdcl3 / Temp: Ambient / N.Reg: XXXXXXXXXX
Usuari: san / Mostra: Xaml365t25
Nom: AGUSTIN MARTINEZ LAPORTA
Data: 15/11/12 / Ope.: A.MARTINEZ
Experiment: s2pul
Pulse Sequence: s2pul
127.935
77.313
76.996
76.679
200
180
160
140
120
100
80
60
40
20
ppm


PhO2S
N
O
CCl3
O
O

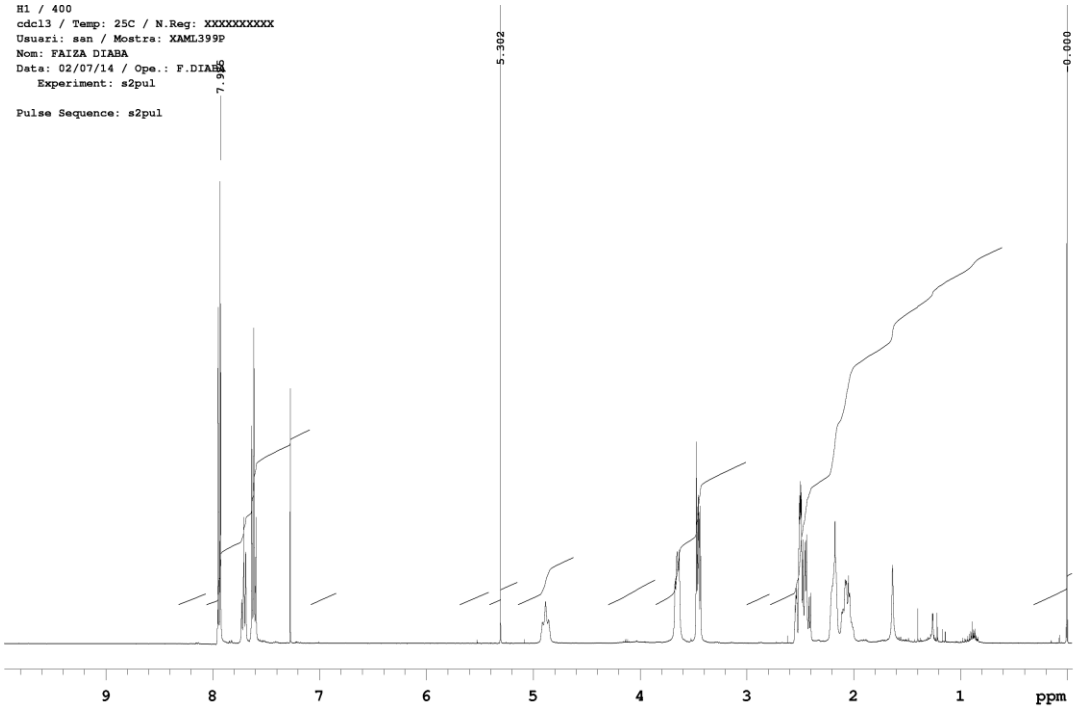
15

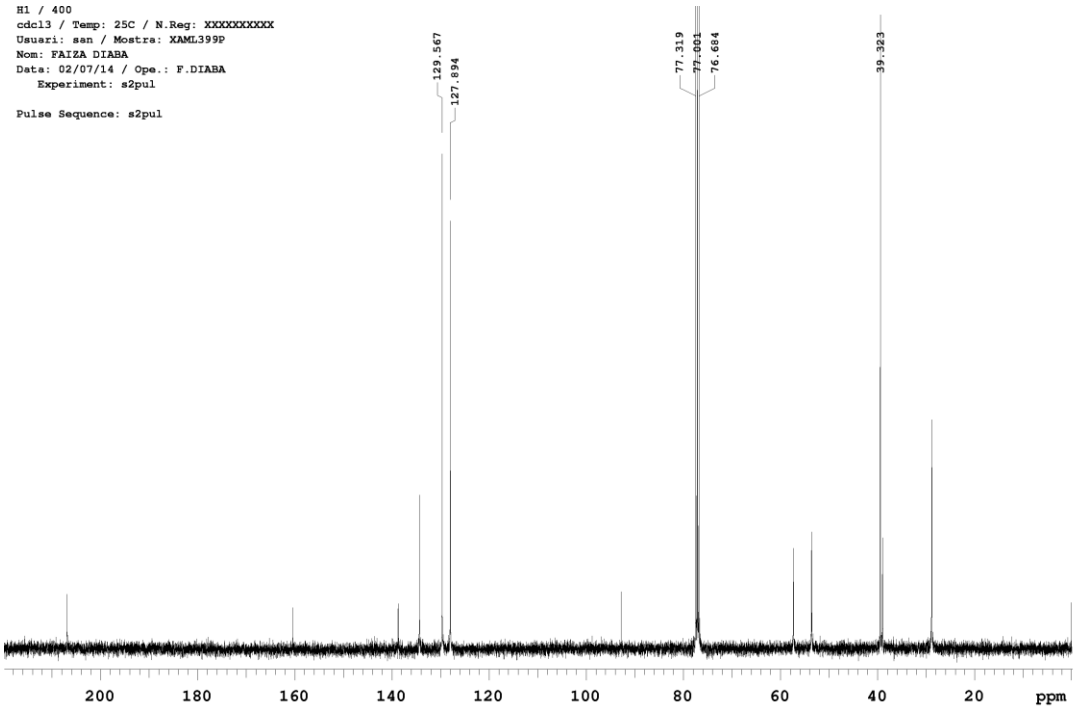

H1 / Mercury-400F
cdcl3 / Temp: Ambient / N.Reg: XXXXXXXXXX
Usuari: san / Mostra: Xaml392
Nom: AGUSTIN MARTINEZ LAPORTA
Data: 26/02/13 / Ope.: A.MARTINEZ
Experiment: s2pul
Pulse Sequence: s2pul
3.950
9
8
7
6
5
4
3
2
1
ppm

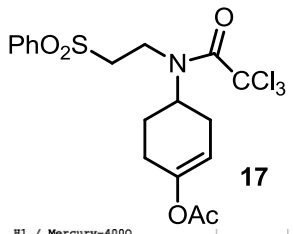

H1 / Mercury-400F
cdcl3 / Temp: Ambient / N.Reg: XXXXXXXXXX
Usuari: san / Mostra: Xaml392
Nom: AGUSTIN MARTINEZ LAPORTA
Data: 26/02/13 / Ope.: A.MARTINEZ
Experiment: s2pul
Pulse Sequence: s2pul
77.316
76.999
76.681
129.478
127.930
64.574
64.341
33.662
26.904
200
180
160
140
120
100
80
60
40
20
ppm


PhO2S
N
O
CCl3
O

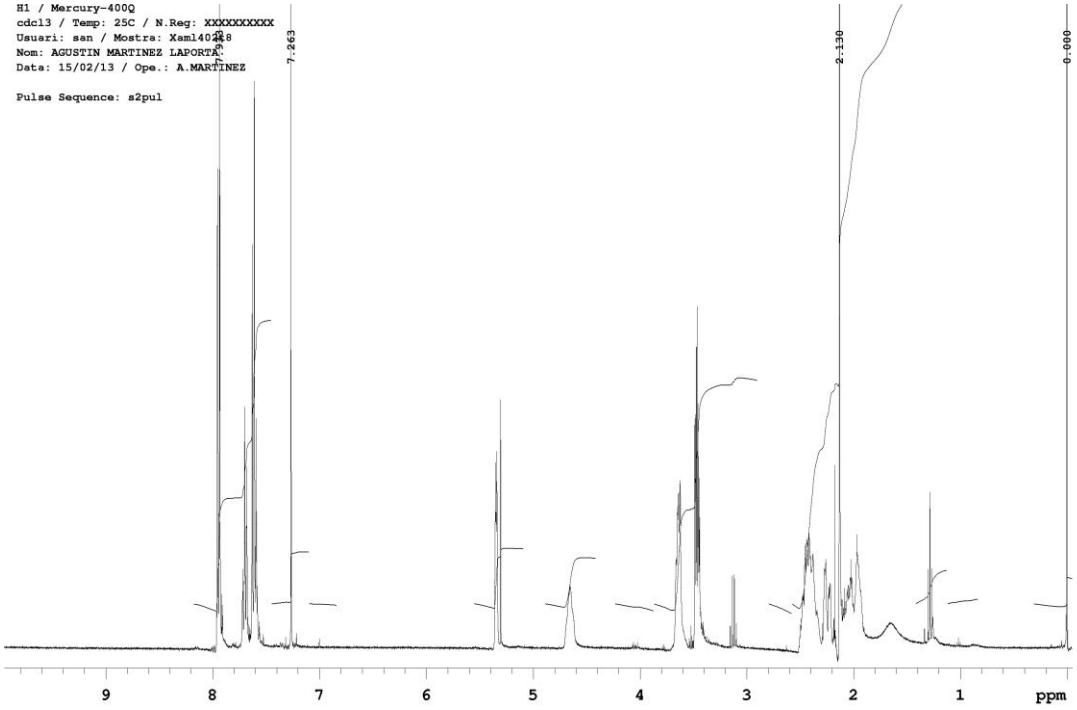
16

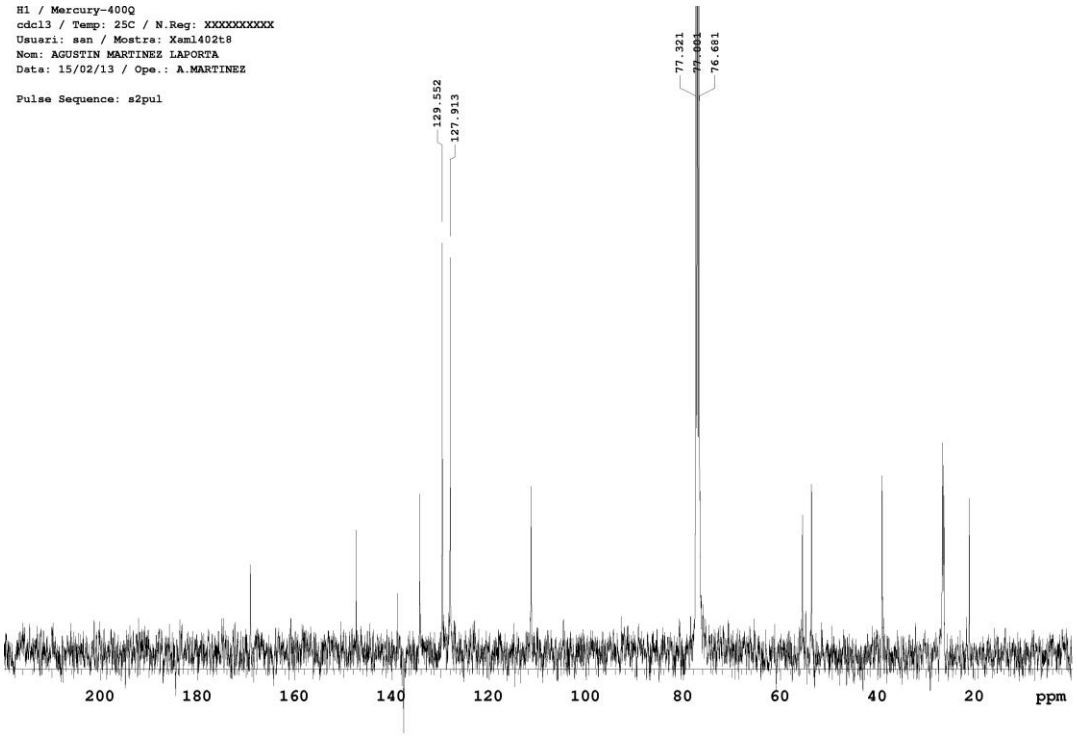

H1 / 400
cdcl3 / Temp: 25C / N.Reg: XXXXXXXXXX
Usuari: san / Mostra: XAML399P
Nom: FAIZA DIABA
Data: 02/07/14 / Ope.: F.DIABA
Experiment: s2pul
Pulse Sequence: s2pul
7.980
5.302
0.000
9
8
7
6
5
4
3
2
1
ppm

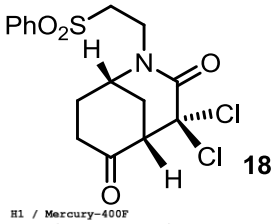

H1 / 400
cdcl3 / Temp: 25C / N.Reg: XXXXXXXXXX
Usuari: san / Mostra: XAML399P
Nom: FAIZA DIABA
Data: 02/07/14 / Ope.: F.DIABA
Experiment: s2pul
Pulse Sequence: s2pul
129.567
127.894
77.319
77.001
76.684
39.323
200
180
160
140
120
100
80
60
40
20
ppm


PhO2S
N
O
CCl3
OAc

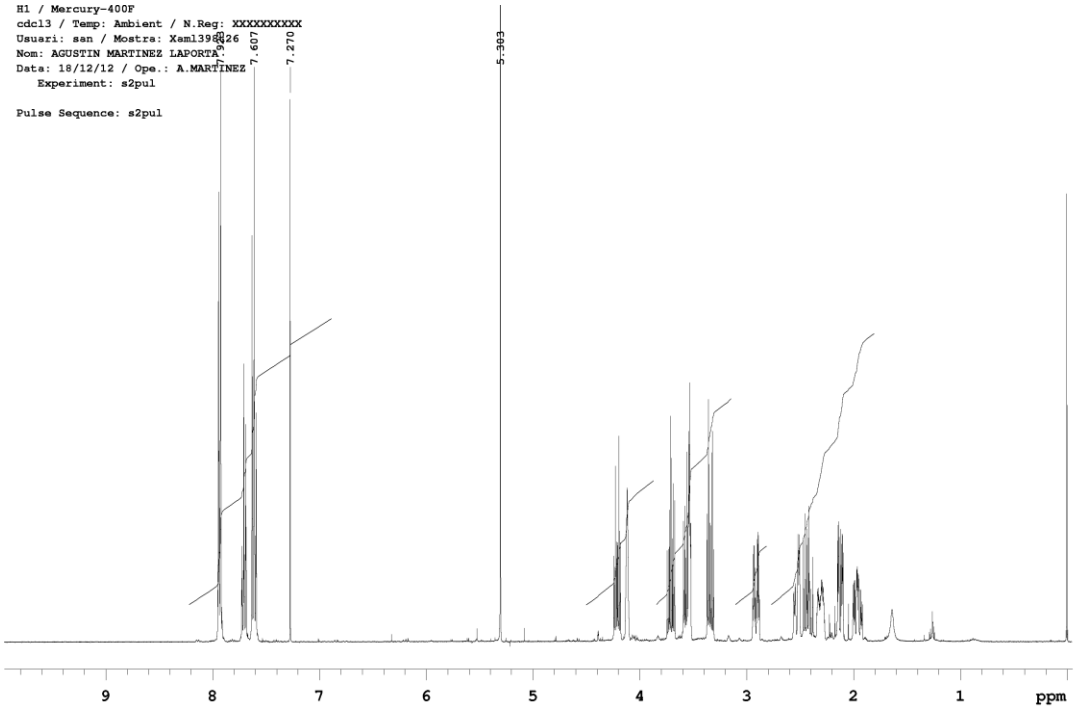
17

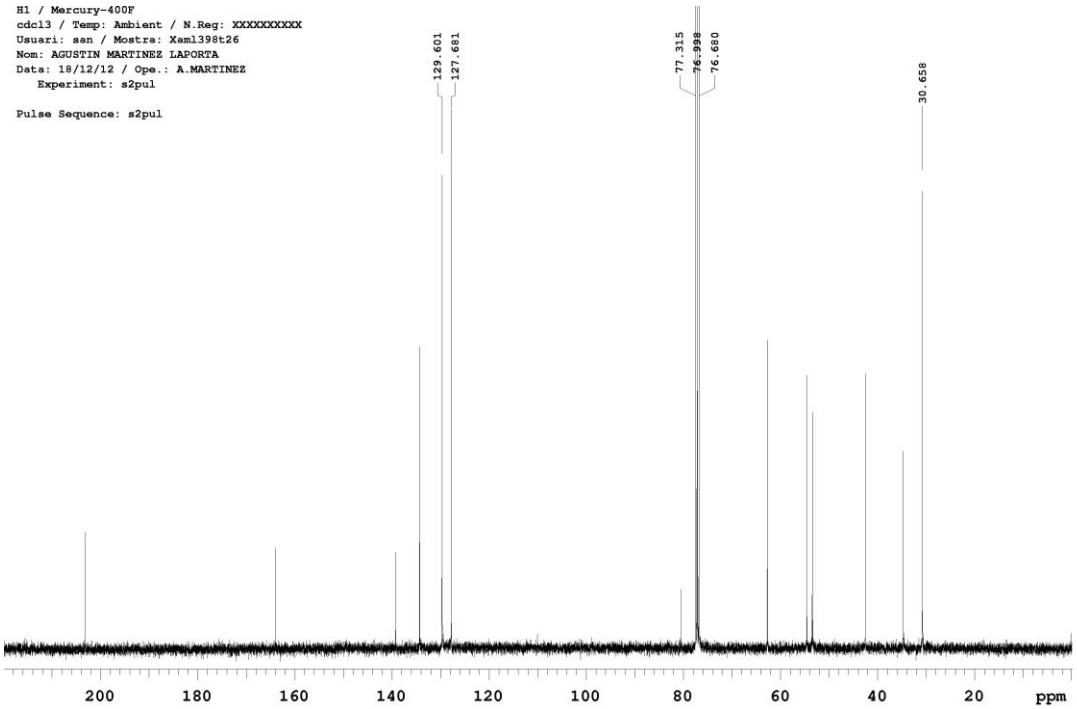

H1 / Mercury-400Q
cdcl3 / Temp: 25C / N.Reg: XXXXXXXXXX
Usuari: san / Mostra: Xaml402t8
Nom: AGUSTIN MARTINEZ LAPORTA
Data: 15/02/13 / Ope.: A.MARTINEZ
Pulse Sequence: s2pul
7.263
2.130
0.000
9
8
7
6
5
4
3
2
1
ppm

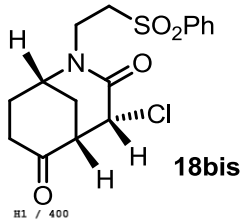

H1 / Mercury-400Q
cdcl3 / Temp: 25C / N.Reg: XXXXXXXXXX
Usuari: san / Mostra: Xaml402t8
Nom: AGUSTIN MARTINEZ LAPORTA
Data: 15/02/13 / Ope.: A.MARTINEZ
Pulse Sequence: s2pul
129.552
127.913
77.321
77.001
76.681
200
180
160
140
120
100
80
60
40
20
ppm


PhO2S
H
N
O
Cl
Cl
H
O

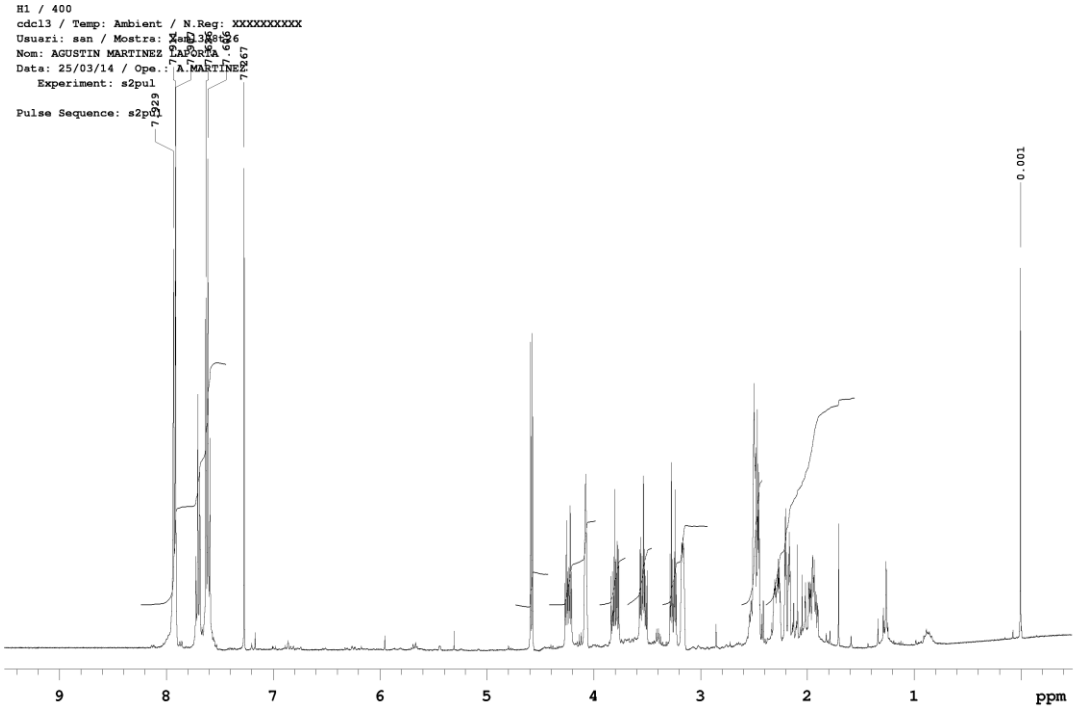
18

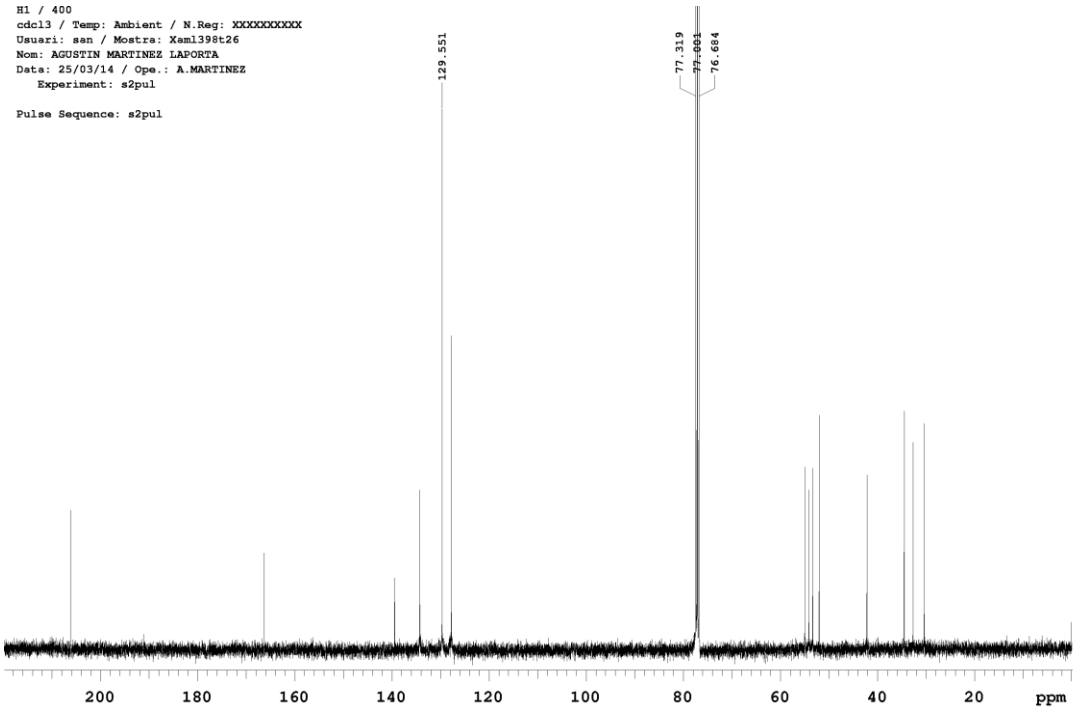

H1 / Mercury-400F
cdcl3 / Temp: Ambient / N.Reg: XXXXXXXXXX
Usuari: san / Mostra: Xaml398t26
Nom: AGUSTIN MARTINEZ LAPORTA
Data: 18/12/12 / Ope.: A.MARTINEZ
Experiment: s2pul
Pulse Sequence: s2pul
7.607
7.270
5.303
9
8
7
6
5
4
3
2
1
ppm

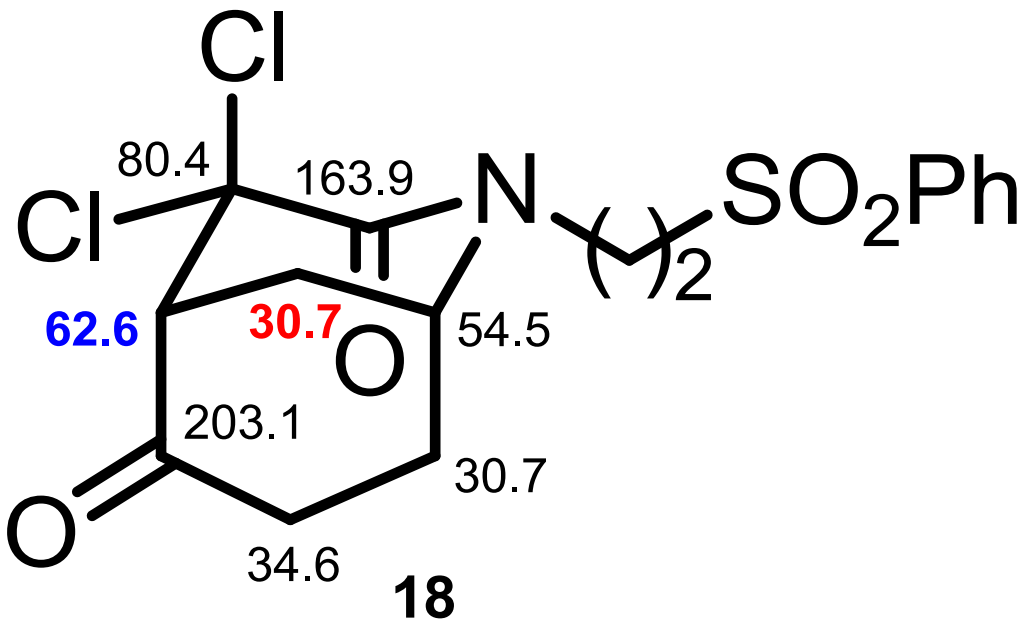

H1 / Mercury-400F
cdcl3 / Temp: Ambient / N.Reg: XXXXXXXXXX
Usuari: san / Mostra: Xaml398t26
Nom: AGUSTIN MARTINEZ LAPORTA
Data: 18/12/12 / Ope.: A.MARTINEZ
Experiment: s2pul
Pulse Sequence: s2pul
129.601
127.681
77.315
76.998
76.680
30.658
200
180
160
140
120
100
80
60
40
20
ppm


H
N
O
SO2Ph
Cl
H
H
O

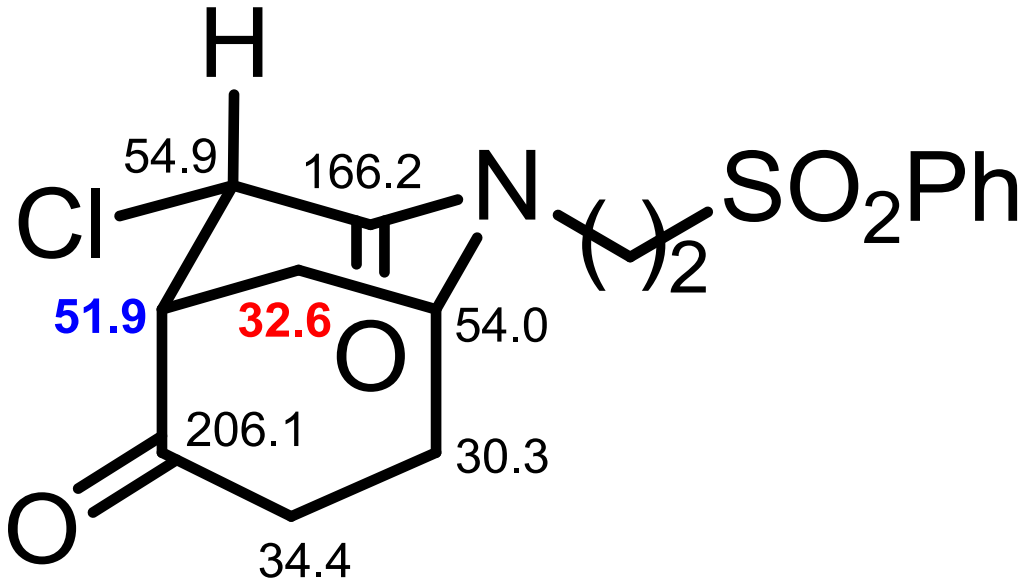
18bis


H1 / 400
cdcl3 / Temp: Ambient / N.Reg: XXXXXXXXXX
Usuari: san / Mostra: Xaml398t26
Nom: AGUSTIN MARTINEZ LAPORTA
Data: 25/03/14 / Ope.: A.MARTINEZ
Experiment: s2pul
Pulse Sequence: s2pul
7.923
7.667
0.001
9
8
7
6
5
4
3
2
1
ppm


H1 / 400
cdcl3 / Temp: Ambient / N.Reg: XXXXXXXXXX
Usuari: san / Mostra: Xaml398t26
Nom: AGUSTIN MARTINEZ LAPORTA
Data: 25/03/14 / Ope.: A.MARTINEZ
Experiment: s2pul
Pulse Sequence: s2pul
129.551
77.319
77.001
76.684
200
180
160
140
120
100
80
60
40
20
ppm

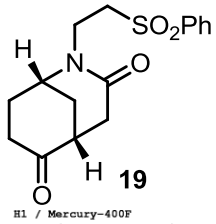


18

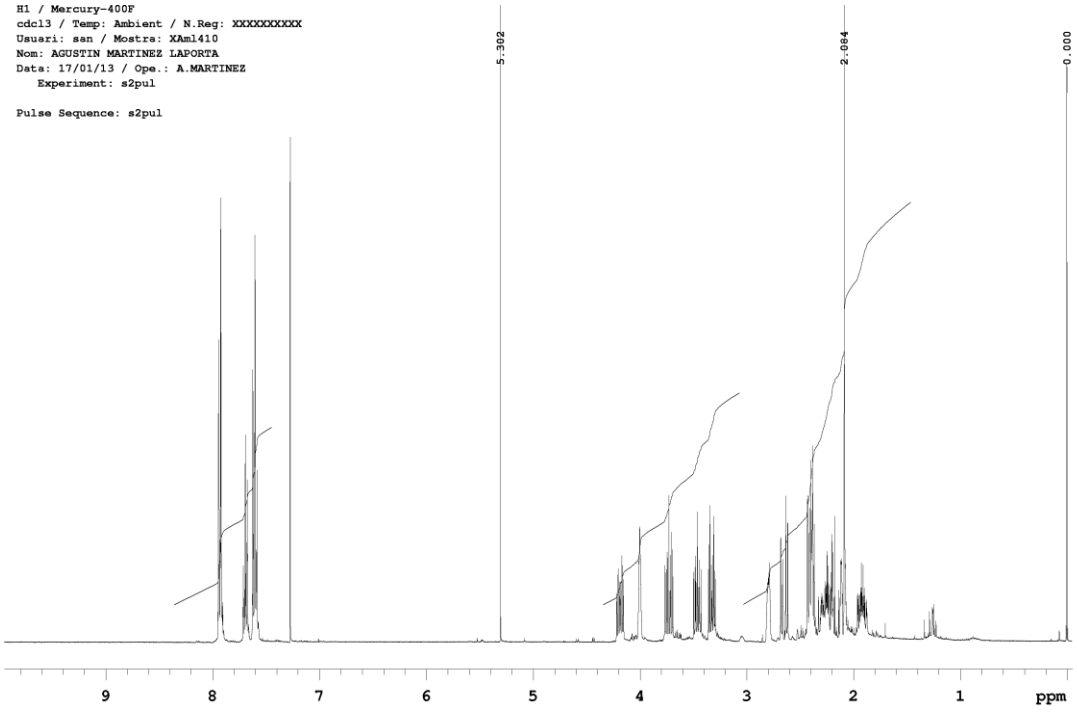


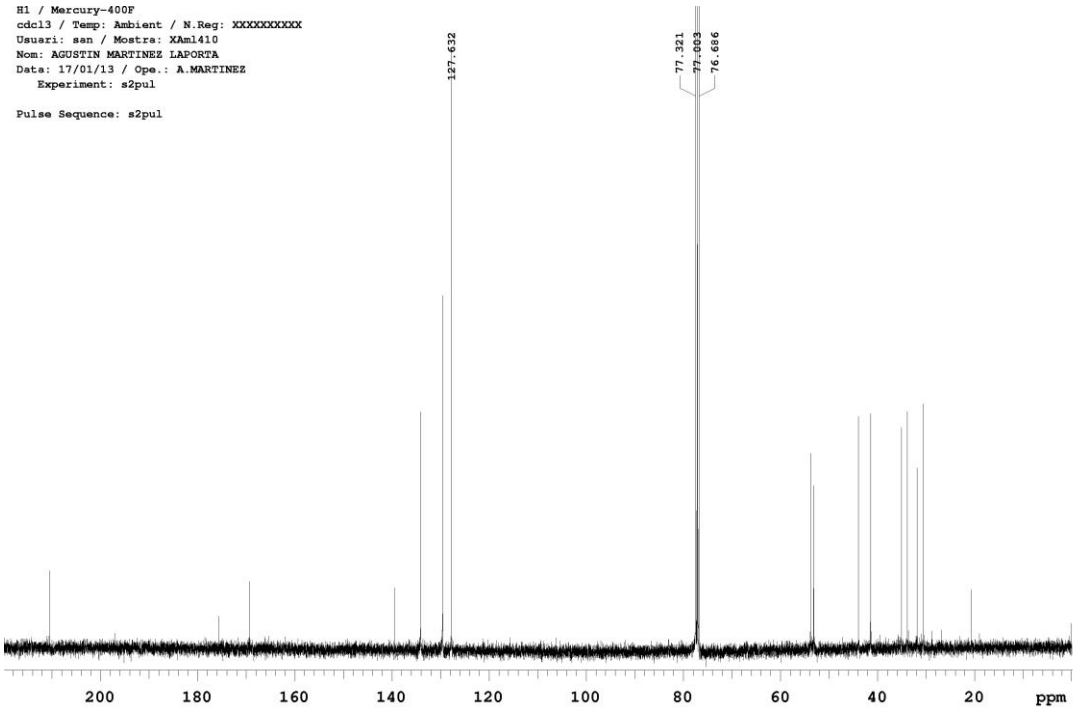
18bis

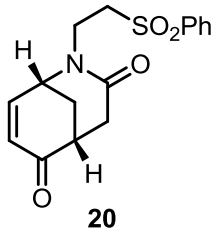
^{13}C chemical shifts of 18 and 18bis


SO2Ph
H
N
O
H
O

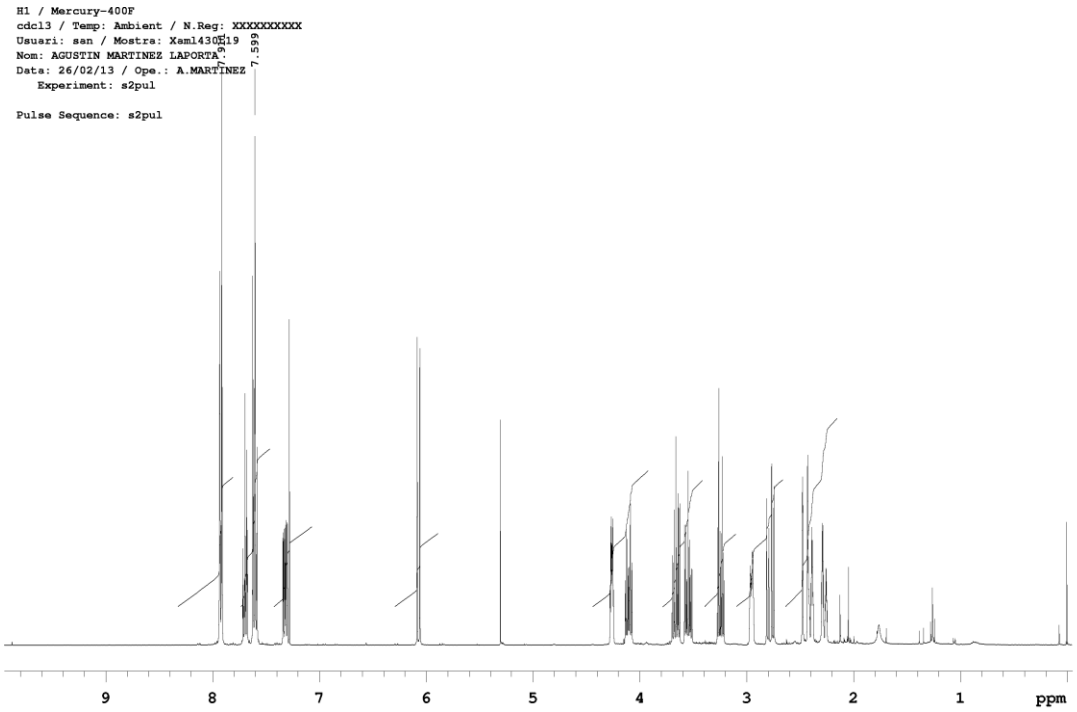
19

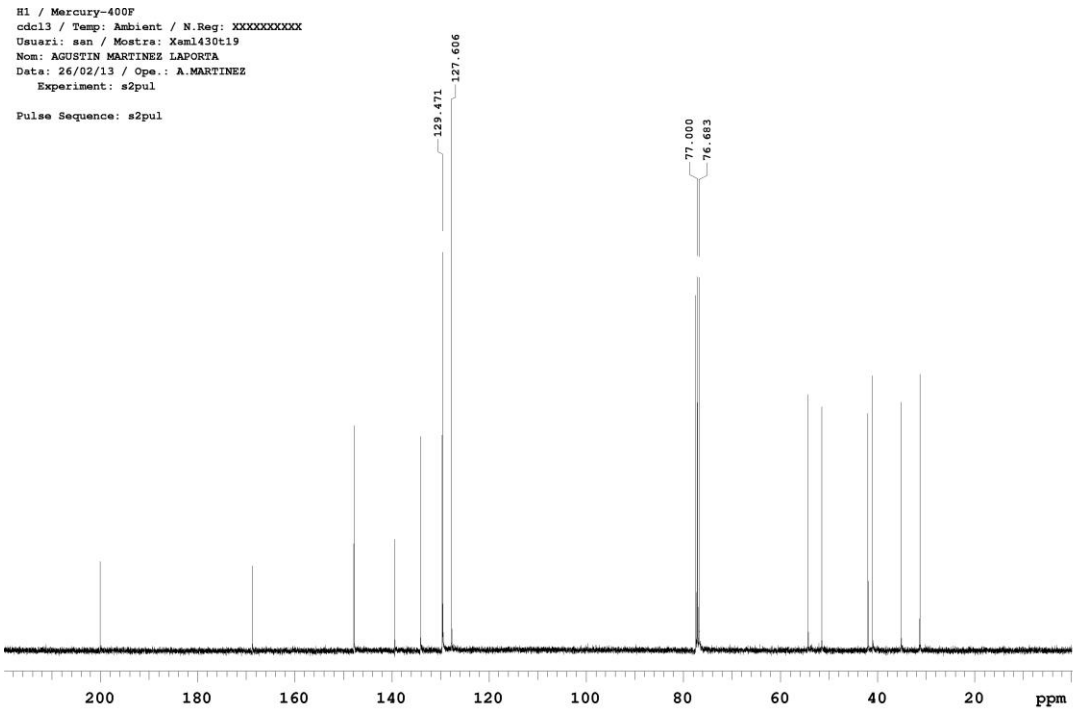

H1 / Mercury-400F
cdcl3 / Temp: Ambient / N.Reg: XXXXXXXXXX
Usuari: san / Mostra: XAm1410
Nom: AGUSTIN MARTINEZ LAPORTA
Data: 17/01/13 / Ope.: A.MARTINEZ
Experiment: s2pul
Pulse Sequence: s2pul
5.302
2.084
0.000
9
8
7
6
5
4
3
2
1
ppm

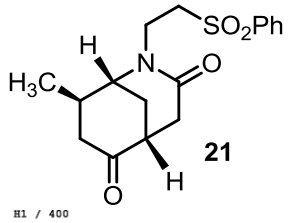

H1 / Mercury-400F
cdcl3 / Temp: Ambient / N.Reg: XXXXXXXXXX
Usuari: san / Mostra: XAm1410
Nom: AGUSTIN MARTINEZ LAPORTA
Data: 17/01/13 / Ope.: A.MARTINEZ
Experiment: s2pul
Pulse Sequence: s2pul
127.632
77.321
77.003
76.686
200
180
160
140
120
100
80
60
40
20
ppm


SO2Ph
H
N
O
O
H

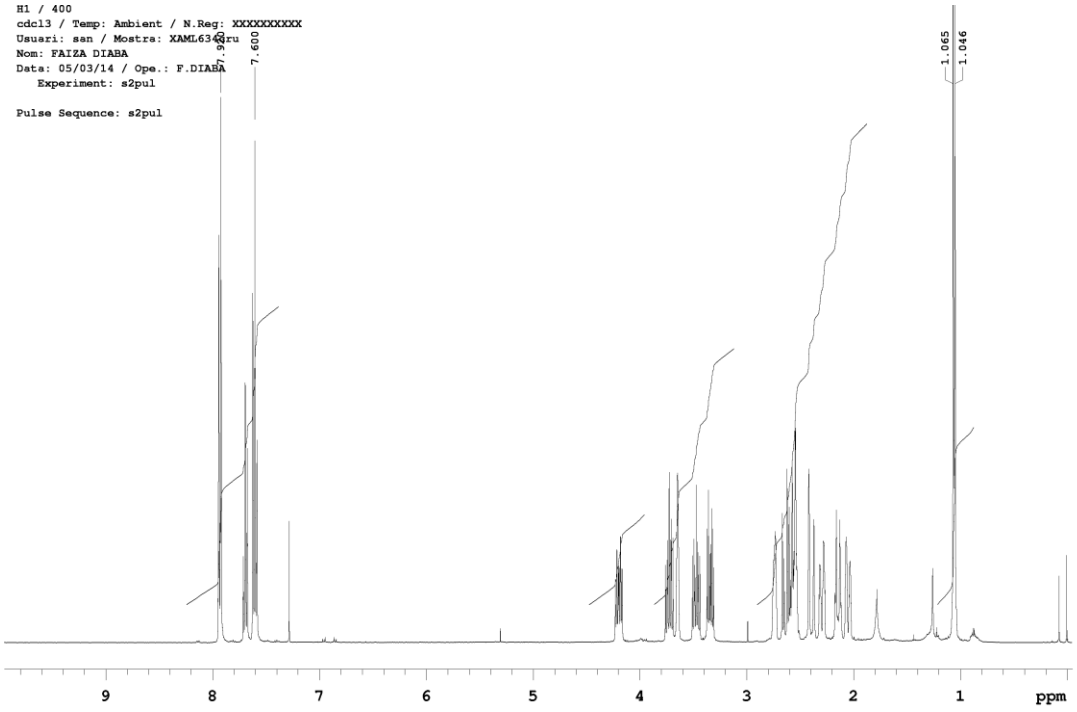
20

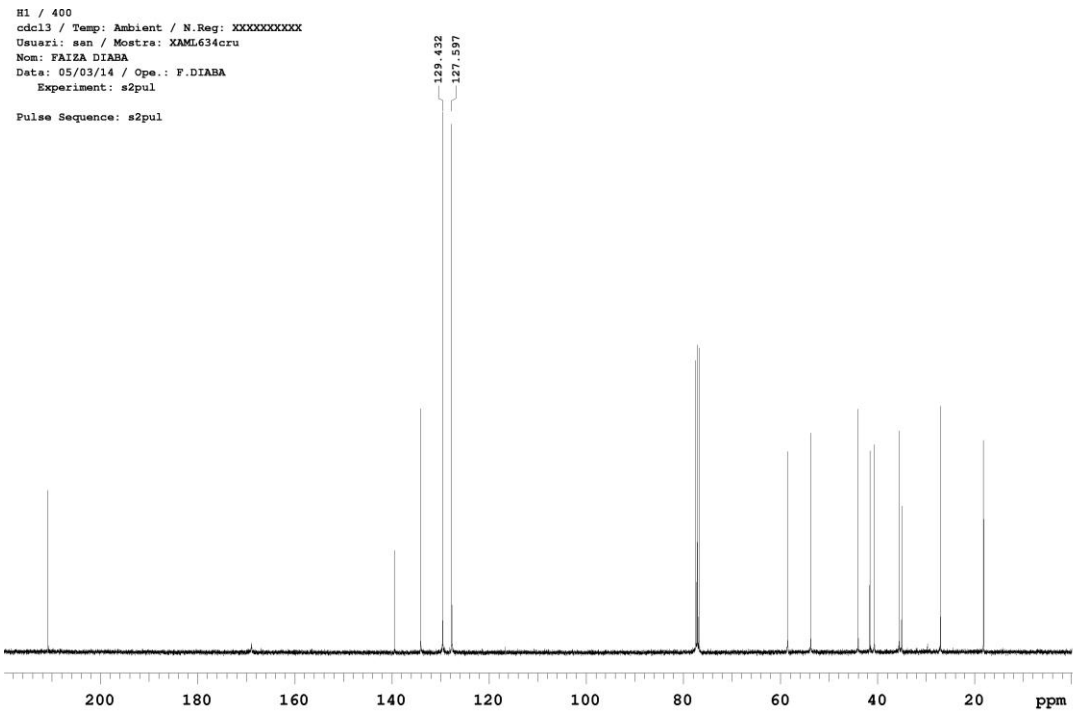

H1 / Mercury-400F
cdcl3 / Temp: Ambient / N.Reg: XXXXXXXXXX
Usuari: san / Mostra: Xaml430t19
Nom: AGUSTIN MARTINEZ LAPORTA
Data: 26/02/13 / Ope.: A.MARTINEZ
Experiment: s2pul
Pulse Sequence: s2pul
7.979
7.599
9
8
7
6
5
4
3
2
1
ppm

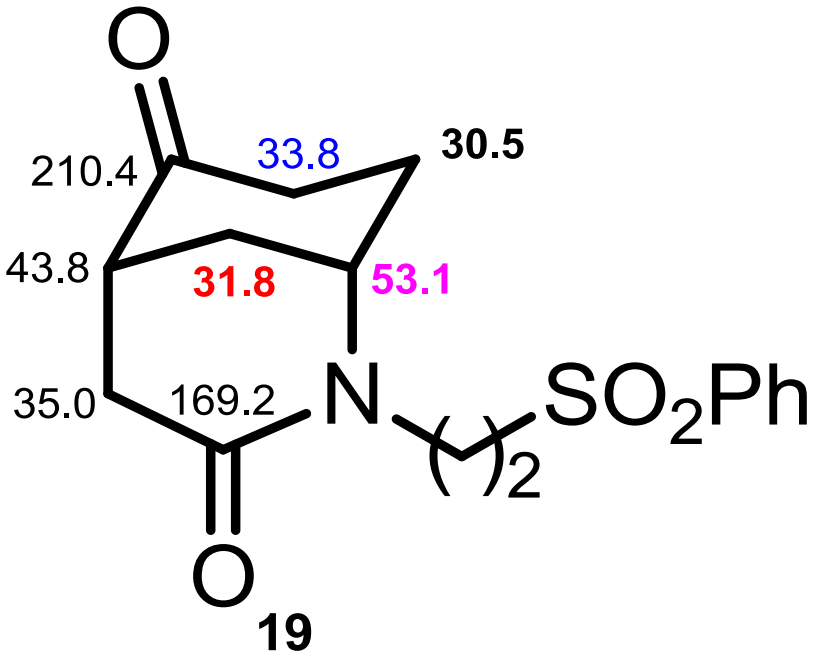

H1 / Mercury-400F
cdcl3 / Temp: Ambient / N.Reg: XXXXXXXXXX
Usuari: san / Mostra: Xaml430t19
Nom: AGUSTIN MARTINEZ LAPORTA
Data: 26/02/13 / Ope.: A.MARTINEZ
Experiment: s2pul
Pulse Sequence: s2pul
129.471
127.606
77.000
76.683
200
180
160
140
120
100
80
60
40
20
ppm

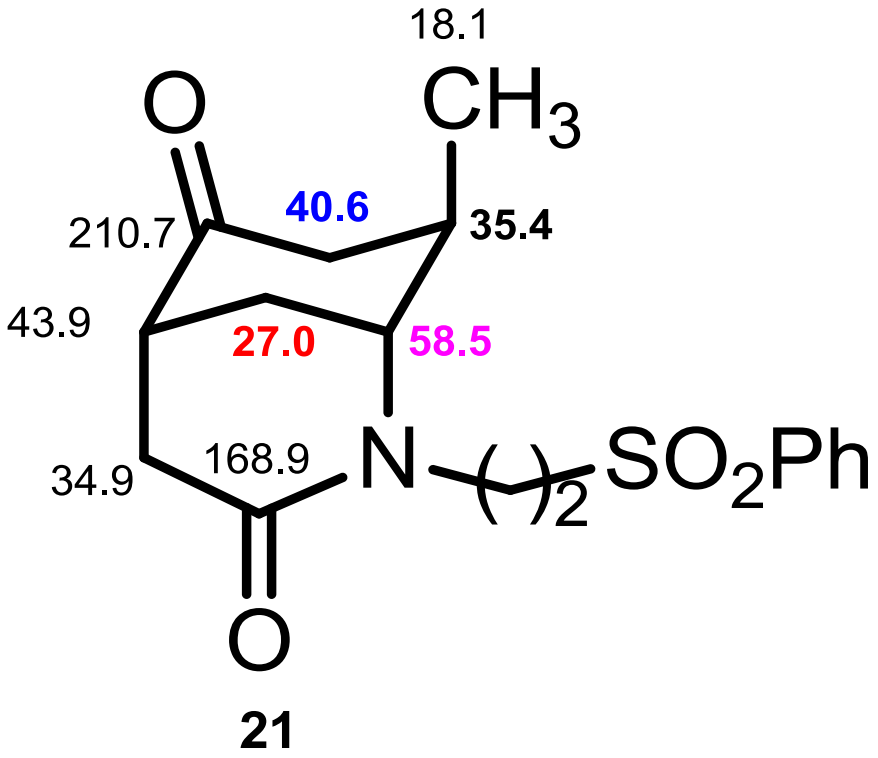

SO2Ph
H
N
O
H3C
O
H

21

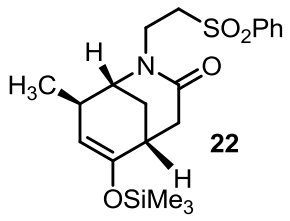

H1 / 400
cdcl3 / Temp: Ambient / N.Reg: XXXXXXXXXX
Usuari: san / Mostra: XAML634cru
Nom: FAIZA DIABA
Data: 05/03/14 / Ope.: F.DIABA
Experiment: s2pul
Pulse Sequence: s2pul
7.928
7.600
1.065
1.046
9
8
7
6
5
4
3
2
1
ppm


H1 / 400
cdcl3 / Temp: Ambient / N.Reg: XXXXXXXXXX
Usuari: san / Mostra: XAML634cru
Nom: FAIZA DIABA
Data: 05/03/14 / Ope.: F.DIABA
Experiment: s2pul
Pulse Sequence: s2pul
129.432
127.597
200
180
160
140
120
100
80
60
40
20
ppm

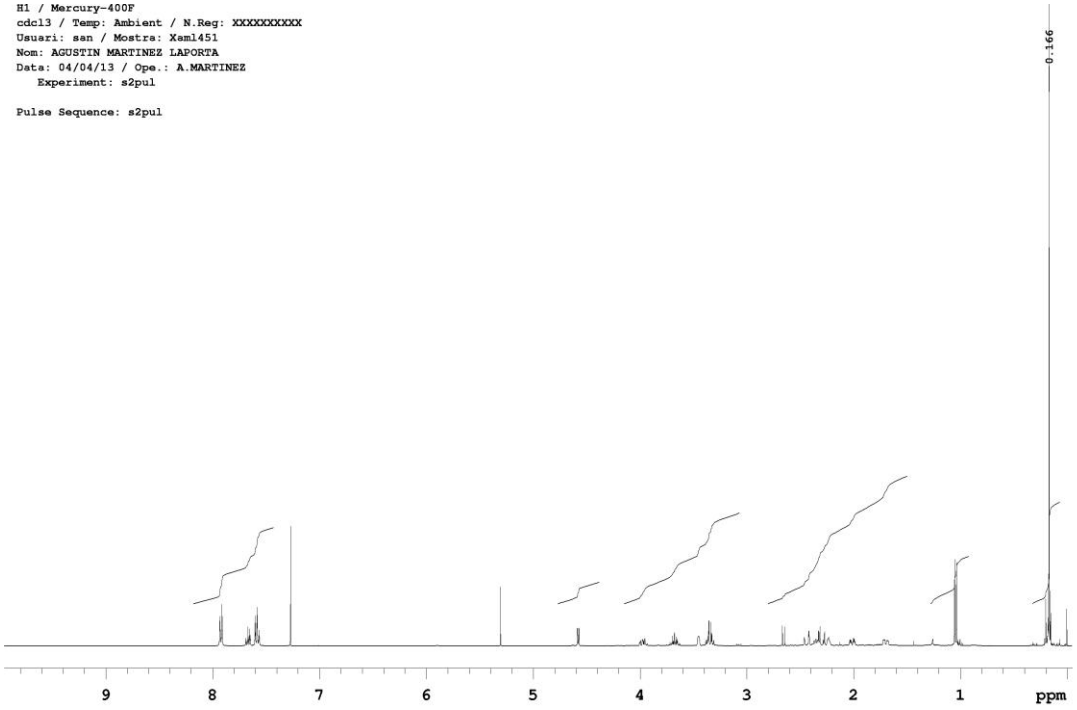


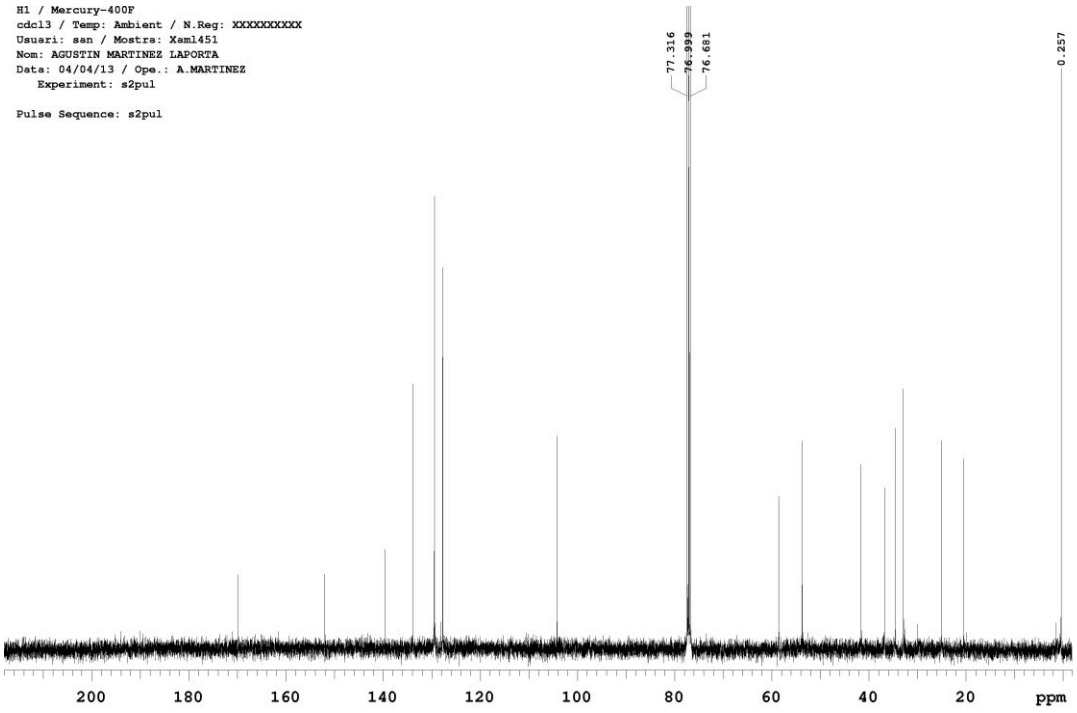


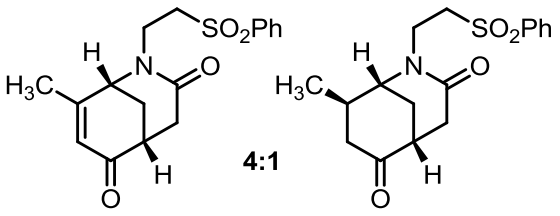
^{13}C chemical shifts of 19 and 21


SO2Ph
H
N
O
H3C
H
OSiMe3

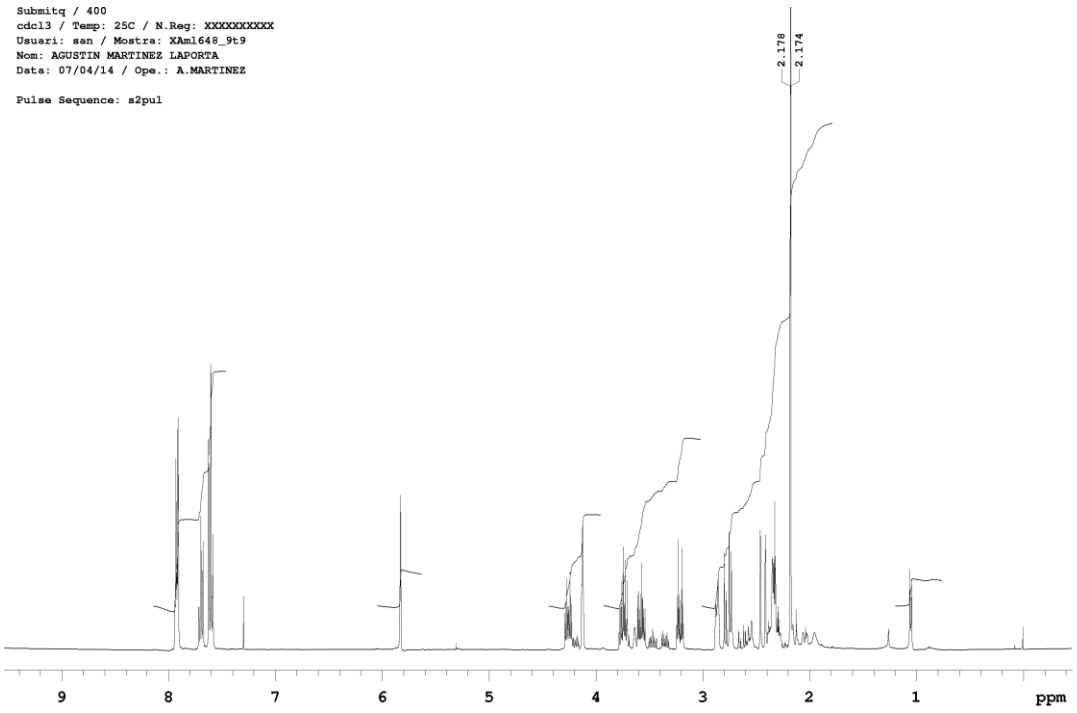
22

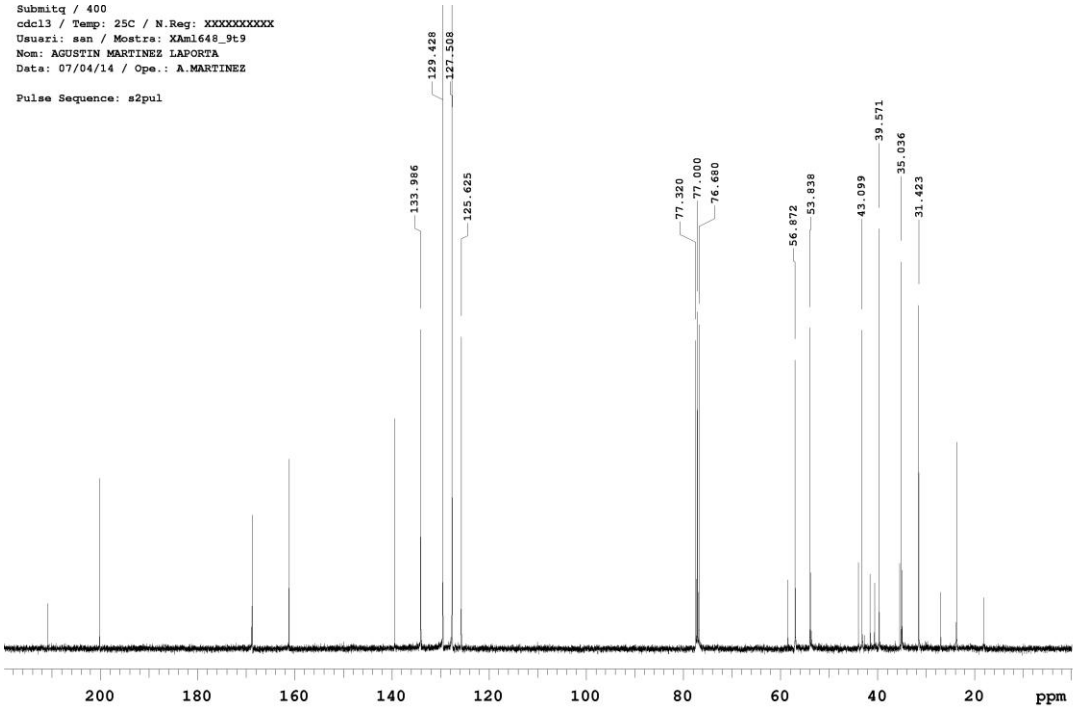

H1 / Mercury-400F
cdcl3 / Temp: Ambient / N.Reg: XXXXXXXXXX
Usuari: san / Mostra: Xaml451
Nom: AGUSTIN MARTINEZ LAPORTA
Data: 04/04/13 / Ope.: A.MARTINEZ
Experiment: s2pul
Pulse Sequence: s2pul
0.166
9
8
7
6
5
4
3
2
1
ppm

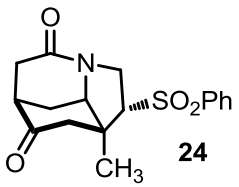

H1 / Mercury-400F
cdcl3 / Temp: Ambient / N.Reg: XXXXXXXXXX
Usuari: san / Mostra: Xaml451
Nom: AGUSTIN MARTINEZ LAPORTA
Data: 04/04/13 / Ope.: A.MARTINEZ
Experiment: s2pul
Pulse Sequence: s2pul
77.316
76.999
76.681
0.257
200
180
160
140
120
100
80
60
40
20
ppm


SO2Ph
H
N
O
H3C
H
O
4:1
SO2Ph
H
N
O
H3C
H
O

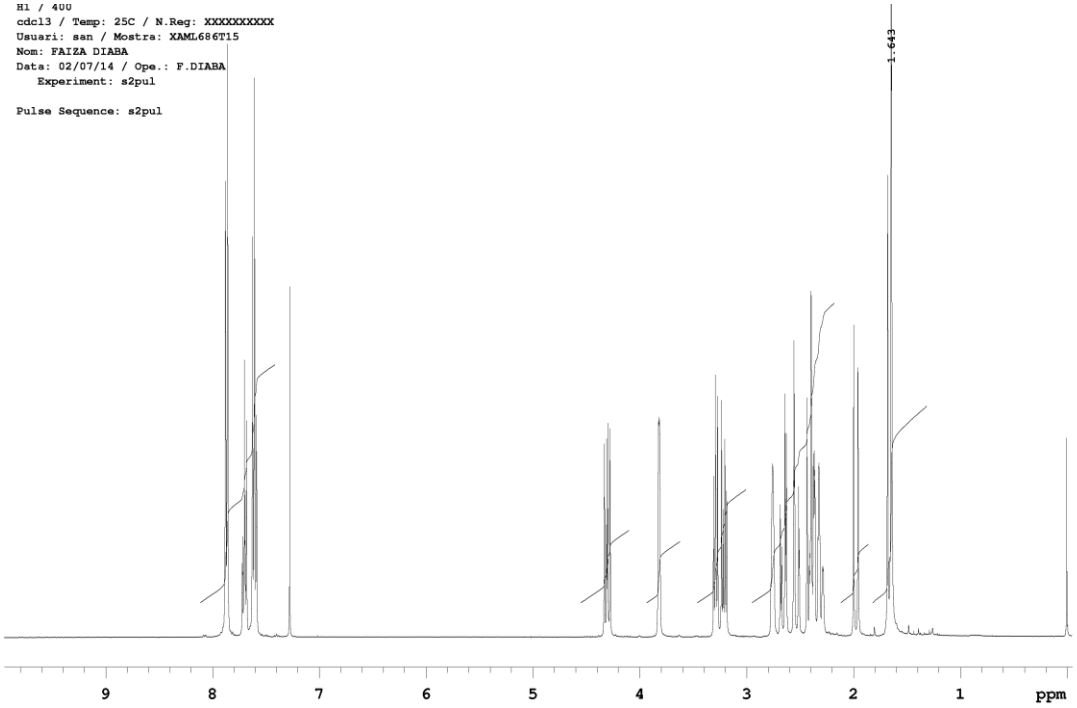
23 **21**

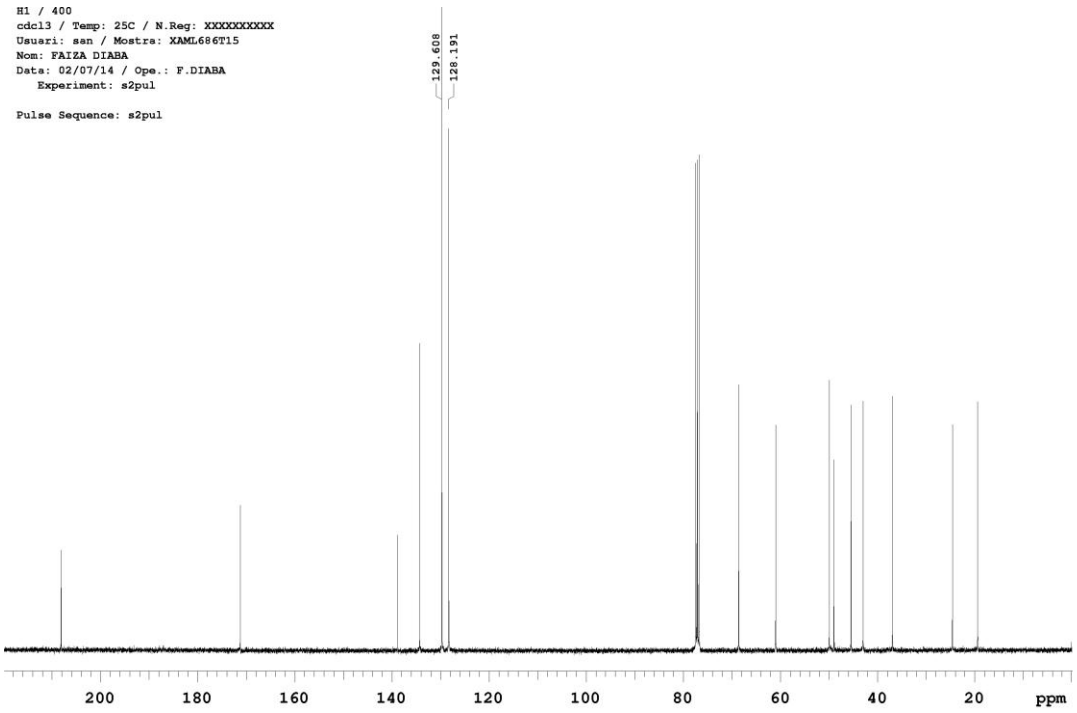

Submitq / 400
cdcl3 / Temp: 25C / N.Reg: XXXXXXXXXX
Usuari: san / Mostra: XAml648_9t9
Nom: AGUSTIN MARTINEZ LAPORTA
Data: 07/04/14 / Ope.: A.MARTINEZ
Pulse Sequence: s2pul
2.178
2.174
9
8
7
6
5
4
3
2
1
ppm


Submitq / 400
cdcl3 / Temp: 25C / N.Reg: XXXXXXXXXX
Usuari: san / Mostra: XAml648_9t9
Nom: AGUSTIN MARTINEZ LAPORTA
Data: 07/04/14 / Ope.: A.MARTINEZ
Pulse Sequence: s2pul
133.986
129.428
127.508
125.625
77.320
77.000
76.680
56.872
53.838
43.099
39.571
35.036
31.423
200
180
160
140
120
100
80
60
40
20
ppm


O
N
SO2Ph
O
CH3

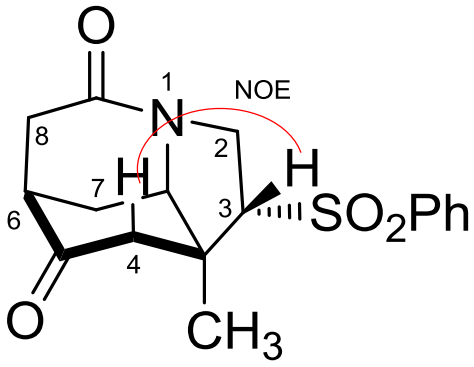
24


H1 / 400
cdcl3 / Temp: 25C / N.Reg: XXXXXXXXXX
Usuari: san / Mostra: XAML686T15
Nom: FAIZA DIABA
Data: 02/07/14 / Ope.: F.DIABA
Experiment: s2pul
Pulse Sequence: s2pul
1.643
9
8
7
6
5
4
3
2
1
ppm

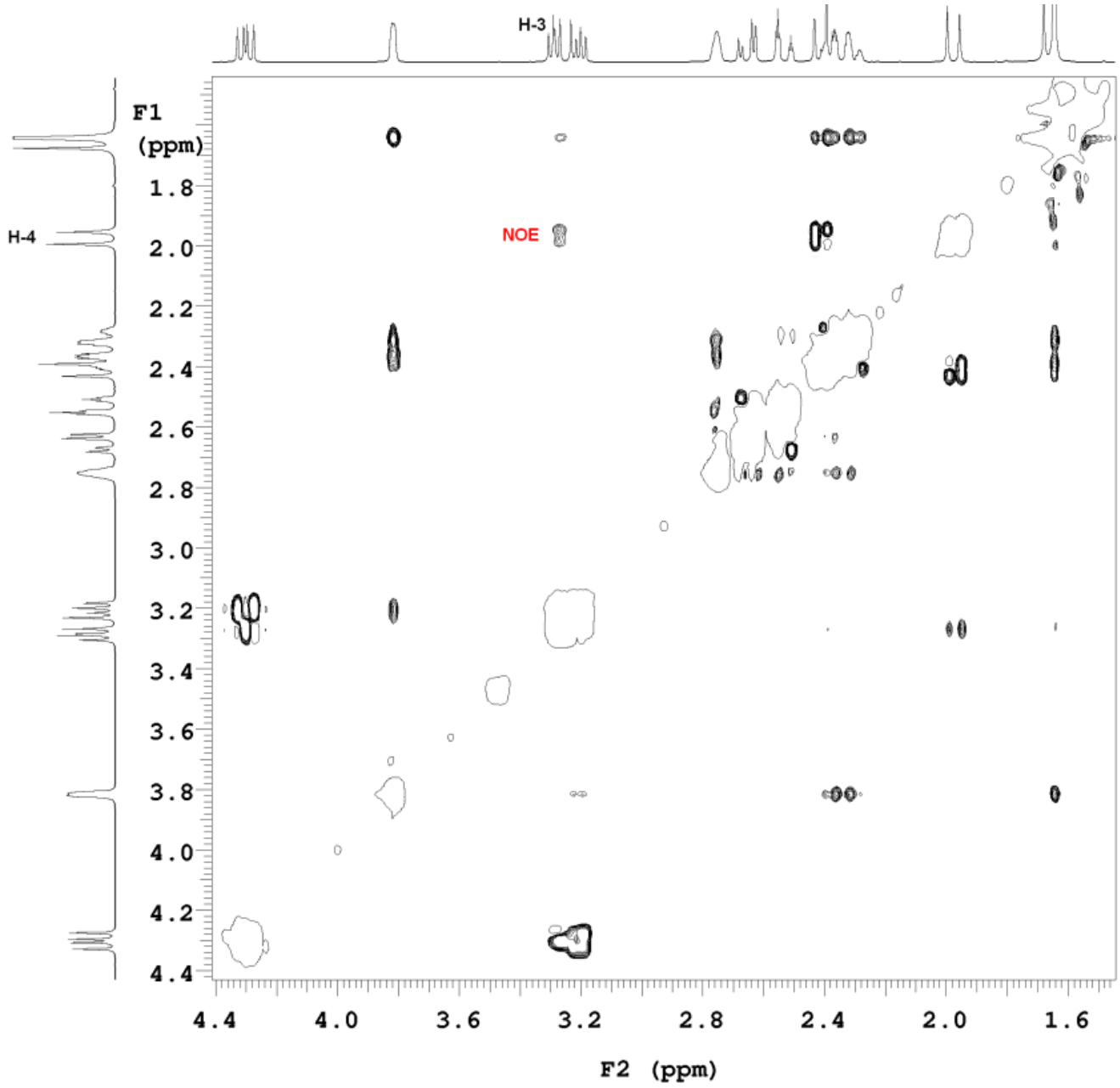

H1 / 400
cdcl3 / Temp: 25C / N.Reg: XXXXXXXXXX
Usuari: san / Mostra: XAML686T15
Nom: FAIZA DIABA
Data: 02/07/14 / Ope.: F.DIABA
Experiment: s2pul
Pulse Sequence: s2pul
129.608
128.191
200
180
160
140
120
100
80
60
40
20
ppm

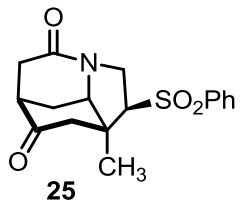
H1 / 400
cdcl3 / Temp: 25C / N.Reg: XXXXXXXXXX
Usuari: san / Mostra: XAML685t8
Nom: FAIZA DIABA
Data: 08/06/14 / Ope.: F.DIABA
Experiment: noesy
H1_data are in file H1

Pulse Sequence: NOESY

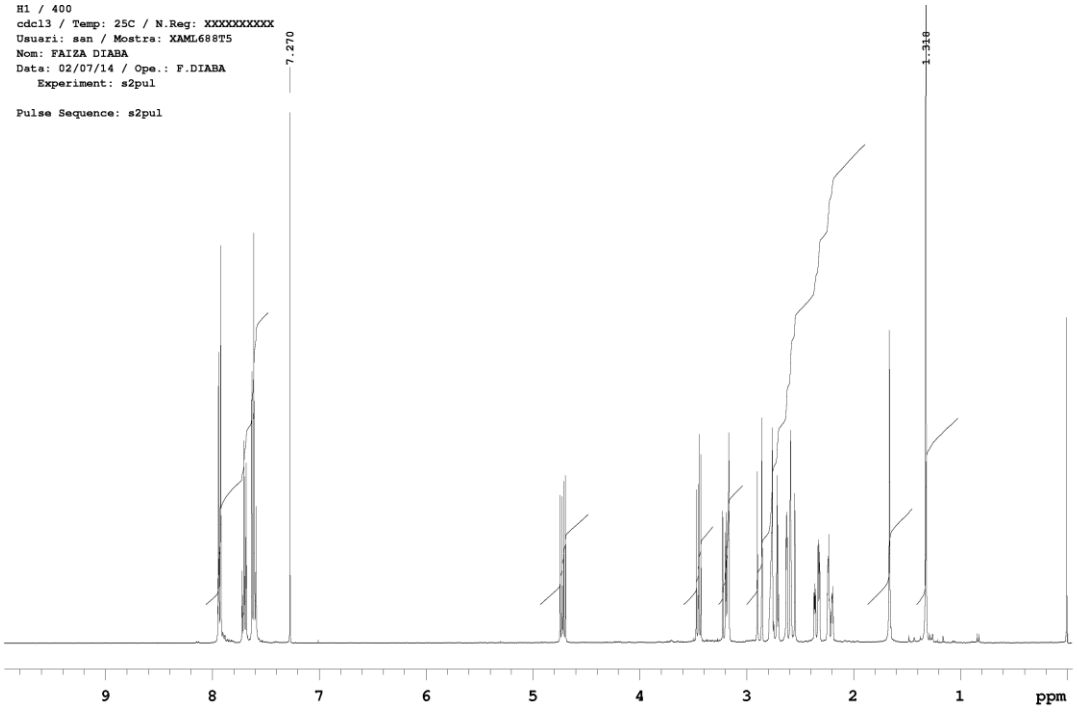


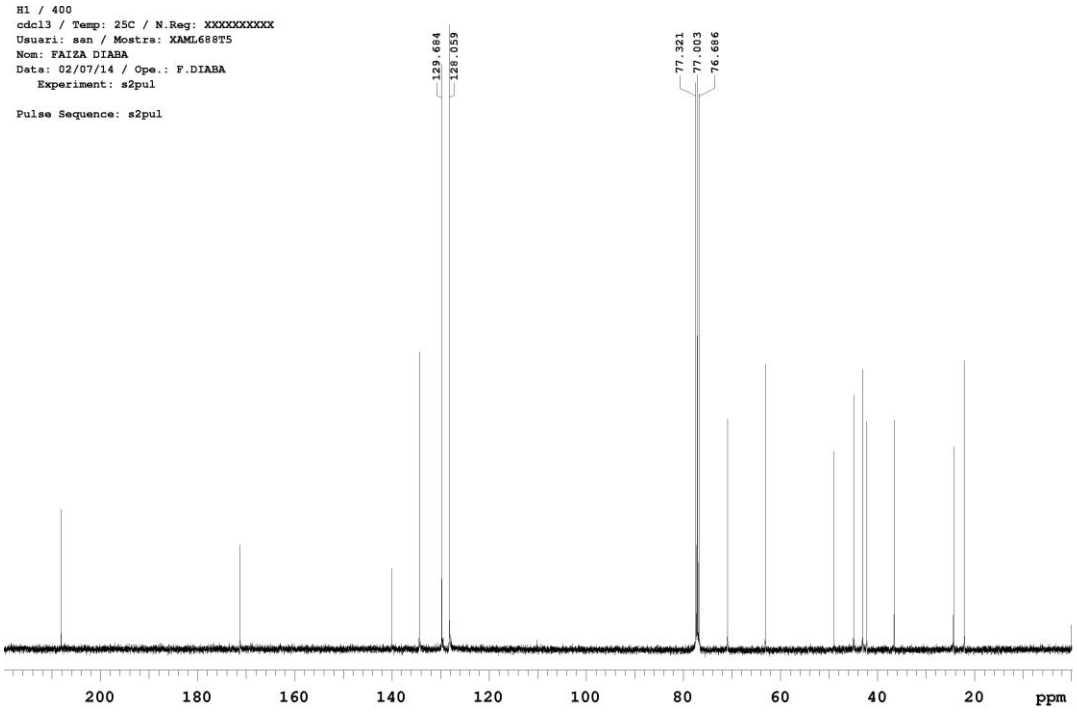
24




O
N
SO2Ph
O
CH3

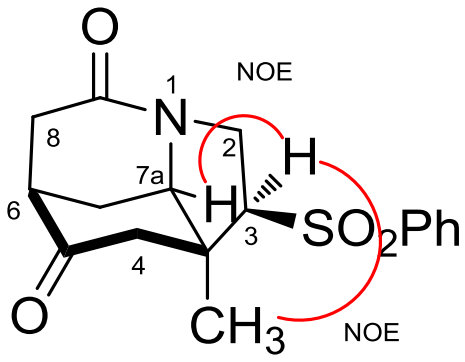
25


H1 / 400
cdcl3 / Temp: 25C / N.Reg: XXXXXXXXXX
Usuari: san / Mostra: XAML688T5
Nom: FAIZA DIABA
Data: 02/07/14 / Ope.: F.DIABA
Experiment: s2pul
Pulse Sequence: s2pul
7.270
1.310
9
8
7
6
5
4
3
2
1
ppm

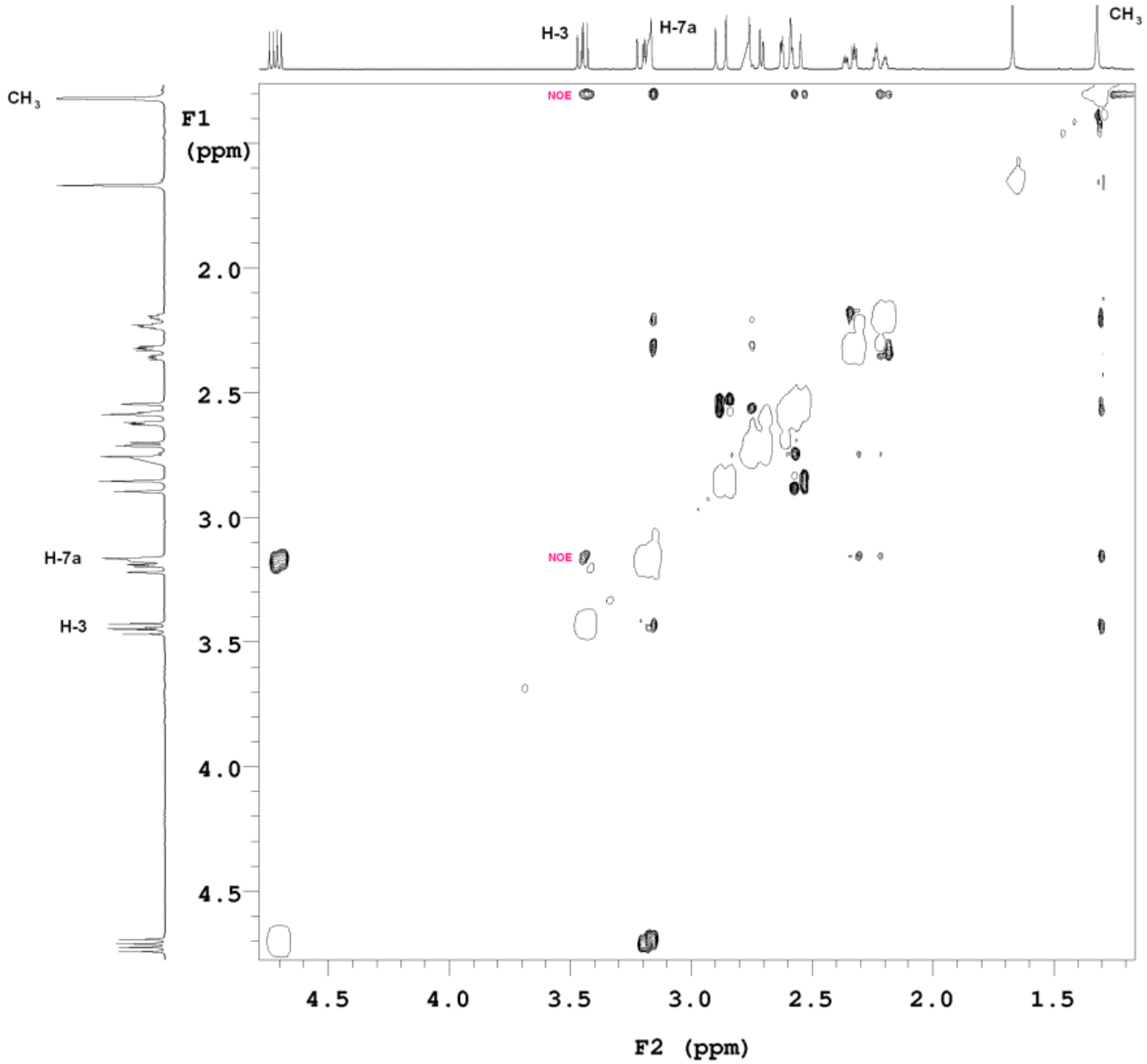

H1 / 400
cdcl3 / Temp: 25C / N.Reg: XXXXXXXXXX
Usuari: san / Mostra: XAML688T5
Nom: FAIZA DIABA
Data: 02/07/14 / Ope.: F.DIABA
Experiment: s2pul
Pulse Sequence: s2pul
129.684
128.059
77.321
77.003
76.686
200
180
160
140
120
100
80
60
40
20
ppm

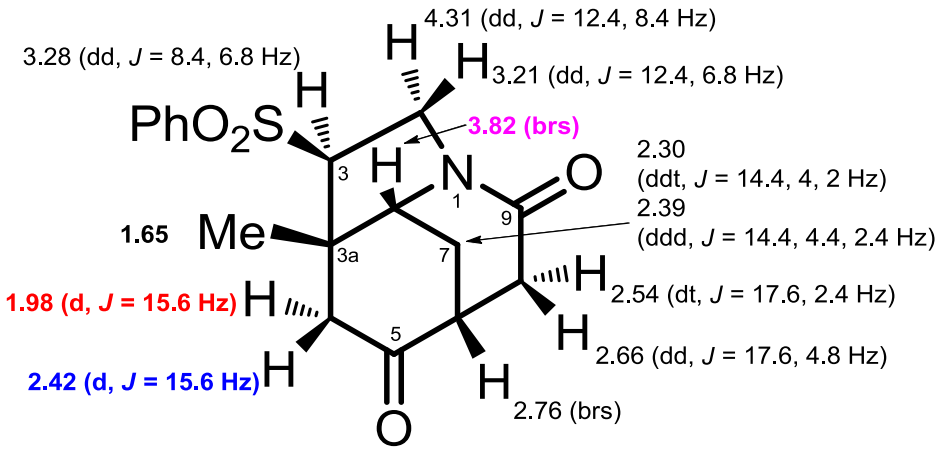
H1 / 400
cdcl3 / Temp: 25C / N.Reg: XXXXXXXXXX
Usuari: san / Mostra: SAML688T5
Nom: FAIZA DIABA
Data: 03/07/14 / Ope.: F.DIABA
Experiment: noesy
H1_data are in file H1

Pulse Sequence: NOESY

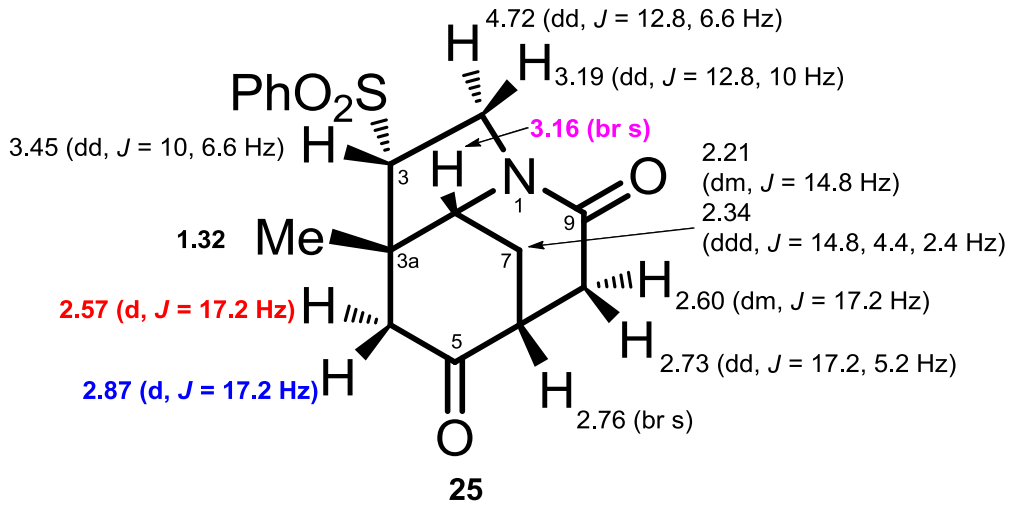


25



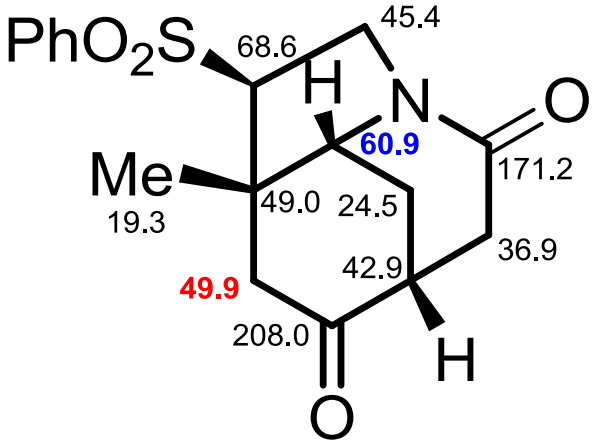


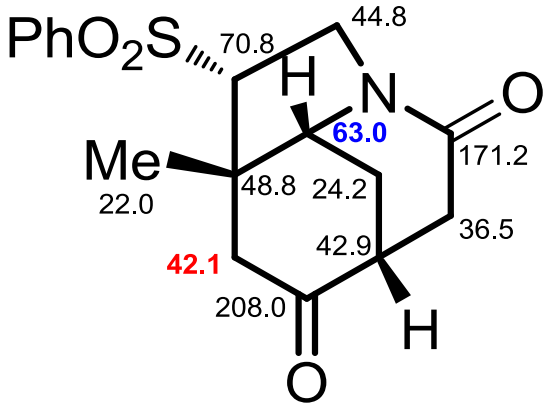
24



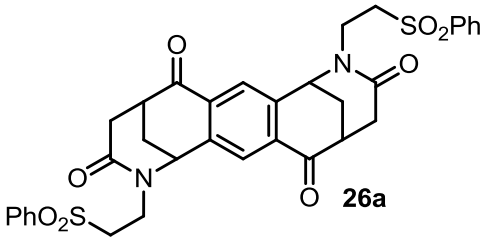
25

^{1}H Chemical shifts of 24 and 25

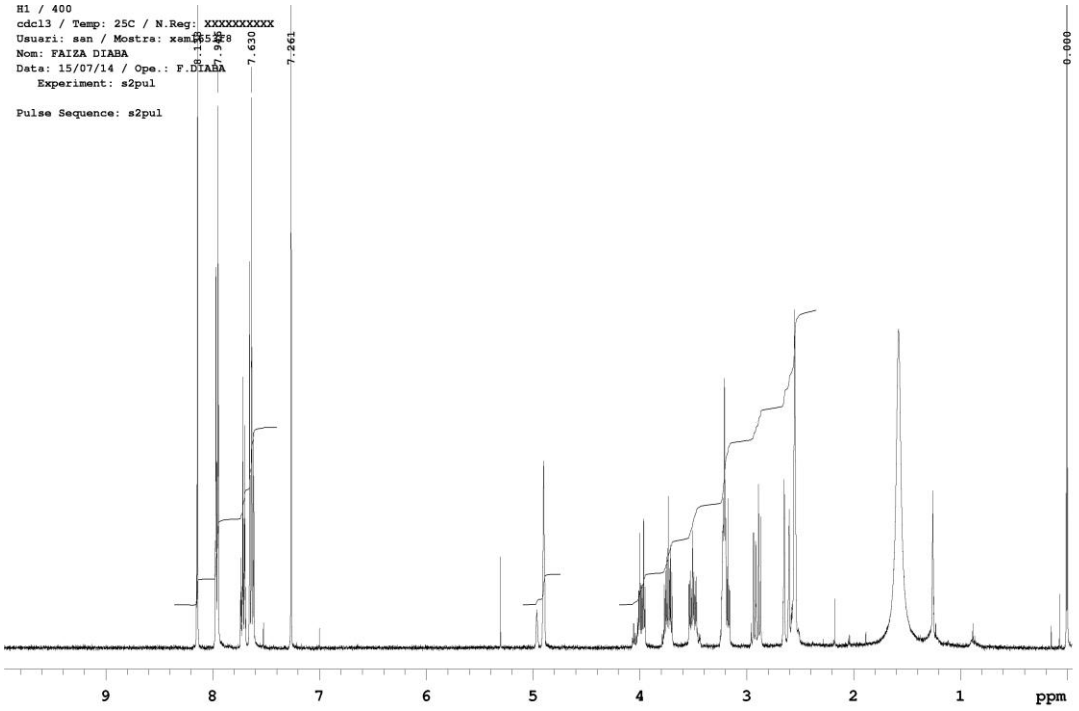


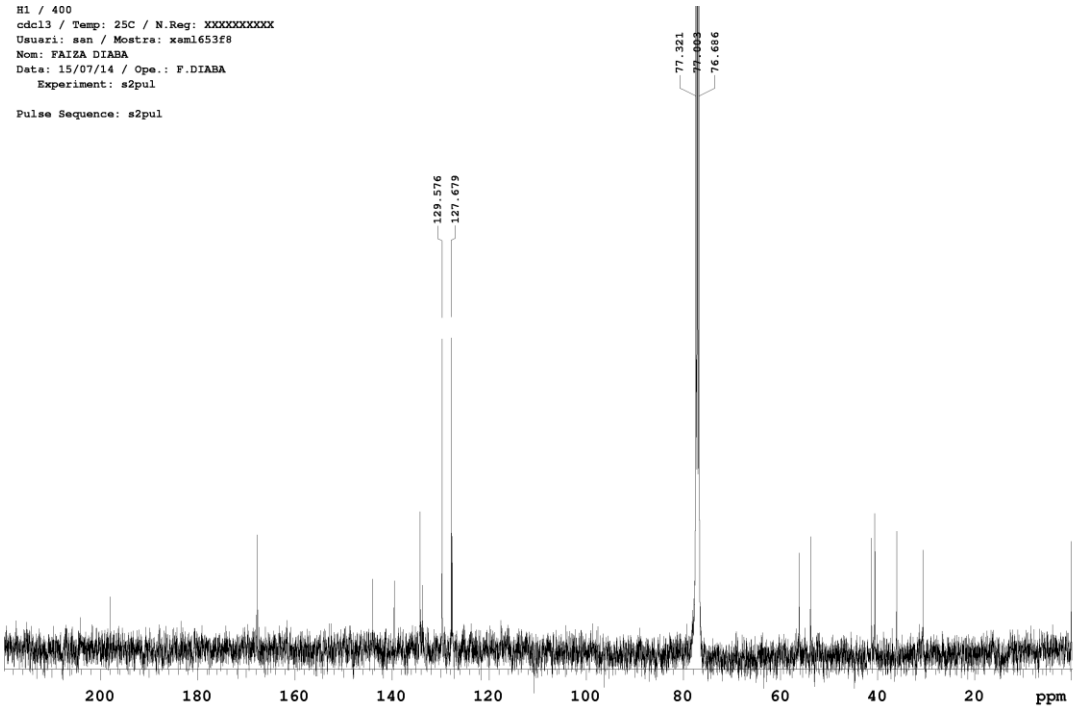


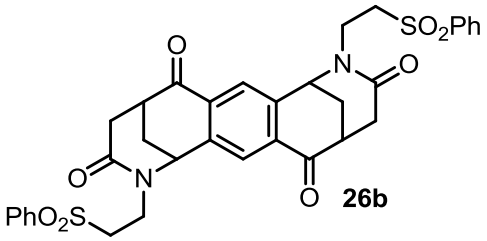
^{13}C Chemical shifts of 24 and 25


O
N
O
O
N
O
O
SO_2Ph
PhO_2S

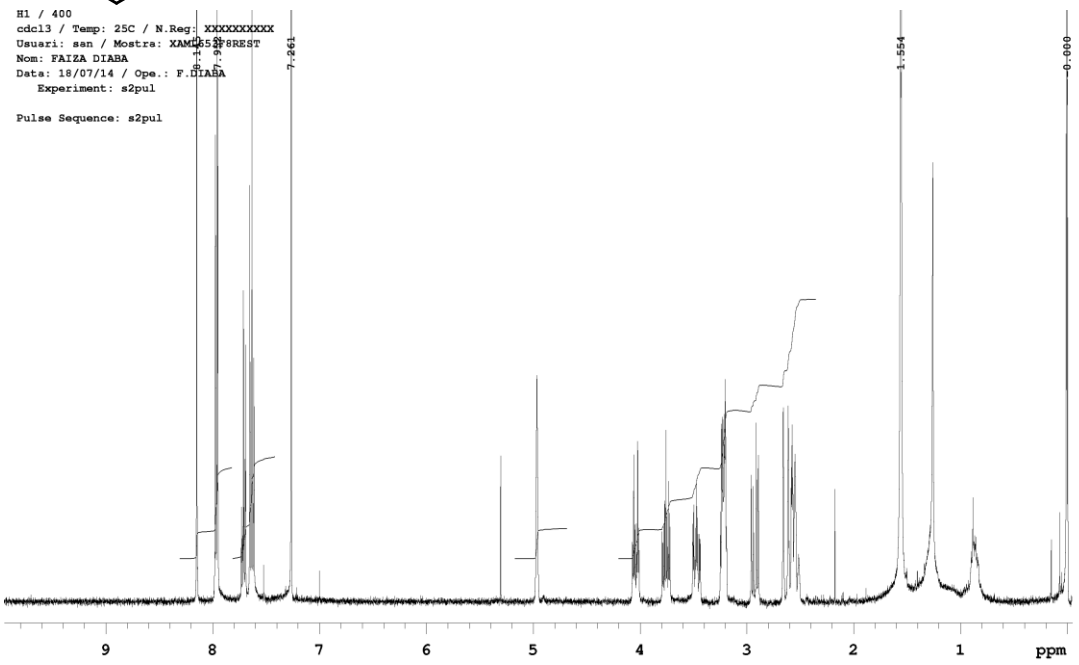
26a

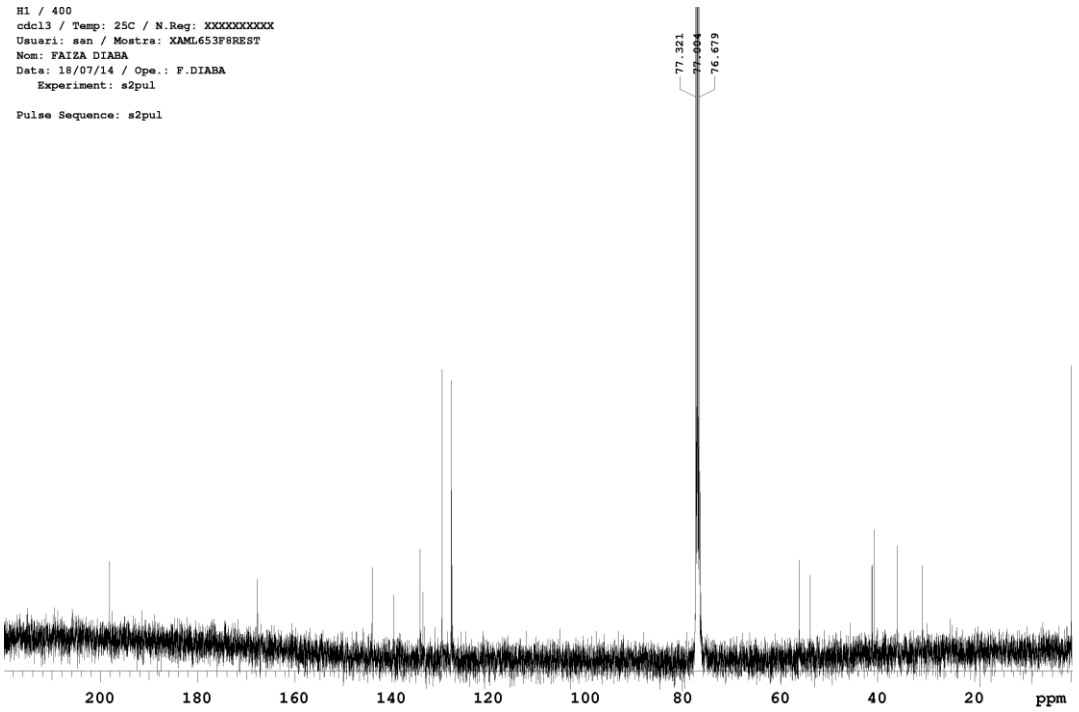

H1 / 400
cdcl3 / Temp: 25C / N.Reg: XXXXXXXXXX
Usuari: san / Mostra: xaml653f8
Nom: FAIZA DIABA
Data: 15/07/14 / Ope.: F.DIABA
Experiment: s2pul
Pulse Sequence: s2pul
8.153
7.948
7.630
7.261
0.000
9
8
7
6
5
4
3
2
1
ppm


H1 / 400
cdcl3 / Temp: 25C / N.Reg: XXXXXXXXXX
Usuari: san / Mostra: xaml653f8
Nom: FAIZA DIABA
Data: 15/07/14 / Ope.: F.DIABA
Experiment: s2pul
Pulse Sequence: s2pul
129.576
127.679
77.321
77.003
76.686
200
180
160
140
120
100
80
60
40
20
ppm


SO2Ph
O
N
O
O
N
O
PhO2S

26b


H1 / 400
cdcl3 / Temp: 25C / N.Reg: XXXXXXXXXX
Usuari: san / Mostra: XAML653F8REST
Nom: FAIZA DIABA
Data: 18/07/14 / Ope.: F.DIABA
Experiment: s2pul
Pulse Sequence: s2pul
7.261
1.554
0.000
9
8
7
6
5
4
3
2
1
ppm


H1 / 400
cdcl3 / Temp: 25C / N.Reg: XXXXXXXXXX
Usuari: san / Mostra: XAML653F8REST
Nom: FAIZA DIABA
Data: 18/07/14 / Ope.: F.DIABA
Experiment: s2pul
Pulse Sequence: s2pul
77.321
77.004
76.679
200
180
160
140
120
100
80
60
40
20
ppm

Cartesian coordinates (in Å) and total energies (in a. u.. ZPVE included) of all the stationary points discussed in the text. All calculations have been performed at the M06-2X/6-31+G(d) level.

23-an: E= -1411.718723

C	-3.647775000	1.811464000	0.270011000
C	-4.000077000	0.829461000	-0.866392000
C	-2.726530000	0.463115000	-1.626750000
C	-1.750600000	-0.150353000	-0.624409000
H	-4.332556000	1.705959000	1.118604000
H	-4.753685000	1.285562000	-1.516990000
H	-2.940729000	-0.253772000	-2.427702000
H	-2.271247000	1.353020000	-2.078468000
H	-0.828045000	-0.469993000	-1.120503000
H	-3.771488000	2.839591000	-0.087772000
N	-1.348633000	0.866422000	0.357611000
C	-2.219488000	1.791761000	0.824873000
O	-1.918632000	2.668062000	1.637336000
C	-2.381029000	-1.378252000	0.039640000
C	-3.719727000	-1.472795000	0.172076000
H	-4.182234000	-2.346030000	0.627856000
C	-4.636654000	-0.419717000	-0.280524000
C	0.119221000	1.030503000	0.626718000
H	0.543606000	1.416697000	-0.312495000
H	0.170522000	1.828588000	1.368355000
O	-5.850971000	-0.517652000	-0.168061000
C	-1.470320000	-2.469606000	0.504146000
H	-0.793540000	-2.771666000	-0.304818000
H	-0.809515000	-2.097707000	1.294037000
H	-2.040104000	-3.335544000	0.855212000
C	0.827014000	-0.195671000	1.071709000
H	1.041438000	-0.369921000	2.120358000
S	1.832718000	-1.021238000	0.042273000
O	1.303421000	-0.973464000	-1.348435000
O	2.201270000	-2.330033000	0.626516000
C	3.449715000	-0.202737000	-0.149615000
C	3.661027000	0.704673000	-1.186603000
C	4.441510000	-0.413019000	0.809557000
C	4.862732000	1.410576000	-1.256896000
H	2.886321000	0.830616000	-1.937644000
C	5.640763000	0.290381000	0.734239000
H	4.262895000	-1.139968000	1.597601000
C	5.853776000	1.208433000	-0.296935000
H	5.027923000	2.116222000	-2.067731000
H	6.415012000	0.121102000	1.478875000
H	6.790314000	1.757486000	-0.354335000

TS1: E= -1411.710318

C	3.654152000	1.900128000	-0.042861000
C	4.151512000	0.463223000	0.099458000
C	3.554818000	-0.104943000	1.383620000
C	2.056509000	-0.259641000	1.139628000
H	3.896280000	2.310202000	-1.027680000
H	5.247088000	0.458218000	0.118576000
H	3.977604000	-1.085950000	1.627749000
H	3.742787000	0.570906000	2.228956000
H	1.532455000	-0.549530000	2.059215000
H	4.131219000	2.547162000	0.705077000

N	1.472944000	1.023914000	0.723058000
C	2.149008000	2.047975000	0.131128000
O	1.598562000	3.080789000	-0.247447000
C	1.848444000	-1.351882000	0.093554000
C	2.656895000	-1.295540000	-1.015153000
H	2.562548000	-2.033125000	-1.809221000
C	3.752682000	-0.358952000	-1.141981000
C	0.006315000	0.956086000	0.585614000
H	-0.426965000	0.861442000	1.589871000
H	-0.304001000	1.913429000	0.158428000
O	4.442448000	-0.242493000	-2.156474000
C	1.218703000	-2.654317000	0.510707000
H	0.467539000	-2.518678000	1.291260000
H	0.734323000	-3.141530000	-0.339678000
H	2.009575000	-3.323919000	0.884128000
C	-0.335370000	-0.251273000	-0.237176000
H	-0.283088000	-0.159107000	-1.320560000
S	-1.696179000	-1.137628000	0.231701000
O	-1.685218000	-1.334249000	1.700068000
O	-1.852892000	-2.310552000	-0.651133000
C	-3.207780000	-0.175380000	-0.052255000
C	-3.687820000	0.677993000	0.939979000
C	-3.827703000	-0.231029000	-1.299888000
C	-4.795286000	1.483812000	0.677726000
H	-3.199822000	0.686130000	1.910900000
C	-4.935373000	0.573803000	-1.555342000
H	-3.440806000	-0.917866000	-2.047767000
C	-5.419380000	1.435013000	-0.568780000
H	-5.175026000	2.148273000	1.449834000
H	-5.425537000	0.526923000	-2.524643000
H	-6.283065000	2.063251000	-0.771043000

TS2: E= -1411.704355

C	2.242880000	2.108518000	-0.581613000
C	3.312691000	1.011715000	-0.532664000
C	3.550970000	0.629601000	0.923224000
C	2.263499000	-0.009785000	1.424508000
H	1.789592000	2.167472000	-1.576848000
H	4.226624000	1.392571000	-1.002052000
H	4.369564000	-0.092655000	1.015586000
H	3.795768000	1.513219000	1.529495000
H	2.354676000	-0.250577000	2.494928000
H	2.688127000	3.089554000	-0.369386000
N	1.161000000	0.950318000	1.328638000
C	1.081597000	1.939767000	0.383735000
O	0.115420000	2.695511000	0.317511000
C	1.966631000	-1.308615000	0.661421000
C	2.361875000	-1.349989000	-0.666528000
H	2.208387000	-2.253228000	-1.252906000
C	2.915660000	-0.223586000	-1.363873000
C	-0.091099000	0.336949000	1.787174000
H	-0.015252000	0.153519000	2.867876000
H	-0.887197000	1.072948000	1.628521000
O	3.179479000	-0.208270000	-2.570587000
C	1.987968000	-2.597786000	1.453554000
H	1.489453000	-2.495996000	2.423332000
H	1.491114000	-3.394094000	0.891319000
H	3.030720000	-2.903458000	1.629634000
C	-0.245421000	-0.977133000	1.071364000
H	-0.658885000	-1.812536000	1.633831000

S	-0.959839000	-0.916938000	-0.484092000
O	-1.132513000	-2.297379000	-0.973071000
O	-0.257831000	0.081585000	-1.305373000
C	-2.632512000	-0.248455000	-0.324004000
C	-2.802142000	1.136505000	-0.307534000
C	-3.712832000	-1.109720000	-0.140736000
C	-4.078509000	1.658255000	-0.094274000
H	-1.940382000	1.784412000	-0.461759000
C	-4.985070000	-0.578121000	0.060728000
H	-3.542845000	-2.182677000	-0.176855000
C	-5.167596000	0.806179000	0.088952000
H	-4.220899000	2.735670000	-0.076622000
H	-5.835776000	-1.242816000	0.190326000
H	-6.160352000	1.220080000	0.248151000

24-an: E= -1411.735473

C	-3.606014000	1.756310000	-0.291691000
C	-3.927331000	0.272942000	-0.097876000
C	-3.329113000	-0.488821000	-1.271229000
C	-1.820977000	-0.388398000	-1.158869000
H	-3.936384000	2.341124000	0.571057000
H	-5.013600000	0.141902000	-0.046089000
H	-3.612152000	-1.547302000	-1.246415000
H	-3.667931000	-0.075373000	-2.232639000
H	-1.328825000	-0.781551000	-2.061560000
H	-4.102728000	2.161884000	-1.186161000
N	-1.356209000	0.995833000	-0.987352000
C	-2.115201000	2.004895000	-0.428670000
O	-1.604656000	3.065366000	-0.086745000
C	-1.265502000	-1.123058000	0.080656000
C	-2.113510000	-0.798195000	1.284652000
H	-1.723858000	-1.115708000	2.252418000
C	-3.363808000	-0.192091000	1.268648000
C	0.040025000	0.914807000	-0.585364000
H	0.672191000	0.849701000	-1.478992000
H	0.312773000	1.806605000	-0.020773000
O	-4.094303000	0.069880000	2.267602000
C	-1.153631000	-2.636343000	-0.162425000
H	-0.538166000	-2.888911000	-1.036024000
H	-0.728704000	-3.132709000	0.714217000
H	-2.162104000	-3.034839000	-0.311701000
C	0.131430000	-0.393980000	0.248093000
H	0.318766000	-0.207593000	1.309084000
S	1.603230000	-1.319580000	-0.260451000
O	1.593645000	-1.549671000	-1.713294000
O	1.813455000	-2.442524000	0.660470000
C	2.927789000	-0.148566000	0.059515000
C	3.482346000	0.567974000	-0.996359000
C	3.363360000	0.030679000	1.370621000
C	4.493414000	1.490005000	-0.729695000
H	3.127191000	0.385070000	-2.006632000
C	4.369587000	0.958081000	1.627972000
H	2.923106000	-0.561938000	2.168173000
C	4.931552000	1.687284000	0.579056000
H	4.937950000	2.054660000	-1.544295000
H	4.717298000	1.110187000	2.645657000
H	5.715354000	2.411685000	0.782865000

25-an: E= -1411.726412

C	-3.683461000	1.577115000	0.035073000
C	-3.874976000	0.076691000	-0.194957000
C	-3.343110000	-0.243939000	-1.582044000
C	-1.841187000	-0.055408000	-1.536651000
H	-3.957540000	1.848775000	1.058550000
H	-4.938726000	-0.168916000	-0.106130000
H	-3.554302000	-1.281847000	-1.864638000
H	-3.788820000	0.409340000	-2.347368000
H	-1.413610000	-0.111121000	-2.552348000
H	-4.305035000	2.173645000	-0.649733000
N	-1.438562000	1.240396000	-0.968300000
C	-2.237332000	2.002564000	-0.138035000
O	-1.777887000	2.982534000	0.435216000
C	-1.137283000	-1.091846000	-0.635283000
C	-1.871080000	-1.199325000	0.676690000
H	-1.374762000	-1.736337000	1.483202000
C	-3.150273000	-0.715682000	0.926813000
C	-0.028330000	1.149349000	-0.587233000
H	0.624586000	1.660413000	-1.304870000
H	0.095915000	1.615909000	0.393800000
O	-3.803969000	-0.812543000	2.005378000
C	-0.973881000	-2.445761000	-1.344875000
H	-0.446187000	-2.352206000	-2.308067000
H	-0.410432000	-3.132928000	-0.707497000
H	-1.960085000	-2.885643000	-1.523080000
C	0.252181000	-0.369280000	-0.566157000
H	0.848939000	-0.662833000	-1.440939000
S	1.334826000	-0.852290000	0.794326000
O	1.528408000	-2.305545000	0.724580000
O	0.975537000	-0.200893000	2.050322000
C	2.893316000	-0.108859000	0.278809000
C	3.200505000	1.183259000	0.696444000
C	3.755767000	-0.834397000	-0.538387000
C	4.395406000	1.763453000	0.272880000
H	2.514080000	1.709785000	1.354384000
C	4.949575000	-0.248181000	-0.953414000
H	3.490888000	-1.849844000	-0.820869000
C	5.265858000	1.050081000	-0.551012000
H	4.648312000	2.770905000	0.590683000
H	5.635186000	-0.805841000	-1.585356000
H	6.197437000	1.505201000	-0.876790000

24: E= -1412.284673

C	-3.594063000	1.830475000	-0.140288000
C	-3.942863000	0.341979000	-0.301290000
C	-3.122546000	-0.194102000	-1.476054000
C	-1.651336000	-0.085402000	-1.124095000
H	-4.051631000	2.273576000	0.748375000
H	-5.017679000	0.229076000	-0.468667000
H	-3.364631000	-1.239381000	-1.696614000
H	-3.337011000	0.387148000	-2.380354000
H	-1.033279000	-0.365364000	-1.986199000
H	-3.985625000	2.375324000	-1.008746000
N	-1.248569000	1.263954000	-0.707457000
C	-2.101964000	2.119330000	-0.041356000
O	-1.689845000	3.069425000	0.603843000
C	-1.209107000	-0.933874000	0.091561000
C	-2.123117000	-0.593237000	1.300643000
H	-2.019051000	-1.349727000	2.084420000
H	-1.833502000	0.371263000	1.743858000

C	-3.599981000	-0.479127000	0.938365000
C	0.115396000	1.139373000	-0.194809000
H	0.827103000	1.272337000	-1.015095000
H	0.297253000	1.909348000	0.555433000
O	-4.458936000	-1.016502000	1.601521000
C	-1.258976000	-2.437054000	-0.180510000
H	-0.737757000	-2.697070000	-1.107000000
H	-0.799609000	-3.002522000	0.633900000
H	-2.303290000	-2.758757000	-0.267174000
C	0.190213000	-0.307999000	0.382748000
H	0.419666000	-0.326743000	1.453027000
S	1.561897000	-1.234965000	-0.360287000
O	1.367345000	-1.252415000	-1.814126000
O	1.713893000	-2.478636000	0.395247000
C	2.984664000	-0.214004000	-0.013125000
C	3.501469000	0.607389000	-1.011301000
C	3.545386000	-0.269505000	1.261391000
C	4.604026000	1.406732000	-0.715041000
H	3.055091000	0.596170000	-2.001812000
C	4.643314000	0.537485000	1.546001000
H	3.140144000	-0.952844000	2.002607000
C	5.167202000	1.374886000	0.560127000
H	5.024990000	2.050469000	-1.481150000
H	5.096319000	0.504691000	2.532054000
H	6.026155000	1.999723000	0.786244000

25: E= -1412.283710

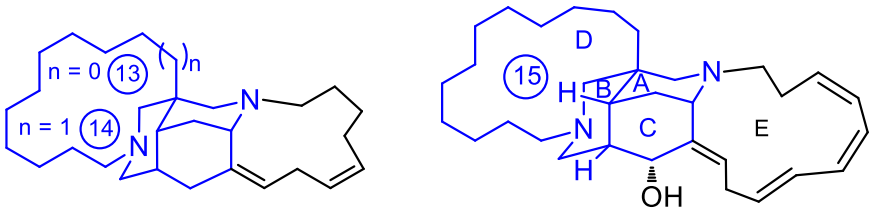
C	-3.541049000	1.708128000	0.213332000
C	-3.912532000	0.265914000	-0.166116000
C	-3.361385000	0.005541000	-1.568207000
C	-1.849755000	0.105228000	-1.507328000
H	-3.776524000	1.938401000	1.256108000
H	-4.998325000	0.141800000	-0.127307000
H	-3.642272000	-0.987894000	-1.935450000
H	-3.759078000	0.741479000	-2.276908000
H	-1.435513000	0.019934000	-2.522836000
H	-4.133512000	2.394600000	-0.404811000
N	-1.364553000	1.366756000	-0.938476000
C	-2.072251000	2.064339000	0.023394000
O	-1.545444000	2.931635000	0.697030000
C	-1.157349000	-0.944846000	-0.605877000
C	-1.798736000	-0.892599000	0.806597000
H	-1.526492000	-1.777094000	1.390087000
H	-1.425042000	-0.026377000	1.370520000
C	-3.316433000	-0.781584000	0.772807000
C	0.076168000	1.204239000	-0.715019000
H	0.656735000	1.629677000	-1.538803000
H	0.346401000	1.719912000	0.210228000
O	-4.025376000	-1.491355000	1.451511000
C	-1.218431000	-2.357076000	-1.180077000
H	-0.888202000	-2.368564000	-2.225989000
H	-0.577307000	-3.032096000	-0.607466000
H	-2.241880000	-2.747250000	-1.140927000
C	0.270323000	-0.335405000	-0.637182000
H	0.792783000	-0.715176000	-1.523747000
S	1.340759000	-0.844212000	0.731093000
O	1.421807000	-2.305459000	0.678216000
O	0.920316000	-0.158979000	1.953183000
C	2.927053000	-0.176955000	0.258265000
C	3.309105000	1.071920000	0.742243000

C	3.737086000	-0.918101000	-0.599442000
C	4.537091000	1.594938000	0.341401000
H	2.662619000	1.604166000	1.434543000
C	4.961200000	-0.383807000	-0.991636000
H	3.417384000	-1.903174000	-0.928082000
C	5.356020000	0.870848000	-0.524691000
H	4.857066000	2.563710000	0.712314000
H	5.610724000	-0.949714000	-1.652320000
H	6.312980000	1.282700000	-0.831612000

7. Síntesis del fragmento diazatetracíclico ABCD de las madangaminas

7.1 Introducción

Después de lograr la síntesis del esqueleto azatriciclico del FR901483 y de los alcaloides de tipo calicifilina A, nos interesamos por la preparación de otro tipo de productos naturales: las madangaminas (ver introducción p. 20). En concreto nos planteamos la preparación del esqueleto tetracíclico de las madangaminas F, D y E formado por el núcleo central diazatricíclico y el hemisferio oeste D completamente hidrogenado para los tres compuestos naturales con 15, 14 y 13 eslabones, respectivamente (Esquema 7.1).

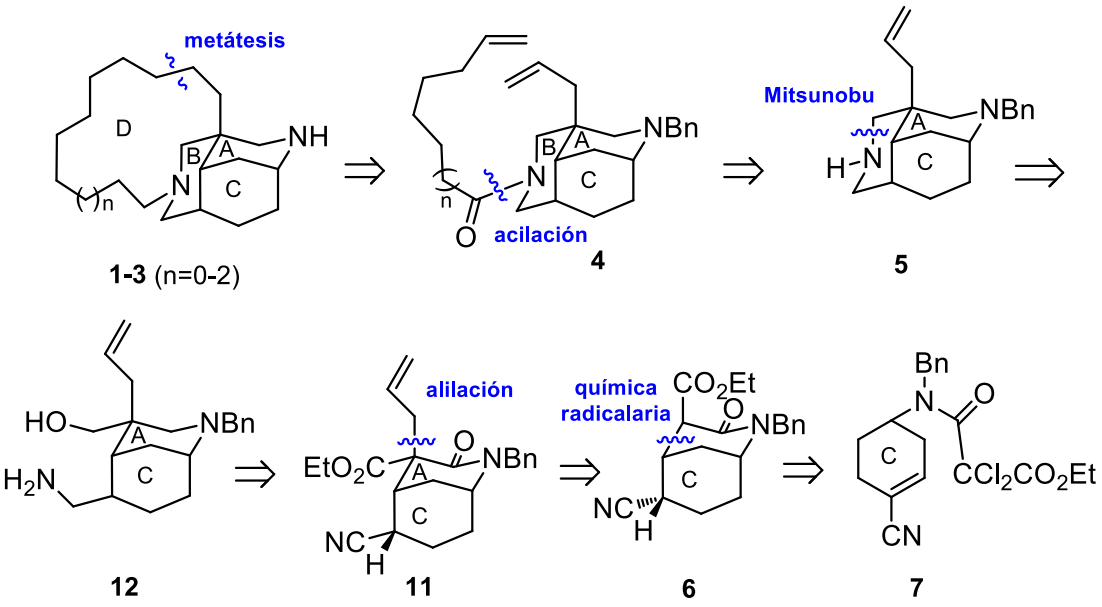


Madangaminas E y D Madangamina F

7.1. Madangaminas E, D y F

Nuestra estrategia sintética (Figura 7.2) conlleva la construcción primero del sistema diazatricíclico, presente en todas las madangaminas, y posterior cierre del macrociclo D por RCM. Esta última se llevaría a cabo desde el dieno **4** preparado por acilación de la amina secundaria **5** con el cloruro de ácido de 9, 10 y 11 carbonos respectivamente. El cierre del tercer anillo piperidínico en **5** se conseguiría mediante una Mitsunobu en el aminoalcohol **12** que a su vez provendría de la reducción de **11**. Finalmente el morfano (2-azabiciclo[3.3.1]nonano) alilado **11** con las funciones y la estereoquímica adecuada (con el nitrilo en posición ecuatorial) seria accesible desde la malonamida **7** utilizando la química radicalaria desarrollada en nuestro grupo de investigación.[1]

[1] (a) Para el trabajo seminal acerca de reacciones radicalarias en condiciones reductoras, en nuestro grupo de investigación, véase: Quirante, J.; Escolano, C.; Massot, M.; Bonjoch, J. *Tetrahedron* **1997**, *53*, 1391-1402.

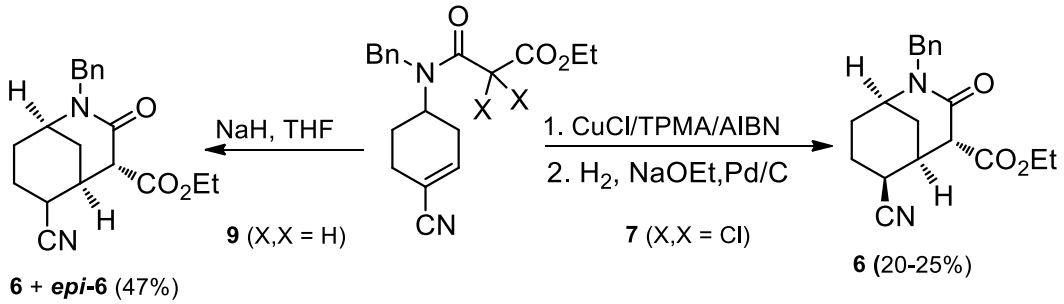


7.2 Estrategia sintética para acceder al esqueleto ABCD de las madangamina E, D y F

7.2 Discusión y resultados

7.2.1 Síntesis del sistema 2-azabiciclo[3.3.1]nonano (AC)

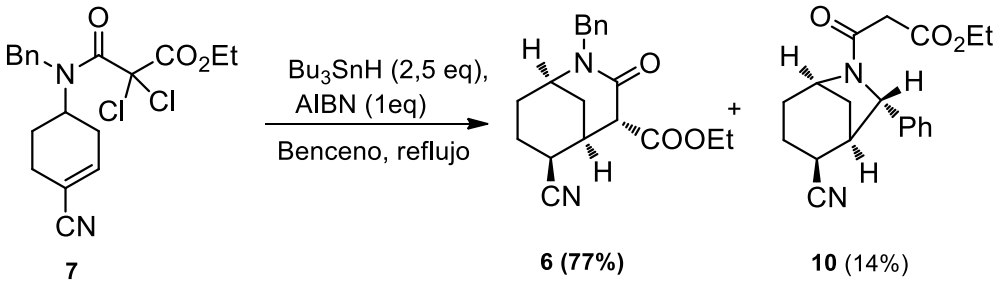
En estudios anteriores a esta parte de la tesis doctoral (capitulo 3) se consiguió la síntesis del morfano **6,** con la esterequimica adecuada para la síntesis del esqueleto tetracíclico, utilizando la química radicalaria con transferencia de átomo pero con bajo rendimiento (20-25%) y con una etapa de reducción adicional del derivado clorado. La preparación de **6** se intentó también mediante una reacción de Michael a partir de **9** (X = H, H), por tratamiento con NaH sin ninguna mejoría apreciable ya que la reacción dio una mezcla de epímeros en el carbono 6 con un rendimiento total del 47% (esquema 7.3).



7.3. Antecedentes de la síntesis del morfano **9**

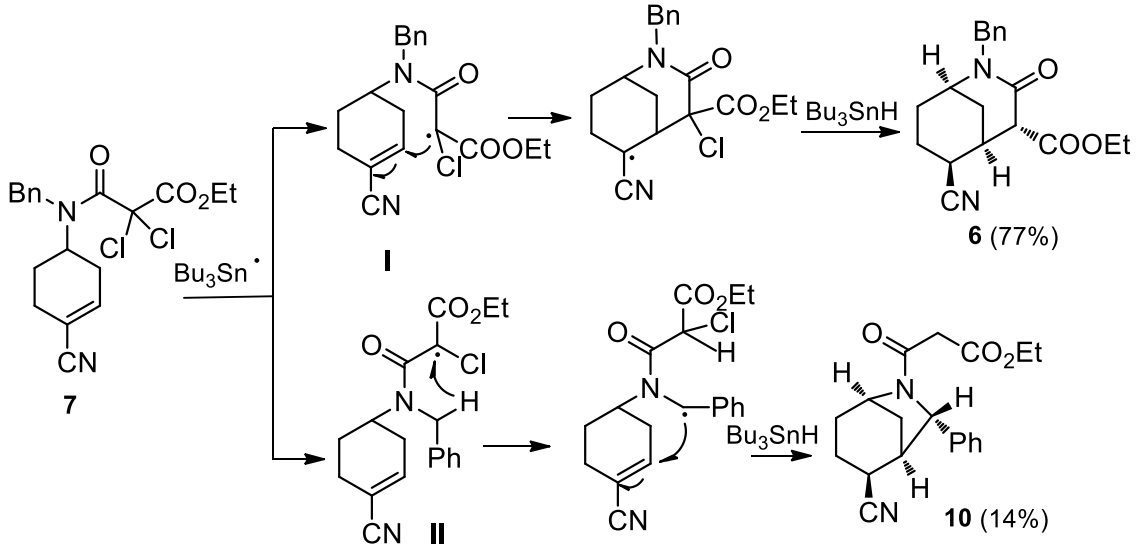
A la vista de estos resultados se optó por la vía radicalaria en condiciones reductoras. Afortunadamente al tratar **7** con 2,5 eq. de Bu_3SnH y 1 eq. de AIBN al reflujo del benceno se obtuvo **6** como único diastereomero de la reacción y con un

buen rendimiento (esquema 7.3). Además, se aisló también el normorfano **10** con un rendimiento del 14%. La utilización de $(TMS)_3SiH$ como agente reductor no dio mejores resultados.



7.3 Síntesis del morfano **6**

El inesperado normorfano **10** proviene del radical α-dicarbonilico en su conformación no reactiva **II** después de una migración de hidrógeno 1,4 y generación de un radical bencílico que se adiciona sobre el nitrilo α,β-insaturado (Esquema 7.4). Este fenómeno se ha observado repetidamente en nuestro grupo de investigación en las reacciones radicalarias de *N*-(1-feniletil)tricloroacetamidas[2], pero nunca en las *N*-benciltricloroacetamidas.

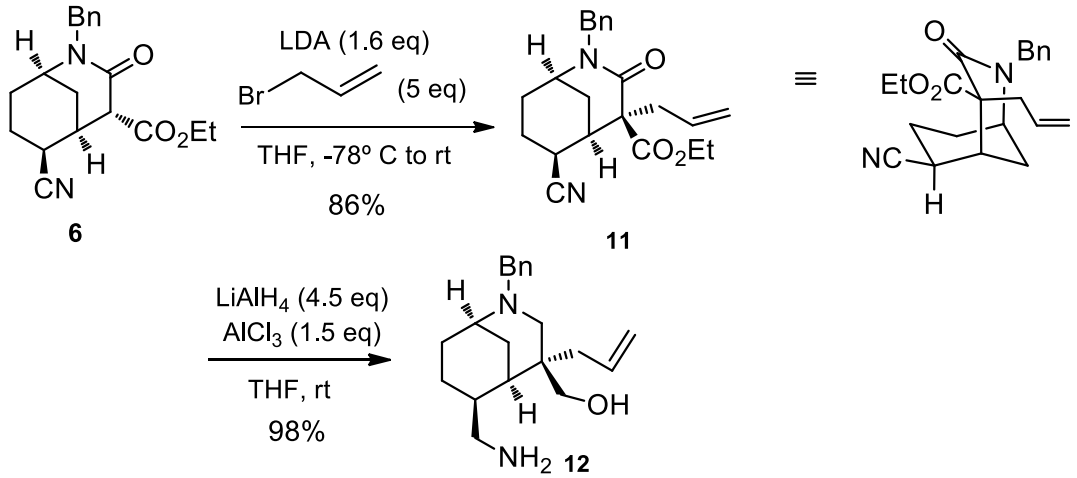


7.4 Mecanismos de la formación de **6** y **10**

[2] (a) Quirante, J.; Torra, M.; Diaba, F.; Escolano, C.; Bonjoch, J. *Tetrahedron: Asymmetry* **1999**,*10*, 2339-2410. (b) Quirante, J.; Diaba, F.; Vila, X.; Bonjoch, J.; Lago, E.; Molins, E. *C. R. Chim.* **2001**, *4*, 513-521; c) Diaba, F.; Montiel, J. A.; Bonjoch, J. *Tetrahedron* **2013**, *69*, 4883-4889.

7.2.2 Síntesis del esqueleto diazatriciclico ABC

Una vez obtenido el morfano **6** con la estereoquímica adecuada nuestro siguiente objetivo fue la instalación del grupo alilo en el carbono 4 que nos permitiría construir el centro cuaternario "C9" de las madangaminas promoviendo al mismo tiempo que el grupo ester se dispusiese en una posición ecuatorial necesaria para la formación del tercer anillo piperidínico y más adelante la formación del macrociclo D. Al tratar el morfano **6** con LDA (1.6 eq) y bromuro de alilo (5 eq) en THF a -78 ºC y después a temperatura ambiente durante 48 h se obtuvo el compuesto **11** como único diastereómero en un muy buen rendimiento (86%) y una excelente estereoselectividad. La alilación tiene lugar exclusivamente por la cara Si más accesible del enolato. Cabe destacar que en los primeros intentos de alilación del morfano **6** se nos formaba una pequeña cantidad del compuesto ***epi*-11** debido a la epimerización de la posición α al grupo CN, que no sólo hacía bajar el rendimiento de **11** sino que dificultaba enormemente el proceso de purificación. La siguiente etapa fue el cierre del anillo B de las madangaminas utilizando un proceso de Mitsunobu sobre el aminoalcohol resultante de la reducción simultánea de las grupos lactama, éster y nitrilo utilizando como agente reductor el alano. Al tratar **11** con un exceso de alano (AlH_3)[3] generado *in situ* por reacción de $LiAlH_4$ (4.5 eq) y $AlCl_3$ (1.5 eq) se obtuvo el diaminoalcohol **12** en un excelente rendimiento (98%) (esquema 7.5.).

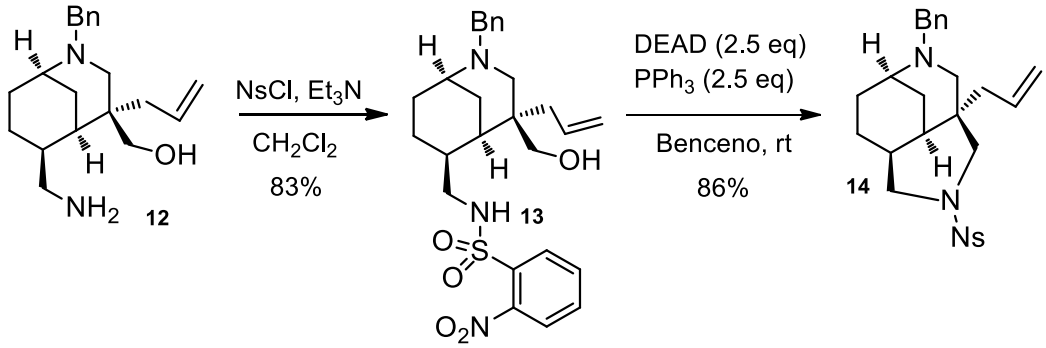


7.5 Preparación del aminoalcohol **12**

Una vez obtenido el compuesto **12** se ensayó la ciclación directa de este aminoalcohol. Desafortunadamente, los primeros intentos de ciclación directa utilizando cloruro de tionilo[4] o probando la reacción de Mitsunobu[5] por tratamiento con DIAD, resultaron infructuosos. Se optó entonces por nosilar la amina primaria de **12** y obtener una sulfonamida más ácida que pudiera dar con éxito la reacción de

[3] Quirante, J.; Paloma, L.; Diaba, F.; Vila, X.; Bonjoch, J. *J. Org. Chem*. **2008**, *73*, 768-771.
[4] Xu, F.; Simmons, B.; Reamer, R. A.; Corley, E.; Murry, J.; Tschaen, D. *J. Org. Chem*. **2008**, *73*, 312-315.
[5] Cui, M.; Song, H.; Feng, A.; Wang, Z.; Wang, Q. *J. Org. Chem*. **2010**, *75*, 7018-7021.

Mitsunobu para formar el anillo B. Al tratar el diaminoalcohol **12** con cloruro de 2-nitrobenceno sulfonilo (1.1 eq) y trietilamina (1 eq) en CH_2Cl_2 se obtuvo la sulfonamida **13** en un 83% de rendimiento. Para satisfacción nuestra, la reacción de **13** con DEAD (2.5 eq) y PPh_3 (2.5 eq) en benceno y a temperatura ambiente durante 24 h proporcionó el diazatriciclo **14** en un 86% de rendimiento (esquema 7.6).



7.6 Formación de la sulfonamida **13** y reacción de Mitsunobu

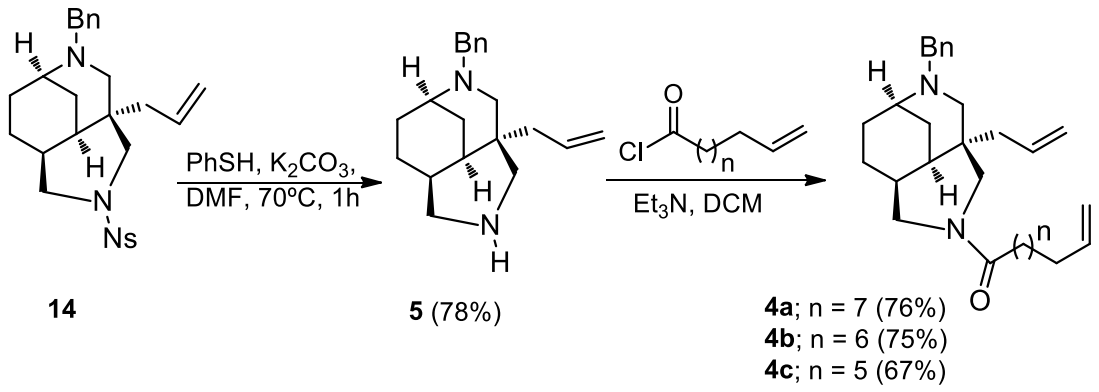
7.2.3 Construcción del esqueleto tetracíclico ABCD

A continuación, nuestros esfuerzos se centraron en construir el anillo D saturado de las madangaminas E, D y F utilizando un mismo intermedio sintético, tal como la amina secundaria **5**, que se obtuvo por tratamiento de la nosilamida **14** con tiofenol (1.2 eq) y K_2CO_3 como base en DMF a 70 ºC con un 78% de rendimiento.,

Como se había mencionado antes, el macrociclo D de las madangaminas F, D y E está completamente hidrogenado y sólo se diferencia por su tamaño (15 eslabones en la madangamina F, 14 eslabones en la madangamina D y 13 eslabones en la madangamina E) y siempre parte del centro cuaternario C9 y termina en N7. Así pues, el acoplamiento entre la amina **5** y un ácido orgánico de longitud adecuada en su cadena carbonada y con doble enlace terminal, permitiría obtener un dieno que sería precursor del tetraciclo ABCD por metátesis de cierre de anillo y posterior hidrogenación.

- ABCD madangamina F → ácido 10-undecenoico
- ABCD madangamina D → ácido 9-decenoico
- ABCD madangamina E → ácido 8-nonenoico

El acoplamiento entre los ácidos orgánicos y la amina **5**, que constituye nuestro material de partida común para las tres series, se consiguió con buen rendimiento a través de los correspondientes cloruros de ácido preparados por tratamiento con un exceso de cloruro de tionilo a 80 ºC (esquema 7.7).



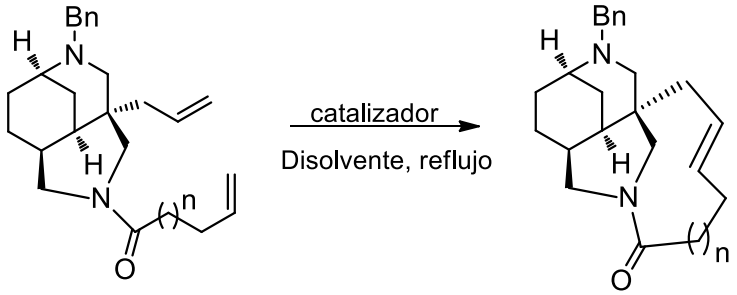
7.7 Preparación de los dienos **4**

A partir de los compuestos **4** pasamos a ensayar la reacción de metátesis de cierre de anillo (RCM), empezando con el dieno **4a** que daría el macrociclo de 15 eslabones. Siguiendo los procesos ya descritos para este tipo de macrociclaciones,[6] el dieno **4a** se trató con el catalitzador de Grubbs I (10%) a reflujo de diclorometano y en condiciones de alta dilución (0.245 mM) para evitar la posible formación de dímeros. Sin embargo y después de 8 h de reacción se recuperó el producto de partida **4a** casi inalterado (entrada 1). La adición de ácido *p*-toluensulfónico[7] como aditivo para protonar la amina terciaria y evitar así su coordinación con el catalizador de Grubbs no supuso ninguna mejoría (entrada 2). Adicionalmente se realizó un último ensayo con el catalizador de Grubbs I en condicione más concentradas (2.917 mM) sin éxito (entrada 3).

Curiosamente al realizar la reacción con el catalizador de Grubbs II y en condiciones bastantes concentradas (2.917 mM) para este tipo de reacciones se obtuvo el compuesto de la RCM con muy buen rendimiento (entrada 4) y como único diastereómero (isómero E)[8]. La aplicación de las mismas condiciones al dieno **4b** proporciono con el mismo rendimiento **15b** como único compuesto de la reacción (entrada 5). Como se esperaba, debido a la tensión que presenta (Figura 7.9.), la formación del anillo de 13 eslabones a partir de **4c** resulto más dificultosa y la reacción en las condiciones anteriores no dio ningún compuesto de RCM (entrada 6).[9] La utilización del catalizador de Grubbs I o Hoveyda-Grubbs II tampoco permitió aislar el compuesto **13c** (entradas 7 y 8). Estos resultados nos empujaron a explorar condiciones más drásticas como realizar la reacción al reflujo de tolueno. El primer ensayo con el catalizador de grubbs II condujo al tetraciclo **15c** con un rendimiento

[6] (a) Ballette, R.; Pérez, M.; Proto, S.; Amat, M.; Bosch, J. *Angew. Chem. Int. Ed*. **2014**, *53*, 6202-6205. (b) Becker, M. H.; Chua, P.; Downham, R.; Douglas, C. J.; Garg, N. K.; Hiebert, S.; Jaroch, S.; Matsuoka, R. T.; Middleton, J. A.; Ng, F. W.; Overman, L. E. *J. Am. Chem. Soc.* **2007**, 129, 11987–12002.
[7] Wright, D. L.; Schulte II, J. P.; Page, M. A.; *Org. Lett*. **2000**, *2*, 1847-1850.
[8] Lee, C. W.; Grubbs, R. H. *Org. Lett*. **2000**, *2*, 2145-2147.
[9] Anslyn, E.; Dougherty, D. *Modern Physical Organic Chemistry*. University Science: Sausulito, 2005.

bajo del 30% (entrada 9). El uso de benzoquinona[10] como aditivo mejora levemente el rendimiento del proceso (entrada 10).



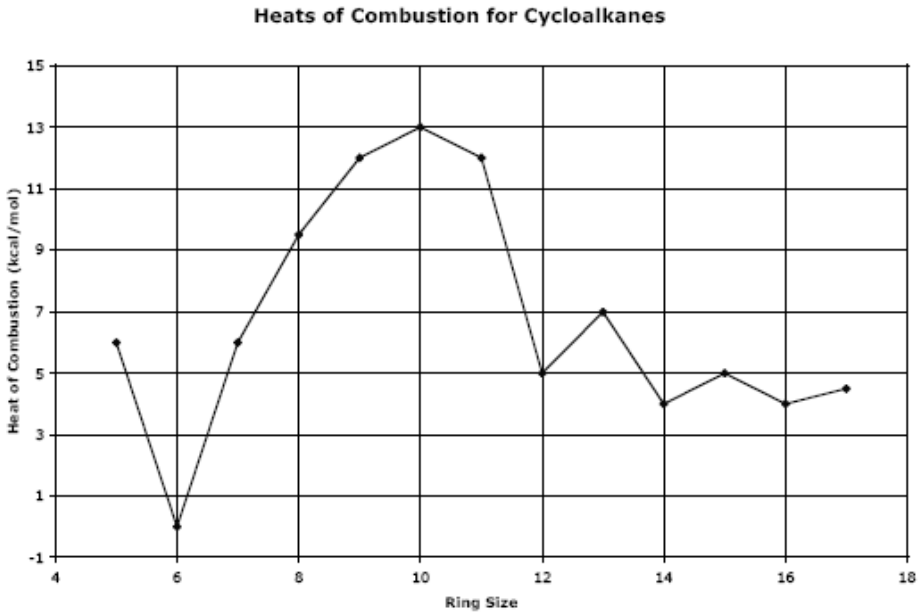
4a
4b
4c

15a; n = 7
15b; n = 6
15c; n = 5

Entrada	**4**	Catalizador (10%)	disolvente	Concentración (aditivos)	**15** (%)
1	**4a**	Grubbs I	CH_2Cl_2	0.245 mM	-
2	**4a**	Grubbs I	CH_2Cl_2	0.249 mM (p-TsOH, 1.5 eq)	-
3	**4a**	Grubbs I	CH_2Cl_2	2.917 mM	-
4	**4a**	Grubbs II	CH_2Cl_2	3.187 mM	**15a** (66)
5	**4b**	Grubbs II	CH_2Cl_2	3.343 mM	**15b** (66)
6	**4c**	Grubbs II	CH_2Cl_2	3.450 mM	-
7	**4c**	Grubbs I	CH_2Cl_2	3.287 mM	-
8	**4c**	Hoveyda-Grubbs II	CH_2Cl_2	3.411 mM	-
9	**4c**	Grubbs II	Tolueno	2.301 mM	**15c** (30)
10	**4c**	Grubbs II	tolueno	3.343 mM (1,4-benzoquinona 0.2 eq)	**15c** (43)

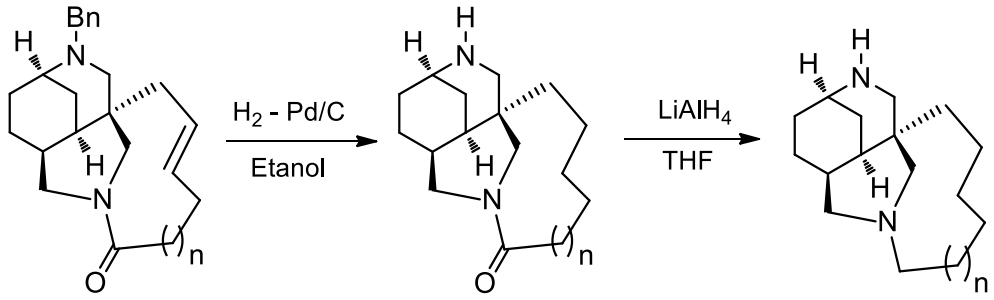
7.8 Reacción de RCM de los dienos **4**.

[10] Hong, S. H.; Sanders, D. P.; Lee, C. W.; Grubbs, R. H. *J. Am. Chem. Soc*. **2005**, *127*, 17160-17161.



7. 9 Calores de combustión de los cicloalcanos

Por último la síntesis se concluyó con la reducción del doble enlace utilizando una hidrogenación catalítica, que también desbencilo la amina del anillo A, y la reducción de la lactama a amina (esquema 7.6).



15a
15b
15c

16a; n = 7 (82%)
16b: n = 6 (67%)
16c; n = 5 (98%)

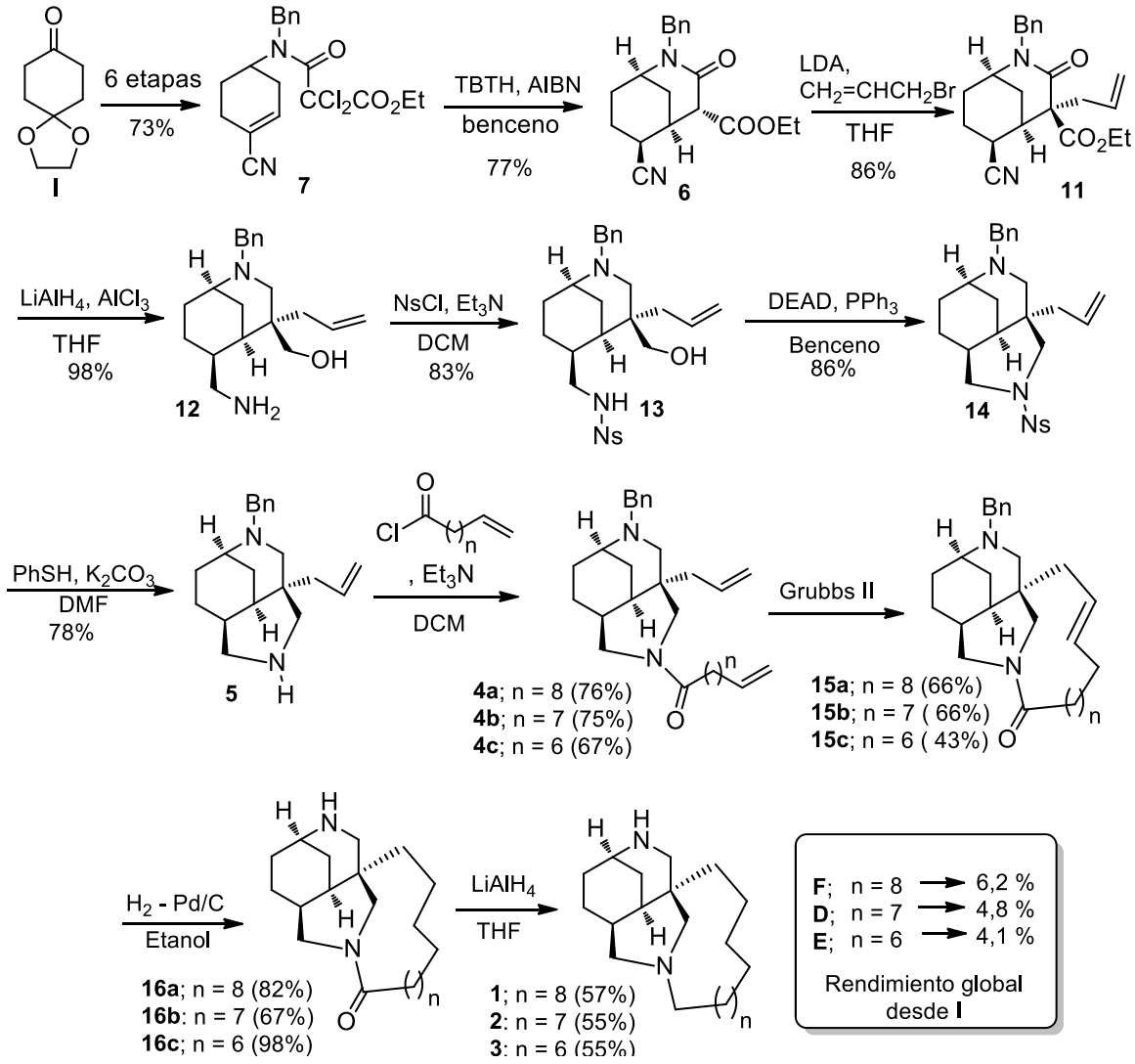
1; n = 7 (57%)
2: n = 6 (55%)
3; n = 5 (55%)

7.6 Etapas finales en la preparación de **1, 2** y **3**

Finalmente, puede mencionarse que este trabajo abre una nueva vía para la síntesis de madangaminas, ya que una funcionalización adecuada en C(3) permitiría la síntesis del macrodiclo E oriental y la obtención de las mismas.

7.3 Resumen

En esta última parte de la tesis se ha conseguido la síntesis del esqueleto ABCD de las madangaminas F, D y E en un total de 17 etapas a partir de 1,4-ciclohexanodiona monoetilenacetal utilizando el mismo intermedio sintético **5** para las 3 series con un rendimiento global del 5%. El proceso incluye como etapas clave la reacción radicalaria intramolecular de un α,α-dicloro-β-amidoéster para formar de manera diastereoselectiva el 2-azabiciclo [3.3.1]nonano **6** con tres de los cuatro centros esterogénicos de estos productos naturales ya fijados. A continuación, una alilación diastereoselectiva permitió la génesis del centro esterogénico cuaternario C(9) y una reacción de Mitsunobu la formación del anillo B para tener el núcleo diazatricíclico **5**, intermedio común para la síntesis de las 3 series. El ensamblaje del macrociclo D occidental de las madangaminas F, D y E se ha alcanzado mediante reacciones de RCM sobre aminas no protegidas y sin utilizar condiciones extremas de alta dilución.



Esquema 7. 6. Resumen de la síntesis de los diazatetraciclos **1**, **2** y **3**.

7. Synthesis of Tetracyclic ABCD Fragments of Madangamines D, E and F

Diaba, F.; Pujol-Grau, C.; Martínez-Laporta, A.; Fernández, I.; Bonjoch, J.

Org. Lett. (en proceso de redacción).

Synthesis of Tetracyclic ABCD Fragments of Madangamines D, E, and F

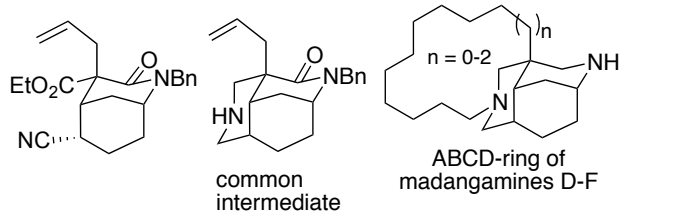
Faïza Diaba*,†, Climent Pujol-Grau†, Agustín Martínez-Laporta†, Israel Fernández‡, and Josep Bonjoch*,†

† Laboratori de Química Orgànica, Facultat de Farmàcia, IBUB, Universitat de Barcelona, Av. Joan XXIII s/n, 08028-Barcelona, Spain

‡ Departamento de Química Orgánica I, Facultad de Ciencias Químicas, Universidad Complutense Madrid, 28040-Madrid, Spain

Supporting Information Placeholder

ABSTRACT: Syntheses of the tetracyclic core of madangamines D, E, and F were achieved, featuring as key steps a reductive radical process from an ethoxycarbonyldichloroacetamide to build the morphan nucleus, a Mitsunobu-type aminocyclization to achieve the common diazatricyclic intermediate, and ring closing metathesis for the macrocyclization step leading to 15- to 13-membered rings.



Madangamines are a group of 3-alkylpiperidine marine alkaloids embodying a pentacyclic skeleton.[1] The six madangamines isolated so far have in common a perhydro-6,4-(iminomethano)isoquinoline core (ABC ring),[2-4] and a western macrocycle of 13 to 15 members. Madangamines A-E contain an eastern polyunsaturated ring and madangamine F shows a greater oxidation state in rings B and E. (Figure 1). Their biological activities, coupled with a highly complex structure, have made these alkaloids attractive synthetic targets. However, only one member of this family, madangamine D, has been achieved by total synthesis, in recent work by Amat and Bosch.[5] Four other approaches have been developed to access the madangamine ABC diazatricyclic core,[6] using either hydroisoquinolines[7] or 2-azabicyclo[3.3.1]nonanes (morphans) as intermediate platforms.[8]

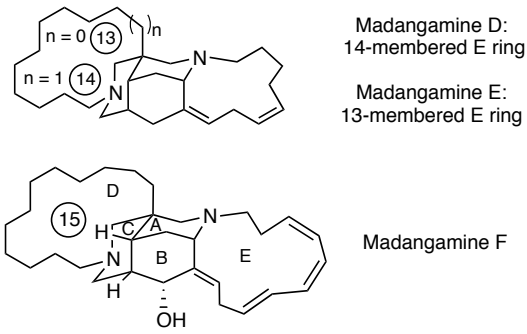
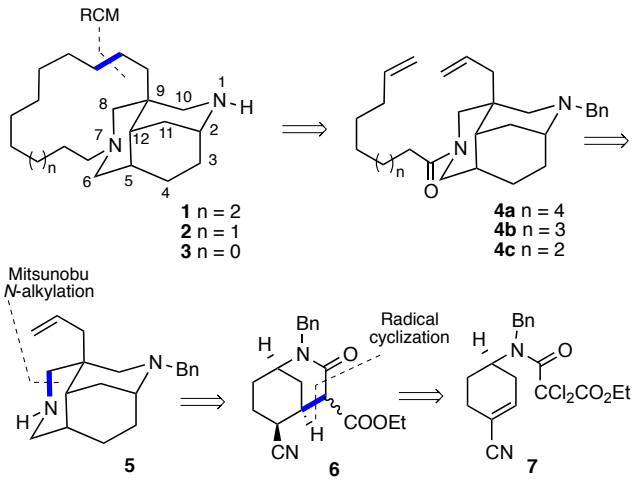


Figure 1. Madangamines D-F embodying a macrocyclic saturated D-membered ring

Scheme 1. Retrosynthetic Strategy for Synthesis of the Tetracyclic ABCD Rings of Madangamines



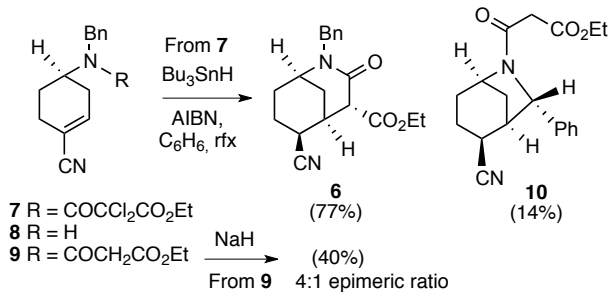
Here, we report a synthetic approach to the tetracyclic core(s) of madangamines D-F from a common precursor. As depicted in Scheme 1, the synthetic strategy we pursued toward our goal, macrocycles **1**-**3**, leads back, via the dienes **4** to diazatricyclic compound **5**, which served as a strategic point of divergence en route to these target-

ed compounds. The polyfunctionalized morphan[9] **6** was envisaged as an early-stage intermediate, whereas the nitrile at C(5) and the ester at C(9) stemming from the morphan radical cyclization would have to be reduced to arrive at an intermediate incorporating the required backbone. Morphan **6** could be accessed by the reductive radical cyclization of dichloroamido ester **7**. Moreover, selective introduction of an allyl group at C(9) would be needed after the morphan cyclization step.

The usefulness of radical synthetic methods for constructing valuable intermediates in target-oriented natural product synthesis has been established in the last twenty years.[10,11] In particular, trichloroacetamides are able to generate radical species for the building of nitrogen-containing rings either in reductive[12] or atom transfer radical cyclizations.[13] As a variation, we herein introduce an alkoxycarbonyldichloroacetamide (Scheme 2) as a radical precursor to build a valuable polyfunctionalized azabicyclic intermediate, which allowed us to develop an approach to the tetracyclic skeletons of madangamines E-F.

The synthesis began with the 4-benzylaminocyclohex-1-encarbonitrile (**8**), which was available in six steps from the monoethylene acetal of 1,4-cyclohexanedione using a protocol that does not require any chromatographic purification.[14] This secondary amine was acylated with 2,2-dichloro-2-ethoxycarbonylacetyl chloride[15] and the resulting dichloroamido ester **7** was treated with Bu_3SnH to induce a reductive radical cyclization[16] leading to the bridged morphan nucleus **6** in 77% yield (Scheme 2). Notably, attempts to obtain **6** by an ionic intramolecular Michael reaction from amido ester **9**, also available from **8**, gave poor results, not only because of the overall yield but also, and even more importantly, due to the low stereocontrol. The lack of diastereoselectivity (**6** was isolated as a 4:1 epimeric mixture at C(5), using NaH as the base) seems inherent to the process, since it is known that the equatorial protonation of exocyclic α-cyano cyclohexyl anions can occur, leaving an axial cyano substituent.[17]

Scheme 2. Radical vs Ionic Cyclization toward the Morphan Ring



Some interesting results were observed in the radical cyclization: (i) the formation of **6** was diastereoselective, the stereochemistry at C(5) and C(9) in morphan **6** being well defined, since the cyano group at C(5) was equatorially located by a kinetic axial delivering of the hydrogen from the Bu_3SnH and the ester group at C-9 has an axial disposition, and (ii) a normorphan compund **8** was also isolated as a minor by-product.[18] The α-amidoyl radical of the general structure NC(O)-CClCO2Et• coming from 7 preferred the *Z* rotamer **INT3** rather than the *E* rotamer **INT1 required for the cyclization step** (Figure 2). DFT calculations (see Supporting Information) established that the two rotamers differ in 6.2 Kcal. However, the TS1 leading to the morphan cyclization required only an activation of 5.3 Kcal/mol, whereas INT3, which is unable to undergo a direct cyclization, required an activation of 14.8 Kcal/mol to undergo a 1,4-H radical translocation, which TS3 then predicts to be diastereoselective. The latter arose from the radical derived from the most stable rotamer that was unable to undergo radical cyclization, but through a very demanding energetic process underwent a 1,4-H radical translocation followed by radical cyclization to the normorphan nucleus. The major and desired compound was formed from the less stable rotamer, but through a less demanding radical intermediate rendered the morphan cyclized compound via a kinetic controlled process (Scheme 2). A profile of the process based on DFT calculations is included in the Supporting Information.

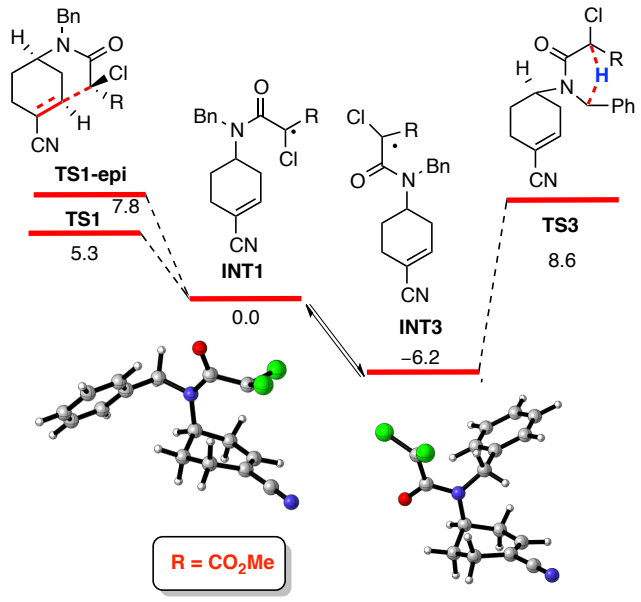
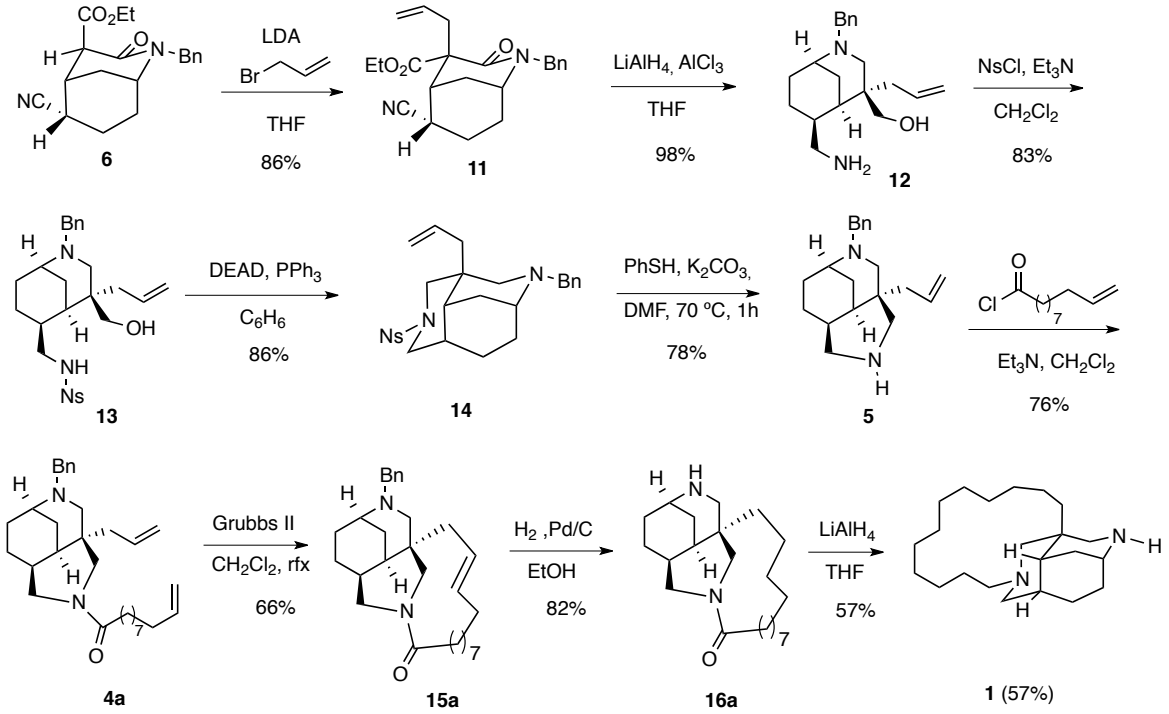


Figure 1. Rotamers of the starting radical enable: (a) radical cyclization; (b) 1,4-hydrogen translocation.

The allylation takes place from the top face under a sterically controlled kinetic reaction to give exclusively **11**[19] (Scheme 4). The configuration in the stereogenic quaternary center in **12** was established unequivocally from a NOESY NMR spectrum in which the methylene proton of

Scheme 3. Synthesis of the Tetracyclic Core of Madangamine F

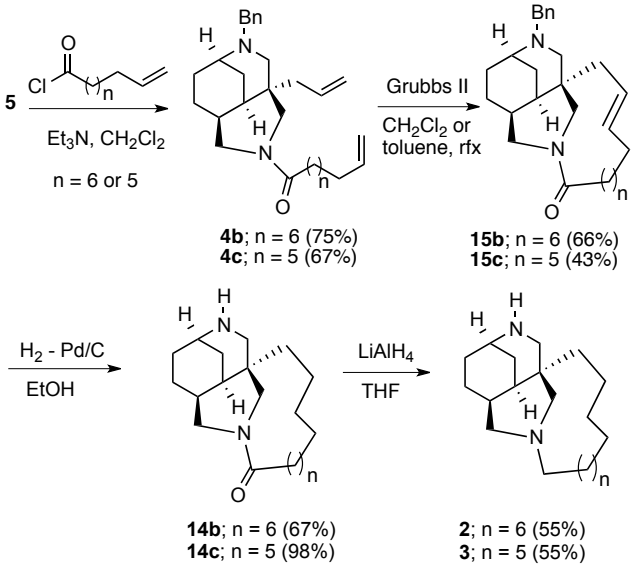


the side chain at δ 2.65 give a cross-peak with the pro-S H-9 at δ 2.20. In the next step, the reduction of the carbonyl lactam, nitrile, and ester groups took place in only one operational step by treatment with alane, generated in situ from $LiAlH_4$ and $AlCl_3$. The process gave the diamino alcohol **12 in high yield**. For the ring closure of the piperidine A ring, a Fukuyama protocol was used involving an initial nosylation and further alkylation through a Mitsunobu process. Removal of the nosyl group rendered the secondary amine 5, which constitutes the common advanced synthetic intermediate en route to the three diazatetracyclic targets.

Amide bond formation between secondary amine **5** and 10-undecenoic acid chloride afforded the RCM precursor **4a** in 83% yield. The ring-closing metathesis (RCM)[20] of 4a was undertaken using Grubbs 2nd generation catalyst in a 3.3 mM in CH_2Cl_2 to give the cyclized product 15a in 66%. Finally, adjustment of the oxidation level by hydrogenation to give **16a**, followed by reduction with $LiAlH_4$ rendered the target **1**. The overall yield for the synthesis of the tetracyclic ring of madangamine F (**1**) was 6.2% over 17 steps.

Having achieved the first target, we pursued the synthetic access to the 14- and 13-macrocyclic ring analogs using the same synthetic protocol, using the secondary amine 5 as a common intermediate. Thus, treatment of **5** with 9-decenoic and 8-nonenoic acid chlorides respectively led to the amides **4b** and **4c** in good yields. RCM from **4b** took place in the same reaction conditions as used from **4c** (Scheme 4). As expected, the formation of the 13-membered ring was sterically more demanding and the cyclization did not proceed when using **4a** in CH_2Cl_2 as a solvent, but when using toluene at 80 ºC and 1,4-benzoquinone as an additive,[21] macrocycle **15c** was isolated in 43%. Its hydrogenation allowed us to isolate the tetracyclic compound **14c, which** by a latter reduction of the lactam rendered **3 (53% over two steps)**.

Scheme 4. Synthesis of tetracyclic ABCD ring of Madangamines D and E



In summary, a 17-step approach for the construction of the ABCD ring system of madangamines F, E, and D has been successfully developed. We have shown that radical chemistry is a powerful reaction for the stereoselective syntheses of the highly functionalized AB ring system. The synthetic pathway allowed access to the three different ABCD fragments of madangamines from a common intermediate. This chemistry will pave the way for the total synthesis of madangamines.

ASSOCIATED CONTENT

Supporting Information

Experimental procedures, spectroscopic and analytical data, and copies of NMR spectra of new compounds. The complete profile of the radical process leading to **6** and **10** is also included. This material is available free of charge via the Internet at http://pubs.acs.org.

AUTHOR INFORMATION

Corresponding Author

* E-mail: josep.bonjoch@ub.edu
* E-mail: faiza.diaba@ub.edu

Notes

The authors declare no competing financial interest.

ACKNOWLEDGMENT

Support of this research was provided by the Spanish Ministry of Economy and Competitiveness (Project CTQ2013-/BQU).

REFERENCES

(1) (a) Andersen, R. J.; van Soest, R. W. M.; Kong, F. Alkaloids: Chemical and Biological Perspectives ; Pelletier, S. W. Ed.; Pergamon-Elsevier Oxford, 1996 ; Vol. 10, pp 301-355. (b) Berlinck, R. G. S. "Polycyclic Diamine Alkaloids from marine sponges. Topics in Heterocyclic chemistry " Springer Berlin, Heidelberg, 2007, 10 , 211-238.

(2) Madandamine A: Kong, F.; Andersen, R. J.; Allen, T. M. *J. Am. Chem. Soc.* **1994** , *116* , 6007-6008.

(3) Madangamines B-E: Kong, F.; Graziani, E. I.; Andersen, R. J. *J. Nat. Prod.* **1998** , *61*, 267-271.

(4) Madangamine F: Oliveira, J. H. H. L.; Nascimento, A. M.; Kossuga, M. H.; Cavalcanti, B. C.; Pessoa, C. O.; Moraes, M. O.; Macedo, M. L.; Ferreira, A. G.; Hajdu, E.; Pinheiro, U. S.; Berlinck, R. G. S. *J. Nat. Prod.* **2007**, *70* , 538-543.

(5) (a) Ballette, R.; Pérez, M.; Proto, S.; Amat, M.; Bosch, J. *Angew. Chem. Int. Ed.* **2014**, *53*, 6202–6205; (b) For a preliminary ABCD ring approach, see: Amat, M.; Ballette, R.; Proto, S.; Pérez, M.; Bosch, J. Chem. Commun. 2013, 49, 3149–3151.

(6) For approaches to the ABC tricyclic fragment of madangamines from hydroisoquinolines (BC rings), see: (a) Matzanke, N.; Gregg, R. J.; Weinreb, S. M.; Parvez, M. J. Org. Chem. 1997, 62, 1920–1921. (b) Quirante, J.; Paloma, L.; Diaba, F.; Vila, X.; Bonjoch, J, J. Org. Chem. 2008, 73, 768–771. (c) Amat, M.; Pérez, M.; Proto, S.; Gatti, T.; Bosch, J. *Chem. Eur. J.* **2010**, *16*, 9438–9441

(7) For approaches from 2-azabicyclo[3.3.1]nonanes (AB rings), see: (a) Yamazaki, N.; Kusanagi, T.; Kibayashi, C. *Tetrahedron Lett.* **2004**, *45* , 6509–6512. (c) Tong, H. M.; Martin, M.-T.; Chiaroni, A.; Bénéchie, M.; Marazano, C. *Org. Lett.* **2005**, *7*, 2437–2440.

(8) (a) For the synthesis of the ACE rings, see: Yoshimura, Y.; Inoue, J.; Yamazaki, N.; Aoyagi, S.; Kibayashi, C. *Tetrahedron Lett.* **2006**, *47*, 3489–3492. (b) Proto, S.; Amat, M.; Pérez, M.; Ballette, R.; Romagnoli, F.; Mancinelli, A.; Bosch, J. *Org. Lett.* **2012**, *14*, 3916–3919.

(9) For a review of 2-azabicyclo[3.3.1]nonanes and their application to natural product synthesis, see: Bonjoch, J.; Diaba, F.; Bradshaw, B. *Synthesis* **2011**, 993-1018.

(10) For a classical review, see: Jasperse C.P.; Curran D.P.; Flevig T.L. *Chem. Rev.* **1991**,*91*, 1237-1286.

(11) Bonjoch, J.; Bradshaw, B.; Diaba, F. In Stereoselective Synthesis of Drugs and Natural Products; Andrushko, V.; Andrushhko, N. Eds.; Wiley-VCH: New York 2013; pp 733-768.

(12) (a) . (b) Quirante, J.; Escolano, C.; Merino, A.; Bonjoch, J. *J. Org. Chem.* **1998**, *63*, 968-976. (c) Cassayre, J.; Quiclet-Sire, B.; Saunier, J.-B.; Zard, S. Z. *Tetrahedron Lett.* **1998**, *39*, 8995-8998. (c) J. Cassayre, S. Z. Zard, *Synlett* **1999**, 501-503.

(13) a) Seijas, J. A.; Vázquez-Tato, M. P.; Castedo, L.; Estévez, R. J.; Onega, M. G.; Ruiz, M. *Tetrahedron* **1992**, *48*, 1637-1642. (b); (c) Li, Q.; Li, G.; Ma, S.; Feng, P.; Shi, Y. *Org. Lett*. **2013**, *15*, 2601-2603. (d) Diaba, F.; Martínez-Laporta, A.; Bonjoch, J. *J. Org. Chem.* **2014**, *79*, 9365-9372.

(14) see Supporting Information.

(15) Castelfranchi, G.; Perrotti, E. *Ann. Chim*. (Rome) **1957**, *47*, 1201-1224.

(16) Treatment of dichloro ester 7 under atom transfer radical cyclization conditions gave a mixture of compounds: Diaba, F.; Martínez-Laporta, A.; Bonjoch, J. *Eur. J. Org. Chem.* **2014**,

(17) For protonation of cyclohexyl anions, see: Lüning, U.; Baumgartner, H.; Manthey, C.; Meynhardt, B. *J. Org. Chem.* **1996**, *61*, 7922-7926. See also: Klein, J. *Tetrahedron* **1974**, *30*, 3349-3353. Hoz, S.; Azran, C.; Sella, A. *J. Am. Chem. Soc.* **1996**, *118*, 5456-5461.

(18) The reductive cyclization of the analogous trichloroacetamide of **7** (Cl atom instead of CO_2Et) exclusively gave the cyclized morphan in 84% yield, no quantity of a normorphan compound being detected.

(19) Using a reverse addition,, a minor amount of the epimer at C() was also isolated (see Supporting Information).

(20)

(21) 1,4-Benzoquinone acts as scavenger of ruthenium hydride species that might be formed during reaction and cause decomposition: (a) Hong, S. H.; Sanders, D. P.; Lee, C. W.; Grubbs, R. H. *J. Am. Chem. Soc*. **2005**, *127*, 17160-17161. (b) Toya, H.; Satoh, T.; Okano, K.; Takasu, K.; Ihara, M.; Takahashi, A.; Tanaka, H.; Tokuyama, H. *Tetrahedron* **2014**, *70*, 8129-8141.

Supporting information

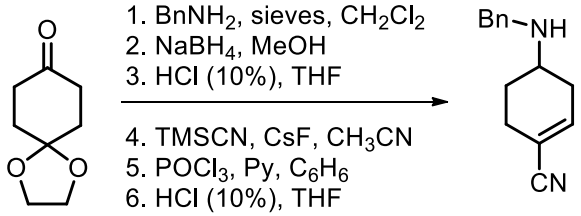
Synthesis of Tetracyclic ABCD Fragments of Madangamines D, E and F

Diaba, F.; Pujol-Grau, C.; Martínez-Laporta, A.; Fernández, I.; Bonjoch, J.

Org. Lett. (en proceso de redacción).

EXPERIMENTAL SECTION

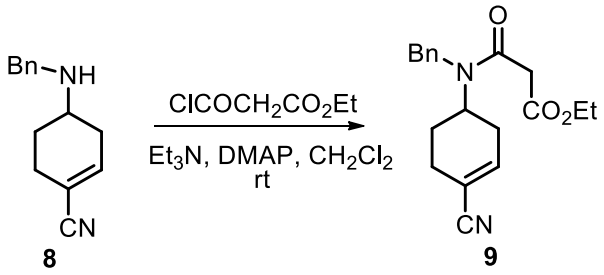
General. ^{1}H and ^{13}C NMR spectra were recorded in $CDCl_3$ solution. ^{1}H Chemical shifts are reported as δ values (ppm) relative to internal Me_4Si and ^{13}C NMR specra are referenced to the deuterated solvent signal ($CDCl_3$: 77.00 ppm). All NMR data assignments are supported by COSY and HSQC experiments. Infrared spectra were recorded on a Nicolet 320 FT-IR spectrophotometer. TLC was performed on SiO_2 (silica gel 60 F_{254}, Merck) or on Al_2O_3 (aluminium oxide 60 F254 neutral, Merck). The spots were located by UV light or a 1% $KMnO_4$ aqueous solution. Chromatography refers to flash chromatography and was carried out on SiO_2 (Silica Flash P60, Wet & Dry, 200-500 mesh) and when indicated on Al_2O_3 (aluminium oxide 90 standardized, Merck). Dry CH_2Cl_2 and toluene used in ring closing metathesis reactions were purged with dry argon before use. Drying of the organic extracts during reaction work-up was performed over anhydrous Na_2SO_4.



8

4-(Benzylamino)cyclohex-1-ene-1-carbonitrile (8). *Part 1*: A mixture of 1,4-cyclohexanedione monoethylene acetal (15 g, 93.2 mmol), benzylamine (13.7 mL, 125.4 mmol) and molecular sieves (30 g) in CH_2Cl_2 (150 mL) was stirred at rt for 4 h then the suspension was filtered on a celite pad and concentrated. The residue was dissolved in MeOH (150 mL) and $NaBH_4$ (3.63 g, 94 mmol) was added portionwise at 0 ºC then stirring was prolonged for an additional hour at rt. The mixture was concentrated, water and CH_2Cl_2 were added, the layers were separated and the aqueous layer was extracted with CH_2Cl_2. The combined organic layers were dried, concentrated, dissolved in THF (15 mL) and treated with a 10% HCl aqueous solution (350 mL) overnight. The mixture was basified with 2.5 N NaOH aqueous solution and extracted with CH_2Cl_2. The organics were dried and concentrated to yield the corresponding aminoketone enough pure to be used in the next step without further purification. *Part 2*: To a solution of the previous product (3 g, 14.77 mmol) in acetonitrile (15 mL) were

added TMSCN (2.1 mL, 16.5 mmol) and CsF (50 mg, 0.33 mmol 2%) and the mixture was stirred at rt overnight. The mixture was then filtered on a celite pad, concentrated and to the resulting residue were added pyridine (25 mL), benzene (5 mL) and $POCl_3$ (4.32 mL). The mixture was heated to reflux for 5 h. concentrated and the residue was partitioned between water and CH_2Cl_2, the layers were separated and the aqueous layer was extracted with CH_2Cl_2. The combined organic layers were dried, concentrated and treated with THF (45 mL) and 10% HCl aqueous solution (60 mL) at 85 ºC for 5 h. The reaction mixture was then basified with a 2.5 N NaOH aqueous solution and extracted with CH_2Cl_2. The organics were dried, concentrated and the residue purified by chromatography (CH_2Cl_2/AcOEt 9:1 to 1:1) to yield **8** (2.71 g, 86% over the 6 steps).

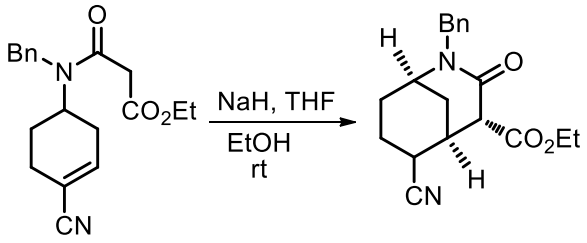


8 **9**

Ethyl 3-[benzyl(4-cyanocyclohex-3-en-1-yl)amino]-3-oxopropanoate (9).

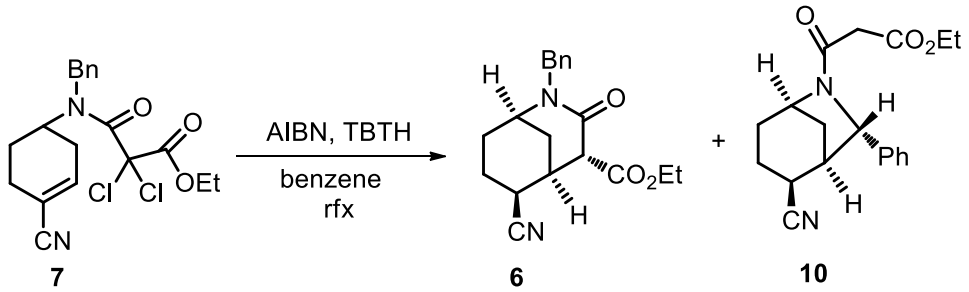
To a solution of **8** (1.01 g, 4.76 mmol) in CH_2Cl_2 (13 mL) were added Et_3N (1 mL, 7.14 mmol), ethylmalonyl chloride (0.73 mL, 5.71 mmol) and the mixture was stirred at rt overnight. Water was added and the mixture was extracted with CH_2Cl_2. The organics were dried, concentrated and purified by chromatography (hexane/AcOEt 3:1 to AcOEt) to yield **9** as a colourless viscous oil (1.13 g, 73%). **^{1}H NMR** ($CDCl_3$, ratio of conformers: 3:1, 400 MHz): δ 1.27 and 1.32 (2 t, *J* = 7.2 Hz, 3H, CH_3), 1.68-1.92 (m, 2H), 2.40-2.60 (m, 4H), 3.38 and 3.61 (2 s, 2H, CH_2N), 3.94 and 4.55 (2 m, 1H), 4.18 and 4.24 (2 q, *J* = 7.2 Hz, 2H), 4.51 and 4.60 (2 s, 2H), 6.50 (brs, 1H, HC=), 7.18-7.43 (m, 5H).**^{13}C NMR** ($CDCl_3$, 100 MHz) δ major rotamer, minor rotamer: 14.0 and 14.1 (CH_3), 25.3 and 27.0 (CH_2), 27.1 and 27.3 (CH_2), 29.0 and 30.5 (CH_2), 41.8 and 41.6 (CH_2), 48.1 and 44.6 (CH_2), 50.0 and 53.2 (CH), 61.4 and 61.7 (CH_2), 111.9 and 112.1 (C), 118.8 and 118.4 (CN), 125.7, 126.6 (CH), 127.7 and 126.9 (CH), 129.0, 128.4 (CH), 136.9 and 138.2 (C), 143.1 and 142.3 (CH=), 167.3 and 166.1 (CO), 167.4 and 167.5 (CO).

- ***Synthesis of morphan 6 using Michael conditions***



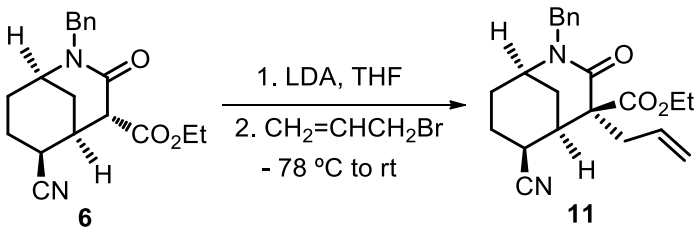
To a solution of **7** (200 mg, 0.61 mmol) in THF (5 ml) was added 60% NaH dispersion in mineral oil (46.6 mg, 1.2 mmol) and the mixture was stirred at rt overnight. AcOEt and 1N HCl aqueous solution (2 mL) were added and the layers were separated. The aqueous was extracted with AcOEt and the combined organics were dried, concentrated and purified by chromatography (hexane/AcOEt 1:1) to yield the corresponding morphans as an inseparable 4:1 mixture of epimers **6**[1] and ***epi*-6** (93 mg, 47%).

- ***Synthesis of morphan 6 using radical conditions***



A solution of **7** (1.10 g, 2.78 mmol) in benzene (20 ml) was heated to reflux (90º) and then a solution of TBTH (1.9 ml, 6.85 mmol) and AIBN (483 mg, 2.94 mmol) in benzene (7 ml) was added over 1 h using a syringe pump. The reaction was prolonged for an additional 3 h then it was concentrated and purified by chromatography (hexane to hexane/AcEt 1:3) to yield **6** (700 mg, 2.145 mmol, 77 %) and then **10**[1] (125 mg, 0.385 mmol, 14%).

[1] For NMR data **6** and **10** see: Diaba, F.; Matínez-Laporta, A.;Bonjoch, J.; *Eur.J. Org. Chem*. **2014,** 2371–2378.

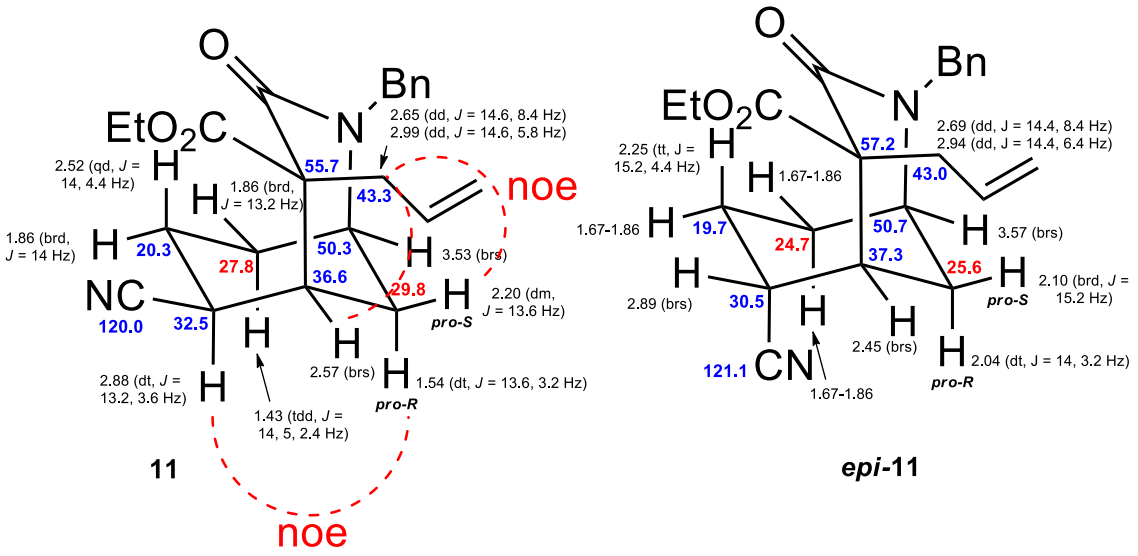


(1*RS*,4*SR*,5*RS*,6*SR*)-Ethyl 4-allyl-2-benzyl-6-cyano-3-oxo-2-azabicyclo [3.3.1]nonane-4-carboxylate (11).

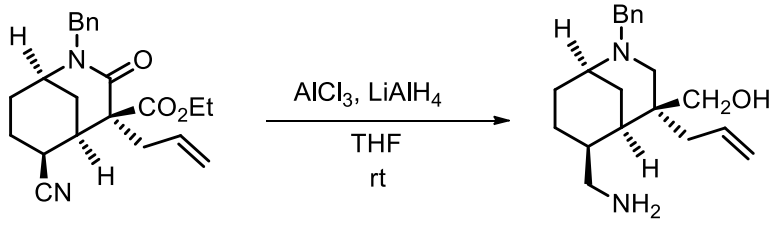
To a solution of diisopropylamine (0.31 ml, 2.207 mmol) in THF (6 ml) at -78 ºC was added a 1.6 M solution of BuLi in THF (1.23 ml, 1.962 mmol) dropwise. The mixture was stirred at this temperature for 5 min then transferred via a cannula to the reaction flask containing **6** (400 mg, 1.226 mmol) in THF (12 ml) at -78ºC and stirred for an additional 15 min. Allyl bromide (0.53 ml, 6.132 mmol) was then add dropwise, the reaction was allowed to reach rt and stirred for 48 h. AcOEt (20 mL) was added and the resulting solution was washed with a saturated aqueous NH_4Cl solution and the aqueous were extracted with EtOAc. The organics were dried, concentrated and purified by chromatography (CH_2Cl_2/EtOAc 9:1) to afford **11** (385 mg, 1. 051 mmol, 86%) as a crystalline solid. **IR** (NaCl, neat): 3074, 3029, 2979, 2940, 2237, 1731, 1634 cm^{-1}; **^{1}H NMR** ($CDCl_3$, 400 MHz): δ 1.35 (t, *J* = 7.2 Hz, 3H, CH_3), 1.43 (tdd, *J* = 14, 5, 2.4 Hz, 1H, H-8ax), 1.54 (dt, *J* = 13.6, 3.2 Hz, 1H, H-9-pro*R*), 1.86 (brd, *J* = 14 Hz, 1H, H-7eq), 1.90 (brd, *J* = 13.2 Hz, 1H, H-8eq), 2.20 (dm, *J* = 13.6 Hz, 1H, H-9-*proS*), 2.52 (qd, *J* = 14, 4.4 Hz, 1H, H-7ax), 2.57 (brs, 1H, H-5), 2.65 (dd, *J* = 14.6, 8.4 Hz, 1H), 2.88 (dt, *J* = 13.2, 3.6 Hz, 1H, H-6), 2.99 (dd, *J* = 14.6, 5.8 Hz, 1H), 3.53 (brs, 1H, H-1), 4.08 (d, *J* = 14.8 Hz, 1H, CH_2Ar), 4.35 (q, J = 7.2 Hz, 2H, CH_2O), 5.11 (m, 2H, CH_2=), 5.16 (d, *J* = 14.4 Hz, 1H, CH_2Ar), 6.12 (m, 1H, CH=), 7.25-7.36 (m, 5H, H-Ar). **^{13}C NMR** ($CDCl_3$, 100 MHz): δ 13.5 (CH_3), 20.3 (C-7), 27.8 (C-8), 29.8 (C-9), 32.5 (C-6), 36.6 (C-5), 43.3 (CH_2), 48.8 (CH_2Ar), 50.3 (C-1), 55.7 (C-4), 61.7 (CH_2O), 118.4 (CH_2=), 120.0 (CN), 127.6, 128.0, 128.7 (Ar-CH), 134.7 (CH=), 137.4 (*ipso*-C), 169.2 (CO), 170.7 (CO). HRMS (ESI-TOF) m/z: $[M+H]^+$ calculated for $C_{22}H_{27}N_2O_3$ 367.2016; found 367.2021.

(1*RS*,4*SR*,5*RS*,6*RS*)-Ethyl 4-allyl-2-benzyl-6-cyano-3-oxo-2-azabicyclo [3.3.1]nonane-4-carboxylate (*epi*-11 at C-6).

To a solution 4:1 mixture of **6** and ***epi*-6** (107, 0.328 mmol) in THF (3 mL) at -78 ºC was added a 2M solution of LDA in THF (0.26 mL, 0.525 mmol) and the mixture was stirred for 15 min. Allyl bromide (0.15 ml, 1.72 mmol) was then add dropwise, the reaction was allowed to reach rt and stirred for 48 h. AcOEt (5 mL) was added and the resulting solution was washed with a saturated aqueous NH_4Cl solution and the aqueous were extracted with EtOAc. The organics were dried, concentrated and purified by chromatography (CH_2Cl_2/EtOAc 9:1) to afford ***epi*-11** (17 mg, 14%) and then **11** (74 mg, 62%).**^{1}H NMR** ($CDCl_3$, 400 MHz): δ 1.34 (t, *J* = 6.8 Hz, 3H, CH_3), 1.67-1.86 (m, 3H, H-7eq and CH_2-8), 2.04 (dt, *J* = 14, 3.2 Hz, 1H, H-9-pro*R*), 2.10 (brd, *J* = 15.2 Hz, 1H, H-9-*proS*), 2.25 (tt, *J* = 15.2, 4.4 Hz, 1H, H-7ax), 2.45 (brs, 1H, H-5), 2.69 (dd, *J* = 14.4, 8.4 Hz, 1H), 2.89 (brs, 1H, H-6), 2.94 (dd, *J* = 14.4, 6.4 Hz, 1H), 3.57 (brs, 1H, H-1), 3.98 (d, *J* = 14.8 Hz, 1H, CH_2Ar), 4.23 (dq, *J* = 10.8, 6.8 Hz, 1H, CH_2O), 4.33 (dq, *J* = 10.8, 6.8 Hz, 1H, CH_2O), 5.12 (m, 2H, CH_2=), 5.22 (d, *J* = 14.8 Hz, 1H, CH_2Ar), 5.99 (m, 1H, CH=), 7.25-7.36 (m, 5H, H-Ar). **^{13}C NMR** ($CDCl_3$, 100 MHz): δ 14.1 (CH_3), 19.7 (C-7), 24.7 (C-8), 25.6 (C-9), 30.5 (C-6), 37.3 (C-5), 43.0 (CH_2), 48.7 (CH_2Ar), 50.7 (C-1), 57.2 (C-4), 61.8 (CH_2O), 118.9 (CH_2=), 121.1 (CN), 127.7, 128.0, 128.7 (Ar-CH), 133.8 (CH=), 137.3 (*ipso*-C), 168.7 (CO), 171.0 (CO).



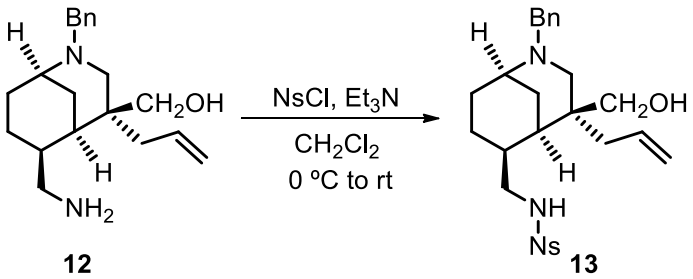
^{1}H and ^{13}C NMR data of 11 and *epi*-11



11 **12**

(1*RS*,4*SR*,5*RS*,6*SR*)-4-Allyl-4-hydroxymethyl-6-aminomethyl-2-benzyl-2-azabicyclo[3.3.1]nonane (12).

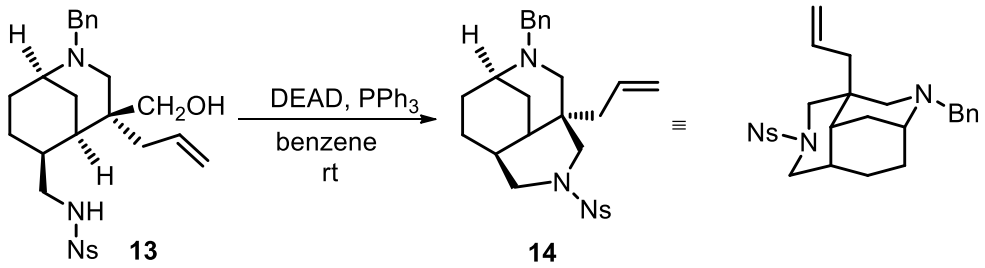
To a solution of $AlCl_3$ (462 mg, 3.461 mmol) in THF (10.6 ml) was added a 1M solution of $LiAlH_4$ in THF (10.38 ml, 10.38 mmol) and the mixture was stirred for 15 min. A solution of **11** (845 mg, 2.31 mmol) in THF (9ml) was then added dropwise via cannula and the reaction was stirred overnight. The mixture was cooled to 0ºC and quenched with a 30% aqueous KOH. The reaction mixture was extracted sequentially with CH_2Cl_2, $CHCl_3$, and $CHCl_3$/i-PrOH (4:1) keeping the aqueous phase basic with NaOH 2.5 N. The organics were dried and concentrated to yield **12** (709 mg, 2.255 mmol, 98 %) enough pure to be used in the next step without further purification. **IR** (NaCl, neat): 3356, 3175, 3065, 3026, 2927, 2864, 1635, 1600, 1584 cm^{-1}; **^{1}H NMR** ($CDCl_3$, 400 MHz): δ 1.36 (dm, *J* = 12.8 Hz, 1H, H-9), 1.40 (ddd, *J* = 13.6, 10.4, 4 Hz, 1H, H-8ax), 1.61 (m, 2H, CH_2-7), 1.99 (brs, 1H, H-5), 2.03 (m, 1H, H-6), 2.27 (m, 3H, H-8eq and CH_2-3), 2.35 (dm, *J* = 12.8 Hz, 1H, H-9), 2.43 (dd, J = 13.6, 7.6 Hz, 1H), 2.61 (dd, *J* = 13.6, 7.6 Hz, 1H), 2.78 (t, *J* = 11.6 Hz, 1H, CH_2NH_2), 3.91 (brs, 1H, H-1), 3.00 (dd, *J* = 11.6, 6.4 Hz, 1H, CH_2NH_2), 3.18 (d, *J* = 12.4 Hz, 1H, CH_2OH), 3.54 (d, *J* = 12.8 Hz, 1H, CH_2Ar), 3.57 (d, *J* = 10.4 Hz, 1H, CH_2OH), 3.75 (d, *J* = 13.2 Hz, 1H, CH_2Ar), 4.95 (m, 2H, CH_2=), 5.91 (m, 1H, CH=), 7.19-7.37 (m, 5H, H-Ar). **^{13}C NMR** ($CDCl_3$, 100 MHz): δ 25.1 (C-8), 28.3 (C-7), 31.1 (C-5), 33.7 (C-9), 41.6 (CH_2), 43.4 (C-4), 45.2 (C-6), 47.2 (CH_2NH_2), 52.3 (C-1), 53.2 (C-3), 59.8 (CH_2Ar), 67.6 (CH_2OH), 117.1 (CH_2=), 126.7, 128.1, 128.5 (Ar-CH), 136.1 (CH=), 140.0 (*ipso*-C). HRMS (ESI-TOF) m/z: $[M+H]^+$ calculated for $C_{20}H_{31}N_2O$ 315.2431; found 315.2437.



12 **13**

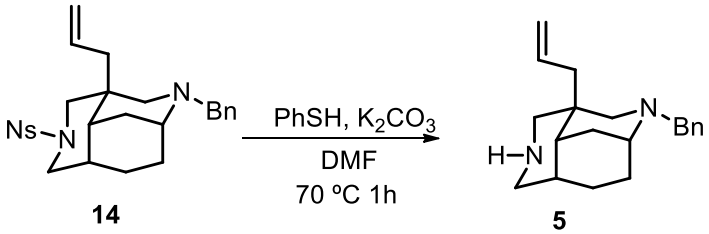
(1*RS*,4*SR*,5*RS*,6*SR*)-*N*-{[4-Allyl-2-benzyl-4-(hydroxymethyl)-2-azabicyclo [3.3.1]non-6-yl]methyl}-2-nitrobenzenesulfonamide (13).

To a solution of **12** (300 mg, 0.954 mmol) in CH_2Cl_2 (2.5 ml) were added successively triethylamine (0.14 ml, 0.954 mmol) and 2-nitrobenzenesulfonyl chloride (237 mg, 1.049 mmol) at 0ºC and then the mixture was stirred at rt for 3h. Water was added and the mixture was successively extracted with CH_2Cl_2, $CHCl_3$, and $CHCl_3$/i-PrOH (4:1). The organics were dried, concentrated, and purified by chromatography (CH_2Cl_2/EtOAc 90:10) to afford **13** (203 mg, 0.793 mmol, 83%). **IR** (NaCl, neat): 3554, 3296, 3071, 3026, 2928, 1835, 1593, 1541 cm^{-1}; **^{1}H NMR** ($CDCl_3$, 400 MHz): δ 1.15 (dt, *J* = 13.2, 2.8 Hz, 1H, H-9), 1.36 (m, 1H, H-8ax), 1.50 (qd, *J* = 12.8, 6 Hz, 1H, H-7ax), 1.62 (m, 1H, H-7eq), 1.92 (brs, 1H, H-5), 2.07 (m, 1H, H-6), 2.14 (dm, *J* = 13.2 Hz, 1H, H-9), 2.20 (d, *J* = 11.6 Hz, 1H, H-3), 2.23 (m, 1H, H-8eq), 2.26 (d, *J* = 11.6 Hz, 1H, H-3), 2.46 (dd, *J* = 14, 7.6 Hz, 1H), 2.52 (dd, *J* = 14, 7.6 Hz, 1H), 2.84 (brs, 1H, H-1), 3.05 (dd, *J* = 14, 11.6 Hz, 1H, CH_2NH_2), 3.33 (dd, *J* = 14, 5.6 Hz, 1H, CH_2NH_2), 3.38 (d, *J* = 11.6 Hz, 1H, CH_2OH), 3.43 (d, *J* = 11.6 Hz, 1H, CH_2OH), 3.51 (d, *J* = 13.6 Hz, 1H, CH_2Ar), 3.71 (d, *J* = 13.6 Hz, 1H, CH_2Ar), 5.04 (m, 2H, CH_2=), 5.77 (m, 1H, CH=), 7.00 (brs, 1H, NH), 7.18-7.32 (m, 5H, H-Ar), 7.70 (m, 2H, H-Ar), 7.83 (m, 1H, H-Ar), 8.14 (m, 1H, H-Ar). **^{13}C NMR** ($CDCl_3$, 100 MHz): δ 24.6 (C-8), 27.2 (C-7), 31.2 (C-5), 33.7 (C-9), 42.2 (CH_2), 42.9 (C-4), 44.9 (C-6), 48.9 (CH_2NH_2), 52.3 (C-1), 53.7 (C-3), 59.8 (CH_2Ar), 68.0 (CH_2OH), 117.8 (CH_2=), 125.1, 126.8, 128.2, 128.3, 130.4, 132.6, 133.0 (Ar-CH), 135.4 (Ar-C), 136.0 (CH=), 139.6, 147.9 (Ar-C). HRMS (ESI-TOF) m/z: $[M+H]^+$ calculated for $C_{26}H_{34}N_3O_5S$ 500.2214; found 500.2220.



(4*RS*,4a*SR*,6*SR*,8a*RS*)-4-Allyl-9-benzyl-2-((2-nitrophenyl)sulfonyl) perhydro -6,4-(iminomethano)isoquinoline (14).

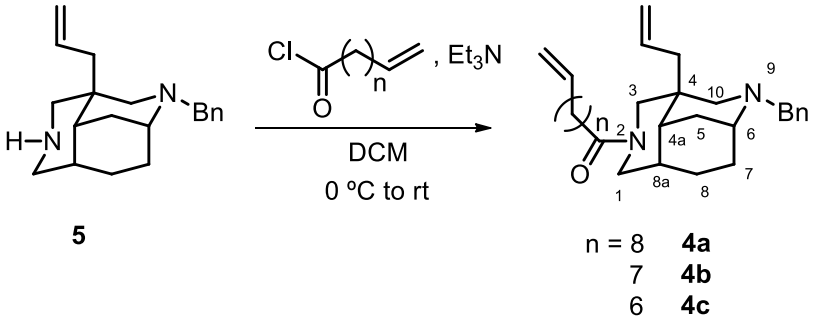
To a stirred solution of **14** (396 mg, 0.793 mmol) and PPh_3 (547 mg, 1.982 mmol) in benzene (8 ml) was slowly added DEAD (0.873 ml, 1.982 mmol) at rt and the mixture was stirred overnight. The reaction mixture was then concentrated and the residue purified by chromatography on alumina (hexane to hexane/CH_2Cl_2 50:50) to give the tricyclic derivative **15** (330 mg, 0.685 mmol, 86%) as a needle-crystalline solid. **IR** (NaCl, neat): 3074, 3026, 2895, 2795, 1637, 1589, 1544 cm^{-1}; **^{1}H NMR** ($CDCl_3$, 400 MHz): δ 1.37 (dt, *J* = 12.8, 2.8 Hz, 1H, H-5), 1.38 (m, 1H, H-7ax), 1.51 (brs, 1H, H-4a), 1.67 (m, 1H, H-8eq), 1.95 (m, 1H, H-8a), 2.04 (m, 1H, H-8ax), 2.19 (dm, *J* = 12.8 Hz, 1H, H-5), 2.25 (m, 1H, H-7eq), 2.36 (m, 3H, H-10 and CH_2), 2.51 (d, *J* = 12.4 Hz, 1H, H-3), 2.75 (dd, *J* = 12, 2.8 Hz, H-1), 2.82 (brs, 1H, H-6), 2.97 (d, *J* = 12.4 Hz, 1H, H-10), 3.33 (dd, *J* = 12.4, 1.6 Hz, 1H, H-3), 3.60 (d, *J* = 13.6 Hz, 1H, CH_2Ar), 3.64 (dt, *J* = 12, 1.6 Hz, 1H, H-1), 3.76 (d, *J* = 13.6 Hz, 1H, CH_2Ar), 5.00 (m, 2H, CH_2=), 5.64 (m, 1H, CH=), 7.00 (brs, 1H, NH), 7.19-7.36 (m, 5H, H-Ar), 7.55 (m, 1H, H-Ar), 7.66 (m, 2H, H-Ar), 7.86 (m, 1H, H-Ar). **^{13}C NMR** ($CDCl_3$, 100 MHz): δ 24.3 (C-7), 25.2 (C-8), 30.6 (C-5), 34.3 (C-8a), 35.0 (C-4a), 36.3 (C-4), 41.2 (CH_2), 50.1 (C-6), 52.0 (C-1), 53.2 (C-3), 54.1 (C-10), 59.6 (CH_2Ar), 118.6 (CH_2=), 123.8, 126.6, 128.1, 128.4, 130.6, 131.3 (Ar-CH), 131.6 (Ar-C), 133.3 (Ar-CH), 133.4 (CH=), 139.8, 148.5 (Ar-C). HRMS (ESI-TOF) m/z: $[M+H]^+$ calculated for $C_{26}H_{32}N_3O_4S$ 482.2108; found 482.2109.



14 **5**

(4*RS*,4a*SR*,6*SR*,8a*RS*)-4-Allyl-9-benzylperhydro-6,4-(iminomethano) isoquinoline (5).

A mixture of **14** (326 mg, 0.677 mmol), K_2CO_3 (373 mg, 2.708 mmol) and thiophenol (0.083 ml, 0.812 mmol) in DMF (6.3 ml) was stirred at reflux for 1h. Water and a 2.5 N aqueous NaOH solution (2ml) were added and the mixture was extracted with CH_2Cl_2. The organics were dried, concentrated and purified by chromatography using alumina (CH_2Cl_2 to CH_2Cl_2 / MeOH 99:1) to give **5** (157 mg, 0.530 mmol, 78%) as an orange viscous oil. **IR** (NaCl, neat): 3352, 3071, 3026, 2922, 2886, 2794, 1636, 1598 cm^{-1}; **^{1}H NMR** ($CDCl_3$, 400 MHz): δ 1.30 (dt, *J* = 12.4, 2.8 Hz, 1H, H-5), 1.39 (qdd, *J* = 13.6, 7.6, 3.6 Hz 1H, H-7ax), 1.54 (brs, 1H, H-4a), 1.54 (m, 1H, H-8eq), 1.71 (m, 2H, H-8a and NH), 1.95 (qd, *J* = 13.2, 7.2 Hz, 1H, H-8ax), 2.20 (dm, *J* = 12.4 Hz, 1H, H-5), 2.27 (m, 4H, H-7eq, H-10 and CH_2), 2.41 (d, *J* = 12.8 Hz, 1H, H-3), 2.50 (d, *J* = 12.8 Hz, 1H, H-3), 2.70 (dd, *J* = 12.4, 1.2 Hz, H-1), 2.74 (dd, *J* = 12.4, 3.2 Hz, H-1), 2.82 (brs, 1H, H-6), 2.89 (d, *J* = 12 Hz, 1H, H-10), 3.60 (d, *J* = 13.6 Hz, 1H, CH_2Ar), 3.80 (d, *J* = 13.6 Hz, 1H, CH_2Ar), 4.95 (m, 2H, CH_2=), 5.68 (m, 1H, CH=), 7.18-7.38 (m, 5H, H-Ar). **^{13}C NMR** ($CDCl_3$, 100 MHz): δ 25.0 (C-7), 25.6 (C-8), 31.1 (C-5), 34.3 (C-8a), 35.5 (C-4a), 35.8 (C-4), 42.0 (CH_2), 50.8 (C-6), 52.0 (C-1), 54.0 (C-3), 55.1 (C-10), 60.0 (CH_2Ar), 117.3 (CH_2=), 126.6, 128.1, 128.4 (Ar-CH), 134.7 (CH=), 140.2 (*ipso*-C). HRMS (ESI-TOF) m/z: $[M+H]^+$ calculated for $C_{20}H_{29}N_2$ 297.2325; found 297.2333.



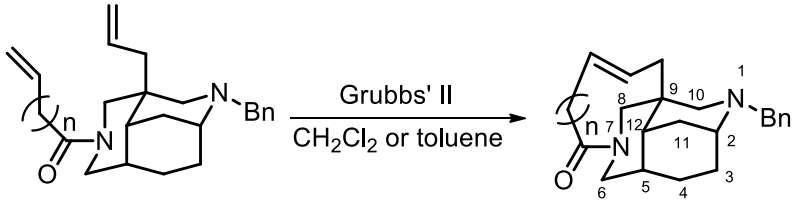
A solution of 10-undecenoic acid (0.21 ml, 1.012 mmol) and thionyl chloride (0.56 ml, 7.66 mmol) was stirred at reflux for 1.5 h and then concentrated. The residue was diluted in CH_2Cl_2 (0.4 ml) and was added dropwise to a solution of **5** (250 mg, 0,843 mmol) and triethylamine (0.24 ml, 1.687 mmol) in CH_2Cl_2 (0.8 ml) at 0 ºC. The mixture was allowed to reach rt and stirred for 6 h. Water was then added and the mixture extracted with CH_2Cl_2. The organics were dried, concentrated and purified by chromatography (Hexane/EtOAc 8:2) to give **4a** (296 mg, 0.639 mmol, 76**%**) as a brown oil.

(4*RS*,4a*SR*,6*SR*,8a*RS*)-4-Allyl-9-benzyl-2-(undec-10-enoyl)perhydro-6,4-(iminomethano)isoquinoline (4a). 2 rotamers: IR (NaCl, neat): 3072, 3025, 2924, 2852, 1646 cm^{-1}; **^{1}H NMR** ($CDCl_3$, 400 MHz): δ 1.33 (m, 12.5H) , 1.64 (m, 5H), 1.91 (brs, 1H), 2.04 (m, 2H), 2.12-2.50 (m, 7H), 2.54 (dd, *J* = 13.2, 3.2 Hz, 0.5H), 2.60 (d, *J* = 12 Hz, 0.5H), 2.65 (d, *J* = 11.2 Hz, 0.5H) , 2.78 and 2.81 (2 brs, 1H), 2.84 (d, *J* = 14 Hz, 0.5H), 3.07 (dd, *J* = 13.6, 3.2 Hz, 0.5H), 3.27 (dd, *J* = 13.6, 1.6 Hz, 0.5H) , 3.53 (d, *J* = 13.6 Hz, 0.5H), 3.54 (d, *J* = 13.6 Hz, 0.5H), 3.60 (d, *J* = 13.2 Hz, 0.5H), 3.71 (d, *J* = 13.6 Hz, 0.5H), 3.75 (d, *J* = 13.6 Hz, 0.5H), 4.21 (dd, *J* = 13.6, 2 Hz, 0.5H), 4.49 (d, *J* = 12.8 Hz, 0.5H), 4.90-5.07 (m, 4H, CH_2=), 5.62-5.87 (m, 2H, CH=), 7.16-7.35 (m, 5H, H-Ar). **^{13}C NMR** ($CDCl_3$, 100 MHz): δ 24.4 and 24.5 (CH_2), 25.2 (CH_2), 25.3 and 25.4 (CH_2), 28.8 (CH_2), 29.0 (CH_2), 29.3 (CH_2), 29.4 and 29.5 (CH_2), 30.6 (CH_2), 33.3 (CH_2), 33.7 (CH_2), 34.7 and 35.2 (CH), 35.4 and 35.7 (CH), 36.7 and 37.0 (C-4), 41.2 and 41.4 (CH_2), 47.3 and 48.8 (CH_2), 49.7 and 50.6 (CH), 51.3 and 53.0 (CH_2), 54.3 and 55.0 (CH_2), 59.5, 59.8 (CH_2), 114.1 (CH_2=), 118.1 and 118.4 (CH_2=), 126.6 and 126.7,128.0 and 128.1, 128.2 and 128.3 (Ar-CH), 133.6 and 133.9 (CH=), 139.1 (CH=), 139.8 (*ipso*-C), 172.6 and 172.6 (CO). HRMS (ESI-TOF) m/z: $[M+H]^+$ calculated for $C_{31}H_{47}N_2O$ 463.3683; found 463.3686.

(4*RS*,4a*SR*,6*SR*,8a*RS*)-4-Allyl-9-benzyl-2-(dec-9-enoyl)perhydro-6,4-(iminomethano)isoquinoline (4b). Operating as above from 9-decenoic acid (0.22 ml, 1.096 mmol), thionyl chloride (0.61 ml, 8.297 mmol), **5** (250 mg, 0,843 mmol), triethylamine (0.24 ml, 1.687 mmol) and after chromatography **4b** was obtained as a brownish oil (286 mg, 0.637 mmol, 75%). **2 rotamers: IR** (NaCl, neat): 3073, 3026, 2995, 2853, 1642 cm^{-1}; **^{1}H NMR** ($CDCl_3$, 400 MHz): δ 1.33 (m, 10.5H) , 1.64 (m, 5H), 1.91 (brs, 1H), 2.04 (m, 2H), 2.12-2.50 (m, 7H), 2.55 (dd, *J* = 12.8, 3.2 Hz, 0.5H), 2.59 (d, *J* = 12.4 Hz, 0.5H), 2.65 (d, *J* = 12 Hz, 0.5H) , 2.81 (brs, 1H), 2.84 (d, *J* = 13.6 Hz, 0.5H), 3.08 (dd, *J* = 13.2, 3.2 Hz, 0.5H), 3.27 (dd, *J* = 14, 2 Hz, 0.5H) , 3.54 (d, *J* = 13.6 Hz, 0.5H), 3.56 (d, *J* = 14.4 Hz, 0.5H), 3.60 (d, *J* = 13.6 Hz, 0.5H), 3.72 (d, *J* = 14 Hz, 0.5H), 3.76 (d, *J* = 13.6 Hz, 0.5H), 4.21 (dd, *J* = 13.6, 1.6 Hz, 0.5H), 4.50 (d, *J* = 12.8 Hz, 0.5H), 4.90-5.07 (m, 4H, CH_2=), 5.62-5.87 (m, 2H, CH=), 7.17-7.36 (m, 5H, H-Ar). **^{13}C NMR** ($CDCl_3$, 100 MHz): δ 24.4 and 24.5 (CH_2), 25.2 (CH_2), 25.3 (CH_2), 28.8 (CH_2), 28.9 and 28.9 (CH_2), 29.2 (CH_2), 29.4 (CH_2), 30.5 and 30.6 (CH_2), 33.3 and 33.4 (CH_2), 33.7 (CH_2), 34.7 and 35.2 (CH), 35.4 and 35.7 (CH), 36.7 and 37.1 (C-4), 41.2 and 41.4 (CH_2), 47.3 and 48.8 (CH_2), 49.7 and 50.6 (CH), 51.3 and 53.0 (CH_2), 54.3 and 54.9 (CH_2), 59.5, 59.8 (CH_2), 114.1 (CH_2=), 118.1 and 118.5 (CH_2=), 126.6 and 126.7,128.0 and 128.1, 128.3 and 128.4 (Ar-CH), 133.5 and 133.9 (CH=), 139.1 (CH=), 139.6 (*ipso*-C), 172.7 (CO). HRMS (ESI-TOF) m/z: $[M+H]^+$ calculated for $C_{30}H_{45}N_2O$ 449.3526; found 449.3515.

(4*RS*,4a*SR*,6*SR*,8a*RS*)-4-Allyl-9-benzyl-2-(non-9-enoyl)perhydro-6,4-(iminomethano)isoquinoline (16c). Operating as above from 8-nonenoic acid (0.19 ml, 1.096 mmol), thionyl chloride (0.61 ml, 8.297 mmol), **5** (250 mg, 0,843 mmol), triethylamine (0.24 ml, 1.687 mmol) and after chromatography **4c** was obtained as a brown viscous oil (244 mg, 0.561 mmol, 67%). **2 rotamers: IR** (NaCl, neat): 3074, 2926, 2855, 1641 cm^{-1}; **^{1}H NMR** ($CDCl_3$, 400 MHz): δ 1.33 (m, 8.5H) , 1.64 (m, 5H), 1.91 (brs, 1H), 2.04 (m, 2H), 2.12-2.50 (m, 7H), 2.55 (dd, *J* = 13.2, 3.6 Hz, 0.5H), 2.59 (d, *J* = 12.4 Hz, 0.5H), 2.65 (d, *J* = 11.6 Hz, 0.5H) , 2.80 (brs, 1H), 2.84 (d, *J* = 14 Hz, 0.5H), 3.08 (dd, *J* = 13.2, 3.6 Hz, 0.5H), 3.27 (dd, *J* = 13.6, 1.6 Hz, 0.5H) , 3.54 (d, *J* = 13.6 Hz, 0.5H), 3.55 (d, *J* = 13.6 Hz, 0.5H), 3.60 (d, *J* = 13.6 Hz, 0.5H), 3.72 (d, *J* = 14 Hz, 0.5H), 3.76 (d, *J* = 14 Hz, 0.5H), 4.21 (dd, *J* = 13.2, 1.6 Hz, 0.5H), 4.49 (d, *J* = 13.2 Hz, 0.5H),

4.89-5.07 (m, 4H, CH_2=), 5.62-5.87 (m, 2H, CH=), 7.17-7.36 (m, 5H, H-Ar). **^{13}C NMR** ($CDCl_3$, 100 MHz): δ 24.4 and 24.5 (CH_2), 25.1 (CH_2), 25.3 (CH_2), 28.7 (CH_2), 28.8 (CH_2), 29.2 and 29.3 (CH_2), 30.5 and 30.6 (CH_2), 33.3 (CH_2), 33.7 (CH_2), 34.7 and 35.2 (CH), 35.4 and 35.7 (CH), 36.8 and 37.0 (C-4), 41.2 and 41.4 (CH_2), 47.3 and 48.8 (CH_2), 49.7 and 50.6 (CH), 51.3 and 53.0 (CH_2), 54.3 and 54.9 (CH_2), 59.5, 59.8 (CH_2), 114.2 (CH_2=), 118.1 and 118.4 (CH_2=), 126.6 and 126.7, 128.0 and 128.1, 128.3 (Ar-CH), 133.5 and 133.9 (CH=), 139.0 (CH=), 139.7 (*ipso*-C), 172.6 and 172.7 (CO). HRMS (ESI-TOF) m/z: $[M+H]^+$ calculated for $C_{29}H_{43}N_2O$ 435.3370; found 435.3363.



n = 8 **4a**
n = 7 **4b**
n = 6 **4c**

n = 8 **15a**
n = 7 **15b**
n = 6 **15c**

To a solution of **4a** (300 mg, 0.649 mmol) in DCM (200 ml) heated to reflux (55ºC) was added a solution of Grubbs' 2nd generation catalyst (55.4 mg, 0.065 mmol) diluted in DCM (10 ml) in one portion through the septum. The solution was stirred at this temperature for 5 h then the solvent was evaporated under reduced pressure and the residue was purified by chromatography (Hexane/EtOAc 50:50) to afford **15a** (175 mg, 0.403 mmol, 64%) and **4a** (35 mg, 0.117 mmol, 12%).

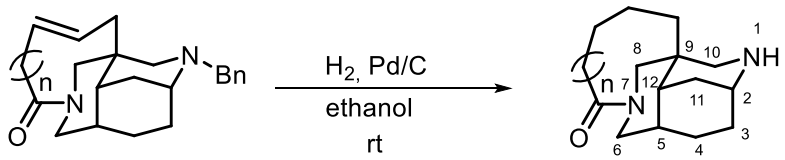
15a: **IR** (NaCl, neat): 3025, 2924, 2851, 1642 cm^{-1}; **^{1}H NMR** ($CDCl_3$, 400 MHz): δ 0.84-1.72 (m, 18H), 1.91 (m, 3H), 2.20 (m, 4H), 2.44 (d, *J* = 11.6 Hz, 1H, H-10), 2.52 (d, *J* = 11.6 Hz, 1H, H-10), 2.56 (dd, *J* = 12.8, 3.2 Hz, H-6), 2.73 (d, *J* = 13.6 Hz, H-8), 2.86 (brs, 1H, H-2), 3.01 (dd, *J* = 12.8, 8 Hz, 1H), 3.33 (dd, *J* = 13.6, 2 Hz, 1H, H-8), 3.52 (d, *J* = 13.2 Hz, 1H, CH_2Ar), 3.77 (d, *J* = 13.2 Hz, 1H, CH_2Ar), 4.44 (d, *J* = 12.8 Hz, 1H, H-6), 5.02 (dt, *J* = 15.2, 6.8 Hz, 1H, CH=), 5.18 (dt, *J* = 15.2, 6.8 Hz, 1H, CH=), 7.20-7.37 (m, 5H, H-Ar). **^{13}C NMR** ($CDCl_3$, 100 MHz): δ 22.9 (CH_2), 24.7 (CH_2), 25.5 (CH_2), 25.6 (CH_2), 26.1 (CH_2), 27.1 (CH_2), 27.4 (CH_2), 27.6 (CH_2), 31.0 (CH_2), 32.2 (CH_2), 35.0 (CH_2), 35.1 (CH), 37.2 (C-9), 39.3 (CH), 39.8 (CH_2), 47.2 (C-6), 51.5 (C-2 and C-10), 54.1 (C-8),

60.3 (CH_2Ar), 125.6 (CH=), 126.8, 128.2, 128.6 (Ar-CH), 134.9 (CH=), 140.0 (*ipso*-C), 173.6 (CO). HRMS (ESI-TOF) m/z: $[M+H]^+$ calculated for $C_{29}H_{43}N_2O$ 435.3370; found 435.3376.

13b: Operating as above from **4b** (60mg, 0.134 mmol) in DCM (40 mL) and a solution of 2nd generation Grubbs catalyst (11.4 mg, 0.0134 mmol) in DCM (2 mL), after chromatography **15b** was obtained (37 mg, 0.088 mmol, 66%) as a white solid. **IR** (NaCl, neat): 3027, 2924, 2851, 1643 cm^{-1}; **^{1}H NMR** ($CDCl_3$, 400 MHz): δ 0.90-1.76 (m, 16H), 1.92 (m, 3H), 2.18 (m, 4H), 2.48 (d, *J* = 11.6 Hz, 1H, H-10), 2.54 (d, *J* = 11.6 Hz, 1H, H-10), 2.58 (dd, *J* = 12.8, 3.6 Hz, H-6), 2.62 (d, *J* = 14 Hz, H-8), 2.86 (brs, 1H, H-2), 3.02 (dd, *J* = 12.8, 6.8 Hz, 1H), 3.44 (dd, *J* = 13.6, 1.6 Hz, 1H, H-8), 3.53 (d, *J* = 13.2 Hz, 1H, CH_2Ar), 3.77 (d, *J* = 13.2 Hz, 1H, CH_2Ar), 4.38 (d, *J* = 12.8 Hz, 1H, H-6), 5.01 (dt, *J* = 15.6, 6.8 Hz, 1H, CH=), 5.17 (dt, *J* = 15.2, 7.2 Hz, 1H, CH=), 7.20-7.37 (m, 5H, H-Ar). **^{13}C NMR** ($CDCl_3$, 100 MHz): δ 22.5 (CH_2), 24.6 (CH_2), 24.7 (CH_2), 25.3 (CH_2), 25.9 (CH_2), 27.4 (CH_2), 27.5 (CH_2), 30.7 (CH_2), 30.8 (CH_2), 33.9 (CH_2), 34.7 (CH), 37.2 (C-9), 38.6 (CH_2), 38.9 (CH), 47.2 (C-6), 51.0 (C-10), 51.2 (C-2), 54.4 (C-8), 60.1 (CH_2Ar), 126.8 (Ar-CH), 126.9 (CH=), 128.1, 128.6 (Ar-CH), 133.8 (CH=), 139.9 (*ipso*-C), 173.7 (CO). HRMS (ESI-TOF) m/z: $[M+H]^+$ calculated for $C_{28}H_{41}N_2O$ 421.3213; found 421.3214.

13c: To a solution of **4c** (94 mg, 0.216 mmol) and 1,4-benzoquinone (5 mg, 0.043 mmol) in toluene (50 ml) heated to reflux (110º C) was added a solution of 2nd generation Grubbs' catalyst (18 mg, 0.0216 mmol) in toluene (2 ml) in one portion through the septum. The mixture was stirred at this temperature for 50 min then the solvent was evaporated under reduced pressure and the residue purified by chromatography (Hexane/EtoAc 1:1) to afford **15c** (38 mg, 0.093 mmol, 43%) as a white solid. **IR** (NaCl, neat): 3023, 2926, 2854, 1644 cm^{-1}; **^{1}H NMR** ($CDCl_3$, 400 MHz): δ 0.98 (m, 1H), 1.12 (m, 1H), 1.20-1.84 (m, 13H), 1.94 (br s, 1H, H-5), 2.06-2.40 (m, 5H), 2.49 (d, *J* = 14.4 Hz, 1H, H-8), 2.50 (d, *J* = 11.6 Hz, 1H, H-10), 2.60 (dd, *J* = 12.8, 3.6 Hz, 1H, H-6), 2.64 (d, *J* = 12.8 Hz, H-10), 2.80 (brs, 1H, H-2), 3.16 (dd, *J* = 12.8, 5.2 Hz, 1H), 3.55 (d, *J* = 15.2 Hz, 1H, H-8), 3.59 (d, *J* = 14 Hz, 1H, CH_2Ar), 3.76 (d, *J* = 13.2 Hz, 1H, CH_2Ar), 4.28 (d, *J* = 12.8 Hz, 1H, H-6), 5.13 (ddd, *J* = 15.2, 10, 5.2 Hz, 1H, CH=), 5.27 (ddd,

J = 15.2, 9.6, 4.4 Hz, 1H, CH=), 7.20-7.38 (m, 5H, H-Ar). **^{13}C NMR** ($CDCl_3$, 100 MHz): δ 21.9 (CH_2), 22.8 (CH_2), 24.6 (CH_2), 26.0 (CH_2), 26.9 (CH_2), 27.2 (CH_2), 30.8 (CH_2), 31.7 (CH_2), 34.7 (CH_2), 34.9 (C-5), 36.0 (C-9), 38.8 (C-12), 39.1 (CH_2), 47.1 (C-6), 50.5 (C-2), 51.9 (C-10), 55.2 (C-8), 59.7 (CH_2Ar), 125.9 (CH=), 126.7, 128.1, 128.2 (Ar-CH), 135.5 (CH=), 140.0 (*ipso*-C), 173.5 (CO). HRMS (ESI-TOF) m/z: $[M+H]^+$ calculated for $C_{27}H_{39}N_2O$ 407.3057; found 407.3060.



n = 8 **15a**
n = 7 **15b**
n = 6 **15c**

n = 8 **16a**
n = 7 **16b**
n = 6 **16c**

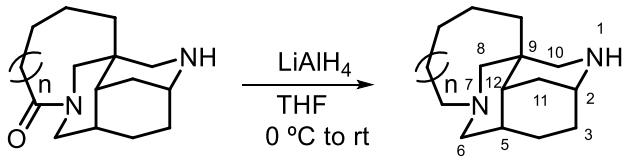
A suspension of **15a** (150 mg, 0.345 mmol) and 10% Pd/C (75 mg) in ethanol (22 ml) was stirred under 1 atm H_2 at rt overnight. The mixture was then filtered on a short celite pad which was washed with CH_2Cl_2 then with MeOH. The solution was concentrated and the residue purified by chromathography (Al_2O_3, CH_2Cl_2 to CH_2Cl_2/MeOH 95:5) to afford **16a** (93 mg, 0.268 mmol, 82%).

16a: IR (NaCl, neat): 3315, 2926, 2856, 1636 cm^{-1}; **^{1}H NMR** ($CDCl_3$, 400 MHz): δ 0.93 (m, 1H), 1.16-1.56 (m, 19H), 1.57-2.04 (m, 7H), 2.16 (m, 3H), 2.51 (m, 1H), 2.63 (dd, *J* = 13.2, 3.2 Hz, 1H, H-6), 2.72 (d, *J* = 13.2 Hz, 1H, H-10), 2.73 (d, *J* = 13.2 Hz, H-8), 2.99 (brs, 1H, H-2), 3.18 (d, *J* = 13.2 Hz, H-10), 3.67 (dd, *J* = 13.6, 1.6 Hz, 1H, H-8), 4.42 (d, *J* = 13.2 Hz, 1H, H-6). **^{13}C NMR** ($CDCl_3$, 100 MHz): δ 22.5 (CH_2), 24.2 (CH_2), 25.4 (CH_2), 26.2 (CH_2), 26.4 (CH_2), 26.6 (CH_2), 27.4 (CH_2), 28.2 (CH_2), 30.2 (CH_2), 31.9 (CH_2), 33.2 (CH_2), 34.6 (C-5), 34.6 (CH_2), 36.2 (C-9), 38.2 (C-12), 44.9 (C-2), 45.8 (C-10), 47.4 (C-6), 54.9 (C-8), 173.9 (CO). HRMS (ESI-TOF) m/z: $[M+H]^+$ calculated for $C_{22}H_{39}N_2O$ 347.3057; found 347.3060.

16b: Operating as above from **15b** (99 mg, 0.235 mmol) and 10% Pd/C (50mg) in ethanol (15 ml). After chromathography **16b** was isolated (52 mg, 0.156 mmol, 67%). **IR** (NaCl, neat): 3300, 2928, 2861, 1641 cm^{-1}; **^{1}H NMR** ($CDCl_3$,

400 MHz): δ 0.77 (m, 1H), 1.00-2.04 (m, 24H), 2.12 (m, 2H), 2.44 (m, 2H), 2.64 (dd, *J* = 12.8, 3.6 Hz, 1H, H-6), 2.75 (d, *J* = 13.2 Hz, 1H, H-10), 2.80 (d, *J* = 13.6 Hz, H-8), 2.99 (brs, 1H, H-2), 3.16 (dd, *J* = 13.2, 1.6 Hz, H-10), 3.59 (d, *J* = 13.6 Hz, 1H, H-8), 4.37 (d, *J* = 13.2 Hz, 1H, H-6). **^{13}C NMR** ($CDCl_3$, 100 MHz): δ 20.8 (CH_2), 22.5 (CH_2), 23.6 (CH_2), 24.9 (CH_2), 25.6 (CH_2), 25.7 (CH_2), 26.7 (CH_2), 27.9 (CH_2), 30.0 (CH_2), 32.2 (CH_2), 33.7 (CH_2), 33.8 (CH_2), 34.8 (C-5), 37.4 (C-9), 38.9 (C-12), 45.0 (C-2), 45.3 (C-10), 47.4 (C-6), 54.1 (C-8), 173.7 (CO). HRMS (ESI-TOF) m/z: $[M+H]^+$ calculated for $C_{21}H_{37}N_2O$ 333.2900; found 333.2905.

16c: Operating as above from **15c** (44 mg, 0.108 mmol) and 10% Pd/C (22mg) in ethanol (7 ml). After chromathography **16c** was isolated (34 mg, 0.107 mmol, 98 %). **IR** (NaCl, neat): 2926, 2854, 1641 cm^{-1}; **^{1}H NMR** ($CDCl_3$, 400 MHz): δ 0.87 (m, 1H), 1.00-2.20 (m, 26H), 2.59 (m, 1H), 2.77 (dd, *J* = 12.8, 3.6 Hz, 1H, H-6), 2.84 (d, *J* = 12.8 Hz, 1H, H-10), 2.94 (d, *J* = 13.6 Hz, H-8), 3.03 (brs, 1H, H-2), 3.16 (d, *J* = 12.4 Hz, H-10), 3.62 (d, *J* = 13.6 Hz, 1H, H-8), 4.20 (d, *J* = 12.8 Hz, 1H, H-6). **^{13}C NMR** ($CDCl_3$, 100 MHz): δ 22.0 (CH_2), 23.4 (CH_2), 23.6 (CH_2), 24.1 (CH_2), 25.4 (CH_2), 25.5 (CH_2), 26.1 (CH_2), 26.6 (CH_2), 29.6 (CH_2), 29.7 (CH_2), 32.0 (CH_2), 33.1 (CH_2), 34.3 (CH_2), 34.5 (C-5), 35.6 (C-9), 40.1 (C-12), 44.6 (C-2), 47.3 (C-6), 47.9 (C-10), 52.3 (C-8), 173.5 (CO). HRMS (ESI-TOF) m/z: $[M+H]^+$ calculated for $C_{20}H_{35}N_2O$ 319.2744; found 319.2735.



n = 8 **16a**
n = 7 **16b**
n = 6 **16c**

n = 8 **1**
n = 7 **2**
n = 6 **3**

To a solution of **16a** (80 mg , 0.231 mmol) in THF (3 ml) was added a 1M THF solution of $LiAlH_4$ (0.69 ml, 0.69 mmol) at 0ºC and the mixture was stirred for 3h at rt. The reaction was then quenched with some drops of water dried over Na_2SO_4 and finally filtered over a short pad of celite which was washed with CH_2Cl_2, then with MeOH. The resulting solution was concentrated and purified

by chromatography (Al_2O_3, CH_2Cl_2 to CH_2Cl_2/MeOH 9:1) to afford **1** as a white solid (43 mg, 0.129 mmol, 57%).

1: m.p. 233 ºC (the HCl salt). **IR** (NaCl, neat): 3302, 2926, 2854, 2804, 2762 cm^{-1}; **^{1}H NMR** ($CDCl_3$, 400 MHz): δ 1.10 (m, 1H), 1.30 (m, 21H), 1.59 (m, 2H), 1.70 (d, *J* = 11.6 Hz, 1H), 1.73 (m, 1H), 1.83 (m, 2H), 2.01 (m, 1H), 2.08 (dm, *J* = 13.2 Hz, 1H), 2.20 (dd, *J* = 11.2, 3.6 Hz, 1H), 2.27 (m, 2H), 2.42-2.64 (m, 4H), 3.09 (brs, 1H, H-2), 3.54 (d, *J* = 13.2 Hz, H-6), 3.80 (br s, 1H, NH). **^{13}C NMR** ($CDCl_3$, 100 MHz): δ 21.1 (CH_2), 23.4 (CH_2), 25.8 (CH_2), 26.0 (CH_2), 26.4 (CH_2), 26.5 (CH_2), 26.6 (CH_2), 27.0 (CH_2), 27.3 (CH_2), 28.4 (CH_2), 29.6 (CH_2), 30.8 (CH_2), 34.8 (CH_2), 35.2 (C-5), 35.4 (C-9), 36.2 (C-12), 45.4 (C-2), 47.7 (C-6), 57.7 (CH_2), 60.5 (CH_2), 61.0 (CH_2). HRMS (ESI-TOF) m/z: $[M+H]^+$ calculated for $C_{22}H_{41}N_2$ 333.3264; found 333.3266.

2: Operating as above from **16b** (52 mg, 0.156 mmol), a 1M THF solution of $LiAlH_4$ THF (0.47 ml, 0.47 mmol) in THF (2 ml) and after chromatography **2** was obtained as a white solid (27 mg, 0.085 mmol, 55%). **IR** (NaCl, neat): 2926, 2858, 2796, 2759 cm^{-1}; **^{1}H NMR** ($CDCl_3$, 400 MHz): δ 0.95 (m, 1H), 1.31 (m, 20H), 1.57 (m, 1H), 1.71 (m, 3H), 1.81 (m, 1H, H-5), 1.88 (m, 1H), 1.93-2.07 (m, 2H), 2.24 (m, 3H), 2.45 (d, *J* = 10.8 Hz, 1H), 2.57 (d, *J* = 13.6 Hz, 1H), 2.64 (d, *J* = 10.4 Hz, 1H), 2.69 (m, 1H), 2.97 (brs, 1H, H-2), 3.47 (d, *J* = 13.6 Hz, H-6). **^{13}C NMR** ($CDCl_3$, 100 MHz): δ 20.8 (CH_2), 23.9 (CH_2), 24.6 (CH_2), 25.7 (CH_2), 25.9 (CH_2), 26.3 (CH_2), 26.4 (CH_2), 26.8 (CH_2), 27.9 (CH_2), 30.2 (CH_2), 31.8 (CH_2), 34.4 (CH_2), 35.3 (C-5), 35.9 (C-9), 37.2 (C-12), 45.3 (C-2), 47.5 (C-6), 57.2 (CH_2), 60.0 (CH_2), 60.7 (CH_2). HRMS (ESI-TOF) m/z: $[M+H]^+$ calculated for $C_{21}H_{39}N_2$ 319.3108; found 319.3110.

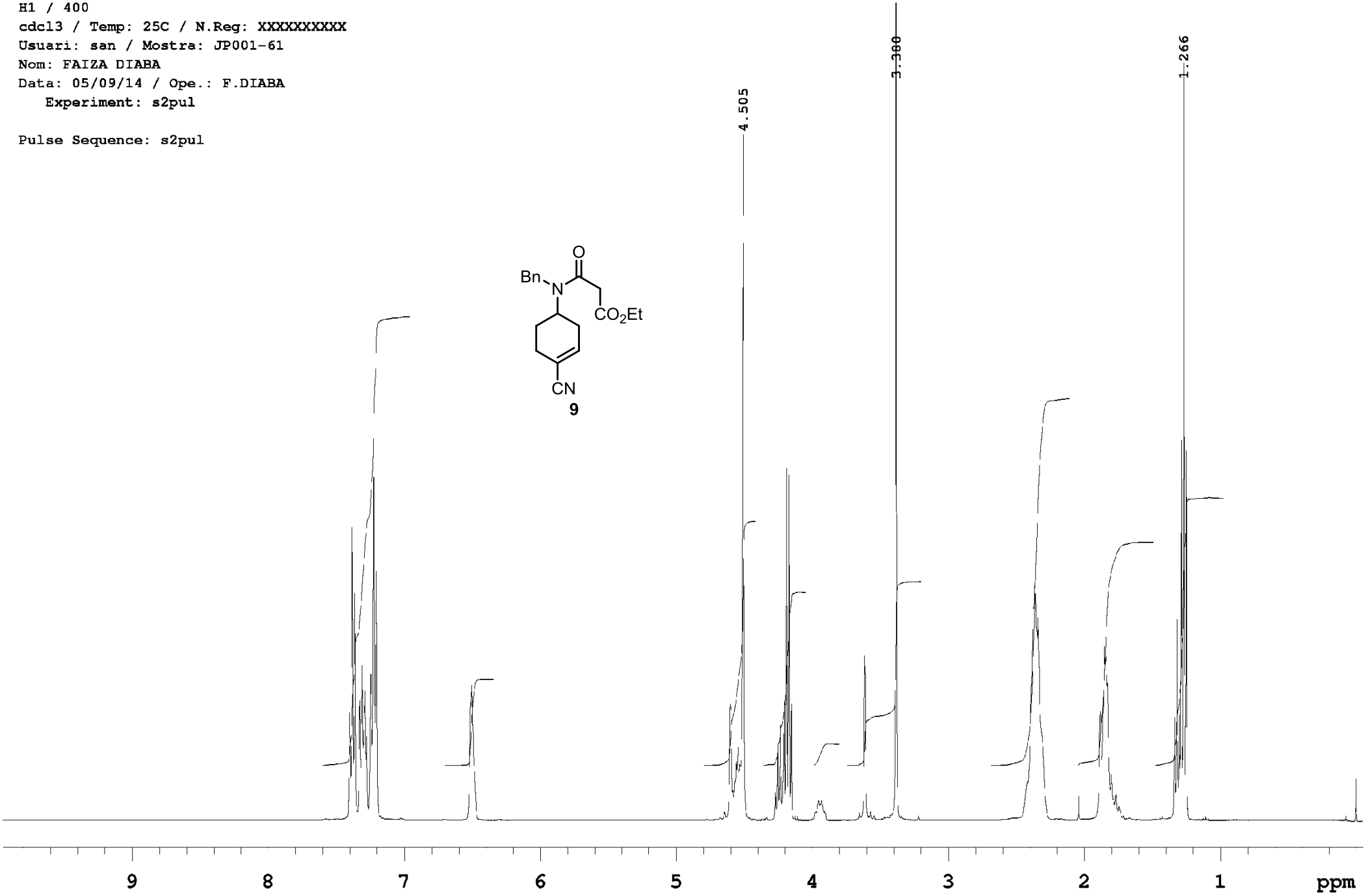
3: Operating as above from **16c** (34 mg, 0.107 mmol), a 1M THF solution of $LiAlH_4$ THF (0.32 ml, 0.32 mmol) in THF (1 ml) and after chromatography **3** was obtained as a white solid (18 mg, 0.255 mmol, 55**%**). **^{1}H NMR** ($CDCl_3$, 400 MHz): δ 1.20-1.95 (m, 27H), 2.00 (dm, *J* = 13.2 Hz, 1H), 2.15 (m, 1H), 2.23 (m, 1H), 2.31 (dd, *J* = 10.8 Hz, 1H), 2.41 (d, *J* = 10.8 Hz, 1H), 2.55 (d, *J* = 11.6 Hz, 1H), 2.58 (d, *J* = 13.6 Hz, 1H, H-6), 2.66 (ddd, *J* = 12.8, 9.2, 3.6 Hz, 1H), 2.98 (brs, 1H, H-2), 3.49 (d, *J* = 13.6 Hz, H-6). **^{13}C NMR** ($CDCl_3$, 100 MHz): δ 22.0

(CH_2), 24.4 (CH_2), 24.9 (CH_2), 26.7 (CH_2), 20.3 (CH_2), 31.7 (CH_2), 34.2 (CH_2), 35.2 (C-5), 35.4 (C-9), 36.4 (C-12), 45.4 (C-2), 49.0 (C-6), 57.0 (CH_2), 60.1 (CH_2), 61.6 (CH_2). HRMS (ESI-TOF) m/z: $[M+H]^+$ calculated for $C_{20}H_{37}N_2$ 305.2951; found 305.2955.

^{1}H, ^{13}C, COSY and HSQC spectra of compounds
1-16

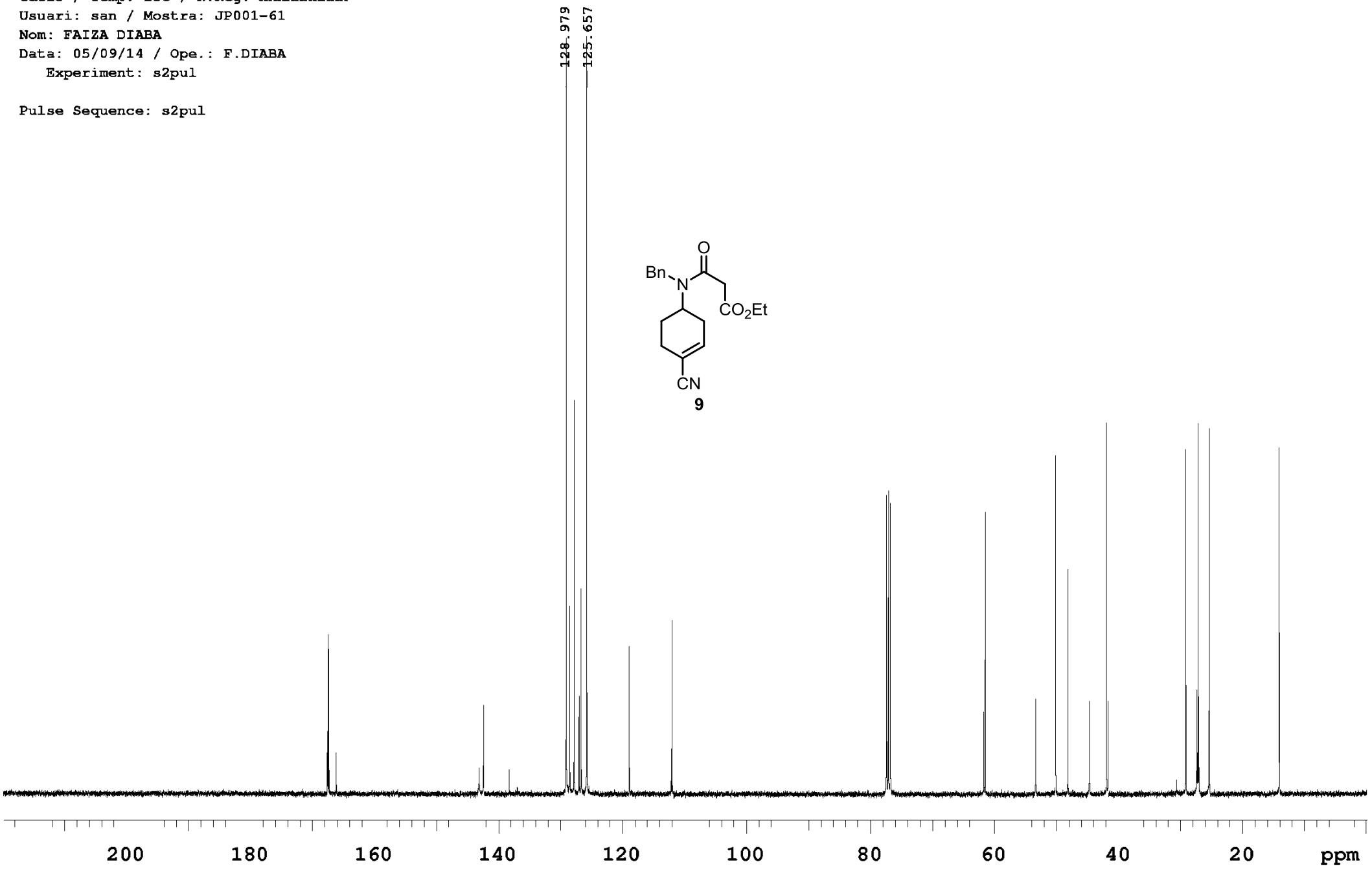
H1 / 400
cdcl3 / Temp: 25C / N.Reg: XXXXXXXXXX
Usuari: san / Mostra: JP001-61
Nom: FAIZA DIABA
Data: 05/09/14 / Ope.: F.DIABA
Experiment: s2pul

Pulse Sequence: s2pul



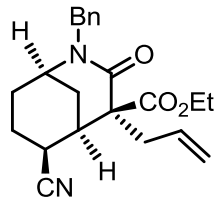
H1 / 400
cdcl3 / Temp: 25C / N.Reg: XXXXXXXXXX
Usuari: san / Mostra: JP001-61
Nom: FAIZA DIABA
Data: 05/09/14 / Ope.: F.DIABA
Experiment: s2pul

Pulse Sequence: s2pul



H1 / 400
cdcl3 / Temp: Ambient / N.Reg: XXXXXXXXXX
Usuari: san / Mostra: XCP41-5CRYS
Nom: FAIZA DIABA
Data: 21/05/14 / Ope.: F.DIABA
Experiment: s2pul

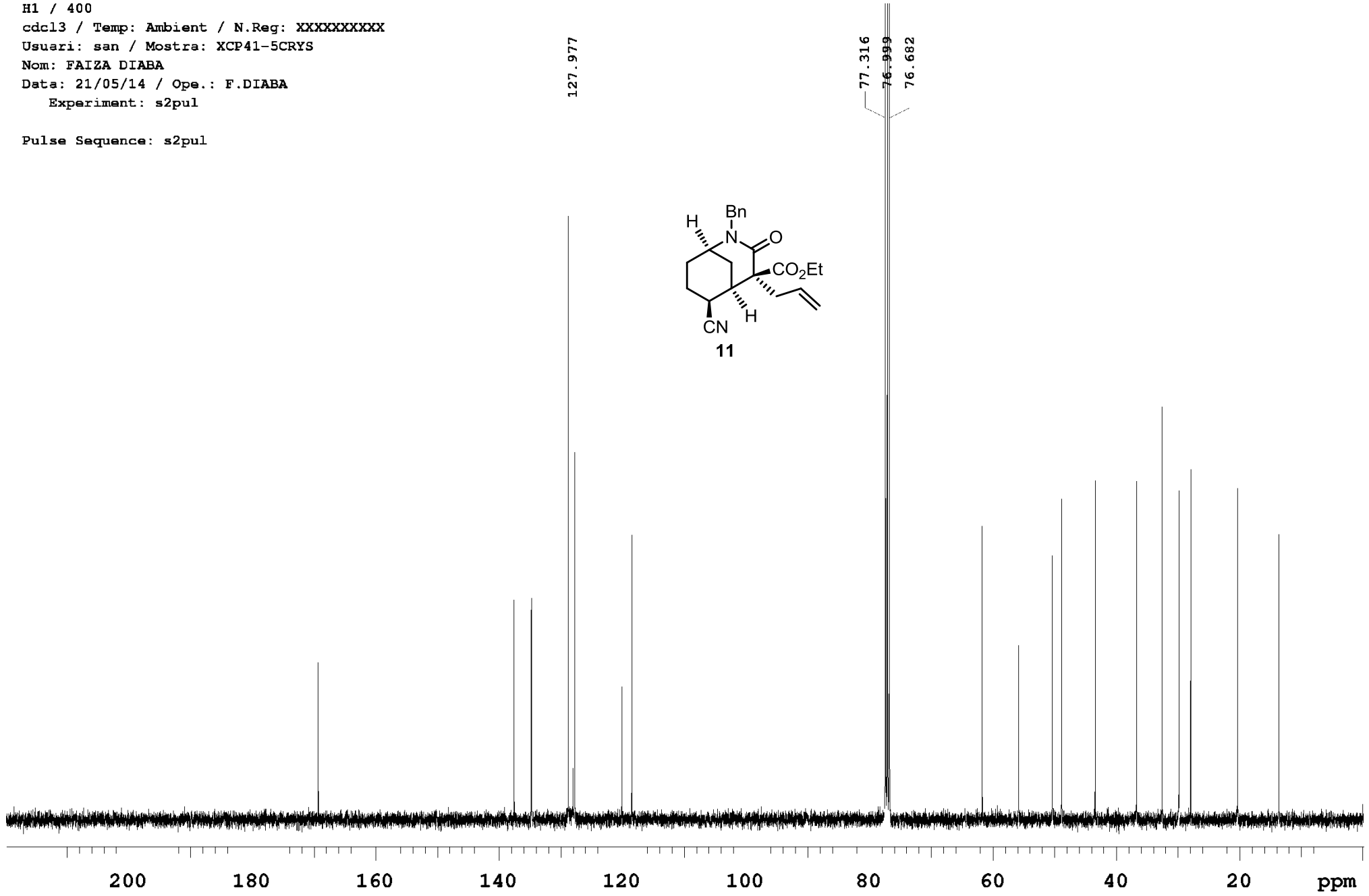
Pulse Sequence: s2pul



11

H1 / 400
cdcl3 / Temp: Ambient / N.Reg: XXXXXXXXXX
Usuari: san / Mostra: XCP41-5CRYS
Nom: FAIZA DIABA
Data: 21/05/14 / Ope.: F.DIABA
Experiment: s2pul

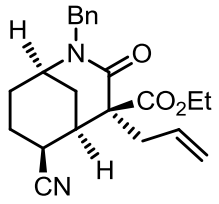
Pulse Sequence: s2pul



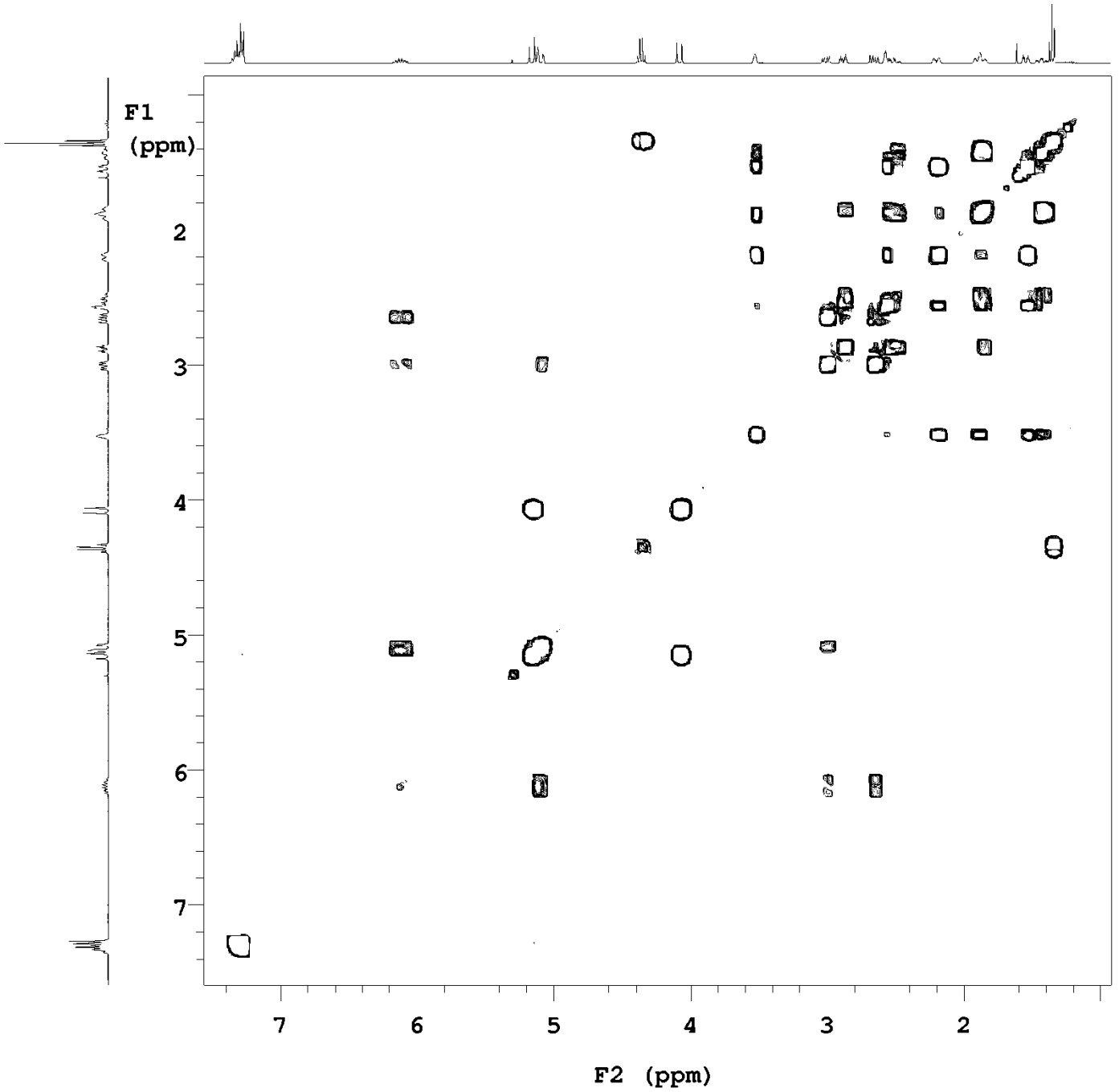
11

H1 / 400
cdcl3 / Temp: Ambient / N.Reg: XXXXXXXXXX
Usuari: san / Mostra: XCP41-5CRYS
Nom: FAIZA DIABA
Data: 21/05/14 / Ope.: F.DIABA
Experiment: gcosy

Pulse Sequence: gCOSY

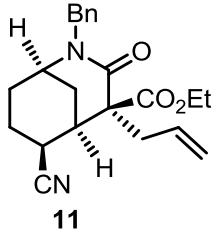


11

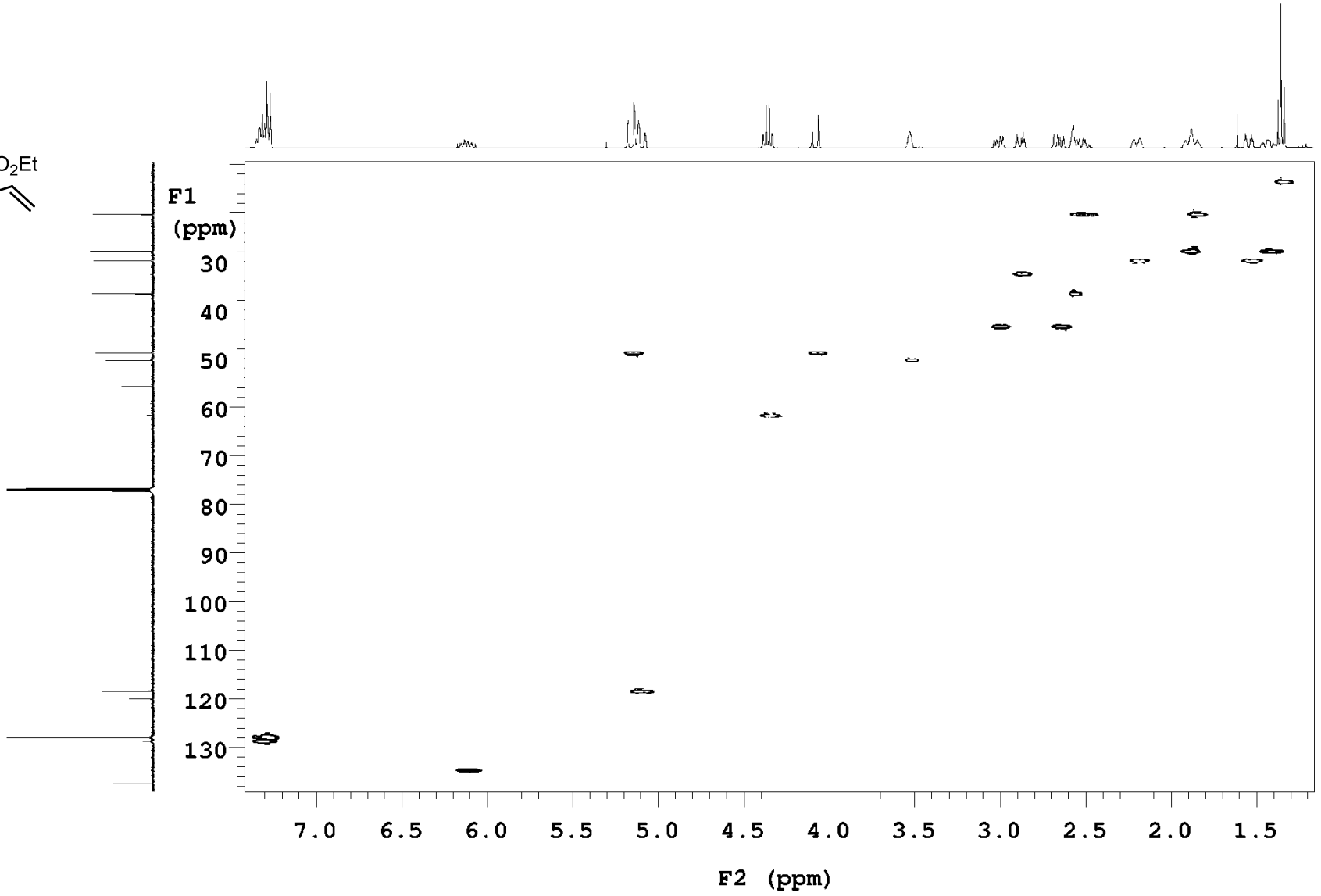


H1 / 400
cdcl3 / Temp: Ambient / N.Reg: XXXXXXXXXX
Usuari: san / Mostra: XCP41-5CRYS
Nom: FAIZA DIABA
Data: 21/05/14 / Ope.: F.DIABA
Experiment: ghsqcad

Pulse Sequence: gHSQCAD

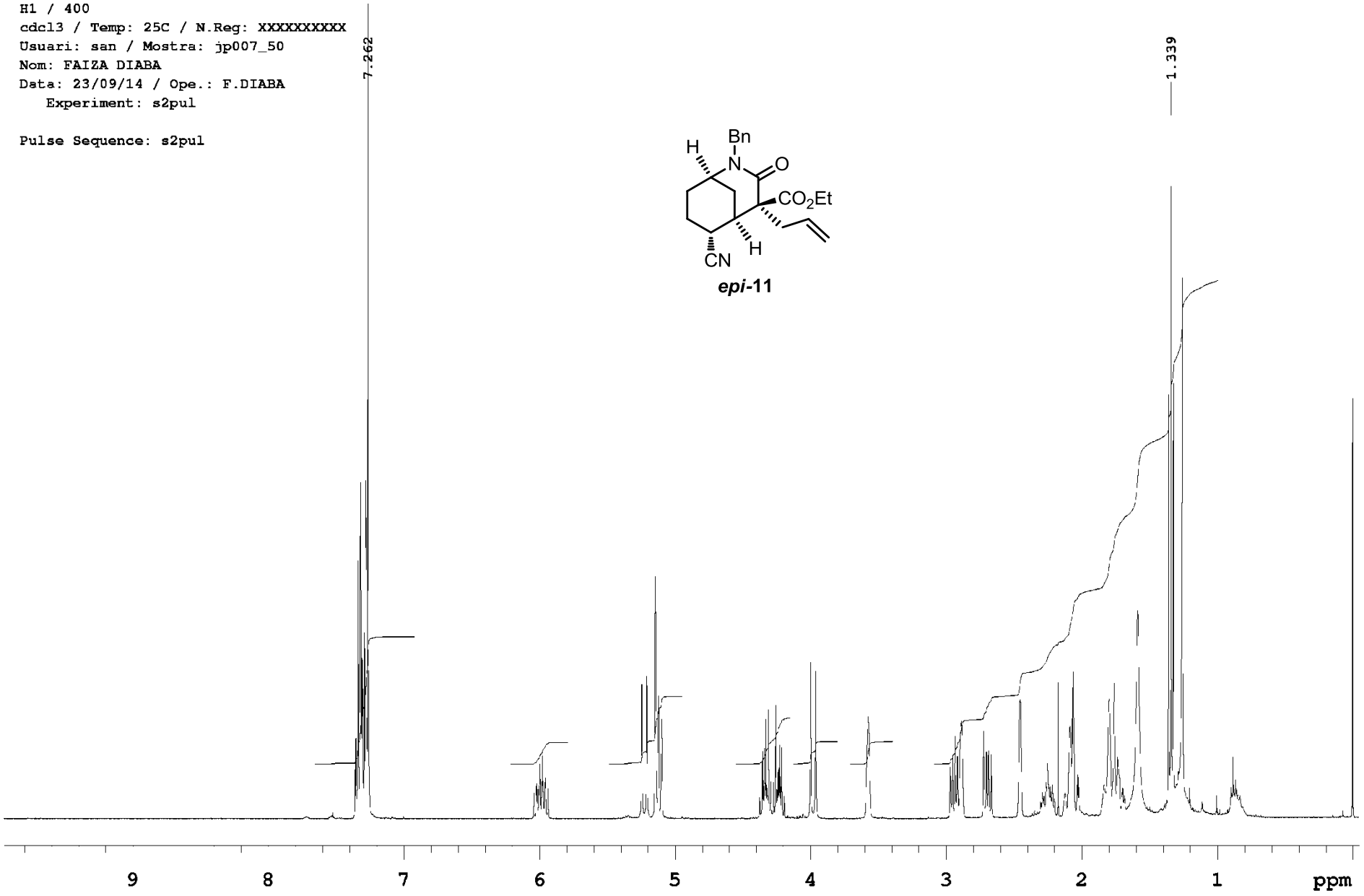


11



H1 / 400
cdcl3 / Temp: 25C / N.Reg: XXXXXXXXXX
Usuari: san / Mostra: jp007_50
Nom: FAIZA DIABA
Data: 23/09/14 / Ope.: F.DIABA
Experiment: s2pul

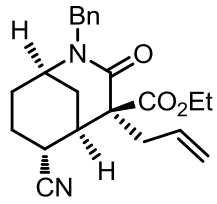
Pulse Sequence: s2pul



epi-11

H1 / 400
cdcl3 / Temp: 25C / N.Reg: XXXXXXXXXX
Usuari: san / Mostra: jp007_50
Nom: FAIZA DIABA
Data: 23/09/14 / Ope.: F.DIABA
Experiment: s2pul

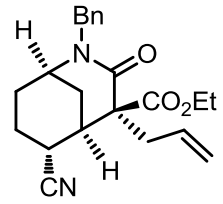
Pulse Sequence: s2pul



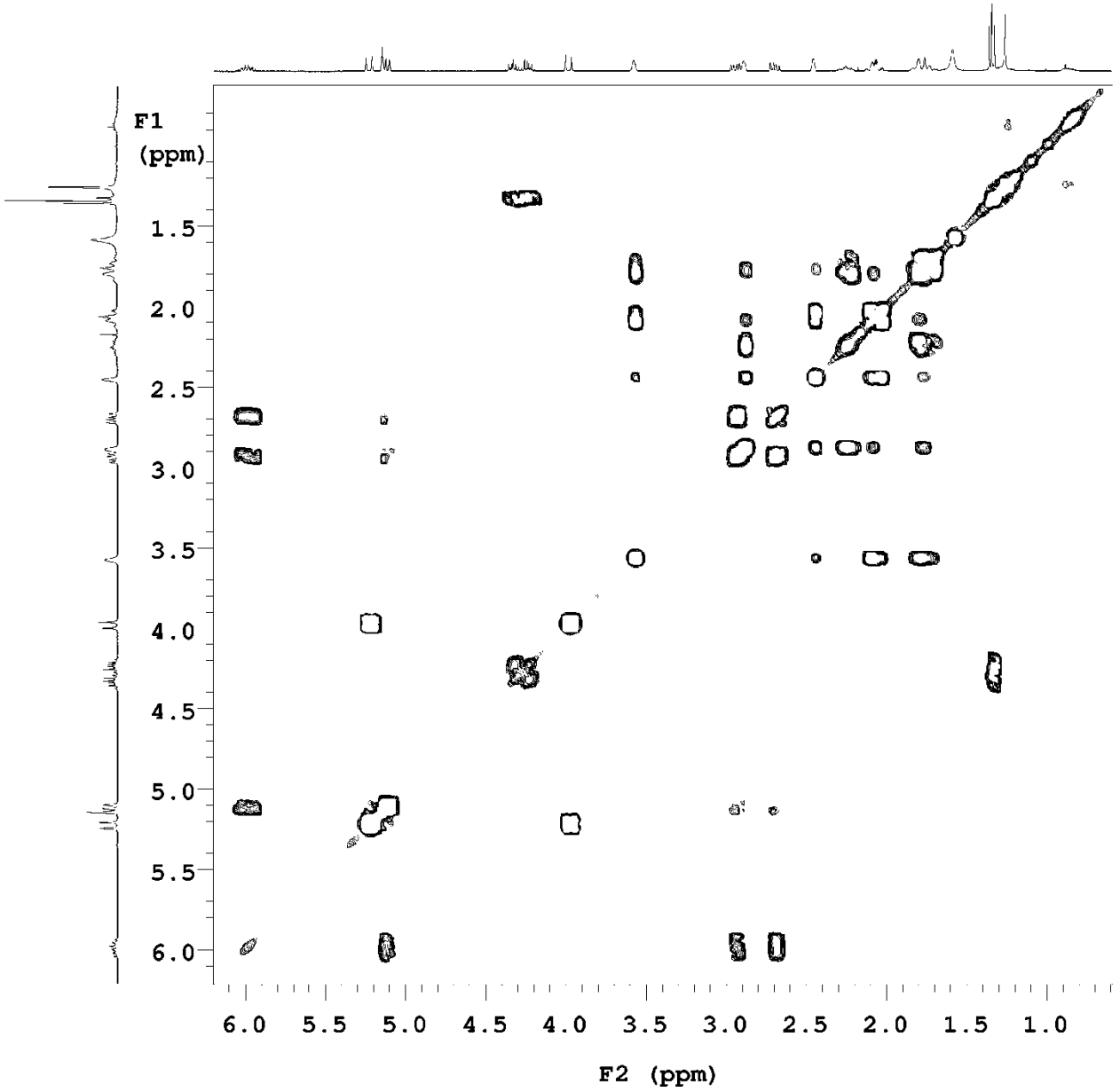
***epi*-11**

H1 / 400
cdcl3 / Temp: 25C / N.Reg: XXXXXXXXXX
Usuari: san / Mostra: jp007_50
Nom: FAIZA DIABA
Data: 23/09/14 / Ope.: F.DIABA
Experiment: gcosy

Pulse Sequence: gCOSY

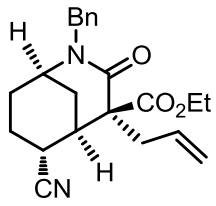


epi-11

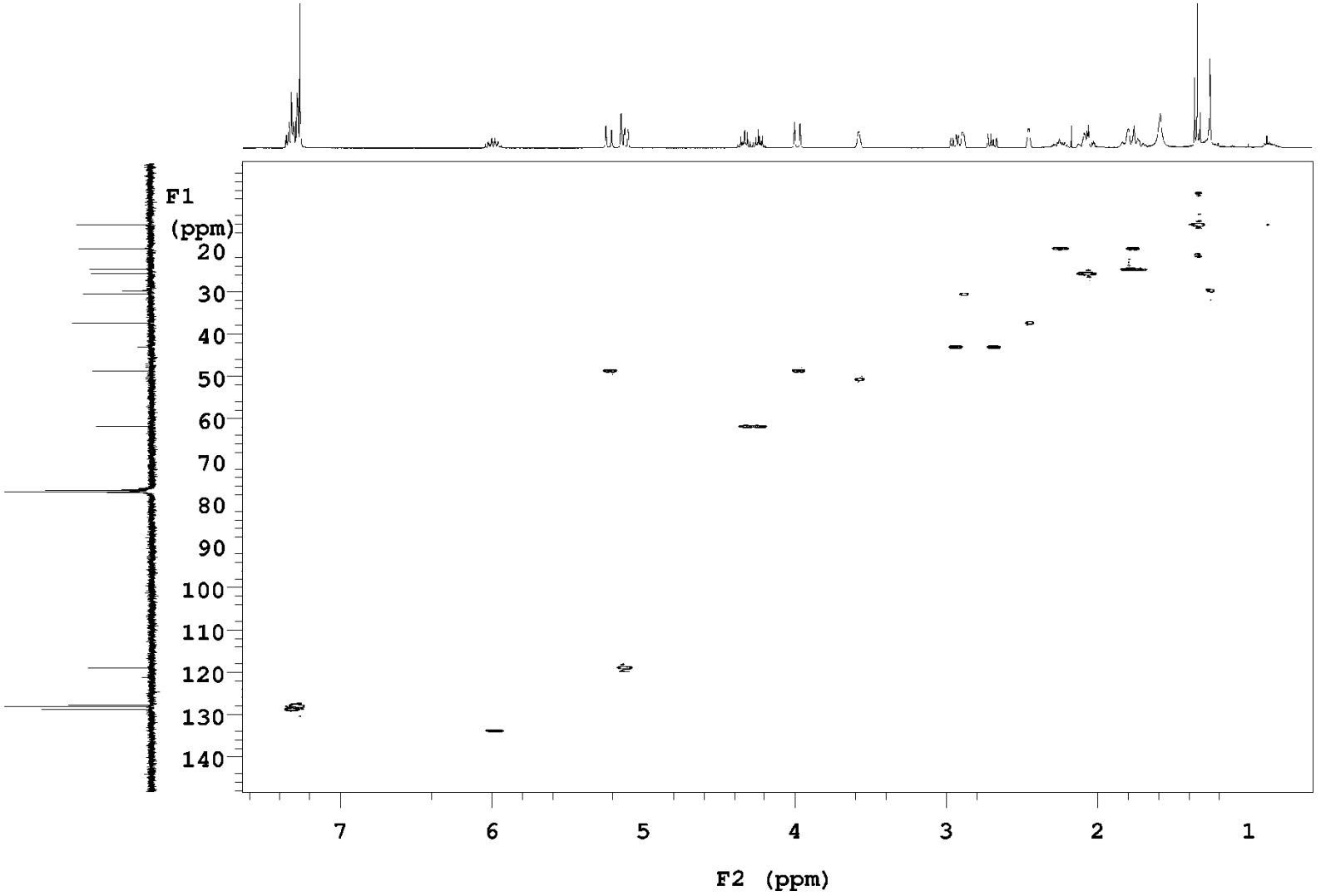


H1 / 400
cdcl3 / Temp: 25C / N.Reg: XXXXXXXXXX
Usuari: san / Mostra: jp007_50
Nom: FAIZA DIABA
Data: 23/09/14 / Ope.: F.DIABA
Experiment: ghsqcad

Pulse Sequence: gHSQCAD

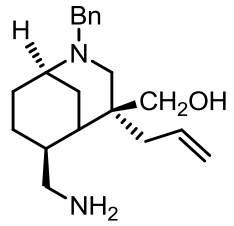


epi-11



H1 / 400
CDCl3 / Temp: Ambient / N.Reg: XXXXXXXXXX
Usuari: san / Mostra: CP027-1
Nom: FAIZA DIABA
Data: 28/04/14 / Ope.: F.DIABA
Experiment: s2pul

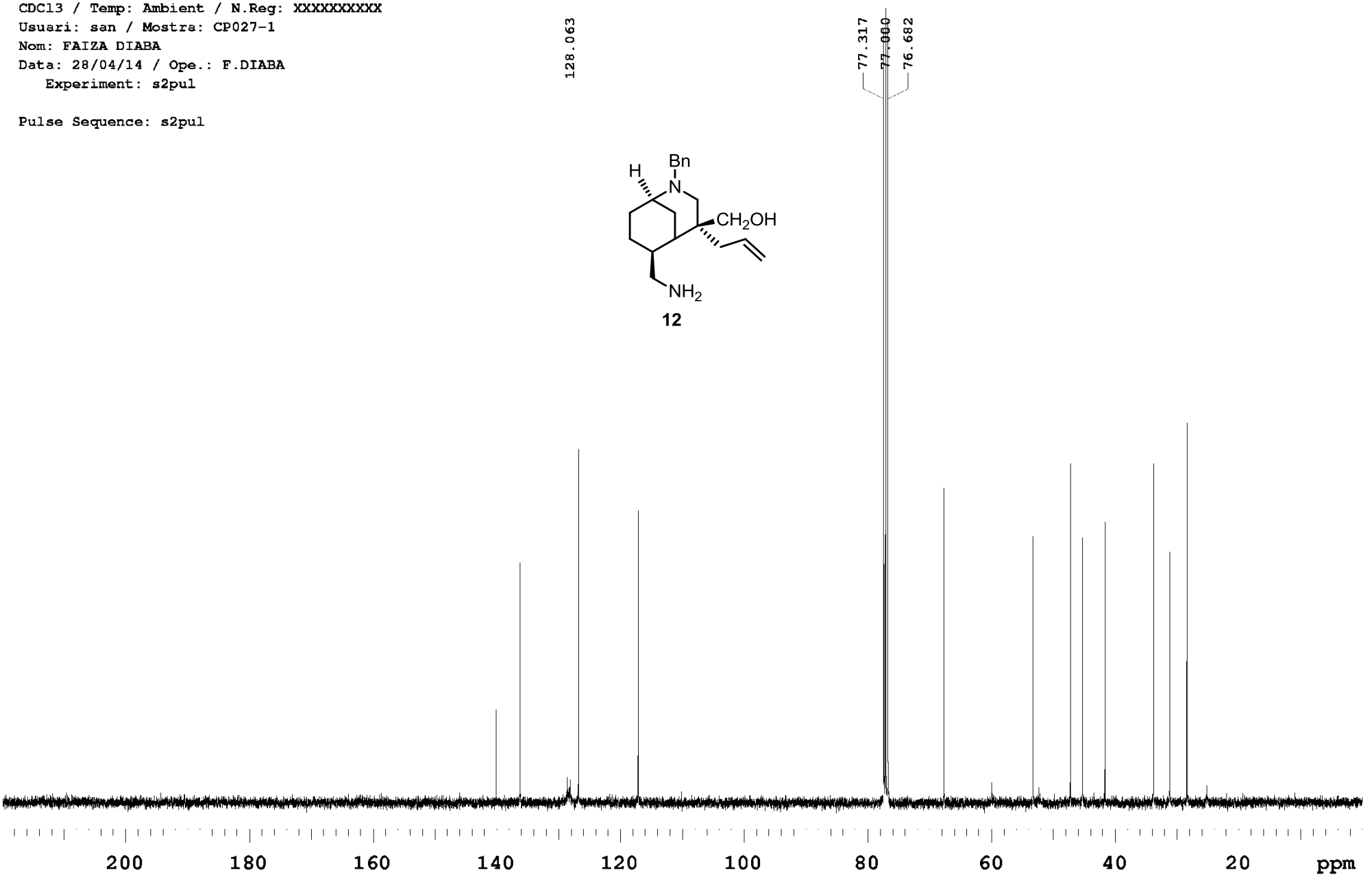
Pulse Sequence: s2pul



12

H1 / 400
CDCl3 / Temp: Ambient / N.Reg: XXXXXXXXXX
Usuari: san / Mostra: CP027-1
Nom: FAIZA DIABA
Data: 28/04/14 / Ope.: F.DIABA
Experiment: s2pul

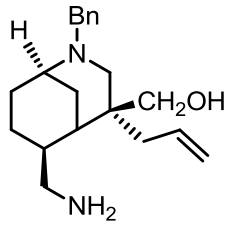
Pulse Sequence: s2pul



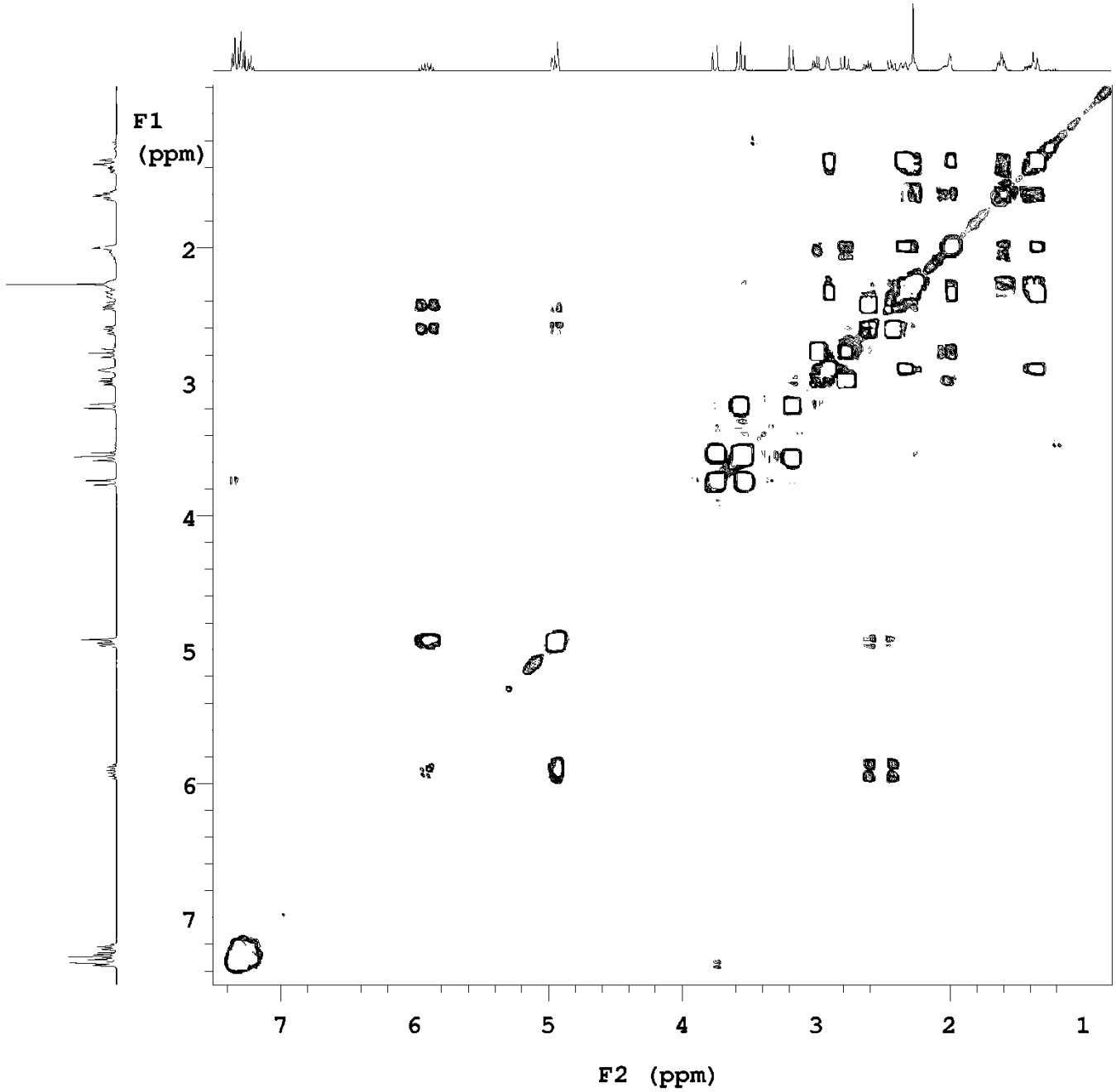
12

H1 / 400
CDCl3 / Temp: Ambient / N.Reg: XXXXXXXXXX
Usuari: san / Mostra: CP027-1
Nom: FAIZA DIABA
Data: 28/04/14 / Ope.: F.DIABA
Experiment: gcosy

Pulse Sequence: gCOSY

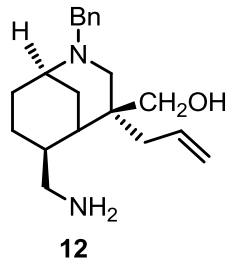


12

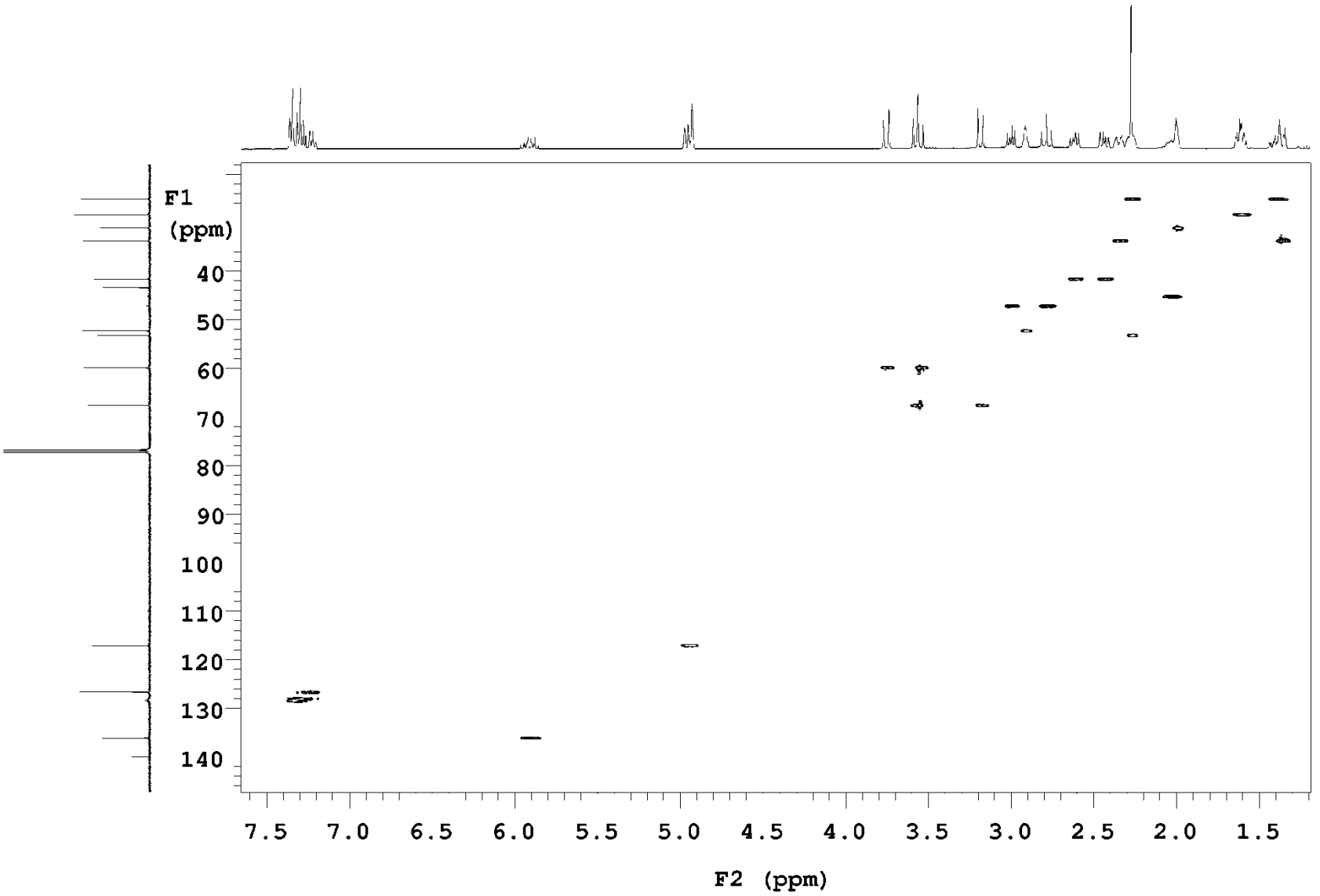


H1 / 400
CDCl3 / Temp: Ambient / N.Reg: XXXXXXXXXX
Usuari: san / Mostra: CP027-1
Nom: FAIZA DIABA
Data: 28/04/14 / Ope.: F.DIABA
Experiment: ghsqcad

Pulse Sequence: gHSQCAD

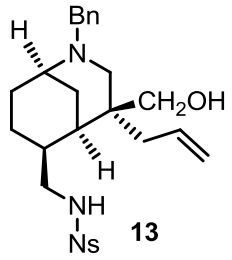


12



H1 / 400
cdcl3 / Temp: Ambient / N.Reg: XXXXXXXXXX
Usuari: san / Mostra: CP046-6
Nom: FAIZA DIABA
Data: 29/05/14 / Ope.: F.DIABA
Experiment: s2pul

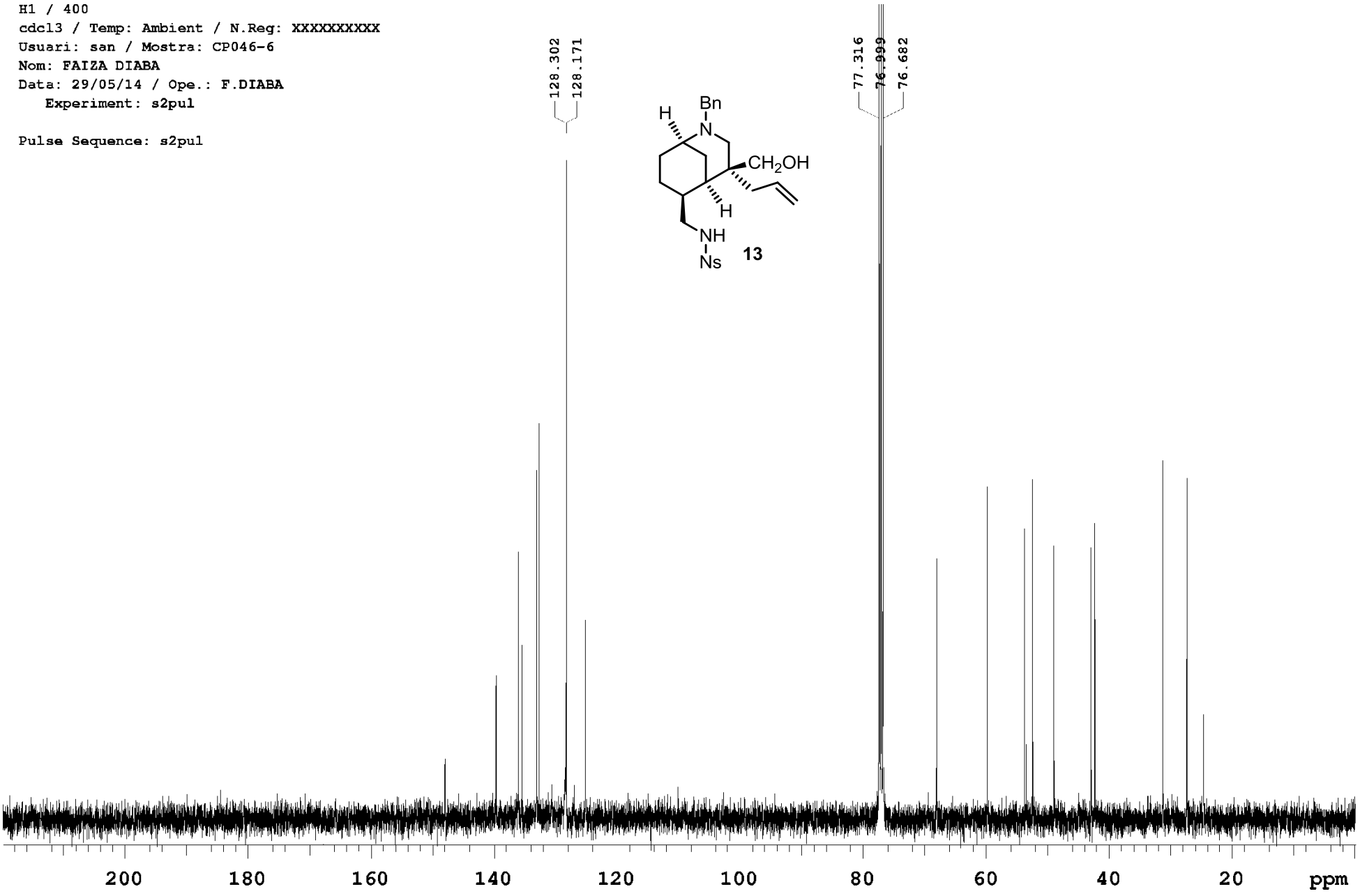
Pulse Sequence: s2pul



13

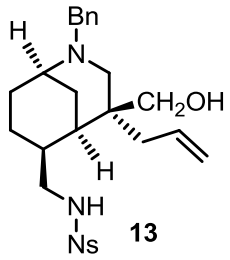
H1 / 400
cdcl3 / Temp: Ambient / N.Reg: XXXXXXXXXX
Usuari: san / Mostra: CP046-6
Nom: FAIZA DIABA
Data: 29/05/14 / Ope.: F.DIABA
Experiment: s2pul

Pulse Sequence: s2pul

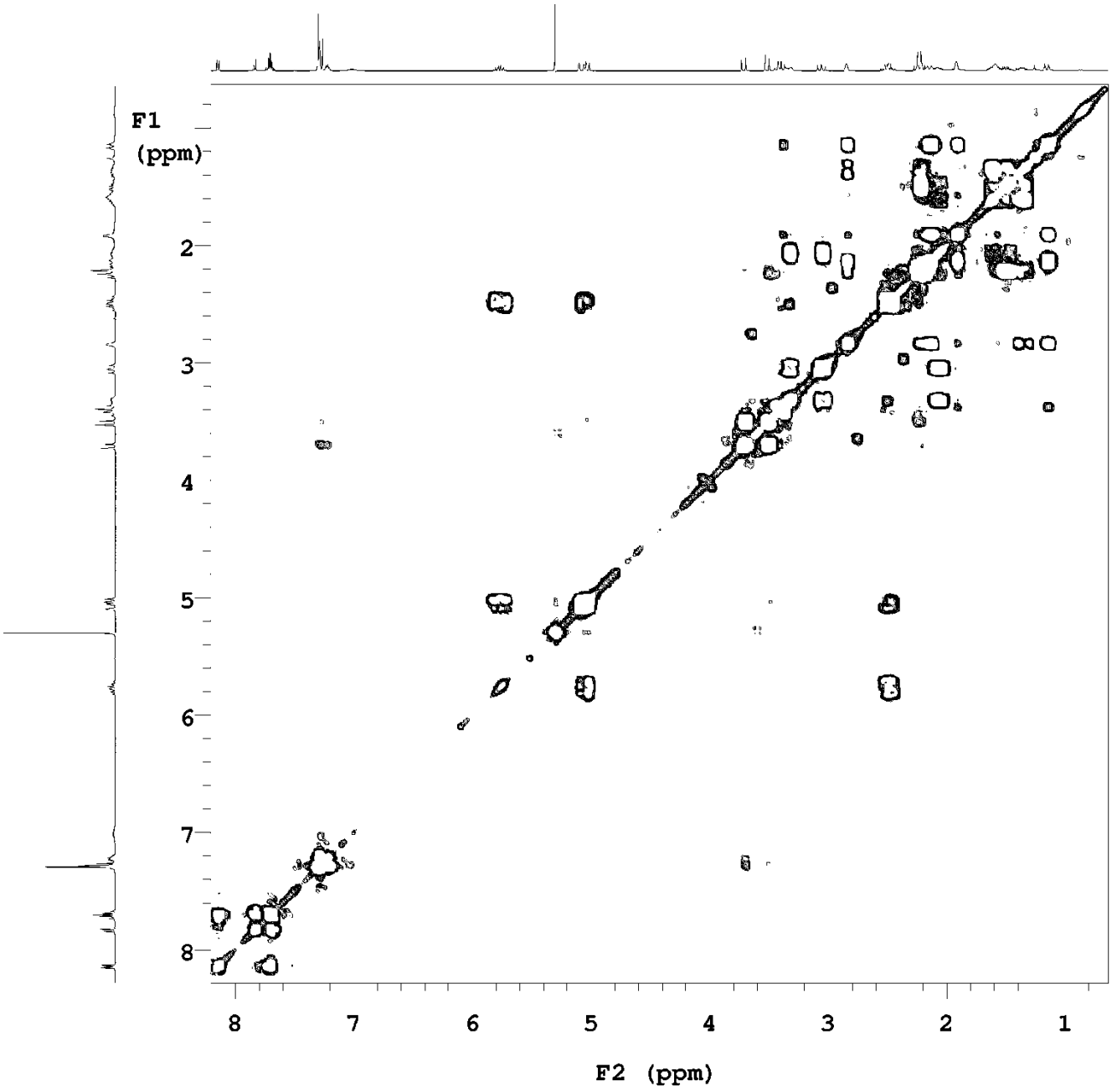


H1 / 400
cdcl3 / Temp: Ambient / N.Reg: XXXXXXXXXX
Usuari: san / Mostra: CP046-6
Nom: FAIZA DIABA
Data: 29/05/14 / Ope.: F.DIABA
Experiment: gcosy
H1_data are in file H1

Pulse Sequence: gCOSY

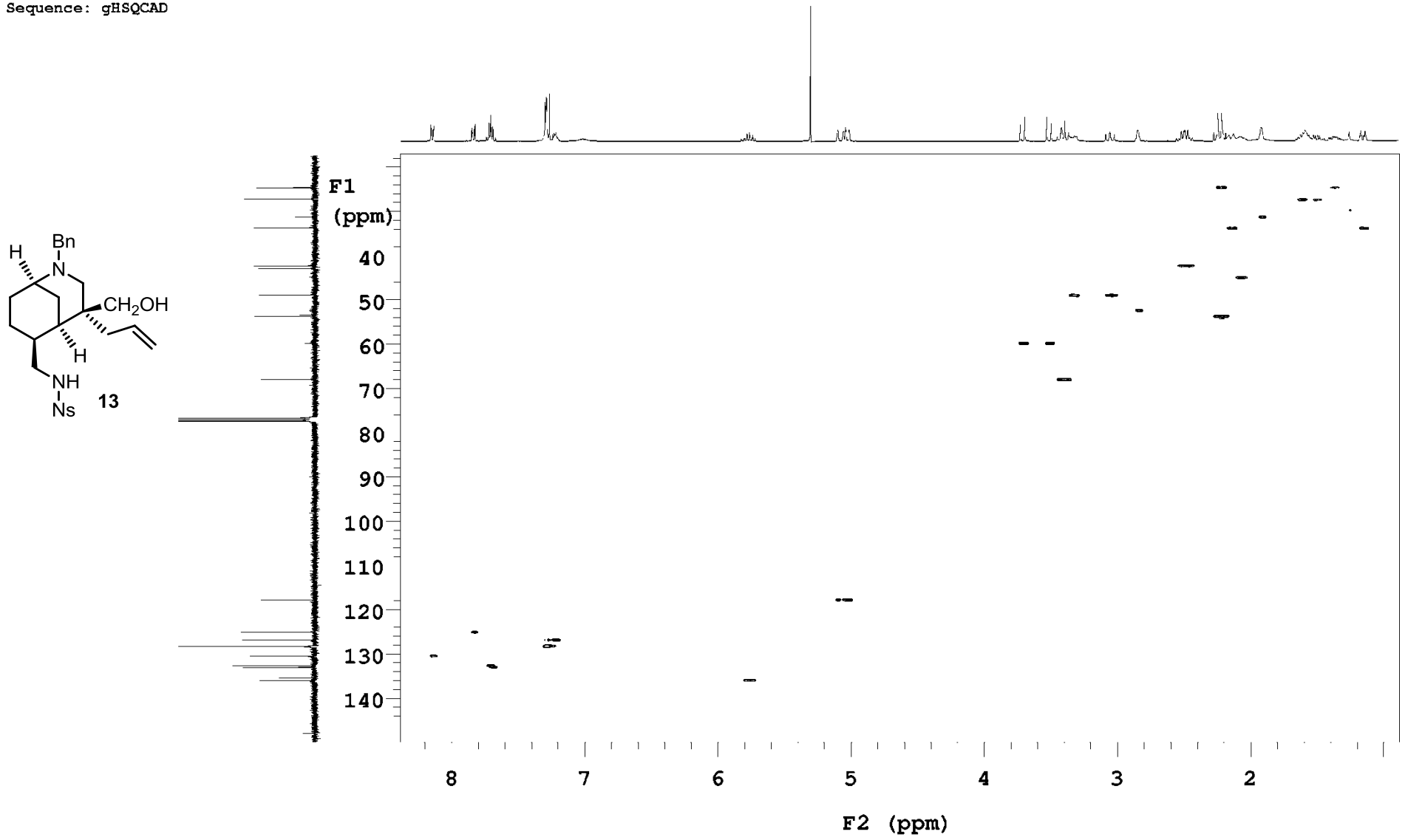


13



H1 / 400
cdcl3 / Temp: Ambient / N.Reg: XXXXXXXXXX
Usuari: san / Mostra: CP046-6
Nom: FAIZA DIABA
Data: 29/05/14 / Ope.: F.DIABA
Experiment: ghsqcad

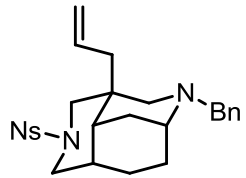
Pulse Sequence: gHSQCAD



H1 / 400
cdcl3 / Temp: 25C / N.Reg: XXXXXXXXXX
Usuari: san / Mostra: XCP049-31
Nom: FAIZA DIABA
Data: 10/06/14 / Ope.: F.DIABA
Experiment: s2pul

Pulse Sequence: s2pul

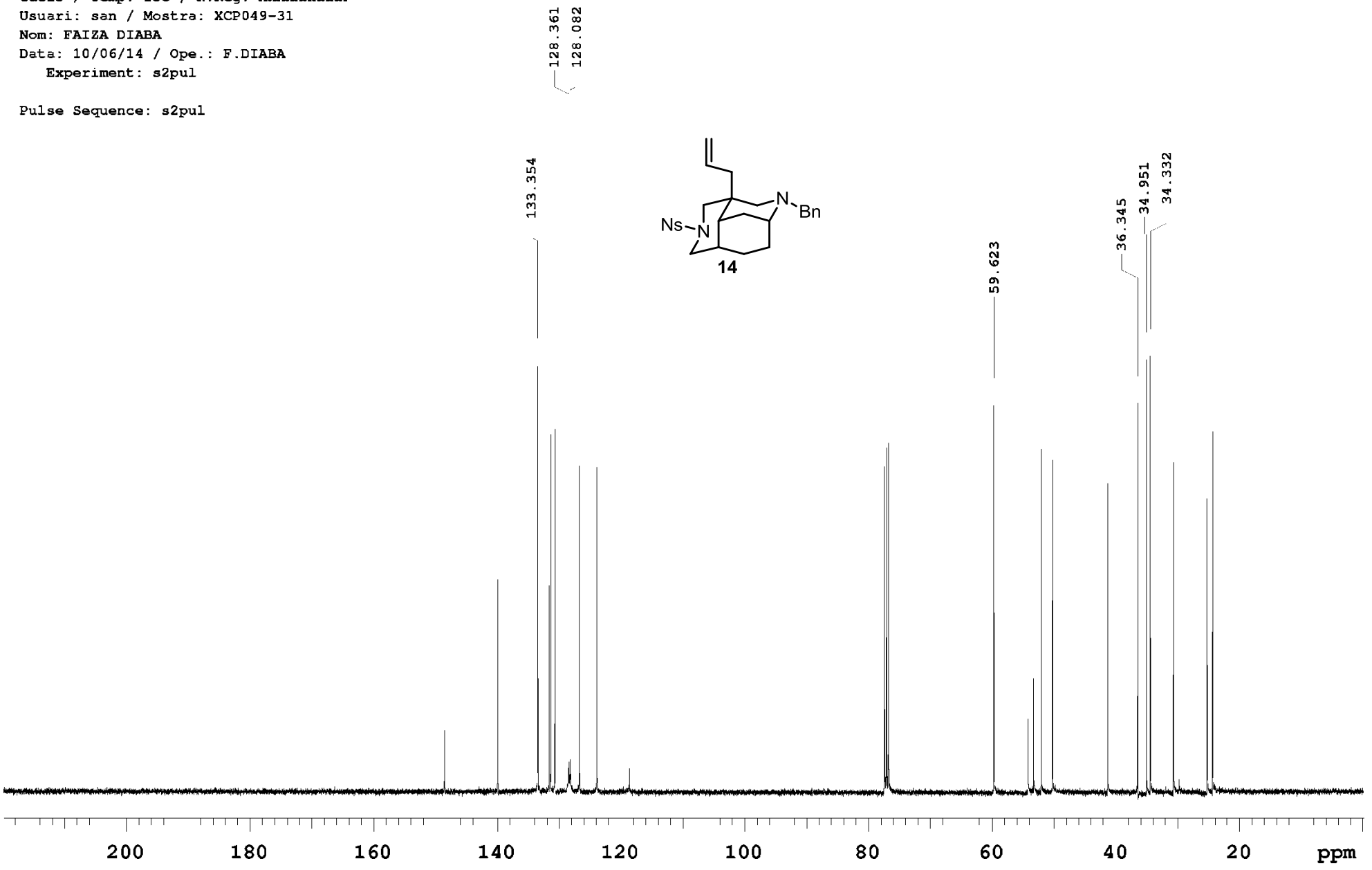
7.660
7.329
7.290



14

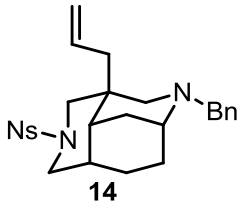
H1 / 400
cdcl3 / Temp: 25C / N.Reg: XXXXXXXXXX
Usuari: san / Mostra: XCP049-31
Nom: FAIZA DIABA
Data: 10/06/14 / Ope.: F.DIABA
Experiment: s2pul

Pulse Sequence: s2pul

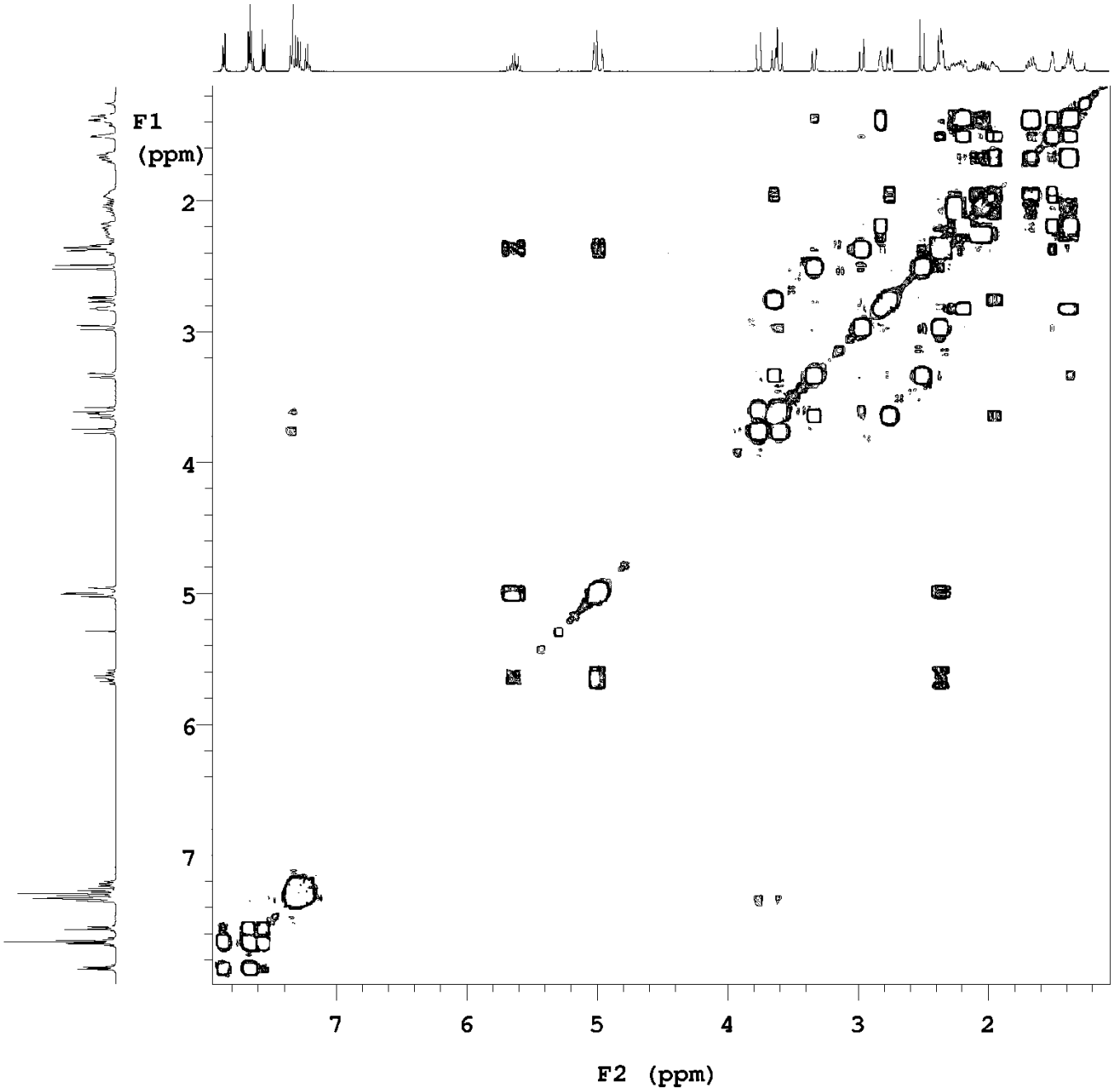


H1 / 400
cdcl3 / Temp: 25C / N.Reg: XXXXXXXXXX
Usuari: san / Mostra: XCP049-31
Nom: FAIZA DIABA
Data: 10/06/14 / Ope.: F.DIABA
Experiment: gcosy

Pulse Sequence: gCOSY

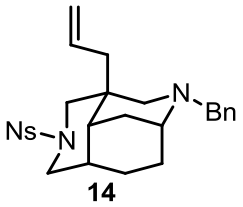


14

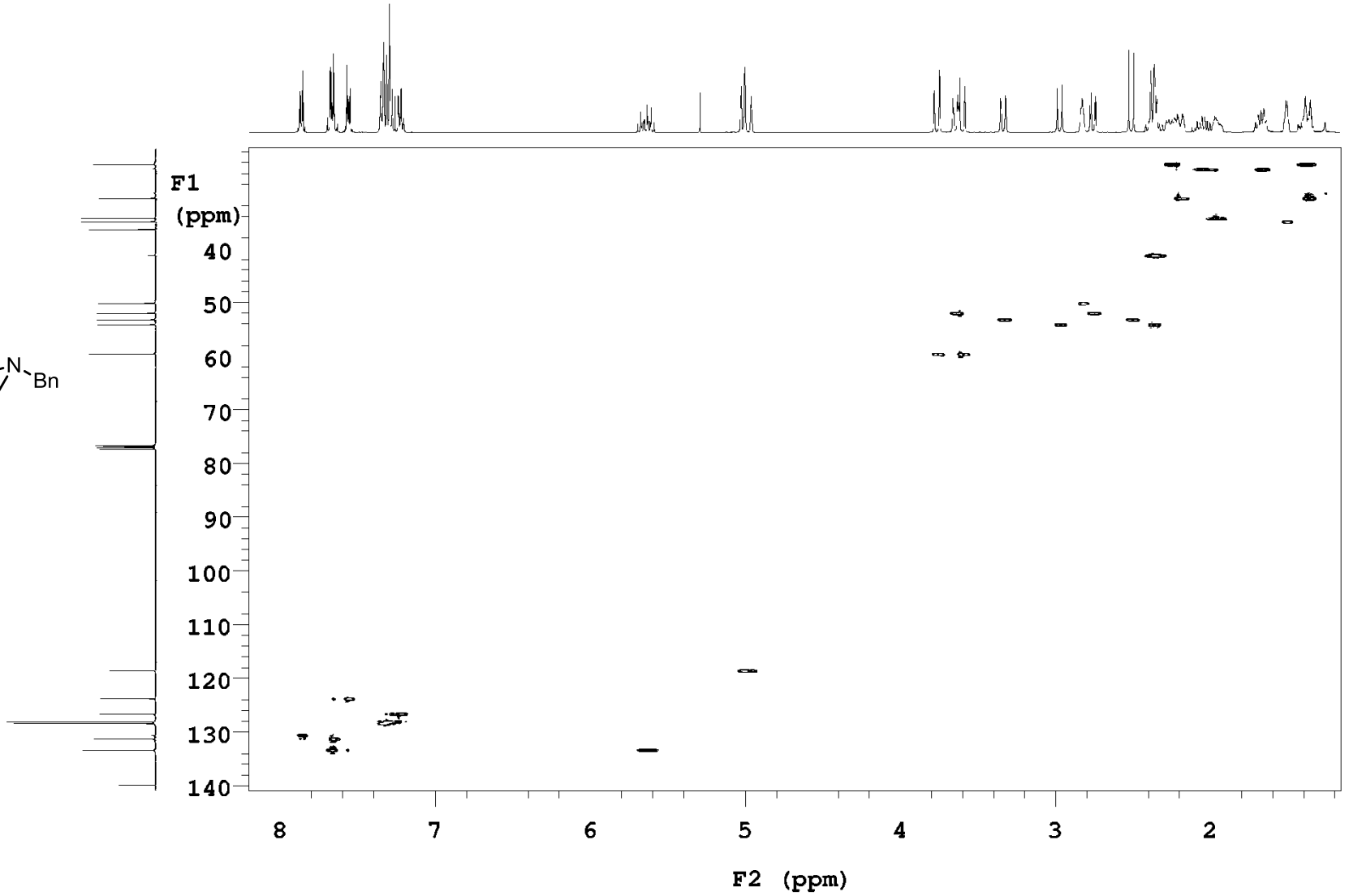


H1 / 400
cdcl3 / Temp: 25C / N.Reg: XXXXXXXXXX
Usuari: san / Mostra: XCP049-31
Nom: FAIZA DIABA
Data: 10/06/14 / Ope.: F.DIABA
Experiment: ghsqcad

Pulse Sequence: gHSQCAD

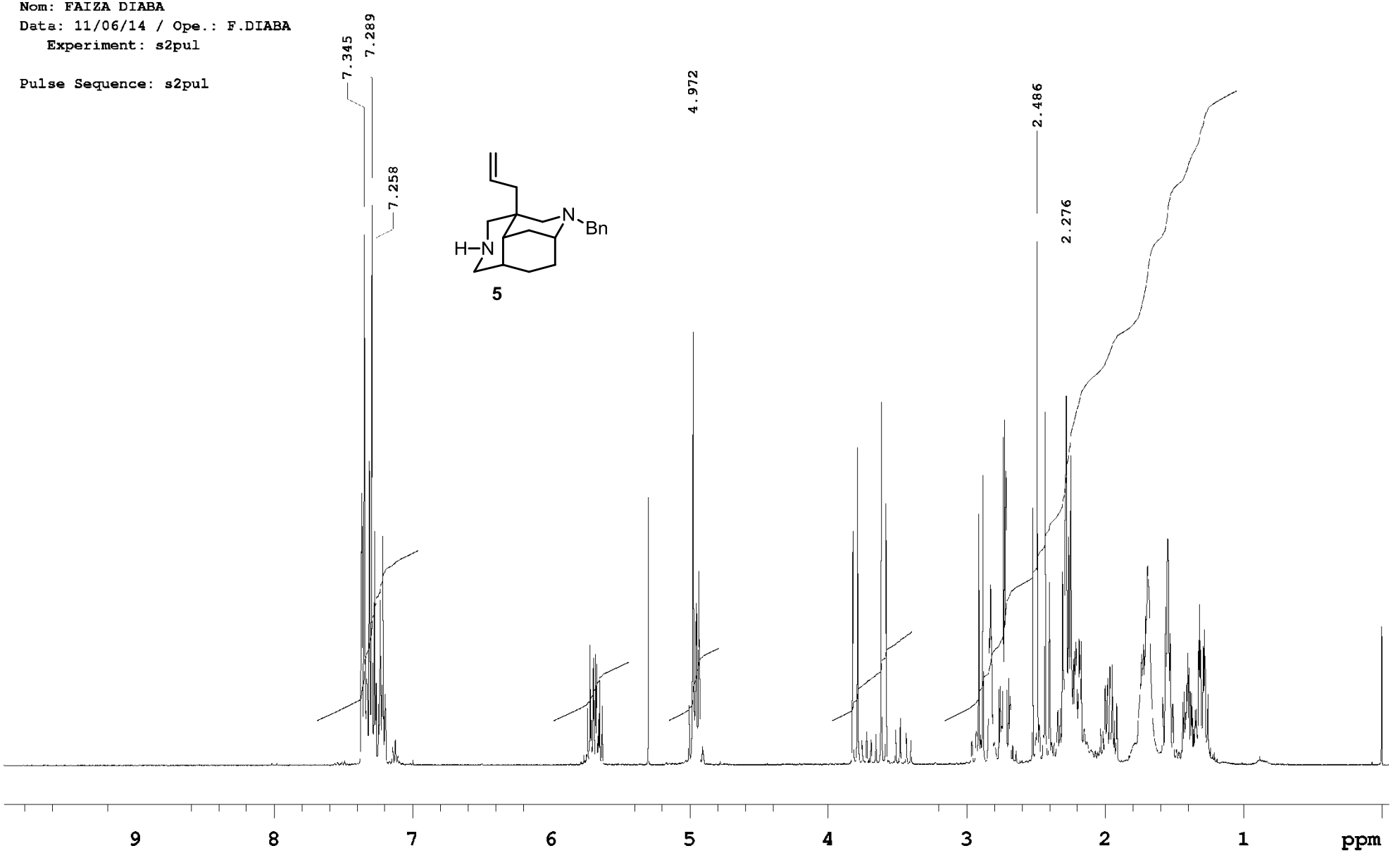


14



H1 / 400
cdcl3 / Temp: 25C / N.Reg: XXXXXXXXXX
Usuari: san / Mostra: CP052-14
Nom: FAIZA DIABA
Data: 11/06/14 / Ope.: F.DIABA
Experiment: s2pul

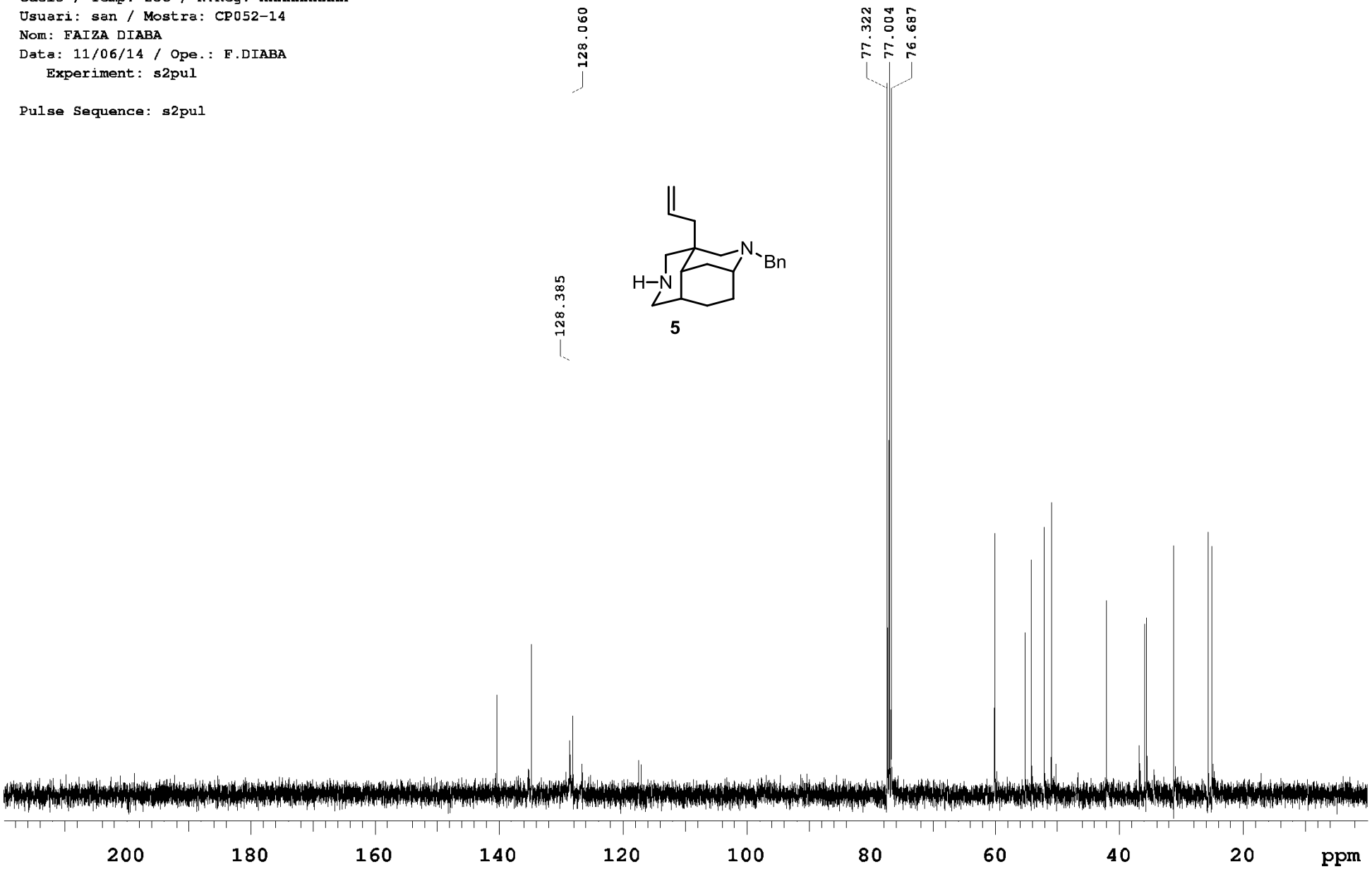
Pulse Sequence: s2pul



5

H1 / 400
cdcl3 / Temp: 25C / N.Reg: XXXXXXXXXX
Usuari: san / Mostra: CP052-14
Nom: FAIZA DIABA
Data: 11/06/14 / Ope.: F.DIABA
Experiment: s2pul

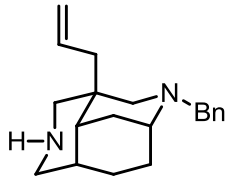
Pulse Sequence: s2pul



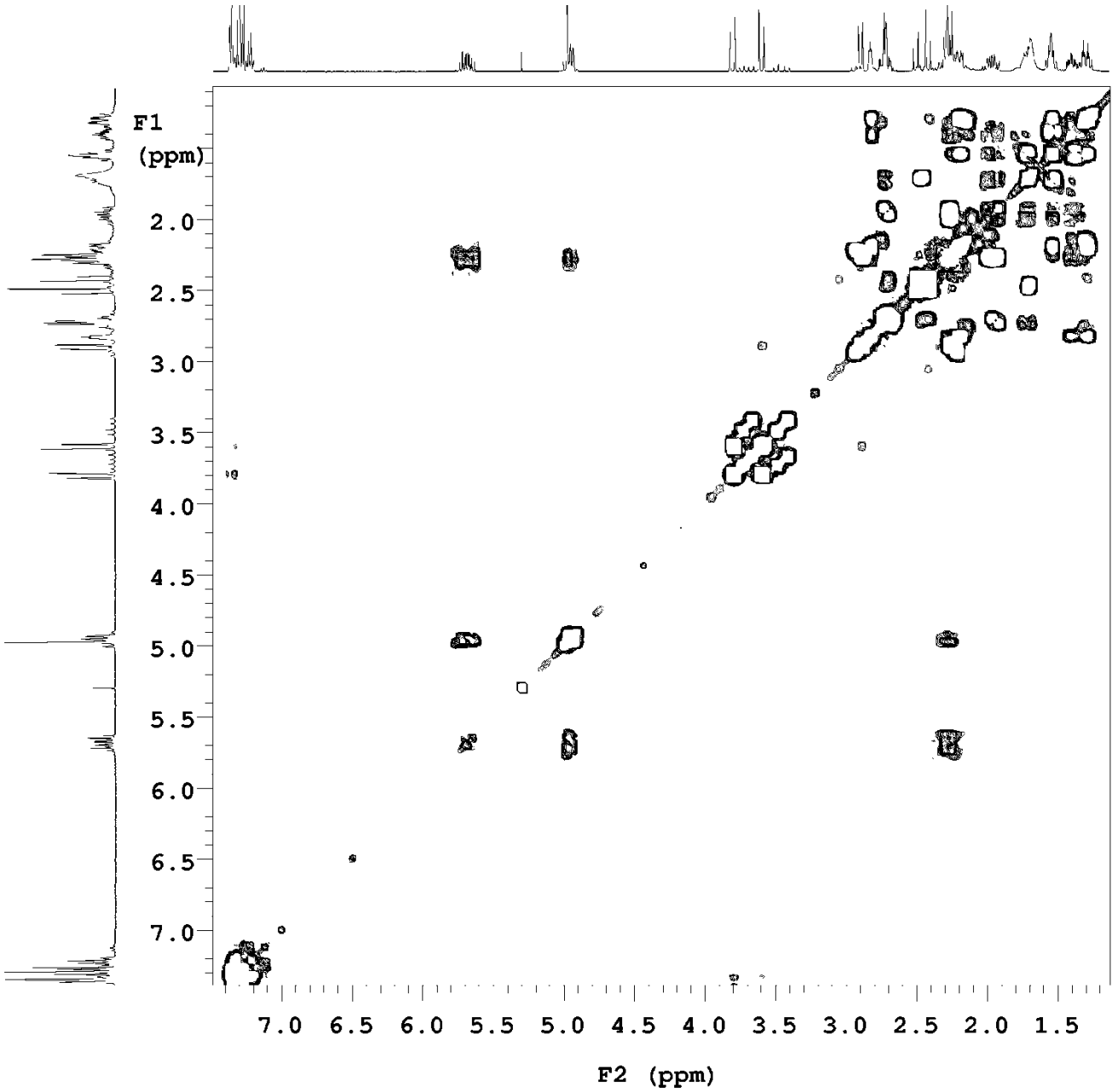
5

H1 / 400
cdcl3 / Temp: 25C / N.Reg: XXXXXXXXXX
Usuari: san / Mostra: CP052-14
Nom: FAIZA DIABA
Data: 11/06/14 / Ope.: F.DIABA
Experiment: gcosy

Pulse Sequence: gCOSY

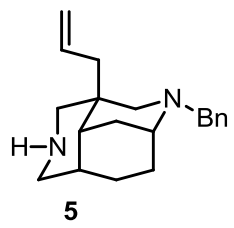


5

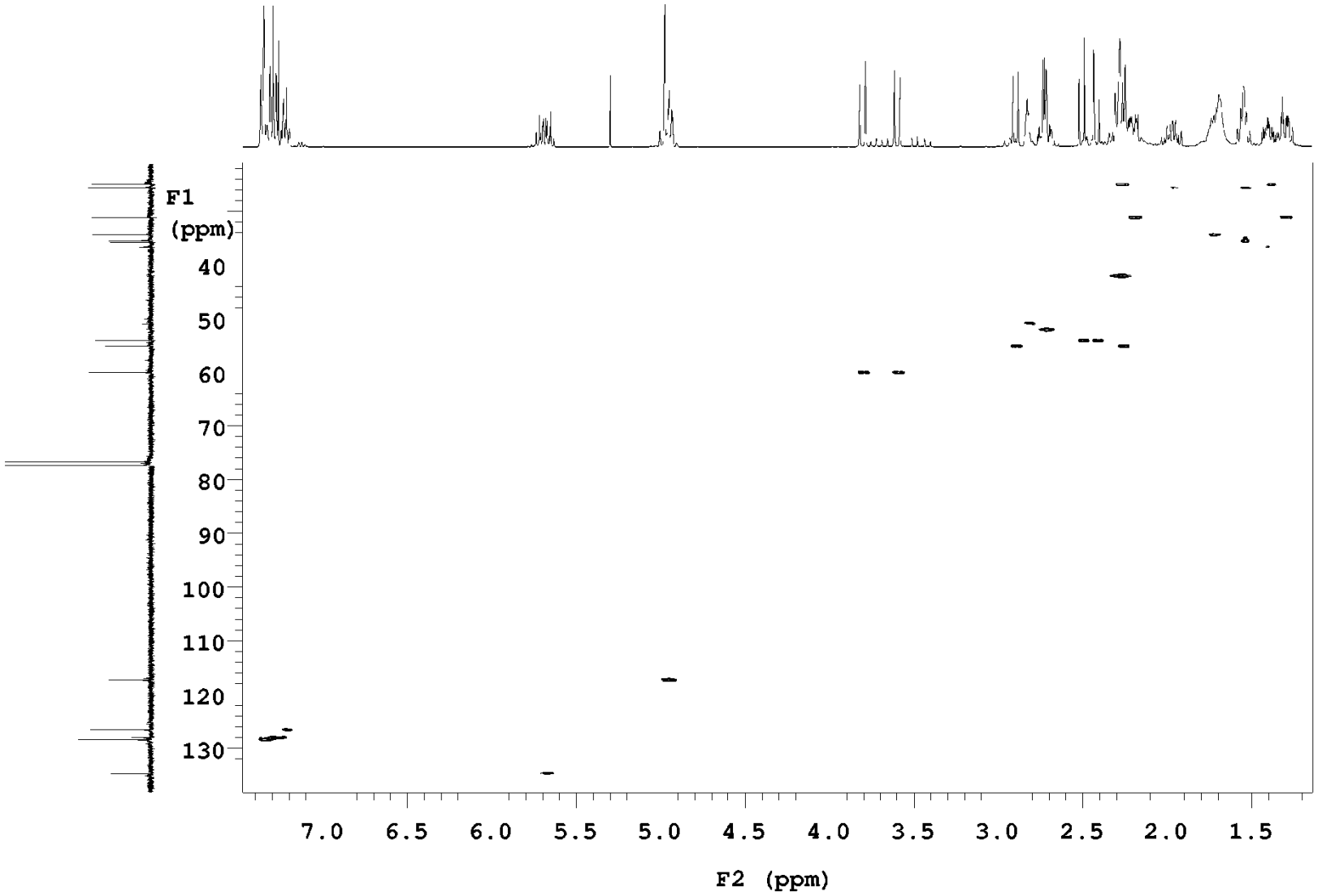


H1 / 400
cdcl3 / Temp: 25C / N.Reg: XXXXXXXXXX
Usuari: san / Mostra: CP052-14
Nom: FAIZA DIABA
Data: 11/06/14 / Ope.: F.DIABA
Experiment: ghsqcad

Pulse Sequence: gHSQCAD

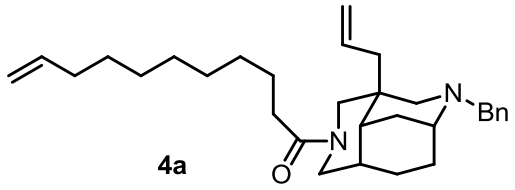


5



H1 / 400
cdcl3 / Temp: 25C / N.Reg: XXXXXXXXXX
Usuari: san / Mostra: CP054-23
Nom: FAIZA DIABA
Data: 16/06/14 / Ope.: F.DIABA
Experiment: s2pul

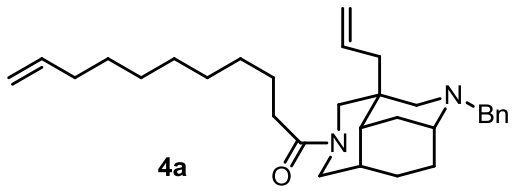
Pulse Sequence: s2pul



4a

H1 / 400
cdcl3 / Temp: 25C / N.Reg: XXXXXXXXXX
Usuari: san / Mostra: CP054-23
Nom: FAIZA DIABA
Data: 16/06/14 / Ope.: F.DIABA
Experiment: s2pul

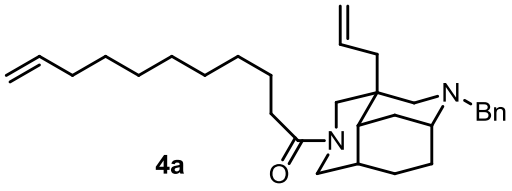
Pulse Sequence: s2pul



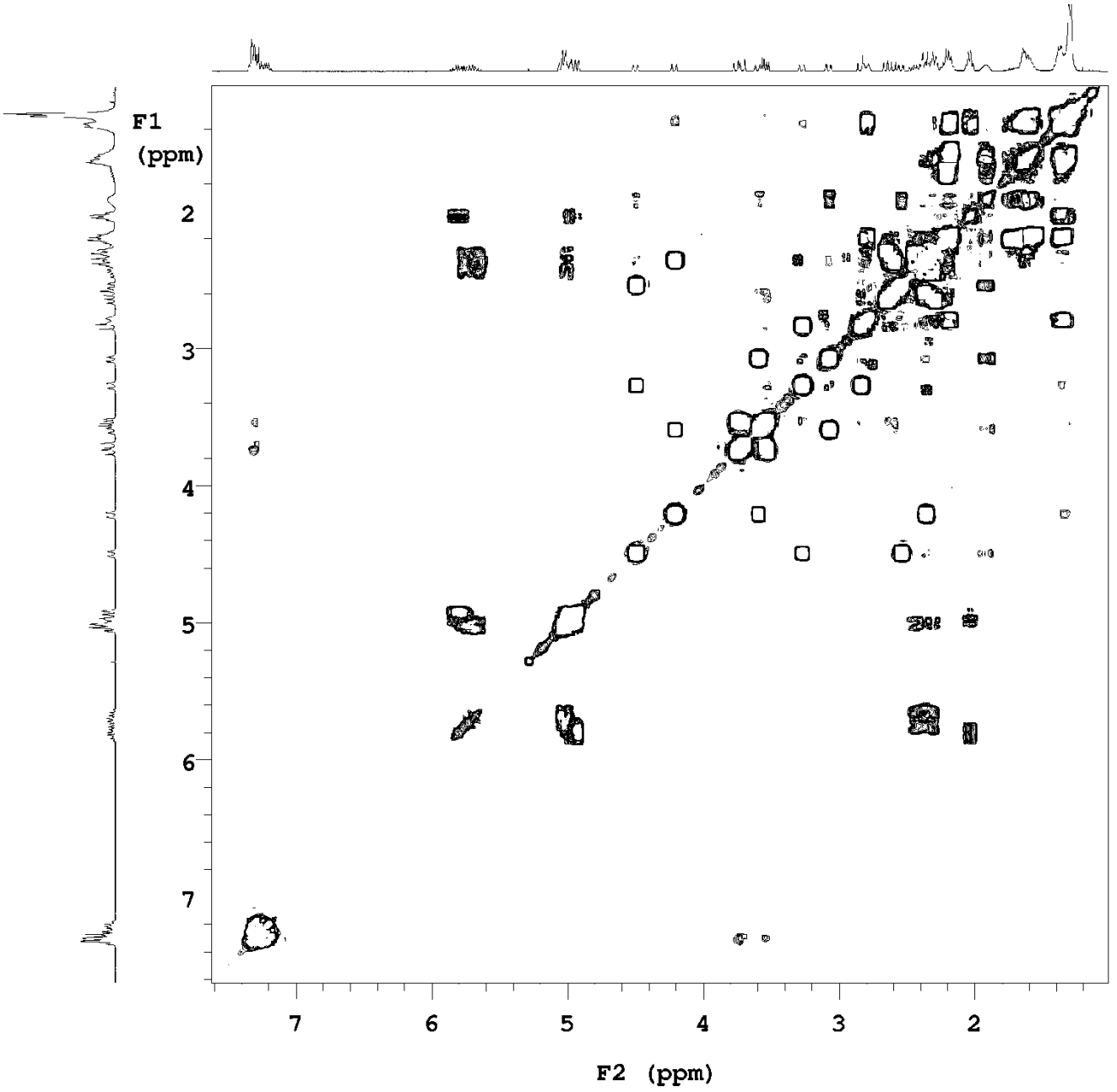
4a

H1 / 400
cdcl3 / Temp: 25C / N.Reg: XXXXXXXXXX
Usuari: san / Mostra: CP054-23
Nom: FAIZA DIABA
Data: 16/06/14 / Ope.: F.DIABA
Experiment: gcosy

Pulse Sequence: gCOSY



4a

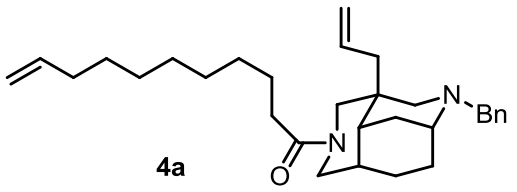


H1 / 400
cdcl3 / Temp: 25C / N.Reg: XXXXXXXXXX
Usuari: san / Mostra: CP054-23
Nom: FAIZA DIABA
Data: 16/06/14 / Ope.: F.DIABA
Experiment: ghsqcad

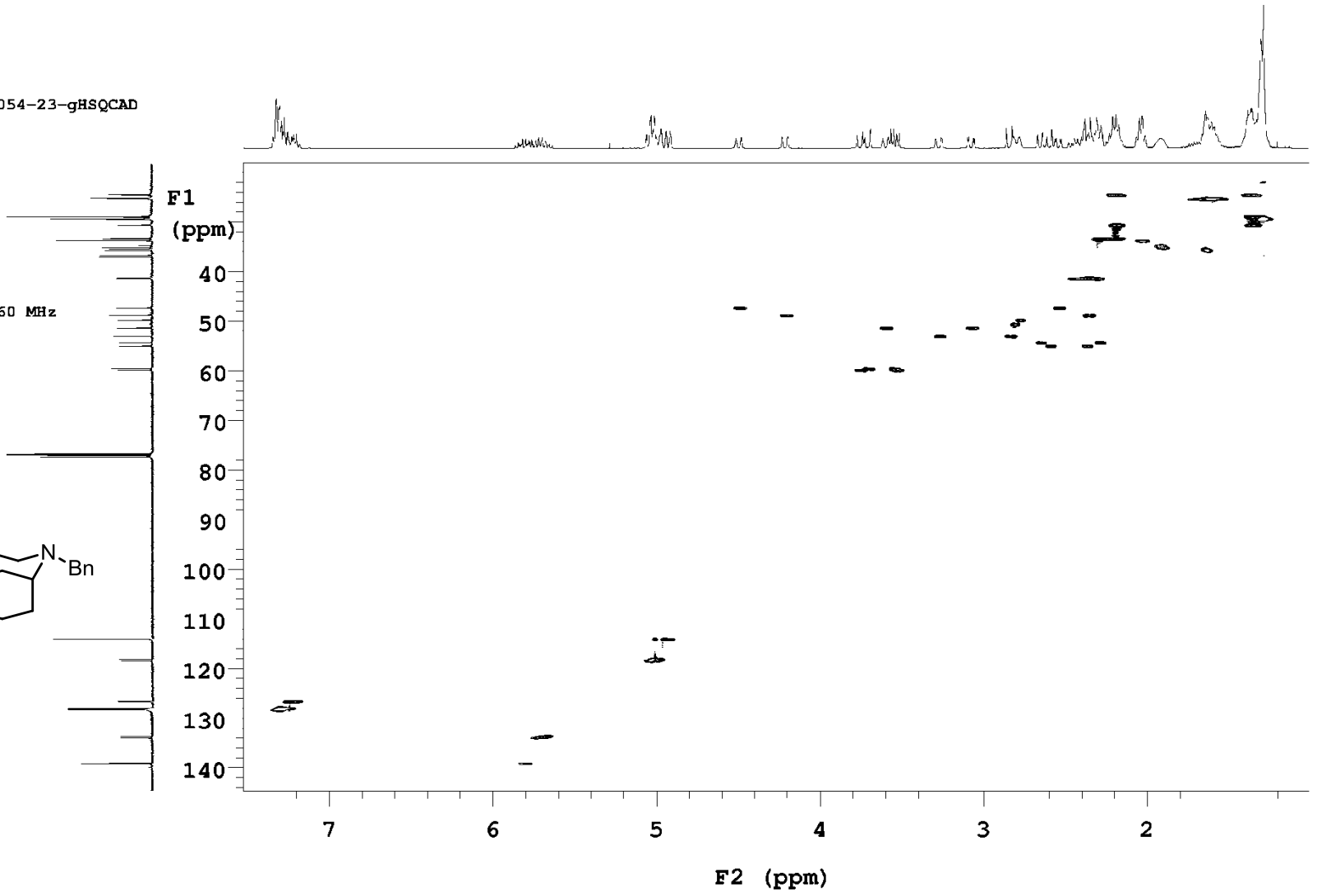
Pulse Sequence: gHSQCAD

Solvent: cdcl3
Temp. 25.0 C / 298.1 K
User: 1-14-87
File: V400A_17062014_CP054-23-gHSQCAD
INOVA-500 "menhir"

PULSE SEQUENCE: gHSQCAD
Relax. delay 1.000 sec
Acq. time 0.150 sec
Width 4807.7 Hz
2D Width 20115.7 Hz
8 repetitions
2 x 256 increments
OBSERVE H1, 399.9428160 MHz

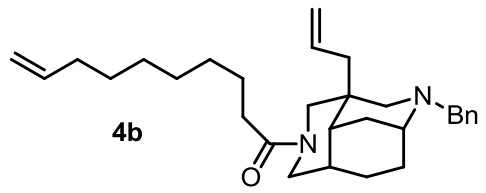


4a



H1 / 400
cdcl3 / Temp: 25C / N.Reg: XXXXXXXXXX
Usuari: san / Mostra: CP070-16
Nom: FAIZA DIABA
Data: 14/07/14 / Ope.: F.DIABA
Experiment: s2pul

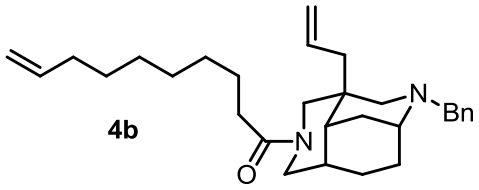
Pulse Sequence: s2pul



4b

H1 / 400
cdcl3 / Temp: 25C / N.Reg: XXXXXXXXXX
Usuari: san / Mostra: CP070-16
Nom: FAIZA DIABA
Data: 14/07/14 / Ope.: F.DIABA
Experiment: s2pul

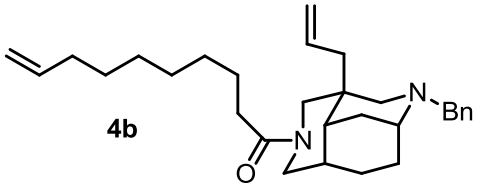
Pulse Sequence: s2pul



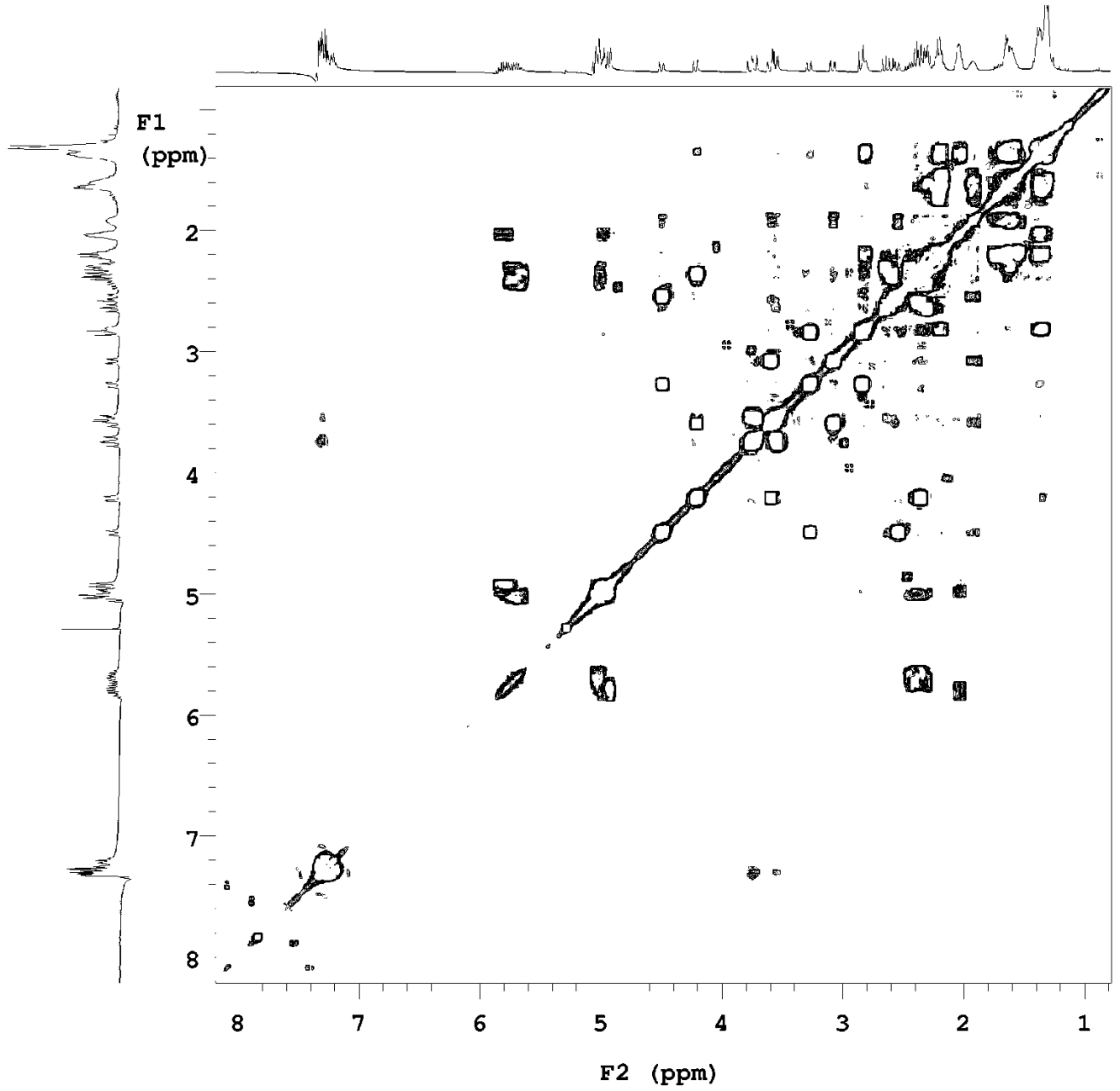
4b

H1 / 400
cdcl3 / Temp: 25C / N.Reg: XXXXXXXXXX
Usuari: san / Mostra: CP070-16
Nom: FAIZA DIABA
Data: 14/07/14 / Ope.: F.DIABA
Experiment: gcosy

Pulse Sequence: gCOSY



4b

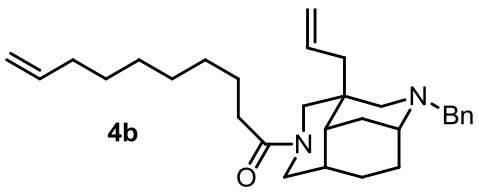


H1 / 400
cdcl3 / Temp: 25C / N.Reg: XXXXXXXXXX
Usuari: san / Mostra: CP070-16
Nom: FAIZA DIABA
Data: 14/07/14 / Ope.: F.DIABA
Experiment: ghsqcad

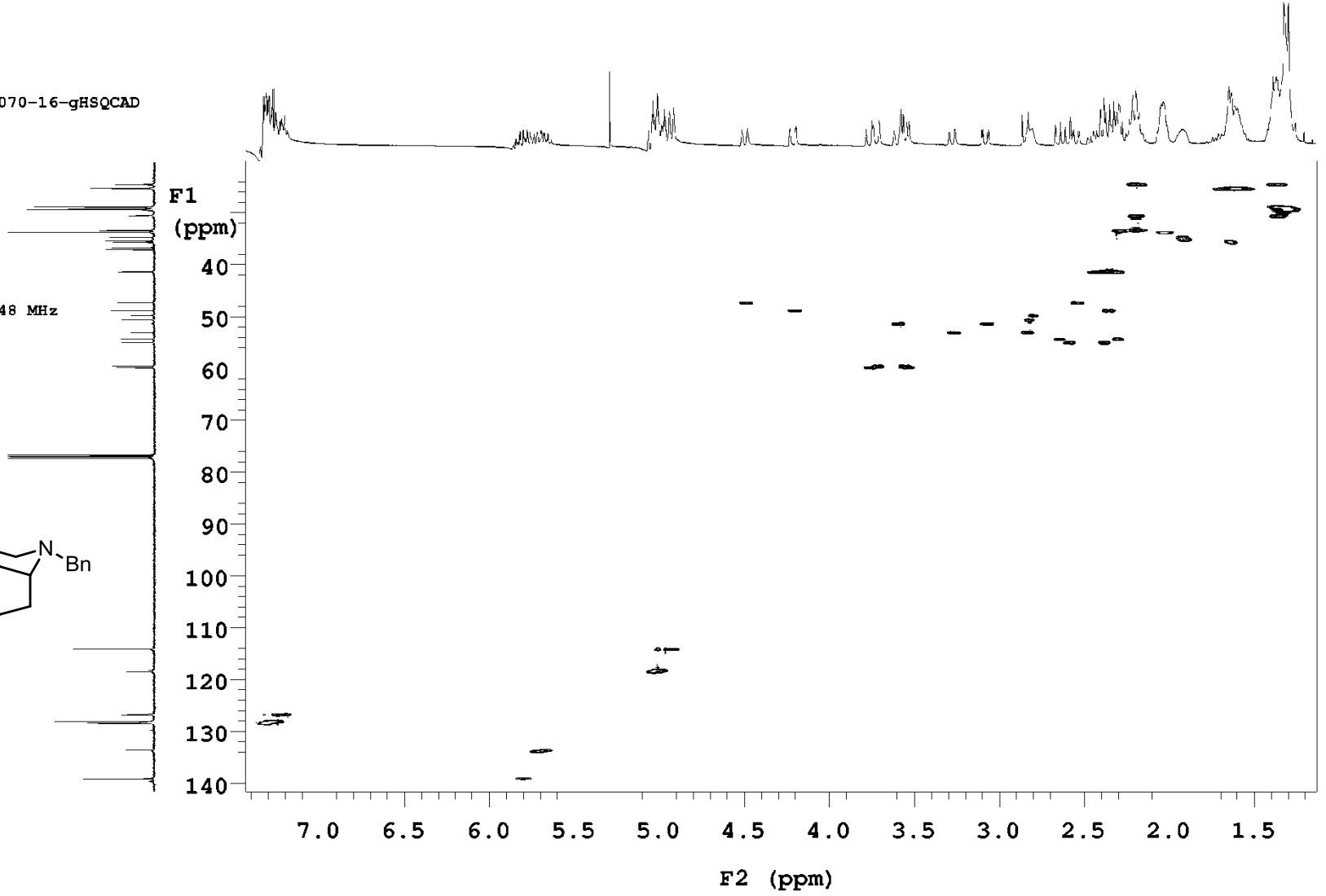
Pulse Sequence: gHSQCAD

Solvent: cdcl3
Temp. 25.0 C / 298.1 K
User: 1-14-87
File: V400A_15072014_CP070-16-gHSQCAD
INOVA-500 "menhir"

PULSE SEQUENCE: gHSQCAD
Relax. delay 1.000 sec
Acq. time 0.150 sec
Width 4807.7 Hz
2D Width 20115.7 Hz
8 repetitions
2 x 256 increments
OBSERVE H1, 399.9428148 MHz

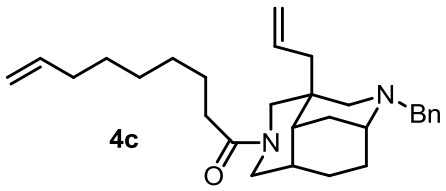


4b



H1 / 400
cdcl3 / Temp: 25C / N.Reg: XXXXXXXXXX
Usuari: san / Mostra: CP071-13
Nom: FAIZA DIABA
Data: 14/07/14 / Ope.: F.DIABA
Experiment: s2pul

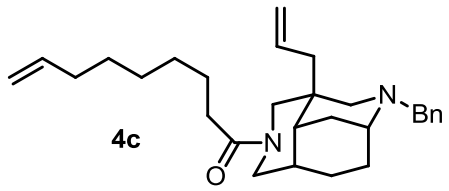
Pulse Sequence: s2pul



4c

H1 / 400
cdcl3 / Temp: 25C / N.Reg: XXXXXXXXXX
Usuari: san / Mostra: CP071-13
Nom: FAIZA DIABA
Data: 14/07/14 / Ope.: F.DIABA
Experiment: s2pul

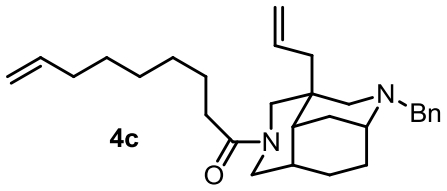
Pulse Sequence: s2pul

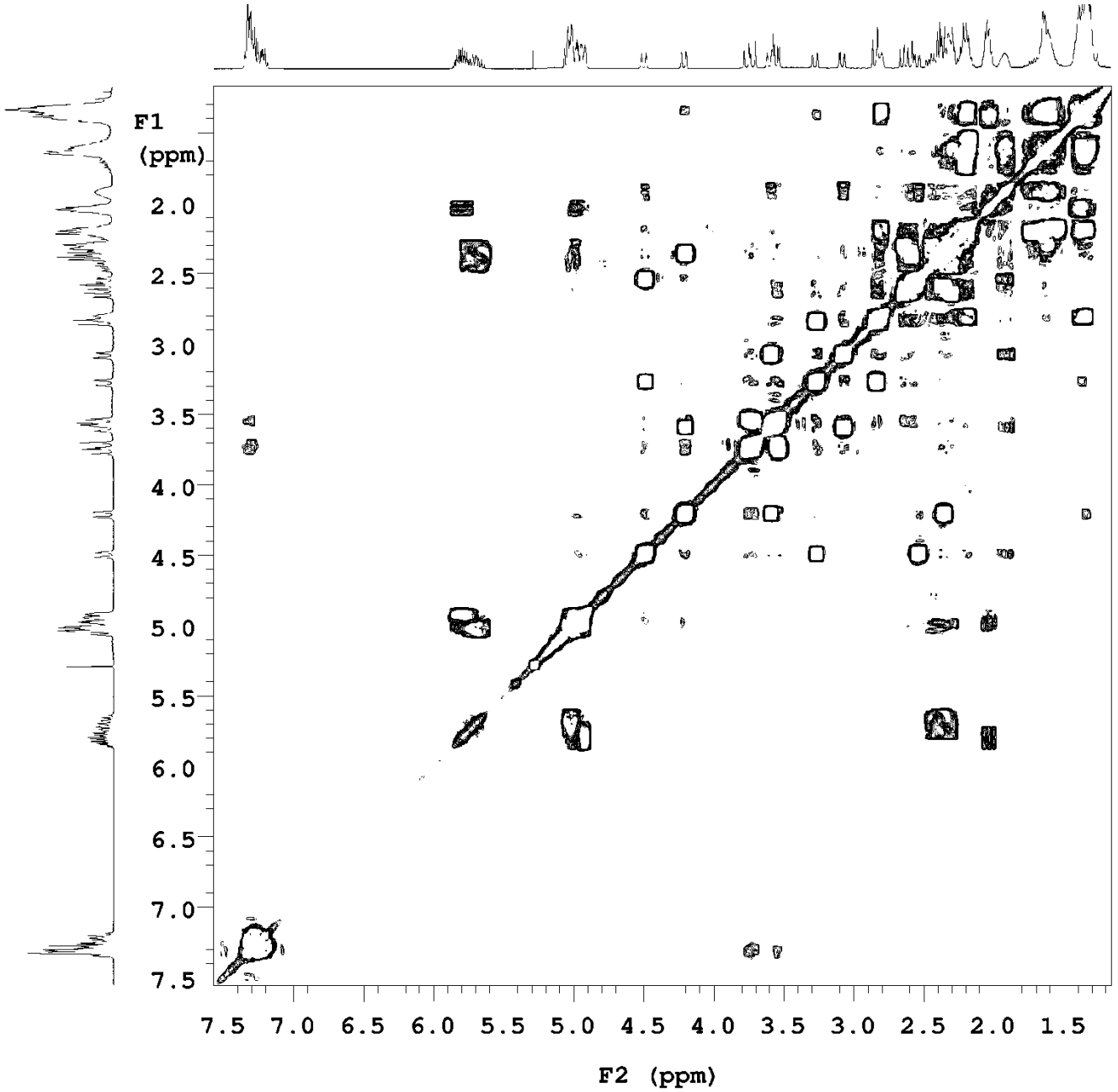


4c

H1 / 400
cdcl3 / Temp: 25C / N.Reg: XXXXXXXXXX
Usuari: san / Mostra: CP071-13
Nom: FAIZA DIABA
Data: 14/07/14 / Ope.: F.DIABA
Experiment: gcosy

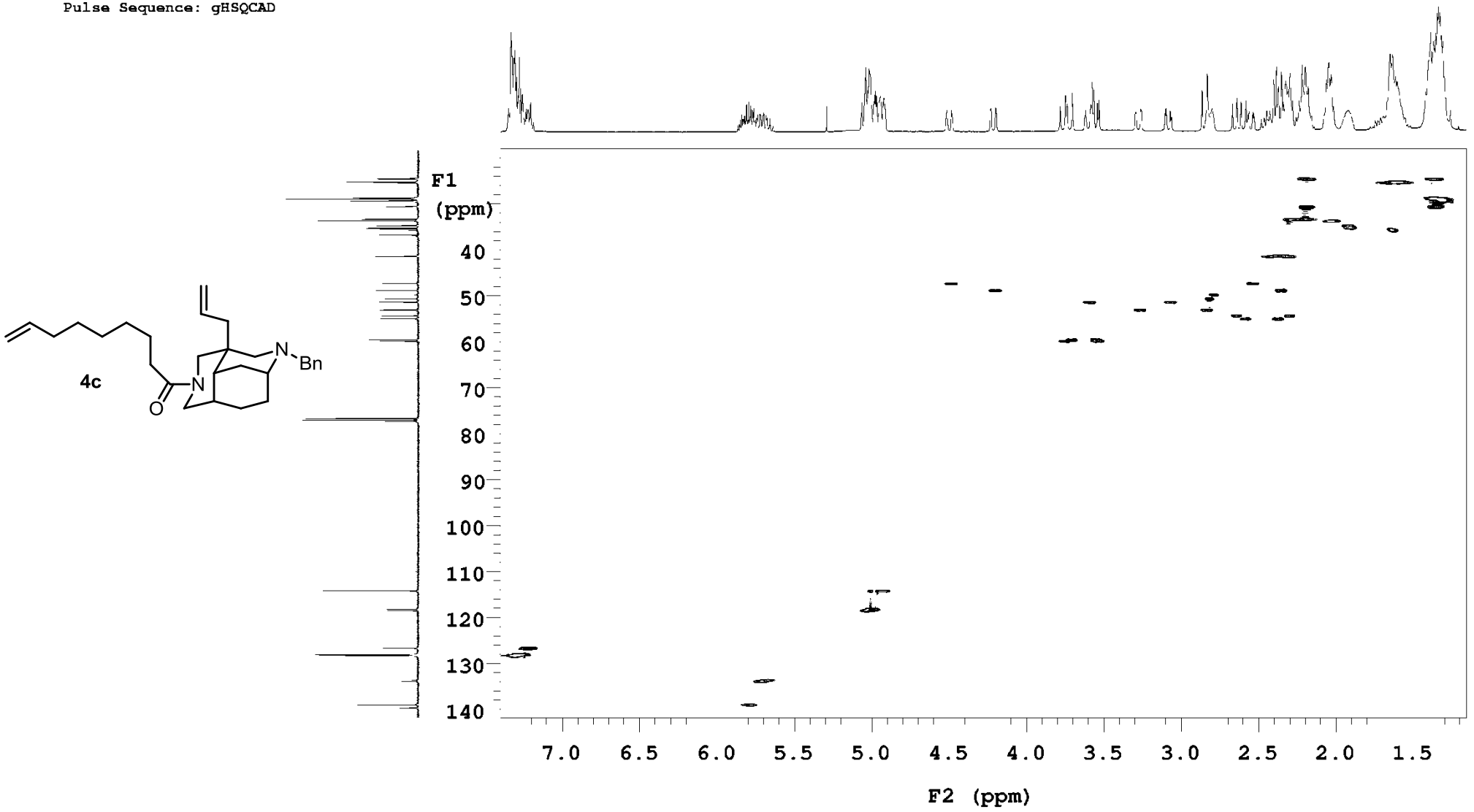
Pulse Sequence: gCOSY

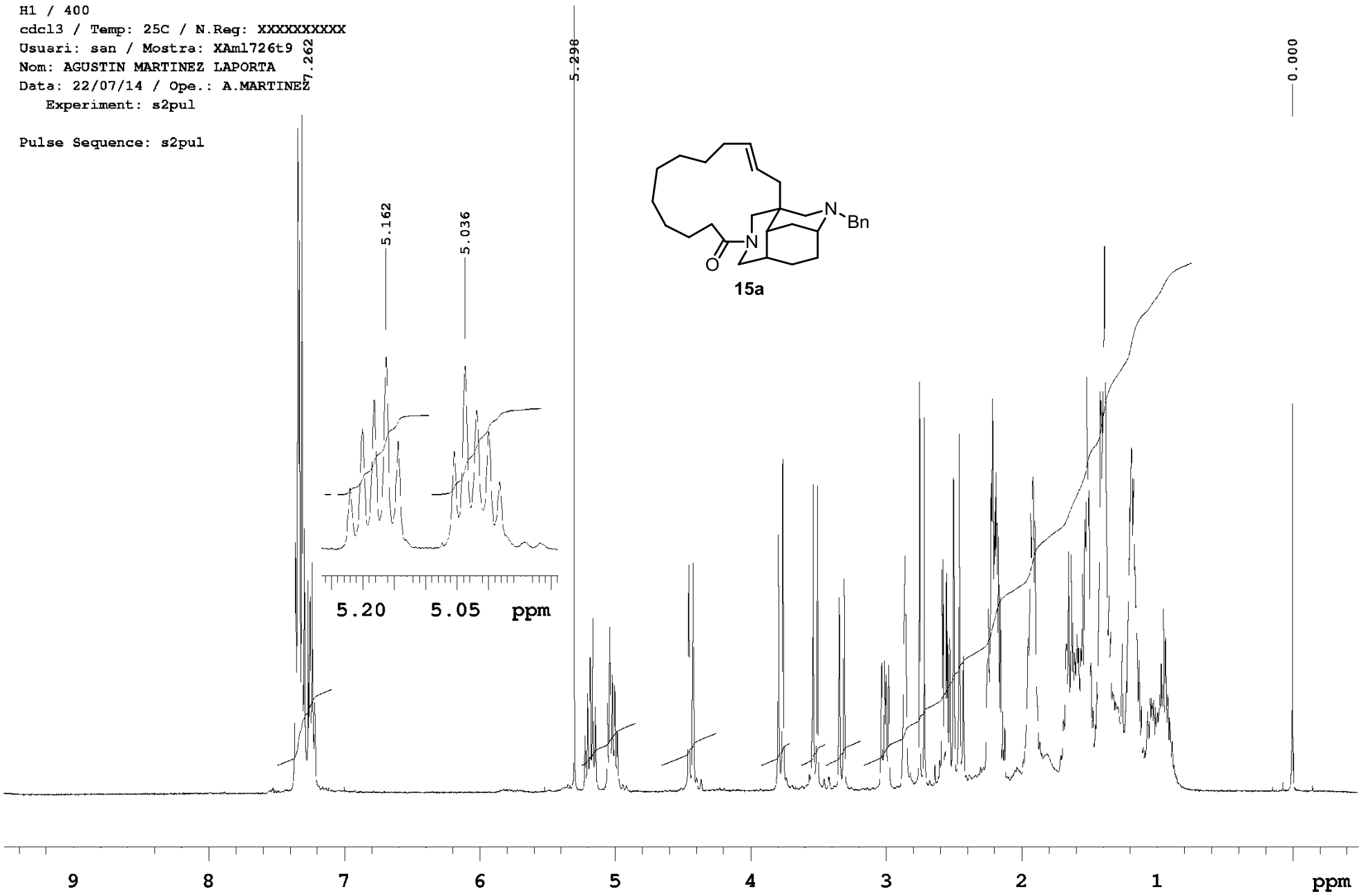




H1 / 400
cdcl3 / Temp: 25C / N.Reg: XXXXXXXXXX
Usuari: san / Mostra: CP071-13
Nom: FAIZA DIABA
Data: 14/07/14 / Ope.: F.DIABA
Experiment: ghsqcad

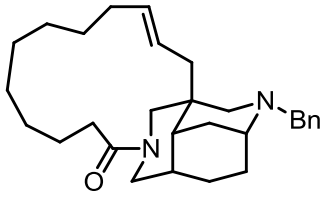
Pulse Sequence: gHSQCAD




H1 / 400
cdcl3 / Temp: 25C / N.Reg: XXXXXXXXXX
Usuari: san / Mostra: XAml726t9
Nom: AGUSTIN MARTINEZ LAPORTA
Data: 22/07/14 / Ope.: A.MARTINEZ
Experiment: s2pul
Pulse Sequence: s2pul
7.262
5.298
0.000
5.162
5.036
5.20
5.05
ppm
N
Bn
N
O
15a
9
8
7
6
5
4
3
2
1
ppm

H1 / 400
cdcl3 / Temp: 25C / N.Reg: XXXXXXXXXX
Usuari: san / Mostra: XAm1726t9
Nom: AGUSTIN MARTINEZ LAPORTA
Data: 22/07/14 / Ope.: A.MARTINEZ
Experiment: s2pul

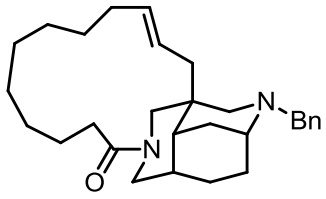
Pulse Sequence: s2pul



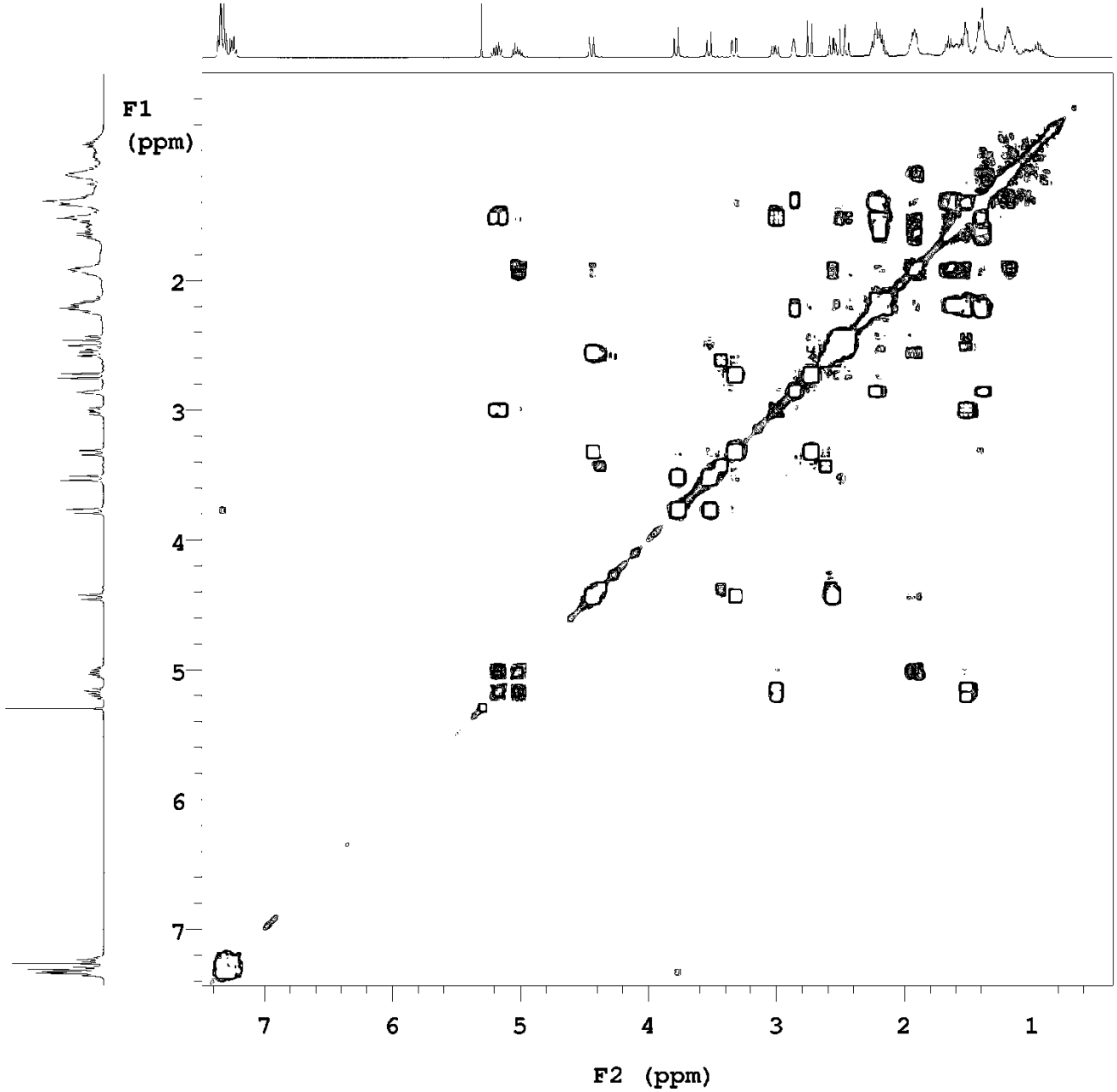
15a

H1 / 400
cdcl3 / Temp: 25C / N.Reg: XXXXXXXXXX
Usuari: san / Mostra: CP059-12
Nom: FAIZA DIABA
Data: 25/06/14 / Ope.: F.DIABA
Experiment: gcosy
H1_data are in file H1

Pulse Sequence: gCOSY

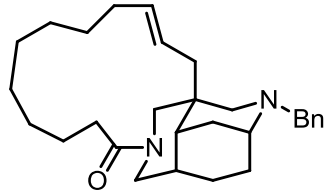


15a

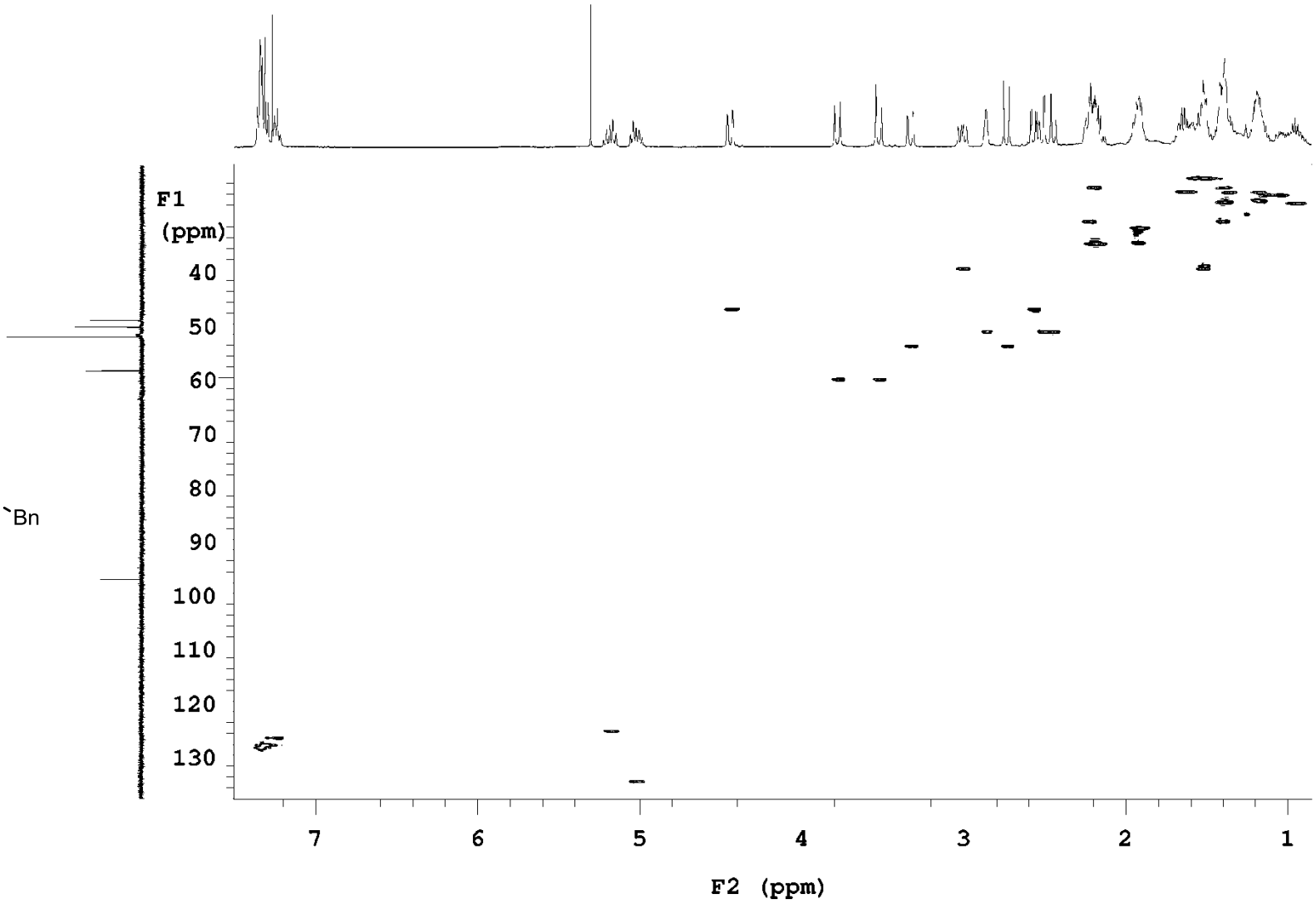


H1 / 400
cdcl3 / Temp: 25C / N.Reg: XXXXXXXXXX
Usuari: san / Mostra: CP059-12
Nom: FAIZA DIABA
Data: 25/06/14 / Ope.: F.DIABA
Experiment: ghsqcad

Pulse Sequence: gHSQCAD

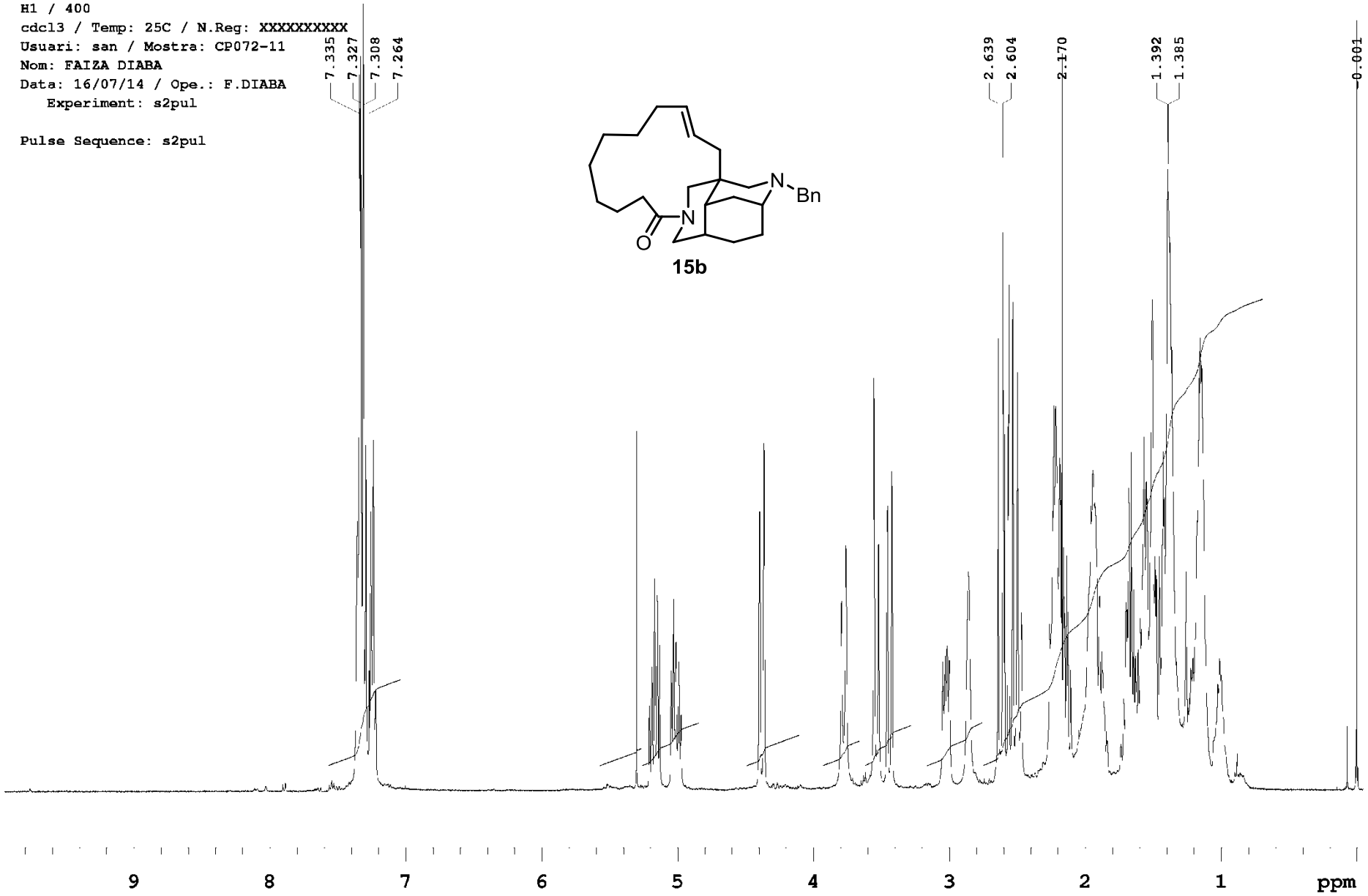


15a



H1 / 400
cdcl3 / Temp: 25C / N.Reg: XXXXXXXXXX
Usuari: san / Mostra: CP072-11
Nom: FAIZA DIABA
Data: 16/07/14 / Ope.: F.DIABA
Experiment: s2pul

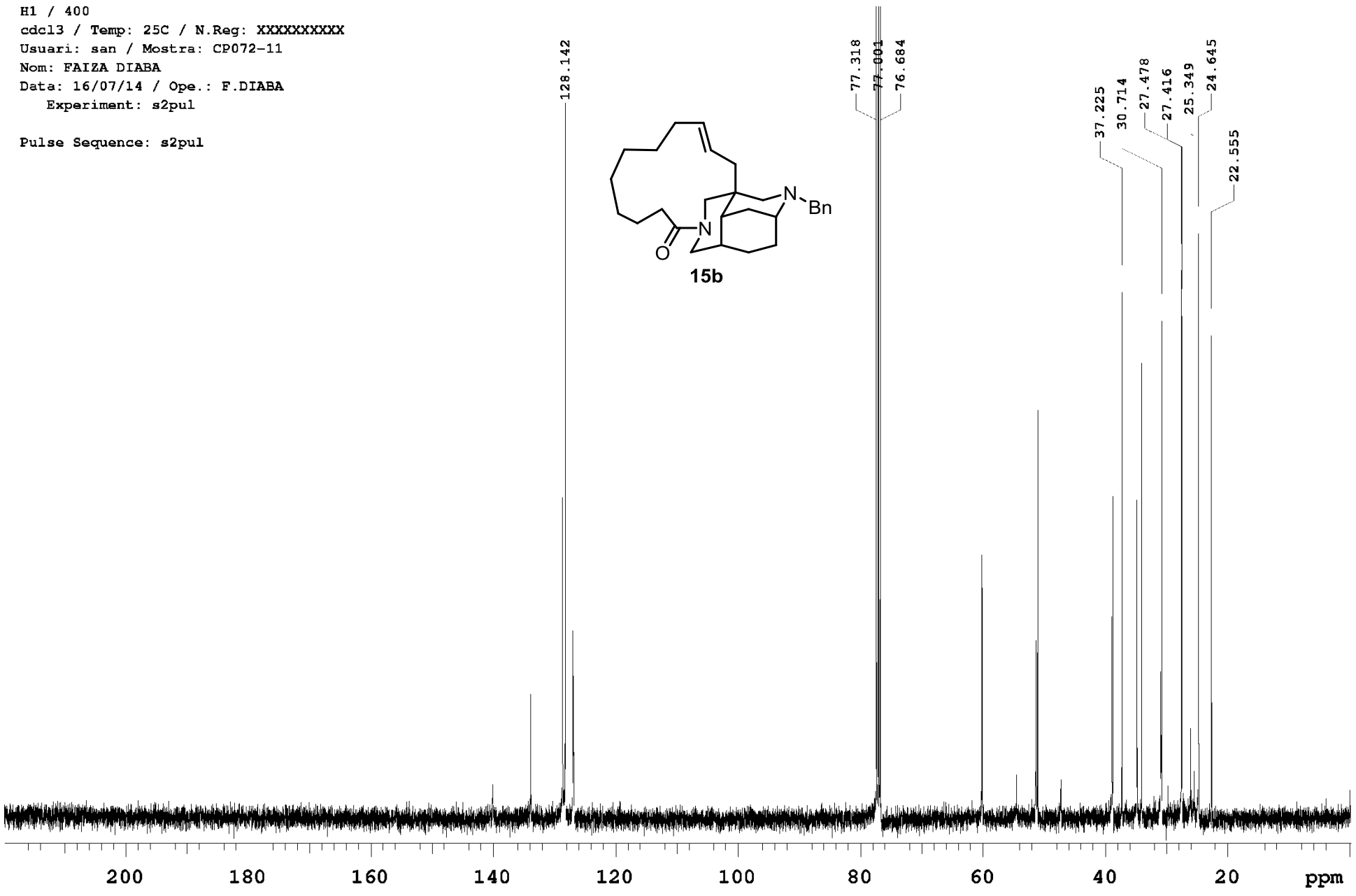
Pulse Sequence: s2pul



15b

H1 / 400
cdcl3 / Temp: 25C / N.Reg: XXXXXXXXXX
Usuari: san / Mostra: CP072-11
Nom: FAIZA DIABA
Data: 16/07/14 / Ope.: F.DIABA
Experiment: s2pul

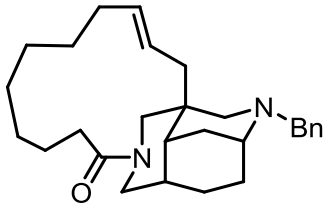
Pulse Sequence: s2pul



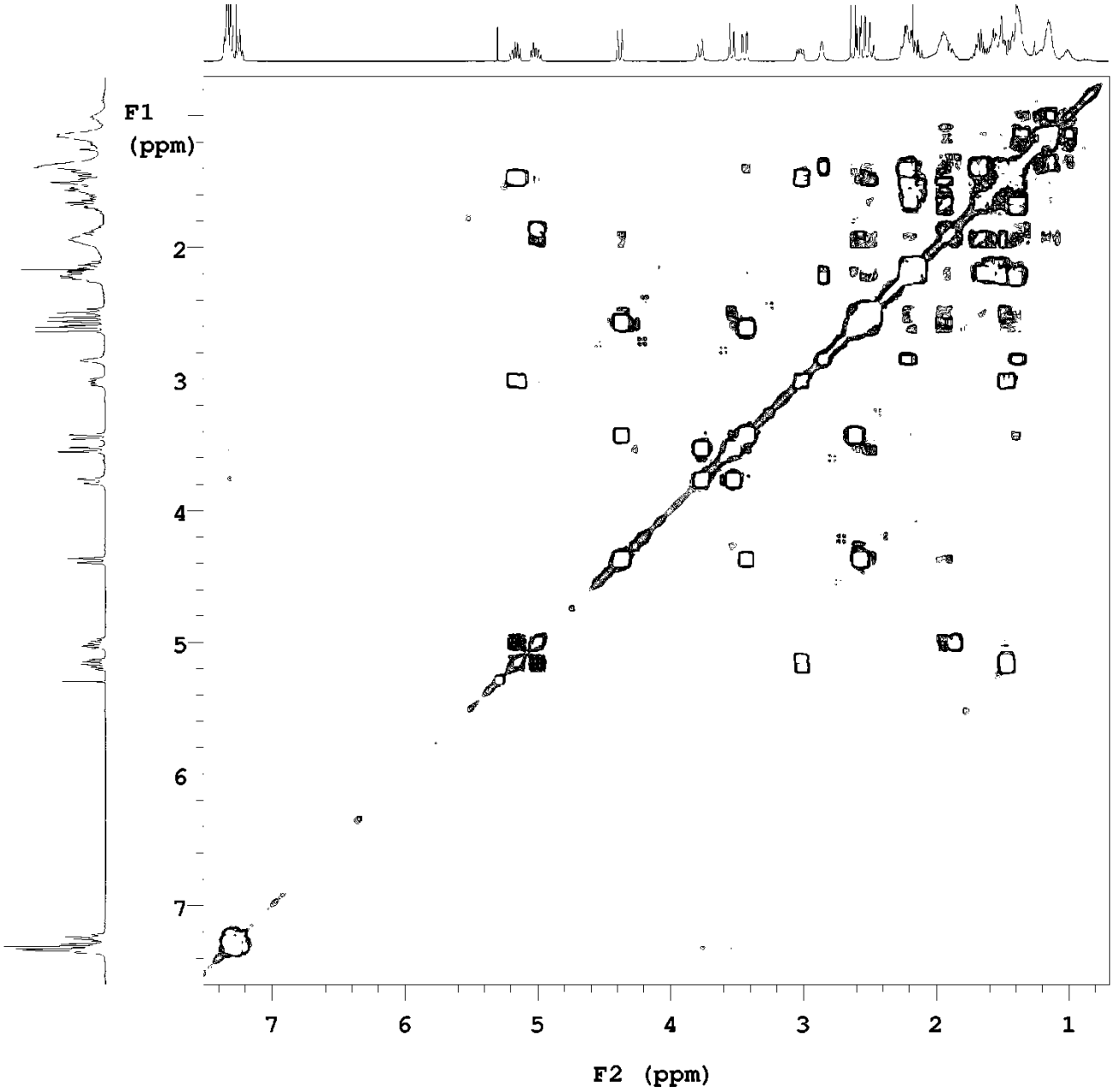
15b

H1 / 400
cdcl3 / Temp: 25C / N.Reg: XXXXXXXXXX
Usuari: san / Mostra: CP072-11
Nom: FAIZA DIABA
Data: 16/07/14 / Ope.: F.DIABA
Experiment: gcosy

Pulse Sequence: gCOSY

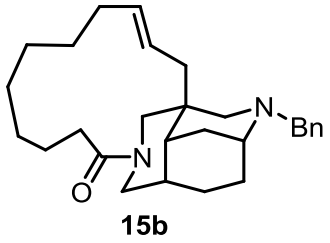


15b

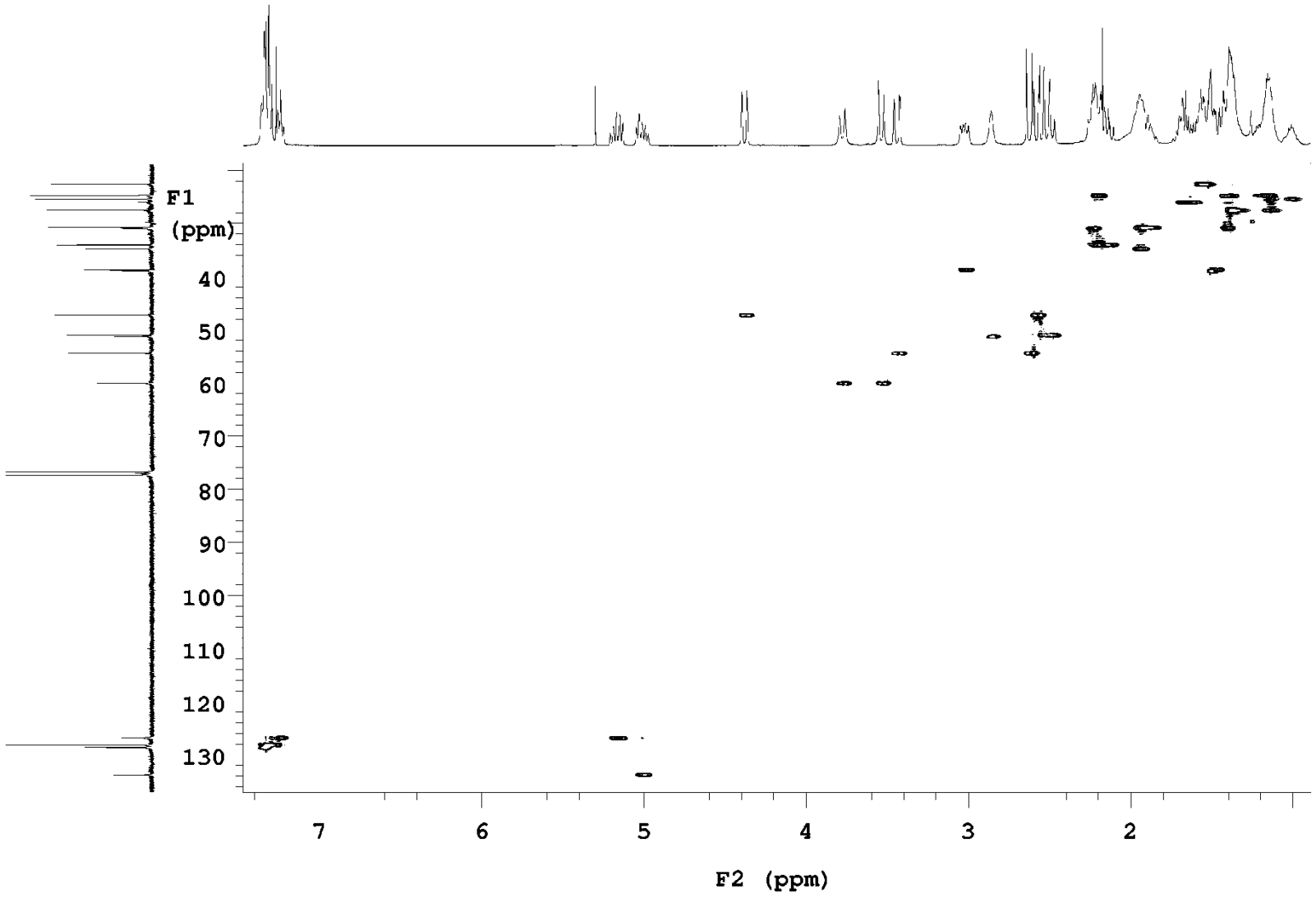


H1 / 400
cdcl3 / Temp: 25C / N.Reg: XXXXXXXXXX
Usuari: san / Mostra: CP072-11
Nom: FAIZA DIABA
Data: 16/07/14 / Ope.: F.DIABA
Experiment: ghsqcad

Pulse Sequence: gHSQCAD

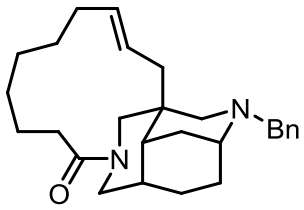


15b



H1 / 400
cdcl3 / Temp: 25C / N.Reg: XXXXXXXXXX
Usuari: san / Mostra: CP087-10
Nom: FAIZA DIABA
Data: 29/07/14 / Ope.: F.DIABA
Experiment: s2pul

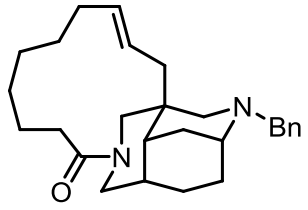
Pulse Sequence: s2pul



15c

H1 / 400
cdcl3 / Temp: 25C / N.Reg: XXXXXXXXXX
Usuari: san / Mostra: CP087-10
Nom: FAIZA DIABA
Data: 29/07/14 / Ope.: F.DIABA
Experiment: s2pul

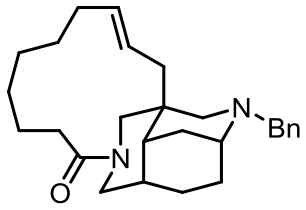
Pulse Sequence: s2pul



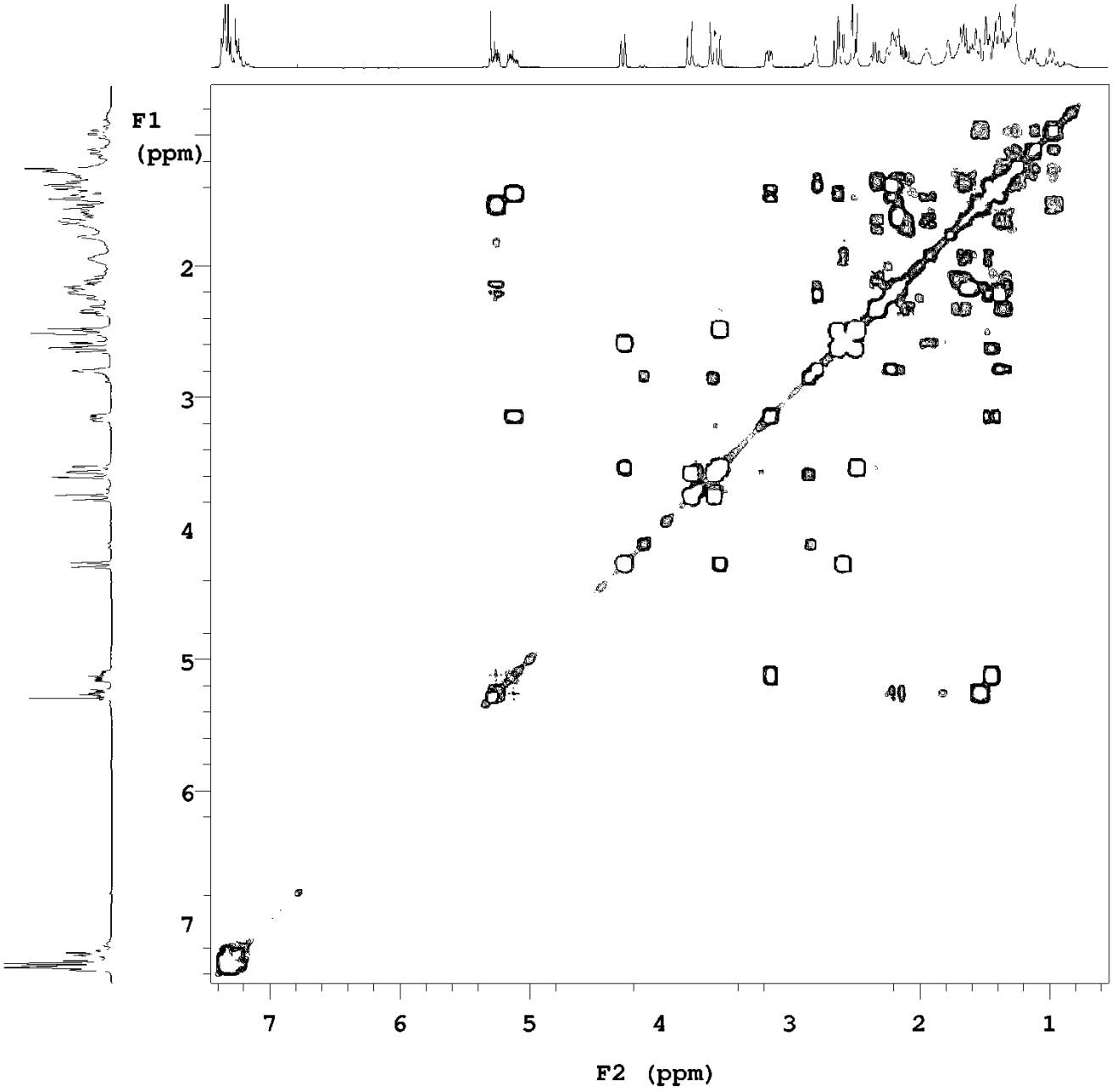
15c

H1 / 400
cdcl3 / Temp: 25C / N.Reg: XXXXXXXXXX
Usuari: san / Mostra: CP087-10
Nom: **FAIZA DIABA**
Data: 29/07/14 / Ope.: F.DIABA
Experiment: gcosy
H1_data are in file H1

Pulse Sequence: gCOSY

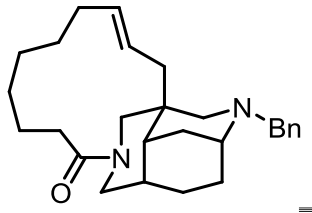


15c

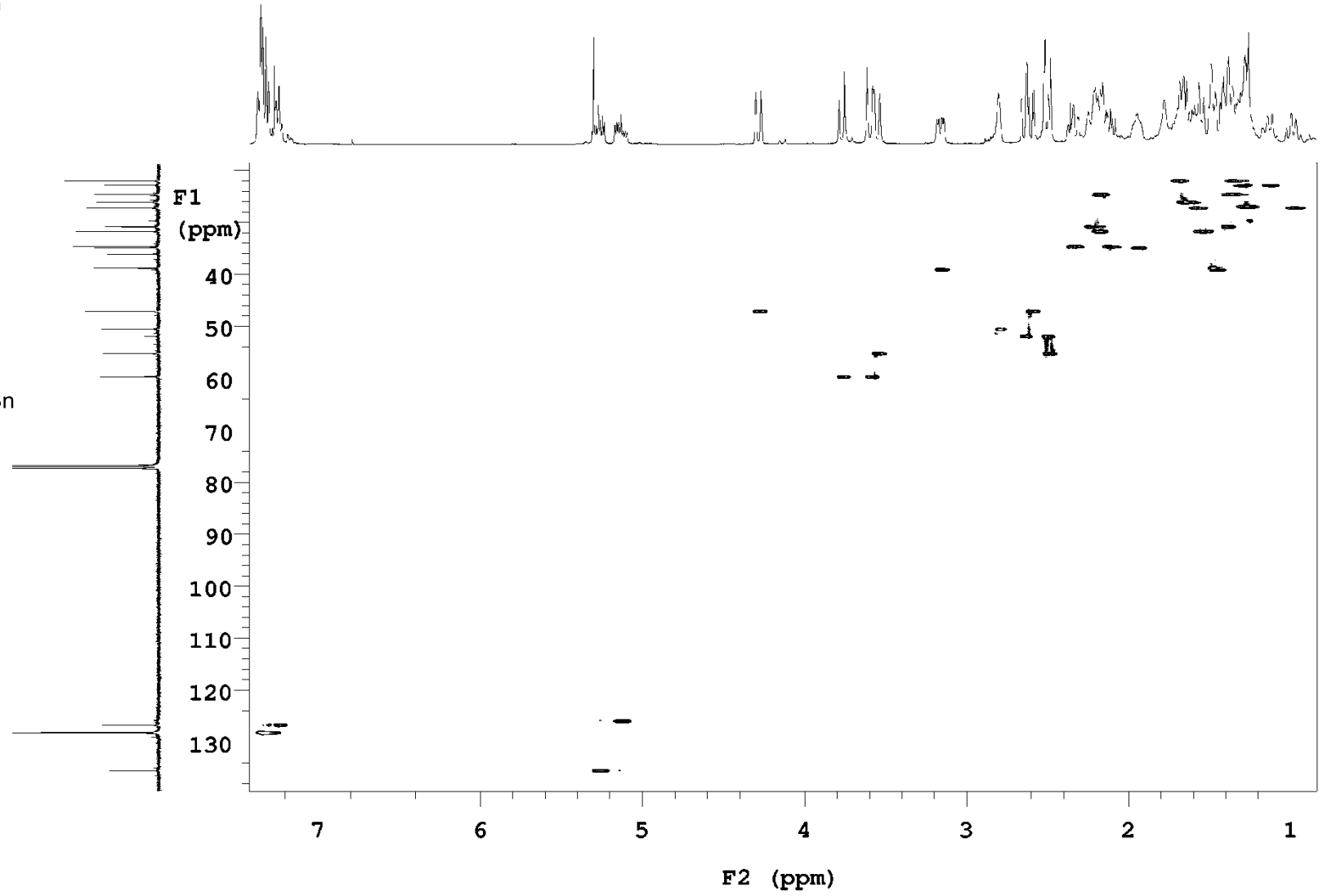


H1 / 400
cdcl3 / Temp: 25C / N.Reg: XXXXXXXXXX
Usuari: san / Mostra: CP087-10
Nom: FAIZA DIABA
Data: 29/07/14 / Ope.: F.DIABA
Experiment: ghsqcad

Pulse Sequence: gHSQCAD

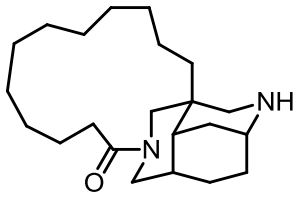


15c



H1 / 400
cdcl3 / Temp: 25C / N.Reg: XXXXXXXXXX
Usuari: san / Mostra: XAml728t3
Nom: AGUSTIN MARTINEZ LAPORTA
Data: 24/07/14 / Ope.: A.MARTINEZ
Experiment: s2pul

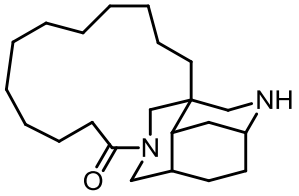
Pulse Sequence: s2pul



16a

H1 / 400
cdcl3 / Temp: 25C / N.Reg: XXXXXXXXXX
Usuari: san / Mostra: XAml728t3
Nom: AGUSTIN MARTINEZ LAPORTA
Data: 24/07/14 / Ope.: A.MARTINEZ
Experiment: s2pul

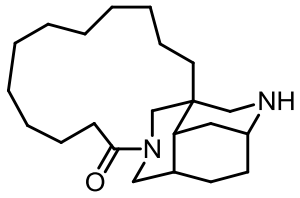
Pulse Sequence: s2pul



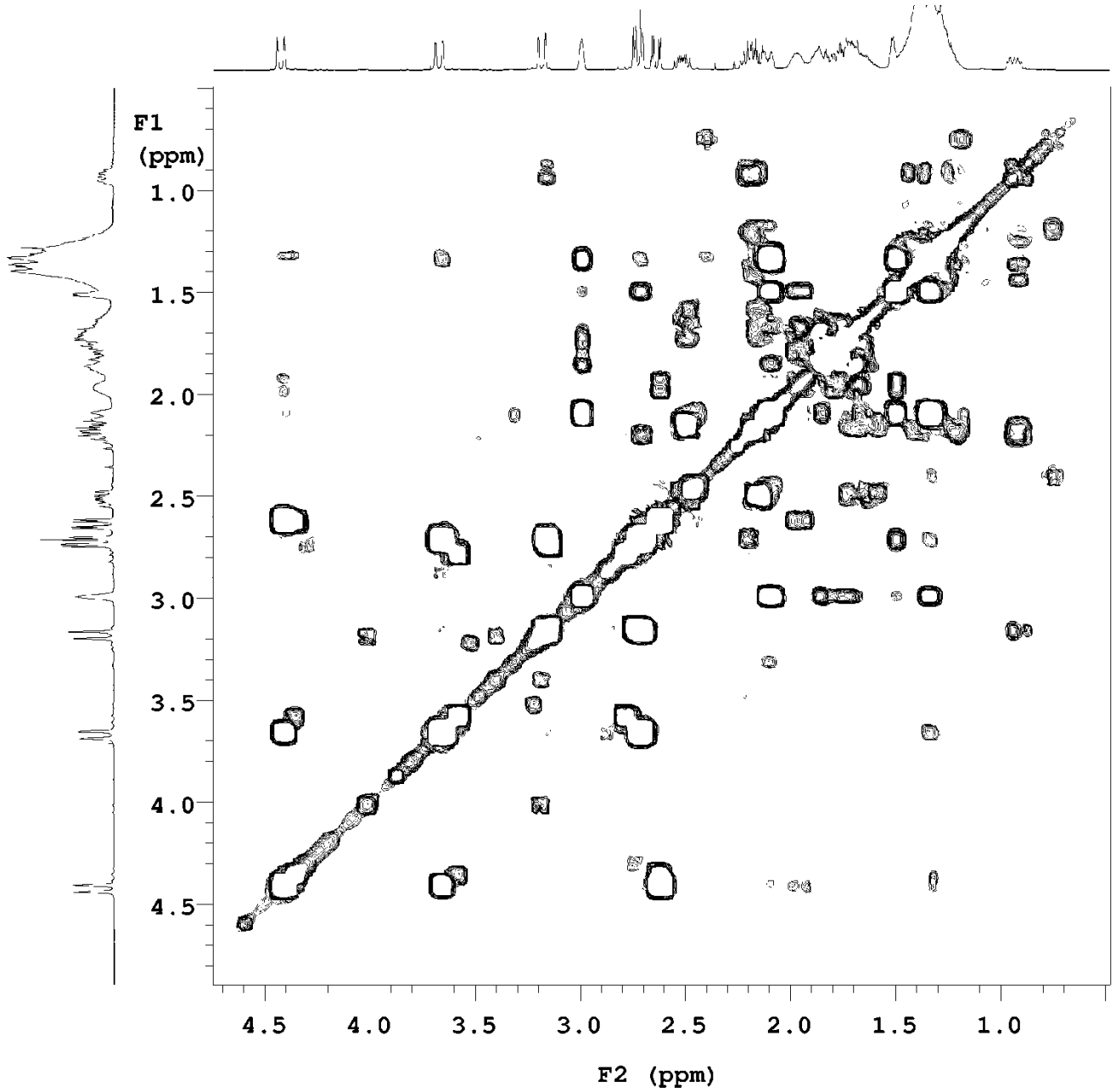
16a

H1 / 400
cdcl3 / Temp: 25C / N.Reg: XXXXXXXXXX
Usuari: san / Mostra: CP062-10
Nom: **FAIZA DIABA**
Data: 27/06/14 / Ope.: F.DIABA
Experiment: gcosy

Pulse Sequence: gCOSY



16a

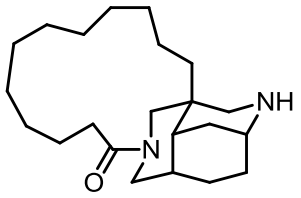


H1 / 400
cdcl3 / Temp: 25C / N.Reg: XXXXXXXXXX
Usuari: san / Mostra: CP062-10
Nom: FAIZA DIABA
Data: 27/06/14 / Ope.: F.DIABA
Experiment: ghsqcad

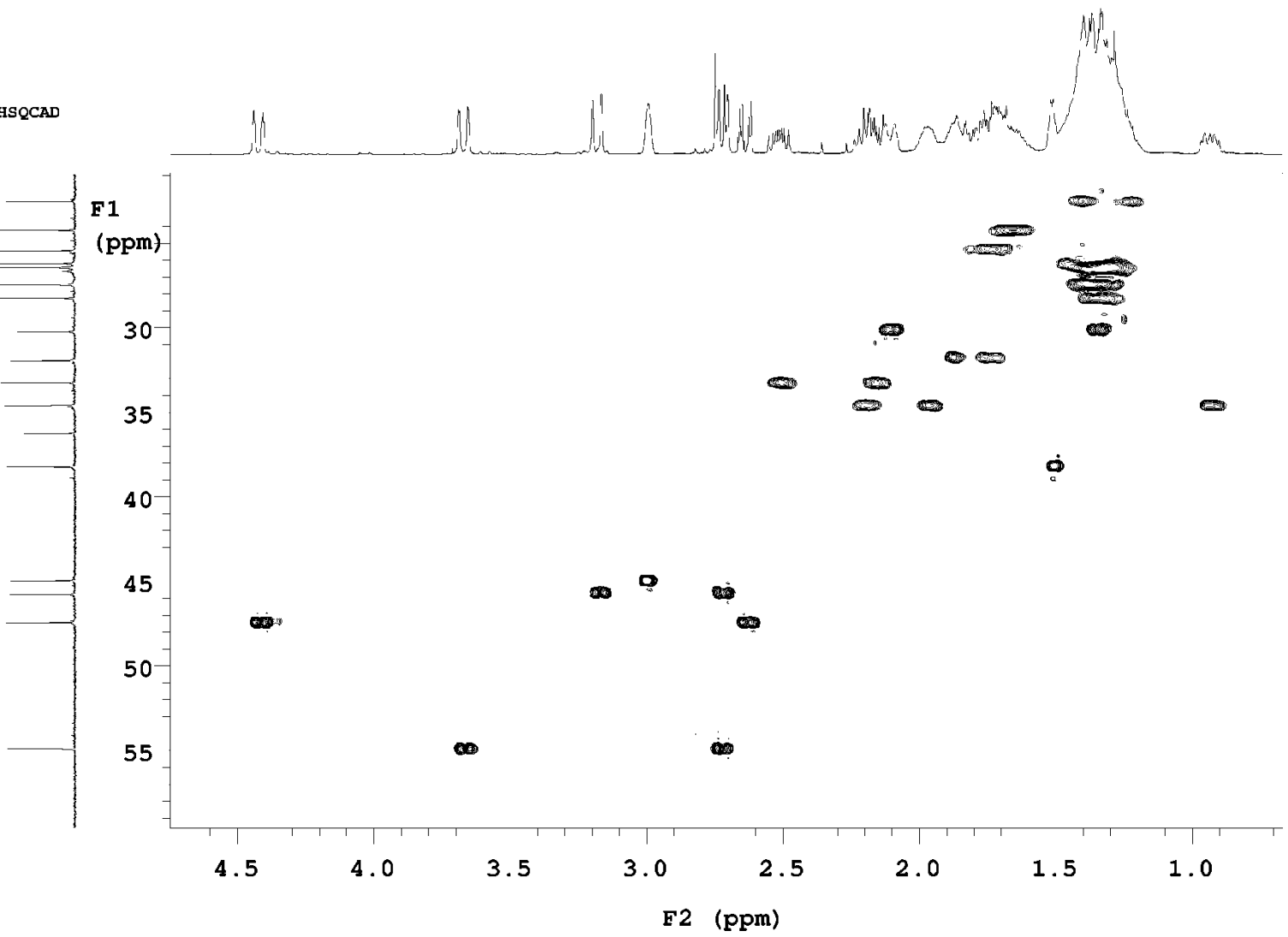
Pulse Sequence: gHSQCAD

Solvent: cdcl3
Temp. 25.0 C / 298.1 K
User: 1-14-87
File: V400A_28062014_CP062-10-gHSQCAD
INOVA-500 "menhir"

PULSE SEQUENCE: gHSQCAD
Relax. delay 1.000 sec
Acq. time 0.150 sec
Width 4807.7 Hz
2D Width 20115.7 Hz
8 repetitions
2 x 256 increments
OBSERVE H1, 399.9428125 MHz

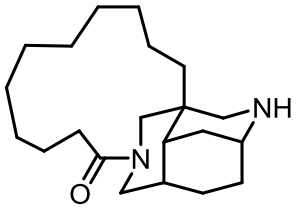


16a



H1 / 400
cdcl3 / Temp: 25C / N.Reg: XXXXXXXXXX
Usuari: san / Mostra: CP080-7
Nom: FAIZA DIABA
Data: 22/07/14 / Ope.: F.DIABA
Experiment: s2pul

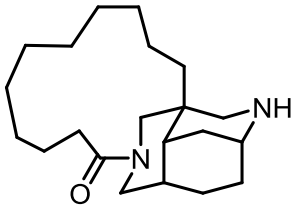
Pulse Sequence: s2pul



16b

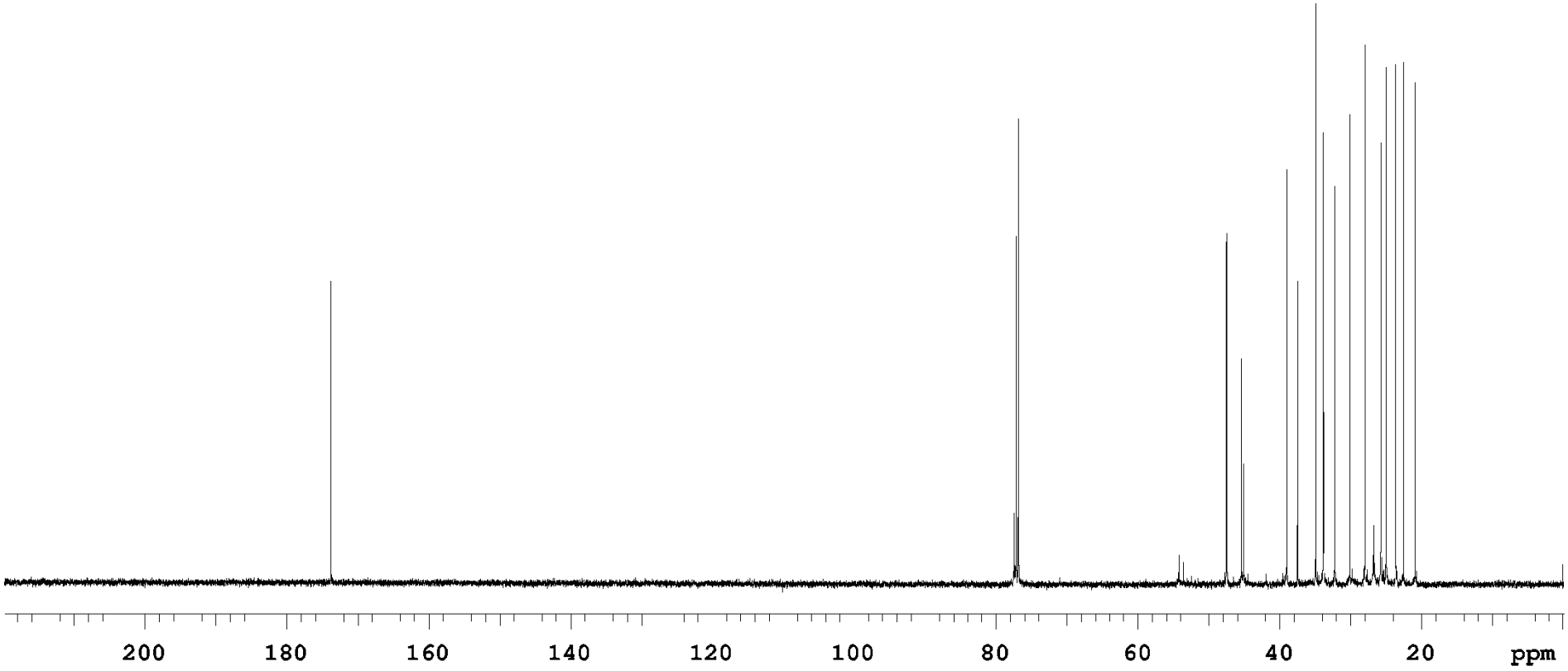
H1 / 400
cdcl3 / Temp: 25C / N.Reg: XXXXXXXXXX
Usuari: san / Mostra: CP080-7
Nom: FAIZA DIABA
Data: 22/07/14 / Ope.: F.DIABA
Experiment: s2pul

Pulse Sequence: s2pul



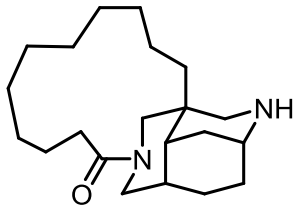
16b

26.678

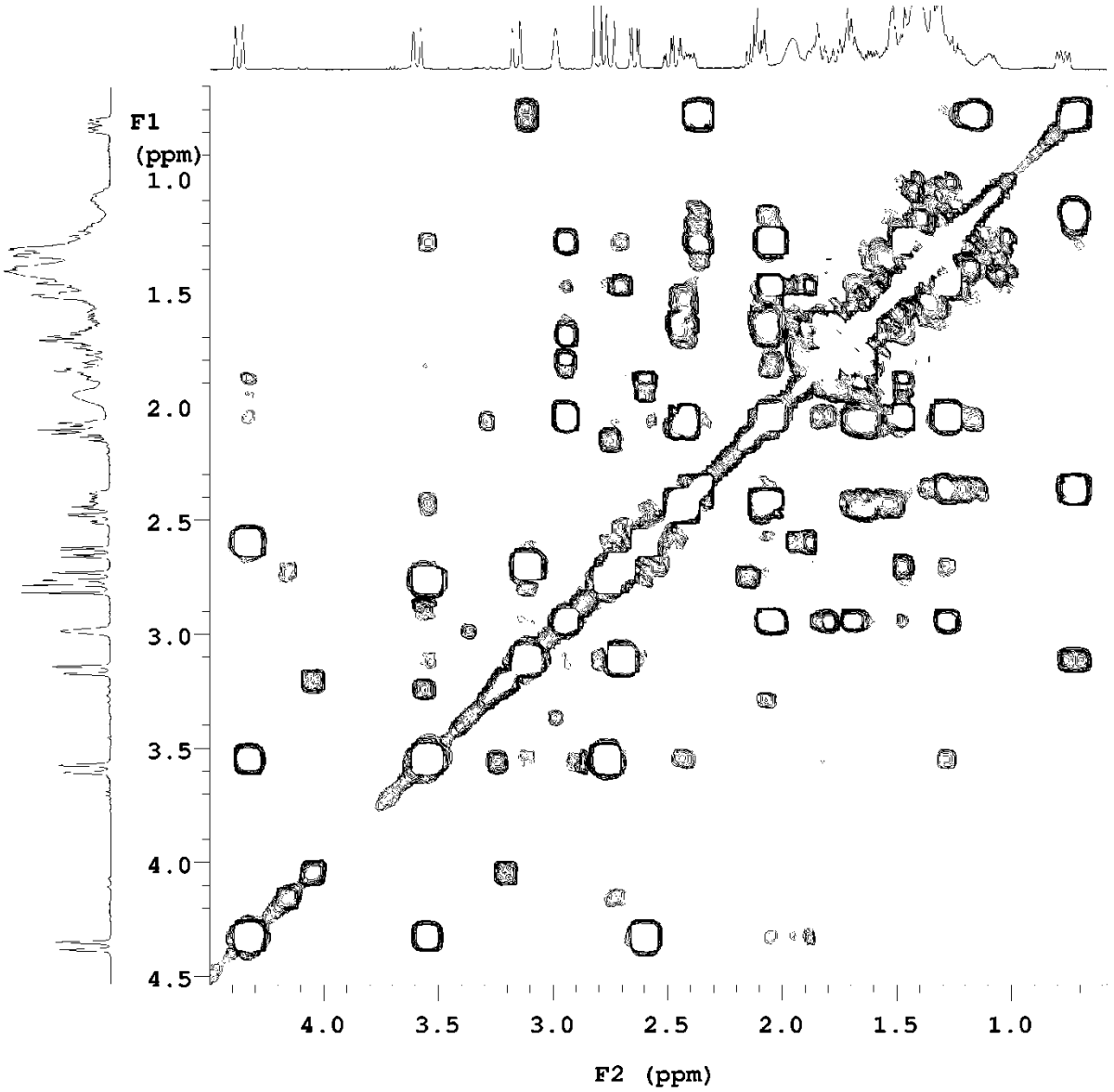


H1 / 400
cdcl3 / Temp: 25C / N.Reg: XXXXXXXXXX
Usuari: san / Mostra: CP080-7
Nom: FAIZA DIABA
Data: 22/07/14 / Ope.: F.DIABA
   Experiment: gcosy
H1_data are in file H1

Pulse Sequence: gCOSY

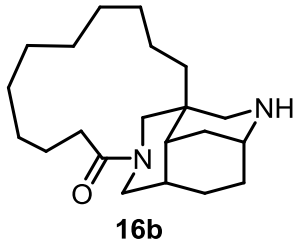


16b

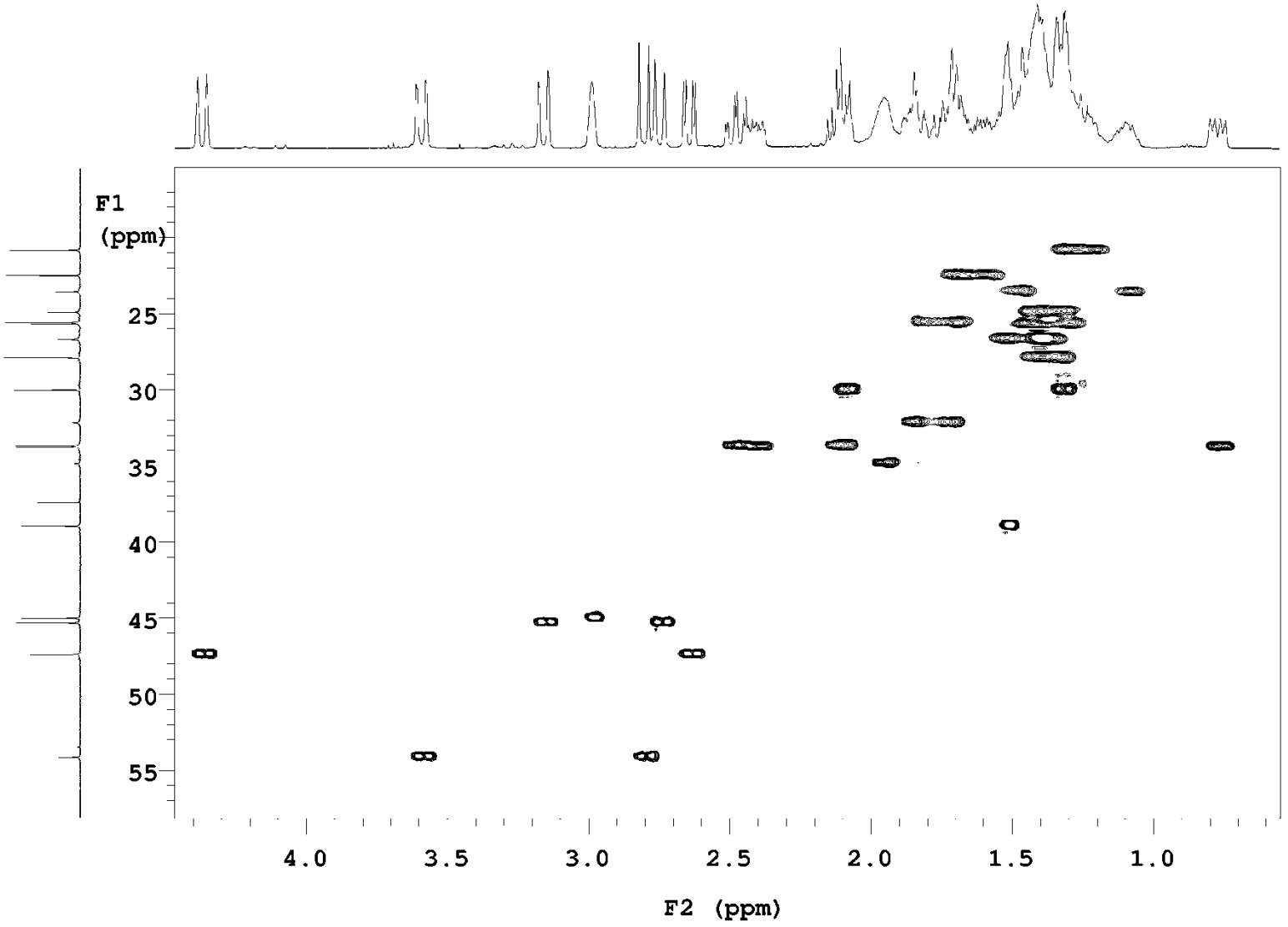


H1 / 400
cdcl3 / Temp: 25C / N.Reg: XXXXXXXXXX
Usuari: san / Mostra: CP080-7
Nom: FAIZA DIABA
Data: 22/07/14 / Ope.: F.DIABA
Experiment: ghsqcad

Pulse Sequence: gHSQCAD

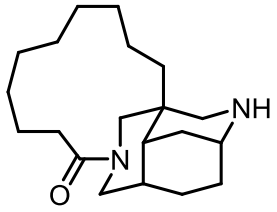


16b



H1 / 400
cdcl3 / Temp: 25C / N.Reg: XXXXXXXXXX
Usuari: san / Mostra: CP088-1
Nom: FAIZA DIABA
Data: 29/07/14 / Ope.: F.DIABA
Experiment: s2pul

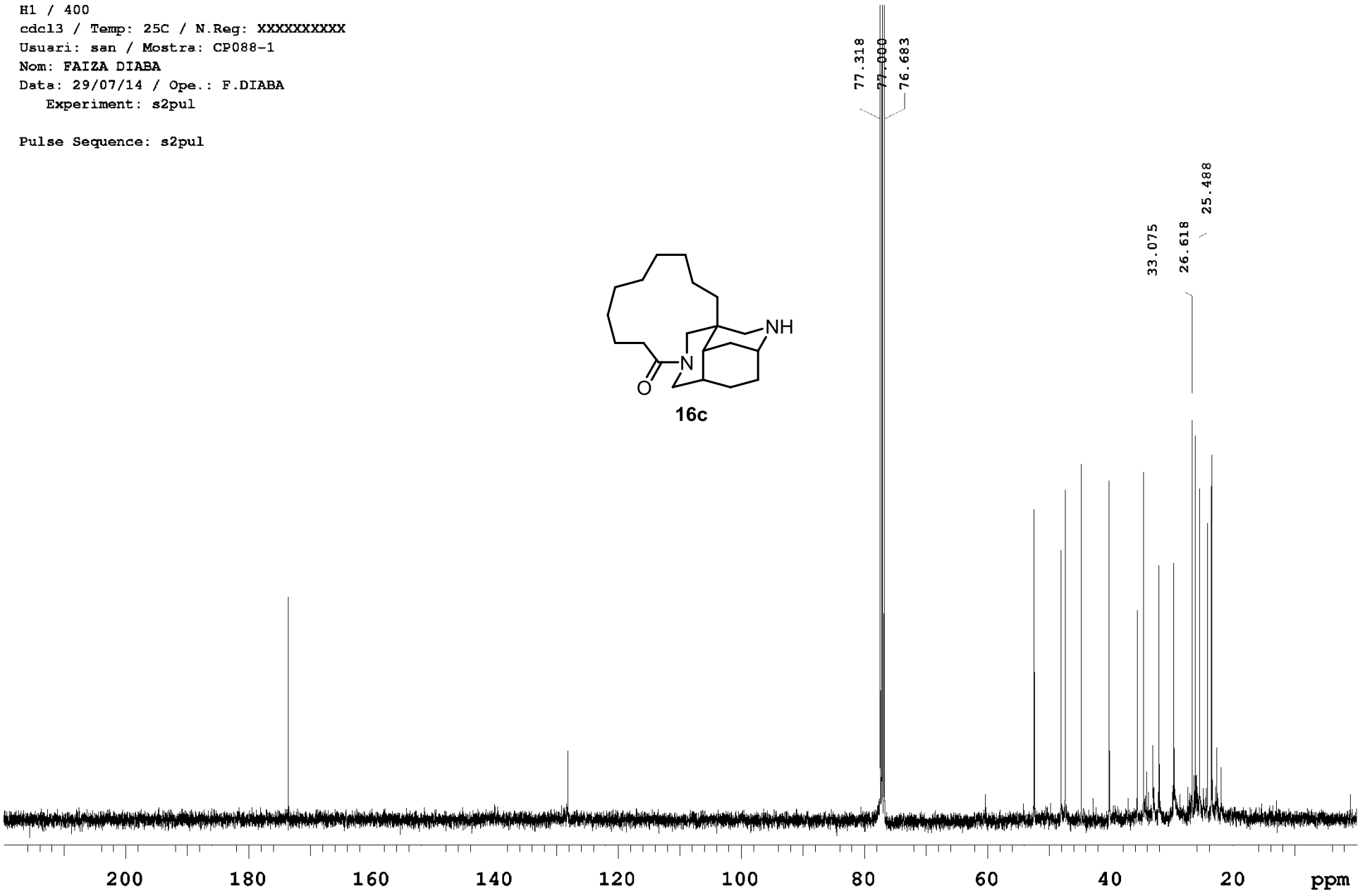
Pulse Sequence: s2pul



16c

H1 / 400
cdcl3 / Temp: 25C / N.Reg: XXXXXXXXXX
Usuari: san / Mostra: CP088-1
Nom: **FAIZA DIABA**
Data: 29/07/14 / Ope.: F.DIABA
Experiment: s2pul

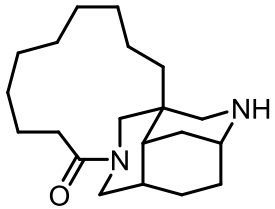
Pulse Sequence: s2pul



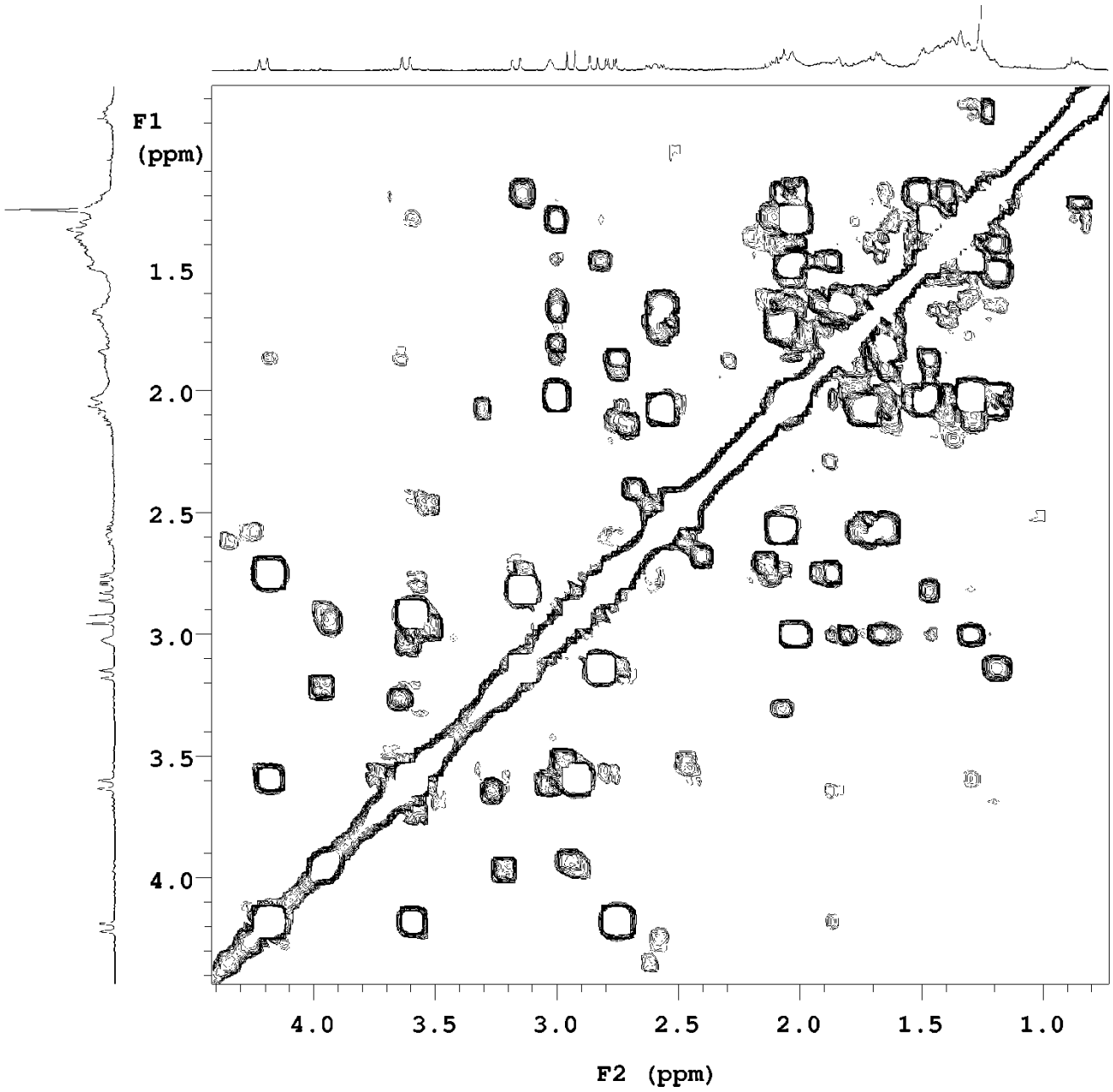
16c

H1 / 400
cdcl3 / Temp: 25C / N.Reg: XXXXXXXXXX
Usuari: san / Mostra: CP088-1
Nom: FAIZA DIABA
Data: 29/07/14 / Ope.: F.DIABA
Experiment: gcosy
H1_data are in file H1

Pulse Sequence: gCOSY

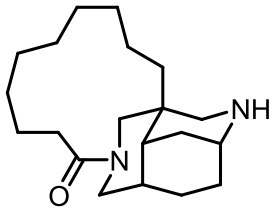


16c

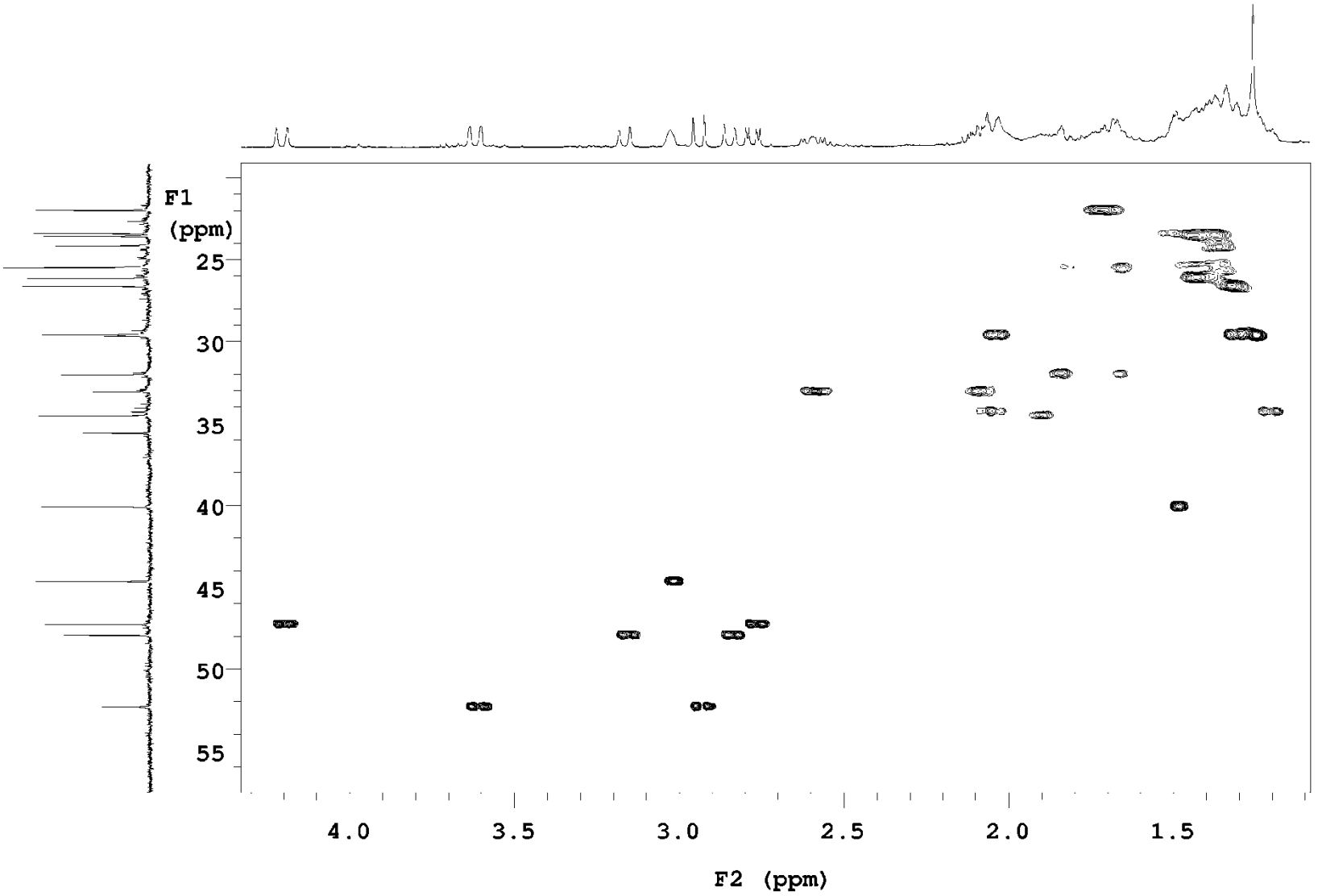


H1 / 400
cdcl3 / Temp: 25C / N.Reg: XXXXXXXXXX
Usuari: san / Mostra: CP088-1
Nom: FAIZA DIABA
Data: 29/07/14 / Ope.: F.DIABA
Experiment: ghsqcad

Pulse Sequence: gHSQCAD

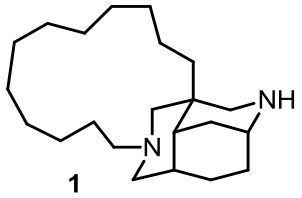


16c



H1 / 400
cdcl3 / Temp: 25C / N.Reg: XXXXXXXXXX
Usuari: san / Mostra: AML729-11
Nom: FAIZA DIABA
Data: 30/07/14 / Ope.: F.DIABA
Experiment: s2pul

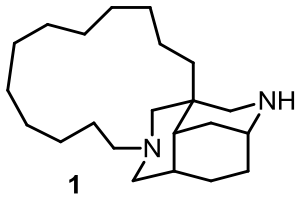
Pulse Sequence: s2pul



1

H1 / 400
cdcl3 / Temp: 25C / N.Reg: XXXXXXXXXX
Usuari: san / Mostra: AML729-11
Nom: FAIZA DIABA
Data: 30/07/14 / Ope.: F.DIABA
Experiment: s2pul

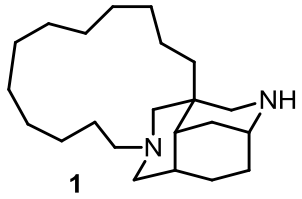
Pulse Sequence: s2pul



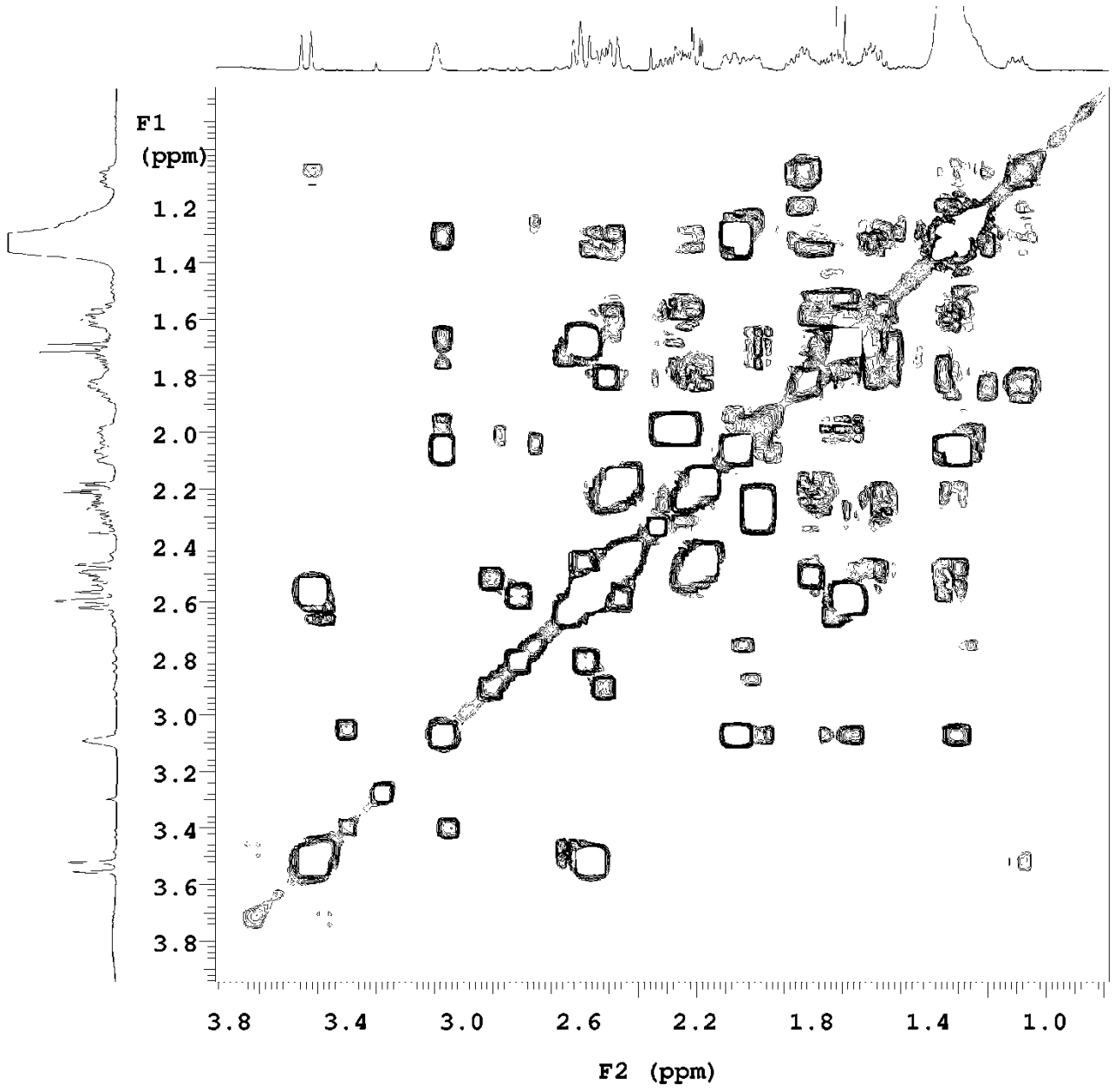
1

H1 / 400
cdcl3 / Temp: 25C / N.Reg: XXXXXXXXXX
Usuari: san / Mostra: AML729-11
Nom: FAIZA DIABA
Data: 30/07/14 / Ope.: F.DIABA
Experiment: gcosy

Pulse Sequence: gCOSY

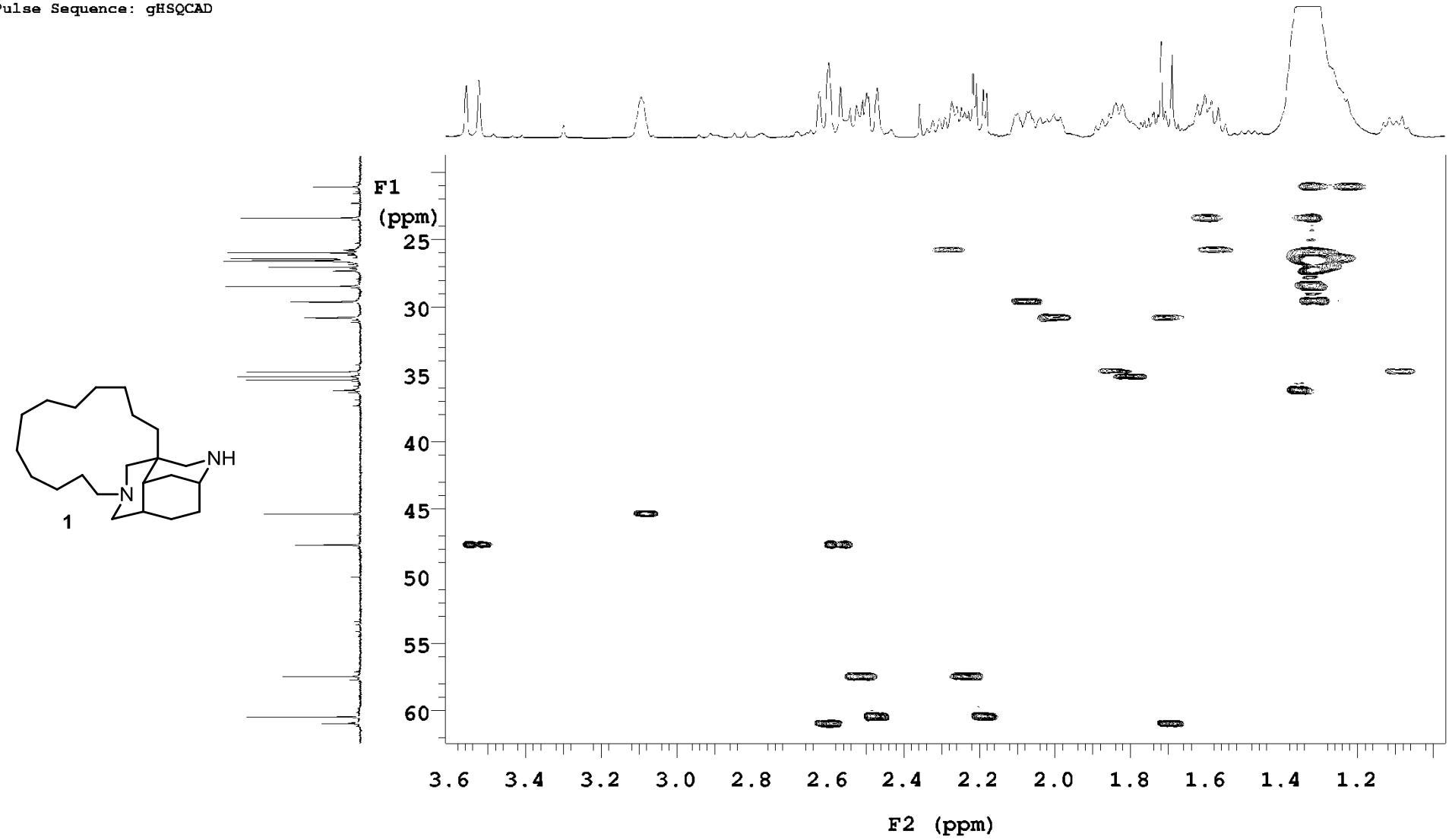


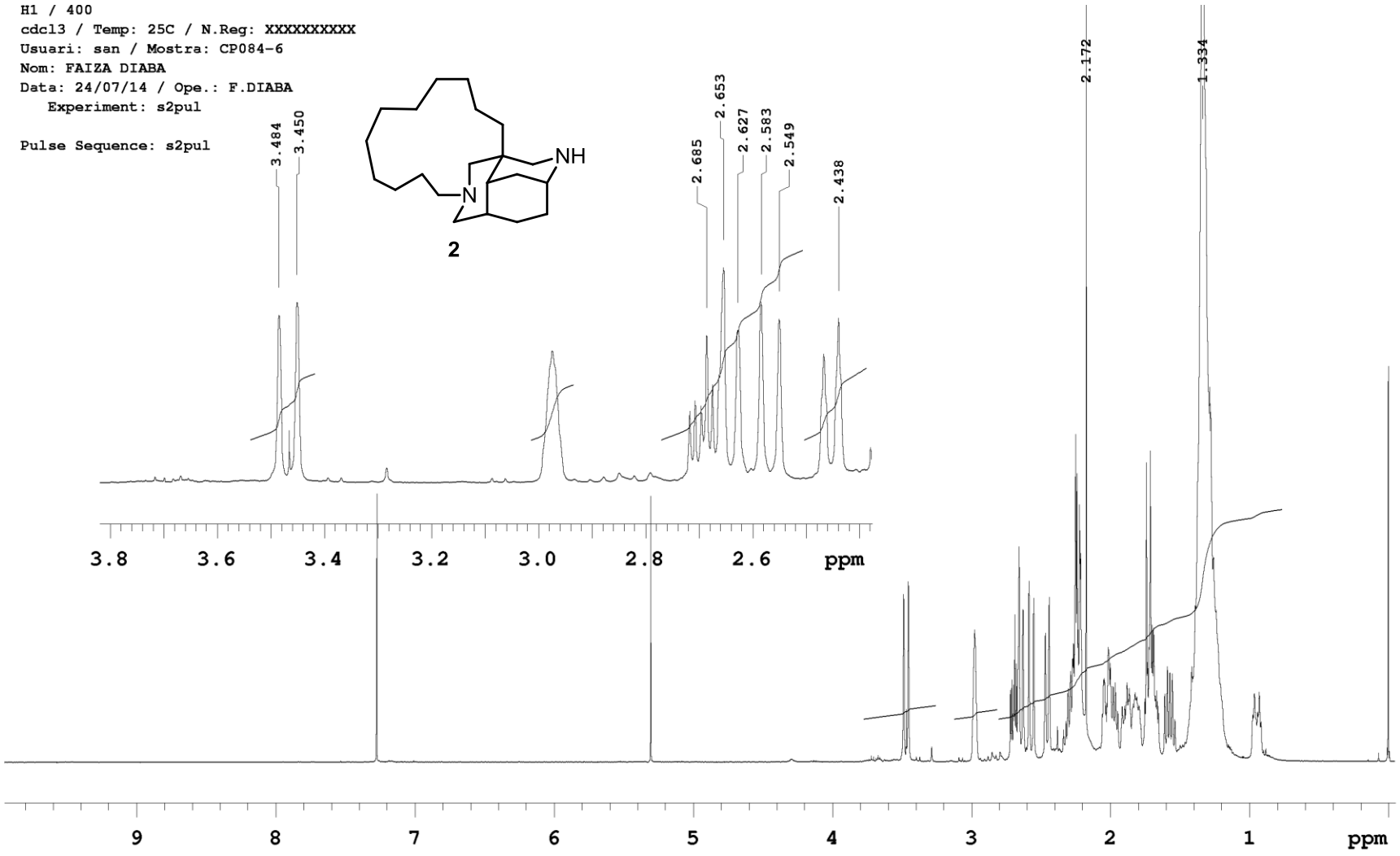
1



H1 / 400
cdcl3 / Temp: 25C / N.Reg: XXXXXXXXXX
Usuari: san / Mostra: AML729-11
Nom: FAIZA DIABA
Data: 30/07/14 / Ope.: F.DIABA
Experiment: ghsqcad

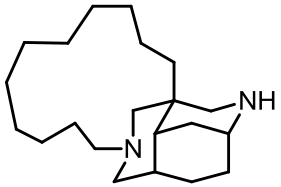
Pulse Sequence: gHSQCAD




H1 / 400
cdcl3 / Temp: 25C / N.Reg: XXXXXXXXXX
Usuari: san / Mostra: CP084-6
Nom: FAIZA DIABA
Data: 24/07/14 / Ope.: F.DIABA
Experiment: s2pul
Pulse Sequence: s2pul
NH
N
2
3.484
3.450
2.685
2.653
2.627
2.583
2.549
2.438
2.172
1.334
3.8
3.6
3.4
3.2
3.0
2.8
2.6
ppm
9
8
7
6
5
4
3
2
1
ppm

H1 / 400
cdcl3 / Temp: 25C / N.Reg: XXXXXXXXXX
Usuari: san / Mostra: CP084-6
Nom: FAIZA DIABA
Data: 29/07/14 / Ope.: F.DIABA
Experiment: s2pul

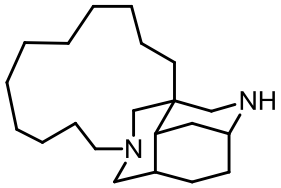
Pulse Sequence: s2pul



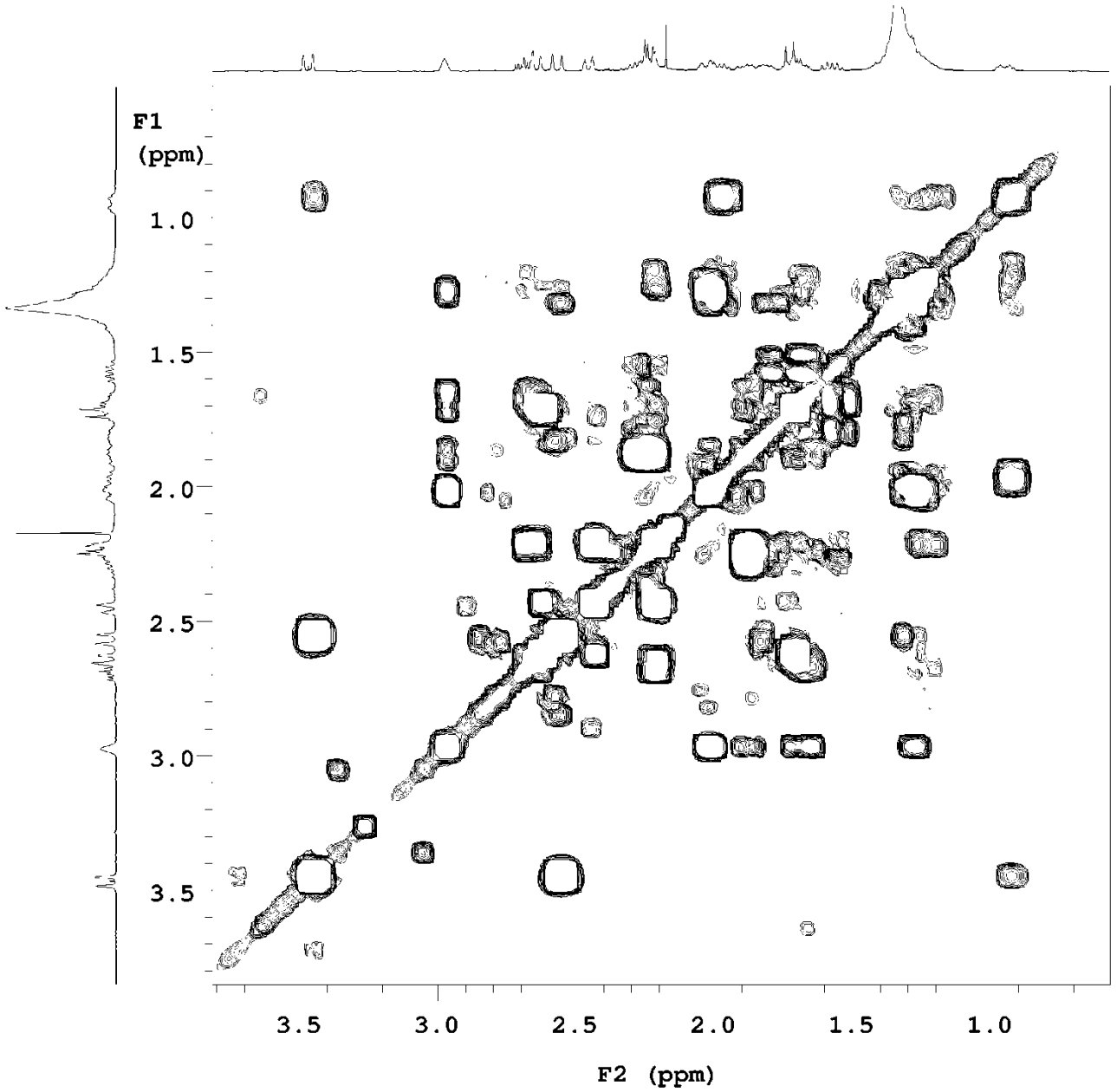
2

H1 / 400
cdcl3 / Temp: 25C / N.Reg: XXXXXXXXXX
Usuari: san / Mostra: CP084-6
Nom: FAIZA DIABA
Data: 29/07/14 / Ope.: F.DIABA
Experiment: gcosy
H1_data are in file H1

Pulse Sequence: gCOSY

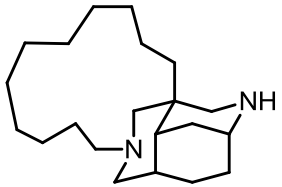


2

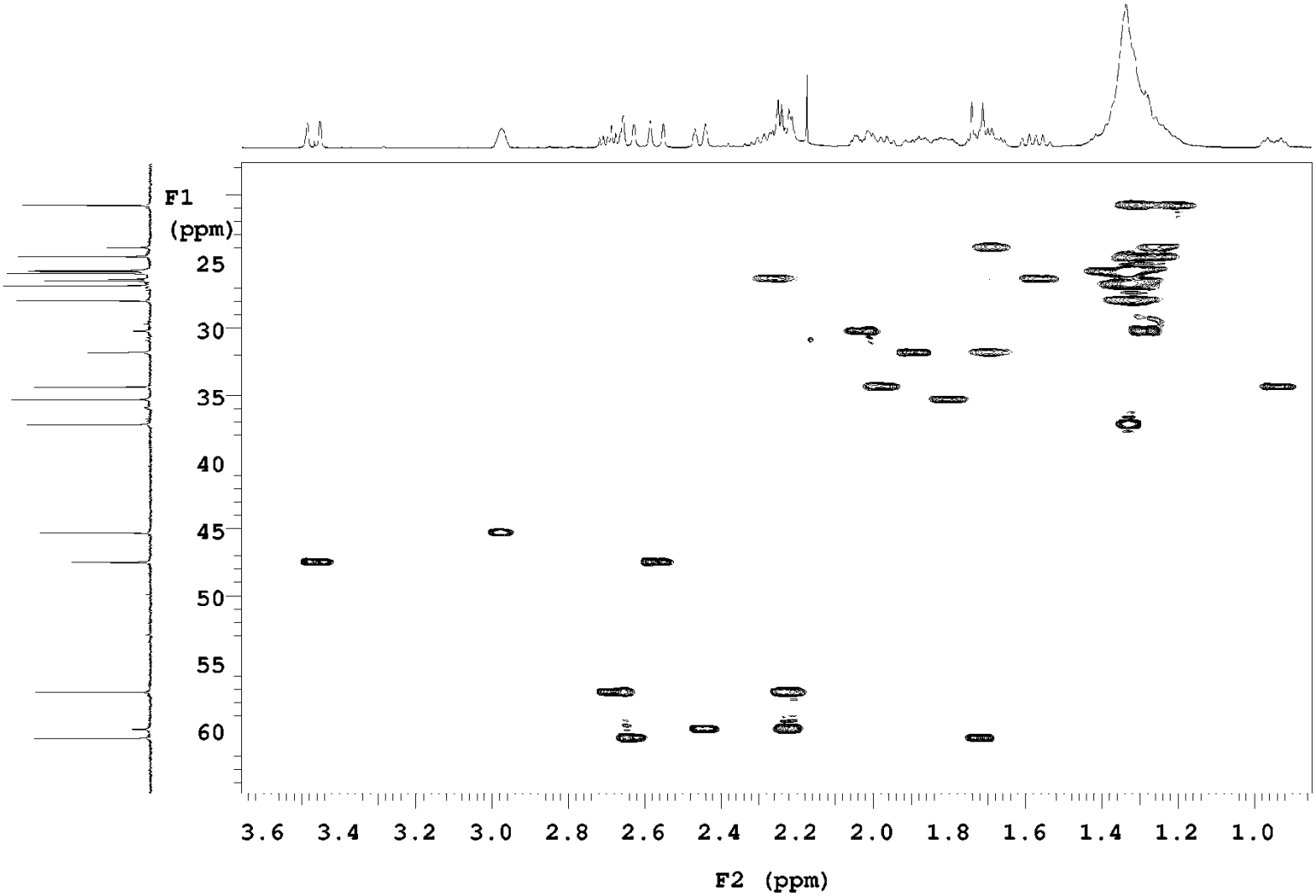


H1 / 400
cdcl3 / Temp: 25C / N.Reg: XXXXXXXXXX
Usuari: san / Mostra: CP084-6
Nom: FAIZA DIABA
Data: 29/07/14 / Ope.: F.DIABA
Experiment: ghsqcad

Pulse Sequence: gHSQCAD

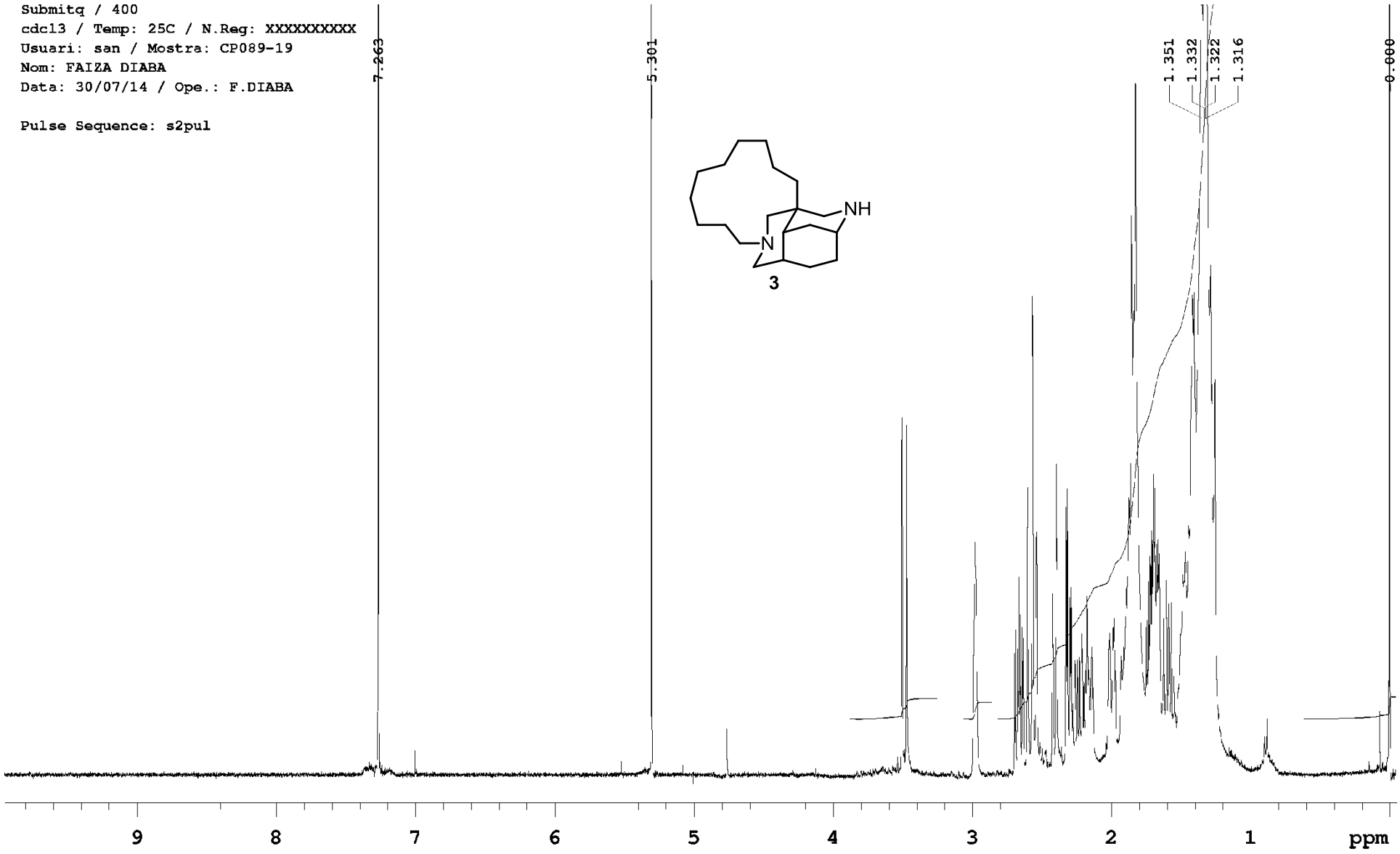


2



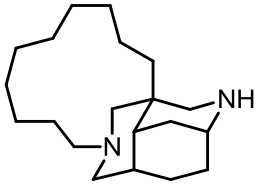
Submitq / 400
cdcl3 / Temp: 25C / N.Reg: XXXXXXXXXX
Usuari: san / Mostra: CP089-19
Nom: FAIZA DIABA
Data: 30/07/14 / Ope.: F.DIABA

Pulse Sequence: s2pul



Submitq / 400
cdcl3 / Temp: 25C / N.Reg: XXXXXXXXXX
Usuari: san / Mostra: CP089-19
Nom: FAIZA DIABA
Data: 30/07/14 / Ope.: F.DIABA

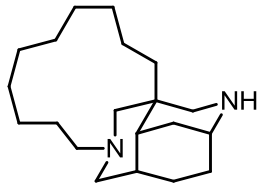
Pulse Sequence: s2pul



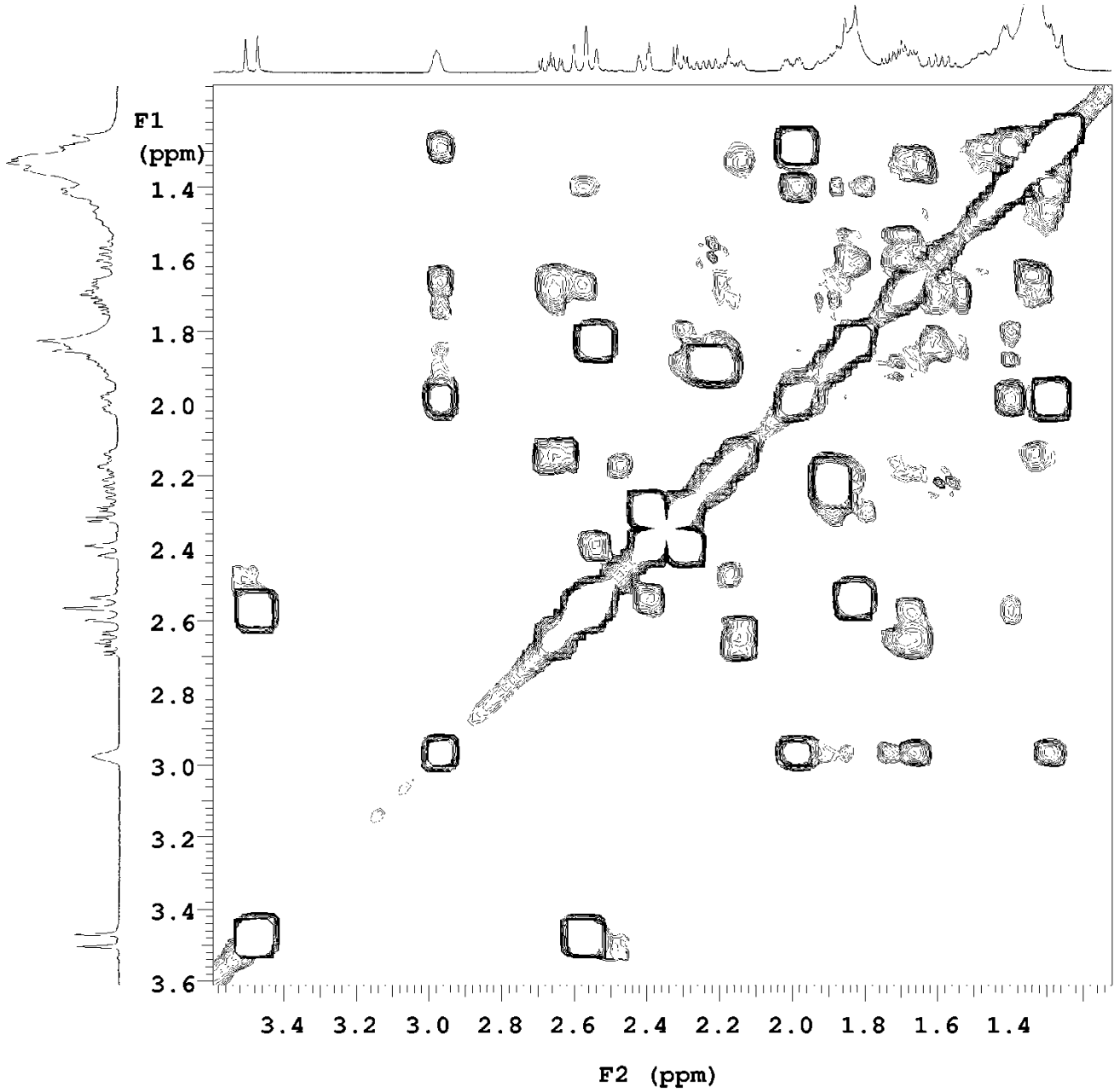
3

Submitq / 400
cdcl3 / Temp: 25C / N.Reg: XXXXXXXXXX
Usuari: san / Mostra: CP089-19
Nom: FAIZA DIABA
Data: 30/07/14 / Ope.: F.DIABA
H1_data are in file H1

Pulse Sequence: gCOSY

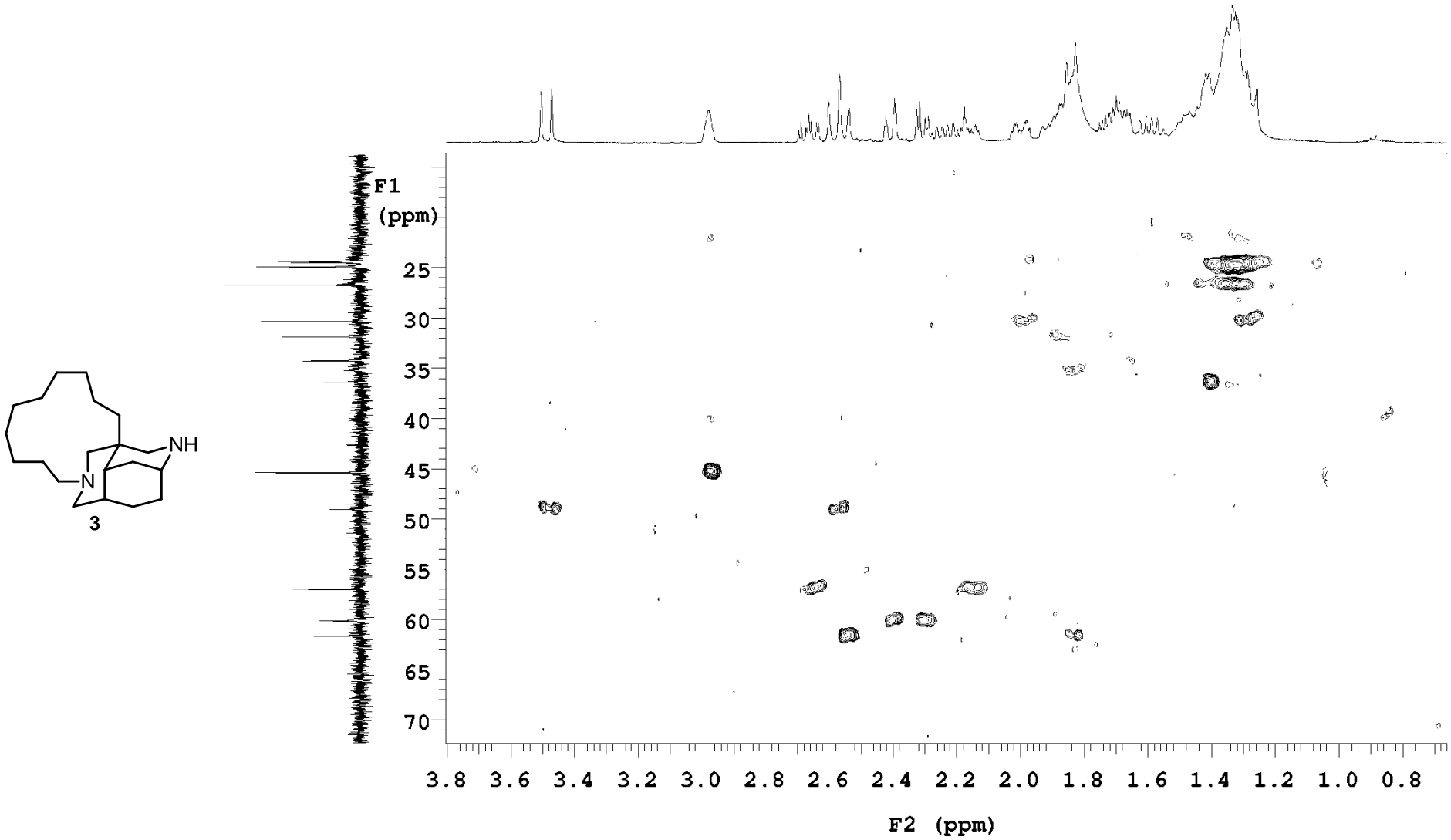


3



Submitq / 400
cdcl3 / Temp: 25C / N.Reg: XXXXXXXXXX
Usuari: san / Mostra: CP089-19
Nom: FAIZA DIABA
Data: 30/07/14 / Ope.: F.DIABA

Pulse Sequence: gHSQC

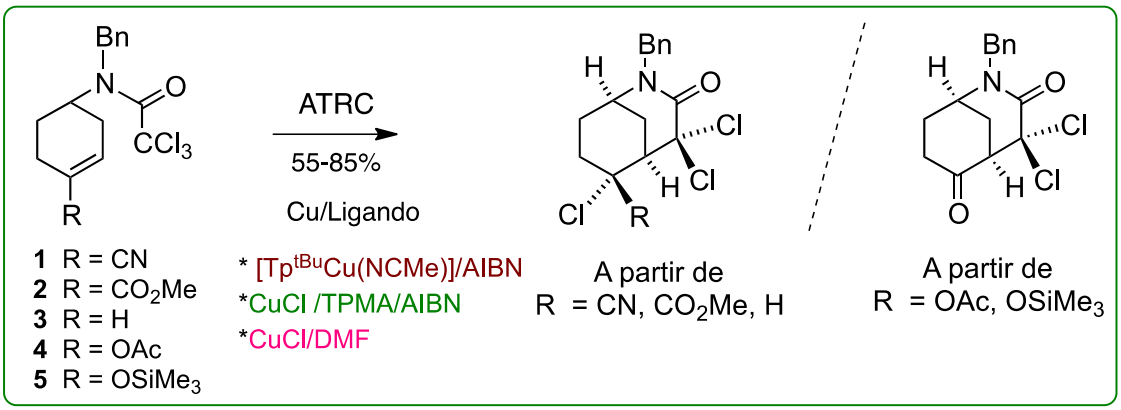


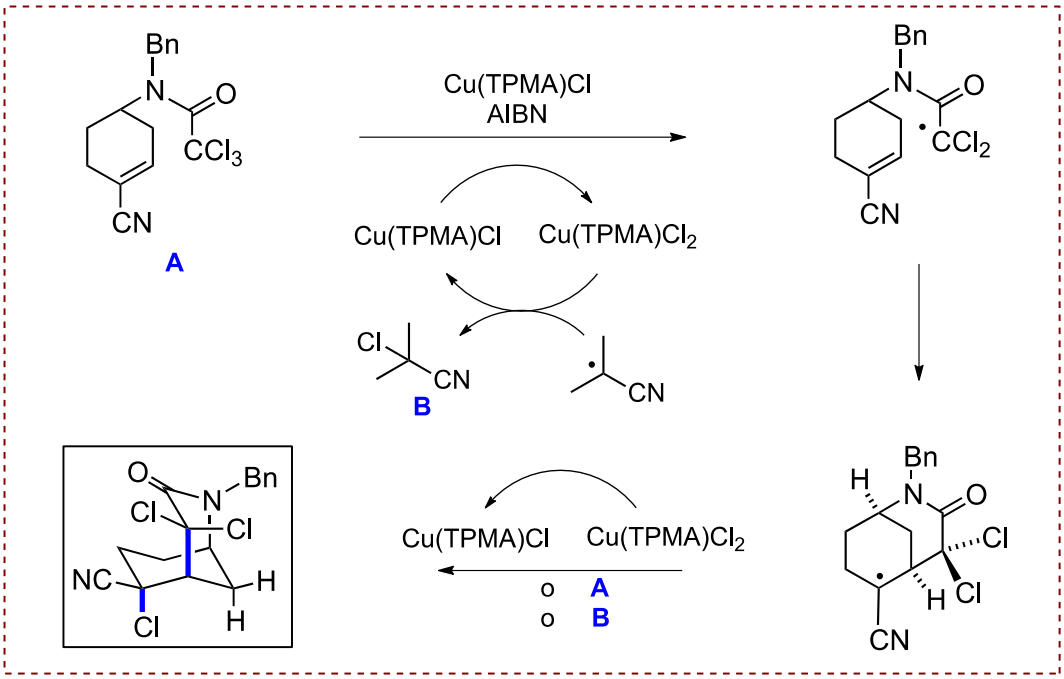
8. CONCLUSIONES

1

La reacción de ciclación radicalaria con transferencia de átomo (ATRC) a partir de tricloroacetamidas en procesos 6-*exo-trig* es factible para sintetizar 2-azabiciclo[3.3.1]nonanos polifuncionalizados. El proceso es catalizado por Cu(I) y la cuestión clave para la eficiencia del proceso reside en la factibilidad de la regeneración de la especie de Cu(I) activa en el medio de reacción a partir del Cu(II) que se genera en la primera etapa del proceso radicalario.

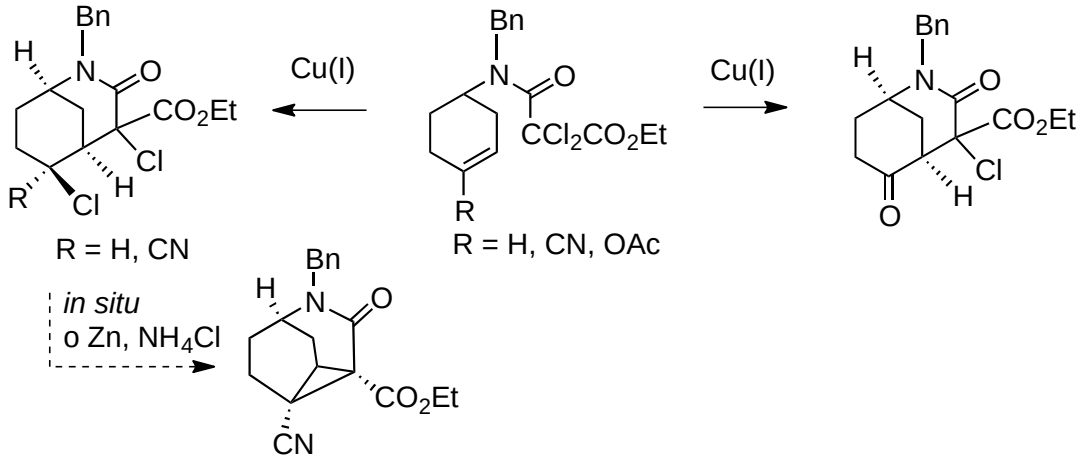
Este proceso de regeneración, que ha de permitir la reducción de la cantidad de catalizador utilizada, puede inducirse completando el sistema catalítico con una agente reductor que reestablezca el ciclo catalítico regenerando el complejo de Cu(I) activo a partir de la forma oxidada. En este tesis se ha implementado en diversos procesos de ATRC la metodología ICAR ("initiator for continuous activator regeneration ") en la que la descomposición de un iniciador radicalaria convencional como es el AIBN interacciona con la forma oxidada para regenerar satisfactoriamente la especie activa.





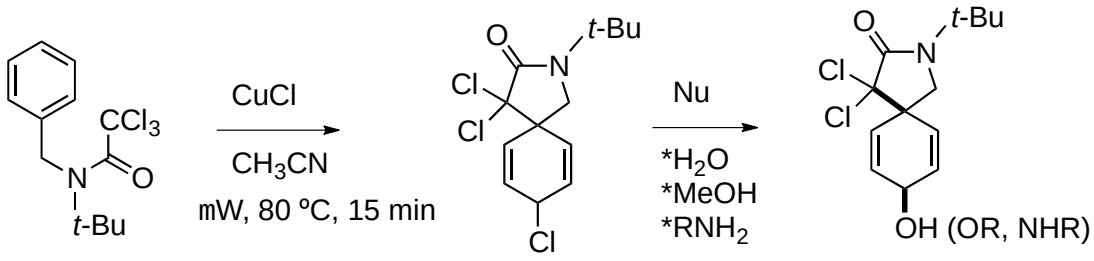
2

Se ha constatado que radicales de tipo electrofílico con dos grupos atrayentes de electrones reaccionan de manera satisfactoriamente en las condiciones de ATRC frente a cualquier tipo de aceptor radicalario. Así la reacción intramolecular de etoxicarbonildicloroacetamidas transcurre frente a dobles enlaces de alquenos, nitrilos α,β-insaturados y acetatos de enol. El proceso conduce a morfanos polifuncionalizados, y en el caso de que los productos azabicíclicos contengan un unidad de 1,3-dicloalcano con estreoquímica antiperiplanar, éstos continúan evolucionando para generar un sistema ciclopropánico incrustrado en el anillo de morfano.

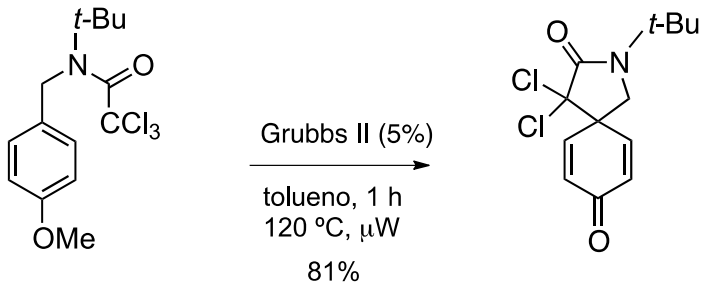


3

La reacción de desaromatización de bencenos no activados es posible mediante un ipso-ciclación de *N*-tricloroacetilbencilaminas en un procesos de ciclación radicalaria con transferencia de átomo. La transformación catalizada por CuCl transcurre de manera regioselectiva conduciendo a 2-azaespiro[4.5]decadienos, en los que los cloruros alílicos inicialmente formados son lábiles y sufren sustitución en los procesos de *quenching* utilizando agua (alcoholes), metanol (éteres) o alilamina (aminas). En los procesos que conducen a alcoholes es factible su oxidación para generar una dienona. El grupo *N-terc*-butilo que por cuestiones conformacionales favorece el proceso de ciclación radicalaria, puede ser fácilmente eliminado en los productos de ciclación mediante un tratamiento ácido fuerte.

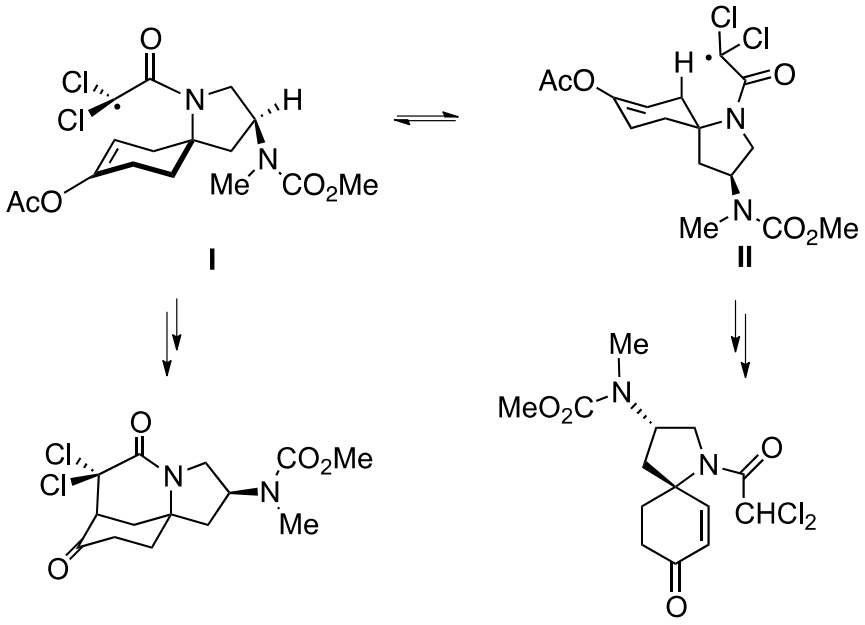


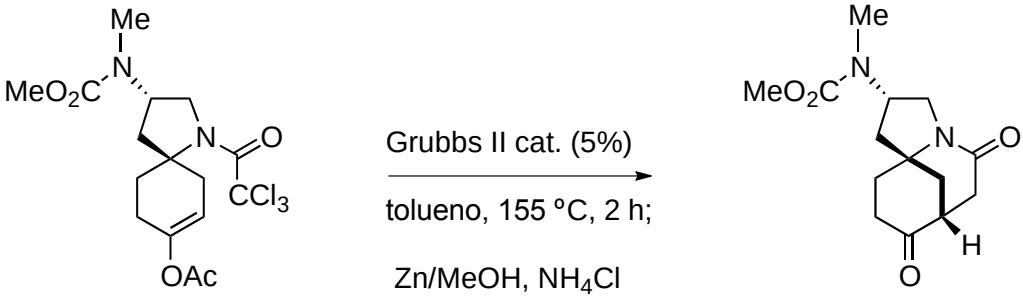
La reacción de desaromatización radicalaria transcurre de manera éxitosa utilizando 4-metoxi derivados análogos, utilizando el catalizador de Grubbs II para inducir el proceso de espirociclación, seguido de la transferencia del átomo de cloro. En estas condiciones de reacción se aisla directamente la ciclohexandienona, fruto de la extrusión formal de cloruro de metilo del producto azaespiránico.



4

La ciclación radicalaria de 2-azaespiro[4.5]decanos via tricloroacetamidas, que no transcurre de manera satisfactoria mediante un método reductivo (Bu_3SnH, AIBN), procede con rendimiento aceptables utilizando un método ATRC. Así utilizando el cataizador de Grubbs II (5%) es factible el proceso ya que la vida media del radical carbamoildiclorometilo es mayor en ausencia de un dador de hidrógeno y así es factible que el bajo porcentaje del confórmero reactivo frente al acetato de enol (**I**) pueda evolucionar de manera productiva para generar el sistema azatricíclico característico del inmunosupresor FR901483. El problema conformacional que aparece en este proceso de ciclación se constata en el hecho que se aisla un subproducto, que proviene de la evolución del radical diclorocarbamoilo, en la conformación inicial **II**, mediante un proceso de transposición 1,5 de H que inhabilita, en un proceso colateral, un mejor rendimiento en la síntesis del sistema azatricíclico presente en el FR901483.

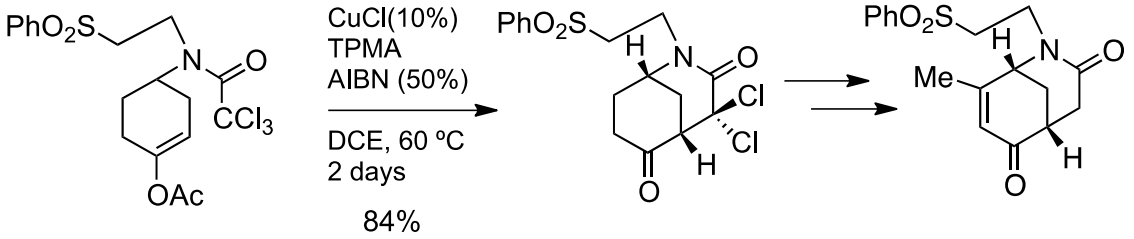




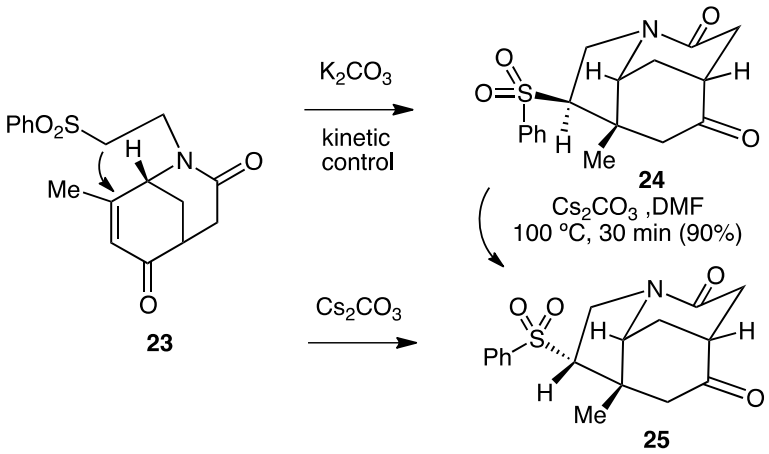
Núcleo del FR901483

5

La sulfona azabicíclica requerida para la síntesis del fragmento ABC de los alcaloides Dapniphyllum del grupo de la calicifilina A, mediante una nueva aproximación, se obtiene con excelentes rendimientos mediante la ciclación con transferencia de átomo, descrita en esta tesis, de tricloroacetamidas sobre acetatos de enol.



Frente al número escaso de precedentes en reacciones de Michael basadas en carbaniones estabilizados por un grupo sulfona, se ha establecido que mediante el uso de una base débil K_2CO_3 o Cs_2CO_3 es factible el proceso sobre un aceptor de tipo enona β-substituído (**23** → **24** o **25**). El proceso según la base empleada es estereodivergente pudiéndose obtener un epímero u otro de manera preferente. Los cálculos computacionales sugieren que el proceso no es en ningún caso de control termodinámico ya que ambos epímeros son isoenergéticos. Se trata pues de un nuevo ejemplo del llamado efecto cesio que proporciona resultados bien diferenciados de los obtenidos con otras bases alcalinas. Este hecho puede tener aplicaciones en el diseño de procesos para la elaboración de intermedios de síntesis avanzados con control diastereoselectivo.



6

La ciclación radicalaria de (etoxicarbonil)dicloroacetamidas frente a nitrilos α,β-insaturados transcurre de manera sintéticamente útil utilizando el método reductivo, que permite la formación con rendimientos superiores al 70% del producto deseado. Por el contrario, el método ATRC en este caso no es eficaz, al menos en las condiciones utilizadas (CuCl, TPMA, AIBN), ya que en el medio de la reacción uno de los epímeros diclorados que se forman evoluciona in situ a un compuesto ciclopropánico, que implica una reducción drástica del rendimiento del proceso (conclusión 2).

El acceso a este sistema azabicíclico polifuncionalizado permite el acceso de manera rápida y eficiente a los sistemas diazatetracíclicos de las madangaminas D, E y F, productos naturales marinos. La reacción de alilación para generar el centro cuaternario de las madangaminas transcurre de manera totalmente diastereoselectiva, ya que el bromuro de alilo se acerca al enolato del metileno activo de manera axial para minimizar los efectos estéricos en esta formación del enlace C-C.

El control en la formación de los centro estereogénicos permite el cierre del sistema azatricíclico de las madangaminas y el uso de este tipo de compuesto en una síntesis divergente de los sistemas tetracíclicos de las madangaminas D, E y F.