Chloroacetamides as Valuable Synthetic Tools to Access Nitrogen-Containing Heterocycles Using Both Radical and Non-Radical Processes

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Memòria presentada per Juan Andrés Montiel Achong per optar al títol de doctor per la Universitat de Barcelona

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ABBREVIATIONS AND ACRONYMS

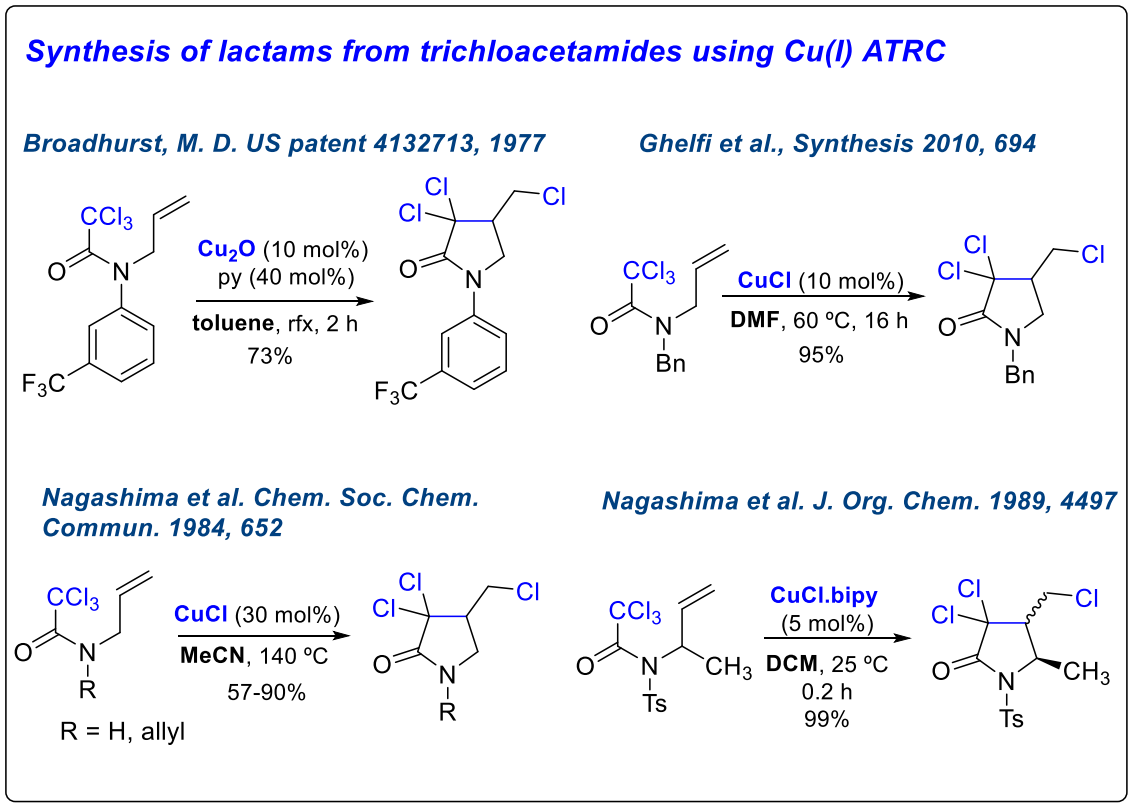
AIBN	2,2'-azobis(iso-butyronitrile)
aq.	Aqueous
ATRC	Atom Transfer Radical Cyclization
ax	axial
Bn	Benzyl group
br	broad
Bu	Butyl group
c	concentration
^{13}C NMR	carbon-13 nuclear magnetic resonance
°C	degrees Celsius
calcd	calculated
cat.	Catalytic
Celite®	filtration agent
COSY	correlation spectroscopy
Cy	cyclohexyl group
d	day(s), doublet (spectra)
δ	Chemical shift
DCE	1,2-Dichloroethane
DCM	Dichloromethane
dd	doublet of doublets
ddd	doublet of doublet of doublets
DMF	N,N-dimethylformamide
DMP	Dess-Martin periodinane
DMSO	dimethyl sulfoxide
dr	diastereomeric ratio
dt	doublet of triplets
equiv.	Equivalent
eq	equatorial
Et	ethyl group
EWG	electron withdrawing groups
g	gram
[H]	Reduction
^{1}H-NMR	proton nuclear magnetic resonance
HRMS	high resolution mass spectrum
HSQC	heteronuclear single quantum correlation spectroscopy
Hz	Hertz
IR	infrared spectroscopy
J	coupling constant
LiHMDS	lithium bis(trimethylsilyl)azide
Lit.	Literature
LUMO	Lowest Unoccupied Molecular Orbital
M	molar
m	multiplet
M	metal or molar
M+	molecular ion
m/z	mass to charge ratio
Me	methyl group
mg	milligram
min	minute(s)

mL	milliliter
MoC	Memory of Chirality
mol	mole(s)
mp	melting point
MS	mass spectrometry
Ms	mesyl group (methylsulfonyl)
Mw or μW	Microwave
nOe	nuclear Overhauser effect
NOESY	2D nuclear Overhauser effect spectroscopy
p. or pp.	Page
PCC	pyridinium chlorochromate
Ph	Phenyl Group
ppm	parts per million
q	Quartet
R	generalized alkyl group or substituent
R	rectus (configurational)
ref.	Reference
rt	room temperature
rfx.	Reflux
s	singlet
S	sinister (configurational)
sat.	Saturated
t	triplet
t	tertiary
td	triplet of doublets
TBTA	Allyltributyltin
TBTH	tributyltin hydride
TEA	triethylamine
TEMPO	2,2,6,6-tetramethylpiperidin-1-yl)oxidanyl
TFA	trifluoroacetic acid
THF	tetrahydrofuran
TLC	thin layer chromatography
TMS	trimethylsilyl group
TsOH	*p*-toluenesulfonic acid
TTMSS	Tris(trimethylsilyl)silane
UV	ultraviolet
wt	weight
yd	yield

Chapter 1

Introduction and Objectives

Haloacetamides are valuable intermediates for the synthesis of lactams using radical and non-radical processes. Trichloroacetamides in particular, introduced in the 1980s, have been widely used for the preparation of favored *γ*-lactams and less favored *β*- and *δ*-lactams using atom transfer radical cyclizations (ATRC) or radical reductive cyclizations through the ambiphilic dichloromethylcarbamoyl radical.[1]

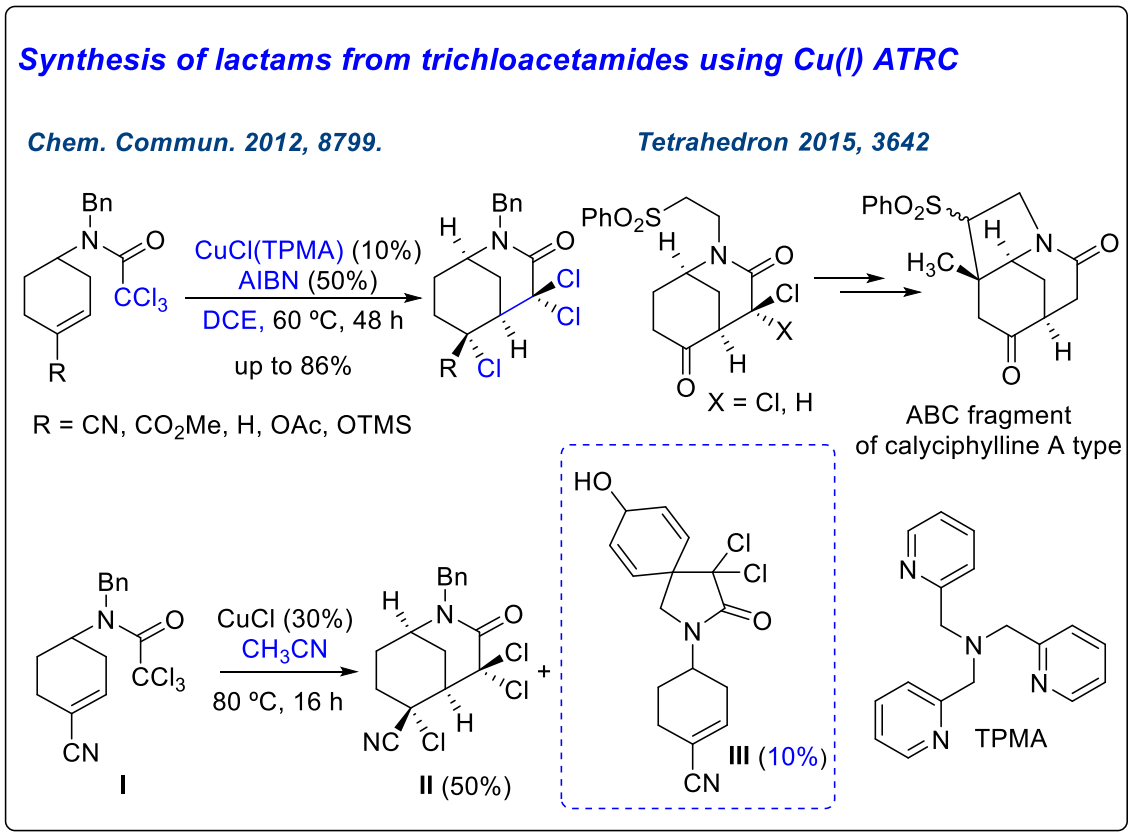


Scheme 1.1.

Using the first strategy, the reactions were usually carried out in the presence of Cu(I)[2] or Ru(II)[3] catalysts with far fewer reported examples of Fe-$FeCl_3$[4], Ni-AcOH[5] or Ti(III).[6] Usage of Cu(I) catalysts in ATRC from trichloro-

[1] For a recent review see: Coussanes, G.; Vila, X.; Diaba, F.; Bonjoch, J. *Synthesis* **2016** (accepted).
[2] For a recent review see: Clark, A. J. *Eur. J. Org. Chem.* **2016**, 2231–2243.
[3] Nagashima, H.; Wakamatsu, H.; Ozaki, N.; Ishii, T.; Watanabe, M.; Tajima, T.; Itoh, K. *J. Org. Chem.* **1992**, *57*, 1682-1689.
[4] (a) Tseng, C.K.; Teach, E.G.; Simons, R.W. *Synth. Commun.* **1984**, 1027–1031. (b) Benedetti, M.; Forti, V.; Ghelfi, G.; Pagnoni, U.M.; Onzoni, R. *Tetrahedron* **1997**, *53*, 14031–14042. (c) De Campo, F.; Lastécouères, D.; Verlhac, J. B. *Chem. Commun.* **1998**, 2117-2118.
[5] Cassayre, J.; Quiclet-Sire, B.; Saunier, J.B.; Zard, S. Z. *Tetrahedron Lett.*, **1998**, *39*, 8995 -8998.
[6] Diaba, F.; Gomez-Bengoa, E.; Cuerva, J. M.; Bonjoch, J.; Justicia, J. *RSC Advances* **2016**, *6*, 55360-55365.

acetamides in the presence of Cu_2O was first reported by Stauffer Chemical company in 1977 for the synthesis of herbicides. Later, CuCl was introduced by Nagashima for the synthesis of *γ*-lactams from trichloroacetamides in acetonitrile at high temperatures. Usage of "ligand-free-like" conditions by Ghelfi and bidentated ligands by Nagashima allowed the reactions to proceed at lower temperatures and using catalytic amounts of CuCl (Scheme 1.1).



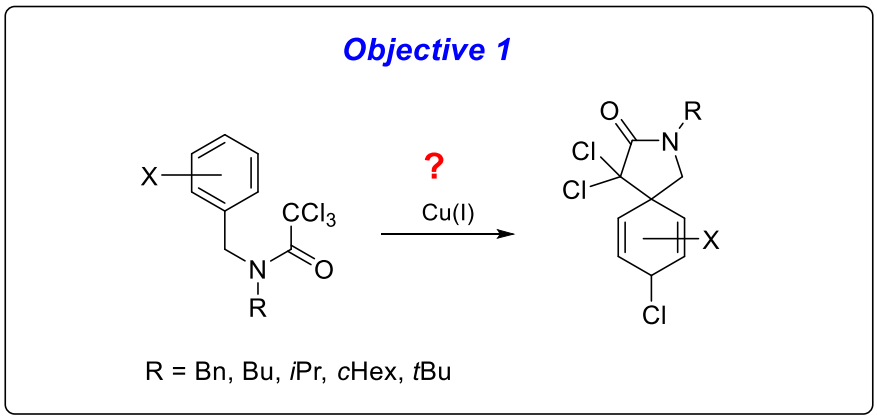
Scheme 1.2.

In our research group, ATRC using CuCl was successfully used for the synthesis of polyfunctionalized 2-azabicyclo[3.3.1]nonanes from trichloro-acetamides with electron-deficient, neutral and electron-rich alkenes.[7] The best results were obtained using CuCl-TPMA (10%) and AIBN (50%) as an initiator for continuous activator regeneration in 1,2-dichloroethane (DCE) at 60 ºC in a sealed tube for 48 h. The methodology was then applied to the synthesis of the ABC fragment of Calyciphylline A-type alkaloids[8] but before settling DCE as the

[7] Diaba, F.; Martínez-Laporta, A.; Bonjoch, Pereira, A.; Muñoz-Molina, J. M., Pérez, P. J.; Belderrain, T. R. *Chem. Commun.* **2012**, *48*, 8799-8801.
[8] Diaba, F.; Martínez-Laporta, A.; Coussanes, G.; Fernández, I.; Bonjoch, J. *Tetrahedron* **2015**, *71*, 3642-3651.

best solvent to achieve this transformation, other solvents were examined such as DMF and acetonitrile. In the presence of the latter besides the expected morphan **II,** azaspiro derivative **III** was also isolated (Scheme 1.2).

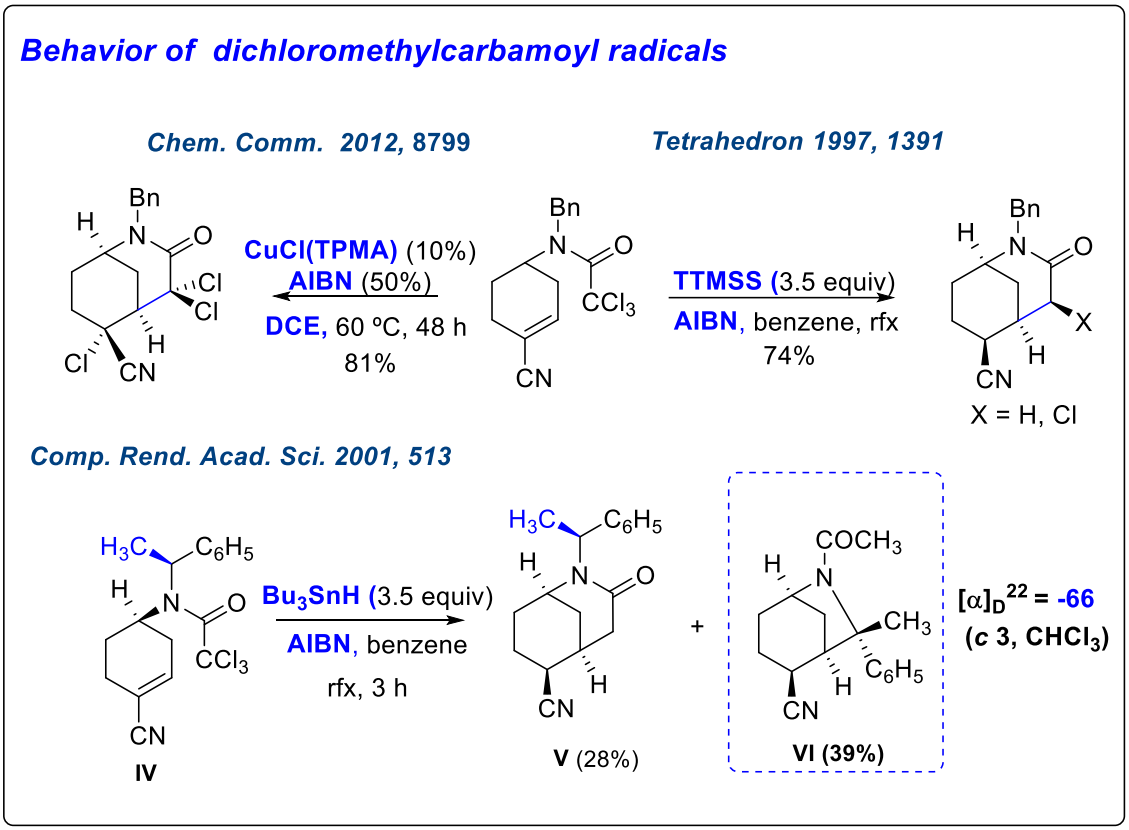
Since this dearomative spirocyclization in the presence of Cu(I) is unprecedented together with the fact that dearomative radical spirocyclization in general have received very little attention encouraged us to investigate this reaction. The process was studied starting from benzyltrichloroacetamides with different substituents on the nitrogen to achieve the synthesis of 2-azaspiro[4.5]decanes present in many natural and synthetic compounds (Scheme 1.3). The results obtained are detailed in chapter 2.



Scheme 1.3.

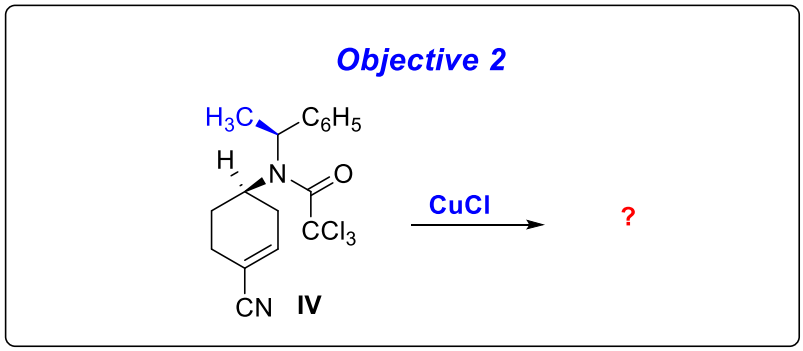
In our research group 2-azabicyclo[3.3.1]nonane derivatives were also prepared from trichloroacetamides using radical reductive conditions in the presence of AIBN, TBTH or TTMSS and in refluxing benzene.[1] When the reaction was achieved from *N*-(α-methylbenzyl)trichloroacetamides instead of benzyltrichloroacetamides, besides the expected morphan **V,** normorphans **VI** were also isolated. **VI** derive from an 1,4-H transfer and subsequent 5-exo-trig cyclization (Scheme 1.4). This process involving memory of chirality (MoC) with complete inversion of stereochemistry at the benzylic center is unprecedented.[9]

[9] For a recent review see: Gloor, C. S.; Dénès, F.; Renaud, P. *Free Radical Res.* **2016**, 1-10; DOI: 10.1080/10715762.2016.1232485.



Scheme 1.4.

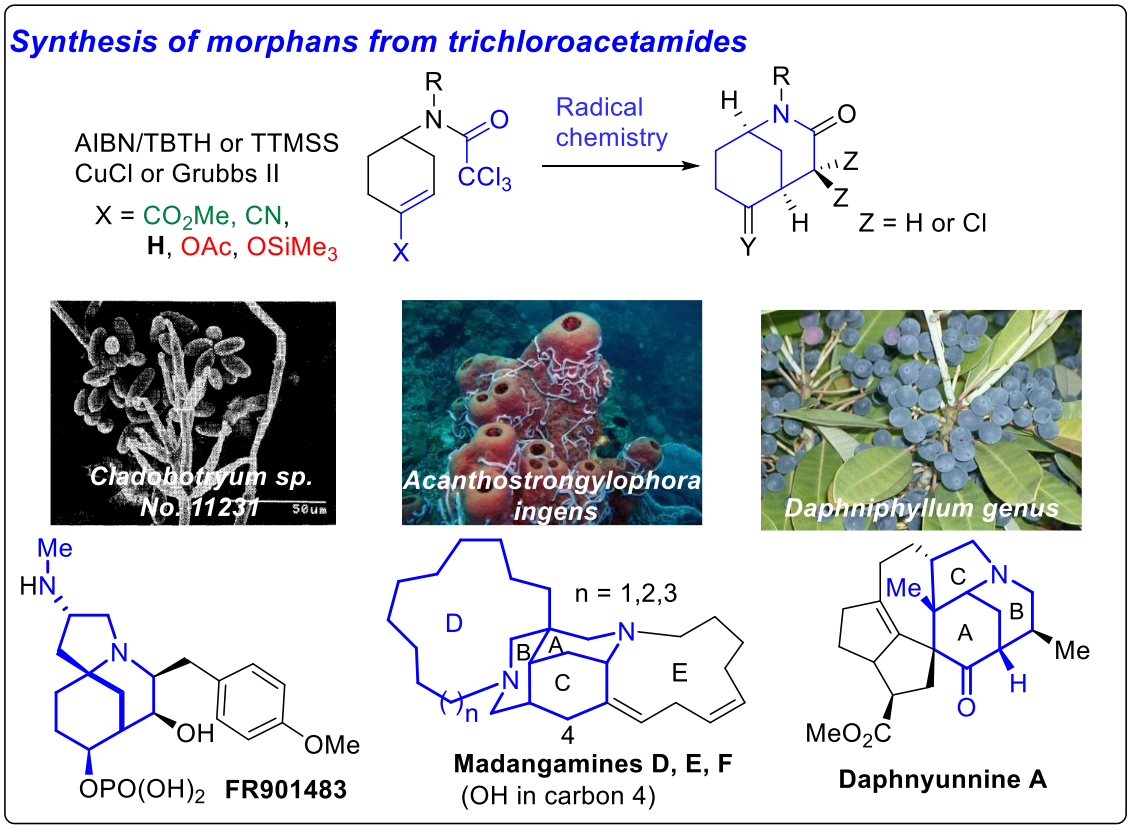
As a continuation of this work, we decided to explore ATRC in the presence of CuCl from trichloroacetamide **IV** to see if the behavior of this substrate under non-reductive conditions (Scheme 1.5) follows the same pattern observed before. This study constitutes the second objective of this thesis and the corresponding results are reported in chapter 3.



Scheme 1.5

In our research group, radical chemistry from trichloacetamido-cyclohexenes with different kind of double bonds: electron-poor, neutral and electron-rich and either using reductive conditions or under ATRC in the presence of CuCl or Grubbs II generation catalyst, allowed the preparation of different

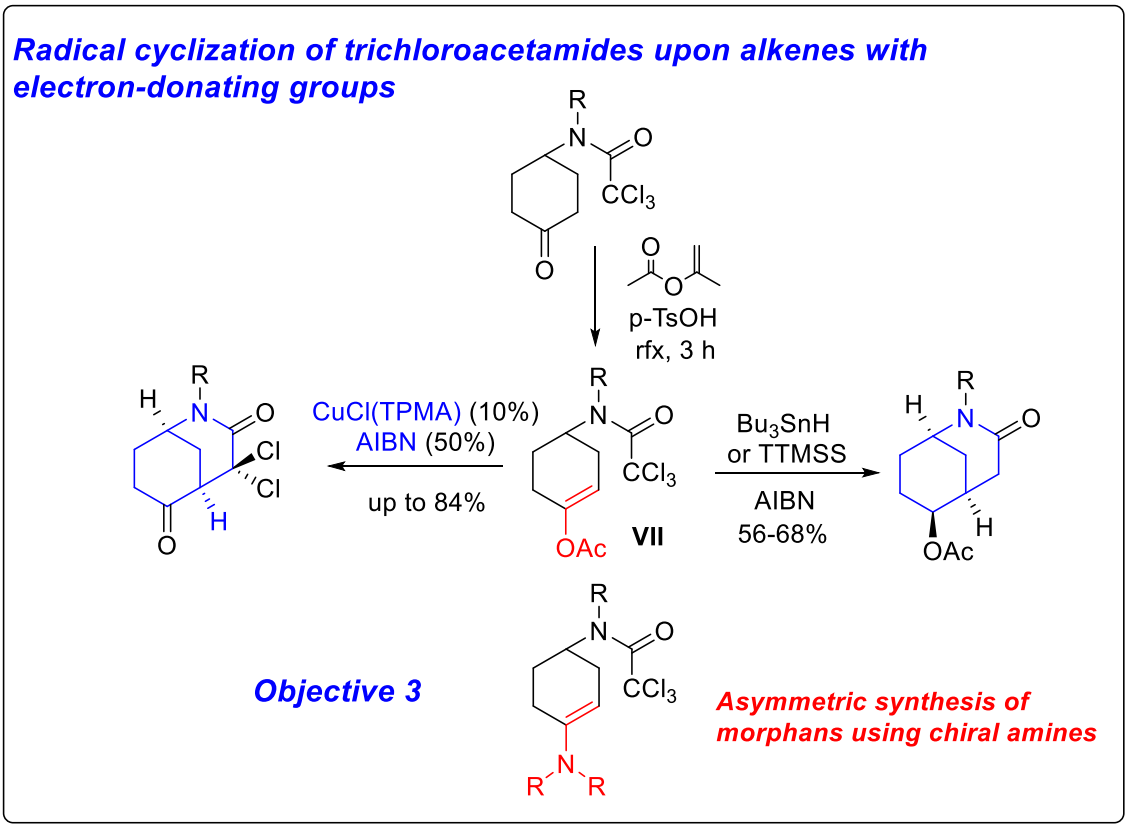
functionalized morphans. These were used later to achieve the synthesis of the main azatricyclic core of the potent immunosuppressant FR901483[10] isolated in 1996 by Fujisawa laboratories.[11] ABCD diazatetracyclic structure of madangamines D, E and F was also achieved.[12] These alkaloids were isolated in the 1990s from marine sponges[13] and present, especially for madangamine F significant *in vitro* cytotoxic activity against a variety of tumor cell lines. Finally, one of the morphan intermediates prepared using radical chemistry was also successfully used to achieve the tricyclic ABC fragment of Daphnyunnine A-type alkaloids,[14] a family of natural compounds isolated in the last decade from *Daphniphyllum* genus[15] (Scheme 1.6)



Scheme 1.6.

[10] Diaba, F.; Martínez-Laporta, A.; Bonjoch, J. *J. Org. Chem*. **2014**, *79*, 9365−9372.
[11] 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.
[12] Diaba, F.; Pujol-Grau, C.; Martínez-Laporta, A.; Fernández, I.; Bonjoch, J. *Org. Lett*. **2015**, *17*, 568−571.
[13] Amat, M.; Pérez, M.; Ballette, R.; Proto, S.; Bosch, J. *The Alkaloids,* **2015**, *74*, 159-199.
[14] Diaba, F.; Martínez-Laporta, A.; Coussanes, G.; Fernández, I.; Bonjoch, J. *Tetrahedron* **2015**, *71*, 3642-3651.
[15] For a review, see: Kang, B.; Jakubec, P.; Dixon, D. J. *Nat. Prod. Rep*. **2014**, *31*, 550-562.

As outlined before, radical chemistry using ATRC or reductive conditions for the synthesis of morphans, was also achieved from trichloroacetamides with electron-rich alkenes, namely enolacetates **VII**. These were prepared from the corresponding ketone by reaction with isopropenyl acetate in acid medium.

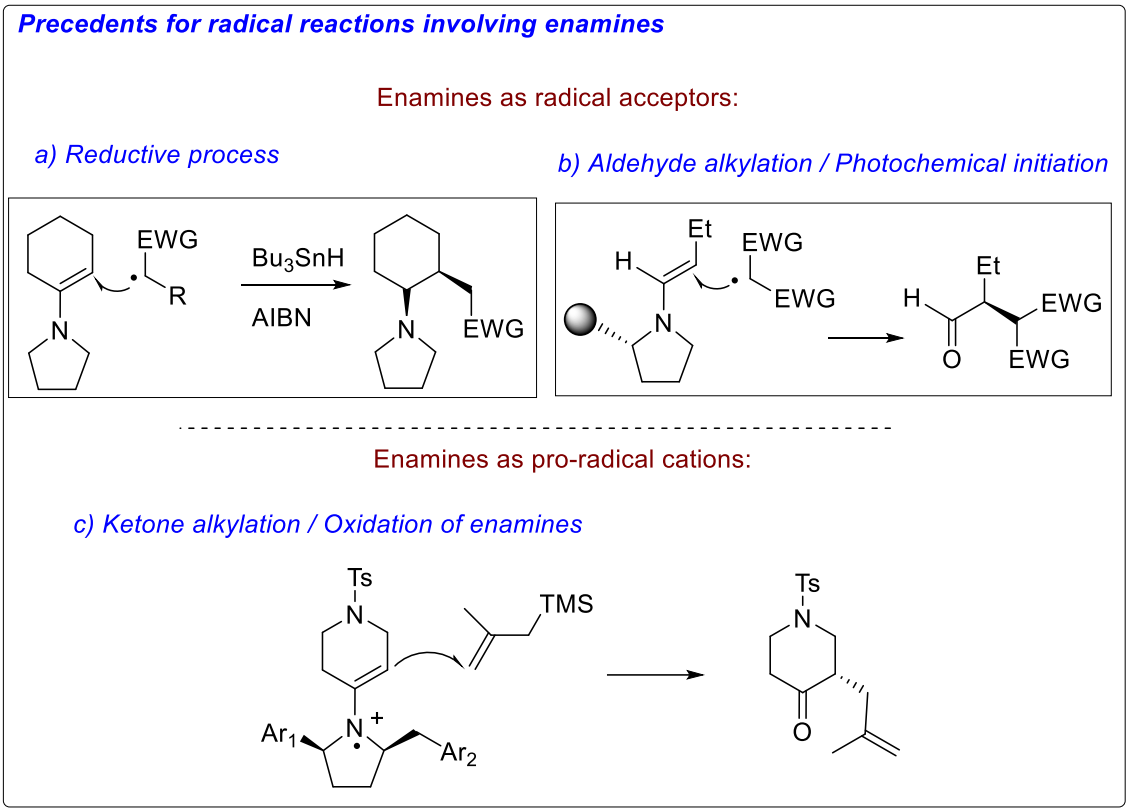


Scheme 1.7.

The third objective of this project was to examine the methodology of radical cyclization upon alkenes bearing electron-donating groups. Thus, the use of enamines as radical acceptors was a central target of this research project. A possible extension, using chiral amines, to an asymmetric version for morphan synthesis was also considered (Scheme 1.7). The results of this investigation are summarized in chapter 4 and 5.

The precedents for radical reactions involving enamines are depicted in Scheme 1.8. Although some examples of radical reductive additions to preformed enamines have been reported, leading to amino compounds,[16] the

[16] (*a*) For intermolecular radical processes involving enamines leading to amino compounds, see *inter alia*: Renaud, P.; Schubert, S. *Angew. Chem. Int. Ed*. **1990**, *29*, 433-434; (*b*) Schubert, S.; Renaud, P.; Carrupt, P.-A.; Schenk, K. *Helv. Chim. Acta* **1993**, *76*, 2473-2489. For intramolecular radical processes involving enamines leading to amino compounds, see *inter alia*: (*c*) Ripa, L.; Hallberg, A. *J. Org. Chem*. **1998**, *63*, 84-91; (*d*) Aurrecoechea, J. M.; Coy, C. A.; Patiño O. J., *J. Org. Chem*. **2008**, *73*, 5194-5197.



Scheme 1.8

non-reductive radical reaction upon transient enamines to achieve α-alkylated ketones is unprecedented.[17,18] The most closely related studies to our goal (radical cyclization of trichloroacetamides upon enamines) were developed by Melchiorre, using photo-organocatalysis, in which an α-alkylation of cyclic ketones was promoted by a radical ion pair.[19] The recent emergence of photochemical procedures[20] has allowed the radical α-alkylation of aldehydes, with transient enamines acting as radical acceptors.[21] In a conceptually different approach, the enamine acts as a pro-radical, instead of a radical acceptor as in the above procedures, and a preformed[22] or transient enamine undergoes

[17] (*a*) For reactions upon preformed enamines leading to alkylated ketones using photo-induced radical reactions, see: (a) Russell, G. A.; Wang, K. *J. Org. Chem.*, **1991**, *56*, 3475-3479; (b) Hu, B.; Chen, H.; Liu, Y.; Dong, W.; Ren, K.; Xie, X.; Xu, H.; Zhang, Z. *Chem. Commun.* **2014**, *50*, 13547-13550.

[18] For Et_3B-initiated addition of an alkyl radical to preformed *N*-silyloxy enamines, see: Song, H.-J.; Lim, C. J. ; Kim, S. *Chem. Commun.* **2006**, 2893-2895.

[19] Arceo, E.; Bahamonde, A.; Bergonzini, G.; Melchiorre, P. *Chem. Sci.* **2014**, *5*, 2438-2442.

[20] (*a*) Narayanam, J. M. R.; Stephenson, C. R. J. *Chem. Soc. Rev.* **2011**, *40*, 102-113. (*b*) Prier, C. K.; Rankic, D. A.; MacMillan, D. W. C. *Chem. Rev.* **2013**, *113*, 5322-5363. (c) Romero, N. A.; Nicewicz, D. A. *Chem. Rev.* **2016**, *116*, 10075-10166.

[21] (a) Shih, H.-W.; Vander Wai, M. N.; Grange, R. L.; MacMillan, D. W. C. *J. Am.Chem. Soc*. **2010**, *132*, 13600-13603. (b) Bahamonde,A.; Melchiorre, P. *J. Am. Chem. Soc.* **2016**, *138*, 8019-8030.

[22] Narasaka, K.; Okauchi, T.; Tanaka, K.; Murakami, M. *Chem. Lett.* **1992**, 2099-2102.

oxidation.[23] The resulting cation radical can react with a wide range of radical acceptors, the organocatalyzed version being introduced in MacMillan´s seminal work (Scheme 1.8).

Finally, our last objective was to explore the potential of dichloro- and monochloroacetamides for the synthesis of nitrogen-containing heterocycles using non-radical processes. Dichloro- or monochloroacetamides tethered to β- or γ-ketones could be valuable intermediates to access functionalized pyrrolidines and piperidines taking advantage of both the acidic character of the proton and the leaving group property of the chloro atom on the carbon next to the carbonyl group (Scheme 1.9). Indeed monohaloketones have been widely used in the Darzens condensation, one of the classical C–C and C–O bond-forming processes.[24] Nevertheless, only few examples were reported for intermolecular Darzens reaction where the substrate is a haloacetamide[25] and even fewer for the intramolecular process.[26] Additionally, we decided to study Darzens reaction from dichloroacetamides since these substrates have been scarcely investigated and only few examples of intermolecular condensation were reported.[27]

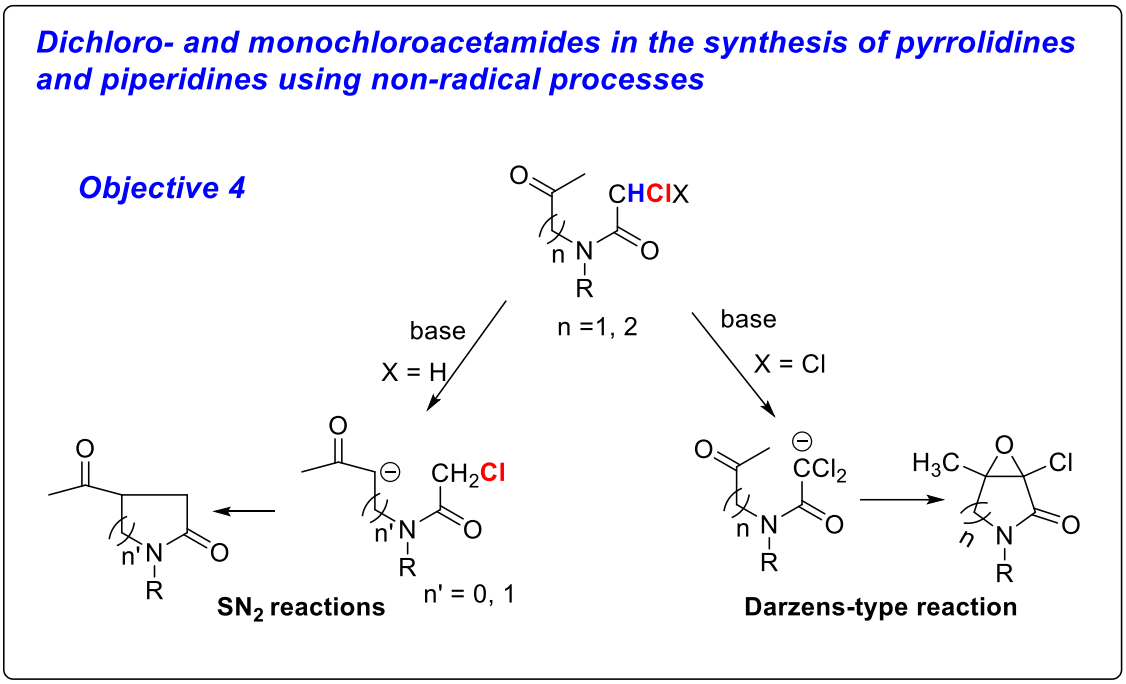
[23] (*a*) Nicewicz, D. A.; MacMillan, D. W. C. *Science* **2008**, *322*, 77-80. (b) Mastracchio, A.; Warkentin, A. A.; Walji, A. M.; MacMillan, D. W. C. *Proc. Natl. Acad. Sci. U.S.A.* **2010**, *107*, 20648-20651.

[24] For selective reviews on Darzens reactions, see: (a) Rosen, T. In Comprehensive Organic Synthesis; Trost, B. M., Fleming, I., Eds.; Pergamon: Oxford, 1991; Vol. 2, pp 409–439. (b) Ballester, M. *Chem. Rev.***1955**, *55*, 283-300. (c) Arai, S.; Shirai, Y.; Ishida, T.; Shioiri, T. *Tetrahedron* **1999**, *55*, 6375-6386. (d) Yuan, J. Y.; Liao, X. C.; Wang, H. M.; Tang, M. S*.; J. Struct. Chem.* **2008**, *49*, 818-827. (e) Sweeney, J. *Eur. J. Org. Chem.* **2009**, 4911-4919.

[25] For intermolecular Darzens reaction from haloacetamides see: (a) Tung, C. C.; Speziale, A. J.; Frazier, H. W. J. Org. Chem. 1963, 28, 1514-1521. (b) Figueroa-Valverde, L.; Diaz-Cedillo, F.; Ortega-Morales, O.; Garcia-Cervera, E.; Rosas-Nexticapa, M.; Pool-Gomez, E.; Lopez-Ramos, M.; Rodriguez-Hurtado, F.; Chan-Salvador, M. Steroids **2016**, *112*, 20-35. (c) Li, B.; Li, C. *J. Org. Chem.* **2014**, *79*, 8271-8277 and the references therein. (d) Ma, N.; Wu, K.; Huang, L. Eur. J. Med. Chem. **2008**, *43*, 893-896. (e) Komori, K.; Taniguchi, T.; Mizutani, S.; Monde, K. Kuramochi, K.;Tsubaki, K. *Org. Lett.* **2014**, *16*, 1386-1389. (f) Mizutani, S.; Komori, K.; Taniguchi, T.; Monde, K.; Kuramochi, K.; Tsubaki, K. *Angew. Chem., Int.* Ed. **2016**, *55*, 9553-9556.

[26] For intramolecular Darzens reaction from haloacetamides see: (a) Fisyuc, A. S.; Poendaev, N. V. Molecules, **2002**, *7*, 119-123. (b) Guo, J.; Sun, X.; Yu, S. *Org. Biomol. Chem*. **2014**, *12*, 265-268.

[27] (a) Mamedov, V. A.; Nuretdinov, I. A.; Subgatullina, F. G. *Russ. Chem. Bull.* **1988**, *37*, 1950-1951. (b) Mamedov, V. A.; Litvinov, I. A.; Kataeva, O. N.; Rizvanov, I. Kh.; Nuretdinov, I. A. *Monatsh. Chem.* **1994**, *125*, 1427-1435.

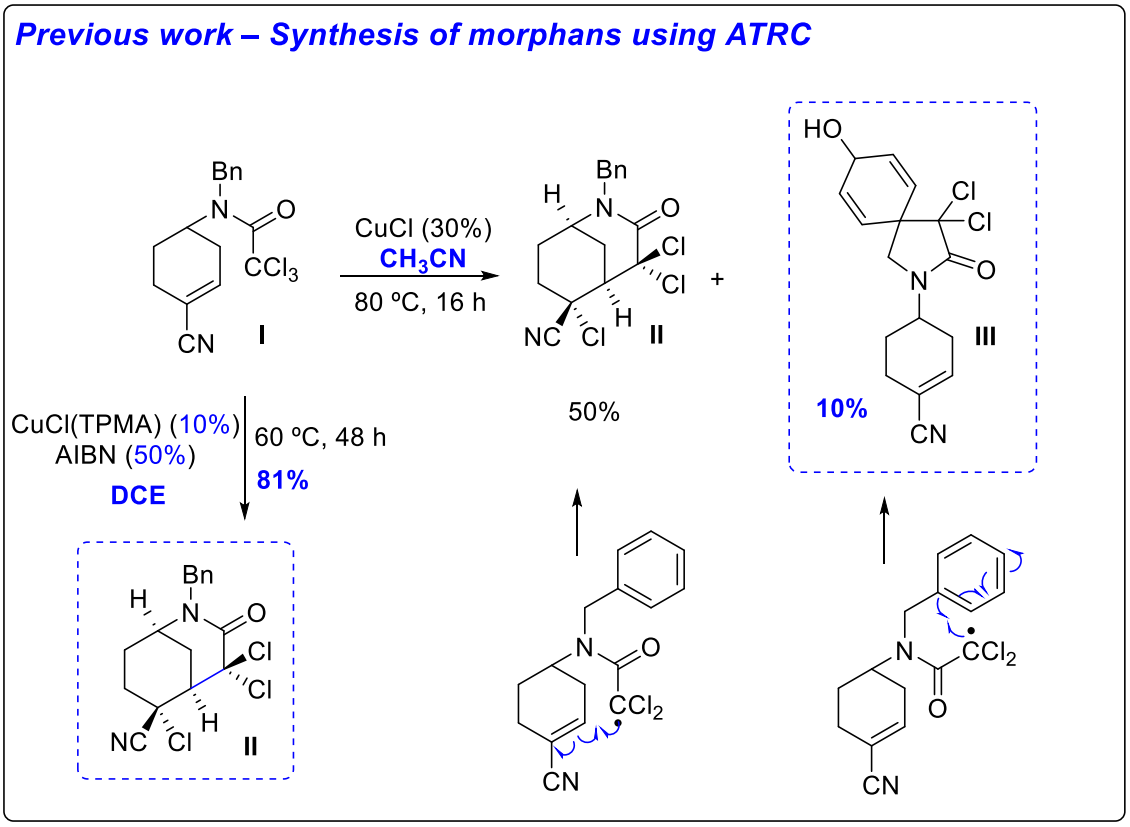

Dichloro- and monochloroacetamides in the synthesis of pyrrolidines and piperidines using non-radical processes
Objective 4
CHClX
n =1, 2
base
X = H
base
X = Cl
CH2Cl
n' = 0, 1
SN2 reactions
CCl2
H3C
Cl
Darzens-type reaction

Scheme 1.9.

Chapter 2

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

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

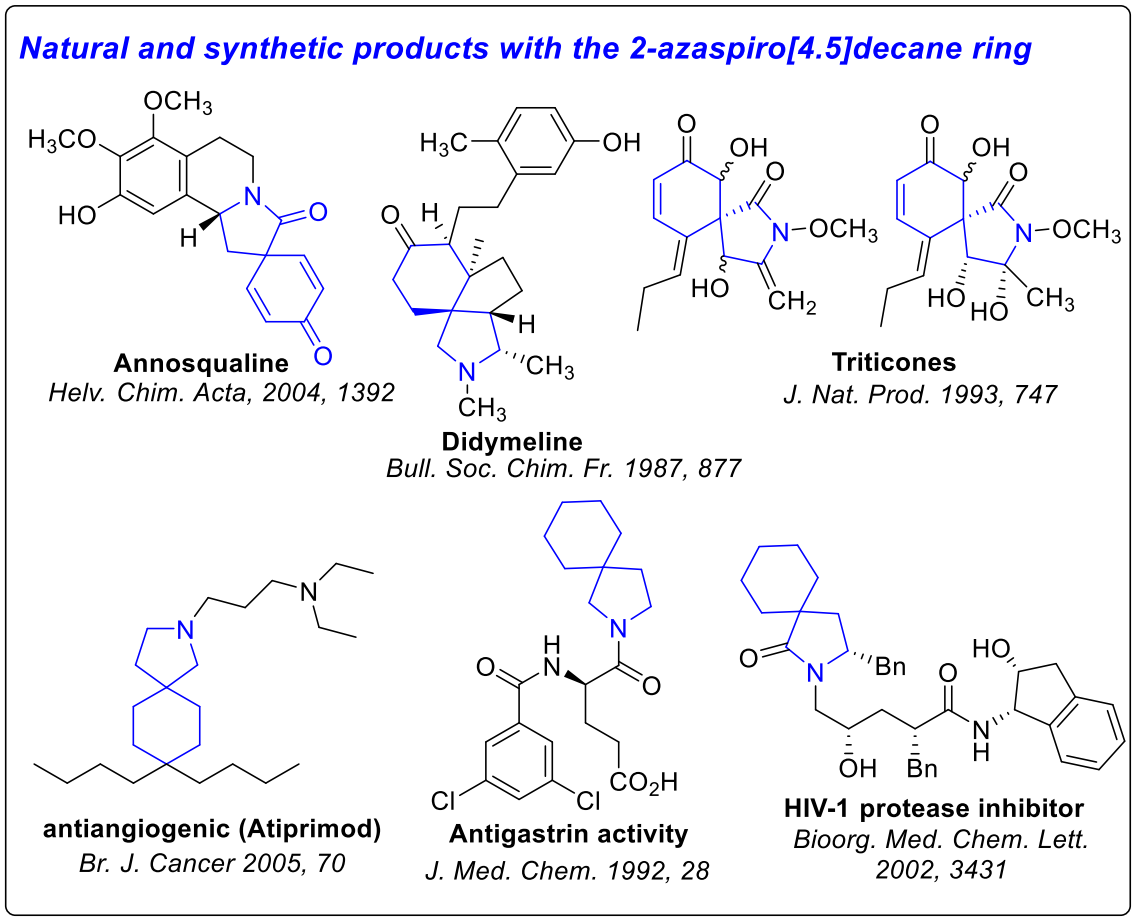


Scheme 2.1.

Few years ago in our research group a new synthetic route for the preparation of morphans from trichloroacetamidocyclohexenes using ATRC in the presence of CuCl was described.[1] During the preliminary study, before settling 1,2-dichloroethane (DCE) as the best solvent for this transformation, the reaction was investigated in the presence of other solvents such as DMF and acetonitrile. In the presence of the latter, besides the previous morphan **II** obtained with a lower yield, spirocyclic derivative **III** was also isolated (Scheme 2.1). Unlike morphan **II**, which results from cyclization of the dichlorocarbamoyl radical on the cyclohexene double bond in the *E*-rotamer, **III** comes from a dearomative spirocyclization in the *Z*-rotamer followed by a displacement of the chlorine atom in the *p*-chloroderivative by water during the aqueous workup (Scheme 2.1).

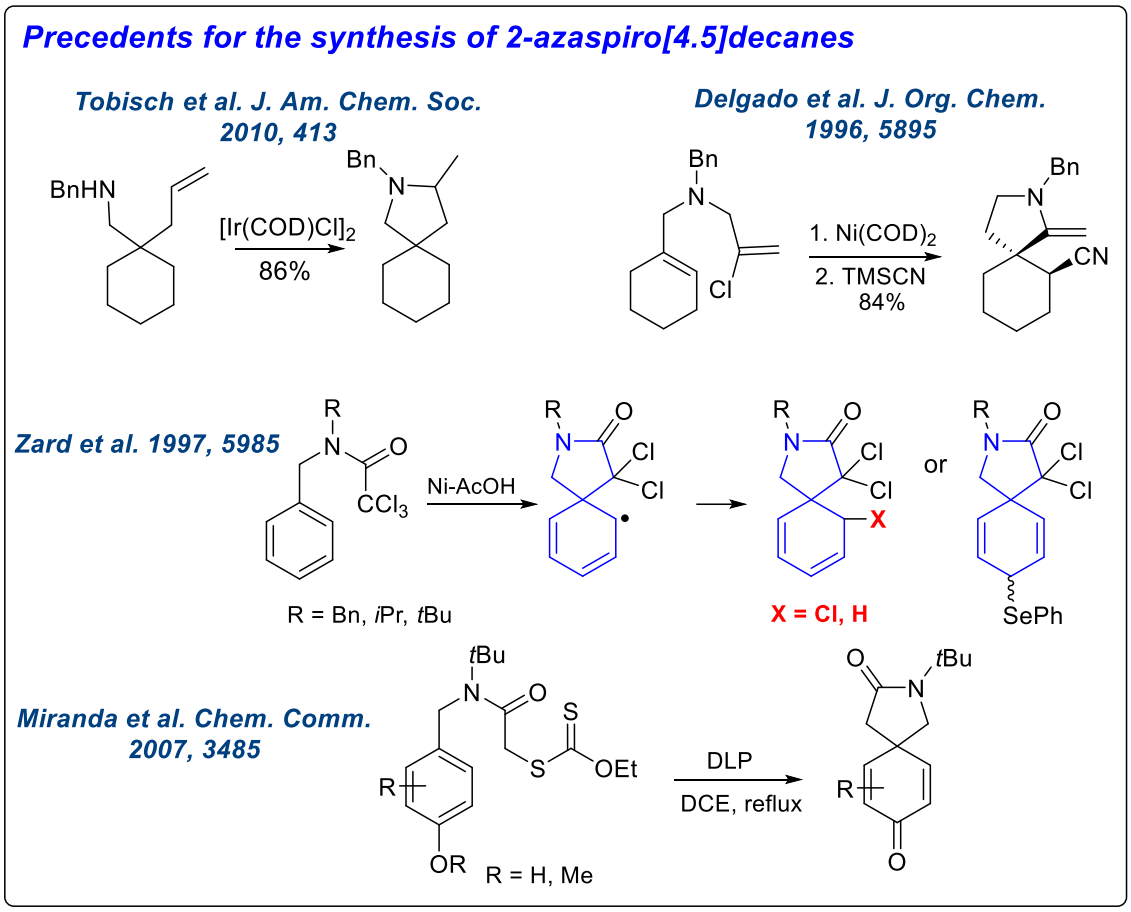
[1] Diaba, F.; Martínez-Laporta, A.; Bonjoch, J.; Pereira, A.; Muñoz-Molina, J. M.;Pérez, J. P.; Belderrain, T. R. *Chem. Commun*. **2012**, *48*, 8799−8801.

This unexpected result was the beginning of an investigation aimed at making the spirocyclization the exclusive process by changing the substituent on the nitrogen to a non-acceptor radical.



Scheme 2.2.

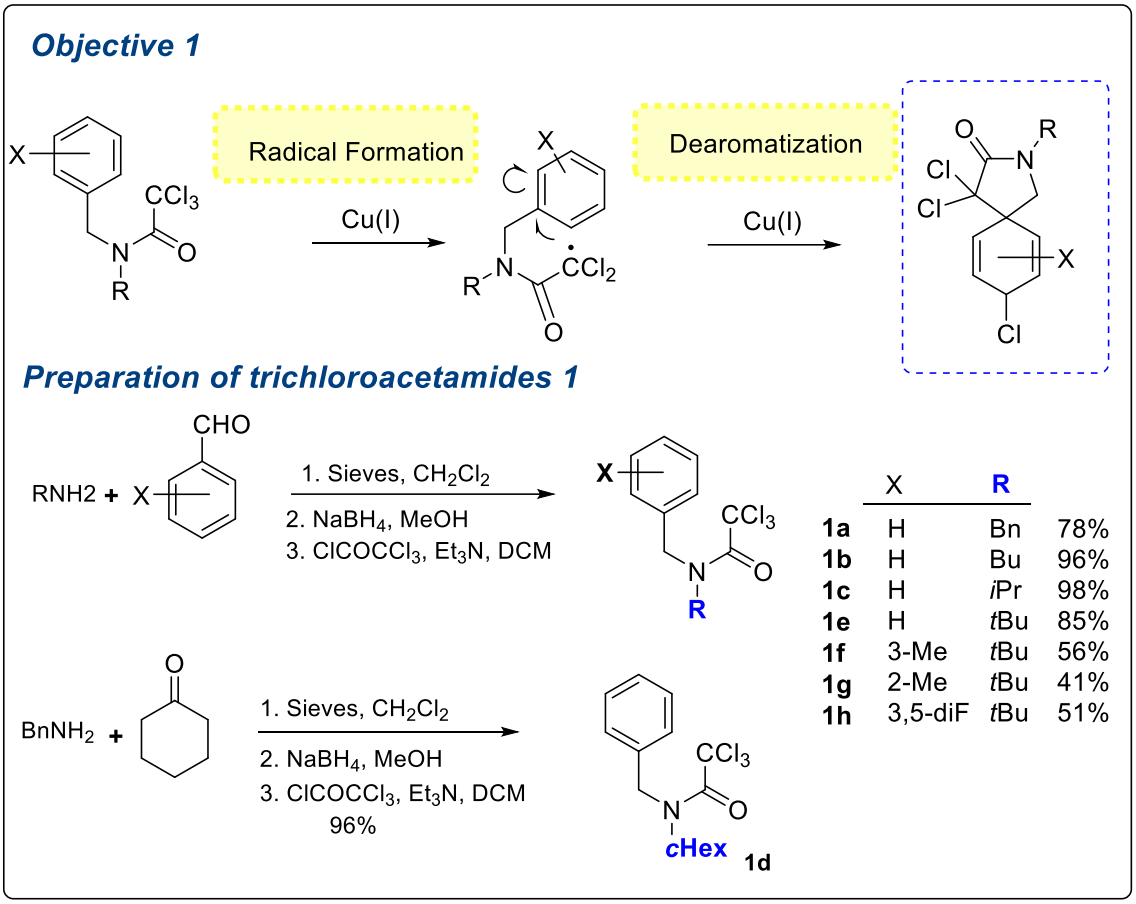
Our interest in undertaking this study was boosted by the fact that the 2-azaspiro[4.5]decane ring is found in a few number of natural compounds. Among these are annosqualine isolated from the stems of *Annona squamosal L.*, Didymeline isolated from *Didymeles Madagascariensis* and fungal metabolites triticones from the culture broth of the plant pathogenic fungus *Drechslera tritici-repentis*. Additionally, several synthetic products embodying this spirobicyclic structure display diverse biological activities such as antiangiogenic for Atiprimod, a substance developed by the company GlaxoSmithKline, antigastrin and even HIV-1 protease inhibition (Scheme 2.2).



Scheme 2.3.

More interesting was the fact that 2-azaspirodecanes are generally prepared from cyclohexyl- or cyclohexenylmethylamines or through a dearomative process involving a spirocyclization on phenol derivatives in an oxidative process most of the time. To our knowledge, at the beginning of this project, there was only one example of a dearomative spirocyclization on non-activated benzenes reported by Zard and coworkers using radical chemistry. In this work, formation of the *o*-chloro derivative is reported using a large excess of Ni in acetic acid, nevertheless the *p*-derivative was isolated when diphenyldiselenide was employed as a radical trap. Additionally, another xanthate-based oxidative spirocyclization from *p*-oxygenated *N*-benzylacetamides for the preparation of azaspirocyclic cyclohexadienones was reported by Miranda and coworkers using dilauryl peroxide in more than stoichiometric amount (Scheme 2.3).

Taking into account all these considerations, the first objective of this work was to investigate the scope of the radical spirocyclization in the presence of CuCl from *N*-benzyltrichloroacetamides with different substituents on the nitrogen atom (Scheme 2.4).



Scheme 2.4.

The trichloroacetamides mentioned before, indicated in scheme 2.4., were easily prepared using a reductive amination from the corresponding aldehydes or ketones and alkyl amines followed by acylation of the resulting secondary amine with trichloroacetyl chloride. Thus, a series of trichloroacetamides bearing different alkyl groups ranging from the bulky *t*-butyl to the linear non-demanding butyl groups was prepared. Subsequently, more trichloroacetamides were prepared, bearing a *t*-butyl group on the nitrogen and different substituents on the benzene ring in order to establish the influence of these on the course of the reaction (Scheme 2.4).

Having in hands the different benzyltrichloroacetamides (**1a**-**1e**) we set out to explore the ATRC using CuCl as a catalyst as we chose trichloacetamide **1e** with the bulky *t*-Bu group on the nitrogen to develop the methodology. This choice is based on the fact that this substituent locks the substrate in a configuration where it is positioned syn to the carbonyl oxygen[2] prone to cyclization.[3] Indeed, examination of NMR spectra for both **1e** and *n*-butyl derivative **1b** revealed a single set of signals in both ^{1}H and ^{13}C spectra for the former (Figure 2.1), whereas the latter showed two sets of signals corresponding to the two rotamers especially for the protons and carbons close to the nitrogen (Figure 2.2). Additionally the *t*-butyl group is easily removed in acid media.

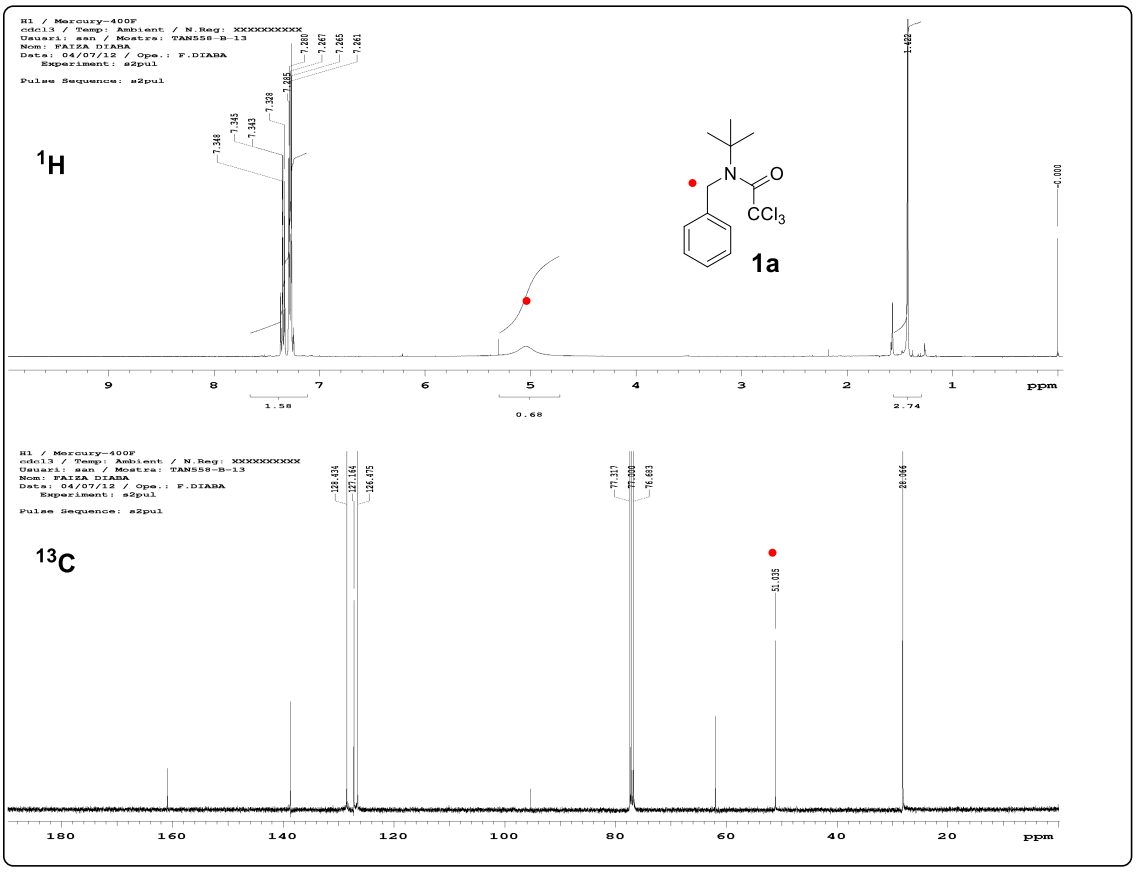


Figure 2.1.

[2] Lewin, A.; Frucht, M.; Chen, K.; Benedetti, E.; Di Blasio, B. *Tetrahedron* **1975**, *31*, 207-215.
[3] (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.

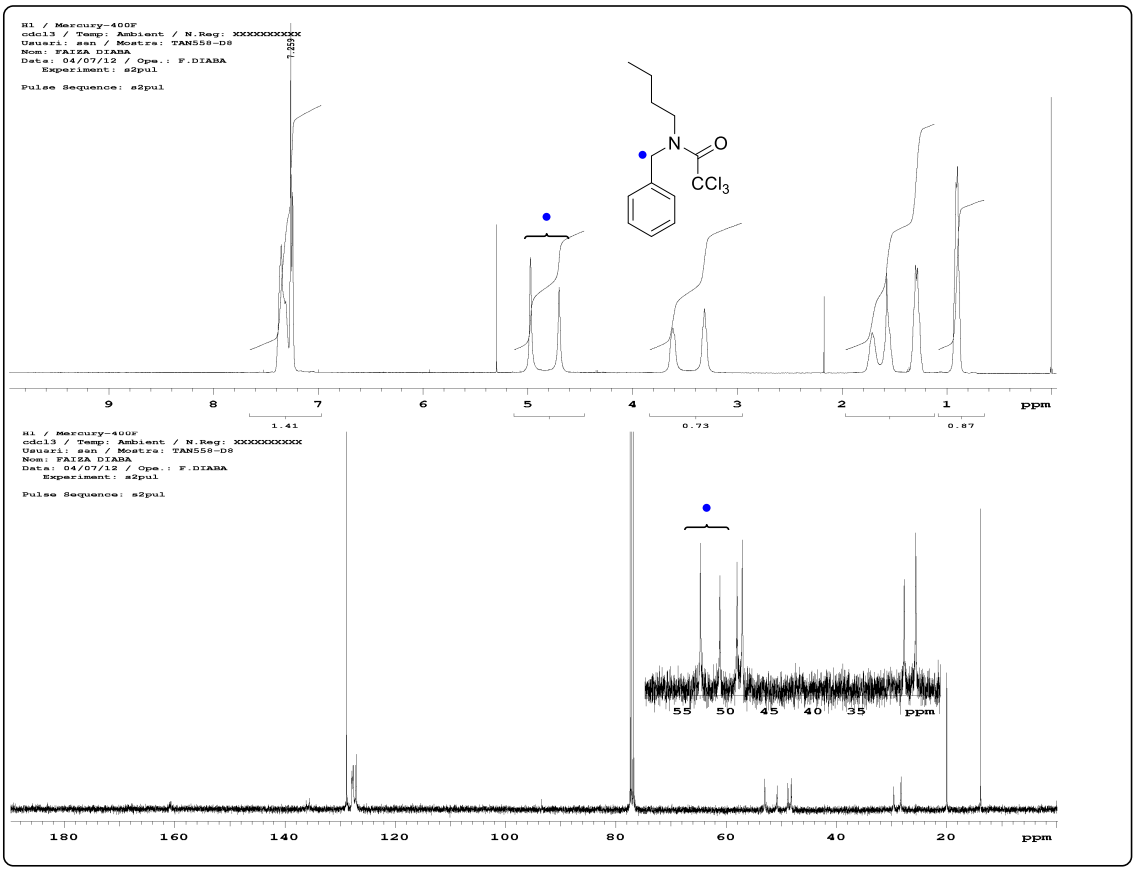
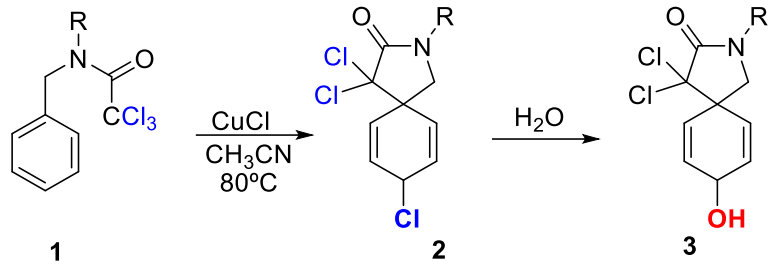

H1 / Mercury-400F
cdcl3 / Temp: Ambient / N.Req: XXXXXXXXXX
Usuari: asn / Mostra: TAN558-D8
Nom: FAIZA DIABA
Data: 04/07/12 / Ope.: F.DIABA
Experiment: s2pul
Pulse Sequence: s2pul
7.259
N
O
CCl3
9
8
7
6
5
4
3
2
1
ppm
1.41
0.73
0.87
55
50
45
40
35
180
160
140
120
100
80
60
40
20

Figure 2.2.

Table 2.1. Synthesis of 2-azaspirodeca[4.5]dienes **3**



1 **2** **3**

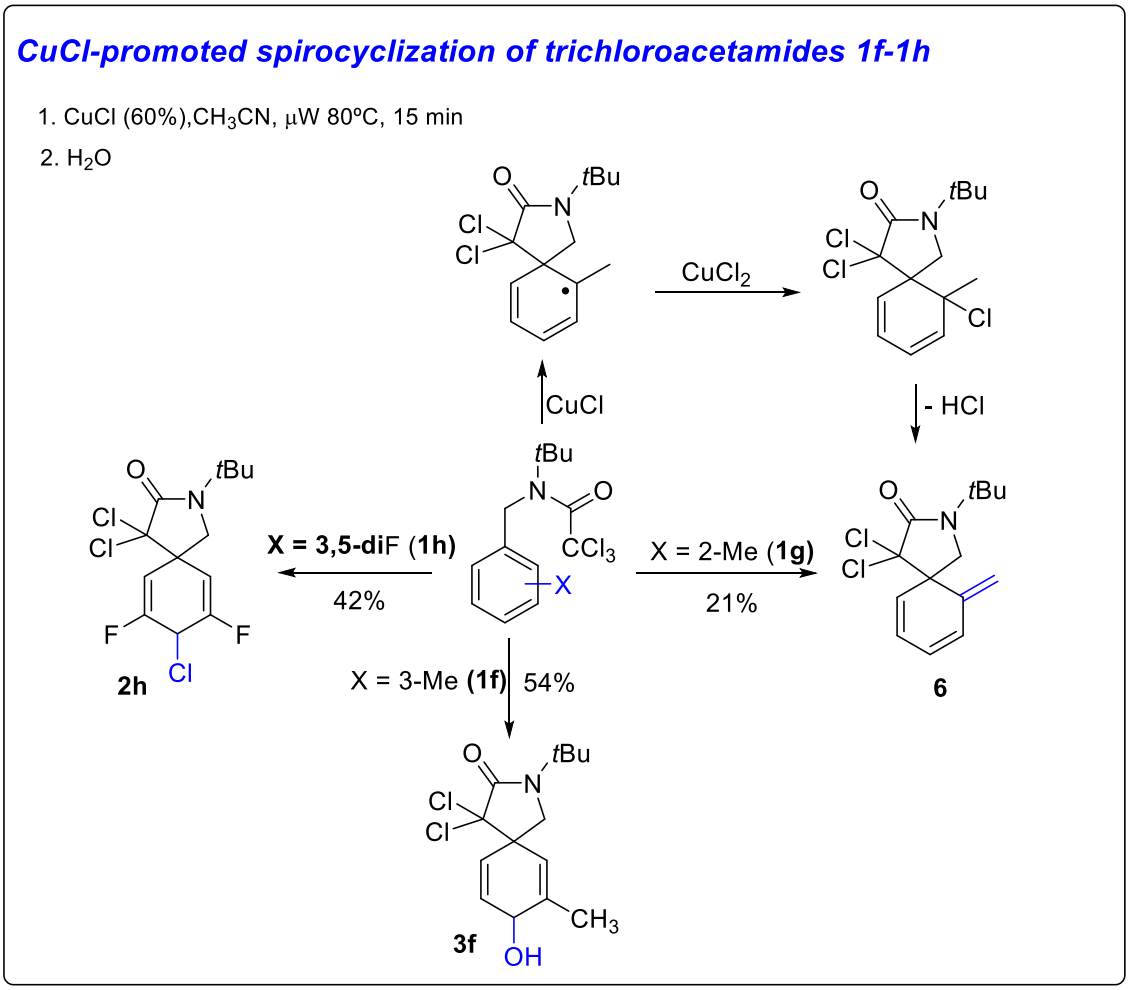
Entry	*R*	*CuCl*	*Time*	***3** (Yield)*	***3** (LP:MP)*[4]
1	*t*Bu (**1e**)	30%	16 h	65%	1.4:1
2	*t*Bu (**1e**)	30%	15 min (µW)	49%	3:2
3	*t*Bu (**1e**)	60%	15 min (µW)	74%	3:2
4	*t*Bu (**1e**)	60%	30 min (µW)	68%	3:2
5	*i*Pr (**1c**)	60%	15 min (µW)	42%	2:3
6	*c*Hex (**1d**)	60%	15 min (µW)	29%	3:2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

The first reaction was achieved using 30% of CuCl in acetonitrile and at 80 ºC. After heating for 16 h and elimination of the solvent, we were pleased to find that the cyclization took place providing spirolactam **2e** as a mixture of two epimers. Nevertheless, purification of **2e** provided a mixture of compounds showing the instability of the chloroderivatives. Fortunately, after a simple treatment with water the corresponding alcohols were formed and were easily separated by chromatography in a 65% yield (entry 1). Using microwave activation allowed us to shorten the reaction time to 15 min but did not bring any improvement to the reaction yield (entry 2). The best results were obtained when the catalyst loading was increased to 60% giving **3e** in 74% yield (entry 3).

The optimal reaction conditions were then applied to the rest of trichloroacetamides **1a**-**1d**, obtaining in all cases alcohols **3** as a mixture of

[4] LP and MP refer to the less polar and the more polar alcohols respectively.

epimers. As it was expected **1a** and **1b** with undemanding substituents on the nitrogen gave the worst results (entries 7 and 8) whereas the isopropyl and cyclohexyl derivatives **1c** and **1d** provided alcohols **3c** and **3d** respectively, with slightly better yields (entries 5 and 6).

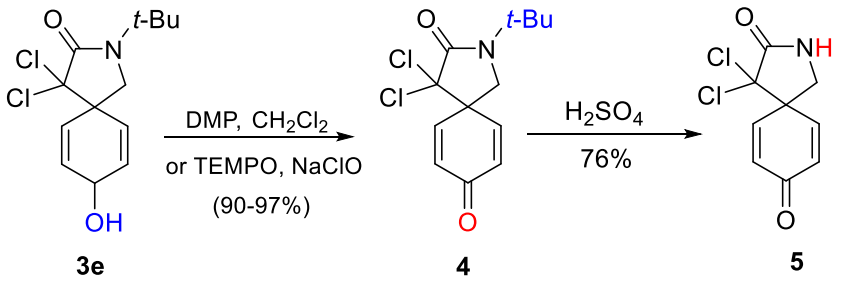


Scheme 2.5.

After settling the *t*-butyl group as the best substituent for the spirocyclization process, we then explored the scope of this reaction on a number of substituted benzene derivatives (Scheme 2.5). Whereas the 3-methylsubstituted benzene **1f** provided a result similar to that observed in the unsubstituted series, 2-methyl substituted benzene displayed a completely different behavior, since the trapping of the radical takes place at carbon 2, further elimination in the chloride intermediate provided azaspirodecane **6** with an exocyclic double bond. Finally, the 3,5-difluorobenzylacetamide **1h** afforded

chloroderivative **2h** which showed a low reactivity towards water and was stable enough to be purified by chromatography.

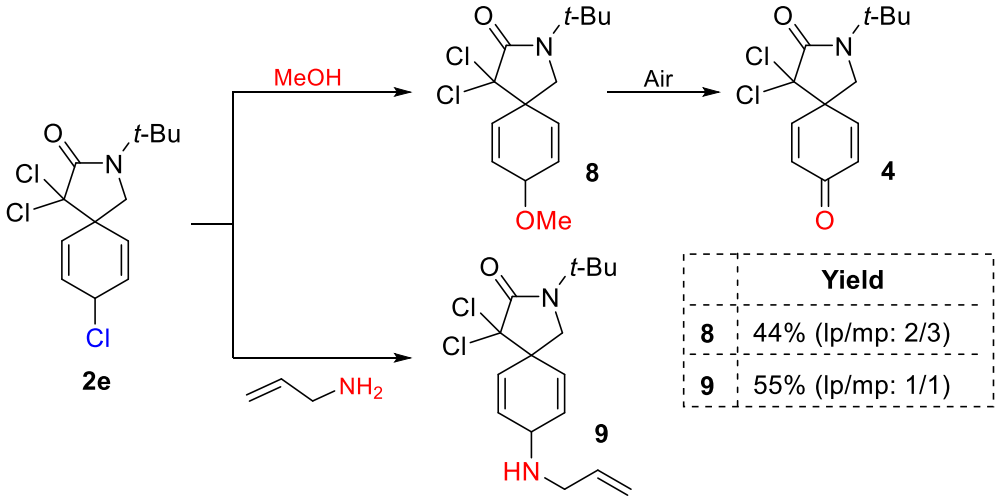
Synthesis of azaspirocyclohexadienone 5



Scheme 2.6.

The mixture of alcohols **3e** was oxidized to ketone **4** in excellent yields using Dess-Martin periodinane or TEMPO and further treatment with sulfuric acid provided secondary amide **5** in 76% yield (Scheme 2.6).

Trapping of chloride 2e with MeOH and allylamine



Scheme 2.7.

This investigation was concluded studying the reactivity of chloroderivative **2e** formed after ATRC with other trapping reagents like methanol and allylamine. Thus treatment of the reaction crude with methanol provided the corresponding mixture of ethers **8** which was sensitive to air and convert to ketone **4** on standing.

Likewise, when allylamine was used in the quenching step epimeric mixture **9** was obtained (Scheme 2.7).

Dearomative radical spirocyclization from *N*-benzyltrichloroacetamides revisited using a copper(I)-mediated atom transfer reaction leading to2-azaspiro[4.5]decanes.

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

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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-

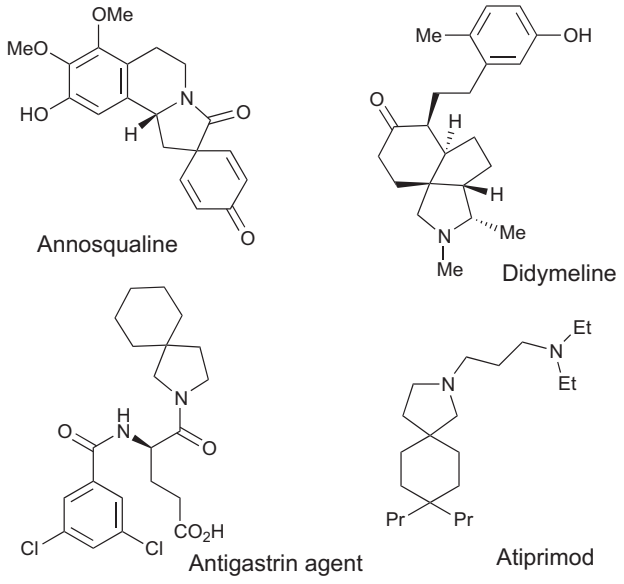

Fig. 1. Structures of 2-azaspiro[4.5]decane natural and unnatural products.

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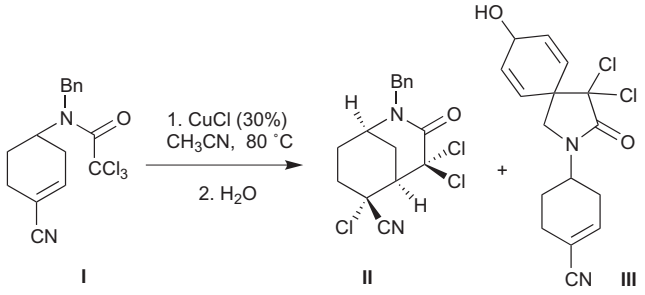
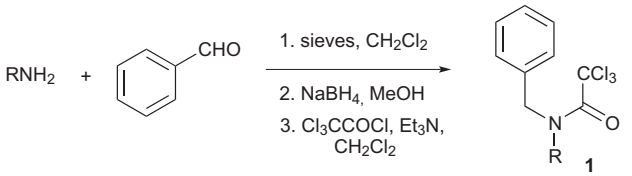
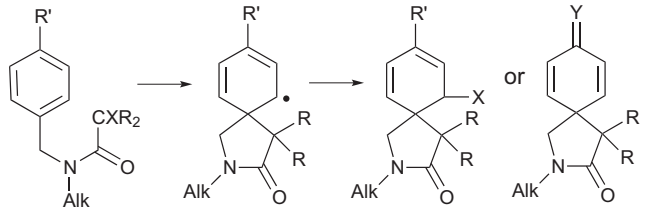


Scheme 1. Radical cyclization of trichloroacetamide **I**.



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%).

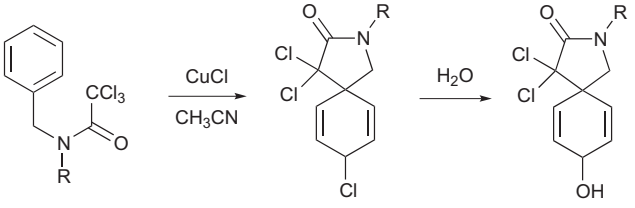
Table 1
Dearomative radical spirocyclization



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]

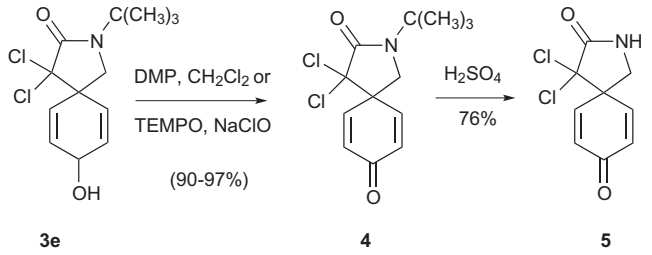
Using 30% of CuCl and after 16 h of heating at 80 °C, we were pleased to see that the main signals in the ^{1}H NMR spectrum of the crude product belonged to a mixture of epimers of spirolactam **2**. However, purification of **2** on silica gel gave a mixture of compounds, showing the instability of 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**.

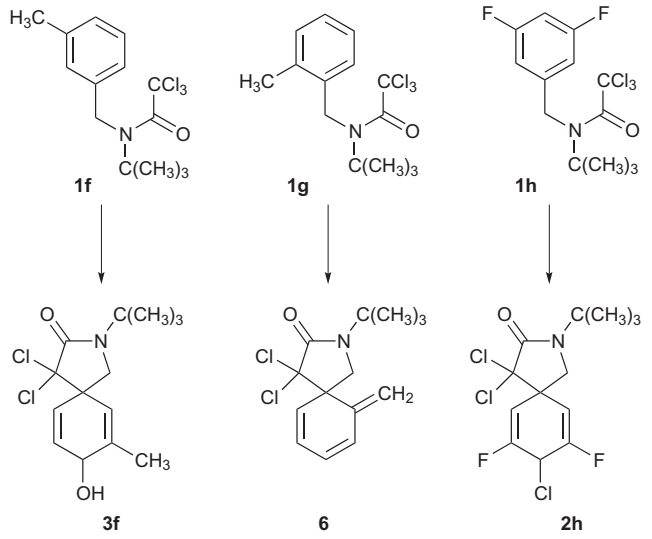
To optimize the process we decided to use microwave activation, but the same catalyst loading, a 15-minute reaction time and further treatment with water gave the same mixture of alcohols with a lower yield of 49% (entry 2). The best results were obtained with 60% of CuCl, which gave **3e** in 74% yield (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).

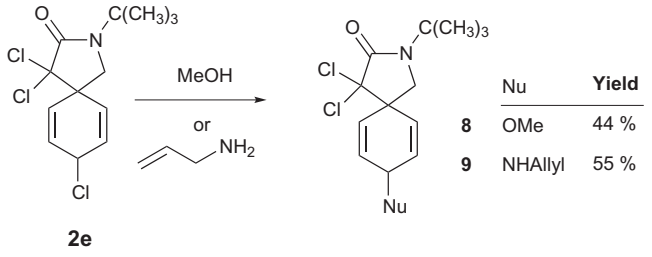
We next sought to explore the scope of the reaction and examined a number of substituted benzene derivatives (Scheme 4). Starting materials were prepared following the same reaction



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]

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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

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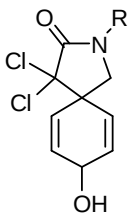
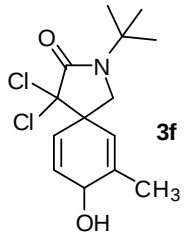
Table 1. ^{13}C NMR chemical shifts of 2-azaspiro[4.5]decanes **3**[a]





3f

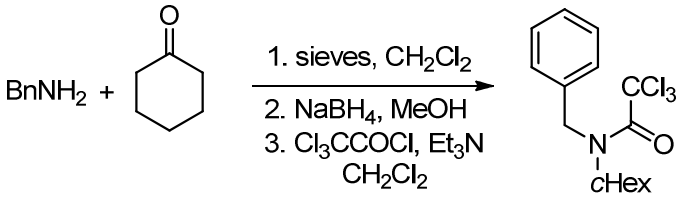
	3a R = Bn		**3b** R = Bu		**3c** R = *i*Pr		**3d** **R** = *c*Hex		**3e** R = *t*Bu		**3f**	
	LP	**MP**	**LP**	**MP**	**LP**	**MP**	**LP**	**MP**	**LP**	**MP**	**LP**	**MP**
C-1	53.8	53.3	54.5	54.0	49.6	49.1	50.2	50.6	52.3	52.7	52.5	52.8
C-3	165.8	165.8	165.2	165.7	165.0	165.0	165.1	165.1	165.3	165.3	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.

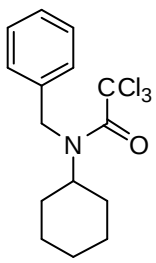
General. ^{1}H and ^{13}C NMR spectra were recorded in $CDCl_3$ solution. Chemical shifts are reported as δ values (ppm) relative to internal Me_4Si. All NMR data assignments are supported by COSY and HSQC experiments. Infrared spectra were recorded on a Nicolet 320 FT-IR spectrophotometer. TLC was performed 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%).

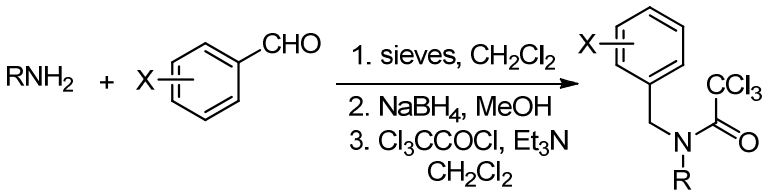


***N*-Benzyl-2,2,2-trichloro-*N*-cyclohexylacetamide (1d)**

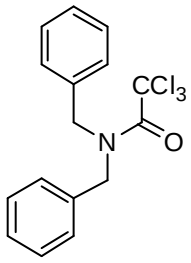
IR (NaCl, neat): 3086, 3063, 3030, 2936, 2859, 1971, 1951, 1873, 1854, 1806, 1775, 1667, 1495, 1453, 1418, 1362, 1325, 1284, 1243, 1161, 1141, 1029, 997, 891, 840, 823, 811, 736, 700, 670, 605, 531 cm^{-1}; ^{1}H

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



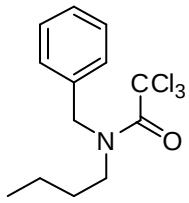
	X	R	
1a	H	Bn	78%
1b	H	Bu	96%
1c	H	*i*Pr	98%
1e	H	*t*Bu	85%
1f	3-Me	*t*Bu	56%
1g	2-Me	*t*Bu	41%
1h	3,5-diF	*t*Bu	51%



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

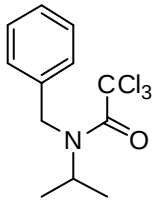
IR (NaCl, neat): 3063, 3027, 2919, 2870, 1954, 1863, 1812, 1679, 1494, 1452, 1420, 1361, 1304, 1282, 1225, 1198, 1160, 1077, 1030, 947, 848, 813, 739, 698, 665, 506 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz): δ 4.58 (s, 2H, CH_2Ar), 4.91 (s, 2H, CH_2Ar), 7.12-7.46 (m, 10H, ArH); ^{13}C NMR ($CDCl_3$, 100 MHz): 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.



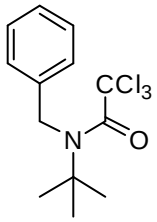
***N*-Benzyl-*N*-butyl-2,2,2-trichloroacetamide (1b)**

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.



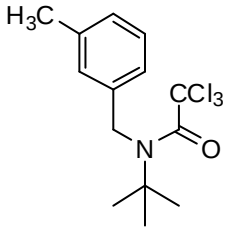
***N*-Benzyl-2,2,2-trichloro-*N*-isopropylacetamide (1c)**[1]

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.

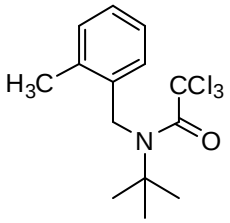


***N*-tert-Butyl-2,2,2-trichloro-*N*-(3-methylbenzyl)acetamide (1f)**[2]

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,

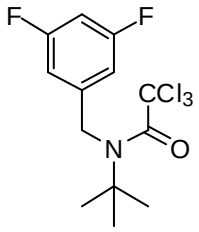
[2] J. Boivin, M. Yousfi, S. Z. Zard, *Tetrahedron lett.* 1997, **38**, 5985-5988

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]

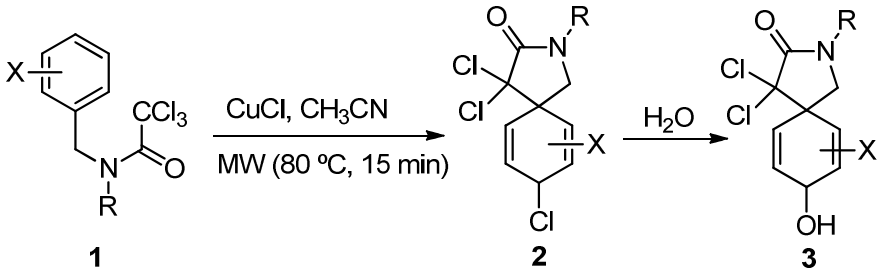
IR (NaCl, neat): 3067, 2969, 2930, 1679, 1606, 1476, 1460, 1382, 1365, 1350, 1254, 1226, 1183, 1145, 1101, 1050, 982, 885, 840, 823, 812, 768, 753, 696, 666, cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 1.45 (s, 9H, 3 CH_3), 2.28 (s, 3H, CH_3), 4.93 (brs, 2H, CH_2Ar), 7.12-7.24 (m, 3H, ArH), 7.34 (d, 1H, *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)**

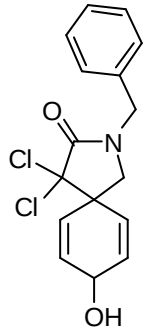
IR (NaCl, neat): 3078, 3064, 3018, 3000, 2976, 2931, 1668, 1625, 1598, 1475, 1451, 1384, 1365, 1351, 1319, 1304, 1256, 1219, 1181, 1153, 1120, 998, 983, 964, 887, 869, 849, 836, 814, 720, 669, 646 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 1.44 (s, 9H, 3 CH_3), 5.01 (brs, 2H, CH_2Ar), 6.72 (tt, 1H, *J* = 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.



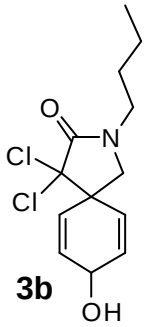
2-Benzyl-4,4-dichloro-8-hydroxy-2-azaspiro[4.5]deca-6,9-dien-3-one (3a)

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.

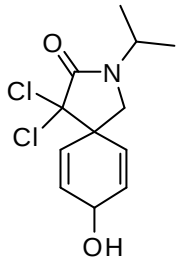
2-Butyl-4,4-dichloro-8-hydroxy-2-azaspiro[4.5]deca-6,9-dien-3-one (3b)



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.

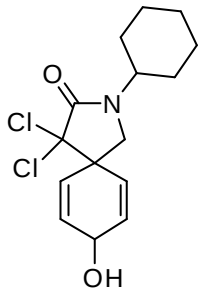


4,4-Dichloro-8-hydroxy-2-isopropyl-2-azaspiro[4.5]deca-6,9-dien-3-one (3c)

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),

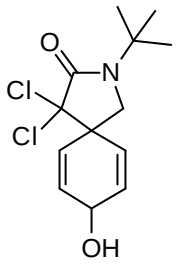
3.28 (s, 2H, CH_2-1), 4.41 (sept, 1H, *J* = 7.2 Hz, CH), 4.66 (brs, 1H, H-8), 5.87 (dq, 2H, *J* = 10.4, 2 Hz, H-6 and H-10), 6.24 (ddt, 2H, *J* = 10.4, 2.8, 2 Hz, H-7 and H-9); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 19.2 (CH_3), 44.2 (CH), 49.1 (C-1), 49.6 (C-5), 62.4 (C-8), 89.8 (C-4), 125.8 (C-6 and C-10), 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.

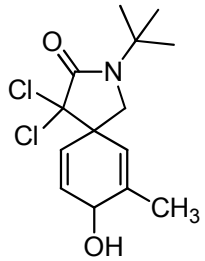


2-*tert*-Butyl-4,4-dichloro-8-hydroxy-2-azaspiro[4.5]deca-6,9-dien-3-one (3e)

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.

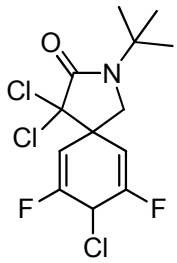
More polar: IR (NaCl, neat): 3254, 3034, 2972, 2871, 1713, 1474, 1400, 1367, 1306, 1245, 1216, 1015, 923, 885, 777, 741, 694, 682, 563, 516 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz): δ 1.43 (s, 9H, 3 CH_3), 1.58 (brs, 1H, OH), 3.34 (s, 2H, CH_2-1), 4.52 (brs, 1H, H-8), 5.96 (dq, 2H, *J* = 10.4, 1.6 Hz, H-6 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.

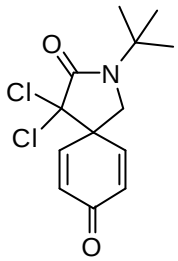
- **Oxidation of alcohols 3e**

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%).

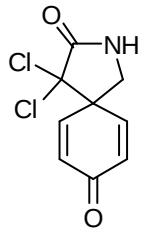


2-*t*ert-Butyl-4,4-dichloro-2-azaspiro[4.5]deca-6,9-diene-3,8-dione (4)

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.

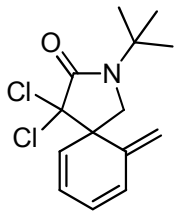
- ***tert*-Butyl group cleavage**

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)

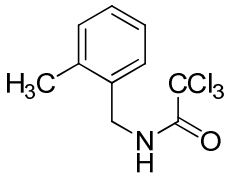
IR (NaCl, neat): 3214, 3154, 3047, 2986, 2873, 2798, 1739, 1668, 1627, 1408, 1366, 1322, 1272, 1252, 1215, 1187, 1093, 1062, 978, 866, 825, 726 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 3.57 (d, 2H, *J* = 1.2 Hz, CH_2-1), 6.53 (dm, 2H, *J* = 10 Hz, H-7 and H-9), 7.04 (dm, 2H, *J* = 10 Hz, H-6 and H-10), 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)

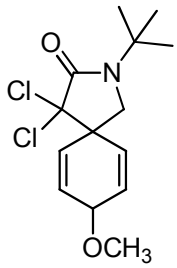
IR (NaCl, neat): 3042, 2959, 2920, 2872, 1712, 1596, 1563, 1476, 1403, 1369, 1296, 1284, 1274, 1258, 1214, 1151, 1121, 1097, 1011, 925, 896, 882, 867, 836, 766, 736, 697, 683, 653 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 1.45 (s, 9H, 3 CH_3), 3.39 (d, 1H, *J* = 10.4 Hz, CH_2-1), 3.56 (d, 1H, *J* = 10.4 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.



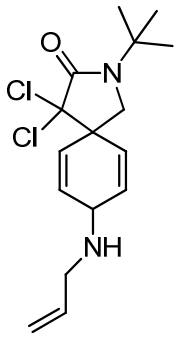
2,2,2-Trichloro-*N*-(2-methylbenzyl)acetamide (7)

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.

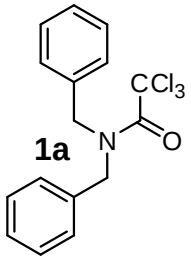


8-Allylamino-2-*tert*-butyl-4,4-dichloro-2-azaspiro[4.5]deca-6,9-dien-3-one (9)

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**



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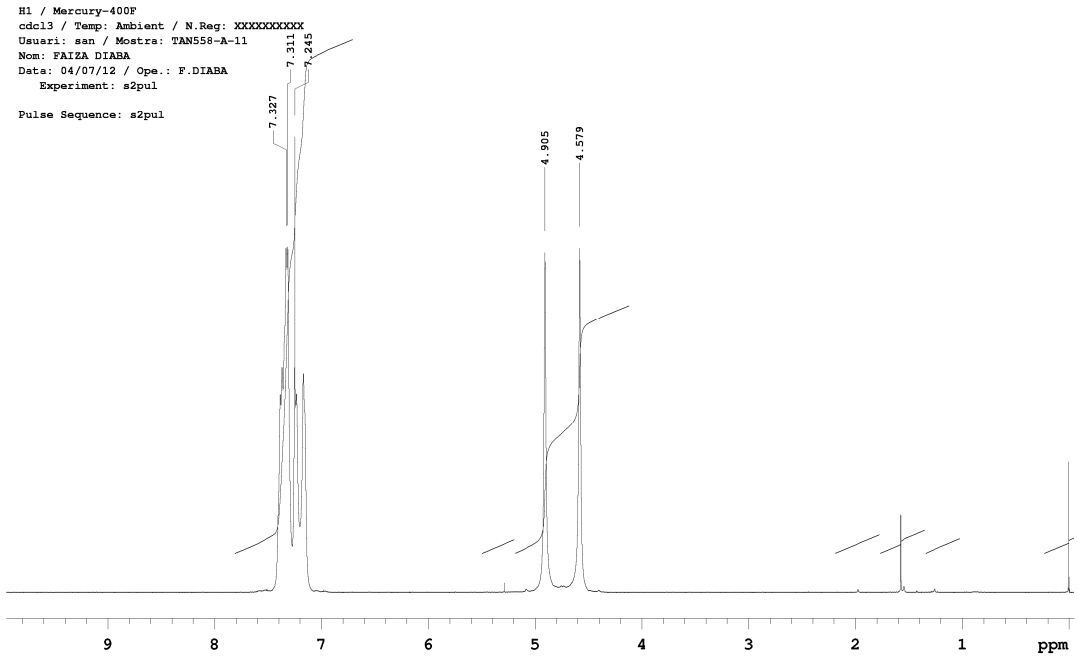
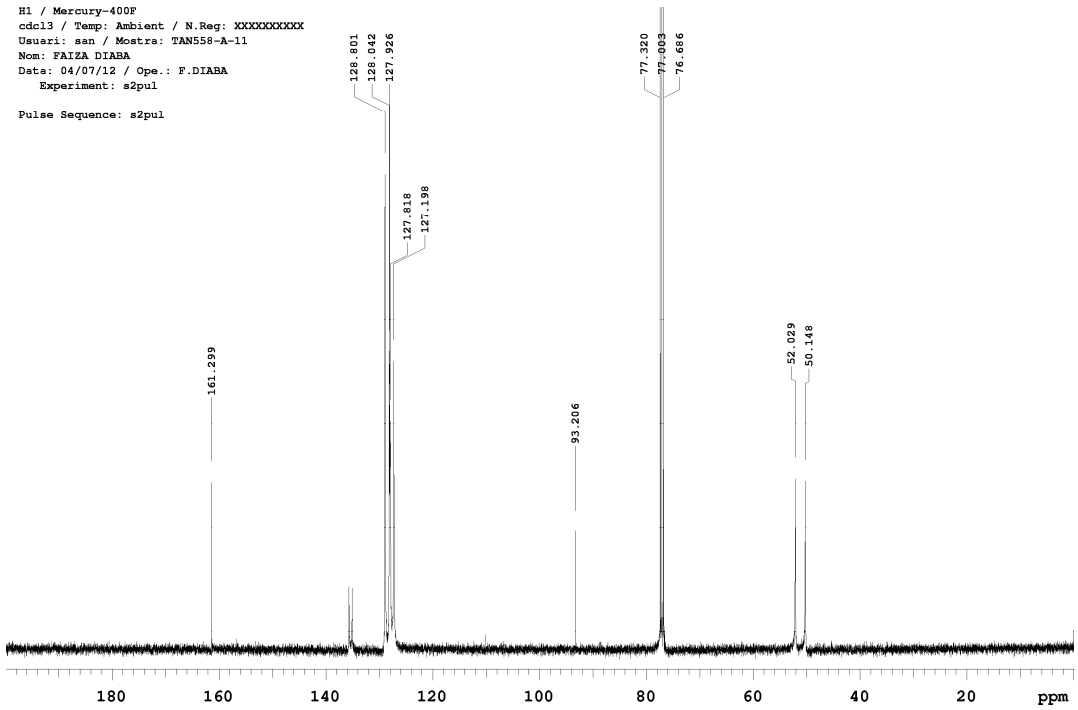
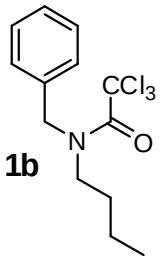
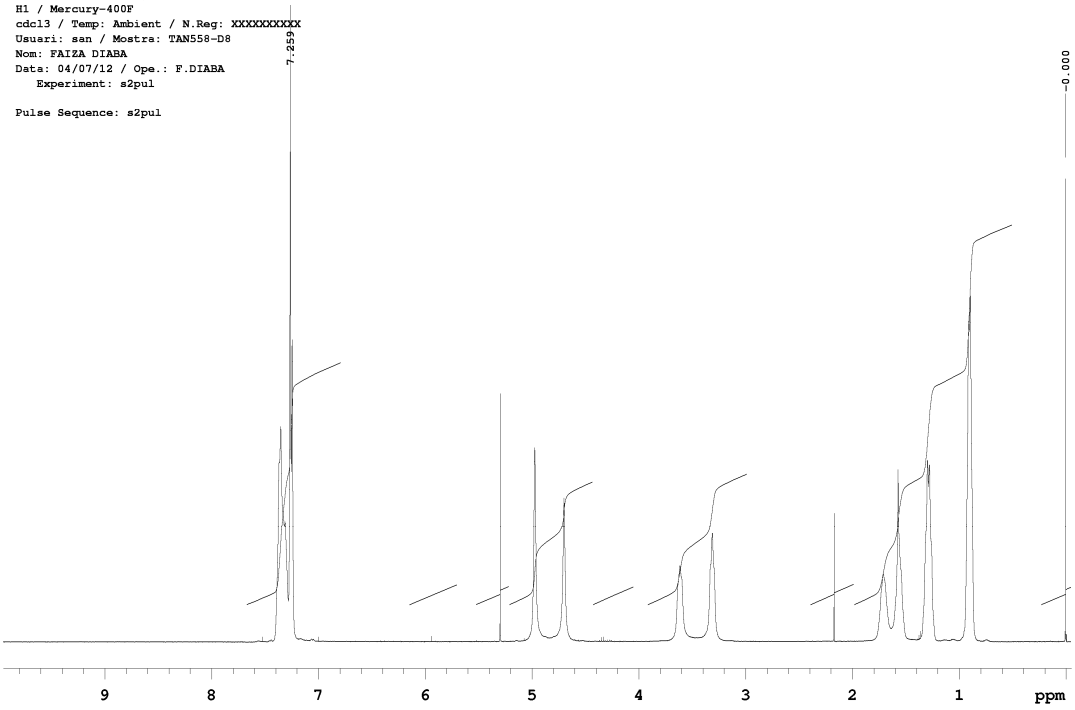





CCl3
N
O

1b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Data: 04/07/12 / Ope.: F.DIABA
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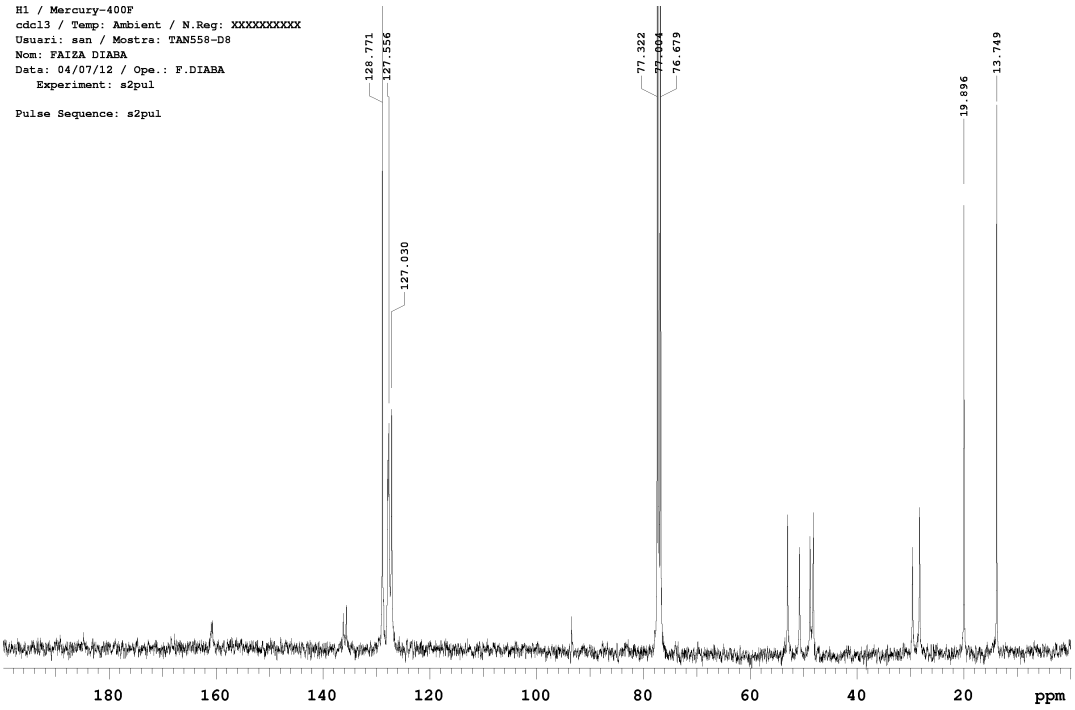
9
8
7
6
5
4
3
2
1
ppm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Data: 04/07/12 / Ope.: F.DIABA
Experiment: s2pul
Pulse Sequence: s2pul
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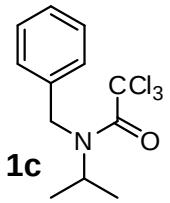
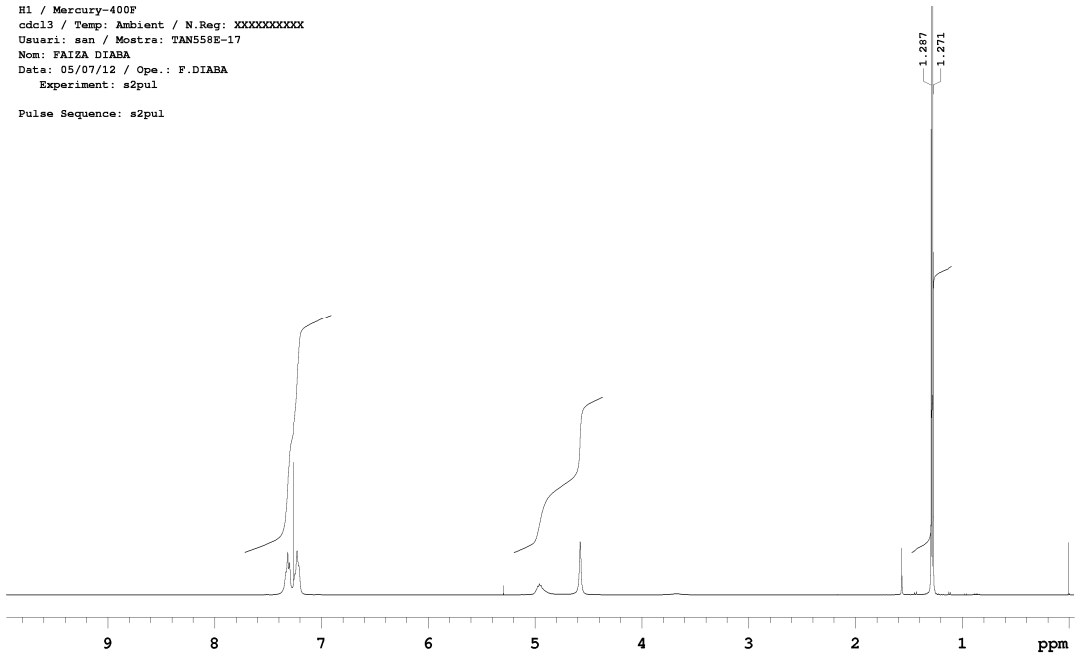
80
60
40
20
ppm


CCl3
N
O

1c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Data: 05/07/12 / Ope.: F.DIABA
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Pulse Sequence: s2pul
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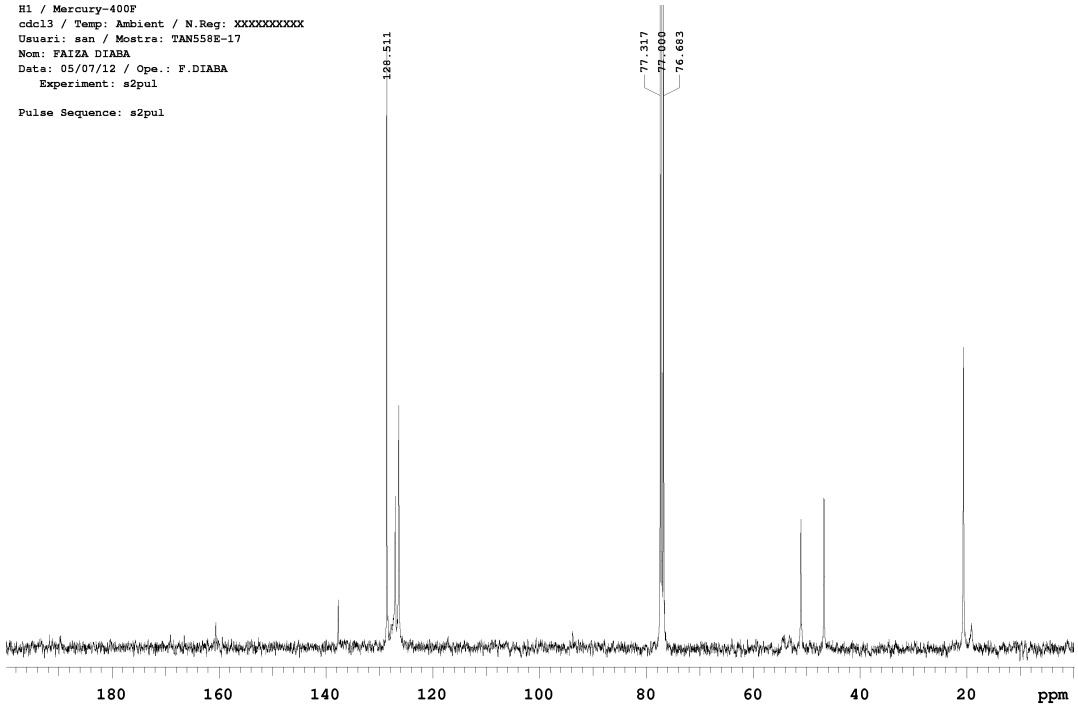
9
8
7
6
5
4
3
2
1
ppm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Data: 05/07/12 / Ope.: F.DIABA
Experiment: s2pul
Pulse Sequence: s2pul
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77.000
76.683
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160
140
120
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80
60
40
20
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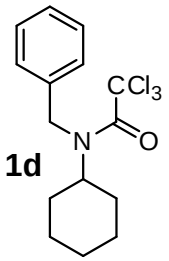
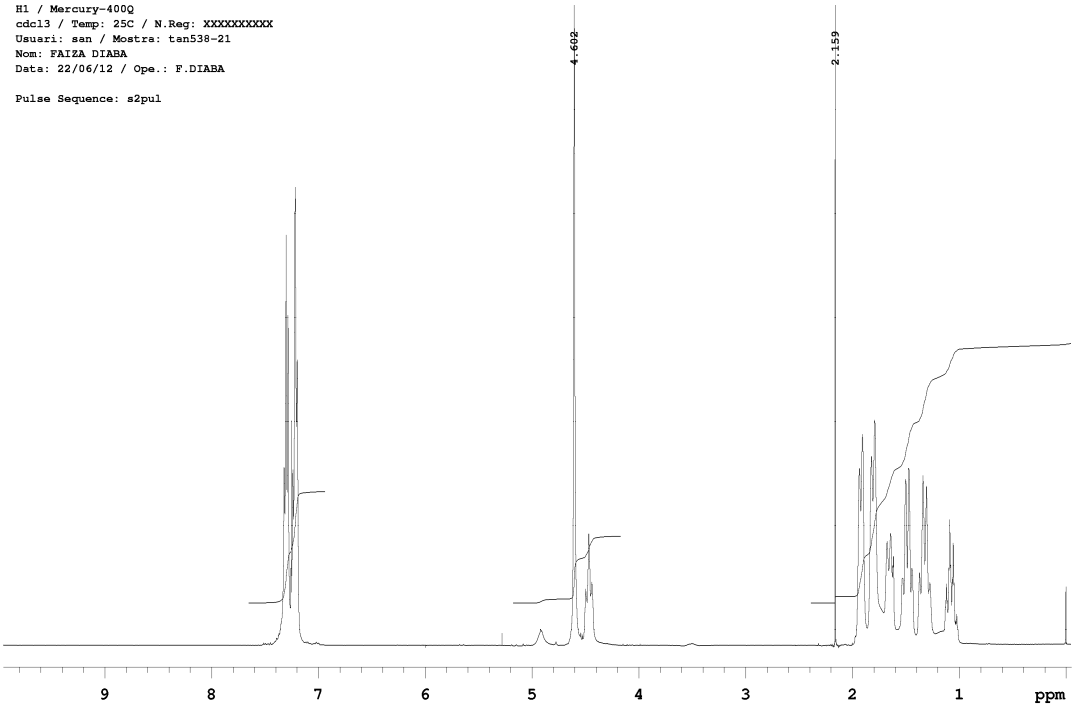

CCl3
O
N

1d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Data: 22/06/12 / Ope.: F.DIABA
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7
6
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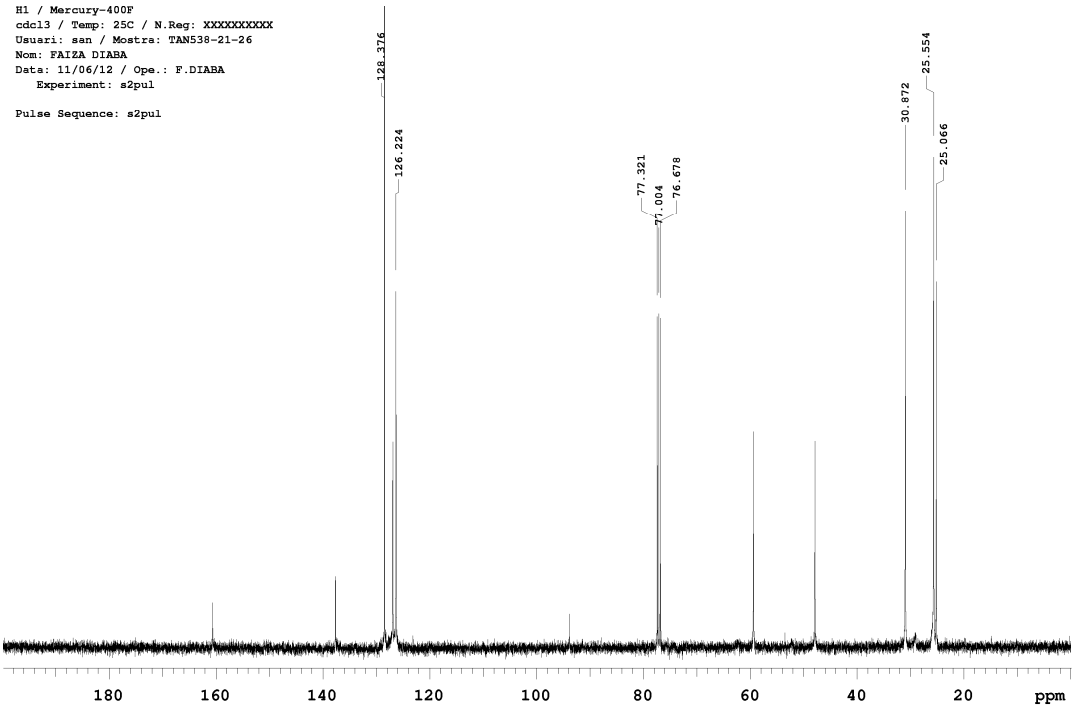
4
3
2
1
ppm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60
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20
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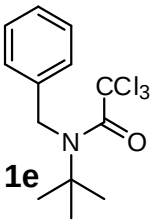
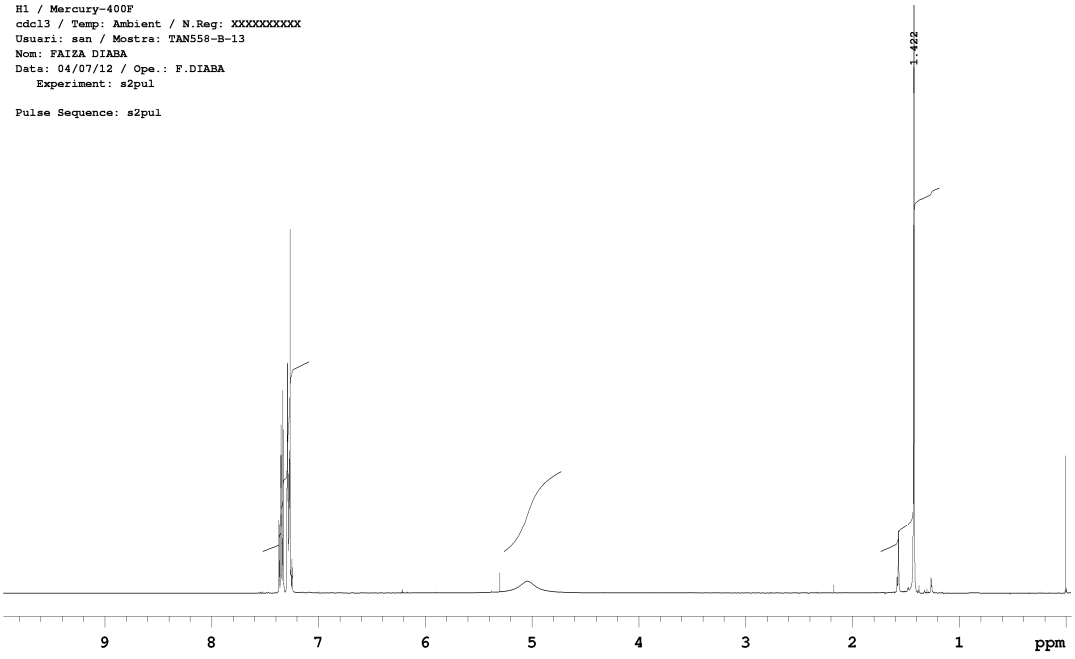

CCl3
N
O

1e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7
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3
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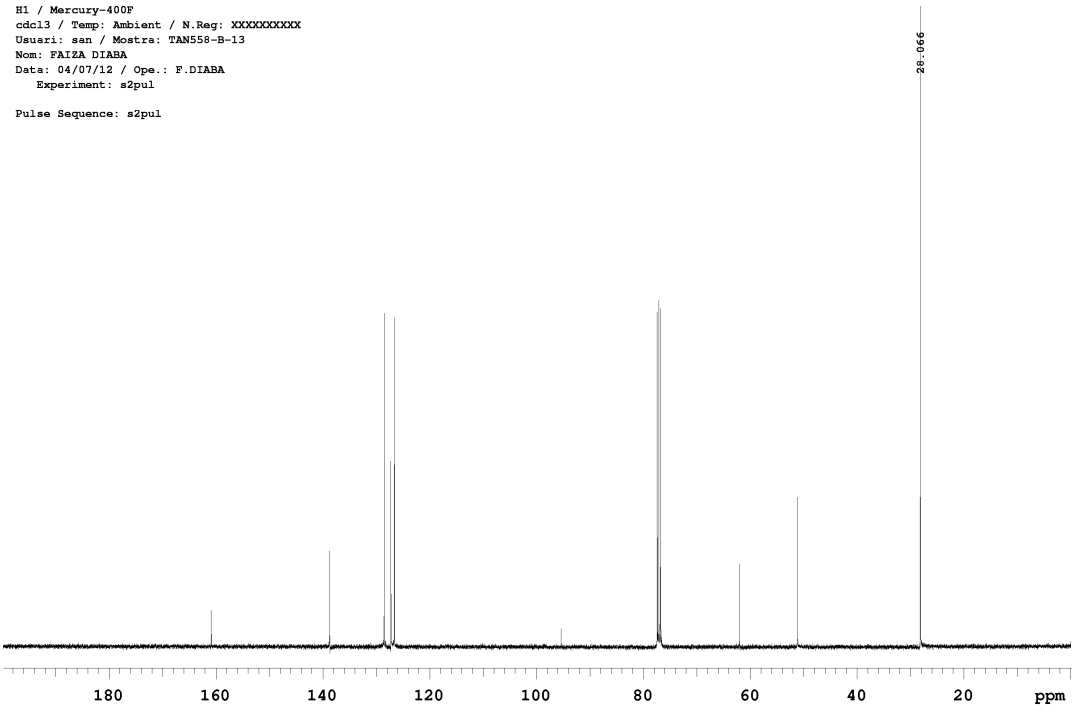
ppm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Usuari: san / Mostra: TAN558-B-13
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Data: 04/07/12 / Ope.: F.DIABA
Experiment: s2pul
Pulse Sequence: s2pul
28.066
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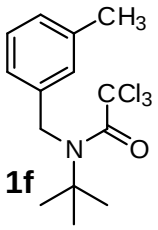
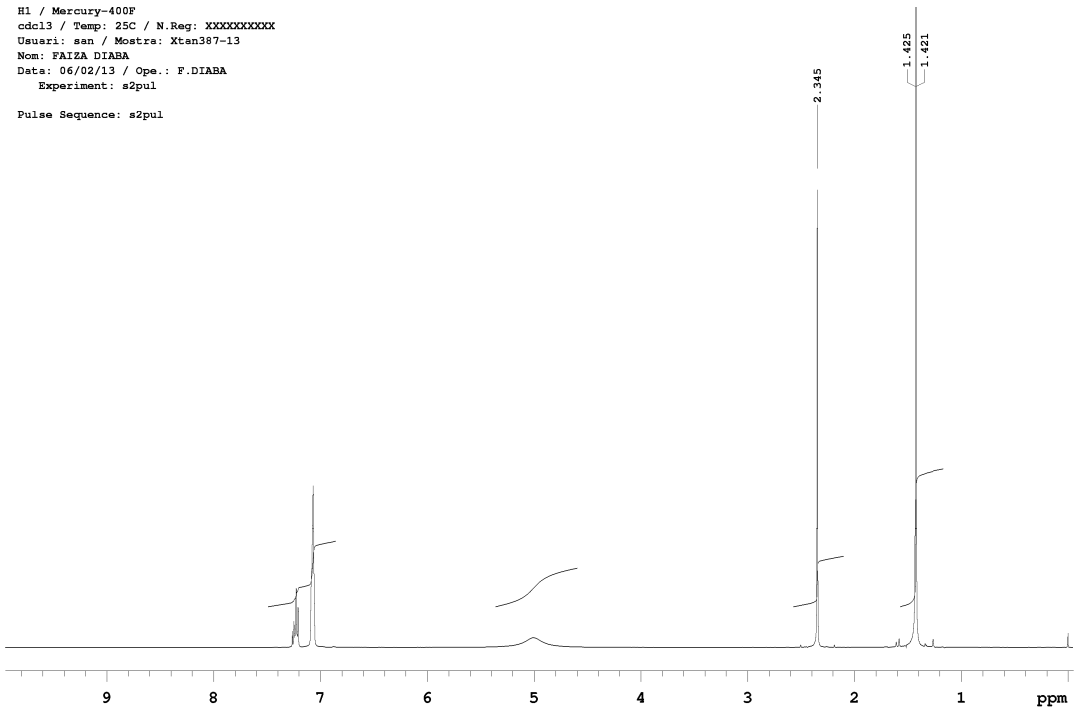
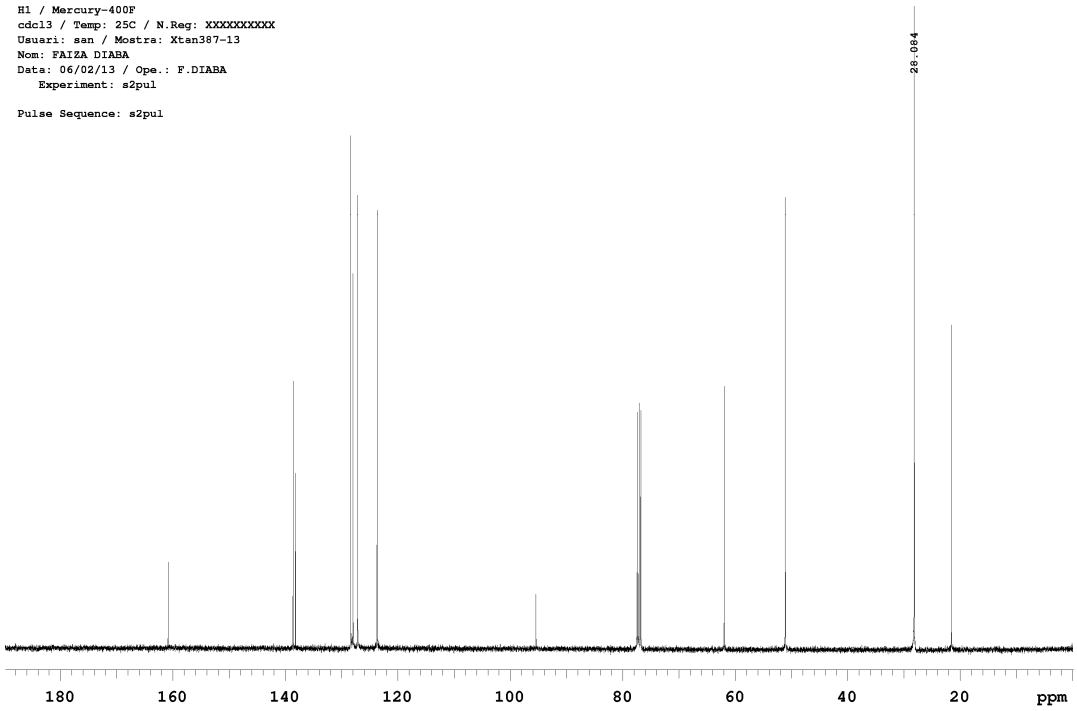
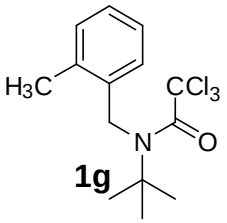
160
140
120
100
80
60
40
20
ppm


CH3
CCl3
N
O

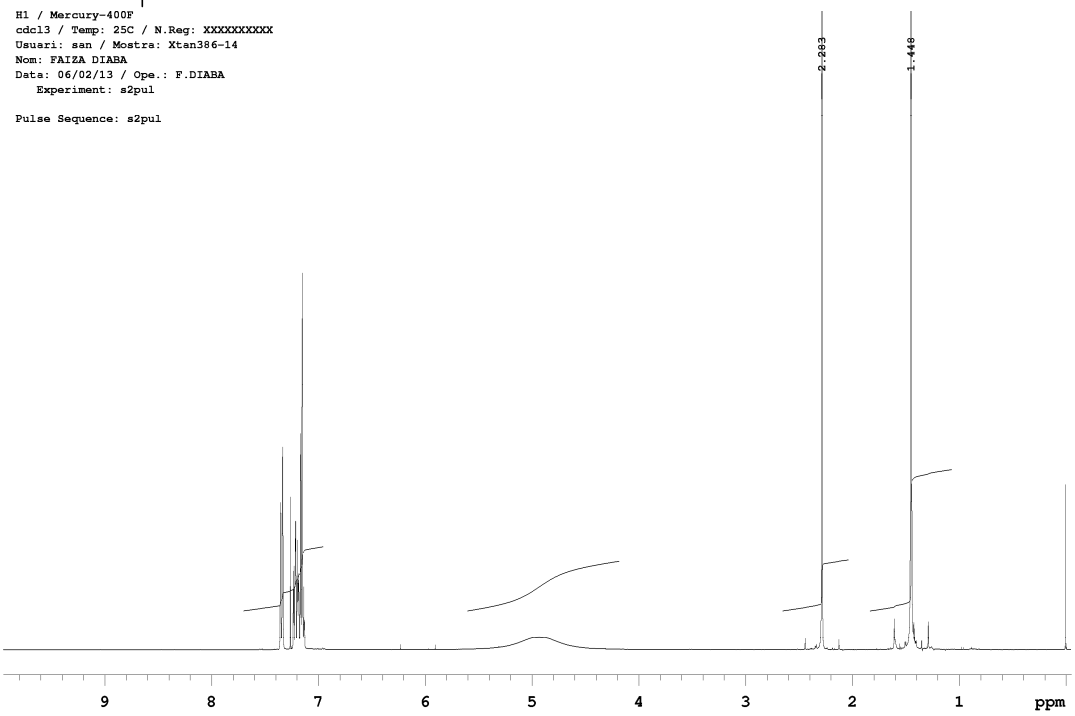
1f

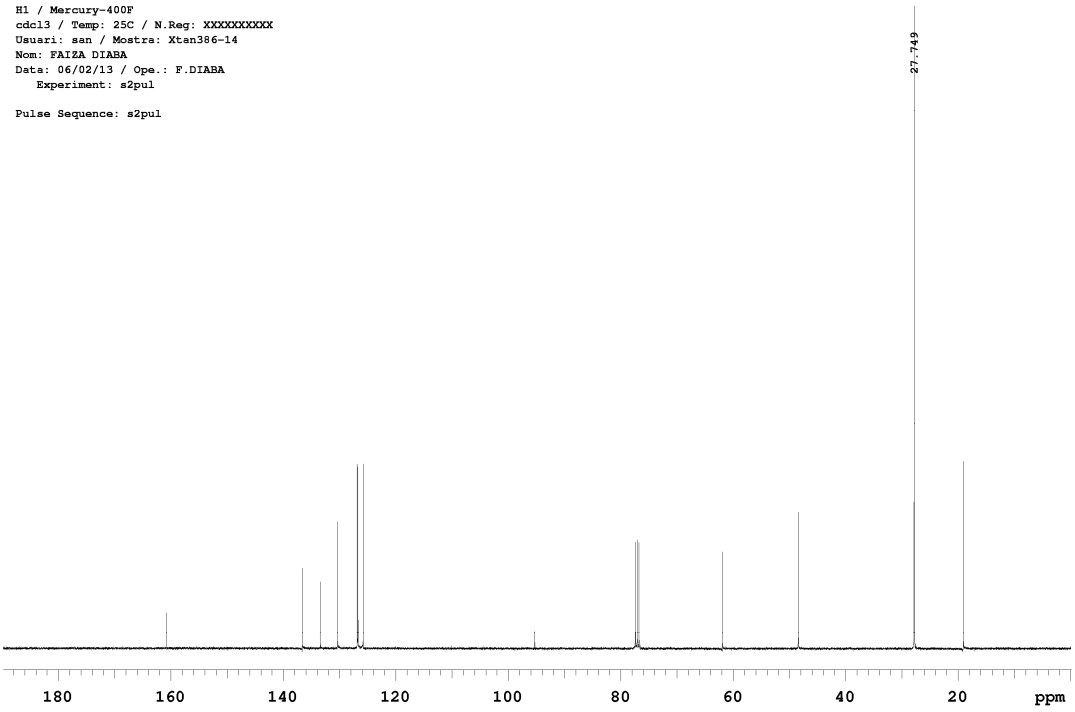

H1 / Mercury-400F
cdcl3 / Temp: 25C / N.Reg: XXXXXXXXXX
Usuari: san / Mostra: Xtan387-13
Nom: FAIZA DIABA
Data: 06/02/13 / Ope.: F.DIABA
Experiment: s2pul
Pulse Sequence: s2pul
2.345
1.425
1.421
9
8
7
6
5
4
3
2
1
ppm

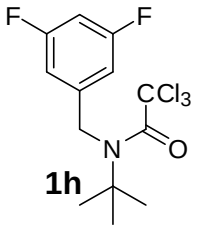

H1 / Mercury-400F
cdcl3 / Temp: 25C / N.Reg: XXXXXXXXXX
Usuari: san / Mostra: Xtan387-13
Nom: FAIZA DIABA
Data: 06/02/13 / Ope.: F.DIABA
Experiment: s2pul
Pulse Sequence: s2pul
28.084
180
160
140
120
100
80
60
40
20
ppm


H3C
CCl3
N
O

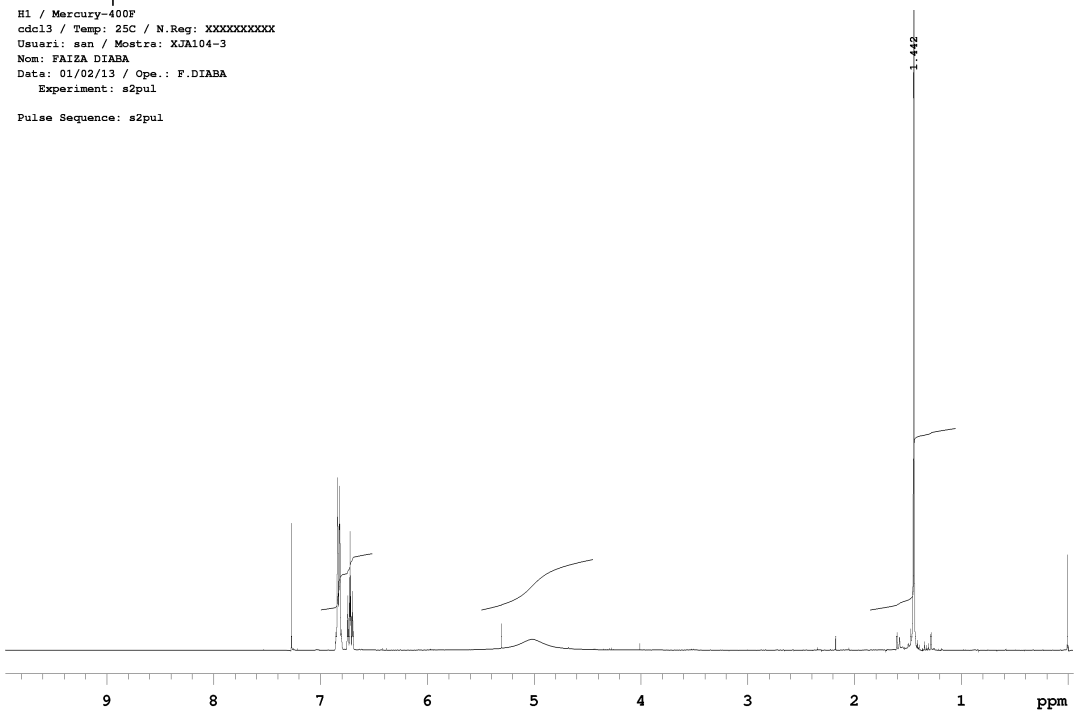
1g

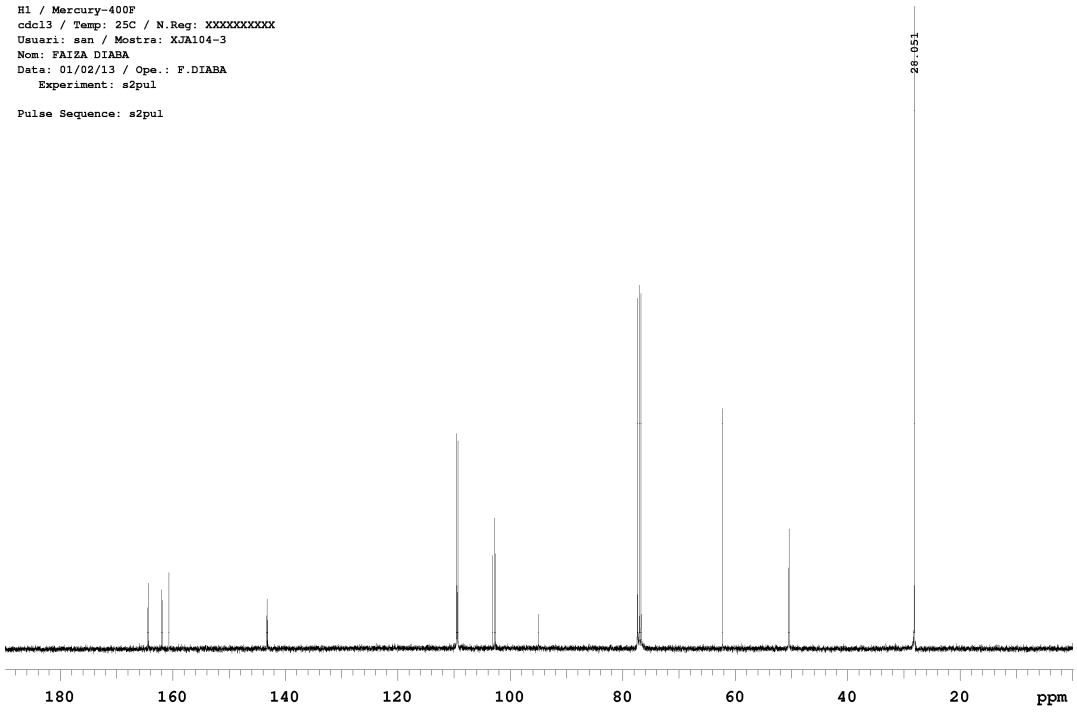

H1 / Mercury-400F
cdcl3 / Temp: 25C / N.Reg: XXXXXXXXXX
Usuari: san / Mostra: Xtan386-14
Nom: FAIZA DIABA
Data: 06/02/13 / Ope.: F.DIABA
Experiment: s2pul
Pulse Sequence: s2pul
2.283
1.448
9
8
7
6
5
4
3
2
1
ppm

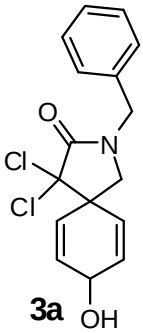

H1 / Mercury-400F
cdcl3 / Temp: 25C / N.Reg: XXXXXXXXXX
Usuari: san / Mostra: Xtan386-14
Nom: FAIZA DIABA
Data: 06/02/13 / Ope.: F.DIABA
Experiment: s2pul
Pulse Sequence: s2pul
27.749
180
160
140
120
100
80
60
40
20
ppm


F
F
CCl3
N
O

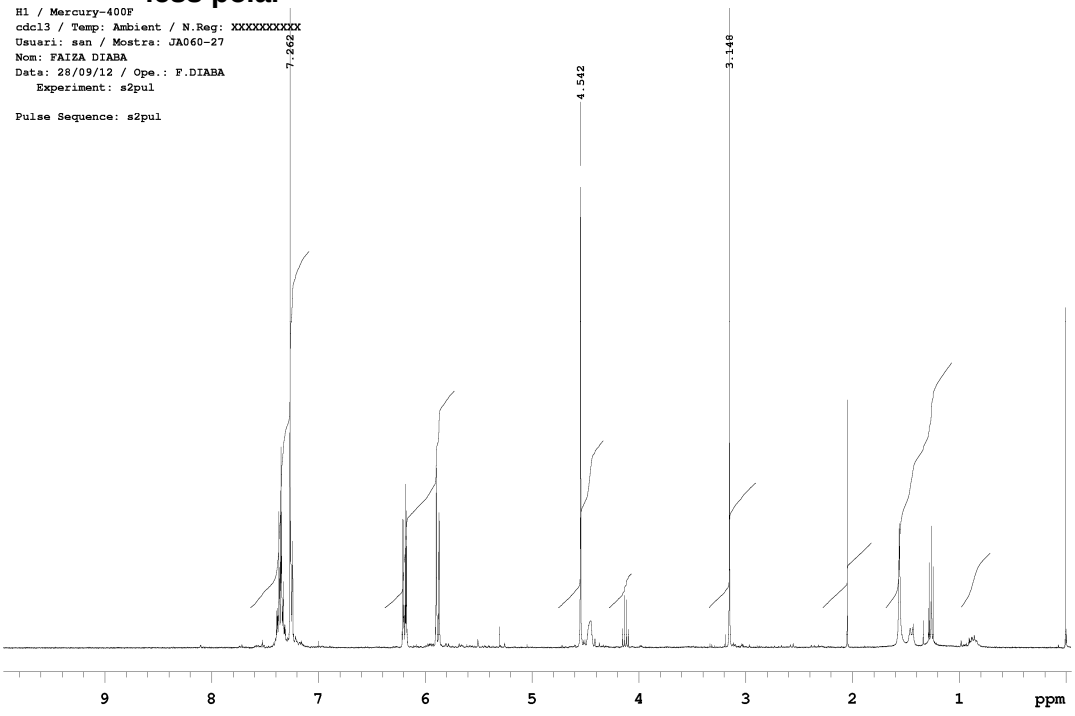
1h

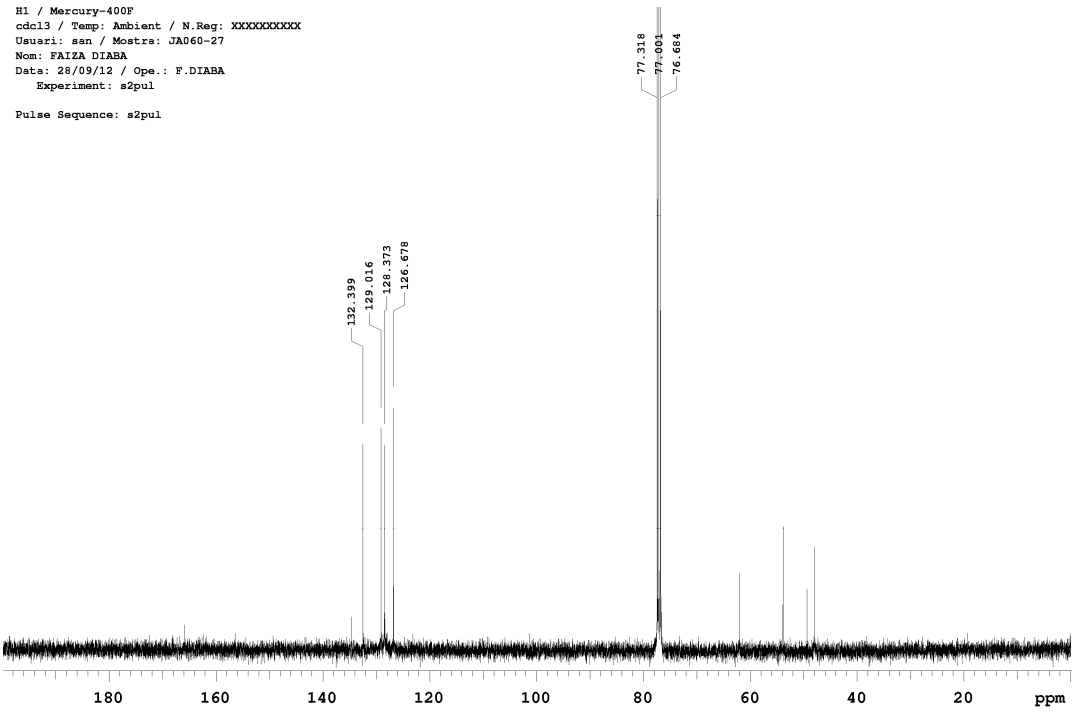

H1 / Mercury-400F
cdcl3 / Temp: 25C / N.Reg: XXXXXXXXXX
Usuari: san / Mostra: XJA104-3
Nom: FAIZA DIABA
Data: 01/02/13 / Ope.: F.DIABA
Experiment: s2pul
Pulse Sequence: s2pul
1.442
9
8
7
6
5
4
3
2
1
ppm

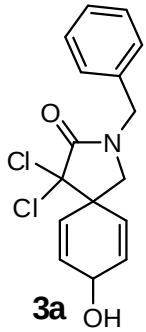

H1 / Mercury-400F
cdcl3 / Temp: 25C / N.Reg: XXXXXXXXXX
Usuari: san / Mostra: XJA104-3
Nom: FAIZA DIABA
Data: 01/02/13 / Ope.: F.DIABA
Experiment: s2pul
Pulse Sequence: s2pul
28.051
180
160
140
120
100
80
60
40
20
ppm



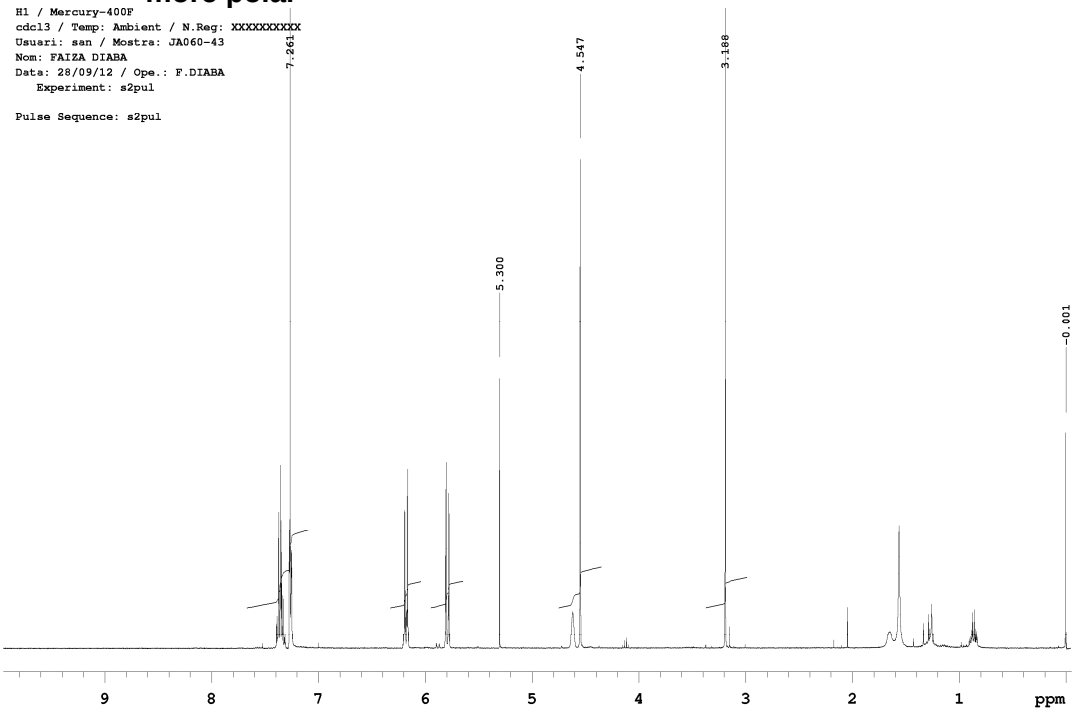
3a **less polar**

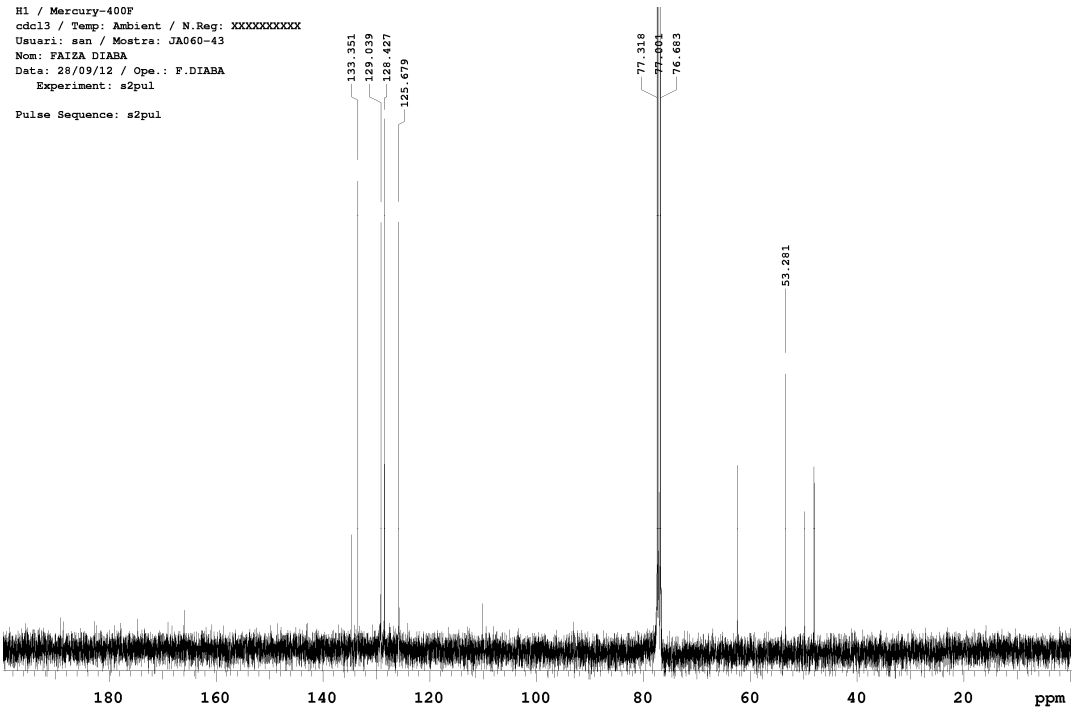


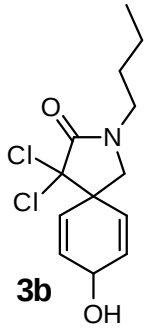




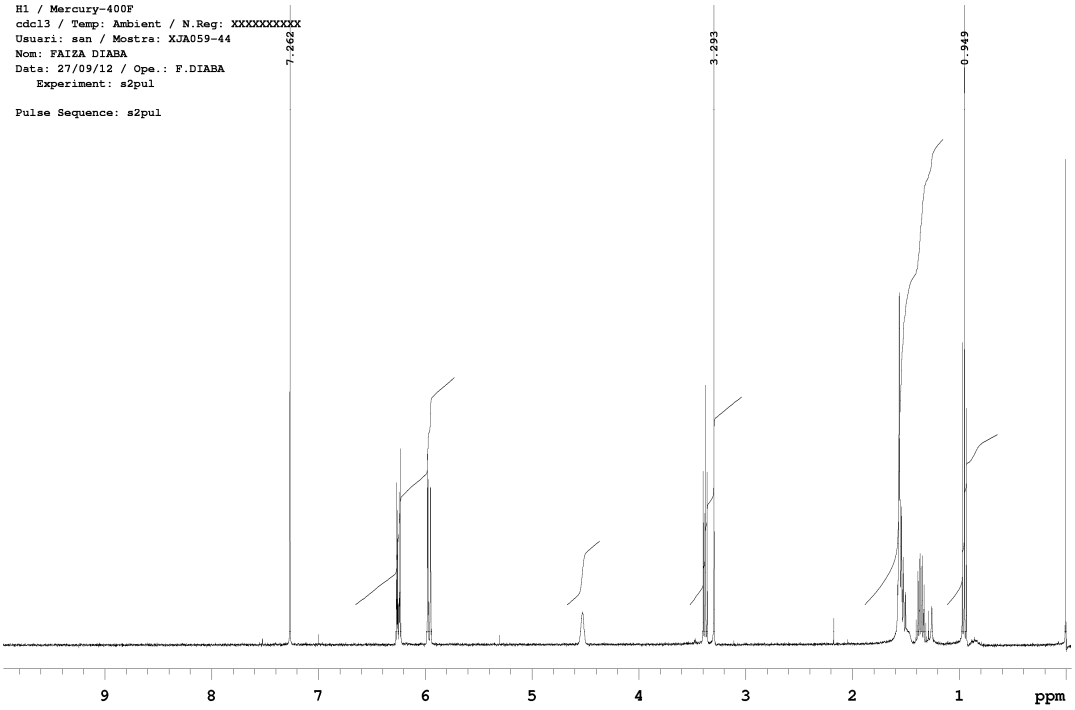
3a **more polar**

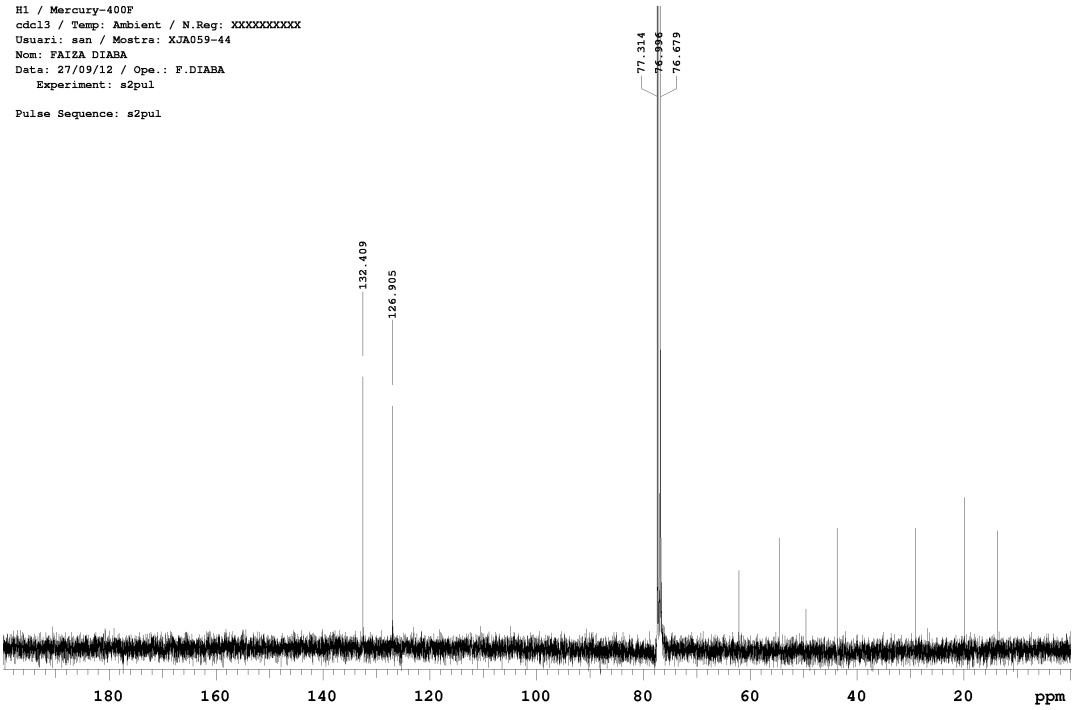


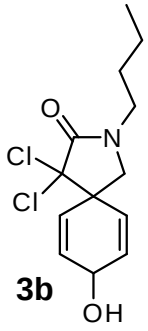




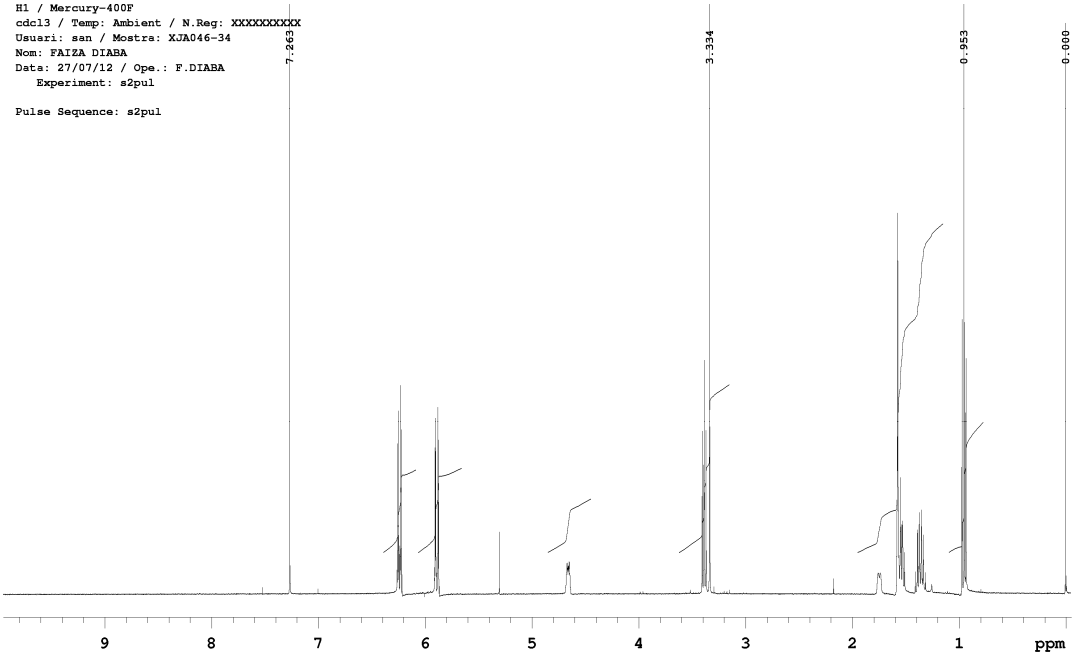
3b **Less polar**

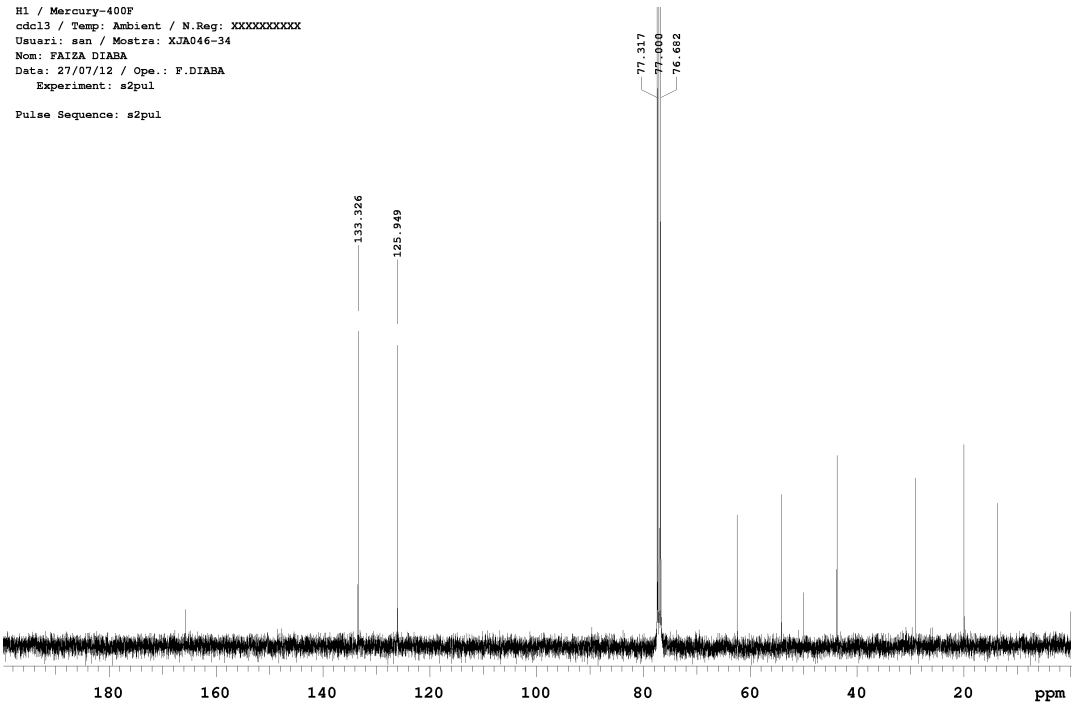


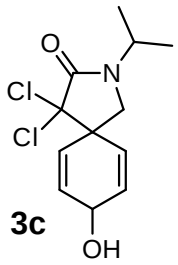




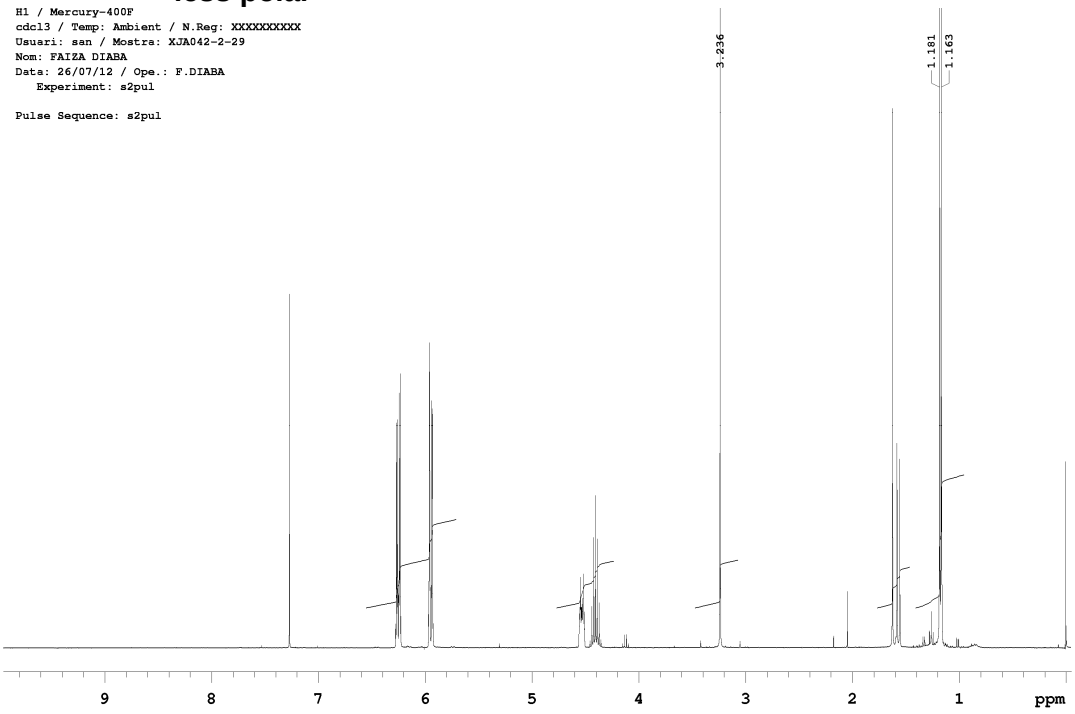
3b **More polar**

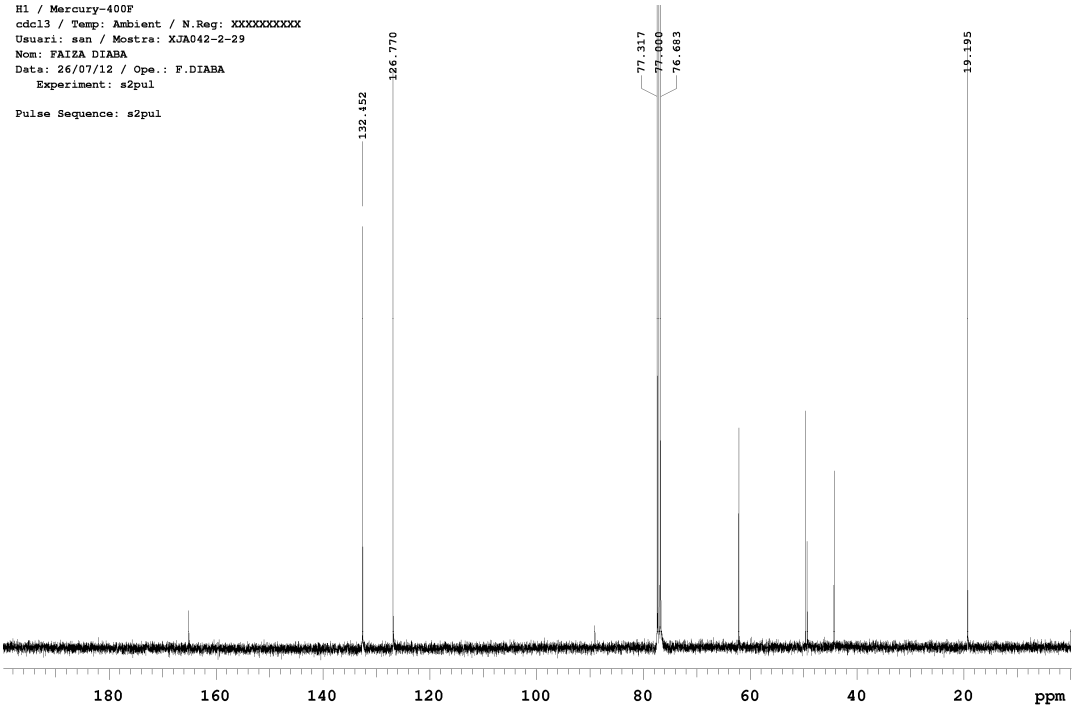


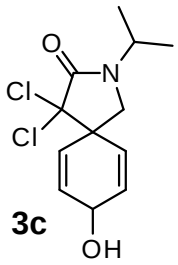




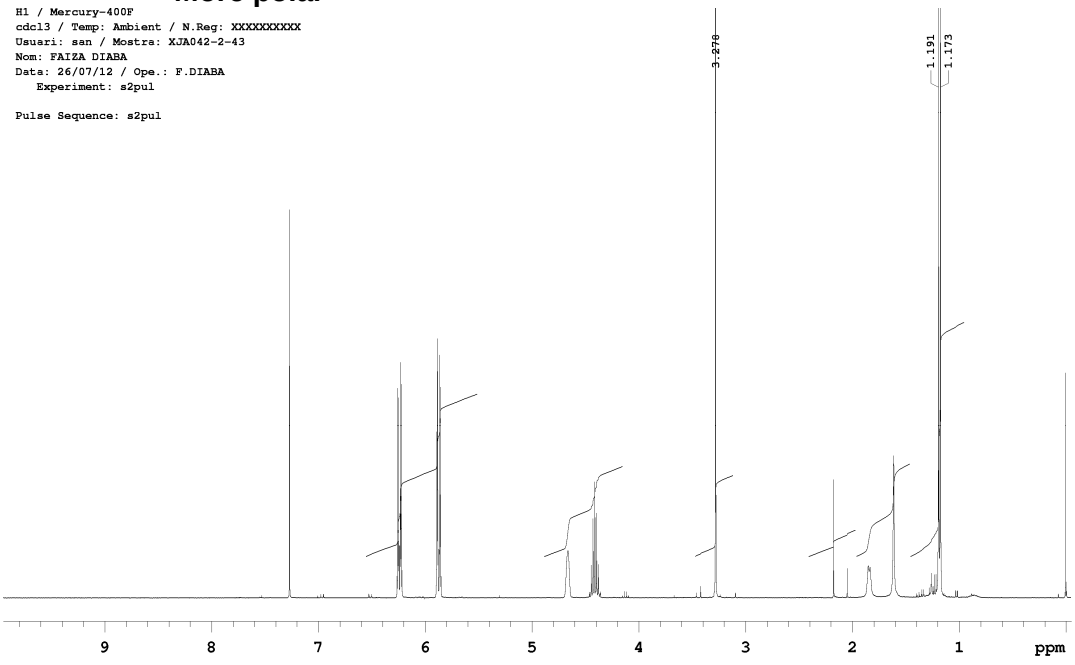
3c **less polar**

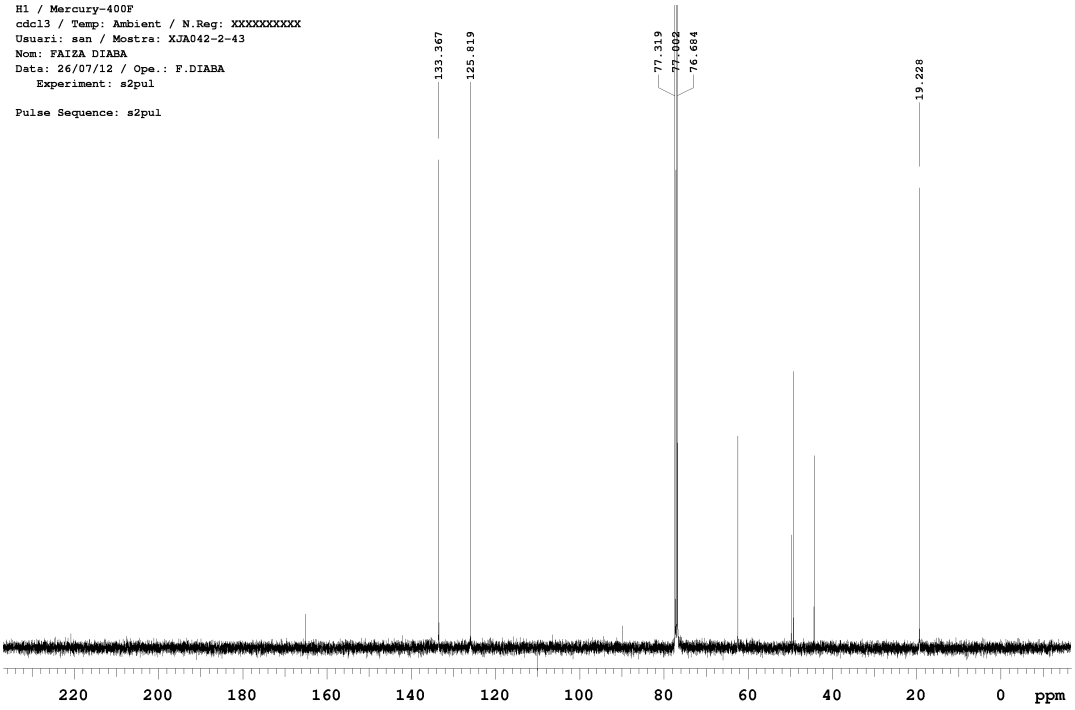


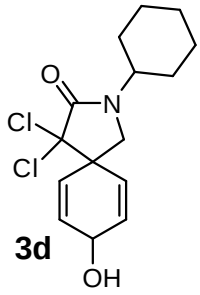




3c **More polar**

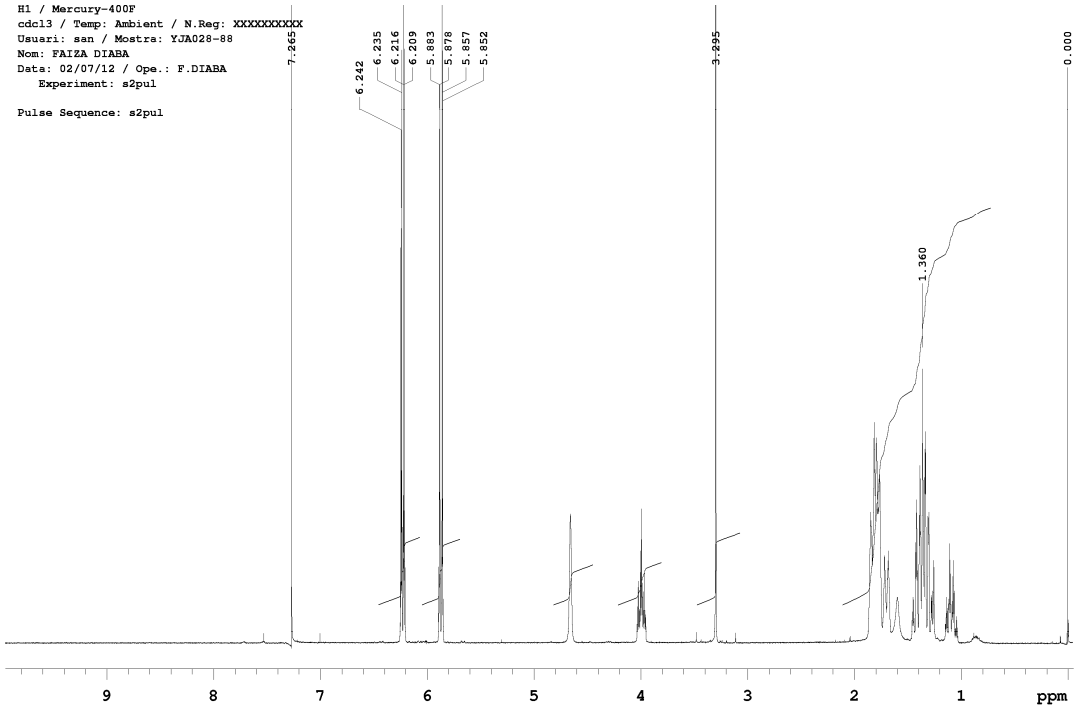


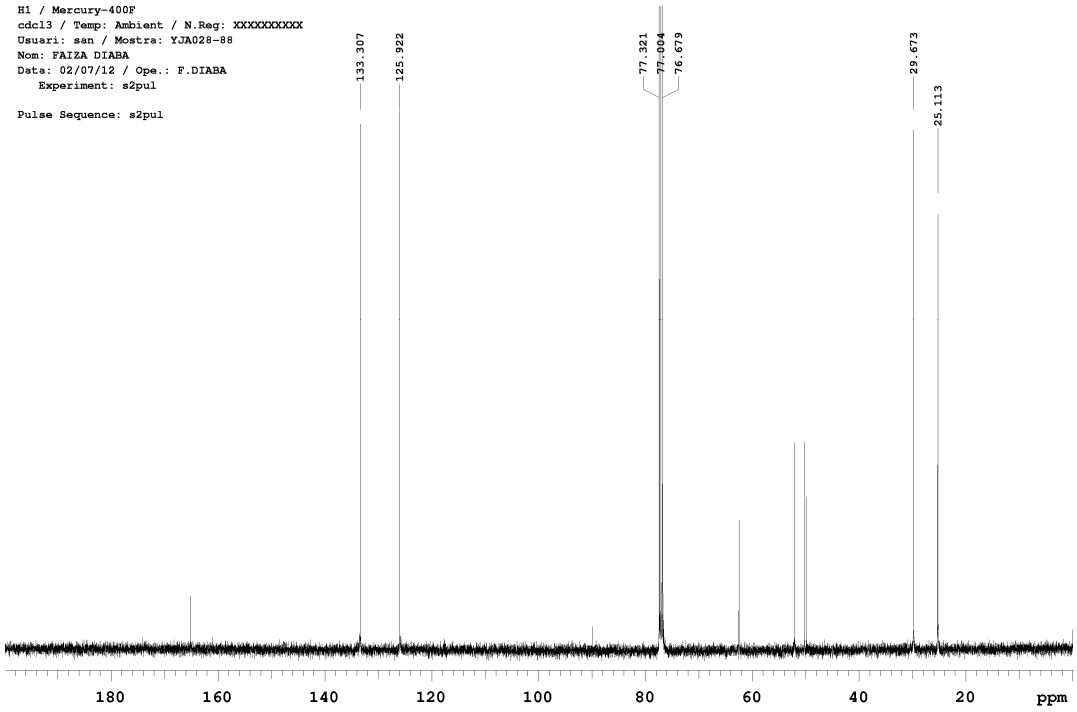


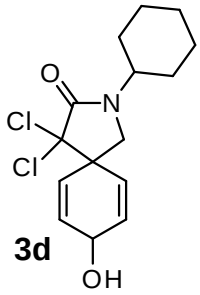


3d

Less polar

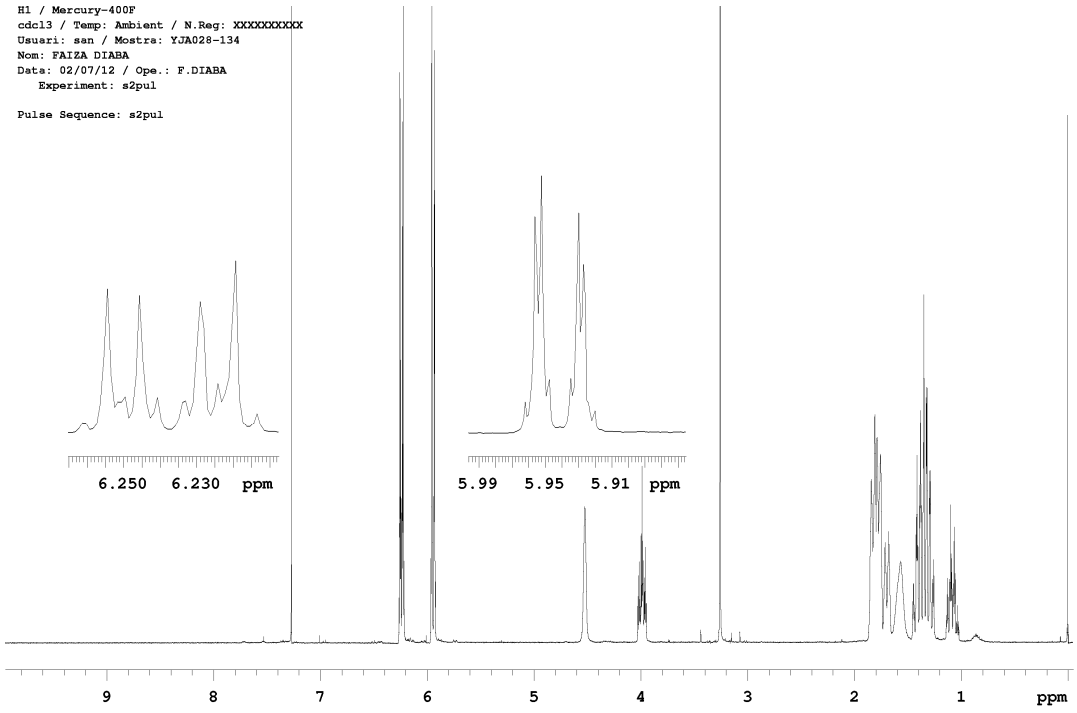


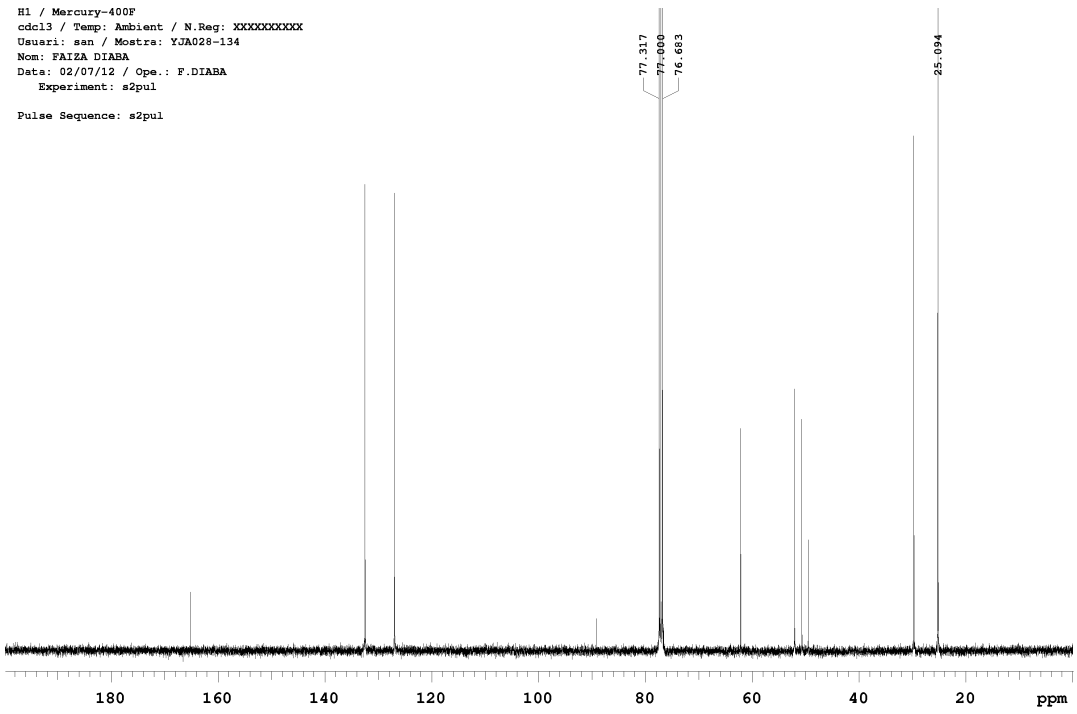


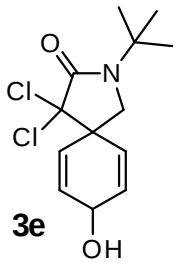


3d

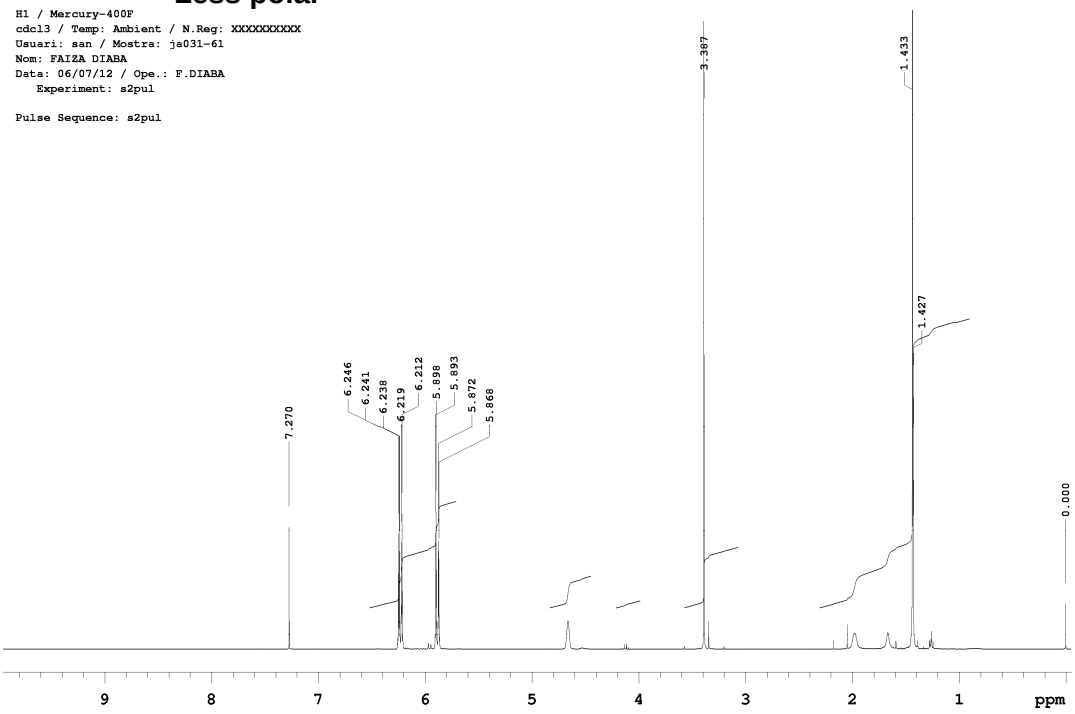
More polar

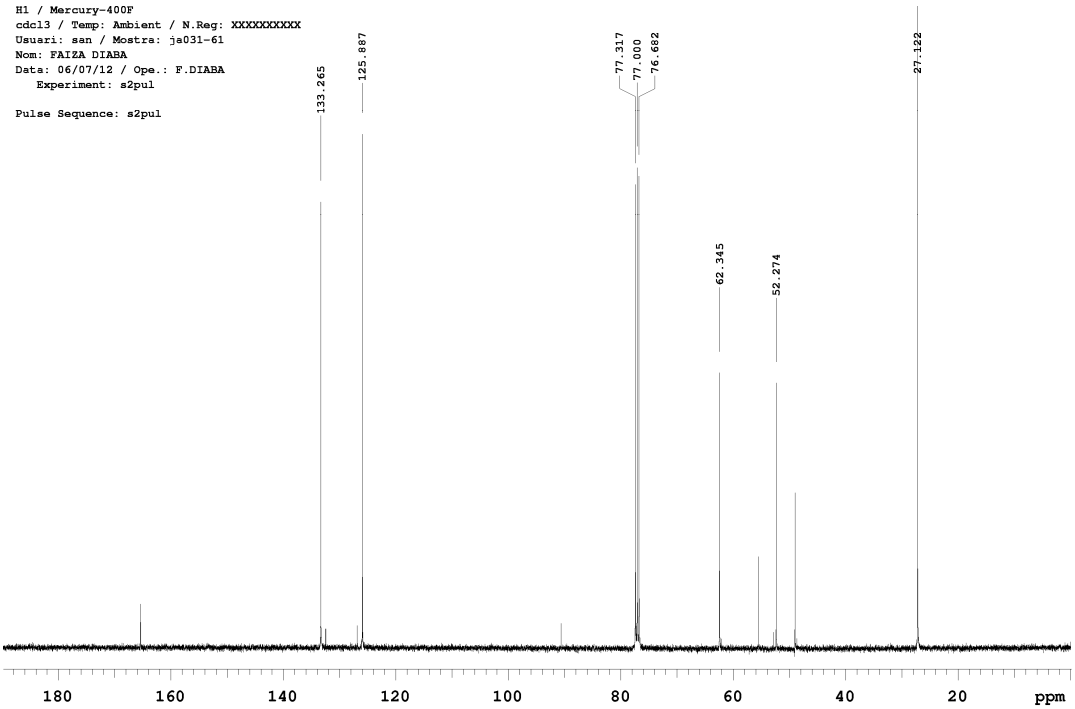


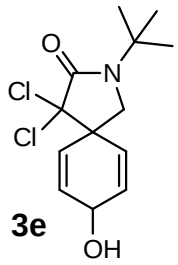




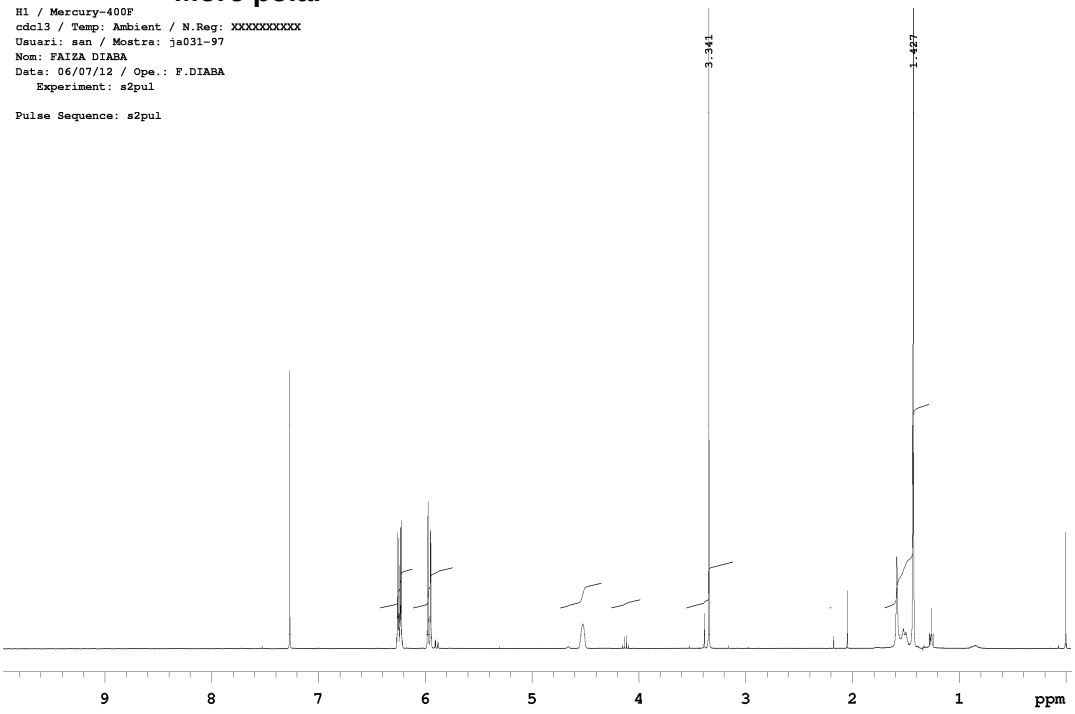
3e **Less polar**

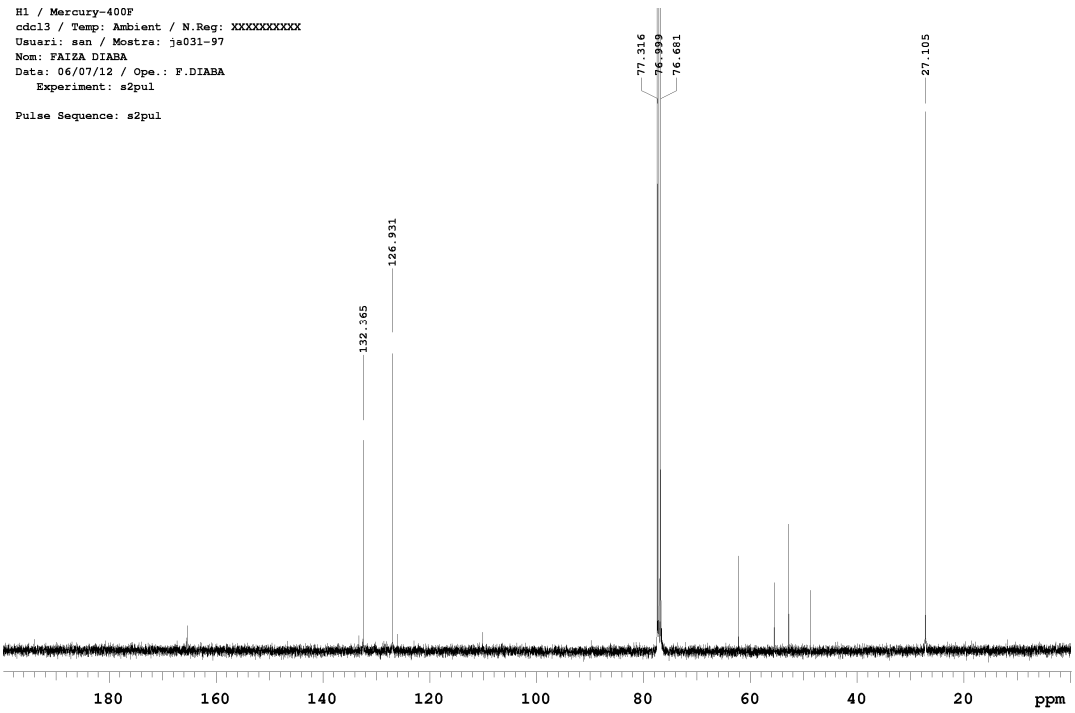


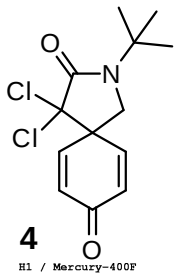




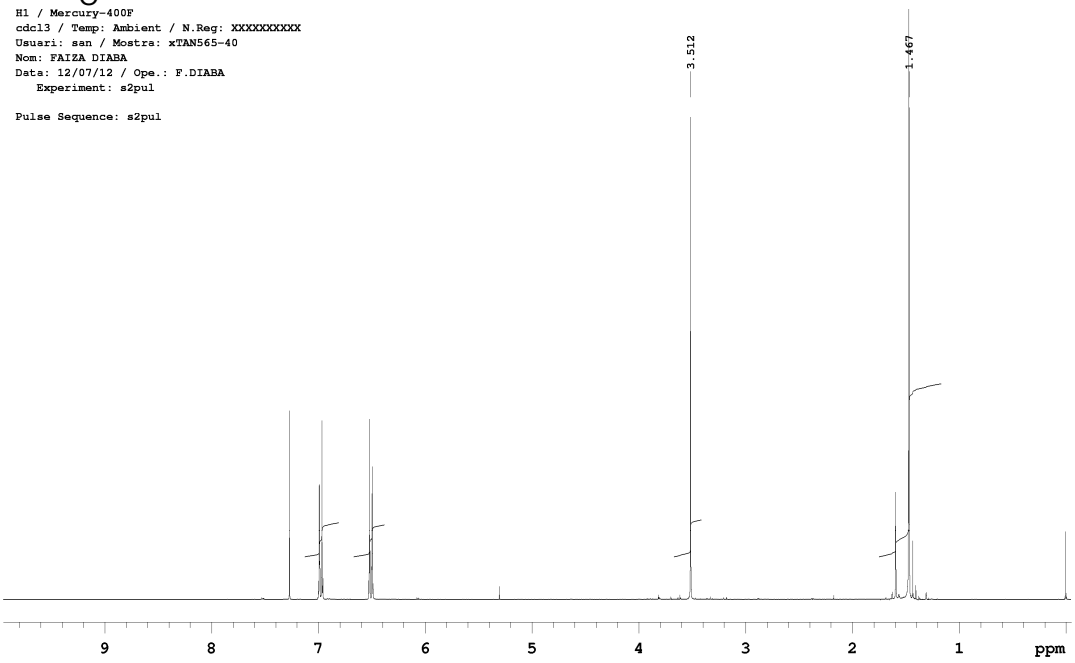
3e **More polar**

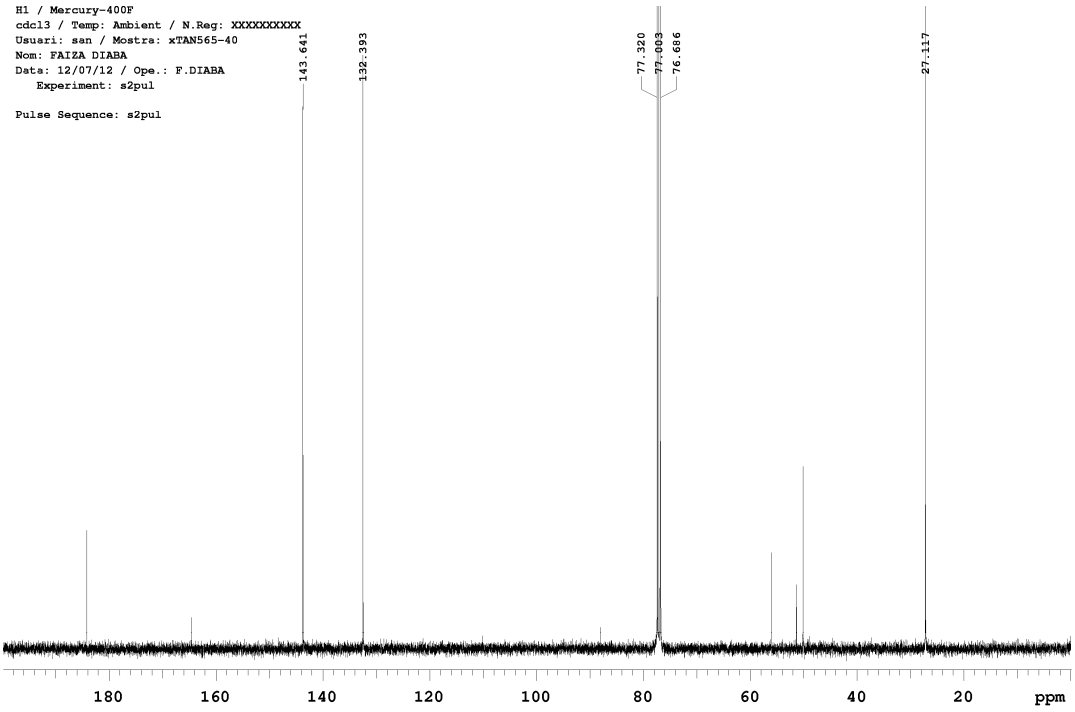


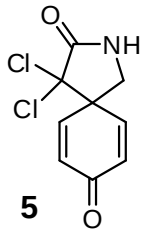



O
N
Cl
Cl
O

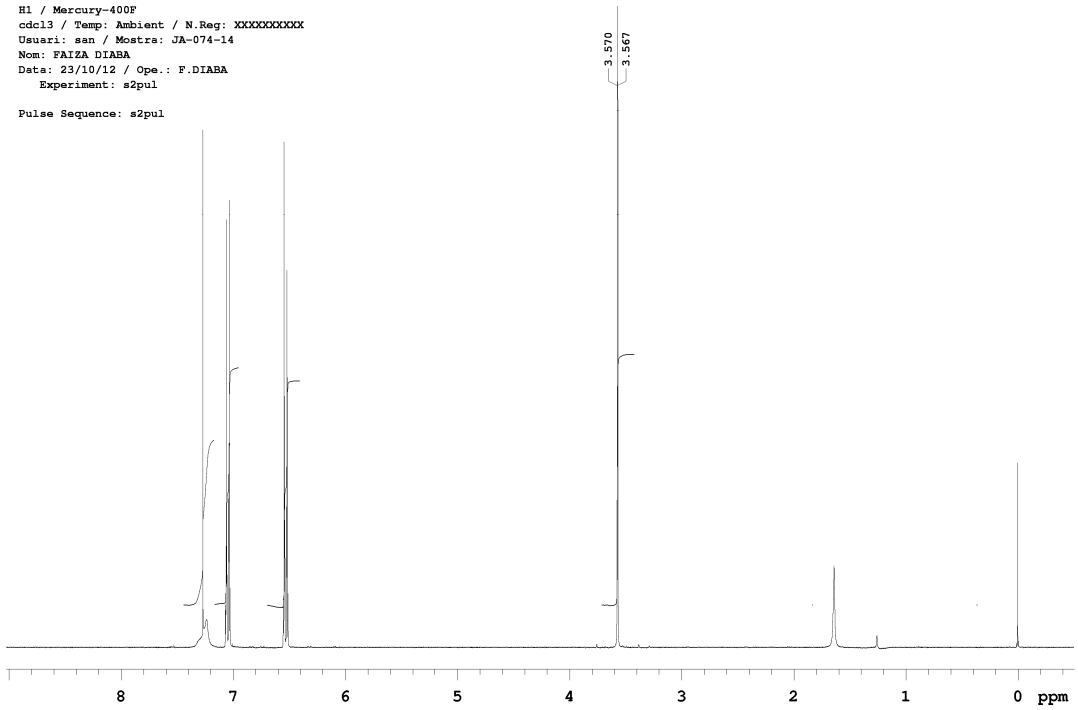
4

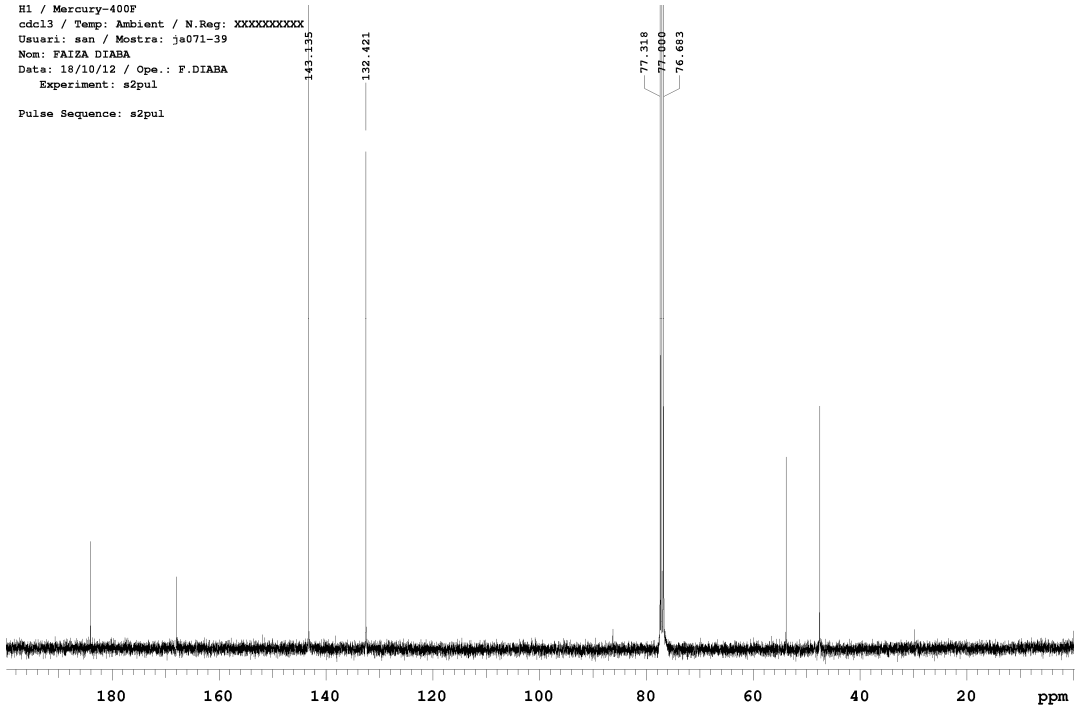

H1 / Mercury-400F
cdcl3 / Temp: Ambient / N.Reg: XXXXXXXXXX
Usuari: san / Mostra: xTAN565-40
Nom: FAIZA DIABA
Data: 12/07/12 / Ope.: F.DIABA
Experiment: s2pul
Pulse Sequence: s2pul
3.512
1.467
9
8
7
6
5
4
3
2
1
ppm

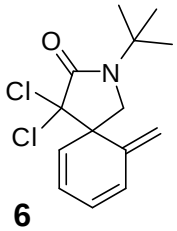

H1 / Mercury-400F
cdcl3 / Temp: Ambient / N.Reg: XXXXXXXXXX
Usuari: san / Mostra: xTAN565-40
Nom: FAIZA DIABA
Data: 12/07/12 / Ope.: F.DIABA
Experiment: s2pul
Pulse Sequence: s2pul
143.641
132.393
77.320
77.003
76.686
27.117
180
160
140
120
100
80
60
40
20
ppm


O
NH
Cl
Cl
O

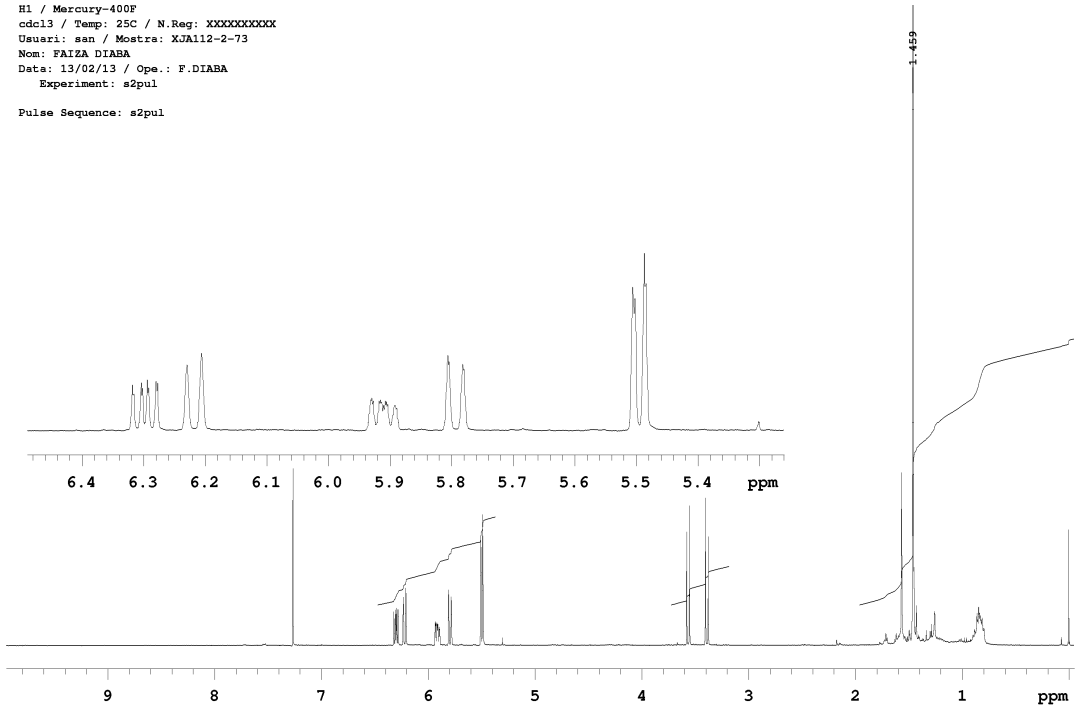
5

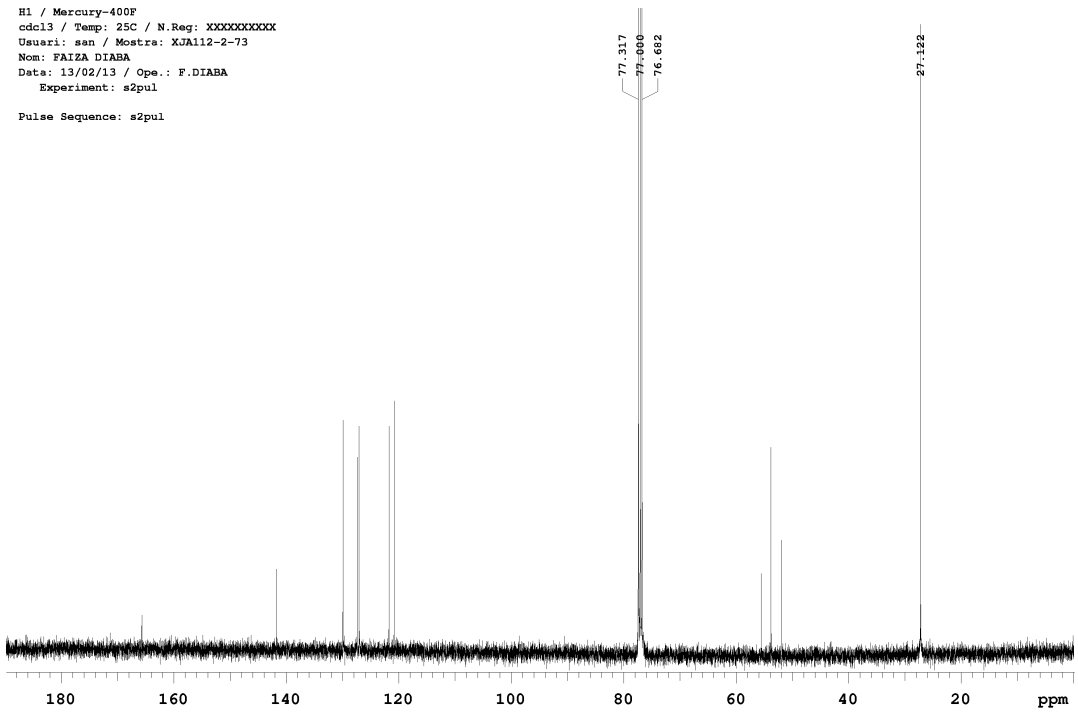

H1 / Mercury-400F
cdcl3 / Temp: Ambient / N.Reg: XXXXXXXXXX
Usuari: san / Mostra: JA-074-14
Nom: FAIZA DIABA
Data: 23/10/12 / Ope.: F.DIABA
Experiment: s2pul
Pulse Sequence: s2pul
3.570
3.567
8
7
6
5
4
3
2
1
0
ppm

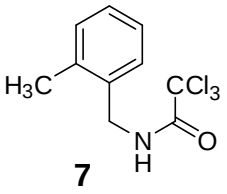

H1 / Mercury-400F
cdcl3 / Temp: Ambient / N.Reg: XXXXXXXXXX
Usuari: san / Mostra: js071-39
Nom: FAIZA DIABA
Data: 18/10/12 / Ope.: F.DIABA
Experiment: s2pul
Pulse Sequence: s2pul
143.135
132.421
77.318
77.000
76.683
180
160
140
120
100
80
60
40
20
ppm


O
N
Cl
Cl

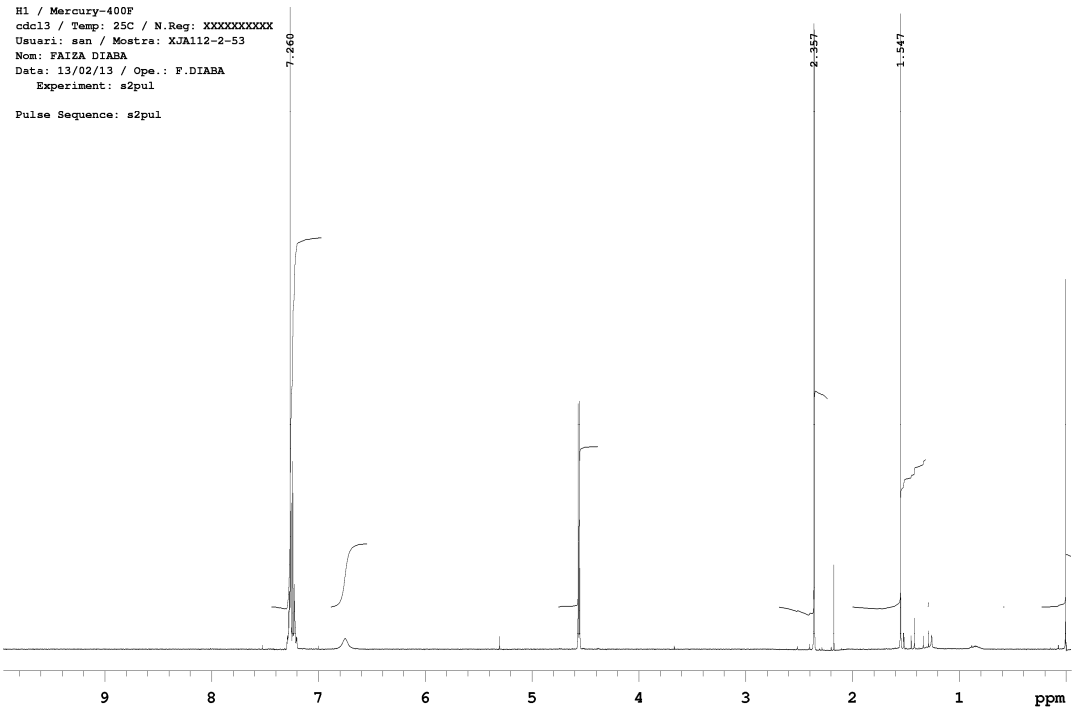
6


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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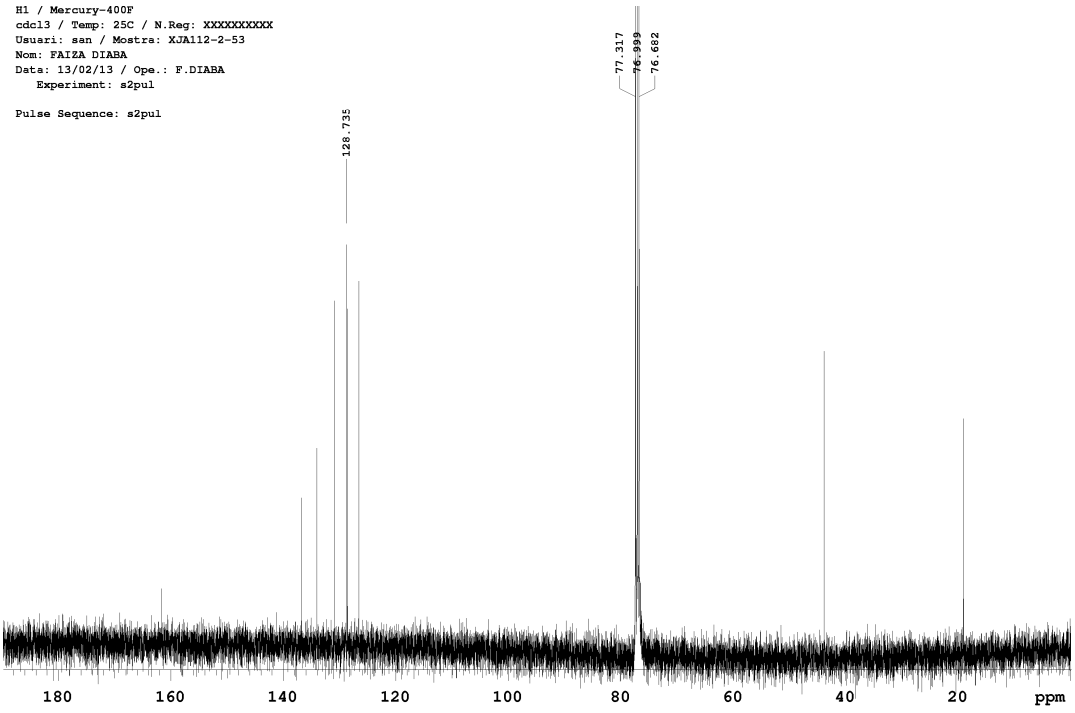
Usuari: san / Mostra: XJA112-2-53
Nom: FAIZA DIABA
Data: 13/02/13 / Ope.: F.DIABA
Experiment: s2pul
Pulse Sequence: s2pul
7.260
2.357
1.547
9
8
7
6
5
4
3
2
1
ppm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Nom: FAIZA DIABA
Data: 13/02/13 / Ope.: F.DIABA
Experiment: s2pul
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76.999
76.682
128.735
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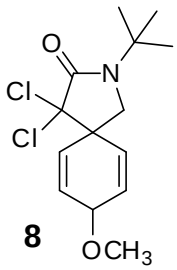
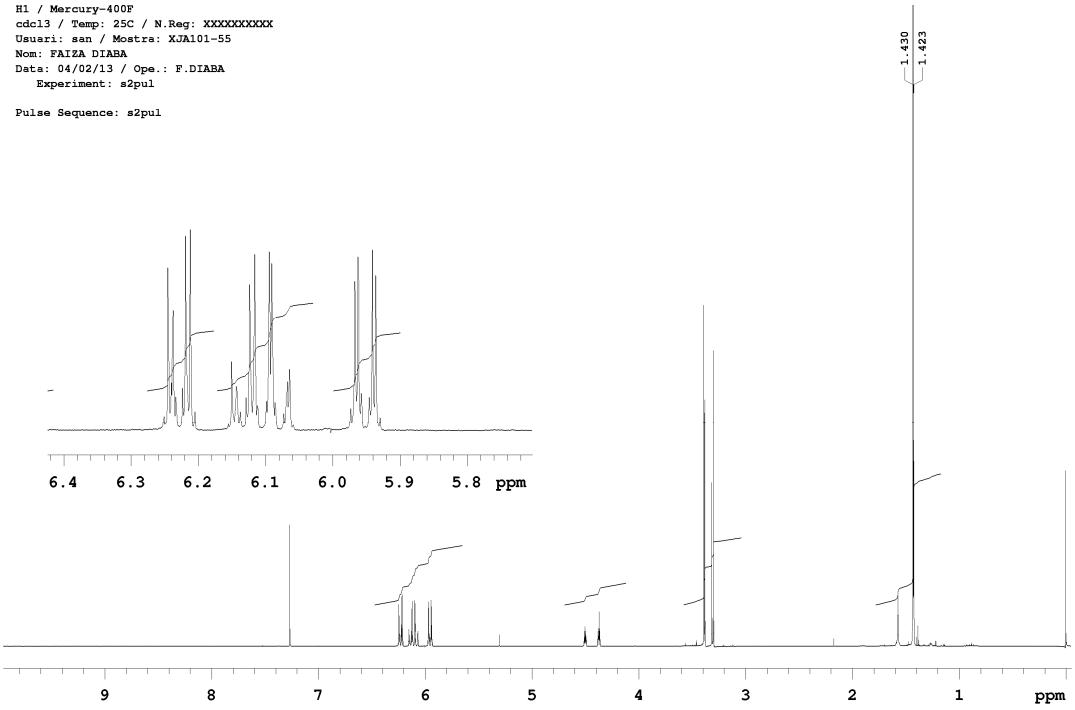
160
140
120
100
80
60
40
20
ppm


O
N
Cl
Cl
OCH3

8


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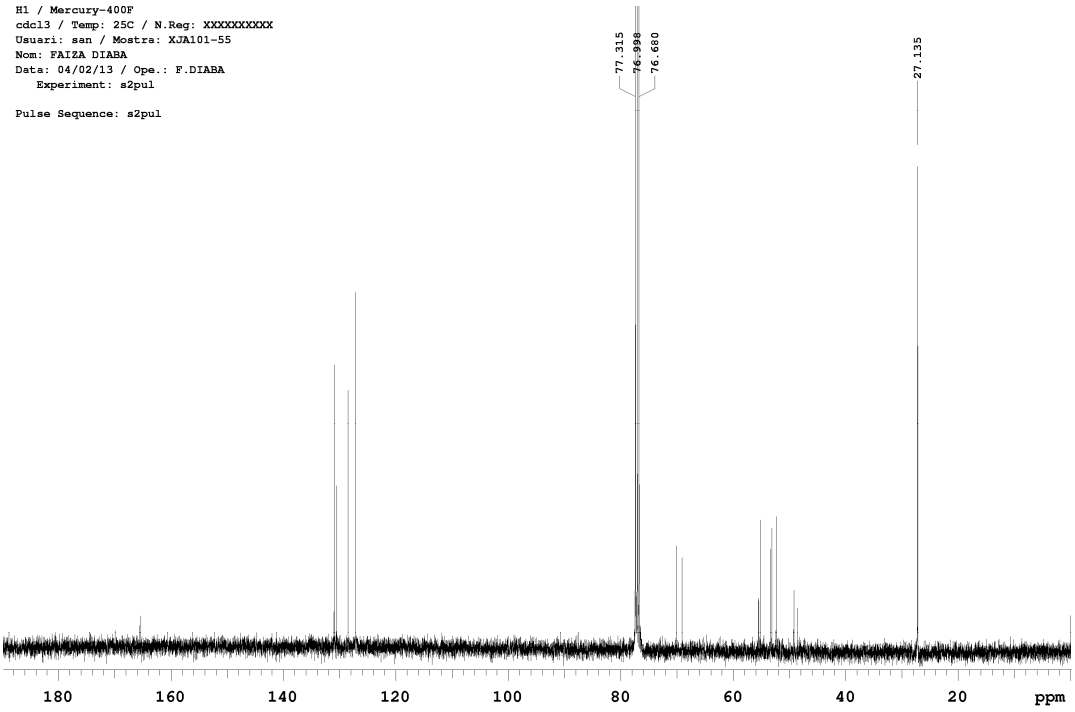
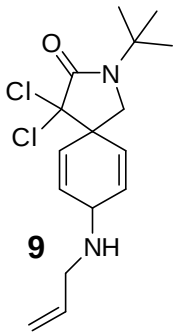
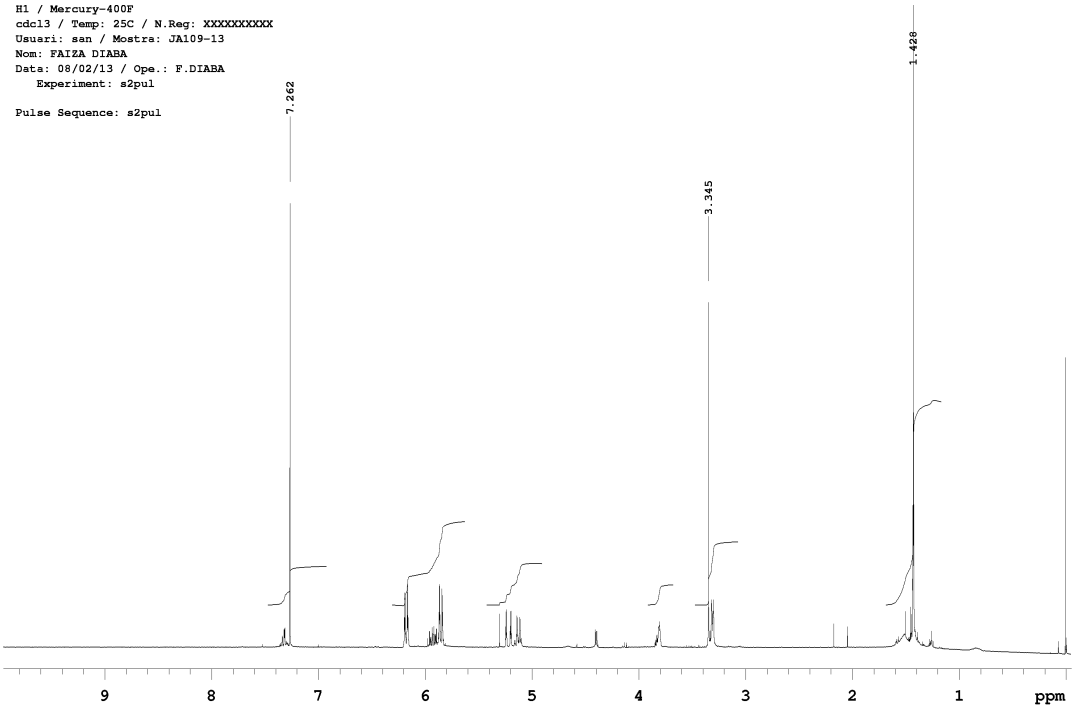
Usuari: san / Mostra: XJA101-55
Nom: FAIZA DIABA
Data: 04/02/13 / Ope.: F.DIABA
Experiment: s2pul
Pulse Sequence: s2pul
1.430
1.423
6.4 6.3 6.2 6.1 6.0 5.9 5.8 ppm
9 8 7 6 5 4 3 2 1 ppm


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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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
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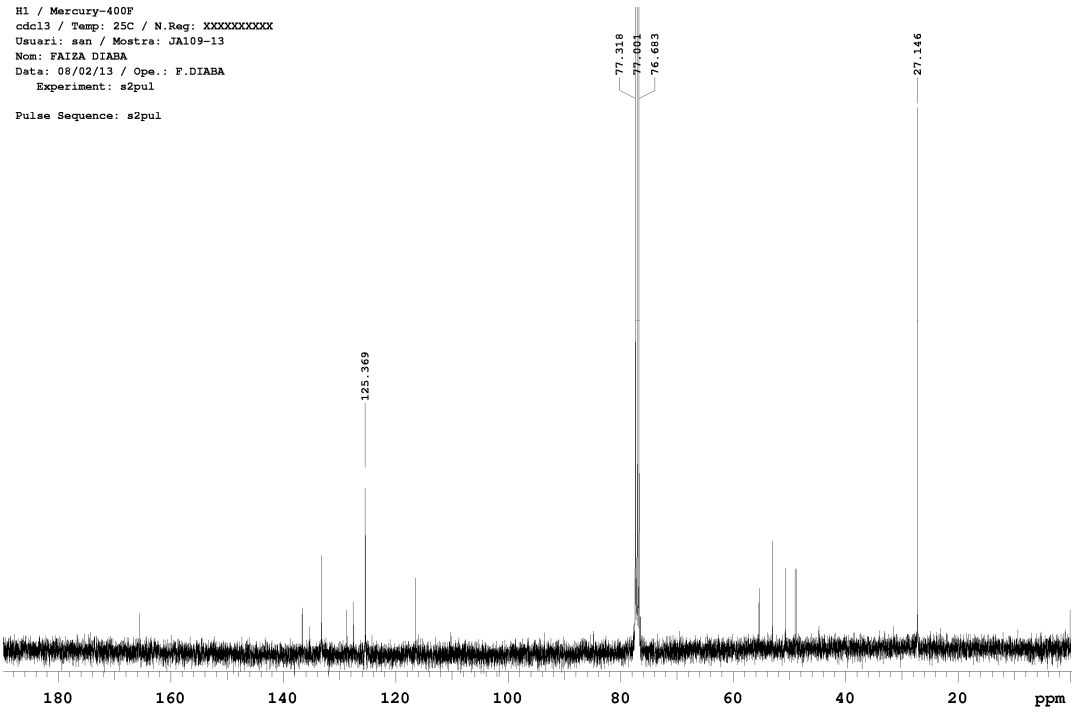
3.345
1.428
9
8
7
6
5
4
3
2
1
ppm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Usuari: san / Mostra: JA109-13
Nom: FAIZA DIABA
Data: 08/02/13 / Ope.: F.DIABA
Experiment: s2pul
Pulse Sequence: s2pul
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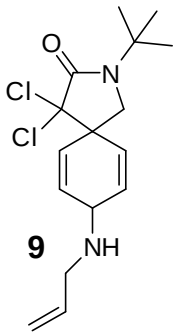
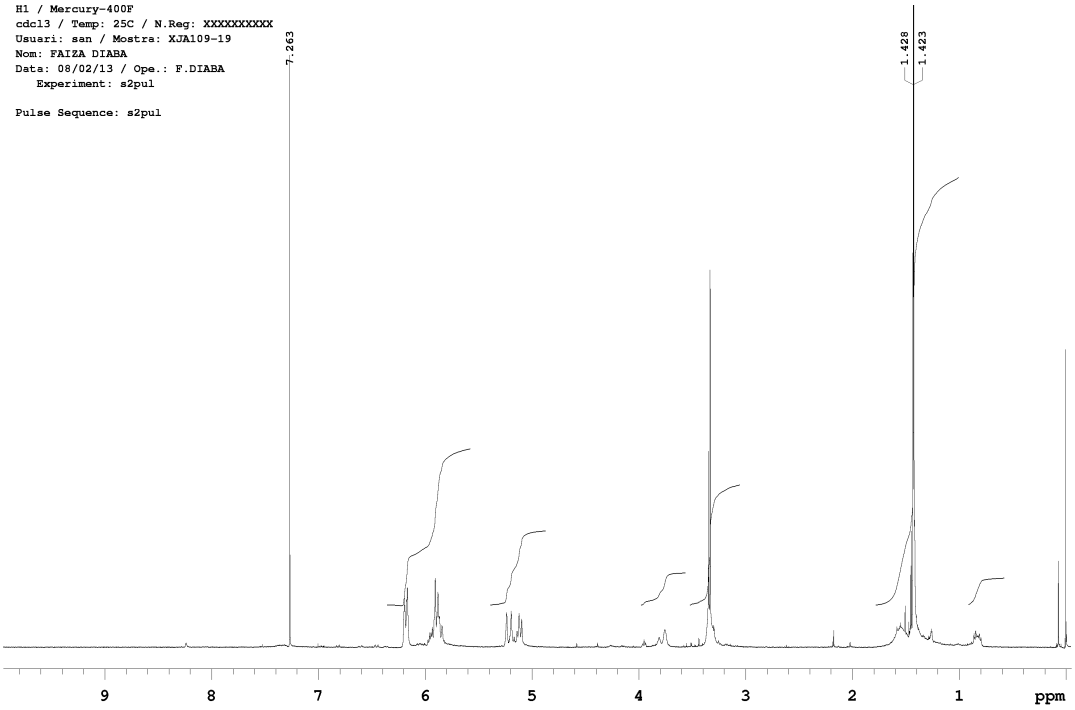
77.001
76.683
27.146
125.369
180
160
140
120
100
80
60
40
20
ppm


O
N
Cl
Cl
9
NH

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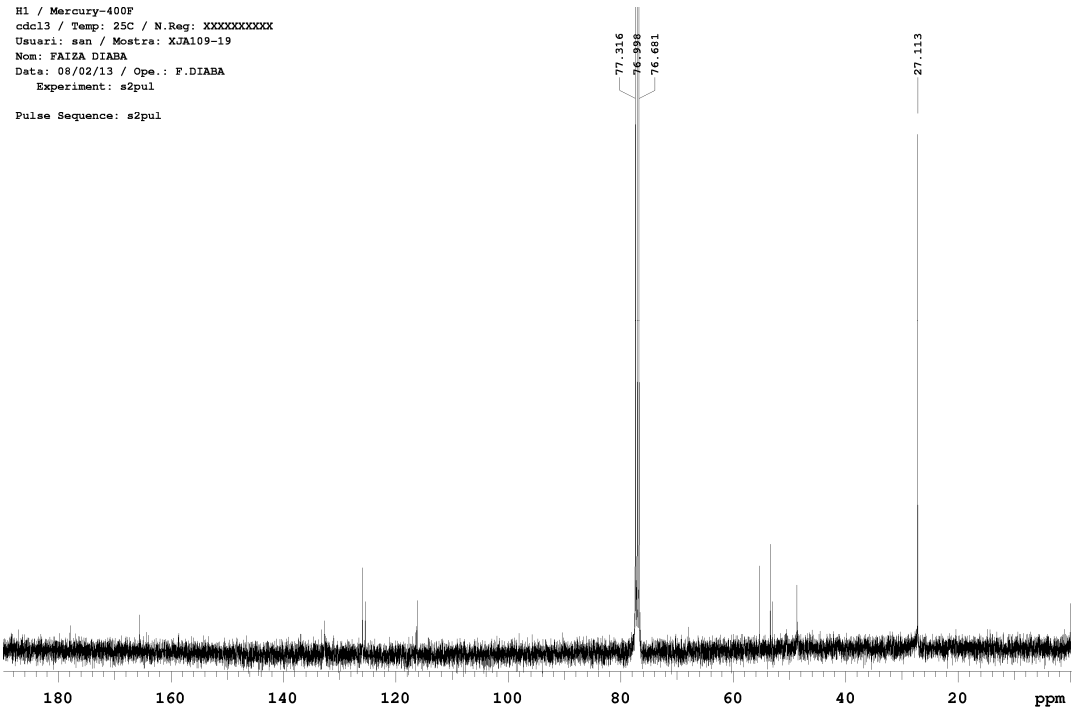
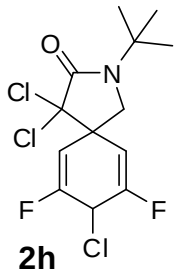
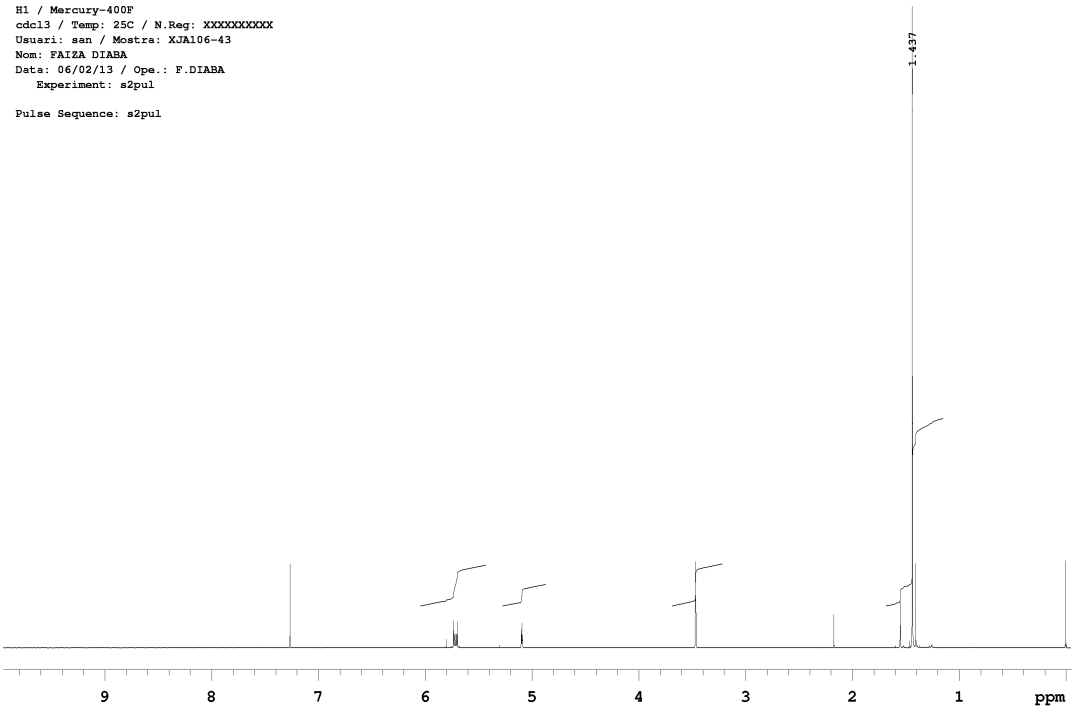
cdcl3 / Temp: 25C / N.Reg: XXXXXXXXXX
Usuari: san / Mostra: XJA109-19
Nom: FAIZA DIABA
Data: 08/02/13 / Ope.: F.DIABA
Experiment: s2pul
Pulse Sequence: s2pul
7.263
1.428
1.423
9
8
7
6
5
4
3
2
1
ppm

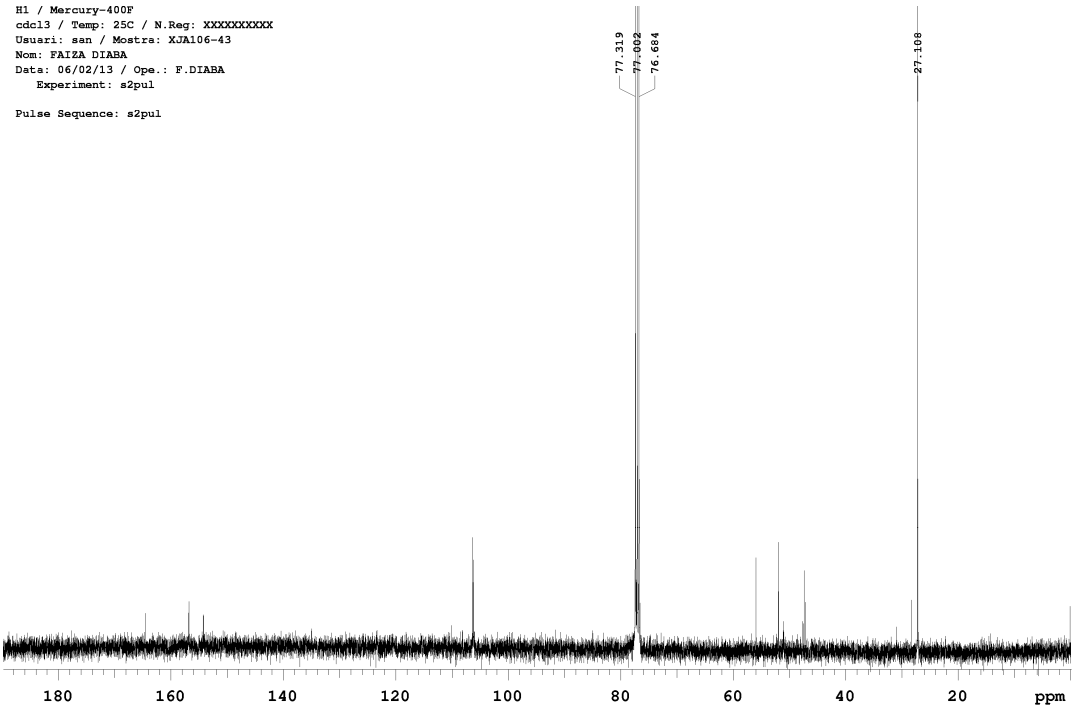

H1 / Mercury-400F
cdcl3 / Temp: 25C / N.Reg: XXXXXXXXXX
Usuari: san / Mostra: XJA109-19
Nom: FAIZA DIABA
Data: 08/02/13 / Ope.: F.DIABA
Experiment: s2pul
Pulse Sequence: s2pul
77.316
76.998
76.681
27.113
180
160
140
120
100
80
60
40
20
ppm

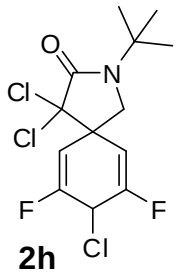


2h

Less polar

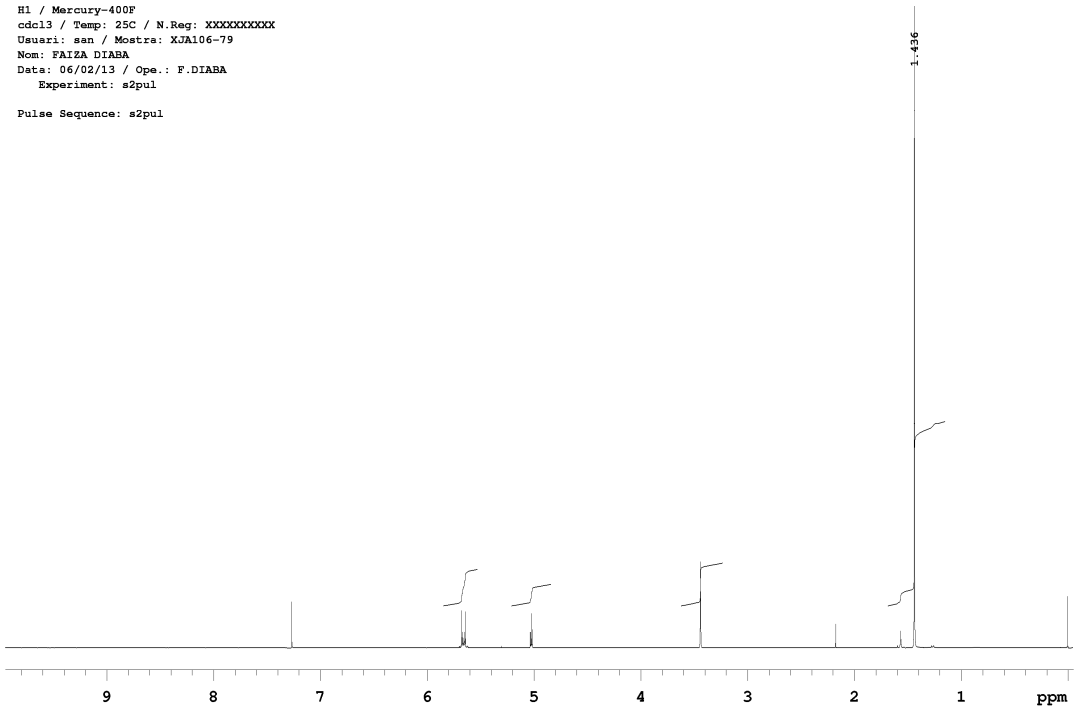


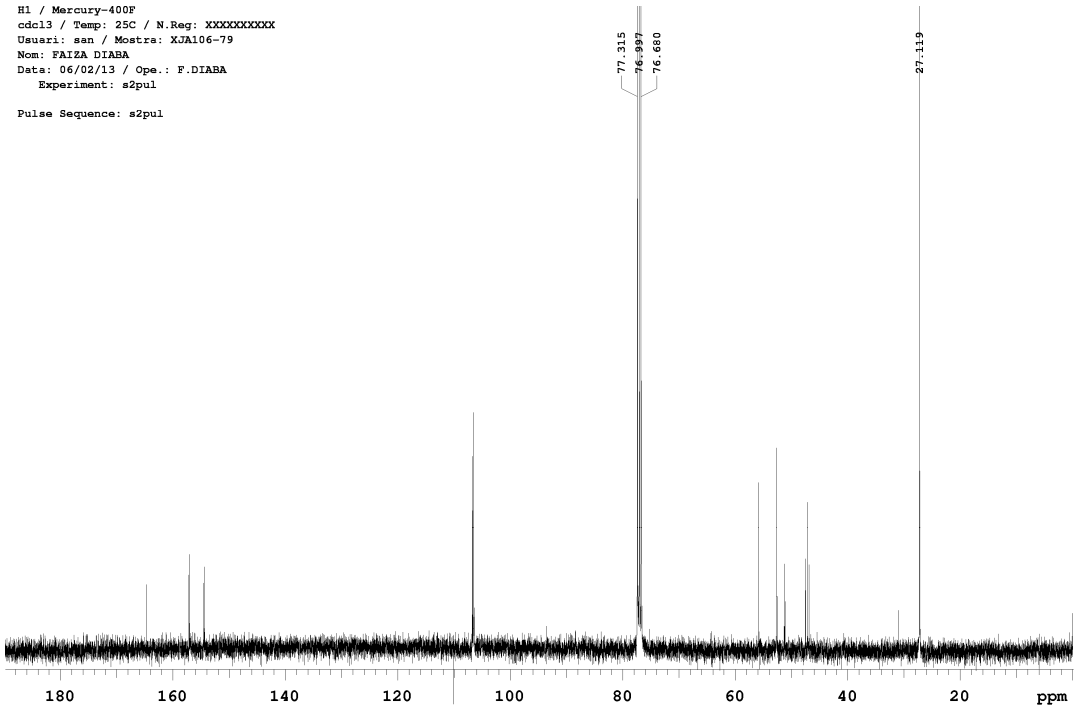




2h

More polar

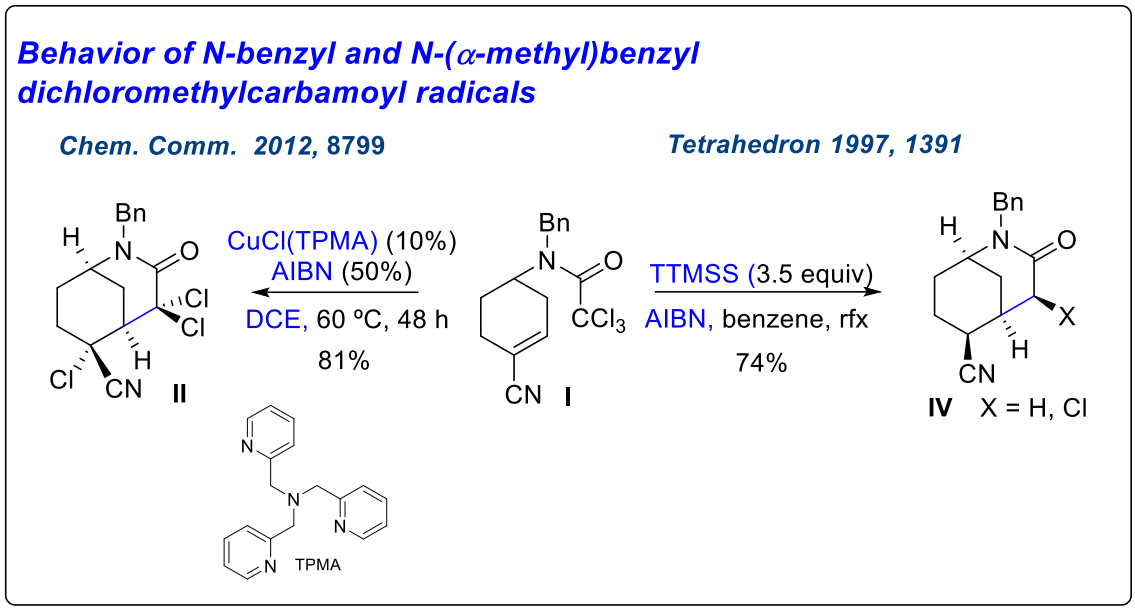




Chapter 3

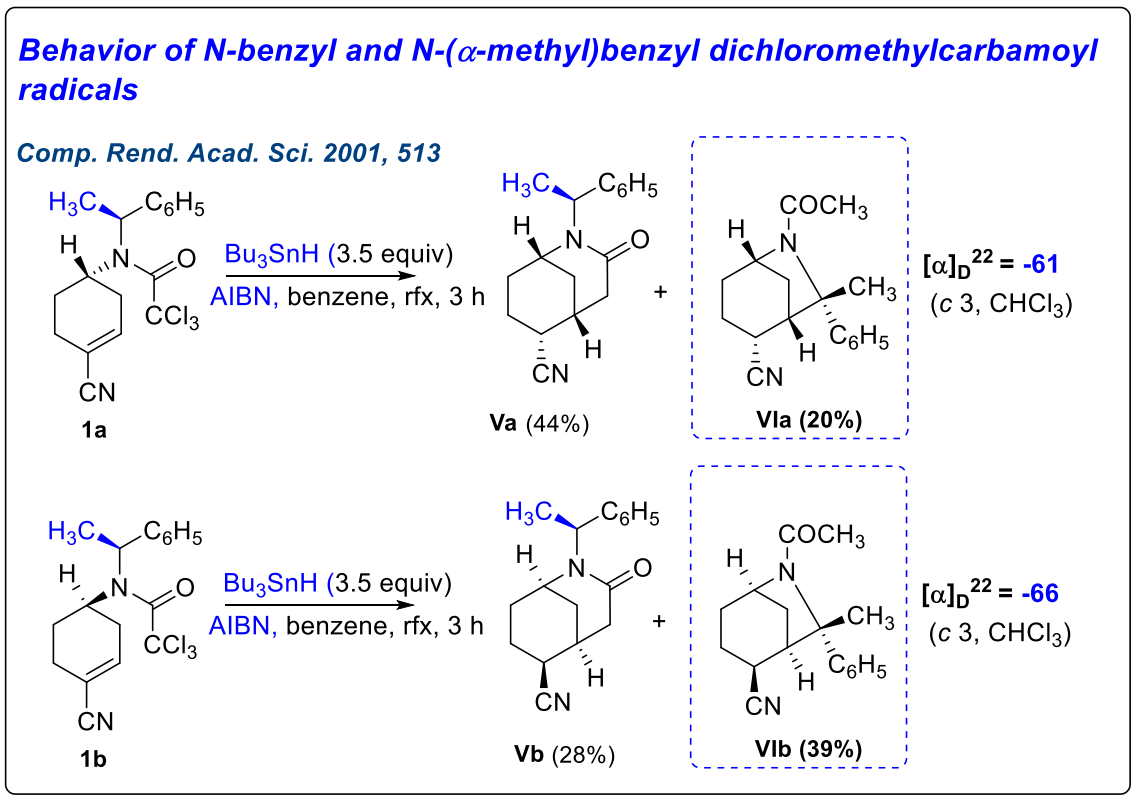
Unusual rearrangement and dearomatization reactions in Cu(I)-catalyzed atom transfer radical cyclizations from N-(1-phenylethyl)trichloroacetamides

Tetrahedron. **2013**, 69, 4883-4889.



Scheme 3.1.

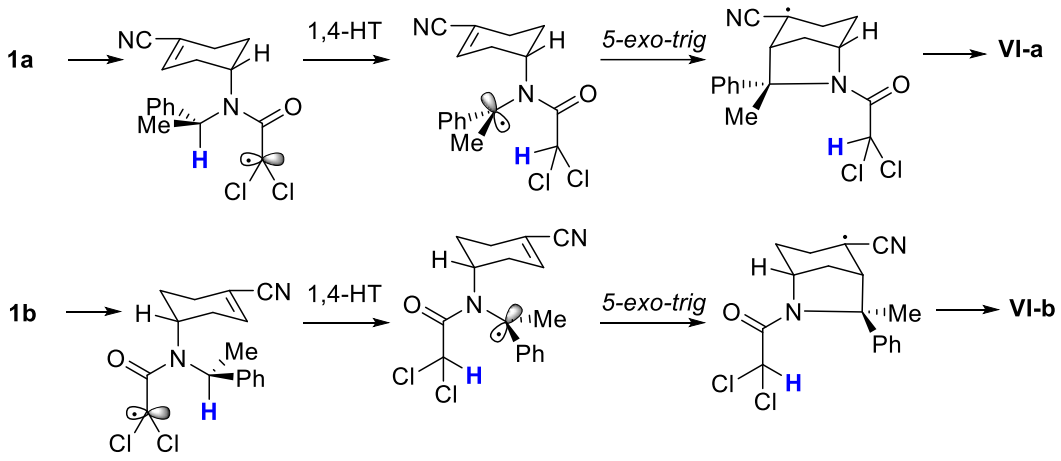
In our research group, azabicyclo[3.3.1]nonane derivatives were successfully prepared from trichloroacetamides using ATRC in the presence of CuCl as well as radical reductive conditions in the presence of AIBN, TBTH or TTMSS in refluxing benzene (Scheme 3.1).



Scheme 3.2.

Nevertheless, when the reaction was achieved from *N*-(α-methylbenzyl)trichloroacetamides type **1** instead of benzyltrichloroacetamides **I**, under reductive conditions, besides the expected morphans **V,** normorphans **VI** were also isolated (Scheme 3.1). **VI** derive from a 1,4-H transfer and subsequent 5-*exo*-trig cyclization as it is detailed in Scheme 3.2. This process involving memory of chirality (MoC) with complete inversion of stereochemistry at the benzylic center is unprecedented (Scheme 3.2).[1]

Heterofacial mechanism for the formation of normorphan VI



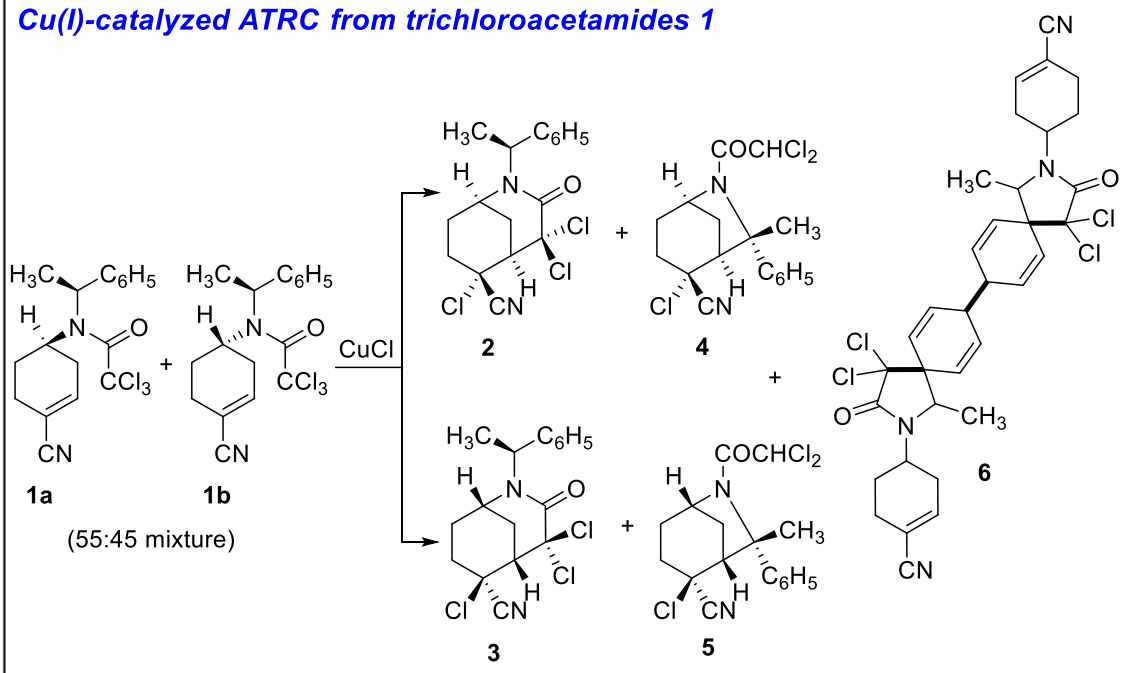
Scheme 3.2.

As a continuation of this work, we decided to explore ATRC in the presence of CuCl from trichloroacetamides type **1** to see if the behavior of these substrates under non-reductive conditions follows the same pattern observed before.

[1] For a recent review see: Gloor, C. S.; Dénès, F.; Renaud, P. *Free Radical Res.* **2016**, 1-10; DOI: 10.1080/10715762.2016.1232485.

Table3.1.

Cu(I)-catalyzed ATRC from trichloroacetamides 1



Entry (Method)	*Reaction Conditions*	***2*** / ***3*** *(Ratio)*	***4*** / ***5*** *(Ratio)*	***6***	***7-9***
1 (A)	CuCl (0.3),TPMA (0.3) DCE, 80ºC, 4h	25% (1.2:1)	29% (1.2:1)	17%	--
2 (B)	CuCl (0.3),TPMA (0.3) DCE, μW, 80ºC, 15min	19% (2:1)	25% (3:2)	24%	--
3 (C)	CuCl (0.6), CH_3CN, μW 80ºC, 15 min	15% (1.5:1)	--	--	**7** (31%)
4 (D)	CuCl / TPMA (0.1) AIBN (0.5) DCE, 60ºC, 48h	25% (1.1/1.0)	39%(1:2)	10%	--
5 (E)	$CuCl_2$ / TPMA (0.1) AIBN (0.5) DCE, 60ºC, 48h	<5%	<5%	-	**8** (15%) **9** (5%)

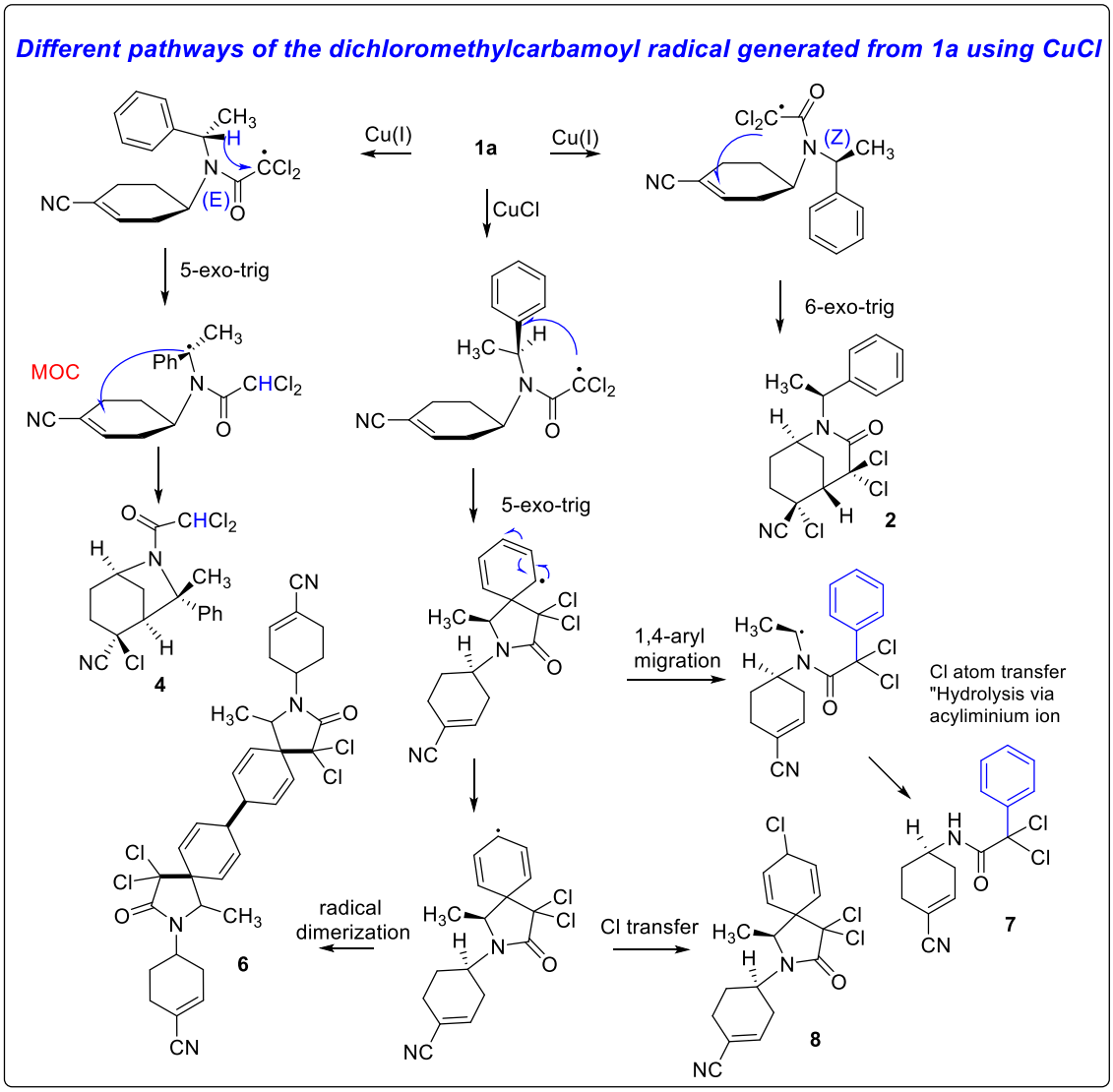
Our investigation began by applying the conditions developed previously for the ATRC to **1** (55:45 mixture of epimers **1a** and **1b**). The results obtained for the different conditions used are summarized in Table 3.1. First, treatment of **1** with CuCl(TPMA) (30%) in 1,2-DCE at 80ºC for 4 hours provided a highly complex mixture of compounds. After an exhaustive and meticulous chromatographic purification, morphans **2** and **3** were isolated in 25% and normorphans **4** and **5** in 29% yield in 1.2:1 ratio for both series (entry 1). Additionally, a minor quantity of

dimeric **6** (17%) was also obtained as a mixture of diastereomers. Thereafter, microwave activation was employed in order to decrease reaction time (entry 2); while still retaining equal amounts of reagents and performing the reaction in a shorter time (15 min). In spite of this, morphans and normorphans were recovered in lower yields, yet higher for the dimeric compounds **6**. Interestingly, when CH_3CN was used as a solvent and ligand for Cu(I), a new type of compound was formed (entry 3). Hence only morphan-type compounds and the rearranged 2,2-dichloro-2-phenylacetamide **7** were isolated, the latter being the major product of these reaction conditions. Finally, we applied our recently described ATRC reaction conditions for the synthesis of morphans, in which AIBN was used to ensure the regeneration of Cu(I) in the reaction medium. Thus, using CuCl/TMPA/AIBN in a molar ratio of 0.1/0.1/0.5 with respect to trichloroacetamide and operating at 60 ºC (entry 4), we obtained the best overall yield (64%) for morphans and normorphans from **1**, while the formation of dearomatized compounds diminished (entry 4). Finally, we carried out the reaction using air-stable copper(II) complexes (Table 3.1., entry 5), which unlike copper(I)/TPMA complexes do not need to be managed in inert atmosphere. Moreover, AIBN not only reduces copper(II) to copper(I), but also acts as an oxygen scavenger. However, using the best reaction conditions found for **1**, replacing CuCl by $CuCl_2$, gave poor results, with a conversion of only 50%. Notably, non-dimeric compounds **8** (14%) and **9** (5%), arising from a dearomative cyclization process, were isolated.[2] Additionally, less than 5% of morphans and normorphans **2**-**5** were also formed, the starting material **1** being recovered in 48% yield.

An overview of all the results obtained in the different essays showed that as it was expected, reaction of this type of trichloroacetamides under radical conditions follows two main pathways depending on the reaction conditions, leading to morphans **2** and **3** and normorphans **4** and **5**. However, these are not the only routes the dichlorocarbamoyl radical devises for this substrate in the presence of CuCl since it exhibits a complete different behavior when the two previously optimized conditions were applied onto the starting material mixture **1** (Scheme 3.3.). Employing the optimum radical cyclization conditions for the

[2] For the structures of **7** and **8** see scheme 3.3., **9** has the same structure of **8** but with a carbonyl group instead of a chloro atom in the allylic position.

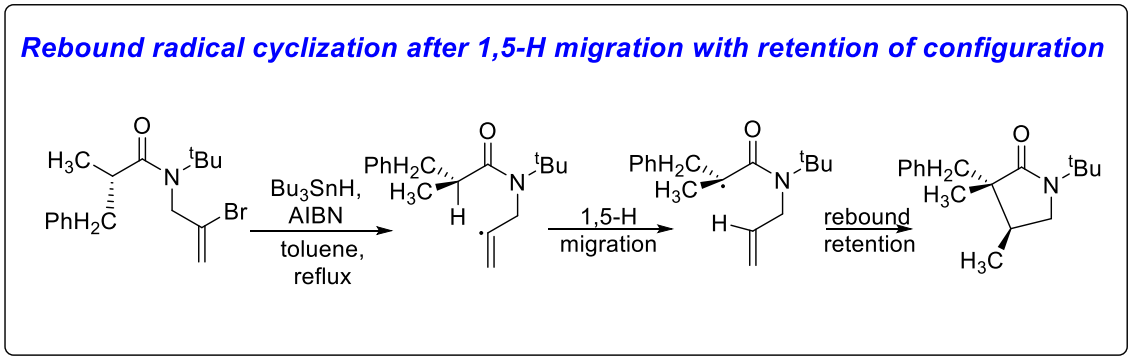
synthesis of morphans led us to three types of products. The initially formed 1-(carbamoyl)dichloromethyl radical with the amide *Z* conformation underwent cyclization upon the α,β-unsaturated nitrile and after chlorine atom transfer diastereoselectively gave **2**. The configuration of the new stereogenic center bearing the transferred chlorine atom was in an axial disposition in the resulting rigid azabicyclic ring. In contrast, the same radical in its *E* conformation evolved through different reaction pathways. The quantitatively most important was a stereospecific process involving a 1,4-hydrogen transfer, which generated a benzylic radical that reacted with the unsaturated nitrile leading to the normorphan derivative, in which the stereogenic benzylic carbon underwent a configurational inversion. It is worth noting that this reaction pathway has never



Scheme 3.3.

been observed in radical reactions using *N*-(1-phenylethyl)trichloroacetamides other than the previous studies reported by our research group (Scheme 3.2.).

The stereochemistry of the compounds with the normorphan ring established that the radical 1,4-H translocation and further cyclization occur with memory of chirality. Interestingly, Curran[3] reported during this investigation an example of memory of chirality in rebound cyclizations of α-amide radicals with retention of configuration, initiated from a 1,5-hydrogen transfer from an α-methine carboxamide to a vinyl radical (Scheme 3.4). In our case the pathway involves a memory of chirality in rebound cyclizations of benzyl radicals with inversion of configuration, initiated from a 1,4-hydrogen atom transfer from a benzylic methine hydrogen to a 1-(carbamoyl)dichloromethyl radical.



Scheme 3.4.

A third reaction pathway appeared along with the standard radical reaction and the 1,4-hydrogen transfer that allowed the normorphan formation. Thus, a competitive reaction from the same radical intermediate that underwent the 1,4-hydrogen translocation was the ipsocyclization on the benzene ring. Surprisingly, the cyclohexadienyl radical was not trapped by a chlorine atom, as occurred in compound **8**, but evolved to the dimeric compounds **6** by a radical coupling. Although the stereochemistry of the diastereomeric mixture **6** could not be ascertained due to the difficulty in isolating pure samples of the isomeric compounds, the structure of **6** was established. The molecular formula of **6**, $C_{34}H_{34}Cl_4N_4O_4$ was deduced from high-resolution FABMS measurements of its ammonium molecular cluster ion (m/z 688.1774) and NMR data. As far as we know, there are no precedents for the formation of compounds such as **6**, from a

[3] Sasmal, A.; Taniguchi, T.; Wipf, P.; Curran, D. P. *Can. J. Chem*. **2013**, *90*, 1-5.

radical cyclization upon a benzene ring with loss of aromaticity and later dimerization.[4] Finally, the fourth structural type (**7**) formed from **1** in these radical conditions was only isolated in the reaction when using microwave irradiation and acetonitrile as the solvent. The 1,4-aryl migration reaction from carbon to carbon has been documented,[5,6] although never previously observed in our studies on radicals from *N*-benzyltrichloroacetamides. As depicted in Scheme 3.3., the same radical intermediate formed in the spiroannulation process that gives the dimeric compounds **6** evolved through a 1,4-phenyl migration to an α-aminoethyl radical. This was probably trapped by a chlorine atom transfer, giving a 1-chloroethylacetamide, which through an acyliminium salt and hydrolysis in the workup led to the acetamide **7** with concomitant loss of acetaldehyde.

[4] A related dearomatization followed by a dimerization process of cyclohexadienyl radicals was observed in a classical study of the decomposition of aryl diazonium salts using copper: Hey, D. H.; Rees, C. W.; Todd, A. R. *J. Chem. Soc*. *C* **1967**, 1518-1525.

[5] (a) Studer, A.; Bossart, M. *Tetrahedron* **2001**, *57*, 9649-9667; (b) Robertson, J.; Palframan, M. J.; Shea, S. A.; Tchabanenko, K.; Unsworth, W. P.; Winters, C. *Tetrahedron* **2008**, *64*, 11896-11907.

[6] For 1,4-phenyl radical transfer starting from haloacetamides or related compounds, see: (a) Ishibashi, H.; Nakamura, N.; Ito, K.; Kitayama, S.; Ikeda, M. *Heterocycles* **1990**, *31*, 1781-1784; (b) Clark, A. J.; Coles, S. R.; Collis, A.; Debure, T.; Guy, C.; Murphy, N. P.; Wilson, P. *Tetrahedron Lett.* **2009**, *50*, 5609-5612; (c) Fuentes, L.; Quintero, L.; Cordero-Vargas, A.; Eustaquio, C.; Terán, J. L.; Sartillo-Piscil, F. *Tetrahedron Lett*. **2011**, *52*, 3630-3632; (d) Sandoval-Lira, J.; Hernández-Pérez, J. M.; Sartillo-Piscil, F. *Tetrahedron Lett.* **2012**, *53*, 6689-6693.

Unusual rearrangement and dearomatization reactions in Cu(I)-catalyzed atom transfer radical cyclizations from *N*-(1-phenylethyl)trichloroacetamides.

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Unusual rearrangement and dearomatization reactions in Cu(I)-catalyzed atom transfer radical cyclizations from *N*-(1-phenylethyl)trichloroacetamides

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ABSTRACT

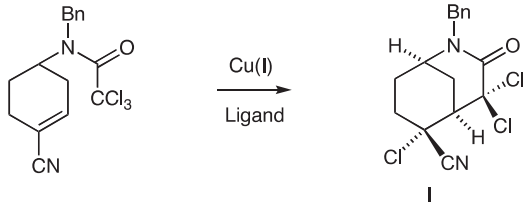
Atom transfer radical cyclization of *N*-(α-methyl)benzyl substituted trichloroacetamide upon α,β-unsaturated nitriles in compounds **1**, using CuCl, trispyridylmethylamine (TPMA), and AIBN as a reducing agent, gives morphan derivatives (**2** and **3**) and the unusual normorphans **4** and **5**, as well as the unexpected azaspirodecanes **6**. Stereospecific formation of normorphans involves memory of chirality in the cyclization step and azaspirodecanes are generated by a radical dearomative ipsocyclization followed by a radical dimerization.

1. Introduction

Trichloroacetamides are carboradical precursors that have been applied in the synthesis of nitrogen-containing heterocycles embodying a lactam ring by intramolecular atom transfer[1–4] and hydride reductive[5–7] radical processes. The most frequently used catalysts for atom transfer radical cyclizations (ATRC) are Cu(I)[2,8–10] and Ru(II)[1,3,4,11,12] reagents with several ligand types, with far fewer reported examples of Fe–$FeCl_3$[10c,13] or Ni–AcOH.[14] For radical reductive cyclizations, the Bu_3SnH/AIBN procedure is the most general,[15] TTMSS also being used as the reducing agent.[16,17]

Recently, we have shown under several reaction conditions that Cu(I) is a useful catalyst for the synthesis of polyfunctionalized 2-azabicyclo[3.3.1]nonanes[18] starting from *N*-trichloroacetamides tethered with cyclohexenes (Scheme 1).[19]

As a continuation of this work, we were interested in exploring this ATRC process using trichloroacetamide **1** (a mixture of epimers **1a** and **1b**) as the starting material in which the *N*-benzyl substituent was replaced by an α-methylbenzyl substituent. In a previous study we found that the reaction of **1**, using Bu_3SnH as the promoter of a reductive cyclization process evolved unexpectedly, since besides the envisaged morphans **II** and **III**, normorphans **IV** and **V** were also isolated (Scheme 2).[20] To understand this formation of normorphan compounds from an unusual initial 1,4-hydrogen transfer, the reaction was also studied from a theoretical point of view using density functional theory (DFT) methods.[21]



Scheme 1. ATRC leading to 2-azabicyclo[3.3.1]nonane I.

With the aim of gaining further insight into this curious mode of reactivity exhibited by *N*-(α-methylbenzyl)trichloro-acetamides, we decided to study the behavior of diastereomers **1** under the reaction conditions of Cu(I)-tris(2-pyridylmethyl)amine (TPMA) and evaluate if the 1,4-hydrogen transfer is also a competitive reaction pathway in the ATRC.

2. Results and discussion

We began our studies under Cu(I) radical-generating conditions with the reaction of **1** (55:45 mixture of epimers **1a** and **1b**, respectively)[22] using CuCl (30% catalyst) and TPMA (30%) in

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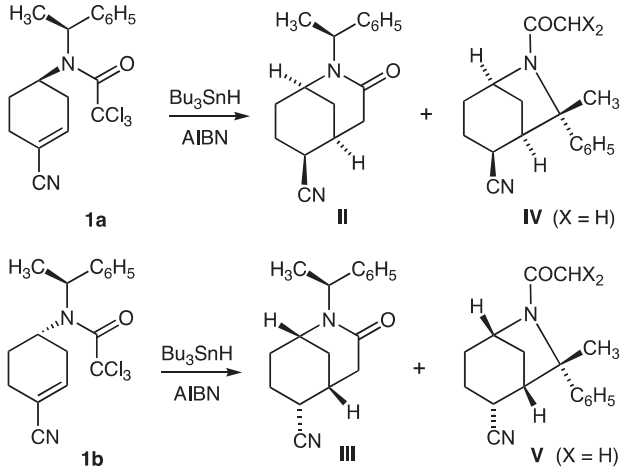


Scheme 2. Reductive radical cyclization of **1** (Ref. 20).

dichloroethane (80 °C, 4 h) (Table 1, entry 1). The reaction mixture was highly complex, generating morphan, normorphan, and azaspirodecane rings (**2**–**6**), as depicted in Scheme 3. A careful chromatographic purification established that morphans **2** and **3** had been formed in 25% yield and normorphans **4** and **5** in 29% yield in a 1.2:1 ratio in both series. Minor amounts of compounds were also obtained from a spiroannulation that led to dearomatized and dimeric compounds **6** as a diastereomeric mixture. The use of microwave irradiation shortened the reaction time to 15 min (entry 2), but resulted in worse yields of compounds **2**–**5**, and only a slight increase in compounds **6** generated by radical cyclization upon the benzene ring. Interestingly, when CH_3CN was used as a solvent and ligand for Cu(I), a new type of compound was formed (entry 3). Thus, only morphan-type compounds and the rearranged 2,2-dichloro-2-phenylacetamide **7** were isolated, the latter being the major product of these reaction conditions. Finally, we applied our recently described ATRC reaction conditions for the synthesis of morphans,[20] in which AIBN was used to ensure the regeneration of Cu(I) in the reaction medium.[23] Thus, using CuCl/TMPA/AIBN in a molar ratio of 0.1/0.1/0.5 with respect to trichloroacetamide and operating at 60 °C (entry 4), we obtained the best overall yield (64%) for morphans and normorphans from **1**, while the formation of dearomatized compounds diminished (Scheme 3). Finally, we carried out the reaction using air-stable copper(II) complexes (Table 1, entry 5), which unlike copper(I)/TPMA complexes do not need to be managed in inert atmosphere. Moreover, AIBN not only reduces copper(II) to copper(I), but also acts as an oxygen scavenger. However, using the best reaction conditions found for **1**, replacing CuCl by $CuCl_2$, gave poor results, with a conversion of only 50%. Notably, non-dimeric compounds **8** (14%) and **9** (5%), arising from a dearomative cyclization process, were isolated (Fig. 1). Additionally, less than 5% of morphans and normorphans **2**–**5** were also formed, the starting material **1** being recovered in 48% yield. The most significant NMR data used for the structural elucidation of morphans **2** and **3**, and normorphans **4** and **5** are included in Figs 2 and 3 (see below).

An overview of all the processes from trichloroacetamide **1a** is depicted in Scheme 4 (the same processes also occurred from the diastereomer **1b**, although the four types of compounds were obtained in a different ratio, as shown in Table 1). The ATRC from trichloroacetamides **1**, like the reductive cyclization, led to the competitive generation of morphan (**2**–**3**) and normorphan compounds (**4**–**5**). The initially formed 1-(carbamoyl)dichloromethyl radical with the amide *Z* conformation underwent cyclization upon the α,β-unsaturated nitrile and after chlorine atom transfer diastereoselectively gave **2**. The configuration of the new stereogenic center bearing the transferred chlorine atom was in an axial disposition in the resulting rigid azabicyclic ring.

In contrast, the same radical in its *E* conformation evolved through different reaction pathways. The quantitatively most important was a stereospecific process involving a 1,4-hydrogen transfer,[20,24] which generated a benzylic radical that reacted with the unsaturated nitrile leading to the normorphan derivative, in which the stereogenic benzylic carbon underwent a configurational inversion. It is notable that this reaction pathway has never been observed in radical reactions using *N*-(1-phenylethyl)trichloroacetamides[25,26] other than in our previous studies on related compounds.[20,27] The stereochemistry of the compounds with the normorphan ring established that the radical 1,4-H translocation and further cyclization occur with memory of chirality. Interestingly, Curran has recently reported an example of memory of chirality in rebound cyclizations of α-amide radicals with retention of configuration, initiated from a 1,5-hydrogen transfer from an α-methine carboxamide to a vinyl radical.[28] In our case the pathway involves a memory of chirality in rebound cyclizations of benzyl radicals with inversion of configuration, initiated from a 1,4-hydrogen atom transfer from a benzylic methine hydrogen to a 1-(carbamoyl)dichloromethyl radical. Notably, in this ATRC protocol working at 60 °C (Method D) compound **1b** was more prone to giving the 1,4-hydrogen translocation than **1a**, leading to normorphan **5**, whereas at a higher temperature (Method A) **1a** gave the normorphan compound **4** in a higher ratio but lower yield.

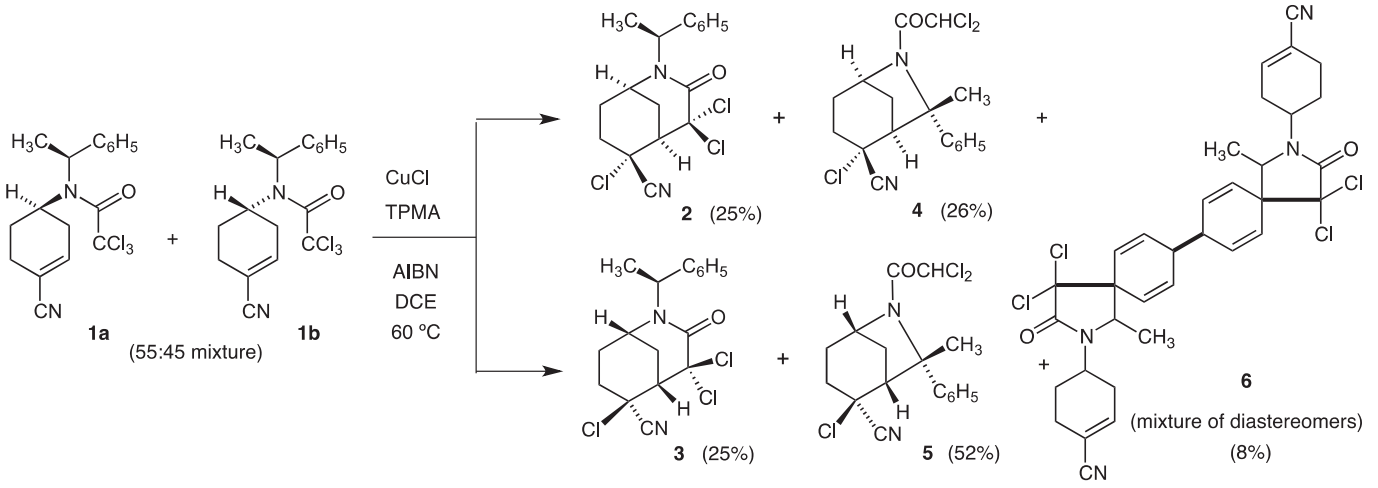
As an explanation of this memory of chirality,[28,29] we assume that the radical intermediate arising from a 1,4-hydrogen atom shift exhibits a high activation barrier for rotation around the C–N single bond.[30] Its absolute chirality is thus preserved during the course of the reaction, which involves a configuration inversion at C-7 of the normorphans. Undoubtedly, the phenyl group also contributes to the geometric stabilization of the radical intermediate.[31]

To ensure that compound **4** was derived from the cyclization of **1a**, with configuration inversion at the benzylic carbon, and was not *ent*-**4**, arising from cyclization of **1b** with configuration retention, we decided to correlate trichloroderivative **4** with dechlorinated normorphan **10**. The absolute configuration of **10** (**IV** in Scheme 2) was established some years ago[20] by X-ray crystal structure analysis and the specific rotation value is known, $[\alpha]_D^{23}$ −66 (*c* 3, $CHCl_3$). Reduction of **4** with Zn[32] gave nitrile **10**, which unfortunately was contaminated with its epimer at C-2, indicating that the reduction was not highly diastereoselective (Scheme 5). The NMR data of the

Table 1
CuCl-catalyzed cyclization of trichloroacetamides **1**[a]

Entry (method)	Reaction conditions[b,c]	**2**/**3** ratio	**4**/**5** ratio	**6**	**7**–**9**
1 (A)	CuCl (0.3) TPMA (0.3) DCE, 80 °C	25% (1.2:1)	29% (1.2:1)	17%	—
2 (B)	CuCl (0.3) TPMA (0.3) DCE, μW 80 °C	19% (2:1)	25% (3:2)	24%	—
3 (C)	CuCl (0.6) CH_3CN, μW 80 °C	15% (1.5:1)	—		**7** 31%
4 (D)	CuCl (0.1) TPMA (0.1) AIBN (0.5) DCE, 60 °C	25% (1.1/1.0)	39% (1:2)	10%	—
5 (E)	$CuCl_2$ (0.1) TPMA (0.1) AIBN (0.5) DCE, 60 °C	<5%	<5%	—	**8** 15% **9** 5%

[a] For structures of compound **2**–**7**, see Schemes 3 and 4. For compounds **8**–**9**, see Fig. 1.
[b] Reaction times: (A) 4 h; (B) 15 min; (C) 15 min; (D and E) 48 h.
[c] Conversion: (A) 100%; (B) 100%; (C) 66%; (D) 100%; (E) 50%.



Scheme 3. Cu(I)-catalyzed atom transfer cyclization reactions from trichloroacetamides **1**. Yields refer to isolated compounds and the processes from **1a** and **1b** are considered separately.

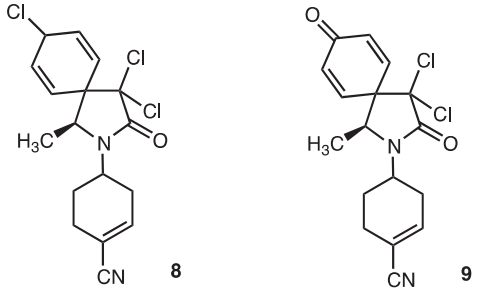


Fig. 1. Compounds **8** and **9** isolated using $CuCl_2$ as initial reagent.

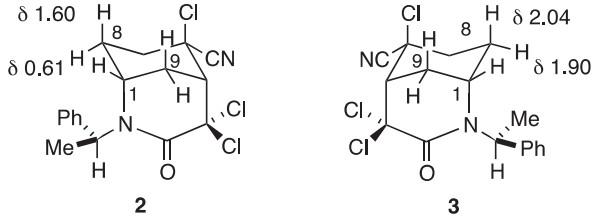


Fig. 2. Key NMR data for stereochemical assignment of morphans **2** and **3**.

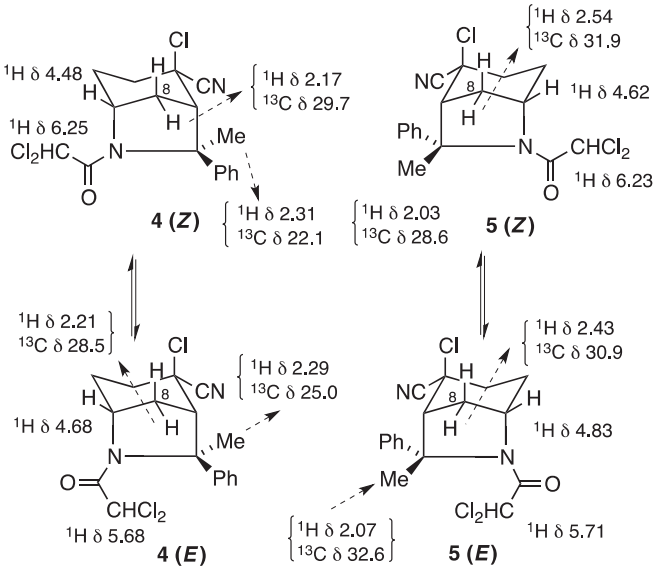


Fig. 3. Key NMR data for stereochemical assignment of normorphans.

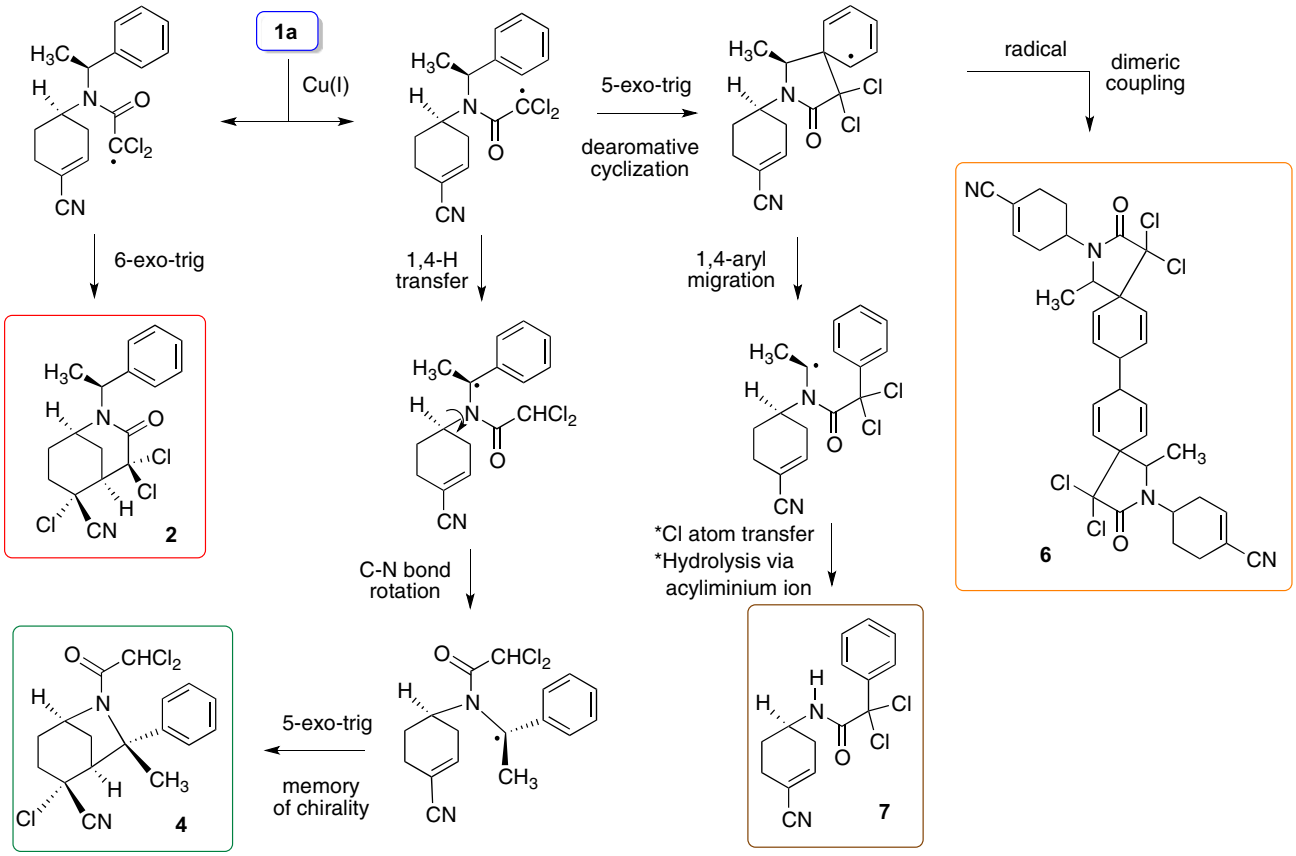
purified reaction mixture matched the published data of the two rotamers of **10** and showed a new set of signals attributable to compound **11**.

Disappointingly, we were not able to obtain a pure sample of **10**, nor the specific rotation for the synthesized **10**. However, the specific rotation for the impure sample was $[\alpha]_D^{23}$ −55 (*c* 1, $CHCl_3$) with a levorotatory character, as reported for **10**. In conclusion, the precedents for this reaction type and the experimental results[33] reported here support the postulated memory of chirality for the cyclization of trichloroacetamides **1** leading to normorphans, involving a configuration inversion at the radical carbon.

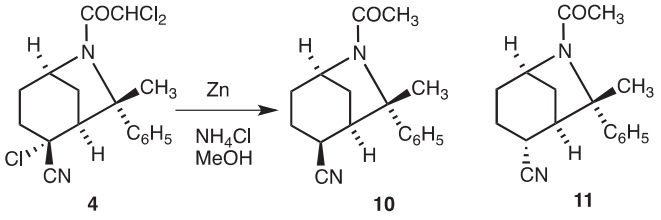
A third reaction pathway appeared along with the standard radical reaction and the 1,4-hydrogen transfer that allowed the normorphan formation. Thus, a competitive reaction from the same radical intermediate that underwent the 1,4-hydrogen translocation was the ipsocyclization on the benzene ring.[34,35] Surprisingly, the cyclohexadienyl radical was not trapped by a chlorine atom, as occurred in compound **8** (Fig. 1), but evolved to the dimeric compounds **6** by a radical coupling. Although the stereochemistry of the diastereomeric mixture **6** could not be ascertained due to the difficulty in isolating pure samples of the isomeric compounds, the structure of **6** was established. The molecular formula of **6**, $C_{34}H_{34}Cl_4N_4O_4$ was deduced from high-resolution FABMS measurements of its ammonium molecular cluster ion (*m*/*z* 688.1774) and NMR data, which is discussed below. As far as we know, there are no precedents for the formation of compounds, such as **6** from a radical cyclization upon a benzene ring with loss of aromaticity and later dimerization.[36]

Finally, the fourth structural type (i.e., **7**) formed from **1** in the radical conditions was only isolated in the reaction when using microwave irradiation and acetonitrile as the solvent. The 1,4-aryl migration reaction from carbon to carbon has been documented,[37,38] although never previously observed in our studies on radicals from *N*-benzyltrichloroacetamides. As depicted in Scheme 4, the same radical intermediate formed in the spiroannulation process that gives the dimeric compounds **6** evolved through a 1,4-phenyl migration to an α-aminoethyl radical. This was probably trapped by a chlorine atom transfer, giving a 1-chloroethylacetamide, which through an acyliminium salt and hydrolysis in the workup led to the acetamide **7** with concomitant loss of acetaldehyde.

The spectroscopic data of morphans **2** and **3** are similar to those of the previously reported dechlorinated compounds at C-6 and C-4 (Table 2 for ^{13}C NMR data). Hence, the isomer showing H-8eq (*δ* 0.61) and CH_3 (*δ* 15.6) at high fields was assigned the absolute



Scheme 4. Overview of the different pathways of the radical dichloromethylcarbamoyl generated from **1a** using Cu(I).



Scheme 5. Reduction of **4** leading to normorphan (−)-**10**.

Table 2
^{13}C NMR chemical shifts (δ) of morphans[a]

Compound	C-1	C-3	C-4	C-5	C-6	C-7	C-8	C-9	CH	CH_3	CN
2	46.4	162.8	83.6	53.1	59.6	29.3	24.9	27.0	53.7	15.6	118.9
3	46.4	163.3	83.7	53.3	59.6	29.6	26.8	26.6	54.2	17.0	118.8
II–Cl[b]	46.7	165.9	57.7	31.3	35.7	20.2	29.3	33.8	52.3	15.7	120.7
III–Cl[b]	46.6	166.3	57.7	31.6	36.1	20.5	31.2	33.7	53.1	17.1	120.6

[a] In $CDCl_3$ (100 MHz). Values assigned on the basis of COSY and HMQC experiments.
[b] Compounds **II**–Cl and **III**–Cl show the structure of **II** and **III** depicted in Scheme 2, but with an equatorial chlorine atom at C-4 and are described in Ref. 20.

configuration (1*R*,5*R*,6*R*). When the isomer showed H-8eq (δ 1.90) and CH_3 (δ 17.0) at lower fields, the absolute configuration (1*S*,5*S*,6*S*) was assigned for the three stereogenic atoms in the carbocyclic ring. The stereochemistry at C-6 in compounds **2** and **3** (Fig. 2) was deduced from the chemical shift of H-8ax (δ 1.60 and δ 2.04, respectively), which appeared deshielded (ca. 0.7 ppm) with respect to the chemical shift found in the analogous dechlorinated compounds (δ 0.90 and δ 1.42).[20,39] This deshielding anisotropic effect is due to the chlorine atom[40] having a 1,3-diaxial relationship with H-8ax in both morphans. Moreover, the axial chlorine atom also exerts a deshielding effect (ca. 0.5 ppm) on H-7ax, which has an antiplanar disposition compared with the analogous compounds lacking this heteroatom. The phenomenon was observed in both **2** (δ 2.01) and **3** (δ 2.29), compared with the values for the dechlorinated compounds in which H-7ax appears at δ 1.49 and δ 1.82, respectively. This stereochemical assignment agrees 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 that locates the chlorine in an axial disposition.

The ^{1}H and ^{13}C NMR spectra patterns of normorphans **4** and **5**, in which most of the signals are duplicated due to the presence of *Z* and *E* rotamers,[41] resemble those of the previously reported normorphans lacking the chlorine atom at C-2 (Table 3). Hence, isomer **4**, showing chemical shifts δ_H 2.31 and δ_C 22.1 for the methyl group at C-7 (major *Z* rotamer), was assigned the absolute configuration

Table 3
^{13}C NMR chemical shifts (δ) of normorphans[a]

Compound	C-1	C-2	C-3	C-4	C-5	C-7	C-8	$CHCl_2$	CO	7-CH_3	CN
4											
Z major	55.9	58.3	32.9	27.7	55.8	72.7	29.7	65.2	161.5	22.1	119.5
E minor	58.1	58.1	33.5	24.6	57.7	70.6	28.5	64.5	164.5	25.0	119.9
5	56.8	59.3	32.2	27.7	56.2	72.3	31.9	66.1	161.8	28.6	117.2
	59.8	59.1	32.6	25.7	57.2	70.3	30.9	64.8	164.9	32.6	116.9
IV–Cl[b]	47.7	30.2	21.5	29.7	56.2	72.2	34.3	65.2	161.1	22.5	121.1
	50.5	30.2	23.1	28.5	58.0	70.1	33.2	64.8	164.1	24.5	121.4
V–Cl[b]	48.2	31.0	21.6	30.6	56.7	71.8	36.6	66.1	161.5	27.5	119.7
	51.4	31.0	21.8	29.7	57.5	69.9	35.5	65.0	164.6	31.0	119.8

[a] In $CDCl_3$ (100 MHz). Values assigned on the basis of COSY and HMQC experiments.
[b] Compounds **IV**–Cl and **V**–Cl show the structure of **IV** and **V** (X=Cl) depicted in Scheme 2, and are described in Ref. 20.

(1*S*,2*R*,5*R*,7*S*), while isomer **5**, showing chemical shifts δ_H 2.03 and δ_C 28.6 for the methyl group at C-7 (major *Z* rotamer), was assigned the absolute configuration (1*R*,2*S*,5*S*,7*S*). Again, the stereochemistry of the quaternary carbon with chlorine and cyano groups was assigned taking into account the ^{1}H chemical shift of the axial proton bearing a 1,3-diaxial relationship with the axial substituent at C-2. Thus, the H-4ax resonates at δ 1.90 and 1.94 in compounds **4** and **5**, respectively, in a deshielded chemical shift (ca. 0.3 ppm) with respect to the values reported for the dechlorinated normorphans (Fig. 3).

The NMR data for spiro dimeric compounds **6**, each one being a mixture of epimers presumably at the spiro carbon atom, while not allowing a configurational assignment, did enable us to clearly identify the formation of spirocyclohexanediene derivatives. Additionally, the calculation of their dimeric structure was based on the HRMS data. The ^{1}H pattern of the olefinic signals and the chemical shift (δ ~3.1) of allylic protons allowed the ground structure of the spirocyclohexanediene ring to be deduced. The counterpart of the five-membered lactam was inferred by the absorption at 1715 cm^{-1} in the IR spectra and the ^{13}C NMR chemical shifts of the four carbons at δ 166.3 (s), 89.3 (s), 53.5 (s), and 40.2 (d), as average values.

3. Conclusion

In summary, under the atom transfer reaction cyclization conditions, the radical reaction course from **1** followed three different pathways. One evolved as expected to morphans **2** and **3** through an ATRC. Another led to normorphans **3** and **4** through an initial 1,4-hydrogen transfer and rebound cyclization with memory of chirality followed by chorine trapping of the generated radical. In a third pathway, the initially formed 1-(carbamoyl)dichloromethyl radical underwent ipsocyclization upon the benzene ring to give a cyclohexadienyl radical. This in turn evolved to **6** as a diastereoisomeric mixture via radical coupling dimerization or, in specific reaction conditions, to the dichloroacetamide **7**, via a 1,4-aryl radical migration.

4. Experimental section

4.1. General procedures

^{1}H and ^{13}C NMR spectra were recorded in a $CDCl_3$ solution at 400 MHz and 100 MHz, respectively. In addition, 2D NMR COSY and HMQC experiments were performed on a Varian instrument. Chemical shifts are reported as δ values (ppm) relative to internal Me_4Si. Infrared spectra were recorded on a Nicolet 205 FT-IR spectrophotometer. HRMS were determined on a Agilent LC/MSD-TOF apparatus. Optical rotations were taken on a Perkin–Elmer 241 polarimeter with a 1 mL (L=1 dm) cell TLC was performed on SiO_2 (silica gel 60 F_{254}, Merck). The spots were located by UV light and a 1% $KMnO_4$ or 1.5% K_2PtCl_6 aqueous solution. Chromatography refers to flash column chromatography and was performed on SiO_2 (silica gel 60, SDS, 230–400 mesh). TPMA refers to tris(2-pyridylmethyl)amine. Unless noted, the reactions were carried out in argon atmosphere.

4.2. Cyclization reaction procedure

4.2.1. Method A. To a suspension of CuCl (9.2 mg, 0.093 mmol 30%) in 1,2-dichloroethane (2 mL) were successively added TPMA (27 mg, 0.093 mmol) and nitrile **1** (55:45 mixture of epimers **1a** and **1b**, 115 mg, 0.31 mmol), and the mixture was heated at 80 °C for 4 h in a sealed tube. The solution was allowed to reach rt, water (2 mL) was added and extracted with CH_2Cl_2. The organics were dried, concentrated and the residue purified by chromatography (hexane/EtOAc 80:20 to hexane/EtOAc 50:50) to yield 62 mg of a 1:1.15 mixture of morphans **2** and **3** and normorphans **4**–**5**, respectively, (54% overall yield) and 18 mg (17%) of dimeric derivatives **6**. The individual yields with respect to the epimeric ratio of the starting material **1** were: normorphan **4** (22%), morphan **2** (25%), morphan **3** (25%), and normorphan **5** (26%).

4.2.2. Method B. In a 10 mL vessel were placed nitrile **1** (100 mg, 0.27 mmol), CuCl (8 mg, 0.081 mmol, 30%), TPMA (23 mg, 0.080 mmol), and 1,2-dichloroethane (1 mL). The mixture was stirred and heated to 80 °C using microwave irradiation for 15 min. After cooling to rt, water (1 mL) was added and the mixture was stirred for an additional hour and extracted with CH_2Cl_2. The organics were dried, concentrated and purified by chromatography (hexane/EtOAc 80:20 to hexane/EtOAc 50:50) to give 44 mg of a 1:1.25 mixture of morphans (19%) and normorphans (25%) and 22 mg of compounds 6 (24%).

4.2.3. Method C. In a 10 mL vessel were placed nitrile **1** (100 mg, 0.27 mmol), CuCl (16 mg, 0.161 mmol, 60%), and acetonitrile (1 mL). The mixture was stirred and heated to 80 °C using microwave irradiation for 15 min. After cooling to rt, water (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 (hexane/AcOEt 85:15 to hexane/EtOAc 70:30) to give 33 mg of recovered starting material **1**, 15 mg (15%) of a 1.5:1 mixture of morphans **2** and **3** and 26 mg (31%) of **7**.

4.2.4. Method D (method of choice). To a suspension of CuCl (2.7 mg, 0.027 mmol 10%) in 1,2-dichloroethane (2 mL) were successively added TPMA (8 mg, 0.027 mmol), nitrile **1** (100 mg, 0.27 mmol), AIBN (22 mg, 0.13 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, stirred with 2 mL of water for an additional hour and extracted with CH_2Cl_2. The organics were dried, concentrated and the residue purified by chromatography (hexane/EtOAc 80:20 to hexane/EtOAc 50:50) to yield 70 mg of a 45:55 mixture of morphans and normorphans and 9 mg (10%) of dimeric derivatives **6**.

The separation of the different morphans and normorphans was achieved using an additional chromatography (cyclohexane/EtOAc 90:10). Normorphan **4** (15 mg, 26%), morphan **2** (14 mg, 25%), morphan **3** (12 mg, 25%), and finally normorphan **5** (23 mg, 52%) were sequentially eluted. Overall yield of the process was 64% (2:3 ratio morphan/normorphan compounds).

4.2.5. Method E. To a suspension of $CuCl_2$ (4.6 mg, 0.034 mmol 10%) in 1,2-dichloroethane (2 mL) were successively added TPMA (10 mg, 0.037 mmol), nitrile **1** (129 mg, 0.34 mmol), and AIBN (29 mg, 0.17 mmol 50%), and the mixture was heated at 60 °C for 2 days under air in a sealed tube. The solution was allowed to reach rt, stirred with 1 mL of water for an additional hour and extracted with CH_2Cl_2. The organics were dried, concentrated and the residue purified by chromatography (hexane/EtOAc 80:20 to hexane/EtOAc 50:50) to yield 62 mg of **1** (48%), 19 mg (15%) of **8**, and 7 mg (5%) of **9**.

4.3. Spectral data for compounds 2–7

*4.3.1. (1R,5R,6R)-4,4,6-Trichloro-2-[(S)-1-phenylethyl]-3-oxo-2-azabicyclo[3.3.1]nonane-6-carbonitrile (**2**).* $[\alpha]_D^{23}$ −63 (*c* 0.6, $CHCl_3$); IR (NaCl, neat): 3059, 3030, 2926, 2855, 2243, 2216, 1670, 1602, 1494, 1446, 1369, 1297, 1270, 1206, 1159, 1095, 990, 826, 805, 779, 735, 701, 635, 612, 573 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 0.61 (dm, 1H, J=14.4 Hz, H-8eq), 1.60 (m, 1H, H-8ax), 1.61 (d, 3H, J=6.8 Hz, CH_3), 2.00 (m, 2H, H-7), 2.58 (td, 2H, J=3.2, 1.2 Hz, H-9), 3.34 (m, 1H, H-5), 3.68 (m, 1H, H-1), 5.94 (q, 1H, J=6.8 Hz, CH), 7.30–7.42 (m, 5H,

ArH); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 15.6 (CH_3), 24.9 (C-8), 27.0 (C-9), 29.4 (C-7), 46.5 (C-1), 53.1 (C-5), 53.7 (CH), 59.6 (C-6), 83.6 (C-4), 118.9 (CN), 127.8, 128.6, 128.9 (Ar), 138.7 (*ipso*-C), 162.8 (C-3). HRMS (ESI-TOF): calcd for $C_{17}H_{18}Cl_3N_2O$ 371.0479 (M^++1). Found 371.0478.

*4.3.2. (1S,5S,6S)-4,4,6-Trichloro-2-[(S)-1-phenylethyl]-3-oxo-2-azabicyclo[3.3.1]nonane-6-carbonitrile (**3**).* IR (NaCl, neat): 3058, 2919, 2850, 2216, 1671, 1495, 1435, 1368, 1296, 1269, 1204, 1160, 990, 824, 733, 699, 632, 575 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 1.64 (d, 3H, *J*=7.2 Hz, CH_3), 1.90 (dm, 1H, *J*=14.8 Hz, H-8eq), 2.04 (m, 1H, H-8ax), 2.29 (m, 2H, H-7), 2.33 (dm, 1H, *J*=14.8 Hz, H-9), 2.43 (dt, 1H, *J*=14.8, 3.2 Hz, H-9), 3.34 (br s, 2H, H-1 and H-5), 5.95 (q, 1H, *J*=7.2 Hz, CH), 7.30–7.44 (m, 5H, ArH); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 17.1 (CH_3), 26.6 (C-9), 26.8 (C-8), 29.6 (C-7), 46.4 (C-1), 53.3 (C-5), 54.2 (CH), 59.6 (C-6), 83.7 (C-4), 118.8 (CN), 127.2, 128.3, 129.0 (Ar), 138.7 (*ipso*-C), 163.3 (C-3). HRMS (ESI-TOF): calcd for $C_{17}H_{18}Cl_3N_2O$ 371.0479 (M^++1). Found 371.0490.

*4.3.3. (1S,2R,5R,7S)-2-Chloro-6-(1,1-dichloroacetyl)-7-phenyl-7-methyl-6-azabicyclo[3.2.1]octane-2-carbonitrile (**4**).* $[\alpha]_D^{23}$ −46 (*c* 1.0, $CHCl_3$); IR (NaCl, neat): 3058, 3004, 2961, 2244, 1678, 1494, 1465, 1446, 1399, 1265, 1243, 1210, 1175, 1057, 844, 808, 733, 701, 664, 549 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz), 8:2 mixture of *Z*/*E* rotamers: Major rotamer (*Z*) δ 1.91 (m, 1H, H-4ax), 2.05 (m, 2H, H-8 and H-4eq), 2.21 (d, 1H, *J*=12.8 Hz, 1H, H-8), 2.31 (s, 3H, CH_3), 2.46 (dd, 1H, *J*=15.6, 5.2 Hz, H-3eq), 2.70 (ddd, 1H, *J*=15.6, 12.4, 6.4 Hz, 1H, H-3ax), 2.79 (br s, 1H, H-1), 4.48 (t, 1H, *J*=5.2 Hz, H-5), 6.25 (s, 1H, $CHCl_2$), 7.15 (dm, *J*=7 Hz, 1H, ArH), 7.25–7.38 (m, 4H, ArH). Minor rotamer (*E*) 1.88 (m, 2H, H-4ax and H-8), 2.17 (d, 1H, *J*=12 Hz, H-8), 2.29 (s, 3H, CH_3), 2.46 (m, 2H, H-3eq and H-4eq), 2.58 (ddd, *J*=15.6, 12, 6.4 Hz, 1H, H-3ax), 2.79 (br s, 1H, H-1), 4.68 (t, 1H, *J*=5.2 Hz, H-5), 5.68 (s, 1H, $CHCl_2$), 7.20–7.47 (m, 5H, ArH); ^{13}C NMR ($CDCl_3$, 100 MHz): Major rotamer δ 22.1 (CH_3), 27.7 (C-4), 29.7 (C-8), 32.9 (C-3), 55.8 (C-5), 55.9 (C-1), 58.1 (C-2), 65.2 ($CHCl_2$), 72.7 (C-7), 119.5 (CN), 125.0, 127.4, 128.6 (Ar), 142.6 (*ipso*-C), 161.5 (CO). Minor rotamer δ 24.6 (C-4), 25.0 (CH_3), 28.5 (C-8), 33.5 (C-3), 57.7 (C-5), 58.3 (C-1 and C-2), 64.5 ($CHCl_2$), 70.6 (C-7), 119.9 (CN), 125.2, 128.5, 129.3 (Ar), 143.5 (*ipso*-C), 164.5 (CO). HRMS (ESI-TOF): calcd for $C_{17}H_{18}Cl_3N_2O$ 371.0479 (M^++1). Found 371.0476.

*4.3.4. (1R,2S,5S,7S)-2-Chloro-6-(1,1-dichloroacetyl)-7-phenyl-7-methyl-6-azabicyclo[3.2.1]octane-2-carbonitrile (**5**).* $[\alpha]_D^{23}$ −51 (*c* 1.0, $CHCl_3$); IR (NaCl, neat): 3058, 3026, 2999, 2950, 2217, 1678, 1496, 1446, 1396, 1266, 1243, 1212, 1071, 10,027, 811, 764, 734, 703, 668 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz), 7:3 mixture of *Z*/*E* rotamers: Major rotamer (*Z*) δ 1.94 (tdd, 1H, *J*=12.4, 6, 1.6 Hz, H-4ax), 2.03 (s, 3H, CH_3), 2.12 (dd, *J*=15.6, 6.4 Hz, 1H, H-3eq), 2.25 (dm, 1H, *J*=12.4 Hz, H-4eq), 2.53 and 2.61 (2d, 2H, *J*=12.8, H-8), 2.73 (ddd, 1H, *J*=15.6, 12.4, 6.4 Hz, H-3ax), 2.91 (br s, 1H, H-1), 4.62 (t, 1H, *J*=5.2 Hz, H-5), 6.23 (s, 1H, $CHCl_2$), 7.15 (dm, 1H, *J*=6.8 Hz, ArH), 7.30–7.46 (m, 4H, ArH). Minor rotamer (*E*) δ 1.88 (tdd, 1H, *J*=13, 6, 1.6 Hz, 1H, H-4ax), 2.07 (s, 3H, CH_3), 2.13 (m, 1H, H-3eq), 2.33 (m, 1H, H-4eq), 2.54 (m, 2H, CH_2-8), 2.61 (m, 1H, H-3ax), 2.91 (br s, 1H, H-1), 4.83 (t, 1H, *J*=5.2 Hz, H-5), 5.71 (s, 1H, $CHCl_2$), 7.30–7.59 (m, 5H, ArH); ^{13}C NMR ($CDCl_3$, 100 MHz): Major rotamer δ 27.7 (C-4), 28.6 (CH_3), 31.9 (C-8), 32.2 (C-3), 56.2 (C-5), 56.8 (C-1), 59.1 (C-2), 66.1 ($CHCl_2$), 72.3 (C-7), 117.2 (CN), 126.3, 127.7, 128.2, 128.8, 129.1 (Ar–CH), 135.7 (*ipso*-C), 161.8 (CO). Minor rotamer δ 24.6(C-4), 30.9 (C-8), 32.6 (CH_3), 32.6 (C-3), 57.2 (C-5), 59.1 (C-2), 59.8 (C-1), 64.8 ($CHCl_2$), 70.3 (C-7), 116.9 (CN), 125.4, 128.4, 128.9, 129.8, 130.6 (Ar–CH), 136.7 (*ipso*-C), 164.9 (CO). HRMS (ESI-TOF): calcd for $C_{17}H_{18}Cl_3N_2O$ 371.0479 (M^++1). Found 371.0485.

*4.3.5. 4,4′-(4,4,4′,4′-Tetrachloro-1,1′-dimethyl-3,3′-dioxo-[8,8′-bi2,2′-diazaspiro[4.5]decane]-6,6′,9,9′-tetraene-2,2′-diyl)bis(cyclohex-1-enecarbonitrile) (**6**).* IR (NaCl, neat): 3034, 2976, 2939, 2251, 2216, 1716, 1671, 1640, 1431, 1371, 1310, 1223, 1172, 1087, 980, 910, 857, 732, 693, 647 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 1.16 (m, 6H, CH_3), 1.88 (br, 2H), 2.40 (m, 8H), 2.84 and 3.04 (2m, 1H each, CH_2), 3.10 and 3.15 (2 br s, 1H each, CH), 3.57 (br s, 2H, CHN), 3.64 (m, 2H, CHMe), 5.52 (m, 2H, =CH), 5.80–6.20 (m, 6H, =CH), 6.58 (br s, 2H, =CH); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 14.2, 14.4 (CH_3), 24.1, 25.3, 27.1, 27.2, 27.9, 28.9 (CH_2), 40.0, 40.3, 40.5 (CH), 49.4, 49.5 (CH), 53.4, 53.5 (C), 59.5, 59.6, 59.7, 59.8 (CHMe), 89.2, 89.7 (C), 112.1, 112.2 (C), 118.7, 118.8 (CN), 123.7, 123.9, 124.0, 124.3 (=CH), 131.5, 132.4, 132.6, 133.2, 133.6 (=CH), 142.4, 142.6, 142.7 (=CH), 166.2, 166.3, 166.4 (CO). HRMS (ESI-TOF): calcd for $C_{34}H_{38}Cl_4N_5O_4$ 688.1774 ($M+NH_4$)$^+$. Found 688.1779.

*4.3.6. 2,2-Dichloro-N-(4-cycanocyclohex-3-en-1-yl)-2-phenylacetamide (**7**).* IR (NaCl, neat): 3331, 2924, 2851, 2215, 1681, 1517, 1446, 1315, 1265, 1195, 1086, 888, 827, 727, 691 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 1.77 (m, 1H), 2.01 (m, 1H), 2.17 (m, 1H), 2.40 (m, 2H), 2.69 (dm, *J*=19.2 Hz, 1H), 4.11 (m, 1H), 6.57 (m, 1H), 6.72 (br s, 1H, NH), 7.42 (m, 3H, ArH), 7.70 (m, 2H, ArH); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 25.1 (CH_2), 26.5 (CH_2), 31.5 (CH_2), 44.9 (CH), 88.0 (CCl_2), 112.6 (C), 118.6 (CN), 126.5, 128.5, 130.0 (Ar–CH), 139.1 (*ipso*-C), 141.6 (CH), 165.2 (C=O). HRMS (ESI-TOF): calcd for $C_{15}H_{15}Cl_2N_2O$ 309.0556 (M^++1). Found 309.0555.

*4.3.7. 4-((S)-4,4,8-Trichloro-1-methyl-3-oxo-2-azaspiro[4.5] deca-6,9-dien-2-yl)cyclohex-1-enecarbonitrile (**8**).* IR (NaCl, neat): 3047, 2926, 2852, 2215, 1719, 1639, 1428, 1370, 1309, 1222, 1188, 1172, 1086, 979, 924, 855, 835, 797, 730, 692 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 1.13 and 1.15 (2 d, 3H, *J*=6.4 Hz, CH_3), 1.89 (m, 1H), 2.42 (m, 4H), 2.89 and 3.07 (2 m, 1H), 3.58 (m, 1H), 3.72 (q, 1H, *J*=6.8 Hz), 5.00 (tt, 1H, *J*=3.6, 1.2 Hz), 5.66 and 5.69 (2ddd, 1H, *J*=10.4, 2.4, 1.2 Hz), 6.04 (dm, 1H, *J*=10.4 Hz), 6.27 (dm, 1H, *J*=10.4 Hz), 6.35 (dm, 1H, *J*=10.4 Hz), 6.58 (br s, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 14.1 and 14.2 (CH_3), 24.1 and 25.4 (CH_2), 27.2 and 27.3 (CH_2), 27.9 and 28.9 (CH_2), 49.2 and 49.5 (CH), 53.2 (C), 59.1 and 59.2 (CH), 87.8 (CCl_2), 112.1 and 112.2 (=C), 118.7 (CN), 125.8 (=CH), 126.3 (=CH), 130.5 (=CH), 132.2 (=CH), 142.3 and 142.5 (=CH), 166.1 (CO). HRMS (ESI-TOF): calcd for $C_{17}H_{18}Cl_3N_2O$ 371.0479 (M^++1). Found 371.0478.

*4.3.8. 4-((S)-4,4-Dichloro-1-methyl-3,8-dioxo-2-azaspiro[4.5] deca-6,9-dien-2-yl)cyclohex-1-enecarbonitrile (**9**).* IR (NaCl, neat): 3058, 2936, 2853, 2215, 1722, 1668, 1633, 1434, 1371, 1319, 1263, 1219, 1172, 1124, 1080, 1031, 980, 924, 871, 847, 734, 693 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 1.20 and 1.21 (2 d, 3H, *J*=6.8 Hz, CH_3), 1.82 (m, 1H), 2.44 (m, 4H), 2.89 and 3.11 (2 m, 1H), 3.62 (m, 1H), 3.97 (q, 1H, *J*=6.8 Hz), 6.54 (dt, 1H, *J*=10.4, 1.6 Hz), 6.59 (br s, 1H), 6.60 (dd, 1H, *J*=10.4, 1.6 Hz), 6.67 and 6.68 (ddd, 1H, *J*=10.4, 3.2 Hz), 7.05 (ddd, 1H, *J*=10.4, 3.2, 0.8 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 14.3 (CH_3), 24.0 and 25.5 (CH_2), 27.1 and 27.3 (CH_2), 27.8 and 29.0 (CH_2), 49.9 (CH), 55.9 (C), 57.8 and 57.9 (CH), 86.6 (CCl_2), 112.3 (=C), 118.5 (CN), 132.7 (=CH), 134.3 (=CH), 142.0 (=CH), 142.1 and 142.2 (=CH), 142.2 and 142.4 (=CH), 165.3 (CO), 184.1 (CO). HRMS (ESI-TOF): calcd for $C_{17}H_{17}Cl_2N_2O_2$ 351.0661 (M^++1). Found 351.0650.

4.4. (1*R*,2*S*,5*R*,7*S*)-6-Acetyl-7-methyl-7-phenyl–6-azabicyclo [3.2.1]octane-2-carbonitrile (10)

To a solution of **4** (27 mg, 0.07 mmol) in MeOH (2 mL) were added at 0 °C NH_4Cl (23 mg, 0.43 mmol) followed by Zn (47.5 mg, 0.73 mmol) portionwise. The mixture was allowed to reach rt, stirred for a further 2 h, filtered on a Celite pad, and concentrated. The residue was taken up in CH_2Cl_2 and the resulting solution was washed with brine, and dried. Purification by chromatography (CH_2Cl_2/AcOEt 90:10 to CH_2Cl_2/EtOAc 80:20) gave 14 mg (72%) of

dehalogenated normorphan **9**[20] and its epimer **10** as a minor compound.

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Supplementary data

Copies of the ^{1}H and ^{13}C NMR spectra for all new compounds. Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.tet.2013.04.042.

References and notes

1. Nagashima, H.; Wakamatsu, H.; Ozaki, N.; Ishii, T.; Watanabe, M.; Tajima, T.; Itoh, K. *J. Org. Chem.* **1992**, *57*, 1682–1689.
2. Iwamatsu, S.; Kondo, H.; Matsubara, K.; Nakashima, H. *Tetrahedron* **1999**, *55*, 1687–1706.
3. Seigal, B. A.; Fajardo, C.; Snapper, M. L. *J. Am. Chem. Soc.* **2005**, *127*, 16329–16332.
4. McGonagle, F. I.; Brown, L.; Cooke, A.; Sutherland, A. *Org. Biomol. Chem.* **2010**, *8*, 3418–3425.
5. Goodall, K.; Parsons, A. F. *Tetrahedron* **1996**, *52*, 6739–6758.
6. Quirante, J.; Escolano, C.; Massot, M.; Bonjoch, J. *Tetrahedron* **1997**, *53*, 1391–1402.
7. Vila, X.; Quirante, J.; Paloma, L.; Bonjoch, J. *Tetrahedron Lett.* **2004**, *45*, 4661–4664.
8. Clark, A. *J. Chem. Soc. Rev.* **2002**, *31*, 1–11.
9. (a) Pintauer, T.; Matyjaszewski, K. *Chem. Soc. Rev.* **2008**, *37*, 1087–1097; (b) Eckenhoff, W. T.; Pintauer, T. *Catal. Rev. Sci. Eng.* **2010**, *52*, 1–59; (c) Pintauer, T. *Eur. J. Inorg. Chem.* **2010**, 2449–2460.
10. (a) Bregoli, M.; Felluga, F.; Frenna, V.; Ghelfi, F.; Pagnoni, U. M.; Parsons, A. F.; Petrillo, G.; Spinelli, D. *Synthesis* **2011**, 1267–1278; (b) Casolari, R.; Felluga, F.; Frenna, V.; Ghelfi, F.; Pagnoni, U. M.; Parsons, A. F.; Spinelli, D. *Tetrahedron* **2011**, *67*, 408–416; (c) Benedetti, M.; Forti, L.; Ghelfi, G.; Pagnoni, U. M.; Onzoni, R. *Tetrahedron* **1997**, *53*, 14031–14042.
11. Edlin, C. D.; Faulkner, J.; Quayle, P. *Tetrahedron Lett.* **2006**, *47*, 1145–1151.
12. Thommes, K.; Fernéndez-Zúmel, M. A.; Buron, C.; Godinat, A.; Scopelliti, R.; Severin, K. *Eur. J. Org. Chem.* **2011**, 249–255.
13. Tseng, C. K.; Teach, E. G.; Simons, R. W. *Synth. Commun.* **1984**, 1027–1031.
14. Cassayre, J.; Quiclet-Sire, B.; Saunier, J. B.; Zard, S. Z. *Tetrahedron Lett.* **1998**, *39*, 8995–8998.
15. Quirante, J.; Escolano, C.; Merino, A.; Bonjoch, J. *J. Org. Chem.* **1998**, *63*, 968–976.
16. Quirante, J.; Escolano, C.; Diaba, F.; Bonjoch, J. *J. Chem. Soc., Perkin Trans. 1* **1999**, 1157–1162.
17. Gandon, L. A.; Russell, A. G.; Güveli, T.; Brodwolf, A. E.; Kariuki, B. M.; Spencer, N.; Snaith, J. S. *J. Org. Chem.* **2006**, *71*, 5198–5207.
18. Bonjoch, J.; Diaba, F.; Bradshaw, B. *Synthesis* **2011**, 993–1018.
19. Diaba, F.; Martínez-Laporta, A.; Bonjoch, J.; Pereira, A.; Muñoz-Molina, J. M.; Pérez, P. J.; Belderrain, T. R. *Chem. Commun.* **2012**, 8799–8801.
20. Quirante, J.; Diaba, F.; Vila, X.; Bonjoch, J.; Lago, E.; Molins, E. *C. R. Chim.* **2001**, *4*, 513–521.
21. Marin, M.-L.; Zaragoza, R. J.; Miranda, M. A.; Diaba, F.; Bonjoch, J. *Org. Biomol. Chem.* **2011**, *9*, 3180–3187.
22. Due to the troublesome separation of enantiopure epimers **1a** and **1b**, we decided to carry out the studies with the epimeric mixture since the reaction products were easier to separate.
23. 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 copper complex (activator) by the abstraction of a halogen atom from the higher oxidation state complex (deactivator), see Ref. 9.
24. For the rare 1,4-hydrogen atom transfer in radical processes, see: (a) Journet, M.; Malacria, M. *Tetrahedron Lett.* **1992**, *33*, 1893–1896; (b) Gulea, M.; Lopez-Romero, J. M.; Fensterbak, L.; Malacria, M. *Org. Lett.* **2000**, *2*, 2591–2594; (c) Cassayre, J.; Zard, S. Z. *J. Organomet. Chem.* **2001**, *624*, 316–326.
25. Ishibashi, H.; Kameoka, C.; Kodama, K.; Kawanami, H.; Hamada, M.; Ikeda, M. *Tetrahedron* **1997**, *53*, 9611–9622.
26. Rodríguez-Soria, V.; Quintero, L.; Sartillo-Piscil, F. *Tetrahedron* **2008**, *64*, 2750–2754.
27. Quirante, J.; Torra, M.; Diaba, F.; Escolano, C.; Bonjoch, J. *Tetrahedron: Asymmetry* **1999**, *10*, 2339–2410.
28. Sasmal, A.; Taniguchi, T.; Wipf, P.; Curran, D. P. *Can. J. Chem.* **2013**, *90*, 1–5.
29. (a) Buckmelter, A. J.; Kim, A. I.; Rychnovsky, S. D. *J. Am. Chem. Soc.* **2000**, *122*, 9386–9390; (b) Griesbeck, A. G.; Kramer, W.; Lex, J. *Angew. Chem., Int. Ed.* **2001**, *40*, 577–579.
30. (a) Bordwell, F. G.; Lynch, T. Y. *J. Am. Chem. Soc.* **1989**, *111*, 7558–7562; (b) Renaud, P.; Giraud, L. *Synthesis* **1996**, 913–926; (c) Welle, F. M.; Beckhaus, H.-D.; Rüchardt, C. *J. Org. Chem.* **1997**, *62*, 552–558.
31. Autrey, S. T.; Alnajjar, M. S.; Nelson, D. A.; Franz, J. A. *J. Org. Chem.* **1991**, *56*, 2197–2202.
32. Cid, M. M.; Pombo-Villar, E. *Helv. Chim. Acta* **1993**, *76*, 1591–1607.
33. Additionally, we carried out a reaction with a sample composed mainly of **1b**, using CuCl (30 mol %), TPMA (30 mol %) in DCE, under microwave irradiation for 15 min. The ^{1}H NMR spectrum of the crude showed the signals of normorphan **5**.
34. Radical spirocyclization upon benzyl derivatives (i.e., lacking the methyl group at the benzylic position) from trichloroacetamides evolves through a cyclohexanedienyl radical trapping with a chlorine atom: Diaba, F.; Montiel, J. A.; Martínez-Laporta, A.; Bonjoch, J. *Tetrahedron Lett.* **2013**, *54*, 2619–2622.
35. For a related reaction upon an indole ring leading to spiroindolines, see: (a) Stevens, C. V.; Van Meenem, E.; Eeckhout, Y.; Vanderhoydonck, B.; Hooghe, W. *Chem. Commun.* **2005**, 4827–4829; (b) Van der Jeught, S.; De Vos, N.; Masschelein, K.; Ghiviriga, I.; Stevens, C. V. *Eur. J. Org. Chem.* **2010**, 5444–5453.
36. A related dearomatization followed by a dimerization process of cyclohexadienyl radicals was observed in a classical study of the decomposition of aryl diazonium salts using copper: Hey, D. H.; Rees, C. W.; Todd, A. R. *J. Chem. Soc. C* **1967**, 1518–1525.
37. (a) Studer, A.; Bossart, M. *Tetrahedron* **2001**, *57*, 9649–9667; (b) Robertson, J.; Palframan, M. J.; Shea, S. A.; Tchabanenko, K.; Unsworth, W. P.; Winters, C. *Tetrahedron* **2008**, *64*, 11896–11907.
38. For 1,4-phenyl radical transfer starting from haloacetamides or related compounds, see: (a) Ishibashi, H.; Nakamura, N.; Ito, K.; Kitayama, S.; Ikeda, M. *Heterocycles* **1990**, *31*, 1781–1784; (b) Clark, A. J.; Coles, S. R.; Collis, A.; Debure, T.; Guy, C.; Murphy, N. P.; Wilson, P. *Tetrahedron Lett.* **2009**, *50*, 5609–5612; (c) Fuentes, L.; Quintero, L.; Cordero-Vargas, A.; Eustaquio, C.; Terán, J. L.; Sartillo-Piscil, F. *Tetrahedron Lett.* **2011**, *52*, 3630–3632; (d) Sandoval-Lira, J.; Hernández-Pérez, J. M.; Sartillo-Piscil, F. *Tetrahedron Lett.* **2012**, *53*, 6689–6693.
39. Quirante, J.; Escolano, C.; Diaba, F.; Torra, M.; Bonjoch, J. *Magn. Reson. Chem.* **2000**, *38*, 891–893.
40. Abraham, R. J.; Warne, M. A.; Griffiths, L. *J. Chem. Soc., Perkin Trans. 2* **1997**, 881–886.
41. For recent NMR studies on *Z* and *E* rotamers in bridged azapolycyclic compounds, see: Sulima, A.; Cheng, K.; Jacobson, A. E.; Rice, K. C.; Gawrisch, K.; Lee, Y.-S. *Magn. Reson. Chem.* **2013**, *51*, 82–88.

Unusual rearrangement and dearomatization reactions in Cu(I)-catalyzed atom transfer radical cyclizations from N-(1-phenylethyl)trichloroacetamides

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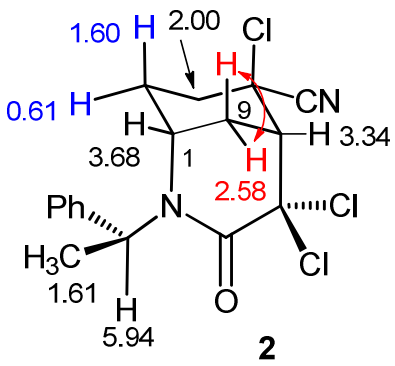
Supporting information

- ^{1}H NMR and ^{13}C NMR spectra of product **2-9**

H1 / Mercury-400F
cdcl3 / Temp: Ambient / N.Reg: XXXXXXXXXX
Usuari: san / Mostra: JA094-26
Nom: FAIZA DIABA
Data: 19/12/12 / Ope.: F.DIABA
Experiment: s2pul

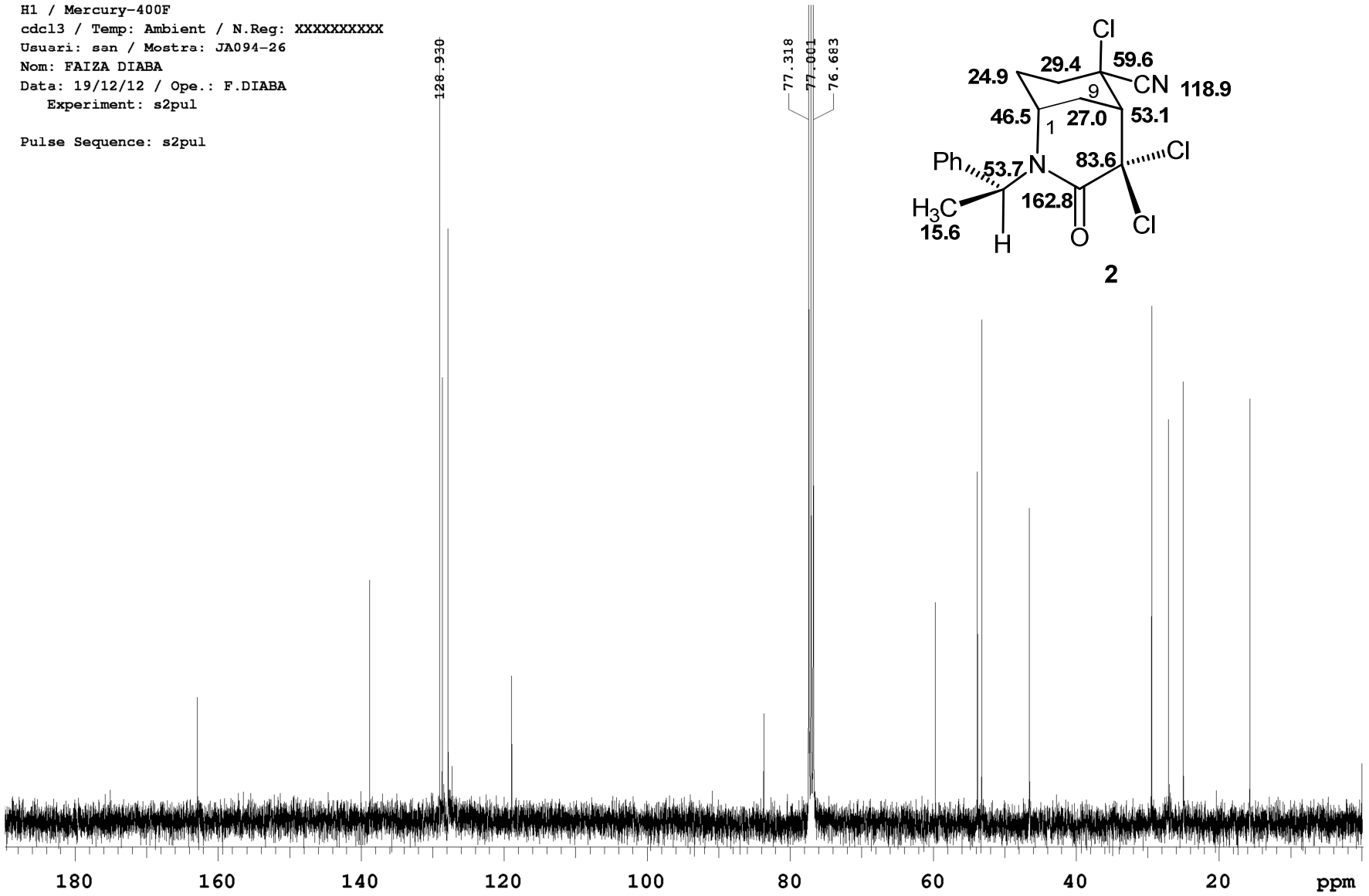
Pulse Sequence: s2pul



2

H1 / Mercury-400F
cdcl3 / Temp: Ambient / N.Reg: XXXXXXXXXX
Usuari: san / Mostra: JA094-26
Nom: FAIZA DIABA
Data: 19/12/12 / Ope.: F.DIABA
Experiment: s2pul

Pulse Sequence: s2pul



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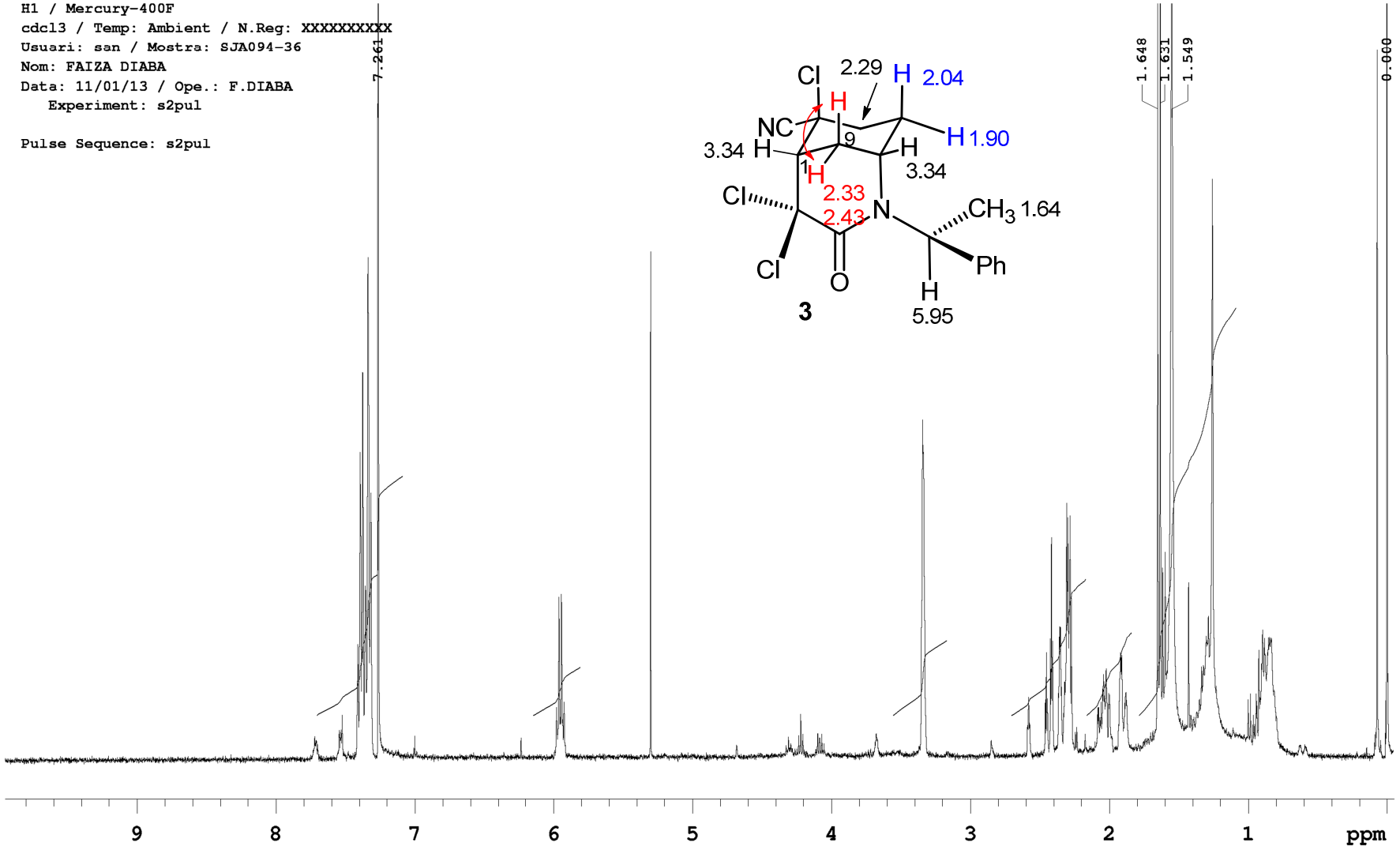
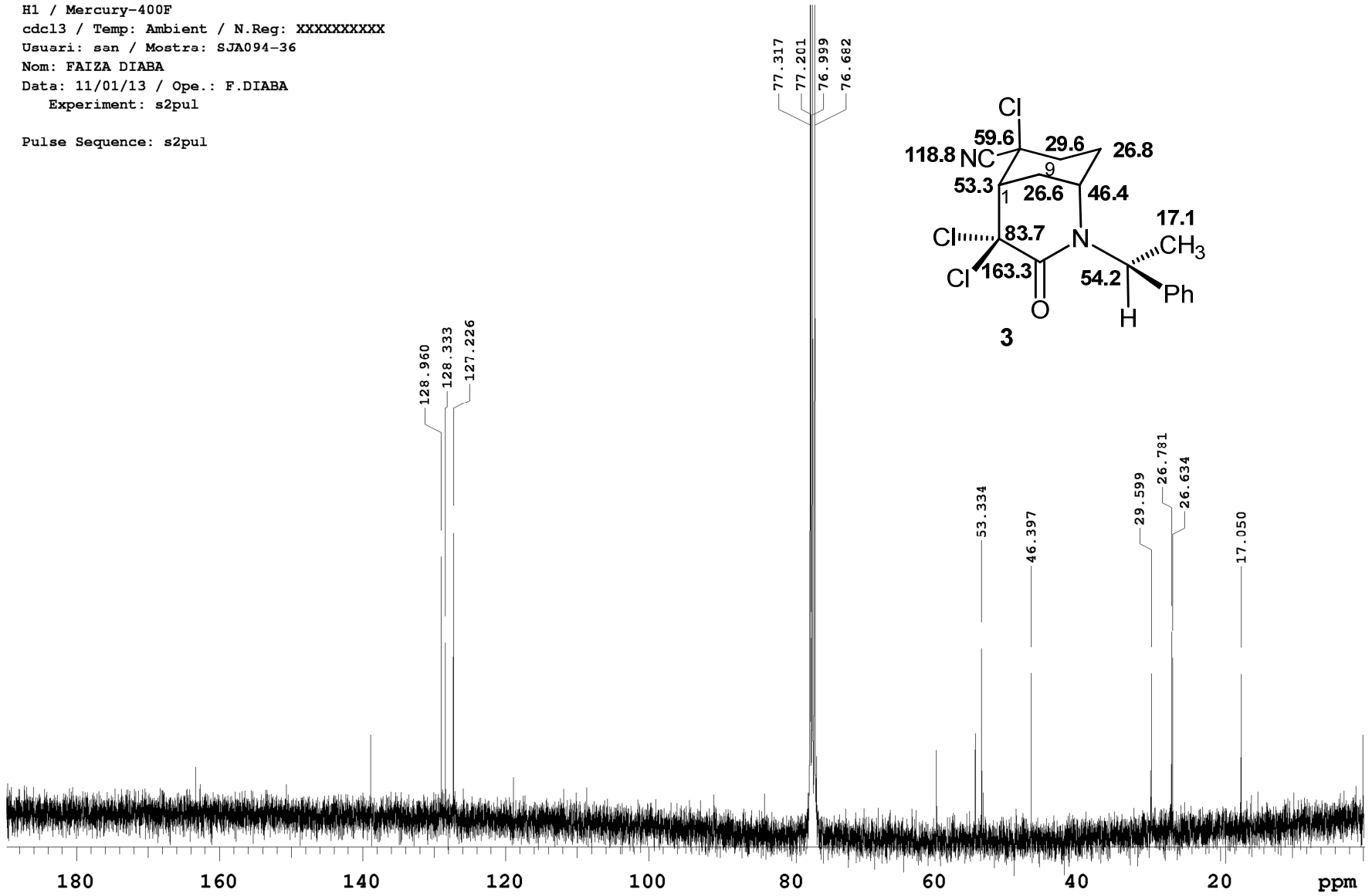

H1 / Mercury-400F
cdcl3 / Temp: Ambient / N.Reg: XXXXXXXXXX
Usuari: san / Mostra: SJA094-36
Nom: FAIZA DIABA
Data: 11/01/13 / Ope.: F.DIABA
Experiment: s2pul
Pulse Sequence: s2pul
7.261
1.648
1.631
1.549
0.000
Cl
2.29
H 2.04
H
NC
H 1.90
3.34 H
9
H
3.34
1
H
2.33
2.43
Cl
N
CH3 1.64
Cl
Ph
O
H
5.95
3
9
8
7
6
5
4
3
2
1
ppm

H1 / Mercury-400F
cdcl3 / Temp: Ambient / N.Reg: XXXXXXXXXX
Usuari: san / Mostra: SJA094-36
Nom: FAIZA DIABA
Data: 11/01/13 / Ope.: F.DIABA
Experiment: s2pul

Pulse Sequence: s2pul



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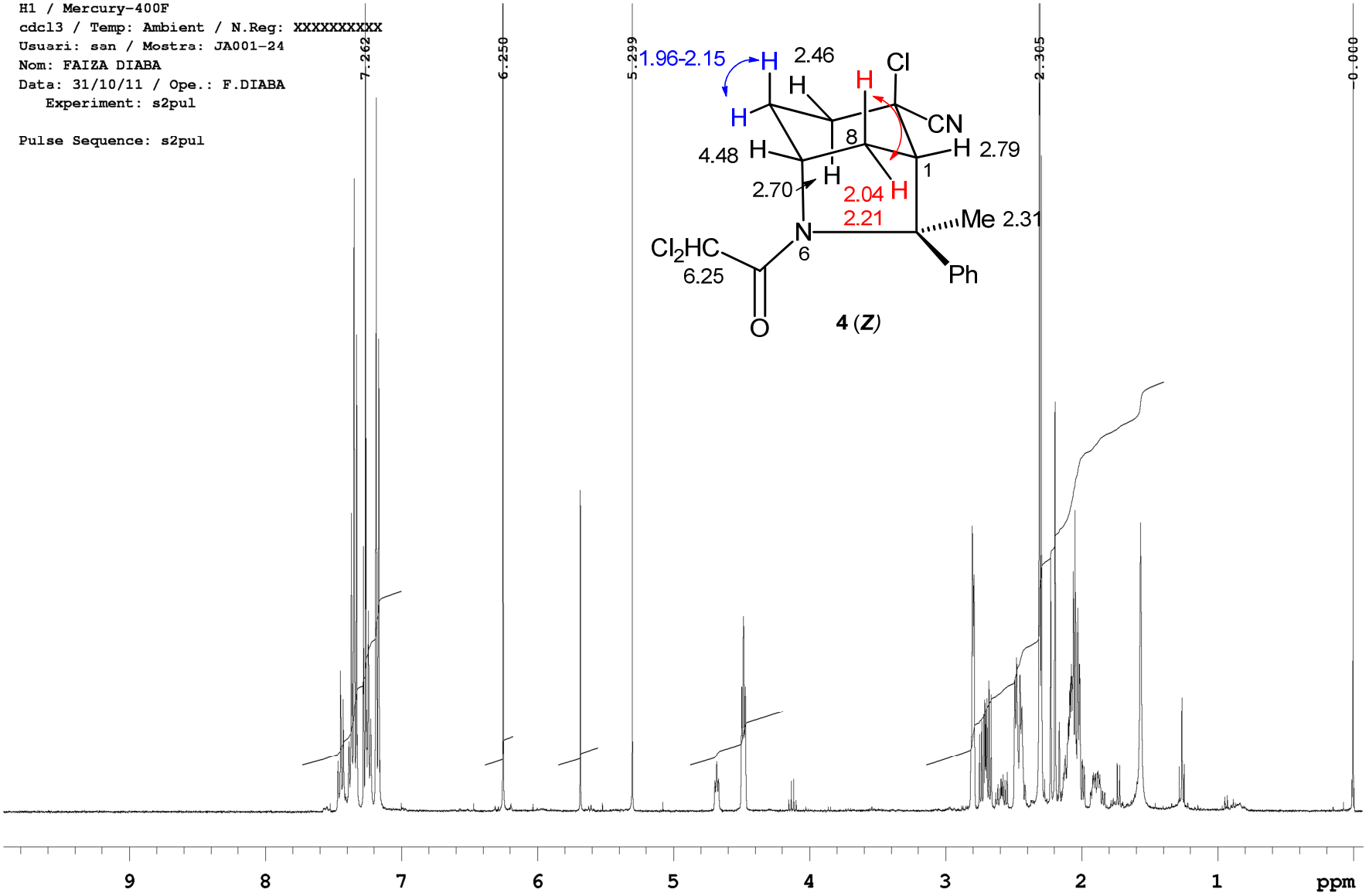
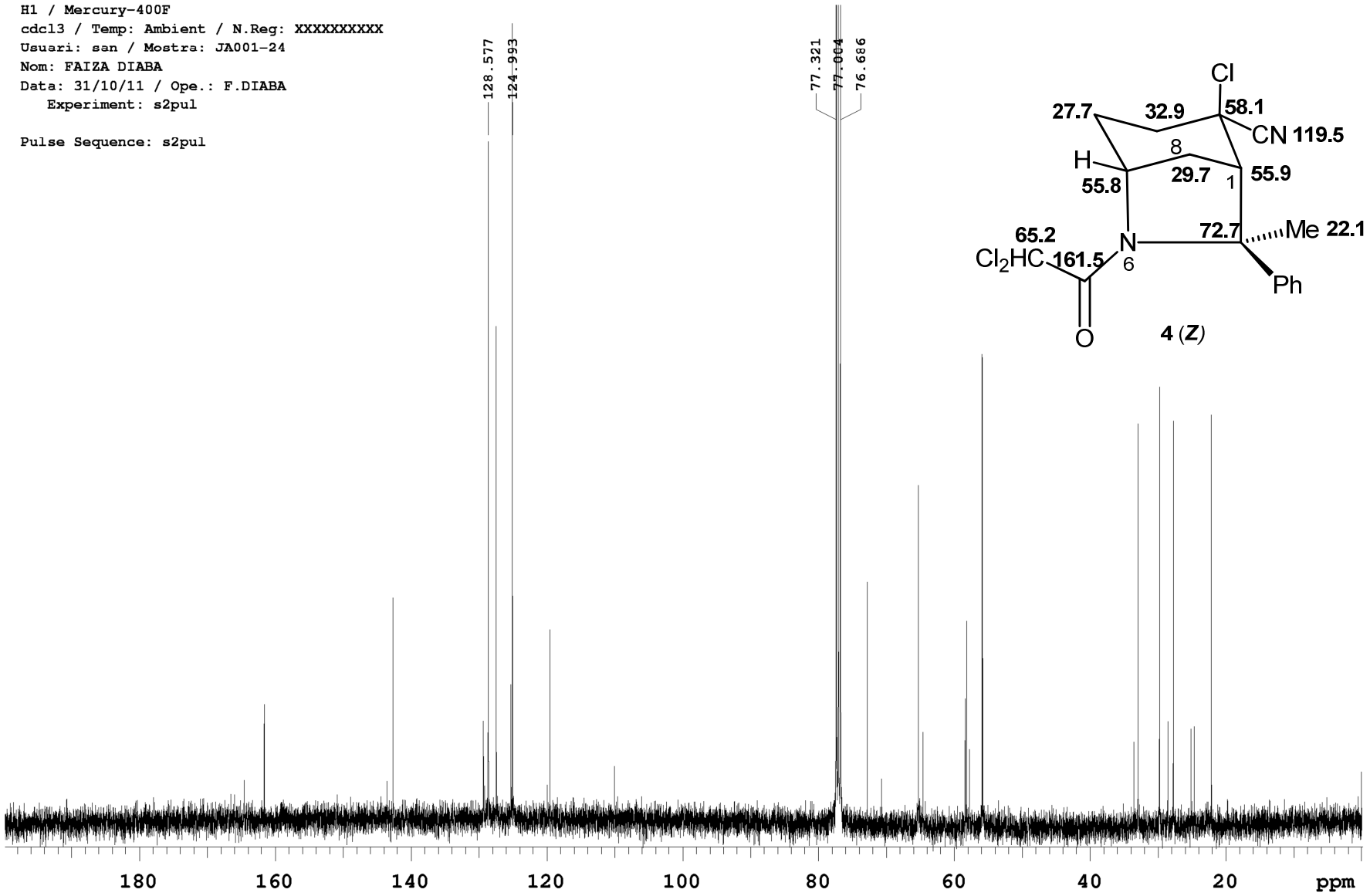

H1 / Mercury-400F
cdcl3 / Temp: Ambient / N.Reg: XXXXXXXXXX
Usuari: san / Mostra: JA001-24
Nom: FAIZA DIABA
Data: 31/10/11 / Ope.: F.DIABA
Experiment: s2pul
Pulse Sequence: s2pul
7.262
6.250
5.299
2.305
0.000
1.96-2.15
2.46
Cl
CN
4.48
2.79
2.70
2.04
2.21
Me 2.31
Cl2HC
6.25
Ph
4 (Z)
9
8
7
6
5
4
3
2
1
ppm

H1 / Mercury-400F
cdcl3 / Temp: Ambient / N.Reg: XXXXXXXXXX
Usuari: san / Mostra: JA001-24
Nom: FAIZA DIABA
Data: 31/10/11 / Ope.: F.DIABA
Experiment: s2pul

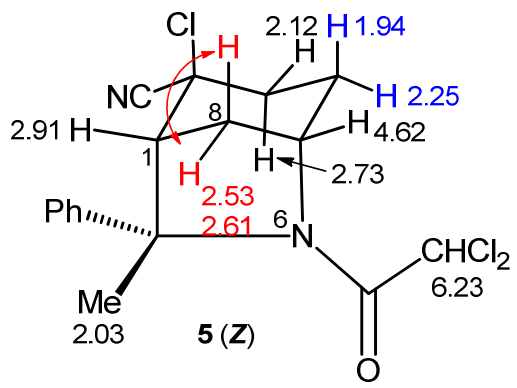
Pulse Sequence: s2pul

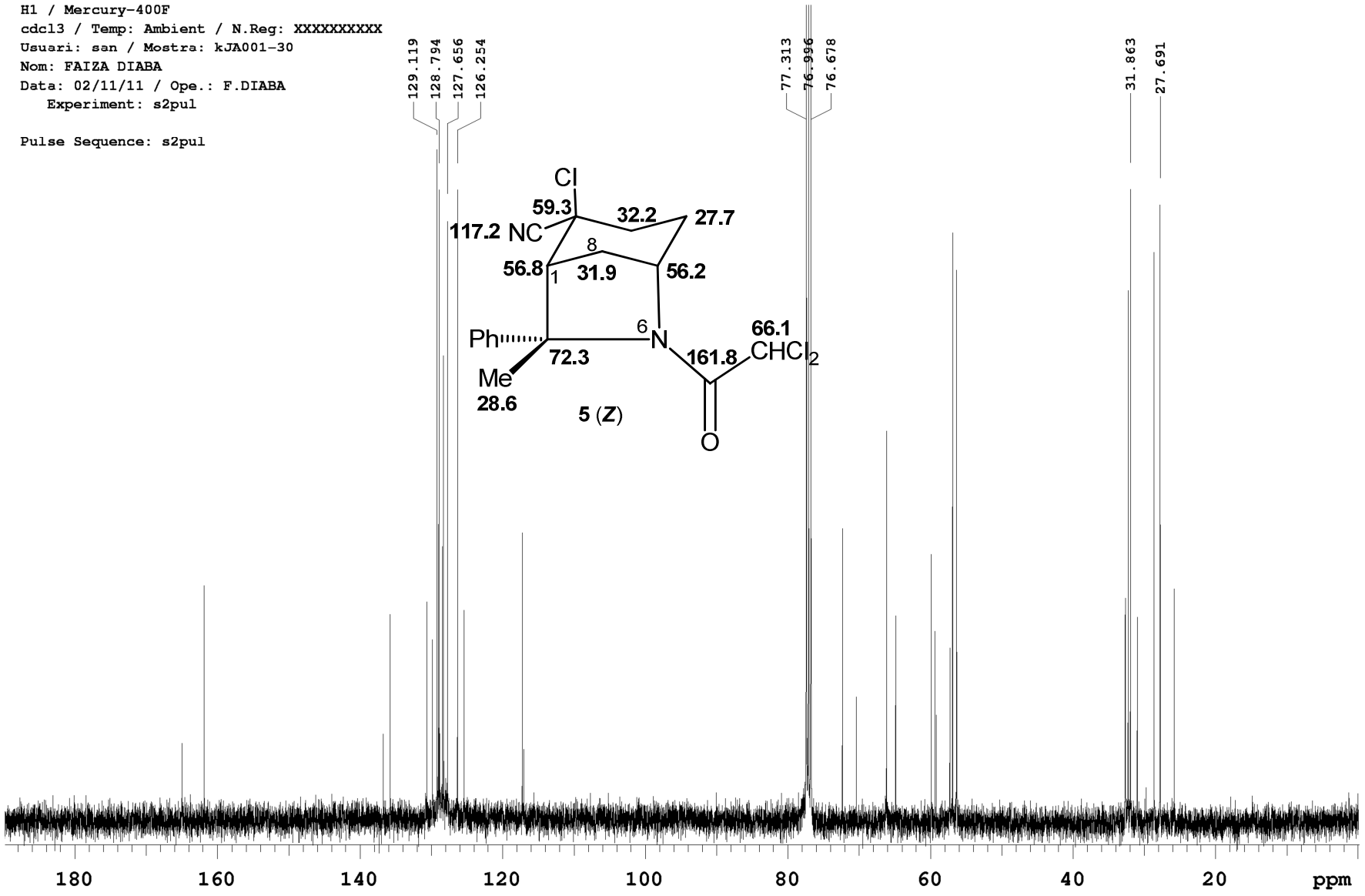


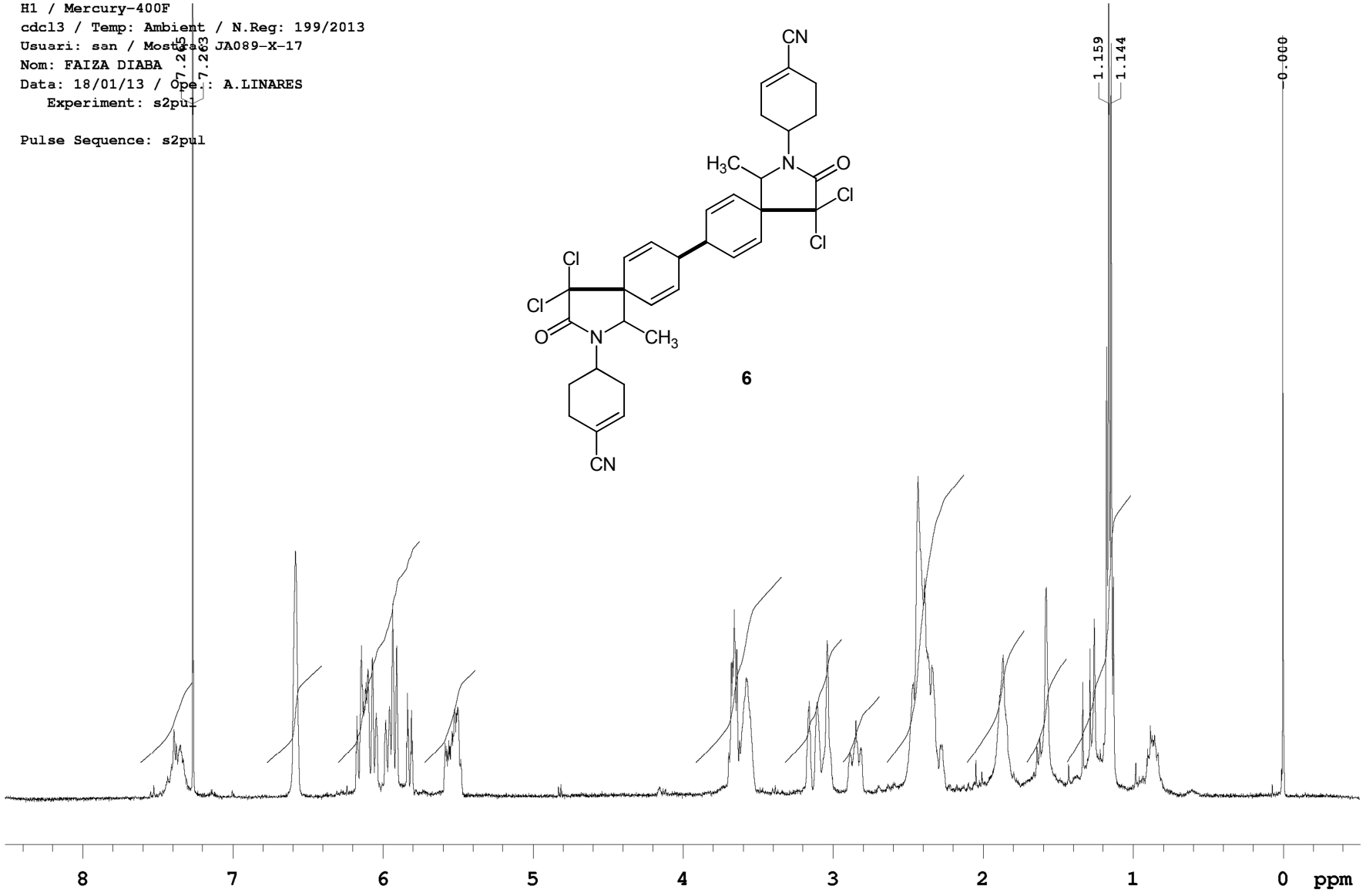
4 (*Z*)

H1 / Mercury-400F
cdcl3 / Temp: Ambient / N.Reg: XXXXXXXXXX
Usuari: san / Mostra: kJA001-30
Nom: FAIZA DIABA
Data: 02/11/11 / Ope.: F.DIABA
Experiment: s2pul

Pulse Sequence: s2pul

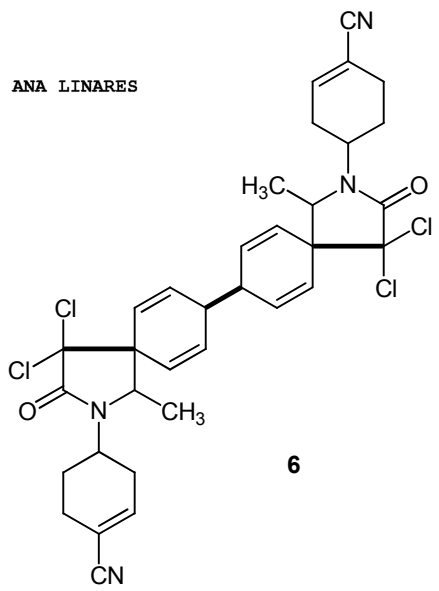



H1 / Mercury-400F
cdcl3 / Temp: Ambient / N.Reg: XXXXXXXXXX
Usuari: san / Mostra: kJA001-30
Nom: FAIZA DIABA
Data: 02/11/11 / Ope.: F.DIABA
Experiment: s2pul
Pulse Sequence: s2pul
129.119
128.794
127.656
126.254
77.313
76.996
76.678
31.863
27.691
Cl
59.3
32.2
27.7
117.2 NC
8
56.8
1
31.9
56.2
6
N
66.1
CHCl2
Ph
72.3
161.8
Me
28.6
O
5 (Z)
180
160
140
120
100
80
60
40
20
ppm

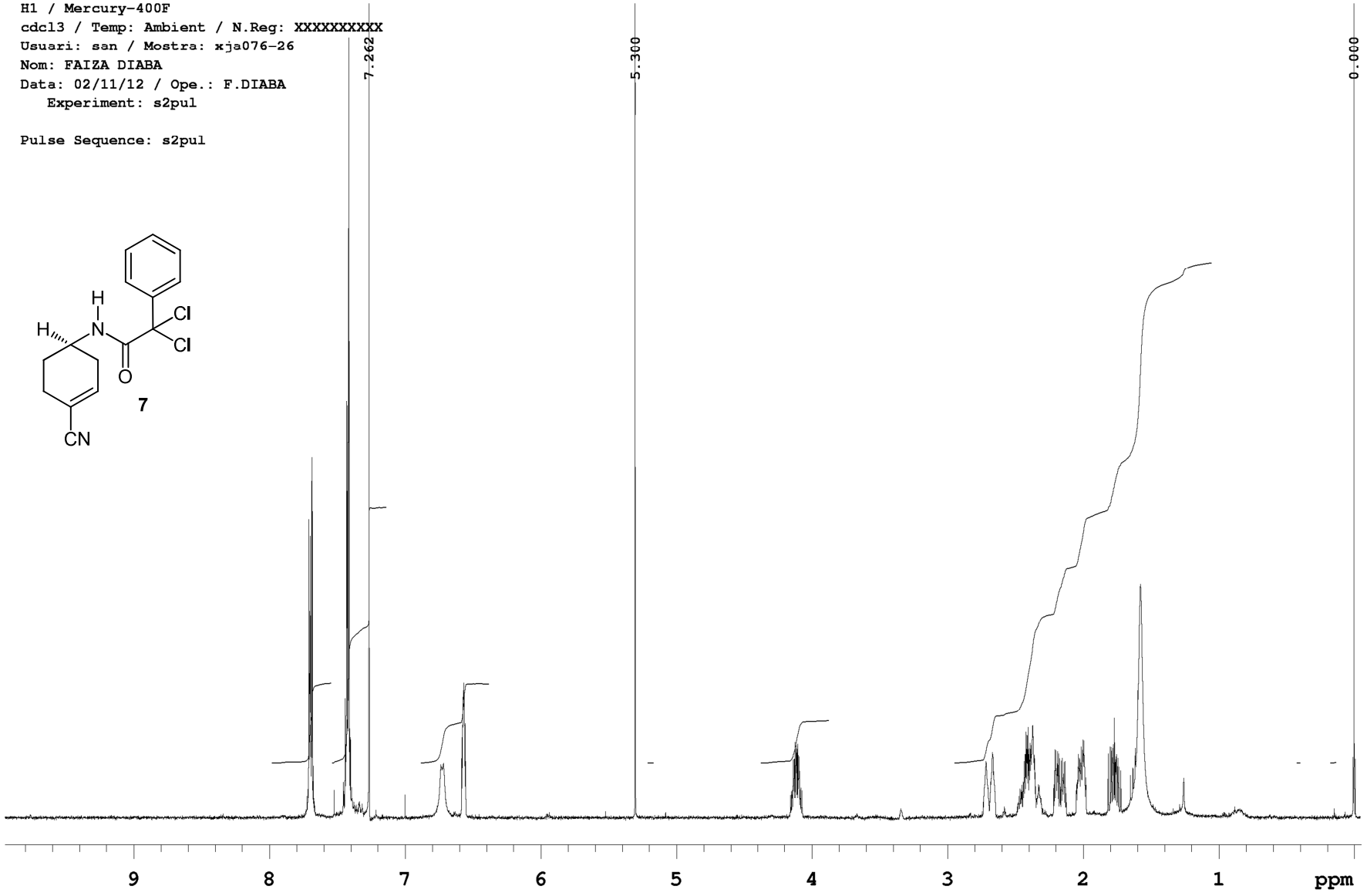

H1 / Mercury-400F
cdcl3 / Temp: Ambient / N.Reg: 199/2013
Usuari: san / Mostra: JA089-X-17
Nom: FAIZA DIABA
Data: 18/01/13 / Ope.: A.LINARES
Experiment: s2pul
Pulse Sequence: s2pul
7.255
7.263
1.159
1.144
0.000
CN
H3C
N
O
Cl
Cl
Cl
Cl
O
N
CH3
CN
6
8
7
6
5
4
3
2
1
0
ppm

Equip: Mercury-400F
C13 / Solvent: cdcl3 / Temp: 25 C
N.Reg: 199/2013
Usuari: san / Mostra: JA089-X-17
Nom: FAIZA DIABA _
Data: 18/01/13 15:15:27 h./ Ope.: ANA LINARES

Pulse Sequence: s2pul

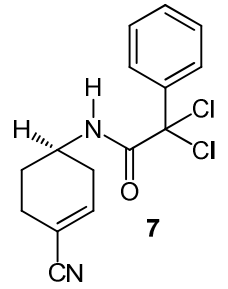


6


H1 / Mercury-400F
cdcl3 / Temp: Ambient / N.Reg: XXXXXXXXXX
Usuari: san / Mostra: xja076-26
Nom: FAIZA DIABA
Data: 02/11/12 / Ope.: F.DIABA
Experiment: s2pul
Pulse Sequence: s2pul
7.262
5.300
0.000
H
N
Cl
Cl
O
CN
7
9
8
7
6
5
4
3
2
1
ppm

H1 / Mercury-400F
cdcl3 / Temp: Ambient / N.Reg: XXXXXXXXXX
Usuari: san / Mostra: xja076-26
Nom: FAIZA DIABA
Data: 02/11/12 / Ope.: F.DIABA
Experiment: s2pul

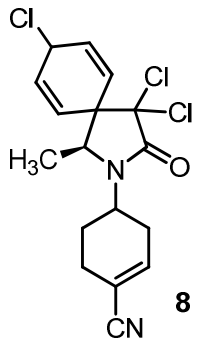
Pulse Sequence: s2pul



7

Equip: Mercury-400F
H1 / Solvent: CDCl3 / Temp: 25 C
N.Reg: 937/2013
Usuari: san / Mostra: ja118-17
Nom: FAIZA DIABA _
Data: 07/03/13 14:20:01 h./ Ope.: ANA LINARES

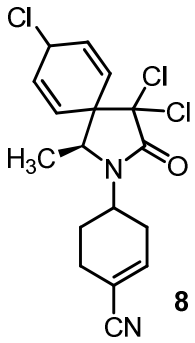
Pulse Sequence: s2pul



8

Equip: Mercury-400F
C13 / Solvent: cdcl3 / Temp: 25 C
N.Reg: 937/2013
Usuari: san / Mostra: ja118-17
Nom: FAIZA DIABA _
Data: 08/03/13 07:52:35 h./ Ope.: ANA LINARES

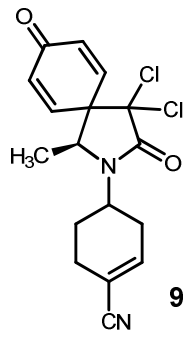
Pulse Sequence: s2pul



8

Equip: Mercury-400F
H1 / Solvent: cdcl3 / Temp: 25 C
N.Reg: 881/2013
Usuari: san / Mostra: JA118-23
Nom: FAIZA DIABA _
Data: 05/03/13 13:57:28 h./ Ope.: ANA LINARES

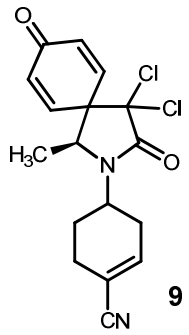
Pulse Sequence: s2pul



9

Equip: Mercury-400F
C13 / Solvent: cdcl3 / Temp: 25 C
N.Reg: 881/2013
Usuari: san / Mostra: JA118-23
Nom: FAIZA DIABA _
Data: 05/03/13 14:04:35 h./ Ope.: ANA LINARES

Pulse Sequence: s2pul



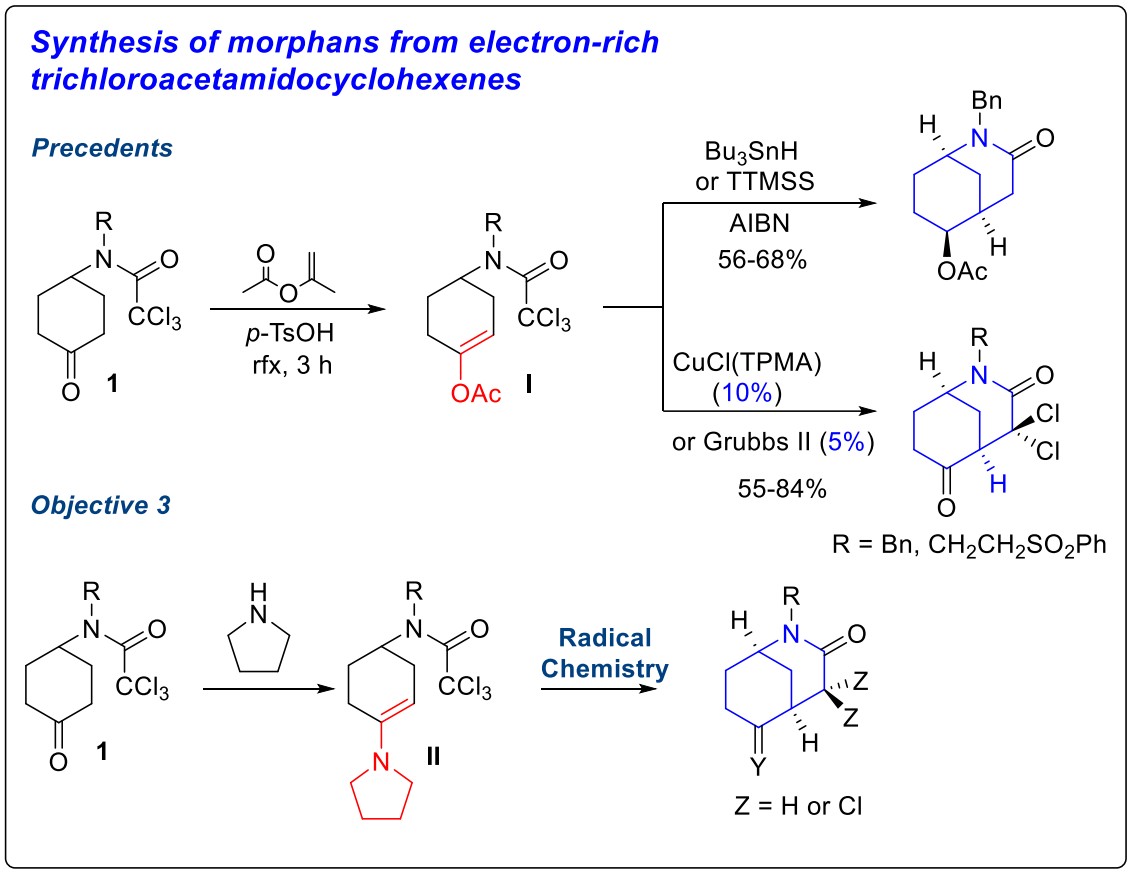
9

Chapter 4

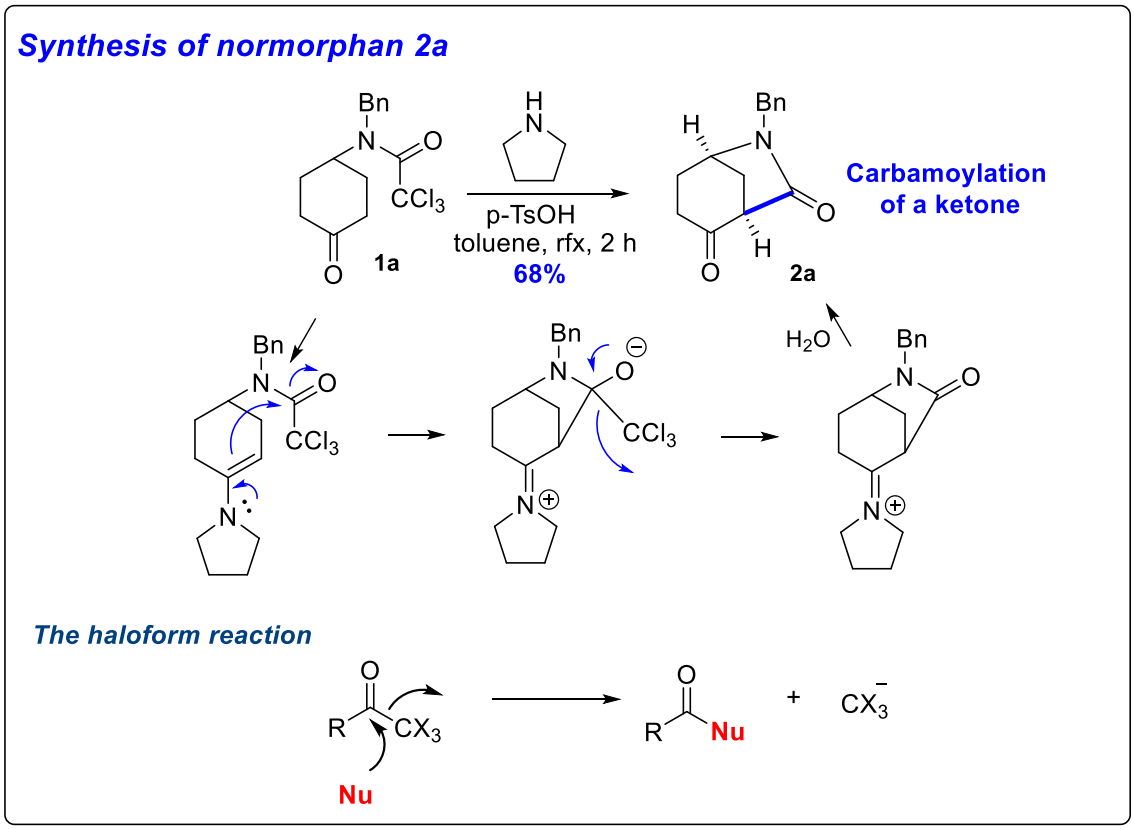
Synthesis of Normorphans through an Efficient Intramolecular Carbamoylation of Ketones

Org. Lett. **2015**, *17*, 3860-3863.

The third objective of this thesis work was to expand the methodology developed in our research group for the radical cyclization of trichloroacetamides upon electron-rich alkenes, namely enol acetates **I**, prepared from ketone **1** by reactions with isopropenylacetate in acid media, to the corresponding enamines **II** as radical acceptors (Scheme 4.1). Thus a study was carried out to examine the scope of the radical cyclization from enamines **II** under reductive or non-reductive conditions and then plan an asymmetric synthesis of morphans using chiral amines.

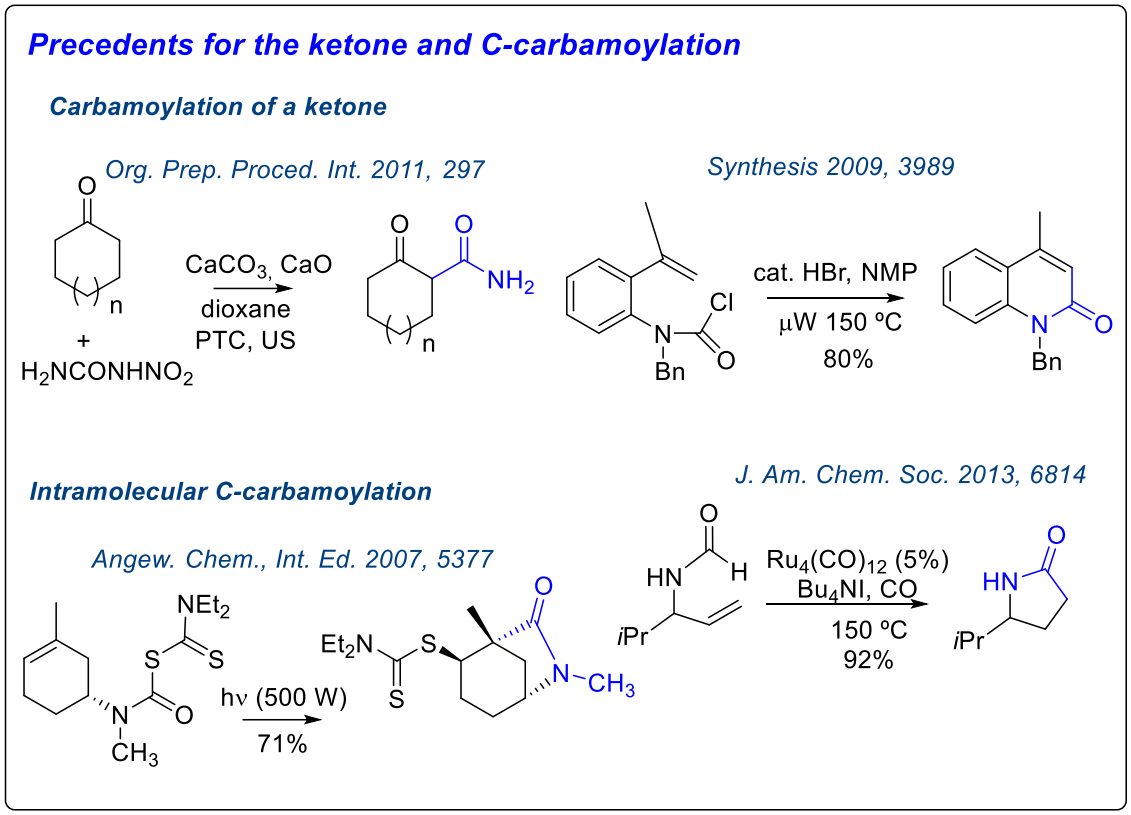


Scheme 4.1.



Scheme 4.2.

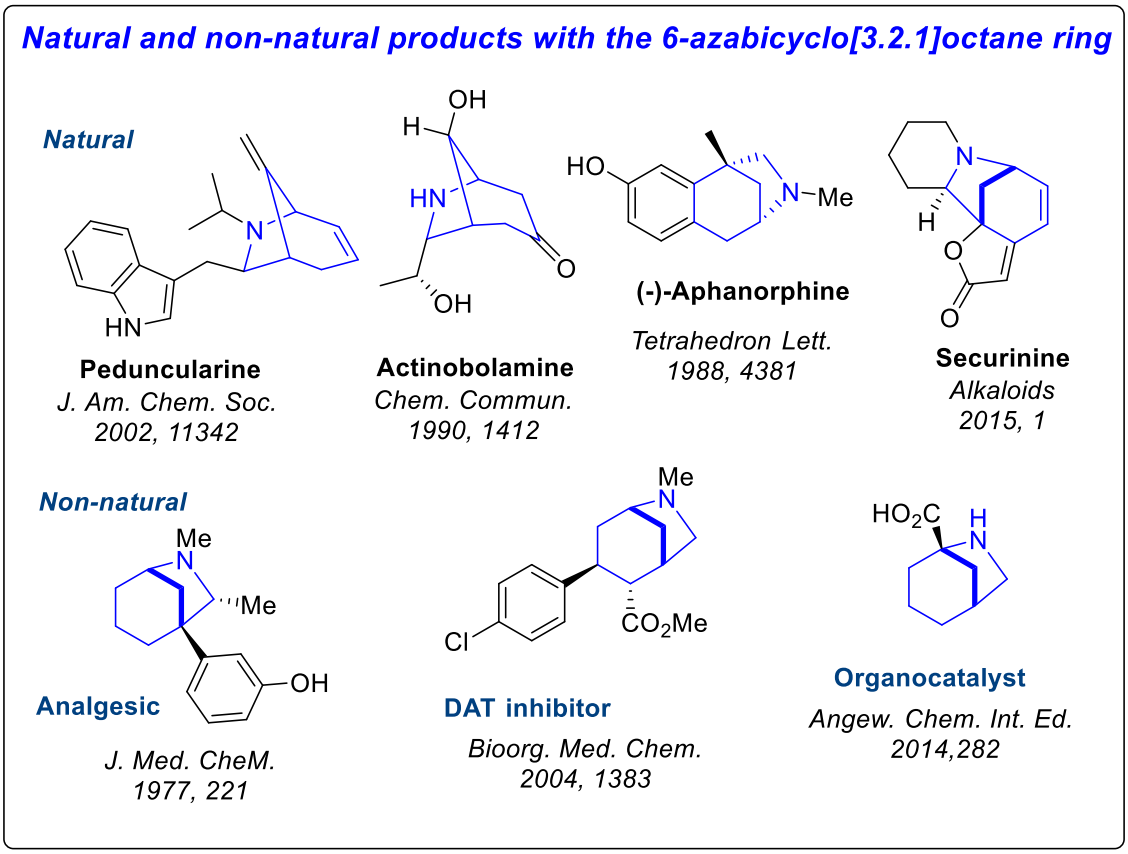
Using the classical conditions for the preparation of enamines, ketone **1a** was treated with pyrrolidine (1.2 equiv) and a catalytic amount of *p*-TsOH in refluxing benzene for two hours. Surprisingly, after solvent removal no signals in the ^{1}H NMR spectrum of the expected enamine were detected, instead those corresponding to normorphan **2a** were unmistakable. The new C-C bond formed in **2a** results from a nucleophilic attack of the enamine generated in situ on the trichloroacetamide carbonyl group with the concomitant release of a trichloromethyl anion as a leaving group (Scheme 4.2). Indeed, a peak corresponding to $CHCl_3$ was observed in the ^{1}H NMR spectrum of the crude reaction mixture when it was recorded in deuterated benzene. The iminium intermediate is then, converted to the corresponding ketone during purification.



Scheme 4.3.

Even if reactions featuring a trihalomethyl anion as a leaving group are well established (*e.g.*, the haloform reaction), they have not been reported from trichloroacetamides using enamines as nucleophiles.

Additionally, the reaction itself is a carbamoylation of a ketone. To our knowledge there is only one example in the literature describing an intermolecular α-carbamoylation of a ketone from the corresponding enolate and nitrourea under ultrasound activation and phase transfer catalysis. Moreover, in the literature, there are only three examples of intramolecular C-carbamoylation: i) photomediated radical reactions of dithiocarbamates, ii) electrophilic cyclization upon alkenes for the preparation of α,β-unsaturated lactams and iii) ruthenium catalyzed hydrocarbamoylation of allylic formamides (Scheme 4.3).

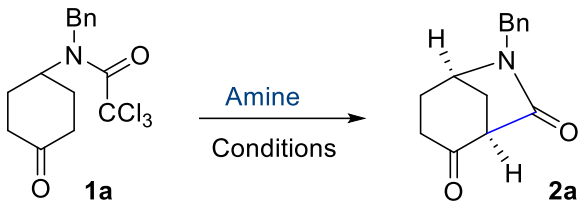


Scheme 4.4.

Interestingly, the 6-azabicyclo[3.2.1]octane (normorphan) ring is present in many natural compounds including peduncularine, the principal alkaloid of the Tasmanian shrub *Aristotelia peduncularis* (*Elaeocarpaceae*), actinobolamine the main degradation product of the antitumor compound actinobolin, aphanorphine, isolated from the blue-green alga *Aphanizomenon flos-aquae* and also in securinine, an alkaloid with a fused indolizidine ring structure found in the shrub *Securinega suffructicosa*. Additionally various synthetic compounds embodying the normorphan moiety are pharmacologically interesting showing among others analgesic property and dopamine reuptake inhibition.

Taking in account all these considerations, we decided to investigate this unprecedented reaction as a new efficient route for the obtention of normorphans.

Table 2.1.Synthesis of normorphan **2a**

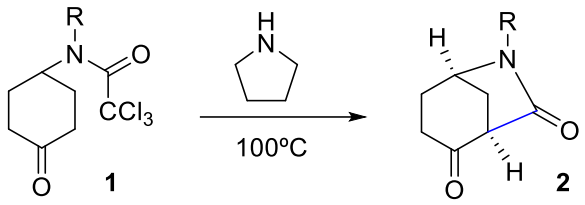


Entry	*Amine (eq)*	*Conditions*	*Reaction Time*	**2a** *Yield (%)*
1	Pyrrolidine (1.2)	*p*-TsOH, Toluene, rfx	2 h	68
2	Pyrrolidine (1.2)	*p*-TsOH, Toluene, μW 120 °C	15 min	53
3	Pyrrolidine (1.2)	*p*-TsOH, CH_3CN, μW 120 °C	15 min	56
4	Pyrrolidine (2)	Toluene, μW 100 °C (A)	5 min	85
5	Pyrrolidine (1.2)	100 °C solvent free	15 min	78
6	Pyrrolidine (0.5)	100 °C solvent free (B)	5 min	94
7	Pyrrolidine (0.25)	100 °C solvent free	5 min	80
8	$BnNH_2$ (1)	100 °C solvent free	5 min	50
9	Allylamine (5)	100 °C solvent free	5 min	58

Thus, starting from **1a**, to improve the reaction conditions, microwave heating was explored in initial experiments to accelerate the process. At 120 °C, after only 15 min, a full conversion was observed, but the target **2a** was isolated in only a moderate yield (53%, Table 4.1., entry 2). No improvement was obtained by switching to acetonitrile as the solvent (entry 3), but when the reaction was carried out with more than a stoichiometric amount of pyrrolidine and without the TsOH catalyst, **2a** was isolated in a better yield (85%, entry 4) after only 5 min heating at 100 ºC . A similar result was attained using solvent-free mode and conventional heating in a sealed tube (78%, entry 5). Moreover, when a substoichiometric amount of pyrrolidine (0.5 equiv) was used, the yield improved further to reach 91–94% in a 1 g scale synthesis (entry 6). Finally, it was found that the pyrrolidine loading can be diminished to 20–25% with little effect on the yield (entry 7). Additionally, the process was also activated by the use of primary amines (e.g., benzylamine and allylamine), although large amounts were required and the yield was lower (entries 8–9).

Table 4.2. Synthesis of normorphans **2b**-**2e**

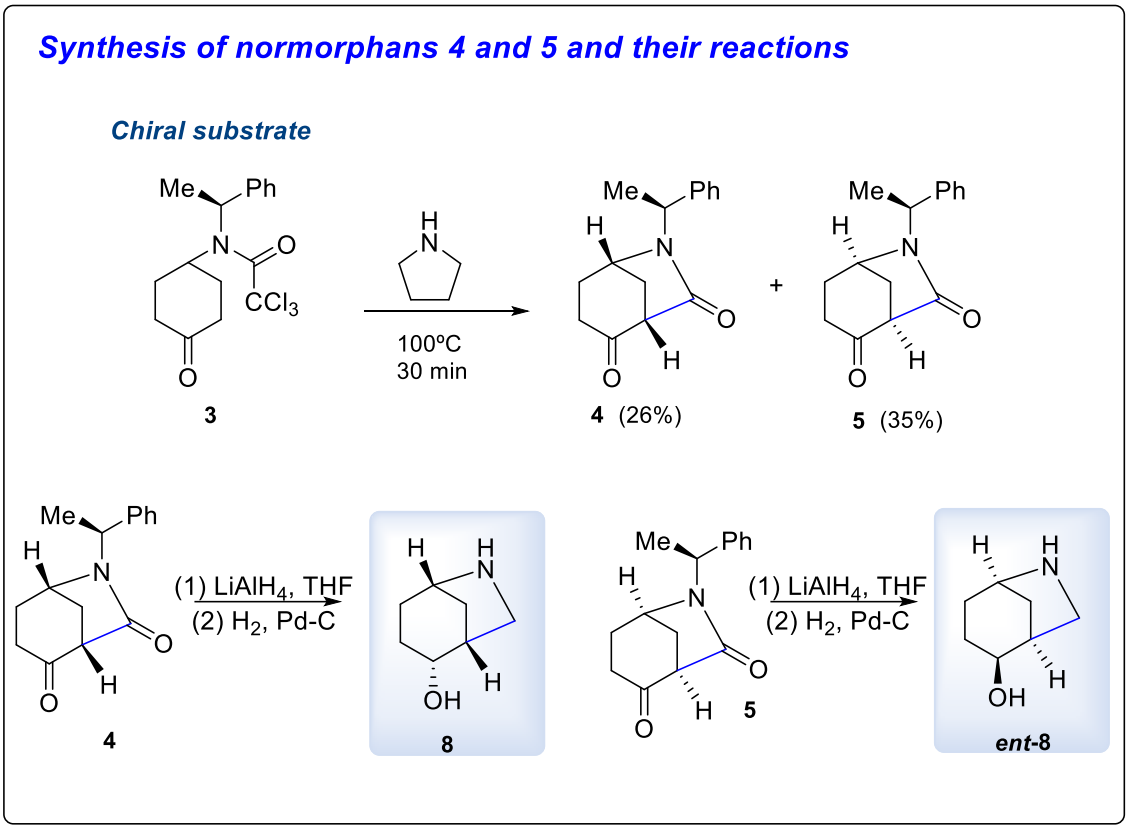
Methodology applied to other nitrogen-substituted trichloroacetamides



Entry	*R*	*Conditions*	*Pyrrolidine (eq)*	*Time*	***2** yield (%)*
1	Me (**1b**)	A	2	5 min	96
2	Me (**1b**)	B	5	5 min	55
5	Allyl (**1c**)	A	2	5 min	82
6	Allyl (**1c**)	B	1	5 min	78
3	*i*Pr (**1d**)	A	2	5 min	60
4	*i*Pr (**1d**)	B	5	10 min	50
7	$CH_2CH(OEt)_2$ (**1e**)	A	2	5 min	88
8	$CH_2CH(OEt)_2$ (**1e**)	B	1	5 min	71

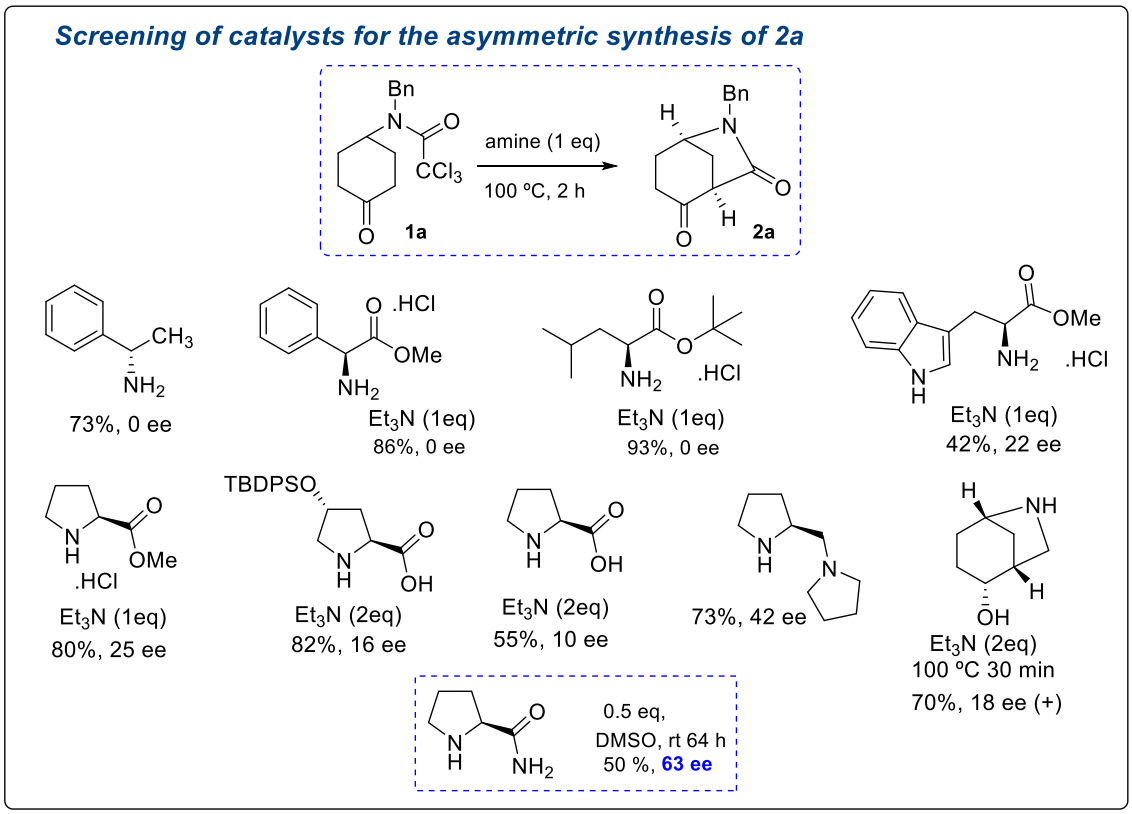
A: μW, 100 ºC, Toluene B: Solvent free, 100 ºC

The applicability of the methodology was subsequently explored on trichloroacetamides in which the benzyl group was replaced by primary or α-branched alkyl groups (compounds **1b**−**1e**). We tested the best set of reaction conditions previously obtained for the model starting material **1a**: the microwave protocol with toluene as a solvent (Method A) and the solvent-free procedure under conventional heating (Method B). When using compounds other than the *N*-benzyl derivative **1a**, method B afforded lower yields than method A, which was attributed to the low homogeneity of the trichloroacetamide (**1b**−**1e**) and pyrrolidine mixture. The microwave procedure worked very well with trichloroacetamides bearing linear substituents at the nitrogen atom, while the yield decreased when the α-position was branched (isopropyl substituent as in **1d**).



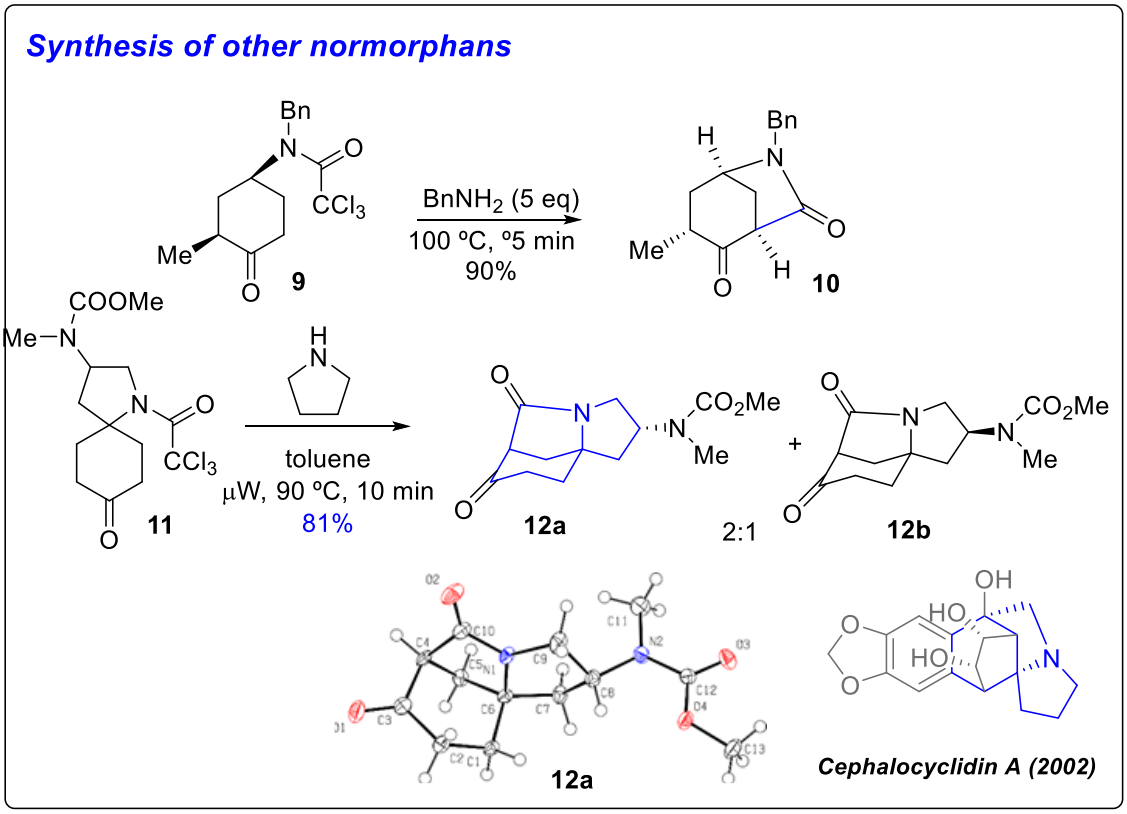
Scheme 4.5.

The methodology was also applied to enantiopure trichloroacetamide **3**. Unlike **1**, **3** required 2 equiv of pyrrolidine and a prolonged reaction time to achieve a full conversion, leading to the diastereomers **4** and **5** in a 1:1.3 ratio and acceptable yields (Scheme 4.5). The two diastereomers **4** and **5** were submitted to $LiAlH_4$ reduction to provide the corresponding amino alcohols which after debenzylation gave enantiopure normorphans **8** and its enantiomer ***ent*-8**. We then used these new sterically demanding secondary amines to explore the asymmetric organocatalyzed synthesis of normorphan **2**.



Scheme 4.6.

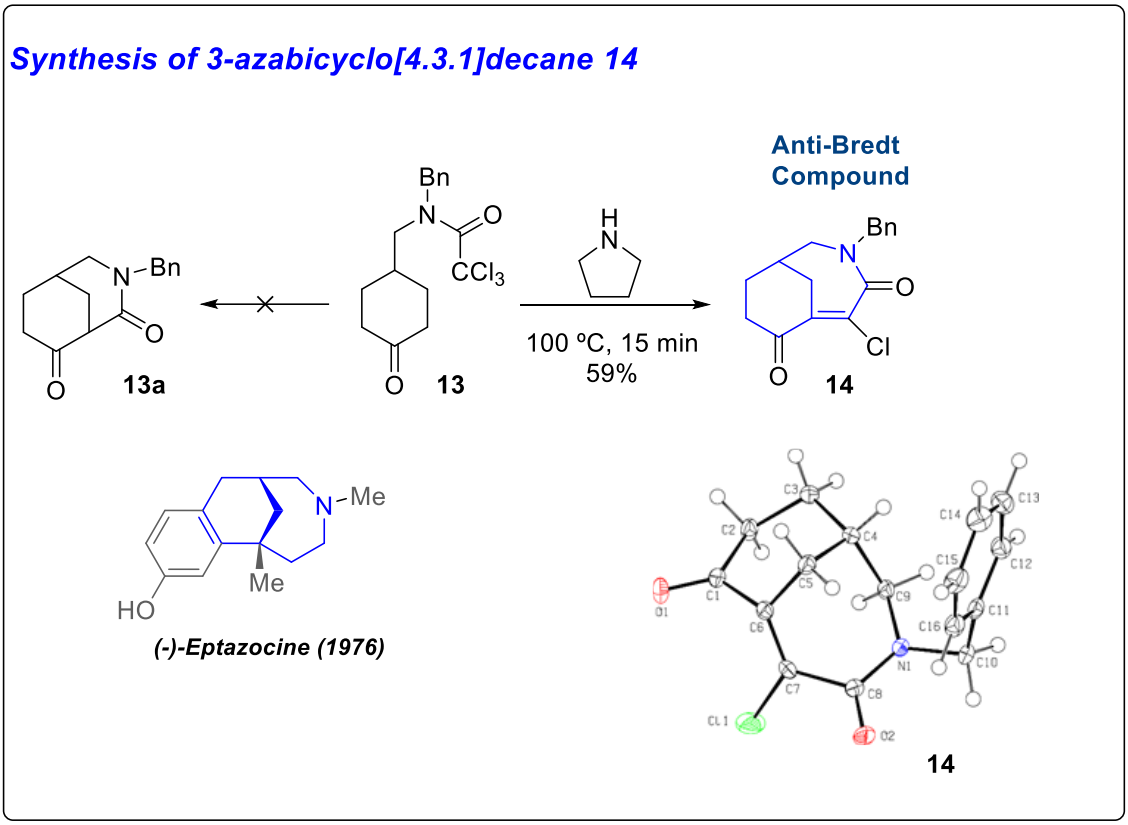
When trichloroacetamide **1a** was treated with **8**, the chemical yield of the carbamoylation was good (70% yield), but the enantioselectivity was very poor [(+)-**2a** < 20% ee]. A short screening of organocatalysts gave disappointing results (Scheme 4.6); although chemical yields ranged from good to excellent, the enantiomeric excess was again unsatisfactory, except for (*S*)-prolinamide. When the latter was used (0.5 equiv, DMSO, rt, 64 h), the reaction afforded (−)-**2a** in 50% yield and 63% ee. These preliminary results are in line with previously noted difficulties in the organocatalyzed desymmetrization of 4-aminocyclohexanones.



Scheme 4.7.

After these disappointing results, we examined the scope of the intramolecular carbamoylation reaction for the synthesis of more structurally complex normorphan compounds. First, α-methyl-substituted cyclohexanone **9** was treated with benzylamine to promote the carbamoylation of the ketone, the process took place regioselectively from the less substituted carbon, leading to normorphan **10**, which was also obtained after treating **9** with pyrrolidine (1.5 equiv, solvent-free, 73%). Interestingly, an epimerization at C-3 occurred in the basic reaction medium.

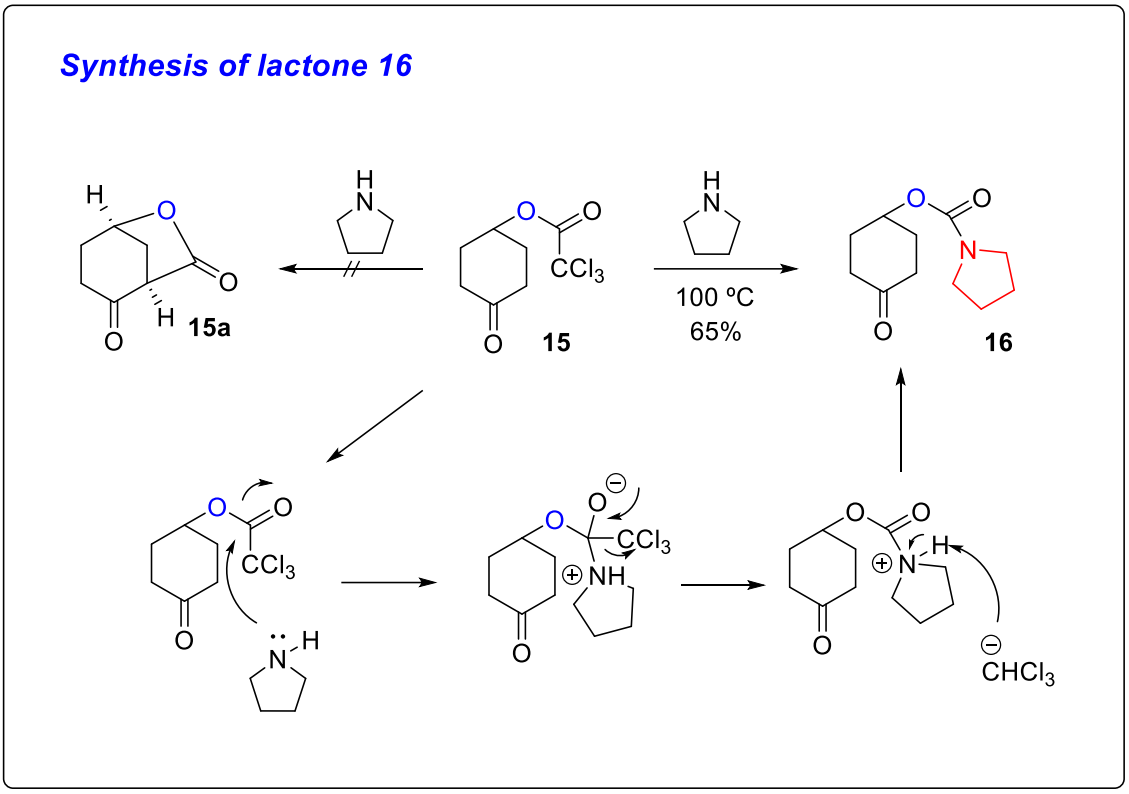
Application of the carbamoylation conditions to azaspirodecane **11** led to the epimeric mixture of azatricyclic compounds **12a** and **12b** (2:1 ratio) in a good yield. This heterocycle constitutes the ring core of the pentacyclic natural product cephalocyclidin A. The structure of the major compound **12a** was determined by X-ray crystallographic analysis (Scheme 4.7).



Scheme 4.8.

Additionally, we were interested in extending this reaction to achieve the six-membered ring scaffold from trichloroacetamide **13** (Scheme 6). However, the enlargement of the side chain bearing the trichloroacetamide moiety had a significant impact on the reaction course. Thus, treatment of **13** with pyrrolidine gave the anti-Bredt compound **14** instead of lactam **13a**. The structure of this unprecedented type of anti-Bredt ring (3-azabicyclo[4.3.1]dec-5-ene) which constitutes the backbone of synthetic analgesic Eptazocine, [1] was elucidated by NMR data and secured by X-ray crystallographic analysis.

[1] Takemoto, T.; Sodeoka, M.; Sasai, H.; Shibasaki, M. *J. Am. Chem. Soc.*, **1993**, *115* , 8477-8478.



Scheme 4.9.

Finally, as it was expected treatment of trichloroacetate **15** with pyrrolidine at 100 ºC yielded the corresponding carbamate **16** alone rendering the presence of the nitrogen atom as indispensable for this cyclization to succeed (Scheme 4.9).

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Organic LETTERS

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Synthesis of Normorphans through an Efficient Intramolecular Carbamoylation of Ketones

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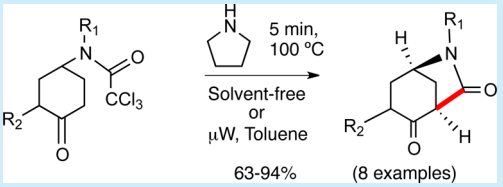
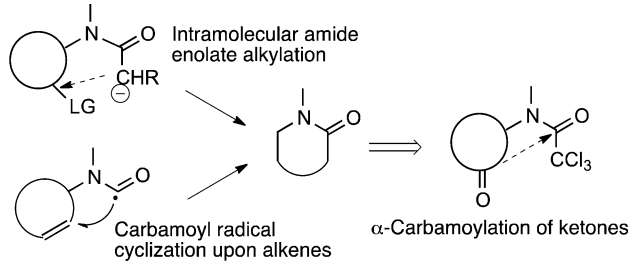
Supporting Information

ABSTRACT: An unexpected C−C bond cleavage was observed in trichloroacetamide-tethered ketones under amine treatment and exploited to develop a new synthesis of normophans from 4-amidocyclohexanones. The reaction involves an unprecedented intramolecular haloform-type reaction of trichloroacetamides promoted by enamines (generated in situ from ketones) as counter-reagents. The methodology was applied to the synthesis of compounds embodying the 6-azabicyclo[3.2.1]octane framework.



Methodologies involving the inter- or intramolecular formation of carbon−carbon bonds at the α-position of ketones are important tools for the construction of molecular frameworks in organic synthesis.[1] Nevertheless, to our knowledge, the α-carbamoylation of ketones remains an "orphan" procedure.[2,3] Whereas the feasibility of using intramolecular amide enolate alkylation (IAEA) in lactam synthesis is known,[4] the umpolung version in which the amide carbonyl acts as an acceptor against an α-carbonyl (ketone) group, such as a nucleophile, is unreported. The only procedures for the intramolecular C-carbamoylation described to date are carbamoyl radical,[5] electrophilic,[6] and Ru-catalyzed[7] cyclizations upon alkenes (Scheme 1).

Scheme 1. Intramolecular Carbamoylation



As part of our continuing interest in synthesizing lactams from trichloroacetamides,[8] we report here an efficient method to synthesize the azabicyclic normorphan ring, based on an intramolecular carbamoylation of ketones. The 6-azabicyclo [3.2.1]octane (normorphan) nucleus is the backbone of peduncularine[9] and actinobolamine,[10] and appears as a structural subunit in several other alkaloids.[11] Additionally, various normorphans are pharmacologically interesting[12] (Figure 1).

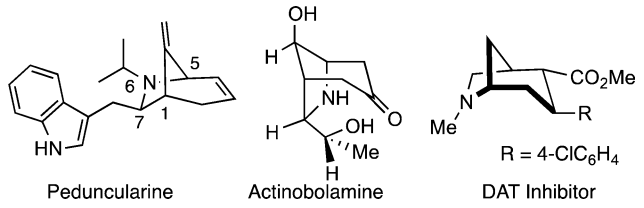


Figure 1. Normorphan compounds.

Among the vast array of synthetic procedures to achieve compounds embodying the 6-azabicyclo[3.2.1]octane skeleton,[13,14] a scarcely used approach involves a ring-closing C1−C7 bond formation. Apart from our studies on the radical cyclization of α-aminomethyl radicals,[15] and those of Grainger using carbamoyl radicals,[5,11] there are no other precedents for this disconnection in a synthetic plan toward the aforementioned bridged azabicyclic ring.

We began with the aim of extending our methodology for the radical cyclization of trichloroacetamides upon electron-rich alkenes, previously reported using enol acetates (i.e., **1A**) as radical acceptors,[8b] to the corresponding enamines, i.e. **1B** (Scheme 2). During this study, it was serendipitously discovered that when ketone **1**[8b] was treated with pyrrolidine (1.2 equiv) and a catalytic amount of TsOH in toluene at reflux, normorphan **2** was isolated in 68% yield (Scheme 2) instead of the expected enamine of **1**. After this surprising result, a synthetic study of the methodology toward 6-azabicyclo[3.2.1]octanes using amine-promoted carbocyclization of trichloroacetamide-tethered ketones was undertaken.

Although organic reactions featuring trichloromethyl as a leaving group are well established (e.g., the haloform

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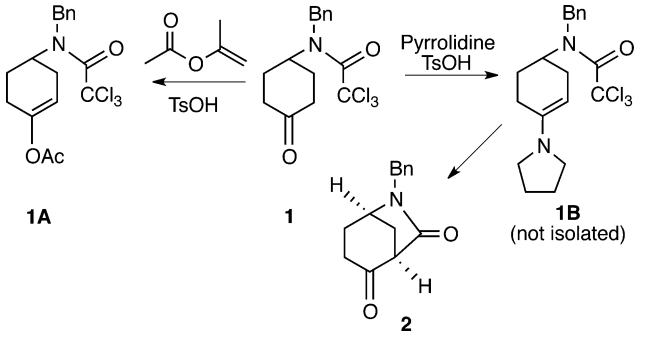
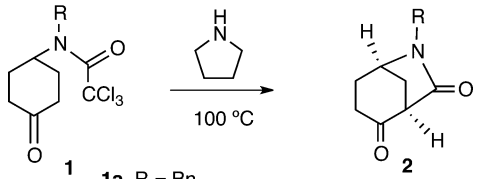
Scheme 2. Enol Acetate vs Enamine Formation from Trichloroacetamide 1



reaction),[16] they have not been reported from trichloroacetamides using enamines as nucleophiles.

To improve the reaction conditions, microwave heating was explored in initial experiments to accelerate the process. At 120 °C, after only 15 min, a full conversion was observed, but the target **2** was isolated in only a moderate yield (53%, Table 1, entry 1). No improvement was obtained by switching to acetonitrile as the solvent (entry 2), but when the reaction was carried out in solvent-free mode without the TsOH catalyst and using conventional heating in a sealed tube, **2** was isolated in a better yield (78%, entry 3). Moreover, when a substoichiometric amount of pyrrolidine (0.5 equiv) was used, the yield improved further to reach 91−94% after only 5 min of reaction in a 1 g scale synthesis (entry 4). Finally, it was found that the pyrrolidine loading can be diminished to 20−25% with little effect on the yield (entry 5). Additionally, the process was also activated by the use of primary amines (e.g., benzylamine and allylamine), although large amounts were required and the yield was lower (entries 7−8).

Table 1. Synthesis of Normorphans 2[a]



entry	compd	method[a]	amine (equiv)	time (min)	yield (%)[b]
1	**1a**	B[c]	1.2	15	53[c]
2	**1a**	B[c]	1.2	15	56[c]
3	**1a**	A	1.2	15	78
4	**1a**	A	0.5	5	94[d]
5	**1a**	A	0.25	5	80
6	**1a**	B	2	5	85
7	**1a**	A	1[e]	5	50
8	**1a**	A	5[f]	5	58[g]
9	**1b**	A	5	5	55[h]
10	**1b**	B	2	5	96
11	**1c**	A	1	5	78
12	**1c**	B	2	5	82
12	**1d**	A	5	10	50
13	**1d**	B	2	5	60
14	**1e**	A	1	5	71
15	**1e**	B[i]	2	5	88

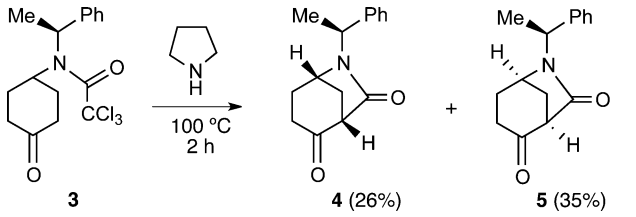
[a]Unless otherwise noted, the reaction was carried out with 200 mg of **1a** or 100 mg of **1b**−**1e**, using pyrrolidine as the amine. *Method A*: The reaction was carried out from trichloroacetamide **1** at 100 °C in solvent-free mode. *Method B*: μW, 100 °C in toluene (1 mL). [b]Yields refer to pure compounds isolated by flash chromatography. [c]At 120 °C, μW, *p*-TsOH (0.06 equiv), and solvent (2 mL): toluene or acetonitrile (entries 1 and 2). [d]1 g scale. [e]Benzylamine was used. [f]Allylamine was used. [g]35% of **1** was recovered. [h]31% of **1** was recovered. [i]200 mg scale.

The new type of C−C bond formation here described is probably based on a nucleophilic attack of an enamine generated in situ on a trichloroacetamide carbonyl group, with a concomitant release of the trichoromethyl anion as a leaving group. Indeed, a peak corresponding to $CHCl_3$ was observed when recording the NMR spectrum of the crude reaction mixture in deuterated benzene.

The applicability of the methodology was subsequently explored on trichloroacetamides in which the benzyl group was replaced by primary or α-branched alkyl groups (compounds **1b**−**1e**). We tested two reaction conditions: the solvent-free procedure under conventional heating (Method A), used in the *N*-benzyl series, and a microwave protocol with toluene as a solvent (Method B, Table 1, entries 9−15). When using compounds other than the *N*-benzyl derivative **1a**, Method A afforded lower yields than Method B, which was attributed to the low homogeneity of the trichloroacetamide (**1b**−**1e**) and pyrrolidine mixture. The microwave procedure worked very well with trichloroacetamides bearing linear substituents at the nitrogen atom, while the yield decreased when the α-position was branched (isopropyl or α-methylbenzyl substituents, as in **1e** and **3**).

The methodology was also applied to enantiopure trichloroacetamide **3**. Unlike **1**, **3** required 2 equiv of pyrrolidine and a prolonged reaction time to achieve a full conversion, leading to the diastereomers **4** and **5** in a 1:1.3 ratio and acceptable yield (Scheme 3).

Scheme 3. Cyclization of Trichloroacetamide 3



Evidence for the configuration of **4** (1*S*,5*S*) and **5** (1*R*,5*R*) was provided by NOESY experiments, which showed off-diagonal cross-peaks connecting H-4eq and CH_3 in **4** and H-4eq and aromatic protons in **5**. This stereochemical elucidation agrees with the chemical shift of H-4eq, which is shielded (δ 1.04) in **5** with regard to **4** (δ 2.20), indicating that H-4eq is held below the benzene ring in **5** (see Supporting Information (SI)).

The two diastereomers **4** and **5** were submitted to $LiAlH_4$ reduction to provide the corresponding amino alcohols **6** and **7**, respectively (not shown; see SI), which after debenzylation gave enantiopure normorphan **8** and its enantiomer ***ent*-8** (Scheme 4). We then used these new sterically demanding secondary amines (i.e., **8**)[17] to explore the asymmetric organocatalyzed synthesis of normorphan **2**.

When trichloroacetamide **1** was treated with **8**, the chemical yield of the carbamoylation was good (70% yield), but the

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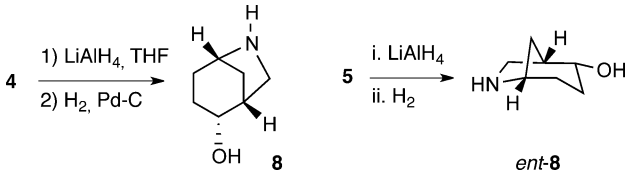
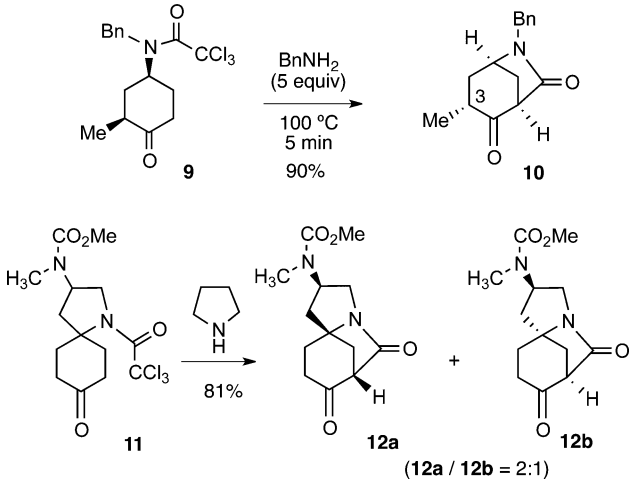
Scheme 4. Synthesis of Enantiopure 8 and *ent*-8



enantioselectivity was very poor [(+)-**2** < 20% ee). A short screening of organocatalysts gave disappointing results (see SI); although chemical yields ranged from good to excellent, the enantiomeric excess was again unsatisfactory, except for (*S*)-prolinamide. When the latter was used (0.5 equiv, DMSO, rt, 64 h), the reaction afforded (−)-**2** in 50% yield and 63% ee. These preliminary results are in line with previously noted difficulties in the organocatalyzed desymmetrization of 4-aminocyclohexanones.[18,19]

At this point, to examine the scope of the intramolecular carbamoylation reaction, the synthesis of more structurally complex normorphan compounds was undertaken (Scheme 5).

Scheme 5. Synthesis of Other Normorphans

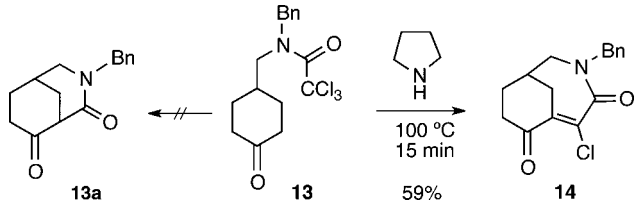


When the α-methyl-substituted cyclohexanone **9**[20] was treated with benzylamine to promote the carbamoylation of the ketone, the process took place regioselectively from the less substituted carbon, leading to the normorphan **10**, which was also obtained after treating **9** with a secondary amine such as pyrrolidine (1.5 equiv, solvent-free, 73%). Interestingly, an epimerization at C3 occurred in the basic reaction medium.

The reaction was extended to additional substrates, including the azaspiranic trichloroacetamide **11**,[21] which led to the azatricyclic compound **12** as an epimeric mixture (2:1 ratio) in a good overall yield. This new heterocycle constitutes the ring core of the structurally unique pentacyclic alkaloid cephalocyclidin A.[22] The structure of the major compound **12a** was determined by X-ray crystallographic analysis (see SI).

Additionally, we were interested in extending this reaction to achieve the six-membered ring scaffold from trichloroacetamide **13**[23] (Scheme 6). However, the enlargement of the side chain bearing the trichloroacetamide moiety had a significant impact on the reaction course. Thus, treatment of **13** with pyrrolidine gave the anti-Bredt compound **14**[24] instead of lactam **13a**. The structure of this unprecedented type of anti-Bredt ring (3-azabicyclo[4.3.1]dec-5-ene)[25] was elucidated by NMR data and secured by X-ray crystallographic analysis (Figure 2).

Scheme 6. Synthesis of anti-Bredt Azabicyclo 14



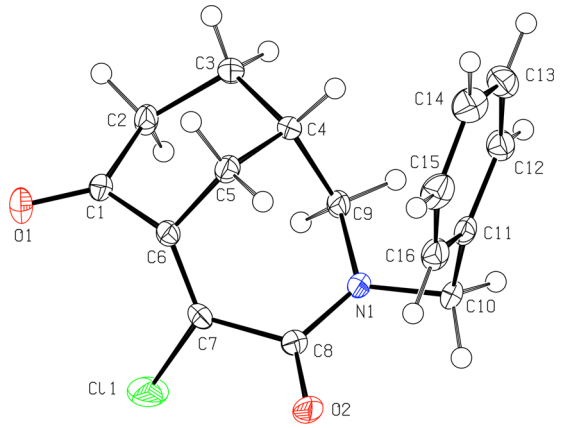


Figure 2. X-ray structure of **14**.

Not unexpectedly, trichloroacetate **15** behaved differently under pyrrolidine treatment, leading to the corresponding carbamate **16** (see ref 26).[26] Thus, the presence of the nitrogen atom (i.e., the trichloroacetamide group) is essential for the accomplishment of the process since the oxygenated analog did not provide a cyclization product.

In summary, a direct synthesis of the 6-azabicyclo[3.2.1]-octane ring, prevalent in a range of biologically active compounds, from an unprecedented α-carbamoylation of ketones is reported. The process involves an intramolecular reaction of trichloroacetamides promoted by enamines (generated in situ from ketones) as counter-reagents. The lactam functionalization of this heterocycle promises several future applications, notably including the conversion of this building block to the corresponding homoderivative bearing a morphan nucleus.[27]

■ ASSOCIATED CONTENT

Supporting Information

Experimental procedures, spectroscopic and analytical data, NMR spectra of new compounds, and X-ray data for **12a** and **14** (CIF). The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.5b01832.

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Notes

The authors declare no competing financial interest.

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■ REFERENCES

(1) (a) *Stereoselective Synthesis of Drugs and Natural Products*; Andrushko, V., Andrushko, N., Eds.; Wiley-VCH: New York, 2013; part 2.1, Chapters 7−28. (b) Vander Wal, M. N.; Dilger, A. K.; MacMillan, D. W. C. *Chem. Sci.* **2013**, *4*, 3075−3079.

(2) (a) For a related transformation involving an intramolecular trapping of an isocyanate arising from a *N*-monosubstituted trichloroacetamide, by a dienolate generated from an enone, see: Nishikawa, T.; Koide, Y.; Adachi, M.; Isobe, M. *Bull. Chem. Soc. Jpn.* **2010**, *83*, 66−68. (b) For an example of intermolecular carbamoylation of ketones using nitrourea under sonochemical PTC, see: Pazdera, P.; Simbera, J. *Org. Prep. Proced. Int.* **2011**, *43*, 297−301.

(3) For intermolecular C-carbamoylation processes not involving ketone compounds, see *inter alia*: (a) Lemoucheux, L.; Seitz, T.; Rouden, J.; Lasne, M.-C. *Org. Lett.* **2004**, *6*, 3703−3706. (b) Yasui, Y.; Tsuchida, S.; Miyabe, H.; Takemoto, Y. *J. Org. Chem.* **2007**, *72*, 5898−5900. (c) Yoshimitsu, T.; Matsuda, K.; Nagaoka, H.; Tsukamoto, K.; Tanaka, T. *Org. Lett.* **2007**, *9*, 5115−5118. (d) Kamijo, S.; Hoshikawa, T.; Inoue, M. *Tetrahedron Lett.* **2011**, *52*, 2885−2888. (e) Roy, S.; Roy, S.; Gribble, G. W. *Tetrahedron* **2012**, *68*, 9867−9923.

(4) Latif, M.; Yun, J. I.; Seshadri, K.; Kim, H. R.; Park, C. H.; Park, H.; Kim, H.; Lee, J. *J. Org. Chem.* **2015**, *80*, 3315−3520.

(5) Grainger, R. S.; Welsh, E. *Angew. Chem., Int. Ed.* **2007**, *46*, 5377−5380. For carbamoylation of methoxybenzenes: (b) Millán-Ortiz, A.; López-Valdez, G.; Cortez-Guzmán, F.; Miranda, L. D. *Chem. Commun.* **2015**, *51*, 8345−8348.

(6) (a) Yasui, Y.; Takemoto, Y. *Chem. Rec.* **2008**, *8*, 386−394. (b) Yasui, Y.; Kakinokihara, I.; Takeda, H.; Takemoto, Y. *Synthesis* **2009**, *2009*, 3989−3993.

(7) (a) Armanino, N.; Carreira, E. M. *J. Am. Chem. Soc.* **2013**, *135*, 6814−6817. (b) Li, B.; Park, Y.; Chang, S. *J. Am. Chem. Soc.* **2014**, *136*, 1125−1131.

(8) Using Bu_3SnH or $(TMS)_3SiH$, see: (a) Quirante, J.; Escolano, C.; Merino, A.; Bonjoch, J. *J. Org. Chem.* **1998**, *63*, 968−976. (b) Quirante, J.; Escolano, C.; Diaba, F.; Bonjoch, J. *J. Chem. Soc., Perkin Trans. 1* **1999**, 1157−1162. (c) Diaba, F.; Pujol-Grau, C.; Martínez-Laporta, A.; Fernández, I.; Bonjoch, J. *Org. Lett.* **2015**, *17*, 568−571. Using Cu(I)/AIBN, see: (d) 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. Using Grubbs' catalyst, see: (e) Diaba, F.; Martínez-Laporta, A.; Bonjoch, J. *J. Org. Chem.* **2014**, *79*, 9365−9372.

(9) (a) Roberson, C. W.; Woerpel, K. A. *J. Am. Chem. Soc.* **2002**, *124*, 11342−11348. (b) Hodgson, D. M.; Shelton, R. E.; Moss, T. A.; Dekhane, M. *Org. Lett.* **2010**, *12*, 2834−2837 and references therein. .

(10) Holmes, A. B.; Kee, A.; Ladduwahetty, T.; Smith, D. F. *J. Chem. Soc., Chem. Commun.* **1990**, 1412−1414.

(11) Betou, M.; Male, L.; Steed, J. W.; Grainger, R. S. *Chem. - Eur. J.* **2014**, *20*, 6505−6517 and references therein. .

(12) For normorphans as dopamine transporter inhibitors, see: Quirante, J.; Vila, X.; Bonjoch, J.; Kozikowski, A. P.; Johnson, K. M. *Bioorg. Med. Chem.* **2004**, *12*, 1383−1391.

(13) For classical approaches, see: Bonjoch, J.; Mestre, E.; Cortés, R.; Granados, R.; Bosch, J. *Tetrahedron* **1983**, *39*, 1723−1728 and references therein. .

(14) For some recent procedures, see: (a) Winkler, J. D.; Fitzgerald, M. E. *Synlett* **2009**, *2009*, 562−564. (b) Campbell, C. L.; Hassler, C.; Ko, S. S.; Voss, M. E.; Guaciaro, M. A.; Carter, P. H.; Cherney, R. J. *J. Org. Chem.* **2009**, *74*, 6368−6370. (c) Casavant, B. J.; Hosseini, A. S.; Chemler, S. R. *Adv. Synth. Catal.* **2014**, *356*, 2697−2702. (d) Liu, T.; Mei, T.-S.; Yu, J.-Q. *J. Am. Chem. Soc.* **2015**, *137*, 5871−5874.

(15) Quirante, J.; Vila, X.; Escolano, C.; Bonjoch, J. *J. Org. Chem.* **2002**, *67*, 2323−2328.

(16) For some examples on the leaving ability of CX_3 groups, see: (a) Zucco, C.; Lima, C. F.; Rezende, M. C.; Vianna, J. F.; Nome, F. *J. Org. Chem.* **1987**, *52*, 5356. (b) Morimoto, H.; wiedemann, S. H.; Yamaguchi, A.; Harada, S.; Chen, Z.; Matsunaga, S.; Shibasaki, M. *Angew. Chem., Int. Ed.* **2006**, *45*, 3146−3150. (c) Gerfaud, T.; Wei, H.-L.; Neuville, L.; Zhu, J. *Org. Lett.* **2011**, *13*, 6172−6175. (d) Zhu, C.; Wei, W.; Du, P.; Wan, X. *Tetrahedron* **2014**, *70*, 9615−9620.

(17) For the use of normorphans as organocatalysts, see: List, B.; Coric, I.; Grygorenko, O.; Kaib, P. S. J.; Komarov, I.; Lee, A.; Leutzch, M.; Pan, S. C.; Tymtsunik, A. V.; van Gemmere, M. *Angew. Chem., Int. Ed.* **2014**, *53*, 282−285.

(18) Diaba, F.; Bonjoch, J. *Org. Biomol. Chem.* **2009**, *7*, 2517−2519.

(19) For a recent first example of very efficient organocatalytic desymmetrization of prochiral 4-aminocyclohexanones, see: Yamagata, A. D. G.; Datta, S.; Jackson, K. E.; Stegbauer, L.; Paton, R. S.; Dixon, D. J. *Angew. Chem., Int. Ed.* **2015**, *54*, 4899−4903.

(20) Racemic **9** was prepared in a six-step sequence (see Supporting Information).

(21) Diaba, F.; Martínez-Laporta, A.; Bonjoch, J. *J. Org. Chem.* **2014**, *79*, 9365−9372.

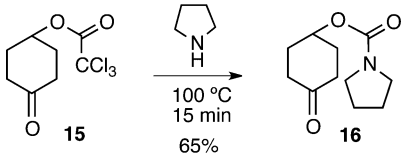
(22) Kobayashi, J.; Yoshinaga, M.; Yoshida, N.; Shiro, M.; Morita, H. *J. Org. Chem.* **2002**, *67*, 2283−2286.

(23) Vila, X.; Quirante, J.; Paloma, L.; Bonjoch, J. *Tetrahedron Lett.* **2004**, *45*, 4661−4664.

(24) For natural products with bridgehead double bonds, see: Mak, J. Y. W.; Pouwer, R. H.; Williams, C. M. *Angew. Chem., Int. Ed.* **2014**, *53*, 13664−13688.

(25) For synthetic approaches to 3-azabicyclo[4.3.1]decanes, see: (a) Hall, H. K., Jr. *J. Org. Chem.* **1963**, *28*, 3213−3214. (b) Orvieto, F.; Botta, M.; Corelli, F.; Harper, S. *Synth. Commun.* **1999**, *29*, 3635−3649.

(26)



(27) For classical examples of the normorphan transformation to morphan compounds, see: (a) Legseir, B.; Henin, J.; Massiot, G.; Vercauteren, J. *Tetrahedron Lett.* **1987**, *28*, 3573−3576. (b) Nkiliza, J.; Vercauteren, J.; Léger, J.-M. *Tetrahedron Lett.* **1991**, *32*, 1787−1790.

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Supporting information

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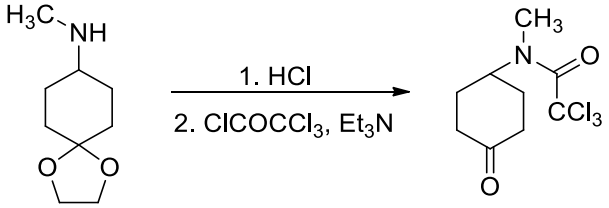
EXPERIMENTAL SECTION

1. General information. ^{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 and ^{13}C NMR spectra are referenced to the deuterated solvent signal ($CDCl_3$: 77.00 ppm) and (CD_3OD, 49.3 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). Drying of the organic extracts during reaction work-up was performed over anhydrous Na_2SO_4. HPLC analyses for the determination of enantiomeric excess were carried out using a DAICEL CHIRALPAK IC column (250×4.6 mm I.D., 5 μm; Chiral Technologies Europe) on a Waters model 2487 Dual Absorbance Detector and set at the wavelength of 230 nm. The HPLC resolution of compound **2a** was achieved using isopropanol, 0.5 mL min^{-1} as the mobile phase.

2. Synthesis of trichloroacetamides 1[1]



1b

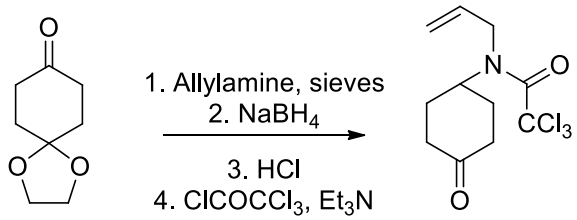
4-(*N*-Methyltrichloroacetamido)-1-cyclohexanone (1b)

A mixture of 4-(*N*-methyl)aminocyclohexane ethylene acetal[2] (1.5 g, 8.76 mmol) and 10 % HCl aqueous solution (50 mL) was stirred at rt overnight. The mixture was basified with 10% NaOH solution and extracted with CH_2Cl_2. The organics were dried, concentrated and the residue treated with Et_3N (1.6 mL, 11.5 mmol) and trichloroacetyl chloride (1 mL, 9 mmol) in CH_2Cl_2 (5 mL) at 0 ºC then at rt for 1h. The mixture was poured into water and extracted with CH_2Cl_2. After chromatography (Hexane/CH_2Cl_2 3:2 to CH_2Cl_2) **1b** was isolated as a white solid (1.5 g, 63%): mp 120-121 °C; IR (KBr) 3051, 3014, 2965, 2887, 2826, 1718, 1662 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.90-2.30 (m, 4H), 2.51 (brs, 4H), 2.95 and 3.24 (2 br s, 3H, CH_3), 4.84 (br s, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 28.1 and 28.5 (CH_2), 30.8 and 32.5 (CH_3), 39.5 (CH_2),

[1] For the synthesis of **1a**, see: Quirante, J.; Escolano, C.; Diaba, F.; Bonjoch, J. *Heterocycles* **1999**, *50*, 731-738. For the synthesis of **3**, see: Quirante, J.; Torra, M.; Diaba, F.; Escolano, C.; Bonjoch, J. *Tetrahedon: Asymmetry* **1999**, *10*, 2399-2410.

[2] W. J. Greenlee, Y. Huang, J. M. Kelly, S. W. McCombie, A. Stamford and Y. Wu, in US 2005/0038100 A1, Schering-Plough Corp., USA, **2005**.

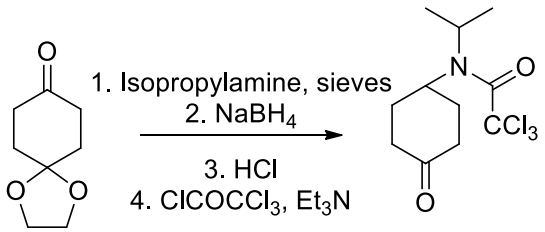
55.2 and 56.2 (CH), 93.4 (CCl_3), 160.3 (CO), 208.6 (CO); HRMS (ESI-TOF) *m/z*: $[M+H]^+$ calcd for $C_9H_{13}Cl_3NO_2$ 272.0006; found 272.0008.



1c

4-(*N*-Allyltrichloroacetamido)-1-cyclohexanone (1c)

A mixture of allylamine (1.6 mL, 20.81 mmol), 1,4-cyclohexanedione monoethylene acetal (2.5 g, 16 mmol) and 4 Å molecular sieves (2 g) in CH_2Cl_2 (10 mL) was stirred at rt for 4 h, filtered on a short celite pad, and concentrated. The residue was dissolved in MeOH (20 ml) and treated with $NaBH_4$ (1.21 g, 19.2 mmol) at 0 ºC and stirred at rt for 1 h. The mixture was concentrated, water was added and the mixture was extracted with CH_2Cl_2. The organics were dried, concentrated and the resulting viscous oil was dissolved in THF (3 mL) and treated with 10% HCl solution (30 mL) overnight. The mixture was basified with 2.5 NaOH solution and extracted with CH_2Cl_2. The organics were dried, concentrated and to the resulting residue in CH_2Cl_2 (25 mL) were added dropwise at 0 ºC Et_3N (4.46 mL, 32.01 mmol) and trichloroacetyl chloride (2.67 mL, 24.01 mmol). The mixture was stirred at rt for 1 h, water was added and the mixture was extracted with CH_2Cl_2. The organics were dried, concentrated and purified by chromatography (Hexane:CH_2Cl_2, 1:1) to yield **1c** as a white solid (2.3 g, 48% for the 4 steps): mp 104-105 °C; IR (KBr) 3013, 2957, 2947, 2877, 2860, 1728, 1674 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 2.06 and 2.22 (2 br s, 4H), 2.48 (br s, 4H), 2.96 and 4.38 (2 br s, 2H, CH_3), 4.94 (br s, 1H), 5.15-5.40 (m, 2H), 5.85 (br s, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 27.6 and 29.3 (CH_2), 39.5 (CH_2), 47.0 and 51.6 (CH_2), 56.8 (CH), 93.4 (CCl_3), 117.4 and 118.9 (CH_2), 132.6 and 133.9 (CH), 159.7 (CO), 207.8 (CO); HRMS (ESI-TOF) *m/z*: $[M+H]^+$ calcd for $C_{11}H_{15}Cl_3NO_2$ 298.0163; found 298.0172.

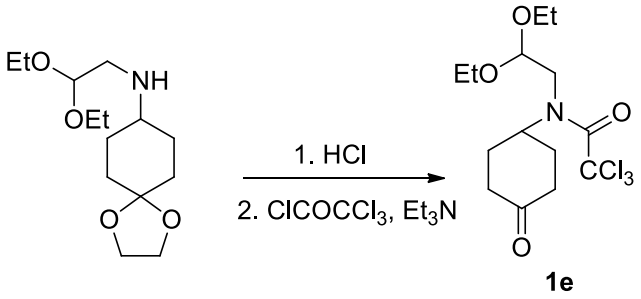


1d

4-(*N*-Isopropyltrichloroacetamido)-1-cyclohexanone (1d)

Operating as above from isopropylamine (2.15 mL, 25.02 mmol) and 1,4-cyclohexanedione monoethylene acetal (3 g, 18.6 mmol), **1d** was obtained as a white solid (2.3 g, 48% for the 4

steps): mp 130-131 °C; IR (KBr) 2972, 2889, 1719, 1679 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 1.34 and 1.44 (2 d, *J* = 6.8 Hz, 3H each, CH_3), 1.86 (m, 1H), 2.07 (m, 1H), 2.25 (m, 1H), 2.30-2.60 (m, 4H), 2.85 (qd, *J* = 12.8, 4.8 Hz, 1H), 3.53 (m, 1H), 4.84 3.53 (m, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 19.5 and 19.7 (CH_3), 26.6 and 28.6 (CH_2), 39.4 and 39.5 (CH_2), 49.8 and 53.6 (CH), 51.1 and 57.1 (CH), 94.1 and 94.4 (CCl_3), 158.3 and 158.8 (CO), 208.0 and 209.7 (CO); HRMS (ESI-TOF) *m/z*: $[M+H]^+$ calcd for $C_{11}H_{17}Cl_3NO_2$ 300.0319; found 300.0326.



1e

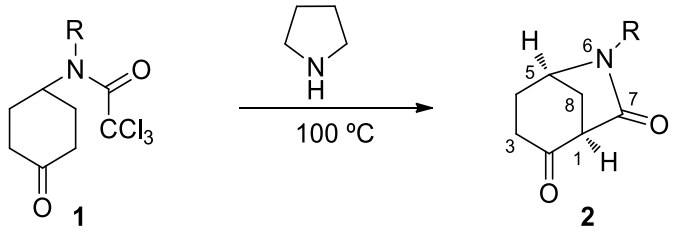
4-[*N*-(2,2-Diethoxyethyl)trichloroacetamido]-1-cyclohexanone (1e)

A mixture of *N*-(2,2-diethoxyethyl)-4-aminocyclohexanone ethylene acetal[3] (3 g, 11 mmol) and 10 % HCl solution (30 mL) was stirred at rt overnight. The mixture was basified with solid K_2CO_3 and extracted with CH_2Cl_2. The organics were dried, concentrated to yield 4-[(2,2-diethoxyethyl)amino]cyclohexanone as a yellowish oil enough pure to be used in the next step without further purification: IR (NaCl) 3327, 2977, 2933, 2906, 2873, 1719 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 1.23 (t, *J* = 7.0 Hz, 6H, CH_3), 1.70 (m, 2H), 2.09 (m, 2H), 2.31 (ddd, *J* = 14.8, 10, 5.6 Hz, 2H), 2.49 (dt, *J* = 14.8, 6 Hz, 2H), 2.79 (d, *J* = 5.6 Hz, 2H), 2.97 (tt, *J* = 8, 3.6 Hz, 1H), 3.57 (m, 2H), 3.73 (m, 2H), 4.61 (t, *J* = 5.6 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 15.2 (CH_3), 31.8 (CH_2), 38.2 (CH_2), 49.6 (CH_2), 53.4 (CH), 62.2 (CH_2), 102.0 (CH), 211.1 (CO); HRMS (ESI-TOF) *m/z*: $[M+H]^+$ calcd for $C_{12}H_{24}NO_3$ 230.1751; found 230.1758.

To a mixture of the previous 4-[(2,2-diethoxyethyl)amino]cyclohexanone and Et_3N (1.8 mL, 12.8 mmol) in CH_2Cl_2 (15 mL) was added trichloroacetyl chloride (1.15 mL, 10.2 mmol) dropwise at 0 ºC and the mixture was stirred at rt for 1h. The mixture was poured into water and extracted with CH_2Cl_2. After chromatography (CH_2Cl_2) **1e** was isolated as a pale yellow solid (2.86 g, 69% for the 2 steps): mp 79-80 °C; IR (KBr) 2975, 28961719, 1675 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 1.20 (td, *J* = 7.2 Hz, 6H, CH_3), 2.06 (qd, *J* = 12, 5.6 Hz, 2H), 2.20 (m, 2H), 2.37-2.54 (m, 4H), 3.33 (d, *J* = 5.2 Hz, 2H), 3.55 (m, 2H), 3.76 (m, 2H), 4.85 (tt, *J* = 11.6, 3.6 Hz, 1H), 4.89 (t, *J* = 5.2 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 15.4 (CH_3), 29.3 (CH_2), 39.6 (CH_2), 48.9 (CH_2), 56.8 (CH), 64.7 (CH_2), 93.4 (CCl_3), 99.4 (CH), 160.6 (CO), 208.1 (CO); HRMS (ESI-TOF) *m/z*: $[M+Na]^+$ calcd for $C_{14}H_{22}Cl_3NNaO_4$ 396.0507; found 396.0509.

[3] Diaba, F.; Bonjoch, J. *Org. Biomol. Chem.* **2009**, *7*, 2517-2519.

3. Cyclization procedures



*3.1. Typical procedure using solvent-free conditions (**Method A**)*

(1*RS*,5*RS*)-6-Benzyl-6-azabicyclo[3.2.1]octane-2,7-dione (2a)[4]

A mixture of **1a** (1 g, 2.87 mmol) and pyrrolidine (0.12 mL, 1.46 mmol) was heated at 100 ºC for 5 min in a sealed tube. After chromatography (CH_2Cl_2 to CH_2Cl_2/EtOAc 3:1) **2a** was obtained as a white solid (0.614 g, 94%): mp 90-92 °C; IR (KBr) 3087, 3065, 3032, 3006, 2969, 2955, 2916, 2894, 1725, 1686, 1602 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 1.78-1.88 (m, 1H, H-4), 2.01 (m, 1H, H-4), 2.03 (d, *J* = 12 Hz, 1H, H-8), 2.34-2.49 (m, 2H, 3-CH_2), 2.60 (dtd, *J* = 12, 5.2, 2.8 Hz, 1H, H-8), 3.24 (d, *J* = 5.2 Hz, 1H, H-1), 3.79 (m, 1H, H-5), 4.31 and 4.78 (2d, *J* = 15.0 Hz, 1H each, CH_2Ar), 7.29-7.39 (m, 5H, ArH). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 27.0 (C-4), 34.8 (C-3), 35.8 (C-8), 45.3 (CH_2Ar), 54.4 (C-5), 58.0 (C-1), 128.0, 128.1, 128.8 (CHAr), 136.2 (C-*ipso*), 170.8 (C-7), 202.1 (C-2); HRMS (ESI-TOF) *m/z*: $[M+H]^+$ calcd for $C_{14}H_{16}NO_2$ 230.1176; found 230.1174.

3.2. *Typical procedure using microwave activation* (***Method B***)

In a 10 mL vessel, a mixture of **1a** (0.1 g, 0.29 mmol) and pyrrolidine (0.048 mL, 0.58 mmol) in toluene (1 mL) was heated with stirring to 100 ºC using microwave irradiation for 5 min. After chromatography (CH_2Cl_2 to CH_2Cl_2/EtOAc 3:1) **2a** was obtained as a white solid (56 mg, 85%).

(1*RS*,5*RS*)-6-Methyl-6-azabicyclo[3.2.1]octane-2,7-dione (2b)

IR (NaCl) 2955, 2885, 1723, 1686 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 1.97 (m, 1H, H-4ax), 2.07 (d, *J* = 11.6 Hz, 1H, H-8ax), 2.34 (m, 1H, H-4eq), 2.38-2.56 (m, 2H, CH_2-3), 2.66 (m, H-8eq), 2.96 (s, 3H, CH_3), 3.16 (d, *J* = 5.2 Hz, 1H, H-1), 3.84 (br s, 1H, H-5); ^{13}C NMR (100 MHz, $CDCl_3$) δ 26.4 (C-4), 28.1 (CH_3), 34.6 (C-3), 35.1 (C-8), 56.8 (C-5), 57.7 (C-1), 171.1 (C-7), 202.1 (C-2); HRMS (ESI-TOF) *m/z*: $[M+H]^+$ calcd for $C_8H_{12}NO_2$ 154.0863; found 154.0865.

(1*RS*,5*RS*)-6-Allyl-6-azabicyclo[3.2.1]octane-2,7-dione (2c)

IR (NaCl) 3083, 2957, 2920, 2883, 1722, 1690 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 1.94 (dtd, *J* = 14.4, 8.8, 2 Hz, 1H, H-4ax), 2.07 (d, *J* = 12 Hz, 1H, H-8ax), 2.29 (dm, *J* = 14.4 Hz, 1H, H-4eq), 2.43-2.56 (m, 2H, 3-CH_2), 2.64 (dtd, *J* = 12, 5.2, 2.8 Hz, 1H, H-8eq), 3.20 (d, *J* = 5.6 Hz,

[4] For the yields corresponding to the other substrates, see the article.

1H, H-1), 3.70 (ddt, *J* = 15.6, 6.8, 1.2 Hz, 1H), 3.91 (m, 1H, H-5), 4.28 (ddt, *J* = 15.6, 5.6, 1.6 Hz, 1H), 5.28 (m, 2H), 5.84 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 27.2 (C-4), 34.8 (C-3), 35.7 (C-8), 44.0 (CH_2), 54.4 (C-5), 58.1 (C-1), 118.7 (CH_2), 132.1 (CH), 170.7 (C-7), 202.1 (C-2); HRMS (ESI-TOF) *m/z*: $[M+H]^+$ calcd for $C_{10}H_{14}NO_2$ 180.1019; found 180.1020.

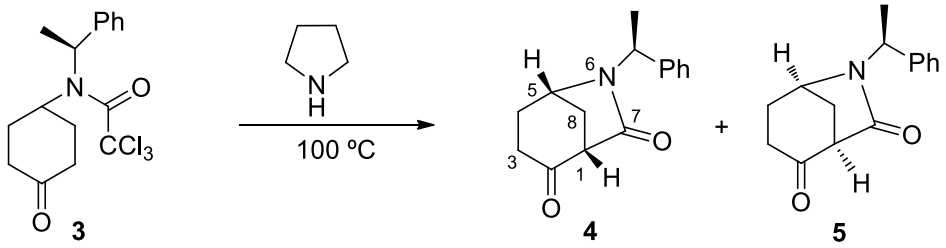
(1*RS*,5*RS*)-6-Isopropyl-6-azabicyclo[3.2.1]octane-2,7-dione (2d)

m.p. 86-87 °C; IR (KBr) 2972, 2945, 2879, 1716, 1679 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.27 (d, *J* = 6.8 Hz, 6H, CH_3), 2.02 (m, 1H, H-4ax), 2.05 (d, *J* = 11.6 Hz, 1H, H-8ax), 2.23 (m, 1H, H-4eq), 2.48-2.66 (m, 3H, 3-CH_2 and H-8eq), 3.16 (d, *J* = 4.8 Hz, 1H, H-1), 4.04 (br s, 1H, H-5), 4.37 (heptet, *J* = 6.8, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 20.2 and 20.6 (CH_3), 30.1 (C-4), 34.9 (C-3), 37.4 (C-8), 43.6 (CH), 52.0 (C-5), 58.7 (C-1), 170.4 (C-7), 202.7 (C-2); HRMS (ESI-TOF) *m/z*: $[M+H]^+$ calcd for $C_{10}H_{16}NO_2$ 182.1176; found 182.1176.

(1*RS*,5*RS*)-6-(2,2-diethoxyethyl)-6-azabicyclo[3.2.1]octane-2,7-dione (2e)

IR (NaCl) 2976, 2932, 2885, 1725, 1694 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.22 (2 t, *J* = 6.8 Hz, 6H, CH_3), 1.92 (dtd, *J* = 13.6, 7.6, 2 Hz, 1H, H-4ax), 2.07 (d, *J* = 11.6 Hz, 1H, H-8ax), 2.38 (m, 1H, H-4eq), 2.44-2.60 (m, 2H, 3-CH_2), 2.64 (dtd, *J* = 11.6, 5.6, 2.8 Hz, 1H, H-8eq), 3.16 (d, *J* = 5.6 Hz, 1H, H-1), 3.25 (dd, *J* = 14, 6.4 Hz, 1H), 3.57 (m, 2H), 3.66 (dd, *J* = 14, 4.4 Hz, 1H), 3.75 (m, 2H), 4.08 (br s, 1H, H-5), 4.65 (dd, *J* = 6.4, 4 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 15.2 and 15.3 (CH_3), 27.2 (C-4), 34.9 (C-3), 35.9 (C-8), 44.3 (CH_2), 56.3 (C-5), 57.8 (C-1), 62.9 and 63.4 (CH_2), 100.7 (CH), 171.4 (C-7), 202.5 (C-2); HRMS (ESI-TOF) *m/z*: $[M+H]^+$ calcd for $C_{13}H_{21}NNaO_4$ 278.1363; found 278.1371.

4. Cyclization of 3 and related reactions



A mixture of **3** (1g, 2.76 mmol) and pyrrolidine (0.453 mL, 5.51 mmol) was heated at 100 ºC in a sealed tube for 30 min. After chromatography (hexane/EtOAc 3:2 to 2:3), **4** (96 mg, 14%), a mixture of **4** and **5** (174 mg, 26%, 1:1.2) and **5** (142 mg, 21%), were sequentially isolated.

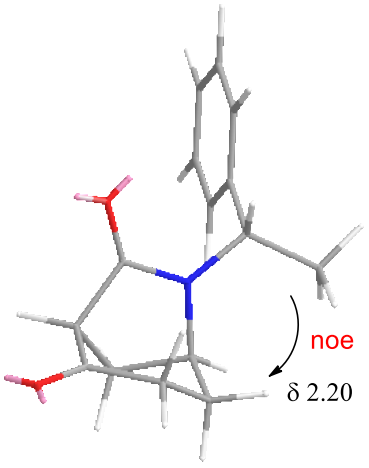
(1*S*,5*S*)-6-[(*S*)-1-Phenylethyl]-6-azabicyclo[3.2.1]octane-2,7-dione (4)

$[\alpha]_D^{23}$ = +195.8 (*c* 1, $CHCl_3$); mp 144-145 °C; IR (NaCl, neat) 3057, 3027, 2969, 2978, 2955, 2892, 2876, 1711, 1677 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.67 (d, *J* = 7.0 Hz, 3H, CH_3), 1.89-1.98 (m, 1H, H-4), 1.95 (d, *J* = 12 Hz, 1H, H-8), 2.18-2.27 (m, 1H, H-4), 2.41-2.48 (dm, *J*

= 12 Hz, 1H, H-8), 2.54 (dd, *J* = 17.2, 7.0 Hz, 1H, H-3), 2.64 (ddd, *J* = 17.2, 10.8, 8.8 Hz, 1H, H-3), 3.22 (d, *J* = 5.2 Hz, 1H, H-1), 3.66 (br s, 1H, H-5), 5.51 (q, *J* = 7.0 Hz, 1H), 7.29-7.41 (m, 5H, ArH); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 17.1 (CH_3), 30.2 (C-4), 35.1 (C-3), 37.4 (C-8), 50.2 (CH), 52.6 (C-5), 58.6 (C-1), 127.0, 127.9, 128.8 (CHAr), 139.9 (C-*ipso*), 170.6 (C-7), 202.6 (C-2); HRMS (ESI-TOF) *m/z*: $[M+H]^+$ calcd for $C_{15}H_{18}NO_2$ 244.1332; found 244.1325.

(1*R*,5*R*)-6-[(*S*)-1-Phenylethyl]-6-azabicyclo[3.2.1]octane-2,7-dione (5)

$[\alpha]_D^{23}$ = -347.5 (*c* 1, $CHCl_3$); m.p. 90-92 °C; IR (NaCl, neat) 3060, 3029, 2971, 2879, 1721, 1686 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.00-1.09 (m, 1H, H-4), 1.48-1.58 (m, 1H, H-4), 1.65 (d, *J* = 7.2 Hz, 3H, CH_3), 1.98 (d, *J* = 11.2 Hz, 1H, H-8), 2.10 (ddd, *J* = 17.2, 10.4, 8.8 Hz, 1H, H-3), 2.19 (dd, *J* = 17.2, 7.2 Hz, 1H, H-3), 2.53-2.61 (dm, *J* = 11.2 Hz, 1H, H-8), 3.19 (d, *J* = 5.6 Hz, 1H, H-1), 3.97 (br s, 1H, H-5), 5.59 (q, *J* = 7.2 Hz, 1H), 7.31-7.38 (m, 3H, ArH), 7.42-7.47 (m, 2H, ArH); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 16.3 (CH_3), 28.4 (C-4), 35.0 (C-3), 37.3 (C-8), 49.2 (CH), 51.8 (C-5), 58.4 (C-1), 127.2, 128.2, 128.7 (CHAr), 139.7 (C-*ipso*), 170.1 (C-7), 202.6 (C-2); HRMS (ESI-TOF) *m/z*: $[M+H]^+$ calcd for $C_{15}H_{18}NO_2$ 244.1332; found 244.1325.



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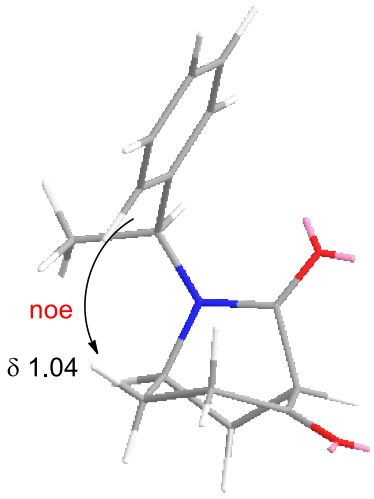
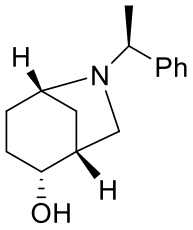


5

*Reduction of **4** and **5** with $LiAlH_4$*

(1*S*,2*R*,5*S*)-6-[(*S*)-1-Phenylethyl]-6-azabicyclo[3.2.1]octan-2-ol (6)

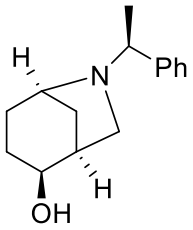
To a solution of **4** (100 mg, 0.411 mmol) in THF (3 mL) was added a 1 M solution of $LiAlH_4$ in THF (1.23 mL, 1.23 mmol) and the mixture was stirred at rt for 3 h. The mixture was quenched with few drops of water, filtered on a short celite pad wich was rinsed with MeOH. The combined filtrates were dried, concentrated and purified by chromatography (Al_2O_3, CH_2Cl_2 to CH_2Cl_2/MeOH 95:5) yielding the corresponding aminoalcohol **6** as a white solid (80 mg, 84%).



$[\alpha]_D^{23}$ = -18.2 (*c* 1, $CHCl_3$); mp 108-109 °C; IR (NaCl, neat) 3364, 3060, 3024, 2931, 2863, 1666, 1598 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 1.19 (tdd, *J* = 12.8, 5.2, 1.6 Hz, 1H, H-4ax), 1.27 (d, *J* = 11.2 Hz, 1H, H-8ax), 1.32 (d, *J* = 6.4 Hz, 3H, CH_3), 1.46-1.58 (tdd, *J* = 12.7, 10.0, 6.4 Hz, 1H, H-3ax), 1.65-1.74 (m, 1H, H-4eq), 1.83 (dtd, *J* = 11.2, 5.6, 2.4 Hz, 1H, H-8eq), 1.86-1.94 (m, 1H, H-3eq), 2.31 (br s, 1H, H-1), 2.65 (dd, *J* = 10, 5.6 Hz, H-7*pro*-R), 2.83 (d, *J* = 10 Hz, H-7*pro*-S), 3.08 (br t, *J* = 4.4 Hz, 1H, H-5), 3.68 (q, *J* = 6.4 Hz, 1H), 3.74 (ddd, *J* = 10.4, 6, 2.4 Hz, 1H, H-2), 7.21 (tt, *J* = 7.6, 1.6 Hz, 1H, ArH), 7.25-7.32 (m, 2H, ArH), 7.33-7.37 (m, 2H, ArH); ^{13}C NMR ($CDCl_3$, 100 MHz,) δ 23.8 (CH_3), 29.3 (C-3), 29.7 (C-4), 34.5 (C-8), 43.2 (C-1), 51.4 (C-7), 54.9 (C-5), 62.1 (CH), 71.5 (C-2), 126.6, 127.2, 128.2 (CHAr), 147.0 (C-*ipso*); HRMS (ESI-TOF) *m/z*: $[M+H]^+$ calcd for $C_{15}H_{22}NO$ 232.1696; found 232.1693.

(1*R*,2*S*,5*R*)-6-[(*S*)-1-Phenylethyl]-6-azabicyclo[3.2.1]octan-2-ol (7)

Operating as above from **5** (200 mg, 0.822 mmol), a 1 M solution of $LiAlH_4$ in THF (2.46 mL, 2.46 mmol) and THF (5 mL) aminoalcohol **7** was obtained as a white solid (137 mg, 72%).

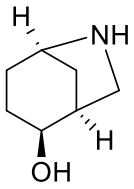


$[\alpha]_D^{23}$ = -26.9 (*c* 1, $CHCl_3$); m.p. 96-98 °C; IR (NaCl, neat): 3300, 3078, 3021, 2970, 2931, 2868, 2773, 1951, 1878, 1813, 1637, 1601 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 1.15 (tdd, *J* = 13.2, 5.6, 1.2 Hz, 1H, H-4ax), 1.27 (d, *J* = 11.2 Hz, 1H, H-8ax), 1.36 (d, *J* = 6.4 Hz, 3H, CH_3), 1.42-1.54 (tdd, *J* = 13.0, 10.2, 6.8 Hz, 1H, H-3ax), 1.62-1.70 (m, 1H, H-4eq), 1.83-1.93 (m, 2H, H-3eq and H-8eq), 2.34 (br s, 1H, H-1), 2.86 (d, *J* = 10.4 Hz, H-7 *pro*-S), 2.90 (dd, *J* = 10.4, 5.6 Hz, H-7 *pro*-R), 2.99 (br t, *J* = 4 Hz, 1H, H-5), 3.75 (q, *J* = 6.4 Hz, 1H), 3.76 (m, 1H, H-2), 7.21 (tt, *J* = 7.6, 1.6 Hz, 1H, ArH), 7.25-7.31 (m, 2H, ArH), 7.35-7.39 (m, 2H, ArH); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 24.4 (CH_3), 28.9 (C-3), 29.2 (C-4), 35.3 (C-8), 42.8 (C-1), 50.7 (C-7), 53.9 (C-5), 60.5 (CH), 71.6 (C-2), 126.6, 127.4, 128.1 (CHAr), 146.2 (C-*ipso*); HRMS (ESI-TOF) *m/z*: $[M+H]^+$ calcd for $C_{15}H_{22}NO$ 232.1696; found 232.1694.

*Debenzylation of **6** and **7***

(1*R*,2*S*,5*R*)-6-Azabicyclo[3.2.1]octan-2-ol (*ent*-8)

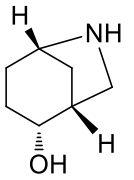
A suspension of **7** (110 mg, 0.48 mmol) and 10% Pd/C (11 mg, 10%) in EtOH (5 mL) was stirred under 1 atm H_2 at rt for 2 days. The mixture was then filtered on a short celite pad which was washed with EtOH. The solution was concentrated and the residue was purified by chromatography (Al_2O_3, CH_2Cl_2 to $CH_2Cl_2(NH_3)$/MeOH 70:30) to afford *ent*-**8** as a white solid (49 mg, 82%).



$[\alpha]_D^{23}$ = -7.69 (*c* 1.26, MeOH); mp 163-165 °C; IR (NaCl, neat) 3305, 2938, 2878 cm^{-1}; ^1H NMR (CD_3OD, 400 MHz) δ 1.39-1.52 (m, 2H), 1.55 (d, *J* = 11.6 Hz, 1H, H-8*ax*), 1.63 (m, 1H, H-4eq), 1.76 (dtd, *J* = 11.6, 5.6, 2.4 Hz, 1H, H-8eq), 1.82 (m, 1H, H-3eq), 2.30 (br s, 1H, H-1), 2.83 (dd, *J* = 10.8, 5.6 Hz, 1H, H-7*pro*-R), 3.14 (d, *J* = 10.8 Hz, 1H, H-7*pro*-S), 3.35 (br t, *J* = 4.8 Hz, 1H, H-5), 3.72 (ddd, *J* = 9.6, 6, 2.8 Hz, 1H, H-2); ^{13}C NMR (100 MHz, CD_3OD) δ 28.6 (C-3), 31.7 (C-4), 37.3 (C-8), 43.7 (C-1), 46.0 (C-7), 54.9 (C-5), 71.9 (C-2); HRMS (ESI-TOF) *m/z*: $[M+H]^+$ calcd for $C_7H_{14}NO$ 128.1070; found 128.1070.

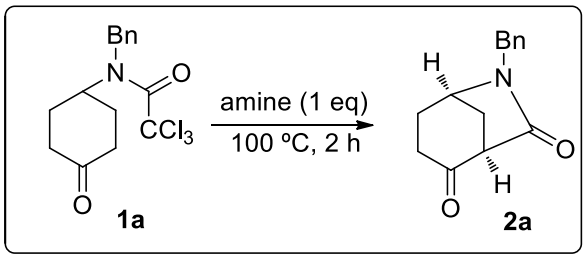
(1*S*,2*R*,5*S*)-6-Azabicyclo[3.2.1]octan-2-ol (8)

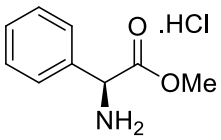
A mixture of aminoalcohol **6** (300 mg, 1.296 mmol), 10 % Pd/C (60 mg, 20%) in MeOH (28 mL) was stirred under 1 atm H_2 at rt for 3 d. After filtration, concentration and chromatography **8** was isolated (107 mg, 65%), **6** was also recovered (54 mg).



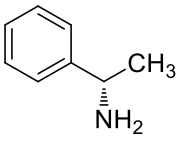
$[\alpha]_D^{23}$ = +7.27 (*c* 0.7, MeOH);

5. Screening of catalysts for the asymmetric synthesis of 2a

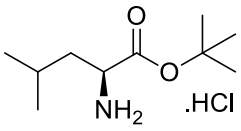




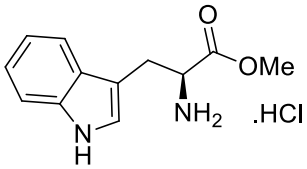
Et_3N (1eq)
86%, 0 ee



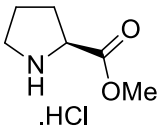
73%, 0 ee



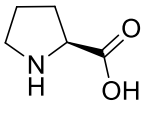
Et_3N (1eq)
93%, 0 ee



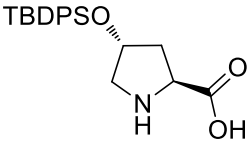
Et_3N (1eq)
42%, 22 ee



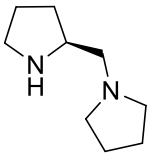
Et_3N (1eq)
80%, 25 ee



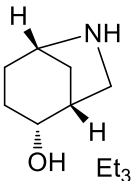
Et_3N (2eq)
55%, 10 ee



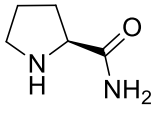
Et_3N (2eq)
82%, 16 ee



73%, 42 ee

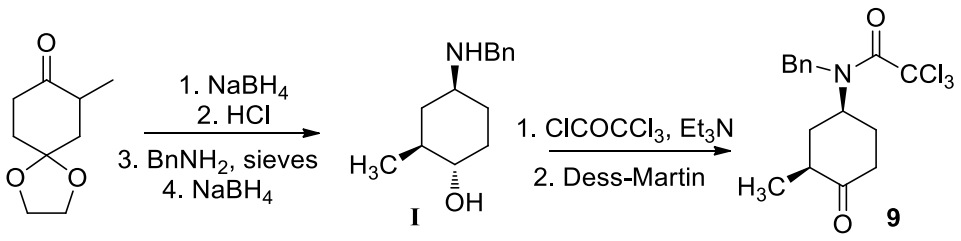


Et_3N (2eq)
100 ºC 30 min
70%, 18 ee (+)



0.5 eq,
DMSO, rt 64 h
50 %, **63 ee**

6. Preparation of 9



(1*RS*,2*RS*,4*RS*)-4-(Benzylamino)-2-methylcyclohexanol (I)

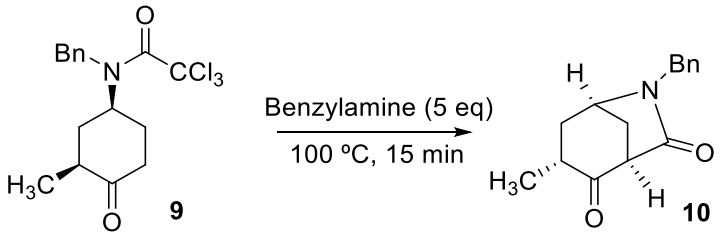
To a mixture of 7-methyl-1,4-dioxaspiro[4.5]decan-8-one (4 g, 23.5 mmol) in MeOH (40 mL) at 0 ºC was added $NaBH_4$ (0.98 g, 25.85 mmol) portionwise and the mixture was stirred at rt for 1 h. The mixture was then concentrated, brine was added and the aqueous extracted with CH_2Cl_2. The organics were dried, concentrated and the residue was treated with 10% HCl solution (40 mL) and THF (4 mL) overnight. The mixture was extracted with $CHCl_3$, the organics were dried, concentrated and to the resulting residue (2.6 g) dissolved in CH_2Cl_2 (30 mL) were added benzylamine (2.17 mL, 19.85 mmol) and 4 Å molecular sieves (6 g). The mixture was stirred at rt for 4 h then it was filtered on a short celite pad and concentrated to yield a viscous oil which was treated with $NaBH_4$ (0.83 g, 21.9 mmol) in MeOH (25 mL) at 0 ºC then at rt for 1 h. The mixture was concentrated, brine was added and the aqueous extracted with $CHCl_3$. The organics were dried, concentrated and the residue was left at -25 ºC with some drops of ether. After about 2 days **I** crystallize alone (1.4 g, 27% for the 4 steps): m.p. 97-98 °C; IR (KBr) 3265, 3168, 3066, 3030, 2986, 2946, 2921, 2869, 2821, 1605 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 1.94 (m, 1H), 1.02 (d, *J* = 6.4 Hz, 3H, CH_3), 1.12-1.24 (m, 1H), 1.26-1.44 (m, 2H), 1.52 (br s, 1H, NH), 1.88-1.01 (m, 3H), 2.56 (tt, *J* = 11.2, 3.6 Hz, 1H), 3.14 (td, *J* = 10.8, 4.4 Hz, 1H), 3.80 (s, 2H), 7.21-7.36 (m, 5H, ArH); ^{13}C NMR (100 MHz, $CDCl_3$) δ 18.5 (CH_3), 31.8 (CH_2), 33.8 (CH_2), 38.5 (CH), 40.4 (CH_2), 51.3 (CH_2), 55.5 (CH), 76.1 (CH), 126.9, 128.0, 128.4 (CHAr), 140.6 (C-*ipso*); HRMS (ESI-TOF) *m/z*: $[M+H]^+$ calcd for $C_{14}H_{22}NO$ 220.1696; found 220.1701.

(2*RS*,4*RS*)-4-(*N*-Benzyltrichloroacetamido)-3-methylcyclohexanone (9)

To a solution of **I** (700 mg, 3.19 mmol) in CH_2Cl_2 (15 ml) were added triethylamine (0.67 ml, 4.79 mmol) and trichloroacetyl chloride (0.39 ml, 3.51mmol) dropwise at 0 ºC. The mixture was stirred at rt for 1 h, water was added and the aqueous extracted with CH_2Cl_2. The organics were dried, concentrated and purified by chromatography (Hex/CH_2Cl_2 1:1 to CH_2Cl_2/AcOEt 9:1) to yield the corresponding trichloroacetamide (810 mg, 70%, 2.22 mmol) which was dissolved in CH_2Cl_2 (40 ml) and treated with Dess-Martin Periodinane (1.88 g, 4.44 mmol) for 1 h at rt. The mixture was then washed with saturated $NaHCO_3$ solution then with saturated $Na_2S_2O_3$. The organics were dried, concentrated and purified by chromatography (Al_2O_3, Hex:CH_2Cl_2 1:1) to

yield **9** (726 mg, 91%): mp 92-93 °C; IR (NaCl) 3089, 3064, 3031, 2970, 2935, 2870, 1716, 1675 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 1.00 (br s, 3H, CH_3), 1.71 (m, 1H), 1.84-1.64 (m, 6H), 4.54 (d, *J* = 14.4 Hz, 1H), 4.67 (d, *J* = 14.4 Hz, 1H), 5.12 (br s, 1H), 7.11-7.42 (m, 5H, ArH); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 14.3 (CH_3), 30.4 (CH_2), 38.3 (CH_2), 39.5 (CH_2), 43.2 (CH), 47.7 (CH_2), 57.1 (CH), 93.5 (CCl_3), 126.2, 127.2, 128.6 (CHAr), 136.9 (C-*ipso*), 160.5 (CO), 209.3 (CO); HRMS (ESI-TOF) *m/z*: $[M+H]^+$ calcd for $C_{16}H_{19}Cl_3NO_2$ 362.0476; found 362.0476.

7. Cyclization of 9

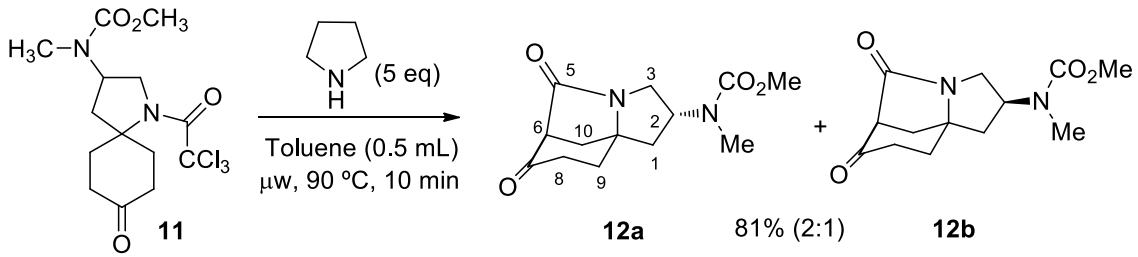


A mixture of **9** (50 mg, 0.14 mmol) and benzylamine (0.075 ml, 0.69 mmol) was heated in a sealed tube at 100 ºC for 15 min. After chromatography (CH_2Cl_2 to CH_2Cl_2/AcOEt 9:1) **10** was obtained contaminated with the other diastereomer (30 mg, 90%, 91:9).

(1*RS*,3*RS*,5*RS*)-6-Benzyl-3-methyl-6-azabicyclo[3.2.1]octane-2,7-dione (10)

IR (NaCl) 2962, 2930, 2872, 2858, 1720, 1688 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 1.05 (d, *J* = 6.8 Hz, 3H, CH_3), 1.46 (ddd, *J* = 13.8, 10.8, 1.6 Hz, 1H, H-4ax), 1.96 (d, *J* = 12 Hz, 1H, H-8ax), 2.26 (ddt, *J* = 13.8, 8, 3.2, 1H, H-4eq), 2.51 (m, 1H, H-3), 2.59 (dtd, *J* = 11.6, 4.8, 2.8 Hz, 1H, H-8eq), 3.27 (d, *J* = 5.2 Hz, 1H, H-1), 3.75 (br s, 1H, H-5), 4.26 and 4.84 (2d, *J* = 14.8 Hz, 1H each, CH_2Ar), 7.25-7.40 (m, 5H, ArH); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 13.9 (CH_3), 36.8 (C-4), 37.2 (C-8), 39.6 (C-3), 45.3 (CH_2Ar), 54.7 (C-5), 57.8 (C-1), 128.0, 128.2, 128.9 (CHAr), 136.2 (C-*ipso*), 171.7 (C-7), 204.3 (C-2); HRMS (ESI-TOF) *m/z*: $[M+H]^+$ calcd for $C_{15}H_{18}NO_2$ 244.1332; found 244.1338.

8. Cyclization of 11



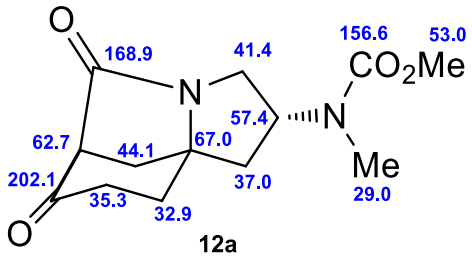
In a 10 mL vessel, a mixture of **11**[5] (39 mg, 0.1 mmol) and pyrrolidine (0.042 mL, 0.5 mmol) in toluene (0.5 mL) was heated with stirring to 90 ºC using microwave irradiation for 10 min. After careful chromatography (CH_2Cl_2 to CH_2Cl_2/EtOAc 1:1), **12b** (7 mg, 26%) and **12a** (15 mg, 55%) were sequentially obtained.

(2*RS*,6*SR*,9a*SR*)-2-[*N*-(Methoxycarbonyl)-*N*-methylamino]-tetrahydro-1*H*,5*H*-6,9a-methanopyrrolo[1,2-*a*]azepine-5,7(6*H*)-dione (12a).

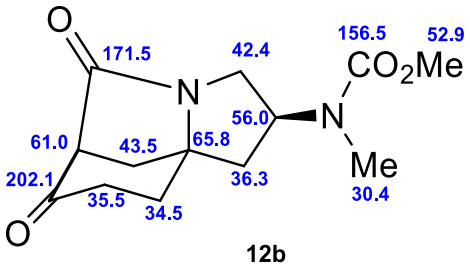
IR (KBr) 2953, 2919, 2873, 1723, 1694 cm^{-1}; 1H NMR ($CDCl_3$, 400 MHz) 1.93-1.05 (m, 2H, H-1 and H-9), 2.08 (dd, *J* = 12.8, 7.7 Hz, 1H, H-1), 2.14-2.24 (m, 1H, H-9), 2.40 (d, *J* = 11.6 Hz, 1H, H-10ax), 2.50-2.56 (m, 1H, H-10eq), 2.60 (dd, *J* = 17.6, 7.2 Hz, 1H, H-8eq), 2.72 (dt, *J* = 17.6, 9.6 Hz, 1H, H-8ax), 2.85 (s, 3H, CH_3), 3.26 (d, 1H, *J* = 4.8 Hz, H-6), 3.43 (dd, *J* = 11.6, 8 Hz, 1H, H-3), 4.50 (dd, *J* = 11.6, 8.8 Hz, 1H, H-3), 3.74 (s, 3H, CH_3), 5.35 (br s, 1H, H-2); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 29.0 (CH_3), 32.9 (C-9), 35.3 (C-8), 37.0 (C-1), 41.4 (C-3), 44.1 (C-10), 53.0 (CH_3), 57.4 (C-2), 62.7 (C-6), 67.0 (C-9a), 156.6 (CO), 168.9 (C-5), 202.1 (C-7). HRMS (ESI-TOF) *m/z*: $[M+H]^+$ calcd for $C_{13}H_{19}N_2O_4$ 267.1339; found 267.1341.

(2*RS*,6*RS*,9a*RS*)-2-[*N*-(Methoxycarbonyl)-*N*-methylamino]-tetrahydro-1*H*,5*H*-6,9a-methanopyrrolo[1,2-*a*]azepine-5,7(6*H*)-dione (12b).

IR (KBr) 2955, 2915, 2880, 1721, 1694 cm^{-1}; 1H NMR ($CDCl_3$, 400 MHz) 1.99 (dd, *J* = 13.2, 10.8 Hz, 1H, H-1), 2.16 (m, 2H, CH_2-9), 2.23 (dd, *J* = 13.2, 8.8 Hz, 1H, H-1), 2.34 (d, *J* = 11.6 Hz, 1H, H-10ax), 2.48 (dd, *J* = 11.6, 4.8 Hz, 1H, H-10eq), 2.61 (dt, *J* = 18, 4.8 Hz, 1H, H-8eq), 2.75 (dt, *J* = 18, 8.8 Hz, 1H, H-8ax), 2.90 (s, 3H, CH_3), 3.07 (br s, 1H, H-3), 3.21 (d, 1H, *J* = 4.8 Hz, H-6), 3.72 (s, 3H, CH_3), 3.97 (dd, *J* = 11.6, 7.2 Hz, 1H, H-3), 4.62 (tdd, *J* = 10.4, 8.8, 7.6 Hz, 1H, H-2); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 30.4 (CH_3), 34.5 (C-9), 35.5 (C-8), 36.3 (C-1), 42.4 (C-3), 43.5 (C-10), 52.9 (CH_3), 56.0 (C-2), 61.0 (C-6), 65.8 (C-9a), 156.5 (CO), 171.5 (C-5), 202.1 (C-7); HRMS (ESI-TOF) *m/z*: $[M+H]^+$ calcd for $C_{13}H_{19}N_2O_4$ 267.1339; found 267.1340.



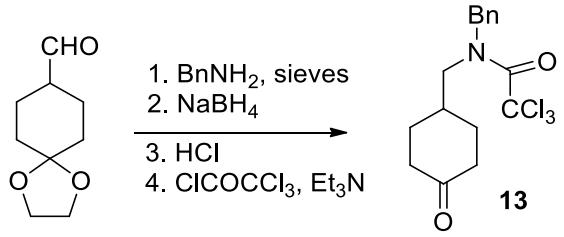
12a



12b

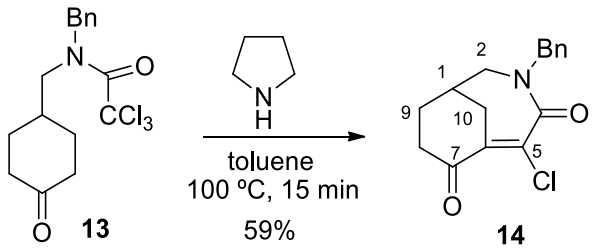
[5] Diaba, F.; Martínez-Laporta, A.; Bonjoch, J. *J. Org. Chem*. **2014**, *79*, 9365−9372.

9. Preparation of 13



Part 1: A mixture of 1,4-dioxaspiro[4.5]decane-8-carbaldehyde[6] (3.32 g, 19.5 mmol), benzylamine (2.40 mL) and molecular sieves (4 Å, 6 g) in CH_2Cl_2 (16 mL) was stirred at rt for 4.5 h. The mixture was filtered on a celite pad, concentrated and treated with $NaBH_4$ (1.48 g, 39.0 mmol) in MeOH at 0 ºC and at rt for 4 h. The mixture was concentrated, brine was added and the aqueous extracted with CH_2Cl_2. The organics were dried, concentrated and purified by chromatography (EtOAc/MeOH 9:1) to yield the corresponding secondary amine (3.46 g, 68%). *Part 2:* A solution of the previous amine (1 g, 3.83 mmol) in 2N HCl solution (115 mL) was stirred at rt overnight. The mixture was basified with 2.5 N NaOH solution and extracted with CH_2Cl_2. The organics were dried, concentrated to yield 4-[(benzylamino)methyl]cyclohexanone (787 mg, 94%) which was used in the next step without further purification. *Part 3*: To a solution of the previous amino ketone (391 mg, 1.80 mmol) in CH_2Cl_2 (3 mL) were added successively Et_3N (0.28 mL, 2 mmol) and trichloroacetyl chloride (0.30 mL, 2.70 mmol) at 0 ºC then the mixture was stirred at rt for 2 h. The mixture was diluted in CH_2Cl_2, washed with 1M HCl solution then with brine. The organics were dried, concentrated and purified by chromatography (hexane/EtOAc 1:1) to yield trichloroacetamide **13** (605 mg, 93%) as a yellowish solid: mp 112-114 ºC; IR (KBr) 3031, 2934, 2860, 1713, 1675; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.37-1.52 (m, 2H), 1.95-2.06 (m, 2H), 2.23-2.45 (m, 5H), 3.31 (d, *J* = 6.8 Hz, 2H, NCH_2), 5.04 (s, 2H, CH_2Ar), 7.22-7.42 (m, 5H, ArH); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 30.2 (2 CH_2), 33.9 (CH), 40.2 (2 CH_2), 52.7 CH_2), 54.2 CH_2), 93.2 (CCl_3), 127.0, 128.1, 128.9 (CHAr), 135.1 (C-*ipso*), 161.3 (CO), 210.8 (CO). HRMS (ESI-TOF) *m/z*: $[M+H]^+$ calcd for $C_{16}H_{19}Cl_3NO_2$ 362.0476; found 362.0475.

10. Cyclization of 13

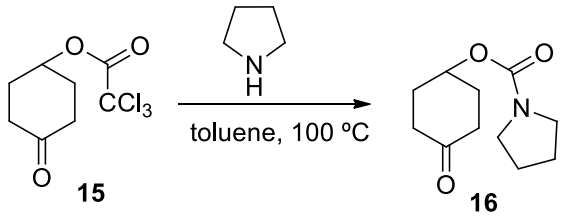


[6] Rosowsky, A.; Forsch, R. A.; Moran, R. G. *J. Med. Chem*. **1989**, *32*, 709-715.

3-Benzyl-5-chloro-3-azabicyclo[4.3.1]dec-5-ene-4,7-dione (14)

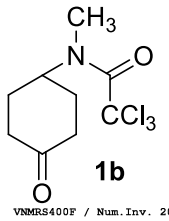
A mixture of **13** (100 mg, 0.27 mmol) and pyrrolidine (0.11 mL, 1.38 mmol) in toluene (0.1 mL) was heated at 100 ºC for 15 min in a sealed tube. After chromatography (CH_2Cl_2 to CH_2Cl_2/AcOEt 95:5) **14** was obtained as a white solid (47 mg, 59%): IR (KBr) 3061, 3031, 2944, 2884, 1718, 1652 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 1.56-1.65 (m, 1H, H-9), 1.96 (dtd, *J* = 14.4, 8.4, 5.6 Hz, 1H, H-9), 2.25 (dd, *J* = 12.8, 2.4 Hz, 1H, H-8), 2.42 (m, 1H, H-1), 2.59 (ddd, *J* = 12.8, 4, 2.8 Hz, 1H, H-8), 3.63 (m, 2H, CH_2-10), 3.34 (d, *J* = 8.8 Hz, 1H, CH_2-2), 4.47 (d, *J* = 14.0 Hz, 1H, CH_2Ar), 4.89 (d, *J* = 14.0 Hz, 1H, CH_2Ar), 7.30-7.39 (m, 5H, ArH); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 26.4 (C-9), 34.4 (C-8), 39.0 (C-1), 40.8 (C-10), 49.4 (C-2), 50.9 (CH_2Ar), 118.8 (C-5), 128.1, 128.6, 129.0 (CHAr), 136.6 (C-*ipso*), 140.4 (C-6), 164.9 (C-4), 198.2 (C-7); HRMS (ESI-TOF) *m/z*: $[M+H]^+$ calcd for $C_{16}H_{17}ClNO_2$ 290.0942; found 290.0953.

11. Reaction of 15 with pyrrolidine

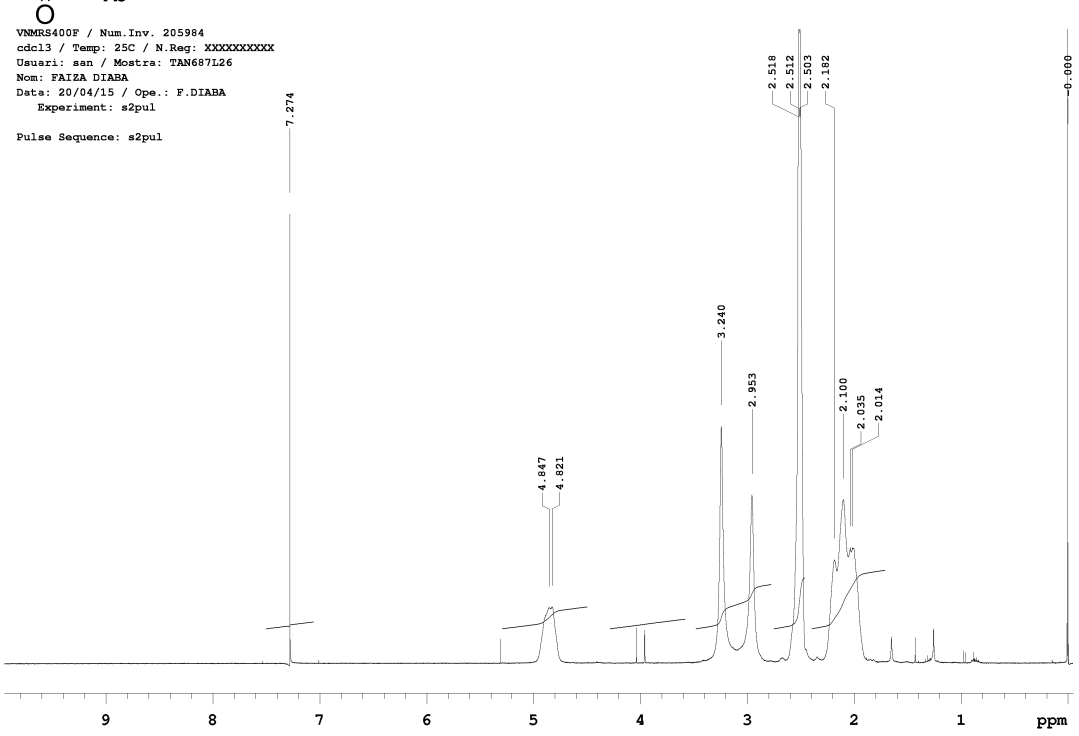


A mixture of **15**[7] (70 mg, 0.27 mmol) and pyrrolidine (0.033 ml, 0.40 mmol) in toluene (0.05 mL) was heated in a sealed tube at 100 ºC for 15 min. After chromatography (CH_2Cl_2), **16** was isolated as a yellowish oil (37 mg, 65%): IR (NaCl) 2955, 2875, 1699 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 1.83-1.95 (m, 4H), 2.00-2.19 (m, 4H), 2.36 (dt, *J* = 14.8, 6.4 Hz, 2H), 2.56 (ddd, *J* = 15.4, 10, 6 Hz, 2H), 3.34-3.45 (m, 4H), 5.12 (m, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 24.9 (CH_2), 25.7 (CH_2), 30.9 (2 CH_2), 37.3 (2 CH_2), 45.8 (CH_2), 46.1 (CH_2), 68.6 (CH), 154.2 (CO), 210.4 (CO); HRMS (ESI-TOF) *m/z*: $[M+H]^+$ calcd for $C_{11}H_{18}NO_3$ 212.1281; found 212.1274.

[7] Kleinpeter, E.; Heydenreich, M.; Koch, A.; Linker, T. *Tetrahedron* **2012**, *68*, 2363-2373.


CH3
N
O
CCl3
O

1b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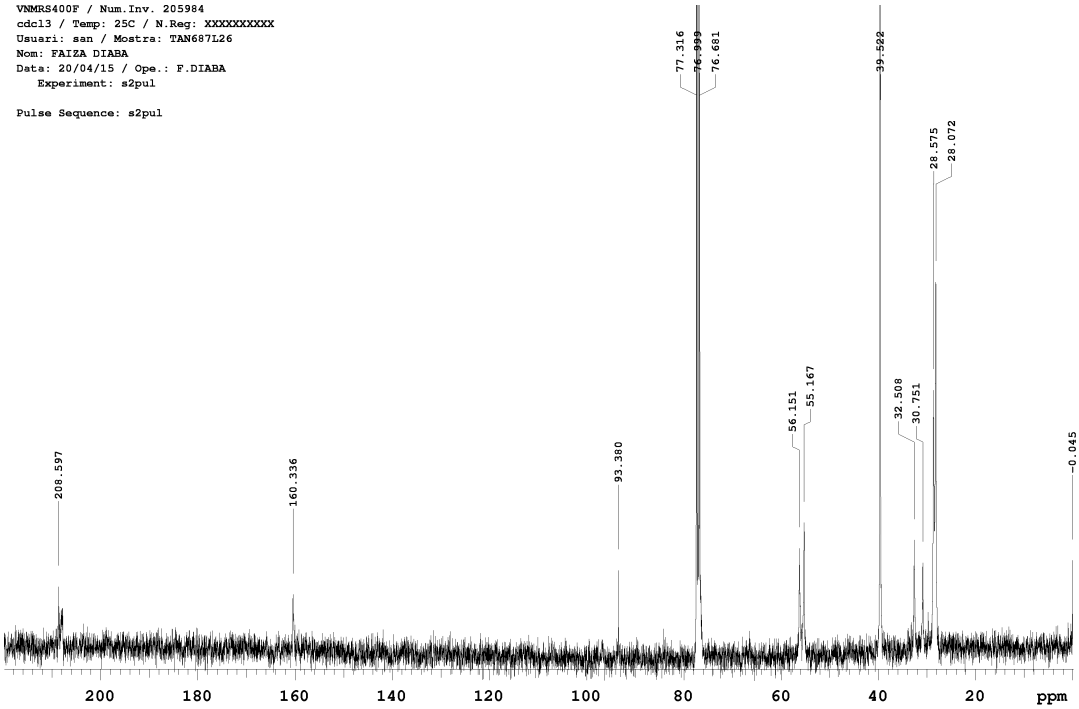
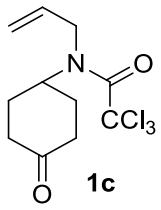
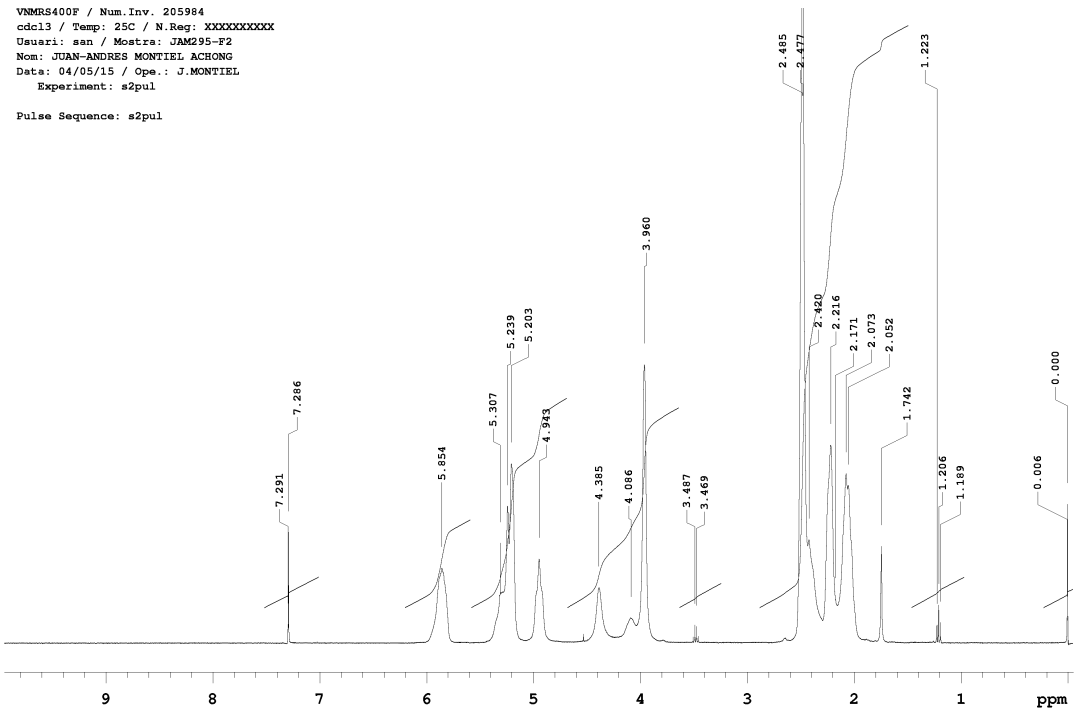
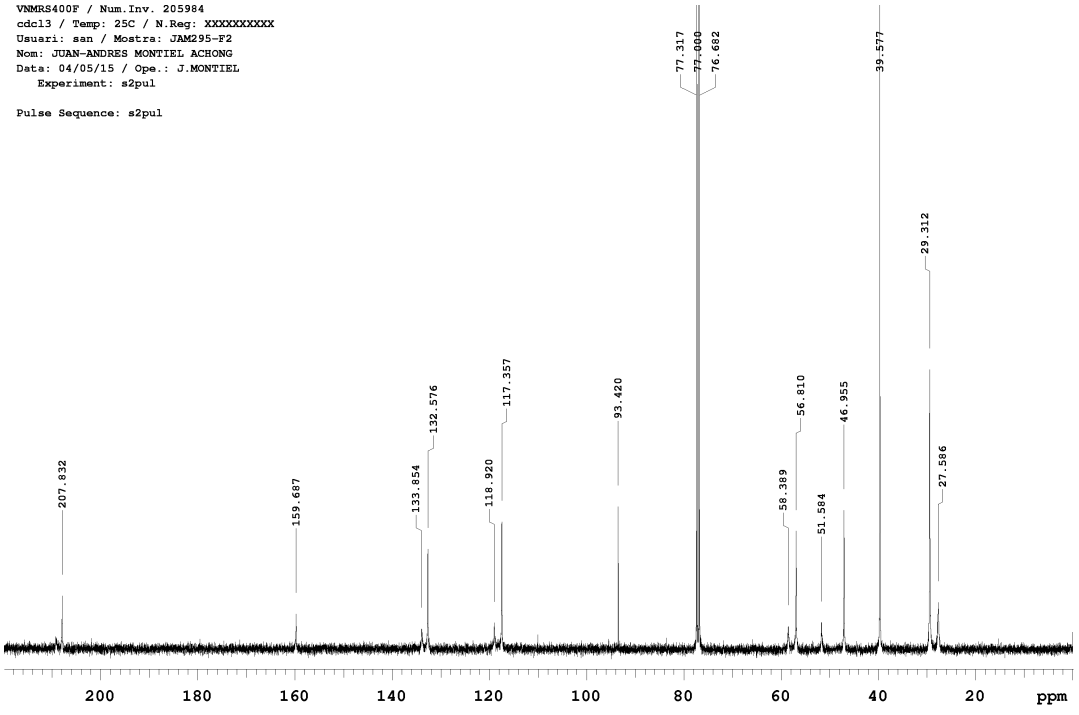
cdcl3 / Temp: 25C / N.Reg: XXXXXXXXXX
Usuari: san / Mostra: TAN687L26
Nom: FAIZA DIABA
Data: 20/04/15 / Ope.: F.DIABA
Experiment: s2pul
Pulse Sequence: s2pul
7.274
4.847
4.821
3.240
2.953
2.518
2.512
2.503
2.182
2.100
2.035
2.014
0.000
9
8
7
6
5
4
3
2
1
ppm

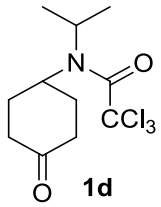

VNMRS400F / Num.Inv. 205984
cdcl3 / Temp: 25C / N.Reg: XXXXXXXXXX
Usuari: san / Mostra: TAN687L26
Nom: FAIZA DIABA
Data: 20/04/15 / Ope.: F.DIABA
Experiment: s2pul
Pulse Sequence: s2pul
208.597
160.336
93.380
77.316
76.999
76.681
56.151
55.167
39.502
32.508
30.751
28.575
28.072
-0.045
200
180
160
140
120
100
80
60
40
20
ppm


N
O
CCl3
O

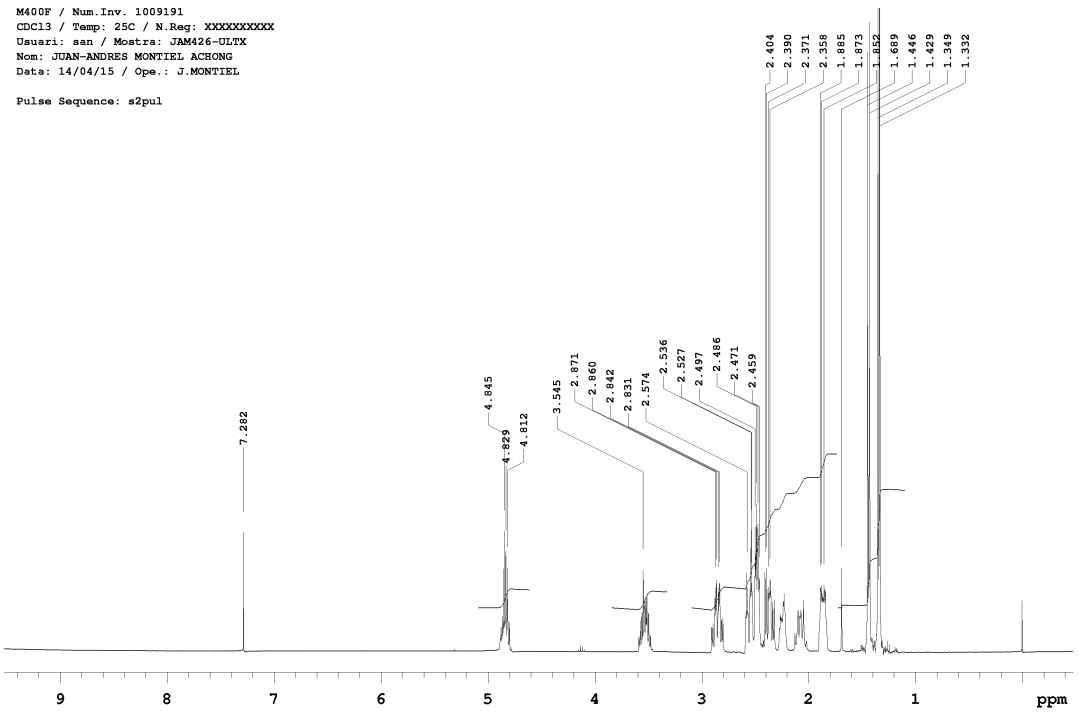
1c

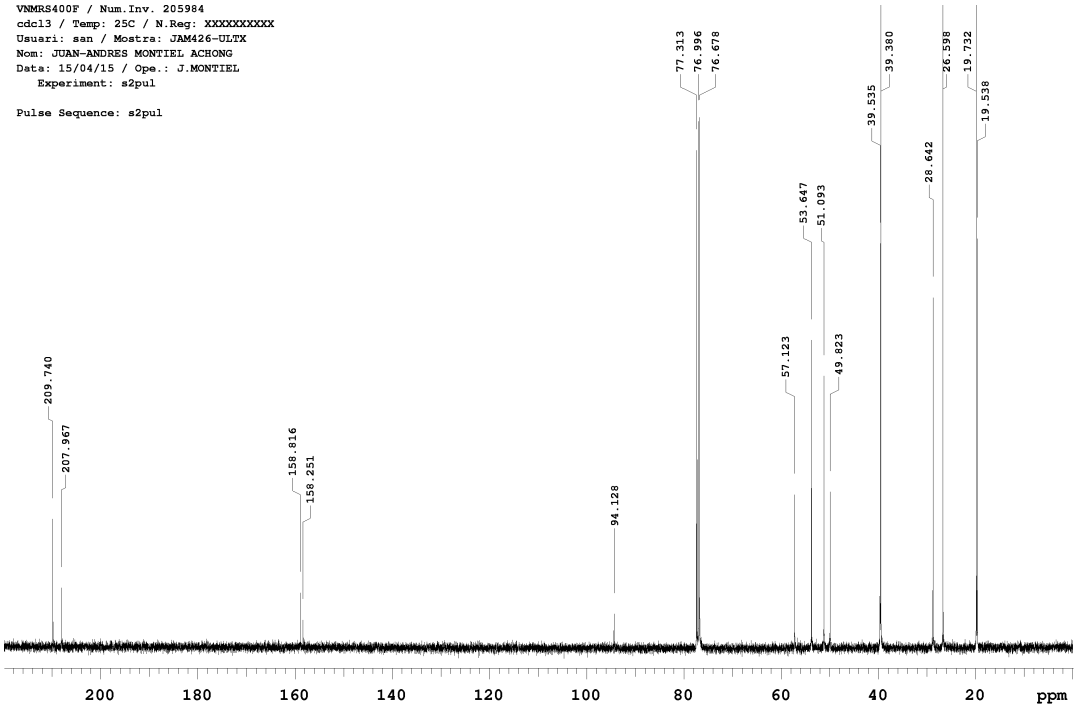

VNMRS400F / Num.Inv. 205984
cdcl3 / Temp: 25C / N.Reg: XXXXXXXXXX
Usuari: san / Mostra: JAM295-F2
Nom: JUAN-ANDRES MONTIEL ACHONG
Data: 04/05/15 / Ope.: J.MONTIEL
Experiment: s2pul
Pulse Sequence: s2pul
7.291
7.286
5.854
5.307
5.239
5.203
4.943
4.385
4.086
3.960
3.487
3.469
2.485
2.477
2.420
2.216
2.171
2.073
2.052
1.742
1.223
1.206
1.189
0.006
0.000
9
8
7
6
5
4
3
2
1
ppm

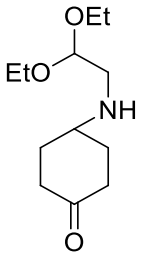

VNMRS400F / Num.Inv. 205984
cdcl3 / Temp: 25C / N.Reg: XXXXXXXXXX
Usuari: san / Mostra: JAM295-F2
Nom: JUAN-ANDRES MONTIEL ACHONG
Data: 04/05/15 / Ope.: J.MONTIEL
Experiment: s2pul
Pulse Sequence: s2pul
207.832
159.687
133.854
132.576
118.920
117.357
93.420
77.317
77.000
76.682
58.389
56.810
51.584
46.955
39.577
29.312
27.586
200
180
160
140
120
100
80
60
40
20
ppm

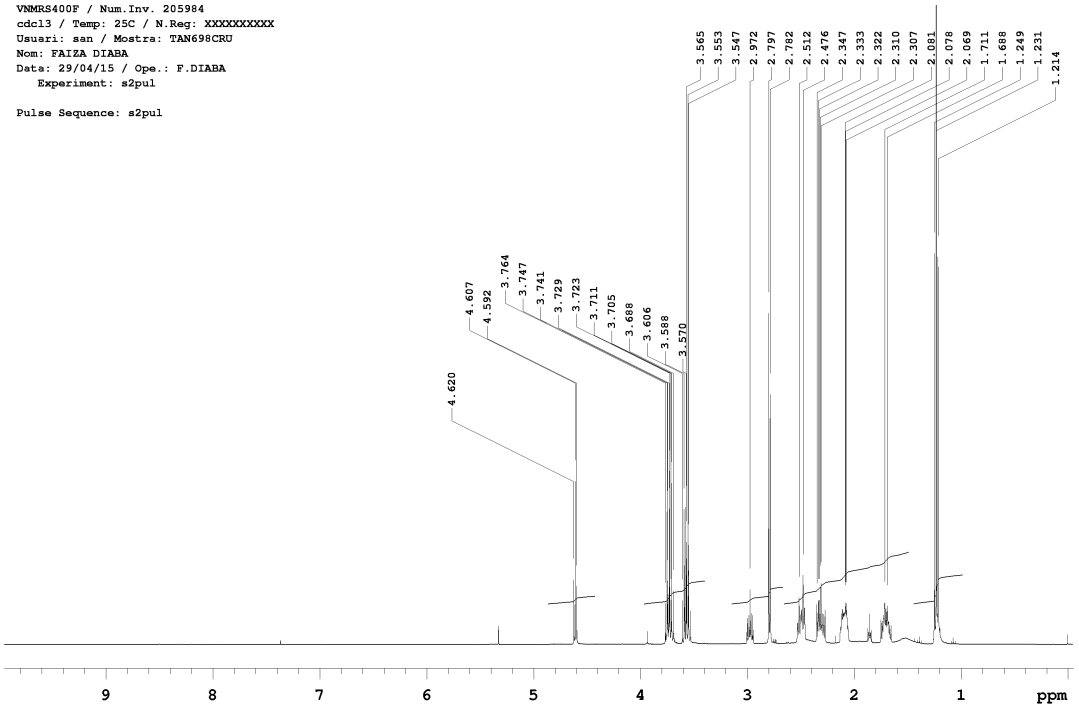

N
O
CCl3
O

1d


M400F / Num.Inv. 1009191
CDCl3 / Temp: 25C / N.Reg: XXXXXXXXXX
Usuari: san / Mostra: JAM426-ULTX
Nom: JUAN-ANDRES MONTIEL ACHONG
Data: 14/04/15 / Ope.: J.MONTIEL
Pulse Sequence: s2pul
7.282
4.845
4.829
4.812
3.545
2.871
2.860
2.842
2.831
2.574
2.536
2.527
2.497
2.486
2.471
2.459
2.404
2.390
2.371
2.358
1.885
1.873
1.852
1.689
1.446
1.429
1.349
1.332
9
8
7
6
5
4
3
2
1
ppm


VNMRS400F / Num.Inv. 205984
cdcl3 / Temp: 25C / N.Reg: XXXXXXXXXX
Usuari: san / Mostra: JAM426-ULTX
Nom: JUAN-ANDRES MONTIEL ACHONG
Data: 15/04/15 / Ope.: J.MONTIEL
Experiment: s2pul
Pulse Sequence: s2pul
209.740
207.967
158.816
158.251
94.128
77.313
76.996
76.678
57.123
53.647
51.093
49.823
39.535
39.380
28.642
26.598
19.732
19.538
200
180
160
140
120
100
80
60
40
20
ppm


OEt
EtO
NH
O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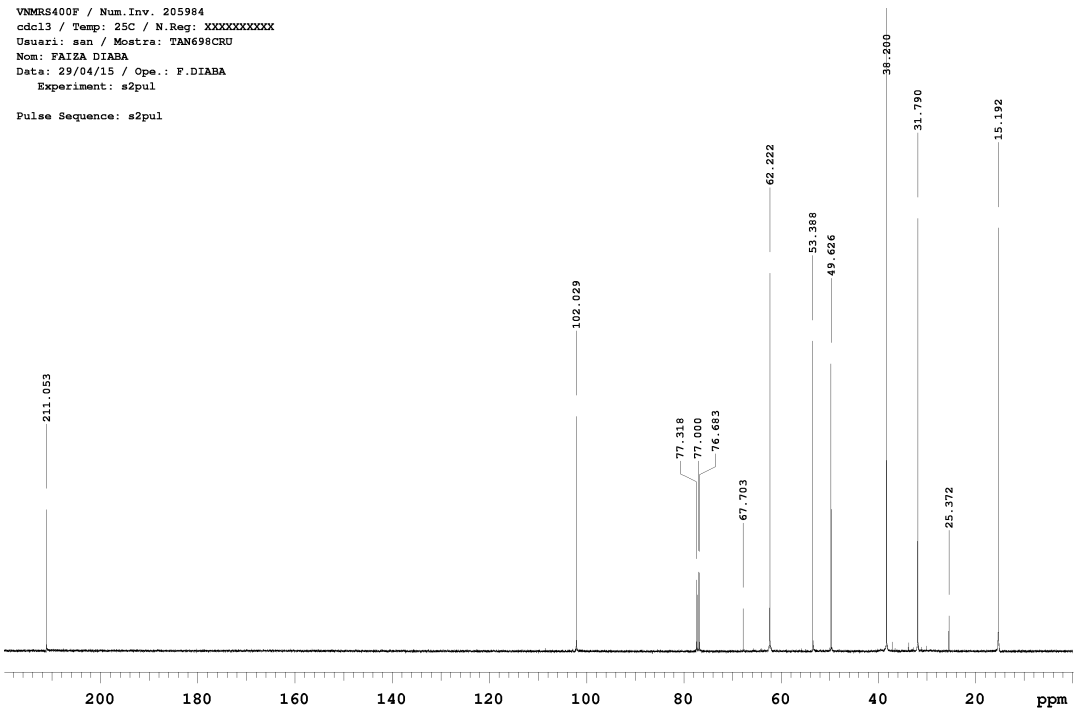
cdcl3 / Temp: 25C / N.Reg: XXXXXXXXXX
Usuari: san / Mostra: TAN698CRU
Nom: FAIZA DIABA
Data: 29/04/15 / Ope.: F.DIABA
Experiment: s2pul
Pulse Sequence: s2pul
4.620
4.607
4.592
3.764
3.747
3.741
3.729
3.723
3.711
3.705
3.688
3.606
3.588
3.570
3.565
3.553
3.547
2.972
2.797
2.782
2.512
2.476
2.347
2.333
2.322
2.310
2.307
2.081
2.078
2.069
1.711
1.688
1.249
1.231
1.214
9
8
7
6
5
4
3
2
1
ppm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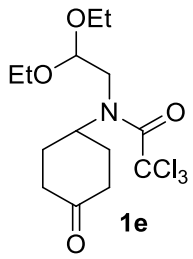
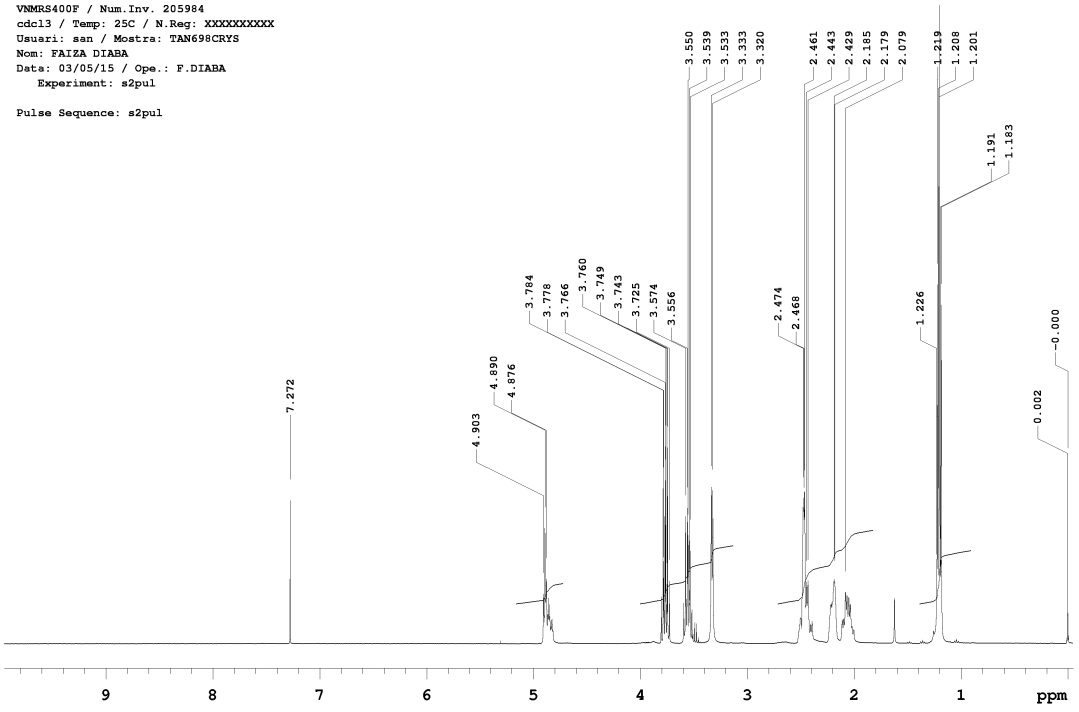
cdcl3 / Temp: 25C / N.Reg: XXXXXXXXXX
Usuari: san / Mostra: TAN698CRU
Nom: FAIZA DIABA
Data: 29/04/15 / Ope.: F.DIABA
Experiment: s2pul
Pulse Sequence: s2pul
211.053
102.029
77.318
77.000
76.683
67.703
62.222
53.388
49.626
38.200
31.790
25.372
15.192
200
180
160
140
120
100
80
60
40
20
ppm


OEt
EtO
N
O
CCl3
O

1e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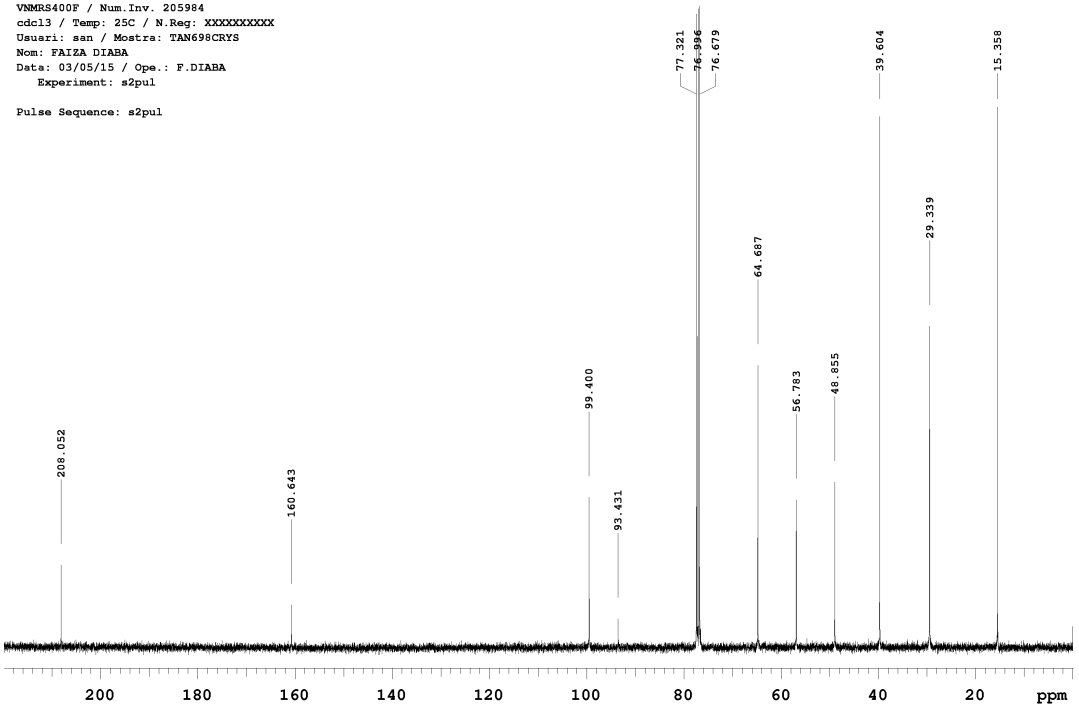
cdcl3 / Temp: 25C / N.Reg: XXXXXXXXXX
Usuari: san / Mostra: TAN698CRYS
Nom: FAIZA DIABA
Data: 03/05/15 / Ope.: F.DIABA
Experiment: s2pul
Pulse Sequence: s2pul
3.550
3.539
3.533
3.333
3.320
2.461
2.443
2.429
2.185
2.179
2.079
1.219
1.208
1.201
1.191
1.183
3.784
3.778
3.766
3.760
3.749
3.743
3.725
3.574
3.556
2.474
2.468
1.226
0.000
0.002
7.272
4.890
4.876
4.903
9
8
7
6
5
4
3
2
1
ppm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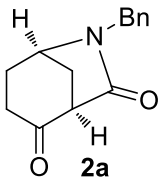
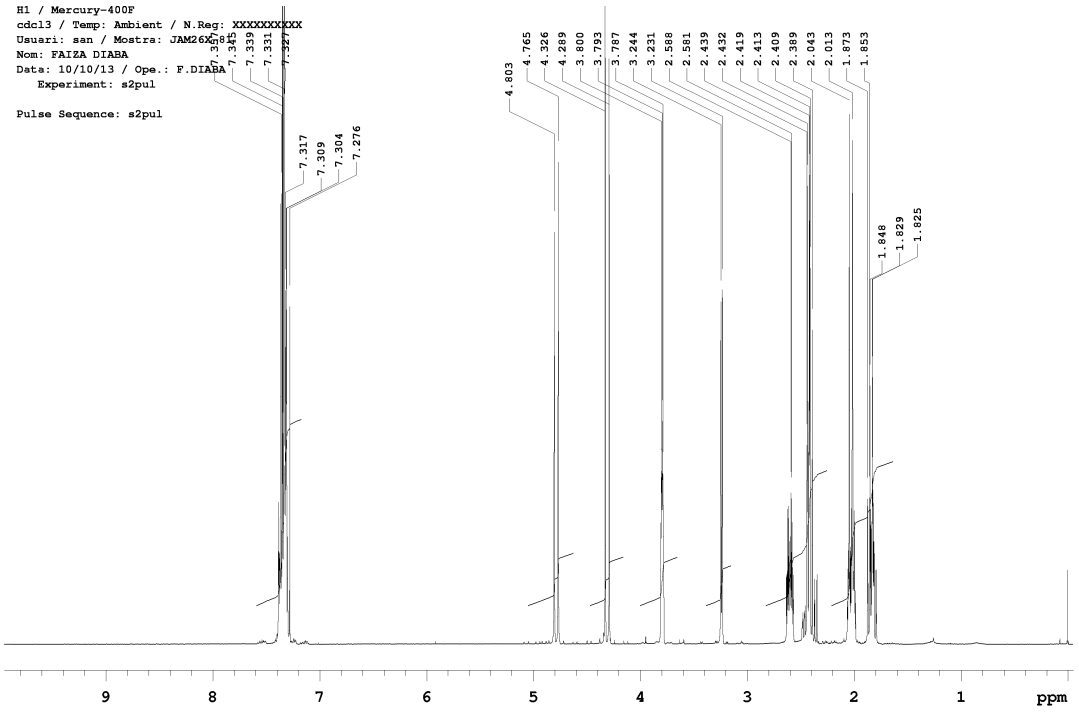
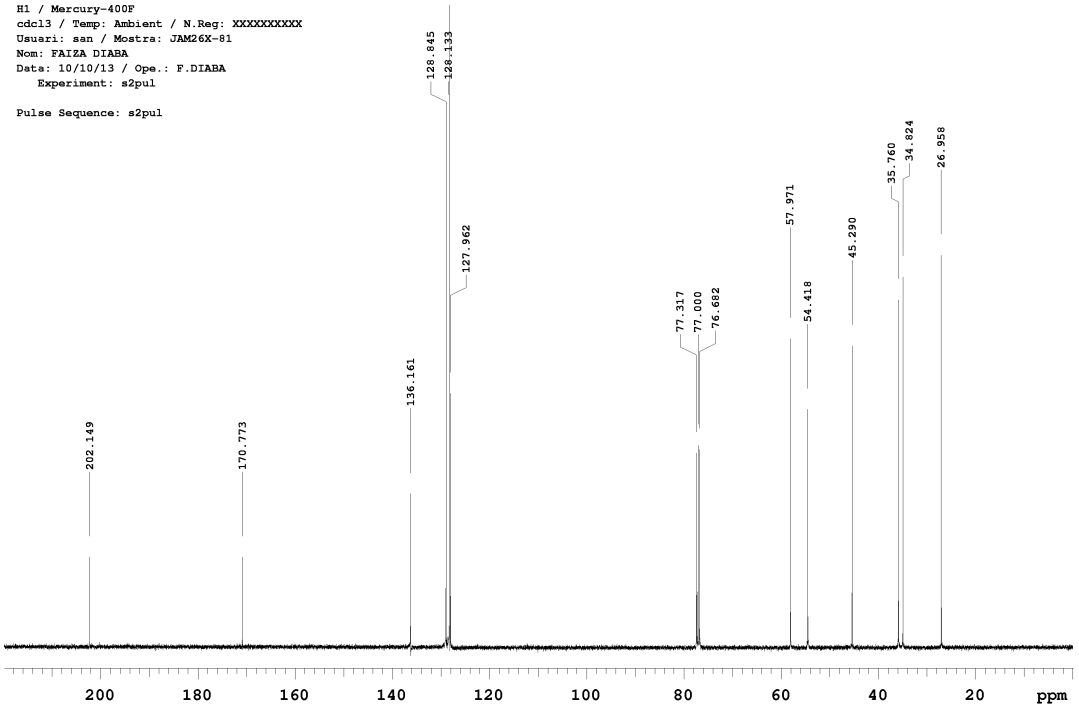
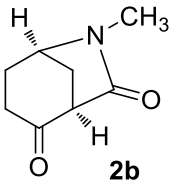
cdcl3 / Temp: 25C / N.Reg: XXXXXXXXXX
Usuari: san / Mostra: TAN698CRYS
Nom: FAIZA DIABA
Data: 03/05/15 / Ope.: F.DIABA
Experiment: s2pul
Pulse Sequence: s2pul
77.321
76.996
76.679
39.604
15.358
64.687
29.339
56.783
48.855
99.400
208.052
160.643
93.431
200
180
160
140
120
100
80
60
40
20
ppm


H
N
Bn
O
H
O
O

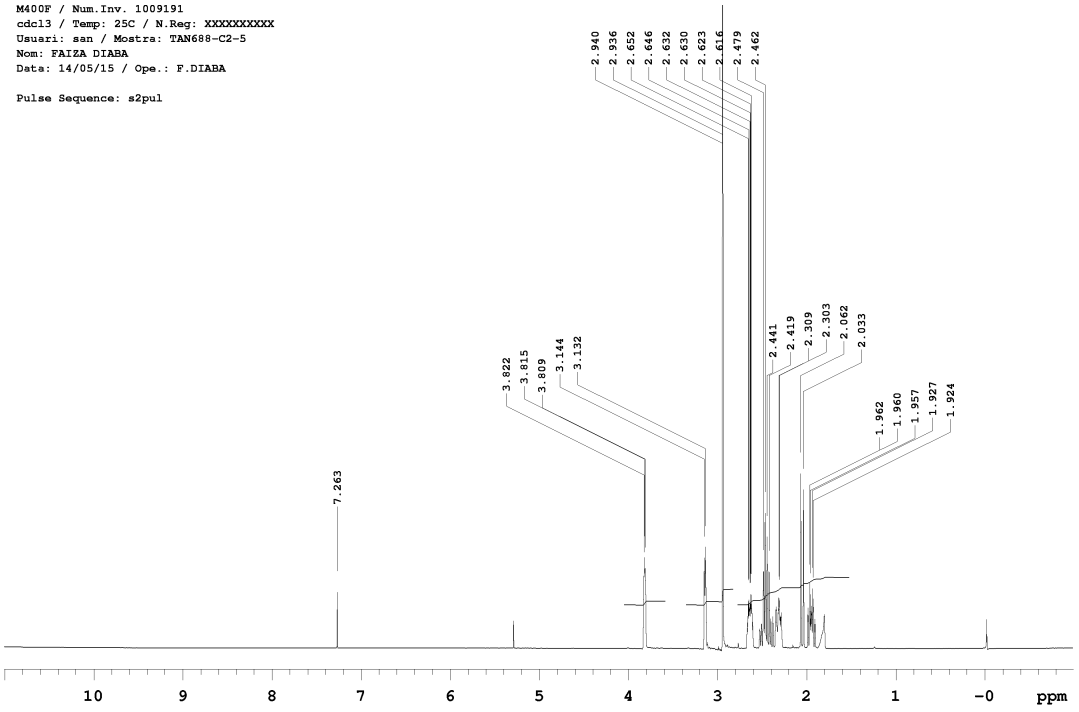
2a


H1 / Mercury-400F
cdcl3 / Temp: Ambient / N.Reg: XXXXXXXXXX
Usuari: san / Mostra: JAM26X-81
Nom: FAIZA DIABA
Data: 10/10/13 / Ope.: F.DIABA
Experiment: s2pul
Pulse Sequence: s2pul
7.345
7.339
7.331
7.327
7.317
7.309
7.304
7.276
4.803
4.765
4.326
4.289
3.800
3.793
3.787
3.244
3.231
2.588
2.581
2.439
2.432
2.419
2.413
2.409
2.389
2.043
2.013
1.873
1.853
1.848
1.829
1.825
9
8
7
6
5
4
3
2
1
ppm


H1 / Mercury-400F
cdcl3 / Temp: Ambient / N.Reg: XXXXXXXXXX
Usuari: san / Mostra: JAM26X-81
Nom: FAIZA DIABA
Data: 10/10/13 / Ope.: F.DIABA
Experiment: s2pul
Pulse Sequence: s2pul
202.149
170.773
136.161
128.845
128.133
127.962
77.317
77.000
76.682
57.971
54.418
45.290
35.760
34.824
26.958
200
180
160
140
120
100
80
60
40
20
ppm


H
N
CH3
O
H
O

2b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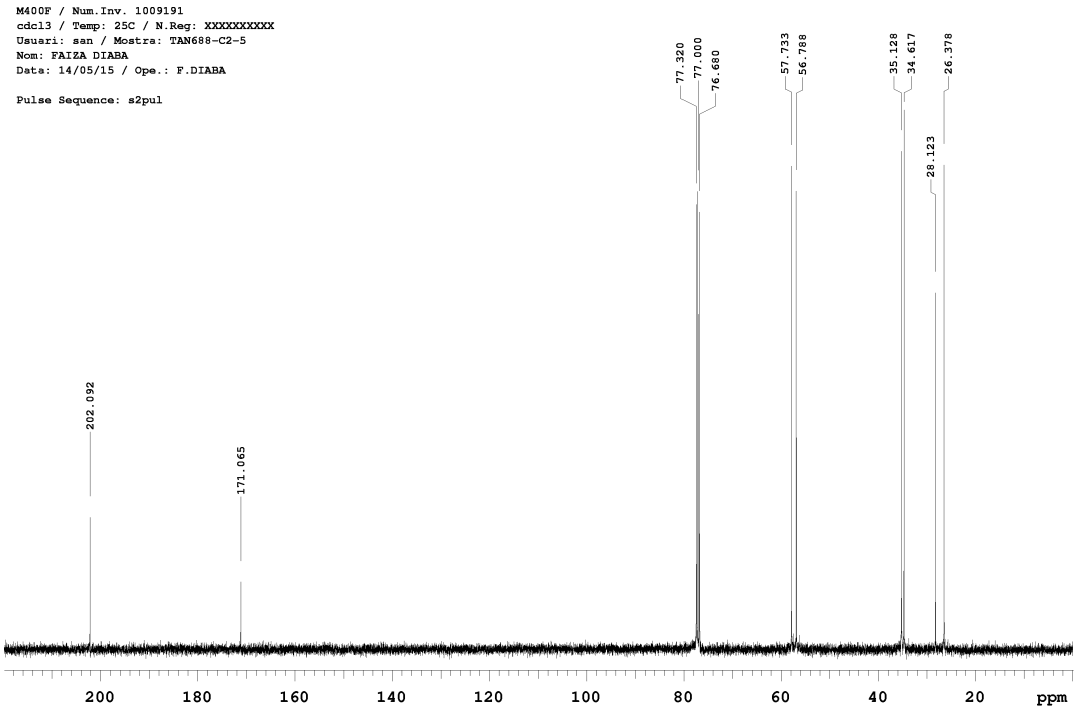
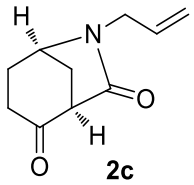
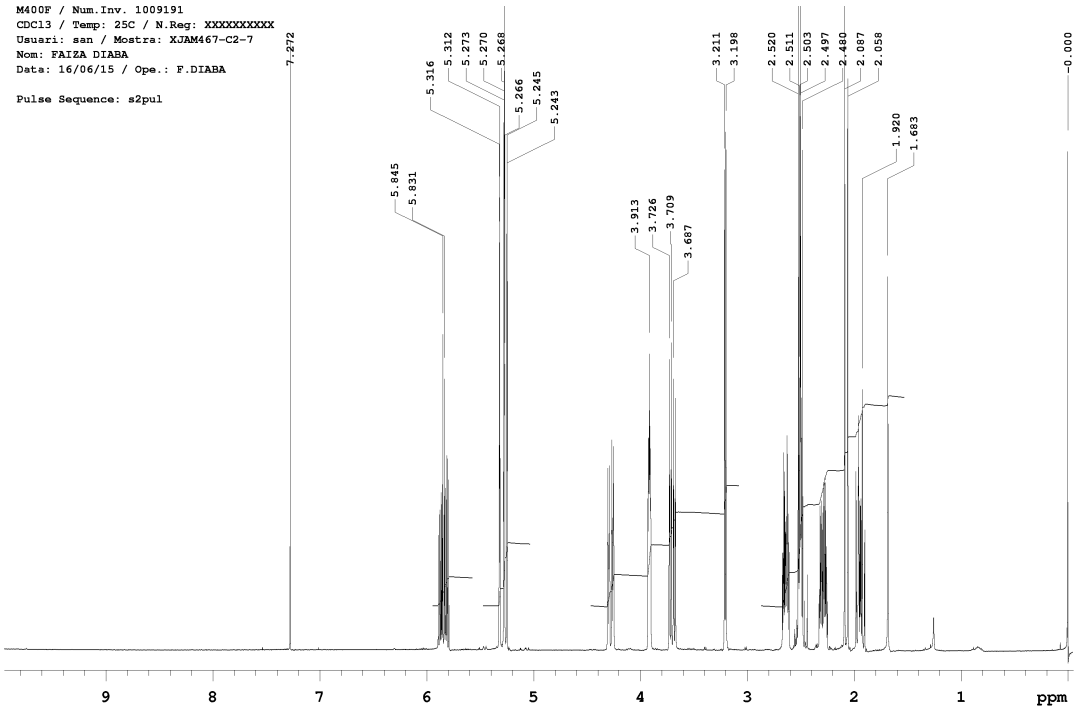
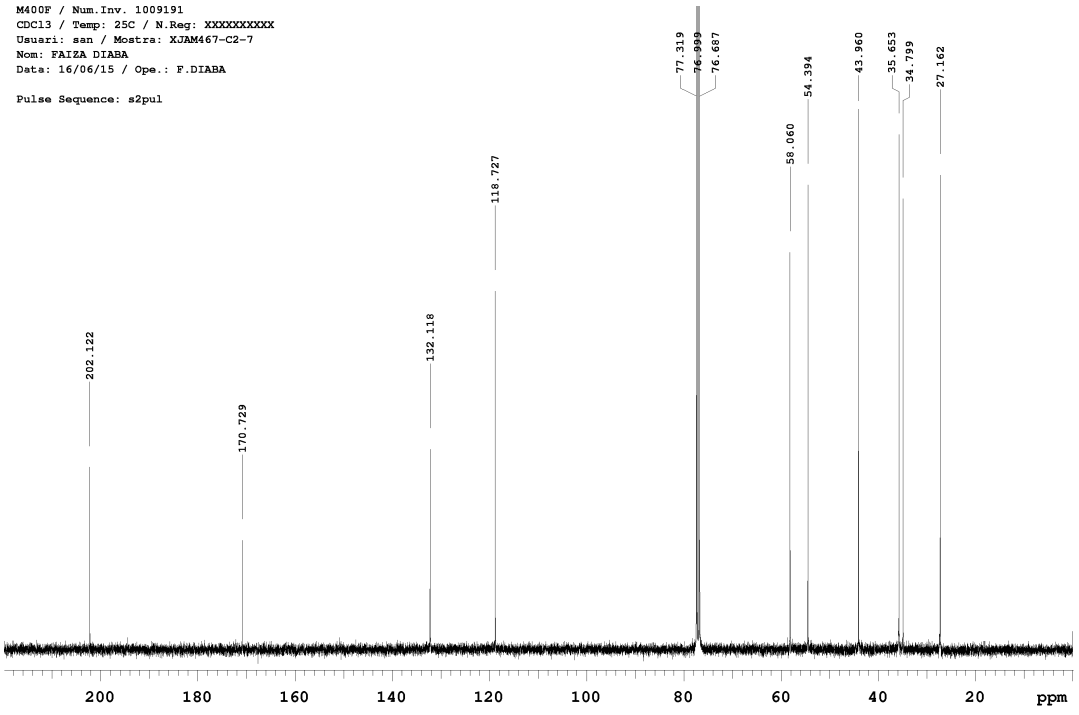
cdcl3 / Temp: 25C / N.Reg: XXXXXXXXXX
Usuari: san / Mostra: TAN688-C2-5
Nom: FAIZA DIABA
Data: 14/05/15 / Ope.: F.DIABA
Pulse Sequence: s2pul
2.940
2.936
2.652
2.646
2.632
2.630
2.623
2.616
2.479
2.462
3.822
3.815
3.809
3.144
3.132
2.441
2.419
2.309
2.303
2.062
2.033
1.962
1.960
1.957
1.927
1.924
7.263
10
9
8
7
6
5
4
3
2
1
-0
ppm

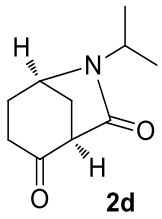

M400F / Num.Inv. 1009191
cdcl3 / Temp: 25C / N.Reg: XXXXXXXXXX
Usuari: san / Mostra: TAN688-C2-5
Nom: FAIZA DIABA
Data: 14/05/15 / Ope.: F.DIABA
Pulse Sequence: s2pul
77.320
77.000
76.680
57.733
56.788
35.128
34.617
26.378
28.123
202.092
171.065
200
180
160
140
120
100
80
60
40
20
ppm


H
N
O
O
H
O

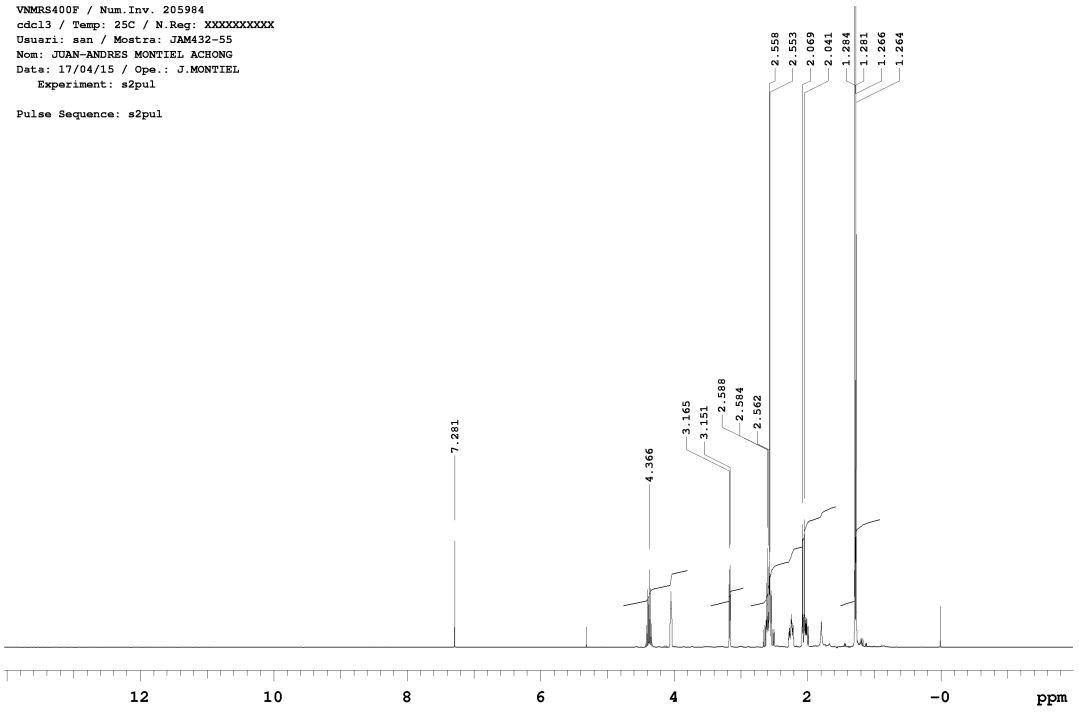
2c

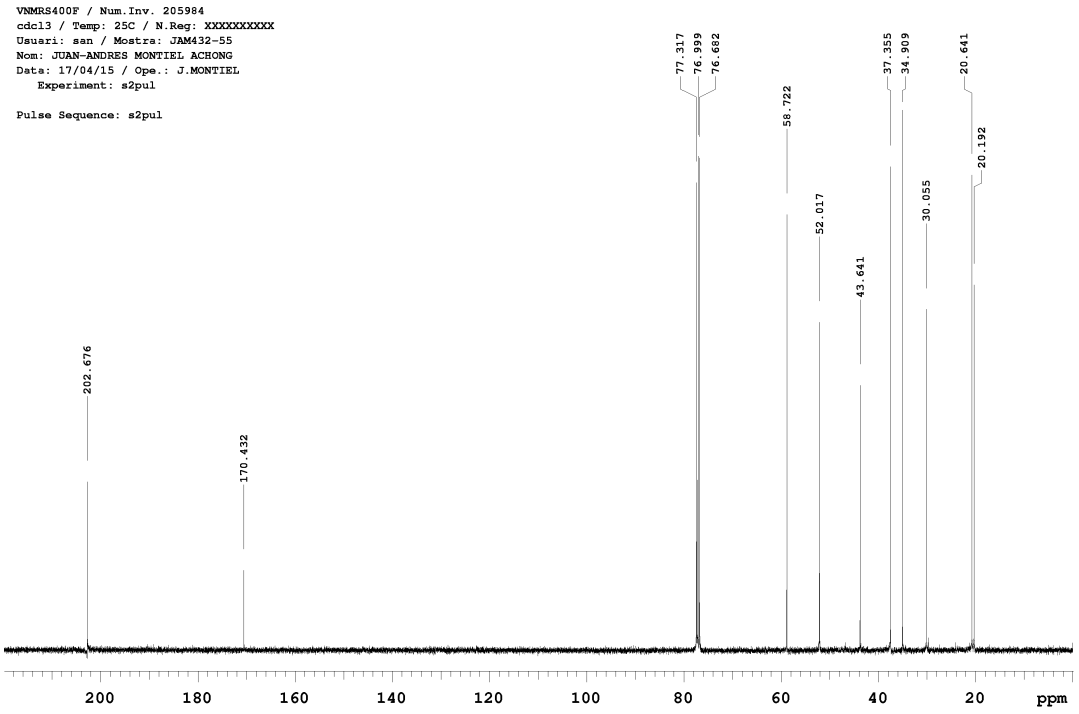

M400F / Num.Inv. 1009191
CDCl3 / Temp: 25C / N.Reg: XXXXXXXXXX
Usuari: san / Mostra: XJAM467-C2-7
Nom: FAIZA DIABA
Data: 16/06/15 / Ope.: F.DIABA
Pulse Sequence: s2pul
7.272
5.316
5.312
5.273
5.270
5.268
5.266
5.245
5.243
5.845
5.831
3.913
3.726
3.709
3.687
3.211
3.198
2.520
2.511
2.503
2.497
2.480
2.087
2.058
1.920
1.683
0.000
9
8
7
6
5
4
3
2
1
ppm

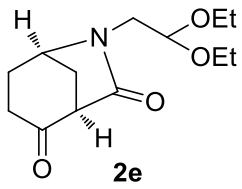

M400F / Num.Inv. 1009191
CDCl3 / Temp: 25C / N.Reg: XXXXXXXXXX
Usuari: san / Mostra: XJAM467-C2-7
Nom: FAIZA DIABA
Data: 16/06/15 / Ope.: F.DIABA
Pulse Sequence: s2pul
77.319
76.999
76.687
58.060
54.394
43.960
35.653
34.799
27.162
202.122
170.729
132.118
118.727
200
180
160
140
120
100
80
60
40
20
ppm


H
N
O
H
O

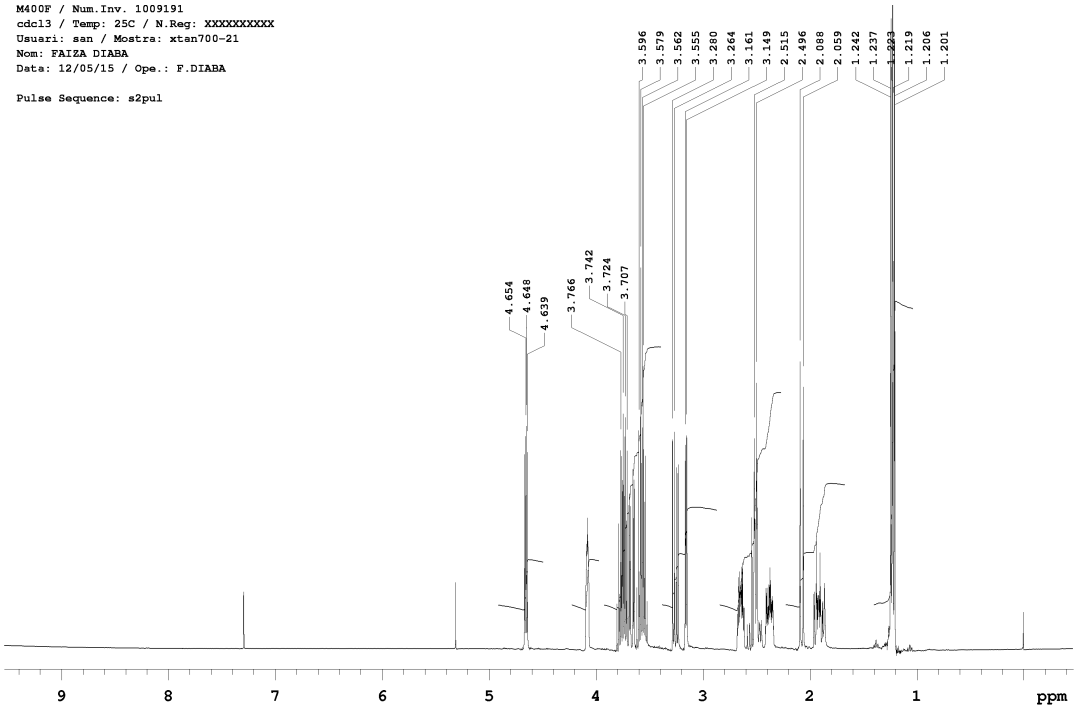
2d

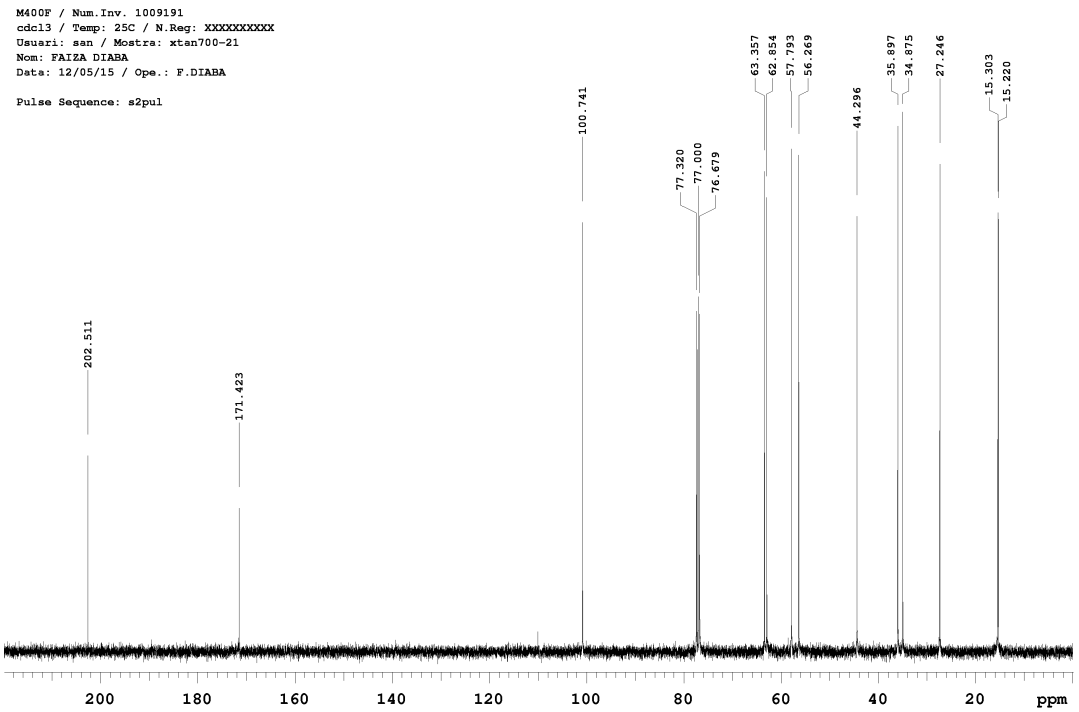

VNMRS400F / Num.Inv. 205984
cdcl3 / Temp: 25C / N.Reg: XXXXXXXXXX
Usuari: san / Mostra: JAM432-55
Nom: JUAN-ANDRES MONTIEL ACHONG
Data: 17/04/15 / Ope.: J.MONTIEL
Experiment: s2pul
Pulse Sequence: s2pul
2.558
2.553
2.069
2.041
1.284
1.281
1.266
1.264
7.281
4.366
3.165
3.151
2.588
2.584
2.562
12
10
8
6
4
2
-0
ppm

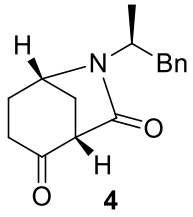

VNMRS400F / Num.Inv. 205984
cdcl3 / Temp: 25C / N.Reg: XXXXXXXXXX
Usuari: san / Mostra: JAM432-55
Nom: JUAN-ANDRES MONTIEL ACHONG
Data: 17/04/15 / Ope.: J.MONTIEL
Experiment: s2pul
Pulse Sequence: s2pul
77.317
76.999
76.682
58.722
52.017
43.641
37.355
34.909
30.055
20.641
20.192
202.676
170.432
200
180
160
140
120
100
80
60
40
20
ppm


H
N
OEt
OEt
O
H
O

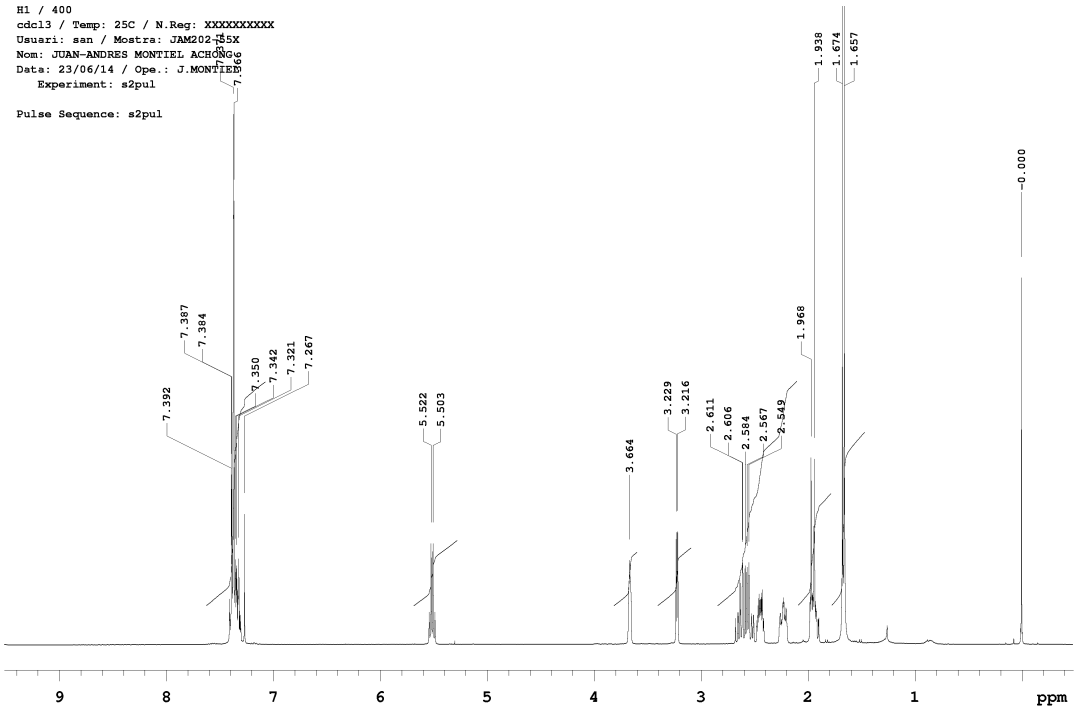
2e

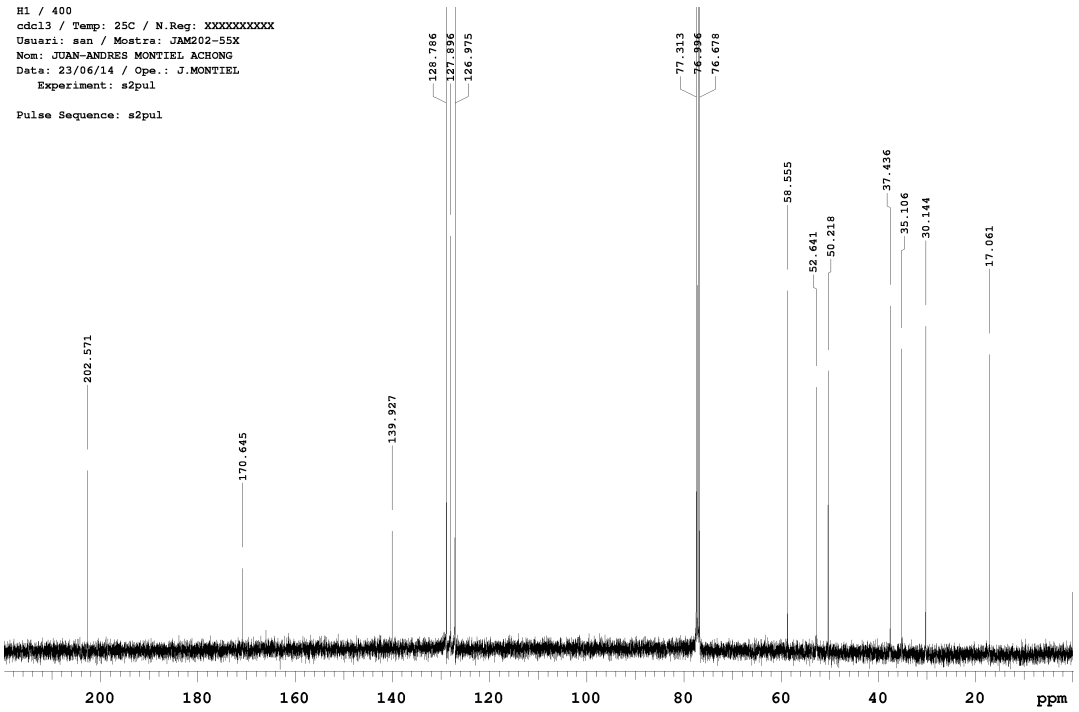

M400F / Num.Inv. 1009191
cdcl3 / Temp: 25C / N.Reg: XXXXXXXXXX
Usuari: san / Mostra: xtan700-21
Nom: FAIZA DIABA
Data: 12/05/15 / Ope.: F.DIABA
Pulse Sequence: s2pul
3.596
3.579
3.562
3.555
3.280
3.264
3.161
3.149
2.515
2.496
2.088
2.059
1.242
1.237
1.223
1.219
1.206
1.201
4.654
4.648
4.639
3.766
3.742
3.724
3.707
9
8
7
6
5
4
3
2
1
ppm

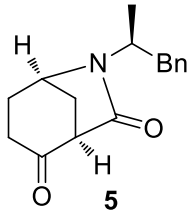

M400F / Num.Inv. 1009191
cdcl3 / Temp: 25C / N.Reg: XXXXXXXXXX
Usuari: san / Mostra: xtan700-21
Nom: FAIZA DIABA
Data: 12/05/15 / Ope.: F.DIABA
Pulse Sequence: s2pul
63.357
62.854
57.793
56.269
44.296
35.897
34.875
27.246
15.303
15.220
100.741
77.320
77.000
76.679
202.511
171.423
200
180
160
140
120
100
80
60
40
20
ppm


H
N
Bn
O
H
O

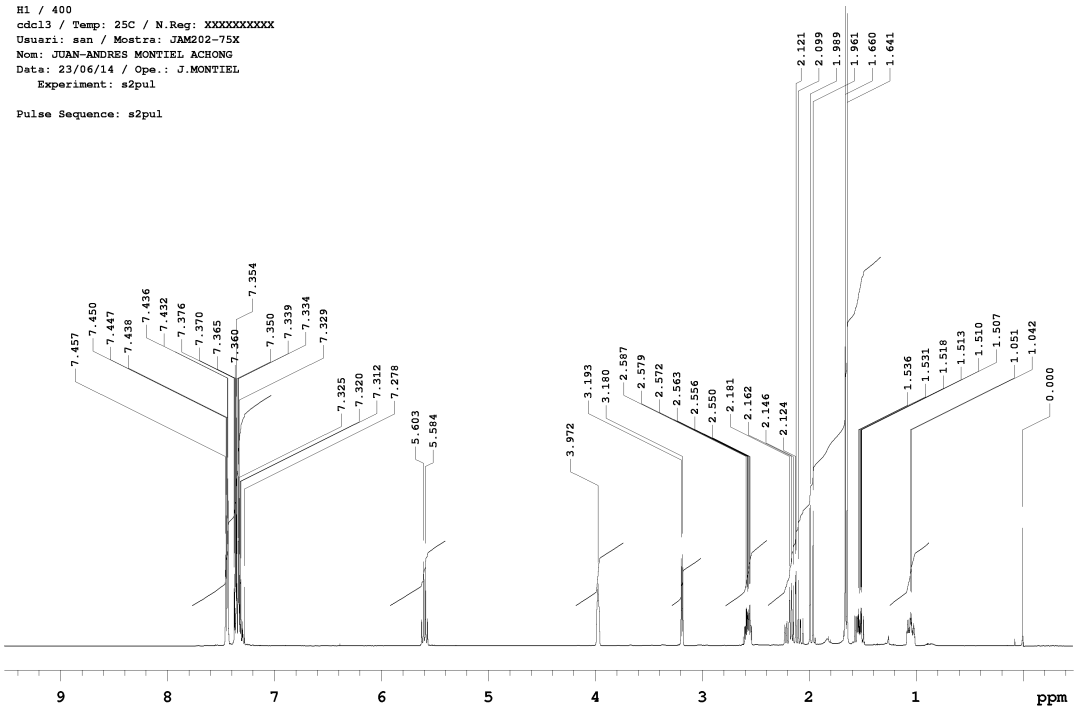
4

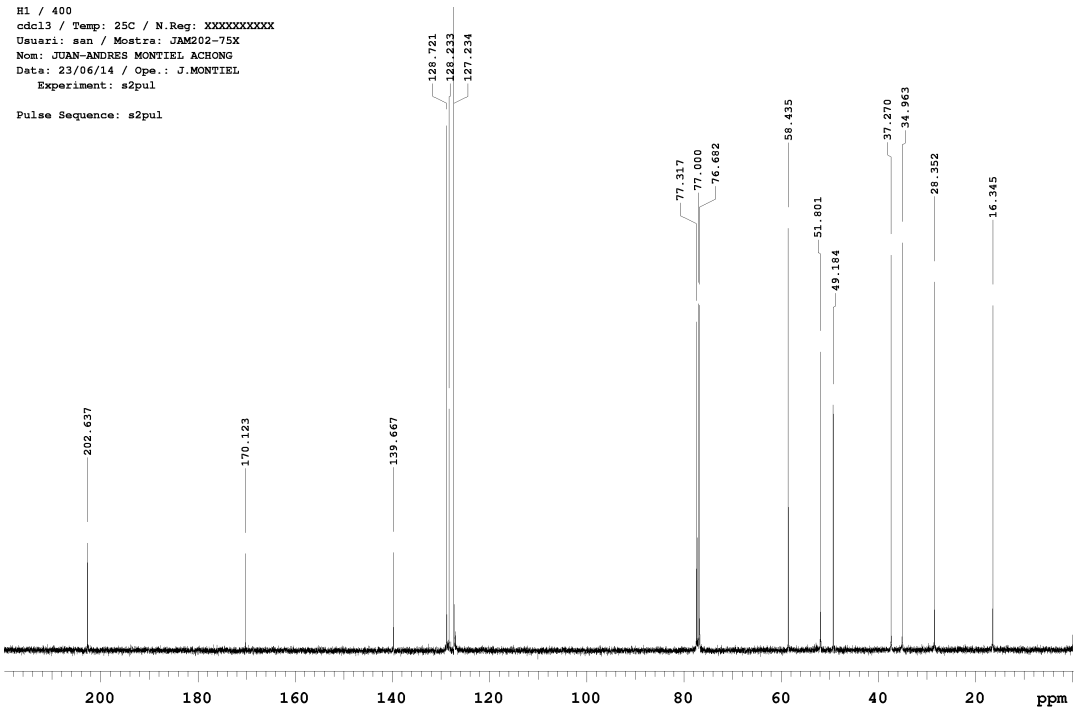

H1 / 400
cdcl3 / Temp: 25C / N.Reg: XXXXXXXXXX
Usuari: san / Mostra: JAM202-55X
Nom: JUAN-ANDRES MONTIEL ACHONG
Data: 23/06/14 / Ope.: J.MONTIEL
Experiment: s2pul
Pulse Sequence: s2pul
7.392
7.387
7.384
7.350
7.342
7.321
7.267
5.522
5.503
3.664
3.229
3.216
2.611
2.606
2.584
2.567
2.549
1.968
1.938
1.674
1.657
0.000
9
8
7
6
5
4
3
2
1
ppm

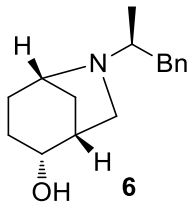

H1 / 400
cdcl3 / Temp: 25C / N.Reg: XXXXXXXXXX
Usuari: san / Mostra: JAM202-55X
Nom: JUAN-ANDRES MONTIEL ACHONG
Data: 23/06/14 / Ope.: J.MONTIEL
Experiment: s2pul
Pulse Sequence: s2pul
202.571
170.645
139.927
128.786
127.896
126.975
77.313
76.996
76.678
58.555
52.641
50.218
37.436
35.106
30.144
17.061
200
180
160
140
120
100
80
60
40
20
ppm


H
N
Bn
O
H
O

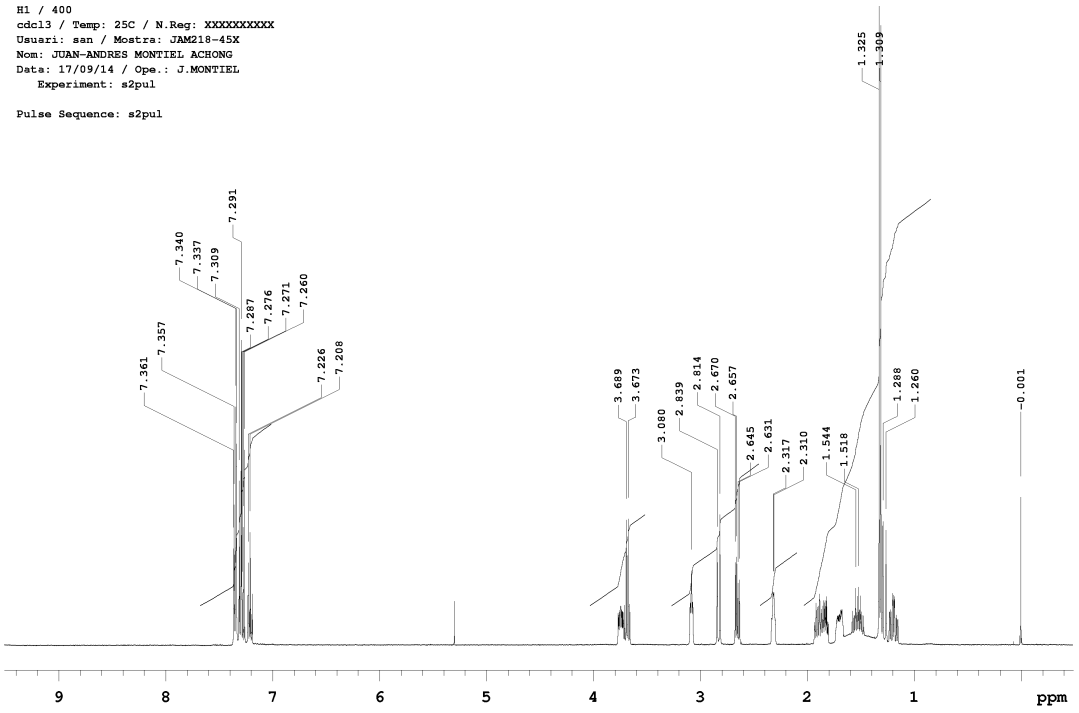
5

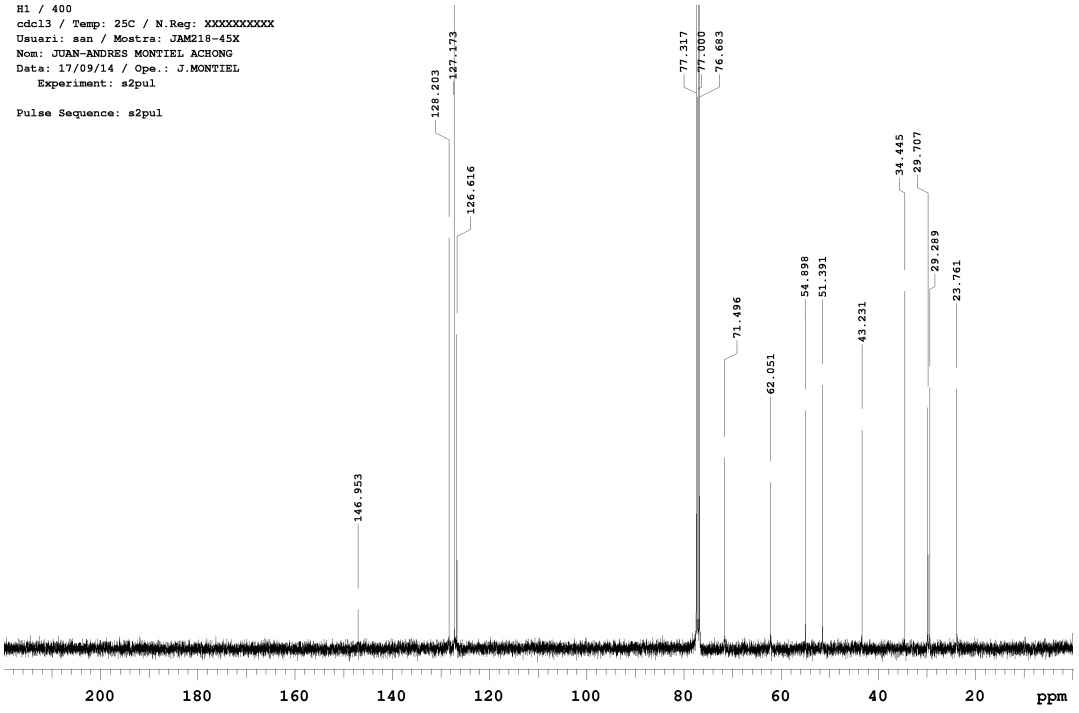

H1 / 400
cdcl3 / Temp: 25C / N.Reg: XXXXXXXXXX
Usuari: san / Mostra: JAM202-75X
Nom: JUAN-ANDRES MONTIEL ACHONG
Data: 23/06/14 / Ope.: J.MONTIEL
Experiment: s2pul
Pulse Sequence: s2pul
7.457
7.450
7.447
7.438
7.436
7.432
7.376
7.370
7.365
7.360
7.354
7.350
7.339
7.334
7.329
7.325
7.320
7.312
7.278
5.603
5.584
3.972
3.193
3.180
2.587
2.579
2.572
2.563
2.556
2.550
2.181
2.162
2.146
2.124
2.121
2.099
1.989
1.961
1.660
1.641
1.536
1.531
1.518
1.513
1.510
1.507
1.051
1.042
0.000
9
8
7
6
5
4
3
2
1
ppm

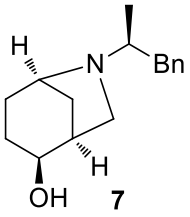

H1 / 400
cdcl3 / Temp: 25C / N.Reg: XXXXXXXXXX
Usuari: san / Mostra: JAM202-75X
Nom: JUAN-ANDRES MONTIEL ACHONG
Data: 23/06/14 / Ope.: J.MONTIEL
Experiment: s2pul
Pulse Sequence: s2pul
202.637
170.123
139.667
128.721
128.233
127.234
77.317
77.000
76.682
58.435
51.801
49.184
37.270
34.963
28.352
16.345
200
180
160
140
120
100
80
60
40
20
ppm


H
N
Bn
H
OH

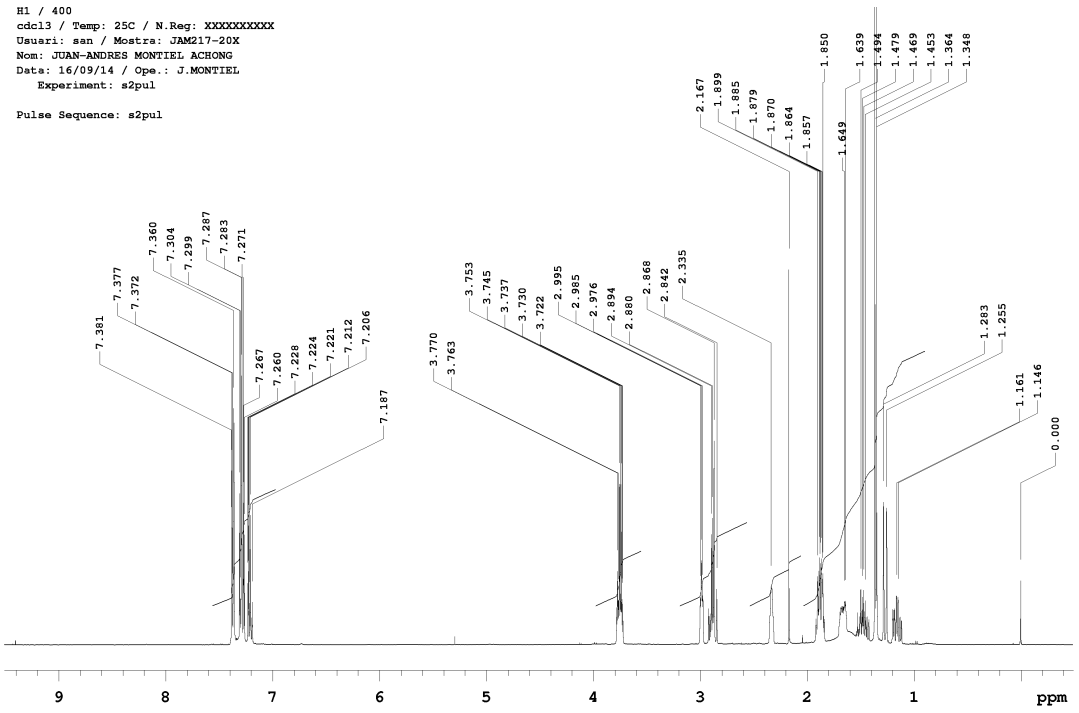
6

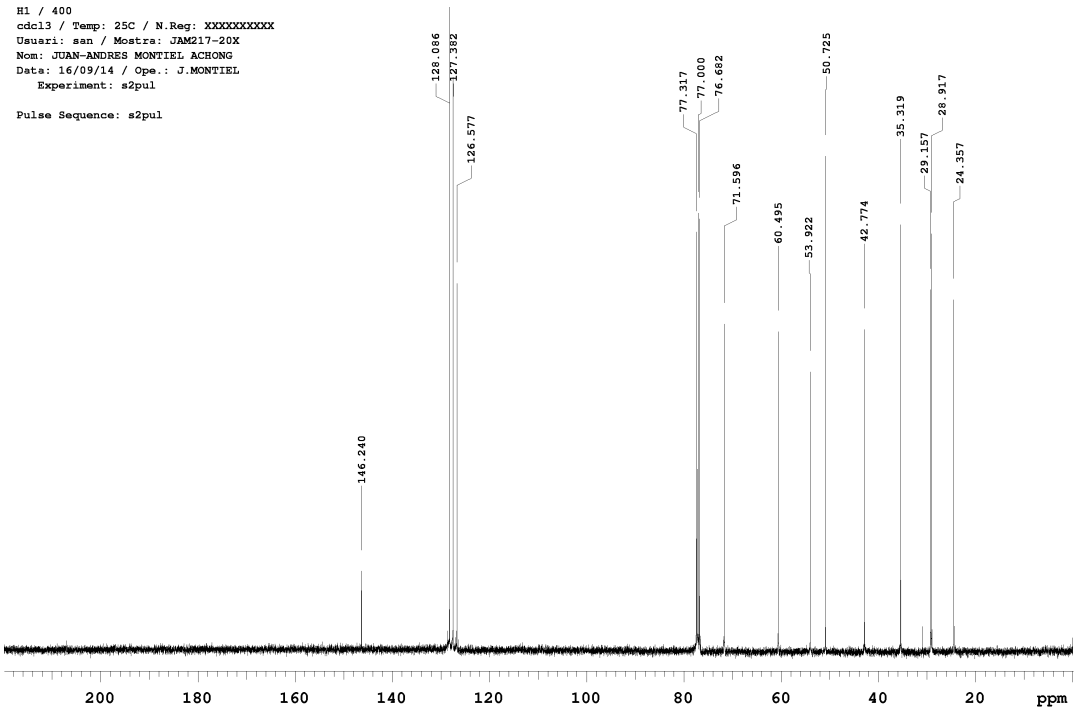

H1 / 400
cdcl3 / Temp: 25C / N.Reg: XXXXXXXXXX
Usuari: san / Mostra: JAM218-45X
Nom: JUAN-ANDRES MONTIEL ACHONG
Data: 17/09/14 / Ope.: J.MONTIEL
Experiment: s2pul
Pulse Sequence: s2pul
7.361
7.357
7.340
7.337
7.309
7.291
7.287
7.276
7.271
7.260
7.226
7.208
3.689
3.673
3.080
2.839
2.814
2.670
2.657
2.645
2.631
2.317
2.310
1.544
1.518
1.325
1.309
1.288
1.260
0.001
9
8
7
6
5
4
3
2
1
ppm

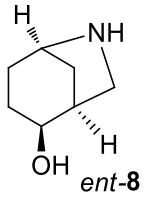

H1 / 400
cdcl3 / Temp: 25C / N.Reg: XXXXXXXXXX
Usuari: san / Mostra: JAM218-45X
Nom: JUAN-ANDRES MONTIEL ACHONG
Data: 17/09/14 / Ope.: J.MONTIEL
Experiment: s2pul
Pulse Sequence: s2pul
146.953
128.203
127.173
126.616
77.317
77.000
76.683
71.496
62.051
54.898
51.391
43.231
34.445
29.707
29.289
23.761
200
180
160
140
120
100
80
60
40
20
ppm


H
N
Bn
H
OH

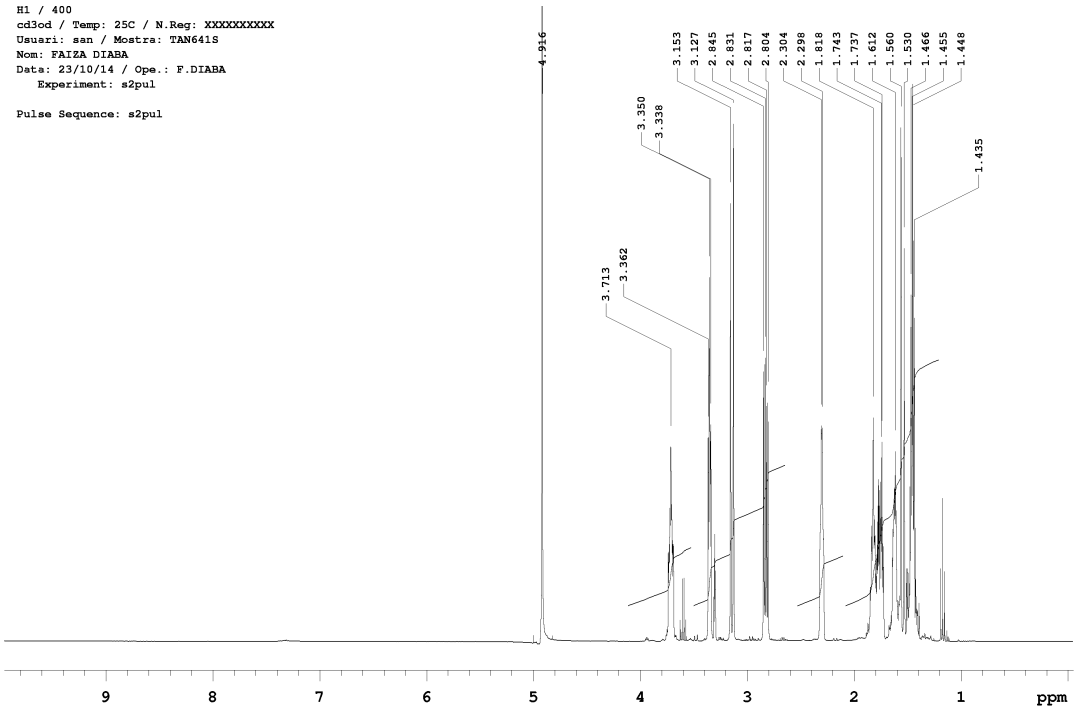
7

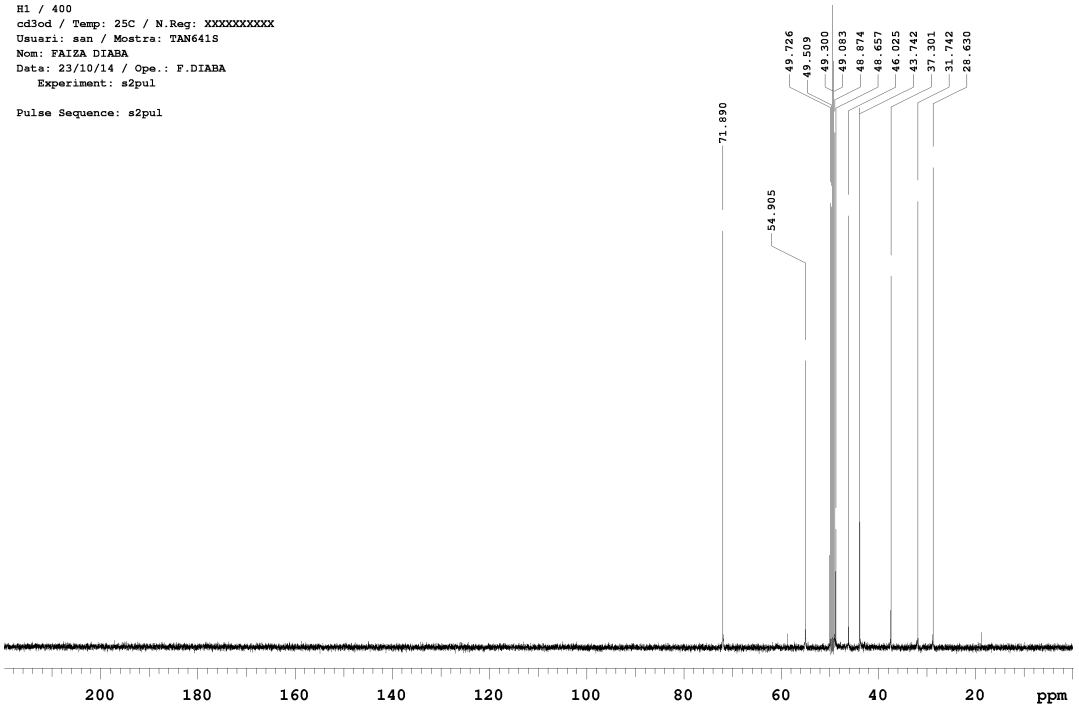

H1 / 400
cdcl3 / Temp: 25C / N.Reg: XXXXXXXXXX
Usuari: san / Mostra: JAM217-20X
Nom: JUAN-ANDRES MONTIEL ACHONG
Data: 16/09/14 / Ope.: J.MONTIEL
Experiment: s2pul
Pulse Sequence: s2pul
7.381
7.377
7.372
7.360
7.304
7.299
7.287
7.283
7.271
7.267
7.260
7.228
7.224
7.221
7.212
7.206
7.187
3.770
3.763
3.753
3.745
3.737
3.730
3.722
2.995
2.985
2.976
2.894
2.880
2.868
2.842
2.335
2.167
1.899
1.885
1.879
1.870
1.864
1.857
1.850
1.649
1.639
1.494
1.479
1.469
1.453
1.364
1.348
1.283
1.255
1.161
1.146
0.000
9
8
7
6
5
4
3
2
1
ppm

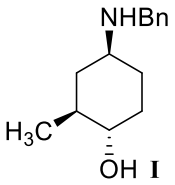

H1 / 400
cdcl3 / Temp: 25C / N.Reg: XXXXXXXXXX
Usuari: san / Mostra: JAM217-20X
Nom: JUAN-ANDRES MONTIEL ACHONG
Data: 16/09/14 / Ope.: J.MONTIEL
Experiment: s2pul
Pulse Sequence: s2pul
146.240
128.086
127.382
126.577
77.317
77.000
76.682
71.596
60.495
53.922
50.725
42.774
35.319
29.157
28.917
24.357
200
180
160
140
120
100
80
60
40
20
ppm


H
NH
H
OH

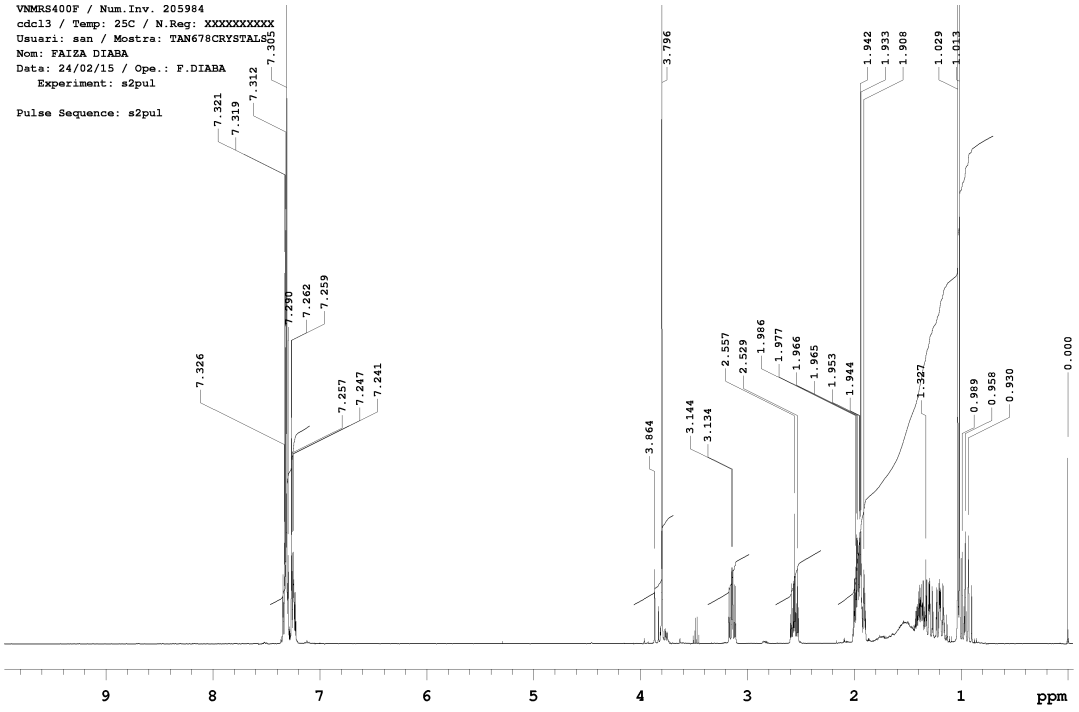
ent-**8**

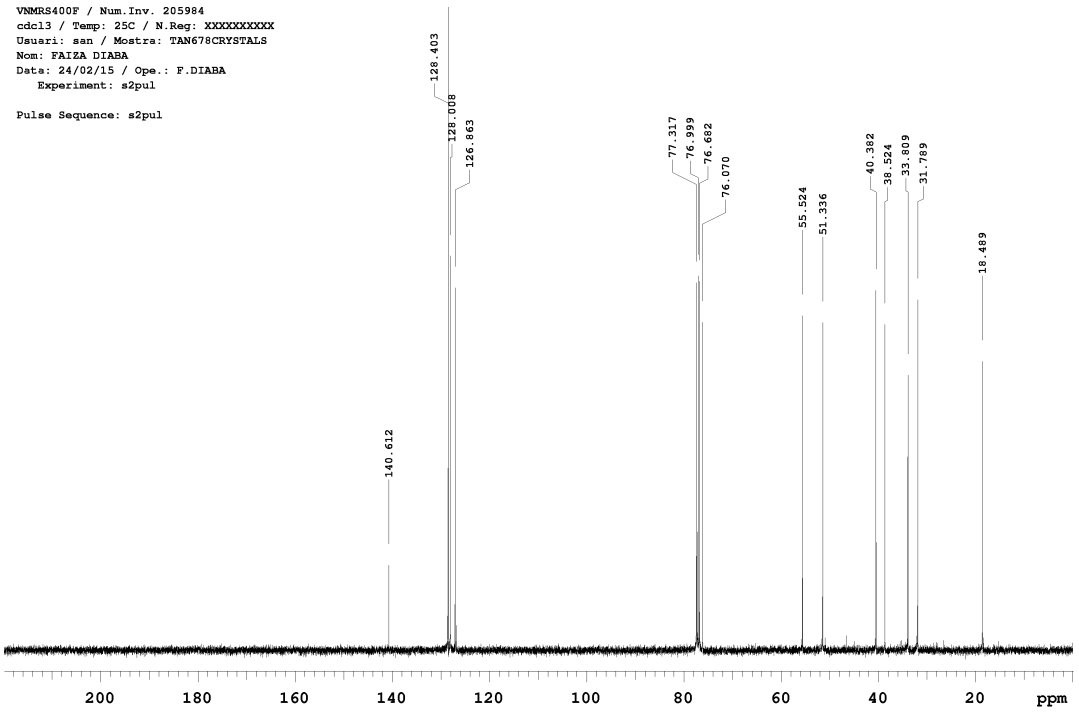

H1 / 400
cd3od / Temp: 25C / N.Reg: XXXXXXXXXX
Usuari: san / Mostra: TAN641S
Nom: FAIZA DIABA
Data: 23/10/14 / Ope.: F.DIABA
Experiment: s2pul
Pulse Sequence: s2pul
4.916
3.713
3.362
3.350
3.338
3.153
3.127
2.845
2.831
2.817
2.804
2.304
2.298
1.818
1.743
1.737
1.612
1.560
1.530
1.466
1.455
1.448
1.435
9
8
7
6
5
4
3
2
1
ppm

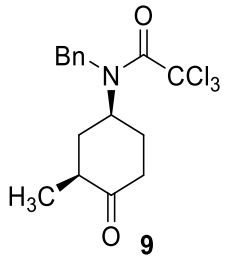

H1 / 400
cd3od / Temp: 25C / N.Reg: XXXXXXXXXX
Usuari: san / Mostra: TAN641S
Nom: FAIZA DIABA
Data: 23/10/14 / Ope.: F.DIABA
Experiment: s2pul
Pulse Sequence: s2pul
71.890
54.905
49.726
49.509
49.300
49.083
48.874
48.657
48.025
43.742
37.301
31.742
28.630
200
180
160
140
120
100
80
60
40
20
ppm


NHBn
H3C
OH

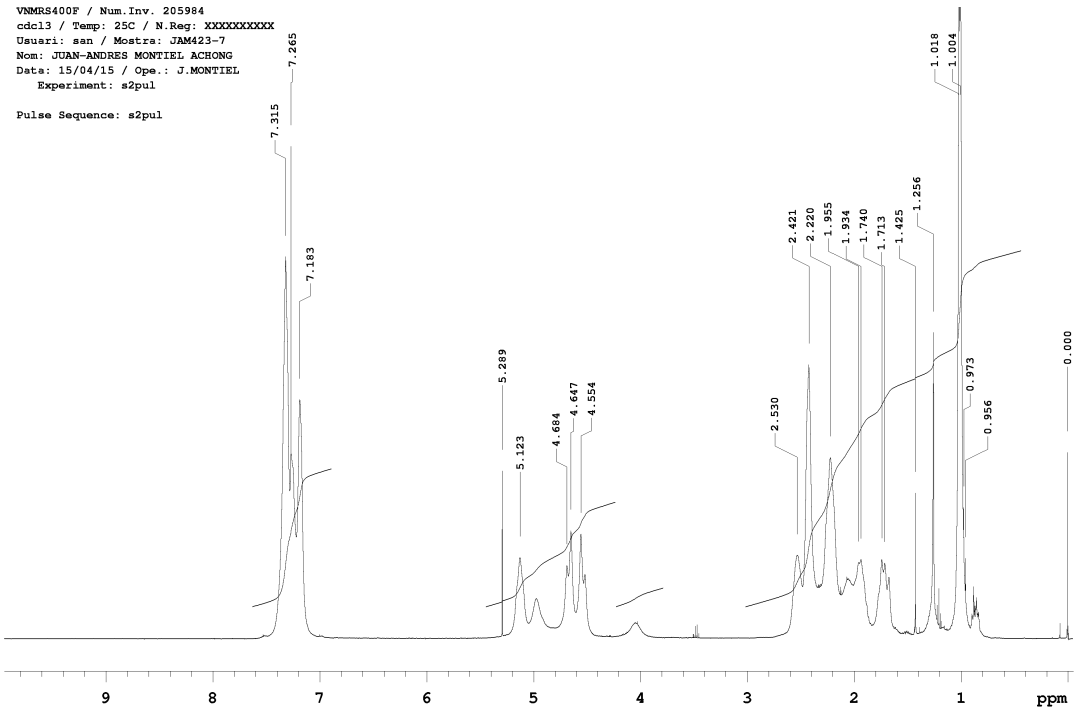
I

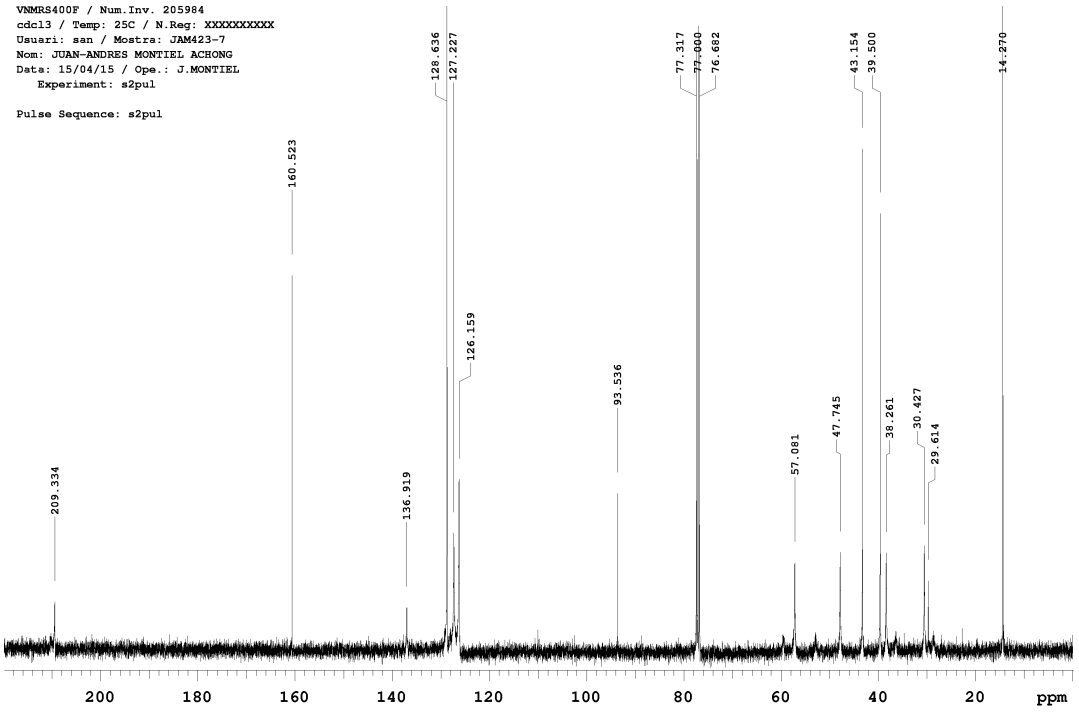

VNMRS400F / Num.Inv. 205984
cdcl3 / Temp: 25C / N.Reg: XXXXXXXXXX
Usuari: san / Mostra: TAN678CRYSTALS
Nom: FAIZA DIABA
Data: 24/02/15 / Ope.: F.DIABA
Experiment: s2pul
Pulse Sequence: s2pul
7.326
7.321
7.319
7.312
7.305
7.290
7.262
7.259
7.257
7.247
7.241
3.864
3.796
3.144
3.134
2.557
2.529
1.986
1.977
1.966
1.965
1.953
1.944
1.942
1.933
1.908
1.327
1.029
1.013
0.989
0.958
0.930
0.000
9
8
7
6
5
4
3
2
1
ppm

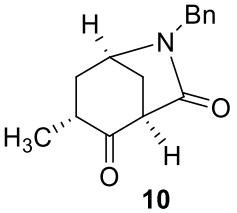

VNMRS400F / Num.Inv. 205984
cdcl3 / Temp: 25C / N.Reg: XXXXXXXXXX
Usuari: san / Mostra: TAN678CRYSTALS
Nom: FAIZA DIABA
Data: 24/02/15 / Ope.: F.DIABA
Experiment: s2pul
Pulse Sequence: s2pul
140.612
128.403
128.008
126.863
77.317
76.999
76.682
76.070
55.524
51.336
40.382
38.524
33.809
31.789
18.489
200
180
160
140
120
100
80
60
40
20
ppm


O
Bn
N
CCl3
H3C
O

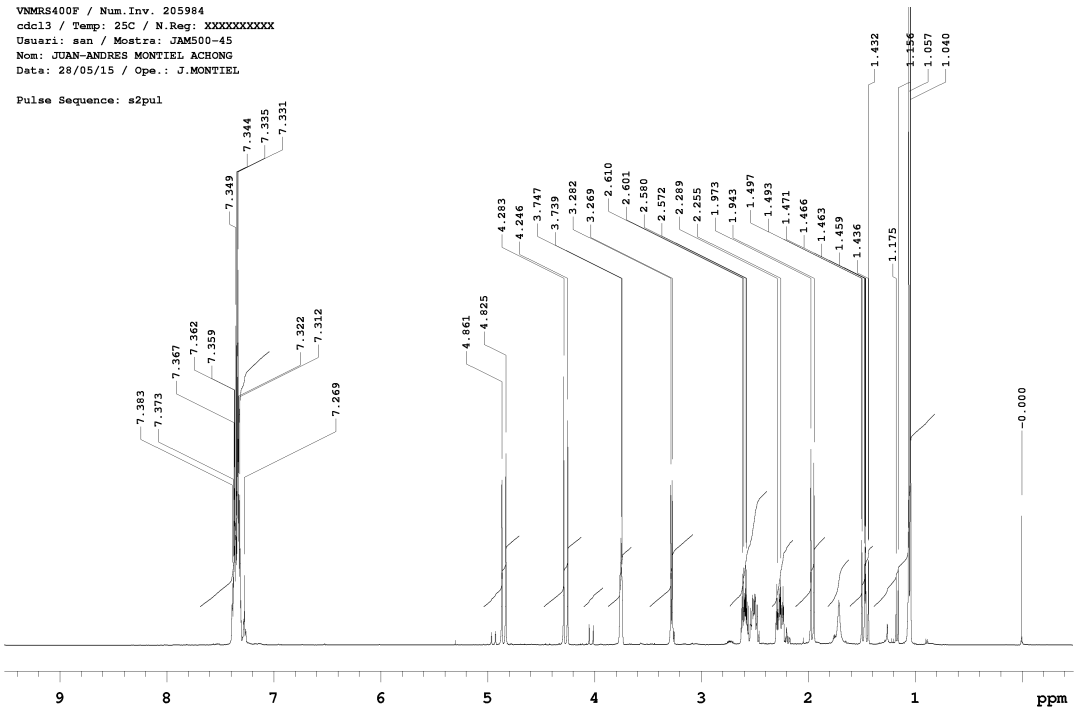
9

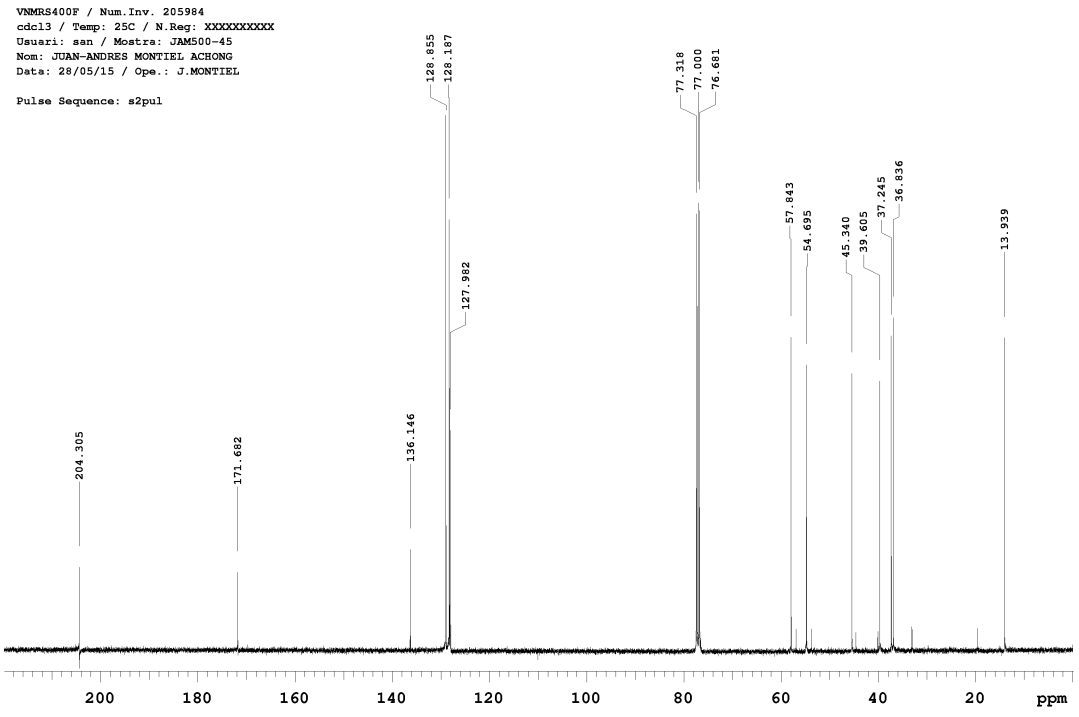

VNMRS400F / Num.Inv. 205984
cdcl3 / Temp: 25C / N.Reg: XXXXXXXXXX
Usuari: san / Mostra: JAM423-7
Nom: JUAN-ANDRES MONTIEL ACHONG
Data: 15/04/15 / Ope.: J.MONTIEL
Experiment: s2pul
Pulse Sequence: s2pul
7.265
7.315
7.183
5.289
5.123
4.684
4.647
4.554
2.530
2.421
2.220
1.955
1.934
1.740
1.713
1.425
1.256
1.018
1.004
0.973
0.956
0.000
9
8
7
6
5
4
3
2
1
ppm

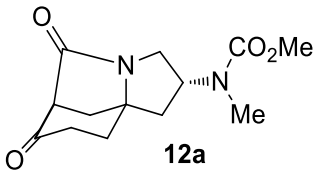

VNMRS400F / Num.Inv. 205984
cdcl3 / Temp: 25C / N.Reg: XXXXXXXXXX
Usuari: san / Mostra: JAM423-7
Nom: JUAN-ANDRES MONTIEL ACHONG
Data: 15/04/15 / Ope.: J.MONTIEL
Experiment: s2pul
Pulse Sequence: s2pul
160.523
128.636
127.227
126.159
93.536
77.317
77.000
76.682
57.081
47.745
43.154
39.500
38.261
30.427
29.614
14.270
209.334
136.919
200
180
160
140
120
100
80
60
40
20
ppm


H
N
Bn
O
H3C
O
H

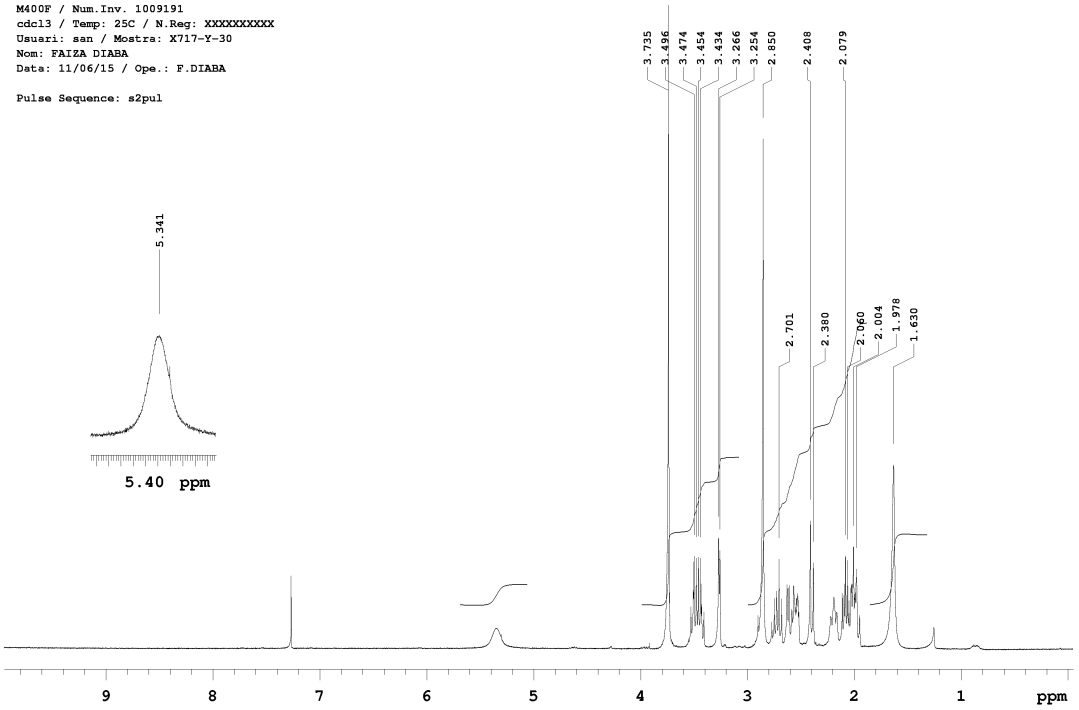
10

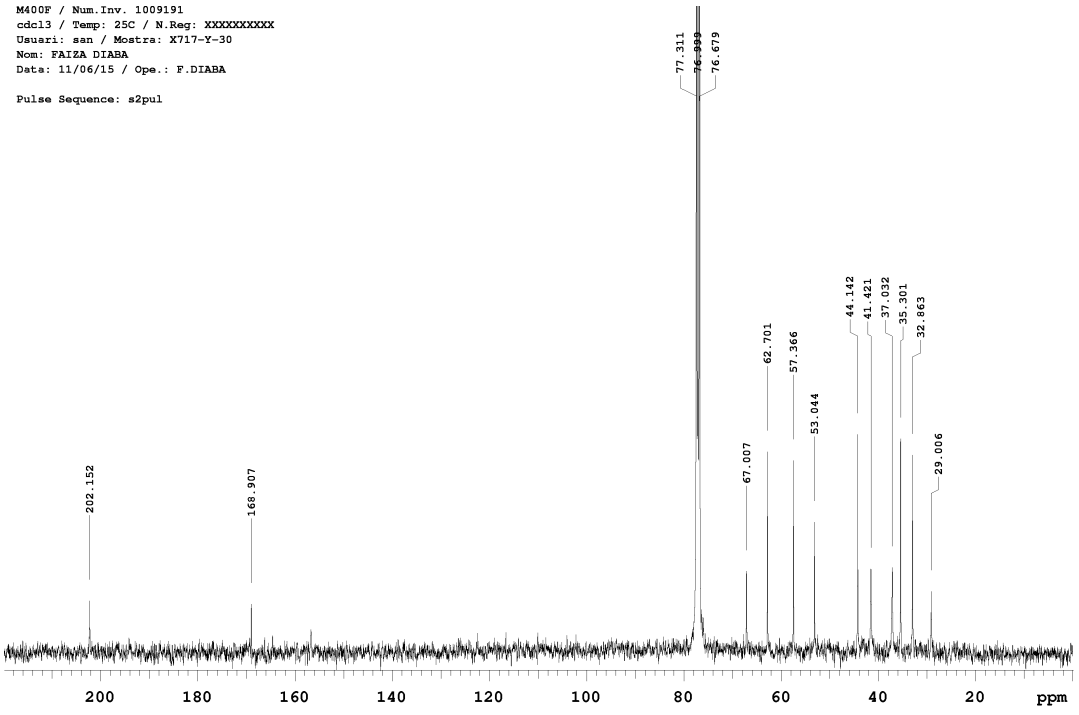

VNMRS400F / Num.Inv. 205984
cdcl3 / Temp: 25C / N.Reg: XXXXXXXXXX
Usuari: san / Mostra: JAM500-45
Nom: JUAN-ANDRES MONTIEL ACHONG
Data: 28/05/15 / Ope.: J.MONTIEL
Pulse Sequence: s2pul
7.383
7.373
7.367
7.362
7.359
7.349
7.344
7.335
7.331
7.322
7.312
7.269
4.861
4.825
4.283
4.246
3.747
3.739
3.282
3.269
2.610
2.601
2.580
2.572
2.289
2.255
1.973
1.943
1.497
1.493
1.471
1.466
1.463
1.459
1.436
1.432
1.175
1.156
1.057
1.040
0.000
9
8
7
6
5
4
3
2
1
ppm

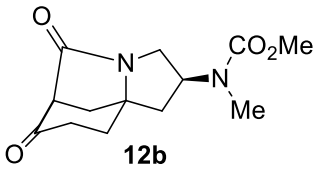

VNMRS400F / Num.Inv. 205984
cdcl3 / Temp: 25C / N.Reg: XXXXXXXXXX
Usuari: san / Mostra: JAM500-45
Nom: JUAN-ANDRES MONTIEL ACHONG
Data: 28/05/15 / Ope.: J.MONTIEL
Pulse Sequence: s2pul
204.305
171.682
136.146
128.855
128.187
127.982
77.318
77.000
76.681
57.843
54.695
45.340
39.605
37.245
36.836
13.939
200
180
160
140
120
100
80
60
40
20
ppm


O
N
CO2Me
N
Me
O

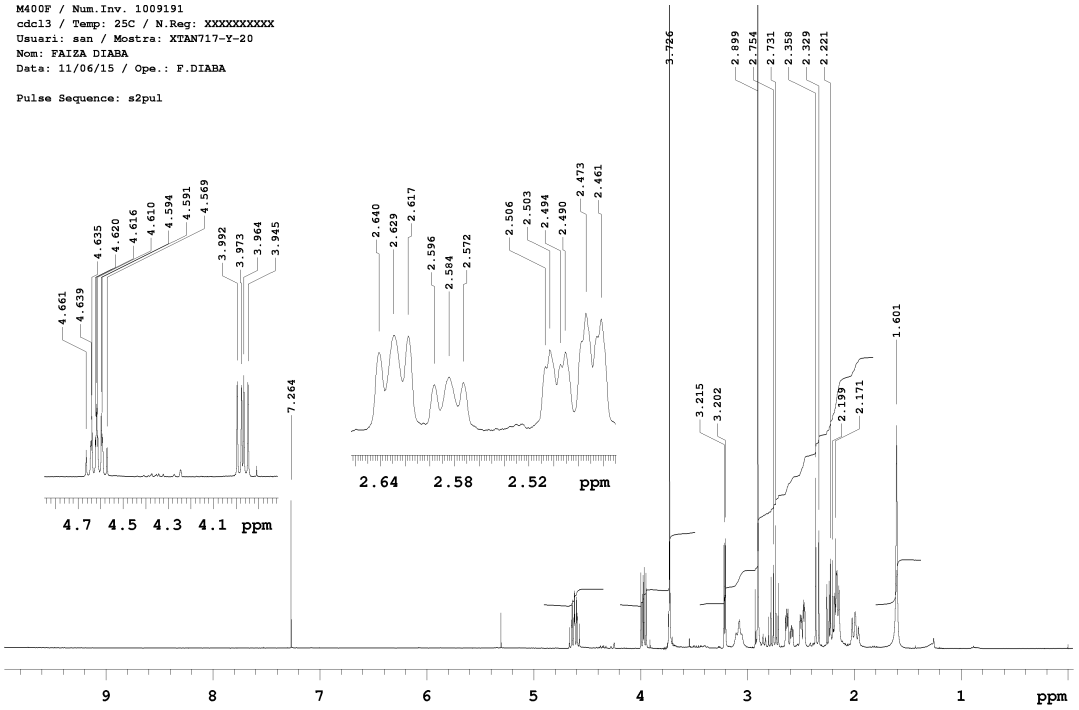
12a

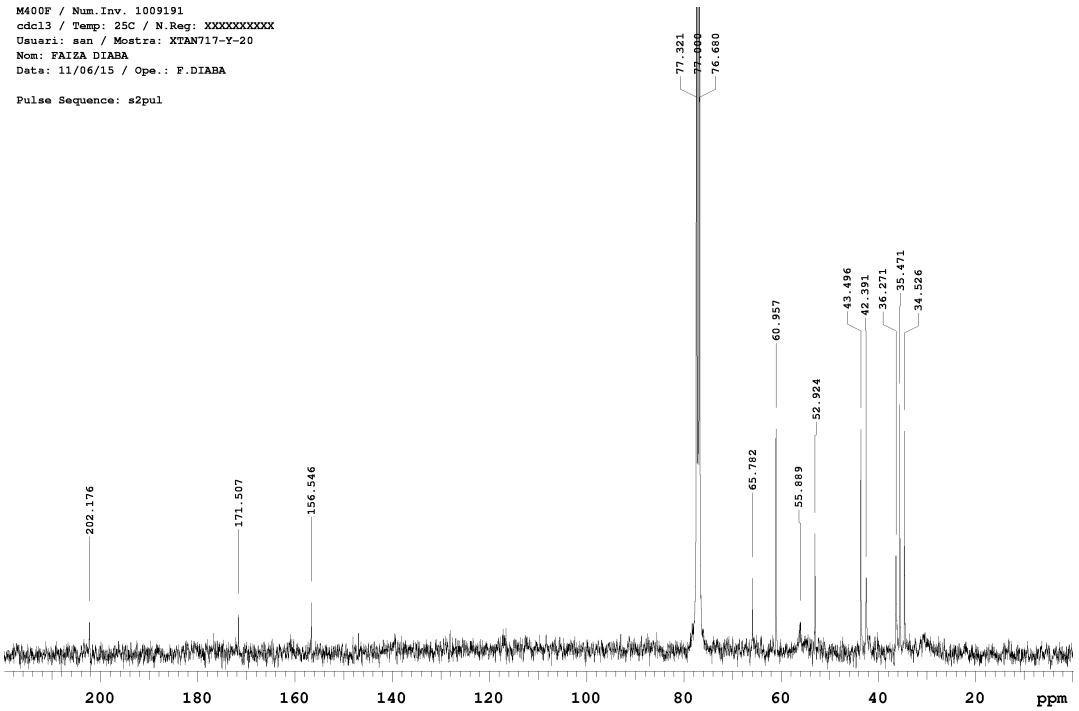

M400F / Num.Inv. 1009191
cdcl3 / Temp: 25C / N.Reg: XXXXXXXXXX
Usuari: san / Mostra: X717-Y-30
Nom: FAIZA DIABA
Data: 11/06/15 / Ope.: F.DIABA
Pulse Sequence: s2pul
3.735
3.496
3.474
3.454
3.434
3.266
3.254
2.850
2.408
2.079
5.341
2.701
2.380
2.060
2.004
1.978
1.630
5.40 ppm
9
8
7
6
5
4
3
2
1
ppm

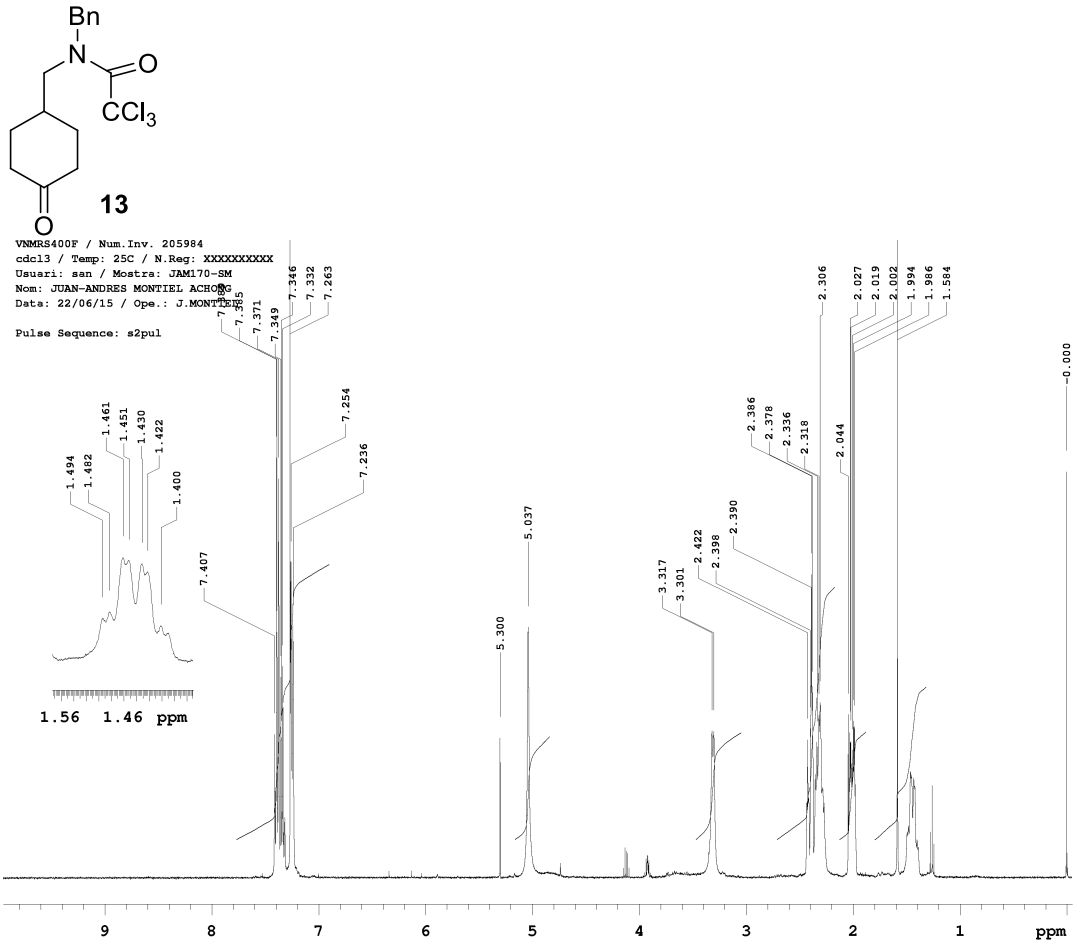

M400F / Num.Inv. 1009191
cdcl3 / Temp: 25C / N.Reg: XXXXXXXXXX
Usuari: san / Mostra: X717-Y-30
Nom: FAIZA DIABA
Data: 11/06/15 / Ope.: F.DIABA
Pulse Sequence: s2pul
77.311
76.999
76.679
202.152
168.907
67.007
62.701
57.366
53.044
44.142
41.421
37.032
35.301
32.863
29.006
200
180
160
140
120
100
80
60
40
20
ppm

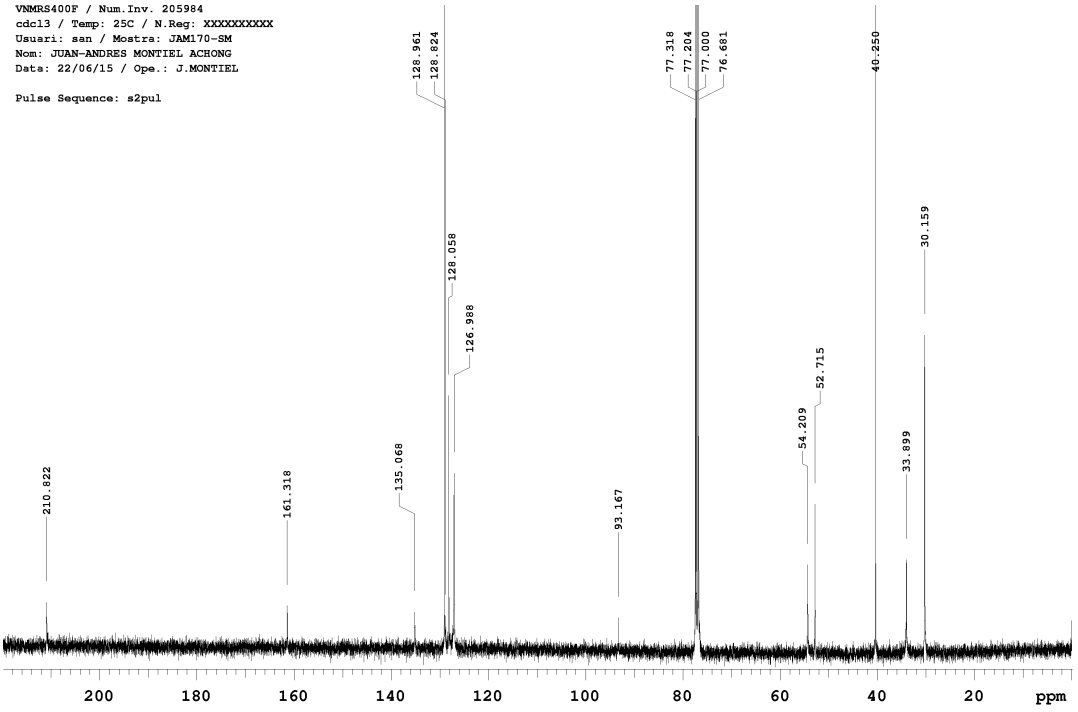

O
N
CO2Me
N
Me
O

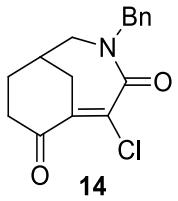
12b


M400F / Num.Inv. 1009191
cdcl3 / Temp: 25C / N.Reg: XXXXXXXXXX
Usuari: san / Mostra: XTAN717-Y-20
Nom: FAIZA DIABA
Data: 11/06/15 / Ope.: F.DIABA
Pulse Sequence: s2pul
4.661
4.639
4.635
4.620
4.616
4.610
4.594
4.591
4.569
3.992
3.973
3.964
3.945
7.264
2.640
2.629
2.617
2.596
2.584
2.572
2.506
2.503
2.494
2.490
2.473
2.461
3.726
3.215
3.202
2.899
2.754
2.731
2.358
2.329
2.221
2.199
2.171
1.601
4.7 4.5 4.3 4.1 ppm
2.64 2.58 2.52 ppm
9 8 7 6 5 4 3 2 1 ppm

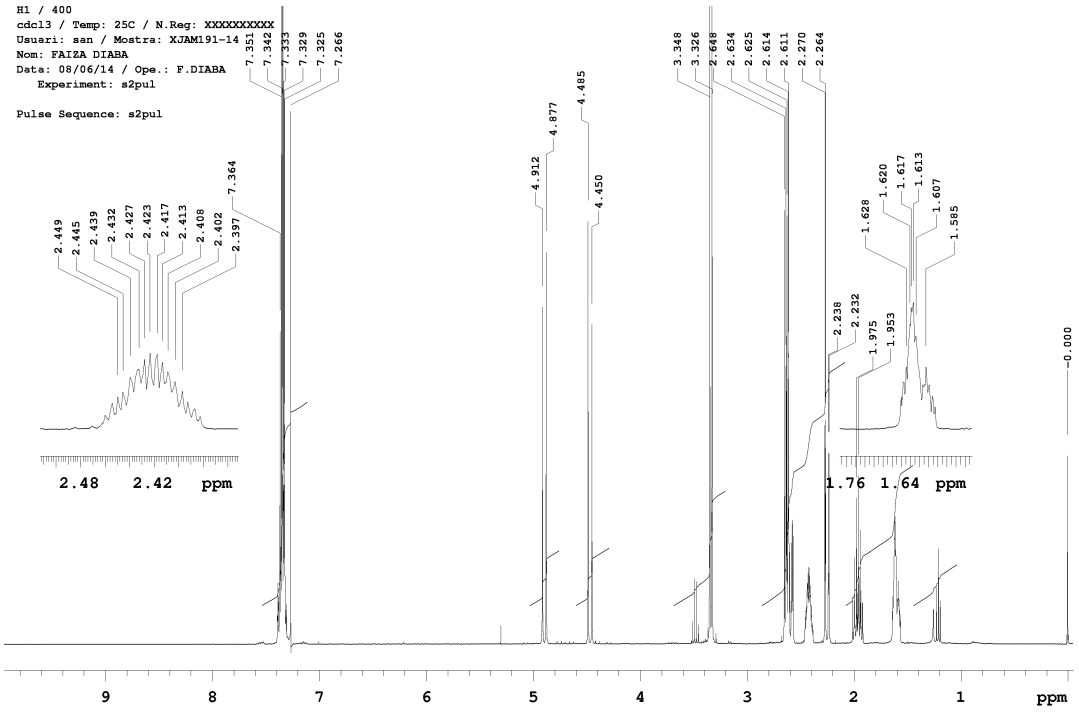

M400F / Num.Inv. 1009191
cdcl3 / Temp: 25C / N.Reg: XXXXXXXXXX
Usuari: san / Mostra: XTAN717-Y-20
Nom: FAIZA DIABA
Data: 11/06/15 / Ope.: F.DIABA
Pulse Sequence: s2pul
77.321
77.000
76.680
202.176
171.507
156.546
65.782
60.957
55.889
52.924
43.496
42.391
36.271
35.471
34.526
200 180 160 140 120 100 80 60 40 20 ppm

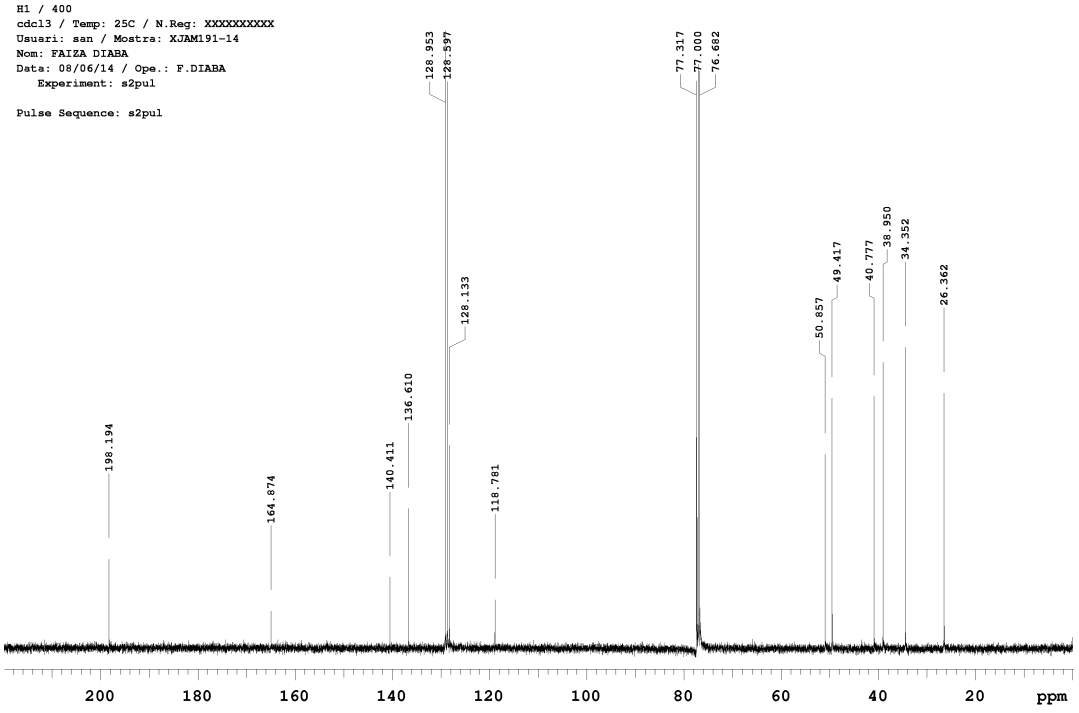

Bn
N
O
CCl3
O
13
VNMRS400F / Num.Inv. 205984
cdcl3 / Temp: 25C / N.Reg: XXXXXXXXXX
Usuari: san / Mostra: JAM170-SM
Nom: JUAN-ANDRES MONTIEL ACHONG
Data: 22/06/15 / Ope.: J.MONTIEL
Pulse Sequence: s2pul
1.56 1.46 ppm
ppm

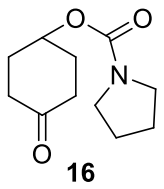

VNMRS400F / Num.Inv. 205984
cdcl3 / Temp: 25C / N.Reg: XXXXXXXXXX
Usuari: san / Mostra: JAM170-SM
Nom: JUAN-ANDRES MONTIEL ACHONG
Data: 22/06/15 / Ope.: J.MONTIEL
Pulse Sequence: s2pul
ppm


Bn
N
O
Cl
O

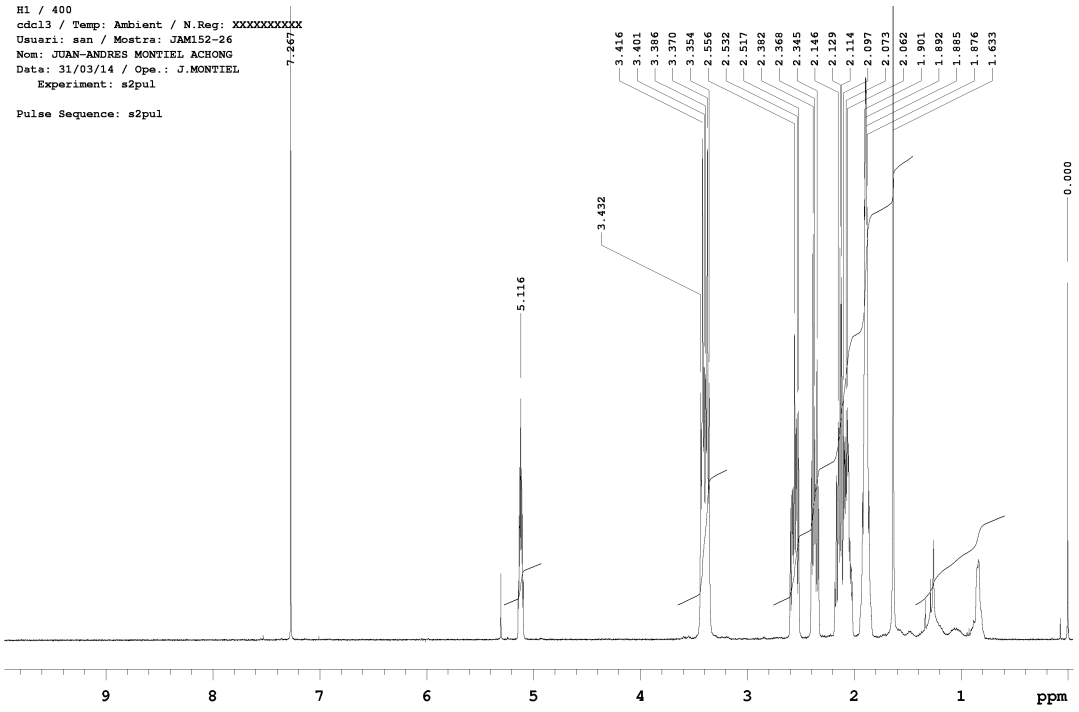
14

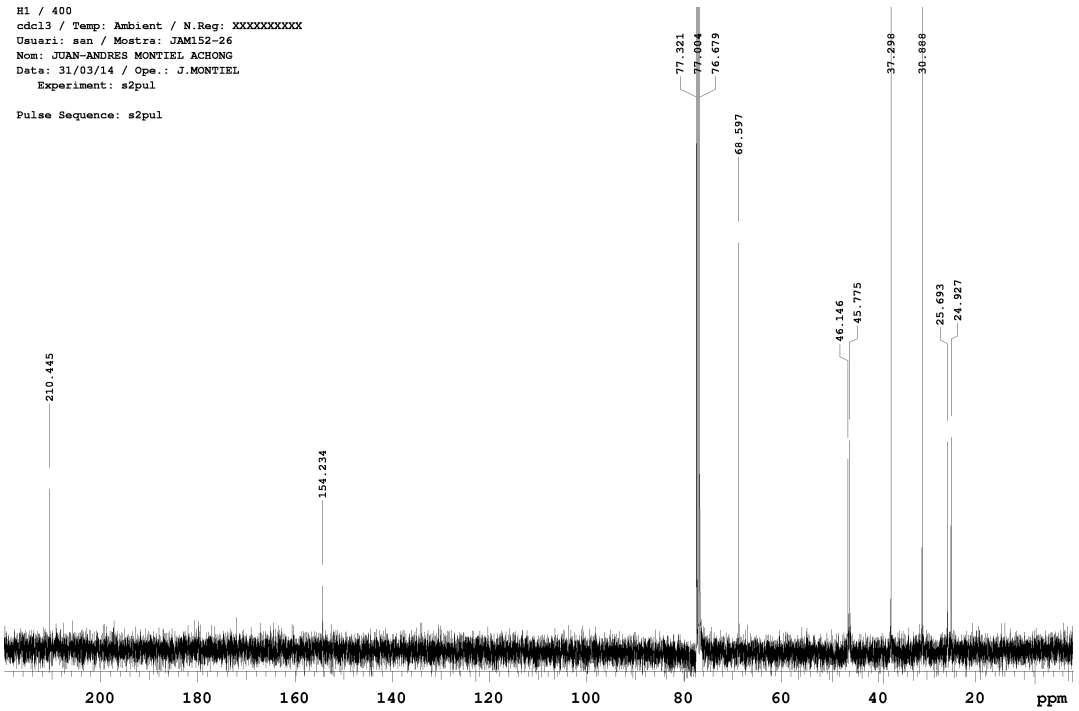

H1 / 400
cdcl3 / Temp: 25C / N.Reg: XXXXXXXXXX
Usuari: san / Mostra: XJAM191-14
Nom: FAIZA DIABA
Data: 08/06/14 / Ope.: F.DIABA
Experiment: s2pul
Pulse Sequence: s2pul
7.351
7.342
7.333
7.329
7.325
7.266
4.912
4.877
4.485
4.450
3.348
3.326
2.648
2.634
2.625
2.614
2.611
2.270
2.264
2.449
2.445
2.439
2.432
2.427
2.423
2.417
2.413
2.408
2.402
2.397
7.364
1.628
1.620
1.617
1.613
1.607
1.585
2.238
2.232
1.975
1.953
0.000
2.48 2.42 ppm
1.76 1.64 ppm
9 8 7 6 5 4 3 2 1 ppm


H1 / 400
cdcl3 / Temp: 25C / N.Reg: XXXXXXXXXX
Usuari: san / Mostra: XJAM191-14
Nom: FAIZA DIABA
Data: 08/06/14 / Ope.: F.DIABA
Experiment: s2pul
Pulse Sequence: s2pul
128.953
128.597
77.317
77.000
76.682
128.133
198.194
164.874
140.411
136.610
118.781
50.857
49.417
40.777
38.950
34.352
26.362
200 180 160 140 120 100 80 60 40 20 ppm



16


H1 / 400
cdcl3 / Temp: Ambient / N.Reg: XXXXXXXXXX
Usuari: san / Mostra: JAM152-26
Nom: JUAN-ANDRES MONTIEL ACHONG
Data: 31/03/14 / Ope.: J.MONTIEL
Experiment: s2pul
Pulse Sequence: s2pul
7.267
5.116
3.432
3.416
3.401
3.386
3.370
3.354
2.556
2.532
2.517
2.382
2.368
2.345
2.146
2.129
2.114
2.097
2.073
2.062
1.901
1.892
1.885
1.876
1.633
0.000
9
8
7
6
5
4
3
2
1
ppm


H1 / 400
cdcl3 / Temp: Ambient / N.Reg: XXXXXXXXXX
Usuari: san / Mostra: JAM152-26
Nom: JUAN-ANDRES MONTIEL ACHONG
Data: 31/03/14 / Ope.: J.MONTIEL
Experiment: s2pul
Pulse Sequence: s2pul
77.321
77.004
76.679
68.597
37.298
30.688
46.146
45.775
25.693
24.927
210.445
154.234
200
180
160
140
120
100
80
60
40
20
ppm

X-Ray Crystallographic Data

CCDC 1408342-1408343 contain the supplementary cristallographic 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

X-Ray Crystallographic Data for compound **12a**

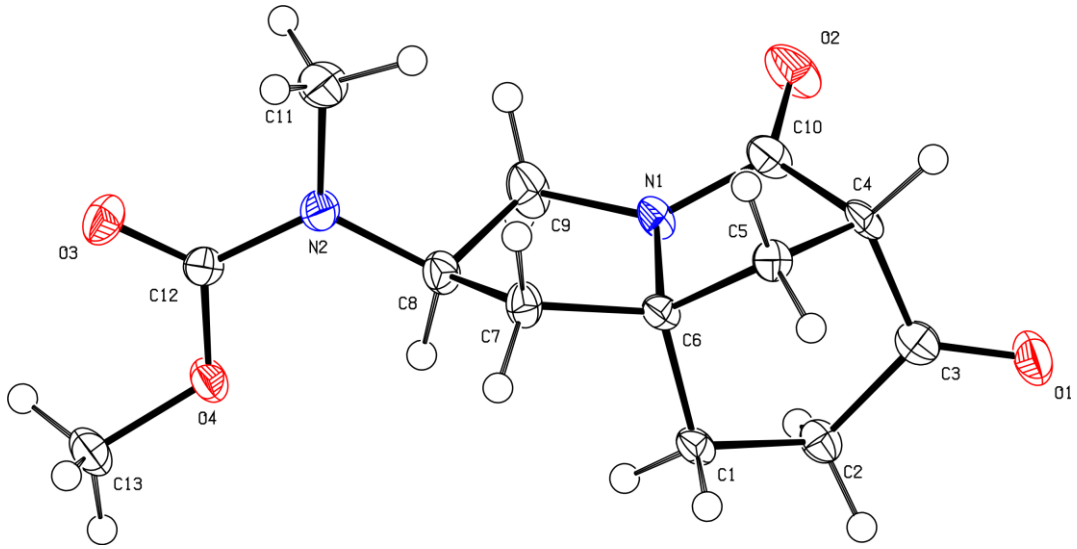


Table 1. Crystal data and structure refinement for **12a**

Identification code	mo_D43TB103_0m_a	
Empirical formula	C13 H18 N2 O4	
Formula weight	266.29	
Temperature	100(2) K	
Wavelength	0.71073 Å	
Crystal system	Monoclinic	
Space group	P 21/n	
Unit cell dimensions	a = 9.4119(2) Å	α= 90°.
	b = 7.6136(2) Å	β= 104.1660(10)°.
	c = 18.3824(5) Å	γ= 90°.
Volume	1277.20(6) $Å^3$	
Z	4	
Density (calculated)	1.385 Mg/m^3	
Absorption coefficient	0.103 mm^{-1}	
F(000)	568	
Crystal size	0.336 x 0.206 x 0.178 mm^3	
Theta range for data collection	2.285 to 30.513°.	
Index ranges	-13<=h<=12, -10<=k<=9, -20<=l<=26	
Reflections collected	3200	

Independent reflections	2481 [R(int) = 0.0372]
Completeness to theta = 25.000°	60.1 %
Absorption correction	Semi-empirical from equivalents
Max. and min. transmission	0.7461 and 0.4606
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	2481 / 0 / 174
Goodness-of-fit on F^2	0.895
Final R indices [I>2sigma(I)]	R1 = 0.0568, wR2 = 0.1220
R indices (all data)	R1 = 0.0905, wR2 = 0.1328
Extinction coefficient	n/a
Largest diff. peak and hole	0.284 and -0.293 e.$Å^{-3}$

Table 2. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters ($Å^2$x 10^3) for mo_D43TB103_0m_a. U(eq) is defined as one third of the trace of the orthogonalized U^{ij} tensor.

	x	y	z	U(eq)
O(1)	785(2)	9039(2)	4229(1)	29(1)
O(2)	4468(2)	11574(2)	4113(1)	32(1)
O(3)	10084(2)	5308(2)	3197(1)	24(1)
O(4)	9023(2)	4414(2)	4112(1)	22(1)
N(1)	4987(2)	8704(2)	3864(1)	16(1)
N(2)	8056(2)	6683(3)	3371(1)	21(1)
C(1)	3682(2)	5984(3)	4052(1)	17(1)
C(2)	2802(2)	7050(3)	4508(1)	19(1)
C(3)	1923(2)	8547(3)	4096(1)	20(1)
C(4)	2548(2)	9465(3)	3504(1)	18(1)
C(5)	2850(2)	8020(3)	2965(1)	17(1)
C(6)	4182(2)	7158(3)	3482(1)	16(1)
C(7)	5341(2)	6289(3)	3145(1)	19(1)
C(8)	6802(2)	6737(3)	3708(1)	19(1)
C(9)	6578(3)	8562(3)	4047(2)	27(1)
C(10)	4108(3)	10105(3)	3865(1)	22(1)
C(11)	8105(3)	7911(4)	2768(2)	33(1)
C(12)	9129(2)	5463(3)	3538(1)	17(1)
C(13)	10019(3)	2946(3)	4247(2)	28(1)

X-Ray Crystallographic Data for compound **14**

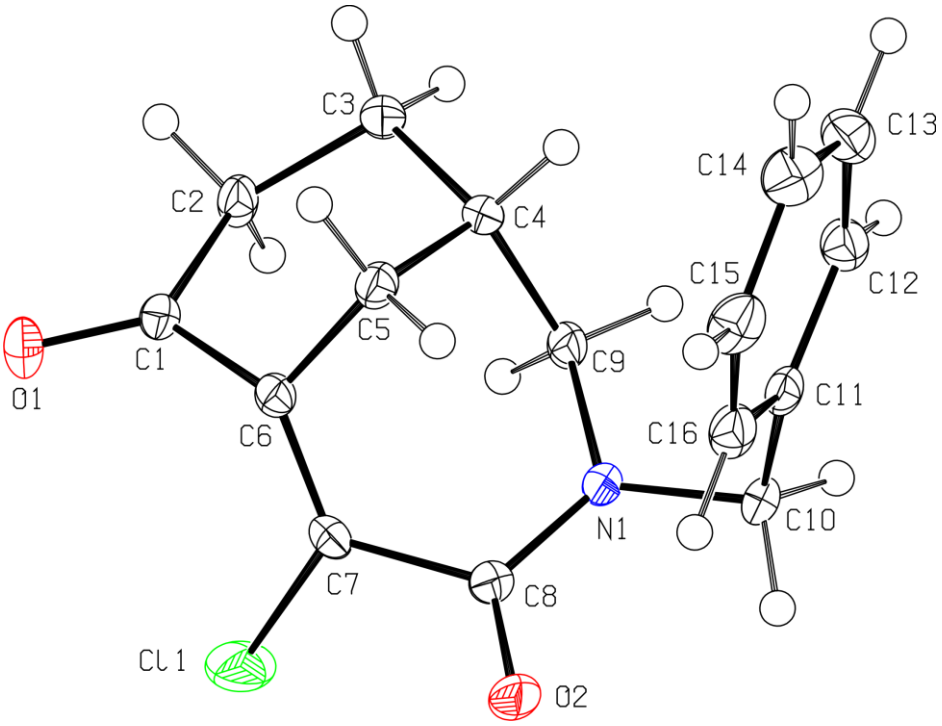


Table 1. Crystal data and structure refinement for mo_D43TB83_0ma_a.

Identification code	mo_D43TB83_0ma_a	
Empirical formula	C16 H16 Cl N O2	
Formula weight	289.75	
Temperature	100(2) K	
Wavelength	0.71073 Å	
Crystal system	Orthorhombic	
Space group	P n a 21	
Unit cell dimensions	a = 7.9657(2) Å	α = 90°.
	b = 14.5166(3) Å	β = 90°.
	c = 12.0126(3) Å	γ = 90°.
Volume	1389.08(6) $Å^3$	
Z	4	
Density (calculated)	1.385 Mg/m^3	
Absorption coefficient	0.275 mm^{-1}	
F(000)	608	
Crystal size	0.505 x 0.337 x 0.224 mm^3	
Theta range for data collection	2.201 to 30.539°.	
Index ranges	-9<=h<=11, -20<=k<=16, -16<=l<=16	
Reflections collected	4291	

Independent reflections	3139 [R(int) = 0.0232]
Completeness to theta = 25.242°	99.8 %
Absorption correction	Semi-empirical from equivalents
Max. and min. transmission	0.7461 and 0.6682
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	3139 / 1 / 181
Goodness-of-fit on F^2	1.098
Final R indices [I>2sigma(I)]	R1 = 0.0467, wR2 = 0.1283
R indices (all data)	R1 = 0.0493, wR2 = 0.1370
Absolute structure parameter	0.02(4)
Extinction coefficient	n/a
Largest diff. peak and hole	1.000 and -0.631 e.$Å^{-3}$

Table 2. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters ($Å^2$x 10^3)
for mo_D43TB83_0ma_a. U(eq) is defined as one third of the trace of the orthogonalized U^{ij} tensor.

	x	y	z	U(eq)
Cl(1)	4431(1)	6960(1)	3593(1)	43(1)
O(1)	2462(2)	6473(1)	6000(2)	22(1)
O(2)	6843(2)	5313(2)	2716(2)	26(1)
N(1)	8298(2)	5708(2)	4287(2)	16(1)
C(1)	3939(3)	6269(2)	6051(2)	16(1)
C(00K)	5119(3)	6664(2)	6922(2)	20(1)
C(2)	6659(3)	6070(2)	7258(2)	22(1)
C(3)	5942(3)	4954(2)	5762(2)	17(1)
C(4)	7394(3)	5483(2)	6308(2)	18(1)
C(5)	4879(3)	5695(2)	5233(2)	15(1)
C(6)	5337(3)	6019(2)	4225(2)	18(1)
C(7)	6894(3)	5643(2)	3657(2)	18(1)
C(8)	8279(3)	6092(2)	5428(2)	18(1)
C(9)	9850(3)	5242(2)	3907(2)	19(1)
C(10)	9998(3)	4309(2)	4461(2)	18(1)
C(11)	10880(3)	4211(2)	5452(2)	21(1)
C(12)	10842(3)	3379(2)	6038(3)	25(1)
C(13)	9924(4)	2639(2)	5618(3)	27(1)
C(14)	9085(4)	2724(2)	4610(3)	26(1)
C(15)	9123(3)	3554(2)	4031(3)	23(1)

Chapter 5

Intramolecular Radical Non-Reductive Alkylation of Ketones via Transient Enamines

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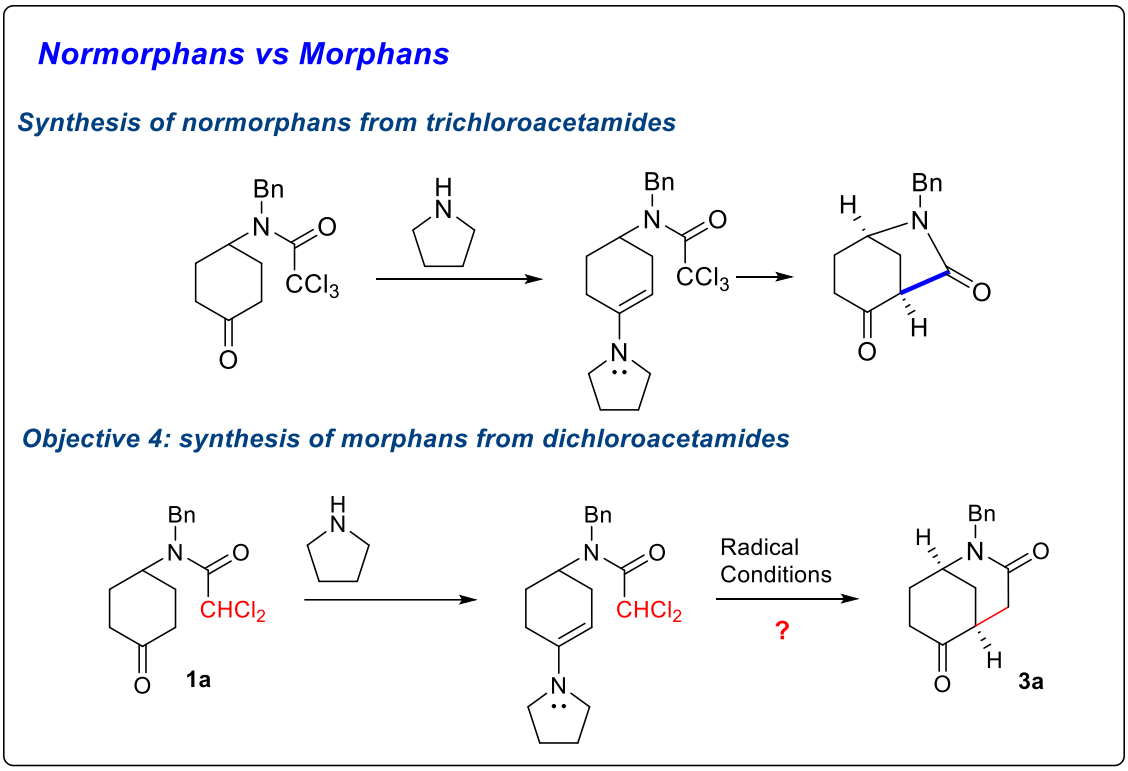
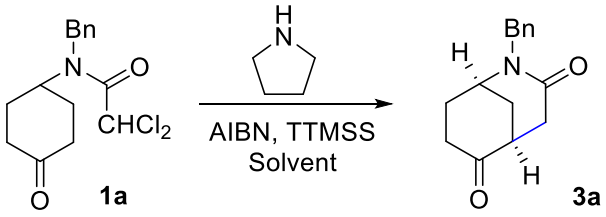


Scheme 5.1

In the previous chapter, we reported a new route for the synthesis of normorphans from trichloroacetamides through the corresponding enamines. The process involves a nucleophilic substitution induced by the enamine formed *in situ* upon the amide carbonyl group. This result prevented us from continuing our radical cyclizations upon electron-donating substituted alkenes. Nevertheless, we envisioned that replacing one of chlorine atoms of the trichloromethyl group by a hydrogen would guarantee the formation of the enamine and thus suppress the nucleophilic attack on the acetamide allowing us to proceed with our radical cyclizations.

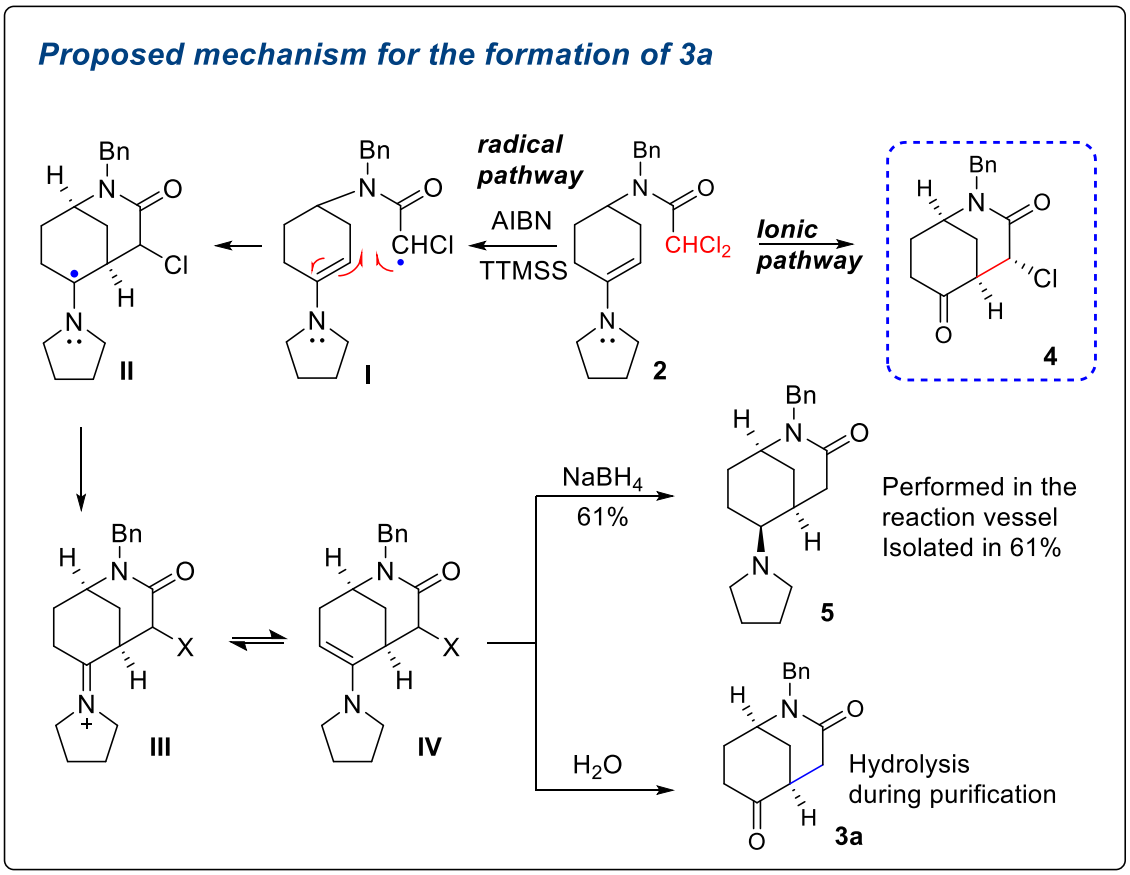
Table 2.1. Synthesis of morphan **3a**



Entry	*Amine (eq)*	*TTMSS (eq)*	*AIBN (eq)*	*Conditions*	*Yield (%)*
1	1	1.1	1	benzene, reflux 1.5 h	32
2	2	2	1	benzene, reflux 1.5 h	45
3	2	2	1	benzene, reflux 4 h	39
4	2	2	1	benzene, μW 80 °C 10 min	47
5	2	1	2	benzene, μW 80 °C 5 min	39
6	5	2	1	benzene, μW 80 °C 5 min **(B)**	**77**
7	5	2	0.5	benzene, μW 60 °C 5 min	60
8	5	1.2	1	benzene, μW 80 °C 5 min	65
9	5	1.5	0.5	benzene, μW 80 °C 5 min	54
10	5	2	1	benzene, μW 60 °C 5 min	57
11	5	2	1	toluene, μW 80 °C, 5min	42
12	5	2	1	toluene, μW 60 °C, 5min **(C)**	**75**

After ensuring formation of the enamine by treatment of **1a** with pyrrolidine (1 equiv) under reflux of benzene for only 5 min, the mixture was submitted to standart radical conditions in which TTMSS (1.1 equiv) and AIBN (1 equiv) were added slowly (30 min). After an additional hour and purification by chromatography, we were glad to find that not only the cyclization had taken place on the enamine double bond, but the ketone functionality was preserved, providing morphan **3a** in moderate yield (Table 1, entry 1). Increasing the quantity of both pyrrolidine and TTMSS to 2 equiv. increased the yield slightly to 45% (entry 2), and a similar yield was obtained when all the reagents were put together in a one-pot reaction after 4 h of reflux (entry 3). The reaction time was dramatically reduced to 5-10 min under microwave heating at 80 ºC (entries 4 and 5) and the best result (77%) was obtained with 5 equiv of pyrrolidine (entry

6). Running the reactions with a lower loading of either TTMSS or AIBN, or both, provided **3a** with lower yields, 54-65%, (entries 7-9), while switching to toluene under the same optimized conditions significantly reduced the yield (entry 11). Curiously, a better yield was obtained when the reaction was carried out using toluene as a solvent but at a lower temperature (entry 12).



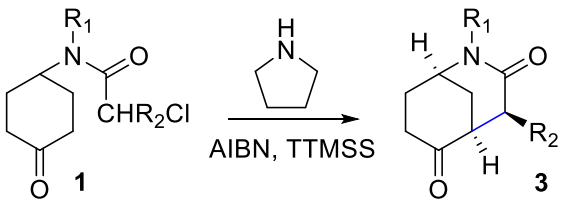
Scheme 5.2.

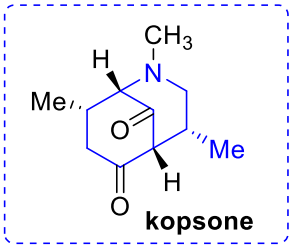
Regarding the mechanism leading to **3a**, in order to rule out the ionic pathway we performed some control experiments using the best conditions previously achieved (table 5.1, entry 5), and by omitting in the reaction vessel: a) AIBN; b) TTMSS and c) both AIBN/TTMSS. In all cases morphan **4** was isolated in low yields (5-10%), with the partial recovery of starting material, suggesting that even if the ionic pathway might ensue, the radical pathway proposed in scheme 5.2. is more favored for this reaction.

Thus, after the generation of enamine **2**, the chloromethylcarbamoyl radical **I** (generated in the presence of AIBN and TTMSS) adds to the electron-rich double bond and leads to α-aminoalkyl radical **II**, which can be oxidized *in*

situ to the corresponding iminium salt **III** and hydrolyzed during purification. The iminium salt could also be formed through a chlorine atom-transfer to the α-amino radical, followed by elimination of the chlorine atom at C-6. Nevertheless, when the reaction was carried out in deuterated benzene, the ^{1}H and ^{13}C NMR spectra of the reaction crude showed signals corresponding to a cyclization intermediate different from those of **2a**. In particular, the presence of a proton at δ 3.88 and signals at δ 88.1 for the corresponding methine carbon and a quaternary carbon at δ 145.9 for C-7 and C-6, respectively, is in accordance with those expected from enamine **IV**. The latter is formed by deprotonation of iminium **III** promoted by pyrrolidine. Indeed, after completion of the reaction, a white precipitate corresponding to the conjugated acid of pyrrolidine was isolated. To confirm the structure of **IV**, ketone **3a** was treated with 1 equiv of pyrrolidine in deuterated benzene in an NMR tube. After only 15 min, signals belonging to **IV** (40% conversion) were observed. Additionally, the reaction mixture was submitted to reduction using $NaBH_4$ in methanol in the same reaction vessel, and after purification, amine **5** was isolated alone in 61% yield.

Table 5.2. Synthesis of morphans **3b**, **3d**-**3f**



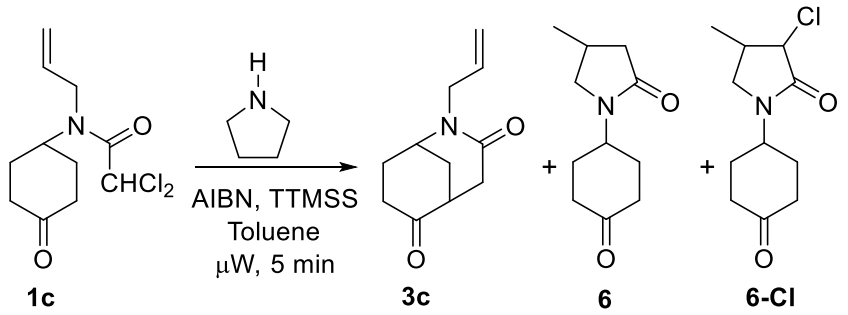


1	*R¹*	*R²*	*Method*	*AIBN (eq)*	*Temp. (ºC)*	*Yield (%)*
1b	Me	Cl	B	1	60	**71**
1b	Me	Cl	C	1	60	36
1d	*i*Pr	Cl	B	1	60	38
1d	*i*Pr	Cl	C	0.25	60	**45**
1e	*t*Bu	Cl	B	1	80	25
1e	*t*Bu	Cl	C	0.25	60	**70**
1e	*t*Bu	Cl	C[a]	0.25	60	58
1f	Bn	Me	C[b]	1	60	**40**
1f[c]	Bn	Me	C[b]	1	60	26
1g	Bn	H	B or C	1	80 or 60	-

Method B: μW, Benzene, 5 min, TTMSS (2eq); **Method C**: μW, Toluene, 5 min, TTMSS (2eq) [a] *t*-BuOH used as solvent. [b] 1 equiv. TTMSS. [c] Br instead of Cl

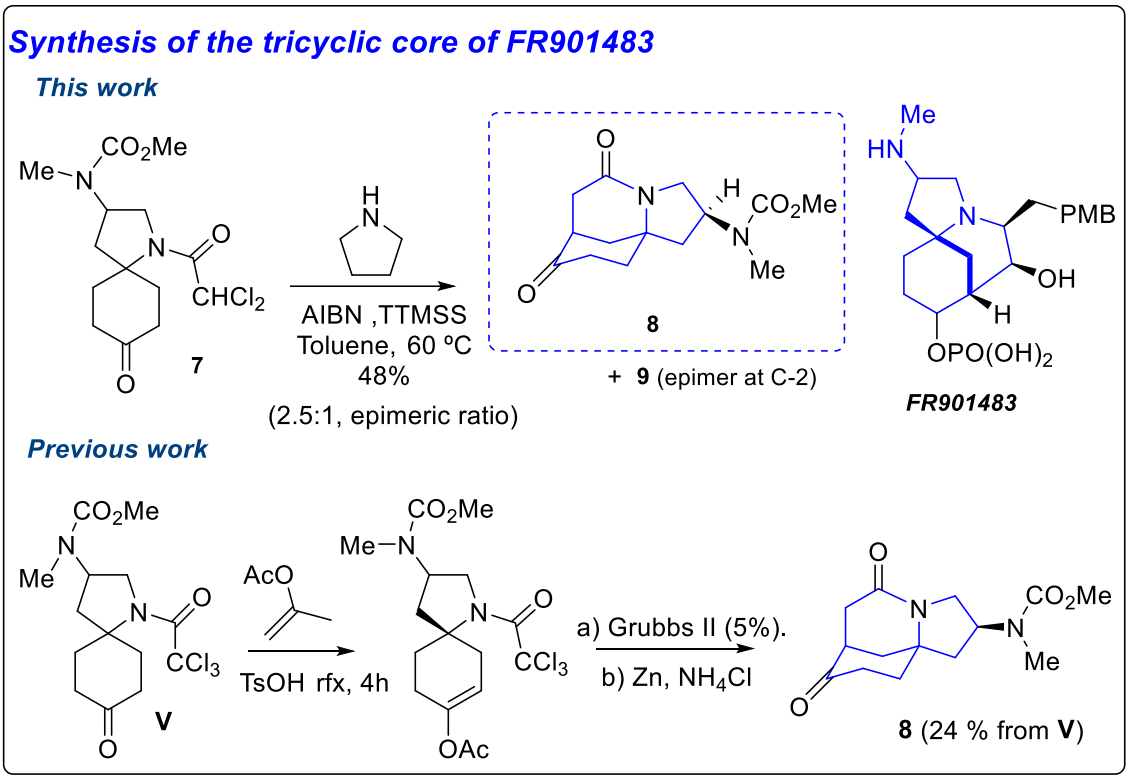
The best reaction conditions were then applied, with slight modifications to dichloroacetamides **1b**-**1e** where the benzyl group was substituted by methyl, allyl, isopropyl, and *t*-butyl groups respectively. In all cases, morphan derivatives **2b**-**2e** were obtained in moderate to good yields (table 5.2), except in the case of **1c** where the 5-*exo* cyclization on the allyl chain competes with the 6-*endo* process obtaining an inseparable mixture of compounds (table 5.3, entry 1). Only when a substoichiometric quantity of AIBN was used, morphan **3c** was isolated in a poor yield (entry 2). As expected, when pyrrolidine was omitted from the reaction mixture leaving the alkene chain alone with the chlorocarbamoil radical, pyrrolidinone **6** was isolated in an acceptable yield (entry 3). The reaction was also extended to chloro- and bromopropanamide **1f** and **1g** for the synthesis of the corresponding morphan related to kopsone. In both cases morphan **3f** was isolated as a unique diastereomer with the right relative configuration in an acceptable yield (table 5.2).

Table 5.3. Synthesis of **3c** and **6**



1c **3c** **6** **6-Cl**

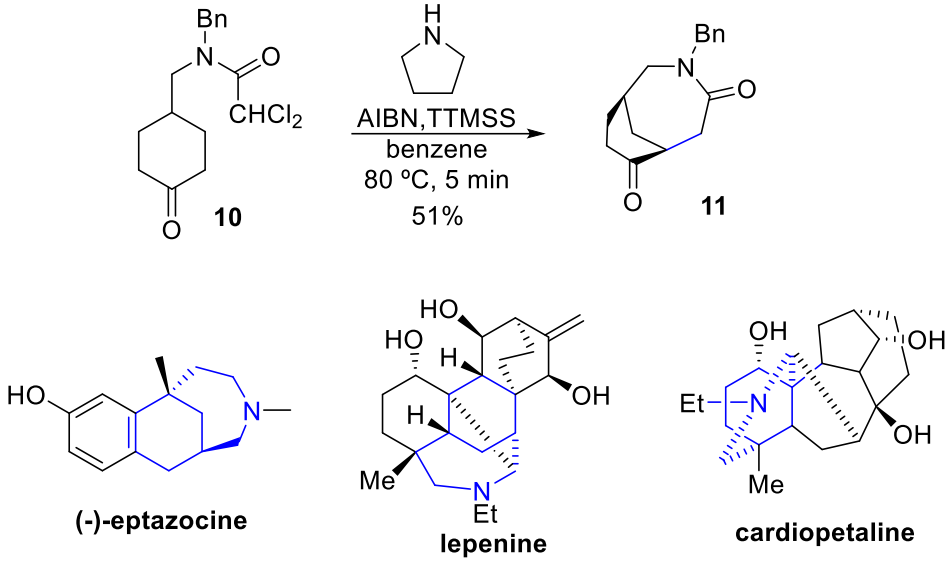
Entry	*AIBN (eq)*	*Amine (eq)*	*Temp. (ºC)*	***3c** Yd. (%)*	***6** Yd. (%)*	***6-Cl** Yd. (%)*
1	1	5	80	Mixture	--	--
2	0.25	5	80	22	--	11
3	1	--	60	--	57	--



Scheme 5.3.

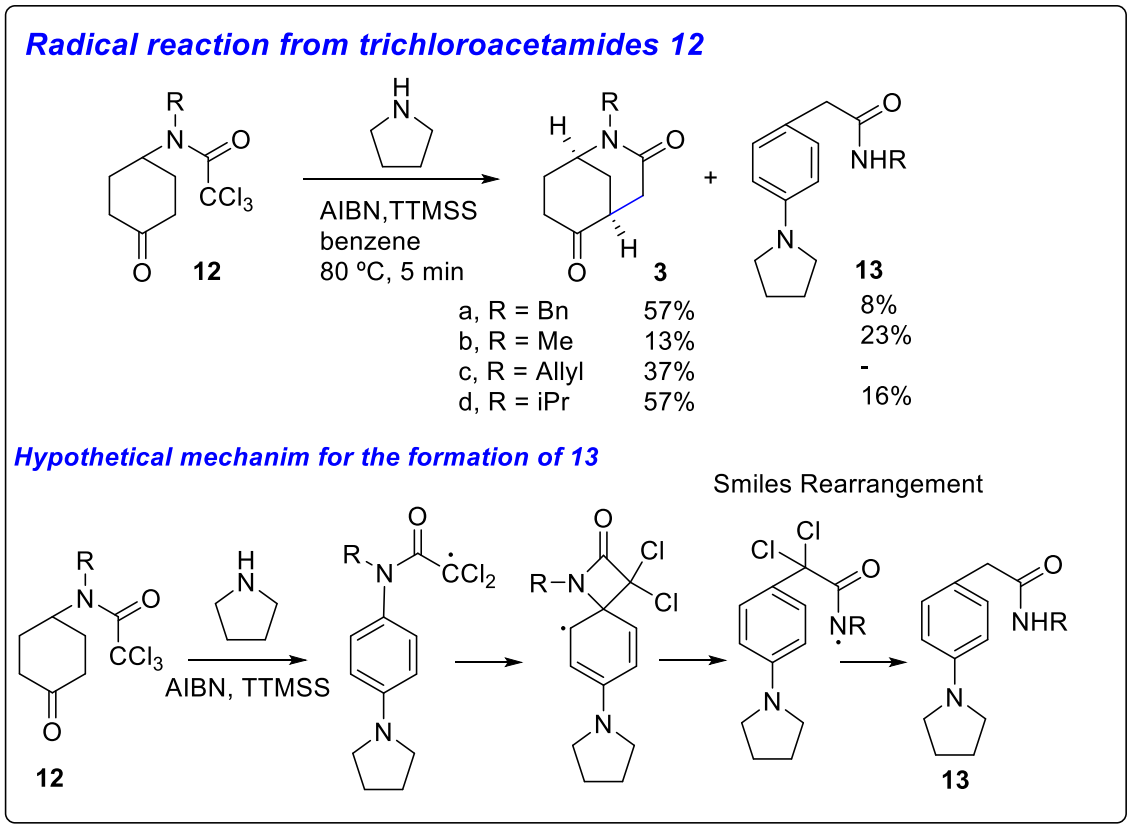
As an application of the methodology developed herein we carried the reaction with azaspirodichloroacetamide **7** for the synthesis of an advanced intermediate of the potent immunosuppressant FR901483. The best results were obtained using toluene as a solvent and at 60 ºC (conditions C) obtaining the diazatricyclic derivative **8** with 34% of yield together with its epimer at C-2 (14%). It's worth noting that the same product was obtained in a previous work from the corresponding trichloroacetamidocyclohexanone **V** using a three steps sequence involving: i) preparation of the enol acetate, ii) ATRC in the presence of Grubbs II catalyst, iii) reduction of the dichloro derivative using zinc (Scheme 5.3).

Synthesis of 3-azabicyclo[4.3.1]decane 11



Scheme 5.4.

Additionally, we found that the reaction worked quite well for the preparation of the 7-membered ring derivative **11** from dichloroacetamide **10**. The best results were obtained with benzene as a solvent and using the original optimized conditions. Although the 3-azabicyclo[4.3.1]decane ring is embedded in numerous natural products and some synthetic pharmacologically active compounds, there are few synthetic procedures for this bridged azabicyclic system (Scheme 5.4).



Scheme 5.5.

With these results in hand, we were curious to check our reaction conditions on trichloroacetamides **12** which readily react with pyrrolidine conducing to the corresponding normorphans. When trichloroacetamides **12** were treated with pyrrolidine in the presence of AIBN and TTMSS in benzene at 80 ºC, morphans **3** were obtained with low to acceptable yields, normorphans **9** being isolated as traces. Even this shows that the formation of the radical and its addition to the enamine is faster than addition of the enamine on the carbonyl group, with substrates **12a**, **12b**, and **12d** a new type of compounds **13** was isolated resulting from a Smiles rearrangement through a four membered ring after aromatization (Scheme 5.5).

Intramolecular Radical Non-Reductive Alkylation of Ketones via Transient Enamines.

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Intramolecular radical non-reductive alkylation of ketones *via* transient enamines†

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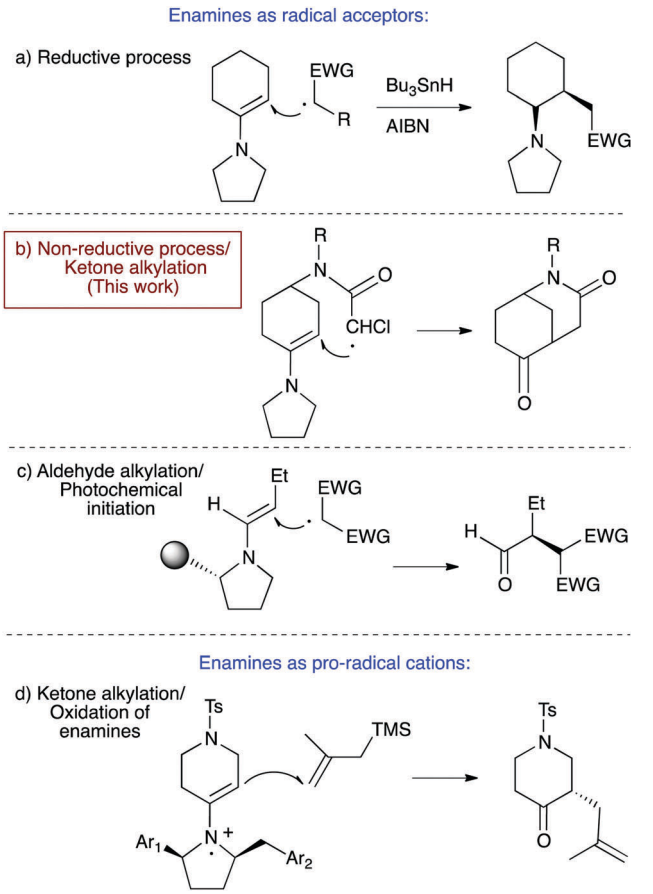
Radical cyclization of dichloroacetamide-tethered ketones using pyrrolidine, AIBN and TTMSS under microwave activation gave 2-azabicyclo[3.3.1]nonan-3,6-diones. In a five-minute one-pot process, after the generation of an enamine, intramolecular addition of a carbamoylchloromethyl radical, and oxidation of the α-aminoalkyl radical intermediate, the resulting iminium salt evolved to the corresponding enamine and, after a workup, to the alkylated ketone.

The Stork alkylation of carbonyl compounds through their corresponding enamines is a classic process in organic synthesis that underwent a strong revival with the advent of organocatalysis (from aldehydes and ketones),[1] and has recently evolved further with the use of radical reactions (from aldehydes).[2] To date, a radical version of the ionic procedure using transient enamines from ketones remains almost unexplored. Although some examples of radical reductive additions to preformed enamines have been reported, leading to amino compounds (Scheme 1a),[3] the non-reductive radical reaction upon transient enamines to achieve α-alkylated ketones is unprecedented.[4,5] Reported here is the development of an intramolecular α-alkylation of ketones (Scheme 1b). The most closely related studies were developed by Melchiorre, using photoorganocatalysis, in which an α-alkylation of cyclic ketones was promoted by a radical ion pair.[6] The recent emergence of photochemical procedures[7] has allowed the radical α-alkylation of aldehydes, with transient enamines acting as radical acceptors (Scheme 1c).[8] In a conceptually different approach, the enamine acts as a pro-radical, instead of a radical acceptor as in the above procedures, and a preformed[9] or transient enamine undergoes oxidation.[10] The resulting cation radical can react with a wide range of radical acceptors, the organocatalyzed version being introduced in MacMillan's seminal work (Scheme 1d).

In a previous work, when we attempted to prepare the enamine tether with a trichloroacetamide, we found the unexpected α-carbamoylation of the ketone in a process in which the initially formed enamine induced a substitution in the amide carbonyl group.[11] This result prevented us from continuing the radical cyclization studies from trichloroacetamides involving electron-donating substituted alkenes[12,13] (Scheme 2). However, we envisioned that replacing the trichloroacetamide with a dichloroacetamide would suppress the nucleophilic attack on



Scheme 1 Radical reactions involving enamines.

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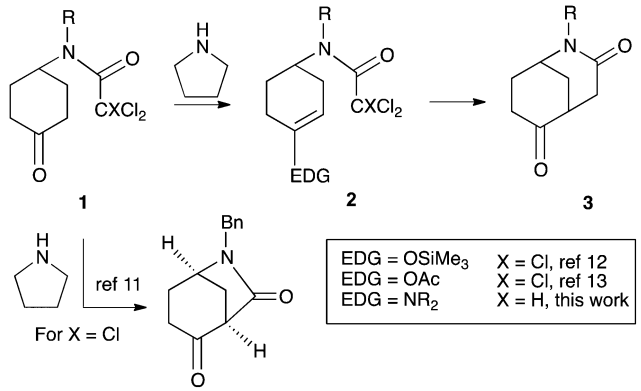
† Electronic supplementary information (ESI) available: Experimental procedures, characterization data and copies of NMR spectral data. See DOI: 10.1039/c6cc08356k



Scheme 2 Radical cyclization with enamines.

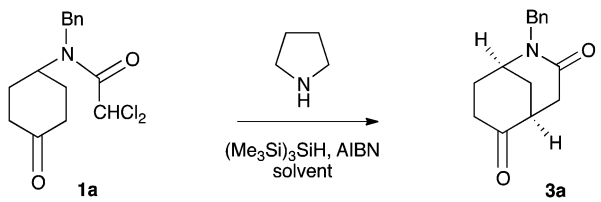
the acetamide group. Here, we report an efficient one-pot procedure for intramolecular α-alkylation of ketone-tethered dichloroacetamides (*e.g.* **1**) based on a radical-polar crossover reaction in the presence of AIBN and $(Me_3Si)_3SiH$ (TTMSS) under microwave activation, where an *in situ* generated enamine (*e.g.* **2**) is the radical acceptor in the cyclization process (Scheme 2).

We began by preparing enamine **2** from ketone **1a** with pyrrolidine (1 equiv.) in refluxing benzene (for only 5 min) under standard radical reaction conditions, in which TTMSS (1.1 equiv.) and AIBN (1 equiv.) were added slowly (30 min). After an additional hour and workup, we were encouraged to find that not only had the cyclization taken place on the enamine double bond, but the ketone functionality was also preserved, providing morphan **3a** in moderate yield (Table 1, entry 1). Increasing the quantity of both pyrrolidine and TTMSS to 2 equiv. increased the yield slightly to 45% (entry 2), and a similar yield was obtained when all the reagents were put together in a one-pot reaction after 4 h at reflux (entry 3). The reaction time was dramatically reduced to 5–10 min under microwave heating at 80 °C (entries 4 and 5) and the best results (75–80%) were obtained with 5 equiv. of pyrrolidine (entry 6). Running the reactions with a lower loading of either TTMSS or AIBN, or both, provided **3a** with lower yields, 54–65%, (entries 7–9), while switching to toluene under the same optimized conditions significantly reduced the yield (entry 11). Curiously, a better yield was obtained when the reaction was carried out using toluene as a solvent but at a lower temperature (compare entries 10 and 11 with 12).

Before postulating a mechanism for the cyclization, the following blank experiments were performed using the best reaction conditions (Table 1, entry 6): (i) without AIBN; (ii) without TTMSS, and (iii) with pyrrolidine alone, in order to discard an ionic mechanism. In all cases, minor amounts (5–10%) of morphan **4** were isolated (see Scheme 3), and the starting material was partially recovered. This suggests that although a competitive ionic process might occur, the radical pathway proposed in Scheme 3 would be more favored.

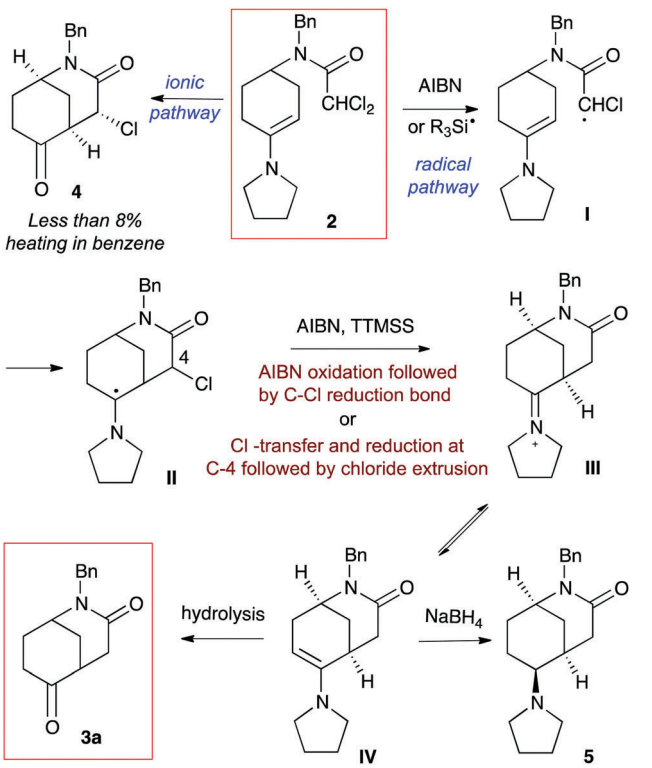
The formation of **3a** could be explained by the following scenario. After the generation of enamine **2**, addition of the chloromethylcarbamoyl radical **I** (generated in the presence of AIBN and TTMSS) to the electron-rich double bond occurs and leads to the formation of α-aminoalkyl radical **II**, which can be oxidized *in situ*[14] to the corresponding iminium salt **III** and

Table 1 Synthesis of morphan **3a**



Entry	Method[a]	Amine (equiv.)	TTMSS (equiv.)	AIBN (equiv.)	Yield[b] (%)
1	A	1	1.1	1	32
2	A	2	2	1	45
3	A	2	2	1	39[c]
4	B	2	2	1	47[d]
5	B	2	2	1	39
6	B	5	2	1	77
7	B	5	2	0.5	60
8	B	5	1.2	1	65
9	B	5	1.5	0.5	54
10	B	5	2	1	57[e]
11	C	5	2	1	42[f]
12	C	5	2	1	75

[a] Unless otherwise noted, the reaction was carried out from 200 mg of **1a**. Method A: the reaction was carried out in benzene (4 mL) under reflux for 1 h after addition of a solution of TTMSS and AIBN over 30 min. Method B: μW, 80 °C in benzene (1 mL) for 5 min. Method C: μW, 60 °C in toluene (1 mL) for 5 min. [b] Yields refer to pure compounds isolated by flash chromatography. [c] **1a** and all the reagents were put together in a one-pot reaction under reflux of the solvent for 4 h. [d] Time reaction: 10 min. [e] At 60 °C. [f] At 80 °C.



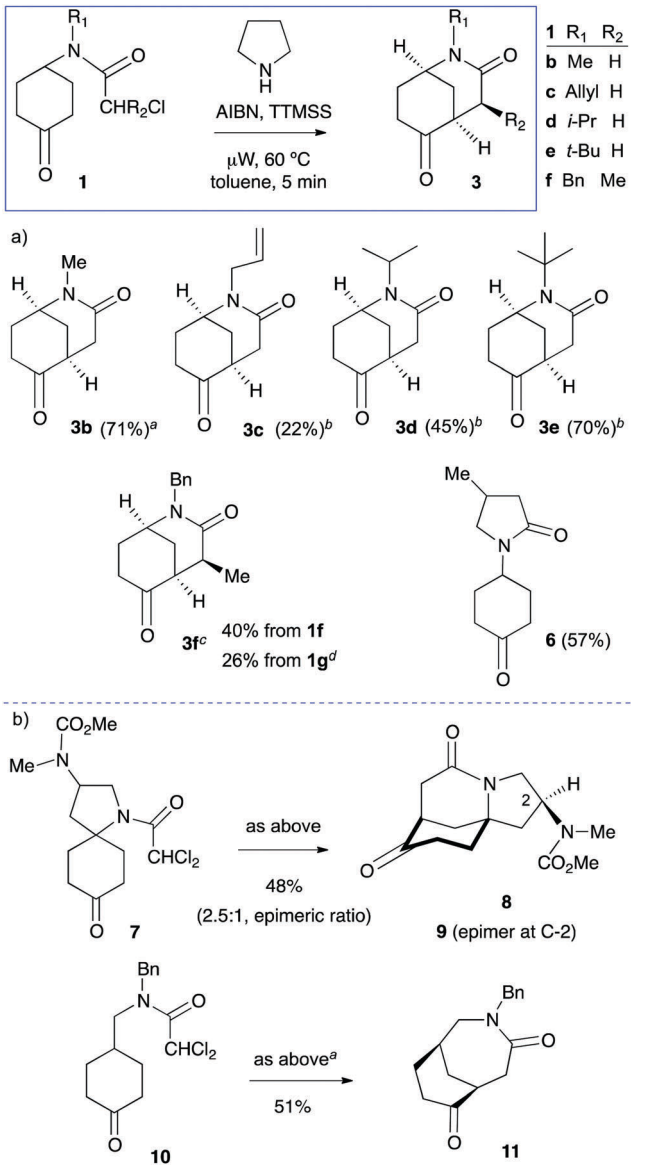
Scheme 3 Proposed radical cyclization pathway.

hydrolyzed during purification. The iminium salt could also be formed through a chlorine atom-transfer to the α-amino radical, followed by elimination of the chlorine atom at C-6.[15] Nevertheless, when the reaction was carried out in deuterated benzene, the ^{1}H and ^{13}C NMR spectra of the reaction crude showed signals corresponding to a cyclization intermediate different from those of **3a**. In particular, the presence of a proton at δ 3.88 and signals at δ 88.1 for the corresponding methine carbon and a quaternary carbon at δ 145.9 for C-7 and C-6, respectively, is in accordance with those expected from enamine **IV**. The latter is formed by deprotonation of iminium **III** promoted by pyrrolidine. Indeed, after completion of the reaction, a white precipitate corresponding to the conjugated acid of pyrrolidine was isolated. To confirm the structure of **IV**, ketone **3a** was treated with 1 equiv. of pyrrolidine in deuterated benzene in an NMR tube. After only 15 min, signals corresponding to **IV** (40% conversion) were observed. Additionally, the reaction mixture was submitted to reduction using $NaBH_4$ in methanol in the same reaction vessel, and after purification amine **5** alone was isolated in 61% yield.[16]

After slight modifications, the best reaction conditions were then applied to dichloroacetamides **1b–1e** with different substituents in the nitrogen atom (Scheme 4a). In all cases, morphan derivatives (**3b–3e**) were obtained in moderate to good yields except in the case of **3c**, where the 5-*exo* cyclization on the allyl chain competes with the 6-*exo* process. As expected, when working without pyrrolidine, the only compound isolated was lactam **6**. The reaction was also extended to chloro- and bromopropanamides **1f** and **1g**, and in both cases, morphan **3f** was isolated as a unique diastereomer.[17] When using chloroacetamide **1** (R_2 = H), the reaction did not work. The reaction was extended to additional substrates (Scheme 4b), including dichloroacetamide **7**, which led to compound **8** with the azatricyclic core of FR901483[13b] as an epimeric mixture (2.5 : 1 ratio, **8**/**9**) in a 48% overall yield. Additionally, we found that the reaction worked quite well for the preparation of the 7-membered ring derivative **11** from dichloroacetamide **10**. Although the 3-azabicyclo[4.3.1]decane ring is embedded in numerous natural products[18] and some synthetic pharmacologically active compounds,[19] there are only a few synthetic procedures for this bridged azabicyclic system.[20]

With these results in hand, we were interested in exploring the above reaction conditions with trichloroacetamides **12**, which readily react with pyrrolidine, leading to the corresponding normorphans.[11] When **12a–d** were treated with pyrrolidine in the presence of AIBN and TTMSS (2 equiv.) in benzene at 80 °C, morphans **3a–d** were obtained in low to acceptable yields (Scheme 5).[21] This result showed that the formation of the radical and its addition to the enamine is faster than the nucleophilic attack of the enamine on the carbonyl group. Also, as shown previously, in the formation of **3** from dichloroacetamides, the radical pathway is favored over an ionic reaction. In addition, a new type of compound **13** was isolated from trichloroacetamides **12**, arising from an unusual radical Smiles rearrangement through a four-membered ring[22] after aromatization of the initially formed 4-aminocyclohexene ring.[23]

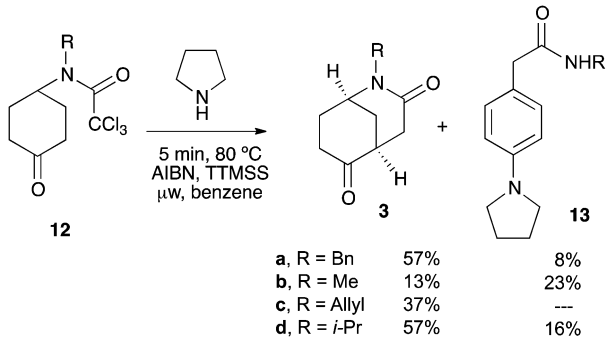
In summary, a new intramolecular addition of radicals (carrying electron-withdrawing groups) to the distal terminus



Scheme 4 Scope of the radical cyclization. Reaction performed from 100 mg of dichloroacetamide, pyrrolidine (5 equiv.), AIBN (1 equiv.), and TTMSS (2 equiv.). Yield after isolation by chromatography. [a] In benzene. At 80 °C for **10**. [b] 0.25 equiv. of AIBN were used. [c] 1 equiv. of TTMSS was used. [d] As **1f**, Br instead Cl.

of an enamine double bond is reported in the context of a straightforward route to morphans[24] from dichloroacetamidocyclohexanones using a one-pot reaction in the presence of pyrrolidine, AIBN and TTMSS under microwave activation. This five-minute reaction provides 2-azabicyclo[3.3.1]nonane derivatives with their carbonyl function being preserved. The process is of interest from the mechanistic point of view and compares favorably with the two-step synthesis of morphans from silyl enol ethers.[12] Further studies are in course to explore the scope of this methodology for the synthesis of other nitrogen-containing heterocycles.

Financial support for this research was provided by the Ministry of Economy and Competitiveness of Spain (Project CTQ2013-41338-P).



Scheme 5 Radical reaction from trichloroacetamides.

Notes and references

1 For enamine-mediated stereoselective catalytic reactions, see: (*a*) C. F. Barbas, III, *Angew. Chem., Int. Ed.*, 2008, **47**, 42; (*b*) B. List, *Angew. Chem., Int. Ed.*, 2010, **49**, 1730.

2 E. Arceo, I. D. Jurberg, A. Álvarez-Fernández and P. Melchiorre, *Nat. Chem.*, 2013, **5**, 750.

3 For intermolecular radical processes involving enamines leading to amino compounds, see *inter alia*: (*a*) P. Renaud and S. Schubert, *Angew. Chem., Int. Ed.*, 1990, **29**, 433; (*b*) S. Schubert, P. Renaud, P.-A. Carrupt and K. Schenk, *Helv. Chim. Acta*, 1993, **76**, 2473. For intramolecular radical processes involving enamines leading to amino compounds, see *inter alia*: (*c*) L. Ripa and A. Hallberg, *J. Org. Chem.*, 1998, **63**, 84; (*d*) J. M. Aurrecoechea, C. A. Coy and O. J. Patiño, *J. Org. Chem.*, 2008, **73**, 5194.

4 For reactions upon preformed enamines leading to alkylated ketones using photo-induced radical reactions, see: (*a*) G. A. Russell and K. Wang, *J. Org. Chem.*, 1991, **58**, 3475; (*b*) B. Hu, H. Chen, Y. Liu, W. Dong, K. Ren, X. Xie, H. Xu and Z. Zhang, *Chem. Commun.*, 2014, **50**, 13547.

5 For Et_3B-initiated addition of an alkyl radical to preformed *N*-silyloxy enamines, see: H.-J. Song, C. J. Lim and S. Kim, *Chem. Commun.*, 2006, 2893.

6 E. Arceo, A. Bahamonde, G. Bergonzini and P. Melchiorre, *Chem. Sci.*, 2014, **5**, 2438.

7 (*a*) J. M. R. Narayanam and C. R. J. Stephenson, *Chem. Soc. Rev.*, 2011, **40**, 102; (*b*) C. K. Prier, D. A. Rankic and D. W. C. MacMillan, *Chem. Rev.*, 2013, **113**, 5322; (*c*) N. A. Romero and D. A. Nicewicz, *Chem. Rev.*, 2016, **116**, 10075.

8 (*a*) H.-W. Shih, M. N. Vander Wai, R. L. Grange and D. W. C. MacMillan, *J. Am. Chem. Soc.*, 2010, **132**, 13600; (*b*) A. Bahamonde and P. Melchiorre, *J. Am. Chem. Soc.*, 2016, **138**, 8019.

9 K. Narasaka, T. Okauchi, K. Tanaka and M. Murakami, *Chem. Lett.*, 1992, 2099.

10 (*a*) D. A. Nicewicz and D. W. C. MacMillan, *Science*, 2008, **322**, 77; (*b*) A. Mastracchio, A. A. Warkentin, A. M. Walji and D. W. C. MacMillan, *Proc. Natl. Acad. Sci. U. S. A.*, 2010, **107**, 20648.

11 F. Diaba, J. A. Montiel, G. Serban and J. Bonjoch, *Org. Lett.*, 2015, **17**, 3860.

12 For silyl enol ethers as radical acceptors, see: (*a*) J. Quirante, C. Escolano, F. Diaba and J. Bonjoch, *J. Chem. Soc., Perkin Trans. 1*, 1999, 1157; (*b*) J. Quirante, M. Torra, F. Diaba, C. Escolano and J. Bonjoch, *Tetrahedron: Asymmetry*, 1999, **10**, 2399.

13 For enol acetates as radical acceptors in ATRC processes, see: (*a*) F. Diaba, A. Martínez-Laporta, J. Bonjoch, A. Pereira, J. M. Muñoz-Molina, P. J. Pérez and T. R. Belderrain, *Chem. Commun.*, 2012, **48**, 8799; (*b*) F. Diaba, A. Martínez-Laporta and J. Bonjoch, *J. Org. Chem.*, 2014, **79**, 9365; (*c*) F. Diaba, A. Martínez-Laporta, G. Coussanes, I. Fernández and J. Bonjoch, *Tetrahedron*, 2015, **71**, 3642.

14 α-Amino radicals are known to be easily oxidized to iminium derivatives: (*a*) H. Fujihara, S. Fuke, M. Yoshihara and T. Maeshima, *Chem. Lett.*, 1981, 1271; (*b*) Ref. 4*a*; (*c*) J. Santamaria, *J. Pure Appl. Chem.*, 1995, **67**, 141. For oxidation of a radical intermediate by-hydrogen-atom abstraction promoted by AIBN, see: (*d*) M. L. Bennasar, T. Roca and F. Ferrando, *Org. Lett.*, 2006, **8**, 561 and references therein.

15 A similar atom-transfer mechanism has been reported for the alkylation of enamides with electrophilic radicals: G. K. Friestad and Y. Wu, *Org. Lett.*, 2009, **11**, 819.

16 Traces of the C-6 epimer of **5** were also observed in the NMR spectra, but not isolated.

17 The equatorial disposition of the methyl group was revealed by the absence of a γ-effect at C-9. For ^{13}C NMR data of morphans, see: J. Quirante, C. Escolano, F. Diaba, M. Torra and J. Bonjoch, *Magn. Reson. Chem.*, 2000, **38**, 891.

18 *Inter alia*, see: (*a*) Y. Nishiyama, Y. Han-ya, S. Yokoshima and T. Fukuyama, *J. Am. Chem. Soc.*, 2014, **136**, 6598; (*b*) K. Fujioka, N. Miyamoto, H. Toya, K. Okano and H. Tokuyama, *Synlett*, 2016, 621; (*c*) Y. Nishiyama, S. Yokoshima and T. Fukuyama, *Org. Lett.*, 2016, **18**, 2359.

19 Q. Chen, X. Huo, Z. Yang and X. She, *Chem. – Asian J.*, 2012, **7**, 2543.

20 (*a*) H. K. Hall Jr., *J. Am. Chem. Soc.*, 1960, **82**, 1209; (*b*) H. K. Hall Jr., *J. Org. Chem.*, 1963, **28**, 3213; (*c*) F. Orvieto, M. Botta, F. Corelli and S. Harper, *Synth. Commun.*, 1999, **29**, 3635; (*d*) C. F. Heinrich, I. Fabre and L. Miesch, *Angew. Chem., Int. Ed.*, 2016, **55**, 5170.

21 Normorphans, as in Scheme 1, were isolated in a negligible ratio if any as minor compounds.

22 (*a*) E. Bacqué, M. El Quacemi and S. Z. Zard, *Org. Lett.*, 2005, **7**, 3817; (*b*) Z.-M. Chen, X.-M. Zhang and Y.-Q. Tu, *Chem. Soc. Rev.*, 2015, **44**, 5220.

23 For aromatization of 4-aminocyclohexenes to anilines, see: (*a*) T. Ishikawa, E. Uedo, R. Tani and S. Saito, *J. Org. Chem.*, 2001, **66**, 186; (*b*) J. Cossy and D. Belotti, *Org. Lett.*, 2002, **4**, 2557; (*c*) M. T. Barros, S. S. Dey and C. D. Maycock, *Eur. J. Org. Chem.*, 2013, 742; (*d*) K. Taniguchi, X. Jin, Y. Yamaguchi and N. Mizuno, *Catal. Sci. Technol.*, 2016, **6**, 3929.

24 For a review on 2-azabicyclo[3.3.1]nonanes (morphans), see: J. Bonjoch, F. Diaba and B. Bradshaw, *Synthesis*, 2011, 993.

Electronic Supplementary Material (ESI) for ChemComm.

Supporting information

for

Intramolecular radical non-reductive alkylation of ketones via transient enamines

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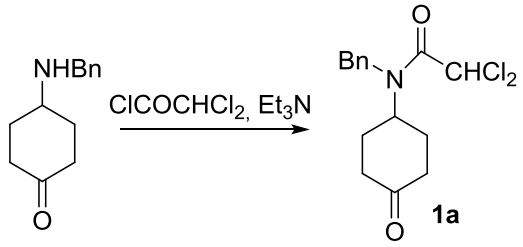
EXPERIMENTAL SECTION

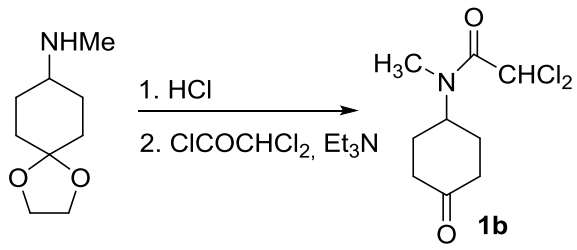
1. General information. ^{1}H and ^{13}C NMR spectra were recorded in $CDCl_3$ solution. Chemical shifts are reported as δ values (ppm) relative to internal Me_4Si and in benzene-D_6 (7.16 ppm), ^{13}C NMR spectra are referenced to the deuterated solvent signal ($CDCl_3$: 77.00 ppm) and benzene-D_6 (128.4 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). Drying of the organic extracts during reaction work-up was performed over anhydrous Na_2SO_4.

1. Synthesis of dichloroacetamides 1a-1g, 7 and 10

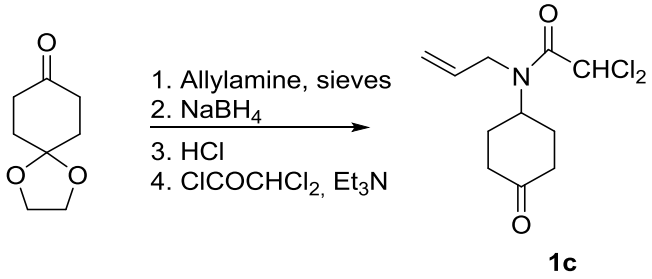


1a: To a solution of 4-(benzylamino)cyclohexan-1-one[1] (11 g, 54.11 mmol) and triethylamine (11.31 mL, 81.16 mmol) in CH_2Cl_2 (110 mL) was added dichloroacetyl chloride (6.24 mL, 64.93 mmol) dropwise at 0 ºC. The mixture was stirred at rt for 1 h then poured into water and extracted with CH_2Cl_2. The organic extracts were dried, concentrated and purified by chromatography (CH_2Cl_2/EtOAc 1:1) to yield **1a** as a white solid (10.5 g, 62%): mp 86-88 °C; IR (NaCl) 3088, 3062, 3029, 2956, 2873, 1716, 1670 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz, 2 rotamers) δ 1.82-2.02 (m, 2H), 2.02-2.20 (m, 2H), 2.36-2.56 (m, 4H), 4.59 and 4.62 (2 s, 2H), 4.80 (m, 1H), 6.08 and 6.39 (2 s, 1H), 7.14-7.46 (m, 5H, ArH); ^{13}C NMR ($CDCl_3$, 100 MHz, 2 rotamers) δ 28.6 and 30.0 (CH_2), 39.5 and 39.6 (CH_2), 45.8 and 47.4 (CH_2), 54.0 and 55.9 (CH), 64.9 and 66.5 (CH), 125.5 and 126.4 (CH), 127.2 and 128.2 (CH), 128.6 and 129.3 (CH), 136.1 and 137.3 (C), 163.8 and 164.8 (CO), 207.9 and 208.7 (CO); HRMS (ESI-TOF) m/z: $[M+H]^+$ calcd for $C_{15}H_{18}Cl_2NO_2$ 314.0709; found 314.0710.

[1] Diaba, F.; Pujol-Grau, C.; Martínez-Laporta, A.; Fernández, I.; Bonjoch, J. *Org. Lett.* **2015**, *17*, 568-571.



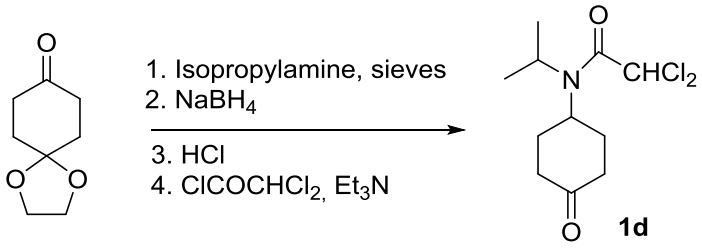
1b: A mixture of 4-(methylamino)cyclohexanone ethylene acetal[2] (3.82 g, 22.31 mmol) and 10% HCl solution (100 mL) was stirred at rt overnight. The mixture was basified with 10% NaOH solution and extracted with CH_2Cl_2. The organic extracts were dried, concentrated and the residue (1.3 g, 10.22 mmol) was treated with Et_3N (2.14 mL, 15.33 mmol) and dichloroacetyl chloride (1.18 mL, 12.26 mmol) in CH_2Cl_2 (15 mL) at 0 ºC then at rt for 1 h. The mixture was poured into water and extracted with CH_2Cl_2. The organic extracts were dried, concentrated and after chromatography (Al_2O_3, CH_2Cl_2) **1b** was isolated as a white solid (1.05 g, 43% over the 2 steps): mp 126-127 °C; IR (NaCl) 3004, 2953, 2873, 1716, 1664 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz, 2 rotamers) δ 1.84-2.24 (m, 4H), 2.42-2.62 (m, 4H), 2.88 and 3.07 (2 s, 3H), 4.67 and 4.85 (2 m, 1H), 6.27 and 6.29 (2 s, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz, 2 rotamers) δ 28.2 and 29.0 (CH_2), 28.6 and 30.0 (CH_3), 39.5 (CH_2), 52.4 and 54.9 (CH), 65.6 and 66.4 (CH), 163.2 and 163.5 (CO), 208.0 and 208.7 (CO); HRMS (ESI-TOF) m/z: $[M+H]^+$ calcd for $C_9H_{14}Cl_2NO_2$ 238.0396; found 238.0395.



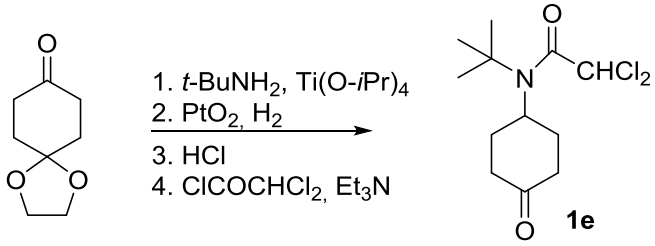
1c: A mixture of allylamine (1.6 mL, 20.81 mmol), 1,4-cyclohexanedione monoethylene acetal (2.5 g, 16.0 mmol) and 4 Å molecular sieves (2 g) in CH_2Cl_2 (10 mL) was stirred at rt for 4 h then filtered on a short celite pad and concentrated. The residue was treated with $NaBH_4$ (1.21 g, 19.2 mmol) in MeOH (20 ml) at 0 ºC then at rt for 1 h. The mixture was concentrated, quenched with water extracted with CH_2Cl_2. The organic extracts were dried, concentrated and the resulting viscous oil was treated with 10% HCl solution (30 mL) overnight. The mixture was basified with 10% NaOH solution and extracted with

[2] W. J. Greenlee, Y. Huang, J. M. Kelly, S. W. McCombie, A. Stamford and Y. Wu, in US 2005/0038100 A1, Schering-Plough Corp., USA, **2005**.

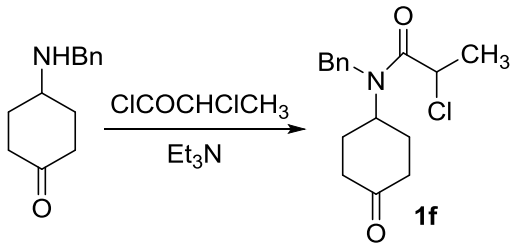
CH_2Cl_2. The organic extracts were dried, concentrated and the residue was treated with Et_3N (4.46 mL, 32.01 mmol) and dichloroacetyl chloride (2.67 mL, 24.01 mmol) in CH_2Cl_2 (25 mL) at 0 ºC then at rt for 1 h. The mixture was poured into water and extracted with CH_2Cl_2. The organic extracts were dried, concentrated and purified by chromatography (CH_2Cl_2) to yield **1c** as a white solid (1.3 g, 43% over the 4 steps): mp 84-86 °C; IR (NaCl) 3007, 2985, 2959,2923, 1717, 1665 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz, 2 rotamers) δ 1.84-2.26 (m, 4H), 2.40-2.60 (m, 4H), 3.88-4.04 (m, 2H), 4.66-4.86 (M, 1H), 5.12-5.38 (m, 2H), 5.76-5.96 (m, 1H), 6.20 and 6.31 (2 s, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz, 2 rotamers) δ 28.7 and 29.8 (2 CH_2), 39.6 (2 CH_2), 45.1 and 45.9 (CH_2), 53.3 and 55.6 (CH), 64.7 and 66.5 (CH), 116.9 and 117.5 (CH_2), 133.0 and 133.7 (CH), 162.9 and 164.5 (CO), 208.1 and 208.8 (CO); HRMS (ESI-TOF) m/z: $[M+H]^+$ calcd for $C_{11}H_{16}Cl_2NO_2$ 264.0553; found 264.0556.



1d: Operating as above from isopropylamine (2.15 mL, 24.97 mmol) and 1,4-cyclohexanedione monoethylene acetal (3 g, 18.6 mmol), **1d** was obtained as a white solid (1.72 g, 34% for the 4 steps): mp 133-135 °C; IR (NaCl) 3044, 3004, 2967, 2891, 1715, 1655 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz, 2 rotamers) δ 1.34 and 1.41 (2 d, J = 6.8 Hz, 6H), 1.85 and 2.23 (2 m, 2H), 2.06 and 2.83 (2 qd, J = 12.4, 5.2 Hz, 2H), 2.30-2.241 (m, 2H), 2.47-2.58 (m, 2H), 3.36-3.60 (m, 1H), 4.45-4.60 (m, 1H), 6.17 (s, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz, 2 rotamers) δ 19.6 and 20.3 (CH_3), 27.0 and 29.1 (CH_2), 39.5 (CH_2), 48.5 and 49.6 (CH), 52.6 and 55.9 (CH), 67.0 and 67.8 (CH), 162.0 and 162.4 (CO), 208.2 and 209.7 (CO); HRMS (ESI-TOF) m/z: $[M+H]^+$ calcd for $C_{11}H_{18}Cl_2NO_2$ 266.0709; found 266.0707.



1e: To a mixture of *t*-butylamine (4.04 mL, 38.42 mmol) and 1,4-cyclohexanedione monoethylene acetal (3 g, 19.2 mmol) was added titanium(IV) isopropoxide[3] (7.10 mL, 24.01 mmol) and the mixture was stirred at rt under argon atmosphere for 2.5 h. Ethanol (60 mL) and PtO_2 (0.3 g, 10%) were then added and the mixture was stirred under a hydrogen atmosphere (50 psi) and at rt overnight. The mixture was then filtered on a short celite pad and concentrated to yield a viscous oil which was treated with 10% HCl (38 ml) overnight. The mixture was basified with a saturated Na_2CO_3 solution and extracted with CH_2Cl_2. The organic extracts were dried, concentrated and the residue was treated with Et_3N (2.74mL , 19.67 mmol) and dichloroacetyl chloride (1.51 mL, 15.75 mmol) in CH_2Cl_2 (40 mL) at 0 ºC then at rt for 1 h. The mixture was poored into water and extracted with CH_2Cl_2. The organic extracts were dried, concentrated and purified by chromatography (CH_2Cl_2) to yield **1e** as a white solid (2.06 g, 38%). mp 183-184 °C; IR (NaCl) 3071, 2979, 2960, 2923, 2882, 1708, 1670 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz, 1 rotamer) δ 1.53 (s, 9H), 2.04-2.17 (m, 2H), 2.33-2.58 (m, 6H), 4.11 (br s, 1H), 6.28 (s, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz, 1 rotamer) δ 29.6 (CH_3), 30.5 (CH_2), 40.3 (CH_2), 55.1 (CH), 59.3 (C), 67.4 (CH), 166.5 (CO), 208.8 (CO); HRMS (ESI-TOF) m/z: $[M+H]^+$ calcd for $C_{12}H_{20}Cl_2NO_2$ 280.0866; found 280.0862.

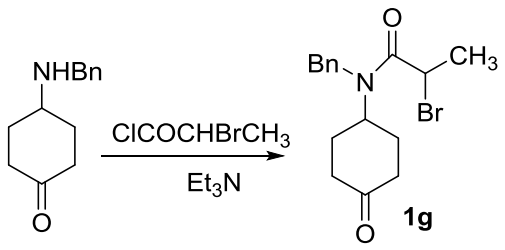


1f

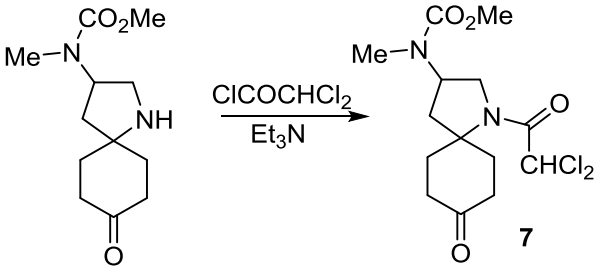
1f: To a solution of 4-(benzylamino)cyclohexanone (1g, 4.92 mmol), and triethylamine (1.03 mL, 7.38 mmol) in CH_2Cl_2 (10 mL) was added 2-chloropropionyl chloride (0.62 mL, 6.40 mmol) dropwise at 0 ºC. The mixture was stirred at rt for 1 h then poured into water and extracted with CH_2Cl_2. The organic extracts were dried, concentrated and purified by chromatography (CH_2Cl_2) to yield **1f** as a yellowish oil (1.1 g, 76%): IR (NaCl) 3087, 3061, 3030, 2954, 2871, 1716, 1653 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz, 2 rotamers) δ 1.63 (d, *J* = 6.4 Hz, 3H), 1.68-2.18 (m, 4H), 2.30-2.58 (m, 4H), 4.32-4.52 (m, 2H), 4.68-4.98 (m, 2H), 7.14-7.41 (m, 5H); ^{13}C NMR ($CDCl_3$, 100 MHz, 2 rotamers) δ 20.8 and 21.1 (CH_3), 28.8 and 30.2 (CH_2), 289.0 and 30.9 (CH_2), 39.6 and 39.7 (CH_2), 45.1 and 46.7 (CH_2), 50.0 and 50.1 (CH), 52.4 and 55.4 (CH), 125.3 and 126.4 (CH), 126.9 and 127.6 (CH), 128.4 and 129.0 (CH), 137.4 and 138.2 (C), 169.0 and 170.1 (CO), 208.1 and

[3] Palmer, J. T. et al. *J. Med. Chem.* **2005**, *48*, 7520-7534.

209.1 (CO); HRMS (ESI-TOF) m/z: $[M+H]^+$ calcd for $C_{16}H_{21}ClNO_2$ 294.1255; found 294.1254.



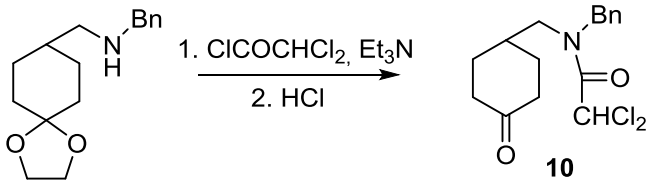
1g: To a solution of 4-(benzylamino)cyclohexanone (1g, 4.92 mmol) and triethylamine (1.03 mL, 7.38 mmol) in CH_2Cl_2 (10 mL) was added 2-bromopropionyl chloride (0.67 mL, 6.40 mmol) dropwise at 0 ºC. The mixture was stirred at rt for 1 h then poured into water and extracted with CH_2Cl_2. The organic extracts were dried, concentrated and purified by chromatography (CH_2Cl_2) to yield **1f** as a yellowish oil (1.01 g, 60%): IR (NaCl) 3087, 3060, 3029, 2956, 2871, 1716, 1652 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz, 2 rotamers) δ 1.65-1.77 (m, 0.9 H), 1.78 and 1.94 (2 d, *J* = 6.8 Hz, 3H, CH_3), 1.86-2.04 (m, 2H), 2.07-2.18 (m, 1.1 H), 2.31-2.59 (m, 4H), 4.32 (q, *J* = 6.8 Hz, 1H), 4.42 (d, *J* = 18.4 Hz, 1H), 4.80 (d, *J* = 18.4 Hz, 1H), 4.97 (tt, *J* = 12, 4 Hz, 1H), 7.12-7.41 (m, 5H); ^{13}C NMR ($CDCl_3$, 100 MHz, 2 rotamers) δ 21.4 and 21.9 (CH_3), 28.6 and 30.0 (CH_2), 29.1 and 31.1 (CH_2), 38.8 and 39.3 (CH), 39.7 (CH_2), 39.8 and 39.9 (CH_2), 45.2 and 47.0 (CH_2), 52.6 and 55.8 (CH), 125.2 and 126.5 (CH), 127.0 and 127.7 (CH), 128.6 and 129.1 (CH), 137.5 and 138.4 (C), 169.3 and 170.5 (CO), 208.2 and 209.3 (CO); HRMS (ESI-TOF) m/z: $[M+H]^+$ calcd for $C_{16}H_{21}BrNO_2$ 338.0750; found 338.0745.



7: To a solution of 3-[(Methoxycarbonyl)(methyl)amino]-1-azaspiro[4.5]deca-8-one[4] (0.3 g, 1.25 mmol) and triethylamine (0.26 mL, 1.87 mmol) in CH_2Cl_2 (10 mL) was added dichloroacetyl chloride (0.14 mL, 1.5 mmol) at 0 ºC. The mixture was stirred at rt for 1 h then poured into water and extracted with CH_2Cl_2. The organic extracts were dried, concentrated and purified by chromatography (CH_2Cl_2 to CH_2Cl_2/MeOH 99.5:0.5) to yield **7** as a white solid (0.31 g, 70%): mp 76-77 °C; IR (NaCl): 3010, 2955, 2913, 2886, 1713,

[4] Diaba, F.; Martínez-Laporta, A.; Bonjoch, J. *J. Org. Chem.* **2014**, *79*, 9365-9372.

1694, 1680, 1674 cm^{-1}; ^1H RMN (400 MHz): δ 1.72-1.85 (m, 2H), 2.04 (td, *J* = 12.4 Hz, 1.2 Hz, 1H), 2.28-2.40 (m, 2H), 2.44-2.54 (m, 2H), 2.68 (dtd, *J* = 15.6, 5.2, 1.6 Hz, 1H), 2.91 (s, 3H, CH_3N), 2.94 (m, 1H), 3.20 (td, *J* = 12.8, 5.2 Hz, 1H), 3.60 (t, *J* = 10 Hz, 1H, H-2), 3.76 (s, 3H, CH_3O), 4.01 (dd, *J* = 10, 8 Hz, 1H, H-2), 4.84 (br s, 1H, H-3), 6.05 (s, 1H, $CHCl_2$). ^{13}C RMN (100 MHz): δ 29.4 (CH_2 and CH_3), 33.0 (CH_2), 37.7 (CH_2), 38.2 (CH_2), 48.1 (CH_2), 52.0 (CH), 53.1 (CH_3), 65.2 (C), 66.8 (CH), 156.9 (CO), 161.8 (CO), 209.5 (CO); HRMS (ESI-TOF): Calcd for $C_{14}H_{21}Cl_2N_2O_4$ 351.0873 (M+1). Found 351.0877.



10: To a solution of 4-[(benzylamino)methyl]cyclohexanone ethylene acetal[5] (7.18 g, 27.47 mmol), and triethylamine (5.74 mL, 41.21 mmol) in CH_2Cl_2 (70 mL) was added dichloroacetyl chloride (3.17 mL, 32.96 mmol) dropwise at 0 ºC. The mixture was stirred at rt for 1 h then poured into water and extracted with CH_2Cl_2. The organic extracts were dried, concentrated and treated with 10% HCl (100 mL) and THF (10 mL) overnight. The mixture was extracted with CH_2Cl_2, the organic extracts were dried, concentrated and purified by chromatography (CH_2Cl_2) to yield **10** as a white solid (5.13 g, 58%): mp 99-101 °C; IR (NaCl) 3030, 2932, 2861, 1711, 1670 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz, 2 rotamers) δ 1.36-1.56 (m, 2H), 1.94-2.08 (m, 2H), 2.08-2.50 (m, 5H), 3.31 and 3.38 (2 d, *J* = 6.8 Hz, 2H), 4.71 and 4.77 (2 s, 2H), 6.21 and 6.35 (2 s, 1H), 7.15-7.45 (m, 5H, ArH); ^{13}C NMR ($CDCl_3$, 100 MHz, 2 rotamers) δ 30.1 (CH_2), 34.4 and 35.5 (CH), 40.2 (CH_2), 49.9 and 52.2 (CH_2), 51.7 and 51.9 (CH_2), 64.5 and 65.2 (CH), 126.3 and 127.8 (CH), 127.9 and 128.3 (CH), 128.9 and 129.3 (CH), 135.1 and 135.8 (C), 164.5 and 164.6 (CO), 209.8 and 210.9 (CO). HRMS (ESI-TOF) m/z: $[M+H]^+$ calcd for $C_{16}H_{20}Cl_2NO_2$ 328.0866; found 328.0889.

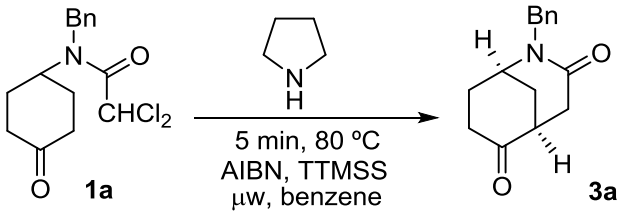
2. Synthesis of enamine 2

A mixture of **1a** (100 mg, 0.32 mmol) and pyrrolidine (0.027 mL, 0.32 mmol) in benzene (1 mL) was heated to reflux for 5 min then concentrated to yield enamine **2** as a yellowish oil. ^1H NMR (C_6D_6, 400 MHz, 2 rotamers) δ 1.38-1.64 (m, 6H), 1.88-2.10 (m, 2H), 2.10-2.30 (m, 2H), 2.66-2.86 (m, 4H), 4.02 (m, 1H, CH=), 4.19 and 4.76 (2 m, 1H), 4.40 (d, *J* = 15.2 Hz, 1H), 4.49 (d, *J* = 15.2 Hz, 1H), 5.94 and 6.16 (2 s, 1H), 6.85-7.25 (m, 5H,

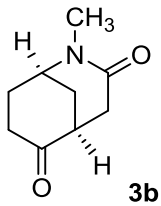
[5] Diaba, F.; Montiel, J. A.; Serban, G.; Bonjoch, J. *Org. Lett.* **2015**, *17*, 3860−3863.

ArH); ^{13}C NMR ($CDCl_3$, 100 MHz, 2 rotamers, some of the signals corresponding to the minor rotamer are not listed) δ 25.4 (CH_2), 28.1 (CH_2), 28.8 (CH_2), 29.7 (CH_2), 46.4 (CH_2), 47.84 (CH_2), 53.8 and 55.9 (CH), 66.5 and 67.3 (CH), 90.0 and 90.3 (CH=), 126.3 (CH), 127.4 and 127.5 (CH), 128.9 and 129.0 (CH), 129.5 (CH), 138.3 and 139.5 (C), 142.3 and 142.5 (C), 164.4 and 164.7 (CO).

3. Synthesis of morphans 3a-3f

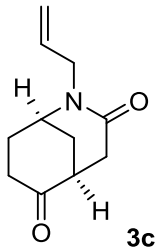


Typical procedure for the radical cyclization using microwave activation from 1a. In a 10 mL vessel were placed **1a** (200 mg, 0.64 mmol), pyrrolidine (0.266 mL, 3.18 mmol), AIBN (105 mg, 0.64 mmol) and TTMSS (0.39 mL, 1.27 mmol) in benzene (1 mL) and the mixture was heated with stirring to 80 ºC using microwave irradiation for 5 min. After chromatography (CH_2Cl_2) **3a**[6] was obtained as a white solid (120 mg, 77%)[7].



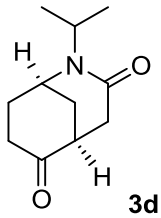
3b: IR (NaCl) 2942, 2880, 1708, 1624 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.81-1.91 (m, 1H, H-8ax), 2.11 (ddt, *J* = 13.6, 3.2, 2.4 Hz, 1H, H-9), 2.26 (dq, *J* = 13.6, 3.2 Hz, 1H, H-9), 2.29-2.38 (m, 1H, H-8eq), 2.38-2.44 (m, 2H, CH_2-7), 2.44 (d, *J* = 18.4 Hz, 1H, H-4), 2.70 (dd, *J* = 18.4, 6.8 Hz, 1H, H-4), 2.83 (m, 1H, H-5), 3.05 (s, 3H, CH_3), 3.67 (m, 1H, H-1); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 29.7 (C-8), 31.9 (C-9), 33.8 (CH_3), 33.9 (C-7), 35.0 (C-4), 44.4 (C-5), 53.3 (C-1), 168.4 (C-3), 210.8 (C-6); HRMS (ESI-TOF) m/z: $[M+H]^+$ calcd for $C_9H_{14}NO_2$ 168.1019; found 168.1017.

[6] For NMR data of **3a** see: Quirante, J.; Escolano, C.; Diaba, F.; Bonjoch, J. *J. Chem. Soc., Perkin Trans. 1* **1999**, 1157–1162.
[7] For the yields of **3b**-**3f** see the article.



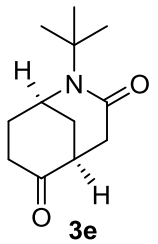
3c

3c: IR (NaCl) 2933, 2885, 2853, 1712, 1637 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.85 (tdd, *J* = 14, 5.6, 2.4 Hz, 1H, H-8ax), 2.13 (ddt, *J* = 13.6, 2.8, 2.4 Hz, 1H, H-9), 2.20 (dq, *J* = 13.6, 3.2 Hz, 1H, H-9), 2.27-2.35 (m, 1H, H-8eq), 2.35-2.53 (m, 3H, CH_2-7 and H-4), 2.74 (dd, *J* = 18.4, 7.2 Hz, 1H, H-4), 2.84 (m, 1H, H-5), 3.60 (dd, *J* = 15.2, 6.4 Hz, 1H), 3.74 (m, 1H, H-1), 4.61 (ddt, *J* = 15.2, 5.6, 1.2 Hz, 1H), 5.19-5.26 (m, 2H), 5.80-5.92 (m, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 30.2 (C-8), 32.2 (C-9), 34.0 (C-7), 34.9 (C-4), 44.2 (C-5), 48.1 (CH_2), 50.3 (C-1), 117.7 (CH_2), 132.9 (CH), 167.9 (C-3), 210.9 (C-6); HRMS (ESI-TOF) m/z: $[M+H]^+$ calcd for $C_{11}H_{16}NO_2$ 194.1176; found 194.1168.



3d

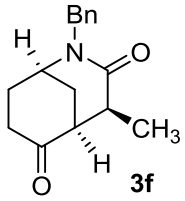
3d: mp 114-115 °C; IR (NaCl) 2966, 2942, 2873, 1714, 1620 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.27 (d, *J* = 6.8 Hz, 3H, CH_3), 1.30 (d, *J* = 6.8 Hz, 3H, CH_3), 1.93 (tdd, *J* = 13.6, 4.8, 2.4 Hz, 1H, H-8ax), 2.08 (dq, *J* = 13.2, 3.2 Hz, 1H, H-9), 2.14 (dq, *J* = 13.2, 2 Hz, 1H, H-9), 2.19-2.29 (m, 1H, H-8eq), 2.36 (dd, *J* = 15.6, 4.8 Hz, 1H, H-7), 2.45 (dd, *J* = 18.8, 1.2 Hz, 1H, H-4), 2.56 (ddd, *J* = 15.6, 14, 6.8 Hz, 1H, H-7), 2.71 (dd, *J* = 18.8, 7.6 Hz, 1H, H-4), 2.79 (m, 1H, H-5), 3.82 (br s, 1H, H-1), 4.64 (sept, *J* = 6.8 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 20.0 (CH_3), 20.7 (CH_3), 33.0 (C-8), 33.4 (C-9), 33.8 (C-7), 35.4 (C-4), 43.7 (C-5), 47.0 (C-1), 47.4 (CH), 167.9 (C-3), 211.2 (C-6); HRMS (ESI-TOF) m/z: $[M+H]^+$ calcd for $C_{11}H_{18}NO_2$ 196.1332; found 196.1332.



3e

3e: mp 133-135 °C; IR (NaCl) 2990, 2959, 2943, 2913, 2870, 1716, 1622 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.54 (s, 9H, CH_3), 1.93 (tdd, *J* = 14, 5.2, 2.8 Hz, 1H, H-8ax), 2.08-

2.19 (m, 2H, CH_2-9), 2.19-2.27 (m, 1H, H-8eq), 2.34 (dd, *J* = 15.2, 5.2 Hz, 1H, H-7), 2.37-2.45 (m, 1H, H-4), 2.53 (ddd, *J* = 15.2, 14, 6.8 Hz, 1H, H-7), 2.68-2.76 (m, 2H, H5 and H-4), 4.09 (m, 1H, H-1); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 28.7 (CH_3), 33.2 (C-7), 33.7 (C-8 and C-9), 37.1 (C-4), 43.8 (C-5), 47.4 (C-1), 58.0 (C), 168.5 (C-3), 211.3 (C-6); HRMS (ESI-TOF) m/z: $[M+H]^+$ calcd for $C_{12}H_{20}NO_2$ 210.1489; found 210.1487.

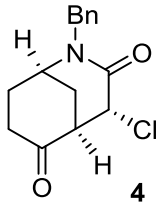


3f

3f: mp 189-191 °C; IR (NaCl) 3062, 3029, 2961, 2936, 2870, 1710, 1635 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.22 (d, *J* = 6.8 Hz, 3H, CH_3), 1.74 (ddd, *J* = 13.2, 5.2, 2.4 Hz, 1H, H-8ax), 2.07 (dt, *J* = 13.2, 2.4 Hz, 1H, H-9), 2.14-2.26 (m, 2H, H-8eq and H-9), 2.27-2.34 (m, 1H, H-7), 2.40 (dd, *J* = 15.2, 4.8 Hz, 1H, H-7), 2.78 (m, 2H, H-4 and H-5), 3.68 (br s, 1H, H-1), 4.04 (d, *J* = 15 Hz, 1H), 5.35 (d, *J* = 15 Hz, 1H), 7.25-7.38 (m, 5H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 14.5 (CH_3), 29.3 (C-8), 32.9 (C-9), 35.1 (C-7), 39.4 (C-4), 48.5 (CH_2), 50.6 (C-1 and C-5), 127.6 (CH), 127.9 (CH), 128.8 (CH), 137.4 (C), 171.9 (C-3), 210.5 (C-6); HRMS (ESI-TOF) m/z: $[M+H]^+$ calcd for $C_{16}H_{20}NO_2$ 258.1489; found 258.1485.

4. Obtention of 4

In a 10 mL vessel were placed **1a** (100 mg, 0.32 mmol), pyrrolidine (0.13 mL, 1.59 mmol) and benzene (1 mL) and the mixture was heated with stirring to 80 ºC using microwave irradiation for 5 min. The mixture was then purified by chromatography (CH_2Cl_2) to provide recovered **1a** (31 mg, 31%) and **4** (6 mmg, 7%) as a white solid.

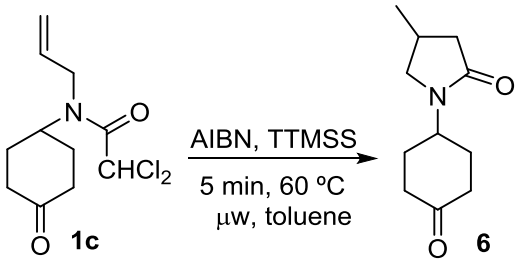


4

4: mp 85-87 °C; IR (NaCl) 3065, 3055, 3031, 2944, 2932, 2875, 2864, 2852, 1714, 1652 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.81 (tdd, *J* = 12.8, 5.6, 2.4 Hz, 1H, H-8ax), 1.99 (dm, *J* = 14.4 Hz, 1H, H-9), 2.17-2.26 (m, 1H, H-8eq), 2.35 (ddd, *J* = 16.4, 12.8, 7.2 Hz, 1H, H-7ax), 2.49 (dd, *J* = 16.4, 6 Hz, 1H, H-7eq), 2.70 (dq, *J* = 14.4, 3.2 Hz, 1H, H-9), 3.08 (br s, 1H, H5), 3.73 (br s, 1H, H-1), 4.03 (d, *J* = 15 Hz, 1H), 4.37 (t, *J* = 1.6 Hz, 1H, H-4), 5.39 (d, *J* = 15 Hz, 1H), 7.28-7.40 (m, 5H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 27.5 (C-9),

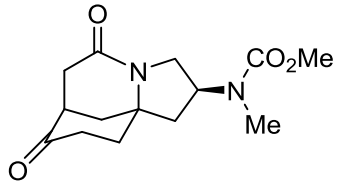
28.9 (C-8), 35.0 (C-7), 48.5 (CH_2), 50.3 (C-1), 53.4 (C-5), 54.1 (C-4), 127.8 (CH), 128.0 (CH), 129.0 (CH), 136.3 (C), 165.7 (C-3), 206.7 (C-6); HRMS (ESI-TOF) m/z: $[M+H]^+$ calcd for $C_{15}H_{17}ClNO_2$ 178.0942; found 178.0937.

5. Synthesis of 6



In a 10 mL vessel were placed **1c** (100 mg, 0.38 mmol), AIBN (63 mg, 0.38 mmol) and TTMSS (0.23 mL, 0.76 mmol) in toluene (1 mL) and the mixture was heated with stirring to 60 ºC using microwave irradiation for 5 min. After chromatography (CH_2Cl_2 to AcOEt) **6** was obtained as a white solid (42 mg, 57%). mp 70-71 °C; IR (NaCl) 2957, 2872, 1715, 1668 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 1.13 (d, J = 7.2 Hz, 3H, CH_3), 1.78-1.93 (m, 2H), 1.98-2.09 (m, 3H), 2.38-2.62 (m, 6H), 2.89 (dd, J = 9.6, 6 Hz, 1H), 3.46 (dd, J = 9.6, 7.6 Hz, 1H), 4.48 (tt, J = 12, 4 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 19.7 (CH_3), 26.6 (CH), 29.2 (CH_2), 29.3 (CH_2), 39.6 (CH_2), 48.2 (CH), 50.0 (CH_2), 174.2 (CO), 209.3 (CO); HRMS (ESI-TOF) m/z: $[M+H]^+$ calcd for $C_{11}H_{18}NO_2$ 196.1332; found 196.1334.

6. Synthesis of 8

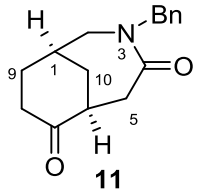


8

In a 10 mL vessel were placed **7** (100 mg, 0.28 mmol), pyrrolidine (0.12 mL, 1.43 mmol), AIBN (47 mg, 0.29 mmol) and TTMSS (0.18 mL, 0.57 mmol) in toluene (0.5 mL) and the mixture was heated with stirring to 60 ºC using microwave irradiation for 5 min. After chromatography (CH_2Cl_2 to CH_2Cl_2/AcOEt/MeOH 49.5:49.5:1) **8** (27 mg, 34%) then **9** (11 mg, 14%) were isolated.[8]

[8] For NMR data of **8** and **9** see ref. 4.

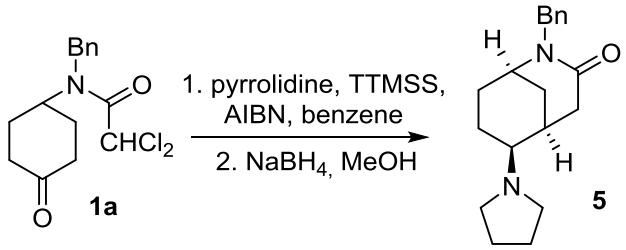
7. Synthesis of 11



11

In a 10 mL vessel were placed **10** (100 mg, 0.30 mmol), pyrrolidine (0.13 mL, 1.52 mmol), AIBN (50 mg, 0.30 mmol) and TTMSS (0.19 mL, 0.61 mmol) in benzene (1 mL) and the mixture was heated with stirring to 80 ºC using microwave irradiation for 5 min. After chromatography (CH_2Cl_2 to CH_2Cl_2/AcOEt 1:1) **11** was obtained (40 mg, 51%) as a white solid. mp 200-202 °C; IR (NaCl) 3060, 3029, 2928, 2868, 1708, 1641 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 1.64-1.72 (m, 1H, H-9), 1.85-2.02 (m, 3H, H-9 and CH_2-10), 2.05 (br s, 1H, H-1), 2.33 (ddd, *J* = 17, 7.6, 2.8 Hz, 1H, H-8), 2.54 (ddd, *J* = 17, 10.8, 8.4 Hz, 1H, H-8), 2.77 (br s, 1H, H-6), 2.76-2.90 (m, 2H, CH_2-5), 3.44 (m, 2H, CH_2-2), 4.49 (d, *J* = 14.8 Hz, 1H, CH_2Ar), 4.79 (d, *J* = 14.8 Hz, 1H, CH_2Ar), 7.27-7.36 (m, 5H, ArH); ^{13}C NMR ($CDCl_3$, 100 MHz) 27.3 (C-9), 27.8 (C-1), 33.6 (C-10), 34.7 (C-8), 38.5 (C-5), 42.2 (C-6), 50.8 (C-2), 51.7 (CH_2Ar), 127.7 (CH), 128.5 (CH), 128.7 (CH), 137.2 (C), 171.7 (C-4), 211.6 (C-7); HRMS (ESI-TOF) m/z: $[M+H]^+$ calcd for $C_{16}H_{20}NO_2$ 258.1489; found 258.1487.

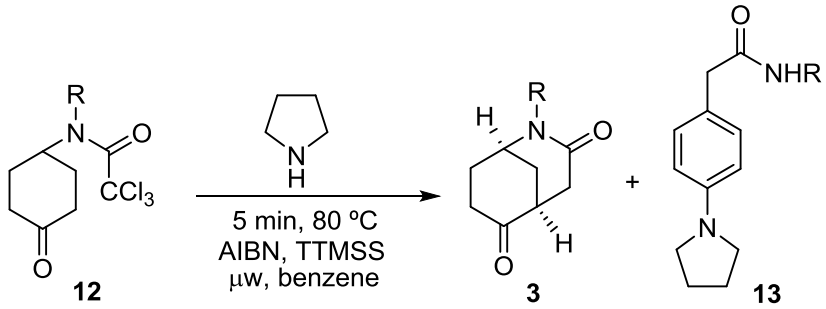
8. Synthesis of 5



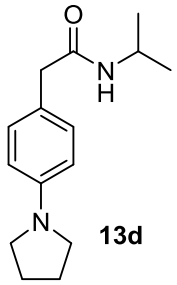
In a 10 mL vessel were placed **1a** (200 mg, 0.64 mmol), pyrrolidine (0.266 mL, 3.18 mmol), AIBN (105, 0.64 mmol) and TTMSS (0.39 mL, 1.27 mmol) in benzene (1 mL) and the mixture was heated with stirring to 80 ºC using microwave irradiation for 5 min. MeOH (0.5 mL) was added and the mixture was treated with $NaBH_4$ (25 mg, 0.64 mmol) at 0 ºC then at rt for 1 h. The reaction mixture was concentrated, water was added and the mixture extracted with CH_2Cl_2. The organic extracts were dried, concentrated and purified by chromatography (CH_2Cl_2 to (CH_2Cl_2,NH_3)/MeOH 9.5:0.5) to yield **5** as a white

solid (115 mg, 61%).[9] mp 89-91 °C; IR (NaCl) 3029, 2932, 2872, 2777, 1634 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 1.32-1.48 (m, 2H, H-7 and H-8), 1.64 (dd, *J* = 13.2, 2 Hz, 1H, H-9), 1.77 (br s, 6H), 1.91 (dq, *J* = 13.2, 2.8 Hz, 1H, H-9), 2.16 (br s, 1H, H-6), 2.35 (br s, 1H, H-5), 2.44 (dd, *J* = 18, 7.2 Hz, 1H, H-4), 2.56 (br s, 4H), 2.98 (d, *J* = 18 Hz, 1H, H-4), 3.41 (br s, 1H, H-1), 3.95 (d, *J* = 15.2 Hz, 1H), 5.23 (d, *J* = 15.2 Hz, 1H), 7.22-7.34 (m, 5H, ArH); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 22.9 (C-7), 23.3 (CH_2), 27.9 (C-8), 30.8 (C-5), 31.3 (C-4), 31.5 (C-9), 48.2 (CH_2), 50.6 (C-1), 51.5 (CH_2), 66.0 (C-6), 127.2 (CH), 127.8 (CH), 128.5 (CH), 137.9 (C), 171.0 (C-3); HRMS (ESI-TOF) m/z: $[M+H]^+$ calcd for $C_{19}H_{27}N_2O$ 299.2118; found 299.2125.

9. Radical cyclization from trichloroacetamides 12a-12d



Typical procedure for the radical cyclization using microwave activation from 12d. In a 10 mL vessel were placed **12d** (100 mg, 0.33 mmol), pyrrolidine (0.14 mL, 1.66 mmol), AIBN (54.6 mg, 0.33 mmol) and TTMSS (0.20 mL, 0.66 mmol) in benzene (1 mL) and the mixture was heated with stirring to 80 ºC using microwave irradiation for 5 min. After chromatography (CH_2Cl_2) **13d** (14 mg, 16%) was isolated then **2d** (37 mg, 57%).[10]

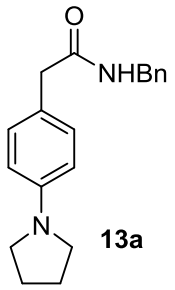


13d

13d: IR (NaCl) 3249, 3069, 2960, 2929, 2870, 2818, 1643, 1617 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 1.04 (d, *J* = 6.8 Hz, 6H, CH_3), 2.01 (m, 4H), 3.29 (m, 4H), 3.44 (s, 2H), 4.05 (m, 1H), 5.21 (br s, 1H, NH), 6.54 (d, *J* = 8.4 Hz, 2H), 7.06 (d, *J* = 8.4 Hz, 2H); ^{13}C NMR

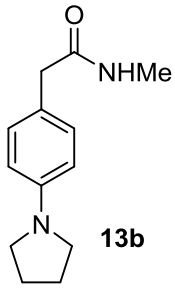
[9] The other epimer at C-6 was observed as traces in some fractions but was not isolated.
[10] For the products obtained with the other substrates and their yields see the article.

($CDCl_3$, 100 MHz) δ 22.6 (CH_3), 25.4 (CH_2), 41.2 (CH), 43.1 (CH_2), 47.6 (CH_2), 112.1 (CH), 121.1 (C), 130.3 (CH), 147.1 (C), 171.4 (CO); HRMS (ESI-TOF) m/z: $[M+H]^+$ calcd for $C_{15}H_{23}N_2O$ 247.1804; found 247.1799.



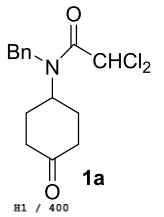
13a

13a: ^1H NMR ($CDCl_3$, 400 MHz) δ 1.98-2.02 (m, 4H), 3.24-3.30 (m, 4H), 3.55 (s, 2H), 4.40 (d, *J* = 6 Hz, 2H), 5.75 (br s, 1H, NH), 6.53 (d, *J* = 8.4 Hz, 2H), 7.09 (d, *J* = 8.4 Hz, 2H), 7.15-7.32 (m, 5H, ArH); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 25.4 (CH_2), 42.9 (CH_2), 43.4 (CH_2), 47.6 (CH_2), 112.1 (CH), 119.9 (C), 127.3 (CH), 127.4 (CH), 128.6 (CH), 130.4 (CH), 138.4 (C), 147.2 (C), 172.2 (CO); HRMS (ESI-TOF) m/z: $[M+H]^+$ calcd for $C_{19}H_{23}N_2O$ 295.1805; found 295.1796.

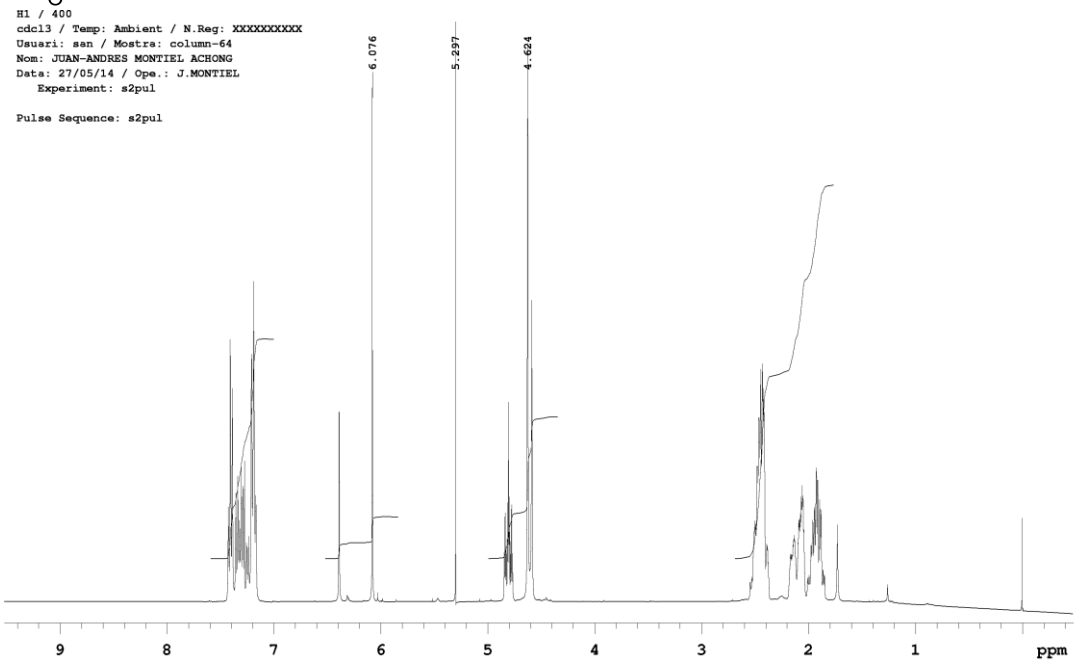


13b

13b: IR (NaCl) 3292, 3094, 2964, 2926, 2850, 2822, 1646, 1617 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 2.01 (m, 4H), 2.73 (d, *J* = 4.8 Hz, 3H, CH_3), 3.28 (m, 4H), 3.48 (s, 2H), 5.38 (br s, 1H, NH), 6.54 (d, *J* = 8.4 Hz, 2H), 7.07 (d, *J* = 8.4 Hz, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 25.5 (CH_2), 26.4 (CH_3), 42.8 (CH_2), 47.6 (CH_2), 112.1 (CH), 121.0 (C), 130.5 (CH), 147.3 (C), 172.9 (CO); HRMS (ESI-TOF) m/z: $[M+H]^+$ calcd for $C_{13}H_{19}N_2O$ 219.1492; found 219.1489.


O
Bn
N
CHCl2
O

1a


H1 / 400
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Usuari: san / Mostra: column-64
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Data: 27/05/14 / Ope.: J.MONTIEL
Experiment: s2pul
Pulse Sequence: s2pul
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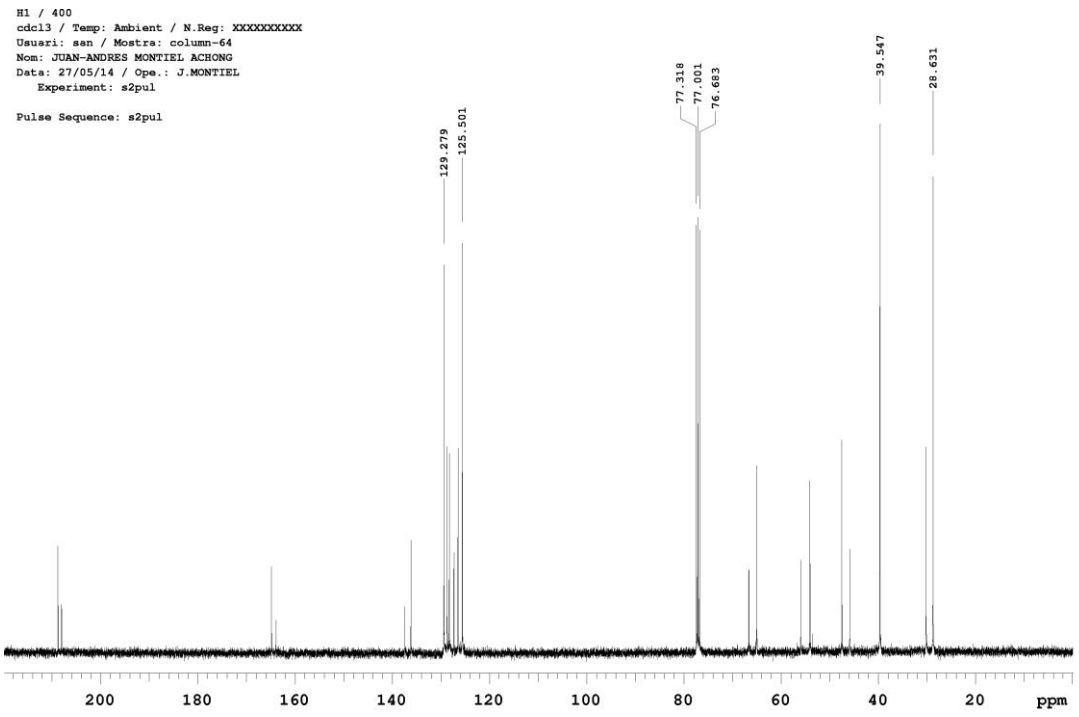
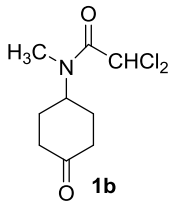
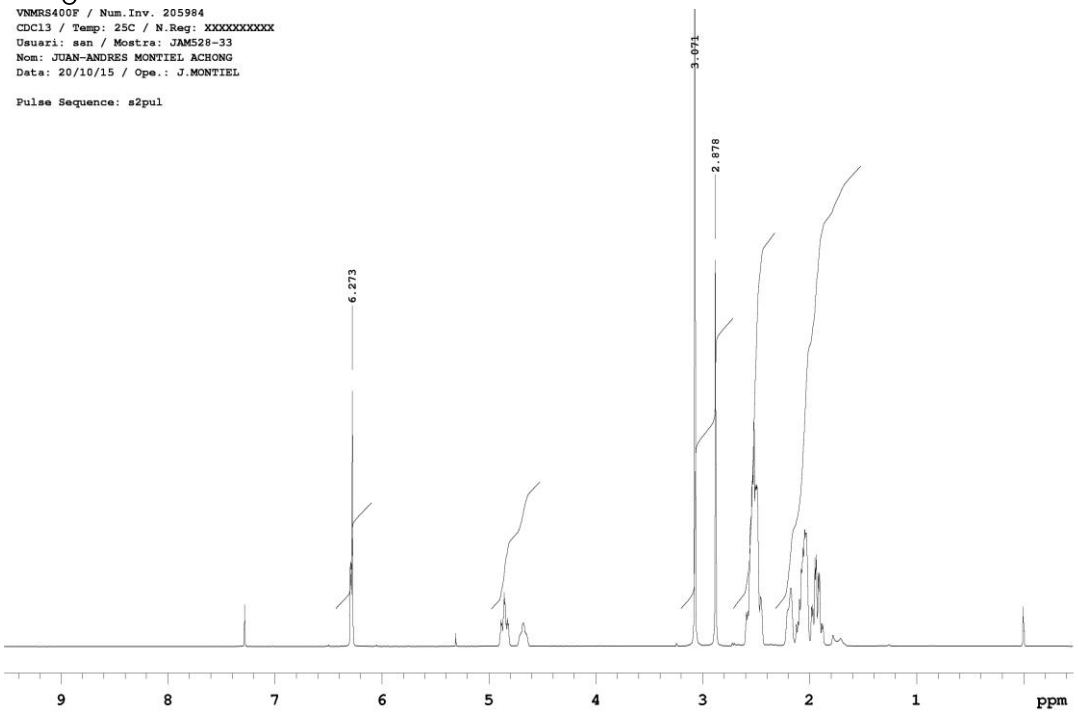
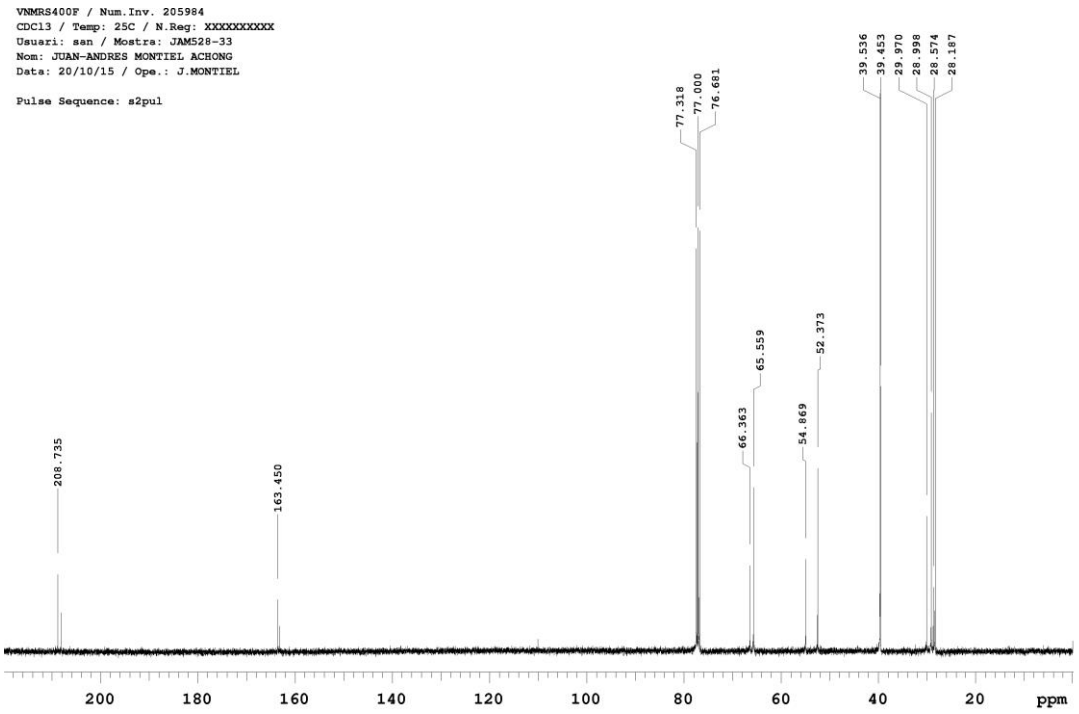
5.297
4.624
9
8
7
6
5
4
3
2
1
ppm


H1 / 400
cdcl3 / Temp: Ambient / N.Reg: XXXXXXXXXX
Usuari: san / Mostra: column-64
Nom: JUAN-ANDRES MONTIEL ACHONG
Data: 27/05/14 / Ope.: J.MONTIEL
Experiment: s2pul
Pulse Sequence: s2pul
129.279
125.501
77.318
77.001
76.683
39.547
28.631
200
180
160
140
120
100
80
60
40
20
ppm


O
H3C
N
CHCl2
O

1b


VNMRS400F / Num.Inv. 205984
CDCl3 / Temp: 25C / N.Reg: XXXXXXXXXX
Usuari: san / Mostra: JAM528-33
Nom: JUAN-ANDRES MONTIEL ACHONG
Data: 20/10/15 / Ope.: J.MONTIEL
Pulse Sequence: s2pul
3.071
2.878
6.273
9
8
7
6
5
4
3
2
1
ppm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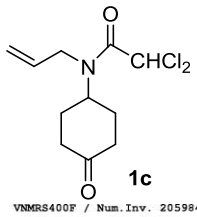
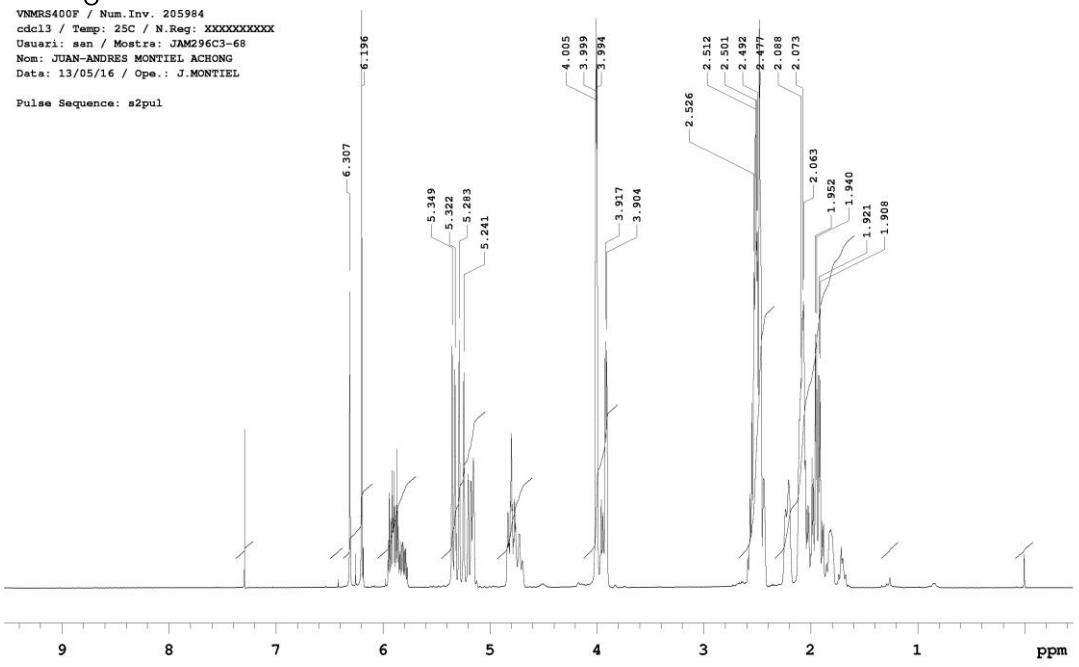
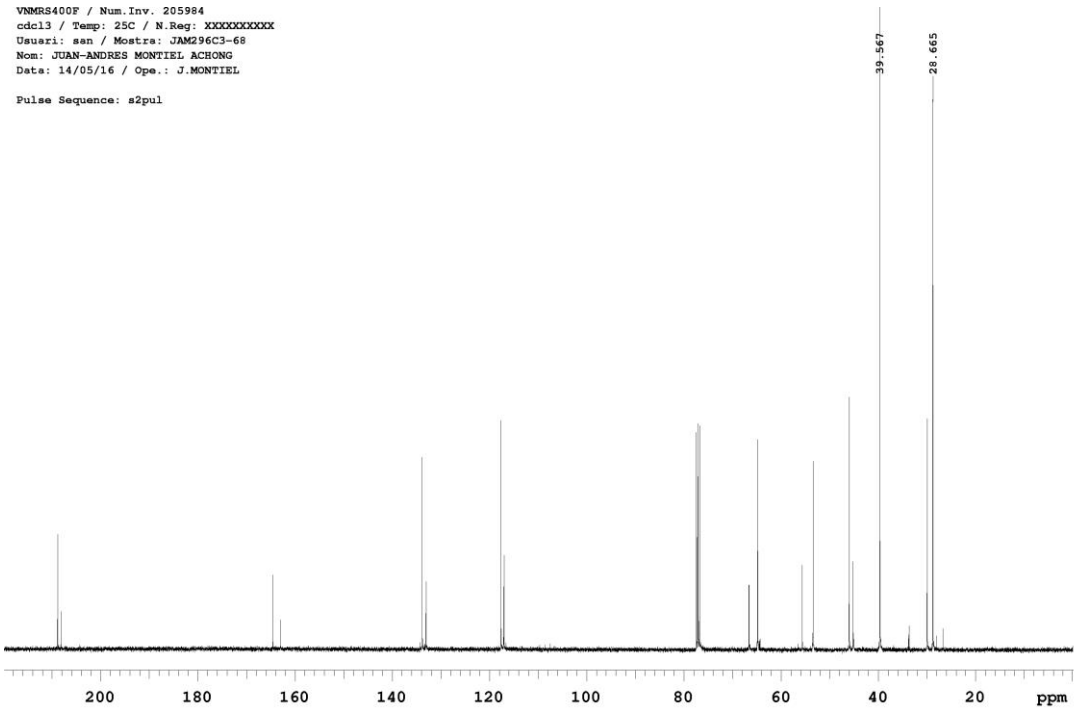
CDCl3 / Temp: 25C / N.Reg: XXXXXXXXXX
Usuari: san / Mostra: JAM528-33
Nom: JUAN-ANDRES MONTIEL ACHONG
Data: 20/10/15 / Ope.: J.MONTIEL
Pulse Sequence: s2pul
39.536
39.453
29.970
28.998
28.574
28.187
77.318
77.000
76.681
65.559
52.373
66.363
54.869
208.735
163.450
200
180
160
140
120
100
80
60
40
20
ppm


O
N
CHCl2
O

1c


VNMRS400F / Num.Inv. 205984
cdcl3 / Temp: 25C / N.Reg: XXXXXXXXXX
Usuari: san / Mostra: JAM296C3-68
Nom: JUAN-ANDRES MONTIEL ACHONG
Data: 13/05/16 / Ope.: J.MONTIEL
Pulse Sequence: s2pul
6.307
6.196
5.349
5.322
5.283
5.241
4.005
3.999
3.994
3.917
3.904
2.526
2.512
2.501
2.492
2.477
2.088
2.073
2.063
1.952
1.940
1.921
1.908
9
8
7
6
5
4
3
2
1
ppm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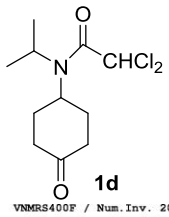
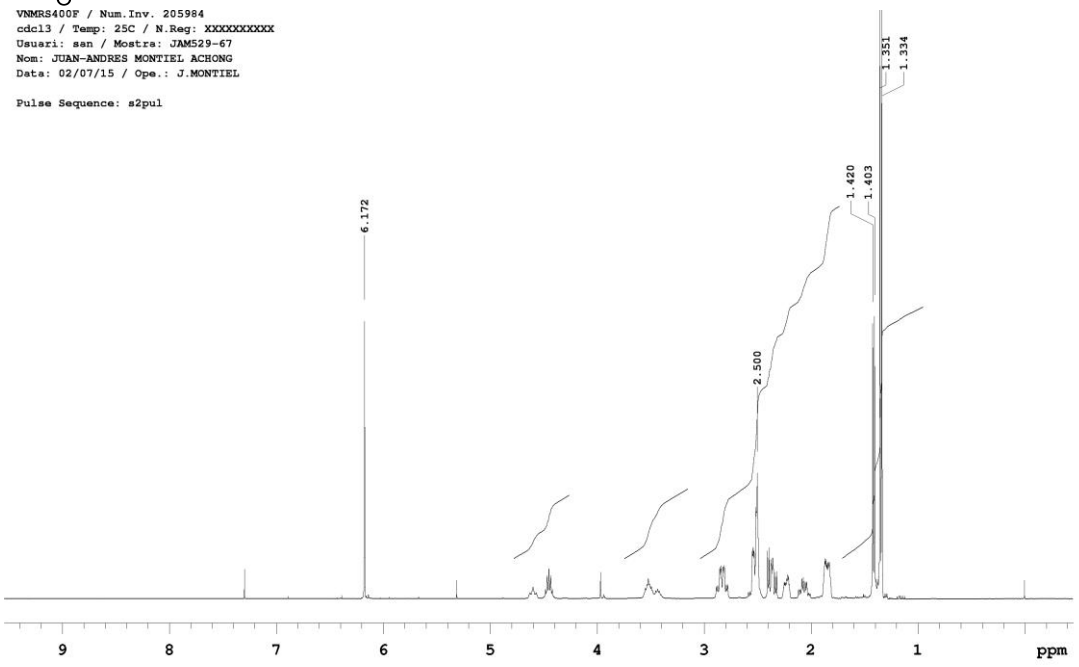
cdcl3 / Temp: 25C / N.Reg: XXXXXXXXXX
Usuari: san / Mostra: JAM296C3-68
Nom: JUAN-ANDRES MONTIEL ACHONG
Data: 14/05/16 / Ope.: J.MONTIEL
Pulse Sequence: s2pul
39.567
28.665
200
180
160
140
120
100
80
60
40
20
ppm


O
N
CHCl2
O

1d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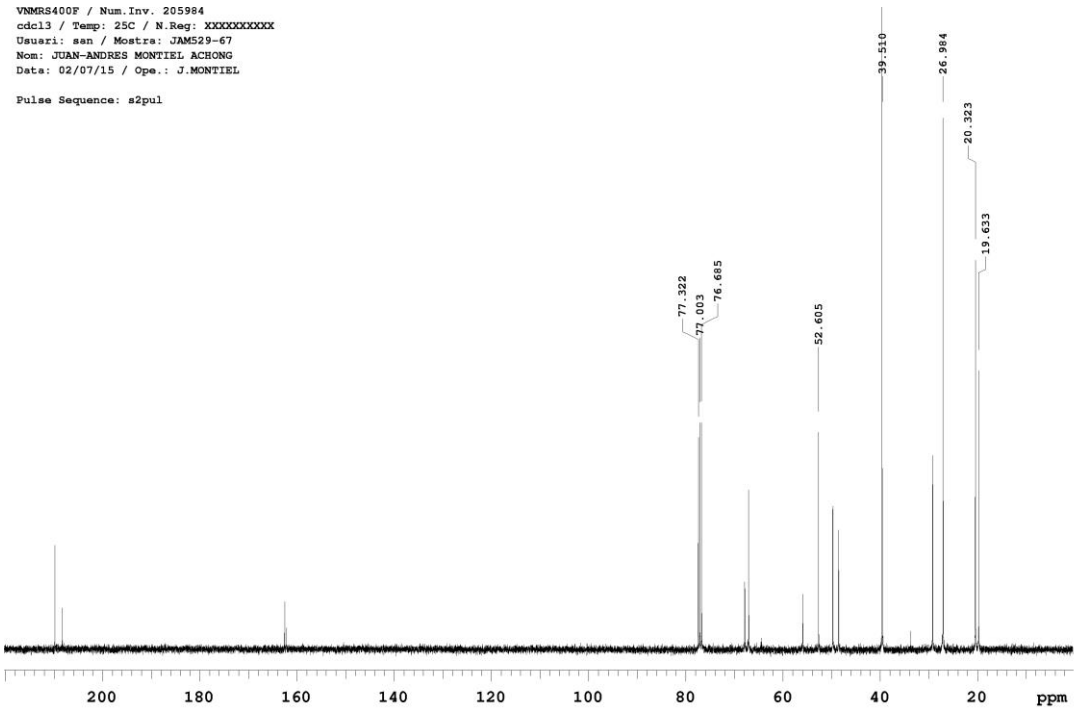
cdcl3 / Temp: 25C / N.Reg: XXXXXXXXXX
Usuari: san / Mostra: JAM529-67
Nom: JUAN-ANDRES MONTIEL ACHONG
Data: 02/07/15 / Ope.: J.MONTIEL
Pulse Sequence: s2pul
6.172
2.500
1.420
1.403
1.351
1.334
9
8
7
6
5
4
3
2
1
ppm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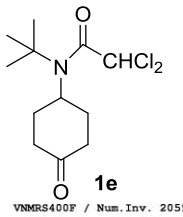
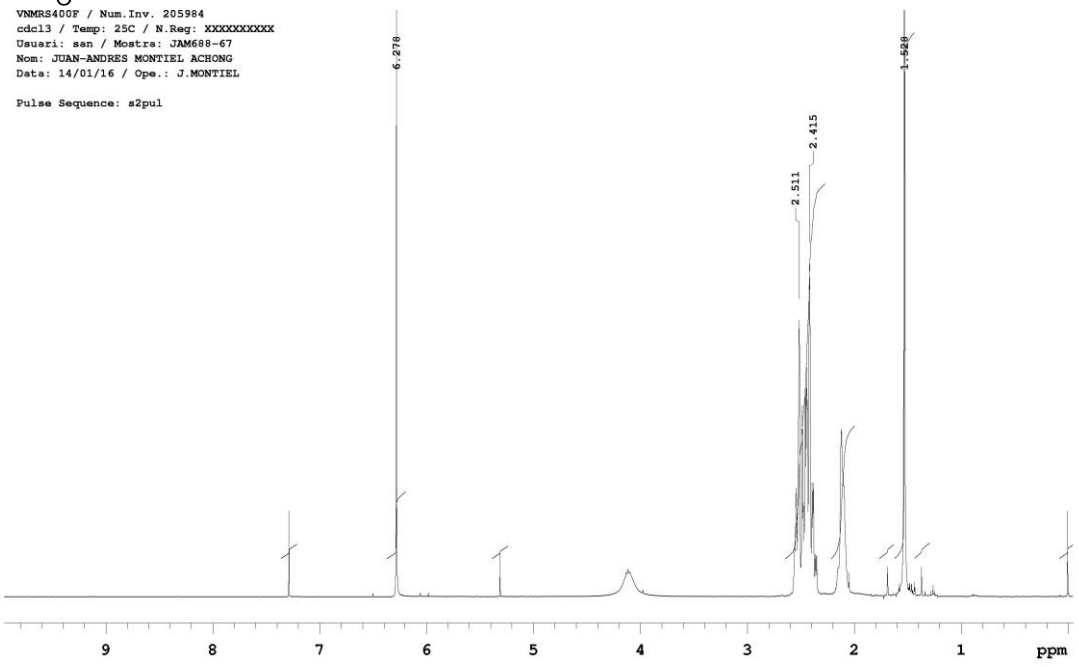
cdcl3 / Temp: 25C / N.Reg: XXXXXXXXXX
Usuari: san / Mostra: JAM529-67
Nom: JUAN-ANDRES MONTIEL ACHONG
Data: 02/07/15 / Ope.: J.MONTIEL
Pulse Sequence: s2pul
77.322
77.003
76.685
52.605
39.510
26.984
20.323
19.633
200
180
160
140
120
100
80
60
40
20
ppm


O
N
CHCl2
O

1e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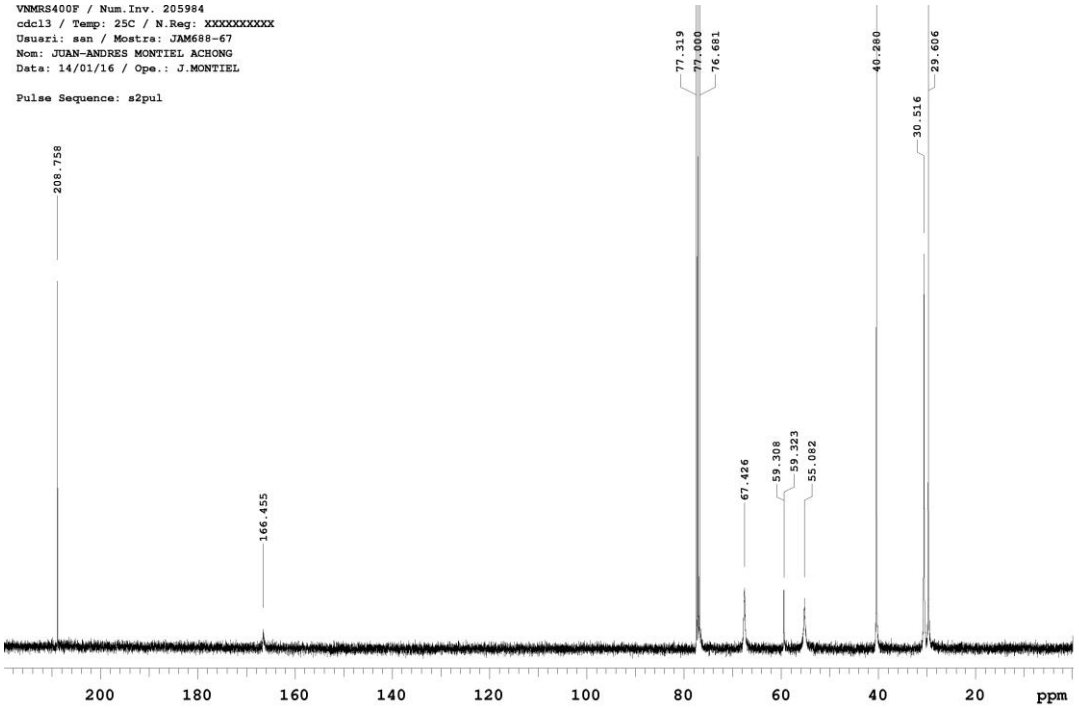
cdcl3 / Temp: 25C / N.Reg: XXXXXXXXXX
Usuari: san / Mostra: JAM688-67
Nom: JUAN-ANDRES MONTIEL ACHONG
Data: 14/01/16 / Ope.: J.MONTIEL
Pulse Sequence: s2pul
6.270
2.511
2.415
1.528
9
8
7
6
5
4
3
2
1
ppm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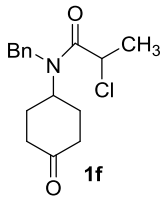
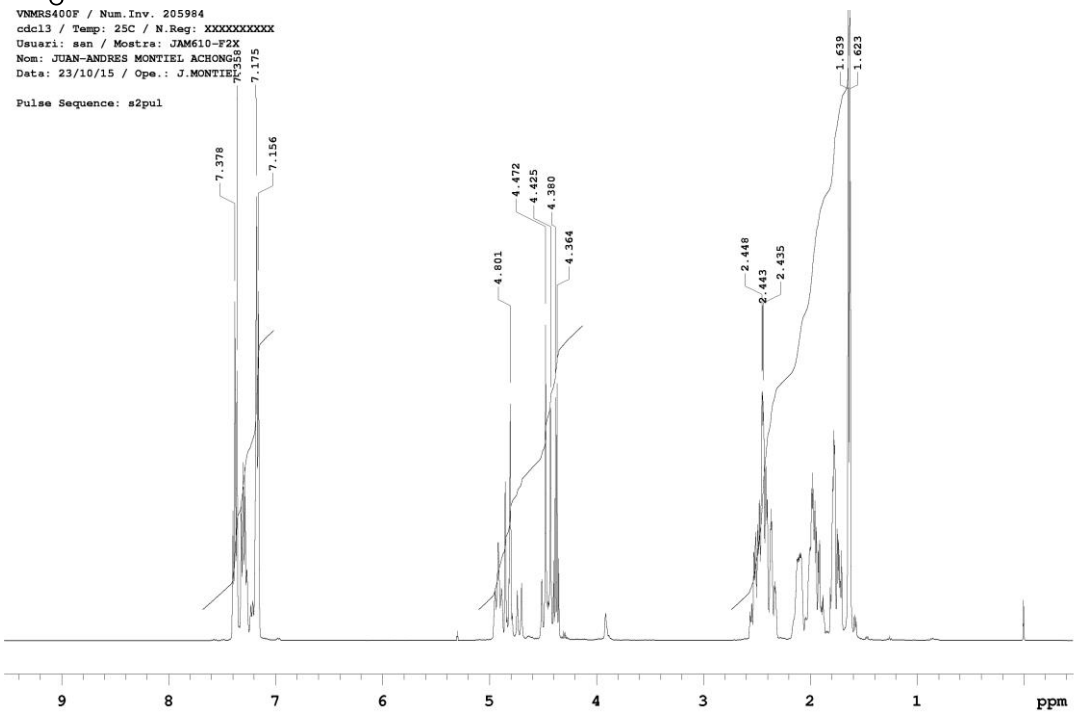
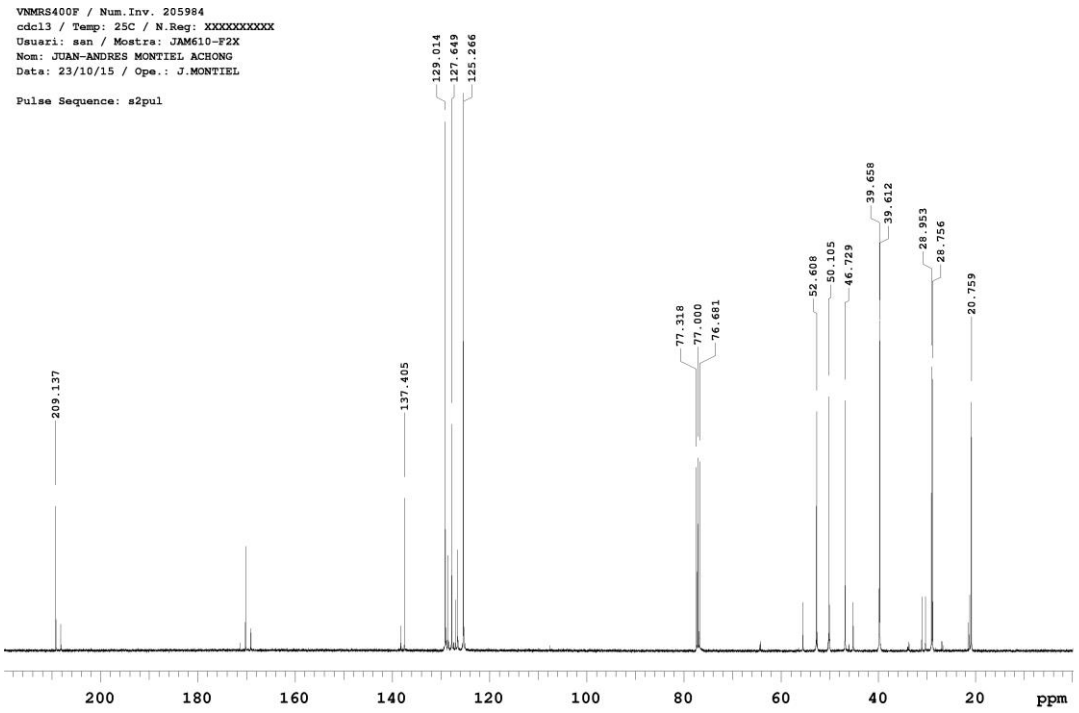
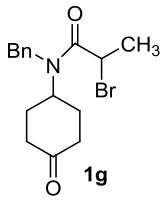
cdcl3 / Temp: 25C / N.Reg: XXXXXXXXXX
Usuari: san / Mostra: JAM688-67
Nom: JUAN-ANDRES MONTIEL ACHONG
Data: 14/01/16 / Ope.: J.MONTIEL
Pulse Sequence: s2pul
208.758
166.455
77.319
77.000
76.681
67.426
59.308
59.323
55.082
40.280
30.516
29.606
200
180
160
140
120
100
80
60
40
20
ppm


O
Bn
N
CH3
Cl
O

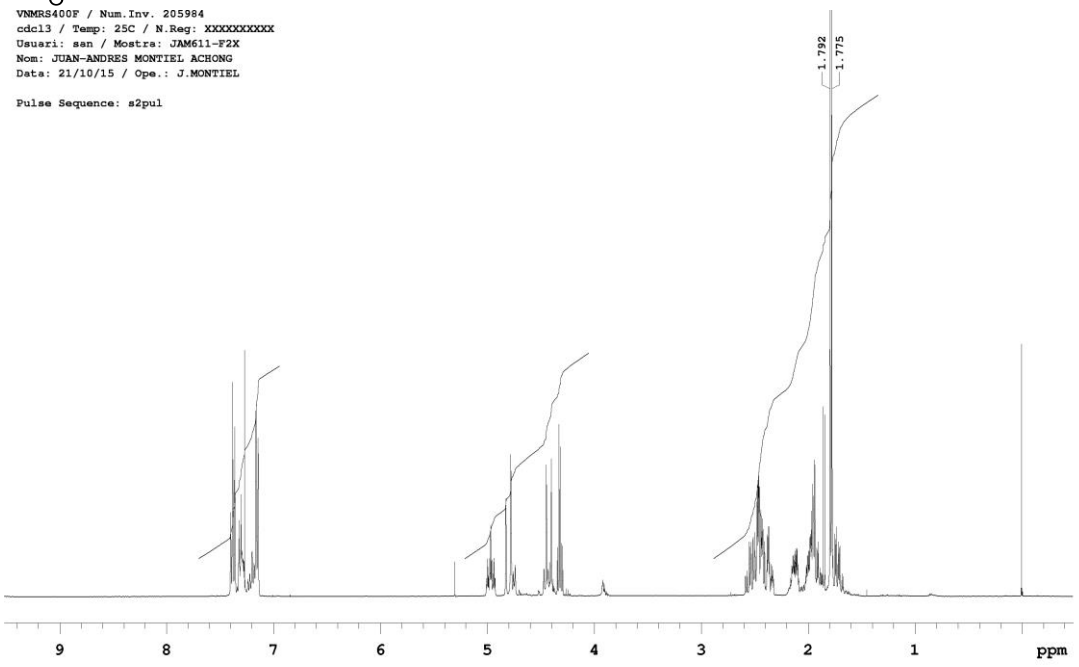
1f


VNMRS400F / Num.Inv. 205984
cdcl3 / Temp: 25C / N.Reg: XXXXXXXXXX
Usuari: san / Mostra: JAM610-F2X
Nom: JUAN-ANDRES MONTIEL ACHONG
Data: 23/10/15 / Ope.: J.MONTIEL
Pulse Sequence: s2pul
7.378
7.175
7.156
4.472
4.425
4.380
4.364
4.801
2.448
2.443
2.435
1.639
1.623
9
8
7
6
5
4
3
2
1
ppm


VNMRS400F / Num.Inv. 205984
cdcl3 / Temp: 25C / N.Reg: XXXXXXXXXX
Usuari: san / Mostra: JAM610-F2X
Nom: JUAN-ANDRES MONTIEL ACHONG
Data: 23/10/15 / Ope.: J.MONTIEL
Pulse Sequence: s2pul
209.137
137.405
129.014
127.649
125.266
77.318
77.000
76.681
52.608
50.105
46.729
39.658
39.612
28.953
28.756
20.759
200
180
160
140
120
100
80
60
40
20
ppm


O
Bn
N
CH3
Br
O

1g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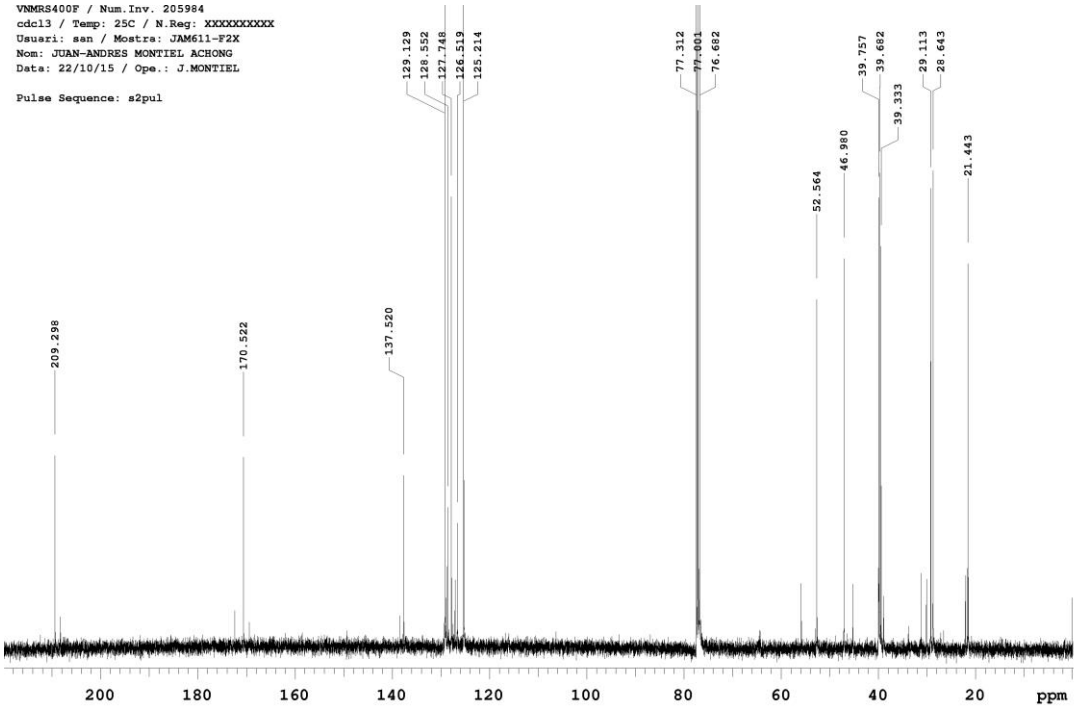
cdcl3 / Temp: 25C / N.Reg: XXXXXXXXXX
Usuari: san / Mostra: JAM611-F2X
Nom: JUAN-ANDRES MONTIEL ACHONG
Data: 21/10/15 / Ope.: J.MONTIEL
Pulse Sequence: s2pul
1.792
1.775
9
8
7
6
5
4
3
2
1
ppm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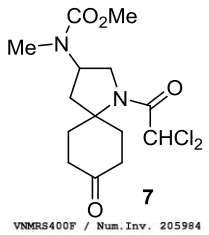
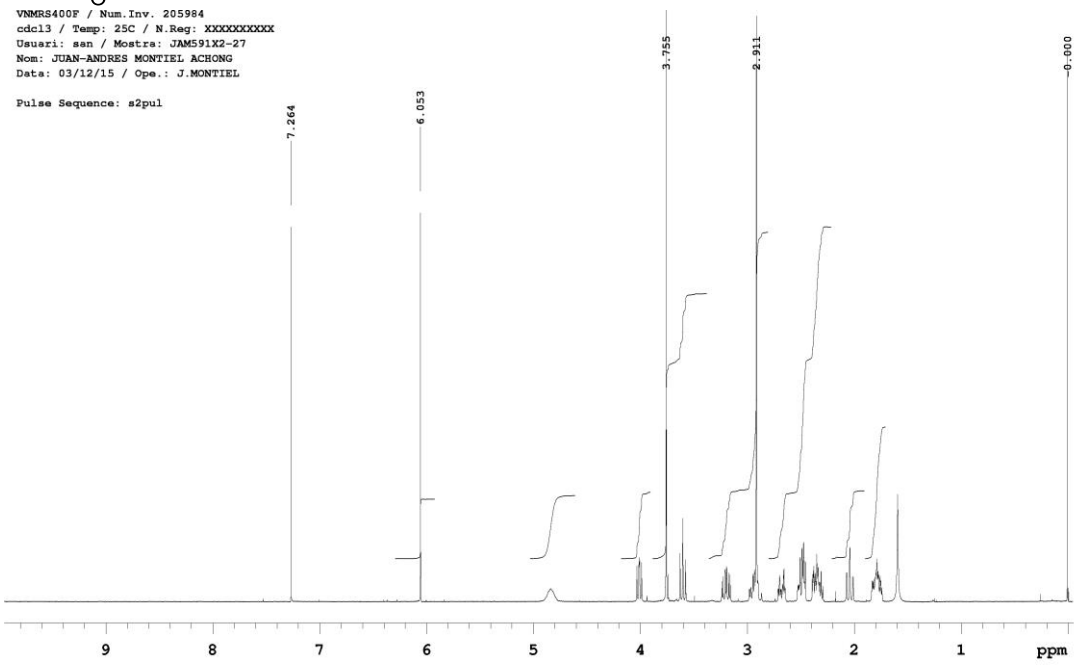
cdcl3 / Temp: 25C / N.Reg: XXXXXXXXXX
Usuari: san / Mostra: JAM611-F2X
Nom: JUAN-ANDRES MONTIEL ACHONG
Data: 22/10/15 / Ope.: J.MONTIEL
Pulse Sequence: s2pul
209.298
170.522
137.520
129.129
128.552
127.748
126.519
125.214
77.312
77.001
76.682
52.564
46.980
39.757
39.682
39.333
29.113
28.643
21.443
200
180
160
140
120
100
80
60
40
20
ppm


CO2Me
Me
N
N
O
CHCl2
O

7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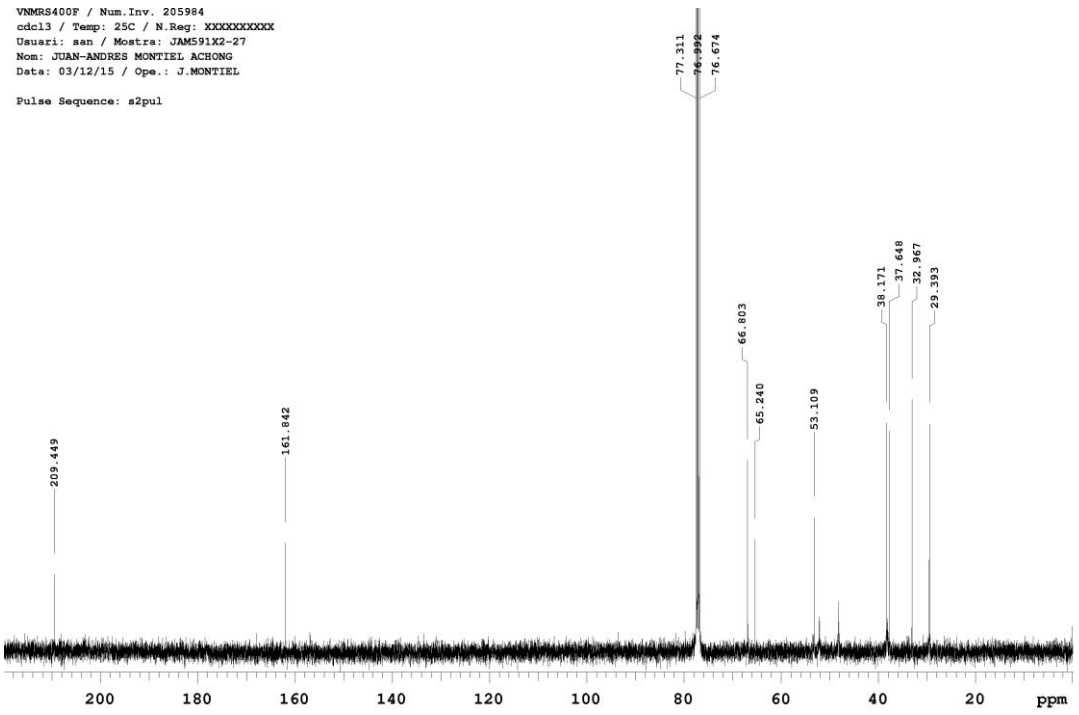
cdcl3 / Temp: 25C / N.Reg: XXXXXXXXXX
Usuari: san / Mostra: JAM591X2-27
Nom: JUAN-ANDRES MONTIEL ACHONG
Data: 03/12/15 / Ope.: J.MONTIEL
Pulse Sequence: s2pul
7.264
6.053
3.755
2.911
0.000
9
8
7
6
5
4
3
2
1
ppm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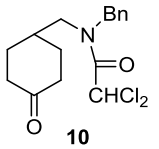
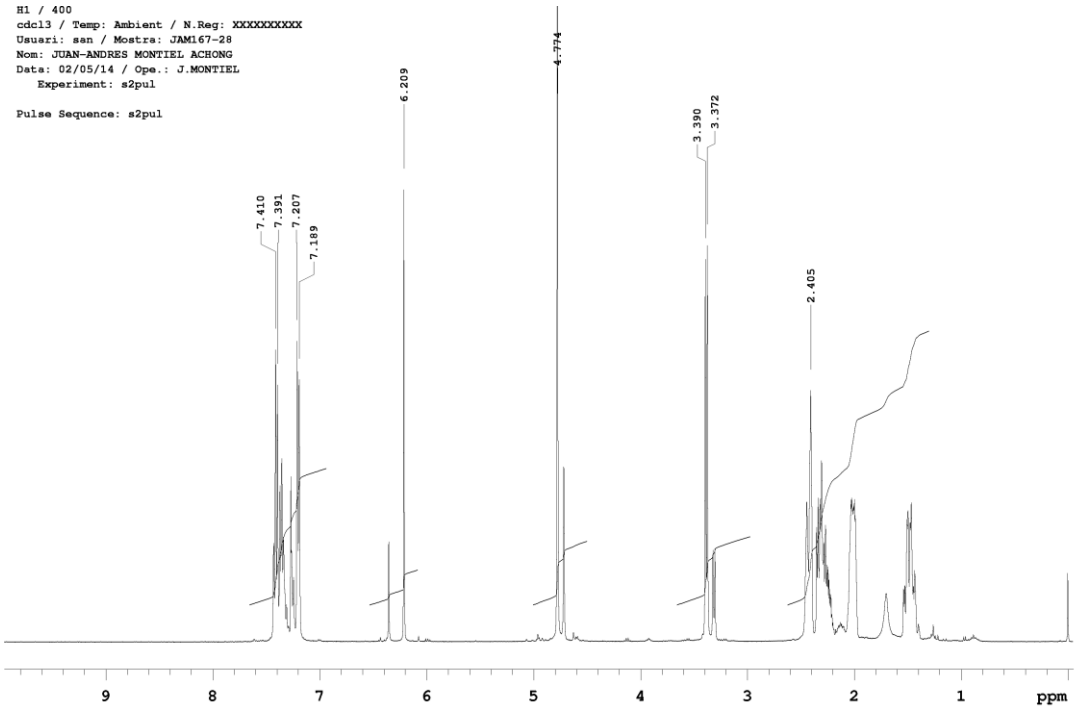
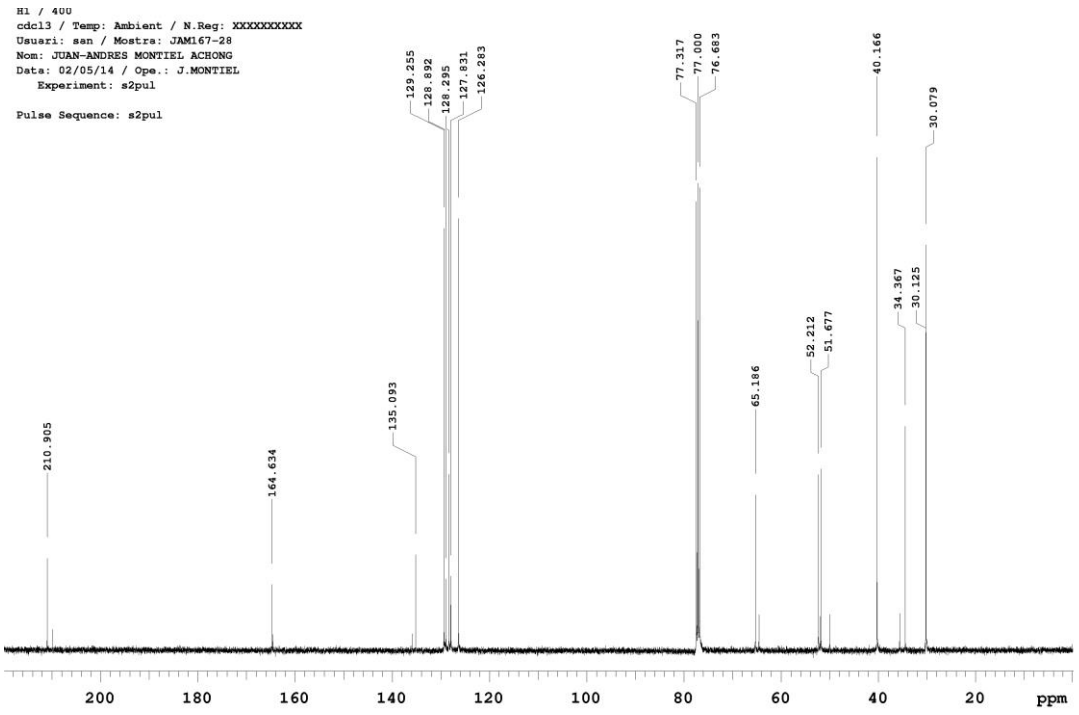
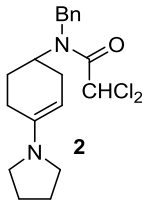
cdcl3 / Temp: 25C / N.Reg: XXXXXXXXXX
Usuari: san / Mostra: JAM591X2-27
Nom: JUAN-ANDRES MONTIEL ACHONG
Data: 03/12/15 / Ope.: J.MONTIEL
Pulse Sequence: s2pul
77.311
76.992
76.674
66.803
65.240
53.109
38.171
37.648
32.967
29.393
209.449
161.842
200
180
160
140
120
100
80
60
40
20
ppm


Bn
N
O
CHCl2
O

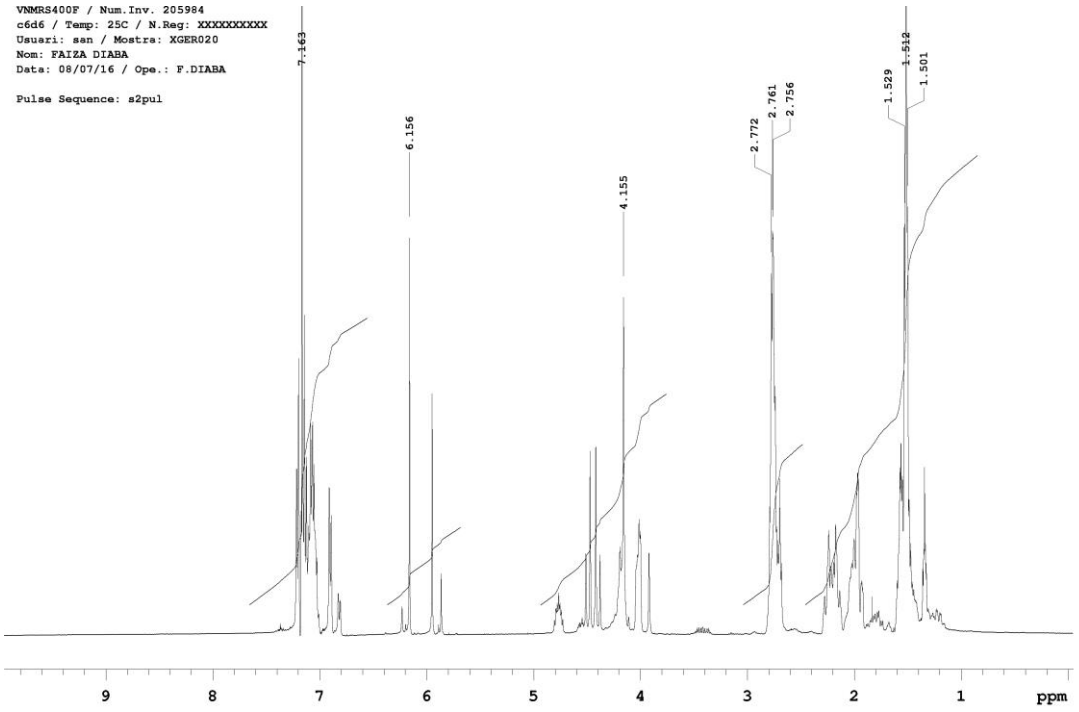
10

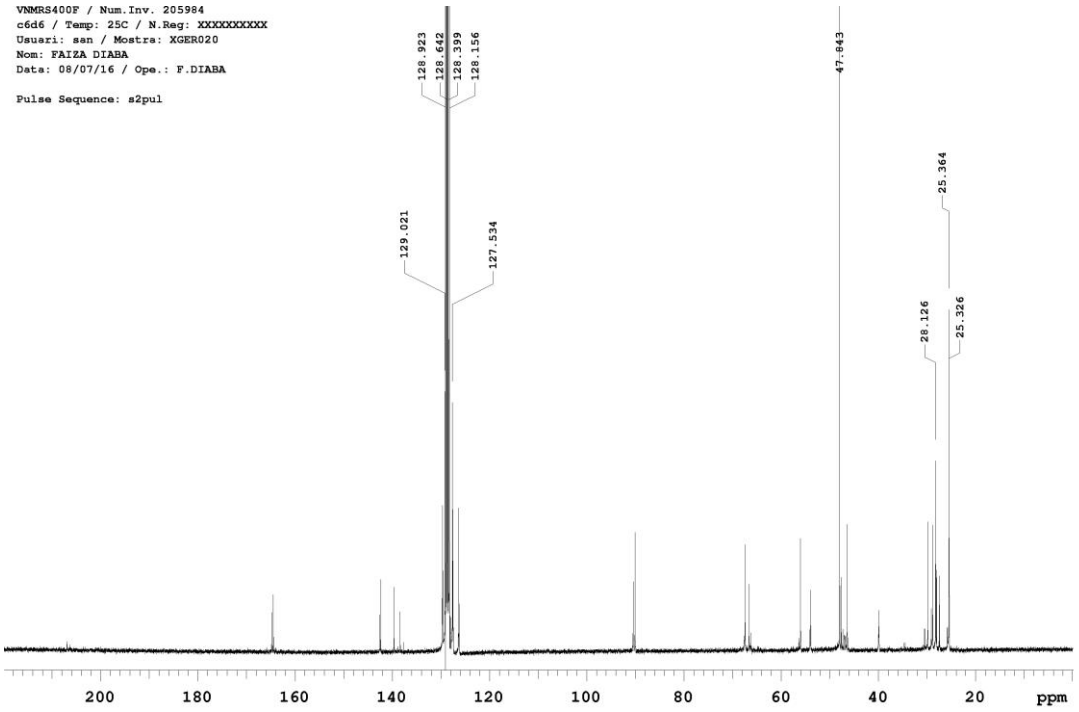

H1 / 400
cdcl3 / Temp: Ambient / N.Reg: XXXXXXXXXX
Usuari: san / Mostra: JAM167-28
Nom: JUAN-ANDRES MONTIEL ACHONG
Data: 02/05/14 / Ope.: J.MONTIEL
Experiment: s2pul
Pulse Sequence: s2pul
7.410
7.391
7.207
7.189
6.209
4.774
3.390
3.372
2.405
9
8
7
6
5
4
3
2
1
ppm

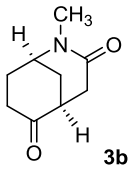

H1 / 400
cdcl3 / Temp: Ambient / N.Reg: XXXXXXXXXX
Usuari: san / Mostra: JAM167-28
Nom: JUAN-ANDRES MONTIEL ACHONG
Data: 02/05/14 / Ope.: J.MONTIEL
Experiment: s2pul
Pulse Sequence: s2pul
129.255
128.892
128.295
127.831
126.283
77.317
77.000
76.683
40.166
30.079
34.367
30.125
52.212
51.677
65.186
135.093
164.634
210.905
200
180
160
140
120
100
80
60
40
20
ppm


Bn
N
O
CHCl2
N

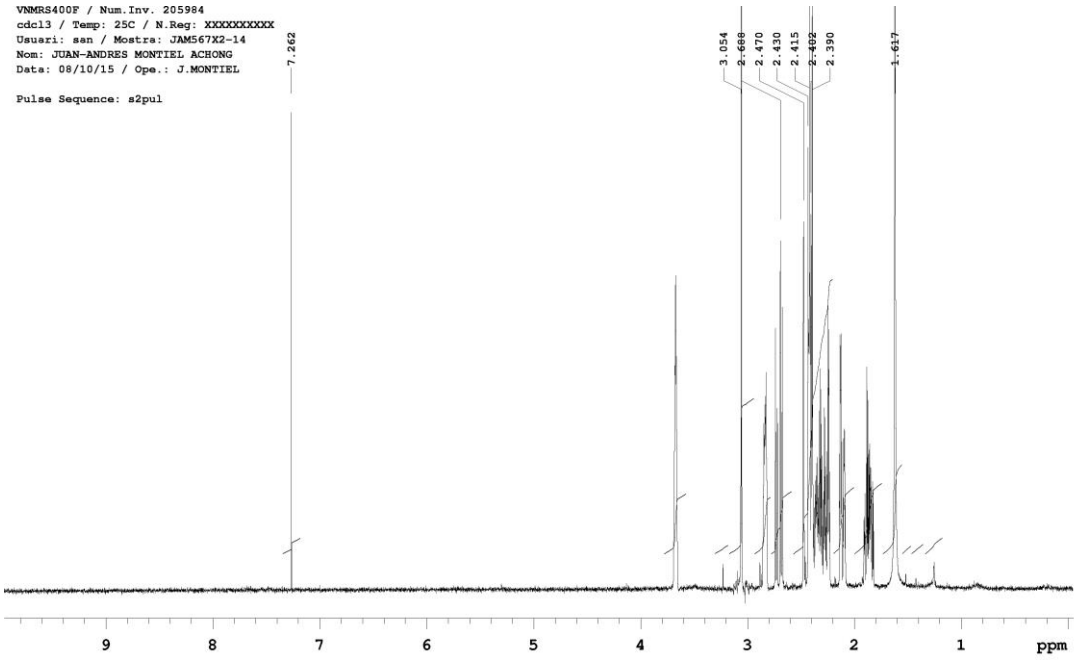
2

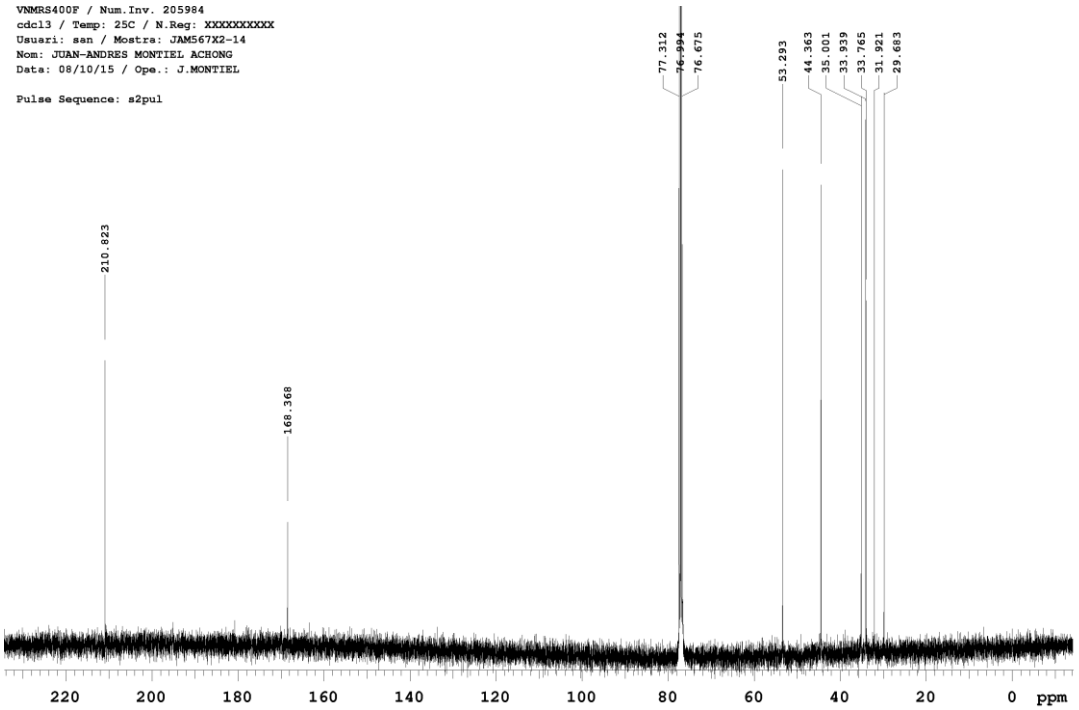

VNMRS400F / Num.Inv. 205984
c6d6 / Temp: 25C / N.Reg: XXXXXXXXXX
Usuari: san / Mostra: XGER020
Nom: FAIZA DIABA
Data: 08/07/16 / Ope.: F.DIABA
Pulse Sequence: s2pul
7.163
6.156
4.155
2.772
2.761
2.756
1.529
1.512
1.501
9
8
7
6
5
4
3
2
1
ppm

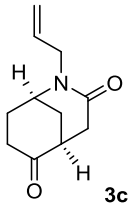

VNMRS400F / Num.Inv. 205984
c6d6 / Temp: 25C / N.Reg: XXXXXXXXXX
Usuari: san / Mostra: XGER020
Nom: FAIZA DIABA
Data: 08/07/16 / Ope.: F.DIABA
Pulse Sequence: s2pul
128.923
128.642
128.399
128.156
129.021
127.534
47.643
25.364
28.126
25.326
200
180
160
140
120
100
80
60
40
20
ppm


CH3
H
N
O
O
H

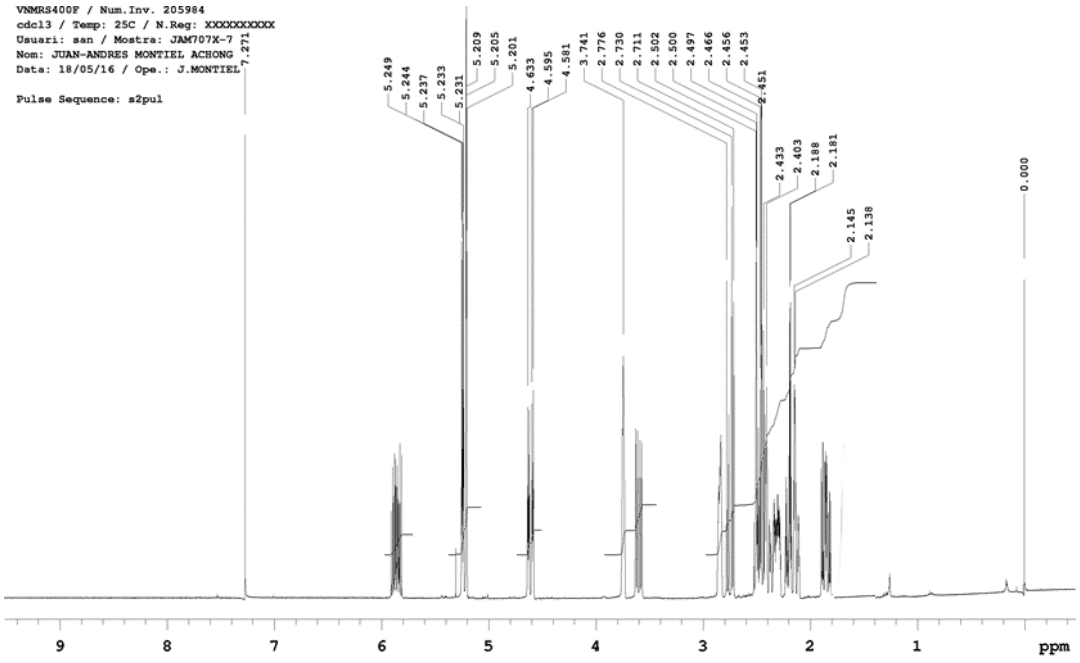
3b

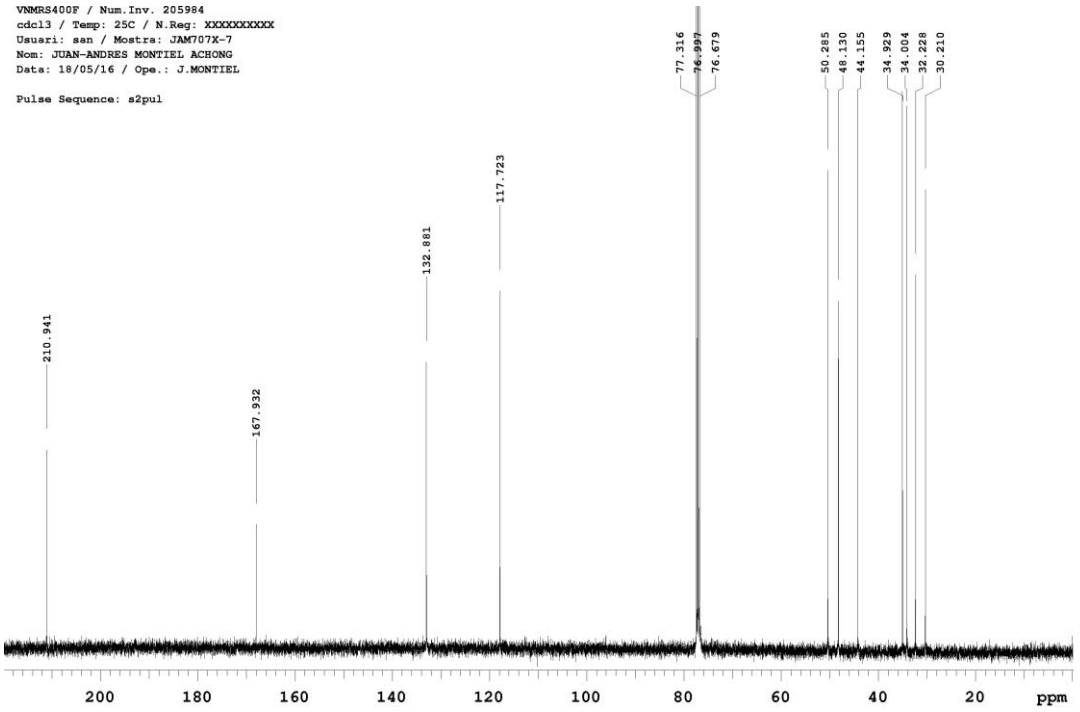

VNMRS400F / Num.Inv. 205984
cdcl3 / Temp: 25C / N.Reg: XXXXXXXXXX
Usuari: san / Mostra: JAM567X2-14
Nom: JUAN-ANDRES MONTIEL ACHONG
Data: 08/10/15 / Ope.: J.MONTIEL
Pulse Sequence: s2pul
7.262
3.054
2.680
2.470
2.430
2.415
2.402
2.390
1.617
9
8
7
6
5
4
3
2
1
ppm

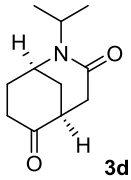

VNMRS400F / Num.Inv. 205984
cdcl3 / Temp: 25C / N.Reg: XXXXXXXXXX
Usuari: san / Mostra: JAM567X2-14
Nom: JUAN-ANDRES MONTIEL ACHONG
Data: 08/10/15 / Ope.: J.MONTIEL
Pulse Sequence: s2pul
77.312
76.994
76.675
53.293
44.363
35.001
33.939
33.765
31.921
29.683
210.823
168.368
220
200
180
160
140
120
100
80
60
40
20
0
ppm



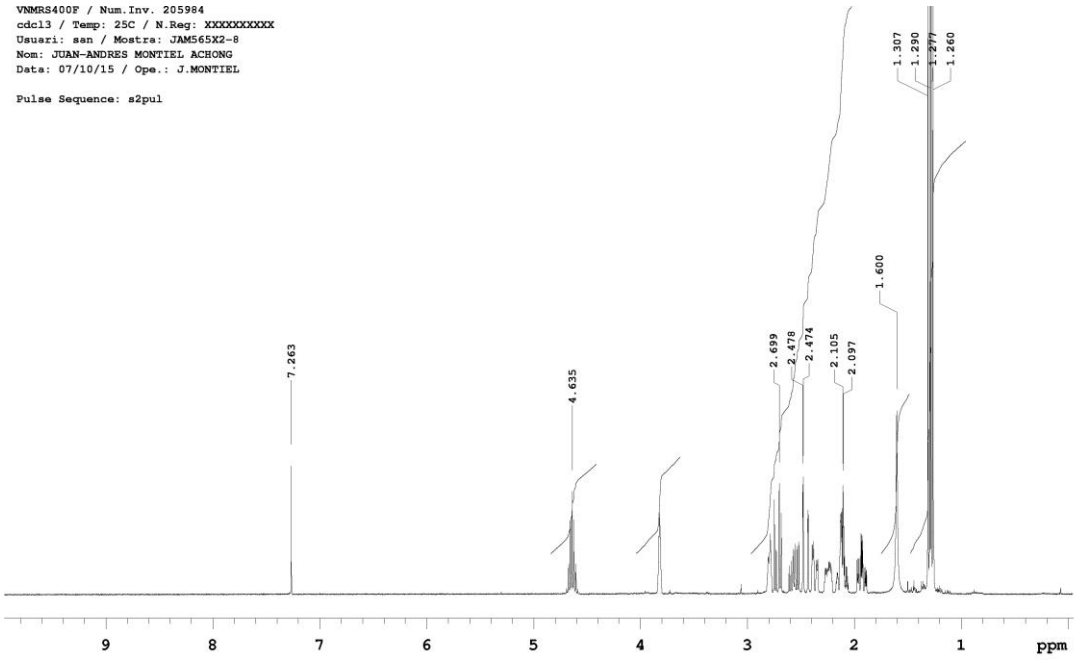
3c

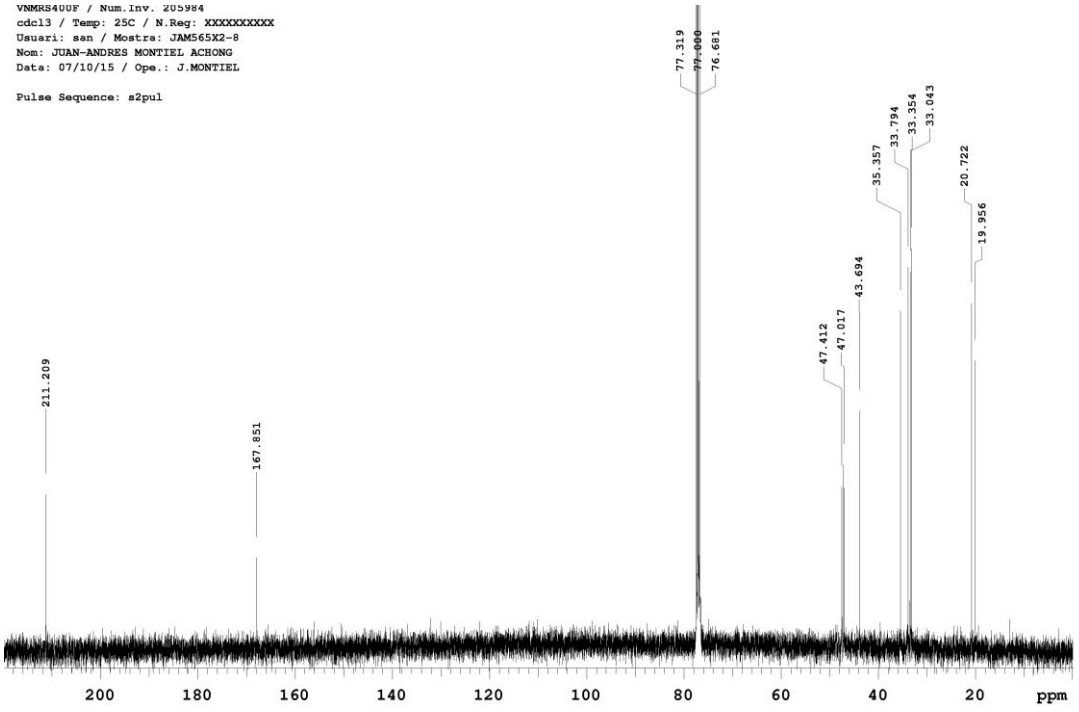

VNMRS400F / Num.Inv. 205984
cdcl3 / Temp: 25C / N.Reg: XXXXXXXXXX
Usuari: san / Mostra: JAM707X-7
Nom: JUAN-ANDRES MONTIEL ACHONG
Data: 18/05/16 / Ope.: J.MONTIEL
Pulse Sequence: s2pul
7.271
5.249
5.244
5.237
5.233
5.231
5.209
5.205
5.201
4.633
4.595
4.581
3.741
2.776
2.730
2.711
2.502
2.500
2.497
2.466
2.456
2.453
2.451
2.433
2.403
2.188
2.181
2.145
2.138
0.000
9
8
7
6
5
4
3
2
1
ppm

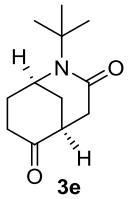

VNMRS400F / Num.Inv. 205984
cdcl3 / Temp: 25C / N.Reg: XXXXXXXXXX
Usuari: san / Mostra: JAM707X-7
Nom: JUAN-ANDRES MONTIEL ACHONG
Data: 18/05/16 / Ope.: J.MONTIEL
Pulse Sequence: s2pul
210.941
167.932
132.881
117.723
77.316
76.997
76.679
50.285
48.130
44.155
34.929
34.004
32.228
30.210
200
180
160
140
120
100
80
60
40
20
ppm



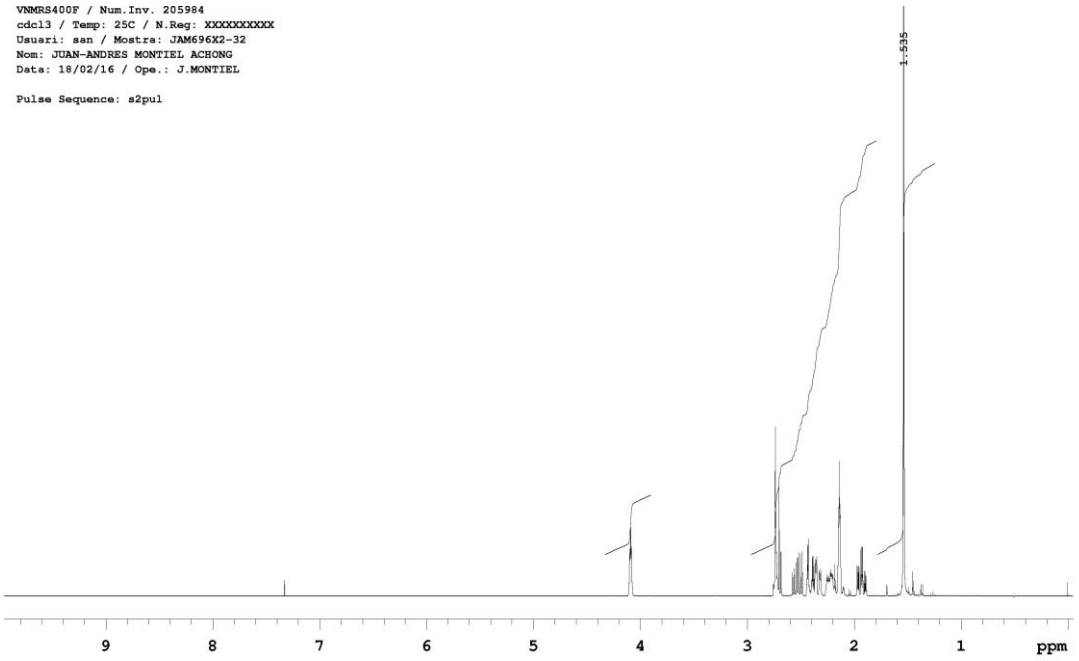
3d

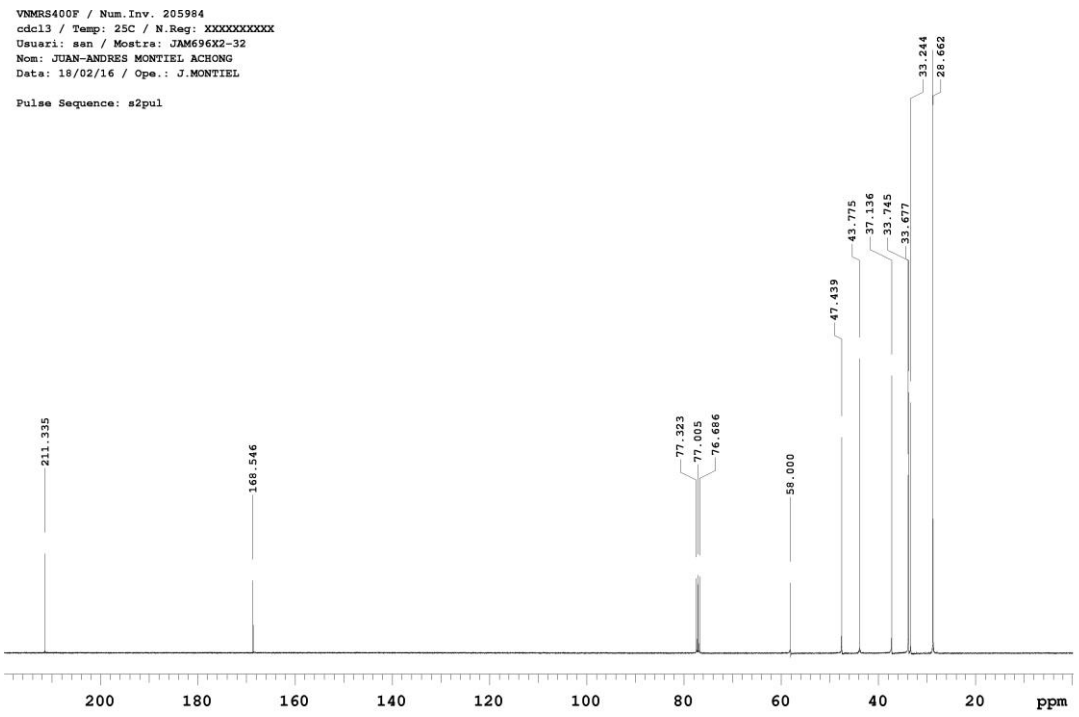

VNMRS400F / Num.Inv. 205984
cdcl3 / Temp: 25C / N.Reg: XXXXXXXXXX
Usuari: san / Mostra: JAM565X2-8
Nom: JUAN-ANDRES MONTIEL ACHONG
Data: 07/10/15 / Ope.: J.MONTIEL
Pulse Sequence: s2pul
7.263
4.635
2.699
2.478
2.474
2.105
2.097
1.600
1.307
1.290
1.277
1.260
9
8
7
6
5
4
3
2
1
ppm

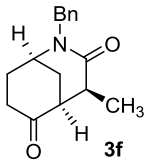

VNMRS400F / Num.Inv. 205984
cdcl3 / Temp: 25C / N.Reg: XXXXXXXXXX
Usuari: san / Mostra: JAM565X2-8
Nom: JUAN-ANDRES MONTIEL ACHONG
Data: 07/10/15 / Ope.: J.MONTIEL
Pulse Sequence: s2pul
211.209
167.851
77.319
77.000
76.681
47.412
47.017
43.694
35.357
33.794
33.354
33.043
20.722
19.956
200
180
160
140
120
100
80
60
40
20
ppm


H
N
O
O
H

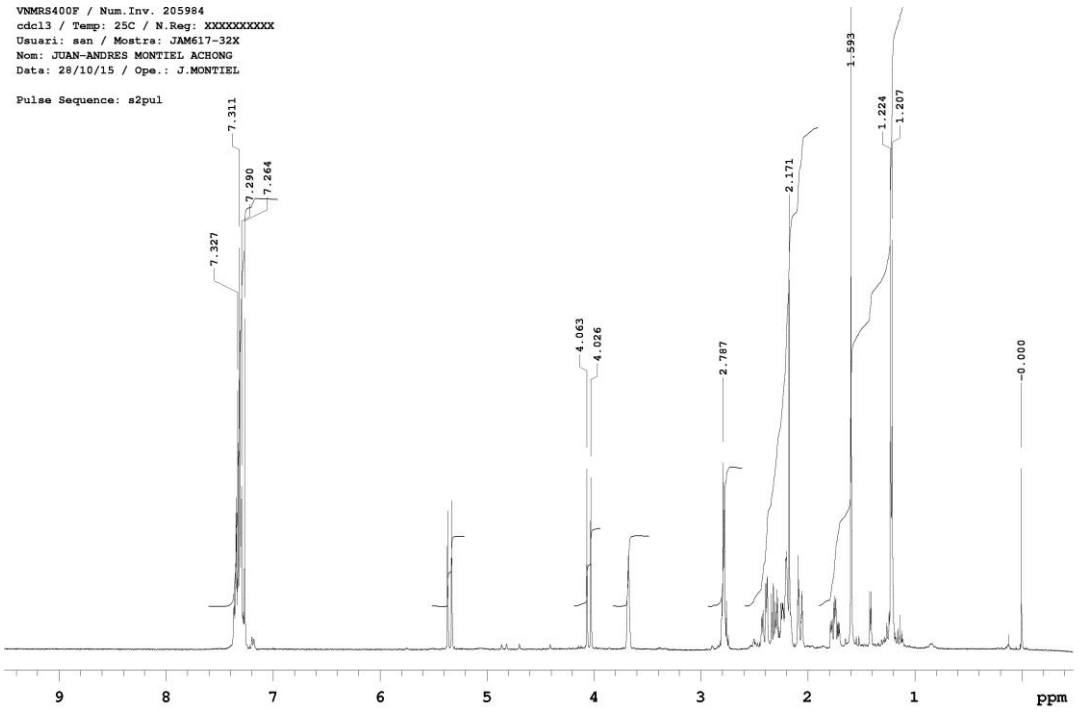
3e

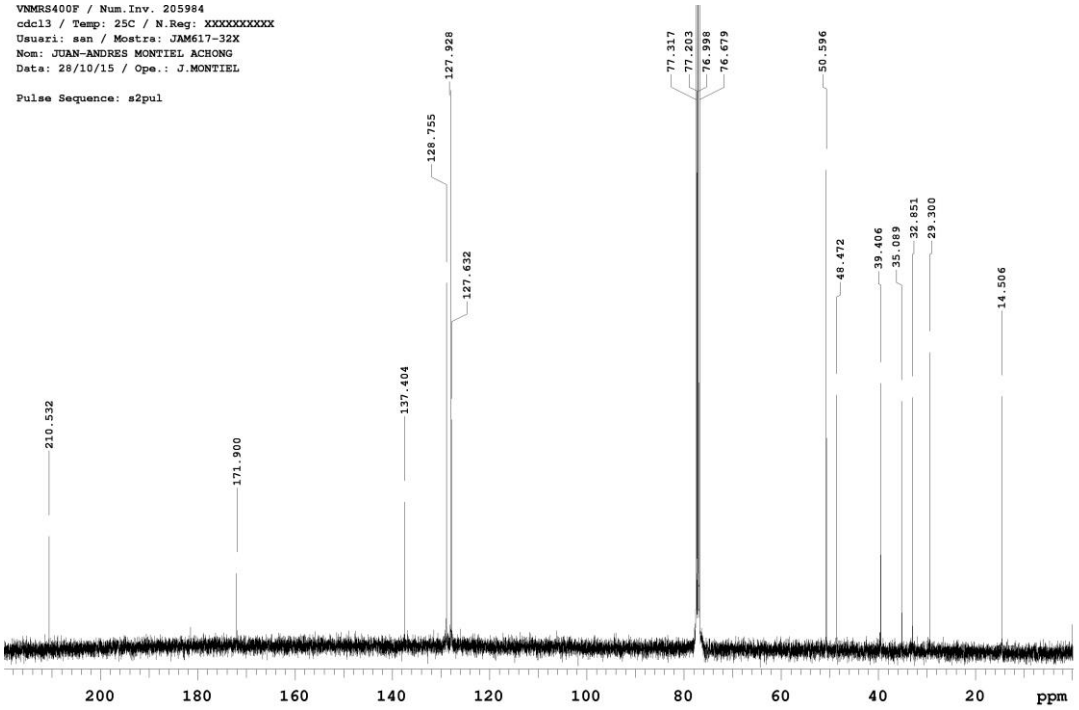

VNMRS400F / Num.Inv. 205984
cdcl3 / Temp: 25C / N.Reg: XXXXXXXXXX
Usuari: san / Mostra: JAM696X2-32
Nom: JUAN-ANDRES MONTIEL ACHONG
Data: 18/02/16 / Ope.: J.MONTIEL
Pulse Sequence: s2pul
1.535
9
8
7
6
5
4
3
2
1
ppm

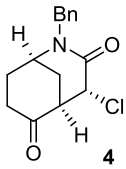

VNMRS400F / Num.Inv. 205984
cdcl3 / Temp: 25C / N.Reg: XXXXXXXXXX
Usuari: san / Mostra: JAM696X2-32
Nom: JUAN-ANDRES MONTIEL ACHONG
Data: 18/02/16 / Ope.: J.MONTIEL
Pulse Sequence: s2pul
211.335
168.546
77.323
77.005
76.686
58.000
47.439
43.775
37.136
33.745
33.677
33.244
28.662
200
180
160
140
120
100
80
60
40
20
ppm


Bn
H
N
O
CH3
H
O

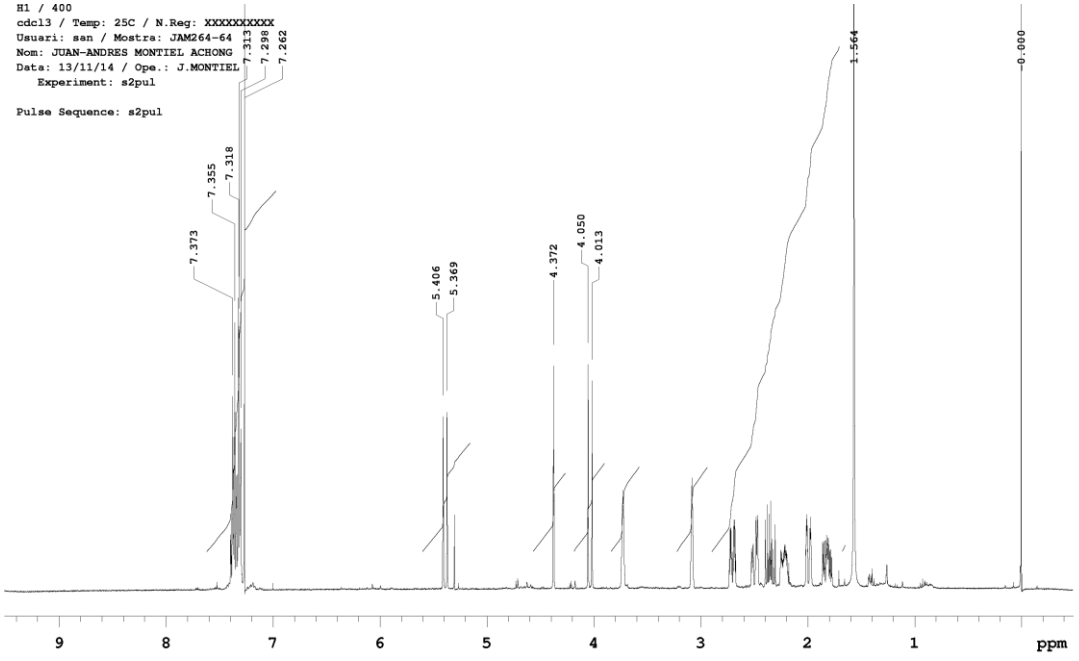
3f

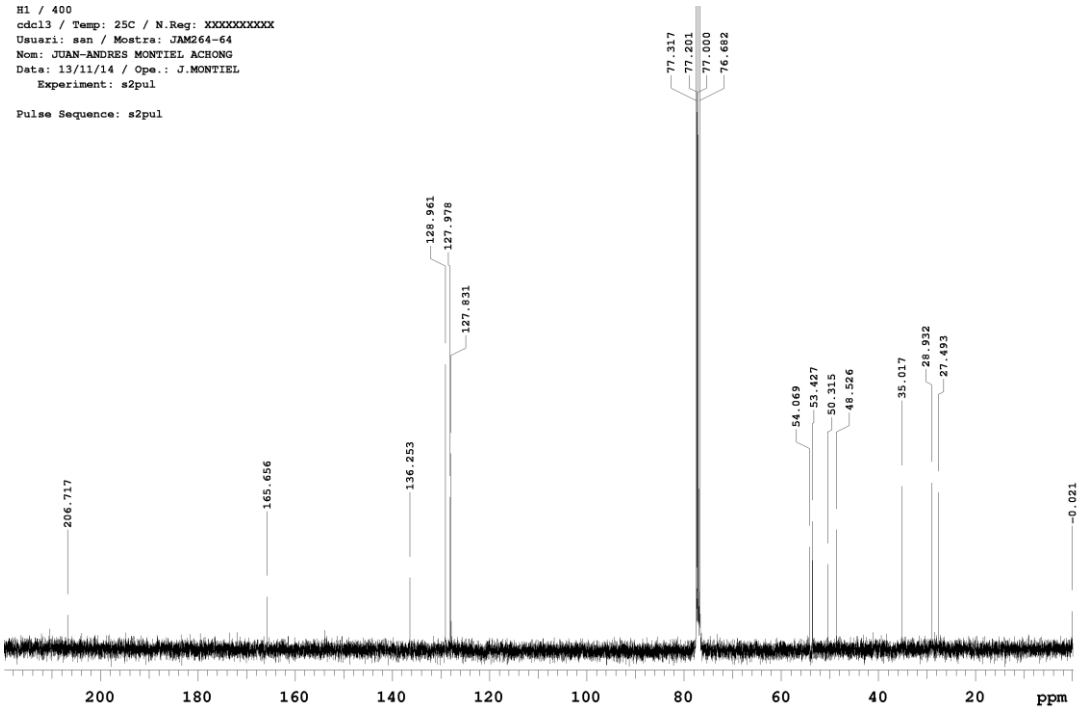

VNMRS400F / Num.Inv. 205984
cdcl3 / Temp: 25C / N.Reg: XXXXXXXXXX
Usuari: san / Mostra: JAM617-32X
Nom: JUAN-ANDRES MONTIEL ACHONG
Data: 28/10/15 / Ope.: J.MONTIEL
Pulse Sequence: s2pul
7.311
7.290
7.264
7.327
4.063
4.026
2.787
2.171
1.593
1.224
1.207
0.000
9
8
7
6
5
4
3
2
1
ppm

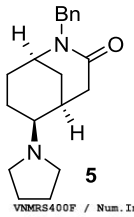

VNMRS400F / Num.Inv. 205984
cdcl3 / Temp: 25C / N.Reg: XXXXXXXXXX
Usuari: san / Mostra: JAM617-32X
Nom: JUAN-ANDRES MONTIEL ACHONG
Data: 28/10/15 / Ope.: J.MONTIEL
Pulse Sequence: s2pul
210.532
171.900
137.404
128.755
127.928
127.632
77.317
77.203
76.998
76.679
50.596
48.472
39.406
35.089
32.851
29.300
14.506
200
180
160
140
120
100
80
60
40
20
ppm


Bn
H
N
O
Cl
H
O

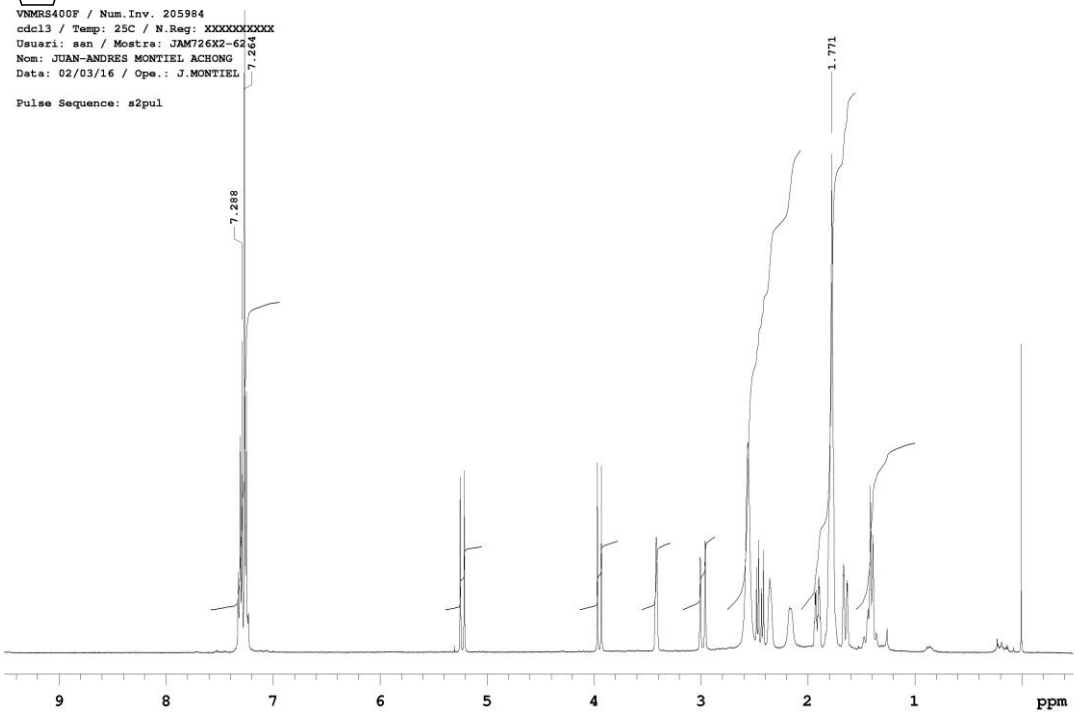
4

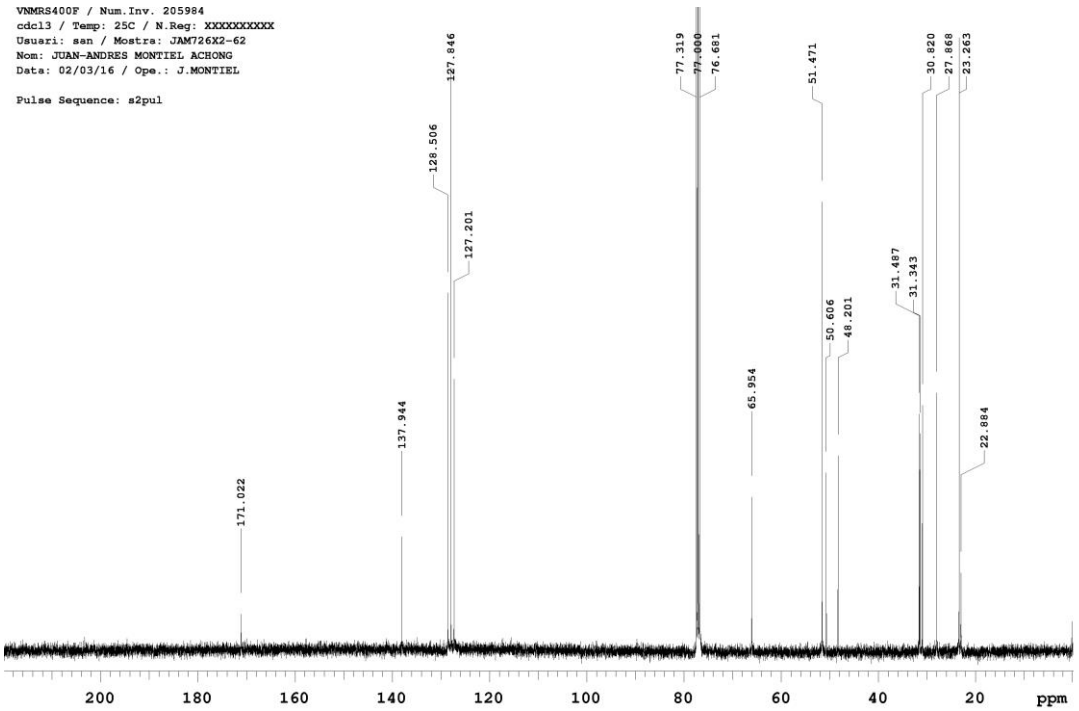

H1 / 400
cdcl3 / Temp: 25C / N.Reg: XXXXXXXXXX
Usuari: san / Mostra: JAM264-64
Nom: JUAN-ANDRES MONTIEL ACHONG
Data: 13/11/14 / Ope.: J.MONTIEL
Experiment: s2pul
Pulse Sequence: s2pul
7.373
7.355
7.318
7.313
7.298
7.262
5.406
5.369
4.372
4.050
4.013
1.564
0.000
9
8
7
6
5
4
3
2
1
ppm

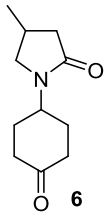

H1 / 400
cdcl3 / Temp: 25C / N.Reg: XXXXXXXXXX
Usuari: san / Mostra: JAM264-64
Nom: JUAN-ANDRES MONTIEL ACHONG
Data: 13/11/14 / Ope.: J.MONTIEL
Experiment: s2pul
Pulse Sequence: s2pul
77.317
77.201
77.000
76.682
128.961
127.978
127.831
206.717
165.656
136.253
54.069
53.427
50.315
48.526
35.017
28.932
27.493
0.021
200
180
160
140
120
100
80
60
40
20
ppm


Bn
H
N
O
H
N

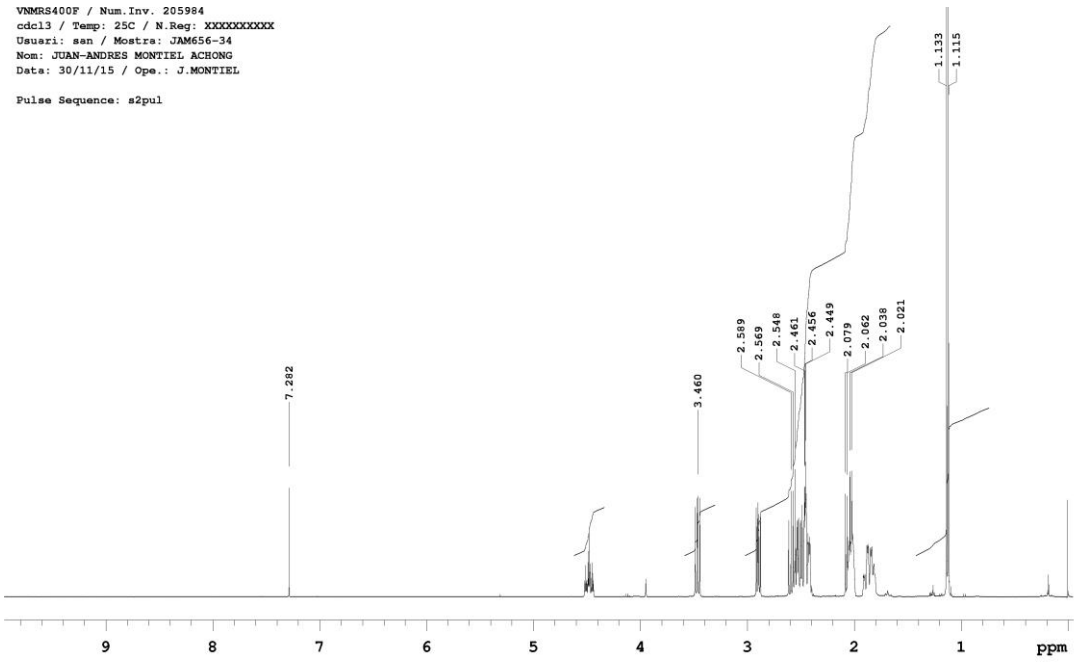
5

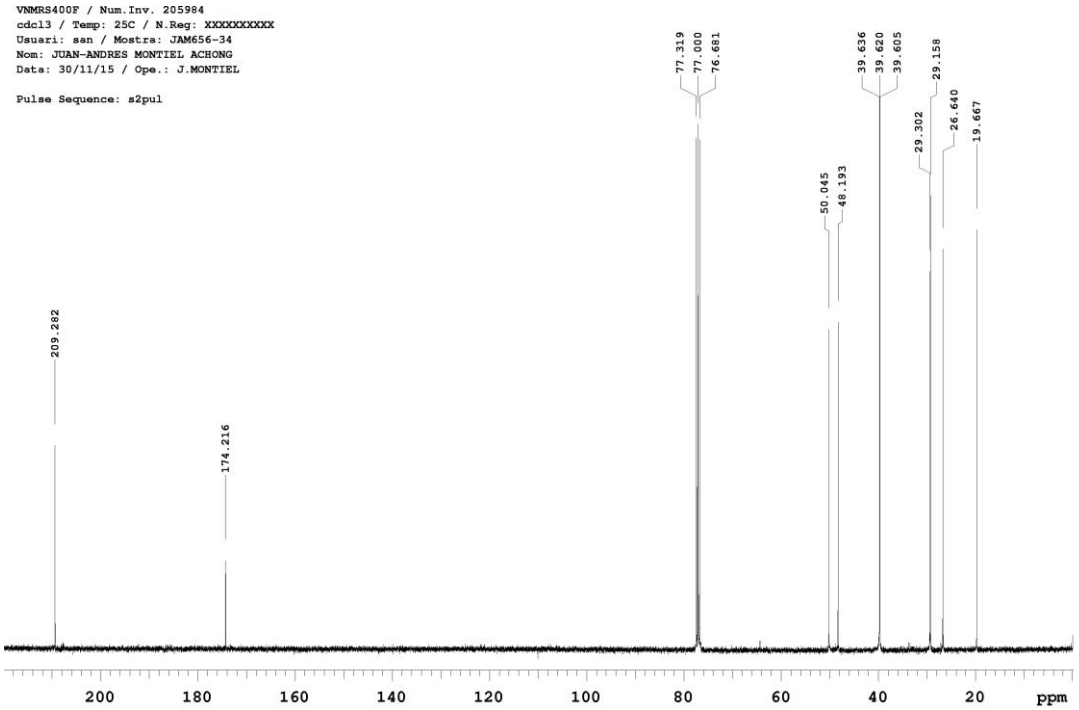

VNMRS400F / Num.Inv. 205984
cdcl3 / Temp: 25C / N.Reg: XXXXXXXXXX
Usuari: san / Mostra: JAM726X2-62
Nom: JUAN-ANDRES MONTIEL ACHONG
Data: 02/03/16 / Ope.: J.MONTIEL
Pulse Sequence: s2pul
7.264
7.288
1.771
9
8
7
6
5
4
3
2
1
ppm

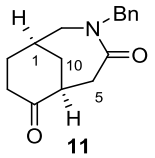

VNMRS400F / Num.Inv. 205984
cdcl3 / Temp: 25C / N.Reg: XXXXXXXXXX
Usuari: san / Mostra: JAM726X2-62
Nom: JUAN-ANDRES MONTIEL ACHONG
Data: 02/03/16 / Ope.: J.MONTIEL
Pulse Sequence: s2pul
171.022
137.944
128.506
127.846
127.201
77.319
77.000
76.681
65.954
51.471
50.606
48.201
31.487
31.343
30.820
27.868
23.263
22.884
200
180
160
140
120
100
80
60
40
20
ppm


N
O
O

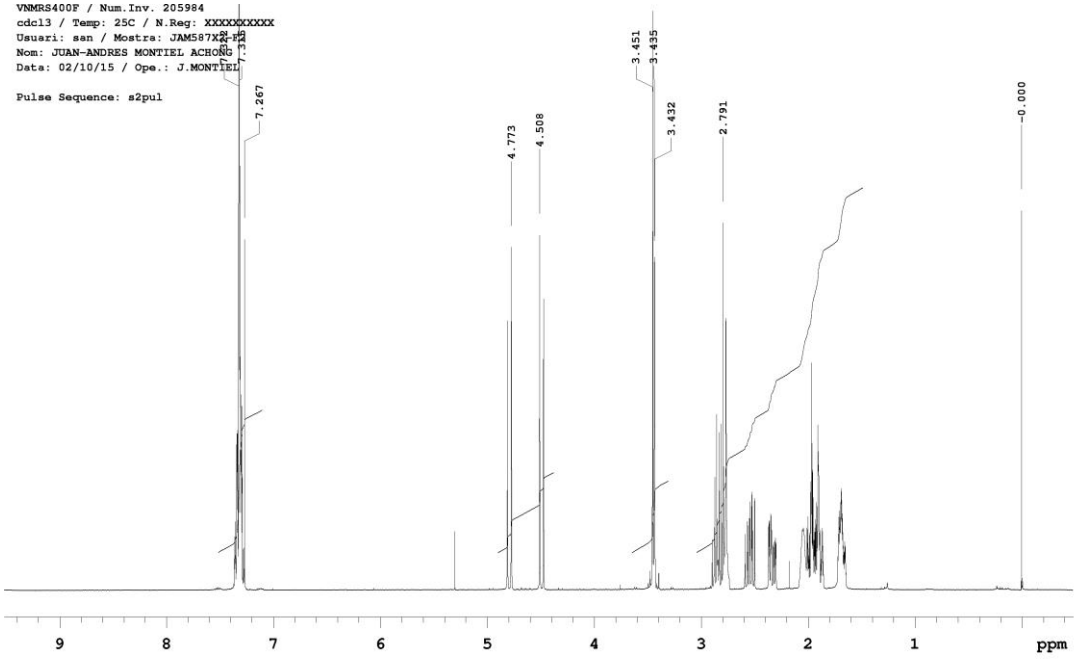
6

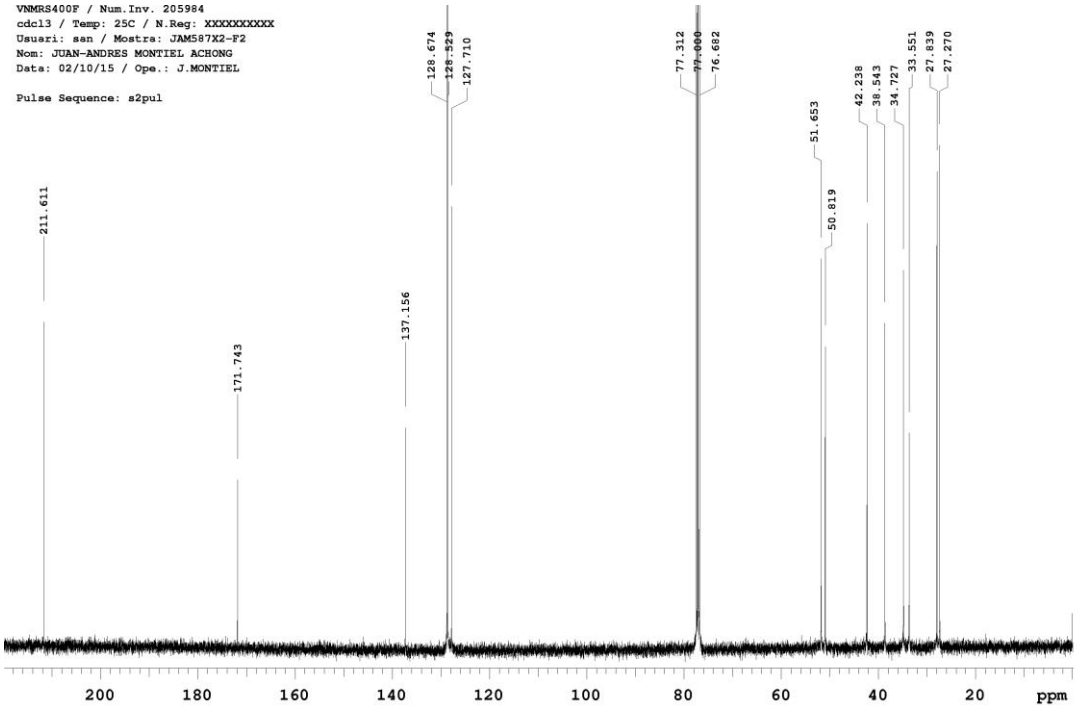

VNMRS400F / Num.Inv. 205984
cdcl3 / Temp: 25C / N.Reg: XXXXXXXXXX
Usuari: san / Mostra: JAM656-34
Nom: JUAN-ANDRES MONTIEL ACHONG
Data: 30/11/15 / Ope.: J.MONTIEL
Pulse Sequence: s2pul
7.282
3.460
2.589
2.569
2.548
2.461
2.456
2.449
2.079
2.062
2.038
2.021
1.133
1.115
9
8
7
6
5
4
3
2
1
ppm


VNMRS400F / Num.Inv. 205984
cdcl3 / Temp: 25C / N.Reg: XXXXXXXXXX
Usuari: san / Mostra: JAM656-34
Nom: JUAN-ANDRES MONTIEL ACHONG
Data: 30/11/15 / Ope.: J.MONTIEL
Pulse Sequence: s2pul
77.319
77.000
76.681
39.636
39.620
39.605
29.158
29.302
26.640
19.667
50.045
48.193
209.282
174.216
200
180
160
140
120
100
80
60
40
20
ppm


H
N
Bn
O
1
10
5
H
O

11


VNMRS400F / Num.Inv. 205984
cdcl3 / Temp: 25C / N.Reg: XXXXXXXXXX
Usuari: san / Mostra: JAM587X2-F2
Nom: JUAN-ANDRES MONTIEL ACHONG
Data: 02/10/15 / Ope.: J.MONTIEL
Pulse Sequence: s2pul
7.315
7.267
4.773
4.508
3.451
3.435
3.432
2.791
0.000
9
8
7
6
5
4
3
2
1
ppm


VNMRS400F / Num.Inv. 205984
cdcl3 / Temp: 25C / N.Reg: XXXXXXXXXX
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Nom: JUAN-ANDRES MONTIEL ACHONG
Data: 02/10/15 / Ope.: J.MONTIEL
Pulse Sequence: s2pul
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171.743
137.156
128.674
128.529
127.710
77.312
77.000
76.682
51.653
50.819
42.238
38.543
34.727
33.551
27.839
27.270
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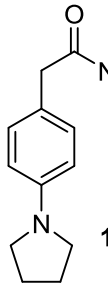
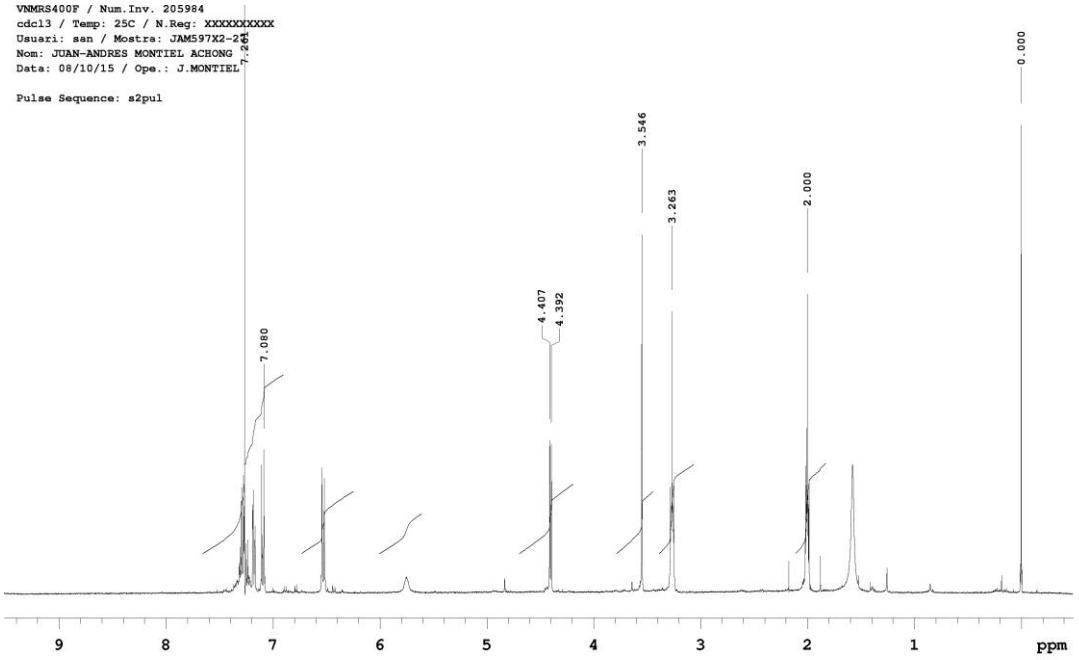
180
160
140
120
100
80
60
40
20
ppm


O
NHBn
N

13a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Nom: JUAN-ANDRES MONTIEL ACHONG
Data: 08/10/15 / Ope.: J.MONTIEL
Pulse Sequence: s2pul
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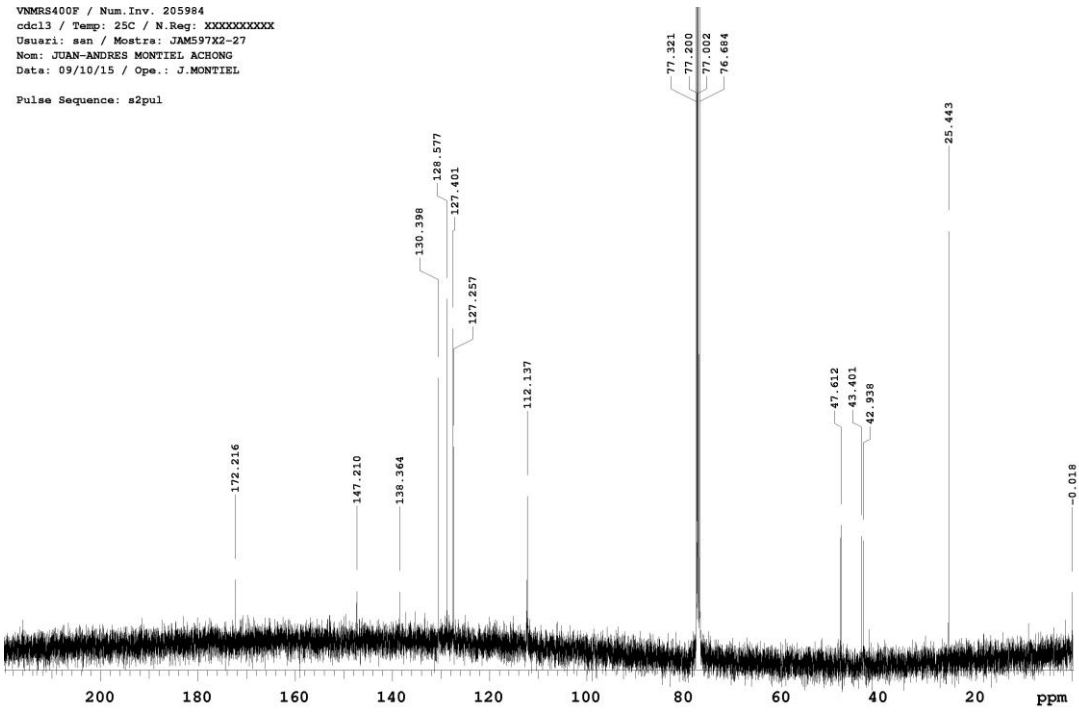
7.080
4.407
4.392
3.546
3.263
2.000
0.000
9
8
7
6
5
4
3
2
1
ppm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Nom: JUAN-ANDRES MONTIEL ACHONG
Data: 09/10/15 / Ope.: J.MONTIEL
Pulse Sequence: s2pul
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77.200
77.002
76.684
128.577
127.401
130.398
127.257
112.137
25.443
47.612
43.401
42.938
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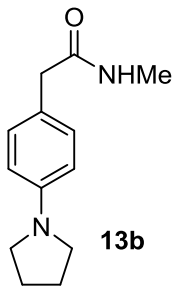
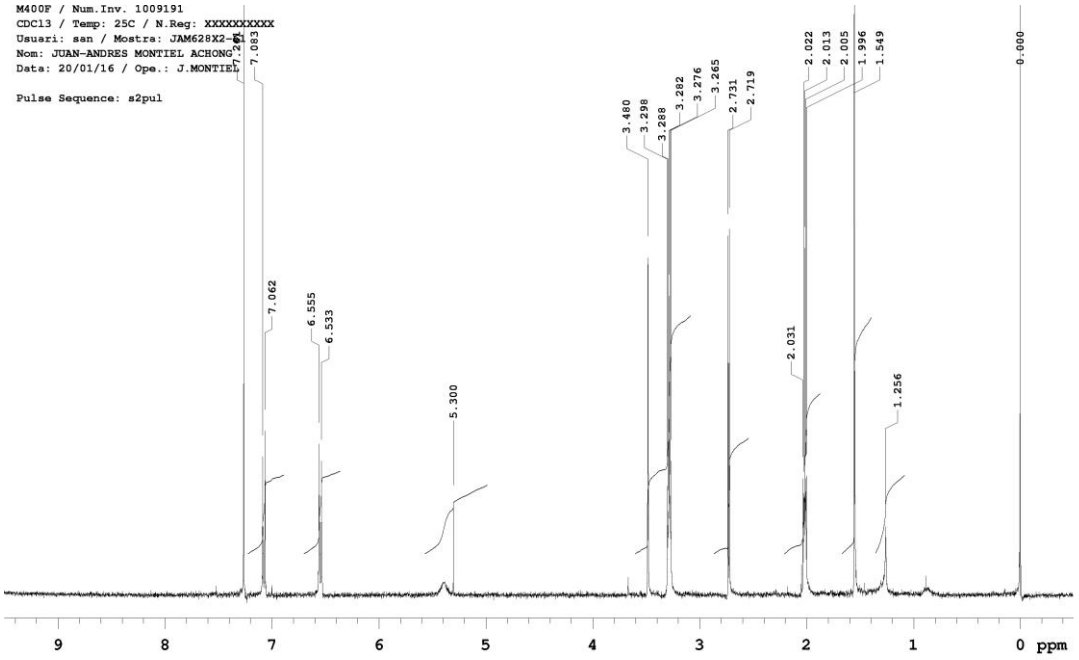
147.210
138.364
-0.018
200
180
160
140
120
100
80
60
40
20
ppm


O
NHMe
N

13b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Nom: JUAN-ANDRES MONTIEL ACHONG
Data: 20/01/16 / Ope.: J.MONTIEL
Pulse Sequence: s2pul
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7.062
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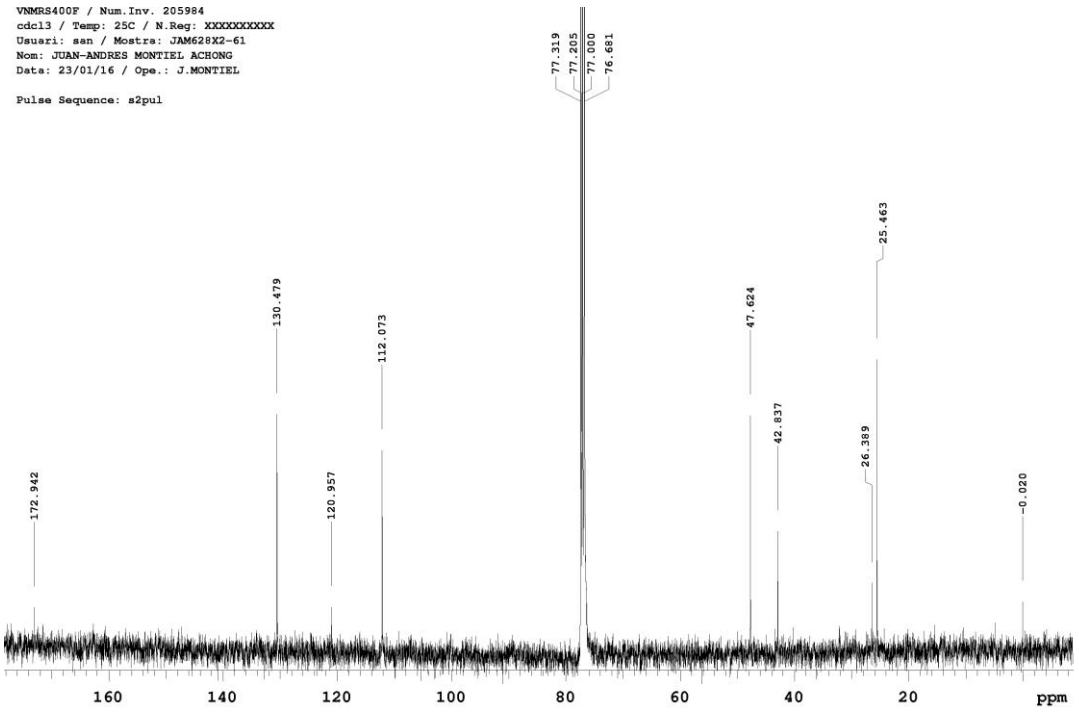
6.533
5.300
3.480
3.298
3.288
3.282
3.276
3.265
2.731
2.719
2.031
2.022
2.013
2.005
1.996
1.549
1.256
0.000
9
8
7
6
5
4
3
2
1
0 ppm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Data: 23/01/16 / Ope.: J.MONTIEL
Pulse Sequence: s2pul
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77.000
76.681
172.942
130.479
120.957
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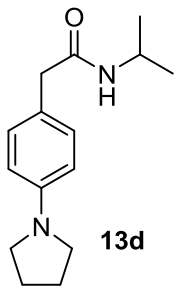
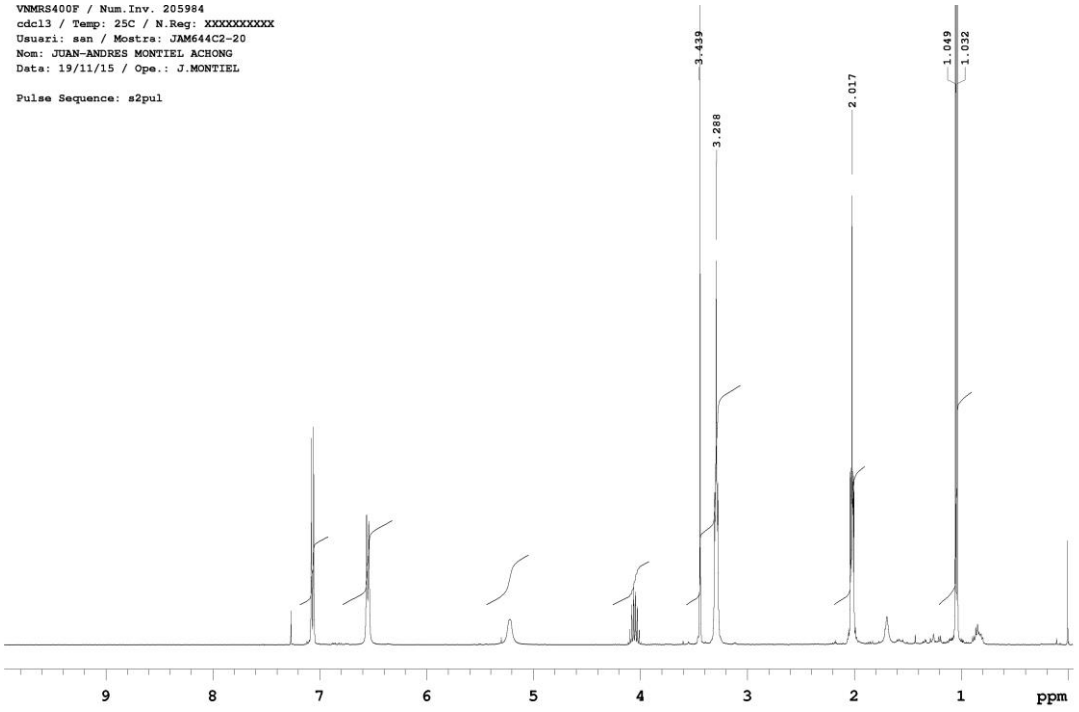
42.837
26.389
25.463
-0.020
160
140
120
100
80
60
40
20
ppm



13d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Nom: JUAN-ANDRES MONTIEL ACHONG
Data: 19/11/15 / Ope.: J.MONTIEL
Pulse Sequence: s2pul
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1.049
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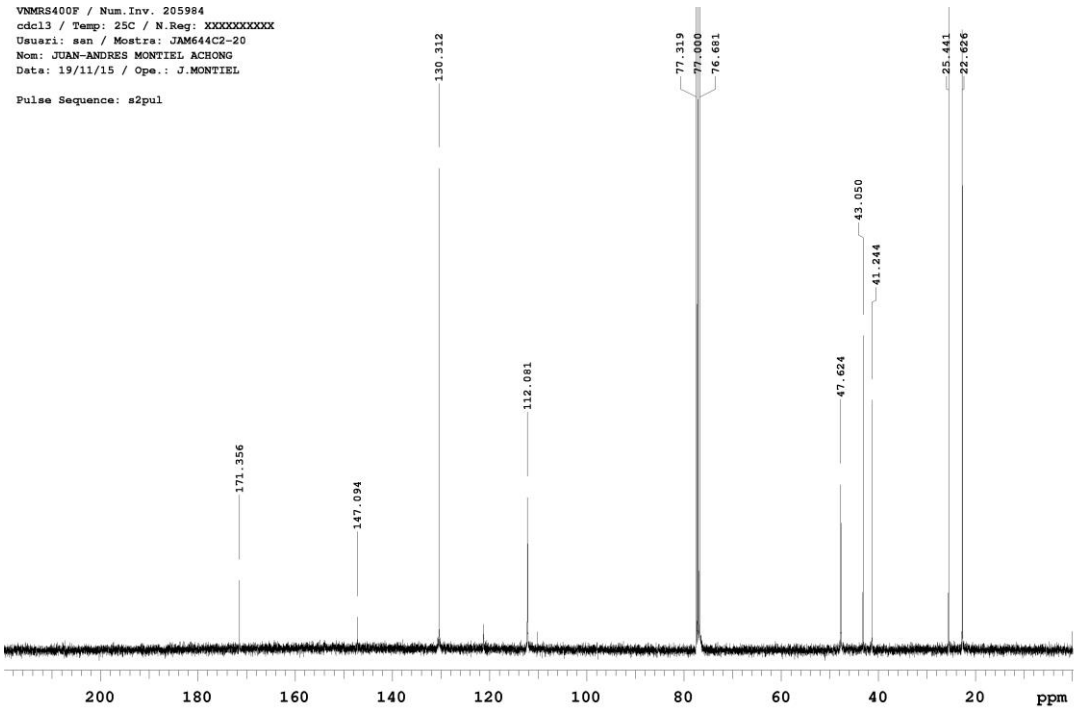
9
8
7
6
5
4
3
2
1
ppm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Usuari: san / Mostra: JAM644C2-20
Nom: JUAN-ANDRES MONTIEL ACHONG
Data: 19/11/15 / Ope.: J.MONTIEL
Pulse Sequence: s2pul
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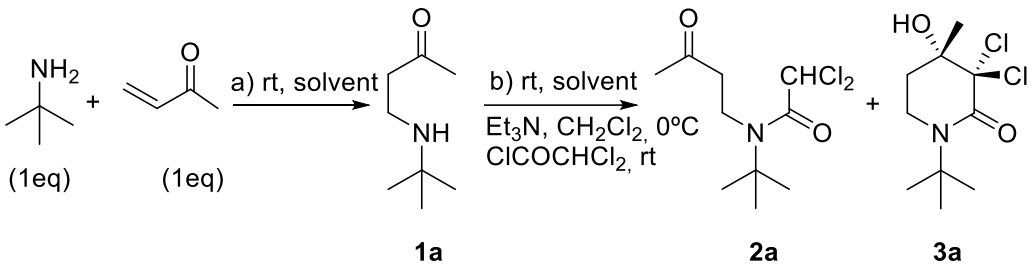
147.094
130.312
112.081
77.319
77.000
76.681
47.624
43.050
41.244
25.441
22.626
200
180
160
140
120
100
80
60
40
20
ppm

Chapter 6

Synthesis of functionalized pyrrolidines and piperidines from monochloro and dichloroacetamides using non-radical processes

Unpublished results

Table 6.1. Synthesis of lactam **3a**.



1a **2a** **3a**

Entry	*Solvent a*	*Solvent b*	*Conditions*	***2a** Yield (%)*	***3**aYield (%)*
1	Toluene	CH_2Cl_2	E	13	45
2	Toluene	Toluene	E	6	18
3	CH_2Cl_2	CH_2Cl_2	E	17	30
4	Toluene	CH_2Cl_2	E^{α}	31	45
5	Toluene	CH_2Cl_2	F	35	40

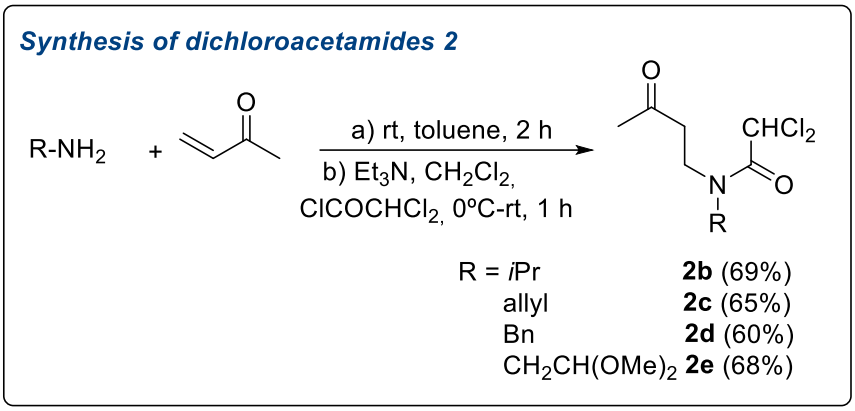
E: a) At rt for 2h; b) Add Et_3N (1.5eq) and dichloroacetylchloride (1.2eq) at 0º then at rt for 1h.

F: One pot μW. 5min. 60ºC. $^{\alpha}$ 2 eq of methylvinylketone for 4 h.

In the last part of this PhD we decided to investigate the synthesis of lactams from dichloro- and monochloroacetamides tethered to β- and γ-ketones using Darzens conditions.

Our study began by the preparation of dichloroacetamide **2a** with a *tert*-butyl group on the nitrogen using a one-pot procedure. First *tert*-Butylamine was treated with methyl vinyl ketone in toluene for one hour at rt[1] then triethylamine and dichloroacetyl chloride were incorporated to the reaction mixture at 0 ºC. After an additional hour of stirring at rt, we were delighted to see that the reaction went farther providing piperidinone **3a** (45%) besides the expected dichloroacetamide **2a** (13%) (Table 6.1., entry 1). The best results were obtained when 2 equiv. of methyl vinyl ketone were used and by prolonging the reaction time for the acylation step (entry 4). Using microwave activation for both steps reduced the reaction time dramatically (5 min each) without altering the global yield of the process (entry 5).

[1] Calow, A. D. J.; Carbó, J. J.; Cid, J.; Fernández, E.; Whiting, A. *J. Org. Chem*. **2014**, *79*, 5163-5172.

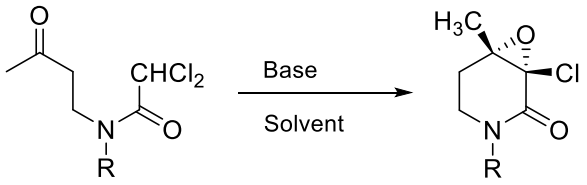


Scheme 6.1.

The methodology was then applied, to other amines providing the corresponding dichloroacetamides **2b**-**2e** with acceptable yields (Scheme 6.1).

Table 6.2. Darzens reaction from dichloroacetamides **2**

Epoxidation of compounds 2

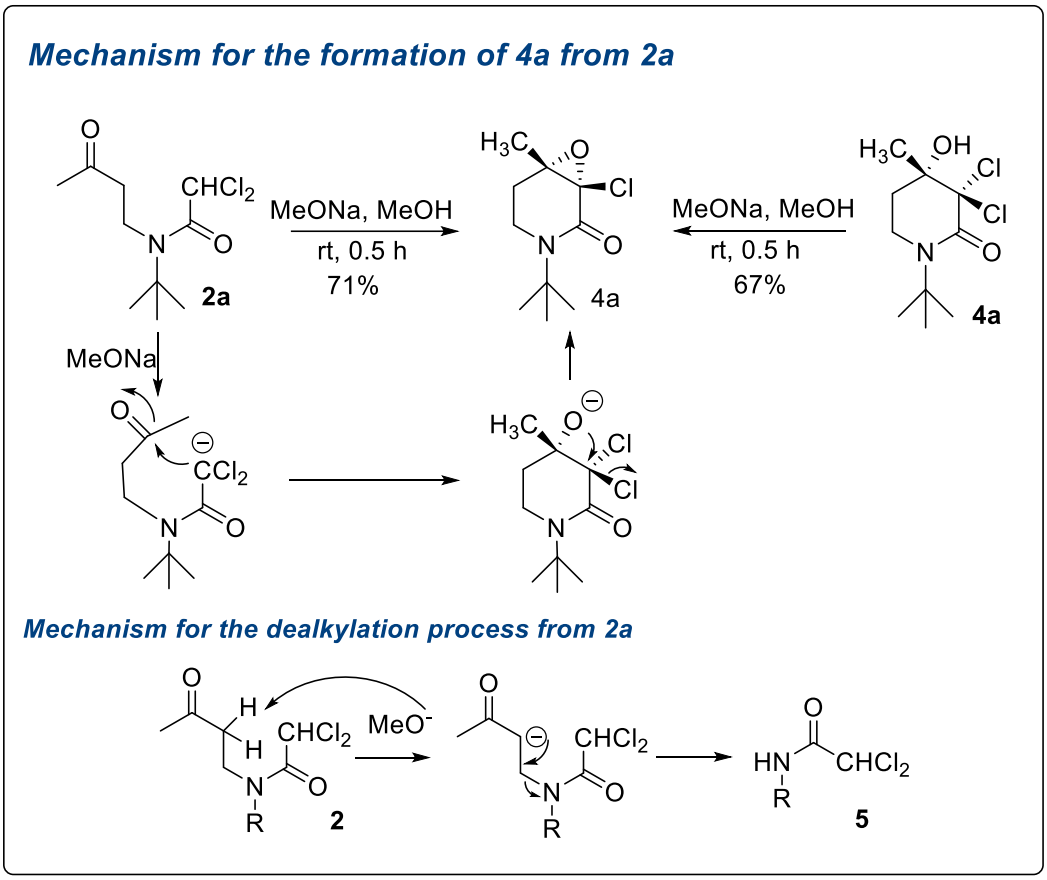


2 **4**

Entry	*R (**2**)*	*Base (equiv)*	*Conditions*	***4** Yield (%)*
1	*t*Bu (**2a**)	NaOMe (1.5)	MeOH, rt, 30 min	**4a** (67)
2	*t*Bu (**2a**)	NaOMe (1.0)	MeOH, rt, 30 min	**4a** (71)
3	*t*Bu (**2a**)	NaOMe (0.5)	MeOH, rt, 15 min	**4a** (33)*
4	*t*Bu (**2a**)	NaOMe (0.5)	Toluene, rt, 15 min	**4a** (72)
5	*t*Bu (**2a**)	*t*BuOK (1)	Toluene, rt, 30 min	**4a** (54)
6	*i*Pr (**2b**)	NaOMe (0.5)	Toluene, rt, 15 min	**4b** (61)
7	*i*Pr (**2b**)	*t*BuOK (1)	Toluene, rt, 30 min	**4b** (60)
8	Allyl (**2c**)	NaOMe (0.5)	Toluene, rt, 15 min	**4c** (63)
9	Allyl (**2c**)	*t*BuOK (1)	Toluene, rt, 30 min	**4c** (83)
10	Bn (**2d**)	NaOMe (0.5)	Toluene, rt, 15 min	**4d** (62)
11	Bn (**2d**)	*t*BuOK (1)	Toluene, rt, 30 min	**4d** (74)
12	$CH_2CH(OCH_3)_2$ (**2e**)	NaOMe (0.5)	Toluene, rt, 15 min	**4e** (46)
13	$CH_2CH(OCH_3)_2$ (**2e**)	*t*BuOK (1)	Toluene, rt, 30 min	**4e** (37)

*30% of S.M recovered

With dichloroacetamides **2** in hands, we set out to explore their behavior under Darzens conditions (Table 6.2). Thus, when **2a** was treated with 1.5 equiv sodium methoxide in methanol, epoxide **4a** was isolated in 67% yield (entry 1). A better yield was obtained when a stoichiometric amount of MeONa was used (entry 2) and a similar yield furnished when a substoichiometric quantity NaOMe was employed in toluene (compare entry 3 and 4). Switching to the more hindered *t*BuOK, gave **4a** with a lower yield (entry 5). The best reaction conditions using either NaOMe or *t*BuOK were then applied to dichloroacetamides **2b**-**2e** providing in all cases the corresponding epoxides **4** with acceptable to good yields.

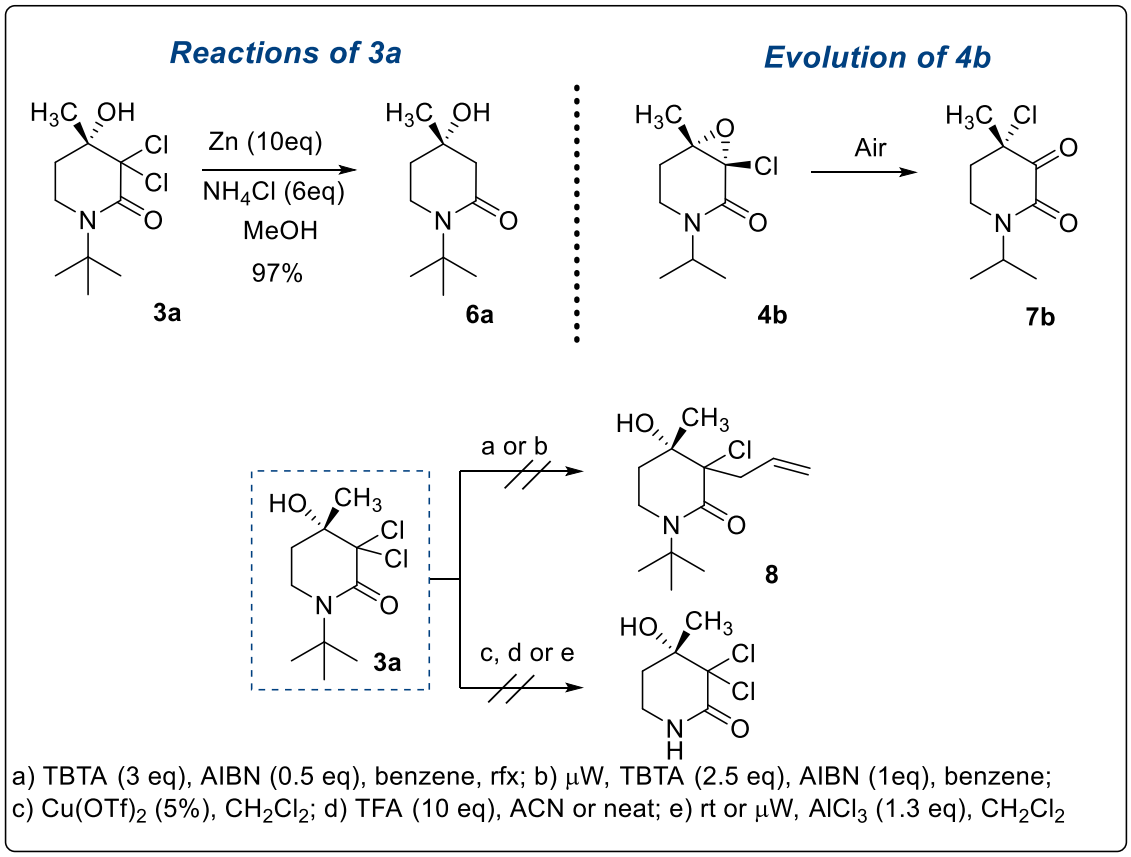


Scheme 6.2.

Formation of **4a** from **2a** could explained by the following scenario. After deprotonation, the α-dichloroamide adds to the carbonyl group and then an intramolecular SN_2 reaction provided epoxide **4a** (Scheme 6.2).

On the other hand, in some essays we isolated traces of amides **5** resulting from a dealkylation process. Indeed, the α-hydrogen adjacent to the carbonyl group, could be abstracted by the base triggering the cleavage of the carbon-nitrogen bond *via* a retro-aza-Michael reaction.[2]

[2] For examples of the dealkylation of amides in the presence of bases see: (a) Sahasrabudhe, K.; Gracias, v.; Furness, K.; Smith, B. T.; Katz, K. E.; Reddy, D. S.; Aube, J. J. Am. Chem. Soc. **2003**, *125*, 7914-7922. (b) Swindell, C. S.; Patel, B. P.; deSolmsl, S. J. *J.* Org. *Chem.* **1987**, *52*, 2346-2355.

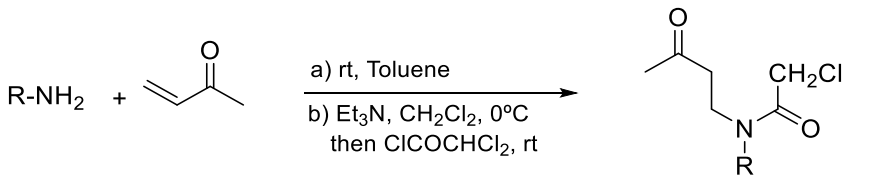


Scheme 6.2.

Even if we did not have time to explore all the synthetic possibilities of the intermediates prepared herein, piperidinone **3a** was successfully dehalogenated by treatment with Zn powder, to afford **6a** with an excellent yield. Nevertheless, our allylation attempts using radical chemistry furnished the allylated derivatives **8** in very poor yields. Additionally, we observed that epoxides **4** were instable providing the corresponding diones on standing.[3]

[3] (a) Mamedov, V.A.; Nuretdinov, I.A.; Subgatullina, F.G. *Russ Chem Bull*, **1988**, *37*, 1950-1951. (b) Mamedov, V.A., Litvinov, I.A., Kataeva, O.N. et al. *Monatsh. Chem.* **1994**, 125, 1427-1435.

Synthesis of chloroacetamides 9



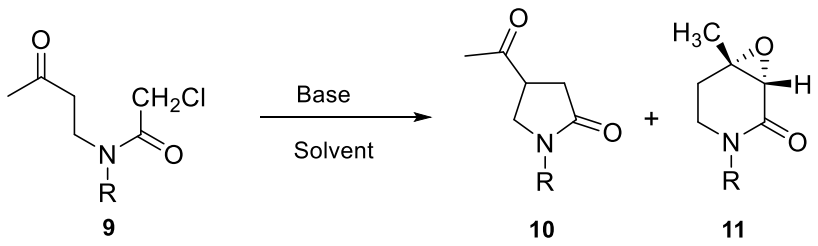
R= *t*Bu **9a** (39%)
Bn **9b** (67%)
Allyl **9c** (43%)

Scheme 6.3

After the results obtained with dichloroacetamides **2** for the preparation of epoxides **4** we were encouraged to see the behavior of monochloroacetamides **9** under the optimized cyclization conditions. Amides **9** were prepared using the same methodology reported previously for **2** (Scheme 6.3).

Table 6.3. Synthesis of **10** and **11** from **9**

Base-catalyzed cyclization of 9 into 10 and 11

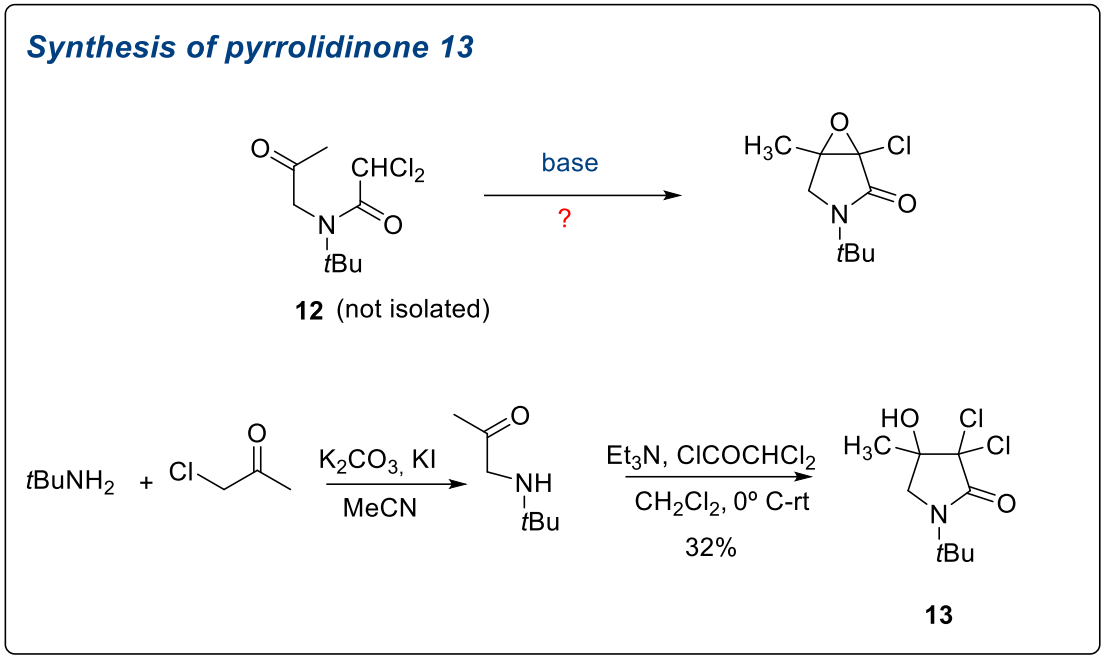


9 **10** **11**

R (9)	*Base (equiv)*	*Solvent*	*10 Yield (%)*	*11 Yield (%)*
*t*Bu (**9a**)	NaOMe (1.5)	MeOH, rt 30min	**10a** (32)	--
*t*Bu (**9a**)	*t*BuOK (1)	Toluene, rt 30min	**10a** (63)	--
Bn (**9b**)	NaOMe (0.5)	MeOH, rt 30min	**10b** (traces)	**11b** (35)
Bn (**9b**)	*t*BuOK (1)	Toluene, rt 30min	--	**11b** (47)
Allyl (**9c**)	*t*BuOK (1)	Toluene, rt 30min	--	**11c** (60)

When chloroacetamides **9** were treated with either MeONa or *t*BuOK, two main pathways were observed. Starting from **9a** with the bulky *t*-butyl group on the nitrogen atom only pyrrolidine **10a** was isolated resulting from a nucleophilic attack of the enolate generated from the ketone on the chloromethyl group.

Nevertheless piperidone **11b** and **11c** were isolated alone when the reaction was achieved from **9b** and **9c** respectively and in the presence *t*BuOK as a base (table 6.3).



Scheme 6.4

Finally, we decided to investigate Darzens reaction from dichloroacetamide **12,** which could be prepared from chloropropanone and *tert*-butylamine and further acylation with dichloroacetyl chloride. However, when the one-pot reaction was performed, pyrrolidine **13** was isolated alone with a moderate yield (32%, from *t*BuNH$_2$). After formation of **12** (not detected in the reaction crude), the cyclization took place spontaneously to afford polyfunctionalized pyrrolidine **13**.

Supporting information

for

Chapter 6

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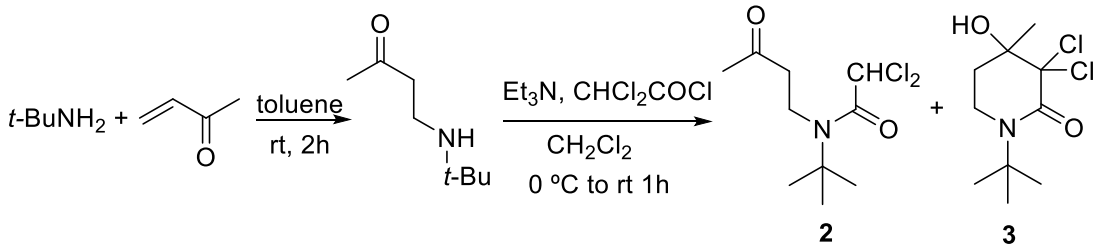
EXPERIMENTAL SECTION

1. General information. ^{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 and ^{13}C NMR spectra 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). 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). Drying of the organic extracts during reaction work-up was performed over anhydrous Na_2SO_4.

1. Synthesis of 2a – 3a



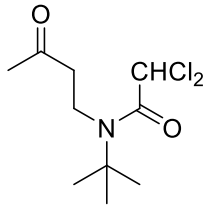
*1.1. Typical procedure (**Method A**)*

A mixture of *tert*-butylamine (2.818 mL, 27.34 mmol) in toluene (100 mL) was added methyl vinyl ketone (4.435 mL, 54.68 mmol), were stirred at rt for 2 h. CH_2Cl_2 (12 mL), Et_3N (5.72 mL, 41.04 mmol) and dichloroacetylchloride (3.16 mL, 32.85 mmol) were added successively at 0ºC. The mixture was stirred at rt for 1 h, then poured into water and extracted with CH_2Cl_2. The organics were dried, concentrated and purified by chromatography (CH_2Cl_2, SiO_2), to afford **2a** (31%) and **3a** (45%)

*1.2. Typical procedure using microwave activation (**Method B**)*

In a 10 mL vessel, a mixture of *tert*-butylamine (0.144 mL, 1.37 mmol) and methyl vinyl ketone (0.13 mL, 1.37 mmol) in toluene (1 mL) was heated with stirring at 60 ºC using microwave irradiation for 5 min. Then CH_2Cl_2 (0.5 mL), Et_3N (0.29 mL, 2.05 mmol) and dichloroacetylchloride (0.16 mL, 1.64 mmol) were added successively and heated at 60 ºC using microwave irradiation for 5 min. After chromatography (CH_2Cl_2, SiO_2), **2a** (122 mg, 35%) and **3a** (140 mg, 40%) were isolated.

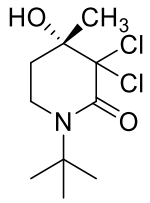
***N*-(*tert*-butyl)-2,2-dichloro-*N*-(3-oxobutyl)acetamide (2a)**



2a

IR (NaCl) 1713, 1673 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz, 1 rotamer): δ 1.46 (s, 9H, *t*-Bu), 2.20 (s, 3H, CH_3), 2.82 (t, *J* = 7.2 Hz, 2H, CH_2CO), 3.71 (t, *J* = 7.2 Hz, 2H, CH_2N), 6.42 (s, 1H, $CHCl_2$); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 28.3 (CH_3), 30.3 (CH_3), 39.4 (CH_2), 45.1 (CH_2), 58.8 (C), 66.5 (CH), 164.1 (CO), 205.6 (CO); HRMS (ESI-TOF) m/z: [M+H]+ Calcd for $C_{10}H_{18}Cl_2NO_2$ 254.0709 $[M+H]^+$; Found 254.0707.

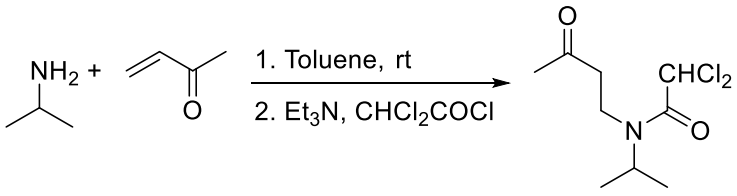
1-(*tert*-butyl)-3,3-dichloro-4-hydroxy-4-methylpiperidin-2-one (**3a)**



3a

IR (NaCl) ν 2966, 2930, 1671 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 1.45 (s, 9H, *t*-Bu), 1.60 (s, 3H, CH_3), 2.05 (ddd, *J* = 14.4 Hz, 5.6 Hz, 3.2 Hz, 1H, H-5), 2.42 (ddd, *J* = 14.4 Hz, 10.8 Hz, 6.4 Hz, 1H, H-5), 2.53 (br s, 1H, OH), 3.35 (ddd, *J* = 12 Hz, 6.4 Hz, 3.2 Hz, 1H, H-6), 3.49 (ddd, *J* = 12 Hz, 10.8, 5.6 Hz, 1H, H-6); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 24.6 (CH_3), 27.6 (CH_3), 31.1 (C-5), 39.3 (C-6), 58.8 (C), 75.1 (C-4), 92.4 (C-3), 163.6 (C-2); HRMS (ESI-TOF): Calcd for $C_{10}H_{18}Cl_2NO_2$ 254.0709 (M^++1). Found 254.0701.

2. Synthesis of 2b-e

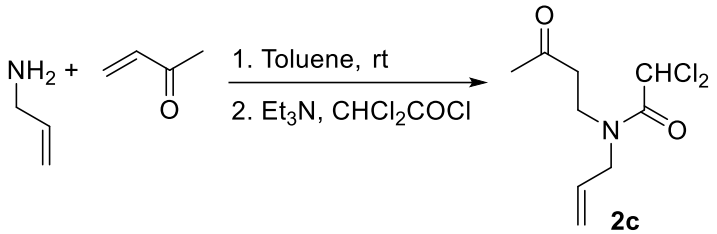


2b

2,2-dichloro-*N*-isopropyl-*N*-(3-oxobutyl) (2b):

To a solution of isopropylamine (2.349 mL, 27.34 mmol) in toluene (100 mL) was added methyl vinyl ketone (2.279 mL, 27.35 mmol).The mixture was stirred at rt for 2 h. Then CH_2Cl_2 (12 mL), Et_3N (5.72 mL, 41.04 mmol) and dichloroacetylchloride (3.16 mL, 32.85 mmol) were added successively at 0ºC. The mixture was stirred at rt for 1 h, then poured into water and extracted with CH_2Cl_2. The organics were dried, concentrated and purified

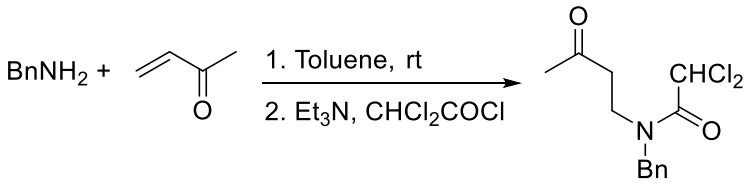
by chromatography (CH_2Cl_2, SiO_2), to afford **2b** (4.52 g, 69%) as a solid. IR (NaCl) 2977, 2941, 1717, 1670 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz, 82:18 rotamer ratio) *major rotamer* δ 1.26 (d, *J* = 6.8 Hz, 6H, 2 CH_3), 2.16 (s, 3H, CH_3), 2.80 (t, *J* = 7.6 Hz, 2H, CH_2CO), 3.47 (t, *J* = 7.6 Hz, 2H, CH_2N), 4.41 (sept, *J* = 6.8 Hz ,1H), 6.23 (s, 1H); *minor rotamer* δ 1.23 (d, *J* = 7.2 Hz, 6H, 2 CH_3), 2.21 (s, 3H, CH_3), 2.83 (t, *J* = 7.2 Hz, 2H, CH_2CO), 3.61 (t, *J* = 7.2 Hz, 2H, CH_2N), 4.34 (sept, *J* = 7.2 Hz ,1H), 6.44 (s, 1H);^{13}C NMR ($CDCl_3$, 100 MHz) *major rotamer* 20.4 (CH_3), 30.0 (CH_3), 36.9 (CH_2N), 41.9 (CH_2CO), 49.3 (CH), 65.9 (CH), 163.0 (CO), 206.8 (CO); *minor rotamer* 19.7 (CH_3), 30.2 (CH_3), 38.6 (CH_2N), 44.0 (CH_2CO), 48.9 (CH), 65.1 (CH), 163.5 (CO), 205.5 (CO); HRMS (ESI-TOF) m/z: $[M+H]^+$ Calcd for $C_9H_{16}Cl_2NO_2$ 240.0553 $[M+H]^+$; Found 240.0556.



2c

2,2-dichloro-*N*-allyl-*N*-(3-oxobutyl) (2c):

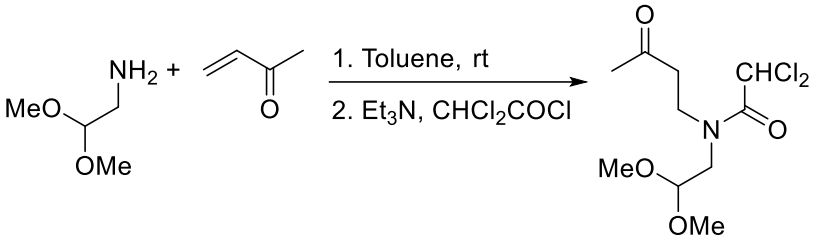
Operating as above from allylamine (2.051 mL, 27.34 mmol) and methyl vinyl ketone (2.279 mL, 27.35 mmol). Then CH_2Cl_2 (12 mL), Et_3N (5.72 mL, 41.04 mmol) and dichloroacetylchloride (3.16 mL, 32.85 mmol) were added (3.16 mL, 32.85 mmol), to afford **2c** (4.21g, 65%) . IR (NaCl) 3089, 3014, 2991, 1718, 1675 cm-1; ^1H NMR ($CDCl_3$, 400 MHz, 70:30 rotamer ratio) *major rotamer* δ 2.16 (s, 3H, CH_3), 2.82 (t, *J* = 6.8 Hz, 2H, CH_2CO), 3.58 (t, *J* = 6.8 Hz, 2H, CH_2N), 4.15 (dt, *J* = 4.8, 2 Hz ,2H), 5.18-5.32 (m, 2H), 5.78-5.91 (m, 1H), 6.17 (s, 1H); *minor rotamer* δ 2.19 (s, 3H, CH_3), 2.82 (t, *J* = 6.8 Hz, 2H, CH_2CO), 3.71 (t, *J* = 6.8 Hz, 2H, CH_2N), 3.97 (br d, *J* = 5.2 Hz ,2H), 5.16-5.26 (m, 2H), 5.72-5.83 (m, 1H), 6.68 (s, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) *major rotamer* 30.1 (CH_3), 41.1 (CH_2 CO), 43.2 (CH_2N), 51.7 (CH_2), 64.7 (CH), 117.9 (CH_2), 132.3 (CH), 164.0 (CO), 206.9 (CO); *minor rotamer* 30.2 (CH_3), 41.7 (CH_2CO), 41.9 (CH_2N), 49.0 (CH_2), 65.0 (CH), 117.9 (CH_2), 131.8 (CH), 163.7 (CO), 205.8 (CO); HRMS (ESI-TOF) m/z: $[M+H]^+$ Calcd for $C_9H_{14}Cl_2NO_2$ 238.0396 $[M+H]^+$; Found 238.0399.



2d

2,2-dichloro-*N*-benzyl-*N*-(3-oxobutyl)acetamide (**2d)**:

Operating as above from benzylamine (3.761 mL, 27.34 mmol) and methyl vinyl ketone (2.279 mL, 27.35 mmol). Then CH_2Cl_2 (12 mL), Et_3N (5.72 mL, 41.04 mmol) and dichloroacetylchloride (3.16 mL, 32.85 mmol) were added (3.16 mL, 32.85 mmol), to afford **2d** (5.33g, 68%) as a solid. IR (NaCl) 3087, 3063, 3030, 3008, 2946, 1714, 1668 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz, 57:43 rotamer ratio): *major rotamer* δ 2.11 (s, 3H, CH_3), 2.78 (t, *J* = 6.8 Hz, 2H, CH_2CO), 3.57 (t, *J* = 6.8 Hz, 2H, CH_2N), 4.76 (s, 2H, CH_2N), 6.22 (s, 1H), 7.19-7.40 (m, 5H, ArH) ; *minor rotamer* δ 2.03 (s, 3H, CH_3), 2.73 (t, *J* = 6.4 Hz, 2H, CH_2CO), 3.65 (t, *J* = 6.4 Hz, 2H, CH_2N), 4.60 (s, 2H, CH_2N), 6.83 (s, 1H), 7.19-7.40 (m, 5H, ArH); ^{13}C NMR ($CDCl_3$, 100 MHz) *major rotamer* 30.0 (CH_3), 40.7 (CH_2CO), 43.0 (CH_2N), 52.4 (CH_2Ar), 64.8 (CH), 126.4 (CH), 128.0 (CH), 129.0 (CH), 135.3 (C), 164.0 (CO), 206.7 (CO); *minor rotamer* 30.0 (CH_3), 41.2 (CH_2CO), 41.7 (CH_2N), 49.4 (CH_2Ar), 65.0 (CH), 127.5 (CH), 127.6 (CH), 128.7 (CH), 136.1 (C), 164.2 (CO), 205.9 (CO); HRMS (ESI-TOF) m/z: $[M+H]^+$ Calcd for $C_{13}H_{16}Cl_2NO_2$ 288.0553 $[M+H]^+$; Found 288.0547.

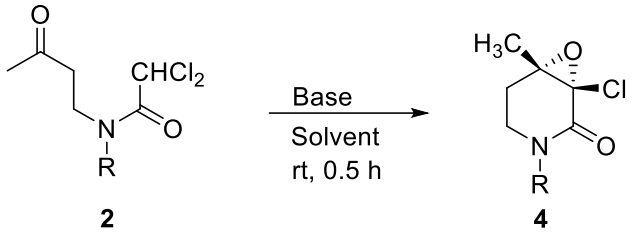


2e

2,2-dichloro-*N*-benzyl-*N*-(3-oxobutyl)acetamide (**2e)**:

Operating as above from 2,2-dimethoxyethan-1-amine (5.19 mL, 47.63 mmol) and methyl vinyl ketone (3.58 mL, 57.36 mmol). Then CH_2Cl_2 (20 mL), Et_3N (9.95 mL, 71.45 mmol) and dichloroacetylchloride (5.49 mL, 57.16 mmol) were added succesively, to afford **2e** (9.26g, 68%) as a solid. IR (NaCl) ν 2996, 2942, 2918, 2836, 1715, 1678 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz, 63:37 rotamer ratio): *major rotamer* δ 2.17 (s, 3H, CH_3), 2.84 (t, *J* = 6.4 Hz, 2H, CH_2CO), 3.45 (s, 6H, OCH_3), 3.57 (d, *J* = 5.2 Hz, 2H, CH_2N), 3.62 (t, *J* = 6.6 Hz, 2H, CH_2N),), 4.39 (t, *J* = 6 Hz, 2H, CH_2N), 6.60 (s, 1H) ; *minor rotamer* δ 2.19 (s, 3H, CH_3), 2.84 (t, *J* = 6.4 Hz, 2H, CH_2CO), 3.35 (d, *J* = 5.2 Hz, 2H, CH_2N), 3.43 (s, 6H, OCH_3), 3.72 (t, *J* = 6 Hz, 2H, CH_2N), 4.59 (t, *J* = 5.4 Hz, 2H, CH_2N), 6.84 (s, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) *major rotamer* 30.2 (CH_3), 41.3 (CH_2CO), 44.3 (CH_2N), 51.7 (CH_2N), 55.9(OCH_3), 103.1 (CH), 165.0 (CO), 207.2 (CO); *minor rotamer* 30.2 (CH_3), 41.3 (CH_2CO), 43.9 (CH_2N), 49.9 (CH_2N), 55.9(OCH_3), 64.9 (CH), 102.7 (CH), 164.5 (CO), 206.2 (CO); HRMS (ESI-TOF) m/z: $[M+H]^+$ Calcd for $C_{13}H_{16}Cl_2NO_2$ 286.0607 $[M+H]^+$; Found 286.0611.

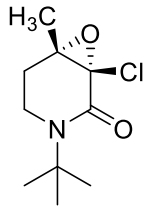
3. Synthesis of piperidinone 4



2 **4**

*3.1. Typical procedure using sodium methoxide (**Method A**)*

3-*tert*-butyl-1-chloro-6-methyl-7-oxa-3-azabicyclo[4.1.0]heptan-2-one (4a)

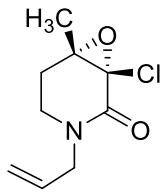


4a

To a solution **2a** (100 mg, 0.3934 mmol) in toluene (1 mL) was added sodium methoxide 30%wt (0.038 mL, 0.197 mmol). The mixture was stirred at rt for 15 minutes. The solution was quenched with water and extracted with CH_2Cl_2. The organics were dried, concentrated and purified by chromatography (CH_2Cl_2, SiO_2), to yield **4a** (62 mg, 72%). IR (NaCl) ν 2983, 2934, 1673 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 1.43 (s, 9H, *t*-Bu), 1.66 (s, 3H, CH_3), 2.05 (ddd, *J* = 14.8, 12.8, 5.6 Hz, 1H, H-5), 2.21 (ddd, *J* = 14.8 Hz, 4, 2 Hz, 1H, H-5), 3.16 (td, *J* = 12.8, 4 Hz, 1H, H-6), 3.31 (ddd, *J* = 12.8, 5.6, 2 Hz, 1H, H-6); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 17.9 (CH_3), 28.2 (CH_3), 30.5 (C-5), 37.7 (C-6), 59.0 (C), 65.3 (C-4), 80.9 (C-3), 162.4 (C-2); HRMS (ESI-TOF): Calcd for $C_{10}H_{17}ClNO_2$ 218.0942 (M^++1). Found 218.0047.

*3.2. Typical procedure using Potassium Tert-butoxide (**Method B**)*

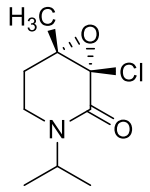
3-allyl-1-chloro-6-methyl-7-oxa-3-azabicyclo[4.1.0]heptan-2-one (4c)



4c

To a solution of **2c** (100 mg, 0.420 mmol) in toluene (1 mL) was added potassium *tert*-butoxide 1M (0.420 mL, 0.420 mmol). The mixture was stirred at rt for 30 minutes. Then quenched with water and extracted with CH_2Cl_2. The organics were dried, concentrated and purified by chromatography (CH_2Cl_2, SiO_2), to afford **4c** (70 mg 83%). IR (NaCl) ν 3083, 3008, 2928, 2855, 1675 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 1.68 (s, 3H, CH_3), 2.13 (ddd, *J* = 15.2, 12.8, 5.6 Hz, 1H, H-5), 2.23 (ddd, *J* = 15.2 Hz, 4.8, 2 Hz, 1H, H-5), 2.97 (ddd, *J* = 12.8, 6, 2 Hz, 1H, H-6), 3.34 (td, *J* = 12.8, 4.8 Hz, 1H, H-6), 3.92 (ddt, *J* = 15.2, 6, 1.2 Hz, 1H), 4.10 (ddt, *J* = 15.2, 6, 1.6 Hz, 1H), 5.14-5.22 (m, 2H), 5.67-5.78 (m, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 18.3 (CH_3), 29.3 (C-5), 41.1 (C-6), 51.1 (CH_2), 65.9 (C-4), 79.3 (C-3), 118.2 (CH_2), 131.9 (CH), 162.3 (C-2); HRMS (ESI-TOF) m/z: $[M+H]^+$ Calcd for $C_9H_{13}ClNO_2$ 202.0629; found 202.0631.

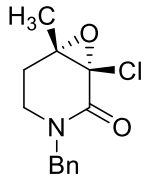
3-isopropyl-1-chloro-6-methyl-7-oxa-3-azabicyclo[4.1.0]heptan-2-one (4b)



4b

Operating as above from **2b** (100 mg, 0.348 mmol) and potassium *tert*-butoxide 1M (0.348 mL, 0.348 mmol) in toluene (1 mL), **4b** was isolated (51 mg, 60%) as a solid. IR (NaCl) ν 2976, 2932, 2923, 2932, 2874, 1667 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 1.10 (d, *J* = 6.8 Hz, 3H, CH_3), 1.11 (d, *J* = 6.8 Hz, 3H, CH_3), 1.68 (s, 3H, CH_3), 2.02 (ddd, *J* = 14.8, 12.8, 6 Hz, 1H, H-5), 2.26 (ddd, *J* = 14.8 Hz, 4, 2 Hz, 1H, H-5), 3.02 (ddd, *J* = 12.8, 6, 2 Hz, 1H, H-6), 3.13 (td, *J* = 12.8, 4.4 Hz, 1H, H-6); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 18.1 (CH_3), 19.3 (CH_3), 19.4 (CH_3), 29.6 (C-5), 34.8 (C-6), 46.1 (CH), 65.4 (C-4), 79.7 (C-3), 161.7 (C-2);

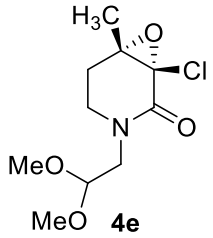
3-benzyl-1-chloro-6-methyl-7-oxa-3-azabicyclo[4.1.0]heptan-2-one (4d)



4d

Operating as above from **2d** (100 mg, 0.348 mmol) and potassium *tert*-butoxide 1M (0.348 mL, 0.348 mmol) in toluene (1 mL), **4d** was isolated (64.5 mg, 74%) as a solid. IR (NaCl) ν 3086, 3062, 3030, 2961, 2928, 1654cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.68 (s, 3H, CH_3), 2.07 (ddd, *J* = 14.8, 12.4, 5.6 Hz, 1H, H-5), 2.17 (ddd, *J* = 14.8 Hz, 4.4, 2 Hz, 1H, H-5), 2.93 (ddd, *J* = 12.4, 5.6, 2 Hz, 1H, H-6), 3.30 (td, *J* = 12.4, 4.4 Hz, 1H, H-6), 4.47 (d, *J* = 14.8 Hz, 1H, CH_2N), 4.72 (d, *J* = 14.8 Hz, 1H, CH_2N), 7.21-7.36 (m, 5H, ArH) ; ^{13}C NMR ($CDCl_3$, 100 MHz) δ 18.3 (CH_3), 29.3 (C-5), 41.2 (C-6), 51.9 (CH_2N), 65.9 (C-4), 79.3 (C-3), 127.8 (CH), 128.0 (CH), 128.7 (CH), 136.1 (C), 162.8 (C-2)

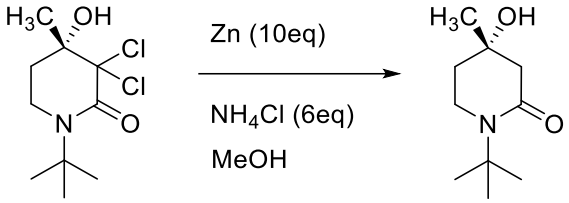
1-chloro-3-(2,2-dimethoxyethyl)-6-methyl-7-oxa-3-azabicyclo[4.1.0]heptan-2-one (4e)



4e

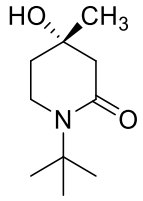
Operating as above from **2e** (200 mg, 0.699 mmol) and sodium methoxide 30%wt (0.348 mL, 0.348 mmol) in toluene (2 mL), **4e** was isolated (80 mg, 46%) as a solid. IR (NaCl) ν 2990, 2939, 2835, 1672 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.68 (s, 3H, CH_3), 2.16 (m, 2H, H-5), 3.13 (ddd, *J* = 15.2, 7.6, 2.4 Hz, 1H, CH_2N), 3.41 (d, *J* = 4.8 Hz, 6H, OCH_3), 3.44 (d, *J* = 5.2 Hz, 2H, H-1), 3.48 (td, *J* = 12.2 Hz, 1H, CH_2N), 4.69(t, *J* = 5.4 Hz, 1H, CH); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 18.2 (CH_3), 29.4 (C-5), 43.9 (C-6), 51.4 (CH_2N), 55.2 (OCH_3) 66.0 (C-4), 79.3 (C-3), 102.9 (CH), 162.8 (C-2); HRMS (ESI-TOF): Calcd for $C_{10}H_{17}ClNO_4$ 250.0841 (M^++1). Found 250.0846.

4. Preparation of 6



3a **6a**

1-(*tert*-butyl)-4-hydroxy-4-methylpiperidin-2-one (6a)



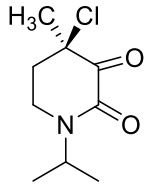
6a

To a solution of **3a** (734 mg, 2.888 mmol) in MeOH (7 mL) at 0ºC was added NH4Cl (927 mg, 17.329 mmol) and Zn powder (1.88g, 28.89 mmol) portionwise. The solution was stirred at rt overnight, filtered on a celite pad, concentrated and purified by chromatography (CH_2Cl_2 to CH_2Cl_2/MeOH 1%, SiO_2) to yield **6a** (516 mg, 97%)

IR (NaCl): ν = 3407, 3342, 3272, 2965, 2928, 1615, 1599, 1576 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz): δ = 1.32 (s, 3H, CH_3) 1.46 (s, 9H, *t*-Bu), 1.73 (ddd, *J* = 13.6 Hz, 10 Hz, 5.6 Hz, 1H, H-5), 1.88 (m, 1H, H-5), 2.44 (bs, 1H, OH), 2.6 (d, *J* = 17.6 Hz, 1H, H-3), 2.68 (d, *J* = 17.6 Hz, 1H, H-3), 3.38 (ddd, *J* = 12.4 Hz, 5.6 Hz, 4.4 Hz, 1H, H-6), 3.55 (ddd, *J* = 12.4 Hz, 10 Hz, 4.8 Hz, 1H, H-6); ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 28.2 (CH_3), 28.8 (CH_3), 35.8 (C-5), 41.1 (C-3), 48.2 (C-6), 58.6 (C), 67.5 (C), 171.5 (C-2); HRMS (ESI-TOF): Calcd for $C_{10}H_{20}NO_2$ 186.1489 (M^++1). Found 186.1484.

5. Degradation Products

4-chloro-1-isopropyl-4-methylpiperidine-2,3-dione (7b)

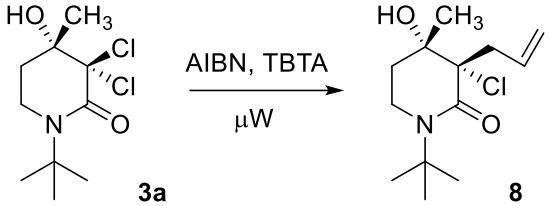


7b

IR (NaCl) ν 2993, 2971, 2932, 2917, 2872, 1739, 1653 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 1.20 (d, *J* = 6.8 Hz, 3H, CH_3), 1.24 (d, *J* = 7.2 Hz, 3H, CH_3), 1.78 (s, 3H, CH_3), 2.33 (ddd, *J* = 16, 14.8, 5.2 Hz, 1H, H-5), 2.48 (ddd, *J* = 14.8 Hz, 6.4, 0.8 Hz, 1H, H-5), 3.34 (ddd, *J* = 13.2, 7.2, 2.4 Hz, 1H, H-6), 3.13 (ddd, *J* = 14.8, 13.2, 4 Hz, 1H, H-6), 4.85 (p, *J* = 13.6, 6.8 Hz, 1H, H-1); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 18.1 (CH_3), 19.1 (CH_3), 25.3

(CH_3), 36.3 (C-5), 36.9 (C-6), 45.9 (CH), 66.3 (C-4), 155.8 (C-2), 184.3 (C-3); HRMS (ESI-TOF): Calcd for $C_9H_{15}ClNO_2$ 204.0786 (M^++1). Found 204.0785.

6. Preparation of 8 and *epi*-8

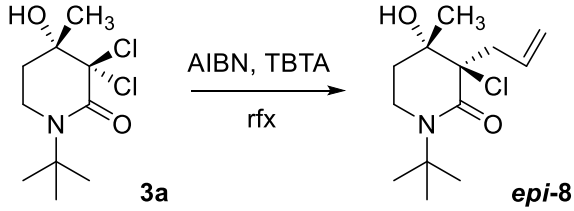


3a **8**

In a 10 mL vessel, a mixture of **3a** (100 mg, 0.39 mmol), AIBN (32 mg, 0,20 mmol) and TBTA (0.305 mL, 0.98 mmol) in benzene (1 mL) was heated with stirring at 100 ºC using microwave irradiation for 45 min. After chromatography (CyHex:AcOEt 9:1, SiO_2), it was obtained **8**(6 mg, 6%),

(3*S*,4*S*)-3-allyl-1-(*tert*-butyl)-3-chloro-4-hydroxy-4-methylpiperidin-2-one (8)

^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.45 (s, 9H, CH_3) 1.48 (s, 3H, CH_3), 1.83 (ddd, J = 14, 10.4, 4 Hz, 1H, H-5), 2.35 (ddd, *J* = 16, 8.8, 2 Hz, 1H, H-5), 2.80 (ddt, *J* = 14.4, 9.6, 0.8 Hz, 1H, H-6), 2.76 (ddt, *J* = 14.8, 9.6, 1.2 Hz, 1H, CH_2), 2.89 (ddt, *J* = 14.8, 9.6, 1.2 Hz, 1H, CH_2), 3.46 (ddd, *J* = 15.2, 11.6, 6 Hz, 1H, H-6), 5.01-5.22 (m, 2H), 6.01-6.11 (m, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 25.1 (CH_3), 27.8 (CH_3), 32.5 (C-5), 39.6 (C-6), 41.8 (CH_2), 58.0 (C-1), 73.8 (C-3), 74.4 (C-4),117.6 (CH_2), 136.5(CH), 167.5 (C-2); HRMS (ESI-TOF) m/z: [M+H]+ Calcd for $C_{13}H_{23}ClNO_2$ 260.1412; found 260.1412.



3a ***epi*-8**

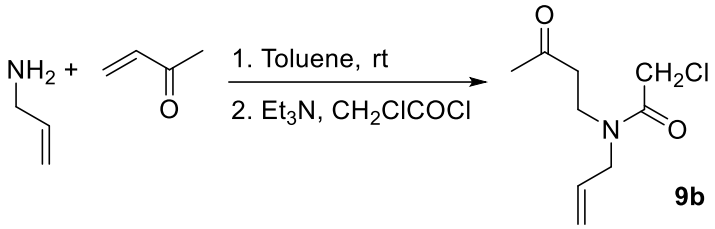
A mixture of **3a** (100 mg, 0.39 mmol), AIBN (32 mg, 0.20 mmol) and TBTA (0.305 mL, 0.98 mmol) in benzene (1 mL) was heated to reflux for 4 h. After chromatography (CyHex:AcOEt 9:1, SiO_2), ***epi*-8** was isolated as an amorphous solid (32 mg, 16%).

(3*S*,4*S*)-3-allyl-1-(*tert*-butyl)-3-chloro-4-hydroxy-4-methyl-piperidin-2-one (*epi*-8)

^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.35 (s, 9H, CH_3) 1.49 (s, 3H, CH_3), 1.83 (ddd, J = 14, 10.4, 4 Hz, 1H, H-5), 2.14 (dt, *J* = 11.2, 5.6 Hz, 1H, H-5), 2.80 (ddt, *J* = 14.4, 9.6, 0.8 Hz, 1H, H-6), 3.31 (ddd, J = 11.6, 5.2, 1H, CH_2), 3.26 (ddd, J = 11.6, 5.2 Hz, 1H, H-6), 3.40 (ddd, J = 14.4, 8.4, 6 Hz, 1H, CH_2), 5.03-5.08 (m, 2H), 5.90-6.00 (m, 1H); ^{13}C NMR ($CDCl_3$,

100 MHz) δ 24.1 (CH_3), 27.8 (CH_3), 32.9 (C-5), 39.7 (C-6), 42.9 (CH_2), 58.1 (C-1), 73.8 (C-3), 74.4 (C-4),118.0 (CH_2), 133.6 (CH), 167.8 (C-2); HRMS (ESI-TOF) m/z: [M+H]+ Calcd for $C_{13}H_{23}ClNO_2$ 260.1412; found 260.1414.

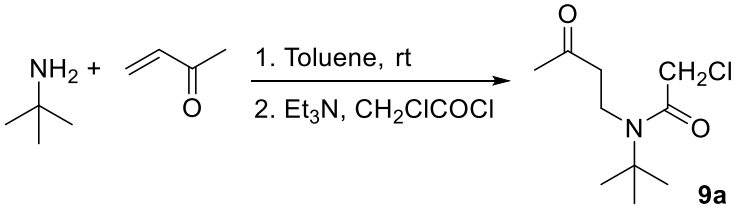
7. Preparation of 9 and 10



7.1. Typical procedure

_N_-allyl-2-chloro-_N_-(3-oxobutyl)acetamide (9b)

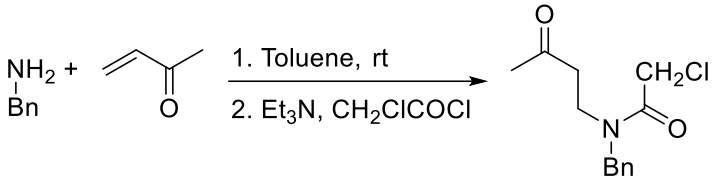
To a solution of allylamine (1.00 mL, 13.36 mmol) in toluene (50 mL) was added methyl vinyl ketone (1.08 mL, 13.36 mmol) and stirred at rt for 2 h. Then, CH_2Cl_2 (4 mL), Et_3N (2.79 mL, 20.04 mmol) and 2-chloroacetylchloride (1.28 mL, 16.04 mmol) were added successively at 0ºC. The mixture was stirred for 1 h, then poured into water and extracted with CH_2Cl_2. The organics were dried, concentrated and purified by chromatography (CH_2Cl_2, SiO_2), to yield **9b** (1.83g, 67%) as a yellow oil. cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz, 70:30 rotamer ratio) *major rotamer* δ 2.16 (s, 3H, CH_3), 2.81 (t, J = 6.6 Hz, 2H, CH_2CO), 3.56 (t, J = 6.6 Hz, 2H, CH_2N), 4.02 (s, 2H), 4.04 (dt, J = 4.8, 1.6 Hz, 2H), 5.18-5.26 (m, 2H), 5.77-5.87 (m, 1H); *minor rotamer* δ 2.18 (s, 3H, CH_3), 2.81 (t, J = 6.6 Hz, 2H, CH_2CO), 3.63 (t, J = 6.8 Hz, 2H, CH_2N), 3.96 (br d, J = 5.6 Hz ,2H), 4.23 (s, 2H), 5.15-5.19 (m, 2H), 5.72-5.82 (m, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) *major rotamer* 30.1 (CH_3), 41.1 (CH), 41.5 (CH_2CO), 42.4 (CH_2N), 51.6 (CH_2), 117.5 (CH_2), 132.7 (CH), 166.9 (CO), 207.2 (CO); *minor rotamer* 30.3 (CH_3), 41.1 (CH), 41.9 (CH_2CO), 42.2 (CH_2N), 48.2 (CH_2), 117.2 (CH_2), 132.5 (CH), 166.5 (CO), 205.9 (CO); HRMS (ESI-TOF): Calcd for $C_9H_{15}ClNO_2$ 204.0786 (M^++1). Found 204.0785.



_N_-(_tert_-butyl)-2-chloro-_N_-(3-oxobutyl)acetamide (9a)

Operating as above from *tert*-butylamine (1 mL, 9.515 mmol) and methyl vinyl ketone (0.772 mL, 9.515 mmol), Then CH_2Cl_2 (4 mL), Et_3N (1.99 mL, 14.27 mmol) and chloroacetylchloride (0.91 mL, 11.42 mmol) were added successively, to afford **9a** (822 mg, 39%) as a yellow oil. ; ^1H NMR ($CDCl_3$, 400 MHz) δ 1.44 (s, 9H, CH_3), 2.19 (s, 3H,

CH_3), 2.78 (ddd, *J* = 8, 4.4, 1.6 Hz, 1H, CH_2O), 3.64 (ddd, *J* = 7.6, 4.4, 1.6 Hz, 2H, CH_2N), 4.1 (s, 2H, CH_2Cl); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 28.5 (CH_3), 30.3 (CH_3), 39.8 (CH_2N), 44.0 (CH_2Cl), 45.2 (CH_2CO), 57.9 (C), 166.8 (CO), 206.7 (CO); HRMS (ESI-TOF): Calcd for $C_{10}H_{19}ClNO_2$ 220.1099 (M^++1). Found 220.1101.

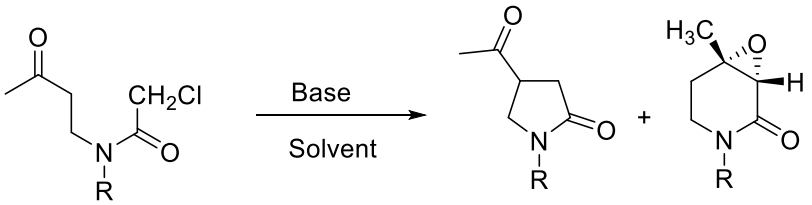


9c

***N*-benzyl-2-chloro-*N*-(3-oxobutyl)acetamide (9c)**

Operating as above from benzylamine (1 mL, 9.15 mmol) and methyl vinyl ketone (0.743 mL, 9.15 mmol), Then CH_2Cl_2 (4 mL), Et_3N (1.91 mL, 13.73 mmol) and chloroacetylchloride (0.88 mL, 10.99 mmol) were added successively, to afford **9c** (1g, 43%) as a yellow oil. IR (NaCl) ν 3086, 3062, 3031, 2999, 2948, 1714, 1657 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz, 57:43 rotamer ratio): *major rotamer* δ 2.13 (s, 3H, CH_3), 2.80 (t, *J* = 6.4 Hz, 2H, CH_2CO), 3.59 (t, *J* = 6.8 Hz, 2H, CH_2N), 4.05 (s, 2H, CH_2Cl), 4.67 (s, 2H, CH_2N), 7.18-7.40 (m, 5H, ArH) ; *minor rotamer* δ 2.02 (s, 3H, CH_3), 2.68 (t, *J* = 6.6 Hz, 2H, CH_2CO), 3.61 (t, *J* = 6.4 Hz, 2H, CH_2N), 4.32 (s, 2H, CH_2Cl), 4.59 (s, 2H, CH_2N), 7.18-7.40 (m, 5H, ArH); ^{13}C NMR ($CDCl_3$, 100 MHz) *major rotamer* 30.1 (CH_3), 41.3 (CH_2Cl), 41.3 (CH_2CO), 42.7 (CH_2N), 52.7 (CH_2Ar), 52.7 (CH), 126.4 (CH), 128.0 (CH), 129.1 (CH), 136.0 (C), 164.2 (CO), 207.2 (CO); *minor rotamer* 30.2 (CH_3), 41.3 (CH_2Cl), 41.7 (CH_2CO), 42.2 (CH_2N), 48.9 (CH_2Ar), 48.9 (CH), 127.6 (CH), 127.8 (CH), 128.8(CH), 136.8 (C), 167.2 (CO), 205.9 (CO); HRMS (ESI-TOF) m/z: $[M+H]^+$ Calcd for $C_{13}H_{17}ClNO_2$ 254.0942 $[M+H]^+$; Found 254.0941.

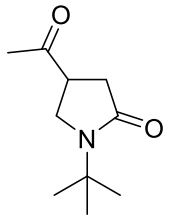
8. Preparation of 10 and 11



9 **10** **11**

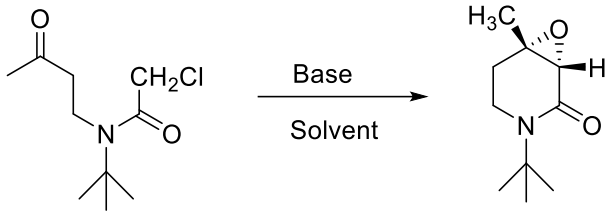
*8.1. Typical procedure using Sodium Methoxide (**Method A**)*

4-acetyl-1-(*tert*-butyl)pyrrolidin-2-one (10a)



10a

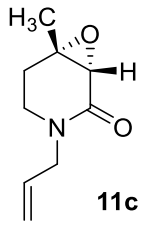
To a solution of **9a** (266 mg, 1.21 mmol) in MeOH (3 mL) was added sodium methoxide 30%wt (0.23 mL, 1.21 mmol). The mixture was stirred at rt for 30 minutes. The solution was quenched with water and extracted with CH_2Cl_2. The organics were dried, concentrated and purified by chromatography (CH_2Cl_2, SiO_2), to afford **10a** (70 mg, 32%) IR (NaCl) ν 3465, 3433,2975, 2933, 1714, 1684 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 1.40 (s, 9H, CH_3), 2.21 (s, 3H, CH_3), 2.51 (dd, *J* = 16.8, 8 Hz, 1H, H-3), 2.62 (dd, *J* = 16.4 Hz, 10 Hz, 1H, H-3), 3.13-3.22 (m, 1H, H-5), 3.54 (dd, *J* = 4.8, 1.2 Hz, 1H, H-6), 3.67 (dd, *J* = 6.4, 3.6 Hz, 1H, H-6); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 27.6 (CH_3), 28.4 (CH_3), 35.3 (C-3), 43.3 (C-4), 46.2 (C-5), 54.3 (C), 172.2 (C=O), 206.4 (C=O); HRMS (ESI-TOF): Calcd for $C_{10}H_{18}NO_2$ 184.1332 (M^++1). Found 184.1332.



9a **11a**

*8.2. Typical procedure using Potassium Tert-butoxide (**Method B**)*

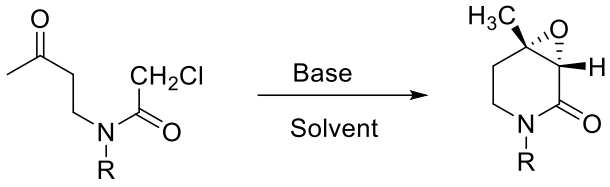
3-allyl-6-methyl-7-oxa-3-azabicyclo[4.1.0]heptan-2-one (11c)



11c

To a solution of **9c** (200 mg, 0.98 mmol) in toluene (2 mL) was added potassium *tert*-butoxide 1M (0.98 mL, 0.98 mmol), were stirred at rt for 30 minutes. The solution was quenched with water and extracted with CH_2Cl_2. The organics were dried, concentrated and purified by chromatography (CH_2Cl_2, SiO_2), to afford **11c** (98 mg, 60%). IR (NaCl) ν

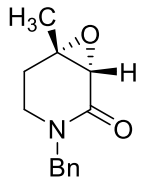
3081, 3016, 2919, 1660 cm-1; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.48 (s, 3H, CH_3), 2.03 (ddd, J = 14.8, 12.4, 6 Hz, 1H, H-5), 2.12 (ddd, J = 14.4, 4, 2 Hz, 1H, H-5), 2.93 (ddd, J = 12.4, 5.6, 1.6 Hz, 1H, H-6), 3.31 (s, H-3),3.38 (td, J = 12.8, 4.4 Hz, 1H, H-6), 3.86 (ddt, J = 15.2, 6.4, 1.2 Hz, 1H), 4.07 (ddt, J = 15.2, 5.6, 1.2 Hz, 1H), 5.13-5.19 (m, 2H), 5.67-5.78 (m, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 20.5 (CH_3), 29.3 (C-5), 41.1 (C-6), 49.4 (CH_2), 57.6 (C-3), 59.9 (C-4), 117.6 (CH_2), 132.3 (CH), 166.8 (C-2); HRMS (ESI-TOF) m/z: [M+H]+ Calcd for $C_9H_{14}NO_2$ 168.1019; found 168.1023.



9 **11**

R=Allyl, Bn

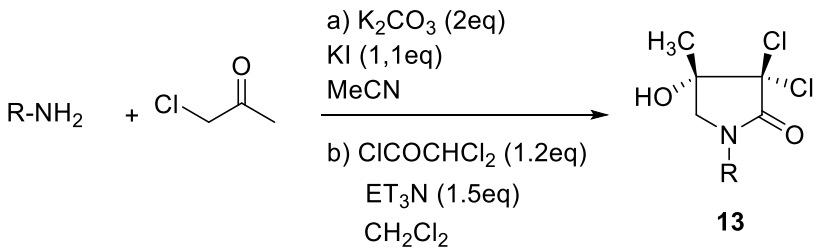
3-benzyl-6-methyl-7-oxa-3-azabicyclo[4.1.0]heptan-2-one (11b)



11b

Operating as above from **9b** (250 mg, 0.985 mmol) and potassium *tert*-butoxide 1M (0.985 mL, 0.985 mmol) in toluene (2.5 mL), **11b** was isolated (112 mg, 47%). IR (NaCl) ν 3086, 3062, 3030, 2962, 2928, 1655 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.48 (s, 3H, CH_3), 1.94 (ddd, *J* = 14.4, 12.4, 6 Hz, 1H, H-5), 2.06 (ddd, *J* = 14.4 Hz, 4, 1.2 Hz, 1H, H-5), 2.89 (ddd, *J* = 12.4, 6, 1.6 Hz, 1H, H-6), 3.34 (td, *J* = 12.4, 4.4 Hz, 1H, H-6), 3.38 (s, H-3), 4.47 (d, *J* = 11.2 Hz, 1H, CH_2N), 4.72 (d, *J* = 11.2 Hz, 1H, CH_2N), 7.21-7.36 (m, 5H, ArH) ; ^{13}C NMR ($CDCl_3$, 100 MHz) δ 20.5 (CH_3), 29.3 (C-5), 41.2 (C-6), 50.2 (CH_2N), 57.6 (C-3), 59.9 (C-4), 127.5 (CH), 127.9 (CH), 128.7 (CH), 136.6 (C), 167.2 (C-2); HRMS (ESI-TOF): Calcd for $C_{13}H_{16}NO_2$ 218.1176 (M^++1). Found 218.1176.

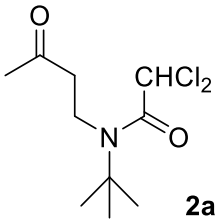
9. Preparation of 13.



1-(*tert*-butyl)-3,3-dichloro-4-hydroxy-4-methylpyrrolidin-2-one (13)

To a solution of *tert*-butylamine (0.5 mL, 4.76 mmol) and potassium carbonate (1.3g, 9.515 mmol) in acetonitrile (14 mL) at 0ºC was added chloroacetone (0.392 mL, 4.76 mmol), and potassium iodide (870 mg, 5.24 mmol). The mixture was stirred at rt for 4 h. The resulting solution was filtered on a celite pad, concentrated and purified by a flash chromatography (CH_2Cl_2, SiO_2) to yield 1-(*tert*-butylamino)propan-2-one (94%). CH_2Cl_2 (12 mL), Et_3N (0.94 mL, 6.74 mmol) and dichloroacetylchloride (0.52 mL, 5.40 mmol) were added successively at 0ºC. The mixture was stirred at rt for 1 h, then poured into water and extracted with CH_2Cl_2. The organics were dried, concentrated and purified by chromatography (CH_2Cl_2, SiO_2), to yield **13** (370 mg, 32% global) as an oil.

IR (NaCl) ν 3429, 3401, 3379, 2979, 2936, 2916, 2896, 1703 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 1.39 (s, 3H, CH_3), 1.53 (s, 9H, CH_3), 2.77 (br s, OH), 3.41 (d, J = 10 Hz, 1H, CH_2), 3.45 (d, J = 10 Hz, 1H, CH_2); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 20.7 (CH_3), 27.1 (CH_3), 53.9 (C-5), 55.2 (C), 76.2 (C-4), 90.1 (CCl_2), 165.3 (C=O); HRMS (ESI-TOF): Calcd for $C_9H_{15}ClNO_2$ 240.0553 (M^++1). Found 240.0556.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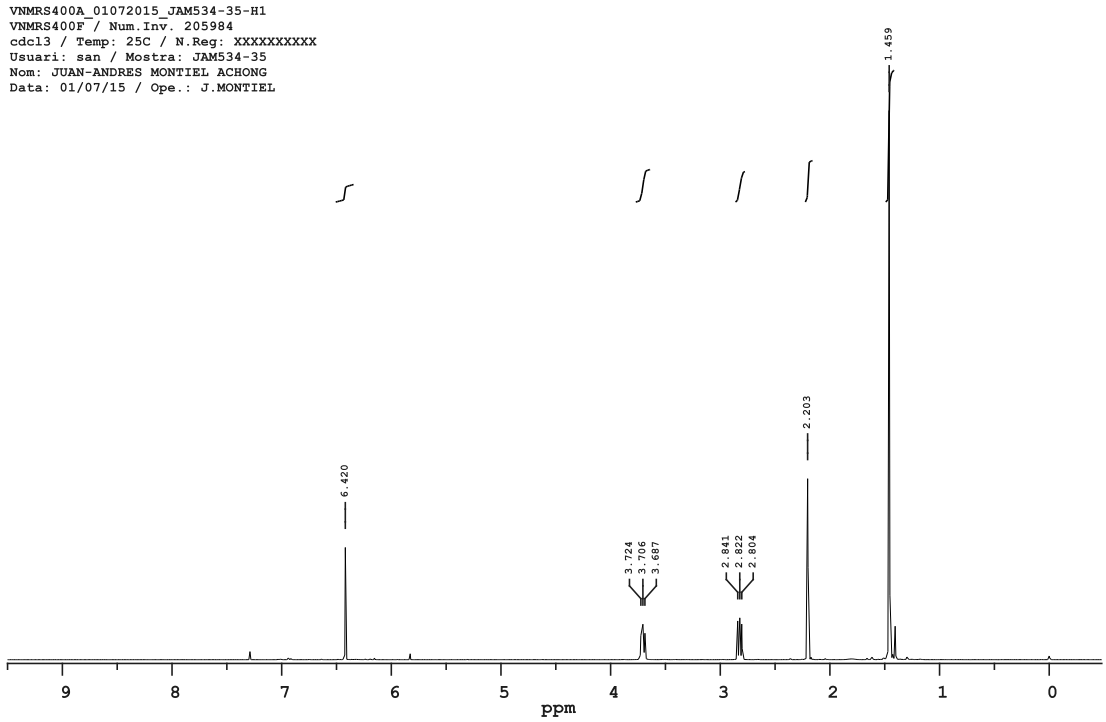
CHCl2
N
O

2a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cdcl3 / Temp: 25C / N.Reg: XXXXXXXXXX
Usuari: san / Mostra: JAM534-35
Nom: JUAN-ANDRES MONTIEL ACHONG
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2.841
2.822
2.804
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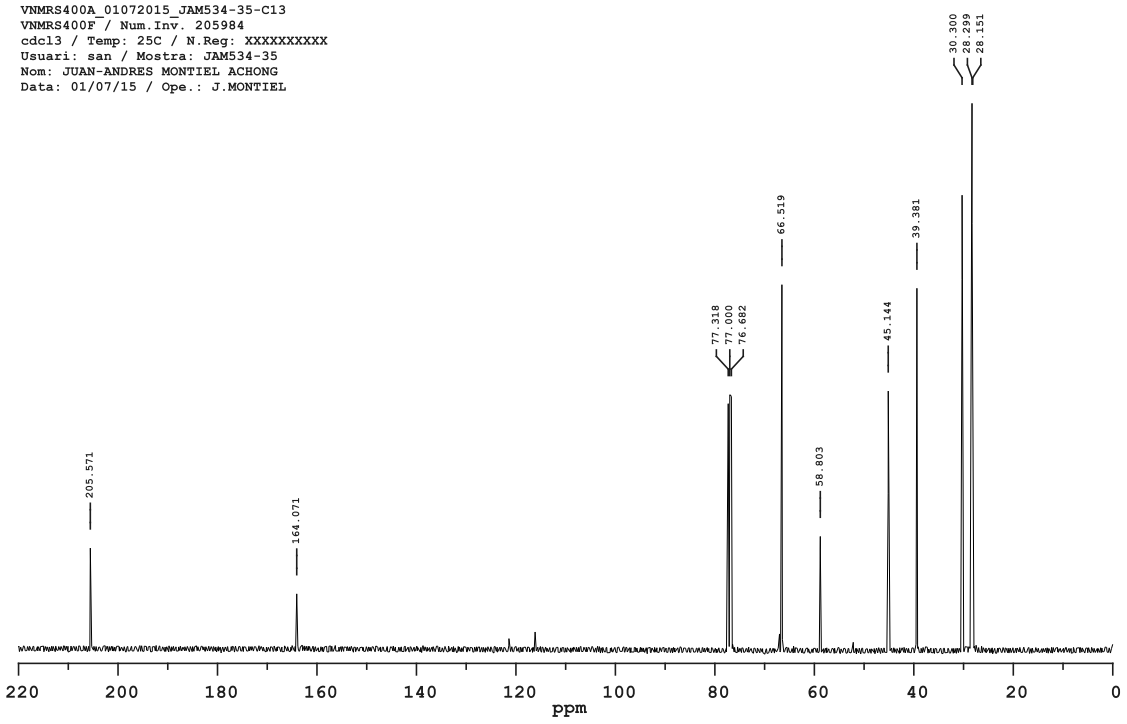
8
7
6
5
4
3
2
1
0
ppm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77.000
76.682
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200
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160
140
120
100
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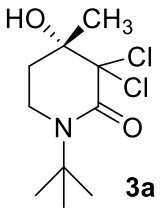
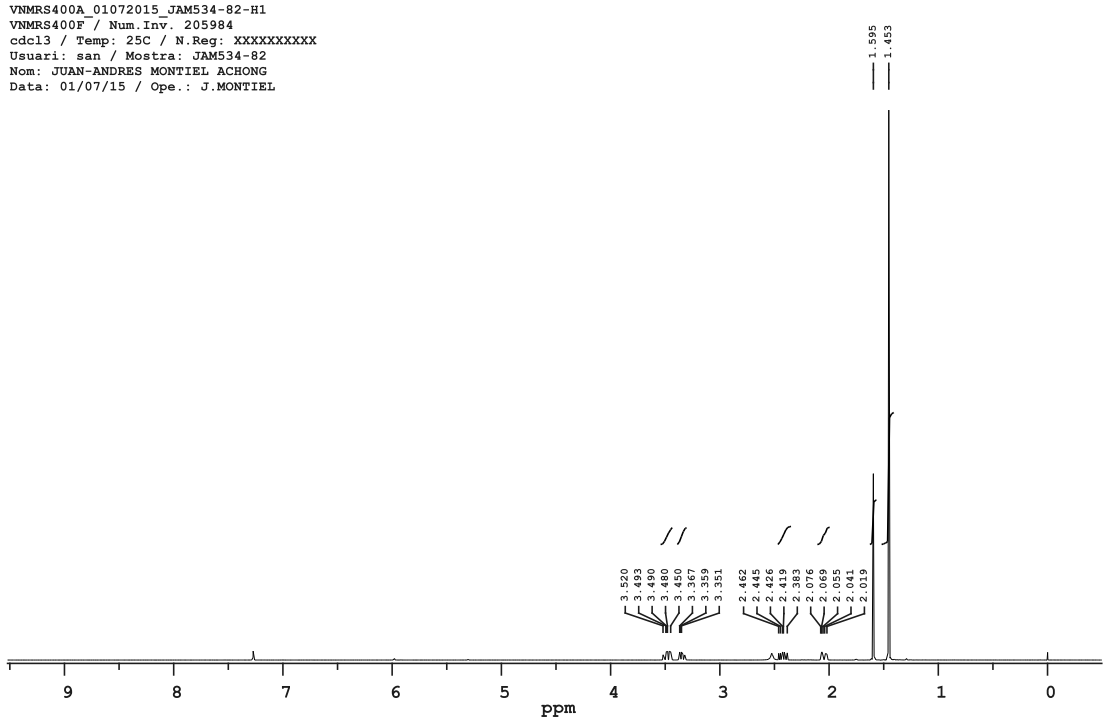
40
20
0
ppm


HO
CH3
Cl
Cl
N
O

3a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cdcl3 / Temp: 25C / N.Reg: XXXXXXXXXX
Usuari: san / Mostra: JAM534-82
Nom: JUAN-ANDRES MONTIEL ACHONG
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3.490
3.480
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2.419
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6
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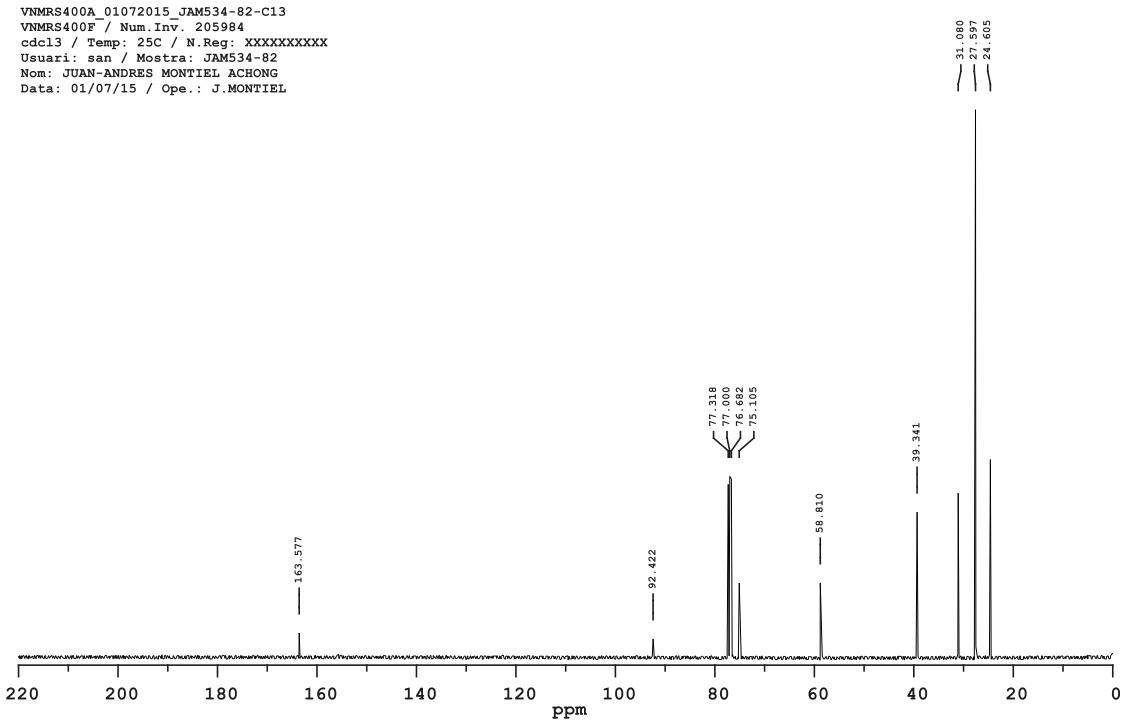
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cdcl3 / Temp: 25C / N.Reg: XXXXXXXXXX
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Nom: JUAN-ANDRES MONTIEL ACHONG
Data: 01/07/15 / Ope.: J.MONTIEL
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77.000
76.682
75.105
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160
140
120
100
80
60
40
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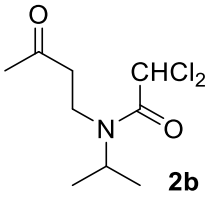
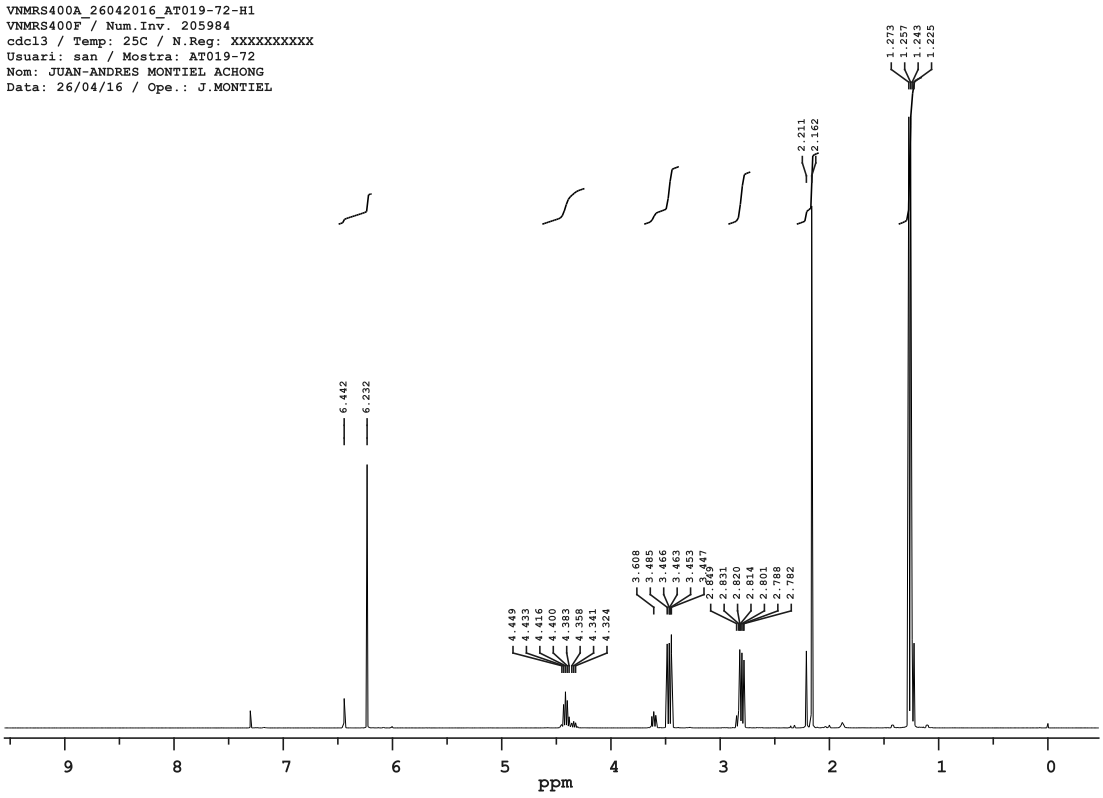
0
ppm


O
CHCl2
N
O

2b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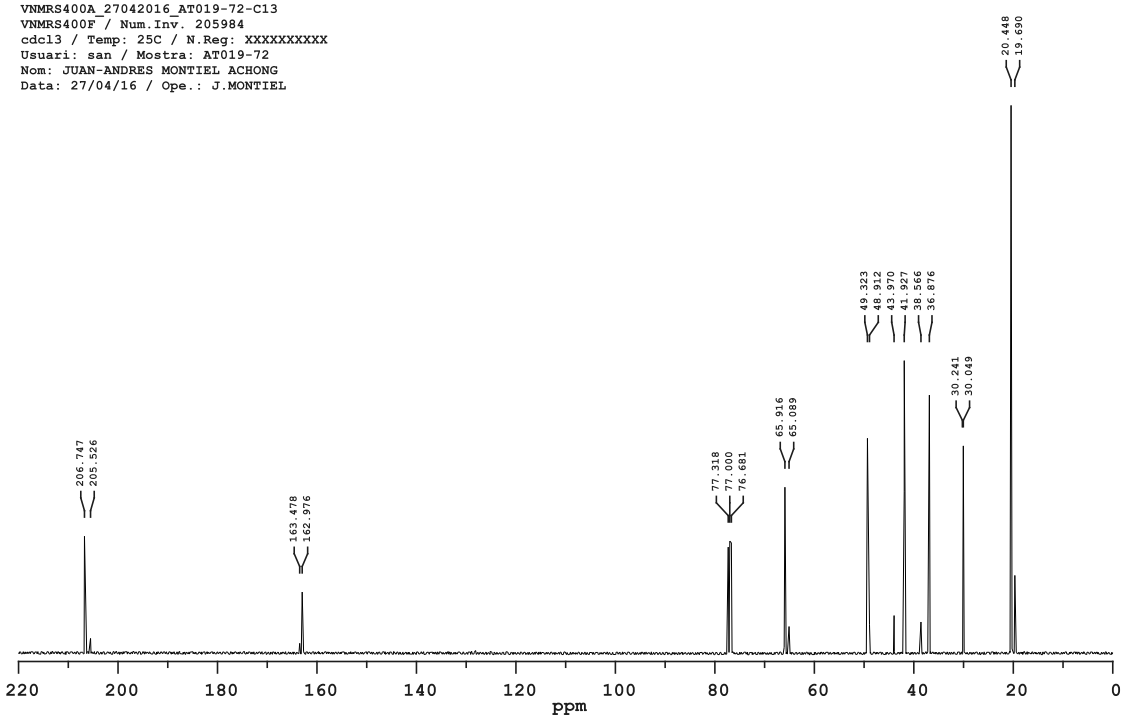
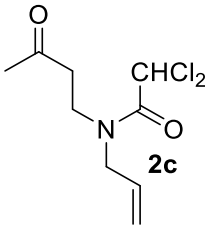
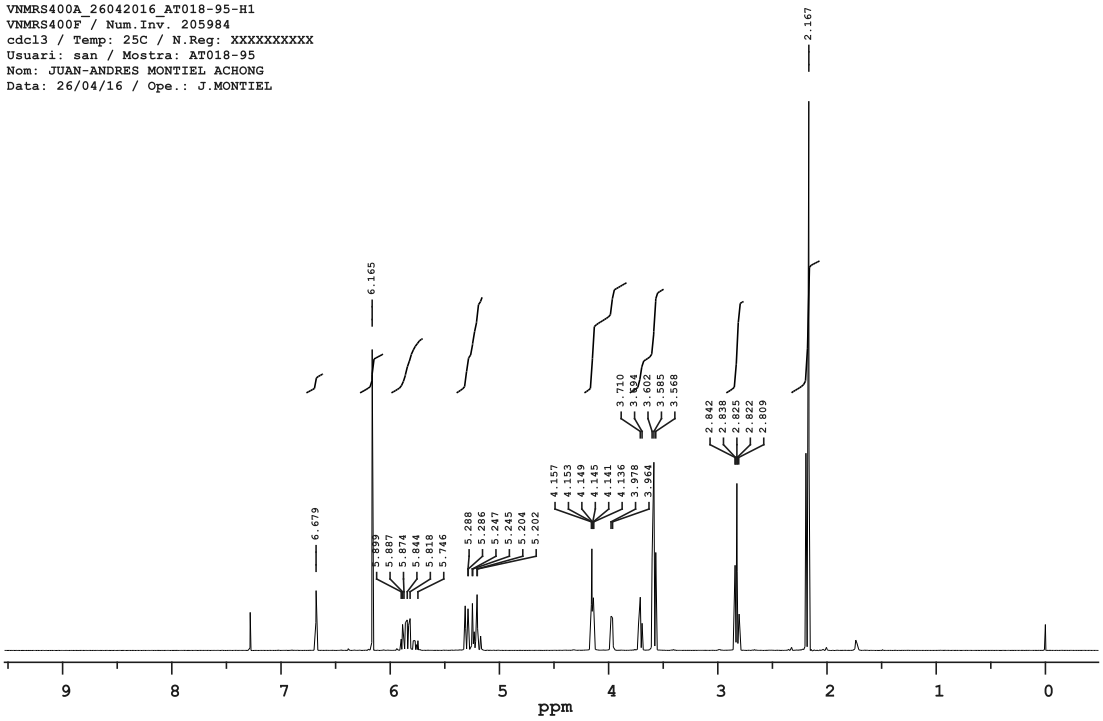
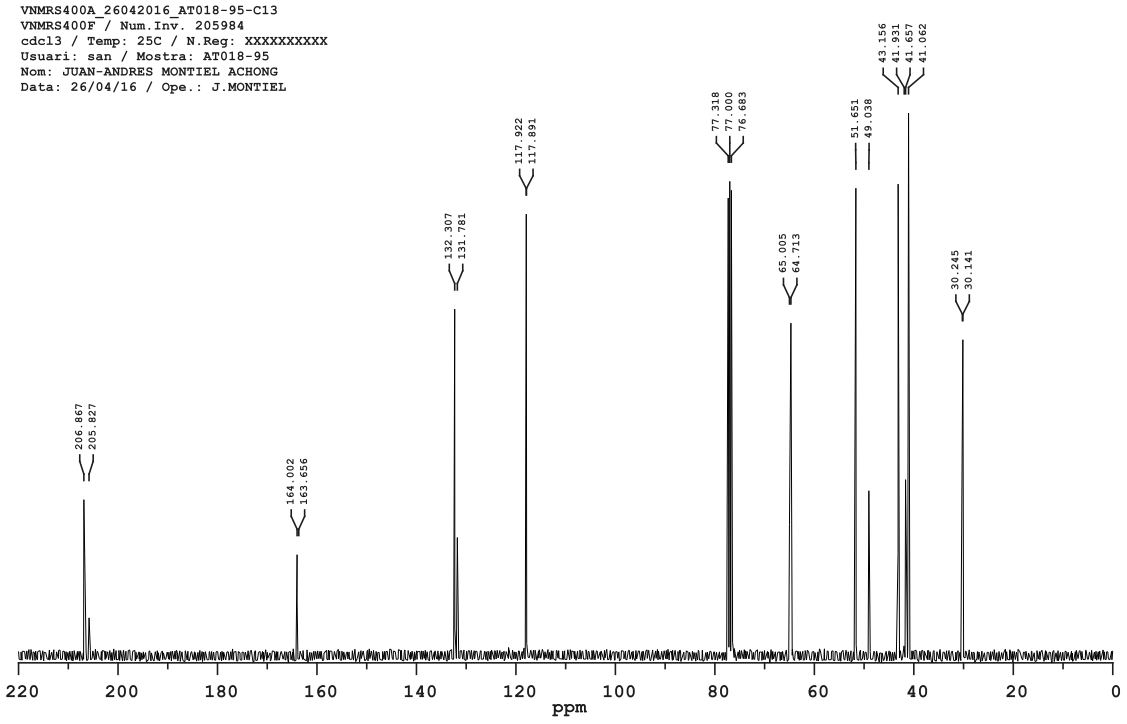
cdcl3 / Temp: 25C / N.Reg: XXXXXXXXXX
Usuari: san / Mostra: AT019-72
Nom: JUAN-ANDRES MONTIEL ACHONG
Data: 26/04/16 / Ope.: J.MONTIEL
6.442
6.232
4.449
4.433
4.416
4.400
4.383
4.358
4.341
4.324
3.608
3.485
3.466
3.463
3.453
2.847
2.831
2.820
2.814
2.801
2.788
2.782
2.211
2.162
1.273
1.257
1.243
1.225
9
8
7
6
5
4
3
2
1
0
ppm

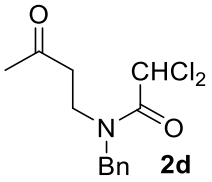

VNMRS400A_27042016_AT019-72-C13
VNMRS400F / Num.Inv. 205984
cdcl3 / Temp: 25C / N.Reg: XXXXXXXXXX
Usuari: san / Mostra: AT019-72
Nom: JUAN-ANDRES MONTIEL ACHONG
Data: 27/04/16 / Ope.: J.MONTIEL
206.747
205.526
163.478
162.976
77.318
77.000
76.681
65.916
65.089
49.323
49.312
43.370
41.927
38.566
36.876
30.241
30.049
20.448
19.690
220
200
180
160
140
120
100
80
60
40
20
0
ppm


O
CHCl2
N
O

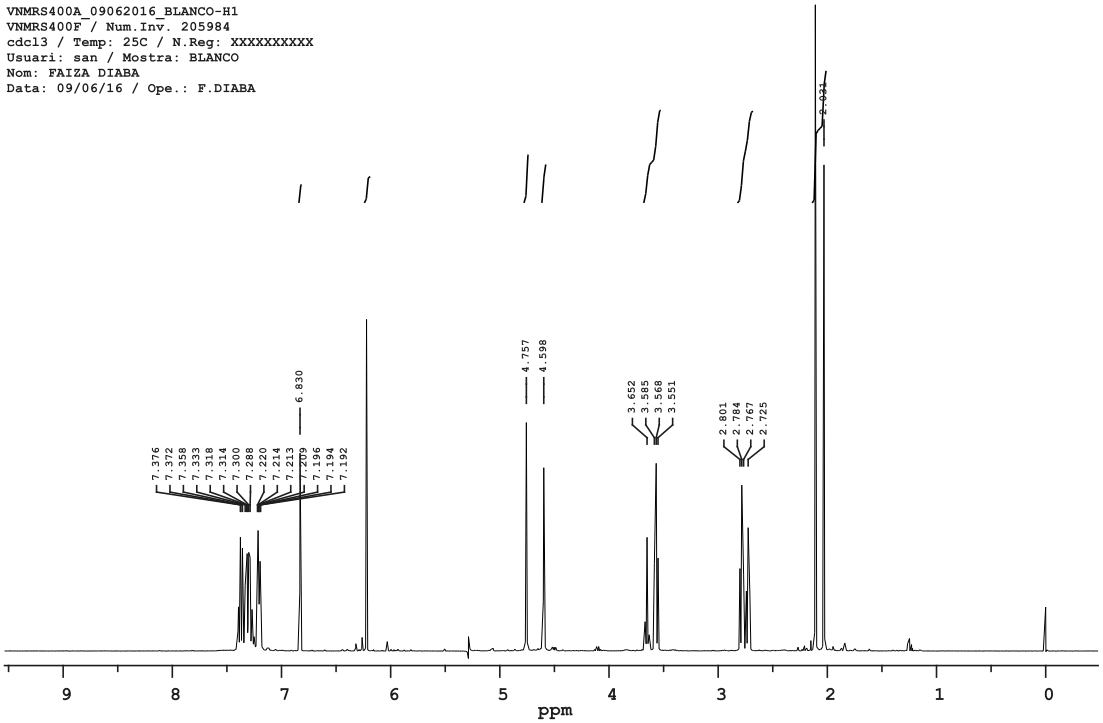
2c

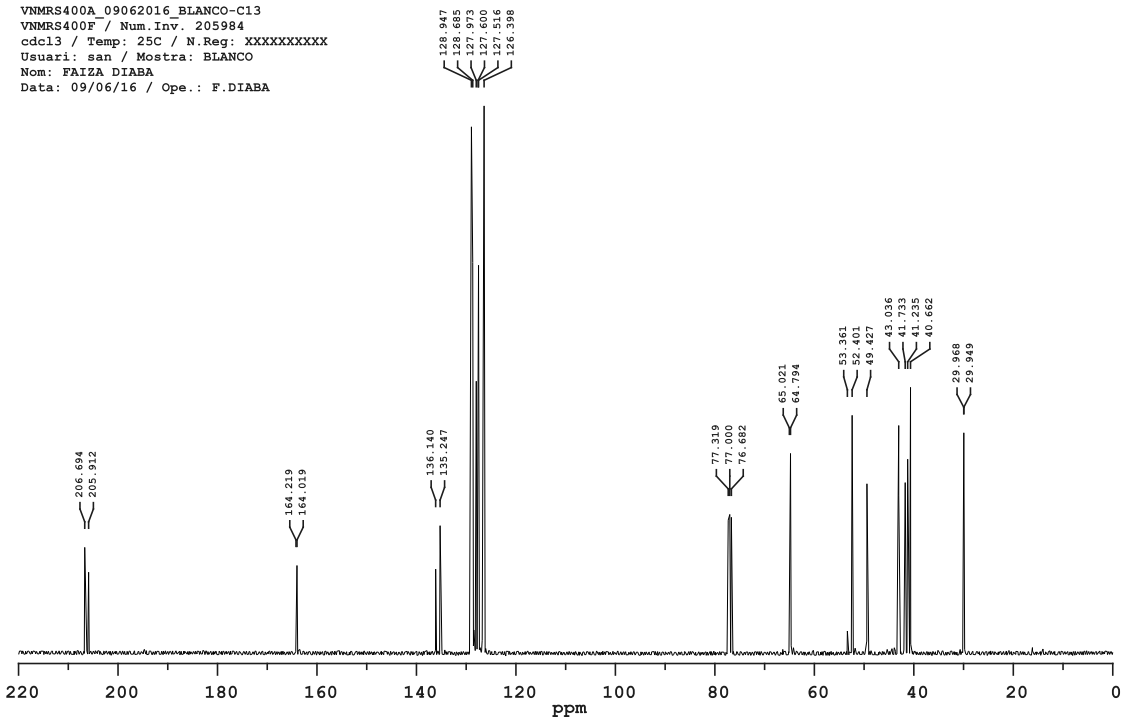

VNMRS400A_26042016_AT018-95-H1
VNMRS400F / Num.Inv. 205984
cdcl3 / Temp: 25C / N.Reg: XXXXXXXXXX
Usuari: san / Mostra: AT018-95
Nom: JUAN-ANDRES MONTIEL ACHONG
Data: 26/04/16 / Ope.: J.MONTIEL
2.167
6.165
6.679
5.899
5.887
5.874
5.844
5.818
5.746
5.288
5.286
5.247
5.245
5.204
5.202
4.157
4.153
4.149
4.145
4.141
4.136
3.978
3.964
3.710
3.624
3.602
3.585
3.568
2.842
2.838
2.825
2.822
2.809
9
8
7
6
5
4
3
2
1
0
ppm

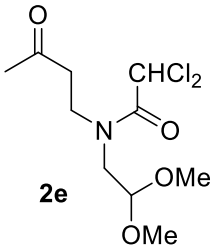

VNMRS400A_26042016_AT018-95-C13
VNMRS400F / Num.Inv. 205984
cdcl3 / Temp: 25C / N.Reg: XXXXXXXXXX
Usuari: san / Mostra: AT018-95
Nom: JUAN-ANDRES MONTIEL ACHONG
Data: 26/04/16 / Ope.: J.MONTIEL
206.867
205.827
164.002
163.656
132.307
131.781
117.922
117.891
77.318
77.000
76.683
65.005
64.713
51.651
49.038
43.156
41.931
41.657
41.062
30.245
30.141
220
200
180
160
140
120
100
80
60
40
20
0
ppm


O
CHCl2
N
O
Bn

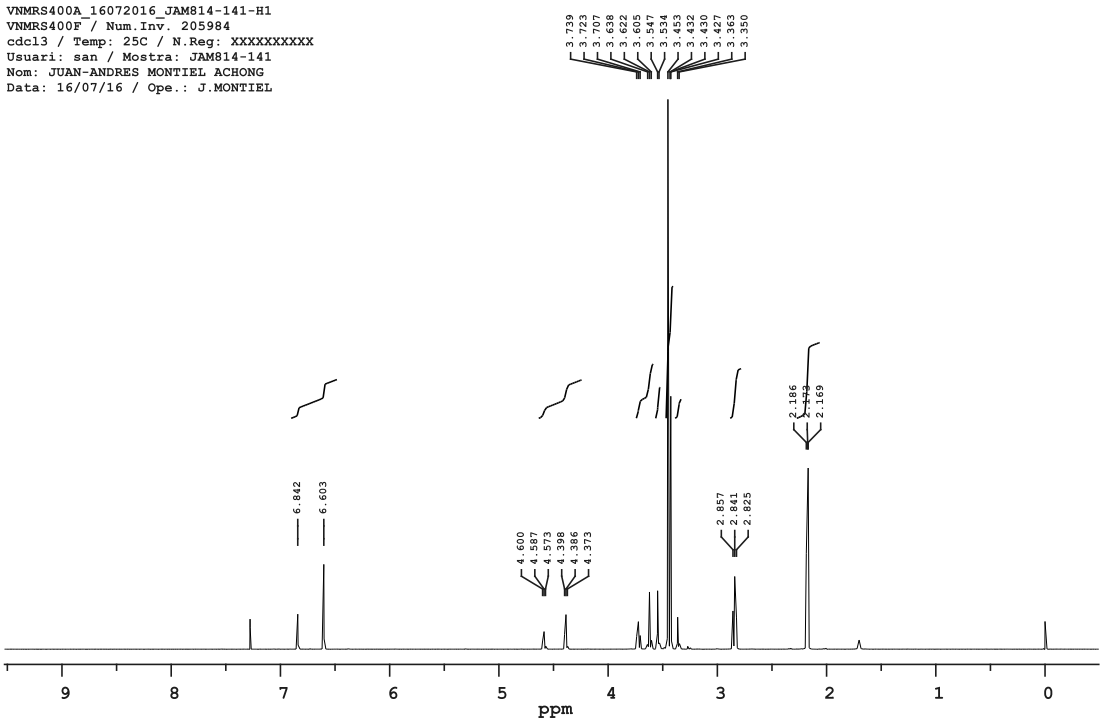
2d

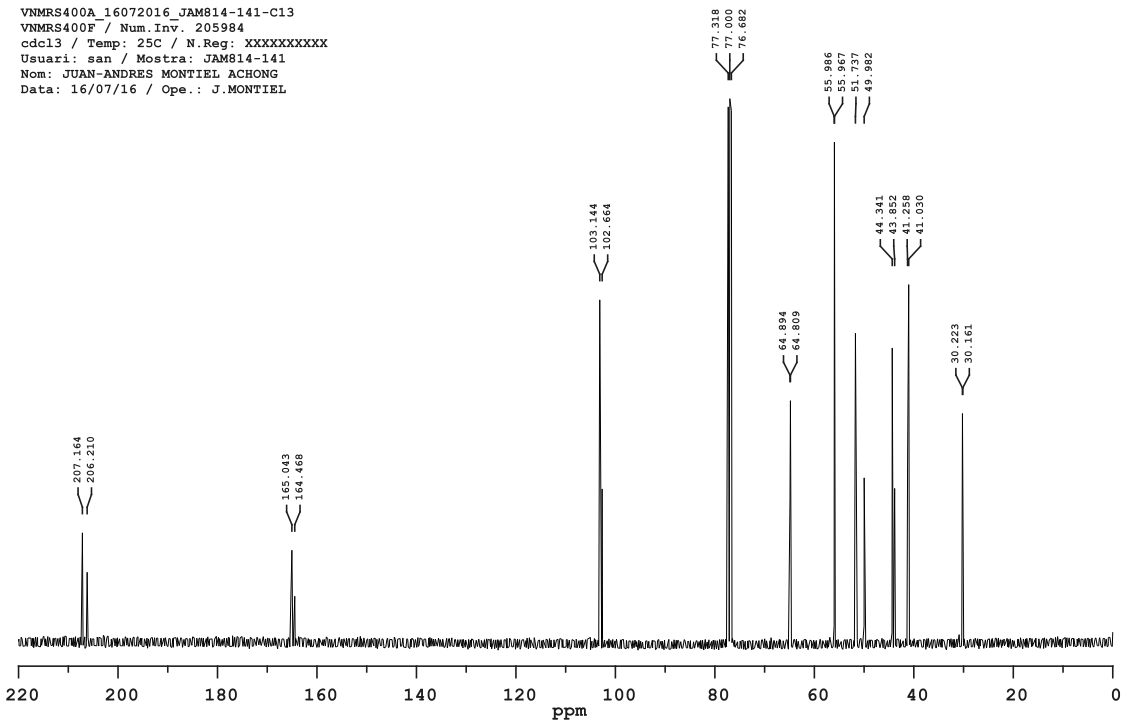

VNMRS400A_09062016_BLANCO-H1
VNMRS400F / Num.Inv. 205984
cdcl3 / Temp: 25C / N.Reg: XXXXXXXXXX
Usuari: san / Mostra: BLANCO
Nom: FAIZA DIABA
Data: 09/06/16 / Ope.: F.DIABA
7.376
7.372
7.358
7.333
7.318
7.314
7.300
7.288
7.220
7.214
7.203
7.196
7.194
7.192
6.830
4.757
4.598
3.652
3.585
3.568
3.551
2.801
2.784
2.767
2.725
2.031
9
8
7
6
5
4
3
2
1
0
ppm

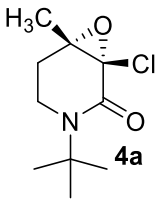

VNMRS400A_09062016_BLANCO-C13
VNMRS400F / Num.Inv. 205984
cdcl3 / Temp: 25C / N.Reg: XXXXXXXXXX
Usuari: san / Mostra: BLANCO
Nom: FAIZA DIABA
Data: 09/06/16 / Ope.: F.DIABA
206.694
205.912
164.219
164.019
136.140
135.247
128.947
128.685
127.973
127.600
127.516
126.398
77.319
77.000
76.682
65.021
64.794
53.361
52.401
49.427
43.036
41.733
41.235
40.662
29.968
29.949
220
200
180
160
140
120
100
80
60
40
20
0
ppm

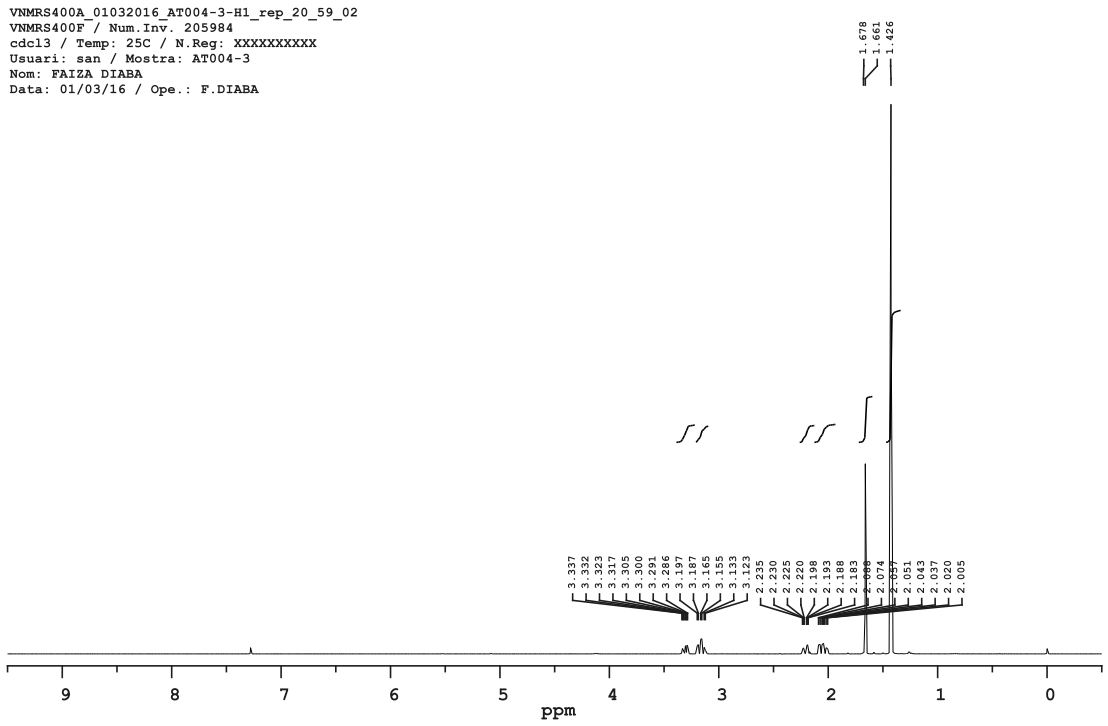

O
CHCl2
N
O
OMe
OMe

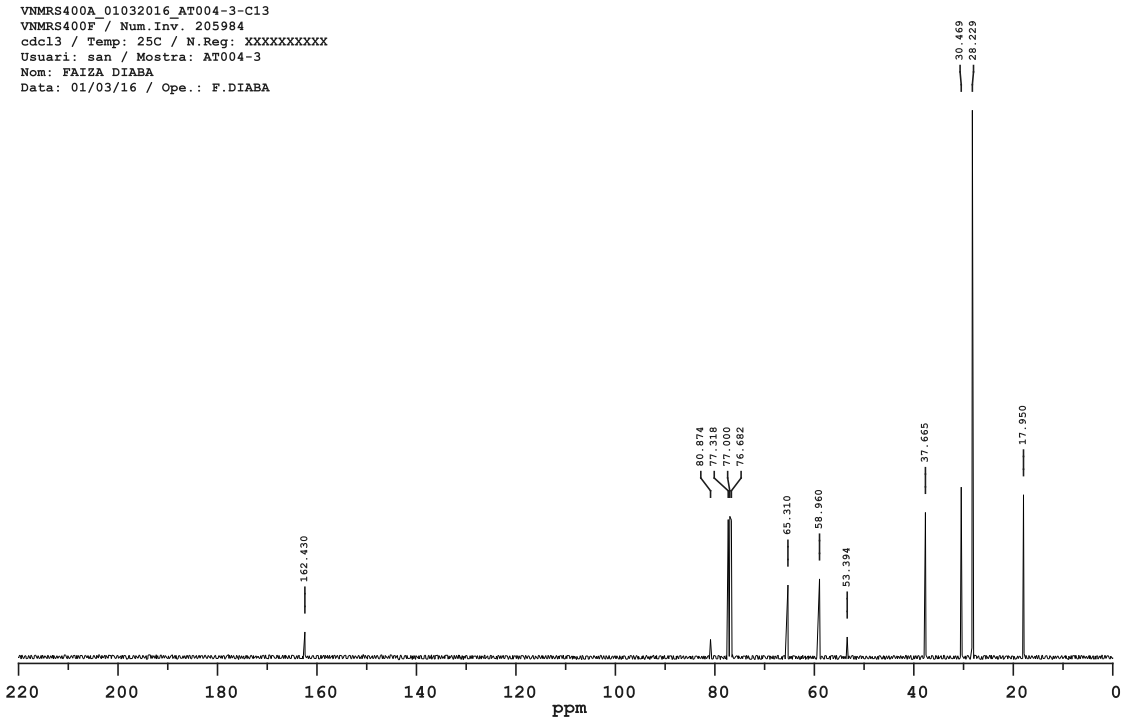
2e

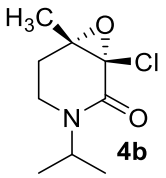

VNMRS400A_16072016_JAM814-141-H1
VNMRS400F / Num.Inv. 205984
cdcl3 / Temp: 25C / N.Reg: XXXXXXXXXX
Usuari: san / Mostra: JAM814-141
Nom: JUAN-ANDRES MONTIEL ACHONG
Data: 16/07/16 / Ope.: J.MONTIEL
3.739
3.723
3.707
3.638
3.622
3.605
3.547
3.534
3.453
3.432
3.430
3.427
3.363
3.350
6.842
6.603
4.600
4.587
4.573
4.398
4.386
4.373
2.857
2.841
2.825
2.186
2.169
9
8
7
6
5
4
3
2
1
0
ppm


VNMRS400A_16072016_JAM814-141-C13
VNMRS400F / Num.Inv. 205984
cdcl3 / Temp: 25C / N.Reg: XXXXXXXXXX
Usuari: san / Mostra: JAM814-141
Nom: JUAN-ANDRES MONTIEL ACHONG
Data: 16/07/16 / Ope.: J.MONTIEL
77.318
77.000
76.682
55.986
55.967
51.737
49.982
103.144
102.664
64.894
64.809
44.341
43.852
41.258
41.030
30.223
30.161
207.164
206.210
165.043
164.468
220
200
180
160
140
120
100
80
60
40
20
0
ppm

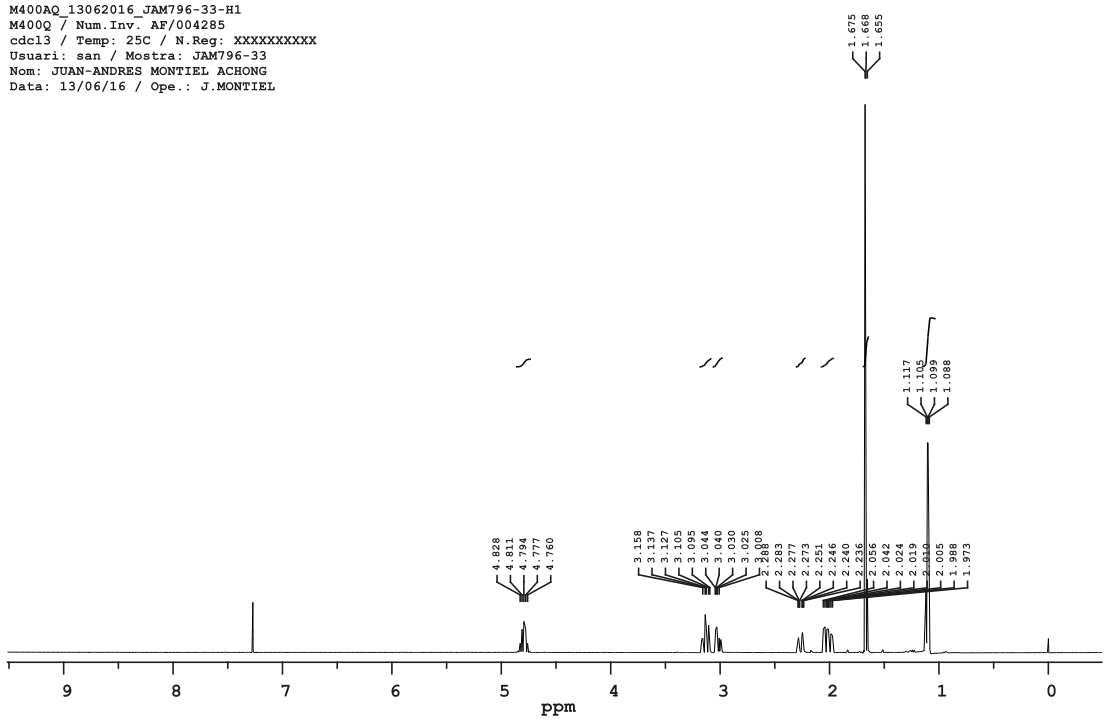

H3C
O
Cl
N
O
4a

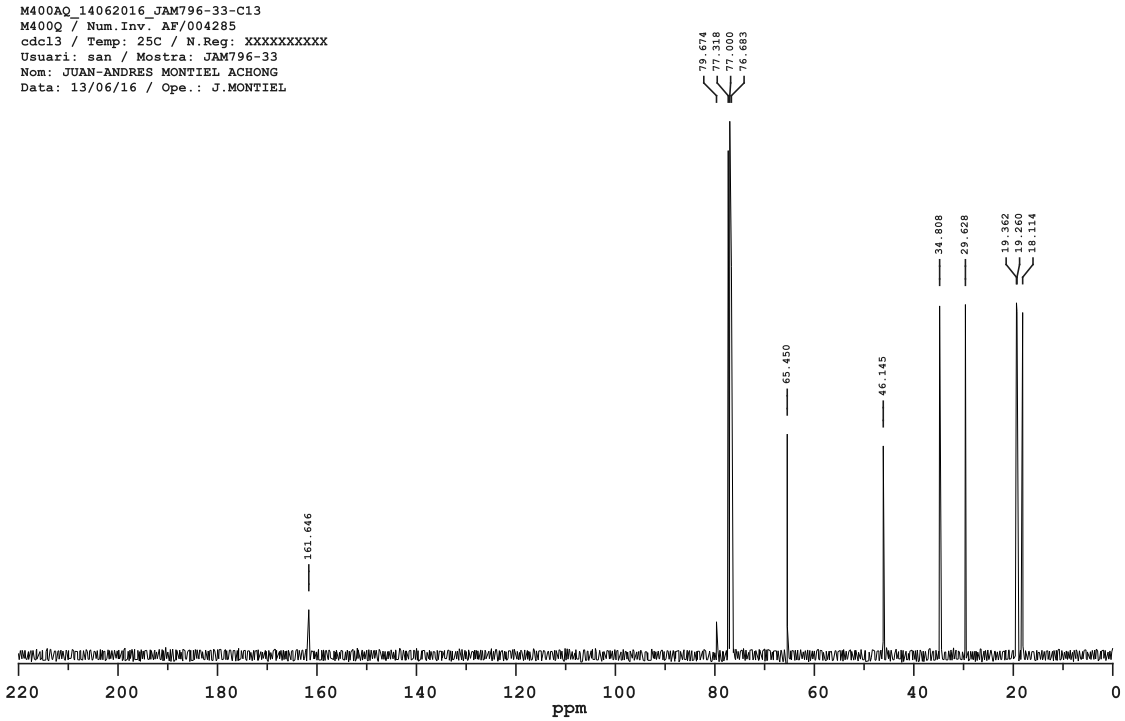

VNMRS400A_01032016_AT004-3-H1_rep_20_59_02
VNMRS400F / Num.Inv. 205984
cdcl3 / Temp: 25C / N.Reg: XXXXXXXXXX
Usuari: san / Mostra: AT004-3
Nom: FAIZA DIABA
Data: 01/03/16 / Ope.: F.DIABA
1.678
1.661
1.426
3.337
3.332
3.323
3.317
3.305
3.300
3.291
3.286
3.197
3.187
3.165
3.155
3.133
3.123
2.235
2.230
2.225
2.220
2.198
2.193
2.188
2.183
2.074
2.051
2.043
2.037
2.020
2.005
9
8
7
6
5
4
3
2
1
0
ppm

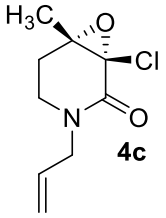

VNMRS400A_01032016_AT004-3-C13
VNMRS400F / Num.Inv. 205984
cdcl3 / Temp: 25C / N.Reg: XXXXXXXXXX
Usuari: san / Mostra: AT004-3
Nom: FAIZA DIABA
Data: 01/03/16 / Ope.: F.DIABA
30.469
28.229
80.874
77.318
77.000
76.682
65.310
58.960
53.394
37.665
17.950
162.430
220
200
180
160
140
120
100
80
60
40
20
0
ppm


H3C
O
Cl
N
O

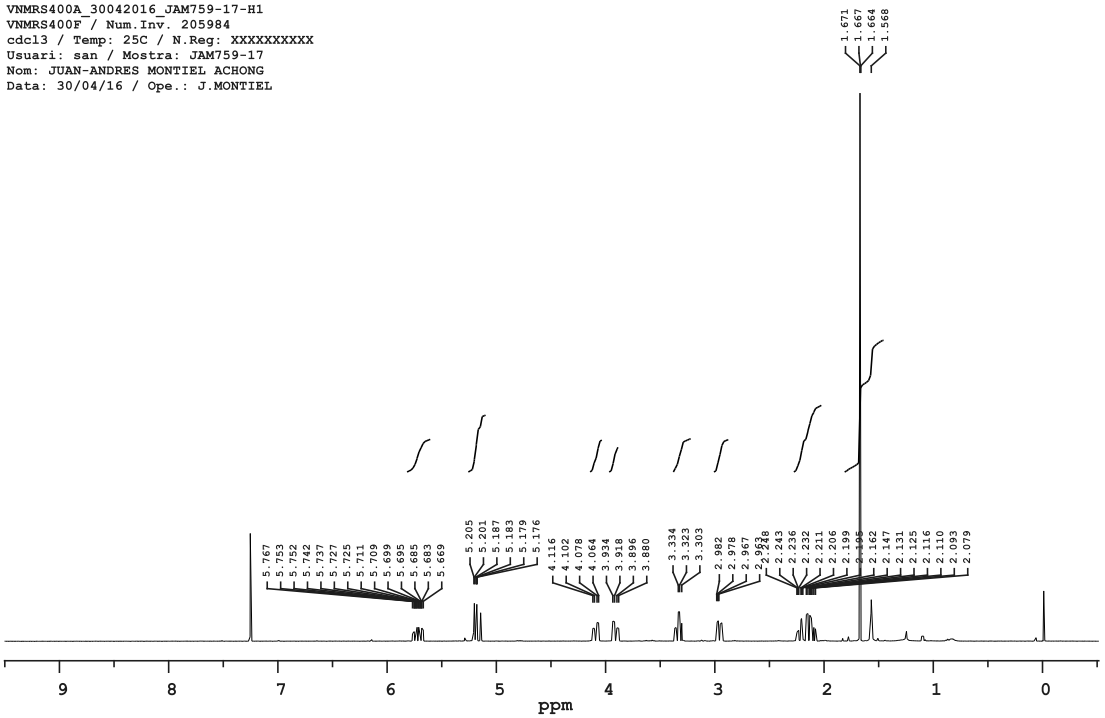
4b

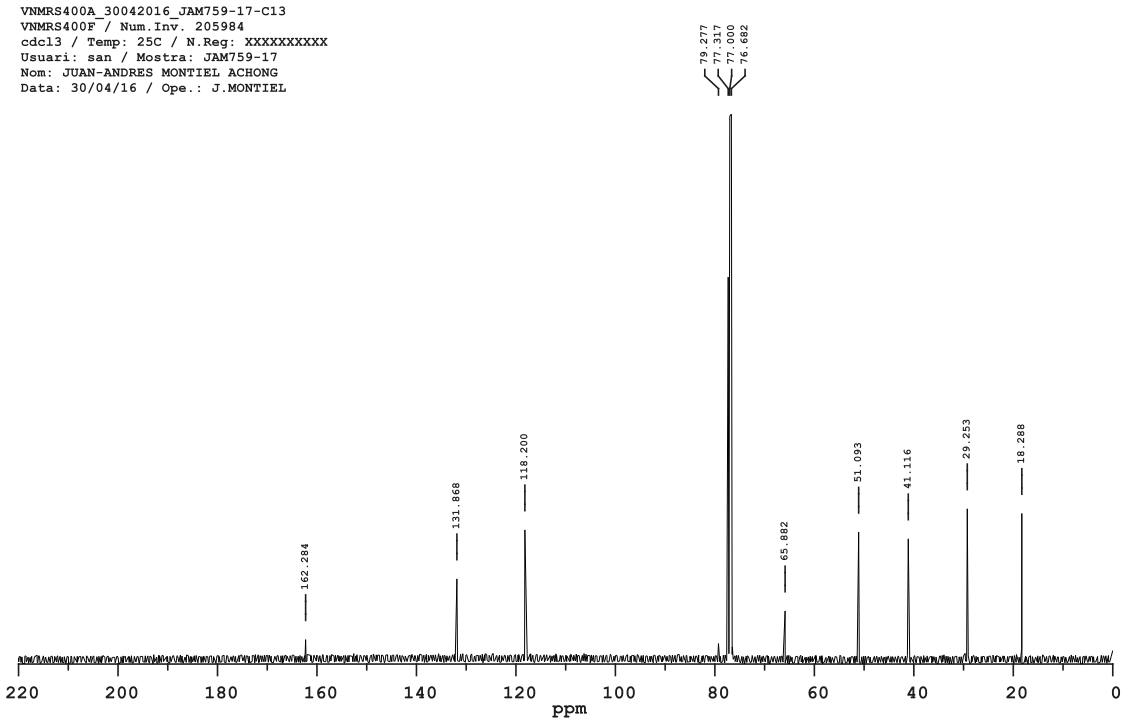

M400AQ_13062016_JAM796-33-H1
M400Q / Num.Inv. AF/004285
cdcl3 / Temp: 25C / N.Reg: XXXXXXXXXX
Usuari: san / Mostra: JAM796-33
Nom: JUAN-ANDRES MONTIEL ACHONG
Data: 13/06/16 / Ope.: J.MONTIEL
1.675
1.668
1.655
1.117
1.105
1.099
1.088
4.828
4.811
4.794
4.777
4.760
3.158
3.137
3.127
3.105
3.095
3.044
3.040
3.030
3.025
2.808
2.283
2.277
2.273
2.251
2.246
2.240
2.236
2.056
2.042
2.024
2.019
2.010
2.005
1.988
1.973
9
8
7
6
5
4
3
2
1
0
ppm

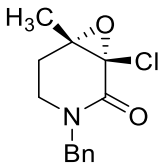

M400AQ_14062016_JAM796-33-C13
M400Q / Num.Inv. AF/004285
cdcl3 / Temp: 25C / N.Reg: XXXXXXXXXX
Usuari: san / Mostra: JAM796-33
Nom: JUAN-ANDRES MONTIEL ACHONG
Data: 13/06/16 / Ope.: J.MONTIEL
79.674
77.318
77.000
76.683
65.450
46.145
34.808
29.628
19.362
19.260
18.114
161.646
220
200
180
160
140
120
100
80
60
40
20
0
ppm


H3C
O
Cl
N
O

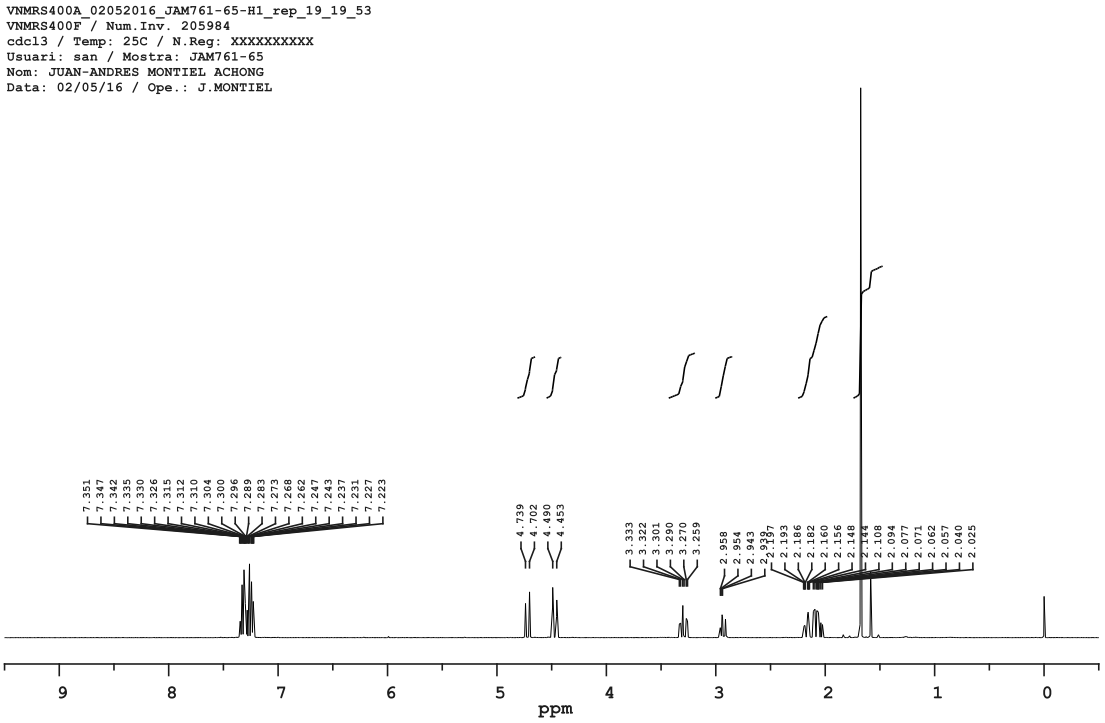
4c

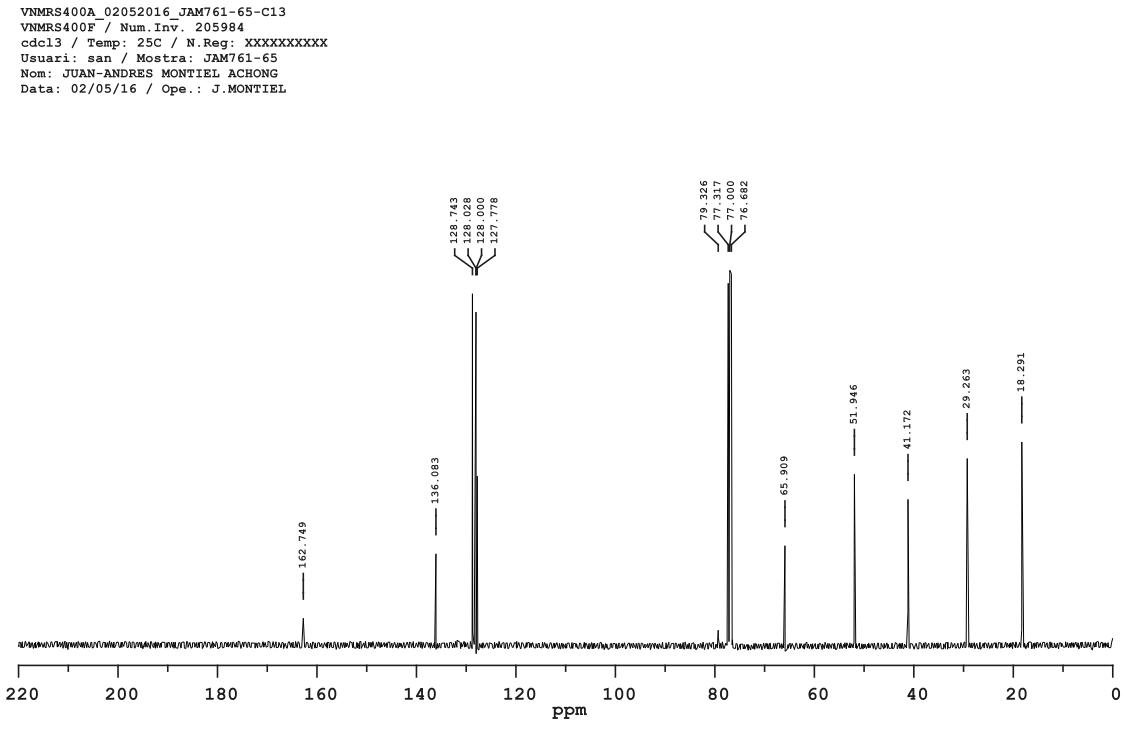

VNMRS400A_30042016_JAM759-17-H1
VNMRS400F / Num.Inv. 205984
cdcl3 / Temp: 25C / N.Reg: XXXXXXXXXX
Usuari: san / Mostra: JAM759-17
Nom: JUAN-ANDRES MONTIEL ACHONG
Data: 30/04/16 / Ope.: J.MONTIEL
1.671
1.667
1.664
1.568
5.767
5.753
5.752
5.742
5.737
5.727
5.725
5.711
5.709
5.699
5.695
5.685
5.683
5.669
5.205
5.201
5.187
5.183
5.179
5.176
4.116
4.102
4.078
4.064
3.934
3.918
3.896
3.880
3.334
3.323
3.303
2.982
2.978
2.967
2.963
2.958
2.243
2.236
2.232
2.211
2.206
2.199
2.105
2.162
2.147
2.131
2.125
2.116
2.110
2.093
2.079
9
8
7
6
5
4
3
2
1
0
ppm

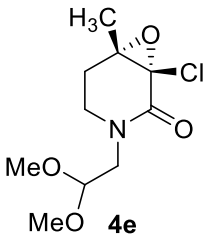

VNMRS400A_30042016_JAM759-17-C13
VNMRS400F / Num.Inv. 205984
cdcl3 / Temp: 25C / N.Reg: XXXXXXXXXX
Usuari: san / Mostra: JAM759-17
Nom: JUAN-ANDRES MONTIEL ACHONG
Data: 30/04/16 / Ope.: J.MONTIEL
79.277
77.317
77.000
76.682
162.284
131.868
118.200
65.882
51.093
41.116
29.253
18.288
220
200
180
160
140
120
100
80
60
40
20
0
ppm


H3C
O
Cl
N
O
Bn

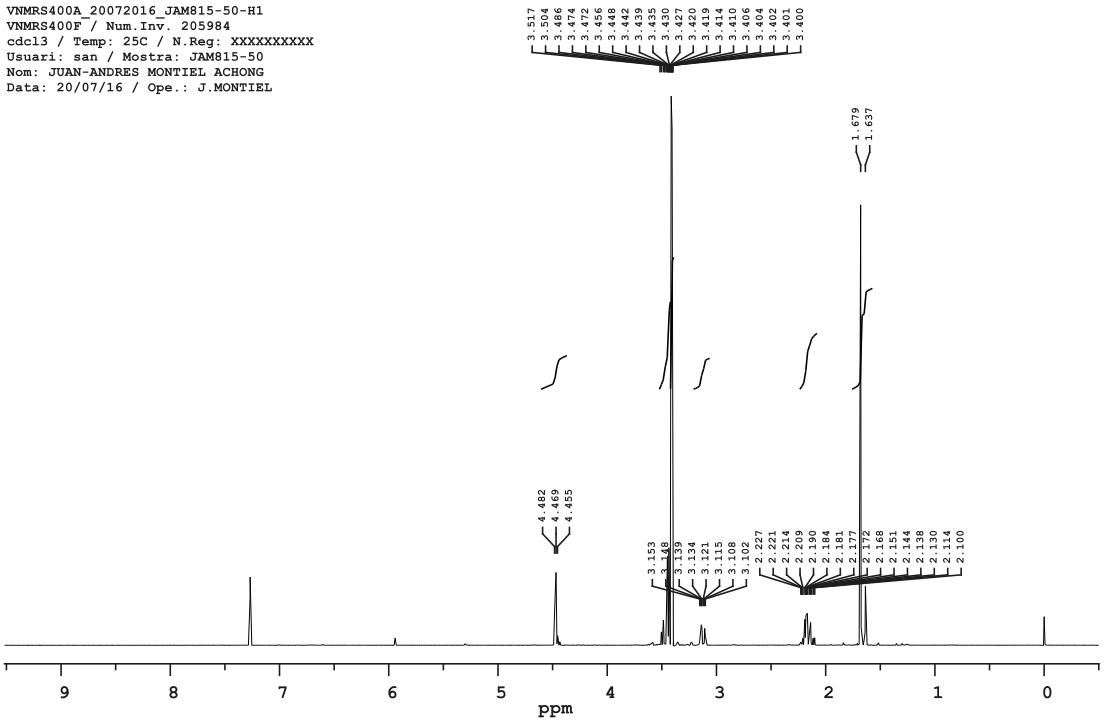
4d

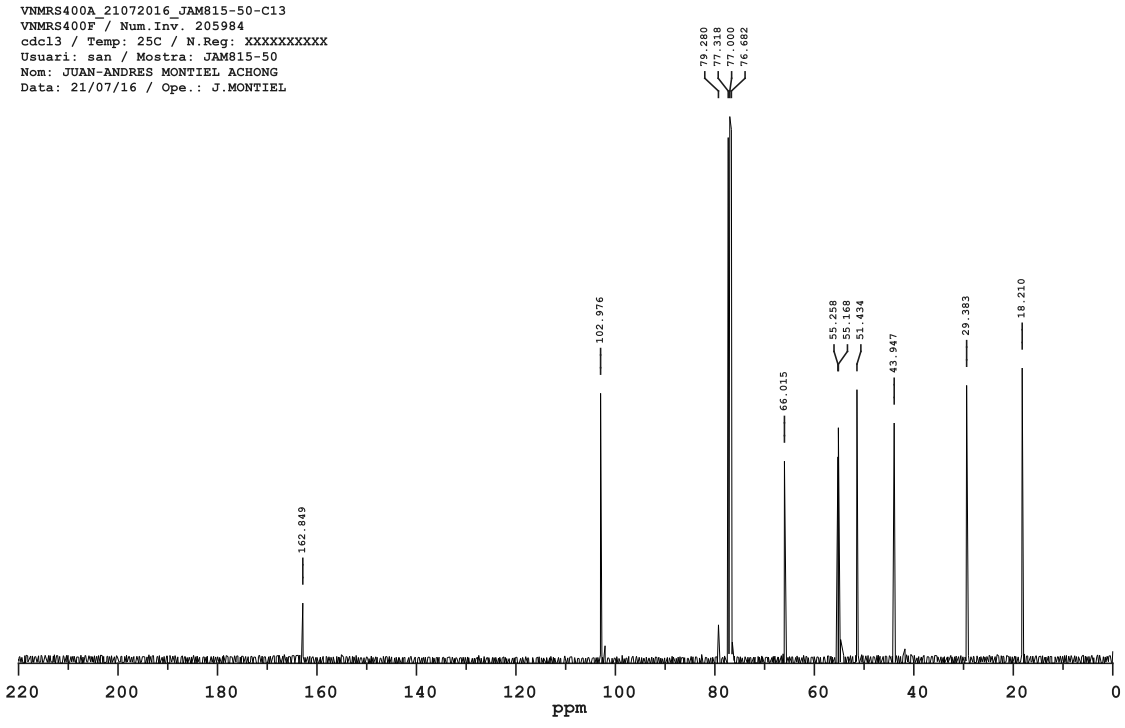

VNMRS400A_02052016_JAM761-65-H1_rep_19_19_53
VNMRS400F / Num.Inv. 205984
cdcl3 / Temp: 25C / N.Reg: XXXXXXXXXX
Usuari: san / Mostra: JAM761-65
Nom: JUAN-ANDRES MONTIEL ACHONG
Data: 02/05/16 / Ope.: J.MONTIEL
7.351
7.347
7.342
7.335
7.330
7.326
7.315
7.312
7.310
7.304
7.300
7.286
7.283
7.273
7.268
7.262
7.247
7.243
7.237
7.231
7.227
7.223
4.739
4.702
4.490
4.453
3.333
3.322
3.301
3.290
3.270
3.259
2.958
2.954
2.943
2.939
2.197
2.193
2.186
2.182
2.160
2.156
2.148
2.104
2.098
2.094
2.077
2.071
2.062
2.057
2.040
2.025
9
8
7
6
5
4
3
2
1
0
ppm

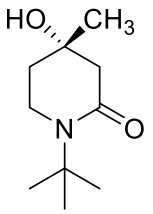

VNMRS400A_02052016_JAM761-65-C13
VNMRS400F / Num.Inv. 205984
cdcl3 / Temp: 25C / N.Reg: XXXXXXXXXX
Usuari: san / Mostra: JAM761-65
Nom: JUAN-ANDRES MONTIEL ACHONG
Data: 02/05/16 / Ope.: J.MONTIEL
162.749
136.083
128.743
128.028
128.000
127.778
79.326
77.317
77.000
76.682
65.909
51.946
41.172
29.263
18.291
220
200
180
160
140
120
100
80
60
40
20
0
ppm


H3C
O
Cl
N
O
MeO
MeO

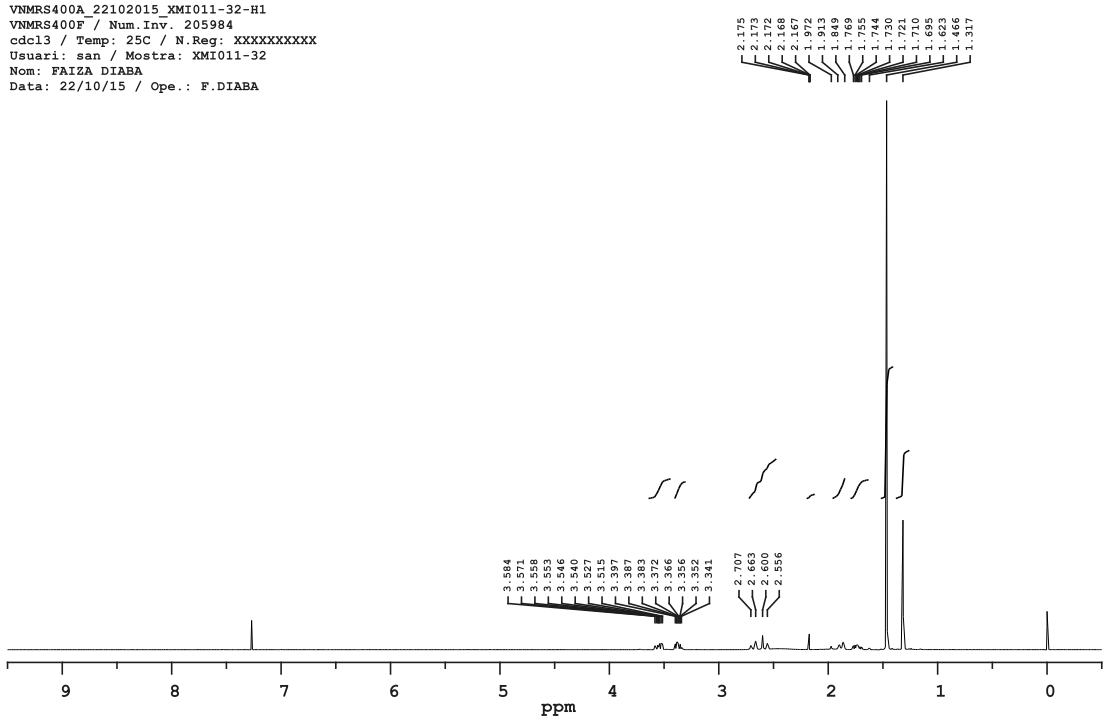
4e

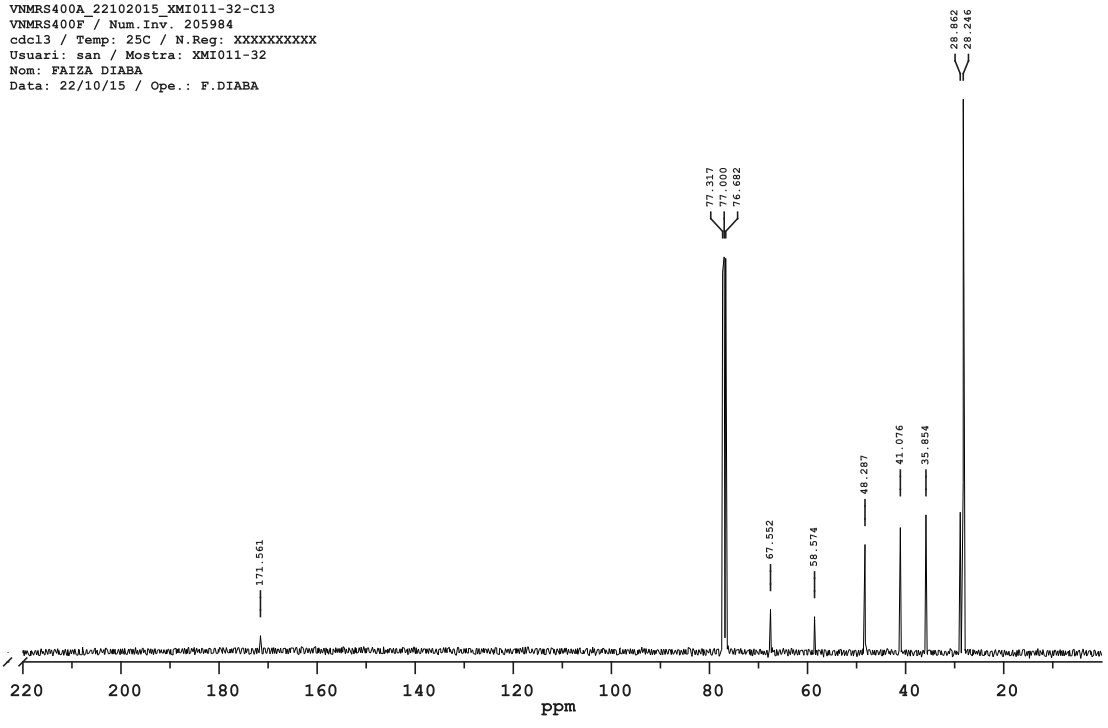

VNMRS400A_20072016_JAM815-50-H1
VNMRS400F / Num.Inv. 205984
cdcl3 / Temp: 25C / N.Reg: XXXXXXXXXX
Usuari: san / Mostra: JAM815-50
Nom: JUAN-ANDRES MONTIEL ACHONG
Data: 20/07/16 / Ope.: J.MONTIEL
3.517
3.504
3.486
3.474
3.472
3.456
3.448
3.442
3.439
3.435
3.430
3.427
3.420
3.419
3.414
3.410
3.406
3.404
3.402
3.401
3.400
1.679
1.637
4.482
4.469
4.455
3.153
3.148
3.139
3.134
3.121
3.115
3.108
3.102
2.227
2.221
2.214
2.209
2.190
2.184
2.181
2.177
2.172
2.168
2.151
2.144
2.138
2.130
2.114
2.100
9
8
7
6
5
4
3
2
1
0
ppm

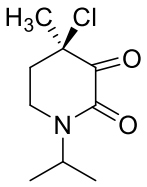

VNMRS400A_21072016_JAM815-50-C13
VNMRS400F / Num.Inv. 205984
cdcl3 / Temp: 25C / N.Reg: XXXXXXXXXX
Usuari: san / Mostra: JAM815-50
Nom: JUAN-ANDRES MONTIEL ACHONG
Data: 21/07/16 / Ope.: J.MONTIEL
79.280
77.318
77.000
76.682
162.849
102.976
66.015
55.258
55.168
51.434
43.947
29.383
18.210
220
200
180
160
140
120
100
80
60
40
20
0
ppm


HO
CH3
N
O

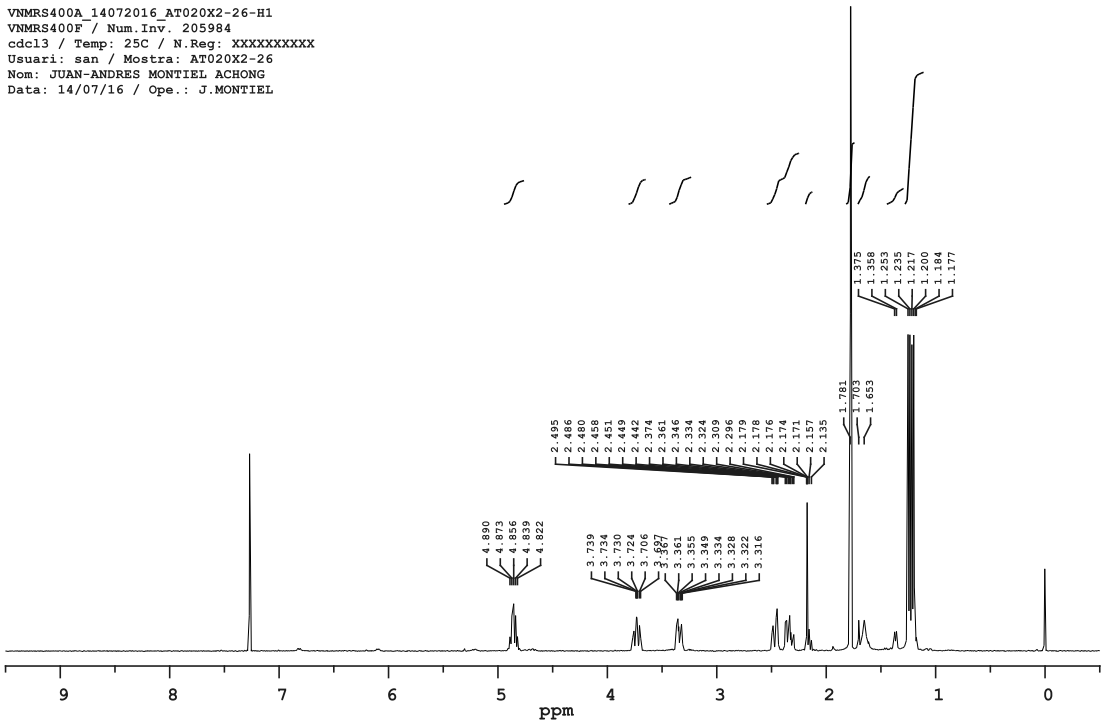
6

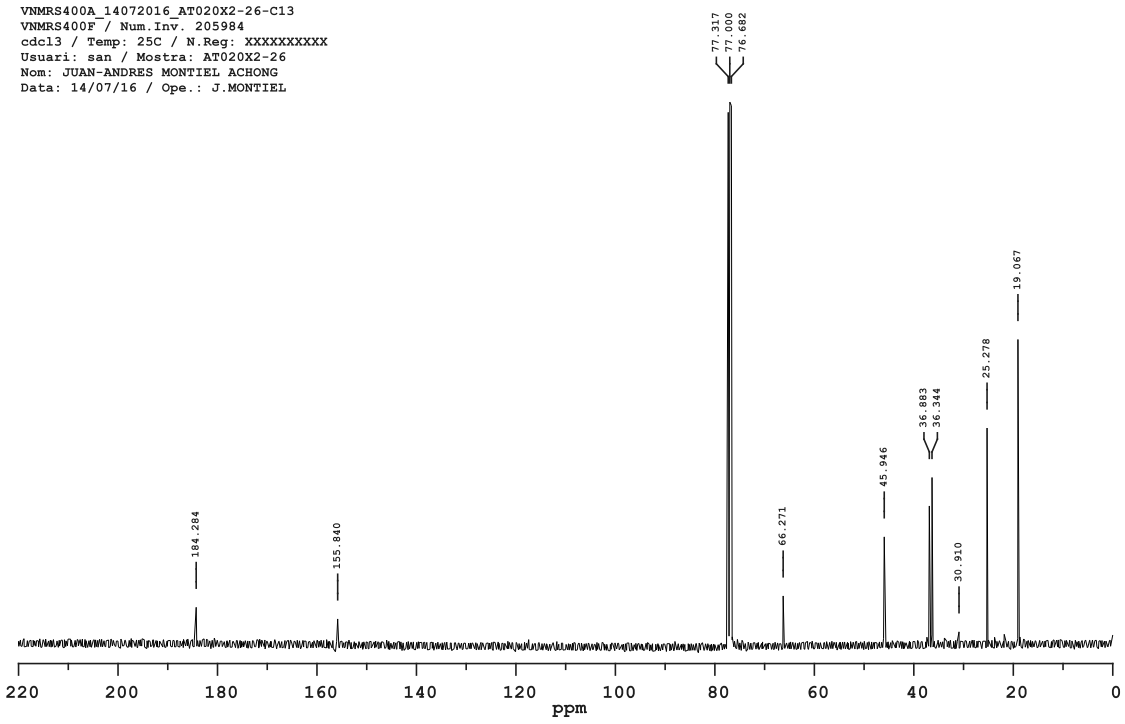

VNMRS400A_22102015_XMI011-32-H1
VNMRS400F / Num.Inv. 205984
cdcl3 / Temp: 25C / N.Reg: XXXXXXXXXX
Usuari: san / Mostra: XMI011-32
Nom: FAIZA DIABA
Data: 22/10/15 / Ope.: F.DIABA
2.175
2.173
2.172
2.168
2.167
1.972
1.913
1.849
1.769
1.755
1.744
1.730
1.721
1.710
1.695
1.623
1.466
1.317
3.584
3.571
3.558
3.553
3.546
3.540
3.527
3.515
3.397
3.387
3.383
3.372
3.366
3.356
3.352
3.341
2.707
2.663
2.600
2.556
9
8
7
6
5
4
3
2
1
0
ppm

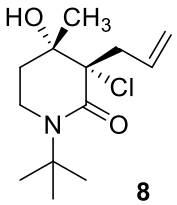

VNMRS400A_22102015_XMI011-32-C13
VNMRS400F / Num.Inv. 205984
cdcl3 / Temp: 25C / N.Reg: XXXXXXXXXX
Usuari: san / Mostra: XMI011-32
Nom: FAIZA DIABA
Data: 22/10/15 / Ope.: F.DIABA
28.862
28.246
77.317
77.000
76.682
171.561
67.552
58.574
48.287
41.076
35.854
220
200
180
160
140
120
100
80
60
40
20
ppm


H3C
Cl
O
O
N

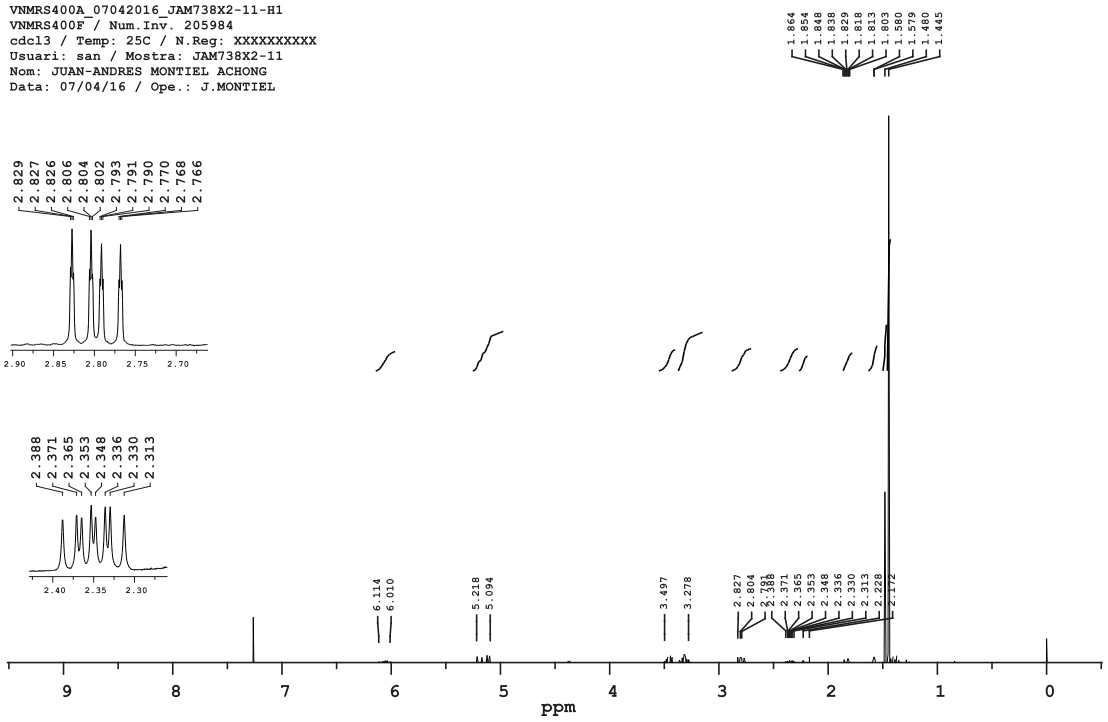
7b

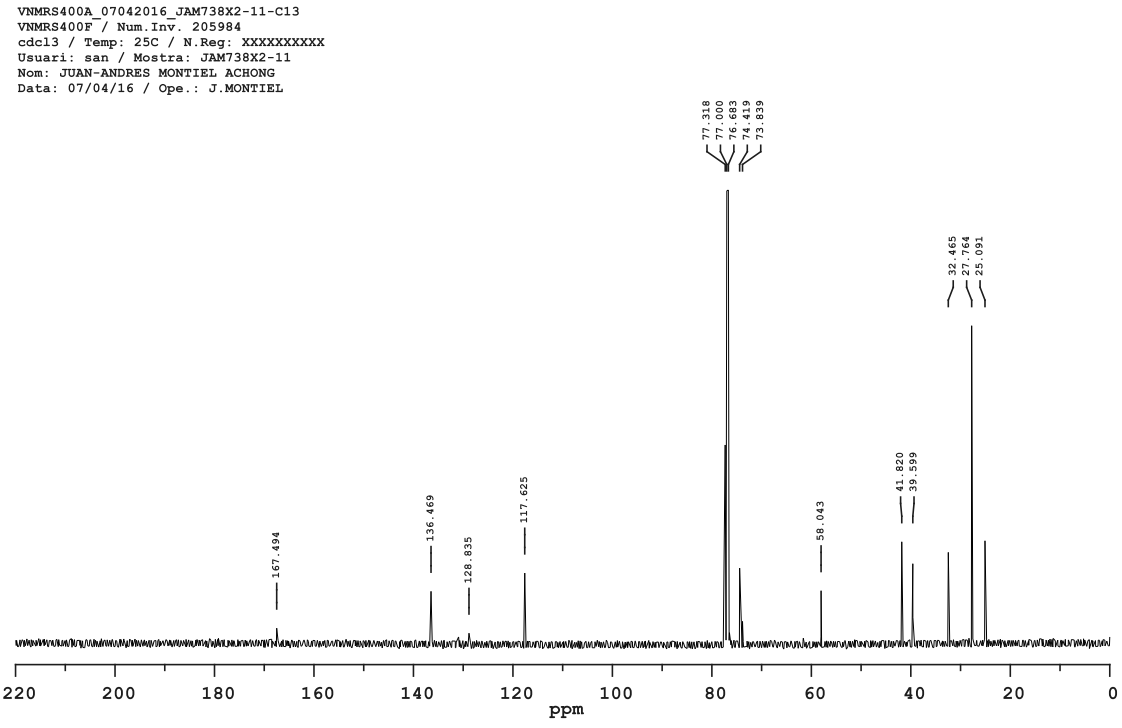

VNMRS400A_14072016_AT020X2-26-H1
VNMRS400F / Num.Inv. 205984
cdcl3 / Temp: 25C / N.Reg: XXXXXXXXXX
Usuari: san / Mostra: AT020X2-26
Nom: JUAN-ANDRES MONTIEL ACHONG
Data: 14/07/16 / Ope.: J.MONTIEL
1.375
1.358
1.253
1.235
1.217
1.200
1.184
1.177
1.781
1.703
1.653
2.495
2.486
2.480
2.458
2.451
2.449
2.442
2.374
2.361
2.346
2.334
2.324
2.309
2.296
2.179
2.178
2.176
2.174
2.171
2.157
2.135
4.890
4.873
4.856
4.839
4.822
3.739
3.734
3.730
3.724
3.706
3.361
3.355
3.349
3.334
3.328
3.322
3.316
9
8
7
6
5
4
3
2
1
0
ppm

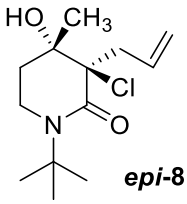

VNMRS400A_14072016_AT020X2-26-C13
VNMRS400F / Num.Inv. 205984
cdcl3 / Temp: 25C / N.Reg: XXXXXXXXXX
Usuari: san / Mostra: AT020X2-26
Nom: JUAN-ANDRES MONTIEL ACHONG
Data: 14/07/16 / Ope.: J.MONTIEL
77.317
77.000
76.682
184.284
155.840
66.271
45.946
36.883
36.344
30.910
25.278
19.067
220
200
180
160
140
120
100
80
60
40
20
0
ppm


HO
CH3
Cl
N
O

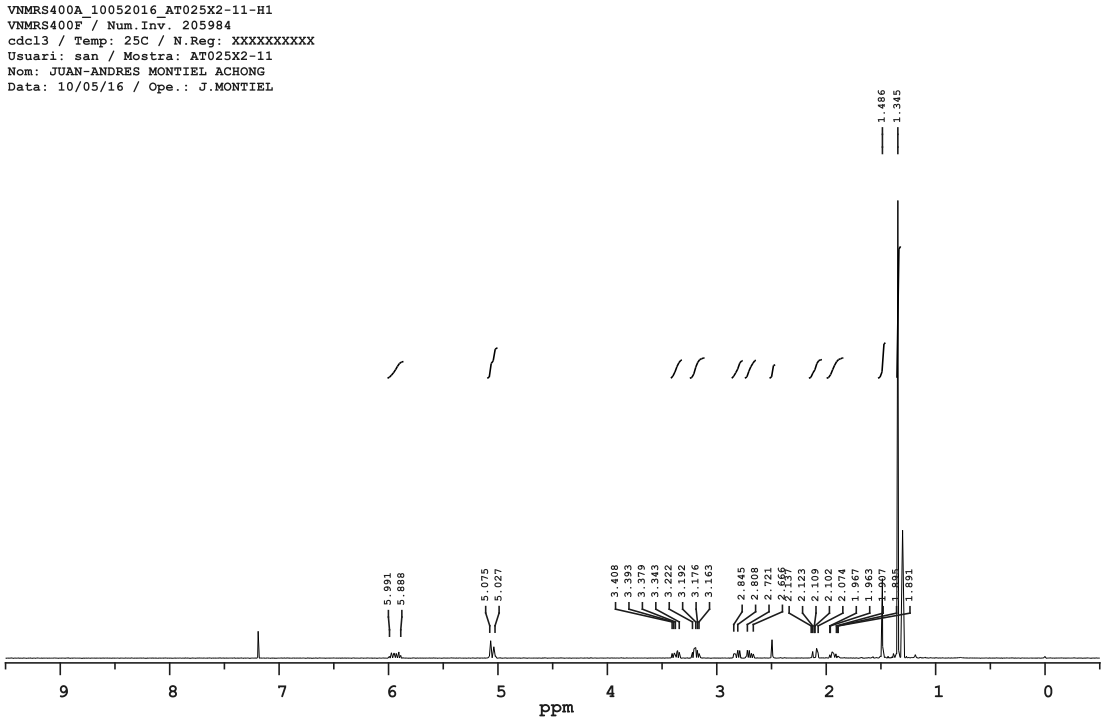
8

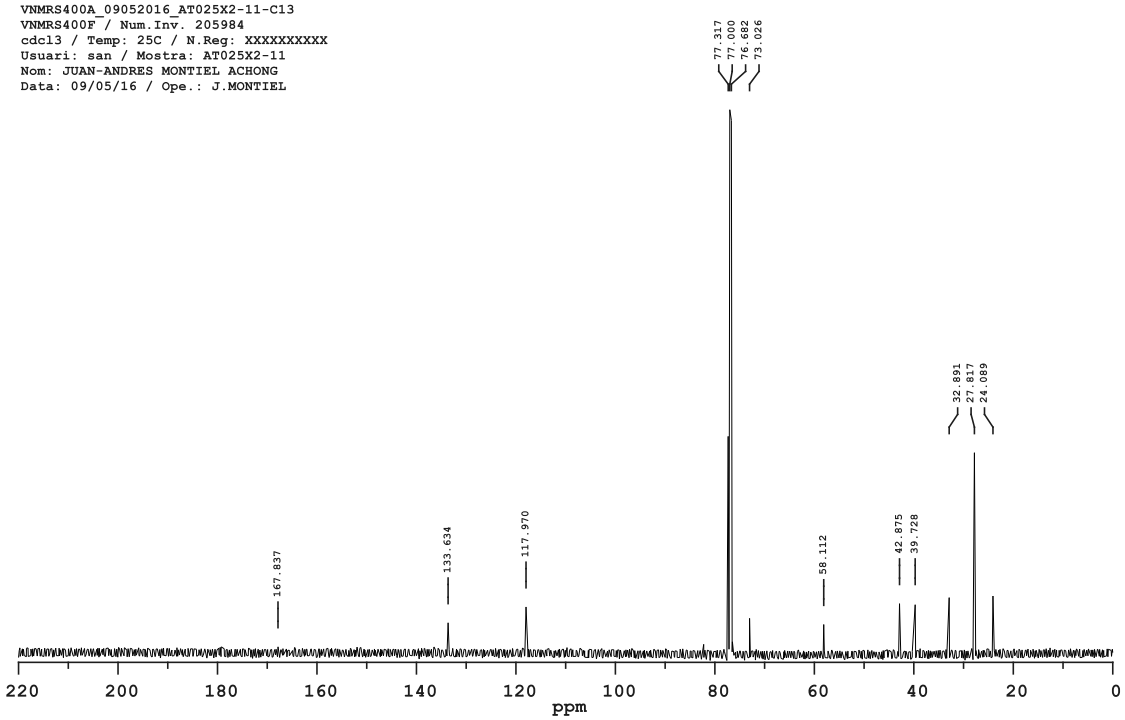

VNMRS400A_07042016_JAM738X2-11-H1
VNMRS400F / Num.Inv. 205984
cdcl3 / Temp: 25C / N.Reg: XXXXXXXXXX
Usuari: san / Mostra: JAM738X2-11
Nom: JUAN-ANDRES MONTIEL ACHONG
Data: 07/04/16 / Ope.: J.MONTIEL
1.864
1.854
1.848
1.838
1.829
1.818
1.813
1.803
1.580
1.579
1.480
1.445
2.829
2.827
2.826
2.806
2.804
2.802
2.793
2.791
2.790
2.770
2.768
2.766
2.388
2.371
2.365
2.353
2.348
2.336
2.330
2.313
6.114
6.010
5.218
5.094
3.497
3.278
2.827
2.804
2.781
2.388
2.371
2.365
2.353
2.348
2.336
2.330
2.313
2.228
2.172
ppm

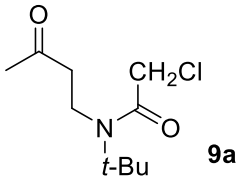

VNMRS400A_07042016_JAM738X2-11-C13
VNMRS400F / Num.Inv. 205984
cdcl3 / Temp: 25C / N.Reg: XXXXXXXXXX
Usuari: san / Mostra: JAM738X2-11
Nom: JUAN-ANDRES MONTIEL ACHONG
Data: 07/04/16 / Ope.: J.MONTIEL
77.318
77.000
76.683
74.419
73.839
32.465
27.764
25.091
167.494
136.469
128.835
117.625
58.043
41.820
39.599
ppm


HO
CH3
Cl
N
O

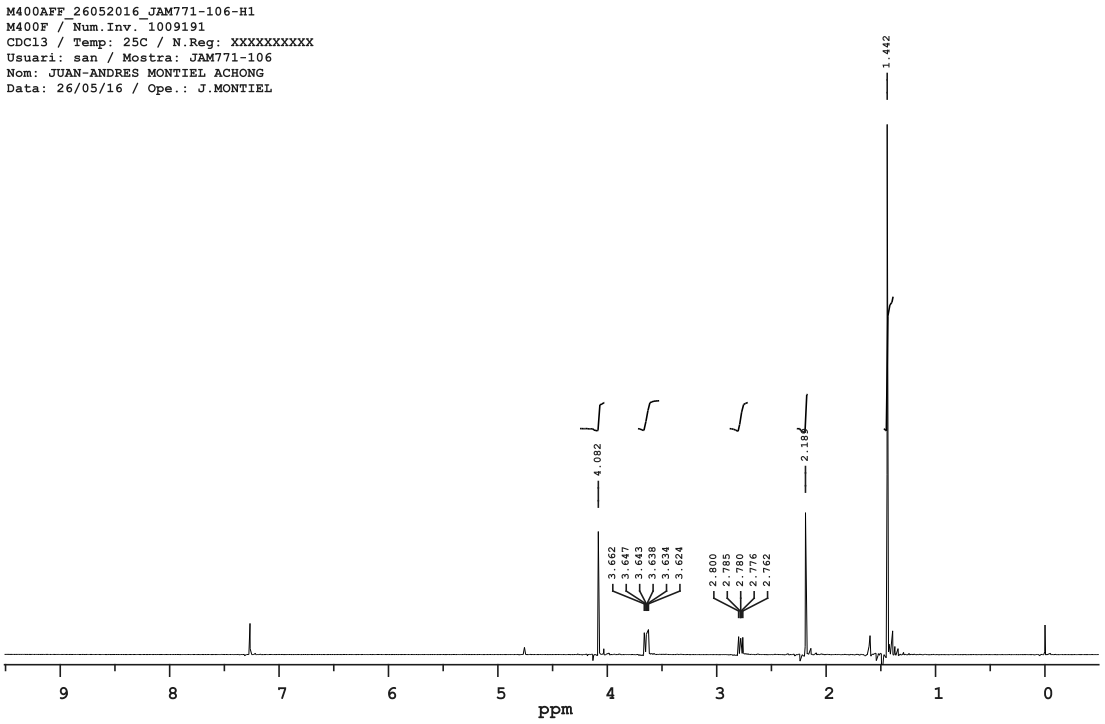
***epi*-8**

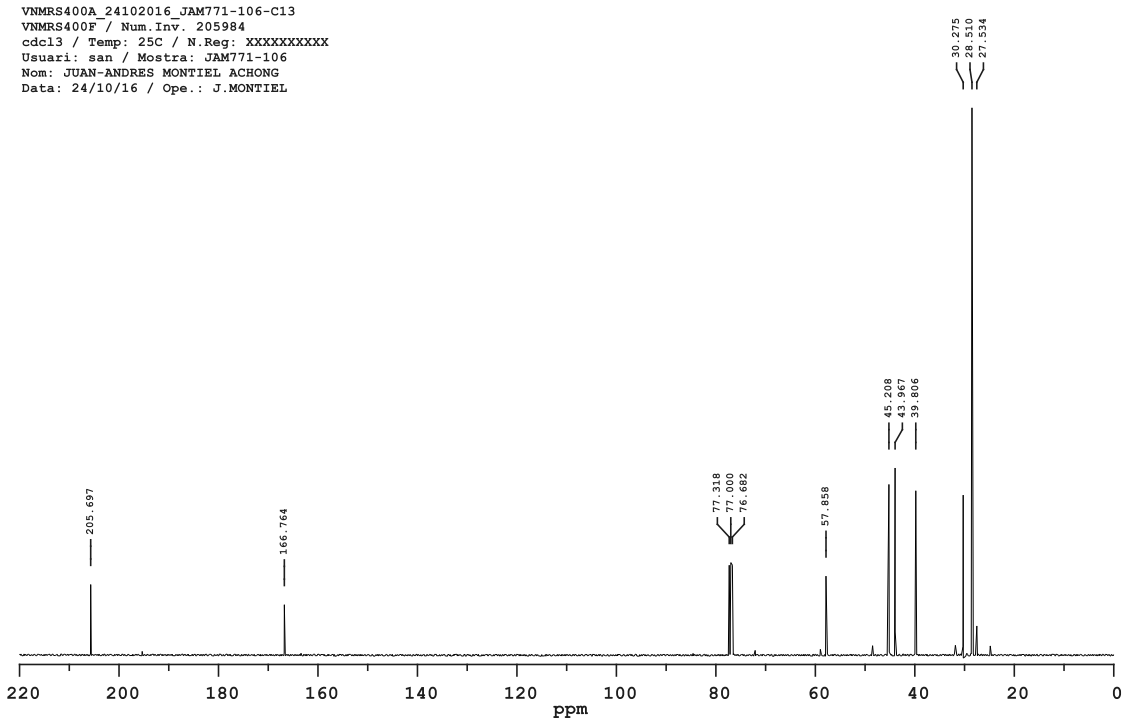

VNMRS400A_10052016_AT025X2-11-H1
VNMRS400F / Num.Inv. 205984
cdcl3 / Temp: 25C / N.Reg: XXXXXXXXXX
Usuari: san / Mostra: AT025X2-11
Nom: JUAN-ANDRES MONTIEL ACHONG
Data: 10/05/16 / Ope.: J.MONTIEL
1.486
1.345
5.991
5.888
5.075
5.027
3.408
3.393
3.379
3.343
3.222
3.192
3.176
3.163
2.845
2.808
2.721
2.123
2.109
2.102
2.074
1.967
1.963
1.907
1.891
9
8
7
6
5
4
3
2
1
0
ppm

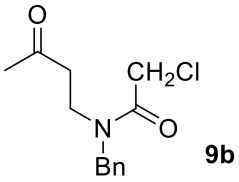

VNMRS400A_09052016_AT025X2-11-C13
VNMRS400F / Num.Inv. 205984
cdcl3 / Temp: 25C / N.Reg: XXXXXXXXXX
Usuari: san / Mostra: AT025X2-11
Nom: JUAN-ANDRES MONTIEL ACHONG
Data: 09/05/16 / Ope.: J.MONTIEL
77.317
77.000
76.682
73.026
32.891
27.817
24.089
167.837
133.634
117.970
58.112
42.875
39.728
220
200
180
160
140
120
100
80
60
40
20
0
ppm


O
CH2Cl
N
O
t-Bu

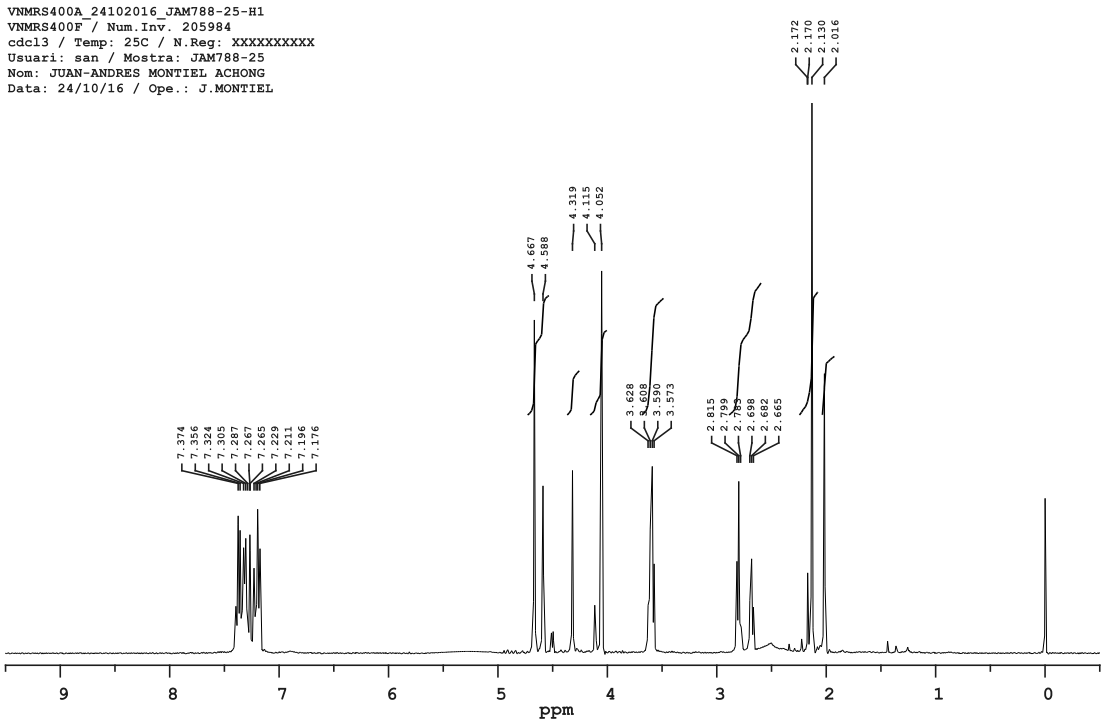
9a

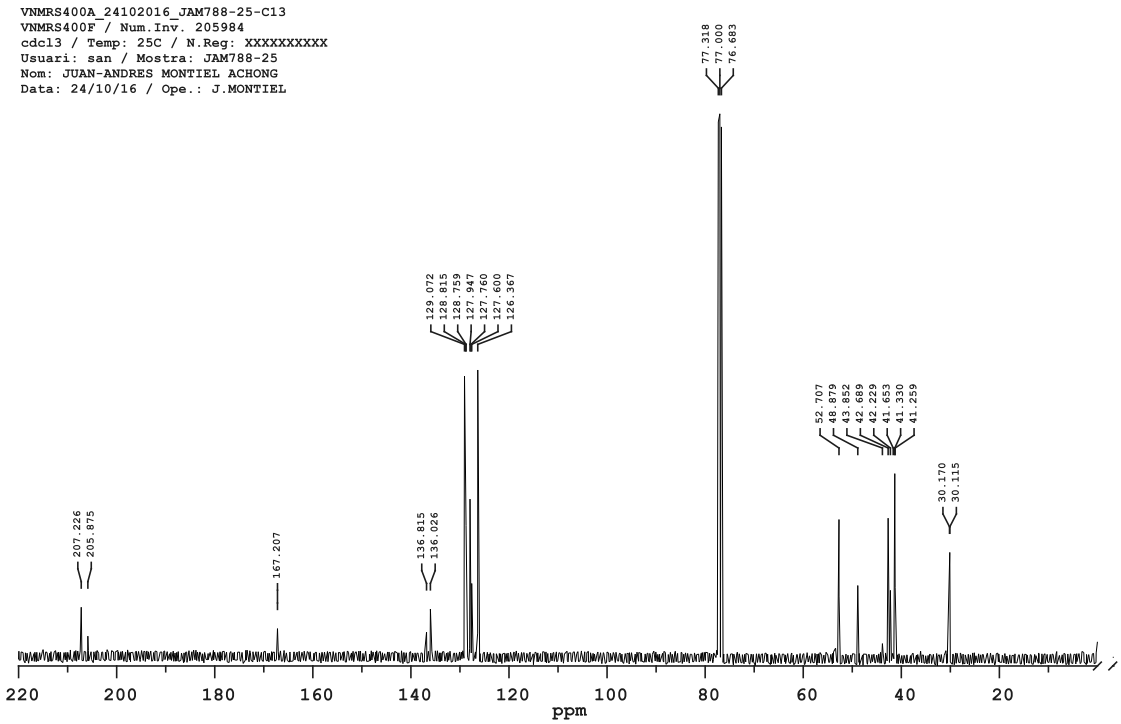

M400AFF_26052016_JAM771-106-H1
M400F / Num.Inv. 1009191
CDCl3 / Temp: 25C / N.Reg: XXXXXXXXXX
Usuari: san / Mostra: JAM771-106
Nom: JUAN-ANDRES MONTIEL ACHONG
Data: 26/05/16 / Ope.: J.MONTIEL
1.442
4.082
3.662
3.647
3.643
3.638
3.634
3.624
2.800
2.785
2.780
2.776
2.762
2.188
9
8
7
6
5
4
3
2
1
0
ppm

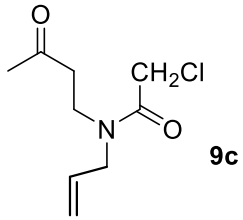

VNMRS400A_24102016_JAM771-106-C13
VNMRS400F / Num.Inv. 205984
cdcl3 / Temp: 25C / N.Reg: XXXXXXXXXX
Usuari: san / Mostra: JAM771-106
Nom: JUAN-ANDRES MONTIEL ACHONG
Data: 24/10/16 / Ope.: J.MONTIEL
30.275
28.510
27.534
45.208
43.967
39.806
77.318
77.000
76.682
57.858
205.697
166.764
220
200
180
160
140
120
100
80
60
40
20
0
ppm


O
CH2Cl
N
O
Bn

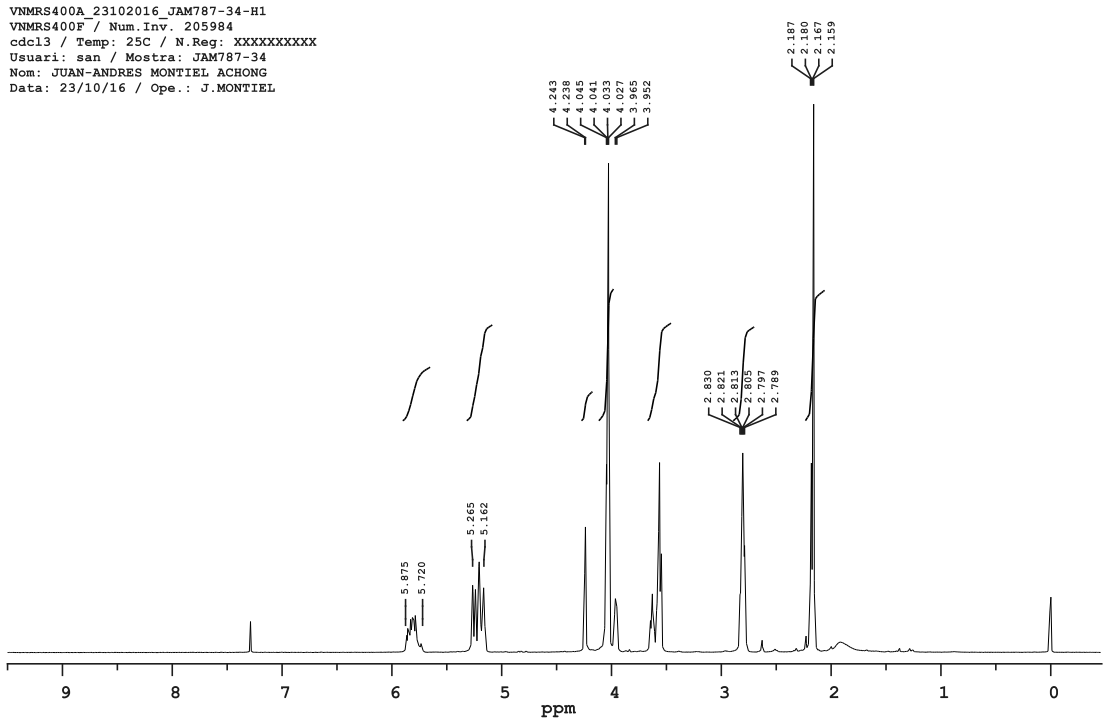
9b

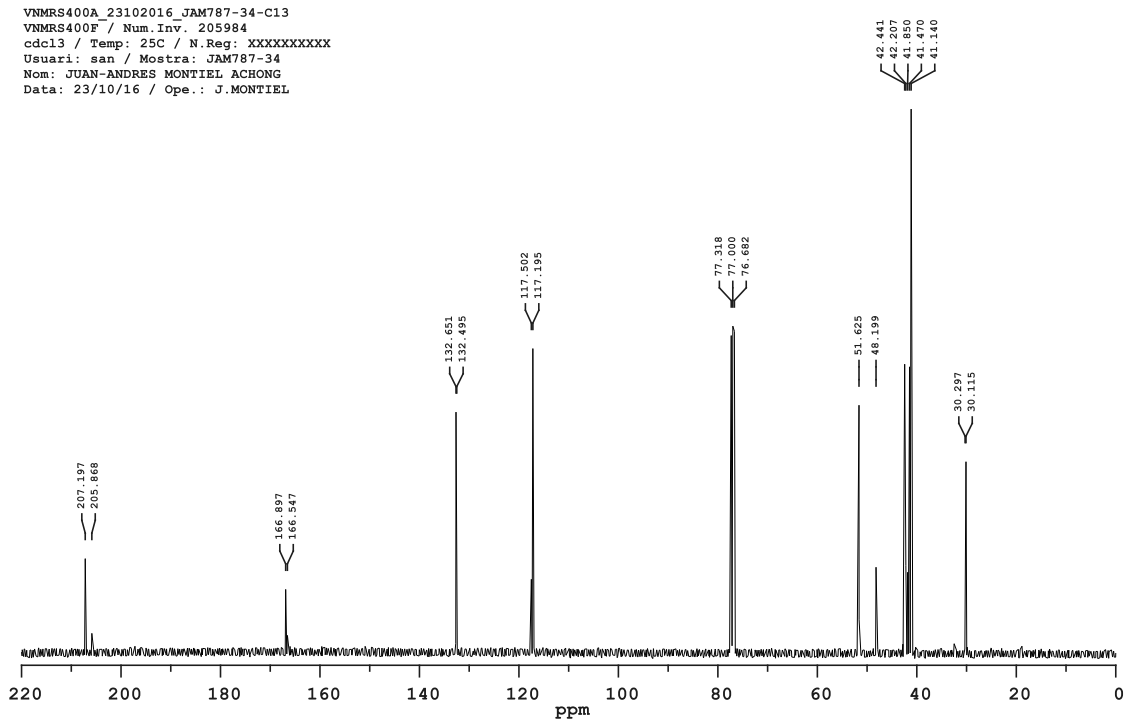

VNMRS400A_24102016_JAM788-25-H1
VNMRS400F / Num.Inv. 205984
cdcl3 / Temp: 25C / N.Reg: XXXXXXXXXX
Usuari: san / Mostra: JAM788-25
Nom: JUAN-ANDRES MONTIEL ACHONG
Data: 24/10/16 / Ope.: J.MONTIEL
2.172
2.170
2.130
2.016
4.667
4.588
4.319
4.115
4.052
3.628
3.608
3.590
3.573
2.815
2.799
2.783
2.698
2.682
2.665
7.374
7.356
7.324
7.305
7.287
7.265
7.229
7.211
7.196
7.176
9
8
7
6
5
4
3
2
1
0
ppm

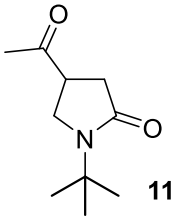

VNMRS400A_24102016_JAM788-25-C13
VNMRS400F / Num.Inv. 205984
cdcl3 / Temp: 25C / N.Reg: XXXXXXXXXX
Usuari: san / Mostra: JAM788-25
Nom: JUAN-ANDRES MONTIEL ACHONG
Data: 24/10/16 / Ope.: J.MONTIEL
77.318
77.000
76.683
129.072
128.811
128.759
127.947
127.760
127.600
126.367
52.707
48.879
43.852
42.689
42.229
41.653
41.330
41.259
30.170
30.115
207.226
205.875
167.207
136.815
136.026
220
200
180
160
140
120
100
80
60
40
20
ppm


O
CH2Cl
N
O

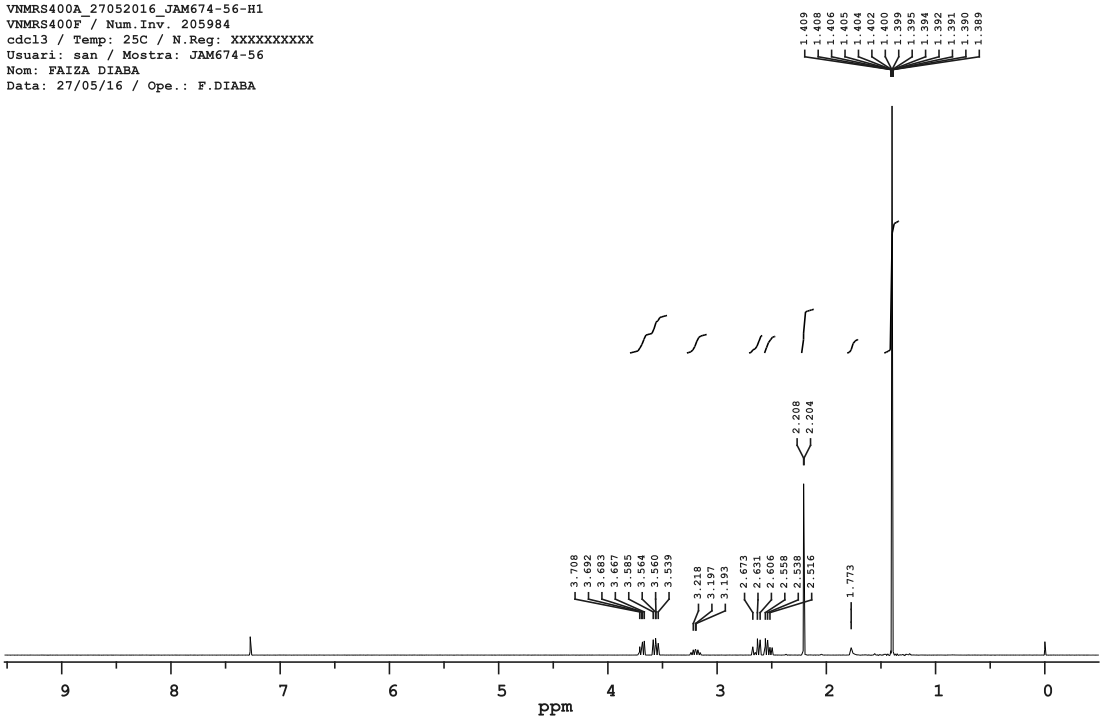
9c

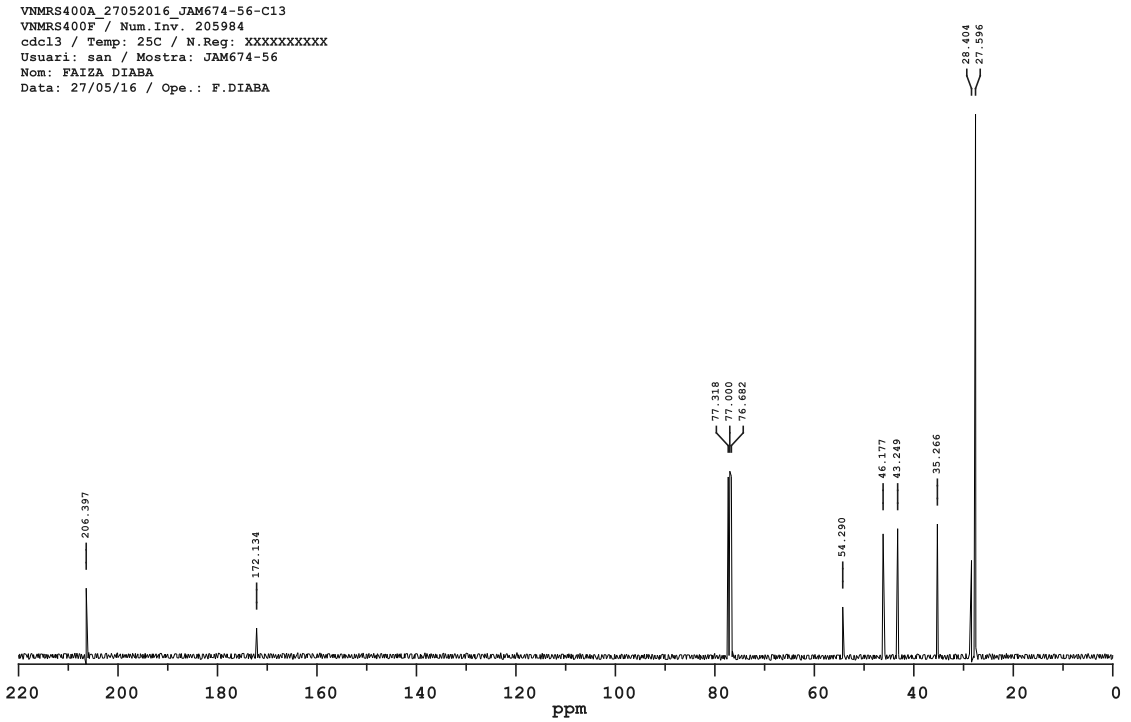

VNMRS400A_23102016_JAM787-34-H1
VNMRS400F / Num.Inv. 205984
cdcl3 / Temp: 25C / N.Reg: XXXXXXXXXX
Usuari: san / Mostra: JAM787-34
Nom: JUAN-ANDRES MONTIEL ACHONG
Data: 23/10/16 / Ope.: J.MONTIEL
4.243
4.238
4.045
4.041
4.033
4.027
3.965
3.952
2.187
2.180
2.167
2.159
2.830
2.821
2.813
2.805
2.797
2.789
5.875
5.720
5.265
5.162
9
8
7
6
5
4
3
2
1
0
ppm

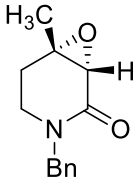

VNMRS400A_23102016_JAM787-34-C13
VNMRS400F / Num.Inv. 205984
cdcl3 / Temp: 25C / N.Reg: XXXXXXXXXX
Usuari: san / Mostra: JAM787-34
Nom: JUAN-ANDRES MONTIEL ACHONG
Data: 23/10/16 / Ope.: J.MONTIEL
42.441
42.207
41.850
41.470
41.140
77.318
77.000
76.682
117.502
117.195
132.651
132.495
51.625
48.199
30.297
30.115
207.197
205.868
166.897
166.547
220
200
180
160
140
120
100
80
60
40
20
0
ppm


O
O
N
O

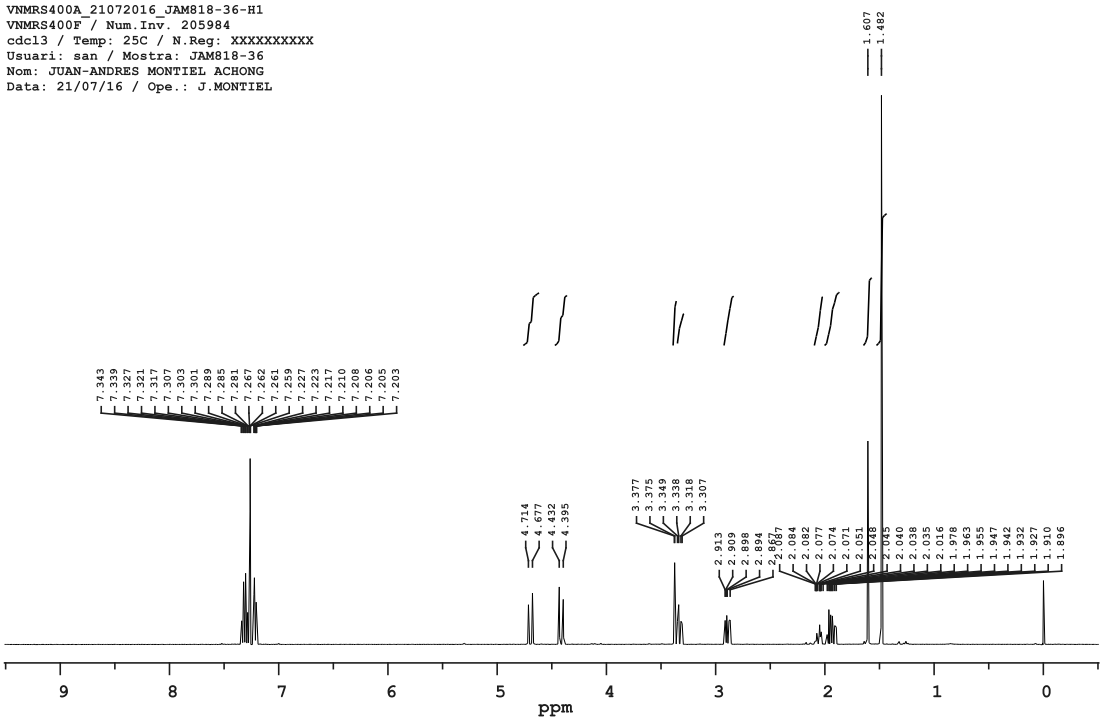
11


VNMRS400A_27052016_JAM674-56-H1
VNMRS400F / Num.Inv. 205984
cdcl3 / Temp: 25C / N.Reg: XXXXXXXXXX
Usuari: san / Mostra: JAM674-56
Nom: FAIZA DIABA
Data: 27/05/16 / Ope.: F.DIABA
1.409
1.408
1.406
1.405
1.404
1.402
1.400
1.399
1.395
1.394
1.392
1.391
1.390
1.389
2.208
2.204
3.708
3.692
3.683
3.667
3.585
3.564
3.560
3.539
3.218
3.197
3.193
2.673
2.631
2.606
2.558
2.538
2.516
1.773
9
8
7
6
5
4
3
2
1
0
ppm


VNMRS400A_27052016_JAM674-56-C13
VNMRS400F / Num.Inv. 205984
cdcl3 / Temp: 25C / N.Reg: XXXXXXXXXX
Usuari: san / Mostra: JAM674-56
Nom: FAIZA DIABA
Data: 27/05/16 / Ope.: F.DIABA
28.404
27.596
77.318
77.000
76.682
46.177
43.249
35.266
54.290
206.397
172.134
220
200
180
160
140
120
100
80
60
40
20
0
ppm


H3C
O
H
N
O
Bn

12b


VNMRS400A_21072016_JAM818-36-H1
VNMRS400F / Num.Inv. 205984
cdcl3 / Temp: 25C / N.Reg: XXXXXXXXXX
Usuari: san / Mostra: JAM818-36
Nom: JUAN-ANDRES MONTIEL ACHONG
Data: 21/07/16 / Ope.: J.MONTIEL
1.607
1.482
7.343
7.339
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7.321
7.317
7.307
7.303
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7.289
7.285
7.281
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7.261
7.259
7.227
7.223
7.217
7.210
7.208
7.206
7.205
7.203
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3.377
3.375
3.349
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3.318
3.307
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2.898
2.894
2.887
2.084
2.082
2.077
2.074
2.071
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2.048
2.045
2.040
2.038
2.035
2.016
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1.955
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6
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4
3
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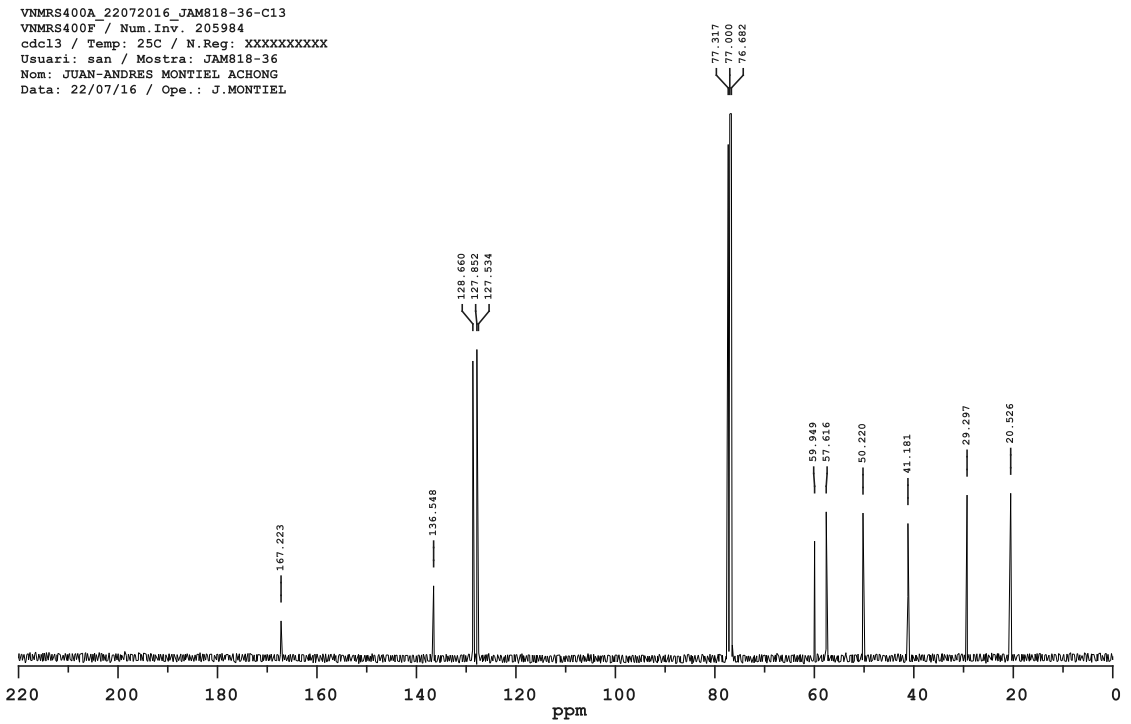
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76.682
128.660
127.852
127.534
167.223
136.548
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120
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60
40
20
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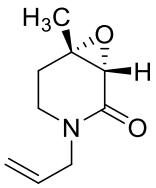
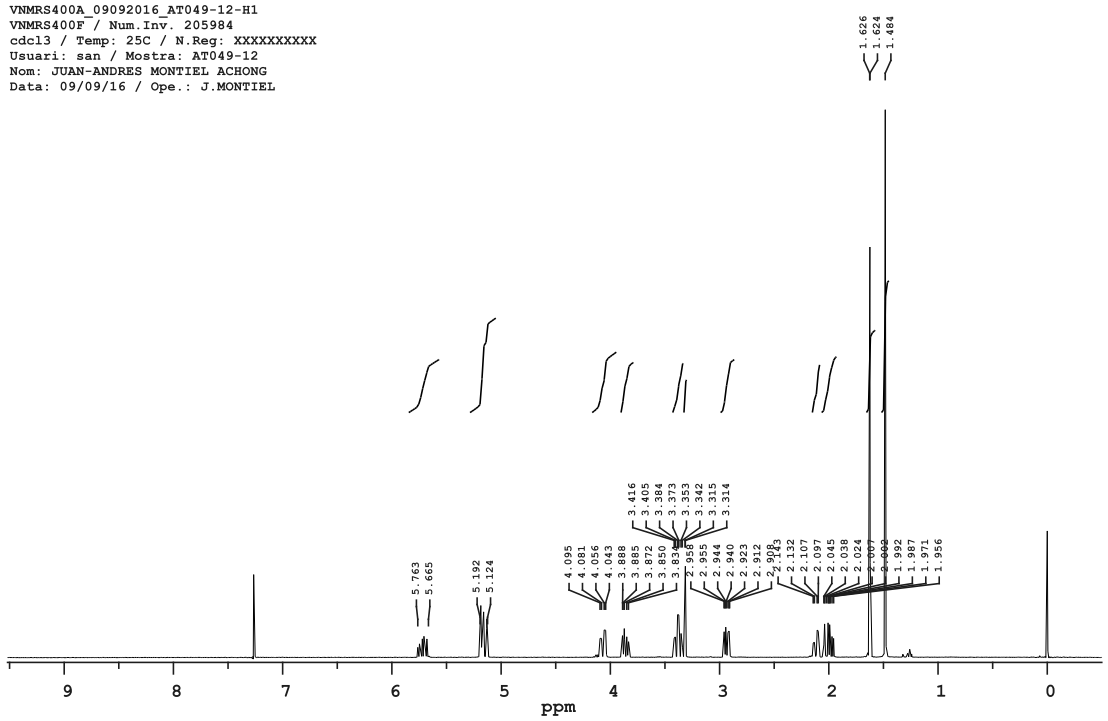

H3C
O
H
N
O

12c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3.342
3.315
3.314
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4.081
4.056
4.043
3.888
3.885
3.872
3.850
2.958
2.955
2.944
2.940
2.923
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2.132
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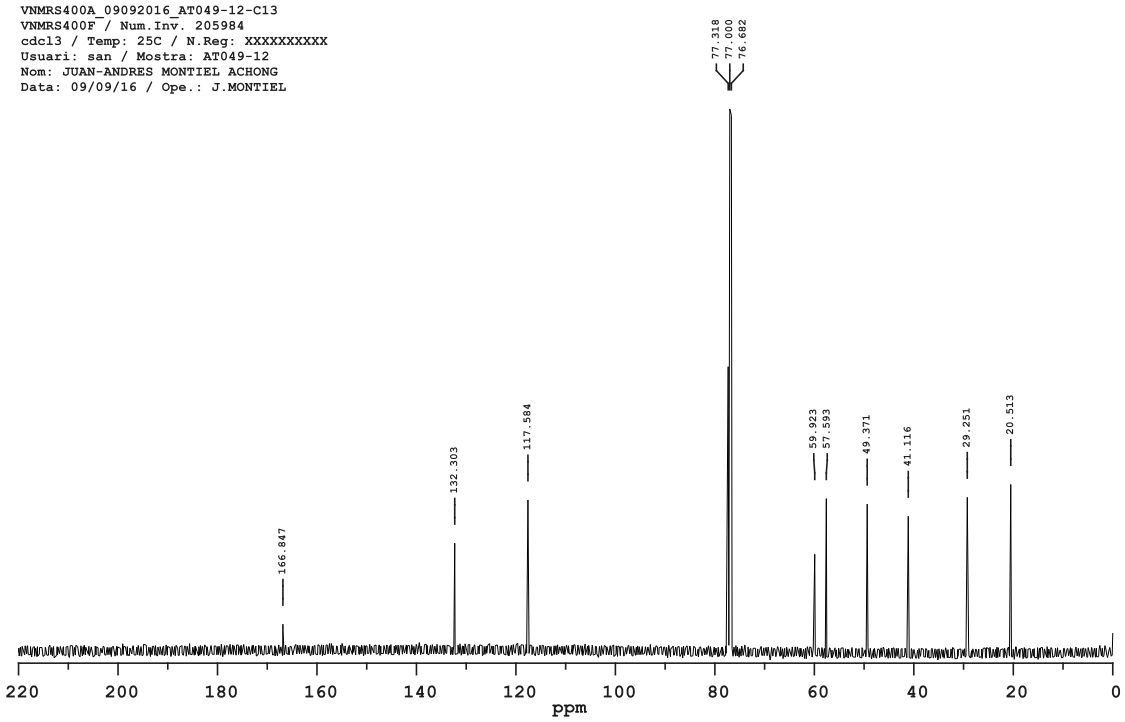
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Nom: JUAN-ANDRES MONTIEL ACHONG
Data: 09/09/16 / Ope.: J.MONTIEL
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76.682
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132.303
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59.923
57.593
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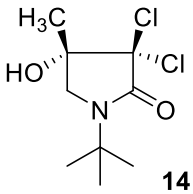
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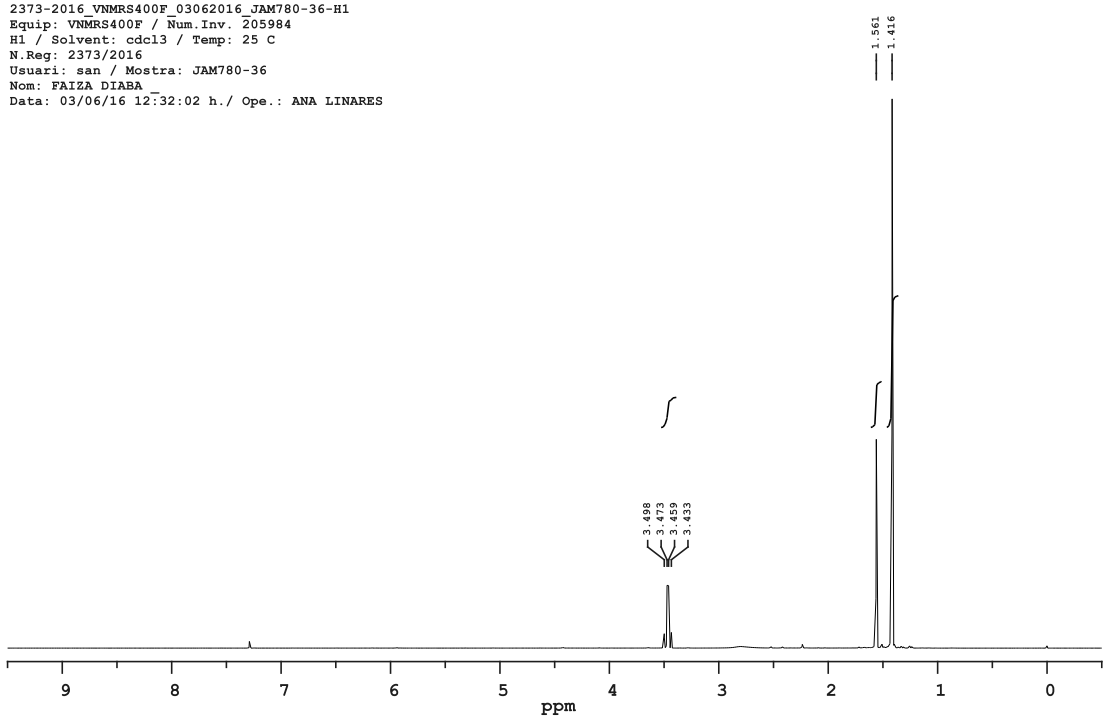
Cl
HO
Cl
N
O

14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H1 / Solvent: cdcl3 / Temp: 25 C
N.Reg: 2373/2016
Usuari: san / Mostra: JAM780-36
Nom: FAIZA DIABA _
Data: 03/06/16 12:32:02 h./ Ope.: ANA LINARES
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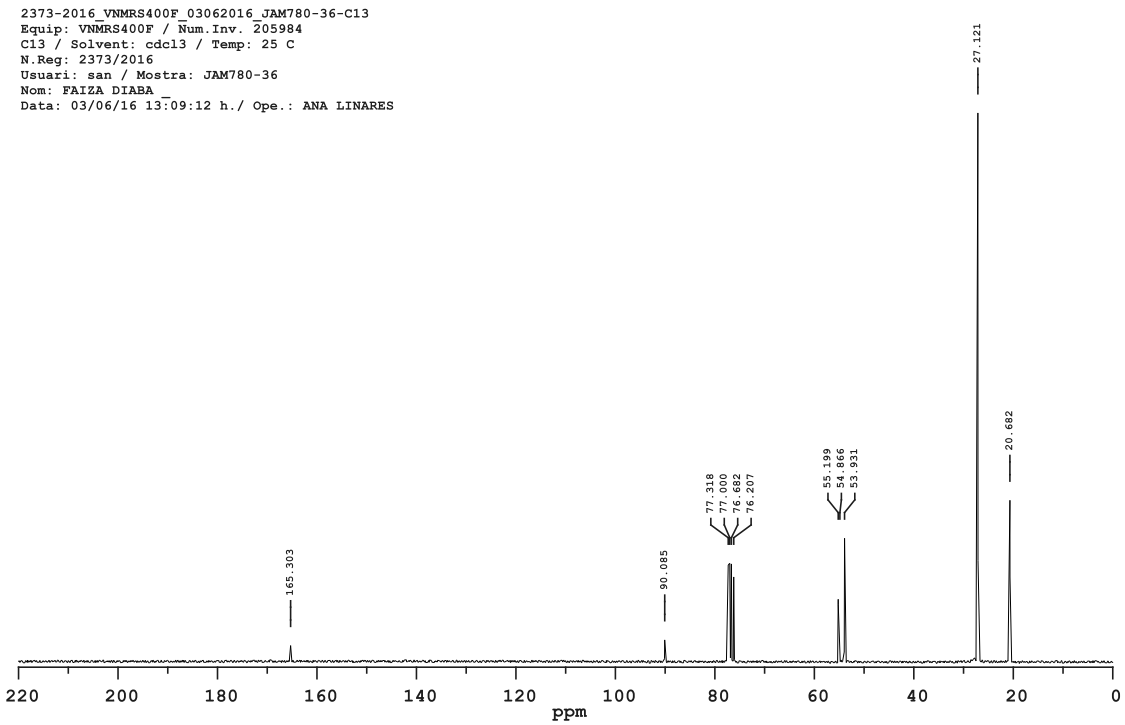
8
7
6
5
4
3
2
1
0
ppm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Usuari: san / Mostra: JAM780-36
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54.866
53.931
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200
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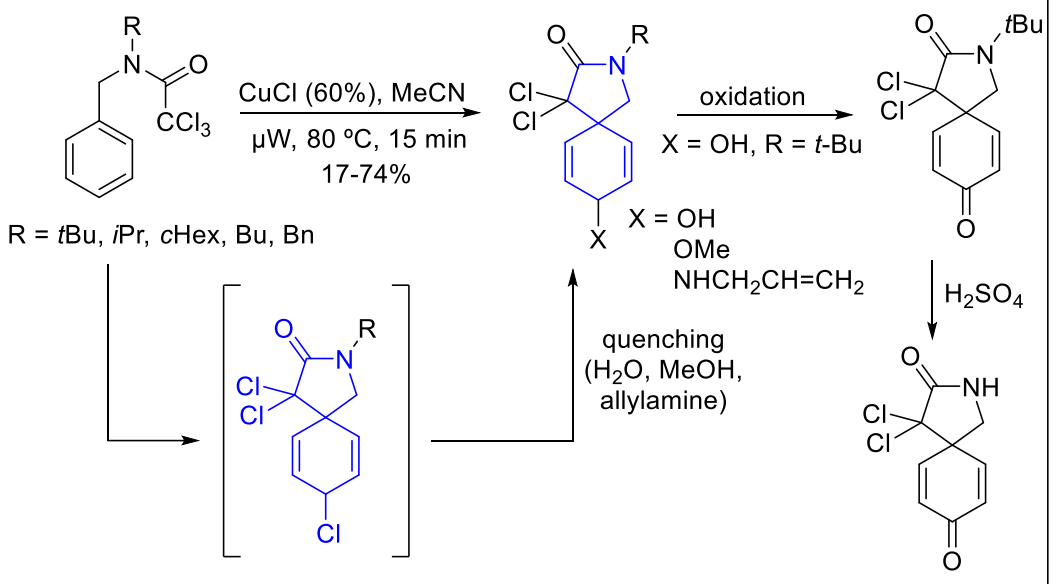
80
60
40
20
0
ppm

Conclusions

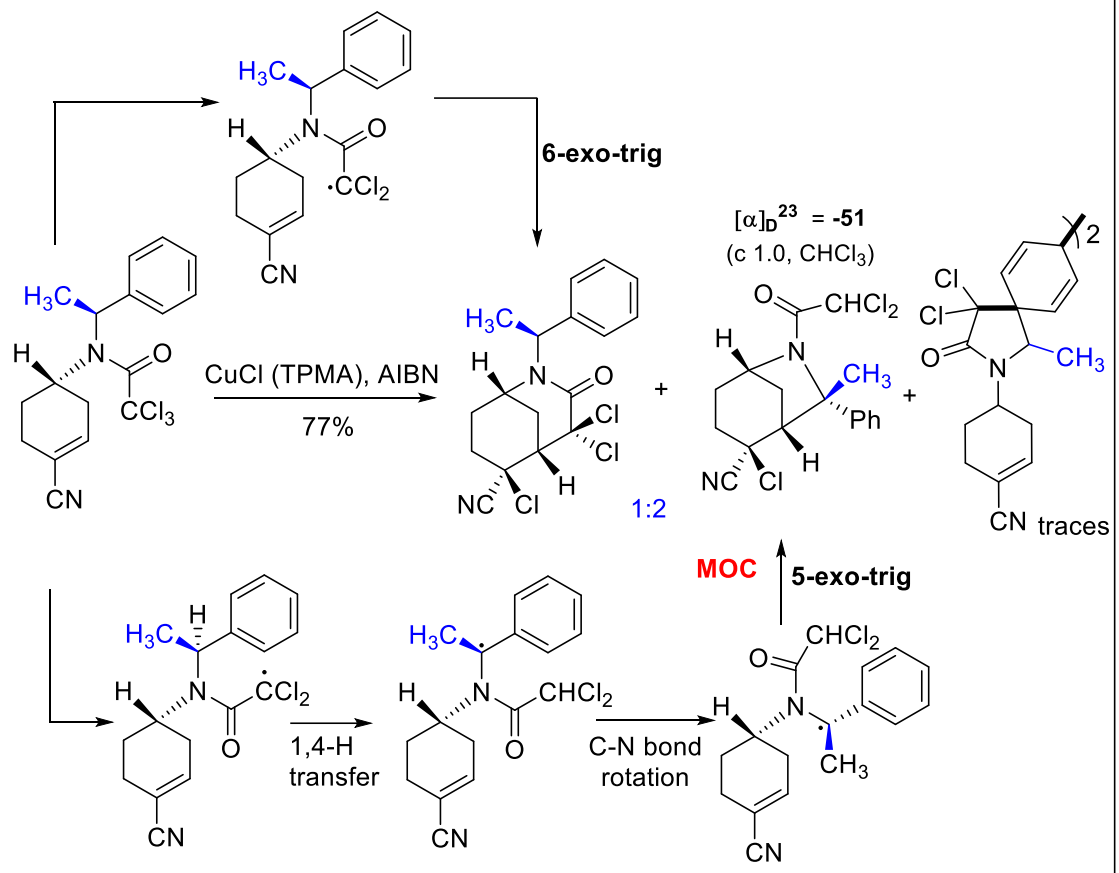
CuCl mediated ATRC for the synthesis of 2- azaspiro[4.5]decanes



Diaba, F.; **Montiel, J. A.**; Martínez-Laporta, A.; Bonjoch, J. *Tetrahedron Lett.* **2013**, *54*, 2619-2622.

In conclusion, during this PhD work we have demonstrated that chloroacetamides are valuable and versatile intermediates for the synthesis of different nitrogen containing heterocycles using either radical or non-radical processes. In the first place, we reported the first dearomative spirocyclization under ATRC conditions using a Cu(I) catalyst to access 2-azaspiro[4.5]decanes by treatment of benzyltrichloroacetamides with substoichiometric quantities of CuCl, in acetonitrile and with microwave activation. The results obtained with the different trichloroacetamides used in this study show the importance of having a bulky group on the nitrogen to achieve the cyclization process. The unstable chlorides obtained at the end of the reaction, were easily transformed into more stable alcohols, ethers or amines by a simple quenching with water, methanol or allylamine respectively. Additionally, oxidation of the epimeric alcohol mixture to the corresponding ketone and further cleavage of the *t*-butyl group provided a polyfunctionalized 2-azaspiro[4.5]decane derivative, which can be used as a building block to construct more complex structures.

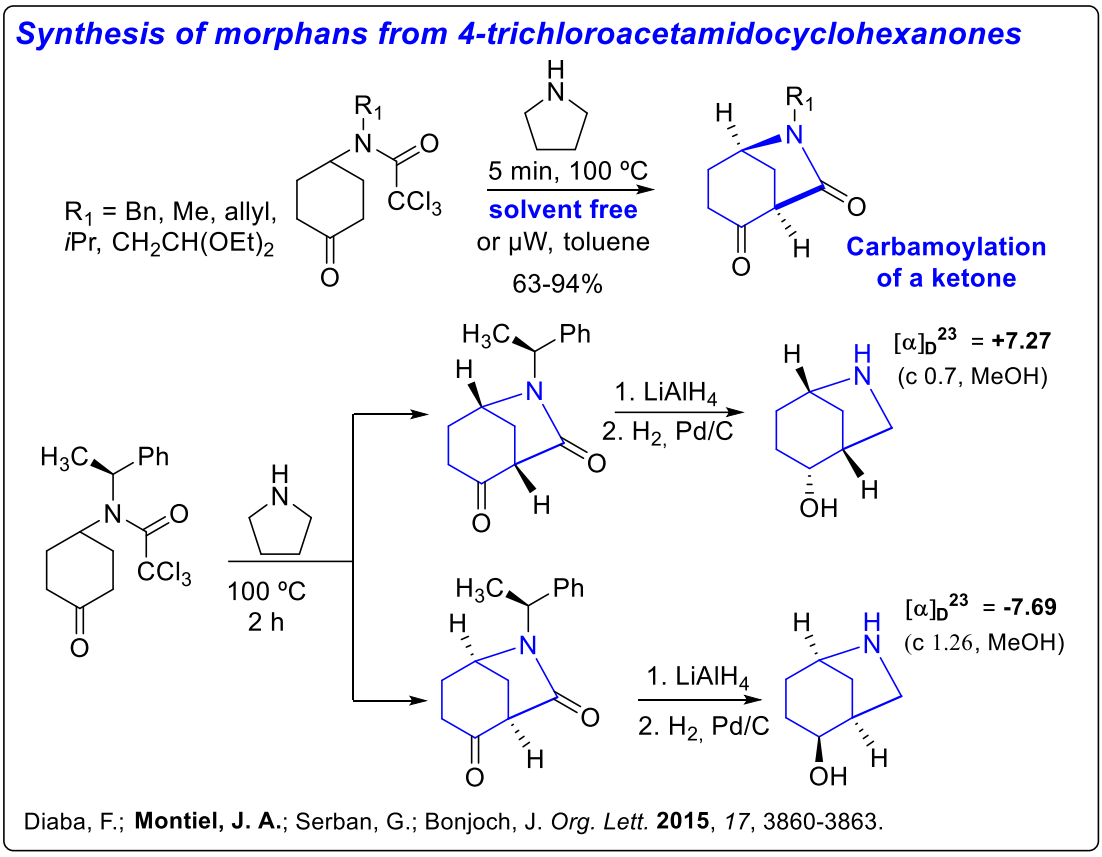
CuCl mediated ATRC from N-(α-methylbenzyl)trichloroacetamides



Diaba, F.; **Montiel, J. A.**; Bonjoch, J. *Tetrahedron* **2013**, *69*, 4883-4889.

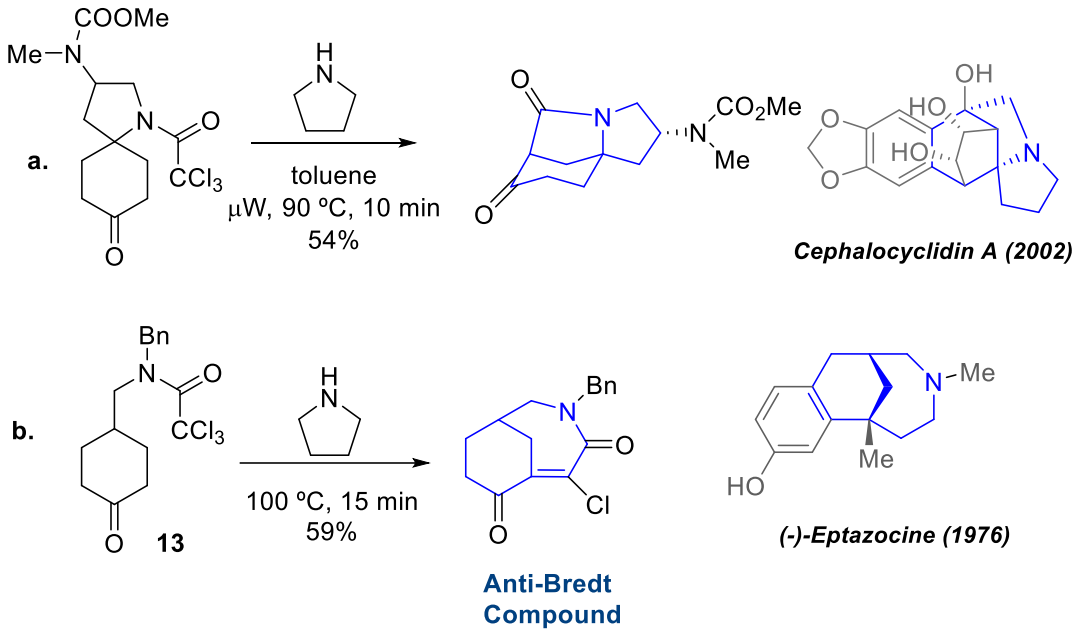
In the second place, when *N*-(α-methylbenzyl)trichloroacetamides were submitted to the ATRC conditions described before for the synthesis of morphans, the radical course of the reaction followed two main pathways. The first one, as expected, provided morphans through an ATRC from the 1-(carbamoyl)dichloromethyl radical with the amide *Z*-conformation, which underwent cyclization upon the α,β-unsaturated nitrile followed by a diastereoselective chlorine atom transfer. In the second pathway, as observed under reductive conditions, the same radical in its *E* conformation underwent a 1,4-hydrogen transfer generating a benzylic radical that reacts with the unsaturated α,β-nitrile with configurational inversion at the quaternary stereogenic center. Here also, after a diastereoselective chlorine transfer, normorphan derivatives were isolated. It is worth noting that this stereospecific formation of normorphans involving memory of chirality (MoC) in the radical

cyclization, together with the one reported earlier by our research group, are examples of this scarce phenomenon.



Additionally, as a result of an investigation aimed at the preparation of enamine from 4-trichloroacetamidocyclohexanone and pyrrolidine, we discovered a new route for the synthesis of 6-azabicyclo[3.2.1]octane ring (normorphan) present in many natural and non-natural compounds . The 5 min reaction was achieved under solvent-free conditions or using microwave activation in toluene. The process involves an unprecedented intramolecular α-carbamoylation of ketones or an intramolecular haloform-type reaction of trichloroacetamides promoted by enamine (generated in situ) as counter-reagents. The methodology was applied to enantiopure *N*-(α-methylbenzyl)trichloroacetamidocyclohexanone providing the expected normorphans which were separated and converted to the corresponding amino alcohols for their future use as organocatalysts.

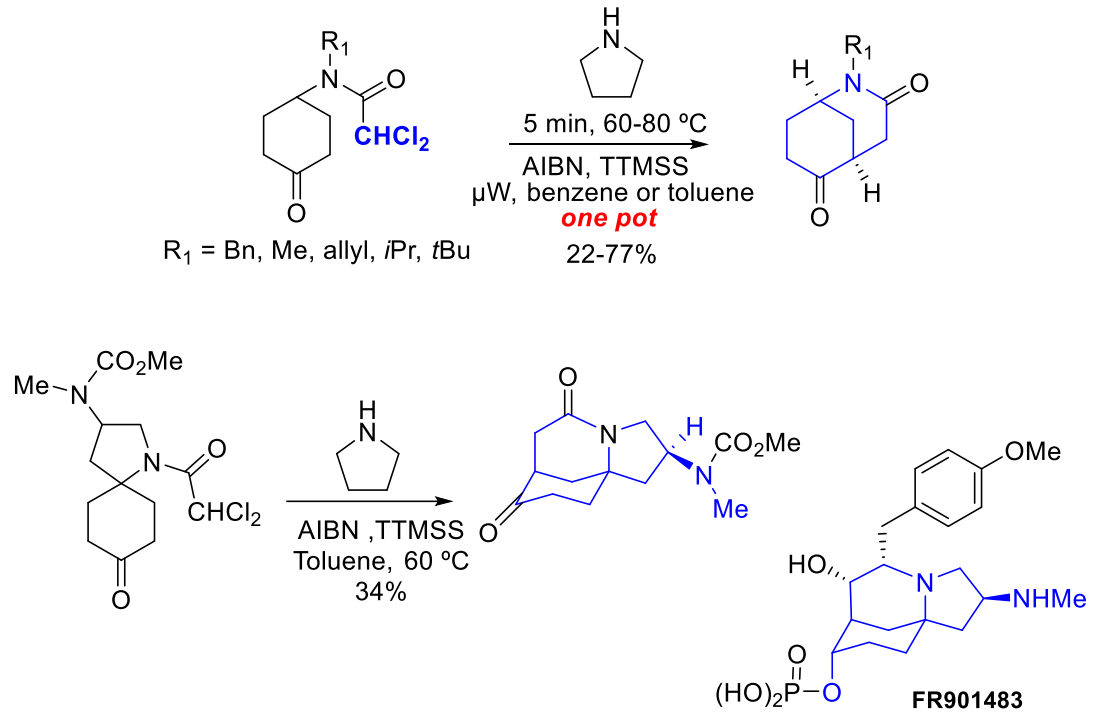
Carbamoylation of ketones from trichloroacetamides



Diaba, F.; **Montiel, J. A.**; Serban, G.; Bonjoch, J. *Org. Lett.* **2015**, *17*, 3860-3863.

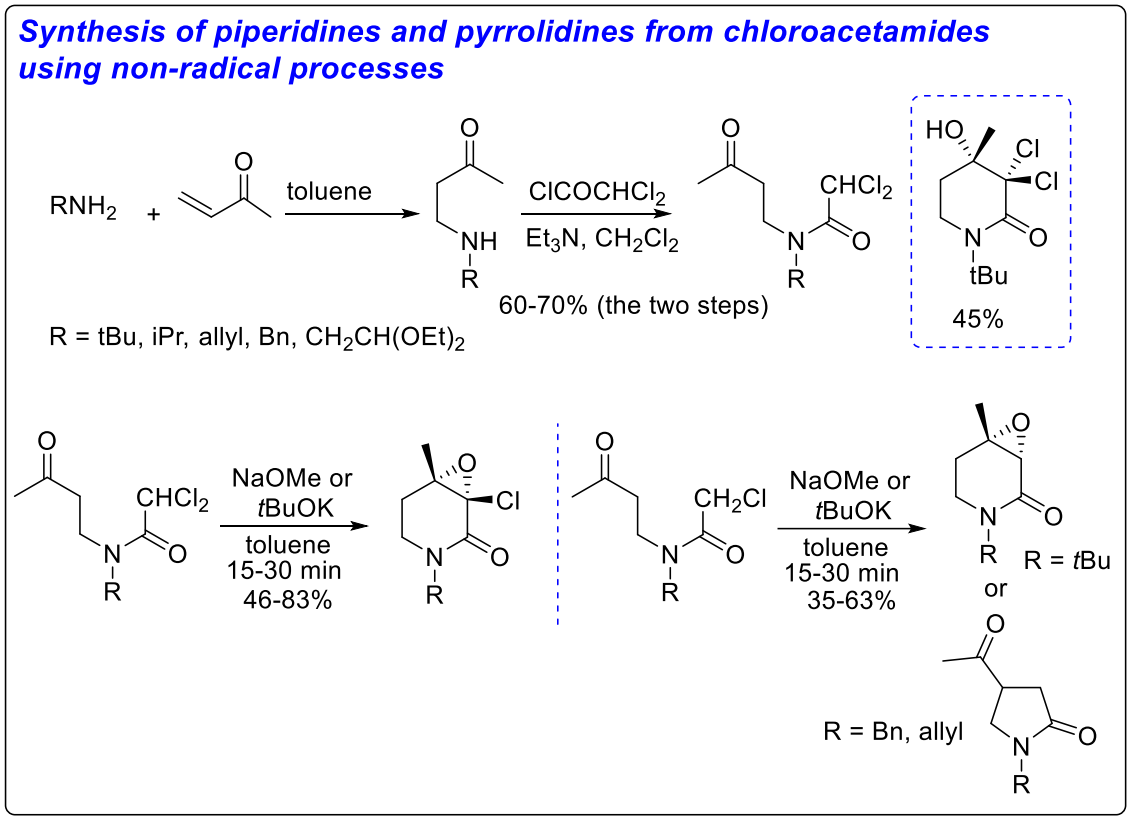
The methodology was successfully extended to additional substrates to provide the azatricyclic structure that constitutes the ring core of the pentacyclic natural product cephalocyclidin A (a). Additionally, enlargement of the side chain bearing the trichloroacetamide had a significant impact on the course of the reaction since it provided the anti-Bredt seven-membered ring alone (b). The structure of this unprecedented type of anti-Bredt ring (3-azabicyclo[4.3.1]dec-5-ene) is present in many natural compounds with few reported methodologies for its preparation.

Radical synthesis of morphans from 4-dichloroacetamidocyclohexanones



Diaba, F.; **Montiel, J. A.**; Bonjoch, J. *Chem. Comm*. **2016**, *52,* 14031-14034

The results previously obtained with trichloroacetamides led us to use dichloroacetamides instead to achieve the radical process. Thus a new route for the synthesis of 2-azabicyclo[3.3.1]nonanes was reported using a radical cyclization of dichloroacetamide-tethered ketones in the presence of pyrrolidine, AIBN and TTMSS and under microwave activation. In a five-minute one-pot process, after the generation of an enamine, intramolecular addition of a carbamoylchloromethyl radical, and oxidation of the α-aminoalkyl radical intermediate, the resulting iminium salt evolved to the corresponding enamine and, after a workup, to the alkylated ketone. The methodology was successfully applied to the synthesis of the tricyclic core of immunosuppressant FR901483 and also to the preparation of the 3-azabicyclo[4.3.1]decane structure through formation of the seven membered ring.



The synthesis of functionalized pyrrolidines and piperidines from linear monochloro- and dichloroacetamides using non-radical chemistry was investigated. These chloroacetamides were easily prepared from methyl vinyl ketone and the corresponding amine followed by treatment with dichloro or chloroacetyl chloride in a *one-pot* reaction. Here also, the *t*-butyl group on the nitrogen allowed the reaction to go further providing the corresponding polyfunctionalized piperidine with an acceptable yield. The cyclization process was also achieved using Darzens conditions in the presence of sodium methoxide or potassium *t*-butoxide to afford the above mentioned epoxides with good yields.

Application of the methodology to monochloroacetamides provided the piperidine or the pyrrolidine ring depending on the nature of the substituent on the nitrogen atom.