Síntesi total de productes marins amb l'estructura triptòfan-pirroloindole

Pau Ruiz Sanchis

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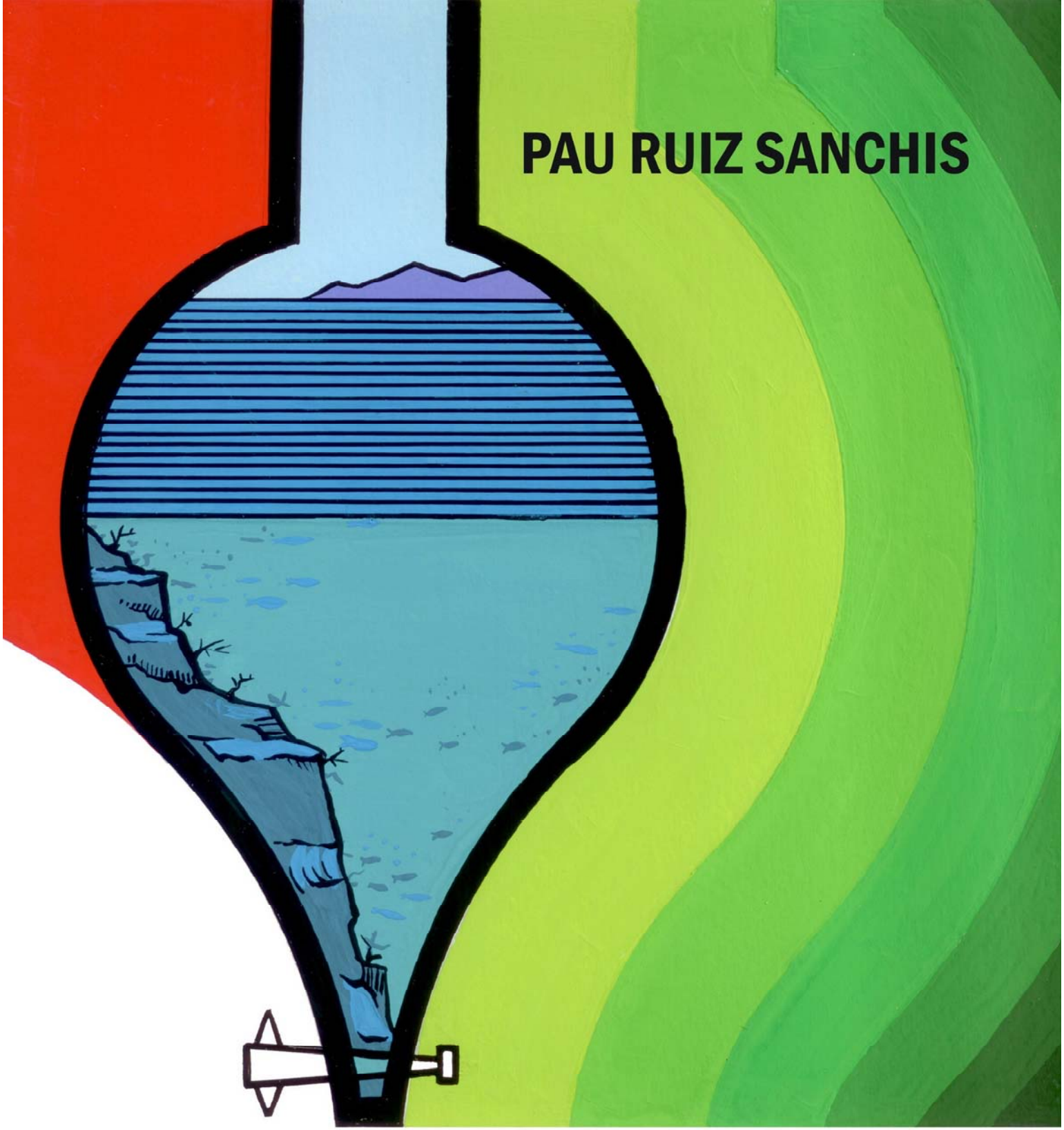
PAU RUIZ SANCHIS



SÍNTESI TOTAL DE PRODUCTES MARINS AMB L'ESTRUCTURA TRIPTÒFAN-PIRROLOINDOLE

UNIVERSITAT DE BARCELONA

FACULTAT DE FARMÀCIA

DEPARTAMENT DE FARMACOLOGIA I QUÍMICA TERAPÈUTICA

SÍNTESI TOTAL DE PRODUCTES MARINS AMB L'ESTRUCTURA TRIPTÒFAN-PIRROLOINDOLE

Pau Ruiz Sanchis

2011

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SÍNTESI TOTAL DE PRODUCTES MARINS AMB L'ESTRUCTURA TRIPTÒFAN-PIRROLOINDOLE

Memòria presentada per:

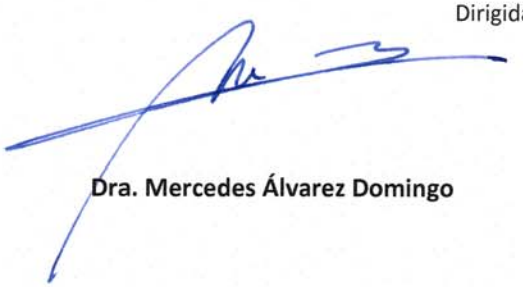
Pau Ruiz Sanchis

per optar al títol de Doctor per la Universitat de Barcelona.

Programa de doctorat: QUÍMICA ORGÀNICA EN LA INDÚSTRIA QUÍMICO FARMACÈUTICA

Bienni 2006-2008

Dirigida per:



Dra. Mercedes Álvarez Domingo **Dr. Fernando Albericio Palomera**

Barcelona, 2011

Al meu abuelo,

a mos pares, a Llum

i a Lore.

El treball descrit en aquesta memòria s'ha realitzat a l'Institut de Recerca Biomèdica de Barcelona (IRBB) ubicat al Parc Científic de Barcelona. Aquest treball ha gaudit dels següents ajuts:

Projecte "Combiestrategias para el Descubrimiento de Nuevos Fármacos Peptídicos y/o Heterocíclicos" finançat per la Comissió de Ciència i Tecnologia (CTQ2009-07758/BQU). Grup de recerca reconegut per la Generalitat de Catalunya, Química Combinatòria per al Desenvolupament de Nous Compostos (2009SGR 1024). Centro de Investigación Biomédica en Red, de Bioingeniería, Biomateriales y Nanomedicina (CIBER-BBN 0074) finançat pel Ministerio de Sanidad y Consumo a través de l'Instituto de Salud Carlos III. Conveni PharmaMar S.A. – Parc Científic de Barcelona amb el projecte "Síntesis de Nuevos Agentes Terapéuticos".

P.R.S. ha rebut una beca predoctoral de l'IRBB (02/06-IRB).

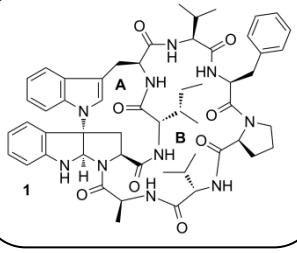
ÍNDEX GENERAL

ÍNDEX D'ABREVIATURES

A-549	Línia cel·lular humana de càncer de pulmó
aa	Aminoàcid
abs.	Absolut
AIBN	2,2'-Azobisisobutironitril
Ala	L-Alanina
Al·loc	Al·liloxicarbonil
anh.	Anhidre
Boc	*terc*-Butoxicarbonil
Br-HPI	3a-Bromo-HPI
bs	Senyal ampla
Cbz	Benziloxicarbonil
CCF	Cromatografia de capa fina
d	Doblet
DCM	Diclorometà
DCP	Dicetopiperazina
DDQ	2,3-Dicloro-5,6-dicianobenzoquinona
DIEA	*N*,*N*-Diisopropiletilamina
DIPC	*N*,*N*'-Diisopropilcarbodiimida
DMF	*N*,*N*-Dimetilformamida
DMSO	Dimetilsulfòxid
EDC	1-Etil-3-(3-dimetilaminopropil)carbodiimida
EMEA	European Medicines Agency
ESI	Ionització amb electroesprai
FDA	Food and Drug Administration
Fmoc	Fluorenilmetiloxicarbonil
Ftal	Ftalimida
gHSQC	Heterocorrelació via detecció inversa
HATU	Hexafluorofosfat de 2-(1*H*-7-azabenzotriazol-1-il)-1,1,3,3-tetrametiluroni
HBTU	Hexafluorofosfat de 2-(1*H*-benzotriazol-1-il)-1,1,3,3-tetrametiluroni
HMPA	Hexametilfosforamida
HOAt	1-Hidroxi-7-azabenzotriazol
HOBt	Hidroxibenzotriazol
HPI	1,2,3,3a,8,8a-Hexahidropirrolo[2,3-*b*]indole
HPLC	Cromatografia líquida d'alta resolució
HRMS	Espectroscòpia de masses d'alta resolució

HT-29	Línia cel·lular humana de càncer de colon
HTS	Bioanàlisi d'alt rendiment
Ile	L-Isoleucina
IR	Infraroig
LIMS	Sistema de gestió d'informació del laboratori
m	Multiplet
MDA-MB-231	Línia cel·lular humana de càncer de mama
Moc	Metoxicarbonil
MTBE	Metil *terc*-butil èter
MW	Microones
NBS	*N*-Bromosuccinimida
NHMDS	Bis(trimetilsilil)amidur de sodi
NIS	*N*-Iodosuccinimida
NOE	Efecte nuclear Overhauser
Ns	2-Nitrofenilsulfonil
PDA	Photodiode array
Phe	L-Fenilalanina
Pip	Piperidina
PNZ	*p*-Nitrobenziloxicarbonil
PPTS	*p*-Toluensulfonat de piridini
Pro	L-Prolina
py	Piridina
PyAOP	Hexafluorofosfat de (7-azabenzotriazol-1-iloxi)-trispirrolidinofosfoni
PyOxP	Hexafluorofosfat de O-[(ciano-(etoxicarbonil)metiliden)-amino]-iloxitripirrolidinofosfoni
Red-Al	Bis(2-metoxietoxi)aluminihidrur de sodi
RMN	Ressonància magnètica nuclear
RPMI	Medi Roswell Park Memorial Institute
s	Singlet
sat.	Saturat
SRB	Sulforodamina B
t	Triplet
t.a.	Temperatura ambient
TEA	Trietilamina
TFA	Àcid trifluoroacètic
THF	Tetrahidrofurà
TMSI	Iodur de trimetilsilil
Tr	Trifenilmetil (tritil)
Troc	2,2,2-Tricloroetoxicarbonil
Trp	L-Triptòfan
UV	Ultraviolat
Val	L-Valina
VLC	Cromatografia líquida amb buit

ÍNDEX DE COMPOSTOS



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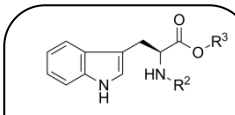

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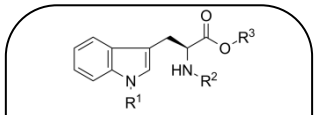
2b R^2= Troc, R^3= Me
2c R^2= Al·loc, R^3= Me
2d R^2= Boc, R^3= Me
2e R^2= Ftal, R^3= Me
2f R^2= Cbz, R^3= Me
2g R^2= Moc, R^3= *t*Bu
2h R^2= Troc, R^3= *t*Bu
2i R^2= Al·loc, R^3= *t*Bu
2j R^2= Cbz, R^3= *t*Bu
2k R^2= N^{α}-Al·loc-Ala, R^3=Me



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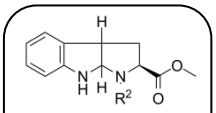
3b R^1= $PhSO_2$, R^2= Moc, R^3= *t*Bu
3c R^1= $PhSO_2$, R^2= Boc, R^3= Me
3d R^1= $PhSO_2$, R^2= Cbz, R^3= Me
3e R^1= $PhSO_2$, R^2= Cbz, R^3= *t*Bu
3f R^1= Ns, R^2= Troc, R^3= Me
3g R^1= Ns, R^2= Troc, R^3= *t*Bu
3h R^1= Ns, R^2= Cbz, R^3= *t*Bu
3i R^1= R^2= Boc, R^3= Me
3j R^1= Boc, R^2= Troc, R^3= Me
3k R^1= Boc, R^2= N^{α}-Al·loc-Ala, R^3= Me



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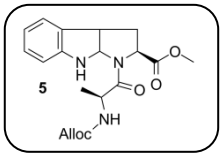
4b R^2= Troc
4c R^2= Cbz



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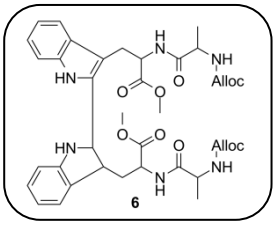

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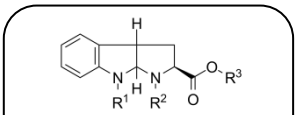

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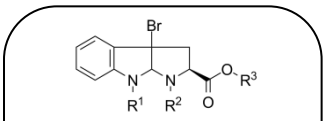
7b R^1= $PhSO_2$, R^2= Moc, R^3= *t*Bu
7c R^1= Ns, R^2= Troc, R^3= Me



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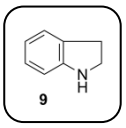
8b R^1= $PhSO_2$, R^2= Moc, R^3= *t*Bu
8c R^1= Ns, R^2= Troc, R^3= Me
8d R^1= $PhSO_2$, R^2= Boc, R^3= Me
8e R^1= $PhSO_2$, R^2= Cbz, R^3= Me
8f R^1= $PhSO_2$, R^2= Cbz, R^3= *t*Bu
8g R^1= Ns, R^2= Troc, R^3= *t*Bu
8h R^1= Ns, R^2= Cbz, R^3= *t*Bu
8i R^1= R^2= Boc, R^3= Me
8j R^1= Boc, R^2= Troc, R^3= Me
8k R^1= Boc, R^2= N^{α}-Al·loc-Ala, R^3= Me



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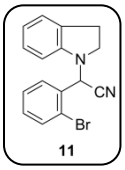

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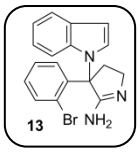

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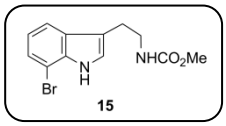

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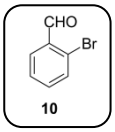

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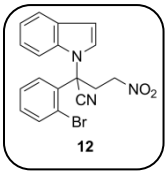

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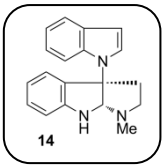

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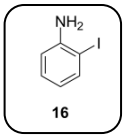

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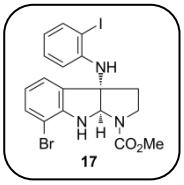

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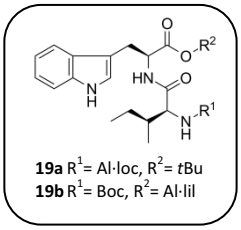

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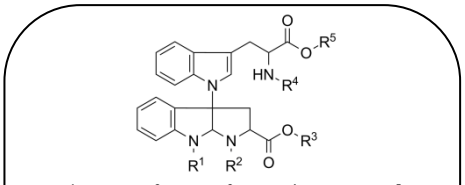
19b R^1= Boc, R^2= Al·lil



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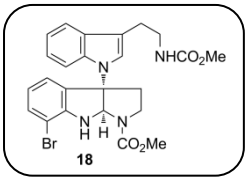
20b R^1= $PhSO_2$, R^2=R^4= Moc, R^3=R^5= Me
20c R^1= $PhSO_2$, R^2=R^4= Moc, R^3=R^5= Me
20d R^1= $PhSO_2$, R^2= Moc, R^3= *t*Bu, R^4= Boc-Ile, R^5= Al·lil
20e R^1= Ns, R^2= Troc, R^3=R^5= Me, R^4= Al·loc
20f R^1= Ns, R^2= Troc, R^3= Me, R^4= Al·loc, R^5= *t*Bu
20g R^1= Ns, R^2= Troc, R^3=R^5= Me, R^4= Ftal
20h R^1= $PhSO_2$, R^2= Cbz, R^3= Me, R^4= Boc-Ile, R^5= Al·lil
20i R^1= $PhSO_2$, R^2= Cbz, R^3= *t*Bu, R^4= Boc-Ile, R^5= Al·lil
20j R^1= $PhSO_2$, R^2=R^4= Cbz, R^3= *t*Bu, R^5= Me
20k R^1=R^2= Boc, R^3=R^5= Me, R^4= Moc
20l R^1=R^2= Boc, R^3=R^5= Me, R^4= Ftal



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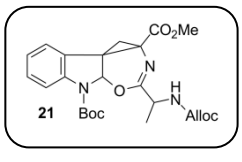

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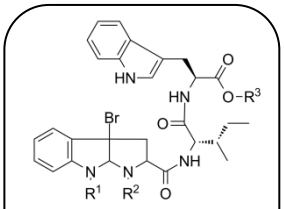

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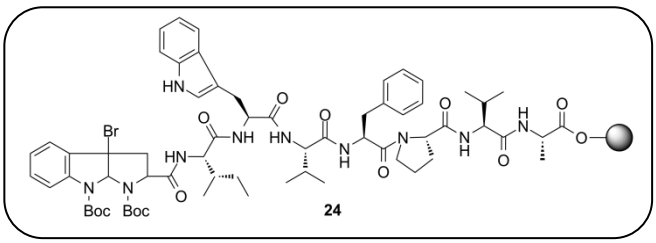
22b R^1=R^2= Boc, R^3= Bn



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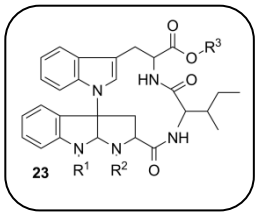

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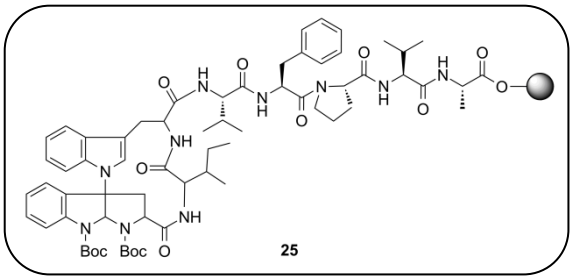

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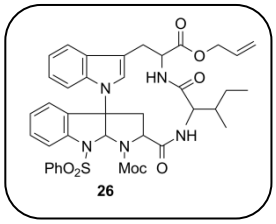

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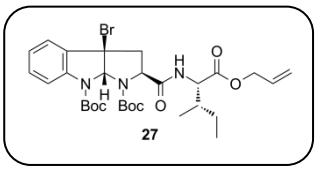

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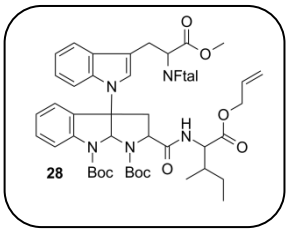

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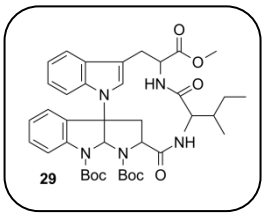

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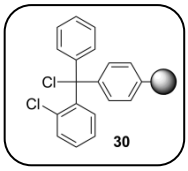

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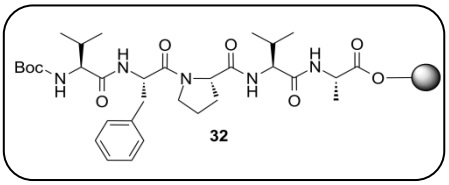

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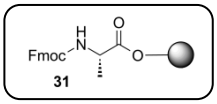

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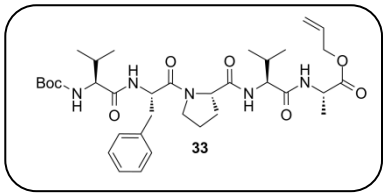

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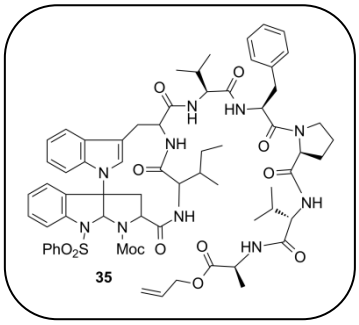

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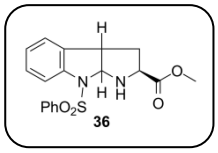

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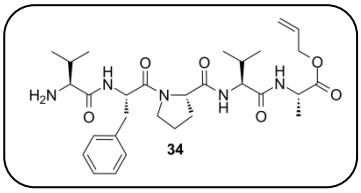

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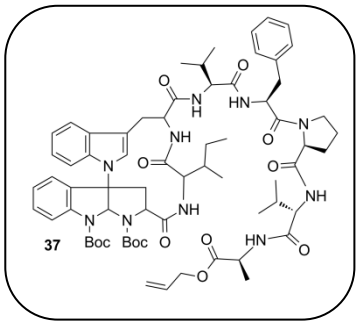

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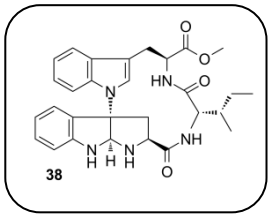

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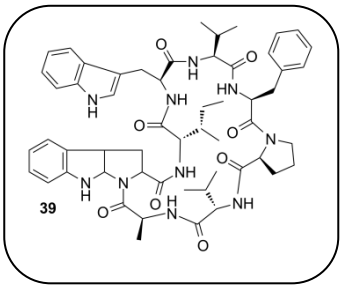

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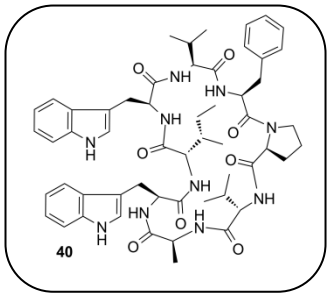

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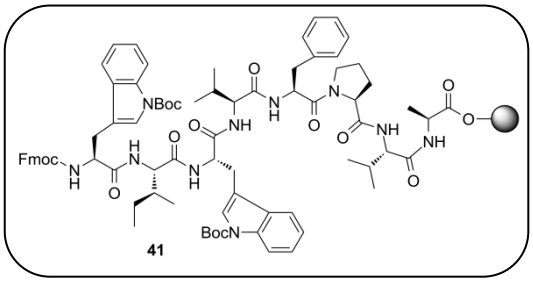

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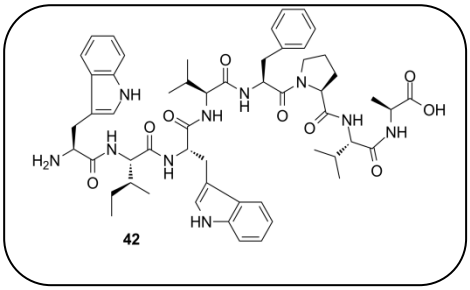

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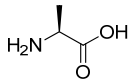
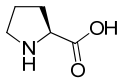
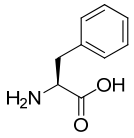
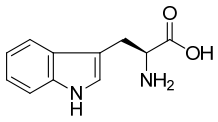
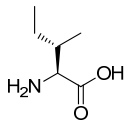
1.1 Aminoàcids

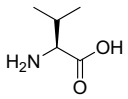
L-Alanina (Ala) 

L-Prolina (Pro) 

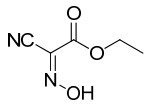
L-Fenilalanina (Phe) 

L-Triptòfan (Trp) 

L-Isoleucina (Ile) 

L-Valina (Val) 

1.2 Agents d'acoblament

2-Ciano-2-hidroximinoacetat d'etil 

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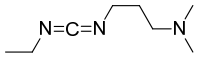
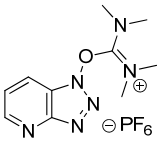
1-Etil-3-(3-dimetilaminopropil)carbodiimida 

HATU
Hexafluorofosfat de 2-(1*H*-7-azabenzotriazol-1-il)-1,1,3,3-tetrametiluroni 

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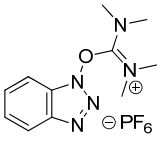
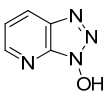
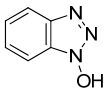
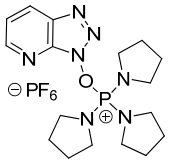
Hexafluorofosfat de 2-(1*H*-benzotriazol-1-il)-1,1,3,3-tetrametiluroni 

HOAt
1-Hidroxi-7-azabenzotriazol 

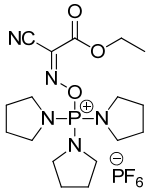
HOBt
Hidroxibenzotriazol



PyAOP
Hexafluorofosfat de (7-azabenzotriazol-1-iloxi)-tripirrolidinofosfoni

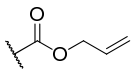


PyOxP
Hexafluorofosfat de *O*-[(ciano-(etoxicarbonil)metiliden)-amino]-iloxitripirrolidinofosfoni

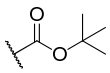


1.3 Grups protectors

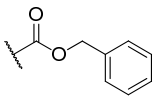
Al·loc
Al·liloxicarbonil



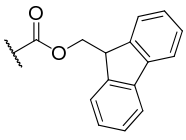
Boc
terc-Butoxicarbonil



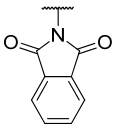
Cbz
Benziloxicarbonil



Fmoc
Fluorenilmetiloxicarbonil

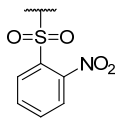


Ftal
Ftalimida

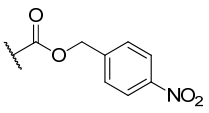


Moc
Metoxicarbonil

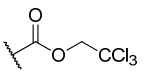
Ns
2-Nitrofenilsulfonil



PNZ
p-Nitrobenziloxicarbonil



Troc
2,2,2-Tricloroetoxicarbonil



Annex 1

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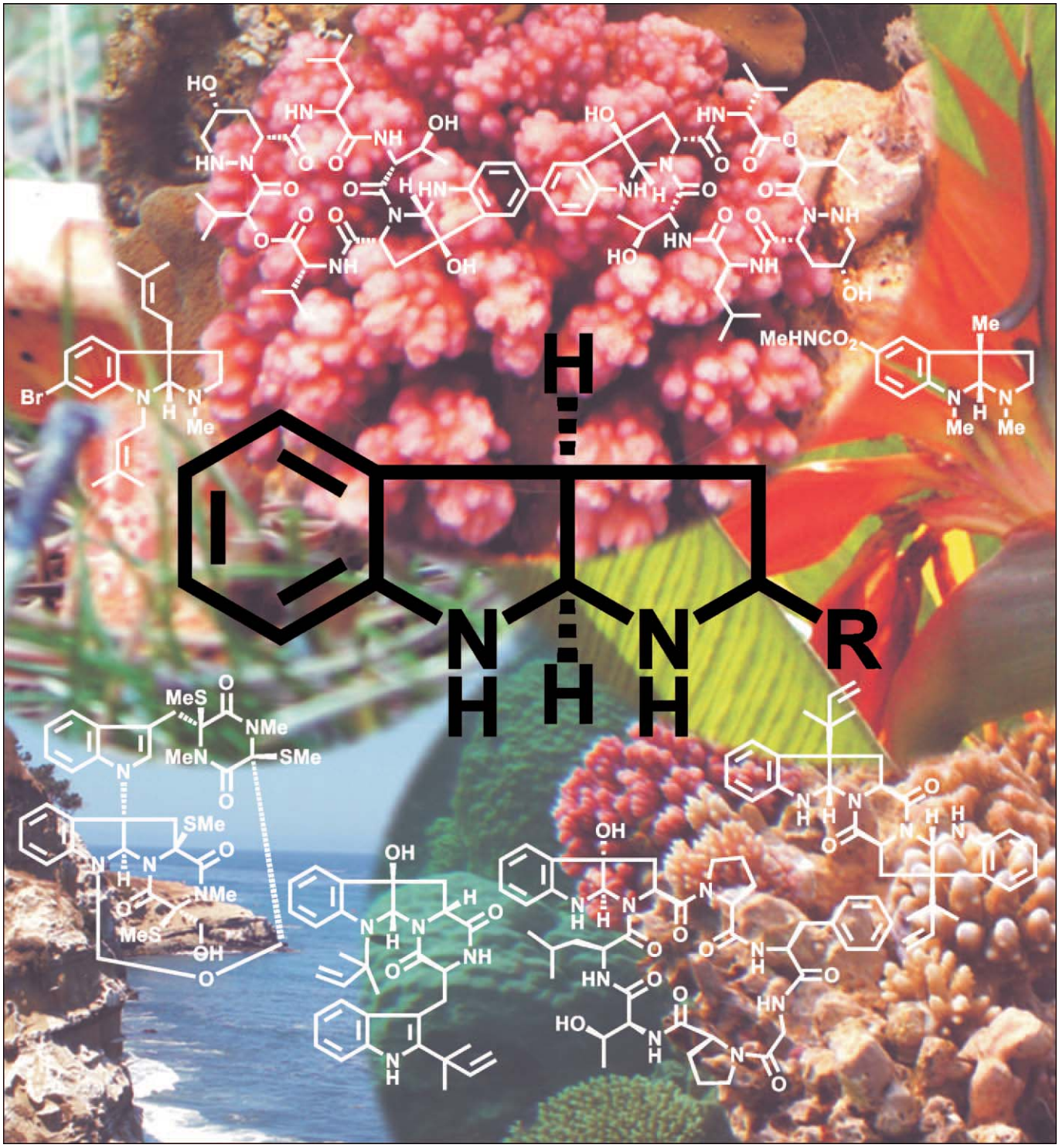
Structure, Bioactivity and Synthesis of Natural Products with Hexahydropyrrolo[2,3-*b*]indole

Pau Ruiz-Sanchis,[a, d] Svetlana A. Savina,[a, b] Fernando Albericio,*[a, b, c] and Mercedes Álvarez*[a, b, d]



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Abstract: Research on natural products containing **h**exahydro**p**yrrolo[2,3-*b*]**i**ndole (HPI) has dramatically increased during the past few years. Newly discovered natural products with complex structures and important biological activities have recently been isolated and synthesized. This review summarizes the structures, biological activities, and synthetic routes for natural compounds containing HPI, emphasizing the different strategies for assembling this motif. It covers a broad range of molecules, from small alkaloids to complex peptides.

Keywords: alkaloids · heterocycles · natural products · peptides

Introduction

From the lushest forests to the deepest oceans, from the simplest organisms to the most complex, nature is replete with compounds containing either a hexahydropyrrolo[2,3-*b*]indole (HPI) unit, or the corresponding 2-carboxylate or 2-carboxamide (both abbreviated HPIC) (Scheme 1). Biosynthetically, the simplest of these compounds stem from the amino acid Trp, whereas the more complex ones derive from Trp-containing peptides. Some HPI- and HPIC-containing compounds contain two Trp or more units.

Structure and Bioactivity

The first structures reported to contain HPI or HPIC were alkaloids; however, advances in the isolation and characterization of natural products later enabled identification of medium-sized cyclic peptides containing HPI or HPIC and exhibiting myriad biological activities. Some of these products are very small and are based around an HPI core, for example, (+)-alline (**1**),[1,2] a small alkaloid with a hydroxyl group at C^{3a} and a methyl group at N^b. (−)-Physostigmine (**2**), isolated from the seeds of the Calabar bean plant (*Physostigma venenosum*) is a cholinesterase inhibitor. (−)-Physostigmine is currently used to treat myasthenia gravis, glaucoma, Alzheimer's disease and delayed gastric emptying, and has recently been employed to treat orthostatic hypotension.[3] Further examples of these compounds alkylated at C^{3a} include the flustramines A–M (**3**–**7**), a family of alkaloids isolated from the marine organism *Flustra foliacea*:[4–9] the flustramides A, B (**8**), and E;[10,11] dihydroflustramine C (**9**);[12] (3a*R**,8a*S**)-6-bromo-3a-[(2*E*)-3,7-dimethyl-2,6-octadienyl]-1,2,3,3a,8,8a-hexahydropyrrolo[2,3-*b*]indol-7-ol;[13] debromoflustramines B[8] and H;[9] five recently discovered alkaloids isolated from the plant *Selaginella moellendorfii*;[14] the flustraminols A and B,[6] both part of the flustramines family and characterized by a hydroxyl group at C^{3a}; and (−)-pseudophrynaminol (**10**), extracted from the Australian frog *Pseudophryne coriacea*[15] (Scheme 1).

The HPIC unit is found in products such as the okaramines A–Q (**11**), isolated from the fungus *Penicillium simplicissum*.[16–22] In okaramines the HPIC is condensed to a diketopiperazine (DKP) unit formed from a second amino acid. Leptosins D–F (**12**–**14**),[23] gliocladines C–E (**15**–**17**),[24] gliocladins A–C,[25] plectosphaeroic acids A–C (**18**, **19**),[26] (+)-asperazine (**20**),[27] and naseseazines A and B[28] have an analogous DKP unit containing an extra indole, bound between C^3 and C^{3a} (except for in the case of (+)-asperazine and the naseseazines, in which the indole binds via C^7 and C^6, respectively). Brevicompanines A–H (**21**: A, **22**: B), *allo*-brevicompanine B and fructigenine B[29–31] are also alkylated at C^{3a}; as is ardeemin, isolated from a strain of *Aspergillus fischeri*;[32] roquefortines C, D (**23**), F and G;[33–36] and aszonalenin (**24**).[37] Brevianamide E (**25**),[38] the sporidesmins[39–42] and notoamide D[43] are all hydroxylated at C^{3a} (Scheme 1).

Natural compounds containing two or more HPI or HPIC units are shown in Scheme 2. These include amauromine (**26**) and gypsetin (**27**), dimeric alkaloids in which two HPIC units are condensed through a DKP. Amauromine, obtained from the culture broth of *Amauroascus* sp, has vasodilating activity,[44,45] and gypsetin is an inhibitor of acyl-CoA.[46,47] Natural products containing two HPI units comprise the botanical compound (−)-chimonanthine (**28**)[48–51] or its optical antipode, (+)-chimonanthine, found in the skin of the Colombian poison dart frog, *Phyllobates terribilis*[49] and in *Psychotria colorata* flowers.[52] Chimonanthines are dimeric HPIs linked between the C^{3a} of each unit. Related compounds include *meso*-chimonanthine;[53] (−)-chimonanthidine (**29**);[51] (−)-calycanthidine (**30**);[51] N^b-desmethyl-*meso*-

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chimonanthine;[50] and the antifungal agent (−)-folicanthine (**31**)[54] which was isolated from both *Calycanthus floridus*[55,56] and the seeds of *Chimonanthus praecox*.[51] The absolute configuration of (−)-**31** was determined by chemical correlation with (−)-**28**[51] and the total synthesis of its enantiomer (+)-**31**.[57] Furthermore, psycholeine,[58] *meso*-pseudophrynamine A[15] and the recently isolated flustramines O (**32**) and P (**33**)[9] each have two HPI units (Scheme 2).

Natural compounds containing more than two HPI units comprise idiospermuline (**34**)[59] and the hodgkinsines (**35**),[50,52,60,61] with three HPI units; psychopentamine[62] and quadrigemines A, B, C (**36**), and I,[50,52,58,61,63] with four. Quadrigemine C is a weak antagonist of the SRIF (somatostatin) receptor, like psycholeine and *meso*-pseudophrynamine A. Isopsychotridines A and B (**37**)[61] and psychotridine, with five;[50,61] oleoidine,[50] with six; and caledonine,[50] with seven.

Another important group comprises dimeric HPICs linked by the C^{3a} of each unit, each of which contains a DKP. These include the neurokinin antagonists (+)-WIN64821 (**38**) and (+)-WIN64745 (**39**), both isolated from a strain of *Aspergillus* sp.;[64–66] (−)-ditryptophenaline (**40**), obtained from *Aspergillus flavus*;[67] the antiviral agent (+)-asperdimin (**41**), isolated from extracts of *Aspergillus niger*;[68] chaetocin (**42**), isolated from the fermentation broth of *Chaetomium minutum*;[69] verticillins A (**43**), B, and C, obtained from *Verticillium* sp., exhibit antimicrobial activity against Gram-positive bacteria and potent antitumor activity in HeLa cell lines;[70–72] gliocladines A (**44**) and B (**45**);[24] 11,11′-dideoxyverticillin A and 11′-deoxyverticillin A;[24,73] melinacidins;[74–76] Sch52900 and Sch52901;[24] and some leptosins A (**46**), B (**47**), and C (**48**).[23] Leptosins C and F, isolated from the marine fungus *Leptoshaeria* sp., have inhibitory activity against topoisomerases I and II[77] (Scheme 2).

Several products isolated (Scheme 3) recently feature a bond between the C^{3a} of an HPI or HPIC unit and the N^1 of a modified tryptamine or Trp, such as that found in the alkaloid psychotrimine (**49**).[62] Another noteworthy example is the epipolythiodioxopiperazine family, whose members exhibit numerous bioactivities, including antitumor, antimicrobial, antinematodal and cytotoxicity; notable members include the chetomin (**50**), chaetocochins A (**51**), B (**52**), and C, and dethio-tetra(methylthio)chetomin, all isolated from the solid-state fermented rice culture of the fungus *Chaetomium cochliodes*.[78–84] An extra degree of complexity is shown in kapakahines C (**53**) and D (**54**), which are macrocyclic peptides formed through a bond between the N^8 of an HPIC located at the *N*-terminal of the linear structure and the C^{4a} of an α-carboline unit, located close to the *C*-terminal.[85]

Natural products with an HPIC integrated into the peptide chain include omphalotins B–I (D: **55**),[86,87] phakellistatin 3 (**56**) and isophakellistatin 3;[88] himastatin (**57**), in which the HPIC is part of a depsipeptide-chain;[89,90] its structure and stereochemistry was revised after the total synthesis.[91,92] Other similar natural products are chloptosin

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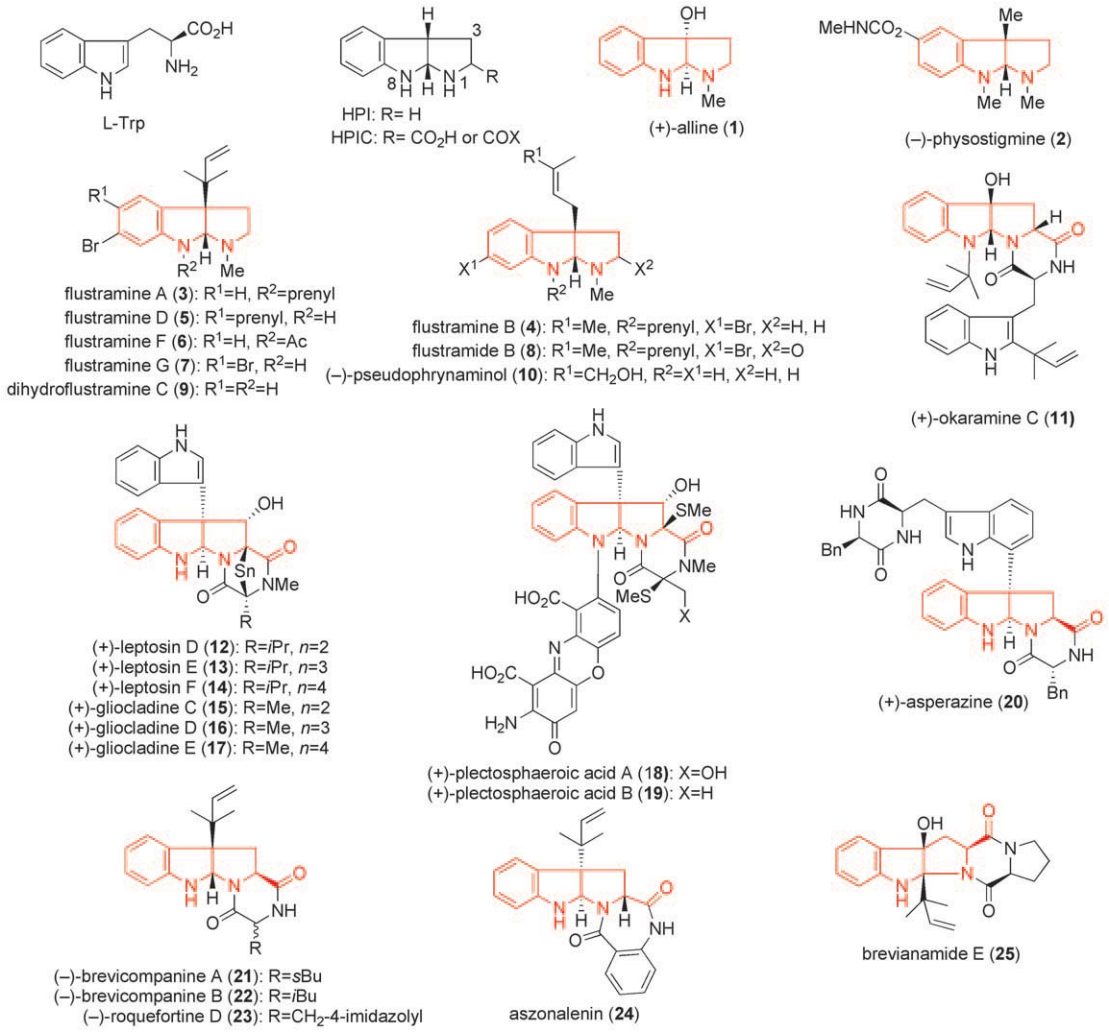

Scheme 1. Natural products containing a single HPI or HPIC unit (shown in red).

(**58**);[93] NW-G01, an antibiotic isolated from *Streptomyces alboflavus*;[94] and kutznerides 1–9 (1: **59**)[95,96] (Scheme 4).

Most of these complex structures have only recently been isolated. The literature contains a few reviews, although these appear to cover only specific aspects of these compounds. These include works by Schmidt and Movassaghi,[97] on biosynthetic hypotheses; Steven and Overman,[98] on syntheses of poly-HPI compounds; and Crich and Banerjee,[99] on the stereochemistry of HPI containing-compounds, as well as classical publications on the Calabar bean alkaloids,[100,101] phenserine,[102] chimonanthine and related natural products,[103,104] chaetocin and related natural products,[105] and the chemistry of cyclic tautomers of tryptamines and Trp.[106,107]

This article provides an exhaustive overview of the structure, synthesis and bioactivity of HPI and HPIC containing natural products from all of the aforementioned structural classes, emphasizing the synthetic routes to polycyclic compounds of this type published until December 2009. Alkaloids containing a poly-HPI linked at the quaternary carbons, such as quadrigemine C, have been omitted here because they have already been covered in an excellent report by Steven and Overman.[98]

Syntheses of Natural Products Containing HPI or HPIC

Several procedures have been developed for the synthesis of HPI and HPIC units, chiefly in the context of natural product syntheses. Scheme 5 illustrates known routes to tricyclic HPI and HPIC.

The most widely used starting materials for the synthesis of tricyclic HPI and HPIC are functionalized indoles (or oxidized indoles), tryptamines or Trp's (see Scheme 5). Routes A through C comprise bond formation between N^b and C^{8a}. In route D, the bonds C^{8a}–N^b and C^2–N^b are formed from a diketo derivative of indole. Route E entails introduction of C^2 by formation of the bonds N^b–C^2 and C^2–C^3, using dichloroketene and an indolyl sulfylimine. In route F, HPI is performed by reductive cyclization. Route G affords HPI after the rearrangement of an acyloxy group. Route H in-

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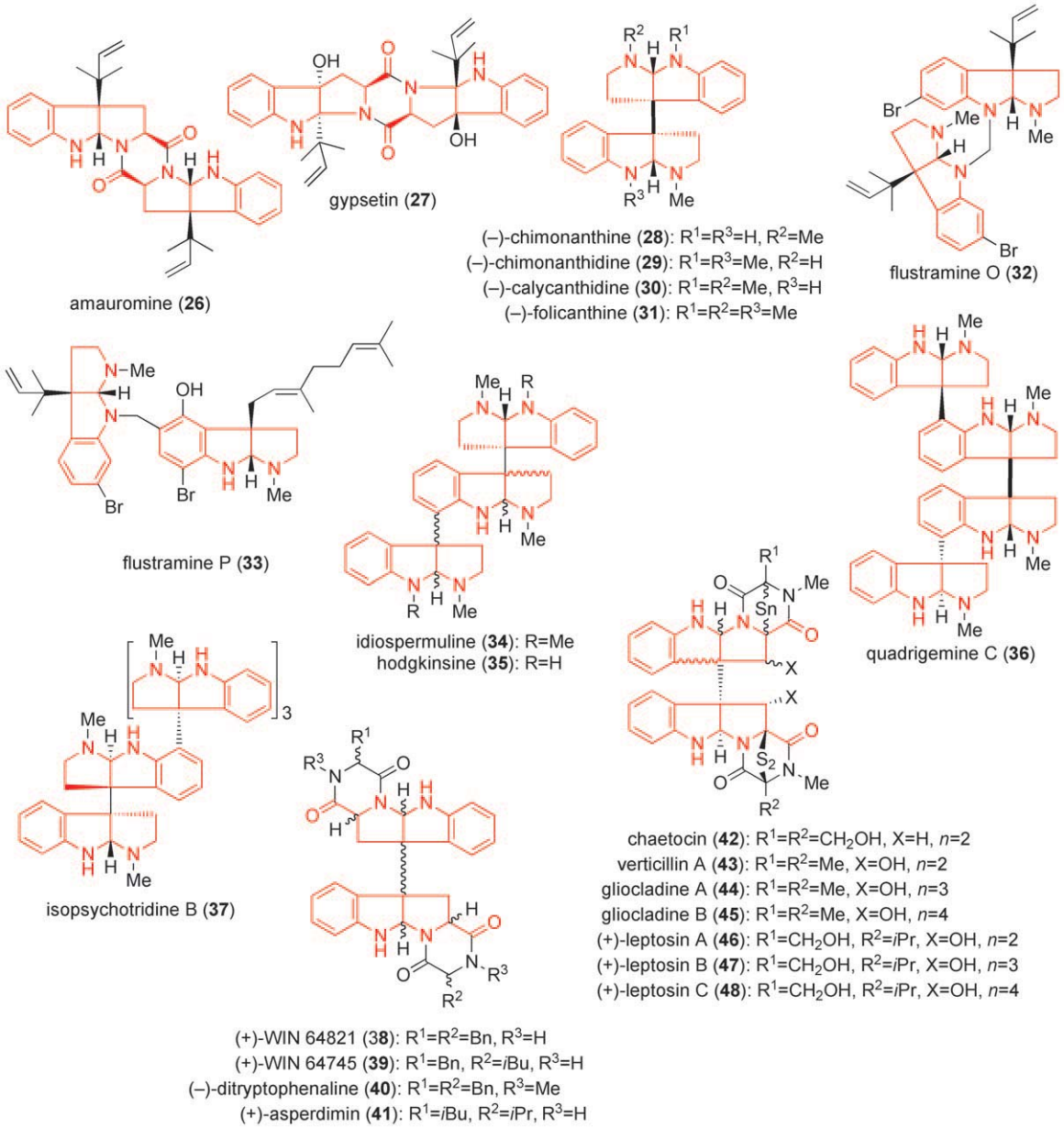

Scheme 2. Natural products containing two or more HPI or HPIC units (shown in red).

volves bond formation between N^8 and C^{8a} from a 3-(nitrocyclohex-1-enyl)pyrrolidin-2-one. Route I comprises Fischer indolization, namely, via condensation of phenylhydrazines with latent aldehydes. Route J involves simultaneous formation of the bonds N^8–C^{8a} and N^b–C^{8a}. Lastly, route K, in which HPIC is assembled via formation of the bonds C^{3a}–C^{8a} and N^b–C^2, is based on the aza-Pauson–Khand reaction (APKR).

Acid-catalyzed cyclization

In route A (Scheme 5), HPIC ring closure is acid-catalyzed. This involves protonation of indole at C^3, followed by capture of the resulting indoline by the protected amine of the lateral chain. This procedure has been extensively used, starting from protected tryptamine, Trp or even more complex compounds.

The Trp derivative **60** cyclized in 85% H_3PO_4 to yield two diastereomers of the corresponding HPIC in a thermodynamic ratio of 9:1 (**61**/**62**, *endo*/*exo*).[108] However, if these products are not stabilized in solution by acylation or sulfonylation of N^8, they degenerate back to the starting material (Scheme 6).[106]

A solution of N^{α}-methoxycarbonyl-L-Trp **60** in trifluoroacetic acid (TFA) gave, after equilibration, mainly the *endo*-HPIC **61** plus minor amounts of the *exo*-HPIC **62** and starting material. Addition of trifluoroacetic acid anhydride (TFAA) to the solution afforded the two corresponding trifluoroacetyl analogues.[109]

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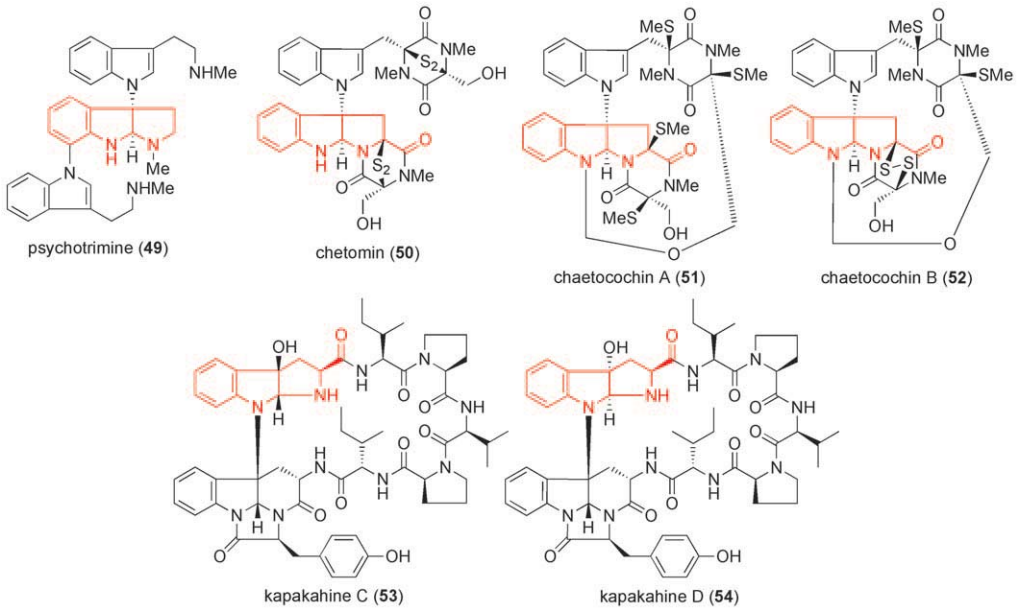
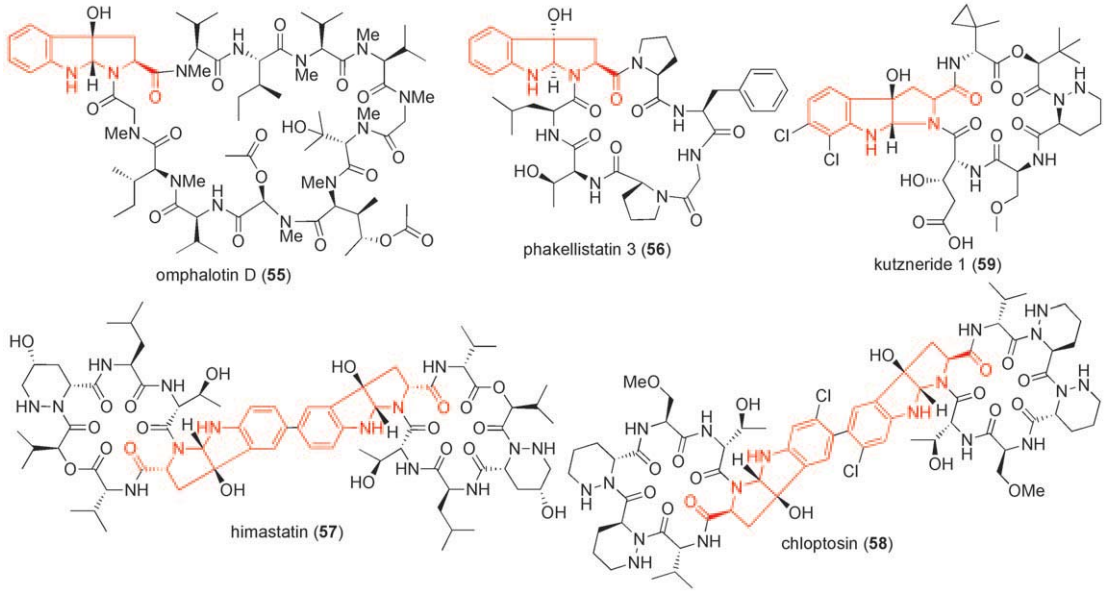


Scheme 3. Natural products containing an HPI or HPIC unit (show in red) bound through C^{3a} to the *N* of an HPIC unit, tryptamine or Trp.



Scheme 4. Natural products containing HPIC (shown in red) as part of a peptide chain.

Treatment of **60** with TFAA in dry pyridine afforded a complex mixture. The main constituents were the adduct **63** (50%) and the N^1-trifluoroacetylated Trp **64**.[110] The exact structure of **63**, including the stereochemistry of its three stereogenic centers, were unequivocally established by X-ray analysis (Scheme 7).[111]

Crich et al. described a diastereoselective synthesis of the non-naturally occurring (+)-debromoflustramine B (**69**) and related compounds from the L-Trp-derived HPIC **65**.[112] Diastereomerically and enantiomerically pure sulfonamide **65** obtained by phenylsulfonylation of **61** was used to prepare HPI alkaloids. The main transformations comprised functionalization and C–C bond formation at C^{3a}; Barton et al.[113] reductive decarbomethoxylation at C^2; and sequential selective deprotection and alkylation of the two nitrogen centers (Scheme 8).

Sequential oxidation-cyclization (A, Scheme 5)

This methodology exploits the reactivity of compounds such as tryptamine or Trp at their 3-substituted indole position to oxidants such as 2,2-dimethyldioxirane (DMDO), *N*-bromo-

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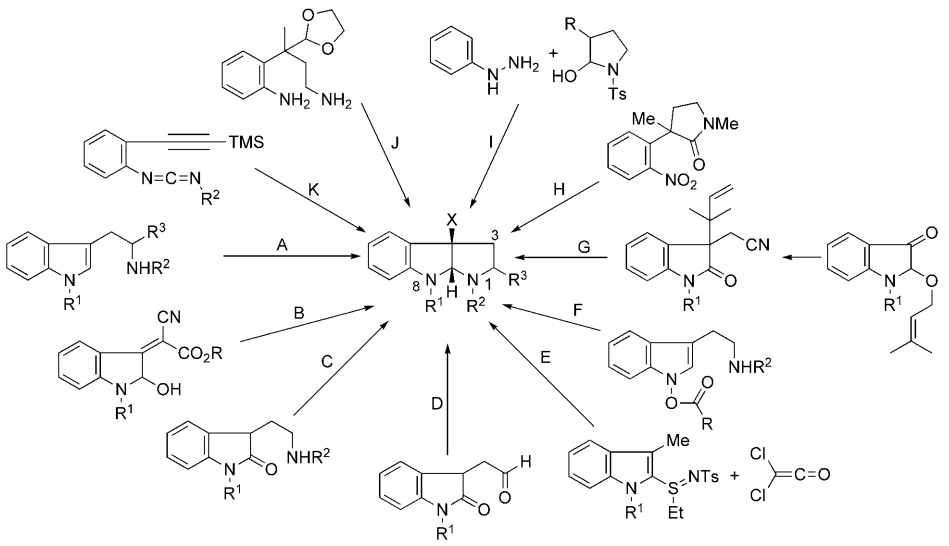
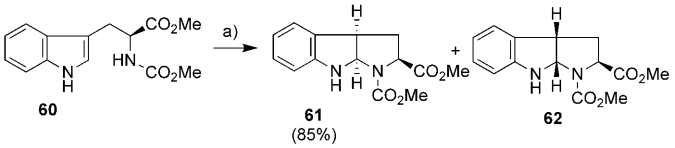
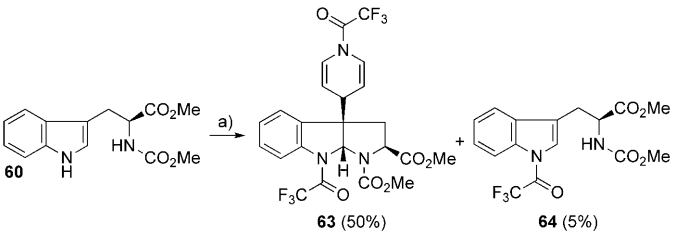


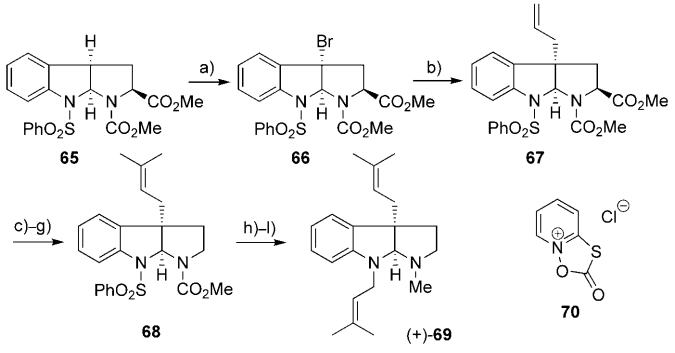
Scheme 5. Synthetic strategies for constructing tricyclic HPI and HPIC.



Scheme 6. Acid-catalyzed cyclization of *N*-protected-L-Trp **60**.[108] a) 85% H_3PO_4.



Scheme 7. Cyclization of protected *N*-protected-L-Trp **60**.[110] a) TFAA, Pyr.

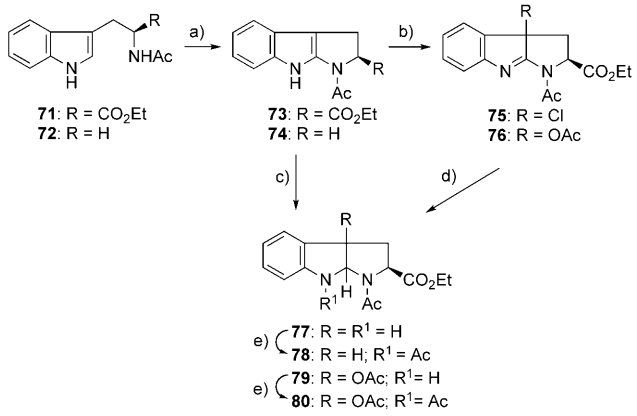


Scheme 8. Synthesis of (+)-debromoflustramine B (**69**) by Crich.[112] a) NBS, CCl_4, Δ, 60–70%; b) $Bu_3SnCH_2CH{=}CH_2$, Δ, 80%; c) $NaIO_4$, OsO_4, 83%; d) $Ph_3P{=}CMe_2$, 64%; e) KOH, MeOH, 89%; f) **70**, Et_3N; g) *t*BuSH, *hv*, 61% (2 steps); h) KOH, MeOH, Δ, 99%; i) $NaBH_3CN$, HCHO, AcOH; j) KOH, MeOH, 79% (2 steps); k) Na, NH_3; l) prenyl bromide, 57% (2 steps). NBS = *N*-bromosuccinimide.

succinimide (NBS), and phenylselenyl chlorides, whereby the resulting imine or iminium salt intermediate is captured by the lateral nitrogen.

Bromination–cyclization:
Witkop et al. prepared the tricyclic pyrrolo[2,3-*b*]indoles **73** and **74** by reacting Trp **71** and tryptamine **72**, respectively, with NBS at pH 9.2 in a very dilute solution at room temperature.[114,115] Compound **73** was slowly reduced over Rh/Al_2O_3 (as catalyst) in EtOAc to yield HPIC **77**, which was then acetylated with Ac_2O in pyridine to give **78**. Reaction of *t*BuOCl with **73** gave the unstable 3a-chloroindolenine **75**. Analogously, oxidation of **73** with $Pb(OAc)_4$ in CH_2Cl_2 gave the 3a-acetoxyindolenine **76**, which was rapidly reduced by $NaBH_4$ in MeOH to the 3a-acetoxyindoline **79**, which in turn was converted to the corresponding diacetyl derivative **80** for structural characterization (Scheme 9).

Lobo and Prabhakar reported a total synthesis of (−)-debromoflustramine B (**69**) from the Witkop HPIC **81** (Scheme 10).[116,117] Their route starts with consecutive C^{3a} allylation of **81**, followed by reduction and N^8-allylation to afford a diastereomeric mixture of *endo* and *exo* methyl



Scheme 9. Cyclization of tryptamine and Trp by Witkop et al.[114] a) NBS, pH 9.2; b) *t*BuOCl or $Pb(OAc)_4$, 23–57%; c) H_2, Rh/Al_2O_3, 30%; d) $NaBH_4$, MeOH, 0°C; e) Ac_2O, Pyr.

esters. These esters had to be transformed into the corresponding Barton esters[118] for separation. Oxidative removal of 2-carboxylate from *exo*-**83** using $Sb(SPh)_3$, followed by reduction, N^b-deprotection and methylation furnished (−)-**69**. Likewise, *endo*-**83** gave (+)-**69** (not shown).

Using Br_2 or NBS without base enabled bromination-cyclization of protected Trp or derivatives. Danishefsky et al.

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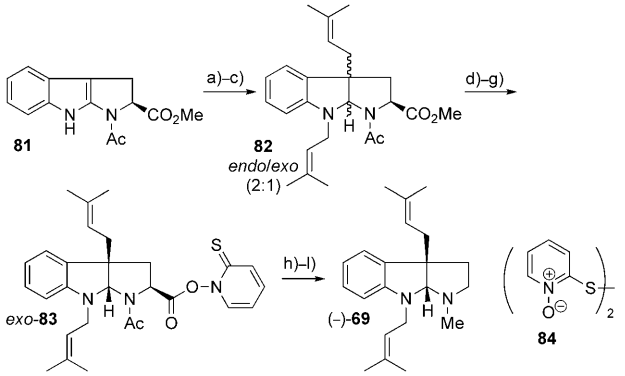
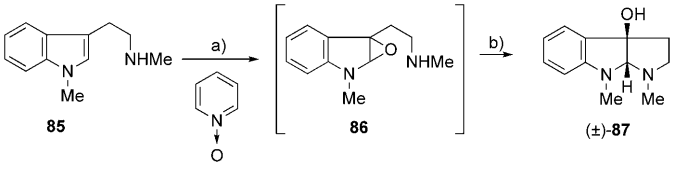


Scheme 10. Total synthesis of (−)-debromoflustramine B (**69**).[116] a) NaH, DMF, prenyl bromide, 60%; b) $NaBH_3CN$, MeOH, 85%; c) K_2CO_3, THF, prenyl bromide, 71%; d) NaOH, aq. MeOH; e) H_3O^+; f) **84**, PBu_3, CH_2Cl_2, 0°C, 62% (3 steps); g) diastereomeric separation; h) $Sb(SPh)_3$, O_2, Et_2O, 0 → 18°C, 64%; i) xylene, Δ, 72%; j) 4.7 M NaOMe, MeOH, NH_2NH_2, H_2O, Δ, 54%; k) $LiAlH_4$, Et_2O, 0°C, 70%; l) NaH, MeI, THF, 46%.

pursued NBS cyclization[91,119] in preliminary studies on the total synthesis and structural characterization of himastatin (**57**). In the total synthesis of (+)-11,11′-dideoxyverticillin A, Movassaghi et al. used bromine and acetonitrile to obtain 3a-bromo-HPIC.[120] de Lera et al. studied the mechanism and proposed the addition of pyridinium *p*-toluenesulfonate (PPTS) to improve the yield of the bromocyclized product in the reaction with NBS.[121]

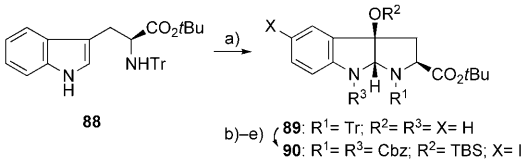
Synthesis of 3a-hydroxy-HPIC: Photochemical oxidation of N^b,N^1-dimethyltryptamine (**85**) in CH_2Cl_2 using pyridine *N*-oxide as oxygen source afforded the HPI (±)-**87**.[122] The proposed mechanism involves opening of intermediate 2,3-oxide **86** by methylamine residue (Scheme 11).

Photocyclization of *N*-methoxycarbonyltryptamine in the presence of (−)-nicotine followed by treatment with triphenylphosphine produced 3-hydroxy-1-methoxycarbonyl-HPI with modest enantioselectivity.[123] Similar results were obtained using protected Trp.



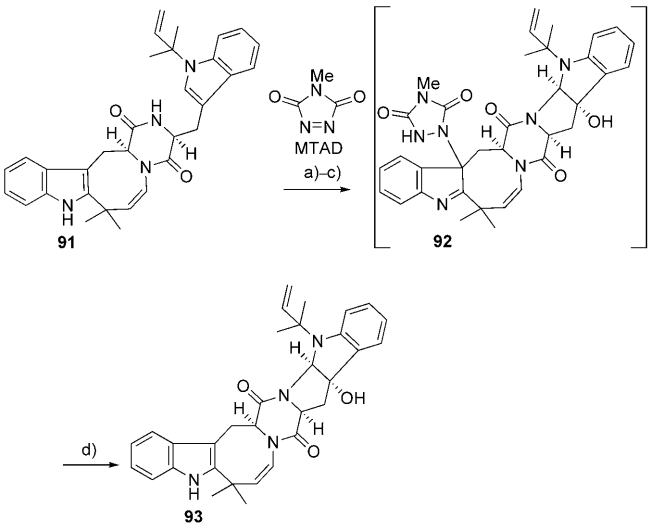
Scheme 11. Photochemical oxidation of N^b,N^1-dimethyltryptamine (**85**) by pyridine *N*-oxides.[122] a) *hν*, 253–7 nm; b) 11%.

Danishefsky et al. developed a route to 3a-hydroxy-HPIC based on oxidative cyclization of Trp,[92] in work on the total synthesis of himastatin (**57**). They also revised and confirmed stereochemistry of the natural product. The *tert*-butyl ester of N^α-Tr-L-Trp (**88**) reacts with DMDO to give **89**. Protecting groups exchange and iodination at position 5 gave **90** which was later dimerized (Scheme 12).



Scheme 12. Tandem oxidation-cyclization of Trp by Danishefsky et al.[92] a) DMDO, CH_2Cl_2, −78°C, 70%; b) AcOH, MeOH, CH_2Cl_2; c) CbzCl, Pyr, CH_2Cl_2; d) TBSCl, DBU, MeCN; e) ICl, 2,6-di-*tert*-butylpyridine, CH_2Cl_2, 75%.

Oxidative cyclization was the key step in the enantioselective total synthesis of the complex alkaloid okaramine N (**93**) by Corey et al.[124] They developed a new method for the selective differentiation of the two indole subunits of **91**. The commercially available reagent *N*-methyl-1,3,4-triazoline-2,5-dione (MTAD) was used in a novel application: reversible blocking of the *N*-unsubstituted indole subunit, which enabled oxidative ring-closure between the DKP and the *N*-substituted indole ring. The bisindole **91** underwent highly selective reaction with MTAD to form exclusively the ene product at C^3 of the *N*-unsubstituted indole subunit. Subsequent photooxidation, employing methylene blue as photosensitizer under sunlamp irradiation, followed by reduction of the resulting product by Me_2S in MeOH, afforded the hydroxylated octacycle **92** cleanly (with only a minor amount of diastereomer). The blocking group was eliminated by thermolysis of the mixture of **92** and the diastereomer to furnish **93** in good total yield (Scheme 13).



Scheme 13. Enantioselective synthesis of okaramine N (**93**).[124] a) MTAD, CH_2Cl_2, −5°C; b) O_2, *hν*, MeOH, methylene blue, −28°C; c) SMe_2, MeOH, −28 → −10°C; d) 110°C, 70% (4 steps).

Phenylselenocyclization: The total synthesis of amauromine **26** from **95** (Scheme 14) has been reported. The keystone of this approach was kinetic stereoselective synthesis of **95** from N^i,N^α-diBoc protected L-Trp methyl ester via selenocyclization reaction.[125] Treatment of protected Trp **94** with *N*-phenylselenophthalimide (*N*-PSP) and PPTS gave **95**. The

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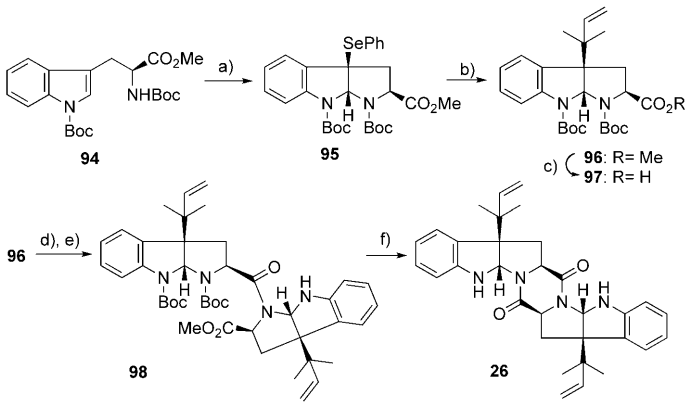
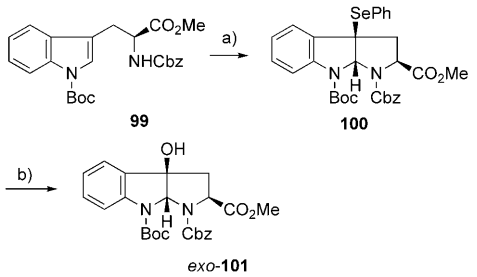


Scheme 14. Total synthesis of amauromine (**26**).[125] a) *N*-PSP, CH_2Cl_2, PPTS, 93%; b) MeOTf, 2,6-di(*tert*-butyl)pyridine, $Me_2C{=}CHCH_2SnBu_3$, CH_2Cl_2, −78°C → reflux, 60% (9:1 *exo*/*endo*); c) NaOH, THF, MeOH, H_2O, reflux, 98%; d) TMSI, MeCN, 0°C, 83%; e) **97**, BOP-Cl, Et_3N, CH_2Cl_2, 58%; f) TMSI, MeCN, 0°C, 58%. BOP = (benzotriazol-1-yloxy)-tris(dimethylamino)phosphonium chloride.

synthesis of **95** was the first construction of *exo*-HPIC from a protected Trp in a high diastereoselective manner. Transformation of phenylselanylHPIC **95** with methyl trifluoromethanesulfonate (MeOTf) in the presence of 2,6-di(*tert*-butyl)pyridine and prenyltri(*n*-butyl)tin gave the angular reverse prenyl derivative **97**.

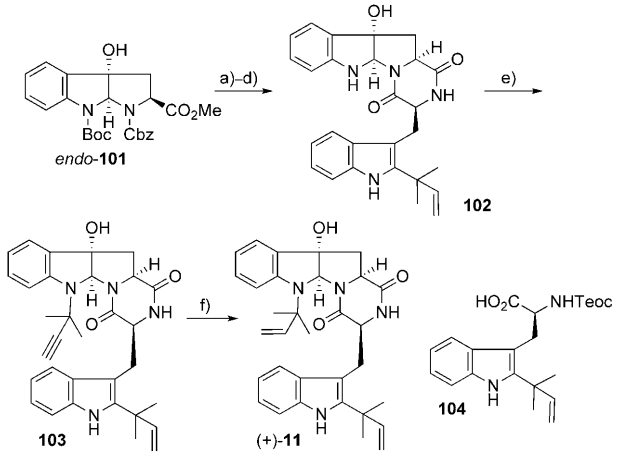
Roquefortine D (**23**) was prepared from the inverse prenylated-HPI **97**, which was reacted with protected His under peptide coupling conditions followed by removal of both *N*-*tert*-butoxycarbonyl (Boc) groups, cyclization, and finally, photolytic elimination of the *o*-nitrobenzyl protecting group (ONB) of the resulting imidazole.[126,127]

Ley et al. described a path to stereocontrolled synthesis of the 3a-hydroxypyrrolo[2,3-*b*]indole skeleton (Scheme 15).[128] The procedure is based on a two-step selenocyclization–oxidative deselenation sequence. Treatment of **99** in the conditions described by Danishefsky[125] gave **100** as a simple diastereomer with an excellent yield. The following oxidation with *m*-chloroperbenzoic acid (mCPBA) gave the desired product *exo*-**101**.



Scheme 15. Two-step route to 3a-hydroxy HPIC *exo*-**101** by Ley et al.[128] a) *N*-PSP, PPTS, Na_2SO_4, CH_2Cl_2, 93%; b) wet *m*CPBA, K_2CO_3, CH_2Cl_2, 0→25°C, quant.

The same group later used this two-step sequence in an elegant and concise total synthesis of (+)-okaramine C (**11**) by epimerization at C^2 of **100** to obtain *endo*-**101**, formation of the DKP with the Trp **104** and introduction of isoprenyl on N^8 (Scheme 16). Isoprenyl group was afforded after partial reduction of the alkyne introduced by N^8-alkylation using 2-bromo-2-methylbut-3-yne.[129]

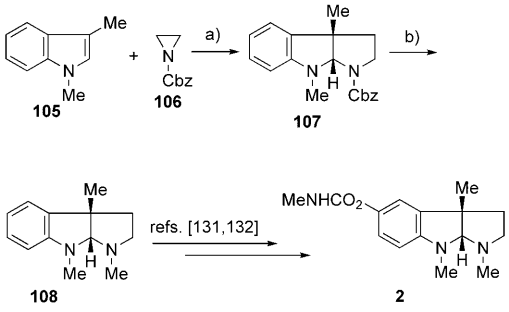


Scheme 16. Total synthesis of (+)-okaramine C (**11**).[129] a) H_3PO_4 aq., CH_2Cl_2; b) H_2, Pd/C, MeOH, 93% (2 steps); c) HATU, DMF, **104**, Et_3N, 95%; d) TASF, DMF, 97%; e) $HC{\equiv}CC(Me)_2Br$, CuCl, THF, DIEA, RT, 88%; f) Lindlar's cat., H_2, 99:1 MeOH/Pyr, 95%. HATU = 2-(7-aza-1*H*-benzotriazole-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate; TASF = tris(dimethylamino)sulfonium difluorotrimethylsilicate.

Alkylative cyclization

Cyclization with electrophiles (A, Scheme 5): This procedure uses the reactivity of indole nucleous of tryptamine or tryptophan with alkylating agents over the substituted 3-position, followed by in situ capture of the resulting indoline by the protected lateral amine.

Nakagawa and Kawahara described a concise synthesis of desoxyeseroline (**108**),[130] a precursor of physostigmine (**2**) (Scheme 17 < xschr17).[131] Their route was based on a Lewis acid-catalyzed alkylative cyclization of 1,3-dimethylindole with *N*-benzyloxycarbonyl (Cbz) protected aziridine to form compound **107**, which is readily converted into physostigmine. They tested several Lewis acids, finding $Sc(OTf)_3$ and TMSCl in dichloromethane to be the best conditions.



Scheme 17. Alkylative cyclization of 1,3-dimethylindole.[130] a) $Sc(OTf)_3$, TMSCl, CH_2Cl_2, −30°C, 52%; b) Red-Al, toluene, reflux, 95%.

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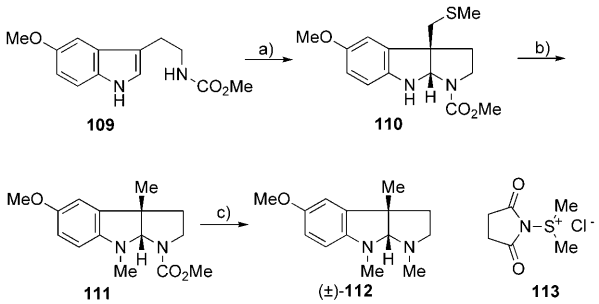
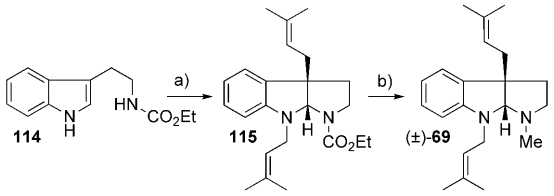
Reaction of N^b-protected tryptamine with allyl bromides afforded the N^b-protected 3a,8-bisallyl-HPI,[133] (±)-debromoflustramides B and E and (±)-debromoflustramines B and E have been prepared using this procedure.[134]

Nakagawa et al. synthesized (±)-esermethole (**112**) using an alkylative cyclization.[135] Reaction of Corey–Kim reagent (**113**) with tryptamine carbamate **109** and iPr$_2$NEt gave the HPI **110**. Simultaneous reductive methylation and desulfurization of **110** were achieved by hydrogenation using Raney Ni (W2) and aqueous HCHO to give **111**, which was then reduced with Red-Al to give (±)-**112** in quantitative yield (Scheme 18).



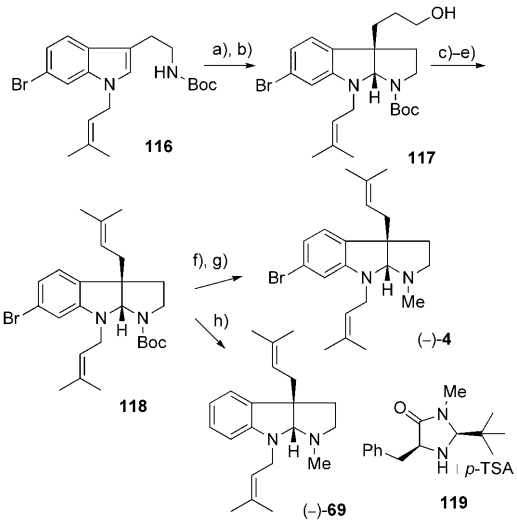
Scheme 18. Synthesis of (±)-esermethole (**112**) by Nakagawa et al.[135] a) **113**, iPr$_2$NEt, −78 °C, 88 %; b) H_2, Ni-Raney (W2), aq. HCHO, EtOH, reflux, 80 %; c) Red-Al, toluene, reflux, 96 %.

The Ganesan group published a fast and elegant three-step total synthesis of (±)-debromoflustramine B (**69**) via zinc triflate-mediated biomimetic alkylative cyclization from tryptamine (Scheme 19).[136]



Scheme 19. Total synthesis of (±)-debromoflustramine B (**69**) by Ganesan et al.[136] a) Prenyl bromide (4 equiv), Zn(OTf)$_2$, Bu$_4$NI, iPr$_2$NEt, toluene, RT, 70 %; b) Red-Al, toluene, reflux, 96 %.

(−)-Flustramine B (**4**) and (−)-debromoflustramine B (**69**) were enantioselectively synthesized in routes based on organocatalytic preparation of pyrroloindoline (Scheme 20). Addition of tryptamine **116** to α,β-unsaturated aldehydes in the presence of imidazolidinone catalysts **119** gave the cyclized pyrroloindoline adduct **117** in high yield and with excellent



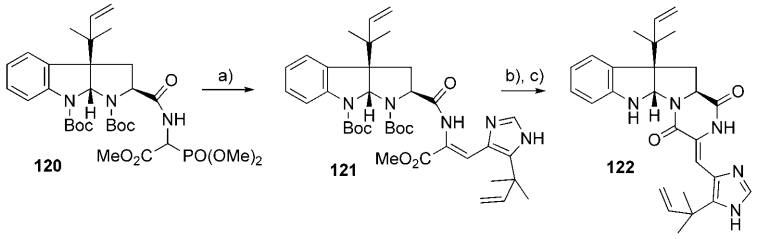
Scheme 20. Enantioselective syntheses of (−)-flustramine B (**4**) and (−)-debromoflustramine B (**69**).[137] a) Propenal, **119**; b) NaBH$_4$, MeOH, 78 %, 90 % *ee* (2 steps); c) MsCl; d) NO$_2$PhSeCN, H$_2$O$_2$, 89 % (2 steps); e) Grubbs metathesis, 2-methyl-2-butene, 94 %; f) TMSI; g) NaBH$_4$, HCHO, 89 % (2 steps); h) LiAlH$_4$, 91 %.

enantioselectivities. Adduct **117** was transformed into (−)-**4** and (−)-**69** using common synthetic procedures, in excellent yields and with high *ee* values.[137]

A one-pot synthesis of (±)-deoxypseudophrynaminol[138] was afforded with moderate yield from the commercially available N^b-methyltryptamine by transformation into the corresponding Grignard reagent, followed by addition of 4-bromo-2-methyl-2-butene, the target in moderate yield. Similar chemistry was recently exploited to synthesize isoroquefortine C and roquefortine C.[139]

A slightly modified version of this strategy recently enabled preparation of isoroquefortine E (**122**).[140] A Horner–Wadsworth–Emmons reaction was the key step to building the dehydroamino acid **121**, which was then underwent DKP formation (Scheme 21).

(−)-Ardeemin (**127**) and its *N*-acyl analogues have been synthesized from L-Trp in 20 steps in approximately 2 % overall yield (Scheme 22).[141] One-pot reaction of **123** with the diazoester **128** gave the chiral 3a-substituted HPI **124** containing the proper configuration in three stereocenters. (−)-**127** was prepared from the tetracyclic compound **124** via the following steps: transformation of the ethyl acetate



Scheme 21. Synthesis of isoroquefortine E (**122**).[140] a) 5-Isoprenyl-1*H*-imidazole-4-carbaldehyde, DBU, CH$_2$Cl$_2$, 24 %; b) TMSI; c) Et$_3$N, 78 % (2 steps).

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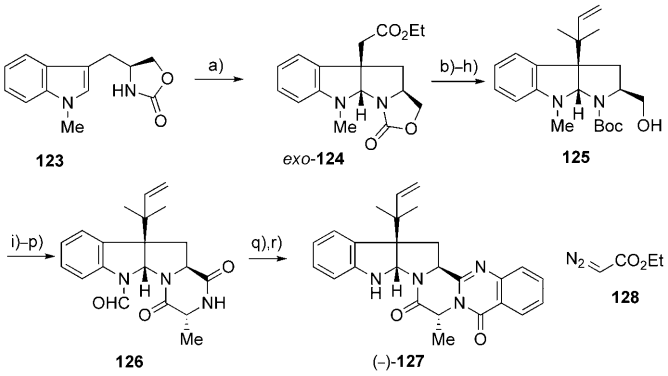
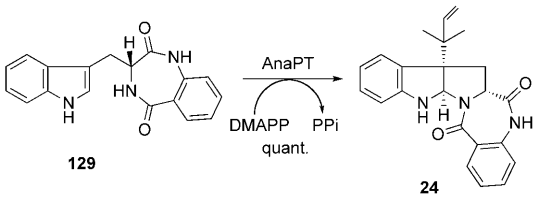


Scheme 22. Total synthesis of (−)-ardeemin (**127**).[141] a) **128**, $Cu(OTf)_2$, CH_2Cl_2, −35 °C, 82 %; b) LDA, MeI, THF, −78 °C → RT; c) LDA, MeI, THF, −78 °C → RT, 72 % (2 steps); d) $LiBH_4$, THF, MeOH, 0 °C, 61 %; e) DMP, CH_2Cl_2, RT, 92 %; f) Ph_3PMeI, LHMDS, THF, −78 °C → RT, 93 %; g) KO*t*Bu, aq *t*BuOH, quant.; h) $(Boc)_2O$, CH_2Cl_2, RT, 95 %; i) DMP, CH_2Cl_2, RT, 92 %; j) PCC, CH_2Cl_2, RT, 76 %; k) $NaClO_2$, NaH_2PO_4 buffer, RT, quant.; l) $ClCO_2iBu$, Et_3N, D-Ala-OMe, CH_2Cl_2, 0 °C, 81 %; m) TMSI, MeCN, 0 °C, 98 %; n) LiOH, aq. MeOH, 95 %; o) $ClCO_2iBu$, Et_3N, CH_2Cl_2, 0 °C → RT, 71 %; p) diastereomeric separation; q) *n*BuLi, *o*-azidobenzoic anhydride, THF, −78 °C, 42 %; r) nBu_3P, benzene, RT, 93 %. LDA = lithium diisopropylamide; LHMDS = lithium hexamethyldisilazide. PCC = pyridinium chlorochromate.

substituent into the corresponding isoprenyl group, hydrolysis of the cyclic carbamate, and orthogonal protection of both amino groups to give **125**, which was converted into the DKP **126**. Finally, formation of the last benzopyrimidone condensed-ring by acylation with *o*-azidobenzoic anhydride followed by cyclization.

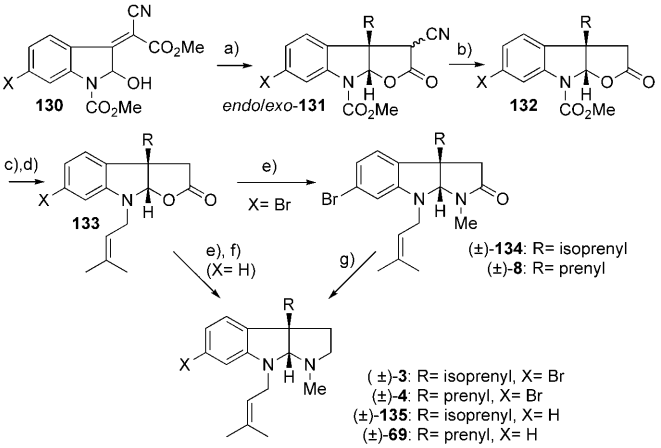
Li et al. recently devised an innovative route to aszonalenin (**24**) and similar alkaloids structure. They employed the enzyme AnaPT, a prenyltransferase, to catalyze the prenylation of (*R*)-benzodiazepinedione **129** in the presence of dimethyl allyl diphosphate (DMAPP) to afford **24** (Scheme 23).[142]



Scheme 23. Enzyme catalyzed synthesis of aszonalenin (**24**) by Li et al.[142]

Cyclization with nucleophiles (B, Scheme 5): This procedure is based on a Michael addition of a nucleophile on the 3-position of 2-hydroxyindolin-3-ylideneacetate followed by in situ lactonization.

The Joseph-Nathan group devised total syntheses of (±)-flustramines A (**3**) and B (**4**), (±)-flustramides A (**134**) and B (**8**), and (±)-debromoflustramines A (**135**) and B (**69**) (Scheme 24).[143,144] A conjugate addition of a prenylmagnesium bromide specie to 2-hydroxyindolenines **130** to give



Scheme 24. Total syntheses of (±)-flustramines A (**3**) and B (**4**), (±)-flustramides A (**134**) and B (**8**), and (±)-debromoflustramines A (**135**) and B (**69**).[144] a) RMgBr, THF/Et_2O, 30–47 %; b) Al_2O_3, THF, H_2O, reflux, 64–95 %; c) NaOMe, MeOH, reflux; d) prenyl bromide, K_2CO_3, acetone, reflux, 60–70 % (2 steps); e) $MeNH_2$, MeOH, 92–98 %; f) $LiAlH_4$, THF, reflux, 98 %; g) $EtN(Me)_2$, AlH_3, THF, 96–97 %.

the C^3-epimeric lactone **131**. Decyanation of the resulting α-cyano-γ-lactones with wet alumina in refluxing THF, followed by *N*-deprotection and allylation, gave compounds **133**, which, upon *N*-methyl insertion under the appropriate conditions, afforded the desired target natural compounds.

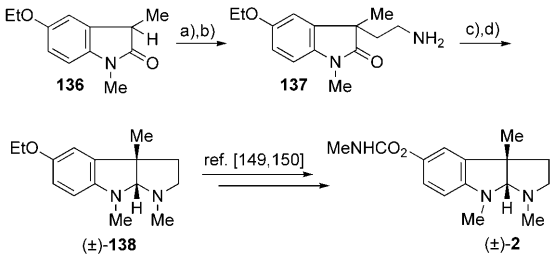
Same procedure was used by for the synthesis of dihydroflustramine C (**9**) and flustramine E.[145]

Successive alkylation cyclization of oxoindoles (C, Scheme 5)

Pyrrolidine formation of HPIC from 2-oxoindoles consists in an enolate alkylation followed by N^b–C^{8a} reductive bond formation.

Julian and Pilk synthesized (±)-eserethole (**138**)[146] based on their previous work on HPI assembly.[147,148] Their approach was actually part of a formal synthesis of physostigmine (**2**).[149–150] The route shown in Scheme 25 comprises α-alkylation of the oxoindole **136**, followed by reduction of the nitrile, *N*-methylation, and finally, reductive cyclization to give the racemic (±)-**138**.

The Julian and Pilk procedure has been used extensively to prepare Calabar alkaloids. It has been modified to im-



Scheme 25. Synthesis of (±)-eserethole (**138**).[146] a) $ClCH_2CN$, NaOEt (or Na), 84 %; b) H_2, Pd, 91 %; c) PhCHO, then MeI followed by hydrolysis, 86 %; d) Na, EtOH, 99 %.

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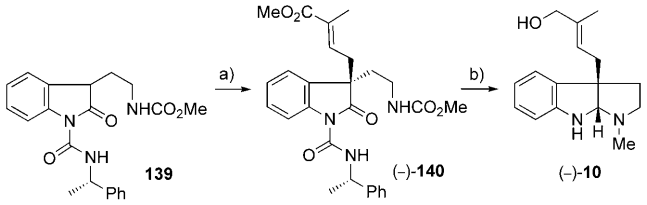
prove the oxoindole preparation,[151–160] adapted to the use of protecting groups,[161–164] performed with chemical resolution of different intermediates,[163,165–168] and combined with asymmetric alkylation of oxindole.[169,170] Furthermore, a modified Julian and Pilk procedure has been used to prepare numerous analogues of physostigmine (**2**) and related alkaloids.[166,171–175] A. Bossi reported an interesting version[176] to prepare a 3-aminoethyloxoindole from 5-methoxytryptamine.

A total synthesis of (−)-pseudophrynaminol (**10**) based on diastereoselective α-alkylation of the chiral oxoindole **139** with methyl 4-bromo-2-methylbut-2-enoate (Scheme 26)



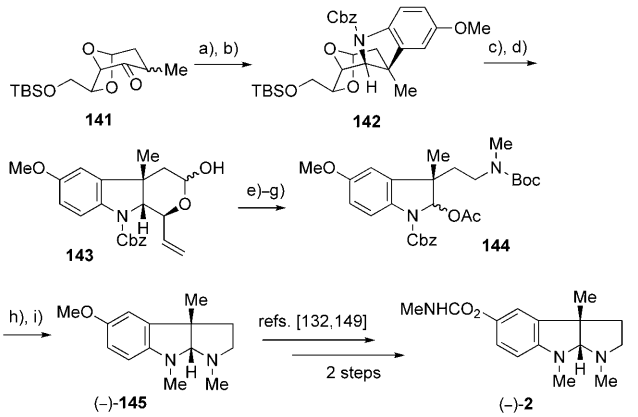
Scheme 26. Total synthesis of (−)-pseudophrynaminol (**10**).[177] a) Methyl 4-bromotiglate, NaOMe, MeOH, 0 °C, 75 %, 51 % d.e.; b) $LiAlH_4$, dioxane, reflux, 76 %.

has been reported.[177] The yield and diastereoselectivity of the process strongly depend on the solvent and base used. Separation of the two isomers, followed by reduction of (−)-**140** with $LiAlH_4$, gave (−)-**10**. The 1-phenylethylcarbamoyl substituent on the oxoindole nitrogen not only acts as a protecting group, but also as a prochiral group for asymmetric induction in the diastereoselective alkylation, enabling separation of diastereomer (−)-**140**. Moreover, this group is readily eliminated during reduction of the methyl ester and the carbamate.

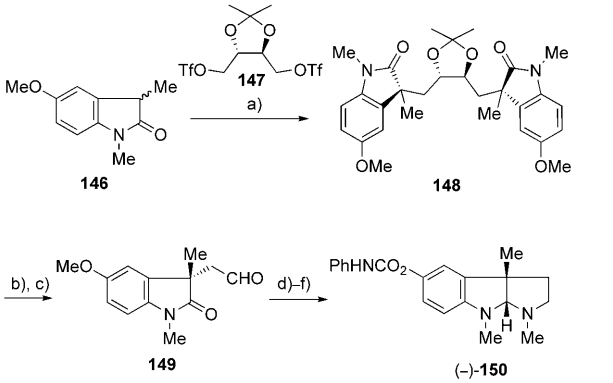
Identical final ring formation for the Calabar alkaloids (−)-physovenine and (−)-**2** was performed using a chiral building block for the diastereocontrolled construction of indoline **142**, a precursor of compound **144** (Scheme 27).[132,178] The oxidation level of compound **144** obviates reduction after the cyclization to form the HPI skeleton.

Hayashi employed a similar route oxoindole alkylation in the total synthesis of CPC-1.[179] Overman's group used the same cyclization strategy (D, Scheme 5) for an elegant total synthesis of (−)-phenserine (**150**),[180] in which alkylation of compound **146** with the chiral bistriflate **147** was the key step in the preparation of **149**, in excellent yield and with more than 99 % *ee* (Scheme 28).

Same last steps (D, Scheme 5) were used in an efficient route to either enantiomer of (−)-physostigmine (**2**), and their respective congeners, is summarized in Scheme 29.[181–183] It is based on versatile, asymmetric preparation of HPIs having carbon substituents at C^{3a}, starting from (*Z*)-butenoic acid **151** and *N*-methyl-*p*-anisidine (**154**). The central step is catalytic asymmetric Heck cyclization of (*Z*)-2-methyl-2-butenanilide (**155**) to form oxindole alde-



Scheme 27. Synthesis of (−)-physostigmine (**2**).[132,178] a) $ArNHNH_2$, HCl, Pyr/H_2O 9:1, reflux; b) $LiAlH_4$, THF, 0 °C then Cbz-Cl, aq. K_2CO_3, 70 % (2 steps); c) TBAF, THF, 89 %; d) Zn, AcOH/EtOH 1:9, 97 %; e) $MeNH_2$·HCl, $NaBH_3CN$, MeOH, 90 °C, 83 %; f) Boc_2O, $NaHCO_3$, MeOH, 94 %; g) $Pb(OAc)_4$, benzene, 60 °C; h) 10 % HCl, EtOAc, reflux, 80 % (2 steps); i) H_2, 10 % Pd/C, 36 % HCHO, MeOH, 80 %.



Scheme 28. Total synthesis of (−)-phenserine (**150**) by Overman et al.[180] a) KHMDS, THF/DMPU (98:2), −78 °C, 70 %; b) *p*TsOH, MeOH, H_2O; c) $NaIO_4$, THF, H_2O, 92 % (2 steps), >90 % *ee*; d) $MeNH_2$·HCl, $LiAlH_4$, $MgSO_4$, THF, 90 %; e) BBr_3, CH_2Cl_2, 91 %; f) NaH, PhNCO, THF, 82 %. DMPU = 1,3-dimethyl-3,4,5,6-tetrahydro-2(1*H*)-pyrimidinone; KHMDS = potassium bis(trimethylsilyl)amide.

hyde (*S*)-**149**. The same group later prepared several derivatives with aryl substituents at C^{3a} of the HPI.[184]

Joseph-Nathan synthesized (−)-debromoflustramine B (**69**) and its enantiomer via the racemic lactone **133** (Scheme 30). Reaction of **133** with (*S*)-1-phenylethylamine provided the diastereomeric lactams **157**, which were separated, then independently reacted with methylamine and reduced to provide the desired targets.[185]

Trost described the earliest examples of molybdenum catalyzed enantioselective allylation of prochiral nucleophiles, reported an interesting route to (−)-esermethole (**145**) based on this chemistry (Scheme 31).[186] Excellent yields and good-to-excellent enantioselectivities were obtained with a large variety of functionalities at the three positions of the starting oxoindole **146**, which provided 3-allyloxoindole (**159**) with 82 % *ee*. Oxidation of the terminal double

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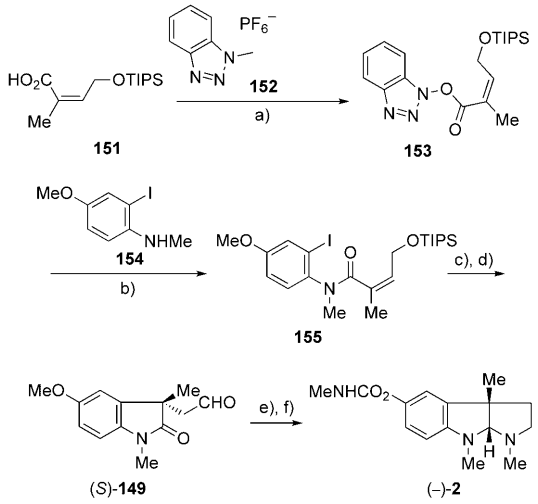
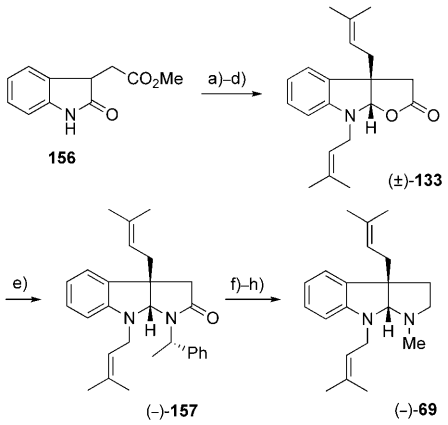


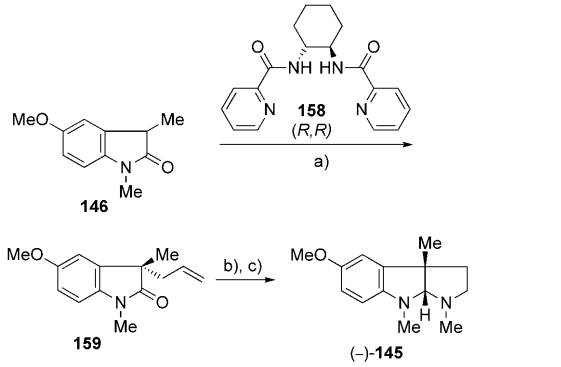
Scheme 29. Asymmetric synthesis of (−)-physostigmine (**2**).[183] a) Et_3N, CH_2Cl_2, 23 °C; b)60 °C, 67 % (2 steps); c) 10 % $[Pd_2(dba)_3]\cdot CHCl_3$, 23 %, (*S*)-BINAP, PMP, DMA, 100 °C; d) 3 M HCl, 23 °C, 84 % (2 steps), 95 % *ee*; e) $MeNH_2$·HCl, Et_3N, $LiAlH_4$, THF, reflux, 88 %; f) BBr_3, CH_2Cl_2, 23 °C, then Na, Et_2O, MeNCO, 63 %. BINAP = 2,2′-bis(diphenylphosphino)-1,1′-binaphthyl. PMP = 1,2,2,6,6-pentamethylpiperidine.



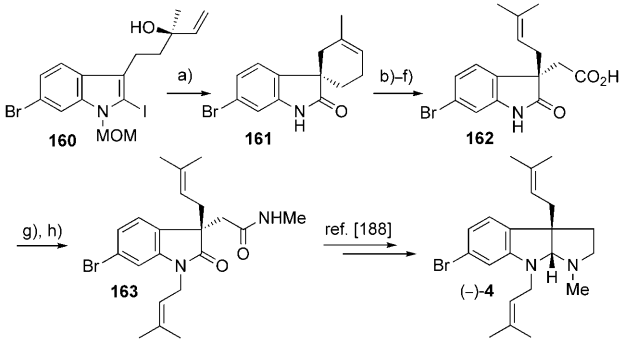
Scheme 30. Synthesis of (−)-debromoflustramine B (**69**).[185] a) Prenyl bromide, 15 % aq. NaOH, CH_2Cl_2, TBAHS, −5 °C, 76 %; b) 15 % aq. NaOH, MeOH, 40–50 °C, 87 %; c) NaH, THF, RT; d) $LiBHEt_3$, THF, 25–30 °C, 64 % (2 steps); e) (*S*)-1-phenylethylamine, 55 °C, then diastereomeric separation, 39 %; f) 50 % aq. AcOH, benzene, sealed tube, 180 °C, 30 %; g) 40 % aq. $MeNH_2$, MeOH, 98 %; h) $LiAlH_4$, THF, 99 %.

bond in **159** and reductive cyclization of the resulting aldehyde with methylamine afforded (−)-**145**.

A total synthesis of (−)-flustramine B (**4**) starting from the spiro compound **161**, enantioselectively prepared via one-pot intramolecular Ullmann coupling and Claisen rearrangement of the iodoindole **160**, has been reported (Scheme 32).[187] Compound **161** into **162** was transformed by double-bond oxidation, Wittig reaction and isomerization. *N*-Prenylation of the resulting product, and subsequent N^b–C^{8a} bond formation, yielded (−)-**4**.[188]



Scheme 31. Synthesis of (−)-esermethole (**145**) by enantioselective allylation of 2-oxoindole by Trost.[186] a) $[Mo(C_7H_8)(CO)_3]$, LiO*t*Bu, allyl *tert*-butyl carbonate, THF, 98 %, 82 % *ee*; b) OsO_4, NMO, NaIO4, 92 %, 82 % *ee*; c) $MeNH_2$, Et_3N, $LiAlH_4$, THF, reflux. NMO = *N*-methylmorpholine-*N*-oxide.



Scheme 32. Total synthesis of (−)-flustramine B (**4**).[187] a) CuCl, 2-aminopyridine, NaOMe, MeOH, triglyme, 100 °C, 69 %; b) OsO_4, NMO, acetone, H_2O, RT; c) $NaIO_4$, THF, H_2O, RT; d) $NaClO_2$, NaH_2PO_4−2 H_2O, 2-methyl-2-butene, *t*BuOH, H_2O, THF, RT, 84 % (3 steps); e) Ph_3PMeBr, *n*BuLi, THF, −25 °C to RT; f) H_2SO_4, then $MgSO_4$, 1,4-dioxane, 60 °C; g) prenyl bromide, K_2CO_3, acetone, reflux, 18 % (3 steps); h) aq. $MeNH_2$, MeOH, RT, 67 %.

Synthesis of HPI system by rearrangements processes

[3.3]-Sigmatropic rearrangements (E, F, G, Scheme 5): Marino et al. showed that 2-(methylsulfinyl)indole reacts with dichloroketene to produce a lactone[189] useful for assembling an HPI core. The same group later established that lactonization of chiral vinyl sulfoxides with dichloroketene occurs with complete control of the relative and absolute configurations. They employed a then new class of sulfoxylating agents, *N*-(alkylsulfinyl)oxazolidinones, to prepare the starting chiral indolyl sulfoxide. They reported that the size of the alkyl group on the sulfoxide positively correlates with the degree of asymmetric induction.[190] Lactonization of isopropyl indolyl sulfoxide **164**, followed by desulfonylation and dechlorination, gave **165** (in good enantiomeric excess), which was then transformed into (−)-**2** (Scheme 33).

A close procedure (E, Scheme 5) was developed by Padwa for the synthesis of (±)-desoxyeseroline (**108**) using an efficient route to highly functionalized γ-lactams

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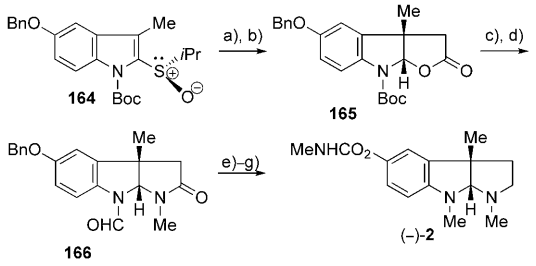
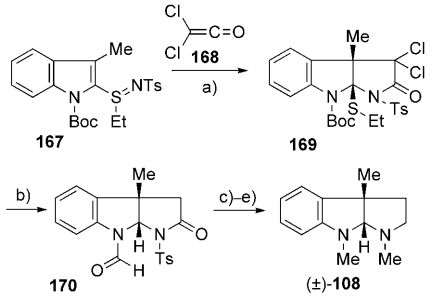


Scheme 33. Enantioselective synthesis of (−)-physostigmine (**2**).[190] a) Zn/CuCl, Cl_3CCOCl, THF, 0 °C; b) nBu_3SnH, AIBN, toluene, reflux, 37 % (2 steps), 70–75 % *ee*; c) HCO_2H, then $MeCO_2CHO$, 94 %; d) $MeNH_2$, −30 °C to RT, then H_2SO_4 cat., DMF, 115 °C, 68 %; e) BH_3·THF, 0 °C to reflux, 64 %; f) Ni-Raney (W2), THF, reflux; g) Na cat., MeNCO, 60 % (2 steps). AIBN = azobisisobutyronitrile;

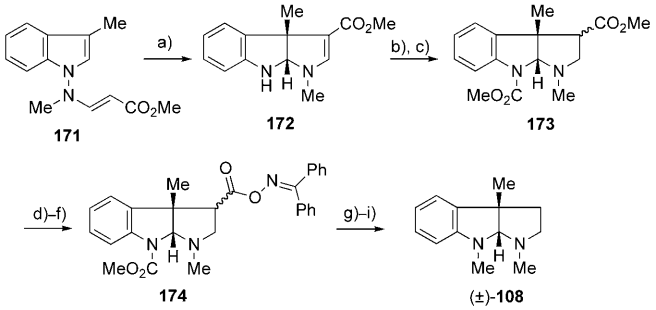


Scheme 34. Synthesis of (±)-desoxyeseroline (**108**).[191] a) Zn/Cu, THF, Cl_3CCOCl, 78 %; b) Zn, AcOH, TMEDA, EtOH, then HCO_2H, 72 %; c) Na, naphthalene, THF, 81 %; d) MeI, NaH, THF, 87 %; e) BH_3·THF, THF, 80 %. TMEDA = tetramethylethylenediamine.

(Scheme 34).[191] This route comprised reaction of the indolyl sulfylimine **167** with the highly electrophilic dichloroketene to generate a zwitterionic intermediate. Subsequent [3.3]-sigmatropic rearrangement, followed by intramolecular trapping of the Pummerer cation by the amido anion, furnished the γ-lactam product **169** in good yield. Reduction of this compound with Zn and AcOH, followed by treatment with HCO_2H, provided **170**. Removal of the *N*-tosyl group, followed by *N*-methylation and subsequent reduction of the lactam and the formamide, afforded (±)-**108** in good total yield.

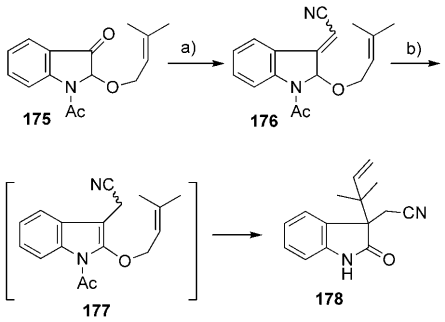
A formal synthesis of (±)-physostigmine (**2**) via 3,3-rearrangement of a bis(enamine) was described by Lobo, Prabhakar et al.[192,193]

(±)-Desoxyeseroline (**108**) was obtained via [3.3]-sigmatropic rearrangement of the *N*-methylvinylamino skeleton of **171** (F, Scheme 5). Thermolysis of the enaminoester **171** in *o*-dichlorobenzene gave the tricyclic compound **172** in excellent yield. Compound **172** was easily transformed into the carbamate **173** by a two-step sequence of *N*-methoxycarbonylation and catalytic hydrogenation. The best conditions they found for removing the carboxylic ester at C^3 comprised irradiation of the benzophenone oxime ester **174** in THF/*i*PrOH containing a large excess of *tert*-butylthiol (Scheme 35).



Scheme 35. Synthesis of (±)-desoxyeseroline (**108**) via [3,3]-sigmatropic rearrangement.[193] a) *o*-$Cl_2C_6H_4$, reflux, 91 %; b) $ClCO_2Me$, DMAP, Et_2O, 0 °C to RT, 81 %; c) H_2, PtO_2, MeOH, 45 psi, 93 %; d) aq. NaOH, MeOH, reflux; e) $ClCO_2iBu$, THF, −20 °C; f) $Ph_2C{=}NOH$, Et_3N, 75 % (3 steps); g) *hv*, *i*PrOH, THF, excess *t*BuSH, 92 %; h) $LiAlH_4$, THF, reflux, 69 %; i) aq. HCHO, $NaBH_3CN$, 67 %.

There is a utile route to 3-allyl-3-cyanomethylindolin-2-ones which is also amenable to prepare structurally diverse libraries of 3a-allyl-HPI that is based on domino reactions of 2-allyloxyindolin-3-ones of the type **175** (Scheme 36).[194,195] The process comprises olefination, isomerization, Claisen rearrangement, and deacetylation to give 3-allyl-3-cyanomethylindolin-2-ones of the type **178**. Reductive cyclization enabled preparation of 3a-allyl-HPI-containing alkaloids (G, Scheme 5).



Scheme 36. Synthesis of 3-allyl-3-cyanomethylindolin-2-one (**178**).[195] a) $Ph_3P{=}CHCN$, toluene, reflux, 70 %; b) DBU, 80 °C, 72 %.

(±)-Flustramines A (**3**) and C, (±)-flustramide A, and (+)- and (−)-debromoflustramine A were ultimately obtained by this route.[196]

While studying nucleophilic substitution in indoles, the Somei group reacted *N*-methoxyindole derivatives with alkoxides to obtain useful route for the synthesis of (±)-debromoflustramine B (**69**).[197] Further studies of the same authors conducted to the synthesis of 3a-oxygenated HPIC[198,199] by a rearrangement of the 1-benzoyloxy group of tryptamine **179** followed by cyclization to give the tricyclic system **181** (F, Scheme 5). The stereoselectivity of the process was demonstrated by heating (−)-**182** in refluxing DMF to produce (−)-**183** as the sole product (Scheme 37).

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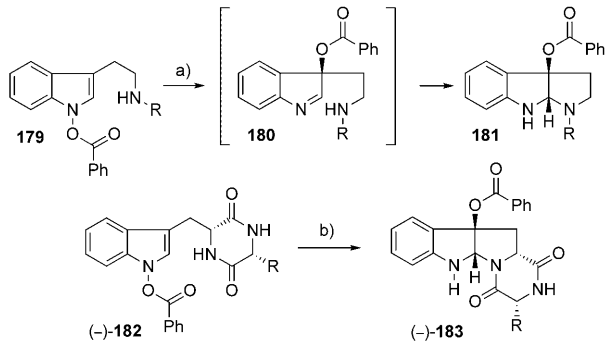
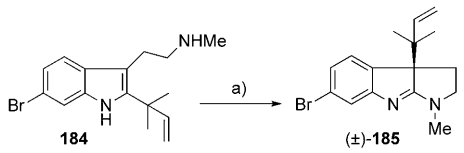


Scheme 37. Somei's synthesis of 3a-oxygenated HPI **183**.[198] a) Heating; b) DMF, reflux.

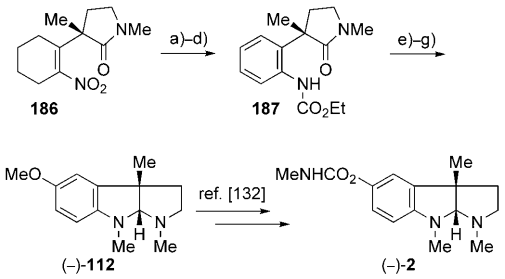
[1.2]-Rearrangements: (±)-Flustramine C (**185**) was synthesized in five steps starting from N^b-methyltryptamine. The key step was biomimetic oxidation of the natural product deformylflustrabromine (**184**), causing selective [1.2]-rearrangement of the inverse isoprenyl group and simultaneous cyclization (Scheme 38).[200]



Scheme 38. Synthesis of flustramine C (**185**).[200] a) NBS, THF, RT, 90%.

Formation of HPI by elaboration of indole heterocyclic ring

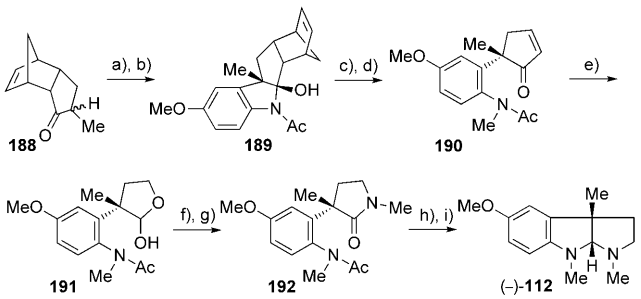
Reductive cyclization (H, Scheme 5): A formal total synthesis of (−)-physostigmine (**2**) was accomplished from the chiral nitro olefin **186** (Scheme 39) and stereochemistry of



Scheme 39. Synthesis of (−)-esermethole (**112**).[131] a) Br_2, KO*t*Bu, 83%; b) KO*t*Bu, DMSO; c) H_2, PtO_2; d) $ClCO_2Et$, 29% (3 steps); e) $LiAlH_4$; f) NBS, 35% (2 steps); g) NaOMe, CuI, 35%.

the product was confirmed.[131] Aromatization of cyclohexene, reduction of the nitro group, and subsequent aniline protection gave **187**, which was submitted to reductive cyclization. Bromination of the aromatic ring, followed by copper-catalyzed methoxy–bromine exchange afforded (−)-esermethole (**112**), which was later converted to (−)-physostigmine. This work constituted the first total synthesis of (−)-**2**.[132]

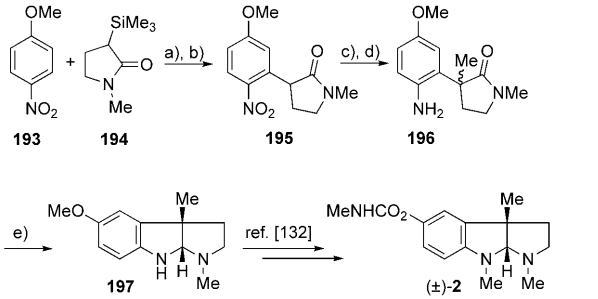
(−)-Physovenine and (−)-**2** were enantioselectively synthesized from the optically active enone **188**, which was first transformed into the enone **190** via Fischer indolization and retro-Diels–Alder chemistries.[201] Oxidation of **190** to the lactam **192**, followed by reductive cyclization, gave (−)-esermethole (**112**) (Scheme 40). The product was subsequently



Scheme 40. Enantiocontrolled total syntheses of (−)-ersemethole (**112**).[201] a) *p*-$MeOC_6H_4NHNH_2$·HCl, aq. Pyr (1:10), reflux, 82%; b) Ac_2O, Pyr; c) NaH, MeI, DMF/THF 1:1, 86% (2 steps); d) *o*-$Cl_2C_6H_4$, reflux, 66%; e) O_3, MeOH, then $NaBH_4$, −78°C to RT, 10% HCl then $NaIO_4$, 62%; f) Ag_2CO_3 on Celite, benzene, reflux, 88%; g) 40% aq. $MeNH_2$, sealed tube, 180°C, 76%; h) *i*Bu_2AlH, CH_2Cl_2, −78°C, then NH_4OH; i) $LiAlH_4$, THF, reflux, 34% (2 steps).

transformed into (−)-physostigmine via (−)-eseroline in two steps as had previously been described.[132] The Takano group used the same route to assemble the non-naturally occurring (+)-**2**.[202]

An efficient formal total synthesis of (±)-physostigmine (**2**) in which a new vicarious nucleophilic substitution reaction between *p*-nitroanisole and a *C*-silylated derivative of *N*-methylpyrrolidinone was exploited to give **195**.[203] α-Methylation and reductive cyclization of **195** provided the key intermediate *N*-demethylesermethole (**197**) in high yield, which was transformed into the (±)-**2** as had previously been described (Scheme 41).[132]



Scheme 41. Formal total synthesis of (±)-physostigmine (**2**).[203] a) TASF, THF, −78°C to RT; b) DDQ, 85% (2 steps); c) MeI, CsOH·H_2O, CH_3Ph, TBAB, RT, 94%; d) H_2, 10% Pd/C, EtOAc, 50 psi, quant.; e) $LiAlH_4$, THF, 60%.

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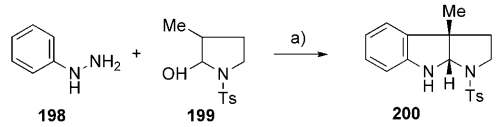
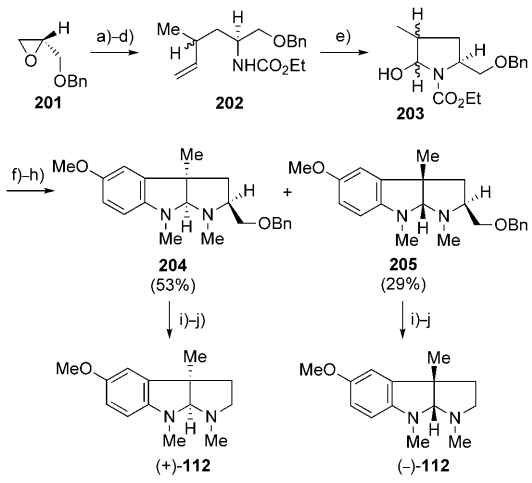
Fischer indole synthesis (I, Scheme 5): An efficient method of preparation of HPI system involves the condensation of hydrazines with latent aldehydes to deliver indoline-containing products (Scheme 42) following an interrupted Fischer indolization sequence.[204] This approach amenable to complex targets was applied with good to excellent yields to several examples.



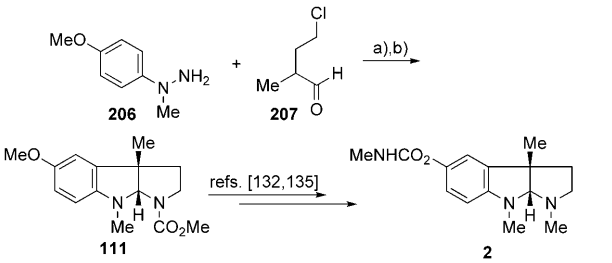
Scheme 42. Preparation of HPI by Fischer indolization.[204] a) AcOH/H_2O 1:1; 100 °C, 88 %.

A chiral synthetic route to both enantiomers of esermethole (**112**) was established starting from (*S*)-*O*-benzylglycidol (**201**),[205] which provided a diastereomeric mixture of hemiacetals **203** in excellent yield (Scheme 43). Fischer indolization of **203** with 4-methoxyphenylhydrazine hydrochloride, followed by dimethylation, gave the HPI derivatives **204** and **205**, which were readily separated. Compounds **204** and **205** were transformed into (+)-**112** and (−)-**112**, respectively, via the following sequence: *O*-debenzylation under Birch conditions; removal of the hydroxymethyl group by Swern oxidation of the alcohol; transformation of the resulting aldehyde into a cyanide; and finally, reductive elimination of cyanide from the formed α-aminonitrile.

Nishida et al. devised an efficient formal synthesis of physostigmine (**2**) whose key step is a modified Fischer indole synthesis using *N*-methyl-*N*-(*p*-methoxyphenyl)hydrazine and the aldehyde **207** (Scheme 44).[206] Transformation of **111** into **2** had been previously described.[135] The authors later made this chemistry enantioselective by using chiral hydrazines, which they readily prepared from commercially available chiral amines.[207]



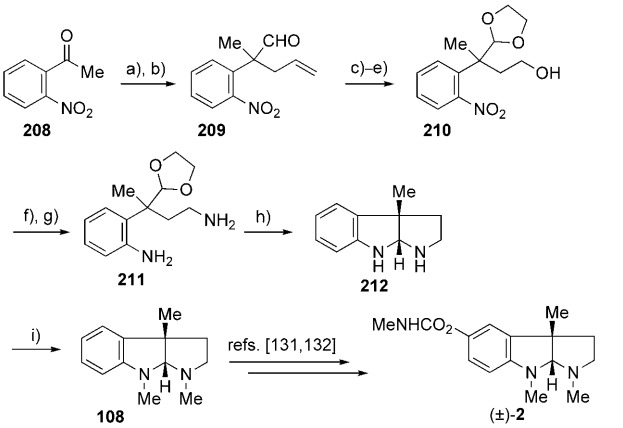
Scheme 43. Synthesis of (+)- and (−)-esermethole (**112**).[205] a) MeCH=$CHCH_2MgCl$, THF, 0 °C, 90 %; b) phthalimide, PPh_3, DIAD; c) $NH_2NH_2{\cdot}H_2O$, EtOH, reflux; d) $ClCO_2Et$, Et_3N, CH_2Cl_2, 72 % (3 steps); e) 2 % mol OsO_4, $NaIO_4$, THF/H_2O 2:1, then $NaIO_4$, THF, H_2O, 94 %; f) *p*-$MeOC_6H_4NHNH_2{\cdot}HCl$, Pyr, reflux, 95 %; g) 35 % HCHO, $NaBH_3CN$, MeOH; h) $LiAlH_4$, THF, reflux; i) Na liq. NH_3, 92 %→ quant.; j) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, then hydroxylamine-*O*-sulfonic acid, then $NaBH_4$, EtOH, reflux, 22–25 %.



Scheme 44. Synthesis of HPI by modified Fischer indole synthesis.[206] a) MeOH, reflux; b) $ClCO_2Me$, Na_2CO_3, CH_2Cl_2, H_2O, 0 °C to RT, 80 % (2 steps).

Synthesis of HPI by simultaneous formation of N^b–C^{8a} and N^8–C^{8a} bonds (J, Scheme 5)

Kulkarni et al. recently reported a novel total synthesis of (±)-**2** (Scheme 45).[208] Wittig olefination and posterior



Scheme 45. Synthesis of (±)-physostigmine (**2**) by Kulkarni et al.[208] a) CH_2=$CHCH_2OCH_2PPh_3Cl$, NaO*t*Bu, THF, 0 °C; b) xylene, reflux, 85 % (2 steps); c) *p*-TSA, ethylene glycol, toluene, reflux; d) O_3, SMe_2, CH_2Cl_2, 0 °C, 88 % (2 steps); e) $NaBH_4$, aq. THF, 92 %; f) DIAD, PPh_3, phthalimide, CH_3NH_2, reflux, 68 %; g) Ni-Raney, H_2, MeOH, 82 %; h) *p*-TSA, aq. THF, reflux, 65 %; i) aq. HCHO, 10 % Pd/C, EtOAc, H_2, 90 %.

Claisen rearrangement of *o*-nitroacetophenone afforded the aldehyde **209**. Protection of the formyl group, oxidation of the double bond, and reduction of the aldehyde in the resulting intermediate afforded the cyclic acetal **210**. Functional group transformation of **210** gave the diamine **211**, whose acetal was hydrolyzed with *p*-TSA to furnish the HPI **212**. Finally, bis-*N*-methylation of **212** and introduction of carbamate on position 5 following a literature protocol[131] yielded (±)-**2**.

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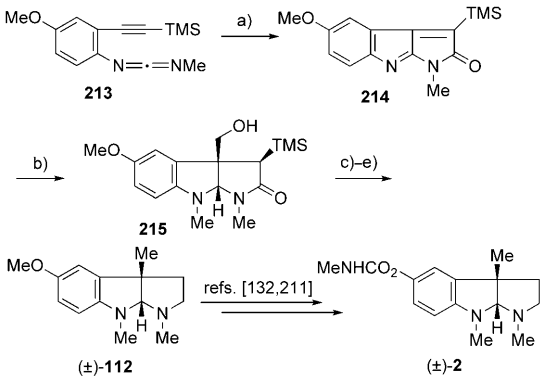


Scheme 46. Formal synthesis of (±)-physostigmine (**2**) by aza-Pauson–Khand formation of HPI.[210] a) $[Co_2(CO)_8]$, TMTU, benzene, CO (1 atm), 70 °C, 55 %; b) $NaCNBH_3$, aq. HCHO, AcOH, MeCN, 0 °C, 79 %; c) TBAF, THF, reflux, 96 %; d) I_2, PPh_3, imidazole, $CHCl_3$, reflux, 78 %; e) $LiAlH_4$, THF, reflux, 83 %. TMTU = Tetramethylthiourea.

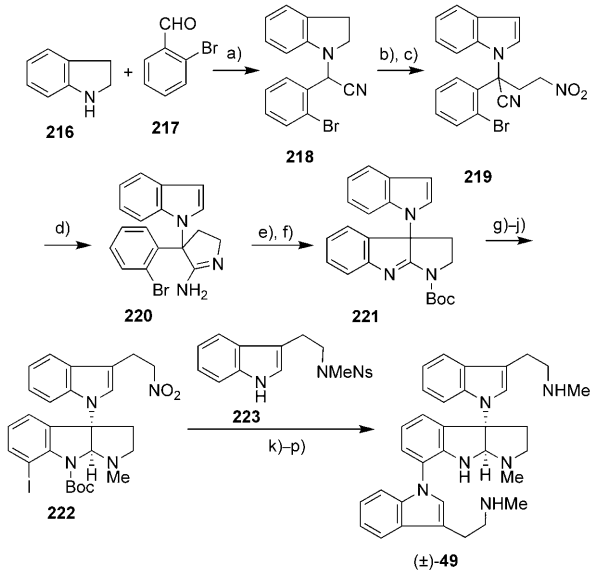
Aza-Pauson–Khand cyclocarbonylation (K, Scheme 5)

(±)-Physostigmine **2** has also been synthesized by subjecting an alkynecarbodiimide to an APKR with $[Co_2(CO)_8]$ as catalyst (Scheme 46).[209,210] Under $[Co_2(CO)_8]$-catalyzed cyclocarbonylation conditions, the carbodiimide **213** was transformed into the pyrrolo[2,3-*b*]indol-2-one **214**. One-pot reduction, hydroxymethylation, and *N*-methylation of **214** gave **215** as a single stereoisomer in good yield. Removal of the TMS and hydroxyl groups in **215**, followed by reduction of the resulting lactam, gave (±)-esermethole **112** in high yields.

(±)-Flustramine B (**4**), (±)-debromoflustramine B (**69**), (±)-debromoflustramide B, (±)-debromoflustramine E, (±)-flustramine E and (±)-debromoflustramide E were prepared[210] from pyrrolo[2,3-*b*]indol-2-ones via APKR of alkynecarbodiimides.

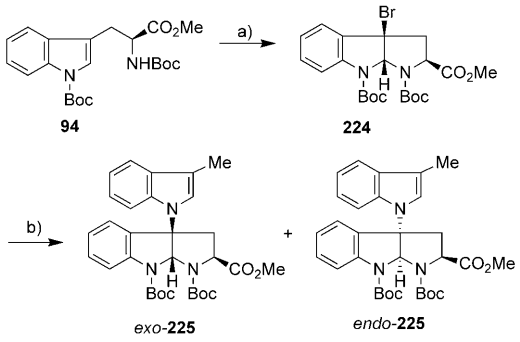
Synthesis of natural products containing an N^1–C^{3a} bond

Takayama et al. were the first to synthesize a natural product containing a N^1–C^{3a} bond characteristic of psychotrimine (**49**).[212] In fact, the N^1–C^{3a} bond was the first bond formed in their sequence (Scheme 47), via Strecker reaction of 2-bromobenzaldehyde and indoline to give **218**. Introduction of a nitro-chain α to the cyano group of **218**, and oxidation of the indoline, gave compound **219**, containing all the atoms needed for elegant construction of 3a-indolyl-HPI **221**. Reduction of the nitro group in **219** gave the primary amine, which spontaneously cyclized to amidine **220**, whose pyrrolidine nitrogen was then Boc-protected. Finally, copper-mediated intramolecular amination afforded **221**, which was then transformed into **222** via reduction of the Boc-protecting group to methyl, protection of N^8, regioselective iodination, and lastly, introduction of nitroethyl at position 3 of the indole. Finally, conversion of the nitro group in **222** into the NMe, followed by copper mediated intermolecular coupling of iodide **222** with tryptamine **223** and subsequent deprotection afforded **49**.



Scheme 47. Synthesis of (±)-psychotrimine (**49**) by Takayama et al.[212] a) KCN, aq. HCl, MeCN, RT, 92 %; b) NHMDS, CH_2=$CHNO_2$, THF, −78 °C; c) DDQ, 1,4-dioxane, 50 °C, 90 % (2 steps); d) Fe powder, aq. HCl, EtOH, reflux; e) Boc_2O, *i*Pr_2NEt, MeCN, RT, 88 % (2 steps); f) CuI, K_3PO_4, DMSO, 80 °C, 91 %; g) Red-Al, toluene, 0 to 90 °C, 60 %; h) NHMDS, Boc_2O, THF, −78 to 0 °C; i) *s*BuLi, TMEDA, I_2, THF, −78 to 0 °C, 87 % (2 steps); j) $InBr_3$, CH_2=$CHNO_2$, CH_2Cl_2, RT, 86 %; k) Fe powder, AcOH, EtOH, dioxane, reflux; l) NsCl, Et_3N, CH_2Cl_2, RT, 93 % (2 steps); m) DBU, Me_2SO_4, DMF, 0 °C, 94 %; n) TMSOTf, 2,6-lutidine, CH_2Cl_2, 0 °C to RT, 87 %; o) **223**, CuI, K_3PO_4, *N*,*N*′-dimethylethylenediamine, 1,4-dioxane, 90 °C, 72 %; p) PhSH, Cs_2CO_3, MeCN, RT, 81 %. NHMDS = sodium bis(trimethylsilyl)amide. Ns = 4-nitrobenzenesulfonyl (nosyl).

Rainier and Espejo described an alternate strategy to N^1–C^{3a} bond formation: reaction of an 3a-bromo-HPIC and an indole derivative.[213] Compound **224** was subjected to base-catalyzed nucleophilic substitution with indole derivatives, yielding a mixture of diastereomers in which the *endo* product was predominant (Scheme 48).



Scheme 48. Synthesis of 3a-indolyl-HPIC by Rainier and Espejo.[213] a) NBS, PPTS, CH_2Cl_2, RT, 92 %; b) 3-methylindole, KO*t*Bu, MeCN, 0 °C, 43 %.

Baran et al. prepared psychotrimine (**49**) via an elegant synthesis based on the simultaneous formation of the tricyclic system of HPI and the N–C^{3a} bond (Scheme 49).[214] The

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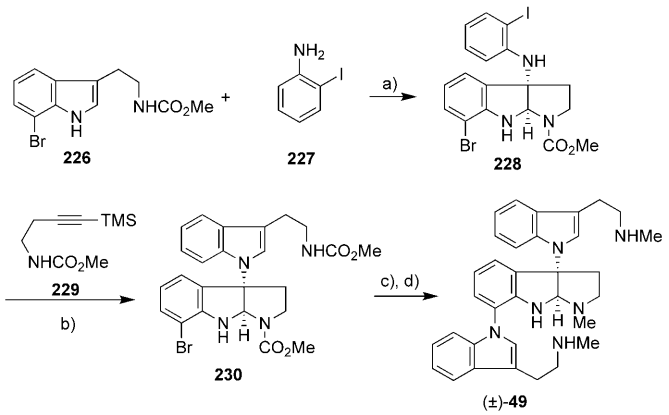
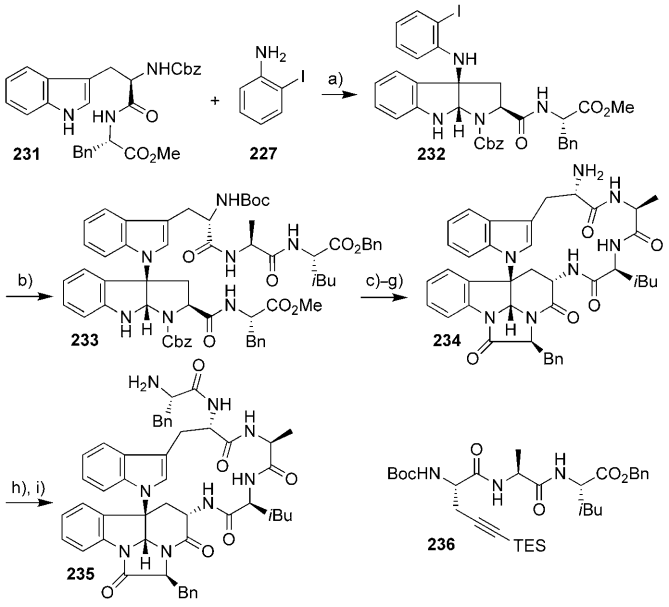


Scheme 49. Synthesis of (±)-psychotrimine (**49**) by Baran et al.[214] a) NIS, Et_3N, MeCN, −45 to 23 °C, 61–67 %; b) $Pd(OAc)_2$, Na_2CO_3, LiCl, DMF, 102 °C, 85 %; c) CuI, (±)-*trans*-*N*,*N*′-dimethyl-1,2-cyclohexanediamine, K_2CO_3, N^b-(methoxycarbonyl)tryptamine, 1,4-dioxane, 101 °C, 89 %; d) Red-Al, toluene, 110 °C, 89 %. NIS = *N*-iodosuccinimide.

starting material was bromotryptamine **226**, which was reacted with NIS and 2-iodoaniline to form HPI derivative **228**. Chemoselective Larock annulation[215] between **228** and an alkyne afforded **230**. Transformation of **230** into (±)-**49** follows a similar procedure as that detailed in Scheme 47.

Recently, Baran et al. employed a similar strategy to synthesize kapakahines B (**235**) and F (**234**) (Scheme 50).[216] Reaction of the dipeptide **231** with *o*-iodoaniline and NIS under simultaneous cyclization-amination gave compound



Scheme 50. Synthesis of kapakahines B (**235**) and F (**234**) by Baran et al.[216] a) NIS, MeCN, −45 to −35 °C, 65 %; b) $Pd(OAc)_2$, NaOAc, LiCl, **236**, DMF, 100 °C, 49 %; c) 10 % Pd/C, H_2, MeOH; d) EDC, HOAt, CH_2Cl_2/DMF 20:1, 70 % (2 steps); e) LiOH, THF/H_2O/MeOH; f) $(COCl)_2$, Et_3N, CH_2Cl_2; g) TFA/CH_2Cl_2 1:10, 64 % (3 steps); h) Boc-Phe-OH, EDC, HOBt, Et_3N, CH_2Cl_2; i) TFA/CH_2Cl_2 1:10, 81 % (2 steps). HOAt = 1-hydroxy-7-azabenzotriazole; HOBt = 1-hydroxybenzotriazole.

232. Larock annulation of **232** with the tripeptide **236** gave **233**. Interestingly, the HPIC-opening in this synthesis occurs after the Cbz elimination and the new double-ring closure, to give the α-carboline condensed to an imidazolidinone unit characteristic of kapakahines.

Summary and Outlook

From the isolation of physostigmine in 1864 to the last decades, many natural products containing HPI and HPIC have been isolated. Furthermore, a new characteristic trait has been reported in some recently isolated natural products: a bond between the C^{3a} of the HPI or HPIC and the N^1 of a tryptamine or Trp. Some of these compounds are macrocyclic peptides, which contain both the HPIC and the Trp in the peptide chain.

This report has covered synthetic routes to natural products containing one or more HPI and/or HPIC units. The smallest and simplest of these compounds have been prepared via classical indole chemistry, whereas the larger, more complex structures have inspired new synthetic methodologies that exploit a full arsenal of transformations, including oxidative cyclization, Pd-catalyzed reactions as Larock annulations, and enzyme-catalyzed reactions between others. Researchers will undoubtedly harness this new chemistry to further advance work on natural products containing HPIs and/or HPICs.

Many of these natural products present a wide range of biological activities, encompassing acyl-CoA inhibitors, neuropeptide neurotransmitter antagonists, topoisomerase inhibitors, and antibiotics. Thus, it is easy to envisage that in a near future, some of these natural products or their analogues will enter into clinical trials, which will require the need of having bigger quantities. The synthetic routes described in this review should be the base for developing industrial strategies required for these natural products which can be considered as potential drugs.

Acknowledgements

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Annex 2

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Orthogonal Protecting Groups in the Synthesis of Tryptophanyl-Hexahydropyrroloindoles

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Keywords: Natural products / Heterocycles / Amino acids / Protecting groups

The synthesis of various polycyclic systems containing a C^{3a}-N^{i} bond between a hexahydropyrrolo[2,3-*b*]indole and an indole tryptophan is described here. A series of experiments was run to determine the best combination of five orthogonal protecting groups and the best reaction conditions for formation of said bond, which is a common feature among many recently discovered marine natural products.

Introduction

The tricyclic motif hexahydropyrrolo[2,3-*b*]indole (HPI) is present in many natural compounds with important bioactivities.[1] These compounds all feature a substituent at the 3a-position of the HPI, such as a methyl group, in (–)-physostigmine;[2] a prenyl, in flustramines,[3] brevicompanines[4] and roquefortines;[5] and a newly discovered HPI linked by one aromatic carbon, in idiospermuline,[6] psychotridine[7] and quadrigemine.[8] Recently isolated natural compounds such as psychotrimine,[9] chaetomin and the chaetocochins[10] contain an unusual bond between the 3a-position of the HPI and the indole nitrogen of either a tryptamine or a tryptophan (Figure 1). Kapakahines are natural products with a bond between the C^{4a} of an α-carboline and the indole nitrogen of an *N*-Trp.[11]

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Supporting information for this article is available on the WWW under http://www.eurjoc.org/ or from the author.

To date, four total syntheses of psychotrimine have been reported.[12] Takayama *et al*. were the first to synthesize this compound,[12a] assembling the HPI motif from a phenylacetonitrile that contains an indoline at the appropriate α-nitrile position. In contrast, Newhouse and Baran[12b] prepared psychotrimine via simultaneous formation of the HPI and the *N*-C^{3a} bond. They later employed the same strategy to prepare kapakahines B and F[13], and (+)-psychotetramine.[14]

During the course of the present work, Rainier *et al.* published a study on *N*-C^{3a} bond formation via bromo-displacement of 3a-bromo-HPIC with the *N*-anion of indole.[15] The same group harnessed this chemistry to prepare kapakahines E and F,[16] and more recently, described a mechanism for the substitution.[17]

Compound **1**, which contains a bond between the C^{3a} of HPI and the *N* of an indole, could be used as a scaffold for the synthesis of many natural products and analogs. In the work reported here, **1** was synthesized via nucleophilic substitution of the bromine at position 3a of 3a-bromo-HPI with an *N*-indole anion (Figure 2). To ensure chemoselectivity during this chemistry, five orthogonal protecting groups were required. Studies to determine the best protecting groups and conditions for this bond formation were then performed and are described herein.

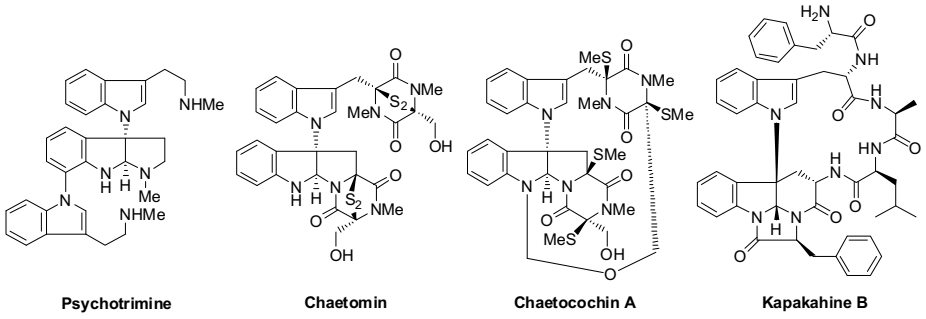


Figure 1. Natural products containing a bond between the C^{3a} of an HPI, or the C^{4a} of an α-carboline, and the indole nitrogen of either a tryptamine or a tryptophan.

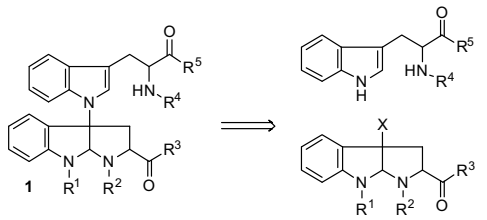


Figure 2. Retrosynthesis of compound **1**.

Results and Discussion

First of all, various bromo analogs of 3a-bromo-1,2,3,3a,8,8a-hexahydropyrrolo[2,3-*b*]indole-2-carboxylate (3a-Br-HPI; **3**) were synthesized using two different procedures, which were subsequently compared for performance (Table 1). The first one follows the route described by Taniguchi and Hino,[18] based on cyclization of a protected Trp in acidic medium, followed by aniline protection and subsequent benzylic bromination of HPI-2-carboxylate. The second procedure is an one-step bromination-cyclization of a totally protected Trp using *N*-bromosuccinimide (NBS) and pyridinium *p*-toluenesulfonate (PPTS).[19] The resulting products **3** and their stereochemistries (*endo/exo*) are listed in Table 1. Although a three (two amino and one carboxylic protecting groups) orthogonal systems is desirable, the use of the same amino protecting groups (R^1 = R^2) for both amino groups were also studied (Table 1, Entries 2, 3, and 16) having in mind the different nucleophilicity of both amino functions. For the carboxylic protection, common esters such as methyl, *t*-butyl, and allyl were tested. On the other hand, for the amino function both alkoxycarbonyl, i.e., *tert*-butoxycarbonyl (Boc), allyloxycarbonyl (Alloc), benzyloxycarbonyl (Cbz), 2,2,2-trichloroetoxycarbonyl (Troc), and metoxycarbonyl (Moc), and and sulfonyl, i.e., 2-nitrobenzenesulfonyl (Nosyl) and SO_2Ph were tested. Additionally, , protected amino acids (R^2 and R^3 Table 1, Entries 14-16) were assayed with the idea of studying the size and/or the electronic properties of protecting groups.

The overall transformation of L-Trp-OMe (the starting material) into **3** was highly demanding, as illustrated by the yields, which ranged from poor to moderate. Method B, which is shorter, gave better yields for the same set of protecting groups (Table 1: Entries 7, 12 and 13) and has the important additional advantage of being amenable to use of various protecting groups for the α-amino group (R^2). Cyclization with H_3PO_4 (Method A) gave better yields when methoxycarbonyl (R^2=Moc) was used as N^{α}-Trp protecting group compared to when trichloroethoxycarbonyl (R^2=Troc) was used (see Table 1: Entries 12 and 7, respectively).

Despite various attempts in diverse conditions, we were unable to remove the Moc group from the N^1 of HPI-2-carboxylate.[21] Furthermore, to the best of our knowledge,[1] to date there have not been any reports of the Moc group being removed from the N^8 of HPI-2-carboxylate; instead, this group typically is reduced to obtain the desired *N*-Me product.[12b,22]

Compounds **3b** and **3c** possess two Boc groups at positions N^1 and N^8 which could be cleaved simultaneously; however, the amine of N^1 is more reactive than the aniline of N^8, which enabled chemoselective acylation of N^1 as reported by Danishefsky *et al.*.[23]

The ^{1}H-NMR signals corresponding to the protecting groups of R^2—namely, the signals for the CH_2 of Cbz or Troc, and for the CH_3 of Moc—are broad or split, because the protons are diastereotopic.

The difference in stereochemistry of the products **3** obtained from each method is noteworthy. Comparison of the ^{1}H-NMR spectra of the products **3g** obtained from Method A and from Method B revealed significant differences in the signals for the proton at position 2 (δ 4.67 vs. 3.98 ppm, respectively) and for the methyl ester (δ 3.21 vs. 3.74 ppm, respectively). Based on these data, the stereochemistry of the product from Method A was determined to be ***endo*-3g**, and that of the product from Method B, ***exo*-3g** (see Figure 3). The diamagnetic anisotropy of the phenyl ring shields the *endo*-methyl group (δ 3.21 ppm) and the *exo*-H2 (δ 3.98 ppm).[24] The same phenomenon occurred with the *endo/exo* **3l** and **3m** obtained with the appropriate method (see Supporting Information).

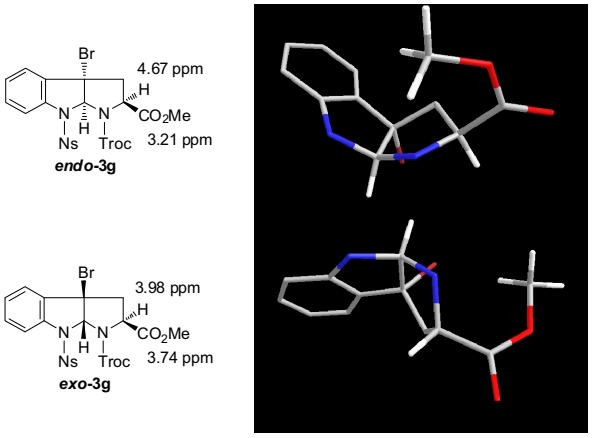
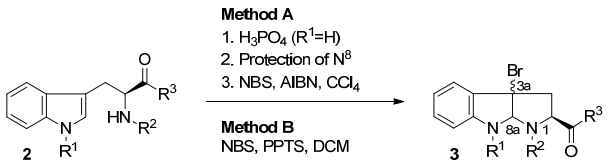


Figure 3. Comparison of the ^{1}H-NMR data for *endo* and *exo* **3g** (left). Three-dimensional models of the corresponding tricyclic systems (right).[25]

Compounds **3a**, **3b**, **3d**, **3k**, **3n**-**3p** (Table 1: Entries 1, 2, 4, 11, 14-16) only showed one diastereomer on NMR data. Their stereochemistry assignments were determined by comparing the chemical shifts of proton and substituent at C^2 of HPI.

To obtain a more versatile intermediate during synthesis of **3n**, **3o** and **3p** via Method B, protected Ala or Ile were used as N^{α}- and *O*-protecting groups respectively. However, the synthesis of compound **6** required an indirect route (see Table 1, footnote d), because subjecting dipeptide **4**, which was N^{α}-Alloc-Ala protected, to the acidic conditions for cyclization furnished the dimer **5** (Figure 4). Formation of **5** could be explained based on electrophilic substitution between **4** and the indoline that had formed after its protonation.

Table 1. Synthesis of the bromo compounds **3a-p**.



#	Comp.	R^1	R^2	R^3	Method (Yield %)	*endo*:*exo*
1	3a	Boc	Alloc	OMe	B (83)	*exo*
2	3b	Boc	Boc	OAllyl	B (30)[a]	*exo*
3	3c	Boc	Boc	OMe	B (86)	4:96[b]
4	3d	Boc	Cbz	OMe	B (78)	*exo*
5	3e	Boc	Troc	OMe	B (77)	11:89[c]
6	3f	Nosyl	Cbz	OtBu	B (80)	7:93[c]
7	3g	Nosyl	Troc	OMe	A (9) B (57)	*endo* 8:92[c]
8	3h	Nosyl	Troc	OtBu	B (59)	6:94[b]
9	3i	SO_2Ph	Boc	OMe	B (92)	7:93[b]
10	3j	SO_2Ph	Cbz	OMe	B (82)	4:96[b]
11	3k	SO_2Ph	Cbz	OtBu	B (83)	*exo*
12	3l	SO_2Ph	Moc	OMe	A (37) B (96)	*endo* 5:95[b]
13	3m	SO_2Ph	Moc	O*t*Bu	A (28) B (58)	91:9[c] 25:75[c]
14	3n	Boc	N^{α}-Alloc-Ala	OMe	B (47)	*exo*
15	3o	Boc	Alloc	Ile-OMOM	B (47)[d]	*exo*
16	3p	Boc	Boc	Ile-OAllyl	B (41)[d]	*exo*

[a] **3b**, **3o** and **3p** were synthesized from **3c**, **3a** and **3c**, respectively, after hydrolysis and subsequent esterification or coupling with the protected Ile (see Supporting Information). [b] Ratio determined by HPLC.[20] [c] Ratio determined by ^{1}H-NMR. [d]

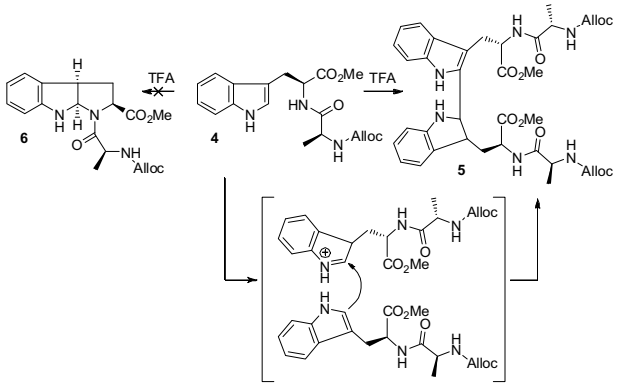


Figure 4. Dimerization of **4** under acidic conditions.

Consequently, in the first step of the HPI formation in Method A, working with an N^{α}-carbamate protecting group at this position, instead an amide bond, is rather important.

The second part of this work comprised formation of the bond between the C^{3a} of the HPI and the N^{i} of the Trp. Several pairs of base and solvent were tested to generate the indole anion that would drive the substitution to give compound **1**.[26] The best conditions found comprised NaH in DMF at 70 ºC for 1.5 h. Every bromo derivative (**3a-p**) was tested with several protected Trp's. A distinguishing data point in the ^{13}C-NMR data for compounds **1** and **3** is the chemical shift of the quaternary C^{3a}, which is less shielded in **1** (δ 72.4 to 82.2 ppm) than in **3** (δ 53.7 to 67.9 ppm). The results of these substitutions are summarized in Table 2.

The best yields of **1** in the nucleophilic substitution were found using **3a**, **3l**, **3m** and **3p** (Table 2: Entries 1 and 7-10, respectively). Moderate yields were obtained for the substitutions with bromides **3c**, **3d** and **3g** (Entries 3-6). However, very poor yields (< 10%, data not shown) were observed when bromides **3b**, **3e**, **3f**, **3h-k** and **3n** were reacted with different protected versions of **7**, which contains two additional protecting groups.

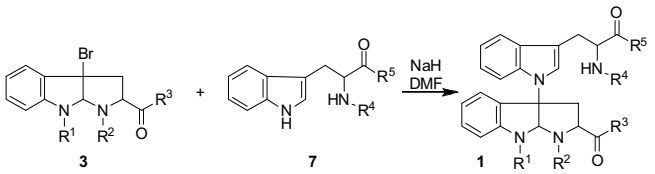


Table 2. Nucleophilic substitution at the C3a of 3a-Br-HPI

#	3[a]	R^4	R^5	3[b]	7[b]	1[b]	Comp (%)[c]
1	**exo-3a**	Phth	OMe	39	18	43	**1a** (41)
2	**3c**	Moc	OMe	49	22	29	**1b** (20)
3	**3c**	Phth	OMe	66	11	24	**1c** (21)
4	**exo-3d**	Phth	OMe	28	14	58	**1d** (26)
5	**endo-3g**	Alloc	OMe	24	21	48	**1e** (29)
6	**exo-3g**	Alloc	OtBu	62	22	15	**1f** (22)
7	**endo-3l**	Alloc-Ile	OtBu	-	24	50	**1g** (41)
8	**endo-3l**	Moc	OMe	-	1	91	**1h** (77)
9	**endo-3m**	Boc-Ile	OAllyl	29	20	48	**1i** (30)
10	**3p**	Phth	OMe	13	42	11	**1j** (30)

[a] See Table 1 for the protecting groups used in each compound **3**. [b] Percentage of each compound in the reaction crude (as measured by HPLC).[20]. [c] Yield of isolated compound.

The phthalamide (Phth) was introduced as R^4 because it is orthogonal to all protecting groups used in the first reactions (Table 2: Entries 1, 3, 4 and 10), as it eliminates all the N^{α} acid protons in **7.** The wide range of yields in the resulting substitution (from 21 to 41%) demonstrates the importance of the protecting groups in the starting bromide. The bromides **3l** and **3m** have the same protecting groups in both amino groups of HPI (R^1 = SO_2Ph, R^2 = Moc). Interestingly, the yield was lower when the group at R^5 was *tert*-butyl ester (**1g**, Entry 7) compared to methyl ester (**1h**, Entry 8). Likewise, the yield was lower when R^3 was *tert*-butyl ester (**1i**, Entry 9) compared to methyl ester (**1h**, Entry 8). The same trend was observed for **1f** (Entry 6) and **1e** (Entry 5), although to a lesser extent: the *tert*-butyl in **1f** is more sterically hindered than the methyl ester in **1e**. The results obtained with a protected Ile-Trp dipeptide as nucleophile (Entries 7 and 9), and with a Br-HPI and a protected Ile (Entry 10), are interesting, as they can serve as the stepping stone to synthesis of peptides found in natural compounds. Additionally, owing to this Ile protection, **1j** (R^3= Ile-OAllyl, Entry 10) was obtained in higher yield than was **1c** (R^3= OMe, Entry 3), whose protecting groups are the same, except for at R^3.

Reaction of bromide **3n** and N^{α}-Phth-Trp-OMe unexpectedly gave compound **8**. The product was characterized by mono- and bi-dimensional NMR and by HRMS (see Supporting Information). Important spectroscopy data for compound **8** are the lack of Br, the α-proton of the Trp, and the fact that the two protons of the cyclopropane CH_2 (2d, J = 15.4 Hz, at δ 3.43 and 3.91 ppm) only exhibit a geminal coupling constant. The significant difference in the chemical shift of the α-proton of the Ala in **3n** (δ 5.02 ppm) and that of the Ala in **8** (δ 4.11 ppm) could be justified by the different electronic effects in each compound. One hypothetical mechanism for formation of **8** begins with deprotonation of the C^2 of the HPI, made possible by the basic conditions, followed by intramolecular bromine displacement and subsequent formation of cyclopropane, to afford intermediate **B** (see Figure 5). The high strain in **B** could drive opening of the aminal and subsequent cyclization, to give a more relaxed cyclohexane (see Figure 5).

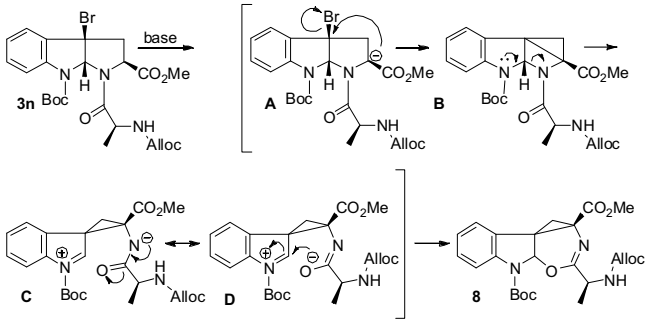


Figure 5. Hypothetical mechanism for formation of **8**.

This is the first time that the authors of this paper have isolated a compound such as **8** after the nucleophilic substitution reaction with the aforementioned conditions. Recently, J.D. Rainier *et al.* have reported the behavior of **3c** under basic conditions of KO*t*Bu and have isolated a tetracycle-containing compound that resembles **B**.[27]

Conclusions

In conclusion, various analogs of 3a-bromo-1,2,3,4,4a,8,8a-hexahydropyrrolo[2,3-*b*]indole-2-carboxylate (**3**), protected with different combinations of three orthogonal protecting groups, were prepared by two different routes. The routes were then compared for performance. Method A, based on sequential cyclization, protection and bromination, provided the thermodynamic *endo*-compound; whereas Method B, based on *one pot* bromination-cyclization of a fully protected Trp, afforded mainly the kinetic *exo*-bromide. The influence of the protecting groups on formation of the *N*-C^{3a} bond between the Trp and HPI to give compounds **1f**, **1g**, and **1i** (containing five orthogonal protecting groups) and compounds **1a**, **1d**, **1e** and **1j** (containing four orthogonal protecting groups) also was evaluated. Some of these compounds contain a protected Ile as the R^4 to protect the α-amino Trp; the orthogonal protecting groups enable synthetic versatility for constructing more structurally complex molecules. The protecting groups in the bromides **3** determined the yields of compounds **1a**, **1c**, **1d** and **1j**, whose starting N^{α}-Phth-Trp-OMe **7** is the same. Moreover, the importance of the carbamate protecting group at R^2 should be emphasized: unexpectedly, compound **5** was obtained from an attempted cyclization of **4** in acidic medium (using an Ala amide bond for protecting the N in **4**) and compound **8** was obtained from an attempted nucleophilic substitution of the bromine at C^{3a} of **3n**.

Experimental Section

General procedure for the synthesis of 1: A solution of **6** (3.0 mmol) in dry DMF (10 mL) was added to a suspension of 60% NaH in mineral oil (1.2 eq.) in dry DMF (20 mL), and the resulting mixture was stirred at room temperature for 15 min. A solution of **3** (3.0 mmol) in dry DMF (10 mL) was then added. The mixture was stirred at 70 °C for 1.5 h. The reaction mixture was then cooled to room temperature and quenched with H_2O. The aqueous phase was saturated with NaCl and extracted with EtOAc. The organic solution was dried over anhyd. Na_2SO_4. The solvent was removed, and the residue was purified by column chromatography on silica gel to afford **1**.

Compound 1a: Purified by flash chromatography (hexane/EtOAc, from 90:10 to 50:50), *endo*:*exo* (57:43) mixture. ^{1}H-NMR (400 MHz, $CDCl_3$): δ (ppm) 1.48 and 1.49 (2s, 9H); 2.82 and 2.92 (2d, J = 13.0 Hz, 1H); 3.17 and 3.21 (2s, 3H); 3.33-3.45 (m, 1H); 3.49-3.68 (m, 2H); 3.76 (s, 3H); 4.59-4.74 (m, 2H); 4.88 (t, J = 9.8 Hz, 1H); 5.08-5.16 (m, 1H); 5.17-5.31 (m, 2H); 5.85-5.99 (m, 1H); 6.62-6.88 (m, 3H); 6.95-7.14 (m, 4H); 7.30 (dd, J = 7.4 and 14.8 Hz, 1H); 7.57 (t, J = 6.8 Hz, 1H); 7.68 (dd, J = 3.1 and 5.5 Hz, 1H); 7.71 (dd, J = 3.0 and 5.6 Hz, 1H); 7.73-7.79 (m, 3H). ^{13}C-NMR (100 MHz, $CDCl_3$): δ (ppm) 24.4 (t); 28.1 (3q); 38.1 (t); 52.2 (q); 52.3 (d); 52.5 and 52.8 (q); 53.4 (s); 59.3 and 59.4 (d); 66.6 (t); 79.6 (d); 82.2 (2s); 110.6 (s); 111.2 and 111.3 (d); 117.6 and 117.7 (t); 119.2 and 119.3 (d); 120.0 (d); 122.3 and 122.4 (d); 123.4 (4d); 124.4 and 124.7 (d); 129.7 (s); 129.8 (s); 130.9 (d); 131.6 (s); 131.7 (s); 132.5 (d); 134.0 (3d); 134.7 (s); 143.3 (s); 143.4 (s); 151.8 (s); 151.9 (s); 167.2 (s); 167.4 (s); 169.4 (s); 170.6 (s). IR (KBr): ν (cm^{-1}) 2952, 1716, 1390, 1255, 1158, 1019, 721. HRMS (ESI) calculated for $C_{41}H_{40}N_4O_{10}Na$ *m/z* ($M+Na^+$) 771.2642, found 771.2634.

Compound 1b: Purified by flash chromatography (hexane/EtOAc, from 80:20 to 50:50). ^{1}H-RMN (400 MHz, $CDCl_3$): δ (ppm) 1.50 (s, 9h); 1.52 (s, 9H); 2.98-3.20 (m, 3H); 3.23 (s, 3H); 3.54-3.65 (m, 7H); 4.60 (m, 1H); 4.90 (bs, 1H); 5.19 (t, J = 8.3 Hz, 1H); 6.69 (d, J = 7.3 Hz, 1H); 6.75 (s, 1H); 7.07-7.33 (m, 5H); 7.35-7.42 (m, 1H); 7.52 (t, J = 7.5 Hz, 1H); 7.67 (bs, 1H). ^{13}C-RMN (100 MHz, $CDCl_3$): δ (ppm) 27.6 (t); 28.2 (3q); 28.3 (3q); 38.4 (t); 52.2 (q); 52.3 (q); 52.4 (q); 54.5 (d); 59.4 (d); 72.5 (s); 79.8 (d); 81.6 (s); 82.4 (s); 109.3 (s); 111.6 (d); 119.4 (d); 120.2 (2d); 122.5 (d); 123.6 (d); 124.9 (d); 125.3 (d); 130.2 (s); 131.0 (d); 131.1 (s); 134.8 (s); 143.5 (s); 152.2 (s); 156.6 (s); 164.3 (s); 171.5 (s); 172.3 (s). IR (KBr): ν (cm^{-1}) 3352, 2978, 1719, 1394, 1368, 1158, 740. HRMS (ESI+) calculated for $C_{36}H_{45}N_4O_{10}$ *m/z* ($M+H^+$) 693.3130, found 693.3118.

Compound 1c: Purified by flash chromatography (MeCN/H_2O, from 30:70 to 90:10). ^{1}H-RMN (400 MHz, $CDCl_3$): δ (ppm) 1.46 and 1.48 (2s, 9H); 1.50 and 1.52 (2s, 9H); 2.77 and 2.90 (2d, *J* = 12.9 Hz, 1H); 3.17 and 3.21 (2s, 3H); 3.38 (dd, *J* = 9.3 and 12.9 Hz, 1H); 3.50-3.66 (m, 2H); 3.76 (s, 3H); 4.83 (bs, 1H); 5.08-5.18 (m, 1H); 6.64-6.75 (m, 3H); 6.82 (t, *J* = 7.6 Hz, 1H); 7.03-7.14 (m, 4H); 7.24-7.31 (m, 1H); 7.57 (dd, *J* = 7.6 and 7.8 Hz, 1H); 7.66-7.79 (m, 4H). ^{13}C-RMN (100 MHz, $CDCl_3$): δ (ppm) 24.4 (t); 28.2 (3q); 28.3 (3q); 38.8 (t); 52.1 (q); 52.6 (d); 52.8 (q); 59.3 (d); 72.4 (s); 79.6 (d); 79.7 (s); 82.0 (s); 110.4 (s); 111.4 (d); 119.2 (d); 119.9 (d); 122.3 (d); 123.1 (d); 123.4 (2d); 124.4 (d); 124.7 (d); 125.0 (d); 128.9 (s); 129.7 (s); 130.8 (d); 131.7 (s); 134.0 (s and 2d); 134.7 (s); 143.5 (s); 151.8 (2s); 167.2 (s); 167.4 (s); 169.4 (s); 171.0 (s). IR (KBr): ν (cm^{-1}) 2977, 1716, 1390, 1255, 1158, 1019, 739, 721. HRMS (ESI+) calculated for $C_{42}H_{45}N_4O_{10}$ *m/z* ($M+H^+$) 765.3130, found 765.3091.

Compound 1d: Purified by flash chromatography (hexane/EtOAc, from 90:10 to 50:50), *endo*:*exo* (69:31) mixture. ^{1}H-NMR (400 MHz, $CDCl_3$): δ (ppm) 1.45 (s, 9H); 2.80 (d, *J* = 13.0 Hz, 1H); 3.16 and 3.20 (2s, 3H); 3.37 (dt, *J* = 9.3 and 13.0 Hz, 1H); 3.49-3.68 (m, 2H); 3.76 (s, 3H); 4.88 (t, *J* = 10.6 Hz, 1H); 5.07-5.30 (m, 3H); 6.62-6.89 (m, 3H); 7.02-7.10 (m, 4H); 7.26-7.36 (m, 6H); 7.54-7.61 (m, 1H); 7.66 (dd, *J* = 3.1 and 5.5 Hz, 1H); 7.70 (dd, *J* = 3.1 and 5.5 Hz, 1H); 7.74 (dd, *J* = 3.1 and 5.5 Hz, 1H); 7.76 (dd, *J* = 3.1 and 5.5 Hz, 2H). ^{13}C-NMR (400 MHz, $CDCl_3$): δ (ppm) 24.4 (t); 28.1 (3q); 38.3 (t); 52.2 (q); 52.5 (d); 52.8 (q); 59.4 (d); 67.5 (t); 72.4 (s); 79.7 (d); 82.2 (s); 110.5 (s); 111.3 (d); 119.2 (d); 120.0 (d); 122.4 (2d); 123.4 (4d); 124.6 (d); 127.8 (d); 128.0 (d); 128.4 (3d); 129.7 (s); 130.9 (d); 131.6 (s); 134.0 (2d); 134.7 (s); 136.2 (s); 143.2 (s); 143.4 (s); 151.8 (s); 167.2 (s); 167.3 (s); 169.4 (s); 169.4 (s); 170.6 (s). IR (KBr): ν (cm^{-1}) 2952, 1716, 1389, 1255, 1158, 1020, 721. HRMS (ESI) calculated for $C_{45}H_{42}N_4O_{10}Na$ *m/z* ($M+Na^+$) 821.2799, found 821.2804.

Compound 1e: Purified by flash chromatography (hexane/EtOAc, from 70:30 to 60:40). ^{1}H-RMN (500 MHz, $CDCl_3$): δ (ppm) 2.81-2.95 (m, 1H); 2.98 (d, *J* = 13.4 Hz, 1H); 3.07 (ddd, *J* = 5.0, 5.4 and 14.8 Hz, 1H); 3.27 (s, 3H); 3.57 and 3.63 (2s, 3H); 3.62-3.68 (m, 1H); 4.06-4.17 and 4.59-4.67 (2m, 1H); 4.74-4.82 and 5.27-5.33 (2m, 1H); 4.50-4.57 (m, 3H); 4.96-5.08 (m, 1H); 5.09-5.30 (m, 3H); 5.80-5.96 (m, 1H); 6.32 and 6.43 (2s, 1H); 6.80 and 6.93 (2d, *J* = 13.7 Hz, 1H); 7.10 (dd, *J* = 7.6 and 8.1 Hz, 1H); 7.12-7.18 (m, 2H); 7.21 (bs, 1H); 7.37 (bs, 1H); 7.39-7.49 (m, 4H); 7.52-7.59 (m, 1H); 7.62 (dd, *J* = 2.9 and 8.1 Hz, 1H); 7.86 (bs, 1H). ^{13}C-RMN (125 MHz, $CDCl_3$): δ (ppm) 27.7 and 27.8 (t); 37.9 (t); 52.3 (q); 52.6 (q); 54.1 and 54.4 (d); 59.4 and 60.1 (d); 65.8 (t); 72.9 and 74.0 (s); 74.6 and 75.3 (t); 81.0 and 81.7 (d); 94.8 and 95.3 (s); 109.3 (s); 110.9 (d); 117.8 and 117.9 (t); 119.7 (d); 119.8 (d); 120.5 (d); 122.8 (d); 124.0 and 124.2 (d); 124.8 (d); 125.8 (d); 126.2 (d); 126.5 (s); 129.7 (d); 130.2 (s); 130.5 (s); 131.5 (d); 132.1 (d); 132.6 (d); 133.3 (d); 133.8 and 133.9 (s); 143.0 and 143.1 (s); 147.3 (s); 151.6 and 152.6 (s); 155.4 and 155.5 (s); 169.9 (s); 171.9 and 172.0 (s). IR (KBr): ν (cm^{-1}) 3369, 2953, 1733, 1545, 1402, 1368, 1231, 1174, 1055, 852, 740, 580. HRMS (ESI+) calculated for $C_{37}H_{35}N_5O_{12}SCl_3$ *m/z* ($M+H^+$) 878.1063, found 878.1059.

Compound 1f: Purified by flash chromatography (MeCN/H_2O, from 0:100 to 70:30). ^{1}H-RMN (400 MHz, $CDCl_3$): δ (ppm) 1.22 and 1.34 (2s, 9H); 2.74-3.11 (m, 3H); 3.27 (s, 3H); 3.49-3.68 (m, 1H); 4.45 (bs, 1H); 4.49-4.58 (m, 2H); 4.59-4.84 (m, 2H); 5.02 (bs, 1H); 5.09-5.33 (m, 3H); 5.79-5.96 (m, 1H); 6.36 and 6.46 (2s, 1H); 6.82 and 6.94 (2d, *J* = 18.7 Hz, 1H); 7.04-7.25 (m, 4H); 7.29-7.58 (m, 6H); 7.62 (d, *J* = 8.3 Hz, 1H); 7.75-7.97 (m, 1H). ^{13}C-RMN (100 MHz, $CDCl_3$): δ (ppm) 27.8 and 28.0 (3q); 27.9 (t); 37.9 (t); 52.6 (q); 54.4 and 54.6 (d); 59.4 (d); 65.7 (t); 74.6 (s); 75.3 (t); 81.6 (s); 82.2 (d); 109.5 (s); 110.8 (d); 117.8 (t); 119.8 (d); 120.2 (d); 120.5 (d); 122.7 (d); 124.2 (d); 124.6 (d); 125.8 (d); 126.3 (s); 126.7 (d); 129.7 (d); 130.5 (s); 131.7 (d); 132.1 (d); 132.7 (d); 133.3 (d); 133.7 (s); 137.9 (s); 143.1 (s); 147.4 (s); 155.6 (s); 155.7 (s); 169.9 (s); 170.6 (s). IR (KBr): ν (cm^{-1}) 3419, 2979, 1733, 1545, 1368, 1230, 1173, 1129, 1055, 740, 581. HRMS (ESI+) calculated for $C_{40}H_{41}N_5O_{12}SCl_3$ *m/z* ($M+H^+$) 920.1538, found 920.1578.

Compound 1g: Purified by flash chromatography (hexane/EtOAc, 60:40). ^{1}H-NMR (400 MHz, $CDCl_3$): δ (ppm) 0.81-0.88 (m, 6H); 1.00-1.12 (m, 1H); 1.31 (s, 9H); 1.39 (bs, 1H); 1.72-1.82 (m, 1H); 2.67 (dd, J = 4.7 and 14.7 Hz, 1H); 2.82 (d, J = 13.3 Hz, 1H); 3.08 (dd, J = 5.9 and 14.7 Hz, 1H); 3.21 (s, 3H); 3.50 (m, 1H); 3.83 (s, 3H); 3.89 (dd, J = 6.6 and 8.4 Hz, 1H); 4.54 (m, 2H); 4.64 (m, 1H); 4.92 (bs, 1H); 5.21 (d, J = 10.5 Hz, 1H); 5.26-5.34 (m, 2H); 5.83 (bs, 1H); 5.84-5.96 (m, 1H); 6.10 (d, J = 7.7 Hz, 1H); 6.70 (bs, 1H); 6.90 (t, J = 7.8 Hz, 2H); 7.15 (bs, 2H); 7.16-7.22 (m, 2H); 7.23-7.35 (m, 4H); 7.50 (t, J = 7.3 Hz, 2H); 7.77 (d, J = 8.0 Hz, 1H). ^{13}C-NMR (100 MHz, $CDCl_3$): δ (ppm) 11.4 (q); 15.3 (q); 24.7 (t); 27.6 (t); 28.0 (3q); 37.2 (t); 37.8 (d); 52.3 (q); 53.3 (q and d); 59.2 (d); 59.5 (d); 65.8 (t); 73.4 (s); 81.9 (s); 82.1 (d); 109.2 (s); 110.9 (d); 117.7 (t); 119.9 (2d); 120.5 (d); 122.7 (d); 124.3 (d); 125.7 (d); 126.4 (2d); 126.7 (d); 128.5 (2d); 130.3 (s); 130.6 (s); 131.7 (d); 132.2 (d); 132.7 (d); 133.5 (s); 138.2 (s); 143.2 (s); 154.8 (s); 155.9 (s); 170.1 (s); 170.5 (s); 170.6 (s). IR (KBr): ν (cm^{-1}) 3367, 2954, 1721, 1447, 1363, 1170 cm^{-1}. HRMS (ESI) calculated for $C_{45}H_{54}N_5O_{11}S$ *m/z* ($M+H^+$) 872.3541, found 872.3557.

Compound 1h: Purified by flash chromatography (hexane/EtOAc, 60:40). ^{1}H-NMR (400 MHz, $CDCl_3$): δ (ppm) 2.66 (dd, *J* = 9.5 and 5.3 Hz, 1H); 2.79 (d, *J* = 13.3 Hz, 1H); 3.03-3.14 (m, 1H); 3.20 (s, 3H); 3.42-3.54 (m, 1H); 3.58-3.68 (m, 6H); 3.84 (s, 3H); 4.42-4.57 (m, 1H); 4.91 (bs, 1H); 5.10 (d, *J* = 8.1 Hz, 1H); 5.73 (s, 1H); 6.71 (bs, 1H); 6.87 (t, *J* = 7.5 Hz, 2H); 7.12-7.35 (m, 5H); 7.43-7.58 (m, 3H); 7.80 (bd, *J* = 7.8 Hz, 1H). ^{13}C-NMR (100 MHz, $CDCl_3$): δ (ppm) 28.0 (t); 37.5 (t); 52.5 (3q); 53.5 (q); 54.8 (d); 59.4 (d); 73.6 (s); 82.1 (d); 109.4 (s); 111.2 (d); 119.8 (d); 120.2 (d); 120.7 (d); 123.0 (d); 124.3 (d); 124.5 (s); 125.8 (s); 126.6 (2d); 126.8 (d); 128.7 (2d); 130.5 (s); 132.1 (2d); 132.4 (d); 133.7 (s); 138.3 (s); 143.5 (s); 156.5 (s); 170.6 (s); 172.3 (s). IR (KBr): ν (cm^{-1}) 3328, 2964, 1722, 1676, 1448, 1368, 1170. HRMS (ESI) calculated for $C_{34}H_{35}N_4O_{10}S$ *m/z* ($M+H^+$) 691.2074, found 691.2079.

Compound 1i: Purified by flash chromatography (MeCN/H_2O, from 30:70 to 50:50). ^{1}H-NMR (400 MHz, $CDCl_3$): δ (ppm) 0.84 (m, 6H); 1.07 (m, 1H); 1.18 (s, 9H); 1.40 (s, 10H); 1.80 (m, 1H); 2.80 (m, 2H); 3.10 (dd, *J* = 5.9 and 14.6 Hz, 1H); 3.50 (dd, *J* = 10.1 and 13.4, 1H); 3.81 (s, 3H); 3.85 (m, 1H); 4.41 (dd, *J* = 5.7 and 13.2 Hz, 1H); 4.51 (dd, *J* = 5.7 and 13.2 Hz, 1H); 4.70-4.87 (m, 2H); 5.10 (bs, 1H); 5.20 (m, 2H); 5.70 (m,1H); 5.78 (bs, 1H); 6.20 (d, *J* = 7.0 Hz, 1H) 6.65 (bs, 1H); 6.85 (t, *J* = 7.6, 2H); 7.25 (m, 8H); 7.50 (m, 2H); 7.80 (d, *J* = 7.6 Hz, 1H). ^{13}C-NMR (100 MHz, $CDCl_3$): δ (ppm) 11.6 (q); 15.4 (q); 24.7 (t); 27.7 (3q); 28.2 (t); 28.4 (3q); 31.5 (q); 36.6 (q); 37.3 (t); 37.7 (d); 53.2 (d); 59.1 (d); 60.0 (d); 66.0 (t); 79.8 (s); 82.1 (d); 82.3 (s); 109.0 (d); 111.1 (d); 118.8 (t); 119.6 (d); 120.1 (s); 120.6 (d); 122.8 (d); 124.4 (d); 126.0 (d); 126.5 (d); 126.6 (d); 128.6 (2d); 130.4 (d); 131.0 (s); 131.4 (d); 131.7 (d); 132.3 (d); 133.7 (s); 138.3 (s); 141.7 (s); 143.2 (s); 145.0 (s); 155.6 (s); 162.7 (s); 168.8 (s); 171.0 (s); 171.3 (s). IR (KBr): ν (cm^{-1}) 3323, 2965, 2929, 1716, 1448, 1367, 1171. HRMS (ESI) calculated for $C_{48}H_{60}N_5O_{11}S$ *m/z* ($M+H^+$) 914.4010, found 914.3986.

Compound 1j: Purified by flash chromatography (hexane/EtOAc 70:30) ^{1}H-NMR (400 MHz, $CDCl_3$): δ (ppm) 0.85-1.03 (m, 6H); 1.13 (dd, *J* = 3.2 and 6.7 Hz, 2H); 1.54 (s, 9H); 1.56 (s, 9H); 2.52 (bs, 1H); 2.68-2.90 (m, 1H); 2.97-3.15 (m, 1H); 3.54-3.66 (m, 2H); 3.77 (s, 3H); 3.94-4.07 (m, 1H); 4.49-4.73 (m, 3H); 5.08-5.31 (m, 3H); 5.75-5.90 (m, 1H); 6.50 (d, *J* = 7.7 Hz, 1H); 6.65 (d, *J* = 11.2 Hz, 1H); 6.75 (d, *J* =9.2 Hz, 1H); 6.87-7.18 (m, 5H); 7.33-7.41 (m, 1H); 7.61 (dd, *J* = 6.1 and 7.4 Hz, 1H); 7.66-7.83 (m, 5H); 7.87-8.01 (bs, 1H). ^{13}C-NMR (100 MHz, $CDCl_3$): δ (ppm) 10.7 and 11.3 (q); 15.8 and 16.8 (q); 24.3 (t); 25.8 and 27.4 (t); 28.2 (6q); 34.1 and 34.4 (d); 39.9 (t); 52.2 and 52.3 (d); 52.8 (q); 56.8 and 58.2 (d); 61.2 (d); 61.5 (s); 66.3 (t); 78.4 (d); 78.7 (s); 83.1 (2s); 109.7 (s); 110.7 (d); 111.0 (d); 116.0 and 116.1 (d); 118.8 (t); 119.4 (d); 120.3 (d); 122.8 (d); 123.3 (d); 123.4 (d); 123.5 and 123.6 (s); 124.5 (2d); 126.4 (s); 129.9 (s); 131.4 (d); 131.5 (d); 131.7 (s); 134.1 (2d); 134.3 (s); 134.4 (s); 151.2 (s); 167.1 (s); 167.3 (s); 168.0 (s); 168.1 (s); 169.3 (2s). IR (KBr): ν (cm^{-1}) 3413, 2969, 1718, 1483, 1455, 1388, 1253, 1162, 1019, 739, 720. HRMS (ESI+) calculated for $C_{46}H_{49}N_5O_{11}$ *m/z* (M–*t*Bu) 847.3429, found 847.3658.

Supporting Information (see footnote on the first page of this article)

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[20] Column: Waters XBridge C_{18} (75 x 4.6 mm, 2.5 µm); eluent and gradient: MeCN/H_2O (from 30:70 to 100:0 in 8 minutes).

[21] Several reaction conditions were tested to remove the Moc group from methyl N^1-(methoxycarbonyl)-N^8-(phenylsulphonyl)HPI-2-carboxylate (**S6**, see Supporting Information): the reagents comprised LiOH, LiSBn, $LiSCH_2CH_2OH$ or TMSI; the solvents tested were THF, H_2O, 1,4-dioxane, MeOH and HMPA; and the temperatures, from rt to solvent reflux temperature. Several of these tests were performed on MW.

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[25] The 3D model of Br-HPI ***endo-*** and ***exo*-3g** was calculated with Gaussian® 03W V 6.0 (Gaussian Inc.) and built with ChemBio3D V 11.0 (CambridgeSoft).

[26] Base-solvent pairs such as NaH/THF, NaHMDS/THF, K*t*BuO/MeCN or proton sponge/THF did not provide better yields.

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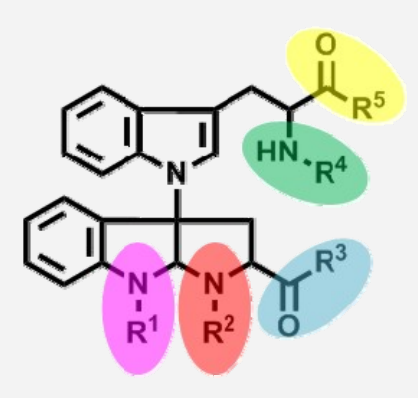
Entry for the Table of Contents

Layout 1:

Trp-HPI

Several Tryptophanyl-Hexahydropyrroloindoles (Trp-HPI) with four or five orthogonal protecting groups have been synthesized. This polyheterocyclic system is the scaffold of many natural products, recently isolated.



Pau Ruiz-Sanchis, Svetlana A. Savina, Gerardo A. Acosta, Fernando Albericio,* and Mercedes Álvarez*

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Orthogonal Protecting Groups in the Synthesis of Tryptophanyl-Hexahydropyrroloindoles

Keywords: Natural products / Heterocycles / Amino acids / Protecting groups

Supporting Information

Orthogonal Protecting Groups in the Synthesis of Tryptophanyl-Hexahydropyrroloindoles

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General data

Reagents and solvents were purified according to *Purification of Laboratory Chemicals* (Armarego, W. and Chai, C.; Elsevier; 2003). Automatic flash chromatography was done in an Isco Combiflash medium pressure liquid chromatograph with Redisep silica gel columns (47-60 μm). ^{1}H- and ^{13}C-NMR spectra were recorded on a Varian Mercury 400 MHz. Multiplicity of the carbons was assigned with DEPT and gHSQC experiments, although standard abbreviations according to off-resonance decoupling are used here: (s) singlet, (d) doublet, (t) triplet and (q) quartet. For ^{1}H-NMR, the following additional abbreviations are used: (m) multiplet, (bs) broad singlet and (bd) broad doublet. Spectra were referenced to the residual solvent peak of $CDCl_3$. IR spectra were obtained on a Thermo Nicolet FT-IR spectrometer. HRMS was performed on an Acquity UPLC Binary Sol MGR (Waters-Corporation) by the Mass Spectrometry Core Facility at the IRBB. Analytical HPLC was performed on a Waters Alliance 2695 separation module equipped with a Waters 996 PDA detector (λ = 254 nm) and Waters XBridge C_{18} column (75 x 4.6 mm, 2.5 μm), in runs of 8 min. Microwave-assisted reactions were carried out in a CEM Discover microwave oven.

Experimental section

N^{α}-Protection of L-Trp-OMe (R^2= Alloc, Boc, Cbz, Moc, Troc, N^{α}-Alloc-Ala)

A solution of L-Trp-OMe·HCl (5.4 g, 21.2 mmol) and Et_3N (2.9 mL, 21.2 mmol) in dry CH_2Cl_2 (85 mL) was added to a solution of either di-*tert*-butyldicarbonate (5.5 g, 25.4 mmol) or an appropriate chloroformate (1.5 eq) in CH_2Cl_2 (3 mL/mmol). The reaction mixture was stirred for 2 h at rt. The organic solution was washed with brine, and then dried over Na_2SO_4. The solvent was removed, and the crude was purified by flash chromatography (hexanes/EtOAc) to afford the desired product in 80 to 99% yield.

If R^2= N^{α}-Alloc-Ala. A solution of Alloc-Ala-OH dicyclohexylamine salt (4.1 g, 11.7 mmol), EDC·HCl (2.3 g, 11.9 mmol) and HOBt (1.6 g, 11.9 mmol) in dry CH_2Cl_2 (20 mL) was added to a solution of Trp-OMe (2.9 g, 11.5 mmol) and DIEA (4.2 mL, 24.1 mmol) in dry CH_2Cl_2 (16 mL). The mixture was stirred for 4 h at rt. The organic solution was washed with sat. NH_4Cl, 10% $NaHCO_3$, water and brine, dried over Na_2SO_4, and then concentrated. The resulting crude was purified by flash chromatography (CH_2Cl_2/MeOH, 99:1) to obtain the desired product in 58% yield.

Syntheses of N^{α}-protected-Trp-O*t*Bu analogs (2f, 2h, 2k, 2m; R^1= H)

Hydrolysis of the methyl ester. N^{α}-protected-Trp-methyl ester (9.9 mmol) was dissolved in 10:1 THF/H_2O (168 mL) and 2M LiOH (15 mL, 30,0 mmol), and the solution was stirred at rt for 3 h. The solution was then diluted with water and subsequently brought to pH 5 by dropwise addition of 2N HCl. The aqueous solution was saturated with NaCl and the phases were separated. The aqueous layer was extracted with THF. The combined organic layers were dried over Na_2SO_4 and concentrated *in vacuo* to give the carboxylic acid in quantitative yield.

Formation of the tert-butyl ester. A mixture of N^{α}-protected-Trp (8.4 mmol), $BnEt_3NCl$ (1.9 g, 8.4 mmol) and K_2CO_3 (7.6 g, 54.7 mmol) in MeCN (25 mL) was vigorously stirred for 5 h. *t*-BuBr (9.9 mL, 88.4 mmol) was then added, and the solution was heated at 50 ºC for 2 h. The reaction mixture was treated with MeCN (13 mL), and then stirred for 24 h. The solvent was evaporated off and the resulting solid was dissolved in 2:1 EtOAc/H_2O. The aqueous solution was extracted with EtOAc. The combined organic layers were washed with brine and dried over Na_2SO_4. The solvent was removed to give the *tert*-butyl N^{α}-protected-Trp carboxylates **2f** (84%), **2k** (84%), **2h** (55%) or **2m** (58%).

Syntheses of N^{α},N^{i}-protected-Trp-alkyl esters (2a-2n)

Compounds **2c**[1] and **2l**[2] have previously been reported.

N^{α}-Protected-Trp alkyl ester (13.3 mmol), Bu_4NHSO_4 (0.4 g, 1.3 mmol) and crushed NaOH (1.6 g, 39.9 mmol) were mixed in CH_2Cl_2 (26 mL). Di-*tert*-butyl dicarbonate (4.3 g, 19.9 mmol) was then added slowly, and the resulting mixture was stirred for 15 h at rt. The solvent was evaporated off, the crude was dissolved in 1:1 sat. NH_4Cl/EtOAc and extracted with EtOAc. The organic layer was washed with H_2O and dried over Na_2SO_4. The solvent was removed, and the crude was purified by flash chromatography (hexanes/EtOAc, 80:20 to 60:40) to give **2a** (68%), **2d** (32%), **2e** (42%) or **2n** (16%).

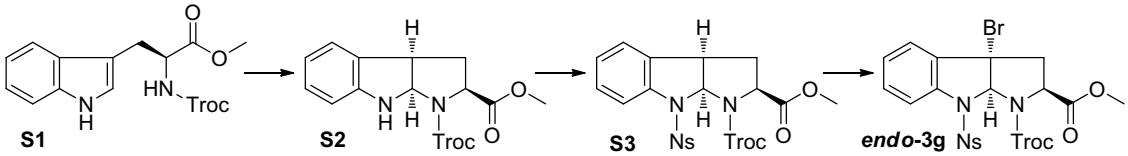
For Nosyl protection, either N^{α}-Cbz-Trp-OtBu, N^{α}-Troc-Trp-OMe or N^{α}-Troc-Trp-O*t*Bu (2.5 mmol) was treated with 2-nitrobenzenesulfonyl chloride (0.7 g, 3.1 mmol), which provided the corresponding 8-(2-nitrobenzenesulfonyl) analogs **2f** (80%), **2g** (43%) or **2h** (46%), respectively.

For SO_2Ph protection, either N^{α}-Boc-Trp-OMe, N^{α}-Cbz-Trp-OMe, N^{α}-Cbz-Trp-O*t*Bu, or N^{α}-Moc-Trp-O*t*Bu (23.9 mmol) was treated with $PhSO_2Cl$ (3.7 mL, 28.7 mmol) in CH_2Cl_2 (120 mL). The reaction mixture was stirred for 2 h to give **2i** (87%), **2j** (92%), **2k** (80%) or **2m** (93%), respectively.

Synthesis of 3a-bromo-1,2,3,3a,8,8a-hexahydropyrrolo[2,3-*b*]indole-2-carboxylate (3)

Method A: three-step synthesis for *endo*-3g, *endo*-3l and *endo*-3m

*endo-(2S, 3aS, 8aS)-Methyl 3a-bromo-8-(2-nitrobenzenesulfonyl)-1-trichloroethylcarbonyl--1,2,3,3a,8,8a-hexahydropyrrolo[2,3-b]indole-2-carboxylate (**endo-3g**)*

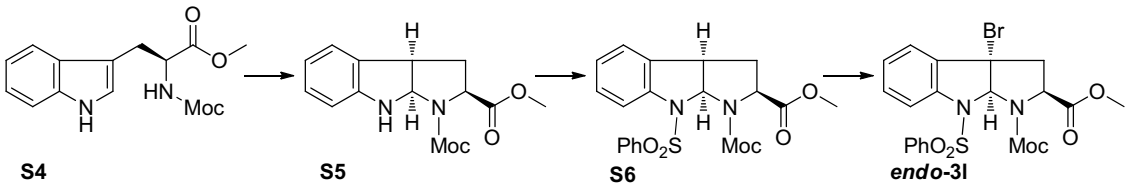


A solution of N^{α}-Troc-Trp-OMe (1.0 g, 2.5 mmol) and trifluoroacetic acid (6.3 mL) was stirred for 30 minutes at rt, and then slowly poured into a mixture of CH_2Cl_2 (30.5 mL) and 15% Na_2CO_3 (76.2 mL). The aqueous layer was extracted with CH_2Cl_2. The combined organic layers were dried over Na_2SO_4. The solvent was removed and the resulting residue was dried *in vacuo* to give **S2** in quantitative yield.

2-Nitrobenzenesulfonyl chloride (2.0 g, 9.2 mmol) was slowly added to a mixture of the previously **S2** (0.9 g, 2.3 mmol) and pyridine (3.0 mL) cooled to 0 ºC and the reaction mixture was stirred at rt for 2 h. The organic solvent was removed *in vacuo* and the residue was dissolved in EtOAc. The organic solution was washed with 2M HCl, 15% Na_2CO_3 and brine, dried over Na_2SO_4 and concentrated *in vacuo*. The resulting residue was purified by flash chromatography (hexanes/EtOAc, 3:1) to give **S3** (0.9 g, 65%).

AIBN (0.1 g, 0.7 mmol) was added to a solution of **S3** (0.9 g, 1.5 mmol) in dry CCl_4 (28 mL) under N_2. The solution was heated to reflux, and then treated with NBS (0.3 g, 1.5 mmol), the resulting mixture was stirred for 2 h. The crude was then cooled to rt and the precipitate was filtered off. The organic layer was concentrated *in vacuo* and the resulting residue was purified by flash chromatography (hexanes/EtOAc, 80:20 to 60:40) to give ***endo*-3g** (0.1 g, 14%). The starting material was recovered.

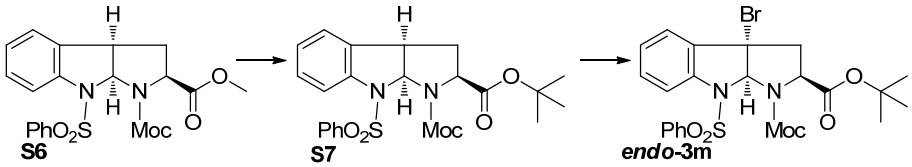
*endo-(2S, 3aS, 8aS)-Methyl 3a-bromo-1-methoxycarbonyl-8-benzenesulfonyl-1,2,3,3a,8,8a-hexahydropyrrolo[2,3-b]indole-2-carboxylate (**endo-3l**).*



[1] S.P. Marsden, K.M. Depew, S.J. Danishefsky; *J. Am. Chem. Soc.*,**1994**, *116*, 11143-11144.
[2] D. Crich, X. Huang; *J. Org. Chem.*, **1999**, *64*, 7218-7223

A solution of N^{α}-Moc-Trp-OMe (1.0 g, 3.6 mmol) and 85% H_3PO_4 (11 mL) was stirred under N_2 at rt for 3 h. The reaction mixture was then slowly poured into a mixture of CH_2Cl_2 (43 mL) and 15% Na_2CO_3 (109 mL), and the resulting mixture was extracted with CH_2Cl_2. The combined organic layer was dried over Na_2SO_4. The solvent was removed and the residue was dried *in vacuo* to give **S5** in quantitative yield.
Benzenesulfonyl chloride (0.8 mL, 6.4 mmol) was slowly added to a mixture of **S5** (0.9 g, 3.2 mmol) and pyridine (4 mL) cooled to 0 ºC and the reaction mixture was stirred at rt for 15 h. The organic solvent was then removed *in vacuo* and the residue was dissolved in EtOAc. The organic solution was washed with 2M HCl, 15% Na_2CO_3 and brine, dried over Na_2SO_4 and concentrated *in vacuo*. The resulting residue was purified by flash chromatography (hexanes/EtOAc, 3:1) to give **S6** (1.1 g, 80%).
***endo*-3l** was obtained with 49% yield from **S6** following the same reported method for ***endo*-3g**.

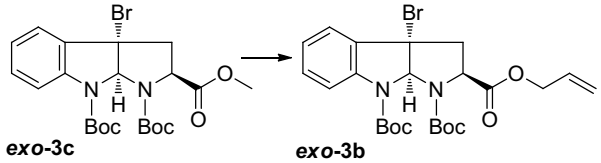
*endo-(2S, 3aS, 8aS)-tert-Butyl 3a-bromo-1-methoxycarbonyl-8-benzenesulfonyl-1,2,3,3a,8,8a-hexahydropyrrolo[2,3-b]indole-2-carboxylate (**endo-3m**).*



To a solution of **S6** (5.0 g, 12.0 mmol) in 10:1 THF/H_2O (204 mL) was added 2M LiOH (12.0 mL, 24.0 mmol). The reaction mixture was stirred at reflux temperature for 2.5 h. The solution was diluted with water and subsequently brought to pH 5 by dropwise addition of 2N HCl. The aqueous solution was saturated with NaCl and extracted with THF. The combined organic layers were dried over Na_2SO_4, and then concentrated *in vacuo* to give the carboxylic acid in quantitative yield.
Following the aforementioned method to generate a *tert*-butyl ester, **S7** was obtained with 81% yield.
***endo*-3m** was obtained in 46% yield from **S7** following the same method reported for ***endo*-3g**.

Method B: One-pot bromocyclization for *exo*-3a, *exo*-(3c-3n)
To a solution of PPTS (1.9 g, 7.4 mmol) and NBS (1.3 g, 7.4 mmol) was added N^{α}-N^{i}-protected-Trp alkyl ester (7.4 mmol) in anhydrous CH_2Cl_2 (67 mL) under N_2. The reaction mixture was stirred at rt for 4 h. The crude mixture was washed with 15% $NaHCO_3$, 10% $Na_2S_2O_4$ and brine, and then dried over Na_2SO_4. The solvent was evaporated off, and the crude was purified by flash chromatography (see the following section for yields and solvent systems).

Synthesis of *exo*-3b



2M LiOH (1.5 mL, 3.0 mmol) was added to a solution of ***exo*-3c** (0.5 g, 1.0 mmol) in 10:1 THF/H_2O (17 mL). The solution was stirred at reflux for 5 h. The solution was then diluted with water and subsequently brought to pH 5 by dropwise addition of 2N HCl. The aqueous layer was saturated with NaCl and extracted with THF. The combined organic layers were dried over Na_2SO_4 and concentrated *in vacuo* to give the carboxylic acid in quantitative yield.
To a solution of the aforementioned acid (0.7 g, 1.5 mmol) in MeOH (10 mL) was added Cs_2CO_3 (0.5 g, 1.6 mmol), and the solution was stirred for 30 min at rt. The reaction mixture was then concentrated, treated with dry DMF (5 mL) and AllylBr (0.25 mL, 3.0 mmol), and finally, stirred at rt for 4 h. The organic solution was diluted with EtOAc and washed with 5% $NaHCO_3$ and brine. The organic phase was dried over $MgSO_4$, and then concentrated *in vacuo*. The resulting residue was purified by flash chromatography (hexanes/EtOAc, 80:20 to 70:30) to give ***exo*-3b** (0.2 g, 30%).

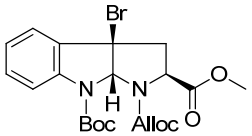
Synthesis of *exo*-3o and *exo*-3p
***exo*-3a** or ***exo*-3c** were hydrolyzed following the aforementioned method for hydrolysis of a methyl ester of ***exo*-3c**.
A solution of DIEA (0.63 mL, 3.6 mmol) and either Ile-OMOM (0.6 g, 3.6 mmol, for ***exo*-3o**) or Ile-OAllyl (0.6 g, 3.6 mmol, for ***exo*-3p**) in CH_2Cl_2 (14 mL) was added to a solution of the acid obtained (3.0 mmol) from either ***exo*-3a**

or ***exo*-3c**, respectively, in CH_2Cl_2 (23 mL). The mixture was stirred at -10 °C for 10 min, and then treated with HBTU (1.1 g, 3.0 mmol), and the resulting mixture was stirred at rt for 21 h. The mixture was washed with 5% $NaHCO_3$, sat. NH_4Cl and brine, dried over Na_2SO_4, and concentrated *in vacuo*. The resulting crude was purified by flash chromatography (hexanes/EtOAc, 70:30) to afford ***exo*-3o** (47%) or ***exo*-3p** (41%).

Compounds Characterization:

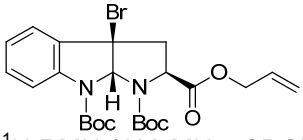
***endo*-3l**,[3] has been reported previously.

exo-Methyl 1-allyloxycarbonyl-3a-bromo-8-(_tert_-butyloxycarbonyl)-1,2,3,3a,8,8a-hexahydropyrrolo[2,3-_b_]indole-2-carboxylate (_exo_-3a).



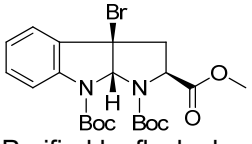
Purified by flash chromatography (hexanes:EtOAc 30:70) 83% yield; *exo*.
^{1}H-RMN (400 MHz, $CDCl_3$): δ (ppm) 1.59 (s, 9H); 2.86 (dd, *J* = 10.3 and 12.7 Hz, 1H); 3.26 (dd, *J* = 6.5 and 12.7 Hz, 1H); 3.74 (s, 3H); 3.97 (dd, *J* = 6.5 and 10.3 Hz, 1H); 4.43-4.70 (m, 2H); 5.14-5.29 (m, 2H); 5.75-5.94 (m, 1H); 6.40 (s, 1H); 7.13 (dd, *J* = 7.5 and 7.6 Hz, 1H); 7.33 (dd, *J* = 7.5 and 8.1 Hz, 1H); 7.37 (d, *J* = 7.6 Hz, 1H); 7.60 (bs, 1H).
^{13}C-RMN (100 MHz, $CDCl_3$): δ (ppm) 28.2 (3q); 41.8 (t); 52.6 (q); 59.5 (d); 59.7 (s); 66.4 (t); 82.3 (s); 83.8 (d); 117.7 (t); 118.4 (d); 123.2 (d); 124.5 (d); 130.8 (d); 132.2 (d); 132.5 (s); 141.3 (s); 152.0 (s); 171.1 (s).
IR (KBr): v (cm^{-1}) 2978, 1717, 1479, 1405, 1334, 1156, 1017, 754.
HRMS (ESI+) calculated for $C_{21}H_{25}BrN_2O_6Na$ *m/z* ($M+Na^+$) 503.0794, found 503.0800.

exo-Allyl 3a-bromo-1,8-di-_tert_-butyloxycarbonyl-1,2,3,3a,8,8a-hexahydropyrrolo[2,3-_b_]indole-2-carboxylate (3b).



^{1}H-RMN (400 MHz, $CDCl_3$): δ (ppm) 1.40 (s, 9H); 1.59 (s, 9H); 2.82 (dd, J = 10.3 and 12.6 Hz, 1H); 3.23 (dd, J = 6.4 and 12.6 Hz, 1H); 3.91 (dd, J = 6.4 and 10.3 Hz, 1H); 4.56-4.70 (m, 2H); 5.23-5.37 (m, 2H); 5.85-5.96 (m, 1H); 6.39 (s, 1H); 7.12 (t, J = 7.6 Hz, 1H); 7.32 (dd, J = 7.6 and 8.0 Hz, 1H); 7.36 (d, 7.6 Hz, 1H); 7.54 (bs, 1H).
^{13}C-RMN (100 MHz, $CDCl_3$): δ (ppm) 28.2 (6q); 41.9 (t); 59.5 (d); 59.7 (s); 66.0 (t); 82.3 (2s); 83.8 (d); 119.0 (t); 123.2 (2d); 124.4 (d); 130.6 (d); 131.5 (d); 133.1 (s); 141.5 (s); 152.2 (s); 171.0 (s).
IR (KBr): v (cm^{-1}) 2979, 1722, 1604, 1479, 1395, 1333, 1256, 1161, 1017, 851, 752.
HRMS (ESI+) calculated for $C_{48}H_{62}Br_2N_4O_{12}Na$ *m/z* ($2M+Na^+$) 1067.2629, found 1067.2601.

exo-Methyl 3a-bromo-1,8-di(_tert_-butyloxycarbonyl)-1,2,3,3a,8,8a-hexahydropyrrolo[2,3-_b_]indole-2-carboxylate (3c)

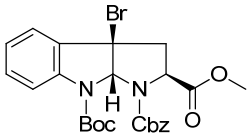


Purified by flash chromatography (hexanes:EtOAc 80:20); 86% yield; *endo*:*exo* 4:96.
^{1}H-RMN (400 MHz, $CDCl_3$): δ (ppm) 1.40 (s, 9H); 1.59 (s, 9H); 2.82 (dd, J = 10.3 and 12.6 Hz, 1H); 3.20 (dd, J = 6.3 and 12.6 Hz, 1H); 3.74 (s, 3H); 3.89 (dd, J = 6.3 and 10.3 Hz, 1H); 6.39 (s, 1H); 7.12 (dd, J = 7.5 and 7.6 Hz, 1H); 7.32 (dd, J = 7.5 and 8.1 Hz, 1H); 7.36 (d, J = 7.6 Hz, 1H); 7.56 (bs, 1H).

[3] M. Bruncko, D. Crich, R. Samy, *J. Org. Chem.* **1994**, *59*, 5543-5549.

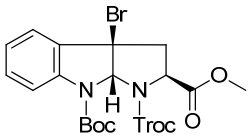
^{13}C-RMN (100 MHz, $CDCl_3$): δ (ppm) 28.5 (3q); 28.6 (3q); 42.2 (t); 52.7 (q); 59.8 (d); 60.1 (s); 81.8 (s); 82.6 (s); 84.1 (d); 119.2 (d); 123.5 (d); 124.7 (d); 130.9 (d); 140.7 (s); 141.9 (s); 152.5 (s); 163.6 (s); 171.8 (s).
IR (KBr): v (cm^{-1}) 2979, 1720, 1394, 1333, 1161, 733.
HRMS (ESI+) calculated for $C_{22}H_{30}BrN_2O_6S$ *m/z* ($M+H^+$) 497.1282, found 497.1276.

exo-Methyl 1-benzyloxycarbonyl-3a-bromo-8-_tert_-butyloxycarbonyl-1,2,3,3a,8,8a-hexahydropyrrolo[2,3-_b_]indole-2-carboxylate (3d)



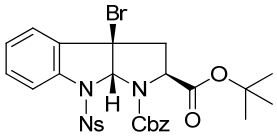
Purified by flash chromatography (hexanes:EtOAc from 90:10 to 70:30); 78% yield; *exo*.
^{1}H-RMN (400 MHz, $CDCl_3$): δ (ppm) 1.54 (bs, 9H); 2.85 (dd, *J* = 10.2 and 12.8 Hz, 1H); 3.26 (dd, *J* = 6.6 and 12.8 Hz, 1H); 3.65 (bs, 3H); 3.98 (dd, *J* = 6.6 and 10.2 Hz, 1H); 5.20 (bs, 2H); 6.43 (s, 1H); 7.13 (t, *J* = 7.5 Hz, 1H); 7.25-7.38 (m, 7H); 7.61 (m, 1H).
^{13}C-RMN (100 MHz, $CDCl_3$): δ (ppm) 28.1 (3q); 41.8 (t); 52.4 (q); 59.5 (d); 59.7 (s); 67.4 (t); 82.4 (s); 83.9 (d); 118.3 (d); 123.2 (d); 124.6 (d); 128.0 (s); 128.4 (4d); 130.8 (2d); 132.5 (s); 141.3 (s); 152.0 (s); 171.1 (s).
IR (KBr): v (cm^{-1}) 2978, 1717, 1478, 1410, 1335, 1157, 1018, 855, 753.
HRMS (ESI+) calculated for $C_{25}H_{27}BrN_2O_6Na$ *m/z* ($M+Na^+$) 553.0950, found 553.0950.

exo-Methyl 1-trichloroethoxycarbonyl-3a-bromo-8-(_tert_-butyloxycarbonyl)-1,2,3,3a,8,8a-hexahydropyrrolo[2,3-_b_]indole-2-carboxylate (3e).



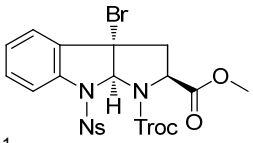
Purified by flash chromatography (hexanes:EtOAc 30:70) 77% yield; *endo:exo* (11:89).
^{1}H-RMN (400 MHz, $CDCl_3$): δ (ppm) 1.61 (s, 9H); 2.88 (dd, *J* = 10.0 and 13.0 Hz, 1H); 3.33 (dd, *J* = 6.5 and 13.0 Hz, 1H); 3.76 (s, 3H); 4.05-4.13 (m, 1H); 4.75 and 4.78 (2s, 2H); 6.45 (bs, 1H); 7.14 (t, *J* = 7.6 Hz, 1H); 7.34 (dd, *J* = 7.6 and 7.9, 1H); 7.38 (d, *J* = 7.6 Hz, 1H); 7.68 (bs, 1H).
^{13}C-RMN (100 MHz, $CDCl_3$): δ (ppm) 29.6 (q); 43.5 (t); 53.7 (s); 54.2 (q); 60.7 (d); 76.5 (t); 84.0 (s); 85.7 (d); 96.1 (s); 119.2 (d); 124.6 (d); 125.2 (s); 125.8 (d); 132.3 (d); 142.6 (s); 153.3 (2s); 172.2 (s).
IR (KBr): v (cm^{-1}) 2979, 1719, 1479, 1401, 1156, 1063, 754, 577.
HRMS (ESI+) calculated for $C_{20}H_{23}BrCl_3N_2O_6$ *m/z* ($M+H^+$) 570.9805, found 570.9791.

exo-tert-Butyl 1-benzyloxycarbonyl-3a-bromo-8-(2-nitrobenzenesulfonyl)-1,2,3,3a,8,8a-hexahydropyrrolo[2,3-_b_]indole-2-carboxylate (3f).



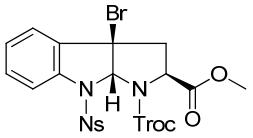
Purified by flash chromatography (hexanes:EtOAc 80:20) 80% yield; *endo:exo* (7:93).
^{1}H-RMN (400 MHz, $CDCl_3$): δ (ppm) 1.34 (s, 9H); 2.80 (dd, *J* = 10.5 and 12.2 Hz, 1H); 3.10-3.19 (m, 1H); 3.79 (bs, 1H); 4.90 and 4.93 (2s, 1H); 5.20 (bs, 1H); 6.54 (s, 1H); 7.25-7.47 (m, 10H); 7.55-7.65 (m, 3H).
^{13}C-RMN (100 MHz, $CDCl_3$): δ (ppm) 27.9 (3q); 43.3 (t); 59.2 (s); 60.3 (d); 67.5 (t); 82.4 (d); 85.4 (s); 119.3 (d); 123.9 (2d); 124.2 (d); 127.0 (s); 128.1 (2d); 128.3 (2d); 128.4 (d); 129.9 (s); 131.1 (d); 131.4 (2d); 134.1 (d); 134.4 (s); 139.8 (s); 148.6 (s); 168.7 (s); 171.1 (s).
IR (KBr): v (cm^{-1}) 2978, 1719, 1546, 1463, 1370, 1217, 1152, 1063, 594.
HRMS (ESI+) calculated for $C_{29}H_{29}BrN_3O_8S$ *m/z* ($M+H^+$) 658.0859, found 658.0856.

***endo*-Methyl 3a-bromo-8-(2-nitrobenzenesulfonyl)-1-trichloroethoxycarbonyl-1,2,3,3a,8,8a-hexahydropyrrolo[2,3-*b*]indole-2-carboxilate (3g)**



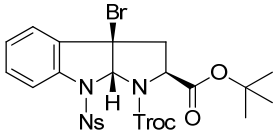
^{1}H-RMN (400 MHz, $CDCl_3$): δ (ppm) 3.08-3.19 (m, 1H); 3.21 (s, 3H); 3.35 (d, *J* = 13.2 Hz, 1H); 4.50 (m, 2H); 4.67 (d, *J* = 8.6 Hz, 1H); 6.59 (s, 1H); 7.21 (t, *J* = 7.2 Hz, 1H); 7.33-7.50 (m, 3H); 7.57 (t, *J* = 7.6 Hz, 1H); 7.69 (t, *J* = 7.6 Hz, 1H); 7.79 (bd, *J* = 7.2 Hz, 1H); 8.03 (bs, 1H).
^{13}C-RMN (100 MHz, $CDCl_3$): δ (ppm) 44.5 (t); 52.5 (q); 58.8 (s); 59.6 (d); 75.0 (t); 86.5 (d); 94.6 (s); 117.9 (d); 121.0 (s); 124.4 (d); 124.8 (d); 125.9 (d); 129.6 (d); 131.4 (d); 132.1 (d); 132.6 (s); 133.6 (d); 134.0 (s); 141.3 (s); 148.0 (s); 169.4 (s); 175.6 (s).
IR (KBr): v (cm^{-1}) 2994, 1736, 1545, 1463, 1376, 1228, 1175, 1048, 852, 767, 583.
HRMS (ESI+) calculated for $C_{21}H_{18}BrCl_3N_3O_8S$ *m/z* ($M+H^+$) 655.9064, found 655.9041.

***exo*-Methyl 3a-Bromo-8-(2-nitrobenzenesulfonyl)-1-trichloroethoxycarbonyl-1,2,3,3a,8,8a-hexahydropyrrolo[2,3-*b*]indole-2-carboxilate (3g)**



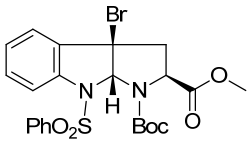
Purified by flash chromatography (DCM); 57% yield; *endo*:*exo* (8:92).
^{1}H-RMN (400 MHz, $CDCl_3$): δ (ppm) 2.90 (dd, *J* = 10.1 and 13.0 Hz, 1H); 3.20 (dd, *J* = 6.2 and 13.0 Hz, 1H); 3.74 (s, 3H); 3.93-4.02 (m, 1H); 4.55 and 4.58 (2s, 2H); 6.60 (s, 1H); 7.30 (dd, *J* = 7.4 and 7.6 Hz, 1H); 7.38 (d, *J* = 7.9 Hz, 1H); 7.43 (dd, *J* = 7.4 and 7.9 Hz, 1H); 7.48 (d, *J* = 7.6 Hz, 1H); 7.57 (d, *J* = 7.3 Hz, 1H); 7.64 (dd, *J* = 7.3 and 8.0 Hz, 2H); 7.73-7.83 (m, 1H).
^{13}C-RMN (100 MHz, $CDCl_3$): δ (ppm) 43.7 (t); 52.8 (q); 58.7 (s); 59.5 (d); 75.1 (t); 86.1 (d); 94.8 (s); 119.6 (d); 123.9 (d); 124.3 (d); 127.2 (d); 130.3 (d); 131.3 (d); 131.4 (d); 132.0 (s); 134.1 (s); 134.3 (d); 139.9 (s); 148.9 (s); 160.1 (s); 169.7 (s).
IR (KBr): v (cm^{-1}) 2955, 1750, 1545, 1464, 1373, 1208, 1177, 1061, 774, 595.
HRMS (ESI+) calculated for $C_{21}H_{18}BrCl_3N_3O_8S$ *m/z* ($M+H^+$) 655.9064, found 655.9045.

***exo*-*tert*-Butyl 3a-bromo-8-(2-nitrobenzenesulfonyl)-1-trichloroethoxycarbonyl-1,2,3,3a,8,8a-hexahydropyrrolo[2,3-*b*]indole-2-carboxylate (3h).**



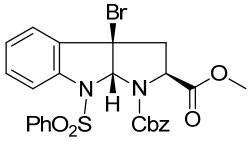
Purified by flash chromatography (hexanes:EtOAc from 80:20 to 70:30) 59% yield; *exo*.
^{1}HRMN (400 MHz, $CDCl_3$): δ (ppm) 1.45 (s, 9H); 2.85 (dd, *J* = 10.5 and 12.4 Hz, 1H); 3.08-3.28 (m, 1H); 3.66-4.08 (m, 1H); 4.22-4.67 (m, 1H); 4.88-5.26 (m, 1H); 6.59 (s, 1H); 7.31 (dd, *J* = 7.4 and 7.5 Hz, 1H); 7.42-7.50 (m, 3H); 7.52-7.71 (m, 4H).
^{13}CRMN (400 MHz, $CDCl_3$): δ (ppm) 28.1 (3q); 43.8 (t); 59.1 (s); 60.7 (d); 74.9 (t); 83.1 (s); 85.5 (d); 95.2 (s); 119.9 (d); 124.2 (d); 124.4 (2d); 127.6 (d); 130.3 (s); 131.6 (2d); 134.5 (d); 137.9 (s); 140.0 (s); 149.0 (s); 167.8 (s); 168.6 (s).
IR (KBr): v (cm^{-1}) 2980, 1741, 1546, 1464, 1371, 1218, 1152, 1062, 851, 773, 595.
HRMS (ESI+) calculated for $C_{24}H_{24}BrCl_3N_3O_8S$ *m/z* ($M+H^+$) 697.9533, found 697.9526.

***exo*-Methyl 8-benzenesulfonyl-3a-bromo-1-*tert*-butoxycarbonyl-1,2,3,3a,8,8a-hexahydropyrrolo[2,3-*b*]indole-2-carboxylate (3i)**



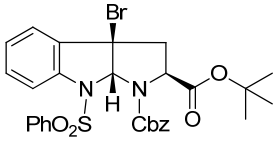
Purified by flash chromatography (hexanes:EtOAc 70:30); 92% yield.
^{1}H-RMN (400 MHz, $CDCl_3$): δ (ppm) 1.54 (bs, 9H); 2.77 (dd, *J* = 10.4 and 12.6 Hz, 1H); 3.06 (dd, *J* = 6.0 and 12.6 Hz, 1H); 3.73 (s, 3H); 3.83 (dd, *J* = 6.0 and 10.4 Hz, 1H); 6.32 (bs, 1H); 7.17 (dd, *J* = 7.5 and 8.0 Hz, 1H); 7.24-7.28 (m, 1H); 7.34 (dd, *J* = 7.1 and 7.5 Hz, 3H); 7.46 (t, J = 7.5 Hz, 1H); 7.57 (d, *J* = 8.0 Hz, 1H); 7.82 (bs, 2H).
^{13}C-RMN (100 MHz, $CDCl_3$): δ (ppm) 28.3 (3q); 43.2 (t); 52.5 (q); 58.6 (s); 59.5 (d); 86.7 (d); 88.9 (s); 118.8 (d); 123.9 (d); 126.4 (d); 128.3 (2d); 128.6 (2d); 129.3 (s); 130.9 (d); 133.4 (d); 134.1 (s); 140.3 (s); 170.8 (s).
IR (KBr): v (cm^{-1}) 2979, 1752, 1702, 1448, 1367, 1032, 1171, 733.
HRMS (ESI+) calculated for $C_{23}H_{26}BrN_2O_6S$ *m/z* ($M+H^+$) 537.0689, found 537.0689.

***exo*-Methyl 8-benzenesulfonyl-1-benzyloxycarbonyl-3a-bromo-1,2,3,3a,8,8a-hexahydropyrrolo[2,3-*b*]indole-2-carboxylate (3j)**



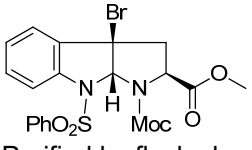
Purified by flash chromatography (hexanes:EtOAc 70:30); 82% yield.
^{1}H-RMN (400 MHz, $CDCl_3$): δ (ppm) 2.78 (dd, *J* = 10.1 and 12.8 Hz, 1H); 3.09 (dd, *J* = 6.3 and 12.8 Hz, 1H); 3.68 (bs, 3H); 3.88 (dd, *J* = 6.3 and 10.1 Hz, 1H); 5.13-5.45 (m, 2H); 6.33 (bs, 1H); 7.18 (dd, *J* = 7.4 and 8.0 Hz, 1H); 7.26 (d, *J* = 6.8 Hz, 2H); 7.29-7.40 (m, 6H); 7.47 (t, *J* = 7.4 Hz, 2H); 7.62 (d, *J* = 8.1 Hz, 1H); 7.79 (bs, 2H).
^{13}C-RMN (100 MHz, $CDCl_3$): δ (ppm) 43.3 (t); 52.4 (q); 59.3 (d); 59.5 (s); 67.9 (t); 86.7 (d); 118.9 (d); 123.8 (2d); 126.4 (d); 128.2 (2d); 128.3 (2d); 128.7 (2d); 128.8 (2d and s); 131.0 (d); 133.5 (d); 133.8 (s); 138.4 (s); 140.2 (s); 170.4 (s).
IR (KBr): v (cm^{-1}) 2953, 1749, 1711, 1408, 1366, 1172, 1029, 755.
HRMS (ESI+) calculated for $C_{26}H_{24}BrN_2O_6S$ *m/z* ($M+H^+$) 571.0533, found 571.0531.

***exo-tert*-Butyl 1-benzyloxycarbonyl-3a-bromo-8-benzenesulfonyl-1,2,3,3a,8,8a-hexahydropyrrolo[2,3-*b*]indole-2-carboxylate (3k).**



Purified by flash chromatography (hexanes/EtOAc from 80:20 to 70:30) 83% yield; *exo*.
^{1}H-RMN (400 MHz, $CDCl_3$): δ (ppm) 1.35 (s, 9H); 2.73 (dd, *J* = 10.2 and 12.7 Hz, 1H); 3.09 (dd, *J* = 6.3 and 12.7 Hz, 1H); 3.78 (bs, 1H); 5.11 (d, *J* = 12.1, 1H); 5.37 (bs, 1H); 6.31 (bs, 1H); 7.17 (t, *J* = 7.6 Hz, 1H); 7.25-7.40 (m, 7H); 7.46 (t, *J* = 7.4 Hz, 2H); 7.47-7.51 (m, 1H); 7.60 (d, *J* = 8.1 Hz, 1H); 7.79 (bs, 2H).
^{13}C-RMN (100 MHz, $CDCl_3$): δ (ppm) 27.7 (3q); 43.3 (t); 59.3 (s); 60.2 (d); 67.6 (t); 82.2 (s); 86.9 (d); 118.8 (d); 123.9 (2d); 126.3 (d); 128.0 (d); 128.2 (d); 128.3 (2d); 128.7 (2d); 129.4 (s); 130.9 (2d); 133.4 (2d); 134.1 (s); 138.5 (s); 140.2 (s); 161.9 (s); 169.0 (s).
IR (KBr): v (cm^{-1}) 2978, 1715, 1463, 1368, 1216, 1172, 1041, 595.
HRMS (ESI+) calculated for $C_{29}H_{30}BrN_2O_6S$ *m/z* ($M+H^+$) 613.1008, found 613.1002.

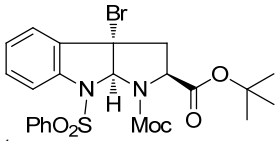
***exo*-Methyl 8-benzenesulfonyl-3a-bromo-1-methoxycarbonyl-1,2,3,3a,8,8a-hexahydropyrrolo[2,3-*b*]indole-2-carboxylate (3l).**



Purified by flash chromatography (hexanes:EtOAc 70:30); 96% yield.

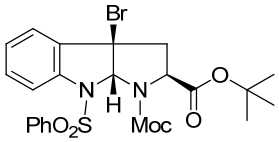
^{1}H-RMN (400 MHz, $CDCl_3$): δ (ppm) 2.81 (dd, *J* = 10.4 and 12.7 Hz, 1H); 3.11 (dd, *J* = 6.0 and 12.7 Hz, 1H); 3.75 (s, 3H); 3.81 (bs, 3H); 3.87 (dd, *J* = 6.0 and 10.4 Hz, 1H); 6.29 (s, 1H); 7.18 (dd, *J* = 7.4 and 7.7 Hz, 1H); 7.27 (bd, J = 7.7 Hz, 1H); 7.31-7.39 (m, 3H); 7.48 (dd, *J* = 7.4 and 7.5 Hz, 1H); 7.60 (d, *J* = 8.2 Hz, 1H); 7.80 (d, *J* = 7.4 Hz, 2H).
^{13}C-RMN (100 MHz, $CDCl_3$): δ (ppm) 43.4 (t); 52.7 (q); 53.0 (q); 59.1 (s); 59.2 (d); 86.7 (d); 118.8 (d); 123.8 (d); 126.4 (d); 128.1 (2d); 128.8 (2d); 131.0 (d); 133.5 (d); 133.7 (s); 138.4 (s); 140.2 (s); 149.3 (s); 170.4 (s).
IR (KBr): v (cm^{-1}) 2954, 1714, 1447, 1366, 1173, 1092, 1027, 733.
HRMS (ESI+) calculated for $C_{20}H_{20}BrN_2O_6S$ *m/z* ($M+H^+$) 495.0220, found 495.0219.

endo-tert-Butyl 8-benzenesulfonyl-3a-bromo-1-methoxycarbonyl-1,2,3,3a,8,8a-hexahydropyrrolo[2,3-*b*]indole-2-carboxylate (3m)



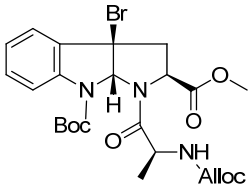
^{1}H-RMN (400 MHz, $CDCl_3$): δ (ppm) 1.08 (s, 9H); 3.04 (dd, *J* = 9.6 and 13.2 Hz, 1H); 3.23 (d, *J* = 13.2 Hz, 1H); 3.65 (s, 3H); 4.49 (d, *J* = 9.6 Hz, 1H); 6.35 (s, 1H); 7.12 (dd, *J* = 7.5 and 7.8 Hz, 1H); 7.27-7.35 (m, 2H); 7.41 (t, *J* = 7.6 Hz, 2H); 7.47-7.55 (m, 2H); 7.86 (d, *J* = 7.6 Hz, 2H).
^{13}C-RMN (100 MHz, $CDCl_3$): δ (ppm) 27.5 (3q); 44.3 (t); 52.7 (s); 52.9 (q); 60.2 (d); 82.0 (s); 87.2 (d); 118.2 (d); 124.5 (d); 125.9 (d); 127.4 (2d); 128.9 (2d); 129.1 (s); 131.0 (d); 133.2 (d); 133.6 (s); 141.6 (s); 157.2 (s); 160.0 (s).
IR (KBr): v (cm^{-1}) 2979, 1721, 1600, 1447, 1369, 1172, 1092, 975, 850, 756, 735.
HRMS (ESI+) calculated for $C_{23}H_{26}BrN_2O_6S$ *m/z* ($M+H^+$) 537.0689, found 537.0687.

exo-tert-Butyl 8-benzenesulfonyl-3a-bromo-1-methoxycarbonyl-1,2,3,3a,8,8a-hexahydropyrrolo[2,3-*b*]indole-2-carboxylate (3m).



Purified by flash chromatography (hexanes/EtOAc from 80:20 to 70:30) 58% yield; *endo:exo* (25:75).
^{1}H-RMN (400 MHz, $CDCl_3$): *exo* product δ (ppm) 1.45 (s, 9H); 2.75 (dd, *J* = 10.3 and 12.7 Hz, 1H); 3.09 (dd, *J* = 6.3 and 12.7 Hz, 1H); 3.75 (dd, *J* = 6.3 and 10.3 Hz, 1H); 3.78 (bs, 3H); 6.28 (s, 1H); 7.18 (t, *J* = 7.6 Hz, 1H); 7.29 (t, *J* = 7.0 Hz, 1H); 7.32-7.40 (m, 3H); 7.42-7.51 (m, 1H); 7.58 (d, *J* = 8.1 Hz, 1H); 7.79 (bd, *J* = 6.9 Hz, 2H).
^{13}C-RMN (100 MHz, $CDCl_3$): *exo* product δ (ppm) 27.8 (q); 43.6 (t); 52.8 (q); 59.2 (s); 60.1 (d); 82.3 (s); 86.9 (d); 118.7 (d); 123.9 (d); 125.1 (s); 126.3 (d); 128.1 (2d); 128.7 (d); 129.4 (d); 130.9 (d); 133.4 (d); 138.5 (s); 140.2 (s); 169.6 (s); 171.5 (s).
IR (KBr): v (cm^{-1}) 2979, 1725, 1447, 1369, 1172, 595.
HRMS (ESI+) calculated for $C_{23}H_{26}BrN_2O_6S$ *m/z* ($M+H^+$) 537.0695, found 537.0681.

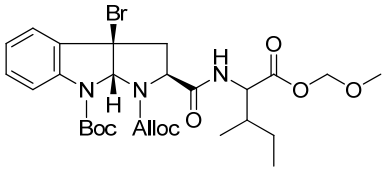
exo-Methyl 2-(_N^α^_-allyloxycarbonyl-Ala-O-yl)-3a-bromo-1-(_tert_-butoxycarbonyl)-1,2,3,3a,8,8a-hexahydropyrrolo[2,3-*b*]indole-2-carboxylate (3n)



Purified by flash chromatography (hexanes/EtOAc from 80:20 to 70:30) 47% yield; *exo*.
^{1}H-RMN (400 MHz, $CDCl_3$): δ (ppm) 1.50 (d, *J* = 6.8 Hz, 3H); 1.62 (s, 9H); 2.79 (dd, *J* = 10.9 and 12.5 Hz, 1H); 3.26 (dd, *J* = 6.2 and 12.5 Hz, 1H); 3.73 (s, 3H); 4.03 (dd, J = 6.2 and 10.9 Hz, 1H); 4.46-4.57 (m, 2H); 5.02 (t, 6.8 Hz, 1H); 5.13-5.29 (m, 2H); 5.43 (bs, 1H); 5.82-5.94 (m, 1H); 6.41 (s, 1H); 7.18 (dd, *J* = 7.3 and 7.4 Hz, 1H); 7.32-7.40 (m, 2H); 7.50 (bs, 1H).
^{13}C-RMN (100 MHz, $CDCl_3$): δ (ppm) 19.3 (q); 28.1 (3q); 40.6 (t); 47.9 (d); 52.5 (q); 60.0 (d); 65.3 (t); 67.9 (s); 84.0 (s); 84.5 (d); 117.3 (t); 120.5 (d); 122.8 (d); 125.6 (d); 128.1 (s); 130.8 (d), 132.9 (d); 133.4 (s); 154.9 (s); 170.3 (s); 173.8 (s).

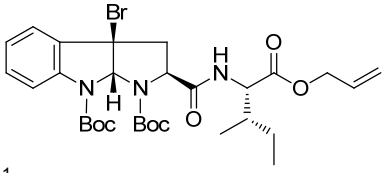
IR (KBr): v (cm^{-1}) 3325, 2979, 1724, 1663, 1478, 1414, 1370, 1333, 1254, 1155, 852, 754.
HRMS (ESI+) calculated for $C_{24}H_{31}BrN_3O_7$ *m/z* ($M+H^+$) 552.1340, found 552.1338.

exo-Methoxymethyloxyisoleucinyl 2-allyloxycarbonyl-3a-bromo-1-(_tert_-butoxycarbonyl)-1,2,3,3a,8,8a-hexahydropyrrolo[2,3-b]indole-2-carbonylate (3o)



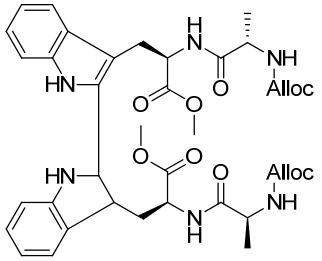
^{1}H-RMN (400 MHz, $CDCl_3$): δ (ppm) 0.91 (t, *J* = 7.5 Hz, 3H); 0.93 (d, *J* = 6.9 Hz, 3H); 1.14-1.24 (m, 1H); 1.39-1.49 (m, 1H); 1.57 (s, 9H); 1.88-1.98 (m, 1H); 2.93 (dd, *J* = 10.1 and 12.8 Hz, 1H); 3.22 (dd, *J* = 6.4 and 12.8 Hz, 1H); 3.47 (s, 3H); 3.85 (dd, *J* = 6.4 and 10.1 Hz, 1H); 4.48-4.65 (m, 3H); 5.12-5.24 (m, 2H); 5.20 (d, *J* = 5.9 Hz, 1H); 5.33 (d, *J* = 5.9 Hz, 1H); 5.76-5.88 (m, 1H); 6.23 (d, *J* = 8.5 Hz, 1H); 6.39 (s, 1H); 7.12 (dd, *J* = 7.5 and 8.3 Hz, 1H); 7.31 (dd, *J* = 7.2 and 8.3 Hz, 1H); 7.36 (d, *J* = 7.5 Hz, 1H); 7.58 (bd, *J* = 7.2 Hz, 1H).
^{13}C-RMN (100 MHz, $CDCl_3$): δ (ppm) 11.6 (q); 15.3 (q); 25.0 (t); 28.2 (3q); 37.8 (d); 41.9 (t); 56.6 (d); 57.9 (q); 59.8 (s); 61.2 (d); 66.3 (t); 82.3 (s); 84.1 (d); 91.1 (t); 117.5 (t); 118.3 (d); 123.2 (d); 124.4 (d); 130.6 (d); 132.3 (d); 132.8 (s); 141.2 (s); 152.0 (s); 169.7 (s); 171.4 (2s).
IR (KBr): v (cm^{-1}) 3333, 2967, 2934, 1718, 1540, 1478, 1369, 1335, 1161, 927, 755.
HRMS (ESI+) calculated for $C_{28}H_{38}BrN_3O_8Na$ *m/z* ($M+Na^+$) 646.1740, found 646.1730.

exo-Allyloxyisoleucinyl 3a-bromo-1,8-(di-_tert_-butoxycarbonyl)-1,2,3,3a,8,8a-hexahydropyrrolo[2,3-_b_]indole-2-carbonylate (3p)



^{1}H-RMN (400 MHz, $CDCl_3$): δ (ppm) 0.88-0.94 (m, 6H); 1.15-1.26 (m, 1H); 1.39 (s, 9H); 1.41-1.49 (m, 1H); 1.58 (s, 9H); 1.86-1.93 (m, 1H); 2.84-2.95 (m, 1H); 3.18 (dd, *J* = 6.3 and 12.8 Hz, 1H); 3.77 (dd, *J* = 6.3 and 10.1 Hz, 1H); 4.58 (dd, *J* = 3.6 and 4.9 Hz, 1H); 4.59-4.63 (m, 2H); 5.26 (ddd, *J* = 1.1 , 2.5 and 10.4 Hz, 1H); 5.33 (ddd, *J* = 1.4 , 2.5 and 17.2, 1H); 5.84-5.95 (m, 1H); 6.28 (d, *J* = 8.5 Hz, 1H); 6.36 (s, 1H); 7.12 (t, *J* = 7.6 Hz, 1H); 7.30 (dd, *J* = 7.6 and 7.9 Hz, 1H); 7.35 (bd, *J* = 7.6 Hz, 1H); 7.50 (bd, *J* = 7.9 Hz, 1H).
^{13}C-NMR (100 MHz, $CDCl_3$) δ (ppm) 11.5 (q); 15.4 (q); 25.1 (t); 28.2 (3q); 28.3 (3q); 38.1 (d); 41.9 (t); 56.5 (d); 59.9 (s); 61.3 (d); 65.8 (t); 81.6 (s); 82.4 (s); 84.1 (d); 118.7 (d); 119.0 (t); 123.3 (d); 124.5 (d); 130.5 (d); 131.5 (d); 133.3 (s); 141.4 (s); 152.3 (s); 169.9 (s); 171.4 (2s).
IR (KBr): v (cm^{-1}) 3343, 2975, 2933, 1721, 1532, 1478, 1394, 1368, 1331, 1165, 853, 751.
HRMS (ESI+) calculated for $C_{30}H_{42}BrN_3O_7$ *m/z* (M) 635.2206, found 635.2628.

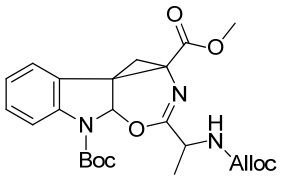
Compound 5



^{1}H-RMN (400 MHz, $CDCl_3$): δ (ppm) 1.18 (s, 3H); 1.20 (s, 3H); 2.17-2.36 (m, 2H); 3.24-3.41 (m, 2H); 3.62 (s, 3H); 3.63 (s, 3H); 3.78 (bs, 1H); 4.09 (t, *J* = 7.1 Hz, 1H); 4.22-4.51 (m, 5H); 4.70 (dd, *J* = 7.6 and 12.0 Hz, 1H); 4.92 (dd, *J* = 6.7 and 12.8 Hz, 1H); 5.13-5.28 (m, 5H); 5.31 (d, *J* = 6.9 Hz, 1H); 5.49 (d, *J* = 6.0 Hz, 1H); 5.76-5.90 (m, 2H); 6.63 (bs, 1H); 6.95 (bd, *J* = 6.4 Hz, 1H); 7.03-7.20 (m, 5H); 7.22 (d, *J* = 8.0 Hz, 1H); 7.31 (t, *J* = 4.4 Hz, 1H); 7.45 (d, *J* = 7.9 Hz, 2H); 9.42 (s, 1H).
^{13}C-RMN (100 MHz, $CDCl_3$): δ (ppm) 17.4 (q); 18.0 (q); 27.1 (t); 35.8 (t); 46.1 (d); 50.2 (d); 50.3 (2d); 52.6 (q); 52.7 (q); 52.9 (d); 60.6 (d); 66.0 (t); 66.2 (t); 109.2 (s); 111.7 (d); 116.0 (d); 118.1 (2t); 118.8 (d); 119.9 (d); 122.8 (s);

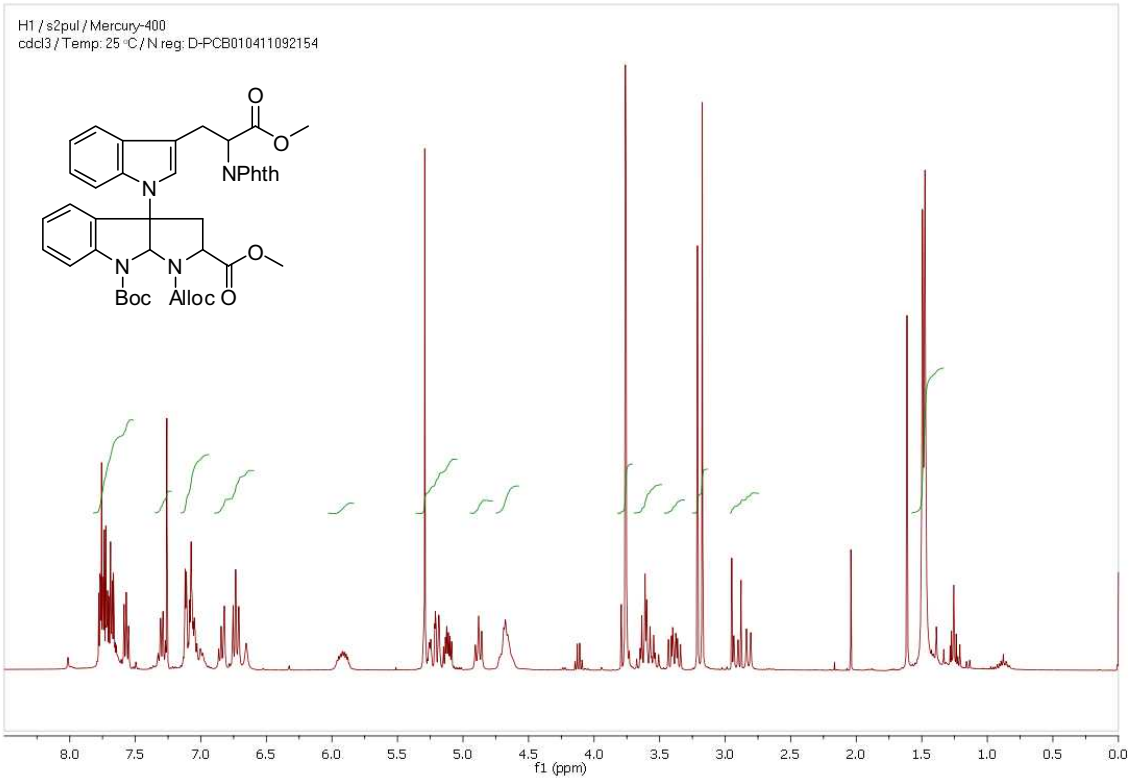
123.2 (d); 124.7 (d); 126.1 (d); 127.6 (s); 127.9 (s); 129.1 (d); 132.1 (d); 132.3 (d); 136.1 (s); 156.4 (s); 160.9 (s); 161.2 (s); 171.8 (s); 172.9 (s); 173.1 (2s).
MS (ESI+) *m/z* = 747 ($M+H^+$, 100%), 374 ($½M+H^+$, 30%).
HPLC (MeCN:H_2O des de 40:60 fins 50:50 en 8 minuts): t_R= 5.52 min.

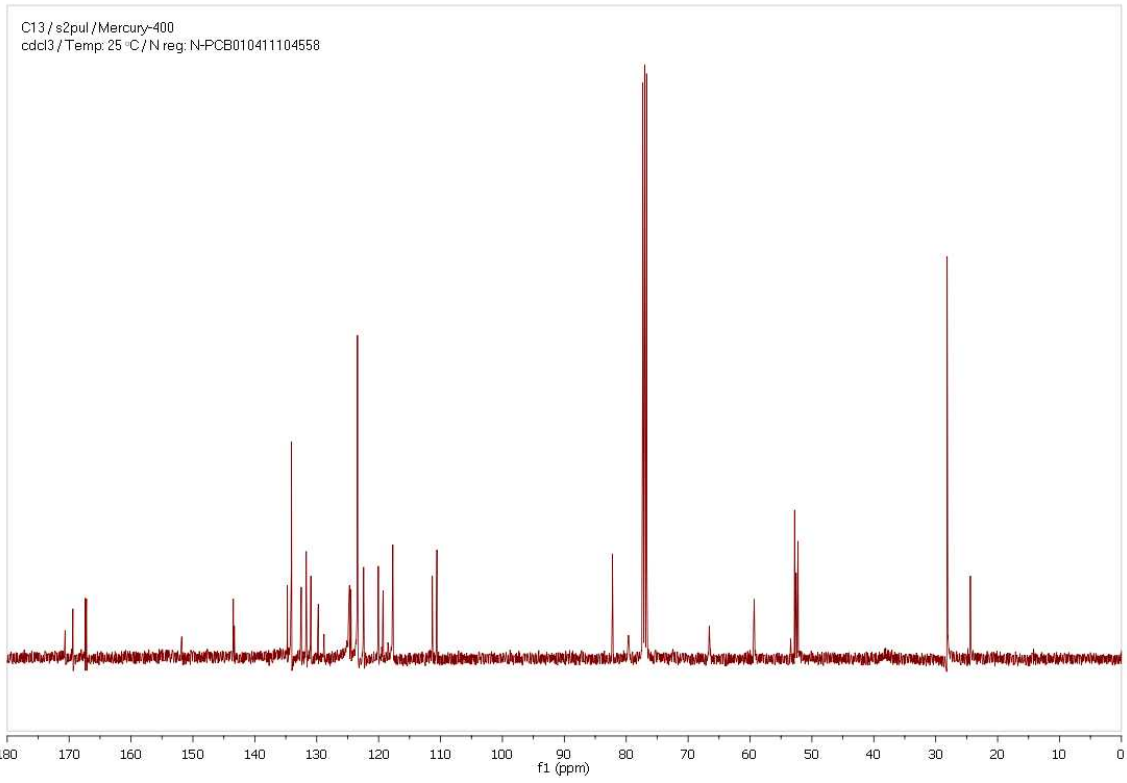
Compound 8



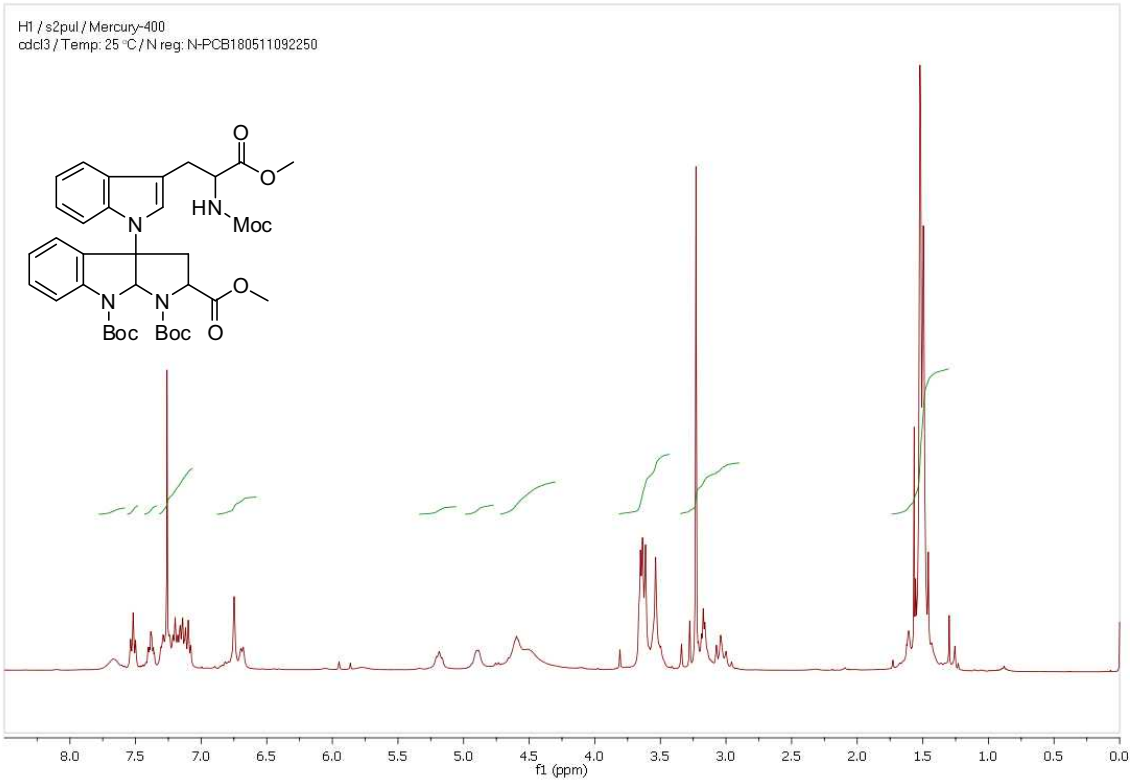
^{1}H-RMN (400 MHz, $CDCl_3$): δ (ppm) 0.66 and 0.77 (2d, *J* = 6,6 Hz, 3H); 1.64 (s, 9H); 3.43 (d, *J* = 15.4 Hz, 1H); 3,81 (s, 3H); 3.91 (d, *J* = 15.4 Hz, 1H); 4.04-4.19 (m, 1H); 4.54-4.77 (m, 2H); 5.15-5.44 (m, 2H); 5.84-5.99 (m, 1H); 7.08 (bs, 1H); 7.14 (dd, *J* = 7.2 and 7.6 Hz, 1H); 7.27 (dd, *J* = 7.2 and 8.2 Hz, 1H); 7.43-7.52 (m, 2H); 8.08 (d, *J* = 8.2 Hz, 1H).
^{13}C-RMN (100 MHz, $CDCl_3$): δ (ppm) 17.0 (q); 28.1 (3q); 28.9 (t); 53.3 (q); 54.9 (d); 66.4 (t); 77.9 (s); 83.8 (s); 113.3 (s); 115.1 (d); 118.1 (t); 119.1 (d); 122.6 (d); 124.4 (d); 125.9 (d); 132.0 (s); 135.0 (s);149.6 (s); 154.0 (s); 170.2 (s); 172.9 (s).
IR (KBr): v (cm^{-1}) 3283, 2931, 1735, 1452, 1370, 1257, 1158, 1082, 747.
HRMS (ESI+) calculated for $C_{48}H_{58}N_6O_{14}Na$ *m/z* ($2M+Na^+$) 965.3909, found 965.3934.

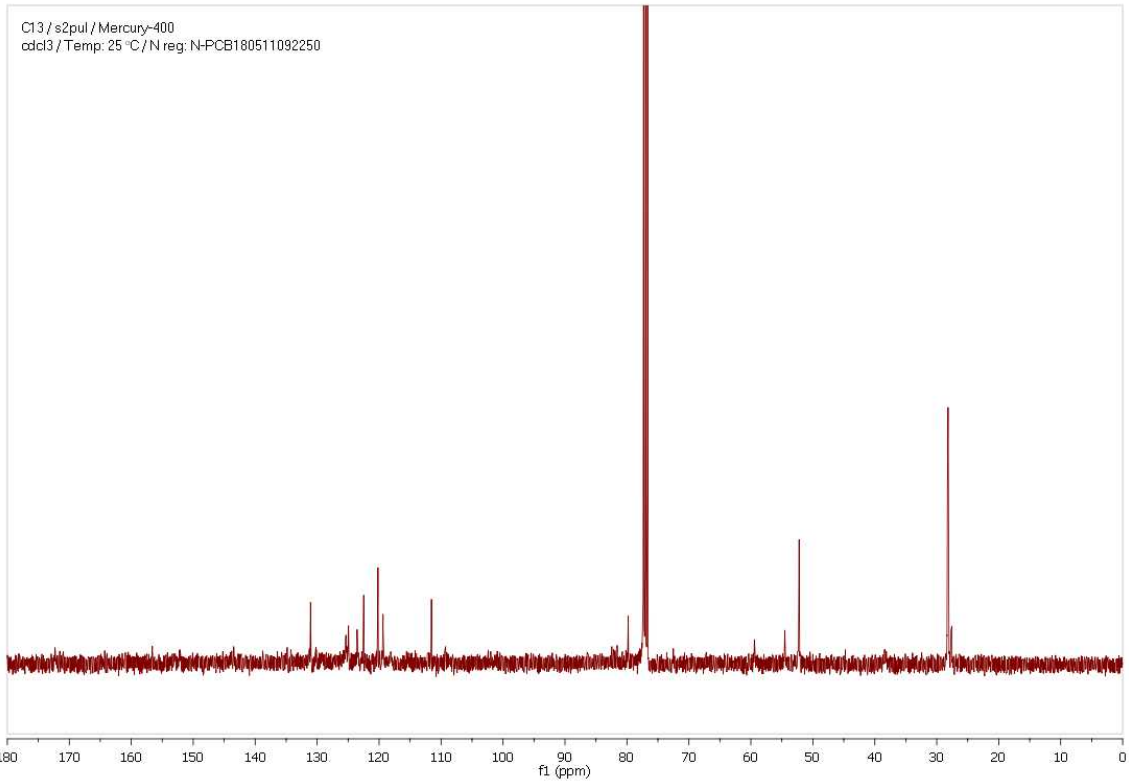
1a.


H1 / s2pul / Mercury-400
cdcl3 / Temp: 25 °C / N reg: D-PCB010411092154
O
O
NPhth
N
N
N
O
Boc
Alloc
O
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

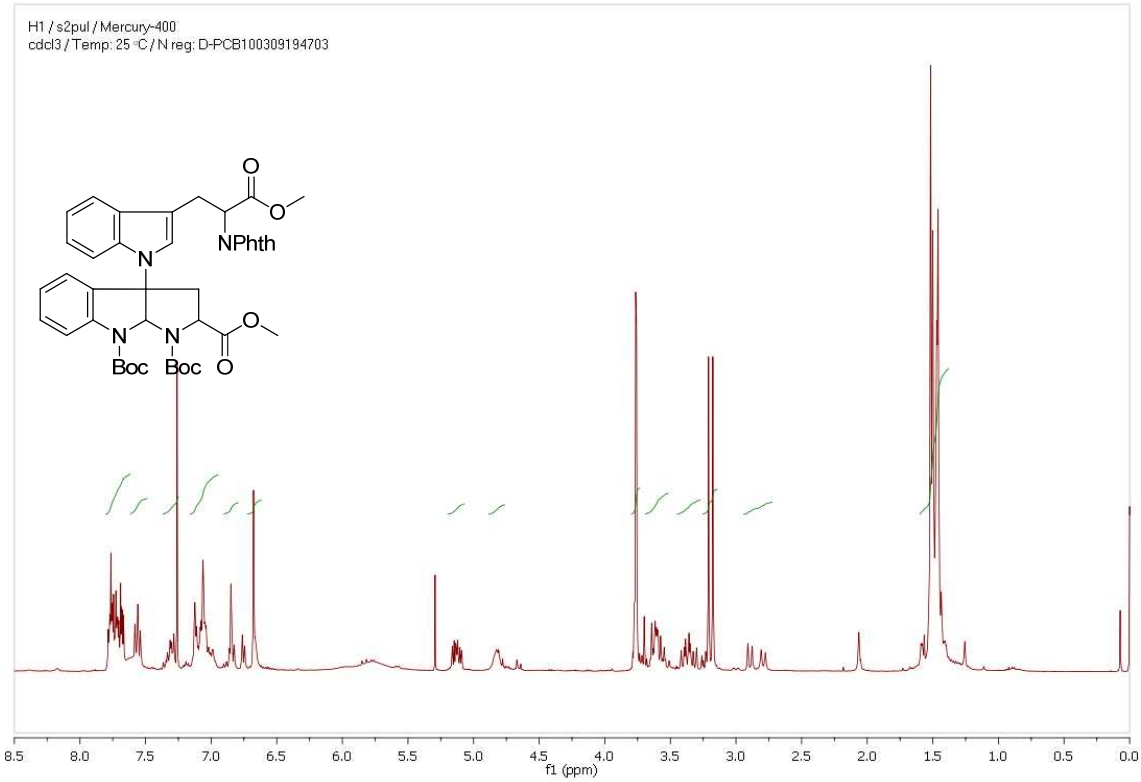

C13 / s2pul / Mercury-400
cdcl3 / Temp: 25 °C / N reg: N-PCB010411104558
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

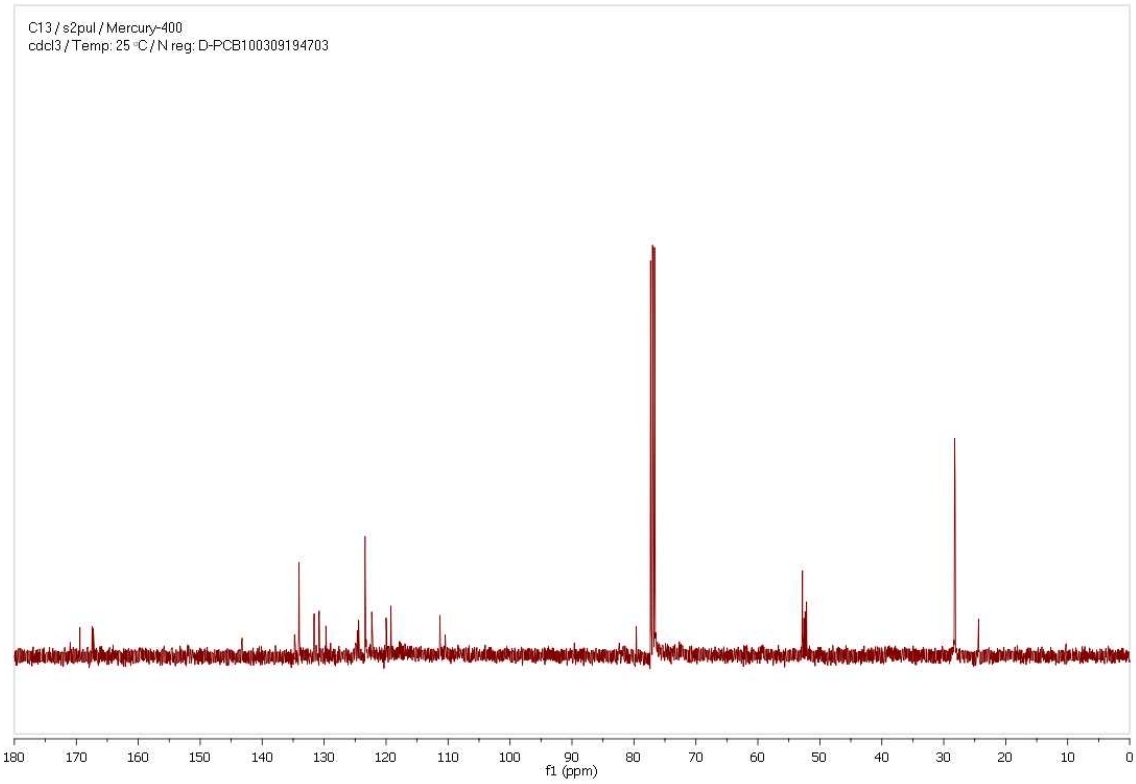
1b.


H1 / s2pul / Mercury-400
cdcl3 / Temp: 25 °C / N reg: N-PCB180511092250
O
O
HN
Moc
N
N
N
Boc
Boc
O
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

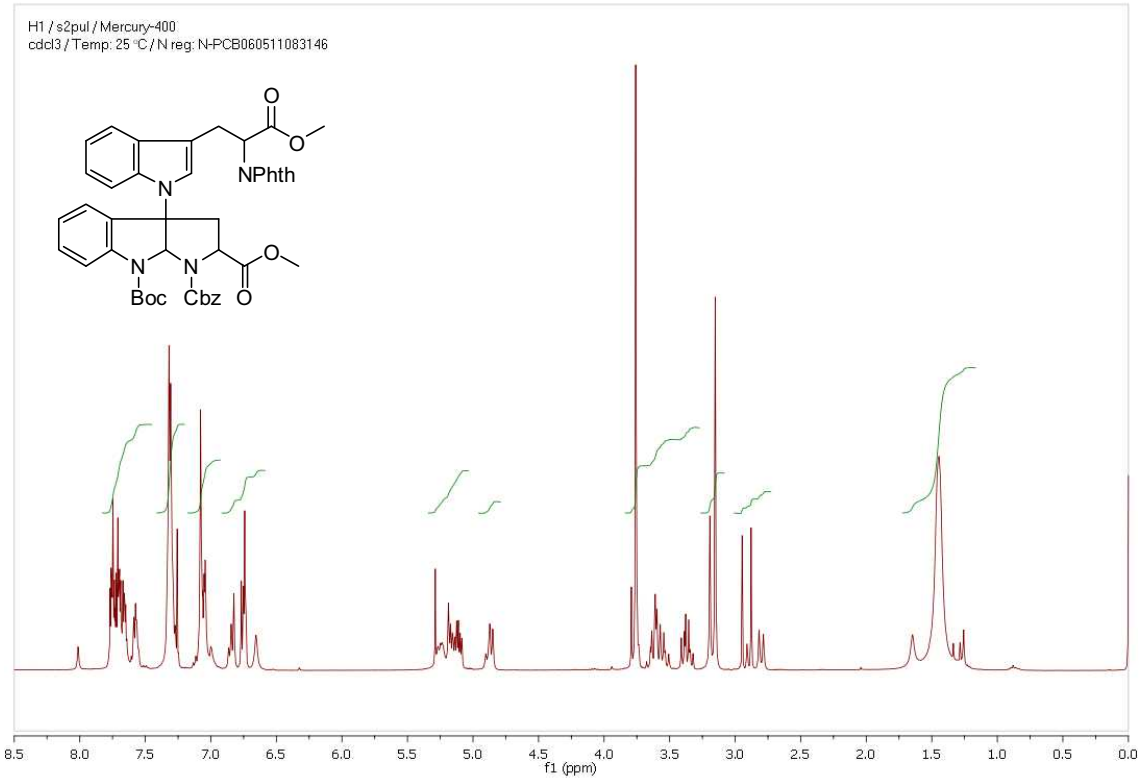

C13 / s2pul / Mercury-400
cdcl3 / Temp: 25 °C / N reg: N-PCB180511092250
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

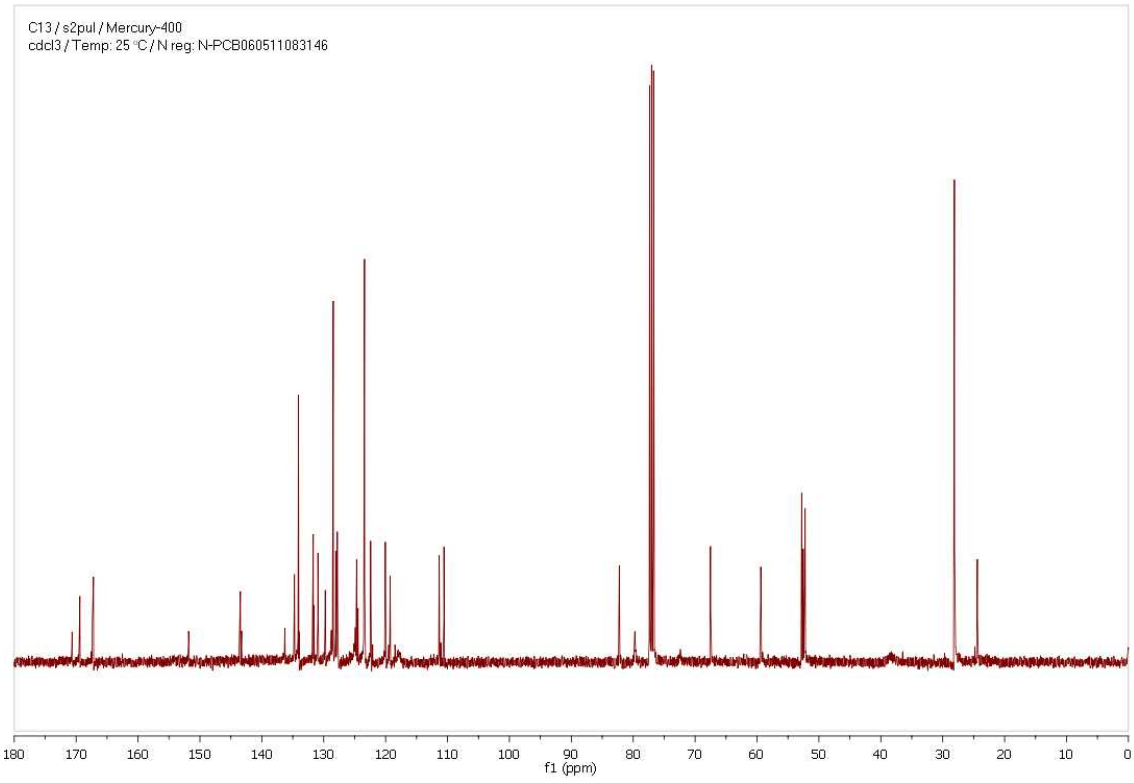
1c.


H1 / s2pul / Mercury-400
cdcl3 / Temp: 25 °C / N reg: D-PCB100309194703
O
O
NPhth
N
N
N
Boc
Boc
O
O
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

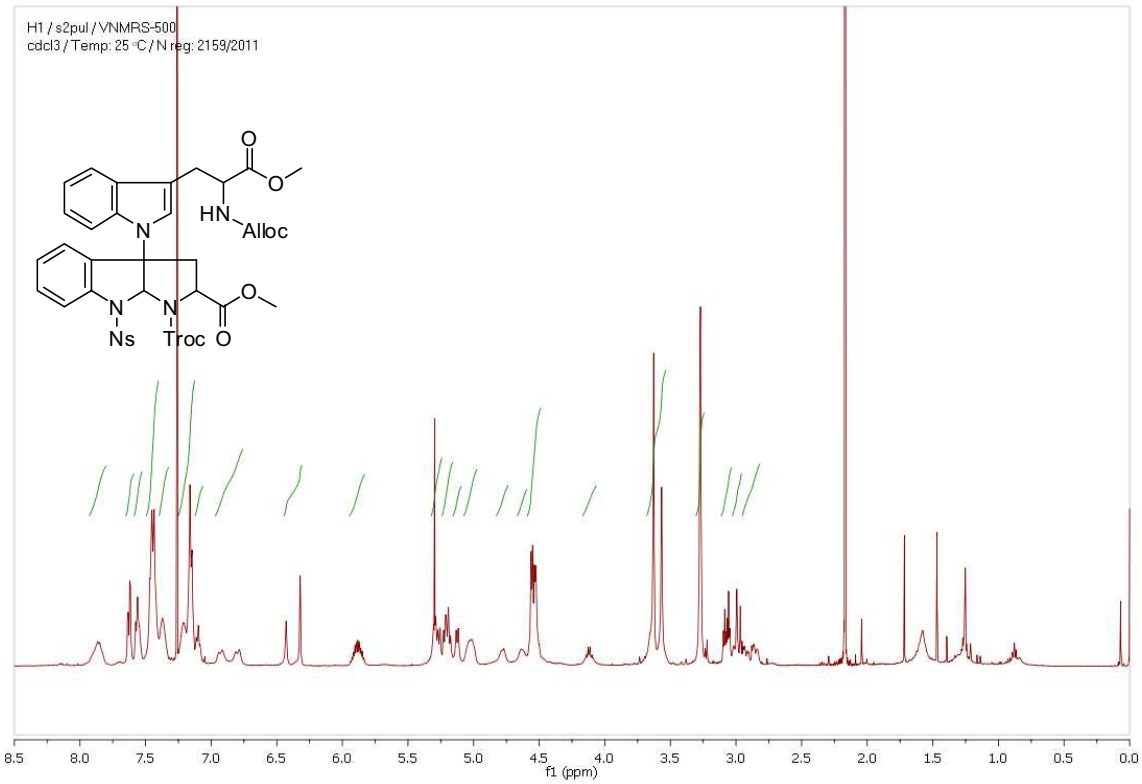

C13 / s2pul / Mercury-400
cdcl3 / Temp: 25 °C / N reg: D-PCB100309194703
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

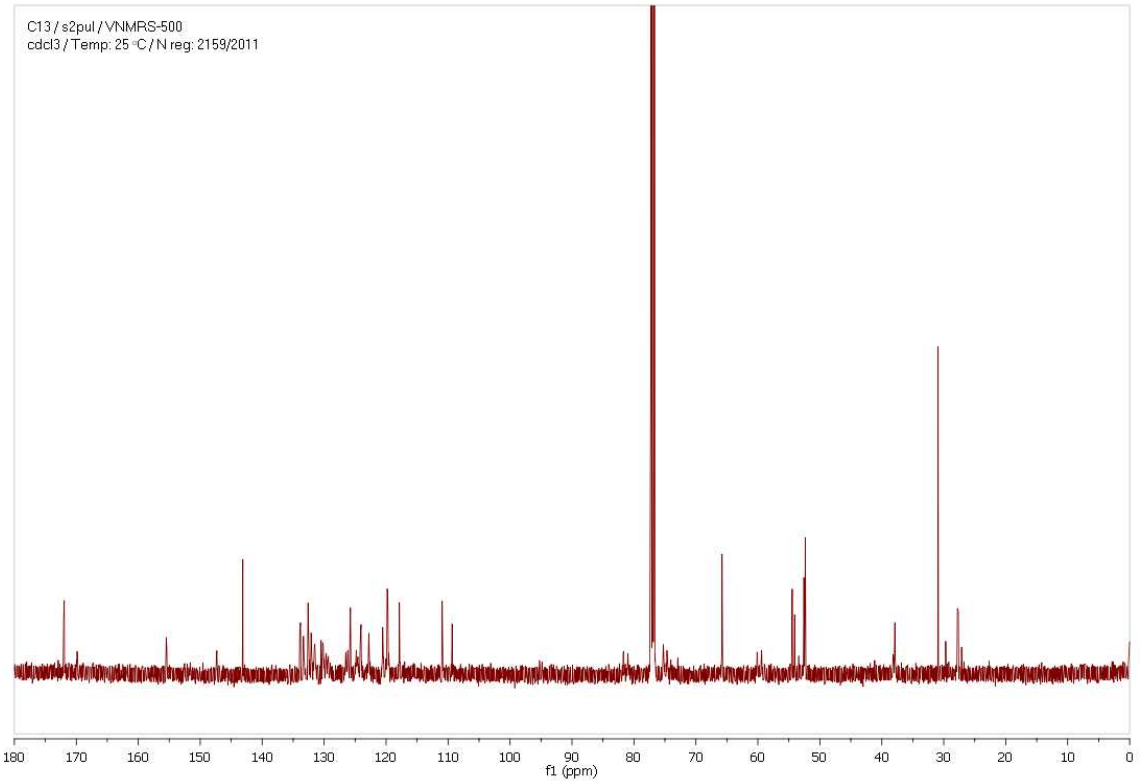
1d.


H1 / s2pul / Mercury-400
cdcl3 / Temp: 25 °C / N reg: N-PCB060511083146
O
O
NPhth
N
N
N
O
Boc
Cbz
O
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

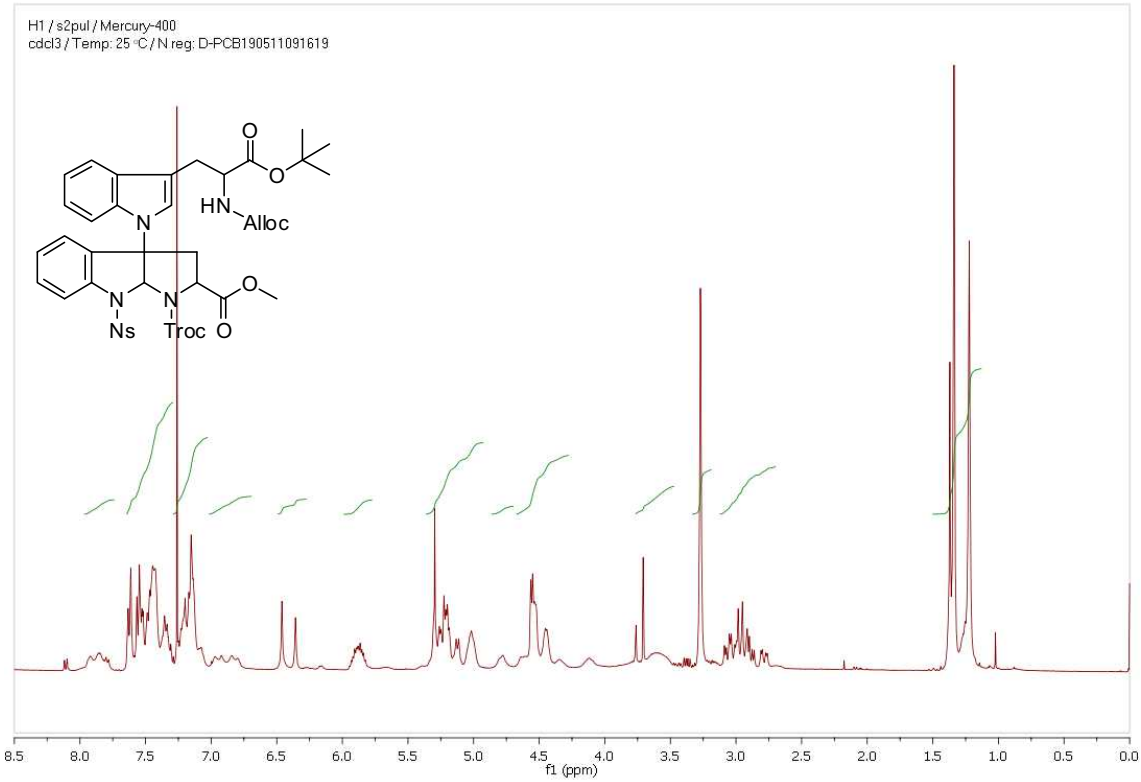

C13 / s2pul / Mercury-400
cdcl3 / Temp: 25 °C / N reg: N-PCB060511083146
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

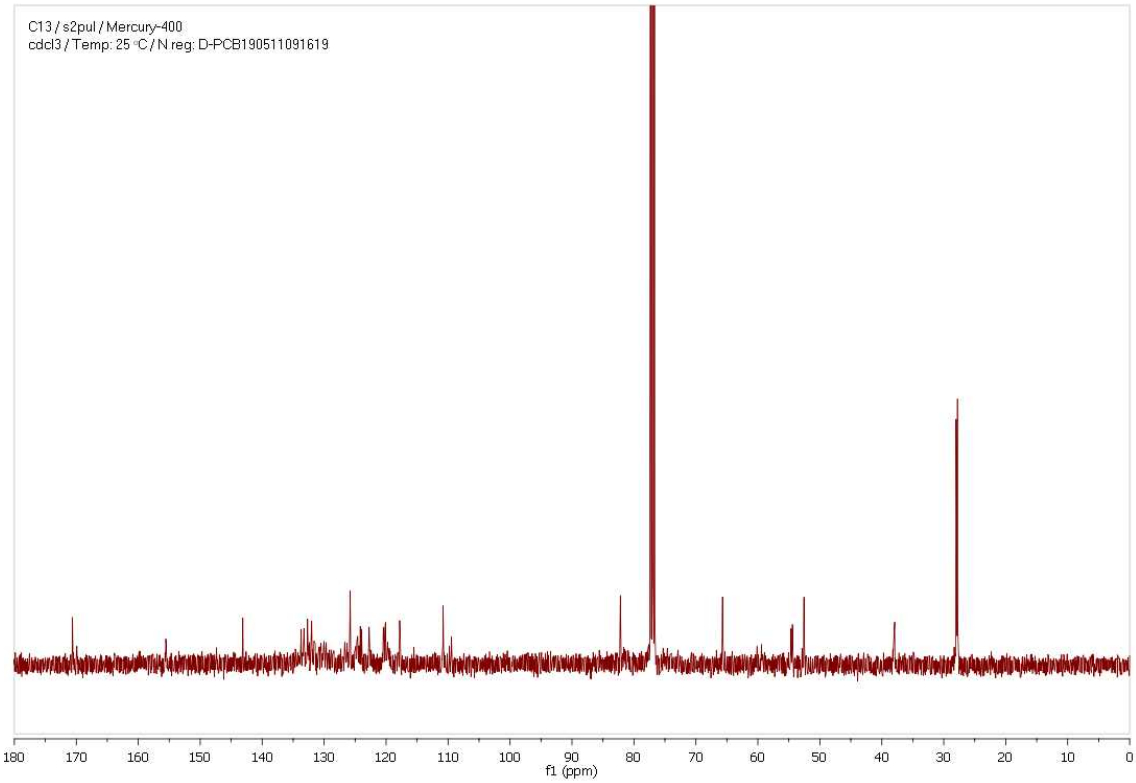
1e.


H1 / s2pul / VNMRS-500
cdcl3 / Temp: 25 °C / N reg: 2159/2011
O
O
HN
Alloc
N
N
N
Ns
Troc
O
O
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

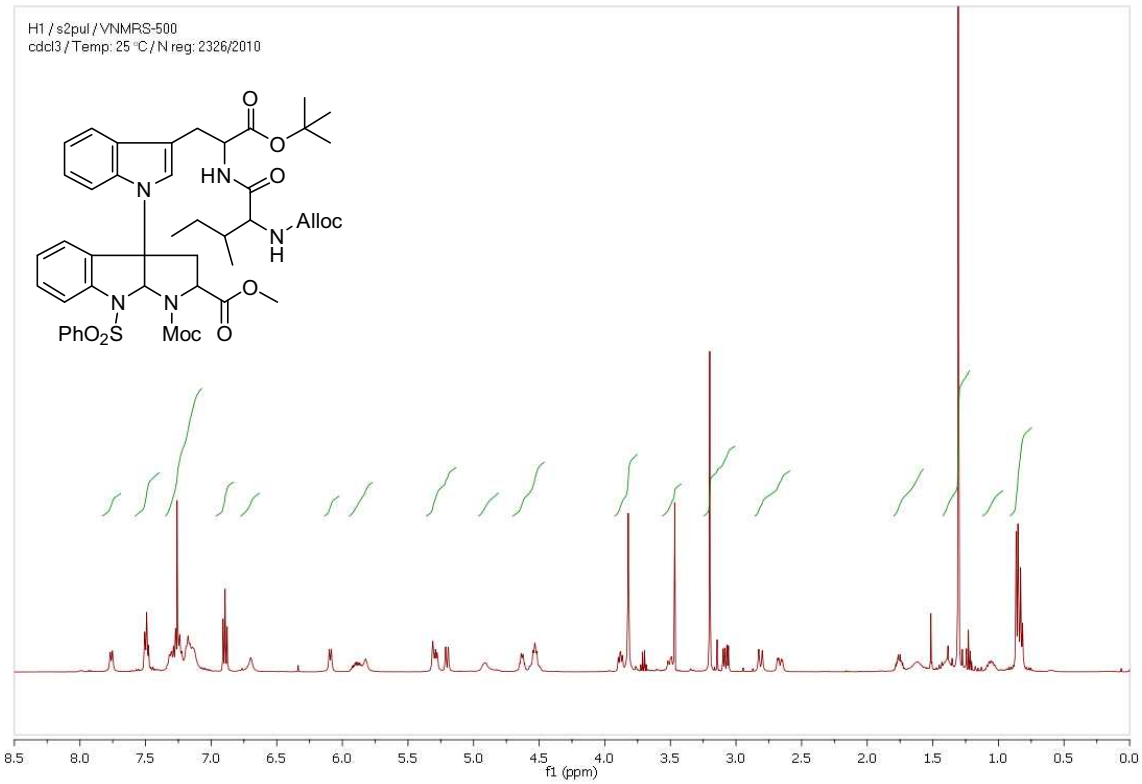

C13 / s2pul / VNMRS-500
cdcl3 / Temp: 25 °C / N reg: 2159/2011
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

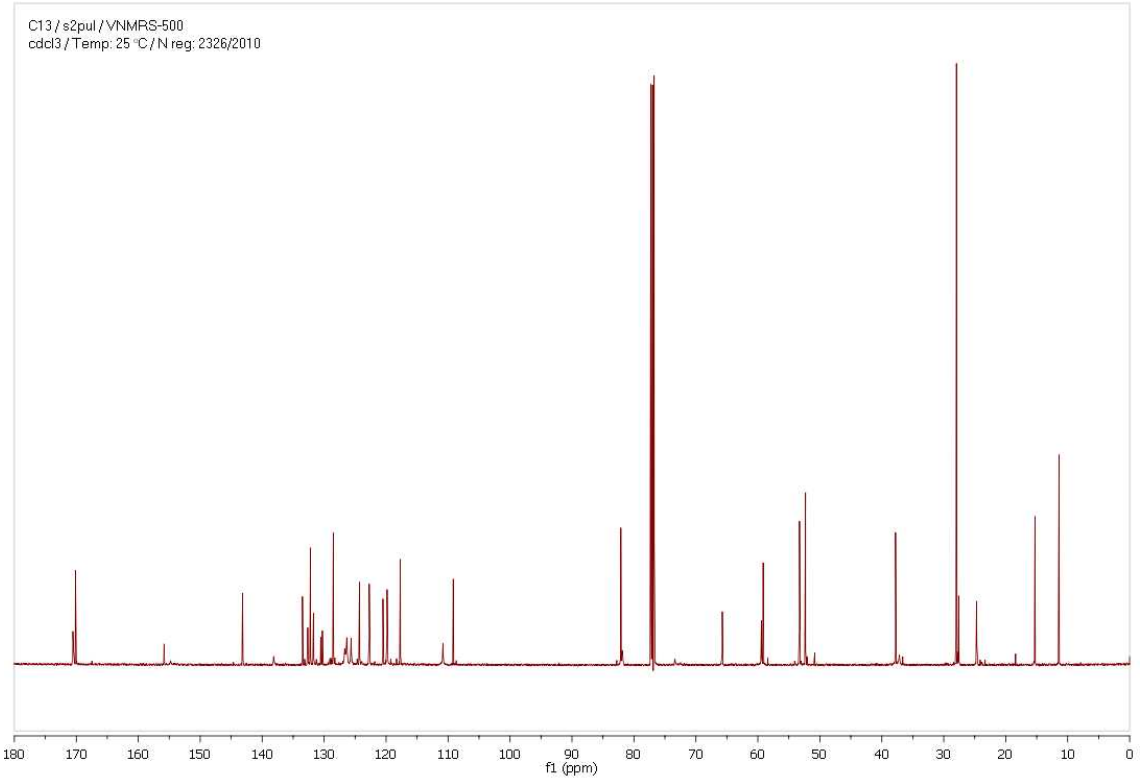
1f.


H1 / s2pul / Mercury-400
cdcl3 / Temp: 25 °C / N reg: D-PCB190511091619
O
O
HN
Alloc
N
N
N
O
Ns
Troc
O
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

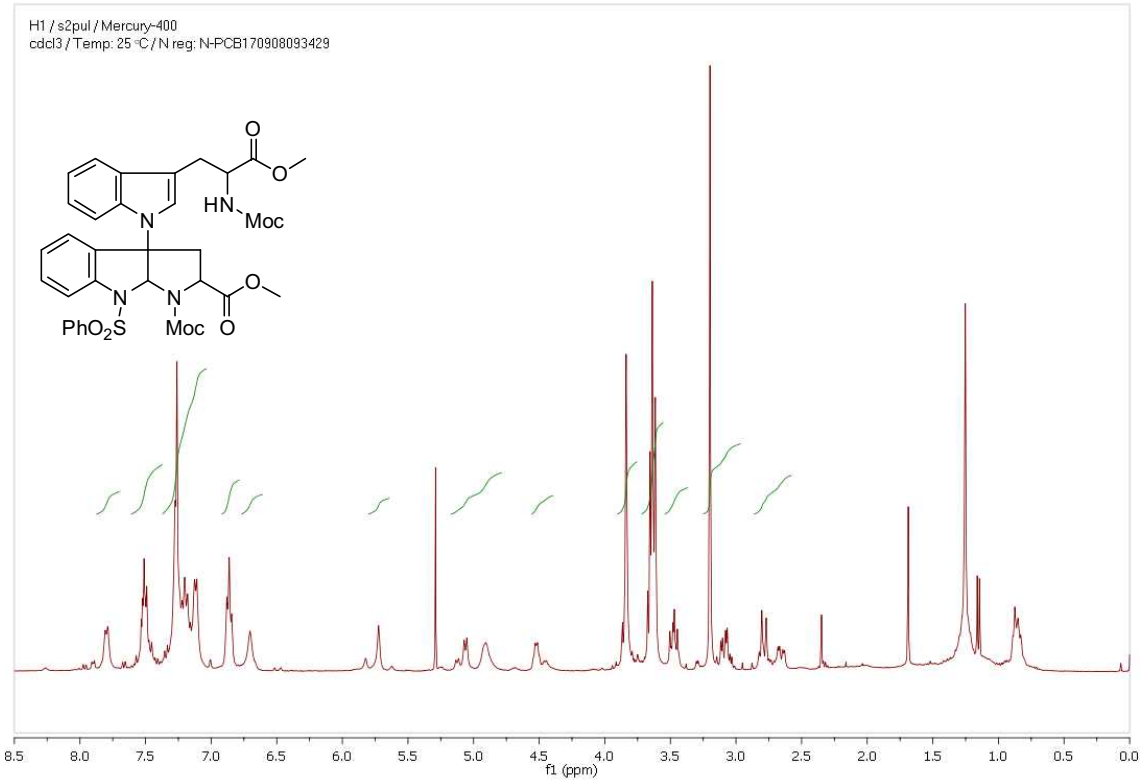

C13 / s2pul / Mercury-400
cdcl3 / Temp: 25 °C / N reg: D-PCB190511091619
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

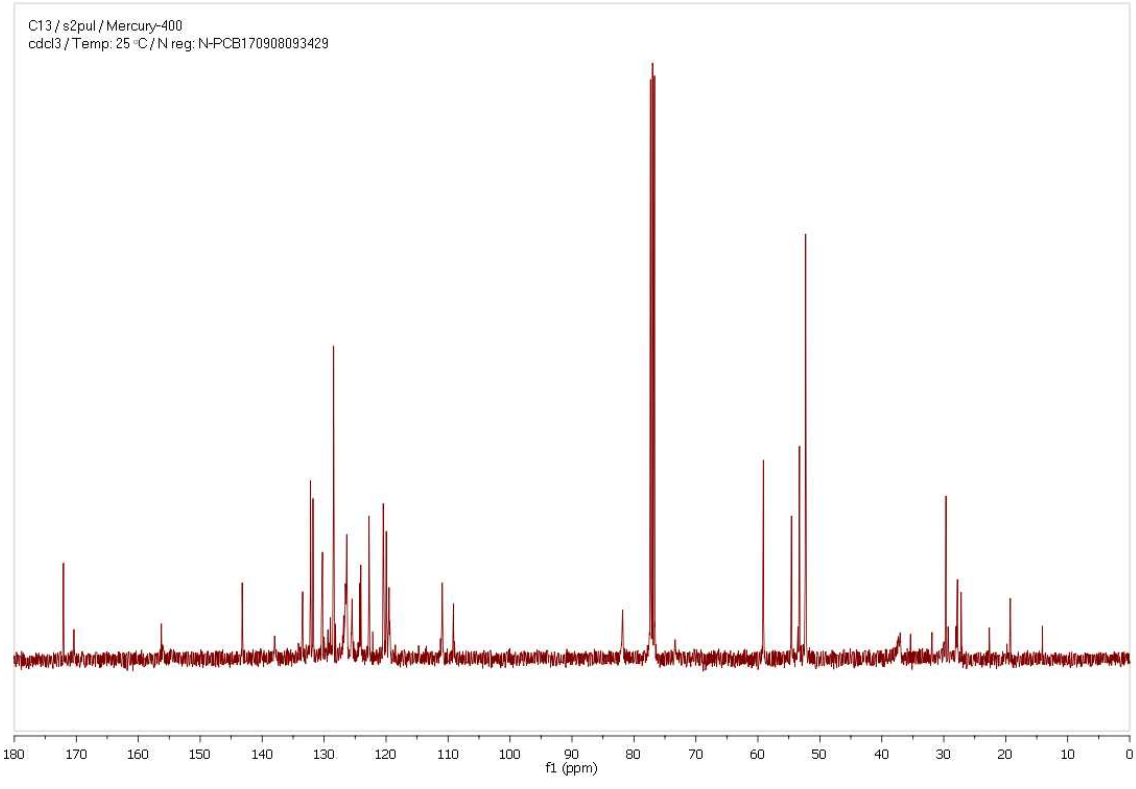
1g.


H1 / s2pul / VNMRS-500
cdcl3 / Temp: 25 °C / N reg: 2326/2010
O
O
HN
O
N
Alloc
N
H
N
N
O
PhO2S
Moc
O
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

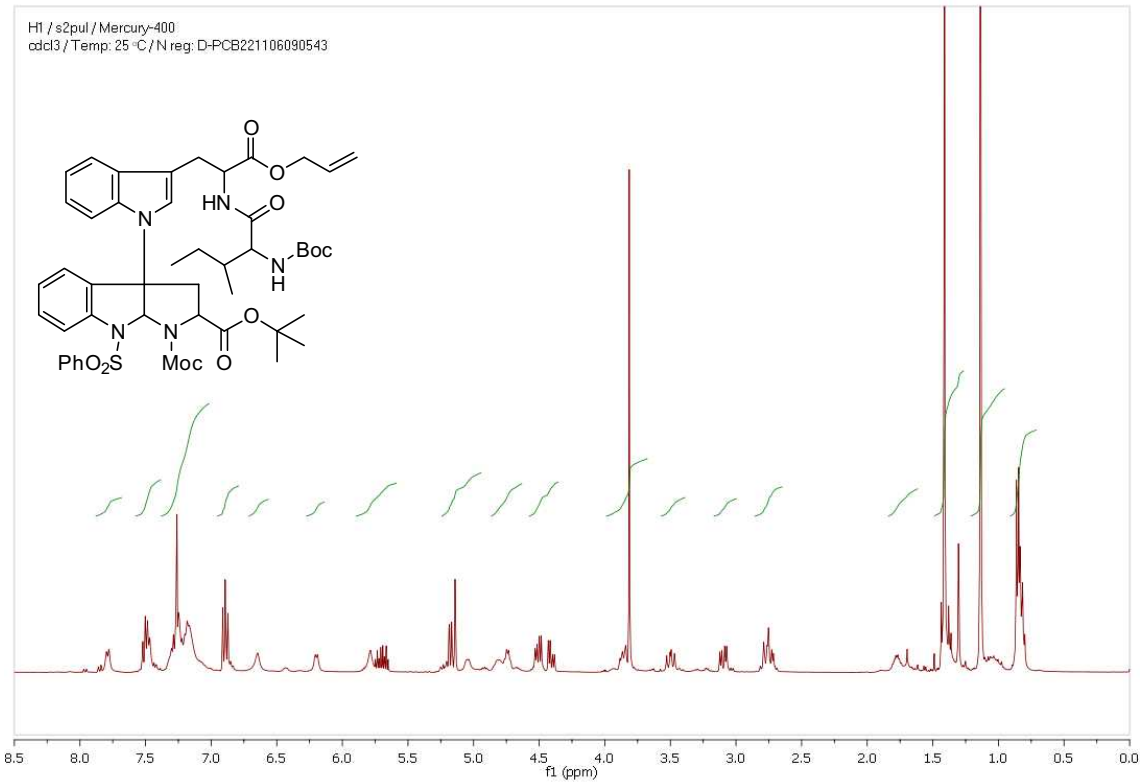

C13 / s2pul / VNMRS-500
cdcl3 / Temp: 25 °C / N reg: 2326/2010
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

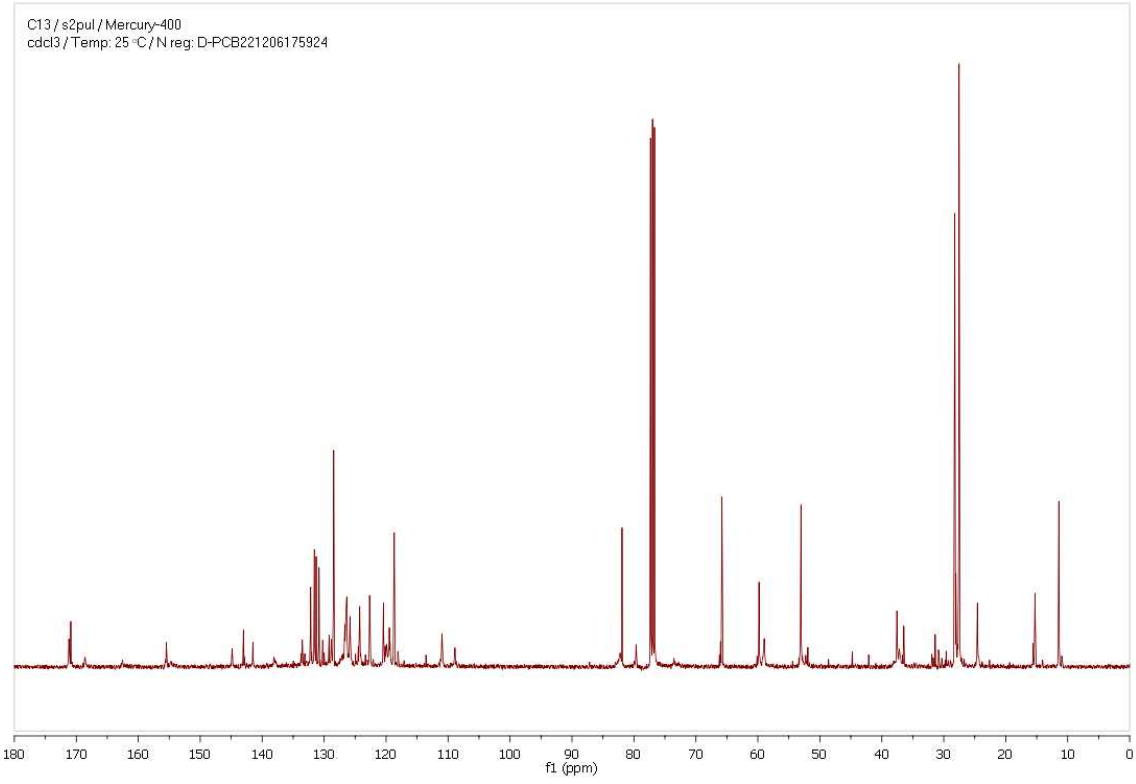
1h.


H1 / s2pul / Mercury-400
cdcl3 / Temp: 25 °C / N reg: N-PCB170908093429
O
O
HN
Moc
N
N
N
O
PhO2S
Moc
O
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

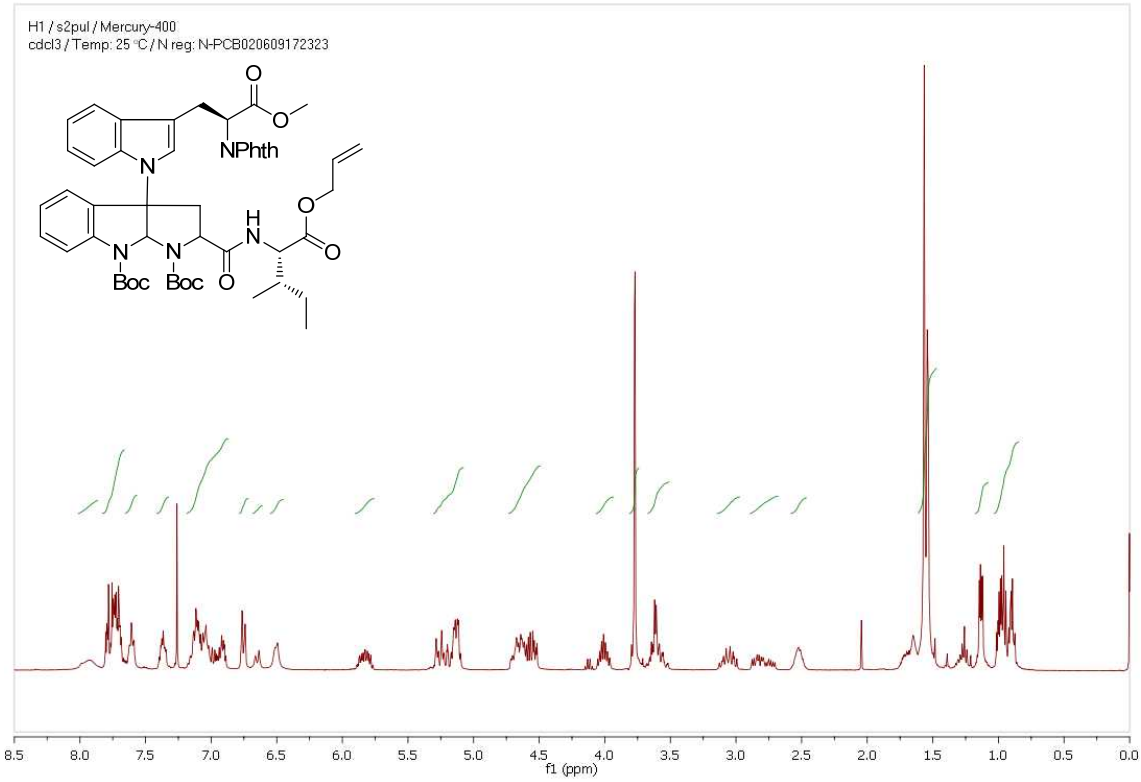

C13 / s2pul / Mercury-400
cdcl3 / Temp: 25 °C / N reg: N-PCB170908093429
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

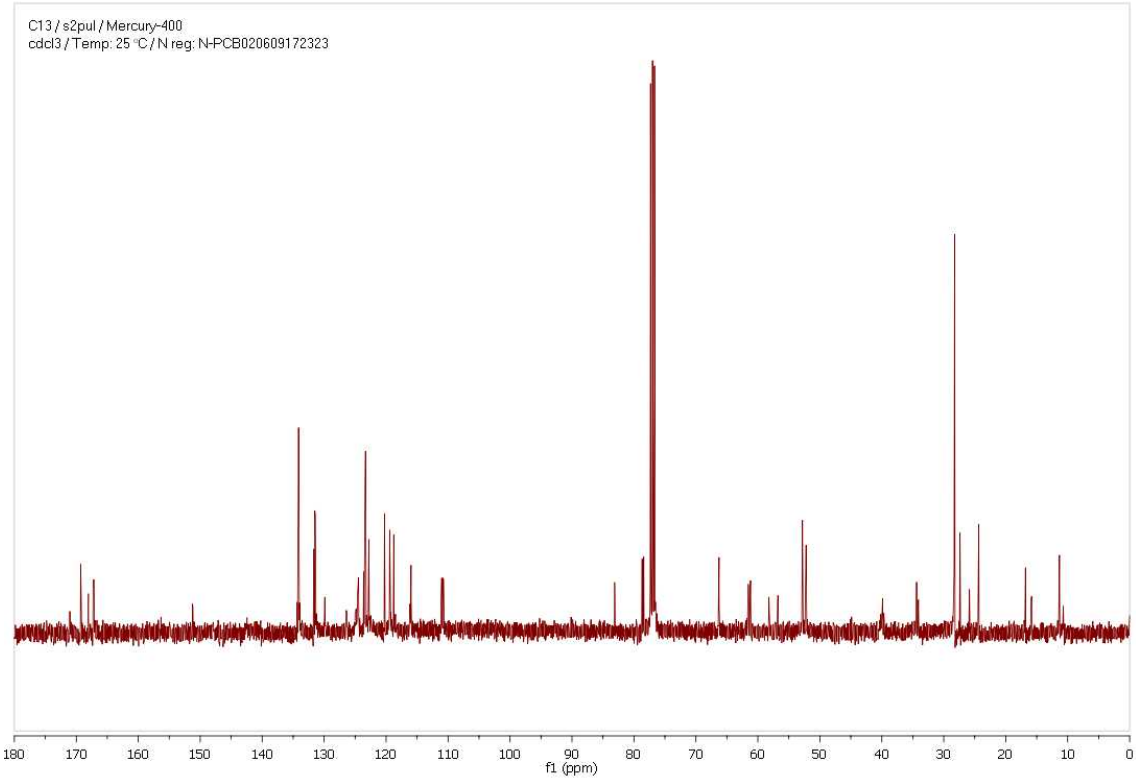
1i.


H1 / s2pul / Mercury-400
cdcl3 / Temp: 25 °C / N reg: D-PCB221106090543
O
O
HN
O
N
Boc
N
H
N
N
O
PhO2S
Moc
O
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

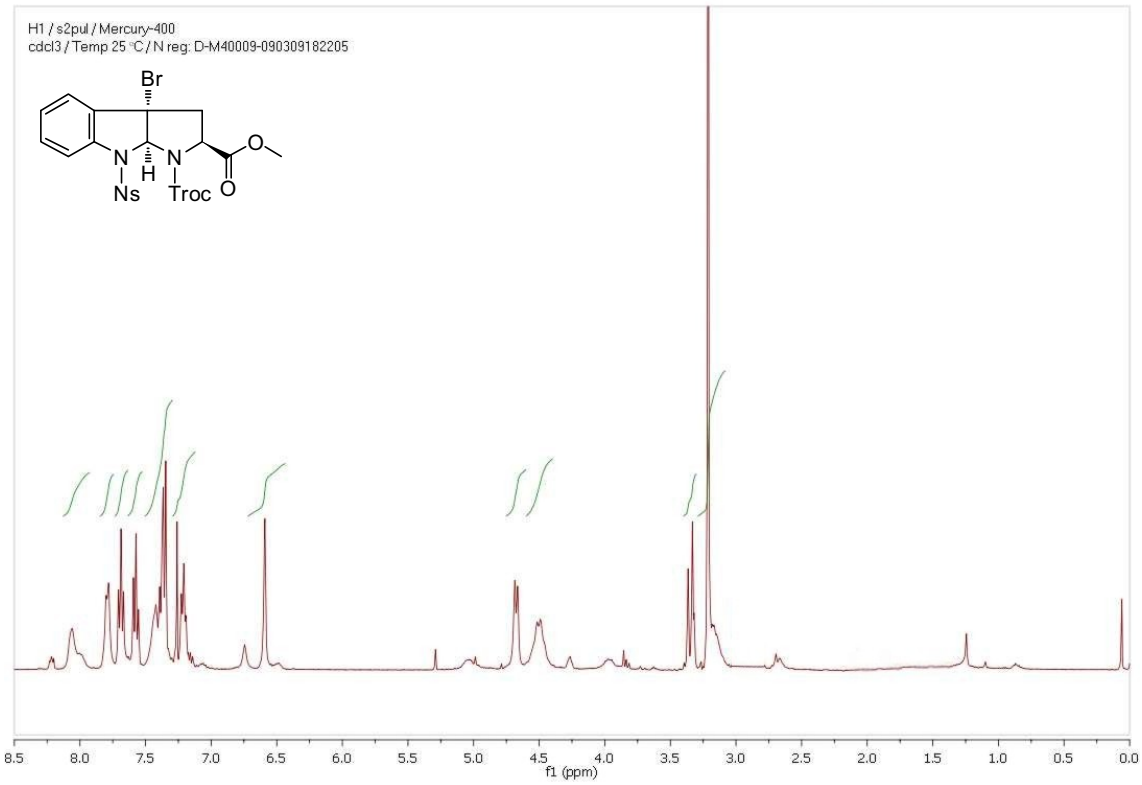

C13 / s2pul / Mercury-400
cdcl3 / Temp: 25 °C / N reg: D-PCB221206175924
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

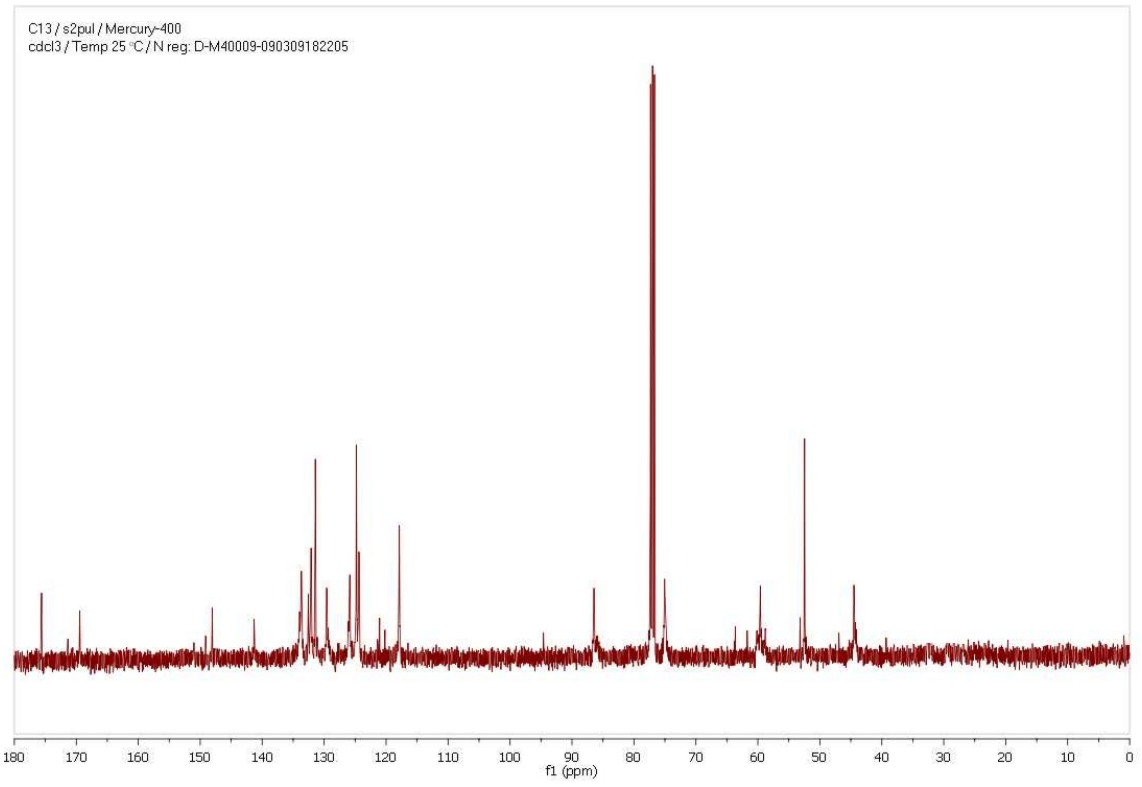
1j.


H1 / s2pul / Mercury-400
cdcl3 / Temp: 25 °C / N reg: N-PCB020609172323
O
O
NPhth
N
O
H
N
N
N
O
O
Boc Boc O
8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)

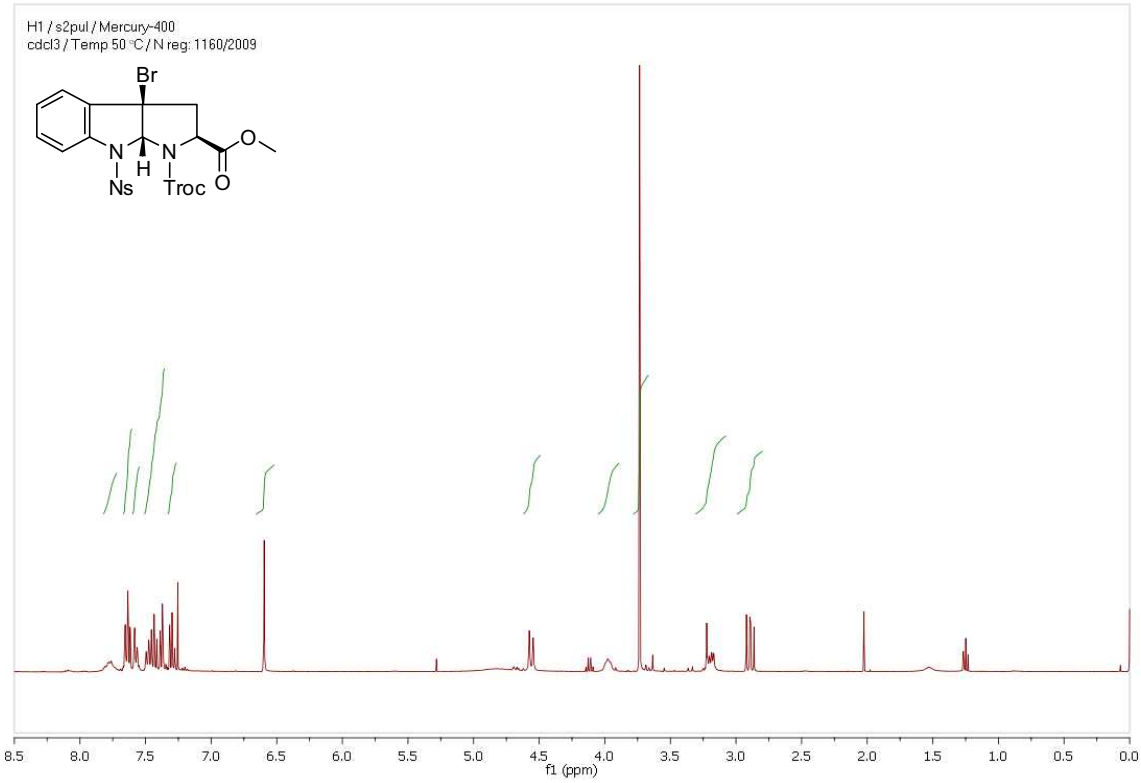

C13 / s2pul / Mercury-400
cdcl3 / Temp: 25 °C / N reg: N-PCB020609172323
180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

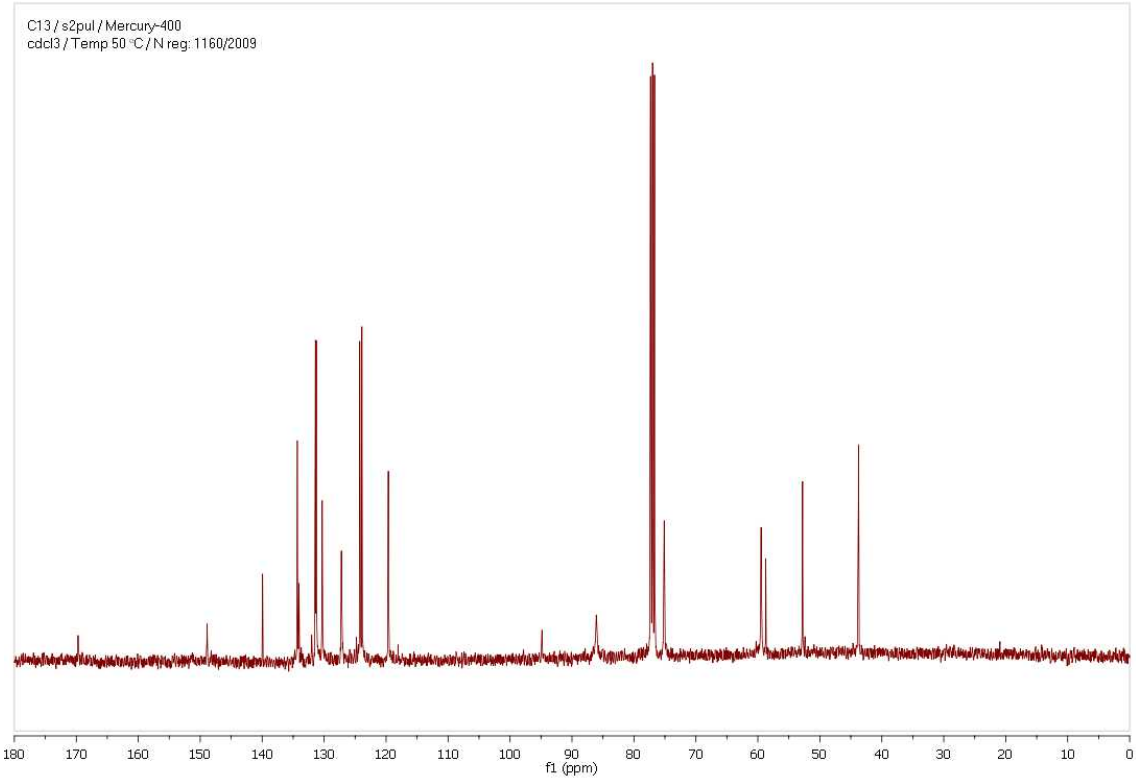
***endo*-3g.**


H1 / s2pul / Mercury-400
cdcl3 / Temp 25 °C / N reg: D-M40009-090309182205
Br
N
H
N
O
O
Ns
Troc
8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)

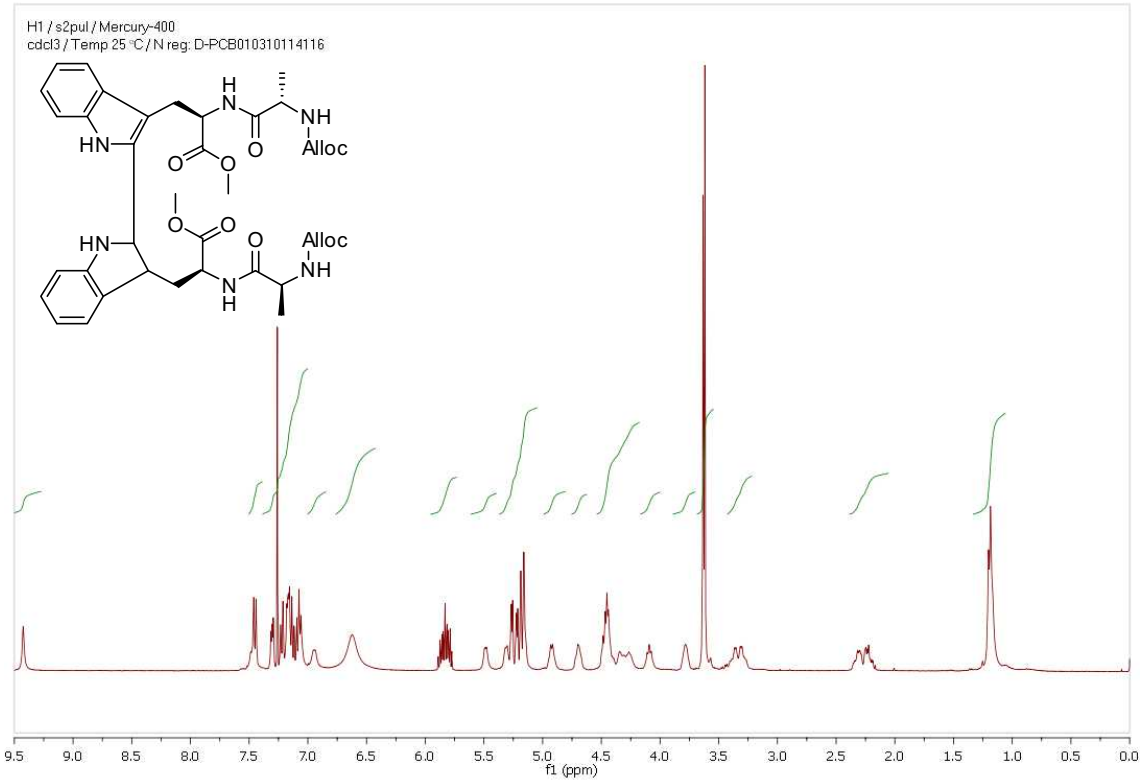

C13 / s2pul / Mercury-400
cdcl3 / Temp 25 °C / N reg: D-M40009-090309182205
180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

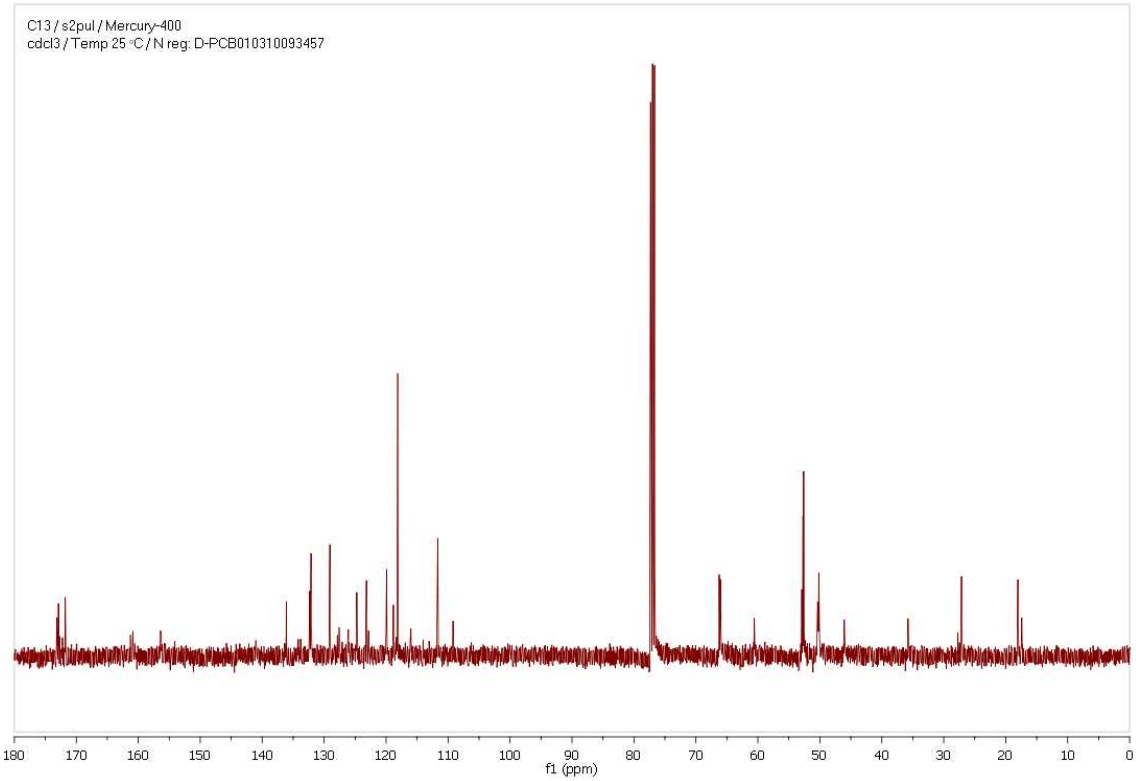
***exo*-3g.**


H1 / s2pul / Mercury-400
cdcl3 / Temp 50 °C / N reg: 1160/2009
Br
N
H
N
Ns
Troc
O
O
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

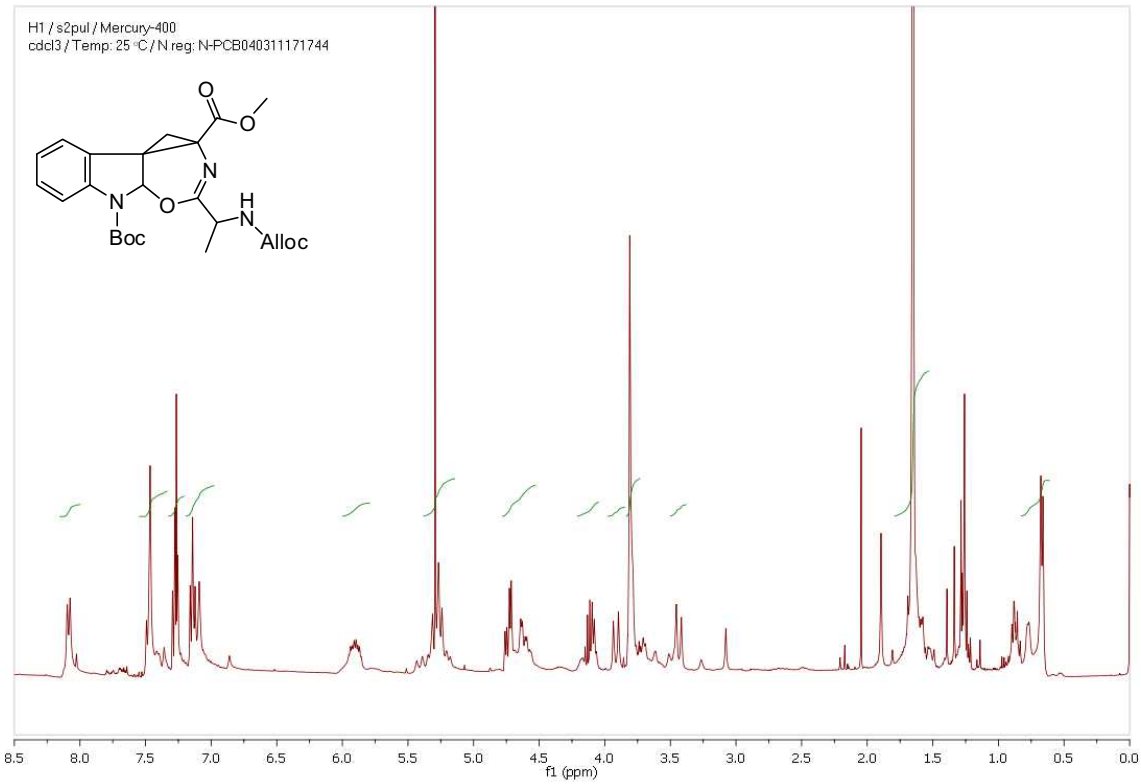

C13 / s2pul / Mercury-400
cdcl3 / Temp 50 °C / N reg: 1160/2009
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

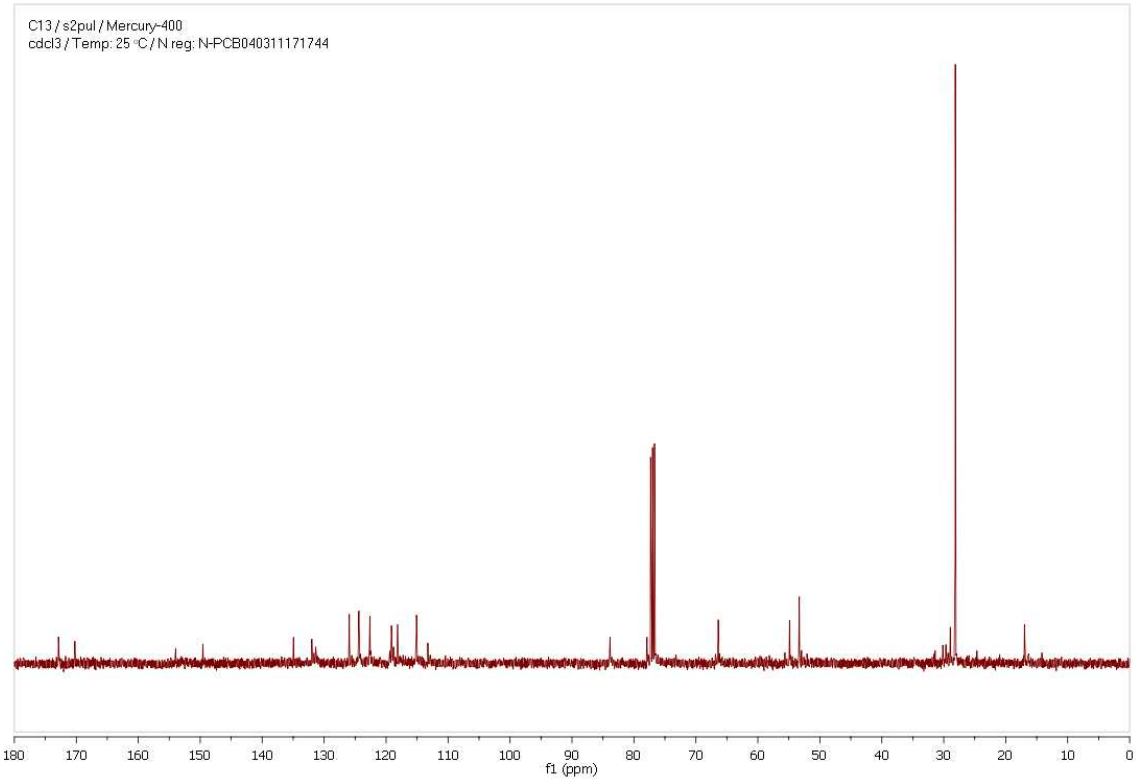
Compost 5

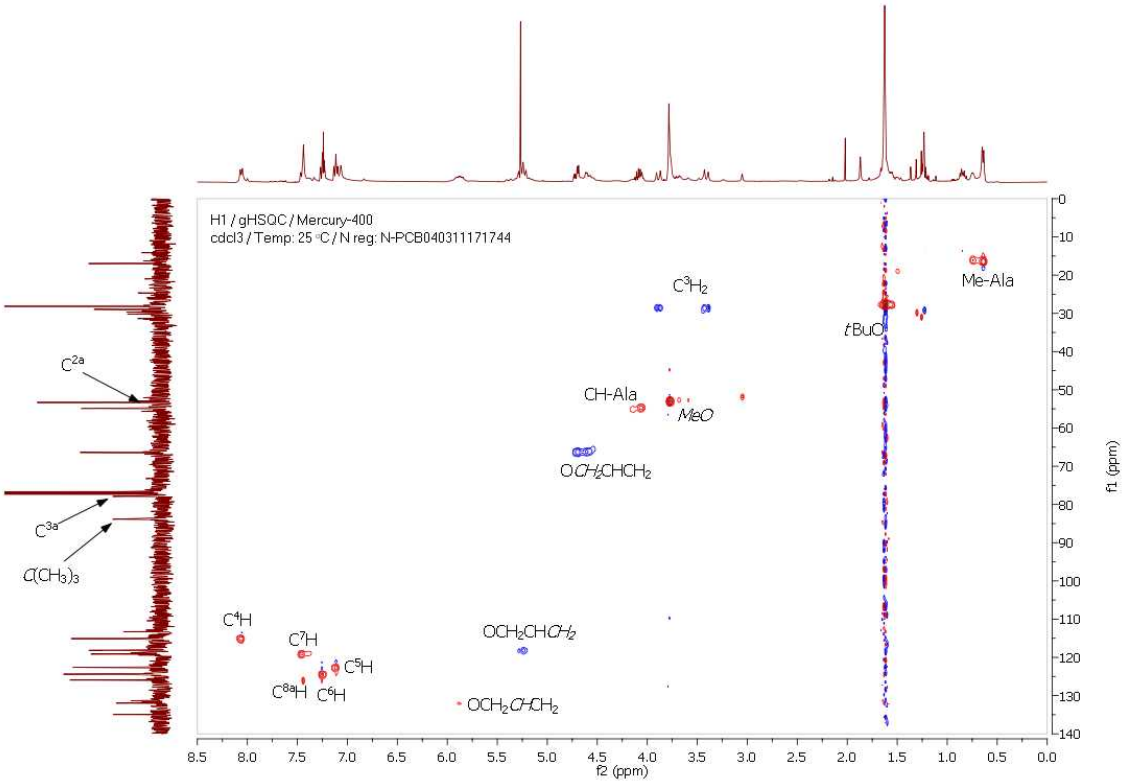

H1 / s2pul / Mercury-400
cdcl3 / Temp 25 °C / N reg: D-PCB010310114116
HN
H
N
NH
Alloc
O
O
O
O
HN
O
O
Alloc
NH
N
H
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)

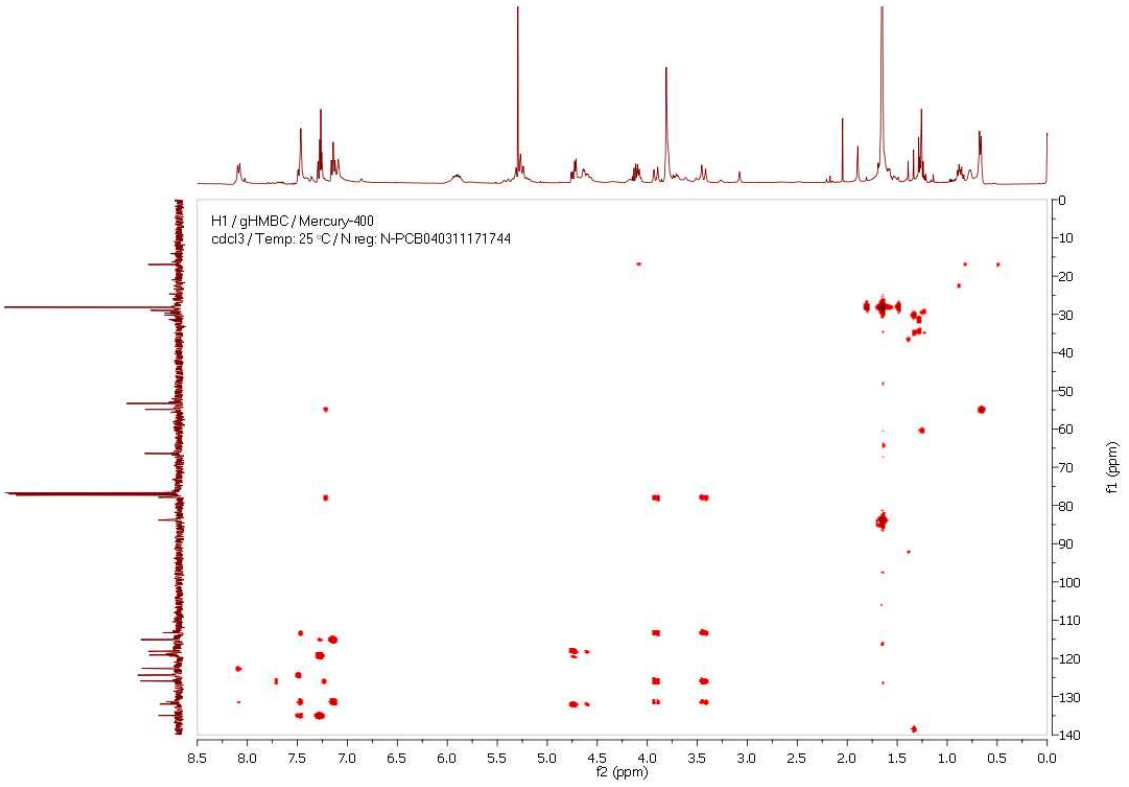

C13 / s2pul / Mercury-400
cdcl3 / Temp 25 °C / N reg: D-PCB010310093457
180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

Compost 8


H1 / s2pul / Mercury-400
cdcl3 / Temp: 25 °C / N reg: N-PCB040311171744
O
O
N
N
O
H
N
Boc
Alloc
8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)


C13 / s2pul / Mercury-400
cdcl3 / Temp: 25 °C / N reg: N-PCB040311171744
180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)


H1 / gHSQC / Mercury-400
cdcl3 / Temp: 25 °C / N reg: N-PCB040311171744
C3H2
Me-Ala
tBuO
CH-Ala
MeO
OCH2CHCH2
C2a
C3a
C(CH3)3
C4H
C7H
C5H
C8aH
C6H
OCH2CHCH2
OCH2CHCH2
f1 (ppm)
f2 (ppm)


H1 / gHMBC / Mercury-400
cdcl3 / Temp: 25 °C / N reg: N-PCB040311171744
f1 (ppm)
f2 (ppm)

Annex 3

Espectres d’RMN

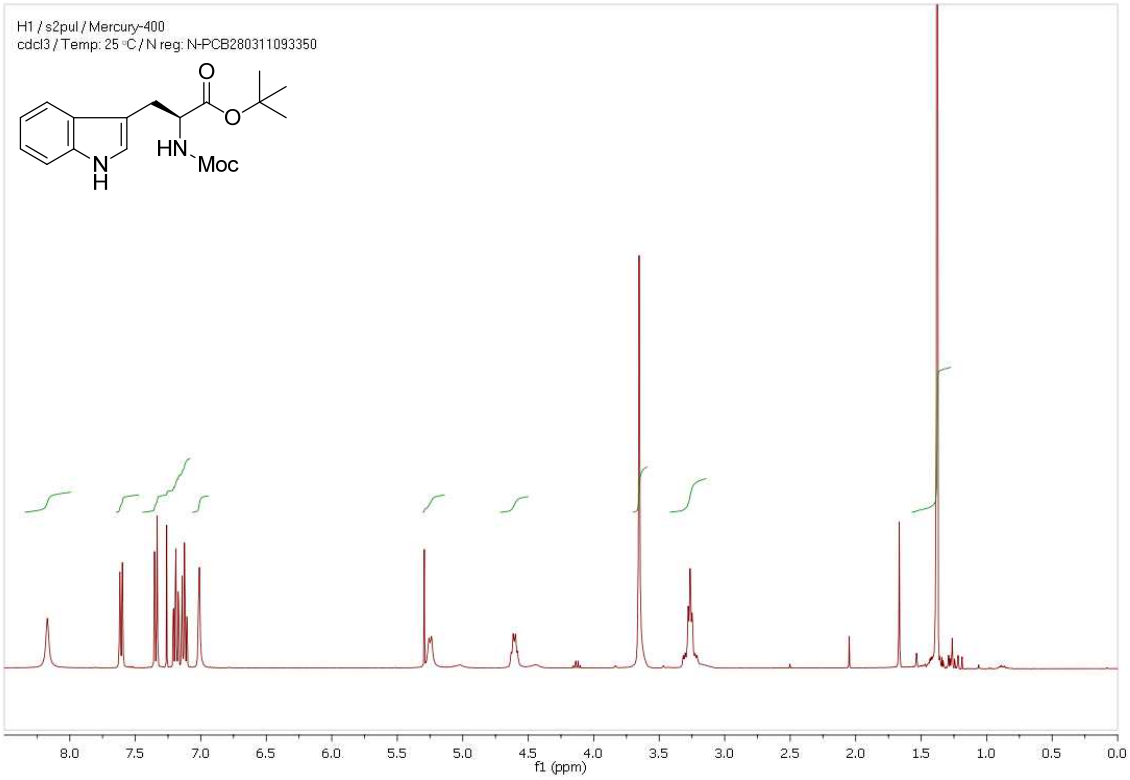
Índex Annex 3

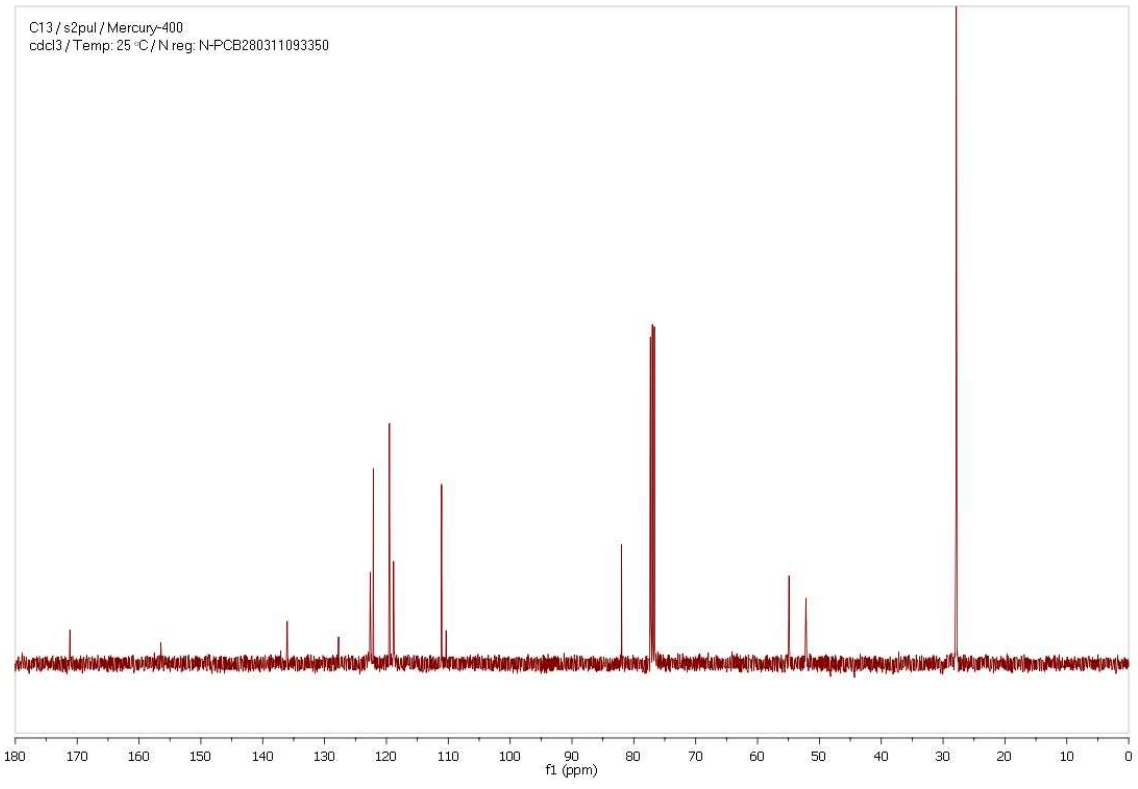
ESPECTRES D'RMN

Espectres d'RMN

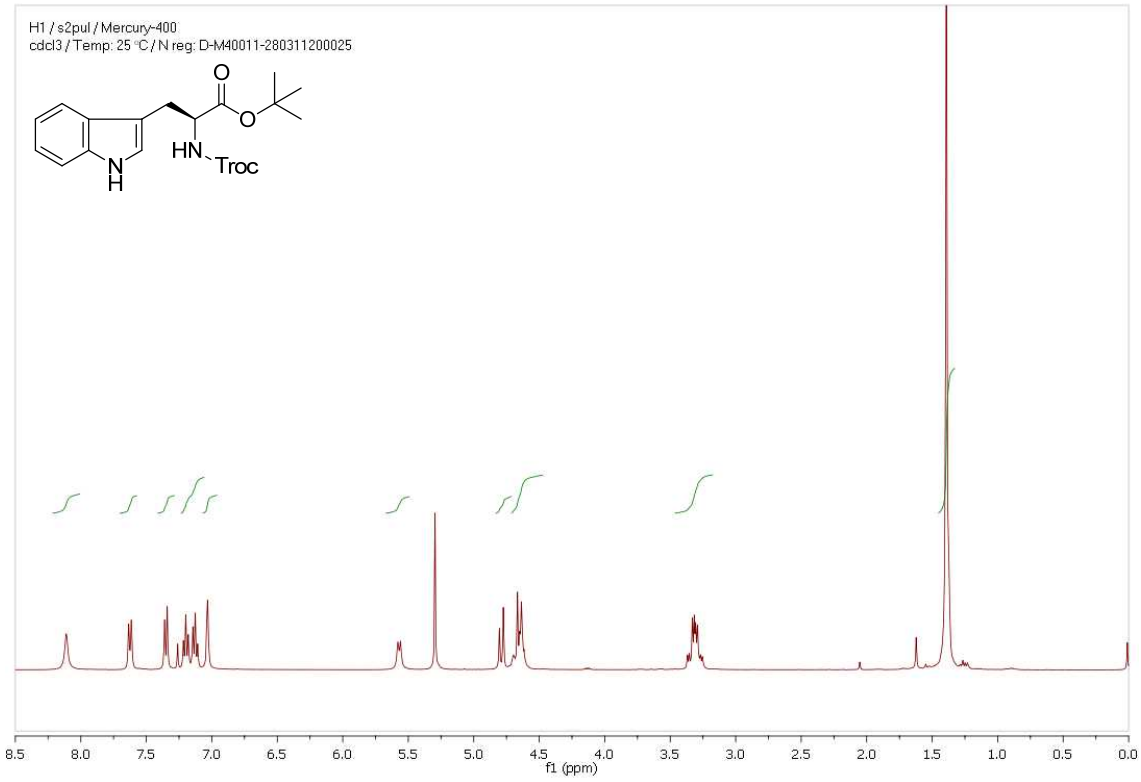
1. Compostos 2

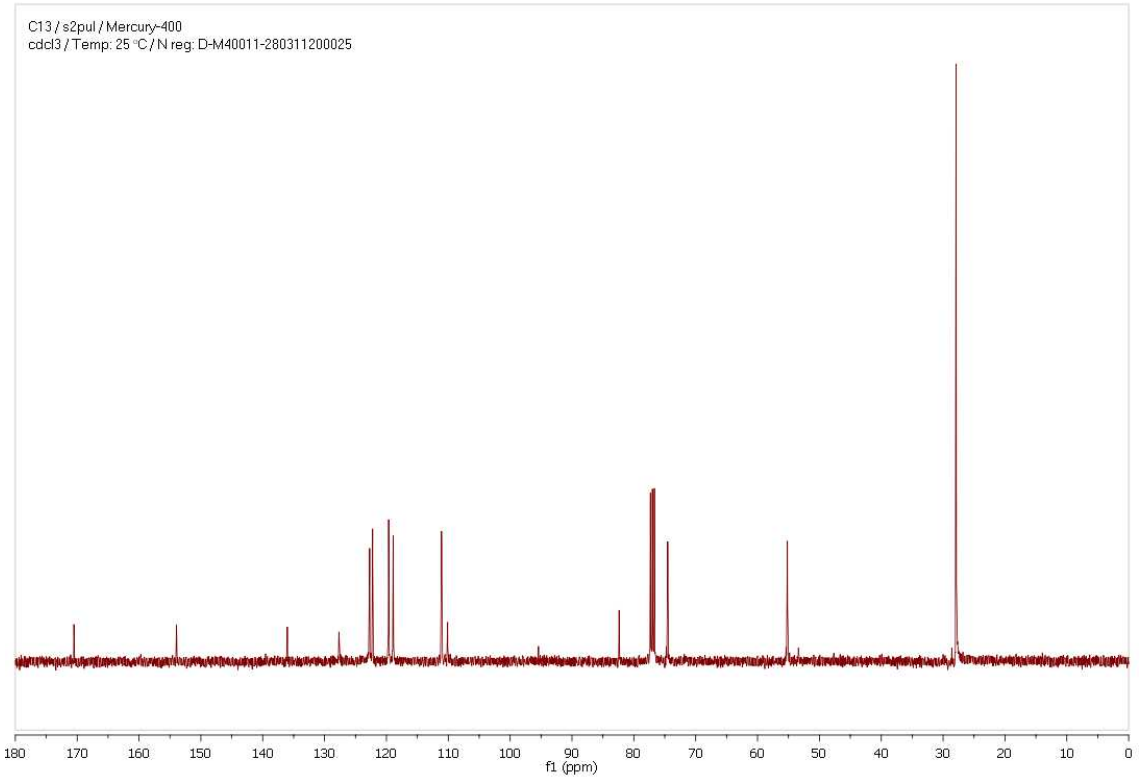
1.1 N^{α}-Moc-Trp-O*t*Bu (2g)



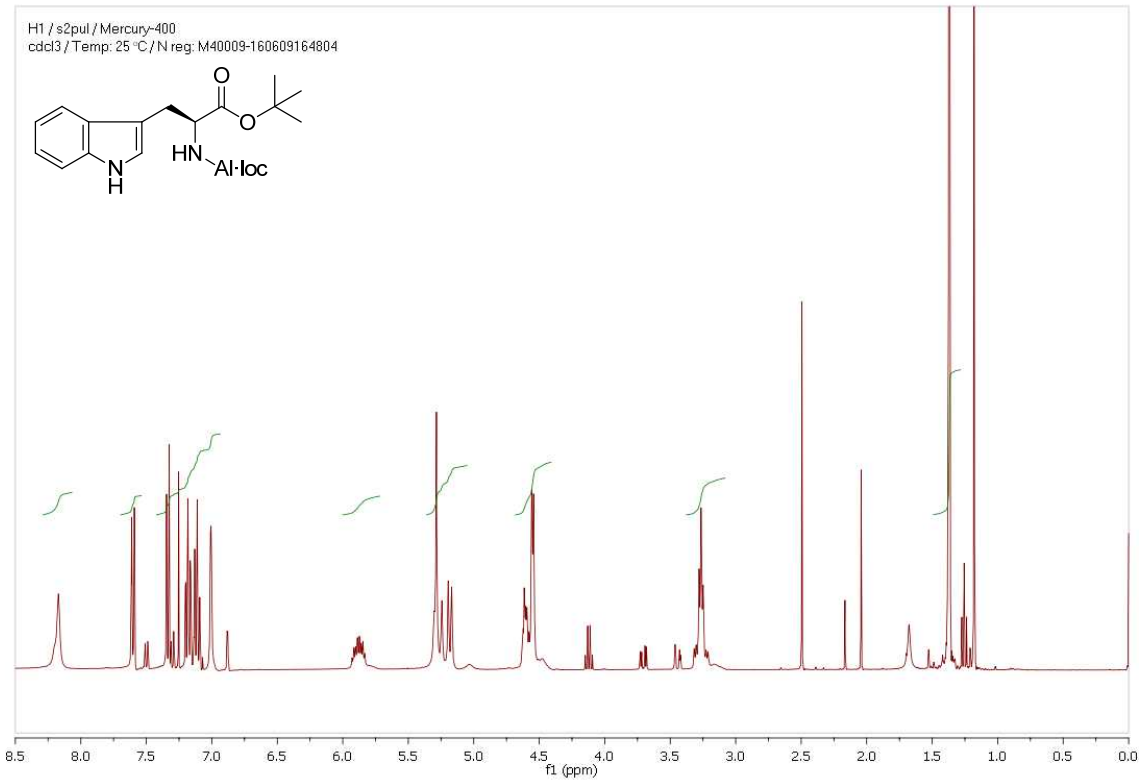


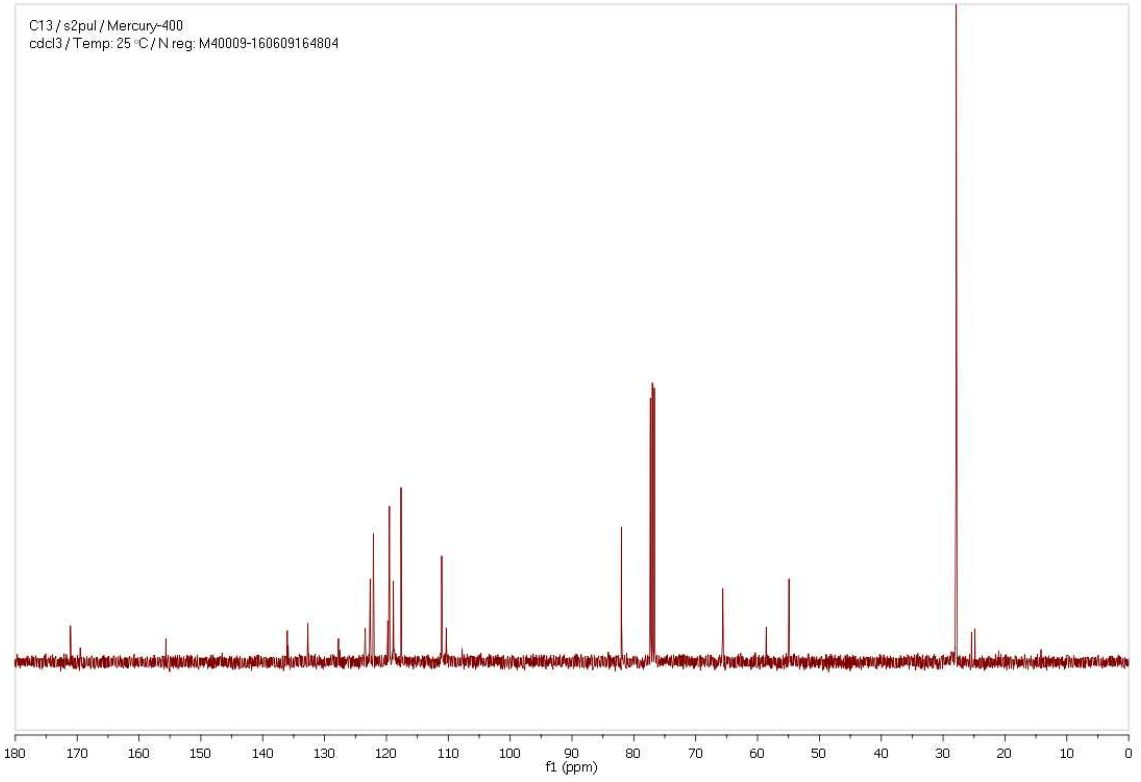
1.2 N^{α}-Troc-Trp-O*t*Bu (2h)



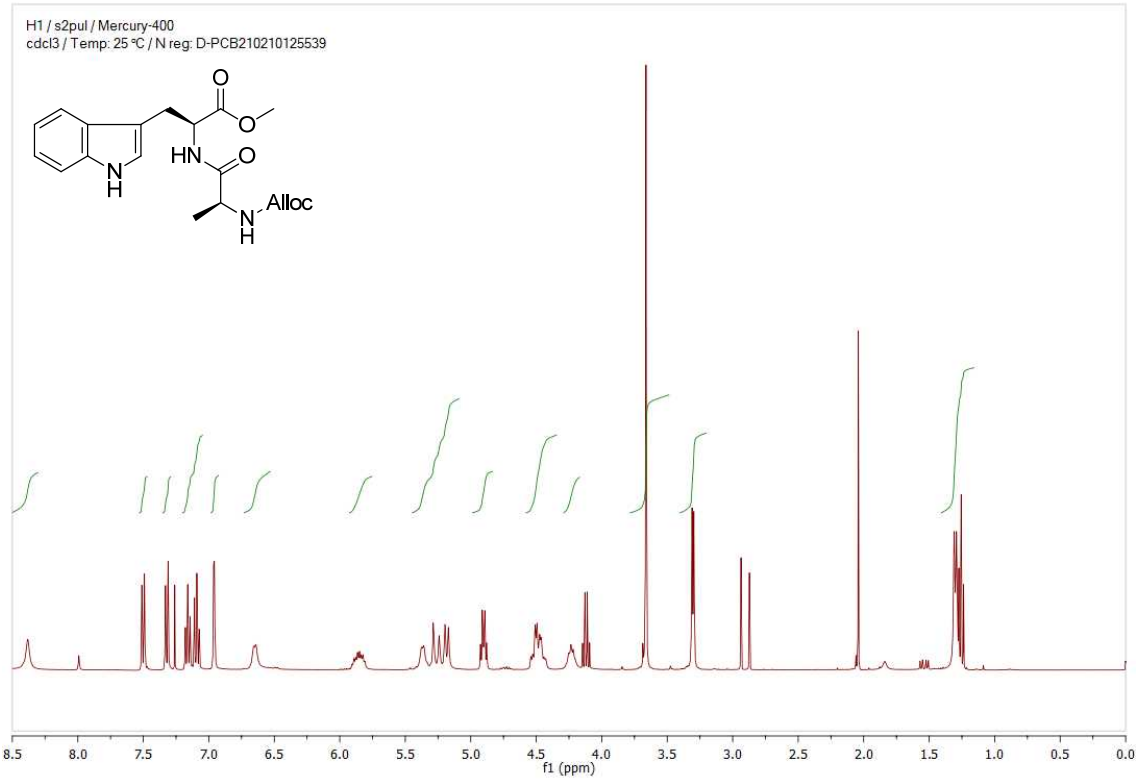


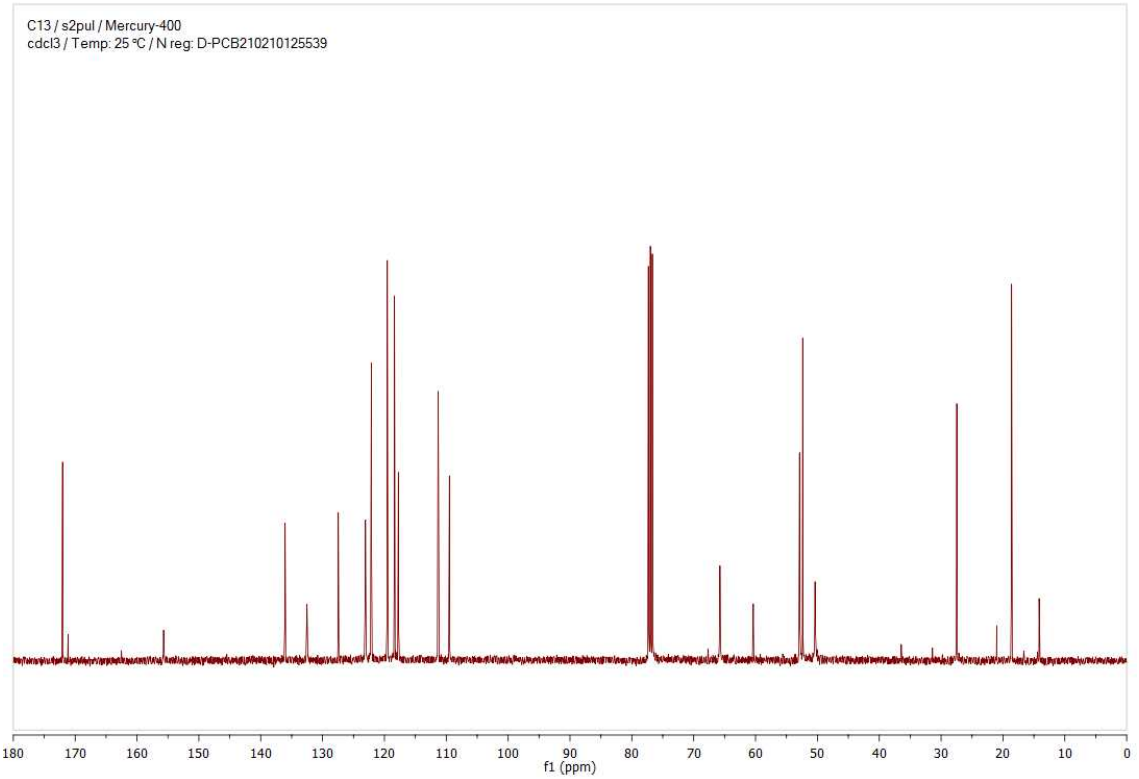
1.3 N^{α}-Al·loc-Trp-O*t*Bu (2i)





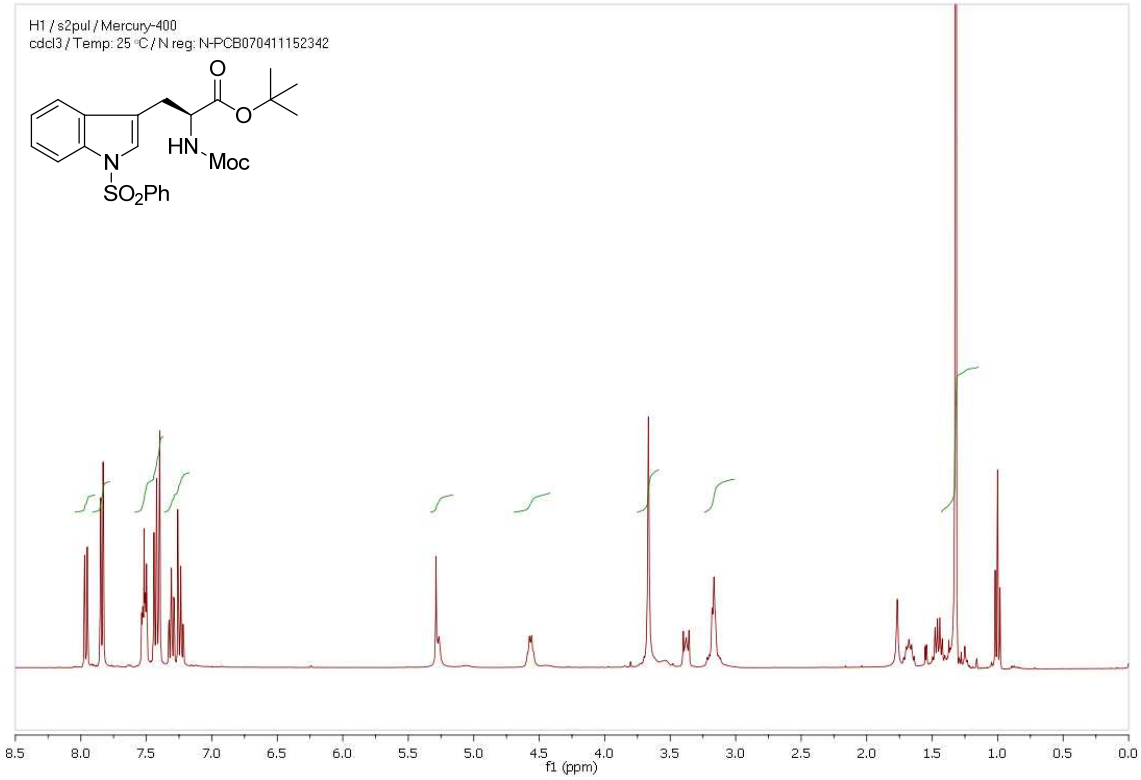
1.4 N^{α}-Al·loc-Ala-Trp-OMe (2k)

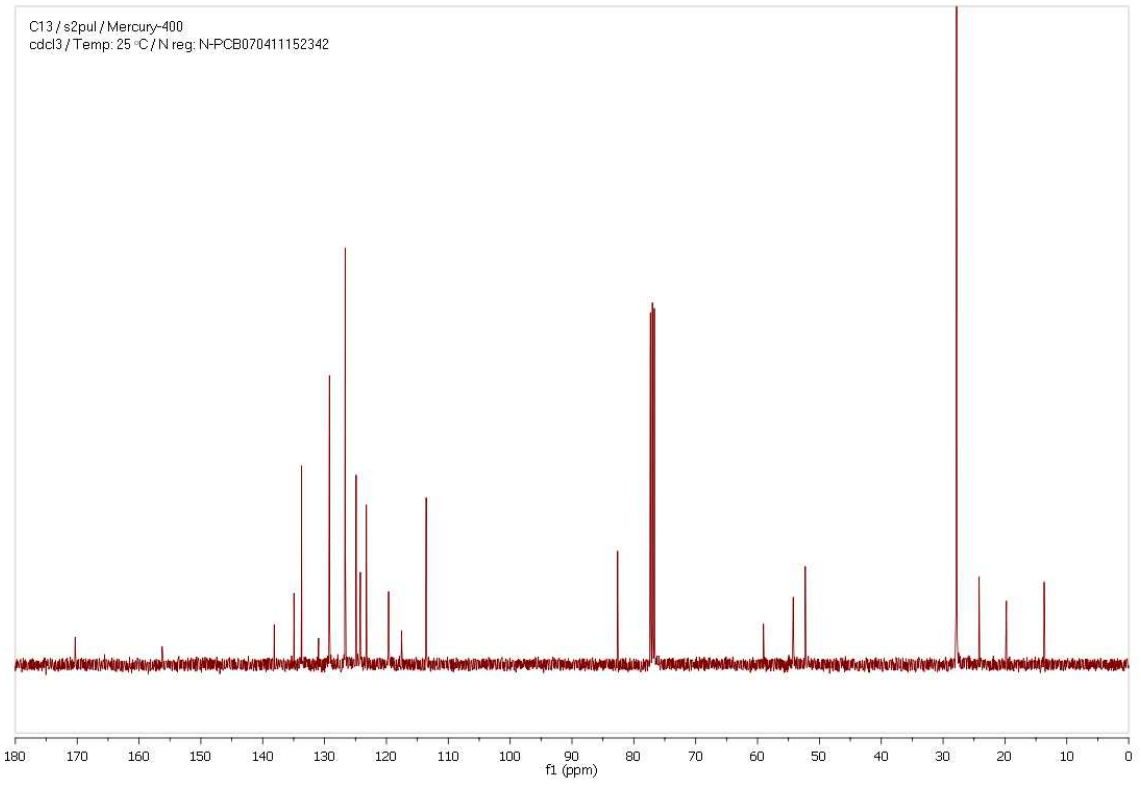




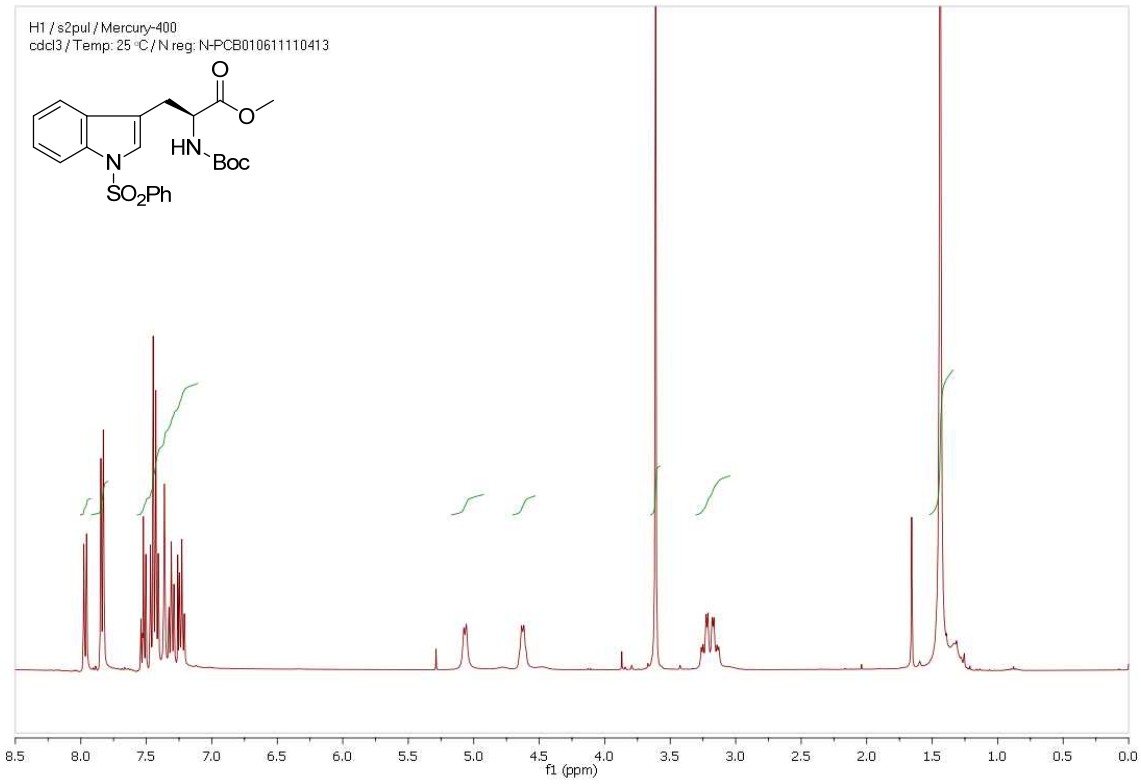
2. Compostos 3

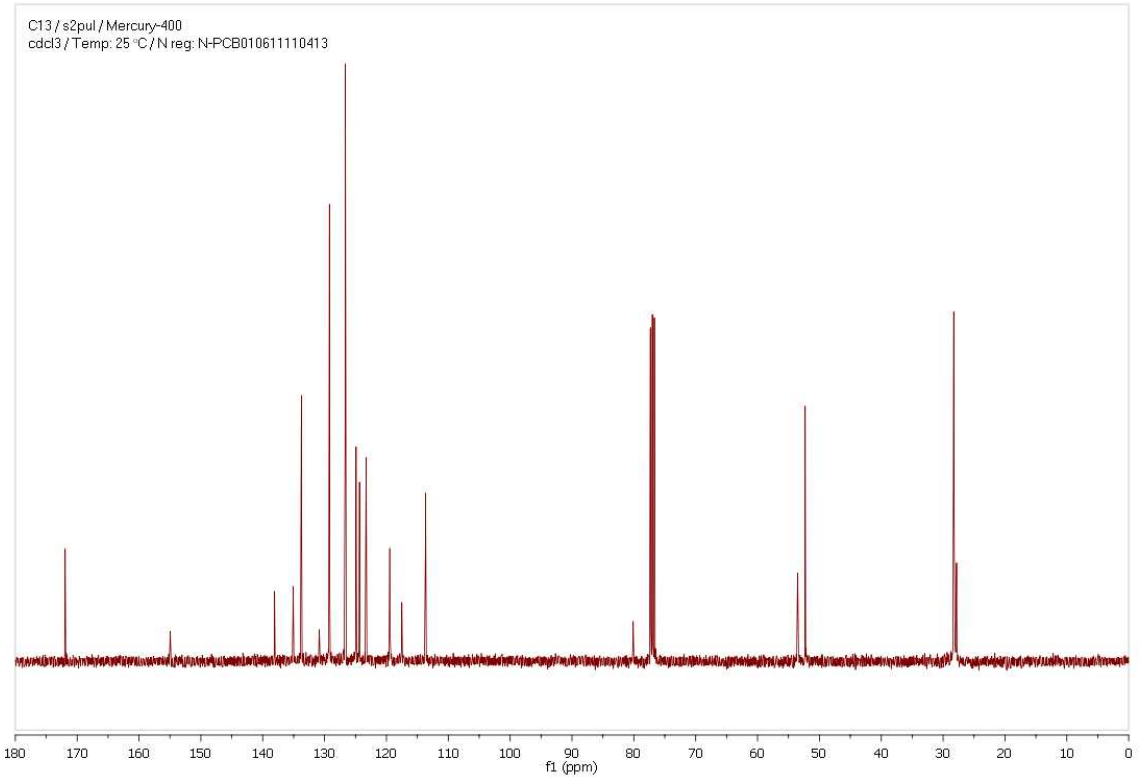
2.1 N^{i}-Fenilsulfonil-N^{α}-metoxicarboniltriptofanat de *terc*-butil (3b)



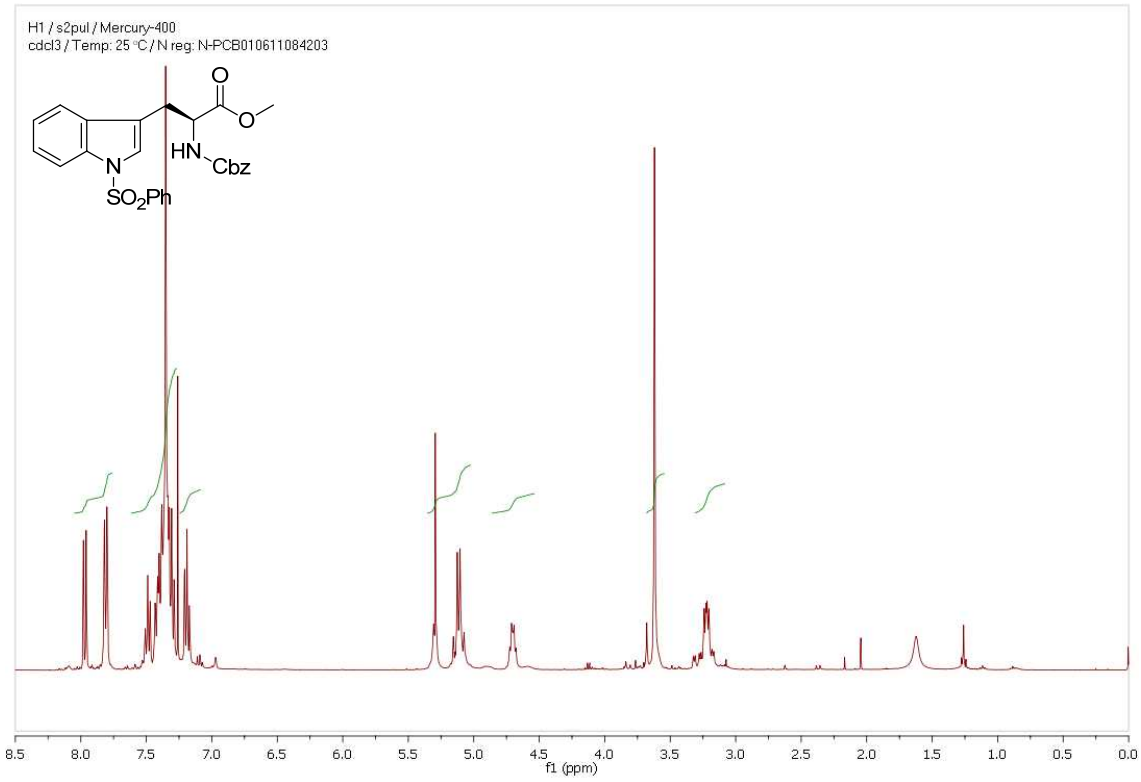


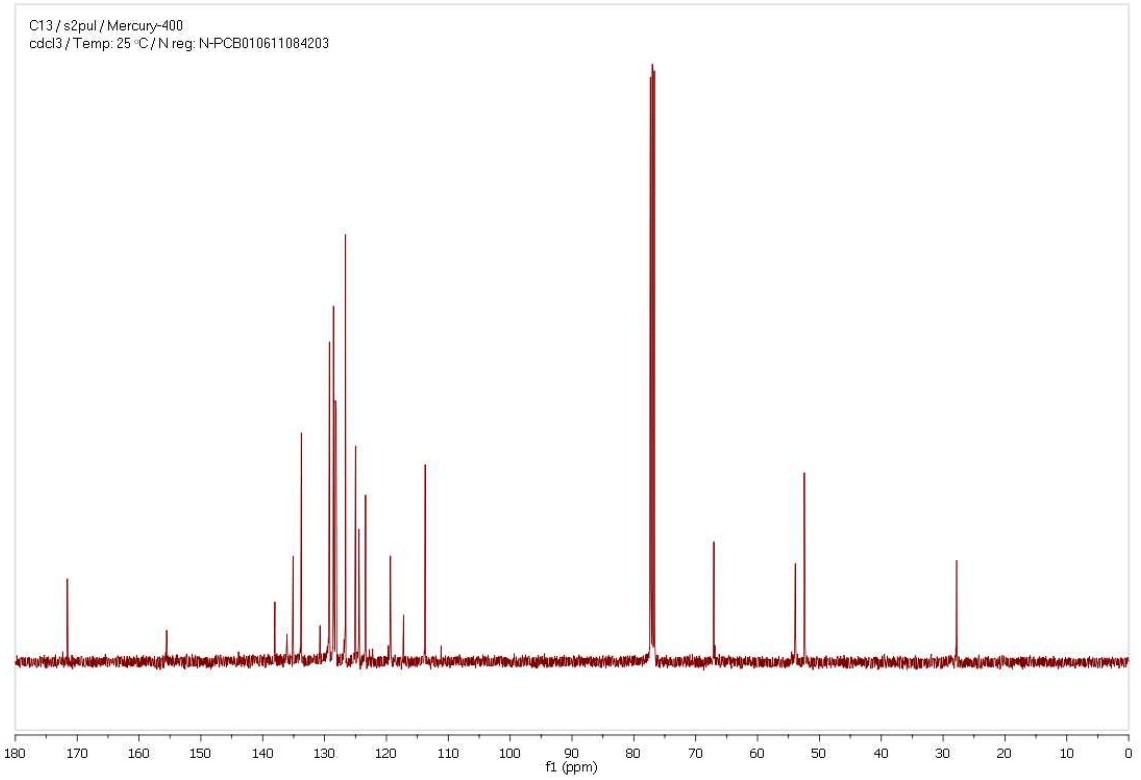
2.2 N^{α}-*terc*-Butoxicarbonil-N^{i}-fenilsulfoniltriptofanat de metil (3c)



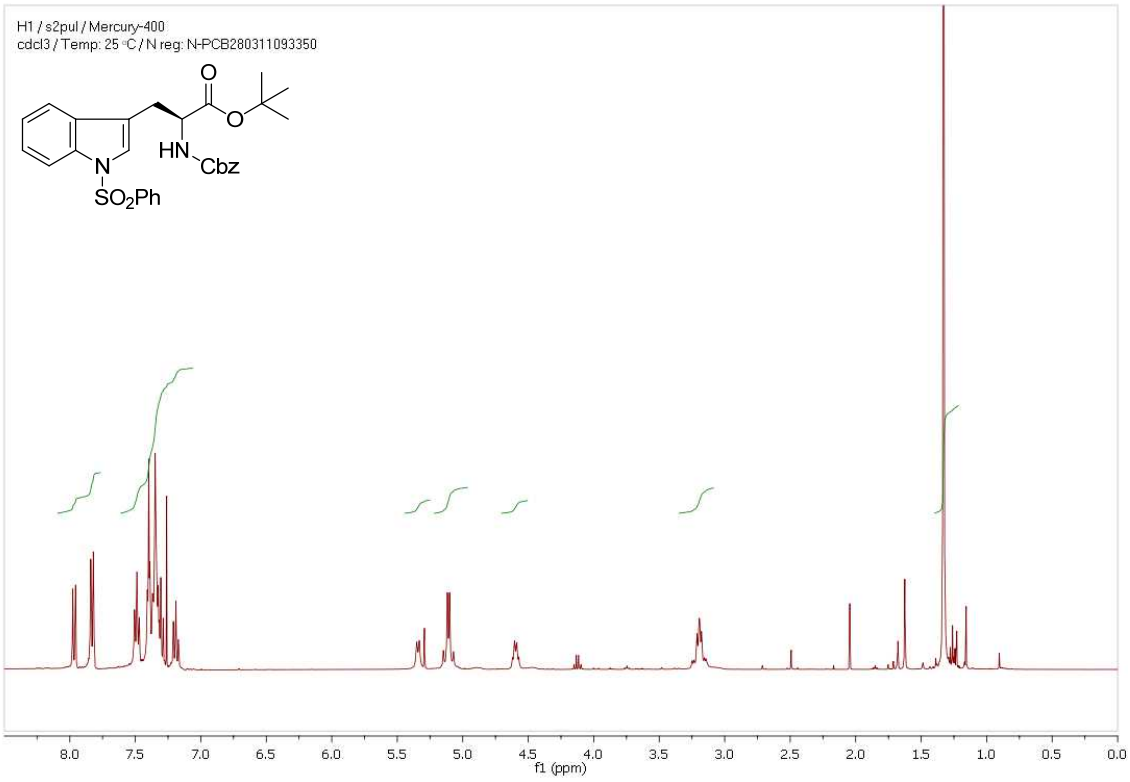


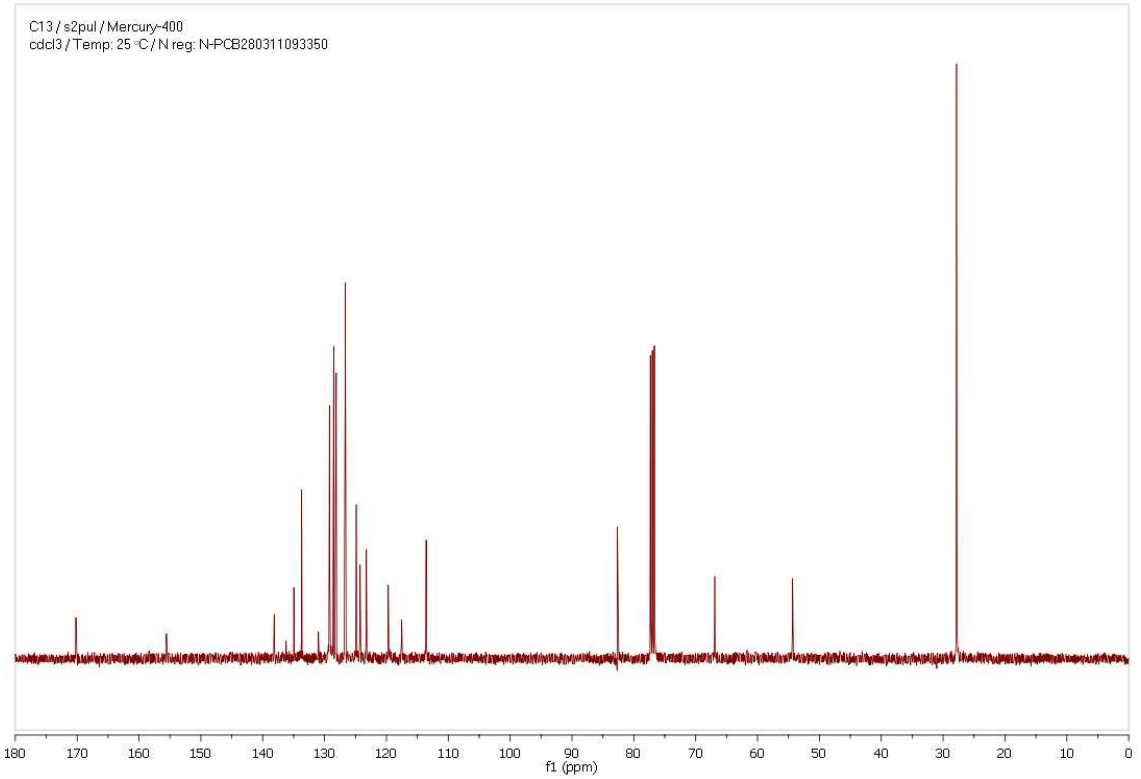
2.3 N^{α}-Benziloxicarbonil-N^{i}-fenilsulfoniltriptofanat de metil (3d)



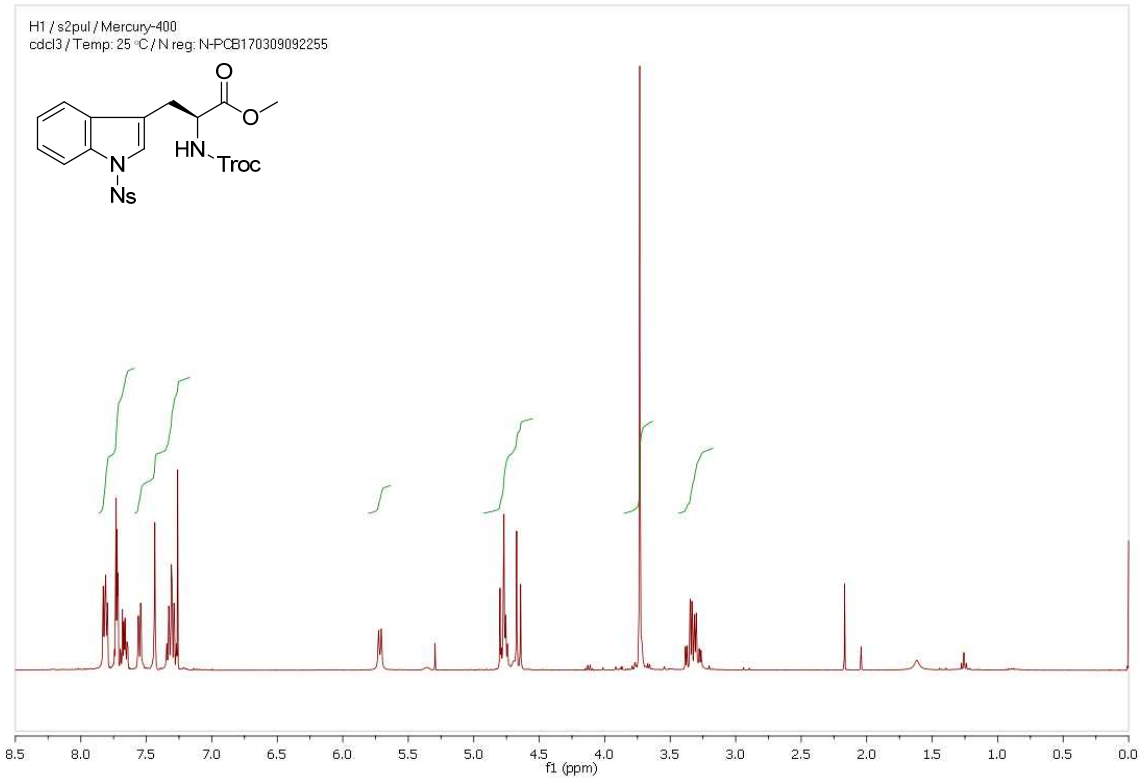


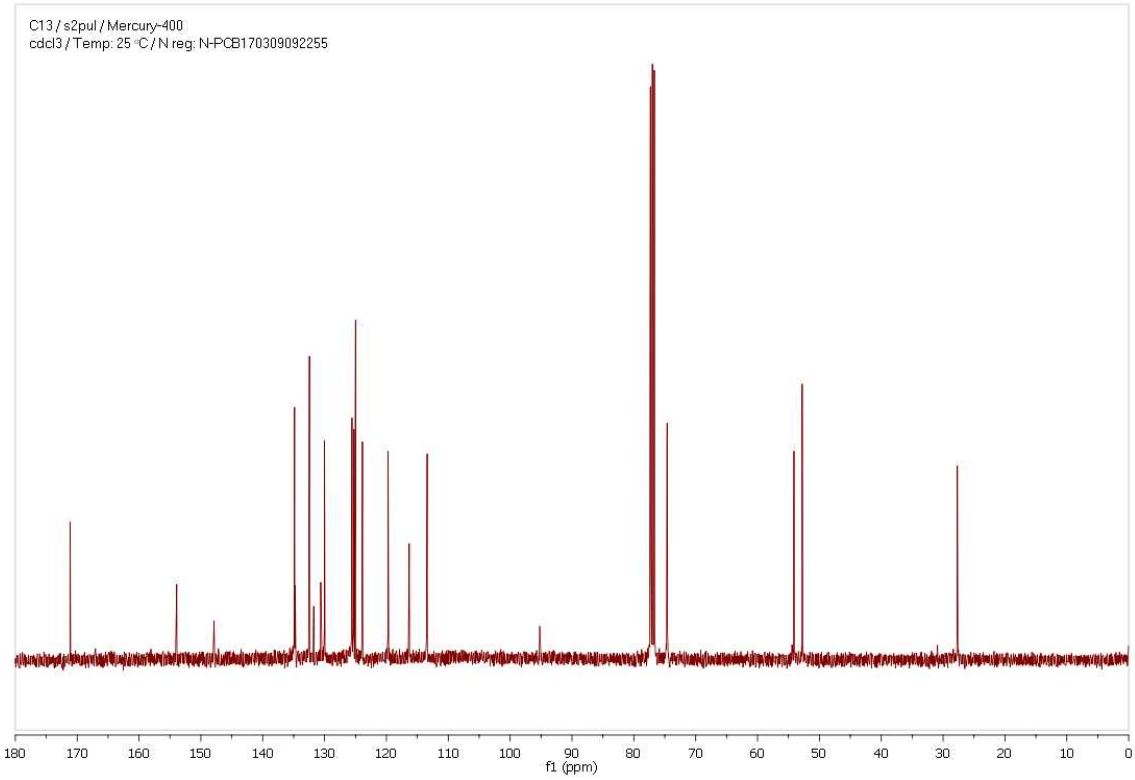
2.4 N^{α}-Benziloxicarbonil-N^{i}-fenilsulfoniltriptofanat de *terc*-butil (3e)



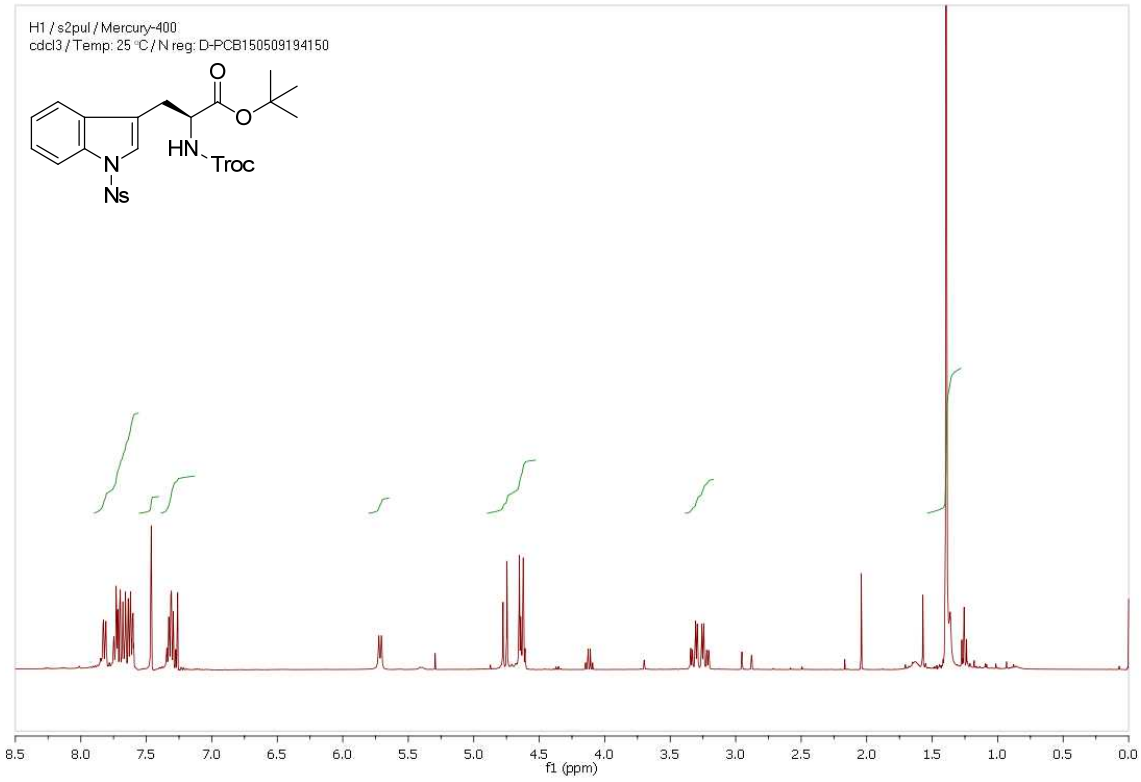


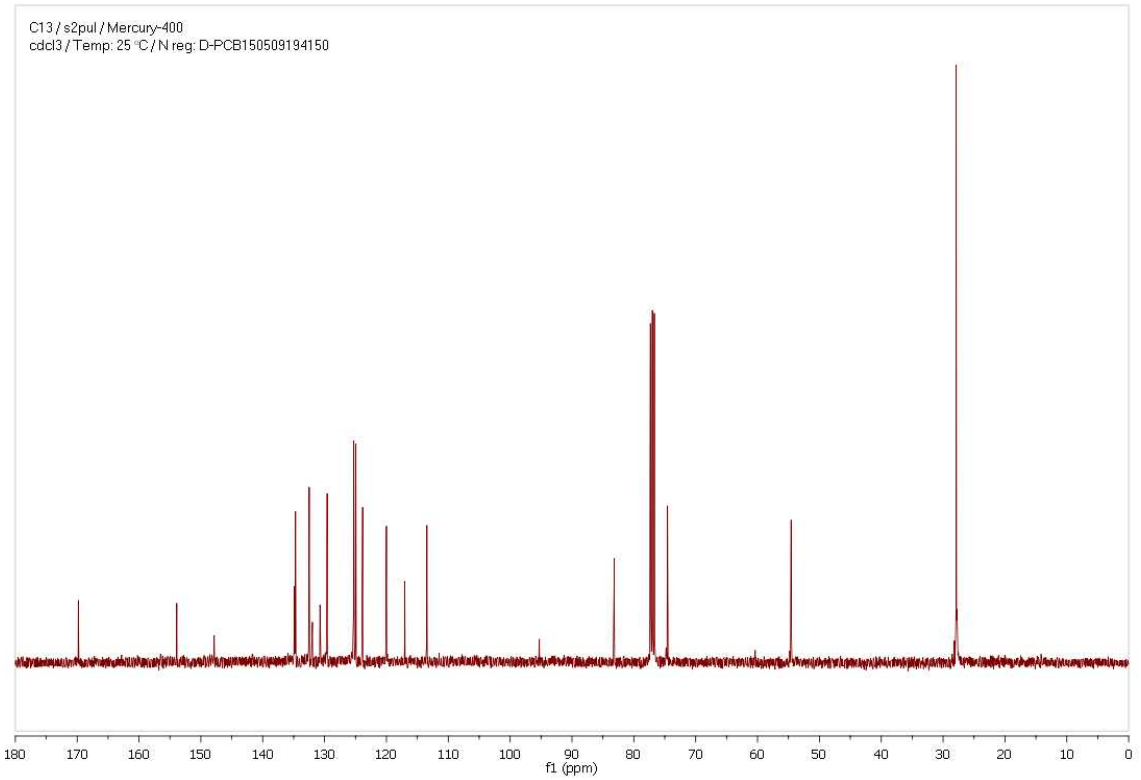
2.5 N^{α}-(2,2,2-Tricloroetoxicarbonil)-N^{i}-((2-nitrofenil)sulfonil)triptofanat de metil (3f)



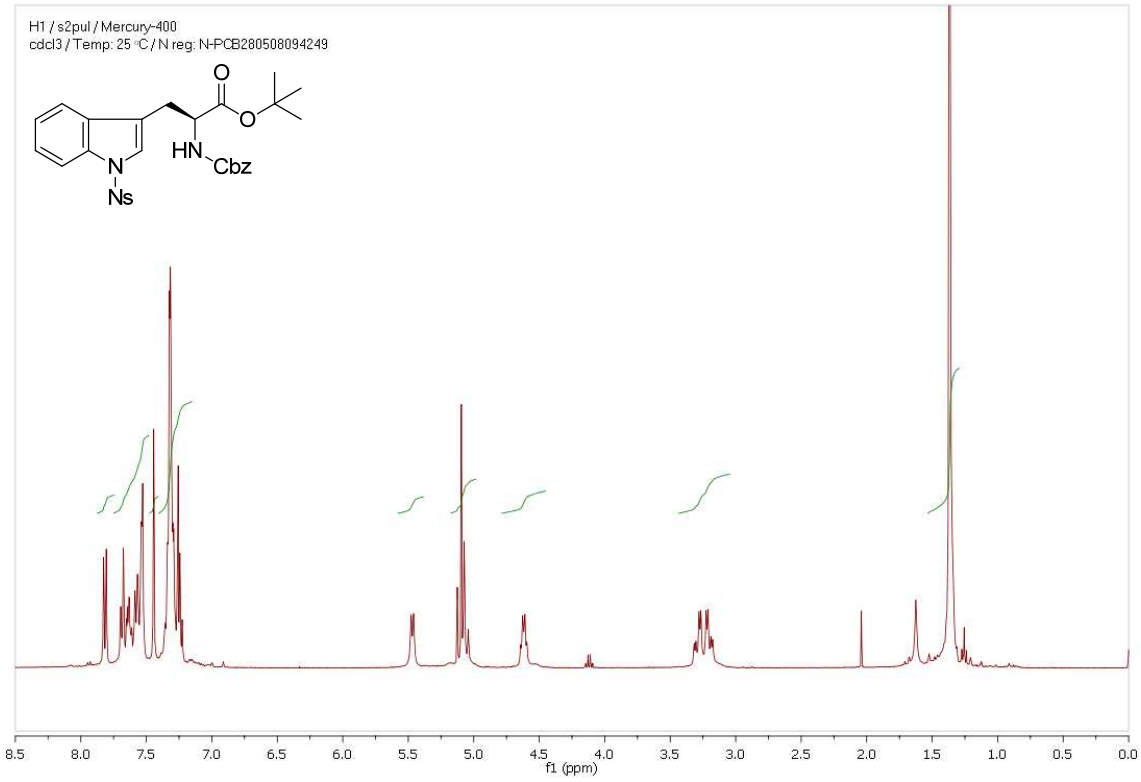


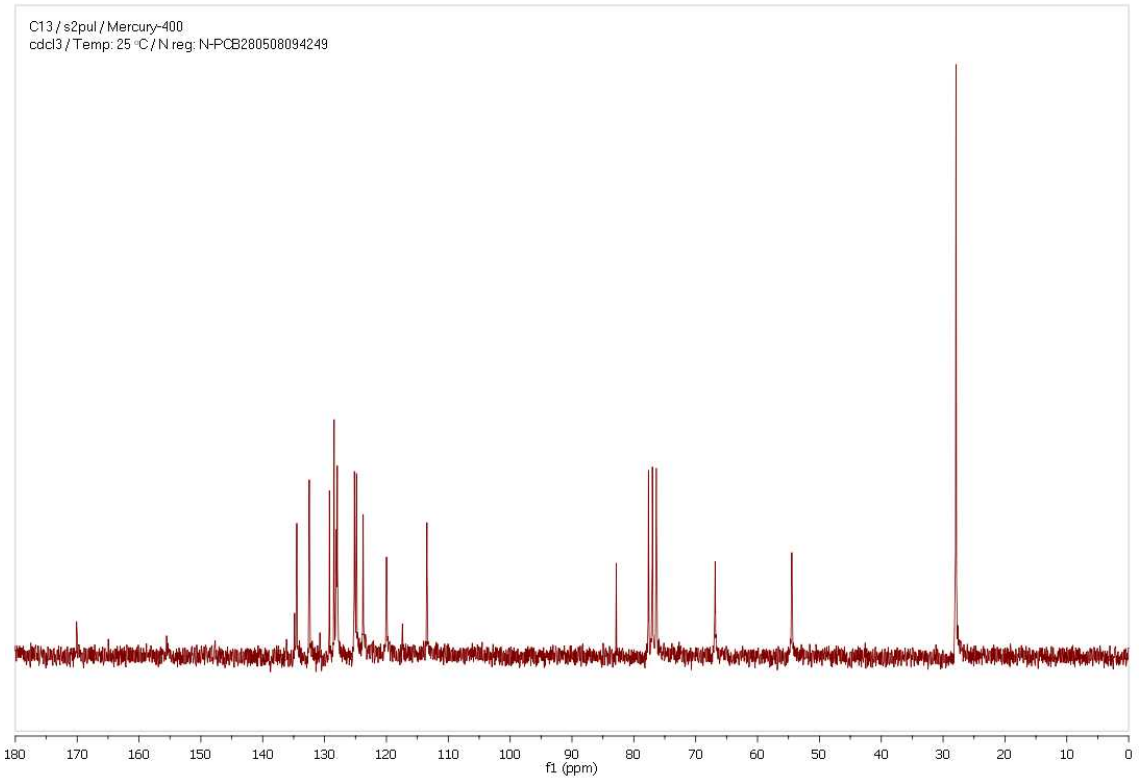
2.6 N^{i}-((2-Nitrofenil)sulfonil)-N^{α}-(2,2,2-tricloroetoxicarbonil)triptofanat de *terc*-butil (3g)



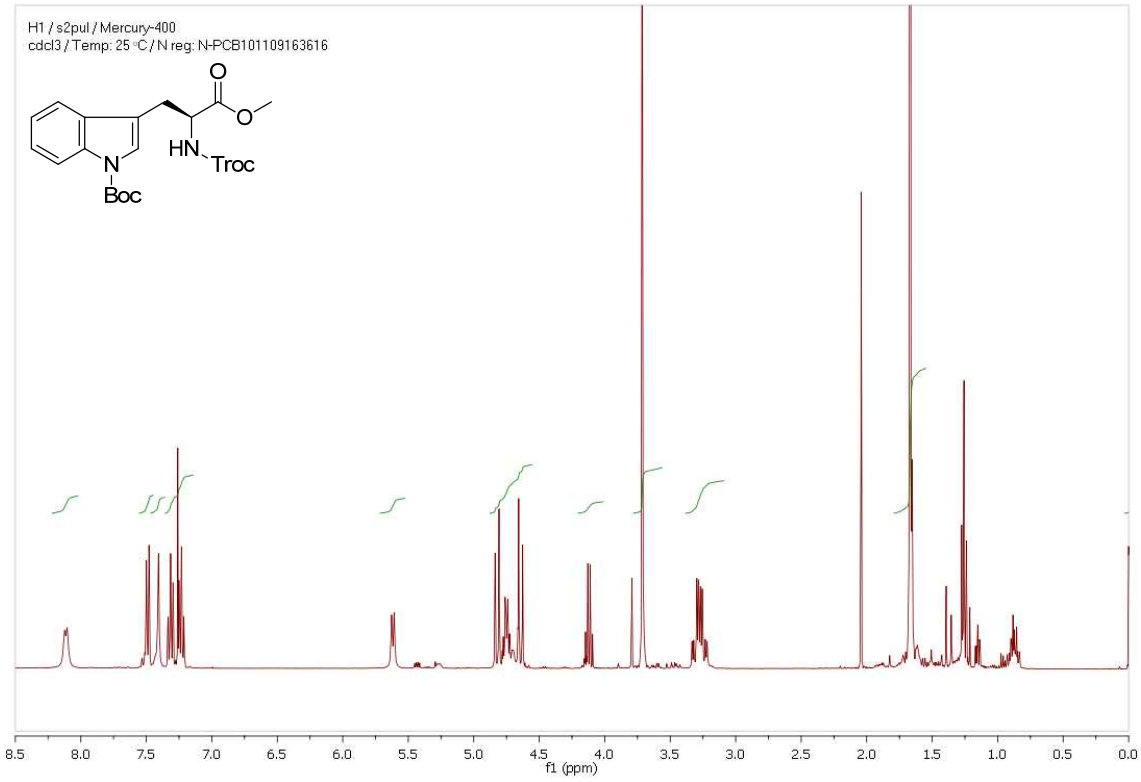


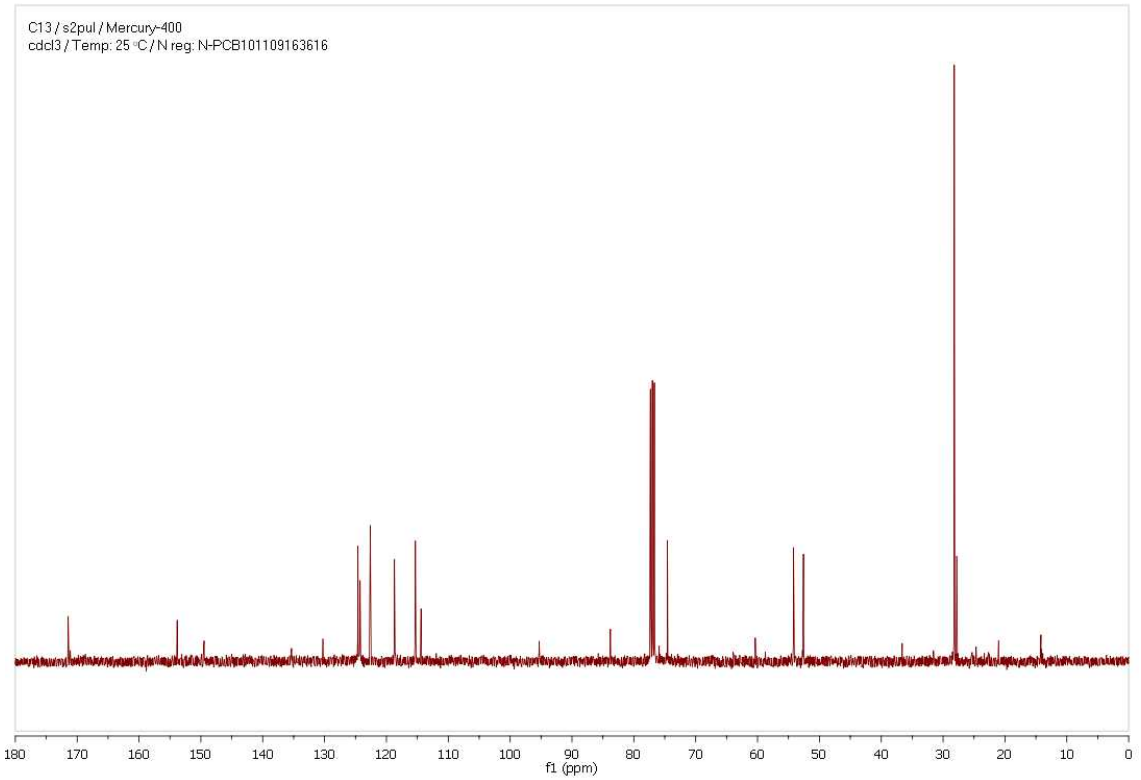
2.7 N^{α}-Benziloxicarbonil-N^{i}-((2-nitrofenil)sulfonil)triptofanat de *terc*-butil (3h)



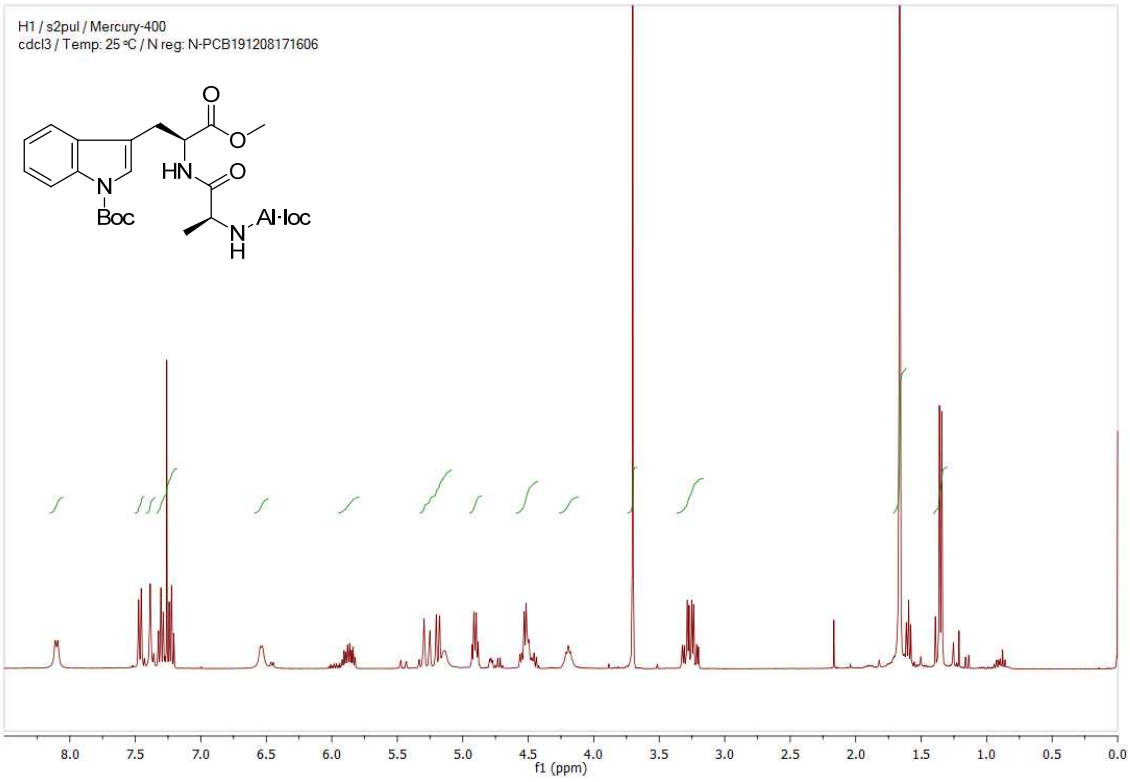


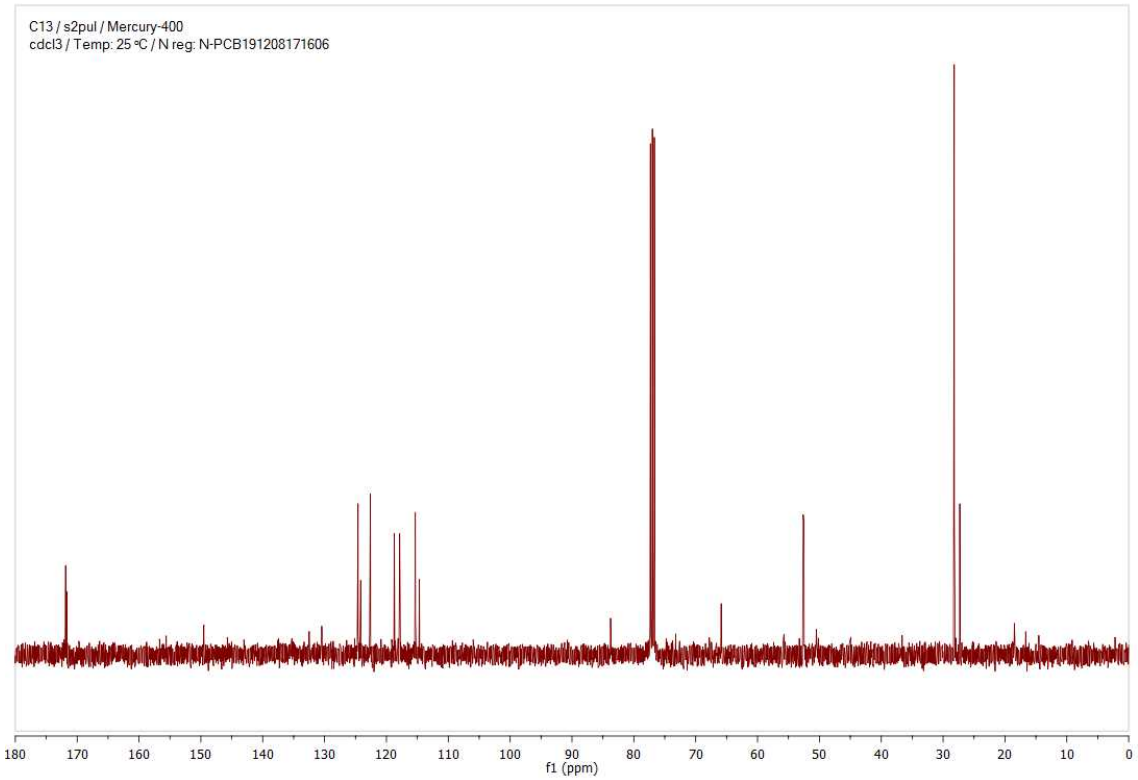
2.8 *N*^{i}-*terc*-Butoxicarbonil-*N*$^{\alpha}$-(2,2,2-tricloroetoxicarbonil)triptofanat de metil (3j)



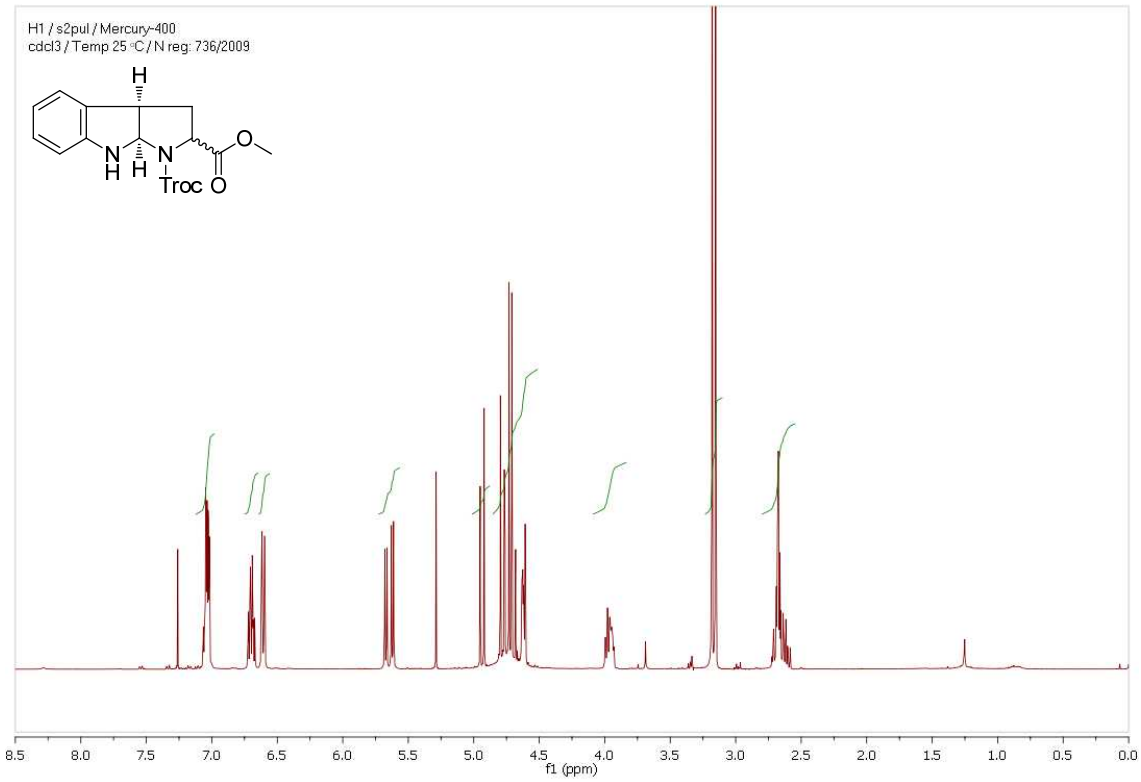


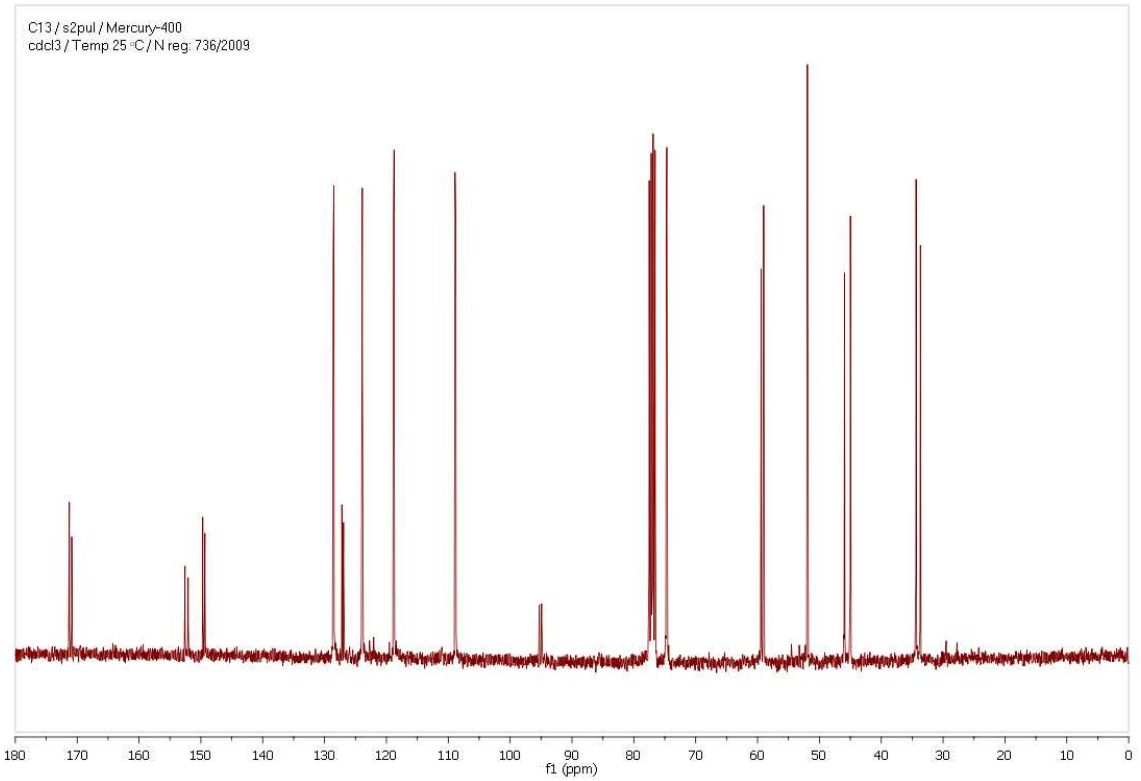
2.9 N^{α}-(N^{α}-Al·liloxicarbonilalaninil)-N^{i}-*terc*-butoxicarboniltriptofanat de metil (3k)



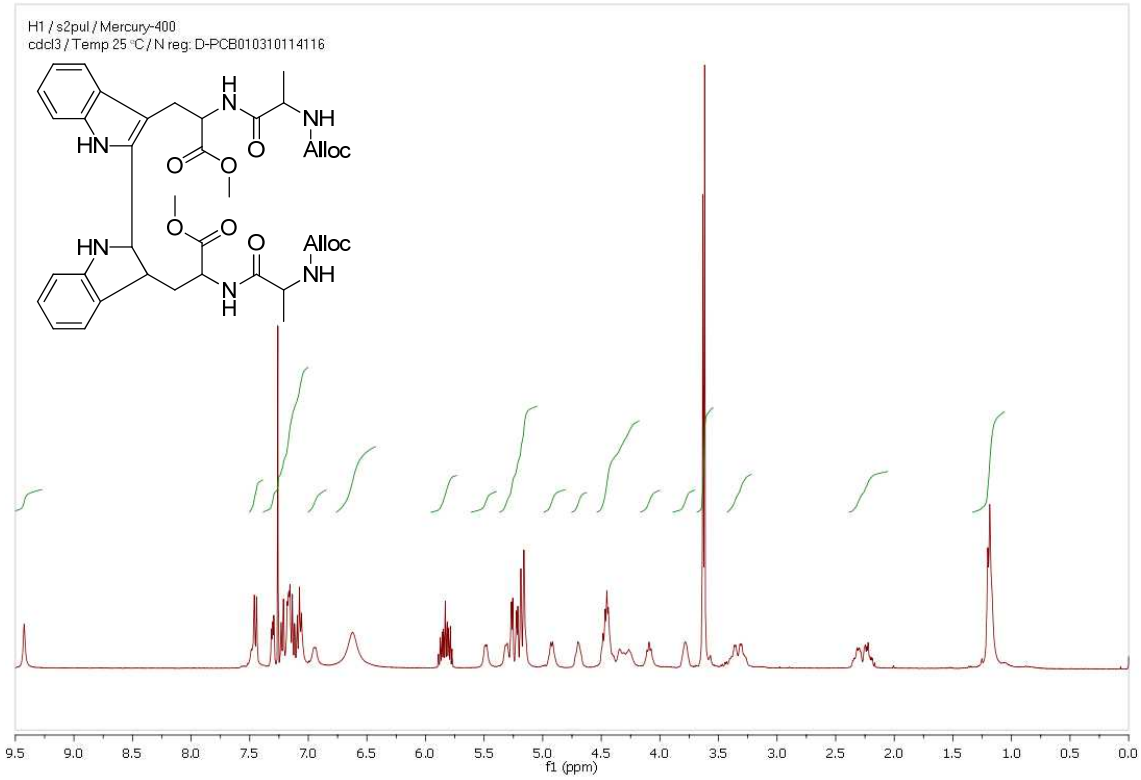


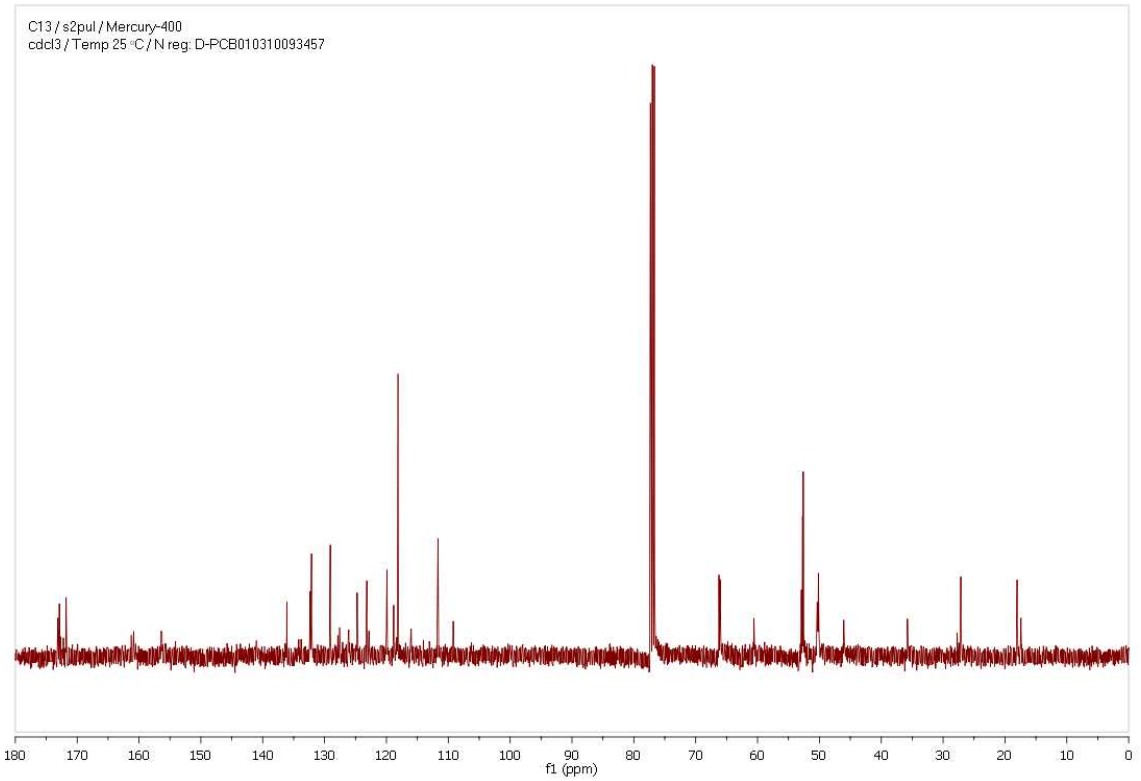
3. 1-(2,2,2-Tricloroetoxicarbonil)-HPI-2-carboxilat de metil (4b)





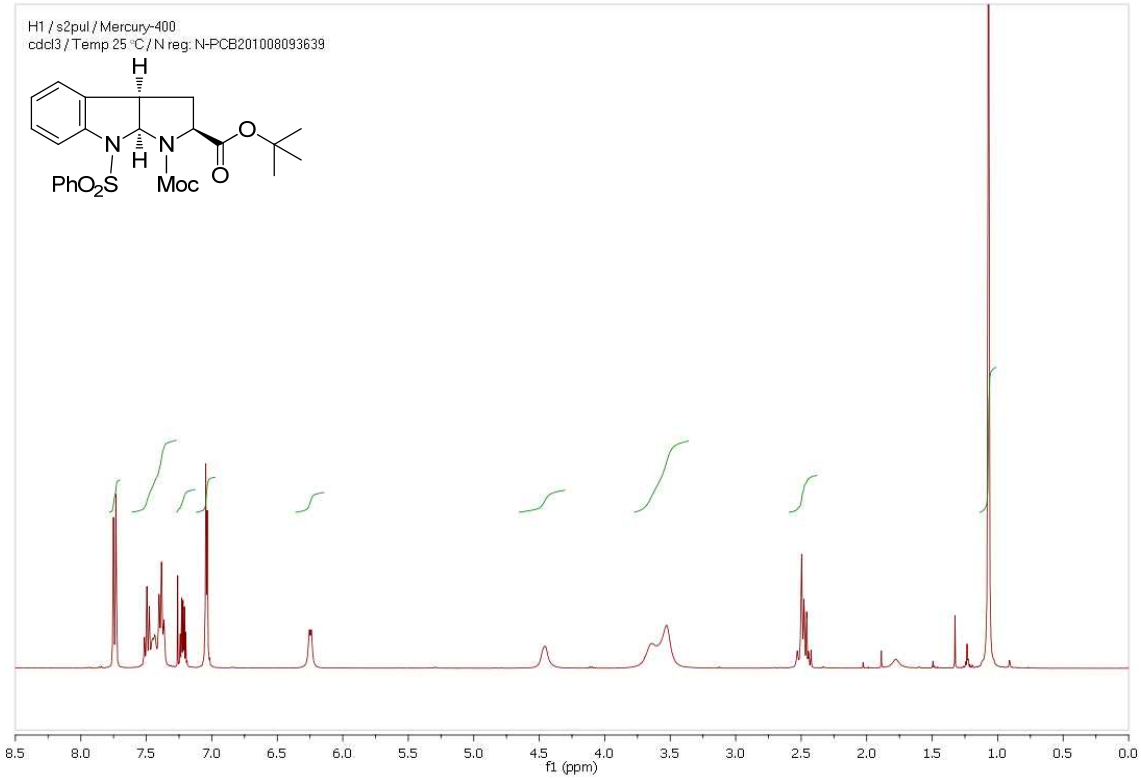
4. Compost 6

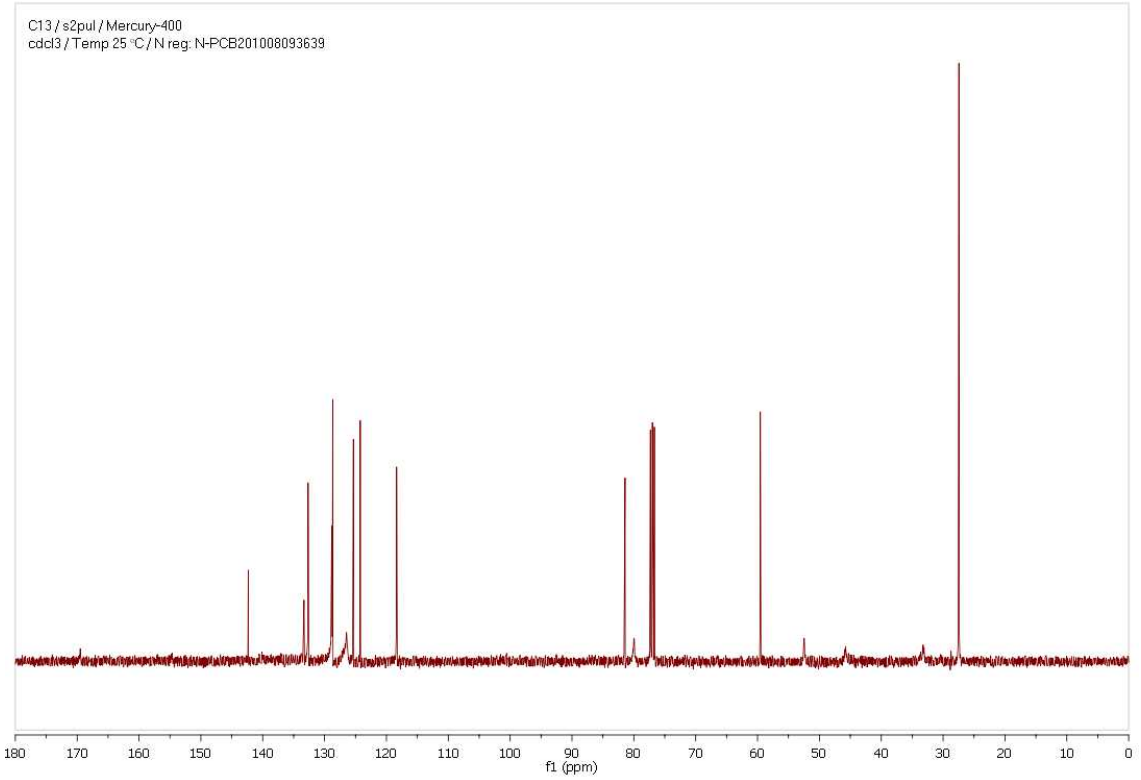

H1 / s2pul / Mercury-400
cdcl3 / Temp 25 °C / N reg: D-PCB010310114116
HN
H
N
O
NH
Alloc
O
O
O
O
HN
O
Alloc
NH
N
H
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)


C13 / s2pul / Mercury-400
cdcl3 / Temp 25 °C / N reg: D-PCB010310093457
180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

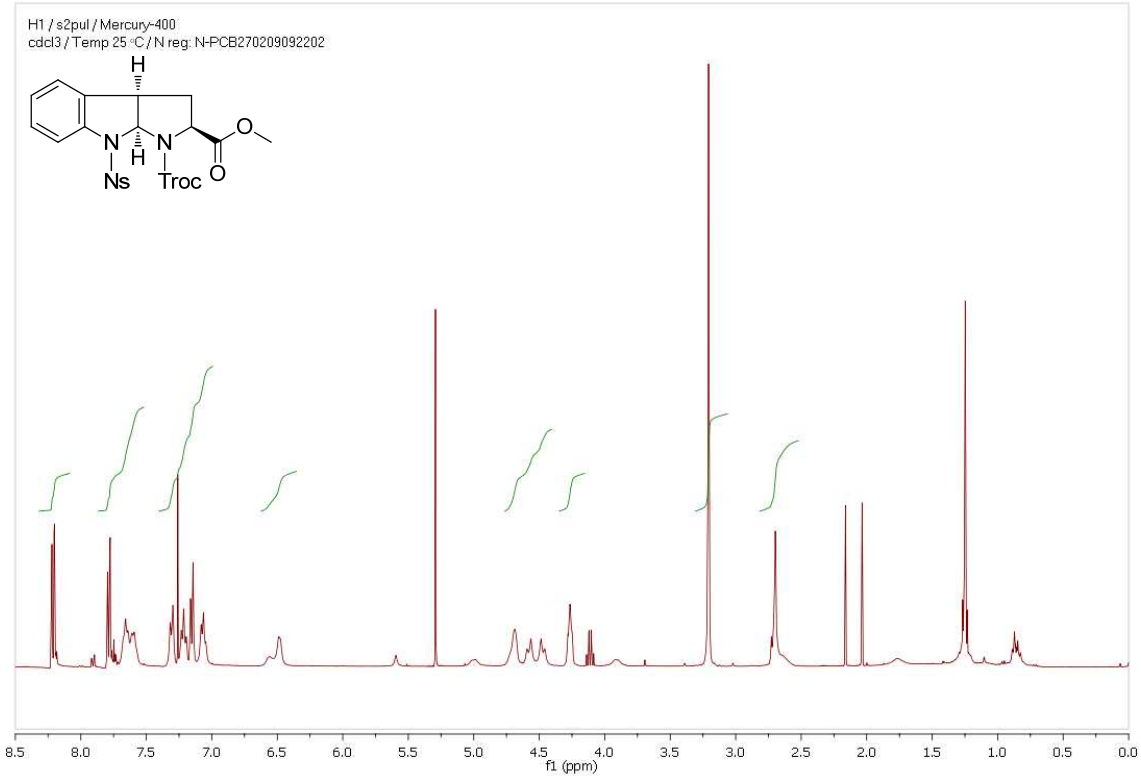
5. Compost 7

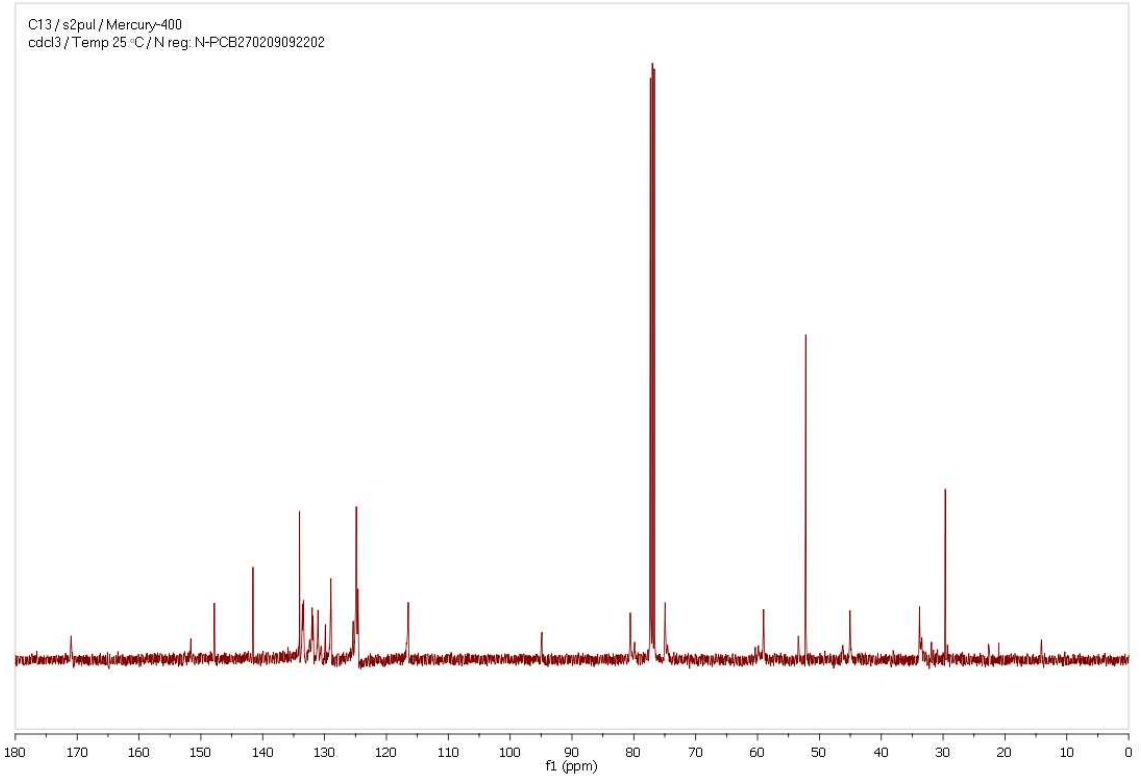
5.1 1-Metoxicarbonil-8-fenilsulfonil-HPI-2-carboxilat de *terc*-butil (7b)





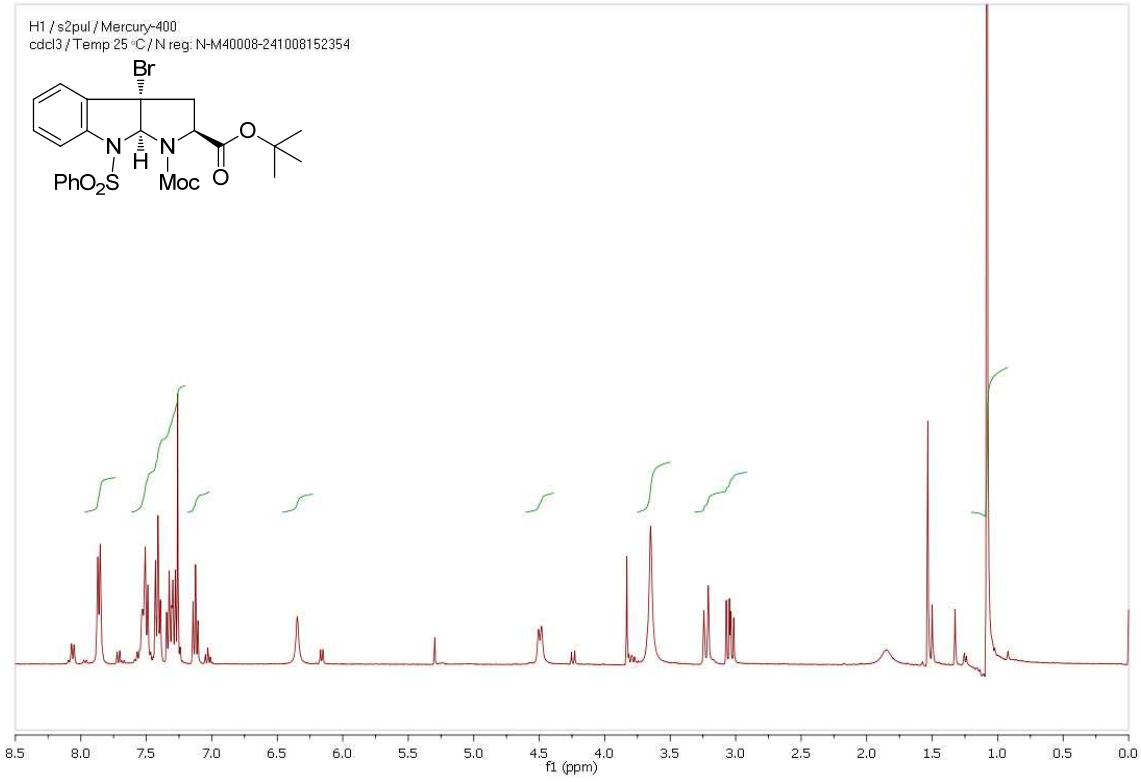
5.2 1-(2,2,2-Tricloroetoxicarbonil)-8-((2-nitrofenil)sulfonil)-HPI-2-carboxilat de metil (7c)

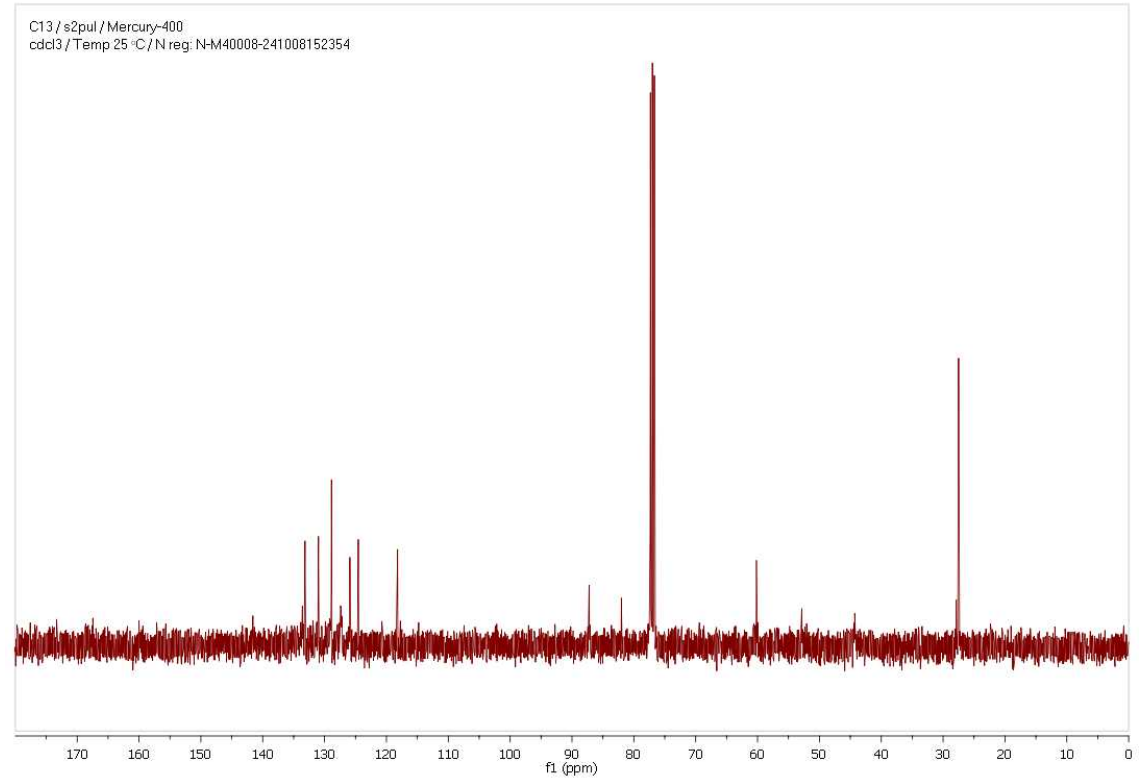




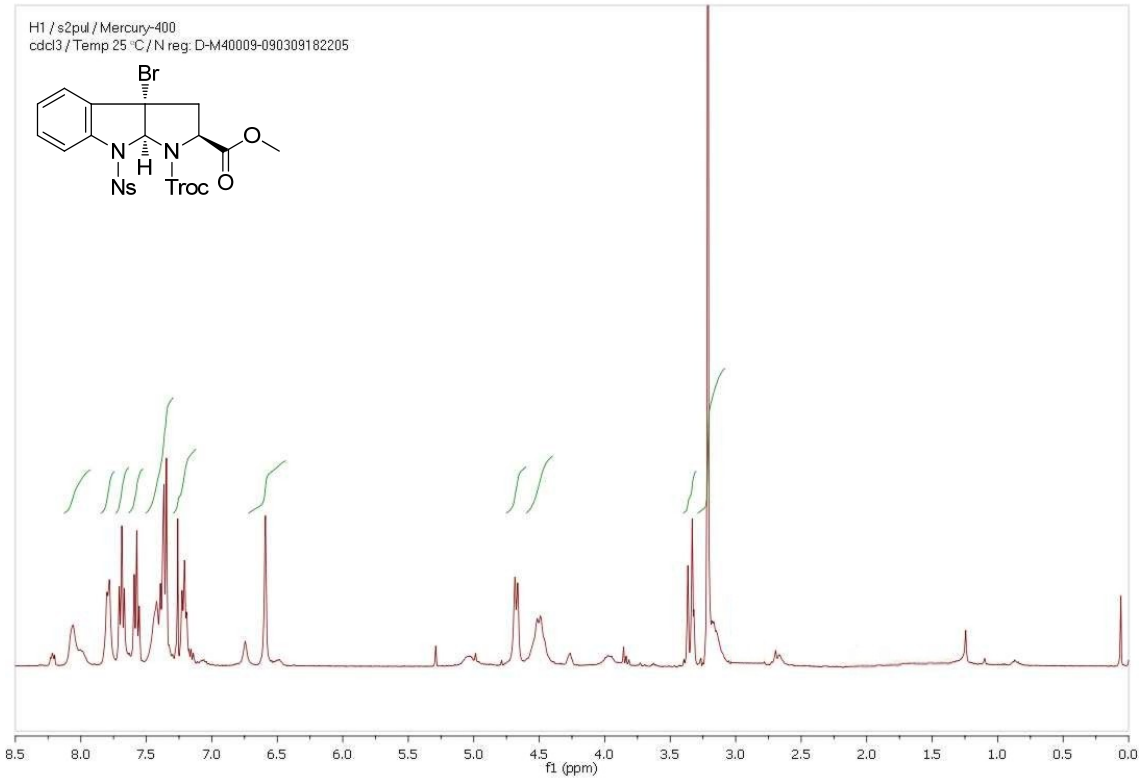
6. Compostos 8

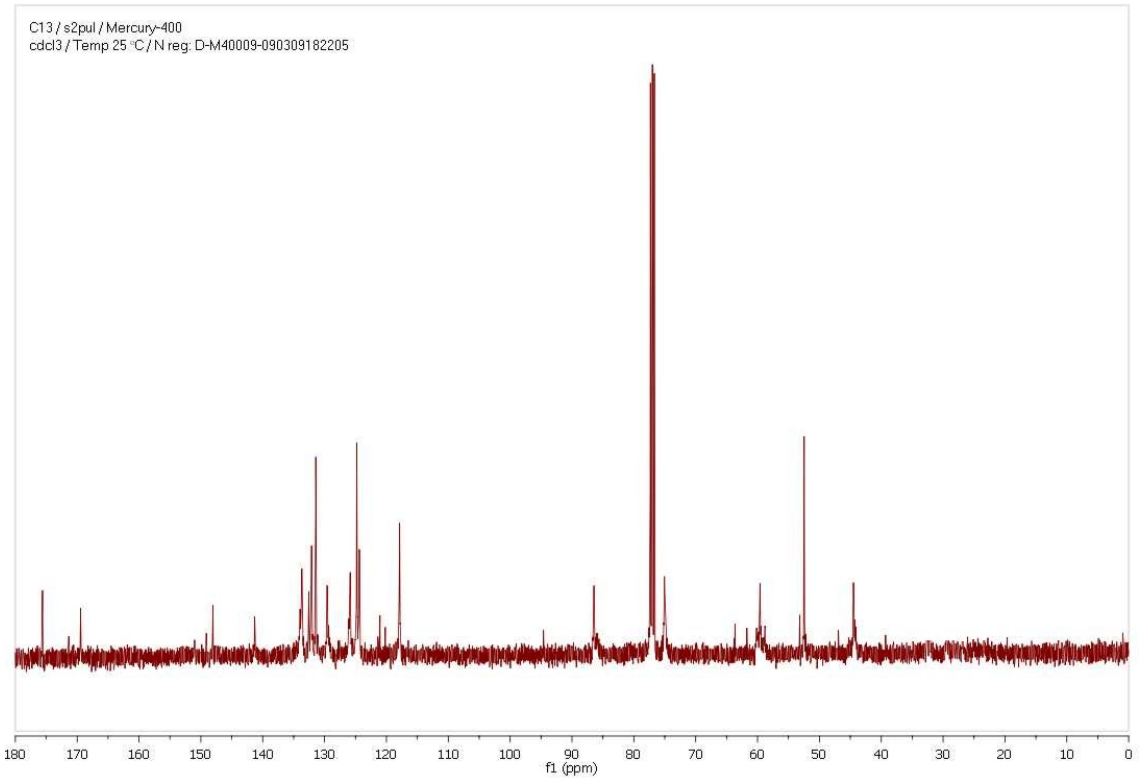
6.1 *endo*-3a-Bromo-8-(fenilsulfonil)-1-(metoxicarbonil)-HPI-2-carboxilat de *terc*-butil (8b)



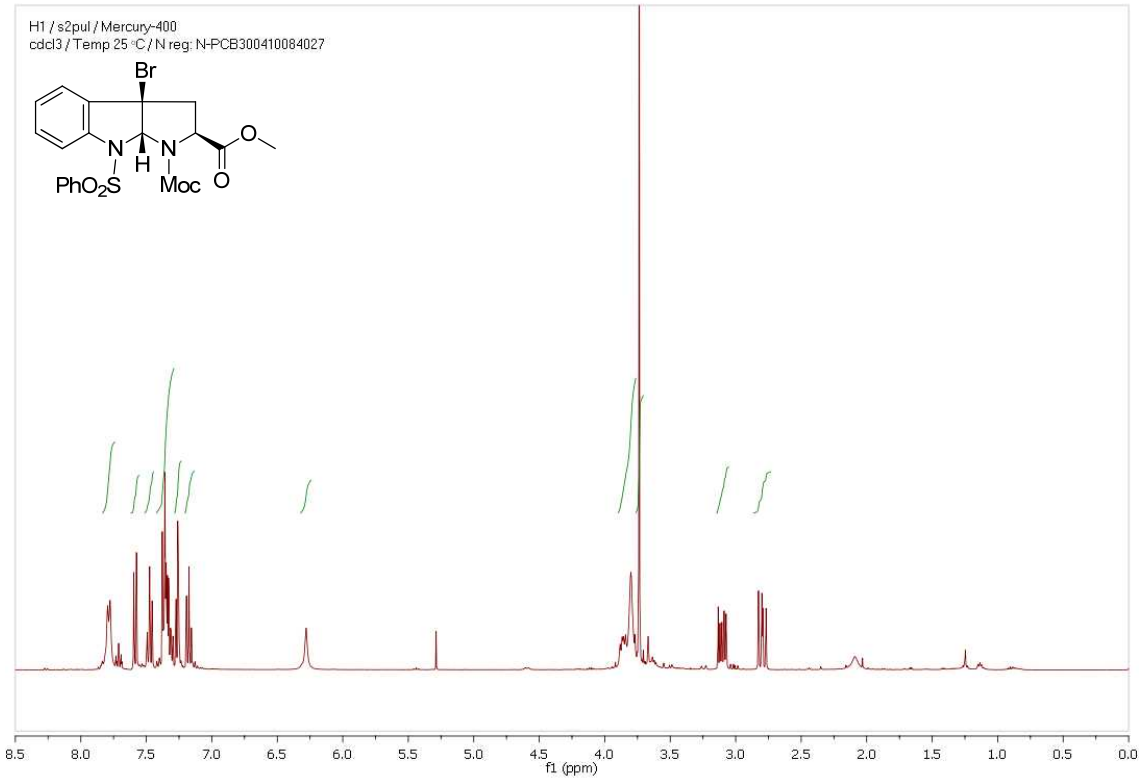


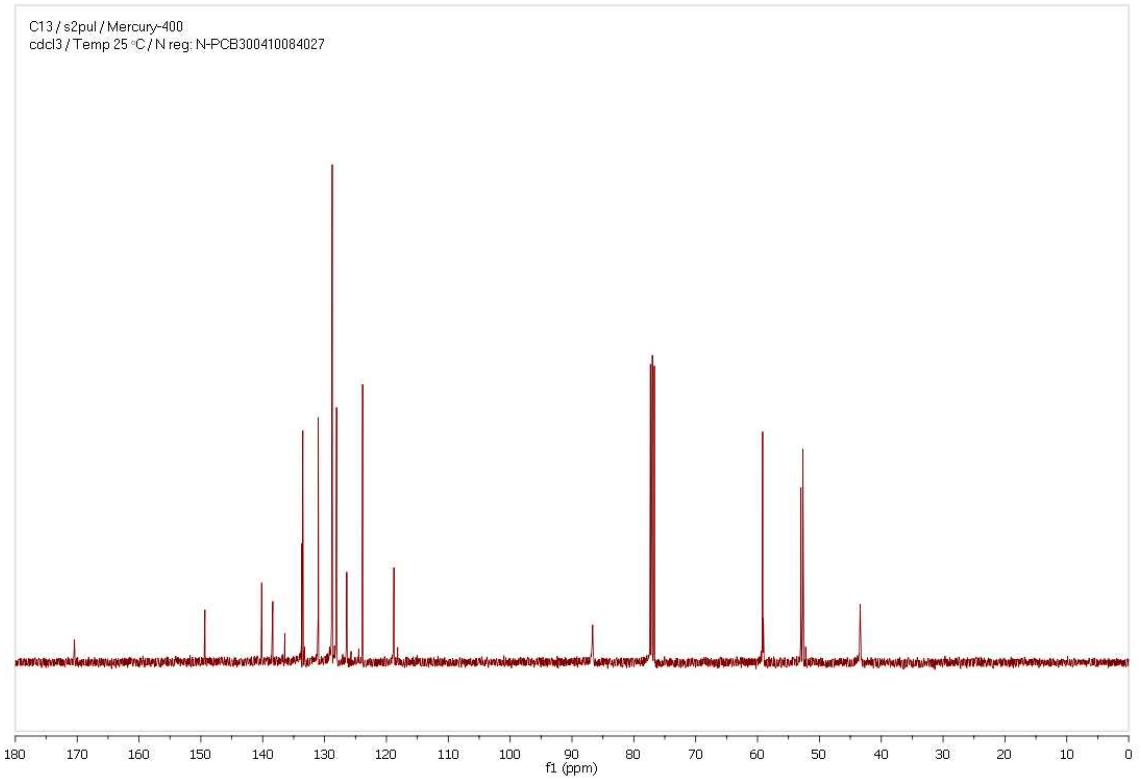
6.2 *endo*-3a-Bromo-8-((2-nitrofenil)sulfonil)-1-(2,2,2-tricloroetoxicarbonil)-HPI-2-carboxilat de metil (8c)



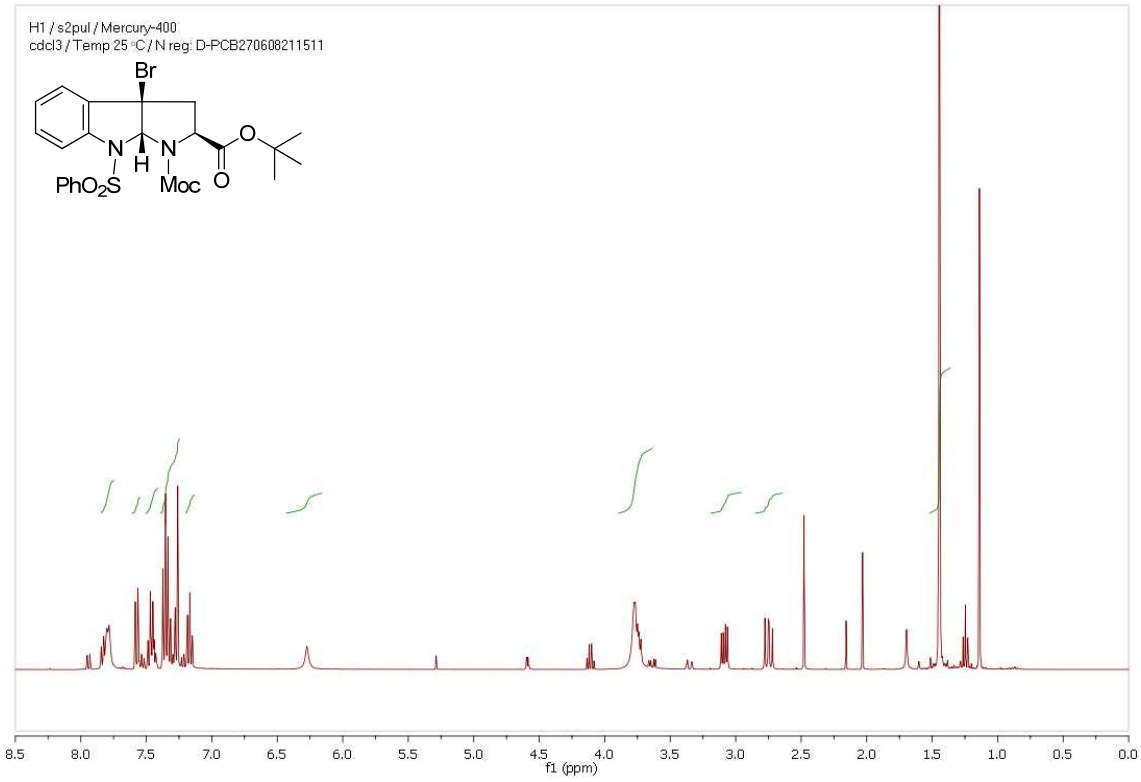


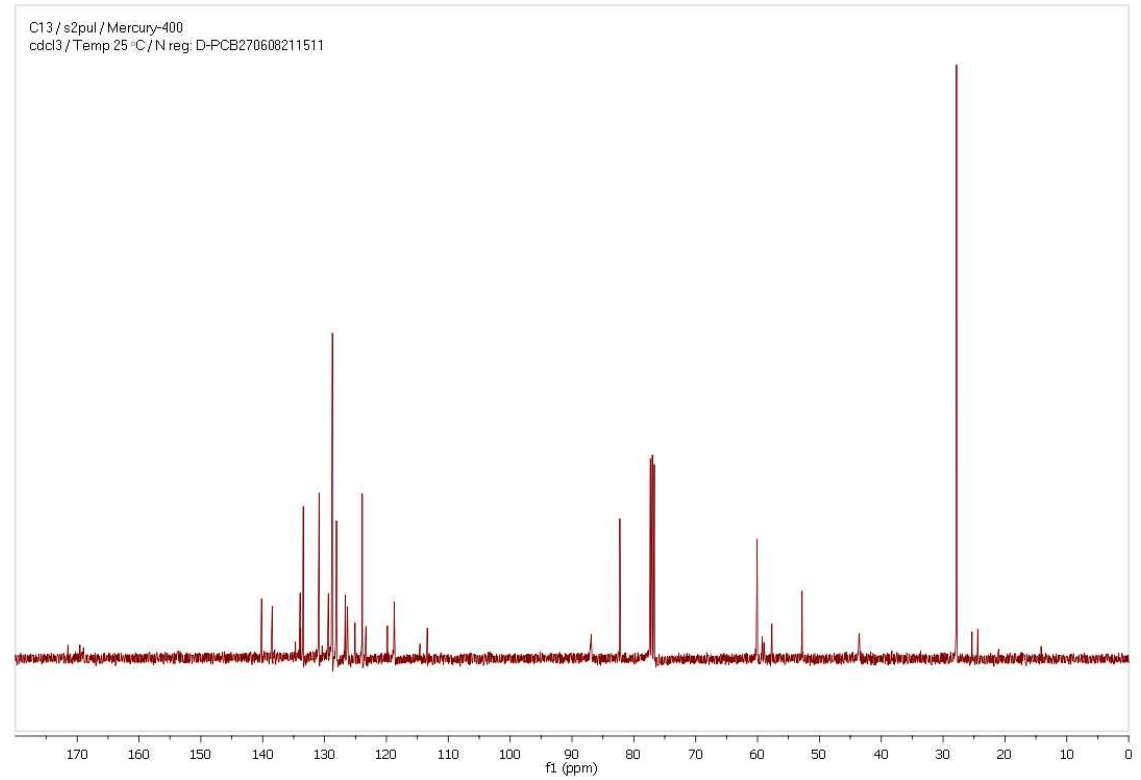
6.3 *exo*-3a-Bromo-8-fenilsulfonil-1-metoxicarbonil-HPI-2-carboxilat de metil (8a).



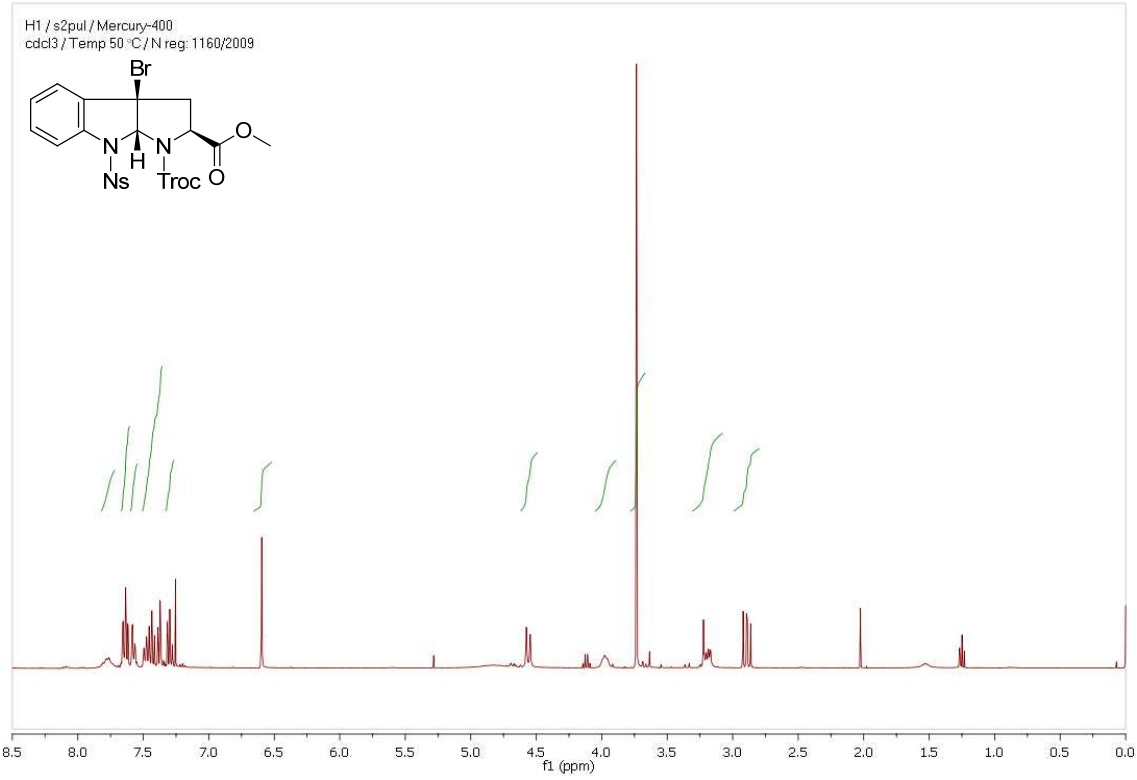


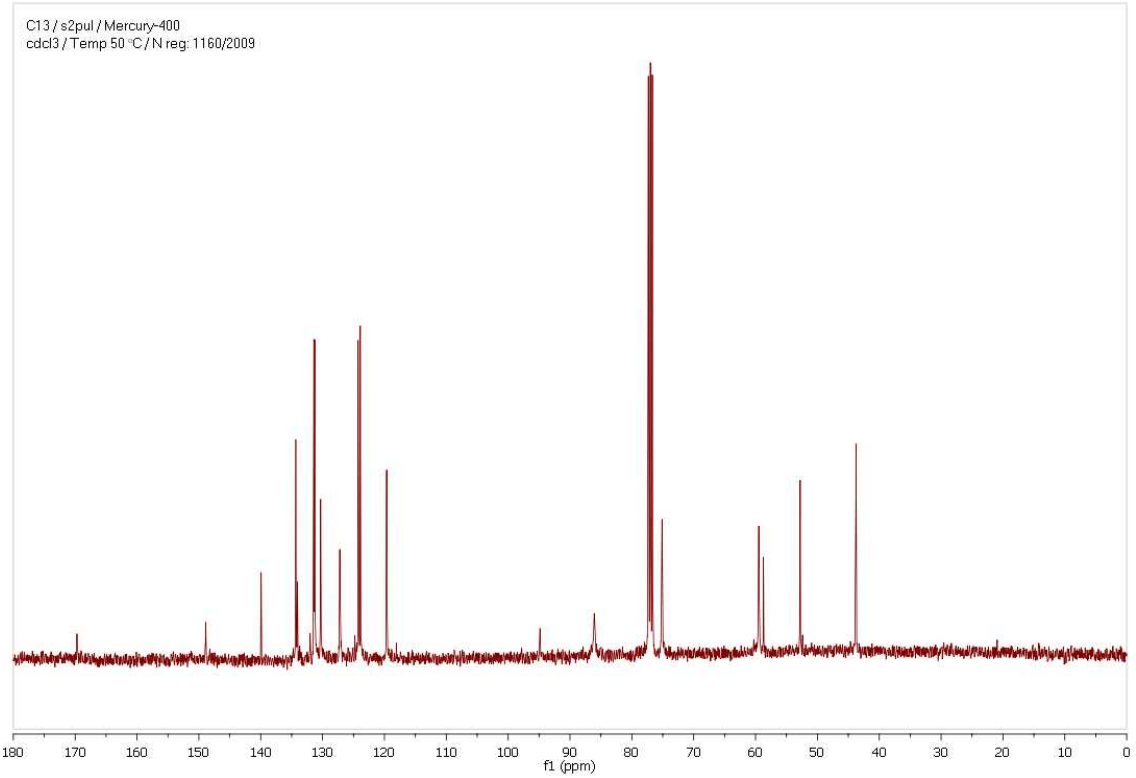
6.4 *exo*-3a-Bromo-8-fenilsulfonil-1-metoxicarbonil-HPI-2-carboxilat de *terc*-butil (8b).



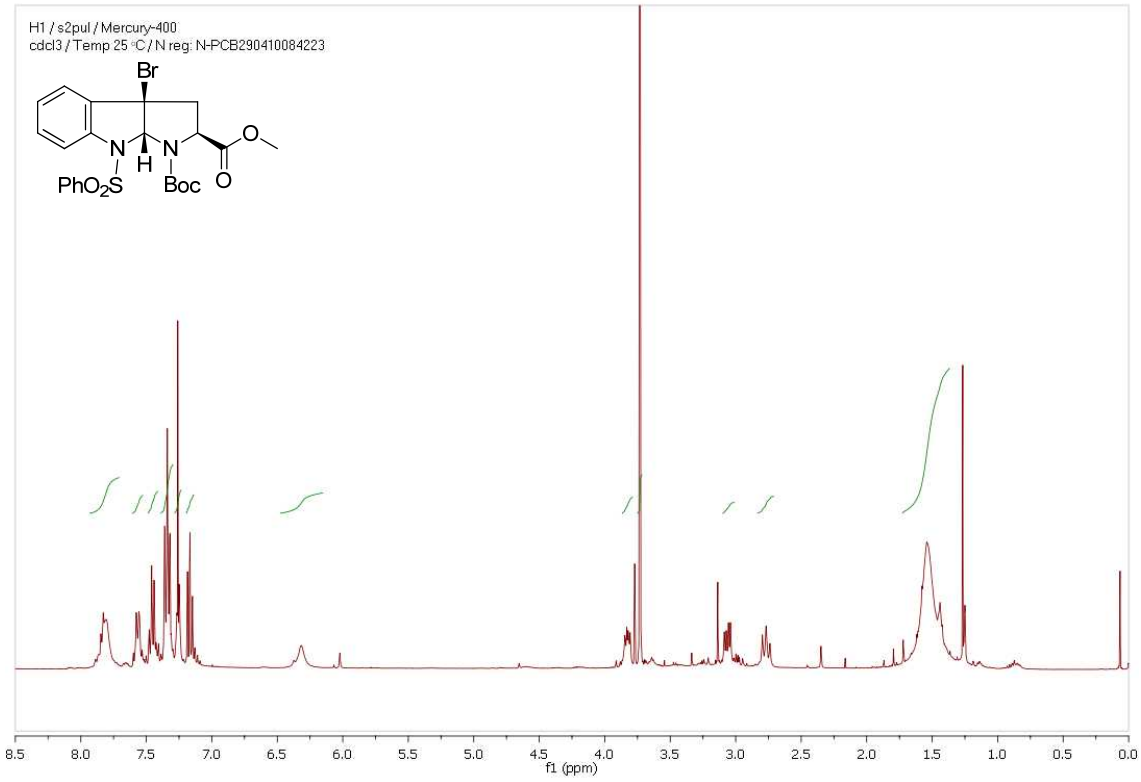


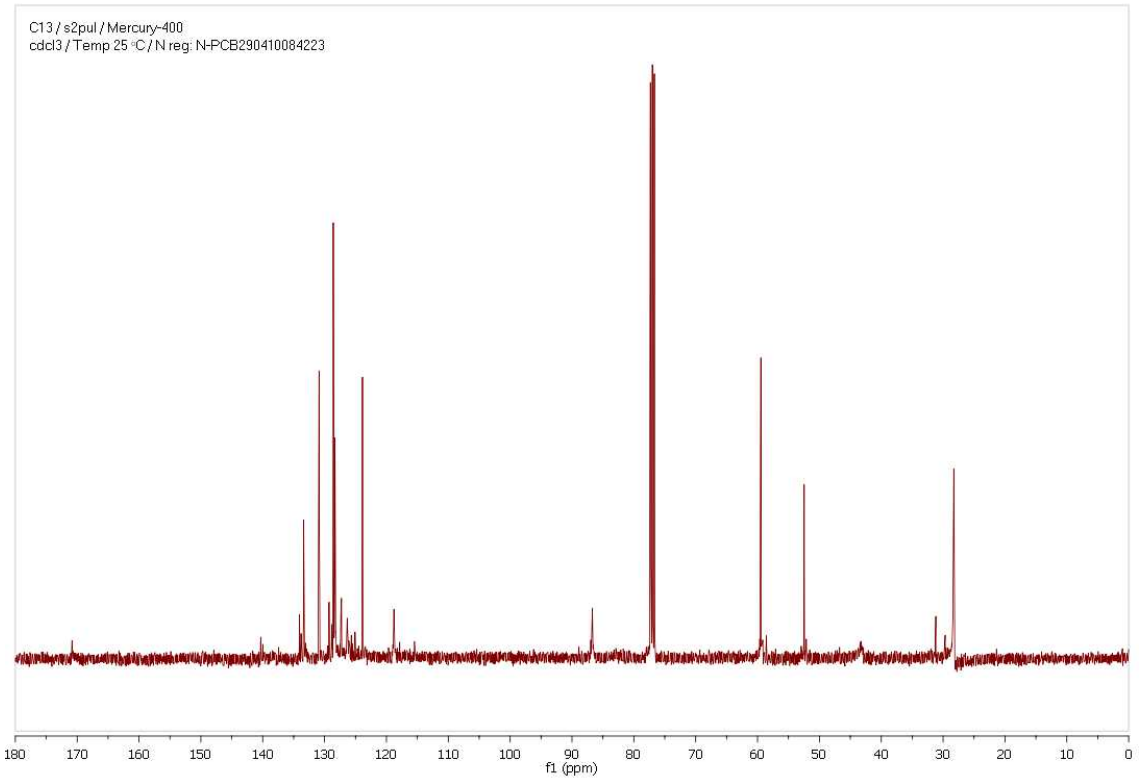
6.5 *exo*-3a-Bromo-8-((2-nitrofenil)sulfonil)-1-(2,2,2-tricloroetoxicarbonil)-HPI-2-carboxilat de metil (8c)



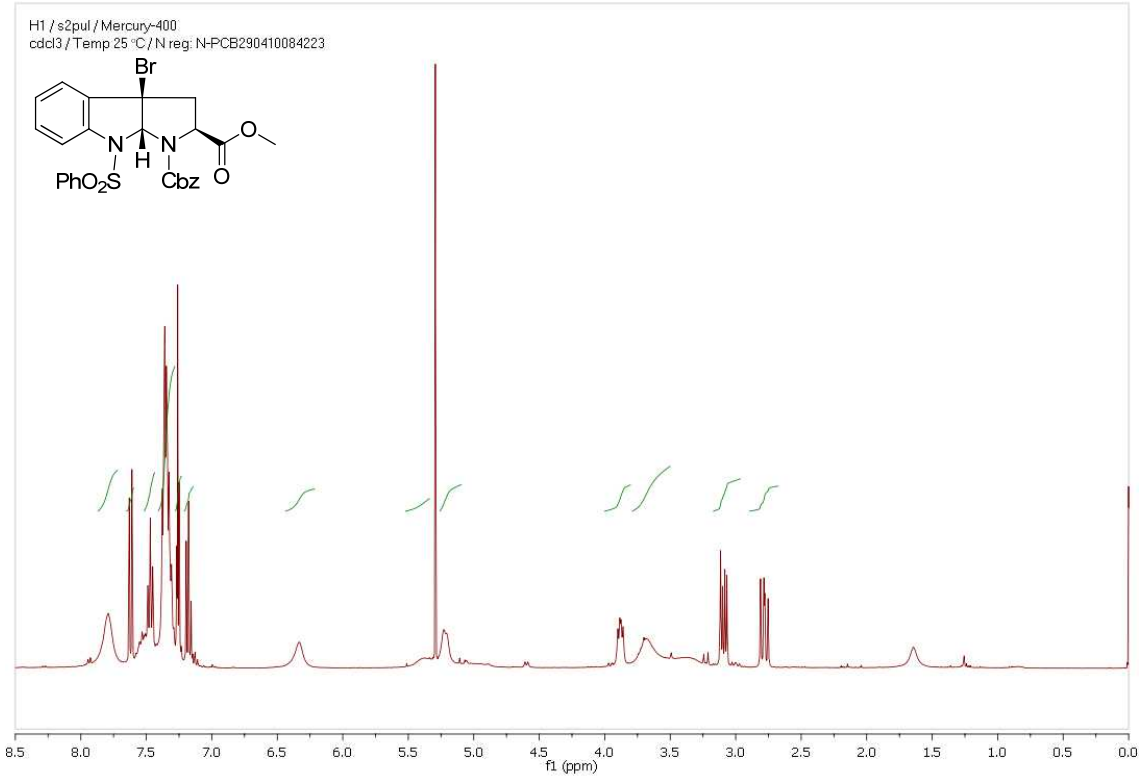


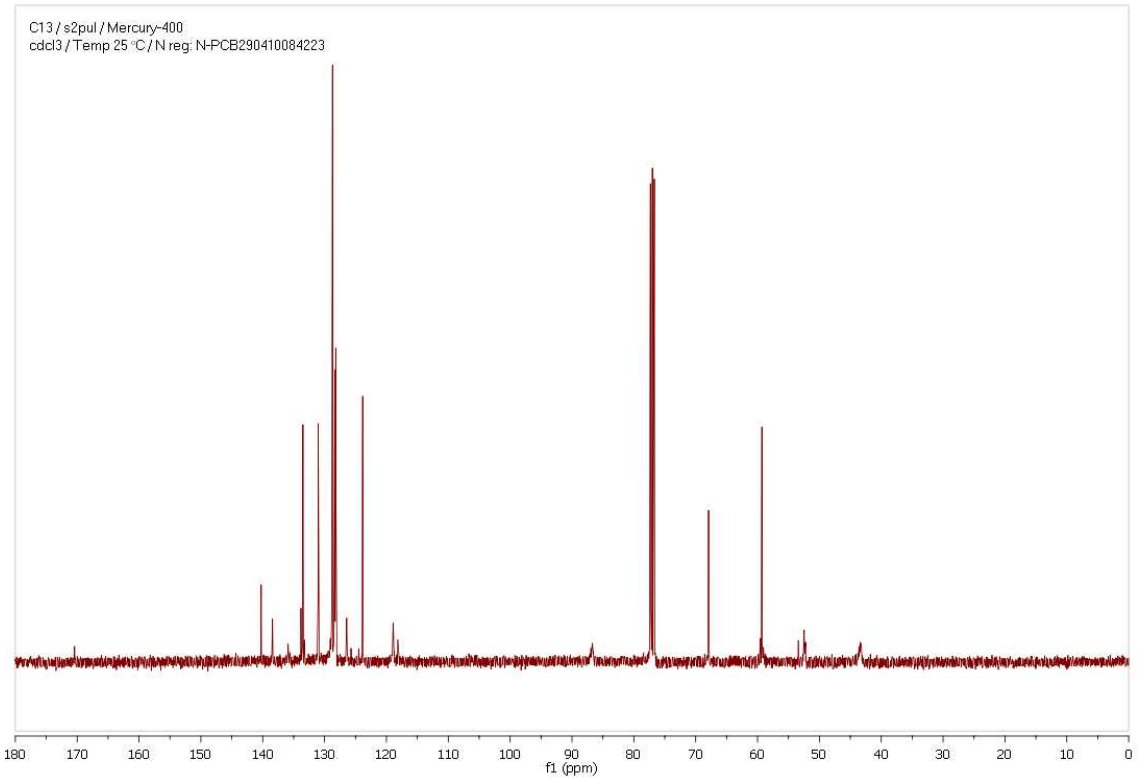
6.6 *exo*-3a-Bromo-1-*terc*-butoxi-8-fenilsulfonil-HPI-2-carboxilat de metil (8d)



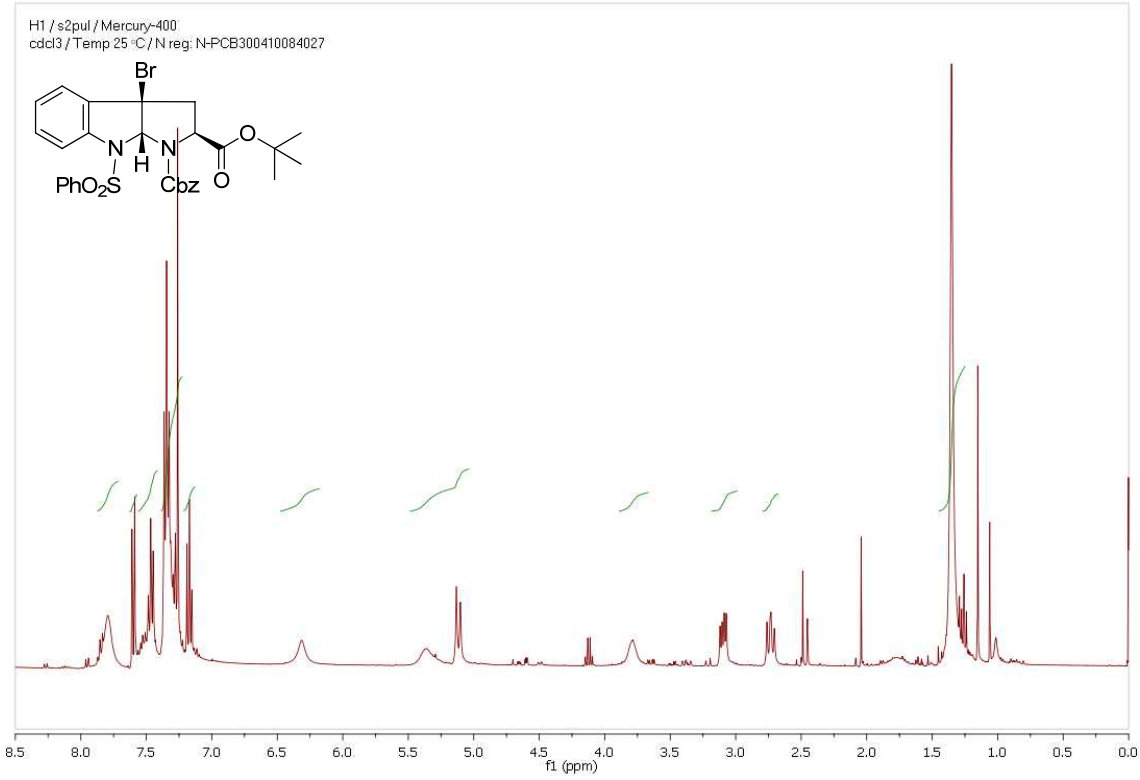


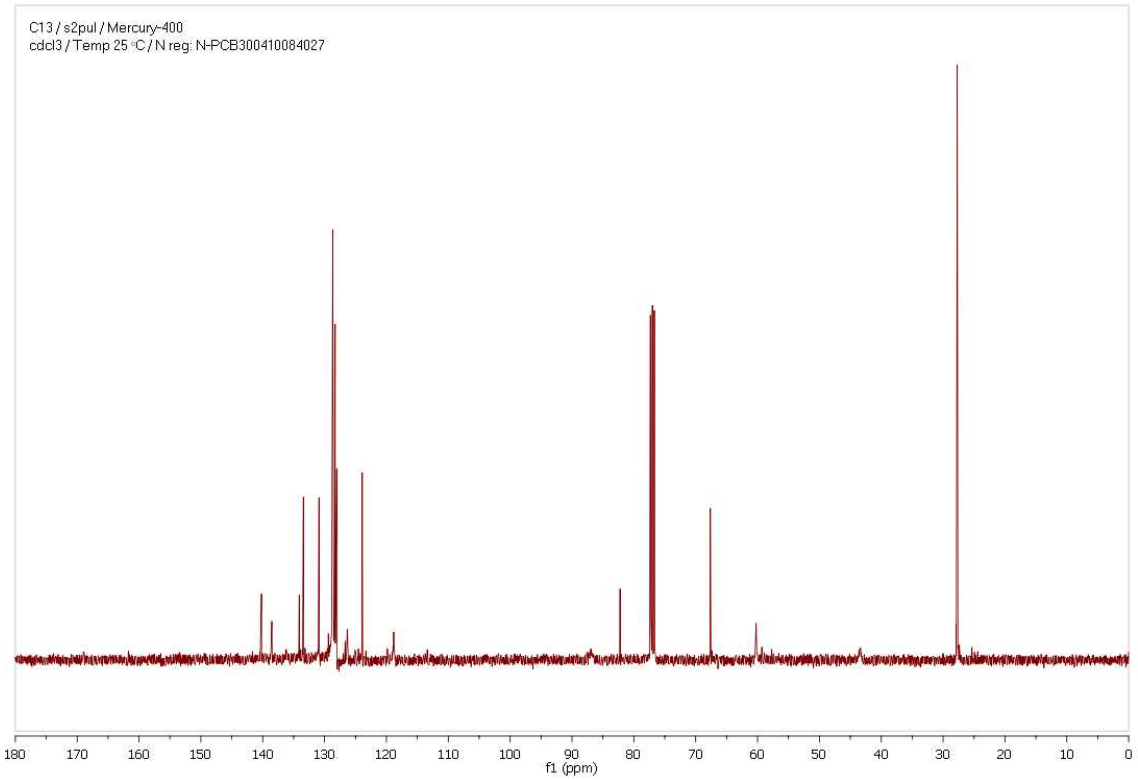
6.7 ***exo*-1-Benziloxicarbonil-3a-bromo-8-fenilsulfonil-HPI-2-carboxilat de metil (8e)**



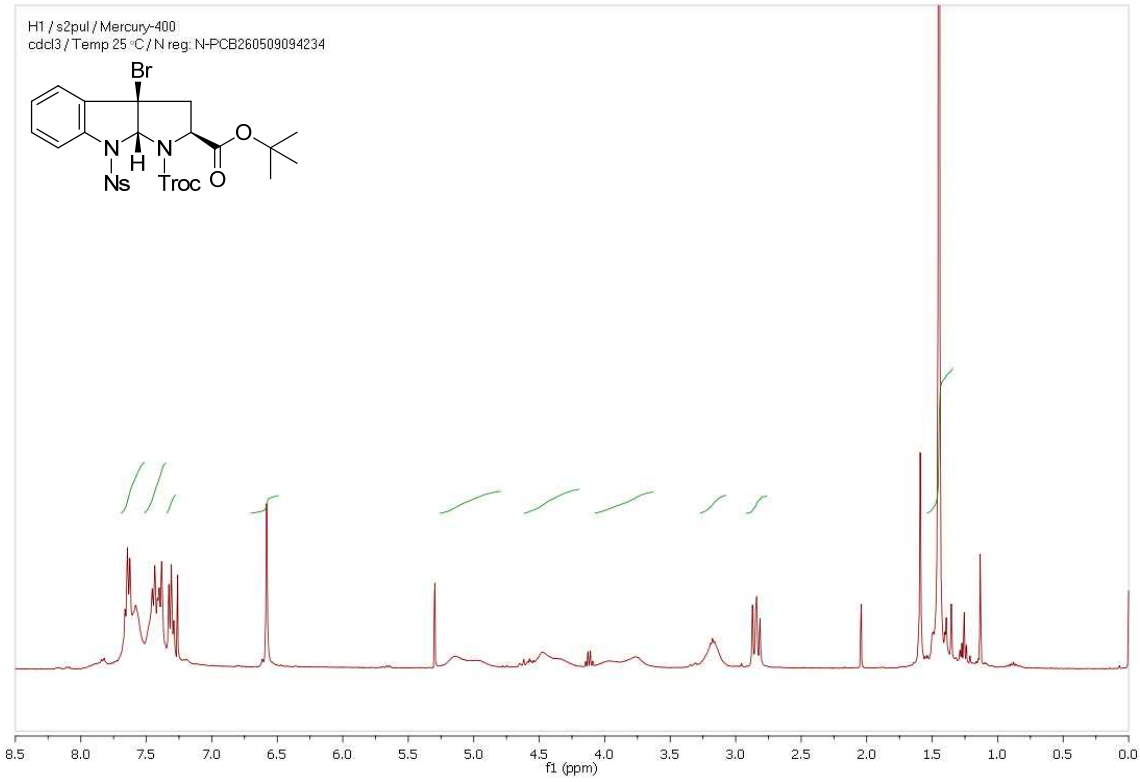


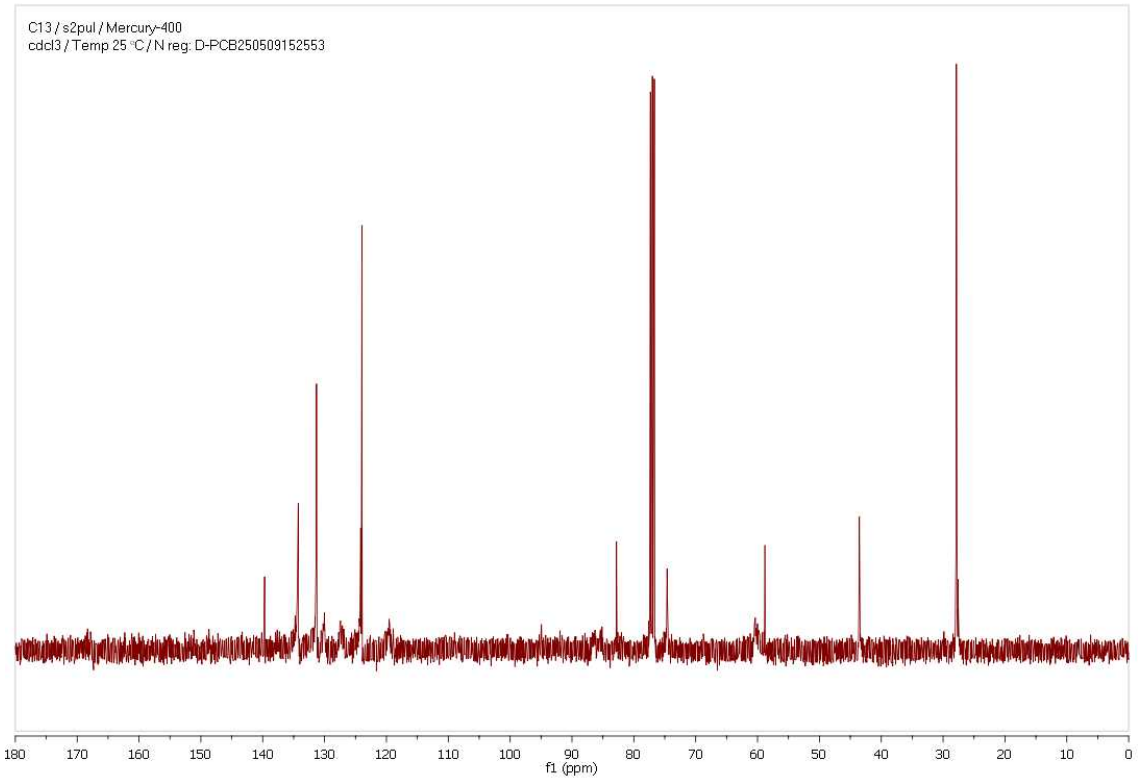
6.8 *exo*-1-Benziloxicarbonil-3a-bromo-8-fenilsulfonil-HPI-2-carboxilat de *terc*-butil (8f)



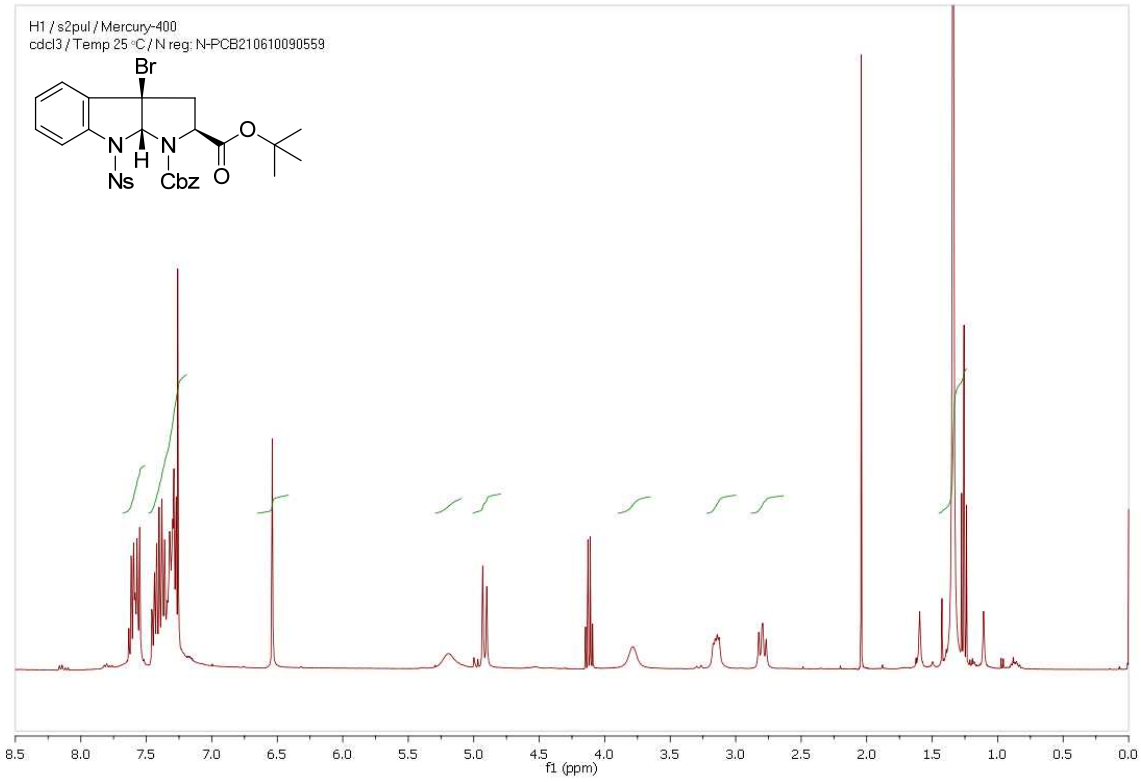


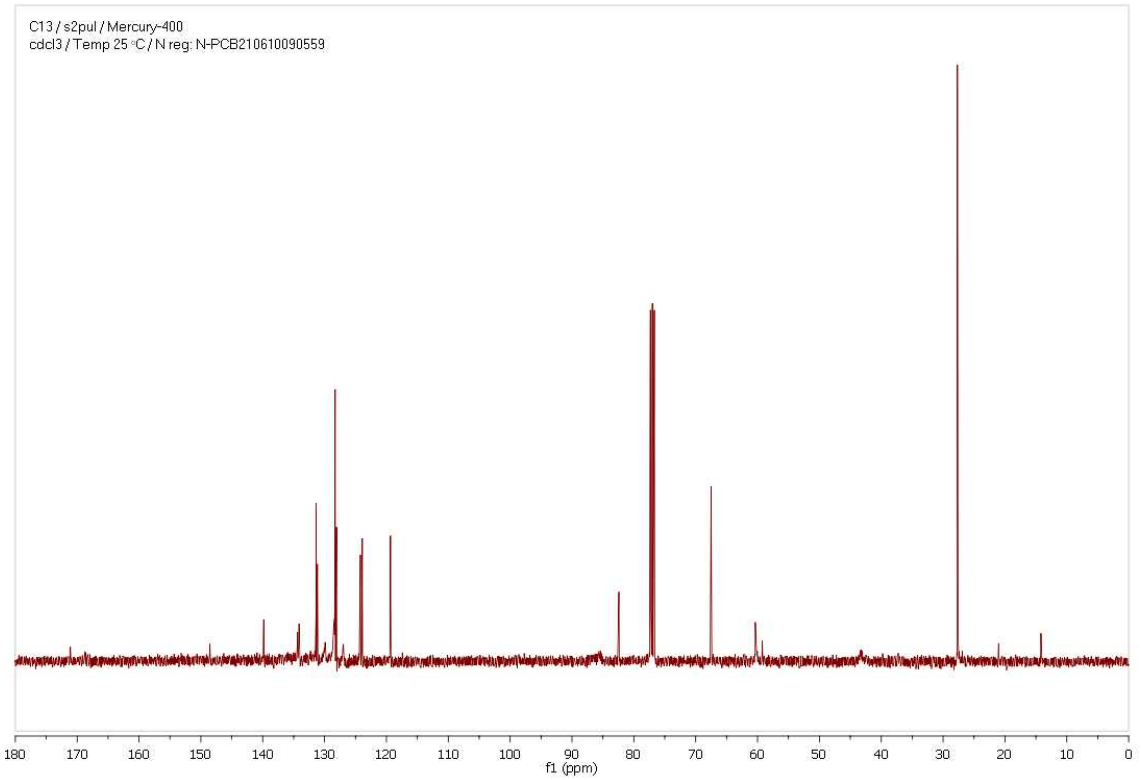
6.9 *exo*-3a-Bromo-8-((2-nitrofenil)sulfonil)-1-(2,2,2-tricloroetoxicarbonil)-HPI-2-carboxilat de *terc*-butil (8g)



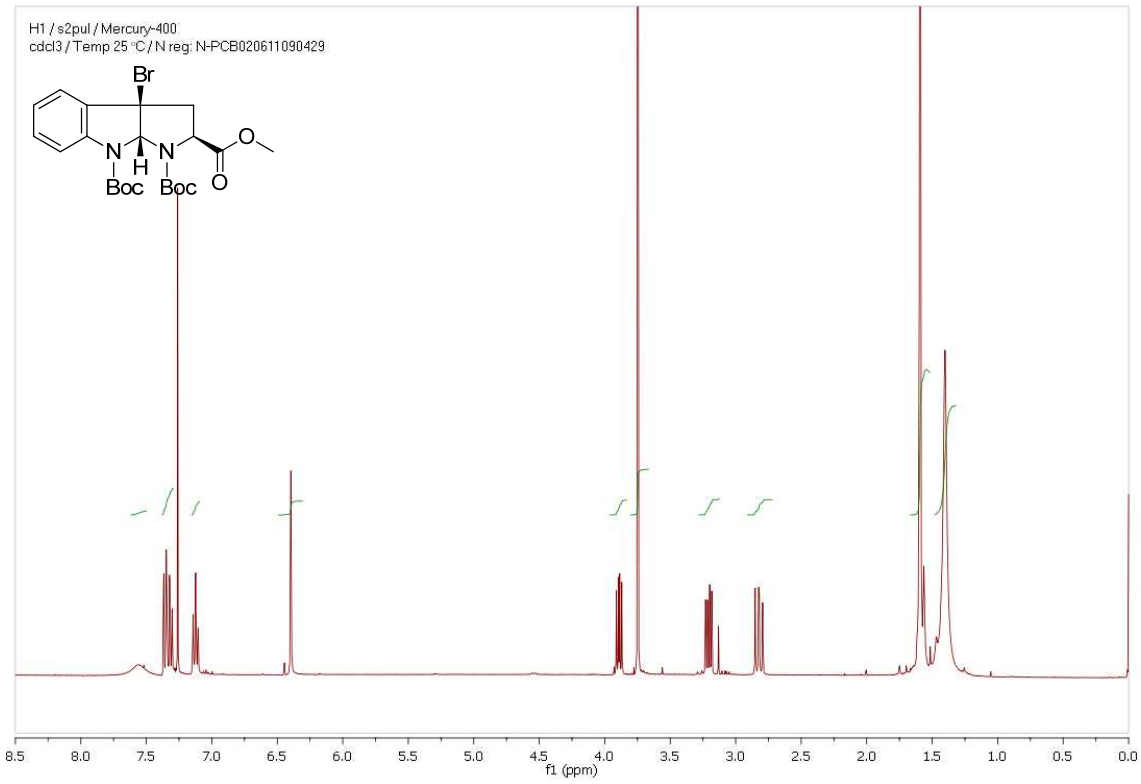


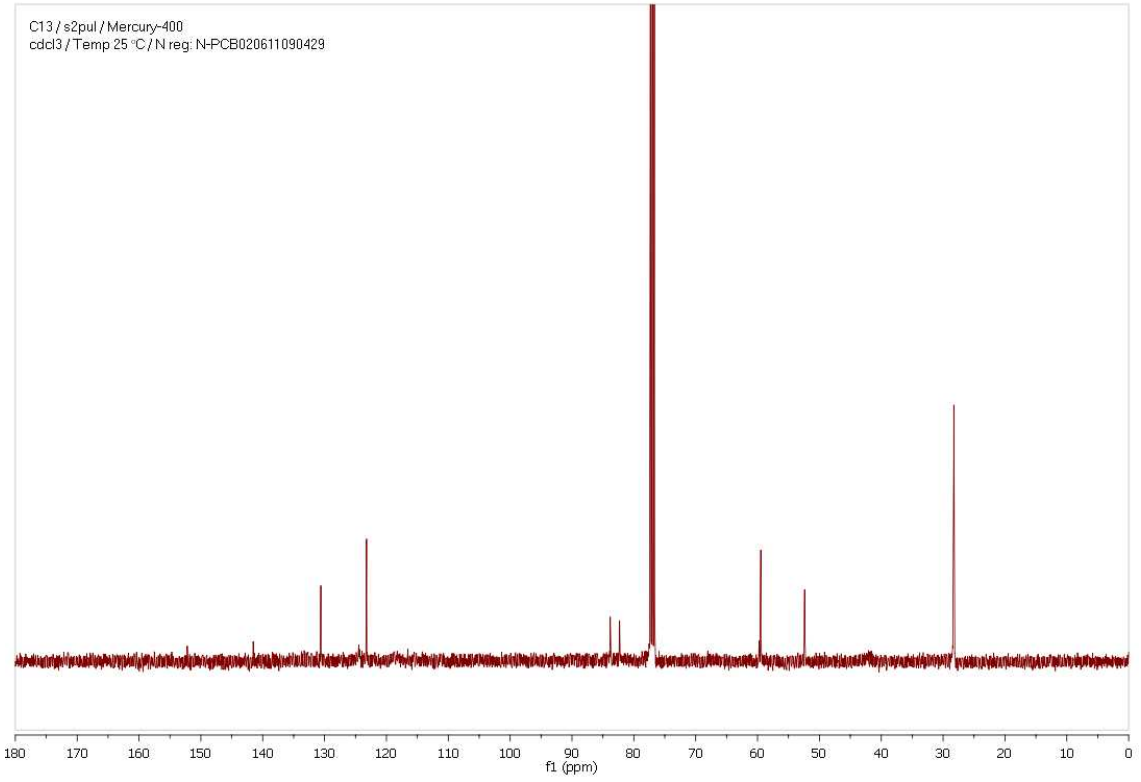
6.10 *exo*-1-Benziloxicarbonil-3a-bromo-8-((2-nitrofenil)sulfonil)-HPI-2-carboxilat de *terc*-butil (8h)



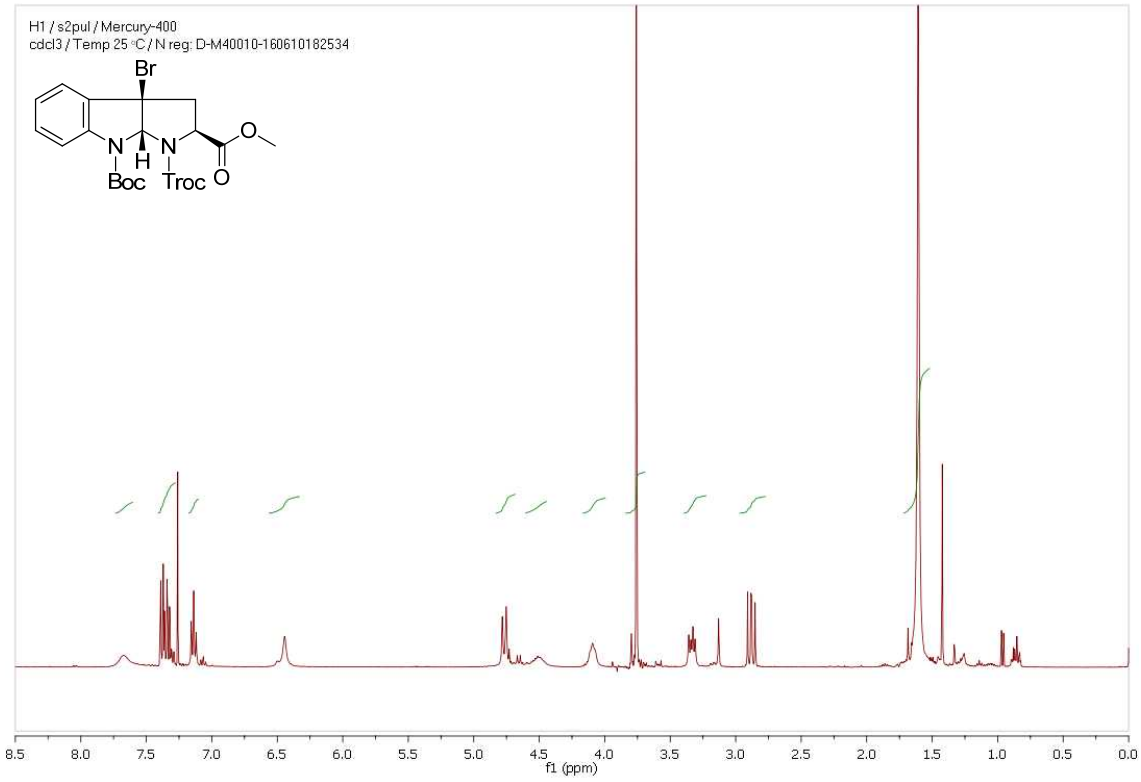


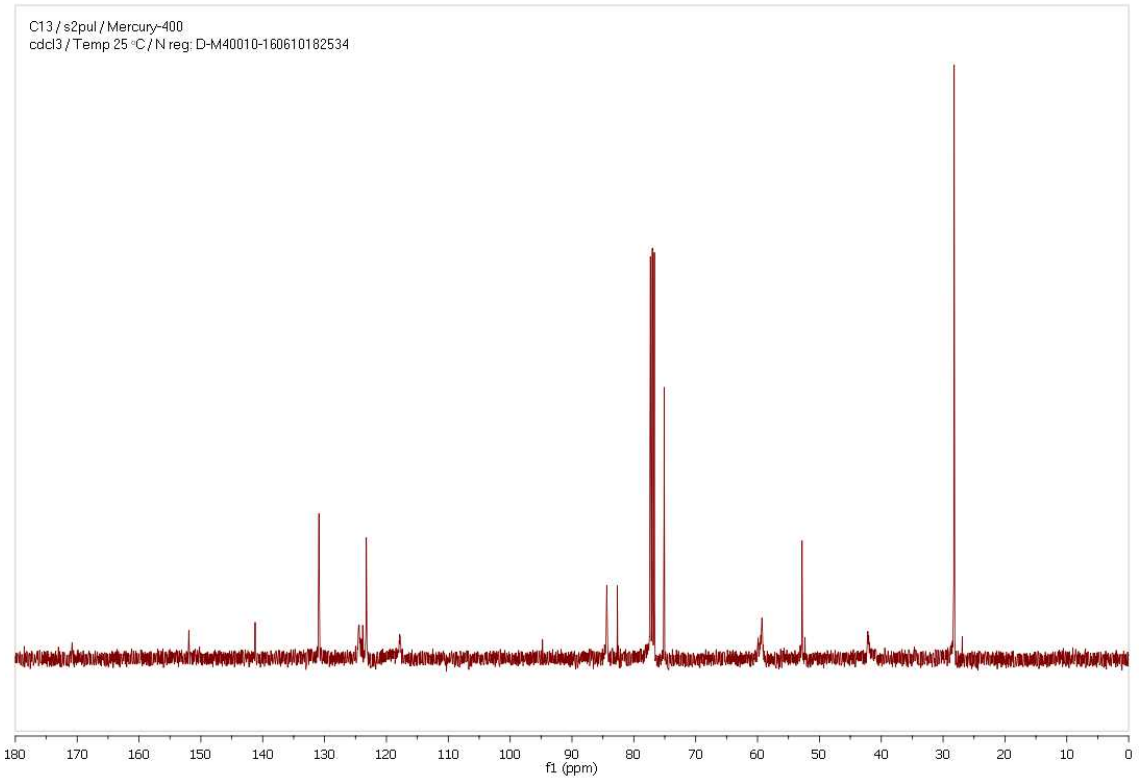
6.11 exo-3a-Bromo-1,8-di-*terc*-butoxicarbonil-HPI-2-carboxilat de metil (8i)



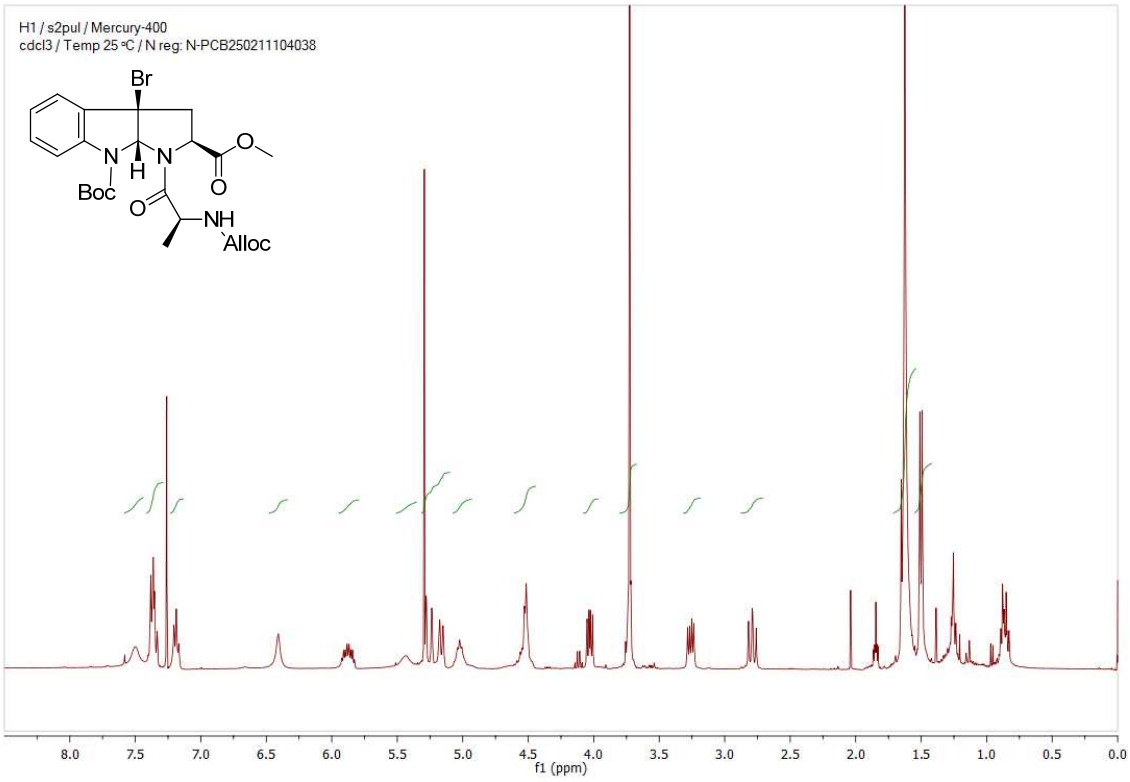


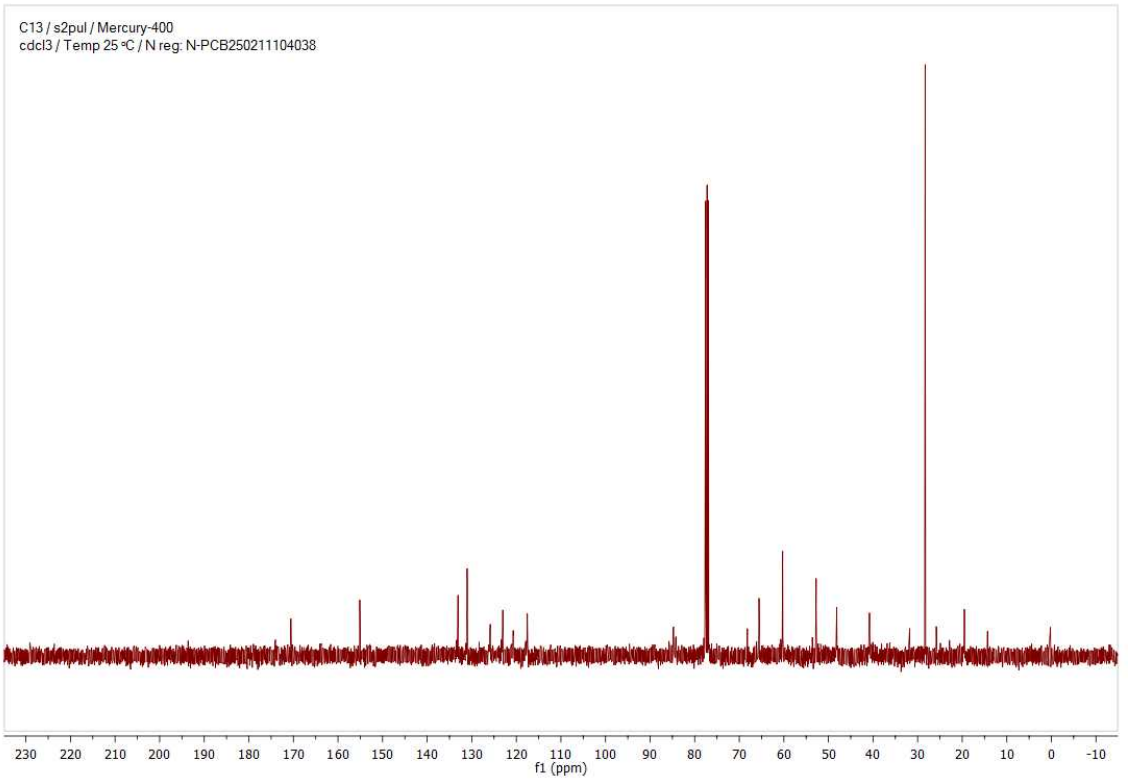
6.12 exo-3a-Bromo-8-*terc*-butoxicarbonil-1-(2,2,2-tricloroetoxicarbonil)-HPI-2-carboxilat de metil (8j)





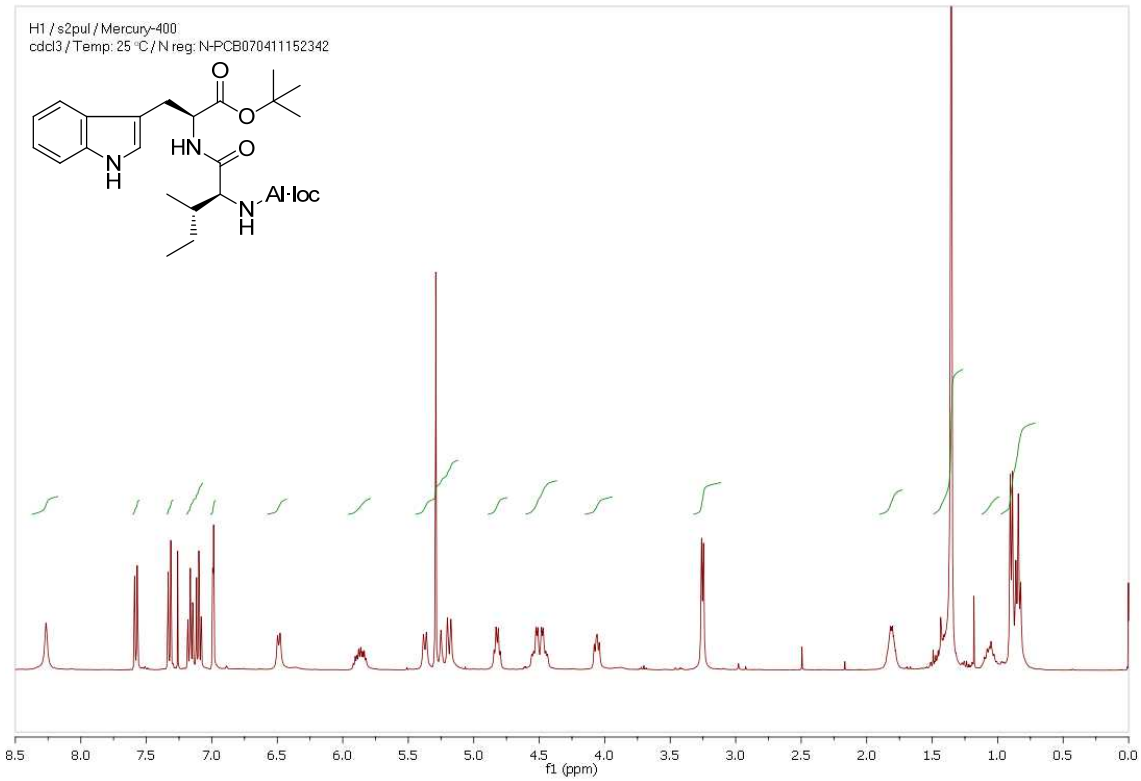
6.13 exo-(*N*$^{\alpha}$-Al·liloxicarbonil-Ala-*O*-yl)-3a-bromo-1-(*terc*-butoxicarbonil)-HPI-2-carboxilat de metil (8k)

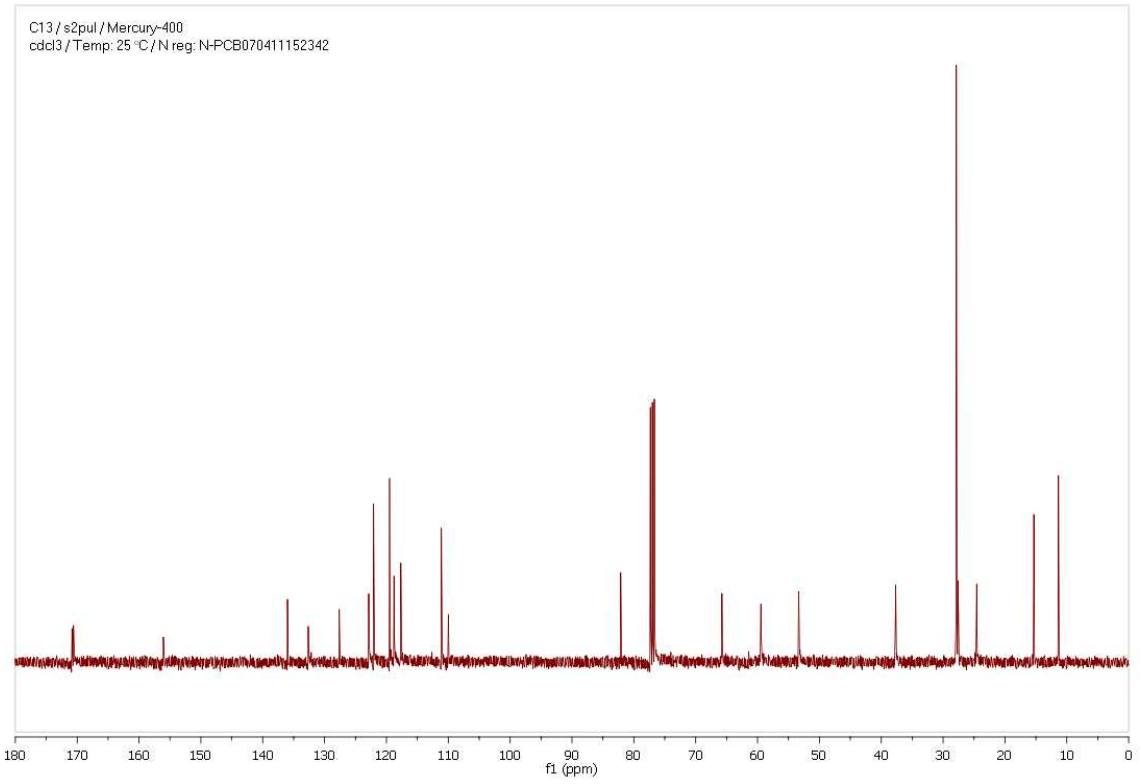




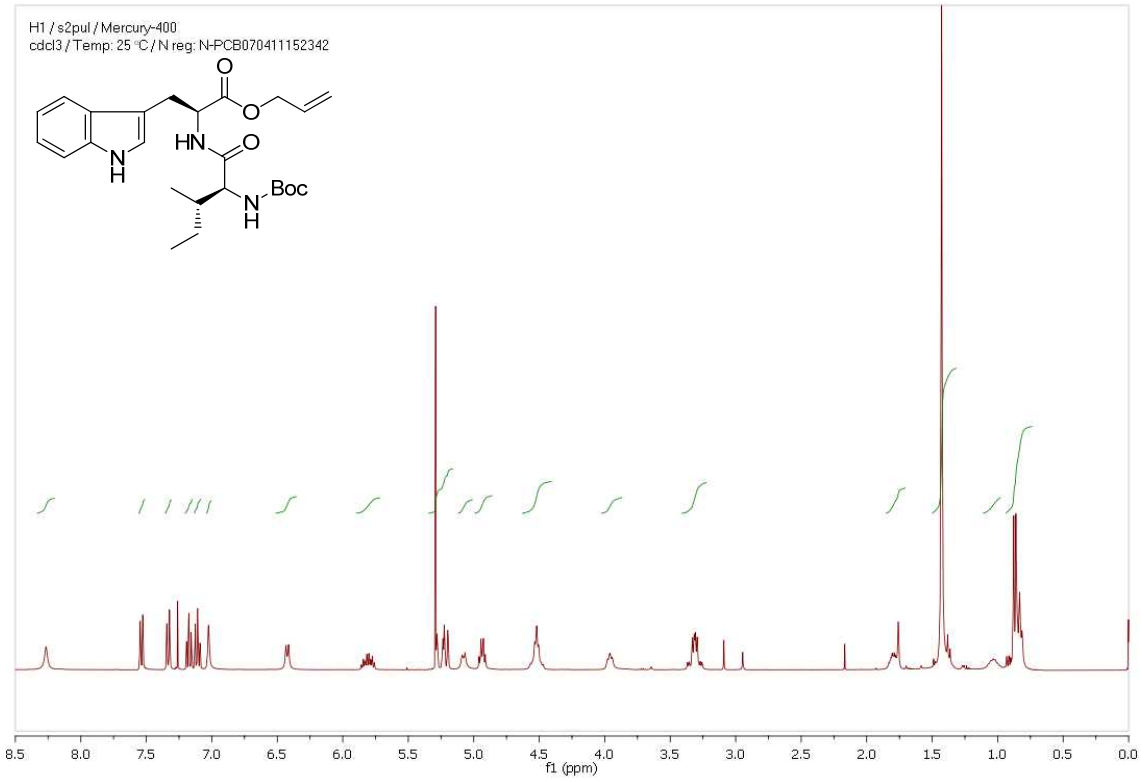
7. Compostos 19

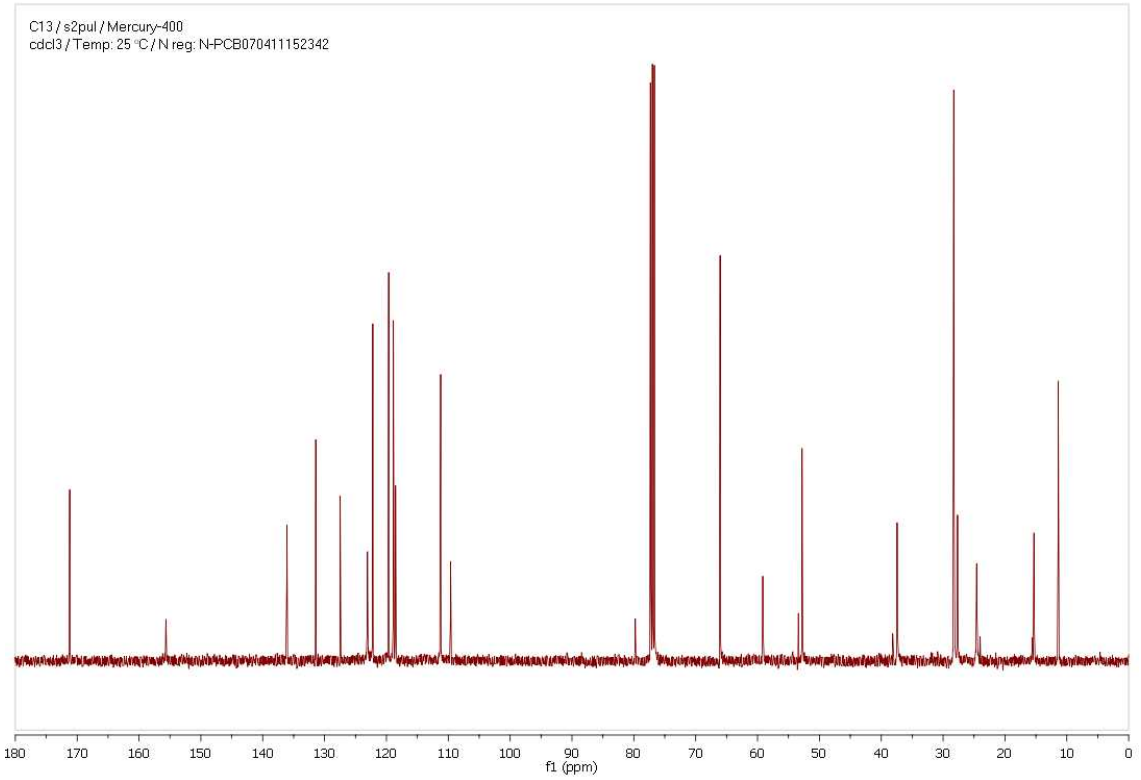
7.1 N^{α}-Al·loc-L-Ile-L-Trp-O*t*Bu (19a)





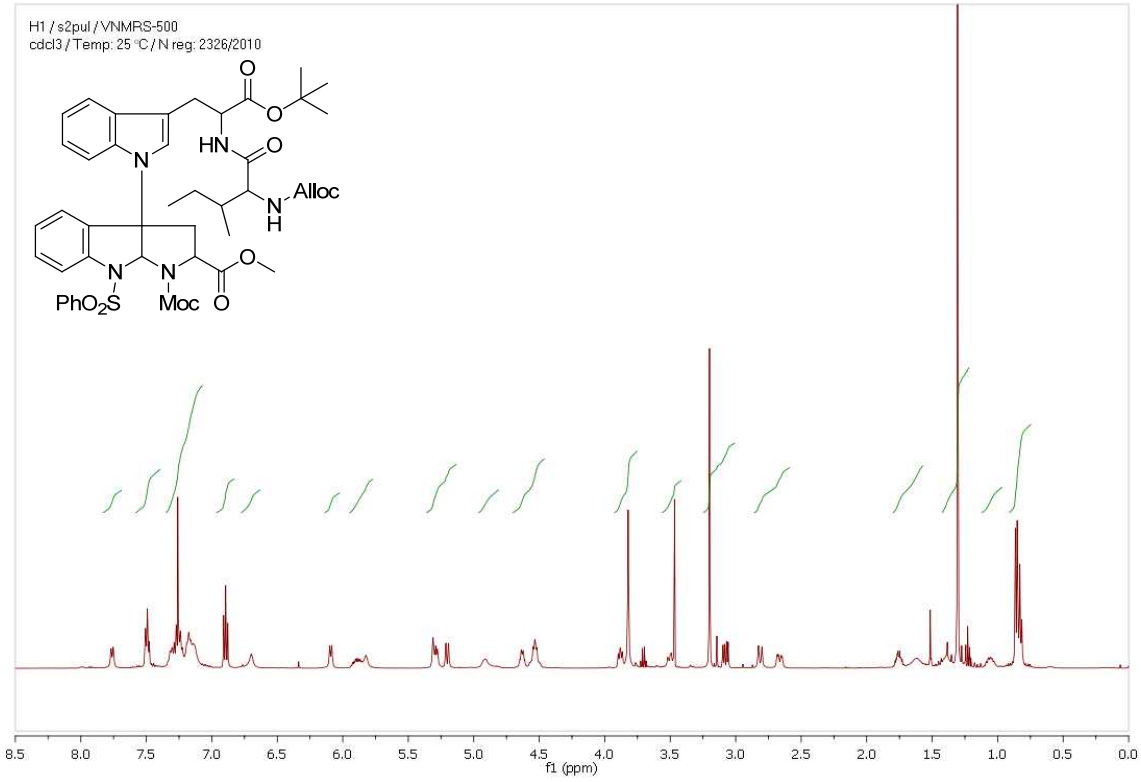
7.2 N^{α}-Boc-L-Ile-L-Trp-OAl·lil (19b)

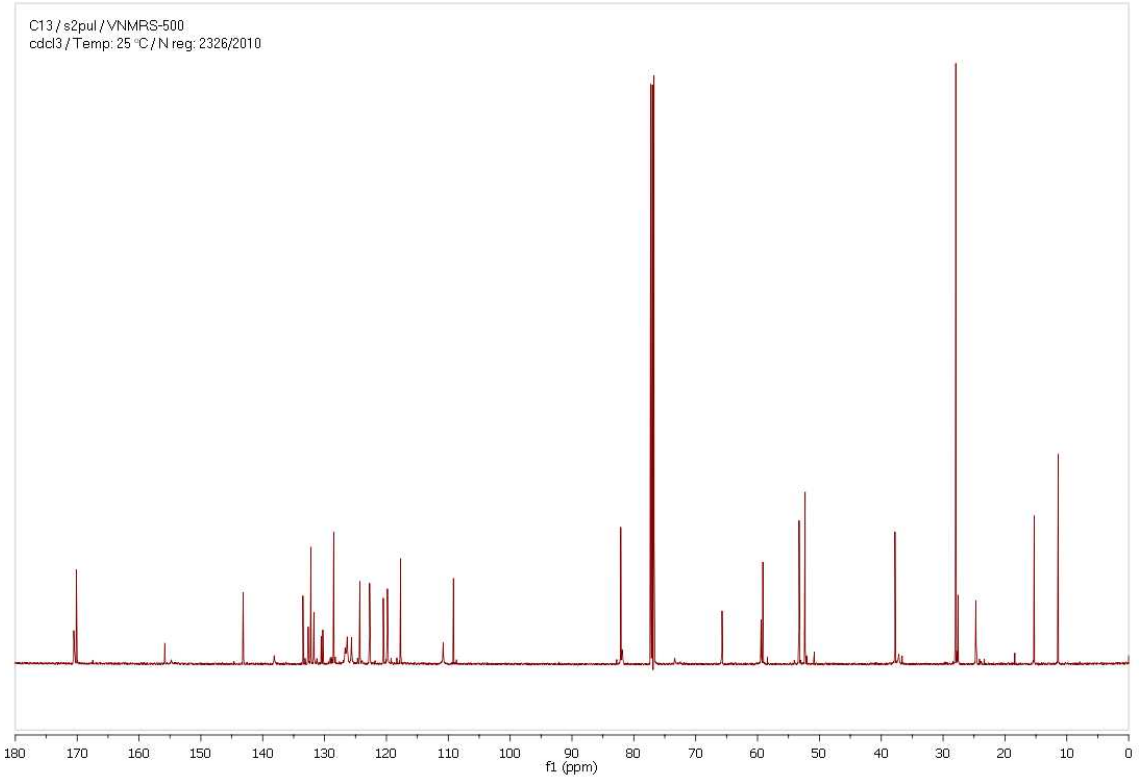




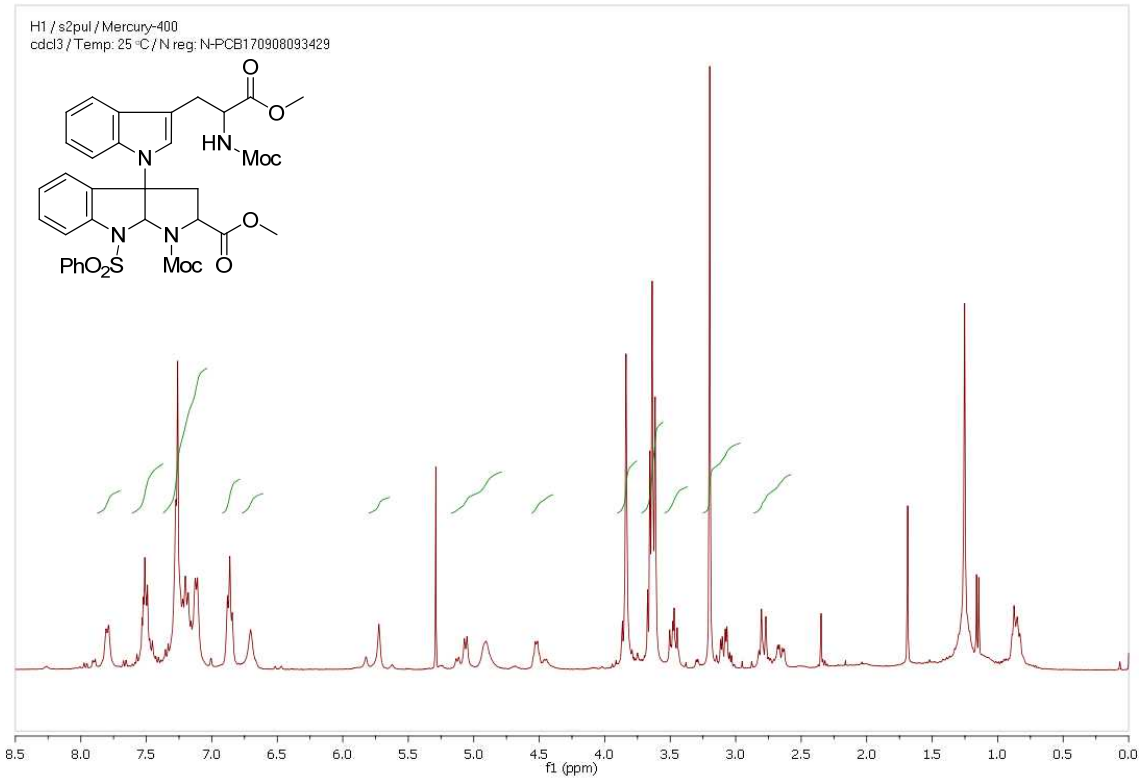
8. Compostos 20

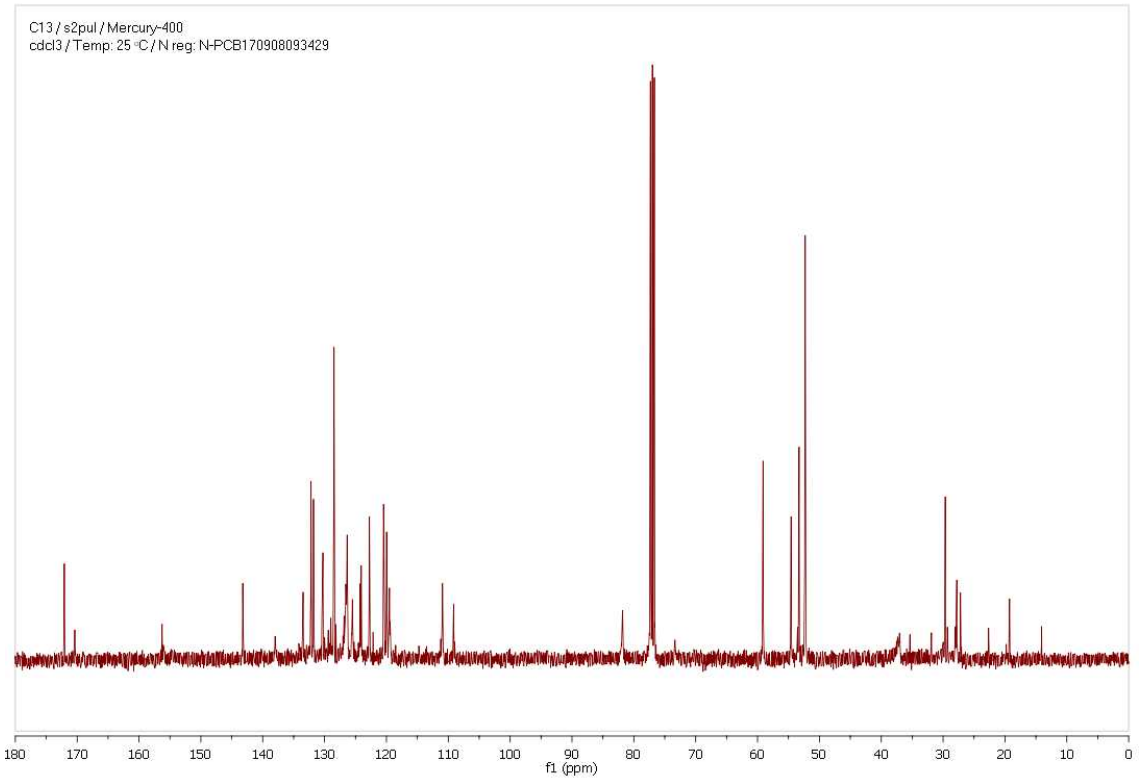
8.1 3a-(N^{α}-Al·loc-L-Ile-L-Trp-O*t*Bu-N^{i}-il)-1-Moc-8-fenilsulfonil-HPI-2-carboxilat de metil (20a)



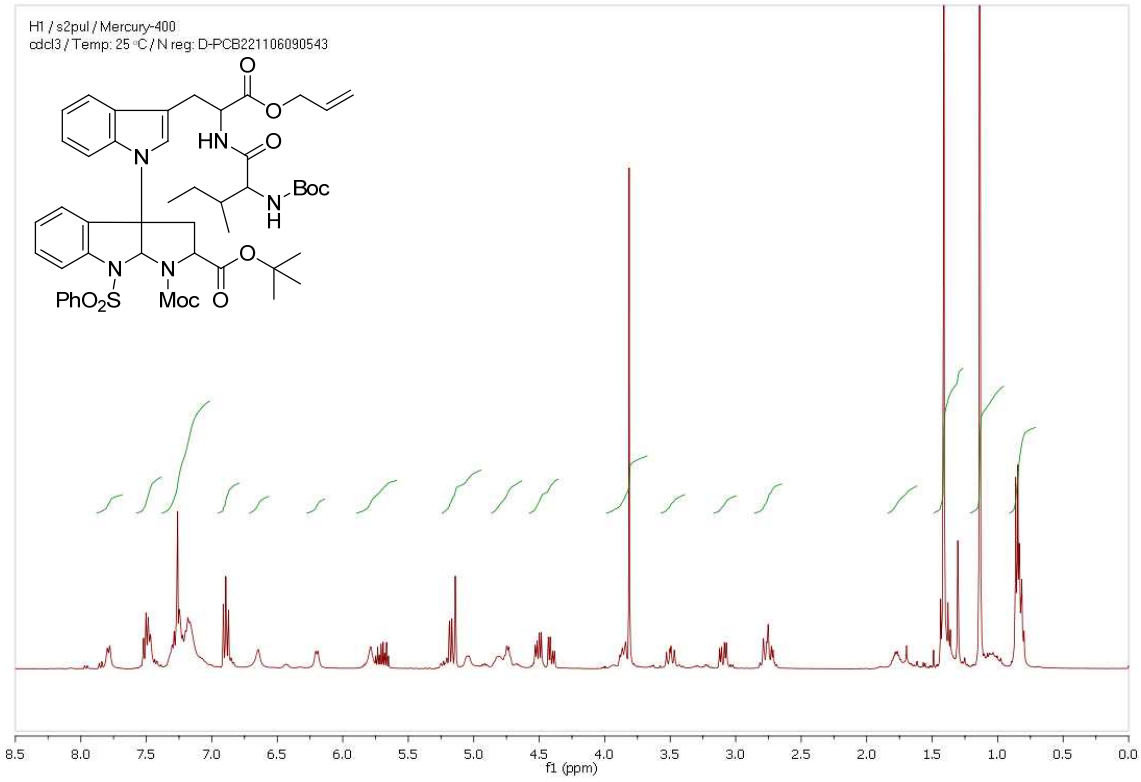


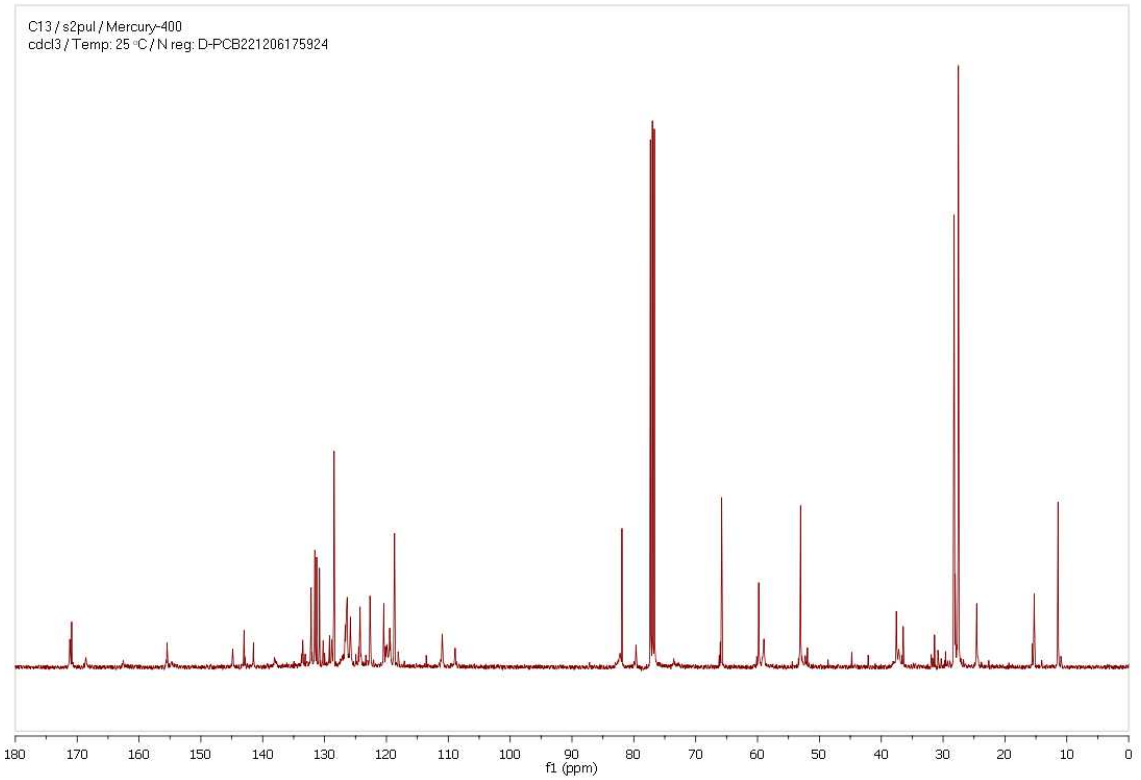
8.2 8-Fenilsulfonil-1-Moc-3a-(N^{α}-Moc-L-Trp-OMe-N^{i}-il)-HPI-2-carboxilat de metil (20b)



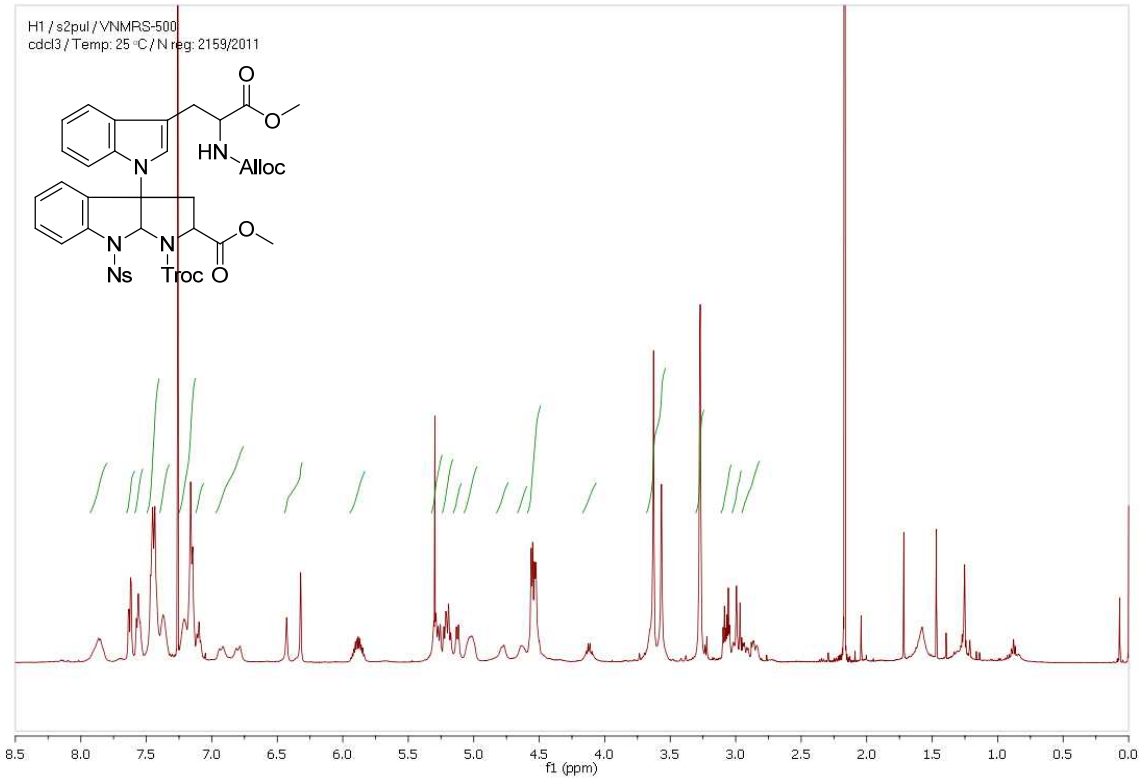


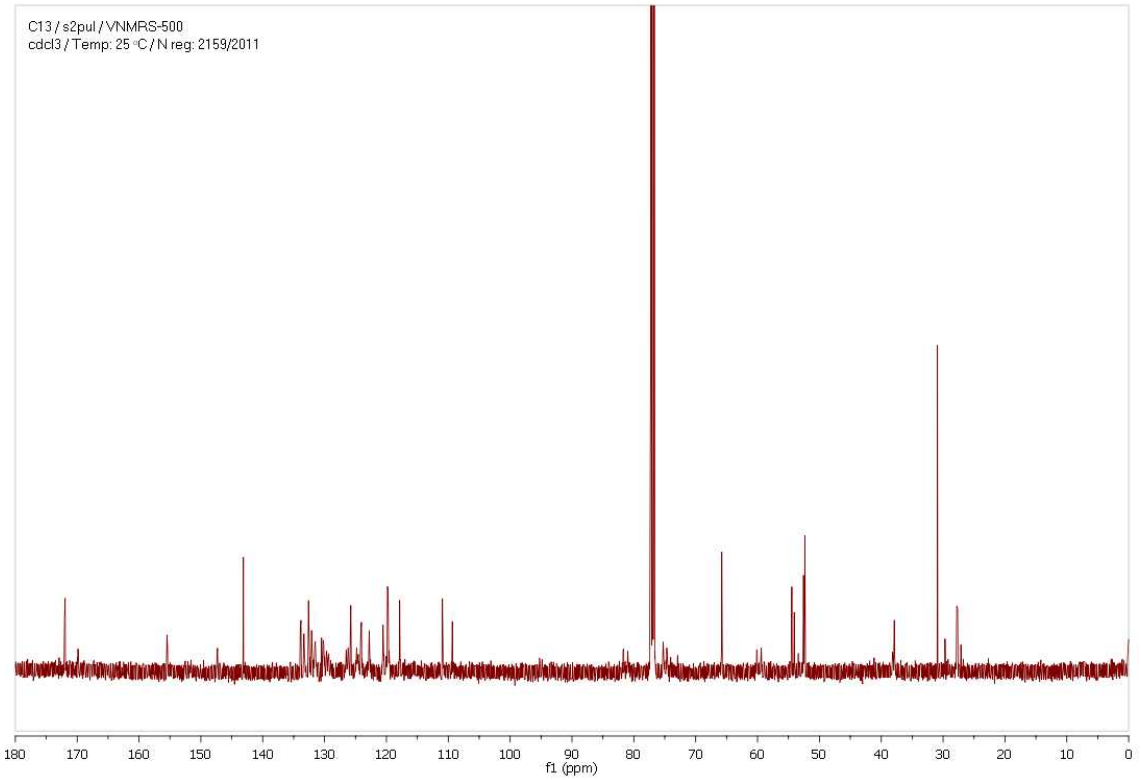
8.3 3a-(N^{α}-Boc-L-Ile-L-Trp-OAl·lil-N^{i}-il)-8-fenilsulfonil-1-Moc-HPI-2-carboxilat de *terc*-butil (20d)



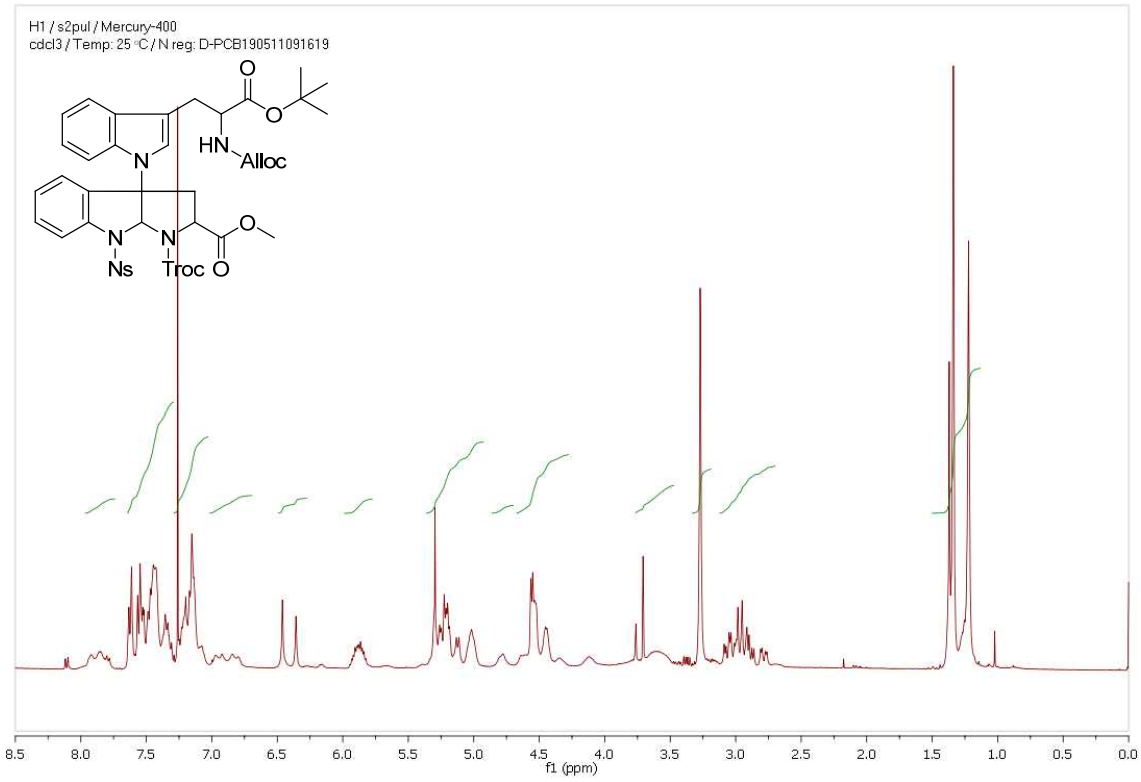


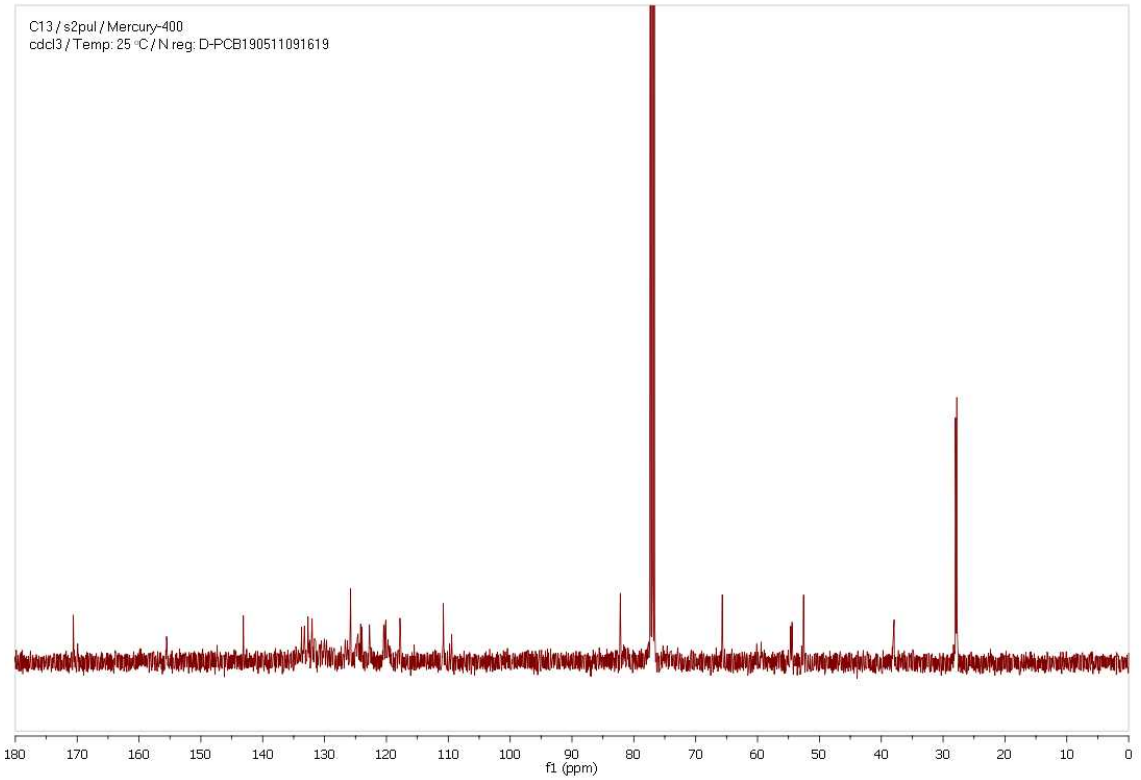
8.4 3a-(N^{α}-Alloc-L-Trp-OMe-N^{i}-il)-8-Nosyl-1-Troc-HPI-2-carboxilat de metil (20e)



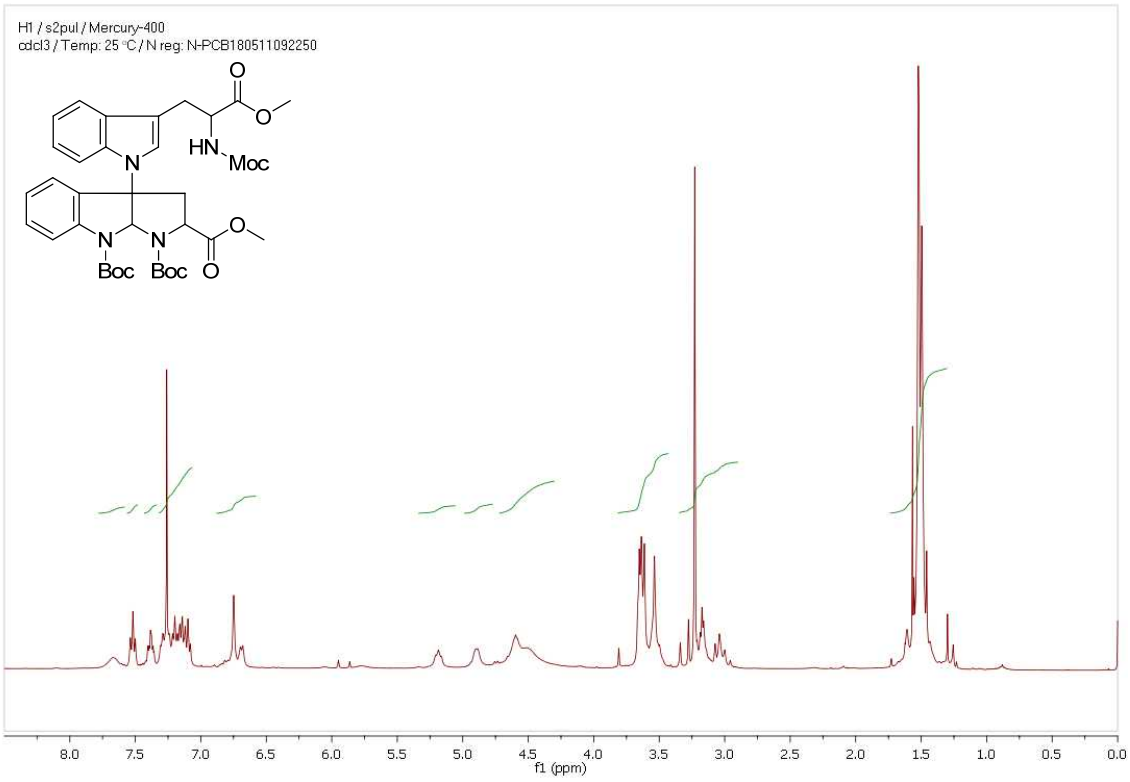


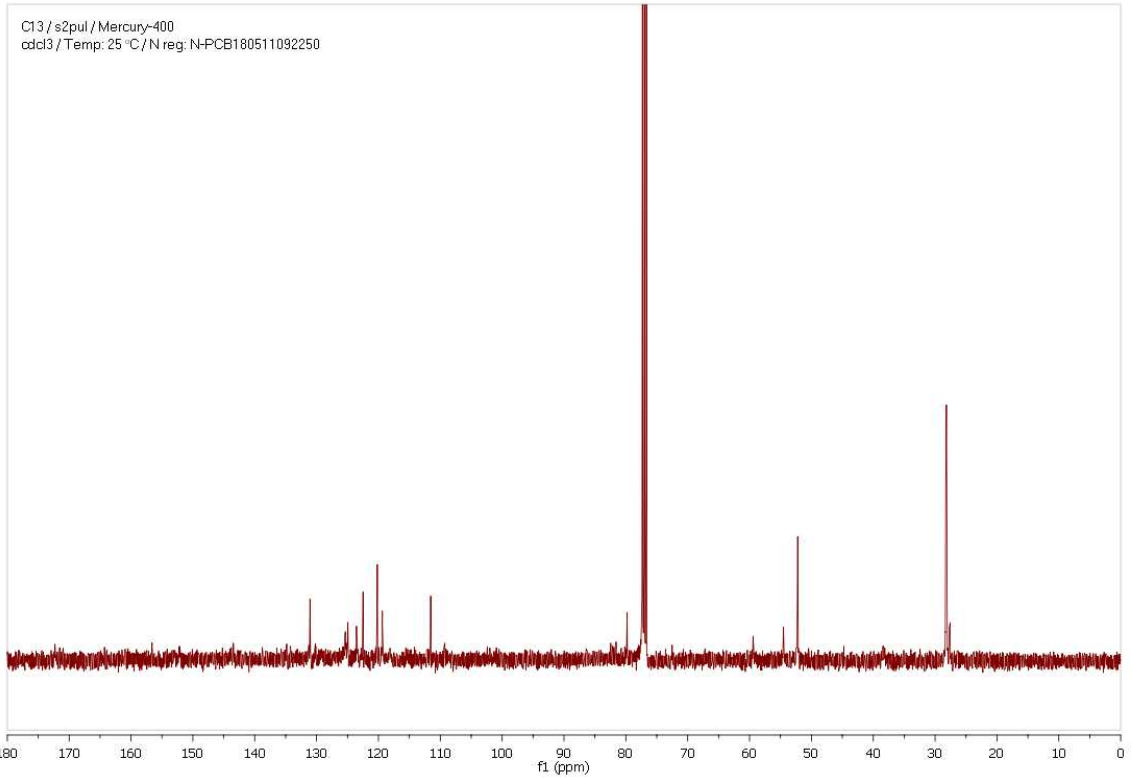
8.5 3a-(N^{α}-Alloc-L-Trp-O*t*Bu-N^{i}-il)-8-Nosyl-1-Troc-HPI-2-carboxilat de metil (20f)



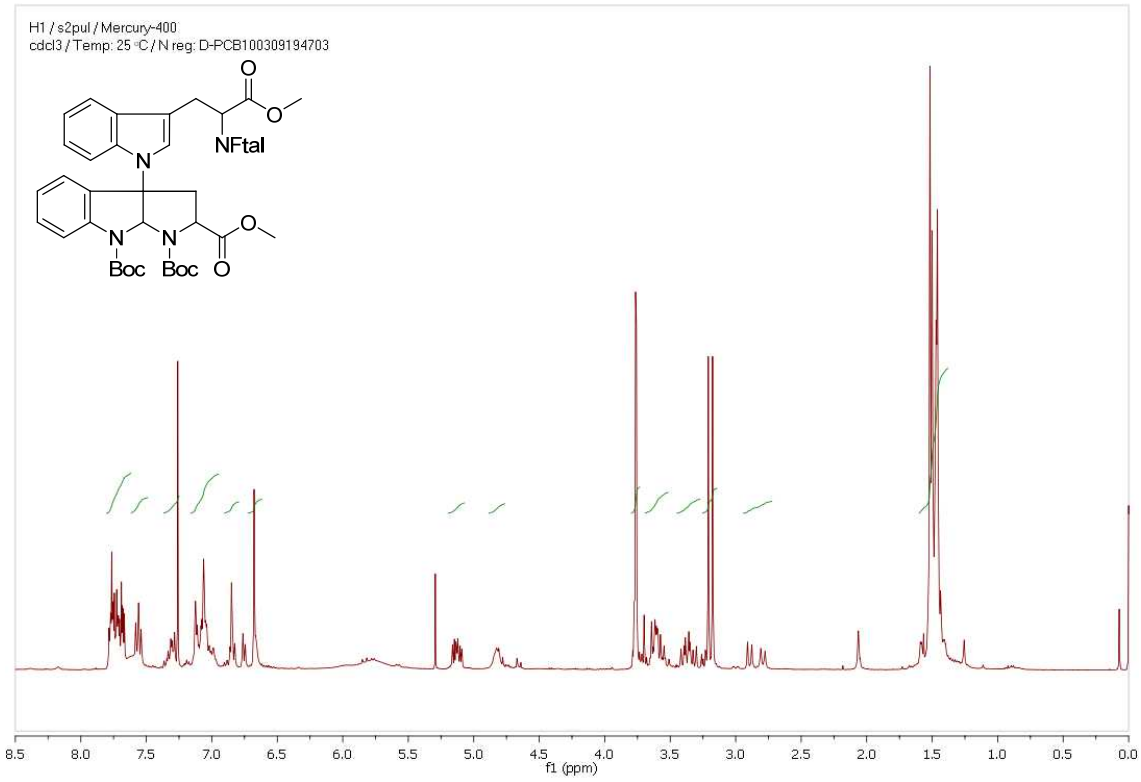


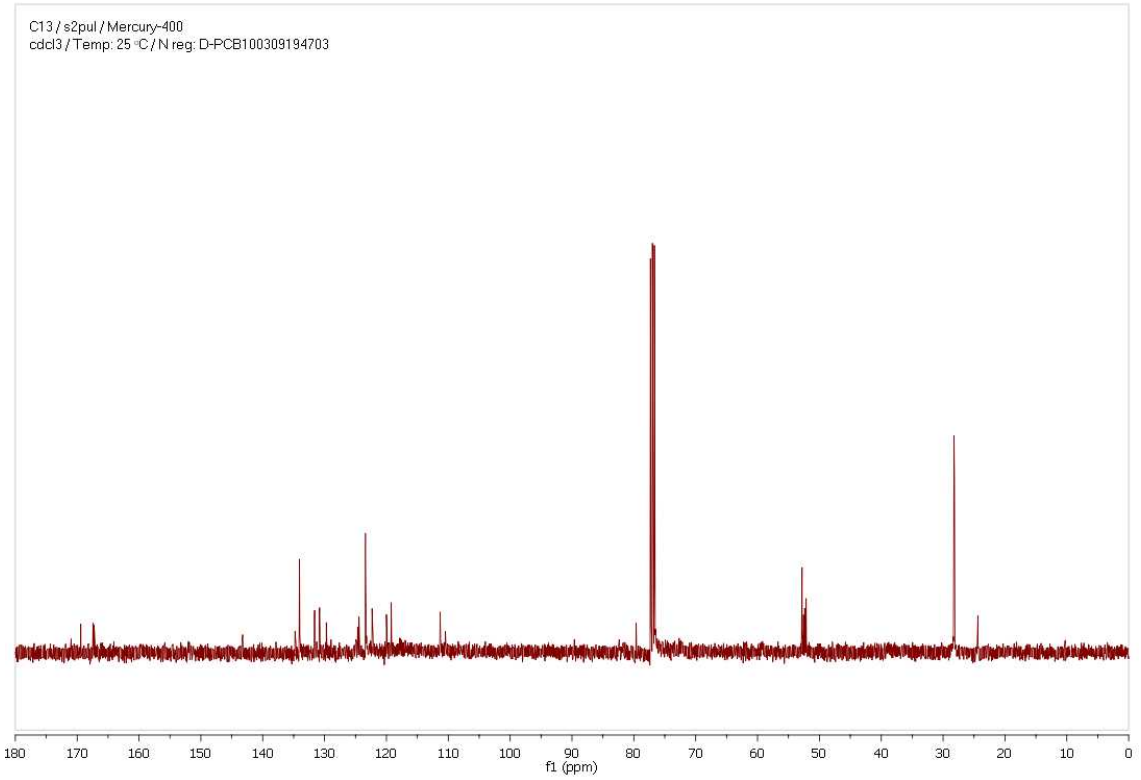
8.6 1,8-diBoc-3a-(N^{α}-Moc-L-Trp-OMe-N^{i}-il)-HPI-2-carboxilat de metil (20k)



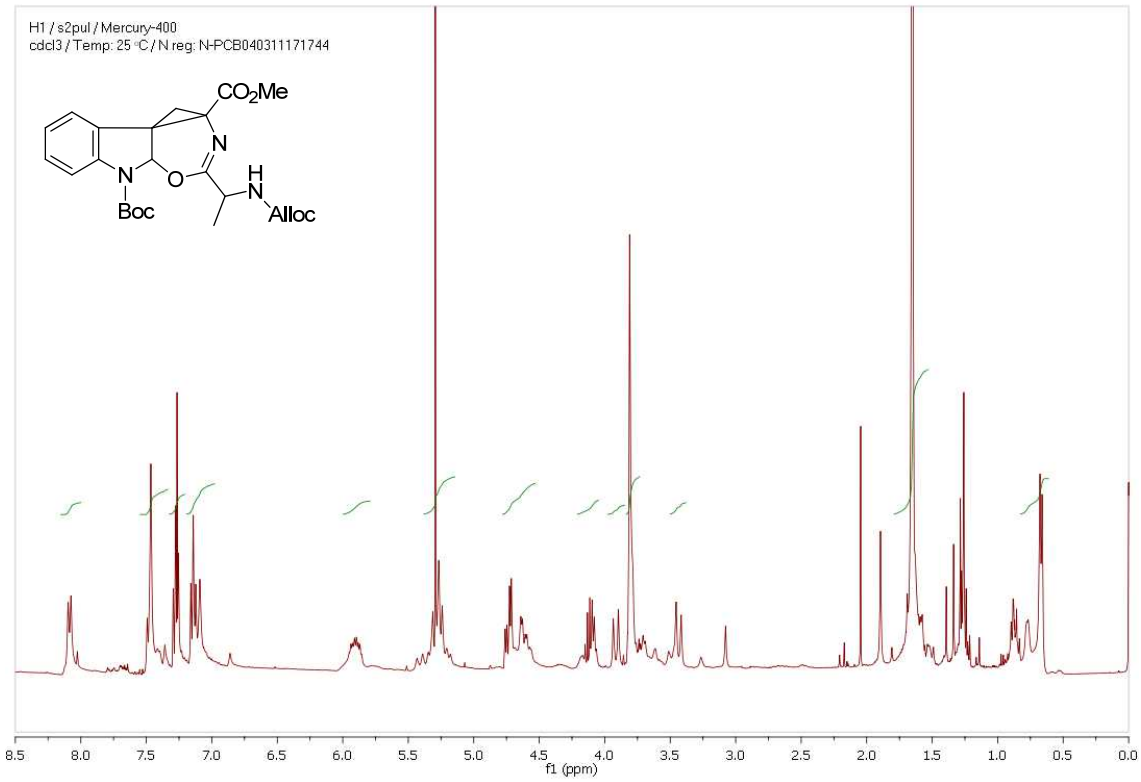


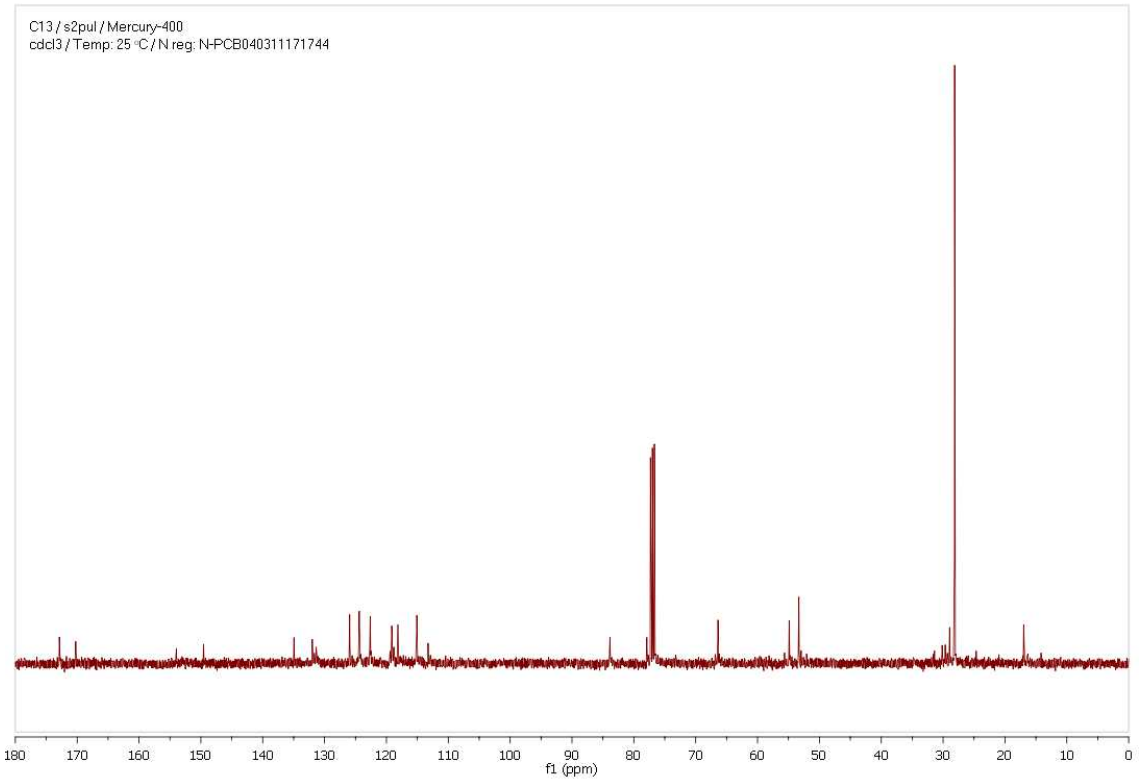
8.7 1,8-diBoc-3a-(N^{α}-Ftal-L-Trp-OMe-N^{i}-il)-HPI-2-carboxilat de metil (20l)





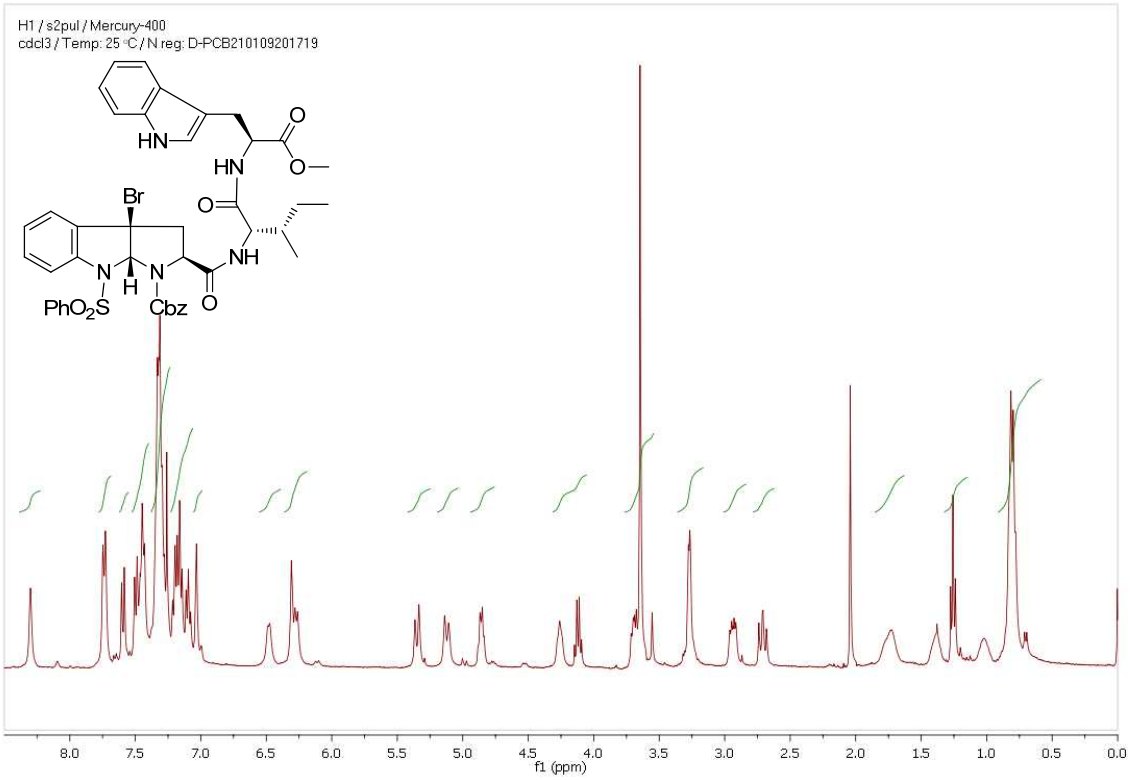
9. Compost 21


H1 / s2pul / Mercury-400
cdcl3 / Temp: 25 °C / N reg: N-PCB040311171744
CO2Me
N
N
Boc
O
H
N
Alloc
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

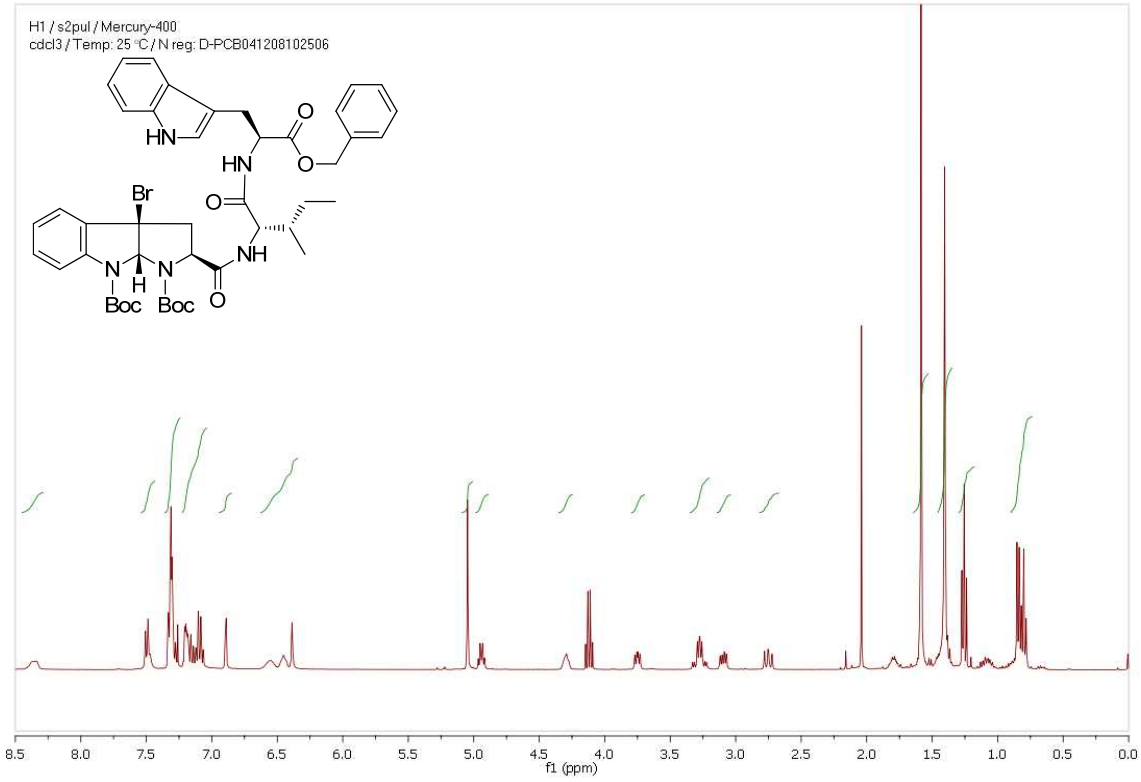

C13 / s2pul / Mercury-400
cdcl3 / Temp: 25 °C / N reg: N-PCB040311171744
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

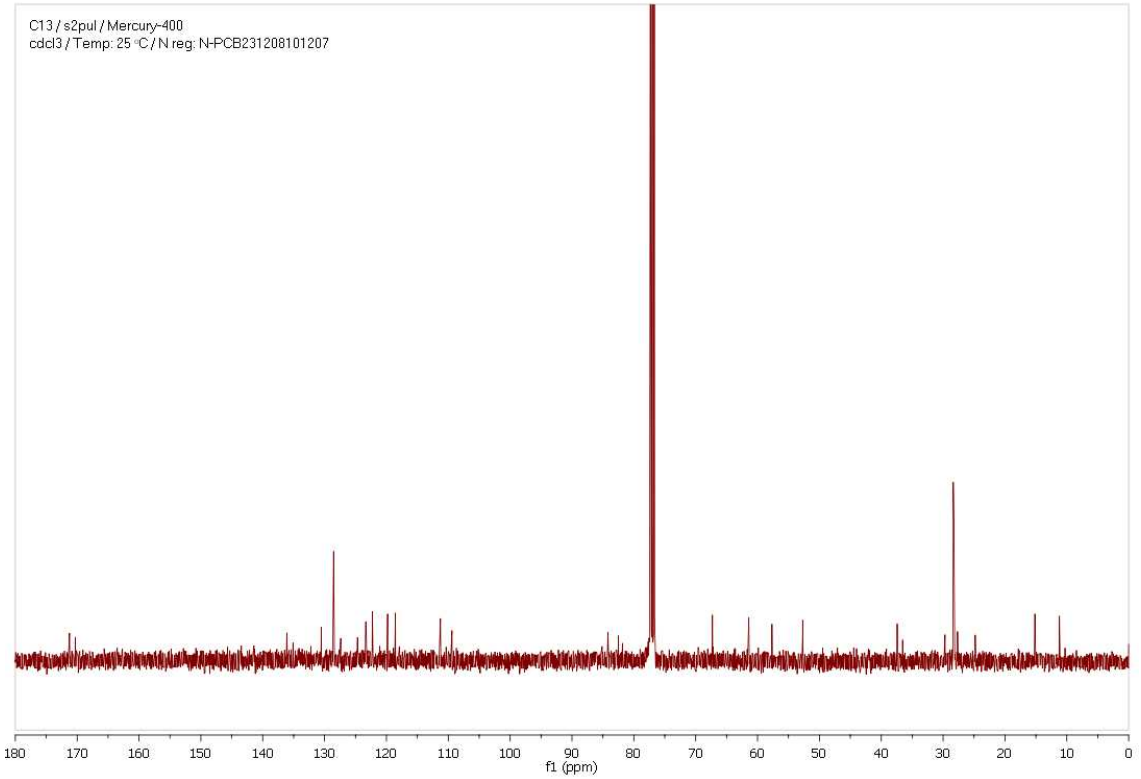
10. Compost 22

10.1 Compost 22a

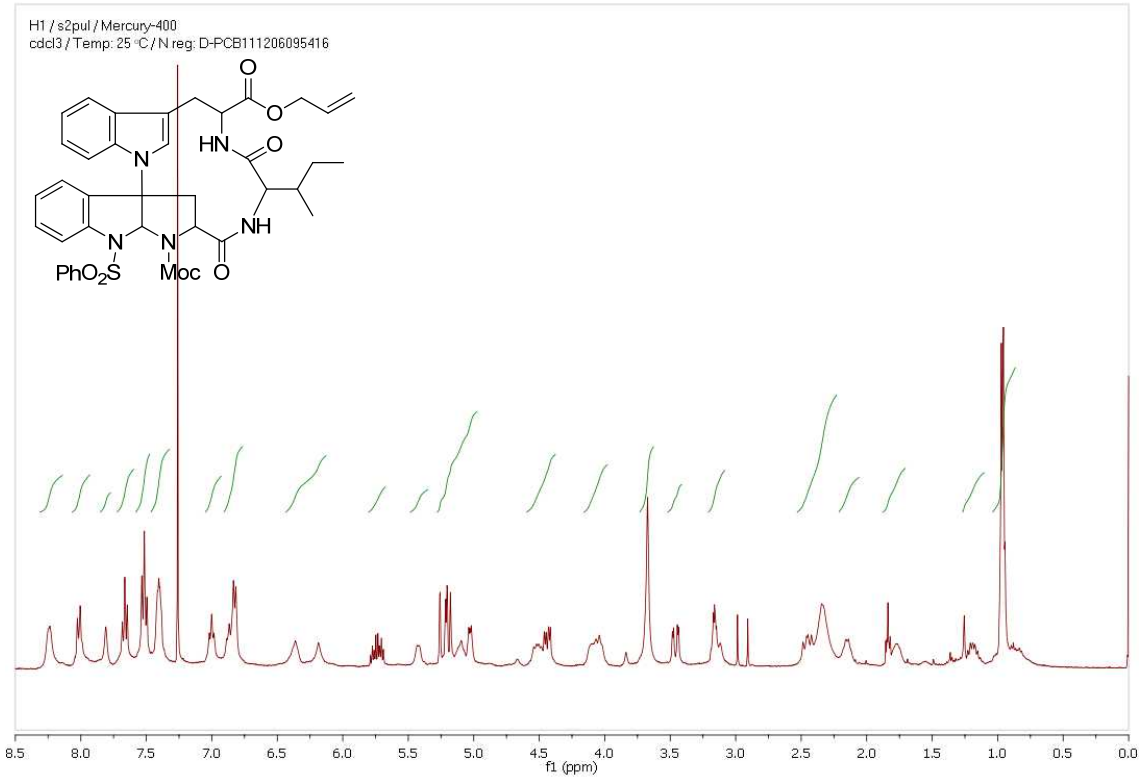


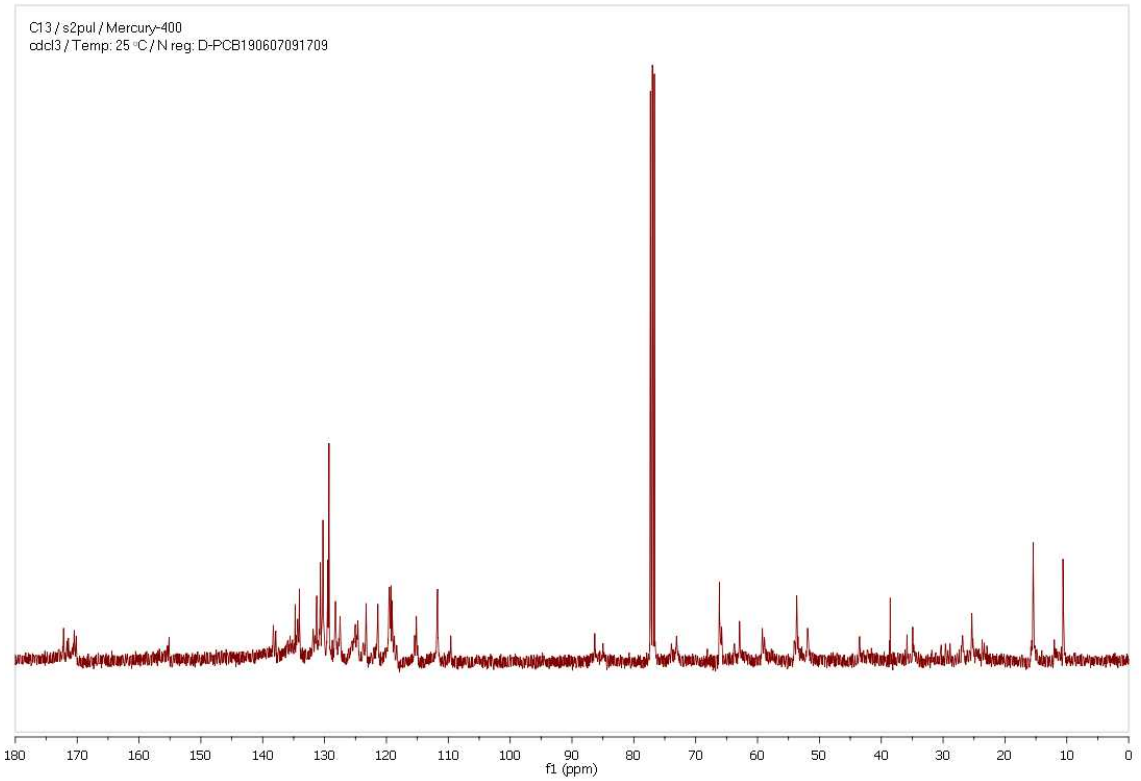
10.2 Compost 22b

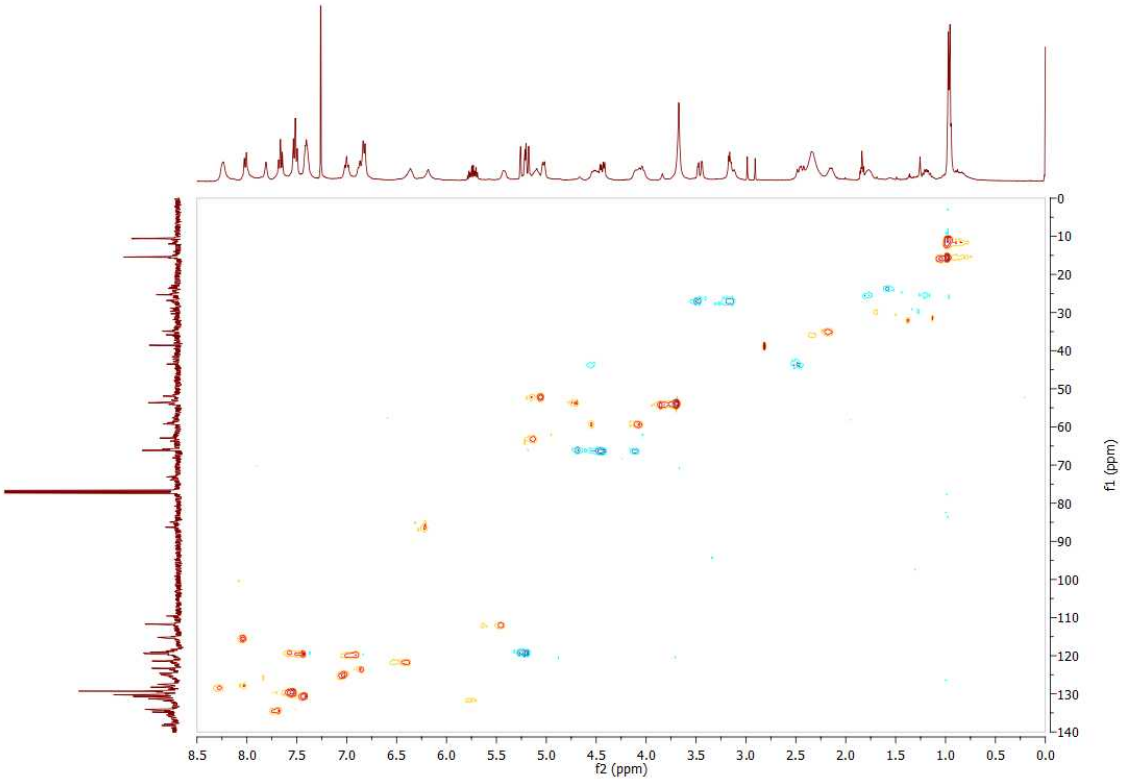




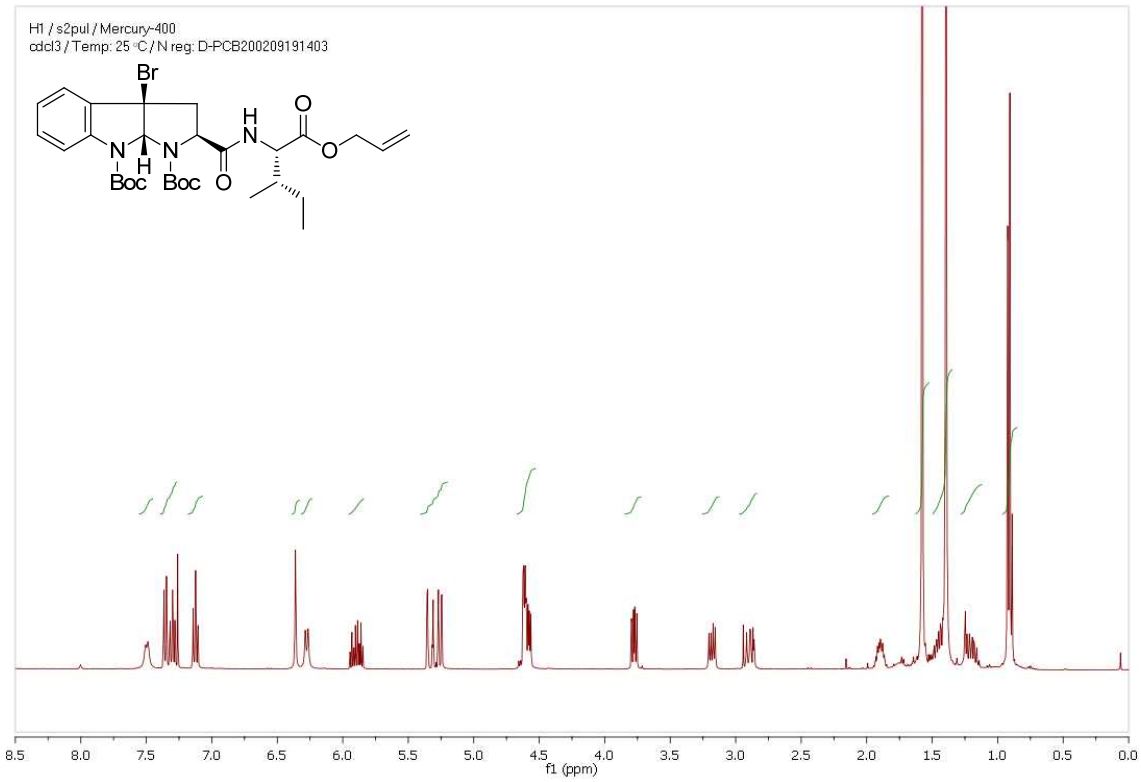
11. Compost 26

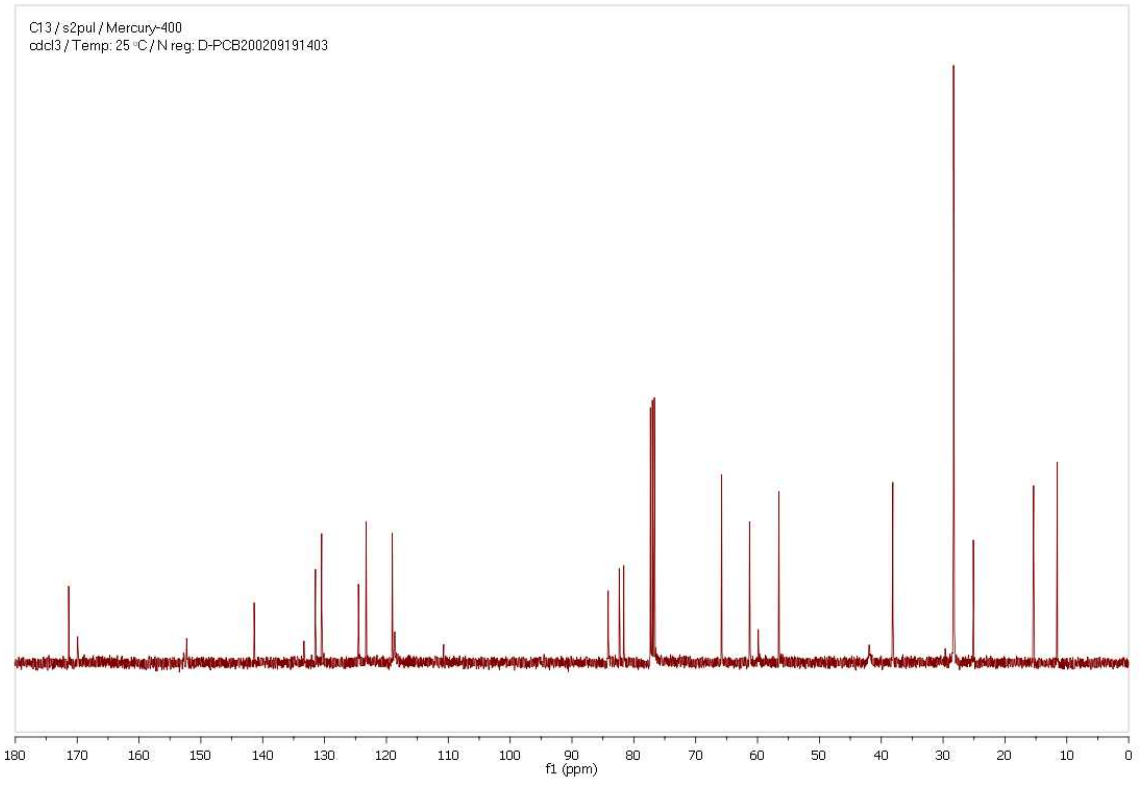




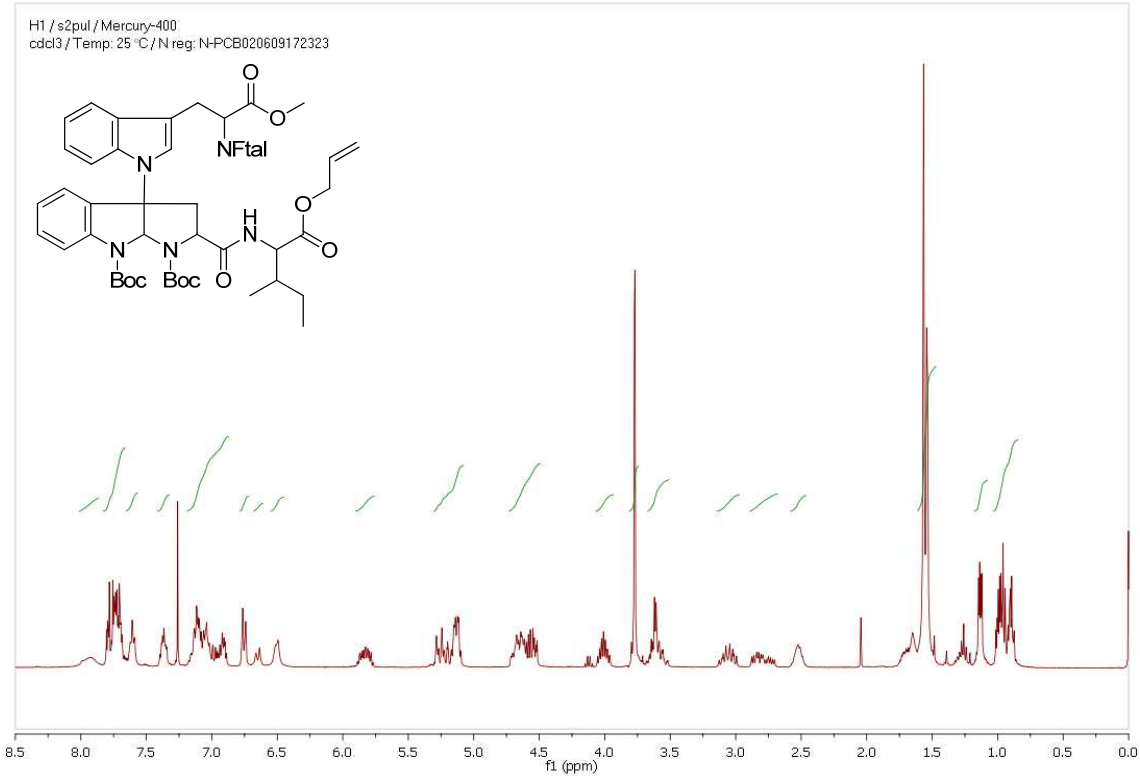

f1 (ppm)
f2 (ppm)

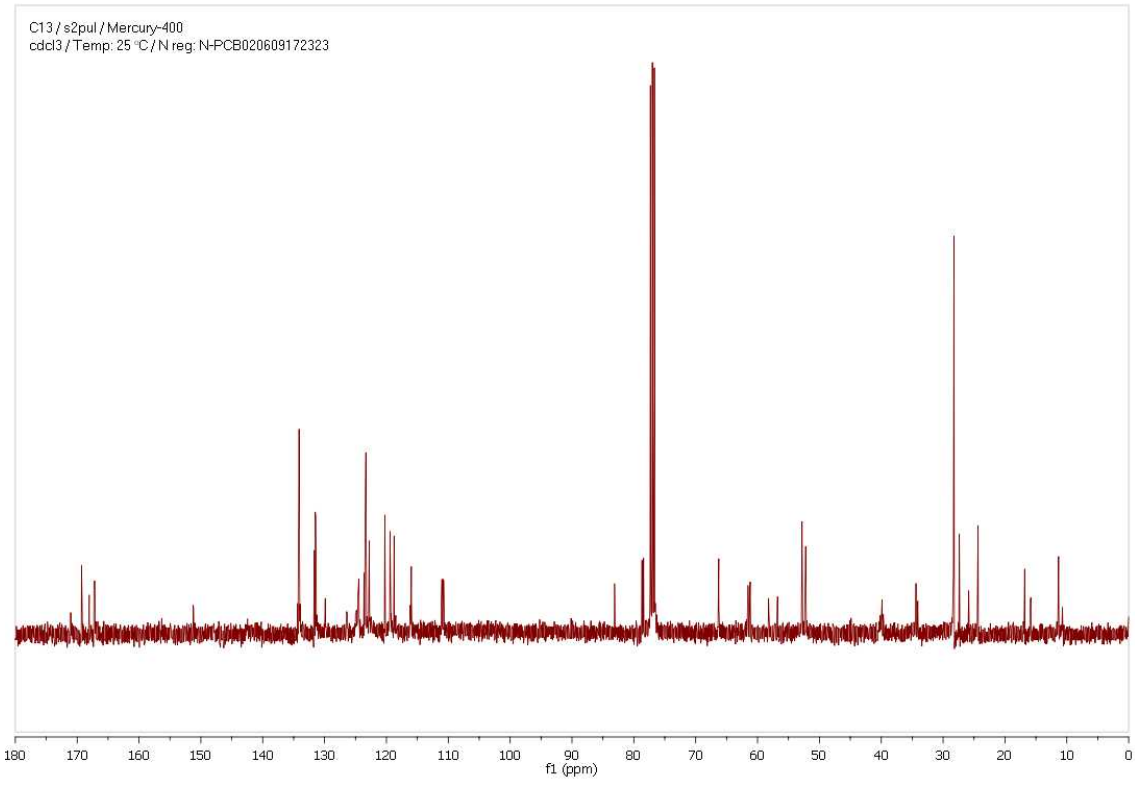
12. 3a-bromo-1,8-(di-*terc*-butoxicarbonil)-HPI-2-carbonil-Ile-OAl·lil (27)



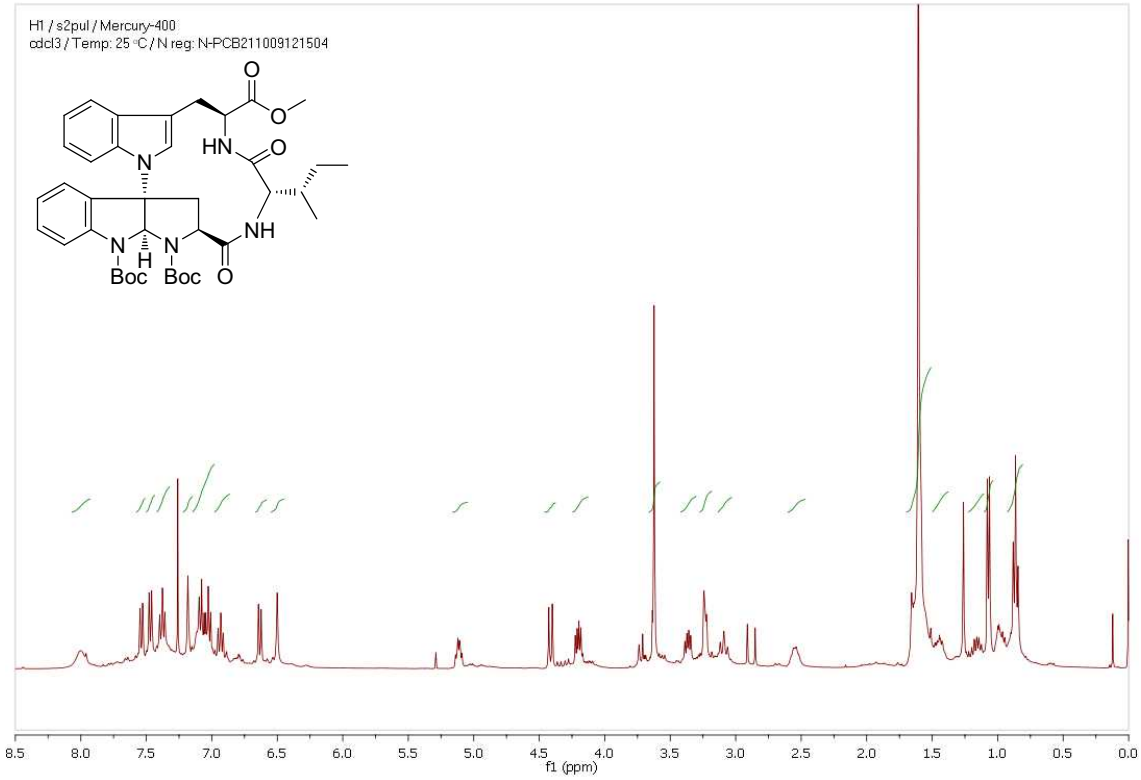


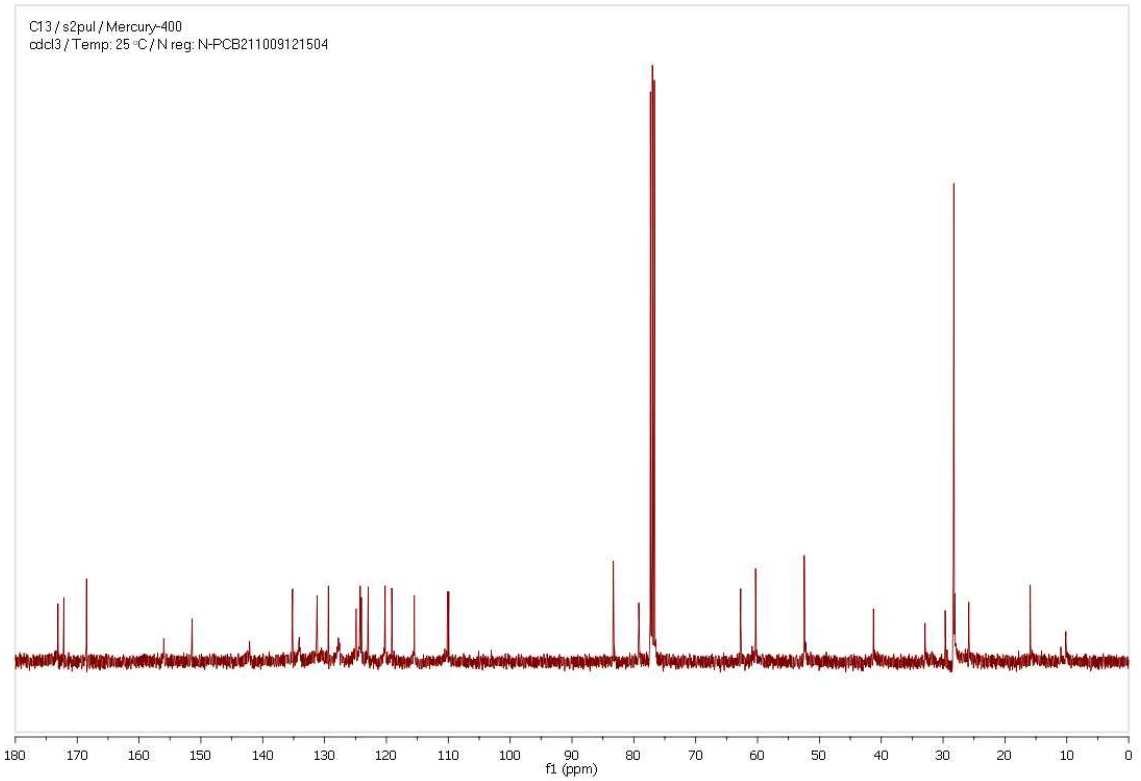
13. 1,8-(di-Boc)-3a-(N^{α}-Ftal-L-Trp-OMe-N^{i}-il)-HPI-2-carbonil-Ile-OAl·lil (28)



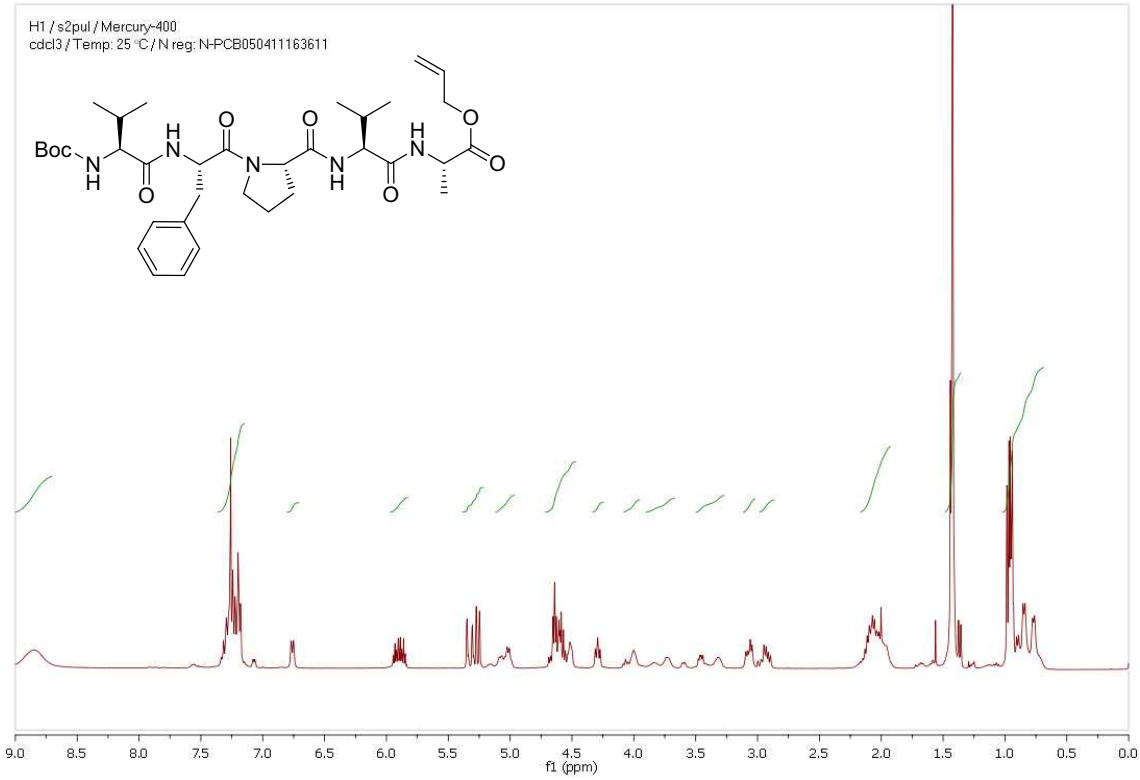


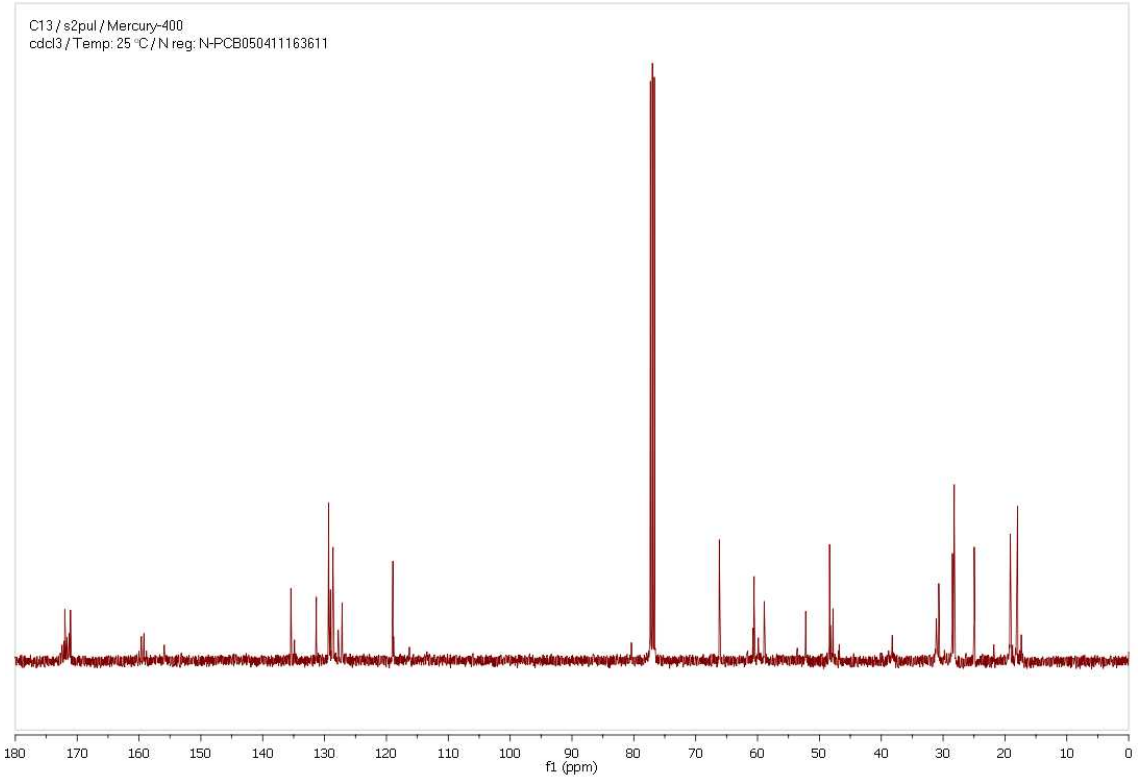
14. Compost 29



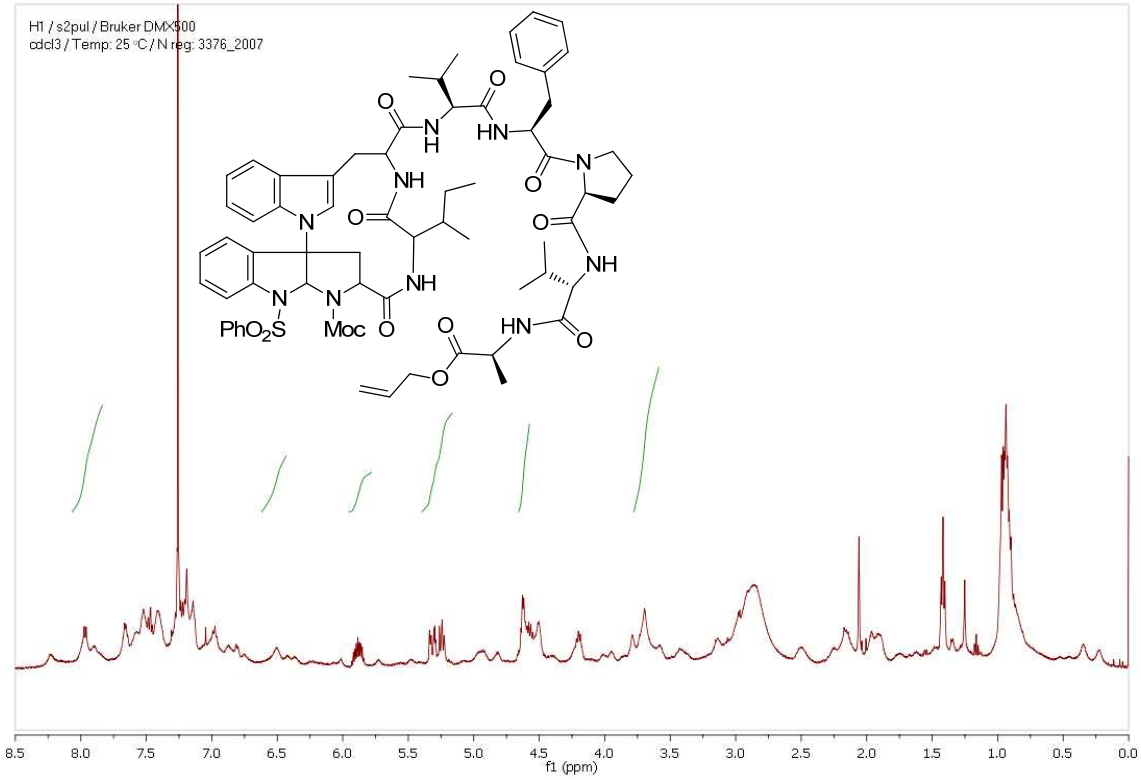


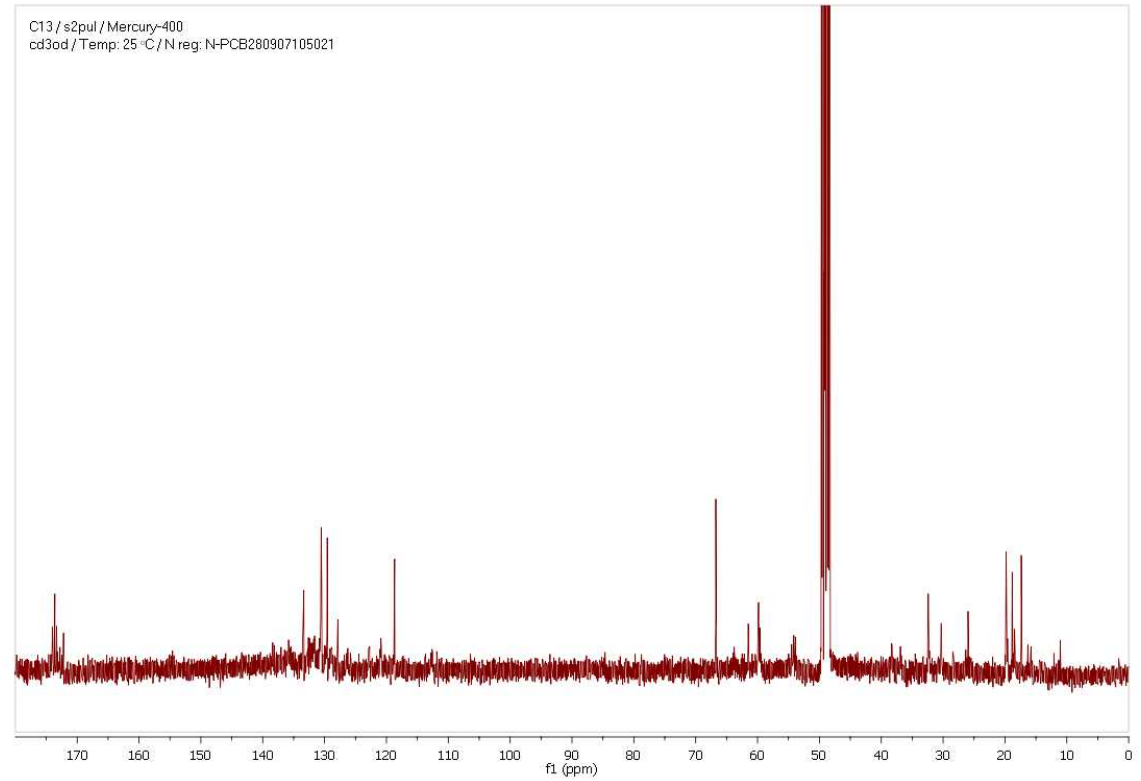
15. N^{α}-Boc-Val-Phe-Pro-Val-Ala-OAl·lil (33)

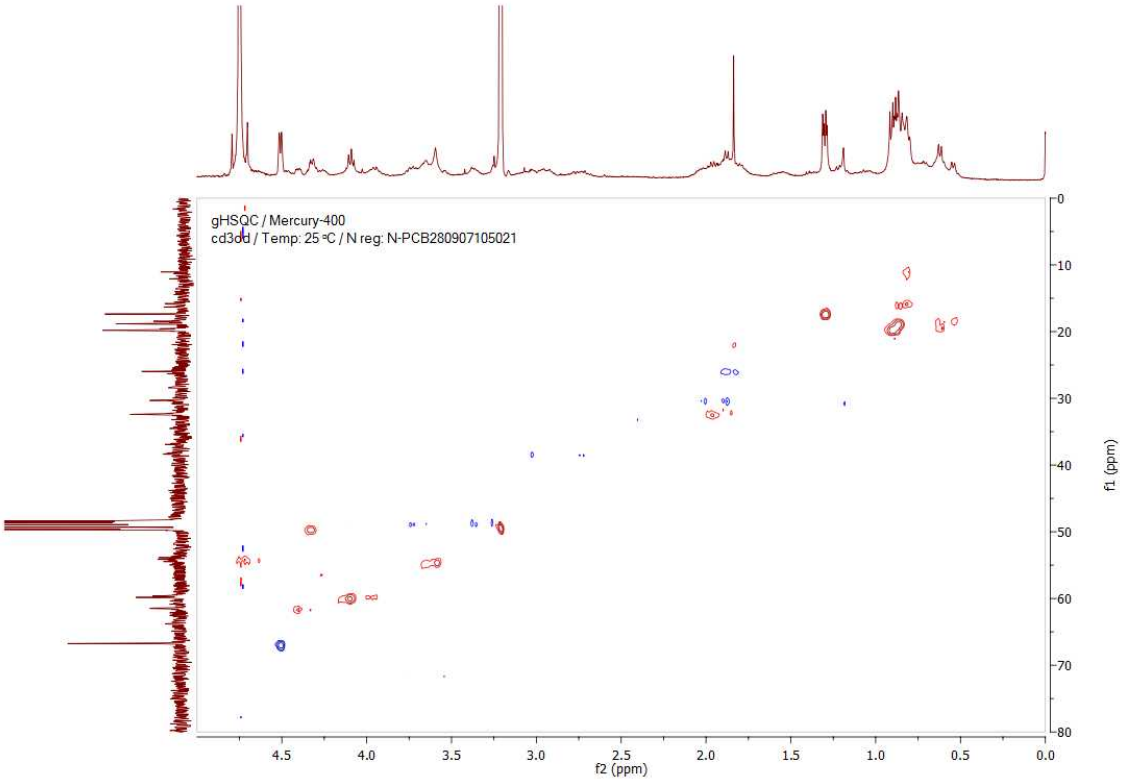




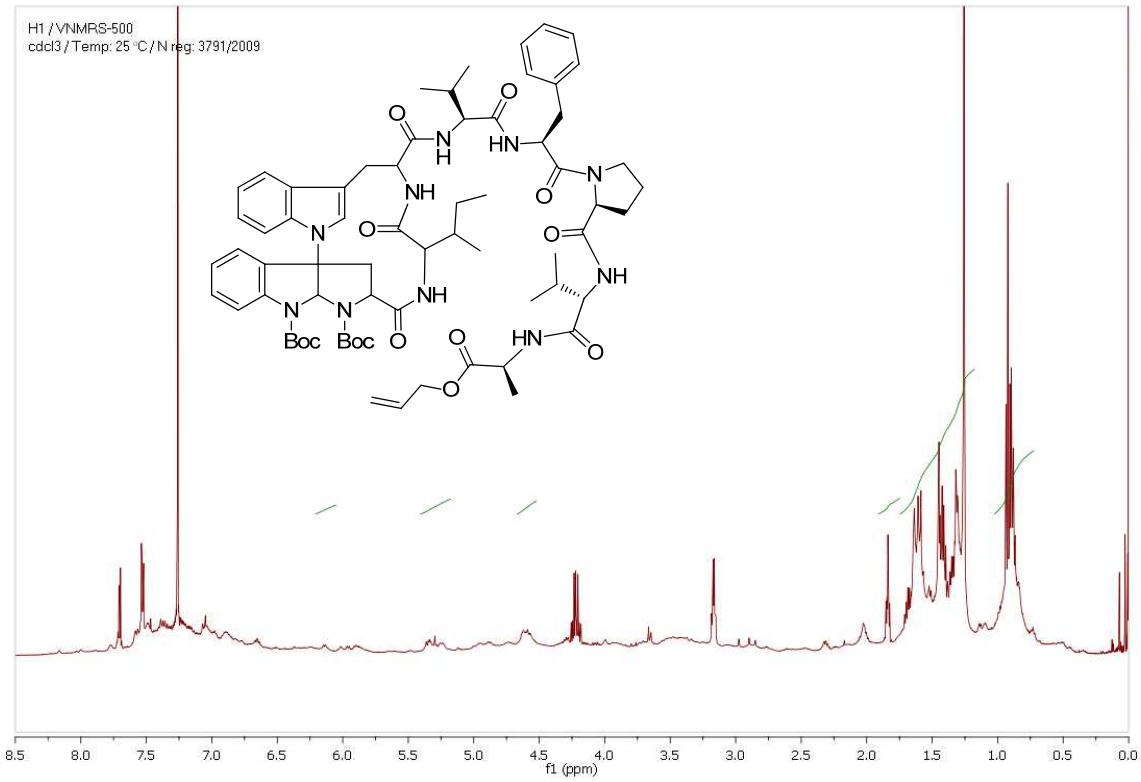
16. Compost 35

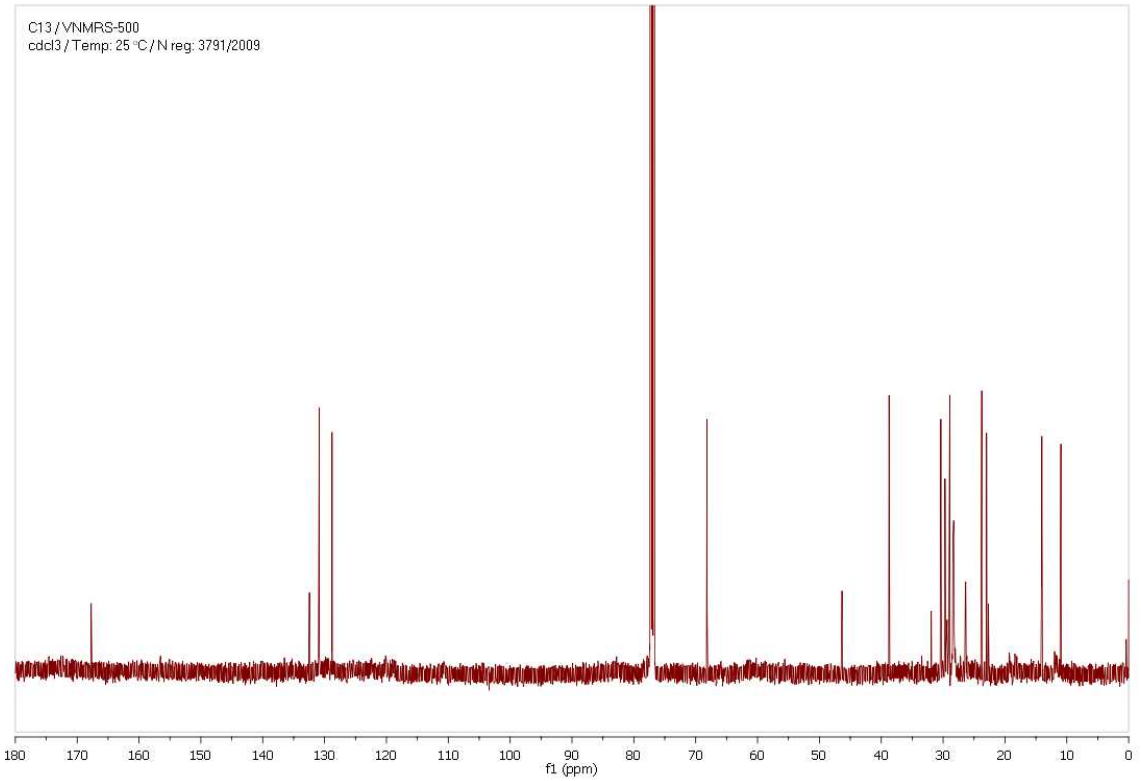


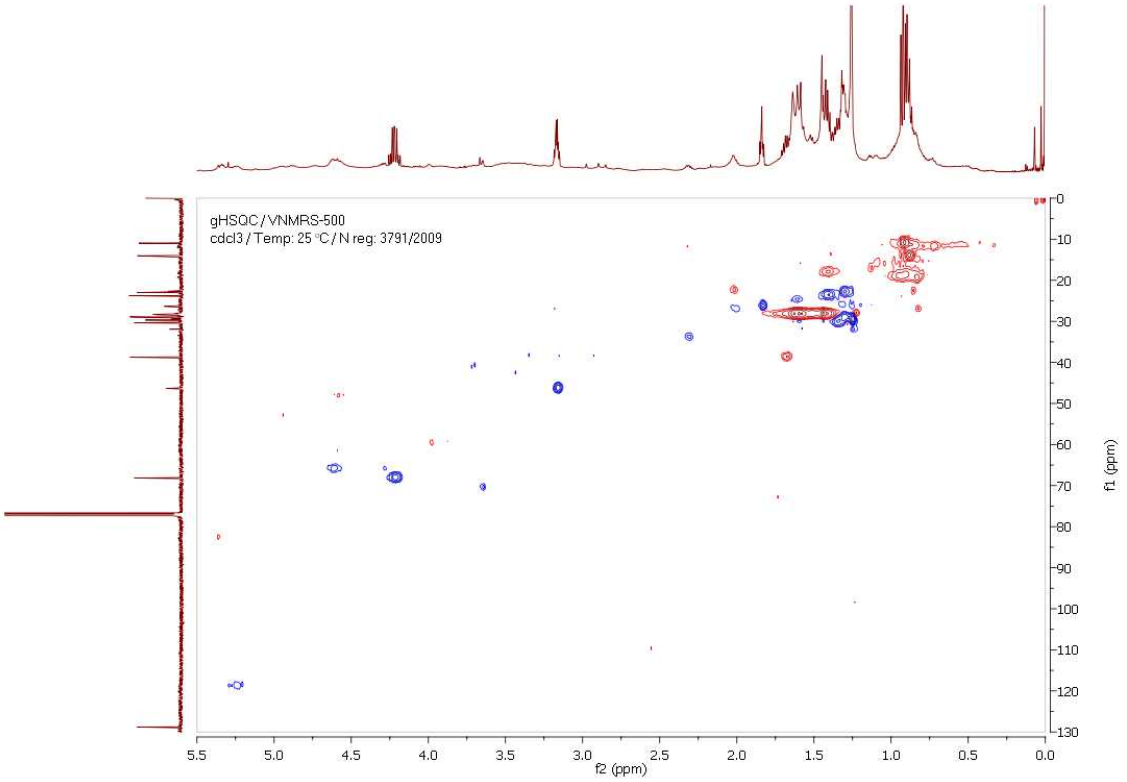



gHSQC / Mercury-400
cd3dd / Temp: 25 °C / N reg: N-PCB280907105021
f2 (ppm)
f1 (ppm)

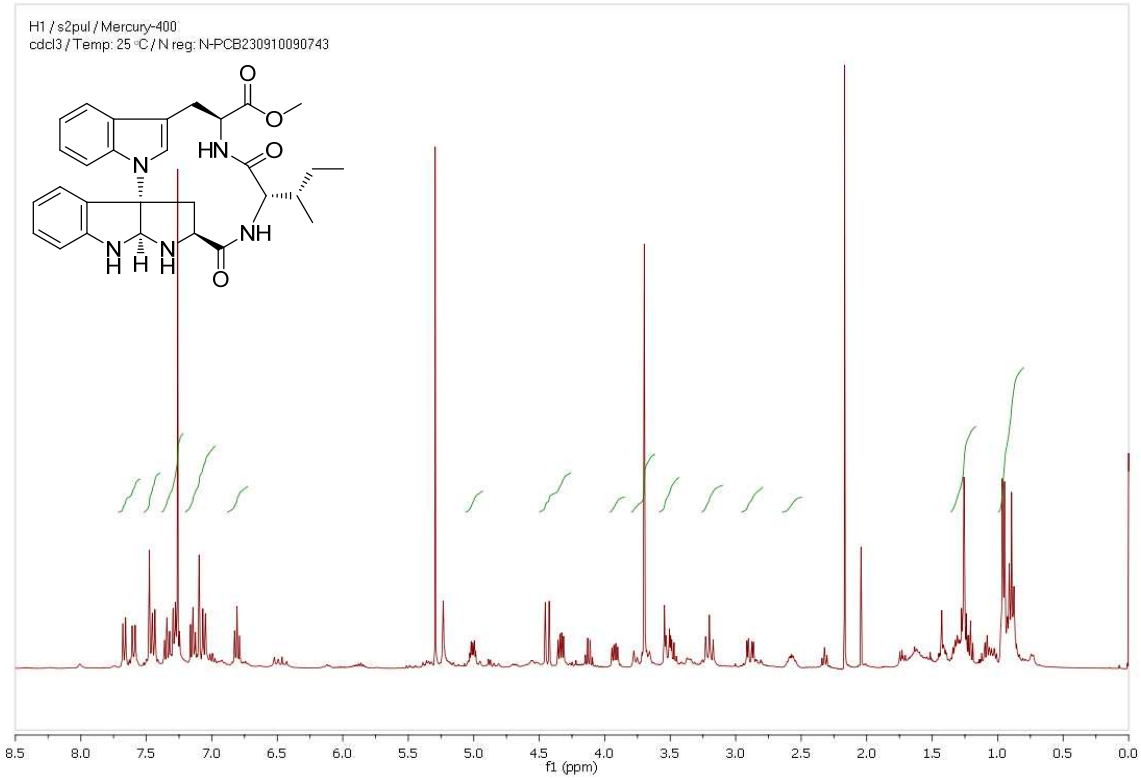
17. Compost 37

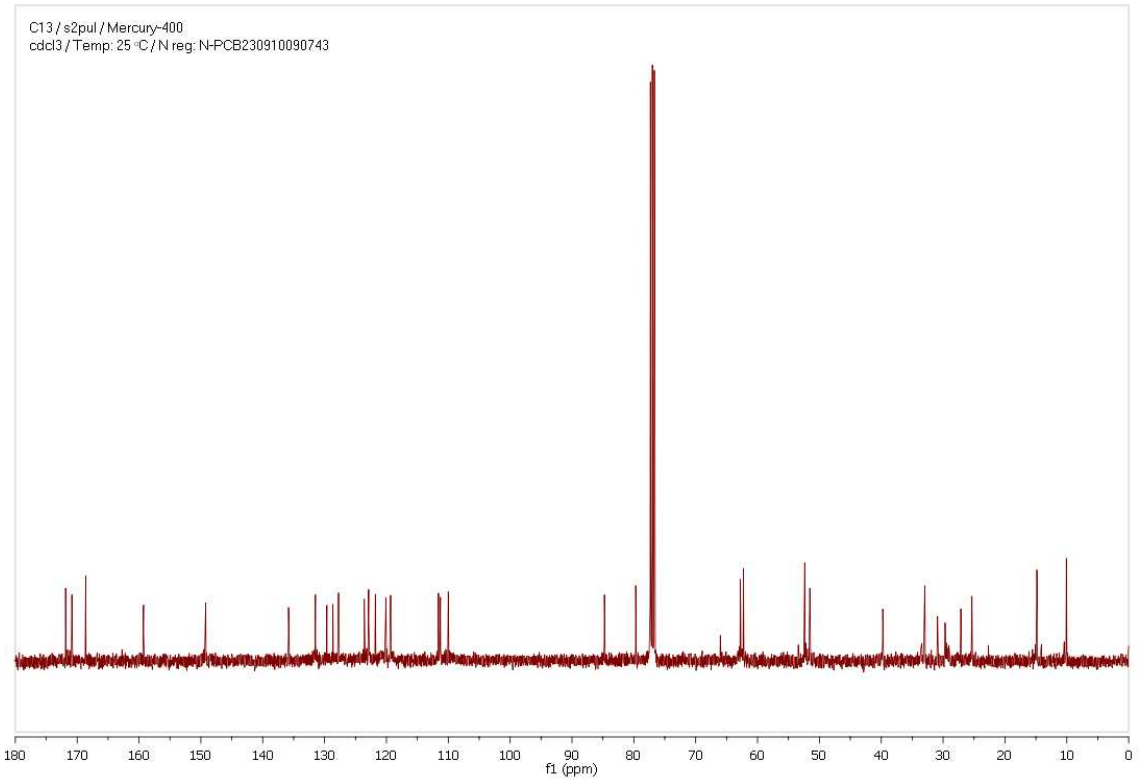




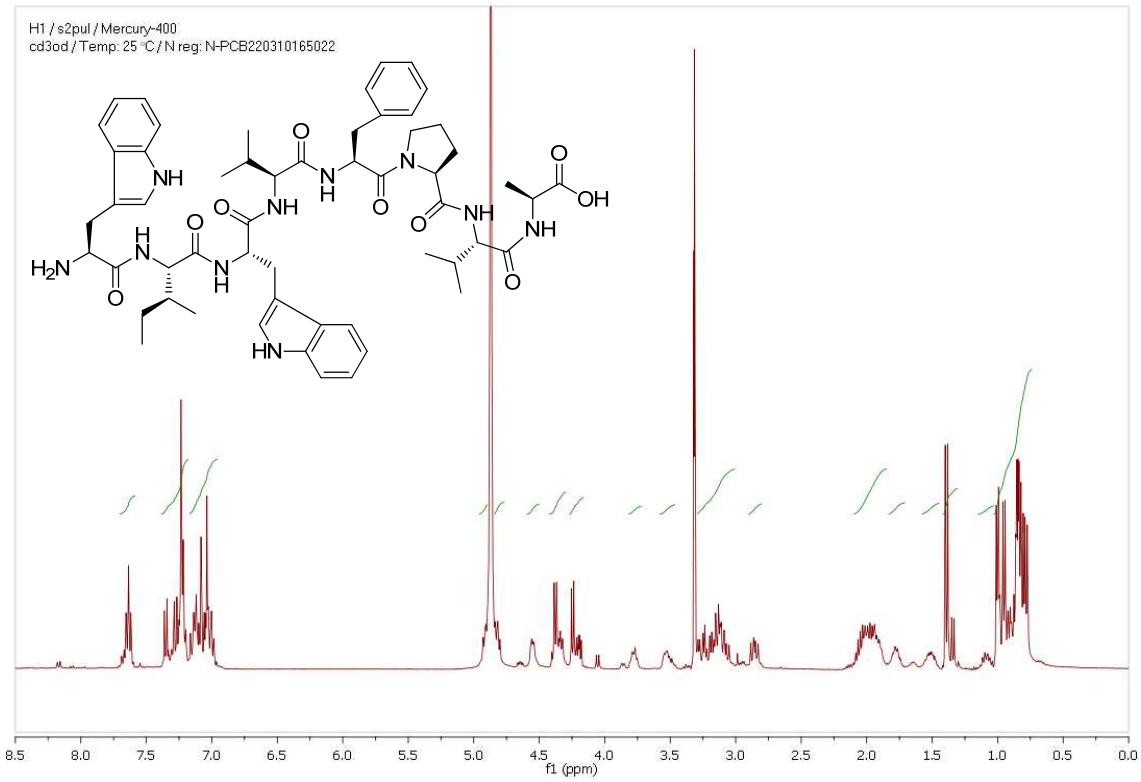

gHSQC / VNMRS-500
cdcl3 / Temp: 25 °C / N reg: 3791/2009
f2 (ppm)
f1 (ppm)

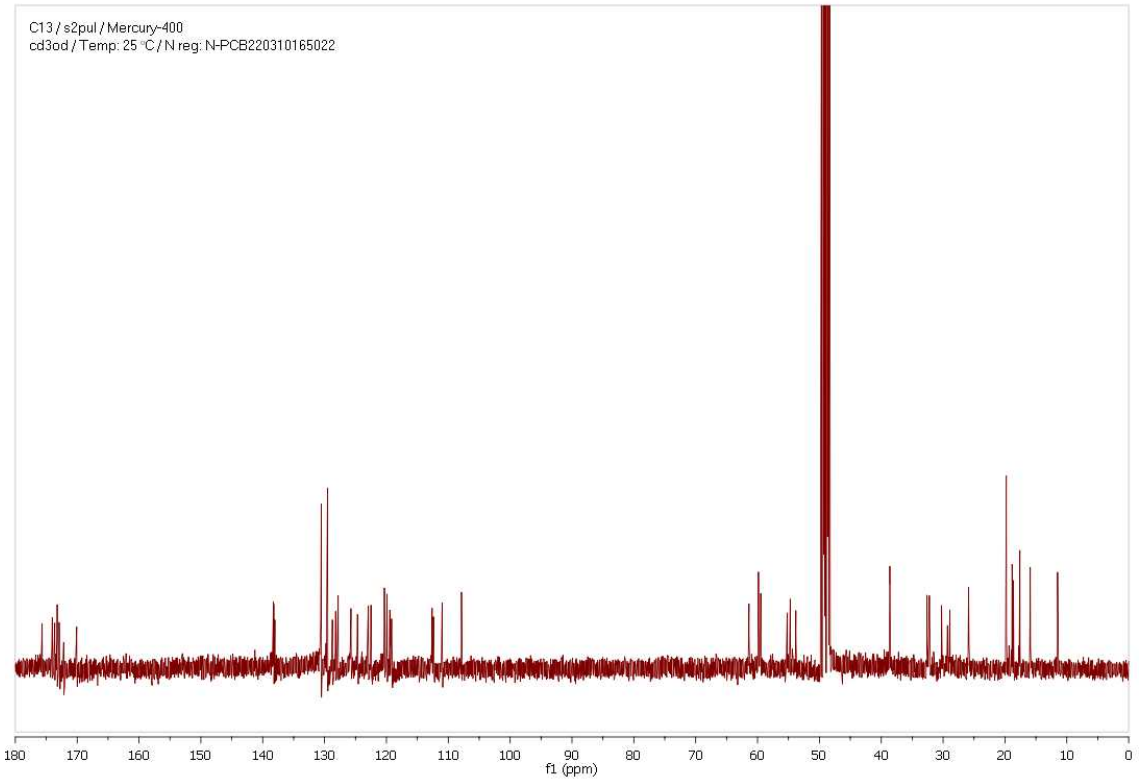
18. Compost 38



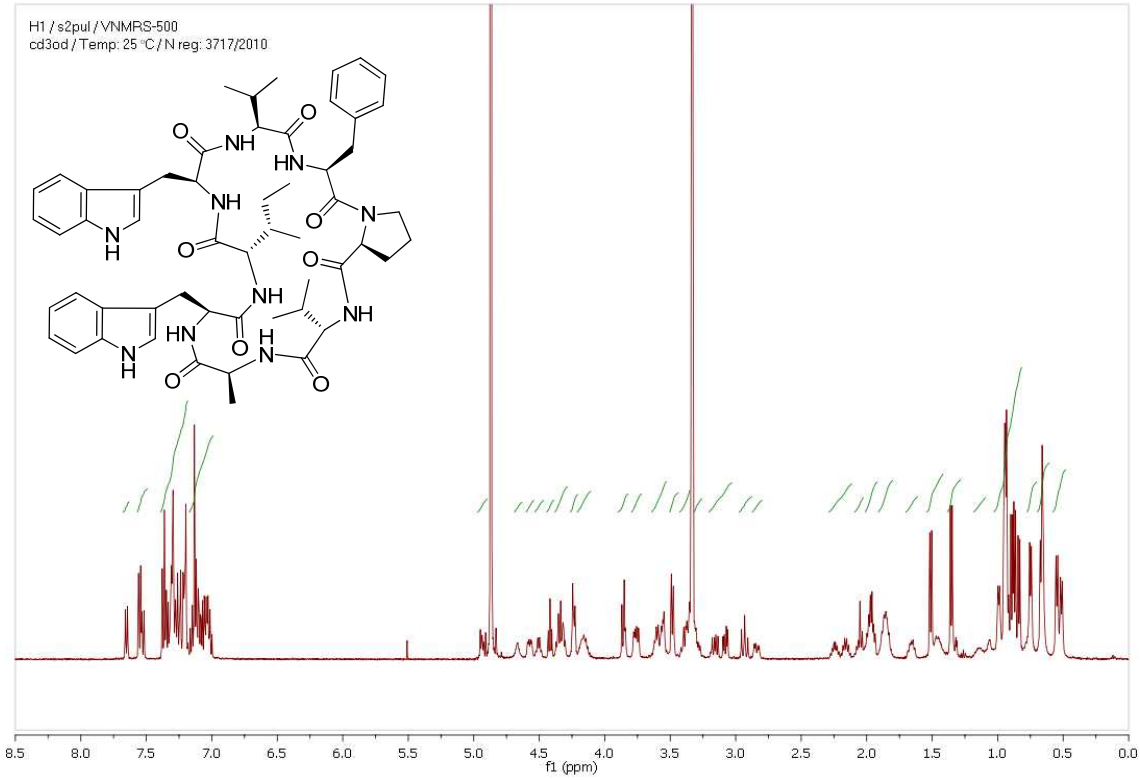


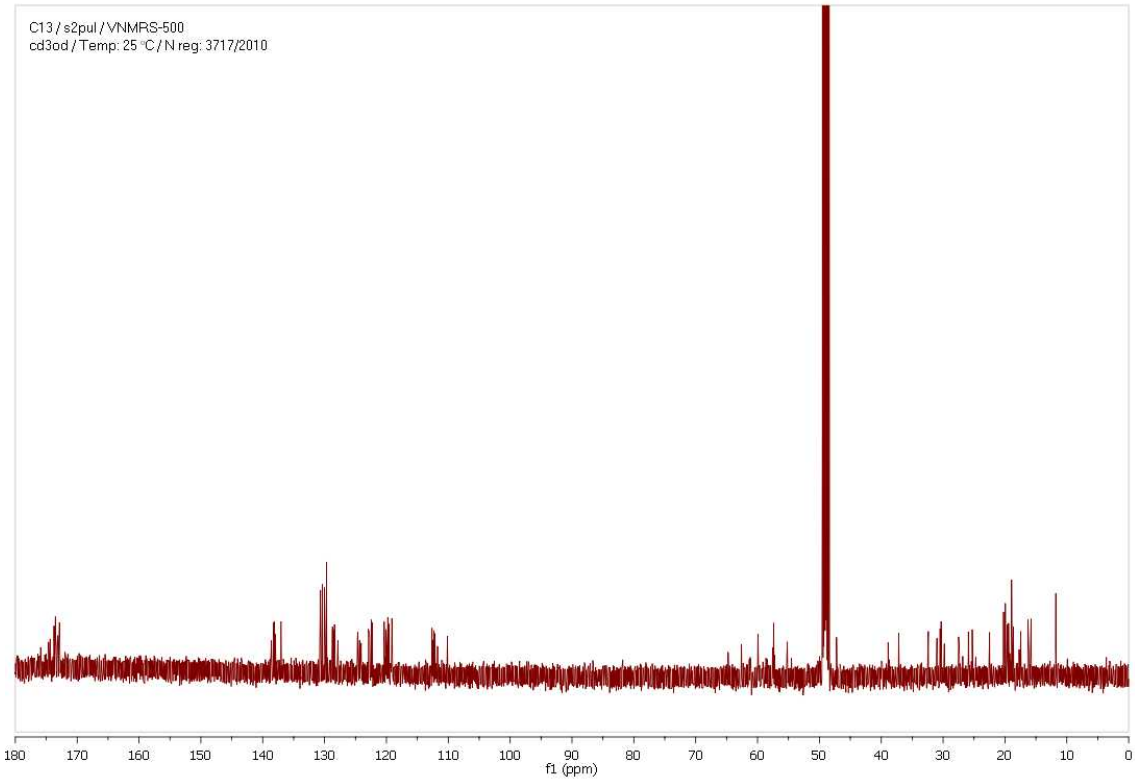
19. Compost Trp-Ile-Trp-Val-Phe-Pro-Val-Ala-OH (42)

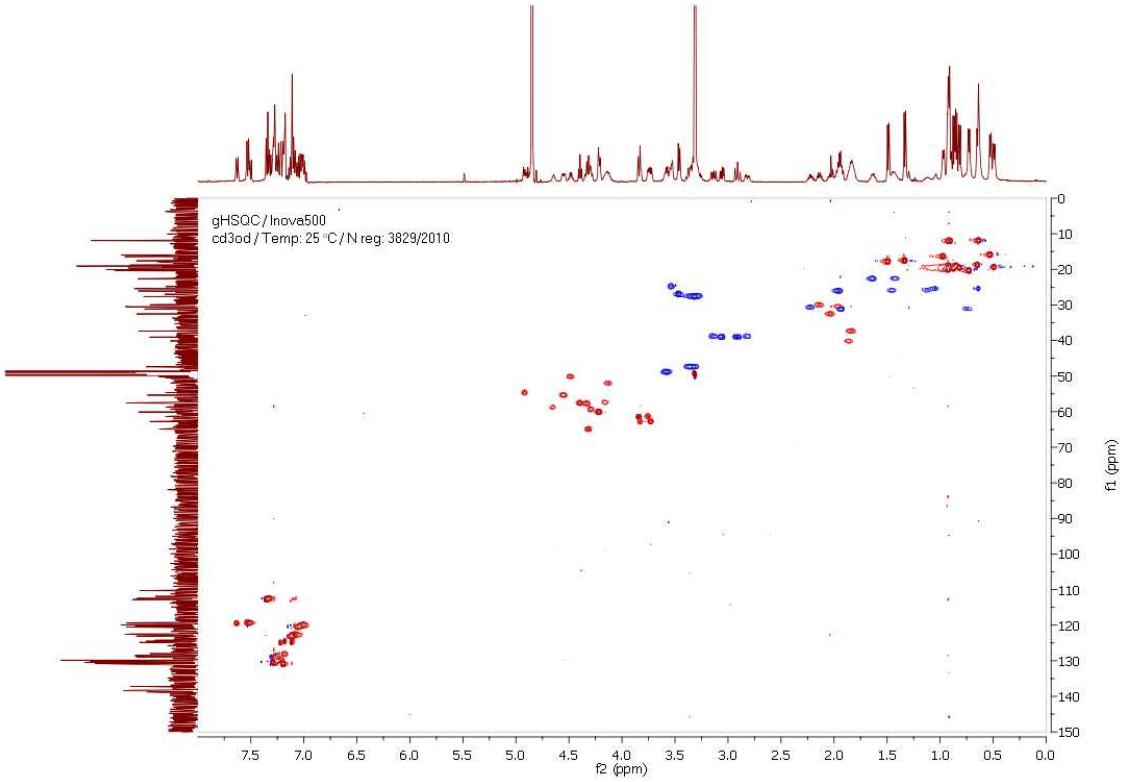


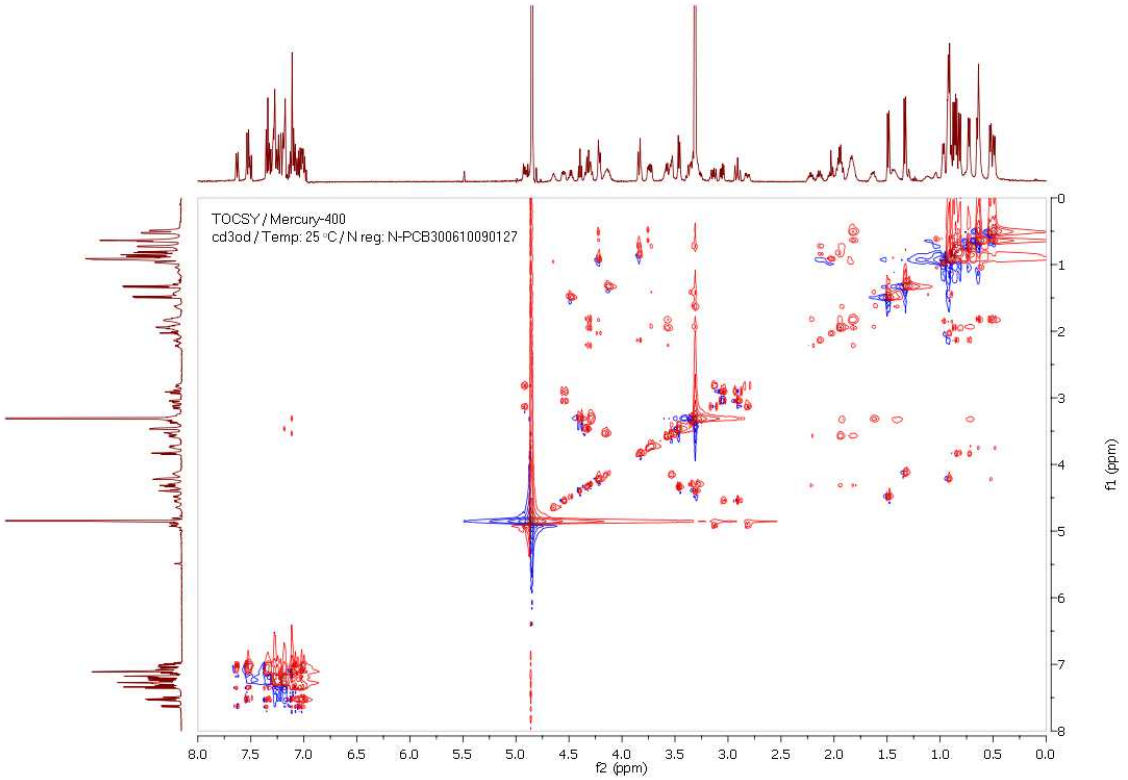


20. Compost ciclat Trp-Ile-Trp-Val-Phe-Pro-Val-Ala (40)






gHSQC / Inova500
cd3od / Temp: 25 °C / N reg: 3829/2010
f2 (ppm)
f1 (ppm)


TOCSY / Mercury-400
cd3od / Temp: 25 °C / N reg: N-PCB300610090127
f2 (ppm)
f1 (ppm)