Total synthesis of (+)-Madangamine D

Roberto Ballette

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UNIVERSITAT DE BARCELONA

FACULTAD DE FARMACIA

DEPARTAMENTO DE FARMACOLOGÍA Y QUÍMICA TERAPEUTICA

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TOTAL SYNTHESIS OF (+)-MADANGAMINE D

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ABBREVIATIONS AND ACRONYMS

$[\alpha]^{22}_{D}$	specific optical rotatory power at λ= 589 nm
^{13}C-NMR	carbon-13 nuclear magnetic resonance
^{1}H-NMR	proton nuclear magnetic resonance
9-BBN	9-borabicyclo[3.3.1]nonane
ACE-Cl	1-Chloroethyl chloroformate
Alloc-Cl	Allyl chloroformate
Anal.	elemental analysis
aq.	aqueous
ax	axial
Boc	*t*-butoxycarbonyl
bp	boiling point
br	broad
c	concentration
calcd.	calculated
CAN	ammonium cerium(IV) nitrate
Cbz	benzyloxycarbonyl
Celite®	filtration agent (90% SiO_2, 4% Al_2O_3, 3.3% Na_2O and K_2O,1.3% Fe_2O_3, 0.5% CaO)
CI	chemical ionization
COSY	H-H correlation spectroscopy
d	chemical shift
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
DCE	1,2 dichloroethane
dd	doublet of doublets
DEAD	diethyl azodicarboxylate
DIBAL-H	diisobutylaluminium hydride
dm	doublet of multiplets
DMAP	4-dimethylaminopyridine
DMF	*N*,*N*-dimethylformamide
DMP	Dess-Martin Periodinane
DNP	2,4-dinitrophenylhydrazine
dt	doublet of triplets
dt	doublet of triplets
EDA	ethylendiamina
EDCl	N-(3-Dimethylaminopropyl)-N′-ethylcarbodiimide hydrochloride
ED_{50}	dose effective in 50% of test subjects
EI	electron impact

epi	epimer
Equiv.	equivalent
eq	equatorial
ESI	electrospry ionization
FGI	functional group interconversion
Funct	functionalization
g	gram(s)
GI_{50}	growth inhibition of 50%
H^+	proton
HOBt	hydroxybenzotriazole
HRMS	high-resolution mass spectrometry
HSQC	H-C heteronuclear single quantum correlation
HWE	Horner-Wadsworth-Emmons reaction
HWE-SGM	Horner-Wadsworth-Emmons Still-Gennari modification reaction
Hz	hertz
i	ipso
i-Pr	isopropyl
IR	infrared
j	coupling constant
KHMDS	potassium bis(trimethylsilyl)amide
LiHMDS	lithium bis(trimethylsilyl)amide
m	multiplet
M	molar
m	meta
m/z	mass to charge ratio
M^+	molecular ion
Mbs	4-methoxyphenyl-sulfonyl
m-CPBA	*meta*-chloroperoxybenzoic acid
Mes	2,4,6-trimethylphenyl (mesityl)
M-SG	metal in silica gel
min.	minute(s)
mmol	millimoles
MOM	methoxymethyl
m.p.	melting point
Ms	methanesulfonyl (mesyl)
MW, mol wt	molecular weight
NaHMDS	sodium bis(trimethylsilyl)amide
Na-SG	sodium in silica gel
NMR	nuclear magnetic resonance
NOESY	nuclear Overhauser effect spectroscopy
Ns	nosyl

Nu	nucleophile
o	ortho
p	para
PCC	pyridinium chlorochromate
PDC	pyridinium dichromate
PG	protecting group
PhtnNH	phthalimide
PMB	*p*-methoxybenzyl
Poc-Cl	propargyl chloroformate
ppm	part(s) per million
PPTS	pyridinium *p*-toluenesulfonate
q	quartet
R	generalized alkyl group or substituent
R_f	retention factor
RCM	ring-closing metathesis
r.t.	room temperature
sat.	saturated
SE	sinthetic equivalent
SES	b-(trimethylsilyl)ethanesulfonyl
t	tertiary
TBAF	tetra-*n*-butylammonium fluoride
TBAI	tetra-*n*-butylammonium iodide
TBDMS	*t*-butyldimethylsilyl
TBDPS	*t*-butyldiphenylsilyl
td	triplet of doublets
Teoc-Cl	2-(trimethylsilyl)-ethyl chloroformate
Teoc-Osu	N-[2-(Trimethylsilyl)ethoxycarbonyloxy]succinimide
TFA	trifluoroacetic acid
Troc-Cl	2,2,2-Trichloroethyl chloroformate

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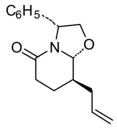
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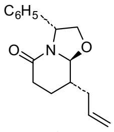
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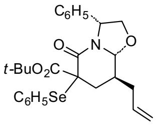
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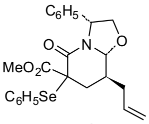
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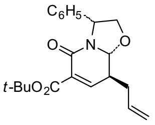
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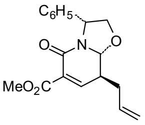
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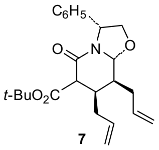
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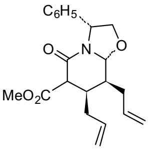
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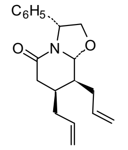
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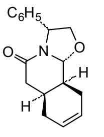
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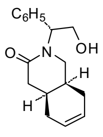
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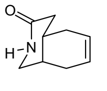
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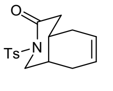
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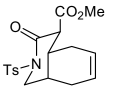
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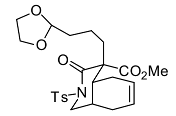
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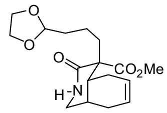
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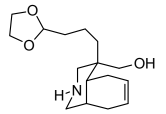
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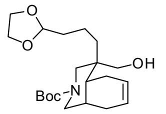
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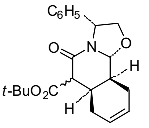
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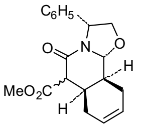
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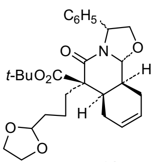
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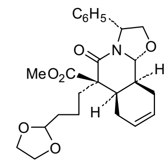
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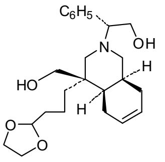
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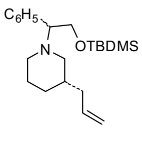
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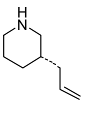
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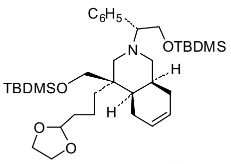
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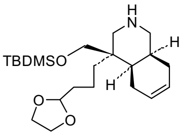
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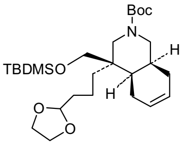
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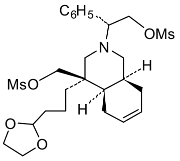
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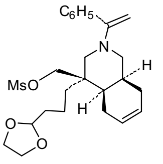
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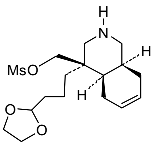
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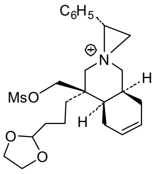
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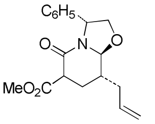
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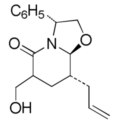
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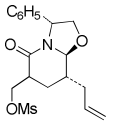
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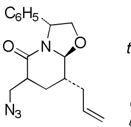
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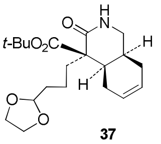
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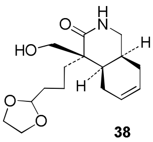
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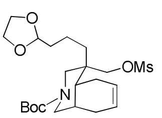
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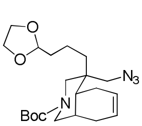
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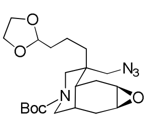
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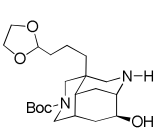
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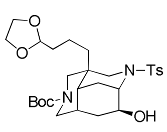
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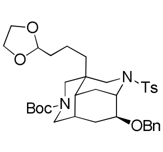
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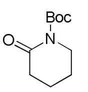
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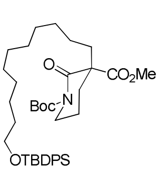
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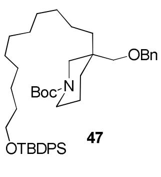
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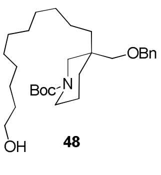
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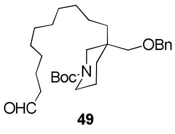
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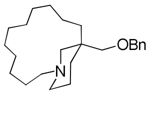
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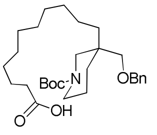
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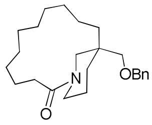
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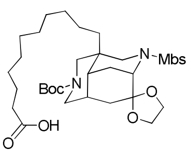
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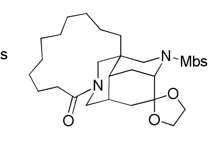
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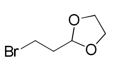
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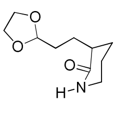
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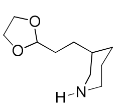
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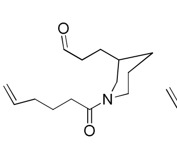
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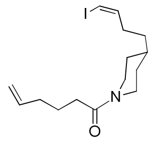
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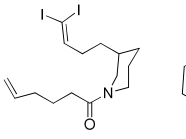
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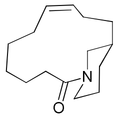
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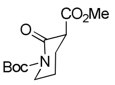
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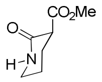
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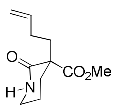
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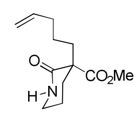
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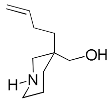
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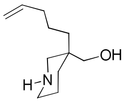
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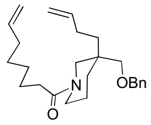
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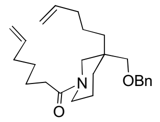
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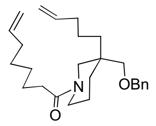
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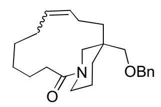
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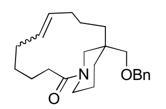
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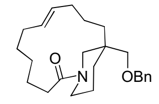
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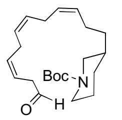
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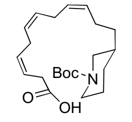
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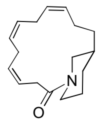
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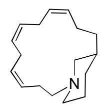
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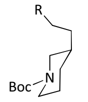
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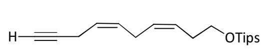
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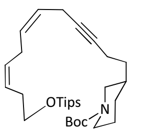
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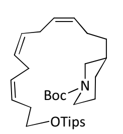
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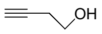
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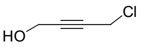
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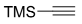
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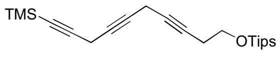
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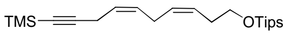
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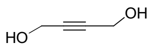
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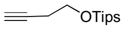
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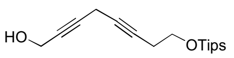
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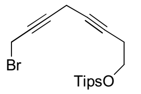
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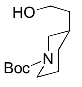
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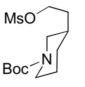
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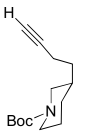
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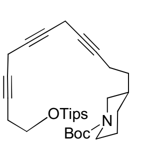
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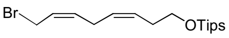
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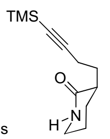
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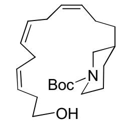
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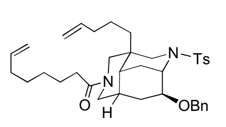
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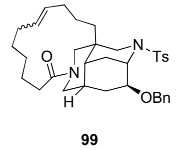
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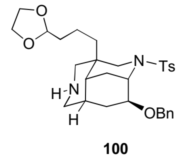
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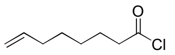
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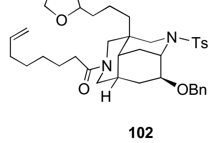
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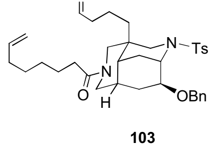
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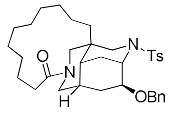

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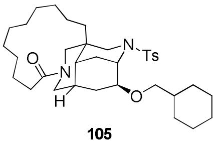

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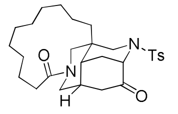

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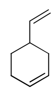

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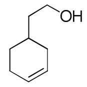

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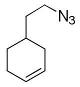

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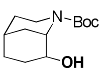

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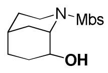

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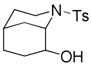

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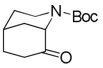

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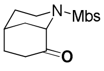

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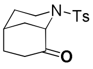

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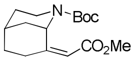

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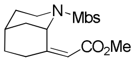

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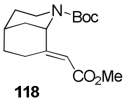

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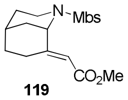

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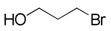

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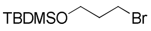

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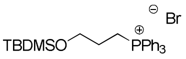
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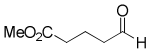

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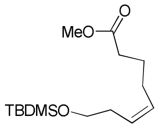
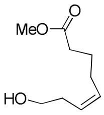
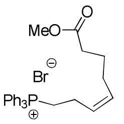

MeO
O
TBDMSO

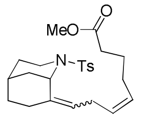
124



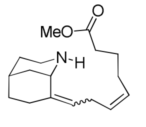
125


MeO
O
Br
Ph_3P

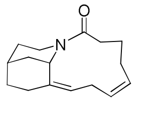
126



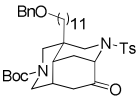
127-128



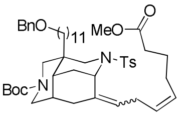
129-130



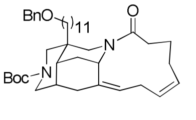
131


BnO
11
N
Ts
Boc
N
O

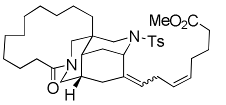
132


BnO
11
MeO
O
N
Ts
Boc
N

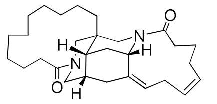
133-134


BnO
11
O
N
Boc
N

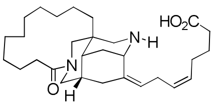
135


MeO_2C
N
Ts
O
N
H

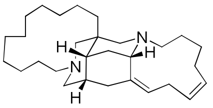
136-137



138



139



Madangamine D

Chapter 1

1.1. INTRODUCTION

Although relatively unexplored until quite late in the last century, marine natural products have become the subject of increasing interest from the biological, ecological, pharmacological, and chemical standpoints.[1,2,3] Many of the marine secondary metabolites possess complex structures not found in terrestrial organisms, and display significant biological activities. The structural diversity of marine natural products makes them attractive candidates as lead compounds for drug discovery.[4,5]

About one third of all marine natural products and more than half of all known alkaloids of marine origin have been isolated from sponges (*Phylum Porifera*), which are among the oldest and most primitive multicellular animals. In particular, sponges in the order Haplosclerida are the source of a great number of structurally diverse but biogenetically related alkaloids, the so-called 3-alkylpiperidine (or 3-alkylpyridine) alkaloids,[6,7] which exhibit a broad spectrum of bioactivity profiles. They include a great variety of skeletal types, such as monomers and oligomers of 3-alkylpyridines, macrocycles containing *bis*-3-alkylpiperidine, *bis*-quinolizidine, *bis*-1-oxaquinolizidine and 3,4'-bipiperidine moieties, and an array of complex polycyclic diamine structures bearing macrocyclic rings (Figure 1.1). These alkaloids usually incorporate a saturated or unsaturated C-8 to C-16 carbon chain attached at the 3-position of the six-membered nitrogen ring, either in the piperidine, tetrahydropyridine, or pyridine oxidation state. 3-Alkylpiperidine alkaloids are also referred to as “manzamine alkaloids”.[8,9] Although this term is usually restricted to β-carboline-containing alkaloids, in some cases its usage encompasses other biogenetically related complex polycyclic diamine alkaloids lacking the β-carboline moiety.[10,11]

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[1] Kornprobst, J-M. *Encyclopedia of Marine Natural Products*; Wiley-VCH: Weinheim, 2010.

[2] Blunt, J. W.; Copp, B. R.; Keyzers, R. A.; Munro, M. H. G.; Prinsep, M. R. *Nat. Prod. Rep.* **2013**, 30, 237–323 and previous reviews in this series.

[3] Morris, J. C. *Nat. Prod. Rep.* **2013**, *30*, 783–805 and previous reviews in this series.

[4] Thakur, N. L.; Thakur, A. N.; Müller, W. E. G. *Nat. Prod. Rad.* **2005**, *46*, 471–477.

[5] Gerwick, W. H.; Moore, B. S. *Chem. Biol.* **2012**, *19*, 85–98.

[6] Andersen, R. J.; Van Soest, R. W. M.; Kong, F. In *Alkaloids: Chemical and Biological Perspectives*; Pelletier, S. W., Ed.; Pergamon Press: New York, 1996; Vol. 10, pp 301–355.

[7] Becking, L. E.; Nakao, Y.; de Voogd, N. J.; van Soest, R. W. M.; Fusetani, N.; Matsunaga, S. In *Porifera Research: Biodiversity, Innovation and Sustainability*; Custódio, M. R.; Lôbo-Hajdu, G.; Hajdu, E.; Muricy, G., Eds.; Museu Nacional: Rio De Janeiro, Brazil, 2007; pp 173–178.

[8] Kaiser, A.; Billot, X.; Gateau-Olesker, A.; Marazano, C.; Das, B. C. *J. Am. Chem. Soc.* **1998**, *120*, 8026–8064.

[9] Duval, R.; Poupon, E. In *Biomimetic Organic Synthesis*; Poupon, E.; Nay, B. Eds.; Wiley-VCH: Weinheim, 2011, Chap 6, pp 181–224.

[10] Peng, J.; Rao, K. V.; Choo, Y.-M.; Hamann, M. T. *Modern Alkaloids: Structure, Isolation, Synthesis and Biology*; Fattorusso, E.; Tagliatela-Scafali, O. Eds.; Wiley-VCH: Weinheim, 2008, Chap 8, pp 189–232.

[11] Hu, J.-F.; Hamann, M. T.; Hill. R.; Kelly, M. In *The Alkaloids: Chemistry and Biology*; Cordell G. A., Ed.; Elsevier: San Diego, CA, 2003; Vol. 60, pp 207–285.

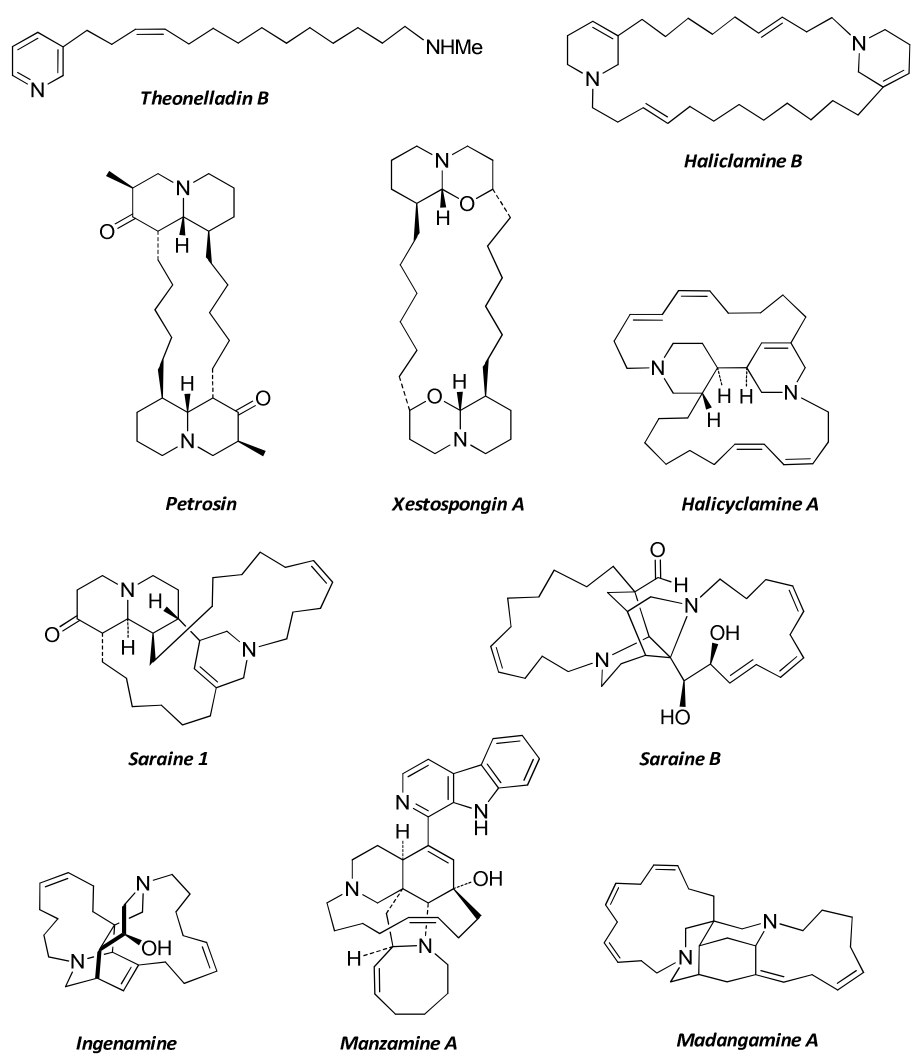
Theonelladin B
NHMe
Haliclamine B
Petrosin
Xestospongin A
Halicyclamine A
Saraine 1
Saraine B
Ingenamine
Manzamine A
Madangamine A

Figure 1.1 Representative 3-alkylpiperidine alkaloids.

The 3-alkylpiperidine alkaloids were first classified according to their structural types by Andersen and coworkers in an excellent review,[6] which also covers biogenetic proposals and phylogenetic distribution. Other general reviews of these marine sponge alkaloids, additionally dealing with synthetic aspects, have been written by Weinreb,[12] Berlinck,[13,14] Rodríguez,[15] and Poupon.[9] Reviews of specific groups of these alkaloids, for instance, simple 3-alkylpyridine (or pyridinium) alkaloids[16] or manzamine-related alkaloids,[10,11,17,18] have also been published.

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[12] Matzanke, N.; Gregg, R. J.; Weinreb, S. M. *Org. Prep. Proced. Int.* **1998**, *30*, 1–51.

[13] Almeida, A. M. P.; Berlinck, R. G. S. *Quim. Nova*, **1997**, *20*, 170–185.

[14] Berlinck, R. G. S. *Top. Heterocycl. Chem.* **2007**, *10*, 211–238.

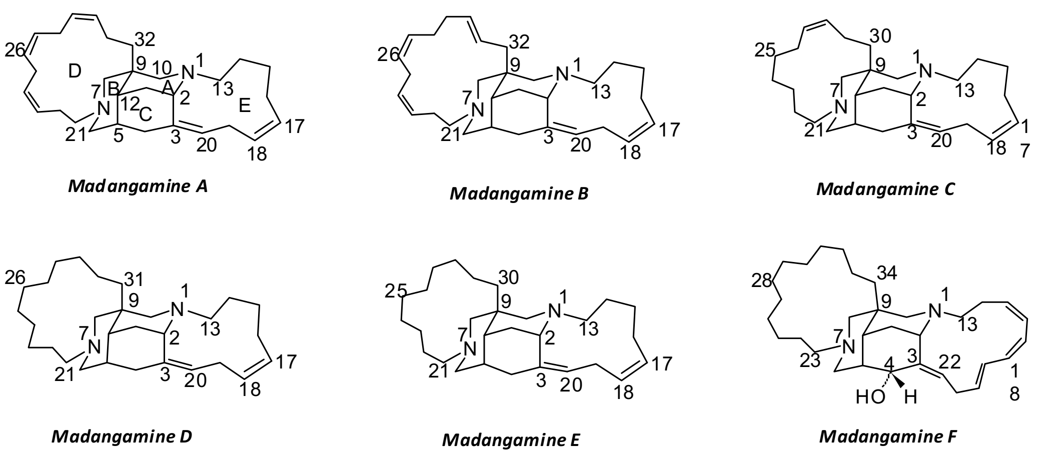
[15] Rodríguez, J. In *Studies in Natural Products Chemistry*; Rahman A.-U., Ed.; Elsevier: Oxford, U.K., 2000; Vol. 24, pp 573–681.

[16] Turk, T.; Sepcic, K.; Mancini, I.; Guella, G. In *Studies in Natural Products Chemistry*; Rahman A.-U., Ed.; Elsevier: Oxford, U.K., 2008; Vol. 35, pp 355–397.

[17] Magnier, E.; Langlois, Y. *Tetrahedron* **1998**, *54*, 6201–6258.

[18] Nishida, A.; Nagata, T.; Nakagawa, M. *Top. Heterocycl. Chem.* **2006**, *5*, 255–280.

The present work is focused on madangamines (Figure 1.2), a small group of complex pentacyclic diamine alkaloids isolated from marine sponges belonging to the order Haplosclerida biogenetically derived from 3-alkylpiperidine precursors. Structurally, madangamines are characterized by a diazatricyclic core (ABC rings), unprecedented among natural products, and two linear carbon bridges connecting N-7 to C-9 (D ring) and N-1 to C-3 (E ring). The peripheral macrocyclic ring D varies in each madangamine both in size (13 to 15-membered) and in the position and degree of unsaturation, whereas E ring is identical in madangamines A-E (two unsaturations; 11-membered) but different in madangamine F (four unsaturations; 13-membered). In addition madangamine F incorporates an alcohol function at C-4, being the first alkaloid of this group to bear a hydroxy substituent.



Madangamine A

Madangamine B

Madangamine C

Madangamine D

Madangamine E

Madangamine F

Figure 1.2 Alkaloids of the madangamine group.

1.2. ISOLATION

As part of a program for the search of bioactive metabolites in extracts of tropical marine sponges, the Andersen group found that the crude extracts of *Xestospongia ingens* Van Soest showed *in vitro* cytotoxicity.[19] This sponge (order Haplosclerida, family Petrosiidae) was collected by hand using scuba on reefs at 15-20 m depth off Madang, in Papua New Guinea. A bioassay-guided fractionation of the extracts resulted in the isolation of madangamines A-E, a new class of pentacyclic alkaloids with an unprecedented skeletal type. The first isolation of an alkaloid of this group, madangamine A, was reported in 1994,[20] and four years later the same team reported[21] the isolation of madangamines B-E. Freshly collected sponge samples were deep frozen on site and transported over dry ice to the laboratory in Vancouver for extraction. Once thawed, the sponges were repeatedly extracted with methanol. The extracts were concentrated to an aqueous suspension, which was diluted with distilled water and then partitioned sequentially against hexanes and EtOAc. The alkaloids were isolated as colorless glass by repeated fractionation of the hexane-soluble fraction using silica gel flash chromatography and then normal-phase HPLC (hexanes, EtOAc, *i*-Pr_2NH). From 200 g wet weight of sponge, the procedure afforded 50-60 mg of madangamine A, 5.5 mg of madangamine B, 11 mg of madangamine C, and 5 mg of an inseparable mixture of madangamines D and E. Other biogenetically related alkaloids isolated from *Xestospongia ingens* were ingenamine,[19] ingamines A and B,[22] ingenamines B-F,[23] xestocyclamines A[24] and B,[23,24] and keramaphidin B[23] (Figure 1.3).

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[19] Kong, F.; Andersen, R. J.; Allen, T. M. *Tetrahedron Lett.* **1994**, *35*, 1643–1646.

[20] Kong, F.; Andersen, R. J.; Allen, T. M. *J. Am. Chem. Soc.* **1994**, *116*, 6007–6008.

[21] Kong, F.; Graziani, E. I.; Andersen, R. *J. Nat. Prod*. **1998**, *61*, 267–271.

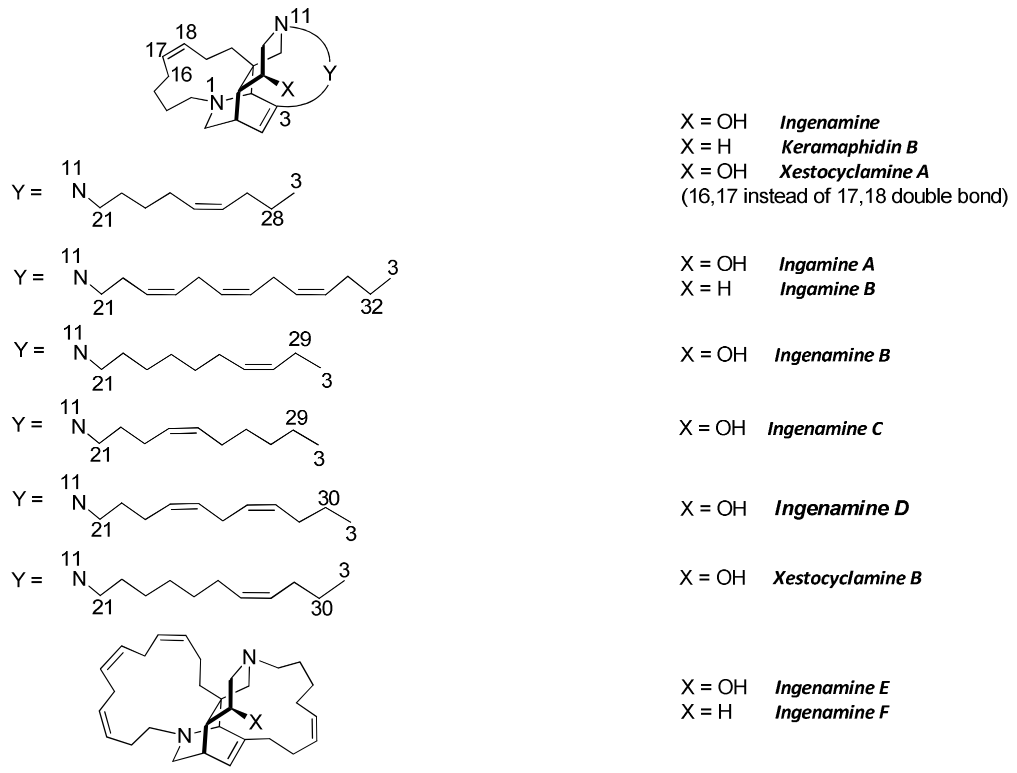
18
17
16
1
N
N
11
X
Y
3
Y =
11
N
21
28
3
X = OH Ingenamine
X = H Keramaphidin B
X = OH Xestocyclamine A
(16,17 instead of 17,18 double bond)
Y =
11
N
21
32
3
X = OH Ingamine A
X = H Ingamine B
Y =
11
N
21
29
3
X = OH Ingenamine B
Y =
11
N
21
29
3
X = OH Ingenamine C
Y =
11
N
21
30
3
X = OH Ingenamine D
Y =
11
N
21
30
3
X = OH Xestocyclamine B
N
N
X
X = OH Ingenamine E
X = H Ingenamine F

Figure 1.3 Other alkaloids isolated from *Xestospongia ingens*.

Pure madangamines A-C and F were isolated as optically active. Although the absolute configuration of the alkaloids has not been unambiguously established, it may be tentatively deduced by correlation with the putative precursor ingenamines.

An intriguing property of madangamines A-E is their low polarity. Thus, during their isolation madangamines dissolve in the hexane layer, in contrast with ingenamine F, an alkaloid with the same molecular formula, which remains in the aqueous layer. This dramatic difference in polarity can be explained taking into account that the tricyclic ABC core of madangamines adopts a rigid chair-chair-chair conformation, in which the nitrogen atom at the 7-position cannot undergo inversion since the cavity of the central core is too small to accommodate the C-21 alkyl substituent. For this reason, the N-7 lone pair is hidden within the tricyclic core, where it is inaccessible for protonation and hydrogen bonding.

---

[22] Kong, F.; Andersen, R. J.; Allen, T. M. *Tetrahedron* **1994**, *50*, 6137–6144.

[23] Kong, F.; Andersen, R. J. *Tetrahedron* **1995**, *51*, 2895–2906.

[24] Rodríguez, J.; Crews, P. *Tetrahedron Lett.* **1994**, *35*, 4719–4722.

In 2007, Berlinck *et al*. reported[25] the isolation of a new alkaloid of this group, madangamine F, from the marine sponge *Pachychalina alcaloidifera* (order Haploscherida, family Niphatidae), which was collected at 10-15 m depth in Ilha do Pai (Father's Island), Nisterói, Rio de Janeiro. Once retrieved, the sponge was immediately immersed in EtOH and shipped to the laboratory at the Universidade de São Paulo, where it was extracted with MeOH. The crude extracts contained a very complex mixture of alkaloids, which were difficult to separate. Starting from 2 Kg of sponge, only a minute amount (4 mg) of madangamine F was isolated. Besides madangamine F, other 3-alkylpiperidine alkaloids isolated from this sponge were haliclonacyclamine F, arenosclerins D and E, ingenamine G, and several cyclostellettamines[26] (Figure 1.4).

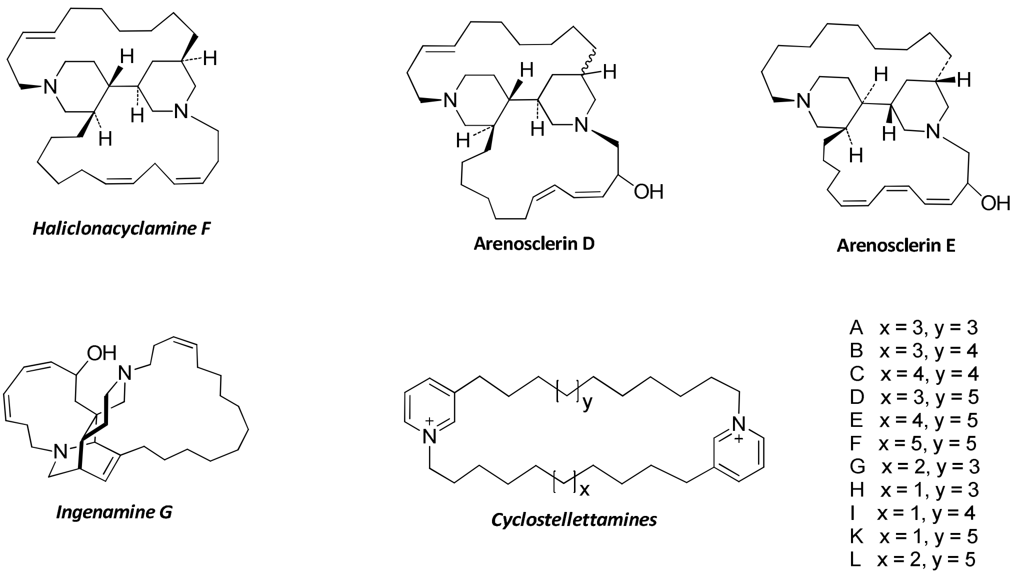

Figure 1.4 Other alkaloids isolated from *Pachychalina alcaloidifera.*

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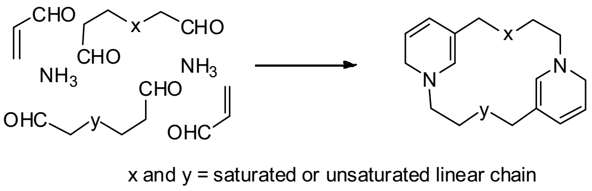
[25] De Oliveira, J. H. H. L.; Nascimento, A. M.; Kossuga, M. H.; Cavalcanti, B. C.; Pessoa, C. O.; Moraes, M. O.; Macedo, M. L.; Ferreira, A. G.; Hajdu, E.; Pinheiro, U. S.; Berlinck, R. G. S. *J. Nat. Prod*. **2007**, *70*, 538–543.

[26] De Oliveira, J. H. H. L.; Grube, A.; Köck, M.; Berlinck, R. G. S.; Macedo, M. L.; Ferreira, A. G.; Hajdu, E. *J. Nat. Prod.*, **2004**, *67*, 1685–1689.

1.3. BIOGENESIS

The imaginative proposal of Baldwin and Whitehead to explain the biogenesis of manzamines,[27,28,29,30] formulated in 1992, also provided the groundwork for a mechanistic rationale for the biosynthesis of 3-alkylpiperidine alkaloids. Despite their structural diversity, all 3-alkylpiperidine alkaloids can biogenetically derive from similar simple building blocks: ammonia, a three carbon acrolein equivalent, and saturated or unsaturated linear long-chain dialdehydes. These units are first assembled into partially reduced 3-alkylpyridine monomers, which can then either polymerize to give oligomers or dimerize to give *bis*-3-alkylpiperidine macrocycles (Scheme 1.1). Subsequent transformations, including intramolecular [4+2] cycloaddition reactions, would lead to the variety of polycyclic skeletons found in these alkaloids.[6,9,12,15,31,32,33]



Scheme 1.1 Proposed biogenesis of dimeric *bis*-3-alkylpiperidine macrocyclic alkaloids.

A plausible biosynthetic pathway to madangamines from partially reduced *bis*-3-alkylpyridine macrocycles is outlined in Scheme 1.2.[6,20] A distinguishing feature of this pathway compared to those leading to other 3-alkylpiperidine polycyclic alkaloids is that it involves a skeletal rearrangement.

---

[27] Baldwin, J. E.; Whitehead, R. C. *Tetrahedron Lett.* **1992**, 2059–2062.

[28] Baldwin, J. E.; Bischoff, L.; Claridge, T. D. W.; Heupel, F. A.; Spring, D. R.; Whitehead, R. C. *Tetrahedron* **1997**, *53*, 2271–2290.

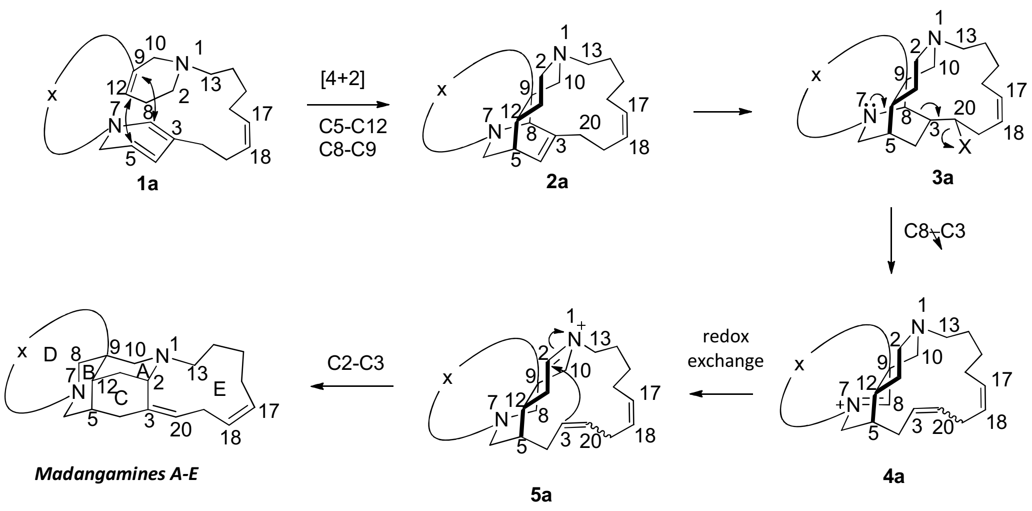
[29] Baldwin, J. E.; Claridge, T. D. W.; Culshaw, A. J.; Heupel, F. A.; Lee, V.; Spring, D. R.; Whitehead, R. C.; Boughtflower, R. J.; Mutton, I. M.; Upton, R. J. *Angew. Chem. Int. Ed.* **1998**, *37*, 2661–2663.

[30] Baldwin, J. E.; Claridge, T. D. W.; Culshaw, A. J.; Heupel, F. A.; Lee, V.; Spring, D. R.; Whitehead, R. C. *Chem. Eur. J.* **1999**, *5*, 3154–3161.

[31] Crews, P.; Cheng, X.-C.; Adamczeski, M.; Rodríguez, J.; Jaspars, M.; Schmitz, F. J.; Traeger, S. C.; Pordesimo, E. O. *Tetrahedron* **1994**, *50*, 13567–13574.

[32] Tsuda, M.; Kobayashi, J. *Heterocycles* **1997**, *46*, 765–793.Whitehead, R. *Annu. Rep. Prog. Chem., Sect. B* **1999**, *95*, 183–205.

[33] Whitehead, R. *Annu. Rep. Prog. Chem., Sect. B* **1999**, *95*, 183–205.

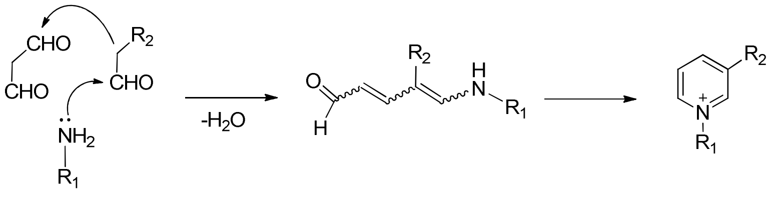


Scheme 1.2 Proposed biogenesis for the madangamine alkaloids.

(For clarity, the madangamine numbering is used throughout the scheme)

Thus, the partially reduced *bis*-3-alkylpyridine macrocycle **1a** would undergo an intramolecular *endo* Diels Alder cycloaddition reaction to generate an ingenamine-type pentacyclic intermediate **2a**. After activation of the carbon 20 and reduction of the tetrahydropyridine double bond, fragmentation of intermediate **3a**, followed by a redox exchange between the two nitrogen atoms of the resulting tetracyclic iminium ion **4a** would give the regioisomeric iminium ion **5a**. A final transannular cyclization would lead to the rearranged skeleton of madangamines.[6,20]

An alternative biosynthetic proposal, suggesting the participation of malonaldehyde, instead of acrolein, as the three carbon unit to generate 3-alkylpyridinium salts via 5-amino-2,4-pentadienal derivatives, has been proposed by Marazano (Scheme 1.3).[8,34]



Scheme 1.3 Alternative biosynthetic pathway to sponge pyridines and pyridinium salts.

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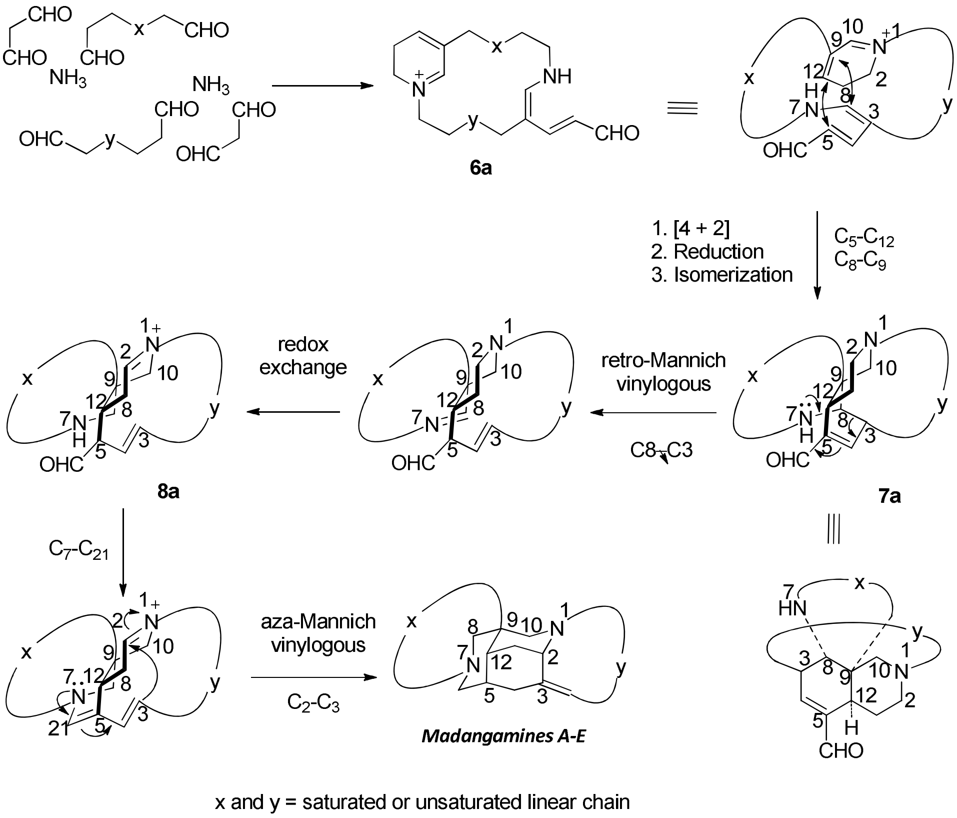
[34] Jakubowicz, K.; Abdeljelil, K. B.; Herdemann, M.; Martin, M.-T.; Gateau-Olesker, A.; Al Mourabit, A.; Marazano, C.; Das, B. C. *J. Org. Chem.* **1999**, *64*, 7381–7387.

In a similar manner, condensation of malonaldehyde, ammonia, and appropriate dialdehydes could produce macrocyclic aminopentadienal derivatives, which can be envisaged as alternative intermediates in the biosynthesis of complex polycyclic 3-alkylpiperidine alkaloids, including the alkaloids of the madangamine group. For instance, the open-chain aminopentadienal moiety in dihydropyridinium derivatives **6a** could participate as the diene in intramolecular Diels-Alder reactions, leading to tetracyclic ircinal-type derivatives **7a**, from which madangamine alkaloids would eventually be generated as outlined in Scheme 1.5, via a vinylogous retro-Mannich fragmentation, an intramolecular redox transfer, cyclization of the resulting amino aldehyde **8a**, and finally, a vinylogous aza-Mannich reaction.[9,35]


CHO
CHO
CHO
NH3
CHO
x
CHO
NH3
CHO
CHO
OHC
y
OHC
6a
NH
CHO
1. [4 + 2]
2. Reduction
3. Isomerization
C5-C12
C8-C9
7a
retro-Mannich vinylogous
C8-C3
redox exchange
8a
C7-C21
aza-Mannich vinylogous
C2-C3
Madangamines A-E
x and y = saturated or unsaturated linear chain

Scheme 1.4 Alternative biosynthetic scheme towards madangamine alkaloids.

(For clarity, the madangamine numbering is used throughout the scheme)

The fact that ingenamine-type intermediates are biosynthetic precursors of madangamines (see Scheme 1.2) allows the absolute configuration of the latter to be tentatively assigned. Thus, madangamine A would biogenetically derive from ingenamine F, an alkaloid with the same carbon skeleton and sign of specific rotation as ingenamine E, whose absolute configuration was determined by Mosher ester methodology as 2*R*, 5*S*, 7*S*, 8*R*, 9*S* (ingenamine numbering).[23] Taking into account that madangamine carbons 5, 9, and 12 correspond to

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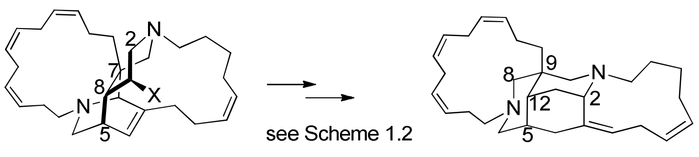
[35] Tong, H. M.; Martin, M.-T.; Chiaroni, A.; Benechie, M.; Marazano, C. *Org. Lett.* **2005**, *7*, 2437–2440.

ingenamine carbons 5, 7, and 9, respectively, and that the configuration of C-2 in madangamines is determined by its bridgehead character, the absolute configuration of madangamines can be assumed to be 2*S*, 5*S*, 9*R*, 12*R* (Scheme 1.5).



X = OH ***Ingenamine E***
X = H ***Ingenamine F***
2*R*, 5*S*, 7*S*, 8*R*

Madangamine A
2*S*, 5*S*, 9*R*, 12*R*

Scheme 1.5 Tentative absolute configuration of madangamine A.

1.4. BIOLOGICAL ACTIVITY

Marine sponges are recognized to be one of the richest sources of pharmacologically active chemicals among marine organisms.[36] In particular, the alkaloids of the 3-alkylpiperidine group, isolated from Haplosclerida sponges, have been found to exhibit a wide range of biological activities, suggesting potential for drug development.

In the case of madangamine alkaloids, extensive pharmacological research has been hampered by the low quantities of samples available from natural sources. Madangamine A has shown significant *in vitro* cytotoxic activity against murine leukemia P388 (ED_{50} 0.93 µg/mL) and human lung A549 (ED_{50} 14 µg/mL), brain U373 (ED_{50} 5.1 µg/mL), and breast MCF-7 (ED_{50} 5.7 µg/mL) cancer cell lines.[20] In turn, madangamine F displays weak cytotoxicity against human CNS SF-295 (ED_{50} 19.8 µg/mL), human breast MDA-MB-435 (ED_{50} 16.2 µg/mL), colon HCT-8 (ED_{50} >25 µg/mL), and leukemia HL-60 (ED_{50} 16.7 µg/mL) cancer cell lines using the MTT cell proliferation assay. No bioactivity data have been reported for madangamines B-E, so these alkaloids are attractive challenges for synthetic organic chemists, not only due to their unprecedented molecular architecture but also as targets for pharmaceutical research.

1.5. SYNTHESIS

The synthesis of alkaloids of the madangamine group has been little explored. The most logical approach to the pentacyclic skeleton of these alkaloids consists in the initial construction of the bridged diazatricyclic ABC core common to all madangamines, with the appropriate substitution and functionality to allow the subsequent building of the peripheral macrocyclic D and E rings.

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[36] Laport, M. S.; Santos, O. C. S.; Muricy, G. *Curr. Pharm. Biotechnol.* **2009**, *10*, 86–105.

Previous to our work in this field, only four synthetic approaches to the diazatricyclic madangamine ABC core[35,37,38,39] and the construction of the 11-membered E macrocycle common to madangamines A-E from a model azabicyclic derivative[40] had been reported. All these studies were performed in the racemic series.

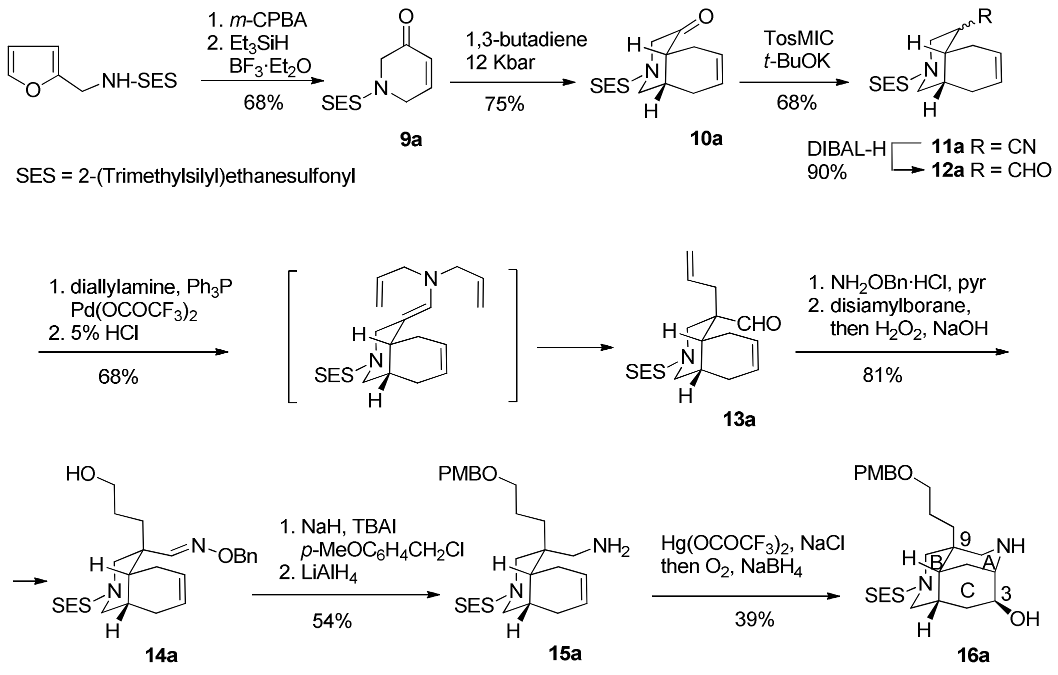
1.5.1. Construction of the Diazatricyclic ABC Core

1.5.1.1 Weinreb's Approach

In 1997 Weinreb reported[37] the first synthesis of the tricyclic core of madangamines. The synthesis started from the SES-protected furfurylamine, which was converted to dihydropyridone **9a** (ring B) by an oxidation-rearrangement sequence (Scheme 1.6). A Diels-Alder reaction with 1,3-butadiene under high pressure conditions produced *cis*-octahydroisoquinolone **10a** (rings AB), from which the quaternary C-9 stereocenter (madangamine numbering) was stereoselectively installed. After a one-carbon homologation with TosMIC and reduction of the resulting nitrile **11a** to aldehyde **12a** (1:1 mixture of epimers), a reaction with diallylamine and $Pd(OCOCF_3)_2$-PPh_3, followed by acidic hydrolysis furnished the α-allyl substituted aldehyde **13a**. This transformation involves the initial generation of an *N*-allyl enamine, which undergoes an *in situ* stereospecific 3-aza-Cope rearrangement from the less congested convex face, and a final hydrolytic step from the resulting α-allyl imine. The formyl group in **13a** was used to construct the piperidine A ring. Thus, once **13a** was converted into an *O*-benzyl oxime, a hydroboration-oxidation reaction led to alcohol **14a**. Protection of the hydroxy group with *p*-methoxybenzyl chloride also produced the elimination of the *O*-benzyl oxime moiety to give a nitrile, which was then reduced to the primary amine **15a**. Finally, closure of the piperidine A ring was accomplished by an intramolecular aminomercuriation with mercuric trifluoroacetate, followed by an oxidative demercuriation process with oxygen and $NaBH_4$. The resulting diazatricyclic derivative **16a** possesses suitable functionality both at C-3 and the C-9 chain to allow the building of the macrocyclic D and E rings of madangamines.

---

[37] Matzanke, N.; Gregg, R. J.; Weinreb R. J.; Parvez, M. *J. Org. Chem.* **1997**, *62*, 1920–1921.
[38] Yamazaki, N.; Kusanagi, T.; Kibayashi, C. *Tetrahedron Lett.* **2004**, *45*, 6509–6512.
[39] Quirante, J.; Paloma, L.; Diaba, F.; Vila, X.; Bonjoch, J. *J. Org. Chem.* **2008**, *73*, 768–771.
[40] Yoshimura, Y.; Inoue, J.; Yamazaki, N.; Aoyagi, S.; Kibayashi, C. *Tetrahedron Lett.* **2006**, *47*, 3489–3492.



Scheme 1.6 Weinreb's synthetic approach to the ABC diazatricyclic core.

1.5.1.2. Kibayashi's Approach

The second approach to the diazatricyclic ABC core of madangamines was reported by Kibayashi in 2004.[40,41] The synthesis starts from cyclohexenone **17a** (ring B) and involves the initial construction of the piperidine A ring to give a functionalized 2-azabicyclo[3.3.1]nonane derivative (rings AB) and the closure of the piperidine C ring in the last synthetic step (Scheme 1.7).

A Michael addition of ethyl cyanoacetate, followed by protection of the cyclohexanone carbonyl group in **18a** as a cyclic acetal led to cyano ester **19a**. Alkylation with formaldehyde, with subsequent protection of the hydroxy group as a MOM-ether provided the substituted cyclohexane derivative **20a** as a mixture of diastereoisomers. Successive reduction of the ester function and, after protection of the resulting alcohol as a MOM-ether, of the cyano group gave the primary amine **21a** as a single diastereoisomer. Reductive amination of **21a** with salicylaldehyde, followed by treatment of the resulting aminophenol **22a** with *p*-toluenesulfonic acid in acetone-H_2O brought about the deprotection of the ketone function and the closure of the piperidine A ring by intramolecular *N*,*O*-acetalization to give the tetracyclic derivative **23a**. Once the 2-azabicyclo[3.3.1]nonane system was assembled, the auxiliary 2-hydroxybenzyl moiety was removed by a Lewis acid-mediated reductive cleavage of the C-O bond, which took place with simultaneous selective deprotection of the axial MOM-ether substituent, followed by *N*-debenzylation by hydrogenolysis.

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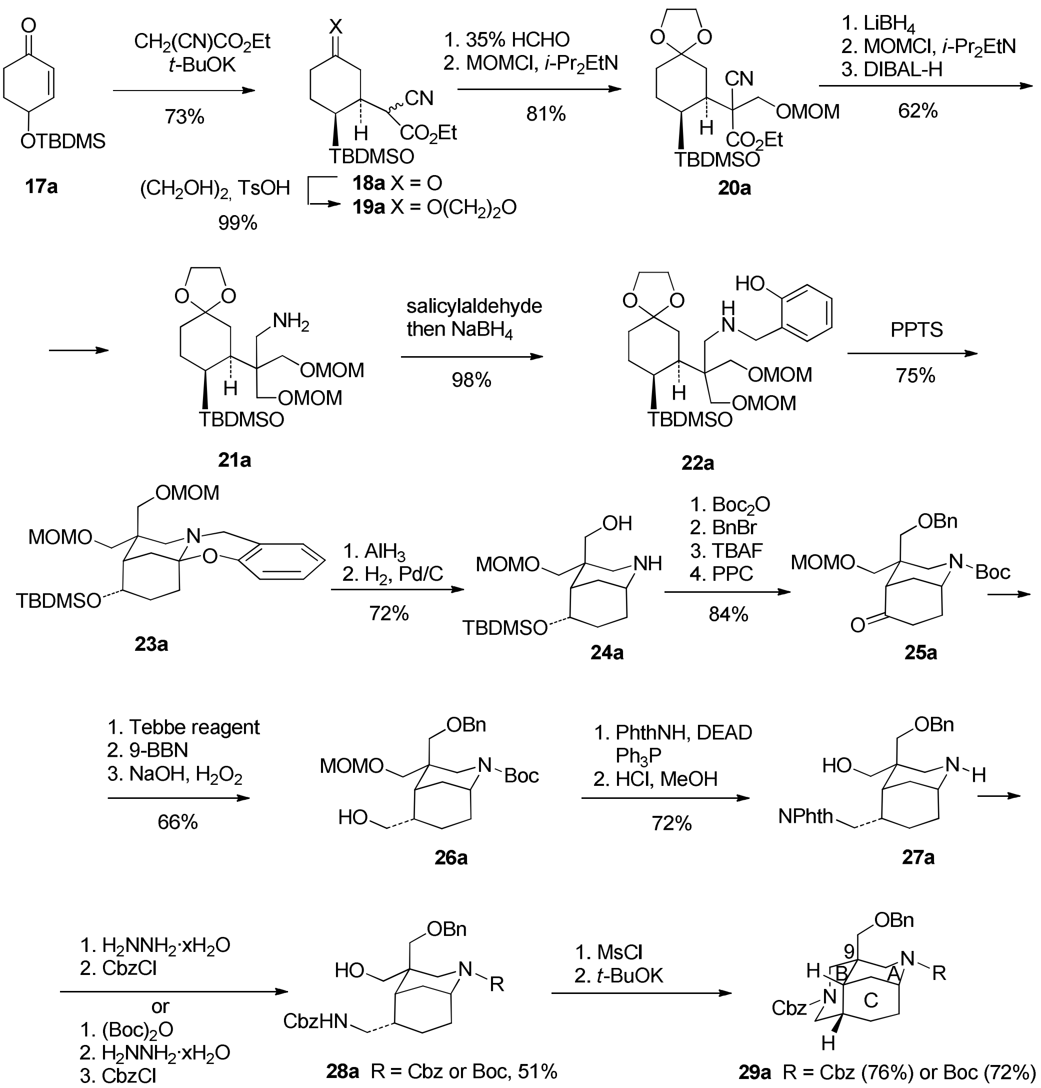
[41] Yoshimura, Y., Kusanagi, T.; Kibayashi, C.; Yamazaki, N.; Aoyagi, S. *Heterocycles* **2008**, *75*, 1329–1354.

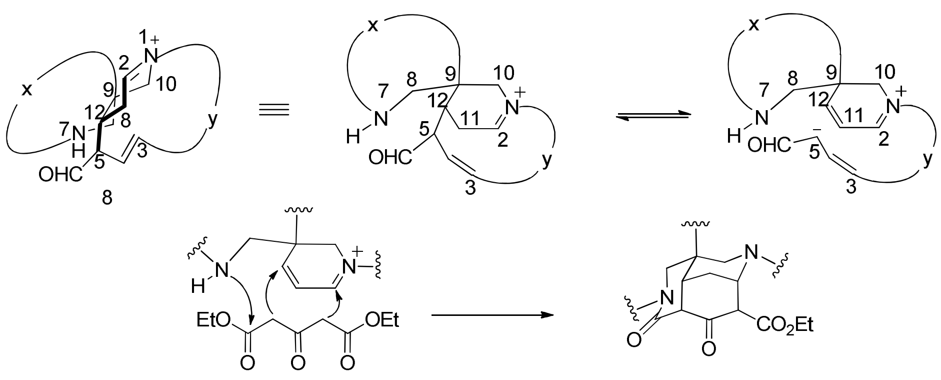
After a sequential protection of the amino and hydroxy groups, a TBAF-induced deprotection of the silylated alcohol and oxidation of the resulting secondary hydroxy group led to ketone **25a**. Tebbe methylenation of **25a**, followed by a hydroboration-oxidation reaction from the most accessible face of the exocyclic methylene substituent gave alcohol **26a** as a single diastereoisomer, from which the nitrogen atom required to construct the piperidine B ring was introduced by a Mitsunobu reaction using phthalimide. Then, a sequence of *N* and *O* protection-deprotection steps led to the functionalized bicyclic derivatives **27a** and **28a**. Finally, mesylation of the hydroxy group of **28a**, followed by exposure of the resulting mesylate to *t*-BuOK completed the synthesis of the model diazatricyclic derivatives **29a**, which bear the quaternary C-9 center present in madangamines and a functionalized substituent at this position, but lack the functionalization required at C-3 (madangamine numbering) to assemble the macrocyclic E ring.


17a
OTBDMS
CH2(CN)CO2Et
t-BuOK
73%
(CH2OH)2, TsOH
99%
18a X = O
19a X = O(CH2)2O
CN
CO2Et
TBDMSO
1. 35% HCHO
2. MOMCl, i-Pr2EtN
81%
20a
OMOM
1. LiBH4
2. MOMCl, i-Pr2EtN
3. DIBAL-H
62%
21a
NH2
salicylaldehyde
then NaBH4
98%
22a
PPTS
75%
23a
1. AlH3
2. H2, Pd/C
72%
24a
1. Boc2O
2. BnBr
3. TBAF
4. PPC
84%
25a
OBn
Boc
1. Tebbe reagent
2. 9-BBN
3. NaOH, H2O2
66%
26a
1. PhthNH, DEAD
Ph3P
2. HCl, MeOH
72%
27a
NPhth
1. H2NNH2·xH2O
2. CbzCl
or
1. (Boc)2O
2. H2NNH2·xH2O
3. CbzCl
28a R = Cbz or Boc, 51%
CbzHN
1. MsCl
2. t-BuOK
9
A
B
C
Cbz
29a R = Cbz (76%) or Boc (72%)

Scheme 1.7 Kibayashi's synthetic approach to the ABC diazatricyclic system.

1.5.1.3. Biomimetic Marazano Approach

A totally different approach to the tricyclic core of madangamines was reported[35] in 2005 by Marazano, based upon his biogenetic proposal[8,34] linking these alkaloids to ircinals (see Scheme 1.4). On the assumption that the hypothetical biogenetic intermediate **8a** is in equilibrium with a dihydropyridinium species, to access the madangamine core skeleton the authors envisaged a biomimetic strategy involving the reaction of an appropriate dihydropyridinium salt with a bis-nuclephile such as an acetonedicarboxylate, as outlined in Scheme 1.8.



Scheme 1.8 Biomimetic strategy.

Dihydropyridinium salt **31a** was initially selected to check the viability of the proposal. This salt was prepared from tetrahydropyridine **30a**, which was accessible in six steps from methyl nicotinate, by treatment of the corresponding *N*-oxide derivative (mixture of two diastereisomers) under Polonovski-Potier reaction conditions (Scheme 1.9)[42]. Reaction of the crude salt **31a** with the sodium salt of diethyl 1,3-acetonedicarboxylate gave a mixture of two diastereoisomeric adducts **32a** (two isolable enol forms) and **33a** in 87% overall yield, the undesired stereoisomers **32a** (axial aminomethyl chain) predominating (69:31 ratio).

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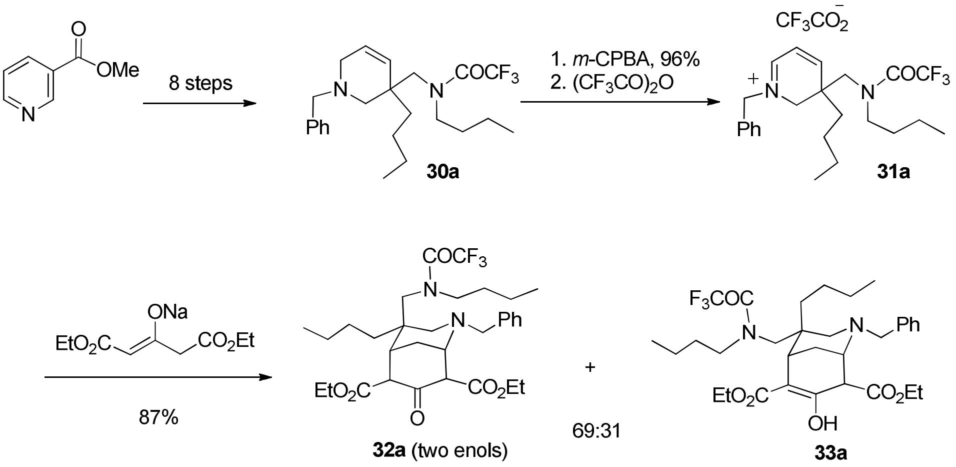
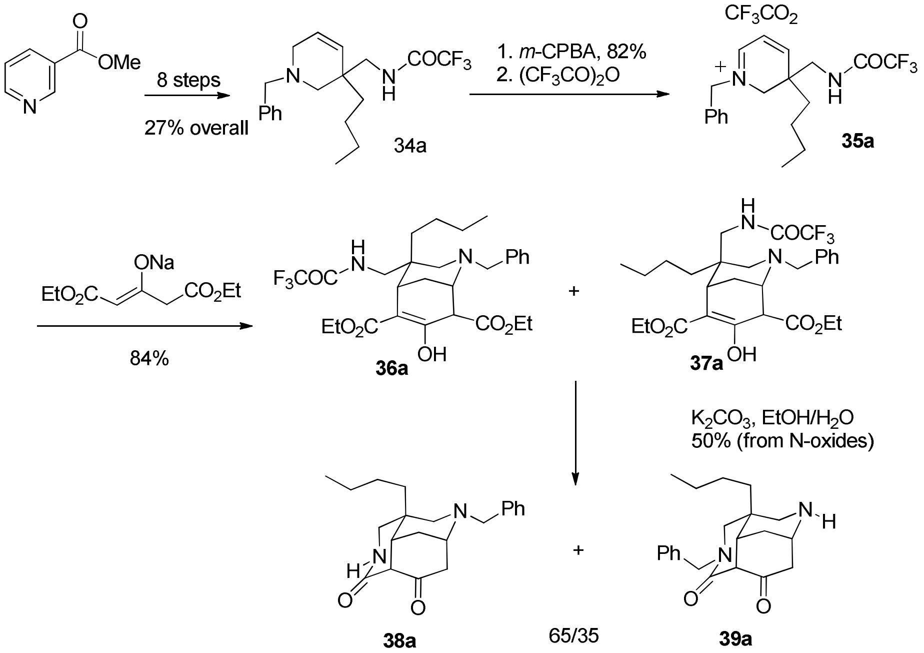
[42] Grierson, D. S. *Org. React.* **1990**, *39*, 85–295.


OMe
8 steps
COCF3
1. m-CPBA, 96%
2. (CF3CO)2O
CF3CO2−
Ph
30a
31a
ONa
EtO2C
CO2Et
87%
32a (two enols)
69:31
33a
F3COC
OH

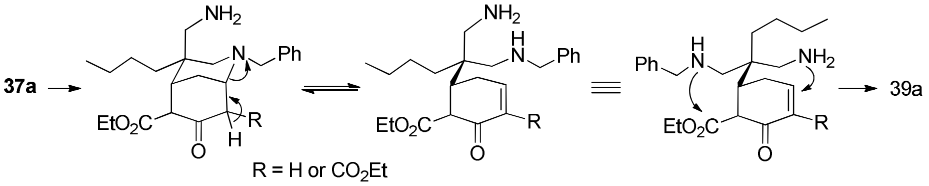
Scheme 1.9 Marazano's biomimetic approach.

This stereochemical problem was overcome using dihydropyridinium salt **35a**, which lacks the *N*-butyl substituent (Scheme 1.10). This salt was generated, as in the above series, from the corresponding tetrahydropyridine derivative **34a**, which, in turn, was prepared in eight steps from methyl nicotinate. Condensation of the crude salt **35a** with the sodium salt of diethyl acetonedicarboxylate resulted in the formation of a mixture of adducts **36a** and **37a**, which were difficult to separate. However, this crude mixture could directly be cyclized to the madangamine tricyclic core models **38a** and **39a** by treatment with K_2CO_3 in EtOH-H_2O at reflux. The formation of **38a** from **36a** involves the hydrolysis of the trifluoroacetamide group followed by lactamization, with concomitant hydrolysis-decarboxylation of the remaining ester group.


OMe
8 steps
27% overall
COCF3
1. m-CPBA, 82%
2. (CF3CO)2O
CF3CO2−
34a
35a
ONa
EtO2C
CO2Et
84%
36a
37a
K2CO3, EtOH/H2O
50% (from N-oxides)
38a
65/35
39a

Scheme 1.10 Marazano's biomimetic approach to the ABC diazatricyclic core.

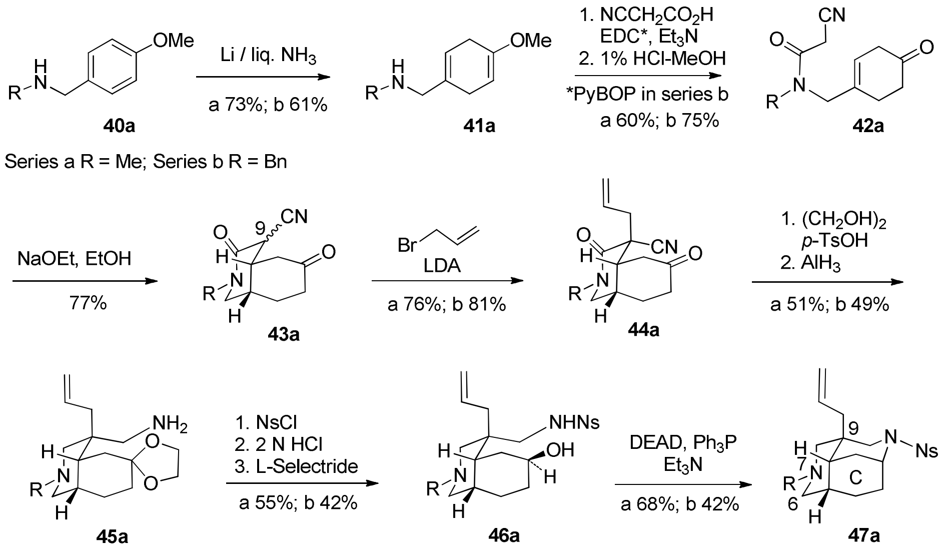
The isolation of **39a** indicates that the “wrong” stereosiomer **37a**, bearing an axial amino chain, undergoes a rearrangement via a retro-Michael process, followed by a Michael addition and lactamization, as outlined in Scheme 1.11.



Scheme 1.11 Proposed mechanism for the formation of tricyclic derivative **39a**.

1.5.1.4.Bonjoch’s Approach

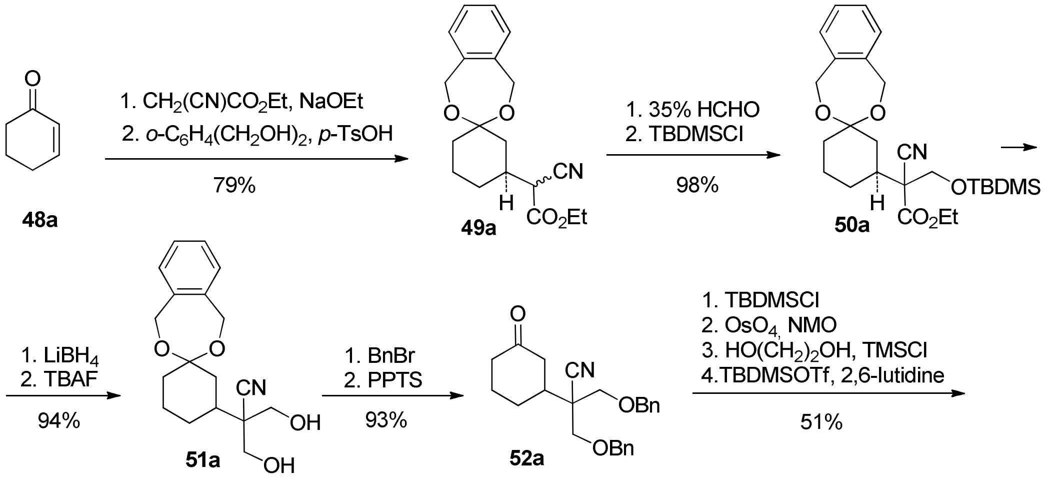
A new synthetic entry to the diazatricyclic core of madangamines was reported by Bonjoch in 2008.[41] The synthesis starts from 4-(aminomethyl)anisole derivatives **40a** (R = Me or Bn), which incorporate the carbocyclic C ring and the C_6–N_7 atoms of the target alkaloids, and involves the successive construction of the piperidine B and A rings (Scheme 1.12). A Birch reduction of **40a**, followed by acylation of the amino group in the resulting dihydro derivatives **41a** with cyanoacetic acid and subsequent hydrolysis of the enol ether moiety gave cyclohexenones **42a**. Treatment of **42a** with a substoichiometric amount of NaOEt caused the isomerization of the carbon-carbon double bond to give an α,β-enone and the closure of the piperidine B ring by an intramolecular Michael addition to give the *cis*-fused perhydroisoquinoline derivatives **43a** as mixtures of C-9 epimers (madangamine numbering). A stereoselective allylation from the most accessible face of **43a** installed the quaternary C-9 stereocenter in **44a**. The cyano group not only provides activation towards the Michael addition and allylation reactions, but is also the precursor of the aminomethyl chain required for the closure of the piperidine A ring. This was accomplished, after the activation of the primary amino group of **45a** as a nosylamide, hydrolysis of the acetal, and reduction of the resulting ketone, by an intramolecular Mitsunobu-type *N*-alkylation from alcohols **46a**. The resulting diazatricyclic derivatives **47a** incorporate a functionalized chain at the quaternary C-9 center but lack functionalization at the carbocyclic ring.

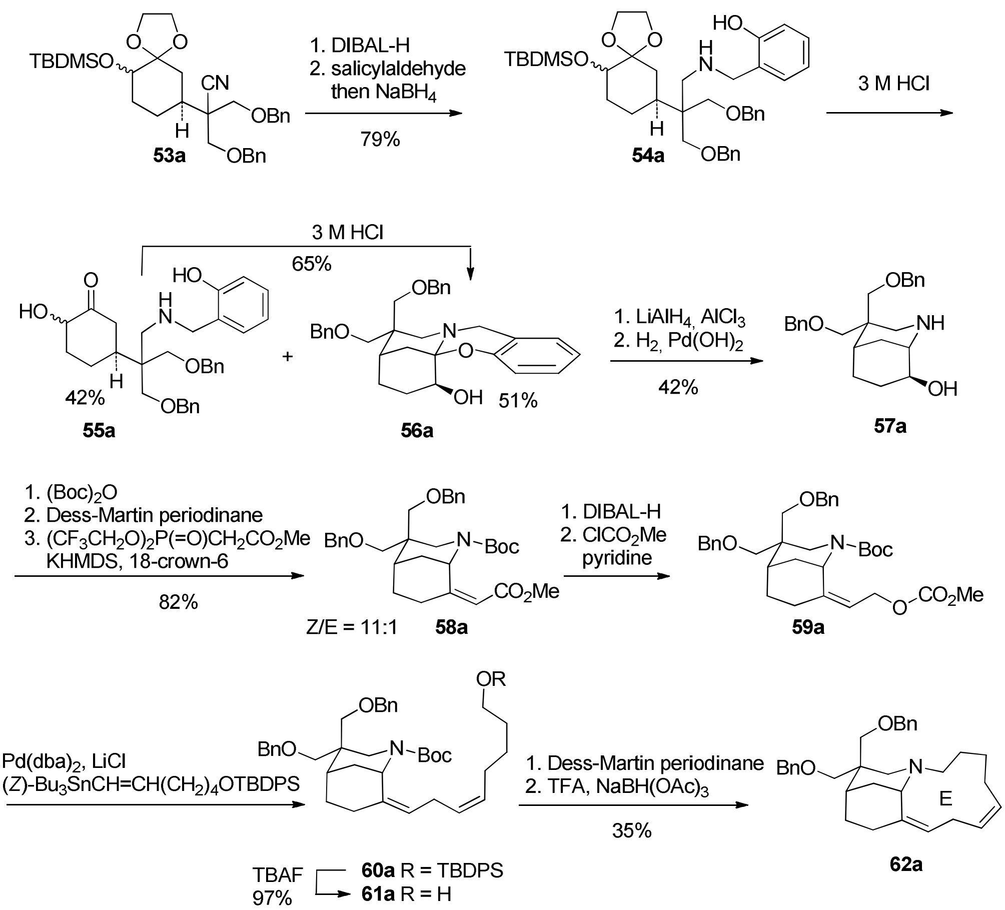

OMe
H
R N
40a
Li / liq. NH3
a 73%; b 61%
OMe
H
R N
41a
1. NCCH2CO2H
EDC*, Et3N
2. 1% HCl-MeOH
*PyBOP in series b
a 60%; b 75%
CN
O
O
R N
42a
Series a R = Me; Series b R = Bn
NaOEt, EtOH
77%
O
9
CN
O
H
R N
H
43a
Br
LDA
a 76%; b 81%
O
CN
O
H
R N
H
44a
1. (CH2OH)2
p-TsOH
2. AlH3
a 51%; b 49%
NH2
O
O
H
R N
H
45a
1. NsCl
2. 2 N HCl
3. L-Selectride
a 55%; b 42%
NHNs
OH
H
H
R N
H
46a
DEAD, Ph3P
Et3N
a 68%; b 42%
9
N
Ns
H
7
R N
C
6
H
47a

Scheme 1.12 Bonjoch's synthetic approach to the ABC diazatricyclic core.

1.5.2. Construction of the ACE System

In 2006 Kibayashi and coworkers reported the first synthesis of the ABE system of madangamine which includes the construction of the unsaturated 11-membered ring bearing a *Z,Z,Z* skipped system of olefins.[40]


O
48a
1. CH2(CN)CO2Et, NaOEt
2. o-C6H4(CH2OH)2, p-TsOH
79%
O
O
CN
H
CO2Et
49a
1. 35% HCHO
2. TBDMSCl
98%
O
O
CN
OTBDMS
H
CO2Et
50a
1. LiBH4
2. TBAF
94%
O
O
CN
OH
OH
51a
1. BnBr
2. PPTS
93%
O
CN
OBn
OBn
52a
1. TBDMSCl
2. OsO4, NMO
3. HO(CH2)2OH, TMSCl
4.TBDMSOTf, 2,6-lutidine
51%


TBDMSO
CN
OBn
H
53a
1. DIBAL-H
2. salicylaldehyde then NaBH4
79%
HO
H
N
54a
3 M HCl
3 M HCl
65%
HO
O
42%
55a
+
BnO
N
O
OH 51%
56a
1. LiAlH4, AlCl3
2. H2, Pd(OH)2
42%
NH
57a
1. (Boc)2O
2. Dess-Martin periodinane
3. (CF3CH2O)2P(=O)CH2CO2Me KHMDS, 18-crown-6
82%
N~Boc
CO2Me
Z/E = 11:1
58a
1. DIBAL-H
2. ClCO2Me pyridine
59a
Pd(dba)2, LiCl
(Z)-Bu3SnCH=CH(CH2)4OTBDPS
OR
TBAF 97%
60a R = TBDPS
61a R = H
1. Dess-Martin periodinane
2. TFA, NaBH(OAc)3
35%
E
62a

Scheme 1.13 Kibayashi's synthetic approach to the E ring of madangamines A-E.

The methodology adopts an intramolecular *N,O*-acetalization for the AC-ring construction while the assembly of the E ring was accomplished using a Still's *Z*-selective Wittig–Horner olefination followed by a cross-coupling reaction and an intramolecular reductive amination. Michael addition of ethyl cyanoacetate to ketone **48a**, followed by protection of the carbonylic group gave cyclic acetal **49a** in a 1:1 diastereomeric mixture. The hydroxymethylation reaction led to the formation of the quaternary carbon center while the protection of the resulting primary alcohol afforded compound **50a**. After the reduction of the ester moiety the two hydroxy groups were protected as benzyl ethers while the hydrolysis of the acetal gave ketone **52a**. After the oxidation of **52a** the resulting α-hydroxylated cyclohexanone was converted in TBDMS- ether while the carbonyl moiety was protected as a cyclic acetal **53a**. Reduction of the nitrile group followed by reaction of the resulting primary amine with salicylaldehyde and $NaBH_4$ gave tetracyclic *N,O*-acetal **54a.** Treatment of compound **54a** with HCl followed by removal of the *N,O*-acetal provided the morphan derivative **57a** which was *N*-protected and oxidize to ketone with Dess-Martin periodinane. A Still-Gennari Wittig-Horner olefination afforded the desired *Z*-isomer of the related ester. A subsequent cross coupling reaction between compound **61a** and an appropriate (*Z*)-vinylstannane derivative gave the skipped diene **62a** as a single isomer. Finally, the 11-membered E ring was constructed through an intramolecular reductive amination that provided the expected ACE system.

1.6. SYNTHETIC BACKGROUND

The development of new methodologies for the enantioselective synthesis of chiral compounds has undergone huge improvements in the last decades. This is of great significance in the field of the synthesis of natural products and biologically active compounds since chirality is crucial for the expression of their bioactivity. In this context, in the last years, we have focused our attention on the search of novel, general methods for the preparation of chiral non-racemic compounds in an enantiopure form with the final aim of applying them to the total synthesis of natural products and biologically active compounds.

Functionalized piperidine structures embody some of the key features found in numerous alkaloids (more than half of the known alkaloids bear a piperidine ring), biologically active compounds, and drugs. This observation prompted us to focus our interest in the search of general procedures for the enantioselective synthesis of piperidine derivatives with a high variety of substitution patterns.[43] With this purpose in mind, we decided to explore the potential of chiral aminoalcohol-derived bicyclic lactams as enantiomeric scaffolds for the stereocontrolled construction of complex piperidine derivatives. Bicyclic lactams were originally developed by A. I. Meyers as chiral templates for the enantioselective synthesis of cycloalkenones and carboxylic acids containing quaternary stereocenters. In subsequent work Meyers also reported some applications to the synthesis of simple α-susbtituted piperidine and tetrahydroquinoline alkaloids, as well as imino-sugars. This seminal work was summarized in three excellent reviews.[44]

Chiral oxazolopiperidone lactams, easily available in a single step by cyclocondensation of oxo-acid derivatives and enantiopure amino-alcohols, bear a tactically versatile functionalized piperidine ring embedded in a conformationally rigid bicyclic system. These structural properties enable the introduction of substituents at virtually all the carbon positions of the heterocycle in a high degree of stereoselectivity giving access to a broad variety of either simple or complex piperidine derivatives.

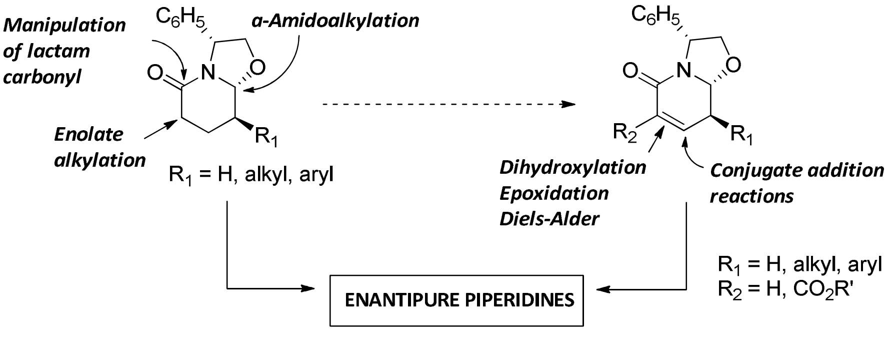


Figure 1.5 Chiral lactams as enantiomeric scaffolds.

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[43] (a) Escolano, C.; Amat, M.; Bosch, J. *Chem. Eur. J.* **2006***, 12*, 8198–8207. (b) Amat, M.; Pérez, M.; Bosch, J. *Synlett* **2011**, 143–160. (c) Amat, M.; Pérez, M.; Bosch, J. *Chem. Eur. J.* **2011***, 17*, 7724–7732.

[44] (a) Romo, D.; Meyers, A. I. *Tetrahedron* **1991**, *47*, 9503–9569. (b) Meyers, A. I.; Brengel, G. P. *Chem. Commun.* **1997**, 1–8. (c) Groaning, M. D.; Meyers, A. I. *Tetrahedron* **2000***, 56*, 9843–9873.

More recently, we have expanded the potential of the methodology to the synthesis of enantiopure *cis*-decahydroquinolines from tricyclic lactams prepared by cyclocondensation of 2-cyclohexanonepropionic acid derivatives and chiral enantiopure amino-alcohols. In most cases phenylglycinol has been used as chiral amino-alcohol due to its availability in both enantiomeric forms and to the benzylic nature of the carbon-nitrogen bond which facilitates the removal of the phenylethanol moiety at an appropriate stage of the sequence. For the synthesis of indole and benzo[*a*]quinolizidine alkaloids we have also used (*S*)-tryptophanol and (*S*)-(3,4-dimethoxyphenyl)alaninol which not only act as source of chirality but also incorporate the aryl ethylamine moiety of the target compound. More recently, we have explored an efficient reductive ring opening of bicyclic lactams leading to chiral aminoalcohols.

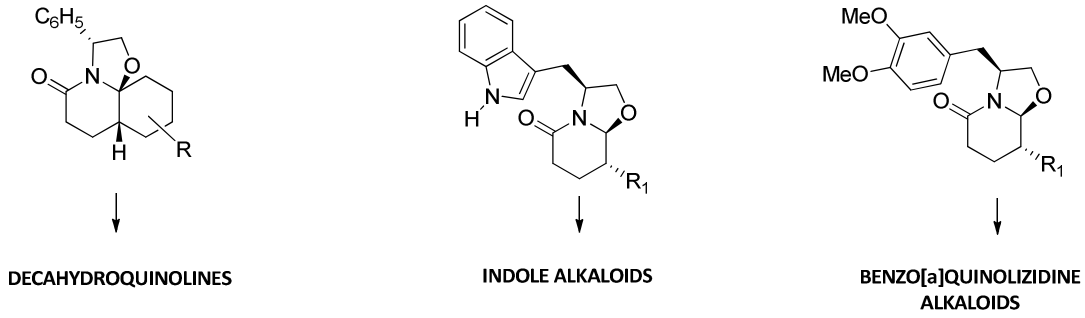

Figure 1.6 Amino-alcohol-derived oxazolopiperidone lactams.

Therefore, we have now in hand a flexible and versatile tool for the preparation in an enantiopure form a broad range of piperidine, *cis*-decahydroquinoline and aminoalcohol derivatives which allows the generation of new stereocenters on the heterocyclic ring with a high degree of stereoselectivity and predictable absolute and relative configuration.[45] The potential of the approach based on the use of chiral bicyclic and tricyclic lactams as enantiomeric scaffolds for the preparation of natural products has been demonstrated in our research group with the synthesis of a variety of alkaloids, some of them depicted in Fig. 1.7.

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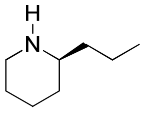
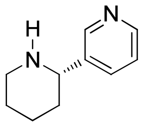
[45] For recent works, see: (a) Amat, M.; Griera, R.; Fabregat, R.; Bosch, J. *Angew. Chem.* **2008**, 120, 3396–3399; *Angew. Chem. Int. Ed.* **2008**, *47*, 3348–3351. (b) Amat, M.; Gómez-Esqué, A.; Escolano, C.; Santos, M. M. M.; Molins, E.; Bosch, J. *J. Org. Chem.* **2009**, *74*, 1205–1211. (c) Amat, M.; Llor, N.; Checa, B.; Molins, E.; Bosch, J. *J. Org. Chem.* **2010**, *75*, 178–189. (d) Amat, M.; Pérez, M.; Bosch, J. *Synlett* **2011**, *2*, 143–160. (e) Amat, M.; Elias, V.; Llor, N.; Subrizi, F.; Molins, E.; Bosch, J. *Eur. J. Org. Chem.* **2010**, *41*, 4017–4026. (f) Pérez, M.; Arioli, F.; Rigacci, G.; Santos, M. M. M.; Gómez-Esqué, A.; Escolano, C.; Florindo, P.; Ramos, C.; Bosch, J.; Amat, M. *Eur. J. Org. Chem.* **2011**, 3858–3863 (g) Amat, M.; Navío, L.; Llor, N.; Molins, E.; Bosch J. *Org. Lett.* **2012**, *14*, 210–213 (h) Amat, M.; Subrizi, F.; Elias, V.; Llor, N.; Molins E.; Bosch, J. *Eur. J. Org. Chem.* **2012**, 1835–1842 (i) Amat, M.; Subrizi, F.; Elias, V.; Llor, N.; Molins E.; Bosch, J. *Eur. J. Org. Chem.* **2012**, 5497–5497 (l) Amat, M.; Ramos, C.; Pérez, M.; Molins, E.; Florindo, P.; Bosch J. *Chem. Commun*. **2013**, *49*, 1954-1956 (m) Amat, M.; Llor, N.; Subrizi, F.; Pérez, M.; Molins, E.; Bosch, J. *Eur. J. Org. Chem.* **2013**, 1246-1252 (n) Amat, M.; Ghirardi, E.; Navío, L.; Griera, R.; Llor, N.; Molins, E.; Bosch. J. *Chem. Eur. J.* **2013**, *19*, 16044–16049.

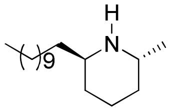
Piperidine derived alkaloids



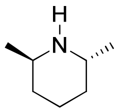
(S)-(+)-Coniine
(both enantiomers)



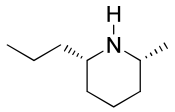
(S)-anabasine



(-)-Solenopsin A

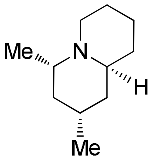


(-)-Lupetidine

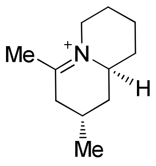


(2R,6S)-Dihydropinidine

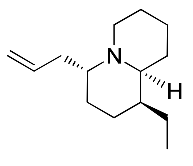
Quinolizidine



(-)-Cermicine C

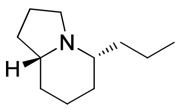


(-)-Senepodine G

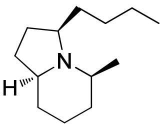


Quinolizidine-4-epi-207I

Indolizidine

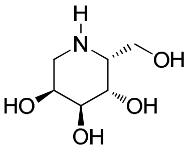


(-)-Indolizidine 167B

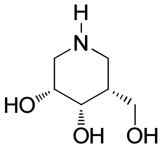


(+)-Monomorine I

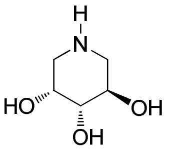
Iminosugars


H
N
OH
HO
OH
OH

Deoxy-D-gulonojirimycin
(1-Deoxy-3,4-diepinojirimycin)

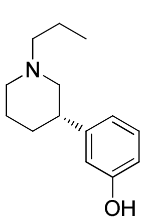


Epiisofagomine
(Isogalactofagomine)
(selective and potent inhibitor of β-galactosidases)

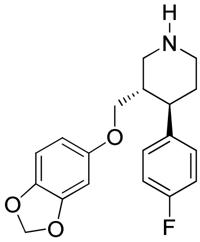


Nor-fuco-deoxynojirimycin

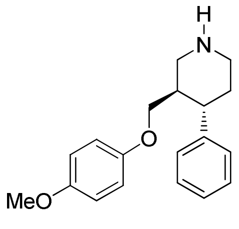
Biologically active compounds



(-)-3PPP
(antipsychotic)

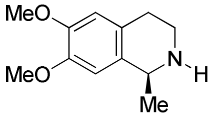


(-)-Paroxetine
(antidepressant)

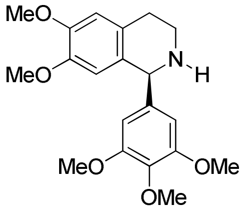


(+)-Femoxetine
(antidepressant)

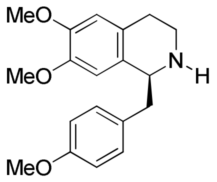
Tetrahydroisoquinoline alkaloids


MeO
MeO
N
H
Me

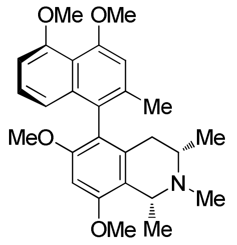
(-)-Salsolidine


MeO
MeO
N
H
MeO
OMe
OMe

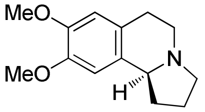
(-)-Norcryptostiline III


MeO
MeO
N
H
MeO

(-)-O,O-Dimethylcoclaurine

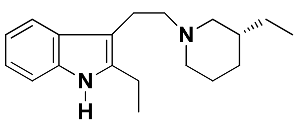

OMe OMe
Me
MeO
Me
N
Me
OMe Me

O-Methylancistrocline
(Formal synthesis)

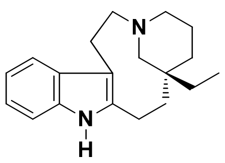


(-)-Crispine A

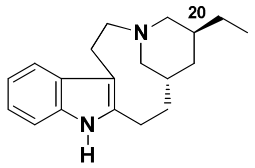
Indole alkaloids



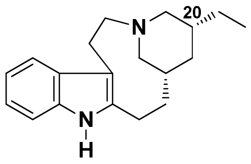
(+)-Decarbomethoxytetrahydrosecodine



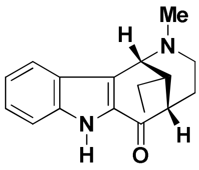
(-)-Quebrachamine



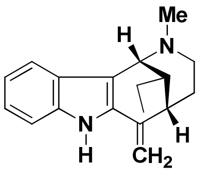
(-)-20S-Dihydrocleavamine



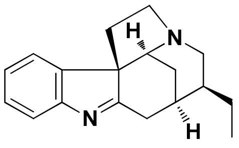
(+)-20R-Dihydrocleavamine



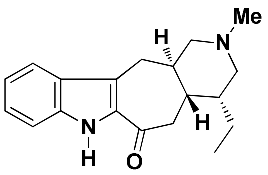
(+)-Dasycarpidone


Me
H
N
H
N
H
CH2

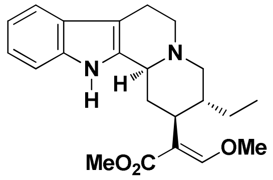
(+)-Uleine



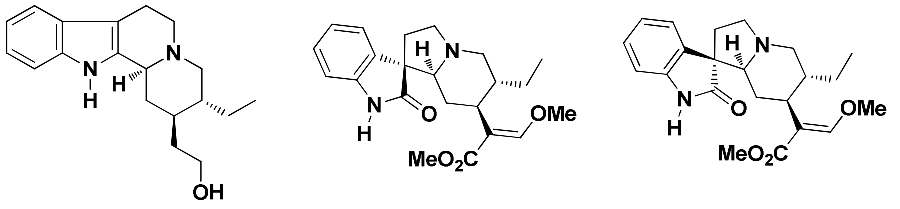
(-)-Tubifoline



(-)-16-Episilicine

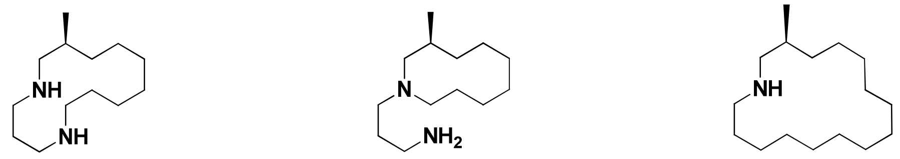

N
N
H
H
MeO2C
OMe

(+)-Dihydrocorynantheine



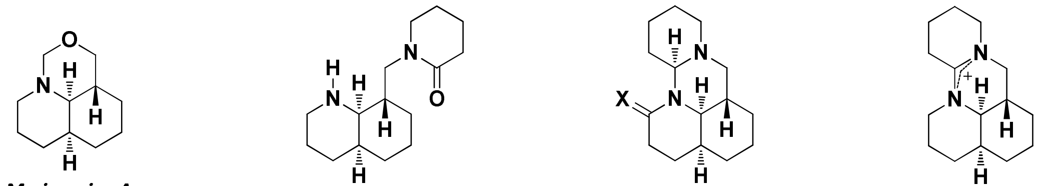
(-)-Dihydrocorynantheol *(-)-Rhynchophylline* *(+)-Isorhynchophylline*

Haliclorensin marine alkaloids



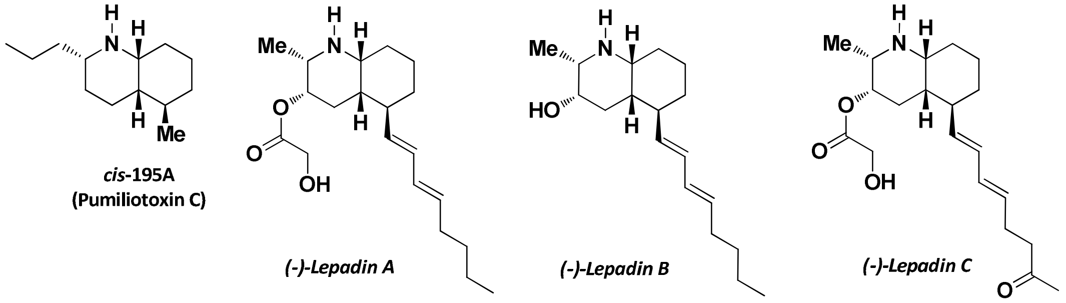
Haliclorensin *Isohaliclorensin* *Haliclorensin C*

Myrioneuron alkaloids



Myrioxazine A *Myrionine* *Schoberine X = H. H* *Myrionamide X = O* *Myrionidine*

Amphibian and marine cis-decahydroquinoline alkaloids



cis-195A (Pumiliotoxin C) *(-)-Lepadin A* *(-)-Lepadin B* *(-)-Lepadin C*

Figure 1.7 Alkaloids prepared from chiral amino-alcohol derived lactams.

As an evolution of this work, we decided to undertake the synthesis of more complex targets in order to demonstrate the scope and synthetic potential of the strategy based on the use of chiral aminoalcohol-derived lactams as enantiomeric scaffolds.[46] With this purpose in mind, we selected the alkaloids of the madangamine group due to their attractive structural architecture and because there was no total synthesis for this group of natural products described in the literature.

---

[46] Enantiomeric scaffolding strategy: (a) Coombs, T. C.; Lee, M. D., IV, Wong, H.; Armstrong, M.; Cheng, B.; Chen, W.; Moretto, A. F.; Liebeskind, L. S. *J. Org. Chem.* **2008**, *73*, 882–888. (b) Wong, H.; Garnier-Amblard, E. C.; Liebeskind, L. S. *J. Am. Chem. Soc.* **2011**, *133*, 7517–7527.

This work was initiated by Dr. Stefano Proto in his Ph. D. Thesis which was defended in March 2012. Due to the complexity inherent to the total synthesis of challenging natural products, such as the alkaloids of the madangamine group, the final goal could not be reached in this Thesis.

The aim of this work was to conclude the total synthesis of madangamine D, which involve:

- to scale up and optimize the procedures for the preparation of starting materials in order to provide enough amounts to reach the target compound.
- to improve the synthetic sequence developed in previous work by reducing the number of steps in the preparation of the diazatricyclic core of madangamines.
- to explore different synthetic pathways that could potentially permit the assembly the macrocyclic D ring of various members of madangamine's family, which are different in size as well in degree and position of unsaturations.
- to set up efficient procedures to solve the final steps of the synthesis.

1.7. SYNTHETIC STRATEGY

The synthetic strategy we devised for the synthesis of madangamines involves the initial construction of the fully functionalized diazatricyclic core common to all madangamines A to E, and the subsequent annulations of the macrocyclic D and E rings.

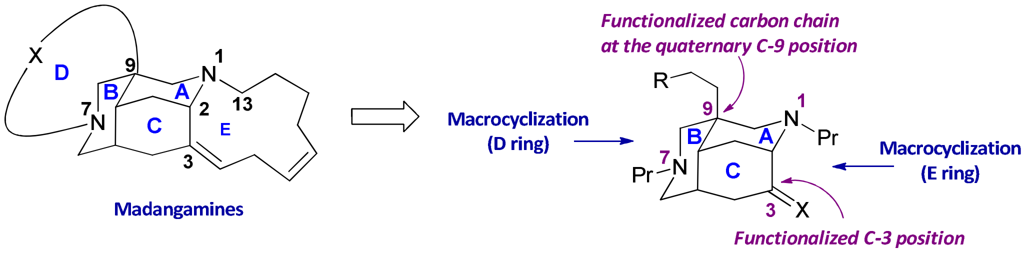


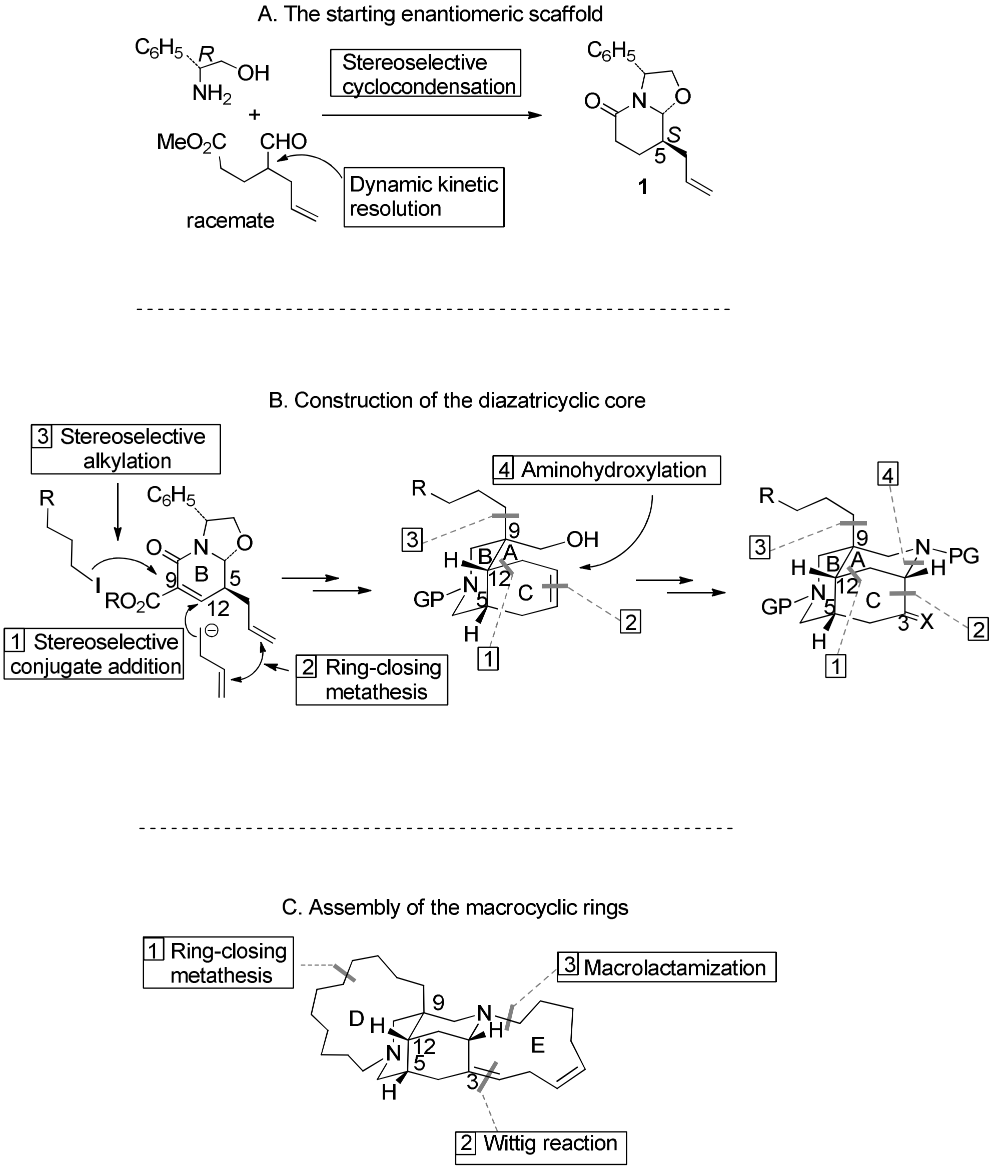
Figure 1.8 General synthetic strategy.

The stereoselective construction of the diazatricyclic core in enantiopure form relies on the use of an allyl-substituted chiral phenylglycinol-derived lactam as enantiomeric scaffold and in our experience in the generation of stereocenters of well-defined configuration at the carbon positions of the piperidine ring of these lactams. Accordingly, the allyl-substituted lactam **1**, with the appropriate absolute configuration at the stereocenter next to the allyl group (corresponding to the 5-position of madangamines) was selected as starting material. A stereoselective conjugate addition on the corresponding unsaturated derivative, in which the double bond is activated by an alcoxycarbonyl group, is used for the introduction of an allyl substituent at C-12, *cis* with respect to the allyl group of the next position (C-5). A RCM of the resulting diallyl derivative is performed for the closure of the carbocyclic ring C of madangamines. The generation of the quaternary stereocenter at the C-9 position by alkylation of an enolate takes advantage of the acidity of the hydrogen next to the carbonyl of the ester and the amide-lactam and of the bended shape of the *cis*-octahydroisoquinoline which allows the selective approach of the alkylating reagent from the less hindered face. In this step a carbon chain with the appropriate functionalization at the terminal position for the closure of the D ring is introduced. The removal of the phenylethanol moiety of the chiral inductor (phenylglycinol) and the closure of the piperidine A ring by an intramolecular aminohydroxylation constitute the final strategic transformations needed to complete the synthesis of the diazatriciclic core of madangamines.[47.]

For the closure of the macrocyclic D ring of madangamines classical macrolactamizations or the more recent but well-established procedure based on ring-closing metathesis (RCM) constitute two of the most popular methods used in the construction of medium and large rings.[45] Ring-closing alkyne metathesis (RCAM) and other palladium-(0) cross-coupling reactions have also proven to be invaluable tools for the intramolecular carbon-carbon formation in the construction of macrocycles with control of the E/Z selectivity. Finally, the elaboration of the unsaturated E ring requires the incorporation at the 3-position of an 8-carbon chain, containing a *Z*-configurated double bond, followed by a macrolactamization. The first step involves a Wittig olefination in which a carbon-carbon double bond with the *Z*-configuration has to be stereoselectively generated.[48]

---

[47] Amat, M.; Ballette, R.; Proto, S.; Pérez, M.; Bosch, J. *Chem. Commun.* **2013,** *49*, 3149–3151.
[48] Ballette, R.; Pérez, M.; Proto, S.; Amat, M.; Bosch, J. *Angew. Chem. Int. Ed*. **2014**, accepted.


A. The starting enantiomeric scaffold

B. Construction of the diazatricyclic core

C. Assembly of the macrocyclic rings

C_6H_5
R
OH
NH_2
+
MeO_2C
CHO
racemate
Stereoselective cyclocondensation
Dynamic kinetic resolution
O
N
S
5
1
3 Stereoselective alkylation
R
I
9
B
12
RO_2C
1 Stereoselective conjugate addition
2 Ring-closing metathesis
4 Aminohydroxylation
A
C
H
GP
OH
N
PG
3
X
1 Ring-closing metathesis
3 Macrolactamization
2 Wittig reaction
D
E

Figure 1.9 Synthetic strategy.

Chapter 2

2.1. INTRODUCTION

In this chapter, our efforts on the synthesis of the diazatricyclic core common to all madangamines (rings A-B-C) from the allyl-substituted phenylglycinol-derived bicyclic lactam **1** are described. This scaffold (**1**) bears the piperidine B ring of madangamines and the stereocenter corresponding to the C-5 position of these natural products. For the sake of clarity, the numbering of madangamines is used for the compounds appearing throughout the text.

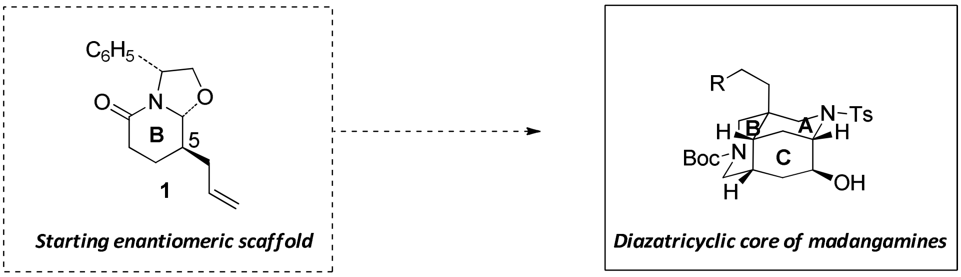
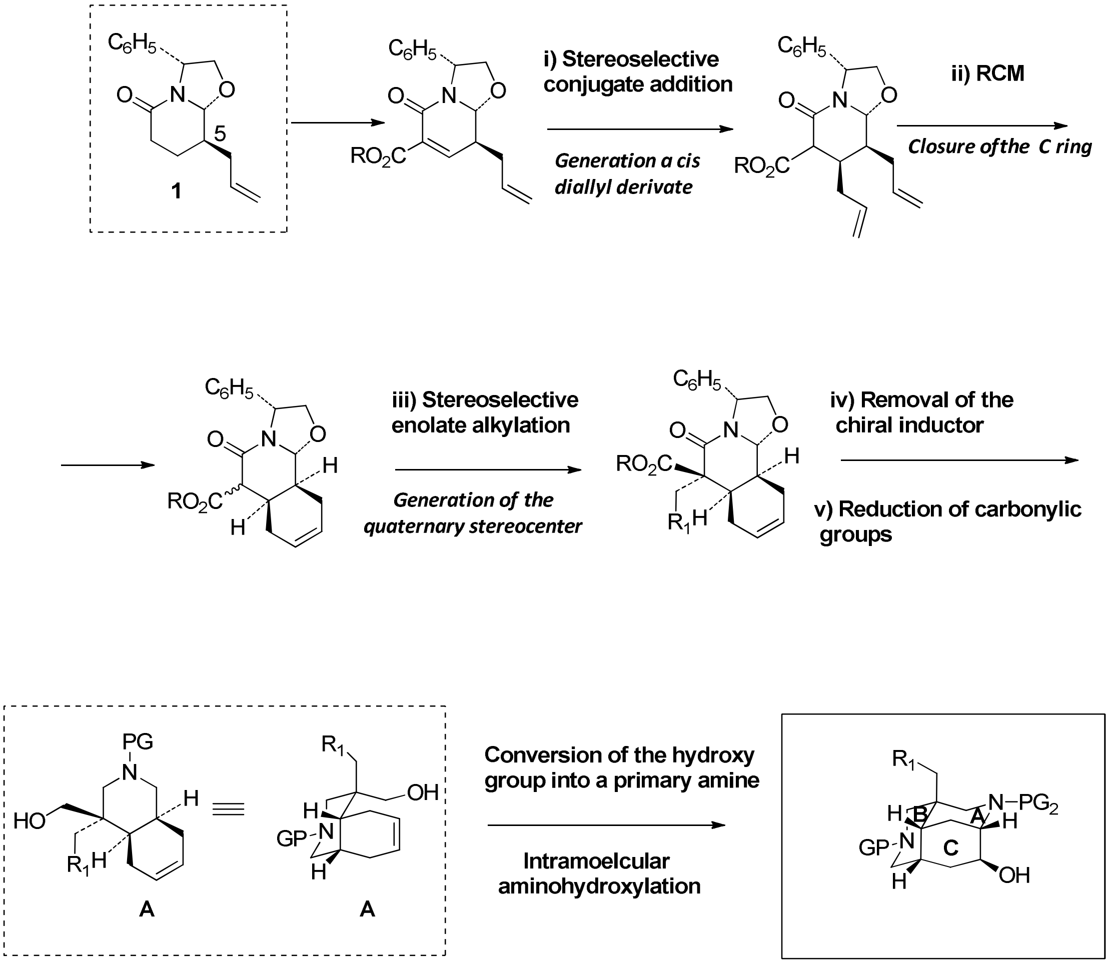

C6H5
O
N
O
B
5
1
Starting enantiomeric scaffold
R
N-Ts
H
B
A
H
Boc-N
C
H
OH
Diazatricyclic core of madangamines

Figure 2.1 Enantiomeric scaffolding strategy.

The synthetic strategy originally devised for the diazatricyclic core of madangamines is depicted in Scheme 2.1. The first stages of the synthesis are oriented to the generation of a *cis*-octahydroisoquinoline (A) with a quaternary stereocenter at the C-9 position holding a hydroxymethyl substituent and a carbon chain appropriately functionalized for the closure of the macrocyclic D ring in subsequent stages of the synthesis.

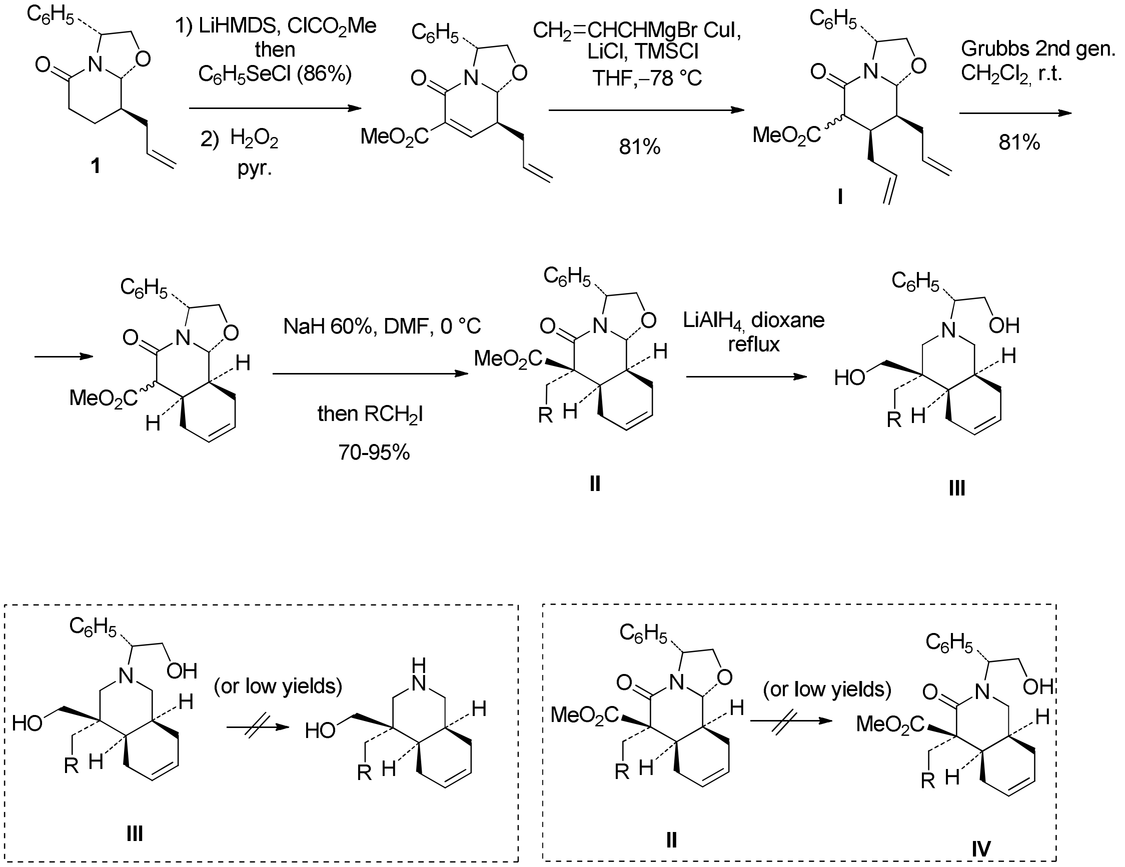
2.2. SYNTHETIC STRATEGY TOWARD THE ABC CORE OF MADANGAMINE

The key steps in the preparation of this cis-octahydroisoquinoline (A) include i) a stereoselective conjugate addition of an allyl group to the unsaturated lactam derived from **1**, ii) a RCM for the closure of the carbocyclic C ring, iii) the alkylation of the enolate of the β-keto-lactam, iv) the removal of the phenylethanol moiety of the chiral inductor, and v) the reduction of the carbonylic groups. In this intermediate A the key stereocenters at the C-5, C-9, and C-12 positions are installed, two of them generated in the conjugate addition (C-12) and in the enolate alkylation (C-9) reactions. Starting from compound A, only the closure of the piperidine A ring is needed to complete the target structure. This transformation can be carried out by conversion of the hydroxymethyl on C-9 into an aminomethyl group followed by an intramolecular amino-hydroxylation of the carbon-carbon double bond present into the *cis*-octahydroisoquinoline system.[47]


1
i) Stereoselective conjugate addition
Generation a cis diallyl derivate
ii) RCM
Closure ofthe C ring
iii) Stereoselective enolate alkylation
Generation of the quaternary stereocenter
iv) Removal of the chiral inductor
v) Reduction of carbonylic groups
A
A
Conversion of the hydroxy group into a primary amine
Intramoelcular aminohydroxylation
C$_6$H$_5$
RO$_2$C
R$_1$
PG
GP
N–PG$_2$
OH
HO
B
A
C

Scheme 2.1 General synthetic plan.

In previous work we prepared a variety of tricyclic lactams **II**, bearing the *cis*-octahydroisoquinoline system and the quaternary stereocenter at C-9, starting from the allyl-substituted bicyclic lactam **1** as illustrated in Scheme 2.2. The reactions involved in this sequence took place in good yields and excellent stereoselectivity. Compounds **I** and **II** were isolated as the only stereoisomers detectable by spectroscopic methods. However, all attempts to remove the phenylethanol moiety of the (*R*)-phenylglycinol, which had played the role of chiral inductor, resulted in failure or provided the expected compound in moderate yields. For the *N*-debenzylation of compounds **III**, the common catalytic hydrogenation could not be used due to the presence of a carbon-carbon double bond. On the other hand, the presence of the hydroxymethyl substituent in **III** made difficult the selective manipulation of both alcohols. Alternatively, all attempts to provoke the reductive ring opening of the oxazolidine ring present in **II** by using Et_3SiH and Lewis acids did not afford the expected compounds **IV**.[49] However, in previous work we found that this reaction works well on bicyclic lactams lacking functional groups such as a methyl carboxylate.


C6H5
1
1) LiHMDS, ClCO2Me then C6H5SeCl (86%)
2) H2O2 pyr.
MeO2C
CH2=CHCHMgBr CuI, LiCl, TMSCl THF, −78 °C
81%
I
Grubbs 2nd gen. CH2Cl2, r.t.
81%
NaH 60%, DMF, 0 °C
then RCH2I
70-95%
II
LiAlH4, dioxane reflux
III
HO
OH
R
H
(or low yields)
III
II
IV

Scheme 2.2 First synthetic plan.

The above results prompted us to modify the synthetic sequence to the diazatricyclic core of madangamines (**XI**) by removing in earlier stages of the synthesis the phenylethanol moiety of the chiral inductor. When tricyclic lactam **V**, lacking the methoxycarbonyl substituent at the C-9 position, was subjected to treatment with Et_3SiH and $TiCl_4$ followed by *N*-debenzylation with sodium in liquid ammonia, the expected compound **VI** was obtained in an excellent 82% yield for the two steps. It is worth mentioning that the presence of an activating group, such an alkyl carboxylate, on the unsaturated lactam is required to obtain good yields in the conjugate addition reaction. The generation of the quaternary stereocenter at the C-9 position by alkylation of the enolate of **VII** took place in excellent stereoselectivity to give compound **VIII** although, in this case, small amounts of the C-9 diastereomer could be detected by spectroscopic methods. On the other hand, the presence of a robust electron withdrawing group, such as tosyl, afforded better results in the enolate alkylation reaction.[50] The final key transformation, involving the closure of the piperidine A ring, was carried out from intermediate **IX** by conversion of the hydroxy group into an azide, stereoselective epoxydation of the alkene to give **X** followed by treatment with trimethylphosphine, which provoked the reduction of the azide and the subsequent intramolecular opening of the epoxide in a one pot reaction. Protection of the resulting secondary amine conducted to the target compound **XI.**[51]

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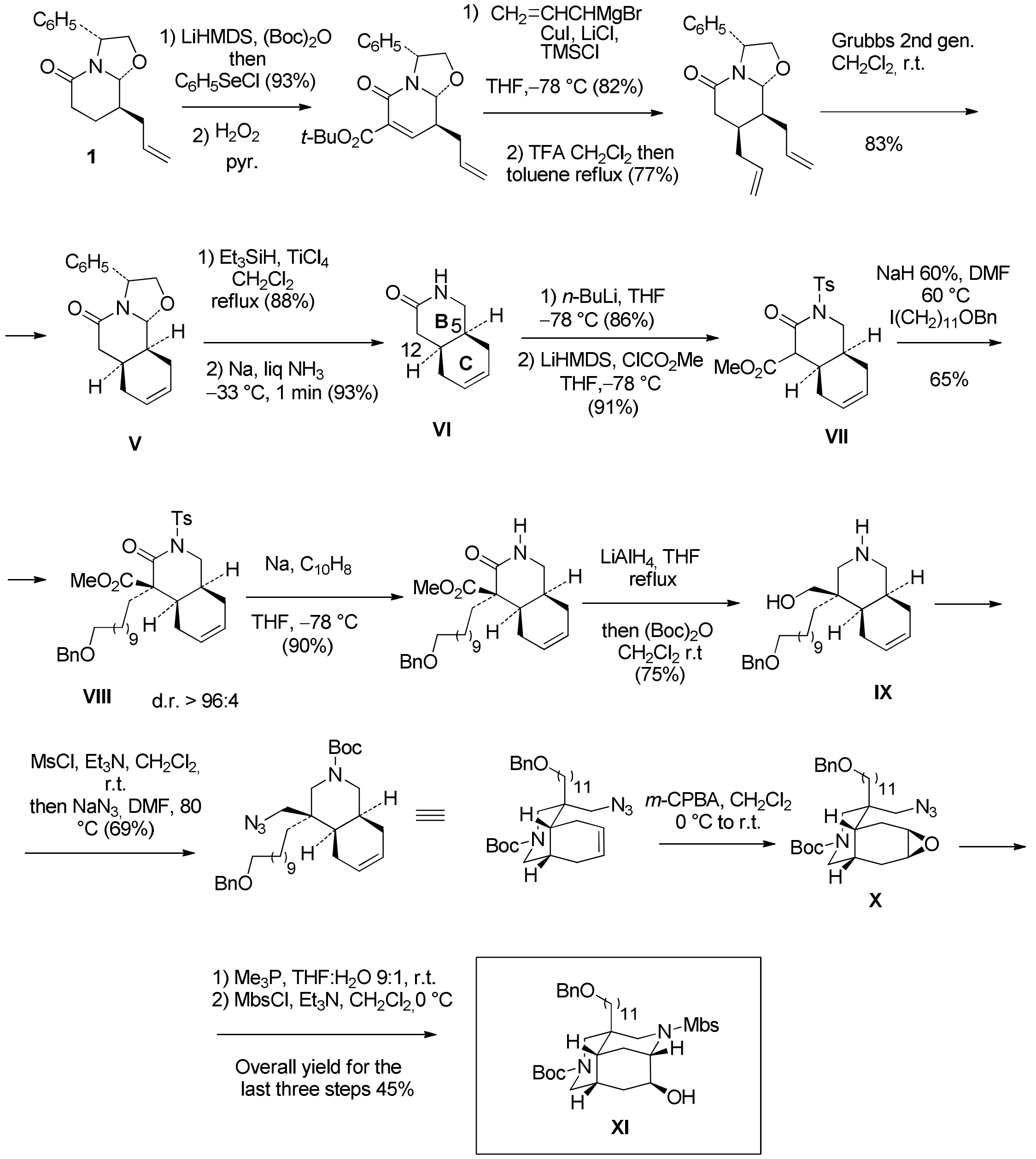
[49] A detailed explanation of all the efforts in the removal of the phenylethanol moiety of the (*R*)-phenylglycinol is included in paragraph 2.4.


1
1) LiHMDS, (Boc)2O then C6H5SeCl (93%)
2) H2O2 pyr.
t-BuO2C
1) CH2=CHCHMgBr CuI, LiCl, TMSCl THF,−78 °C (82%)
2) TFA CH2Cl2 then toluene reflux (77%)
Grubbs 2nd gen. CH2Cl2, r.t.
83%
V
1) Et3SiH, TiCl4 CH2Cl2 reflux (88%)
2) Na, liq NH3 −33 °C, 1 min (93%)
B
C
5
12
VI
1) n-BuLi, THF −78 °C (86%)
2) LiHMDS, ClCO2Me THF,−78 °C (91%)
Ts
MeO2C
VII
NaH 60%, DMF 60 °C I(CH2)11OBn
65%
VIII
d.r. > 96:4
Na, C10H8
THF, −78 °C (90%)
BnO
9
LiAlH4, THF reflux
then (Boc)2O CH2Cl2 r.t (75%)
HO
IX
MsCl, Et3N, CH2Cl2, r.t. then NaN3, DMF, 80 °C (69%)
Boc
N3
11
m-CPBA, CH2Cl2 0 °C to r.t.
X
1) Me3P, THF:H2O 9:1, r.t.
2) MbsCl, Et3N, CH2Cl2 0 °C
Overall yield for the last three steps 45%
N-Mbs
OH
XI

Scheme 2.3 Revised synthetic plan.

---

[50] The use of *N*-Boc derivatives of VII afforded mixtures of the desired compound along with variable amount of the corresponding unprotected compound.

[51] Amat, M.; Pérez, M.; Proto, S.; Gatti, T.; Bosch, J. *Chem. Eur. J.* **2010**, *16*, 9438–9441.

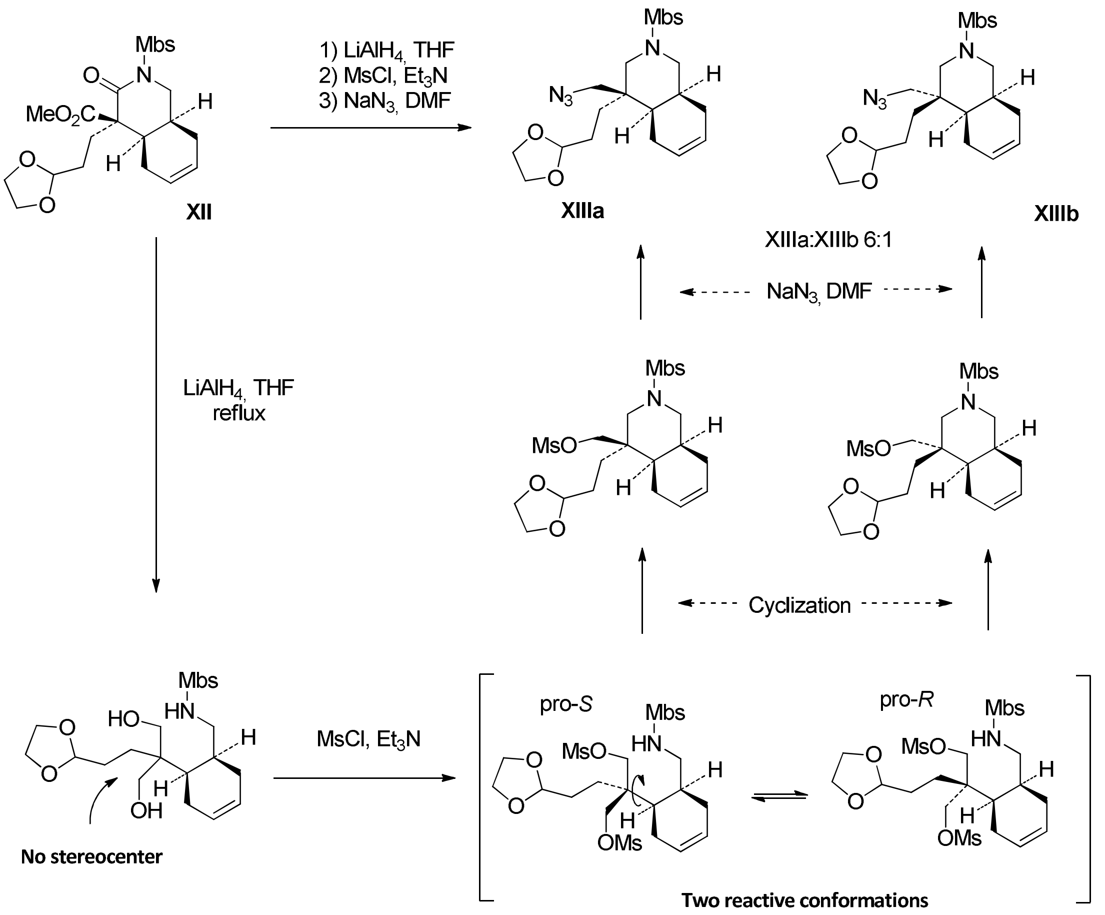
Although the above synthesis allowed us to reach the target compound **XI**, this sequence includes more steps than the originally one (see Scheme 2.3), which is a limitation under a synthetic standpoint considering that the two macrocycles D and E had to be installed yet.

Two main drawbacks can be identified in this sequence:

- The alkyl carboxylate introduced at the beginning of the synthesis to activate the unsaturated lactam has to be taken out for the removal of the chiral inductor and reintroduced later to activate the C-9 position in the enolate alkylation step and as precursor of the aminomethyl substituent needed for the closure of the A ring.

- On the other hand, the protecting *N*-tosyl group present in **VIII** has to be removed before the $LiAlH_4$ reduction of the lactam carbonyl and ester functions and the resulting secondary amine has to be reprotected with an *N*-Boc group. In previous work we observed that treatment of the *N*-*p*-methoxybenzenesulfonyl lactam **XII** with $LiAlH_4$ followed by addition of an excess of mesyl chloride and sodium azide afforded a mixture of the expected compound **XIIIa** and its diastereomer at the C-9 quaternary center **XIIIb**.

This stereochemical result can be accounted for by considering that the reaction of **XII** with $LiAlH_4$ provokes the reduction of the ester and the reductive ring opening of the lactam ring affording a compound with two diastereotopic hydroxymethyl groups. Treatment of this diol with mesyl chloride gives a dimesyltate which undergoes cyclization leading a mixture of epimeric C-9 *cis*-octahydroisoquinolines which are precursors of the isolated azides **XIIIa** and **XIIIb**.


Mbs
1) LiAlH4, THF
2) MsCl, Et3N
3) NaN3, DMF
XII
XIIIa
XIIIb
XIIIa:XIIIb 6:1
NaN3, DMF
LiAlH4, THF
reflux
Cyclization
MsCl, Et3N
No stereocenter
pro-S
pro-R
Two reactive conformations

Scheme 2.4 Isomerization of C-9 stereocenter.

On the grounds of the experience acquired in previous work on the synthesis of marine alkaloids of the madangamine group, mentioned above, in the present chapter we decided to focus our efforts on two main points:

- To scale up and optimize the reactions included in the sequence leading to the diazatricyclic core of madangamines. This was crucial in order to dispose enough amounts to undertake the studies about the construction of rings D and E of madangamines.

- To review the original synthetic sequence trying to find an efficient solution for the removal of the phenylethanol moiety of the chiral inductor avoiding the drawbacks of the synthesis depicted in Scheme 2.2.

2.3. SYNTHESIS OF BC HEART OF MADANGAMINE

As described above the first challenges of our synthesis were represented by the construction of the chiral nonracemic allyl oxazolopiperidone scaffold **1** and its transformation into the fully-functionalized BC azabicyclic heart of madangamines (A). The main features of this synthon include a *cis*-convex isoquinolic structure embodying three contiguous stereocenters and bearing the endocyclic double bond among the C ring. This functionalization, together with the presence at the C-9 position of a hydroxymethyl chain, synthetic equivalent of the aminomethyl fragment, forms the ideal platform for the construction of the piperidinic A ring. On the other hand a suitable carbon chain, installed at the quaternary stereocenter, guarantees the access to the western macrocyclic ring D of madangamines.

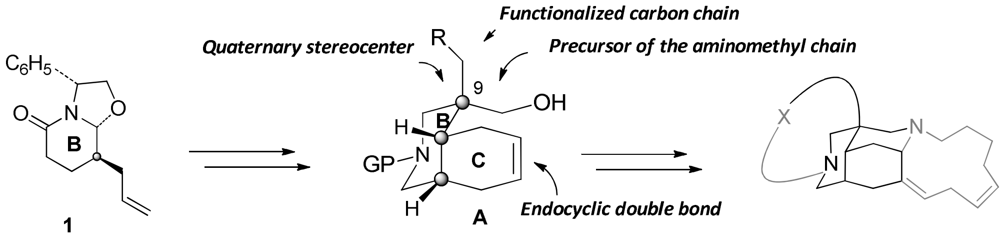


Figure 2.2 BC system of madangamines.

The construction of the BC azabicyclic heart involves as key steps (i) the generation of the first enantiopure intermediate, the bicyclic lactam **1**, by cyclocondensation of (*R*)-phenylglycinol with racemic γ-substituted δ-oxoester, in a process that involves a dynamic kinetic resolution; (ii) a highly stereoselective conjugate addition to unsaturated lactam; (iii) the closure of the carbocyclic ring by a ring-closing olefin metathesis (RCM); and (iv) the stereoselective generation of the C-9 quaternary stereocenter.

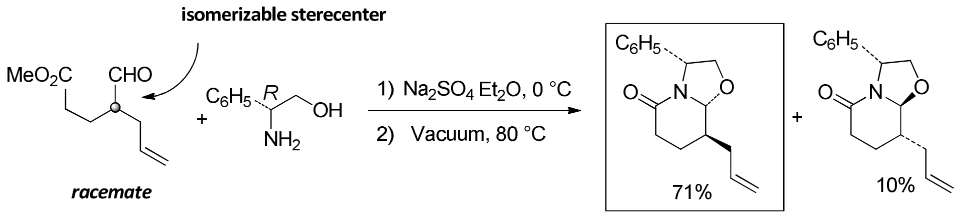
2.3.1. Synthesis of the Enantiopure Bicyclic Lactam: Cyclocondensation reaction

Our route toward the total synthesis of the alkaloid started with the construction of the appropriate chiral oxazolopiperidone lactam **1** which represents a versatile building block for the stereocontrolled construction of the bridged diazatricyclic ABC core of madangamine.

The required bicyclic lactam **1** was prepared in a straightforward way through a cyclondensation reaction of (*R*)-phenylglycinol with racemic 4-formyl-6-heptenoate,[52] which incorporates a labile stereocenter capable of undergoing in situ racemization or epimerization during the reaction. Thus, the starting enantiopure allyl-substituted lactam **1** was obtained in 71% yield, with only a minor amount of the corresponding (8*S*, 8a*S*)-diastereoisomer **2**.

---

[52] For the synthesis of 4-formyl-6-heptenoate, see: (a) Lawton, G.; Saxton, J. E.; Smith, A. J. *Tetrahedron* **1977**, *33*, 1641–1653. (b) Costello, G.; Saxton, J. E. *Tetrahedron* **1986**, *42*, 6047–6069.



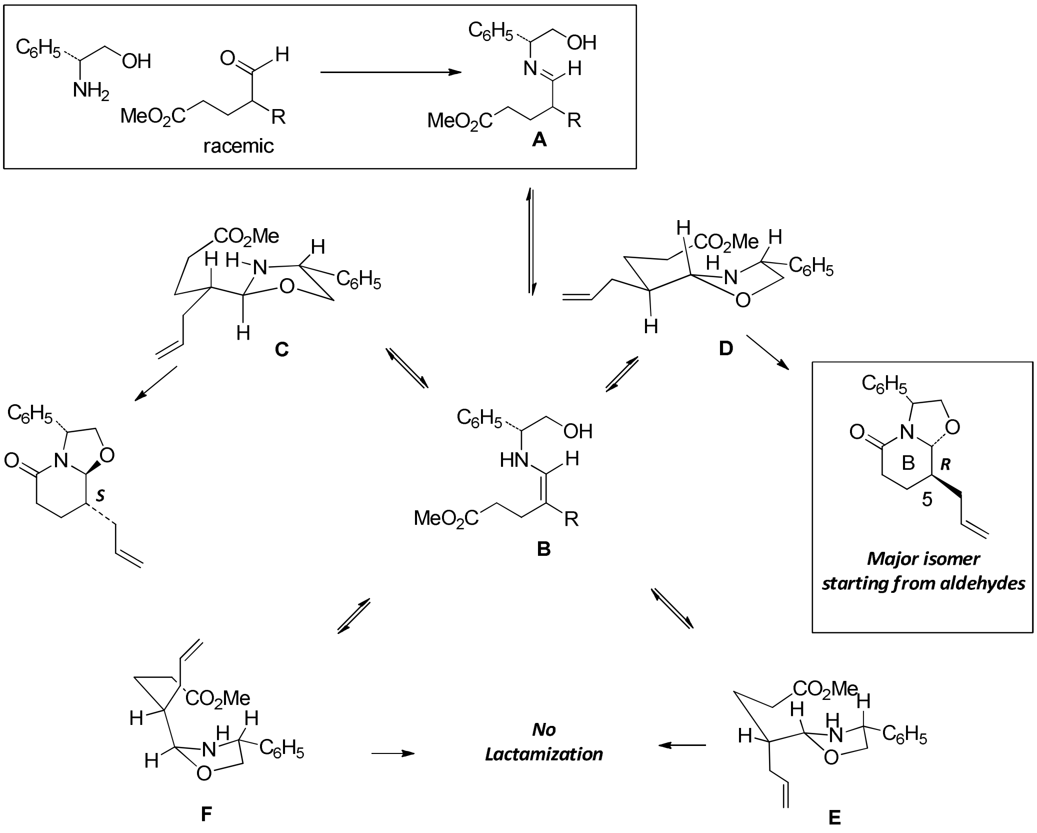
1 **2**

Scheme 2.5 Construction of piperidine B ring.

The high stereoselectivity observed in the reaction can be justified considering that the cyclodehydration involves a dynamic kinetic resolution (DKR) of the racemic substrate.[53] As shown in Scheme 2.6, the mixture of the four diastereomeric oxazolidines (C-F) formed initially by reaction between the (*R*)-phenylglycinol and the racemic aldehyde ester, is in equilibrium through the corresponding imines/enamines (A-B), and the subsequent lactamization takes place through a chairlike transition state in which the substituent allyl is equatorial. The preferential formation of isomers H-3/H-8a *cis* indicates that lactamization occurs faster from the diastereomeric oxazolidine (D) that allows the approach of the carboxylate group to the nitrogen atom by the most accessible face, that is anti with respect to C_6H_5 (from aldehyde esters).

---

[53] For related examples, see: (a) Amat, M.; Cantó, M.; Llor, N.; Ponzo, V.; Pérez, M.; Bosch, J. *Angew. Chem.* **2002***, 114*, 345–348; *Angew. Chem. Int. Ed.* **2002**, 41, 335–338. (b) Amat, M.; Cantó, M.; Escolano, C.; Molins, E.; Espinosa, E.; Bosch, J. *J. Org. Chem.* **2002***, 67*, 5343–5351. (c) Amat, M.; Bassas, O.; Pericàs, M.; Pastó, M.; Bosch, J. *Chem. Comm*. **2005**, 1327–1329. (d) For a review, see: Pellissier, H. *Tetrahedron* **2003***, 59*, 8291–8327.



Scheme 2.6 Dynamic kinetic resolution.

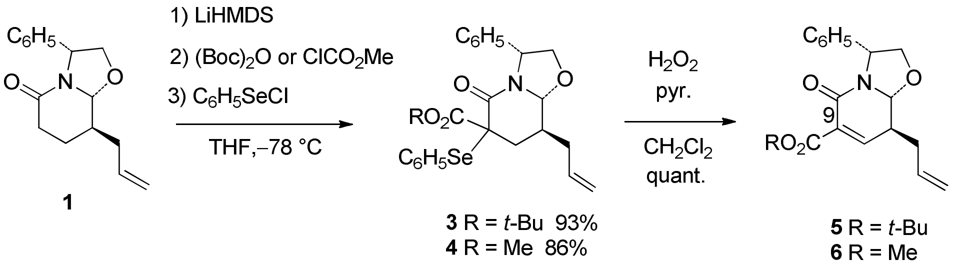
The highly stereoselective process reported herein allowed not only the successful assembly of the piperidine ring B but also the generation of the first stereocenter at C-5 position of the alkaloid. This strategy has proven to be an efficient method to synthesize our starting chiral building block for the enantioselective synthesis of madangamines alkaloids as it can be generated in high quantity and excellent yields.

2.3.2. Generation of the C-12 Stereocenter: Stereoselective Conjugate Addition

With lactam **1** in hand we decided to pursue our synthetic route toward the synthesis of the BC azabicyclic heart of madangamine using, as a key reaction, a highly stereoselective conjugated addition of an organocuprate to the unsaturated lactams **5** and **6**. This strategy can be applied to accomplish the preparation of the required diallyl compound, bearing the appropriate B/C *cis* ring junction, which represents a useful platform for the enantioselective construction of the enantiopure *cis*-isoquinolinic framework (see Scheme 2.8).

Since α,β-unsaturated lactams are poor Michael acceptors, has been necessary the introduction of an activating electron-withdrawing group[54] at the C-9 position in order to improve the reactivity of these compounds towards the addition of organocuprates.[55] In this work we selected the easily removable *tert*-butoxycarbonyl (Boc) group, since can be easily removed under nonreductive conditions without affecting the carbon–carbon double bonds, and the methoxycarbonyl group as activating electron-withdrawing groups.

Thus, the activated allyl unsaturated compounds **5** and **6** were prepared from lactam **1** by a sequential treatment with 2.2 equivalents of LiHMDS, di-*tert*-buty carbonate or the appropriate chloroformate and phenylselenyl chloride. The resulting mixture of selenides epimers **3** and **4** were then oxidized with H_2O_2 in presence of pyridine affording compounds **5** and **6**. These unsaturated lactams are unstable and very sensitive to both mild acid and basic conditions which would provoke the formation of 2-pyridones. For this reason they have to use in the next reaction immediately without further purification.



Scheme 2.7 Preparation of unsaturated lactams.

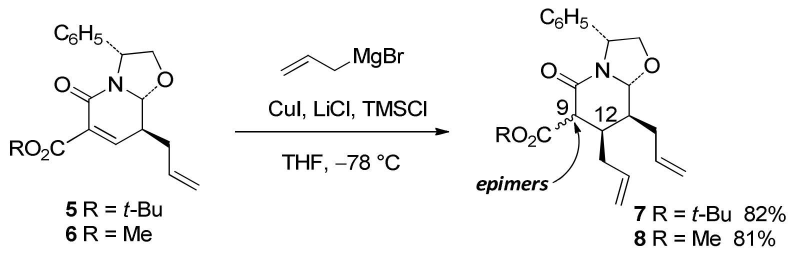
The conjugate addition of an allyl group to the α,β unsaturated lactams **5** and **6** was satisfactorily accomplished, with allylmagnesium bromide in the presence of CuI, LiCl, and TMSCl, in excellent chemical yields and high *exo*-facial diastereoselectivities,[56] leading to *cis*-diallyl lactams **7** and **8** as mixtures of epimers at the isomerizable C-9 stereocenter.

---

[54] (a) Nagashima, H.; Ozaki, N; Washiyama, M.; Itoh, K. *Tetrahedron Lett.* **1985***, 26*, 657–660. (b) Hagen, T. J. *Synlett* **1990**, 63–66.

[55] (a) Overman, L. E.; Robichaud, A. J. *J. Am. Chem. Soc.* **1989***, 111*, 300–308. (b) Herdeis, C.; Kaschinski, C.; Karla, R.; Lotter, H. *Tetrahedron: Asymmetry* **1996***, 7*, 867–884. (c) Muller, M.; Schoenfelder, A.; Didier, B.; Mann, A.; Wermuth, C.-G. *Chem. Commun.* **1999**, 683–684. (d) Lerchner, A.; Carreira, E. M. *J. Am. Chem. Soc.* **2002***, 124*, 14826–14827. (e) Hanessian, S.; van Otterlo, W. A. L.; Nilsson, I.; Bauer, U. *Tetrahedron Lett.* **2002***, 43*, 1995–1998. (f) Cossy, J.; Mirguet, O.; Gomez Pardo, D.; Desmurs, J.-R. *New J. Chem.* **2003***, 27,* 475–482. (g) Pineschi, M.; Del Moro, F.; Gini, F.; Minnaard, A. J.; Feringa, B. L. *Chem. Commun.* **2004**, 1244–1245. (h) Deiters, A.; Pettersson, M.; Martin, S. F. *J. Org. Chem.* **2006***, 71*, 6547–6561.

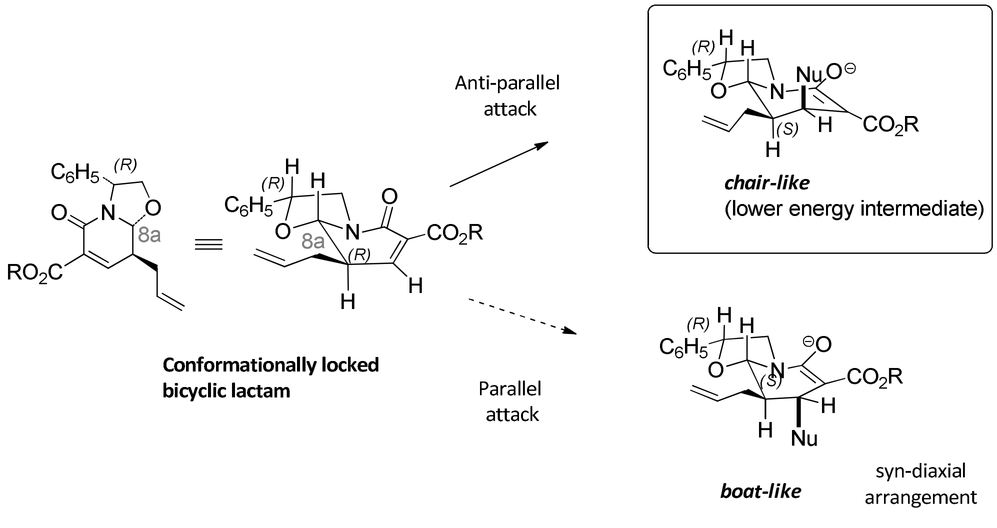
For the stereochemical outcome of the conjugate addition of organocuprates to phenylglycinol-derived lactams, see: Amat, M.; Pérez, M.; Bosch, J. *Chem. Eur. J.* **2011**, *17*, 7724–7732.and references therein.


C$_6$H$_5$
O
N
O
RO$_2$C
MgBr
CuI, LiCl, TMSCl
THF, −78 °C
9
12
epimers
5 R = *t*-Bu
6 R = Me
7 R = *t*-Bu 82%
8 R = Me 81%

Scheme 2.8 Stereoselective conjugate addition.

The stereoselectivity in the attack of organocuprates to the unsaturated lactams can be rationalized by considering that these compounds possess a lock structure, as a result of the presence of an amide bond in a bicyclic system, and the conformation of the six-membered ring is determined by the configuration of the angular position of C-8a. As a consequence, they adopt the pseudochair conformations described in Scheme 2.9, which implies the pseudoequatorial disposition of the allyl substituent.

The nucleophilic attack occurs under stereoelectronic control, axial to the conjugated double bond, preferentially via a chair-like transition state generating the *cis* isomer, kinetically more favored than the *trans* one that would be obtained through a boat-like transition state.[57]


Anti-parallel attack
(R)
H
H
C$_6$H$_5$
O
N
Nu
O$^{\ominus}$
(S)
H
CO$_2$R
H
chair-like
(lower energy intermediate)
C$_6$H$_5$
(R)
O
N
O
8a
RO$_2$C
≡
(R)
H
H
C$_6$H$_5$
O
8a
N
O
CO$_2$R
(R)
H
H
Conformationally locked bicyclic lactam
Parallel attack
(R)
H
H
C$_6$H$_5$
O
N
$^{\ominus}$O
(S)
CO$_2$R
H
H
Nu
boat-like
syn-diaxial arrangement

Scheme 2.9 Stereoelectronic control in conjugate addition.

---

[57] (a) Deslongchamps, P. *Stereoelectronic Effects in Organic Chemistry*; Pergamon Press: Oxford, 1983, p. 221. (b) Perlmutter, P. *Conjugate Addition Reactions in Organic Synthesis*; Pergamon Press: Oxford, 1992, p. 25.

As described earlier, the *cis*-diallyl lactam **7** and **8** were isolated as mixture of epimers at the isomerizable stereocenter C-9 adjacent to both carbonyl groups, but with a complete stereoselectivity in the formation of the new bond. Nevertheless, this result was thought to be inconsequential from the synthetic standpoint, since in the next step, we hoped to remove the activating *tert*-butoxycarbonyl moiety present in **7** or, alternatively, to generate an enolate for the alkylation step in the route that involves the methoxycarbonyl derivative (**8**). The conjugate addition, thus, provides a practical and efficient access to an important compound, direct precursor of the BC ring system, and permits the installation of the second contiguous stereocenter at the C-12 position of madangamines.

2.3.3. First Generation Synthesis of BC bicyclic Heart of Madangamines

Cis-diallyl lactams **7** and **8** seem to be the perfect candidates to allow the entry to the substituted tricyclic lactam **X**, which represents an easy access to BC azabicyclic system of madangamines. Furthermore, as discussed in Section 2.2, we have already developed a general synthetic route which would permit, starting from conjugated adducts **7** and **8**, to reach the construction of a variety of enantiopure tricyclic lactams bearing the crucial quaternary stereocenter at C-9 position in only few synthetic steps and excellent chemical yields.

Unfortunately, at this point, we had to face the main limitation of our original synthetic plan; in fact removal of the chiral inductor from our tricyclic compound resulted in a poor yields or degradation of the starting material under the classical triethylsilane-$TiCl_4$ conditions.

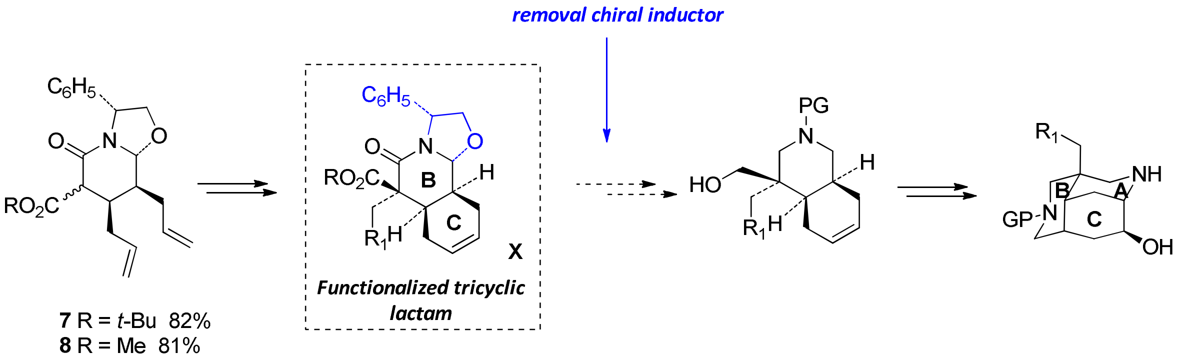


Figure 2.3 Limitation reaction of the original plan.

After a careful analysis, validated by many experimental procedures, we found that the responsible of this restriction was the presence of the electron withdrawing ester moiety at C-9 position of the lactam which prevents the oxazolidine opening reaction, needed to cleavage the chiral inductor.[58] On the other hand its presence is fundamental for the activation of the unsaturated lactams toward the stereoselective conjugate addition. Keeping in mind this limitation we were obliged to extend our synthetic path to permit to reach our synthetic target.

The adapted route involved the use of compound **5**, holding a *tert*-butyl carbonyl ester, which act as activating electron withdrawing substituent and could be easy removed under mild conditions. The cleavage of the chiral inductor in these substrates, lacking of substituents, proceeded smoothly in a two steps sequence which involved the reductive opening oxazolidine reaction followed by *N*-debenzylation of the resulting amido compound.

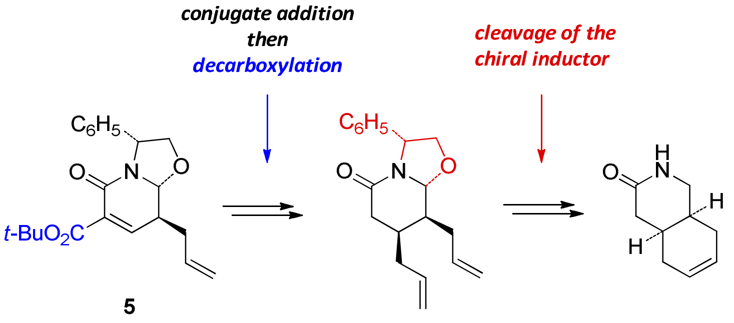

conjugate addition
then
decarboxylation
cleavage of the
chiral inductor
C6H5
O
N
O
t-BuO2C
5
H
N
H
H

Figure 2.4 Adapted synthetic route.

This modified synthetic approach permitted the generation of the enantiopure *cis*-isoquinolic scaffold which required the subsequent installation of the functionalizations to form the quaternary stereocenter at C-9 position. Finally the construction of the substituted BC ring system of madangamine was accomplished by reductions of the both amide and ester moieties.

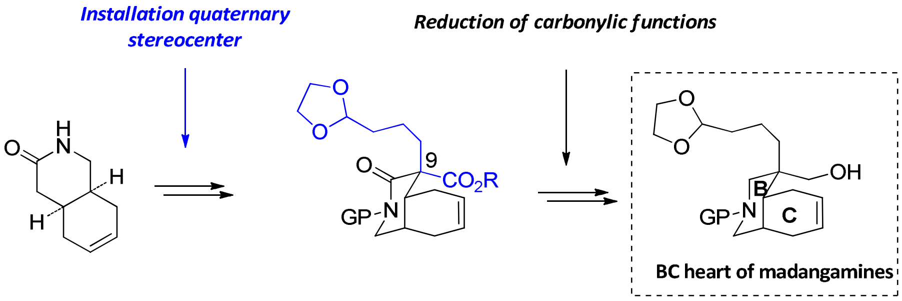

Installation quaternary
stereocenter
Reduction of carbonylic functions
O
9
CO2R
GP-N
OH
B
C
BC heart of madangamines

Figure 2.5 Synthesis of BC heart of madangamines.

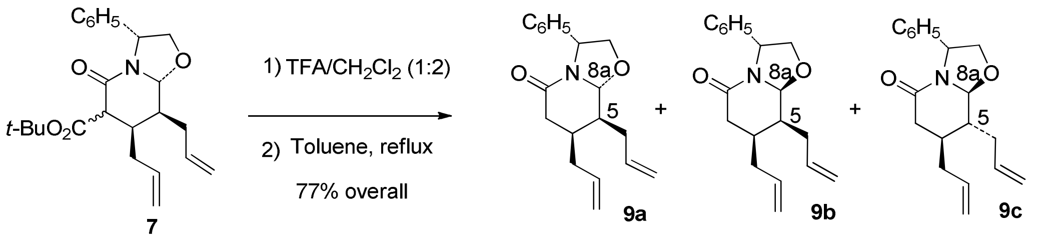
---

[58] Annamaria Tania Minaglia Ph.D thesis, University of Barcelona, 2008.

2.3.3.1 Synthesis of Cis-hexahydroisoquinolone Scaffold

The synthesis of the enantiopure isoquinolinic BC ring system started with the removal the *tert*-butyl carbonyl ester from epimeric compounds **7**, which worked as activating group in the stereoselective conjugate addition. Therefore dienes **7** were treated with a 2:1 mixture solution of DCM/TFA providing the corresponding carboxylic acids. The resulting mixture was finally heat to reflux in toluene to perform the decarboxylation which permitted the access to the enantiopure desired *cis* di-allylic compounds **9**.

It is worth to mention that in most cases the strong acidic reaction conditions provoked the isomerization of the C-8a and C-5 sterecenters affording a mixture of two *cis*-isomers **9a** and **9b**, epimers in the C-8a position, togheter with the undesired more stable *trans*-isomer **9c** which result useless in our syntesis (approximate ratio 2:2:1).

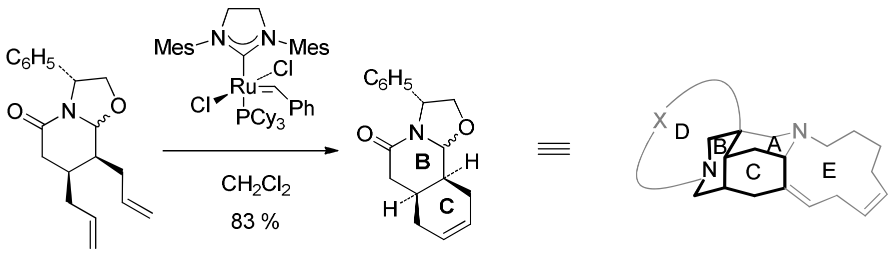


Scheme 2.10 Removal of alkoxycarbonyl moiety.

The *cis*-dienes **9a** and **9b** were finally subjected to a ring-closing metathesis reaction with the 2nd generation Grubbs catalyst which allowed the formation of the unsaturated six-membered C ring[59] and consequentially the synthesis **10** which form the *cis*-isoquinolinic BC system of madangamines.

---

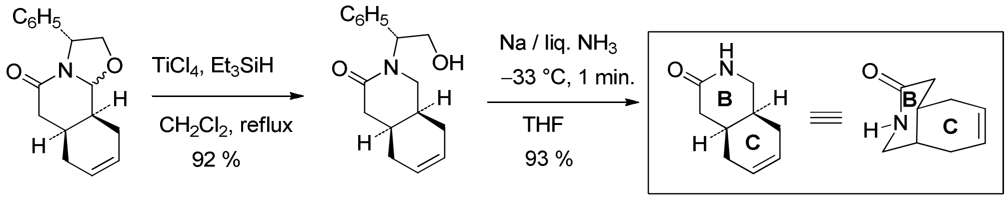
[59] For reviews of the alkene-metathesis reaction, see: (a) Grubbs, R. H.; Chang, S. *Tetrahedron* **1998***, 54*, 4413–4450. (b) Fürstner, A. *Angew. Chem.* **2000***, 112*, 3140–3172; *Angew. Chem. Int. Ed.* **2000,** *39*, 3012–3043. (c) Schmidt, B.; Hermanns, J. *Top. Organomet. Chem.* **2004**, *13*, 223–267. (d) Connon, S. J.; Blechert, S. *Top. Organomet. Chem.* **2004***, 11*, 93–124. For a review of olefin and enyne metathesis, see: Prunet, J.; Grimauld, L. *Comprehensive Organic Functional Group Transformations* II; Katritzky, A. R.; Taylor, R. J. K., Eds.; Elsevier: Oxford, 2005, Vol. 1, pp. 669–722.



9a, 9b **10**

Scheme 2.11 Construction of C ring.

With tricyclic lactam **10** in hand the next issue was represented by the removal of the chiral inductor. Conversion of tricyclic lactam **10** into the desired bicyclic piperidine derivative **12** was accomplished removing the phenylethanol moiety of the chiral inductor by classical reductive opening reductive cleavage of the C8a-O and C-N bonds of the oxazolidine ring. The process was divided in two synthetic steps and the formation of lactam **12** was carried out treating compound **10** with triethylsilane and $TiCl_4$ followed by removal of the benzylic substituent from compound **11** with sodium in liquid ammonia. The outcome of the process demonstrates the efficiency of this methodology in C-9 unsubstituted lactams.



10 **11** **12**

Scheme 2.12 Removal of phenylethanol moiety.

The reaction proceeded with excellent yield affording the desired bicyclic system **12** bearing the endocyclic double bond required for assembly the ABC system of madangamines.

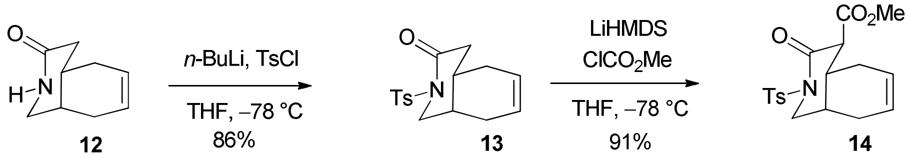
Unfortunately one of the limitations of this process was represented by the difficulty to scale up the debenzylation step. Indeed the reaction works, in an almost quantitative yield, when a maximum of 300 mg of starting material **11** was used while, an increase of quantity coincide unequivocally with a dramatic decrease of the yield due to the formation of complex byproducts.

It is easy to understand that the impossibility to scale this crucial reaction, at this early stage of the synthesis, represents an important drawback of our synthetic strategy.

2.3.4. Generation of the Quaternary C-9 Stereocenter

Once assembled the *cis*-hydroisoquinolone compound **12** the subsequent challenging was represented by the construction of the advanced BC heart of madangamine bearing the crucial quaternary stereocenter at C-9 position.

The functionalization of the BC ring system started with the protection of the bicyclic compound **12** as *N*-tosyl derivate **13** and the re-installation of an ester moiety at the C-9 position which afforded compound **14**. This group acts as a precursor of the desired aminomethyl chain and permits the subsequent alkylation reaction, enhancing the acidity of the proton α-to the carbonyl group.



Scheme 2.13 Functionalization of BC system.

With compound **14** in hand we had to choose an alkylating agent which had to bear an appropriate functionality that could allow, in a later stage, the construction of the macrocyclic D ring of madangamine. Considering that the presence of a double bond is incompatible with our synthetic plan, which involves an aminohydroxylation reaction which proceeds *via* epoxidation of the ciclohexene ring, a suitable chain bearing an acetal function at the terminal position was installed. The easy hydrolysis of the dioxolane moiety affords an aldehyde that would allow access of a wide range of unsaturated compounds including: terminal olefins, *Z*-iodoalkenes or acetylenes. The resulting C-9 functionalized diazatricyclic compounds would represent the ideal platform to perform different type of macrocyclization reactions, some of them discussed in Chapter 3.

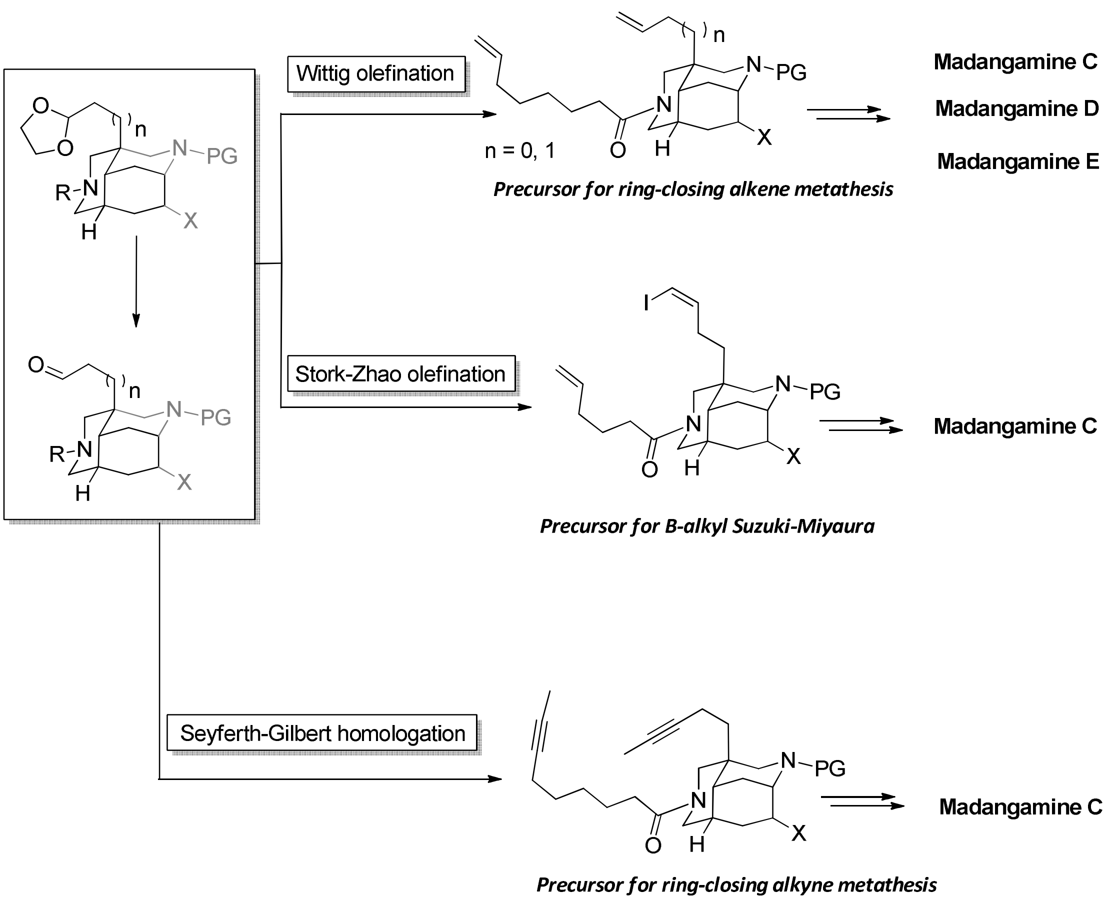
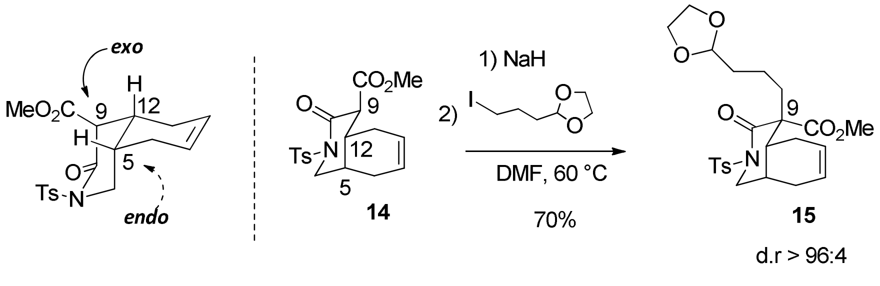

Wittig olefination
n = 0, 1
Precursor for ring-closing alkene metathesis
Madangamine C
Madangamine D
Madangamine E
Stork-Zhao olefination
Precursor for B-alkyl Suzuki-Miyaura
Madangamine C
Seyferth-Gilbert homologation
Precursor for ring-closing alkyne metathesis
Madangamine C
N-PG
R-N
X
H
PG

Figure 2.6 D rings annulation strategies.

The quaternary C-9 stereocenter of madangamines was installed using NaH as base and 3-(3-iodopropyl)-1,3-dioxolane as alkylating agent. The reaction proceeded from compound **14** with an excellent facial stereoselectivity due to the compact convex geometry of the bicyclic system that allowed that the alkylation took place preferentially at the most accessible *exo* face. This strategy permitted the installation of the quaternary stereocenter at C-9 position and compound **15** was generated with an excellent, but not complete, diastereselectivity.


exo
endo
MeO_2C
Ts-N
9
12
5
CO_2Me
14
1) NaH
2)
DMF, 60 °C
70%
15
d.r > 96:4

Scheme 2.14 Stereoselective alkylation.

The achievement of our first goal, represented by the construction of the functionalized BC azabicyclic system of madangamines, would be reached simply treating compound **15** with $LiAlH_4$ which would provoke the reduction of both carbonyl functions leading directly to compound **18**. Unfortunately, as already described in Section 2.2, the electron withdrawing nature of the *N*-tosyl protecting group would induce the opening reaction of the lactam ring B ring affording diol **XIV**.[60]

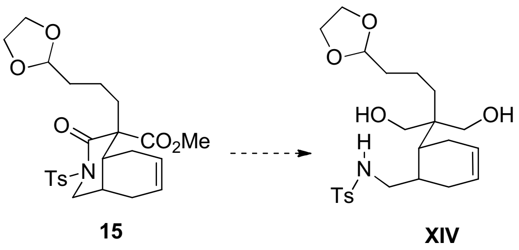
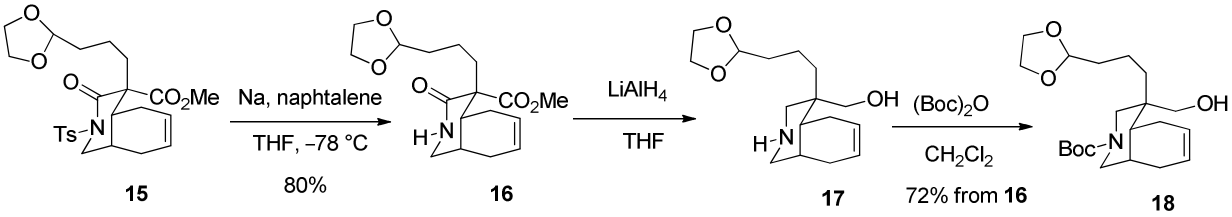


Figure 2.7 A ring opening reaction.

These observations led us to overcome this drawback extending the synthetic sequence with a three steps procedure in which the reduction reaction was performed into *N*-unprotected amide **16.** Thus, after the deprotection of the *N*-sulfonamide **15** with a sodium naphtalenide solution both carbonylic functions were reduced with $LiAlH_4$. The resulting desired aminoalcohol **17** was finally converted to the *N*-Boc derivative **18** with excellent yields.



Scheme 2.15 Synthesis of BC core of madangamine.

The route described herein allows the access to the enantiopure azabicyclic compound **18** holding the three contiguous stereocenters, including the quaternary one, and with the correct functionalizations needed to perform the closure of the A ring and the formation of macrocylic D ring of madangamines.

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[60] (a) Hosaka, T.; Torisawa, Y.; Nakagawa, M. *Tetrahedron Lett.* **1997**, *38*, 3535–3538.

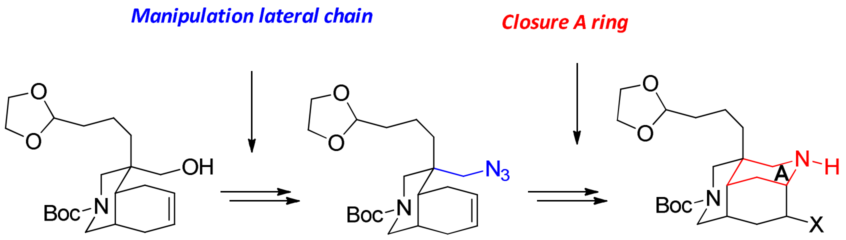
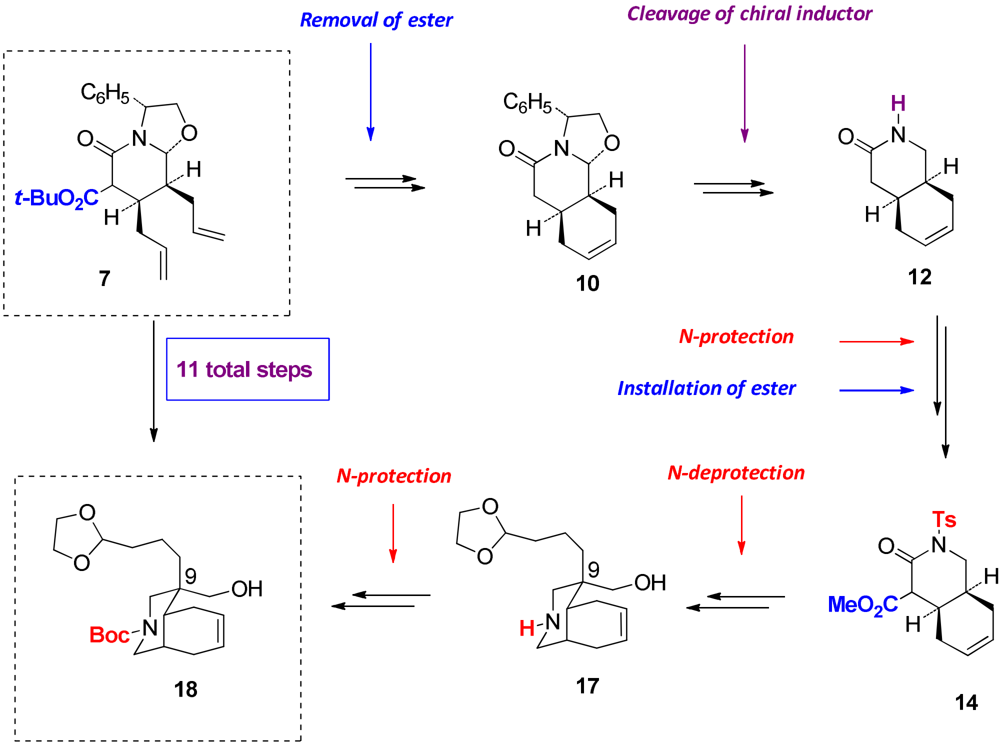

Manipulation lateral chain
Closure A ring
O
O
OH
Boc
N
O
O
N3
Boc
N
O
O
N
H
A
Boc
N
X

Figure 2.8 Synthetic plan toward the tricyclic core.

2.4. AN ALTERNATIVE ROUTE TO THE BC SYSTEM

Even if the synthetic strategy reported above permitted to reach the construction of the BC heart of madangamines, we were obliged to pay an expensive price, from a synthetic point view.

In fact, starting from the elaborated diallyl compound **7**, a total of eleven steps were needed to achieve the synthesis of the bicyclic compound **18**. Analyzing the Scheme 2.16 it is possible to notice that, practically a half of the synthetic steps of this sequence, are redundant and include the installation/cleavage and re-installation of the ester function at the C-9 position and the change of two different nitrogen protecting groups to finally generate the aminoalcohol **18**.


Removal of ester
Cleavage of chiral inductor
C6H5
O
N
O
H
t-BuO2C
H
7
C6H5
O
N
O
H
H
10
H
N
O
H
H
12
11 total steps
N-protection
Installation of ester
N-protection
N-deprotection
O
O
9
OH
Boc
N
18
O
O
9
OH
H
N
17
Ts
N
O
MeO2C
H
H
14

Scheme 2.16 Synthesis of BC system.

Furthermore there are another two observations which are worth to remember:

- Part of the precious starting material is lost during the removal of the activating ester moiety, due the acid-promoted epimerization of the C-5 position.
- The impossibility to scale (over 300 mg) the debenzylation reaction difficulty the production of starting material in a very early stage of the synthesis (see Section 2.3).

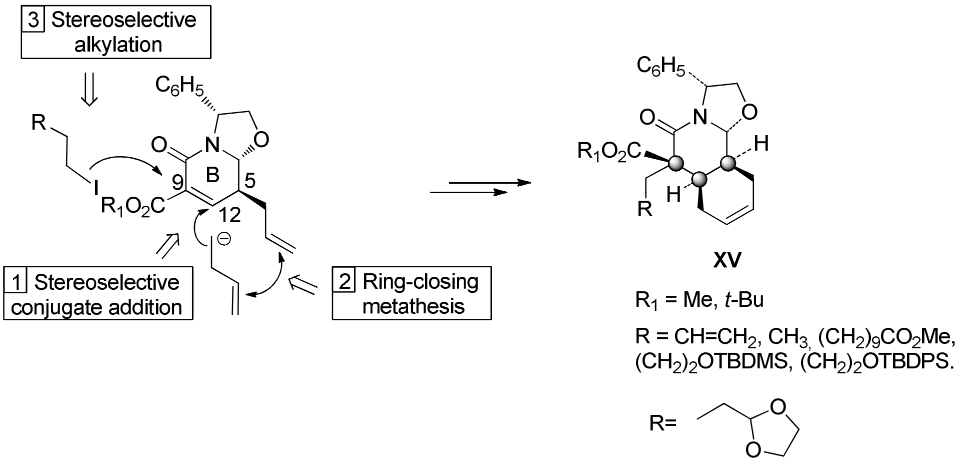
As we mentioned in Section 2.2 the synthetic approach presented until now is a modification of an “original plan” which was designed to overcome the phenyl ethanol removal troubles, attributed to the interfering presence of the methoxycarbonyl function at the C-9 position. The synthetic consequences caused by this single failure were severe and the synthetic tricks necessary to reach our goal complicated the whole process.

Considering that we are still in an early stage of the process and we need to dispose of enough quantity of starting material to achieve the synthesis of the diazatricyclic system and the subsequent annulation of the macrocyclcic rings we decided to tackle our synthetic problems.

2.4.1. Formulation of the Alternative Strategy

We always have been conscious of the existence of two different ways to avoid this unwanted pathway and consequentially reduce significantly the numbers of synthetic steps. Both processes would start with the synthesis of tricyclic lactam **XV** which already incorporates all the above key features, including the methoxycarbonyl function that dually enhances the reactivity of the double bond towards the conjugate addition, and simultaneously acts as a masked aminomethyl moiety, required to construct the piperidine ring A.

Tricyclic system **XV** can be prepared with (1) a stereoselective conjugate addition followed by (2) a ring-closing metathesis, whereas the crucial quaternary stereocenter at C-9 would be installed by (3) a stereoselective alkylation reaction. As mention before in a previous work the synthesis of some alkylated compounds constructed with this three step sequence was studied.


3 Stereoselective alkylation
R
I
C_6H_5
O
N
O
9
B
5
R_1O_2C
12
⊖
1 Stereoselective conjugate addition
2 Ring-closing metathesis
C_6H_5
O
N
O
H
R_1O_2C
R
H
R=
O
O

XV

R_1 = Me, *t*-Bu

R = $CH{=}CH_2$, CH_3, $(CH_2)_9CO_2Me$, $(CH_2)_2OTBDMS$, $(CH_2)_2OTBDPS$.

Figure 2.9 Preparation of functionalized tricyclic lactam.

With these arguments in mind we thought it was worth stopping our journey toward the synthesis of madangamine, come back to our original synthetic plan and concentrate our efforts to achieve the construction of the azabicyclic compound **18** starting from the fully substituted tricyclic lactam **XV** since this process would allow to reach the goal, halving the synthetic sequence with the consequent big save in terms of time and synthetic steps.

To this end, we plan to explore a methodology for the removal of the phenylethanol moiety from the amino alcohol resulting from the $LiAlH_4$-reduction of **XV** while, in an alternative route, we will study the problematic C-O oxazolidine opening reaction from tricyclic lactam **XV**.

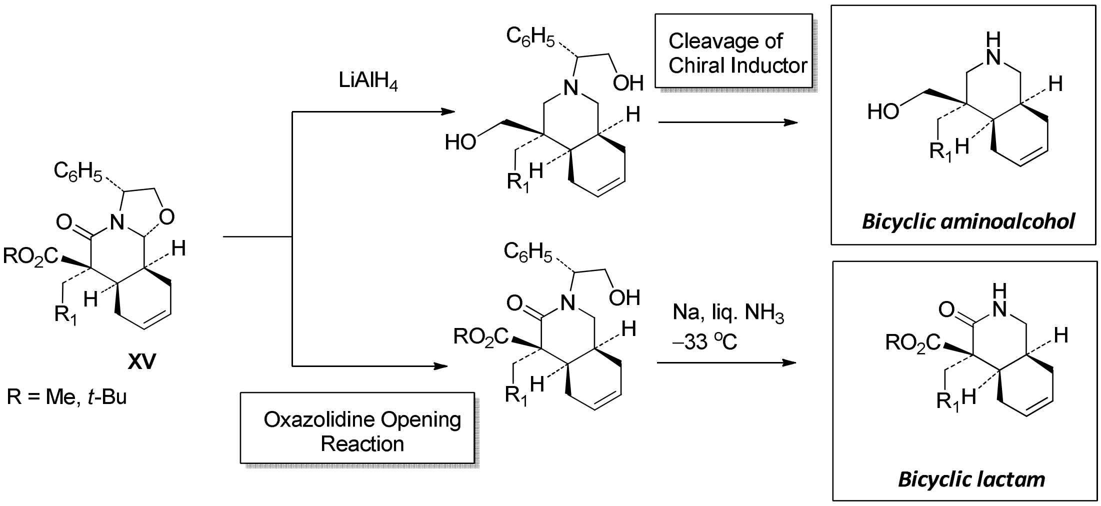
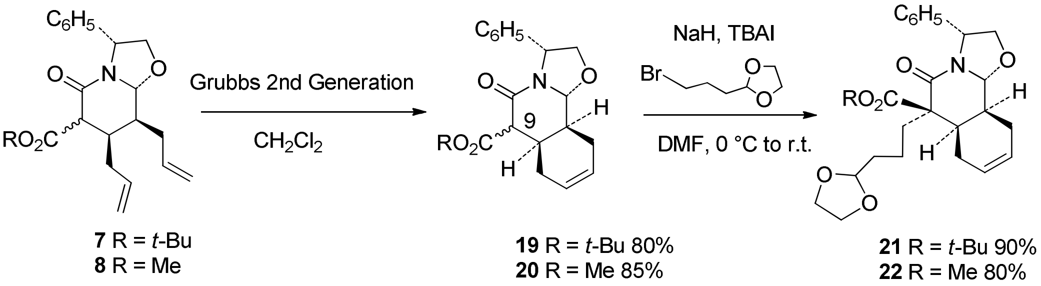

C_6H_5
O
N
O
RO_2C
H
R_1
H
XV
R = Me, *t*-Bu
$LiAlH_4$
C_6H_5
N
OH
H
HO
R_1
H
Cleavage of Chiral Inductor
H
N
H
HO
R_1H
Bicyclic aminoalcohol
C_6H_5
O
N
OH
RO_2C
H
R_1
H
Oxazolidine Opening Reaction
Na, liq. NH_3
−33 °C
H
O
N
RO_2C
H
R_1H
Bicyclic lactam

Figure 2.10 Different strategies for the cleavage of the chiral inductor

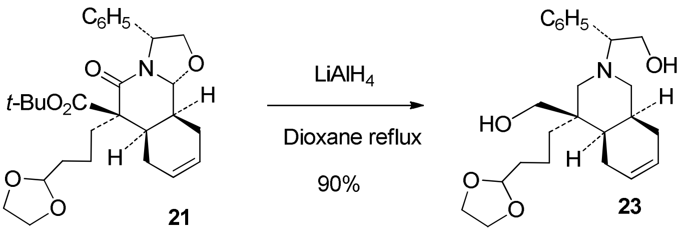
The synthesis of the functionalized tricyclic compounds started with the ring-closing metathesis of the diallyl compounds **7** and **8** which were converted to the tricyclic lactams **19** and **20** using a 2nd generation Grubbs catalyst in dichloromethane. In this case, the alcoxycarbonyl group present in the C-9 position not only increase the acidity of the C=O α position, permitting the subsequent alkylation reaction, but acts as a precursor of the aminomethyl chain required for the synthesis of A ring of the ABC diazatricyclic core of madangamine. Then, the crucial quaternary C-9 stereocenter of madangamines was generated with complete facial selectivity and excellent chemical yields by alkylation of the epimeric mixture of **19** and **20** to give the lactams **21** and **22** as single isomers. The compactly architecture of the starting tricyclic compound clearly forced alkylation to occur from the more accessible *exo*-face.


C6H5
O
N
O
RO2C
Grubbs 2nd Generation
CH2Cl2
9
H
NaH, TBAI
Br
DMF, 0 °C to r.t.
RO2C
7 R = t-Bu
8 R = Me
19 R = t-Bu 80%
20 R = Me 85%
21 R = t-Bu 90%
22 R = Me 80%

Scheme 2.17 Synthesis of tricyclic lactam **21** and **22**.

2.4.2. Cleavage of Phenylethanol Moiety from Amine Derivatives

$LiAlH_4$ reduction of the alkylated compound **21** caused the cleavage of the C-O bond of the oxazolidine ring and the simultaneous reduction of the ester and amide carbonyl groups to give the respective alcohol **23** in excellent yield.

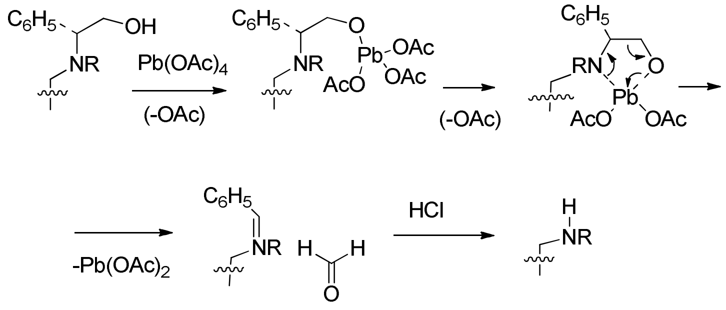

C6H5
O
N
t-BuO2C
H
21
LiAlH4
Dioxane reflux
90%
OH
HO
23

Scheme 2.18 Reduction of tricyclic lactam.

Since the removal of the chiral inductor using a catalytic hydrogenation is incompatible due to the presence of the endocyclic double bond in the C ring, needful to generate the piperidine A ring in a later stage, we decided, as first attempt, to cleavage the phenyl ethanol moiety applying the typical *N*-dealkyl or *N*-debenzylation reactions normally used in tertiary amines.

2.4.2.1. Oxidative Ceavage with Lead Tetraacetate and CAN

We assume that the first reagent had to be tested on our compound was lead tetraacetate since has been successfully used in transformations of 1,2-aminoalcohols to the corresponding amines. The methodology appeared promising and its ability and selectivity in the removal of phenylethanol moieties from both secondary and tertiary amines, has been largely demonstrated in several papers[61].The reaction would involve the oxidative cleavage of the aminoalcohol while an acidic hydrolysis of the resulting imine would afford the corresponding secondary amine.

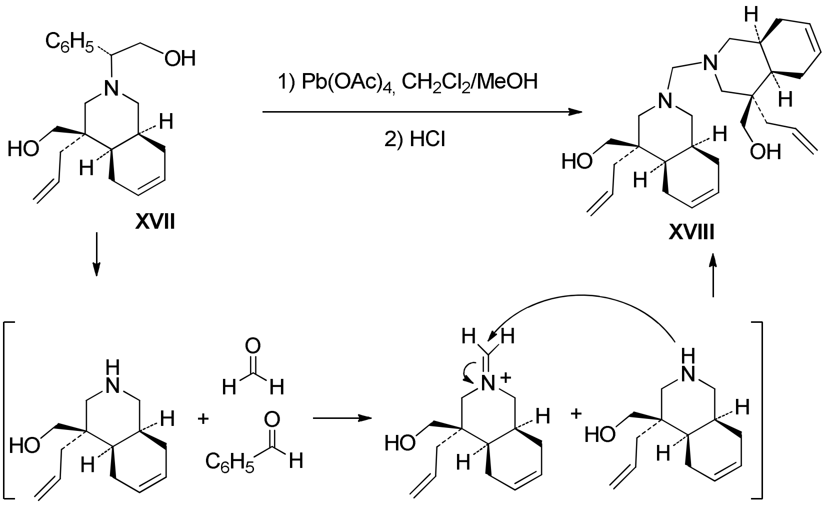


Scheme 2.19 Mechanism of reaction.

In order to test its efficacy we treat aminoalcohol **XVII** with lead tetraacetate in a 2:1 solution of dichloromethane and methanol at low temperature. Unfortunately the use of this procedure resulted unsuccessful and, despite the use of a several different experimental protocols, the expected secondary amine was obtained with poor yield. The only significant result was represented by the aisolation of a small quantity of dimeric compound **XVIII**, formed as a resulting of a side reaction of the secondary amine with the formaldehyde generated during the process.

---

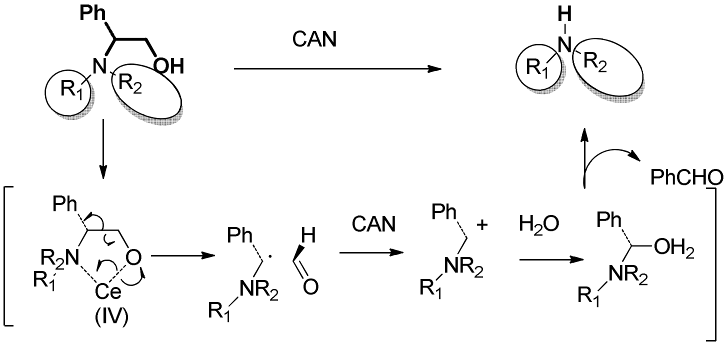
[61] (a) Poerwono, H.; Higashiyama, K.; Yamauchi, T.; Takahashi, H. *Heterocycle* **1997**, *46*, 385–400. (b) Chakraborty, T. K.; Reddy, G. V. *J.Org. Chem.* **1992**, *57*, 5462–5469. (c) Williams, R. M.; Zhai, W.; Aldous, D. J.; Aldous, S. C. *J. Org. Chem.* **1992**, *57*, 6527–6532. (d) Mokhallalati, K.; Pridgen, L. N. *Synth. Commun* **1993**, *14*, 2055–2064. (e) Higashiyama, K.; Inoue, T.; Yamacuchi, T.; Takahashi, H. *J. Chem. Soc. Perkin Trans*. 1 **1995**, 111–115. (f) Mokhallalati, K.; Wu M. J.; Pridgen, L. N. *Tetrahedron Lett.* **1993**, .*34*, 47–50. (g) Wu M. J.; Pridgen, L. N. *J.Org. Chem.* **1991**, *56*, 1340–1344.



Scheme 2.20 Formation of dimer.

In view of these disappointing results we moved our attention to CAN (cerium ammonium nitrate) which represents another oxidative reagent with similar characteristics.[62] Furthermore the reaction conditions, which are normally used, are very mild and mostly functional groups remain unaffected during the reaction.

The mechanism, shown in Scheme 2.21, would suggest that the reaction between the alcohol unit of the chiral inductor and CAN would produce a radical cleavage of the C–C bond which would afford the benzyl radical species and formaldehyde. The radical has to be converted to a cation species by a one-electron transfer oxidation of one more CAN while the addition of water would form a hemiacetal, easily converted to the final compound by the removal of the benzaldehyde.



Scheme 2.21 Mechanism of reaction.

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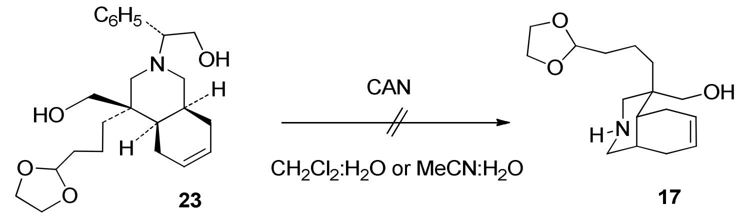
[62] (a) Bull, S. D.; Davies, S. G.; Fenton, G.; Mulvaney, A. W.; Prasad, R. S.; Smith, A. D. *J. Chem. Soc. Perkin Trans.* 1 **2000**, 3765–3774. (b) Fujioka, H.; Hirose, H.; Ohba, Y.; Murai, K.; Nakahara, K.; Kita, Y. *Tetrahedron* **2007**, *63*, 625–637. (c) Lan, H. Q.; Ye, J. L.; Wang, A. E.; Ruan, Y. P.; Huang, P. Q. *Chem. Eur.* **2011**, 17, 958–968.

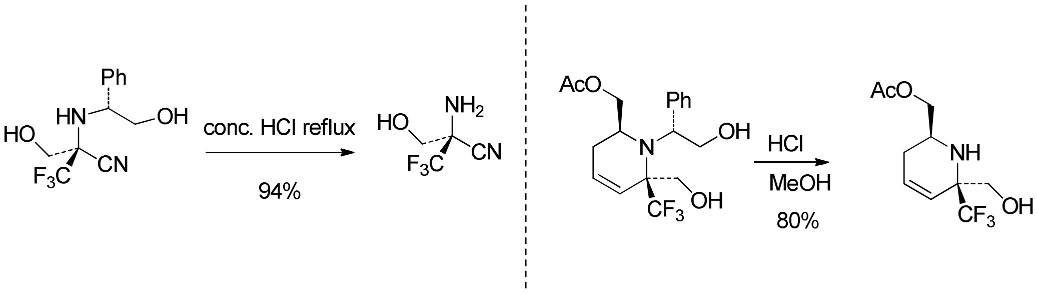
Although CAN is recognized as a good reagent for the selective deprotection hydroxyethyl units from 2-hydroxyethyl amines, no report has described its ability with cyclic amines. Indeed treatment of aminoalcohol **23** with aqueous CAN gave unsatisfactory results.



Scheme 2.22 Reaction with CAN.

2.4.2.2. Acid Mediated Elimination of the Chiral Inductor

Firmly motivated to overcome the problem and inspired by some recent few works concerning the synthesis of fluorinated amino acids[63] we decided to undertake another methodology which would involve the removal of the phenylethanol moiety simply by treatment of the corresponding tertiary amine with acid. Scheme 2.23 illustrates two examples in which a clean removal of the phenylethanol side chain was easily achieved in excellent yield by reaction of the aminoalcohols with a concentrated solution of refluxing HCl.



Scheme 2.23 Removal of chiral inductor with HCl.

Unfortunately the application of this procedure on our compound did not afford the desired secondary amine and, treatment of compound **23** with HCl under several experimental procedures, gave only mixtures of undesired byproducts. This result demonstrate that probably the outcome of the reaction is strictly dependent by the presence of the electron withdrawing trifluoromethyl group at the C-2 position that weakens the benzylic C-N bond promoting the removal of the chiral inductor.

---

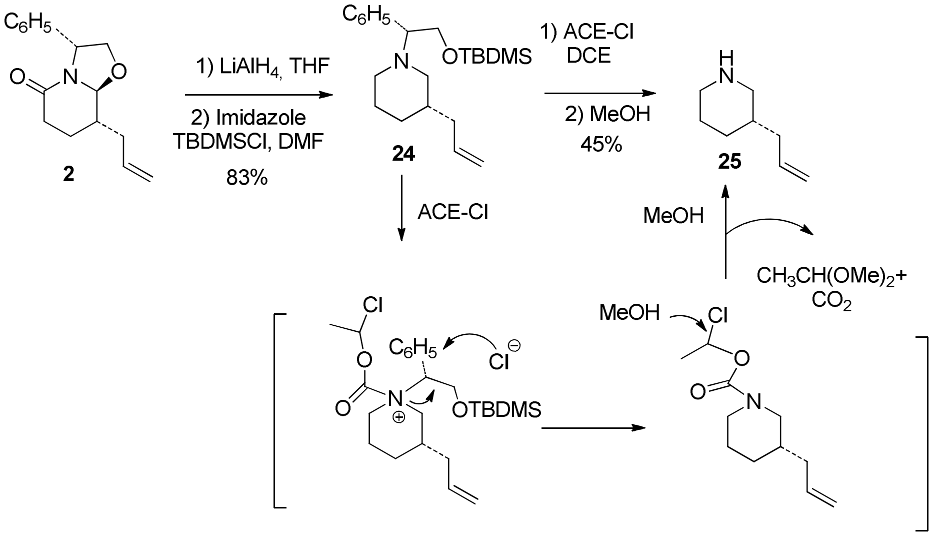
[63] Fustero, S.; Albert, L.; Mateu, N.; Chiva, G.; Miró, J.; González, J.; Aceña, J. L. *Chem. Eur. J.* **2012**, *18*, 3753–3764. (b) Simon, J.; Nguyen, T.; Chelain, E.; Lensen, N.; Pytkowicz, J.; Chaume, G.; Brigaud, T. *Tetrahedron: Assimetry* **2011**, *22*, 309 314.

2.4.2.3. .*Trans*-Acylating Reagents

We next turned our attention to another classic methodology which involves the use of *trans*-acylating reagents which have been largely used to perform the selective *N*-dealkylation of tertiary amines in high yields.[64]

The most popular reactive of this family is 1-chloroethyl chloroformate (ACE-Cl) which has proven to be effective in the removal of the phenylglycinol chiral inductor from tertiary cyclic amines.[65] The reaction proceeds via a nucleophilic attack of the chloride ion at the benzylic position, leading to the formation of the carbamate ester. This intermediate is deACEylated by evaporating the reaction mixture in vacuo and then heating the residue in MeOH (see Scheme 2.24).

Its compatibility with our compound and the easiness to be removed make ACE-Cl the perfect candidate for our cleavage studies on the piperidinic model compound **24**, generated by reduction and TBDMS protection of lactam compound **2**.[66] Subsequent treatment of compound **24** with ACE-Cl in a refluxing solution of 1,2-dichloroethane, followed by heating of the residue in MeOH, afforded allyl piperidine **25** with modest yield.



Scheme 2.24 Debenzylation reaction with ACE-Cl.

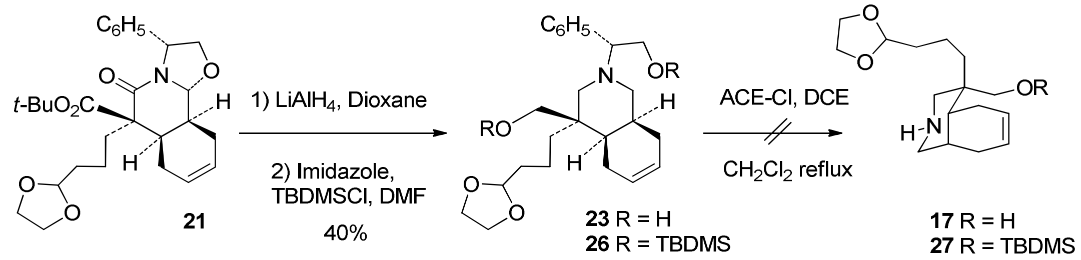
---

[64] (a) Olofson, R. A.; Abbott, D. E. *J. Org. Chem.* **1984***, 49*, 2795–2799. (b) Olofson, R. A.; Martz, J. T.; Senet, J. P.; Piteau, M.; Malfroof, T. *J. Org. Chem.* **1984***, 49*, 2081–2082. (c) Bhat, R. G.; Ghosh, Y.; Chandrasekaran, S. *Tetrahedron Lett.* **2004**, *45,* 7983–7985.

[65] (a) Ennis, M. D.; Hoffman, R. L.; Ghazal, N.B.; Old, D. W.; Mooney, P. A. *J. Org. Chem.* **1996***, 61*, 5813–5817. (b) Agami, C.; Bihan, D.; Hamon, L.; Kadouri-Puchot, C.; Lusinchi, M. *Eur. J. Org. Chem.* **1998***,* 2461–2465.

[66] Lactam 2 is the minor isomer synthesized during the cyclocondensation reaction.

The same methodology was therefore applied on our compound using both unprotected aminoalcohol **23** or TBDMS protected compound **26** but, despite our efforts, the reaction didn't take place and in all cases it was only possible to recover starting or decomposed material. Several attempts were tried to promote the reaction including: (i) the screening of various solvents (ii) the use of a proton sponge[67] or hydrogen carbonate,[68] in order to elude the protonation of the starting amine by the chloridric acid formed in the reaction, or (iii) the introduction of the iodine ion to accelerate the nucleophilic pathway[69] and avoid the formation of byproducts. Under no circumstances were possible to reproduce the results obtained on the model compound and achieve the synthesis of the desired secondary amine. The use of Troc-Cl instead of ACE-Cl gave identical results.[18]



Scheme 2.25 Reaction with ACE-Cl.

2.4.2.4. Dissolving-Metal Reductions

Once we discarded the use of oxidatives and *trans*-acylative methodologies we decided to start the exploration of dissolving-metal reductions.

Reductions of organic compounds using a "solution of electrons" in ammonia are known as dissolving-metal reductions. When alkali metals (lithium, sodium, potassium and calcium) are dissolved in liquid ammonia, metal atoms loose electrons and their solvation gives the typical blue color of the solution. The efficiency of these reactions for the selective cleavage of C-N benzylic compounds has already been proven in the removal of the chiral phenylethanol moiety from our isoquinolinic bicyclic lactam **12** (See Section 2.3).

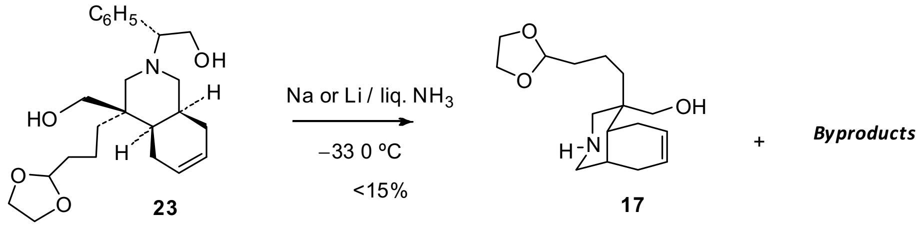
Therefore the application of the conventional procedure with sodium or lithium in liquid ammonia, on our amino alcohol compound **23,** gave the desired secondary amine **17** with poor yield (<15%) together with a complex mixture of byproducts, some of them derived from a dearomatization of the phenyl group.

---

[67] Harmann, B. C.; Hartwig, J. F. *J. Am. Chem. Soc.* **1997**, *119*, 7236–7239.

[68] Yamada, K.; Kurokawa, T.; Tokuyama, H.; Fukuyama, T. *J. Am. Chem. Soc.* **2003**, *125*, 12382–12383.

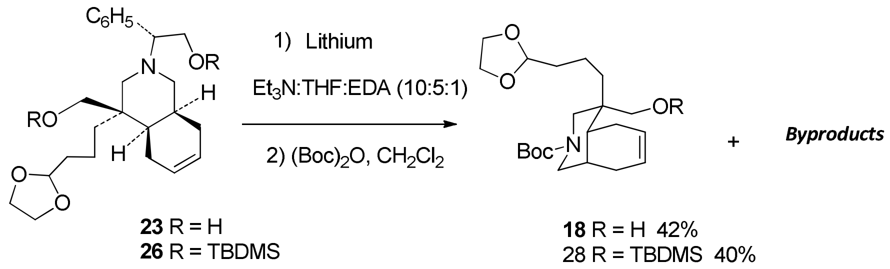
[69] Coe, J. W.; Brooks, P. R.; Vetelino, M. G.; Bashore, C. G.; Bianco, K.; Flick, A. C. *Tetrahedron Lett.* **2011**, *52*, 953–954.



Scheme 2.26 Dissolving metal methodology.

Fortunately, the application of the Benkeser protocol, described by Angle in his synthesis of palaustrine,[70] which employs lithium in a mixture of triethylamine/THF/ethylenediamine instead liquid ammonia,[71] worked. Treatment of both TBDMS and unprotected **23** and **26** compounds with lithium using the Angle conditions gave aminoalcohol **17** that was immediately converted without any purification to the *N*-Boc derivatives **18** or **28**.

Disappointingly, due to the complicated operational procedure, the reaction was sparsely reproducible and sometimes afforded a complex mixture of unwanted compounds. In order to control the course of the reaction avoiding, or at least reducing, the formation of byproducts we tried the use of different solvents, the substitution of lithium with sodium but all our efforts result unsuccessful.



Scheme 2.27 Removal of the chiral inductor with lithium.

We thought that the reason of our failures was the impossibility to dosage the exact quantity of lithium, considering that this metal is sold in wire and has to be cut with a scissor with the consequent different shape and dimensions of the resulting pieces.

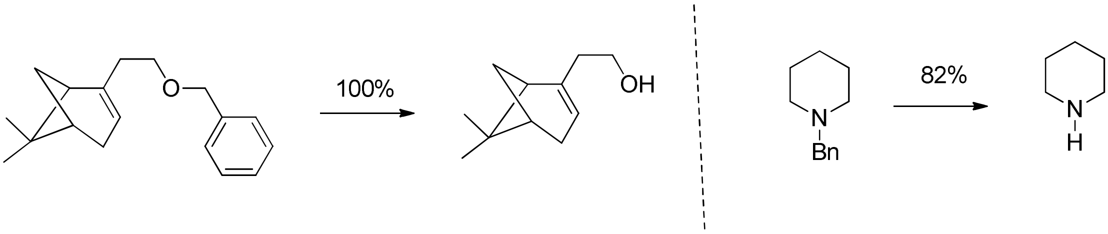
Based on these experimental observations we started again to search for solutions. SiGNa Chemistry has developed a technology for encapsulating alkali metals into nano-structured porous oxides, such as silica gel and alumina. The encapsulation facilitates the manipulation and reduces the dangers associated with the handling of alkali metals while retains its reducing power. The company has developed three categories of alkali metal nanostructured silica materials (M-SG) which differ in the reductive reactivity compared with neat alkali metals.

---

[70] (a) Angle, S. R.; Henry, R. M. *J. Org. Chem.* **1998**, *63*, 7490–7497. (b) Passarella, D.; Angoli, M.; Giardini, A.; Lesma, G.; Silvani, A.; Danieli, B. *Org. Lett.* **2002**, *4*, 2925–2928.

[71] Garst, E. M.; Dolby, J. L.; Esfandiari, S.; Fedoruk, N. A.; Chamberlain, N. C.; Avey, A. A. *J. Org. Chem.* **2000**, *65*, 7098–7104.

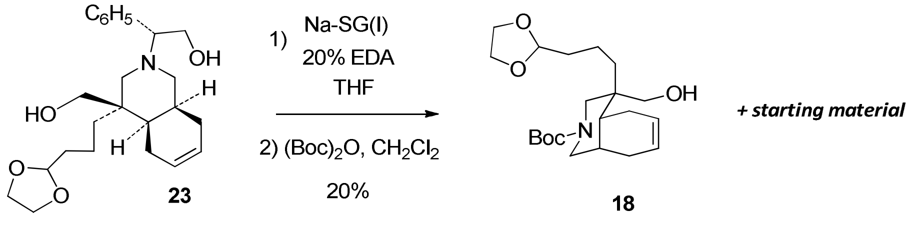
The literature described a large number of applications of the reagents in organic chemistry including cleavage of sulfonamides,[72] ester reductions, Birch reactions and debenzylations.[73] The examples shown in Scheme 2.28 were conducted in ethereal solvents, typically in THF with 2.5–5 equivalents of M-SG(I) at room temperature and demonstrate the efficacy of this class of reagents in debenzylation reactions.



Scheme 2.28 Applications of M-SG.

Even if the only reagent available in the market is formed by a mixture of sodium and potassium[74] we decided to test its ability to cleavage the C-N benzylic bond on our compound. We thought it could replace the lithium metal avoiding at the same time the typical problems related to its manipulation and, as a consequence, the formation of the by-products.

Thus, a solution of compound **23** in THF was treated with Na-SG(I) at room temperature and, after 12 hours the reaction showed the formation of the desired amino product with modest yield. Indeed the best results were observed when a sub-stoichiometric amount of ethylenediamine (EDA) was added. From compound **23** and using the reaction conditions described above, we obtained the *N*-protected amino alcohol **18** in low overall yield, which were not able to improve.



Scheme 2.29 Reaction with Na-SG(I).

---

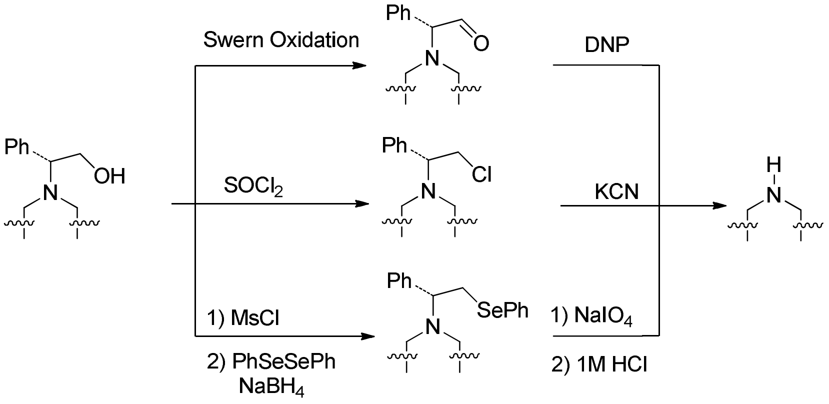
[72] Nandi, P.; Redko, M. Y.; Petersen, K.; Dye, J. L.; Lefenfeld, M.; Vogt, P. F.; Jackson, J. E. *Org. Lett.* **2008**, *10*, 5441–5444.

[73] Nandi, P.; Dye, J. L.; Jackson, J. E. *Tetrahedron Lett.* **2009**, *50*, 3864–3866.

[74] Stabilized lithium-alumina gel materials (M-AG) has been recently developed by the same company but it isn't available in the market yet.

2.4.2.5. Cleavage of Chiral Inductor by Mesylation/Elimination

It is worth mentioning others attempts of removal the phenylglycinol chiral auxiliary from amino-substrates which are reported in the literature and contemplate a two steps sequences.[75]

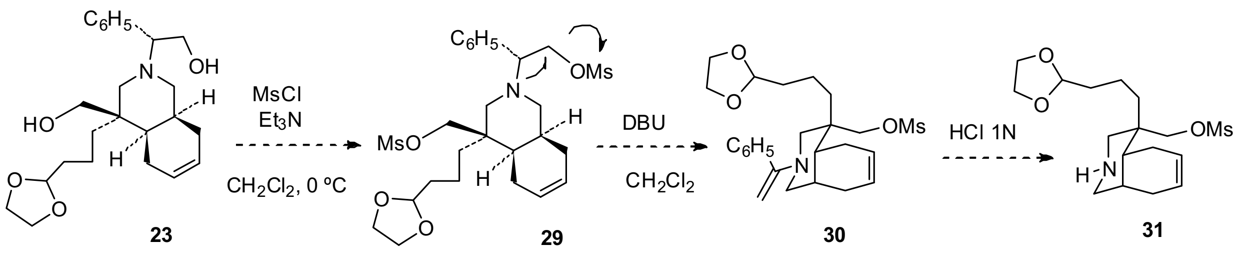


Swern Oxidation
SOCl2
1) MsCl
2) PhSeSePh NaBH4
DNP
KCN
1) NaIO4
2) 1M HCl
Ph
OH
N
O
Cl
SePh
H

Figure 2.11 Miscellaneous methodologies.

None of this methodology is viable for our purpose, due to the presence of the hydroxymethyl chain at the C-9 position of our compound **23**, which would have to be selectively reduced and protected in an early stage of the synthesis. Nevertheless we focused our attention on the formation of the mesyl and chloride intermediates of the last two entries (see Figure 2.12).

Theoretically a mesylation of both primary alcohols would lead to compound **29**, while, a subsequent elimination reaction, would take place only in the hydroxymethyl chain of the phenylethanol fragment affording **30**. In summary a two steps process would generate an enamine which can be hydrolyze with HCl leading to the free amine compound **31**: an advanced intermediate of our synthetic sequence.



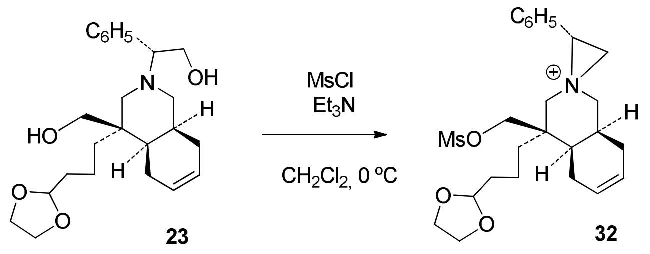
MsCl
Et3N
CH2Cl2, 0 °C
DBU
CH2Cl2
HCl 1N
C6H5
OH
HO
OMs
MsO
H
N
O
23
29
30
31

Scheme 2.30 Mesylation/elimination strategy.

---

[75] (a) Lebeuf, R.; Robert, F.; Schenk, K.; Landais, Y. Org. Lett. 2006, 8, 4755–4758. (b) Andrés, J. A.; Herráiz-Sierra, I.; Pedrosa, R.; Pérez-Encabo, A. *Eur. J. Org. Chem.* **2000**, 1719–1726. (c) Agami, C.; Couty, F.; Evano, G. *Tetrahedron: Assimetry* **2000**, *11*, 4639–4643.

Unfortunately due the nucleophilicity of our tertiary amine we were not able to obtain the double mesylated compound **29** and the reaction led only to the formation of the aziridinium ion **32** which forced us to leave this route.



Scheme 2.31 Formation of aziridinium compound.

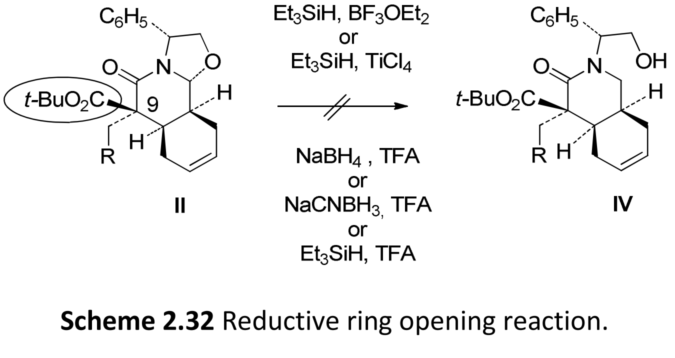
Unsatisfied of all these results, but still motivated to find a way to reduce the number of synthetic steps, we decided to change our strategy and concentrate our efforts exploring alternative methodologies to perform the cleavage of the C-O bond of the oxazolidine.

2.4.3. Removal of the Chiral Inductor from Tricyclic Lactams

2.4.3.1. C-O Bond Cleavage Studies

As already disclosed in the previous sections treatment of tricyclic lactam **II** under classical $TiCl_4$ and triethylsilane conditions did not afford the expected reduced compound **IV**.[76] In view of the difficulty to perform the chemoselective reduction of the oxazolidine C-O bond it was decided to try various combinations of reducing agents and Lewis acids.

Despite the exploration of several reaction conditions and reagents we couldn't achieve the desired compound confirming what was previously mentioned about the influence of the substituent at the C-9 position of lactam.



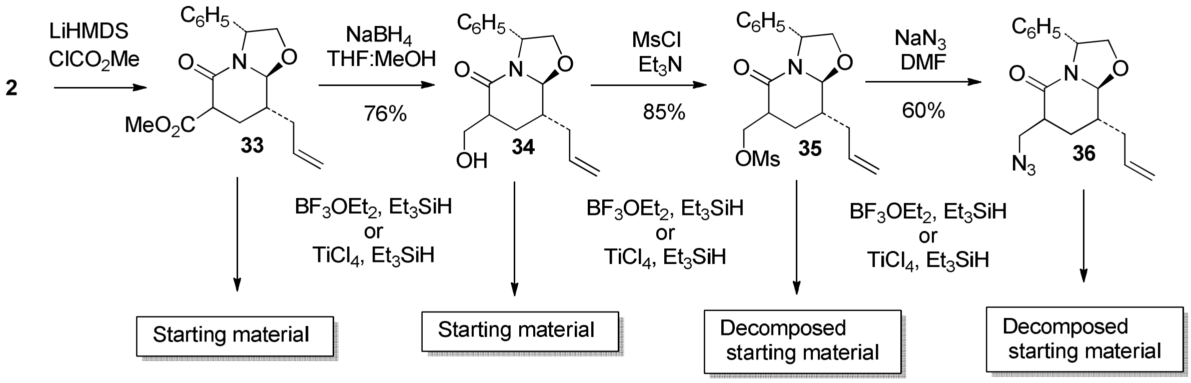
Scheme 2.32 Reductive ring opening reaction.

---

[76] Snyder, L.; Meyers, A.I. *J. Org. Chem.* **1993**, *58*, 36–42.

With the aim of find out a solution and establish if the behavior of these compounds depends on the presence in the piperidine ring of a specific substituent or on the inductive proprieties of the ester group at C-9 position, we decided to use lactams **33**-**36** as model compounds (Scheme 2.33).

Starting compound **33** was prepared with excellent yield treating lactam **2** with a solution of LiHMDS and the appropriate chloroformiate. As predictable, compound **33** was not reduced under $TiCl_4$ and triethylsilane conditions. Thus the ester moiety was transformed into primary alcohol and **34** subjected to reduction with a combination of $Et_3SiH/TiCl_4$ or Et_3SiH/BF_3OEt_2, but in all cases the oxazolidine ring opening reaction didn't take place. The same conditions were then used with the corresponding mesylate **35** and azide **36** derivatives but again the results were unsatisfactory.


2
LiHMDS
ClCO$_2$Me
C$_6$H$_5$
MeO$_2$C
33
NaBH$_4$
THF:MeOH
76%
34
OH
MsCl
Et$_3$N
85%
35
OMs
NaN$_3$
DMF
60%
36
N$_3$
BF$_3$OEt$_2$, Et$_3$SiH
or
TiCl$_4$, Et$_3$SiH
Starting material
Starting material
Decomposed starting material
Decomposed starting material

Scheme 2.33 Attempts on a model lactam.

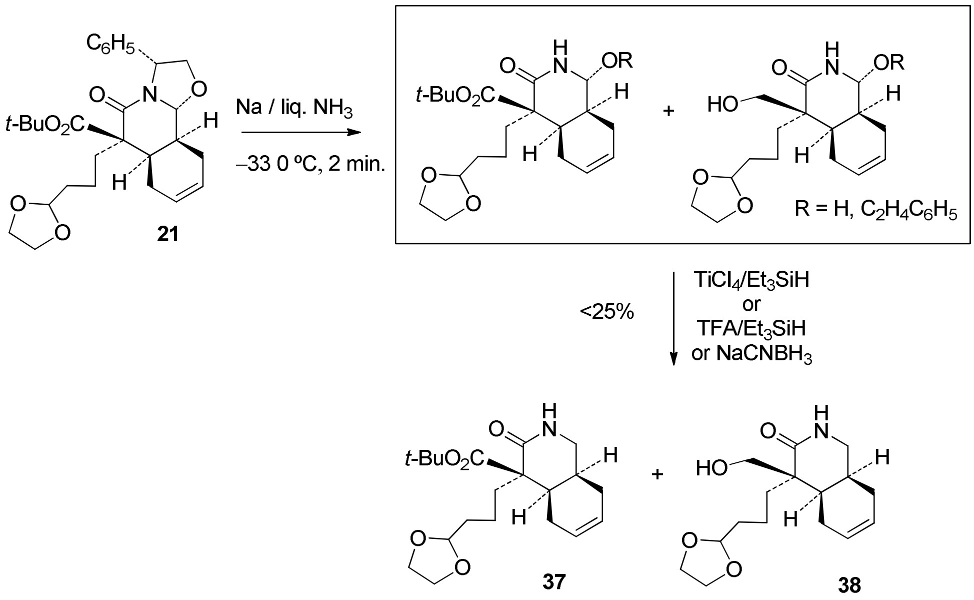
The results presented above point out the interference of some substituents at the C-9 position which dramatically hinder the oxazolidine reduction and suggest the use of a different methodology to overcome the problem.

2.4.3.2. C-N bond Cleavage Studies

In view of these considerations we decide to overturn the process cleaving in the first place the C-N benzylic bond. The C-O bond of resulting hydroxyl- or alkoxy-lactam could be easily reduced in a later stage with conventional methods.

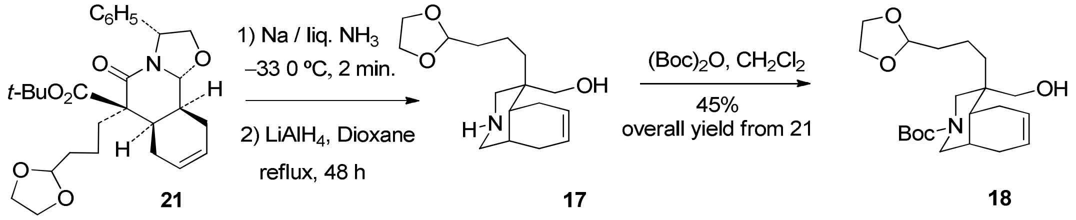
As mentioned above the methodology that involves the use of sodium metal in liquid ammonia is able to cleave the C-N benzylic bond, with excellent yields, in amides but poorly in amines. With these observations in mind our plan to remove the chiral inductor would involve an inversion of the order of the classical two step methodology (see Section 2.3). Hence the C-N reductive opening oxazolidine reaction followed by a Lewis acid-promoted reduction of the resulting hidroxy lactam would led to the free amide compound **XIX**. Subsequent reductions of carbonylic functions with $LiAlH_4$ followed by *N*-Boc protection of the resulting secondary amine would finally afford compound **18.**

Unfortunately, as already argue, dissolving-metal reductions are very effective reactions but, due its complicated experimental protocol, lack in selectivity. Thus, as predictable, the reaction was able to perform the oxazolidine opening reaction and afforded the corresponding alkoxy- and hydroxyl- lactams together with products derived by the reduction of the ester group. Afterwards the complex mixture of unstable compounds was treated with Et_3SiH or $NaCNBH_3$ and alternatively $TiCl_4$ or TFA but, the conversion into the desired free amide compounds **37** and **38**, was obtained with low unacceptable yields (< 25%).


21
Na / liq. NH3
–33 0 °C, 2 min.
R = H, C2H4C6H5
<25%
TiCl4/Et3SiH
or
TFA/Et3SiH
or NaCNBH3
37
38

Scheme 2.34 C-N bond cleavage methodologies.

Interestingly, treatment of the crude resulting unstable products with a high excess of $LiAlH_4$ (15 equiv.) in refluxing dioxane during a period of 48 hours provoked the contemporary reduction of the hemiaminal moieties and both carbonylic groups affording, as only product, the aminoalcohol **17.** The protection of the secondary amine with di-*tert*-butyl-dicarbonate finally gave the desired *N*-Boc derivate **18** with a considerable overall yield of 45%.


21
1) Na / liq. NH3
–33 0 °C, 2 min.
2) LiAlH4, Dioxane
reflux, 48 h
17
(Boc)2O, CH2Cl2
45%
overall yield from 21
18

Scheme 2.35 Cleavage of phenyl ethanol moiety

This methodology represents an important breakthrough in the synthesis of the azabicyclic intermediate **18**. We have definitely found a reliable way to cleave the phenylglicynol chiral inductor from our tricyclic compound and consequently fix our main synthetic hindrance. The advantages resulting from this improvement are outstanding and the return to our "original synthetic plan" permitted the synthesis of the fully-functionalized azabicyclic compound **18** in a faster and scalable easier way.

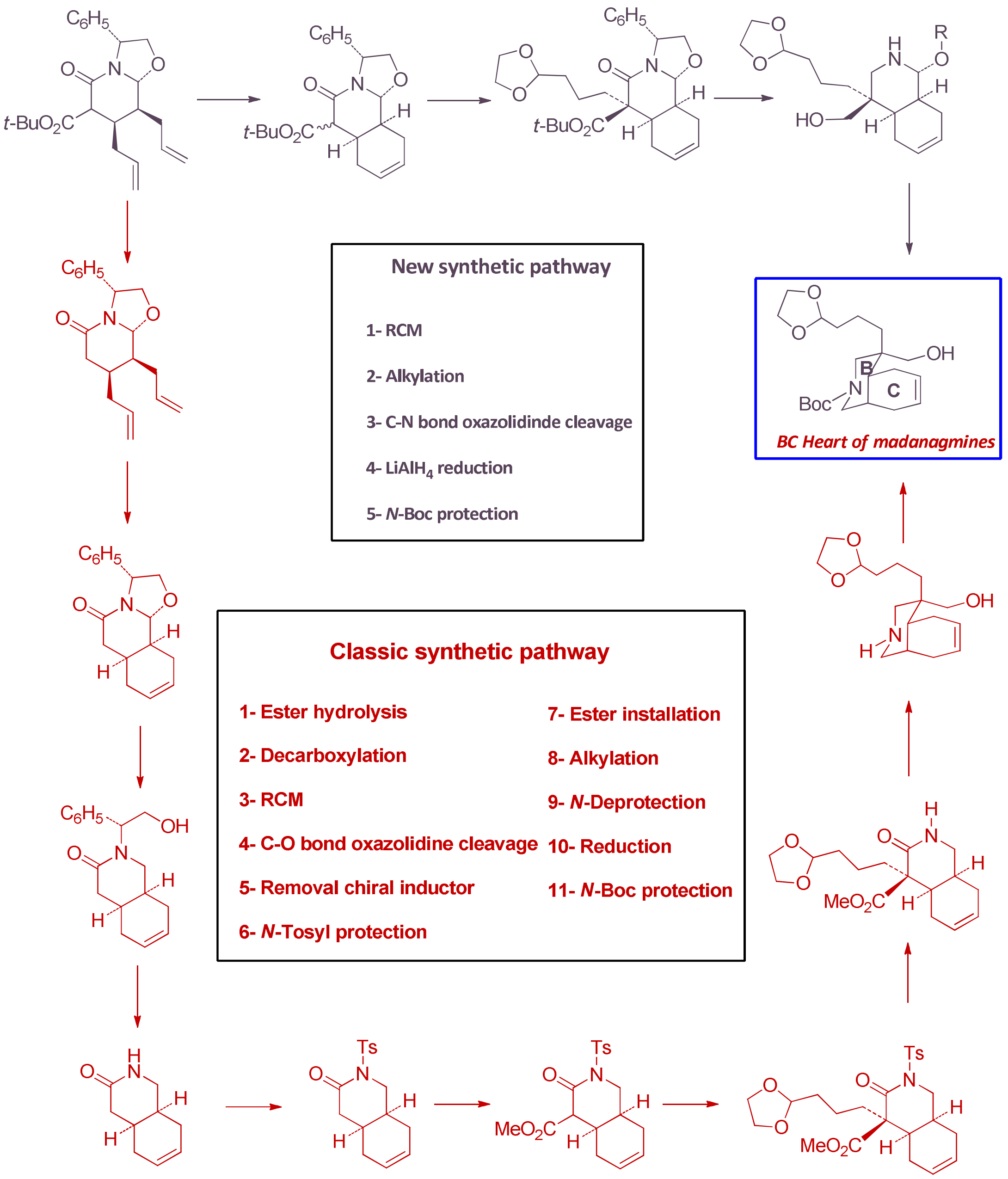

New synthetic pathway
1- RCM
2- Alkylation
3- C-N bond oxazolidinde cleavage
4- LiAlH$_4$ reduction
5- *N*-Boc protection
Classic synthetic pathway
1- Ester hydrolysis
2- Decarboxylation
3- RCM
4- C-O bond oxazolidine cleavage
5- Removal chiral inductor
6- *N*-Tosyl protection
7- Ester installation
8- Alkylation
9- *N*-Deprotection
10- Reduction
11- *N*-Boc protection
BC Heart of madanagmines
B
C
Boc
OH
HO
R
O
N
H
C$_6$H$_5$
t-BuO$_2$C
MeO$_2$C
Ts

Figure 2.12 Synthetic routes toward BC system.

The new synthetic sequence, represented below, excludes the two main drawbacks of the previous strategy represented by the removal and re-introduction of the alkoxycarbonate in the C-9 position and the nitrogen protecting group changes. This route allows the production of an important scaffold, direct precursor of the ABC central core of madangamine, in only five scalable steps, in contrast to the eleven steps of the previous sequence, permitting to save a lot of time and precious starting material during the process.

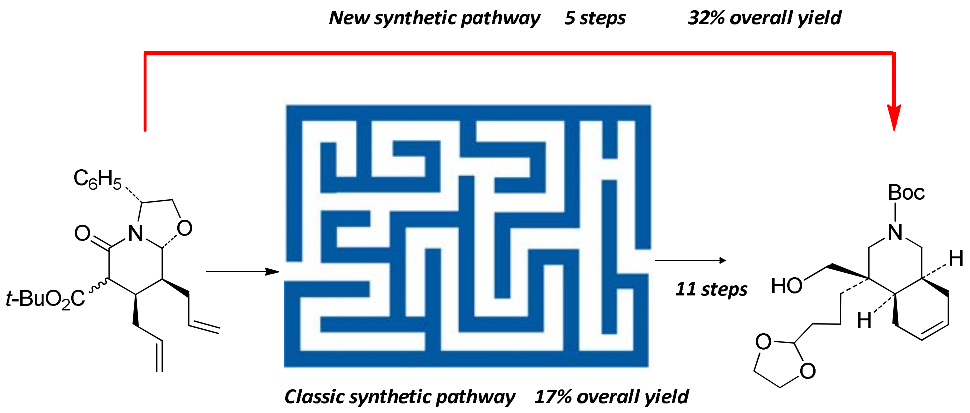


Figure 2.13 Improvements of the new strategy.

2.5. SYNTHESIS OF ABC TRICYCLIC CORE OF MADANGAMINE

With a solid and scalable synthetic sequence, which allows the access to the bicyclic heart of madangamine, the next challenge has been represented by the construction of the central diazatricyclic ring system common to madangamines A-E.

The azabicyclic compound **18** possesses two main features we can use to assemble the ABC system:

- The primary alcohol at the C-9 position, with an appropriate spatial arrangement, which can be easily converted into an aminomethyl moiety.
- The endocyclic double bond in the C ring which would take part in the aminohydroxylation process leading contemporary to the construction of the tricyclic system, the formation of the C-2 stereocenter and the C-3 functionality, essential for the construction of the macrocyclic E ring.

In summary our basic idea is to assemble the piperidine A ring performing an intramolecular aminohydroxylation reaction between the amino moiety, easily obtainable from the primary alcohol, and the unsaturation among the ciclohexene C ring.

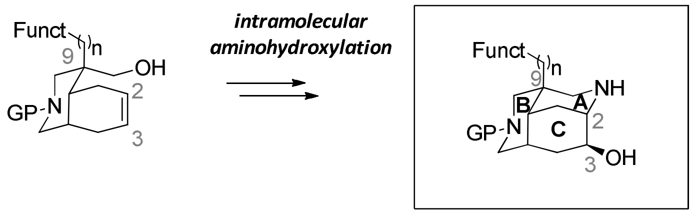
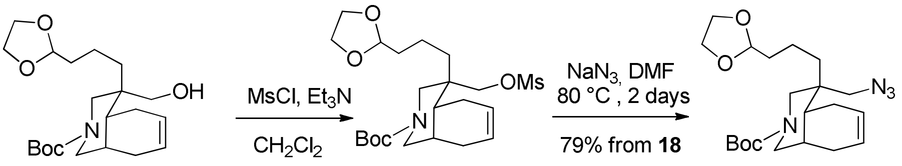


Figure 2.14 Assembly of the diazatricyclcic core.

The synthetic sequence started with transformation of the hydroxyl functional group of **18** into the azide compound which would serve as masked amino functionality. Azide **40** was first tried to introduce under Mitsunobu conditions but the result of the process was unsatisfactory and a two steps sequence synthesis via mesylate was found to be necessary. Even under these conditions the transformation of mesylated compound **39** into the required azide **40** proceeded slowly and required strong reaction conditions to reach a satisfactory conversion.



18 **39** **40**

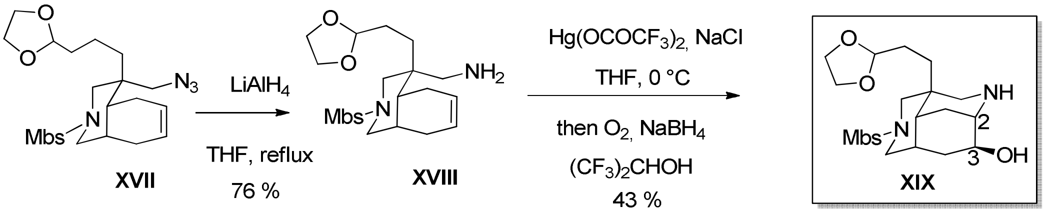
Scheme 2.36 Preparation of azide compounds.

With the bicyclic azide **40** in hands we started our aminohydroxylation studies that would lead to the construction of the diazatricyclic system.

In a first generation synthesis of the ABC system,[51] we were inspired by the construction of the tricyclic core described by Weinreb,[37] which involves an aminomercuriation reaction followed by oxidation.[77] The application of this strategy started with the reduction of the azide **XVII** into the amine **XVIII** and culminated with the first enantiopure synthesis of the diazatricylic system of madangamines **XIX** which confirm the great synthetic potentiality of our retrosynthetic analysis.

---

[77] For further applications of the aminomercuration reaction in total synthesis, see: (a) Saitoh, Y; Moriyama, Y.; Takahashi, T.; Khuong-Huu, Q. *Tetrahedron Lett.* **1980***, 21*, 75–78. (b) Kametani, T.; Suzuki, Y.; Honda, T. *J. Chem. Soc., Perkin Trans.1,* **1986**, 1373–1377. (c) Kalinin, V. N.; Moiseev, S. K.; Bakhmutov, V. I.; Chrepanov, I. A. *J. Organom. Chem.* **1990***, 383*, 85–91. (d) Bai, X.; Mascarella, W.; Bowen, W. D.; Carroll, F. I. *J. Chem. Soc., Chem. Commun.* **1994**, 2401–2402.

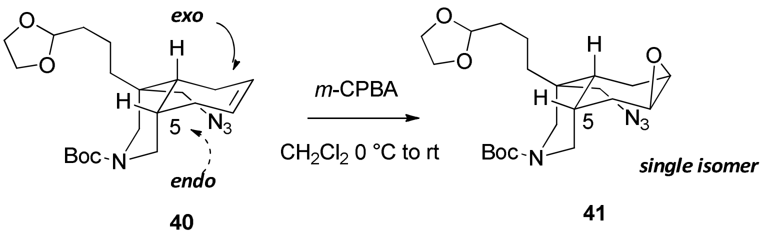


Scheme 2.37 Aminomercuriation methodology.

Unfortunately the process was tedious and a large and complicated experimental protocol was required. Furthermore the low yield associated to the process and the use of some toxic or expensive reagents limit a large scale synthesis of the core, essential condition to reach our final target. Thus we decided to replace this procedure with a more convenient one.

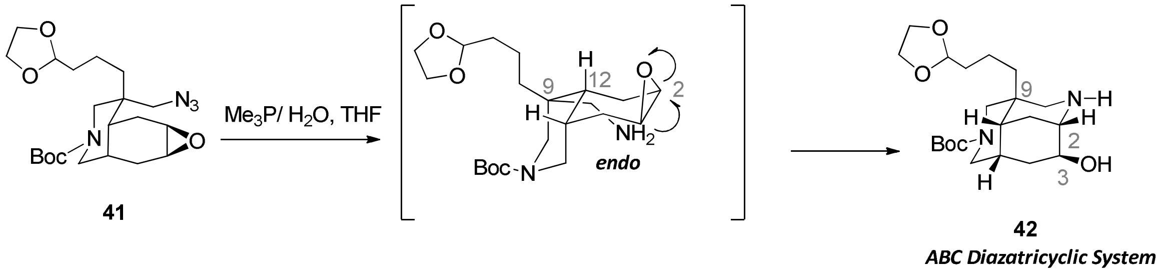
Hence the new methodology, design for the construction of the diazatricyclcic core of madangamine, was centered on the use of an alternative aminohydroxylation reaction. This strategy would avoid the use uncomfortable operational procedure preserving the capability to assemble the piperidinic A ring and installing the C-2 and C-3 stereocenters in an efficient and simple procedure which provided the proper 1,2-amino alcohol.

Our attention was then turned to the possibility to reach our target molecule using, as a key step, a nucleophilic epoxide opening reaction as alternative of the aminomercuriation procedure. The outcome of the process depends on the stereoselechemical course of the epoxidation of the endocyclic double bond which has to be *exo*-selective. The stereospecific *endo*-face nature of the nucleophilic attack at the epoxide ring with an appropriate amine function would guarantee the formation of the 1,2 aminoalcohol with an anti-selectivity. Thus, the azide **40** was treated with *meta*-chloroperbenzoic acid to provoke the cyclohexene double bond epoxidation. As expected the reaction proceeded with a perfect *exo*-selectivity affording the azido-epoxide compound **41** as only isomer. This stereochemical result can be explained taking into account that the epoxidation reaction occurs from the less hindered *exo*-face of the compact convex architecture of our bicyclic system.



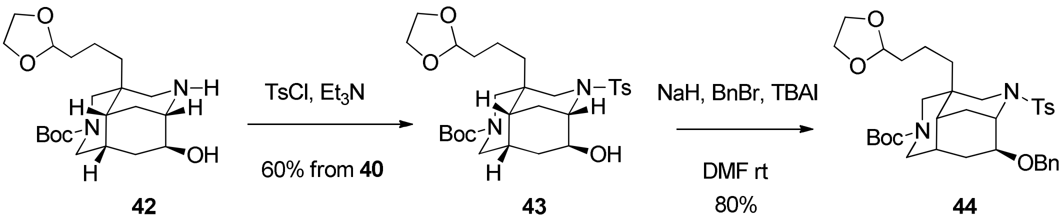
Scheme 2.38 Stereoselective epoxidation.

The resulting epoxide compound **41** was subjected to a selective reduction of the azide function through a mild Staundinger reaction allowing the formation of the resulting amine which underwent a smooth in situ cyclization leading to the closure of the piperidine ring A and the formation of the resulting enantiopure diazatricyclic alcohol **42**. In view of these observations appear evident that the stereochemical course of the reaction has been directed by the geometrical disposition of the aminomethyl chain and its *endo*-nucleophilic attack to the epoxide ring.[51]



Scheme 2.39 Closure of A ring.

The resulting tricyclic system **42** was immediately protected as *N*-tosyl derivatives **43** while the tertiary alcohol at C-3 position was converted in the benzylic ether affording the fully-functionalized ABC diazatricyclic system **44**.



Scheme 2.40 Construction of ABC diazatricyclic ring.

The methodology described set a big improvement in term of yields and simplicity: the aminohydroxilation reaction was carried out without the use of uncomfortable experimental processes and dangerous reagents like mercury or oxygen. The excellent yields of every step permitted to avoid unnecessary chromatographic purifications and *N*-tosyl, *O*-benzyl protected tricylic compound **44** was obtained with excellent yield.

In summary the diazatricyclic core, which would virtually permit the access to madangamine A-E, has been enantioselectively assembled in a fast and scalable way, with the suitable functionality at the C-3 and C-9 positions which would permit to address the construction of both western and eastern macrocyclic D and E rings.

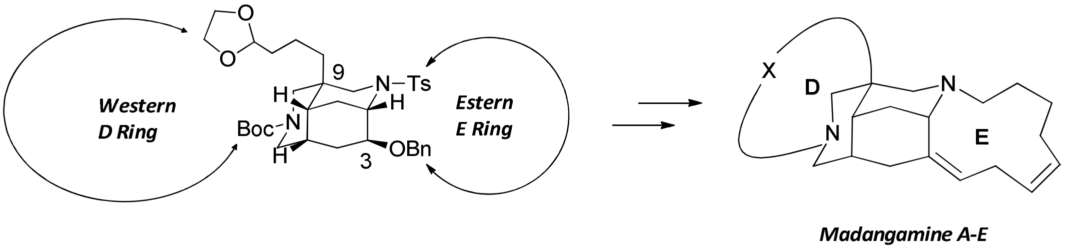

Western
D Ring
Estern
E Ring
9
3
N−Ts
Boc−N
OBn
H
X
D
E
N
Madangamine A-E

Figure 2.15 Fully-functionalized diazatricyclic ring.

Chapter

3.1. INTRODUCTION

With a robust and convenient synthesis of the tricyclic system in hand we focused our attention on the second part of our synthetic plan which involves the construction of the macrocyclic rings of madangamine. Our studies started with the assembly of the western macrocyclic D ring and then proceeded with the construction of the common unsaturated eastern E ring which would permit to complete the first total synthesis of the alkaloid.

One of the most evident advantages of our synthetic approach is that, starting from a common simple building block, we can virtually accede to all type of madangamine. Indeed we can hypothetically introduce any type of carbon chain at the C-9 position, at an early stage of synthesis, allowing the entry to different functionalized diazatricyclic precursors. What we need now is to develop effective strategies for the construction of the macrocyclic rings D from these functionalized-central cores.

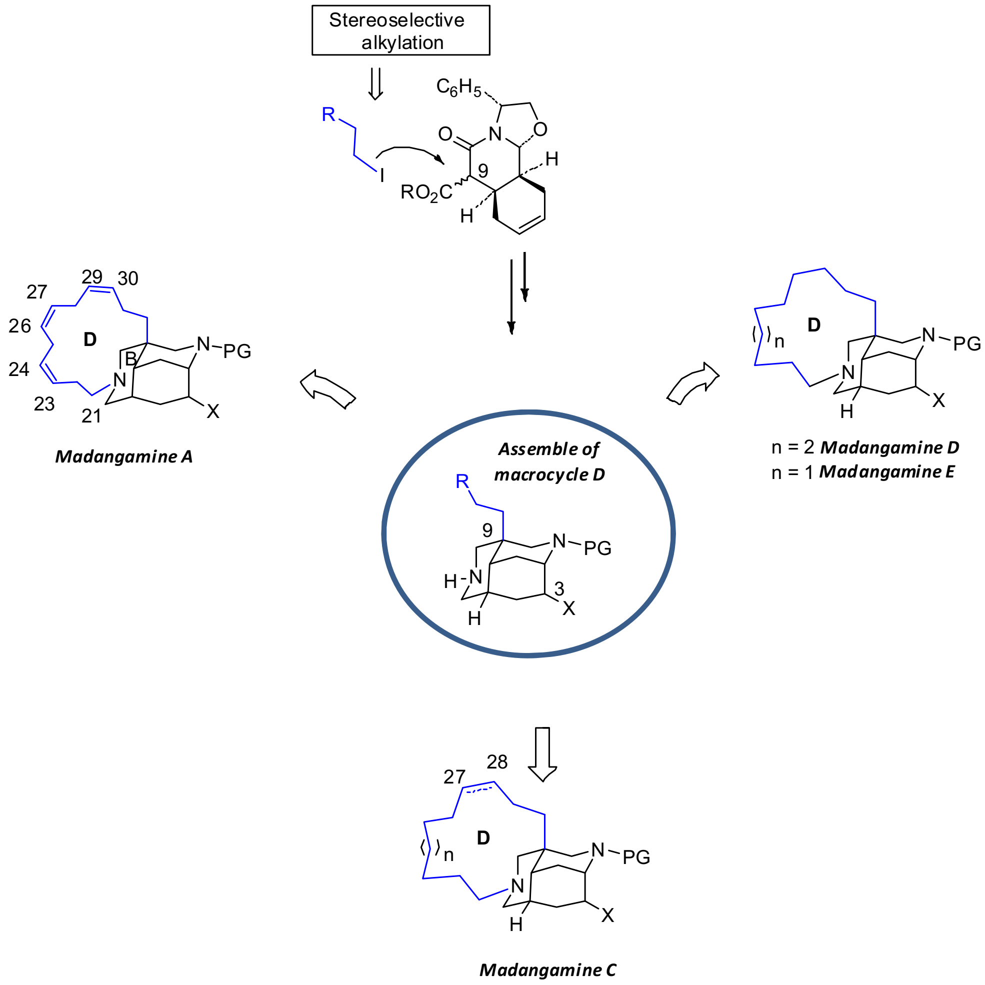

Stereoselective alkylation
R
I
C6H5
O
N
O
9
H
RO2C
H
Assemble of macrocycle D
R
9
N-PG
H-N
3
X
H
27
29
30
26
D
B
N-PG
24
N
23
21
X
Madangamine A
D
( )n
N-PG
N
H
X
n = 2 Madangamine D
n = 1 Madangamine E
27
28
( )n
D
N-PG
N
H
X
Madangamine C

Figure 3.1 Synthetic plan for the annulation of macrocyclic D rings.

In the present section will be presented different approaches to assemble macrocyclic rings of various dimensions, completely unsaturated, presenting a single double bond or a *Z*-skipped system of olefins. The annulation reactions will be studied and optimized on simple piperidinic model compounds and the most promising methodologies will be applied on the diazatricyclic system.

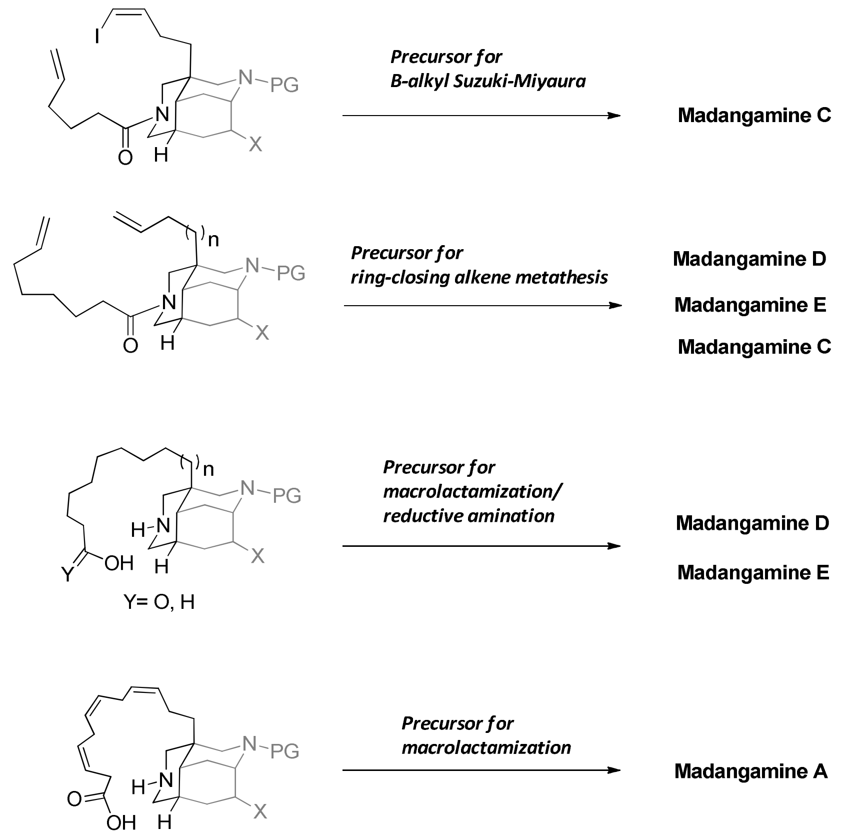

I
N–PG
N
O H
X
Precursor for
B-alkyl Suzuki-Miyaura
Madangamine C
n
Precursor for
ring-closing alkene metathesis
Madangamine D
Madangamine E
Madangamine C
H–N
Y OH
Y= O, H
Precursor for
macrolactamization/
reductive amination
Madangamine D
Madangamine E
O
OH H
Precursor for
macrolactamization
Madangamine A

Figure 3.2 Possible synthetic pathways.

The use of a cheap and easy-to-prepare appropriate simplified model derivatives offers the possibility to work with structures which chemical behavior is, or would expected to be, similar to our diazatricylic compound. In most cases they have permitted to find the best experimental conditions or, at least, to predict the course of the reaction saving a lot of time and precious starting material.[78].

---

[78] Proto, S.; Amat, M.; Pérez, M.; Ballette, R.; Romagnoli, F.; Mancinelli, A.; Bosch, J. *Org. Lett.* **2012**, *14*, 3916–3919.

Once we will found an appropriate and viable methodology for the closure of the western D ring, we will apply it in order to reach the construction the tetracyclic ABCD system. Finally, the assembly of the eastern 11-membered E ring we will be studied to provide first total synthesis of an alkaloid of the madangamine group.

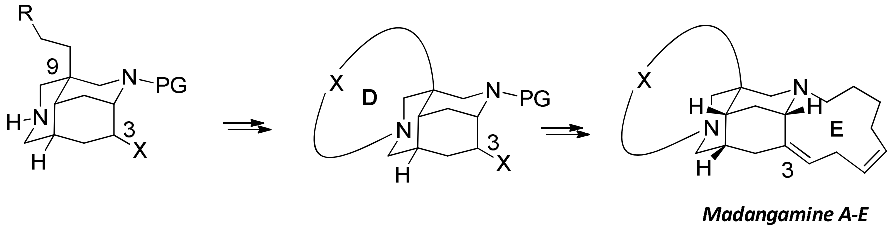

R
9
N
PG
H
N
H
3
X
X
D
N
PG
N
H
3
X
X
H
N
H
N
E
H
3
Madangamine A-E

Figure 3.3 Annulation of E ring.

3.2. CONTRIBUTION FROM PREVIOUS WORK

As already mentioned in the previous section, part of the work presented herein has been made in conjunction with Dr. Stefano Proto with whom I share the first two years of my experimental studies. The outcome of this project has been possible thanks to this collaboration and the chemical heritage he left. Indeed I had the possibility to follow his footprints among the synthetic pathway together with the chance to learn from his errors. His experimental studies ended with the assembly of the tetracyclic ABCD and ABCE systems of madangamine D but, due some complications during the process, he wasn't able to combine the two macrocyclization strategies to finally achieve the goal.

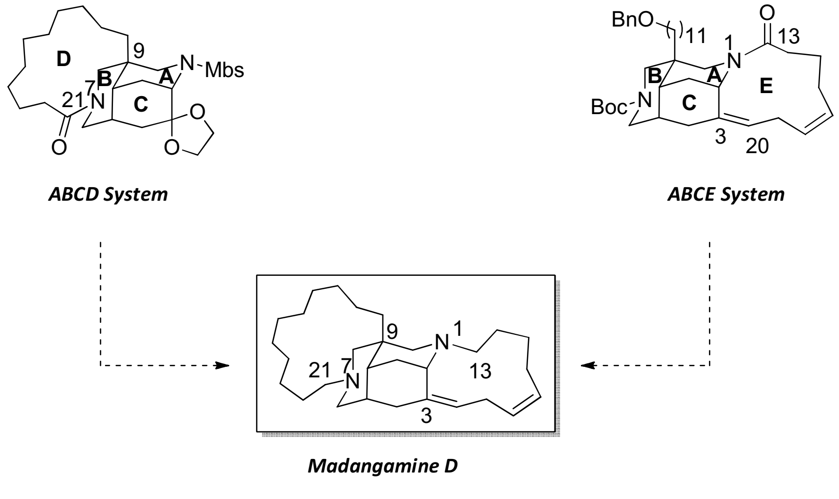

D
9
B
A
N
Mbs
21
7
N
C
O
O
O
ABCD System
BnO
11
1
O
13
B
A
N
E
Boc
N
C
3
20
ABCE System
9
N
1
21
7
N
13
3
Madangamine D

Figure 3.4 Previous work.

3.2.1. Macroclactamization Approach to the ABCD Tetracyclic System

The studies concerning the elaboration of the western D ring of madangamine D started with the exploration of intramolecular macrolactamization and reductive amination reactions from diazatricyclic compound **XX** which incorporates a saturated 11-carbon chain at the C-9 quaternary carbon.

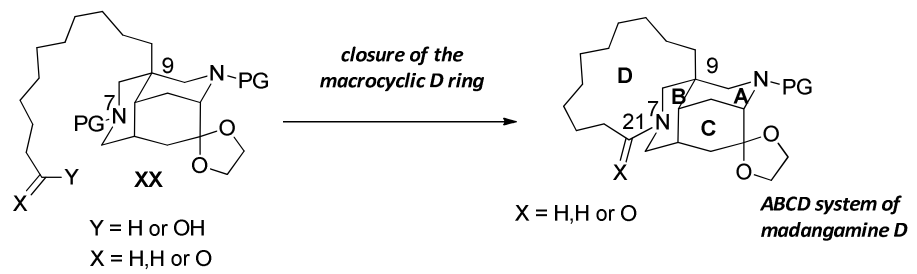
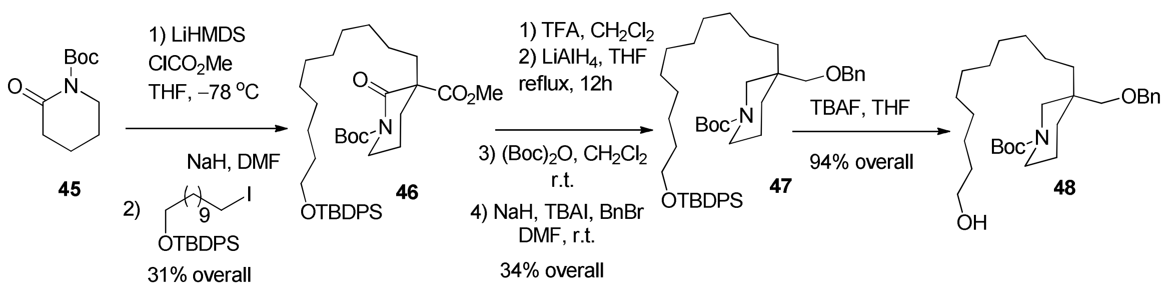

9
N~PG
7
PG~N
O
O
X
Y
XX
Y = H or OH
X = H,H or O
closure of the
macrocyclic D ring
D
9
B
A
N~PG
21
7
N
C
O
O
X
X = H,H or O
ABCD system of
madangamine D

Figure 3.5 Macrolactamization and reductive amination reaction approach.

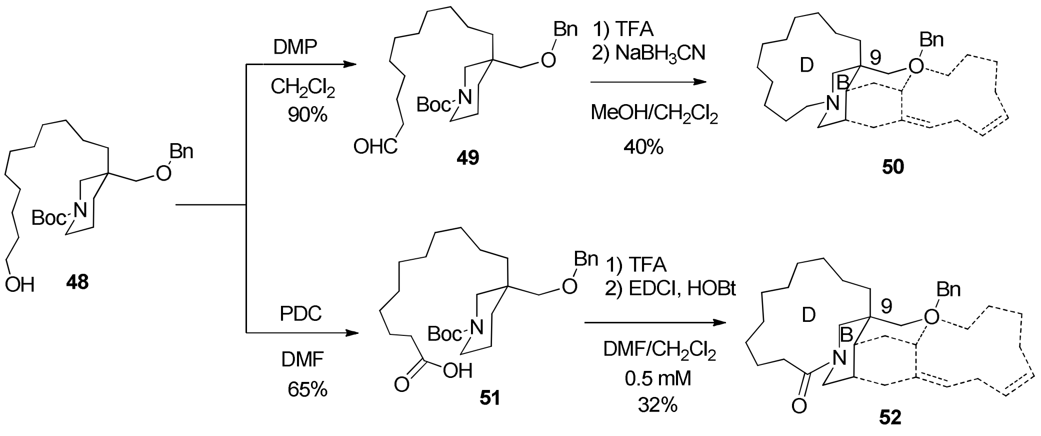
As already mentioned the use of a model compound played a guiding role in all our investigations representing a useful platform we can use to predict the viability of our plans.

Thus, *δ*-valeroctam was used as starting material for the synthesis of the piperidinic model compound and, once protected as *N*-Boc carbamate **45**, was acylated at the α C=O position with methylchloroformiate. This group increased the acidity of the proton at C-3 permitting the subsequent alkylation with the 11-membered iodoalkyl chain. Alkylated compound **46** was then *N*-Boc deprotected and reduced with $LiAlH_4$. Once re-protected as *N*-Boc carbamate the resulting hydroxymethyl chain was converted into the benzyl ester **47** which was finally treated with TBAF to give free alcohol **48**.


Boc
O
N
45
1) LiHMDS
ClCO2Me
THF, −78 °C
NaH, DMF
2)
9
I
OTBDPS
31% overall
O
CO2Me
Boc
N
OTBDPS
46
1) TFA, CH2Cl2
2) LiAlH4, THF
reflux, 12h
3) (Boc)2O, CH2Cl2
r.t.
4) NaH, TBAI, BnBr
DMF, r.t.
34% overall
OBn
Boc
N
OTBDPS
47
TBAF, THF
94% overall
OBn
Boc
N
OH
48

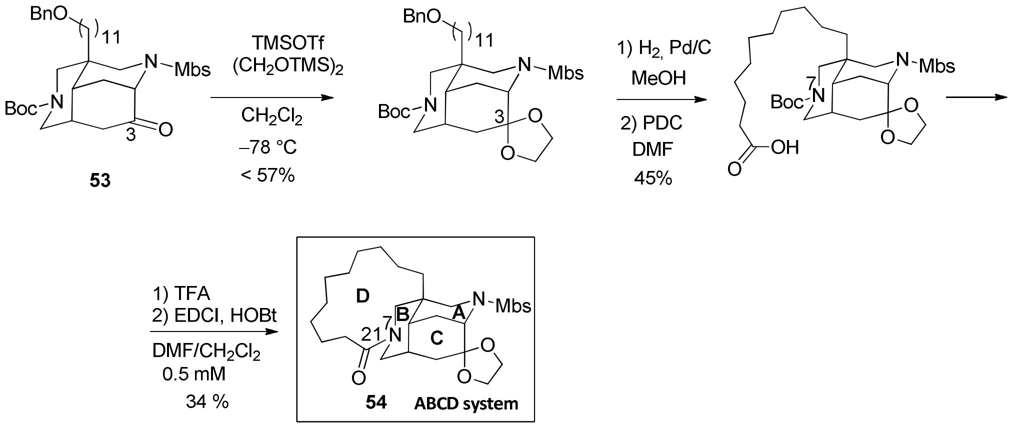
Scheme 3.1 Synthesis of model compound.

Compound **48** was then subjected to oxidation alternatively with Dess-Martin periodinane to aldehide **49** or with PDC to carboxylic acid **51**. The attempts to perform the macrocyclization reaction using a reductive amination approach, starting from the amino-aldehyde compound, allowed to assembly the macrocyclic D ring **50** with 40% yields while, starting from the corresponding aminoacid, the macrolactamization approach gave the D ring **52** with a 32% of yields.


DMP
CH_2Cl_2
90%
PDC
DMF
65%
1) TFA
2) $NaBH_3CN$
MeOH/CH_2Cl_2
40%
1) TFA
2) EDCI, HOBt
DMF/CH_2Cl_2
0.5 mM
32%
Bn
O
Boc
N
OH
OHC
D
B
9
48
49
50
51
52

Scheme 3.2 Macrocyclization reactions.

Having achieved these results, and once we found the best experimental conditions, the same methodologies were then applied on the diazatricylcic system **53**. The more promising reductive-amination reaction led only to the formation of oligomeric products while, with the macrolactamization methodology, it was possible to achieve the first synthesis of the ABCD tetracyclic system of madangamine D **54**.[47]


BnO
11
N-Mbs
Boc-N
3
O
53
TMSOTf
$(CH_2OTMS)_2$
CH_2Cl_2
–78 °C
< 57%
1) H_2, Pd/C
MeOH
2) PDC
DMF
45%
OH
7
1) TFA
2) EDCI, HOBt
DMF/CH_2Cl_2
0.5 mM
34 %
D
B
A
C
21
54
ABCD system

Scheme 3.3 Intramolecular macrolactamization.

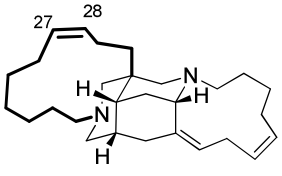
However intramolecular macrolactamization has proven to be a viable process to construct large membered macrocyclic rings, the results herein reported point out some limitations. The elevated number of degrees of freedom of the 11-membered carbon chain, which lack unsaturations, favored the formation of oligomeric products provoking a ruinous loss of material at this stage of the synthesis. Moreover the preceding synthetic steps, especially the protection of the ketone at C-3 and the oxidation of the primary alcohol to carboxylic acid, proceeded with moderate to low yields causing an important drop of the overall yield (<9% from tricyclic compound **XXI**).

3.3. ASSEMBLING OF THE D RING: ANNULATION STUDIES

Thus, with these precious informations in hands, we decided to search for more convenient methodologies, able to assemble the ABCD tetracyclic system of different type of madangamines and capable to provide enough material to complete the first total synthesis of the alkaloid.

3.3.1. Construction of Macrocyclic D Ring of Madangamine C

The western D ring of madangamine C possesses a single isolated *Z*-unsaturation among the macrocycle between positions 27 and 28. This structure represents a very common motif found in different marine natural products like manzamine[79] or nakadomarine[80] which share the same biogenetic origins of our alkaloid.



Madangamine C

Figure 3.6 Structure of madangamine C.

The study of a methodology that could afford *Z*-isolated double bonds in "madangamine type" alkaloids was explored by Winkler[81] in 1998 and later by Fukuyama[82] in 2010. In their works both achieved the formation of the unsaturated ring of nakadomarine A and manzamine A, respectively, via macrocyclization reactions followed by a Lindlar-catalyzed partial hydrogenation of the alkyne.

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[79] Sakai, R.; Higa, T.; Jefford C.W.; Bernardinelli G.; *J. Am. Chem. Soc.* **1986***, 108*, 6404–6405.

[80] (a) Kobayashi, J.; Watanabe, D.; Kawasaki, N.; Tsuda, M. *J. Org. Chem.* **1997***, 62*, 9236–9239. (b) Kobayashi, J.; Tsuda, M.; Ishibashi, M. *Pure Appl. Chem.* **1999***, 71*, 1123–1126.

[81] Winkler, J. D.; Axten, J. M. *J. Am. Chem. Soc.* **1998***, 120*, 6425–6426.

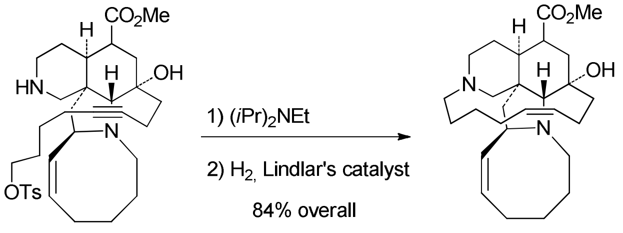
H
CO2Me
HN
H
OH
N
OTs
1) (iPr)2NEt
2) H2, Lindlar's catalyst
84% overall
H
CO2Me
N
H
OH
N

Figure 3.7 Annulation of macrocyclic ring of manzamine.

During the successive years the general strategy used to assemble these types of rings included ring-closing metathesis reactions which always produced a mixture of Z/E isomers[83] in which an HPLC separation to afford the pure Z compounds is needed in many cases.

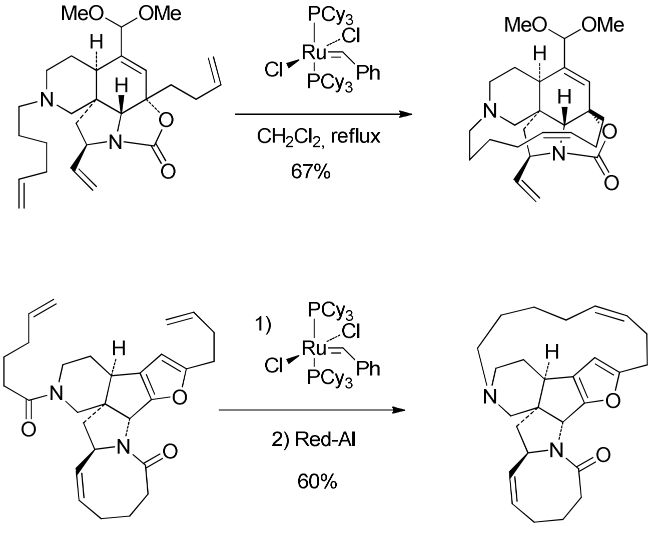
MeO
OMe
H
N
H
O
N
O
PCy3
Cl
Ru
Cl
Ph
PCy3
CH2Cl2, reflux
67%
MeO
OMe
H
N
H
O
N
O
H
N
O
O
H
N
O
1)
PCy3
Cl
Ru
Cl
Ph
PCy3
2) Red-Al
60%
H
N
O
N
O

Figure 3.8 RCM macrocyclization strategies.

An interesting improvement addressed to overcome the lack of stereocontrol for the alkene geometry in RCM macrocyclizations, was introduced by Funk[84] and Fürstner[85]. These authors

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[82] Toma, T.; Kita, Y.; Fukuyama, T. *J. Am. Chem. Soc.* **2010***, 132*, 10233–10235.

[83] (a) Ono, K.; Nakagawa, M.; Nishida, A. *Angew. Chem. Int. Ed.* **2004***, 43*, 2020–2023. (b) Young, I. S.; Kerr, M. A. *J. Am. Chem. Soc.* **2007***, 129*, 1465–1469. (c) Jakubec, P.; Cockfield, D. M.; Dixon, D. J. *J. Am. Chem. Soc.* **2009***, 131*, 16632–16633. (d) Cheng, B.; Wu, F.; Yang, X.; Zhou, Y.; Wan, X.; Zhai, H. *Chem. Eur. J.* **2011***, 17*, 12569–12572. (e) Martin, S. F.; Humphrey, J. M.; Ali, A.; Hillier, M. C. *J. Am. Chem. Soc.* **1999***, 121*, 866–867.

accomplished the synthesis of the *cis*-unsaturated macrocyclic ring of nakadomarine A through a ring-closing alkyne metathesis followed by Lindlar-catalyzed *Z*-stereoselective hydrogenation.

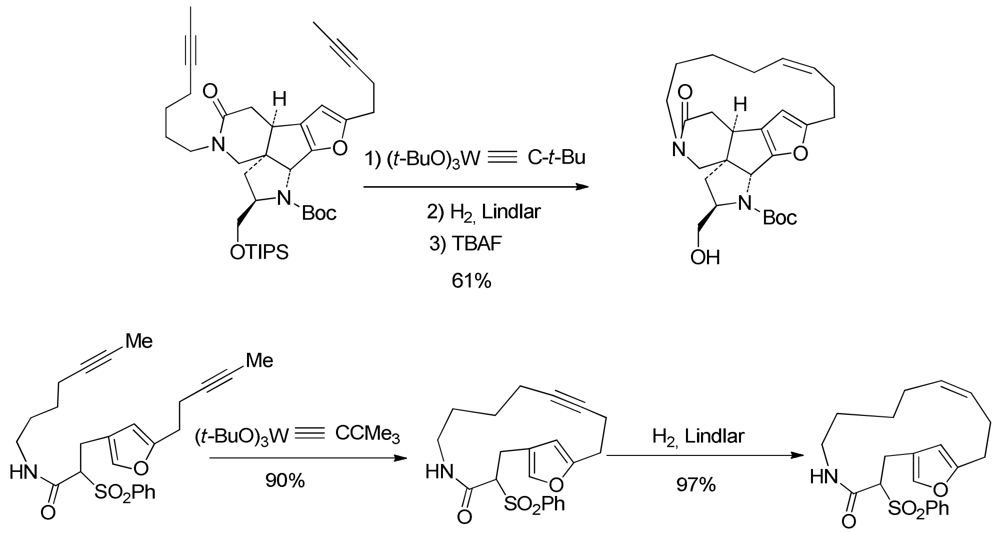

Figure 3.9 Ring-closing enyne metathesis strategies.

3.3.1.1. Intramolecular *B*-Alkyl Suzuky-Miyaura Approach: Model Studies

With the aim to analyze different methodologies able to generate large-dimensioned rings with control on the stereochemical outcome, we decided to explore the use of intramolecular *B*-Suzuki-Miyaura reactions.[86] These cross coupling palladium-catalyzed reactions represent a powerful tool to form C (sp3)-C (sp2) bonds under mild conditions, in good yields and providing access to either *E*- or *Z*-alkenes. In general only few methods have been reported for the highly selective access to *Z*-alkenes, presumably because of the thermodynamic control favors the lower-in-energy *E*-alkenes The cross coupling step in *B*-Suzuki-Miyaura reactions is stereospecific and results in the retention of the stereochemistry of the starting alkenyl halides: the control of the alkene isomer, therefore, has to be established before the cross coupling step.

Hence, starting from an aldehyde derivative bearing a terminal double bond, the Suzuki annulation process for the assembly of a macrocyclic ring involves three steps: the stereoselective formation of a *Z*-iodoalkene, the hydroboration reaction of the terminal olefin

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[84] Nilson, M. G.; Funk, R. L. *Org. Lett.,* **2010***, 12,* 4912–4915.

[85] (a) Fürstner, A.; Grela, K. *Angew. Chem., Int. Ed.* **2000**, *39*, 1234–1236. (b) Fürstner, A.; Guth, O.; Rumbo, A.; Seidel, G. *J. Am. Chem. Soc.* **1999***, 121*, 11108–11113.

[86] (a) Miyaura, N.; Ishiyama, T.; Ishikawa, M.; Suzuki, A. *Tetrahedron Lett.* **1986**, *27*, 6369–6321. (b) Miyaura, N.; Ishiyama, T.; Sasaki, H.; Ishikawa, M.; Satoh, M.; Suzuki, A. *J. Am. Chem. Soc.* **1989**, *111*, 314–321. (c) Oh-e, T.; Miyayra, N.; Suzuki, A. *J. Org. Chem.* **1993**, *58*, 2201–2208. (d) Sato, M.; Miyaura, N.; Suzuki, A. *Chem. Lett.* **1989**, 1405–1408.

with 9-BBN,[87] and finally the palladium-catalyzed coupling reaction of the alkyl borane moiety with the *Z*-iodoalkene.

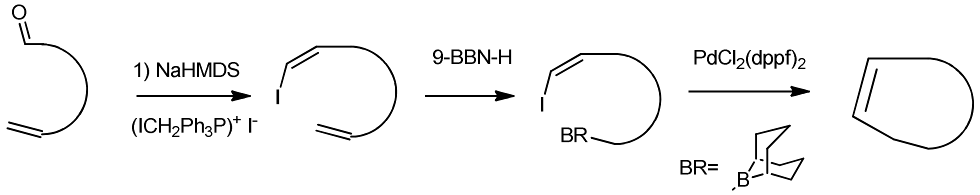
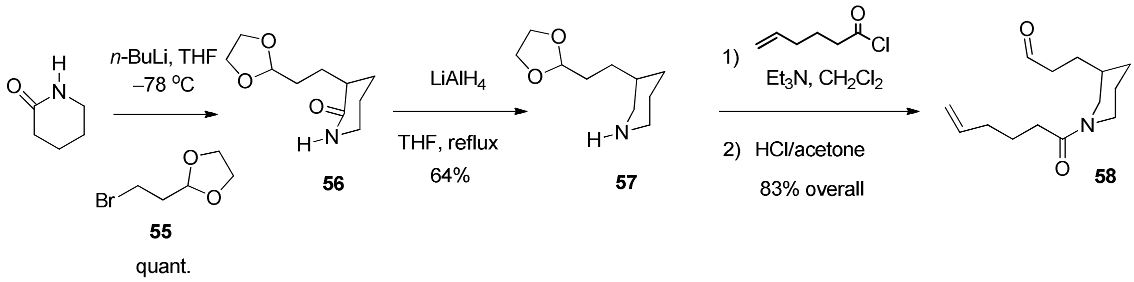

1) NaHMDS
(ICH2Ph3P)+ I-
I
9-BBN-H
I
BR
PdCl2(dppf)2
BR=
B

Figure 3.10 Intramolecular Suzuki annulation.

As already mentioned the reaction will be studied on a piperidinic model compound, synthesized from from commercially available *δ*-valerolactam, which would allow the entry to diolefin compound **59** in only five steps.

The process started with the direct alkylation of the *δ*-valerolactam with **55**[88] which afforded, with quantitative yield, functionalized compound **56**. The reduction of the amide, and the subsequent acylation of the resulting amine **57** with 5-hexenoic acid, was followed by the hydrolysis of the acetal which led to the formation of aldehyde **58**.


n-BuLi, THF
–78 °C
55
quant.
56
LiAlH4
THF, reflux
64%
57
1) Et3N, CH2Cl2
2) HCl/acetone
83% overall
58

Scheme 3.4 Construction of model compound.

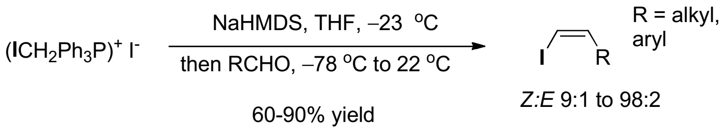
The synthesis of the *Z*-iodoalkene was achieved using the Stork-Zhao Wittig olefination.[89] Thus, the protocol would involve the deprotonation of the iodoalkyl phosphonium salt with sodium hexamethyldisilazane to yield the ylide that would react with aldehydes to generate the *Z*-alkenyl halides in good to excellent selectivity. Not only disubstituted *Z*-alkenyl halides, but also trisubstituted ones can be prepared using this method.[90] These products are useful synthons in organic synthesis, especially in cross coupling reactions.

---

[87] (a) Burgess, K.; Van der Donk, W. A.; Jarstfer, M. B.; Ohlmeyer, M. J. *J. Am. Chem. Soc.* **1991***, 113*, 6139–6144.

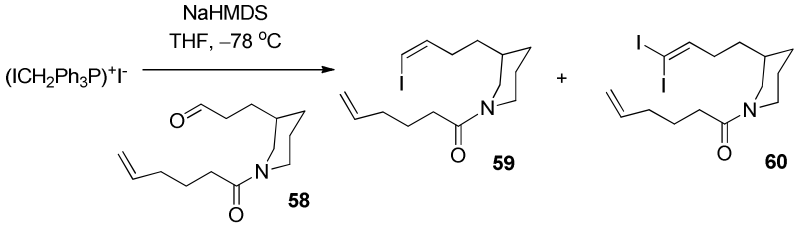
[88] (a) Potts, K. T.; Rochanapruk, T.; Padwa, A.; Coats, S. J.; Hadjiarapoglou, L. *J. Org. Chem*. **1995**, *60,* 3795–3805. (b) Magnus, P.; Rainey, T. *Tetrahedron* **2001***, 57*, 8647–8651.

[89] (a) Stork, G.; Zhao, K. *Tetrahedron Lett.* **1989***, 30*, 2173-2174. (b) Stork, G.; Zhao, K. *J. Am. Chem. Soc.* **1990***, 112*, 5875–5876.



Scheme 3.5 Synthesis of *Z*-iodoalkenes.

Unfortunately the application of this protocol, between aldehyde **58** and the required ylide, gave an inseparable mixture of the *Z*-vinyliodide **59** together with the undesired geminal diiodide **60**.



Scheme 3.6 Stork-Zhao Wittig reaction.

Similar results were obtained by the groups of Bestmann[91] and Menche[92] which tried to avoid the formation of byproducts by simply carrying out the reaction through an “inverted addition” of the phosphonium salt to the base.

As shown in Scheme 3.7 the formation of the undesired geminal iodide **60** can be explained considering an I-H exchange caused by the slow addition of the base. This process could promote the nucleophilic attack of the ylide ***a*** to the phosphonium salt ***b*** which would bring to the formation of dimeric species ***c***. The compound could undergo to another nucleophilic substitution, mediated by a iodide, that would finally lead to the formation of ***d*** and ***e***. The inverse addition of the base should avoid the first nucleophilic attack and consequentially the formation of the dimer ***c***.

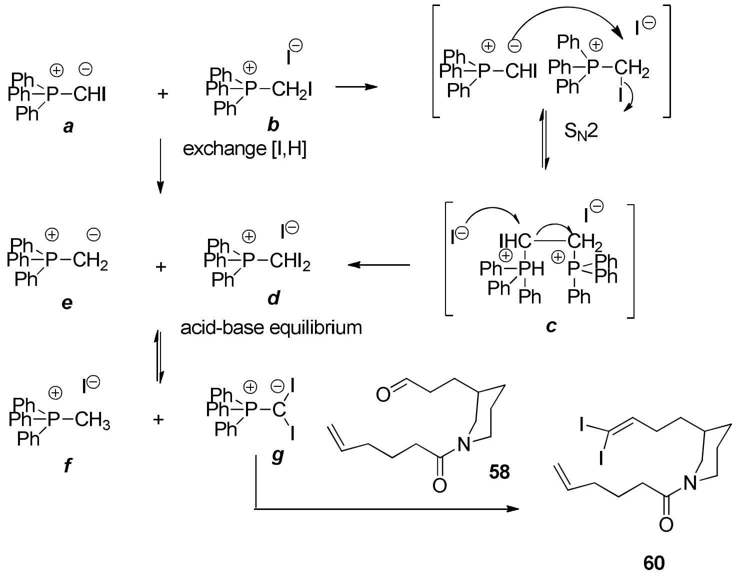
Following this procedure we were able to obtain the *Z*-iodoalkene **59** with a moderate 46% yield in a pure form.

---

[90] Chen, J.; Wang, T.; Zaho, K. *Tetrahedron Lett.* **1994***, 35*, 2827–2828.

[91] Bestmann, H. J.; Rippel, H. C.; Dostalek, R. *Tetrahedron Lett.* **1989***, 30*, 5261–5262.

[92] Li, P.; Li, J.; Arikan, F.; Ahlbrecht, W.; Dieckmann, M.; Menche, D. *J. Org. Chem*. **2010**, *75*, 2429–2444.

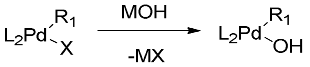


Scheme 3.7 Proposed mechanism of geminal diiodide.

With compound **59** in hand we started to study the intramolecular *B*-Suzuky-Miyaura coupling reaction that would give the unsaturated macrocyclic D ring of madangamine C. In the quest of using these cross coupling reactions, the nature of bases, Pd catalysts, and solvents must be taken into consideration.

Thus, in a first attempt, we decided to use a protocol described by Danishefsky[93] which performed the regioselective terminal hydroboration of the double bond with 9-BBN and the coupling reaction with Pd(0) with a bidentate bis(diphenylphosphino)ferrocene ligand in presence of a thallium base in a very diluted conditions.

The selection of the thallium(I)ethoxyde as base was justified considering its proprieties in increasing the rate of the coupling, probably due to acceleration of the hydroxyl–halogen exchange at palladium.[94, 95]



Scheme 3.8 Hydroxyl–halogen exchange.

A β-hydride elimination can be occurs instead of the reductive elimination when the substrate possess hydrogens in the β-position. For this reason a bidentate palladium catalyst was used. The bis(diphenylphosphino)ferrocene ligand helps to avoid the elimination by enforcing a *cis*-geometry between the substituents and facilitating the reductive elimination.

---

[93] Chemler, R.; Danishefsky, S. J. *Org. Lett.* **2000**, *2*, 2695–2698.

[94] Frank, S. A.; Chen, H.; Kunz, R. K.; Schnaderbeck, M. J.; Roush, W. R. *Org.Lett.* **2000**, *2,* 2691–2694.

[95] Uenishi, J.; Beau, J.; Armstrong, R. W.; Kishi, Y. *J. Am. Chem. Soc*. **1987**, 109, 4756–4658.

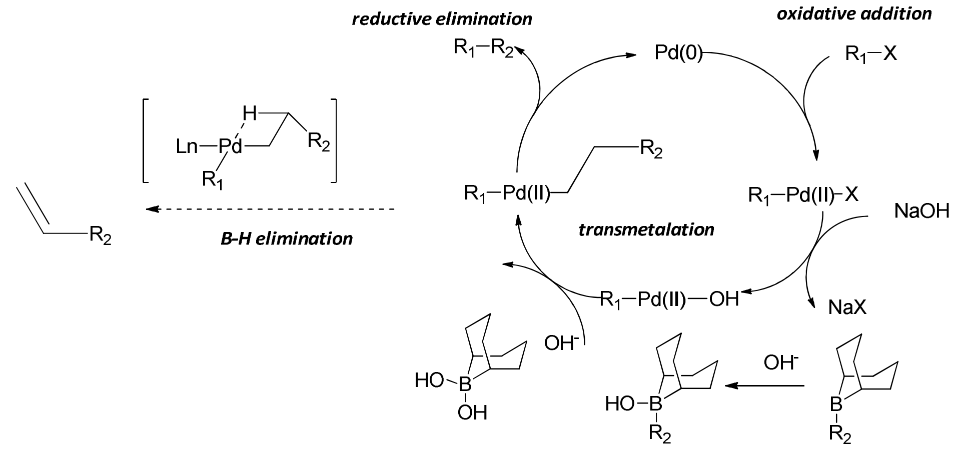
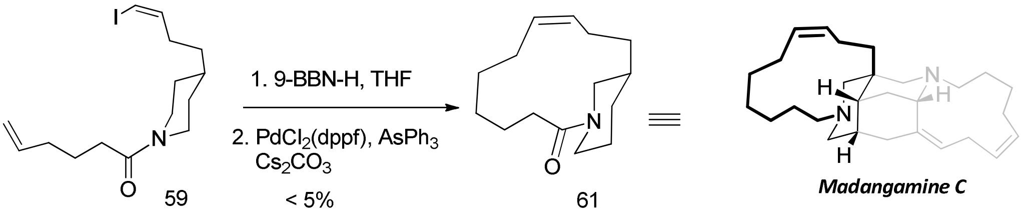

reductive elimination
oxidative addition
R1–R2
Pd(0)
R1–X
Ln–Pd
H
R2
R1
R1–Pd(II)
R2
R1–Pd(II)–X
NaOH
B-H elimination
transmetalation
R1–Pd(II)–OH
NaX
OH-
HO–B
OH
HO–B
R2
OH-
B
R2

Figure 3.11 Catalytic cycle.

With these consideration in mind we carried out the reaction adding the solution of hydroborated compound **59** and the base to the solution of catalyst [$PdCl_2$(dppf)] and $AsPh_3$ *via* a syringe pump over a period of 5 hours. A high dilution of 0.003M was used to avoid the formation of the oligomeric undesired products.

Unfortunately our boronic acid–TlOEt adduct was not soluble not even using of water as a co-solvent. The substitution of the thallium base for cesium carbonate[96] gave only trace of the desired compound **61,** which presence was revealed by a LC-MS analysis, together with oligomeric byproducts.


I
N
O
59
1. 9-BBN-H, THF
2. PdCl2(dppf), AsPh3
Cs2CO3
< 5%
N
O
61
H
N
H
N
H
Madangamine C

Scheme 3.9 Intramolecular Suzuki-Miyaura reaction.

These results underline the difficulty of this task and point out the entropically favorable formation of oligomeric byproducts which was probably promoted by the elevated number of degrees of freedom of both unsaturated chains and the elevated strain energy of the ring. The use of the piperidinic model compound provided important informations regarding the construction of the unsaturated macrocyclic ring, allowing the evaluation of the efficacy of the strategy and avoiding useless waste of valuable material.

---

[96] Trost, B. M.; Lee, C. B. *J. Am. Chem. Soc.* **1998**, 120, 6818–6819.

Due to the poor results obtained in the cyclization step, and the difficulties that involved the construction of the required *Z*-iodoalkene, we decided for the moment to consider alternative approaches and center our attention on other methodologies for the generation of the 13- and 14- membered D rings of madangamine D and E.

3.3.2. Ring-closing Metathesis Strategy: Construction of D Ring of Madangamine D and E

Catalytic ring-closing metathesis is one of the most powerful tools for the construction of carbon-carbon bonds; the market availability of a wide range of catalysts makes these reactions indispensable methodologies to prepare cyclic and acyclic organic compounds. The stability, easiness to handle and the tolerance to a huge variety of functional groups make ruthenium catalysts the most used catalytic systems in metathesis reactions including: ring-closing metathesis (RCM), cross-metathesis (CM), ring-opening metathesis (ROMP) and enyne metathesis (RCEYM).[97]

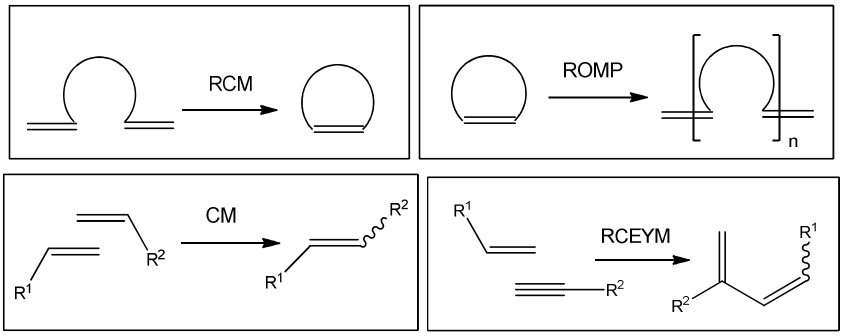


Figure 3.12 Metathesis reactions.

The validity and importance of these processes have been largely demonstrated by hundreds of publications regarding theoretical study and applications but, in this paragraph, we will try to focus our attention on the RCM and, in particularly, on its application in the synthesis of large rings.[98] Our objective is to explore the formation of 13- and 14-member saturated macrocyclic rings[99] of madangamine D and E *via* ring-closing metathesis reactions followed by hydrogenation of the resulting double bonds.

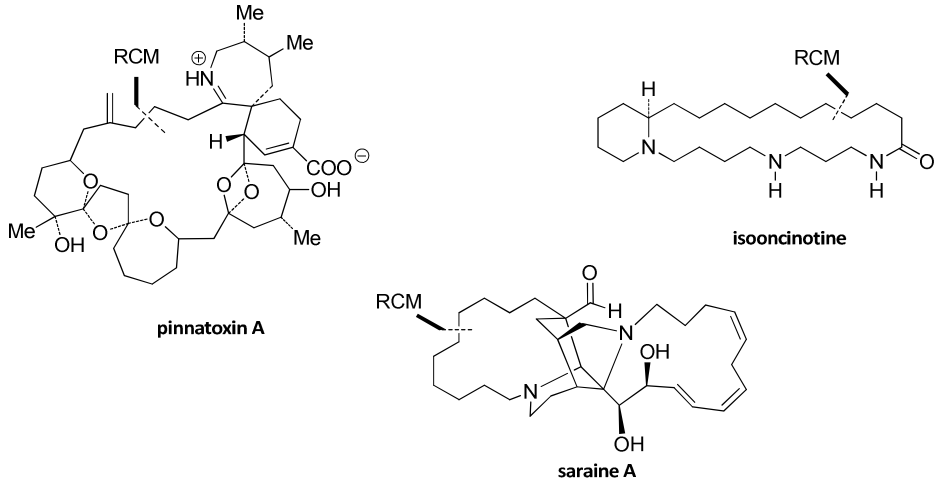
---

[97] Nicolaou, K. C.; Bulger, P. G.; Sarlah, D. *Angew. Chem. Int. Ed.* **2005**, *44*, 4490– 4527.

[98] (a) Gradillas, A.; Pérez-Castells, J. *Angew. Chem. Int. Ed.* **2006**, *45*, 6086–6101. (b) Fürstner, A. *Chem. Commun.* **2011**, *47*, 6505–6511.

[99] Rao, H. S. P.; Rafi, S.; Ratish Kumar, P.; Guravaiah, C.; Muthanna, N. *Tetrahedron Lett.* **2012**, *53*, 6877–6880.

This procedure has been validating during the last years in the synthesis of different large-dimensioned rings of alkaloids such as pinnatoxin A[100], isooncinotine[101] and saraine A. [102]


RCM
Me
Me
HN
H
COO
OH
Me
OH
Me
O
RCM
H
N
N
H
N
H
O
RCM
O
H
N
OH
N
OH

pinnatoxin A

isooncinotine

saraine A

Figure 3.13 Alkaloids containing macrocyclic rings.

Inspired by these recent works we decided to undertake this route and to study the assembly of the macrocyclic D ring of madangamine D and E starting from simple model compounds. Our synthetic plan involves the synthesis of piperidinic dienes bearing unsaturated chains of different lengths, required for the macroannulations of different D rings. Our intention is to validate this methodology and finally to find the best reaction conditions that will be applied in the synthesis of the madangamine alkaloids.

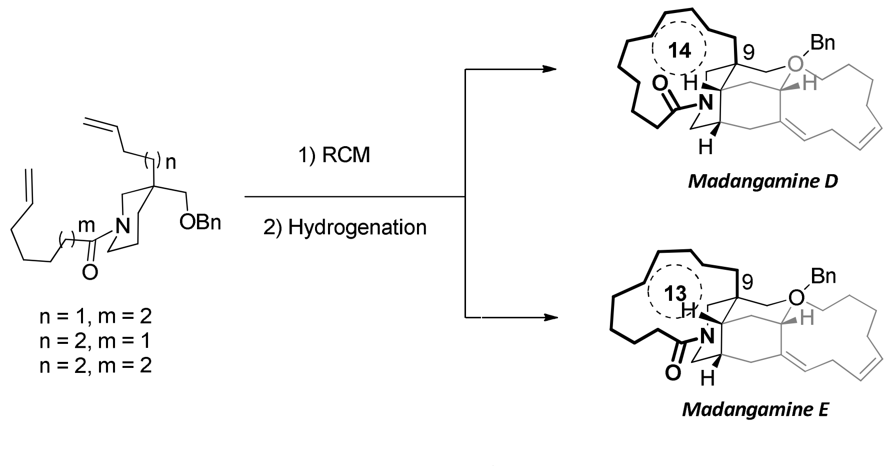

n
m
N
OBn
O
n = 1, m = 2
n = 2, m = 1
n = 2, m = 2
1) RCM
2) Hydrogenation
14
9
Bn
O
H
O
N
H
H
Madangamine D
13
9
Bn
O
H
N
H
O
H
Madangamine E

Figure 3.14 RCM annulation strategy.

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[100] Sakamoto, S.; Sakazaki, H.; Hagiwara, K.; Kamada, K.; Ishii, K.; Noda, T.; Inoue, M.; Hirama, M. *Angew. Chem.* **2004**, *116*, 2200–2204; *Angew. Chem. Int. Ed.* **2004**, *43*, 6505–6510.

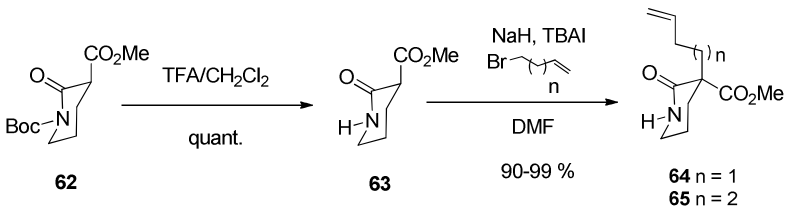
[101] Scheiper, B.; Glorius, F.; Leitner, A.; Fürstner, A. *Proc. Natl. Acad. Sci. USA* **2004**, *101*, 11960–11965.

[102] Garg, K. N.; Hiebert, S.; Overman, L. E. *Angew. Chem. Int. Ed.* **2006**, *45*, 2912–2915.

The main problem related to the construction of large rings is the formation of byproducts, derived by a competitive cross-metathesis reaction, which would provoke the formation of oligomeric compounds. The parameters to control the course of the reaction are: (a) the catalysts, (b) the length of the chains and the site of ring close, (c) the dimension of the macrocyclic rings, (d) the dilution factor, (e) and some parameters such as time, solvent and temperature.[103,]

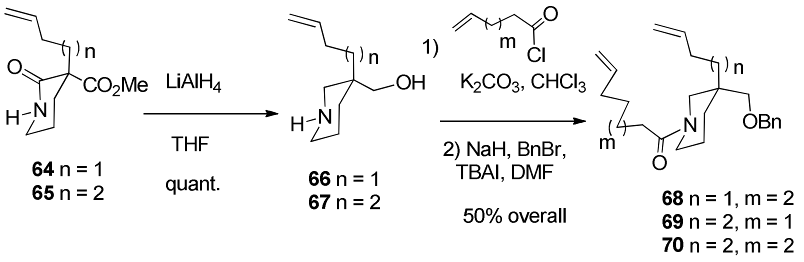
3.3.2.1. Ring-closing Metathesis Approach: Model Studies

The synthesis of our dienes model compounds started from *N*-Boc-protected derivative **62**. The alkylation step was carried out from *N*-unprotected 3-methoxycarbonyl-2-piperidone **63** by treatment with NaH and the corresponding four or five membered bromo-alkene derivatives.


CO2Me
O
Boc-N
62
TFA/CH2Cl2
quant.
CO2Me
O
H-N
63
NaH, TBAI
Br
n
DMF
90-99 %
n
O
CO2Me
H-N
64 n = 1
65 n = 2

Scheme 3.10 Synthesis of piperidinic model system.

The reduction of both carbonylic moieties of compounds **64** and **65** with $LiAlH_4$ afforded amines **66** and **67** while, after the protection of the resulting primary alcohols as benzyl derivates the compounds were acylated with terminal unsaturated chains affording the required dienes **68**, **69** and **70**.


n
O
CO2Me
H-N
64 n = 1
65 n = 2
LiAlH4
THF
quant.
n
OH
H-N
66 n = 1
67 n = 2
1)
m
O
Cl
K2CO3, CHCl3
2) NaH, BnBr, TBAI, DMF
50% overall
n
m
N
O
OBn
68 n = 1, m = 2
69 n = 2, m = 1
70 n = 2, m = 2

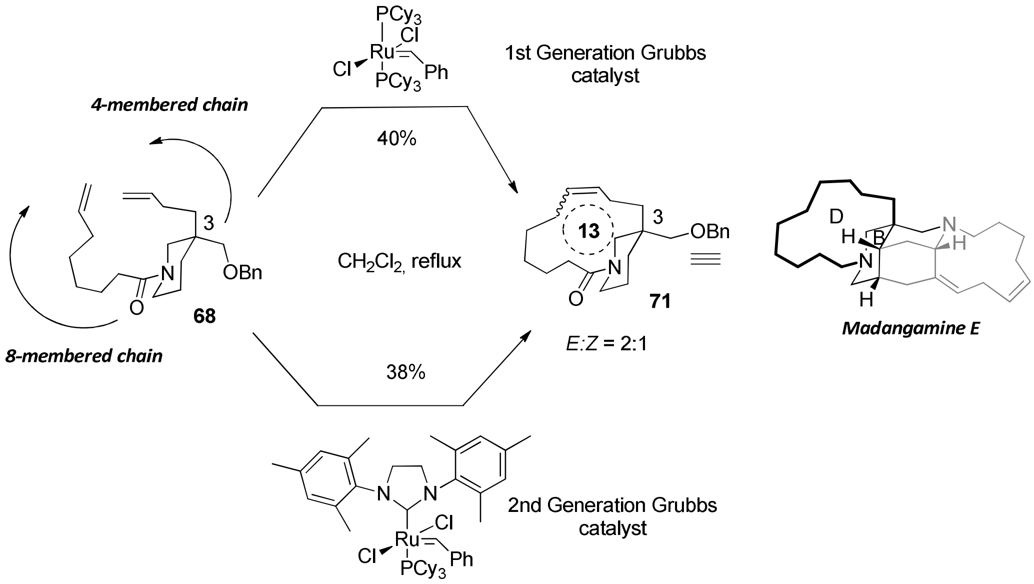
Scheme 3.11 Synthesis of the diene.

---

[103] (a) Clavier, H.; Nolan, S. P. *Chem. Eur. J.* **2007**, *13*, 8029–8036. (b) Yamamoto, K.; Biswas, K.; Gaul, C.; Danishefsky, S. J. *Tetrahedron Lett.* **2003**, *44*, 3297–3299. (c) Conrad, J. C.; Fogg, D. E. *Curr. Org. Chem.*, **2006**, *10*, 185-202.

In our first attempt we decided to study the assembly of the 13-membered D ring of madangamine E starting from compound **68** embodying a four membered carbon chain at the C-3 position and acylated with an eight membered terminal olefin (see Scheme 3.12).

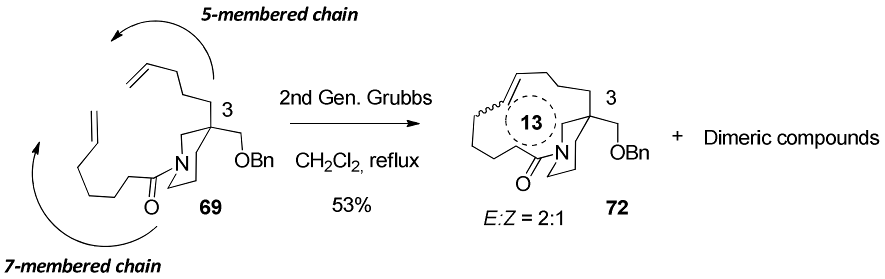
In order to avoid the formation of dimeric products the reaction was carried out in a very high diluted condition (0.4 mM) and diene **68** were slowly added *via* syringe pump to a refluxing solution of the catalyst in dichloromethane. When a 1st generation Grubbs catalyst was used, the desired 13-membered macrocyclic ring **71** was isolated with 40% of yield in an inseparable mixture of *E*/*Z* isomers. In order to increase the yield we next tried the use the 2nd generation Grubbs catalyst and, applying the same synthetic protocol described above, the reaction led to the formation of the desired cycloolefin with 38% of yield.



Scheme 3.12 13-memebered RCM reactions.

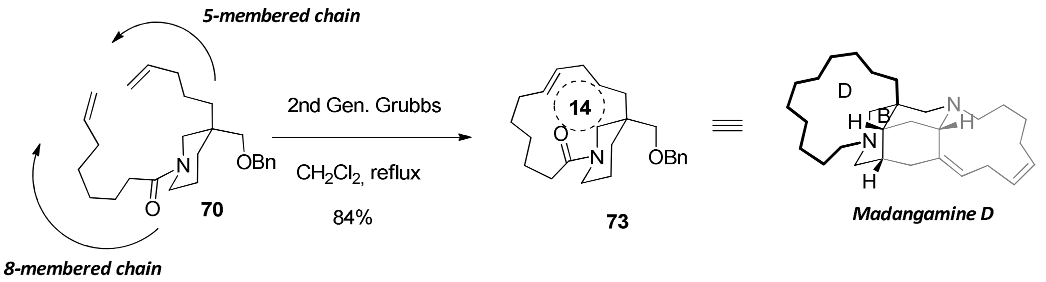
Considering that the rate, products and selectivity of RCM processes are determined by both catalyst and substrate and, taking into account that the use of the 2nd generation Grubbs catalyst didn't improve the yields of the macrocyclization reaction, we decided to change the chains length of diene. Instead of compound **68** we decided to use the diene **69** bearing a five membered carbon chain at C-3 position and a seven membered carbon chain on the nitrogen (n = 2, m = 1). Our intention is to estabilish if these modifications could make more favorable the end to end encounters probabilities of the olefins and increase the effective molarity (EM), defined as the ratio between the rate constant of RCM macrocyclization and the oligomeric reactions.

Thanks to these modifications the reaction showed a little improvement, in terms of yield, and the use of a 2nd generation Grubbs catalyst with diene **69** gave the 13-membered macrocyclic ring **72** with 53% yield together with 25% of dimeric compound.


5-membered chain
7-membered chain
3
N
O
OBn
69
2nd Gen. Grubbs
CH2Cl2, reflux
53%
13
3
N
O
OBn
E:Z = 2:1
72
+ Dimeric compounds

Scheme 3.13 13-membered RCM reaction.

In view of these results we decided to assemble the 14-membered D ring of madangamine D applying the same protocol described above with piperidinic diene **70**. Thus, reaction of compound **70** with a 2nd generation Grubbs catalyst gave surprisingly the unsaturated macrocyclic ring **73** with 84% yields and a complete *E*-stereoselectivity.


5-membered chain
8-membered chain
N
O
OBn
70
2nd Gen. Grubbs
CH2Cl2, reflux
84%
14
O
N
OBn
73
D
B
H
N
H
N
H
Madangamine D

Scheme 3.14 14-memebered RCM reaction.

The results obtained showed a significant difference in the assembly of the 13- and 14-membered macrocyclic rings. We thought we could force the formation of the macrocyclic D ring of madangamine E, and overcame some of the problems related to the high dilution, modifying some of the parameters of the reaction by using a flow chemistry approach.

3.3.2.2. Ring-closing Metathesis Strategy: Flow Chemistry Approach

The low effective molarity (EM) of the dienes **68** and **69**, precursors of macrocyclic D ring of madangamine E, resulted in a competition between ring-closing and cross metathesis reactions.

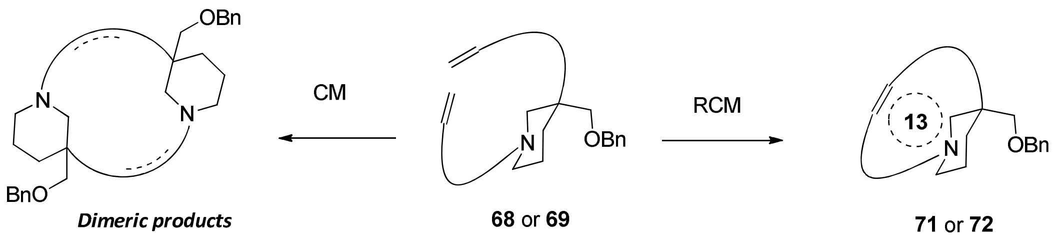


Figure 3.15 RCM versus CM.

To improve the EM values of our problematic diolefinics compounds **68** and **69** and facilitate the synthesis of macrocylic compounds are required high dilutions that, consequently, reduce the kinetics of the reaction. The high temperature often used to overcome this effect has a detrimental impact on the catalysts activity and lifetime.

Flow chemistry represents an attractive solution not only for the opportunity to improve the synthesis of the 13-membered ring but also open the possibility to carry out one of the crucial step of the synthesis of madangamine in a continuous-flow system. We thought we could exploit this technique to avoid the use of extremely diluted condition and the formation of byproducts.[104]

3.3.2.3. Flow Reactors Structure and Main Principles

In flow chemistry,[105] a chemical reaction is performed in a continuously flowing stream in a network of interconnecting channels: where they join one another, the fluids come into contact and the reaction takes place.

In terms of equipment, a typical flow chemistry apparatus is composed by two or more pumps connected with an appropriate reactor. The liquid reagents are collected in tanks, or simply in flasks, and pumped, with independents flow rates through a T-junction, inside the reactor where the reaction takes place. The whole process can be monitored at the end of this circuit, in real time, by diode array UV detectors or mass spectrometry techniques.

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[104] Monfette, S.; Eyholzer, M.; Roberge, D. M.; Fogg, D. E. *Chem. Eur. J.* **2010***, 16*, 11720–11725.

[105] For reviews of flow chemistry see: (a) Wegner, J.; Ceylan, S.; Kirschning, A. *Chem. Commun.* **2011***, 47*, 4583–4592. (b) Pastre, J. C.; Browne, D. L.; Ley, S. V. *Chem. Soc. Rev.* **2013***, 42*, 8849–8869. (c) Jas, G.; Kirschning, A. *Chem. Eur. J.* **2003***, 9*, 5708–5723.

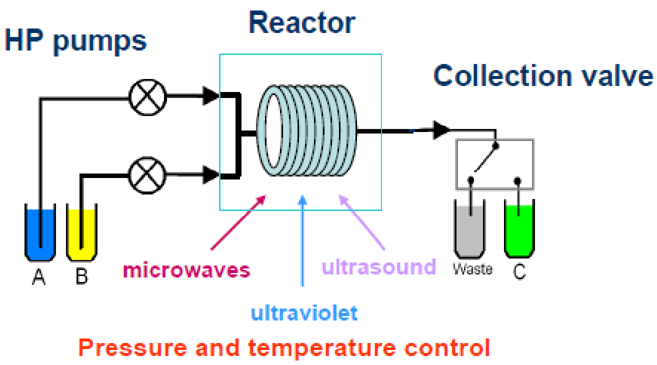


Figure 3.16 Flow reactors structure.

The core of the equipment is represented by the reactor: laboratory scale flow reactors can be generally divided into two classes on the basis of channels size and volume: micro- and meso-flow reactors.[106] Micro-flow reactors present channels having diameter from 10 to 1000 µm, whereas meso-flow reactors are characterized by larger channels with diameter up to 1000 µm.

The main advantages associated with the flow processes can be comprised in two classes: the first one is associated with the small dimensions of the reactor channels and includes the precise control of the reaction conditions, the efficient mass and heat transfer and the possibility of working under superheating conditions. The second aspect is related to the continuous nature of the process and includes the simplicity in reaction, scale-up, the possibility of performing sequential synthetic steps with independent control of reaction conditions and the opportunity to introduce in-line purification by means of supported scavengers.

The main principles of the flow chemistry are:

- The reaction stoichiometry depends not only on the concentration of the reagent but also on the flow rate which can be controlled and changed during the reaction.
- The reaction time is determined by the ratio between the reactor volume and the flow rate.

  RT (min) = Reactor Volume (mL) / Total Flow Rate (mL/min)

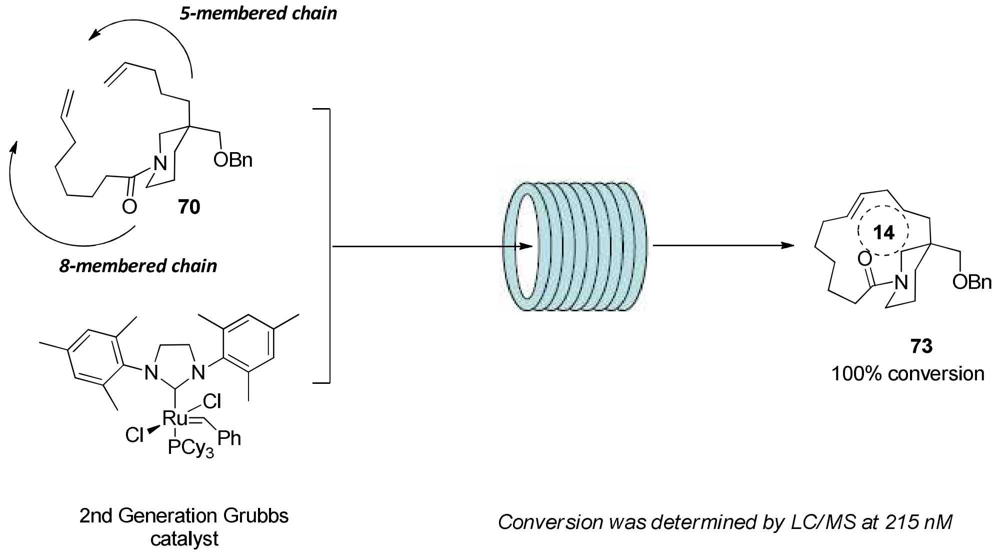
---

[106] Geyer, K.; Codee, J. D. C.; Seeberger, P. H. *Chem. Eur. J.* **2006**, *12,* 8434–8442.

3.3.2.4. Continuous Flow RCM Macrocyclization: Model Studies

Keeping in mind the limitations of our RCM-batch transannulation reactions, and fascinated by the promises of this recent methodology, we decided to explore the efficiency of macrocyclizations performed in a flow system.

Our attempts began with the annulation reaction of compound **70**.with the aim to find the best reaction conditions to carry out the process. Hence, the reaction was performed using a flow apparatus, equipped with a 10 mL reactor, with two constant flow streams of 0.120 mL/min each.[107] The first one was formed by a 0.01 M solution of diene **70** in toluene and the second by a solution of a 2nd generation Grubbs catalyst in the same solvent. The reaction took place at 150 °C leading to a complete conversion of the starting material into compound **73** and confirming the efficiency of the flow technique.


5-membered chain
OBn
70
8-membered chain
14
OBn
73
100% conversion
Cl
Ru
Cl
PCy3
Ph
N
2nd Generation Grubbs catalyst
Conversion was determined by LC/MS at 215 nM

Scheme 3.15 14-memebered RCM-flow reaction.

In view of these promising results we next tested the use of a PEG-supported Hoveyda-Grubbs catalyst under continuous flow chemistry conditions.

The immobilizations of ruthenium catalysts in polymers have been largely exploited during the last decade[108] for the ease of catalysts separation and recycling purposes. The PEG-supported catalyst, synthesized by the group of Yao,[109] was find to be very effective, easy to recover by precipitation with ethylic ether and once recycled could be reused up to six cycles without a substantial decrease in activity.

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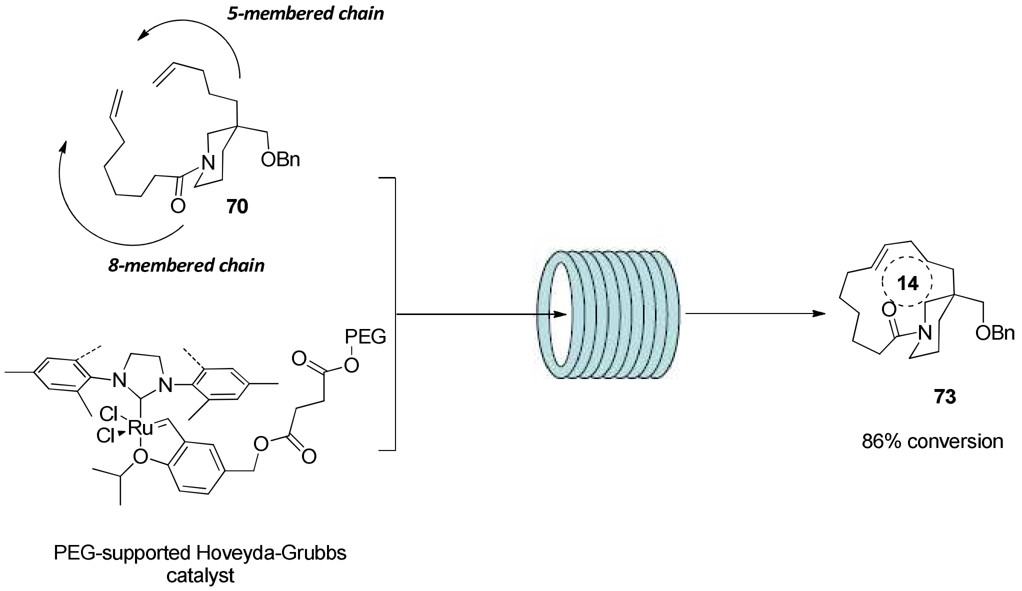
[107] 0.120 mL/min was the minimum flow rate permitted by the apparatus.

[108] (a) Buchmeiser, M. R. *Chem. Rev.* **2009***, 109*, 303–321. (b) Ahmed, M.; Barrett, A. G. M.; Braddock, D. C.; Cramp, S. M.; Procopiou, P. A. *Tetrahedron Lett.* **1999***, 40*, 8657–8662. (c) Halbach, T. S.; Mix, S.; Fischer, D.; Maechling, S.; Krause, J. O.; Sievers, C.; Blechert, S.; Nuyken, O.; Buchmeiser, M. R. *J. Org. Chem.* **2005***, 70*, 4687–4694.

In the macrocyclization reaction of diene **70** with the PEG-supported catalyst was observed 86% of conversion of the starting material and the final product **73** could be easily purified by removal of the organic solvent, treatment of the residue with ethylic ether and filtration.



Scheme 3.16 RCM-flow reaction.

Once we established the best RCM-flow conditions we started to exploit the problematic formation of the 13-membered macrocyclic ring of madangamine E. The same protocol described above was applied in the reactions between diene **68** and the 2nd generation Grubbs catalyst but the results were unsatisfactory: the LC-MS reveled only 50% of conversion and the presence of unreacted starting material and oligomeric byproducts. When compound **69** was used, which differs in the length of both chains, the reaction gave identical results.

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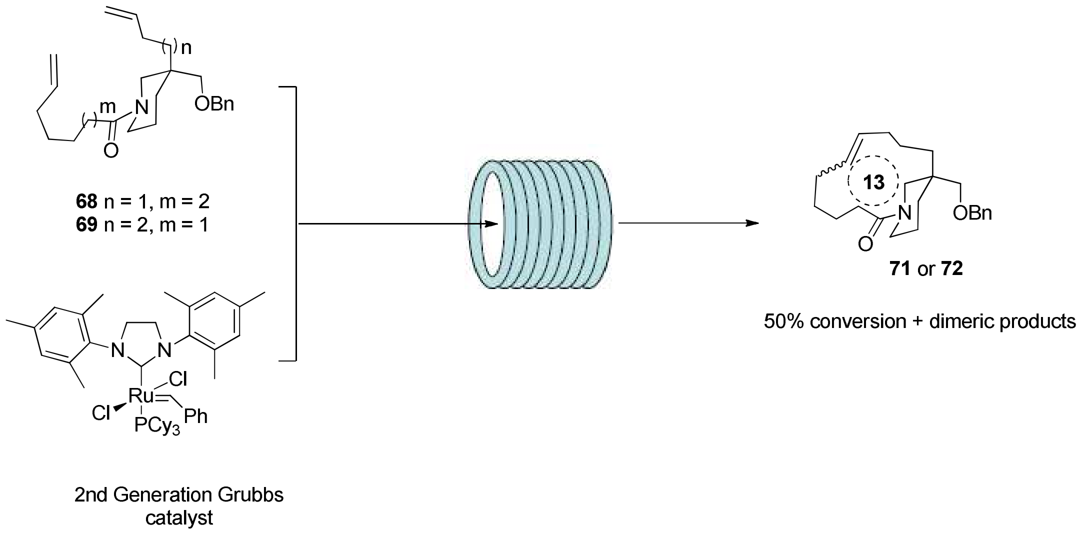
[109] (a) Yao, Q. Angew. Chem., Int. Ed. **2000**, *39*, 3896–3898. (b) Yao, Q.; Motta, A. R. *Tetrahedron Lett.* **2004***,* *45*, 2447–2451.



Scheme 3.17 13-membered RCM-flow reaction.

The results of these experiments pointed out two important facts: the first one is that the low yields related to the formation of the 13-membered cycle can be attributed to the slow reaction rate that didn't permit to reach a complete conversion.[110] The second observation is that both batch and flow reactions demonstrated that an important parameter, in ring-closing macrocyclization reactions, is the size of the ring, no matter which is the position of the unsaturation among the cycle.

The substantial difference, in terms of yields, between the 13- and the 14-membered rings could be explained considering that the success of ring closing reactions is determined largely by strain in the nascent ring system, and the probability of end-to-end encounter between the chains. Figure 3.17 represents the behavior of model lactones[111] and shows how the strain energy increases or decreases depending on the size of the ring due to the transannular interactions. As we can see in the graphic, the ring strain for a 14-membered ring is quite lower than the corresponding 13-membered.

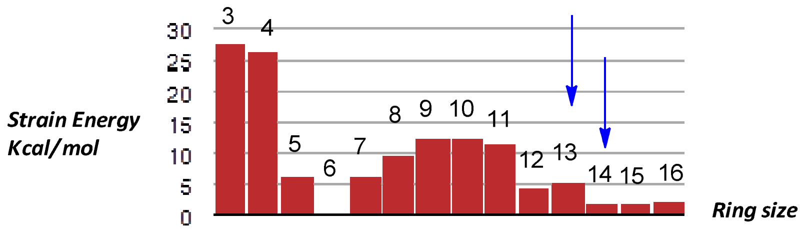


Figure 3.17 Strain energy variations.

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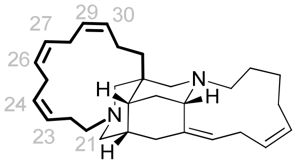
[110] A 10 mL reactor was used with the minimum permitted flow rate, to increase the reaction time we should use a bigger reactor.

[111] Conrad, J. C.; Eelman, M. D.; Duarte Silva, J. A.; Monfette, S.; Parnas, H. H.; Snelgrove, J. L.; Fogg, D. E. *J. Am. Chem. Soc.* **2007**, *129*, 1024–1025.

In summary, the RCM strategy for the synthesis of the macrocyclic D ring of madangamine D and E has been examined including the use of three different ruthenium catalysts. Some of the efforts were directed towards the annulation of the 13-membered ring, which resulted in moderate yields, while the assembly of the larger 14-membered ring was achieved with excellent results. Further studies of RCM reactions resulted in the exploration of flow chemistry techniques however this methodology wasn't able to improve the yields of the problematic 13-membered ring construction of madangamine E.

3.3.3. Construction of D Ring of Madangamine A

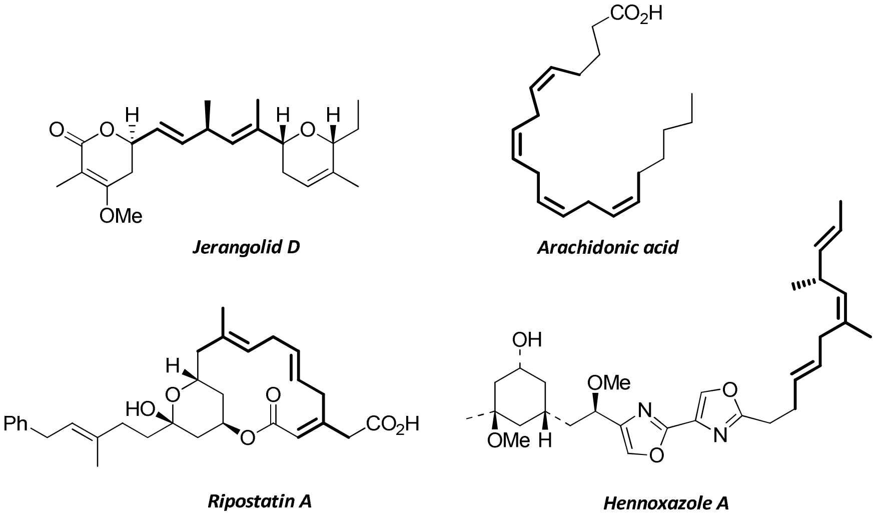
Madangamine A is probably the most important alkaloid of the family due to its structural complexity and its pharmacological proprieties. The main feature is to possess a polyunsaturated D ring composed by 15 carbons with a *Z,Z,Z*-skipped system of olefins.



Madangamine A

Figure 3.18 Structure of madangamine A.

This architectural characteristic is a common motif which can be found in many biologically active compounds such as marine alkaloids, pheromones, and its construction represents a synthetic intriguing challenge for chemists.[112]



Jerangolid D

Arachidonic acid

Ripostatin A

Hennoxazole A

Figure 3.19 Alkaloids containing skipped olefins.

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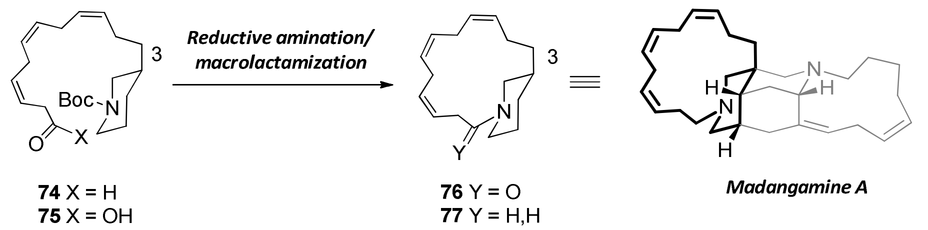
[112] (a) Tang, W.; Prusov, E. V. *Org. Lett.* **2012***, 17*, 4690–4693. (b) Pospısil, J.; Markó, I. E. *J. Am. Chem. Soc.* **2007***, 129*, 3516–3517. (c) Yokokawa, F.; Asano, T.; Shioiri, T. *Org. Lett.* **2000***, 2*, 4169–4172.

Our purpose is to set up a protocol for the construction of this complex macrocyclic ring using a piperidine model and eventually apply the methodology on the synthesis of madangamine A.

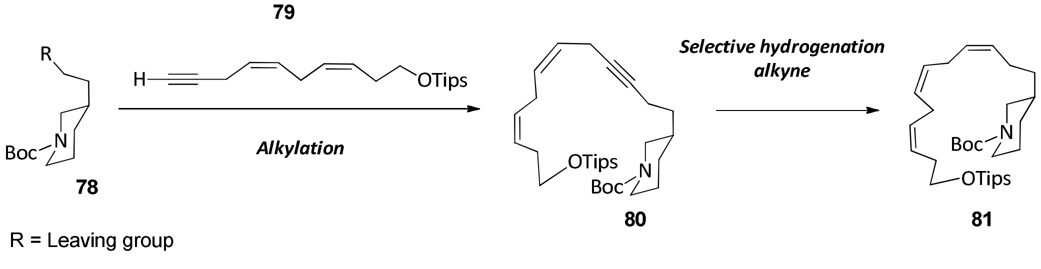
The general strategy would involve first the synthesis of a piperidinic ring, substituted at C-3 position with a 12-membered carbon chain bearing the *Z*-skipped system of olefins and an appropriate terminal functionalization (**74** or **75**). In a second stage of the synthesis we will explore the annulation of the macrocyclic ring through intramolecular macrolactamization or reductive amination reactions. Following this synthetic plan the construction of the D ring of madangamine A **76** and **77** could be achieved, for the first time, in a fast and convergent way.


3
Boc
N
O
X
74 X = H
75 X = OH
Reductive amination/
macrolactamization
3
N
Y
76 Y = O
77 Y = H,H
H
N
H
N
H
Madangamine A

Scheme 3.18 D ring annulation strategy.

3.3.3.1. Synthesis of *Z*-Skipped D Ring of Madangamine A: First Synthetic Approach

In our first synthetic strategy we planned to incorporate the carbon chain **79**, bearing two skipped system of olefins and a terminal alkyne, on the piperidine compound **78**. The stereoselective partial *cis*-hydrogenation of the resulting piperidine-derivate **80** would afford compound **81** which represents our starting point for the macrocylization studies.


79
H
OTips
R
Boc
N
78
R = Leaving group
Alkylation
OTips
N
Boc
80
Selective hydrogenation
alkyne
Boc
N
OTips
81

Scheme 3.19 First synthetic approach.

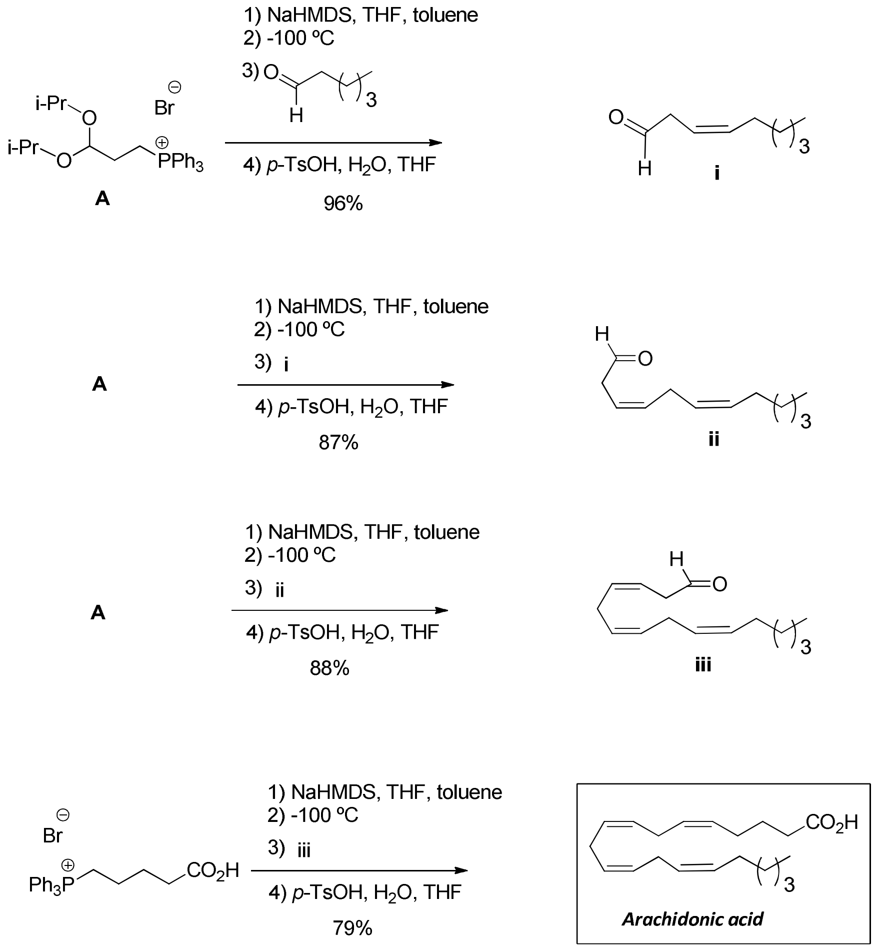
Keeping in mind this synthetic plan, our first challenge was represented by the synthesis of the (*Z,Z*) 1,4-dienic systems, a common feature found in many organic compounds such as polyunsaturated fatty acids (PUFA). The methodologies generally used to build these structures can be divided in two big groups:

- A preparation using sequential Wittig reactions, which would bring directly to the construction of the *Z*-olefin system.

- The synthesis of a poly-alkynil chain and the subsequent selective *cis*-hydrogenation of the resulting triple bonds.

The Wittig reaction is a useful methodology for the generation of olefins and most of its attractiveness is due to the possibility to control the *E*/*Z* geometry of the double bond. The *Z*-skipped system can be achieved through this procedure using the classical *cis*-Wittig reaction conditions that include the use of unstabilized ylides, free-lithium bases and the control of some parameters like dilution and temperature.

The synthesis of arachidonic acid reported by Santelli[113] represents an example of the versatility of this methodology for the synthesis of these *Z*-skipped olefins.


i-Pr
O
i-Pr
O
Br
PPh3
A
1) NaHMDS, THF, toluene
2) -100 °C
3) O
H
3
4) p-TsOH, H2O, THF
96%
O
H
3
i
A
1) NaHMDS, THF, toluene
2) -100 °C
3) i
4) p-TsOH, H2O, THF
87%
H
O
3
ii
A
1) NaHMDS, THF, toluene
2) -100 °C
3) ii
4) p-TsOH, H2O, THF
88%
H
O
3
iii
Br
Ph3P
CO2H
1) NaHMDS, THF, toluene
2) -100 °C
3) iii
4) p-TsOH, H2O, THF
79%
CO2H
3
Arachidonic acid

Scheme 3.20 Synthesis.of arachidonic acid.

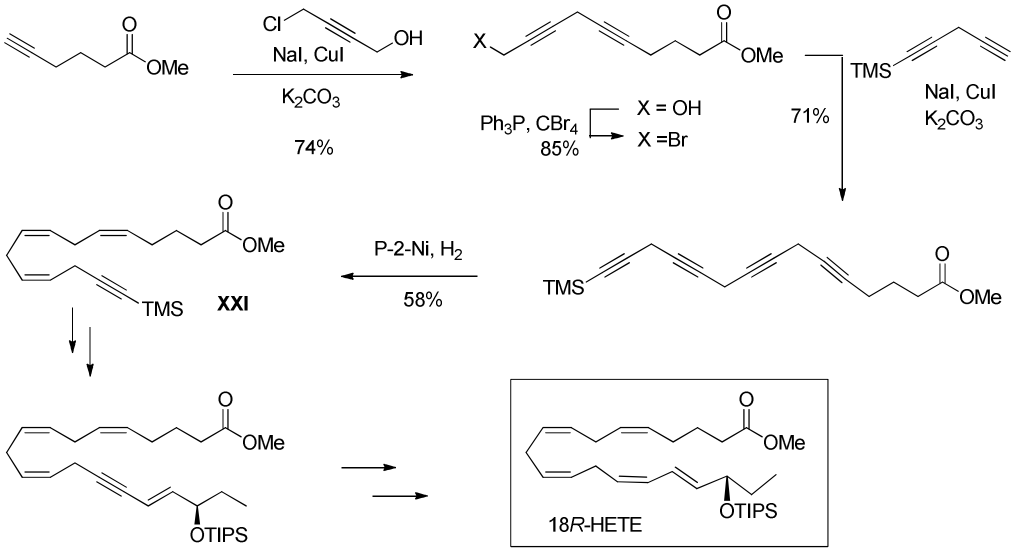
---

[113] Viala, J.; Santelli, M. *J. Org. Chem.* **1988**, *53*, 6121–6123.

As already mentioned the second strategy involves the preparation of a poli-alkynil system by a cross-coupling reaction between a terminal alkyne and propargylic halides. The subsequent semi-hydrogenation of the corresponding acetylenic moiety could be achieved using different methodologies described in literature.

The most classical ones include the hydrogenation with Lindlar catalyst (palladium oxide deposited on calcium carbonate and poisoned with lead acetate and quinolone) or with the nickel based Brown catalyst,[114] while other methodologies like the hydroboration followed by protonolysis or the use of titanium isopropoxide-isopropylmagnesium chloride system[115] seem to be also efficient methods to obtain *Z*-olefins.

An application of this methodology was reported by Chaikof in the synthesis of 18*R*-HETE.[116] As shown below the synthesis of the TMS-protected acetylenic triene **XXI** was achieved by using a Cu (I) coupling reactions and a selective hydrogenation with a Brown catalyst P-2 as a key steps. This catalytic system permits the *Z*-selective hydrogenation of the alkyne without affecting the terminal TMS-acetylenic moiety.



Scheme 3.21 Synthesis of 18*R*-HETE.

The catalyst was obtained through a reaction between sodium borohydride and a solution of nickel salts, when the reaction takes place in aqueous media a black precipitate is formed (P-1-Ni).[117] This material showed an activity comparable with nickel Raney but is non-magnetic and non-pyrophoric. When the same catalytic system was synthesized using a suspension of the nickel salt in ethanol[118] a colloidal black suspension was produced, the material called P-2-Ni showed different characteristics compare to the other. This catalytic system is less effective than the P-1 type but more selective in the hydrogenation of conjugate dienes and in the partial hydrogenation of alkynes in *cis*-olefins while has no activity in the hydrogenation of the terminal TMS-protected alkyne.[119, 111] Furthermore the nickel catalyst can be generated in situ through the reduction of nickel acetate by $NaBH_4$, which makes it straightforward to control the exact catalyst loading for the reaction.

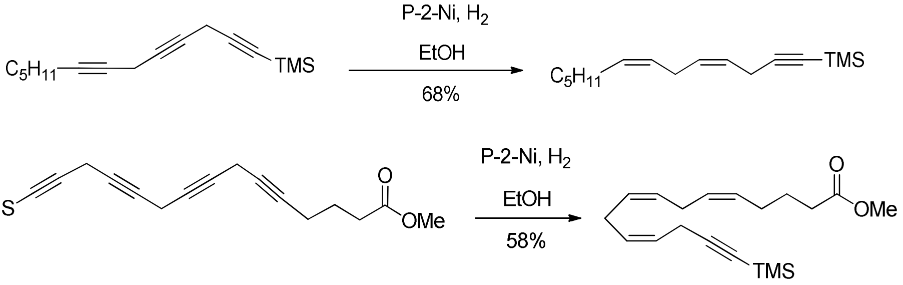
---

[114] (a) Brown, C. A.; Ahuja, V. K.*; J. Chem. Soc. Chem. Commun.* **1973**, 553–554. (b) Brown, C. A.; Ahuja, V. K. *J. Org. Chem.* **1973**, *38*, 2226–2230.

[115] (a) Hungerford, N. L.; Kitching, W. *Chem. Commun.* **1996**, 1697–1698. (b) Harada, K.; Urabe, H.; Sato, F. *Tetrahedron Lett.* **1995***, 36*, 3203–3206

[116] Krishnamurthy, V. R.; Dougherty, A.; Haller, C. A.; Chaikof, E. L. *J. Org. Chem.* **2011**, *76*, 5433–5437.

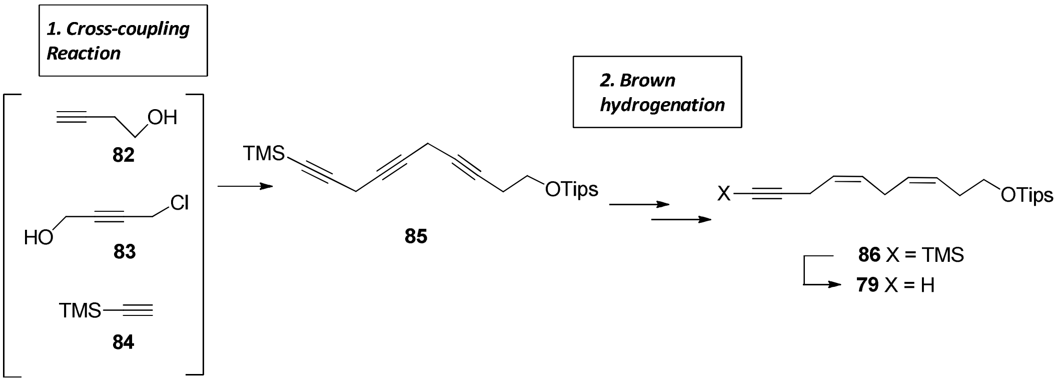
[117] Brown, C. A. *J. Org. Chem.* **1970**, *35*, 1900–1904.



Scheme 3.22 Hydrogenations with P-2-Ni.

3.3.3.2. Construction of Unsaturated Chain

The assembly of our unsaturated chain **79** could be achieved using a Brown hydrogenation of the two central triple bonds of tryine **85** which was obtained after two cross coupling reactions between terminal alkynes and propargylic halides.



Scheme 3.23 Construction of unsaturated chain.

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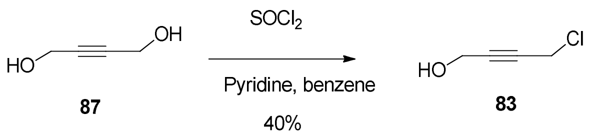
[118] (a) Brown, H. C.; Brown, C. A. *Tetrahedron*, **1966**, *22*, *Suppl. 8 Part I,* 149–164. (b) Brown, C. A.; Brown, H. C. *J. Org. Chem.* **1966**, *31*, 3989–3995.

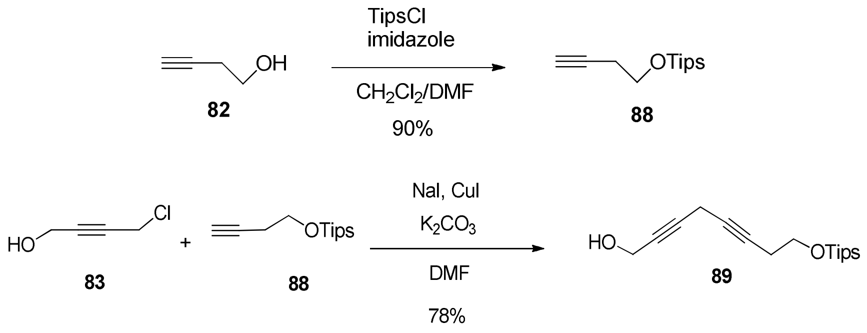
[119] Gueugnot, S.; Alami, M.; Linstrumelle, G., Mambu, L.; Petit, Y.; Larchevêque, M. *Tetrahedron* **1996**, *52*, 6635–6646.

The synthetic sequence started with the 4-chloro butynol **83**,[120] which was prepared by slowly addition of thionyl chloride to a solution of diol **87** *via* syringe pump. After the purification by distillation, compound **83** was obtained with moderate yield.


HO
OH
87
SOCl2
Pyridine, benzene
40%
HO
Cl
83

Scheme 3.24 Synthesis of 4-chloro butynol.

The subsequent reaction between the Tips-protected terminal alkyne **88**, prepared from compound **82**, and the propargylic halide **83** proceeded smoothly, when classical copper cross-coupling conditions were used (CuI, NaI and potassium carbonate as base), affording dyine **89** with excellent yield.


OH
82
TipsCl
imidazole
CH2Cl2/DMF
90%
OTips
88
HO
Cl
83
+
OTips
88
NaI, CuI
K2CO3
DMF
78%
HO
OTips
89

Scheme 3.25 Cross coupling reaction.

Transformation of alcohol **89** into the corresponding bromo-derivative, using the classical Appel reaction, proceeded with very low yield and a two-step synthesis was necessary to synthesize the required propargylic halide **90**. The resulting bromo derivative was then subjected to the second cross-coupling reaction with a terminal TMS-protected alkyne affording the desired tryine **85**.

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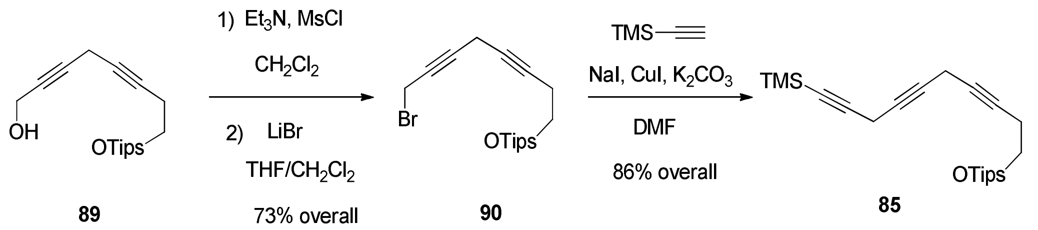
[120] The compound is commercial available but expensive.

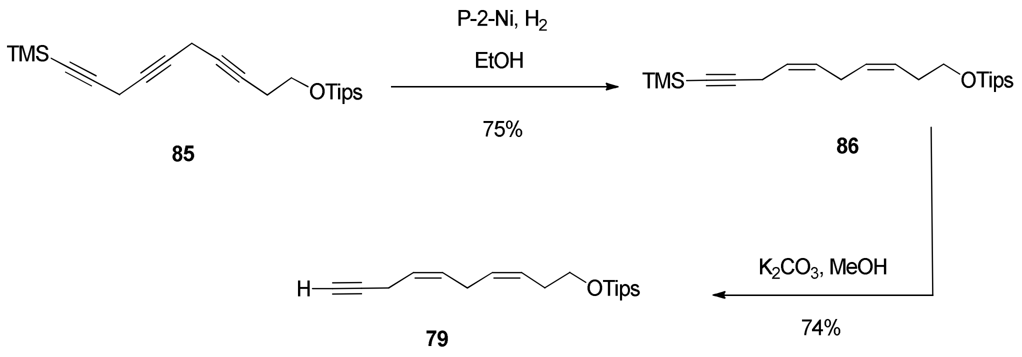

1) Et_3N, MsCl
CH_2Cl_2
2) LiBr
THF/CH_2Cl_2
73% overall
TMS
NaI, CuI, K_2CO_3
DMF
86% overall
OH
OTips
Br
TMS
89
90
85

Scheme 3.26 Synthesis of tryine.

The next challenging issue was represented by the regio- and stereoselective *cis*-reduction of the central alkyne functionalities of **85** to give the desired *Z-Z* diene **86** with the terminal TMS-alkyne function (see scheme 3.27).

Our approach was based on the use of the Brown catalyst which was prepared in situ by treating a vigorously stirred solution of nickel acetate in 95% ethanol with a solution of sodium borohydride under hydrogen atmosphere. The presence of ethylendiamine was found to increase the selectivity in the formation of the *Z*-olefins and to avoid the over reduction of the substrates into alkane.

To our delight, a clean conversion of the skipped triyne **85** into the corresponding *Z-Z* diene-alkyne system **86** was obtained in 75% yield. The subsequent deprotection of the triple bond with potassium carbonate afforded unsaturated compound **79**.

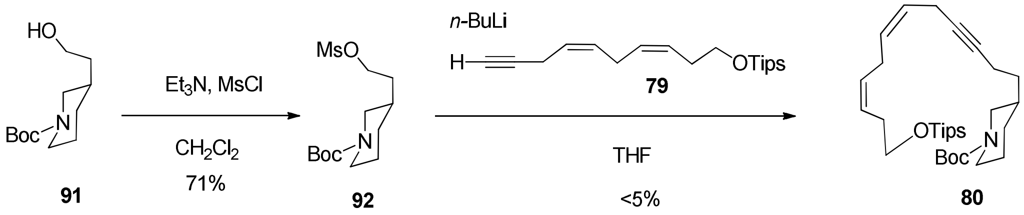

TMS
OTips
85
P-2-Ni, H_2
EtOH
75%
TMS
OTips
86
K_2CO_3, MeOH
74%
H
OTips
79

Scheme 3.27 Synthesis of unsaturated chain.

Following this simple protocol we were able to obtain in few steps the nucleophilic unsaturated chain **79** ready to be incorporated into the piperidine ring.

3.3.3.3. Incorporation of the Unsaturated Chain into the Piperidinic Model Compound

The preparation of the required mesyl-substituted piperidine was achieved using the commercial 3-ethanol piperidine **91** as starting material. Unfortunately the reaction of the piperidine **92** with our unsaturated carbon chain **79** gave unsatisfactory results. When the reaction was conducted using buthyllithium[121] at room temperature, it was possible to observe the formation of a small quantity of product and unreacted starting material, while an increase of the temperature or the reactions time led to the degradation of the chain.



Scheme 3.28 Installation of carbon chain **79**.

We thought that the problem could be found in the poor stability of the unsaturated chain in a basic media which probably caused the isomerization of the double bonds system and didn't allow the formation of the desired anion necessary to perform the alkylation reaction.

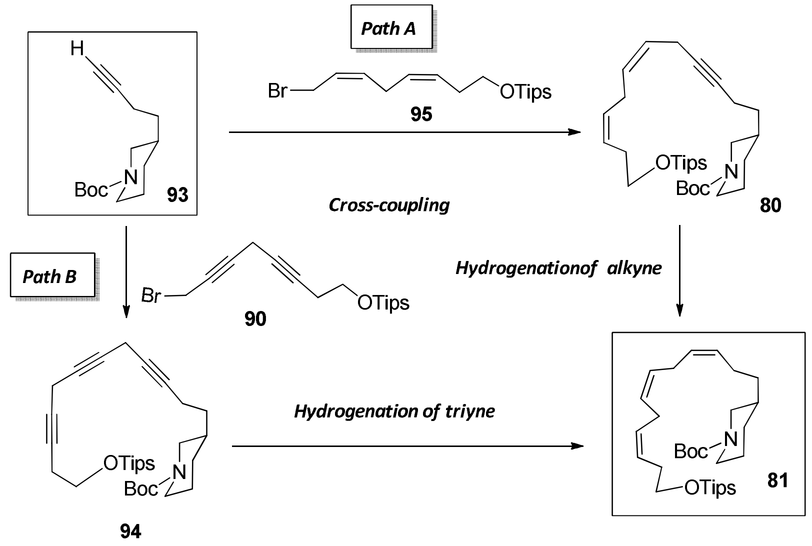
3.3.3.4. Synthesis of *Z*-Skipped D Ring of Madangamine A: Second Synthetic Approach

In order to overcome the alkylation problems we decided to change our strategy using piperidine **93** bearing a side chain at C-3 position with an acetylenic moiety. The new synthetic plan would involve an alkylation reaction between **93** and the unsaturated chain **95**. The subsequent selective reduction of the triple bond of compound **80** would afford the *Z*-triene **81** required in our macrocyclization studies (Path A).

Another alternative approach would contemplate a copper cross-coupling reaction between the piperidine **93** and skipped diyne **90**. The simultaneously hydrogenation of the triyne **94** would lead to the synthesis of the required *Z*-skipped double bond system **81** (Path B).

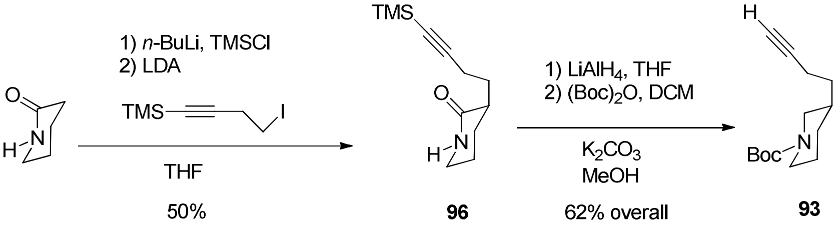
---

[121] (a) Du, Y.; Zheng, J.-F.; Wang, Z.-G.; Jiang, L.-J.; Ruan, Y.-P.; Huang, P.-Q. *J. Org. Chem.* **2010**, *75*, 4619–4622. (b) Schumacher, R. F.; Rosário, A. R.; de Souza, A. C. G.; Menezes, P. H.; Zeni, G. *Org. Lett.* **2010**, *12*, 1952–1955. (c) Davison, E. C.; Fox, M. E.; Holmes, A. B.; Roughley, S. D.; Smith, C. J.; Williams, G. M.; Davies, J. E.; Raithby P. R.; Adams, J. P.; Forbes, I. T.; Press, N. J.; Thompson, M. J. *J. Chem. Soc., Perkin Trans 1*, **2002**, 1494–1514.


Path A
Br
OTips
95
Cross-coupling
93
Boc
N
H
80
OTips
Boc
N
Hydrogenationof alkyne
Path B
Br
90
OTips
94
OTips
Boc
N
Hydrogenation of triyne
81
Boc
N
OTips

Scheme 3.29 Alternative approaches.

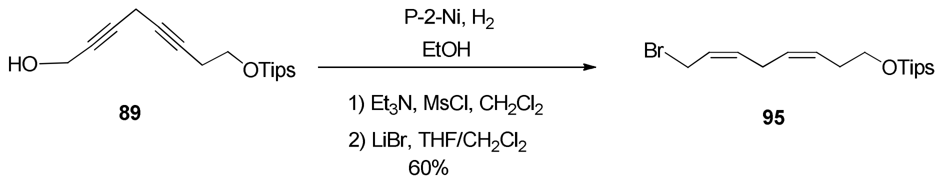
The starting piperidinic material **93** was readily obtained through an alkylation at α C=O position of the *δ*-valerolactam with the appropriate carbon chain. The iodo-derivatives was prepared from TMS-protected 3-butynol and introduced at the C-3 position of the valerolactam giving compound **96**. The subsequent reduction of the amide with $LiAlH_4$, followed by the formation of *N*-Boc carbamate and the deprotection of the triple bond afforded compound **93**.


1) n-BuLi, TMSCl
2) LDA
TMS
I
THF
50%
O
H
N
TMS
O
H
N
96
1) LiAlH4, THF
2) (Boc)2O, DCM
K2CO3
MeOH
62% overall
H
Boc
N
93

Scheme 3.30 Construction piperidine model.

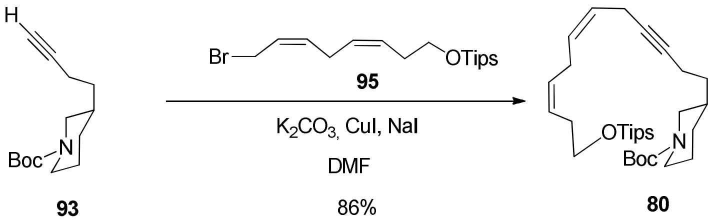
3.3.3.5. Model Studies Toward the Construction of the D Ring of Madangamine A: Path A

The required unsaturated carbon chain was readily available starting from the previously synthesized compound **89**. Thus, the dyine was transformed in the corresponding olefin, through a selective Brown hydrogenation, and subsequently converted into the bromo-derivative **95**.



Scheme 3.31 Synthesis of unsaturated carbon chain **95**.

Finally the cross-coupling reaction between bromo-derivative chain **95** and piperidine **93** took place giving piperidinic compound **80** with excellent yields.

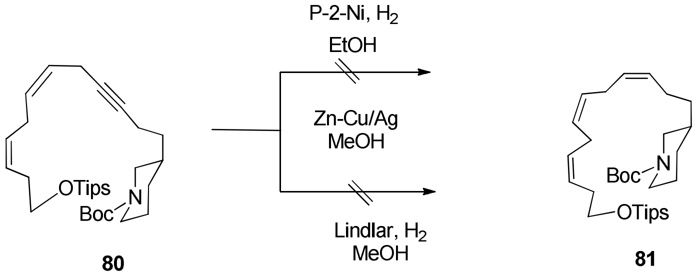


Scheme 3.32 Cross coupling reaction.

The crucial hydrogenation step of the triple bond of compound **80** presented some problems. The use of the Brown's P-2-Ni catalyst resulted unsuccessful and when was substituted with the classical Lindlar's catalyst no conversion to piperidine **81** were observed. A third approach was based on the use of Zn(Cu/Ag) reagent as catalytic system[122] but neither this methodology was able to perform the expected hydrogenation of the triple bond.

---

[122] (a) Näf, F.; Decorzant, R.; Thommen, W.; Willhalm, B.; Ohloff, G. *Helv. Chim. Acta* **1975**, *58*, 1016–1037. (b) Aerssens, M. H. P. J.; Brandsma, L. *J. Chem. Soc., Chem. Commun*. **1984**, 735–736. (c) Boland, W.; Schroer, N.; Sieler, C.; Feigel, M. *Helv. Chim. Acta* **1987**, *70*, 1025–1040.


P-2-Ni, H_2
EtOH
Zn-Cu/Ag
MeOH
Lindlar, H_2
MeOH
OTips
Boc
N
80
81

Scheme 3.33 Catalytic hydrogenation.

The difficulties we found in this step made us leave this synthetic plan and undertake the pathway B.

3.3.3.6. Model Studies Toward the Construction of the D Ring of Madangamine A: Path B

Our new challenge was then represented by the synthesis of the piperidinic model compound **94** embodying the 12-membered carbon chain bearing the tryine system. Selective hydrogenation of the alkyne moieties would lead to the formation of piperidine **XXIII** which represents the platform for our macrocyclization studies.

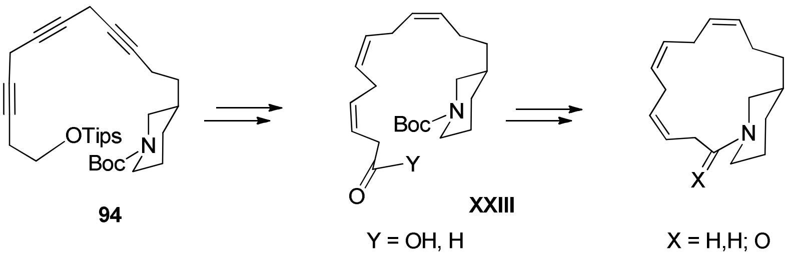
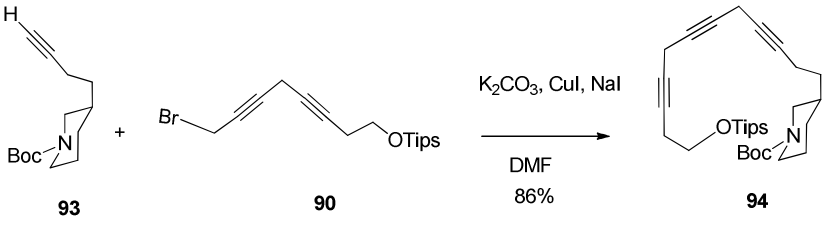

OTips
Boc
N
94
Y
O
XXIII
Y = OH, H
X
X = H,H; O

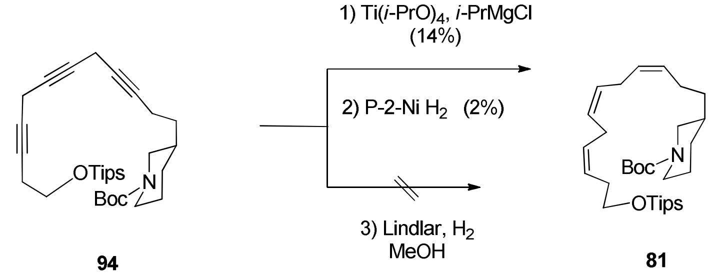
Figure 3.20 Second pathway.

Thus, compound **94** was prepared using a classical copper cross-coupling reaction between the previously synthesized diyne **90** (see Scheme 3.26) with piperidine **93**.


H
Boc
N
93
+
Br
OTips
90
K_2CO_3, CuI, NaI
DMF
86%
94

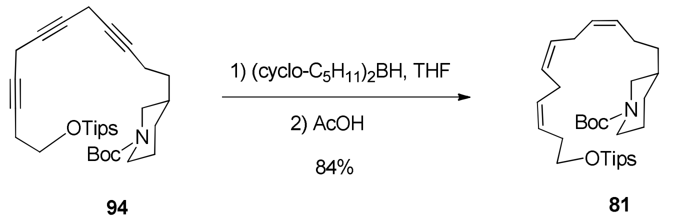
Scheme 3.34. Construction of **94**.

With compound **94** in hand we next tried to perform the selective hydrogenation reaction. In our first attempt we performed the reaction with the Lindlar's catalyst but the reaction gave a mixture of over-reduced product together with unreacted starting material. The use of Brown's catalyst or titanium isopropoxide-isopropylmagnesium chloride system[115] afforded required compound **81** with poor yields and an increase of the load of catalysts lead to the degradation of the compound, probably due to the isomerization of the unsaturated system.



Scheme 3.35 Hydrogenation of alkynes.

Therefore, in our last attempt, we decided to apply another well-known methodology used for the selective *cis*-reduction of the alkyne that involves a hydroboration reaction of the alkyne followed by protonolysis. Thus the use of dicyclohexylborane followed by treatment with acetic acid[123] was finally able to generate our compound **81** bearing the desired *Z,Z,Z*-skipped system of olefins with excellent yields.



Scheme 3.36 Hydroboration/protonolysis reaction.

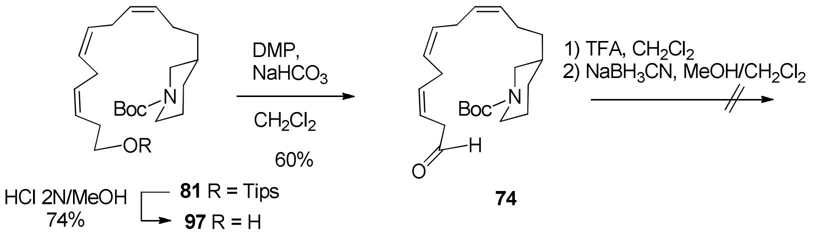
3.3.3.7. Closure of the Macrocyclic D Ring of Madangamine A

With compound **81** in hands we started to study the macrocyclization reactions that, as planned before, included an intramolecular aminoreduction or macrolactamization reactions.

---

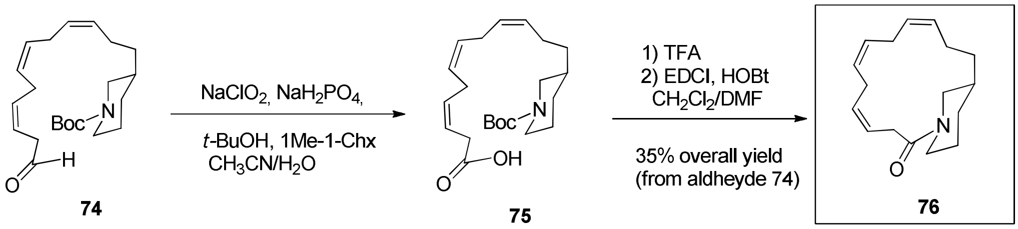
[123] Brudermüller, M.; Musso, H. *Angew. Chem., Int. Ed. Engl.* **1988**, *27*, 298–299.

The deprotection of the primary alcohol from compound **81** was achieved using hydrogen chloride[124] in methanol solution since the classical use of TBAF resulted in an isomerization of the lateral chain. The resulting alcohol **97** was then oxidized with a Dess-Martin reagent to give aldehide **74** that was used to study the intramolecular aminoreduction macrocyclization. Unfortunately the reaction didn't take place and was observed only the formation of complex products probably derived by a degradation of the starting material.


Boc
N
OR
DMP,
NaHCO$_3$
CH$_2$Cl$_2$
60%
HCl 2N/MeOH
74%
81 R = Tips
97 R = H
H
O
74
1) TFA, CH$_2$Cl$_2$
2) NaBH$_3$CN, MeOH/CH$_2$Cl$_2$
77

Scheme 3.37 Reductive amination.

The further oxidation of the aldehyde **74** to carboxylic acid **75** was performed using sodium chlorite. The following deprotection reaction gave the resulting aminoacid that was immediately treated with a combination of EDCl and HOBt which finally afforded compound **76** bearing the desired unsaturated D ring of madangamine A.


Boc
N
H
O
74
NaClO$_2$, NaH$_2$PO$_4$,
t-BuOH, 1Me-1-Chx
CH$_3$CN/H$_2$O
OH
75
1) TFA
2) EDCI, HOBt
CH$_2$Cl$_2$/DMF
35% overall yield
(from aldheyde 74)
76

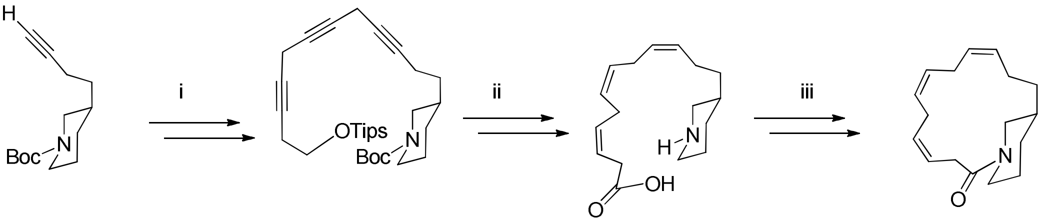
Scheme 3.38 Closure of A ring.

In summary the synthesis of the 15-membered D ring was achieved in a convergent way. The key steps included (i) a cross coupling reaction between the piperidine and the diyne chain (ii) a hydroboration followed by protonolysis and (iii) an intramolecular macrolactamization reaction.[125]

---

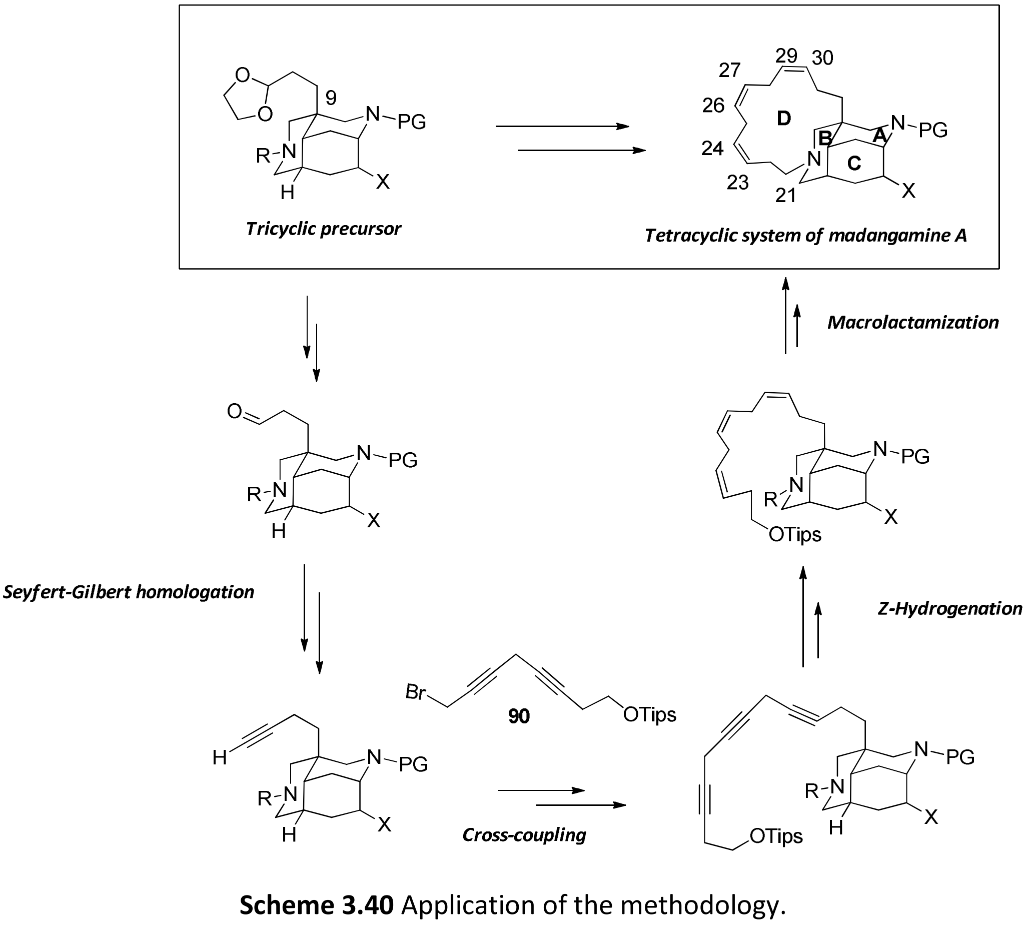
[124] (a) Ogilvie, K. K.; Thompson, E. A.; Quilliam, M. A.; Westmore, J. B. *Tetrahedron Lett.* **1974**, *15*, 2865–2868. (b) Magnus, P.; Giles, M.; Bonnert, R.; Johnson, G.; McQuire, L.; Deluca, M.; Merritt, A.; Kim, C. S.; Vicker, N. *J. Am. Chem. Soc.* **1993**, *115*, 8116–8129.

[125] Campbell, J. E.; Englund, E. E.; Burke, S. D. *Org. Lett.* **2002**, *4*, 2273–2275.


H
Boc
N
i
OTips
Boc
N
ii
H
N
OH
O
iii
N
O

Scheme 3.39 Synthesis of the A ring.

The methodology described could be applied for the synthesis of the D ring of madangamine A using an advanced tricyclic precursor bearing a cyclic acetal, precursor of an aldehyde, at C-9 position. A Seyfert-Gilbert homologation[126] reaction could convert the carbonylic group into a terminal alkyne which could react, through a cross-coupling reaction, with **90.** The result tryine would be converted to the *Z*-skipped system of olefins and cyclized to finally give the tetracyclic ABCD system of madangamine A.


O
O
9
N
PG
R
N
H
X
Tricyclic precursor
27
29
30
26
D
B
A
N
PG
24
N
C
23
21
X
Tetracyclic system of madangamine A
Macrolactamization
O
N
PG
R
N
H
X
N
PG
R
N
X
OTips
Seyfert-Gilbert homologation
Z-Hydrogenation
Br
90
OTips
H
N
PG
R
N
H
X
Cross-coupling
OTips
R
N
N
PG
H
X

Scheme 3.40 Application of the methodology.

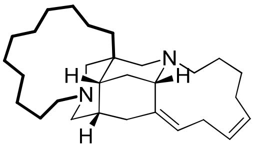
---

[126] (a) Gilbert, J. C.; Weerasooriya, U. *J. Org. Chem.* **1982**, *47*, 1837–1845. (b) Müller, S.; Liepold, B.; Roth, G. J.; Bestmann, H. J. *Synlett* **1996**, 521–522.

In summary, using appropriate simplified piperidine model compounds, we have explored different synthetic routes to construct the 13- and 14-membered D rings of madangamines C-E as well as the all-*cis*-triunsaturated 15-membered D ring of madangamine A.

3.4 CONSTRUCTION OF TETRACYCLIC ABCD SYSTEM

The results obtained in the model compounds pointed out the efficiency of the RCM reactions for the synthesis of large rings. The surprising excellent yields obtained in the construction of the 14-membered D ring, led us to madangamine D as the target molecule for our synthetic endeavor.



Madangamine D

Figure 3.21 Structure of madangamine D.

According to our investigation, the construction of the completely saturated 14-membered D ring could be reached applying the RCM protocol, previously set up on the model compound, followed by hydrogenation reaction of the resulting double bond. Thus, the synthesis of the ABCD tetracyclic system of madangamine D from an advanced tricyclic compound would involve: (i) the incorporation at N-7 position of a carbon chain with a terminal double bond and the generation of the other terminal olefin from the dioxolane; (ii) the macrocyclization by a ring-closing metathesis reaction. We hoped that the chemical behavior of the piperidine model compound could be extrapolated to our complex tricyclic diene.

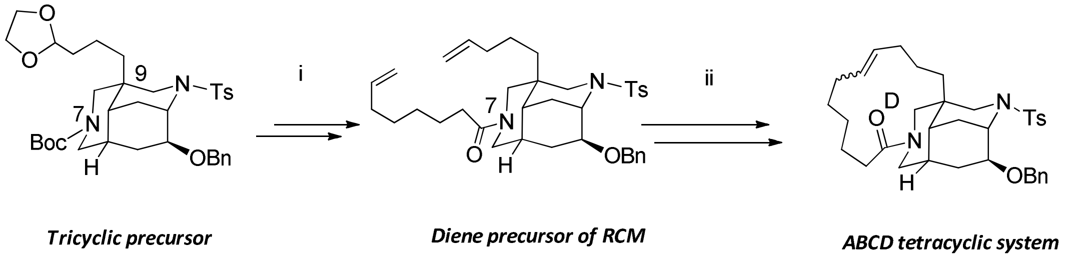
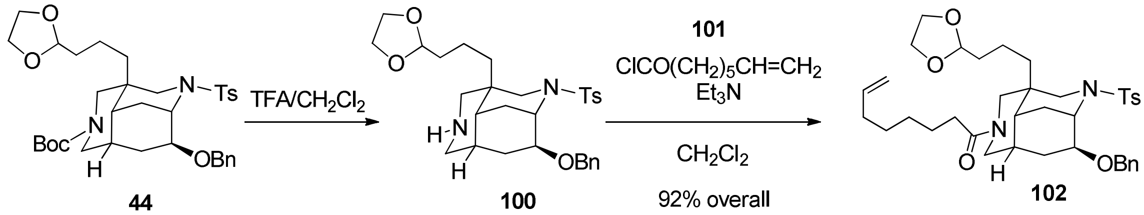


Figure 3.22 RCM strategy.

3.4.1. Assembly of the 14-Membered Ring of Madangamine D

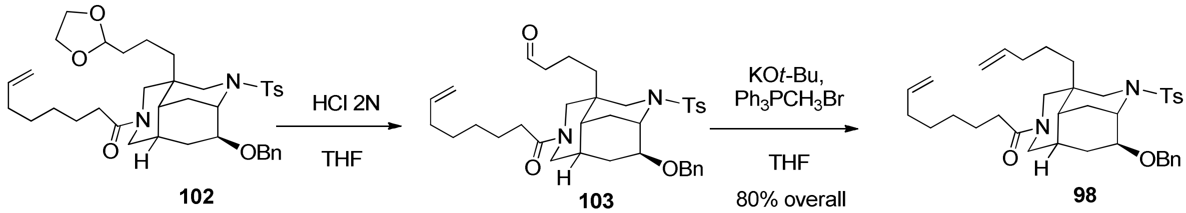
Our purpose by now is the application of the most promising RCM strategy that involve the formation of the required diene bearing a 5-membered carbon chain at C-9 position and a 8-membered chain on the nitrogen of the B ring.

The synthesis of the di-olefin started with the functionalized tricyclic compound **44** which was treated with a mixture of TFA/CH_2Cl_2 in anhydrous conditions which were necessary to perform the Boc-deprotection of the piperidinic B ring without affecting the dioxolane group. The excess of TFA was co-evaporated with toluene and the resulting amine **100** was then acylated with octenoyl chloride **101**, previously prepared from the commercial acid, affording compound **102** with excellent yields.



Scheme 3.41 Preparation of the olefin.

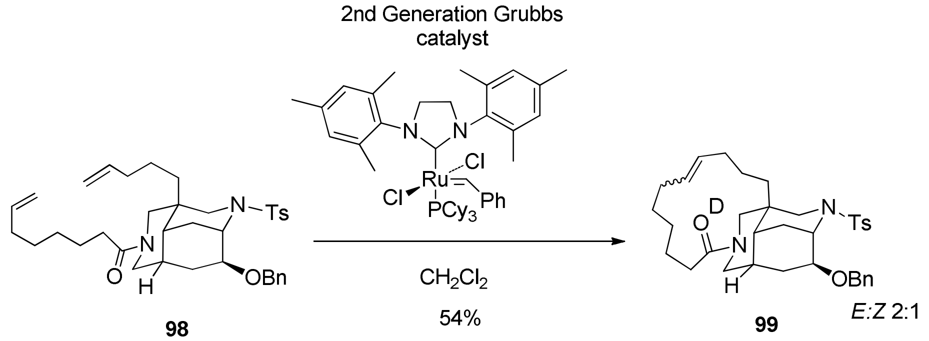
The aldehyde **103** was readily obtained after the acidic hydrolyisis of the dioxolane **102** which was immediately used in the subsequent Wittig methylenation reaction which afforded the desired di-olefin **98**.



Scheme 3.42 Synthesis of the diene **98**.

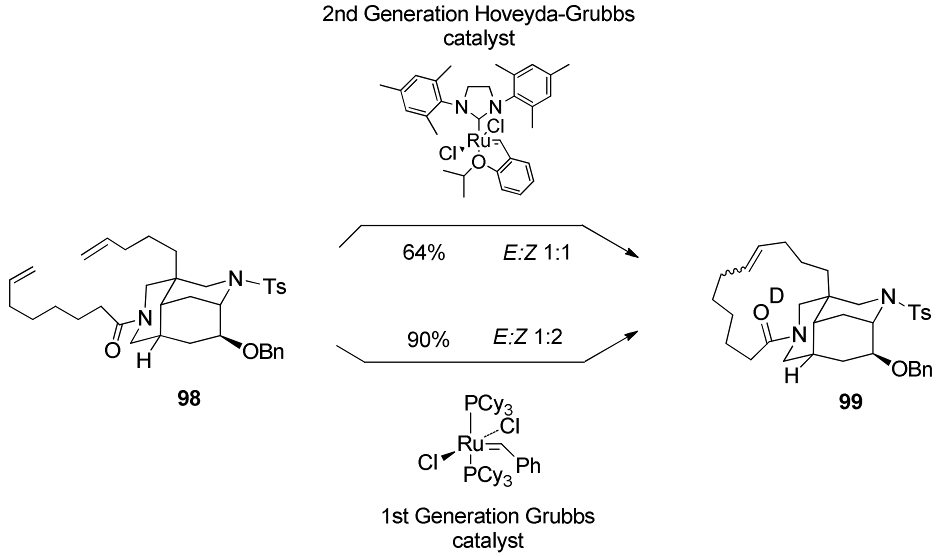
Starting from diene **98** we tried to apply the RCM protocol, described in Section 3.3.2, which involves a slowly addition of the olefin *via* syringe pump in a 0.2 mM refluxing solution of a 2nd generation Grubbs catalyst in dichloromethane. As we hoped the reaction underwent a macrocyclization and afforded the unsaturated tetracyclic system **99** in 54% of yield in a 2:1

mixture of *E*:*Z* isomers. No cross-metathesis products were observed and the reaction permitted the recovery of unreacted starting material.[47]



Scheme 3.43 RCM reaction with 2nd generation Grubbs catalyst.

The results obtained in the RCM macrocyclization reaction were satisfactory but not as excellent as the ones observed in the piperidine model. In our attempts to improve the yield of the reaction we first tried to carry out the reaction avoiding the slow addition of the diene *via* syringe pump, since we thought that the high temperature could inactivate the Grubbs catalyst. We next tried to work in a more concentrated solution but, in both cases, we were not able to improve the yields. Taking into account that our efforts for optimize the metathesis reaction were unsuccessful (change of temperature, catalyst's loading, solvent and time of reaction) and, considering that we were far from the end and a consistent amount of tetracycle compund **99** were needed to complete the synthesis, we decided to carry out the reaction using other ruthenium catalysts. Thus, when the reaction was conducted with a 2nd generation Hoveyda-Grubbs catalyst, we observed a little yield improvement (64%) and a substantial difference in the *E*:*Z* ratio (1:1). To our delight, the reaction of diene **98** with the 1st generation Grubbs catalyst afforded the desired unsaturated tetracyclic system **99** with 90% yield and a complete inversion of the *E*:*Z* ratio selectivity (*E:Z* ratio 1:2), compared with the use of the 2nd generation Grubbs catalyst.


2nd Generation Hoveyda-Grubbs catalyst
64% E:Z 1:1
90% E:Z 1:2
1st Generation Grubbs catalyst
98
99
N–Ts
OBn
H
O
D
Ru
Cl
PCy3
Ph

Scheme 3.44 Annulation of macrocyclic ring D.

Grubbs and coworkers, in a recent study[127] toward the RCM reaction of a 14-membered lactone, have showed the existence of a significant difference of stereoselectivity in the use of the first or second generation Grubbs catalysts. The graphic below shows the sterechemical *E/Z* depedence of the reaction on the the type of catalysts used in the RCM of a 14-membered ring. In addition, the high *trans*-preference observed in the reaction with the 2nd generation catalyst seems to be due to secondary isomerization of the ring-closed product.

These results can be extrapolated to our substrate to explain the observed *E/Z* stereoselectivity.

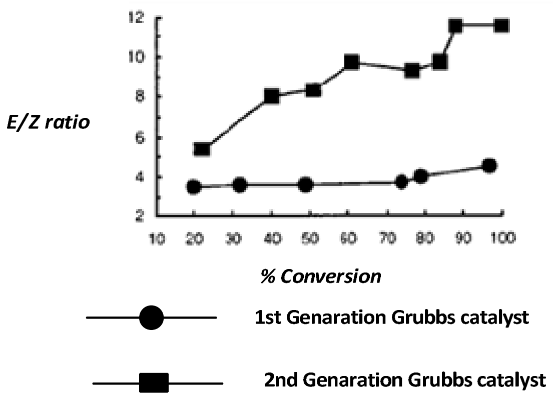
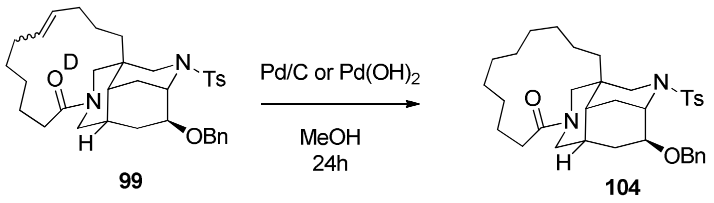


Figure 3.23 Stereoselectivity of Grubbs catalysts.

---

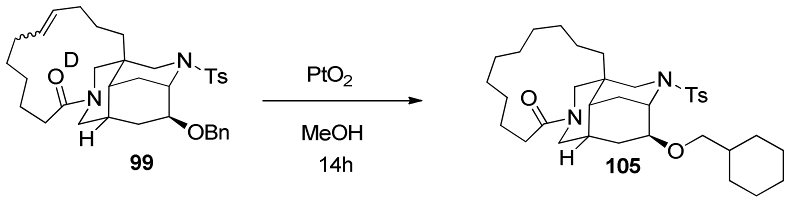
[127] (a) Lee, C. W.; Grubbs, R. H. *Org. Lett.* **2000**, *2*, 2145–2147. (b) For reviews of the alkene-metathesis reaction, see reference 58.

The subsequent hydrogenation at atmospheric pressure of compound **99**, with conventional palladium catalyst [Pd/C or $Pd(OH)_2$] in common solvents, such as methanol, ethanol and THF, led to the formation of tertracyclic system **104** but wasn't able to remove the benzyl group from the tertiary alcohol.


D
O
N
H
N
Ts
OBn
99
Pd/C or Pd(OH)2
MeOH
24h
O
N
H
N
Ts
OBn
104

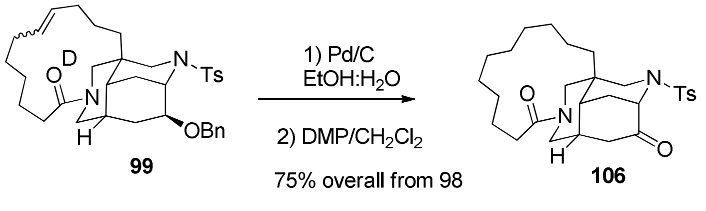
Scheme 3.45 Hydrogenation reactions.

We next tried the use of platinum oxide in methanol at room temperature and atmospheric pressure which tragically caused the hydrogenation of the benzene ring leading to the formation of compound **105**.


D
O
N
H
N
Ts
OBn
99
PtO2
MeOH
14h
O
N
H
N
Ts
O
105

Scheme 3.46 Hydrogenation with PtO_2.

The problem was finally solved changing the solvent. The use of Pd/C catalyst in a 9:1 solution of ethanol and water at last permitted to afford tertiary alcohol which was immediately oxidized to ketone **106** with Dess-Martin periodinane.


D
O
N
H
N
Ts
OBn
99
1) Pd/C
EtOH:H2O
2) DMP/CH2Cl2
75% overall from 98
O
N
H
N
Ts
O
106

Scheme 3.47 Synthesis of the tetracyclic ketone.

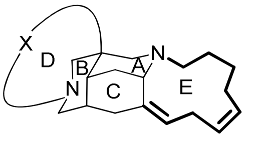
Tetracyclic compound **106** represents an important intermediate in our synthesis since can be produced in high yields with only few steps starting from the functionalized diazatricyclic core. Therefore the presence of the ketone moiety, at C-3 position, makes this compound the perfect candidate to reach the final stage of the synthesis: the elaboration of the last E ring.

In summary we have validated and optimized the RCM methodology previously studied on the piperidinic model compound and we have set up a protocol that permitted to achieve the synthesis of the functionalized tetracyclic ABCD system of madangamine D from diene **98** with an almost quantitative yield and using a very efficient synthetic procedure.

The next phase of our work will include the construction of the eastern E ring of the alkaloid which would lead to complete the first total synthesis of madangamine D.

3.5. ANNULATION OF MACROCYCLIC RING E

The 11- membered E ring common of madangamine A-E possess a peculiar motif formed by a *Z,Z* skipped system of olefins. In Section 3.3.3 we have already presented the features of this structure and point out its complexity from a synthetically point of view. The construction of the E ring of madangamines is even more synthetically intricate since one of the *Z*-olefin, which forms the skipped system, is directly connected with the C ring of the alkaloid.



Madangamine A-E

Figure 3.24 General structure of madangamines.

With the tetracyclic ABCD ketone **106** in hands our synthetic plan for the assembly of the eastern E ring of madangamine will involve two different strategies:

- A stepwise pathway described by Kibayashi which would start with a Still-Gennari modification of the Horner-Wadsworth-Emmons olefination[128] to install the C-3/C-20 *Z*-double bond. The remaining six carbon of the lateral chain would be inserted through a palladium-catalyzed coupling reaction with the appropriate (*Z*)-

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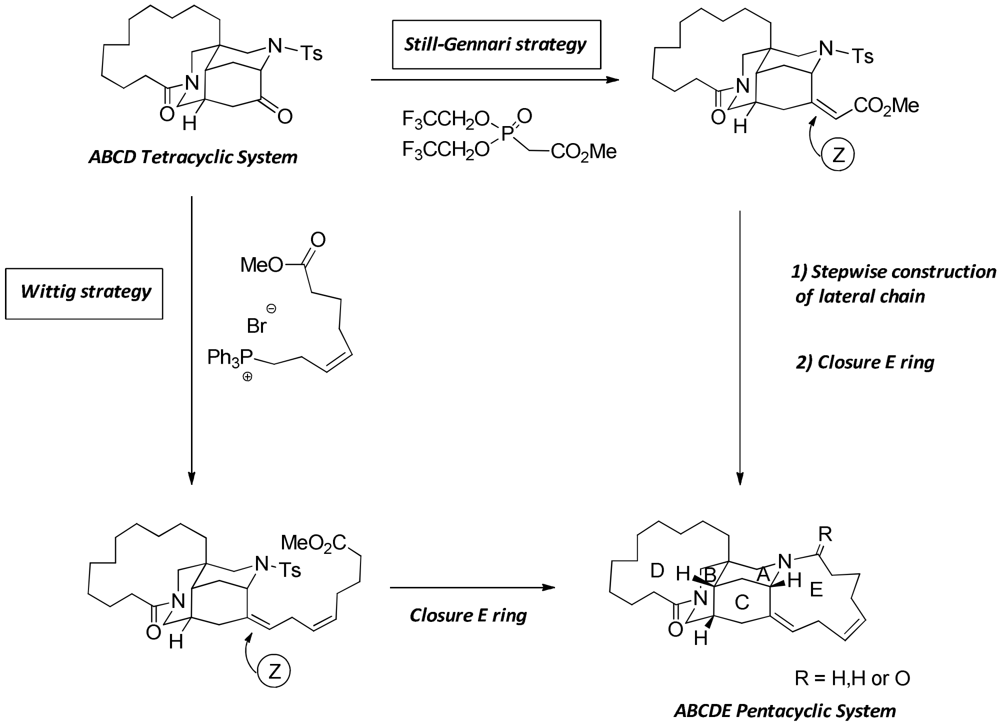
[128] Still, W. C.; Gennari, C. *Tetrahedron Lett.* **1983**, *24*, 4405–4408.

vinylstannane while the annulation of the E ring could be performed with a reductive amination.

- A convergent strategy in which a Wittig reaction between the tetracyclic ketone and a suitable phosphonium salt would incorporate the required 8-membered *Z,Z* skipped chain in a single step. The subsequent intramolecular macrolactamization reaction would afford the desired pentacyclic system.


ABCD Tetracyclic System
Still-Gennari strategy
Wittig strategy
1) Stepwise construction of lateral chain
2) Closure E ring
Closure E ring
R = H,H or O
ABCDE Pentacyclic System

Scheme 3.48 Synthetic strategies.

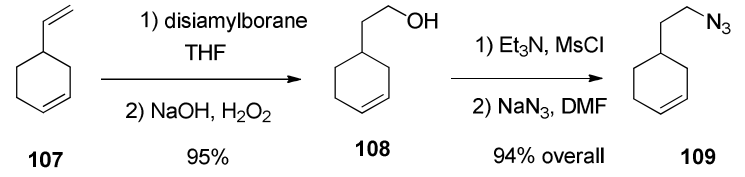
The synthetic plan for the annulation of the E ring will follow the trend used until now, consisting on the exploration of different methodologies first on simple model compounds and the application of the more promising protocol on our tetracyclic system.

3.5.1. Synthesis of Model Compounds

The morphan model was synthesized thanks to the important collaboration of Federica Romagnoli who, despite the short time spent in our laboratories, was able to give a priceless contribution in the project.

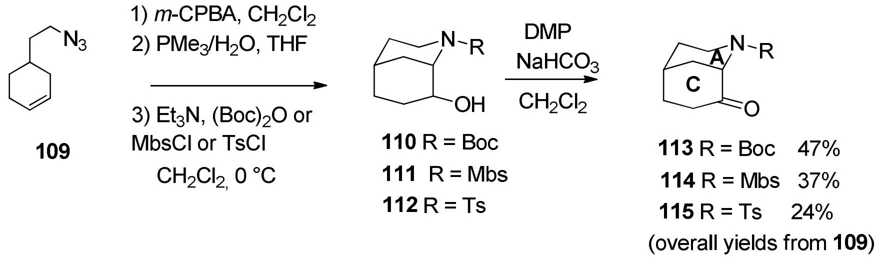
Thus, the AC model compound was constructed, in very few steps, starting from the commercially available 4-vinylcyclohexene and using, as a key step, the intramolecular aminohydroxidation methodology previously described in the synthesis of the ABC core of madangamine.

The hydroboration of the exocyclic double bond of **107** afforded the primary alcohol **108** which was easily converted, through a two steps sequence, to the corresponding azide **109**.


1) disiamylborane
THF
2) NaOH, H_2O_2
95%
OH
1) Et_3N, MsCl
2) NaN_3, DMF
94% overall
N_3
107
108
109

Scheme 3.49 Synthesis of azide **109**.

The construction of the A ring was achieved via epoxidation of the cyclohexene double bond of **109** followed by a Staudinger reduction of the azide moiety. The initially formed amino epoxide underwent a smooth in situ cyclization, directly leading to the corresponding amino alcohols (**110, 111** and **112**), which were then *N*-protected and immediately oxidized to ketones **113**, **114** and **115**.


N_3
109
1) m-CPBA, CH_2Cl_2
2) PMe_3/H_2O, THF
3) Et_3N, $(Boc)_2O$ or
MbsCl or TsCl
CH_2Cl_2, 0 °C
N~R
OH
110 R = Boc
111 R = Mbs
112 R = Ts
DMP
$NaHCO_3$
CH_2Cl_2
N~R
A
C
O
113 R = Boc 47%
114 R = Mbs 37%
115 R = Ts 24%
(overall yields from 109)

Scheme 3.50 Construction of AC morphan models.

This synthetic plan allowed to access to a azabicyclic system which represents not only the AC fragment of madangamine but a model compound, similar to the Kibayashi's one, we can use to test different methodologies to access to the 11-membered *Z,Z* unsaturated E ring.

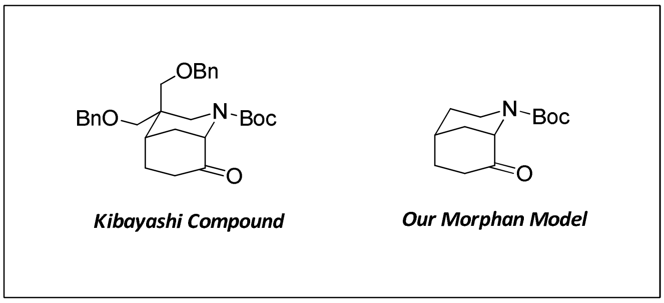
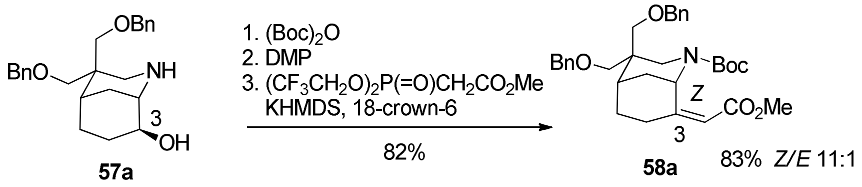

OBn
BnO
N~Boc
O
Kibayashi Compound
N~Boc
O
Our Morphan Model

Figure 3.25 Model compounds.

3.5.2. Annulation of E Ring on Model Compounds

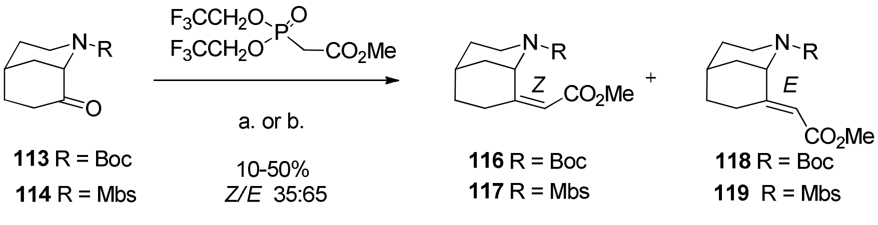
3.5.2.1 Still-Gennary Strategy

The construction of the 11-membered E ring of madangamine was successful achieved by Kibayashi and coworkers in 2006[40] starting from the morphan system **57a**.[129] The methodology used to install the crucial *Z*-unsaturation at the C-3 position involved a Still-Gennari (*Z*)-selective Wittig-Horner olefination, which afforded the resulting ester **58a** with an incredible high *E:Z* ratio of 11:1.


OBn
BnO
NH
3
OH
57a
1. (Boc)2O
2. DMP
3. (CF3CH2O)2P(=O)CH2CO2Me
KHMDS, 18-crown-6
82%
OBn
BnO
N
Boc
Z
CO2Me
3
58a
83% Z/E 11:1

Scheme 3.51 Still-Gennari reaction.

Taking into account that, apparently, this strategy has demonstrated to be particularly effective in the installation of the *Z*-isomer of the related ester, we decided to test the Kibayashi's methodology in our model compounds **113** and **114**. Unfortunately the application of the described Still-Gennari olefination under either the original[119] or slightly modified[130] reaction conditions resulted in the generation of *Z*/*E* mixtures of alkenes, in which the undesired *E*-isomer was predominant (35:65 ratio).


N
R
O
113 R = Boc
114 R = Mbs
F3CCH2O
F3CCH2O
P
O
CO2Me
a. or b.
10-50%
Z/E 35:65
N
R
Z
CO2Me
116 R = Boc
117 R = Mbs
+
N
R
E
CO2Me
118 R = Boc
119 R = Mbs

Conditions: a. KHMDS, 18-crown-6, THF, −78 °C
b. LiCl, DBU, THF,−78 °C

Scheme 3.52 Application of Kibayashi protocol.

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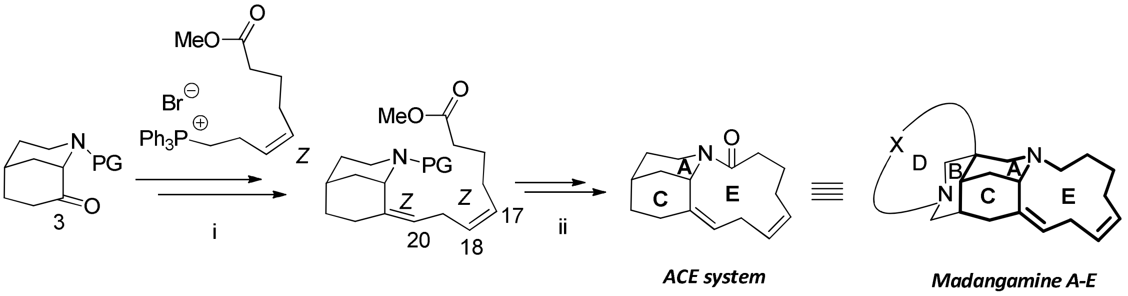
[129] See section 1.5.2

[130] Blanchette, M. A.; Choy, W.; Davis, J. T.; Essenfeld, A. P.; Masamune, S.; Roush, W. R.; Sakai, T. T*etrahedron Lett.* **1984***,* *25*, 2183–2186.

3.5.2.2. Wittig Strategy

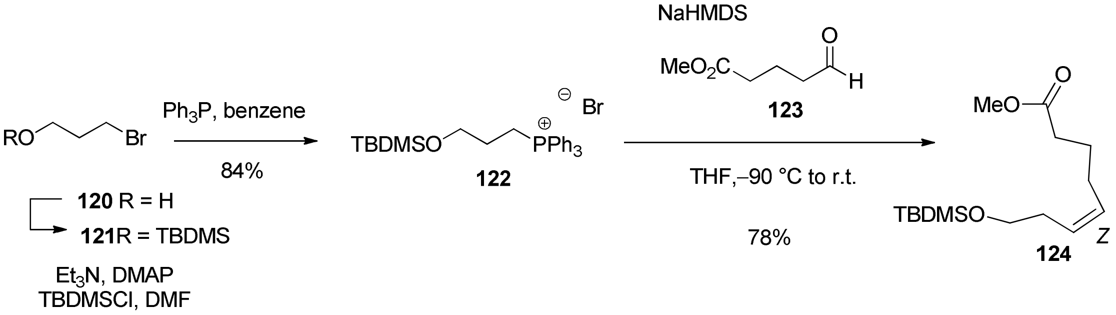
In view of these disappointing results we decided to put aside this stepwise strategy and undertake another synthetic route that would involve (i) the direct installation of the eight-membered carbon chain at C-3 position, and (ii) the subsequent annulation of the E ring through an intramolecular macrolactamization. We were convinced that the required *Z,Z* poli-unsaturated system could be directly installed to our azabicycle model using a *Z*-selective Wittig reaction with an appropriate phosphonium salt. The control over the selectivity of the reaction could be achieved using a suitable "nonstabilized" phosphonium salt. This ideal ylide already contains the central *cis* C-17/C-18 double bond present in the E ring of madangamines, and possesses the ester functionality required for the final macrolactamization.



MeO
O
Br
Ph3P
Z
N
PG
O
3
i
MeO
O
N
PG
Z
Z
17
20
18
ii
N
O
A
C
E
ACE system
X
D
B
A
N
N
C
E
Madangamine A-E

Scheme 3.53 Wittig strategy.

The desired unsaturated chain **124** was prepared, as a single *cis*-isomer, through a Wittig reaction between the phosphonium bromide **122**, prepared starting from 3-bromopropanol, and methyl-5-oxopentanoate **123**.



RO
Br
Ph3P, benzene
84%
120 R = H
121R = TBDMS
Et3N, DMAP
TBDMSCl, DMF
TBDMSO
Br
PPh3
122
NaHMDS
MeO2C
O
H
123
THF,–90 °C to r.t.
78%
MeO
O
TBDMSO
Z
124

Scheme 3.54 Construction of unsaturated chain **124**.

The required Wittig reactive was readily obtained after the deprotection of the silyl ether **124** and the subsequent transformation of the resulting alcohol **125** into the phosphonium salt **126.**[131]

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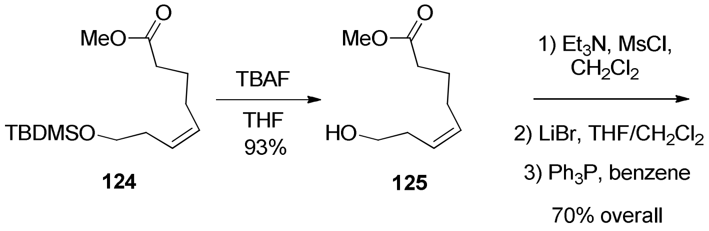
[131] The synthesis of the phosphonium salt 126 was accomplished by modification of known procedures: (a) Zamboni, R.; Milette, S.; Rokach, J. *Tetrahedron Lett.* **1983***, 24*, 4899–4902. (b) Wang, S. S.; Rokach, J.;


MeO
O
TBDMSO
124
TBAF
THF
93%
MeO
O
HO
125
1) Et3N, MsCl, CH2Cl2
2) LiBr, THF/CH2Cl2
3) Ph3P, benzene
70% overall
MeO
O
Br
Ph3P
126

Scheme 3.55 Synthesis of phosphonium salt **126**.

Compound **126** belongs to the nonstabilized class of ylides, which doesn't possess conjugating substituents (e.g., COOMe, CN or SO_2Ar) on the ylidic carbon, and that generally reacts in Wittig reactions under kinetic control giving preferentially *Z*-olefins.

The carbonyl compound and the ylide approach at right angles and large substituents are kept away from each other due to the steric effects. The first step of the Wittig reaction is represented by the formation of the oxaphosphetane in which the steric 1,2 or 1,3 repulsions lead to the distortion of the cycle and the formation of a *syn*-puckered-oxaphosphetane which can undergo in a *syn*-elimination to give preferentially the corrisponding *Z*-alkene.

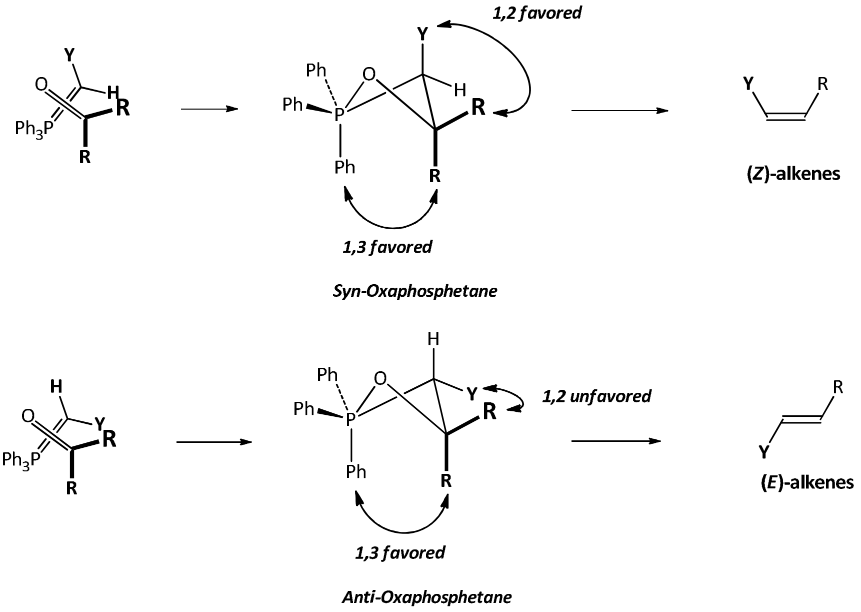

Y
O
H
R
Ph3P
R
Ph
Ph
Ph
O
Y
H
R
R
1,2 favored
1,3 favored
Syn-Oxaphosphetane
Y
R
(Z)-alkenes
H
O
Y
R
Ph3P
R
Ph
Ph
Ph
O
H
Y
R
R
1,2 unfavored
1,3 favored
Anti-Oxaphosphetane
R
Y
(E)-alkenes

Figure 3.26 Stereoselectivity in Wittig reactions.

The critical coupling reaction between phosphonium salt **126** and the morphan model compound **115** conducted to the formation of desired compounds **127** and **128** with an

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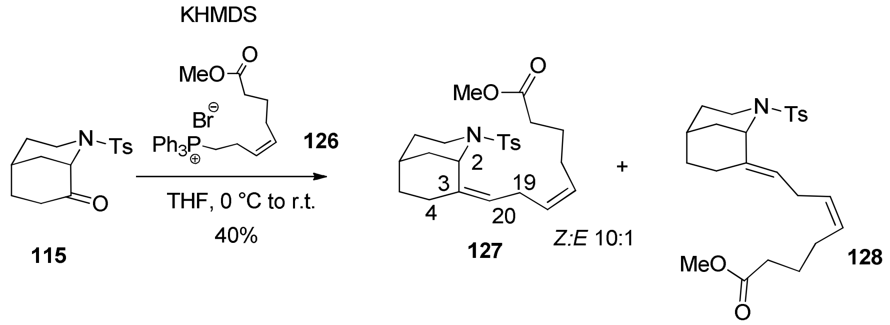
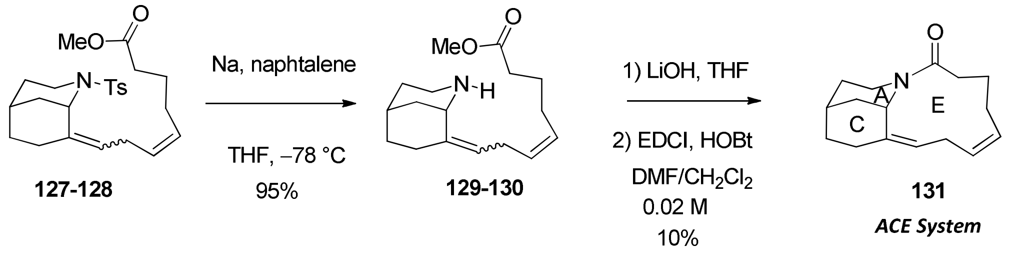
Powell, W. S.; Dekle, C.; Feinmark, S. J. *Tetrahedron Lett.* **1994**, *35*, 4051–4054. (c) Sandri, J.; Viala, J. *J. Org. Chem.* **1995**, *60*, 6627–6630.

excellent *E*:*Z* ratio of 1:10, confirmed by 2D NOESY experiment, which clearly showed the presence of a NOE effects between H-4/H-20 and H-2/H-19.


KHMDS
MeO
O
Br
Ph3P
126
N
Ts
O
115
THF, 0 °C to r.t.
40%
MeO
O
N
Ts
2
3
19
4
20
127
Z:E 10:1
+
N
Ts
MeO
O
128

Scheme 3.56 Wittig reaction.

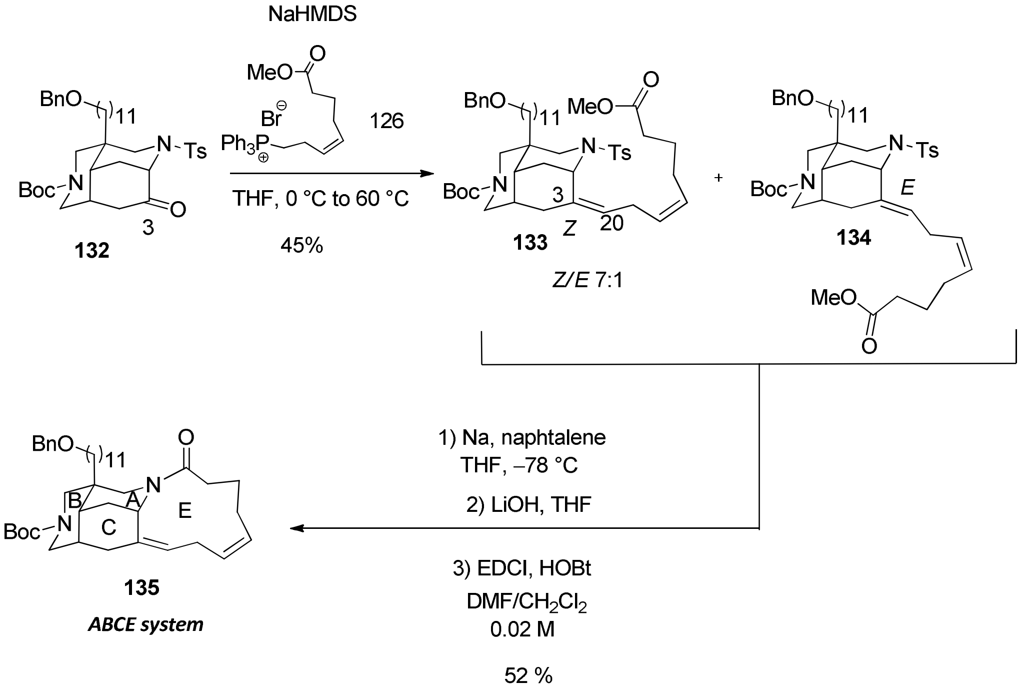
Once we installed the fragment C-13/C-20 on the azabicyclic morphan we applied the macrolactamization protocol that would led to the synthesis of the ACE ring system of madangamine. The synthetic plan involved the removal of the sulfonamide protecting group from **127** and **128**, with a sodium naphtalenide solution, followed by hydrolysis of the ester moiety which provided the resulting amino acids. The crude compounds were finally treated with a HOBt/EDCl mixture of coupling agents that afforded tricyclic lactam **131**, bearing the (*Z*,*Z*)-unsaturated 11-membered ring of the target alkaloids.


MeO
O
N
Ts
127-128
Na, naphtalene
THF, –78 °C
95%
MeO
O
N
H
129-130
1) LiOH, THF
2) EDCI, HOBt
DMF/CH2Cl2
0.02 M
10%
O
N
A
E
C
131
ACE System

Scheme 3.57 Closure of E ring.

Completely satisfied with this results we decided to go a little further and apply the same methodology described for the morphan using the fully-functionalized tricyclic compound **132**.

Thus, the required *Z*-selective Wittig reaction, conducted with potassium hexamethyldisilazide, wasn’t able to afford the desired compound and it has been necessary a substitution with sodium hexamethyldisilazide and a slight warming of the solution to accelerate the reaction. After one hour at 60 °C the desired *Z*-exo-olefin was obtained as a mayor product (*E*:*Z* ratio of 7:1) with 45% of yield. The inseparable mixture of diastereomeric compounds **133** and **134** were transformed into amino acids, and finally subjected to the described intramolecular macrolactamization reaction which provided the ABCE tetracyclic system **135**.

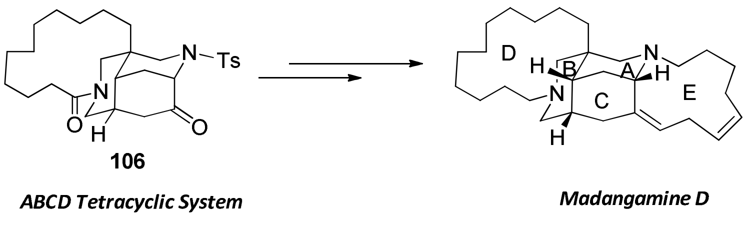

NaHMDS
MeO
O
Br
126
Ph3P
THF, 0 °C to 60 °C
45%
BnO
11
N-Ts
Boc-N
3
O
132
MeO
3
Z
20
133
Z/E 7:1
+
E
134
1) Na, naphtalene
THF, –78 °C
2) LiOH, THF
3) EDCI, HOBt
DMF/CH2Cl2
0.02 M
52 %
B
A
C
E
N
135
ABCE system

Scheme 3.58 Synthesis ABCE system.

These results confirm the efficiency of this procedure for the assembly of the eastern E ring. The synthetic plan for the stereoselective installation of the C-13/C-20 fragment was first achieved using the AC system and then validated on a complex functionalized diazatricyclic ring, while the efficiency of the intramolecular macrolactamization for the construction of the 11-membered ring was confirmed in both models.

3.5.3. Synthesis ABCDE Pentacyclic System of Madangamine D

At this stage the next last challenge was represented by the annulation of the last eastern E ring, which access could be achieved applying the described methodology on the tetracyclic ABCD system of madangamine D.

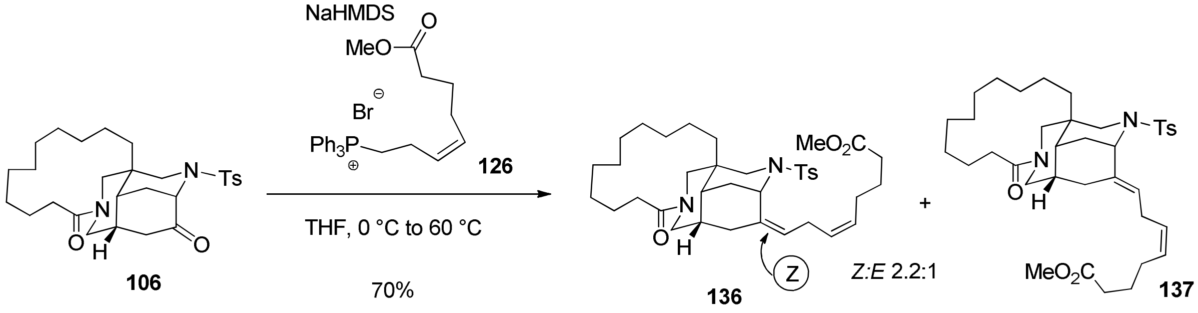

N-Ts
N
O
H
O
106
ABCD Tetracyclic System
D
H
B
A
H
N
N
C
E
H
Madangamine D

Scheme 3.59 From tetracycle to madangamine D.

The incorporation of the (*Z*,*Z*)-unsaturated eight-carbon fragment, required to complete the synthesis of madangamine D, was carry out, as previously described for the models, using the phosphonium salt **126** and the tetracyclic ketone **106**. In our first attempts the reaction gave a mixture of complex products and no traces of the desired compounds were observed. The problem was found in the extremely hygroscopicity of the phosphonium salt which impeded the formation of the ylide.[132] In fact only when **126** was dried by repeated dilution/re-concentration in dry 1:1 THF: toluene, followed by overnight subjection in vacuo with inline phosphorous pentoxide, was able to react with sodium hexamethyldisilazide affording the typical orange color of the ylide.

Apparently this problem was not observed in the previously assays withy the bi- or tricyclic model compounds because of the larger-scale of the reactions. In our case the process was conducted with only few milligrams of products and the presence of a minimum amount of moisture seemed to be detrimental for the outcome of the reaction.

Thus, the reaction between the tetracyclic ketone **106** and the anhydrous Wittig reactive **126** afforded the desired diastereoisomeric mixture of alkenes **136** and **137** with excellent yields but with a loss in stereoselectivity (*E*:*Z* ratio 1:2.2).



Scheme 3.60 Stereoselective Wittig reaction.

The removal of the tosyl group from compounds **136** and **137** permitted an easy separation of the diastereomeric mixture of the amines while the hydrolysis of the ester function afforded the desired carboxylic compound, which was immediately cyclized through an intramolecular macrolactamization reaction to give **138**. The annulation reaction was performed in diluted conditions and, the aminoacid compound, was slowly added *via* syringe pump over a period of six hours to a solution containing the coupling agents.

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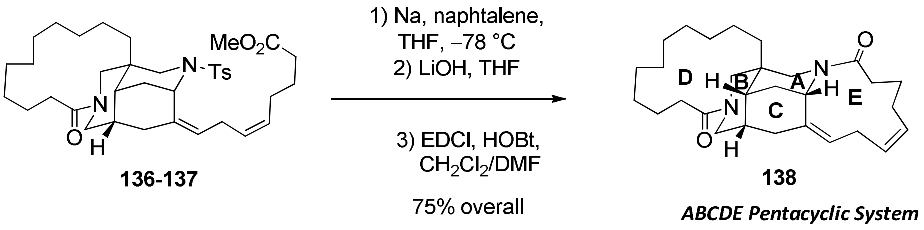
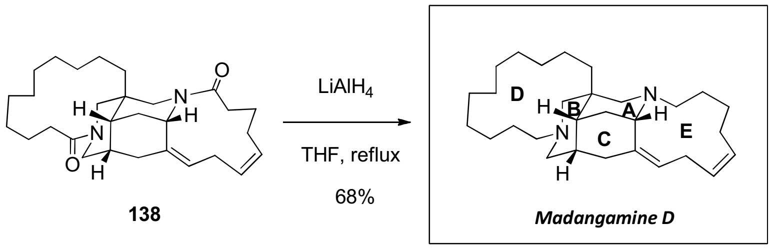
[132] Christiansen, M. A.; Andrus, M. B. *Tetrahedron Lett.* **2012**, *53*, 4805–4808.


MeO$_2$C
N-Ts
N
O
H
136-137
1) Na, naphtalene, THF, −78 °C
2) LiOH, THF
3) EDCI, HOBt, CH$_2$Cl$_2$/DMF
75% overall
O
N
D
H
B
A
H
E
N
C
O
H
138
ABCDE Pentacyclic System

Scheme 3.61 Synthesis of the pentacyclic system.

The methodology described allowed the formation of pentacyclic dilactam compound **138** with excellent yields and the final reduction of both amide with $LiAlH_4$ permitted to access to pure madangamine D. The ^1H and ^{13}C NMR data of our synthetic madangamine were coincident with those reported for the natural product.


O
H
N
H
N
O
H
138
LiAlH$_4$
THF, reflux
68%
D
H
B
N
A
H
E
N
C
H
Madangamine D

Scheme 3.62 Synthesis of madangamine D.

We have reported the first total synthesis of an alkaloid of the madangamine group,[48] and confirmed their absolute configuration which, until now, has only been inferred by correlation with that of their presumed biosynthetic precursors, ingenamines. Synthetic madangamine D possess unambiguous 2*S*, 5*S*, 9*R*, 12*R* absolute configuration and a specific rotation {[α]= + 101.3 (c 0.29, $CHCl_3$)} with the same sign as in the closely related madangamines A-C. According to these data we can confirms the absolute configuration of this alkaloid family assigned by Andersen.[19]

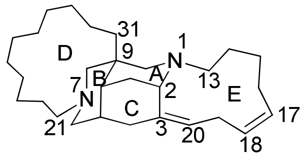
As already discuss in the previous section no biological activity data has been reported to date for madangamine D, since was isolated as inseparable mixture with madangamine E and further pharmacological research has been impeded by the low quantity of alkaloid available.

Thanks to collaboration with Pharmamar Company we could test the biological activity of madangamine D. The alkaloid showed significant in vitro cytotoxic activity against human colon HT29 (GI_{50} 4.4 µg/mL) and pancreas PSN1 (GI_{50} 7.4 µg/mL) cancer cell lines, but was inactive against lung NSCLC A549 and breast MDA-MB-231 cancer cell lines at the highest assayed concentration (>10 µg/mL).

3.6. PRIMERA SÍNTESIS TOTAL DE LA (+)-MADANGAMINA D

La madangamina D es un complejo alcaloide pentacíclico aislado de *Xestospongia ingens,* una esponja de la familia Haplosclerida que se encuentra en las aguas de la costa de la isla de Madang en Papúa Nueva Guinea.

Estructuralmente este alcaloide está constituido por un núcleo diazatricíclico central (anillos ABC) y dos puentes carbonados que forman dos macrociclos. El anillo D está formado por una cadena completamente saturada de 11 carbonos que conecta la posición C-9 con el nitrógeno N-7, mientras que el anillo E, de 11 miembros, posee un sistema insaturado de tipo "skypped" con dos *Z*-olefinas, una de ellas directamente conectada a la posición C-3 del sistema tricíclico central.



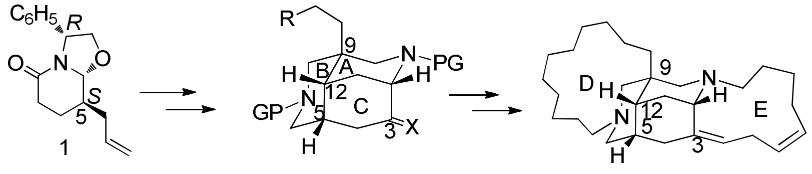
Madangamina D

Figura 3.27 Madangamina D.

Hasta el presente ninguna síntesis total de un alcaloide perteneciente a la familia de las madangaminas ha sido descrita y la actividad biológica de la madangamina D no ha sido estudiada debido a su limitada disponibilidad. En la presente Tesis Doctoral hemos querido sintetizar la madangamina D para confirmar su estructura, incluyendo su configuración absoluta, y preparar suficiente material para un eventual estudio biológico.

Nuestra estrategia sintética implica la utilización de una lactama bicíclica quiral, derivada del fenilglicinol, y a partir de esta, se pretende generar del núcleo diazatricíclico ABC con la funcionalización y la substitución requerida para la posterior construcción de los macrocíclos D y E de la madangamina D.

Construcción del núcleo tricíclico

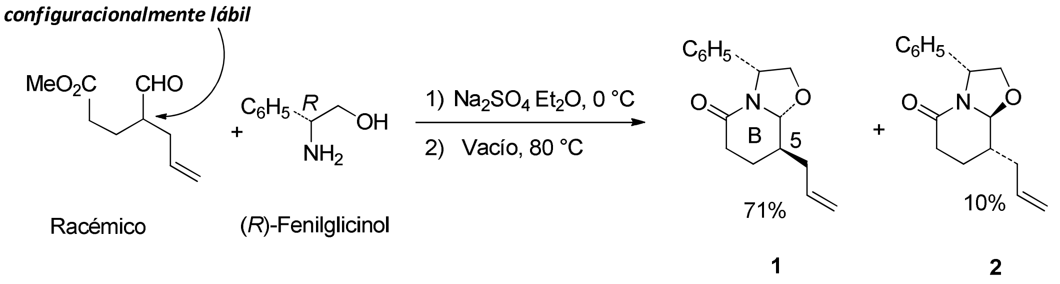


Scaffold enantiomérico de partida

Madangamina D

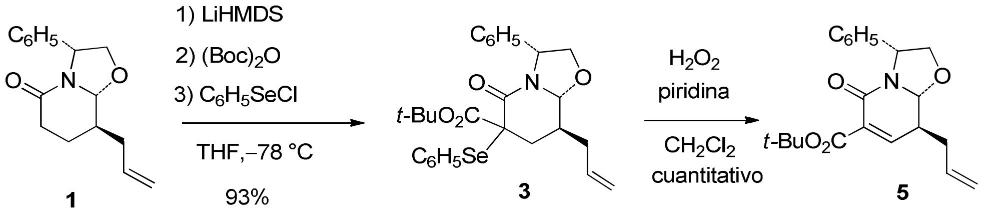
Figura 3.28 Estrategia sintética.

La lactama bicíclica **1** se preparó mediante una reacción de ciclocondensación entre el (*R*)-fenilglicinol y el 4-formil-6-heptonato, obtenido a su vez por adición conjugada del acrilato de metilo al 4-pentenal. La reacción de ciclodeshidratación conduce preferentemente a un solo estereoisómero de los cuatro posibles, debido al proceso de resolución cinética dinámica que tiene lugar por la presencia de un centro estereogénico configuracionalmente lábil en el substrato racémico. En esta etapa no solamente se generó el anillo piperidínico B de las madangaminas sino que además se instauró el primer estereocentro del alcaloide (posición 5 de las madangaminas).


configuracionalmente lábil
MeO2C
CHO
Racémico
+
C6H5
R
OH
NH2
(R)-Fenilglicinol
1) Na2SO4 Et2O, 0 °C
2) Vacío, 80 °C
C6H5
O
N
O
B
5
71%
1
+
C6H5
O
N
O
10%
2

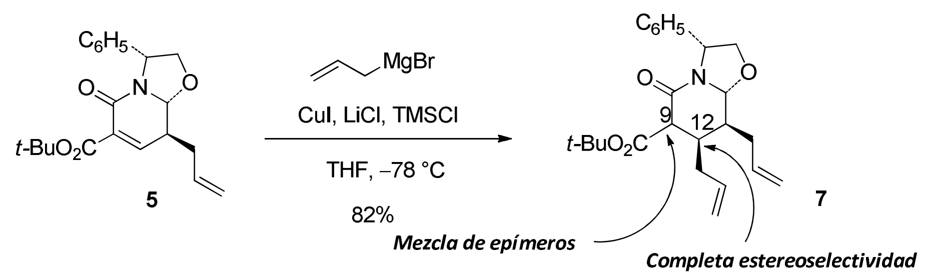
Esquema 3.63 Obtención lactama bicíclica inicial **1**. Generación primer estereocentro.

La lactama insaturada **5** fue preparada en dos etapas a partir del compuesto **1**. La introducción de *tert*-butoxicarbonilo y fenilselenio en posición α respecto al grupo carbonilo de la lactama proporcionó los seleno derivados **3**, como mezcla de isómeros en la posición C-9. La oxidación posterior del selenio con peróxido de hidrógeno en presencia de piridina, proporcionó la lactama insaturada **5**, la cual fue inmediatamente utilizada en la etapa siguiente sin previa purificación. Cabe comentar que la activación del doble enlace mediante la presencia del grupo activante alcoxicarbonilo es imprescindible para que la posterior reacción de adición conjugada tenga lugar.


C6H5
O
N
O
1
1) LiHMDS
2) (Boc)2O
3) C6H5SeCl
THF,–78 °C
93%
C6H5
O
N
O
t-BuO2C
C6H5Se
3
H2O2
piridina
CH2Cl2
cuantitativo
C6H5
O
N
O
t-BuO2C
5

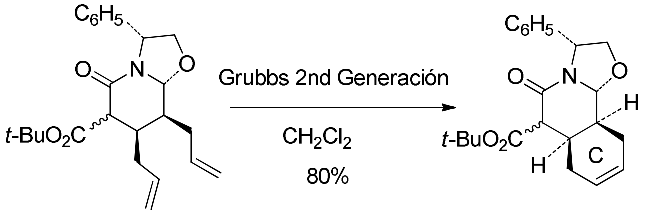
Esquema 3.64 Preparación de la lactama insaturada **5**.

La adicción conjugada del alil cuprato a lactama α,β-insaturada activada **5**, tuvo lugar de forma completamente estereoselectiva en la generación del nuevo enlace, proporcionando la diallyl lactama **7** con excelente rendimiento como mezcla de epímeros en posición 9. La reacción de adición nos permitió instalar el segundo estereocentro de la madangamina en la posición C-12 y obtener la relación *cis* entre los sustituyentes alilo, relación necesaria para la posterior construcción del anillo C.


C6H5
O
N
O
t-BuO2C
5
MgBr
CuI, LiCl, TMSCl
THF, –78 °C
82%
C6H5
O
N
O
9
12
t-BuO2C
7
Mezcla de epímeros
Completa estereoselectividad

Esquema 3.65 Adición conjugada. Generación segundo estereocentro.

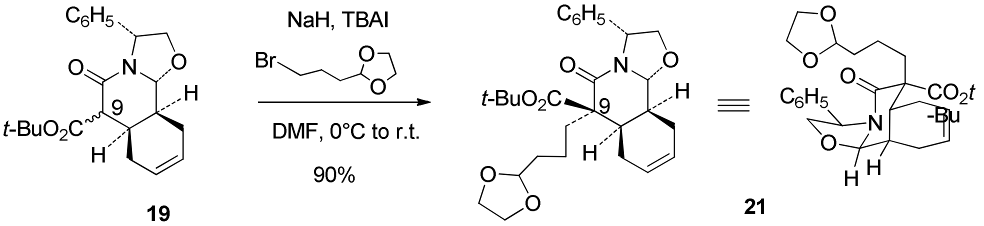
El cierre del anillo carbocíclico tuvo lugar mediante tratamiento de los dienos **7** con el reactivo de Grubbs de segunda generación que, a través de una reacción de ring-closing metátesis, generó la lactama tricíclica **19** con excelente rendimiento. El anillo C, formado a través de esta reacción, posee la instauración requerida para la construcción posterior del anillo piperidínico A necesaria para completar la síntesis del núcleo diazatríciclico de las madangaminas, que queremos construir mediante de reacción de amino-hidroxilación intramolecular.


C6H5
O
N
O
t-BuO2C
Grubbs 2nd Generación
CH2Cl2
80%
H
C

7 **19**

Esquema 3.66 Cierre del anillo carbocíclico C.

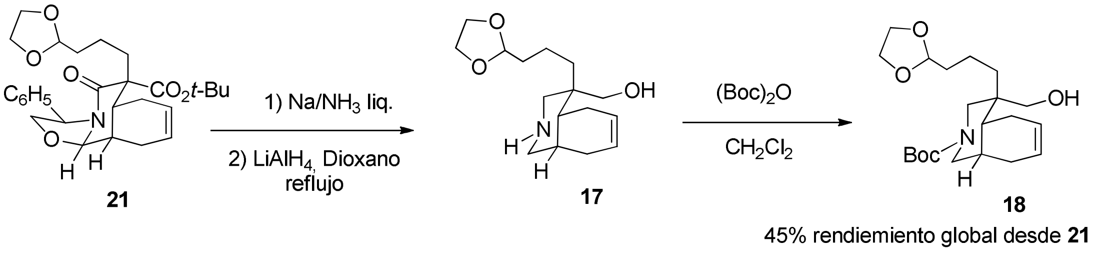
El centro cuaternario presente en la posición 9 de las madangaminas, se instaló aprovechando de la acidez de los protones metilénicos contiguos a los carbonilos del compuesto **19**, mediante de una reacción de alquilación con el agente alquilante 3-(3-bromopropil)-1,3-dioxolano. La reacción tuvo lugar por la cara más accesible del sistema isoquinolínico, proporcionado el compuesto **21** como único isómero, instalando de esta manera el tercer estereocentro del alcaloide.


C6H5
O
N
O
H
9
t-BuO2C
NaH, TBAI
Br
DMF, 0°C to r.t.
90%
CO2t-Bu

19 **21**

Esquema 3.67 Incorporación del centro cuaternario.

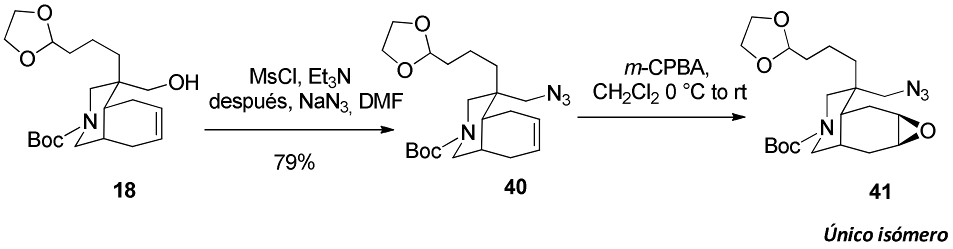
Para la eliminación del inductor quiral empleamos un procedimiento en tres etapas que implica: rotura del enlace C-N bencílico del compuesto **20** mediante tratamiento con una disolución de sodio en amoniaco líquido, posterior reducción de la mezcla compleja de las alcoxi- y oxilactamas resultantes con $LiAlH_4$ y, finalmente, protección del grupo amino presente en **17** en forma de *N*-Boc derivado **18**.


C6H5
CO2t-Bu
N
H
1) Na/NH3 liq.
2) LiAlH4, Dioxano reflujo
OH
(Boc)2O
CH2Cl2
Boc
45% rendiemiento global desde 21

21 **17** **18**

Esquema 3.68 Eliminación del inductor quiral.

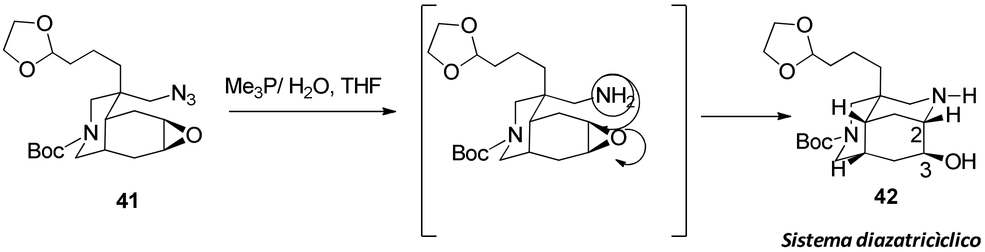
La mesilación del alcohol primario del compuesto **18**, seguido de una reacción de sustitución nucleófila con azida sódica permitió la obtención de la azida **40**. La reacción de este compuesto con *m*-CPBA llevó a la epoxidación del doble enlace presente en el anillo ciclohexénico C en una reacción que, debido a la estructura convexa del sistema bicíclico, proporcionó como único isómero el compuesto **41**.



Esquema 3.69 Preparación del precursor para la cierre del anillo piperidínico A.

La síntesis del núcleo diazatricíclico ABC, común a las madangaminas A-E, se efectuó a través de una reacción de aminohidroxilación intramolecular en la cual, una reducción de Staundinger de la azida **41**, llevó a la formación del intermedio amino-epóxido que experimentó una espontánea ciclación formando el compuesto tricíclico **42**.

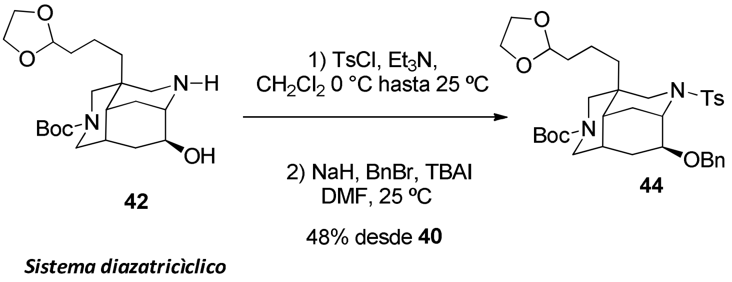
De esta manera se pudo instalar el último estereocentro de las madangaminas (posición C-2) y obtener el sistema tricíclico con la funcionalización y la substitución adecuada en las posiciones C-3 y C-9 necesarias para la posterior construcción de los anillos macrocíclicos D y E.



Esquema 3.70 Síntesis del núcleo diazatricíclico ABC.

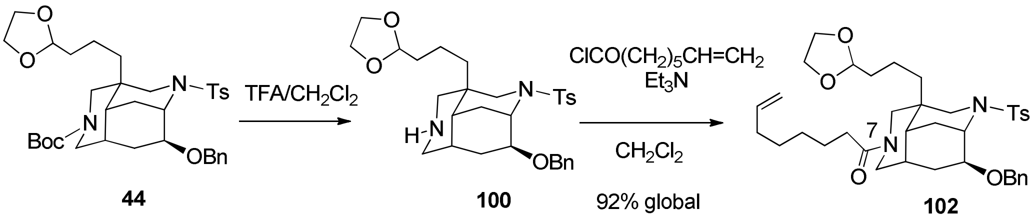
Una vez sintetizado en núcleo central de las madangaminas, la siguiente fase de la síntesis implicó la construcción del anillo D de la madangamina D, completamente saturado y que presenta 14 miembros, macrociclación que queremos realizar mediante una reacción de ring-closing metátesis.

Para ello, en primer lugar a partir del compuesto tricíclico **42** se protegieron las funciones de amina en forma de tosil derivado y de alcohol en forma de benzilo, proporcionando el triciclo **44** de forma satisfactoria.


O
O
N–H
Boc–N
OH
42
1) TsCl, Et3N,
CH2Cl2 0 °C hasta 25 ºC
2) NaH, BnBr, TBAI
DMF, 25 ºC
48% desde 40
O
O
N–Ts
Boc–N
OBn
44
Sistema diazatricìclico

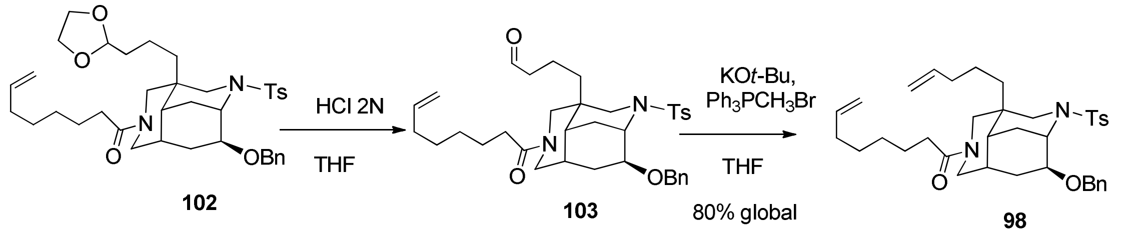
Esquema 3.71 Protección de las funciones de amina y alcohol.

El triciclo **44** fue posteriormente tratado con una disolución de TFA en diclorometano obteniendo la amina segundaria **100**, la cual se aciló inmediatamente con cloruro de octenoilo, previamente preparado a partir del correspondiente ácido, obteniendo el compuesto **102**.


O
O
N–Ts
Boc–N
OBn
44
TFA/CH2Cl2
O
O
N–Ts
H–N
OBn
100
ClCO(CH2)5CH=CH2
Et3N
CH2Cl2
92% global
O
O
N–Ts
7
N
O
OBn
102

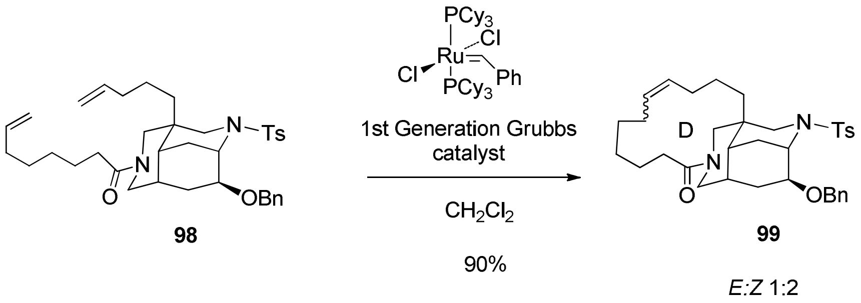
Esquema 3.72 Incorporación de la cadena carbonada en el nitrógeno 7.

El dieno **98**, necesario para la construcción del anillo D, se generó finalmente a partir del compuesto **102** a través de una reacción de olefinación de tipo Wittig entre el aldehído **103**, obtenido a través de una hidrólisis acida del dioxolano, y la correspondiente sal de fosfonio.


O
O
N–Ts
N
O
OBn
102
HCl 2N
THF
O
N–Ts
N
O
OBn
103
KOt-Bu,
Ph3PCH3Br
THF
80% global
N–Ts
N
O
OBn
98

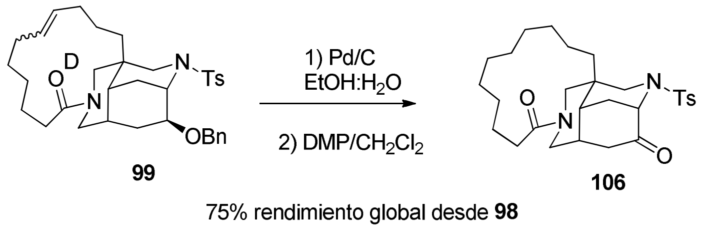
Esquema 3.73 Obtención del dieno precursor del anillo D de la madangamina D.

La cierre del anillo D fue realizada mediante ring-closing metátesis utilizando el catalizador de Grubbs de primera generación, que mostró una actividad superior respecto al de segunda, y que condujo con excelentes rendimientos al sistema tetracíclico ABCD **99** de la madangamina D.


PCy3
Cl
Ru
Cl
Ph
PCy3
1st Generation Grubbs catalyst
CH2Cl2
90%
N
Ts
N
O
OBn
98
D
N
Ts
N
O
OBn
99
E:Z 1:2

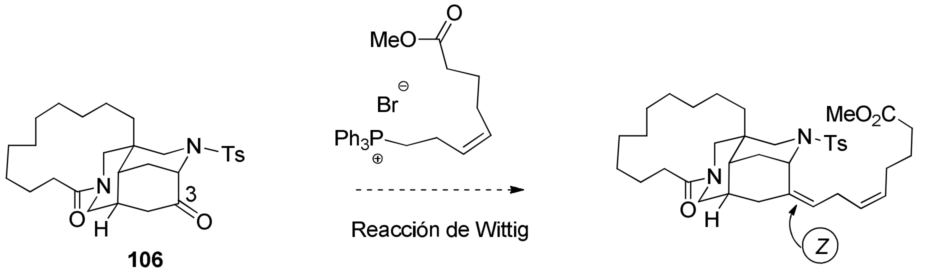
Esquema 3.74 Síntesis del sistema tetracíclico ABCD de la madangamina D

La posterior hidrogenación catalítica, realizada con Pd/C en una disolución de 9:1 de etanol y agua, provocó la reducción del doble enlace del macrociclo con simultánea desbencilación del alcohol terciario **99**, mientras que la oxidación del alcohol resultante con el reactivo de Dess-Martin proporcionó la cetona **106** con excelente rendimiento.


D
O
N
N
Ts
OBn
99
1) Pd/C
EtOH:H2O
2) DMP/CH2Cl2
O
N
N
Ts
O
106
75% rendimiento global desde 98

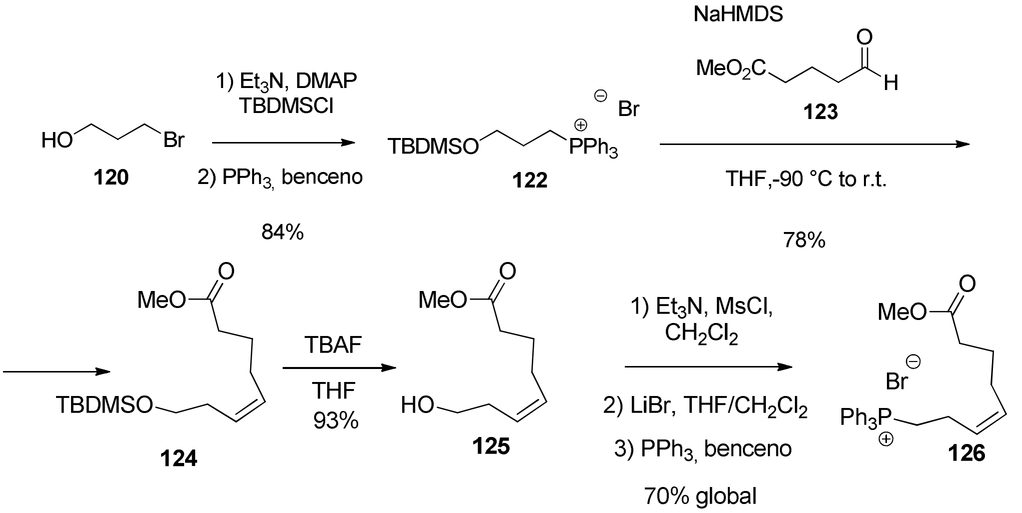
Esquema 3.75 Obtención de la cetona tetracíclica **106.**

El anillo macrocíclico E, mucho más complejo por presentar una doble insaturación, se construyó de manera convergente, mediante una reacción *Z*-estereoselectiva de Wittig entre la cetona **106** y una sal de fosfonio apropiada, previamente sintetizada y caracterizada por la presencia de una *Z*-instauración y de un grupo éster terminal.


N
Ts
N
O
H
3
O
106
MeO
O
Br ⊖
Ph3P ⊕
Reacción de Wittig
MeO2C
N
Ts
N
O
H
Z

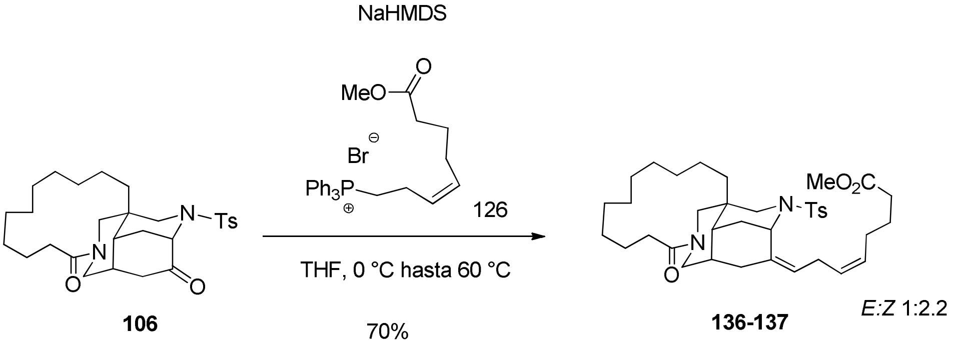
Esquema 3.76 Estrategia para la incorporación cadena en C-3 para la construcción anillo E.

La sal de fosfonio **126** fue sintetizada a partir del ester **124** preprarado mediante una reacción estereoselectiva de Wittig entre el aldehído **123** y el la sal de fosfonio **122**. Tras desprotección del grupo silil éter con TBAF, el alcohol **125** fue finalmente convertido al correspondiente bromuro y, a partir de este, se generó la sal de fosfonio **126**.


HO
Br
120
1) Et_3N, DMAP
TBDMSCl
2) PPh_3, benceno
84%
TBDMSO
Br
PPh_3
122
NaHMDS
MeO_2C
O
H
123
THF,-90 °C to r.t.
78%
MeO
O
TBDMSO
124
TBAF
THF
93%
HO
125
1) Et_3N, MsCl, CH_2Cl_2
2) LiBr, THF/CH_2Cl_2
3) PPh_3, benceno
70% global
Br
Ph_3P
126

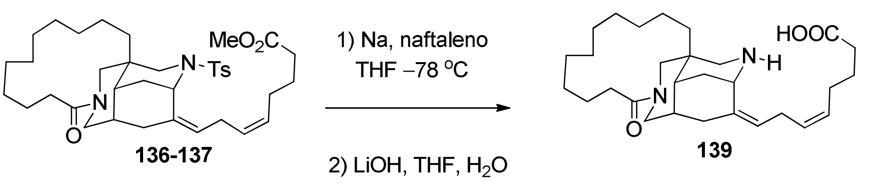
Esquema 3.77 Preparación de la sal de fosfonio **126**.

La posterior reacción de *Z*-olefinacíon selectiva de Wittig entre la cetona **106** y la sal de fosfonio **126** nos permitió incorporar el fragmento to C-3/C-20 al sistema tetracíclico conduciendo a la formación del compuesto **137** con excelentes rendimientos y como mezcla de los isómeros *E* y *Z* (*E:Z* ratio 1:2.2).


NaHMDS
MeO
O
Br
Ph_3P
126
THF, 0 °C hasta 60 °C
70%
N
Ts
N
O
O
106
MeO_2C
136-137
E:Z 1:2.2

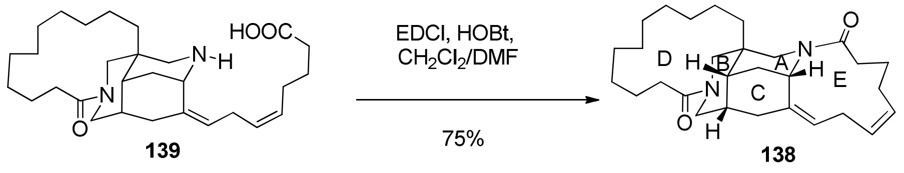
Esquema 3.78 Reacción de Wittig, generación de la *Z*-olefina.

La desprotección del nitrógeno piperidínico del anillo A con una disolución de sodio y naftaleno en THF a baja temperatura y la siguiente hidrólisis del éster con hidróxido de litio condujo a la formación del aminoácido **139**.


MeO_2C
N
Ts
N
O
136-137
1) Na, naftaleno
THF –78 °C
2) LiOH, THF, H_2O
HOOC
N
H
139

Esquema 3.79 Obtención del precursor de macrolactamización.

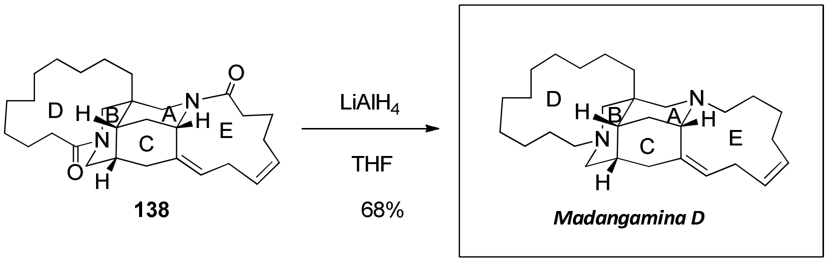
El sistema pentacíclico ABCDE de la madangamina D fue obtenido con excelentes resultados mediante una reacción de macrolactamización intramolecular, en condiciones diluidas, adicionando el aminoácido **139** a través de una *syringe pump* a una disolución de DMF y diclorometano contente los agentes acoplantes EDCl, HOBt.



Sistema pentacíclico ABCDE

Esquema 3.80 Obtención sistema pentacíclico.

Finalmente la reducción de los dos carbonilos de lactama del sistema pentacíclico obtenido proporcionó la madangamina D como único producto.



Esquema 3.81 Obtención de la madagamina D.

La presente estrategia sintética permitió obtener por primera vez la madangamina D en forma enantiopura y establecer su configuración absoluta. La madangamina D sintética posee sin ambigüedades la configuración absoluta 2*S*, 5*S*, 9*R*, 12*R* y una rotación específica {[α] = + 101.3 (*c* 0,29, $CHCl_3$) } con el mismo signo que en las madangamines A-C. De acuerdo con estos datos podemos confirmar la configuración absoluta de esta familia de alcaloides asignado por Andersen.

La actividad biológica la madangamina D, hasta ahora totalmente desconocida debido a su aislamiento en forma de mezcla inseparable con la madangamina E y por la baja cantidad de muestra disponible, fue ensayada en los laboratorios de Pharmamar. El alcaloide mostró significativa actividad citotóxica *in vitro* comparable a la de la madangamina A, siendo activa contra líneas celulares de cáncer HT29 de colon humano (GI_{50} 4,4 µg/mL) y PSN1 páncreas (GI_{50} 7,4 µg/mL), pero fue inactiva contra las líneas celulares de cáncer pulmonar NSCLC A549 y de mama MDA-MB-231 en la concentración más alta ensayada (>10 µg/mL).[48]

Chapter 4

1. Se ha ratificado el potencial sintético de las lactamas bicíclicas quirales con estructura de oxazolopiperidona derivadas del (*R*)-fenilglicinol para la síntesis enantioselectivas de productos naturales complejos que contienen una subunidad de piperidina.

2. Se ha mejorado la metodología sintética anteriormente desarrollada en nuestro grupo de investigación permitiendo acceder al corazón BC de las madangaminas de manera escalable y rápida. La nueva ruta sintética prevé la eliminación del inductor quiral a través de una metodología compatible con la presencia del doble enlace endocíclico en una fase inicial de la síntesis. El compuesto obtenido ya presenta todas las funcionalizaciones necesarias para completar la síntesis del núcleo diazatriciclico común a las madangaminas A-E.

3. En la nueva secuencia sintética se ha conseguido eliminar algunas etapas redundantes incluyendo la eliminación de la función ester y su posterior re-introducción o los cambios de grupos protectores del nitrógeno piperidínico. De esta manera se podido reducir sensiblemente el número de etapas sintéticas y duplicar los rendimientos globales que llevan a la síntesis enantioselectiva del azabicílico correspondiente a los anillos B y C de las madangaminas.

4. Se ha puesto de manifiesto la eficiencia de la reacción de aminohydroxilacción intramolecular capaz de acceder al núcleo diazatricíclico ABC, común a las madangaminas A-E, de forma rápida y económica excluyendo la manipulación de reactivos altamente tóxicos o la utilización de procedimientos experimentales complejos e incómodos.

5. Se han estudiado reacciones de macrociclación de anillos de diferente tamaño pertenecientes a diferentes madangaminas. Las metodologías han sido aplicadas en un modelo piperidínico sencillo con el objetivo de encontrar las mejores condiciones de reacción y poder evaluar su eficacia. Como resultados de estos estudios exploratorios se identificó la reacción de cierre de anillo por metátesis como la más prometedora para acceder al sistema tetracíclico ABCD de la madangamina D.

6. El potencial sintético de las reacciones de ring-closing metátesis como procedimiento para la anulación de anillos macrocíclicos ha sido demostrada con la construcción del anillo de 14 eslabones, permitiendo el acceso manera eficaz al sistema ABCD de la madangamina D.

7. Se ha aplicado con éxito la metodología sintética que presenta una reacción de tipo Wittig, descrita anteriormente en el grupo de investigación, para la introducción de la cadena carbonada instaurada en la posición C-3 del sistema tetracíclico, con una estereoselectividad preferentemente *Z*. Esta ruta, desarrollada precedentemente en un modelo morfánico, permite la formación del

sistema insaturado de tipo *Z*-skipped, mientras que, la siguiente reacción de macrolactamizacción, permite la construcción del anillo E de la madangamina D.

8. La reducción final del compuesto diaminico, permite la obtención del la madangamna D. Por primera vez se ha llevado a cabo la síntesis total de un alcaloide perteneciente a la familia de las madangaminas. La (+)-madangamina D sintetizada permitió confirmar la configuración absoluta asignada por Andersen basada en la correlación con un precursor biogenético común.

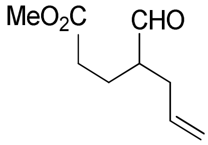
9. Gracias a la obtención del compuesto en estado puro se ha podido ensayar la actividad biológica de este alcaloide y confirmar sus propiedades citotóxicas hacia diferentes líneas celulares, ensayos que hasta el presente no habían podido efectuarse al aislarse conjuntamente con la madangamina E y en poca cantidad de su fuente natural. La madangamina D sintética, así pues, muestra citotoxicidad in vitro contra las líneas celulares de cáncer HT29 de colon humano y PSN1 páncreas, pero es inactivo contra el NSCLC de pulmón A549 y el cáncer de mama MDA-MB-231 líneas de células a la concentración más alta ensayada (10 μg/ml).

Chapter 5

Experimental procedures and spectroscopic data

General Procedures: All air sensitive manipulations were carried out under a dry argon or nitrogen atmosphere. THF and toluene were carefully dried and distilled from sodium/benzophenone prior to use. CH_2Cl_2 was dried and distilled from CaH_2. Other solvents and all standard reagents were purchased from Aldrich, Fluka or Alfa Aesar and were used without further purification.

Analytical thin-layer chromatography was performed on SiO_2 (Merck silica gel 60 F_{254}), and the spots were located with 1% aqueous $KMnO_4$. Chromatography refers to flash chromatography and was carried out on SiO_2 (SDS silica gel 60 ACC, 35-75 mm, 230-240 mesh ASTM). NMR spectra were recorded at 300 or 400 MHz (^{1}H) and 75.4 or 100.6 MHz (^{13}C), and chemical shifts are reported in δ values downfield from TMS or relative to residual chloroform (7.26 ppm, 77.0 ppm) as an internal standard. Data are reported in the following manner: chemical shift, integrated intensity, multiplicity, coupling constant (*J*) in hertz (Hz), and assignment (when possible). Assignments and stereochemical determinations are given only when they are derived from definitive two-dimensional NMR experiments (HSQC-COSY). IR spectra were performed in a spectrophotometer Nicolet Avantar 320 FT-IR and only noteworthy IR absorptions (cm^{-1}) are listed. Optical rotations were measured on Perkin-Elmer 241 polarimeter. $[\alpha]_D$ values are given in 10^{-1} deg cm^2 g^{-1}. High resolution mass spectra (HMRS; LC/MSD TOF Agilent Technologies) were performed by Centres Científics i Tecnològics de la Universitat de Barcelona.

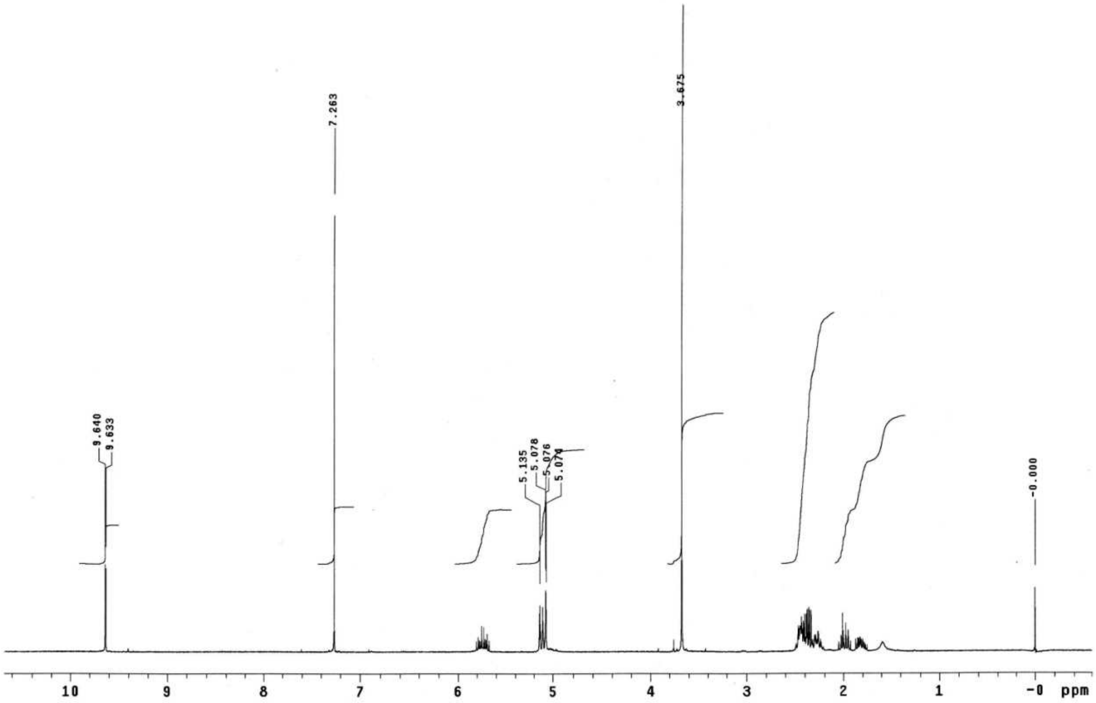


Methyl-4-formyl-6-heptenoate.

4-Pentenal (4.7 ml, 0.047 mol) was added dropwise during 0.5 h to a stirred, ice-cold suspension of anhydrous potassium carbonate (2.0 g, 0.16 mol) in piperidine (12 ml, 0.1 mol). Stirring was continued at room temperature for 2 days and the mixture filtered through sintered glass. The residue was washed thoroughly with ether which was subsequently removed under reduced pressure affording the piperidine enamine of 4-pentenal, as a pale yellow oil. To a solution of the above enamine in dry acetonitrile (75 ml), cooled below 5 °C, was added methyl acrylate (7.5 ml, 0.03 mol) dissolved in 19 ml of dry acetonitrile during 30 min. The mixture was stirred at room temperature for 5 h and then refluxed for 72 h. Glacial acetic acid (10.5 ml) in water (75 ml) was added and the mixture refluxed for further 8 h. Ether (250 ml) was added to the residue and the organic layer was washed with 3 N HCl (100 ml), saturated $NaHCO_3$ (100 ml), brine (100 ml), and finally dried with $MgSO_4$ and filtered. Removal of the organic solvents left methyl-4-formyl-6-heptenoate (5.10 g, 64%) as a brown oil which was used in the next reaction without further purification.

^{1}H NMR (300 MHz, $CDCl_3$): δ 1.80 (m, 1H, H-3), 1.98 (m, 1H, H-3), 2.21-2.51 (m, 5H, 2H-2, H-4, 2H-5), 3.67 (s, 3H, CH_3), 5.09 (m, 2H, H-7), 5.76 (m, 1H, H-6), 9.63 (d, *J* = 2.1 Hz, 1H, CHO).

^{13}C NMR (100.6 MHz, $CDCl_3$): δ 23.2 (C-3), 31.2 (C-5), 32.9 (C-2), 50.3 (CH_3), 51.7 (C-4), 117.6 (C-7), 134.3 (C-6), 173.4 (C-1), 203.7 (CHO).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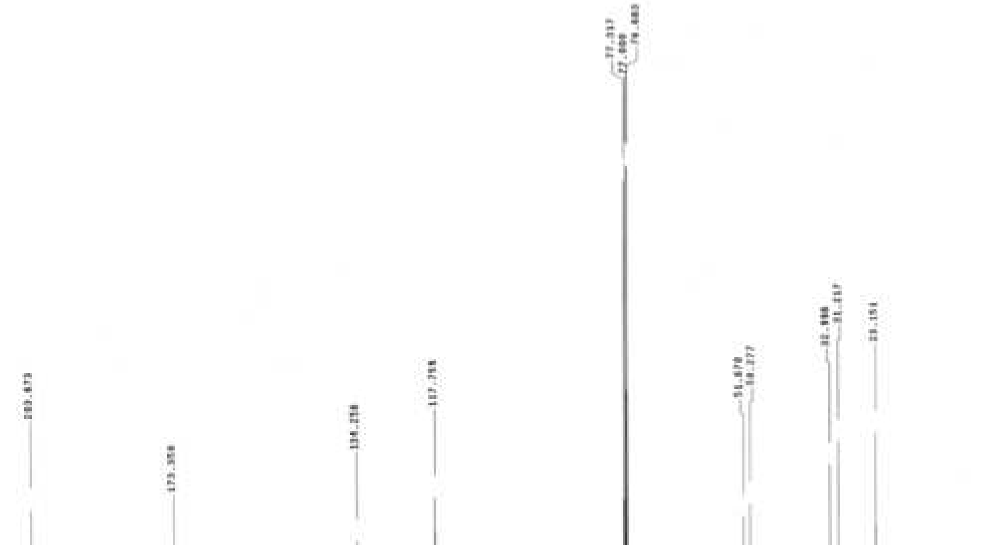
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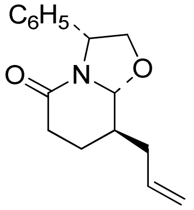


(3*R*,8*R*,8a*R*)-8-Allyl-5-oxo-3-phenyl-2,3,6,7,8,8a-hexahydro-5*H*-oxazolo[3,2-*a*]pyridine (1).

A mixture of racemic methyl 4-formyl-6-heptenoate (4.6 g, 29 mmol), (*R*)-phenylglycinol (3.97 g, 29 mmol), and anhydrous Na_2SO_4 (17.0 g, 12 mmol) in Et_2O (115 mL) was stirred at 0 °C for 2 h. The resulting suspension was filtered through Celite® and concentrated under reduced pressure. The residue was heated at 80 °C for 18 h under vacuum (10-15 mmHg). Flash chromatography (8:2 hexane-EtOAc to EtOAc) of the residue afforded oxazolopiperidone **1** (5.3 g, 71%) and its (8*S*,8a*S*)-diastereoisomer **2** (753 mg, 10%).

Compound **1** (major isomer, lower R_f):

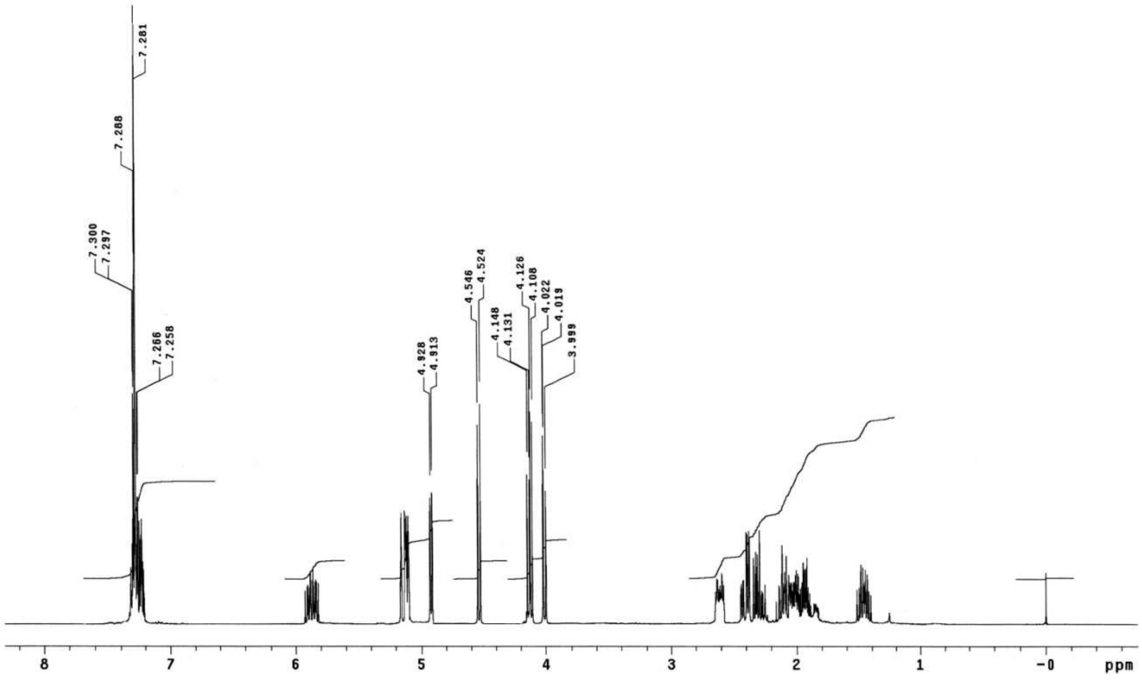
$[\alpha]_D^{22} = -32.8$ (*c* 1.0, EtOH).

IR (film): 1655 (NCO) cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$, COSY, gHSQC): δ 1.45 (dddd, *J* = 13.8, 13.8, 12.0, 7.2 Hz, 1H, H-7), 2.02 (m, 3H, H-7, H-8, CH_2 allyl), 2.30 (ddd, *J* = 18.0, 12.0, 6.6 Hz, 1H, H-6), 2.42 (ddd, *J* = 18.0, 7.2, 1.8 Hz, 1H, H-6), 2.62 (m, 1H, CH_2 allyl), 4.01 (dd, *J* = 9.0, 1.2 Hz, 1H, H-2), 4.11 (dd, *J* = 9.0, 6.9 Hz, 1H, H-2), 4.53 (d, *J* = 8.7 Hz, 1H, H-8a), 4.92 (d, *J* = 6.6 Hz, 1H, H-3), 5.12 (m, 2H, CH_2=), 5.86 (dddd, *J* = 16.5, 10.2, 7.8, 6.0 Hz, 1H, CH=), 7.20-7.30 (m, 5H, C_6H_5).

^{13}C NMR (100.6 MHz, $CDCl_3$): δ 23.6 (C-7), 31.2 (C-6), 35.4 (CH_2 allyl), 39.1 (C-8), 58.9 (C-3), 73.7 (C-2), 91.9 (C-8a), 117.4 (CH_2=), 126.2, 128.4 (C-*o*, *m* C_6H_5), 127.4 (C-*p* C_6H_5), 134.6 (CH=), 141.4 (C-*i* C_6H_5), 167.1 (NCO).

Elemental analysis calcd (%) for $C_{16}H_{19}NO_2\cdot\frac{1}{4}H_2O$: C 73.40, H 7.51, N 5.35; found: C 73.71, H 7.25, N 5.41.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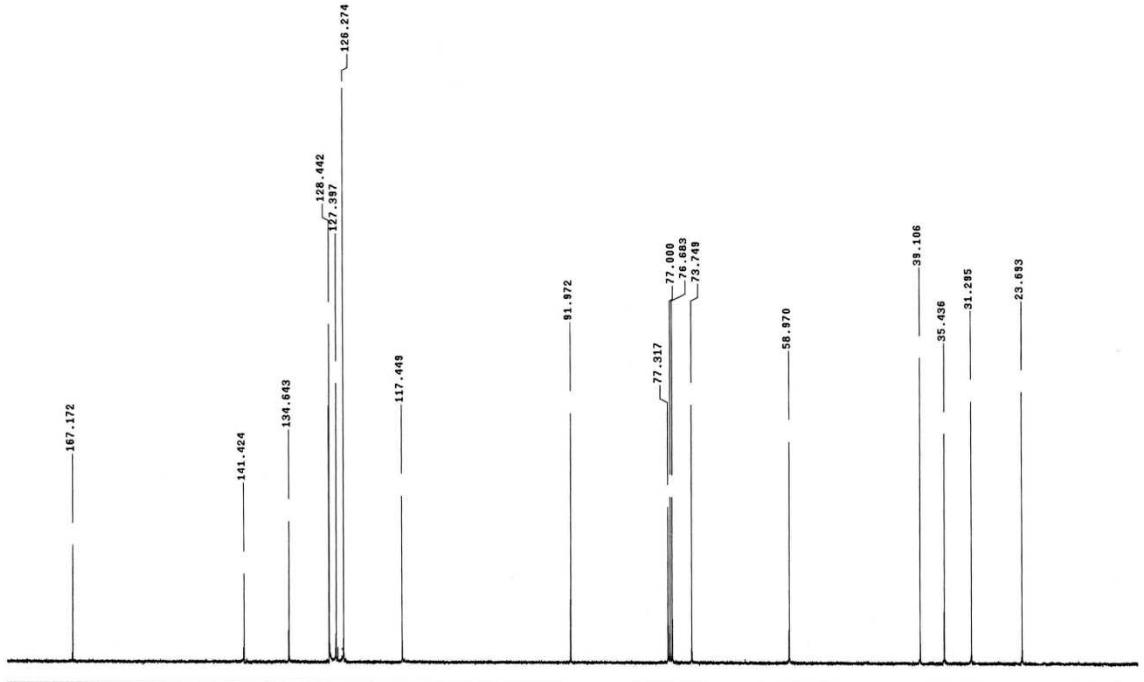
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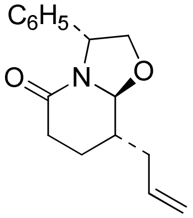


Compound **2** (minor isomer, higher R_f):

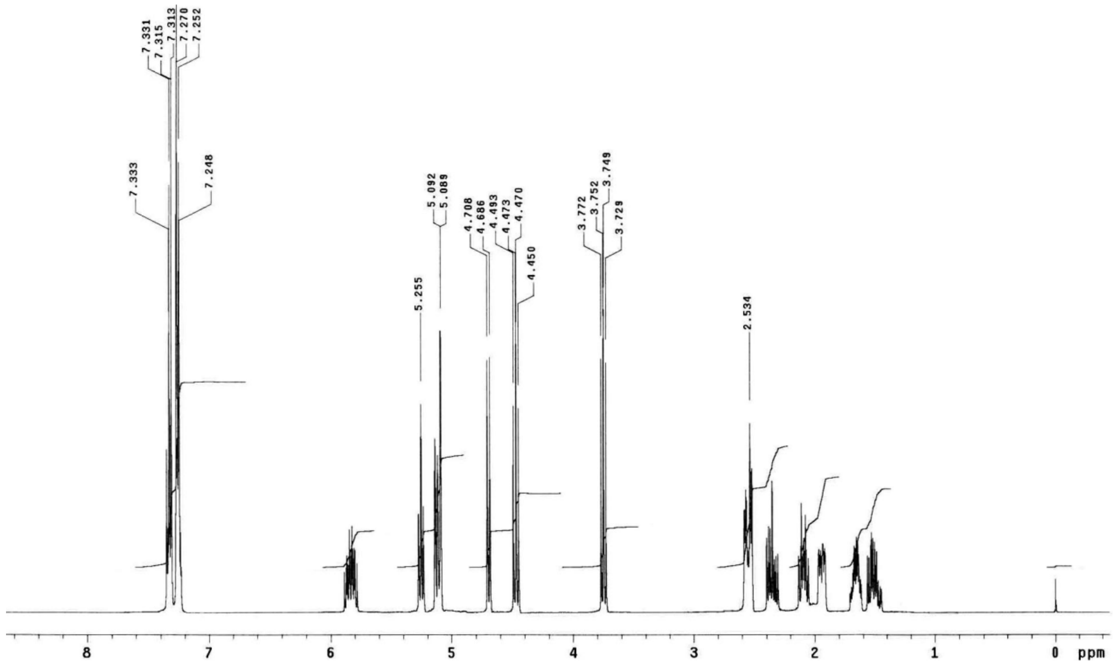
$[\alpha]_D^{22} = -59.9$ (*c* 1.0, EtOH).

IR (film): 1658 (NCO) cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$, COSY, gHSQC): δ 1.53 (m, 1H, H-7), 1.66 (m, 1H, H-8), 1.96 (m, 1H, H-7), 2.07 (dt, *J* = 16.5, 8.4, 8.4 Hz, 1H, CH_2 allyl), 2.35 (ddd, *J* = 18.6, 12.0, 6.6 Hz, 1H, H-6), 2.56 (m, 2H, H-6, CH_2 allyl), 3.75 (dd, *J* = 9.0, 7.8 Hz, 1H, H-2), 4.47 (dd, *J* = 9.0, 8.1 Hz, 1H, H-2), 4.69 (d, *J* = 8.4 Hz, 1H, H-8a), 5.13 (m, 2H, CH_2=), 5.25 (t, *J* = 7.8 Hz, 1H, H-3), 5.83 (dddd, *J* = 16.5, 10.2, 8.1, 6.0 Hz, 1H, CH=), 7.25-7.34 (m, 5H, C_6H_5).

^{13}C NMR (100.6 MHz, $CDCl_3$): δ 22.7 (C-7), 31.3 (C-6), 35.8 (CH_2 allyl), 39.5 (C-8), 58.3 (C-3), 72.3 (C-2), 92.0 (C-8a), 117.4 (CH_2=), 126.0, 128.7 (C-*o*, *m* C_6H_5), 127.5 (C-*p* C_6H_5), 134.6 (CH=), 139.4 (C-*i* C_6H_5), 168.7 (NCO).

Elemental analysis calcd for $C_{16}H_{19}NO_2\cdot\frac{1}{4}H_2O$: C, 73.40; H, 7.51; N, 5.35. Found: C, 73.27; H, 7.25; N, 5.51.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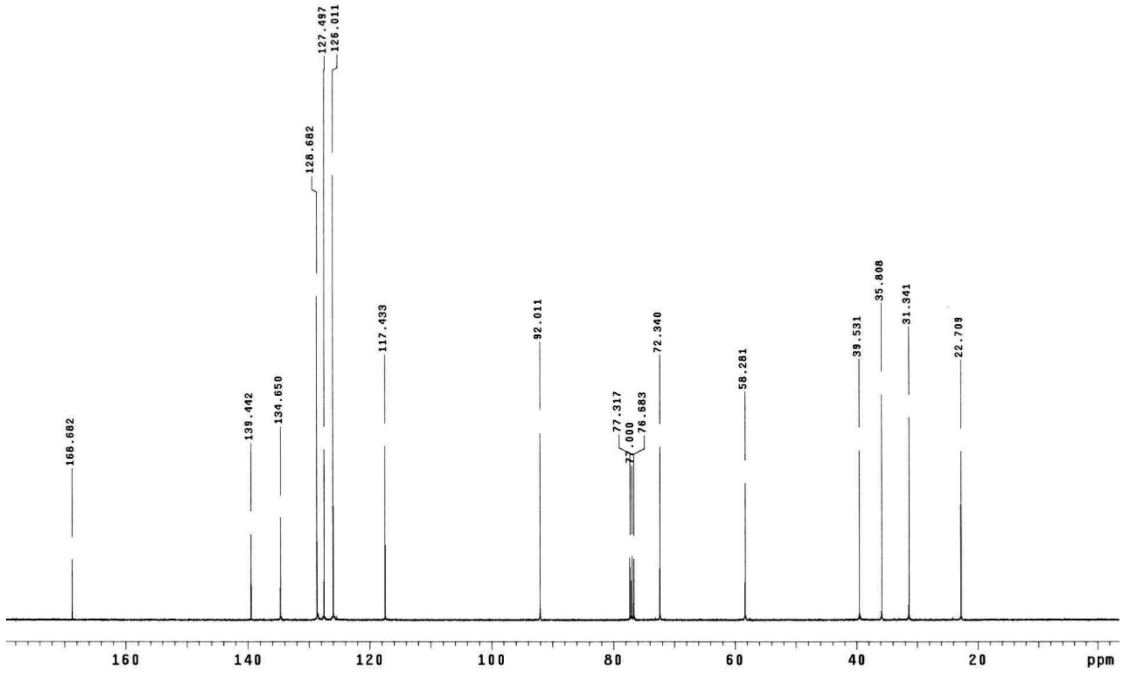
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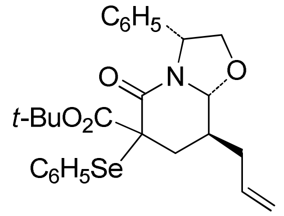


(3*R*,8*S*,8a*R*)-8-Allyl-6-(*tert*-butoxycarbonyl)-5-oxo-3-phenyl-6-(phenylselenyl)-2,3,6,7,8,8a-hexahydro-5*H*-oxazolo-[3,2-*a*]pyridine (3).

Lithium bis(trimethylsilyl)amide (3.85 mL of a 1 M solution in THF, 3.85 mmol) was slowly added at –78 °C to a solution of lactam **1** (450 mg, 1.75 mmol) in anhydrous THF (30 mL), and the resulting mixture was stirred for 90 min. Then, di-*tert*-butyl dicarbonate (420 mg, 1.92 mmol) in THF (2 mL) and, after 90 min of continuous stirring at –78 °C, phenylselenyl chloride (503 mg, 2.62 mmol) in THF (4 mL) were added to the solution. The resulting mixture was stirred for a further 1 h and poured into saturated aqueous NH_4Cl. The aqueous layer was extracted with EtOAc, and the combined organic extracts were dried over anhydrous $MgSO_4$, filtered and concentrated under reduced pressure. Flash chromatography (9:1 to 8:2 hexane-EtOAc) of the resulting oil afforded the C-6 epimers **a** (520 mg) and **b** (320 mg) of the seleno derivatives **3** as brown oils (93% overall yield).

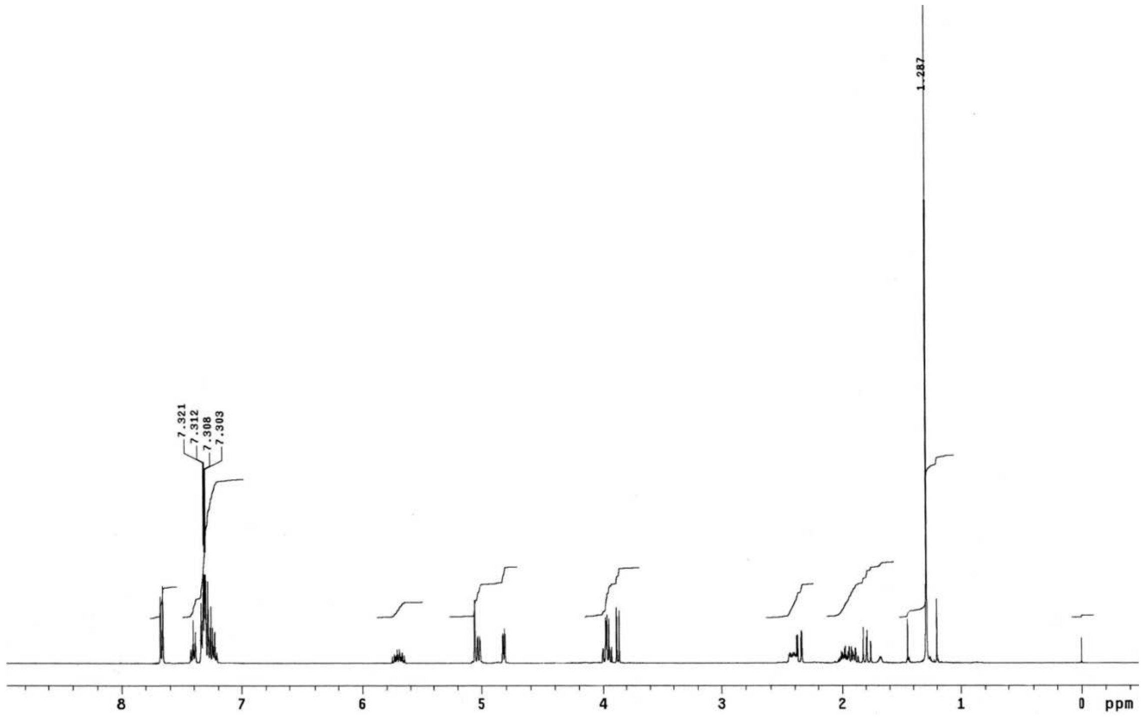
Epimer **a** (major, higher R_f):

IR (film): 1665 (NCO), 1726 (COO) cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$, gHSQC): δ 1.29 [s, 9H, $(CH_3)_3C$], 1.79 (dd, *J* = 14.4, 12.3 Hz, 1H, H-7), 1.93 (m, 1H, CH_2 allyl), 1.98 (m, 1H, H-8), 2.36 (dd, *J* = 14.4, 3.0 Hz, 1H, H-7), 2.43 (m, 1H, CH_2 allyl), 3.87 (d, *J* = 9.0 Hz, 1H, H-8a), 3.95 (dd, *J* = 9.0, 6.0 Hz, 1H, H-2), 3.99 (dd, *J* = 9.0, 2.1 Hz, 1H, H-2), 4.82 (dd, *J* = 6.0, 2.1 Hz, 1H, H-3), 5.03 (3m, 2H, CH_2=), 5.70 (dddd, *J* = 16.5, 10.8, 8.1, 6.6 Hz, 1H, CH=), 7.26-7.68 (m, 10H, C_6H_5).

^{13}C NMR (100.6 MHz, $CDCl_3$): δ 27.5 [$(CH_3)_3C$], 34.5 (CH_2 allyl), 36.7 (C-7), 37.9 (C-8), 55.8 (C-6), 59.3 (C-3), 74.0 (C-2), 82.8 [$(CH_3)_3C$], 91.5 (C-8a), 117.6 (CH_2=), 126.7-128.6, 138.3 (C-*o*, *m, p* C_6H_5), 129.5 (C-*i* C_6H_5), 133.9 (CH=), 140.7 (C-*i* C_6H_5), 163.6 (C=O), 168.7 (C=O).

HRMS calcld for $[C_{27}H_{31}NO_4Se + H]^+$: 514.1491, found: 514.1479.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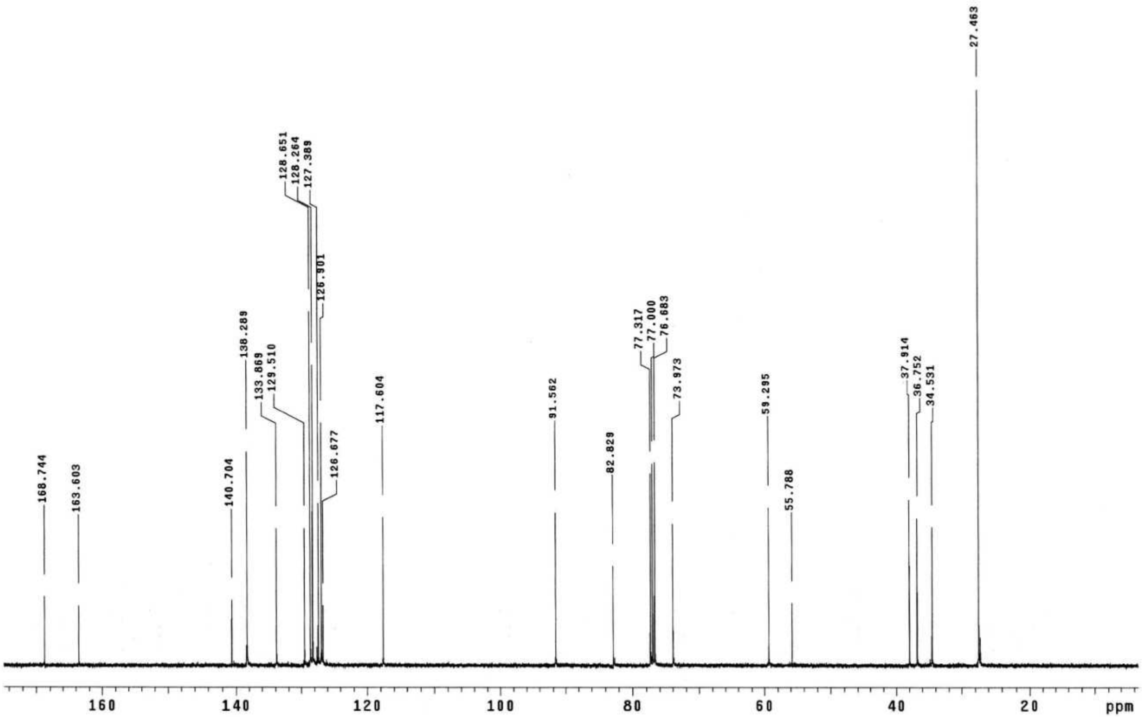
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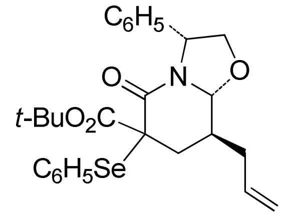


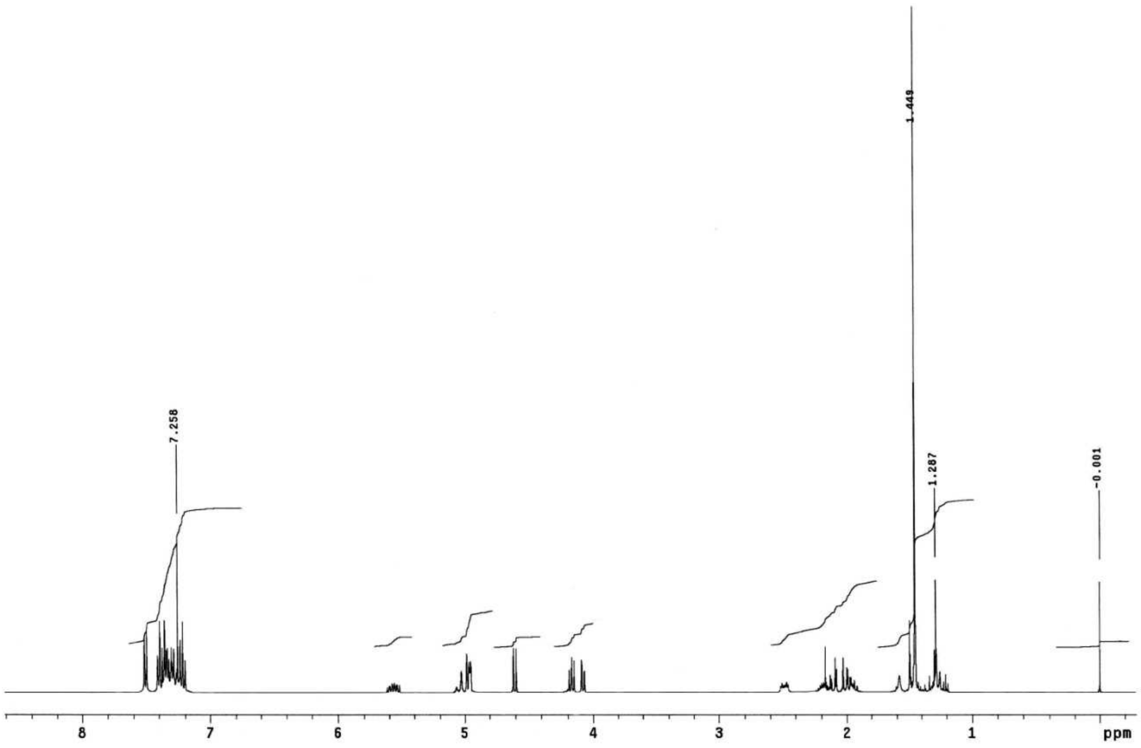
Epimer **b** (minor, lower R*f*):

IR (film): 1661 (NCO), 1732 (COO) cm^{-1}.

^{1}H NMR (400 MHz, CDCl$_3$, gHSQC): δ 1.45 [s, 9H, (CH$_3$)$_3$C], 1.95 (m, 1H, CH$_2$ allyl), 1.99 (dd, *J* = 15.0, 10.8 Hz, 1H, H-7), 2.10 (dd, *J* = 15.0, 4.5 Hz, 1H, H-7), 2.20 (m, 1H, H-8), 2.48 (m, 1H, CH$_2$ allyl), 4.08 (dd, *J* = 9.0, 1.2 Hz, 1H, H-2), 4.17 (dd, *J* = 9.0, 6.6 Hz, 1H, H-2), 4.61 (d, *J* = 8.7 Hz, 1H, H-8a), 4.95 (dd, *J* = 6.6, 1.2 Hz, 1H, H-3), 4.98 (3m, 2H, CH$_2$=), 5.56 (dddd, *J* = 16.5, 10.2, 8.4, 6.0 Hz, 1H, CH=), 7.22-7.52 (m, 10H, C$_6$H$_5$).

^{13}C NMR (100.6 MHz, CDCl$_3$): δ 27.8 [(*C*H$_3$)$_3$C], 34.2 (C-7), 35.2 (CH$_2$ allyl), 36.9 (C-8), 56.8 (C-6), 59.4 (C-3), 73.9 (C-2), 82.9 [(CH$_3$)$_3$*C*], 91.6 (C-8a), 117.5 (CH$_2$=), 126.9-128.6, 138.1 (C-*o*, *m*, *p* C$_6$H$_5$), 129.3 (C-*i* C$_6$H$_5$), 134.2 (CH=), 140.6 (C-*i* C$_6$H$_5$), 163.5 (C=O), 169.5 (C=O).

HRMS calcd for [C$_{27}$H$_{31}$NO$_4$Se + H]$^+$: 514.1491, found: 514.1472.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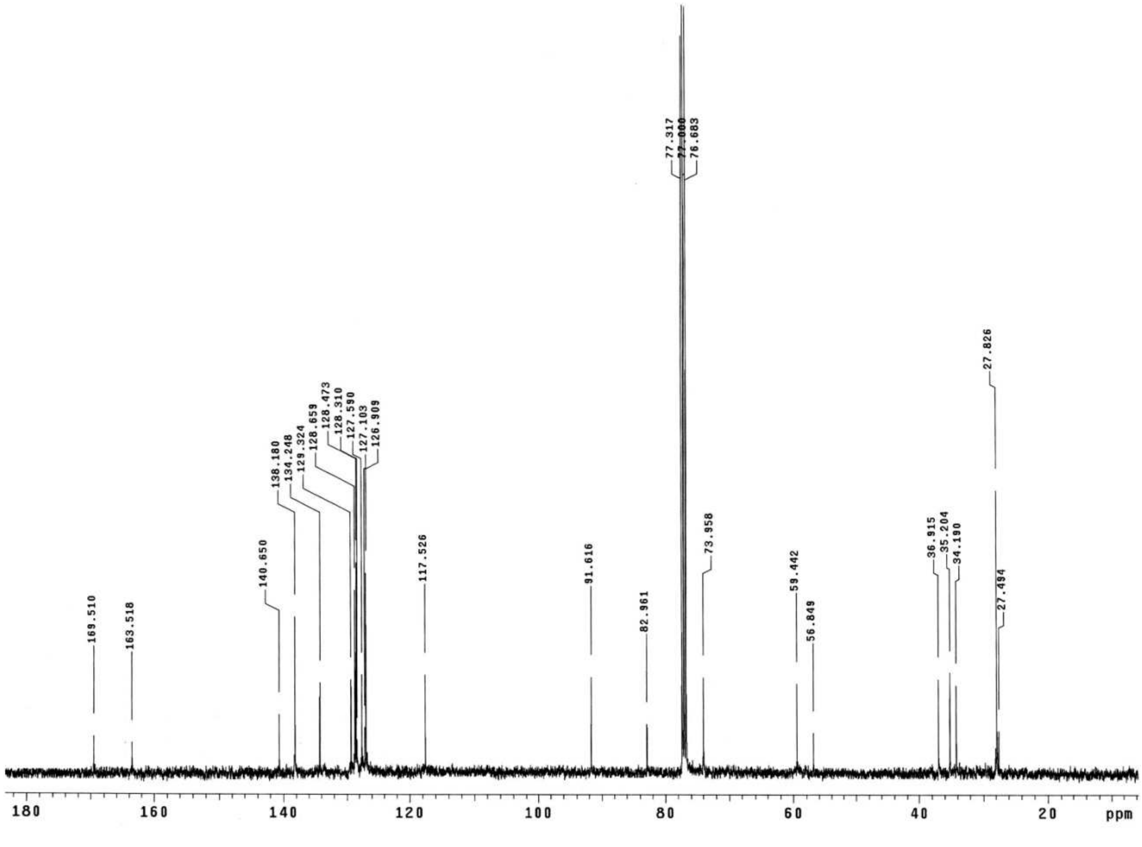
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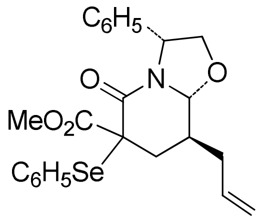


(3*R*,8*S*,8a*R*)-8-Allyl-6-(methoxycarbonyl)-5-oxo-3-phenyl-6-(phenylselenyl)-2,3,6,7,8,8a-hexahydro-5*H*-oxazolo[3,2-*a*]pyridine (4).

Lithium bis(trimethylsilyl) amide (1 M in THF, 10 mL) was slowly added at –78 ºC to a solution of lactam **1** (2.0 g, 1.07 mmol) in anhydrous THF (120 ml), and the resulting mixture was stirred for 90 min. Then, methyl chloroformate (0.6 mL, 7.78 mmol) and, after 90 min of continuous stirring at –78 °C, PhSeCl (2.08 g, 10.8 mmol) were added to the solution. The resulting mixture was stirred for 1 h and poured into saturated aqueous NH_4Cl. The aqueous layer was extracted with EtOAc, and the combined organic extracts were dried and concentrated. Flash chromatography (9:1 hexane-EtOAc to 1:1 hexane-EtOAc) of the resulting oil afforded **4** as a mixture of C-6 epimers (3.14 g, 86% overall yield).

Epimer **a** (higher R_f):

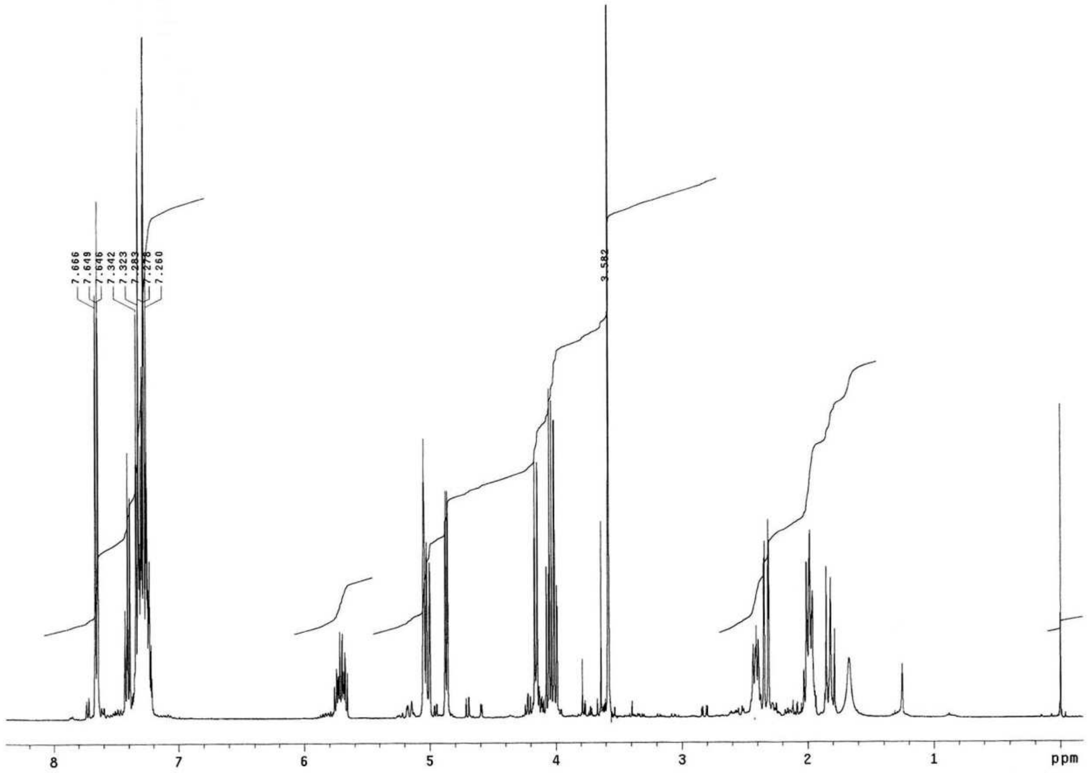
IR (NaCl) 1667, 1725 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$, COSY, gHSQC): δ 1.82 (dd, *J* = 14.0, 12.4 Hz, 1H, CH_2 allyl), 1.98 (m, 2H, H-7, H-8), 2.33 (dd, *J* = 14.0, 2.8 Hz, 1H, CH_2 allyl), 2.41 (m, 1H, H-7), 3.58 (s, 3H, CH_3), 4.00 (dd, *J* = 9.2, 2.0 Hz, 1H, H-2), 4.05 (dd, *J* = 9.2, 6.8 Hz, 1H, H-2), 4.15 (d, *J* = 8.8 Hz, 1H, H-8a), 4.87 (dd, *J* = 6.8, 2.0 Hz, 1H, H-3), 5.03 (m, 2H, CH_2=), 5.71 (dddd, *J* = 16.8, 10.4, 7.6, 6.4 Hz, 1H, CH=), 7.26-7.66 (m, 10H, ArH).

^{13}C NMR (100.6 MHz, $CDCl_3$): δ 34.8 (C-7), 36.6 (CH_2), 37.7 (C-8), 53.0 (CH_3), 54.0 (C-6), 59.4 (C-3), 74.0 (C-2), 91.8 (C-8a), 117.7 (CH_2=), 126.4-138.2 (C-*o*, *m*, *p*), 133.7 (CH=), 140.5 (C-*i*), 163.3 (NCO), 170.8 (COO).

$[\alpha]_D^{22}$ = – 99.3 (*c* 0.7, $CHCl_3$).

HRMS calcd for $C_{24}H_{25}NO_4Se$: 471.0948, found: 471.0955.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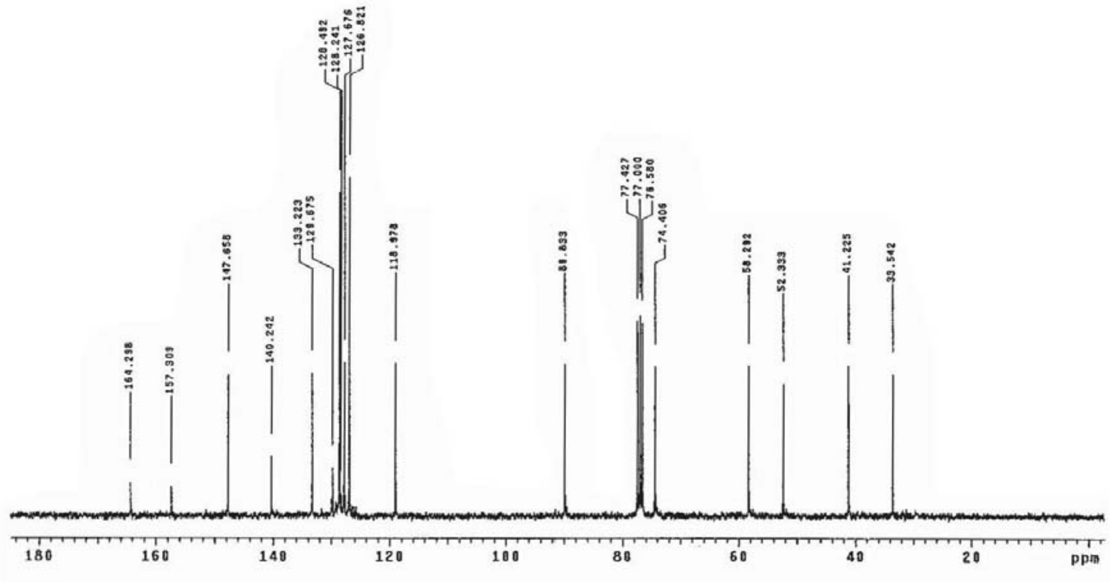
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76.580
74.406
58.282
52.333
41.225
33.542
180
160
140
120
100
80
60
40
20
ppm

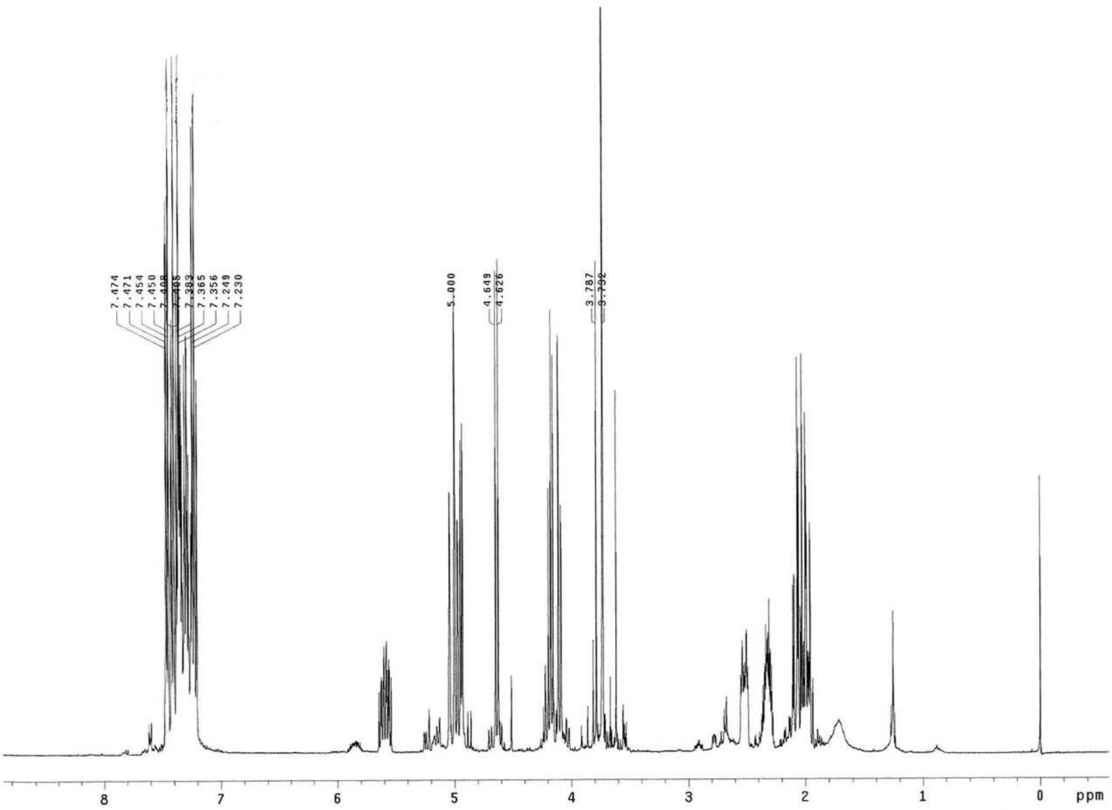
Epimer **b** (lower R_f):

^{1}H NMR (400 MHz, $CDCl_3$, COSY, gHSQC) δ 1.98 (m, 1H, CH_2 allyl), 2.00 (dd, *J* = 15.2, 11.6 Hz, 1H, H-7), 2.08 (dd, *J* = 15.2, 4.0 Hz, 1H, H-7), 2.32 (m, 1H, H-8), 2.52 (m, 1H, CH_2 allyl), 3.73 (s, 3H, CH_3), 4.10 (dd, *J* = 9.2, 1.2 Hz, 1H, H-2), 4.17 (dd, *J* = 9.2, 6.8 Hz, 1H, H-2), 4.63 (d, *J* = 9.2 Hz, 1H, H-8a), 4.97 (m, 3H, H-3, CH_2=), 5.59 (dddd, *J* = 16.0, 10.0, 8.0, 6.0 Hz, 1H, CH=), 7.23-7.47 (m, 10H, ArH).

^{13}C NMR (100.6 MHz, $CDCl_3$) δ 33.6 (C-7), 35.0 (CH_2), 36.5 (C-8), 53.3 (CH_3), 55.6 (C-6), 59.6 (C-3), 73.8 (C-2), 91.6 (C-8a), 117.8 (CH_2=), 126.8-138.3 (C-*o*, *m*, *p*), 134.0 (CH=), 140.5 (C-*i*), 162.8 (NCO), 171.0 (COO).

$[\alpha]_D^{22}$ = + 18.46 (*c* 0.5, $CHCl_3$).

HRMS calcd for $C_{24}H_{25}NO_4Se$: 471.0948, found: 471.0946.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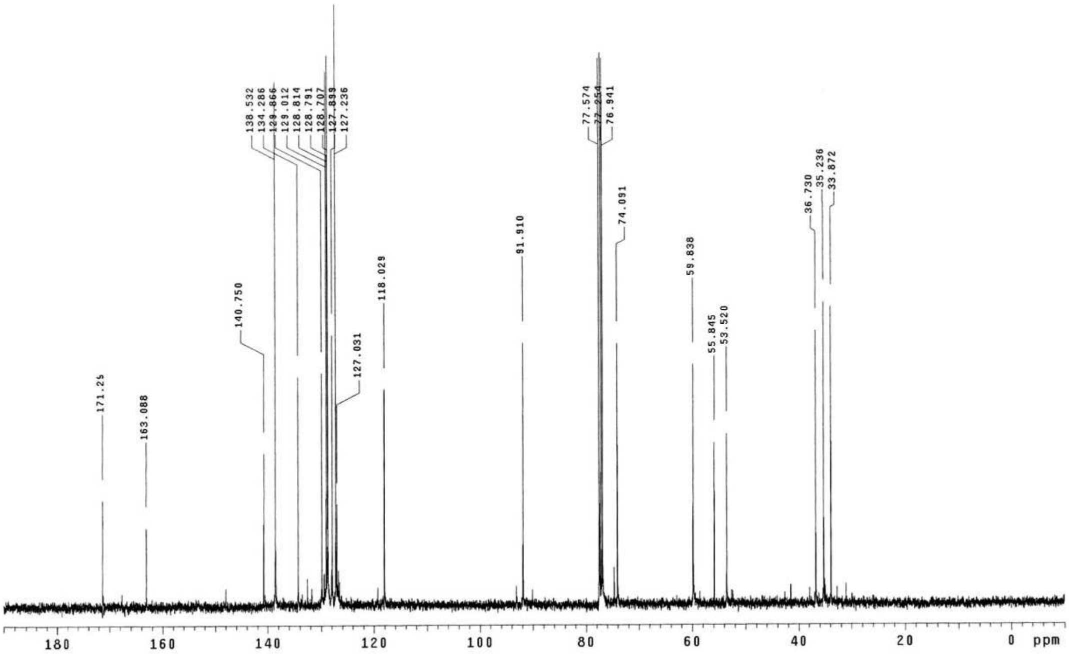
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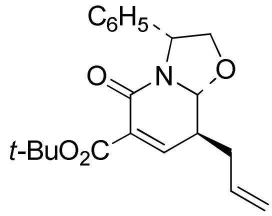


(3*R*,8*S*,8a*R*)-8-Allyl-6-(*tert*-butoxycarbonyl)-5-oxo-3-phenyl-2,3,8,8a-tetrahydro-5*H*-oxazolo[3,2-*a*]pyridine (5).

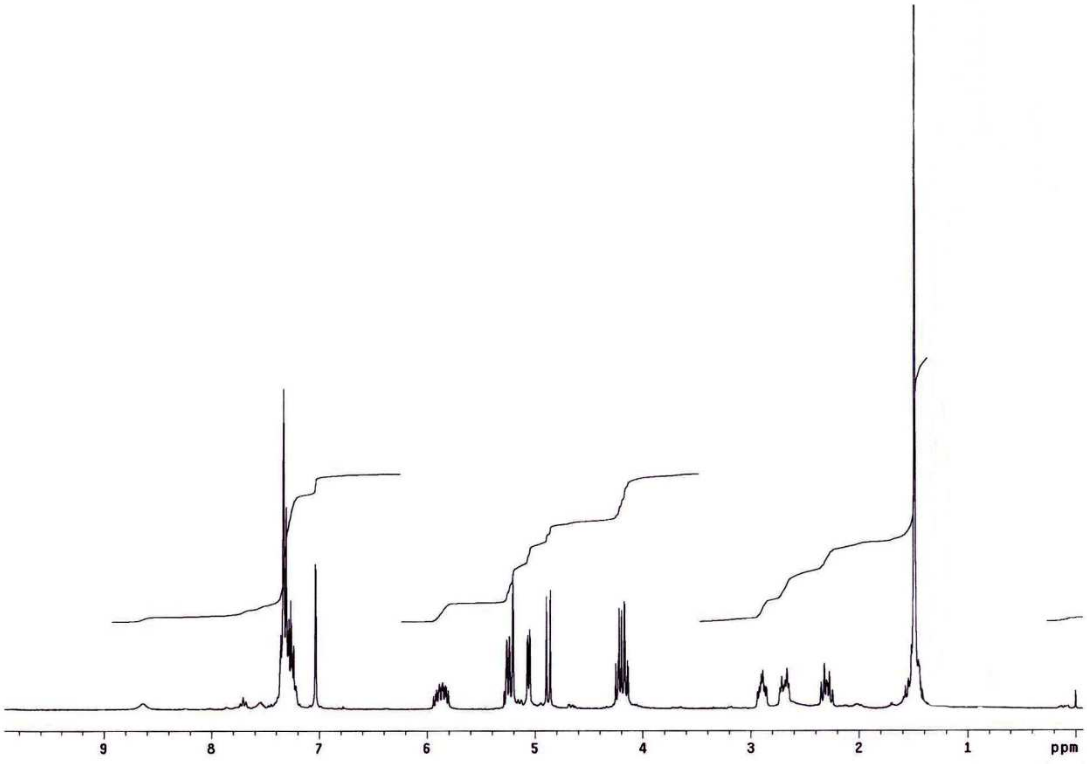
Aqueous H_2O_2 (30%, 0.37 mL, 12.4 mmol) and pyridine (0.17 mL, 2.01 mmol) were added to a solution of the selenides **3** (0.92 g, 1.77 mmol) in CH_2Cl_2 (159 mL). The resulting mixture was stirred at room temperature for 2 h and poured into distilled water. The two phases were separated, and the organic layer was washed with water, dried, filtered and concentrated under reduced pressure to give crude unsaturated lactam **5**, which was used in the next reaction without further purification.

Compound **5** (spectroscopic data from the crude):

IR (film): 1675 (NCO), 1731 (COO) cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ 1.49 [s, 9H, $(CH_3)_3C$], 2.31 (dt, *J* = 14.4, 9.3, 9.3 Hz, 1H, CH_2 allyl), 2.68 (ddm, *J* = 14.4, 4.8 Hz, 1H, CH_2 allyl), 2.89 (dddd, *J* = 10.5, 9.3, 4.8, 1.8 Hz, 1H, H-8), 4.15 (dd, *J* = 9.0, 1.2 Hz, 1H, H-2), 4.22 (dd, *J* = 9.0, 6.6 Hz, 1H, H-2), 4.87 (d, *J* = 10.5 Hz, 1H, H-8a), 5.05 (dd, *J* = 6.6, 1.2 Hz, 1H, H-3), 5.24 (m, 2H, CH_2=), 5.86 (dddd, *J* = 16.5, 10.2, 8.7, 5.7 Hz, 1H, CH=), 7.10-7.20 (m, 6H, H-7, C_6H_5).

^{13}C NMR (75.4 MHz, $CDCl_3$): δ 28.0 [$(CH_3)_3C$], 33.7 (CH_2 allyl), 41.0 (C-8), 58.2 (C-3), 74.5 (C-2), 82.1 [$(CH_3)_3C$], 90.0 (C-8a), 118.7 (CH_2=), 126.6, 128.6 (C-*o*, *m* C_6H_5), 127.6 (C-*p* C_6H_5), 131.6 (C-6), 133.5 (CH=), 140.5 (C-*i* C_6H_5), 145.2 (C-7), 157.6 (C=O), 163.2 (C=O).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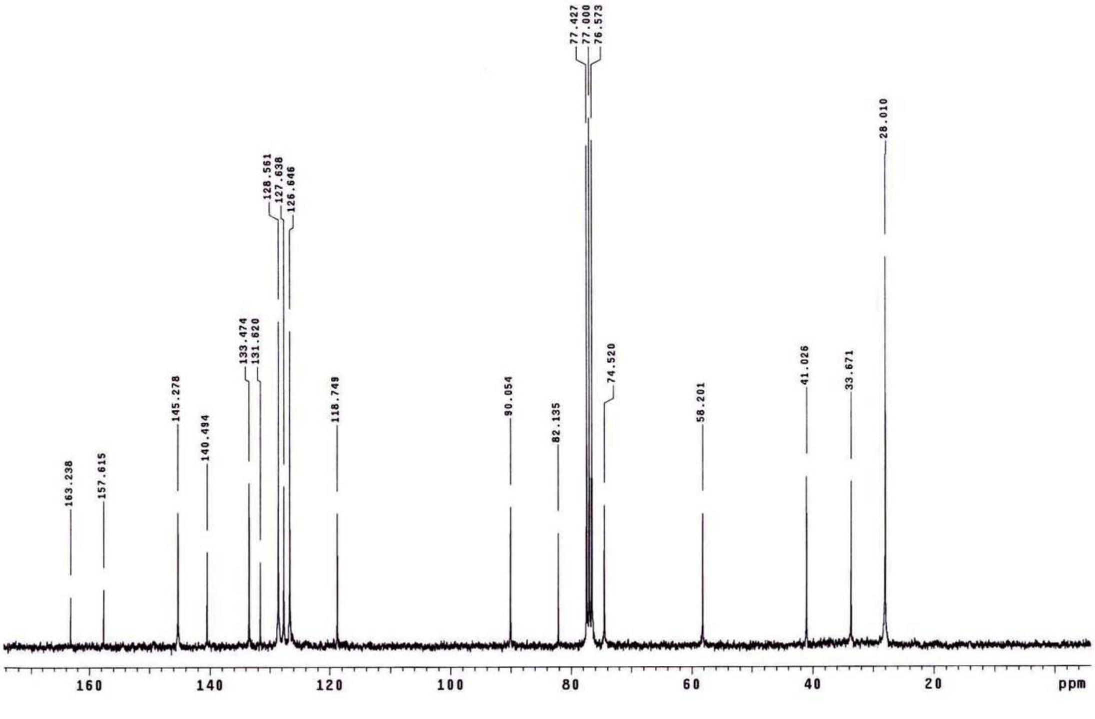
ppm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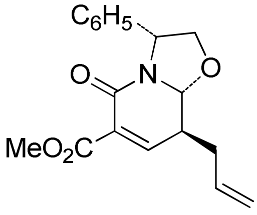
ppm



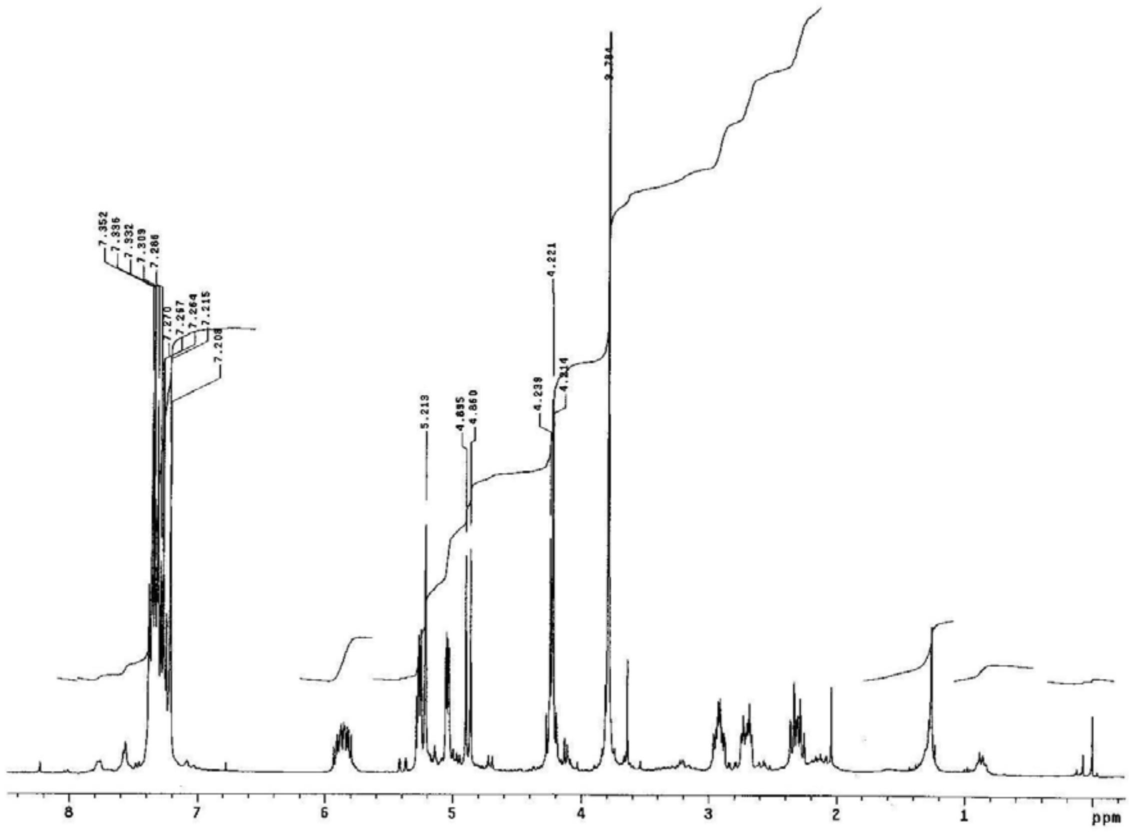
(3*R*,8*S*,8a*R*)-8-Allyl-6-(methoxycarbonyl)-5-oxo-3-phenyl-2,3,8,8a-tetrahydro-5*H*-oxazolo[3,2-*a*]pyridine (6).

30% aqueous H_2O_2 (0.73 mL, 23.8 mmol) and pyridine (0.36 mL, 4.4 mmol) were added to a solution of selenides **4** (1.6 g, 2.8 mmol) in CH_2C1_2 (231 mL), and the resulting mixture was stirred at rt for 2 h. The two phases were separated, and the organic layer was washed with water (10x20 mL), dried, and concentrated to give crude **6** (1.65 g) as an oil, which was kept at –30 °C and used in the next reaction without further purification.

IR (NaCl) 1673, 1741 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ 2.31 (dt, *J* = 14.4, 8.7 Hz, 1H, CH_2 allyl), 2.70 (dm, *J* = 14.4 Hz, 1H, CH_2 allyl), 2.91 (m, 1H, H-8), 3.78 (s, 3H, CH_3), 4.20 (dd, *J* = 9.0, 2.4 Hz, 1H, H-2), 4.24 (dd, *J* = 9.0, 6.0 Hz, 1H, H-2), 4.87 (d, *J* = 10.5 Hz, 1H, H-8a), 5.03 (dd, *J* = 6.0, 2.4 Hz, 1H, H-3), 5.27 (m, 2H, CH_2=), 5.86 (dddd, *J* = 15.3, 10.8, 8.7, 5.7 Hz, 1H, CH=), 7.20-7.36 (m, 5H, ArH).

^{13}C NMR (75.4 MHz, $CDCl_3$): δ 33.5 (CH_2), 41.2 (C-8), 52.3 (CH_3), 58.3 (C-3), 74.4 (C-2), 89.8 (C-8a), 119.0 (CH_2=), 126.8, 128.5 (C-*o*, *m*), 127.7 (C-*p*), 129.7 (C-6), 133.3 (CH=), 140.2 (C-*i*), 147.6 (C-7), 157.3 (COO), 164.3 (NCO).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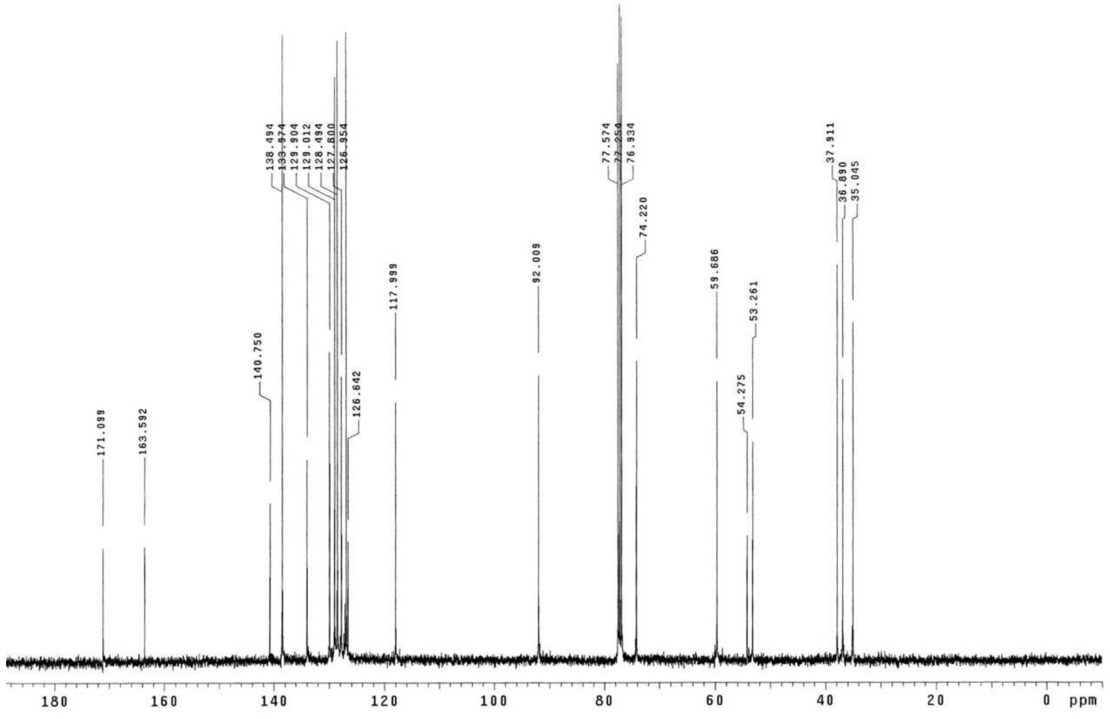
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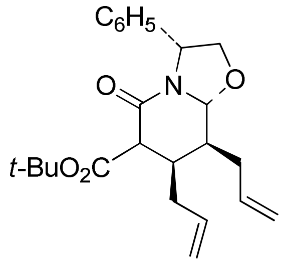


(3*R*,7*R*,8*S*,8a*R*)-6-(*tert*-Butoxycarbonyl)-7,8-diallyl-5-oxo-3-phenyl-2,3,6,7,8,8a-hexahydro-5*H*-oxazolo[3,2-*a*]pyridine (7).

LiCl (301 mg, 7.11 mmol) was dried at 80 °C for 1 h under vacuum (10–15 mmHg) in a two-necked, 100 mL round-bottomed flask. Then, CuI (1.35 g, 7.11 mmol) and THF (20 mL) were added under inert atmosphere, and the mixture was stirred at room temperature for 5 min. The suspension was cooled at –78 °C, and allylmagnesium bromide (7.11 mL of a 1 M solution in Et_2O, 7.11 mmol), TMSCl (0.9 mL, 7.11 mmol), and the crude unsaturated lactam **5** (1.77 mmol) in THF (20 mL) were successively added. The resulting mixture was stirred at –78 °C for 18 h. The reaction was quenched with saturated aqueous NH_4Cl, and filtered through Celite®. The aqueous layer was extracted with EtOAc, and the combined organic extracts were dried over anhydrous $MgSO_4$, filtered and concentrated under reduced pressure. Flash chromatography (9:1 to 7:3 hexane-EtOAc) gave the C-6 epimers **a** (major, 494 mg, 71% from selenide derivative) and **b** (minor, 77 mg, 11% from selenide derivative) of the diallyl derivative **7** as colourless oils (82% overall yield).

Epimer **7a** (major, lower R_f) (6*S*):

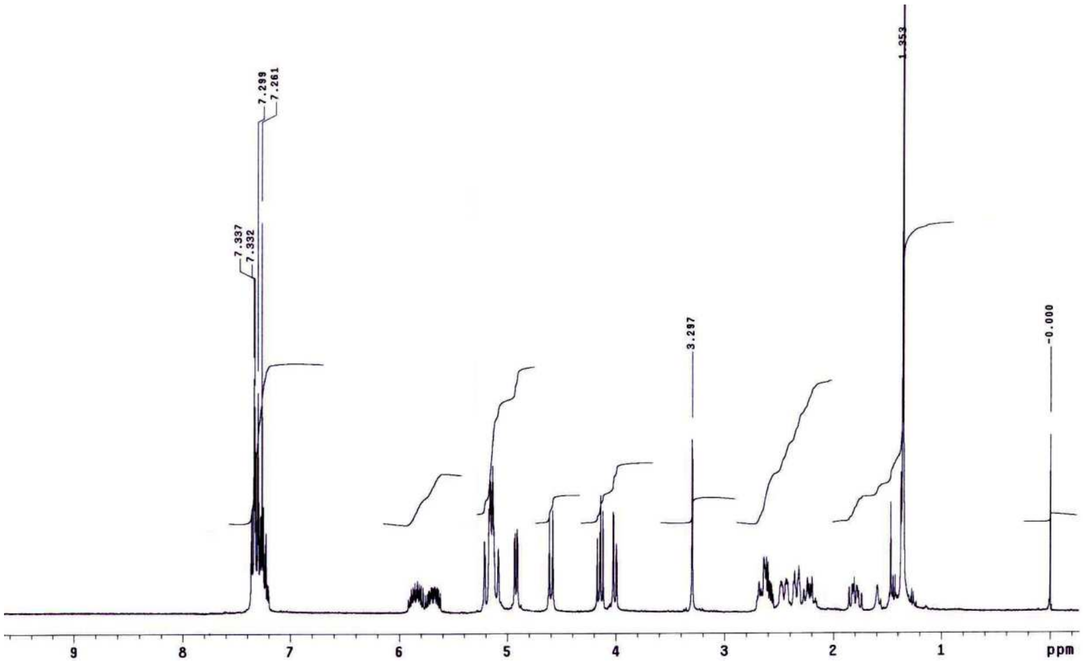
$[\alpha]_D^{22} = -70.7$ (*c* 0.5, $CHCl_3$).

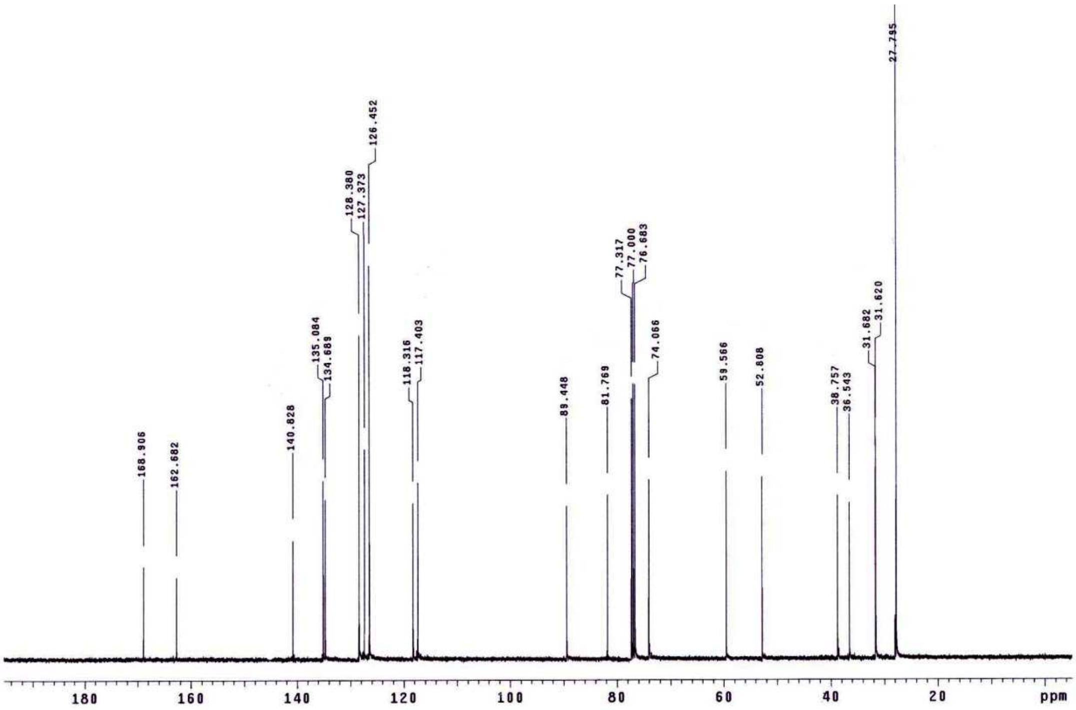
IR (film): 1664 (NCO), 1729 (COO) cm^{-1}.

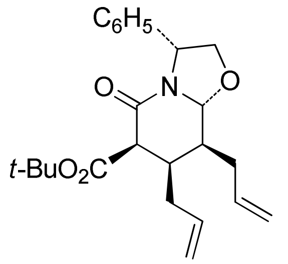
^{1}H NMR (400 MHz, $CDCl_3$, COSY, gHSQC): δ 1.35 [s, 9H, $(CH_3)_3C$], 1.80 (dt, *J* = 12.3, 9.0, 9.0 Hz, 1H, CH_2 allyl), 2.20 (dt, *J* = 13.8, 10.2, 10.2 Hz, 1H, CH_2 allyl), 2.33 (dm, *J* = 11.4 Hz, 1H, H-7), 2.45 (dm, *J* = 13.8 Hz, 1H, CH_2 allyl), 2.63 (m, 2H, H-8, CH_2 allyl), 3.30 (s, 1H, H-6), 4.00 (dd, *J* = 9.0, 1.2 Hz, 1H, H-2), 4.14 (dd, *J* = 9.0, 6.9 Hz, 1H, H-2), 4.60 (d, *J* = 9.6 Hz, 1H, H-8a), 4.92 (dd, *J* = 6.9, 1.2 Hz, 1H, H-3), 5.08-5.21 (m, 4H, CH_2=), 5.68 (dddd, *J* = 15.0, 10.5, 8.4, 4.8 Hz, 1H, CH=), 5.84 (dddd, *J* = 15.3, 9.9, 8.4, 4.8 Hz, 1H, CH=), 7.20-7.35 (m, 5H, C_6H_5).

^{13}C NMR (100.6 MHz, $CDCl_3$): δ 27.8 [$(CH_3)_3C$], 31.6, 31.7 (CH_2 allyl), 36.5 (C-7), 38.7 (C-8), 52.8 (C-6), 59.6 (C-3), 74.1 (C-2), 81.8 [$(CH_3)_3C$], 89.4 (C-8a), 117.4, 118.3 (CH_2=), 126.4, 128.4 (C-*o*, *m* C_6H_5), 127.4 (C-*p* C_6H_5), 134.7, 135.1 (CH=), 140.8 (C-*i* C_6H_5), 162.7 (C=O), 168.9 (C=O).

Elemental analysis calcd (%) for $C_{24}H_{31}NO_4$: C 72.52, H 7.86, N 3.52; found: C 72.49, H 7.94, N 3.40.







Epimer **7b** (minor, higher R*f*) (6*R*):

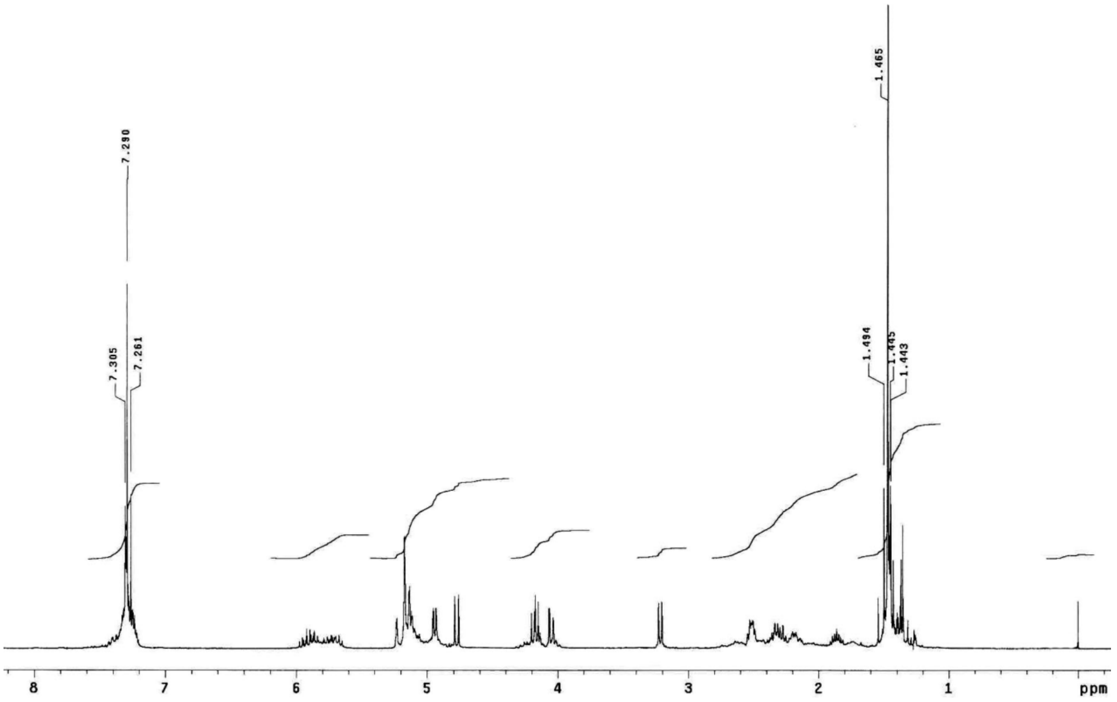
IR (film): 1669 (NCO), 1727 (COO) cm^{-1}.

^{1}H NMR (300 MHz, CDCl$_3$): δ 1.47 [s, 9H, (CH$_3$)$_3$], 1.86 (m, 1H, CH$_2$ allyl), 2.18 (m, 1H, CH$_2$ allyl), 2.33 (m, 2H, H-7, CH$_2$ allyl), 2.51 (m, 2H, H-8, CH$_2$ allyl), 3.21 (d, *J* = 8.1 Hz, 1H, H-6), 4.05 (dd, *J* = 9.0, 1.2 Hz, 1H, H-2), 4.18 (dd, *J* = 9.0, 6.6 Hz, 1H, H-2), 4.77 (d, *J* = 9.0 Hz, 1H, H-8a), 4.94 (dd, *J* = 6.6, 1.2 Hz, 1H, H-3), 5.10-5.17 (m, 4H, CH$_2$=), 5.73 (m, 1H, CH=), 5.89 (m, 1H, CH=), 7.26-7.35 (m, 5H, C$_6$H$_5$).

^{13}C NMR (100.6 MHz, CDCl$_3$): δ 27.8 [(*C*H$_3$)$_3$C], 32.7, 35.5 (CH$_2$ allyl), 36.7 (C-7), 41.6 (C-8), 54.4 (C-6), 59.0 (C-3), 73.8 (C-2), 81.9 [(CH$_3$)$_3$*C*], 89.8 (C-8a), 118.2, 119.4 (CH$_2$=), 126.4, 128.4 (C-*o*, *m* C$_6$H$_5$), 127.5 (C-*p* C$_6$H$_5$), 132.7, 133.4 (CH=), 140.8 (C-*i* C$_6$H$_5$), 163.2 (C=O), 169.7 (C=O).

MS *m/z* (%): 397 (2) [M$^+$], 381 (5), 342 (8), 341 (34), 340 (21), 324 (17), 300 (12), 296 (27), 256 (15), 254 (38), 214 (16), 146 (26), 128 (12), 120 (28), 117 (15), 104 (100).

HRMS calcld for [C$_{24}$H$_{32}$NO$_4$ + H]$^+$: 398.2326, found: 398.2320.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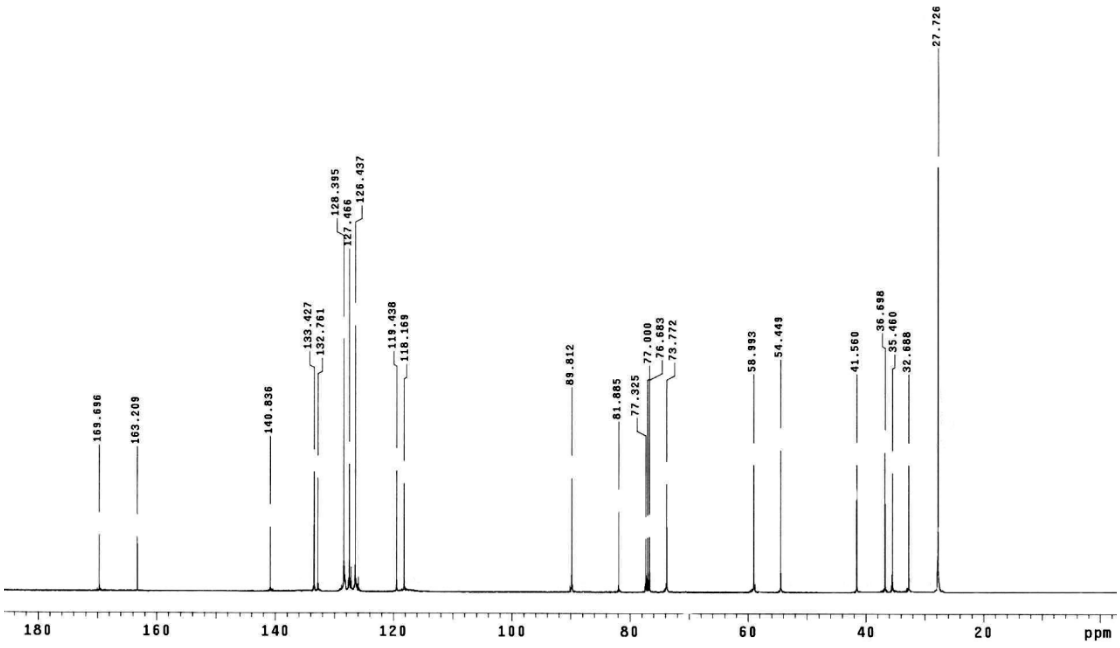
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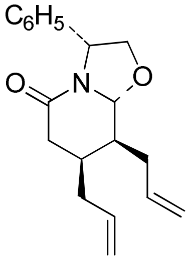


(3*R*,7*S*,8*S*,8a*R*)-7,8-Diallyl-5-oxo-3-phenyl-2,3,6,7,8,8a-hexahydro-5*H*-oxazolo[3,2-*a*]pyridine (9a).

TFA (1.5 mL, 0.02 mmol) was added to a solution of the diallyl derivative **7** (406 mg, 1.02 mmol) in anhydrous CH_2Cl_2 (4 mL) at room temperature under inert atmosphere, and the resulting mixture was stirred for 30 minutes. The reaction was quenched with saturated aqueous Na_2CO_3. The aqueous phase was washed with CH_2Cl_2 (2 × 5 mL), and the combined organic extracts were dried over anhydrous Na_2SO_4, filtered, and concentrated. The crude was then redissolved in anhydrous toluene (15 mL), and the resulting solution was heated at reflux for 18 h. The resulting solution was cooled and poured into brine, the aqueous phase was extracted with EtOAc, and the combined organic extracts were dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. Flash chromatography (7:3 to 6:4 hexane-EtOAc) afforded compound **9a** (233 mg, 77%) as a colourless oil.

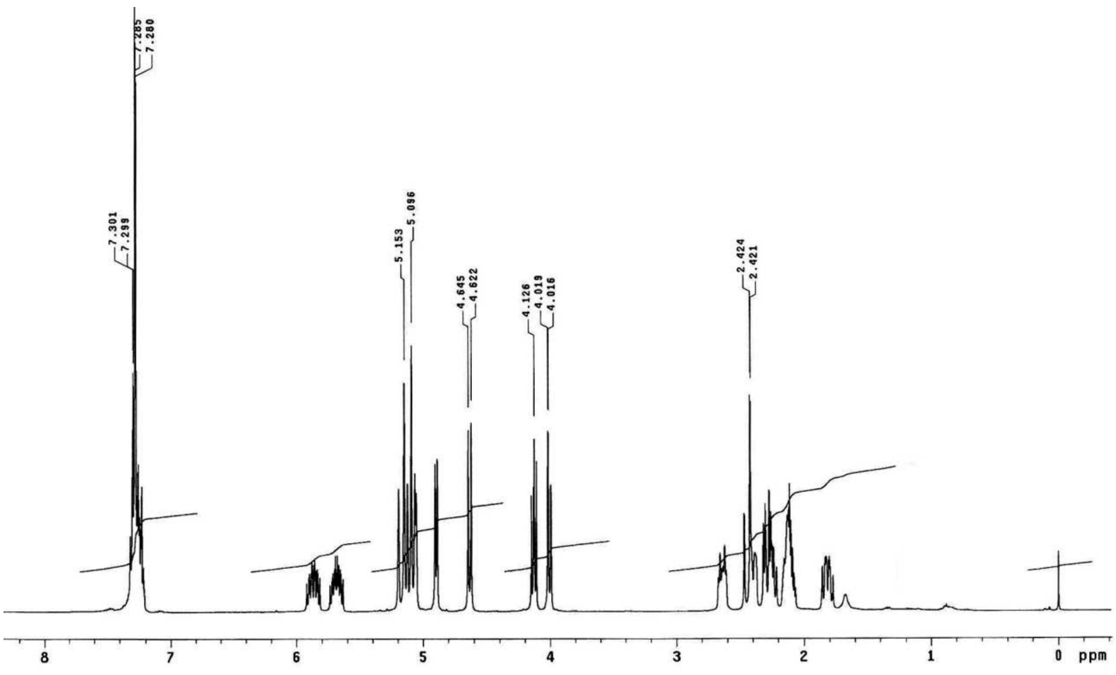
$[\alpha]_D^{22}$ = – 17.0 (*c* 0.2, $CHCl_3$).

IR (film): 1661 (COO) cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$, COSY, gHSQC): δ 1.81 (ddd, *J* = 13.6, 10.8, 8.8 Hz, 1H, CH_2 allyl), 2.13 (m, 2H, H-7, H-8), 2.23 (m, 1H, CH_2 allyl), 2.28 (dd, *J* = 18.0, 6.0 Hz, 1H, H-6), 2.38 (m, 1H, CH_2 allyl), 2.44 (dd, *J* = 18.0, 1.6 Hz, 1H, H-6), 2.64 (dt, *J* = 14.0, 5.2, 5.2 Hz, 1H, CH_2 allyl), 4.00 (dd, *J* = 8.8, 0.8 Hz, 1H, H-2), 4.13 (dd, *J* = 8.8, 6.8 Hz, 1H, H-2), 4.63 (d, *J* = 9.2 Hz, 1H, H-8a), 4.89 (dd, *J* = 6.8, 0.8 Hz, 1H, H-3), 5.05-5.20 (m, 4H, CH_2=), 5.69 (m, 1H, CH=), 5.86 (dddd, *J* = 16.0, 10.4, 8.8, 6.0 Hz, 1H, CH=), 7.26-7.30 (m, 5H, C_6H_5).

^{13}C NMR (100.6 MHz, $CDCl_3$): δ 32.2 (2CH_2 allyl), 32.5 (C-7), 36.3 (C-6), 42.2 (C-8), 59.4 (C-3), 73.8 (C-2), 89.6 (C-8a), 117.3 (CH_2=), 117.6 (CH_2=), 126.3, 128.5 (C-*o*, *m* C_6H_5), 127.4 (C-*p* C_6H_5), 135.0 (CH=), 135.9 (CH=), 141.5 (C-*i* C_6H_5), 166.9 (NCO).

Elemental analysis calcd (%) for $C_{19}H_{23}NO_2\cdot\frac{1}{4}$ H_2O: C 75.59, H 7.85, N 4.64; found: C 75.49, H 7.76, N 4.45.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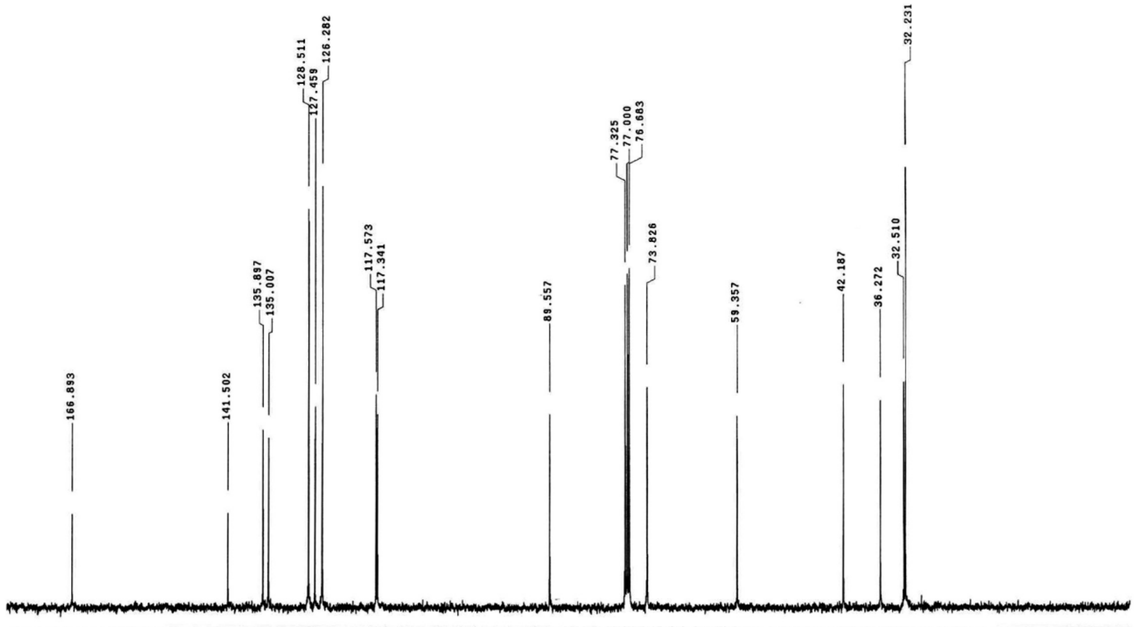
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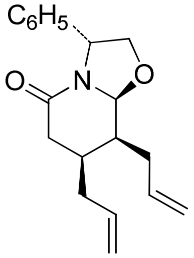


Compound **9b**:

IR (film): 1643 (NCO) cm^{-1}.

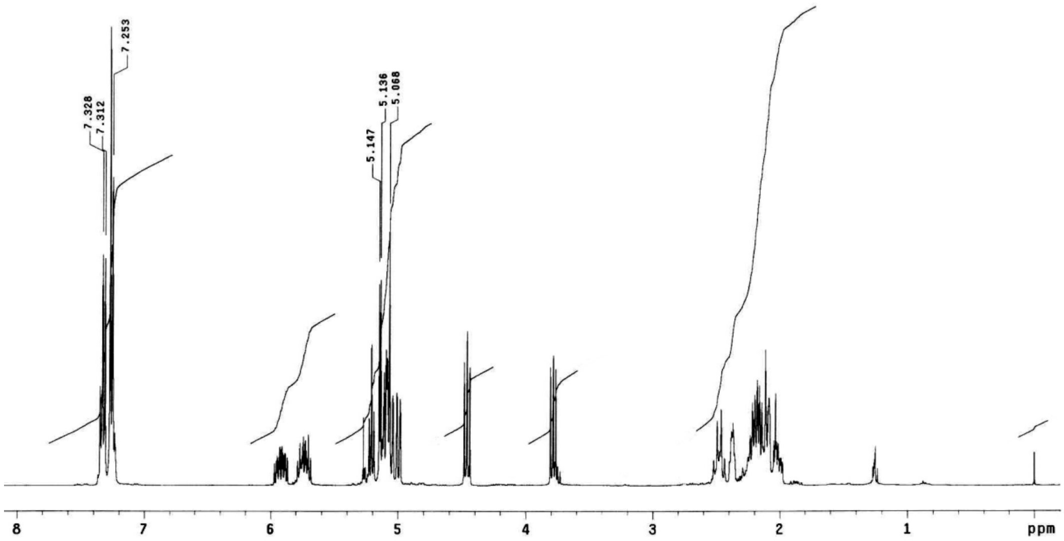
^{1}H-NMR (400 MHz, $CDCl_3$, COSY, gHSQC): δ 2.01 (m, 1H, CH_2 allyl), 2.08-2.23 (m, 5H, H-6, H-7, 3H CH_2 allyl), 2.37 (m, 1H, H-8), 2.49 (m, 1H, H-6), 3.78 (dd, *J* = 9.2, 7.6 Hz, 1H, H-2), 4.46 (dd, *J* = 9.2, 8.0 Hz, 1H, H-2), 4.89-5.11 (m, 4H, CH_2=), 5.14 (d, *J* = 4.4 Hz, 1H, H-8a), 5.20 (t, *J* = 7.6 Hz, 1H, H-3), 5.73 (m, 1H, CH=), 5.91 (dddd, *J* = 17.6, 10.0, 8.0, 6.0 Hz, 1H, CH=), 7.25-7.40 (m, 5H, C_6H_5).

^{13}C-NMR (100.6 MHz, $CDCl_3$): δ 25.9 (CH_2 allyl), 33.8 (C-7), 34.3 (C-6), 36.5 (CH_2 allyl), 39.0 (C-8), 58.1 (C-3), 72.6 (C-2), 91.0 (C-8a), 115.4 (CH_2=), 117.3 (CH_2=), 126.1, 128.7 (C-*o*, *m* C_6H_5), 127.5 (C-*p* C_6H_5), 135.3 (CH=), 137.9 (CH=), 139.3 (C-*i* C_6H_5), 168.1 (NCO).

$[\alpha]_D^{22} = -94.6$ (*c* 2.1, $CHCl_3$).

m.p. 91-93 °C

HRMS calcld for $[C_{19}H_{23}NO_2 + Na]^+$: 320.1621, found: 320.1626.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4
3
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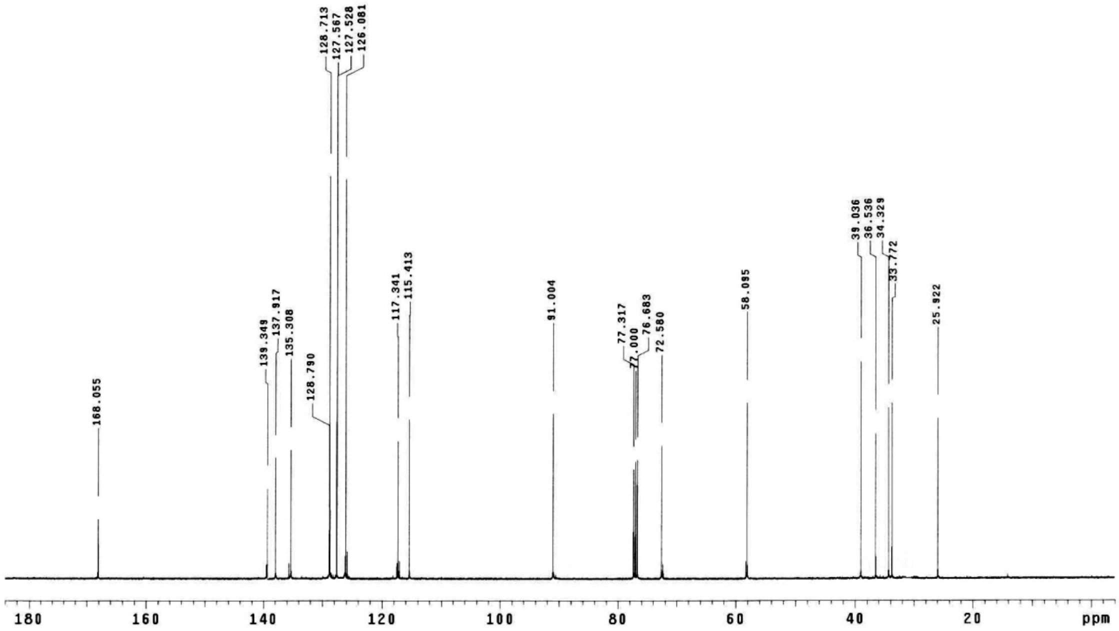
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77.000
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72.580
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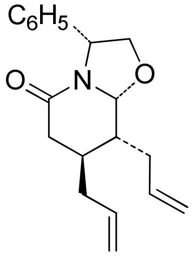


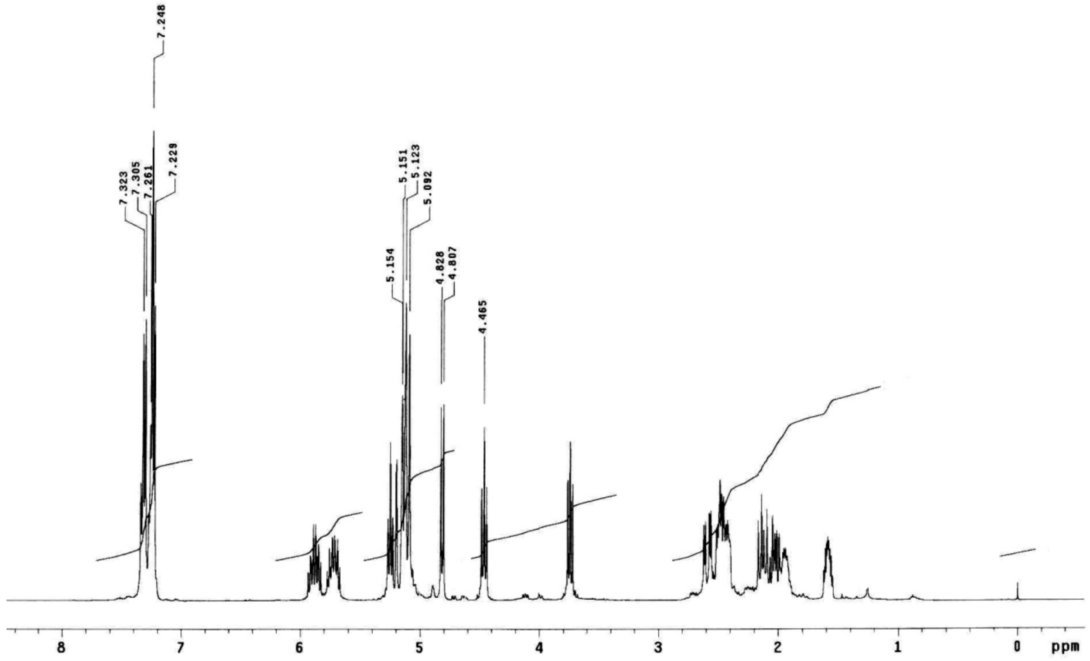
Compound **9c**:

IR (film): 1661 (NCO) cm^{-1}.

^{1}H-NMR (400 MHz, $CDCl_3$, COSY, gHSQC): δ 1.58 (m, 1H, H-8), 1.94 (m, 1H, CH_2 allyl), 1.98 (m, 1H, H-7), 2.10 (dd, *J* = 18.4, 10.8 Hz, 1H, H-6), 2.47 (m, 3H, CH_2 allyl), 2.58 (dd, *J* = 18.4, 5.6 Hz, 1H, H-6), 3.74 (t, *J* = 8.4 Hz, 1H, H-2), 4.46 (t, *J* = 8.4 Hz, 1H, H-2), 4.81 (d, *J* = 8.4 Hz, 1H, H-8a), 5.05-5.20 (m, 4H, CH_2=), 5.25 (t, *J* = 8.4 Hz, 1H, H-3), 5.72 (dddd, *J* = 16.9, 9.6, 7.2, 7.2 Hz, 1H, CH=), 5.88 (dddd, *J* = 16.8, 10.0, 7.6, 6.8 Hz, 1H, CH=), 7.23-7.32 (m, 5H, C_6H_5).

^{13}C-NMR (100.6 MHz, $CDCl_3$): δ 31.7 (C-7), 31.8 (CH_2 allyl), 35.7 (CH_2 allyl), 36.9 (C-6), 42.5 (C-8), 58.2 (C-3), 72.3 (C-2), 90.5 (C-8a), 118.1 (CH_2=), 118.2 (CH_2=), 125.9, 128.6 (C-*o*, *m* C_6H_5), 127.5 (C-*p* C_6H_5), 133.5 (CH=), 134.0 (CH=), 139.3 (C-*i* C_6H_5), 168.3 (NCO).

HRMS calcld for $[C_{19}H_{23}NO_2 + H]^+$: 298.1801, found: 298.1801.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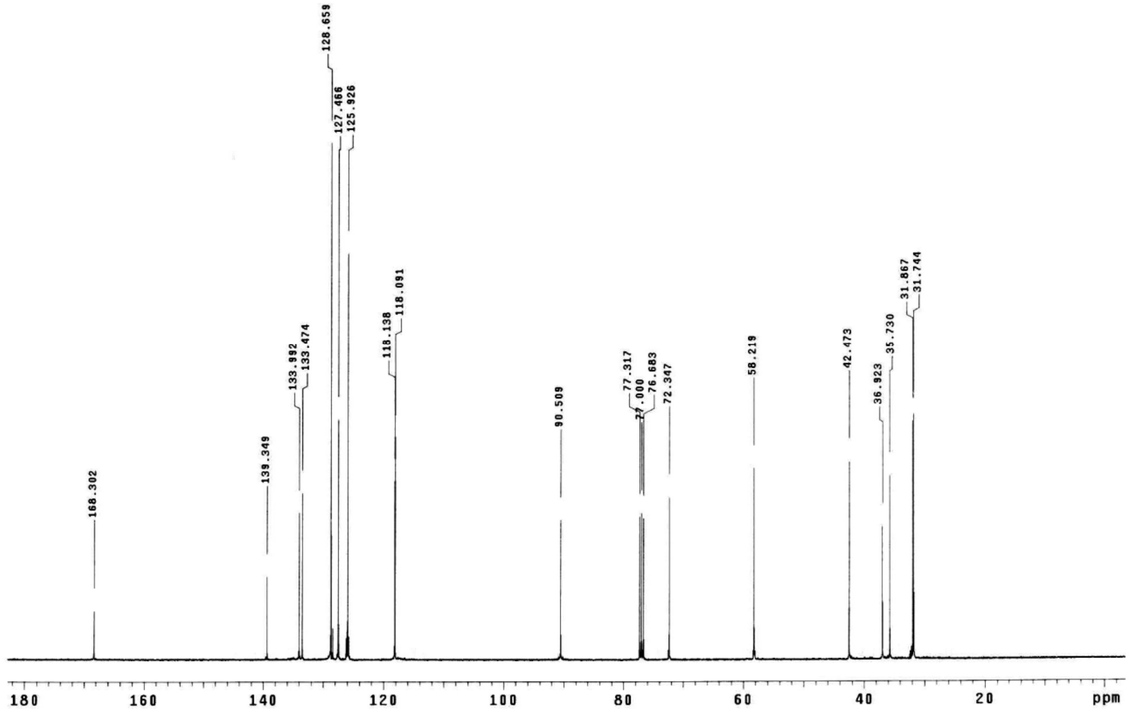
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72.347
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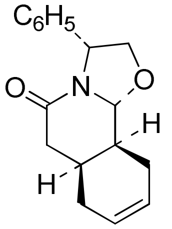
20
ppm



(3*R*,6a*S*,10a*S*,10b*R*)-5-Oxo-3-phenyl-2,3,6,6a,7,10,10a,10b-octahydro-5*H*-oxazolo[3,2-*a*]isoquinoline (10).

Second generation Grubbs catalyst (340 mg, 0.4 mmol) was added to a solution of lactam **9** (1.59 g, 5.3 mmol) in CH_2Cl_2 (756 mL). The mixture was stirred at room temperature for 4 h and concentrated under reduced pressure. Flash chromatography (9:1 to 7:3 hexane-EtOAc) afforded tricyclic lactam **10** (1.18 g, 83%) as a brown solid.

$[\alpha]_D^{22}$ = + 68.6 (*c* 1.0, $CHCl_3$).

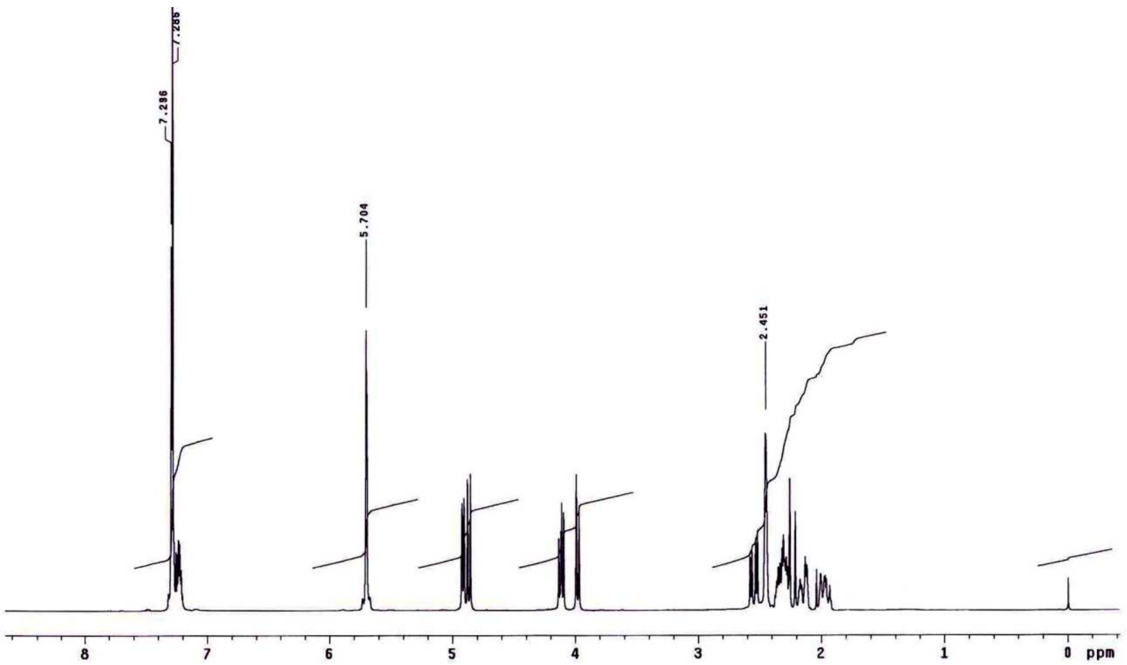
IR (film): 1658 (COO) cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$, COSY, gHSQC): δ1.93-2.03 (m, 1H, H-7), 2.13 (dd, *J* = 16.4, 5.6 Hz, 1H, H-7), 2.23 (d, *J* = 18.0 Hz, 1H, H-6), 2.30 (m, 2H, H-10a, H-6a), 2.45 (s, 2H, H-10), 2.54 (dd, *J* = 18.0, 6.4 Hz, 1H, H-6), 3.98 (d, *J* = 9.2 Hz, 1H, H-2), 4.11 (dd, *J* = 9.2, 6.8 Hz, 1H, H-2), 4.86 (d, *J* = 9.6 Hz, 1H, H-10b), 4.91 (d, *J* = 6.8 Hz, 1H, H-3), 5.70 (m, 2H, H-8, H-9), 7.20-7.30 (m, 5H, C_6H_5).

^{13}C NMR (100.6 MHz, $CDCl_3$): δ25.6 (C-10), 28.5 (C-7), 29.1 (C-6a), 36.0 (C-10a), 38.3 (C-6), 59.4 (C-3), 73.6 (C-2), 87.3 (C-10b), 124.6, 125.1 (C-8, C-9), 127.3, 128.5 (C-*o*, *m* C_6H_5), 127.4 (C-*p* C_6H_5), 141.6 (C-*i* C_6H_5), 166.7 (NCO).

m.p. 138-140 °C.

Elemental analysis calcd (%) for $C_{17}H_{19}NO_2 \cdot {}^1/_4H_2O$: C 74.56, H 7.18, N 5.11; found: C 74.67, H 7.09, N 4.99.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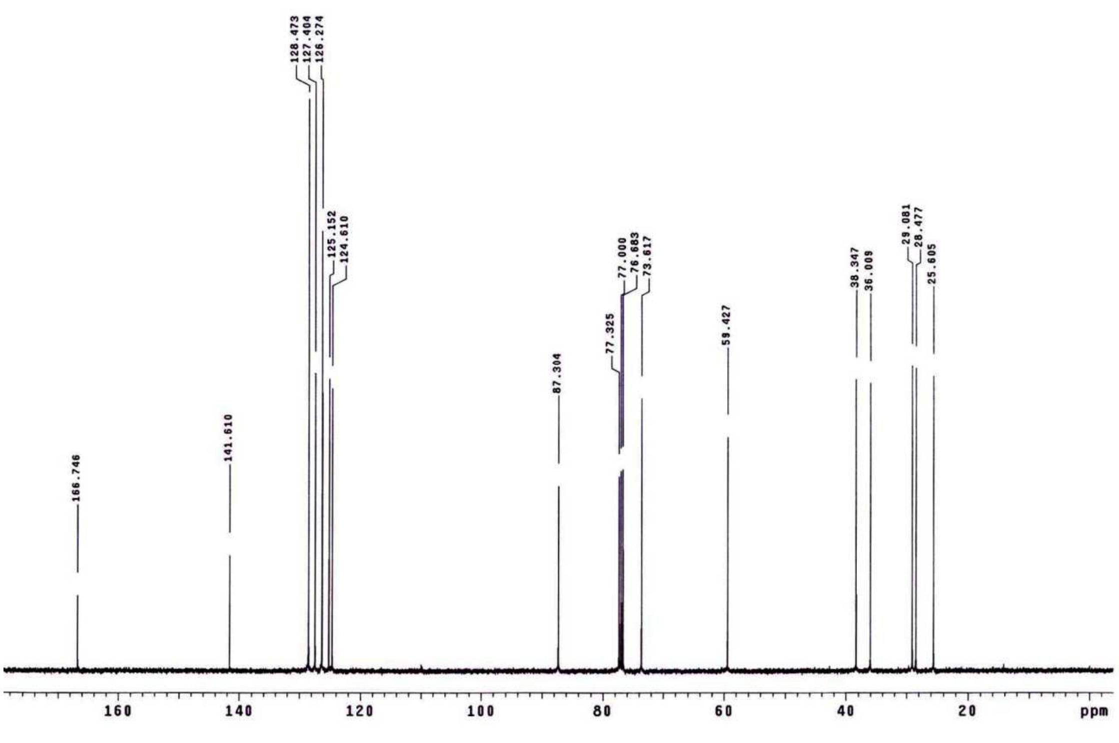
3
2
1
0 ppm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77.000
76.683
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36.009
29.081
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60
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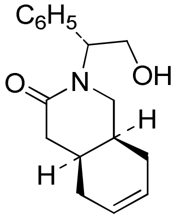
20
ppm



(4a*S*,8a*S*)-2-[(1*R*)-2-Hydroxy-1-phenylethyl]-3-oxo-1,2,3,4,4a,5,8,8a-octahydroisoquinoline (11).

Et_3SiH (155 µL, 0.97 mmol) and $TiCl_4$ (171 µL, 1.56 mmol) were added under inert atmosphere to a solution of lactam **10** (105 mg, 0.39 mmol) in anhydrous CH_2Cl_2 (10 mL), and the resulting dark solution was heated at reflux for 24 h. The mixture was poured into saturated aqueous $NaHCO_3$ (10 mL), and the resulting solution was extracted with CH_2Cl_2. The combined organic extracts were dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. Flash chromatography (9:1 hexane-EtOAc to only EtOAc) gave isoquinoline **11** (98 mg, 92%) as a white solid.

$[\alpha]_D^{22}$ = – 20.5 (*c* 0.4, $CHCl_3$).

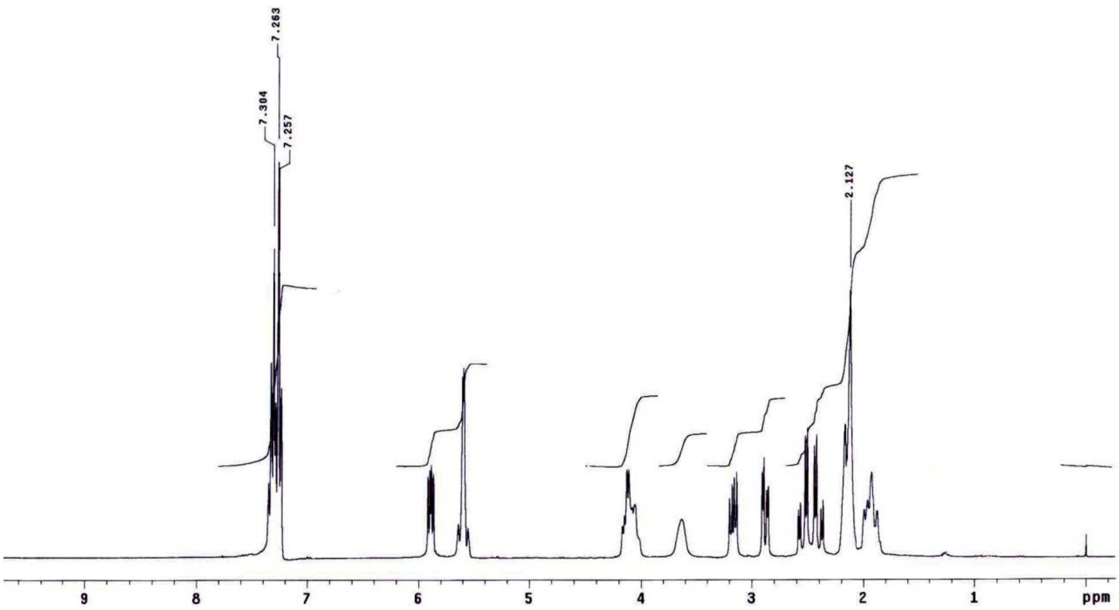
IR (film): 3375 (OH), 1614 (COO) cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$, COSY, gHSQC): δ 1.93 (m, 2H, H-5, H-8), 2.15 (m, 4H, H-5, H-8, H-4a, H-8a), 2.40 (dd, *J* = 18.0, 6.0 Hz, 1H, H-4), 2.54 (dd, *J* = 18.0, 5.6 Hz, 1H, H-4), 2.88 (dd, *J* = 12.0, 4.0 Hz, 1H, H-1), 3.16 (dd, *J* = 12.0, 7.2 Hz, 1H, H-1), 3.64 (br. s, 1H, OH), 4.08 (m, 1H, H-2'), 4.14 (dd, *J* = 11.2, 5.2 Hz, 1H, H-2'), 5.60 (m, 2H, H-6, H-7), 5.89 (dd, *J* = 9.2, 5.2 Hz, 1H, H-1'), 7.10-7.20 (m, 5H, C_6H_5).

^{13}C NMR (100.6 MHz, $CDCl_3$): δ 26.2, 27.6 (C-5, C-8), 28.7 (C-4a), 29.7 (C-8a), 36.0 (C-4), 44.7 (C-1), 57.1 (C-1'), 60.4 (C-2'), 124.3, 124.5 (C-6, C-7), 127.3 (C-*p* C_6H_5), 127.5, 128.3 (C-*o*, *m* C_6H_5), 136.9 (C-*i* C_6H_5), 170.6 (NCO).

m.p. 84-86 °C

Elemental analysis calcd (%) for $C_{17}H_{21}NO_2$: C 75.25, H 7.80, N 5.16; found: C 74.96, H 7.78, N 5.07.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3
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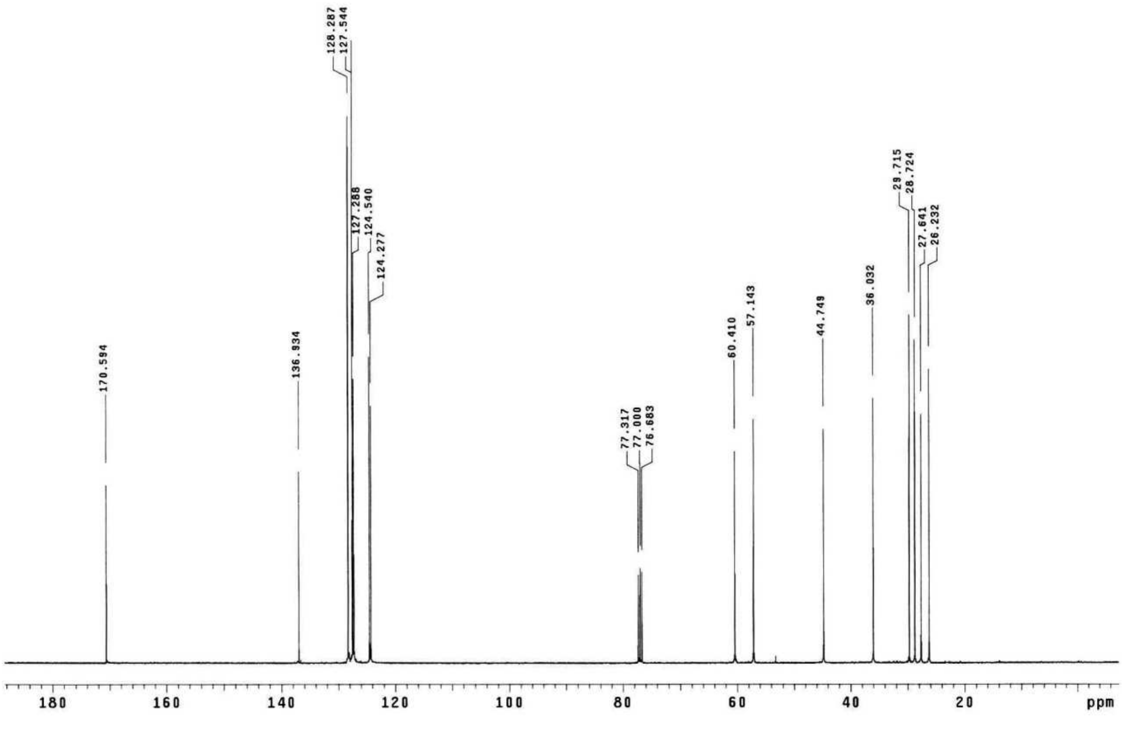
1
ppm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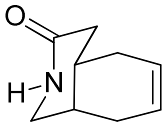


(4a*S*,8a*S*)-3-Oxo-1,2,3,4,4a,5,8,8a-octahydroisoquinoline (12).

Into a three-necked, 100 mL round-bottomed flask equipped with a coldfinger condenser charged with dry ice-acetone were condensed 15 mL of NH_3 at –78 °C, and then a solution of lactam **11** (190 mg, 0.70 mmol) in THF (10 mL) was added. The temperature was raised to –33 °C and sodium metal was added in small portions until the blue colour persisted. The mixture was stirred at –33 °C for 1 min. The reaction was quenched by the addition of solid NH_4Cl until the blue colour disappeared, and then the mixture was stirred at room temperature for 4 h. The resulting residue was digested at room temperature with CH_2Cl_2, and the suspension was filtered through Celite®. The solution was concentrated under reduced pressure. Flash chromatography of the resulting oil (2:1 hexane- EtOAc to 60:1 EtOAc-MeOH) afforded bicyclic lactam **12** (98 mg, 93%) as a white solid.

$[\alpha]_D^{22}$ = – 30.2 (*c* 1.0, MeOH).

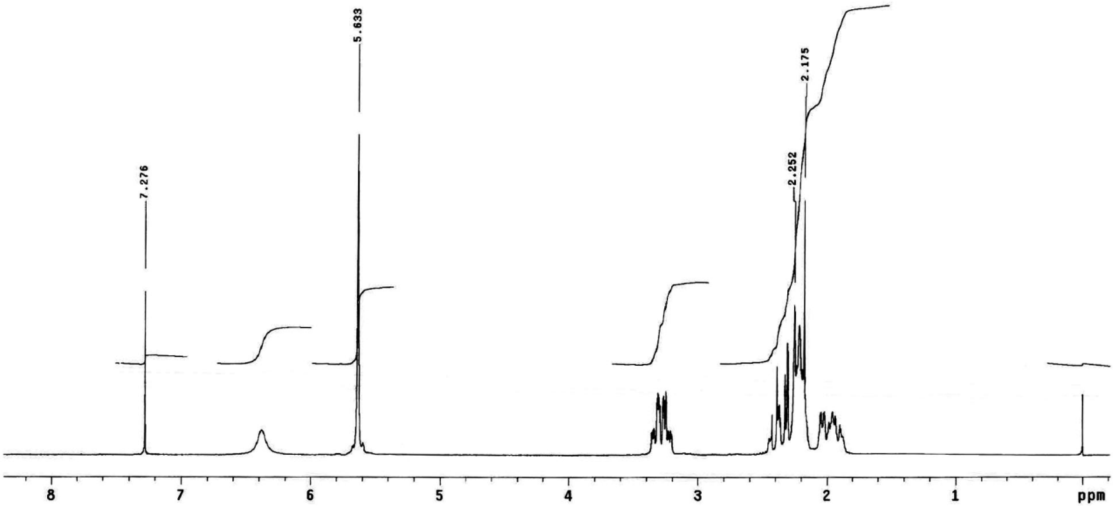
IR (film): 3300 (NH), 1665 (COO) cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$, COSY, gHSQC): δ 1.88-2.04 (m, 2H, H-8, H-5), 2.15-2.30 (m, 4H, H-8, H-5, H-4a, H-8a), 2.30 (dd, *J* = 16.8, 6.4 Hz, 1H, H-4), 2.38 (dd, *J* = 16.8, 4.4 Hz, 1H, H-4), 3.23 (ddd, *J* = 12.0, 6.0, 2.0 Hz, 1H, H-1), 3.31 (ddd, *J* = 12.0, 4.8, 1.6 Hz, 1H, H-1), 5.63 (s, 2H, H-6, H-7), 6.73 (br. s, 1H, NH).

^{13}C NMR (100.6 MHz, $CDCl_3$): δ 26.0 (C-8), 28.3 (C-5), 29.1, 29.2 (C-4a, C-8a), 34.8 (C-4), 44.6 (C-1), 124.5, 124.6 (C-6, C-7), 172.2 (NCO).

m.p. 65-67 °C

Elemental analysis calcd (%) for $C_9H_{13}NO$: C 71.49, H 8.67, N 9.26; found: C 71.42, H 8.58, N 9.16.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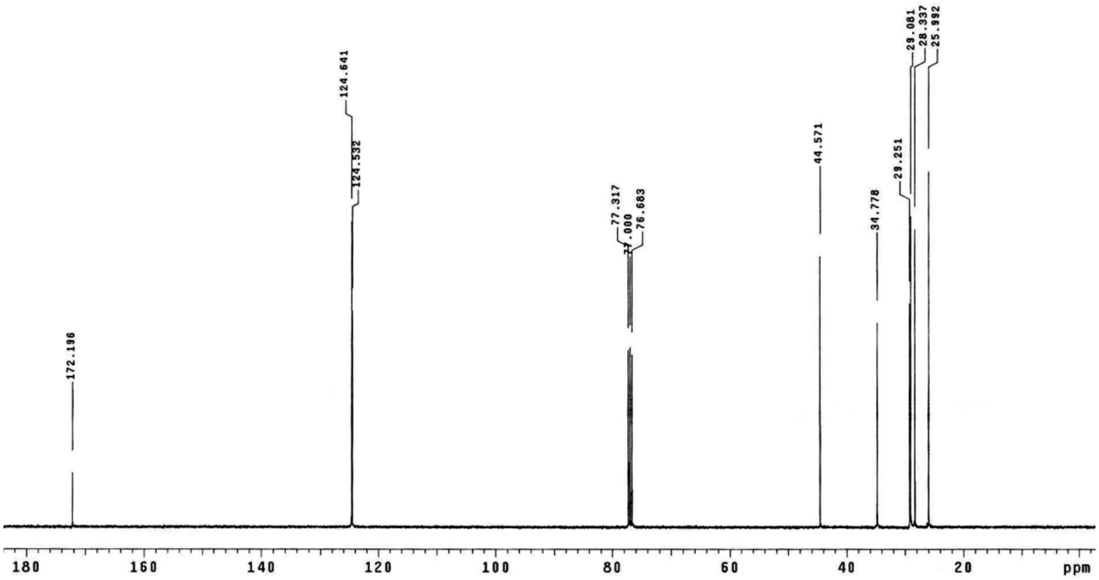
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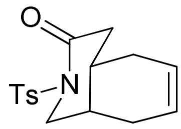
40
20
ppm



(4a*S*,8a*S*)-3-Oxo-2-(*p*-toluenesulfonyl)-1,2,3,4,4a,5,8,8a-octahydroisoquinoline (13).

n-BuLi (1.24 mL of a solution 1.6 M in hexane, 1.98 mmol) was added dropwise at –78 °C to a stirred solution of bicyclic lactam **12** (250 mg, 1.65 mmol) in anhydrous THF (10 mL) under inert atmosphere. After stirring for 45 min at –78 °C, a solution of *p*-toluenesulfonyl chloride (347 mg, 1.82 mmol) in anhydrous THF (2 mL) was added via cannula, and the stirring was continued for 4 h at –78 °C. The reaction was quenched by the addition of saturated aqueous NH_4Cl solution, and the resulting solution was extracted with EtOAc. The combined organic extracts were dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. Flash chromatography (8:2 hexane-EtOAc) afforded lactam **13** (432 mg, 86% yield) as a white solid.

$[\alpha]_D^{22}$ = – 17.5 (*c* 0.14, $CHCl_3$).

IR (film): 1690 (NCO), 1165 (SO_2-O) cm^{-1}.

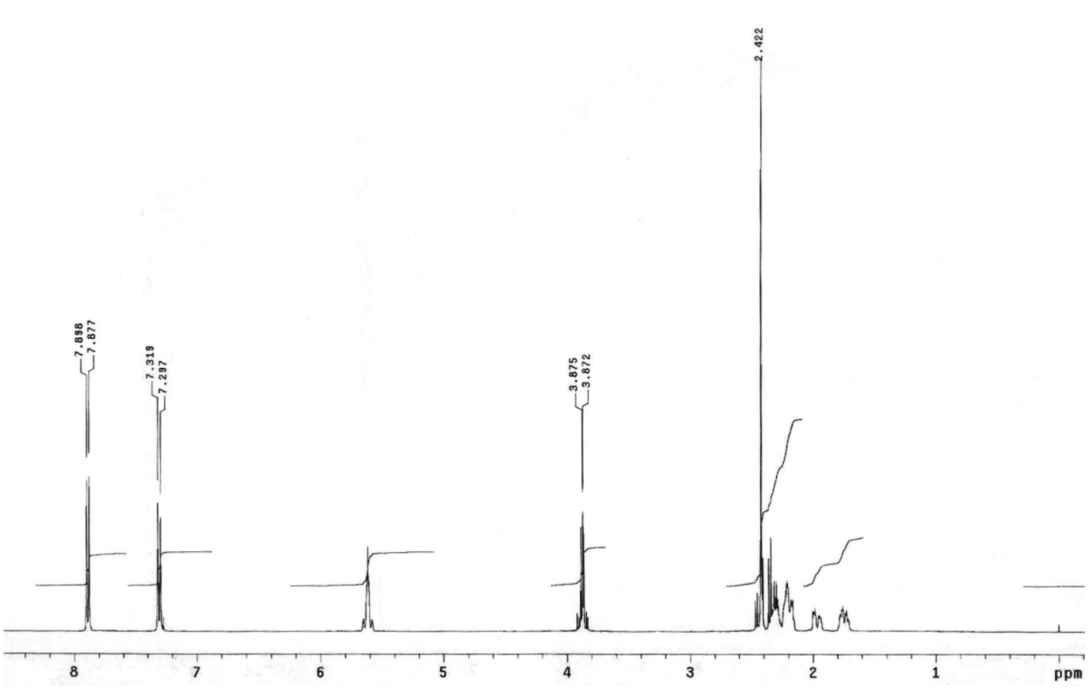
^1H NMR (400 MHz, $CDCl_3$, COSY, gHSQC): δ 1.74 (dm, *J* = 17.2 Hz, 1H, H-5), 1.96 (dm, *J* = 17.2 Hz, 1H, H-8), 2.19 (m, 2H, H-5, H-4a), 2.31 (m, 2H, H-8, H-8a), 2.33 (dd, *J* = 18.0, 7.2 Hz, 1H, H-4), 2.42 (s, 3H, CH_3 Ts), 2.43 (dd, *J* = 18.0, 5.1 Hz, 1H, H-4), 3.85 (dd, *J* = 12.0, 5.1 Hz, 1H, H-1), 3.89 (dd, *J* = 12.0, 6.0 Hz, 1H, H-1), 5.61 (s, 2H, H-6, H-7), 7.30 (d, *J* = 8.8 Hz, 2H, H-*m* Ts), 7.89 (d, *J* = 8.8 Hz, 2H, H-*o* Ts).

^{13}C NMR (100.6 MHz, $CDCl_3$): δ 21.6 (CH_3 Ts), 25.5 (C-8), 27.9 (C-5), 28.9 (C-4a), 30.2 (C-8a), 37.1 (C-4), 49.3 (C-1), 124.1, 124.4 (C-6, C-7), 128.6 (C-*o*), 129.2 (C-*m* Ts), 136.0 (C-*i* Ts), 144.6 (C-*p* Ts), 169.8 (NCO).

m.p. 70-72 °C.

HRMS (ESI) calcd for $[C_{16}H_{19}NO_3S + H]^+$: 306.1158, found: 306.1155.

Elemental analysis calcd (%) for $C_{16}H_{19}NO_3S$: C 62.93, H 6.27, N 4.59; found: C 62.93, H 6.36, N 4.48.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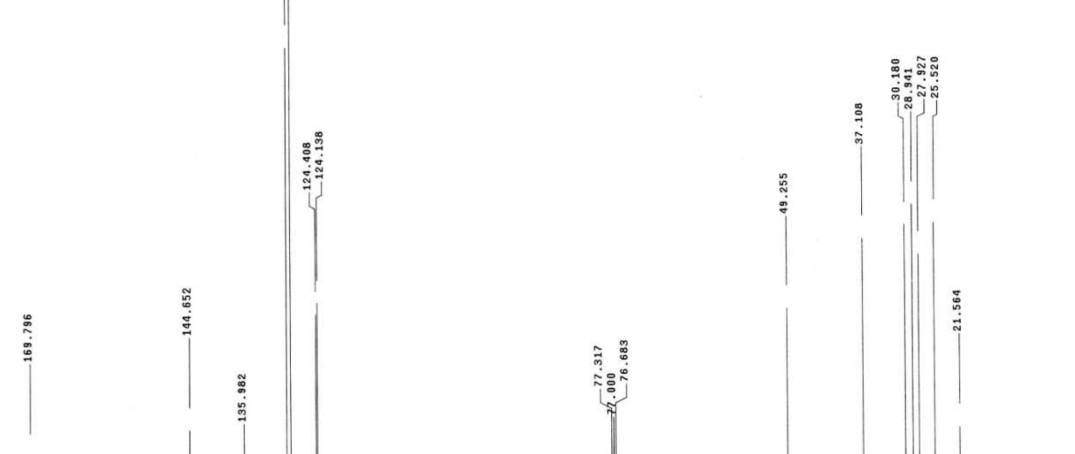
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76.683
49.255
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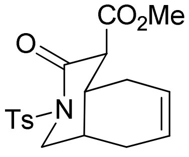


(4a*R*,8a*S*)-4-Methoxycarbonyl-3-oxo-2-(*p*-toluenesulfonyl)-1,2,3,4,4a,5,8,8a-octahydroisoquinoline (14).

Lithium bis(trimethylsilyl)amide (528 µl of a 1 M solution in hexane, 0.53 mmol) was added at –78 °C to a stirred solution of lactam **13** (124 mg, 0.41 mmol) in anhydrous THF (5 mL) under inert atmosphere. After stirring for 1 h at –78 °C, methyl chloroformate (31 µl, 0.41 mmol) was added and stirring was continued for 3 h at –78 °C. The reaction was quenched by the addition of saturated aqueous NH_4Cl, and the resulting solution was extracted with EtOAc. The combined organic extracts were dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. Flash chromatography (9:1 to 7:3 hexane-EtOAc) afforded the *N*-tosyl derivative **14** (136 mg, 91%).

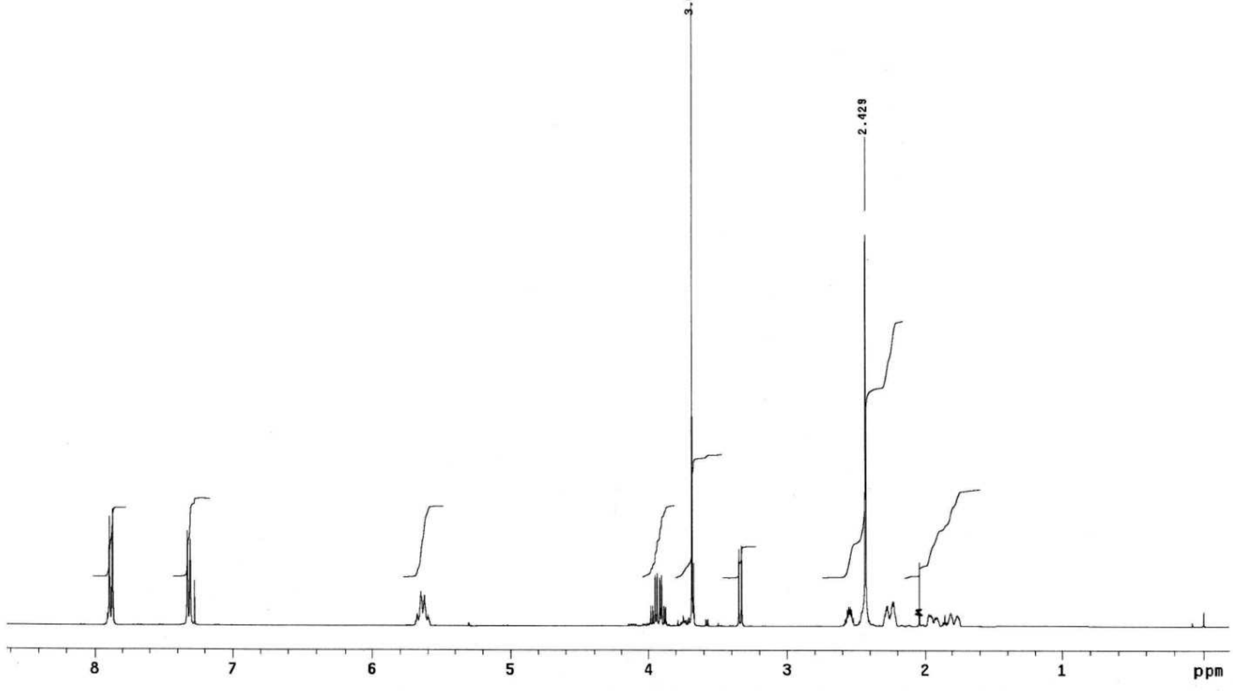
IR (film): 1686 (NCO), 1740 (COO) cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$, COSY, gHSQC): δ 1.77 (dm, *J* = 18.0 Hz, 1H, H-8), 1.93 (m, 1H, H-5), 2.25 (m, 2H, H-5, H-8), 2.43 (s, 3H, CH_3 Ts), 2.45 (m, 1H, H-8a), 2.55 (m, 1H, H-4a), 3.33 (d, *J* = 8.0 Hz, 1H, H-4), 3.68 (s, 3H, CH_3O), 3.89 (dd, *J* = 12.0, 6.0 Hz, 1H, H-1), 3.95 (dd, *J* = 12.0, 4.4 Hz, 1H, H-1), 5.63 (m, 2H, H-6, H-7), 7.31 (d, *J* = 8.4 Hz, 2H, H-*m* Ts), 7.88 (d, *J* = 8.4 Hz, 2H, H-*o* Ts).

^{13}C NMR (100.6 MHz, $CDCl_3$): δ 21.6 (CH_3 Ts), 25.2 (C-5), 27.3 (C-8), 28.8 (C-8a), 33.2 (C-4a), 49.3 (C-1), 52.7 (CH_3O), 53.2 (C-4), 123.8, 124.6 (C-6, C-7), 128.6 (C-*o* Ts), 129.3 (C-*m* Ts), 135.4 (C-*i* Ts), 144.9 (C-*p* Ts), 166.0 (NCO), 169.5 (COO).

HRMS (ESI) calcd for $[C_{18}H_{21}NO_5S + H]^+$: 364.1213, found: 364.1214.

Elemental analysis calcd (%) for $C_{18}H_{21}NO_5S$: C 59.49, H 5.82, N 3.85; found: C 59.45, H 5.84, N 3.83.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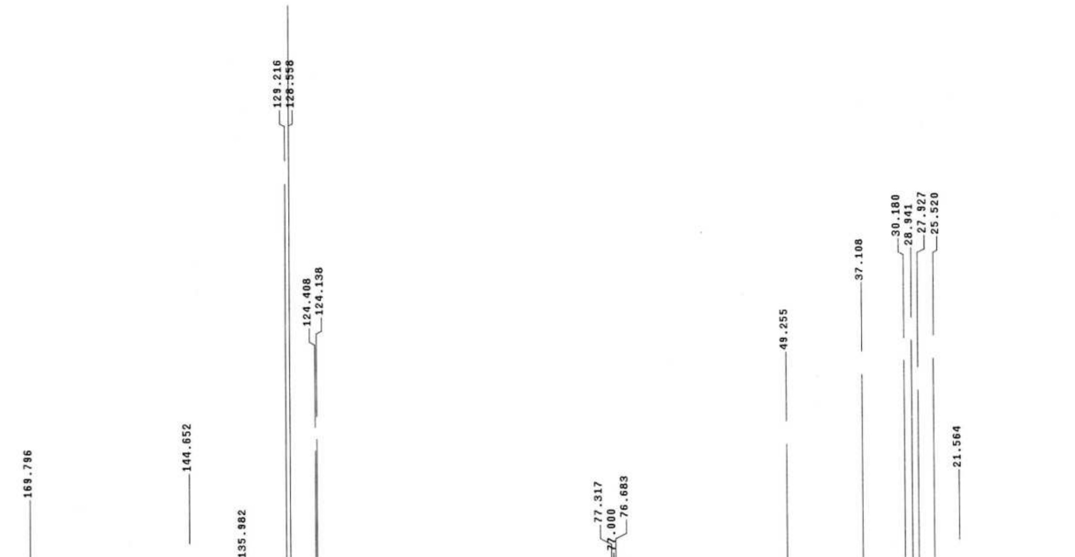
ppm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49.255
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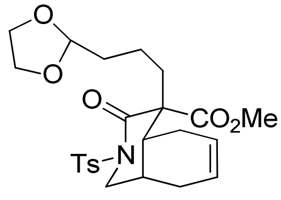
ppm



(4*R*,4a*R*,8a*S*)-4-[3-(1,3-Dioxolan-2-yl)propyl]-4-(methoxycarbonyl)-3-oxo-2-(*p*-toluensulfonyl)-1,2,3,4,4a,5,8,8a-octahydroisoquinoline (15).

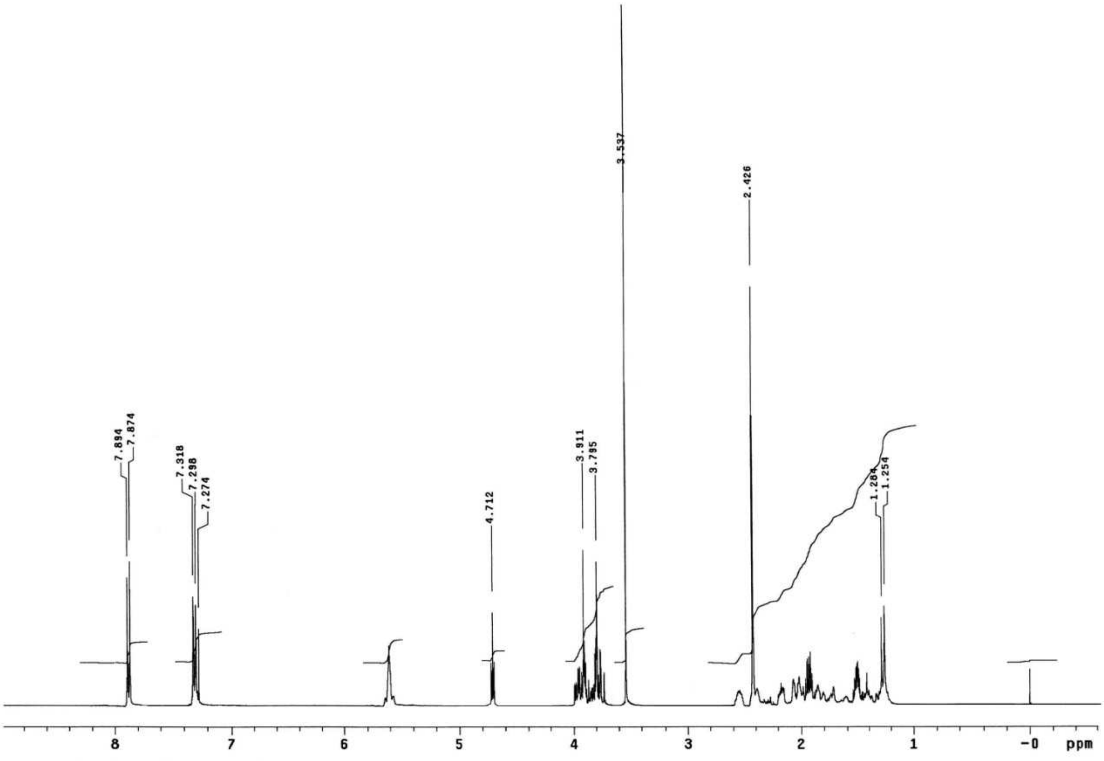
A mixture of lactam **14** (85 mg, 0.24 mmol) and NaH (12 mg of a 60% dispersion in mineral oil, 0.28 mmol) in anhydrous DMF (1 mL) was stirred at 0 °C under argon atmosphere for 1 h. Then, 2-(2-iodoprophyl)-1,3-dioxolane (226 mg, 0.95 mmol) was added, and the solution was stirred at 60 °C for 20 h. After cooling to room temperature, saturated aqueous NH_4Cl was added and was extracted with ethyl acetate. The combined organic extracts were dried, filtered and concentrated under reduced pressure. Flash chromatography (95:5 to 7:3 hexane-EtOAc) afforded compound **15** (113 mg, 70%).

$[\alpha]_D^{22} = -28.28$ (*c* 0.99, $CHCl_3$).

^{1}H NMR (400 MHz, $CDCl_3$, COSY, gHSQC): δ 1.25 (m, 1H, H-2'), 1.42 (m, 1H, H-2'), 1.51 (m, 2H, H-3'), 1.83 (dm, *J* = 17.4 Hz, 1H, H-5), 1.93 (m, 2H, H-1'), 2.00 (dm, *J* = 17.4 Hz, 1H, H-5), 2.03 (dm, *J* = 16.4 Hz, 1H, H-8), 2.17 (ddd, *J* = 9.6, 5.6, 3.2 Hz, 1H, H-4a), 2.41 (dm, *J* = 16.4 Hz, 1H, H-8), 2.43 (s, 3H, CH_3 Ts), 2.55 (m, 1H, H-8a), 3.54 (s, 3H, CH_3O), 3.76 (t, *J* = 12.0 Hz, 1H, H-1ax), 3.80 (m, 2H, CH_2O), 3.90 (m, 2H, CH_2O), 3.96 (dd, *J* = 12.0, 4.8 Hz, 1H, H-1eq), 4.71 (t, *J* = 4.8 Hz, 1H, CHO_2), 5.61 (m, 2H, H-6, H-7), 7.30 (d, J = 8.0 Hz, 2H, H-*m*), 7.88 (d, *J* = 8.4 Hz, 2H, H-*o*).

^{13}C NMR (100.6 MHz, $CDCl_3$): δ 19.6 (C-2'), 21.6 (CH_3 Ts), 24.5 (C-5), 27.8 (C-8), 28.0 (C-8a), 33.9 (C-3'), 37.0 (C-1'), 38.2 (C-4a), 46.9 (C-1), 51.9 (CH_3O), 59.7 (C-4), 64.7 ($2CH_2O$), 104.1 (C-4'), 124.2, 124.4 (C-6, C-7), 128.6, 129.1 (C-*o*, *m*), 135.7 (C-*i*), 144.6 (C-*p*), 168.4 (NCO), 171.0 (CCO).

HRMS calcd for $[C_{24}H_{31}NO_7S + H]^+$: 478.18, found: 478.1888.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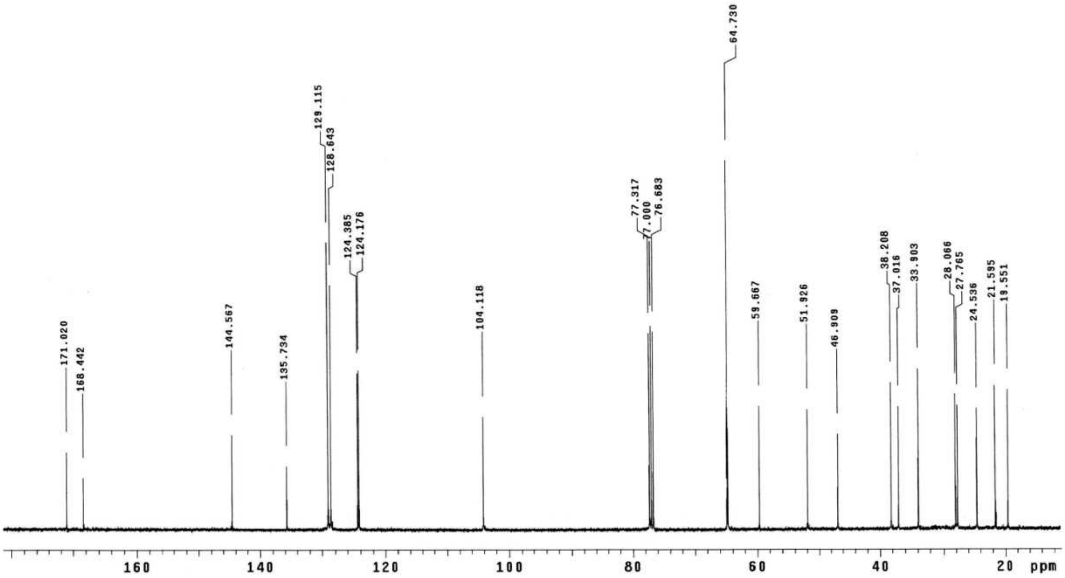
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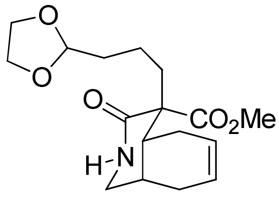
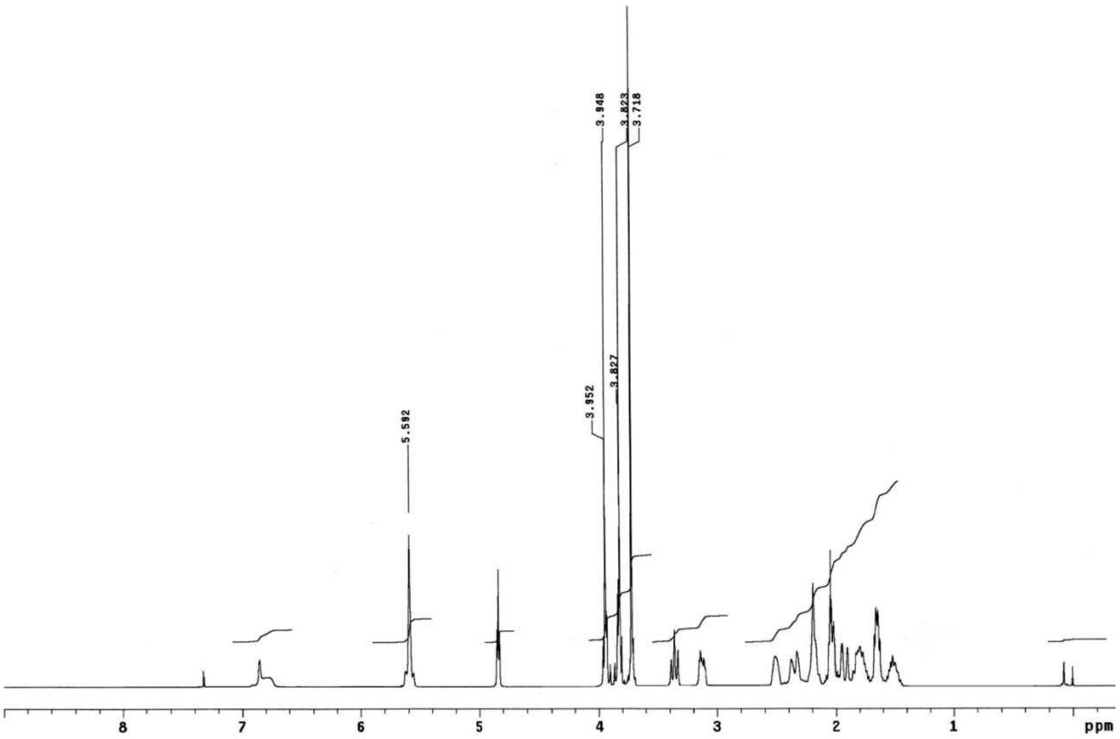


(4*R*,4a*R*,8a*S*)-4-[3-(1,3-Dioxolan-2-yl)propyl]-4-(methoxycarbonyl)-3-oxo-1,2,3,4,4a,5,8,8a-octahydroisoquinoline (16).

Sodium metal (320 mg, 13.3 mmol) was added at room temperature to a solution of naphthalene (890 mg, 13.3 mmol) in THF (20 mL). After stirring for 3 h, part of the mixture (4.55 mL) was added to a solution of sulfonamide **15** (162 mg, 0.35 mmol) in THF (9 mL) at –78 °C. After 15 min, saturated aqueous NH_4Cl was carefully added, and the resulting solution was extracted with ethyl acetate. The combined extracts were washed with brine, dried (Na_2SO_4), and concentrated under reduced pressure. Flash chromatography (9:1 to 1:1 hexane-EtOAc) afforded amide **16** (85 mg, 75%).

^{1}H NMR (400 MHz, $CDCl_3$, COSY, gHSQC): δ 1.51 (m, 1H, H-2’), 1.65 (m, 2H, H-3’), 1.79 (m, 2H, H-2’, H-5), 1.93 (dm, *J* = 18.0 Hz, 1H, H-8), 2.03 (m, 2H, H-1’), 2.19 (m, 2H, H-4a, H-5), 2.35 (dm, *J* = 18.0 Hz, 1H, H-8), 2.51 (m, 1H, H-8a), 3.12 (dt, *J* = 12.0, 4.8 Hz, 1H, H-1), 3.36 (t, *J* = 12.0 Hz, 1H, H-1), 3.75 (s, 3H, CH_3O), 3.82 (m, 2H, CH_2O), 3.94 (m, 2H, CH_2O), 4.84 (t, *J* = 4.8 Hz, 1H, CHO_2), 5.59 (m, 2H, H-6, H-7), 6.84 (br. s, 1H, NH).

^{13}C NMR (100.6 MHz, $CDCl_3$): δ 19.9 (C-2’), 24.5 (C-5), 26.9 (C-8a), 27.8 (C-8), 34.1 (C-3’), 37.1 (C-1’), 38.6 (C-4a), 42.6 (C-1), 51.7 (CH_3O), 57.2 (C-4), 64.6 ($2CH_2O$), 104.2 (C-4’), 124.1, 124.7 (C-6, C-7), 170.4 (NCO), 172.2 (CCO).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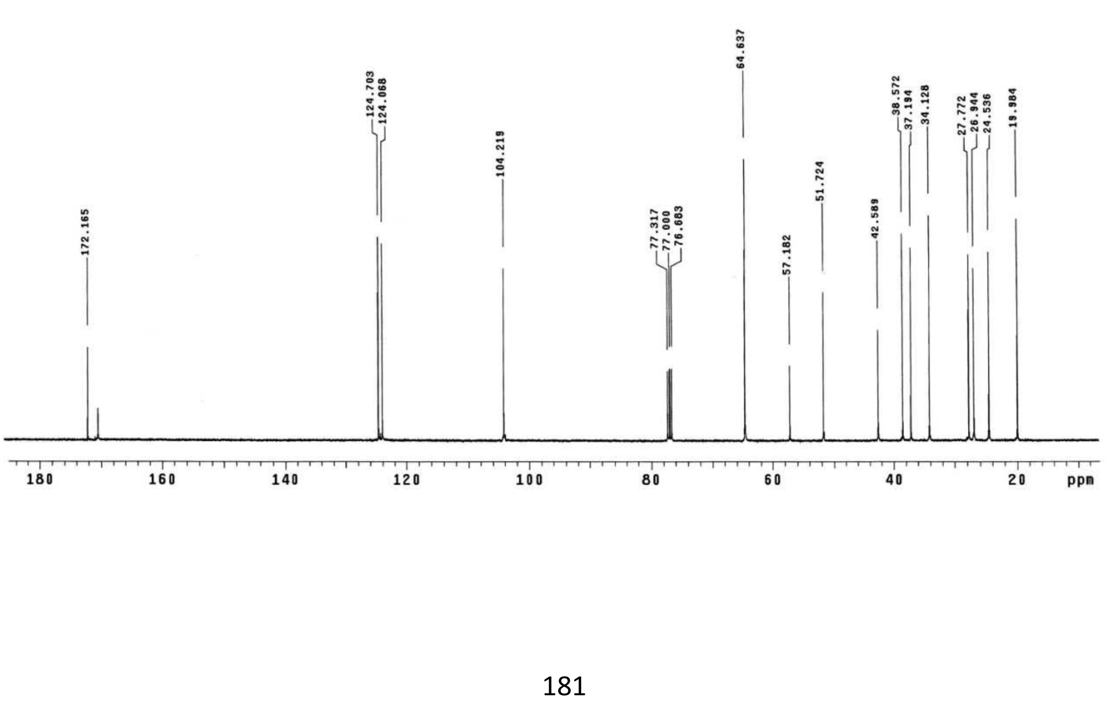
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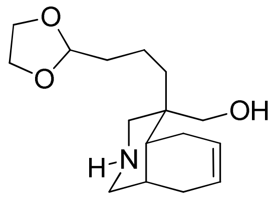
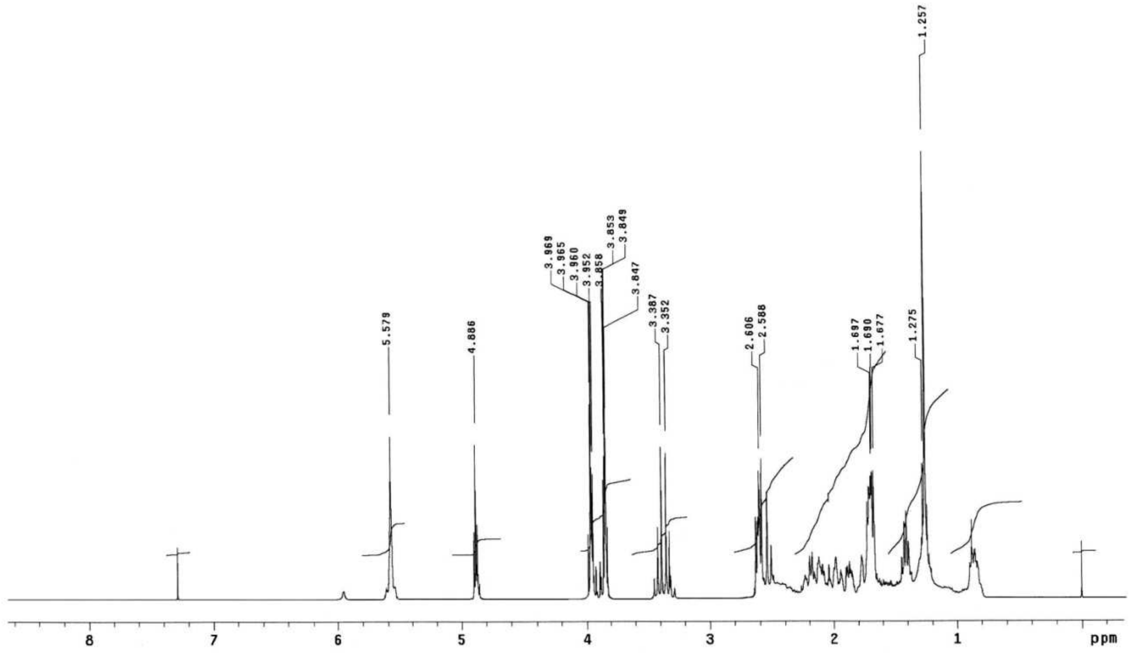


(4*R*,4a*R*,8a*S*)-4-[3-(1,3-Dioxolan-2-yl)propyl]-4-(methoxycarbonyl)-1,2,3,4,4a,5,8,8a-octahydroisoquinoline (17).

Lithium aluminum hydride (237 mg, 6.25 mmol) was added to a solution of compound **16** (404 mg, 1.25 mmol) in anhydrous THF (81 mL) under argon atmosphere at 0 °C and the mixture was stirred at reflux for 5 h. The resulting suspension was cooled to 0 °C, and the reaction was quenched by slowly addition of distilled water. The aqueous layer was extracted with EtOAc, and the combined organic extracts were dried and concentrated to afford aminoalcohol derivate **17** (381 mg) as a yellow oil which was used in the next step without purification.

^{1}H NMR (400 MHz, $CDCl_3$, COSY, gHSQC): δ 1.43 (m, 2H, H-2'), 1.69 (m, 4H, H-1', H-3'), 1.73 (dm, *J* = 18.4 Hz, 1H, H-8), 1.87 (m, 1H, H-4a), 1.96 (dm, *J* = 15.6 Hz, 1H, H-5), 2.03-2.19 (m, 2H, H-8 H-5), 2.23 (m, 1H, H-8a), 2.58 (m, 4H, H-1, H-3), 3.36 (m, 2H, CH_2OH), 3.84, 3.95 (2m, 2H, CH_2O), 4.88 (t, *J* = 4.8 Hz, 1H, CHO_2), 5.58 (m, 2H, H-6, H-7).

^{13}C NMR (100.6 MHz, $CDCl_3$): δ 17.2 (C-2'), 21.9 (C-5), 29.0 (C-8a), 29.3 (C-8), 30.6 (C-1'), 34.0 (C-3'), 34.2 (C-4a), 39.6 (C-4), 46.9, 47.1 (C-1, C-3), 64.4 (CH_2OH), 64.7, 64.8 ($2CH_2O$), 104.5 (C-4'), 124.5, 124.7 (C-6, C-7).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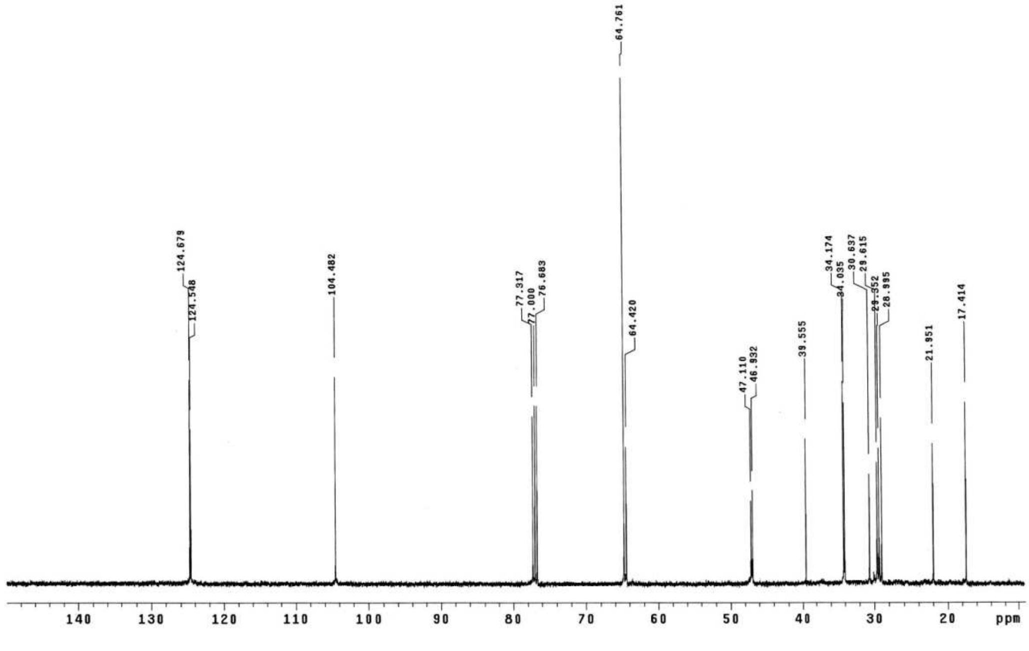
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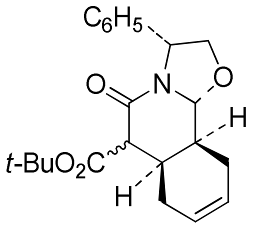


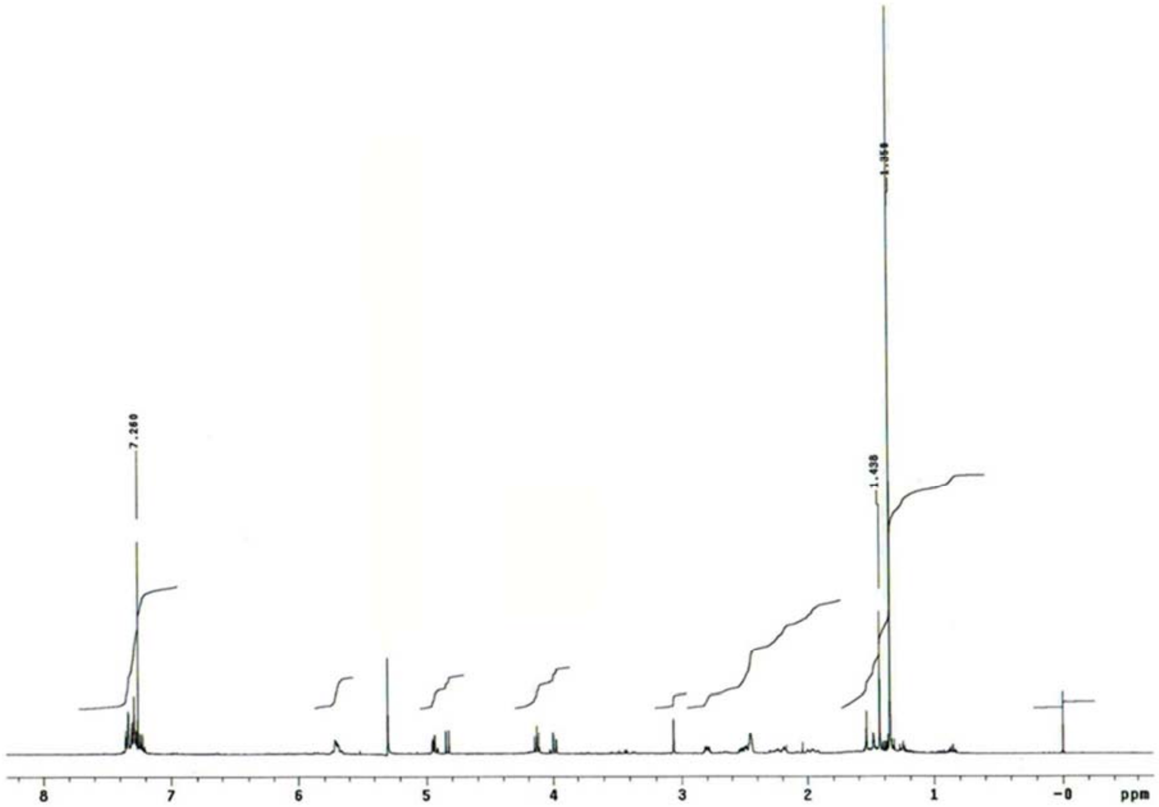
(3*R*,6a*R*,10a*S*,10b*R*)-6-(*tert*-Butotxycarbonyl)-5-oxo-3-phenyl-2,3,6,6a,7,10,10a,10b- octahydro-5*H*-oxazolo[3,2-*a*]isoquinoline (19).

Second generation Grubbs catalyst (200 mg, 5% mol) was added to a stirred solution of diallyl-lactams **7** (1.87 g, 4.71 mmol) in CH_2Cl_2. The resulting mixture was stirred at room temperature for 18 h and then concentrated under reduced pressure. Flash chromatography (hexane to 8:2 hexane-EtOAc) gave the C-6 epimers of lactam **19** (1.38 g, 80%).

^{1}H NMR (400 MHz, $CDCl_3$, COSY, gHSQC): δ 1.35 [s, 9H, $(CH_3)_3C$], 1.96 (tm, *J* = 16.0 Hz, 1H, H-7), 2.19 (m, 1H, H-7), 2.45 (m, 2H, H-10), 2.50 (m, 1H, H-6a), 2.80 (m, 1H, H-10a), 3.06 (s, 1H, H-6), 3.99 (dd, *J* = 8.8, 1.6 Hz, 1H, H-2), 4.13 (dd, *J* = 8.8, 7.2 Hz, 1H, H-2), 4.84 (d, *J* = 10.0 Hz, 1H, H-10b), 4.94 (dd, *J* = 7.2, 1.6 Hz, 1H, H-3), 5.70 (m, 2H, H-8, H-9), 7.20-7.36 (m, 5H, C_6H_5).

^{13}C NMR (100.6 MHz, $CDCl_3$): δ 25.2 (C-10), 27.8 [$(CH_3)C$], 27.9 (C-7), 33.1 (C-10a), 33.4 (C-6a), 53.4 (C-6), 59.5 (C-3), 73.8 (C-2), 81.8 [$(CH_3)C$], 87.1 (C-10b), 124.7, 125.1 (C-8, C-9), 126.4, 128.3 (C-*o*, *m* C_6H_5), 127.4 (C-*p* C_6H_5), 141.1 (C-*i* C_6H_5), 163.5, 168.2 (NCO, COO).

HRMS (ESI) calcd for $[C_{22}H_{27}NO_4 + H]^+$: 370.2013, found: 370.2011.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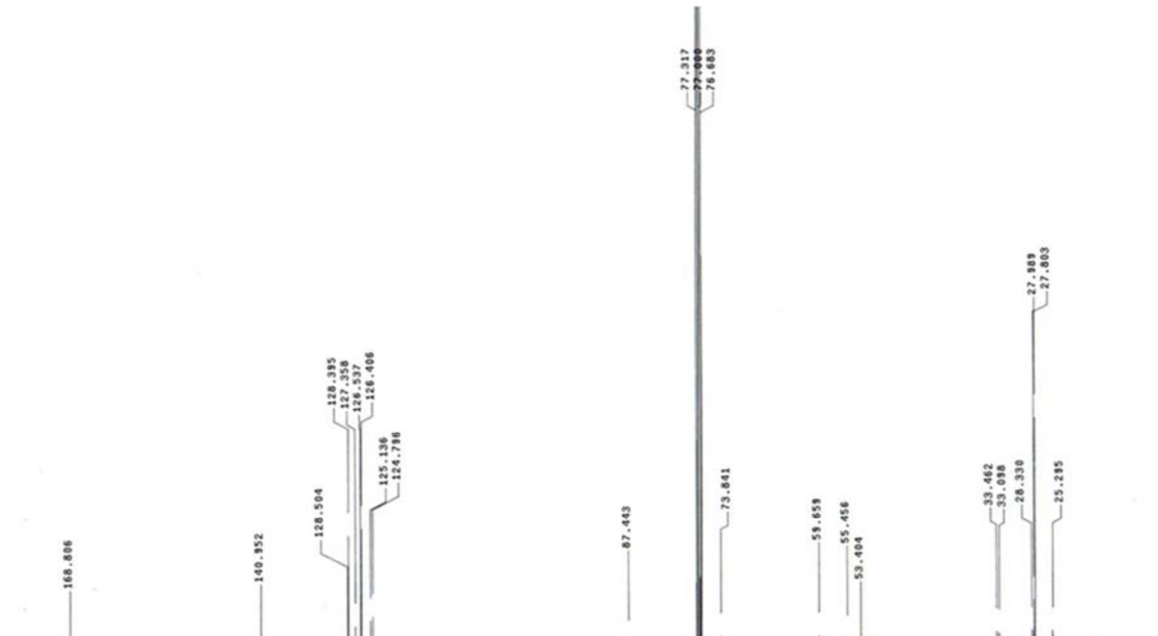
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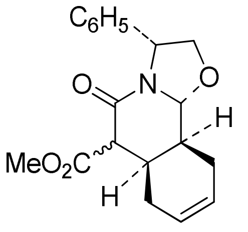


(3*R*,6a*R*,10a*S*,10b*R*)-6-(Methoxycarbonyl)-5-oxo-3-phenyl-2,3,6,6a,7,10,10a,10b-octahydro - 5H-oxazolo[2,3-*a*]isoquinoline (20).

Second generation Grubbs catalyst (642 mg) was added to a solution of lactam **8** (3.58 g, 10.1 mmol) in CH_2Cl_2 (1.44 L). The mixture was stirred for 18 h at room temperature, and the resulting suspension was concentrated. Flash chromatography (4:1 to 3:2 hexane-EtOAc) of the residue gave tricyclic lactam **20** as a mixture of C-6 epimers (2.8 g, 85% yield).

IR (film): 1667, 1738 (CO) cm^{-1}.

Compound (6*R*)-**20** (major):

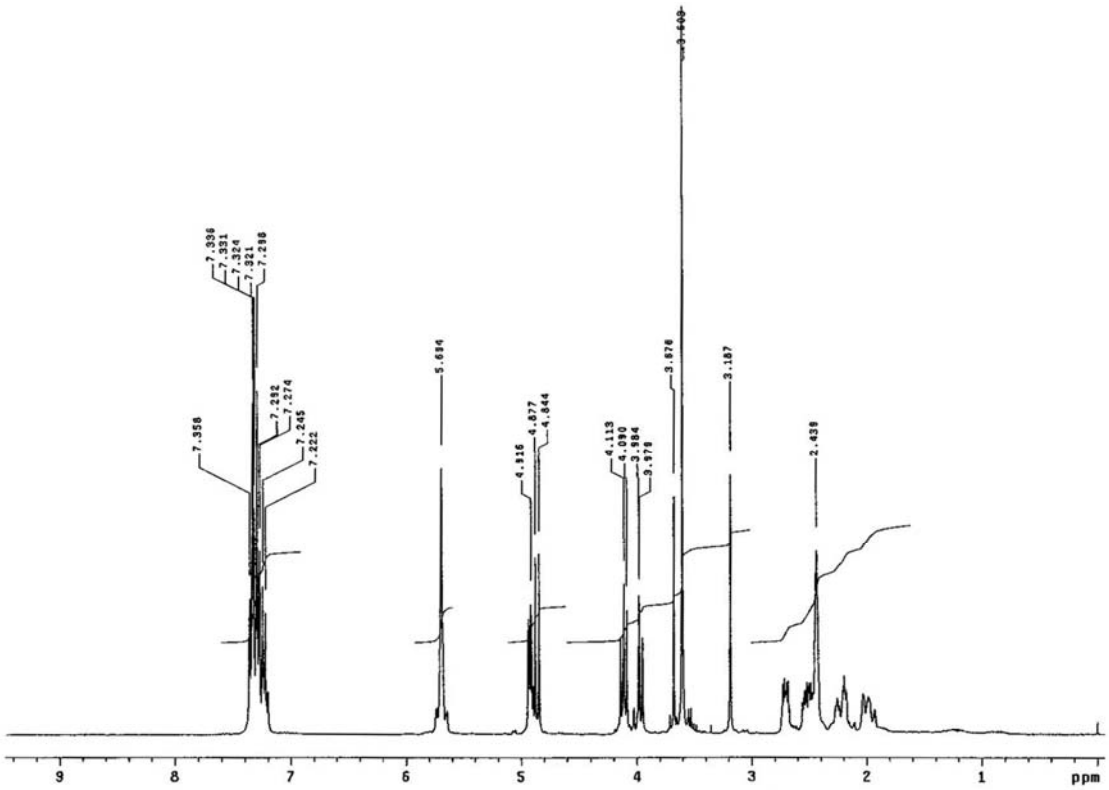
^{1}H NMR (400 MHz, $CDCl_3$, COSY, gHSQC): δ 2.00 (m, 1H, H-7), 2.20 (m, 1H, H-7), 2.43 (m, 2H, H-10), 2.50 (m, 1H, H-6a), 2.70 (m, 1H, H-10a), 3.18 (s, 1H, H-6), 3.60 (s, 3H, CH_3O), 3.96 (dd, *J* = 9.0, 1.2 Hz, 1H, H-2), 4.12 (dd, *J* = 9.0, 6.9 Hz, 1H, H-2), 4.85 (d, *J* = 9.9 Hz, 1H, H-10b), 4.92 (dd, *J* = 6.9, 1.2 Hz, 1H, H-3), 5.69 (m, 2H, H-8, H-9), 7.22-7.35 (m, 5H, C_6H_5).

^{13}C NMR (100.6 MHz, $CDCl_3$): δ 25.1 (C-10), 28.0 (C-7), 32.6 (C-10a), 33.5 (C-6a), 52.2 (CH_3O), 53.9 (C-6), 59.4 (C-3), 73.6 (C-2), 87.1 (C-10b), 124.4, 124.8 (C-8, C-9), 126.8, 128.0 (C-*o*, *m* C_6H_5), 127.2 (C-*p* C_6H_5), 140.6 (C-*i* C_6H_5), 162.0 (NCO), 170.2 (COO).

Compound (6*S*)-**3** (minor):

^{13}C NMR (100.6 MHz, $CDCl_3$, selected resonances): δ 24.7 (C-10), 32.6 (C-10a), 36.7 (C-6a), 51.8 (CH_3), 53.7 (C-6), 59.6 (C-3), 73.3 (C-2), 86.6 (C-10b), 140.9 (C-*i*), 162.4 (NCO), 169.1 (COO).

Anal. Calcd for $C_{19}H_{21}O_4N \cdot \frac{1}{4} H_2O$: C, 68.76; H, 6.53; N, 4.22. Found: C, 68.82; H, 6.90; N, 4.20.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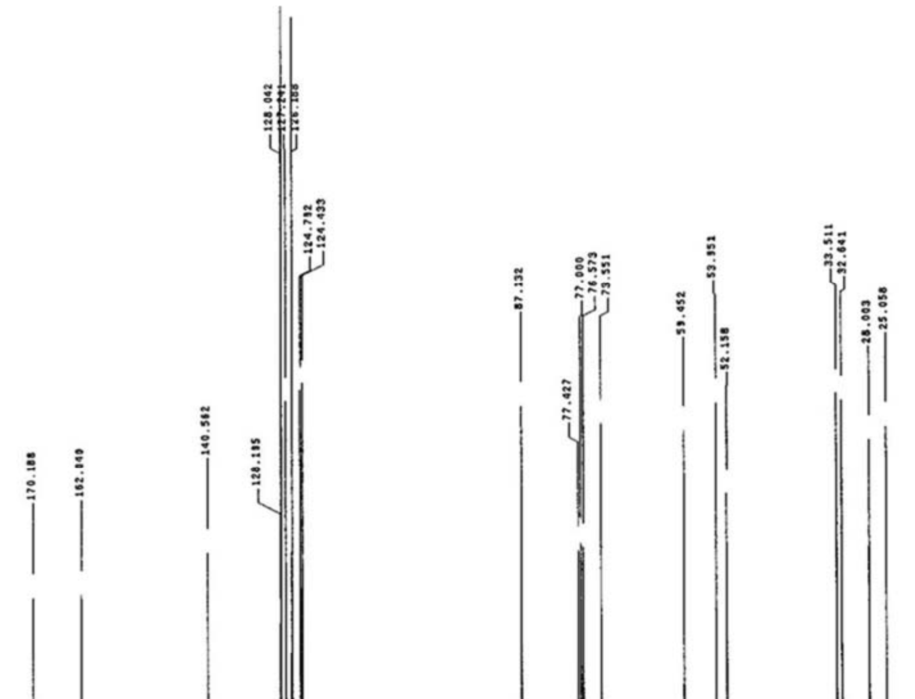
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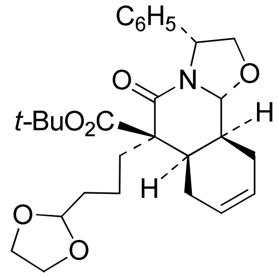

(3*R*,6*R*,6a*R*,10a*S*,10b*R*)-6-(*tert*-Butotxycarbonyl)-6-[3-(1,3-dioxolan-2-yl)propyl]-5-oxo -3-phenyl-2,3,6,6a,7,10,10a,10b-octahydro-5*H*-oxazolo[3,2-*a*]isoquinoline (21).

Lactam **19** (2.0 g, 5.4 mmol) was added to a suspension of NaH (396 mg of a 60% dispersion in mineral oil, 5.9 mmol) in anhydrous DMF (10 mL) at 0 °C under an inert atmosphere, and the resulting mixture was stirred at this temperature for 1 h. 2-(3-Bromopropyl)-1,3-dioxolane[133] (3.87 g, 27.0 mmol) and TBAI (398 mg, 1.08 mmol) were then added at 0 °C, and the mixture was stirred overnight at room temperature. Saturated aqueous NH_4Cl was added, and the mixture was extracted with Et_2O and then with CH_2Cl_2. The combined organic extracts were dried, filtered, and concentrated under reduced pressure. Flash chromatography (hexane to 8:2 hexane-EtOAc) of the resulting residue afforded lactam **21** (2.34 g, 90%).

$[\alpha]_D^{22} = -51.7$ (*c* 0.63, $CHCl_3$).

IR (KBr): 1728, 1659 (C=O) cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$, COSY, gHSQC): δ 1.22 (m, 2H, H-2’), 1.39 (m, 2H, H-3’), 1.45 [s, 9H, $(CH_3)_3C$], 1.81 (dd, *J* = 6.0, 2.0 Hz, 1H, H-1’), 1.84 (dd, *J* = 6.0, 2.4 Hz, 1H, H-1’), 2.00 (dm, *J* = 12.4 Hz, 1H, H-7), 2.17 (dm, *J* = 12.4 Hz, 1H, H-7), 2.23 (m, 1H, H-10), 2.29 (ddd, *J* = 11.6, 5.6, 3.6 Hz, 1H, H-6a), 2.44 (m, 1H, H-10), 2.51 (m, 1H, H-10a), 3.78, 3.88 (2m, 4H, $2CH_2O$), 4.04 (dd, *J* = 8.8, 1.2 Hz, 1H, H-2), 4.13 (dd, *J* = 8.8 Hz, 1H, H-2), 4.63 (t, *J* = 4.8 Hz, 1H, H-4’), 4.89 (m, 2H, H-3, H-10b), 5.69 (m, 2H, H-8, H-9), 7.20-7.35 (m, 5H, C_6H_5).

^{13}C NMR (100.6 MHz, $CDCl_3$): δ 20.0 (C-2’), 25.7, 25.8 (C-5, C-8), 28.0 [$(CH_3)_3C$], 33.6 (C-10a), 34.2 (C-3’), 37.3 (C-1’), 38.9 (C-6a), 46.9 (C-1), 59.1 (C-4), 59.7 (C-3), 64.6, 64.7 ($2CH_2O$), 73.5 (C-2), 81.6 [$(CH_3)_3C$], 87.0 (C-10b), 104.4 (C-4’), 124.1, 125.1 (C-8, C-9), 126.7, 128.3 (C-*o*, *m* C_6H_5), 127.4 (C-*p* C_6H_5), 142.2 (C-*i* C_6H_5), 165.5 (NCO), 170.0 (CCO).

HRMS (ESI) calcd for $[C_{28}H_{37}NO_6 + H]^+$: 484.2694, found: 484.2685.

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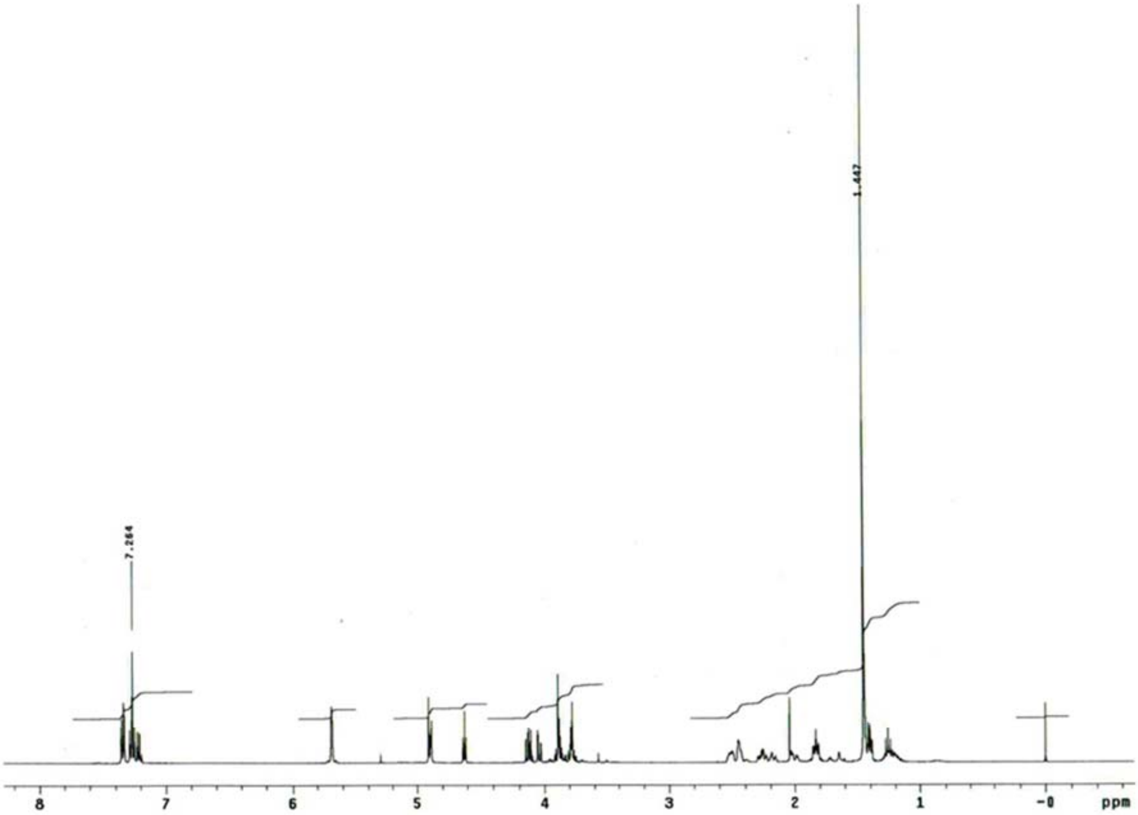
[133] Varseev, G. N.; Maier, M. E. *Org. Lett.* **2005**, *7*, 3881–3884.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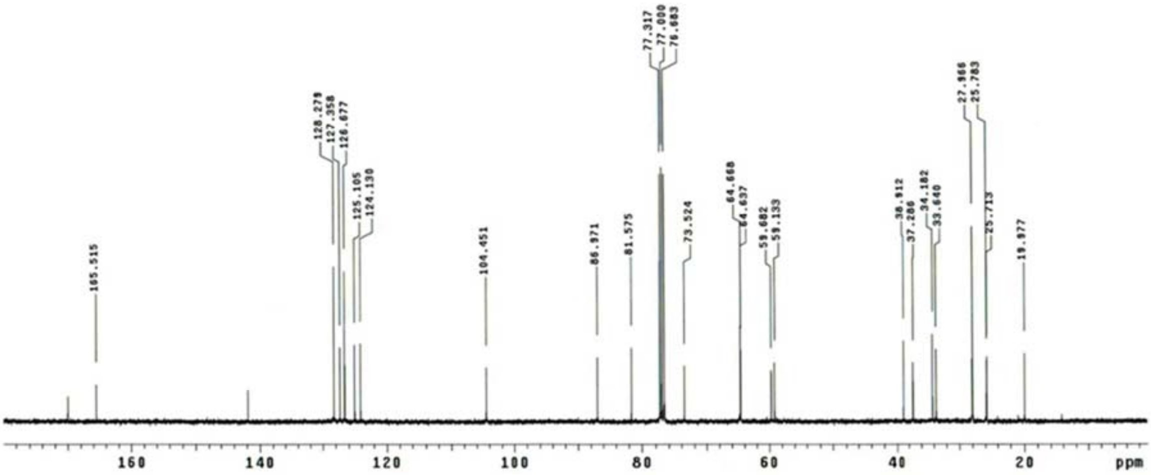
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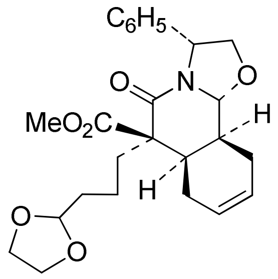


(3*R*,6*R*,6a*R*,10a*S*,10b*R*)-6-[3-(1,3-Dioxolan-2-yl)propyl]-6-(methoxycarbonyl)-5-oxo-3-phenyl-2,3,6,6a,7,10,10a,10b-octahydro-5*H*-oxazolo[3,2-*a*]isoquinoline (22).

A solution of isoquinoline **20** (880 mg, 2.691 mmol) in DMF (2 mL) was added to a cooled (0 °C) suspension of NaH (161 mg of a 60% dispersion in mineral oil, 4.031 mmol) in anhydrous DMF (20 mL) under an inert atmosphere, and the resulting mixture was stirred at 0 °C for 1 h. 2-(3-Bromopropyl)-1,3-dioxolane (1.94 g, 13.4 mmol) and TBAI (198 mg, 0.538 mmol) were added at 0 °C, and the mixture was stirred overnight at room temperature. Saturated aqueous NH_4Cl was added, and the mixture was extracted with diethyl ether and then with CH_2Cl_2. The combined organic extracts were dried, filtered, and concentrated under reduced pressure. Flash chromatography (hexane to 6:4 hexane-EtOAc) of the resulting oil afforded lactam **22** (905 mg, 80%).

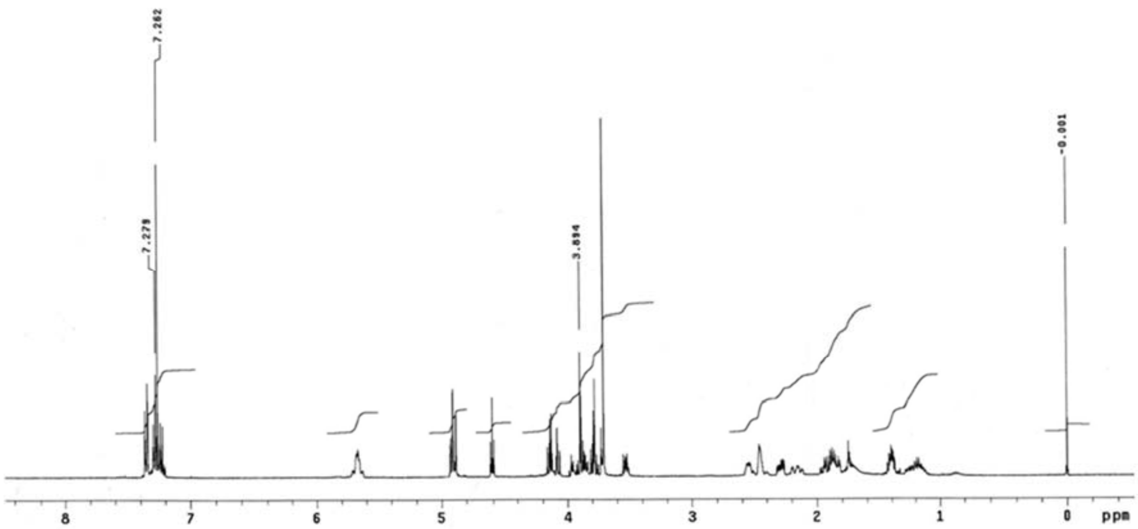
$[\alpha]_D^{22}$ = – 29.7 (*c* 2.1, $CHCl_3$).

IR (film): 1668, 1737 (CO) cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$, COSY, gHSQC): δ 1.13-1.23 (m,2 H, H-2’), 1.40 (m, 2H, H-3’), 1.81-1.97 (m, 3H, 2H-1’, H-7), 2.11-2.20 (3m, 2H, H-7, H-10), 2.28 (ddd, *J* = 12.4, 6.0, 4.0 Hz, 1H, H-6a), 2.45 (m, 1H, H-10), 2.54 (m, 1H, H-10a), 3.70 (s, 3H, CH_3O), 3.77, 3.89 (2m, 4H, CH_2O), 4.07 (dd, *J* = 9.2, 1.6 Hz, 1H, H-2), 4.15 (dd, *J* = 9.2 Hz, 1H, H-2), 4.61 (t, *J* = 4.8 Hz, 1H, H-4’), 4.91 (m, 2H, H-3, H-10b), 5.67 (m, 2H, H-8, H-9), 7.20-7.39 (m, 5H, C_6H_5).

^{13}C NMR (100.6 MHz, $CDCl_3$): δ 19.9 (C-2’), 25.6, 25.7 (C-7, C-10), 33.6 (C-10a), 34.1 (C-3’), 37.4 (C-1’), 39.5 (C-6a), 51.9 (CH_3O), 58.9 (C-6), 59.8 (C-3), 64.6, 64.7 ($2CH_2O$), 73.5 (C-2), 87.5 (C-10b), 104.4 (C-4’), 124.3, 124.7 (C-8, C-9), 126.8, 128.3 (C-*o*, *m* C_6H_5), 127.5 (C-*p* C_6H_5), 141.6 (C-*i* C_6H_5), 165.4 (NCO), 172.1 (CCO).

HRMS calcd for $[C_{25}H_{31}NO_6 + H]^+$: 442.2224, found: 442.2227.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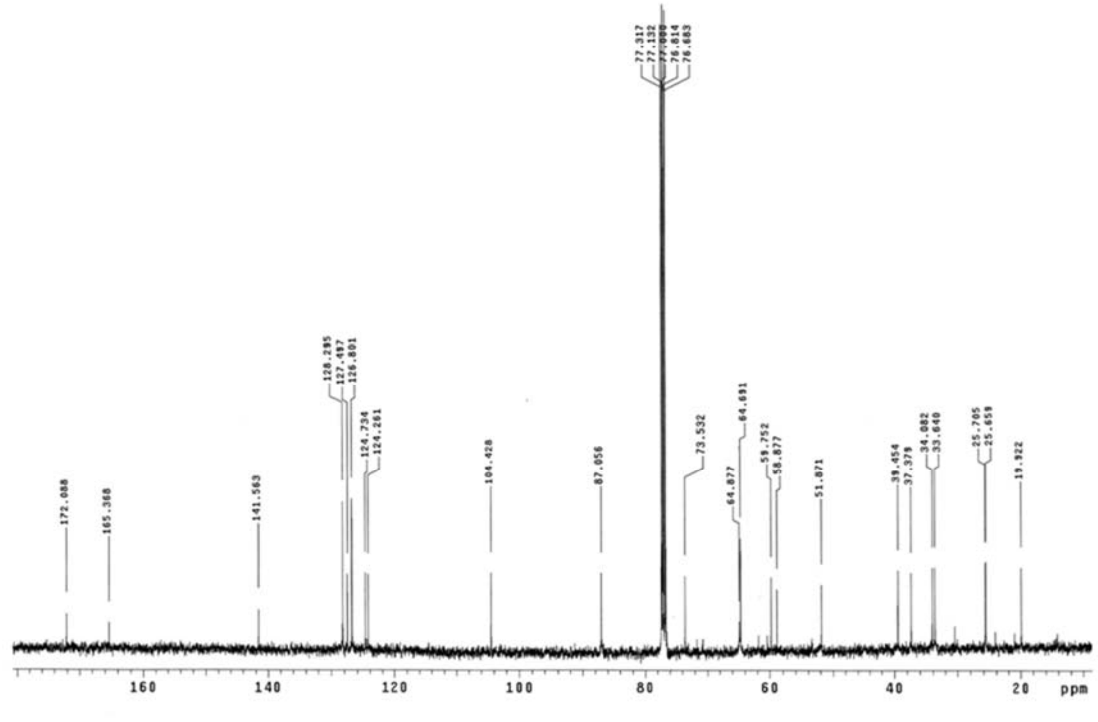
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51.871
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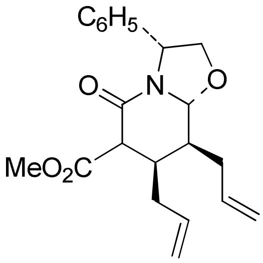


(3*R*,7*R*,8*S*,8a*R*)-7,8-Diallyl-6-(methoxycarbonyl)-5-oxo-3-phenyl-2,3,6,7,8,8a-hexahydro-5*H*-oxazolo[3,2-*a*]pyridine (8).

LiCl (1.2 g, 28.4 mmol) was dried at 80 °C for 1 h under vacuum (10–15 mmHg) in a three-necked, 250 mL round-bottomed flask. Then, CuI (5.4 g, 28.4 mmol) and THF (150 mL) were added under an inert atmosphere, and the mixture was stirred at room temperature for 5 min. The suspension was cooled to –78 °C, and allylmagnesium bromide (28.4 mL of a 1 M solution in Et_2O, 28.4 mmol), TMSCl (3.6 mL, 28.4 mmol), and unsaturated lactam **6** (7.11 mmol) in THF (5 mL) were successively added. The resulting mixture was stirred at –78 °C for 18 h. The reaction was quenched with saturated aqueous NH_4Cl, and the resulting mixture was filtered through Celite®. The aqueous layer was extracted with EtOAc, and the combined organic extracts were dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure. Flash chromatography (9:1 to 7:3 hexane-EtOAc) of the resulting oil gave **8** (2.05 g, 81% yield) as a mixture of C-6 epimers (ratio 2:1).

Epimer **8a** (major) (6*S*):

IR (film): 1665, 1736 (CO) cm^{-1}.

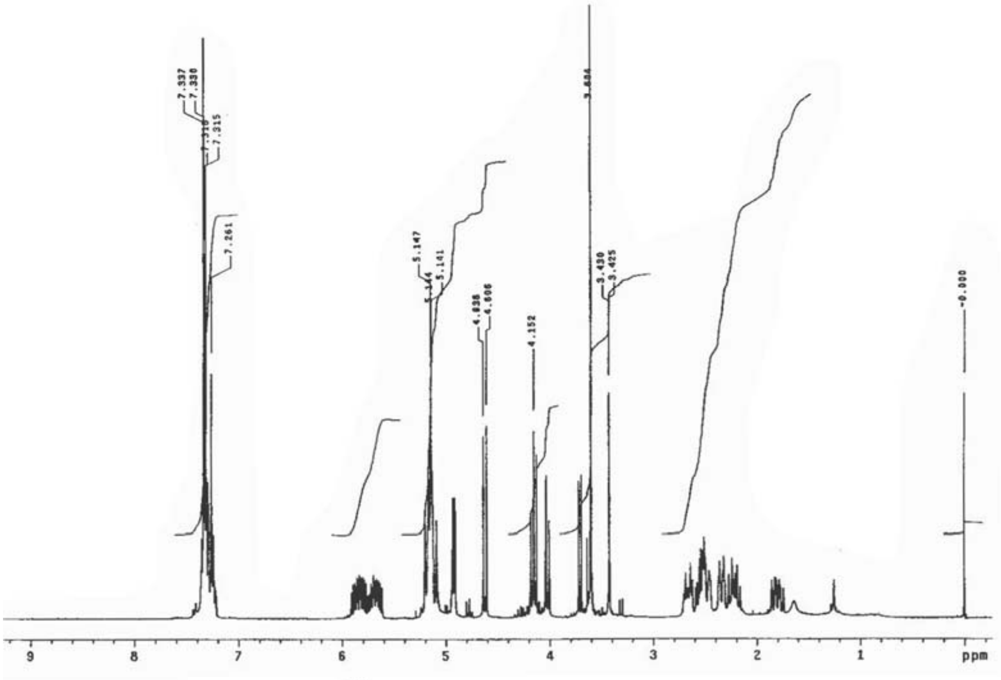
^{1}H NMR (300 MHz, $CDCl_3$, COSY, gHSQC): δ 1.80 (ddd, *J* = 14.1, 12.0, 9.0 Hz, 1H, CH_2 allyl), 2.16 (dt, *J* = 14.1, 9.3, 9.3 Hz, 1H, CH_2 allyl), 2.34 (dm, *J* = 12.0 Hz, 1H, H-7), 2.44-2.70 (m, 3H, H-8, CH_2 allyl), 3.43 (d, *J* = 1.5 Hz, 1H, H-6), 3.60 (s, 3H, CH_3O), 4.02 (dd, *J* = 9.3, 1.8 Hz, 1H, H-2), 4.15 (dd, *J* = 9.3, 7.2 Hz, 1H, H-2), 4.62 (d, *J* = 9.6 Hz, 1H, H-8a), 4.91 (dd, *J* = 7.2, 1.8 Hz, 1H, H-3), 5.14 (m, 4 H, CH_2=), 5.68 (dddd, *J* = 15.0, 10.2, 9.0, 4.8 Hz, 1H, CH=), 5.84 (dddd, *J* = 15.3, 9.9, 8.7, 5.1 Hz, 1H, CH=), 7.26-7.33 (m, 5H, C_6H_5).

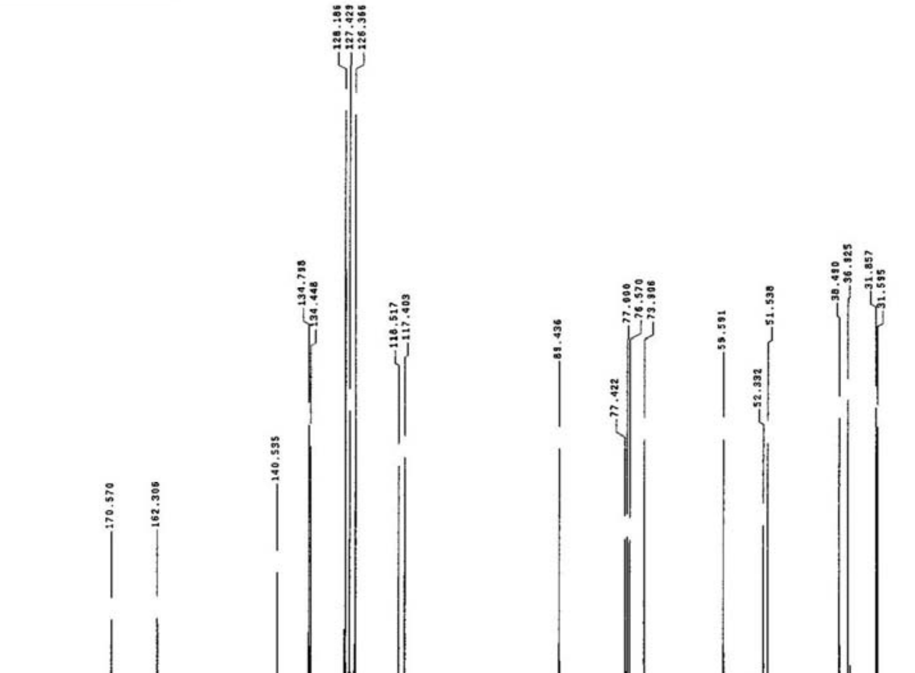
^{13}C NMR (75.4 MHz, $CDCl_3$): δ 31.6, 31.8 (CH_2), 36.9 (C-7), 38.5 (C-8), 51.5 (C-6), 52.3 (CH_3O), 59.6 (C-3), 73.9 (C-2), 89.4 (C-8a), 117.4, 118.5 (CH_2=), 126.4, 128.2 (C-*o*, *m*), 127.4 (C-*p*), 134.4, 134.8 (CH=), 140.5 (C-*i*), 162.3 (NCO), 170.6 (COO).

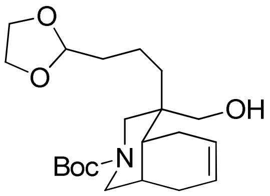
Epimer **8b** (minor) (6*R*):

^{13}C NMR (75.4 MHz, CDCl$_3$): δ 32.8, 35.9 (CH$_2$), 36.5 (C-7), 41.9 (C-8), 52.5 (CH$_3$O), 53.7 (C-6), 59.2 (C-3), 73.8 (C-2), 89.8 (C-8a), 118.4, 119.6 (CH$_2$=), 126.7-128.5 (C-*o*, *m, p*), 132.8, 133.4 (CH=), 140.6 (C-*i*), 162.5 (NCO), 170.8 (COO).

HRMS (ESI) calcd for [C$_{21}$H$_{25}$NO$_4$ + H]$^+$: 356.1783, found: 356.1779.







(4*R*,4a*R*,8a*S*)-2-(*tert*-Butoxycarbonyl)-4-[3-(1,3-dioxolan-2-yl)propyl]-4-(hydroxymethyl)-1,2,3,4,4a,5,8,8a-octahydroisoquinoline (18).

First step: Liquid ammonia (15 mL) was condensed at –78 °C in a three-necked, 100 mL round-bottomed flask equipped with a coldfinger condenser charged with dry ice-acetone, and then a solution of lactam **21** (200 mg, 0.414 mmol) in THF (10 mL) was added. The temperature was raised to –33 °C and sodium metal was added in small portions until the blue color persisted. The mixture was stirred at –33 °C for 2 min. The reaction was quenched by the addition of solid NH_4Cl until the blue colour disappeared, and the mixture was stirred at room temperature for 4 h. The residue was digested at room temperature with CH_2Cl_2, and the resulting suspension was filtered through Celite®. The solution was concentrated under reduced pressure.

Second step: Lithium aluminum hydride (235 mg, 6.21 mmol) was added under an argon atmosphere to a solution of the above residue in anhydrous dioxane (14 mL) and the mixture was stirred at reflux overnight. The resulting suspension was cooled to 0 °C, and the reaction was quenched with distilled water. The aqueous layer was extracted with Et_2O, and the combined organic extracts were dried, filtered, and concentrated to afford the corresponding amino alcohol **17** as a yellow oil, which was used in the next step without purification.

Third step: Di-*tert*-butyl dicarbonate (98 mg, 0.455 mmol) was added dropwise to a solution of the above amino **17** alcohol in anhydrous CH_2Cl_2 (7 mL) at room temperature under an inert atmosphere, and the resulting mixture was stirred for 20 h. The solution was then poured into saturated aqueous NH_4Cl and extracted with CH_2Cl_2. The combined organic extracts were washed with brine, dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure. Flash chromatography (9:1 to 1:1 hexane-EtOAc) of the residue gave carbamate **18** (71 mg, 45% overall yield from **21**).

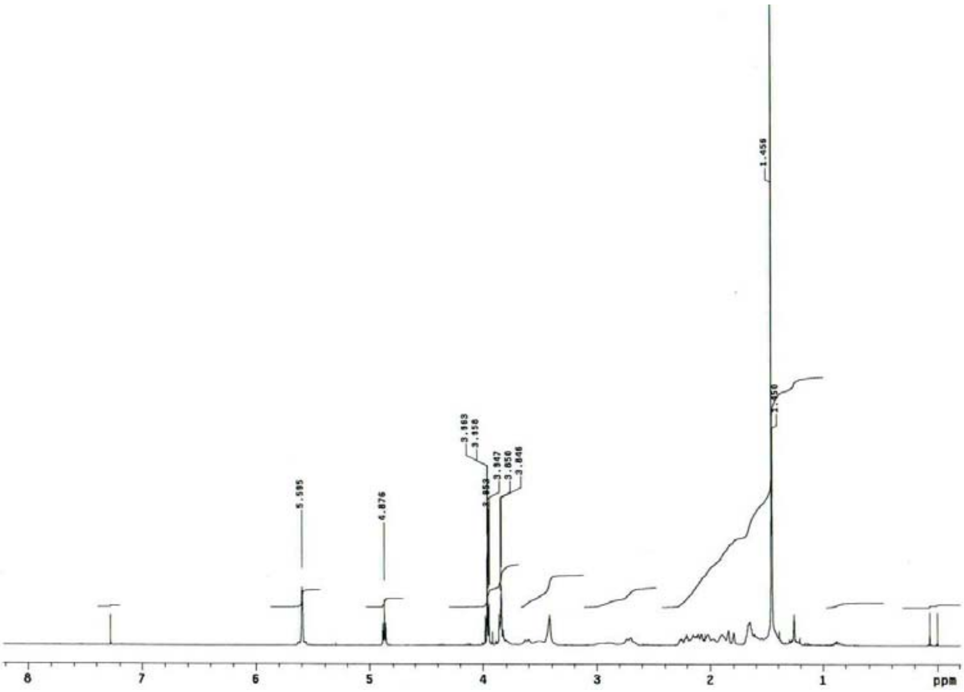
$[\alpha]_D^{22}$ = – 14.4 (c 2.6, $CHCl_3$).

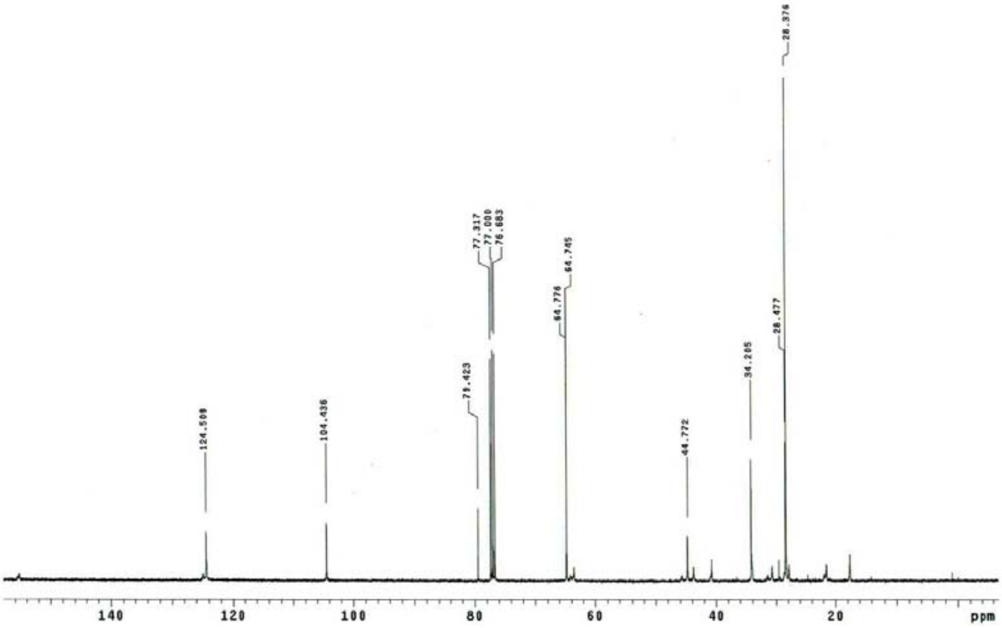
IR (KBr): 3480 (OH), 1688 (C=O) cm^{-1}.

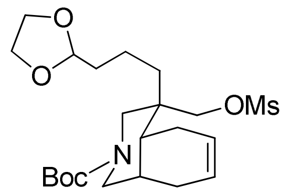
^1H NMR (400 MHz, $CDCl_3$, COSY, gHSQC): δ 1.45 [s, 11H, (CH3)3C), H-2'], 1.50 (m, 2H, H-1'), 1.63 (m, 2H, H-3'), 1.81 (d, *J* = 18.0 Hz, 1H, H-8), 1.90 (m, 1H, H-4a), 1.99 (dm, *J* = 18.8 Hz, 1H, H-5), 2.09 (dm, *J* = 18.8 Hz, 1H, H-5), 2.14 (m, 1H, H-8a), 2.23 (d, *J* = 18.0 Hz, 1H, H-8), 2.70-2.97 (m, 2H, H-1, H-3), 3.42 (s, 2H, CH_2OH), 3.52-3.63 (m, 2H, H-1, H-3), 3.85, 3.95 (2m, 4H, $2CH_2O$), 4.87 (t, *J* = 4.8 Hz, 1H, H-4’), 5.59 (m, 2H, H-6, H-7).

^{13}C NMR (100.6 MHz, CDCl3): δ 17.6 (C-2’), 21.4 (C-5), 27.8 (C-8a), 28.3 [$(CH_3)_3C$)], 28.5 (C-8), 30.7 (C-1’), 34.2 (C-3’, C-4a), 40.8 (C-4), 43.7-45.7 (C-1, C-3), 63.6, 64.2 (CH_2OH), 64.7, 64.8 ($2CH_2O$), 79.4 [$(CH_3)_3C$)], 104.4 (C-4’), 124.5 (C-6, C-7), 155.0 (NCOO).

HRMS (ESI) calcd for $[C_{22}H_{35}NO_5 + H]^+$: 382.2588, found: 382.2585.







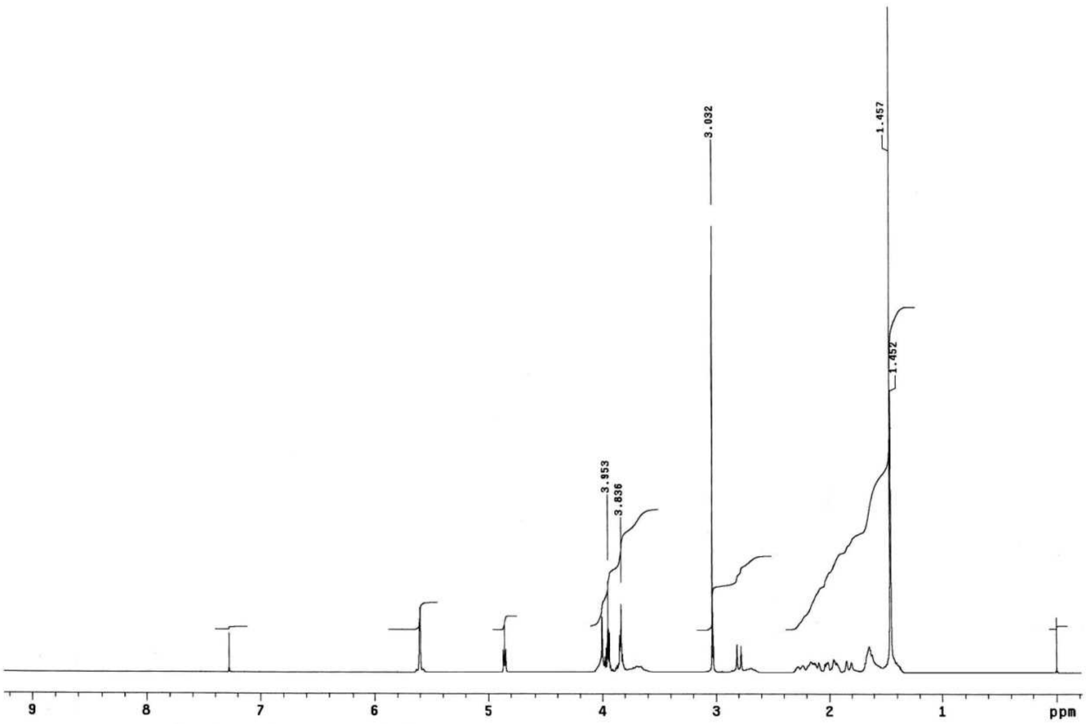
(4*R*,4a*R*,8a*S*)-2-(*tert*-Butoxycarbonyl)-4-[3-(1,3-dioxolan-2-yl)propyl]-4-(methansulfonyloximethyl)-1,2,3,4,4a,5,8,8a-octahydroisoquinoline (39).

Anhydrous Et_3N (2.18 mL, 15.6 mmol) and methanesulfonyl chloride (1.21 mL, 15.6 mmol) were added at 0 °C under an inert atmosphere to a stirred solution of alcohol **18** (1.98 g, 5.21 mmol) in anhydrous CH_2Cl_2 (86 mL), and the resulting mixture was stirred at room temperature for 4 h. The reaction was quenched with a saturated aqueous NH_4Cl solution, and the mixture was extracted with CH_2Cl_2. The combined organic extracts were dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The resulting mesylate **39** was obtained as a yellow oil, which was used in the next step without purification.

^{1}H NMR (400 MHz, $CDCl_3$, COSY, gHSQC): δ 1.42 (m, 2H, H-2'), 1.45, 1.46 [s, 9H, $(CH_3)_3C$)], 1.64 (m, 4H, H-1', H-3'), 1.83 (d, *J* = 17.6 Hz, 1H, H-8), 1.94 (m, 1H, H-4a), 1.99 (dm, *J* = 17.2 Hz, 1H, H-5), 2.10 (dm, *J* = 17.2 Hz, 1H, H-5), 2.16 (m, 1H, H-8a), 2.25 (dm, *J* = 17.6 Hz, 1H, H-8), 2.78-2.81 (2s, 2H, H-1, H-3), 3.03 (s, 3H, CH_3S), 3.66-3.73 (2m, 2H, H-1, H-3), 3.84, 3.95 (2m, 4H, $2CH_2O$), 4.00 (s, 2H, CH_2OS), 4.86 (t, *J* = 4.4 Hz, 1H, H-4'), 5.60 (m, 2H, H-6, H-7).

^{13}C NMR (100.6 MHz, $CDCl^3$): δ 17.2 (C-2'), 21.4 (C-5), 27.8 (C-8a), 28.3 [$(CH_3)_3C$), C-8], 31.0 (C-1'), 33.5 (C-4a), 34.3 (C-3'), 37.1 (CH_3SO), 39.8 (C-4), 43.4-44.6 (C-1, C-3), 64.7, 64.8 ($2CH_2O$), 70.2 (CH_2OS), 79.8 [$(CH_3)_3C$)], 104.1 (C-4'), 123.8, 124.5 (C-6, C-7), 155.0 (NCOO).

HRMS (ESI) calcd for $[C_{22}H_{37}NO_7S + NH_4]^+$: 477.2629, found: 477.2621.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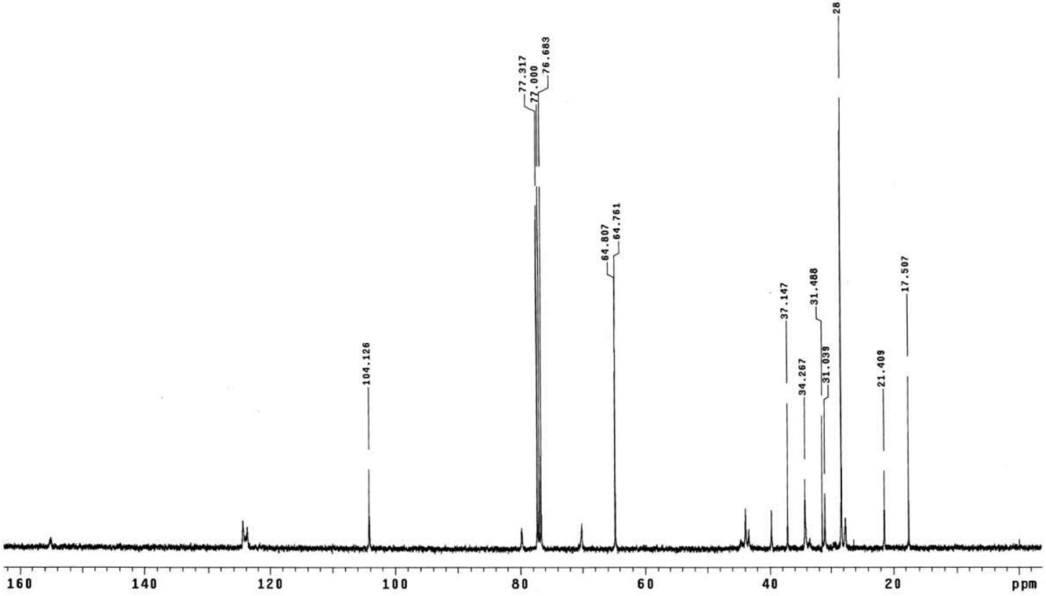
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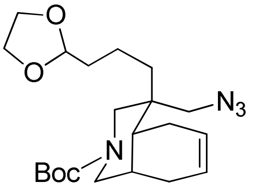


(4*R*,4a*R*,8a*S*)-4-(Azidomethyl)-2-(*tert*-butoxycarbonyl)-4-[3-(1,3-dioxolan-2-yl)propyl]-1,2,3,4,4a,5,8,8a-octahydroisoquinoline (40).

NaN_3 (2.03 g, 31.2 mmol) was added to a solution of the above mesylate **39** (5.21 mmol) in anhydrous DMF (15 mL), and the mixture was heated to 90 °C. After 48 h, more NaN_3 (2.03 g, 31.2 mmol) was added, and the resulting mixture was stirred at 90 °C for an additional 24 h and quenched with distilled water. The aqueous layer was extracted with CH_2Cl_2, and the combined organic extracts were dried, filtered, and concentrated under reduced pressure to give an oil. Flash chromatography (9:1 hexane-EtOAc) afforded azide **40** (1.68 g, 79%).

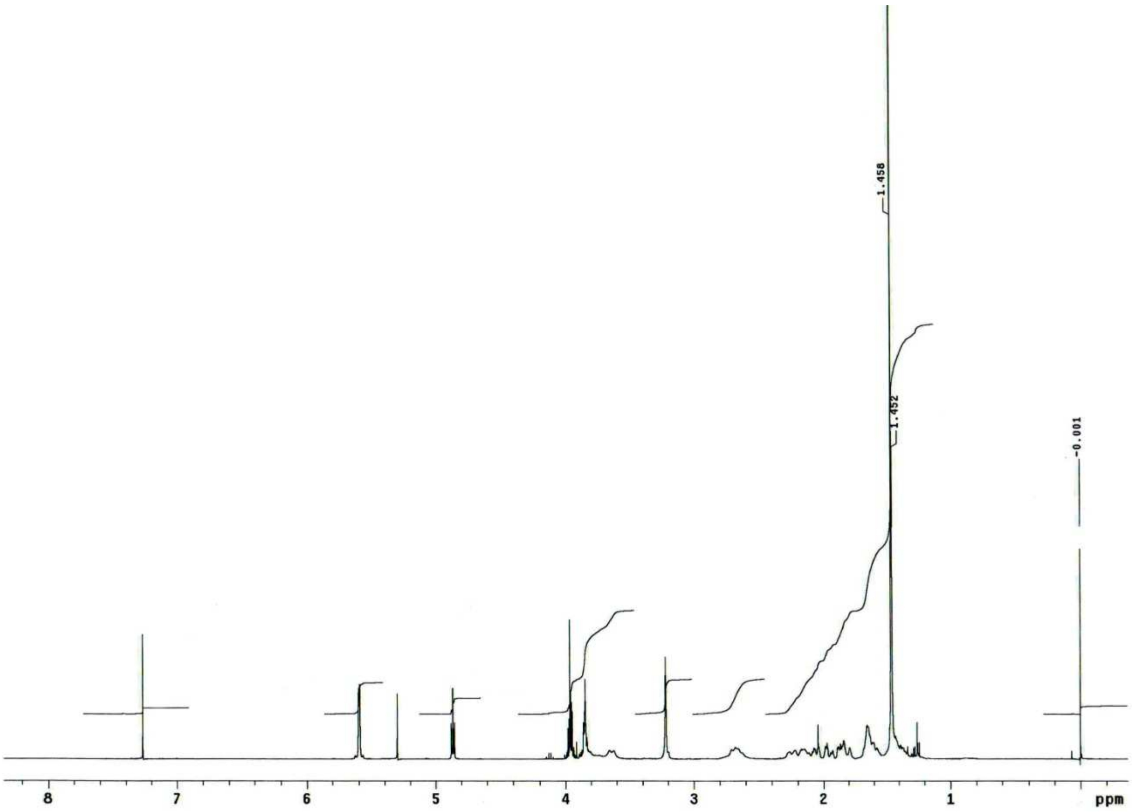
$[\alpha]_D^{22}$ = – 45.3 (c 0.9, $CHCl_3$).

IR (film): 2098 (N_3), 1688 (C=O) cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$, COSY, gHSQC): δ 1.38 (m, 2H, H-2’), 1.42 [s, 10H, $(CH_3)_3C$), H-1’], 1.60 (m, 1H, H-1’), 1.65 (m, 2H, H-3’), 1.81 (d, *J* = 18.4 Hz, 1H, H-8), 1.86 (m, 1H, H-4a), 1.95 (dm, *J* = 17.6 Hz, 1H, H-5), 2.08 (dm, *J* = 17.6 Hz, 1H, H-5), 2.16 (m, 1H, H-8a), 2.24 (m, 1H, H-8), 2.61-2.74 (m, 2H, H-1, H-3), 3.22 (s, 2H, CH_2N_3), 3.62-3.73 (2m, 2H, H-1, H-3), 3.85, 3.95 (2m, 4H, $2CH_2O$), 4.82 (t, *J* = 4.4 Hz, 1H, H-4’), 5.60 (m, 2H, H-6, H-7).

^{13}C NMR (100.6 MHz, $CDCl_3$): δ 17.7 (C-2’), 21.5 (C-5), 27.8 (C-8a), 28.3 [(CH3)3C), C-8], 31.7 (C-1’), 34.5 (C-4a), 34.8 (C-3’), 42.2 (C-4), 43.5-45.0 (C-1, C-3), 54.0 (CH_2N_3), 64.8 ($2CH_2O$), 79.7 [$(CH_3)_3C$)], 104.3 (C-4’), 123.9, 124.6 (C-6, C-7), 155.0 (NCOO).

HRMS (ESI) calcd for $[C_{21}H_{34}N_4O_4 + H]^+$: 407.2653, found: 407.2645.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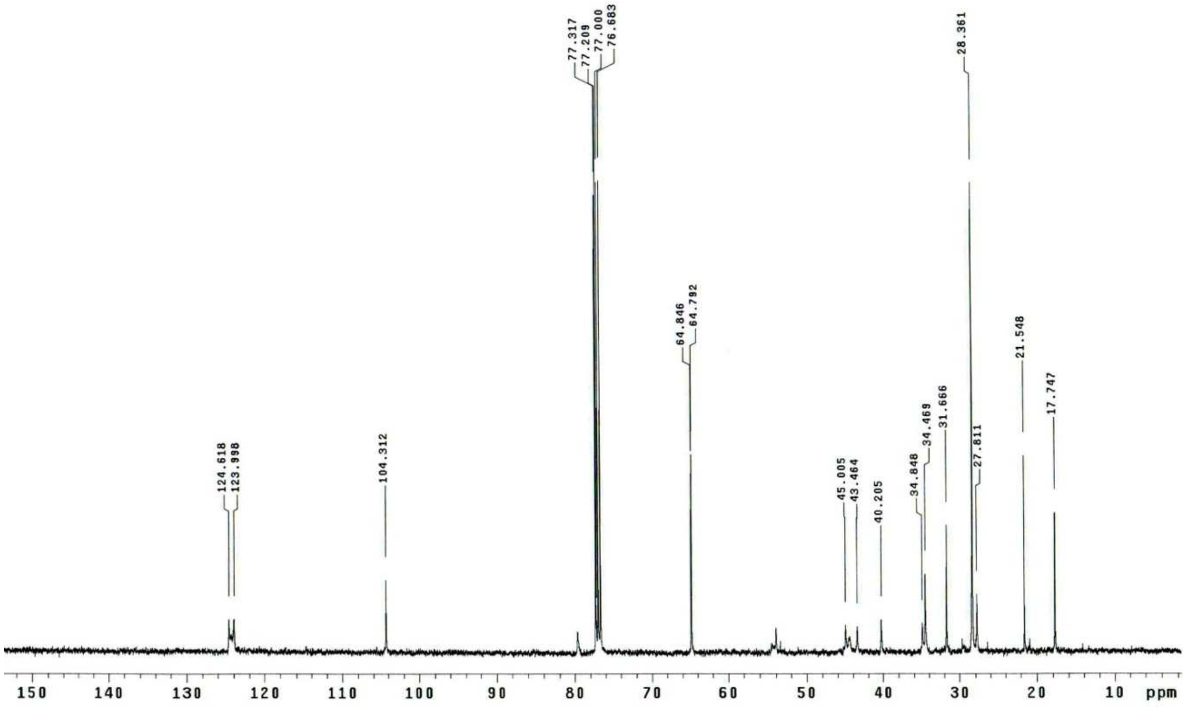
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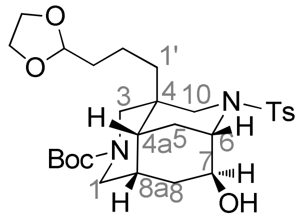


(IUPAC numbering)

(4*R*,4a*R*,6*S*,7*S*,8a*S*)-2-(*tert*-Butoxycarbonyl)-4-[3-(1,3-dioxolan-2-yl)propyl]-7-hydroxy-6,4-(iminomethano)-9-(*p*-toluenesulfonyl)perhydroisoquinoline (43).

First step: m-Chloroperoxybenzoic acid (1.48 g, 6.61 mmol, ≤ 77% of purity) was added to a cold (0 °C) solution of azide **40** (1.22 g, 3.00 mmol) in CH_2Cl_2 (43 mL), and the mixture was allowed to warm slowly to room temperature. After 5 h, the reaction was quenched with saturated aqueous $NaHCO_3$, and the mixture was extracted with CH_2Cl_2. The organic extracts were dried (anhydrous $MgSO_4$), filtered, and concentrated under reduced pressure to give azido epoxide **41**, which was used in the next step without purification.

Second step: Me_3P (4.8 mL of a 1 M solution in DMF, 4.80 mmol) was added to a solution of the above azido epoxide **41** (3.00 mmol) in THF (60 mL), and the mixture was stirred at room temperature for 2 hours. Water (6 mL) was added, and the resulting mixture was stirred overnight at room temperature and concentrated under reduced pressure to afford a diazatricyclic alcohol **42**.

Third step: Et_3N (410 μL, 3.00 mmol) was added dropwise to a stirring solution of the aminoalcohol **42** in anhydrous CH_2Cl_2 (50 mL) at 0 °C. A solution of *p*-toluenesulfonyl chloride (572 mg, 3.00 mmol) in anhydrous CH_2Cl_2 (5 mL) was transferred via a cannula, and the stirring was continued at 0 °C for 2.5 h. The reaction was then quenched with saturated aqueous NH_4Cl, and the aqueous layer was extracted with CH_2Cl_2. The combined organic extracts were dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure to afford the protected tricyclic compound **43** (998 mg, 60% overall yield from the azide **41**) after flash chromatography (9:1 to 1:1 hexane-EtOAc).

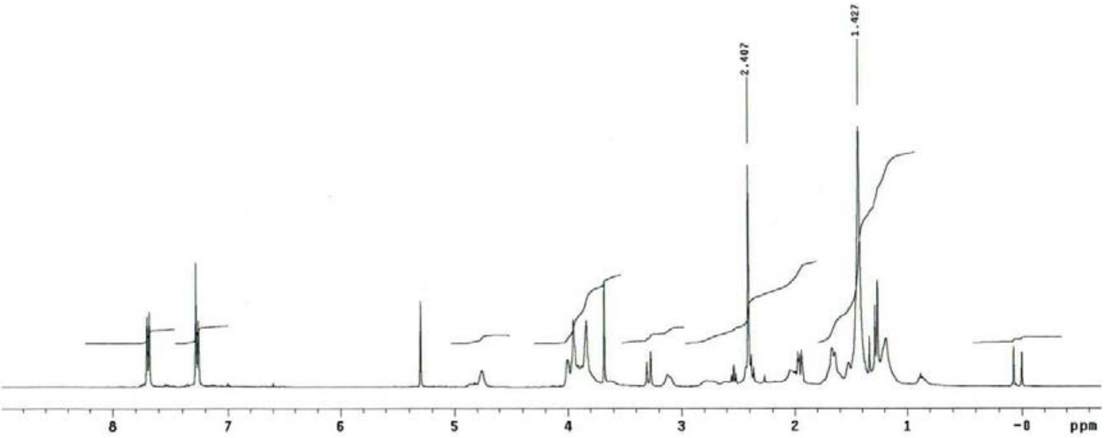
$[\alpha]_D^{22}$ = + 36.1 (*c* 3.1, $CHCl_3$).

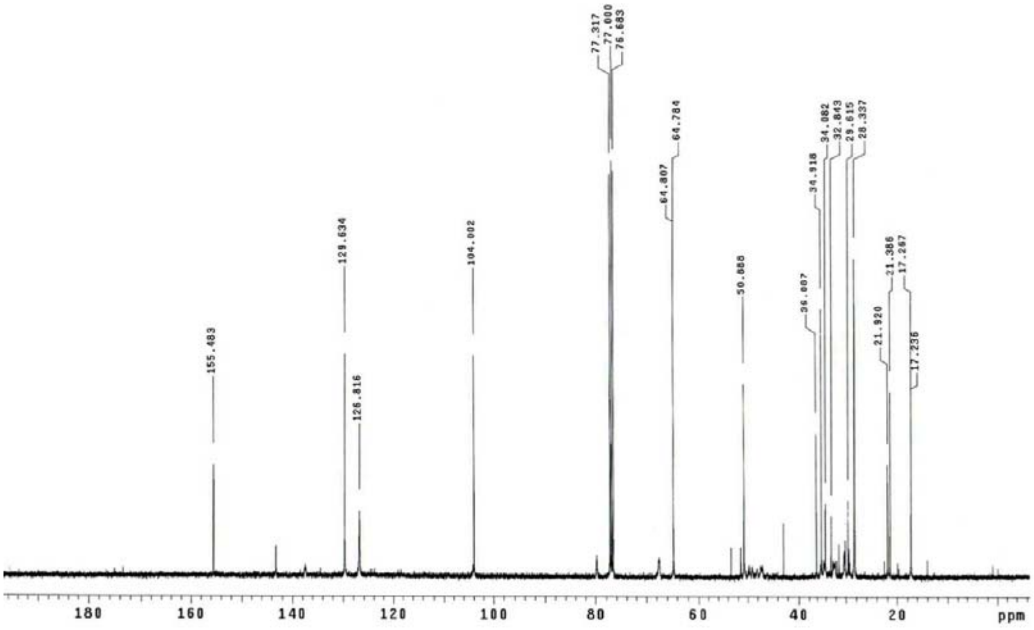
IR (film): 3500 (OH), 1689 (C=O) cm^{-1}.

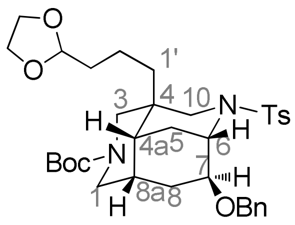
^1H NMR (400 MHz, $CDCl_3$, COSY, gHSQC): δ 1.19 (m, 4H, H-1', H-2'), 1.43 [s, 11H, $(CH_3)_3C$, H-3'], 1.52 (m, 1H, H-4a), 1.60-1.71 (m, 3H, H-5, 2H-8), 1.94 (d, *J* = 14.4 Hz, 1H, H-5), 2.04 (m, 1H, H-8a), 2.43 (s, 3H, CH_3 Ts), 2.60-2.78 (m, 2H, H-1, H-3), 3.12 (m, 1H, H-10), 3.28 (d, *J* = 13.2 Hz, 1H, H-10), 3.84 (m, 2H, CH_2O), 3.87 (m, 1H, H-7), 3.90 (masked, 2H, H-3, H-1), 3.95 (m, 2H, CH_2O), 4.00 (s, 1H, H-6), 4.76 (m, 1H, H-4'), 7.27 (d, *J* = 8.0 Hz, 2H, H-*m* Ts), 7.69 (d, *J* = 8.0 Hz, 2H, H-*o* Ts).

^{13}C NMR (100.6 MHz, $CDCl_3$): δ 17.3 (C-2'), 21.4 (CH_3 Ts), 21.9 (C-5), 28.3 [$(CH_3)_3C$], 30.3 (C-8a), 32.5 (C-8), 32.8 (C-4), 34.0 (C-3'), 34.9 (C-4a), 36.1 (C-1'), 46.0-50.0 (C-10, C-1, C-3), 50.8 (C-6), 64.7, 64.8 ($2CH_2O$), 67.7 (C-7), 79.8 [$(CH_3)_3C$], 104.0 (C-4'), 126.8 (C-*o* Ts), 129.6 (C-*m* Ts), 136.5 (C-*i* Ts), 143.1 (C-*p* Ts), 155.5 (NCOO).

HRMS (ESI) calcd for $[C_{28}H_{42}N_2O_7S + H]^+$: 551.2785, found: 551.2788.







(IUPAC numbering)

(4*R*,4a*R*,6*S*,7*S*,8a*S*)-7-(Benzyloxy)-2-(*tert*-butoxycarbonyl)-4-[3-(1,3-dioxolan-2-yl)propyl]-6,4-(iminomethano)-9-(*p*-toluenesulfonyl)perhydroisoquinoline (44).

NaH (180 mg of a 60% dispersion in mineral oil, 4.53 mmol) was added to a solution of tricyclic compound **43** (1.66 g, 3.02 mmol) in anhydrous DMF (40 mL), and the mixture was stirred at 0 °C for 1 h. Then, benzyl bromide (2.58 g, 15.12 mmol, previously filtered over a neutral alumina pad) and TBAI (223 mg, 0.60 mmol) were added at room temperature, and the resulting suspension was stirred overnight. The reaction was quenched by the addition of distilled water, and the aqueous layer was extracted with Et_2O. The combined organic extracts were dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. Flash chromatography (9:1 to 1:1 hexane-EtOAc) of the residue gave the benzyloxy derivative **44** (1.55 g, 80%) as a colourless oil.

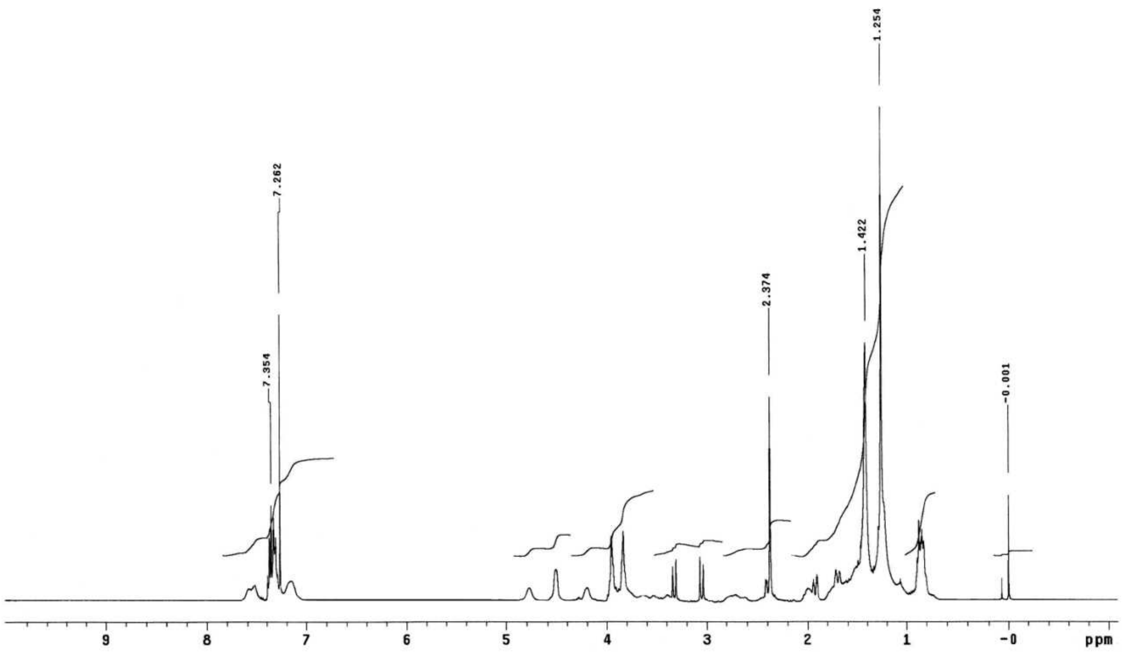
$[\alpha]_D^{22}$ = + 38.8 (*c* 0.75, $CHCl_3$).

IR (film): 1689 (C=O) cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$, COSY, gHSQC): δ 1.25 (s, 4H, H-1′, H-2′), 1.42 [s, 11H, $(CH_3)_3C$, H-3′], 1.50 (m, 2H, H-4a, H-8), 1.70 (dm, *J* = 13.6 Hz, 1H, H-5), 1.75 (m, 1H, H-8), 1.92 (dt, *J* = 13.6, 2.4 Hz, 1H, H-5), 1.99 (m, 1H, H-8a), 2.37 (s, 3H, CH_3 Ts), 2.62-2.70 (2m, 2H, H-1, H-3), 3.04 (d, *J* = 13.2 Hz, 1H, H-10), 3.32 (d, *J* = 13.2 Hz, 1H, H-10), 3.40 (br. s, 1H, H-7), 3.52-3.62 (2m, 2H, H-1, H-3), 3.84, 3.95 (2m, 4H, $2CH_2O$), 4.20 (m, 1H, H-6), 4.51 (m, 2H, CH_2 Bn), 4.78 (m, 1H, H-4′), 7.10-7.60 (m, 9H, C_6H_5, Ts).

^{13}C NMR (100.6 MHz, $CDCl_3$): δ 17.3 (C-2′), 21.4 (CH_3 Ts), 22.6 (C-5), 28.4 [$(CH_3)_3C$], 29.9 (C-8), 30.8 (C-8a), 31.9 (C-4), 34.2 (C-3′), 35.0 (C-4a), 36.1 (C-1′), 43.9 (C-3′), 47.0-49.9 (C-1, C-3), 48.2 (C-10), 51.0 (C-6), 64.8 ($2CH_2O$), 70.5 (CH_2 Bn), 73.4 (C-7), 79.8 [$(CH_3)_3C$], 104.1 (C-4′), 126.7-129.6 (C-*o, m* Ts, C-*o*, *m*, *p* C_6H_5), 137.4 (C-*i* Ts), 138.5 (C-*i* C_6H_5), 143.0 (C-*p* Ts), 155.5 (NCOO).

HRMS (ESI) calcd for $[C_{35}H_{48}N_2O_7S + H]^+$: 641.3255, found: 641.3255.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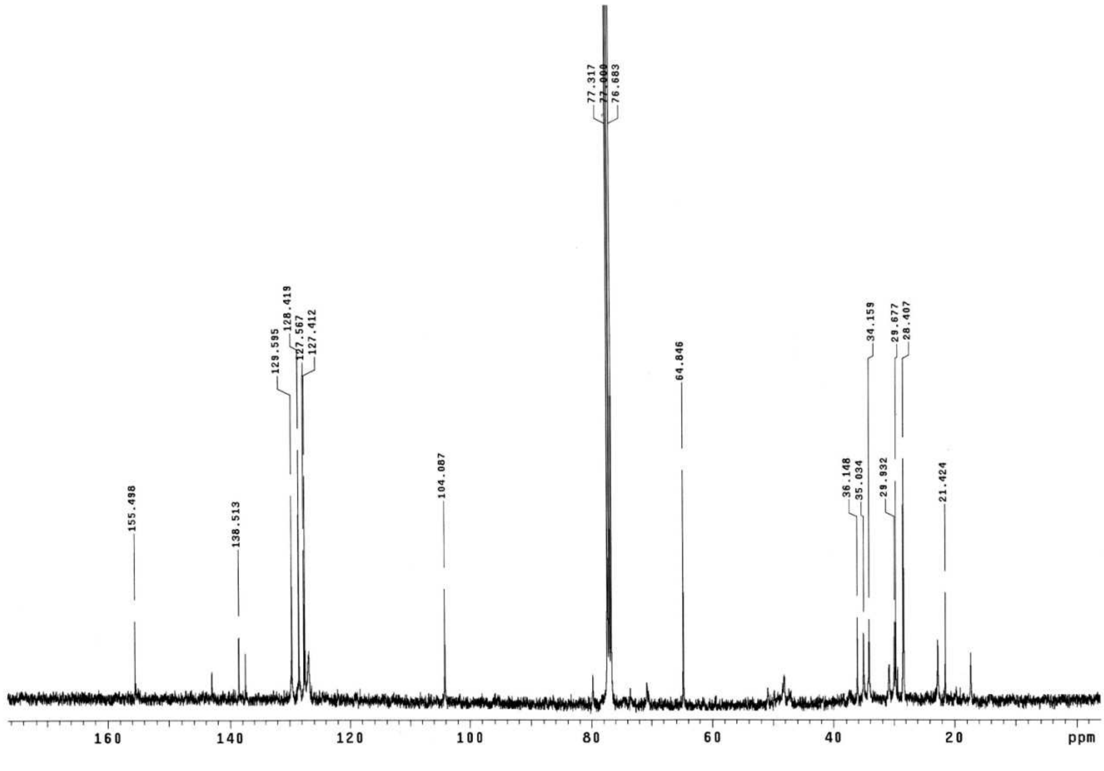
1.422
1.254
-0.001
9
8
7
6
5
4
3
2
1
-0
ppm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77.000
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127.412
64.846
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29.677
28.407
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138.513
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36.148
35.034
29.832
21.424
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140
120
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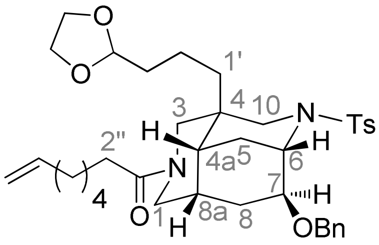
80
60
40
20
ppm



(IUPAC numbering)

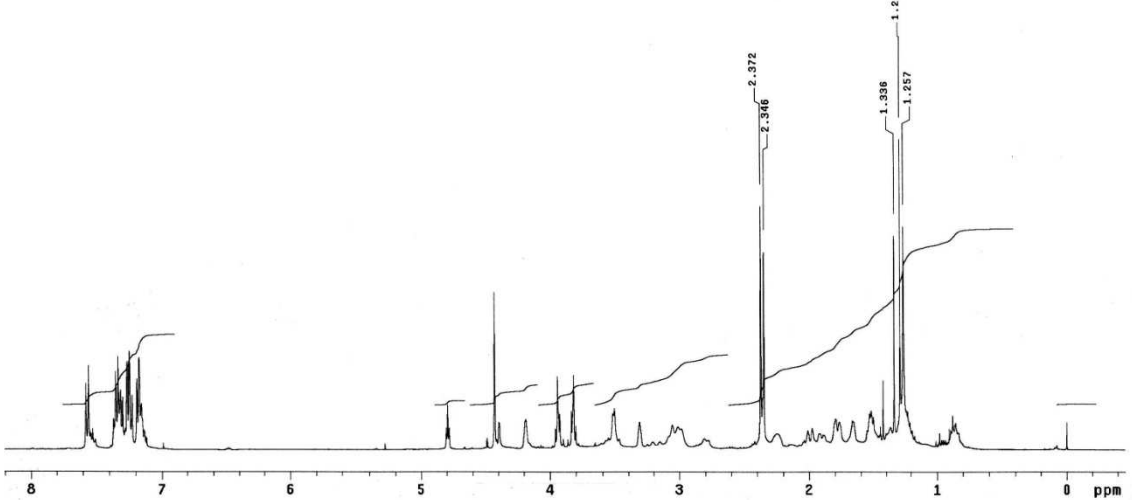
(4*R*,4a*R*,6*S*,7*S*,8a*S*)-7-(Benzyloxy)-4-[3-(1,3-dioxolan-2-yl)propyl]-6,4-(iminomethano)-2-(7-octenoyl)-9-(*p*-toluenesulfonyl)perhydroisoquinoline (102).

First step: TFA (7 mL) was added to a solution of the above tricyclic compound (1.15 g, 1.79 mmol) in anhydrous CH_2Cl_2 (21 mL), and the mixture was stirred at room temperature for 30 minutes. Toluene (2 x 20 mL) was added, and the resulting solution was concentrated under reduced pressure to give the deprotected derivative **100**, which was used in the next step without purification.

^{1}H NMR (400 MHz, $CDCl_3$, COSY, gHSQC): δ 1.22 (m, 2H, H-2’), 1.36 (m, 1H, H-1’), 1.52 (m, 3H, 2H-3’, H-1’), 1.65 (m, 1H, H-4a), 1.78 (dm, *J* = 13.6 Hz, 2H, H-4a, H-8), 1.90 (dm, *J* = 13.6 Hz, 1H, H-8), 1.98 (dm, *J* = 13.6 Hz, 1H, H-5), 2.25 (m, 1H, H-8a), 2.37 (s, 3H, CH_3 Ts), 2.78, 2.98-3.05 (2m, 4H, H-1, H-3), 3.31 (br. s, 1H, H-7), 3.48 (d, *J* = 13.2 Hz, 1H, H-10), 3.53 (d, *J* = 13.2 Hz, 1H, H-10), 3.82, 3.94 (2m, 4H, $2CH_2O$), 4.18 (br. s, 1H, H-6), 4.43 (m, 2H, CH_2 Bn), 4.79 (t, *J* = 4.4 Hz, 1H, H-4’), 7.15-7.57 (m, 9H, C_6H_5, Ts).

^{13}C NMR (100.6 MHz, $CDCl_3$): δ 17.0 (C-2’), 21.4 (CH_3 Ts), 22.5 (C-5), 27.7 (C-8a), 28.9 (C-8), 32.3 (C-4a), 33.1 (C-4), 33.6 (C-3’), 36.0 (C-1’), 46.2 (C-10), 47.6, 48.7 (C-1, C-3), 47.8 (C-6), 64.8 ($2CH_2O$), 70.7 (CH_2 Bn), 72.8 (C-7), 103.7 (C-4’), 126.6-129.8 (C-*o, m* Ts, C-*o*, *m*, *p* C_6H_5), 137.2 (C-*i* Ts), 138.0 (C-*i* C_6H_5), 143.4 (C-*p* Ts).

HRMS (ESI) calcd for $[C_{30}H_{40}N_2O_5S + H]^+$: 541.2731, found: 541.2736.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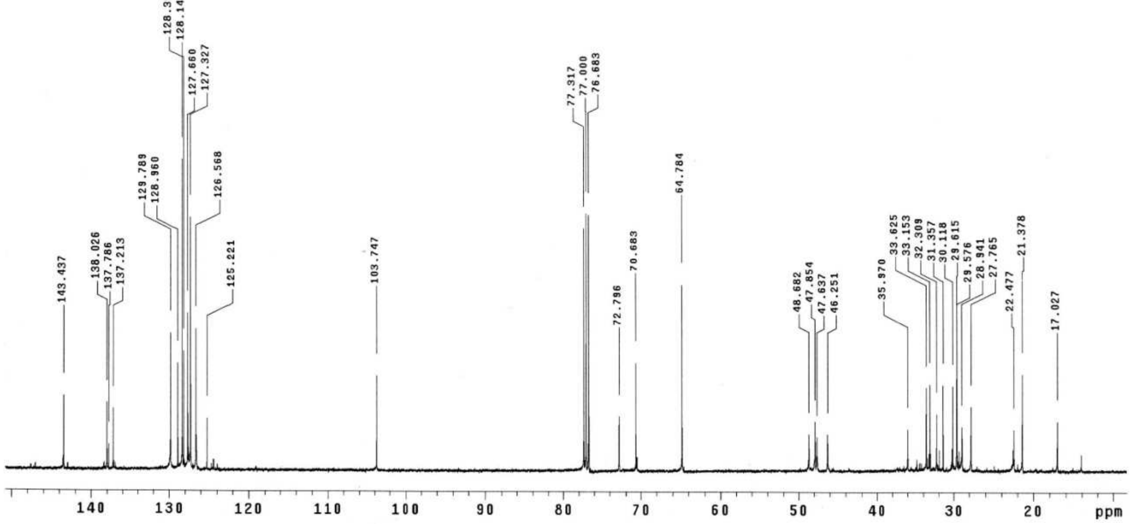
0
ppm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137.213
129.789
128.960
128.395
128.148
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127.327
126.568
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103.747
77.317
77.000
76.683
72.796
70.683
64.784
48.682
47.854
47.637
46.251
35.970
33.625
33.153
32.309
31.357
30.118
29.615
29.576
28.941
27.765
22.477
21.378
17.027
140
130
120
110
100
90
80
70
60
50
40
30
20
ppm

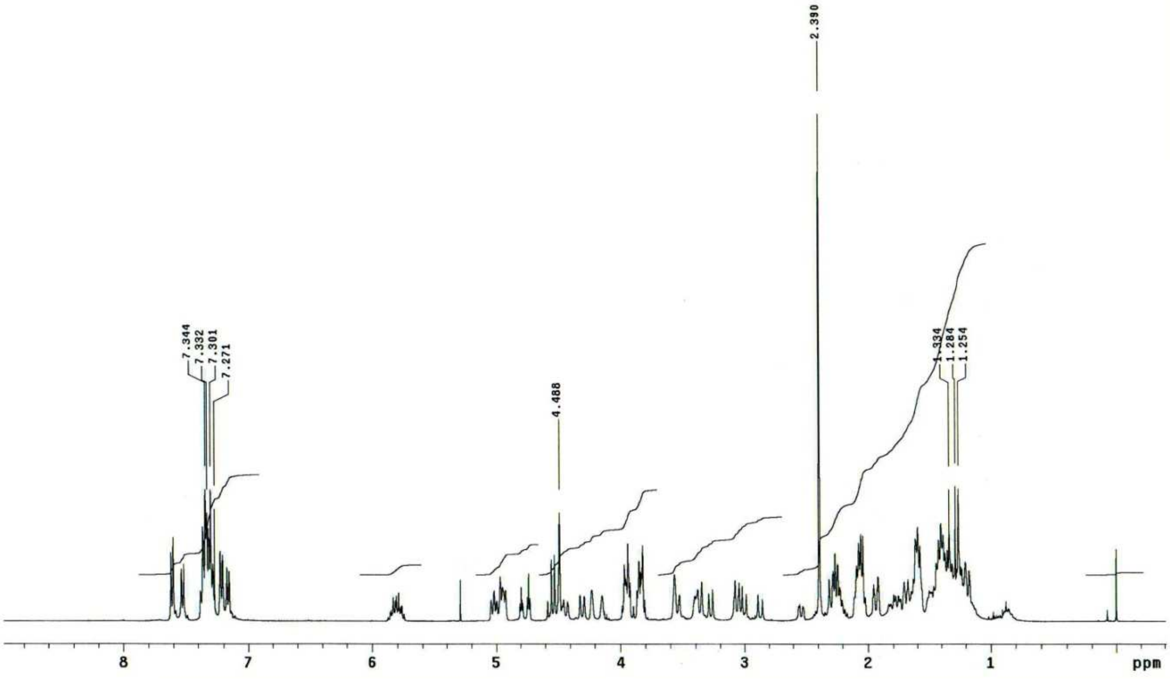
Preparation of 7-octenoyl chloride: A CH_2Cl_2 solution of oxalyl chloride (2 M, 5.8 mL, 11.7 mmol) was added to a mixture of 7-octenoic acid (1.37 mL, 8.97 mmol) and 2 drops of DMF, and the resulting mixture was stirred at room temperature for 15 min. Et_2O was added, and the resulting mixture was filtered and concentrated under reduced pressure to give crude **7-octenoyl chloride.**

Second step: Et_3N (1.30 mL, 9.33 mmol) was added at 0 °C to a solution of the above secondary amine **100** (1.79 mmol) in anhydrous CH_2Cl_2 (85 mL), and the resulting mixture was stirred at 0 °C for 10 min. A solution of the freshly prepared **101** (8.97 mmol) in anhydrous CH_2Cl_2 (4 mL) was added at 0 °C, and the mixture was stirred at 0 °C for 3 h and at room temperature overnight. Distilled water was added, and the resulting mixture was stirred for 20 minutes. The aqueous layer was extracted with CH_2Cl_2, and the combined organic extracts were dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. Flash chromatography (hexane to 8:2 hexane-EtOAc) of the residue afforded amide **102** (1.09 g, 92 %, overall yield from the Boc derivative **44**).

^{1}H NMR (400 MHz, $CDCl_3$, COSY, gHSQC): δ 1.20-1.50 (m, 10H, H-1’, H-2’, H-3’, H-4’’, H-5’’), 1.59 (m, 3H, H-4a, 2H-3’’), 1.64 (m, 1H, H-8), 1.69 (dm, *J* = 13.2 Hz, 1H, H-5), 1.78 (td, *J* = 14.8, 5.6 Hz, 1H, H-8), 1.93 (dt, *J* = 13.2, 2.8 Hz, 1H, H-5), 2.06 (m, 3H, H-8a, 2H-6’’), 2.25 (m, 2H, H-2’’), 2.29, 2.86 (d, *J* = 14.0 Hz, 1H, H-3ax), 2.39 (s, 3H, CH_3 Ts), 2.53, 3.06 (2dd, *J* = 13.2, 2.8 Hz, 1H, H-1), 3.00, 3.27 (2d, *J* = 13.6 Hz, 1H, H-10), 3.05, 3.36 (2d, *J* = 13.6 Hz, 1H, H-10), 3.37, 4.30 (2d, *J* = 13.2 Hz, 1H, H-3), 3.40, 3.56 (2br. s, 1H, H-7), 3.54, 4.43 (2d, *J* = 13.2 Hz, 1H, H-1), 3.82, 3.93 (2m, 4H, $2CH_2O$), 4.14, 4.22 (2br. s, 1H, H-6), 4.50 (d, *J* = 12.4 Hz, 1H, CH_2 Bn), 4.56 (d, *J* = 12.0 Hz, 1H, CH_2 Bn), 4.73, 4.79 (2t, *J* = 4.8 Hz, 1H, H-4’), 4.93-5.04 (m, 2H, CH_2=), 5.80 (tdt, *J* = 13.2, 13.2, 10.0, 6.8, 6.8 Hz, 1H, CH=), 7.05-7.60 (m, 9H, Ts, C_6H_5).

^{13}C NMR (100.6 MHz, $CDCl_3$): δ 17.3, 17.4 (C-2’), 21.4 (CH_3 Ts), 22.3, 22.6 (C-5), 24.9 (C-3’’), 28.6, 28.7, 28.8, 28.9 (C-4’’, C-5’’), 29.7, 30.0 (C-8), 30.4, 31.0 (C-8a), 33.1, 33.2 (C-2’’), 33.5 (C-6’’), 34.4 (C-3’), 34.6, 34.8 (C-4a), 34.9, 35.3 (C-4), 36.1, 36.2 (C-1’), 43.9, 50.5 (C-1), 46.5, 46.8 (C-10), 47.8, 48.4 (C-6), 48.0, 52.2 (C-3), 64.7, 64.8 ($2CH_2O$), 70.5, 70.8 (CH_2 Bn), 73.7, 74.7 (C-7), 103.9, 104.0 (C-4’), 114.3, 144.4 (CH_2=), 126.6-129.6 (C-*o, m* Ts, C-*o*, *m*, *p* C_6H_5), 137.4-138.8 (C-*i* Ts, C_6H_5, CH=), 143.0, 143.2 (C-*p* Ts), 172.6, 172.7 (NCO).

HRMS (ESI) calcd for $[C_{38}H_{52}N_2O_6S + H]^+$: 665.3619, found: 665.3608.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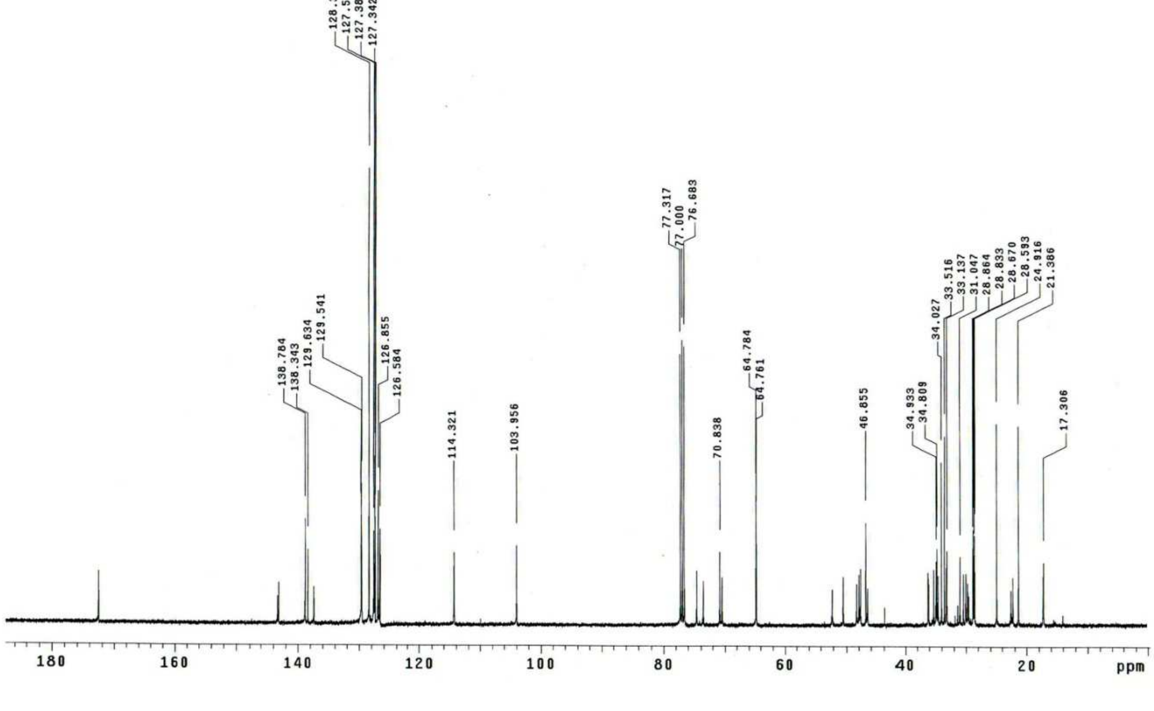
ppm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126.584
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77.317
77.000
76.683
70.838
64.784
64.761
46.855
34.933
34.809
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33.516
33.137
31.047
28.864
28.833
28.670
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17.306
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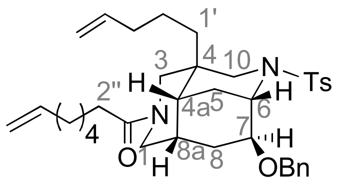


(IUPAC numbering)

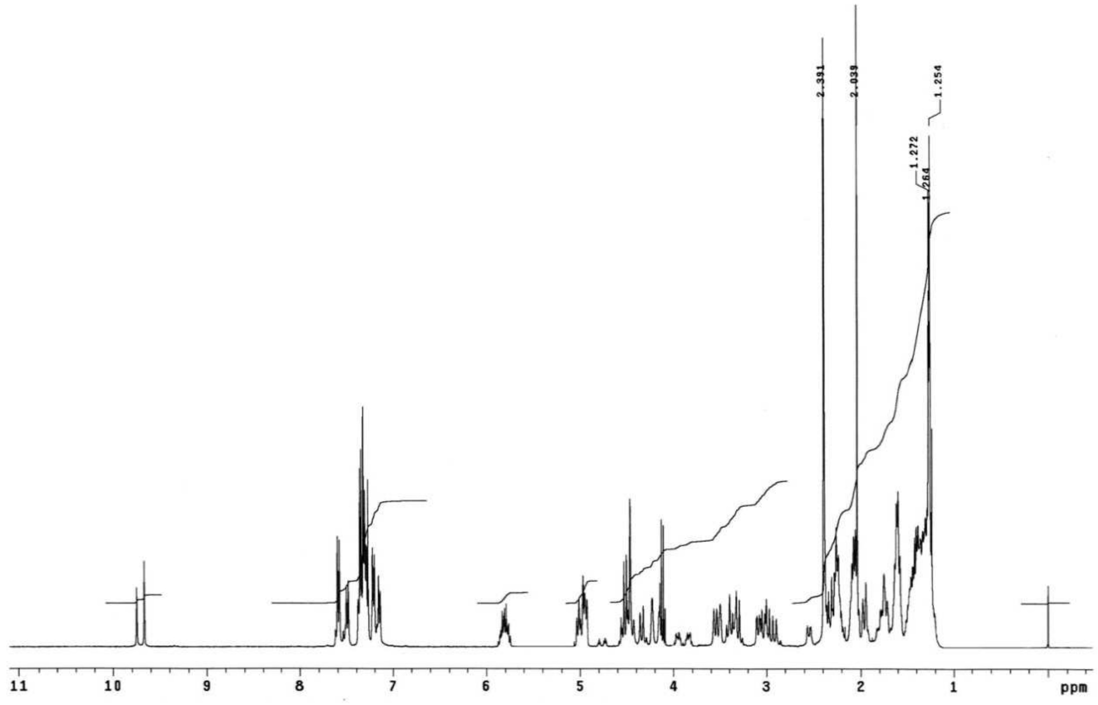
(4*R*,4a*R*,6*S*,7*S*,8a*S*)-7-(Benzyloxy)-6,4-(iminomethano)-2-(7-octenoyl)-4-(4-pentenyl) -2-(*p*-toluenesulfonyl)perhydroisoquinoline (98).

First step: Aqueous HCl (3.0 mL of a 1M solution, 3.0 mmol) was added to a solution of acetal **102** (100 mg, 0.15 mmol) in THF (1.0 mL), and the resulting mixture was stirred at room temperature for 2 h. The reaction was quenched by addition of solid K_2CO_3, and the mixture was basified to pH 8. The resulting mixture was extracted with CH_2Cl_2, and the combined organic extracts were washed with brine, dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure to give the corresponding aldehyde **103** as a yellow oil, which was used in the next step without purification.

^{1}H NMR (400 MHz, $CDCl_3$, COSY, gHSQC): δ 1.25-1.49 (m, 8H, H-1’, H-2’, H-4’’, H-5’’), 1.58-1.65 (m, 4H, H-8, H-4a, 2H-3’’), 1.74 (dm, *J* = 14.0 Hz, 1H, H-5), 1.79 (dd, *J* = 14.0, 6.4 Hz, 1H, H-8), 1.96 (dm, *J* = 14.0 Hz, 1H, H-5), 2.07 (m, 3H, H-8a, 2H-6’’), 2.26 (t, *J* = 7.6 Hz, 4H, H-2’’, H-3’), 2.35, 2.90 (d, *J* = 13.2 Hz, 1H, H-3ax), 2.39 (s, 3H, CH_3 Ts), 2.55, 3.08 (dd, *J* = 13.2, 3.2 Hz, 1H, H-1ax), 2.98, 3.03 (2d, *J* = 13.6 Hz, 1H, H-10ax), 3.29, 3.38 (2d, *J* = 13.6 Hz, 1H, H-10eq), 3.33, 3.50 (2br. s, 1H, H-7), 3.41, 4.34 (2d, *J* = 13.2 Hz, 1H, H-3eq), 3.55, 4.45 (2d, *J* = 13.2 Hz, 1H, H-1eq), 4.14, 4.22 (2br. s, 1H, H-6), 4.48 (d, *J* = 12.0 Hz, 1H, CH_2 Bn), 4.55 (d, *J* = 12.0 Hz, 1H, CH_2 Bn), 4.97 (m, 2H, CH_2=), 5.81 (m, 1H, CH=), 7.13-7.60 (m, 9H, Ts, C_6H_5), 9.67, 9.75 (2s, 1H, CHO).

^{13}C NMR (100.6 MHz, $CDCl_3$): δ 15.3, 15.5 (C-2’), 21.0, 21.4 (CH_3 Ts), 22.4, 22.5 (C-5), 24.9 (C-3’’), 28,6, 28.7, 28.8, 28.9 (C-4’’, C-5’’), 29.7, 30.0 (C-8), 30.5, 31.0 (C-8a), 31.5 (C-4), 33.1, 33.2 (C-2’’), 33.5 (C-6’’), 34.6, 34.9 (C-4a), 35.4, 35.5 (C-1’), 43.9 (C-3’), 46.5, 50.1 (C-1), 46.6 (C-10), 47.8, 52.1 (C-3), 47.9, 48.4 (C-6), 70.4, 70.7 (CH_2 Bn), 73.2, 74.2 (C-7), 114.3, 114.4 (CH_2=), 126.6-129.6 (C-*o, m* Ts, C-*o*, *m*, *p* C_6H_5), 137.3-138.9 (C-*i* Ts, C-*i* C_6H_5, CH=), 143.0 (C-*p* Ts), 172.5, 172.7 (NCO), 201.4, 201.5 (CHO).

HRMS (maldi) calcd for $[C_{36}H_{48}N_2O_5S + Na]^+$: 643.32, found: 643.30.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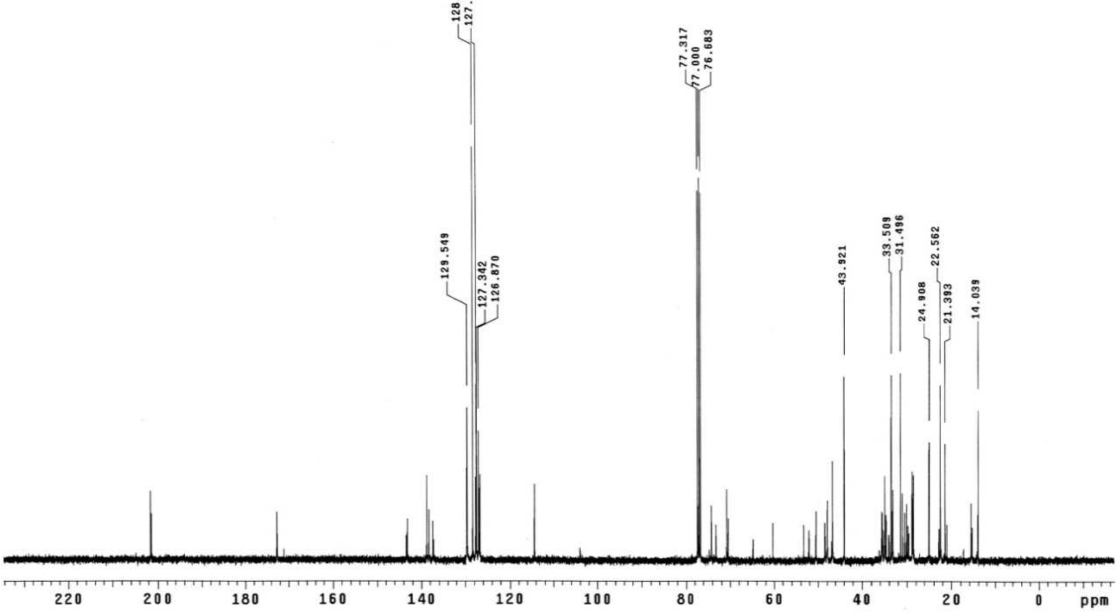
1
ppm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31.496
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21.393
14.039
220
200
180
160
140
120
100
80
60
40
20
0
ppm

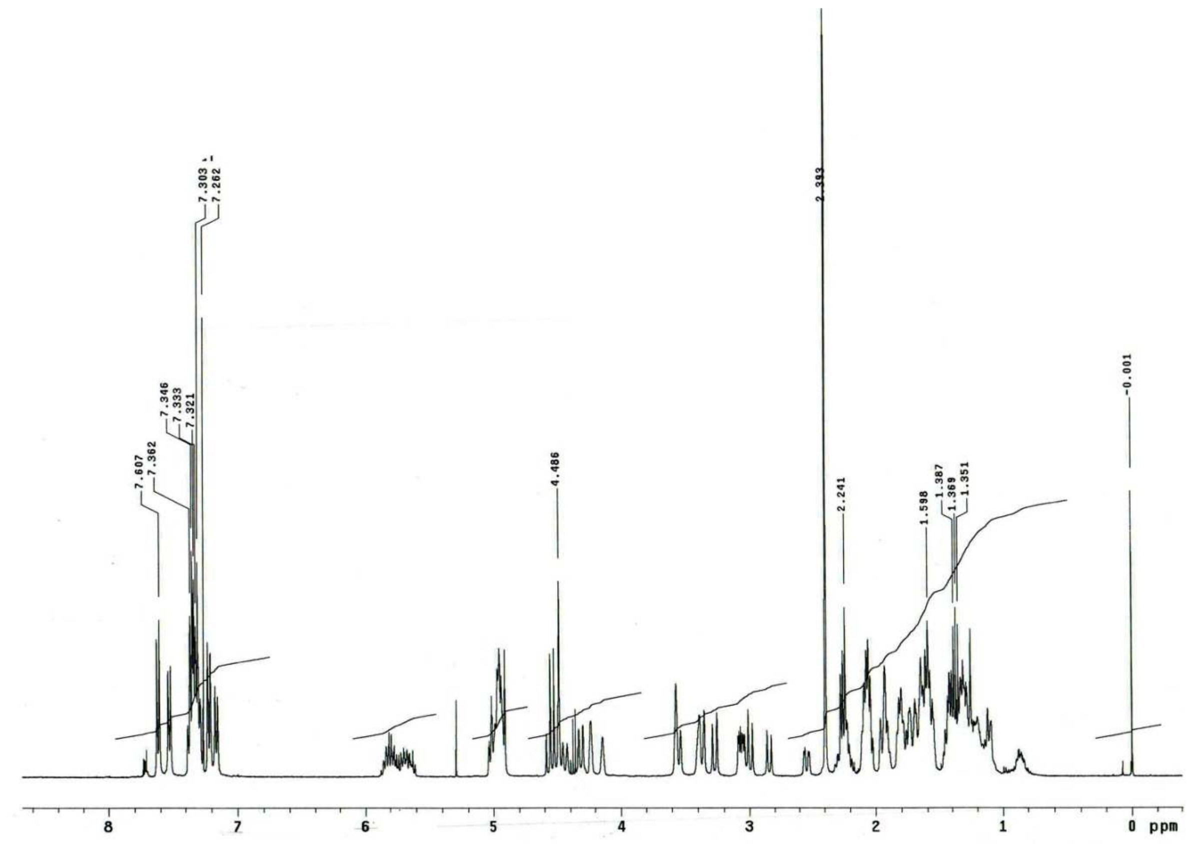
Second step: KO*t*Bu (750 µL of a 1M solution in THF, 0.75 mmol) was added dropwise to a solution of methyltriphenylphosphonium bromide (375 mg, 1.05 mmol) in THF (4 mL), and the solution was stirred at room temperature for 1 h. The resulting yellow suspension was added to a solution of the above aldehyde **103** (0.15 mmol) in THF (4 mL) and the mixture was stirred at room temperature overnight. The reaction was quenched by addition of saturated aqueous NH_4Cl, and the aqueous layer was extracted with Et_2O. The combined organic extracts were dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. Flash chromatography (hexane to 6:4 hexane-EtOAc) of the resulting oil afforded diene **98** (73 mg, 80%).

$[\alpha]_D^{22}$ = + 38.5 (*c* 1.5, $CHCl_3$).

IR (film): 1641 (C=O) cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$, COSY, gHSQC): δ 1.08-1.43 (m, 8H, 2H-1’, 2H-2’, 2H-4’’, 2H-5’’), 1.55 (m, 1H, H-4a), 1.61 (m, 3H, 2H-3’’, H-8), 1.71 (dm, *J* = 14.8 Hz, 1H, H-5), 1.80 (m, 2H, H-3’, H-8), 1.91 (m, 1H, H-3’), 1.94 (dm, *J* = 14.8 Hz, 1H, H-5), 2.06 (m, 3H, H-6’’, H-8a), 2.20, 2.84 (2d, *J* = 14.0 Hz, 1H, H-3ax), 2.26 (t, *J* = 8.0 Hz, 2H, H-2’’), 2.40 (s, 3H, CH_3 Ts), 2.54, 3.07 (2dd, *J* = 12.8, 2.8 Hz, 1H, H-1ax), 2.98, 3.04 (2d, *J* = 13.6 Hz, 1H, H-10ax), 3.26, 3.36 (2d, *J* = 13.6 Hz, 1H, H-10eq), 3.36, 4.31 (2d, *J* = 14.0 Hz, 1H, H-3eq), 3.40, 3.57 (2br. s, 1H, H-7), 3.55, 4.43 (2d, *J* = 12.8 Hz, 1H, H-1eq), 4.14, 4.23 (2br. s, 1H, H-6), 4.51 (d, *J* = 12.0 Hz, 1H, CH_2 Bn), 4.56 (d, *J* = 12.0 Hz, 1H, CH_2 Bn), 4.95 (m, 4H, CH_2=), 5.61-5.90 (m, 2H, CH=), 7.08-7.60 (m, 9H, Ts, C_6H_5).

^{13}C NMR (100.6 MHz, $CDCl_3$): δ 21.0, 21.4 (CH_3 Ts), 22.2, 22.3, 22.4, 22.6 (C-2’, C-5), 24.7, 25.0 (C-3’’), 28.7, 28.8, 28.9 (C-4’’, C-5’’), 30.1, 30.6 (C-8), 31.1, 31.5 (C-8a), 33.2, 33.3 (C-2’’), 33.6 (C-6’’), 34.0 (C-3’), 34.8, 35.3 (C-4a), 35.7, 35.8 (C-1’), 36.6 (C-4), 46.5, 50.6 (C-1), 46.7, 46.8 (C-10), 47.9, 48.4 (C-6), 48.2, 52.3 (C-3), 70.5, 70.9 (CH_2 Bn), 73.7, 74.7 (C-7), 114.3, 114.4, 114.8, 115.1 (2CH_2=), 126.7-129.6 (C-*o*, *m* Ts, C-*o*, *m*, *p* C_6H_5), 137.4, 138.0, 138.1, 138.4, 138.5 (2CH=, C-*i* Ts, C-*i* C_6H_5), 143.1, 143.3 (C-*p* Ts), 172.6, 172.7 (NCO).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2.393
2.241
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1.351
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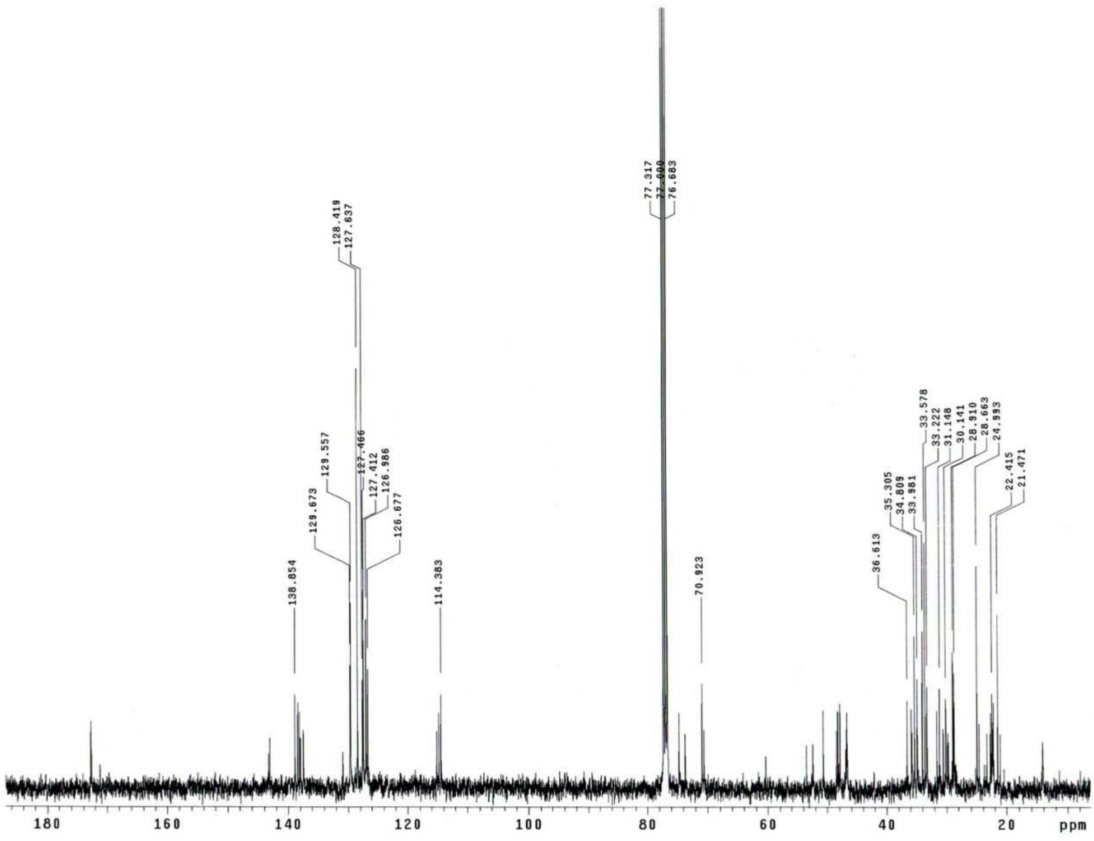
8
7
6
5
4
3
2
1
0 ppm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31.148
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28.663
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20
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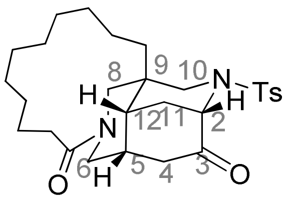


(madangamine numbering)

(2*S*,5*S*,9*R*,12*R*) Tetracyclic keto lactam 106.

Ring-closing metathesis reaction: A solution of compound **98** (202 mg, 0.326 mmol) in CH_2Cl_2 (1.3 L) was sparged with a flow of argon through a gas dispersion tube for 1 h. The solution was heated to reflux and then a solution of 1st generation Grubbs catalyst (27 mg, 0.0326 mmol) in CH_2Cl_2 (10 mL) was added in one portion through the septum. The solution was heated to reflux for 8 h under a flow of argon. DMSO (0.3 mL) was added, and the resulting solution was allowed to cool to room temperature over 12 h. The solvent was evaporated under reduced pressure. Flash chromatography filtration (8:2 to 1:1 hexane-EtOAc) of the residue afforded the unsaturated tetracyclic lactam **99** as a 2:1 mixture of *Z/E* isomers.

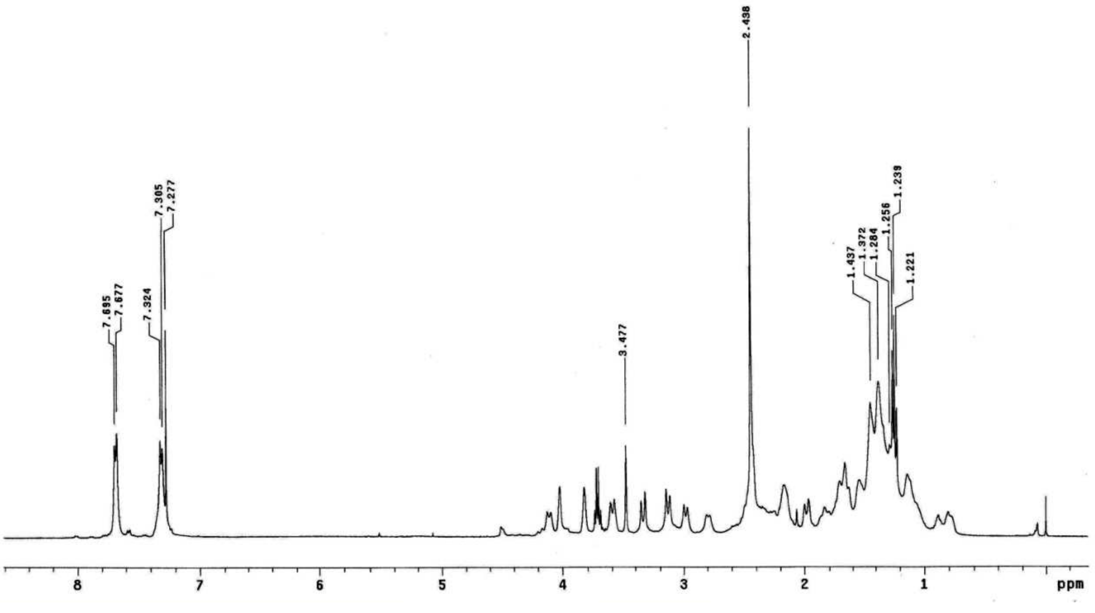
^{1}H NMR (400 MHz, $CDCl_3$, COSY, gHSQC, selected resonances, spectral data of the major isomer (*Z*) from a mixture of isomers): δ 1.36 (m, 1H, H-12), 1.46 (dm, *J* = 13.6 Hz, 1H, H-11), 1.78 (dm, *J* = 10.4 Hz, 1H, H-4), 1.84-2.22 (m, 10H, H-11, H-5, H-4, H-22), 2.44 (s, 3H, CH_3 Ts), 2.53 (m, 1H, H-22), 2.59 (d, *J* = 11.6 Hz, 1H, H-10ax), 2.99 (d, *J* = 11.6 Hz, 1H, H-10eq), 3.04 (d, *J* = 14.0 Hz, 1H, H-6ax), 3.20 (d, *J* = 11.6 Hz, 1H, H-8ax), 3.63 (m, 2H, H-2, H-8eq), 4.22 (m, 1H, H-3), 4.31 (d, *J* = 14.0 Hz, 1H, H-6eq), 4.57 (d, *J* = 11.6 Hz, 1H, CH_2 Bn), 4.64 (d, *J* = 11.6 Hz, 1H, CH_2 Bn), 5.13 (m, 2H, CH=), 7.26-7.36 (m, 7 H, C_6H_5, H-*m* Ts), 7.60 (d, *J* = 8.4 Hz, 2H, H-*o* Ts).

^{13}C NMR (100.6 MHz, $CDCl_3$): δ 21.0 (CH_3 Ts), 21.5 (C-11), 22.6 (CH_2), 25.6 (CH_2), 25.7 (CH_2), 27.6 (CH_2), 28.8 (CH_2), 29.0 (C-5), 30.5 (C-4), 30.9 (CH_2), 31.5 (CH_2), 31.9 (C-22), 36.0 (C-9), 38.4 (CH_2), 40.8 (C-6), 47.6, 49.4 (C-10, C-8), 50.6 (C-2), 71.6 (CH_2 Bn), 77.1 (C-3), 127.1 (C-*o, m, p* C_6H_5, C-*o*, *m* Ts), 131.6, 132.0 (C=), 133.6 (C-*p* Ts), 138.8 (C-*i* C_6H_5), 143.6 (C-*i* Ts), 174.5 (NCO).

HRMS (maldi) calcd for $[C_{35}H_{46}N_2O_4S + Na]^+$: 613.3, found: 613.3.

Hydrogenation step: Pd/C (100 mg, 50% in weight) was added to a solution of the above unsaturated lactam **99** (0.326 mmol) in a 9:1 EtOH-H_2O mixture (20 mL), and the resulting mixture was stirred under a hydrogen atmosphere at room temperature overnight to afford a saturated alcohol as a single product, which was immediately used in the subsequent step.

^{1}H NMR (400 MHz, $CDCl_3$, selected resonances): δ 1.38 (m, 1H, H-12), 1.63-1.79 (m, 3H, 2H-4, H-11), 1.86 (dm, *J* = 13.2 Hz, 1H, H-11), 2.04 (m, 1H, H-5), 2.13 (m, 2H, CH_2), 2.43 (s, 3H, CH_3 Ts), 2.79 (dd, *J* = 113.6, 4.4 Hz, 1H, H-6ax), 2.98 (d, *J* = 12.8 Hz, 1H, H-8ax), 3.13 (d, *J* = 124 Hz, 1H, H-10ax), 3.33 (d, *J* = 12.4 Hz, 1H, H-10eq), 3.59 (d, *J* = 12.8 Hz, 1H, H-8eq), 3.82(br. s, 1H, H-2), 4.02 (br. s, 1H, H-3), 4.10 (d, *J* = 13.6 Hz, 1H, H-6eq), 7.31 (d, *J* = 8.4 Hz, 2H, H-*m* Ts), 7.68 (d, *J* = 8.4 Hz, 2H, H-*o* Ts).



Oxidation step: Dess–Martin periodinane (414 mg, 0.97 mmol) was added to an ice-cold solution of the above alcohol in CH_2Cl_2 (20 mL), and the resulting mixture was stirred at room temperature for 4 h. The solution was poured into a saturated aqueous solution of $NaHCO_3$ and $Na_2S_2O_3$, and the mixture was stirred for 1 h and extracted with CH_2Cl_2. The combined organic extracts were dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. Flash chromatography (7:3 to 1:1 hexane-EtOAc) of the residue afforded ketone **106** (122 mg, 75% from diene **98**).

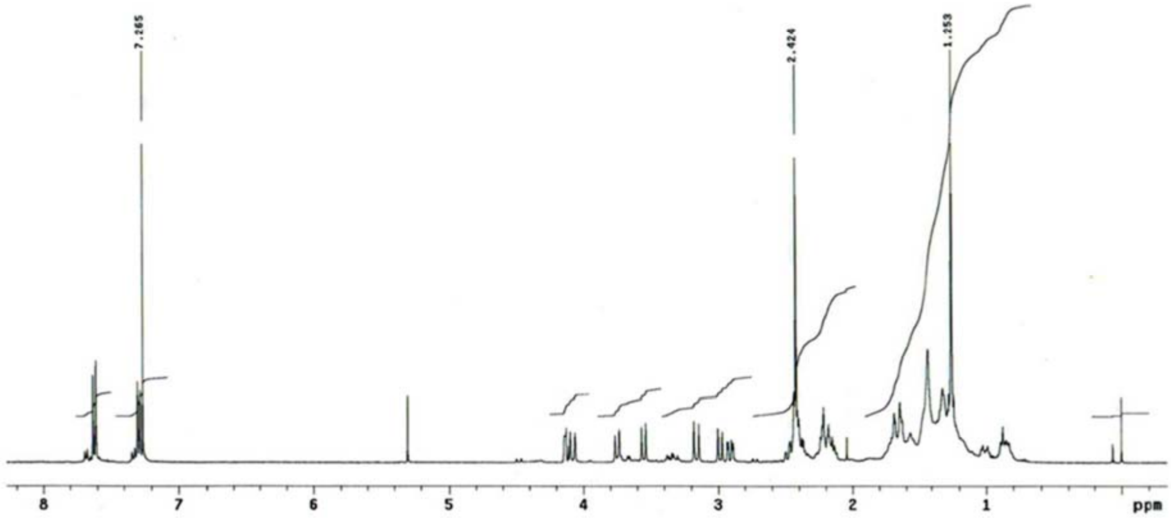
$[\alpha]_D^{22}$ = + 33.8 (*c* 1.4, $CHCl_3$).

IR (film): 1721, 1636 (C=O) cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$, COSY, gHSQC): δ 1.00 (m, 1H, H-31), 1.24-1.42 (m, 16H, CH_2), 1.50-1.65 (m, 2H, H-11, H-12), 2.10-2.22 (m, 4H, H-22, H-5, H-4, H-31), 2.35-2.50 (m, 3H, H-22, H-11, H-4), 2.42 (s, 3H, CH_3 Ts), 2.91 (dd, *J* = 12.8, 1.2 Hz, 1H, H-6ax), 2.98 (d, *J* = 13.2 Hz, 1H, H-10ax), 3.16 (d, *J* = 14.0 Hz, 1H, H-8ax), 3.54 (d, *J* = 13.2 Hz, 1H, H-10eq), 3.75 (d, *J* = 14.0, 1H, H-8eq), 4.08 (d, *J* = 12.8 Hz, 1H, H-6eq), 4.13 (m, 1H, H-2), 7.29 (d, *J* = 7.6 Hz, 2H, H-*m* Ts), 7.62 (d, *J* = 7.6 Hz, 2H, H-*o* Ts).

^{13}C NMR (100.6 MHz, $CDCl_3$): δ 20.7 (CH_2), 21.5 (CH_3 Ts), 22.7 (CH_2), 23.3 (CH_2), 24.1 (CH_2), 25.6 (CH_2), 26.3 (CH_2), 26.4 (CH_2), 27.3 (CH_2), 29.0 (C-11), 33.7 (C-22), 34.8 (CH_2), 35.8 (C-5), 36.6 (C-12), 38.0 (C-9), 43.2 (C-4), 45.2 (C-10), 45.8 (C-6), 50.9 (C-8), 57.4 (C-2), 127.8 (C-*o* Ts), 129.4 (C-*m* Ts), 134.6 (C-*p* Ts), 144.0 (C-*i* Ts), 174.0 (NCO), 205.4 (C=O).

HRMS (maldi) calcd for $[C_{28}H_{40}N_2O_4S + Na]^+$: 523.26, found: 523.30.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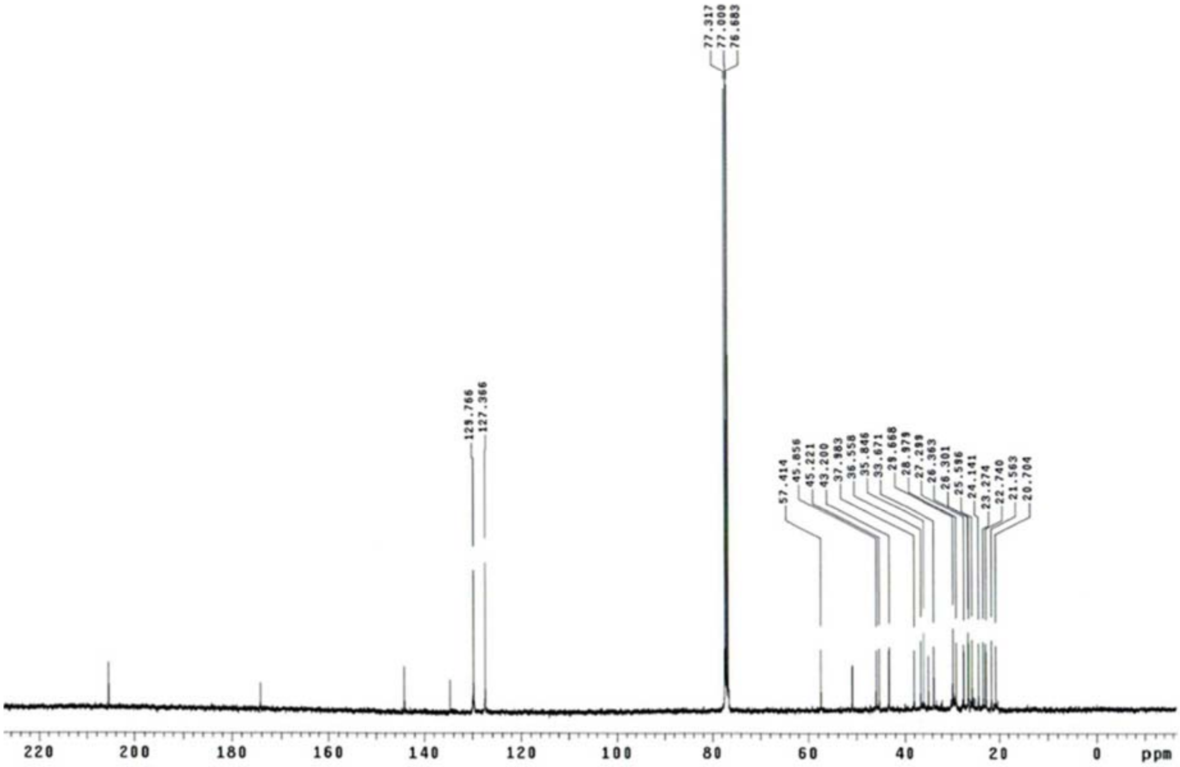
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24.141
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0
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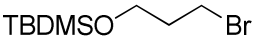
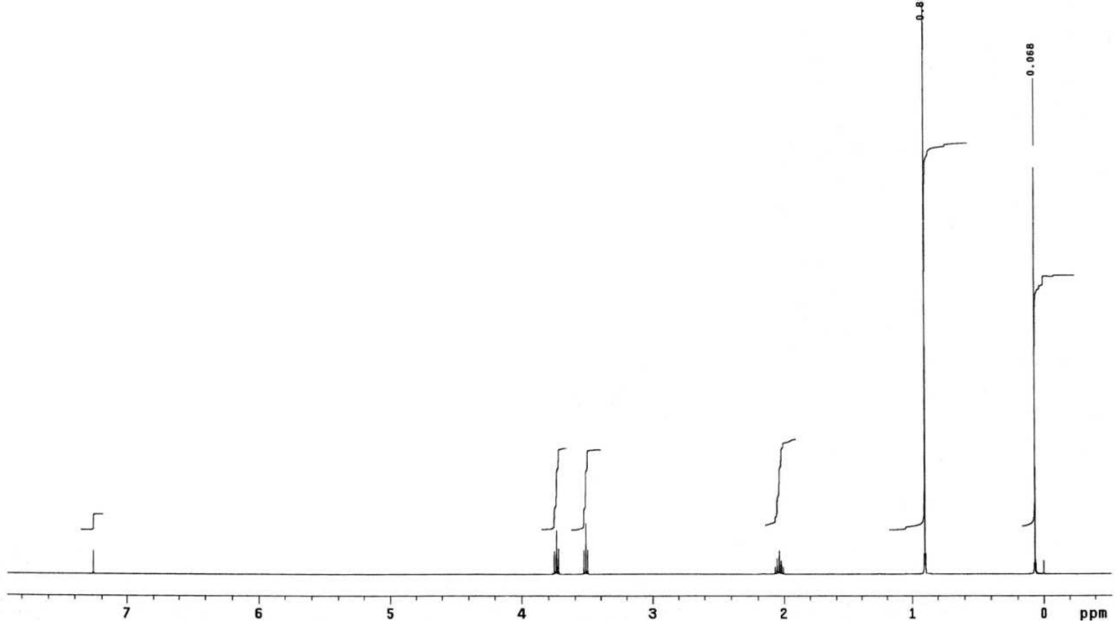


3-Bromo-1-(*tert*-butyldimethylsililoxy)propane (121).

Triethylamine (2.0 mL, 14.2 mmol), dimethylaminopiridine (67 mg, 0.52 mmol) and *tert*-butyldimethylsilane chloride (2.0 g, 13.2 mmol) were added to a solution of 3-bromopropanol (1.0 mL, 11 mmol) in anhydrous THF (16 mL) under inert atmosphere at room temperature. After 18 h stirring at room temperature, saturated NH_4Cl was added and the resulting mixture was extracted with CH_2Cl_2. The combined organic extracts were dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. Flash chromatography (hexane) gave protected alcohol **121** (253 mg, 99%) as colourless oil.

^{1}H RMN (400 MHz, $CDCl_3$): δ 0.07 (s, 6H, CH_3Si), 0.90 [s, 9H, $(CH_3)_3C$], 2.03 (m, 2H, H-2), 3.51 (t, *J* = 6.6 Hz, 2H, H-1), 3.73 (t, *J* = 5.4 Hz, 2H, H-3).

^{13}C NMR (100.6 MHz, $CDCl_3$): δ -5.4 ($2CH_3Si$), 18.3 [$(CH_3)_3\mathit{C}Si$], 25.9 [$(\mathit{C}H_3)_3CSi$], 30.7 (CH_2Br), 35.5 (CH_2), 60.4 (CH_2O).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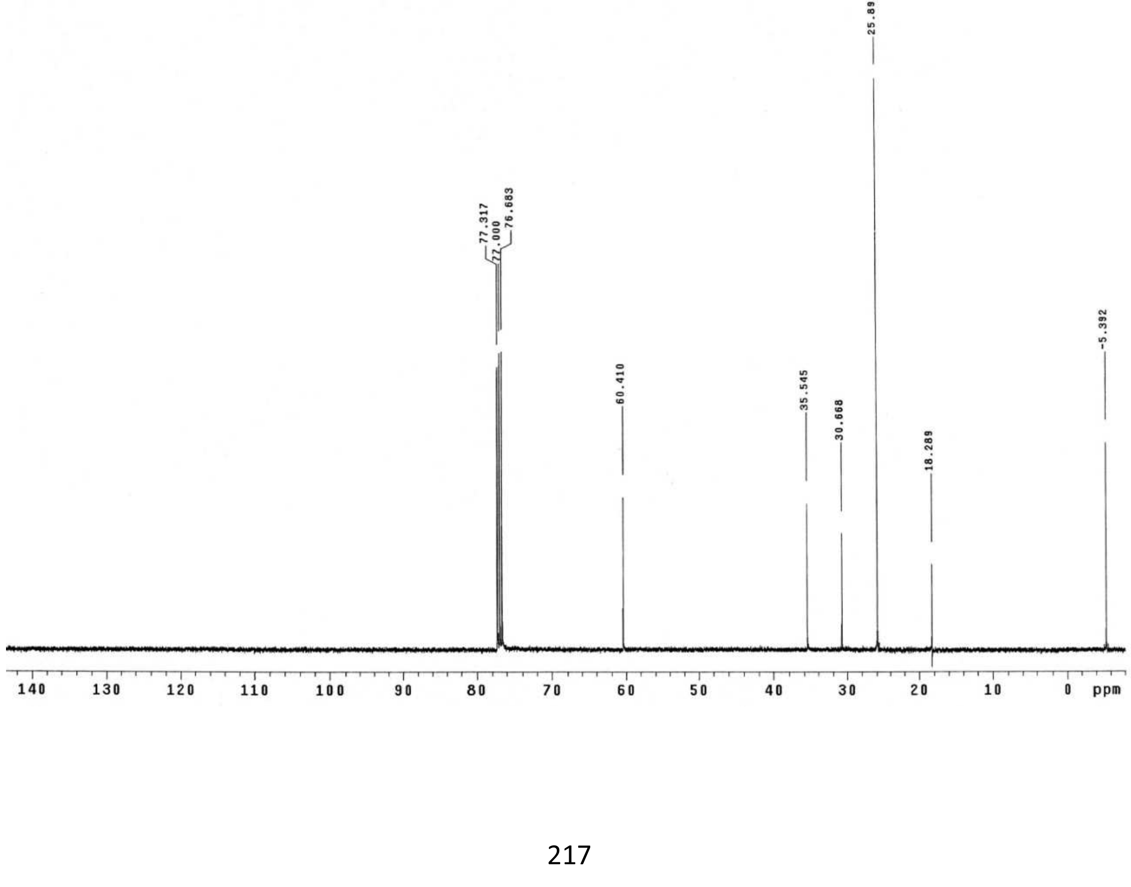
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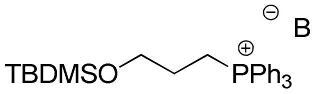
ppm



3-(*tert*-Butyldimethylsilyloxy)propyltriphenylphosphonium bromide (122).

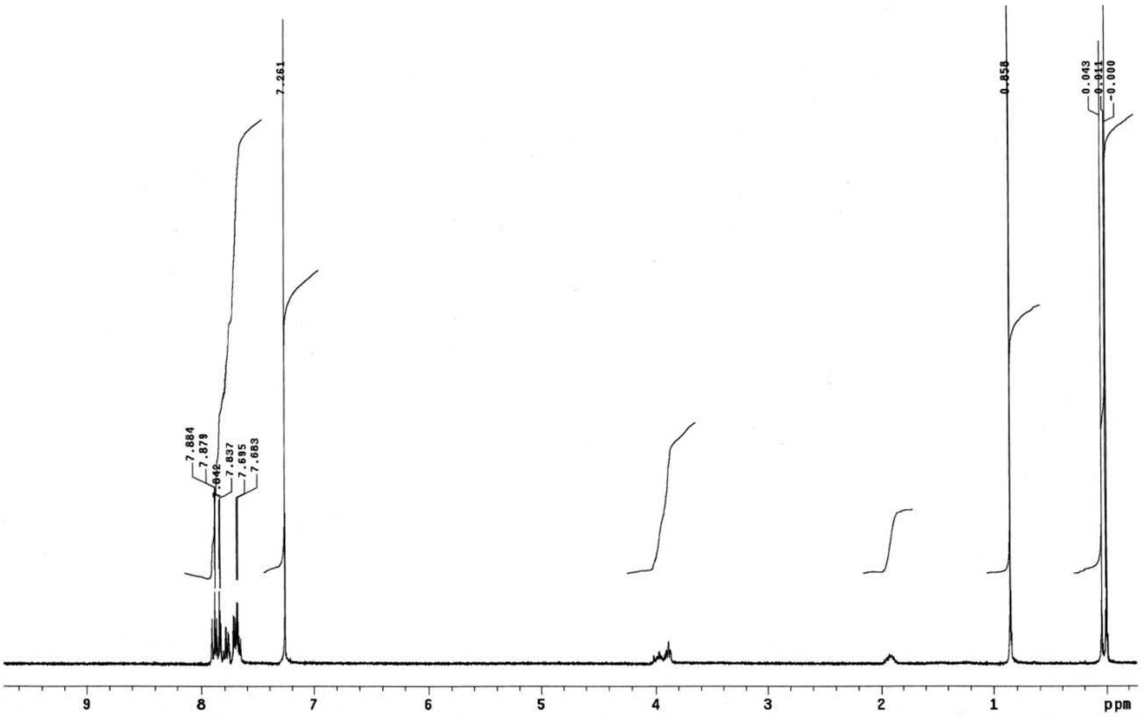
Triphenylphosphine (8.7 g, 33 mmol) was added to a solution of compound **121** (6.9 g, 28 mmol) in anhydrous benzene (5 mL) under argon atmosphere. The mixture was heated at 85 °C for 18 h and then was cooled to room temperature. Ether was added to the resulting solution and a white solid was formed. The residue was filtered and washed several times with ether. Flash chromatography of the resulting solid (CH_2Cl_2 to 96:4 CH_2Cl_2/MeOH) afforded phosphonium salt **122** (12 g, 84%).

^{1}H RMN (300 MHz, $CDCl_3$): δ 0.04 (s, 6H, CH_3Si), 0.85 [s, 9H, $(CH_3)_3C$], 1.95 (m, 2H, H-2), 3.98 (m, 4H, H-1, H-3), 7.69-7.90 (m, 15H, C_6H_5).

^{13}C NMR (100.6 MHz, $CDCl_3$): δ-5.3 ($2CH_3Si$), 18.2 [$(CH_3)_3\mathit{C}Si$], 18.7, 19.2 (CH_2P), 25.9 [$(\mathit{C}H_3)_3CSi$], 26.0, 26.1 (CH_2), 61.6, 61.8 (CH_2O), 118.0, 118.8 (C-*i* C_6H_5), 130.3-133.7 (C-*o*, *m* C_6H_5), 134.9 (C-*p* C_6H_5).

m.p. 216 °C

HRMS (ESI) calcd for $[C_{21}H_{22}OP - TBDMSi + H]^+$: 321.1403, found: 321.1398.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7
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3
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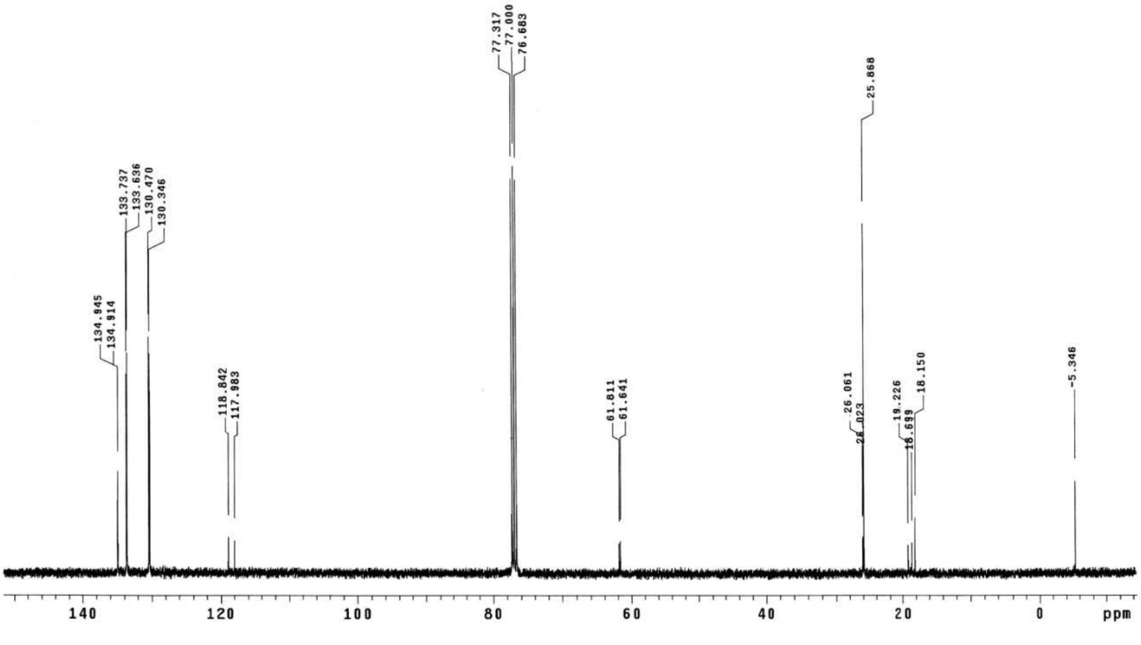
1
ppm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26.061
26.023
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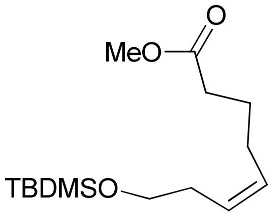


(*Z*)-Methyl 8-(*tert*-butyldimethylsilyloxy)-5-octenoate (124).

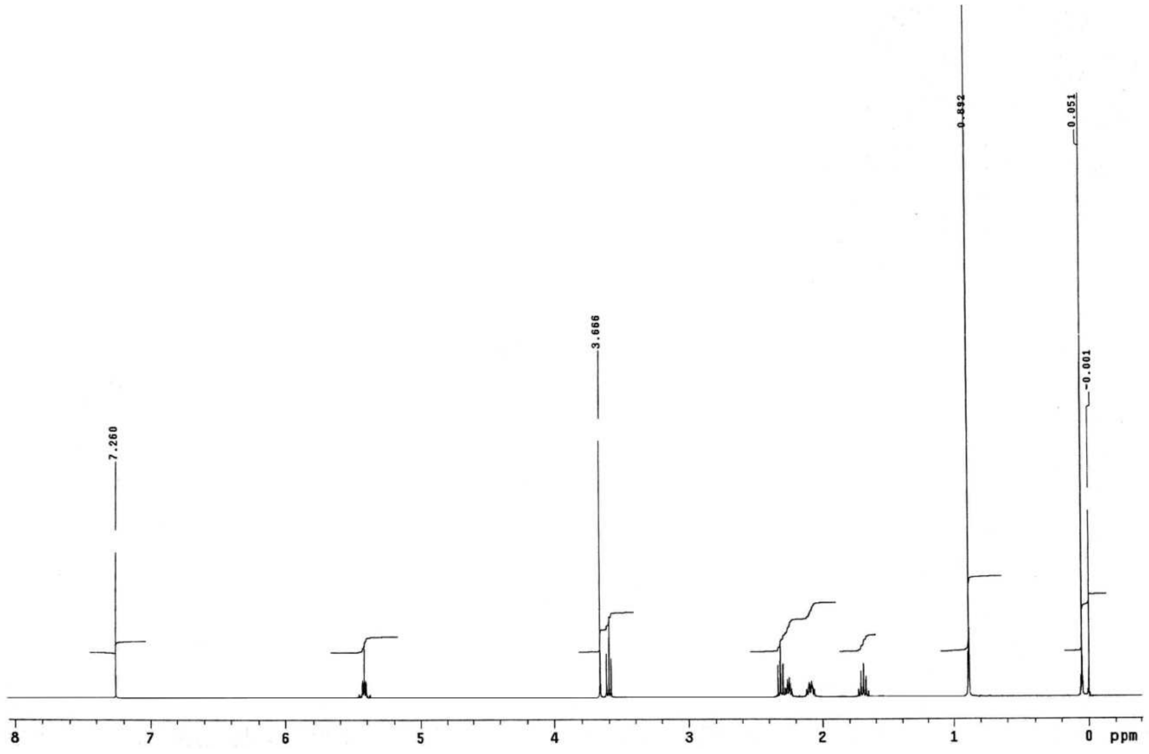
Sodium bis(trimethylsilyl)amide (8.75 mL of a solution 1M in THF, 8.75 mmol) was added dropwise to a solution of compound **122** (4.5 g, 8.75 mmol) in a mixture of solvents formed by THF (99 mL) and toluene (22 mL) at –30 °C under inert atmosphere and the resulting mixture was stirred at room temperature for 4 h. A solution of methyl 4-formylpentanoate **123** (2.2 g, 17.5 mmol) in THF (15 mL) was then added at −78 °C and the mixture was stirred at the same temperature overnight. The reaction was quenched with saturated aqueous NH_4Cl, and the resulting solution was extracted with EtOAc. The combined organic extracts were dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. Flash chromatography (hexane to 8:2 hexane-EtOAc) afforded compound **124** (1.94 g, 78%).

IR (film): 1742 (COO) cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$, COSY, gHSQC): δ 0.05 (s, 6H, CH_3Si), 0.89 [s, 9H, $(CH_3)_3CSi$], 1.69 (m, 2H, 2H-3), 2.08 (m, 2H, 2H-4), 2.25 (m, 2H, 2H-7), 2.31 (t, *J* = 8.0 Hz, 2H, 2H-2), 3.60 (t, *J* = 6.4 Hz, 2H, CH_2OSi), 3.67 (s, 3H, CH_3O), 5.40 (m, 2H, H-5, H-6).

^{13}C NMR (75.4 MHz, $CDCl_3$): δ - 5.3 (CH_3Si), 18.3 [$(CH_3)_3CSi$], 24.8 (C-3), 25.9 [$(CH_3)_3CSi$], 26.7 (C-4), 31.1 (C-7), 33.5 (C-2), 51.5 (CH_3O), 62.9 (C-8), 126.9, 130.3 (C-5, C-6), 174.1 (NCO).

HRMS (ESI) calcd for $[C_{15}H_{30}O_3Si + H]^+$: 287.2000, found: 287.2042.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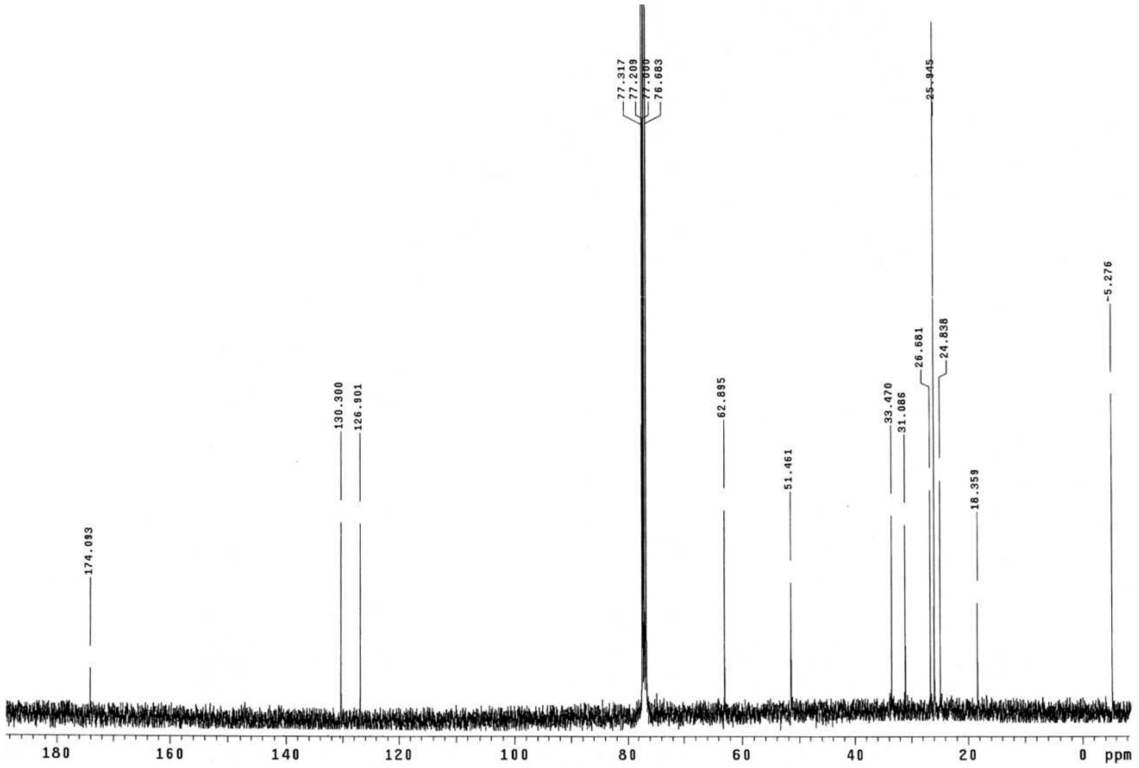
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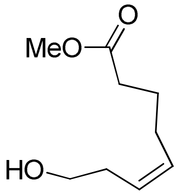


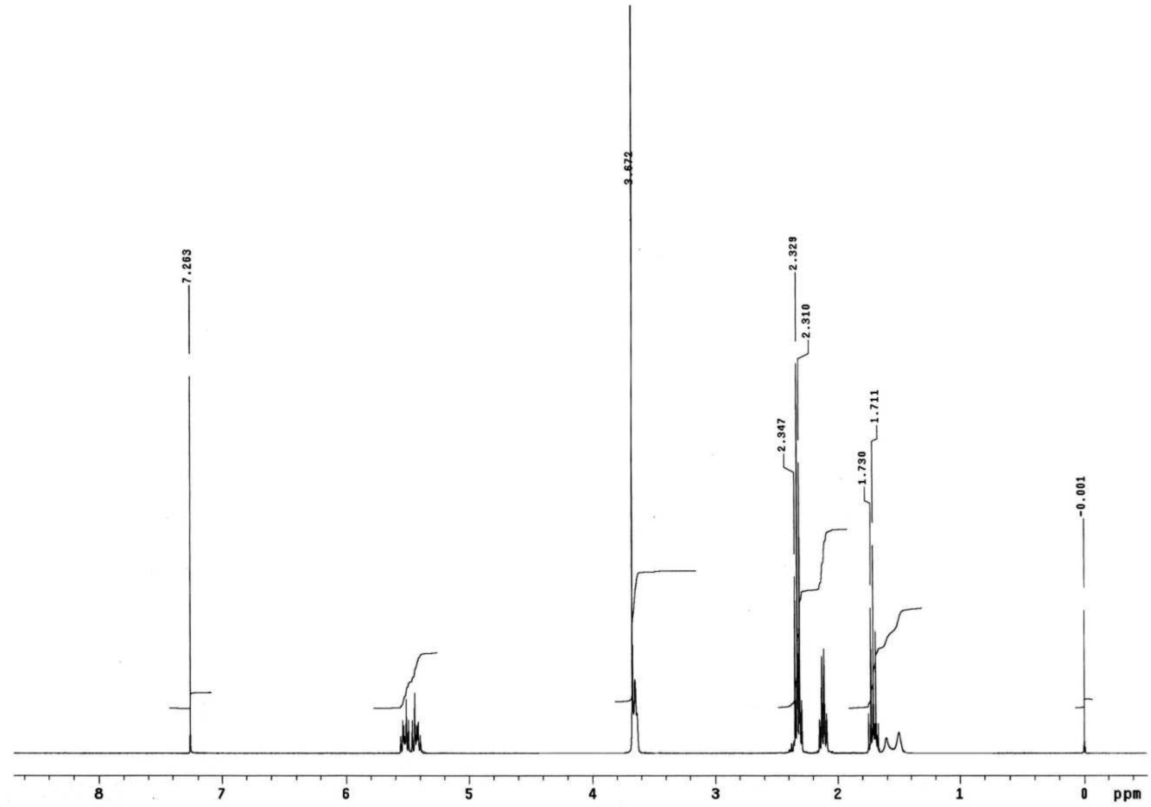
(*Z*)-Methyl 8-hydroxy-5-octenoate (125).

TBAF (1.94 mL of a solution 1 M in THF, 1.94 mmol) was added at 0 °C to a solution of silyl derivative **124** (275 mg, 0.97 mmol) in THF (15 mL) under inert atmosphere and the resulting mixture was stirred overnight at room temperature. The reaction was quenched with saturated aqueous $NaHCO_3$, and the resulting mixture was extracted with EtOAc. The combined organic extracts were dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. Flash chromatography (8:2 to 7:3 hexane-EtOAc) afforded compound **125** (153 mg, 93%).

IR (film): 3465 (OH), 1732 (COO) cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$, COSY, gHSQC): δ 1.71 (m, 2H, H-3), 2.11 (m, 2H, H-4), 2.30 (t, *J* = 6.0 Hz, 2H, H-7), 2.33 (t, *J* = 7.2 Hz, 2H, H-2), 2.65 (t, *J* =6.4 Hz, 2H, C*H*$_2$OH), 3.67 (s, 3H, CH_3O), 5.39-5.55 (2m, 2H, H-5, H-6).

^{13}C-NMR (100.6 MHz, $CDCl_3$): δ 24.8 (C-3), 28.6 (C-4), 30.8 (C-7), 33.4 (C-2), 51.5 (CH_3O), 62.2 (CH_2OH), 126.5(C-6), 131.8 (C-5), 174.1 (NCO).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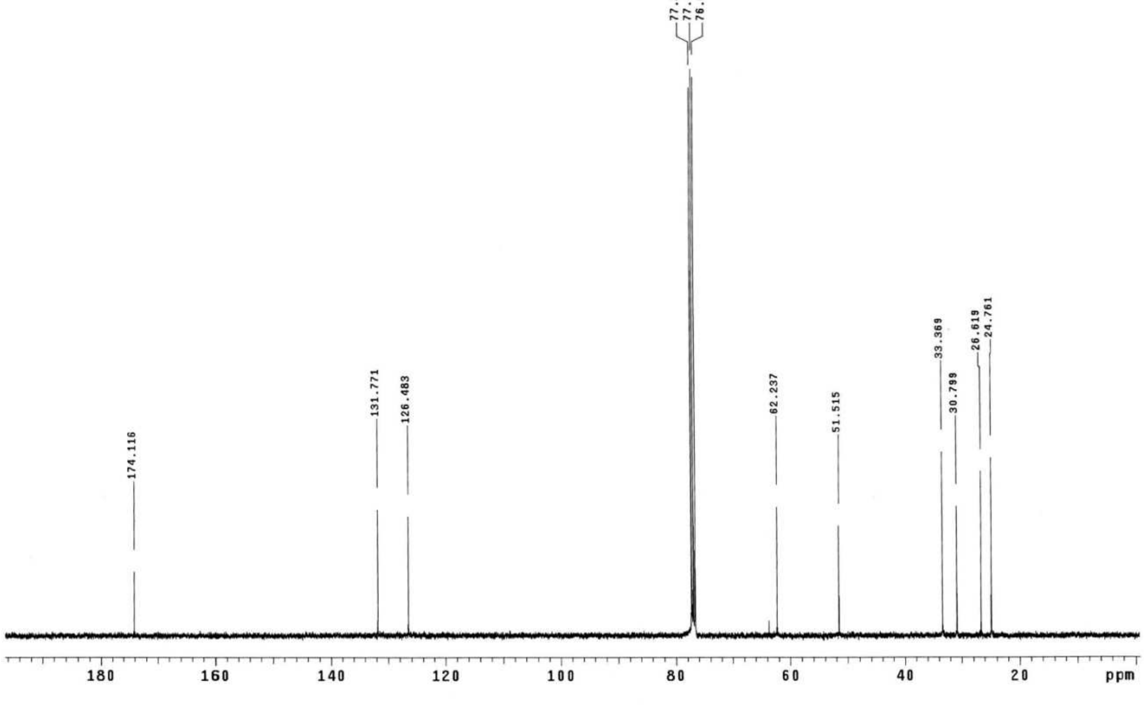
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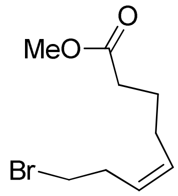


(*Z*)-Methyl 8-(*tert*-butyldimethylsilyloxy)-5-octenoate.

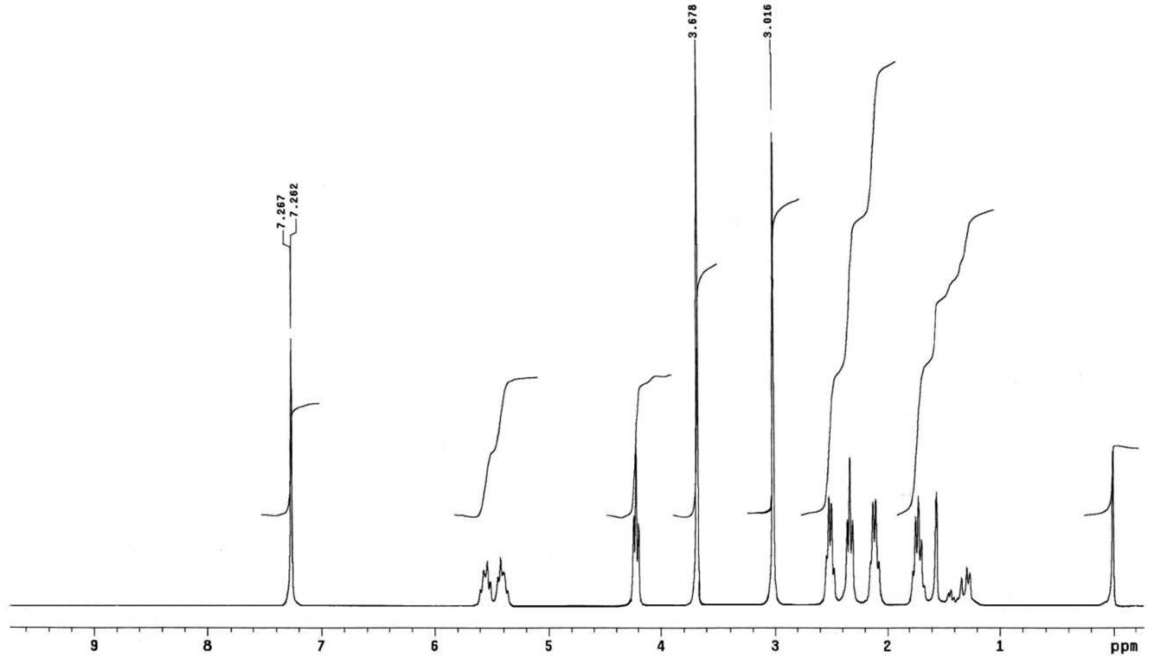
Mesylation step: Triethylamine (190 µL, 1.35 mmol) and mesyl chloride (130 µL, 1.8 mmol) were added dropwise to a solution of alcohol **125** (153 mg, 0.9 mmol) in anhydrous CH_2Cl_2 (12 mL) cooled to 0 °C. After the end of addition, the mixture was allowed to heat slowly to room temperature and was stirred for additional 2 h. Saturated aqueous NH_4Cl was added, and the mixture was extracted with CH_2Cl_2. The combined organic layers were dried over anhydrous Na_2SO_4, filtered, and the solvent was removed under reduced pressure. Flash chromatography (6:4 to 1:1 hexane-EtOAc) afforded the mesyl derivative (239 mg, 99% yield).

Bromination step: A solution of LiBr (2.9 g, 33.3 mmol) in THF (13 mL) was added to a solution of the above crude (818 mg, 3.33 mmol) in CH_2Cl_2 (9.3 mL) at 0 °C under inert atmosphere. The resulting mixture was stirred overnight at room temperature. Distilled water was added, and the mixture was extracted with CH_2Cl_2. The combined organic layers were dried over anhydrous Na_2SO_4, filtered, and the solvent was removed under reduced pressure. Flash chromatography (hexane to 3:7 hexane-EtOAc) afforded bromo derivative (374 mg, 75% yield).

IR (film): 1730 (COO) cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ 1.71 (m, 2H, 2H-3), 2.14 (m, 2H, 2H-4), 2.36 (t, *J* = 7.2 Hz, 2H, 2H-2), 2.55 (qd, *J* = 7.2, 1.2 Hz, 2H, 2H-7), 3.01 (s, 3H, CH_3SO_2), 3.67 (s, 3H, CH_3O), 4.21 (t, *J* = 6.8 Hz, 2H, 2H-8), 5.41 (m, 1H, CH=), 5.56 (m, 1H, CH=).

^{13}C NMR (100.6 MHz, $CDCl_3$): δ 24.5 (C-3), 26.6, 27.3 (C-4, C-7), 32.2 (C-8), 37.4 (CH_3SO_2), 51.5 (CH_3O), 69.0 (C-2), 123.9 (C-6), 132.6 (C-5), 173.8 (NCO).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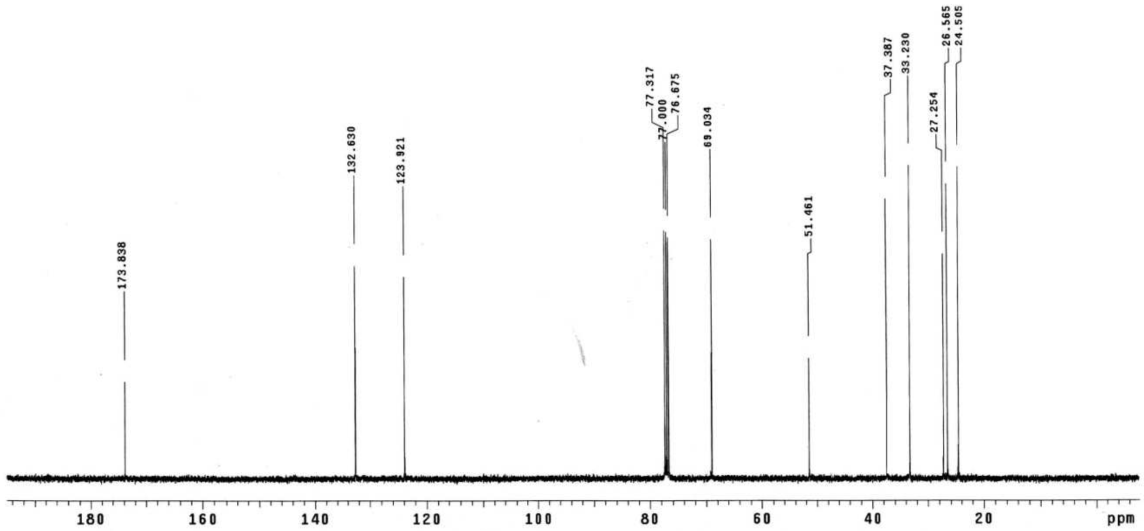
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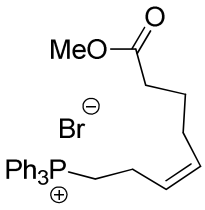
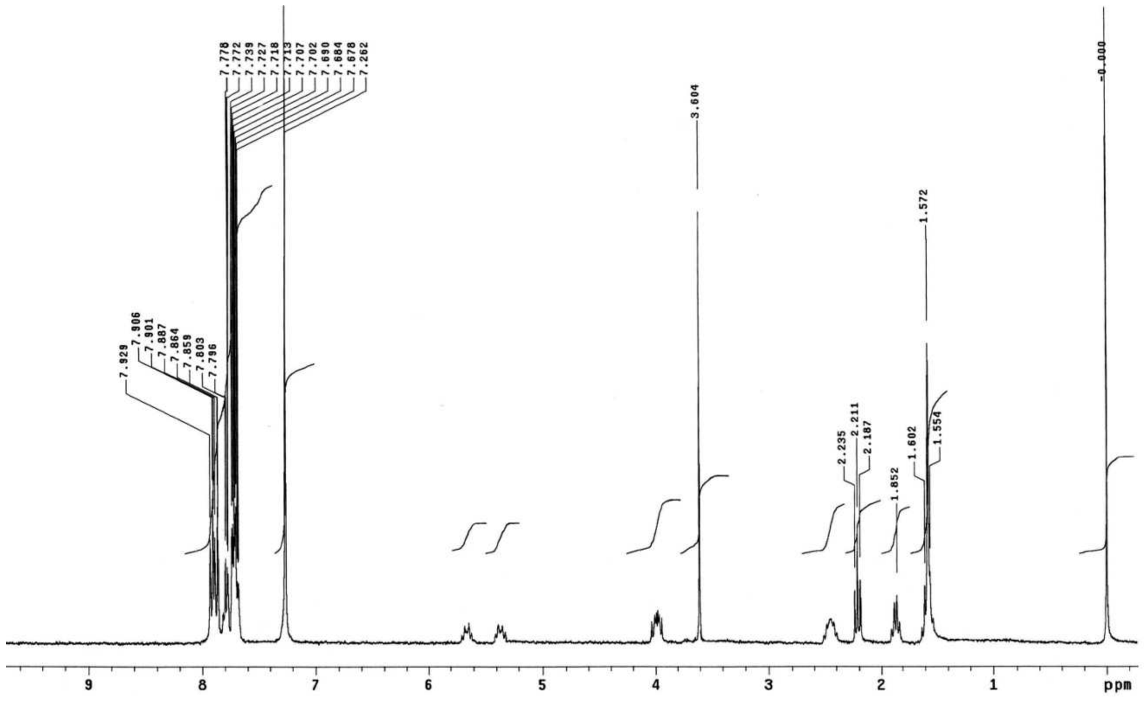


(*Z*)[-8-(Methoxycarbonyl)-3-octen-1-yl]triphenylphosphonium bromide (126).

Triphenylphosphine (113 mg, 0.43 mmol) was added to a solution of the above bromo derivative (100 mg, 0.43 mmol) in anhydrous benzene (1.2 mL) under argon atmosphere. The mixture was heated at 85 °C for 18 h, then was cooled to room temperature and concentrated under reduced pressure. Flash chromatography (hexane to 1:9 hexane-CH_2Cl_2 and then CH_2Cl_2 to 96:4 CH_2Cl_2/MeOH) afforded phosphonium salt **126** (200 mg, 94%).

^{1}H NMR (400 MHz, $CDCl_3$): δ 1.57 (m, 2H, 2H-3), 1.85 (q, *J* = 7.6 Hz, 2H, 2H-4), 2.21 (t, *J* = 7.2 Hz, 2H, 2H-2), 2.43 (m, 2H, 2H-7), 3.60 (s, 3H, CH_3O), 4.00 (m, 2H, 2H-8), 5.38 (m, 1H, CH=), 5.65 (m, 1H, CH=), 7.67-7.92 (m, 15H, C_6H_5).

^{13}C NMR (100.6 MHz, $CDCl_3$): δ 20.3 (C-2), 23.2 (C-1), 24.4 (C-6), 26.5 (C-5), 33.2 (C-7), 51.4 (CH_3O), 117.9, 118.8 (C-*i* C_6H_5), 127.2, 127.4 (CH=), 130.4, 130.5, 133.7, 133.8 (C-*o*, *m* C_6H_5), 131.0 (CH=), 134.9, 135.0 (C-*p* C_6H_5), 173.9 (NCO).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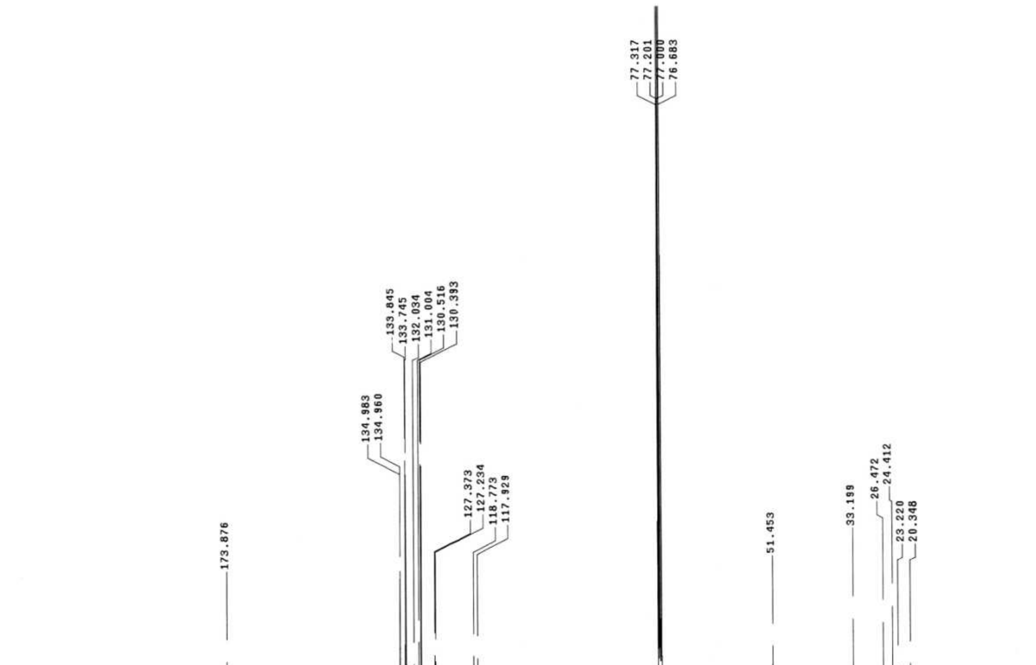
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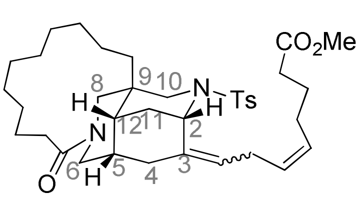
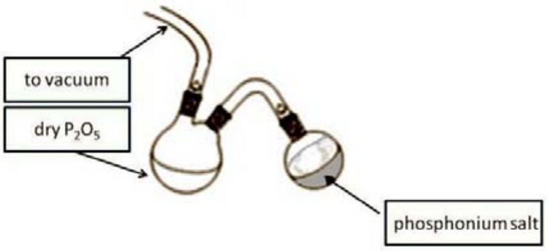


(madangamine numbering)



(2*S*,5*S*,9*R*,12*R*) Tetracyclic derivative 136-137.

(*Z*)-(8-Methoxy-8-oxo-3-octenyl)triphenylphosphonium bromide (**126**)[134] was dried by repeated dilution with anhydrous 1:1 THF-toluene and concentration under reduced pressure, followed by overnight storing under vacuum over a phosphorus pentoxide system[135] (see illustration). Sodium bis(trimethylsilyl)amide (1.03 mL of a 1 M solution in THF, 1.03 mmol) was added to a solution of this phosphonium salt (566 mg, 1.14 mmol) in anhydrous THF (2.0 mL) under an inert atmosphere at 0 °C. After 1 h of stirring at this temperature, a solution of tetracyclic ketone **106** (173 mg, 0.346 mmol) in anhydrous THF (1.0 mL) was added, and the resulting mixture was stirred at 0 °C for 1 h, at room temperature for 90 min, and at 60 °C for 2 h. The reaction was quenched with a saturated aqueous NH_4Cl. The mixture was extracted with EtOAc, and the combined organic extracts were dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. Flash chromatography (hexane to 7:3 hexane-EtOAc) of the residue gave an inseparable mixture of isomers of compounds **136-137** (155 mg, *E/Z* 2.2:1 ratio, 70%).

Major isomer (spectral data from a mixture of isomers):

IR (film): 1733, 1638 (C=O) cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$, COSY, gHSQC): δ 0.80 (m, 1H, H-31), 1.10-1.39 (m, 14H, H-11, CH_2), 1.49 (m, 3H, H-12, CH_2), 1.62 (m, 3H, H-15, CH_2), 1.88 (m, 1H, H-5), 2.01-2.10 (m, 5H, 2H-22, 2H-16, H-4), 2.13 (m, 1H, H-31), 2.21 (m, 1H, H-11), 2.25 (t, *J* = 7.6 Hz, 2H, H-14), 2.34 (s, 3H, CH_3 Ts), 2.35 (m, 1H, H-4), 2.61 (dd, *J* = 13.6, 3.6 Hz, 1H, H-6ax), 2.67 (m, 1H, H-19), 2.86 (m, 1H, H-19), 2.87 (d, *J* = 13.6 Hz, 1H, H-8ax), 2.98 (d, *J* = 12.4 Hz, 1H, H-10ax), 3.45 (d, *J* = 12.4 Hz, 1H, H-10eq), 3.55 (d, *J* = 13.6 Hz, 1H, H-8eq), 3.60 (s, 3H, CH_3O), 4.17 (d, *J* = 13.6 Hz, 1H, H-6),

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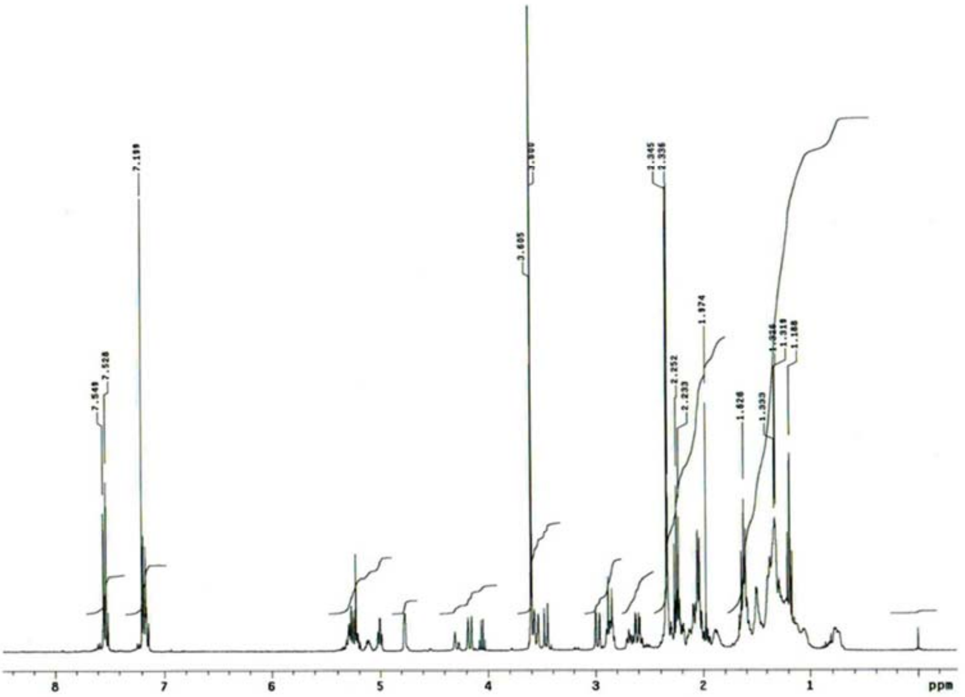
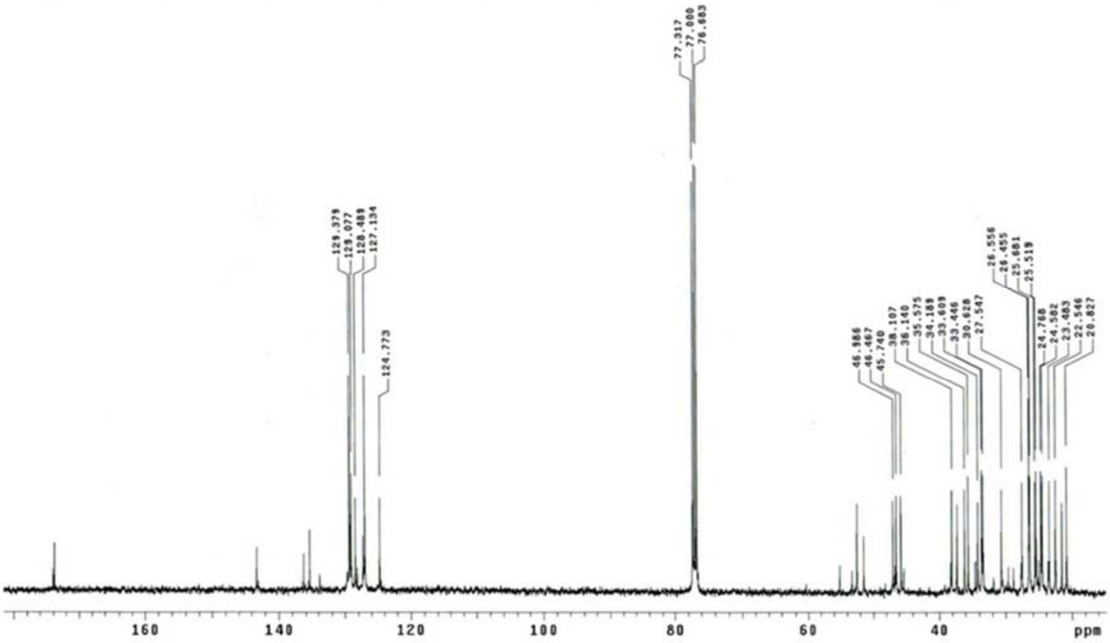
[134] Sandri, J.; Viala, J. *J. Org. Chem*. **1996**, *60*, 6627–6630.

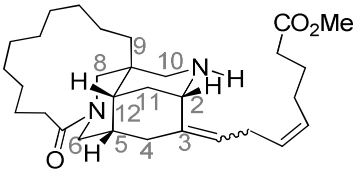
[135] Christiansen, M. A.; Andrus, M. B. *Tetrahedron Lett.* **2012**, *53*, 4805–4808.

4.76 (m, 1H, H-2), 5.00 (tm, *J* = 7.6 Hz, 1H, H-20), 5.21-5.32 (m, 2H, H-17, H-18), 7.17 (d, *J* = 8.4 Hz, 2H, H-*m* Ts), 7.53 (d, *J* = 8.4 Hz, 2H, H-*o* Ts).

^{13}C NMR (100.6 MHz, CDCl$_3$): δ 20.8 (CH$_2$), 21.5 (CH$_3$ Ts), 22.5 (CH$_2$), 23.5 (CH$_2$), 24.6 (CH$_2$), 24.8 (CH$_2$), 25.5 (C-19), 25.7 (CH$_2$), 26.4 (CH$_2$), 26.6 (C-16, CH$_2$), 27.5 (CH$_2$), 30.6 (C-11), 33.5 (C-14), 33.6 (C-4), 34.1 (C-31), 35.6 (C-5), 36.1 (C-22), 37.3 (C-9), 38.1 (C-12), 45.7 (C-10), 46.5 (C-6), 46.9 (C-2), 51.5 (CH$_3$O), 52.6 (C-8), 124.8 (C-20), 127.1 (C-*o* Ts), 128.5, 129.1 (C-17, C-18), 129.4 (C-*m* Ts), 135.4, 136.3 (C-*p* Ts, C-3), 143.2 (C-*i* Ts), 173.8 (NCO, COO).





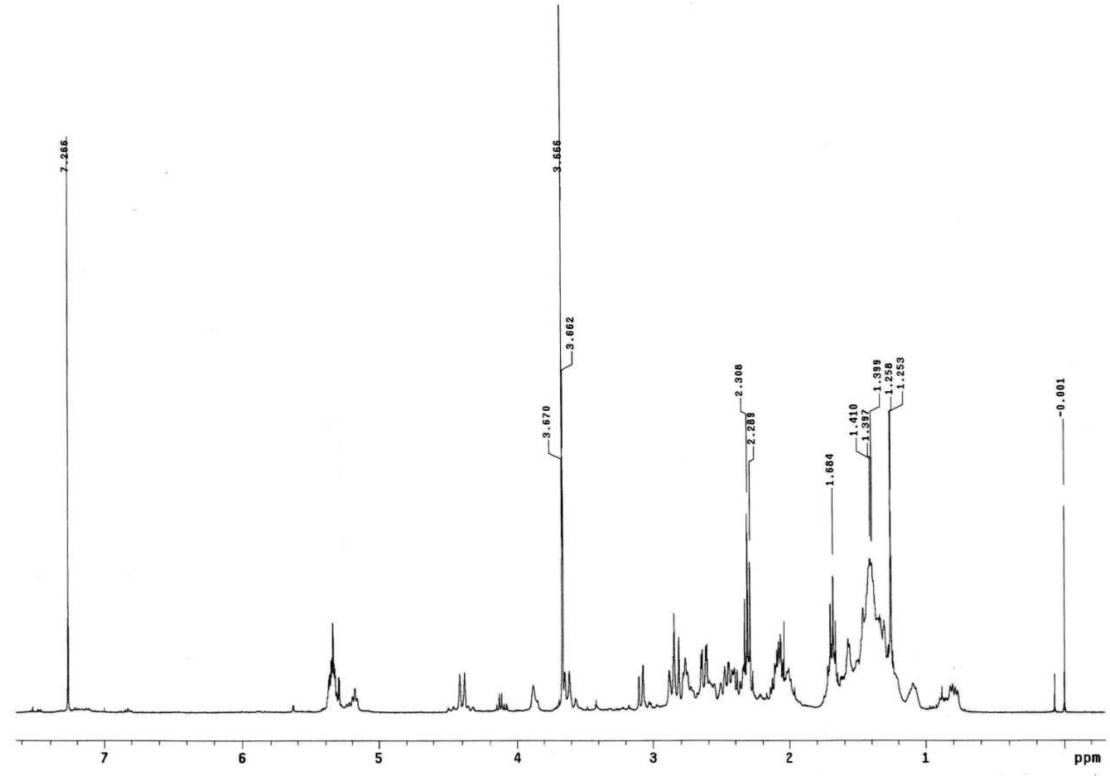


(madangamine numbering)

(2*S*,5*S*,9*S*,12*R*) Tetracyclic secondary amine.

Sodium metal (192 mg, 8.02 mmol) was added at room temperature to a solution of naphthalene (534 mg, 4.16 mmol) in THF (12 mL). After stirring for 2 h, part of the mixture (2.44 mL) was added at –78 °C to a solution of the above tosyl derivatives **136-137** (120 mg, 0.188 mmol) in THF (4.5 mL). After 10 min at –78 °C, a few drops of saturated aqueous NH_4Cl were carefully added, and the resulting solution was dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure. Flash chromatography (1:1 hexane-EtOAc to EtOAc) of the residue afforded the secondary amine (62 mg, 68%).

^{1}H NMR (400 MHz, $CDCl_3$, selected resonances): δ 0.85 (m, 1H, H-31), 1.68 (t, *J* = 7.6 Hz, 2H, H-15), 2.31 (t, *J* = 7.6 Hz, 2H, H-14), 2.64 (dd, *J* = 13.2, 2.8 Hz, H, H-6ax), 2.77 (m, 1H, H-19), 2.84 (d, *J* = 12.4Hz, 1H, H-10ax), 2.86 (d, *J* = 13.6 Hz, 1H, H-8ax), 3.08 (d, *J* = 12.4 Hz, 1H, H-10eq), 3.65 (d, *J* = 13.6 Hz, 1H, H-8eq), 3.66 (s, 3H, CH_3O), 3.81 (br. s, 1H, H-2), 4.40 (d, *J* = 13.2 Hz, 1H, H-6eq), 5.20 (br. t, *J* = 6.4 Hz, 1H, H-20), 5.35 (m, 2H, H-17, H-18).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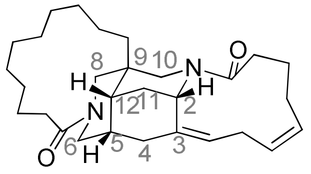
ppm



(madangamine numbering)

Pentacyclic dilactam (138).

First step: An aqueous solution of LiOH (1 M, 3.7 mL, 3.7 mmol) was added to a solution of the above secondary amine (45 mg, 0.092 mmol) in anhydrous THF (3 mL), and the resulting mixture was stirred at room temperature for 3.5 h. The reaction was quenched by addition of saturated aqueous NaCl, and the solution was extracted with EtOAc. The combined organic extracts were dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure to afford the corresponding acid, which was used in the next step without purification.

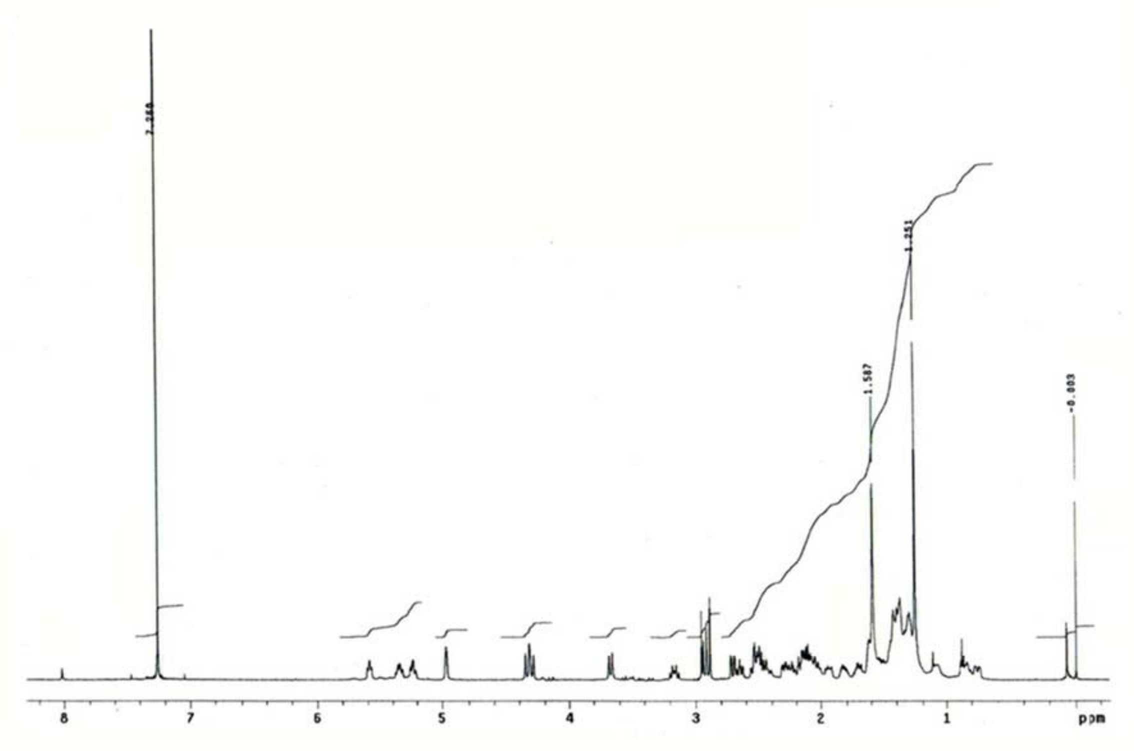
Second step: A solution of the above amino acid (0.092 mmol) in a 9:1 CH_2Cl_2-DMF mixture (3.1 mL) was slowly added with a syringe pump (6 h) to a solution of EDCI (84 mg, 0.441 mmol) and HOBt (60 mg, 0.441 mmol) in 9:1 CH_2Cl_2-DMF (1.5 mL). The mixture was stirred overnight at room temperature, and the resulting solution was then concentrated under reduced pressure. Flash chromatography (9:1 to 6:4 hexane-EtOAc) of the residue afforded pentacyclic dilactam **138** (31 mg, 75%).

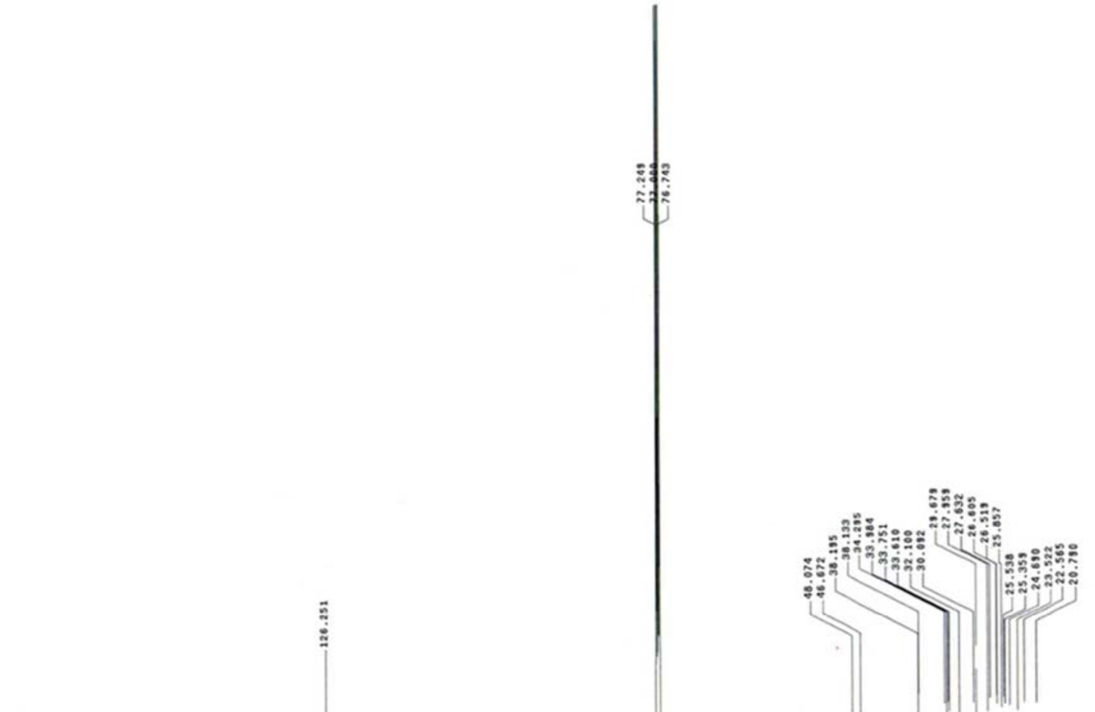
$[\alpha]_D^{22}$ = + 44.0 (*c* 3.5, $CHCl_3$).

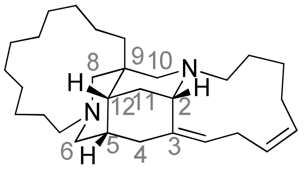
^{1}H NMR (500 MHz, $CDCl_3$, COSY, gHSQC): δ 0.75 (dm, *J* = 14.0 Hz, 1H, H-31), 1.20-1.50 (m, 15H, CH_2, H-11), 1.60 (m, 2H, H-12, CH_2), 1.64 (m, 1H, CH_2), 1.80 (m, 1H, CH_2), 1.90 (m, 1H, CH_2), 1.90 (m, 1H, H-31), 2.00-2.15 (m, 6H, H-5, CH_2), 2.20 (m, 1H, H-11), 2.28 (ddd, *J* = 14.0, 12.0, 3.5 Hz, 1H, H-16), 2.40-2.55 (m, 3H, H-19, 2H-4), 2.60 (ddd, *J* = 14.0, 10.5, 3.5 Hz, 1H, H-16), 2.69 (dd, *J* = 13.5, 3.5 Hz, 1H, H-6), 2.88-3.00 (m, 2H, H-8, H-10), 3.16 (dt, *J* = 15.0, 9.5 Hz, 1H, H-19), 3.65 (d, *J* = 13.5 Hz, 1H, H-10), 4.32 (d, *J* = 13.5 Hz, 1H, H-6), 4.36 (d, *J* = 14.5 Hz, 1H, H-8), 4.97 (br. s, 1H, H-2), 5.20 (td, *J* = 10.5, 4.5 Hz, 1H, H-18), 5.40 (m, 1H, H-17), 5.60 (t, *J* = 8.5 Hz, 1H, H-20).

^{13}C NMR (125 MHz, $CDCl_3$): δ 20.8 (CH_2), 22.6 (CH_2), 23.5 (CH_2), 24.7 (CH_2), 25.4 (CH_2), 25.5 (CH_2), 25.8 (C-19), 26.5 (CH_2), 26.6 (CH_2), 27.6 (CH_2), 27.9 (CH_2), 30.0 (C-11), 32.1 (C-16), 33.6 (CH_2), 33.7 (C-4), 34.0 (C-31), 34.2 (C-5), 38.1 (C-9), 38.2 (C-12), 41.9 (C-10), 46.7 (C-6), 48.1 (C-2), 53.0 (C-8), 126.2 (C-20), 128.0, 128.1 (C-17, C-18), 136.1 (C-3), 174.0, 174.1 (2NCO).

HRMS (ESI) calcd for $[C_{29}H_{44}N_2O_2 + H]^+$: 453.3476, found: 453.3467.







(madangamine numbering)

Madangamine D.

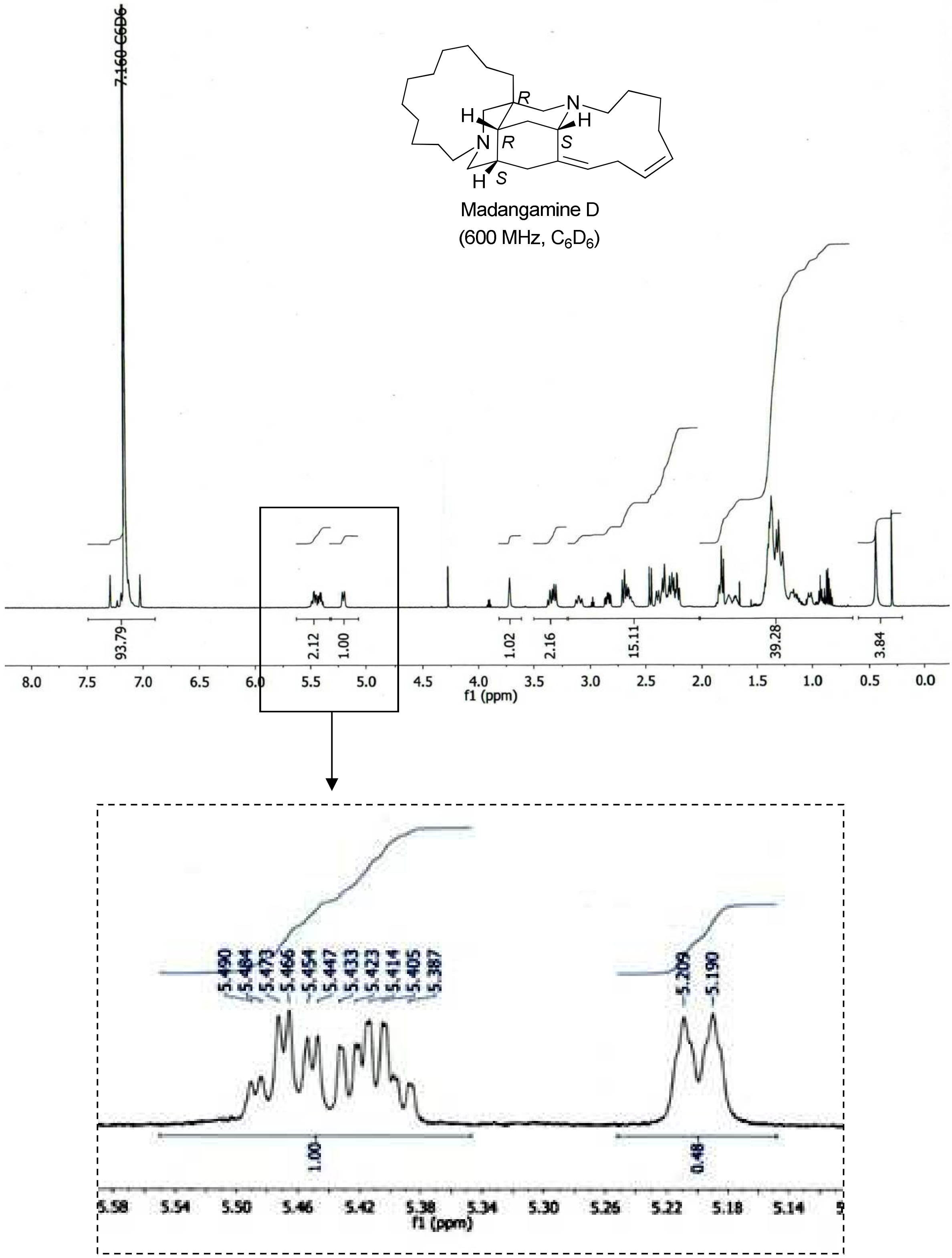
$LiAlH_4$ (9 mg, 0.268 mmol) was added under an argon atmosphere to a solution of pentacyclic dilactam **138** (20 mg, 0.044 mmol) in anhydrous THF (2 mL). The resulting mixture was stirred at 0 °C for 40 minutes and at room temperature for 3 hours. The mixture was cooled, and the reaction was quenched with a few drops of distilled water. The resulting suspension was dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure. Flash chromatography (hexane to 8:2 hexane-EtOAc) of the residue afforded pure madangamine D (13 mg, 68%).

$[\alpha]_D^{22}$ = + 101.3 (*c* 0.29, $CHCl_3$).

^1H NMR (600 MHz, C_6D_6, COSY, gHSQC): δ 1.01 (dm, *J* = 14.0 Hz, 1H, H-31), 1.20-1.45 (m, 23H, CH_2, H-11, H-12), 1.69 (m, 1H, H-14), 1.75 (m, 1H, H-5), 1.79 (d, *J* = 11.2 Hz, 1H, H-8), 1.80 (m, 1H, H-16), 2.19 (dd, *J* = 11.2, 3.6 Hz, 1H, H-6), 2.20-2.30 (m, 4H, H-31, H-16, H-4, H-21), 2.33 (m, 2H, H-19, H-6), 2.38 (dt, *J* = 12.6, 3.6 Hz, 1H, H-11), 2.45 (d, *J* = 12.0 Hz, 1H, H-10), 2.61 (m, 1H, H-13), 2.66 (m, 1H, H-21), 2.69 (d, *J* = 11.2 Hz, 1H, H-8), 2.82 (ddd, *J* = 14.0, 11.2, 6.0 Hz, 1H, H-13), 3.09 (tm, *J* = 13.2 Hz, 1H, H-4), 3.30 (d, *J* = 12.0 Hz, 1H, H-10), 3.35 (t, *J* = 13.2 Hz, 1H, H-19), 3.71 (br. s, 1H, H-2), 5.20 (dm, *J* = 12.0 Hz, 1H, H-20), 5.40 (tdd, *J* = 11.4, 6.0, 1.2 Hz, 1H, H-17), 5.46 (td, *J* = 11.4, 4.2 Hz, 1H, H-18).

^{13}C NMR (150 MHz, C_6D_6): δ 21.6 (CH_2), 24.6 (C-14), 25.2 (C-15), 25.4 (C-16), 26.0 (CH_2), 26.2 (CH_2), 26.3 (CH_2), 26.5 (CH_2), 26.8 (CH_2), 27.0 (C-19), 27.3 (CH_2), 28.5 (CH_2), 30.2 (CH_2), 32.2 (C-11), 35.8 (C-31), 36.8 (C-5), 37.5 (C-9), 37.7 (C-12), 38.6 (C-4), 51.8 (C-2), 54.1 (C-10), 56.3 (C-13), 57.4 (C-21), 59.6 (C-6), 61.0 (C-8), 121.9 (C-20), 129.0 (C-17), 129.1 (C-18), 139.3 (C-3).

HRMS (ESI) calcd for $[C_{29}H_{48}N_2 + H]^+$: 425.3887, found: 425.3890.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H
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N
R
S
H
S
Madangamine D
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1.00
1.02
2.16
15.11
39.28
3.84
8.0
7.5
7.0
6.5
6.0
5.5
5.0
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4.0
3.5
3.0
2.5
2.0
1.5
1.0
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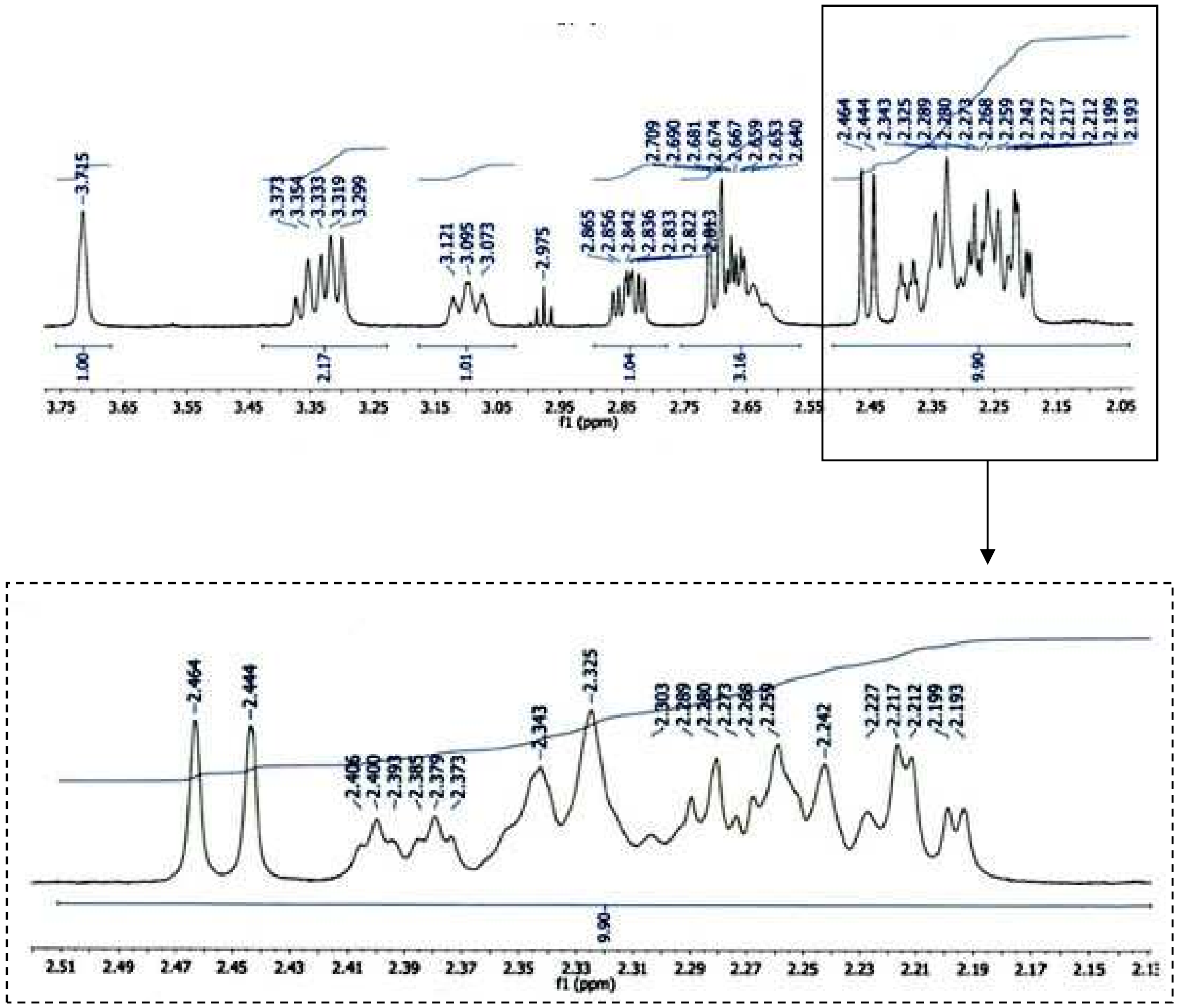
f1 (ppm)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2.667
2.659
2.653
2.640
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2.343
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f1 (ppm)
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2.400
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2.343
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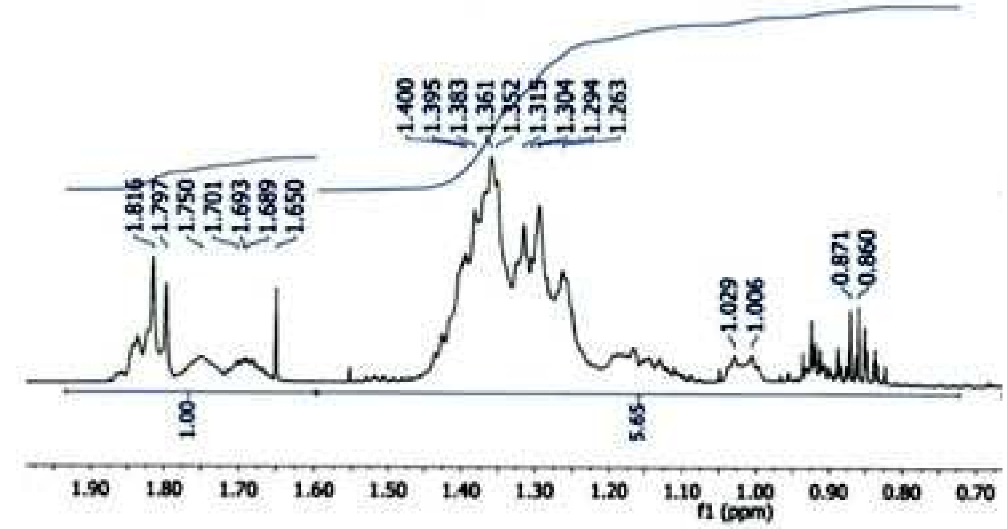
2.217
2.212
2.199
2.193
9.90
2.51 2.49 2.47 2.45 2.43 2.41 2.39 2.37 2.35 2.33 2.31 2.29 2.27 2.25 2.23 2.21 2.19 2.17 2.15
f1 (ppm)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1.383
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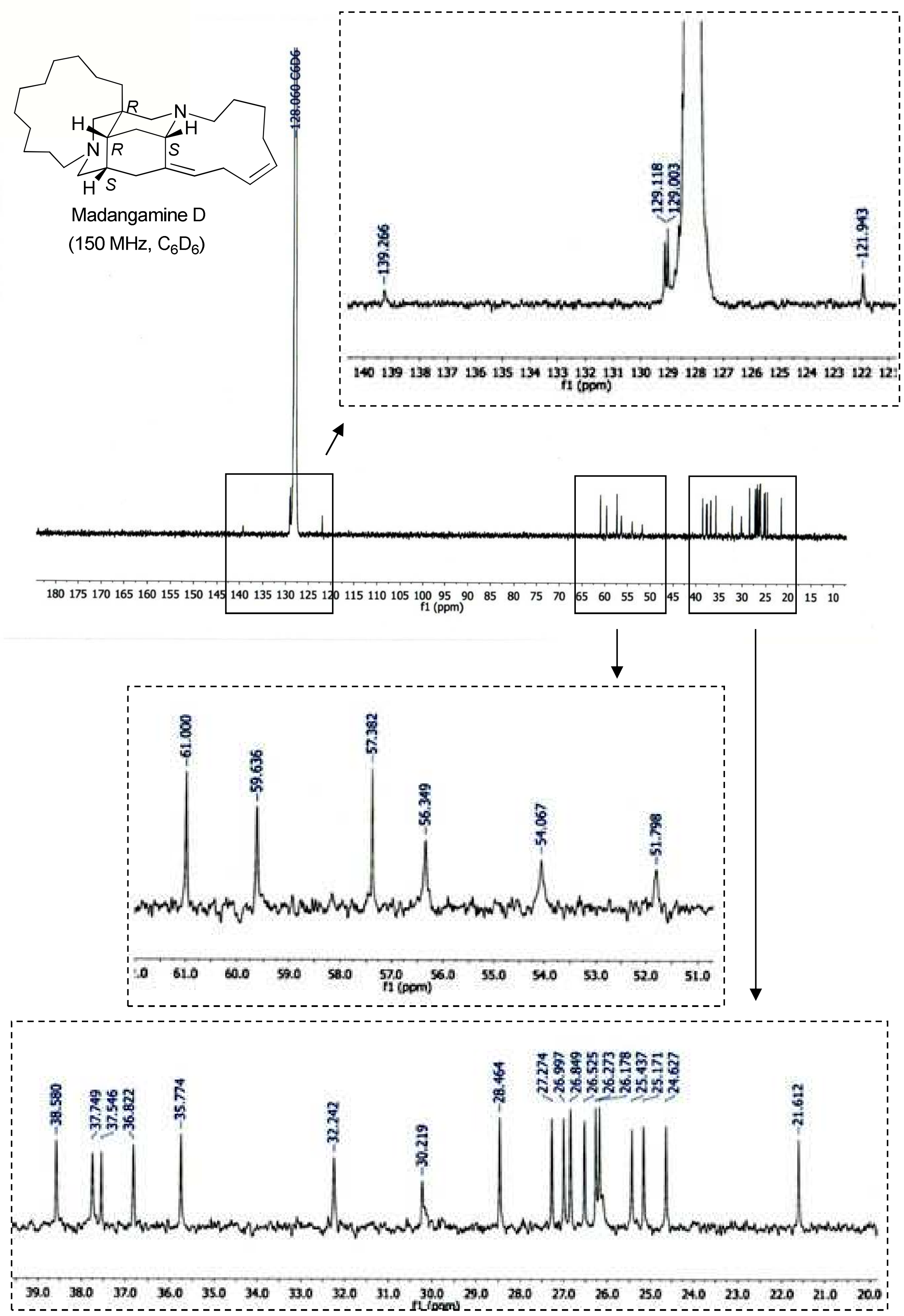
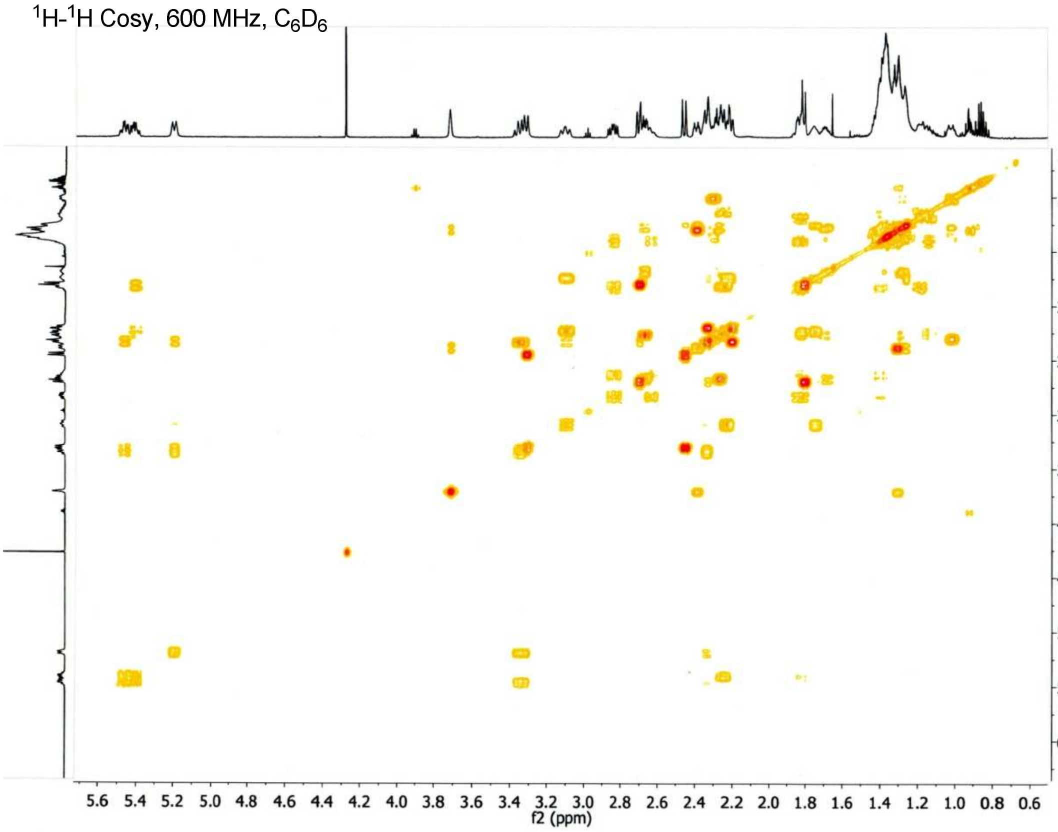
1.304
1.294
1.263
1.029
1.006
0.871
0.860
1.00
5.65
1.90 1.80 1.70 1.60 1.50 1.40 1.30 1.20 1.10 1.00 0.90 0.80 0.70
f1 (ppm)



Madangamine D
(150 MHz, C_6D_6)

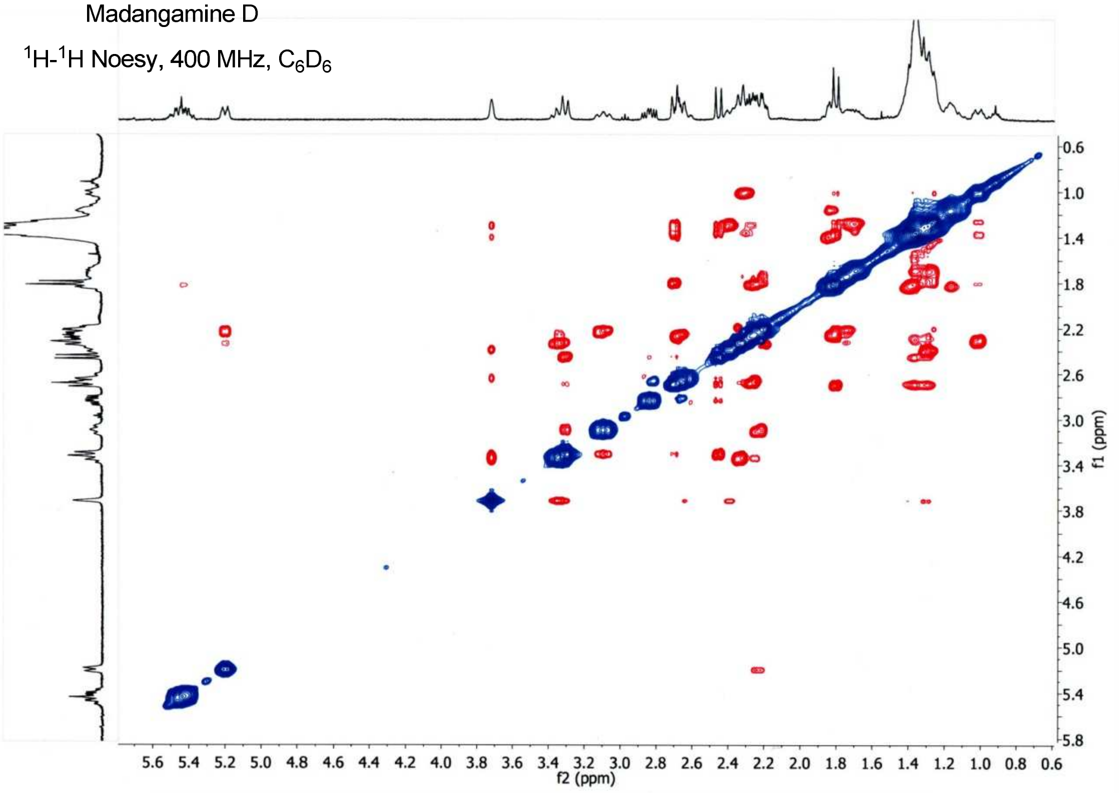
Madangamine D

^{1}H-^{1}H Cosy, 600 MHz, C_6D_6



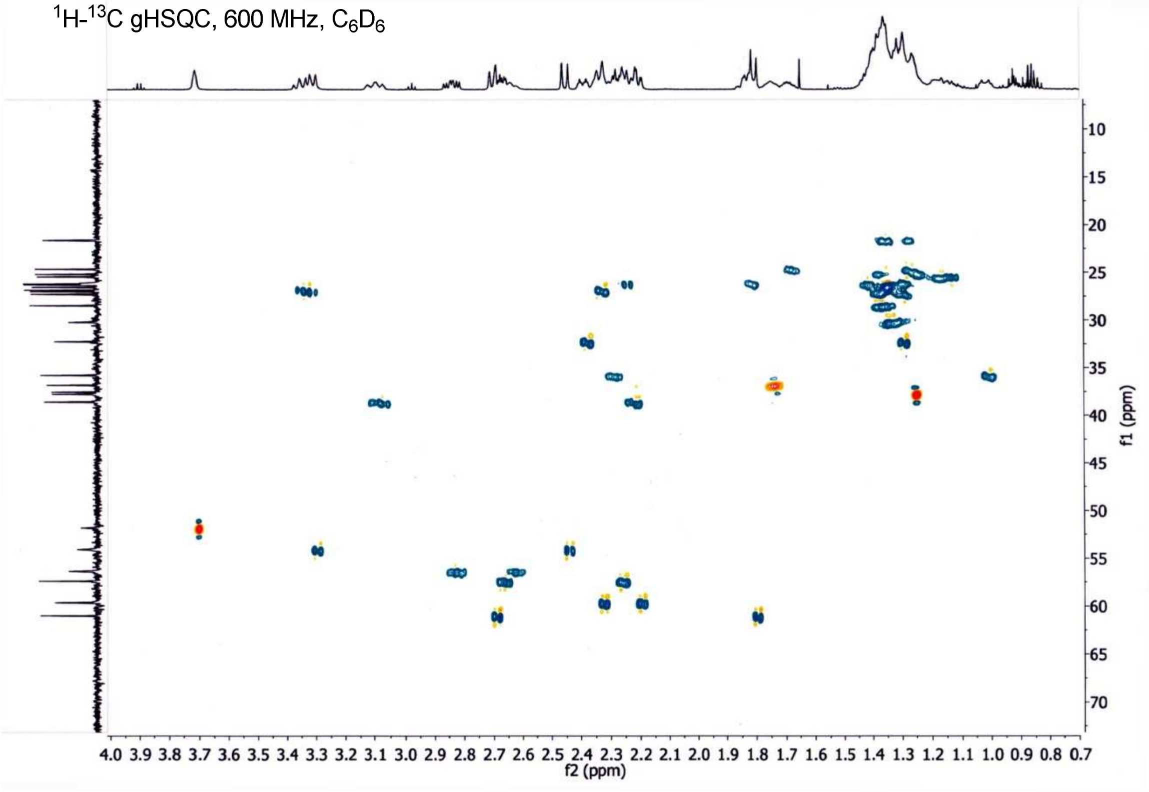
Madangamine D

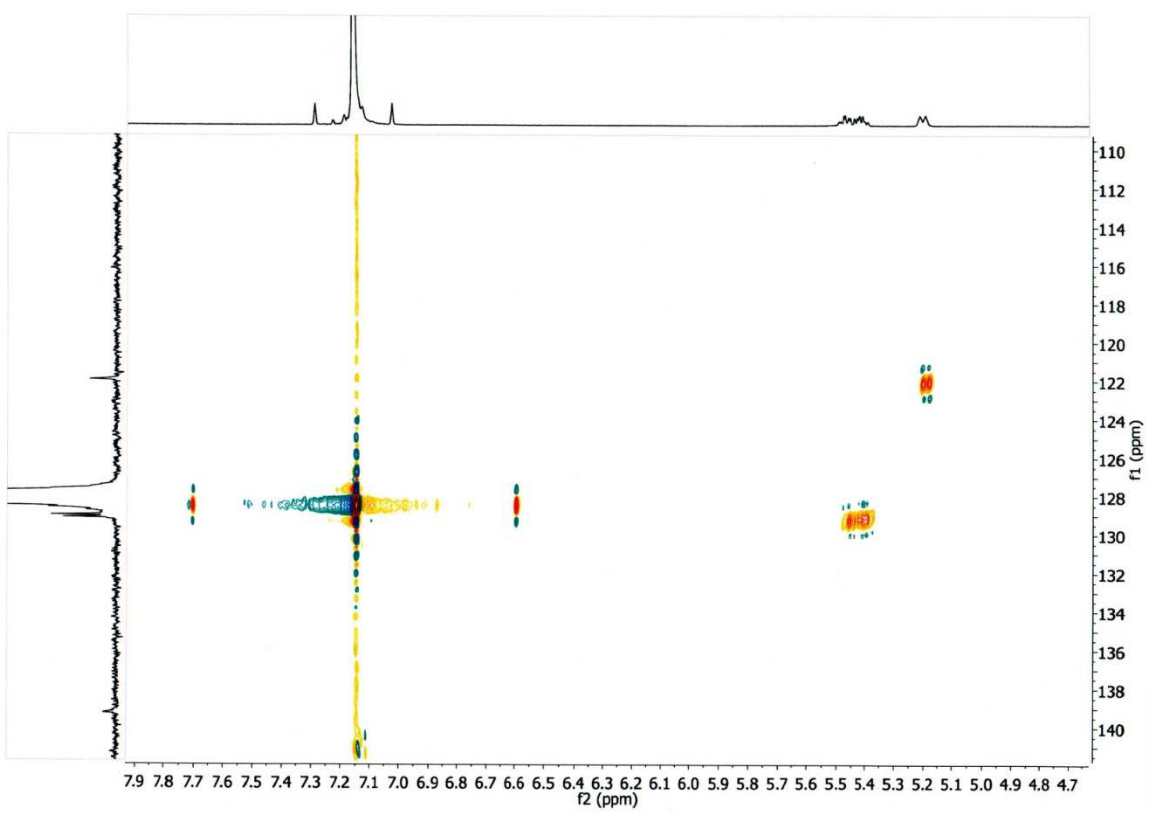
^{1}H-^{1}H Noesy, 400 MHz, C_6D_6

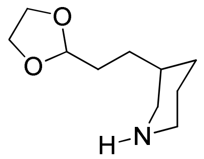


Madangamine D

^{1}H-^{13}C gHSQC, 600 MHz, C$_6$D$_6$







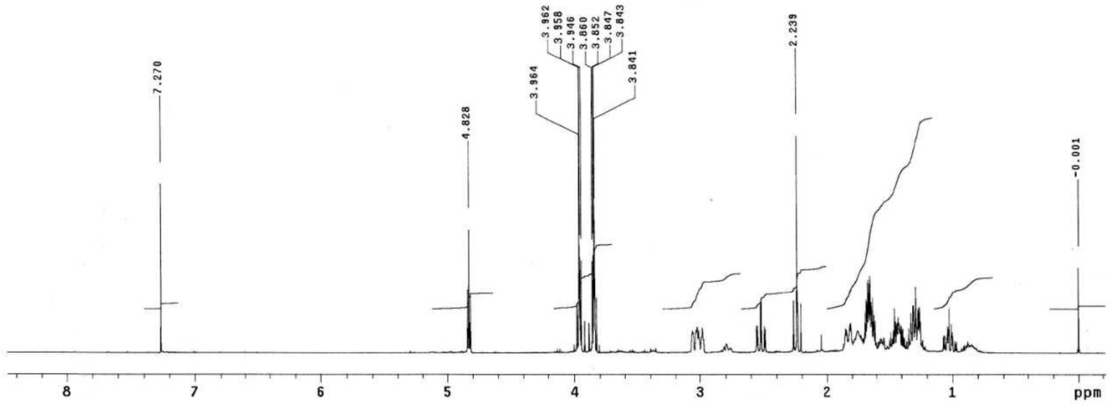
3-[2-(1,3-Dioxolan-2-yl)ethyl]piperidine (57).

Alkylation step: n-BuLi (25.8 mL of a 1.6 M solution in hexane, 45.6 mmol) was added to a solution of δ-valerolactam (2.26 g, 22.8 mmol) in anhydrous THF (75 mL) at −78 °C under inert atmosphere. The resulting mixture was stirred at 0 °C for 1 h. 2-(2-bromoethyl)-1,3-dioxolane (2.73 mL, 22.8 mmol) and TBAI (1.6 g, 4.5 mmol) were then added at 0 °C and the mixture was stirred overnight at the same temperature. Saturated aqueous NaCl was added and the mixture was extracted with CH_2Cl_2. The combined organic extracts were dried, filtered and concentrated under reduced pressure. Flash chromatography (neutral alumina, EtOAc) afforded lactam **56** (4.5 g, quant.)

Reduction step: $LiAlH_4$ (201 mg, 5.3 mmol) was added at room temperature and under inert atmosphere to a solution of lactam **56** (527 mg, 2.6 mmol) in anhydrous THF (25 mL) and the mixture was stirred at reflux overnight. The resulting suspension was cooled to 0 °C, and the reaction was quenched with distilled water. The aqueous layer was extracted with Et_2O, and the combined organic extracts were dried, filtered, and concentrated to afford the corresponding amine **57** (327 mg, 64%) which was used in the next step without purification.

^{1}H NMR (400 MHz, $CDCl_3$, COSY, gHSQC): δ 1.03 (qd, *J* = 12.4, 3.6 Hz, 1H, H-4), 1.23-1.34 (m, 2H, 2H-1’), 1.37-1.49 (m, 2H, H-3, H-5), 1.67 (m, 3H, 2H-2’, H-5), 1.76 (br. s, 1H, NH), 1.95-2.06 (dm, *J* = 12.4 Hz, 1H, H-4), 2.23 (dd, *J* = 12.0, 10.4 Hz, 1H, H-2), 2.51 (td, *J* = 11.6, 2.8 Hz, 1H, H-6), 3.00 (dm, *J* = 11.6 Hz, 2H, H-6), 3.03 (dm, *J* = 12.0 Hz, 2H, H-2), 3.85 (m, 2H, CH_2O), 3.96 (m, 2H, CH_2O), 4.83 (t, *J* = 5.2 Hz, 1H, CHO_2), 6.25 (br. s, 1H, NH).

^{13}C NMR (100.6 MHz, $CDCl_3$): δ 26.6 (C-5), 28.7 (C-1’), 31.1 (C-2’), 31.5 (C-4), 37.7 (C-3), 47.1 (C-6), 53.0 (C-2), 64.8 (2CH_2O), 104.7 (CHO_2).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7
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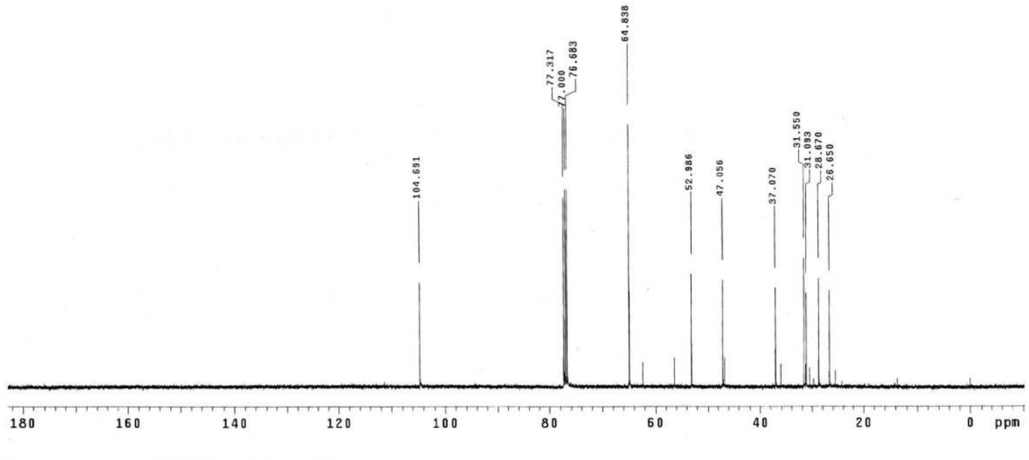
5
4
3
2
1
ppm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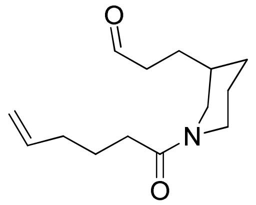
0
ppm



1-(5-hexenoyl)-3-piperidine propionaldehyde (58)

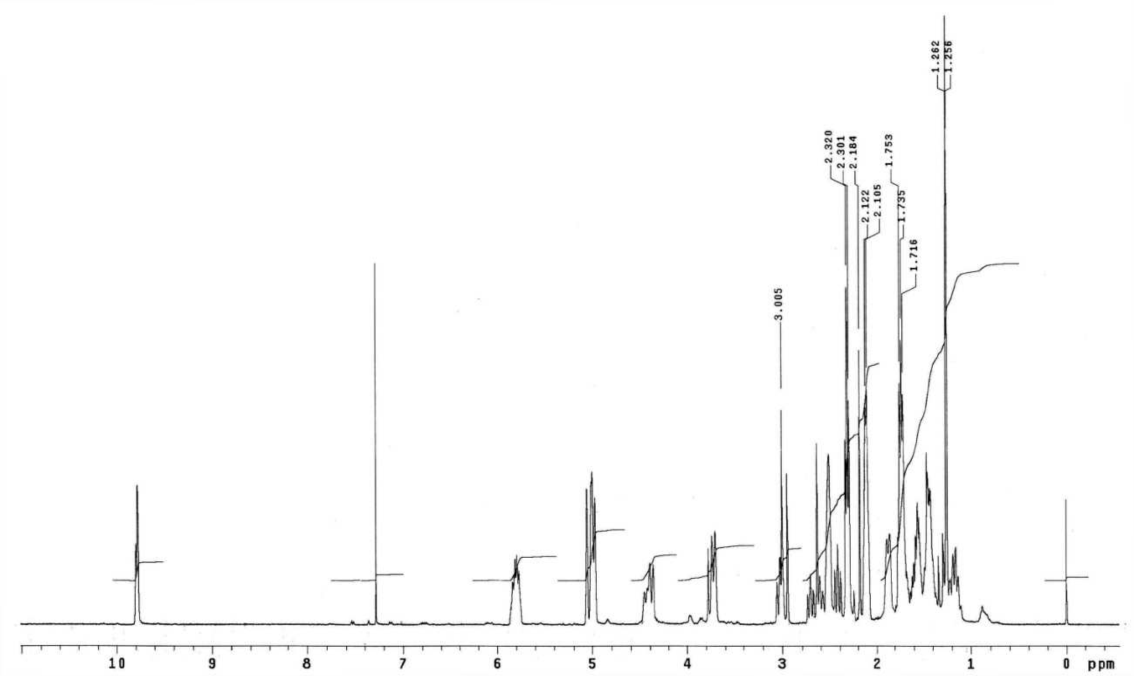
First step: Oxalyl chloride (4.73 mL of a 2 M solution in CH_2Cl_2, 9.47 mmol) were added to a solution of 5-hexenoic acid (5.64 mmol) with 1 drop of DMF at 0 °C and, after the evolution of gas subsided, the resulting mixture was stirred for 15 min then diluted with Et_2O, filtered and concentrated under reduced pressure to give a clear oil.

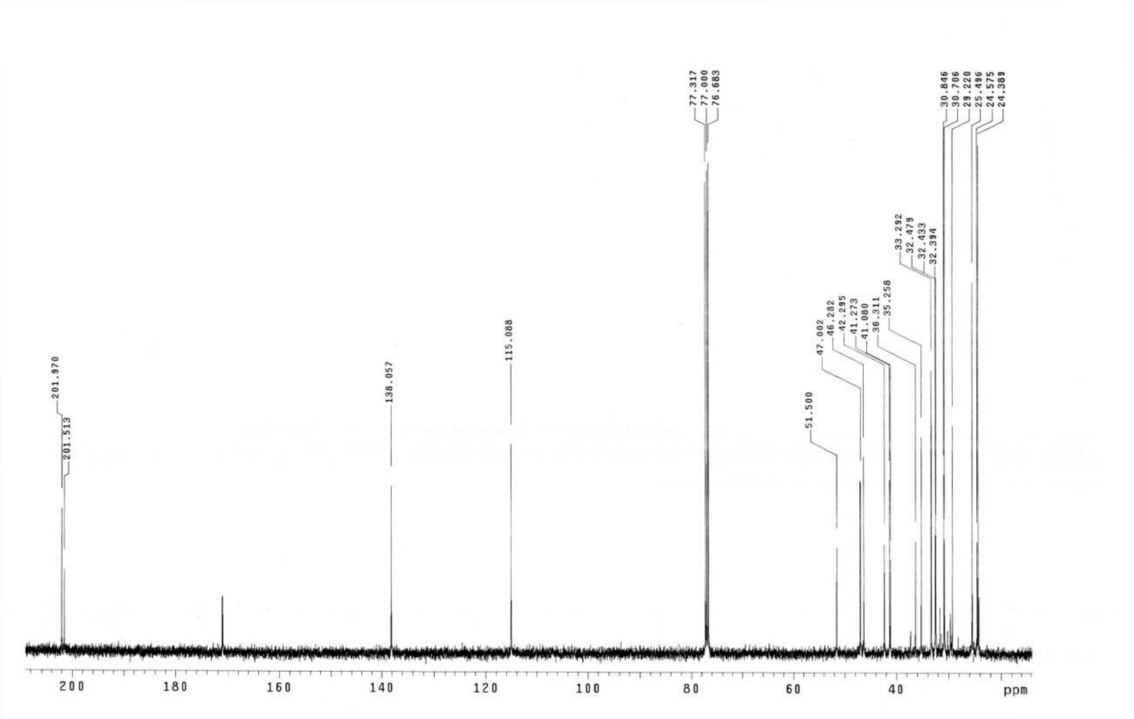
To a solution of amine **57** (292 mg, 1.5 mmol) in CH_2Cl_2 (13 mL) was added Et_3N (4.5 mmol). The solution was stirred for 15 min and then cooled at 0 °C. A solution of 5-hexanoil chloride (2.55 mmol) in CH_2Cl_2 (5 mL) was slowly added. The reaction mixture was stirred at 0 °C for 1h, then gradually warmed to room temperature and stirred overnight. The reaction mixture was cooled at 0 °C, distilled water was then added and the mixture was extracted with CH_2Cl_2. The combined organic extracts were dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. Flash chromatography (9:1 to 7:3 hexane-EtOAc) afforded acylated compound (83%).

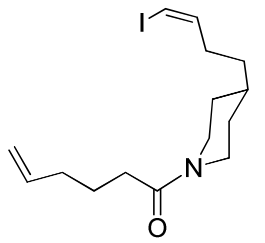
Second step: HCl (6 mL of a 10% solution in H_2O) was added to a solution of the above amide (112 mg, 0.4 mmol) in acetone (15 mL). The resulting mixture was stirred at room temperature for 48 h and then poured into $NaHCO_3$ saturated solution. The acetone was removed under reduced pressure and the aqueous phase was extracted several times with CH_2Cl_2. The combined organic extracts were dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure to give aldehyde **58** (93 mg, 98%) which was used in the next step without purification.

^{1}H NMR (400 MHz, $CDCl_3$, COSY, gHSQC): δ 1.16 (m, 1H, H-4), 1.44 (m, 2H, H-5, H-3), 1.55 (m, 2H, 2H-1'), 1.73 (m, 3H, H-5, 2H-3''), 1.87 (dm, J = 12.4 Hz, 1H, H-4), 2.10 (m, 2H, 2H-4''), 2.32 (t, J = 7.6 Hz, 2H, 2H-2''), 2.42, 2.57 (2td, J = 12.8, 2.8 Hz, 1H, H-6ax), 2.52 (m, 2H, 2H-2'), 2.70, 3.02 (2dd, *J* = 13.2, 10.4 Hz, 1H, H-2ax), 3.71, 3.75 (2d, *J* = 13.2 Hz, 1H, H-2eq), 4.38, 4.44 (2d, *J* = 12.8 Hz, 1H, H-6eq), 4.97-5.05 (m, 2H, CH2=), 5.80 (m, 1H, CH=), 9.78, 9.80 (2s, 1H, CHO).

^{13}C NMR (100.6 MHz, $CDCl_3$): δ 24.4 (C-3''), 25.5 (C-5, C-1'), 29.2 (C-4), 30.7, 30.8 (C-2''), 32.4, 33.5 (C-4''), 33.3 (C-3), 41.1, 41.3 (C-2'), 42.3, 47.0 (C-6), 46.3, 51.5 (C-2), 115.1 (CH_2=), 138.1 (CH=), 171.3 (NCO), 201.5, 201.9 (CHO).





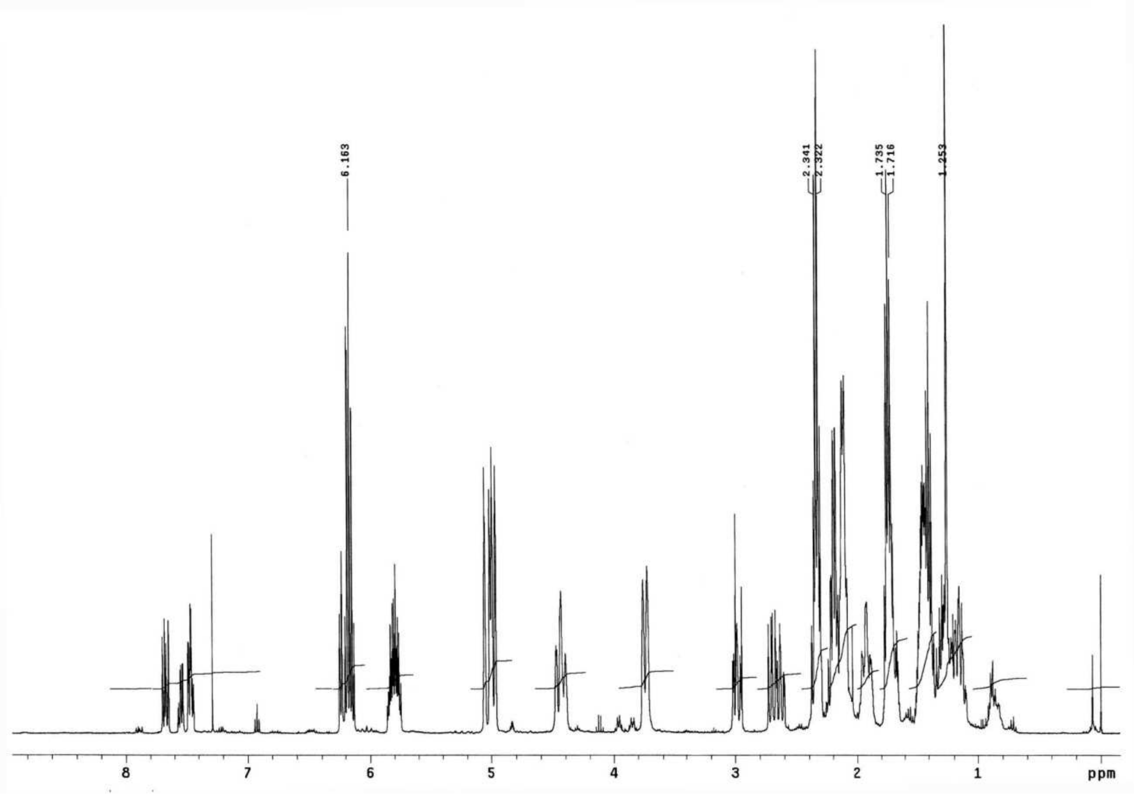


(*Z*)-1-(5-hexenoyl)-3-(4-iodo-3-butenyl)piperidine (59).

A suspension of the phosphonium iodide (362 mg, 0.683 mmol) in 5 mL of THF and 0.12 mL anhydrous HMPA was added to a solution of NaHMDS (1.0 M in THF, 683 µL, 0.683 mmol) in THF (10 mL) at 10-15 °C (ice-water bath). After 1 min, the mixture was cooled to –78 °C and a solution of aldehyde **58** (108 mg, 0.455 mmol) in THF (5.0 mL) was added dropwise. After being stirred at –78 °C for 20 min, the reaction was quenched by addition of aqueous saturated NH_4Cl and water. When the mixture was warmed to room temperature, the insoluble solids were filtered off, the layers of the filtrate were separated and the aqueous layer was extracted with diethyl ether. The combined organic phases were washed with brine, dried over $MgSO_4$, filtered, and concentrated. Flash chromatography (2:8 hexane-EtOAc) of the resulting residue afforded vinyl iodide **59** (76 mg, 46%).

^1H NMR (400 MHz, $CDCl_3$, COSY, gHSQC): δ 1.15 (m, 1H, H-4), 1.39 (m, 2H, 2H-1'), 1.44 (m, 2H, H-3, H-5), 1.73 (m, 3H, H-5, 2H-3”), 1.90 (dt, *J* = 13.2 Hz, 3.36 Hz, 1H, H-4), 2.11 (m, 2H, H-4”), 2.18 (m, 2H, H-2'), 2.33 (m, 2H, 2H-2”), 2.34, 2.61 (m, 2H, H-6ax, 2-H2”), 2.68, 2.99 (m, 1H, H-2ax), 3.72, 3.76 (d, *J* = 14Hz, H-2eq), 4.39, 4.43 (m, J = ,1H, H-6eq), 4.97, 5.05 (m, 2H, CH_2=), 5.79 (m, 1H, CH=), 6.24 (d, *J* = 7.2 Hz, 1H, H-4'), 6.16 (m, 1H, H-3').

^{13}C NMR (100.6 MHz, $CDCl_3$): δ 24.4 (C-3”), 25.7 (C-5), 30.7 (C-4), 31.6 (C-1'), 31.9 (C-2'), 32.5 (C-2”), 33.2 (C-4”), 35.2 (C-3), 42.3, 47.4 (C-6), 46.3, 51.4 (C-2), 115.0 (C-6”), 138.0 (C-5”), 140.4 (C-3'), 140.7 (C-4'), 171.0 (NCO).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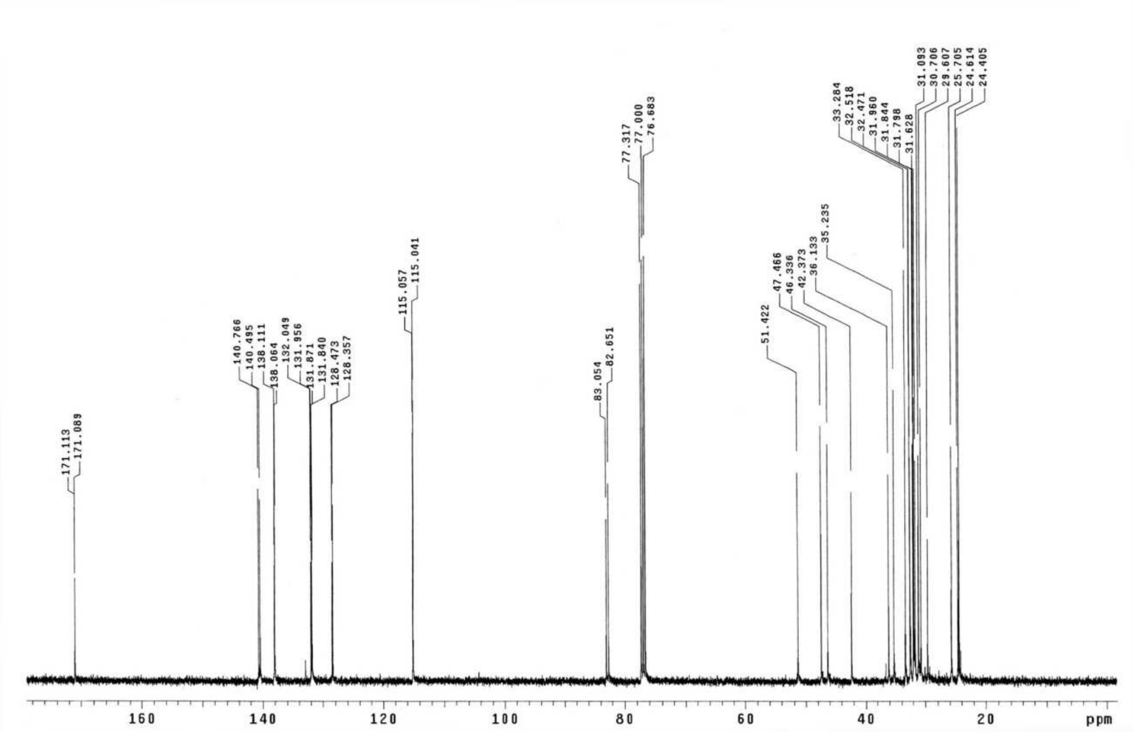
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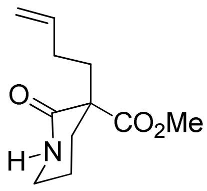


3-(3-Butenyl)-3-(methoxycarbonyl)-2-piperidone (64).

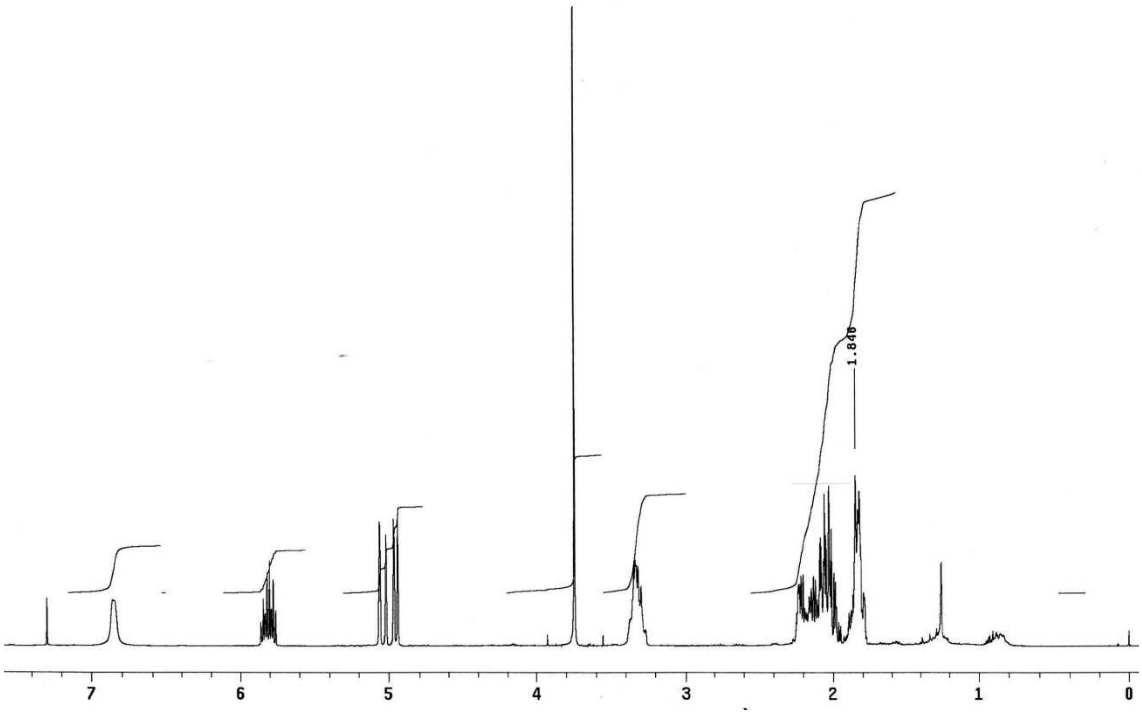
A solution of NaH (127 mg of a 60% dispersion in mineral oil, 3.17 mmol) in DMF (5 mL) was added via transfer to a solution of **3-(methoxycarbonyl)-2-piperidone** (415 mg, 2.64 mmol) in DMF (13 mL) at 0 °C, and the resulting mixture was stirred at 0 °C for 1 h. 4-Bromo-1-butene (1.34 mL, 13.2 mmol) and tetrabutylammonium iodide (195 mg, 0.52 mmol) were then added, and the mixture was stirred at room temperature for 4 h. The reaction was quenched with saturated aqueous NH_4Cl solution, and the resulting mixture was extracted with CH_2Cl_2. The combined organic extracts were dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. Flash chromatography (9:1 to 1:9 hexane-EtOAc) afforded compound **64** (506 mg, 91%).

IR (film): 1731 (COO), 1665 (NCO) cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$, COSY, gHSQC): δ 1.83 (m, 3H, 2H-4, H-5), 1.95-3.25 (m, 4H, H-1', H-2'), 2.21 (m, 1H, H-5), 3.33 (m, 2H, H-6), 3.74 (s, 3H, CH_3O), 4.95 (dd, *J* = 10.0, 1.2 Hz, 1H, CH=), 5.03 (dd, *J* = 16.0, 1.2 Hz, 1H, CH_2=), 5.80 (ddt, *J* = 16.0, 10.0, 5.6 Hz, 1H, CH=), 6.85 (d, *J* = 5.2 Hz, 1H, NH).

^{13}C NMR (100.6 MHz, $CDCl_3$): δ 19.5 (C-4), 28.8 (C-2'), 29.5 (C-5), 34.7 (C-1'), 42.1 (C-6), 52.4 (CH_3O), 53.5 (C-3), 114.7 (CH_2=), 137.8 (CH=), 170.9 (NCO), 173.2 (COO).

HRMS (ESI) calcd for $[C_{11}H_{17}NO_3 + H]^+$: 212.1281, found: 212.1281.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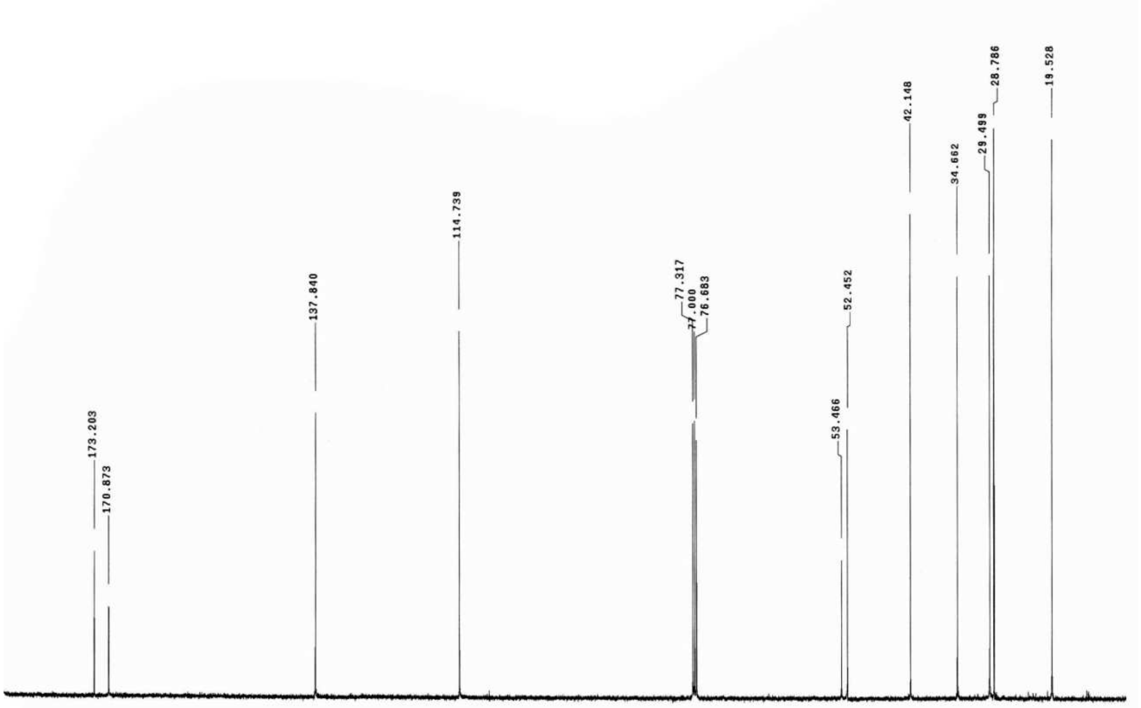
3
2
1
0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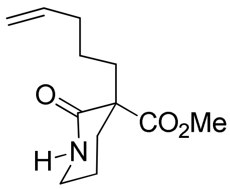


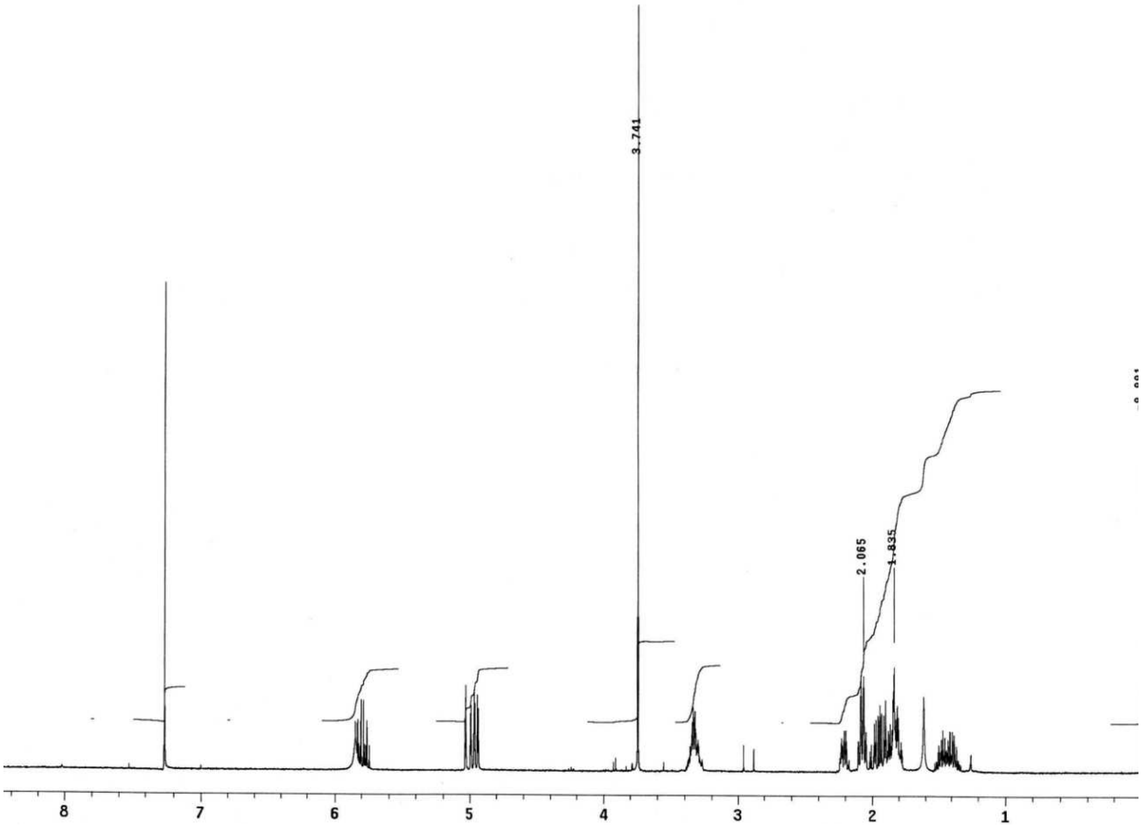
3-(Methoxycarbonyl)-3-(4-pentenyl)-2-piperidone (65).

Operating as described above, from a solution of **3-methoxycarbonyl-2-piperidone** (231 mg, 1.47 mmol) in DMF (5 mL), a suspension of NaH (71 mg of a 60% dispersion in mineral oil, 1.76 mmol) in DMF (5 mL), 5-bromo-1-pentene (0.87 mL, 7.35 mmol), and tetrabutylammonium iodide (108 mg, 0.29 mmol), compound **65** was obtained (380 mg, 99%) after flash cromatography.

IR (film): 1725 (COO), 1665 (NCO) cm^{-1}.

^{1}H NMR (400 MHz, CDCl$_3$, COSY, gHSQC): δ 1.39 (ttd, *J* = 12.4, 12.4, 7.2, 7.2, 4.8 Hz, 1H, H-2’), 1.46 (m, 1H, H-2’), 1.79 (dd, *J* = 10.8, 3.6 Hz, 1H, H-5), 1.82-2.02 (m, 4H, 2H-1’, 2H-4), 2.07 (m, 2H, H-3’), 2.21 (m, 1H, H-5), 3.33 (m, 2H, H-6), 3.74 (s, 3H, CH$_3$O), 4.93-5.04 (m, 2H, CH$_2$=), 5.79 (dddd, *J* = 16.8, 10.0, 6.4, 6.4 Hz, 1H, CH=).

^{13}C NMR (100.6 MHz, CDCl$_3$): δ 19.7 (C-4), 23.9 (C-2’), 29.5 (C-5), 33.9 (C-3’), 35.1 (C-1’), 42.4 (C-6), 52.6 (CH$_3$O), 53.9 (C-3), 114.8 (CH$_2$=), 138.3 (CH=), 170.7 (NCO), 173.4 (COO).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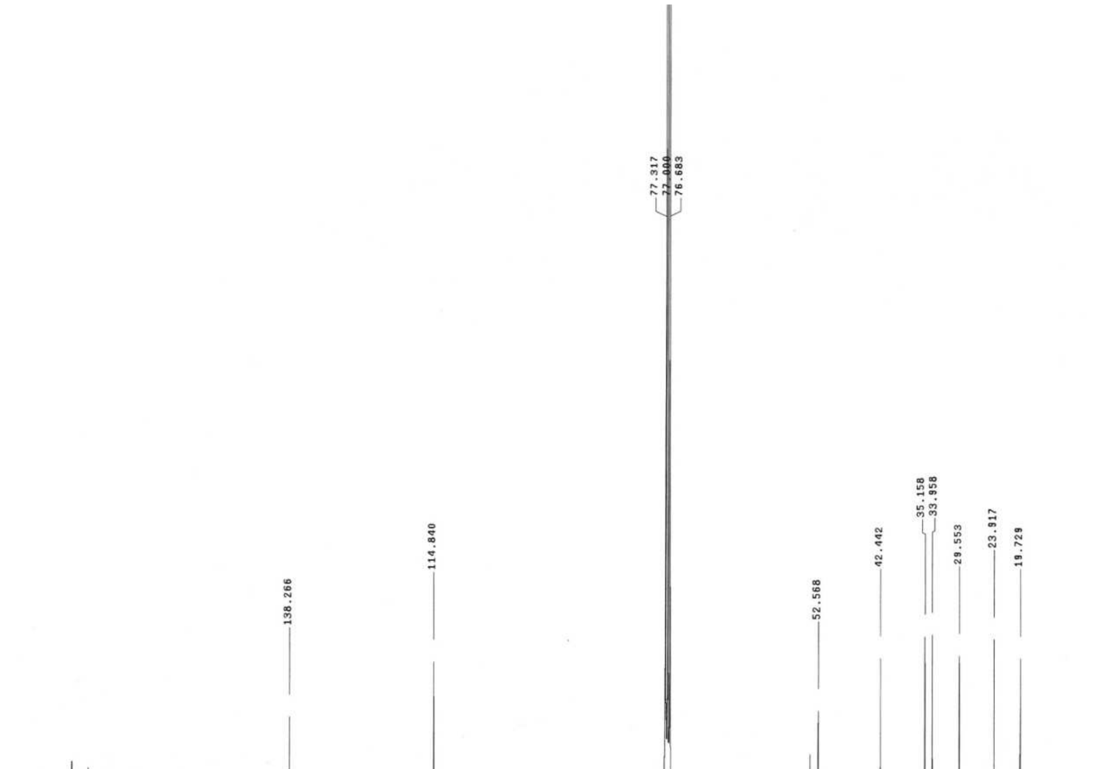
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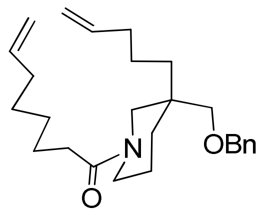


3-(Benzyloxymethyl)-3-(4-pentenyl)-1-(7-octenoyl) piperidine (70).

Reduction step: Lithium aluminum hydride (90 mg, 2.38 mmol) was added to a solution of compound **65** (302 mg, 1.34 mmol) in anhydrous THF (20 mL) under argon atmosphere, and the mixture was heated at reflux for 4 h. The resulting suspension was cooled to room temperature, and the reaction was quenched with distilled water. The aqueous layer was extracted with Et_2O, and the combined organic extracts were dried, filtered, and concentrated to give **3-(hydroxymethyl)-3-(4-pentenyl)piperidine (67)** (220 mg), which was used in the next step without purification.

IR (film): 3400 (NH, OH) cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$, COSY, gHSQC): δ 1.15 (m, 2H, H-1'), 1.24-1.36 (m, 3H, 2H-2', H-4), 1.53 (ddd, *J* = 17.2, 8.4, 4.4 Hz, 1H, H-5), 1.68 (dt, *J* = 14.0, 3.6 Hz, 1H, H-4), 1.89 (m, 1H, H-5), 2.00 (m, 2H, H-3'), 2.55 (d, *J* = 11.6 Hz, 1H, H-2), 2.61 (td, *J* = 11.2, 3.2 Hz, 1H, H-6), 2.84 (br. s, 1H, OH), 2.95 (dd, *J* = 11.2, 4.4 Hz, 1H, H-6), 2.97 (d, *J* = 11.6 Hz, 1H, H-2), 3.67 (s, 2H, CH_2OH), 4.93-5.02 (2m, 2H, CH_2=), 5.78 (ddt, *J* = 16.8, 10.4, 6.8, 6.8 Hz, 1H, CH=).

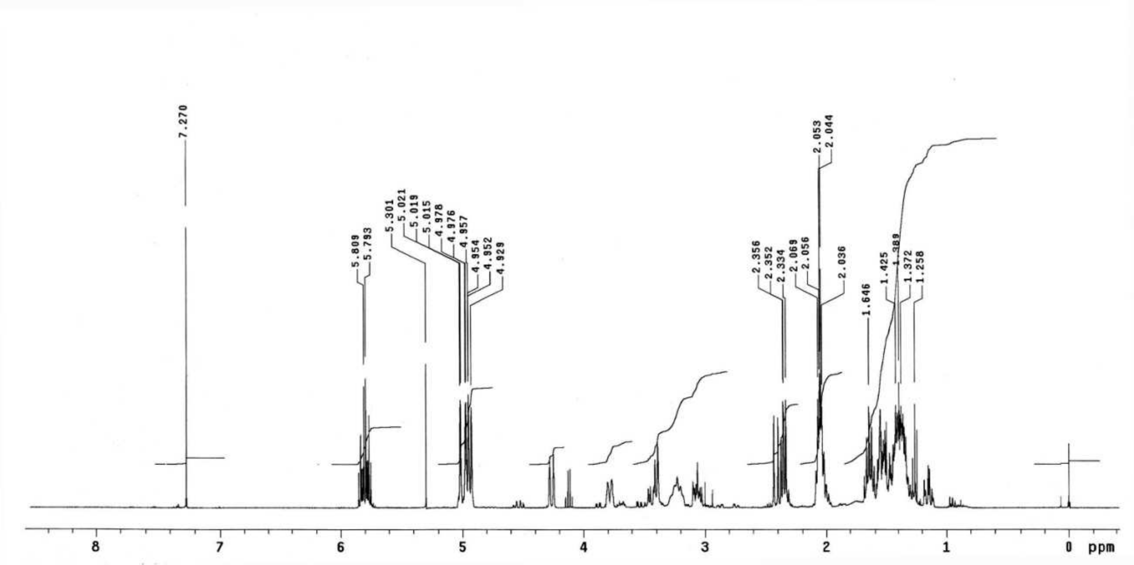
^{13}C NMR (100.6 MHz, $CDCl_3$): δ 22.2 (C-2'), 22.9 (C-5), 33.4 (C-4), 34.5 (C-3'), 35.7 (C-3), 37.2 (C-1'), 46.8 (C-6), 55.6 (C-2), 71.1 (CH_2OH), 114.6 (CH_2=), 138.7 (CH=).

Acylation step: Oxalyl chloride (1.0 mL of a 2 M solution in CH_2Cl_2, 2.0 mmol) was added to a solution of 7-octenoic acid (0.15 mL, 1.0 mmol) in CH_2Cl_2 (4 mL) and two drops of DMF, and the resulting mixture was stirred for 3 h. Et_2O was added, and the resulting mixture was filtered and concentrated under reduced pressure to give crude **7-octenoyl chloride**.

A solution of the above chloride (1.0 mmol) in chloroform (5 mL) was added to a suspension of **67** (157 mg, 0.859 mmol) and K_2CO_3 (273 mg, 1.975 mmol) in chloroform (10 mL), and the mixture was stirred for 1.5 h at room temperature. Distilled water was then added, and the resulting mixture was stirred for 20 minutes. The aqueous layer was extracted with chloroform, and the combined organic extracts were dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. Flash chromatography (8:2 to 1:1 hexane-EtOAc) afforded **3-(hydroxymethyl)-1-(7-octenoyl)-3-(4-pentenyl)piperidine** (130 mg, 50% overall yield for the two steps).

^{1}H NMR (400 MHz, CDCl$_3$, COSY, gHSQC): δ 1.14 (td, *J* = 16.0, 16.0, 4.0 Hz, 1H, H-1'), 1.29-1.47 (m, 7H, 2H-2', 2H-4'', 2H-5'', H-4), 1.49-1.58 (m, 4H, 2H-5, H-4, H-1'), 1.64 (m, 2H, H-3'), 2.05 (m, 4H, H-6'', H-3'), 2.35 (t, *J* = 7.2 Hz, 2H, H-2''), 2.40 (d, *J* = 13.2 Hz, 1H, H-2), 3.06 (dm, *J* = 14.4 Hz, 1H, H-6), 3.22 (d, *J* = 11.2 Hz, 1H, CH$_2$OH), 3.25 (br. s, 1H, OH), 3.39 (d, *J* = 11.2 Hz, 1H, CH$_2$OH), 3.78 (dm, *J* = 14.4 Hz, 1H, H-6), 4.25 (d, *J* = 13.2 Hz, 1H, H-2), 4.92-5.03 (4m, 4H, CH$_2$=), 5.80 (ddt, *J* = 17.2, 10.0, 6.8, 6.8 Hz, 2H, CH=).

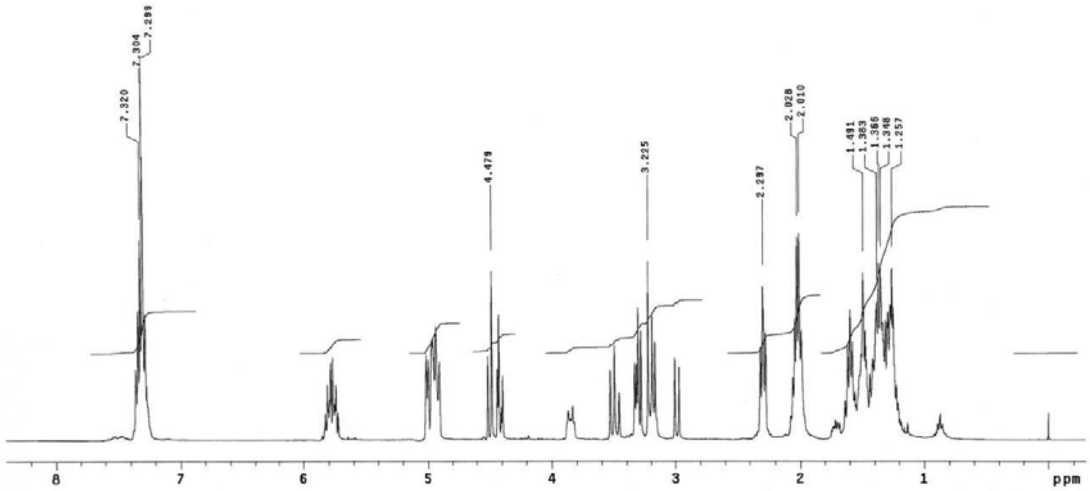
^{13}C NMR (100.6 MHz, CDCl$_3$): δ 22.2 (C-2'), 22.6 (C-5), 25.3 (C-3'), 28.6, 28.9 (C-4'', C-5''), 30.7 (C-4), 33.0 (C-2''), 33.5 (C-6''), 34.4 (C-3'), 35.5 (C-1'), 38.5 (C-3), 47.2 (C-6), 48.9 (C-2), 62.4 (CH$_2$OH), 114.4, 114.5 (CH$_2$=), 138.7, 138.8 (CH=), 172.9 (NCO).



Protection step: A solution of **3-(hydroxymethyl)-1-(7-octenoyl)-3-(4-pentenyl) piperidine** (265 mg, 0.86 mmol) in anhydrous DMF (6 mL) was added under inert atmosphere to a suspension of NaH (83 mg of a 60% dispersion in mineral oil, 2.09 mmol) in DMF (6 mL). The resulting mixture was stirred at 0 °C for 1 h, and then benzyl bromide (410 µL, 3.47 mmol) and tetrabutylammonium iodide (51 mg, 0.14 mmol) were added. The resulting white suspension was stirred at room temperature for 4 h. The reaction was quenched with saturated NH_4Cl solution, and the resulting mixture was extracted with Et_2O and CH_2Cl_2. The combined organic extracts were dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure. Flash chromatography (98:2 to 7:3 hexane-EtOAc) gave compound **70** (327 mg, 95%) as a colourless oil.

^{1}H NMR (400 MHz, $CDCl_3$, COSY, gHSQC): δ 1.25-1.41 (m, 9H, 2H-5'', 2H-4'', 2H-6'', 2H-2', H-4), 1.49 (m, 3H, H-4, 2H-5), 1.59 (t, *J* = 8.4 Hz, 2H, 2H-3''), 2.01 (m, 4H, H-3', H-1'), 2.30 (t, *J* = 8.4 Hz, 2H, H-2''), 2.99, 3.32 (d, *J* = 13.6 Hz, 1H, H-2), 3.18 (d, *J* = 8.8 Hz, 1H, CH_2OBn), 3.21 (m, 1H, H-6), 3.29 (d, *J* = 8.8 Hz, 1H, CH_2OBn), 3.48, 3.52 (d, *J* = 13.6 Hz, 1H, H-2), 3.84 (d, *J* = 13.2 Hz, 1H, H-6), 4.40 (d, *J* = 12.4 Hz, 1H, CH_2 Bn), 4.49 (d, *J* = 12.4 Hz, 1H, CH_2 Bn), 4.96 (4H, CH_2=), 5.78 (m, 2H, CH=), 7.28-7.32 (m, 5H, H-*o*, *m*, *p* C_6H_5).

^{13}C NMR (100.6 MHz, $CDCl_3$): δ 20.8, 21.9 (C-5), 22.1, 22.4 (C-2'), 25.0, 25.3 (C-3''), 28.6, 28.9, (C-4'', C-5''), 30.7, 30.9 (C-4), 32.7 (C-2''), 33.4-34.3 (C-3', C-6'', C-1'), 37.5, 37.7 (C-3), 42.2, 46.3 (C-6), 48.2, 52.6 (C-2), 71.7, 72.9 (CH_2OBn), 73.1 (CH_2 Bn), 114.2-114.6 (CH_2=), 126.8-128.2 (C-*o*, *m*, *p* C_6H_5), 138.2-138.8 (CH=, C-*i* C_6H_5), 171.7, 172.2 (NCO).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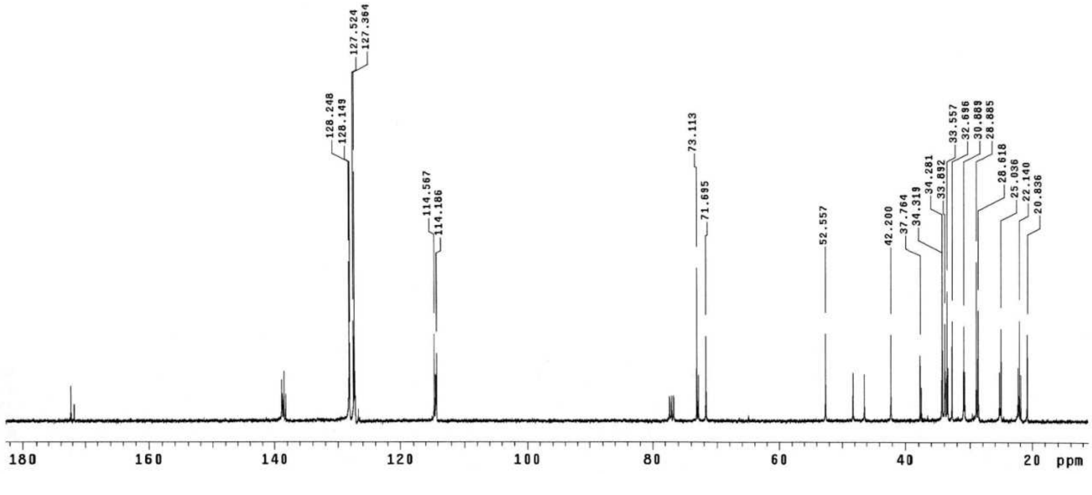
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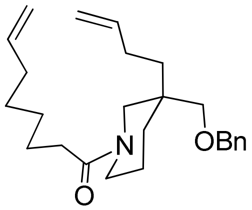


3-(Benzyloxymethyl)-3-(3-butenyl)-1-(1-oxo-7-octenyl)-piperidine (68).

Reduction step: Lithium aluminum hydride (88 mg, 2.34 mmol) was added to a solution of compound **64** (306 mg, 1.44 mmol) in anhydrous THF (25 mL) under argon atmosphere, and the mixture was heated at reflux for 3 h. The resulting suspension was cooled to room temperature, and the reaction was quenched with distilled water. The aqueous layer was extracted with Et_2O, and the combined organic extracts were dried, filtered, and concentrated to give **3-(3-butenyl)-3-(hydroxymethyl)piperidine (66)** (200 mg), which was used in the next step without purification.

IR (film) 3400 (NH, OH) cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$, COSY, gHSQC): δ 1.25 (m, 2H, H-1'), 1.33 (td, *J* = 13.2, 13.2, 5.5 Hz, 1H, H-4), 1.55 (dt, *J* = 13.2, 4.0, 4.0 Hz, 1H, H-5), 1.67 (tm, *J* = 13.2 Hz, 1H, H-4), 1.85-2.05 (m, 3H, H-5, 2H-2'), 2.56 (d, *J* = 12.0 Hz, 1H, H-2), 2.62 (td, *J* = 10.8, 4.0, 4.0 Hz, 1H, H-6), 3.00 (d, *J* = 12.0 Hz, 1H, H-2), 3.65 (d, *J* = 11.6 Hz, 1H, CH_2OH), 3.69 (d, *J* = 11.6 Hz, 1H, CH_2OH), 4.91-5.03 (4m, 2H, CH_2=), 5.78 (ddt, *J* = 16.8, 10.4, 6.8, 6.8 Hz, 1H, CH=).

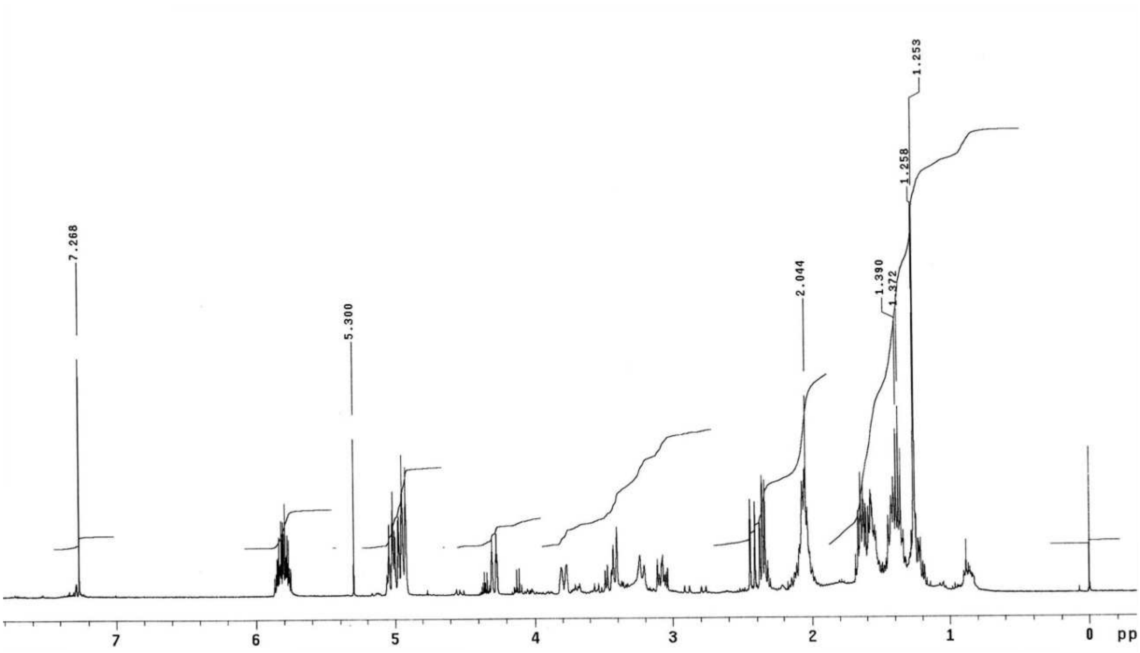
^{13}C NMR (100.6 MHz, $CDCl_3$): δ 22.7 (C-5), 27.3 (C-2'), 33.0 (C-4), 35.7 (C-3), 36.7 (C-1'), 46.6 (C-6), 55.0 (C-2), 70.1 (CH_2OH), 114.3 (CH_2=), 139.1 (CH=).

Acylation step: Oxalyl chloride (1.09 mL of a 2 M solution in CH_2Cl_2, 2.18 mmol) was added to a solution of 7-octenoic acid (0.17 mL, 1.09 mmol) in CH_2Cl_2 (3 mL) and two drops of DMF, and the resulting mixture was stirred for 3 h. Et_2O was added, and the resulting mixture was filtered and concentrated under reduced pressure to give crude **7-octenoyl chloride**.

A solution of the above chloride (1.09 mmol) in CH_2Cl_2 (5 mL) was added to a suspension of piperidine **66** (162 mg, 0.99 mmol) and K_2CO_3 (314 mg, 2.27 mmol) in CH_2Cl_2 (10 mL), and the mixture was stirred for 3 h at room temperature. Distilled water was then added, and the resulting mixture was stirred for 20 minutes. The aqueous layer was extracted with chloroform, and the combined organic extracts were dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. Flash chromatography (8:2 to 1:1 hexane-EtOAc) afforded **3-(3-butenyl)-3-(hydroxymethyl)-1-(7-octenoyl)piperidine** (90 mg, 31%, overall yield for the two steps).

^{1}H NMR (400 MHz, $CDCl_3$, COSY, gHSQC) δ 1.25 (m, 1H, H-6''), 1.38 (m, 5H, H-4, 2H-4'', 2H-5''), 1.52-1.66 (m, 6H, 2H-3'', 2H-5, H-6'', H-4), 2.05 (m, 2H, H-3'), 2.36 (t, *J* = 7.2 Hz, 2H, H-2''), 2.43 (d, *J* = 13.2 Hz, 1H, H-2), 3.09 (d, *J* = 13.6 Hz, 1H, H-6), 3.22 (d, *J* = 11.6 Hz, 1H, CH_2OH), 3.42 (d, *J* = 11.6 Hz, 1H, CH_2OH), 3.79 (dm, *J* = 13.6 Hz, 1H, H-6), 4.28 (d, *J* = 13.2 Hz, 1H, H-2), 4.92-5.05 (4m, 4H, CH_2=), 5.81 (ddddd, *J* = 16.8, 10.0, 6.0, 6.0, 4.0 Hz, 2H, CH=).

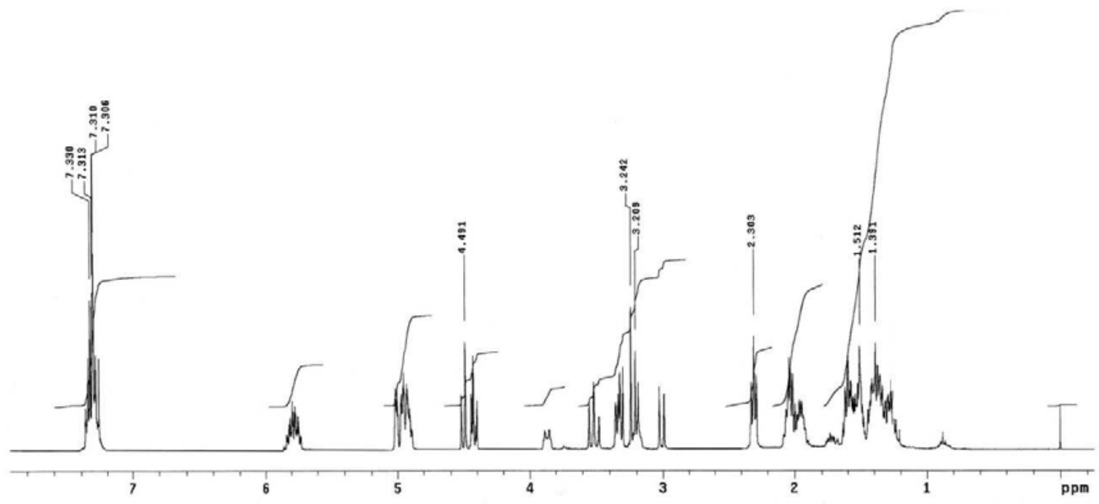
^{13}C NMR (100.6 MHz, $CDCl_3$) δ 22.6 (C-5), 25.3 (C-3''), 28.6, 28.9 (C-4'', C-5''), 30.7 (C-4), 33.0 (C-2''), 33.6 (C-3'), 35.2 (C-6''), 38.6 (C-3), 47.2 (C-6), 48.8 (C-2), 62.3 (CH_2OH), 114.3, 114.4 (CH_2=), 138.8, 139.0 (CH=), 173.0 (NCO).



Protection step: A solution of the above alcohol (186 mg, 0.63 mmol) in anhydrous DMF (4 mL) was added under inert atmosphere to a suspension of NaH (76 mg of a 60% dispersion in mineral oil, 1.9 mmol) in DMF (8 mL). The resulting mixture was stirred at 0 °C for 1 h, and then benzyl bromide (370 µL, 3.17 mmol) and tetrabutylammonium iodide (46 mg, 0.13 mmol) were added. The resulting white suspension was stirred at room temperature for 4 h. The reaction was quenched with saturated NH_4Cl solution, and the resulting mixture was extracted with Et_2O and CH_2Cl_2. The combined organic extracts were dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure. Flash chromatography (98:2 to 7:3 hexane-EtOAc) gave compound **68** (216 mg, 89%) as a colourless oil.

^{1}H NMR (400 MHz, $CDCl_3$, COSY, gHSQC): δ 1.25-1.44 (m, 5H, 2H-5'', 2H-6'', H-4), 1.49-1.62 (m, 5H, 2H-5, 2H-3'', H-4), 1.95 (m, 2H, H-4''), 2.03 (m, 2H, H-3'), 2.30 (t, *J* = 8.4 Hz, 2H, H-2''), 3.01 (d, *J* = 13.6 Hz, 1H, H-2), 3.19, 3.32 (m, 1H, H-6), 3.22 (d, *J* = 13.2 Hz, 1H, CH_2OBn), 3.31 (d, *J* = 12.3 Hz, 1H, CH_2OBn), 3.50, 3.53 (d, *J* = 13.6 Hz, 1H, H-2), 3.86 (d, *J* = 13.2 Hz, 1H, H-6), 4.42 (d, *J* = 12.0 Hz, 1H, CH_2 Bn), 4.51 (d, *J* = 12.0 Hz, 1H, CH_2 Bn), 4.90-5.02 (4H, CH_2=), 5.72-5,84 (m, 2H, CH=), 7.30-7.34 (m, 5H, H-*o*, *m*, *p* C_6H_5).

^{13}C NMR (100.6 MHz, $CDCl_3$): δ 20.8, 21.9 (C-5), 25.1, 25.3 (C-3''), 27.4, 27.6 (C-4''), 28.6, 29.4 (C-5''), 30.8, 30.9 (C-4), 32.8 (C-2''), 33.6 (C-3'), 33.7 (C-6'', 1'), 37.8, 37.6 (C-3), 42.2, 46.4 (C-6), 48.2, 52.6 (C-2), 71.6, 72.8 (CH_2OBn), 73.2 (CH_2 Bn), 114.1-114.3 (CH_2=), 126.9-128.3 (C-*o*, *m*, *p*), 138.2-139.1 (CH=, C-*i*), 171.7, 172.9 (NCO).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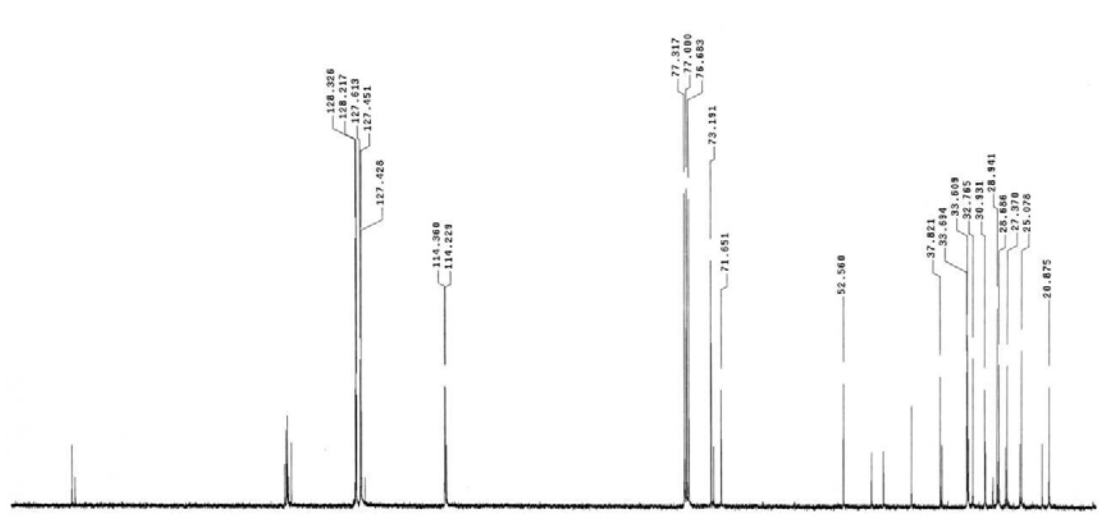
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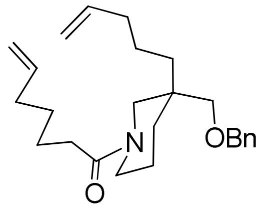


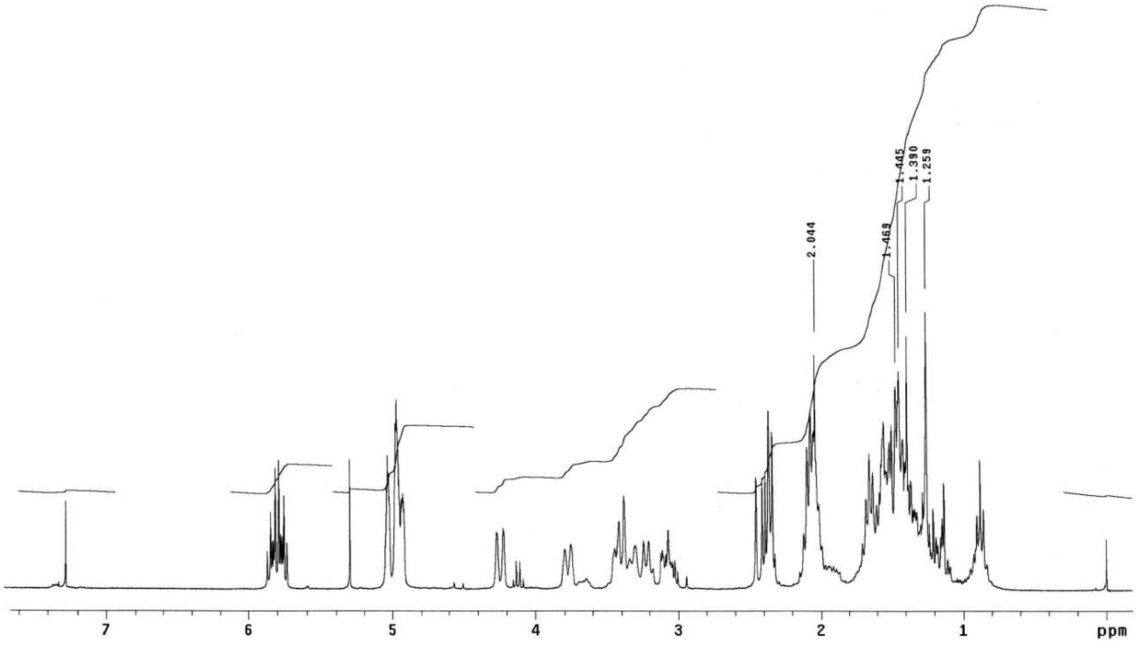
3-(Benzyloxymethyl)-3-(4-pentenyl)-1-(6-heptenoyl) piperidine (69).

Oxalyl chloride (2.9 mL of a 2 M solution in CH_2Cl_2, 5.89 mmol) was added to a solution of 6-heptenoic acid (0.39 mL, 2.9 mmol) in CH_2Cl_2 (7 mL) and two drops of DMF, and the resulting mixture was stirred for 3 h. Et_2O was added, and the resulting mixture was filtered and and concentrated under reduced pressure to give crude **6-heptenoyl chloride**.

A solution of the above chloride (2.9 mmol) in chloroform (5 mL) was added to a suspension of piperidine **67** (540 mg, 2.95 mmol) and K_2CO_3 (937 mg, 6.78 mmol) in chloroform (20 mL), and the mixture was stirred for 3 h at room temperature. Distilled water was then added, and the resulting mixture was stirred for 20 minutes. The aqueous layer was extracted with chloroform, and the combined organic extracts were dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. Flash chromatography (8:2 to 1:1 hexane- EtOAc) afforded **1-(6-heptenoyl)-3-(hydroxymethyl)-3-(4-pentenyl)piperidine** (200 mg, 31% overall yield for the two steps).

^{1}H NMR (400 MHz, $CDCl_3$, COSY, gHSQC): δ 0.88 (t, *J* = 7.5 Hz, 1H, H-1’), 1.13-1.46 (m, 5H, 2H-2’, 2H-4’’, H-4), 1.49-1.58 (m, 4H, 2H-5, H-4, H-1’), 1.65 (m, 2H, H-3’’), 2.02-2.12 (m, 4H, 2H-3’, 2H-5’’), 2.36 (t, *J* = 7.8 Hz, 2H, H-2’’), 2.43 (d, *J* = 13.5 Hz, 1H, H-2), 3.09 (m, 1H, H-6), 3.22 (d, *J* = 10.8 Hz, 1H, CH_2OH), 3.30 (br. s, 1H, OH), 3.40 (d, *J* = 10.8 Hz, 1H, CH_2OH), 3.75 (d, *J* = 13.2 Hz, 1H, H-6), 4.24 (dd, *J* = 13.5, 1.5 Hz, 1H, H-2), 4.92-5.04 (m, 4H, CH_2=), 5.80 (ddt, *J* = 17.4, 10.5, 6.6 Hz, 2H, CH=).

^{13}C NMR (100.6 MHz, $CDCl_3$): δ 22.2 (C-2’), 22.6 (C-5), 24.9 (C-3’’), 28.4 (C-4’’), 30.6 (C-4), 32.9 (C-2’’), 33.4 (C-5’’), 34.4 (C-3’), 35.4 (C-1’), 38.5 (C-3), 47.2 (C-6), 48.9 (C-2), 62.4 (CH_2OH), 114.5, 114.6 (CH_2=), 138.3, 138.7 (CH=), 172.8 (NCO).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6
5
4
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2
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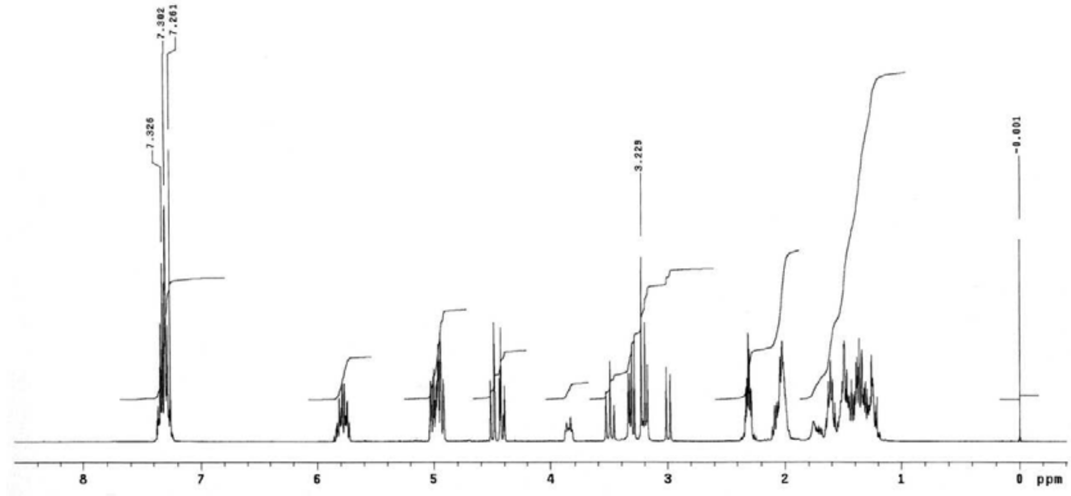
ppm

Protection step: A solution of the above alcohol (198 mg, 0.67 mmol) in anhydrous DMF (6 mL) was added under inert atmosphere to a suspension of NaH (131 mg of a 60% dispersion in mineral oil, 2.02 mmol) in DMF (19 mL). The resulting mixture was stirred at 0 °C for 1 h, and then benzyl bromide (390 µL, 3.37 mmol) and tetrabutylammonium iodide (51 mg, 0.13 mmol) were added. The resulting white suspension was stirred at room temperature for 4 h. The reaction was quenched with saturated NH_4Cl solution, and the resulting mixture was extracted with Et_2O and CH_2Cl_2. The combined organic extracts were dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure. Flash chromatography (98:2 to 7:3 hexane-EtOAc) gave compound **69** (205 mg, 80%) as a colourless oil.

^{1}H NMR (400 MHz, $CDCl_3$, COSY, gHSQC): δ 1.21-1.52 (m, 10H, 2H-2', 2H-4'', 2H-4, 2H-1', 2H-5), 1.60 (m, 2H, H-3''), 1.98-2.10 (m, 4H, 2H-3', 2H-5''), 2.30 (m, 2H, H-2''), 2.98 (d, *J* = 13.2 Hz, H-2), 3.19 (s, 1H, CH_2OH), 3.23 (s, 1H, CH_2OH), 3.20 (d, *J* = 13.2 Hz, H-6), 3.29 (d, *J* = 13.2 Hz, 1H, H-6), 3.21 (d, *J* = 13.2 Hz, 1H, H-2), 3.51, 3.48 (d, *J* = 13.2 Hz, 1H, H-2), 3.84 (dt, *J* = 13.2, 4.8 Hz, 1H, H-6), 4.41 (d, *J* = 12.0 Hz, 1H, CH_2 Bn), 4.50 (d, *J* = 12.0 Hz, 1H, CH_2 Bn), 4.91-5.03 (m, 4H, CH_2=), 5.73-5.84 (m, 2H, CH=), 7.26-7.33 (m, 5H, H-*o*, *m*, *p* C_6H_5).

^{13}C NMR (100.6 MHz, $CDCl_3$): δ 20.9-22.4 (C-2', C-5), 24.7, 24.9 (C-3''), 28.7 (C-4''), 30.8, 30.9 (C-4), 33.3, 33.6 (C-2''), 33.4-34.4 (C-5'', C-3', C-1'), 37.6, 37.8 (C-3), 42.2, 46.4 (C-6), 48.3, 52.6 (C-2), 71.8, 72.9 (CH_2OBn), 73.2 (CH_2 Bn), 114.4, 114.6 (CH_2=), 127.4, 128.3 (C-*o*, *m*, *p* C_6H_5), 138.5, 138.8 (C-*i* C_6H_5), 138.6 (CH=), 170.0, 172.1 (NCO).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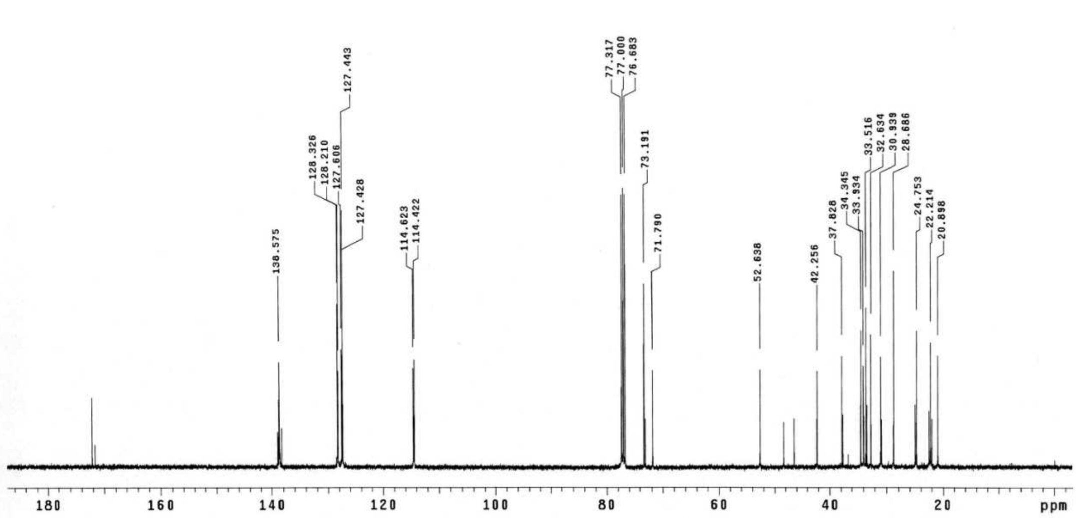
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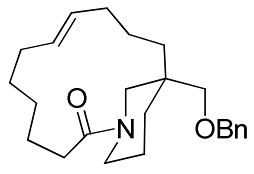


13-(Benzyloxymethyl)-2-oxo-1-azabicyclo[11.3.1]heptadec-8-ene (73).

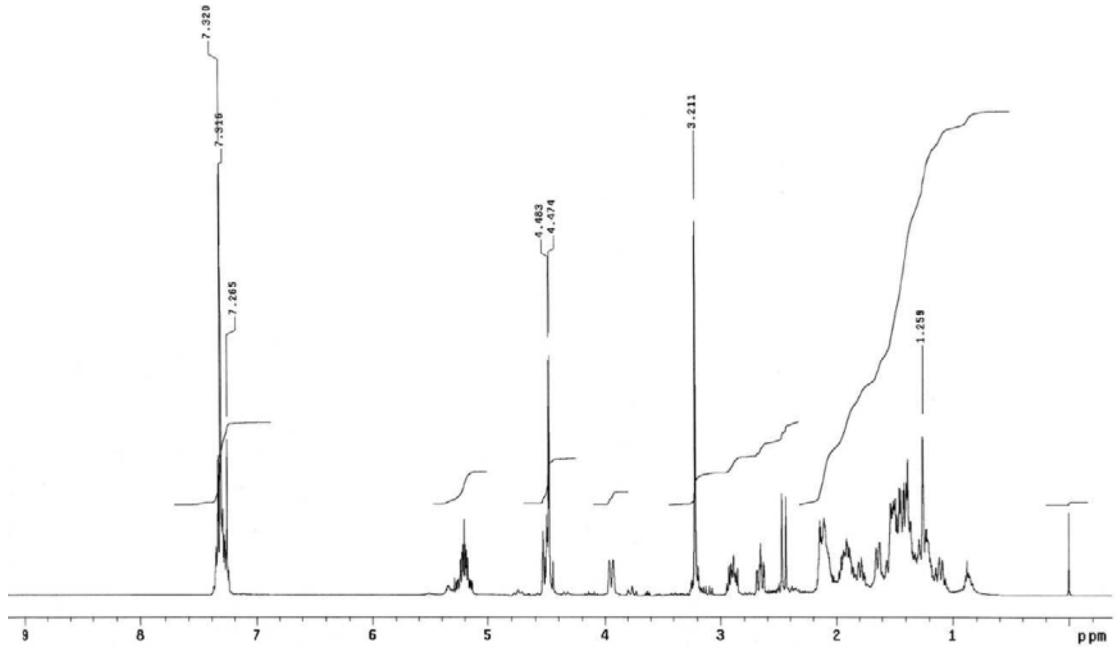
A solution of diene **70** (158 mg, 0.396 mmol) in CH_2Cl_2 (10 mL) was slowly added via a syringe pump (2 h) to a solution of Grubbs second generation catalyst (68 mg, 0.08 mmol) in refluxing CH_2Cl_2 (80 mL). The resulting mixture was heated at reflux for 4 h and concentrated under reduced pressure. Flash chromatography (alumina, 95:5 to 3:7 hexane-EtOAc) afforded macrocyclic compound **73** (115 mg, 84%). Only traces of the *Z* isomer were detected.

E isomer:

^{1}H NMR (400 MHz, $CDCl_3$, COSY, gHSQC): δ 1.08-1.52 (m, 9H, 2H-15, H-14, CH_2), 1.64 (d, *J* = 12.8 Hz, 1H, H-14), 1.78 (m, 1H, CH_2), 1.91 (m, 2H, H-7, H-10), 2.11 (m, 3H, H-7, H-10, H-3), 2.45 (d, *J* = 12.8 Hz, 1H, H-17), 2.66 (t, *J* = 11.2 Hz, 1H, H-3), 2.89 (m, 1H, H-16), 3.21 (s, 2H, CH_2OBn), 3.94 (d, *J* = 12.8 Hz, H-16), 4.45 (d, *J* = 12.4 Hz, 1H, CH_2 Bn), 4.49 (d, *J* = 12.4 Hz, 1H, CH_2 Bn), 4.51 (d, *J* = 12.8 Hz, 1H, H-17), 5.17 (ddd, *J* = 15.2, 7.6, 4.4 Hz, 1H, CH=), 5.24 (ddd, *J* = 15.2, 7.2, 4.8 Hz, 1H, CH=), 7.32 (m, 5H, H-*o*, *m*, *p* C_6H_5).

^{13}C NMR (100.6 MHz, $CDCl_3$): δ 21.6, 21.6 (C-15, CH_2), 25.7, 26.6, 28.1, 28.7 (CH_2), 29.8 (C-14), 31.2, 32.2 (C-7, C-10), 32.0 (C-3), 37.8 (C-13), 47.0 (C-16), 48.7 (C-17), 73.2 (CH_2 Bn), 76.2 (CH_2OBn), 127.3, 128.2 (C-*o*, *m* C_6H_5), 127.4 (C-*p* C_6H_5), 131.6, 131.8 (CH=), 138.6 (C-*i* C_6H_5), 172.2 (NCO).

HRMS (ESI) calcd for $[C_{24}H_{35}NO_2 + H]^+$: 370.2741, found: 370.2741.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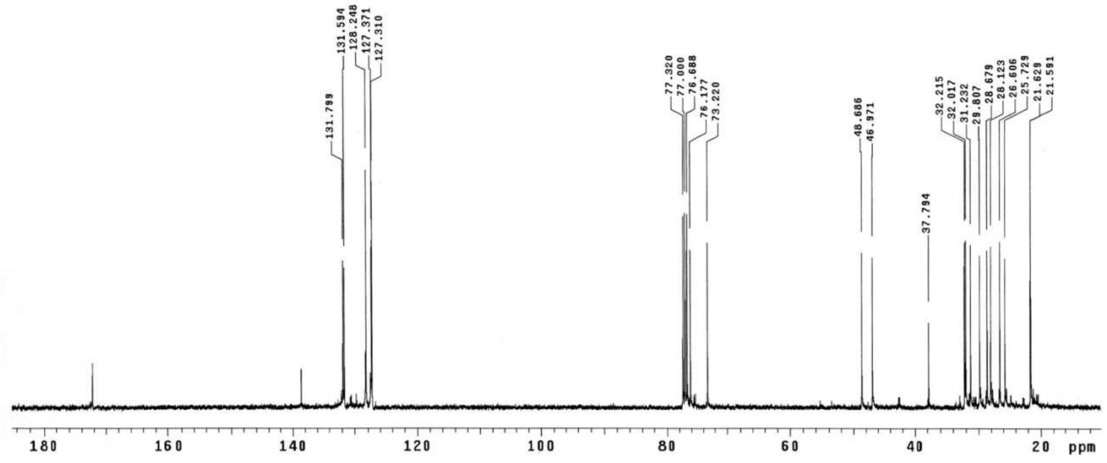
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32.215
32.017
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29.807
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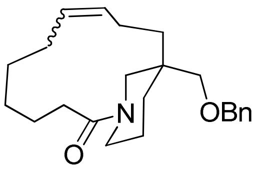


13-(Benzyloxymethyl)-2-oxo-1-azabicyclo[10.3.1]hexadec-8-ene (71).

A solution of diene **68** (216 mg, 0.456 mmol) in CH_2Cl_2 (20 mL) was slowly added via a syringe pump (4 h) to a solution of Grubbs second generation catalyst (77 mg, 0.09 mmol) in refluxing CH_2Cl_2 (60 mL). The resulting mixture was heated at reflux for 8 h and concentrated under reduced pressure. Flash chromatography (alumina, 95:5 to 1:1 hexane-EtOAc) afforded macrocyclic compound **71** (86 mg, 53%) as an inseparable 2:1 mixture of *E*/*Z* isomers and a dimer (40 mg, 25%).

E isomer of compound **71** (spectral data from a 2:1 *E*/*Z* mixture of isomers):

^{1}H NMR (400 MHz, $CDCl_3$, COSY, gHSQC): δ 1.30-2.15 (m, 14H, CH_2), 2.45 (d, *J* = 13.2 Hz, 1H, H-16), 2.58 (m, 2H, H-3), 2.94 (td, *J* = 13.2, 2.8 Hz, 1H, H-15), 3.22 (d, *J* = 8.8 Hz, 1H, CH_2 Bn), 3.28 (d, *J* = 8.8 Hz, 1H, CH_2 Bn), 3.89 (dm, *J* = 13.2 Hz, 1H, H-15), 4.49 (s, 2H, CH_2OBn), 4.53 (d, *J* = 13.2 Hz, 1H, H-16), 5.30 (ddd, *J* = 15.2, 7.2, 3.2 Hz, 1H, CH=), 5.36 (m, 1H, CH=), 7.32 (m, 5H, H-*o*, *m*, *p* C_6H_5).

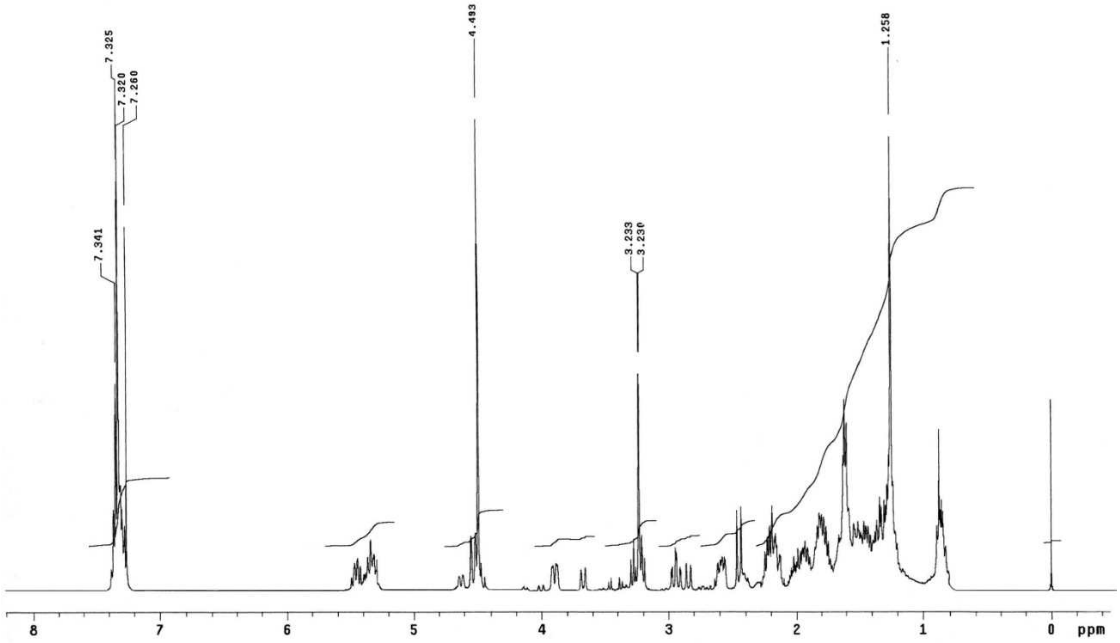
^{13}C NMR (100.6 MHz, $CDCl_3$): δ 21.3 (C-14), 22.0-35.0 (CH_2), 32.8 (C-3), 38.6 (C-12), 46.4 (C-16), 47.8 (C-15), 73.2 (CH_2OBn), 76.3 (CH_2 Bn), 127.3-128.3 (C-*o*, *m*, *p* C_6H_5), 130.0, 130.9 (CH=), 138.5 (C-*i* C_6H_5), 171.7 (C=O).

Z isomer of compound **71** (spectral data from a 2:1 *E*/*Z* mixture of isomers):

^{1}H NMR (400 MHz, $CDCl_3$, COSY, gHSQC): δ 1.30-2.15 (m, 14H, CH_2), 2.40 (dm, *J* = 11.6 Hz, 1H, H-16), 2.58 (m, 2H, H-3), 2.84 (d, *J* = 13.2 Hz, 1H, H-15), 3.20 (d, *J* = 9.2 Hz, 1H, CH_2 Bn), 3.24 (d, *J* = 9.2 Hz, 1H, CH_2 Bn), 3.67 (d, *J* = 13.2 Hz, 1H, H-15), 4.49 (s, 2H, CH_2OBn), 4.62 (dm, *J* = 11.6 Hz, 1H, H-16), 5.36 (m, 1H, CH=), 5.44 (tm, *J* = 9.2 Hz, 1H, CH=), 7.32 (m, 5H, H-*o*, *m*, *p* C_6H_5).

^{13}C NMR (100.6 MHz, $CDCl_3$): δ 20.3 (C-14), 22.2-35.0 (CH_2), 32.8 (C-3), 37.7 (C-12), 42.2 (C-16), 49.1 (C-15), 73.4 (CH_2OBn), 75.7 (CH_2 Bn), 127.3-128.3 (C-*o*, *m*, *p* C_6H_5), 131.8, 132.9 (CH=), 138.3 (C-*i* C_6H_5), 172.2 (C=O).

HRMS (ESI) calcd for $[C_{23}H_{33}NO_2 + H]^+$: 356.2589, found: 356.2589.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0
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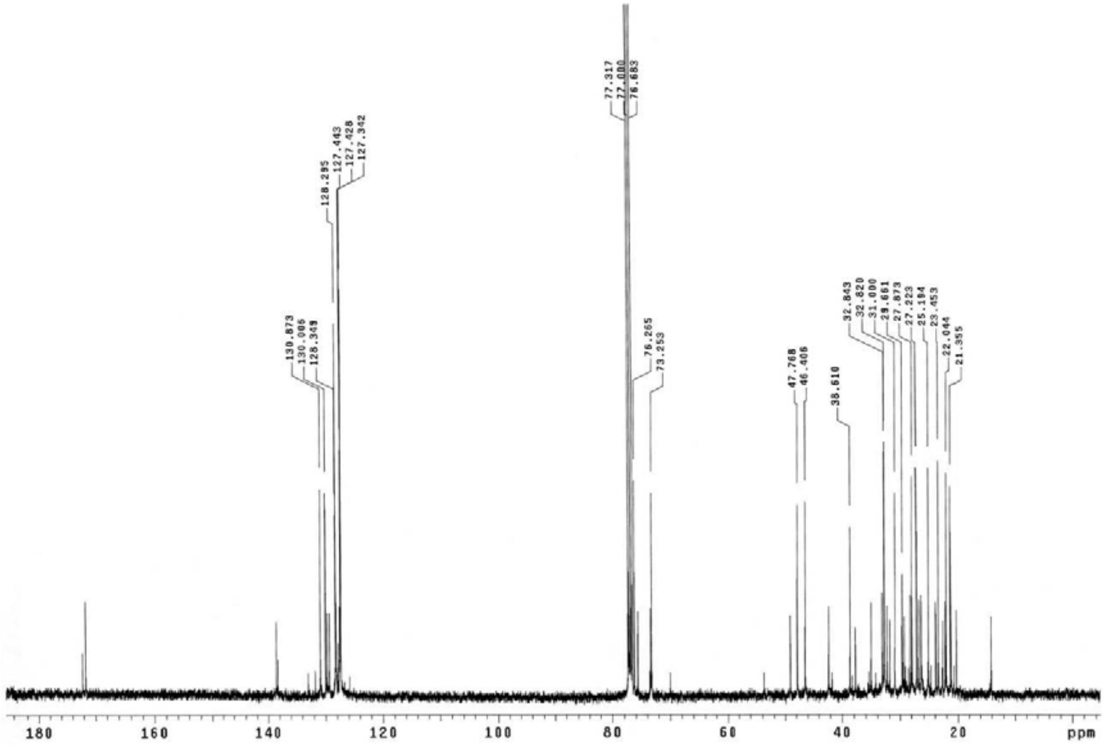
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32.820
31.000
29.661
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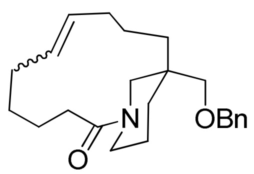


13-(Benzyloxymethyl)-2-oxo-1-azabicyclo[10.3.1]hexadec-8-ene (72).

A solution of diene **69** (71 mg, 0.18 mmol) in CH_2Cl_2 (10 mL) was slowly added via a syringe pump (4 h) to a solution of Grubbs second generation catalyst (31 mg, 0.036 mmol) in refluxing CH_2Cl_2 (35 mL). The resulting mixture was heated at reflux for 6 h and concentrated under reduced pressure. Flash chromatography (alumina, 95:5 to 1:1 hexane-EtOAc) afforded macrocyclic compound **72** (24 mg, 38%) as an inseparable 2:1 mixture of *E*/*Z* isomers.

E isomer of compound **72** (spectral data from a 2:1 *E*/*Z* mixture of isomers):

^{1}H NMR (400 MHz, $CDCl_3$, COSY, gHSQC): δ 1.35-2.35 (m, 14H, CH_2), 2.39 (d, *J* = 13.2 Hz, 1H, H-16), 2.75 (m, 2H, H-3), 2.89 (t, *J* = 12.4 Hz, 1H, H-15), 3.17 (d, *J* = 8.8 Hz, 1H, CH_2 Bn), 3.23 (d, *J* = 8.8 Hz, 1H, CH_2 Bn), 3.76 (dm, *J* = 12.4 Hz, 1H, H-15), 4.34 (d, *J* = 13.2 Hz, 1H, H-16), 4.48 (s, 2H, CH_2OBn), 5.17 (dd, *J* = 15.2, 7.2 Hz, 1H, CH=), 5.25 (m, 1H, CH=), 7.32 (m, 5H, H-*o*, *m*, *p* C_6H_5).

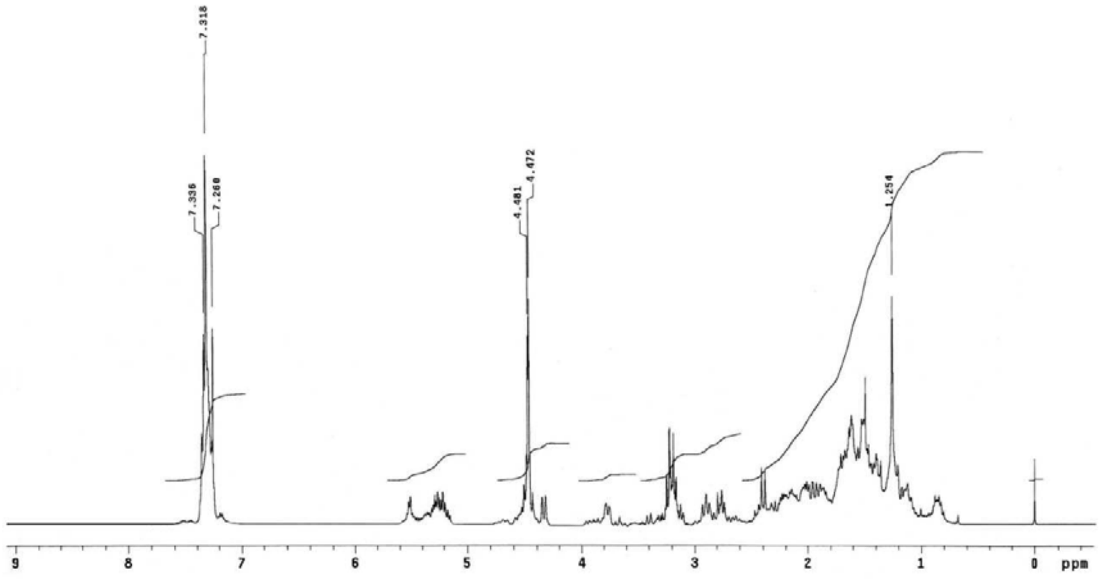
^{13}C NMR (100.6 MHz, $CDCl_3$): δ 20.9 (C-14), 21.4-32.0 (CH_2), 33.5 (C-3), 38.0 (C-12), 46.8 (C-16), 47.6 (C-15), 73.2 (CH_2OBn), 76.4 (CH_2 Bn), 127.3-128.3 (C-*o*, *m*, *p* C_6H_5), 130.5, 132.5 (CH=), 138.6 (C-*i* C_6H_5), 173.0 (C=O).

Z isomer of compound **72** (spectral data from a 2:1 *E*/*Z* mixture of isomers):

^{1}H NMR (400 MHz, $CDCl_3$, COSY, gHSQC): δ 1.35-2.35 (m, 14H, CH_2), 2.39 (d, *J* = 13.2 Hz, 1H, H-16), 2.75 (m, 2H, H-3), 2.76 (masked 1H, H-15), 3.10-3.25 (m, 2H, CH_2 Bn), 3.40 (dm, *J* = 13.6 Hz, 1H, H-15), 4.47 (masked, 1H, H-16), 4.47 (s, 2H, CH_2OBn), 5.35, 5.50 (2m, 2H, CH=), 7.32 (m, 5H, ArH).

^{13}C NMR (100.6 MHz, $CDCl_3$): δ 20.9 (C-14), 21.5-33.6 (CH_2), 33.8 (C-3), 37.8 (C-12), 42.4 (C-16), 48.9 (C-15), 73.3 (CH_2OBn), 76.2 (CH_2 Bn), 127.3-128.3 (C-*o*, *m*, *p*), 130.8, 134.1 (CH=), 138.2 (C-*i*), 172.2 (C=O).

HRMS (ESI) calcd for $[C_{23}H_{33}NO_2 + H]^+$: 356.2589, found: 356.2582.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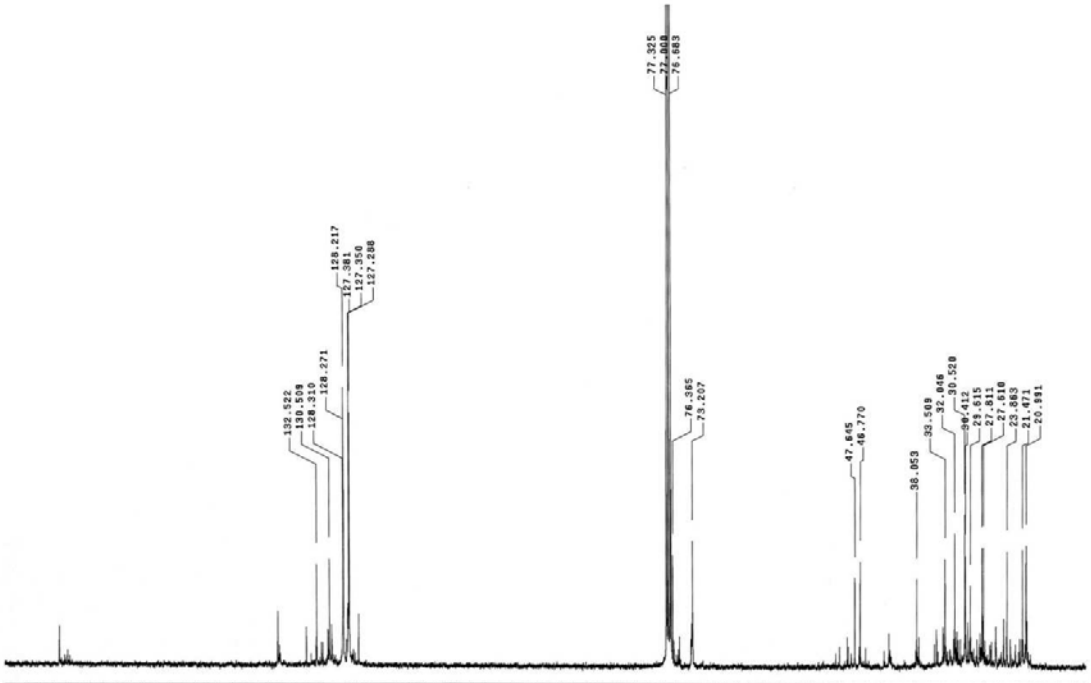
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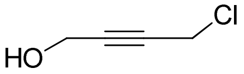


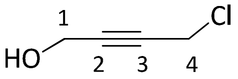
4-Chloro-2-butynol (83).

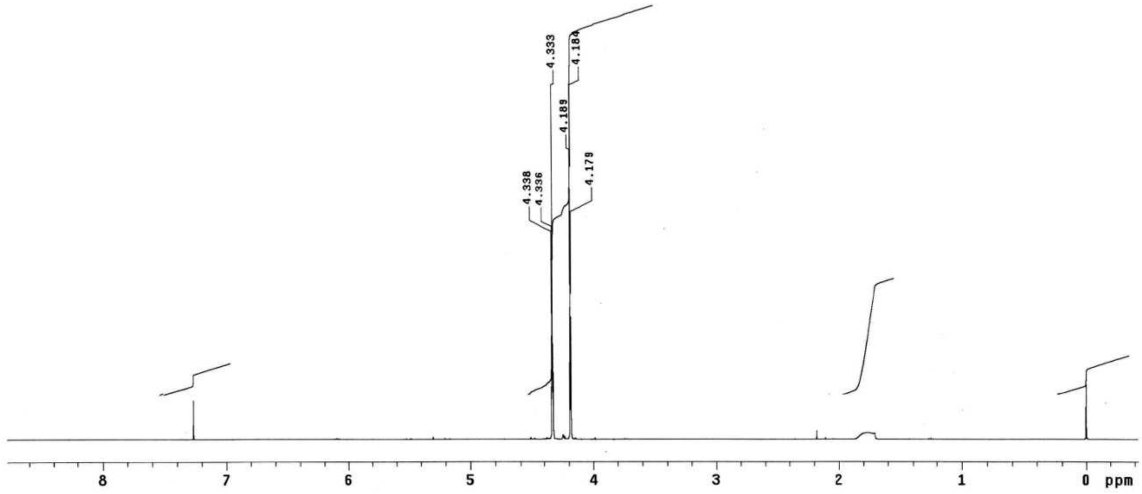
Thionyl chloride (9.3 mL, 24.3 mol) was added dropwise over a period of 6 h to a stirred solution of 2-butyn-1,4-diol (10 g, 11.6 mol) and pyridine (9.35 mL, 12.7 mol) in benzene (12 mL) while the temperature was maintained between 10 to 20 °C. The reaction mixture was then stirred overnight at room temperature. The mixture was poured into ice water and the benzene layer was separated. The aqueous phase was extracted with ether and the combined organic extracts were washed with saturated $NaHCO_3$, followed by water and brine, dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. Distillation (55 °C/0 tor) provided cloro derivative **83** (4.73 mg, 40%) as colorless oil.

IR (film): 3332 (OH) cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$, COSY, gHSQC): δ 2.80 (br. s, 1H, OH), 4.18 (t, J = 2.0 Hz, 2H, H-4), 4.33 (t, J = 2.0 Hz, 2H, H-1).

^{13}C NMR (100.6 MHz, $CDCl_3$): δ 30.3 (C-4), 51.0 (C-1), 80.5, 84.6 (C-2, C-3).

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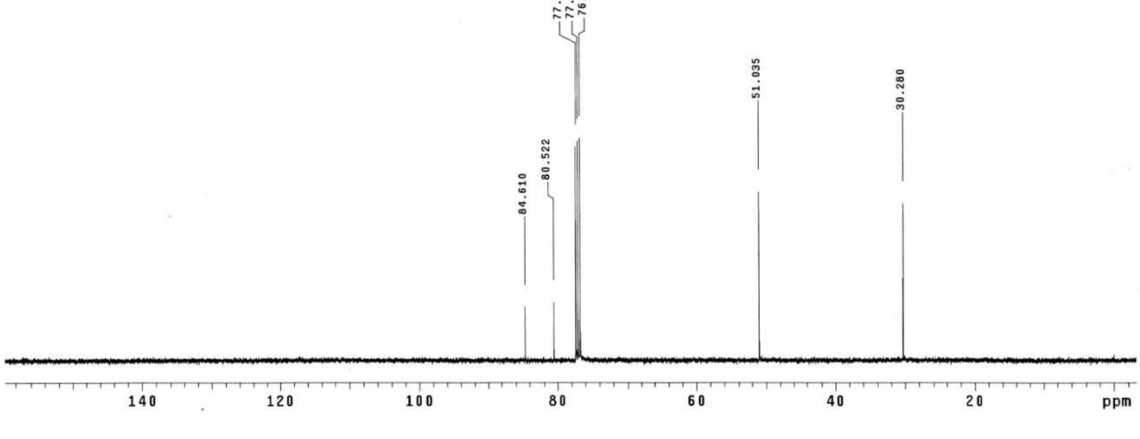
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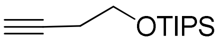
ppm

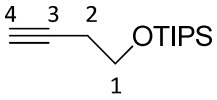


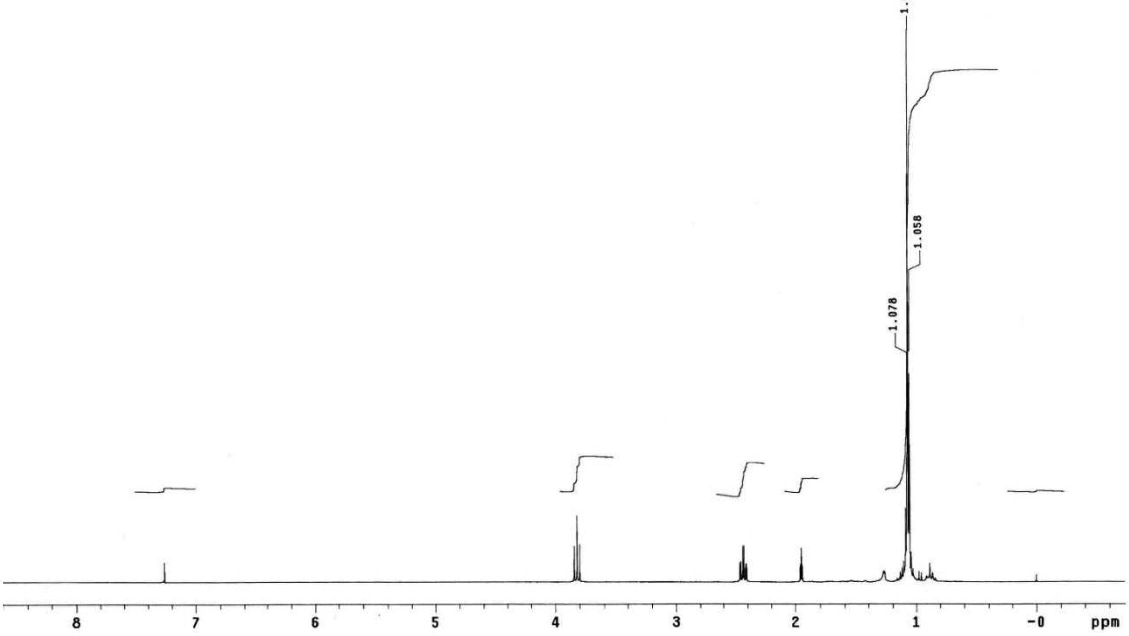
(Triisopropylsilyloxy)-3-butynol (88).

TipsCl (11 mL, 51.5 mmol) was added to a stirred solution of imidazole (3.98 g, 58.4 mmol) and of **3-butynol** (2.6 mL, 34.3 mmol) in CH_2Cl_2 (16 mL) and DMF (8 mL) at 0 ^{o}C, then the mixture was stirred for 4 h at room temperature. The reaction was quenched by addition of saturated NH_4Cl and was extracted with CH_2Cl_2. The combined organic extracts were dried over $MgSO_4$, filtered and concentrated under reduced pressure. Flash chromatography (hexane) gave silyl derivative **88** as colorless oil (7.012 g, 90%).

^{1}H NMR (400 MHz, $CDCl_3$): δ 1.07 [2S, 21H, C*H*(C*H*$_3$)$_2$], 1.95 (t, *J* = 2.4 Hz, 1H, H-4), 2.44 (td, *J* = 7.2, 2.4 Hz, 2H, H-2), 3.82 (t, *J* = 7.2 Hz, 2H, H-1).

^{13}C NMR (100.6 MHz, $CDCl_3$): δ 11.9 [*C*H(CH$_3$)$_2$], 17.9 [CH(*C*H$_3$)$_2$], 22.9 (C-2), 62.0 (C-1), 69.2 (C-4), 81.5 (C-3).

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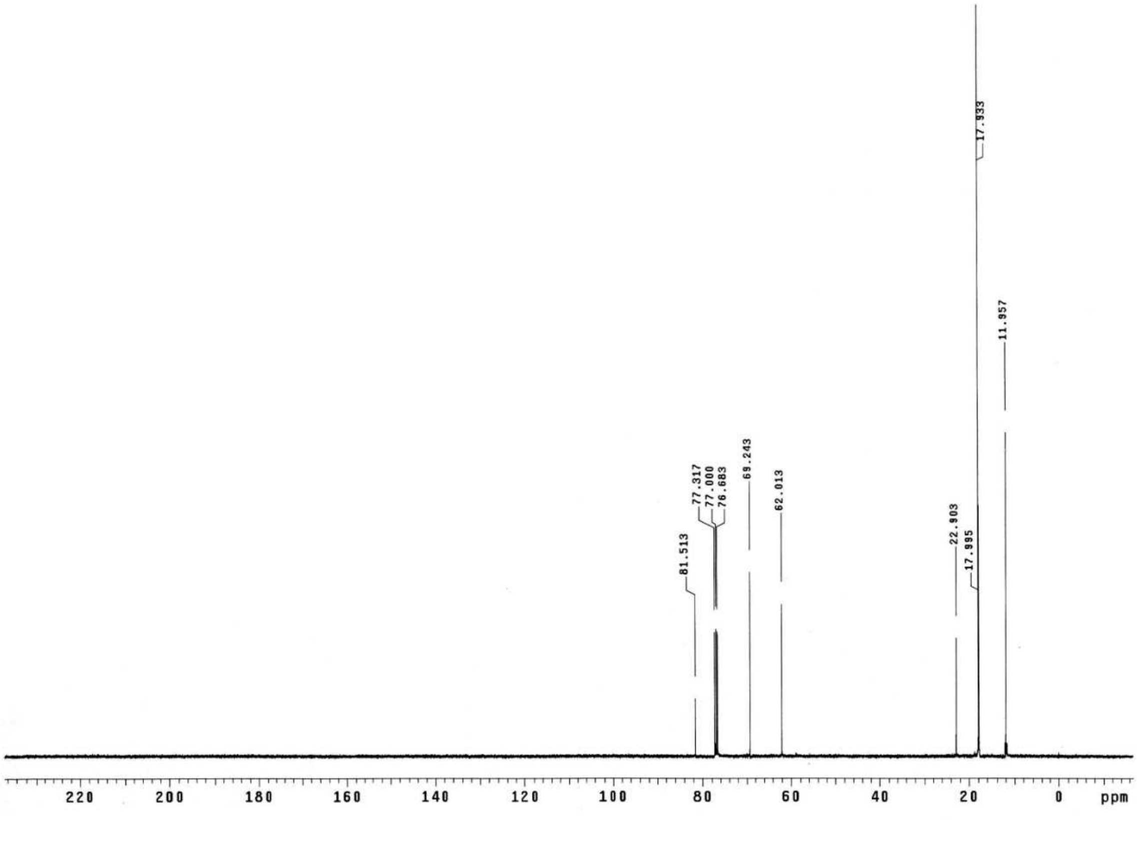
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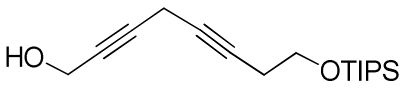


8-[(Triisopropylsilyl)oxy]-2,5-octadiynol (89).

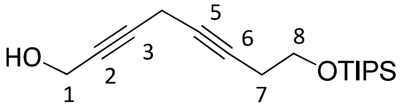
4-Chloro-2-butyn-1-ol (4.05 g, 38.78 mmol) and **1-(triisopropylsilyloxy)-3-butyne** (11.4 g, 50.5 mmol) were added under inert atmosphere to a suspension of CuI (15.17 g, 77.56 mmol), NaI (11.63 g, 77.56 mmol), and K_2CO_3 (8.04 g, 58.17 mmol) in anhydrous DMF (77 mL). The mixture was stirred overnight at room temperature. Saturated aqueous NH_4Cl and EtOAc were added, and the resulting mixture was filtered through a Celite® pad. The two phases were separated, and the aqueous layer was extracted with ether. The combined organic extracts were washed with brine, dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. Flash chromatography (hexane to 8:2 hexane-EtOAc) gave **89** (8.95 g, 78%) as a pale yellow oil.

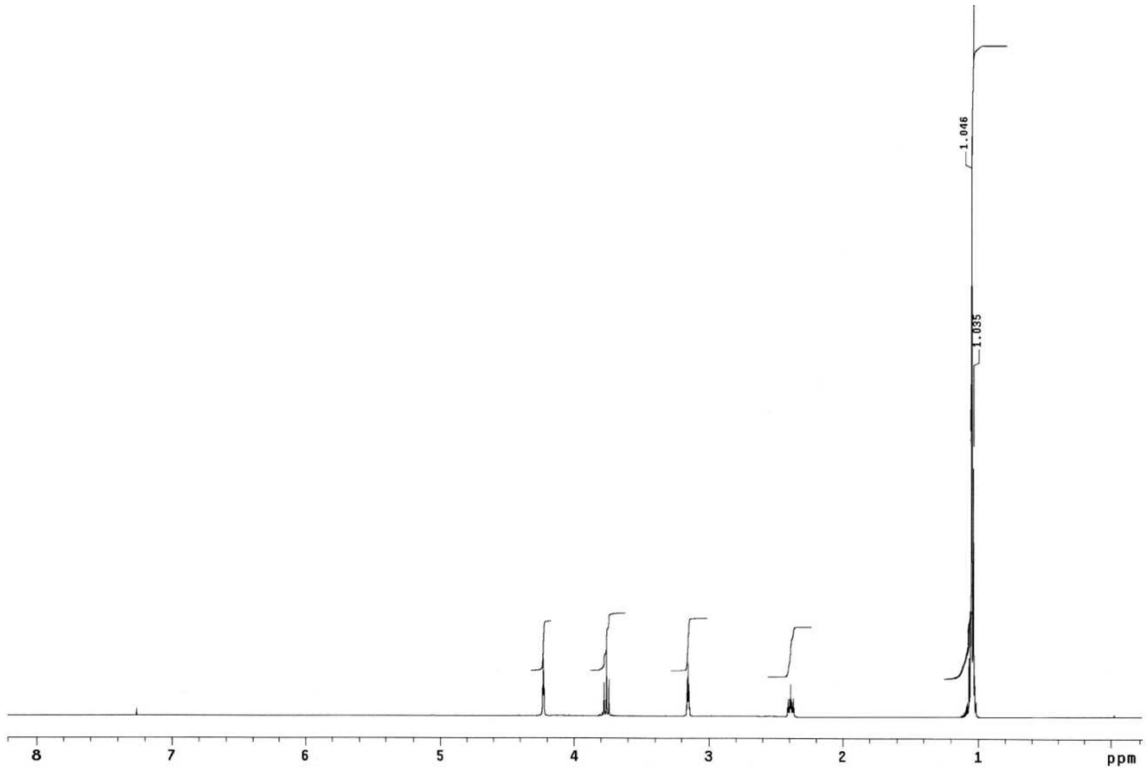
IR (film): 3332 (OH) cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$, COSY, gHSQC): δ 1.03, 1.04 [2S, 21H, C*H*(C*H*$_3$)$_2$], 2.39 (tt, *J* = 7.6, 2.4 Hz, 2H, H-7), 3.15 (m, 2H, H-4), 3.76 (t, *J* = 7.6 Hz, 2H, H-8), 4.23 (t, *J* = 2.4 Hz, 2H, H-1).

^{13}C NMR (100.6 MHz, $CDCl_3$): δ 9.5 (C-4), 11.9 [*C*H(CH$_3$)$_2$], 17.9 [CH(*C*H$_3$)$_2$], 23.1 (C-7), 51.1 (C-1), 62.1 (C-8), 74.5 (C-5), 77.9 (C-3), 78.5 (C-2), 80.3 (C-6).

HRMS calcd for [$C_{17}H_{30}O_2Si$ + H]$^+$: 295.2088, found: 295.2090.

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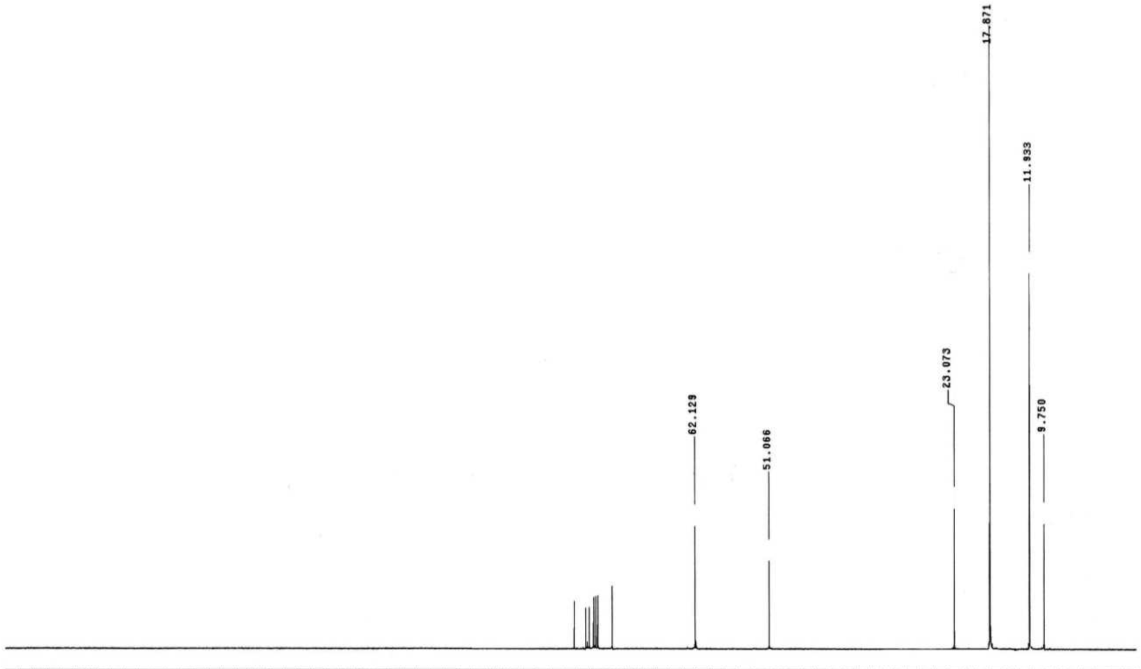
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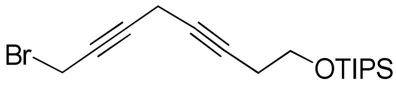


8-Bromo-1-[(triisopropylsilyl)oxy]-3,6-octadiyn (90).

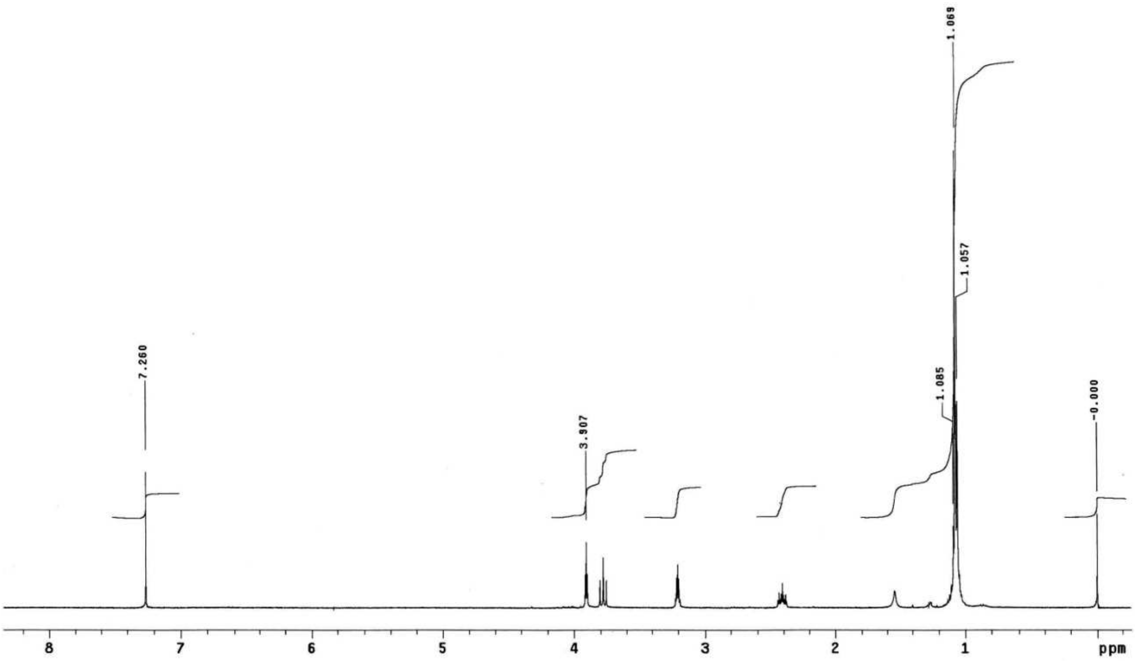
First step: Triethylamine (610 µL, 4.38 mmol) and mesyl chloride (454 µL, 5.84 mmol) were added dropwise to a solution of alcohol **89** (860 mg, 2.92 mmol) in anhydrous CH_2Cl_2 (50 mL) cooled to 0 °C. After the end of addition, the mixture was stirred at 0 °C for 15 min, thus was stirred for additional 1.5 h keeping the temperature between 10 and 20 °C. Saturated aqueous NH_4Cl was added, and the mixture was extracted with CH_2Cl_2. The combined organic layers were washed with water, dried over anhydrous Na_2SO_4, filtered, and the solvent was removed under reduced pressure to afford compound **90**, which was used in the next step without purification.

Second step: A solution of LiBr (2.5 g, 29.2 mmol) in THF (20 mL) was added to a solution of mesyl derivative (2.92 mmol) in CH_2Cl_2 (15 mL) at 0 °C under inert atmosphere. The resulting mixture was stirred at room temperature for 1h. Distilled water was added, and the mixture was extracted with CH_2Cl_2. The combined organic layers were dried over anhydrous Na_2SO_4, filtered, and the solvent was removed under reduced pressure. Flash chromatography (hexane to 3:7 hexane-EtOAc) afforded bromo derivative **90** (760 mg, 73% yield).

^{1}H NMR (400 MHz, $CDCl_3$): δ 1.05, 1.06 [2S, 21H, $CH(CH_3)_2$], 2.41 (m, *J* = 6.8, 2.4 Hz, 2H, H-2), 3.20 (t, *J* = 2.4 Hz, 2H, H-5), 3.78 (t, *J* = 7.2 Hz, 2H, H-1), 3.90 (t, *J* = 2.4 Hz, 2H, H-8).

^{13}C NMR (100.6 MHz, $CDCl_3$): δ 10.1 (C-5), 12.0 [$\mathit{C}H(CH_3)_2$], 14.7 (C-8), 17.9 [$CH(\mathit{C}H_3)_2$], 23.1 (C-2), 62.1 (C-1), 74.0 (C-4), 75.3 (C-6), 78.3 (C-7), 81.8 (C-3).

HRMS calcd for $[C_{17}H_{29}BrOSi + H]^+$: 357.1244, found: 357.1232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2
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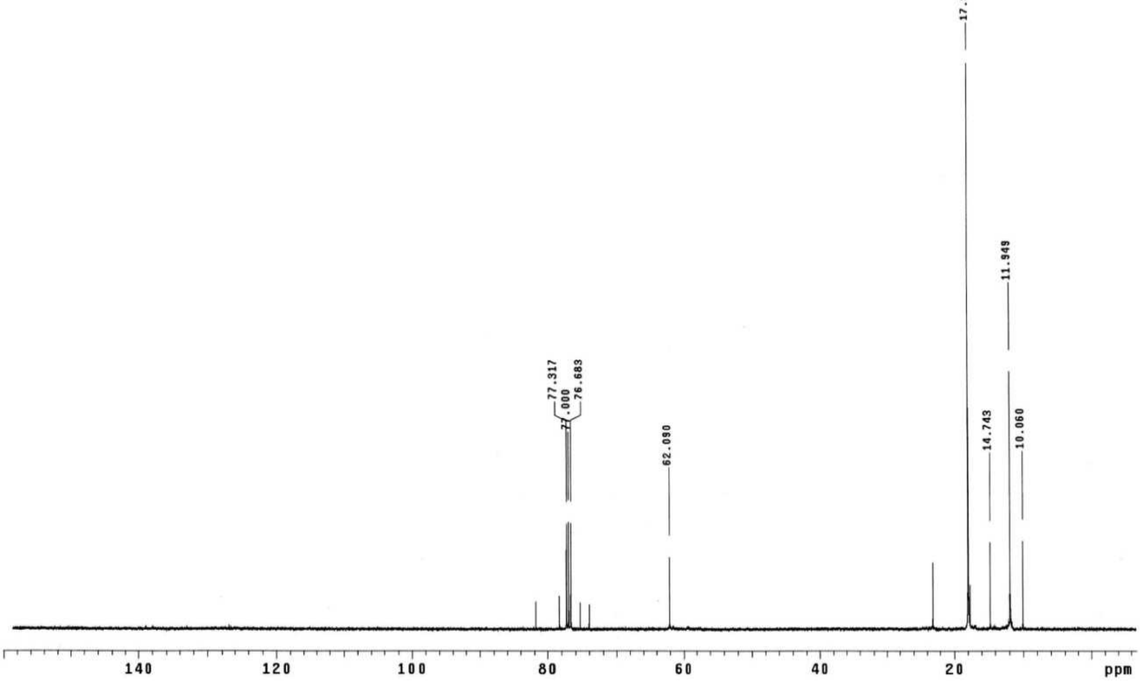
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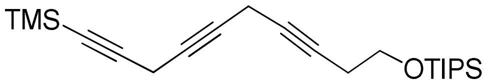


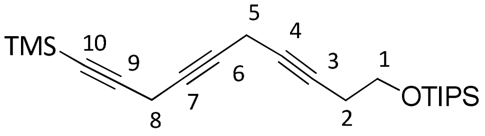
10-(Trimethylsilyl)-1-[(triisopropylsilyl)oxy]-3,6,9-octatriyn (85).

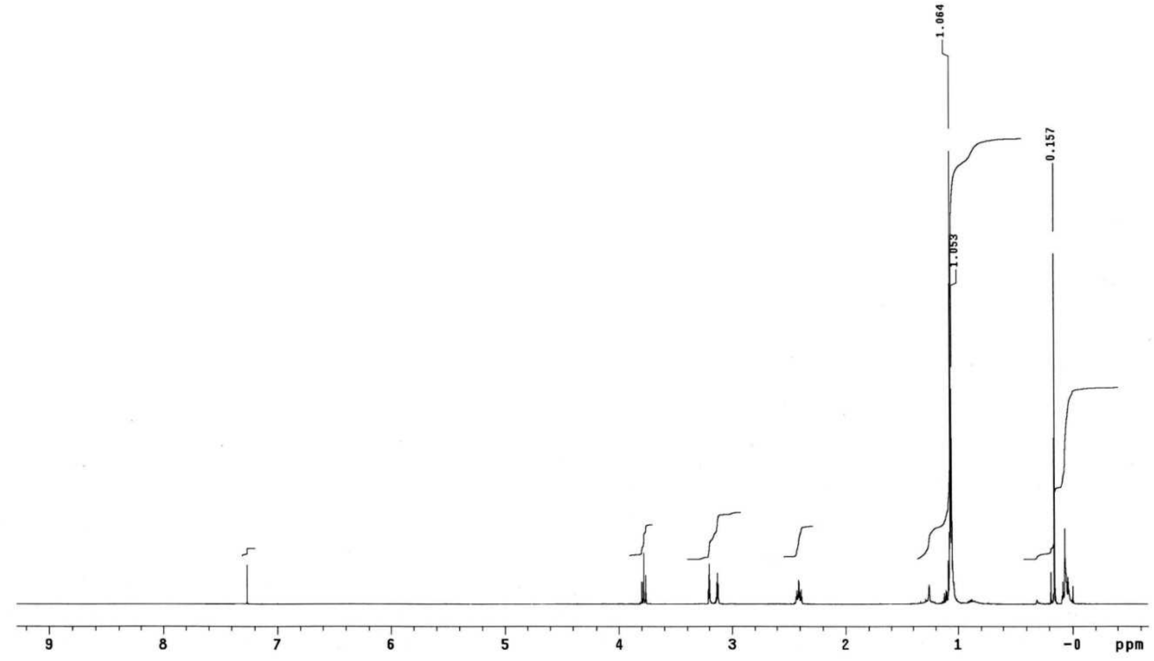
Bromo derivative **90** (760 mg, 2.13 mmol) and ethynyltrimethylsilane (349 µL, 2.04 mmol) were added to a suspension of CuI (816 mg, 4.26 mmol), NaI (638 mg, 4.26 mmol), and K_2CO_3 (441 mg, 3.10 mmol) in of anhydrous DMF (8 mL) under inert atmosphere. The mixture was stirred overnight at room temperature. Saturated aqueous NH_4Cl and EtOAc were then added and the mixture was filtered through a celite pad. The aqueous layer of the filtered mixture was extracted with ether (3 x 20 mL) and the combined organic layers were washed with brine, dried over anhydrous Na_2SO_4, filtered and concentrated under vacuum. Flash chromatography (hexane to 97:3 hexane-EtOAc) gave trialkinyl derivative **85** (685 mg, 86%) as colorless oil.

^{1}H NMR (400 MHz, $CDCl_3$, COSY, gHSQC): δ 0.06, 0.16 [2s, 9H, $(CH_3)_3Si$], 1.05, 1.06 [2s, 21H, $(CH_3)_2CH$)], 2.41 (tt, *J* = 7.2, 2.4 Hz, 2H, H-2), 3.13 (q, *J* = 2.4 Hz, 2H, H-5), 3.20 (t, *J* = 2.4 Hz, 2H, H-8), 3.78 (t, *J* = 7.2 Hz, 2H, H-1).

^{13}C NMR (100.6 MHz, $CDCl_3$): δ -0.1, 1.01 [$(CH_3)_3Si$], 9.8 (C-5), 10.9 (C-8), 12.0 [$(CH_3)_2CH$)], 17.9 [$(CH_3)_2CH$)], 23.1 (C-2), 62.2 (C-1), 73.8, 74.9, 75.1 (C-4, C-6, C-7), 77.7 (C-3), 85.1 (C-9), 99.9 (C-10).

HRMS calcd for $[C_{22}H_{38}OSi_2 + H]^+$: 375.2534, found: 375.2524.

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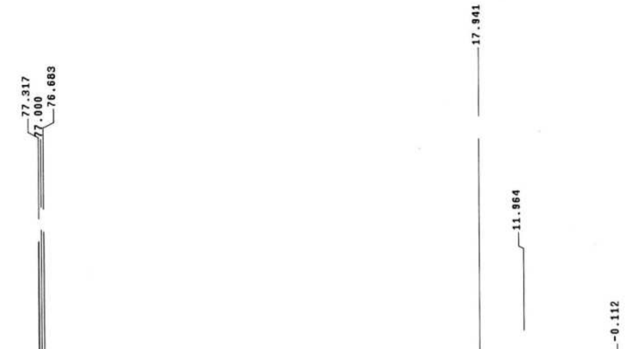
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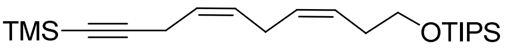


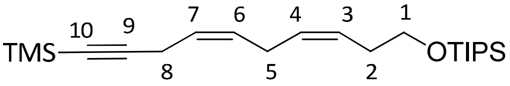
(3*Z*,6*Z*)-10-(Trimethylsilyl)-1-[(triisopropylsilyl)oxy]-3,6-octadien-9-yn (86).

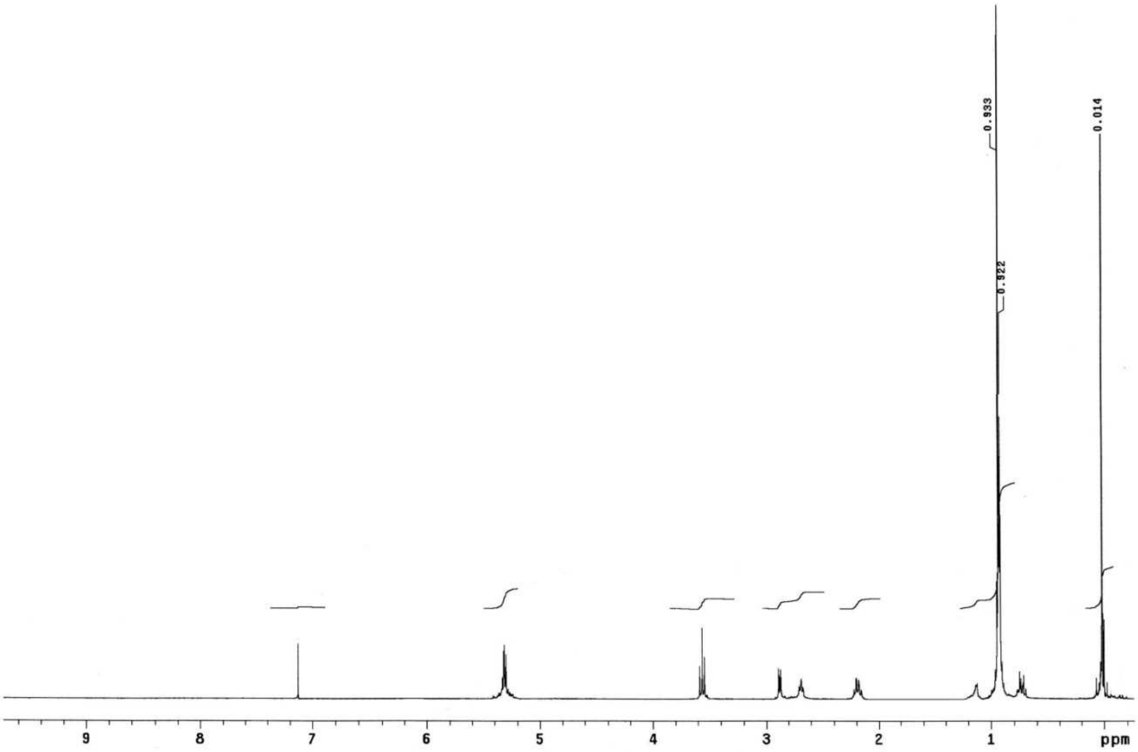
A 1 M solution of $NaBH_4$ in ethanol (730 µL, 0.73 mmol) was added to a stirred suspension of $Ni(OAc)_2\cdot 4H_2O$ (180 mg, 0.73 mmol) in ethanol (12 mL) under an H_2 atmosphere. After the black suspension was stirred for 30 min, ethylenediamine (97 µL, 1.45 mmol) was added followed by a solution of trialkinyl **85** (544 mg, 1.45 mmol) in ethanol (1 mL). The reaction flask was purged three times with H_2 and the reaction mixture was stirred under H_2 atmosphere for 1 h and 45 min. The resulting mixture was filtered through a pad of silica gel with ether. The filtrate was concentrated and the residue was chromatographed to give diene **86** (411 mg, 75% yield) as a colorless oil.

^{1}H NMR (400 MHz, $CDCl_3$, gHSQC): δ 0.01 [s, 9H, $(CH_3)_3Si$], 0.92, 0.93 [2s, 21H, $(CH_3)_2CH$)], 2.19 (q, J = 6.9 Hz, 2H, H-2), 2.68 (t, J = 7.2 Hz, 2H, H-5), 2.87 (dd, J = 4.5, 0.6 Hz, 2H, H-8), 3.78 (t, J = 6.9 Hz, 2H, H-1).

^{13}C NMR (100.6 MHz, $CDCl_3$): δ 0.07 [$(CH_3)_3Si$], 12.0 [$(CH_3)_2CH$)], 18.0 [$(CH_3)_2CH$)], 18.4 (C-8), 25.7 (C-5), 31.3 (C-2), 63.0 (C-1), 84.2 (C-9), 105.3 (C-10), 124.3, 126.8, 128.7, 129.9 (4CH=).

HRMS calcd for $[C_{22}H_{42}OSi_2 + H]^+$: 379.2846, found: 379.2848.

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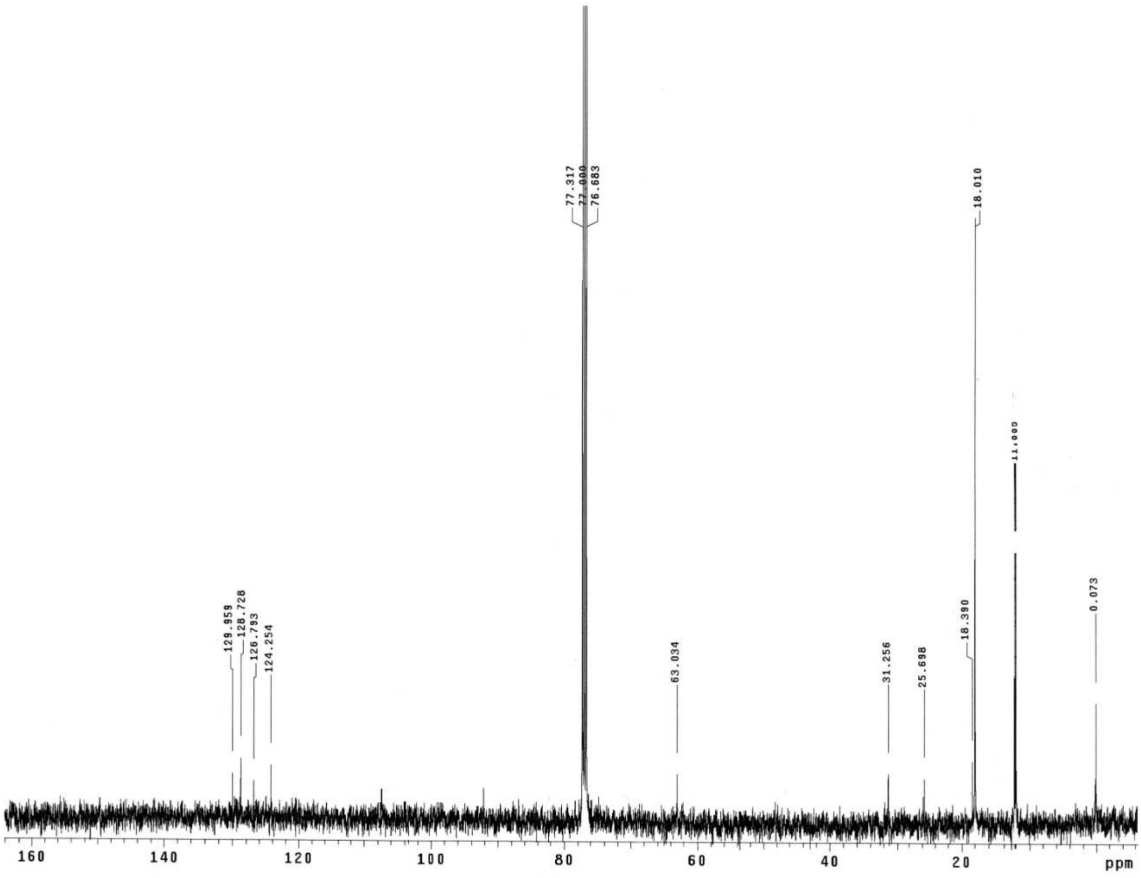
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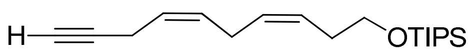
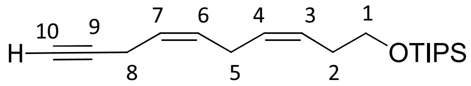


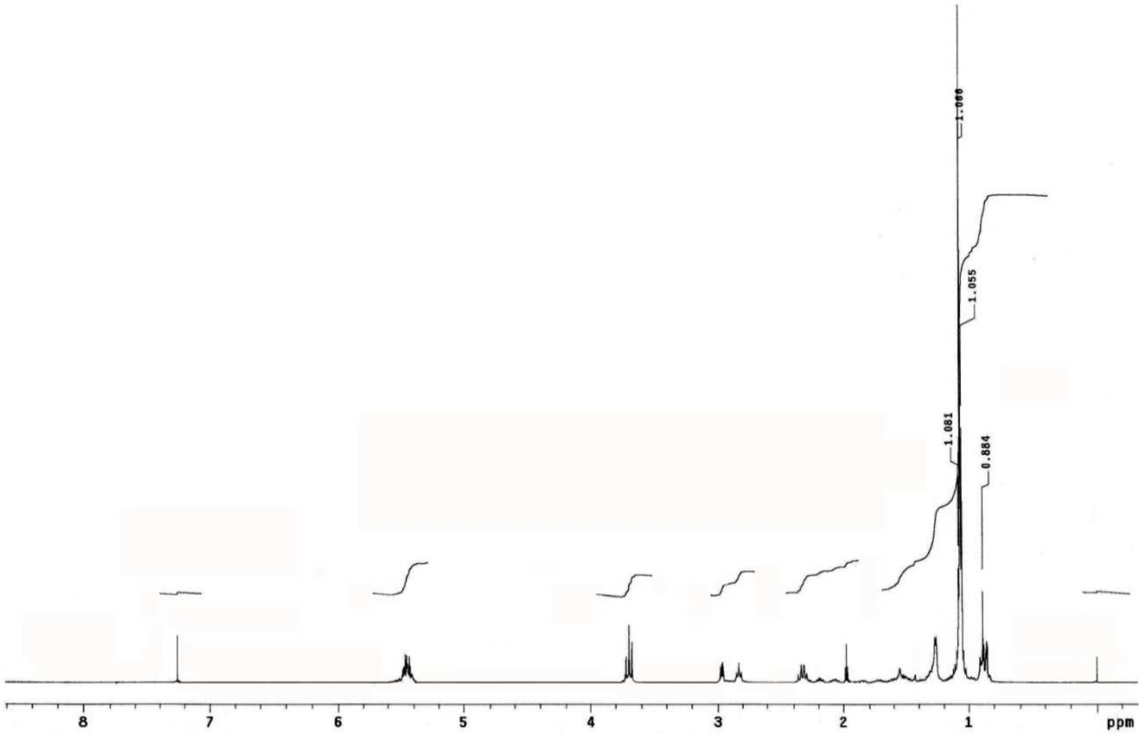
(3*Z*,6*Z*)-1-[(Triisopropylsilyl)oxy]-3,6-octadien-9-yn (79).

K_2CO_3 (80 mg, 0.579 mmol) was added to a stirred solution of diene **86** (146 mg, 0.386 mmol) in anhydrous methanol (2 mL) at 0° C. The reaction was stirred at room temperature for one hour and then methanol was removed under reduced pressure. EtOAc and saturated aqueous NH_4Cl were added and the aqueous layer was extracted with EtOAc. The combined organic extracts were dried over Na_2SO_4, and the solvent was concentrated under reduced pressure. Flash chromatography (hexane) afforded the unstable alkyne derivate **79** (110 mg, 74% yield).

^{1}H NMR (300 MHz, $CDCl_3$): δ 0.92, 0.93 [2s, 21H, (CH_3)$_2$C*H*)], 1.95 (m, 1H, H-10), 2.25 (q, *J* = 6.9 Hz, 2H, H-2), 2.80 (t, *J* = 7.2 Hz, 2H, H-5), 2.97 (dd, *J* = 4.5, 0.6 Hz, 2H, H-8), 3.65 (t, *J* = 6.9 Hz, 2H, H-1), 5.35-5.45 (m, 4H, CH=).

^{13}C NMR (100.6 MHz, $CDCl_3$): δ 12.0 [(CH_3)$_2$*C*H)], 18.0 [(*C*H$_3$)$_2$CH)], 22.6 (C-8), 25.5 (C-5), 31.6 (C-2), 63.0 (C-1), 68.1 (C-10), 82.3 (C-9), 123.9, 126.9, 128.6, 132.0 (4CH=).

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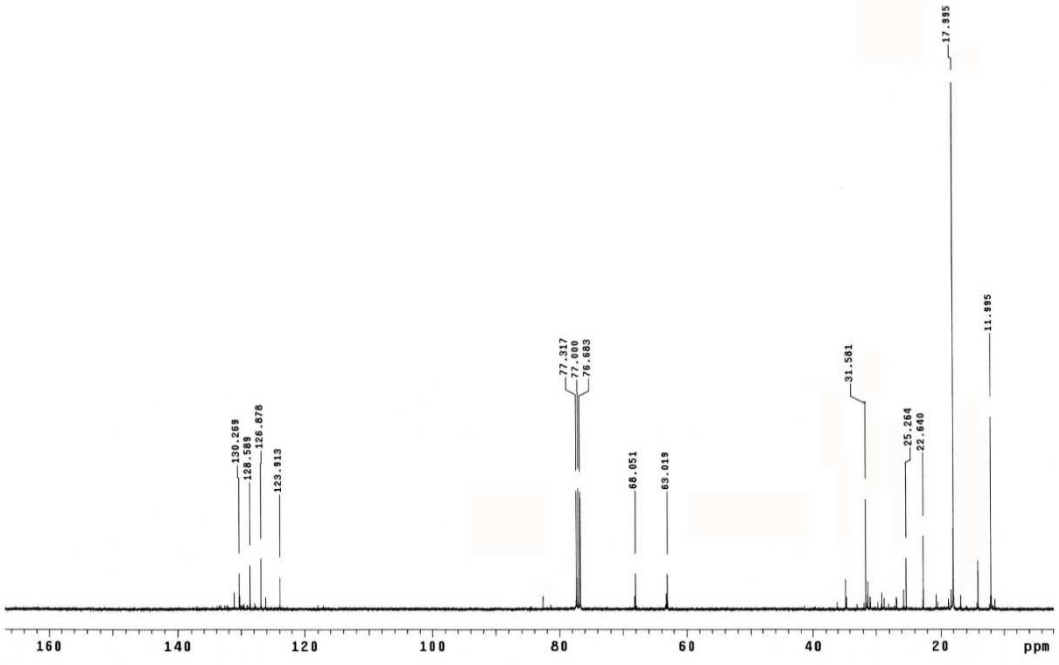
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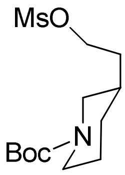


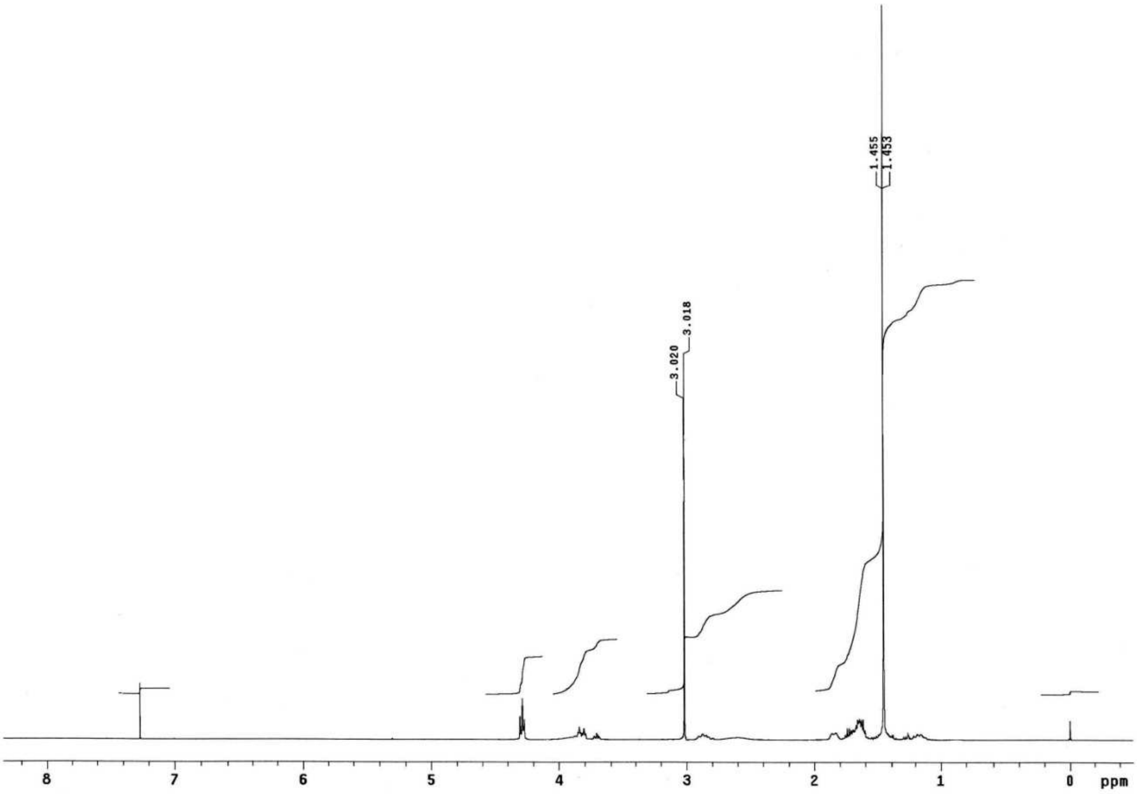
N-(*tert*-Butoxycarbonyl)-3-[(methansulfonyloxy)ethyl]piperidine (92).

Triethylamine (156 µL, 1.12 mmol) and mesyl chloride (116 µL, 1.49 mmol) were added dropwise to a cooled (0 °C) solution of commercial available ***N*-(*tert*-butoxycarbonyl)-3-(2-hydroxyethyl)piperidine** (171 mg, 0.746 mmol) in anhydrous CH_2Cl_2 (10 mL). After the end of addition, the mixture was stirred at 10 °C for 15 min, thus was allowed to heat slowly to room temperature and was stirred for additional 1.5 h. Saturated aqueous NH_4Cl was added, and the mixture was extracted with CH_2Cl_2. The combined organic extracts were dried over anhydrous Na_2SO_4, filtered, and the solvent was removed under reduced pressure. Flash chromatography (9:1 to 7:3 hexane-EtOAc) afforded methansulfonyl derivative **92** (160 mg, 71%).

^{1}H NMR (400 MHz, $CDCl_3$, COSY, gHSQC): δ 1.14 (m, 1H, H-4), 1.42 [s, 10H, $(CH_3)_3C$, H-5], 1.61 (m, 3H, H-5, H-3, H-1’), 1.69 (m, 1H, H-1’), 1.81 (dm, *J* = 12.8 Hz, 1H, H-4), 2.60, 2.83 (br. s, 2H, H-1ax, H-6ax), 3.02 (s, 3H, CH_3S), 3.67, 3.80 (2m, 2H, H-1eq, H-6eq), 4.28 (t, *J* = 6.8 Hz, 2H, H-2’).

^{13}C NMR (100.6 MHz, $CDCl_3$): δ 24.0 (C-5), 28.4 [$(\mathit{C}H_3)_3C$], 30.4 (C-4), 31.0 (C-3), 32.2 (C-1’), 37.4 (CH_3S), 44.5, 49.1 (C-1, C-6), 67.6 (C-2’), 79.5 [$(CH_3)_3\mathit{C}$], 154.7 (NCOO).

HRMS calcd for $[C_{13}H_{25}NO_5S + H]^+$: 308.1526, found: 308.1526.



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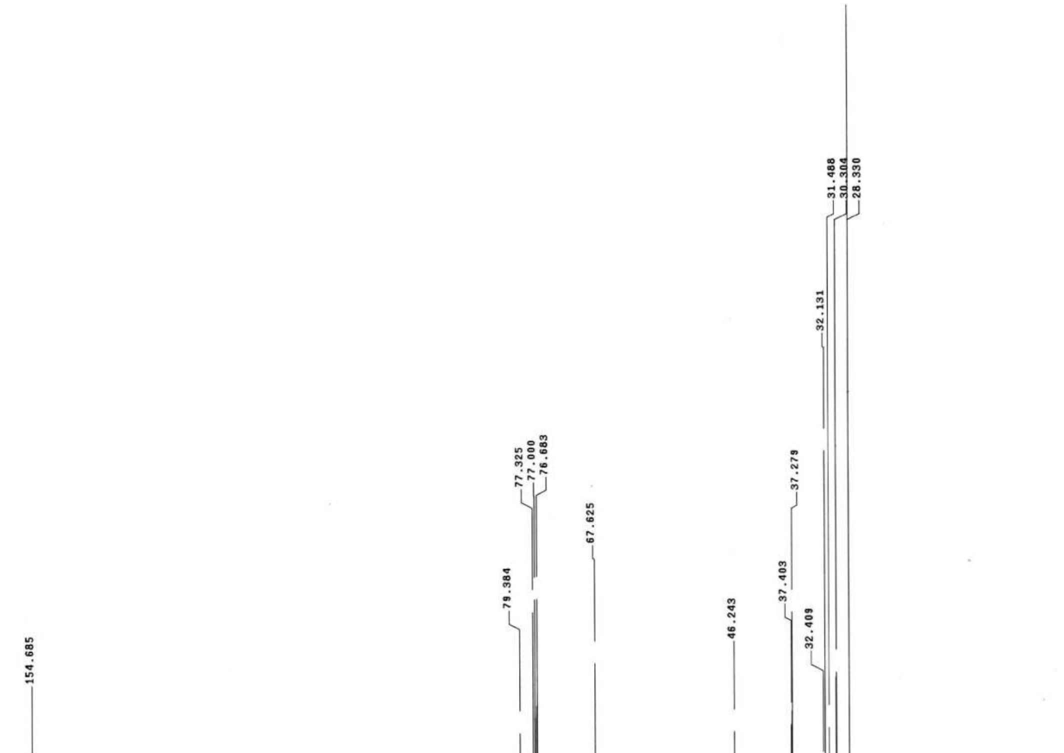

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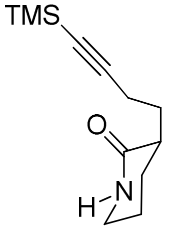


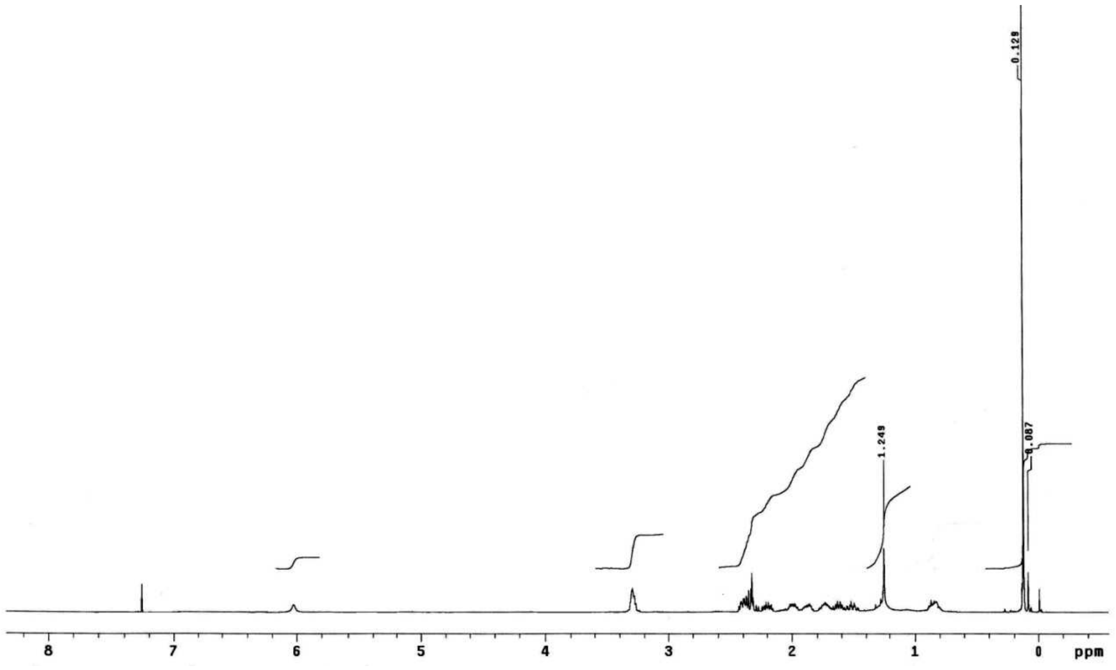
3-[4-(Trimethylsilyl)-3-butynyl]-2-piperidinone (96).

n-BuLi (9.39 mL of a 1.6 M solution in hexane, 15.0 mmol) was added to a stirring solution of *δ*-valerolactam (1.49 g, 15.0 mmol) in anhydrous THF (38 mL) previously cooled at –78 °C. The resulting mixture was stirred for 30 minutes, and then TMSCl (1.91 mL, 15.0 mmol) was added while the solution was allowed to warm to room temperature. LDA (8.27 mL of a 2 M solution in THF, 16.54 mmol) was then added at –78 °C to the above mixture, which was then again allowed to warm to room temperature. After stirring at room temperature for 30 minutes, a solution of **4-iodo-1-(trimethylsilyl)-1-butyne** in THF (10 mL) was added dropwise at 0 °C, and the resulting dark solution was stirred at this temperature for 1 h, and for 3 h at room temperature. The reaction was quenched with saturated aqueous NH_4Cl, and the mixture was extracted with EtOAc. The combined organic extracts were dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure. Flash chromatography (9:1 to 4:6 hexane-EtOAc) afforded piperidone **96** (1.67 g, 50%) as a colourless oil.

^{1}H NMR (400 MHz, $CDCl_3$, COSY, gHSQC): *δ* 0.13 [s, 9H, $(CH_3)_3Si$], 1.51 (dddd, *J* = 13.2, 10.0, 10.0, 2.8 Hz, 1H, H-4), 1.62 (dddd, *J* = 13.6, 8.4, 8.4, 2.8 Hz, 1H, H-1’), 1.73 (m, 1H, H-5), 1.87 (m, 1H, H-5), 1.99 (m, 1H, H-4), 2.19 (m, 1H, H-1’), 2.32-2.43 (m, 3H, 2H-2’, H-3), 3.29 (m, 2H, H-6), 6.02 (br. s, 1H, NH).

^{13}C NMR (100.6 MHz, $CDCl_3$): *δ* 0.1 [$(CH_3)_3Si$], 17.7 (C-2’), 21.5 (C-5), 26.1 (C-4), 30.3 (C-1’), 40.1 (C-3), 42.4 (C-6), 85.0 (C-3’), 106.6 (C-4’), 174.5 (NCO).

HRMS (ESI) calcd for $[C_{12}H_{22}NOSi + H]^+$: 224.1465, found: 224.1465.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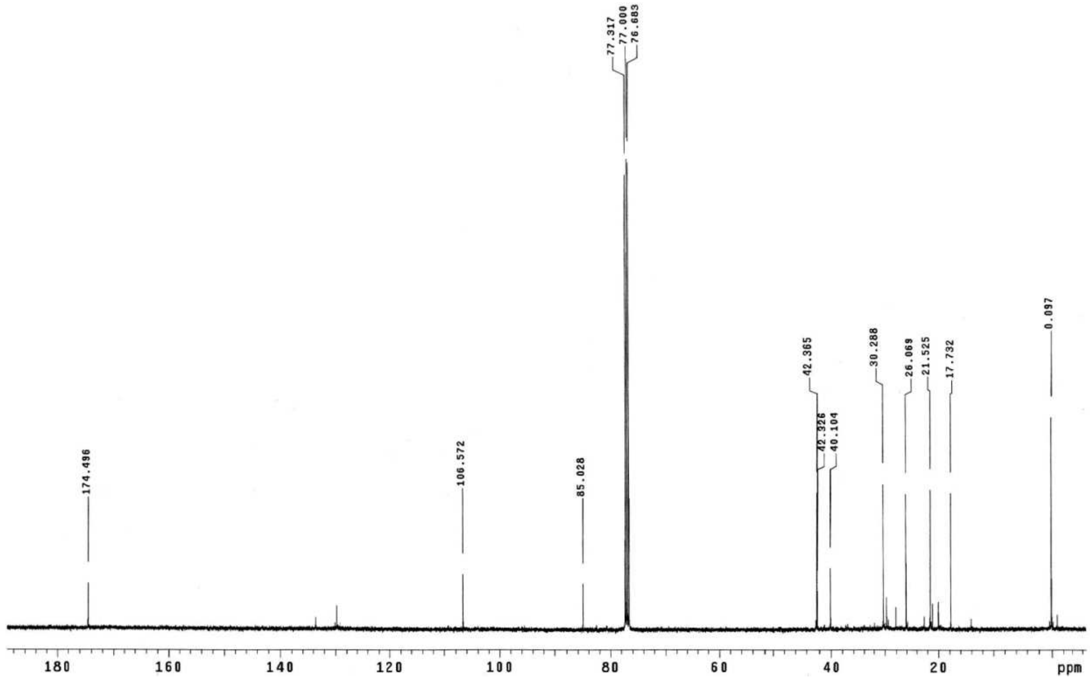
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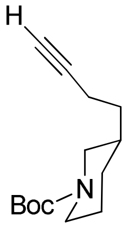


N-(*tert*-Butoxycarbonyl)-3-[4-(trimethylsilyl)-3-butynyl]piperidine (93).

Reduction step: Lithium aluminum hydride (1.53 g, 38.52 mmol) was added under argon atmosphere to a solution of the piperidone **96** (2.86 g, 12.84 mmol) in anhydrous THF (642 mL), and the mixture was stirred at room temperature for 3 h. The resulting suspension was cooled to 0 °C, and the reaction was quenched by the slow addition of water (1.53 mL) and 15% aqueous NaOH (1.53 mL). Anhydrous $MgSO_4$ was added, and the mixture was then filtered through Celite® and concentrated to give **3-[4-(trimethylsilyl)-3-butynyl]piperidine**, which was used in the next step without further purification.

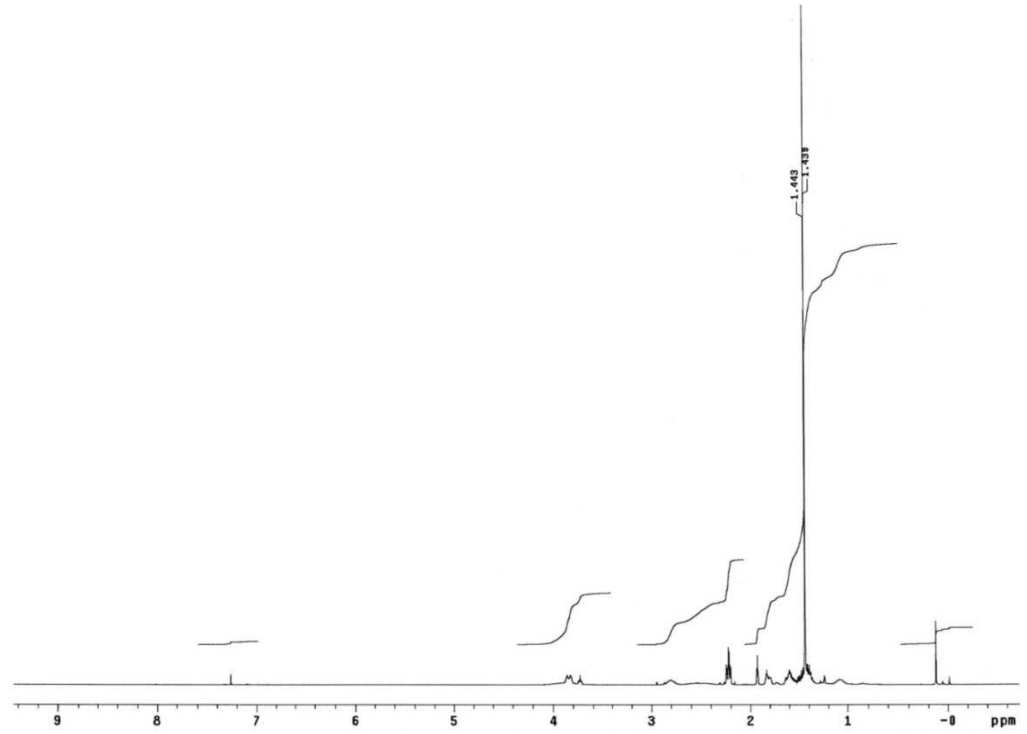
N-Boc protection step: A solution of di-*tert*-butyl dicarbonate (3.36 g, 15.39 mmol) in anhydrous CH_2Cl_2 (33 mL) was added dropwise at room temperature under inert atmosphere to a solution of the above amino derivative (12.84 mmol) in anhydrous CH_2Cl_2 (180 mL). The resulting mixture was stirred overnight, poured into water, and extracted with CH_2Cl_2. The combined organic extracts were dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. Flash chromatography (95:5 hexane-EtOAc) gave the resulting *N*-Boc piperidine derivative (2.97 g, 74%).

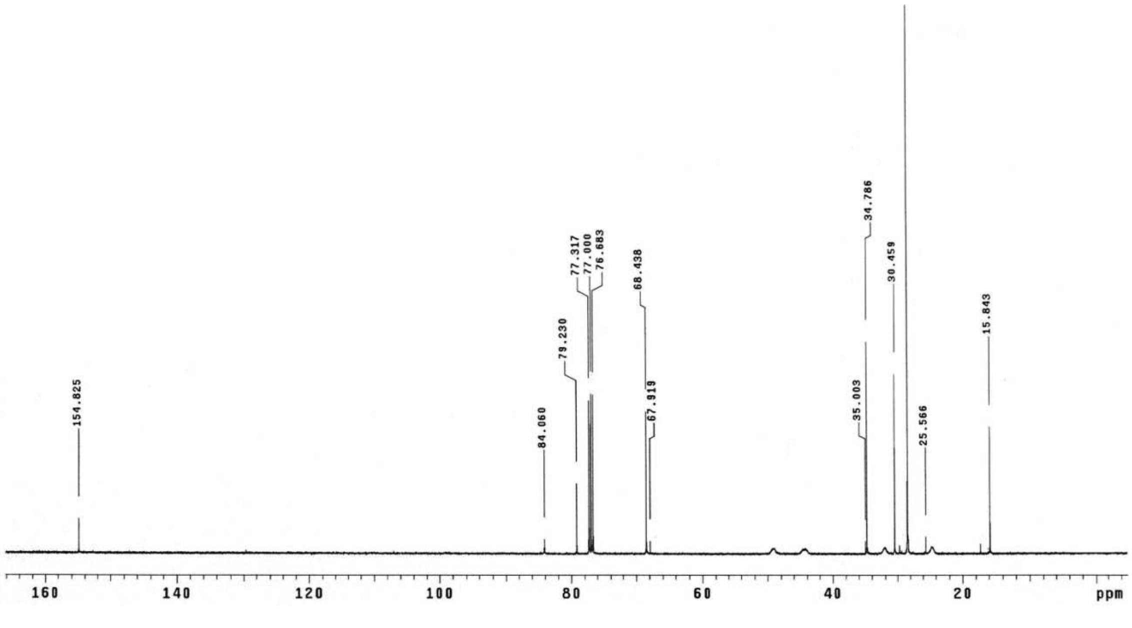
TMS deprotection step: K_2CO_3 (137 mg, 0.99 mmol) was added to a cooled (0 °C) solution of the silyl derivative (204 mg, 0.66 mmol) in anhydrous methanol (3.3 mL). The mixture was allowed to warm to room temperature, stirred overnight, and concentrated under reduced pressure. The reaction was quenched by addition of saturated aqueous NH_4Cl, and the resulting aqueous solution was extracted with EtOAc. The combined organic extracts were dried over Na_2SO_4, filtered, and concentrated under reduced pressure. Flash chromatography (95:5 hexane-EtOAc) afforded compound **93** (131 mg, 84%).

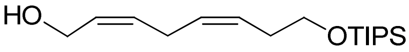
^{1}H NMR (400 MHz, $CDCl_3$, COSY, gHSQC): δ 1.07 (m, 1H, H-1’), 1.35-1.53 (m, 3H, 2H-4, H-5), 1.44 [s, 9H, $(CH_3)_3C$], 1.59 (m, 2H, H-3, H-5), 1.83 (m, 1H, H-1’), 1.93 (m, 1H, H-4’), 2.21 (t, *J* = 7.2 Hz, 2H, H-2’), 2.50, 2.80 (2br. s, 2H, H-2ax, H-6ax), 3.82, 3.85 (2br. s, H-2eq, H-6eq).

^{13}C NMR (100.6 MHz, $CDCl_3$): δ 15.8 (C-2’), 25.6 (C-5), 28.4 [$(\mathit{C}H_3)_3C$], 30.5 (C-1’), 32.3 (C-4), 34.8 (C-3), 44.4, 49.5 (C-2, C-6), 68.4 (C-4’), 79.2 [$(CH_3)_3\mathit{C}$], 84.1 (C-3’), 154.8 (NCOO).

HRMS (ESI) calcd for $[C_{14}H_{23}NO_2 + Na]^+$: 260.1621, found: 260.1621.





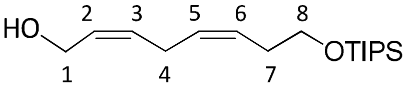


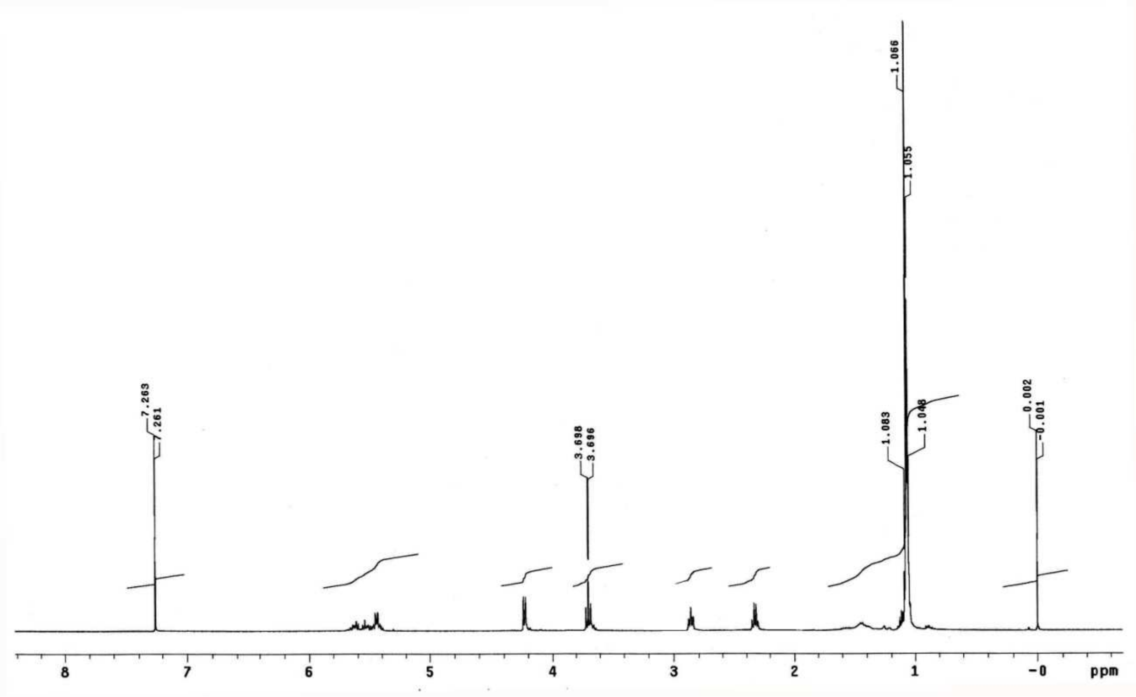
(2*Z*,5*Z*)-8-[(Triisopropylsilyl)oxy]-2,5-octadienol.

A 1 M solution of $NaBH_4$ in ethanol (3.1 mL, 3.06 mmol) was added to a stirred suspension of $Ni(OAc)_2 \cdot 4H_2O$ (760 mg, 3.06 mmol) in ethanol (165 mL) under an H_2 atmosphere. After the black suspension was stirred for 30 min, ethylenediamine (275 µL, 4.08 mmol) was added followed by a solution of compound **89** (3.0 g, 10.2 mmol) in ethanol (5 mL). The reaction flask was purged three times with H_2 and then the reaction mixture was stirred under H_2 atmosphere for 2 h with weak continuous hydrogen bubbling. The resulting mixture was filtered through a pad of silica gel with ether. The filtrate was concentrated and the residue was chromatographed (95:5 to 9:1 hexane-EtOAc) to give the corresponding diene (2.36 g, 78%) as a colorless oil.

^{1}H NMR (400 MHz, $CDCl_3$, COSY, gHSQC): δ 1.06, 1.07 [2s, 21H, $(CH_3)_2CH$)], 2.33 (m, 2H, H-7), 2.86 (t, *J* = 6.8 Hz, 2H, H-4), 3.70 (t, *J* = 6.4 Hz, 2H, H-8), 4.23 (d, *J* = 6.8 Hz, 2H, H-1), 5.40-5.49 (m, 2H, H-5, H-6), 5.54-5.61 (2m, 2H, H-2, H-3).

^{13}C NMR (100.6 MHz, $CDCl_3$): δ 12.0 [$(CH_3)_2CH$)], 18.0 [$(CH_3)_2CH$)], 25.9 (C-4), 31.2 (C-7), 58.6 (C-1), 63.0 (C-8), 127.0, 128.6, 128.8, 131.1 (4CH=).

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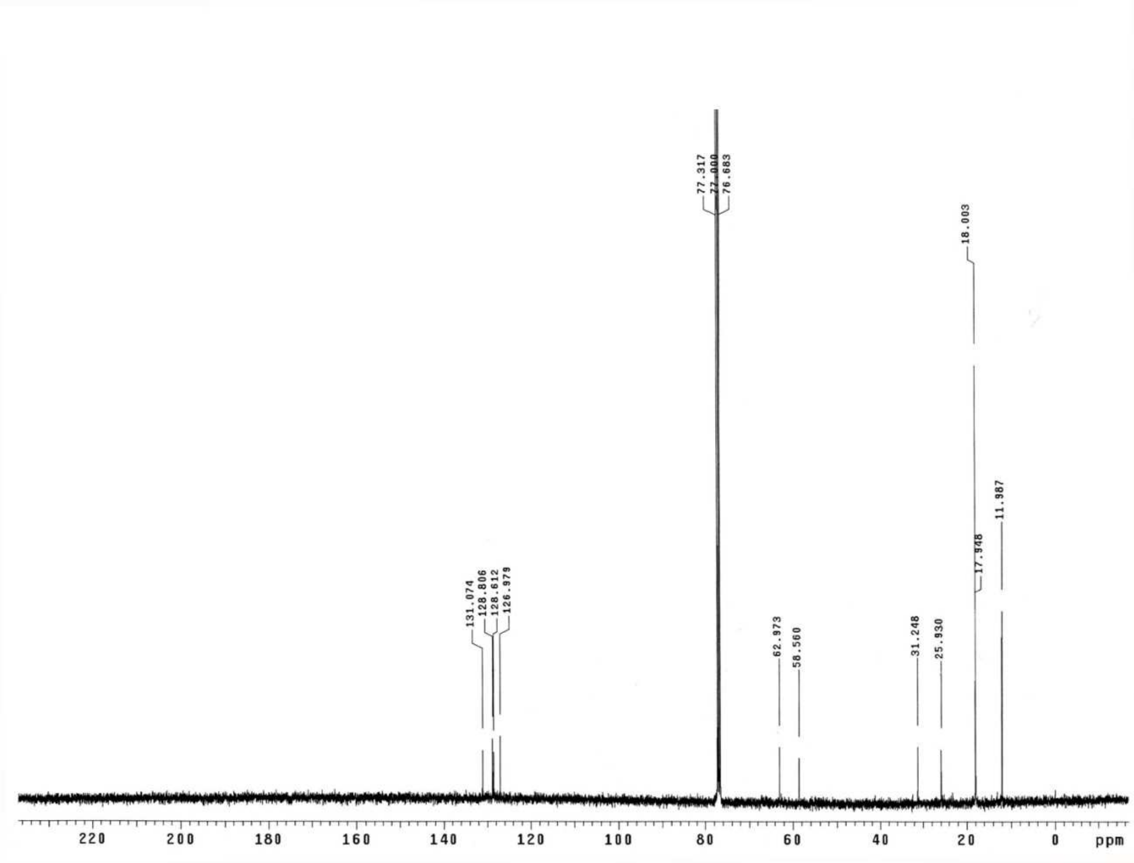
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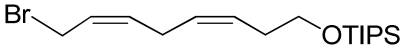
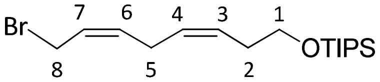


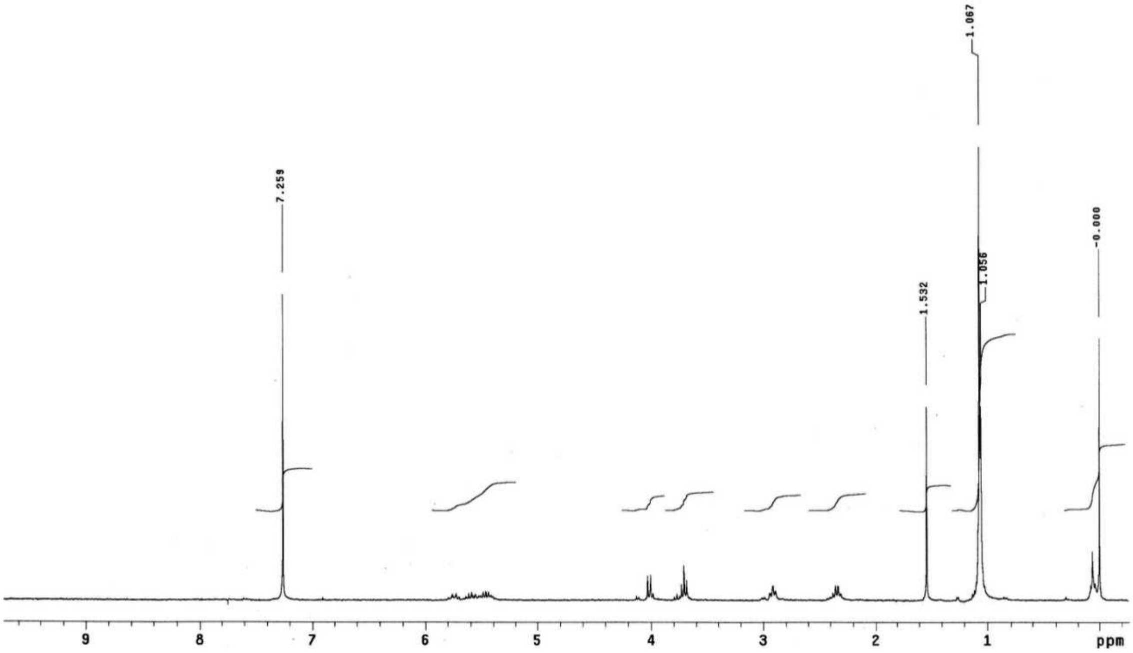
(3*Z*,6*Z*)-8-Bromo-1-[(triisopropylsilyl)oxy]-3,6-octadien (95).

Triethylamine (350 µL, 2.5 mmol) and methansulfonyl chloride (180 µL, 2.31 mmol) were added dropwise to a solution of **(2*Z*,5*Z*)-8-[(triisopropylsilyl)oxy]-2,5-octadienol** (574 mg, 1.93 mmol) in anhydrous CH_2Cl_2 (32 mL) cooled to 0 °C. After the end of addition, the mixture was stirred at 0 °C for 15 min, thus was stirred for additional 2 h keeping the temperature between 10 °C and 20 °C. Saturated aqueous NH_4Cl was added, and the mixture was extracted with CH_2Cl_2. The combined organic extracts were washed with water, dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure to afford a methansulfonyl derivative intermediate.

A solution of LiBr (1.67 g, 19.3 mmol) in anhydrous THF (8 mL) was added to a solution of the above mesyl derivative (1.93 mmol) in anhydrous CH_2Cl_2 (6 mL) at 0 °C under inert atmosphere. The resulting mixture was stirred at room temperature for 1h. Distilled water was added, and the mixture was then extracted with CH_2Cl_2. The combined organic extracts were dried over anhydrous Na_2SO_4, filtered, and the solvent was removed under reduced pressure. Flash chromatography (hexane to 98:2 hexane-Et_2O) afforded bromo derivative **95** (435 mg, 73%).

^{1}H NMR (300 MHz, $CDCl_3$): δ 1.06, 1.07 [2s, 21H, $(CH_3)_2CH$)], 2.36 (m, 2H, H-2), 2.85 (t, J = 6.8 Hz, 2H, H-5), 3.70 (t, J = 6.4 Hz, 2H, H-1), 4.04 (d, J = 6.8 Hz, 2H, H-8), 5.40-5.80 (m, 4H, H-5, H-6, H-2, H-3).

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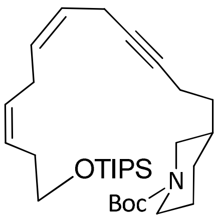


(6*Z*,9*Z*)-*N*-(*tert*-Butoxycarbonyl)-3-[12-(triisopropylsilyloxy)dodeca-6,9-dien-3-inyl]piperidine (80).

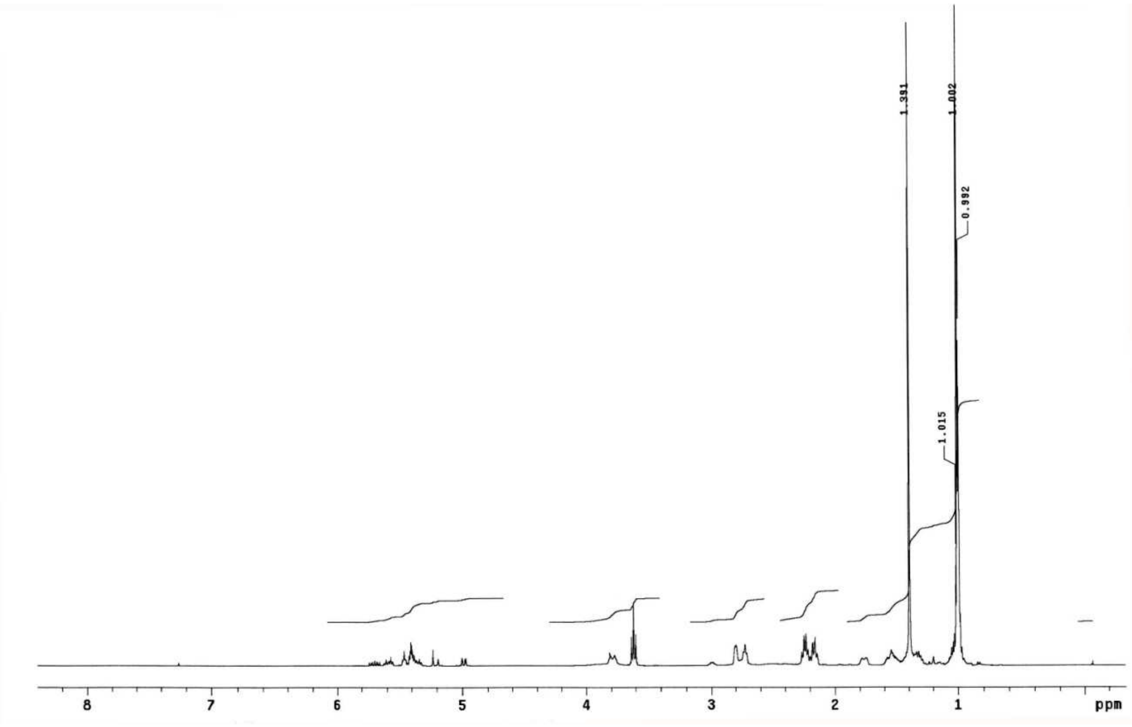
Bromo derivative **95** (500 mg, 1.39 mmol) and piperidine **93** (164 mg, 0.70mmol) were added under inert atmosphere to a suspension of CuI (264 mg, 1.39 mmol), NaI (208 mg, 1.39 mmol), and K_2CO_3 (143 mg, 1.05 mmol) in of anhydrous DMF (1.5 mL). The mixture was stirred overnight at room temperature. Then the mixture was filtered through a Celite® pad and concentrated under vacuum. Flash chromatography (hexane to 97:3 hexane-Et_2O) gave piperidine **80** (312 mg, 86%).

IR (film): 1694 (CO) cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$, COSY, gHSQC): δ 0.99, 1.02 (2s, 22H, SiC*H*(C*H*$_3$)$_2$, H-1’], 1.32 (m, 1H, H-4), 1.39 [m, 11H, C(C*H*$_3$)$_3$, H-4, H-5], 1.49-1.58 (m, 2H, H-3, H-5), 1.76 (m, 1H, H-1’), 2.15 (m, 2H, H-2’), 2.23 (m, 2H, H-11’), 2.30 (masked, 1H, H-6), 2.72 (m, 3H, H-8’ H-2), 2.79 (m, 2H, H-5’), 3.60 (t, *J* = 6.8 Hz, 2H, H-12’), 3.76-3.80 (2m, 2H, H-2, H-6), 5.353-5.46, 5.58 (3m, 4H, CH=).

^{13}C NMR (100.6 MHz, $CDCl_3$): δ 11.8 [Si*C*H(CH$_3$)$_2$], 16.1 (C-2’), 17.8 [SiCH(*C*H$_3$)$_2$], 21.8 (C-5’), 24.3 (C-5), 28.3 [C(*C*H$_3$)$_3$], 30.0 (C-8’), 30.3 (C-1’), 31.0 (C-11’), 32.5 (C-4), 34.8 (C-3), 44.4, 49.8 (C-2, C-6), 62.9 (C-12’), 77.3, 78.9 [C-3’, C-4’, *C*(CH$_3$)$_3$], 125.0, 126.6, 128.7, 129.5 (4CH=), 154.6 (NCO).

HRMS (ESI) calcd for [$C_{31}H_{55}NO_3Si$ + H]$^+$: 518.4024, found: 518.4025.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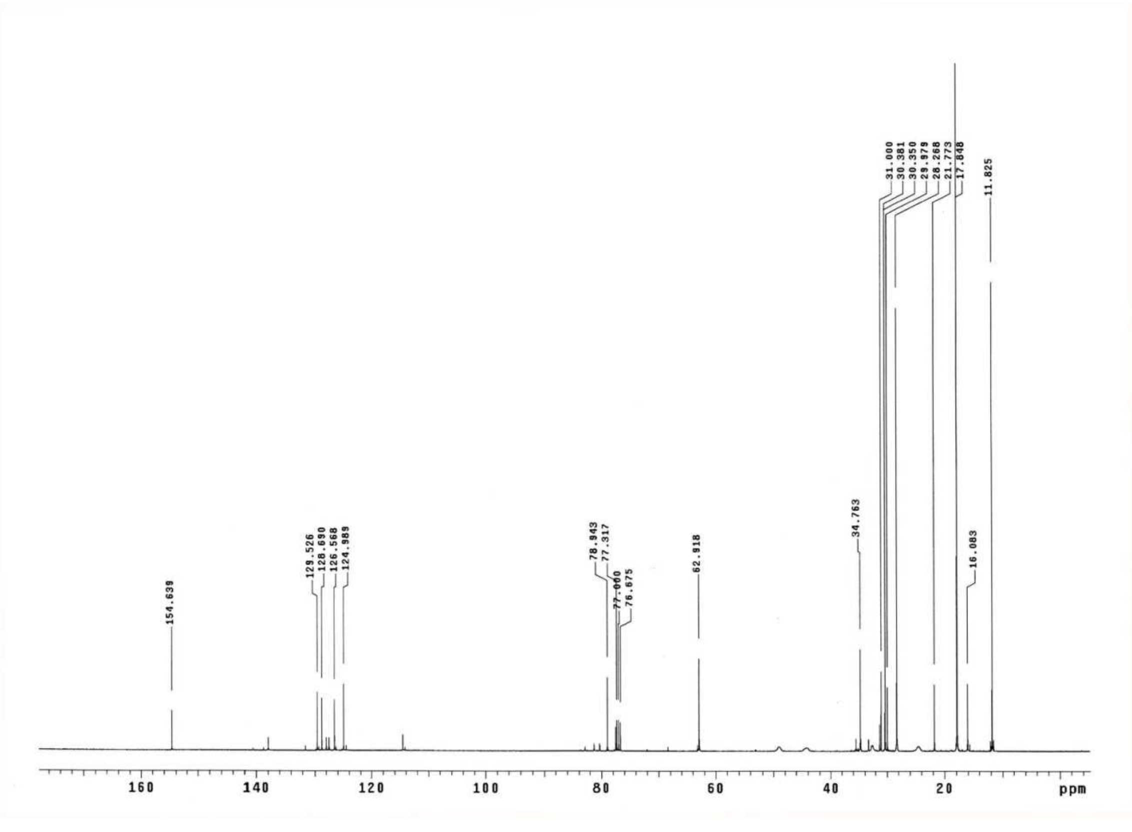
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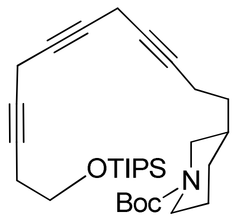


N-(tert-Butoxycarbonyl)-3-[12-(triisopropylsilyloxy)dodeca-3,6,9-triynyl]piperidine (94).

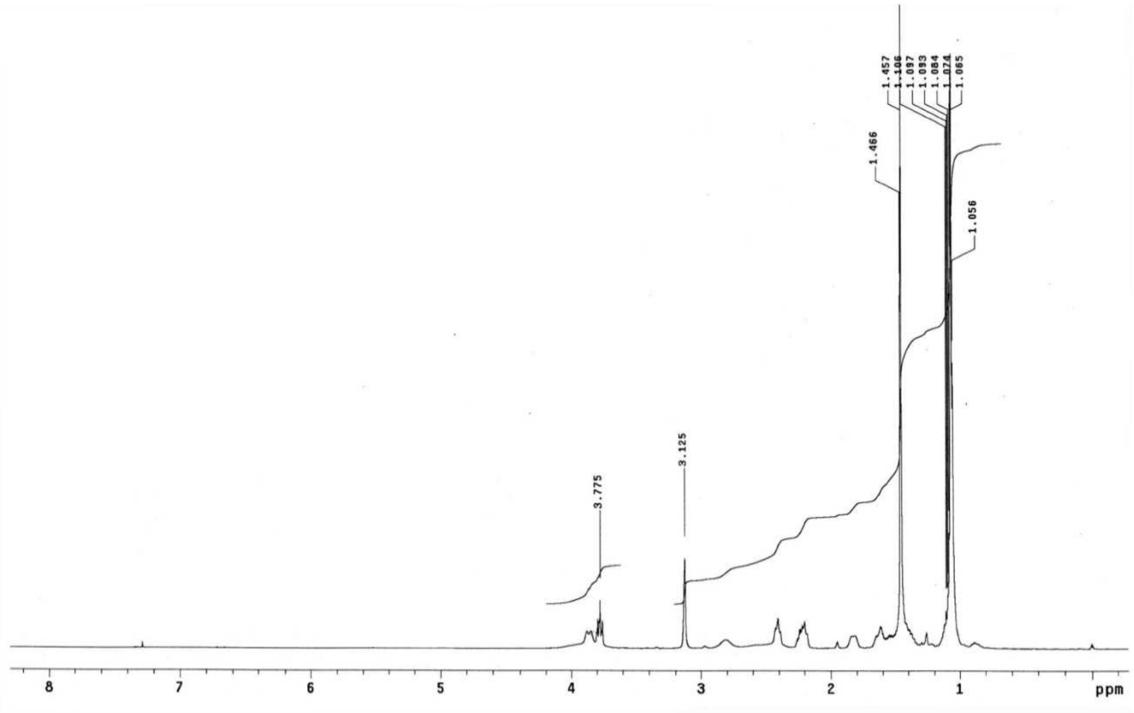
The diyne **90** (500 mg, 1.39 mmol) and compound **93** (164 mg, 0.70 mmol) were added under inert atmosphere to a suspension of CuI (264 mg, 1.38 mmol), NaI (208 mg, 1.38 mmol), and K_2CO_3 (143 mmg, 1.05 mmol) in anhydrous DMF (1.5 mL). The resulting mixture was stirred overnight at room temperature. Saturated aqueous NH_4Cl and EtOAc were added, and the mixture was filtered through a Celite® pad. The two phases are separated, and the aqueous layer was extracted with ether. The combined organic extracts were washed with brine, dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. Flash chromatography (hexane to 94:6 hexane-EtOAc) gave the compound **94** (312 mg, 86%) as a pale yellow oil.

IR (film): 1694 (CO) cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$, COSY, gHSQC): δ 1.08 [m, 22H, Si*C*H(*C*H$_3$)$_2$, H-1'], 1.38 (m, 1H, H-4), 1.49 [m, 11H, $(CH_3)_3C$, H-4, H-5], 1.55 (m, 1H, H-3), 1.61 (m, 1H, H-5), 1.82 (dm, *J* = 11.6 Hz, 1H, H-1'), 2.19 (m, 4H, H-5', H-2'), 2.35 (m, 2H, H-11'), 2.80 (m, 2H, H-2ax, H-6ax), 3.12 (s, 2H, H-8'), 3.77 (t, *J* = 6.8 Hz, 2H, H-12'), 3.84, 3.87 (br. s, 2H, H-2eq, H-6eq).

^{13}C NMR (100.6 MHz, $CDCl_3$): δ 9.7 (C-8'), 11.9 [Si*C*H(CH$_3$)$_2$], 15.8, 16.1 (C-5', C-2'), 17.9 [SiCH(*C*H$_3$)$_2$], 23.1 (C-11'), 24.5 (C-5), 28.4 [C(*C*H$_3$)$_2$], 30.4 (C-1'), 32.2 (C-4), 34.9 (C-3), 44.6, 49.1 (C-6, C-2), 62.1 (C-12'), 74.0, 74.5, 74.7, 74.9, 77.6 (C≡), 79.2, 80.2 [C≡, *C*(CH$_3$)$_2$], 154.8 (NCOO).

HRMS (ESI) calcd for $[C_{31}H_{51}NO_3Si + NH_4]^+$: 531.3976, found: 531.3974.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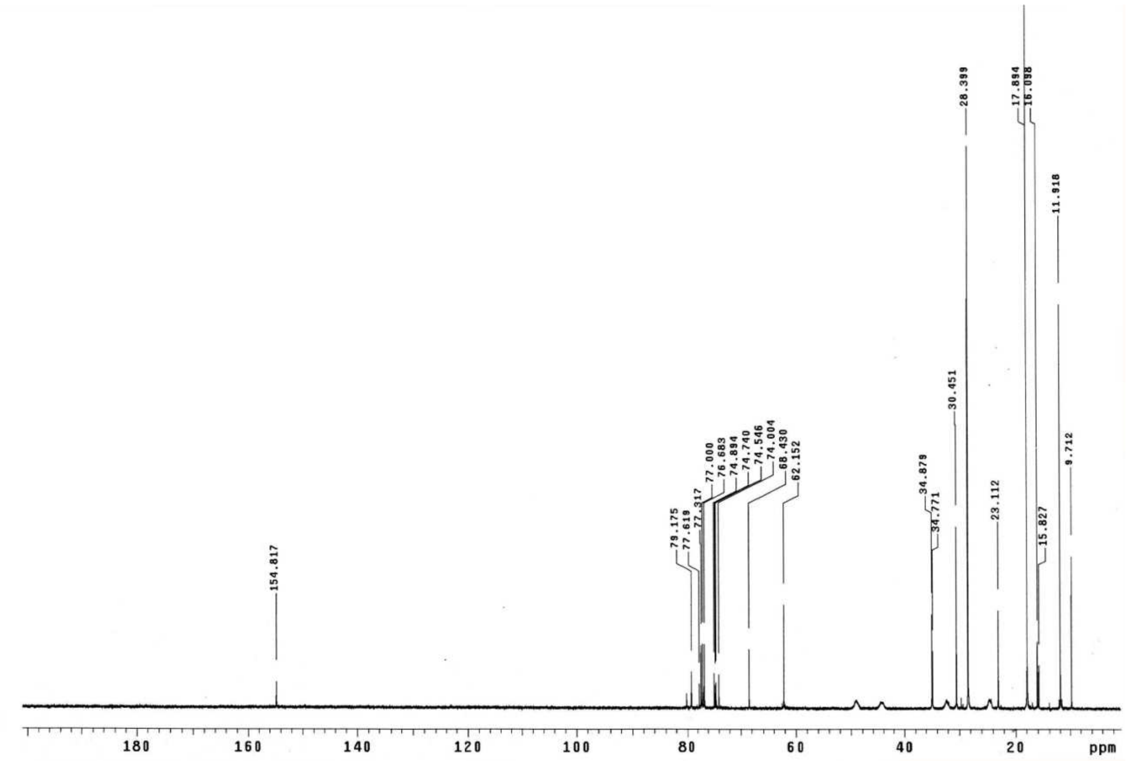
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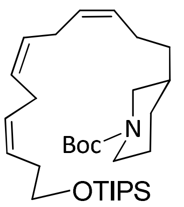


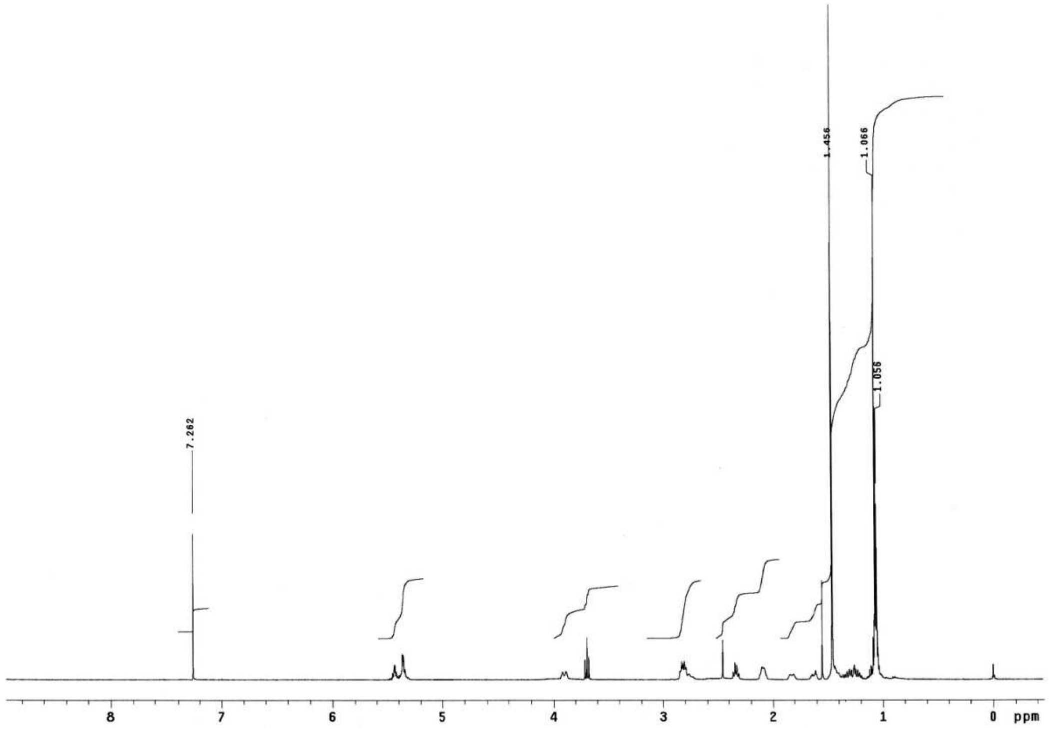
(3*Z*,6*Z*,9*Z*)-*N*-(*tert*-Butoxycarbonyl)-3-[12-(triisopropylsilyloxy)dodeca-3,6,9-trienyl]piperidine (81).

A suspension of dicyclohexylborane (1.14 mmol) was prepared at 0 °C by dropwise addition of cyclohexene (232 μL, 2.28 mmol) to a solution of borane–dimethyl sulfide complex (571 μL of a 2 M solution in THF, 1.14 mmol) in THF (3 mL). The resulting mixture was warmed to 20 °C, stirred for 2 h, and then cooled again at 0 °C. Triyne **94** (140 mg, 0.272 mmol) in anhydrous THF (1.5 mL) was then added, and the mixture was warmed to 20 °C over 2 h and was stirred at room temperature for an additional 2 h. Glacial acetic acid (435 μL) was added dropwise, and the resulting solution was stirred overnight. The solution was then cooled to 0 °C and basified by slow addition of aqueous NaOH (1.63 mL of a 5 M solution) and 30% aqueous H_2O_2 (435 μL). Water was then added, and the resulting mixture was extracted with EtOAc. The combined organic extracts were dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. Flash chromatography (hexane to 95:5 hexane-EtOAc) gave compound **81** (119 mg, 84%) as a colourless oil.

^{1}H NMR (400 MHz, $CDCl_3$, COSY, gHSQC): δ 1.05 (m, 22H, SiC*H*(C*H*$_3$)$_2$, H-1'], 1.25 (m, 2H, 2H-4), 1.40 (m, 1H, H-5), 1.45 [m, 10H, C(C*H*$_3$)$_3$, H-3], 1.61 (m, 1H, H-5), 1.81 (m, 1H, H-1'), 2.08 (m, 2H, H-2'), 2.32 (m, 2H, H-11'), 2.80 (m, 6H, 2H-8', 2H-5', H-2ax, H-6ax), 3.69 (t, *J* = 6.8 Hz, 2H, H-12'), 3.90 (m, 2H, H-2eq, H-6eq), 5.35, 5.43 (CH=).

^{13}C NMR (100.6 MHz, $CDCl_3$): δ 12.0 [Si*C*H(CH$_3$)$_2$], 18.0 [SiCH(*C*H$_3$)$_2$], 24.4 (C-2'), 24.9 (C-5), 25.6, 25.8 (C-8', C-5'), 28.5 [C(*C*H$_3$)$_3$], 30.9 (C-1'), 31.0 (C-11'), 33.5 (C-4), 35.4 (C-3), 44.4, 49.8 (C-2, C-6), 63.0 (C-12'), 79.1 [*C*(CH$_3$)$_3$], 126.3 (C-10'), 128.0, 128.2, 128.3 (C-4', C-6', C-7'), 129.4, 129.9 (C-3', C-9'), 154.9 (NCO).

HRMS (ESI) calcd for $[C_{31}H_{57}NO_3Si + H]^+$: 520.4199, found: 520.4180.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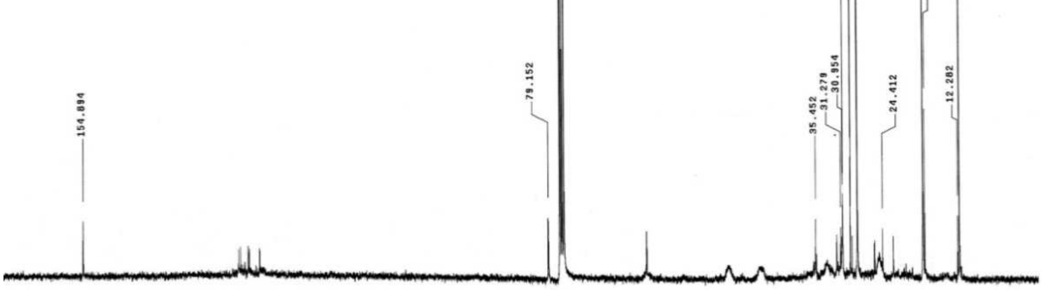
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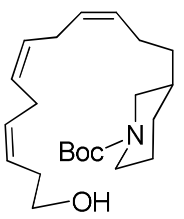


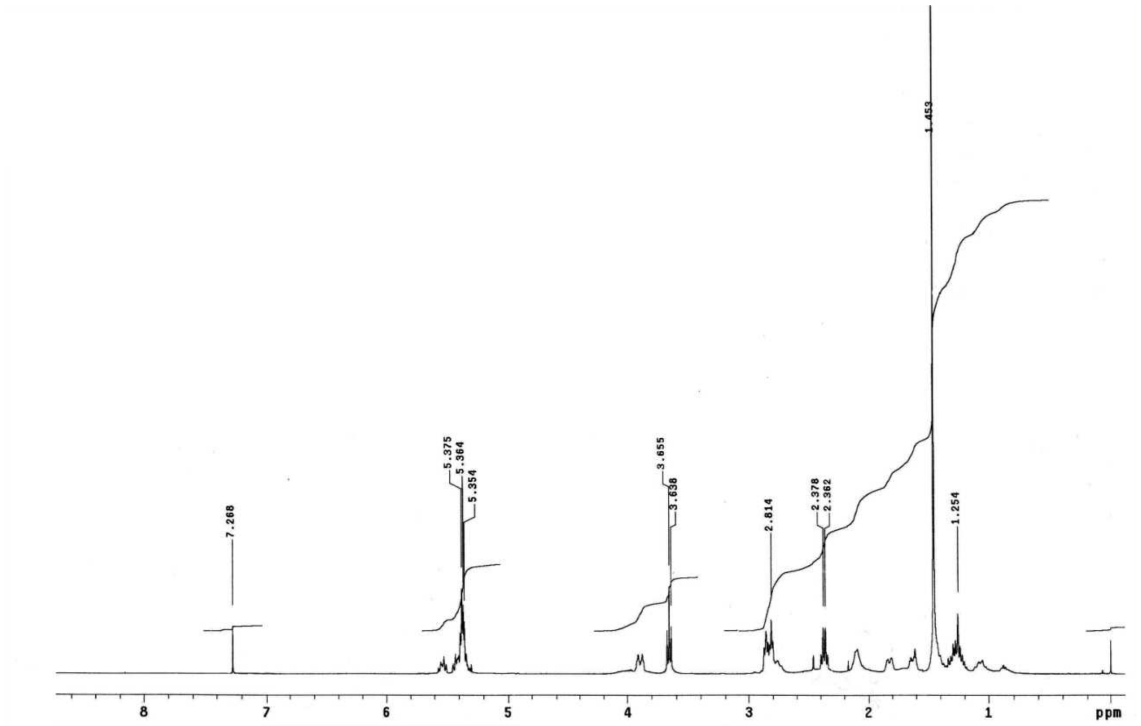
(3*Z*,6*Z*,9*Z*)-*N*-(*tert*-Butoxycarbonyl)-3-[12-hydroxydodeca-3,6,9-trienyl]piperidine (97).

2 N aqueous HCl (3.16 mL) was added to a stirred solution of silyl derivative **81** (119 mg, 0.23 mmol) in methanol (23 mL), and the mixture was stirred for 30 min. The solvent was evaporated under reduced pressure, saturated aqueous NaHCO$_3$ was added, and the resulting mixture was extracted with CH$_2$Cl$_2$. The combined organic extracts were dried over anhydrous Na$_2$SO$_4$, filtered, and concentrated under reduced pressure to give a white foam. Flash chromatography (hexane to 7:3 hexane-EtOAc) gave alcohol **97** (71 mg, 85%) as a colourless oil.

^{1}H NMR (400 MHz, CDCl$_3$, COSY, gHSQC): *δ* 1.25 (m, 4H, H-2', H-4), 1.45 [s, 11H, C(C*H*$_3$)$_3$, H-5, H-3), 1.61 (m, 1H, H-5), 1.81 (dm, *J* = 12.4 Hz, 2H, H-1'), 2.11 (m, 2H, H-5'), 2.37 (m, 2H, H-11'), 2.75 (m, 2H, H-2ax, H-6ax), 2.83 (m, 2H, H-8'), 3.65 (t, *J* = 8.0 Hz, 2H, H-12'), 3.90 (2m, 2H, H-2eq, H-6eq), 5.37 (m, 4H, H-4', H-6', H-7', H-10'), 5.56 (m, 2H, H-3', H-9').

^{13}C NMR (100.6 MHz, CDCl$_3$): *δ* 24.5 (C-5'), 25.0 (C-2'), 25.6 (C-5), 25.8 (C-8'), 28.4 [C(*C*H$_3$)$_2$], 30.9 (C-11'), 31.0 (C-1'), 33.7 (C-4), 35.5 (C-3), 44.8, 49.3 (C-2, C-6), 62.1 (C-12'), 79.2 [*C*(CH$_3$)$_2$], 125.7 (C-10'), 127.8, 127.9, 128.5 (C-4', C-6', C-7') 129.9, 130.9 (C-3', C-9'), 154.9 (NCO).

HRMS (ESI) calcd for [C$_{22}$H$_{37}$NO$_3$ + H]$^+$: 364.2846, found: 364.2841.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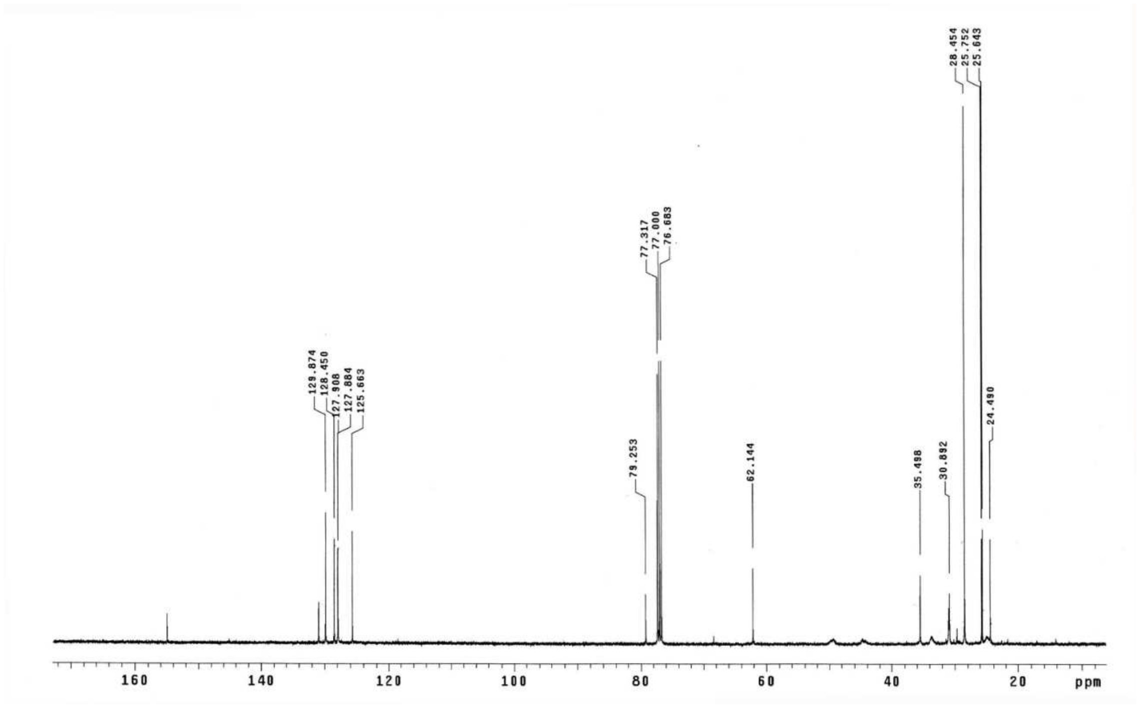
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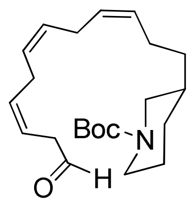


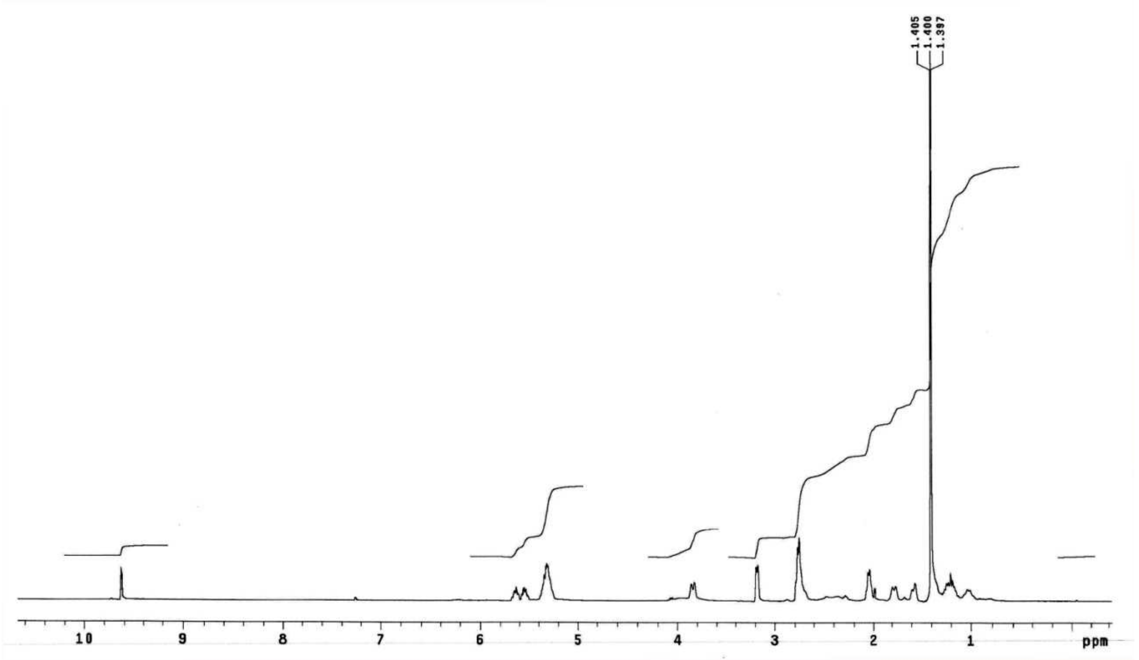
(3*Z*,6*Z*,9*Z*)-*N*-(*tert*-Butoxycarbonyl)-3-piperidinedodeca-3,6,9-trienaldehyde (74).

$NaHCO_3$ (436 mg, 5.19 mmol) and Dess–Martin periodinane (2.24 g, 5.19 mmol) were added to a solution of the alcohol **97** (630 mg, 1.73 mmol) in CH_2Cl_2 (35 mL). After 18 h of stirring at room temperature, a saturated aqueous solution of $NaHCO_3$-$Na_2S_2O_3$ (1:1) was slow added. The resulting mixture was vigorously stirred for 1 h and extracted with CH_2Cl_2. The combined organic extracts were dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. Flash chromatography (hexane to 7:3 hexane-EtOAc) afforded aldehyde **74** (374 mg, 60%), which was immediately used in the next step.

^{1}H NMR (400 MHz, $CDCl_3$, COSY, gHSQC): δ 1.02 (m, 1H, H-1’), 1.20 (m, 2H, H-4), 1.35 (m, 2H, H-5, H-3), 1.41 [s, 9H, C(CH_3)$_3$], 1.57 (m, 1H, H-5), 1.77 (m, 1H, H-1’), 2.04 (m, 2H, H-2’), 2.76 (m, 6H, H-2, H-6, 2H-5’, 2H-8’), 3.18 (d, J = 7.2 Hz, 2H, H-11’), 3.85 (dm, J = 12.8 Hz, 2H, H-2ax, H-6ax), 3.99 (m, 1H, H-2eq, H-6eq), 5.31 (m, 4H, H-4’, H-5’, H-6’, H-7’), 5.63 (m, 2H, H-3’, H-9’), 9.63 (s, 1H, CHO).

^{13}C NMR (100.6 MHz, $CDCl_3$): δ 24.3 (C-2’), 24.8 (C-5), 25.5 (C-5’), 25.8 (C-8’), 28.3 [C(CH$_3$)$_2$], 30.8 (C-1’), 33.4 (C-4), 35.3 (C-3), 42.3 (C-11’), 44.7, 49.2 (C-2, C-6), 79.0 [C(CH$_3$)$_2$], 118.5 (C-10’), 126.8, 127.5, 128.8, (C-4’, C-6’, C-7’), 129.9, 132.9 (C-3’, C-9’), 154.7 (NCO), 199.1 (CHO).

HRMS (ESI) calcd for $[C_{22}H_{35}NO_3 + H]^+$: 362.2676, found: 362.2693.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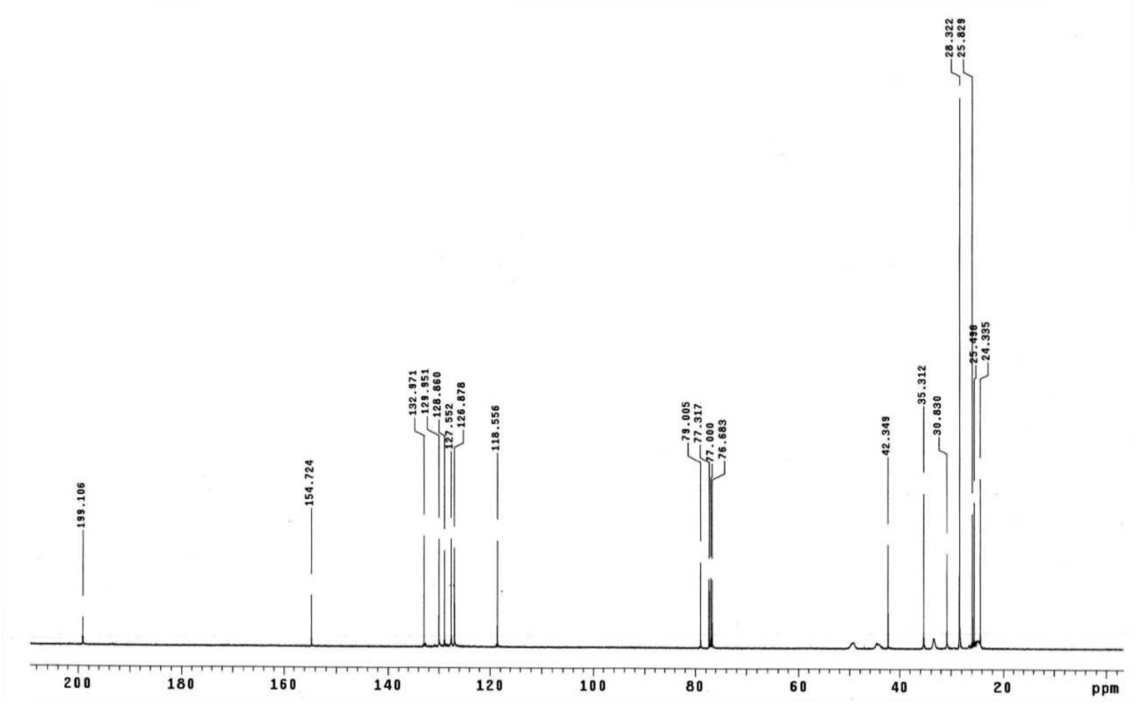
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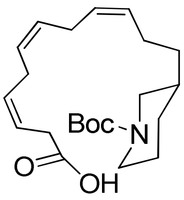
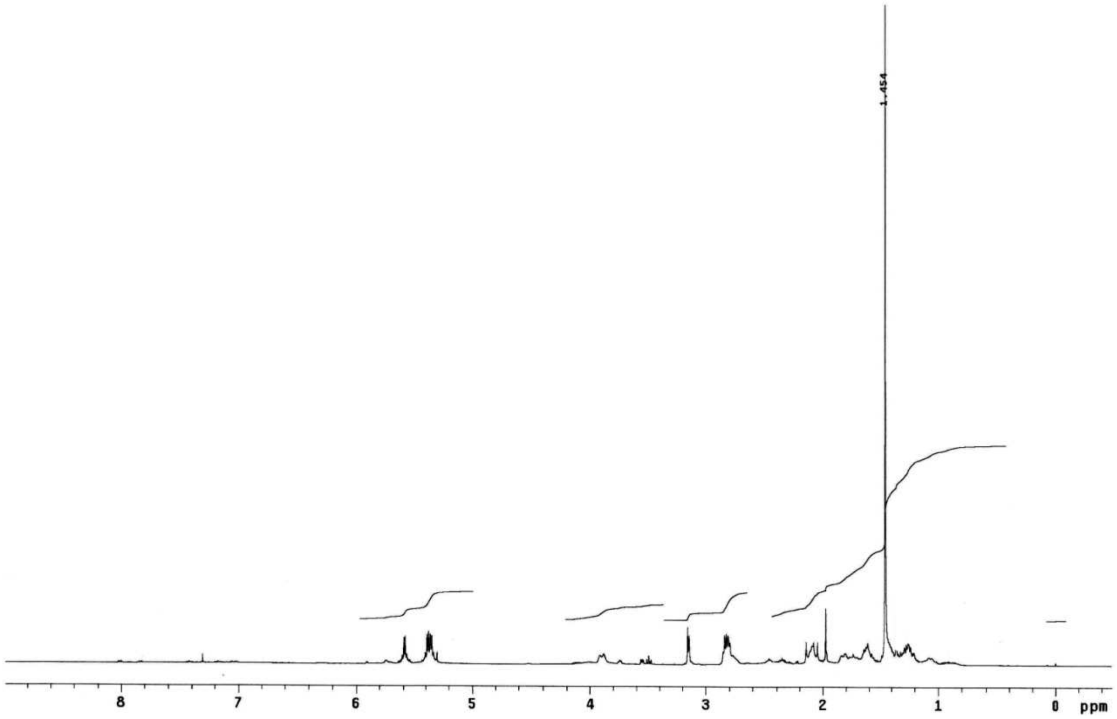


(3*Z*,6*Z*,9*Z*)-*N*-(*tert*-Butoxycarbonyl)-3-piperidinedodeca-3,6,9-trienoic acid (75).

t-BuOH (11 mL) and 1-methyl-1-cyclohexene (1.5 mL) were added to a stirring solution of the above aldehyde **74** (131 mg, 0.36 mmol) in CH_3CN (4 mL). A solution of $NaClO_2$ (80%, 273 mg, 2.4 mmol) and NaH_2PO_4 (300 mg, 2.5 mmol) in water (4 mL) was then added, and the mixture was stirred at room temperature for 1.5 h. Then 0.1 M $Na_2S_2O_3$ and 2 N aqueous HCl solutions were added (until pH=1), and the aqueous solution was extracted with EtOAc. The combined organic extracts were dried over $MgSO_4$, filtered, and concentrated affording the acid **75** as a colourless oil, which was used in the next step without further purification.

^{1}H NMR (400 MHz, $CDCl_3$, selected resonances): δ 1.05 (m, 1H, H-1'), 1.20 (m, 2H, H-4), 1.35 (m, 2H, H-5, H-3), 1.45 (s, 9H, [$C(CH_3)_2$]), 1.60 (m, 1H, H-5), 1.75 (m, 1H, H-1'), 2.00 (m, 2H, H-2'), 2.76 (m, 6H, H-2, H-6, 2H-5', 2H-8'), 3.18 (d, *J* = 7.2 Hz, 2H, H-11'), 3.90 (dm, *J* = 12.8 Hz, H-2, H-6), 5.31 (m, 4H, H-4', H-5', H-6', H-7'), 5.60 (m, 2H, H-3', H-9').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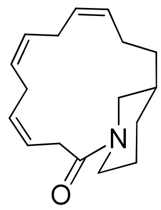


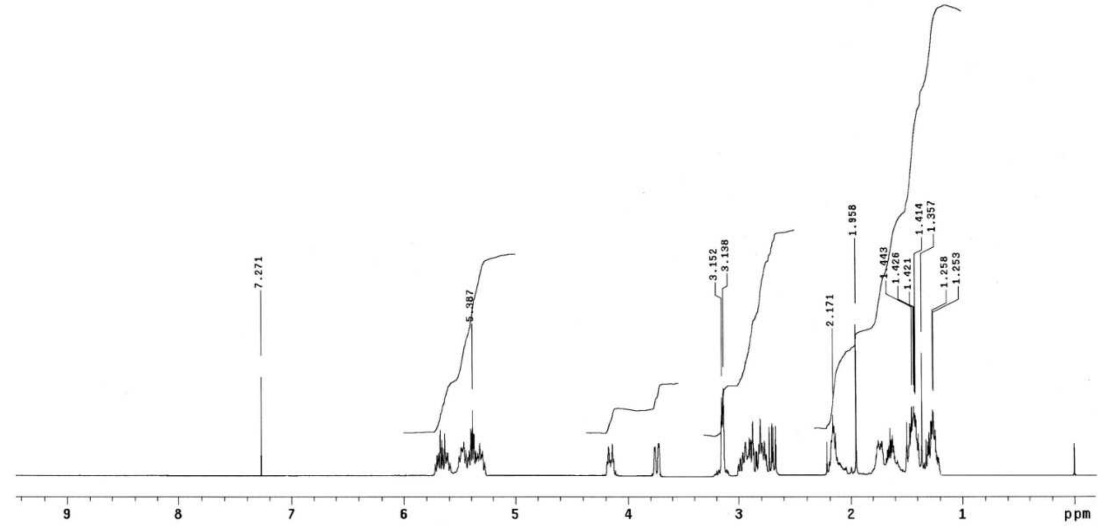
(4*Z*,7*Z*,10*Z*)-2-Oxo-1-azabicyclo[12.3.1]octadeca-4,7,10-triene (76).

TFA (3 mL) was added to a solution of the acid **75** (0.36 mmol) in anhydrous CH_2Cl_2 (10 mL), and the mixture was stirred at room temperature for 30 minutes. Toluene (2 mL) was added, and the solution was concentrated under reduced pressure. A solution of the resulting residue in CH_2Cl_2/DMF (9:1, 2 mL) was added to a solution of HOBt (364 mg, 1.9 mmol) and EDCI (258 mg, 1.9 mmol) in CH_2Cl_2/DMF (9:1, 2 mL). The resulting mixture was stirred overnight at room temperature, and concentrated under reduced pressure. Then 1 N aqueous HCl was added. The solution was washed with EtOAc, neutralized ($NaHCO_3$), and extracted with CH_2Cl_2. The combined organic extracts were dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. Flash chromatography (hexane to 3:7 hexane-EtOAc) gave bicyclic compound **76** (33 mg, 35% overall yield for two steps).

^{1}H NMR (400 MHz, $CDCl_3$, COSY, gHSQC): δ 1.24 (m, 1H, H-4), 1.26 (m, 2H, H-12'), 1.42 (m, 1H, H-5), 1.45 (m,1H, H-3), 1.64 (m, 1H, H-5), 1.75 (m, 1H, H-4), 2.17 (m, 2H, H-11), 2.70 (dd, *J* = 14.0, 9.6 Hz, 1H, H-2ax), 2.80 (m, 2H, H-5'), 2.87 (m, 1H, H-6ax), 2.91 (m, 2H, 2H-8'), 3.14 (dm, *J* = 5.6 Hz, 2H, H-2'), 3.74 (dm, *J* = 13.2 Hz, 1H, H-2eq), 4.15 (dt, *J* = 13.2, 5.6 Hz, 1H, H-6eq), 5.38-5.47 (m, 4H, H-6', H-7', H-9', H-10'), 5.63-5.67 (m, 2H, H-3', H-6').

^{13}C NMR (100.6 MHz, $CDCl_3$): δ 24.5 (C-5), 25.1 (C-11), 26.1 (C-8'), 26.3 (C-5'), 32.3 (C-12), 32.5 (C-4), 32.4 (C-2'), 42.8 (C-6), 50.7 (C-2), 123.9 (C-3'), 126.7 (C-7'), 127.3 (C-9'), 128.1 (C-6'), 128.9 (C-4'), 129.9 (C-10'), 169.6 (NCO).

HRMS (ESI) calcd for $[C_{17}H_{25}NO + H]^+$: 260.2009, found: 260.2010.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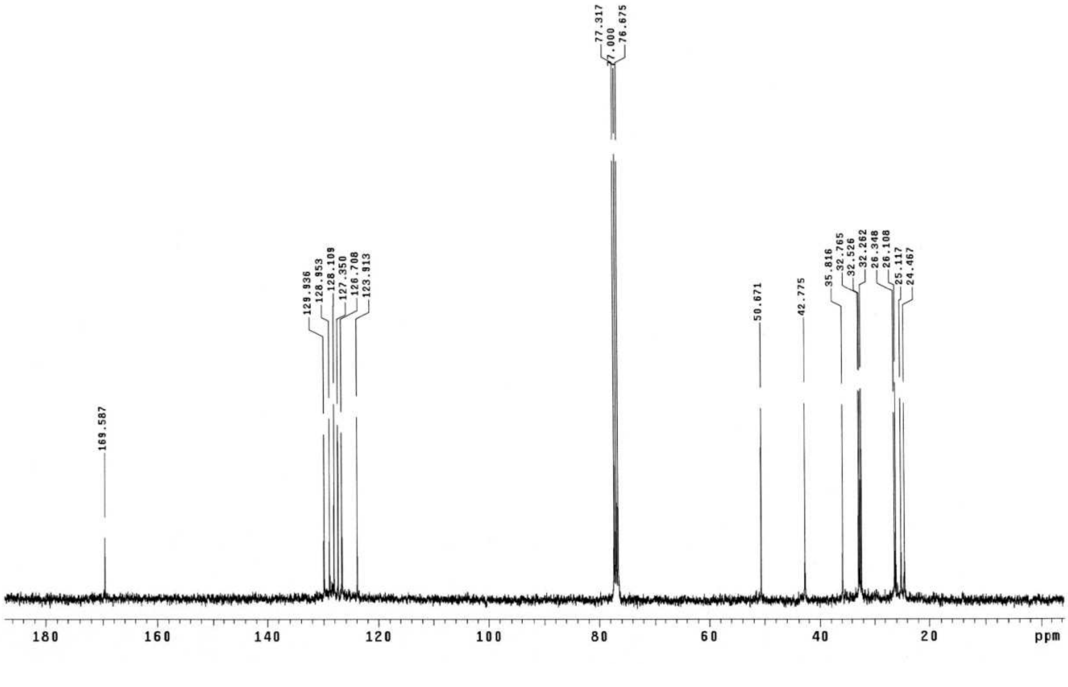
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ppm