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Departament de Química

Indolizidine and Quinolizidine Motifs for the Synthesis of Conformationally Constrained Smac Mimetics and Chloroquine Conjugates

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Abbreviations

Abbreviations

AcOH	Acetic acid	Fmoc	9-Fluorenylmethoxy carbonyl
Boc	*tert*-butoxy carbonyl	HOBt	Hydroxybenzotriazole
Boc_2O	Di-*tert*-butyl dicarbonate	$^{i}Pr_2NH$	Diisopropylamine
Bn	Benzyl	$^{i}PrOH$	isopropanol
BnBr	Benzyl bromide	IR(ATR)	Infrared spectroscopy in attenuated total reflection
Cbz	Carboxybenzyl	KHMDS	Potassium bis(trimethylsilyl)amide
CbzCl	Benzyl chloroformate	LiHMDS	Lithium bis(trimethylsilyl)amide
COSY	Correlation spectroscopy	LDA	Lithium diisopropylamide
DBAD	Di-tert-butylazodi-carboxylate	MeOH	Methanol
DCC	N,N'-Dicyclohexyl-carbodiimide	Mp	Melting point
DIBAL-H	Diisobutylaluminium hydride	Ms	Methanesulfonyl
DMAP	4-dimethylamino-pyridine	MsCl	Methanesulfonyl chloride
DMF	Dimethylformamide	NaHMDS	Sodium bis(trimethylsilyl)amide
DMP	Dess–Martin periodinane	NMR	Nuclear magnetic resonance
DMSO	Dimethylsulfoxide	*n*-BuLi	*n*-Butyllithium
ESI	Electrospray Ionization	*n*-BuONO	tert-Butyl nitrite
Et	Ethyl	PCC	Pyridinium chlorochromate
Et_2O	Diethyl ether	Ph	Phenyl
EtOH	Ethanol	PhOH	phenol
EtOAc	Ethyl acetate	rt	Room temperature

Sec-BuLi	sec-Butyllithium
sm	Starting material
t-Bu	*tert*-butyl
t-BuOH	*tert*-butanol
t-BuOK	Potassium *tert*-butoxide
TBDPS	*tert*-Butyldiphenylsilyl
TBDPSCl	*tert*-Butylchlorodiphenylsilane
THF	Tetrahydrofuran
UV	Ultraviolet

I. Introduction

1.1. INDOLIZIDINE AND QUINOLIZIDINE AS BIOACTIVE SYSTEMS

Indolizidine and quinolizidine are heterobicyclic compounds containing a bridgehead nitrogen atom (Figure 1). The indolizidine and quinolizidine framework is present in many natural and synthetic compounds, some of which display diverse bioactivities.

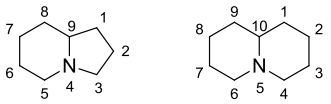

Figure 1. The indolizidine and quinolizidine basic frameworks

In the recent years, our research group has been involved in a project devoted to the stereoselective preparation of chiral indolizidine and quinolizidine derivatives. Some of our targeted compounds were alkaloids isolated from natural sources and their analogs, whilst others have been designed as potential pharmaceutical drugs. This thesis has been developed in this context.

1.1.1 Alkaloids

Indolizidines and quinolizidines are among the motifs most frequently encountered in alkaloids.[1] These two azabicyclic systems may occur in the natural products either in isolation (the so-called "simple izidine" alkaloids) or, more commonly, embedded within fused polycyclic arrays. It has been estimated that between 25% and 30% of all alkaloids possess structures incorporating one or other of these motifs. They occur in extremely diverse organisms as bacteria, fungi, higher plants, invertebrates and vertebrates, including both terrestrial and marine sources.

[1] Michael, J. P. *Beilstein J. Org. Chem.* **2007**, *3*, 1-2.

1.1.1.1. Indolizidine alkaloids

Among the most investigated groups of simple izidine alkaloids are the polyhydroxylated indolizines derived from plants and fungi, which function as potent glycosidase inhibitors, and the alkylindolizidines isolated from the skin of amphibians.

Prototypical examples of the first group are swainsonine from *Swainsona canescens* (Leguminosae/Fabaceae) and castanospermine from the Moreton Bay chestnut *Castanospermum austral* (Figure 2).[2] These compounds have demonstrated activity against the HIV and other viruses, by their ability to inhibit glycosidase enzymes involved in glycoprotein biosynthesis, since the glycoprotein coating is essential for the proliferation of these viruses. This activity has stimulated considerable research on related structures and their mode of action. For instance, 6-*O*-butanoylcastanospermine, known as celgosivir, is currently in clinical trials as an anti-AIDS agent and for the treatment of dengue infections.[3] These alkaloids are also toxic to animals, causing severe gastro-intestinal upset and malnutrition by severely affecting intestinal hydrolases.

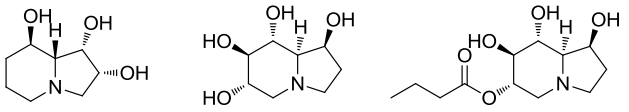

Figure 2. Representative examples of polyhydroxylated indolizine alkaloids

Many indolizidine alkaloids are isolated from the skin extracts of neotropical frogs.[4] Among them, the first class to be discovered was 3,5-disubstituted indolizidines (Figure 3), which occur randomly in extracts of dendrobatid (primarily *Dendrobates*), mantellid (*Mantella*), and bufonid (*Melanophrynisus*) anurans, where they are usually

[2] Dewick, P. M. In *Medicinal Natural Products. A Biosynthetic Approach*; John Wiley and Sons, Ltd, **2002**; pp 305-310.
[3] Rathore, A.P; Paradkar, P. N.; Watanabe, S.; Tan, K. H.; Sung, C.; Connolly, J. E.; Low, J.; Ooi, E. E.; Vasudevan, S. G. *Antiviral Res.* **2011**, *92*, 453-460.
[4] Daly, J. W.; Spande, T. F. In *Alkaloids: Chemical and Biological Perspectives*; Pelletier, S. W., Ed.; Wiley-Inter science: New York, **1986**; Vol. *4*, *pp* 1–274.

minor or trace alkaloids.[5] The parent structure for this class **223AB** was isolated and its gross structure proposed in 1978.[6] Another indolizidine 5*E*,9*E*-**195B** was extracted from a dendrobatid frog in 1986.[7] This alkaloid was an isomer of a 5*Z*,9*Z*-alkaloid, previously isolated from the Pharaoh ant and named monomorine I.[8] There are nearly thirty alkaloids, including stereoisomers, assigned to this class, however little is known of their biological activity. Indolizidine **239CD,** the ω-hydroxyl congener of **223AB,** has a minimum lethal dose for mice of 200 mg, acting as a noncompetitive blocker of nicotinic receptors.[5]

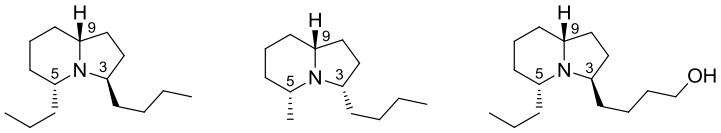

Figure 3. Typical 3,5-disubstituted indolizidine alkaloids

The most populous class among these alkaloids has turned out to be the 5,8-disubstituted indolizidines (Figure 4), which occur in a wide range of dendrobatid and mantellid frogs and represent the largest class of amphibian alkaloids.[9] The structures of the first 5,8-disubstituted indolizidines **205A** and **235B''** were described in 1987.[10] Synthetic **235B'** has been reported to be a very potent and selective blocker of the α4β2 neuronal nicotinic receptor. Alkaloid **205A** greatly enhances the binding of tritiated perhydrohistrionicotoxin (a blocking agent), to a noncompetitive blocker site on the nicotinic receptor channel of electric ray electroplax.[11]

[5] Daly, J. W.; Garraffo, H. M.; Spande, T. F. In *Alkaloids: Chemical and biological Perspectives*; Pelletier, S. W., Ed.; Pergamon: New York, **1999**; Vol.*13*, *pp* 1-161.
[6] Daly, J. W.; Brown, G. B.; Mensah-Dwumah, M.; Myers, C. W. *Toxicon.* **1978**, *16*, 163-188.
[7] Tokuyama, T.; Nishimori, N.; Karle, I. L.; Edwards, M. W.; Daly, J.W. *Tetrahedron.* **1986**, *42*, 3453-3460.
[8] Ritter, F. J.; Rotgans, I. E. M.; Talman, E.; Vermiel, P. E. J.; Stein, F. *Experientia.* **1973**, *29*, 530-531.
[9] Daly. J. W.; Spande. T. F. Garraffo, H. M. *J. Nat. Prod.* **2005**, *68*, 1556-1575.
[10] Tokuyama. T.; Nishimori. N.; Shimada. A.; Daly. J.W. *Tetrahedron*, **1987**, *43*, 643-652.
[11] Daly, J.W.; Nishizawa, Y.; Padgett, W.L.; Tokuyama, T.; Smith, A.L.; Holmes, A.B.; Kibayashi, C.; Aronstam, R.S. *Neurochem. Res.* **1991**, *16*, 1213-1218.

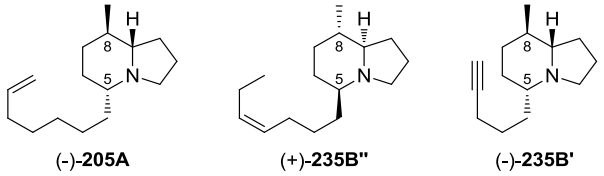

Figure 4. Typical 5,8-disubstituted indolizidine alkaloids

A new major class of indolizidine alkaloids is now proposed to be 6,7-dehydro-5,8-disubstituted indolizidines (Figure 5). They occur relatively commonly as minor or trace alkaloids in dendrobatid, mantellid and bufonid anurans.[9] Another class, 5,6,8-trisubstituted indolizidines, include about seventy alkaloids at present. The structure of the first member **223A** was proposed in 1997.[12] Such alkaloids occur commonly in mantellid frogs, but ants and mites[13] represent also likely sources. Until now, no toxicity or biological activity data have been reported for these two classes of alkaloids.

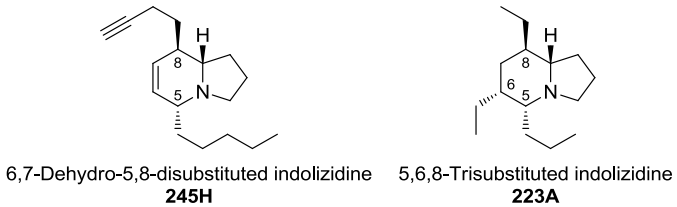

Figure 5. Typical examples of 6,7-dehydro-5,8-disubstituted and 5,6,8-trisubstituted indolizidine alkaloids

1.1.1.2. Quinolizidine alkaloids

Quinolizidine alkaloids are mainly found in plants of the Leguminosae/Fabaceae family. They deter or repel feeding of herbivores, and are toxic to them by a variety of mechanisms. A number of plants (*Laburnum*, *Cytisus*, *Lupinus*) containing significant quantities of these alkaloids must be regarded as potentially toxic to humans, and are known to be responsible for human poisoning.[2] (-)-Lupinine and (-)-sparteine, isolated from *Lupinus luteus* and *Cytisusscoparius*, respectively, are probably the most representative examples (Figure 6).[14]

[12] Garraffo. H.M.; Jain. P.; Spande. T.F.; Daly. J.W. *J. Nat. Prod.* **1997**, *60*, 2-5.
[13] Takeda, W.; Sakata, T.; Shimano, S.; Enami, Y.; Mori, N.; Nishida, R.; Kuwahara, Y. *J. Chem. Ecol.* **2005**, *31*, 2403-2415.
[14] Bunsupa, S.;Yamazaki, M.; Saito; K. *Front. Plant Sci.* **2012**, *3*, 1-7.

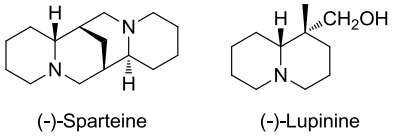

Figure 6. Two representative quinolizidine alkaloids

The 1,4- and 4,6-disubstituted quinolizidines are the more common structural patterns found in amphibian skin.[6] The structure of the parent 1,4-disubstituted quinolizidine alkaloid **217A** (Figure 7) was reported in 1996, from material isolated from a mantellid frog (*Mantella baroni*).[15] At present, about twenty alkaloids are assigned to this class. Most of them occur as trace alkaloids in dendrobatid frogs.[9]

Up to now, only six alkaloids have been assigned as 4,6-disubstituted quinolizidines. The structure of the first one, **195C**, was reported in 1999,[16] and it was found in dendrobatid and mantellid frogs. No biological activity has been reported for this compound, but, presumably, like other frog skin izidines, **195C** will prove to be a noncompetitive blocker of nicotinic receptor-channels.[5]

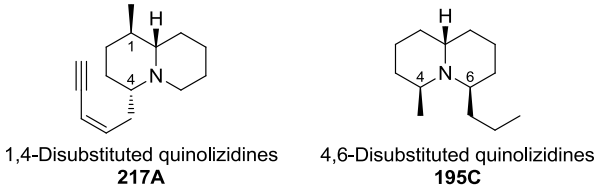

Figure 7. Typical 1,4- and 4,6-disubstituted quinolizidine alkaloids

Prominent alkaloids embedding a quinolizidine skeleton are the phenanthroquinolizidine cryptopleurine and its *cis*-stilbene analog julandine (Figure 8). They were isolated from *Boehmeria platyphylla*[17] and exhibit a range of biological activities, including antiviral, antifungal, antimicrobial, amoebicidal, and anticancer effects.[18]

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[15] Jain, P.; Garraffo, M. H.; Yeh, H. J. C.; Spande, T. F.; Daly, J. W.;Andriamaharavo, N. R.; Andriantsiferana, M. *J. Nat. Prod*. **1996**, *59*, 1174-1178.
[16] Jones, T. H.; Gorman, J. S. T.; Snelling, R. R.; Delabie, J. H. C.; Blum,M. S.; Garraffo, H. M.; Jain, P.; Daly, J. W.; Spande, T. F. *J. Chem. Ecol*. **1999**, *25*, 1179-1193.
[17] Suzuki, H.; Aoyagi, S.; Kibayashi, C. *J. Org. Chem.* **1995**, *60*, 6114-6122.
[18] (a) Pansare, S. V.; Dyapa, R. *Org. Biomol. Chem.* **2012**, *10*, 6776-6784. (b) Michael, J. P. *Nat. Prod. Rep.* **2008**, *25*, 139-165.

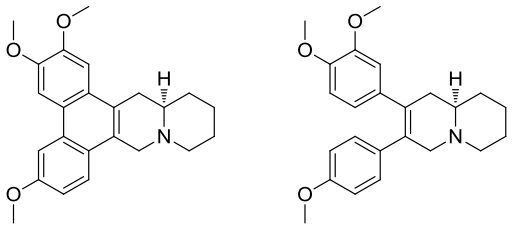


Figure 8. Phenanthroquinolizidine alkaloid

1.1.1.3. Other alkaloids containing indolizidine or quinolizidine substructure

Juliprosopine (Figure 8), which contains an unsaturated indolizidine core, was extracted from *P. glandulosa*. It exhibits remarkable antifungal activity against *C. neoformans* and *A. fumigates*.[19] Embedded quinolizidines also represent scaffolds of interest from a medicinal chemistry perspective. Flueggine B, isolated from *Flueggea virosa*, which is an example of the *Securinega* family, exhibits growth inhibitory activity against MCF-7 and MDA-MB-231 human breast cancer cells.[20] The tricyclic alkaloids known as cylindrines, exhibit a broad range of biological activities.[21] For instance, fasicularin, isolated from the marine invertebrate *Nephteis fasixcularis*, displays modest cytotoxic properties (IC_{50} of 14 μg/mL against Vero cells)[22] and has potential ability to damage DNA.[23] Lycopodine demonstrates a curare-like paralyzing activity[24] and beneficial medicinal properties, such as antipyretic and anticholinesterase activity.[25] Clavepictines A and B show activity against three human solid tumors (A-549, U-251, and SN12K1), with an IC_{50} of 1.8-8.5 μg/mL.[26]

[19] Samoylenko,V.; Ashfaq, M. K.; Jacob, M. R.; Tekwani, B. L.; Khan, S. I.; Manly, S. P.; Joshi, V. C.; Walker, L. A.; Muhammad, I. *J. Nat. Prod.* **2009**, *72*, 92-98.
[20] Zhao, B.; Wang, Y.; Zhang, D.; Jiang, R.; Wang, G.; Shi, J.; Huang, X.; Chen, W.; Che, C.; Ye, W. *Org. Lett.* **2011**, *13*, 3888-3891.
[21] Liu, J. F.; Heathcock, C. H. *J. Org. Chem.* **1999**, *64,* 8263-8266.
[22] Fenster, M. D. B.; Dake, G. R. *Chem. Eur. J.* **2005**, *11*, 639-649.
[23] Dutta, S.; Abe, H.; Aoyagi, S.; Kibayashi, C.; Gates, K. S. *J. Am. Chem. Soc.* **2005**, *127*, 15004-15005.
[24] Bissember, A. C.; Banwell, M. G. *Tetrahedron* **2009**, *65*, 8222-8230.
[25] Yang, H.; Carter, R. G.; Zakharov, L. N. *J. Am. Chem. Soc.* **2008**, *130*, 9238-9239.
[26] Attaway, D. H.; Zaborsky, O. R. In *Marine Biotechnology*. Ed. New York: Springer; **1993**; *Volume 1: Pharmaceutical and Bioactive Natural Products. pp.* 265.

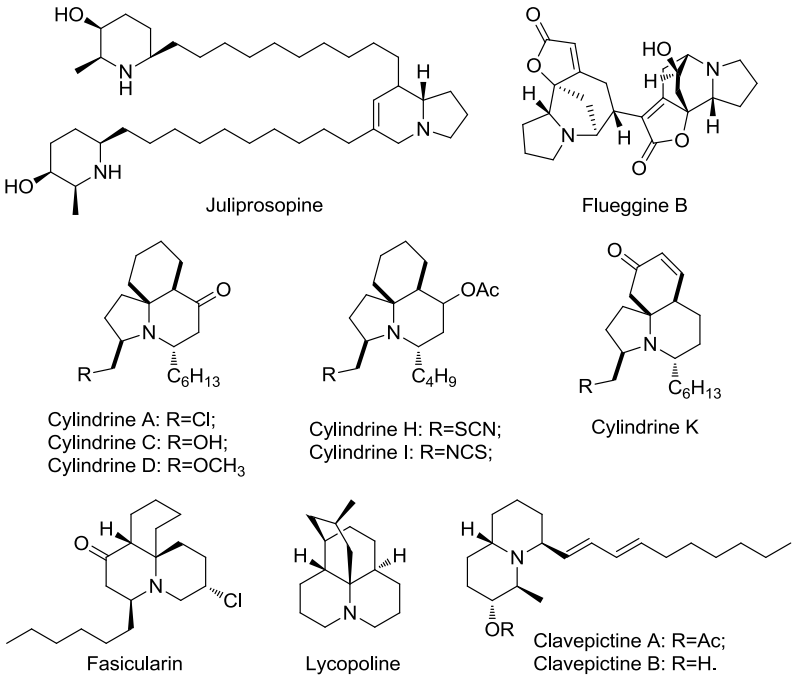


Figure 9. Some alkaloids containing indolizidine or quinolizidine substructure

Benzo[*a*]quinolizidines are of significance since it was found to exist widely in biologically active alkaloids, such as protoemetinol, psychotrine, emetine, and tubulosine (Figure 10). It was reported that psychotrine is a potent inhibitor of HIV-1 reverse transcriptase and emetine shows activity against breast tumor cells.[27]

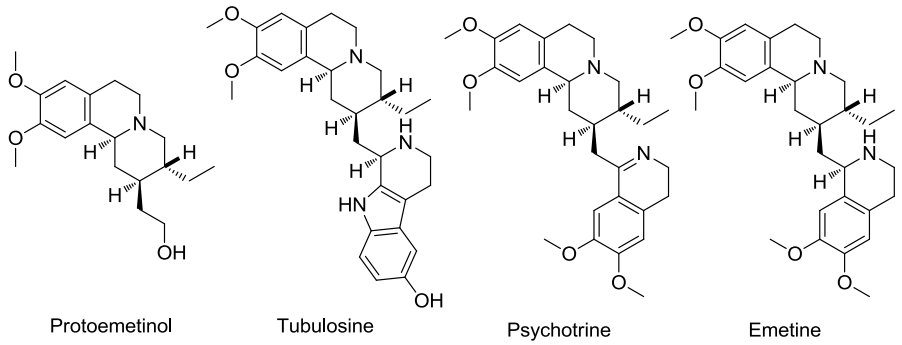


Figure 10. Structures of some benzo[*a*]quinolizidine alkaloids

[27] (a) Chang, J.; Chang, B.; Chuang, Y.; Chang, N. *Tetrahedron* **2008**, *64*, 9685-9688. (b) Zhou, Y. D.; Kim, Y. P.; Mohammed, K. A.; Jones, D. K.; Muhammad, I.; Dunbar, D. C.; Nagle, D. G. *J. Nat. Prod.* **2005**, *68*, 947-950.

1.1.2. Indolizidine and quinolizidine structure in peptidomimetics

The interest in indolizidines and quinolizidines, initially inspired by alkaloids, nowadays extends far beyond natural product chemistry. Considerable effort is being invested in the development of innovative methods for preparing the parent bicyclic systems and, particularly, for the stereocontrolled attachment of substituents. There is a growing interest on the biological activity of compounds containing azabicyclic building blocks and structural, spectroscopic and computational studies on both natural and synthetic indolizidines and quinolizidines are reported regularly. Some of these studies are related to the design and synthesis of rigid bicyclic peptidomimetics.

Naturally occurring peptides have been shown to be valuable molecules that can influence the activity of a desired biological target. Peptides have been important lead compounds in drug discovery, albeit with limited applicability due to their poor pharmacokinetic properties, including rapid metabolism and low bioavailability.[28] The design of peptidomimetic derivatives is an area of active investigation and has generated a considerable amount of work in the synthesis of high affinity and selective new therapeutic agents.[29] They are expected to maintain the features responsible for biological activity as natural peptide counterparts and, at the same time, overcome low metabolic stability in *vivo* and the poor bioavailability.[29a,30]

One of the most efficient strategies to improve stability against biodegradation is the modification of natural proteins by introducing a non peptide unit.[31] Turn motifs reverse the overall direction of a polypeptide chain and play important roles in peptide folding, recognition, and biology.[32] Specifically, the replacement of a dipeptide motif

[28] Sawyer, T. K. In *Peptide-based Drug Design, Controlling Transport and Metabolism;* Taylor, M. D.; Amidon, G. L., Eds.; ACS Professional Reference Book, American Chemical Society: Washington, DC, USA, **1995**; *6*, *pp* 387 – 421.
[29] a)Gante, J. *Angew. Chem., Int. Ed.* **1994**, *33*, 1699-1720. b) Ripka, A. S.; Rich, D. H. *Curr. Opin. Chem. Biol.* **1998**, *2*, 441-452. (c) Surprenant, S.; Lubell, W. D. *Org. Lett.* **2006**, *8*, 2851-2854.
[30] Trabocchi, A.; Scarpi, D.; Guarna, A. *Amino Acids*. **2008**, *34*, 1-24.
[31] Fustero, S.; Chiva, G.; Piera, J.; Sanz-Cervera, J. F.; Volonterio, A.; Zanda, M.; Ramírez de Arellano, C. *J. Org. Chem.* **2009**, *74*, 3122-3132.
[32] Belvisi, L.; Gennari, C.; Mielgo, A.; Potenza, D.; Scolastico, C. *Eur.J.Org.Chem.* **1999**, 389-400.

with a constrained or rigidified counterpart that simulates a *β*-turn in the packaging of polypeptides has become a useful strategy for developing new therapeutic agents.[33]

1.1.2.1. Constrained structures of *β*-turn mimics

The *β*-turn is one of the most important regular secondary structures found in protein epitopes in Nature (another one is the α-helix), which play important roles in stabilizing tertiary structure by initiating folding and facilitating intermolecular recognition.[34] Thus, it is readily amenable to mimetic design. Characterized by specific angular and torsional parameters, the motifs of *β*-turn can exist as type I and type II (Figure 11), where the peptide backbone adopts a U-shape conformation.[33a]

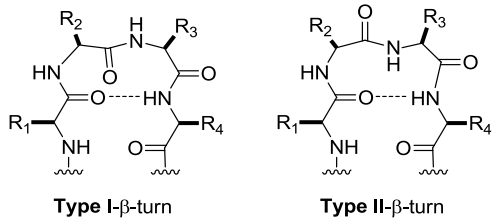


Figure 11. Two types of *β*-turn

Obviously, constrained dipeptide motifs would be a nice mimic of natural *β*-turns and the conformational restriction can be achieved by incorporating one or more rings into the backbone of amino acid chimera.[35] Considering the specific structure of type I-*β*-turn, a composite representation of such motif can be generated (Figure 12). The general structure is formed by fusing two rings (A and B) which have a carbon-nitrogen bond as bonding bridge. It is possible to introduce a third ring C and to replace the carbon by a heteroatom (X, Y and Z could be S, O or N).[35a] When there are only two rings (A and B) and no heteroatom except the nitrogen on the bridge, the structure

[33] a) Whitby, L. R.; Boger, D. L. *Acc. Chem. Res.* **2012**, *45*, 1698-1709. b) Wang, W,; Xiong, C.; Hruby, V. J. *Tetrahedron Letters*. **2001**, *42*, 3159-3161.
[34] (a) Dutt, A.; Fröhlich, R.; Pramanik, A. *Org. Biomol.Chem.* **2005**, *3*, 661-665. (b) Suat, Kee. K.; Jois, S. D. S. J. *Curr. Pharm. Des.* **2003**, *9*, 1209-1212.
[35] (a) Hanessian, S.; McNaughton-Smith, G.; Lombart, H. -G.; Lubell, W. D. *Tetrahedron.* **1997**, *53*, 12789-12854. (b) Bentz , E. L.; Goswami, R.; Moloney, M. G.; Westaway, S. M. *Org. Biomol.Chem.* **2005**, *3*, 2872-2882.

becomes an azabicyclo[X.Y.0]alkane dipeptide, a class of compounds which have gained specific popularity in peptide mimics.

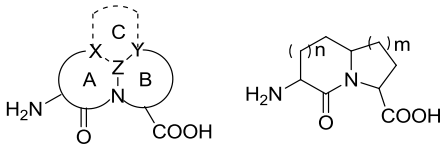


Figure 12. Representation of a general structure of constrained dipeptide motifs and azabicyclo[X.Y.0]alkane dipeptides, m = 0,1,2,3; n = 0,1,2

Thus, azabicyclo[X.Y.0]alkane dipeptides can be building blocks for the construction of conformationally rigid surrogates of peptide structures.[29a,36] These dipeptide analogs can be used to restrain the backtone and side-chain geometry and hence be useful tools for studying conformation-activity relationships.[37] The bicyclic framework restricts the geometry of the backbone by a combination of structural constraints and steric interactions, in such a way that the flexibility of these molecules is influenced by the stereochemistry, the presence of substituents in the heterocyclic system, and the size of the ring.[37,38]

1.1.2.2. Indolizidine and quinolizidine dipeptide mimics

In azabicyclo[X.Y.0]alkane dipeptides, the ring A is a lactam, which may have four to seven atoms (γ-, δ-, or ε-lactam for n equal to 0, 1, or 2, respectively). Yet ring B could be composed by four, five, six or seven atoms (for m equal to 0, 1, 2, or 3, respectively). Rings A and B of different sizes can be combined to form a wide variety of dipeptidomimetics. Indolizidine peptidomimetics display 5/6-bicyclic fused systems and can be classified into γ- and δ-lactams (Figure 13). Both of them generate library members exhibiting different biological activity. Five examples of each type are shown in Table 1.

[36] Halab, L. F.; Gosselin, F.; Lubell, W. D. *Biopolymers (Peptide Science)*. **2000**, *55*, 101-122.
[37] Rao, M. H. V. R.; Pinyol, E.; Lubell, W. D. *J. Org. Chem.* **2007**, *72*, 736-743.
[38] Cluzeau, J.; Lubell, W. D. *Biopolymers (Peptide Science).* **2005**, *80*, 98-150.

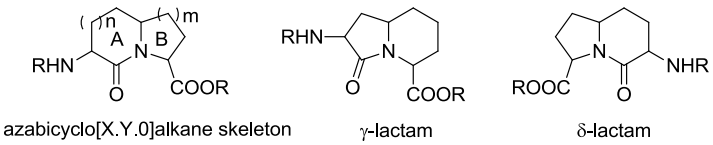
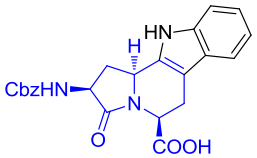
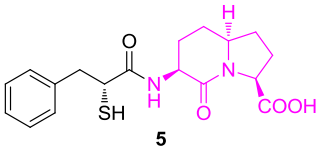
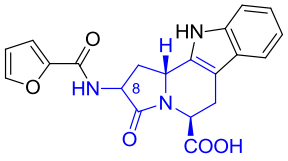
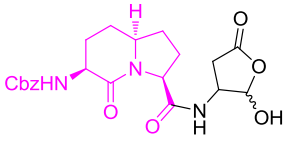
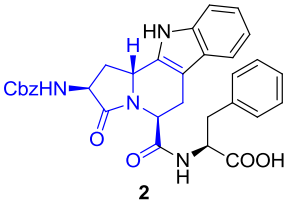
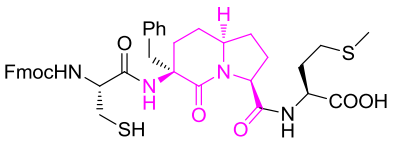
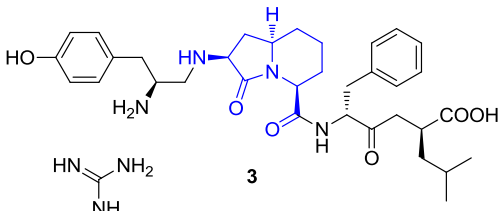
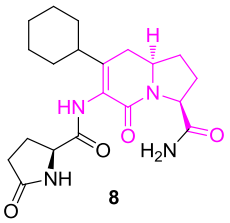
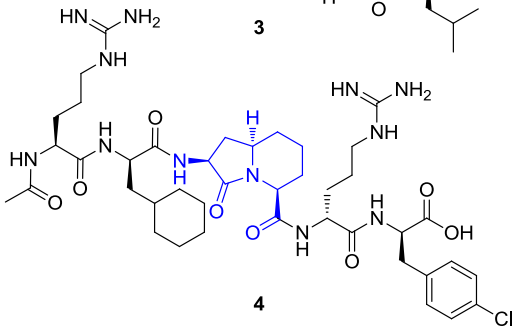
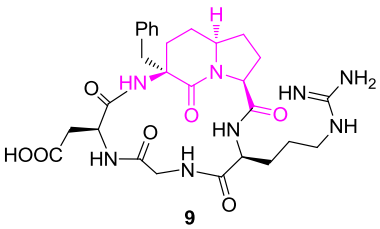


Figure 13. General structure of azabicyclo[X.Y.0]alkane dipeptides and indolizidine dipeptide structure of γ-lactam and δ-lactam

Table 1. Classification of indolizidine peptidomimetics and examples for each type[39-48]

γ-lactam group	δ-lactam group
 IBTM	 5
 (8*S*)-**1** (8*R*)-**1**	 6
 2	 7
 3	 8
 4	 9

The left column of Table 1 displays five γ-lactam analogs which show some biological activity. IBTM is a substituted indolizidine amino acid widely used as restricted dipeptide to generate conformationally constrained *β*-turn mimics.[39] The

[39] Martín-Martínez, M.; De La Figuera, N.; Latorre, M.; García-López, M. T.; Cenarruzabeitia, E.; Del Río, J.; González-Muñiz, R. *J. Med. Chem.* **2005**, *48,* 7667-7674.

IBTM analogs (8*S*)- and (8*R*)-**1** show weak inhibitor effect against a series of matrix metalloproteinases (MMPs).[40] In addition, another IBTM analog, **2**, has shown antagonist activity (IC_{50} = 4.7 nM) at the cholecystokinin (CCK_1) receptor.[41] The analog **3** is less active in *vivo* than Leu-enkephalin, but it reached 68% of the maximum signal obtained with morphine on the μ-receptor and its long-acting effect indicates the requirements of its conformation for interaction with the biological receptor.[42] The hexapeptide mimic **4** displays good affinity for the ORL1 (opioid receptor-like) receptor.[43] A broad spectrum of potential therapeutic applications have been reported for the ORL1 receptor system, for example, ORL1 agonists have been identified as anxiolytics, stimulants of food-intake, analgesics, suppressants of drug abuse, antiepileptics, and for the management of hyponatemic and water-retaining syndromes.

The five compounds in the right column are δ-lactams. Compound **5** is a potent selective ACE (angiotensin converting enzyme) inhibitor (IC_{50} =0.87 nM)[44] and compound **6** was found to be a selective inhibitor of caspase 1 (IC_{50} =36 nM).[45] Furthermore, tetrapeptide **7** exhibited activity against farsenyl transferase (Ftase, IC_{50}=5 μM).[46] Constrained thyroliberin (TRH) tripeptide analog **8** is a partial agonist (K*i* = 2/1.3 μM) for the THR receptor (THR-R) without THR-R1/THR-R2 subtype selectivity.[47] Finally, the cyclic peptide **9** was proved to be a $\alpha_V\beta_3$ (a type of integrin)

[40] D'Alessio, S.; Gallina, C.; Gavuzzo, E.; Giordano, C.; Gorini, B.; Mazza, F.; Paradisi, M. P.; Panini, G.; Pochetti, G. *Eur. J. Med. Chem.* **2001**, *36*, 43-53.
[41] a)De La Figuera, N.; Martín-Martínez, M.; Herranz, R.; García-López, M. T.; Latorre, M.; Cenarruzabeitia, E.; Del Río, J.; González-Muñiz, R. *Bioorg. Med. Chem. Lett.* **1999**, *9*, 43-48; b) Martín-Martínez, M.; Latorre, M.; García-López, M. T.; Cenarruzabeitia, E.; Del Río, J.; González-Muñiz, R. *Bioorg. Med. Chem. Lett.* **2002**, *12*, 109-112.
[42] Gosselin, F.; Lubell, W. D.; Tourwé, D.; Ceusters, M.; Meert, T.; Heylen, L.; Jurzak, M. *J. Pept. Res.* **2001**, *57*, 337-344.
[43] Halab, L.; Becker, J. A.; Darula, Z.; Tourwé, D.; Kieffer, B. L.; Simonin, F.; Lubell, W. D. *J. Med. Chem.* **2002**, *45*, 5353-5257.
[44] St Charles, R.; Matthews, J. H.; Zhang, E.; Tulinsky, A. *J. Med. Chem.* **1999**, *42*, 1376-1383.
[45] Karanewsky, D. S.; Bai, X.; Linton, S. D.; Krebs, J. F.; Wu, J.; Phran, B.; Tomaselli, K. J. *Bioorg. Med. Chem. Lett.* **1998**, *8*, 2757-2762.
[46] Liu, R.; Dong, D. L. Y.; Sherlock, R.; Nestler, H. P.; Gennari, C.; Mielgo, A.; Scolastico, C. *Bioorg. Med. Chem. Lett.* **1999**, *9*, 847-852.
[47] Chu, W.; Perlman, J. H.; Gershengorn, M. C.; Moeller, K. D. *Bioorg. Med. Chem. Lett.* **1998**, *8*, 3093-3096.

specific inhibitor (IC_{50} = 4.1 nM).[48] The integrins are cell surface receptors which play a major role incell-cell and cell-matrix adhesive interactions.

Quinolizidine peptidomimetics present a 6/6-bicyclic fused system and hence they belong to the δ-lactam category. The two examples are shown in Figure 14 were used to investigate the structure-activity requirements of the ORL1 antagonist Ac-Arg-D-Cha-Qaa-D-Arg-D-*p*-ClPhe-NH_2.[49]

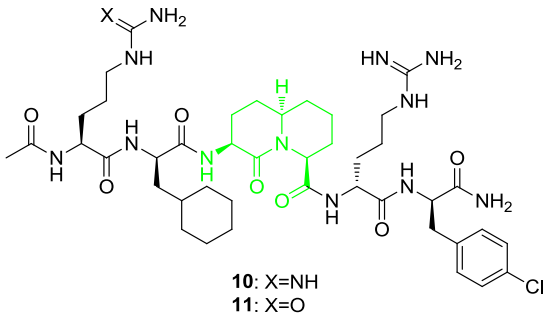


Figure 14. Examples of quinolizidine peptidomimetics

[48] Belvisi, L.; Bernardi, A.; Checchia, A.; Manzoni, L.; Potenza, D.; Scolastico, C.; Castorina, M.; Cupelli, A.; Giannini, G.; Carminati, P.; Pisano, C. *Org. Lett.* **2001**, *3*, 1001-1004.
[49] Van Cauwenberghe, S.; Simonin, F.; Cluzeau, J.; Becker, J. A.; Lubell, W. D.; Tourwé, D. *J. Med. Chem.* **2004**, *47*, 1864-1867.

1.1.3. Indolizidine and quinolizidine dipeptides in Smac mimics

1.1.3.1. Smac protein

Smac/DIABLO (the second mitochondria-derived activator of caspase) has been identified as a pro-apoptotic protein released from mitochondria in response to apoptotic stimuli (Figure 15).[50] Smac protein promotes apoptosis in cells, at least in part, by directly interacting with the anti-apoptotic proteins IAPs (inhibitors of apoptosis proteins), functioning as anti-inhibitors of caspase enzymes (apoptotic proteins directly involved in programmed cell death).[51] Moreover, short Smac peptides fused to a carrier peptide for intracellular delivery have been shown to overcome resistance of cancer cells with high levels of IAPs, to enhance the activity of anticancer drugs *in vitro* and *in vivo*, and to have little toxicity to normal cells and to normal tissues.[52]

Figure 15. Structure of the Smac/DIABLO protein[53]

The IAPs are a class of central apoptosis regulators.[54] The X-linked inhibitor of apoptosis protein (XIAP) is found to be highly expressed in many human tumor cell lines and tumor samples from patients[55] and plays an important role in the resistance of cancer cells to a variety of anticancer drugs.[56] Functioning as an endogenous inhibitor

[50] (a) Du, C.; Fang, M.; Li, Y.; Li, L.; Wang, X. *Cell.* **2000**, *102*, 33-42. (b) Verhagen, A. M.; Ekert, P. G.; Pakusch, M.; Silke, J.; Connolly, L. M.; Reid, G. E.; Moritz, R. L.; Simpson, R. J.; Vaux, D. L. *Cell.* **2000**, *102*, 43-53.
[51] Vucic, D; Deshayes, K; Ackerly, H; Pisabarro, M. T.; Kadkhodayan, S; Fairbrother, W. J.; Dixit, V. M. *J. Biol. Chem.* **2002**, *227*, 12275-12279.
[52] (a) Fulda, S.; Wick, W.; Weller, M.; Debatin, K. M. *Nat. Med.* **2002**, *8*, 808-815. (b) Arnt, C. R.; Chiorean, M. V.; Heldebrant, M, P.; Gores G. J; Kaufmann S. H. *J. Biol. Chem*. **2002**, *277*, 44236-44243. (c) Yang, L.; Mashima, T.; Sato, S.; Mochizuki, M.; Sakamoto, H.; Yamori, T.; Oh-Hara, T.; Tsuruo, T. *Cancer Res*. **2003**, *63*, 831-837.
[53] Chai, J.; Du, C.; Wu, J.W.; Kyin, S.; Wang, X.; Shi, Y. *Nature.* **2000**, *406*, 855-862.
[54] (a) Deveraux, Q. L.; Reed, J. C. *Genes Dev.* **1999**, *13*, 239-252. (b) Schimmer,; A. D. *Cancer. Res*. **2004**, *64*, 7183-7190.
[55] Tamm, I.; Kornblau, S. M.; Segall, H.; Krajewski, S.; Welsh, K.; Kitada, S.; Scudiero, D. A.; Tudor, G.; Qui, Y. H.; Monks, A.; Andreeff, M.; Reed, J. C. *Clin. Cancer Res.* **2000**, *6*, 1796-1803.
[56] Holcik, M.; Gibson, H.; Korneluk, R. G. *Apoptosis.* **2001**, *6*, 253-261.

of XIAP and other IAP proteins,[57] Smac blocks the inhibition of XIAP to caspase-9 by binding to the BIR3 domain in XIAP (Figure 16) through its AVPI tetra-peptide binding motif and competing directly with a similar ATPF tetrapeptide in caspase-9.[58]

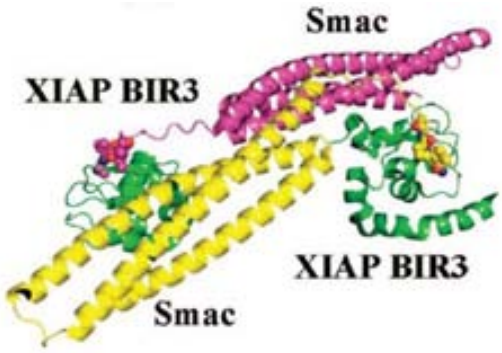


Figure 16. Crystal structure of Smac in complex with XIAP BIR3 protein[53]

As all natural peptides, Smac peptides have typical limitations for being potent therapeutic agents. For instance, they are not cell-permeable and they have poor bioavailability. In recent years, a great deal of attention is focused on the strategy to design small molecules to mimic the Smac AVPI binding motif, with improved binding affinities, cell-permeability, and in *vivo* stability.

1.1.3.2. Design of Smac peptidomimetics

It is revealed that the AVPI tetrapeptide (Figure 17), as N-terminal four residues in Smac, recognize and bind to a surface groove on XIAP BIR3.[58] This structural information has laid the foundation for the design of Smac mimetics at the atomic level.

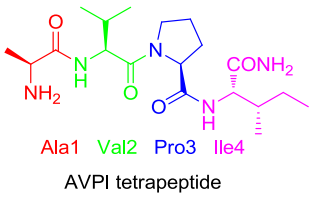


Figure 17. Smac-derived AVPI-NH_2

[57] Dai, Y.; Lawrence, T. S.; Xu, L.; *Am. J. Transl. Res.* **2009**, *1*, 1-15.
[58] (a) Wu, G.; Chai, J.; Suber, T. L.; Wu, J. W.; Du, C.; Wang, X.; Shi, Y. *Nature* **2000**, *408*, 1008-1012; (b) Liu, Z.; Sun, C.; Olejniczak, E. T.; Meadows, R. P.; Betz, S. F.; Oost, T.; Herrmann, J.; Wu, J. C.; Fesik, S. W. *Nature*, **2000**, *408*, 1004-1008.

Some years ago, McLendon's group carried out general modifications of the AVPI tetrapeptide and found an overall structure-activity relationship (SAR) of Smac-based peptides binding to the XIAP BIR3 domain.[59] On this basis, Oost and colleagues modified the AVPI peptide to derive potent Smac peptidomimetics.[60] After their evaluation, several compounds showed extremely high binding affinities to XIAP BIR3 with the K_d values shown (Figure 18).

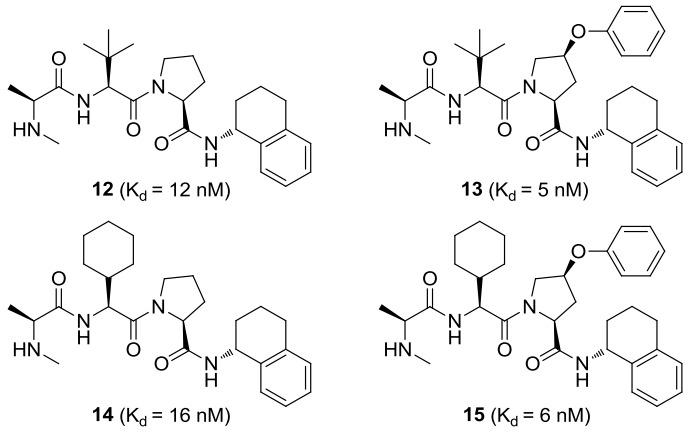


Figure 18. Representative potent Smac peptidomimetics

Apart from their functional antagonism against XIAP BIR3, they are also effective in induction of caspase-3 activation in the MDA-MB-231 human breast cancer cell line. These *in vitro* and *in vivo* data indicate that Smac mimetics may have a therapeutic potential as single agents for the treatment of human cancer.[60]

1.1.3.3. Design of conformationally constrained Smac mimetics

The research on structure-activity relationship suggested that the cyclization of the side chain of Val2 and Pro3 ring could form a bicyclic lactam structure without changing the binding between the AVPI peptide and XIAP BIR3.[61] Accordingly, Wang's laboratory from the University of Michigan designed and synthesized a series of conformationally constrained, bicyclic Smac mimetics **16-21** (Figure 19). Meanwhile,

[59] Kipp, R. A.; Case, M. A.; Wist, A. D.; Cresson, C. M.; Carrell, M.; Griner, E.; Wiita, A.; Albiniak, P. A.; Chai, J.; Shi, Y.; Semmelhack, M. F.; McLendon, G. L. *Biochemistry*, **2002**, *41*, 7344-7349.
[60] Oost, T. K.; Sun, C.; Armstrong, R. C.; Al-assaad, A. S.; Bentz, S. F.; Deckwerth, T. L.; Ding, H.; Elmore, S. W.; Meadows, R. P.; Olejniczak, E. T.; Oleksijew, A.; Oltersdorf, T.; Rosenberg, S. H.; Shoemaker, A. R.; Tomaselli, K. J.; Zou, H.; Fesik, S. W. *J. Med. Chem.* **2004**, *47*, 4417-4426.
[61] Sun, H.; Nikolovska-Coleska, Z.; Yang, C.-Y.; Xu, L.; Liu, M.; Tomita, Y.; Pan, H.; Yoshioka, Y.; Krajewski, K.; Roller, P. P.; Wang, S. *J. Am. Chem. Soc.* **2004**, *126*, 16686-16687.

relative evaluation and biological activity assay were reported.[61,62] As shown, these compounds achieve high binding affinities to XIAP BIR3, especially **19** and **21**.

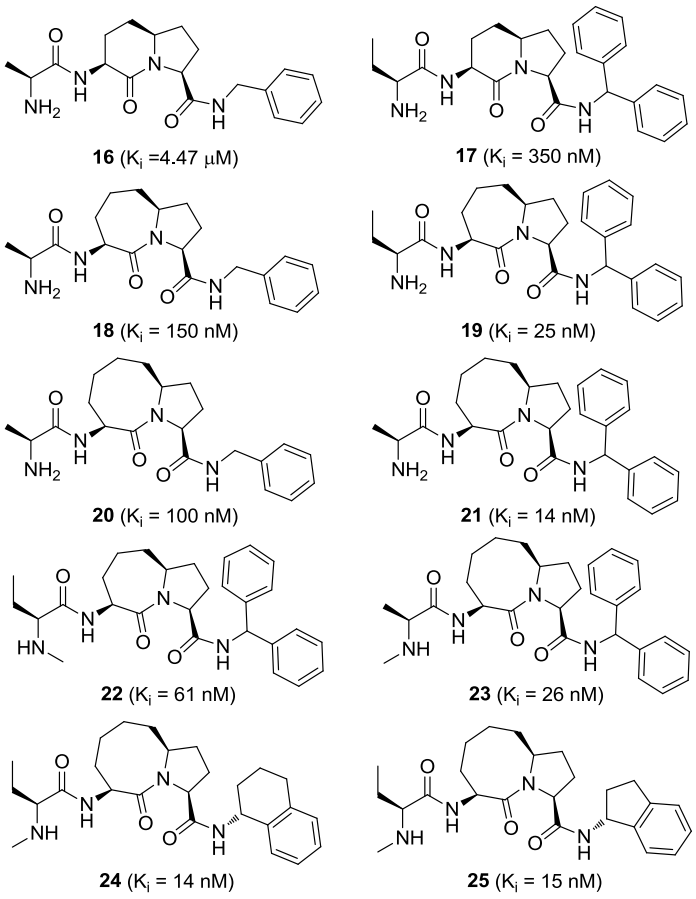


Figure 19. Conformationally constrained Smac peptidomimetics from Wang's group

Since substitution of the free terminal amino group by one methyl group is well tolerated,[59] additional modification was carried out.[61,63] The K_i value of the new analogs showed their closely binding with XIAP BIR3 protein. The inhibitor test of cell growth in the MDA-MB-231 human breast cancer cell line also indicated their potent inhibitor activity, especially for compound **22** with an IC_{50} value of 0.1 μM. In addition, compounds **24** and **25** potently inhibit cancer cell growth in other cancer cell lines.

[62] Sun, H.; Stuckey, J. A.; Nikolovska-Coleska, Z.; Qin, D.; Meagher, J. L.; Qiu, S.; Lu, J.; Yang, C.-Y.; Saito, N. G.; Wang, S. *J. Med. Chem.* **2008,** *51,* 7169-7180.
[63] Sun, H.; Nikolovska-Coleska, Z.; Lu, J.; Qiu, S.; Yang, C.-Y.; Gao, W.; Meagher, J.; Stuckey, J.; Wang, S. *J. Med. Chem.* **2006**, *49*, 7916-7920.

Moreover, other kinds of conformationally constrained Smac mimetics are designed and reported in recent years. Compound **26**[64] (Figure 20) can effectively inhibit cell growth in the MDA-MB-231 breast cancer cell line (IC_{50} = 100 nM) and A-2058 melanoma cell line (IC_{50} = 2 μM). Compound **27** (LBW242), designed by cyclization of the third and fourth residues in the AVPI peptide, binds to XIAP BIR3 with an IC_{50} value of 280 nM.[65]

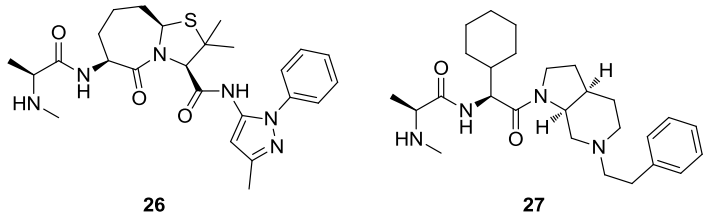


Figure 20. Conformationally constrained Smac peptidomimetics from Genentech and Novartis

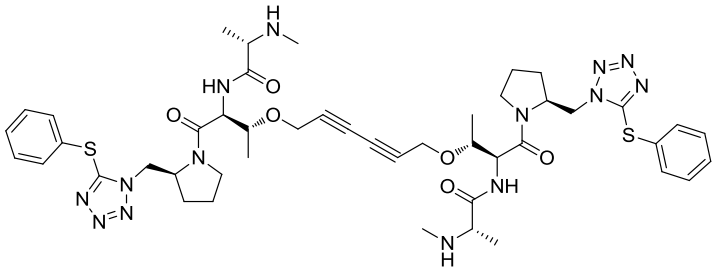
1.1.3.4. Design of bivalent Smac mimetics

The crystal structure showed that Smac protein forms an elongated homodimer (Figure 16)[58] and binds to XIAP protein with a much higher affinity than the Smac AVPI peptide. Thus compounds that contain two "AVPI" binding motifs may mimic the binding mode of Smac protein to XIAP and potentially achieve high binding affinities to XIAP.

The first bivalent small molecule Smac mimetic **28** (Figure 21) was reported in 2004 by Wang and Harran laboratories.[66] It has an affinity higher than Smac peptide and binds to XIAP containing both BIR2 and BIR3.[67] Relevant bioassays demonstrated that compound **28** is effective in cell growth inhibition in ~25% of human non-small carcinoma cell lung cancer cell lines and effectively inhibits tumor growth in the

[64] Zobel, K.; Wang, L.; Varfolomeev, E.; Franklin, M. C.; Elliott, L. O.; Wallweber, H. J.; Okawa, D. C.; Flygare, J. A.; Vucic, D.; Fairbrother, W. J.; Deshayes, K. *ACS Chem. Biol.* **2006**, *1*, 525-533.
[65] (a) Chauhan, D.; Neri, P.; Velankar, M.; Podar, K.; Hideshima, T.; Fulciniti, M.; Tassone, P.; Raje, N.; Mitsiades, C.; Mitsiades, N.; Richardson, P.; Zawel, L.; Tran, M.; Munshi, N.; Anderson, K. C. *Blood*. **2007**, *109*, 1220-1227. (b) Gaither, A.; Porter, D.; Yao, Y.; Borawski, J.; Yang, G.; Donovan, J.; Sage, D.; Slisz, J.; Tran, M.; Straub, C.; Ramsey, T.; Iourgenko, V.; Huang, A.; Chen, Y.; Schlegel, R.; Labow, M.; Fawell, S.; Sellers, W. R.; Zawel, L. *Cancer Res.* **2007**, *67*, 11493-11498.
[66] Li, L.; Thomas, R. M.; Suzuki, H.; De Brabander, J. K.; Wang, X.; Harran, P. G. *Science*. **2004**, *305*, 1471-1474.
[67] Nikolovska-Coleska, Z.; Meagher, J. L.; Jiang, S.; Kawamoto, S. A.; Gao, W.; Yi, H.; Qin, D.; Roller, P. P.; Stuckey, J. A.; Wang, S. *Anal. Biochem.* **2008**, *374*, 87-98.

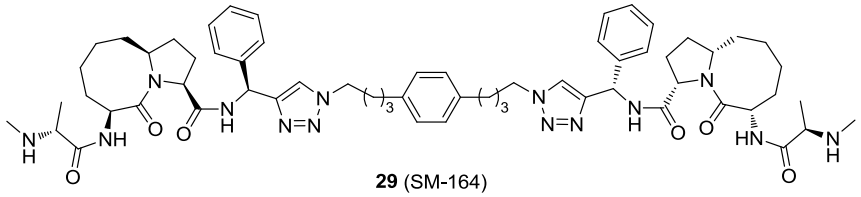
HCC461 xenografts in mice; furthermore, it causes tumor regression in 40% of treated animals.[68]



28 (bivalent Smac mimetic)

Figure 21. First bivalent small-molecule Smac mimetic from the group of Wang and Harran

Afterwards, based upon conformationally constrained monovalent Smac mimetics, many bivalent Smac mimetics were designed and reported. As the most potential mimic, compound **29** (bivalent SM-164, Figure 22) interacts with both domains (BIR2 and BIR3) in XIAP and shows good inhibitor activity.[69] Moreover, it showed to be effective in inhibition of cell growth and induction of apoptosis in cancer cell lines and shows no or little toxicity to animals at effective dose schedules.[70]



29 (SM-164)

Figure 22. Bivalent small-molecule Smac mimetics from Wang's laboratory

1.1.3.5. Summary

Due to the potent pro-apoptotic role of Smac, there has been an enormous interest in the design and synthesis of small-molecule Smac mimetics. To date, intense research has generated potent small-molecule peptidomimetics and nonpeptidic mimetics.

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[68] Petersen, S. L.; Wang, L.; Yalcin-Chin, A.; Li, L.; Peyton, M.; Minna, J.; Harran, P.; Wang, X. *Cancer Cell*. **2007**, *12*, 445-456.

[69] Sun, H.; Nikolovska-Coleska, Z.; Lu, J.; Meagher, J. L.; Yang, C.-Y.; Qiu, S.; Tomita, Y.; Ueda, Y.; Jiang, S.; Krajewski, K.; Roller, P. P.; Stuckey, J. A.; Wang, S. *J. Am. Chem. Soc.* **2007**, *129*, 15279-15294.

[70] Lu, J.; Bai, L.; Sun, H.; Nikolovska-Coleska, Z.; McEachern, D.; Qiu, S.; Miller, R. S.; Yi, H.; Shangary, S.; Sun, Y.; Meagher, J. L.; Stuckey, J. A.; Wang, S. *Cancer Res*. **2008**, *68*, 9384-9393.

A structure-based strategy has been employed to develop monovalent Smac mimetics designed to mimic the Smac AVPI binding motif. Such compounds were found to achieve not only high affinities to XIAP but also effective inhibition of cell growth and induction of apoptosis in cancer cell lines. In particular, Smac mimics based on a constrained AVPI tetrapeptide containing bicyclic lactams have exhibited potency as inhibitors of IAP binding. Besides, bivalent Smac mimetics, containing two "AVPI" binding motifs, have an extremely high affinity, exceeding that of Smac protein, which demonstrate another direction to design Smac mimetics as potent therapeutic agents.

1.1.4. Indolizidine and quinolizidine structure in antimalarial drugs

1.1.4.1. Malaria

Malaria is a mosquito-borne infectious disease of humans and other animals caused by parasitic protozoan (a type of unicellular microorganism) of the genus *Plasmodium*. Commonly, the disease is transmitted by a bite from an infected female *Anopheles* mosquito, which introduces the organisms from its saliva into a person's circulatory system. In the blood, the parasites travel to the liver to mature and reproduce. Malaria is characterized by intermittent high fevers and, in the case of cerebral malaria, neurological complications, such as brain injury and coma.

Malaria remains one of the most prevalent and deadly infectious diseases across Africa, Asia, and the Americas. It causes hundreds of thousands of deaths worldwide each year: estimates range from 660,000 to 1,238,000 deaths in 2010 and the highest mortality occurred in Africa.[71] Moreover, it imposes a heavy social burden that has delayed economic development in regions where it is endemic. For instance, in Africa the economic burden is estimated at $12 billion/year.[72]

For the reason shown above, malaria elimination has recently been reinstated as a global health priority.[73] There is an urgent need to develop efficient drug classes that alleviate symptoms, prevent transmission and provide a radical cure.

1.1.4.2. Indolizidine and quinolizidine structure in antimalarial drugs

Chloroquine (Figure 23) has long been used in the treatment or prevention of malaria. The cause of chloroquine resistance is not completely clear, but it is associated with an increased efflux from the parasite food vacuole and with mutations of Pfcrt genes of *P. falciparum*.[74] Commonly, it is accepted that chloroquine exerts its antimalarial activity by inhibiting hemozoin formation in the digestive vacuole of the

[71] Shetty, P. *Nature* **2012**, *484*, S14-S15.
[72] Kar, S. *Nat. Rev. Drug. Disc.* **2010**, *9*, 511-512.
[73] Flannery, E. L., Chatterjee, A. K. Winzeler, E. A. *Nat. Rev.* **2013**, *11*, 849-862.
[74] Ursos, L. M. B.; Roepe, P. D. *Med. Res. Rev.* **2002**, *22*, 465-491.

parasite.[75] It has been observed that several chloroquine analogs and derivatives retain significant activity against chloroquine-resistant *P. falciparum* strains[76] and it has been suggested that chloroquine analogs containing the side chain basic nitrogen in a piperidine or pyrrolidine ring exhibited a substantial increase in antimalarial activity against chloroquine-resistant strains. The analogs **30**-**33** exhibit from 7 to 10 times more activity than chloroquine and they are either equitoxic or definitely less toxic than chloroquine on murine cells.[77] Compound **31**, which is the best one, indicates a potential way to design and synthesize a new class of potential antimalarial drugs.

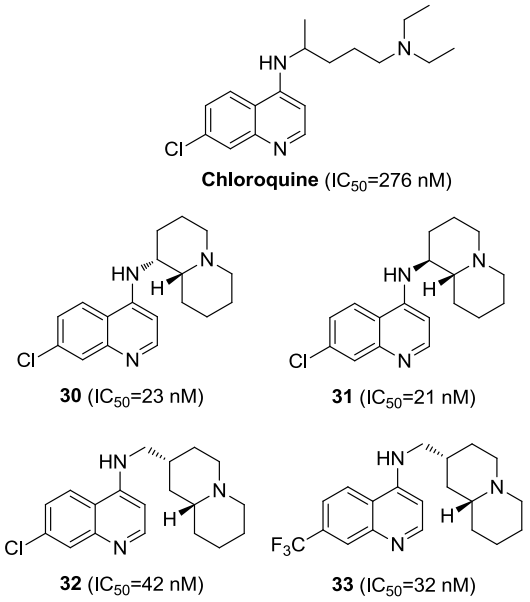


Figure 23. Activity of chloroquine and some analogs with quinolizidine structure against W-2 (CQ-R) strains of *P.falciparum*

Febrifugine (Figure 24), which was isolated from the roots of *Dichroa febrifuga* Lour, shows powerful antimalarial activity against *P. falciparum*. Structure-activity relationship studies performed with febrifugine analogs suggested that in the

[75] (a) Egan, T. J.; Hunter, R.; Kaschula, C. H.; Marques, H. M.; Misplon, A.; Walden, J. *J. Med. Chem.* **2000**, *43*, 283-291. (b) Egan, T. J. *Mini Rev. Med. Chem.* **2001**, *1*, 113-123. (c) Kaschula, C. H.; Egan, T. J.; Hunter, R.; Basilico, N.; Parapini, S.; Taramelli, D.; Pasini, E.; Monti, D. *J. Med. Chem.* **2002**, *45*, 3531-3539.

[76] (a) Ridley, R. G.; Hofheinz, W.; Matile, H.; Jaquet, C.; Dorn, A.; Masciadri, R.; Jolidon, S.; Richter, W. F.; Guenzi, A.; Girometta, M. A.; Urwyler, H.; Huber, W.; Thaithong, S.; Peters, W. *Antimicrob. Agents Chemother.* **1996**, 40, 1846-1854. (b) De, D.; Krogstad, F. M.; Byers, L. D.; Krogstad, D. J. *J. Med. Chem.* **1998**, *41*, 4918-4926. (c) Ryckebusch, A.; Deprez-Poulain, R.; Maes, L.; Debren- Fontain, M.-A.; Mouray, E.; Grellier, P.; Sergheraert, C. *J. Med. Chem.* **2003**, *46*, 542-557.

[77] Sparatore, A.; Basilico, N.; Parapini, S.; Romeo, S.; Novelli, F.; Sparatorec, F.; Taramelli, D. *Bioorg. Med. Chem.* **2005**, *13*, 5338-5345.

4-quinazolinone moiety, the nitrogen atom of the piperidine ring, and the hydroxyl group is necessary for the antimalarial activity and that the absolute configuration of these functional groups plays an important role.[78] The two acetone adducts **34** and **35** were synthesized and evaluated in vitro and it was found that against the chloroquine sensitive FCR-3 strain, both **34** (EC_{50} = 1.6 nM) and **35** (EC_{50} = 2.8 nM) showed much higher antimalarial activity than chloroquine (EC_{50} = 1.8 nM). They proved selective for *Plasmodium falciparum* and also showed high antimalarial activity against the chloroquine-resistant K1 strain.

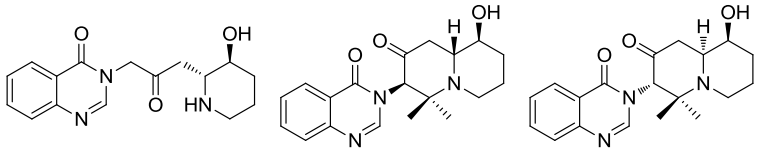


Figure 24. Febrifugine and two analogs

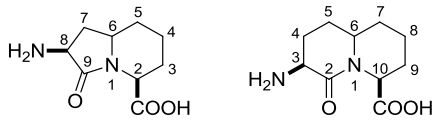
1.1.4.3. Summary

Malaria remains one of the most prevalent and deadly infectious diseases across Africa, Asia, and the Americas. A number of medicines are available for treatment of malaria, but the rapid development of drug resistance is a serious problem. Medicinal agents based on novel mechanisms of action are, therefore, required to overcome the emergence of resistance and to control an ever-increasing number of epidemics caused by the malaria parasite. As shown before, as a result of several works concerning the design of analogs of effective parent compounds (like chloroquine or febrifugine), introduction of indolizidine or quinolizidine structure may induce surprisingly good results.

[78] Takaya, Y.; Tasaka, H.; Chiba, T.; Uwai, K.; Tanitsu, M.; Kim, H. S.; Wataya, Y.; Miura, M.; Takeshita, M.; Oshima, Y. *J. Med. Chem.* **1999**, *42*, 3163-3166.

1.2. SYNTHETIC PRECEDENTS

As shown above, indolizidin-9-one amino acid **36** and quinolizidin-2-one amino acid **37** are important dipeptide analogs having restrained backbone and side-chain conformations (Figure 25). Because of their growing use in the investigation of structure-activity relationships in various biologically active peptides, there is an urgent demand for new methodology for synthesizing their enantiopure isomers. Hence, the introduction of chiral centers in a stereocontrolled manner is an attractive challenge.



36 **37**

Figure 25. Structure of targeted indolizidine and quinolizidine amino acids†

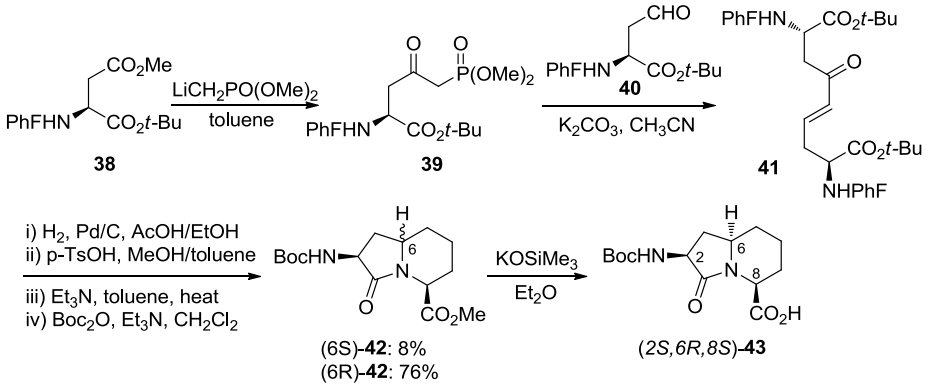
1.2.1. Synthetic precedents of indolizidine amino acids

So far, there are few reports describing the synthesis of indolizidine aminoacids (1-aza-9-oxobicyclo[4.3.0]nonane). The first synthesis, published in 1998, is shown in Scheme 1.[79] It started from β-methyl α-*tert*-butyl-*N*-(PhF)aspartate **38**, which was reacted with (dimethoxyphosphorylmethyl)lithium to form β-ketophosphonate **39**. After a Horner-Wadsworth-Emmons reaction with aldehyde **40**, the protected diamino-dicarboxylate **41** was obtained. Reductive amination of the carbonyl group in intermediate **41**, followed by ester exchange, cyclization to the lactam and amine protection furnished the *N*-(Boc) amino indolizidin-9-one ester **42** as a 9:1 mixture of diastereoisomers. Hydrolysis of the major isomer using $KOSi(CH_3)_3$ in ether provided *N*-(Boc)amino indolizidin-9-one acid **43** with overall yield around 25%.[79,80]

†Atom numbering of ring systems does not follow the IUPAC rules, nitrogen is always numbered as 1 as previously done in reference 23a.

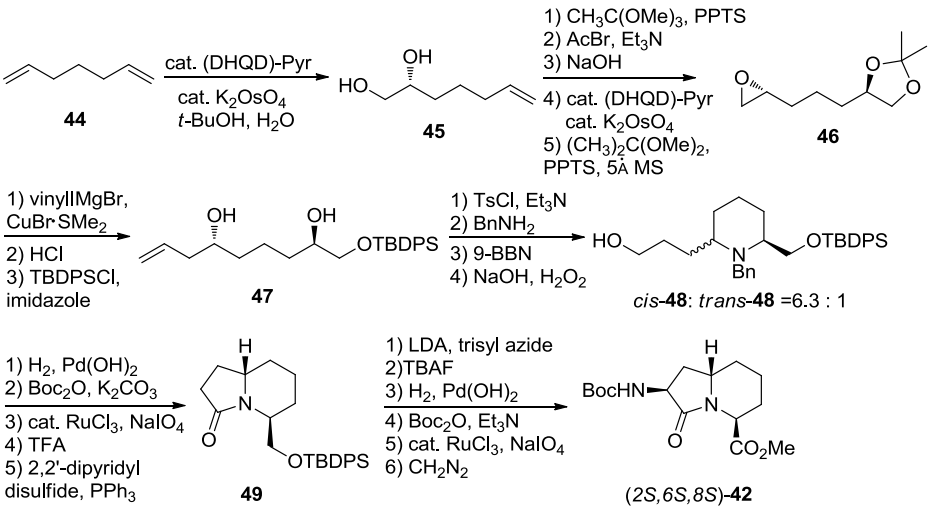
[79] Gosselin, F.; Lubell, W. D. *J. Org. Chem.* **1998**, *63*, 7463-7471.

[80] Halab, L.; Gosselin, F.; Lubell, W. D. *Biopolymers (Peptide Science).* **2000**, *55*, 101-122.



Scheme 1. Synthesis of *N*-(Boc)amino indolizidin-9-one acid **43**

The (2*S*,6*S*,8*S*)-Indolizidin-9-one aminoester (6*S*)-**42** has also been synthesized by a route starting from hepta-1,6-diene, **44**, and featuring two asymmetric dihydroxylation processes (Scheme 2).[81] The product diol of the first one, (*2R*)-**45**, was converted into epoxide and then a second asymmetric dihydroxylation was performed. Nucleophilic addition to the epoxide furnished followed by protecting group manipulation gave diol **47**. After ditosylation of the secondary hydroxyl groups, aminocyclization and hydroboration of the olefin, piperidine *trans*-**48** was generated as a major diastereoisomer. Diastereomerically pure (*2S,6S,8S*)-**42** was obtained after the α-carbonyl amination, followed by several conventional synthetic steps, including the necessary redox reactions.[38,81] The overall yield from diene **44** was 1%.

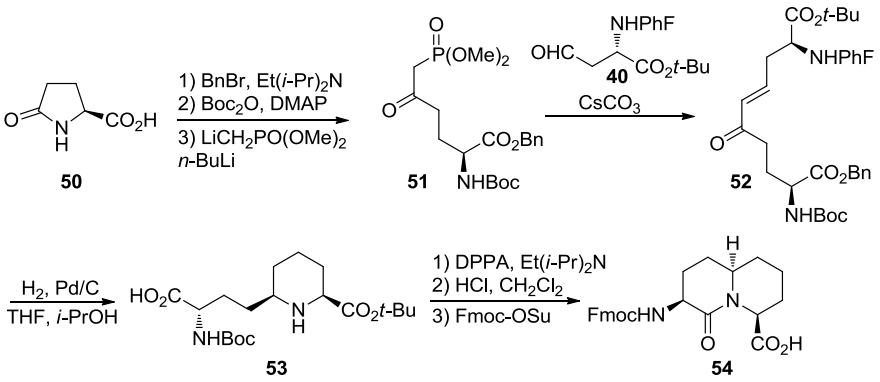


Scheme 2. Synthesis of *N*-(Boc)aminoindolizidin-9-one ester, (*6S*)-**42**

[81] Shimizu, M.; Nemoto, H.; Kakuda, H.; Takahata, H. *Heterocycles.* **2003**, *59*, 245-255.

1.2.2. Synthetic precedents of quinolizidine amino acids

The first synthesis of enantiopure quinolizidin-2-one amino acids was illustrated in 2000 (Scheme 3).[82] The sequence started from L-pyroglutamic acid, **50**, which, after nitrogen protection, was reacted with (dimethoxyphosphorylmethyl)lithium to form β-ketophosphonate **51**. After the Horner-Wadsworth-Emmons reaction with aldehyde **40**, the orthogonally protected linear enone **52** was produced. The following reductive amination gave pipecolate **53** as a single diastereoisomer that submitted to cyclization delivered the (3*S*,6*R*,10*S*)-isomer of the corresponding lactam. Protecting group manipulation furnished the quinolizidinone *N*-(Fmoc) amino acid **54** in 13% overall yield from L-pyroglutamic acid.[38,82]

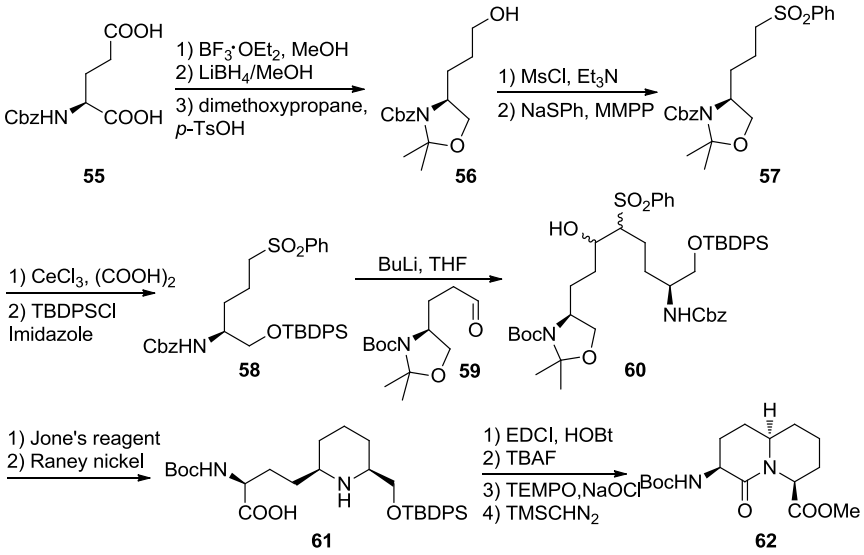


Scheme 3. Synthesis of *N*-(Boc)-aminoquinolizidin-2-one acid **54**

Another diatereoselective approach was reported in 2005, the key step of which involves the coupling reaction of an α-sulfonyl carbanion with a chiral aldehyde (Scheme 4).[83] The sequence started from the *N*-protected glutamic acid **55**, which in several conventional steps was converted to sulfone **58**. Coupling of this sulfone with aldehyde **59**, prepared also from L-glutamic acid, delivered hydroxysulfone **60** that was oxidized with Jone's reagent and then treated with Raney nickel to give piperidine **61**. Lactam formation, followed by alcohol deprotection and subsequent oxidation, furnished a carboxylic acid which was converted to methyl ester **62**, isolated as the

[82] Gosselin, F.; Lubell, W. D. *J.Org.Chem.* **2000**, *65*, 2163-2171.
[83] Truchot, C.; Wang, Q.; Sasaki, N. A. *Eur. J. Org. Chem.* **2005**, 1765-1776.

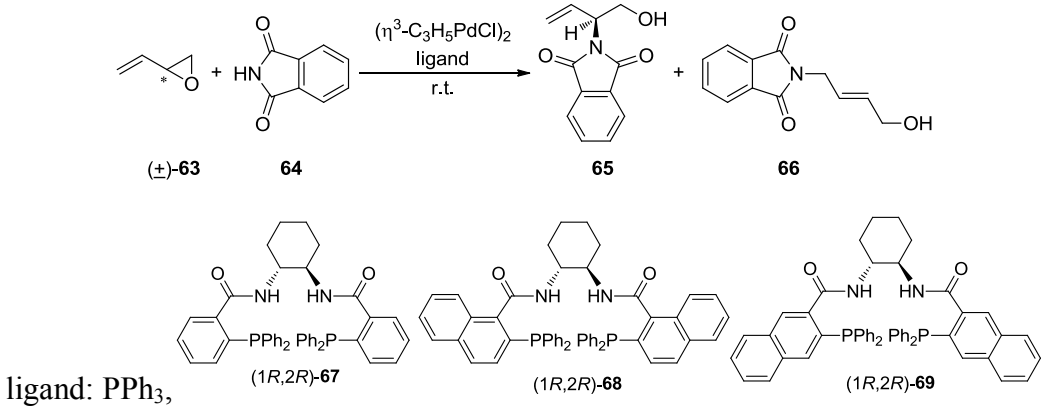
single (3*S*,6*R*,10*S*) isomer.[83] The overall yield from L-glutamic acid derivative **55** was about 21%.



Scheme 4. Synthesis of *N*-(Boc) amino quinolizidin-2-one ester **61**

1.2.3. The asymmetric allylic alkylation as a tool for stereochemical control in the synthesis of aza- bicycloalkanes

In 2000, Trost *et al*. disclosed a dynamic kinetic asymmetric transformation (DYKAT) through a palladium-catalyzed asymmetric allylic alkylation (AAA).[84] Different from traditional kinetic asymmetric reactions, in that reaction both enantiomers of the racemic starting material are converted into a single chiral product.[85] The DYKAT was explored in the context of phthalimide and racemic butadiene monoepoxide in the presence of some chiral phosphine ligands (Scheme 5). Finally they screened out the best chiral ligand **68**, which demonstrates remarkable ability to control both the regio- and the enantioselectivity (Table 2).



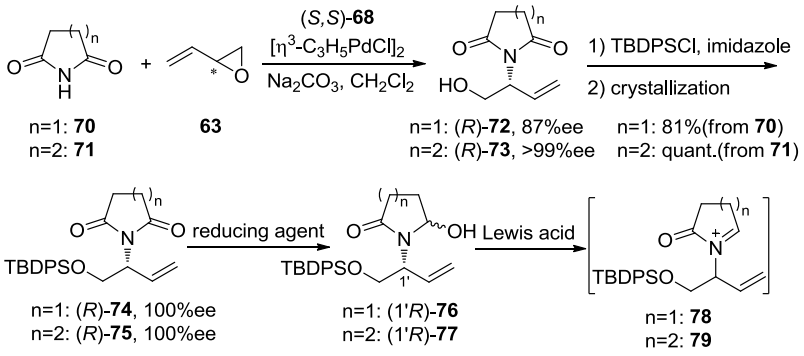
Scheme 5. The AAA between phthalimide and butadiene monoepoxide

Table 2. Attempts and results of amination of racemic butadiene monoepoxide[84]

entry	ligand	solvent	**67**:**68**	yield (%)	ee (%)
1	Ph_3P	THF	4:1	71	N.A
2	(1*R*,2*R*)-**67**	THF	16:1	87	77
3	(1*R*,2*R*)-**67**	CH_2Cl_2	-	83	68
4	(1*R*,2*R*)-**68**	THF	-	86	67
5	(1*R*,2*R*)-**68**	CH_2Cl_2	75:1	99	98
6	(1*R*,2*R*)-**69**	THF	-	94	66
7	(1*R*,2*R*)-**69**	CH_2Cl_2	-	99	55

[84] Trost, B. M.; Bunt, R. C.; Lemoine, R. C.; Calkins, T. L. *J. Am. Chem. Soc.* **2000**, *122*, 5968-5976.
[85] Trost, B. M.; Horne, D. B.; Woltering, M. J. *Chem. Eur. J.* **2006**, *12*, 6607-6620.

Inspired by this work, our group investigated the reaction between succinimide **70** and glutarimide **71** and the same epoxide **63** under similar conditions (Scheme 6). The interest in these reactions was related to an ongoing program on the synthesis of polycyclic alkaloids of the *Securinega* family. After extensive experimentation, the appropriate conditions were found and the expected alkylated products **72** or **73** could be isolated in good yield and excellent enantiomeric excess that, for the glutarimide derivative, was further improved after *O*-silylation.[86] For synthetic purposes, the silylethers **74** and **75** were reduced to the corresponding acylaminals, as precursors of the *N*-acyliminium ions **78** and **79** that were then involved in a vinylogous Mannich reaction. This strategy allowed the successful completion of very short and efficient syntheses of (-)-norsecurinine and securinine (Figure 26). In parallel, other natural products were synthesized in Trost laboratories, employing the AAA as a key step, including (+)-broussonetine G,[85,87] (-)-bulgecinine[85] and an analog of FR900482,[88] although none of them embedded an azabicyclic core.



Scheme 6. The application of DYKAT with succinimide and glutarimide

It was visualized that the AAA of succinimide and glutarimide could be a suitable entry to the enantioselective synthesis of indolizidine and quinolizidine frameworks, respectively, the *N*-acyliminium ions **78** and **79** acting as templates for the construction of these azabicyclic systems.

[86] (a) Alibés, R.; Bayón, P. March, P.; Figueredo.; Font, J.; García, E. G.; Gálvez, D. G. *Org. Lett.* **2005**, *7*, 5107-5109; (b) Gálvez, D. G.; García, E. G.; Alibés, R.; Bayón, P. March, P.; Figueredo.; Font, J. *J. Org. Chem.* **2009**, *74*, 6199-6211**.**

[87] Trost, B. M.; Horne, D. B.; Woltering, M. J. *Angew. Chem. Int. Ed.* **2003**, *42*, 5987-5990.

[88] Trost, B. M.; O'Boyle, B. M.; Torres, W.; Ameriks, M. K. *Chem. Eur. J.* **2011**, *17*, 7890-7903.

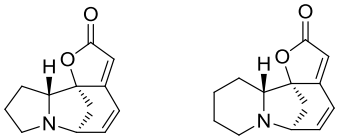


Figure 26. Structure of (-)-norsecurinine and securinine

II. Objectives

As mentioned above, the synthesis of amino acids with indolizidine and quinolizidine skeleton attracts increasing interest among chemists. The introduction of chiral centers in a stereocontrolled manner is an appealing challenge, for which the application of the DYKAT reaction in the *N*-alkylation of succinimide and glutarimide appears as a potential solution. On the other hand, it has been observed that chloroquine analogs, in which a chloroquine residue is linked to a bicyclic skeleton based on nitrogen, exhibited potential antimalarial activity against chloroquine-resistant strains.

Accordingly, the following two objectives were targeted for the present work:

- **Objective 1:** Synthesis of indolizidine peptides (**TM1**) and quinolizidine peptides (**TM2**). The aim of the work was developing a general and enantioselective strategy to asymmetrically synthesize all their stereoisomers. Moreover, the future goal is to obtain some derivatives and establish a protocol for synthesizing analogs of natural peptides Smac/DIABLO.

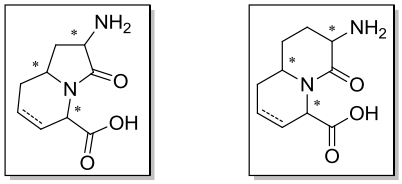


Figure 27. Targeted azabicycloalkane amino acid

- **Objective 2 :** Synthesis of chloroquine analogs containing indolizidine or quinolizidine skeleton and evaluation of their antimalarial activity.

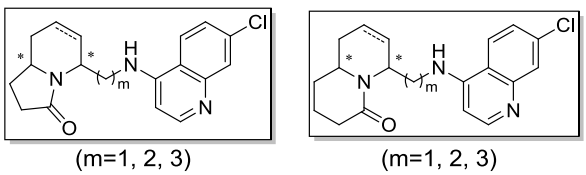


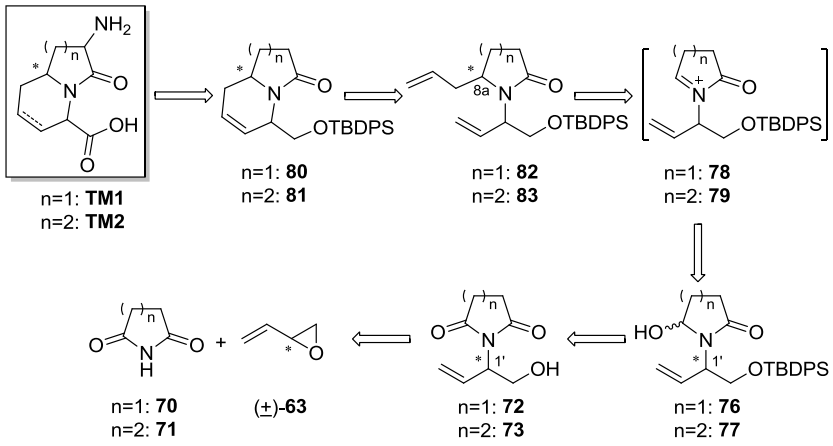
Figure 28. Targeted chloroquine conjugates

III. Results and Discussion

3.1. PREPARATION OF 80 AND 81

3.1.1. Retrosynthetic analysis

Scheme 7 shows our retrosynthetic analysis for the enantioselective preparation of the target compounds **TM1** and **TM2**. The synthesis would be initiated by the asymmetric alkylation of succinimide, **70**, or glutarimide, **71**, with the racemic epoxide (±)-**63**. Thus, the absolute configuration of the stereogenic center $C_{1'}$ of the allyl derivatives **72** and **73** will be controlled by the sense of chirality of the palladium ligand. Reduction of these allylimides would furnish the acylaminal **76** and **77**, precursors of the corresponding acyliminium ions **78** and **79**, which would act as the acceptor partner versus a nucleophilic allylation reagent. This second allylation would deliver a second stereogenic center C_{8a} in dienes **82** and **83**. Afterwards, a metathesis reaction (RCM) should allow the formation of the second ring. Finally, the bicyclic compounds **80** and **81** would be transformed into the target compounds by α-amination and subsequent oxidation.

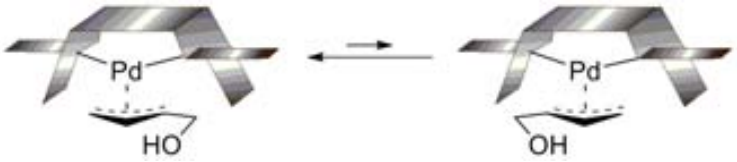


Scheme 7. Retrosynthetic analysis for the target compounds **TM1** and **TM2**.

3.1.2. First allylation step. Synthesis of compounds 74 and 75

As mentioned in the Introduction, the palladium catalyzed asymmetric *N*-allylation of succinimide and glutarimide had been previously studied and optimized in our laboratories by extension of the AAA methodology developed by Trost and coworkers

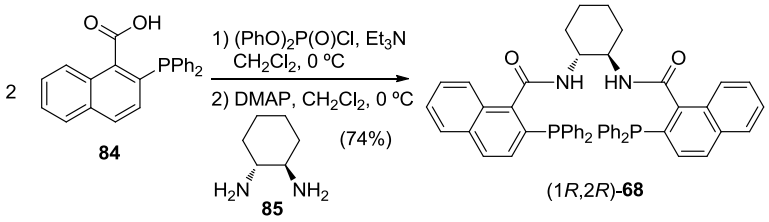
for phtalimide. According to the mechanism proposed by these authors, the palladium catalyzed allylation of imides usually proceeds through a Pd displacement of an allylic leaving group, followed by the allylic complexation of the metal and, finally, its nucleophilic substitution by the imide. Figure 29 depicts the nature of the reactive complex when the allylating reagent is butadiene monoxide. In this DYKAT process, the ligand is essential to control the regio- and stereoselectivity by favoring one of the competitive reaction paths [89] and reequilibration of the diastereomeric reactive palladium complexes I and II is essential to accomplish a good control.



I **II**

Figure 29. Assumed cartoon depiction of the chiral space

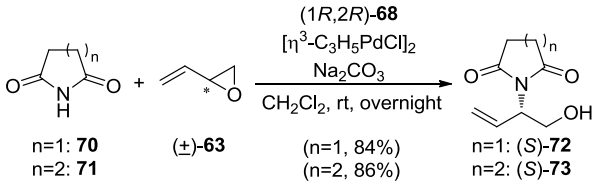
In the present work, the required ligand (1*R*,2R)-**68** was synthesized through the reaction between two molar equivalents of 2-diphenylphosphino-1-naphthoic acid, **84**, and one of (1*R*,2*R*)-cyclohexane-1,2-diamine **85** (Scheme 8).[84] In the process of purification by chromatography, we chose to use neutral alumina as the stationary phase instead of the reported silica gel, because it was found that the ligand (1*R*,2*R*)-**68** has a certain instability in acidic medium. This modification of the purification protocol resulted in an increased performance from the 51% described to 74% yield.



Scheme 8. Preparation of ligand (1*R*,2*R*)-**68**

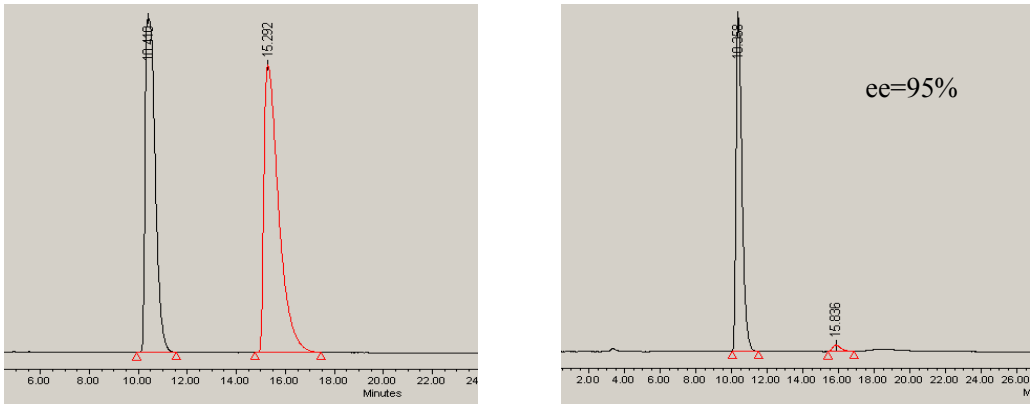
[89] (a) Trost, B. M.; Toste, F. D. *J. Am. Chem. Soc.* **1999**, *121*, 4545-4554. (b) Hayashi, T.; Kawatsura, M.; Uozumi, Y. *J. Am. Chem. Soc.* **1998**, *120*, 1681-1687. (c) Prétot, R.; Pfaltz, A. *Angew. Chem., Int. Ed.* **1998**, *37*, 323-325.

Next, the stereocontrolled AAA of succinimide and glutarimide in the presence of ligand (1*R*,2*R*)-**68** was performed (Scheme 9). The succinimide derivative (*S*)-**72** was obtained in 84% yield by using 0.4 mol% Pd (II), 1.2 mol% of (1*R*,2*R*)-**68** and 5 mol% Na_2CO_3.[86] Besides, the glutarimide derivative (*S*)-**73** was obtained in 86% yield by using double reagent (0.8 mol% Pd (II), 2.4 mol% of (1*R*,2*R*)-**68** and 10 mol% Na_2CO_3).[86b]



Scheme 9. Asymmetric *N*-alkylation of succinimide and glutarimide

The enantiomeric excess of the alcohol (*S*)-**73**, determined by CHPLC through comparison with the racemic sample (Figure 30) was 95%.[90] The enantiomeric exces of its analog (*S*)-**72** was establish in the next synthetic intermediate (*vide infra*).



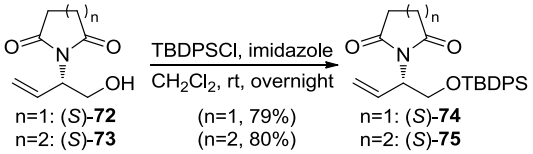
Racemic sample product of AAA

Figure 30. Comparison of the chromatograms of (±)-**73** and product (-)-**73**

For synthetic purposes, we decided to protect the alcohols as silyl ethers. To this aim, compounds (*S*)-**72** and (*S*)-**73** were treated with an excess of *tert*-butyldiphenylsilyl chloride in the presence of imidazole, in CH_2Cl_2 as solvent (Scheme 10). After purification by column chromatography on silica gel and then crystallization in

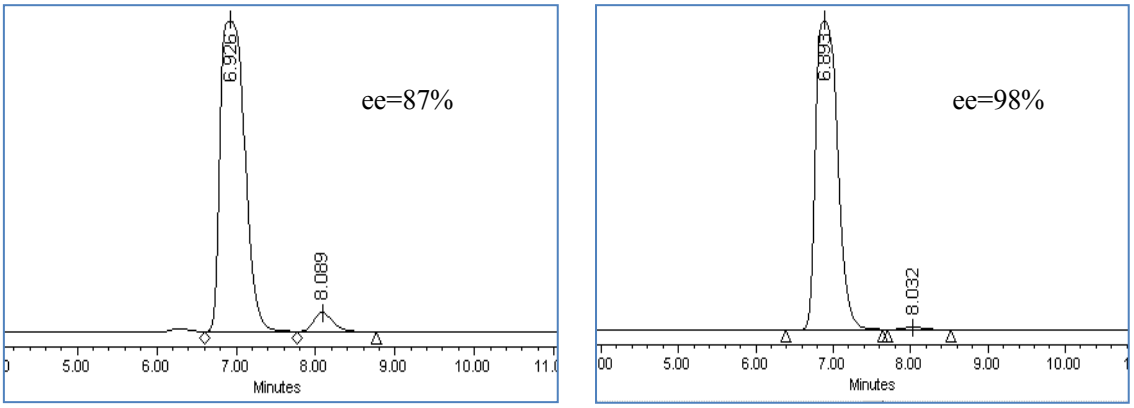
[90] Alujas. S. B. Màster en Experimentació Química, UAB, **2012**.

2-propanol, the silyl ethers (*S*)-**74** and (*S*)-**75** were isolated in 69% and 80% yield, respectively.



Scheme 10. Protection of (*S*)-**72** and (*S*)-**73**

The enantiomeric excess of the silyl ether (*S*)-**74** was determined by CHPLC through analysis of samples before and after crystallization (Figure 31). As shown, the crystallization process improved the ee of (*S*)-**74** from 87% to 98%. In the Figure, the peak at around 6.9 min corresponds to (*S*)-**74**, while the peak around 8.0 min is the signal of (*R*)-**74**.



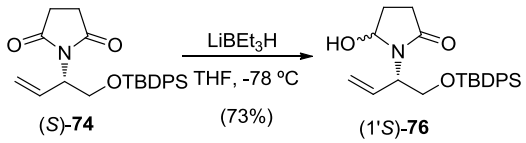
before crystallization after crystallization

Figure 31. Comparison of chromatograms obtained by CHPLC

3.1.3. Synthesis and stereochemical assignment of the key indolizidinone 80

3.1.3.1. Selective reduction and second allylation

The aminal **76**, precursor of the *N*-acyliminium ion **78** that should act as a template for the construction of the azabicyclic system, was obtained by selective reduction of silyl ether (*S*)-**74** (Scheme 11). Based on a protocol previously developed in our group, the silyl ether (*S*)-**74** was treated with 1.6 molar equivalentsalents of $LiBEt_3H$ at -78 °C for 45 minutes. After purification by column chromatography on silica gel, (1'*S*)-**76** was isolated in 73% yield.[86]



Scheme 11. Reduction of (*S*)-**74**

The ^{1}H NMR spectrum of purified (1'*S*)-**76** (Figure 32) shows the splitting of various signals due to the presence of two diastereomers. In particular, the signals at 6.06 and 5.81 ppm were assigned to the olefinic proton $H_{2'}$, the relative area of these signals indicating a diastereoisomeric ratio 1/4.5. Since in the next synthetic step the stereogenic at $C_{2'}$ will be lost due to the formation of the acyliminium ion, the coexistence of diastereomers is irrelevant.

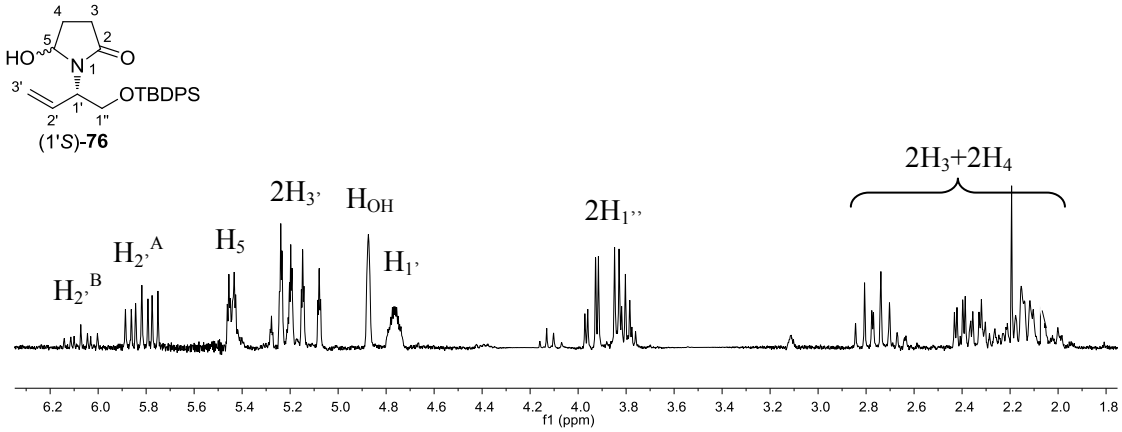
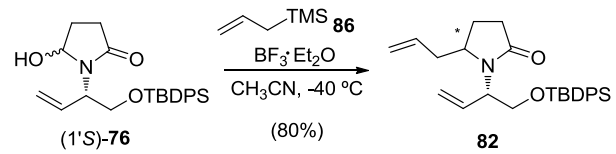


Figure 32. ^{1}H NMR (400 MHz, $CDCl_3$) spectrum of (1'*S*)-**76** as a mixture of diastereoisomers: A=major diastereoisomer; B=minor diastereoisomer

In the allylation of aminals, the Lewis acid exerts a fundamental effect on the formation of the electrophilic *N*-acyliminium ion that, reacting with allyltrimethylsilane as C-nucleophile, will generate the corresponding allylated product.[91] In this work, the aminal (1'*S*)-**76** was tretated with 1.2 molar equivalents of allyltrimethylsilane, **86**, in the presence $BF_3{\cdot}Et_2O$ as the Lewis acid, in CH_3CN as solvent (Scheme 12). After purification by column chromatography on silica gel, the allylated product **82** was isolated in 80% yield as mixture of diastereoisomers.

[91] Giardinà, A.; Mecozzi, T.; Petrini, M. *J. Org. Chem.* **2000,** *65,* 8277-8282.



Scheme 12. Allylation of (1'*S*)-**76**

The ^{1}H NMR spectrum of diene **82** indicates that it exists as a diastereoisomeric mixture. The signals at 6.12 and 5.93 ppm were assigned to protons $H_{2'}$. From the relative area of these two signals, it could be determined a diastereomer ratio of 1/1.1. The spectrum shows also the presence of a second allyl group as expected, the signal at 5.68 ppm corresponding to the proton $H_{2'''}$ for the two diastereomers.

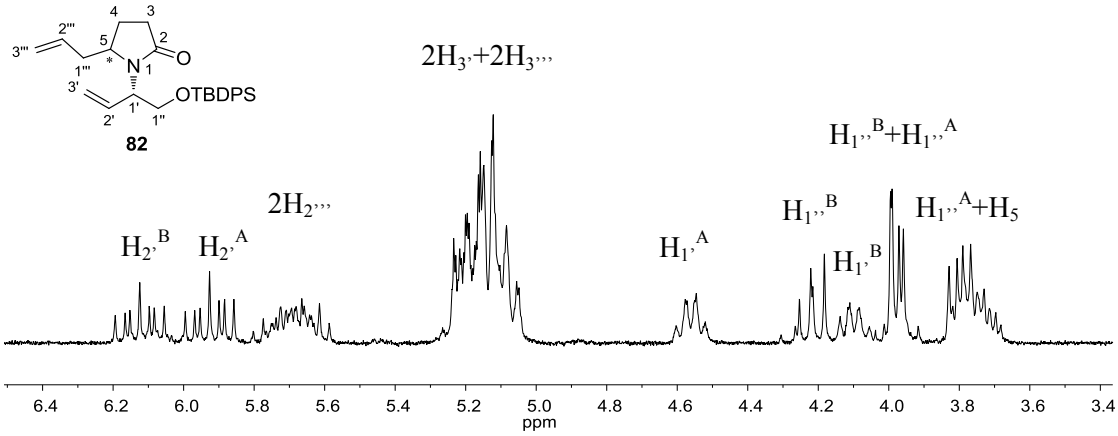
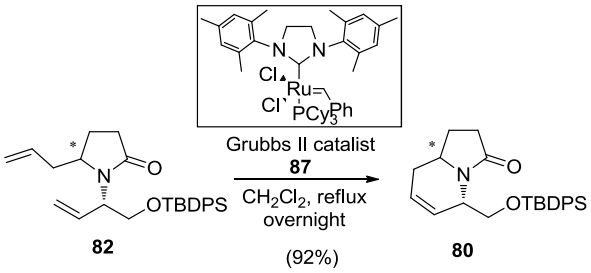


Figure 33. ^{1}H NMR (400 MHz, $CDCl_3$) spectrum of **82** as a mixture of diastereoisomers: A=major diastereoisomer; B=minor diastereoisomer

Considering the objective of the present work, the lack of diastereofacial selectivity of the nucleophilic allylation is not a drawback, since it opens the access to different stereoisomers of the targeted compounds.

3.1.3.2. Ring-closing metathesis of 80. Formation of the indolizidine framework

The ring-closing metathesis reaction was performed in the presence of 5% second generation Grubbs catalyst **87**. The reaction was carried out with the mixture of diastereomers **82** in CH_2Cl_2 as solvent, slowly adding a solution of the catalyst at the reflux temperature (Scheme 13). After purification by column chromatography on silica gel, the bicyclic product **80** was obtained in 92% yield.



Scheme 13. Ring-closing metathesis of **82**

The indolizidinone **80** exists as a balanced mixture of diastereomers that cannot be separated. As shown, its ^{1}H NMR spectrum in $CDCl_3$ shows almost complete overlapping between the groups of signals of each isomer, whilst in C_6D_6 the signals corresponding to each diastereomer could be observed with better resolution.

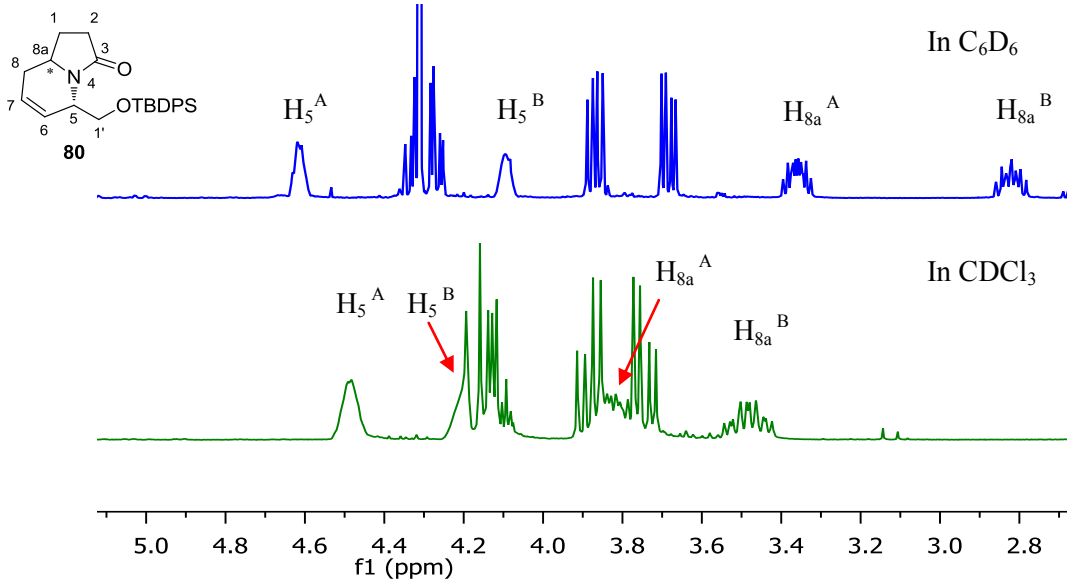
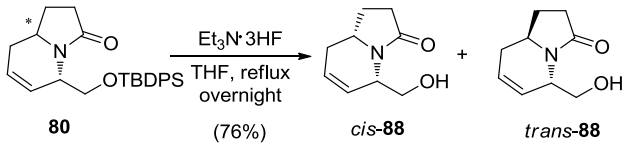


Figure 34. ^{1}H NMR (400 MHz) spectrum of the mixture of diastereomers **80** in different solvents (C_6D_6 and $CDCl_3$): A=major diastereoisomer; B=minor diastereoisomer

As a mean to separate and assign the relative configuration to each isomer, the diastereomeric mixture **80** was deprotected by treatment with $Et_3N{\cdot}3HF$ in THF at the reflux temperature overnight (Scheme 14). The free alcohols **88** could be separately isolated through purification by column chromatography on silica gel, furnishing the less polar isomer *cis*-**88** in 34% yield and the more polar isomer *trans*-**88** in 42% yield.



Scheme 14. Deprotection of **80**

The less polar lactam could be crystallized in a mixture of hexane and AcOEt. Its X-ray diffraction analysis (Figure 35) revealed that the relative configuration between the protons attached to C_5 and C_{8a} was *cis*. Since the configuration of C_5 was confirmed as *S* at the beginning, we know its absolute configuration is (*S*,*S*). Thus, the more polar isomer has the *trans* configuration and should be (*S*,*R*) .

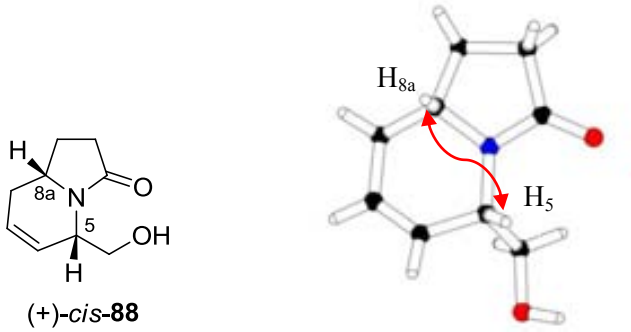
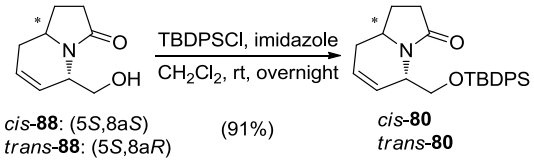


Figure 35. Representation of the result of X-ray diffraction of alcohol *cis*-**88**

Each of diastereoisomers **88** was then separately reprotected by reaction with an excess of *tert*-butyldiphenylsilyl chloride in the presence of imidazole, using CH_2Cl_2 as solvent (Scheme 15). The following purification by column chromatography on silica gel furnished *cis*-**80** and *trans*-**80** with the same yield of 91%.



Scheme 15. Silylation of isomers *cis*-**88** and *trans*-**88**

The silylation of the two isomers was confirmed by comparison of the ^{1}H NMR spectrum of the mixture **80** with those of each isomer *cis*-**80** and *trans*-**80**.

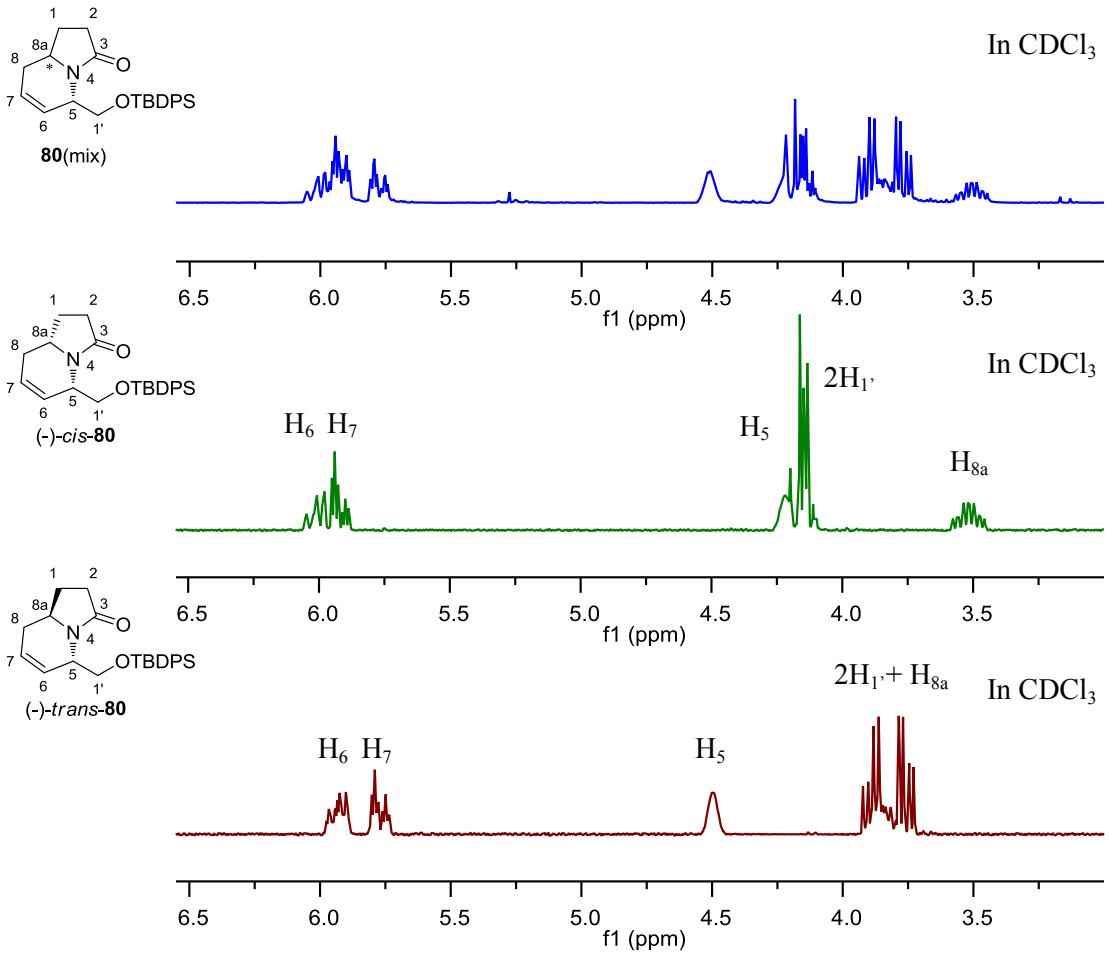
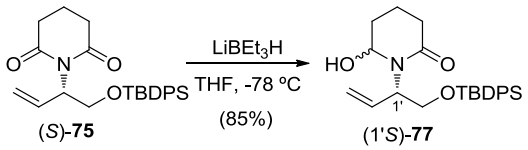


Figure 36. Comparison of the ^{1}H NMR (250 MHz, $CDCl_3$) spectra of the mixture and each isomer of **80**

3.1.4. Synthesis and stereochemical assignment of the key quinolizidinone 81

3.1.4.1. Selective reduction and second allylation

Analogously to the previous transformation on (*S*)-**74**, the reduction of imide (*S*)-**75** was carried out in THF using $LiBEt_3H$ as reducing agent at -78 °C for 45 minutes (Scheme 16). The acylaminal (*S*)-**77** was obtained in 85% yield after purification by column chromatography on silica gel.[86b]



Scheme 16. Reduction of (*S*)-**75**

As can be deduced from its ^1H NMR spectrum (Figure 37), the aminal (*S*)-**77** was formed as a mixture of diastereomers that could not be separarted. The signals at 5.79 and 6.17 ppm were assigned to the internal olefinic protons $H_{2'}$; their relative area evidences a diastereoisomeric ratio of 1/12.

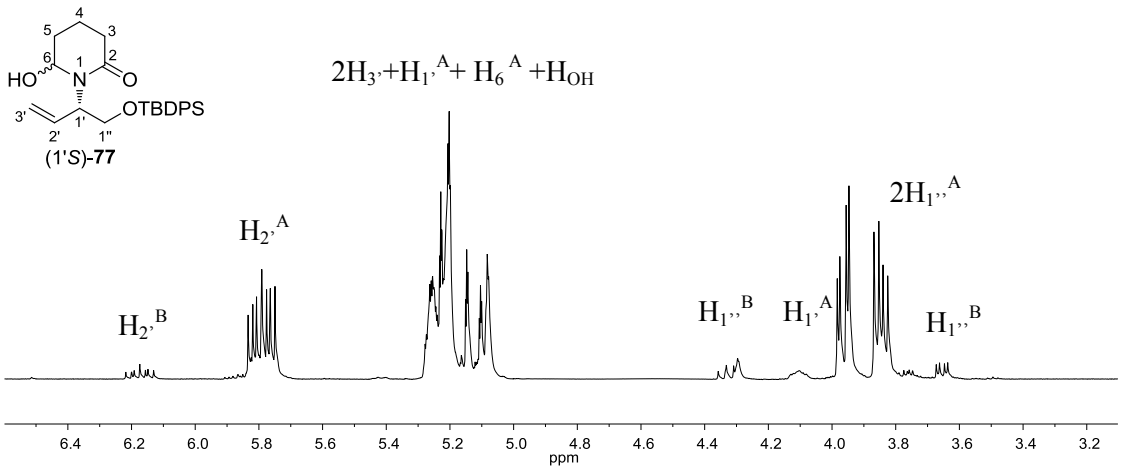
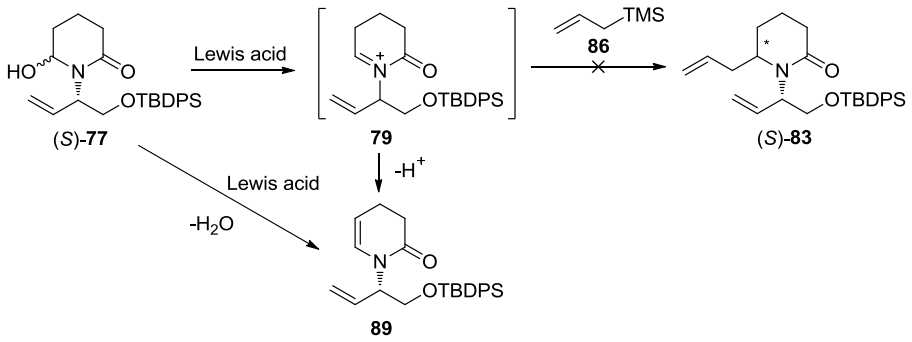


Figure 37. ^1H NMR (400 MHz, $CDCl_3$) spectrum of (1'*S*)-**77** as a mixture of diastereoisomers: A=major diastereoisomer; B=minor diastereoisomer

In contrast with the behavior of its succinimide analog, in this case, the diastereoselectivity of the allylation indicates that one of the two faces of the imide is more accessible to the approach of the reducing agent.

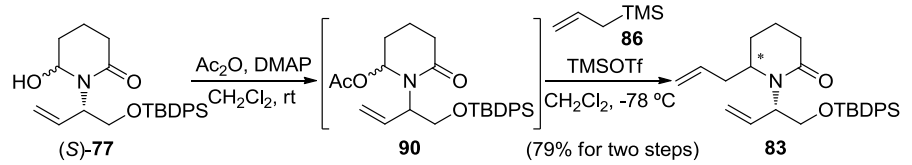
Interestingly, under the same conditions applied to the five-membered analog (1'*S*)-**76**, the nucleophilic allylation of (1'*S*)-**77** gave a different result. Thus, instead of the expected allylated derivative (*S*)-**81**, the enamide **89** was obtained as the major product. This enamide may be formed by direct acid-catalyzed β-elimination of the acylaminal or with the intermediacy of the iminium cation **79**.

After many attempts of avoiding this competitive path under different allylation conditions, the formation of **89** could be circumvented by starting from the acetyl derivative of the aminal.[86b]



Scheme 17. Possible pathways of the formation of enamide **89**

In the event, the aminal (1'*S*)-**77** was treated with acetic anhydride, DMAP and Et_3N in CH_2Cl_2 at room temperature for 14 hours to obtain the acetylated intermediate **90**, which was then tretaed with allyltrimethylsilane, **86**, in the presence of TMSOTf as the Lewis acid promoter at -78 ºC for 4 h (Scheme 18). The allylated product **83** was obtained in 79% yield after purification by column chromatography on silica gel.



Scheme 18. Allylation of (*S*)-**77**

Diene **83** was isolated as a mixture of diastereoisomers with a high predominance of one of them, as shown in its ^1H NMR spectrum (Figure 38). The signals at 6.22 and 6.06 ppm were assigned to the internal olefinic proton $H_{2'}$ and the multiplets at 4.01 and 3.86 ppm to the allylic methylene group ($2xH_{1''}$). From the relative area of these signals

a diastereomer ratio of 1/10 could be determined. Moreover, the signal at 5.68 ppm corresponding to the new internal olefinic proton $H_{2'''}$ shows the presence of the second allyl group.

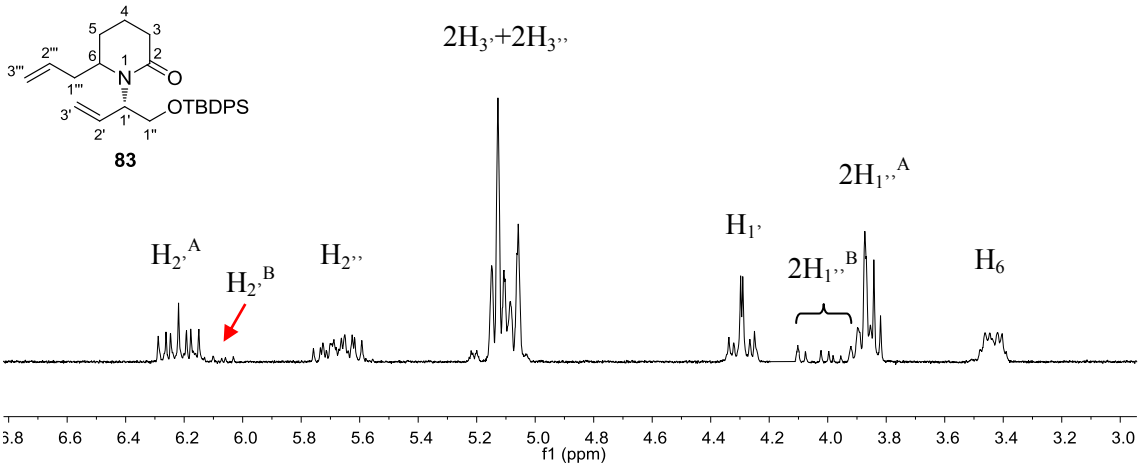
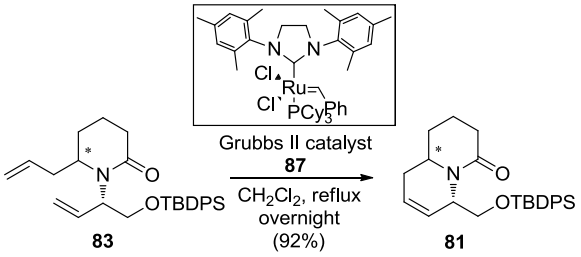


Figure 38. ^{1}H NMR (250 MHz, $CDCl_3$) spectrum of **83** as a mixture of diastereoisomers: A=major diastereoisomer; B=minor diastereoisomer

3.1.4.2. Ring-closing metathesis of 81. Formation of the quinolizidine framework

The ring-closing metathesis of **83** was carried out in CH_2Cl_2 as solvent, slowly adding a solution of 3% second generation Grubbs catalyst **87** at the reflux temperature (Scheme 19). The reaction was run overnight. After purification by column chromatography on silica gel, the expected bicyclic product **81** was obtained in 92% yield.



Scheme 19. Ring-closing metathesis of **83**

The ^{1}H NMR spectrum of the crude material of this reaction shows a mixture of two diastereomers, where the minor one is less than 5% (Figure 39). As shown, the signal corresponding to H_7 and H_8 of the major diastereomer is observed at 6.07 and 5.99 ppm and the signal of the same proton of the minor isomer at 5.92 and 5.77 ppm.

Similarly, the signals at 5.09 and 4.66 ppm are assigned to H_6 of the minor and major isomer, respectively.

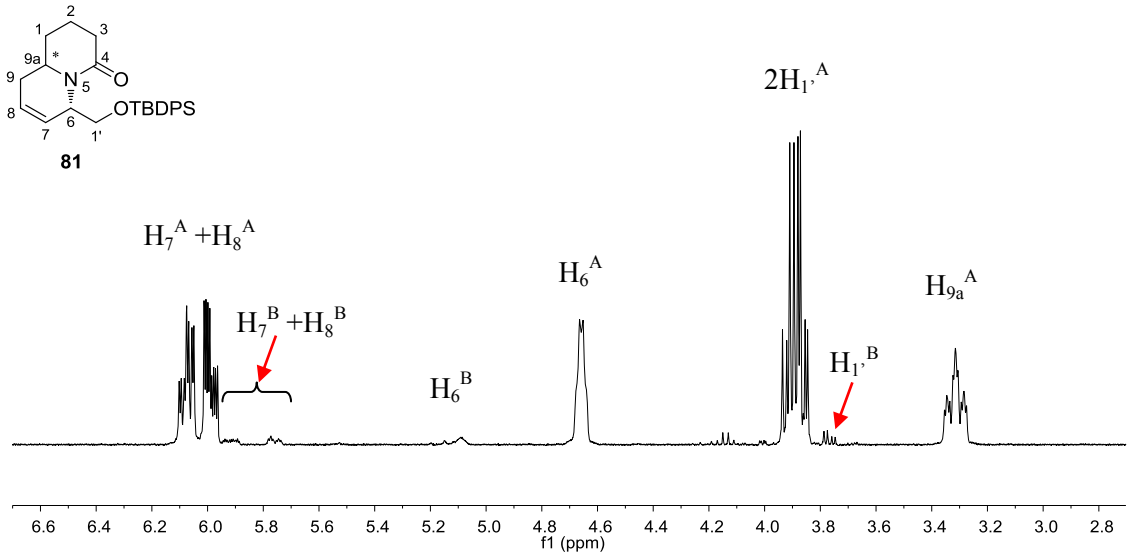
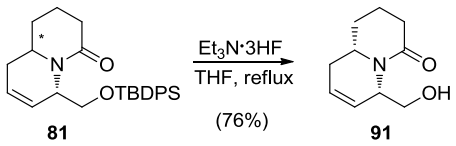


Figure 39. ^{1}H NMR (400 MHz, $CDCl_3$) spectrum of **81** as a mixture of diastereoisomers: A=major diastereoisomer; B=minor diastereoisomer

As before, the bicyclic product **81** was treated with $Et_3N{\cdot}3HF$ in THF at the reflux temperature overnight, to get the corresponding free alcohol (Scheme 20). The unprotected derivative **91** was isolated in 76% yield after purification by column chromatography on silica gel. The alcohol **91** could be crystallized in a mixture of hexane and AcOEt as solvent and the major isomer isolated in pure form. From the result of an X-ray diffraction experiment (Figure 40), the relative configuration between the protons on C_6 and C_{9a} was established as *cis* and the absolute configuration is (*S*,*S*).[90]



Scheme 20. Deprotection of **81**

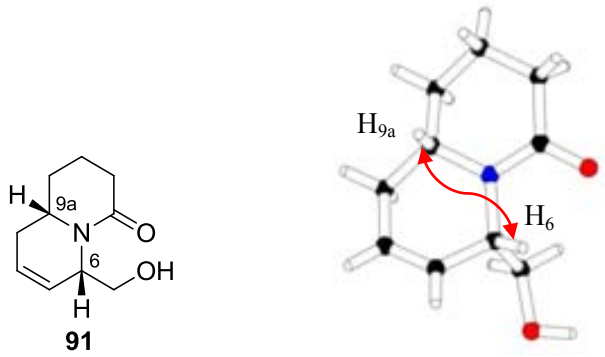
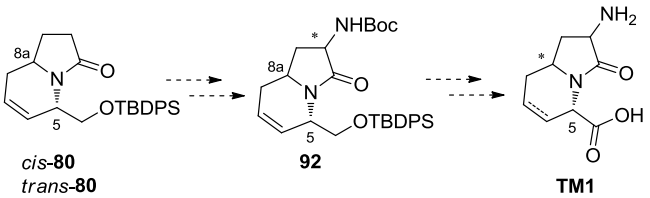


Figure 40. Representation of the result of X-ray diffraction of alcohol **91**

3.2. STUDIES ON THE α-AMINATION OF 80

3.2.1. Direct α-amination and α-alkylation of 80

Sheme 21 displays the strategy initially designed for the synthesis of the target bicyclic peptides. It was intended to perform an α-carbonyl amination, followed by alcohol deprotection and subsequent oxidation to furnish a carboxylic acid. It was foreseen that the most crucial, and probably troublesome, among these steps would be the initial α-amination. This transformation requires strongly basic conditions to form the enolate (which would then react with the nitrogen electrophile) and the presence of a relatively acidic allylic proton at C_5 may cause epimerization/isomerization problems and even regioselectivity complications. Moreover, the desired α-amination would deliver a new stereogenic center, adding complexity to the reaction product.



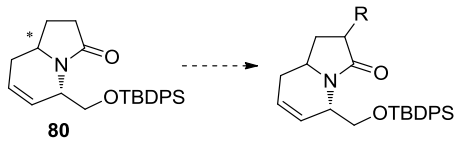
Scheme 21. Planned synthetic strategy for the preparation of **TM1**

3.2.1.1. Attempts of direct α-amination of 80

Table 3 summarizes the conditions and results of different experiments to attempt the α-amination of **80**. The experiments were performed either starting from the *cis* or the *trans* isomer of **80**. As can be seen, none of the assays were successful. In the first trials using *t*-BuOK as the base and *n*-BuONO as the electrophile,[92] only unaltered starting material was recovered. Then, *cis*-**80** was treated with trisyl azide in the presence of lithium diisopropylamide (LDA),[81] which only caused decomposition according to the ^{1}H NMR spectrum of crude reaction material (entry 3). The same occurred when the electrophile was changed to di-*tert*-butyl azodicarboxylate (DBAD)

[92] Allen, N. E.; Boyd, D. B.; Campbell, J. B.; Deeter, J. B.; Elzey, T. K.; Foster, B. J.; Hatfield, L. D.; Hobbs Jr., J. N.; Hornback, W. J.; Hunden, D. C.; Jones, N. D.; Kinnick, M. D.; Morin Jr., J. M.; Munroe, J. E.; Swartzendruber, J. K.; Vogt, D. G. *Tetrahedron* **1989**, *45*, 1905-1928.

(entry 4, 5).[93] However, when the substrate was *trans*-**80** around 25% of the sm remained after treatment with LDA and DBAD from -78°C to rt overnight (entry 5).



Scheme 22. General α-amination of **80**

Table 3. Attempts and results of α-amination of **80**[a]

Entry	SM	-R	Reagent	T	Time	Result
1	*cis*-**80**	=NOH	*tert*-BuOK, *n*-BuONO	0°C -rt	1.5h	*cis*-**80** (60%)
2	*trans*-**80**	=NOH	*tert*-BuOK, *n*-BuONO	0°C -rt	1.5h	*trans*-**80** (90%)
3	*cis*-**80**	$-N_3$	LDA, Trisyl azide	-78°C	0.5-1h	decomposed
4	*cis*-**80**	-NBoc-NHBoc	LDA, DBAD	-78°C -rt	overnight	decomposed
5	*trans*-**80**	-NBoc-NHBoc	LDA, DBAD	-78°C -rt	overnight	*trans*-**80** (25%)

[a] THF was used as solvent in all runs. The results were analyzed by ^{1}H NMR of the crude reaction product

To investigate if these negative results were associated to the insufficient acidity of the α-hydrogen atom of the lactam or to a poor electrophilic character of the amination reagents, we decided to assay the α-alkylation of **80** using benzyl bromide as a highly active electrophile.

Table 4 summarizes the results obtained under the different reaction conditions assayed for the α-benzylation of **80**. As it is shown, the expected compound **93** could only be detected using the first conditions on *cis*-**80**, whereas in the other cases (entry 2-6) the starting material remained mostly unaltered. In the first benzylation experiment, *cis*-**80** was treated with LDA in THF at -78°C and, 20 minutes later, benzyl bromide was added and the reaction mixture stirred at -78°C for 1 h (entry 1). Under these conditions, the purification of the crude material by column chromatography on silica gel furnished compound **93** in 25% yield.

[93] Allin, S. M.; Towler, J.; Gaskell, S. N.; Saha, B.; Martin, W. P.; Bulman Page, P. C.; Edgar, M. *Tetrahedron* **2010**, *66*, 9538-9544.

80 **93**

Scheme 23. General synthesis of α-alkylation of **80**

Table 4. Attempts and results of α-alkylation of **80**[a]

Entry	SM	Reagent	T	Time	Result
1	*cis*-**80**	LDA, Benzyl bromide	-78°C	1.5 h	**93** (25%)
2	*trans*-**80**	LDA, Benzyl bromide	-78°C	1.5 h	*trans*-**80** (>70%)
3	*cis*-**80**	Sec-BuLi[94], Benzyl bromide	-78°C	1.5 h	*cis*-**80** (30%)
4	*trans*-**80**	*sec*-BuLi, Benzyl bromide	-78°C	1.5 h	*trans*-**80** (60%)
5	*cis*-**80**	KHMDS[95], Benzyl bromide	-78°C	>12 h	*cis*-**80** (65%)
6	*trans*-**80**	*tert*-BuOK, Benzyl bromide	rt	1.5 h	*trans*-**80** (85%)

[a] THF was used as solvent in all runs. The results were analyzed by ^{1}H NMR of the crude reaction product

The α-alkylation of lactam *cis*-**80** was confirmed by the upfield shifting of H_{8a} signal from 3.52 to 3.16 ppm, the downfield shifting of H_2 signal from 2.32 to 2.76 ppm, and the appearance of new signals around 3 ppm corresponding to the benzyl group.

[94] Baussanne, I.; Travers, C.; Royer, J. *Tetrahedron: Asymmetry* **1998**, *9*, 797-804.

[95] David A. Evans; Thomas C. Britton; *J. Am. Chem. Soc*. **1990**, *112*, 4011-4030.

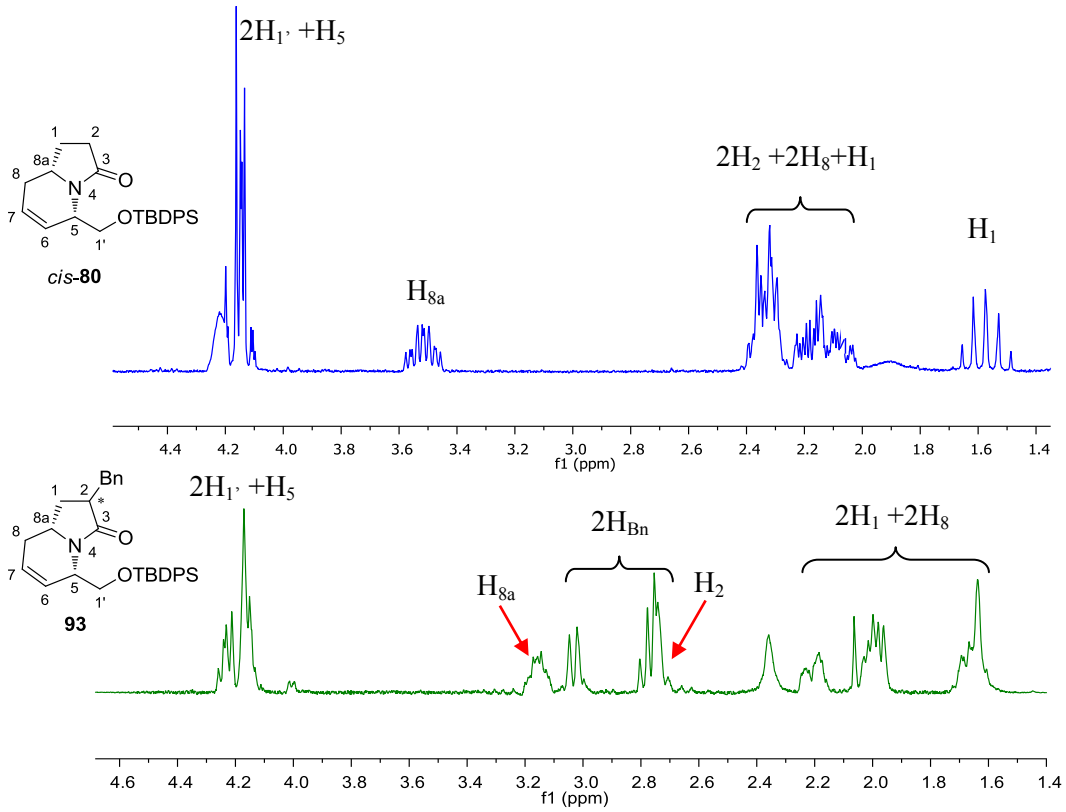
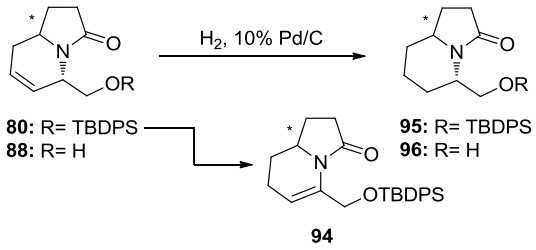


Figure 41. Comparison of the ^{1}H NMR (250 MHz, $CDCl_3$) spectra of *cis*-**80** and **93**

The decomposition of the sm, observed in some degree in all the experiments, led us to suspect that the carbon-carbon double bond present in the substrate may exert a negative influence on its stability under basic conditions. Therefore, we decided to perform the hydrogenation of **80**.

3.2.1.2. Hydrogenation of 80 and attempted α-amination of *trans*-95

Table 5 summarizes the results of the different hydrogenation assays. We observed that the solvent has an important influence on the process: in THF and EtOAc (entry 1-3), hydrogenation and migration of the double bond happened competitively on both diastereoisomers *cis*-**80** and *trans*-**80**; in Methanol (entry 4), both the unsaturated product *cis*-**80** and the isomerized olefin (8a*S*)-**94** were hydrogenated with simultaneous deprotection to form alcohol *cis*-**96**. When the free alcohols *cis*-**88** and *trans*-**88** were used as hydrogenation substrates (entry 5,6), in the presence of 10% Pd/C and Methanol as solvent at room temperature the alcohols *cis*-**96** and *trans*-**96** were respectively isolated in good yield.



Scheme 24. Hydrogenation of **80** and **88**

Table 5. Attempts and results of hydrogenation of **80**[a]

Entry	sm	Solvent	Time	Result
1	*trans*-**80**	THF	overnight	20%(8aR)-**94** + 50%mix (*trans*-**80**+ *trans*-**95**)
2	*cis*-**80**	THF	overnight	*cis*-**80** : (8a*S*)-**94**[b]**= 10:1**[c]
3	*cis*-**80**	EtOAc	5h	*cis*-**95**[b] : (8a*S*)-**94= 3:1**[c]
4	**94**+ *cis*-**80**	Methanol	overnight	60% *cis*-**96**
5	*cis*-**88**	Methanol	overnight	75% *cis*-**96**
6	*trans*-**88**	Methanol	overnight	89% *trans*-**96**

[a] All attempts were run at rt. [b] could not be separated, their structures (*cis*-**95** and (8a*S*)-**94)** were inferred by comparison with *trans*-**95** and (8a*R*)-**94**. [c] The ratio of result was determined by ^{1}H NMR spectrum of crude product.

^{1}H NMR analysis (Figure 42) evidenced the isomerization of *trans*-**80** to (8a*R*)-**94** by the absence of the allylic H_5 signal, before at 4.50 ppm, the upfield shifting of H_6 from 5.93 to 5.43 ppm and the downfield shifting of the α-oxygen protons $H_{1'}$ from 3.89 and 3.76 ppm to 4.96 and 4.80 ppm.

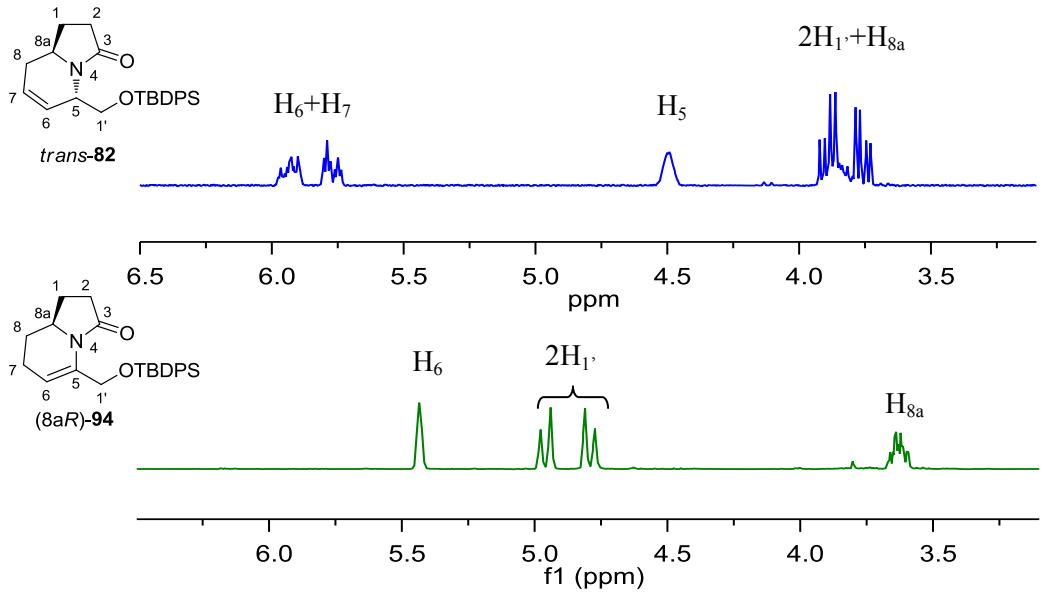


Figure 42. Comparison of the ^{1}H NMR (250 MHz, $CDCl_3$) spectrum of *trans*-**80** and (8a*R*)-**94**

The isomerized product (8a*S*)-**94** derived from *cis*-**80** could not be separated, but it was detected in the spectrum (Figure 43) of the crude product of the second trial (hydrogenation of *cis*-**80** in THF). The new signal at 5.43 ppm was tentatively assigned to the olefinic proton H_6 and the signals at 4.96 and 4.80 ppm to the allylic α-oxygen protons $H_{1'}$.

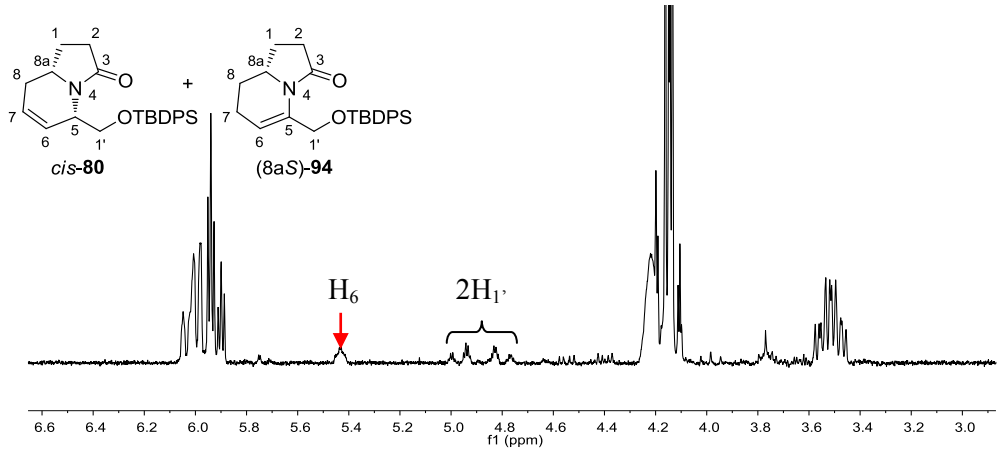


Figure 43. ^{1}H NMR (250 MHz, $CDCl_3$) spectrum of the mixture of *cis*-**80** and (8a*S*)-**94**

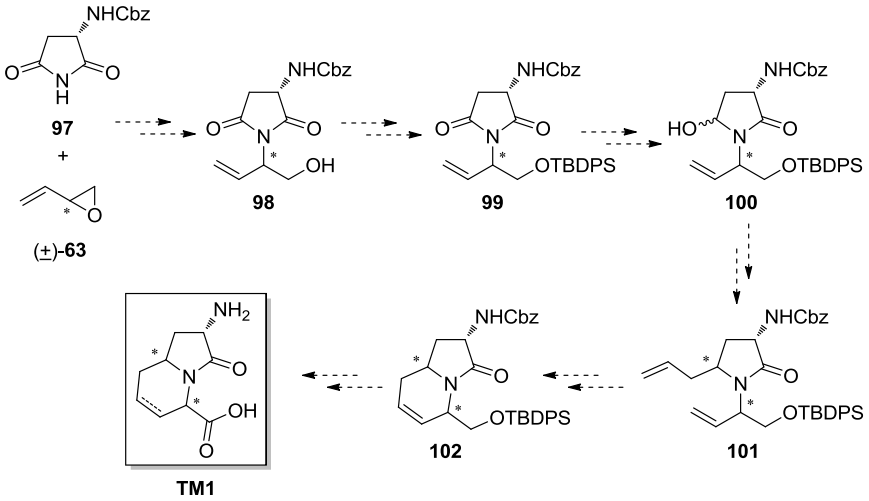
The isolated indolizidinone *trans*-**95** was then used to try the α-amination. Considering the previous results, LDA was selected as the base to form the enolate and trisyl azide and DBAD were assayed as the electrophiles, in THF solution in all cases. Unfortunately, in all these experiments the starting material was recovered unchanged. We can then conclude that the hydrogenation of the double bond enhances the stability of the substrate but displays no positive influence on the α-amination. On view of that, we decided to modify the strategy and try to use an amino-substituted substrate as the starting material for the synthesis.

3.2.2. Synthesis of the α-aminoindolizidone 102

3.2.2.1. Synthetic strategy

In the new strategy (Scheme 25), the synthesis would begin with benzyl (*S*)-(2,5-dioxopyrrolidin-3-yl) carbamate, **97**, a described derivative of succinimide that can be prepared from a chiral pool material and already incorporates a nitrogen atom at the α-carbonyl position. We planned to apply a parallel sequence to that developed for

succinimide: initial palladium catalyzed allylation, followed by silylation, reduction to the acylaminal, second nucleophilic allylation, and ring closing metathesis to form the indolizidine framework. On the contrary to succinimide, the starting substrate **97** is a chiral compound lacking any kind of symmetry. Consequently, it was particularly interesting to study the influence of the preexisting stereogenic center on the stereoselectivity on the first allylation step, which would furnish **98** with a second stereogenic center, as well as on the regioselectivity of the reduction to the acylaminal from the imide **99**, where the two carbonyl groups are not equivalentsalent anymore. If the sequence, analogous to that applied to succinimide, can be successfully adapted to **97** to deliver **102**, then deprotection followed by oxidation of the primary alcohol should furnish the target peptide **TM1**.



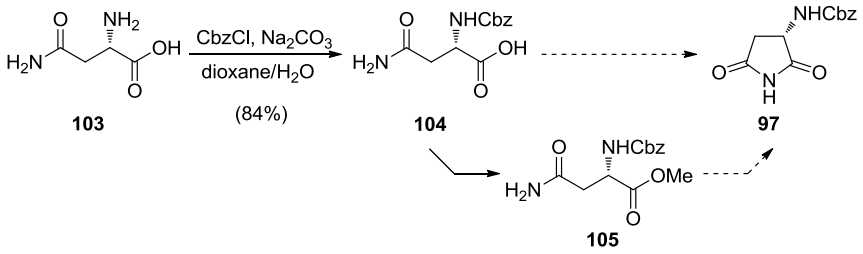
Scheme 25. Alternative synthetic strategy for the preparation of **TM1**

3.2.2.2. Preparation of the succinimide derivative 97

(*S*)-Asparagine **103** (Scheme 26) was the chiral pool material of choice to prepare the enantiopure succinimide derivative **97**. The nitrogen protection was initially attempted by reaction with 1.2 equivalents of CbzCl in the presence of 2 equivalents of Na_2CO_3 in H_2O/acetone as solvent at room temperatute for 3 h,[96] but, under these conditions, only starting material was recovered. However, a second assay using a

[96] Pehere, A. D.; Abell, A. D. *Tetrahedron Lett*. **2011**, *52*, 1493-1494.

mixture of 1,4-dioxane and 10% Na_2CO_3 solution[97] afforded the carbamate **104** in 84% yield.



Scheme 26. Planned synthesis of **97** from (S)-asparagine **103**

The conversion of **104** into the desired succinimide **97** was attempted under various sets of conditions based on literature references, as summarized in Table 6. In most cases (entry 1-3), both under basic or acidic medium, the starting material was recovered unchanged. Only the reaction with DCC in DMF at 80ºC overnight (entry 4) took place, but the product was a complex mixture of unidentified compounds.

Table 6. Attempts and results of cyclization of **104**

Entry	Reagent	Solvent	T	Time	Result
1	K_2CO_3 [98]	DMF	rt	overnight	**104**
2[a]	1) Methanol, H_2SO_4 (cat.) 2) TsOH (cat.) [99]	1) Methanol 2) Toluene	reflux	overnight	**105**
3[a]	1) Methanol, H_2SO_4 (cat.) 2) 5% NaOH, 10% HCl[100]	1) Methanol 2) H_2O	1) reflux 2) 0ºC-rt	1) overnight 2) 2 h	**105**
4	DCC[101]	DMF	80ºC	overnight	complex mixture

[a] 1) and 2) refer to consecutive steps.

As an alternative, a new route starting from L-aspartic acid, **106**, was assayed. In this case, the first step protection was performed with 1.2 equivalent CbzCl in the

[97] Zhang, Z.; Aerschot, A. V.; Hendrix, C.; Busson, R.; David, F.; Sandra, P.; Herdewijn, P. *Tetrahedron* **2000**, *56*, 2513-2522.

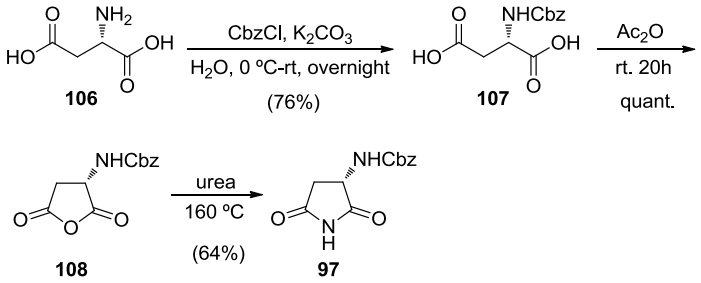
[98] Fringuelli, R.; Pilar Utrilla Navarro, M.; Milanese, L.; Bruscoli, S.; Schiaffella, F.; Riccardi, C.; Simone, C. D. *IL FARMACO*. **2004**, *59*, 271-277.

[99] Park, M.; Lee, Jaewon.; Choi, Jongwon. *Bioorg. Med. Chem. Lett*. **1996**, *6*, 1297-1302.

[100] Sondheimer, E.; Holley, R. W; *J. Am. Chem. Soc*. **1954**, *76*, 2467-2470.

[101] Bhavar, P. K.; Ltd, G. J.; Joshi, N. K.; Lingam, P. R.; Thomas, A. PCT Int. Appl.(2004),WO 2004022536 A1, 20040318.

presence of 2 equivalent of Na_2CO_3 in H_2O as solvent,[102] the crude product was treated with Ac_2O at rt for 20 h to afford quantitatively the anhydride **108**,[103] the crude product of which was treated with urea at 160 ºC to obtain **97** in 64% yield after purification by column chromatography on silica gel.[104]



Scheme 27. Synthesis of **97** from L-aspartic acid **106**

3.2.2.3. First allylation step. Synthesis of 99

Initially, the palladium catalyzed allylation of **97** with racemic butadiene monoxide (Scheme 28) was tried under the same conditions used for succinimide, namely with 0.6 mol% Pd (II), 1.8 mol% of (1*R*,2*R*)-**68** and 8 mol% Na_2CO_3 in dichloromethane at room temperature, but, in this case, the starting material was recovered unchanged. The addition of DMF to the reaction medium, working at refluxing CH_2Cl_2, furnished the expected allylated product **98** but in a low 30% yield. Neither THF nor toluene as solvent, in both cases at the reflux temperature, led to any conversion of the substrate. Fortunately, when the reaction was performed in 1,2-dichloroethane at 60 ºC, the desired olefin **98** was isolated in 68% yield after purification by column chromatography on silica gel, as a single diastereoisomer, according to ^{1}H NMR analyses.

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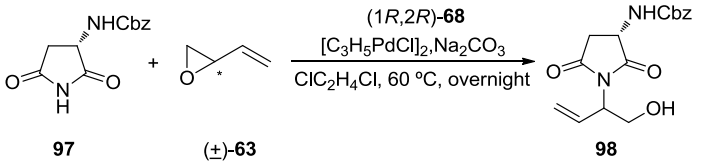
[102] Choi, S. J.; Eo, J. Y.; Kim, H. S.; Kim, Y. T.; Lee, B. G.; Oh, S, S. PCT Int. Appl. (2012), WO 2012148246 A2, 20121101.

[103] Buron, F.; Deguest, G.; Bischoff, L.; Fruit, C.; Marsais, F. *Tetrahedron Asymmetry*. **2007**, *18*, 1625-1627.

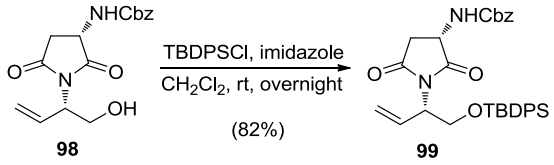
[104] Casteel, D. A.; Leonard, N. J. *J.Org.Chem*. **1985**, *50*, 2450-2456.



Scheme 28. Asymmetric *N*-allylation of **97**

Thus, the ^{1}H NMR spectrum of **98** (Figure 44) present a unique set of signals, in agreement with the expected structure, without evidence of a minor diastereomer. The incorporation of the allyl fragment is evidenced by the signals at 6.01 and 5.25 ppm corresponding to the olefinic protons. Since **98** contains two stereogenic centers, the diastereomeric ratio directly correlates with the stereoselectivity of this reaction. At this point, it was not possible to unequivocally establish the relative configuration of **98**, but we assumed that the absolute configuration of the new stereogenic center depends on the sense of chirality of the catalyst ligand and, hence, we tentatively assigned it as *S*.

Next, the alcohol **98** was reacted with excess *tert*-butyldiphenylsilyl chloride in the presence of imidazole, in CH_2Cl_2 as solvent (Scheme 29). After purification by column chromatography on silica gel, the silyl ether **99** was obtained in 82% yield. As for the precursor alcohol, none of signals on the spectrum of **99** is accompanied by similar minor signals corresponding to another isomer.



Scheme 29. Protection of compound **98**

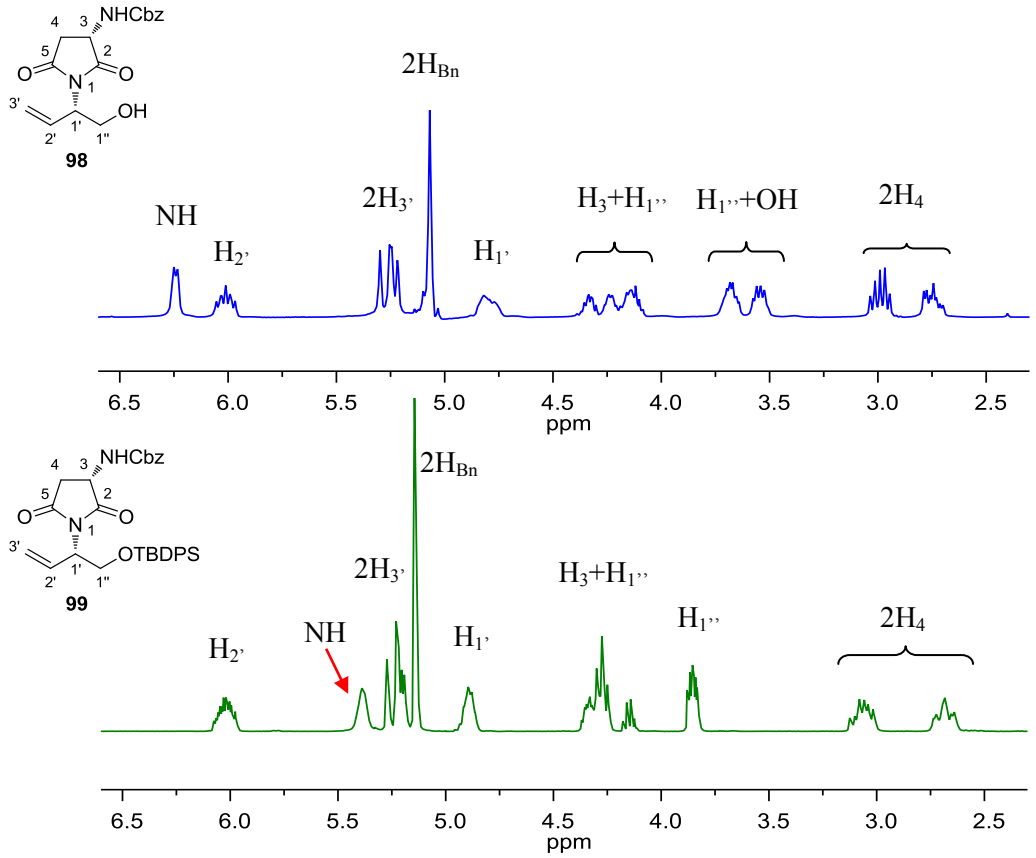
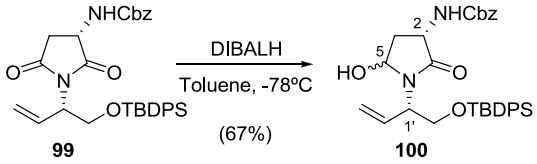


Figure 44. ^{1}H NMR (400 MHz, $CDCl_3$, 323K) spectra of **98** and **99**

3.2.2.4. Regioselective reduction of 99 and second allylation

In this step, we wanted to reduce exclusively the carbonyl group at C_5 without any change on the one at C_2. In a related substrate, in which the protecting group of the α-nitrogen was a lactam, it described a regioselectivity according to our purpose when using DIBAL-H.[105] The reduction was achieved by using DIBAL-H, The silyl ether **99** was treated with 1.5 molar equivalentsalents of DIBAL-H at -78 °C in toluene for 1 h (Scheme 30). After purification by column chromatography on silica gel, the acylaminal **100** was isolated in 67% yield.

[105] Chiyoda, K. Shimokawa, J. Fukuyama, T. *Angew. Chem. Int. Ed.* **2012**, *51*, 2505-2508.



Scheme 30. Selective reduction of compound **99**

In the ^{1}H NMR spectrum of **100** (Figure 45), the splitting of the signal at 1.07/1.09 ppm, corresponding to the methyl groups of the silyl protection, seems to indicate that the sample contains two compounds in a similar proportion. Since the reduction originates a new stereogenic center at the aminal position, we speculated that these two compounds were most probably epimers at C_5. As in the former route from succinimide, the coexistence of epimers at C_5 is inconsequent for the synthesis. However, at this stage of the work, we could not discard the possibility of regioisomers being present. Evidences against this possibility would be presented later on.

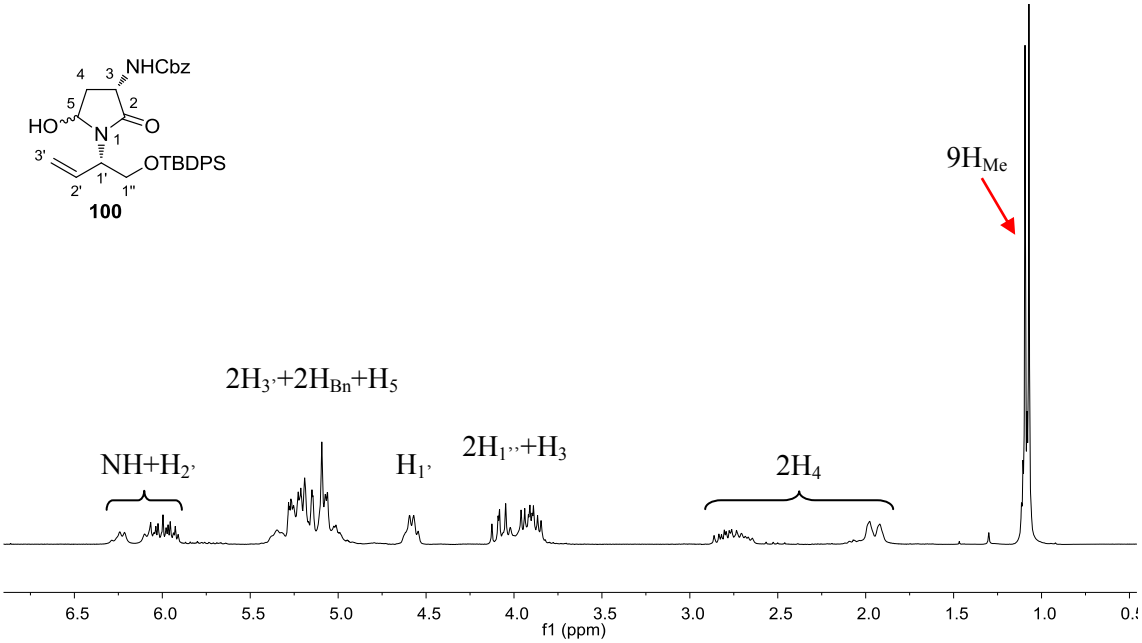
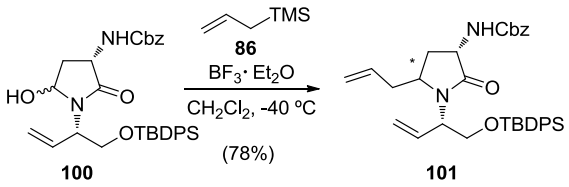


Figure 45. ^{1}H NMR (250 MHz, $CDCl_3$) spectrum of **100**

As for the nucleophilic allylation of (1'*S*)-**76** (see Section **3.1.3.1**), the aminal **100** was treated with 1.2 equivalents of allyltrimethylsilane, **86**, in the presence of 2.5 equivalents of the Lewis acid $BF_3{\cdot}Et_2O$ (Schme 31). After purification by column chromatography on silica gel, the diene **101** was isolated in 78% yield, as mixture of diastereoisomers.



Scheme 31. Allylation of the acylaminal **100**

In the ^{1}H NMR spectrum of the allylated product **101** (Figure 46), the signals at 6.08 and 5.90 ppm were assigned to the preexisting internal olefinic protons $H_{2'}$ of each isomer. From the relative area of these two signals it was calculated an isomeric ratio of 1/1.6. The signal at 5.71 ppm, overlapping for the two isomers, was assigned to the new internal olefinic proton $H_{2'''}$ and it demonstrates the presence of a second allyl group.

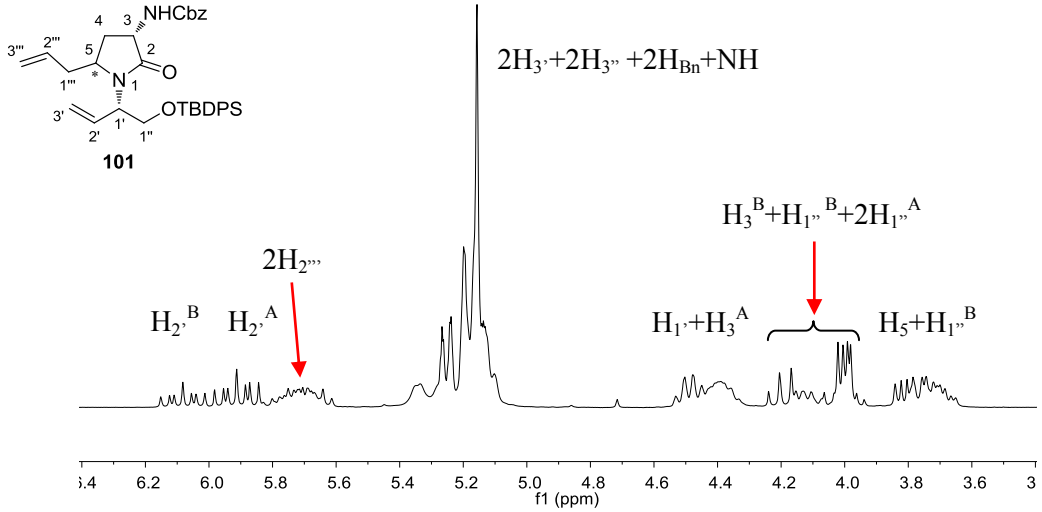
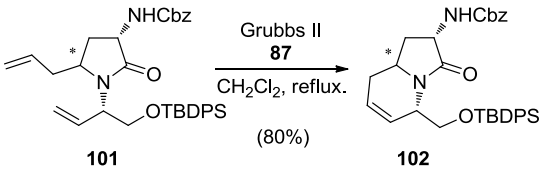


Figure 46. ^{1}H NMR (400 MHz, $CDCl_3$) spectrum of **101** as a mixture of isomers: A=major isomer; B=minor isomer

3.2.2.5. Ring-closing metathesis of 101. Formation of the indolizidine framework

The ring-closing metathesis of **101** was carried out with the mixture of isomers in CH_2Cl_2 as solvent, adding 5% of the second generation Grubbs catalyst **87** at the reflux temperature (Scheme 32). The reaction was run overnight. Purification of the crude reaction product by column chromatography on silica gel led to the isolation of two isomers, in 43% and 37% yield for the more polar (**102a**) and the less polar one (**102b**), respectively.



Scheme 32. Ring-closing metathesis of diene **101**

The 2D-COSY spectrum of the less polar isomer **102b** (Figure 47) confirms the constitution, as can be deduced from the signal assignment shown. H_{8a} is only related with four saturated hydrogens (H_1 and H_8) but shows no relationship with the one next to the amino group (assigned as H_2), which discords the alternative regioisomer, in which the nitrogen substituent of the pyrrolidinone would be next to the ring junction (C_1).

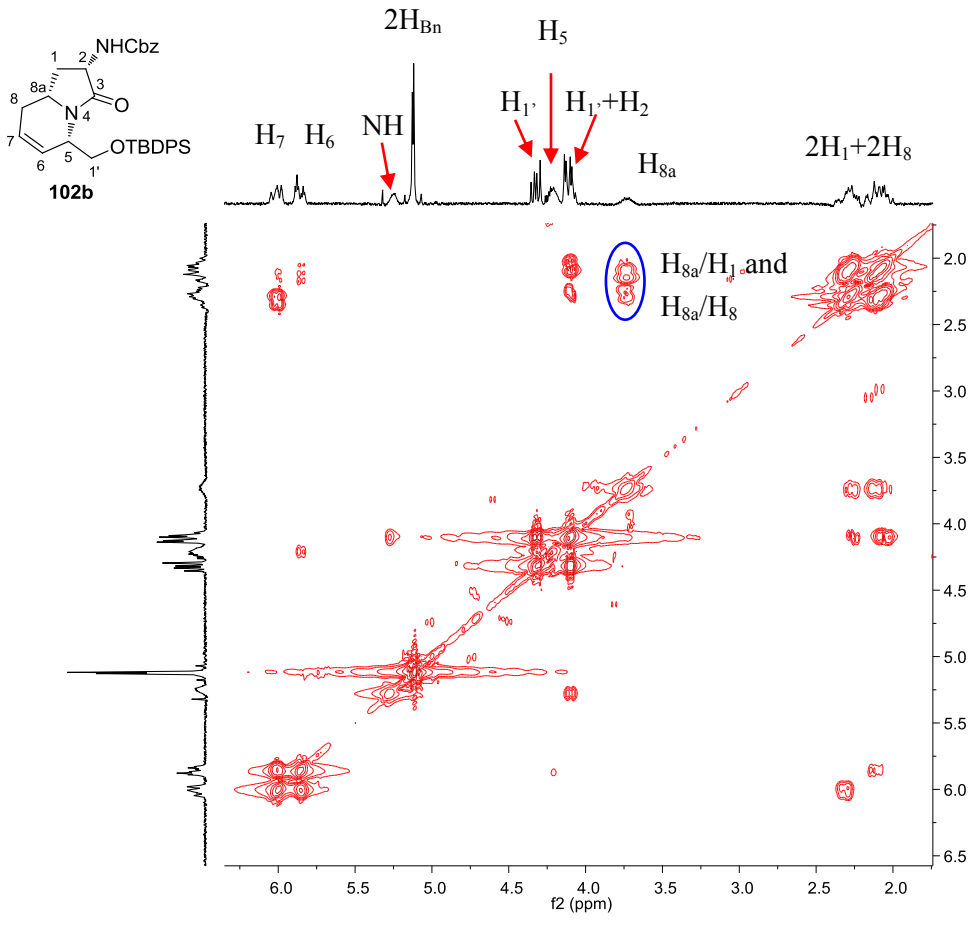


Figure 47. 2D-COSY spectrum (400 MHz, C_6D_6) of **102b**

Similarly, in the 2D-COSY spectrum of the more polar isomer **102a** (Figure 48) H_{8a} shows the same situation, which demonstrates the constitution of **102a**.

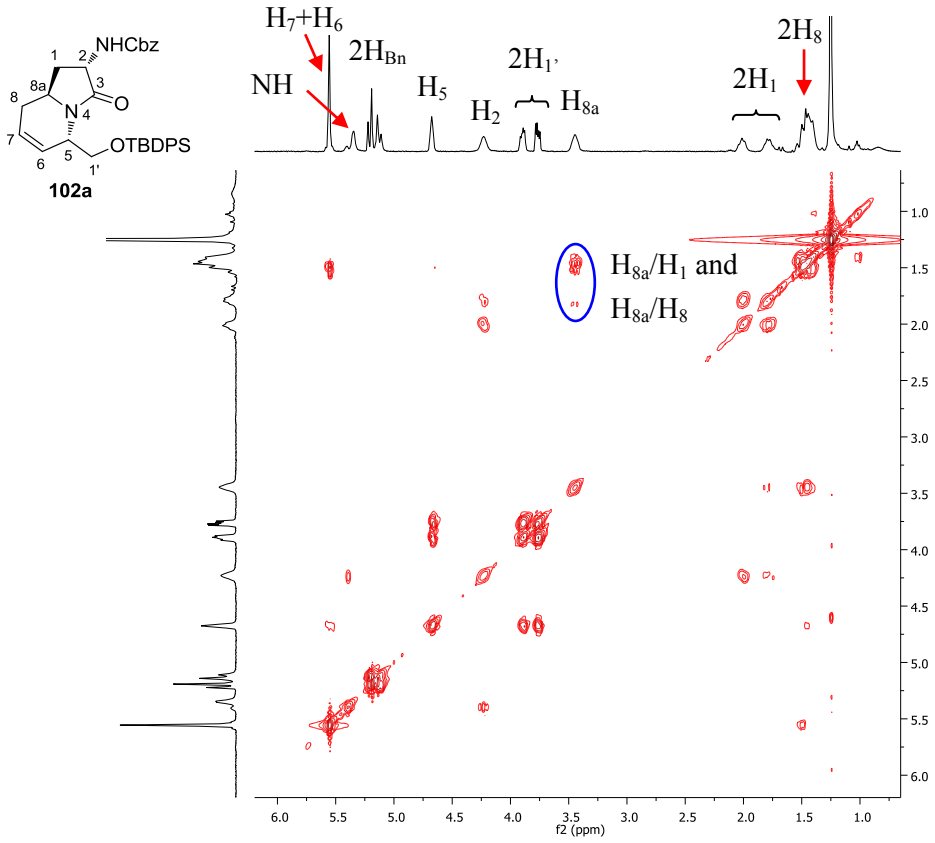
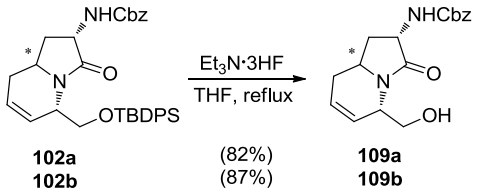


Figure 48. 2D-COSY spectrum (400 MHz, C_6D_6) of **102a**

The relative configuration of this compound was demonstrated after deprotection to the corresponding free alcohol. To this end, the two isomers **102a** and **102b** were independently treated with $Et_3N{\cdot}3HF$ in THF at the reflux temperature overnight (Scheme 33). After purification by column chromatography on silica gel, the corresponding alcohols **109a** and **109b** were isolated in 82% and 87% yield, respectively.



Scheme 33. Deprotection of two epimers of **102**

Fortunately, in the ^1H NMR spectrum of **109b** in C_6D_6, the signals corresponding to H_2, H_5, H_{8a} are sufficiently separated to determine the relative configuration by

NOESY. Firstly, from the two-dimensional COSY spectrum of **109b** (Figure 49), we proceeded to assign the signals to each proton.

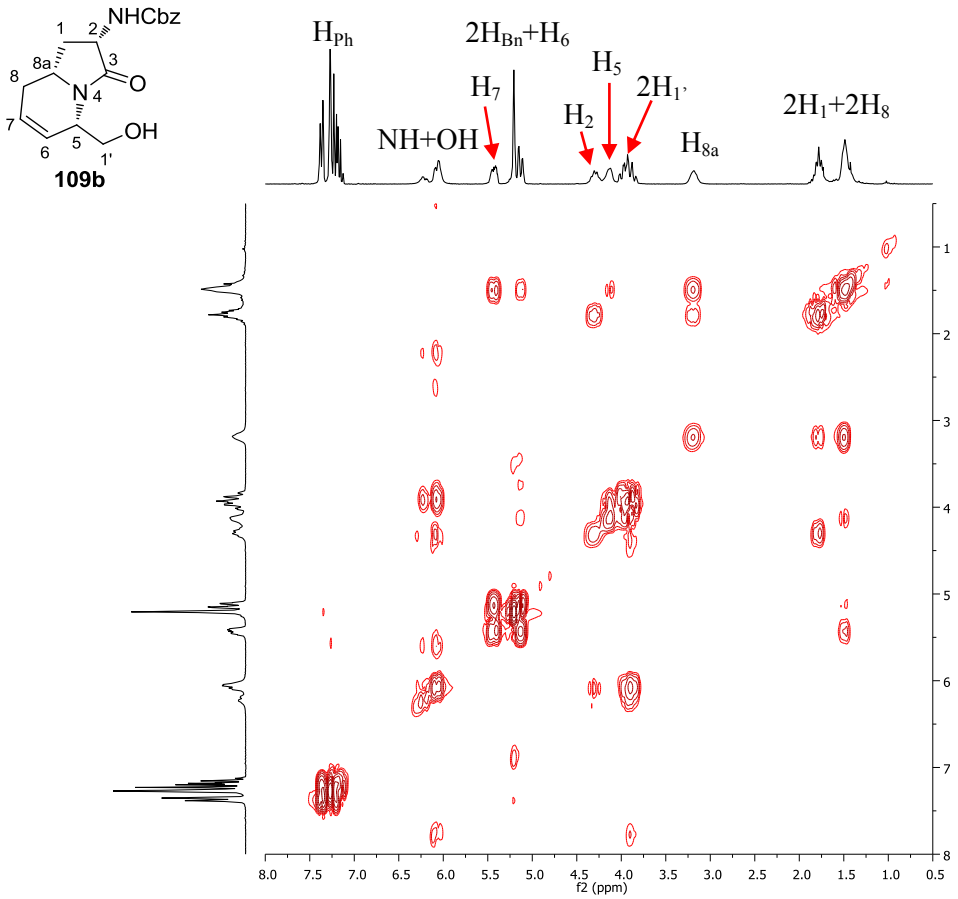


Figure 49. 2D-COSY (400 MHz, C_6D_6) spectrum of alcohol **109b**

Afterwards, a two-dimensional NOESY experiment (Figure 50) showed crossed peaks between the three protons attached to the stereogenic centers, an observation which evidences that H_2, H_5 and H_{8a} are in the same face of the bicyclic system, namely in a relative an all *cis* configuration.

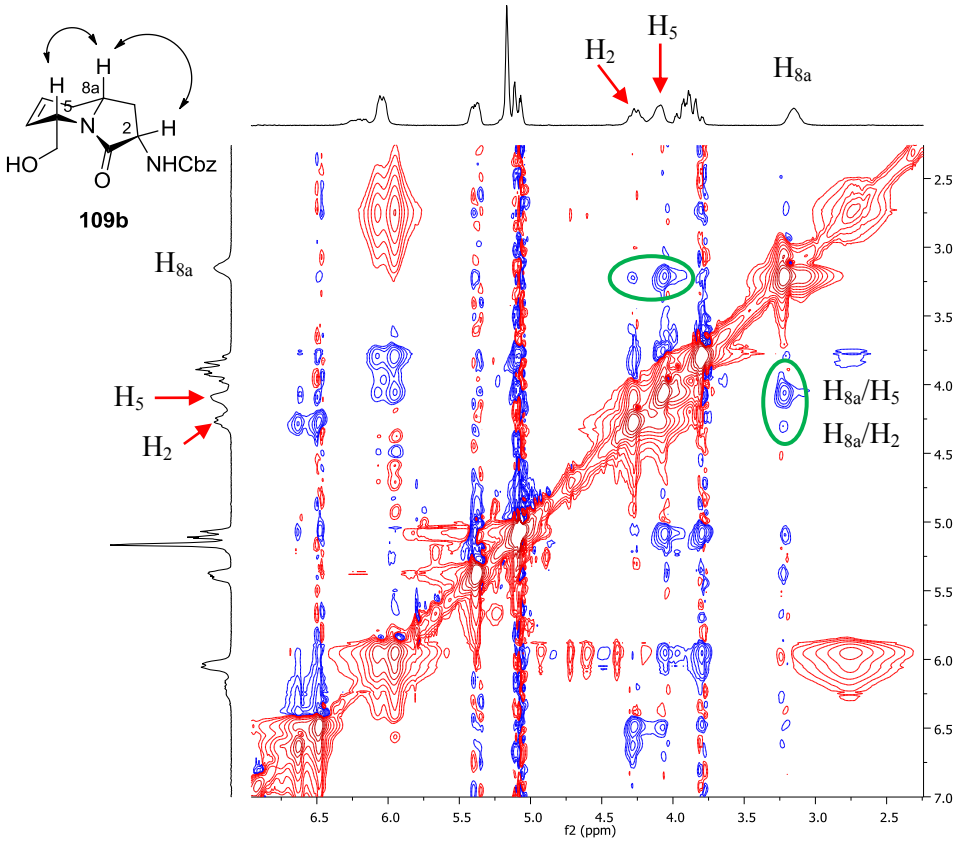


Figure 50. 2D-NOESY spectrum of alcohol **109b**

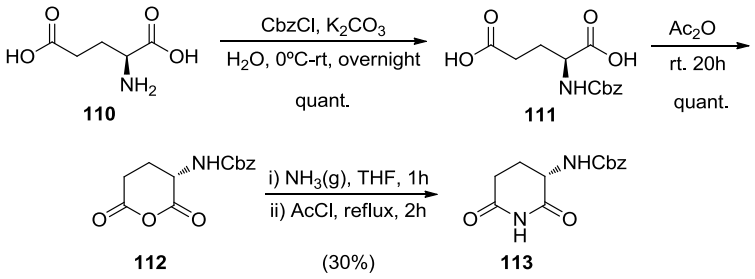
Since the starting material is enatiopure L-aspartic acid which form a *S* configuration on C_2, it can now be unequivocally established that the configuration of **109b** and that of its precursor **102b** is (2*S*,5*S*,8a*S*). Moreover, we can also confirm the absolute configuration tentatively assigned to **98**, meaning that the preexisting stereogenic center in the imide **97** apparently did not have any influence on the steric course of the palladium catalyzed asymmetric allylation. Thus, another alcohol **109a** has the (2*S*,5*S*,8a*R*) configuration.

3.2.3. Studies related to the attempted synthesis of α-aminoquinolizidinones

Since the new strategy worked fine for the synthesis of enantiopure α-aminoindolizidinones, the same methodology was intended for synthesis of the analogous quinolizidines.

3.2.3.1. Preparation of the glutarimide derivative 113

In analogy to the previous work within the succinimide route, the synthesis of the required α-aminoglutarimide started from L-glutamic acid, **110** (Scheme 34). Protection of the amino group by reaction with CbzCl,[102] was followed by cyclization in Ac_2O to afford quantitatively the anhydride **111**,[103] the crude product of which was treated with NH_3(g) in THF as solvent for 1 h.[106] The resulting mixture was concentrated under vacuum and then treated with AcCl at the reflux temperature for 2h to obtain benzyl (*S*)-(2,6-dioxopiperidin-3-yl) carbamate, **113**, in 30% yield after crystallization in EtOAc.



110 **111** **112** **113**

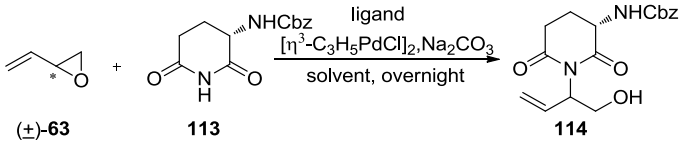
Scheme 34. Synthesis of **113** from L-glutamic acid **110**

3.2.3.2. Asymmetric *N*-allylation of imide 113

Table 7 summarizes the results obtained in the different experiments assayed for the allylation of the imide **113**. The initial experiments (entries 1-4) were performed using the same ligand (1*R*,2*R*)-**68** that had worked efficiently in the parallel allylation of the succinimide analog. Either in 1,2-dichloroethane at different temperatures or in refluxing toluene the reaction did not evolved and the starting material was recovered unchanged. It is important to recall here that the same allylation reaction applied to the unsubstituted glutarimide occurred in methylene chloride at room temperature in 86% yield. Therefore, we reasoned that the steric hindrance caused by the additional protected amino group in **113** may prevent its approach to the intermediate palladium complex and hence the allylation. Consequently, we decided to try the reaction using

[106] Gonzalez, S. V.; Carlsen, P. *Eur. J. Org. Chem*. **2007**, *13*, 3495-3502.

the less sterically demanding PPh_3 ligand. Starting with an enantiomerically pure material as **113**, the introduction of chirality in the ligand is not strictly necessary; independently of the diastereoselectivity of the process, the allylated product will be single enantiomers. All the experiments performed with PPh_3 (entries 5-11) were run in 1,2-dichloroethane and the modified parameters were the temperature and the relative amounts of palladium, ligand and base. Among this series, the best conditions found were those of entry 10, where compound **113** was mixed with 1.6 mol% of Pd (II), 10 mol% of PPh_3, and 20 mol% of Na_2CO_3, then the epoxide (±)-**63** was added and the solution was heated to reflux overnight. Although NMR analysis of the crude reaction products indicates a higher conversion, the allylated compound **114** was isolated in only 10% yield, after two consecutive column chromatography purifications on silica gel.



Scheme 35. Asymmetric N-alkylation of compound **113**

Table 7. Attempts and results of N-alkylation of **113**[a]

Entry	ligand	Solvent	T	Pd(mol%)	L*(mol%)	Na_2CO_3(mol%)	Result
1	(1*R*,2*R*)-**68**	ClC_2H_4Cl	rt	0.8	2.4	10	only **113**
2			56 °C				
3			reflux				
4		toluene	reflux				
5	PPh_3	ClC_2H_4Cl	rt	0.8	10	10	
6			56 °C	0.8	4	10	only **113**
7			reflux	0.8	7	10	
8			reflux	0.8	10	10	**114**(<30%)
9			50 °C	1.6	10	20	**114**(<11%)
10			reflux	1.6	10	20	**114**(<31%)[b]
11			reflux	2.4	15	30	**114**(<28%)

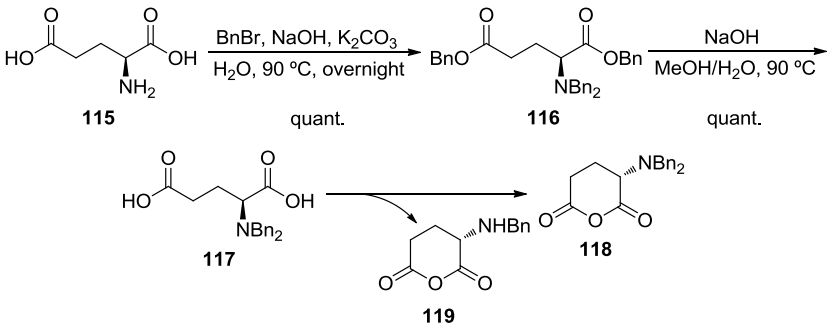
[a] All the experiments are performed overnight, b yield after the first purification through column chromatography, the product of which was not clean enough.

We speculated that a plausible reason for the unsatisfactory performance of this reaction could be the presence of the carbamate protection in **113** that supplies an acidic proton, which can be removed by the base generating a competitive reactive position for the nucleophilic attack. However, a similar reasoning could be applied to the succinimide analog **97**, from which the reaction took place in a reasonable yield. We believe then that the low yield obtained in these reactions may be in part due to partial decomposition of the product during the purification process. In any case, it was considered that this reaction was not amenable to scaling up and it was decided to attempt a change in the nitrogen protection to avoid the presence of a competitive acidic position and, eventually, increase the stability of the product.

3.2.3.3. Preparation of the *N*-benzyl derivative 120

According to a literature precedent,[107] L-glutamic acid, **115**, was quantitatively perbenzylated by treatment with excess benzyl bromide under basic condition in water at 90 ºC overnight (Scheme 36). Hydrolysis of the diester **116** afforded without problems the corresponding *N*,*N*-dibenzylamino diacid **117**. We intended to accomplish the cyclization of **117** to the anhydride **118** and the subsequent oxygen nitrogen exchange to furnish the corresponding imide. However, the cyclization was more troublesome than expected (Table 8). Treatment with Ac_2O at room temperature overnight (entry 1) did not produced any transformation, while heating at reflux for 40 min (entry 2) delivered the expected anhydride in 50% yield after chromatographic purification. In an attempt to improve the yield, the dehydrating agent was changed by acetyl chloride (entry 3), but this modification caused partial debenzylation of the amine.

[107] Banner, D.; Haap, W.; Kuhn, B.; Luebbers, T.; Peters, J.; Schul-Gash, T. PCT Int. Appl. (2013), WO2013076063 A1, 20130520.

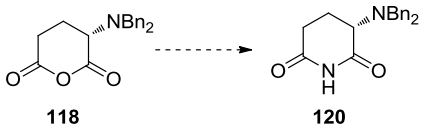


Scheme 36. Preparation of **118** from L-glutamic acid **115**

Table 8. Attempts and results of cyclization of **117**

Entry	Reagent	Temperature	Time	Result and yield
1	Ac_2O	rt	overnight	**117** (100%)
2	Ac_2O	90 ºC	40 min	**118** (50%)
3	AcCl	reflux	5 h	**118** (6%) + **119** (40%)

Unfortunately, all the attempts made in the present work to convert the anhydride **118** into the corresponding imide (Scheme 37, Table 9) were fruitless. The treatment with urea at 160 ºC (entry 1) that worked fine with the succinimide analog failed here. Alternative protocols using ammonium bicarbonate (entry 2) or ammonia in THF followed by acetyl chloride (entry 3) were also unsuccessful, recovering the starting anhydride in all cases.



Scheme 37. General synthesis of preparation of **120**

Table 9. Attempts and results of preparation of **120**[a]

Entry	Reagent	T	Time	Result
1	Urea	160 °C	2 h	**118**
2	NH_4HCO_3[108]	200 °C	1 h	**118**
3	1) NH_3(g),THF; 2) AcCl	1) rt 2) reflux	1) 30 min 2) 5 h	**118**

[a] 1) and 2) refer to consecutive steps

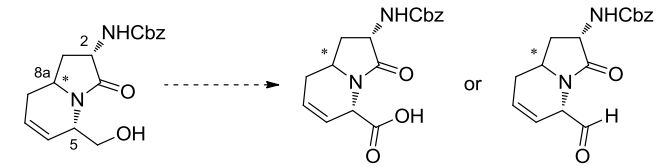
In view of the negative results, this route was temporarily abandoned and will be re-examined in the future.

[108] Braña, M. F.; Acero, N.; Añorbe, L.; Mingarro, D. M.; Llinares, F.; Domínguez, G. *Eur. J. Med. Chem*. **2009**, *44*, 3533-3542.

3.3. ATTEMPTED OXIDATION AND HYDROGENATION OF 109

3.3.1. Oxidation of compounds 109

With the two diastereoisomers of **109** in hands, the only remaining step to the target peptides was the oxidation of the primary alcohol to the corresponding carboxylic acid (Scheme 38). Table 10 summarizes the oxidation experiments separately performed with each isomer. Unfortunately, none of the assayed methods gave satisfactory results. Dess-Martin periodinane (DMP) in dichloromethane at room temperature (entries 1, 2) led to total consumption of **109a** (entry 1), in the ^{1}H NMR spectrum of crude product it is able to see some signals related to the skeleton of **109a** but we cannot isolate or identify any compound in the mixture. The isomer **109b** was more resistant to these conditions (entry 2) and was recovered in part, but still the expected acid could not be detected. A similar result (entry 3) was observed using pyridinium chlorochromate (PCC). The Swern oxidation of **109b** (entry 4) was also ineffective and a complex crude product was also obtained. Besides, the treatment of **109a** with Jones reagent (entry 5) and the oxidation of both isomers with $NaIO_4$, $RuCl_3$ (entries 6, 7) shown negative result either, and practically no clear signals can be seen in ^{1}H NMR analysis.



109b: (2*S*,5*S*,8a*S*)
109a: (2*S*,5*S*,8a*R*)

Scheme 38. General synthesis of oxidation of **109**

Table 10. Attempts and results of oxidation of **109**[a]

Entry	sm	Reagent	Solvent	T	Time	Result
1	**109a**	DMP	CH_2Cl_2	rt	2 h	complex mixture
2	**109b**	DMP	CH_2Cl_2	rt	2 h	**109b**(40%)
3	**109b**	PCC	CH_2Cl_2	rt	overnight	**109b**(<60%)
4	**109b**	DMSO, $(COCl)_2$, Et_3N	CH_2Cl_2	-78ºC-rt	1.5 h	complex mixture
5	**109a**	Jones reagent[109]	Acetone	rt	3 h	decomposed

[109] (a) Takahashi, S.; Kuzuhara, H.; Nakajima, M. *Tetrahedron*. **2001**, *57*, 6915-6926. (b) Frantz, M. C.; Pierce, J. G.; Pierce, J. M.; Li, K.; Wan, Q.; Johnson, M.; Wipf, P. *Org. Lett*. **2011**, *13*, 2318-2321.

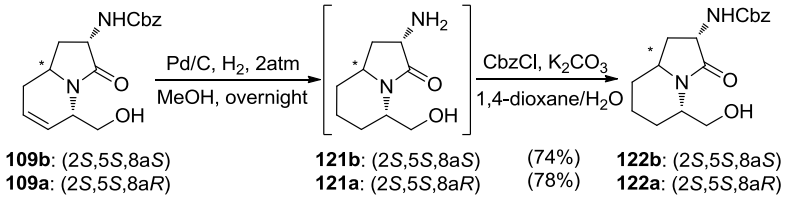
6	**109a**	$NaIO_4$, $RuCl_3 \cdot 3H_2O$[110]	CH_3CN/H_2O	rt	2 h	decomposed
7	**109b**	$NaIO_4$, $RuCl_3 \cdot 3H_2O$	CH_3CN/H_2O	rt	2 h	decomposed

[a] The results were inferred from ^1H NMR analysis of the crude products

Our general conclusion after all these trials was that our substrates were too sensitive to most oxidation conditions and we thought that a possible cause could be the presence of the carbon-carbon double bond, which is a functional group also amenable of being oxidized. With this idea in mind, we decided to undertake the hydrogenation of the double bond prior to the oxidation.

3.3.2. Hydrogenation of compounds 109

The hydrogenation of **109a** and **109b** (Scheme 39) was initially assayed at atmospheric pressure, using 10% of Pd/C as the catalyst in Methanol. Under these conditions, the starting material was recovered unchanged. However, increasing the hydrogen pressure to 2 atm, the conversion was complete after 20 h. ^1H NMR analysis of the crude hydrogenation product unveiled that saturation of the double bond was concomitant with deprotection of the amine. Therefore, the amino alcohols **121a/b** were not purified but reprotected to the corresponding carbamates **122a** and **122b**, with overall yield of 78% and 74%, respectively.



Scheme 39. Hydrogenation of compound **109**

The study on the oxidation of **122a/b** to furnish the corresponding acids is currently in progress.

[110] Hallinan, E. A.; Kramer, S. W.; Houdek, S. C.; Moore, W. M.; Jerome, G. M.; Spangler, D. P.; Stevens, A. M.; Shieh, H. S.; Manning, P. T.; Pitzele, B. S. *Org. Biomol.Chem*. **2003**, *1*, 3527-3534.

3.4. ATTEMPTS TO PREPARE CHLOROQUINE DERIVATIVES

3.4.1. 7-Chloroquinolines as structural feature in antimalarians

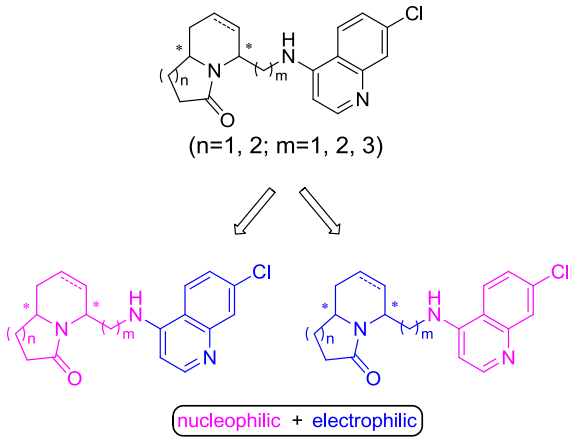
In tropical and subtropical regions, malaria represents a serious health problem affecting 400–500 million people annually.[111] Besides, the resistance to common antimalarials, such as chloroquine or antifolates, is increasing steadily worldwide. At present, the most promising and, so far, successful strategy in fighting malaria is a combinational chemotherapy in order to improve efficacy and delay onset of resistance.[75]

There is a need for new drugs that do not share the same mechanisms of resistance with those that are failing today. The quinoline type compounds continue to attract interest because their mechanisms of action and resistance are unrelated. Recently, it has been observed that chloroquine analogues containing the side chain basic nitrogen in a piperidine or pyrrolidine ring exhibited a substantial increase in antimalarial activity against chloroquine-resistant strains (see **1.1.4.2**). Therefore, a series of compounds, in which our bicyclic structures are linked to chloroquine, were designed.

3.4.2. Design of new chloroquine resistant antimalarial candidates

As it was already mentioned, one of the objectives of the present work was the preparation of chloroquine analogs incorporating an enantiopure indolizidine or quinolizidine fragment. These two fragments would be linked to a tether, the length of which could be moderate in view of the activity result. Scheme 40 shows the targeted molecules, which were plan to be synthesized by reaction of a chloroquine derivative with an indolizidinone or quinolizidinone counterpart. To this end, two alternative approaches were considered depending of the nucleophilic or electrophilic character of each reaction partner.

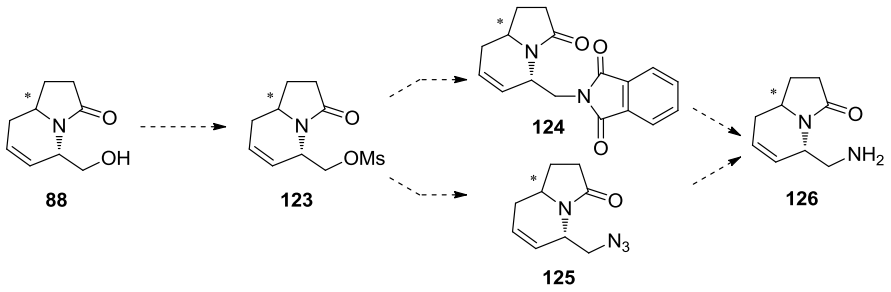
[111] Greenwood, B.; Mutabingwa, T. *Nature* **2002**, *415*, 670-672.



Scheme 40. Alternative approaches to chloroquine analogs incorporating an azabicyclic moiety

3.4.3. Approach based on the reaction of a nucleophilic azabicycle with an electrophilic chloroquine fragment

Among other possibilities, as the nucleophilic azabicyclic derivative we chose to prepare the amine **126** (Scheme 41), because the amino group might be used as the nucleophile in S_NAr reactions versus electron-deficient quinolizidines and also in condensation reactions with activated carbonyl compounds derived from chloroquine. To prepare the amine **126**, we undertook the sequence depicted in the Scheme.



Scheme 41. Intended preparation of amine **126**

3.4.3.1. Preparation of amine 125

The synthesis began with the mesylation of alcohol **88**, the two epimers of which were separately treated with 2 equivalents of MsCl in the presence of Et_3N in CH_2Cl_2 at 0°C for 2h, to produce the mesylates **123** (Scheme 42). These mesylates showed limited stability and were used in the next step without further purification.

Scheme 42. Mesylation of alcohol **88**

A comparison between the ^{1}H NMR spectrum of the starting alcohol *trans*-**88** and that of the corresponding mesylate *trans*-**123** is displayed in Figure 51. The main evidences of the transformation are the appearance of a singlet at 2.98 ppm, corresponding to the methyl group, and the downfield shifting of the signals of the α-oxygen methylene group, from 3.81 and 3.65 ppm to 4.34 and 4.19 ppm. A similar observation is made when going from *cis*-**88** to *cis*-**123**.

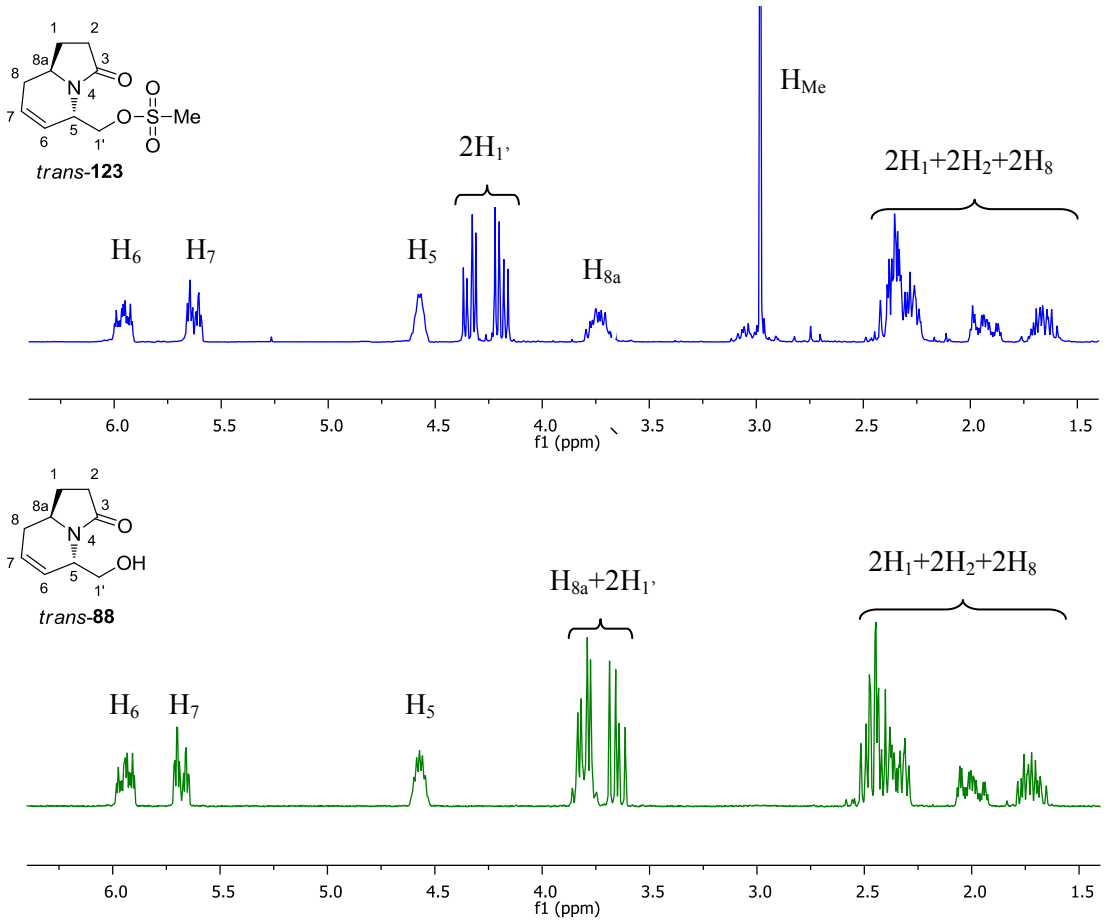
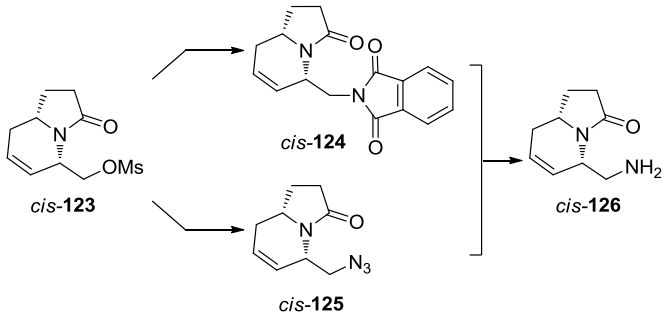


Figure 51. Comparison of the ^{1}H NMR (250 MHz, $CDCl_3$) spectra of *trans*-**123** and *trans*-**88**

Table 11 shows the results obtained for the different conditions assayed for preparation of the primary amine *cis*-**126** (Scheme 43). The Gabriel synthesis proved

ineffective when the using K_2CO_3 in combination with phtalimide in acetonitrile as solvent (entry 1). Better results were obtained treating *cis*-**123** with preformed potassium phtalimide in dimethylformamide (DMF) (entry 2), followed by treatment with hydrazine but the yield was still low. Better results were found through azidation and subsequent reduction (entry 3), a procedure that led to the isolation of the expected amine *cis*-**126** in overall 62% yield. Then, the same set of conditions were applied to the epimeric mesylate *trans*-**123** that conducted to the corresponding primary amine *trans*-**126** in 56% yield for two steps after purification by column chromatography on silica gel.



Scheme 43. Assayed synthesis of amine *cis*-**126** from *cis*-**123**

Table 11. Attempts and results of amination of *cis*-**123**[a]

Entry	Reagent	Solvent	T	Result (yield)
1	phthalimide, K_2CO_3	CH_3CN	reflux	*cis*-**82**
2[b]	1) potassium phthalimide;[112]	1) DMF	1) rt-80°C	1) *cis*-**124** (36%)
	2) aqueous hydrazine	2) EtOH	2) reflux	2) *cis*-**126** (20%)
3[b]	1) NaN_3;[113]	1) DMF	1) 80°C	1) *cis*-**125** (80%)
	2) Ph_3P	2) Et_2O,H_2O	2) 0 °C -rt	2) *cis*-**126** (78%)

[a] All reactions were ran overnight. [b] 1) and 2) refer to consecutive steps.

Figure 52 shows the partial ^{1}H NMR spectra for the series of compounds *cis*-**123**-*cis*-**126**, where the effect of the substituent attached to the exocyclic methylene group is

[112] Wakita, T.; Kinoshita, K.; Kodaka, K.; Yasui, N.; Naoi, A.; Banba, S. *J. Pestic. Sci*. **2004**, *29*, 356-363.

[113] Saito, Y.; Matsumoto, K.; Bag, S. S.; Ogasawara, S.; Fujimoto, K.; Hanawa, K.; Saito, I. *Tetrahedron*. **2008**, *64*, 3578-3588.

clearly observed by the upfield shifting of the double doublet signal of protons $H_{1'}$ in parallel to the increasing electron-withdrawing affinity of the substituent.

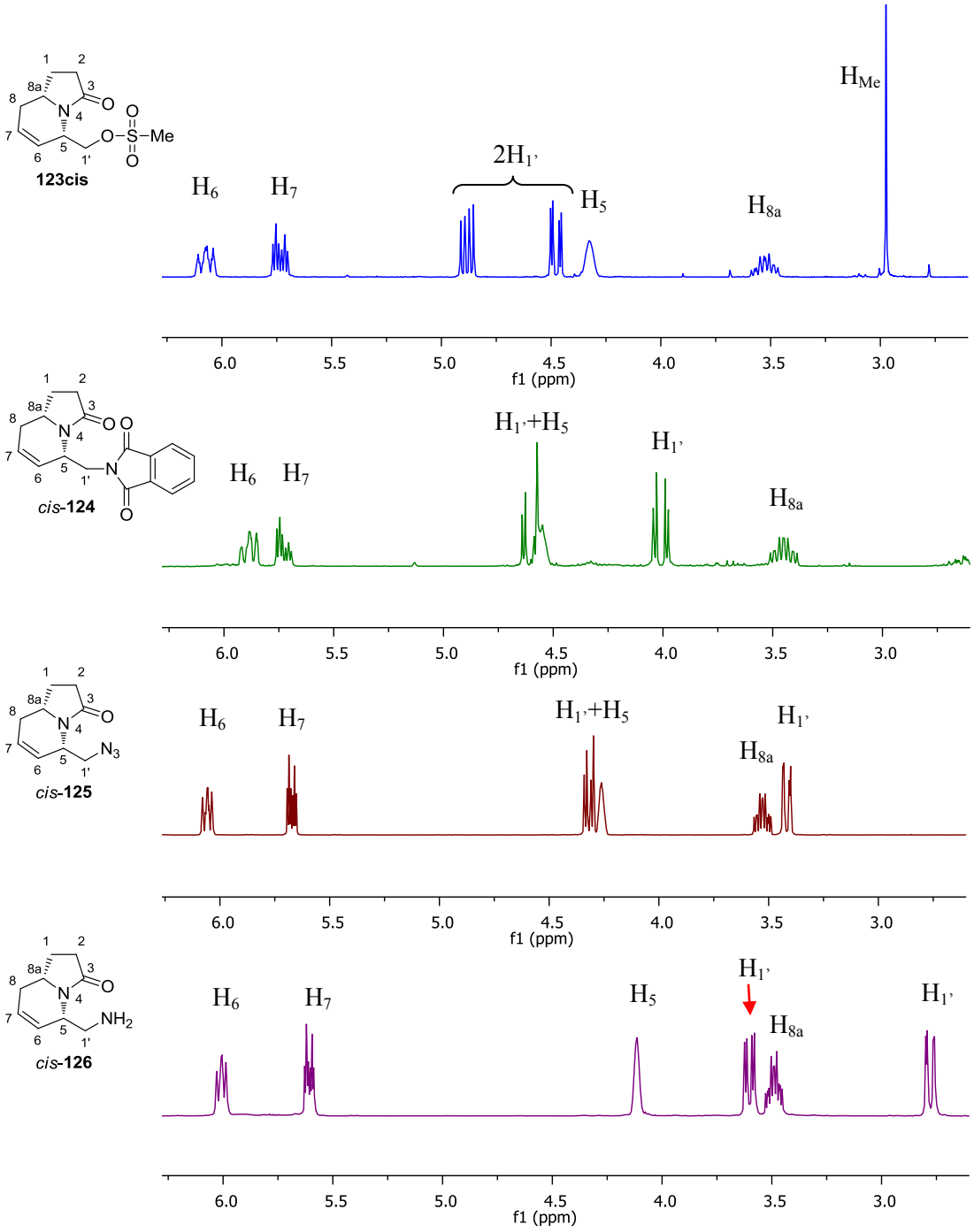
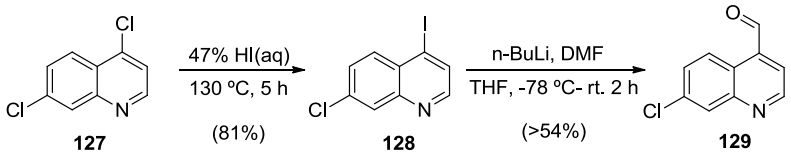


Figure 52. Comparison of the ^{1}H NMR (250 MHz, $CDCl_3$) spectra of *cis*-**123**- *cis*-**126**

3.4.3.2. Preparation quinoline 128 and aldehyde 129

The partners of choice for the reaction with amines *cis*-**126** and *trans*-**126** were 4,7-dichloroquinoline, **127**, and 7-chloroquinoline-4-carbaldehyde, **129**, which can respectively react as electrophiles in S_NAr and condensation processes with amines. The dichloroquinoline **127** is the commercially available and was used as starting material to prepare the aldehyde **129** (Scheme 44). Firstly, 7-chloro-4-iodoquinoline, **128**, was obtained by treating **127** with 47% HI solution at 130 °C for 5 h in 81% yield after crystallization from H_2O.[114] Then the iodo derivative **128** was reacted with DMF in the presence of *n*-BuLi in THF at -78 °C for 15 min and then at room temperature for 2 h.[115] In our hand, this reaction was not reproducible, even though it was performed many times, the expected aldehyde **129** was isolated successfully only once and even after purification by column chromatography on silica gel the purity was not good. As the ^1H NMR spectrum confirmed the main component, the impure product was used to do the next step directly.



Scheme 44. Synthesis of aldehyde **129** from dichloroquinoline **127**

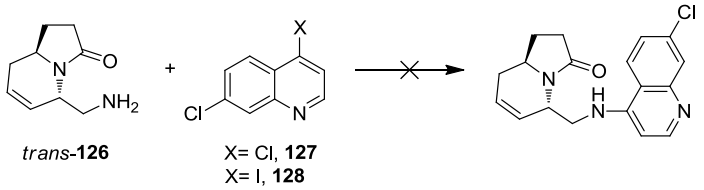
3.4.3.3. Reaction between amine *trans*-125 and 7-chloroquine partners

Firstly, the S_NAr was attempted between the amine *trans*-**126** and the dichloroquinoline **127** (Scheme 45) in the presence of K_2CO_3 in DMF at 140 °C overnight.[77] The ^1H NMR spectrum of the crude reaction product showed unreacted quinoline **127** and indicated the decomposition of *trans*-**126**, while traces of the expected substitution product were not detected. We suspected that at the high temperature required for the S_NAr reaction on **127**, the amine was probably too unstable

[114] Cheruku, S. R.; Vennerstrom, J. L.; *J. Med. Chem*. **2003**, *46*, 3166-3169.

[115] Xu, Y.; Lu, H.; Kennedy, J. P.; Yan, X.; McAllister, L. A.; Yamamoto, N.; Moss, J. A.; Boldt, G. E.; Jiang, S.; Janda, K. D. *J. Comb. Chem*. **2006**, *8*, 531-539.

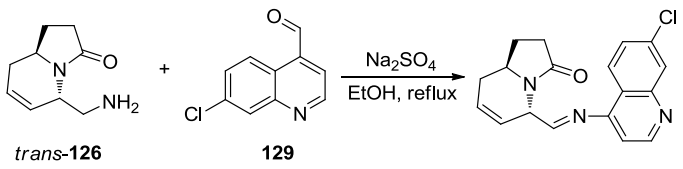
to survive. Therefore, the reaction was then tried with the more reactive iodo derivative **128** that, hopefully, should allow working at lower temperature. The reaction between *trans*-**126** and **128** was assayed in refluxing THF in the presence of Et_3N and in DMF with K_2CO_3 at room temperature, leading in both cases to recovery of the starting amine. When the last conditions were applied heating up to 80 ºC, the amine decomposed and only the quinoline partner was recovered.



trans-**126** X= Cl, **127** X= I, **128**

Scheme 45. Intended S_NAr reaction between amine *trans*-**126** and haloquinolines **127** and **128**

In view of these difficulties, we moved to the alternative route, namely the condensation of the amine with the aldehyde to furnish a Schiff base (Scheme 46). Unfortunately, under the standard conditions shown, both *trans*-**126** and **129** decomposed.



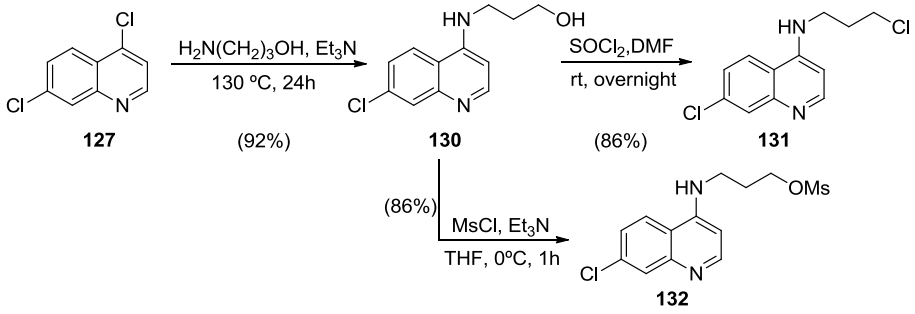
trans-**126** **129**

Scheme 46. Reaction between amine *trans*-**126** and aldehyde **129**

3.4.3.4. Preparation of aminoquinolines 131 and 132 and attempted S_N2 reactions

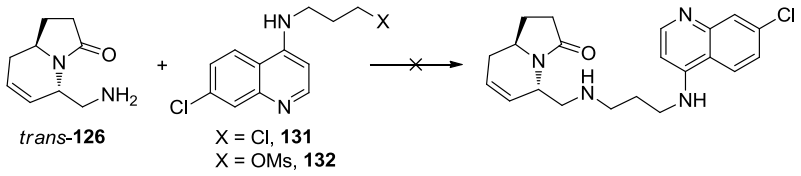
The former negative results, led us to consider the possibility of joining the indolizidine and quinoline fragments through a tether, which could be linked through a S_N2 type reaction. To this end, the quinoline partner should bear a leaving group attached to a sp^3 carbon atom and. Scheme 47 shows the two electrophiles **131** and **132** prepared to this aim. The synthesis of **131** and **132** was accomplished through the intermediacy of the alcohol **130**, which was prepared through S_NAr reaction between the dichloroquinoline **127** and 3-aminopropanol in the presence of Et_3N at 130 ºC for 20

h.[116] The alcohol was then treated with $SOCl_2$ in the presence of DMF to generate **131** in 86% yield.[117] Besides, the alcohol **130** could be mesylated under standard conditions[118] to form **132** in 86% yield.



Scheme 47. Synthesis of chloride **131** and mesylate **132** from **127**

The reaction between amine *trans*-**126** and chloride **131** and mesylate **132** (Scheme 48) was performed in the presence of Et_3N in DMF as solvent at 80°C for 4 h. The analysis of the product indicated decomposition of both starting materials and no traces of the substitution product. Similar results were also observed with the mesylate **132** as the electrophile, despite the softer conditions used in this case, where the solvent was THF and the temperature did not exceed 60°C.



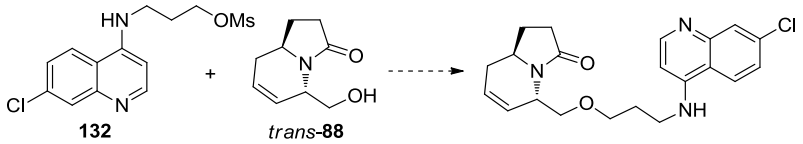
Scheme 48. Attempted reaction of **131**, **132** with *trans*-**126**

[116] (a) Burgess, S. J.; Selzer, A.; Kelly, J. X.; Smilkstein, M. J.; Riscoe, M. K.; Peyton, D. H. *J. Med. Chem*. **2006**, *49*, 5623-5625. (b) Starčević, K.; Pešić, D.; Toplak, A.; Landek, G.; Alihodžić, S.; Herreros, E.; Ferrer, S.; Spaventi, R.; Perić. M. *Eur. J. Med. Chem*. **2012**, *49*, 365-378.

[117] Souza, M. N.; Pais, K. C.; Kaiser, C. R.; Peralta, M. A.; Ferreira, M. L.; Lourenço, M. S. *Bioorg. Med. Chem*. **2009**, *17*, 1474-1480.

[118] (a) Tukulula, M.; Sharma, R. K.; Meurillon, M.; Mahajan, A.; Naran, K.; Warner, D.; Huang, J.; Mekonnen, B.; Chibale, K. *ACS Med. Chem. Lett*. **2013**, *4*, 128-131. (b) Solomon, V.R.; Hu, C.; Lee, H. *Eur.J.Med.Chem.* **2010**, *45*, 3916-3923.

Since we are interested on the influence of the nature of the heteroatoms in the tether on the activity of the analogs, we decided to attempt the S_N2 reaction with alcohol *trans*-**88** as the nucleophile, which shows higher stability than the amine *trans*-**126**. Table 12 summarizes the results of these trials. In all cases, THF was used as the solvent, working at temperatures from 0 ºC to 60 ºC and two bases were assayed, Et_3N and NaH. The alcohol proven indeed to be more stable than the amine and was recovered in all the trials; the mesylate **132** was unreacted in most cases and it was decomposed when the reaction was performed at 60 ºC for 6 h using NaH as base (entry 4). Unfortunately, the substitution product was never detected.



Scheme 49. Attempted reaction between **132** and *trans*-**88**

Table 12. Attempts and results of reaction of **132** with *trans*-**88** and *trans*-**126**[a]

Entry	Reagent	Solvent	T	Time	Result
1	Et_3N	THF	0 °C –rt	2 h	**132**+ *trans*-**88**
2	Et_3N		55 °C	5 h	**132**+ *trans*-**88**
3	NaH		rt	6 h	**132**+ *trans*-**88**
4	NaH		60 °C	6 h	only *trans*-**88**

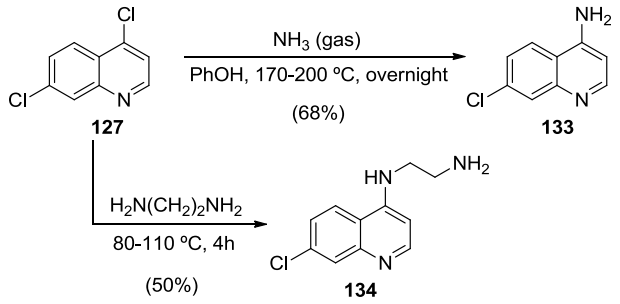
[a] The results were inferred from ^{1}H NMR analysis of the crude products

3.4.4. Approach based on the reaction of an electrophilic azabicycle with a nucleophilic chloroquine fragment

3.4.4.1. Preparation of amines 133 and 134

Scheme 50 shows the preparation of 7-chloroquinolin-4-amine, **133**, and *N*-(7-chloroquinolin-4-yl)ethane-1,2-diamine, **134**, which were the nucleophiles of choice to attempt the linkage to an electrophilic azabicyclic partner. The synthesis of amine **133** was performed by treating the dichloroquinoline **127** with NH_3 gas in PhOH

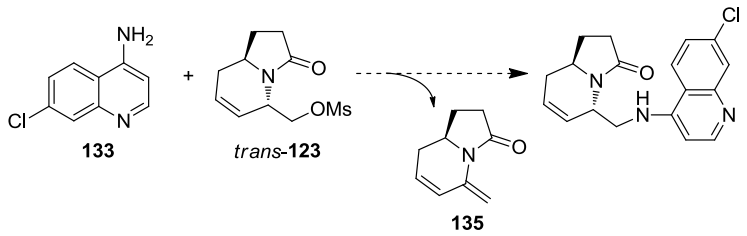
as solvent at 170-200 °C overnight.[119] The amine **134** was obtained through the S_NAr reaction between **127** and ethylenediamine at 80-110°C for 4 h.[117,120]



Scheme 50. Synthesis of amines **133** and **134** from **127**

3.4.4.2. Reaction of mesylate *trans*-123 with amines 133 and 134

Table 13 summarizes the experiments performed to attempt the nucleophilic substitution reaction between amine **133** and mesylate *trans*-**123**. Mixing equimolar amounts of the two reagents in DMF at room temperature (entry 1) or refluxing THF (entry 2), in the presence of Et_3N, for several hours, led them unaffected. When the reaction temperature was raised to 100 ºC, the amine was recovered but the mesylate decomposed. Increasing the equivalents of amine (entries 4 and 5) did not produced significant changes. Finally, the use of NaHMDS as the base instead of Et_3N (entry 6) favored the competitive elimination reaction, generating the olefin **135**.



Scheme 51. Attempted reaction between **133** and *trans*-**123**

[119] (a) Price, C. C.; Leonard, N. J.; Peel, E. W.; Reitsema, R. H. *J. Am. Chem. Soc*. **1946**, *68*, 1807-1808. (b) Elderfield, R. C.; Gensler, W. J.; Birstein, O.; Kreysa, F. J.; Maynard, J. T.; Galbreath, J. *J. Am. Chem. Soc.* **1946**, *68*, 1250-1251.

[120] Carmo, A. M. L.; Silva, F. M. C.; Machado, P. A.; Fontes, A. P. S.; Pavan, F. R.; Leite, C. Q. F.; Leite, S. R. A.; Coimbra, E. S.; Da Silva, A. D. *Biomed Pharmacother*. **2011**, *65*, 204-209.

Table 13. Attempts and results of reaction between **133** and *trans*-**123**[a]

Entry	*trans*-122 : 132	Reagent	Solvent	T	Time	Result
1	**1:1**	Et_3N	DMF	rt	overnight	**133**+ *trans*-**123**
2	**1:1**	Et_3N	THF	reflux		**133**+ *trans*-**123**
3	**1:1**	Et_3N	DMF	100		only **133**
4	**1:2**	/	DMF	rt		**133**+ *trans*-**123**
5	**1:2**	/	DMF	80		**133**+ *trans*-**123**
6	**1:1**	NaHMDS	THF	rt		**133**+**135(27%)**

[a] The results were inferred from ^{1}H NMR analysis of the crude products

The only isolated product **135** (27% yield) was characterized by its ^{1}H NMR spectrum (Figure 53). Compared with the spectrum of the mesylate *trans*-**123**, the loss of the signals corresponding to the exocyclic methylene group and the allylic α-nitrogen proton, and the appearance of two broad singlets at 6.06 and 4.77 ppm evidences the formation of an exocyclic carbon-carbon double bond.

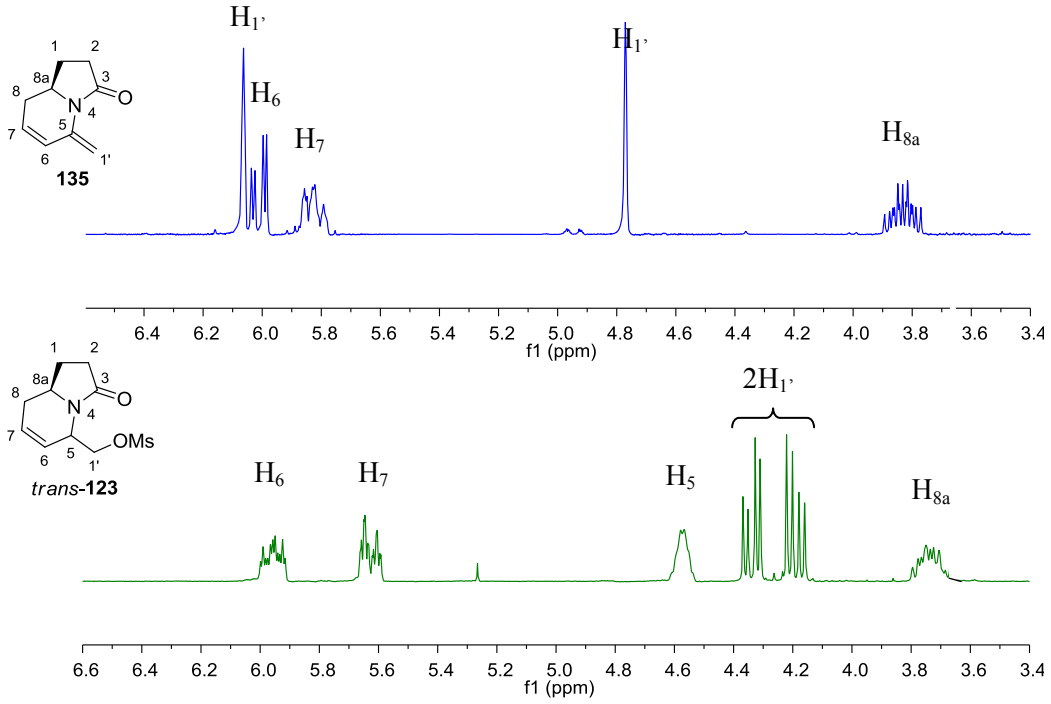
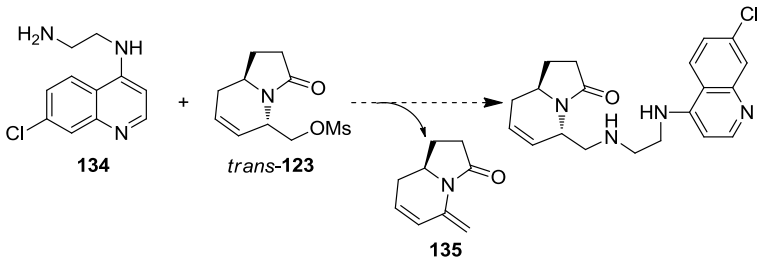


Figure 53. Comparison of the ^{1}H NMR (250 MHz, $CDCl_3$) spectra of mesylate *trans*-**123** and olefin **135**

The results did not improve in the experiments using chloroquinolinediamine **134** as the nucleophile (Scheme 52, Table 14). For this reaction, some trials were made

using K_2CO_3 as an alternative base and EtOH as an alternative solvent, but again the only new compound detected in the crude product was the olefin **135**.



Scheme 52. Attempted reaction between **134** and *trans*-**123**

Table 14. Attempts and results of reaction between **134** and *trans*-**123**

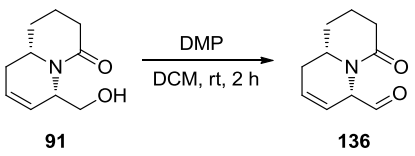
Entry	Reagent	Solvent	T	Result
1	K_2CO_3	EtOH	rt	**134**+ *trans*-**123**
2	K_2CO_3	EtOH	60 ºC	**134**+**135**(70%)
3	K_2CO_3	DMF	rt	**134**+ *trans*-**123**
4	Et_3N	DMF	50 ºC	only *trans*-**123**

[a] All reaction were ran overnight and the results were determined by ^{1}H NMR

3.4.4.3. Preparation of aldehyde 136 and attempted condensation with amine 133

In order to attempt the alternative condensation path to link the chloroquine, an aldehyde was required in the azabicyclic fragment.

The oxidation of alcohol **91** with the DMP reagent in CH_2Cl_2 as solvent at room temperature for 2 h furnished aldehyde **136** quantitively (Scheme 53). Its formation was confirmed by the appearance of a signal at 8.98 ppm in the ^{1}H NMR spectrum of the crude reaction prodcut. However, aldehyde **136** showed a limited stability and hence it was used in the next reaction without further purification.



Scheme 53. Synthesis of aldehyde **136** from **91**

Unexpectedly, the analogous oxidation of the indolizidine derivatives *cis*-**88** and *trans*-**88** met with difficulties (Scheme 54, Table 15). Treatment of *trans*-**88** with the DMP under the same conditions applied to **91** led to a complex mixture of unidentifiable products (entry 1). At lower temperature, for both *cis*-**88** and *trans*-**88** (entries 2 and 3) the conversion was incomplete and yet the reaction mixtures very complex, even some signals related to the skeleton can be seen no compound could be isolated or identified. The Swern oxidation (entries 4 and 5) gave also negative results for both substrates and the treatment with PCC (entries 6 and 7) only caused decomposition, almost no signals can be seen in ^{1}H NMR spectra.

cis-**88**
trans-**88**

Scheme 54. Attempted oxidation of *cis*-**88** and *trans*-**88**

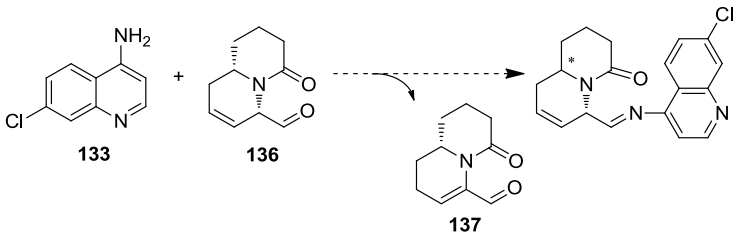
Table 15. Attempts and results of oxidation of *cis*-**88** and *trans*-**88**[a]

Entry	sm	Reagent	T	Time	Result
1	*trans*-**88**	DMP	rt	3 h	complex mixture
2	*trans*-**88**	DMP	0 ºC	30 min	*trans*-**88**+ complex mixture
3	*cis*-**88**	DMP	0 ºC	30 min	*cis*-**88**+ complex mixture
4	*trans*-**88**	DMSO, $(COCl)_2$, Et_3N	-78 ºC- rt	1 h	*trans*-**88**+ complex mixture
5	*cis*-**88**	DMSO, $(COCl)_2$, Et_3N	-78 ºC- rt	1 h	*cis*-**88**+ complex mixture
6	*trans*-**88**	PCC, K_2CO_3	rt	3 h	decomposition
7	*cis*-**88**	PCC, K_2CO_3	rt	3 h	decomposition

[a] CH_2Cl_2 was used as solvent in all runs. The crude reaction product was analyzed by ^{1}H NMR

In view of these difficulties, the next efforts were centered on the condensation reaction between the aldehyde **136** and the amine **133** (Scheme 55). Table 16 summarizes the results observed in this study. The condensation was tried in Methanol as the solvent, in the presence of a dehydrating agent, without or with acid catalysis. Unfortunately, the expected imine was not detected in none of the experiments. The starting aldehyde was totally consumed, while the amine was recovered unaltered. The

only product that we were able to characterize from the complex reaction crude materials was the α,β-unsaturated aldehyde **137**.



Scheme 55. Attempted reaction between **133** and **136**

Table 16. Attempts and results of reaction between **133** and **136**[a]

Entry	Additive	Solvent	T	Time	Result
1	MS, 4 Å	Methanol	reflux	overnight	**137** (10%)+**133**
2	Na_2SO_4	Methanol	rt		**137** (10%)+**133**
3	Na_2SO_4	Methanol /AcOH	rt	3 h	**137** (40%)+**133**

[a] The results were inferred from the ^{1}H NMR spectrum of the crude product

Figure 54 shows significant fragments of the ^{1}H NMR spectra of aldehydes **136** and **137**. The loss of an olefinic proton and the downfield shift of the aldehyde signals evidence the isomerization of **136** to **137**.

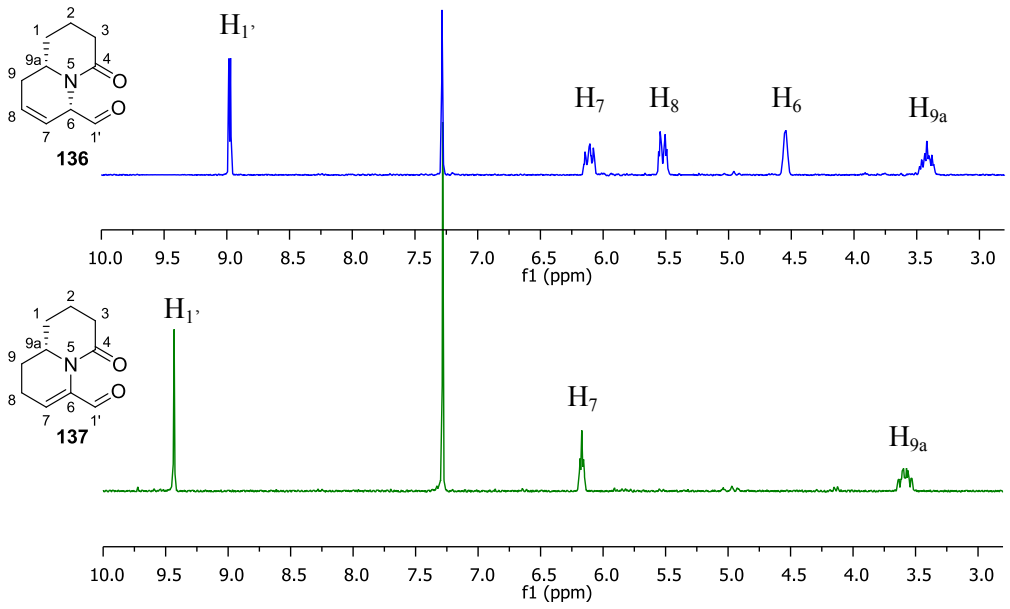
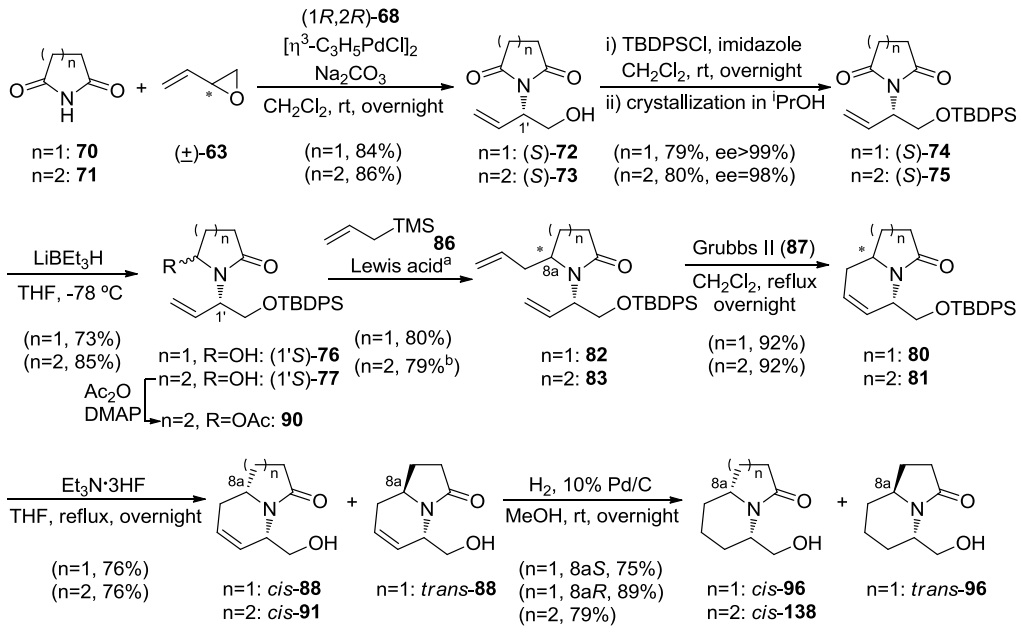


Figure 54. Comparison between the ^{1}H NMR (250 MHz, $CDCl_3$) spectra of **136** and **137**

IV. Summary and Conclusions

This thesis focuses on the stereoselective preparation of chiral indolizidine and quinolizidine derivatives with a double purpose: i) as precursors of conformationally constrained Smac peptidomimetics and ii) to form conjugates with chloroquine residues, in the search for new antimalarial drugs against resistant strains.

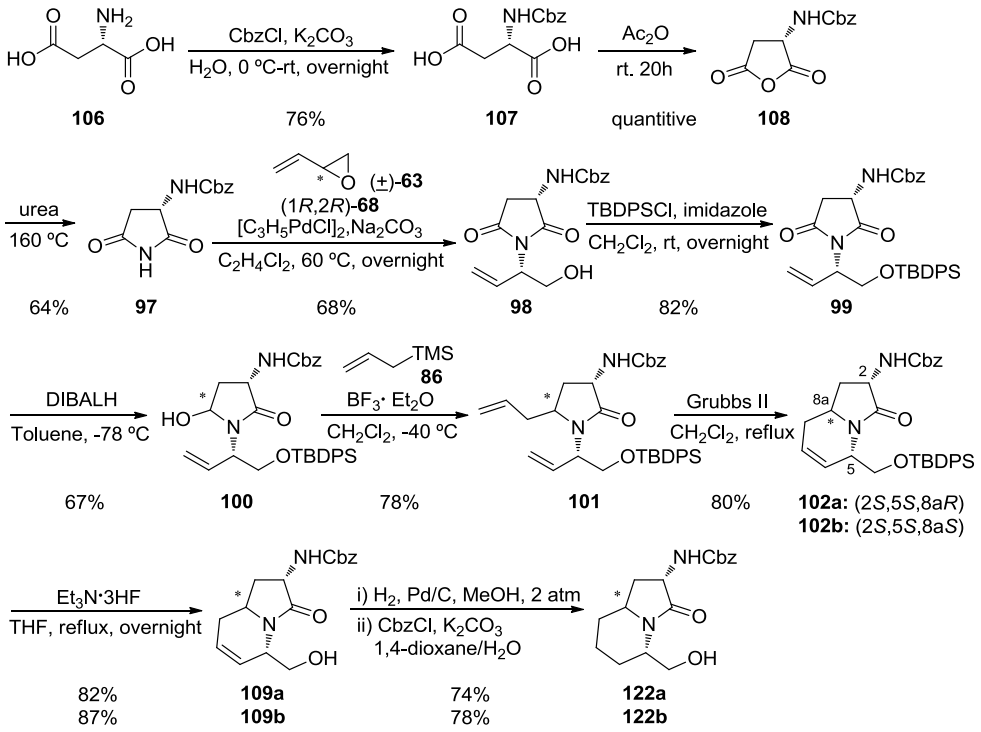
Scheme 56 summarizes the enantioselective preparation of the key targeted indolizidines **80**, *cis*- and *trans*-**88**, and *cis*- and *trans*-**96** and quinolizidines **81**, *cis*-**91** and *cis*-**138**. The first key step of the sequence is the palladium-catalyzed enantioselective allylation of succinimide, **70**, or glutarimide, **71**, with the racemic epoxide (±)-**63**, where the absolute configuration of the sterogenic center $C_{1'}$ of the allyl derivatives **72** and **73** was controlled by the sense of chirality of the palladium ligand. The optical purity can be improved by crystallization in isopropanol of the corresponding silyl ethers. After regioselective reduction and then nucleophilic allylation, the fused bicyclic skeleton was formed through a RCM reaction. In the event, the 5,6-membered bicycle **80** was obtained as a balanced mixture of two epimers, while the 6,6-membered bicycle **81** was formed as an almost exclusive isomer. The configuration of *cis*-**88** and *cis*-**91** was established by X-ray diffraction analysis.



Scheme 56. Enantioselective synthesis of the key targeted indolizidines and quinolizidines

[a] n=1: $BF_3 \cdot Et_2O$, CH_3CN, -40 °C; n=2: TMSOTf, CH_2Cl_2, -78 °C; [b] for two steps

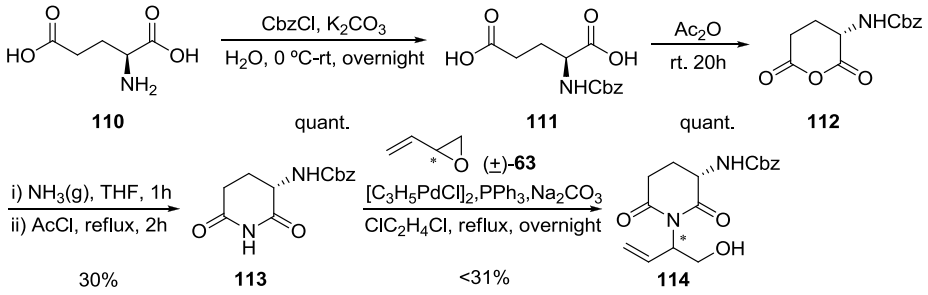
The α-carbonyl amination *en route* to the designed dipeptides was attempted on **81** as the substrate and, unfortunately, despite the many trials, this reaction meat with failure. Therefore, the initial strategy was modified and an amino-substituted substrate of the chiral pool was used as the starting material for the synthesis. The new sequence for the indolizidine derivatives starts from L-aspartic acid, **106**, which is converted in a few steps into the protected α-aminoimide **97** (Scheme 57). The asymmetric allylation of **97** controls the absolute configuration of the sterogenic center $C_{1'}$, which provide the olefin **97** as a unique stereoisomer. A key step of this sequence is the DIBAL-H regioselective reduction of **99**. The subsequent nucleophilic allylation and RCM furnished a balanced mixture of two epimers **102a** and **102b**, which can also provide the saturated analogs **122a** and **122b**. The constitution, relative and absolute configuration of these compounds was inferred from NMR experiments, including COSY and NOESY spectra. The study on the oxidation of **122a** and **122b** to furnish the corresponding acids is currently in progress.



Scheme 57. Alternative sequence for the preparation of the targeted α-aminoindolizidines

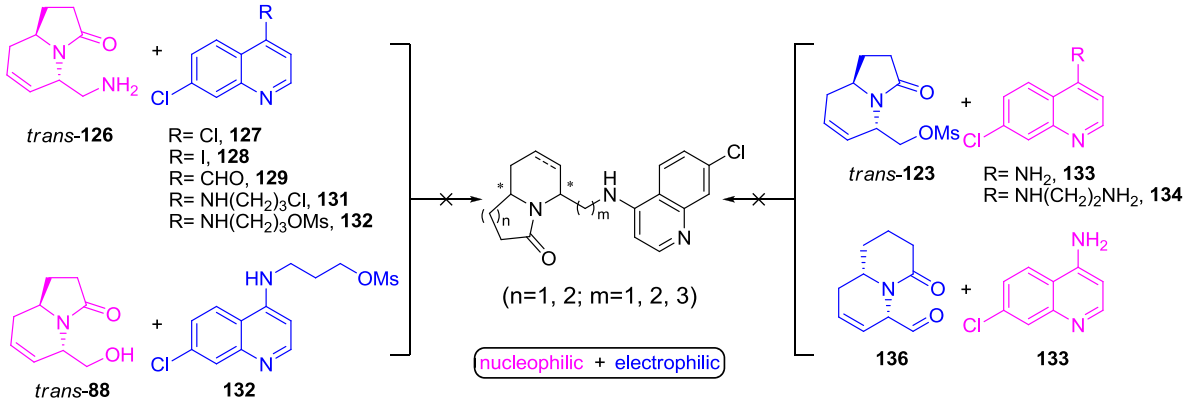
For the α-aminoquinolizidine analogs, a parallel sequence starting from L-glutamic acid **110** was explored (Scheme 58). Unfortunately, using the same palladium ligand

(1*R*,2*R*)-**68** that worked efficiently before, the asymmetric allylation of **113** did not evolve and with PPh_3 as the ligand the expected olefin **114** was produced in poor yield. Several attempts with a different nitrogen protection were also negative. This strategy will be re-examined in the future.



Scheme 58. Preparation of the α-aminoquinolizidine **114**

For the synthesis of chloroquine analogs incorporating an enantiopure indolizidine or quinolizidine fragment, Scheme 59 shows the two general approaches considered, depending on the nucleophilic or electrophilic character of each reaction partner. Unluckily, in the different reactions explored up to now, the expected conjugate was never detected. Apparently, a main general reason for that is the limited stability displayed by the azabicyclic reagents under the required reaction conditions. This part of the research will be continued in the future.



Scheme 59. Alternative approaches to chloroquine analogs incorporating an azabicyclic moiety

V. Experimental Part

5.1. GENERAL COMMENTS

5.1.1. Spectroscopy

Nuclear magnetic resonance spectra were recorded on the NMR Service of the *Universitat Autònoma de Barcelona*. All ^{1}H NMR (250MHz) and ^{13}C NMR (63MHz) spectra were recorded on a Bruker Avance DXP (250MHz) FT NMR spectrometer. All ^{1}H NMR (360MHz) and ^{13}C NMR (90MHz) spectra were recorded on a Bruker Avance (360MHz) FT NMR spectrometer. All ^{1}H NMR (400MHz) and ^{13}C NMR (101MHz) spectra were recorded on a Bruker Avance (400MHz) FT NMR spectrometer. All the spectra have been recorded at a temperature of 298 K without special instruction. Chemical shifts are given in ppm relative to the residual solvent peak ($CDCl_3$: 7.26 for ^{1}H, 77.16 for ^{13}C; DMSO-d_6: 2.50 for ^{1}H, 39.52 for ^{13}C; Acetone-d_6: 2.05 for ^{1}H, 29.84 for ^{13}C). NMR signals were assigned with the help of COSY, DEPT 135 and NOESY experiments. The following abbreviations were used for ^{1}H NMR to indicate the signal multiplicity: s (singlet) , bs (broad singlet) , d (doublet) , bd (broad doublet) , t (triplet), dd (doublet of doublets) , ddd (double double doublet) , dt (double triplet) , ddt (double double triplet), dtd (double triple doublet), m (multiplet) and J to indicate the coupling constants.

Infrared spectra (IR) were acquired by a Tensor 27 Brucker Infrared spectrometer equipped with a MKII Golden Gate diamond ATR unit in single reflectance.

High resolution mass spectrometry (HRMS) experiments were performed by the Chemical Analysis Service of *Universitat Autònoma de Barcelona* on a Bruker microTOF-Q II instrument.

5.1.2. Chromatography

Thin-layer chromatography (TLC) analyses were carried out with Alugram® Sil G/UV_{254} (*0.25 mm thick*) under 254nm UV light and /or deceloped with a $KMnO_4$/NaOH solution.

Flash column chromatography was performed using 230-400 mesh silica with the indicated solvent system according to specific procedures.

Analyses of chiral high performance liquid chromatography (CHPLC) were performed using a Watters 2690 instrument with the Watters 2487 Detector. The analytical chiral column was Daicel Chiralcel OD (25 x 0.46 cm) which is filled with silica-cellulose attached to 3,5-dimethylphenylcarbamate.

5.1.3. Specific Rotation

Specific rotations $[\alpha]_D$ were calculated from the results which were measured with the Propol Automatic Polarimeter Dr. Kermchen, using a 0.05 dm path length quartz cuvette. The concentration and solvent used are indicated in each case.

5.1.4. Melting point

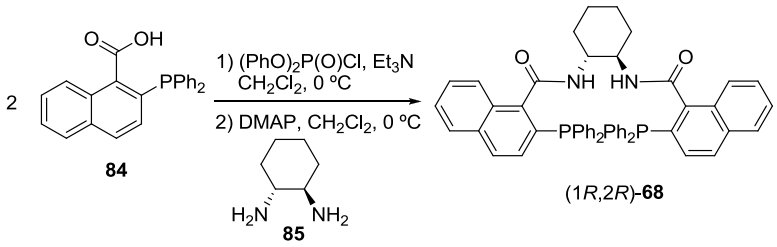
Melting points (Mp) were determined on a REICHERT Koffler hot stage melting point apparatus, and are uncorrected.

5.1.5. Reagents and Solvents

All reagents were purchased from Acros, Alfa Aesar or Sigma-Aldrich and used without further purification. Anhydrous solvents were used when necessary and it is indicated in the procedures. All they were obtained according to the standard methods of drying processes.

5.2. PREPARATION OF DIPEPTIDO AMINO ACIDS

5.2.1.(1*R*,2*R*)-Diamino-1*N*,2*N*-bis(2'-diphenylphosphino-1'-naphthoyl)cyclohexane, (1*R*,2*R*)-68[84]



In a 100 mL Schlenk flask equipped with magnetic stirring, under nitrogen atmosphere, 1.01 g (2.81 mmol) of 2-diphenylphosphino-1-naphthoic acid, **84**, was dissolved in 23 mL of anhydrous CH_2Cl_2. After cooling the solution down to 0 °C, 1.29 mL (9.27 mmol) of Et_3N were added, followed by the dropwise addition of 0.64 mL (3.09 mmol) of diphenyl chlorophosphate over 5 min.

On the other hand, in a 25 mL Schlenk flask equipped with magnetic stirring and nitrogen atmosphere, 161 mg (1.41 mmol) of (1*R*,2*R*)-cyclohexane-1,2-diamine, **85**, were dissolved in 6 mL of anhydrous CH_2Cl_2 at room temperature and, then, 16.7 mg (0.14 mmol) of DMAP were added to the solution.

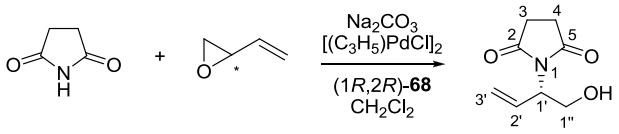
After warming the first solution of **84** to room temperature over 5 h, it was transferred via cannula to the solution of diamine **85**. Afterwards, the mixture was stirred at room temperature for 12 h.

The reaction mixture was then diluted with 27 mL of CH_2Cl_2 and washed with 27 mL of saturated $NaHCO_3$ aqueous solution. The organic phase was dried over anhydrous Na_2SO_4 and then evaporated in vacuum. The crude product was purified by flash column chromatography (gradient, hexane:ethyl acetate, from 9:1 to 3:1), furnishing 872 mg (1.04 mmol, 74% yield) of the ligand (1*R*,2*R*)-**68** as a yellow solid.

$\boldsymbol{R_f}$ = 0.6 (hexane:ethyl acetate, 1:1)

^{1}H NMR (250 MHz, $CDCl_3$): δ 7.87 (d, J = 8.7 Hz, 2H), 7.73 (dd, J'=9.5 Hz, J''=6.0 Hz, 4H), 7.30 (m, 22H), 7.07 (m, 4H), 6.54 (m, 2H), 3.84 (m, 2H), 2.37 (m, 2H), 1.73 (m, 3H), 1.60 (m, 3H)

5.2.2. 1-[(1'*S*)-1'-(Hydroxymethyl)-2'-propenyl]-2,5-pyrrolidinedione, (*S*)-72[86]



70 (±)-**63** (*S*)-**72**

In a 100 mL Schlenk flask equipped with magnetic stirring, under nitrogen atmosphere, a mixture of 11.8 mg (0.03 mmol) of π-allylpalladium chloride dimer, 81 mg (0.10 mmol) of (1*R*,2*R*)-**68**, 43 mg (0.40 mmol) of sodium carbonate and 797 mg (8.05 mmol) of succinimide, **70**, was purged with nitrogen for 1 h. After addition of 100 mL of dichloromethane, the resulting mixture was stirred 10 min at room temperature and, then, butadiene monoepoxide **63** (0.64 mL, 8.00 mmol) was added. The resulting mixture was stirred at room temperature under nitrogen for 14 h.

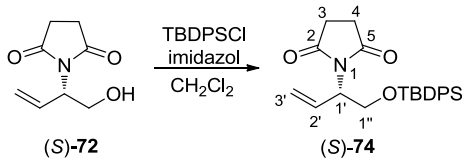
Then the reaction mixture was filtered through Celite, washed with ethyl acetate, and concentrated in vacuum. The residue was purified by flash column chromatography (gradient, hexane:ethyl acetate, from 5:1 to 2:1) to give 1.14g (6.76 mmol, 84% yield) of (*S*)-**72** as a clear oil in 83% enantiomeric excess (determined by CHPLC analysis, ^{i}PrOH:hexane 10:90).

$\boldsymbol{R_f}$ = 0.3 (ethyl acetate)

$[\alpha]_D^{20}$ = -32.8 (c 1.90, CH_2Cl_2)

^{1}H NMR (250 MHz, $CDCl_3$): δ 6.07 (ddd, J=18.2 Hz, J'=10.7 Hz, J''=7.2 Hz, 1H:$1H_{2'}$), 5.25 (m, 2H:$2H_{3'}$), 4.75 (m, 1H:$1H_{1'}$), 4.05 (dd, J=11.6 Hz, J'=8.1 Hz, 1H:$1H_{1''}$), 3.81 (dd, J=11.6 Hz, J'=4.4 Hz , 1H:$1H_{1''}$), 2.73 (s, 4H:$2H_3$+$2H_4$)

5.2.3. 1-{(1'*S*)-1'–[(*tert*-Butyldiphenylsilyloxy)methyl]-2'-propenyl}-2,5-pyrrolidine-dione, (*S*)-74[86]



In a 250 mL Schlenk flask equipped with magnetic stirring, under nitrogen atmosphere, 1.35 g (7.98 mmol) of alcohol (*S*)-**72** was dissolved in 60 mL of anhydrous CH_2Cl_2. After cooling to 0°C in an ice/water bath, 2.72 g (39.90 mmol) of imidazole were added, followed by 4.1 mL (15.96 mmol) of TBDPSCl. The cooling bath was removed and the mixture was stirred at room temperature overnight.

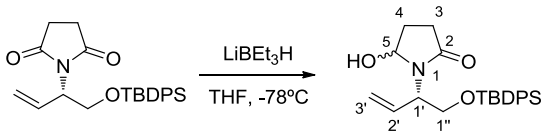
The reaction mixture was then concentrated under vacuum and the residue dissolved in 50 mL of ethyl acetate. After vigorous stirring for 1h, the mixture was filtered through Celite®, washing with ethyl acetate. The overall filtrate was concentrated under vacuum and then purified by flash column chromatography (gradient, hexane:ethyl acetate, from 9:1 to 3:2) to give 2.18g (5.35 mmol, 67% yield) of (*S*)-**74** as white solid, which was crystallized from 2-propanol.

$\boldsymbol{R_f}$ = 0.6 (hexane:ethyl acetate, 1:1)

$\boldsymbol{[\alpha]_D^{20}}$ = 14.4 (c 1.30, CH_2Cl_2)

^{1}H NMR (250 MHz, $CDCl_3$): δ 7.65 (m, 4H:4H_{Ph}), 7.38 (m, 6H:6H_{Ph}), 6.05 (ddd, J=17,9 Hz, J'=10.3 Hz, J''=7.6 Hz, 1H:1$H_{2'}$), 5.16 (m, 2H:2$H_{3'}$), 4.88 (m, 1H:1$H_{1'}$), 4.25 (t, J=10.0 Hz, 1H:1$H_{1''}$), 3.79 (dd, J=10.1 Hz, J'=5.8 Hz, 1H:1$H_{1''}$), 2.57 (s, 4H:2H_3 + 2H_4), 1.00 (s, 9H:9H_{Me})

5.2.4. (5*SR*)-5-Hydroxyl-1-{(1'*S*)-1'–[(*tert*-butyldiphenylsilyloxy)methyl]-2'-propenyl}- 2-pyrrolidinedione, (1'*S*)-76[86]



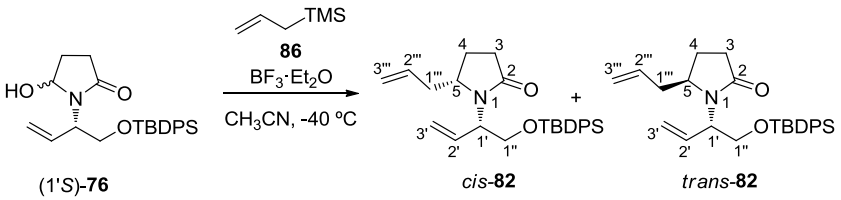
(*S*)-**74** (1'*S*)-**76**

In a 100 mL Schlenk flask equipped with magnetic stirring and nitrogen atmosphere, 1.99 g (4.88 mmol) of (*S*)-**74** were dissolved in 25 mL of anhydrous THF. After cooling down to -78 °C, 7.3 mL (7.32 mmol) of $LiBEt_3H$ (1M in THF) were added dropwise. The reaction was monitored by TLC (hexane:ethyl acetate, 1:1) and it was finished in 45 min. After that time, 40 mL of $NaHCO_3$ saturated solution and 10 mL of 30% H_2O_2 were added at -78 °C, and then the mixture was allowed to warm up to room temperature. It was filtered through Celite® and extracted with CH_2Cl_2 (4 x 30 mL). The organic layers were combined and dried over anhydrous Na_2SO_4, followed by concentration and purification by column chromatography (gradient, hexane:ethyl acetate, from 4:1 to 1:1) that gave 1.46 g (3.56 mmol, 73% yield) of (1'*S*)-**76** (diastereoisomeric mixture) as a colorless oil.

$\boldsymbol{R_f}$ = 0.6 (hexane:ethyl acetate, 1:1)

^{1}H NMR (400 MHz, $CDCl_3$): Isomer A (major) and B (minor); δ 7.62 (m, 4H: $4H_{Ph}$), 7.37 (m, 6H: $6H_{Ph}$), 6.06 (ddd, J=17.5 Hz, J'=10.3 Hz, J''=7.2 Hz, 1H: $1H_{2'}^{B}$), 5.81 (ddd, J=17.4 Hz, J'=10.7 Hz, J''=6.2 Hz, 1H: $1H_{2'}^{A}$), 5.36 (m, 1H: $1H_5$), 5.12 (m, 2H: $2H_{3'}$), 4.94 (d, J=5.6Hz, 1H: $1H_{OH}^{A}$), 4.67 (m, 1H: $1H_{1'}^{A}$), 4.45 (m, 1H: $1H_{1'}^{B}$), 4.39 (d, J=6.1 Hz, 1H: H_{OH}^{B}), 3.83 (m, 2H: $2H_{1''}$), 2.65 (dt, J=17.0 Hz, J''=9.2 Hz, 1H: $1H_4^{A}$), 2.57 (m, 1H: $1H_4^{B}$), 2.32-1.95 (m, 3H: $1H_4$ +$2H_3$), 1.04 (s, $9H_{Me}^{A}$), 1.02 (s, $9H_{Me}^{B}$)

5.2.5. (5*S*)- and (5*R*)-5-Allyl-1-{(1'*S*)-1'–[(*tert*-butyldiphenylsilyloxy)methyl]-2'-propenyl}-2-pyrrolidinedione, 82



In a 250 mL Schlenk flask equipped with magnetic stirring and nitrogen atmosphere, a solution of 982 mg (2.40 mmol) of (1'*S*)-**76** in 50 mL of anhydrous CH_3CN was cooled down to -40℃. To the cold solution were added 420 µL (2.64 mmol) of **86** and, then, 610 µL (4.80 mmol) of $BF_3 \cdot Et_2O$ dropwise. The reaction, monitored by TLC (hexane:EtOAc, 1:1), was finished in 1 h.

After that time, 100 mL of $NaHCO_3$ saturated solution were added, and then the mixture was allowed to warm up to room temperature. After the extraction with CH_2Cl_2 (4 x 50 mL), the organic layers were dried over anhydrous Na_2SO_4 and concentrated under vacuum.

The residue was purified by flash column chromatography (gradient, hexane:EtOAc, from 4:1 to 1:2) to give 832 mg (1.92 mmol, 80% yield) of **82** (*cis*:*trans*, 1:1.1 mixture of diastereoisomers) as a yellow oil.

$\boldsymbol{R_f}$ = 0.6 (hexane:EtOAc, 1:1)

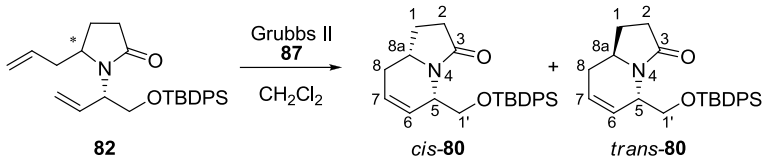
IR (ATR): 3073, 2932, 2858, 1687, 1428, 1259, 1110 cm^{-1}

^{1}H NMR (400 MHz, $CDCl_3$): Isomer A (*trans*-**82**) and B (*cis*-**82**); δ 7.67 (m, 4H: $4H_{Ph}$), 7.40 (m, 6H: $6H_{Ph}$), 6.11 (ddd, J=17.4 Hz, J'=10.5 Hz, J''=7.1 Hz, 1H: $1H_{2'}{}^{B}$), 5.90 (ddd, J=17.1 Hz, J'=10.5 Hz, J''=6.6 Hz, 1H: $1H_{2'}{}^{A}$), 5.66 (m, 1H: $1H_{2'''}$), 5.12 (m, 4H: $2H_{3'}$ + $2H_{3'''}$), 4.55 (m, 1H: $1H_{1'}{}^{A}$), 4.21 (dd, J=8.4 Hz, J'=10.2 Hz, 1H: $1H_{1''}{}^{B}$), 4.08 (m, 1H: $1H_{1'}{}^{B}$), 3.97 (dd, J=6.0 Hz, J'=2.7 Hz, 2H: $2H_{1''}{}^{A}$), 3.75 (m, 2H: $1H_5$+ $1H_{1''}{}^{B}$), 2.49-1.98 (m, 5H: $2H_3$ + $2H_{1'''}$+ H_4), 1.75 (m, 1H: $1H_4$), 1.07 (s, $9H_{Me}{}^{B}$), 1.06 (s, $9H_{Me}{}^{A}$)

^{13}C NMR (100 MHz, $CDCl_3$): δ 175.6 (C_2), 175.0 (C_2), 135.5 (C_{Ph}), 134.4 ($C_{2'}$), 133.5 ($C_{2'}$), 133.4 ($C_{2'''}$), 133.2 ($C_{2'''}$), 129.7 (C_{Ph}), 127.7 (C_{Ph}), 127.6 (C_{Ph}), 118.4 ($C_{3'}$ or $C_{3'''}$), 118.2 ($C_{3'}$ or $C_{3'''}$), 118.0 ($C_{3'}$ or $C_{3'''}$), 117.6 ($C_{3'}$ or $C_{3'''}$), 63.7 ($C_{1''}$), 62.9 ($C_{1''}$), 59.5 (C_5), 59.3 (C_5), 57.0 ($C_{1'}$), 39.4 (C_4 or C_3 or $C_{1'''}$), 38.7 (C_4 or C_3 or $C_{1'''}$), 30.4 (C_4 or C_3 or $C_{1'''}$), 30.1 (C_4 or C_3 or $C_{1'''}$), 26.8 ($C(\underline{C}H_3)_3$), 26.7 ($C(\underline{C}H_3)_3$), 23.9 (C_4 or C_3 or $C_{1'''}$), 23.8 (C_4 or C_3 or $C_{1'''}$), 19.1 ($\underline{C}(CH_3)_3$)

HRMS m/z (ESI+) Calculated for [$C_{27}H_{34}NO_2Si$+Na]: 456.2329; Experimental: 456.2326.

5.2.6. (5*S*,8a*S*)- and (5*S*,8a*R*)-5-[(*tert*-Butyldiphenylsilyloxy)methyl]-1,2,8,8a-tetrahydroindolizine-3-(5*H*)-one, 80



In a 250 mL Schlenk flask, equipped with magnetic stirring and nitrogen atmosphere, a solution of 654 mg (1.51 mmol) of **82** in 150 mL of anhydrous CH_2Cl_2 was warmed up to reflux and, then, 65 mg (0.075 mmol) of 2nd generation Grubbs catalyst **87** were added in 3 portions (one per hour). The mixture was heated under reflux while stirring overnight.

After cooling down to room temperature, the resulting mixture was filtered through silica gel and washed with EtOAc. The residue was concentrated under vacuum and then purified by flash column chromatography (gradient, hexane:EtOAc, from 3:2 to 1:9) to give 563 mg (1.39 mmol, 92% yield) of **80** (*cis*:*trans*, 1:1.2).

$\boldsymbol{R_f}$ = 0.3 (hexane:EtOAc, 1:1)

IR (ATR): 2929, 2855, 1686, 1426, 1263, 1108 cm^{-1}

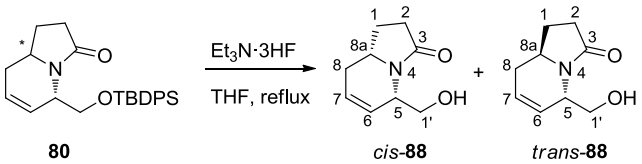
^{1}H NMR (400 MHz, C_6D_6): Isomer A (*trans*-**80**) and B (*cis*-**80**); δ 7.80 (m, 4H: $4H_{Ph}{}^{B}$), 7.74 (m, 4H: $4H_{Ph}{}^{A}$), 7.32 (m, 12H: $12H_{Ph}$), 5.77 (m, 1H: $1H_6{}^{B}$), 5.65 (m, 1H: $1H_7{}^{B}$), 5.59 (m, 2H: $1H_6{}^{A}$ + $1H_7{}^{A}$), 4.63 (m, 1H: $1H_5{}^{A}$), 4.32 (m, 2H: $2H_{1'}{}^{B}$), 4.12 (m, 1H: $1H_5{}^{B}$), 3.90

(dd, J=9.7 Hz, J'=5.4 Hz, 1H: $1H_{1'}{}^{A}$), 3.71 (dd, J=9.9 Hz, J'=4.3 Hz, 1H: $1H_{1'}{}^{A}$), 3.39 (m, 1H: $1H_{8a}{}^{A}$), 2.86 (m, 1H: $1H_{8a}{}^{B}$), 2.01 (m, 2H: $1H_{2}{}^{A}$ + $1H_{2}{}^{B}$), 1.91-1.25 (m, 8H: $1H_{2}{}^{B}$+ $1H_{1}{}^{A}$+ $2H_{8}{}^{A}$+ $2H_{8}{}^{B}$+ $1H_{1}{}^{A}$+ $1H_{1}{}^{B}$), 1.17 (s, $9H_{Me}{}^{B}$), 1.14 (s, $9H_{Me}{}^{A}$), 0.96 (m, 1H: $1H_{1}$)

^{13}C NMR (101 MHz, C_6D_6): Isomer A (*trans*-**80**) and B (*cis*-**80**); δ 174.8 ($C_3{}^{B}$), 172.9 ($C_3{}^{A}$), 136.1 (C_{Ph}), 136.0 (C_{Ph}), 134.2 (C_{Ph}), 134.0 (C_{Ph}), 133.8 (C_{Ph}), 130.1 (C_{Ph}), 130.0 ($C_6{}^{B}$ or $C_7{}^{B}$), 127.0 ($C_6{}^{A}$ or $C_7{}^{A}$), 126.5 ($C_6{}^{A}$ or $C_7{}^{A}$), 125.6 ($C_6{}^{B}$ or $C_7{}^{B}$), 65.3 ($C_{1'}{}^{A}$), 64.3 ($C_{1'}{}^{B}$), 54.9 ($C_5{}^{B}$), 54.7 ($C_{8a}{}^{B}$), 51.9 ($C_5{}^{A}$), 51.4 ($C_{8a}{}^{A}$), 32.3 ($C_8{}^{B}$ or $C_8{}^{A}$), 32.2 ($C_8{}^{B}$ or $C_8{}^{A}$), 31.0 ($C_2{}^{B}$ or $C_2{}^{A}$), 29.8 ($C_2{}^{B}$ or $C_2{}^{A}$), 27.2 ($C(\underline{C}H_3)_3$), 27.1 ($C(\underline{C}H_3)_3$), 27.0 ($C_1{}^{B}$), 25.3 ($C_1{}^{A}$), 19.7 ($\underline{C}(CH_3)_3$), 19.6 ($\underline{C}(CH_3)_3$)

HRMS m/z (ESI+) Calculated for [$C_{25}H_{31}NO_2Si$+Na]: 428.2016; Experimental: 428.2015.

5.2.7. (5*S*,8a*S*)- and (5*S*,8a*R*)-5-(Hydroxymethyl)-1,2,8,8a-tetrahydroindolizine-3-(5*H*)-one, 88



80 *cis*-**88** *trans*-**88**

In a 250 mL Schlenk flask, equipped with magnetic stirring and nitrogen atmosphere, a solution of 360 mg (0.89 mmol) of a mixture of diastereoisomers **80** in 15 mL of anhydrous THF was heated to reflux, followed by the addition of $Et_3N{\cdot}3HF$, 0.87 mL (5.34 mmol). The mixture was stirred under reflux overnight.

The resulting cold mixture was diluted with 10 mL of CH_2Cl_2 and 10 mL of $NaHCO_3$ saturated solution, the layers were separated and the aqueous one extracted with CH_2Cl_2 (4 x 20 mL). The combined organic extracts were dried over anhydrous Na_2SO_4, concentrated under vacuum and then purified by flash column chromatography (gradient, hexane:EtOAc, from 1:1 to EtOAc and then chloroform:methanol, 9:1) to give 51 mg (0.31 mmol, 34% yield) of (+)-(5*S*,8a*S*)-**88**, which was less polar, and 63 mg (0.38 mmol, 42% yield) of (-)-(5*S*,8a*R*)-**88**, which was more polar.

Physical and spectroscopic data of (+)-(5*S*,8a*S*)-**88**

$\boldsymbol{R_f}$ = 0.2 (EtOAc)

IR (ATR): 3352, 3050, 2930, 2857, 1700, 1669, 1648, 1417, 1268, 1105 cm^{-1}

$\boldsymbol{[\alpha]_D^{20}}$ = 62.3 (c 1.35, CH_2Cl_2)

^{1}H NMR (360 MHz, C_6D_6): δ 6.50 (m, 1H:1H_{OH}), 5.32 (ddt, J=10.4 Hz, J''=6.4 Hz, J'''=2.1 Hz, 1H:1H_6), 5.08 (m, 1H:1H_7), 4.00 (m, 1H:1H_5), 3.80 (m, 2H:2$H_{1'}$), 2.71 (m, 1H:1H_{8a}), 1.94 (ddd, J=10.3 Hz, J'=6.0 Hz, J''=2.0 Hz 1H:1H_8), 1.77 (m, 1H:1H_8), 1.50-1.23 (m, 2H:1H_1 + 2H_2), 0,80 (m, 1H:1H_1)

^{13}C NMR (90 MHz, C_6D_6): δ 177.5 (C_3), 126.6 (C_7), 125.9 (C_6), 67.7 ($C_{1'}$), 60.2 (C_5), 56.3 (C_{8a}), 32.7 (C_2), 31.2 (C_8), 26.7 (C_1)

Physical and spectroscopic data of (-)-(5*S*,8aR)-**88**

$\boldsymbol{R_f}$ = 0.1 (EtOAc)

IR (ATR): 3355, 2926, 1662, 1644, 1423, 1265, 1079 cm^{-1}

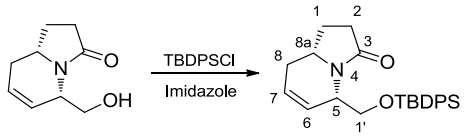
$\boldsymbol{[\alpha]_D^{20}}$ = -211.4 (c 1.20, CH_2Cl_2)

^{1}H NMR (360 MHz, C_6D_6): δ 5.42 (m, 1H:1H_6), 5.36 (dt, J=10.4 Hz, J''=2.6 Hz, 1H: 1H_7), 4.59 (m, 1H: 1H_5), 3.70 (m, 2H: 1$H_{1'}$ + 1H_{OH}), 3.58 (m, 1H: 1$H_{1'}$), 3.17 (m, 1H: 1H_{8a}), 1.98 (m, 2H: 2H_2), 1.53 (m, 2H: 1H_1 + 1H_8), 1.31 (m, 1H: 1H_8), 0.87 (m, 1H: 1H_1)

^{13}C NMR (90 MHz, C_6D_6): δ 175.8 (C_3), 126.2 (C_6 or C_7), 125.7 (C_6 or C_7), 66.1 ($C_{1'}$), 54.0 (C_5), 51.4 (C_{8a}), 32.8 (C_8), 30.5 (C_2), 25.9 (C_1)

HRMS m/z (ESI+) Calculated for [$C_9H_{13}NO_2$+Na]: 190.0838; Experimental: 190.0843.

5.2.8. (-)-(5*S*,8a*S*)-5-[(*tert*-Butyldiphenylsilyloxy)methyl]-1,2,8,8a-tetrahydroindolizine-3-(5*H*)-one, (-)-*cis*-80



(+)-*cis*-**88** (-)-*cis*-**80**

In a 50 mL Schlenk flask, equipped with magnetic stirring and nitrogen atmosphere, 50 mg (0.30 mmol) of alcohol (+)-*cis*-**88** were dissolved in 2 mL of anhydrous CH_2Cl_2. After cooling to 0 ℃ in an ice/water bath, 82 mg (1.20 mmol) of imidazole were added, followed by 0.16 mL (0.6 mmol) of TBDPSCl. The cooling bath was removed and the mixture was stirred at room temperature overnight.

The reaction mixture was concentrated under vacuum and dissolved in 5 mL of EtOAc. After vigorous stirring for 1 h, the mixture was filtered through Celite®, washing with EtOAc. The filtrate was concentrated under vacuum and then purified by flash column chromatography (gradient, from hexane:EtOAc, 1:1 to EtOAc) to give 110 mg (0.27 mmol, 91% yield) of (-)-*cis*-**80**.

R_f = 0.3 (hexane:EtOAc, 1:1)

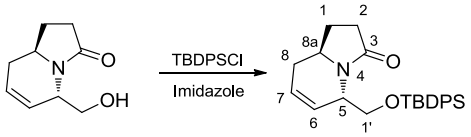
$[\alpha]_D^{20}$ = -63.8 (c 1.45, CH_2Cl_2)

IR (ATR): 3070, 3044, 2929, 2856, 1684, 1421, 1109 cm^{-1}

^{1}H NMR (250 MHz, C_6D_6): δ 7.93 (m, 4H:4H_{Ph}), 7.35 (m, 6H:6H_{Ph}), 5.83 (m, 2H:1H_6 + 1H_7), 4.43 (m, 2H:2$H_{1'}$), 4.24 (m, 1H:1H_5), 2.98 (m, 1H:1H_{8a}), 2.14 (ddt, J=16.7 Hz, J'=9.3 Hz, J''=1.2 Hz, 1H:1H_2), 1.96 (m, 1H:1H_8) 1.84 (m, 2H: 1H_2+1H_8), 1.52 (m, 1H:1H_1), 1.29 (s, 9H:9H_{Me}), 1.12 (m, 1H:1H_1)

^{13}C NMR (101 MHz, C_6D_6): δ 174.3 (C_3), 135.6 (C_{Ph}), 133.7 (C_{Ph}), 129.5 (C_7 or C_6), 125.0 (C_7 or C_6), 63.9 ($C_{1'}$), 54.4 (C_5), 54.2 (C_{8a}), 31.8 (C_8), 30.6 (C_2), 26.7 (C($\underline{C}H_3$)$_3$), 26.5 (C_1), 19.2 ($\underline{C}(CH_3)_3$)

5.2.9. (-)-(5*S*,8a*R*)-5-[(*tert*-Butyldiphenylsilyloxy)methyl]-1,2,8,8a-tetrahydroindolizine-3-(5*H*)-one, (-)-*trans*-80



(-)-*trans*-**88** (-)-*trans*-**80**

In a 10 mL Schlenk flask, equipped with magnetic stirring and nitrogen atmosphere, 50 mg (0.30 mmol) of alcohol (-)-*trans*-**88** were dissolved in 2 mL of anhydrous CH_2Cl_2. After cooling to 0℃ in an ice/water bath, 82 mg (1.20 mmol) of imidazole were added, followed by 0.16 mL (0.6 mmol) of TBDPSCl. The cooling bath was removed and the mixture was stirred at room temperature overnight.

The reaction mixture was concentrated under vacuum and the residue dissolved in 5 mL of EtOAc. After vigorous stirring for 1 h, the mixture was filtered through Celite®, washing with EtOAc. The filtrate was concentrated under vacuum and then purified by flash column chromatography (gradient, hexane:EtOAc, from 1:1 to 100% EtOAc) to give 110 mg (0.27 mmol, 91% yield) of (-)-*trans*-**80**.

$\boldsymbol{R_f}$ = 0.3 (hexane:EtOAc, 1:1)

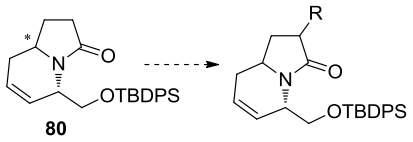
$\boldsymbol{[\alpha]_D^{20}}$ = -161.5 (c 0.94, CH_2Cl_2)

IR (ATR): 3070, 3044, 2929, 2856, 1684, 1421, 1109 cm^{-1}

^{1}H NMR (400 MHz, C_6D_6): δ 7.74 (m, 4H:4H_{Ph}), 7.23 (m, 6H:6H_{Ph}), 5.59 (m, 2H:1H_6 + 1H_7), 4.63 (m, 1H:1H_5), 3.90 (dd, J=9.8 Hz, J'=5.4 Hz, 1H:1$H_{1'}$), 3.71 (dd, J=9.8 Hz, J'=4.3 Hz, 1H:1$H_{1'}$), 3.40 (m, 1H:1H_{8a}), 2.01 (m, 2H:2H_2), 1.75-1.25 (m, 3H:2H_8+1H_1), 1.13 (s, 9H:9H_{Me}), 0.98 (m, 1H:1H_1)

^{13}C NMR (100 MHz, C_6D_6): δ 173.4 (C_3), 136.6 (C_{Ph}), 134.7 (C_{Ph}), 134.4 (C_{Ph}), 130.7 (C_{Ph}), 127.1 (C_7 or C_6), 126.2 (C_7 or C_6), 65.9 ($C_{1'}$), 52.4 (C_5), 52.0 (C_{8a}), 32.8 (C_8), 30.3 (C_2), 27.8 (C($\underline{C}H_3$)$_3$), 25.9 (C_1), 20.1 ($\underline{C}(CH_3)_3$)

5.2.10. Attempted amination of 80



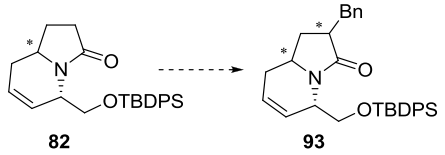
The Table 3 below summarizes the unsuccessful attempts of α-amination of lactam **80**:

Table 3. Attempts and results of α-amination of **80**[a]

Entry	SM	-R	Reagent	T	Time	Result
1	*cis*-**80**	=NOH[92]	*tert*-BuOK, *n*-BuONO	0℃ -rt	1.5h	60% (sm)
2	*trans*-**80**	=NOH	*tert*-BuOK, *n*-BuONO	0℃ -rt	1.5h	90% (sm)
3	*cis*-**80**	$-N_3$[81]	LDA, Trisyl azide	-78℃	0.5-1h	decomposed
4	*cis*-**80**	-NBoc-NHBoc[93]	LDA, DBAD	-78℃ -rt	overnight	complex mixture
5	*trans*-**80**	-NBoc-NHBoc	LDA, DBAD	-78℃ -rt	overnight	25% (sm)

[a] THF was used as solvent in all runs. The results were analyzed by ^{1}H NMR of the crude reaction product

5.2.11. Attempted alkylation of 80



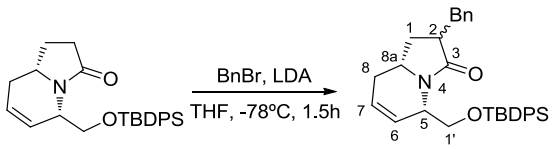
The Table below summarizes the attempts of α-alkylation of lactam **80**:

Table 4. Attempts and results of α-alkylation of **80**[a]

Entry	SM	Reagent	T	Time	Result
1	*cis*-**80**	LDA, Benzyl bromide	-78℃	1.5 h	25% (**93**)
2	*trans*-**80**	LDA, Benzyl bromide	-78℃	1.5 h	>70% (sm)
3	*cis*-**80**	*sec*-BuLi,[94] Benzyl bromide	-78℃	1.5 h	30% (sm)
4	*trans*-**80**	*sec*-BuLi, Benzyl bromide	-78℃	1.5 h	60% (sm)
5	*cis*-**80**	KHMDS,[95] Benzyl bromide	-78℃	>12 h	65% (sm)
6	*trans*-**80**	*tert*-BuOK, Benzyl bromide	rt	1.5 h	85% (sm)

[a] THF was used as solvent in all runs. The results were analyzed by ^{1}H NMR of the crude reaction product

5.2.12. (2*SR*,5*S*,8a*R*)-2-benzylamino-5-[(*tert*-Butyldiphenylsilyloxy)methyl]-1,2,8, 8a-tetrahydroindolizin-3(5*H*)-one, 93



cis-**80** **93**

In a 10 mL Schlenk flask, equipped with magnetic stirring and nitrogen atmosphere, a solution of 17 µL (0.12 mmol) of $^{i}Pr_2N$ in 0.5 mL of anhydrous THF was cooled to -78℃ , followed by the addition of 75 µL (0.12 mmol) of *n*-BuLi. The prepared LDA solution was stirred for 20 min.

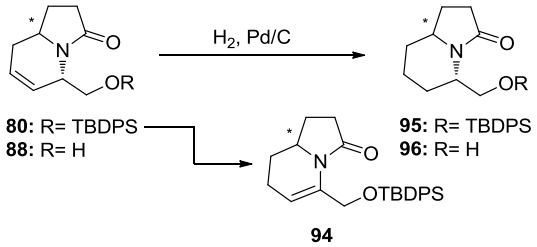
40 mg (0.10 mmol) of *cis*-**80** were dissolved in 0.5 mL anhydrous THF and then transferred into the LDA solution. Followed by the addition of 25 µL (0.10 mmol) of BnBr in 20 min, the resulting mixture was kept at -78℃ for 1.5 h. Then, the solution was quenched with 2 mL NH_4Cl saturated solution, and then allowed to warm up to room temperature. After the extraction with CH_2Cl_2 (3 x 3 mL), the organic layers were dried over anhydrous Na_2SO_4 and concentrated under vacuum. The residue was purified by flash column chromatography (gradient, from hexane to hexane:EtOAc, 5:1) to give 12 mg (0.03 mmol, 25% yield) of **93**.

$\boldsymbol{R_f}$ = 0.8 (EtOAc)

^{1}H NMR (360 MHz, $CDCl_3$): δ 7.67 (m, 4H:4H_{Ph}), 7.41 (m, 6H:6H_{Ph}), 7.26 (m, 5H:5H_{Ph}), 5.95 (m, 1H:1H_6), 5.87 (d, J = 10.2 Hz, 1H:1H_7), 4.24 (dd, J=10.0 Hz, J'=6.7 Hz, 1H:1H_5), 4.15 (m, 2H:2$H_{1'}$), 3.16 (m, 1H:1H_{8a}), 3.03 (m, 1H:1H_{Bn}), 2.76 (m, 2H:1H_2+ 1H_{Bn}), 2.21 (m, 1H:1H_8), 2.00 (m, 2H:1H_8+1H_1), 1.67 (m, 1H:1H_1), 1.07 (s, 9H:9H_{Me})

^{13}C NMR (91 MHz, $CDCl_3$): δ 176.8 (C_3), 139.4 (C_{Ph}), 135.6 (C_{Ph}), 134.8 (C_{Ph}), 129.6 (C_{Ph}), 129.1 (C_{Ph}), 128.4 (C_{Ph}), 127.7 (C_{Ph}), 127.6 (C_{Ph}), 126.4 (C_6 or C_7), 125.7 (C_6 or C_7), 63.4 ($C_{1'}$), 54.3 (C_{8a} or C_5), 53.6 (C_{8a} or C_5), 43.5 (C_2), 36.2 (C_{Bn}), 32.0 (C_8 or C_1), 30.9 (C_8 or C_1), 26.9 (C($\underline{C}H_3$)$_3$), 19.4 ($\underline{C}$(CH_3)$_3$)

5.2.13. Attempted hydrogenation of 80 and 88



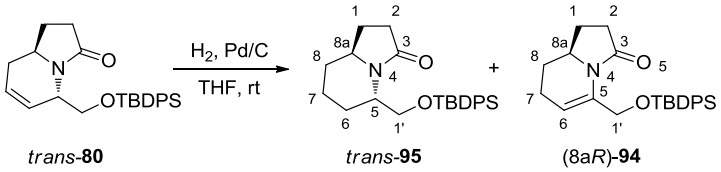
The Table below summarizes the attempts of hydrogenation of lactams **80** and **88**:

Table 5. Attempts and results of hydrogenation of **80**[a]

Entry	sm	Solvent	Time	Result
1	*trans*-**80**	THF	overnight	20%(8aR)-**94** + 50%mix (*trans*-**80**+ *trans*-**95**)
2	*cis*-**80**	THF	overnight	*cis*-**80** : (8a*S*)-**94**[b]**= 10:1**[c]
3	*cis*-**80**	EtOAc	5h	*cis*-**95**[b] : (8a*S*)-**94= 3:1**[c]
4	**94**+ *cis*-**80**	Methanol	overnight	60% *cis*-**96**
5	*cis*-**88**	Methanol	overnight	75% *cis*-**96**
6	*trans*-**88**	Methanol	overnight	89% *trans*-**96**

[a] All attempts were at rt. [b] couldn't be separated successfully and the structure of *cis*-**95** and (8a*S*)-**94** were inferred by comparison with *trans*-**95** and (8a*R*)-**94**. [c] Determined by ^{1}H NMR.

5.2.14. (5*S*,8a*S*)-5-[(*tert*-Butyldiphenylsilyloxy)methyl]hexahydroindolizin-3-(2*H*)-one, *trans*-95



In a 10 mL Schlenk flask equipped with magnetic stirring, 136 mg (0.34 mmol) of *trans*-**80** were dissolved in 5 mL of THF and 15 mg of Pd/C were added at once. The flask was sealed up by a septum and Parafilm® and connected to a balloon filled with H_2. The mixture was stirred at room temperature overnight. After that time, the solution was filtered through Celite®, washing with EtOAc, and concent rated under vacuum. The residue was filtered through short pad of silica gel to give 28 mg (0.07 mmol, 20% yield) of (8a*R*)-**94** and 69 mg of a mixture of *trans*-**80** and *trans*-**95**, which was filtered

through short pad of silica gel again to give an analytical pure sample of *trans*-**95** (11 mg) and 52mg of mixture.

Physical and spectroscopic data of (8a*R*)-**94**

$\boldsymbol{R_f}$ = 0.3 (hexane:EtOAc, 1:1)

$\boldsymbol{[\alpha]_D^{20}}$ = -17.9 (c 1.40, CH_2Cl_2)

IR (ATR): 2928, 2855, 1694, 1657, 1405, 1261, 1111 cm^{-1}

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.71 (m, 4H:4H_{Ph}), 7.41 (m, 6H:6H_{Ph}), 5.43 (s, 1H:1H_6), 4.96 (bd, J=14.9 Hz, 1H:1$H_{1'}$), 4.79 (bd, J=14.9 Hz, 1H:1$H_{1'}$), 3.62 (m, 1H:1H_{8a}), 2.41 (ddd, J=17.0 Hz, J'=11.0 Hz, J''=9.7 Hz, 1H: 1H_2), 2.25 (m, 3H: 1H_2+1H_1+1H_7), 2.04 (bd, J=12.5 Hz, 1H: 1H_7), 1.58 (m, 3H: 1H_1+ 2H_8), 1.09 (s, 9H: 9H_{Me})

^{13}C NMR (101 MHz, $CDCl_3$): δ 172.5 (C_3), 136.9 (C_3), 135.5 (C_{Ph} or C_5), 133.6 (C_{Ph} or C_5), 129.5 (C_{Ph} or C_5), 127.6 (C_{Ph}), 105.9 (C_6), 62.4 ($C_{1'}$), 57.1 (C_{8a}), 31.2 (C_1 or C_2 or C_7 or C_8), 29.9 (C_1 or C_2 or C_7 or C_8), 26.9 (C($\underline{C}H_3$)$_3$), 25.9 (C_1 or C_2 or C_7 or C_8), 22.7 (C_1 or C_2 or C_7 or C_8), 19.3 ($\underline{C}(CH_3)_3$)

Physical and spectroscopic data of *trans*-**95**

$\boldsymbol{R_f}$ = 0.6 (EtOAc)

$\boldsymbol{[\alpha]_D^{20}}$ = -34.1 (c 0.55, CH_2Cl_2)

IR (ATR): 2929, 2855, 1684, 1426, 1109 cm^{-1}

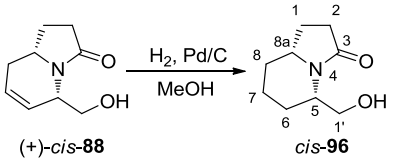
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.66 (m, 4H:4H_{Ph}), 7.43 (m, 6H:6H_{Ph}), 4.39 (m, 1H:1H_5), 3.67 (dd, J=10.4 Hz, J'=6.7 Hz, 2H:2$H_{1'}$), 3.40 (dtd, J=10.9 Hz, J'=7.2 Hz, J''=3.5 Hz, 1H:1H_{8a}), 2.31 (m, 2H:2H_2), 2.10 (m, 1H:1H_1 or 1H_6 or 1H_8), 2.00-1.37 (m, 7H: 1H_1+ 2H_6+2H_7+2H_8), 1.07 (s, 9H:9H_{Me})

^{13}C NMR (101 MHz, $CDCl_3$): δ 173.8 (C_3), 135.6 (C_{Ph}), 135.6 (C_{Ph}), 133.4 (C_{Ph}), 133.2 (C_{Ph}), 129.6 (C_{Ph}), 127.6 (C_{Ph}), 61.7 ($C_{1'}$), 54.2 (C_{8a}), 48.9 (C_5), 33.5 (C_1 or C_2 or C_6 or

C_8), 30.2 (C_1 or C_2 or C_6 or C_8), 26.8 ($C(\underline{C}H_3)_3$), 25.7 (C_1 or C_2 or C_6 or C_8), 24.1 (C_1 or C_2 or C_6 or C_8), 19.2 ($\underline{C}(CH_3)_3$), 19.1 (C_7)

HRMS m/z (ESI+) Calculated for $C_{25}H_{33}NO_2Si$: Experimental:

5.2.15. (5*S*,8a*R*)-5-Hydroxymethyl-1,2,8,8a,7,6-hexahydroindolizine-3-(5*H*)-one, *cis*-96



(+)-*cis*-**88** *cis*-**96**

In a 10 mL Schlenk flask equipped with magnetic stirring, 50 mg (0.30 mmol) of alcohol (+)-*cis*-**88** were dissolved in 2 mL of methanol and 5 mg of palladium on carbon were added at once. The flask was sealed up by a septum and Parafilm® and connected to a balloon filled with H_2. The mixture was stirred at room temperature for 8 h. After that time, the solution was filtered through Celite®, washing with EtOAc, and concentrated under vacuum. The residue was filtered through short pad of silica gel to give 38 mg (0.22 mmol, 75% yield) of *cis*-**96**.

$\boldsymbol{R_f}$ = 0.2 (EtOAc)

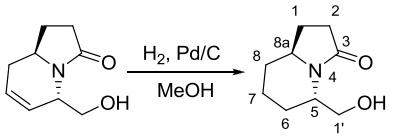
$\boldsymbol{[\alpha]_D^{20}}$ = -7.0 (c 1.40, CH_2Cl_2)

IR (ATR): 3306, 2936, 2859, 1655, 1420, 1267, 1061 cm^{-1}

^{1}H NMR (250 MHz, $CDCl_3$): δ 5.33 (dd, J=8.9 Hz, J'=6.2 Hz, 1H: OH), 3.85 (m, 2H: $2H_{1'}$), 3.44 (m, 1H: $1H_5$), 3.15 (m, 1H: $1H_{8a}$), 2.42 (m, 2H: $2H_2$), 2.22 (m, 1H: $1H_1$ or $1H_6$ or $1H_8$), 2.00-1.22 (m, 7H: $1H_1$+$2H_6$+$2H_7$+$2H_8$)

^{13}C NMR (101 MHz, CDCl3): δ 175.5 (C_3), 63.7 ($C_{1'}$), 60.8 (C_{8a} or C_5), 60.4 (C_{8a} or C_5), 33.1 (C_8 or C_1 or C_2 or C_6), 31.4 (C_8 or C_1 or C_2 or C_6), 27.9 (C_8 or C_1 or C_2 or C_6), 25.1 (C_8 or C_1 or C_2 or C_6), 23.5 (C_7)

5.2.16. (5*S*,8a*S*)-5-Hydroxymethyl-1,2,8,8a,7,6-hexahydroindolizine-3-(5*H*)-one, *trans*-96



(-)-*trans*-**88** *trans*-**96**

In a 10 mL Schlenk flask equipped with magnetic stirring, 20 mg (0.12 mmol) of alcohol (-)-*trans*-**88** was dissolved in 1 mL of methanol and 2 mg of Pd/C were added at once. The flask was sealed up by a septum and Parafilm® and connected to a balloon filled with H_2. The mixture was stirred at room temperature overnight. After that time, the solution was filtered through Celite®, washing with EtOAc, and concentrated under vacuum. The residue was filtered through short pad of silica gel to give 18 mg (0.106 mmol, 89% yield) of *trans*-**96**.

$\boldsymbol{R_f}$ = 0.1 (EtOAc)

$\boldsymbol{[\alpha]_D^{20}}$ = -31.5 (c 1.00, CH_2Cl_2)

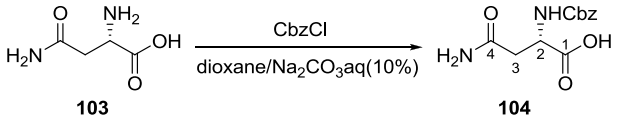
IR (ATR): 3365, 2937, 2854, 1657, 1420, 1265, 1056 cm^{-1}

^{1}H NMR (400 MHz, $CDCl_3$): δ 4.31 (m, 1H: $1H_5$), 3.70 (dd, J=11.0 Hz, J'=9.0 Hz, 1H: $1H_{1'}$), 3.61 (m, 2H: $1H_{1'}$+$1H_{8a}$), 2.76 (bs, 1H: OH), 2.37 (m, 2H: $2H_2$), 2.21 (m, 1H: $1H_1$ or $1H_6$ or $1H_8$), 1.97-1.40 (m, 6H: $1H_1$+$2H_6$+$1H_7$+$2H_8$), 1.15 (m, 1H: $1H_7$)

^{13}C NMR (101 MHz, $CDCl_3$): δ 175.6 (C_3), 61.6 ($C_{1'}$ or C_{8a}), 53.9 ($C_{1'}$ or C_{8a}), 49.9 (C_5), 33.3 (C_8 or C_1 or C_2 or C_6), 30.3 (C_8 or C_1 or C_2 or C_6), 25.8 (C_8 or C_1 or C_2 or C_6), 24.2 (C_8 or C_1 or C_2 or C_6), 19.4 (C_7)

HRMS m/z (ESI+) Calculated for [$C_9H_{15}NO_2$+Na]: 192.0995; Experimental: 192.0996.

5.2.17. *N*-benzyloxycarbonyl-L-asparagine, 104[97]

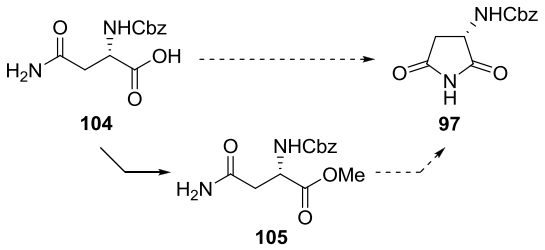


In a 50 mL Schlenk flask equipped with magnetic stirring, 1.32 g L-Asparagine, **103**, (10.00 mmol) was dissolved in a mixture of 15 mL 1,4-dioxane and 25 mL 10% Na_2CO_3 aqueous solution. After cooling down to 0ºC excess of CbzCl (1.71 mL, 12.00 mmol) was added, and then the mixture was warmed up to room temperature and stirred overnight. The solution was poured into 10 mL ice/water solution and then filtered to get **104**, (2.24 g, 8.42 mmol, 84% yield) as white solid.

Mp = 165 ºC; lit [97] mp=164 ºC

^{1}H NMR (400 MHz, DMSO-d_6): δ 7.44 (d, J = 7.7 Hz, 1H: NH), 7.34 (bs, 5H: $5H_{Ph}$), 6.91 (bs, 1H: NH), 5.02 (s, 2H: $2H_{Bn}$), 4.33 (m, 1H: $1H_2$), 2.54 (dd, J=15.5 Hz, J'=5.3 Hz, 1H: $1H_3$), 2.43 (m, 1H: $1H_3$)

5.2.18. Attempted cyclization of 104



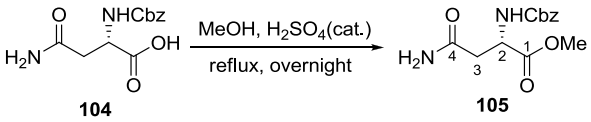
The Table below summarizes the unsuccessful attempts of cyclization of **104**:

Table 6. Attempts and results of cyclization of **104**

Entry	Reagent	Solvent	T	Time	Result
1	K_2CO_3[98]	DMF	rt	overnight	**104**
2[a]	1) Methanol, H_2SO_4 (cat.) 2) TsOH (cat.)[99]	1) Methanol 2) Toluene	reflux	overnight	**105**
3[a]	1) Methanol, H_2SO_4 (cat.) 2) 5% NaOH, 10% HCl[100]	1) Methanol 2) H_2O	1) reflux 2) 0ºC -rt	1) overnight 2) 2 h	**105**
4	DCC[101]	DMF	80ºC	overnight	complex mixture

[a] 1) and 2) refer to consecutive steps.

5.2.19. Methyl-(2*S*)-4-amino-2-{[(benzyloxy)carbonyl]amino}-4-oxobutanoate, 105[99]

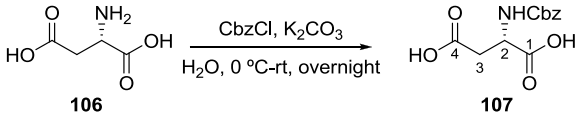


In a 10 mL Schlenk flask equipped with magnetic stirring, 266 mg of **104** (0.50 mmol) was dissolved in 5 mL Methanol. Then, catalytic amount of H_2SO_4 was added and the mixture was warmed up to reflux, which was kept overnight.

After cooling down to rt, 5 mL of $NaHCO_3$ saturated aqueous solution were added. Then, the aqueous phase was extracted with EtOAc (4 x 5 mL), the combined organic layers were dried over anhydrous Na_2SO_4 and concentrated under vacuum to give 283 mg crude ester **105**, which was used in the next step without further purification.

^{1}H NMR (250 MHz, $CDCl_3$): δ 7.37 (s, 5H: $5H_{Ph}$), 5.80 (bd, J = 8.4 Hz, 1H: NH), 5.14 (s, 2H: $2H_{Bn}$), 4.66 (dt, J=9.2 Hz, J'=4.6 Hz, 1H: $1H_2$), 3.70 (s, 3H: H_{Me}), 3.06 (dd, J=17.1 Hz, J'=4.6 Hz, 1H: $1H_3$), 2.87 (dd, J=17.0 Hz, J'=4.6 Hz, 1H: $1H_3$)

5.2.20. (2*S*)-2-{[(Benzyloxy)carbonyl]amino}butanedioic acid, 107[102]

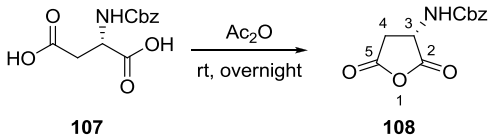


In a 25 mL Schlenk flask equipped with magnetic stirring, 500 mg diacid **106** (3.76 mmol) and 1.04 g K_2CO_3 (7.52 mmol) were dissolved in 10 mL H_2O. After cooling down to 0 ºC, excess of CbzCl (0.75 mL, 5.26 mmol) was added, the mixture was warmed up to room temperature and stirred overnight.

The mixture was washed with Et_2O, the aqueous layer was adjusted with 10% HCl solution to pH=1. Then, it was extracted with EtOAc (4 x 5 mL), the organic layers were combined and dried over anhydrous Na_2SO_4 and concentrated under vacuum to give 760 mg of diacid **107**, which was used in the next step without further purification.

^{1}H NMR (360 MHz, $CDCl_3$) δ 10.11 (bs, 2H: 2OH), 7.28 (m, 5H: $5H_{Ph}$), 6.19 (m, 1H: NH), 5.07 (m, 2H: $2H_{Bn}$), 4.60 (m, 1H: $1H_2$), 2.88 (m, 2H: $2H_3$)

5.2.21. Benzyl-(3S)-2,5-dioxotetrahydro-3-furanylcarbamate, 108[103]

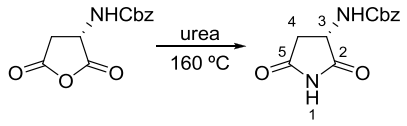


107 **108**

In a 25 mL Schlenk flask equipped with magnetic stirring, **107** (935 mg, 3.76 mmol) were dissolved in 5 mL Ac_2O and stirred at room temperature overnight. Then, it was concentrated under vacuum to give 890 mg of anhydride **108**, which was used in the next step without further purification.

^{1}H NMR (360 MHz, $CDCl_3$): δ 7.33 (m, 5H: $5H_{Ph}$), 6.07 (m, 1H: NH), 5.10 (s, 2H: $2H_{Bn}$), 4.60 (q, J = 8.1 Hz, 1H: $1H_3$), 3.23 (dd, J=18.6 Hz, J'=9.7 Hz, 1H: $1H_4$), 3.08 (dd, J=18.5 Hz, J'=6.9 Hz, 1H: $1H_4$)

5.2.22. (*S*)-Benzyl-(2,5-dioxopyrrolidin-3-yl)carbamate, 97[104]



108 **97**

In a 50 mL Schlenk flask equipped with magnetic stirring, 2.5 g (10.0 mmol) of **108** were warmed up to 160 ºC. Then, 721 mg (12.0 mmol) of urea were added and the mixture was stirred at 160ºC until the foaming ceased.

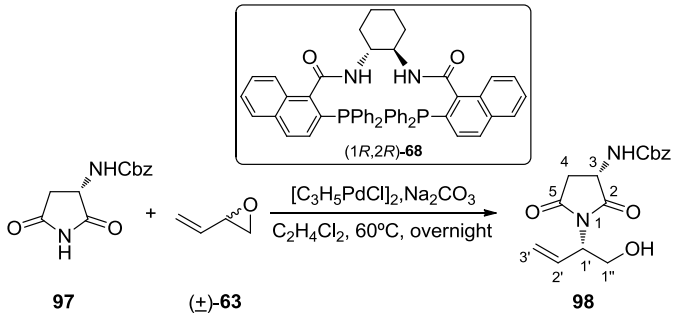
After cooling down to 100ºC, the mixture was diluted with water and left to reach room temperature. Then, it was extracted with $CHCl_3$ (4 x 30 mL), the organic layers were combined and dried over anhydrous Na_2SO_4 and concentrated under vacuum. Purification of the residue by flash column chromatography (gradient, from hexane: EtOAc, 1:1 to EtOAc) furnished 1.59 g (6.41 mmol, 64% yield) of **97** as a white solid.

Mp =105 ºC

$[\alpha]_D^{20}$ = -2.1 (c 1.00, DMF)

^{1}H NMR (250 MHz, $CDCl_3$): δ 8.73 (bs, 1H: NH), 7.29 (s, 5H: $5H_{Ph}$), 6.27 (bs, 1H: NH), 5.05 (s, 2H: $2H_{Bn}$), 4.37 (m, 1H: $1H_3$), 2.82 (m, 2H: $2H_4$)

5.2.23. Benzyl-(3*S*)-1-[(1'*S*)-1'-(hydroxymethyl)-2'-propenyl]-2,5-dioxopyrrolidinyl-carbamate, 98



In a 50 mL Schlenk flask equipped with magnetic stirring, under nitrogen atmosphere, a mixture of 6.4 mg (0.02 mmol) of π-allylpalladium chloride dimer, 44 mg (0.05 mmol) of (1*R*,2*R*)-**68**, 25 mg (0.23 mmol) of sodium carbonate and 720 mg (2.90 mmol) of **97** was purged with nitrogen for 1 h. After addition of 20 mL of CH_2Cl_2, the resulting mixture was stirred 10 min at room temperature, at which point racemic butadiene monoepoxide, **63**, (0.23 mL, 2.90 mmol) was added. The resulting mixture was warmed up to 60ºC and stirred under nitrogen overnight.

Then, the reaction mixture was cooled and filtered through Celite®, washed with EtOAc and concentrated under vacuum. The residue was purified by flash column chromatography (gradient, hexane:EtOAc, from 3:1 to 1:2) to give 627 mg (1.97 mmol, 68% yield) of **98** as a unique diastereoisomer.

R_f = 0.6 (EtOAc)

IR (ATR): 3343, 3058, 2949, 1696, 1518, 1391, 1263, 1196 cm^{-1}

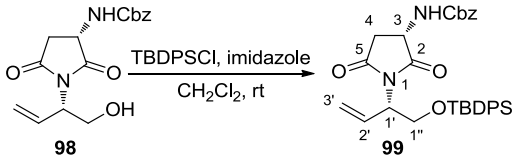
$[\alpha]_D^{20}$ = -13.0 (c 1.55, CH_2Cl_2)

^{1}H NMR (400 MHz, $CDCl_3$, 323K): δ 7.31 (m, 5H: $5H_{Ph}$), 6.03 (m, 2H: $1H_{2'}$+NH), 5.24 (m, 2H: $2H_{3'}$), 5.08 (bs, 2H: $2H_{Bn}$), 4.79 (m, 1H: $1H_3$), 4.29 (m, 1H: $1H_{1'}$), 4.12 (m, 1H: $1H_{1''}$), 3.71 (m, 1H: $1H_{1''}$), 3.21 (m, 1H: OH), 3.01 (m, 1H: $1H_4$), 2.75 (m, 1H: $1H_4$)

^{13}C NMR (101 MHz, $CDCl_3$, 323K)[121]: δ 176.1 (C_5), 176.0 (C_5), 174.5 (C_2), 174.4 (C_2), 156.0 (C_{Cbz}), 135.7 (C_{Ph}), 135.6 (C_{Ph}), 130.9 ($C_{2'}$), 130.8 ($C_{2'}$), 128.5 (C_{Ph}), 128.3 (C_{Ph}), 128.2 (C_{Ph}), 128.0 (C_{Ph}), 119.3 ($C_{3'}$), 67.5 (C_{Bn}), 61.5 ($C_{1''}$), 57.2 ($C_{1'}$), 56.9 ($C_{1'}$), 49.9 (C_3), 49.8 (C_3), 35.6 (C_4)

HRMS m/z (ESI+) Calculated for [$C_{16}H_{18}N_2O_5$]: 318.1216; Experimental: 318.1207.

5.2.24. Benzyl-(3*S*)-1-{(1'*S*)-1'-[*tert*-butyl(diphenyl)silyloxymethyl]-2'-propenyl}2,5-dioxopyrrolidinylcarbamate, 99



In a 100 mL Schlenk flask equipped with magnetic stirring and nitrogen atmosphere, 1.10 g (3.46 mmol) of alcohol **98** were dissolved in 30 mL of anhydrous CH_2Cl_2. After cooling to 0℃ in an ice/water bath, 708 mg (10.40 mmol) of imidazole were added, followed by 1.44 mL (5.54 mmol) of TBDPSCl. The cooling bath was removed and the mixture was stirred at room temperature overnight.

Then, the reaction mixture was concentrated under vacuum and the residue dissolved in 20 mL of EtOAc. After vigorous stirring for 1 h, the solution was filtered through Celite®, washing with EtOAc. The filtrate was concentrated under vacuum and the residue purified by flash column chromatography (gradient, hexane:EtOAc, from 4:1 to 3:2) to give 1.58 g (2.84 mmol, 82% yield) of **99**.

$\boldsymbol{R_f}$ = 0.8 (EtOAc)

IR (ATR): 2929, 2856, 1709, 1510, 1390, 1264, 1111 cm^{-1}

[121] Some of the signals are double, we assume this is due to conformational equilobia on the basis of ^{1}H NMR performed at different temperature.

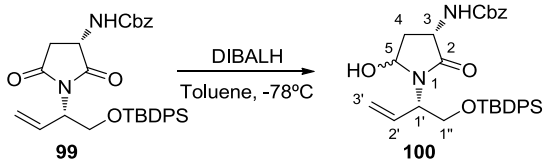
$[\alpha]_D^{20}$ = -0.5 (c 1.80, CH_2Cl_2)

^{1}H NMR (400 MHz, $CDCl_3$, 323K): δ 7. 65 (m, 4H: $4H_{Ph}$), 7.4 (m, 11H: $11H_{Ph}$), 6.02 (m, 1H: $1H_{2'}$), 5.38 (m, 1H: NH), 5.24 (m, 2H: $2H_{3'}$), 5.14 (s, 2H: $2H_{Bn}$), 4.89 (m, 1H: $1H_3$), 4.29 (m, 2H: $1H_{1'}$+$1H_{1''}$), 3.86 (ddd, J=10.4 Hz, J'=5.9 Hz, J''=2.8 Hz, 1H: $1H_{1''}$), 3.06 (m, 1H: $1H_4$), 2.69 (dp, J=15.5 Hz, J'=5.8 Hz, 1H: $1H_4$), 1.05 (s, 9H: $9H_{Me}$)

^{13}C NMR (101 MHz, $CDCl_3$, 323K)[121]: δ 175.1 (C_5), 174.9 (C_5), 173.5 (C_2), 173.4 (C_2), 155.7 (C_{Cbz}), 135.5 (C_{Ph}), 135.4 (C_{Ph}), 133.2 (C_{Ph}), 133.1 (C_{Ph}), 131.0($C_{2'}$), 130.9 ($C_{2'}$), 129.8 (C_{Ph}), 129.7 (C_{Ph}), 128.5 (C_{Ph}), 128.2 (C_{Ph}), 128.0 (C_{Ph}), 127.7 (C_{Ph}), 119.5 ($C_{3'}$), 119.4 ($C_{3'}$), 67.4 (C_{Bn}), 62.0 ($C_{1''}$), 56.7 ($C_{1'}$), 56.6 ($C_{1'}$), 50.1 (C_3), 50.0 (C_3), 36.3 (C_4), 26.7 ($C(\underline{C}H_3)_3$), 19.1 ($\underline{C}(CH_3)_3$)

HRMS m/z (ESI+) Calculated for $[C_{32}H_{36}N_2O_5Si+Na]$:579.2286; Experimental: 579.2286.

5.2.25. Benzyl-(3*S,5SR*)-1-{(1'*S*)-1'-[*tert*-butyl(diphenyl)silyloxymethyl]-2'-propenyl} -2-hydroxy-5-oxopyrrolidinylcarbamate, 100



In a 100 mL Schlenk flask equipped with magnetic stirring and nitrogen atmosphere, 1.42 g (2.55 mmol) of **99** were dissolved in 15 mL of anhydrous toluene. After cooling down to -78 °C, 3.82 mL (3.82 mmol) of a DIBAL-H solution (1M in toluene) was added dropwise. The reaction, monitored by TLC (hexane:EtOAc, 1:1), was finished in 1h.

After that time, 15 mL of a saturated, aqueous solution of potassium sodium tartrate were added at -78 ℃ and the mixture was allowed to warm up to room temperature and kept for 30 min. Then, it was filtered through Celite® and then extracted with CH_2Cl_2 (4 x 25 mL). The organic layers were combined, dried over anhydrous Na_2SO_4, and concentrated under vacuum. Purification of the residue by flash column chromatography

(gradient, hexane:EtOAc, from 4:1 to 1:1) gave 953 mg (1.71 mmol, 67% yield) of **100** as a mixture of epimers.

R_f = 0.5 (hexane:EtOAc, 1:1)

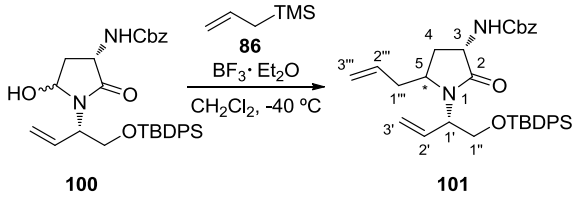
IR (ATR): 3309, 2930, 2856, 1685, 1521, 1427, 1264, 1109 cm^{-1}

^{1}H NMR (250 MHz, $CDCl_3$): Isomer A (major) and B (minor); δ 7.68 (m, 4H: $4H_{Ph}$), 7.42 (m, 11H: $11H_{Ph}$), 6.23 (m, 1H: $1H_{NH}$), 6.00 (m, 1H: $1H_{2''}{}^{A}$+ $1H_{2''}{}^{B}$), 5.20 (m, 6H:$1H_{OH}$+$1H_5{}^{A}$+$1H_5{}^{B}$+$2H_{3''}{}^{A}$+$2H_{3''}{}^{B}$+$2H_{Bn}{}^{A}$+$2H_{Bn}{}^{B}$), 4.57 (m, 1H: $1H_3{}^{A}$+ $1H_3{}^{B}$), 3.97 (m, 3H: $1H_{1'}{}^{A}$+$1H_{1'}{}^{B}$+$2H_{1''}{}^{A}$+$2H_{1''}{}^{B}$), 2.76 (m, 1H: $1H_4{}^{A}$+ $1H_4{}^{B}$), 1.95 (bd, J = 14.4 Hz, 1H: $1H_4{}^{A}$+ $1H_4{}^{B}$), 1.09 (s, 9H: $9H_{Me}{}^{B}$), 1.07 (s, 9H: $9H_{Me}{}^{A}$)

^{13}C NMR (63 MHz, $CDCl_3$)[121]: δ 171.9 (C_2), 156.9 (C_{Cbz}), 156.7 (C_{Cbz}), 136.1 (C_{Ph}), 136.0 (C_{Ph}), 134.6 (C_{Ph}), 130.4 ($C_{2'}$), 129.0 (C_{Ph}), 128.6 (C_{Ph}), 128.5 (C_{Ph}), 128.3 (C_{Ph}), 119.3 ($C_{3'}$), 118.6 ($C_{3'}$), 81.7 (C_5), 81.4 (C_5), 67.6($C_{1''}$), 60.8(C_{Bn}), 58.3 ($C_{1'}$), 57.9 ($C_{1'}$), 51.6 (C_3), 27.3 ($C(\underline{C}H_3)_3$), 27.2 ($C(\underline{C}H_3)_3$), 21.5 (C_4), 19.7 ($\underline{C}(CH_3)_3$), 19.6 ($\underline{C}(CH_3)_3$)

HRMS m/z (ESI+) Calculated for $C_{32}H_{38}N_2O_5Si$: Experimental:

5.2.26. (5*S*)- and (5*R*)-Benzyl-(3*S*)-2-allyl-1-{(1'*S*)-1'-[*tert*-butyl(diphenyl)silyloxy-methyl]-2'-propenyl}-5-oxopyrrolidinylcarbamate, 101



100 **101**

In a 100 mL Schlenk flask equipped with magnetic stirring and nitrogen atmosphere, a solution of 1.30 g (2.33 mmol) of **100** in 30 mL of anhydrous CH_2Cl_2 was cooled down to -40°C, followed by the addition of 0.45 mL (2.80 mmol) of **86**. Then, 0.74 mL (5.82mmol) of $BF_3{\cdot}Et_2O$ were added dropwise. The reaction, monitored by TLC (hexane:EtOAc, 1:1), was finished in 1.5 h.

After that time, 25 mL of $NaHCO_3$ saturated aqueous solution were added and the mixture was allowed to warm up to room temperature. Then, the aqueous phase was extracted with CH_2Cl_2 (4 x 20 mL), the combined organic layers were dried over anhydrous Na_2SO_4 and concentrated under vacuum. The residue was purified by flash column chromatography (gradient, hexane:EtOAc, from 4:1 to 1:1) to give 1.06 g (1.82 mmol, 78% yield) of **101** (mixture of epimers, dr=1:1.6) as a yellow oil.

$\boldsymbol{R_f}$ = 0.8 (hexane:EtOAc, 1:1)

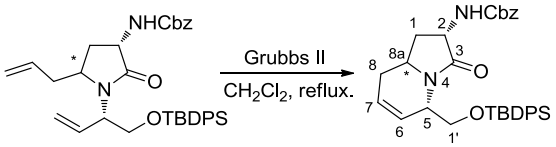
IR (ATR): 2930, 2856, 1686, 1499, 1239, 1109 cm^{-1}

^{1}H NMR (400 MHz, $CDCl_3$): Isomer A (major) and B (minor); δ 7.66 (m, $4H_{Ph}$), 7.40 (m, $11H_{Ph}$), 6.07 (ddd, J=17.4 Hz, J'=10.4 Hz, J''=7.1 Hz, $1H_{2'}{}^{B}$), 5.89 (ddd, J=17.3 Hz, J'=10.5 Hz, J''=6.9 Hz, $1H_{2'}{}^{A}$), 5.67 (m, $1H_{2''}{}^{A}$+ $1H_{2''}{}^{B}$), 5.32 (m, $2H_{3''}{}^{B}$), 5.20 (m, $2H_{3''}{}^{A}$+$2H_{3'''}{}^{A}$+$2H_{3'''}{}^{B}$+$2H_{Bn}{}^{A}$+$2H_{Bn}{}^{B}$), 4.45 (m, H_3+ $H_{1''}{}^{A}$ or $H_{1'}{}^{A}$), 4.07 (m, $2H_{1''}$ or $H_{1''}$ + $H_{1'}$), 3.74 (m, H_5+ $H_{1''}{}^{B}$ or $H_{1'}{}^{B}$), 2.58 (m, 1H: $1H_{1'''}$), 2.38 (m, 1H: $1H_{1'''}$), 2.19 (m, 1H: $1H_4$), 1.93 (m, 1H: $1H_4$), 1.08 (s, 9H: $9H_{Me}{}^{A}$ or $9H_{Me}{}^{B}$), 1.07 (s, 9H: $9H_{Me}{}^{A}$ or $9H_{Me}{}^{B}$)

^{13}C NMR (101 MHz, $CDCl_3$)[121]: δ 172.2 (C_2), 171.7 (C_{Cbz}), 156.4 (C_{Ph}), 136.3 ($C_{2'}$ or $C_{2'''}$), 135.5 ($C_{2'}$ or $C_{2'''}$), 133.4 ($C_{2'}$ or $C_{2'''}$), 133.2 ($C_{2'}$ or $C_{2'''}$), 133.1 (C_{Ph}), 133.0 (C_{Ph}), 132.9 (C_{Ph}), 132.4 (C_{Ph}), 129.9 (C_{Ph}), 129.8 (C_{Ph}), 128.5 (C_{Ph}), 128.0 (C_{Ph}, 127.8 (C_{Ph}), 127.7 (C_{Ph}), 119.1 ($C_{3'}$ or $C_{3'''}$), 118.9 ($C_{3'}$ or $C_{3'''}$), 118.6 ($C_{3'}$ or $C_{3'''}$), 118.4 ($C_{3'}$ or $C_{3'''}$), 66.8 (C_{Bn} or $C_{1''}$), 63.8 (C_{Bn} or $C_{1''}$), 62.7 (C_{Bn} or $C_{1''}$), 57.9 ($C_{1'}$ or C_3 or C_5), 57.3 ($C_{1'}$ or C_3 or C_5), 51.6 ($C_{1'}$ or C_3 or C_5), 51.4 ($C_{1'}$ or C_3 or C_5), 38.5 ($C_{1'''}$), 38.0 ($C_{1'''}$), 33.3 (C_4), 26.8 ($C(\underline{C}H_3)_3$), 26.8 ($C(\underline{C}H_3)_3$), 19.1 ($\underline{C}(CH_3)_3$)

HRMS m/z (ESI+) Calculated for [$C_{35}H_{41}N_2O_4Si$]: 581.2836; Experimental: 581.2852.

5.2.27. (5*S*, 8a*S*)- and (5*S*, 8a*R*)-Benzyl-(2*S*)-5-[*tert*-butyl(diphenyl)silyloxymethyl]-3-oxo-1,2,3,5,8,8a-hexahydro-2-indolizinylcarbamate, 102



101 **102**

In a 250 mL Schlenk flask equipped with magnetic stirring and nitrogen atmosphere, a solution of 700 mg (1.20 mmol) of **101** in 100 mL of anhydrous CH_2Cl_2 was warmed up to reflux, and then 51 mg (0.06 mmol) of the 2nd generation Grubbs catalyst were added in 3 portions (one per hour). The mixture was heated under reflux while stirring overnight.

After cooling down to room temperature, the resulting mixture was filtered through a pad of silica gel, washing with EtOAc. The filtrate was concentrated under vacuum and the residue purified by flash column chromatography (gradient, hexane:EtOAc, from 4:1 to 1:2) to give 246 mg (0.44 mmol, 37% yield) of the minor diastereoisomer **102b** (2*S*,5*S*,8a*S*) and 283 mg (0.51 mmol, 43% yield) of the major diastereoisomer **102a** (2*S*,5*S*,8a*R*).

Physical and spectroscopic data of major diastereoisomer **102a**

$\boldsymbol{R_f}$ = 0.4 (hexane:EtOAc, 1:1)

IR (ATR): 3304, 2929, 2856, 1685, 1513, 1427, 1239, 1110 cm^{-1}

$\boldsymbol{[\alpha]_D}^{\boldsymbol{20}}$ = -69.1 (c 2.10, CH_2Cl_2)

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.68 (m, 4H: $4H_{Ph}$), 7.41 (m, 11H: $11H_{Ph}$), 5.92 (ddd, J=10.1 Hz, J'=5.2 Hz, J''=2.9 Hz, 1H: $1H_7$), 5.75 (m, 1H: $1H_6$), 5.39 (m, 1H: NH), 5.15 (s, 2H: $2H_{Bn}$), 4.53 (m, 1H: $1H_5$), 4.31 (m, 1H: $1H_2$), 3.81 (m, 3H: $2H_{1'}$+$1H_{8a}$), 2.40 (m, 1H: $1H_1$), 2.20 (m, 1H: $1H_8$), 2.03 (m, 2H: $1H_1$+$1H_8$), 1.09 (s, 9H: $9H_{Me}$)

^{13}C NMR (101 MHz, $CDCl_3$)[121]: δ 170.5 (C_3), 156.4 (C_{Cbz}), 136.3 (C_{Ph}), 135.6 (C_{Ph}), 135.5 (C_{Ph}), 133.2 (C_{Ph}), 133.1 (C_{Ph}), 129.8 (C_{Ph}), 129.7 (C_{Ph}), 128.5 (C_{Ph}), 128.1 (C_{Ph}),

128.0(C_{Ph}), 127.7 (C_{Ph}), 126.1 (C_6 or C_7), 125.8 (C_6 or C_7), 66.9 (C_{Bn}), 65.0 ($C_{1'}$), 52.2 (C_{8a} or C_5 or C_2), 51.8 (C_{8a} or C_5 or C_2), 49.4 (C_{8a} or C_5 or C_2), 30.5 (C_8 or C_1), 29.6 (C_8 or C_1), 26.8 ($C(\underline{C}H_3)_3$), 19.2 ($\underline{C}(CH_3)_3$)

Physical and spectroscopic data of minor diastereoisomer **102b**

$\boldsymbol{R_f}$ = 0.6 (hexane:EtOAc, 1:1)

IR (ATR): 3296, 2930, 2889, 1683, 1528, 1427, 1256, 1109 cm^{-1}

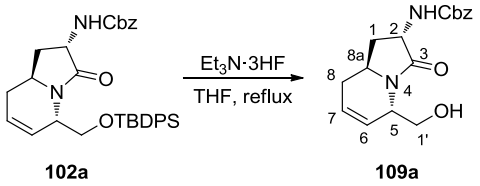
$\boldsymbol{[\alpha]_D}^{20}$ = -31.1 (c 1.95, CH_2Cl_2)

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.66 (m, 4H: $4H_{Ph}$), 7.38 (m, 11H: $11H_{Ph}$), 6.01 (m, 1H: $1H_7$), 5.85 (m, 1H: $1H_6$), 5.28 (s, 1H: NH), 5.12 (m, 2H: $2H_{Bn}$), 4.32 (dd, J=9.6 Hz, J'=5.6 Hz, 1H: $1H_{1'}$), 4.22 (m, 1H: $1H_5$), 4.10 (bd, J=9.6 Hz, 2H: $1H_{1'}$+$1H_2$), 3.74 (m, 1H: $1H_{8a}$), 2.31 (m, 2H: $1H_1$+$1H_8$), 2.08 (m, 2H: $1H_1$+$1H_8$), 1.04 (s, 9H: $9H_{Me}$)

^{13}C NMR (101 MHz, $CDCl_3$)[121]: δ 171.4 (C_3), 156.2 (C_{Cbz}), 136.1 (C_{Ph}), 135.5 (C_{Ph}), 133.5 (C_{Ph}), 133.4 (C_{Ph}), 129.6 (C_{Ph}), 128.5 (C_{Ph}), 128.1 (C_6 or C_7), 128.0 (C_6 or C_7), 127.5 (C_{Ph}), 127.3 (C_{Ph}), 125.8 (C_{Ph}), 66.9 (C_{Bn}), 62.5 ($C_{1'}$), 54.9 (C_{8a} or C_5 or C_2), 53.5 (C_{8a} or C_5 or C_2), 52.0 (C_{8a} or C_5 or C_2), 31.7 (C_8 or C_1), 29.6 (C_8 or C_1), 26.7 ($C(\underline{C}H_3)_3$), 19.3 ($\underline{C}(CH_3)_3$)

HRMS m/z (ESI+) Calculated for [$C_{33}H_{37}N_2O_4Si$+H]: 554.2601; Experimental: 554.2620.

5.2.28. (5*S*, 8a*R*)-Benzyl-(2*S*)-5-(hydroxymethyl)-3-oxo-1,2,3,5,8,8a-hexahydro-2-indolizinylcarbamate, 109a



102a **109a**

In a 10 mL Schlenk flask equipped with magnetic stirring and nitrogen atmosphere, a solution of 90 mg (0.21 mmol) of **102a** in 2 mL of anhydrous THF was warmed up to

reflux, followed by the addition of 0.21 mL (1.26 mmol) of $Et_3N{\cdot}3HF$. The mixture was stirred at the reflux temperature overnight.

The cool reaction mixture was diluted with 5 mL of CH_2Cl_2 and 5 mL of $NaHCO_3$ aqueous saturated solution. The aqueous phase was extracted with CH_2Cl_2 (4 x 3 mL), the combined organic extracts were dried over anhydrous Na_2SO_4 and concentrated under vacuum. Purification of the residue by flash column chromatography (gradient, from hexane:EtOAc, 1:1 to EtOAc and then chloroform:methanol, 9:1) gave 54 mg (0.17 mmol, 82% yield) of **109a**.

$\boldsymbol{R_f}$ = 0.2 (EtOAc)

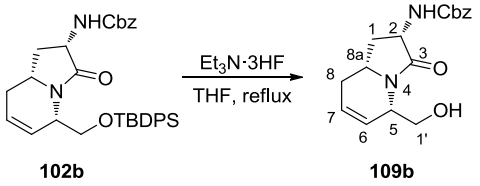
IR (ATR): 3297, 2923, 1673, 1649, 1531, 1454, 1255, 1057 cm^{-1}

$\boldsymbol{[\alpha]_D^{20}}$ = -67.5 (c 1.10, CH_2Cl_2)

^{1}H NMR (400 MHz, $CDCl_3$, 323K): δ 7.32 (m, 5H: $5H_{Ph}$), 6.12 (m, 1H: NH), 5.87 (m, 1H: $1H_7$), 5.62 (m, 1H: $1H_6$), 5.10 (s, 2H: $2H_{Bn}$), 4.46 (m, 1H: $1H_2$), 4.23 (m, 1H: $1H_5$), 3.79 (m, 2H: $2H_{1'}$), 3.57 (m, 1H: $1H_{8a}$), 3.38 (m, 1H: OH), 2.19 (m, 3H: $2H_1$+$1H_8$), 2.02 (m, 1H: $1H_8$)

^{13}C NMR (101 MHz, $CDCl_3$, 323K)[121]: δ 171.7 (C_3), 156.3 (C_{Cbz}), 136.3 (C_{Ph}), 128.3 (C_{Ph}), 127.9 (C_{Ph}), 126.4 (C_6 or C_7), 124.5 (C_6 or C_7), 124.4 (C_6 or C_7), 66.9 (C_{Bn}), 63.6 ($C_{1'}$), 53.2 (C_{8a} or C_5 or C_2), 52.1 (C_{8a} or C_5 or C_2), 49.2 (C_{8a} or C_5 or C_2), 32.9 (C_8 or C_1), 31.5 (C_8 or C_1)

5.2.29. (5*S*, 8a*S*) -Benzyl (2*S*)-5-(hydroxymethyl)-3-oxo-1,2,3,5,8,8a-hexahydro-2-indolizinylcarbamate, 109b



102b **109b**

In a 50 mL Schlenk flask equipped with magnetic stirring and nitrogen atmosphere, a solution of 283 mg (0.51 mmol) of **102b** in 15 mL of anhydrous THF was warmed up

to reflux, followed by the addition of 0.50 mL (3.06 mmol) of $Et_3N{\cdot}3HF$. The mixture was stirred at the reflux temperature overnight.

The cool reaction mixture was diluted with 10mL of CH_2Cl_2 and 10 mL of $NaHCO_3$ aqueous saturated solution. The aqueous phase was extracted with CH_2Cl_2 (4 x 10 mL), the combined organic extracts were dried over anhydrous Na_2SO_4 and concentrated under vacuum. Purification of the residue by flash column chromatography (gradient, hexane:EtOAc, from 3:1 to 1:2) gave 140 mg (0.44 mmol, 87% yield) of **109b**.

$\boldsymbol{R_f}$ = 0.4 (EtOAc)

IR (ATR): 3295, 2924, 1675, 1645, 1533, 1454, 1242, 1040 cm^{-1}

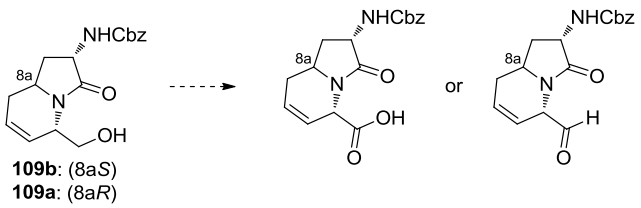
$\boldsymbol{[\alpha]_D}^{\boldsymbol{20}}$ = 16.8 (c 1.35, CH_2Cl_2)

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.37 (m, 5H: $5H_{Ph}$), 5.90 (t, J = 7.6 Hz, 1H: $1H_7$), 5.59 (m, 1H: NH), 5.51 (d, J = 9.5 Hz, 1H: $1H_6$), 5.12 (s, 2H: $2H_{Bn}$), 4.35 (q, J = 7.8 Hz, 1H: $1H_2$), 4.22 (m, 1H: $1H_5$), 3.83 (d, J = 5.1 Hz, 2H: $2H_{1'}$), 3.75 (m, 1H: $1H_{8a}$), 2.30 (m, 4H: $2H_1$+$2H_8$)

^{13}C NMR (101 MHz, $CDCl_3$, 323K)[121]: δ 172.8 (C_3), 156.8 (C_{Cbz}), 136.7 (C_{Ph}), 129.0 (C_{Ph}), 128.6 (C_{Ph}), 128.5 (C_{Ph}), 127.1 (C_6 or C_7), 126.2 (C_6 or C_7), 67.6 (C_{Bn}), 64.6 ($C_{1'}$), 60.3 (C_{8a} or C_5 or C_2), 54.5 (C_{8a} or C_5 or C_2), 52.6 (C_{8a} or C_5 or C_2), 33.3 (C_8 or C_1), 31.9 (C_8 or C_1)

HRMS m/z (ESI+) Calculated for [$C_{17}H_{19}N_2O_4$]: Experimental:

5.2.30. Attempted oxidation of 109



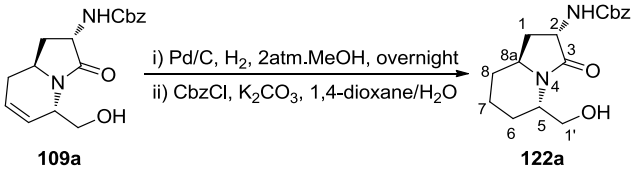
The Table below summarizes the unsuccessful attempts to oxidize **109**:

Table 10. Attempts and results of oxidation of **109**[a]

Entry	sm	Reagent	Solvent	T	Time	Result
1	**109a**	DMP	CH_2Cl_2	rt	2 h	decomposed
2	**109b**	DMP	CH_2Cl_2	rt	2 h	40% sm
3	**109b**	PCC	CH_2Cl_2	rt	overnight	<60% sm
4	**109b**	DMSO, $(COCl)_2$, Et_3N	CH_2Cl_2	-78℃ -rt	1.5 h	complex mixture
5	**109a**	Jones reagent[109]	Acetone	rt	3 h	decomposed
6	**109a**	$NaIO_4$, $RuCl_3 \cdot 3H_2O$[110]	CH_3CN/H_2O	rt	2 h	decomposed
7	**109b**	$NaIO_4$, $RuCl_3 \cdot 3H_2O$	CH_3CN/H_2O	rt	2 h	decomposed

[a] The results were inferred from ^{1}H NMR analysis of the crude products

5.2.31. (5*S*, 8a*S*)- Benzyl-(2*S*)-5-(hydroxymethyl)-3-oxo-octahydro-2-indolizinyl-carbamate, 122a



109a **122a**

A solution of 20 mg (0.06 mmol) of alcohol **109a** in 1 mL of methanol stirring at room temperature was hydrogenated in presence of 2 mg of Pd/C (10%) at 2atm for 20h. After that time, the solution was filtered through Celite®, washing with EtOAc and concentrated under vacuum.

To the residue were added 18 mg (0.13 mmol) of K_2CO_3 and 1 mL of 1,4-dioxane/H_2O (1:1). The mixture was cooled down to 0℃ , followed by the addition of 10 µL (0.07mmol) of CbzCl. The resulting solution was kept at room temperature overnight.

Then, the solution was diluted with 5 mL of H_2O and extracted with CH_2Cl_2 (4 x 2 mL), the combined organic extracts were dried over anhydrous Na_2SO_4 and concentrated under vacuum. Purification of the residue by flash column chromatography (gradient, EtOAc and then chloroform:methanol 9:1) furnished 14 mg (0.04 mmol, 74% yield) of **122a**.

R_f = 0,1 (EtOAc)

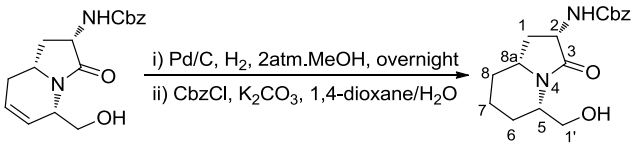
$[\alpha]_D^{20}$ = -13.7 (c 0.70, CH_2Cl_2)

IR (ATR): 3306, 2936, 2858, 1712, 1665, 1533, 1454, 1239, 1043 cm^{-1}

^{1}H NMR (400 MHz, $CDCl_3$, 323K): δ 7.36 (m, 5H: $5H_{Ph}$), 5.98 (s, 1H: NH), 5.12 (m, 2H: $2H_{Bn}$), 4.34 (m, 1H: $1H_2$), 4.17 (m, 1H: $1H_5$), 3.85 (m, 1H: $1H_{1'}$), 3.78 (m, 1H: $1H_{8a}$), 3.59 (dt, *J* = 11.8, 5.1 Hz, 1H: $1H_{1'}$), 2.92 (m, 1H: OH), 2.17 (m, 2H: $2H_1$), 1.86-1.48 (m, 5H: $2H_6$+ $1H_7$+ $2H_8$), 1.16 (m, 1H: $1H_7$)

^{13}C NMR (101 MHz, $CDCl_3$, 323K)[121]: δ 171.7 (C_3), 156.3 (C_{Cbz}), 136.3 (C_{Ph}), 128.3 (C_{Ph}), 127.9 (C_{Ph}), 66.9 (C_{Bn}), 61.1 ($C_{1'}$), 60.8 ($C_{1'}$), 52.1 (C_{8a} or C_5 or C_2), 51.6 (C_{8a} or C_5 or C_2), 50.9 (C_{8a} or C_5 or C_2), 33.3 (33.2) (C_8 or C_6 or C_1), 32.9 (C_8 or C_6 or C_1), 24.4 (C_8 or C_6 or C_1), 19.8 (C_7)

5.2.32. (5*S*, 8a*R*)-Benzyl-(2*S*)-5-(hydroxymethyl)-3-oxooctahydro-2-indolizinyl-carbamate, 122b



109b **122b**

A solution of 38 mg (0.12 mmol) of alcohol **109b** in 2 mL of methanol stirring at room temperature was hydrogenated in presence of 4 mg of Pd/C (10%) at 2atm for 20h. After that time, the solution was filtered through Celite®, washing with EtOAc and concentrated under vacuum.

To the residue were added 33 mg (0.24 mmol) of K_2CO_3 and 2 mL of 1,4-dioxane/H_2O (1:1). The mixture was cooled down to 0ºC, followed by the addition of 19 µL (0.13 mmol) of CbzCl. The resulting solution was kept at room temperature overnight.

Then, the solution was diluted with 5 mL of H_2O and extracted with CH_2Cl_2 (4 x 3 mL), the combined organic extracts were dried over anhydrous Na_2SO_4 and concentrated under vacuum. Purification of the residue by flash column

chromatography (gradient, from hexane:EtOAc, 3:1 to EtOAc) furnished 30 mg (0.09 mmol, 78% yield) of **122b**.

R_f = 0,3 (EtOAc)

$[\alpha]_D^{20}$ = 3.7 (c 1.65, CH_2Cl_2)

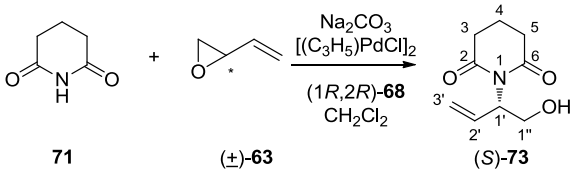
IR (ATR): 3289, 2938, 2869, 1672, 1534, 1454, 1262, 1055 cm^{-1}

^{1}H NMR (400 MHz, $CDCl_3$, 323K): δ 7.37 (m, 5H: $5H_{Ph}$), 5.28 (s, 1H), 5.14 (s, 2H: $2H_{Bn}$), 4.31 (m, 1H: $1H_2$), 3.91 (m, 2H: $2H_{1'}$), 3.46 (m, 1H: $1H_5$), 3.23 (m, 1H: $1H_{8a}$), 2.32 (bt, J=11.4 Hz, 1H: $1H_1$), 2.15 (dt, J=13.3 Hz, J'=8.9 Hz, 1H: $1H_1$), 1.97 (m, 1H: $1H_8$), 1.82 (m, 1H: $1H_8$), 1.67-1.23 (m, 4H: $2H_6$+$2H_7$)

^{13}C NMR (101 MHz, $CDCl_3$)[121]: δ 170.8 (C_3), 156.1 (C_{Cbz}), 136.2 (C_{Ph}), 128.4 (C_{Ph}), 128.0 (C_{Ph}), 127.9 (C_{Ph}), 67.0 (C_{Bn}), 62.9 ($C_{1'}$), 61.3 (C_{8a} or C_5 or C_2), 57.9 (C_{8a} or C_5 or C_2), 52.7 (C_{8a} or C_5 or C_2), 32.9(C_8 or C_6 or C_1), 31.92(C_8 or C_6 or C_1), 27.56 (C_8 or C_6 or C_1), 23.84(C_7)

HRMS m/z (ESI+) Calculated for [$C_{17}H_{21}N_2O_4$]: Experimental:

5.2.33. 1 -[(1'*S*)-1'-(Hydroxymethyl)-2'-propenyl]-2,6-piperidinedione, (*S*)-73[86b]



In a 100 mL Schlenk flask equipped with magnetic stirring, under nitrogen atmosphere, a mixture of 11.7 mg (0.03 mmol) of π-allylpalladium chloride dimer, 80.5 mg (0.10 mmol) of (1*R*,2*R*)-**68**, 42 mg (0.40 mmol) of sodium carbonate and 452 mg (4.00 mmol) of glutarimide, **71**, was purged with nitrogen for 1 h. After addition of 50 mL of dichloromethane, the resulting mixture was stirred 10 min at room temperature at which point racemic butadiene monoepoxide **63** (0.32 mL, 4.00 mmol) was added. The resulting mixture was stirred at room temperature under nitrogen for 14 h.

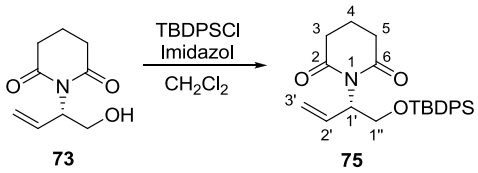
Then the reaction mixture was filtered through Celite®, washing with ethyl acetate, and concentrated under vacuum. The residue was purified by flash column chromatography (gradient, hexane:ethyl acetate, from 5:1 to 2:1) to give 1.20 g (6.55 mmol, 86% yield) of (*S*)-**73** as a clear oil.

R_f = 0.5 (ethyl acetate)

$[\alpha]_D^{20}$ = -13.3 (c 1.40, CH_2Cl_2)

^{1}H NMR (250 MHz, $CDCl_3$): δ 6.14 (ddd, J=17.3 Hz, J'=10.1 Hz, J''=7.0 Hz, 1H: $1H_{2'}$), 5.42 (m, 1H: $1H_{1'}$), 5.23 (m, 2H: $2H_{3'}$), 4.03 (dd, J=11.5 Hz, J'=7.8 Hz, 1H: $1H_{1''}$), 3.86 (dd, J=11.5 Hz, J'=5.0 Hz, 1H: $1H_{1''}$), 2.70 (m, 4H: $2H_3$+$2H_5$), 1.99 (m, 2H: $2H_4$)

5.2.34. 1-{(1'*S*)-1'–[(*tert*-Butyldiphenylsilyloxy)methyl]-2'-propenyl}-2,6-piperidine-dione, (*S*)-75[86b]



In a 250 mL Schlenk flask equipped with magnetic stirring and nitrogen atmosphere, 1.46 g (8.00 mmol) of alcohol **73** were dissolved in 80 mL of anhydrous CH_2Cl_2. After cooling to 0°C in an ice/water bath, 2.18 g (32.00 mmol) of imidazole were added, followed by 4.2 mL (13.00 mmol) of TBDPSCl. The cooling bath was removed and the mixture was stirred at room temperature overnight.

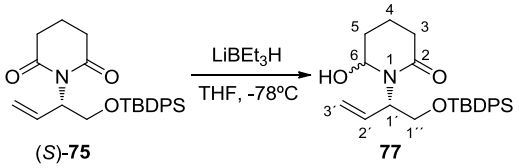
The reaction mixture was concentrated under vacuum and the residue dissolved in 60 mL of ethyl acetate. After vigorous stirring for 1h, the solution was filtered through Celite®, washing with ethyl acetate. The filtrate was concentrated under vacuum and the residue purified by flash column chromatography (gradient, hexane:ethyl acetate, from 9:1 to 3:2) to give 2.53g (6.01 mmol, 75% yield) of (*S*)-**75** as white solid, which was crystallized from ^{i}PrOH.

R_f = 0.7 (hexane:ethyl acetate, 1:1)

$[\alpha]_D^{20}$ = 16.7 (c 1.00, CH_2Cl_2)

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.65 (m, 4H: $4H_{Ph}$), 7.42 (m, 6H: $6H_{Ph}$), 6.06 (ddd, J=17.3 Hz, J'=10.2 Hz, J''=7.2 Hz, 1H: $1H_{2'}$), 5.54 (m, 1H: $1H_{1'}$), 5.16 (m, 2H: $2H_{3'}$), 4.23 (t, J = 9.7 Hz, 1H: $1H_{1''}$), 3.83 (dd, J=10.0 Hz, J'=6.4 Hz, 1H: $1H_{1''}$), 2.64 (t, J = 6.6 Hz, 4H: $2H_3$ + $2H_5$), 1.92 (p, J = 6.5 Hz, 2H: $2H_4$), 1.02 (s, 9H: $9H_{Me}$)

5.2.35. (6*SR*)-6-Hydroxy-1-{(1'*S*)-1'–[(*tert*-butyldiphenylsilyloxy)methyl]-2'-propenyl}-2-piperidinedione, (1'*S*)-77[86b]



(*S*)-**75** **77**

In a 50 mL Schlenk flask equipped with magnetic stirring and nitrogen atmosphere, 1.27 g (3.01 mmol) of **75** were dissolved in 12 mL anhydrous THF. After cooling down to -78 °C, 4.8 mL (4.82 mmol) of a $LiBEt_3H$ solution (1M in THF) were added dropwise. The reaction, monitored by TLC (hexane:ethyl acetate, 1:1), was finished in 1h.

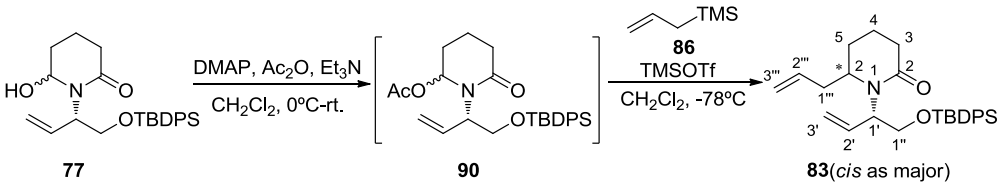
After that time, 40 mL of $NaHCO_3$ aqueous saturated solution of and 10 mL of 30% H_2O_2 were added at -78°C, and the mixture was allowed to warm up to room temperature. Then, it was filtered through Celite® and the filtrate extracted with CH_2Cl_2 (4 x 10 mL), the combined organic extracts were dried over anhydrous Na_2SO_4 and concentrated in vacuum. The residue was purified by column chromatography (gradient, hexane:ethyl acetate, from 3:1 to 1:1) to give 923 mg (2.18 mmol, 73% yield) of (1'*S*)-**77** (mixture of isomers) as a colorless oil.

R_f = 0.4 (hexane:ethyl acetate, 1:1)

^{1}H NMR (400 MHz, $CDCl_3$): Isomer A (major) and B (minor); δ 7.67 (m, 4H: $4H_{Ph}$), 7.44 (m, 6H: $6H_{Ph}$), 6.17 (ddd, J=17.6 Hz, J'=10.5 Hz, J''=7.2 Hz, 1H: $1H_{2'}^{B}$), 5.79 (ddd, J=16.7 Hz, J'=10.6 Hz, J''=5.9 Hz, 1H: $1H_{2'}^{A}$), 5.17 (m, 4H: $1H_6^{A}$ + $1H_6^{B}$ + $2H_{3'}^{A}$+ $2H_{3'}^{B}$+ $1H_{1'}^{A}$+ $1H_{1'}^{B}$), 4.32 (m, 2H: $2H_{1''}^{B}$), 4.10 (m, 1H: $1H_{OH}^{B}$), 3.97 (dd, J=11.2 Hz, J'=3.5 Hz, 1H: $1H_{1''}^{A}$), 3.85 (dd, J=11.3 Hz, J'=6.1 Hz, 1H: $1H_{1''}^{A}$), 2.64 (m, 1H: $1H_5^{A}$),

2.53 (d, J = 1.5 Hz, 1H: $1H_5^B$), 2.36 (m, 2H: $1H_5^A$ + $1H_5^B$ +$1H_3^A$), 2.20 (m, 1H: $1H_3^B$), 2.11 (m, 1H: $1H_3^A$),1.97 (m, 1H: $1H_3^B$), 1.85 (d, J = 3.9 Hz, 2H: $2H_4^B$), 1.75 (m, 2H: $2H_4^A$), 1.09 (s, $9H_{Me}^A$), 1.08 (s, $9H_{Me}^B$)

5.2.36. (6*SR*)-5-Allyl-1-{(1'*S*)-1'–[(*tert*-butyldiphenylsilyloxy)methyl]-2'-propenyl} -2-pyrrolidinedione, 83



In a 50 mL Schlenk flask equipped with magnetic stirring and nitrogen atmosphere, 1.06 g (2.50 mmol) of **77** was dissolved in 15 mL of anhydrous CH_2Cl_2. After cooling to 0℃ in an ice/water bath, 153 mg (1.25 mmol) of DMAP, 0.59 mL (2.50 mmol) of acetic anhydride and 0.87 mL (2.50 mmol) of Et_3N were added. The cooling bath was removed and the mixture was stirred at room temperature overnight.

The reaction mixture was diluted with 15 mL of $NaHCO_3$ saturated solution and 15 mL of water and then extracted with CH_2Cl_2 (4 x 15 mL). The combined organic extracts were dried over anhydrous Na_2SO_4 and concentrated under vacuum. The remaining crude product **90** was used in the next step without further purification.

In a 250 mL Schlenk flask equipped with magnetic stirring and nitrogen atmosphere, a solution of the crude ester **90** in 50 mL of anhydrous CH_3CN was cooled down to -40°C, followed by the addition of 0.79 mL (5.00 mmol) of **86** and then, dropwise, 0.69 mL (3.75 mmol) of TMSOTf. The reaction, monitored by TLC (hexane:EtOAc, 1:1) was finished in 1.5 h.

After that time, the reaction mixture was cooled to -78°C, 100 mL of $NaHCO_3$ saturated solution were added, and then the mixture was allowed to warm up to room temperature. The aqueous solution was extracted with CH_2Cl_2 (4 x 20 mL), the combined organic extracts were dried over anhydrous Na_2SO_4 and concentrated under vacuum. The residue was purified by flash column chromatography (gradient, hexane:EtOAc, from

4:1 to 1:2) to give 678 mg (1.52 mmol, 61% yield) of **83** (mixture of diastereoisomers, 10:1) as a yellow oil.

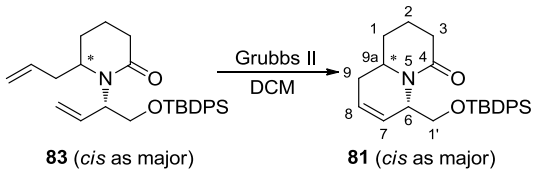
R_f = 0.7 (hexane:EtOAc, 1:1)

IR (ATR): 3071, 2931, 2857, 1637, 1427, 1107 cm^{-1}

^{1}H NMR (400 MHz, $CDCl_3$): Isomer A (major) and B (minor); δ 7.68 (m, 4H: $4H_{Ph}{}^{A}$ + $4H_{Ph}{}^{B}$), 7.41 (m, 6H: $6H_{Ph}{}^{A}$ + $6H_{Ph}{}^{B}$), 6.22 (ddd, J=17.4 Hz, J'=10.6 Hz, J''=6.8 Hz, 1H: $1H_{2'}{}^{A}$), 6.06 (m, 1H: $1H_{2'}{}^{B}$), 5.68 (m, 1H: $1H_{2'''}{}^{A}$+$1H_{2'''}{}^{B}$), 5.11 (m, 4H: $2H_{3'}{}^{A}$ + $2H_{3'}{}^{B}$ + $2H_{3'''}{}^{A}$ + $2H_{3'''}{}^{B}$), 4.29 (td, J=10.0 Hz, J'=4.0 Hz, 1H: $1H_{1'}{}^{A}$+$1H_{1'}{}^{B}$), 4.01 (m, 2H: $2H_{1''}{}^{B}$), 3.86 (m, 2H: $2H_{1''}{}^{A}$), 3.43 (dd, J=10.8 Hz, J'=4.0 Hz, 1H: $1H_6{}^{A}$ + $1H_6{}^{B}$), 2.31 (m, 4H: $4H_3$+ $4H_{1'''}$), 1.75 (ddd, J=21.2 Hz, J'=12.7 Hz, J''=6.3 Hz, 4H: $4H_4$ + $4H_5$), 1.08 (s, 9H: $9H_{Me}{}^{A}$)

^{13}C NMR (63 MHz, $CDCl_3$): δ 169.9 (C_2), 135.7 (C_{Ph}), 135.7 (C_{Ph}), 135.3 (C_{Ph}), 134.6 (C_{Ph}), 133.7 ($C_{2'}$ or $C_{2'''}$), 133.5 ($C_{2'}$ or $C_{2'''}$), 129.8 (C_{Ph}), 127.8 (C_{Ph}), 117.9 ($C_{3'}$ or $C_{3'''}$), 117.1 ($C_{3'}$ or $C_{3'''}$), 66.0 ($C_{1''}$), 64.2 ($C_{1'}$), 59.0 (C_6), 37.7 (C_3), 32.6 ($C_{1'''}$), 27.0 ($C(\underline{C}H_3)_3$), 25.7 (C_4 or C_5), 19.2 (C_4 or C_5), 16.3 ($\underline{C}(CH_3)_3$)

5.2.37. (6*S*,9a*S*)-6-[(*tert*-Butyldiphenylsilyloxy)methyl]-2,3,9,9a-tetrahydro-1*H*-quinolizin-4-(6*H*)-one, 81



83 (*cis* as major) **81** (*cis* as major)

In a 250 mL Schlenk flask equipped with magnetic stirring and nitrogen atmosphere, a solution of 670 mg (1.50 mmol) of **83** (10:1 diastereomeric mixture) in 150 mL of anhydrous CH_2Cl_2 was warmed up to reflux, and then 32 mg (0.04 mmol) the 2nd generation Grubbs catalyst was added in two portions (one per hour). The mixture was kept under reflux while stirring overnight.

After cooling down to room temperature, the resulting mixture was filtered through a short pad of silica gel, washing with EtOAc. The filtrate was concentrated under

vacuum and the residue purified by flash column chromatography (gradient, hexane:EtOAc, from 3:1 to 100% EtOAc) to give 577 mg (1.38 mmol, 92% yield) of **81** as a 10:<0.5 diastereomeric mixture.

R_f = 0.4 (hexane:EtOAc, 1:1)

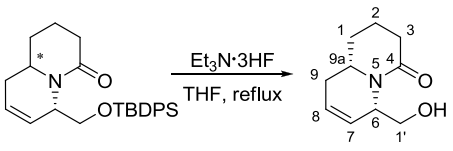
IR (ATR): 2928, 2854, 1668, 1612, 1406, 1095 cm^{-1}

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.67 (m, 4H: $4H_{Ph}$), 7.39 (m, 6H: $6H_{Ph}$), 6.07 (qd, *J* = 6.1, 2.8 Hz, 1H: $1H_7$), 5.99 (m, 1H: $1H_8$), 4.65 (s, 1H: $1H_6$), 3.89 (m, 2H: $2H_{1'}$), 3.31 (ddd, *J* = 11.0, 7.2, 3.0 Hz, 1H: $1H_{9a}$), 2.41 (m, 2H: $2H_3$), 2.16 (m, 2H: $2H_9$), 1.89 (m, 2H: $1H_1$+$1H_2$), 1.75 (m, 1H: $1H_1$), 1.52 (m, 1H: $1H_2$), 1.07 (dd, *J* = 9.0, 3.4 Hz, 9H: $9H_{Me}$)

^{13}C NMR (101 MHz, $CDCl_3$): δ 171.2 (C_4), 135.6 (C_{Ph}), 135.5 (C_{Ph}), 133.7 (C_{Ph}), 133.64 (C_{Ph}), 129.5 (C_{Ph}), 129.4 (C_{Ph}), 127.9 (C_7 or C_8), 127.5 (C_{Ph}), 126.9 (C_7 or C_8), 65.1 ($C_{1'}$), 54.8 (C_{9a}), 53.7 (C_6), 32.7 (C_3 or C_9 or C_1), 31.8 (C_3 or C_9 or C_1), 30.9 (C_3 or C_9 or C_1), 26.8 ($C(\underline{C}H_3)_3$), 20.7 (C_2), 19.2 ($\underline{C}(CH_3)_3$)

HRMS m/z (ESI+) Calculated for $C_{26}H_{33}NO_2Si$: Experimental:

5.2.38. (6*S*,9a*S*)-6-(Hydroxymethyl)-2,3,9,9a-tetrahydro-1*H*-quinolizin-4-(6*H*)-one, 91



81 **91**

In a 50 mL Schlenk flask equipped with magnetic stirring and nitrogen atmosphere, a solution of 264 mg (0.63 mmol) of **81** in 10 mL of anhydrous THF was warmed up to reflux, followed by the addition of 0.62 mL (5.34 mmol) of $Et_3N{\cdot}3HF$. The mixture was stirred under reflux overnight.

After cooling down to room temperature, the reaction mixture was diluted with 10 mL of CH_2Cl_2 and 10 mL of $NaHCO_3$ saturated solution. The layers were separated and

the aqueous one extracted with CH_2Cl_2 (4 x 8 mL). The combined organic extracts were dried over anhydrous Na_2SO_4 and concentrated under vacuum. The residue was purified by flash column chromatography (gradient, from hexane:EtOAc, 2:1 to EtOAc) to give 107 mg (0.59mmol, 94% yield) of **91**.

$\boldsymbol{R_f}$ = 0.1 (EtOAc)

IR (ATR): 3339, 2983, 1612, 1410, 1265, 1034 cm^{-1}

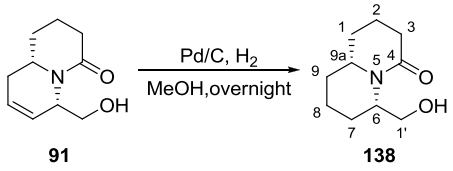
$\boldsymbol{[\alpha]_D}^{20}$ = -35.5 (c 1.30, CH_2Cl_2)

^{1}H NMR (250 MHz, $CDCl_3$): δ 6.03 (m, 1H: $1H_7$), 5.80 (m, 1H: $1H_8$), 4.64 (m, 1H: $1H_6$), 3.78 (dd, J=11.3 Hz, J'=2.5 Hz, 1H: $1H_{1'}$), 3.55 (dd, J=11.5 Hz, J'=6.1 Hz, H: $1H_{1'}$), 3.36 (m, 1H: $1H_{9a}$), 2.53 (dd, J=8.3 Hz, J'=5.5 Hz, 2H: $1H_9$+$1H_3$), 2.15 (m, 2H: $1H_9$+$1H_3$), 1.93 (m, 2H: $1H_1$ + $1H_2$), 1.68 (m, 2H: $1H_1$ + $1H_2$)

^{13}C NMR (101 MHz, $CDCl_3$): δ 173.3 (C_4), 126.9 (C_7 or C_8), 126.6 (C_7 or C_8), 67.2 ($C_{1'}$), 56.7 (C_{9a}), 55.6 (C_6), 32.5 (C_3 or C_9 or C_1), 31.3 (C_3 or C_9 or C_1), 30.5 (C_3 or C_9 or C_1), 20.0 (C_2)

HRMS m/z (ESI+) Calculated for $C_{10}H_{15}NO_2$: Experimental:

5.2.39. (6*S*,9a*R*)-6-(Hydroxymethyl)hexahydro-1*H*-quinolizin-4-(6*H*)–one, 138



In a 10 mL Schlenk flask equipped with magnetic stirring, 50 mg (0.27 mmol) of alcohol **91** were dissolved in 2 mL of methanol and 5 mg of Pd/C were added at once. The flask was sealed up by a septum and Parafilm®, connected to a balloon filled with H_2, and stirred at room temperature for 8 h.

After that time, the solution was filtered through Celite®, washing with EtOAc, and the filtrate concentrated under vacuum. The residue was filtered through a short pad of silica gel to give 39 mg (0.21 mmol, 79% yield) of **138**.

$\boldsymbol{R_f}$ = 0.2 (EtOAc)

$\boldsymbol{[\alpha]_D}^{20}$ = -80.0 (c 0.60, CH_2Cl_2)

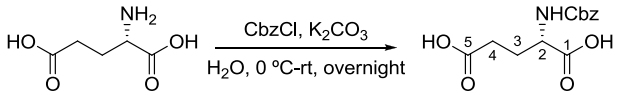
IR (ATR): 3371, 2940, 2872, 1603, 1410, 1343, 1050 cm^{-1}

^{1}H NMR (250 MHz, $CDCl_3$): δ 4.94 (dd, J=7.5 Hz, J'=5.8 Hz, 1H: H_{OH}), 3.82 (m, 2H: $2H_{1'}$), 3.52 (m, 1H: $1H_6$), 3.39 (m, 1H: $1H_{9a}$), 2.42 (m, 2H: $2H_3$), 2.08-1.38 (m, 10H: $2H_1$ + $2H_2$+: $2H_7$ + $2H_8$+ $2H_9$)

^{13}C NMR (101 MHz, $CDCl_3$): δ 171.1 (C_4), 65.3 ($C_{1'}$), 62.0 (C_{9a}), 57.5 (C_6), 33.3 (C_3 or C_9 or C_1 or C_7), 31.7 (C_3 or C_9 or C_1 or C_7), 29.7 (C_3 or C_9 or C_1 or C_7), 25.9 (C_3 or C_9 or C_1 or C_7), 21.3 (C_8 or C_2), 18.5 (C_8 or C_2)

HRMS m/z (ESI+) Calculated for [$C_9H_{17}NO_2$+H]: 184.1338; Experimental: 184.1360.

5.2.40. (2*S*)-2-{[(benzyloxy)carbonyl]amino}pentanedioic acid, 111[102]



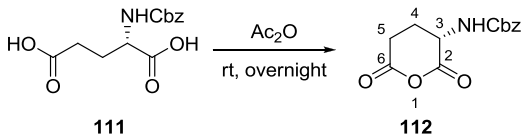
110 **111**

In a 50 mL Schlenk flask equipped with magnetic stirring, 1.50 g diacid **110** (10 mmol) and 2.76 g K_2CO_3 (20 mmol) were dissolved in 25 mL H_2O. After cooling down to 0 ºC, excess of CbzCl (2.00 mL, 14 mmol) was added, the mixture was warmed up and stirred overnight.

The mixture was washed with Et_2O, the aqueous layer was adjusted with 10% HCl solution to pH=1. Then, it was extracted with EtOAc (4 x 20 mL), the organic layers were combined and dried over anhydrous Na_2SO_4 and concentrated under vacuum to give 3 g of diacid **111**, which was used in the next step without further purification.

^{1}H NMR (250 MHz, $CDCl_3$): δ 7.35 (m, 5H: $5H_{Ph}$), 5.59 (m, 1H: NH), 5.13 (s, 2H: $2H_{Bn}$), 4.47 (m, 1H: $1H_2$), 2.42 (m, 2H: $2H_4$), 2.24 (m, 2H: $2H_3$)

5.2.41. Benzyl-(3*S*)-2,6-dioxotetrahydro-2*H*-pyran-3-yl-carbamate, 112[103]

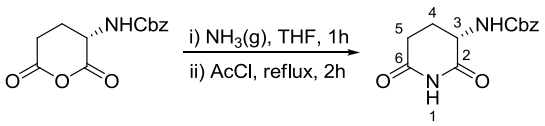


111 **112**

In a 25 mL Schlenk flask equipped with magnetic stirring, 3.0 g **111** were dissolved in 6 mL Ac_2O and stirred at rt overnight. Then, it was concentrated under vacuum to give 2.88 g anhydride **112**, which was used in the next step without further purification.

^{1}H NMR (360 MHz, $CDCl_3$): δ 7.37 (m, 5H: $5H_{Ph}$), 5.66 (s, 1H: NH), 5.15 (s, 2H: $2H_{Bn}$), 4.47 (m, 1H: $1H_3$), 2.98 (m, 2H: $2H_5$), 2.44 (m, 1H: $1H_4$), 1.96 (ddd, J= J'=13.1 Hz, J''=5.4 Hz, 1H: $1H_4$)

5.2.42. (*S*)-Benzyl-(2,5-dioxopyrrolidin-3-yl)carbamate, 113[106]



112 **113**

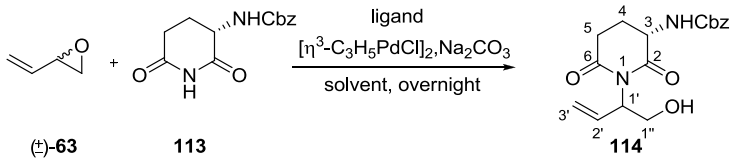
In a 50 mL Schlenk flask equipped with magnetic stirring, 1.75 g (6.65 mmol) **112** were dissolved in 15 mL THF. Meanwhile, gaseous NH_3 was prepared and passed through the solution for 1h to get a white suspention, which was concentrated under vacuum. The result mixture was mixed with 10 mL AcCl and warmed up to reflux for 2h. The result solution was concentrated under vacuum and then dissolved in 20 mL $H_2O/CHCl_3$ (v:v= 1:1), 5 mL $NaHCO_3$ aqueous saturated solution were added to the mixture, followed by the extraction with $CHCl_3$ (4 x 10 mL), the combined organic extracts were dried over anhydrous Na_2SO_4 and concentrated under vacuum to give 525 mg (2.00 mmol)**113** which was crystallized from EtOAc.

Mp =134 ºC

$[\alpha]_D^{20}$ = 16.1 (c 1.05, DMF)

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.39 (m, 5H: $5H_{Ph}$), 6.09 (s, 1H: NH), 5.53 (s, 1H: NH), 5.30 (dd, J=12.0 Hz, J'=7.8 Hz, 2H: $2H_{Bn}$), 4.60 (m, 1H: $1H_3$), 2.79 (dt, J=17.8 Hz, J'=10.0 Hz, 1H: $1H_5$), 2.51 (ddd, J=17.6 Hz, J'=8.7 Hz, J''=3.4 Hz, 1H: $1H_5$), 2.28 (m, 2H: $2H_4$)

5.2.43. Benzyl-(3*S*)-1-[(1'*SR*)-1'-(hydroxymethyl)-2'-propenyl]-2,6-dimethylene-piperidinyl-carbamate, 114



The Table below summarizes the attempts of asymmetric allylation of lactam **113**:

Table 7. Attempts and results of N-alkylation of **113**[a]

Entry	Ligand	Solvent	T	Pd (mol%)	Ligand (mol%)	Na_2CO_3 (mol%)	Result
1	(1*R*,2*R*)-**68**	CH_2ClCH_2Cl	rt	0. 8	2.4	10	only **113**
2			56℃				
3			reflux				
4		toluene	reflux				
5	PPh_3	CH_2ClCH_2Cl	rt	0. 8	10	10	
6			56℃	0. 8	4	10	only **113**
7			reflux	0. 8	7	10	
8			reflux	0. 8	10	10	**114** (<30%)
9			50℃	1.6	10	20	**114** (<11%)
10			reflux	1.6	10	20	**114** (<31%)
11			reflux	2.4	15	30	**114** (<28%)

[a] All the experiments are performed overnight

The procedure for 10th entry is as follow:

In a 25 mL Schlenk flask equipped with magnetic stirring, under nitrogen atmosphere, a mixture of 9 mg (0.02 mmol) of π-allylpalladium chloride dimer, 39 mg (0.15 mmol) of triphenyl phosphine, 32 mg (0.30 mmol) of sodium carbonate and 393 mg (1.50 mmol) of **113** was purged with nitrogen for 1 h. After addition of 10 mL of

1,2-dichloroethane, the resulting mixture was stirred 10 min at room temperature, at which point racemic butadiene monoepoxide, (±)-**63**, (0.12 mL, 1.50 mmol) was added. The resulting mixture was warmed up to reflux and stirred under nitrogen overnight.

Then, the reaction mixture was cooled and filtered through Celite®, washed with EtOAc and concentrated in vacuum. The residue was purified twice by flash column chromatography (gradient, hexane:EtOAc, from 3:1 to 1:1) to give 52 mg (0.16 mmol, 10% yield) of **114**.

R_f = 0.4 (EtOAc)

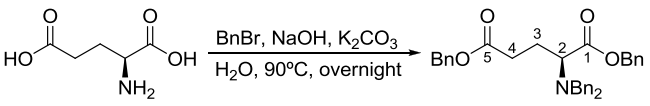
IR (ATR): 3282, 3056, 2925, 1688, 1530, 1455, 1195 cm^{-1}

^{1}H NMR (400 MHz, $CDCl_3$, 323K): δ 7.34 (m, 5H: $5H_{Ph}$), 5.96 (bs, 1H: NH), 5.79 (m, 1H: $1H_{2'}$), 5.27 (m, 2H: $2H_{3'}$), 5.12 (m, 2H: $2H_{Bn}$), 4.57 (bs, 1H: $1H_{1'}$), 4.32 (m, 1H: $1H_{1''}$), 4.18 (m, 2H: $1H_{1''}$+$1H_3$), 2.25 (m, 4H: $2H_4$+$2H_5$)

^{13}C NMR (101 MHz, $CDCl_3$): δ 178.4 (C_6), 171.4 (C_2), 171.3 (C_2), 155.9 (C_{Cbz}), 136.4 (C_{Ph}), 136.3 (C_{Ph}), 134.1 (C_{Ph}), 128.6 (C_{Ph}), 128.5 (C_{Ph}), 128.4 (C_{Ph}), 128.1 ($C_{2'}$), 117.1 ($C_{3'}$), 117.0 ($C_{3'}$), 66.9 ($C_{1''}$ or C_{Bn}), 66.7 ($C_{1''}$ or C_{Bn}), 55.6 ($C_{1'}$), 55.5 (C_3), 29.5 (C_5), 29.2 (C_5), 24.2 (C_4), 24.0 (C_4)

HRMS m/z (ESI+) Calculated for $C_{17}H_{20}N_2O_5$: 332.1372; Experimental: 332.1376.

5.2.44. Dibenzyl-(2*S*)-2-(dibenzylamino)pentanedioate, 116[107]



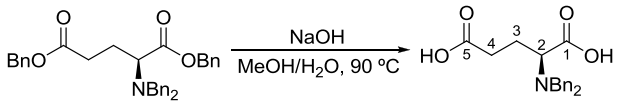
115 116

In a 100 mL Schlenk flask equipped with magnetic stirring, a solution of 1.63 g (40.78 mmol) NaOH and 5.64 g (40.78 mmol) K_2CO_3 in 40 mL H_2O was cooled down to 0 ℃ , followed by the addition of 3.00 g (20.39 mmol) diacid **115**. It was warmed up to 90 ℃ and then 14.55 mL (122.34 mmol) BnBr was added dropwise. The mixture was kept at 90 ℃ overnight.

The cool reaction mixture was diluted with 20 mL H_2O and then extracted with EtOAc (4 x 20 mL), the combined organic extracts were dried over anhydrous Na_2SO_4 and concentrated under vacuum to get quantitative product **116** as colorless oil. The crude product was used to do the next step without further purification.

^{1}H NMR (250 MHz, $CDCl_3$): δ 7.37 (m, 20H: $20H_{Ph}$), 5.24 (dd, J=29.1 Hz, J'=12.5 Hz, 2H: $2H_{Bn}$), 5.01 (dd, J=14.6 Hz, J'=12.5 Hz, 2H: $2H_{Bn}$), 3.92 (d, J = 13.7 Hz, 2H: $2H_{Bn}$), 3.50 (m, 3H: $2H_{Bn}$+ $1H_2$), 2.45 (m, 2H: $2H_4$), 2.10 (q, J = 7.5 Hz, 2H: $2H_3$)

5.2.45. (2*S*)-2-(dibenzylamino)pentanedioic acid, 117[107]



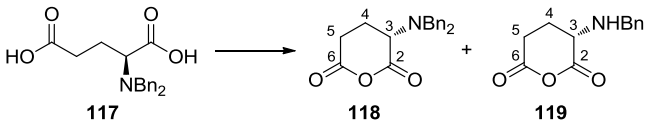
In a 10 mL Schlenk flask equipped with magnetic stirring, a solution of 0.27 g (6.80 mmol) NaOH in 3 mL H_2O was cooled down to 0 ℃ , followed by the addition of 1.72 g (3.39 mmol) diester **116** in 2 mL Methanol all in once. The mixture was warmed up to 90 ℃ and kept for 6 h.

The cool reaction mixture was diluted with 2 mL H_2O and then extracted with (Et_2O:Hexane, 1:1) (3 x 3 mL). The aqueous layer was acidified to pH=2 and extracted with EtOAc (4 x 2 mL), the combined organic extracts were dried over anhydrous Na_2SO_4 and concentrated under vacuum to get 0.85 g (2.60 mmol, 77% yield) acid **117** as white solid. The crude product was used to do the next step without further purification.

Mp= 207-211℃

^{1}H NMR (250 MHz, DMSO-d_6): δ 7.30 (m, 10H: $10H_{Ph}$), 3.81 (d, J = 13.9 Hz, 2H: $2H_{Bn}$), 3.57 (d, J = 14.0 Hz, 2H: $2H_{Bn}$), 3.37 (bs, 2H: 2OH), 3.16 (t, J = 7.5 Hz, 1H: $1H_2$), 2.24 (m, 2H: $2H_4$), 1.88 (q, J = 7.4 Hz, 2H: $2H_3$)

5.2.46. (3*S*)-3-(dibenzylamino)dihydro-2*H*-pyran-2,6-(3*H*)-dione, 118 and (3*S*)-3-(benzylamino)dihydro-2*H*-pyran-2,6-(3*H*)-dione, 119



The Table below summarizes the attempts of cyclization of aminoacid **117**:

Table 8. Attempts and results of cyclization of **117**

Entry	Reagent	Temperature	Time	Result and yield
1	Ac_2O	rt	overnight	**117** (100%)
2	Ac_2O	90℃	40 min	**118** (50%)
3	AcCl	reflux	5 h	**118** (6%) + **119** (40%)

The procedure of the entry 2 is as follow:

In a 25 mL Schlenk flask equipped with magnetic stirring, a solution of 200 mg (0.61 mmol) acid **117** in 2 mL Ac_2O was warmed up to 90 ℃ and kept for 40 min.

The cool reaction mixture was diluted with 2 mL H_2O and then extracted with EtOAc (3 x 3 mL), the combined organic extracts were dried over anhydrous Na_2SO_4 and concentrated under vacuum. The residue was purified by flash column chromatography (gradient, hexane:EtOAc, from 3:1 to 1:1) to give 93 mg (0.30 mmol, 50% yield) of **118**.

Physical and spectroscopic data of **118**

$\boldsymbol{R_f}$ = 0.7 (EtOAc)

$[\alpha]_D^{20}$ = 2.6 (c 1.05, CH_2Cl_2)

^{1}H NMR (250 MHz, $CDCl_3$): δ 7.32 (m, 10H: $10H_{Ph}$), 5.08 (m, 3H: $2H_{Bn}$+$1H_3$), 4.00 (m, 2H: $2H_{Bn}$), 2.33 (m, 4H: $2H_4$+$2H_5$)

The procedure of the entry 3 is as follow:

In a 10 mL Schlenk flask equipped with magnetic stirring, a solution of 50mg (0.15 mmol) acid **117** in 1mL Ac_2O was warmed up to reflux and kept for 6h.

The cool reaction mixture was diluted with 2 mL H_2O and then extracted with EtOAc (3 x 3 mL), the combined organic extracts were dried over anhydrous Na_2SO_4 and concentrated under vacuum. The residue was purified by flash column chromatography (gradient, hexane:EtOAc, from 3:1 to 1:1) to give 3 mg (0.01 mmol, 6% yield) of **118** and 13 mg (0.06 mmol, 40% yield) of **119**.

Physical and spectroscopic data of **119**

$[\alpha]_D^{20}$ = 29.8 (c 0.65, CH_2Cl_2)

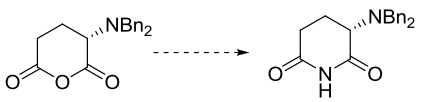
IR (ATR): 2921, 1732, 1634, 1418, 1200 cm^{-1}

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.53 (s, 1H: NH), 7.30 (m, 5H: H_{Ph}), 5.17 (d, J = 14.8 Hz, 1H: 1 H_{Bn}), 3.99 (m, 1H: $1H_3$), 4.02 (d, J = 14.8 Hz, 2H: $1H_{Bn}$+), 2.65 (m, 1H: $1H_5$), 2.51 (ddd, J=17.0 Hz, J'=9.5 Hz, J''=3.5 Hz, 1H: $1H_5$), 2.32 (m, 1H: $1H_4$), 2.19 (m, 1H: $1H_4$)

^{13}C NMR (101 MHz, $CDCl_3$): δ 176.0 (C_2), 175.0 (C_6), 135.3 (C_{Ph}), 128.8 (C_{Ph}), 128.5 (C_{Ph}), 127.9 (C_{Ph}), 58.4 (C_3), 45.6 (C_{Bn}), 29.5 (C_5), 22.8 (C_4)

HRMS m/z (ESI+) Calculated for $C_{12}H_{13}NO_3$: Experimental:

5.2.47. (3*S*)-3-(Dibenzylamino)dihydro-2*H*-pyran-2,6-(3*H*)-dione, 120



118 **120**

The table below summarizes the unsuccessful attempts of converting anhydride **118** into lactam **120**:

Table 9. Attempts and results of preparation of **120**[a]

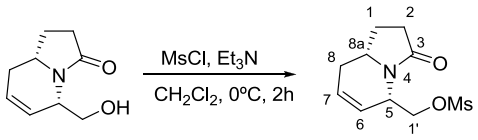
Entry	Reagent	T	Time	Result
1	Urea	160 ℃	2 h	**118**
2	NH_4HCO_3[108]	200 ℃	1 h	**118**
3[a]	1) NH_3(g),THF 2) AcCl	1) rt 2) reflux	1) 30 min 2) 5 h	**118**

[a] 1) and 2) refer to consecutive steps

.

5.3. PREPARATION OF CHLOROQUINE DERIVATIVES

5.3.1. (5*S*,8a*S*)-5-[2-(methylsulfonyl)ethyl]-1,5,8,8a-tetrahydro-3(2*H*)-indolizinone, *cis*-123



cis-**88** *cis*-**123**

In a 10 mL Schlenk flask equipped with magnetic stirring and nitrogen atmosphere, 110 mg (0.66 mmol) of alcohol *cis*-**88** were dissolved in 3 mL of anhydrous CH_2Cl_2. After cooling to 0 ℃ in an ice/water bath, 0.28 mL (1.98 mmol) of Et_3N were added, followed by 0.10 mL (1.32 mmol) of MsCl. The mixture was stirred for 2h at 0 ℃.

Then, the reaction mixture was diluted with 3 mL of CH_2Cl_2 and 5 mL of $NaHCO_3$ aqueous saturated solution. The aqueous phase was extracted with CH_2Cl_2 (4 x 5 mL), the combined organic extracts were dried over anhydrous Na_2SO_4 and concentrated under vacuum to give crude mesylated product *cis*-**123**, which was used in the next step without further purification.

R_f = 0.3 (EtOAc)

^{1}H NMR (250 MHz, $CDCl_3$): δ 6.07 (ddt, J=10.0 Hz, J'=7.0 Hz, J''=1.8 Hz, 1H: $1H_6$), 5.73 (dt, J=10.1 Hz, J'=3.3 Hz, 1H: $1H_7$), 4.88 (dd, J=9.9 Hz, J'=4.8 Hz, 1H: $1H_{1'}$), 4.48 (dd, J=9.9 Hz, J'=2.4 Hz, 1H: $1H_{1'}$), 4.32 (m, 1H: $1H_5$), 3.53 (m, 1H: $1H_{8a}$), 2.97 (m, 3H: $3H_{Me}$), 2.36 (m, 3H: $2H_2$+$1H_8$), 2.14 (m, 2H: $1H_8$+$1H_1$), 1.66 (m, 1H: $1H_1$)

5.3.2. (5*S*,8a*R*)-5-[2-(methylsulfonyl)ethyl]-1,5,8,8a-tetrahydro-3(2*H*)-indolizinone, *trans*-123

trans-**88** *trans*-**123**

In a 10 mL Schlenk flask equipped with magnetic stirring and nitrogen atmosphere, 50 mg (0.30 mmol) of alcohol *trans*-**88** were dissolved in 2 mL of anhydrous CH_2Cl_2.

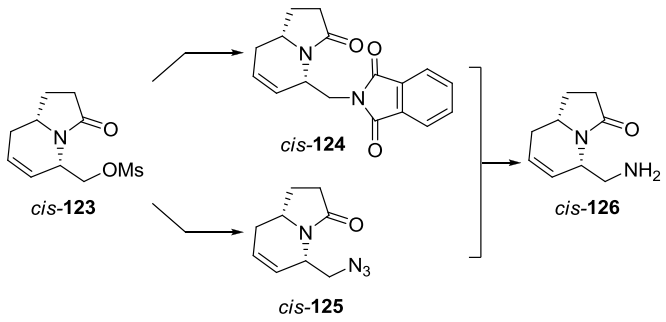
After cooling to 0 ℃ in an ice/water bath, 0.13 mL (0.90 mmol) of Et_3N were added, followed by 46 µL (0.60 mmol) of MsCl. The mixture was stirred for 2h at 0 ℃ .

Then, the reaction mixture was diluted with 2 mL of CH_2Cl_2 and 3 mL of $NaHCO_3$ aqueous saturated solution. The aqueous phase was extracted with CH_2Cl_2 (4 x 3 mL), the combined organic extracts were dried over anhydrous Na_2SO_4 and concentrated under vacuum to give crude mesylated product *trans*-**123**, which was used in the next step without further purification.

R_f = 0.3 (EtOAc)

^{1}H NMR (250 MHz, $CDCl_3$): δ 5.95 (m, 1H: $1H_6$), 5.63 (dtd, J=10.3 Hz, J'=3.3 Hz, J''=1.1 Hz, 1H: $1H_7$), 4.57 (m, 1H: $1H_5$), 4.34 (dd, J=10.4 Hz, J'=4.1 Hz, 1H: $1H_{1'}$), 4.19 (dd, J=10.4 Hz, J'=4.9 Hz, 1H: $1H_{1'}$), 3.69 (m, 1H: $1H_{8a}$), 2.98 (s, 3H: $3H_{Me}$), 2.34 (m, 4H: $1H_1+2H_2+1H_8$), 1.93 (m, 1H: $1H_8$), 1.66 (m, 1H: $1H_1$)

5.3.3. Attempts of amination of *cis*-123



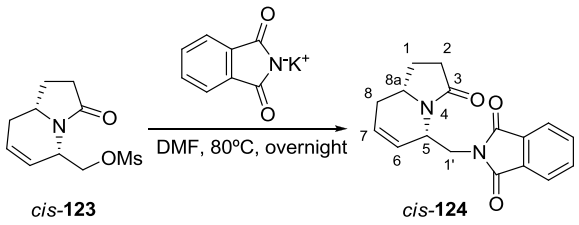
The table below summarizes the attempted S_N2 reactions between the mesylate *cis*-**123** and nitrogen nucleophiles:

Table 11. Attempts and results of amination of *cis*-**123**[a]

Entry	Reagent	Solvent	T	Result (yield)
1	phthalimide, K_2CO_3	CH_3CN	reflux	*cis*-**80**
2[b]	1) potassium phthalimide[112]	1) DMF	1) rt-80℃	1) *cis*-**124** (36%)
	2) aqueous hydrazine	2) EtOH	2) reflux	2) *cis*-**126** (20%)
3[b]	1) NaN_3;[113]	1) DMF	1) 80℃	1) *cis*-**125** (80%)
	2) Ph_3P	2) Et_2O,H_2O	2) 0 ℃ -rt	2) *cis*-**126** (78%)

[a] All reactions were ran overnight. [b] 1) and 2) refer to consecutive steps.

5.3.4. 2-{[(5*S*,8a*S*)-3-oxo-1,2,3,5,8,8a-hexahydro-5-indolizinyl]methyl}-1*H*-isoindole -1,3-(2*H*)-dione, *cis*-124[112]



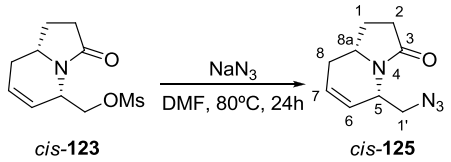
In a 10 mL Schlenk flask equipped with magnetic stirring and nitrogen atmosphere, 86 mg (0.35 mmol) of crude *cis*-**123** and 72 mg (0.39 mmol) of potassium phthalimide were dissolved in 3 mL of anhydrous DMF. After warmming to 80 ℃ the mixture was stirred overnight at the same temperature.

The cooled reaction mixture was diluted with 5 mL of H_2O then extracted with EtOAc (4 x 4 mL), the combined organic extracts were washed with H_2O (1 x 10 mL) and then dried over anhydrous Na_2SO_4. After concentrated under vacuum, the residue was purified by flash column chromatography (gradient, hexane:EtOAc, from 3:1 to 1:2) to give 37 mg (0.12 mmol, 36% yield) of *cis*-**124**.

$\boldsymbol{R_f}$ = 0.4 (EtOAc)

^{1}H NMR (250 MHz, $CDCl_3$): δ 7.79 (m, 4H: $4H_{Ph}$), 5.88 (m, 1H: $1H_6$), 5.74 (m, 1H: $1H_7$), 4.58 (m, 2H: $1H_{1'}$+ $1H_5$), 4.01 (dd, J=13.5 Hz, J'=3.7 Hz, 1H: $1H_{1'}$), 3.46 (m, 1H: $1H_{8a}$), 2.26 (m, 4H: $2H_2$+$1H_8$+$1H_1$), 1.66 (m, 2H: $1H_8$+$1H_1$)

5.3.5. (5*S*,8a*S*)-5-(azidomethyl)-1,2,8,8a-tetrahydroindolizin-3-(5*H*)-one, *cis*-125[113]



In a 10 mL Schlenk flask equipped with magnetic stirring and nitrogen atmosphere, 183 mg (0.75 mmol) of crude *cis*-**123** and 122 mg (1.87 mmol) of NaN_3 were dissolved in 2 mL of anhydrous DMF. The mixture was warmed up to 80 ℃ and stirred for 24h at the same temperature.

The cooled reaction mixture was diluted with 5 mL of H_2O then extracted with Et_2O (4 x 4 mL), the combined organic extracts were dried over anhydrous Na_2SO_4 and concentrated under vacuum, the residue was purified by flash column chromatography (gradient, hexane:EtOAc, from 3:1 to 1:1) to give 116 mg (0.60 mmol, 80% yield) of *cis*-**125**.

R_f = 0.6 (EtOAc)

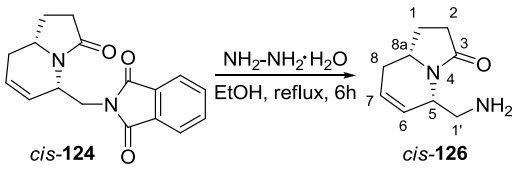
IR (ATR): 2931, 2852, 2013, 1680, 1653, 1405, 1265 cm^{-1}

$[\alpha]_D^{20}$ = -39.8 (c 2.25, CH_2Cl_2)

^{1}H NMR (400 MHz, $CDCl_3$): δ 6.06 (ddt, J=10.3 Hz, J'=7.1 Hz, J''=1.8 Hz, 1H: $1H_6$), 5.67 (dt, J=10.0 Hz, J'=3.3 Hz, 1H: $1H_7$), 4.32 (dd, J=12.0 Hz, J'=4.9 Hz, 1H: $1H_{1'}$), 4.26 (m, 1H: $1H_5$), 3.53 (tdd, J=10.1 Hz, J'=5.7 Hz, J''=3.8 Hz, 1H: $1H_{8a}$), 3.42 (dd, J=12.1 Hz, J'=2.3 Hz, 1H: $1H_{1'}$), 2.37 (m, 3H: $2H_2$+$1H_8$), 2.18 (m, 2H: $1H_8$+ $1H_1$), 1.66 (tt, J=11.5 Hz, J'=9.9 Hz, 1H: $1H_1$)

^{13}C NMR (101 MHz, $CDCl_3$): δ 176.3 (C_3), 127.4 (C_6), 125.8 (C_7), 55.3 (C_{8a}), 52.6 ($C_{1'}$), 51.4 (C_5), 31.8 (C_8 or C_2 or C_1), 30.9 (C_8 or C_2 or C_1), 26.8 (C_8 or C_2 or C_1)

5.3.6. (5*S*,8a*S*)- 5-(Aminomethyl)-1,2,8,8a-tetrahydro-indolizin-3-(5*H*)-one, *cis*-126[112,113]

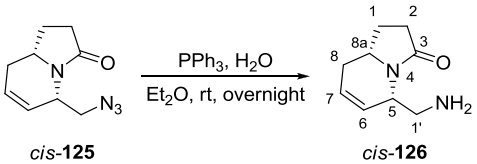


cis-**124** *cis*-**126**

In a 10 mL Schlenk flask equipped with magnetic stirring, 37 mg (0.12 mmol) of *cis*-**124** and 29 µL (0.60 mmol) of hydrazine hydrate were dissolved in 1 mL of EtOH. The mixture was warmed up to reflux and kept for 6h.

The cooled reaction mixture was diluted with 3 mL of H_2O then extracted with CH_2Cl_2 (3 x 3 mL), the combined organic extracts were dried over anhydrous Na_2SO_4 and concentrated under vacuum, the residue was purified by flash column

chromatography (gradient, from 100% EtOAc to 5% Et_3N in EtOAc) to give 4 mg (0.02 mmol, 20% yield) of *cis*-**126**.



cis-**125** *cis*-**126**

In a 10 mL Schlenk flask equipped with magnetic stirring, a solution of 71 mg (0.37 mmol) of *cis*-**125** in 0.60 mL of Et_2O was cooled to 0 ℃ in an ice/water bath, 145 mg (0.55 mmol) of PPh_3 were added. Followed by the addition of 0.15 mL H_2O in 1h, the mixture was warmed up to room temperature and stirred overnight.

The result mixture was acidified with 10% HCl solution to pH=1 then extracted with Et_2O (3 x 2 mL). 5% NaOH solution was added to adjust pH of the aqueous phase to 10, after extraction with CH_2Cl_2 (4 x 3 mL), the combined organic extracts were dried over anhydrous Na_2SO_4 and concentrated under vacuum, the residue was purified by flash column chromatography (gradient, from EtOAc to 5% Et_3N in EtOAc) to give 48 mg (0.29 mmol, 78% yield) of *cis*-**126**.

Physical and spectroscopic data of *cis*-**126**

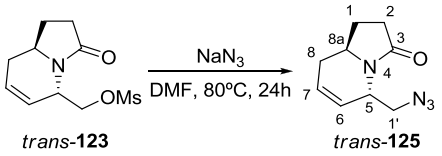
IR (ATR): 3367, 2927, 2853, 1677, 1650, 1408, 1265 cm^{-1}

$[\alpha]_D^{20}$ = -32.1 (c 1.00, CH_2Cl_2)

^{1}H NMR (400 MHz, $CDCl_3$): δ 6.01 (ddt, J=10.5 Hz, J'=7.3 Hz, J''=1.9 Hz, 1H: $1H_6$), 5.61 (dt, J=10.1 Hz, J'=3.2 Hz, 1H: $1H_7$), 4.12 (m, 1H: $1H_5$), 3.60 (dd, J=13.4 Hz, J'=4.5 Hz, 1H: $1H_{1'}$), 3.49 (tdd, J=9.9 Hz, J'=5.7 Hz, J''=3.7 Hz, 1H: $1H_{8a}$), 2.78 (dd, J=13.4 Hz, J'=2.7 Hz, 1H: $1H_{1'}$), 2.33 (m, 3H: $2H_2$+$1H_8$), 2.18 (dddd, J=12.0 Hz, J'=8.0 Hz, J''=5.8 Hz, J'''= 2.1 Hz, 1H: $1H_1$), 1.99 (m, 1H: $1H_8$), 1.61 (m, 1H: $1H_1$)

^{13}C NMR (101 MHz, $CDCl_3$): δ 176.1 (C_3), 127.1 (C_6 or C_7), 126.5 (C_6 or C_7), 55.5 (C_{8a}), 55.4 (C_5), 42.9 ($C_{1'}$), 32.1 (C_8 or C_2 or C_1), 31.1 (C_8 or C_2 or C_1), 26.5 (C_8 or C_2 or C_1)

5.3.7. (5*S*,8a*R*)-5-(azidomethyl)-1,2,8,8a-tetrahydroindolizin-3-(5*H*)-one, *trans*-125[113]



In a 10 mL Schlenk flask equipped with magnetic stirring and nitrogen atmosphere, 81 mg (0.33 mmol) of crude *trans*-**123** and 54 mg (1.87 mmol) of NaN_3 were dissolved in 1 mL of anhydrous DMF. After warming up to 80 ℃ , the mixture was stirred for 24h at the same temperature.

The cooled reaction mixture was diluted with 2 mL of H_2O then extracted with Et_2O (4 x 3 mL), the combined organic extracts were dried over anhydrous Na_2SO_4 and concentrated under vacuum, the residue was purified by flash column chromatography (gradient, hexane:EtOAc, from 3:1 to 1:1) to give 51 mg (0.27 mmol, 80% yield) of *trans*-**125**.

R_f = 0.5 (EtOAc)

IR (ATR): 3038, 2924, 2094, 1679, 1650, 1419, 1262 cm^{-1}

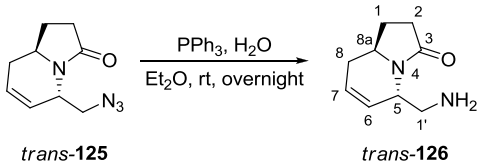
$[\alpha]_D^{20}$ = -298.6 (c 1.00, CH_2Cl_2)

^{1}H NMR (400 MHz, $CDCl_3$): δ 5.98 (ddt, J=10.6 Hz, J'=6.3 Hz, J''=2.2 Hz, 1H: $1H_6$), 5.67 (dtd, J=10.3 Hz, J'=3.1 Hz, J''=1.1 Hz, 1H: $1H_7$), 4.52 (m, 1H: $1H_5$), 3.82 (ddt, J=9.8 Hz, J'=7.3 Hz, J''=4.9 Hz, 1H: $1H_{8a}$), 3.58 (dd, J=12.4 Hz, J'=4.9 Hz, 1H: $1H_{1'}$), 3.41 (dd, J=12.4 Hz, J'=4.5 Hz, 1H: $1H_{1'}$), 2.38 (m, 4H: $1H_1$+$2H_2$+$1H_8$), 1.98 (m, 1H: $1H_8$), 1.71 (m, 1H: $1H_1$)

^{13}C NMR (101 MHz, $CDCl_3$): δ 174.3 (C_3), 127.0 (C_6), 124.6 (C_7), 53.1 (C_{8a}), 51.4 ($C_{1'}$), 49.6 (C_5), 31.9 (C_8 or C_2 or C_1), 29.7 (C_8 or C_2 or C_1), 25.2 (C_8 or C_2 or C_1)

HRMS m/z (ESI+) Calculated for [$C_9H_{12}N_4O$-N]: 178.0980; Experimental: 178.0982.

5.3.8. (5*S*,8a*R*)-5-Aminomethyl-1,2,8,8a-tetrahydro-indolizin-3-(5*H*)-one, *trans*-126[113]



trans-**125** *trans*-**126**

In a 10 mL Schlenk flask equipped with magnetic stirring, a solution of 51 mg (0.27 mmol) of *trans*-**125** in 0.40 mL of Et_2O was cooled to 0 ℃ in an ice/water bath, 105 mg (0.40 mmol) of PPh_3 were added, followed by the addition of 0.10 mL H_2O in 1h, the mixture was warmed up to rt. and stirred overnight.

The result mixture was acidified with 10% HCl solution to pH=1 then extracted with Et_2O (3 x 2 mL). 5% NaOH solution was added to adjust pH of the water phase to 10, after extraction with CH_2Cl_2 (4 x 3 mL), the combined organic extracts were dried over anhydrous Na_2SO_4 and concentrated under vacuum, the residue was purified by flash column chromatography (gradient, from EtOAc to 5% Et_3N in EtOAc) to give 32 mg (0.19 mmol, 71% yield) of *trans*-**126**.

IR (ATR): 3365, 2923, 1661, 1639, 1422, 1309, 1266 cm^{-1}

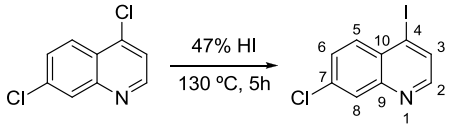
$[\alpha]_D^{20}$ = -207.2 (c 2.10, CH_2Cl_2)

^{1}H NMR (250 MHz, $CDCl_3$): δ 5.85 (m, 1H: $1H_6$), 5.66 (ddd, J=10.3 Hz, J'=4.1 Hz, J''=1.9 Hz, 1H: $1H_7$), 4.37 (s, 1H: $1H_5$), 3.75 (m, 1H: $1H_{8a}$), 2.91 (dd, J=13.1 Hz, J'=4.8 Hz, 1H: $1H_{1'}$), 2.75 (dd, J=13.1 Hz, J'=7.2 Hz, 1H: $1H_{1'}$), 2.34 (m, 4H: $1H_1$+$2H_2$+$1H_8$), 1.96 (dddd, J=13.3 Hz, J'=10.5 Hz, J''=4.9 Hz, J''' = 2.8 Hz, 1H: $1H_8$), 1.70 (m, 1H: $1H_1$)

^{13}C NMR (101 MHz, $CDCl_3$): δ 174.7 (C_3), 125.7 (C_6 or C_7), 125.7 (C_6 or C_7), 52.7 (C_{8a}), 51.1 ($C_{1'}$), 45.1 (C_5), 31.8 (C_8 or C_2 or C_1), 29.7 (C_8 or C_2 or C_1), 24.6 (C_8 or C_2 or C_1)

HRMS m/z (ESI+) Calculated for [$C_9H_{14}N_2O$+H]: 167.1184; Experimental: 167.1185.

5.3.9. 7-chloro-4-iodoquinoline, 128[114]



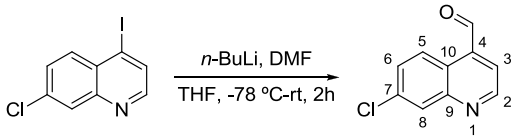
127 **128**

In a 10 mL Schlenk flask equipped with magnetic stirring, 500 mg **127** were added to 4.5 mL 47% HI solution in small portions at room temperature. The resulting suspension was warmed to 130 °C and kept for 5 h, after cooling down to room temperature, it was poured into an ice-water mixture (10 mL), basified with 10 N NaOH, and extracted with $CHCl_3$ (4 x 8 mL). The combined organic extracts was washed with brine, dried over Na_2SO_4, and concentrated in vacuo to give (2.04 mmol, 81% yield) of 590 mg **128**.

mp= 125-127 ℃ ; lit.[114] mp=120-122 ℃

^{1}H NMR (360 MHz, $CDCl_3$) δ 8.46 (d, J = 4.7 Hz, 1H: $1H_2$), 8.07 (d, J = 2.2 Hz, 1H: $1H_5$), 7.99 (m, 2H: $1H_6$+$1H_8$), 7.58 (dd, J=9.0 Hz, J'=2.2 Hz, 1H: $1H_3$)

5.3.10. 7-chloro-4-quinolinecarbaldehyde, 129[115]



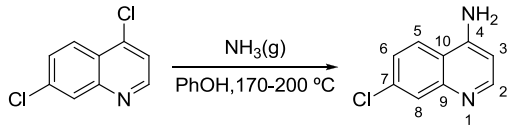
128 **129**

In a 10 mL Schlenk flask equipped with magnetic stirring and nitrogen atmosphere, a solution of 52 mg **128** (0.18 mmol) in 1 mL THF was cooled to -78 °C and 2.5 M *n*-BuLi (110 µL, 0.27 mmol) was added all at once. The resulting black solution was stirred 4 min at -78 °C, then anhydrous DMF (140 µL, 0.18 mmol) was added all at once. The cooling bath was removed after 15 min and the reaction was allowed to warm to rt. After 2 h, the orange solution was quenched with water (2 mL). The reaction was extracted with EtOAc (3 x 2 mL). The combined organic fractions were washed with water (1 x 3 mL) and brine (1 x3 mL), then were dried over Na_2SO_4 and concentrated

under vacuum, the residue was purified by flash column chromatography (hexane:EtOAc, 3:1) to give around 18 mg (0.09 mmol, 52% yield) **129**.

^{1}H NMR (250 MHz, $CDCl_3$): δ 10.47 (s, 1H: CHO), 9.23(d, J = 4.2 Hz, 1H: $1H_5$), 9.03 (d, J = 9.1 Hz, 1H: $1H_2$), 8.23 (d, J = 2.2 Hz, 1H: $1H_8$), 7.81 (d, J = 4.2 Hz, 1H: $1H_6$), 7.70 (dd, J=9.1 Hz, J'=2.2 Hz, 1H: $1H_3$)

5.3.11. 7-chloroquinolin-4-amine, 133[119]



127 **133**

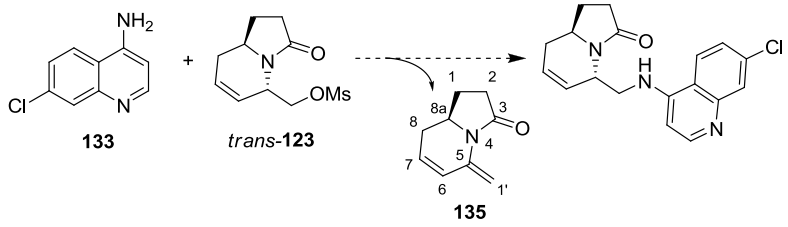
In a 50 mL Schlenk flask equipped with magnetic stirring, a solution of 5.0 g **127** (25.25 mmol) in 15.0 g phenol was warmed to 170 °C and gaseous ammonia was bubbled through it at a moderate rate. The bath was raised to 200 °C and the ammonia passed through the refluxing solution for 2.5 h.

After cooling to room temperature, 7.5 mL glacial acetic acid in 15 mL water was added to dissolve the solidified mixture. Followed by the addition of 50 mL Et_2O, the mixture was filtered and washed with Et_2O to get white precipitate. A second precipitate was obtained from a similar treatment with ether and mother liquor. The combined precipitate was dissolved in 40 to 50 mL hot water and treated with an excess of NaOH. The product was filtered and washed with water to give 4-amino-7-chloroquinolirie hydrate after crystallization from water, which was dried several days to remove the water of hydration to get 3.0 g (16.85 mmol, 68% yield) **133**.

mp= 154-156 ℃ ; lit.[119b]mp= 150-152 ℃

^{1}H NMR (250 MHz, $CDCl_3$) δ 8.54 (d, J = 5.3 Hz, 1H: $1H_2$), 8.00 (t, J = 2.0 Hz, 1H: $1H_5$), 7.71 (m, 1H: $1H_8$), 7.42 (dd, J=8.9 Hz, J'=2.1 Hz, 1H: $1H_6$), 6.61 (m, 1H: $1H_3$), 4.81 (s, 2H: 2NH)

5.3.12. Attempted reaction of the mesylate *trans*-49 with quinolinamine 133



The table below summarizes the attempted S_N2 reactions between the amine **133** and the mesylate *trans*-**123**:

Table 13. Attempts and results of reaction between **133** and *trans*-**123**[a]

Entry	122trans : 132	Reagent	Solvent	T	Result (Yield)
1[b]	**1:1**	Et_3N	DMF	rt	**133** + *trans*-**123**
2[b]	**1:1**	Et_3N	THF	reflux	**133** + *trans*-**123**
3[b]	**1:1**	Et_3N	DMF	100ºC	only **133**
4[b]	**1:2**	-	DMF	rt	**133** + *trans*-**123**
5[b]	**1:2**	-	DMF	80ºC	**133** + *trans*-**123**
6	**1:1**	NaHMDS	THF	rt	**133**+**135**(27%)

[a] All reactions were ran overnight, [b] the results were determined by ^{1}H NMR

In a 10 mL Schlenk flask equipped with magnetic stirring and nitrogen atmosphere, 18 mg (0.10 mmol) of crude **133** and 0.20 mL (0.20 mmol) of NaHMDS solution (1mol/L) were dissolved in 1 mL of anhydrous THF. The mixture was stirred for 1h at room temperature and then 25 mg (0.10 mmol) of mesylate *trans*-**123** were added. The result mixture was stirred for 24h.

The reaction mixture was diluted with 2 mL of CH_2Cl_2 and 2 mL Na_2CO_3 saturated solution then extracted with CH_2Cl_2 (4 x 3 mL), the combined organic extracts were dried over anhydrous Na_2SO_4 and concentrated under vacuum, the residue was purified by flash column chromatography (gradient, hexane:EtOAc, from 3:1 to 1:1) to give 4 mg (0.27 mmol, 27% yield) of **135**.

Physical and spectroscopic data of **135**

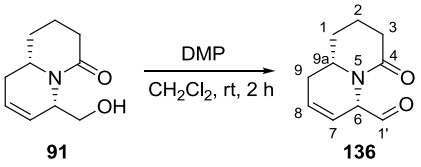
$\boldsymbol{R_f}$ = 0.7 (EtOAc)

^{1}H NMR (250 MHz, $CDCl_3$): δ 6.06 (s, 1H: $1H_{1'}$), 6.01 (dd, J=9.9 Hz, J'=2.9 Hz, 1H: $1H_6$), 5.83 (m, 1H: $1H_7$), 4.77 (s, 1H: $1H_{1'}$), 3.83 (dddd, J=11.2 Hz, J'=8.3 Hz, J''=7.0 Hz, J'''=4.3 Hz, 1H: $1H_{8a}$), 2.48 (m, 3H: $2H_2$+$1H_8$), 2.26 (m, 2H: $1H_1$ + $1H_8$), 1.71 (m, 1H: $1H_1$)

^{13}C NMR (101 MHz, $CDCl_3$): δ 174.3 (C_3), 137.6 (C_5), 127.2 (C_6), 124.4 (C_7), 102.2 ($C_{1'}$), 55.4 (C_{8a}), 32.7 (C_8 or C_2 or C_1), 31.4 (C_8 or C_2 or C_1), 25.5 (C_8 or C_2 or C_1)

HRMS m/z (ESI+) Calculated for $C_9H_{11}NO$: Experimental:

5.3.13. (6*S*,9a*S*)-4-oxo-1,3,4,6,9,9a-hexahydro-2*H*-quinolizine-6-carbaldehyde, 136



In a 10 mL Schlenk flask equipped with magnetic stirring and nitrogen atmosphere, 60 mg (0.33 mmol) of alcohol **91** were dissolved in 2 mL of anhydrous CH_2Cl_2. Then, 1.37 mL (0.66 mmol) of DMP solution (15%wt) were added at room temperature. The mixture was stirred for 2h.

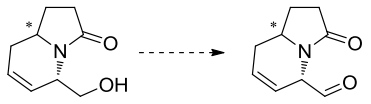
Then, the reaction mixture was diluted with 3 mL of $NaHCO_3$ and $NaS_2O_3 \cdot (H_2O)_5$ saturated solution. After vigorous stirring for 1 h, the solution was extracted with CH_2Cl_2 (4 x 3 mL), the combined organic extracts were dried over anhydrous Na_2SO_4 and concentrated under vacuum to give crude aldehyde **136**, which was used in the next step without further purification.

Physical and spectroscopic data of **136**

R_f = 0.5 (EtOAc)

^{1}H NMR (250 MHz, $CDCl_3$) δ 8.98 (d, J = 3.4 Hz, 1H: $1H_{1'}$), 6.11 (m, 1H: $1H_7$), 5.53 (dt, J = 10.0, 3.0 Hz, 1H: $1H_8$), 4.54 (m, 1H: $1H_6$), 3.44 (m, 1H: $1H_{9a}$), 1.92 (m, 8H: $2H_1$+$2H_2$+$2H_3$+$2H_9$)

5.3.14. Attempted oxidation of alcohol 88



cis-**88**
trans-**88**

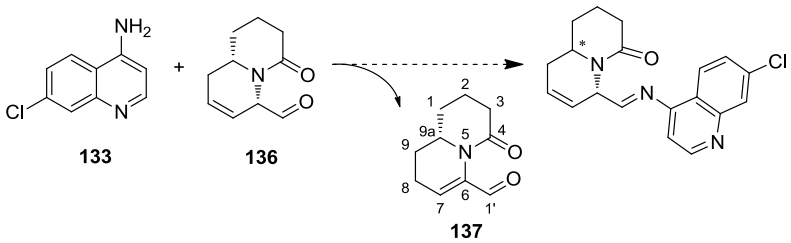
The Table below summarizes the unsuccessful attempts of oxidation of **88**:

Table 15. Attempts and results of oxidation of *cis*-**88** and *trans*-**88**[a]

Entry	sm	Reagent	T	Time	Result
1	*trans*-**88**	DMP	rt	3 h	complex mixture
2	*trans*-**88**	DMP	0℃	30 min	sm+ complex mixture
3	*cis*-**88**	DMP	0℃	30 min	sm+ complex mixture
4	*trans*-**88**	DMSO, $(COCl)_2$, Et_3N	-78℃ - rt	1 h	sm+ complex mixture
5	*cis*-**88**	DMSO, $(COCl)_2$, Et_3N	-78℃ - rt	1 h	sm+ complex mixture
6	*trans*-**88**	PCC, K_2CO_3	rt	3 h	decomposition
7	*cis*-**88**	PCC, K_2CO_3	rt	3 h	decomposition

[a] CH_2Cl_2 was used as solvent in all runs. The crude reaction product was analyzed by ^1H NMR

5.3.15. Attempted condensation between the aldehyde 136 and the quinolinamine 133



133 **136** **137**

The table below summarizes the attempted reactions between **133** and **136**:

Table 16. Attempts and results of reaction between **133** and **136**[a]

Entry	Additive	Solvent	T	Time	Result (Yield)
1	MS 4Å	Methanol	reflux	overnight	**137** (10%)+**133**
2	Na_2SO_4	Methanol	rt	overnight	**137** (10%)+**133**
3	Na_2SO_4	Methanol /AcOH	rt	3h	**137** (40%)+**133**

The procedure for 1st entry is as follow:

In a 10 mL Schlenk flask equipped with magnetic stirring and nitrogen atmosphere, 18 mg (0.10 mmol) of crude **136** and 18 mg (0.10 mmol) of quinolinamine **133** were dissolved in 1 mL of EtOH in the presence of 4Å molecular sieves. The mixture was warmed to reflux and kept for 2h.

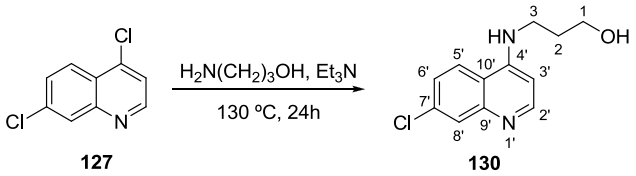
The resulting mixture was diluted with 2 mL of CH_2Cl_2 and concentrated under vacuum, the residue was purified by flash column chromatography (gradient, hexane:EtOAc, from 3:1 to 1:1) to give 2 mg (0.10 mmol, 10% yield) of **137**.

Physical and spectroscopic data of **137**

R_f = 0.3 (EtOAc)

^{1}H NMR (250 MHz, $CDCl_3$): δ 9.43 (s, 1H: $1H_{1'}$), 6.17 (t, J = 3.5 Hz, 1H: $1H_7$), 3.58 (m, 1H: $1H_{9a}$), 2.64 (m, 1H: $1H_3$), 1.96 (m, 11H: $2H_1$+$2H_2$+$1H_3$+$2H_8$+$2H_9$)

5.3.16. 3-[(7-chloro-4-quinolinyl)amino]-1-propanol, 130[116,118]



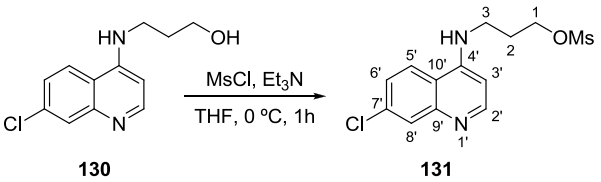
In a 10 mL Schlenk flask equipped with magnetic stirring, a mixture of 4,7-dichloroquinoline **127** (1.02 g, 0.52 mmol) and 3-aminopropanol (80 µL, 1.04 mmol) were warmed with stirring at 130 ℃ for 24 h. After cooling to rt, the reaction was poured into 5 mL water and filtered, and the solid residue was dried then boiled in 10 mL ethyl acetate to give **130** (1.12 g, 91%) as an off-white solid.

mp= 144-146 ℃ ; lit.[118b] mp=140-142 °C

^{1}H NMR (250 MHz, $(CD_3)_2CO$): δ 8.47 (d, J = 5.5 Hz, 1H: $1H_{2'}$), 8.12 (dd, J=8.9 Hz, J'=1.2 Hz, 1H: $1H_{5'}$), 7.85 (d, J = 2.3 Hz, 1H: $1H_{8'}$), 7.40 (dd, J=9.0 Hz, J'=2.3 Hz, 1H:

$1H_{6'}$), 6.56 (d, J = 5.4 Hz, 1H: $1H_{3'}$), 3.78 (t, J = 5.9 Hz, 2H: $2H_1$), 3.51 (m, 2H: $2H_3$), 1.99 (m, 2H: $2H_2$)

5.3.17. 3-[(7-chloro-4-quinolinyl)amino]propyl methanesulfonate, 131[118]



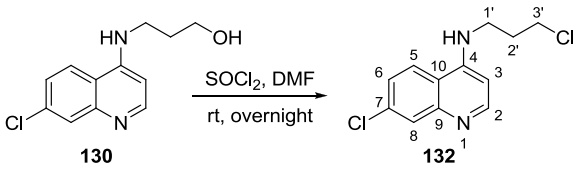
130 **131**

In a 10 mL Schlenk flask equipped with magnetic stirring and nitrogen atmosphere, a suspension of **130** (440. mg, 1.86 mmol) in anhydrous 9 mL THF was cooled to below 0 °C then triethylamine (0.53 mL, 3.72 mmol) was added. MsCl (0.17 mL, 2.2 mmol) was added dropwise and the reaction was stirred in an ice bath for 1h. After dilution with10 mL $NaHCO_3$ saturated solution, the mixture was extracted with CH_2Cl_2 (4 x 8 mL). The combined organic extracts were dried over anhydrous Na_2SO_4 and concentrated under vacuum to give 503 mg (1.60 mmol, 86% yield) of **131**.

mp= 125-127 ℃ ; lit.[118b] mp=124-126 ℃

^{1}H NMR (250 MHz, $CDCl_3$): δ 8.55 (d, J = 5.4 Hz, 1H: $1H_{2'}$), 7.98 (d, J = 2.2 Hz, 1H: $1H_{5'}$), 7.74 (d, J = 9.0 Hz, 1H: $1H_{8'}$), 7.41 (dd, J=8.9 Hz, J'=2.2 Hz, 1H: $1H_{6'}$), 6.45 (d, J = 5.4 Hz, 1H: $1H_{3'}$), 5.56 (s, 1H: NH), 4.44 (t, J = 5.6 Hz, 2H: $2H_1$), 3.60 (q, J = 6.2 Hz, 2H: $2H_3$), 3.08 (s, 3H: $3H_{Me}$), 2.21 (m, 2H: $2H_2$)

5.3.18. 7-chloro-*N*-(3'-chloropropyl)-4-quinolinamine, 132[117]



130 **132**

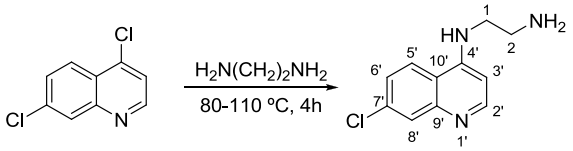
In a 10 mL Schlenk flask equipped with magnetic stirring and nitrogen atmosphere, a mixture of 171 mg **130** (0.72 mmol), 1.0 mL thionyl chloride (14.40 mmol), and catalytic amount of DMF was stirred at room temperature for 24 h. After that, the resulting mixture was neutralized with 5 mL $NaHCO_3$ saturated aqueous solution and

extracted with EtOAc (3 x 5 mL). The combined organic extracts were dried over anhydrous Na_2SO_4 and concentrated under vacuum to give 158 mg (0.62 mmol, 86% yield) of **132** without further purification.

mp= 140-143 ℃ ; lit.[117] mp=130-133 ℃

^{1}H NMR (250 MHz, $CDCl_3$): δ 8.55 (d, J = 5.2 Hz, 1H: $1H_2$), 8.00 (d, J = 2.1 Hz, 1H: $1H_5$), 7.75 (d, J = 8.9 Hz, 1H: $1H_8$), 7.39 (dd, J=9.0 Hz, J'=2.0 Hz, 1H: $1H_6$), 6.49 (d, J = 5.4 Hz, 1H: $1H_3$), 5.48 (s, 1H: NH), 3.73 (dd, J=6.4 Hz, J'=5.6 Hz, 2H: $2H_{3'}$), 3.61 (q, J = 6.4 Hz, 2H: $2H_{1'}$), 2.25 (m, 2H: $2H_{2'}$)

5.3.19. *N*^{1}-(7-chloro-4-quinolinyl)-1,2-ethanediamine, 134[117]



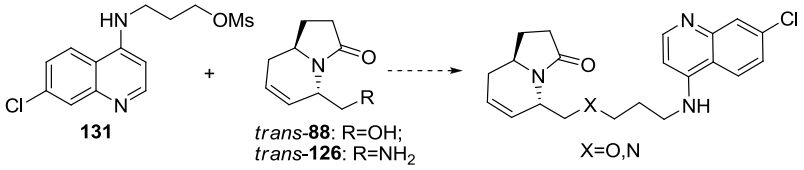
127 134

In a 10 mL Schlenk flask equipped with magnetic stirring, a mixture of 0.5 g 4,7-dichloroquinoline **127** (2.50 mmol) and 0.42 mL 1,2-ethanediamine (6.30 mmol) was warmed to 80 ℃ and kept for 1 h without stirring, then, it was raised to 110 ℃ for 4 h with continued stirring. After cooling to rt, the mixture was diluted with 3 mL CH_2Cl_2 then washed with 10 mL 5% NaOH. After the extraction with CH_2Cl_2 (4 x 5 mL), the combined organic extracts were dried over anhydrous Na_2SO_4 and concentrated under vacuum to give 280 mg (1.27 mmol, 50% yield) of **134**.

mp=136-138 ℃ ; lit.[117] mp=137-139 ℃

^{1}H NMR (250 MHz, $CDCl_3$): δ 8.54 (d, J = 5.3 Hz, 1H: $1H_{2'}$), 7.97 (d, J = 2.2 Hz, 1H: $1H_{5'}$), 7.75 (d, J = 8.9 Hz, 1H: $1H_{8'}$), 7.37 (dd, J=8.9 Hz, J'=2.2 Hz, 1H: $1H_{6'}$), 6.42 (d, J = 5.4 Hz, 1H: $1H_{3'}$), 5.82 (s, 1H: NH), 3.34 (dt, J=6.2 Hz, J'=4.9 Hz, 2H: $2H_1$), 3.13 (dd, J=6.7 Hz, J'=4.8 Hz, 2H: $2H_2$)

5.3.20. Attempted reaction between mesylate 132 and alcohol *trans*-88 or amine *trans*-126



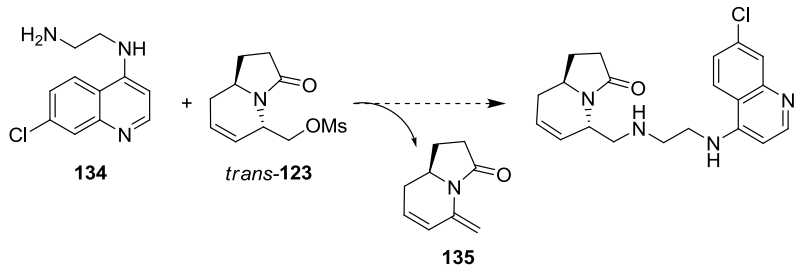
The table below summarizes the attempted reactions:

Table 12. Attempts and results of reaction of **131** with *trans*-**88** and *trans*-**126**[a]

Entry	Reactant	X	Reagent	T	Time	Result
1	*trans*-**88**	O	Et_3N	0 °C -rt	2 h	**133** + *trans*-**88**
2	*trans*-**88**	O	Et_3N	55 °C	5 h	**133** + *trans*-**88**
3	*trans*-**88**	O	NaH	rt	6 h	**133** + *trans*-**88**
4	*trans*-**88**	O	NaH	60 °C	6 h	only *trans*-**88**
5	*trans*-**126**	N	Et_3N	60 °C	overnight	decomposition

[a] All reaction were performed in THF as solvent and the results were determined by ^{1}H NMR

5.3.21. Attempted reaction between mesylate *trans*-123 and the amine 134



The table below summarizes the unsuccessful attempts of reacting *trans*-**123** with **134**:

Table 14. Attempts and results of reaction between **134** and *trans*-**123**[a]

Entry	Reagent	Solvent	T	Result
1	K_2CO_3	EtOH	rt	**134** + *trans*-**123**
2	K_2CO_3	EtOH	60ºC	**135**(70%)+**134**
3	K_2CO_3	DMF	rt	**134** + *trans*-**123**
4	Et_3N	DMF	50 ºC	only *trans*-**123**

[a] All reaction were ran overnight and the results were determined by ^{1}H NMR

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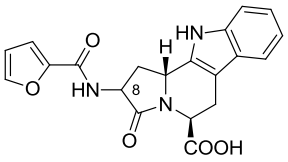
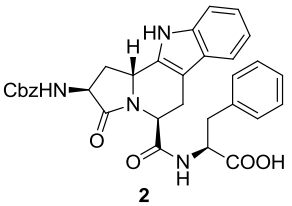


(8S)-**1**
(8R)-**1**



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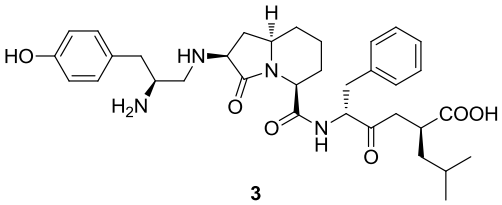

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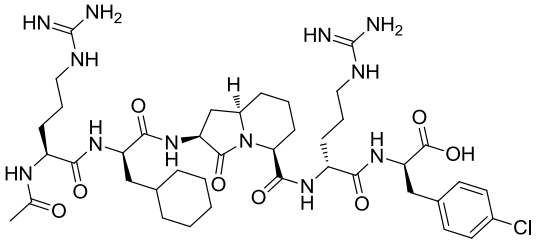

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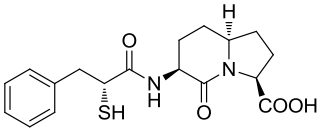

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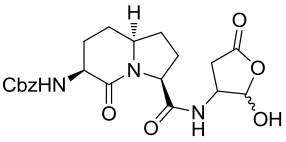

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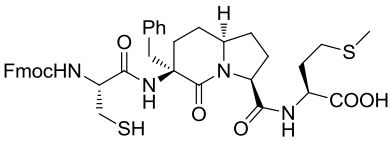

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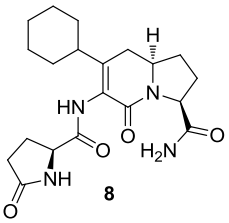

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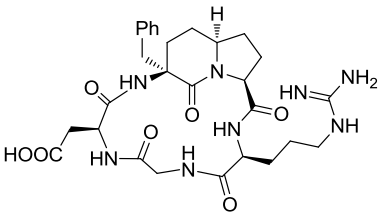

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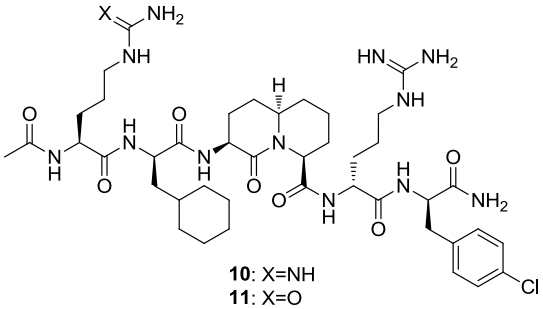

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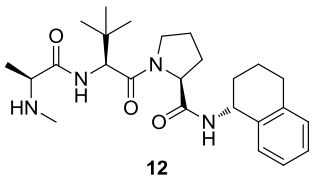
11: X=O



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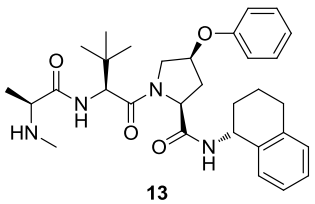

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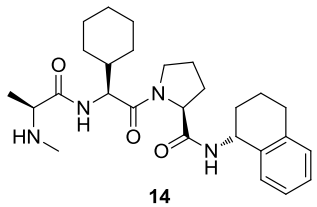

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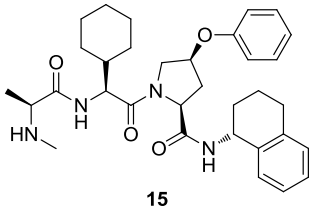

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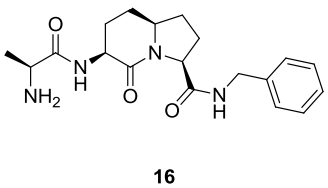

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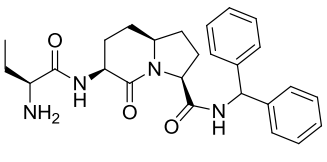

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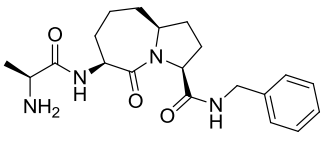

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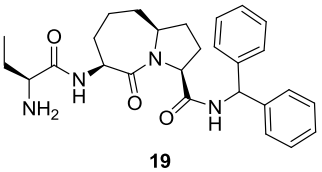

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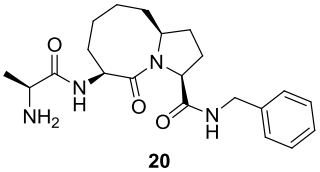

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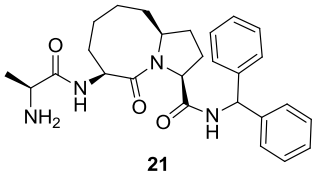

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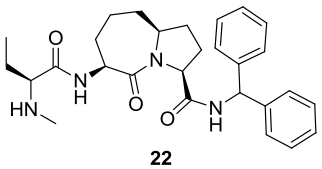

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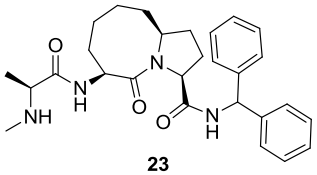

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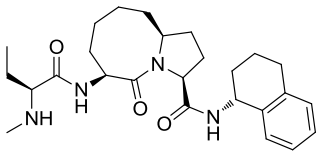

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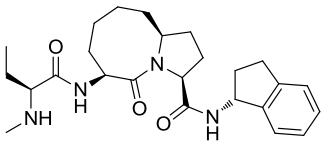

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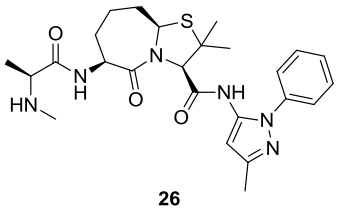

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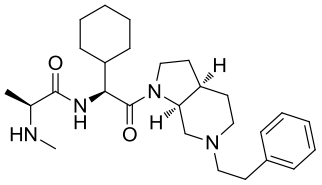

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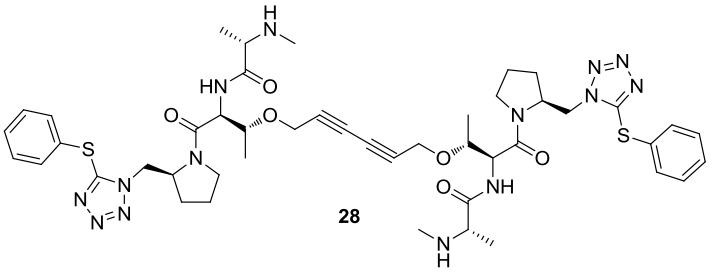

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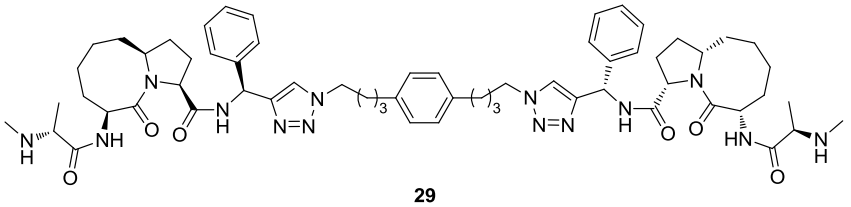

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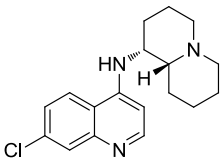

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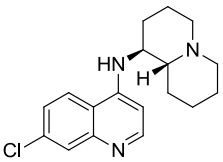

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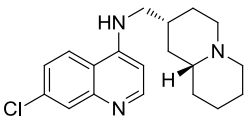

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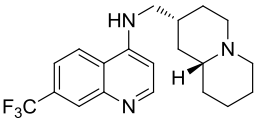

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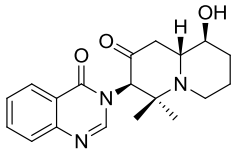

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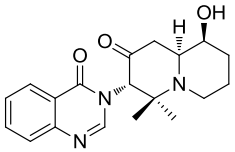

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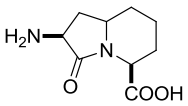

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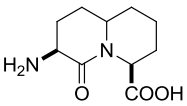

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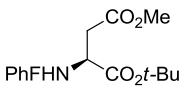

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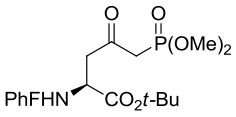

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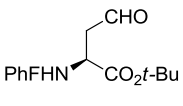

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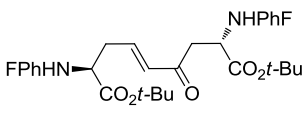

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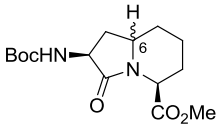
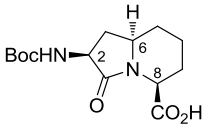
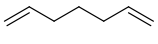


(6*S*)-**42**
(6*R*)-**42**



(*2S,6R,8S*)-**43**



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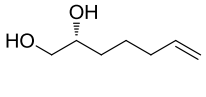

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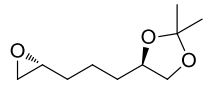

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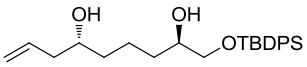

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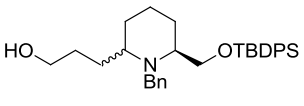
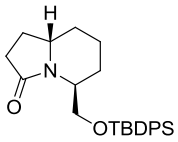


cis-**48**
trans-**48**



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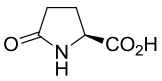

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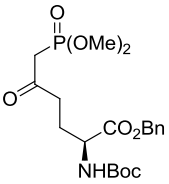

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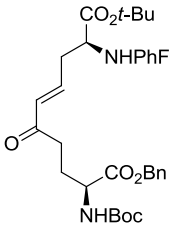

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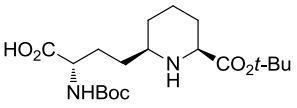

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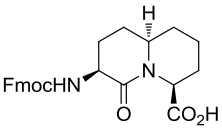

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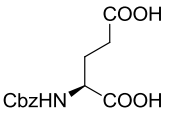

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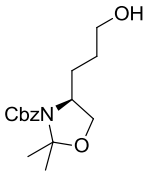

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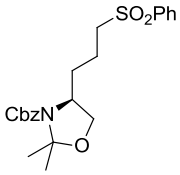

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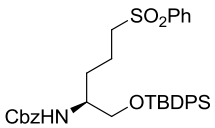

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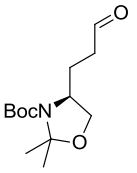

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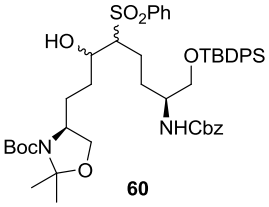

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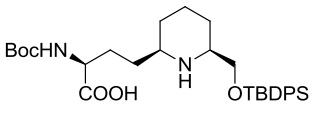
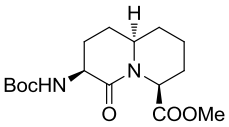
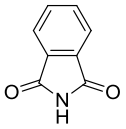


61

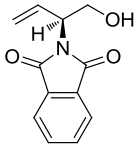


62

(±)-**63**



64



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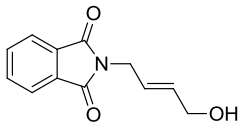

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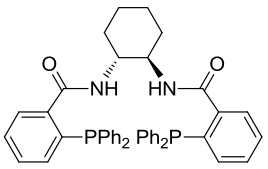

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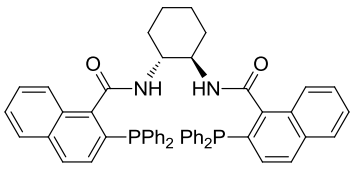

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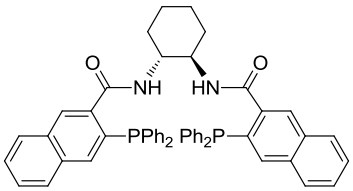
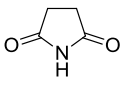


69



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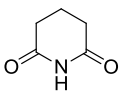
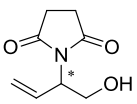
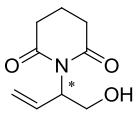


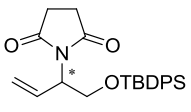
71



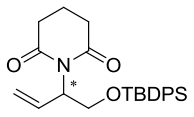
(*R*)-**72**
(*S*)-**72**



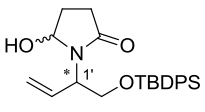
(*R*)-**73**
(*S*)-**73**



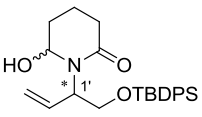
(*R*)-**74**
(*S*)-**74**



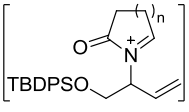
(*R*)-**75**
(*S*)-**75**



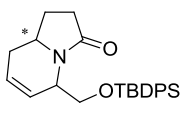
(1'*R*)-**76**
(1'*S*)-**76**



(1'*R*)-**77**
(1'*S*)-**77**



n=1: **78**
n=2: **79**



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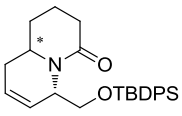
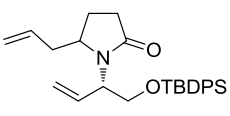
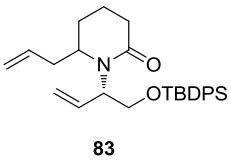


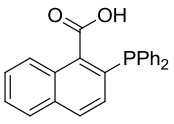
81



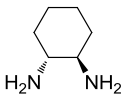
82



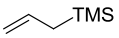
83



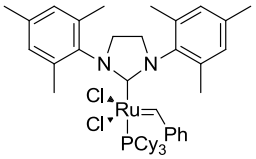
84



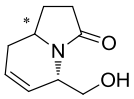
85



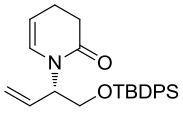
86



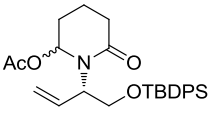
87



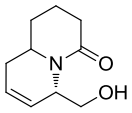
(+)-*cis*-**88**
(-)-*trans*-**88**



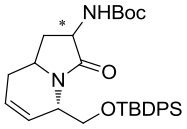
89



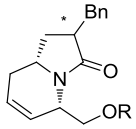
90



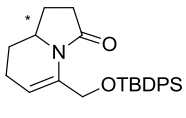
91



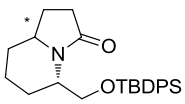
92



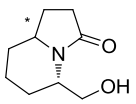
93



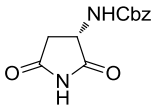
(8a*R*)-**94**
(8a*S*)-**94**



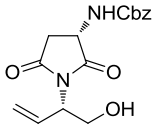
95



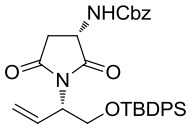
96



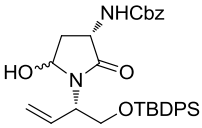
97



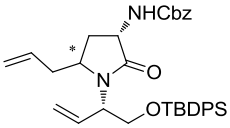
98



99



100



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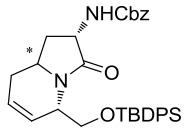
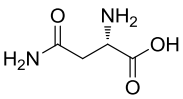
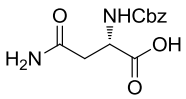


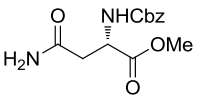
102b: (2*S*,5*S*,8a*S*)
102a: (2*S*,5*S*,8a*R*)



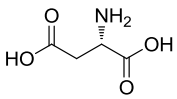
103



104



105



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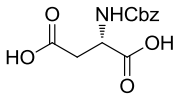
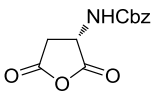
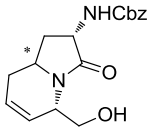


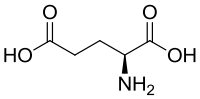
107



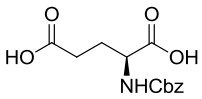
108



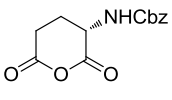
109b: (2*S*,5*S*,8a*S*)
109a: (2*S*,5*S*,8a*R*)



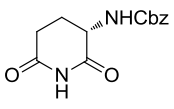
110



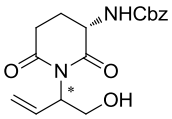
111



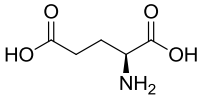
112



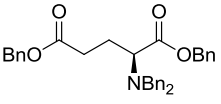
113



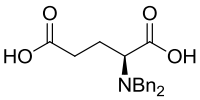
114



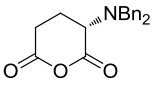
115



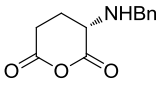
116



117



118



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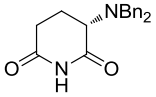
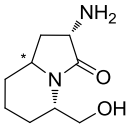
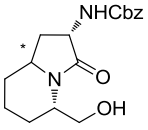


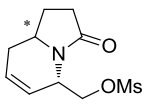
120



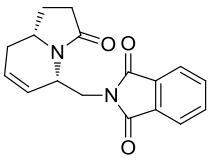
121b: (2*S*,5*S*,8a*S*)
121a: (2*S*,5*S*,8a*R*)



122b: (2*S*,5*S*,8a*S*)
122a: (2*S*,5*S*,8a*R*)



cis-**123**
trans-**123**

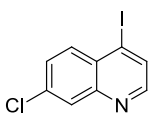


cis-**124**

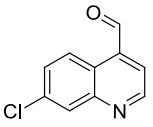
cis-**125**
trans-**125**

cis-**126**
trans-**126**

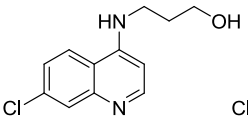
127



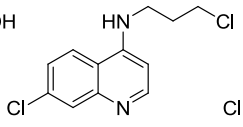
128



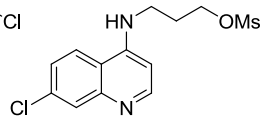
129



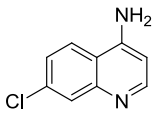
130



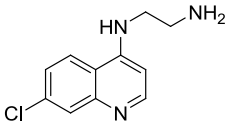
131



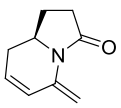
132



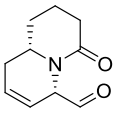
133



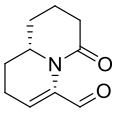
134



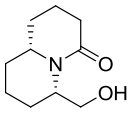
135



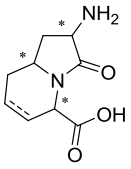
136



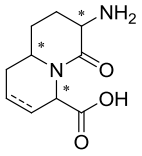
137



138

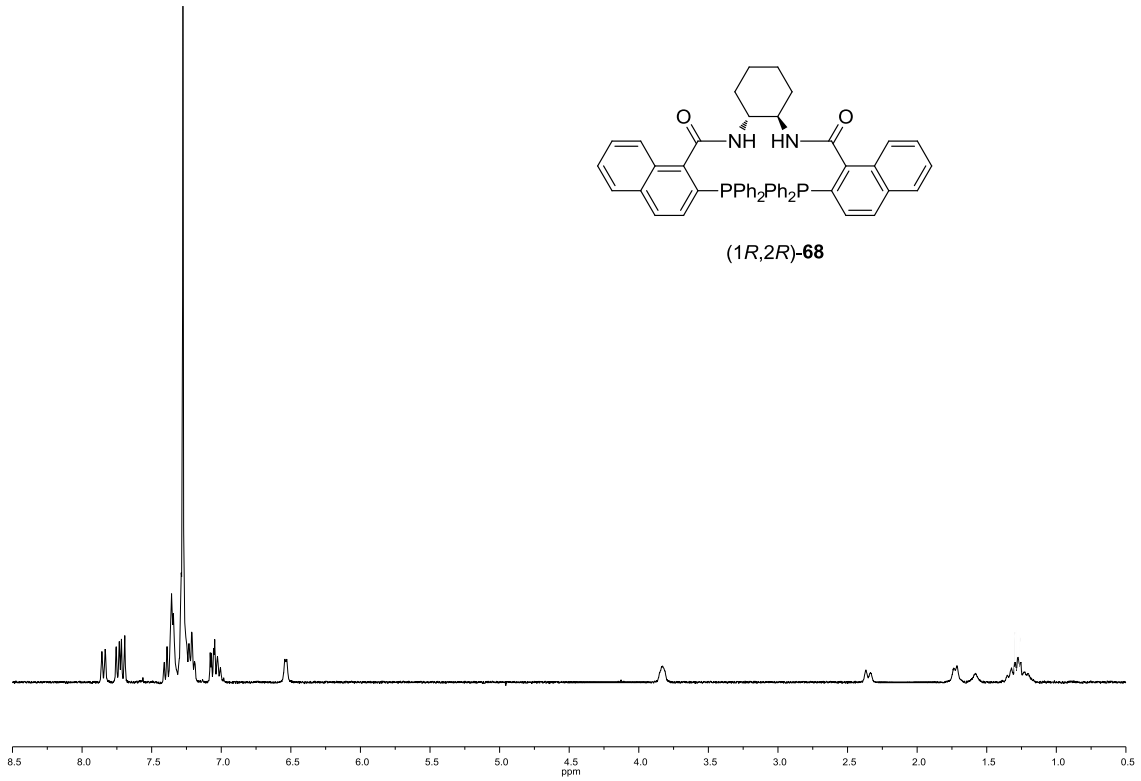


TM1

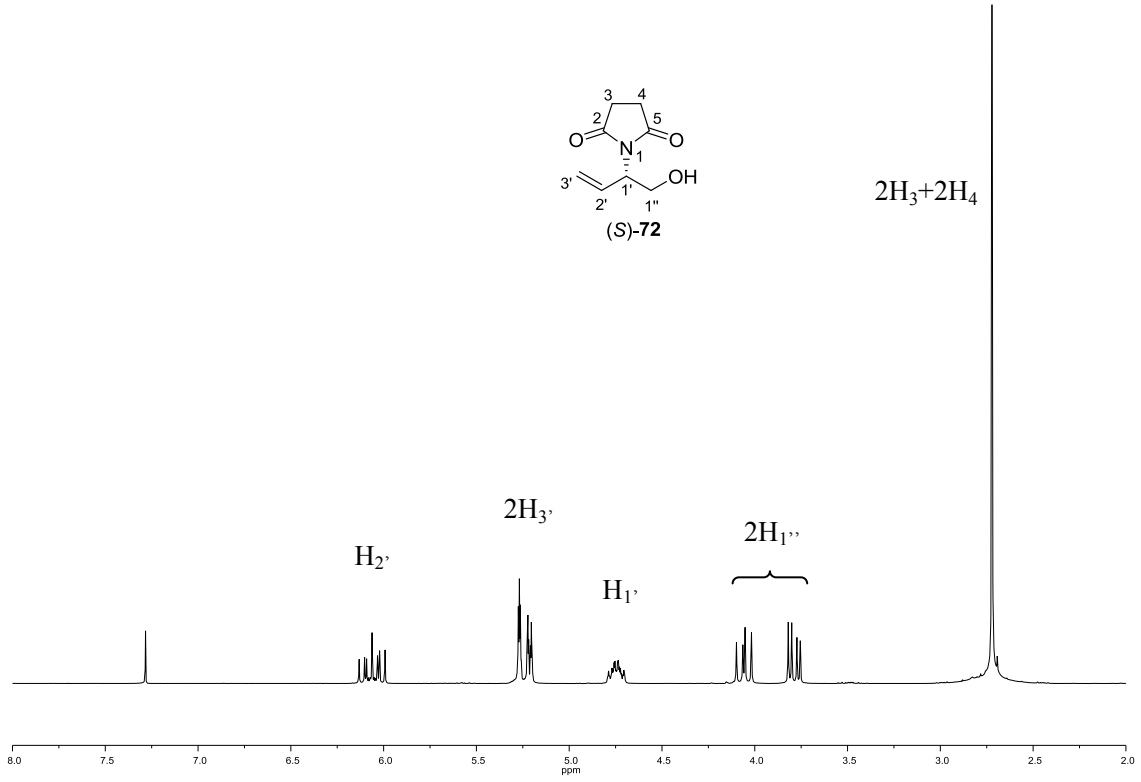


TM2

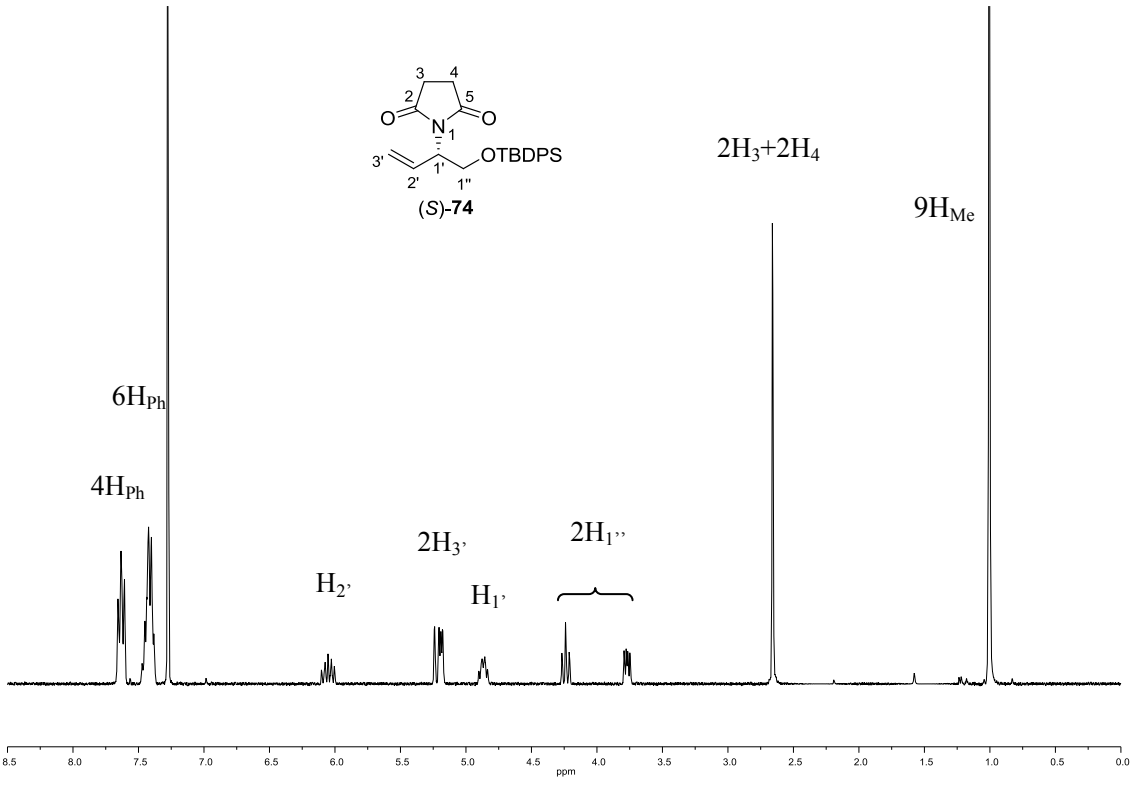
VI. Spectra



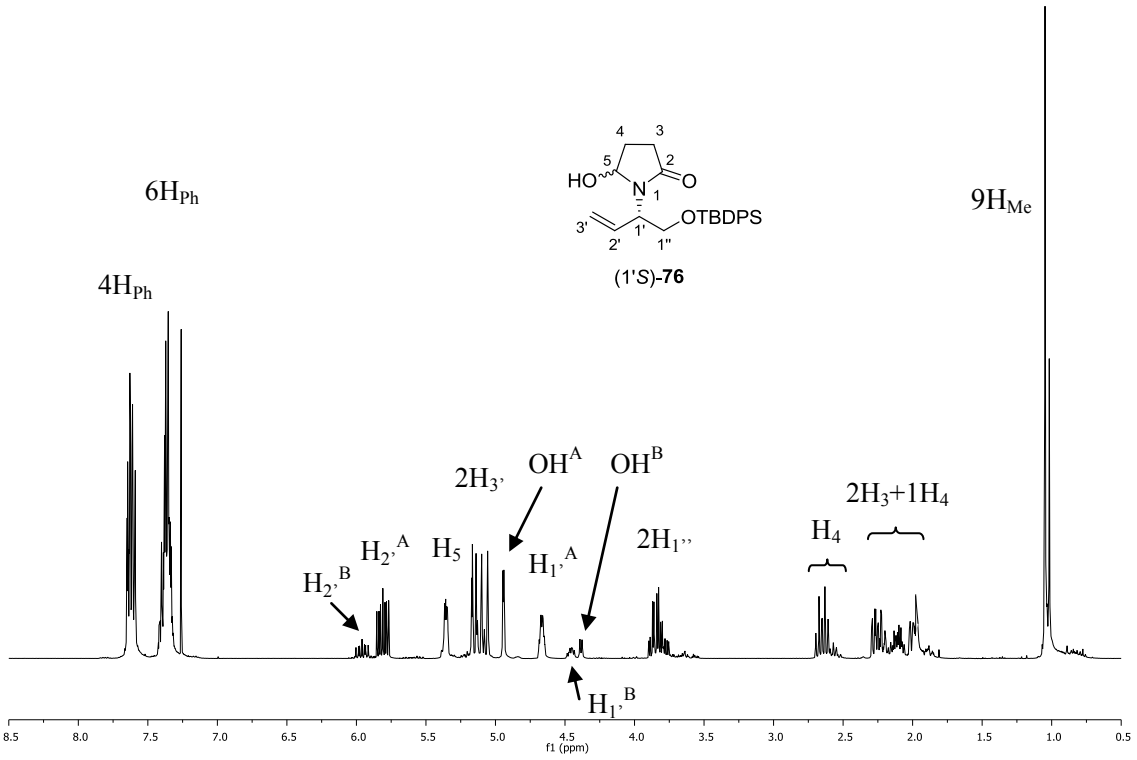
^{1}H NMR ($CDCl_3$, 250 MHz)



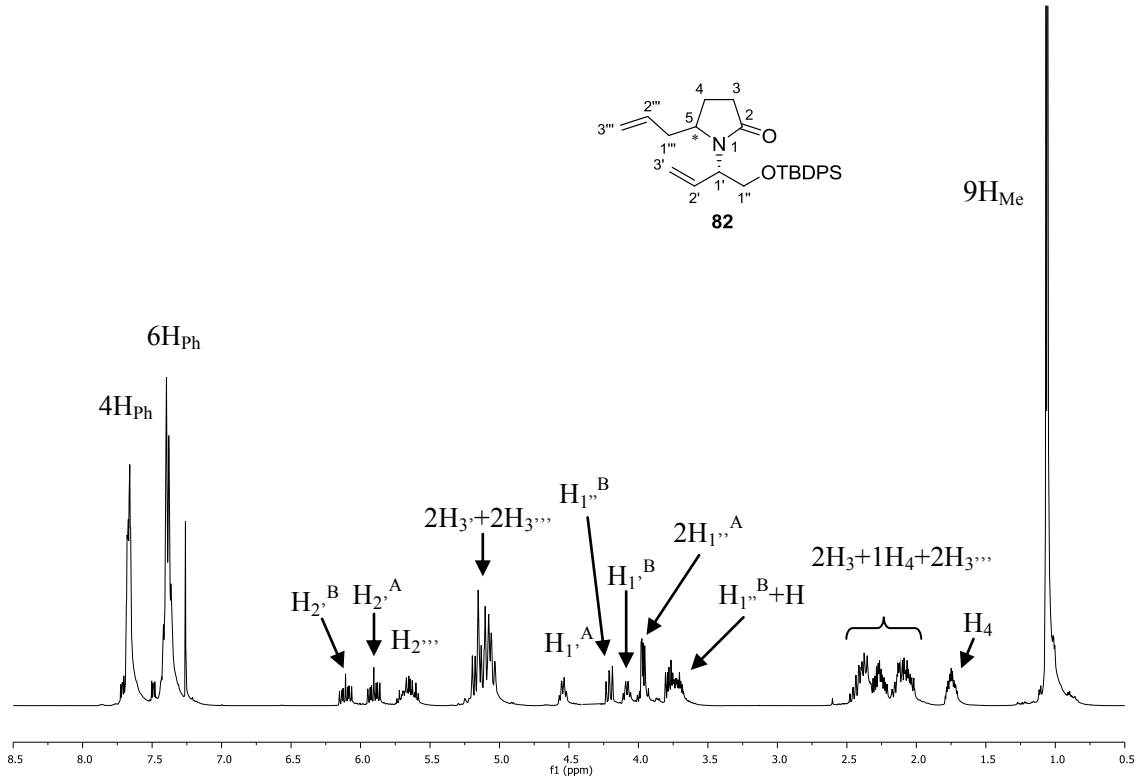
^{1}H NMR ($CDCl_3$, 250 MHz)



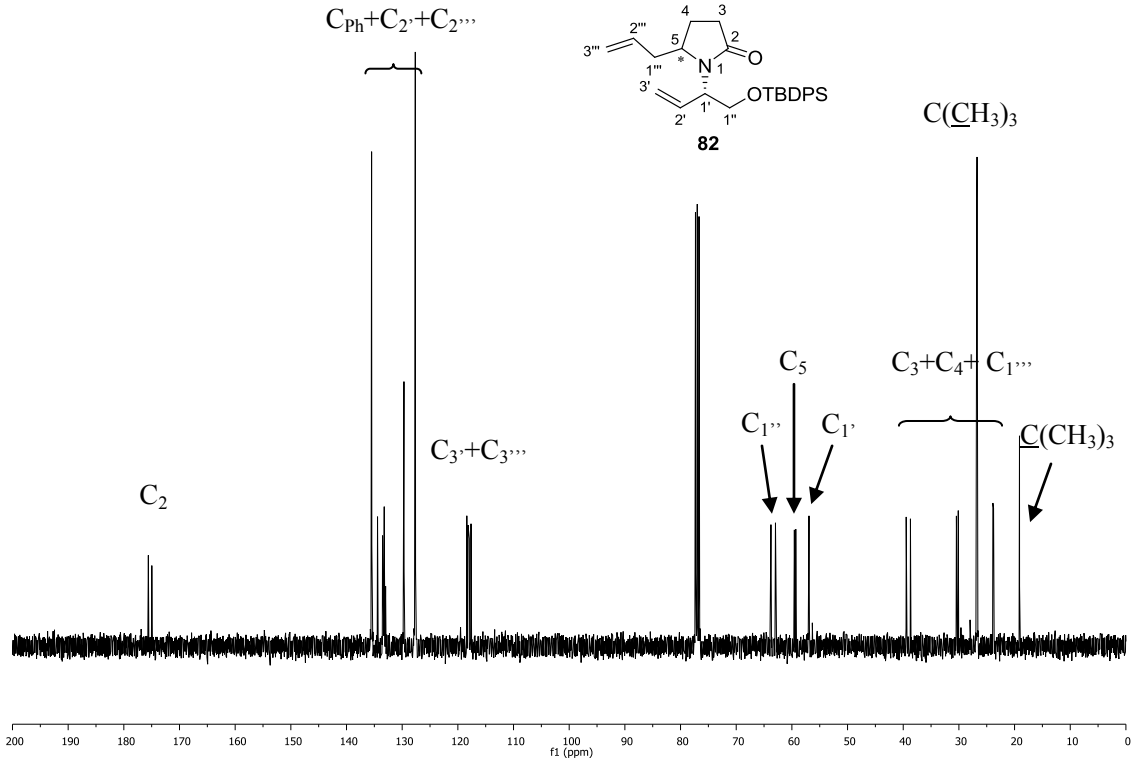
^{1}H NMR ($CDCl_3$, 360 MHz)



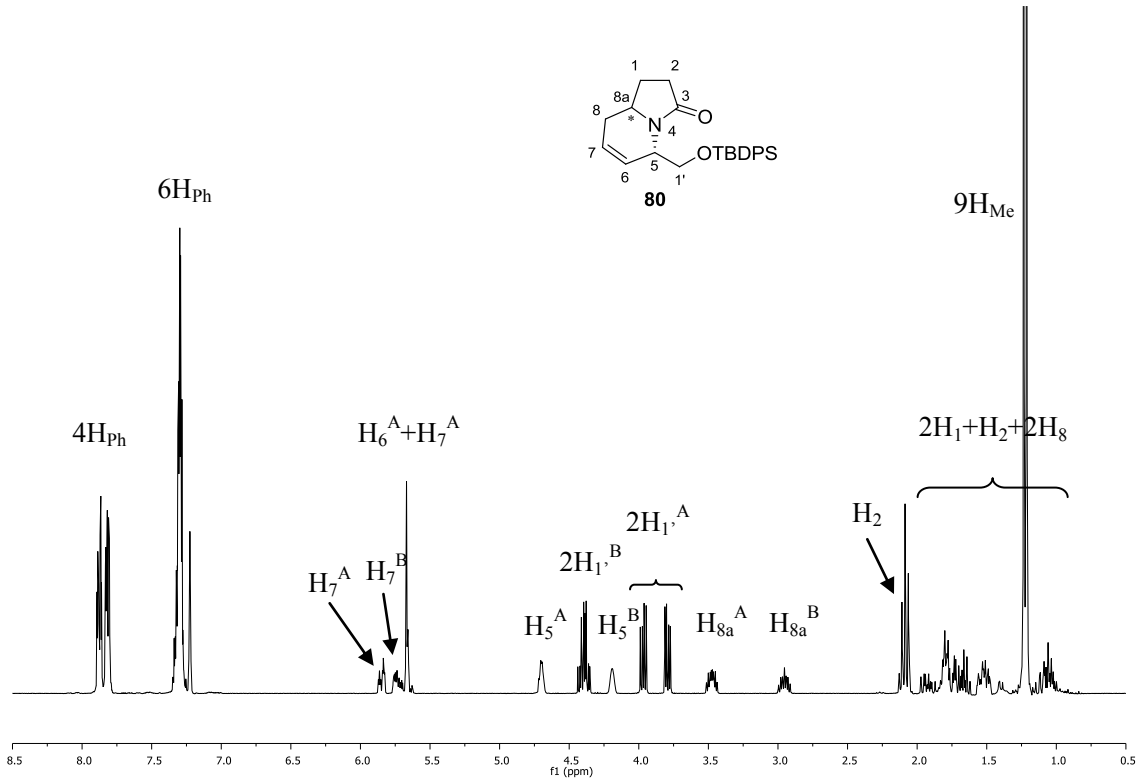
^{1}H NMR ($CDCl_3$, 250 MHz)



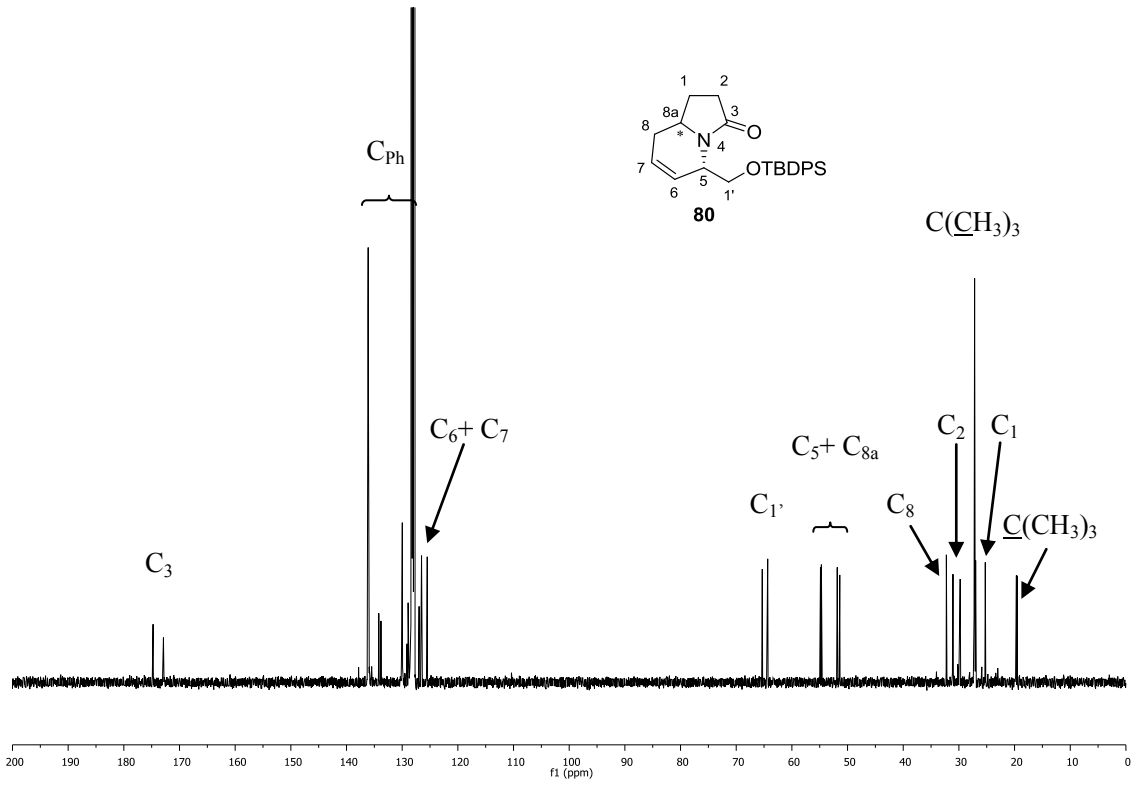
^{1}H NMR ($CDCl_3$, 400 MHz)



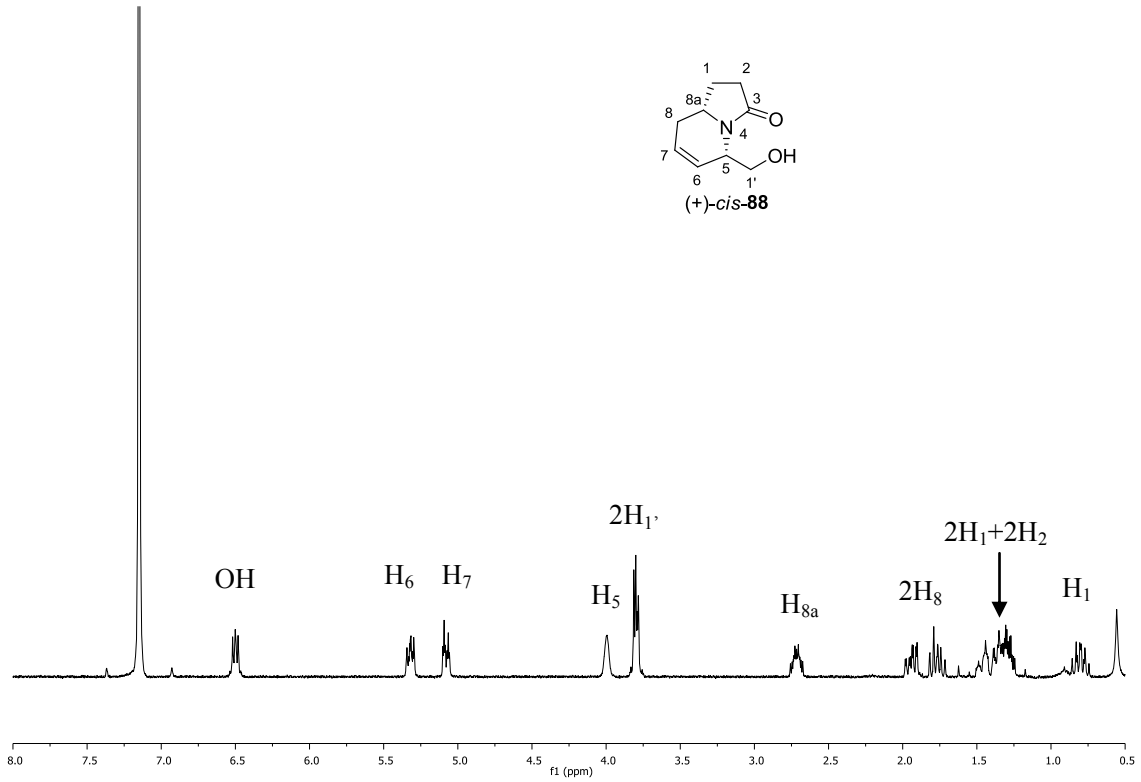
^{13}C NMR ($CDCl_3$, 101 MHz)



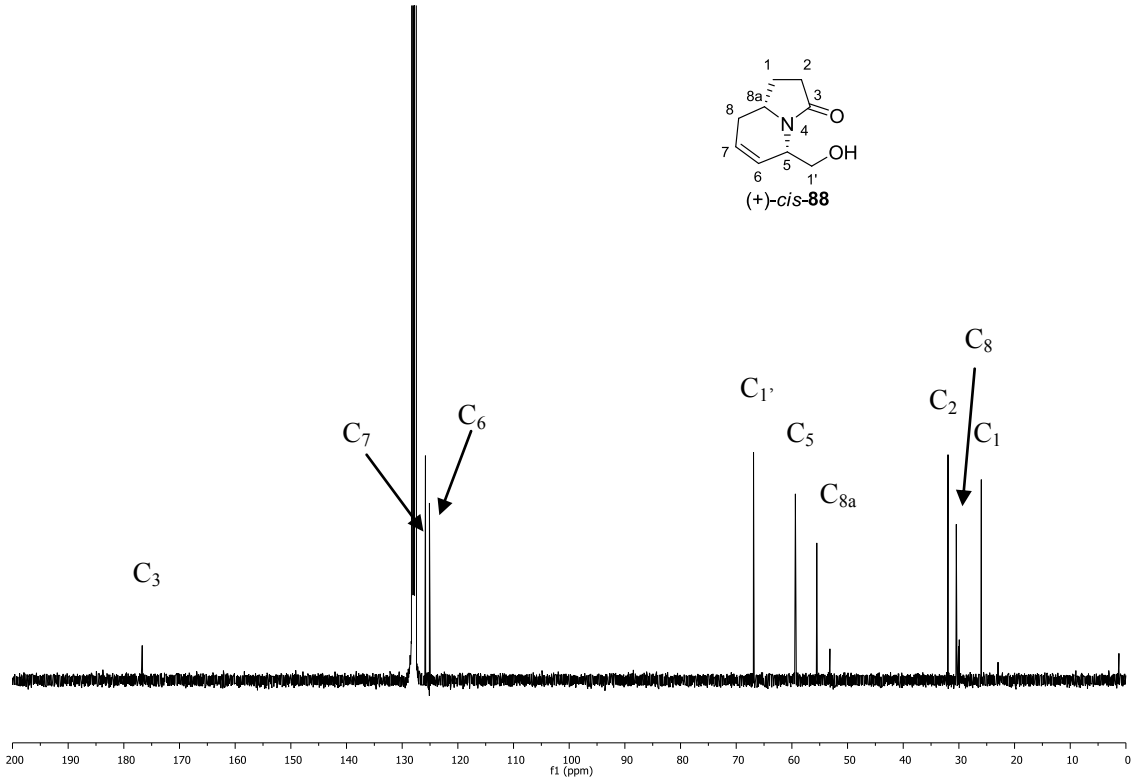
^{1}H NMR (C_6D_6, 400 MHz)



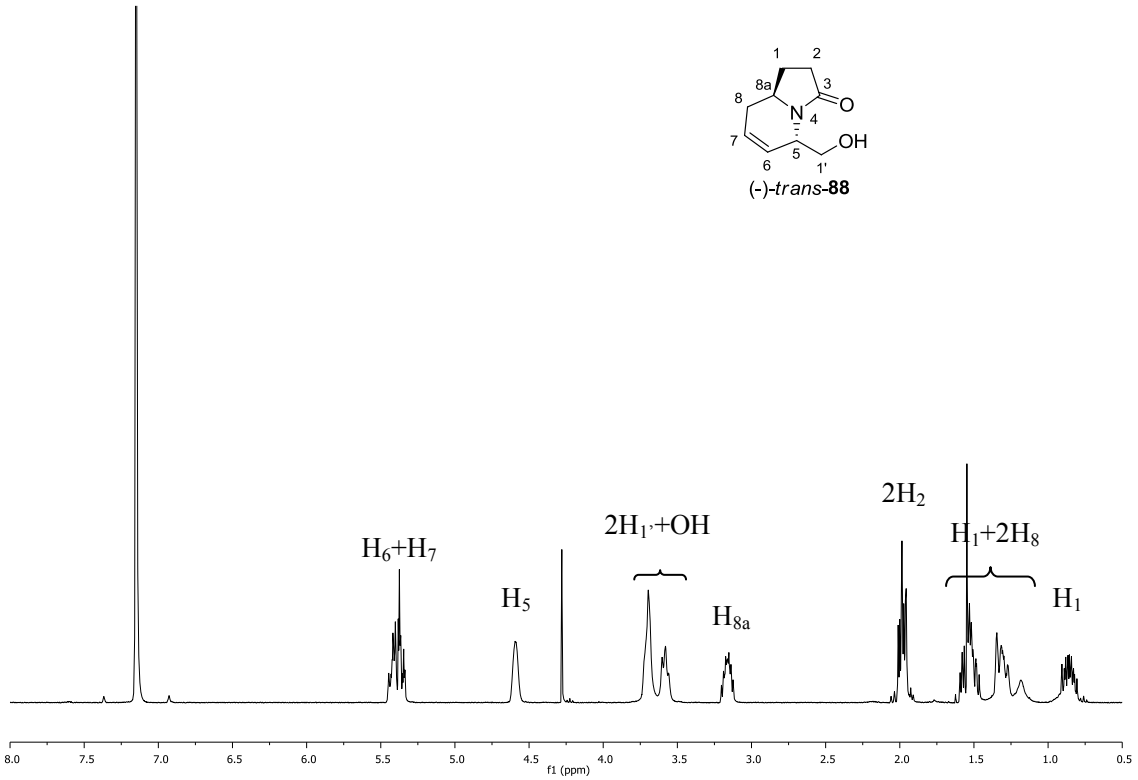
^{13}C NMR (C_6D_6, 101 MHz)



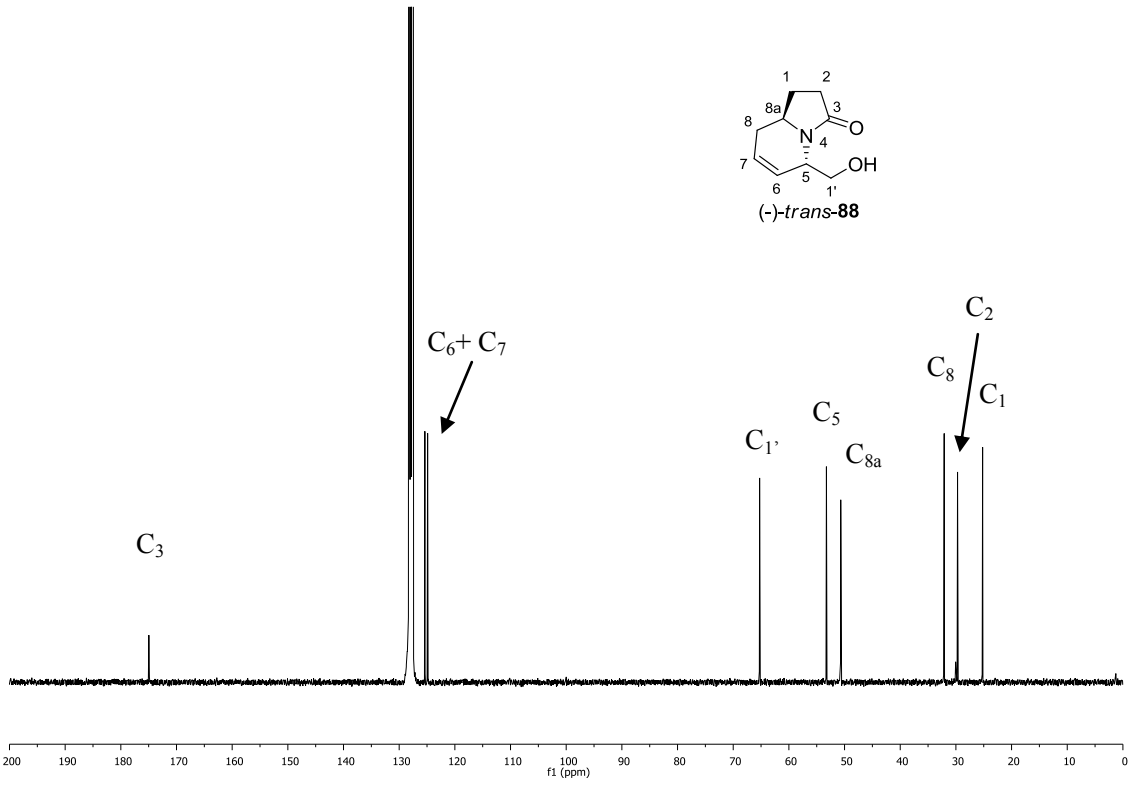
^{1}H NMR (C_6D_6, 360 MHz)



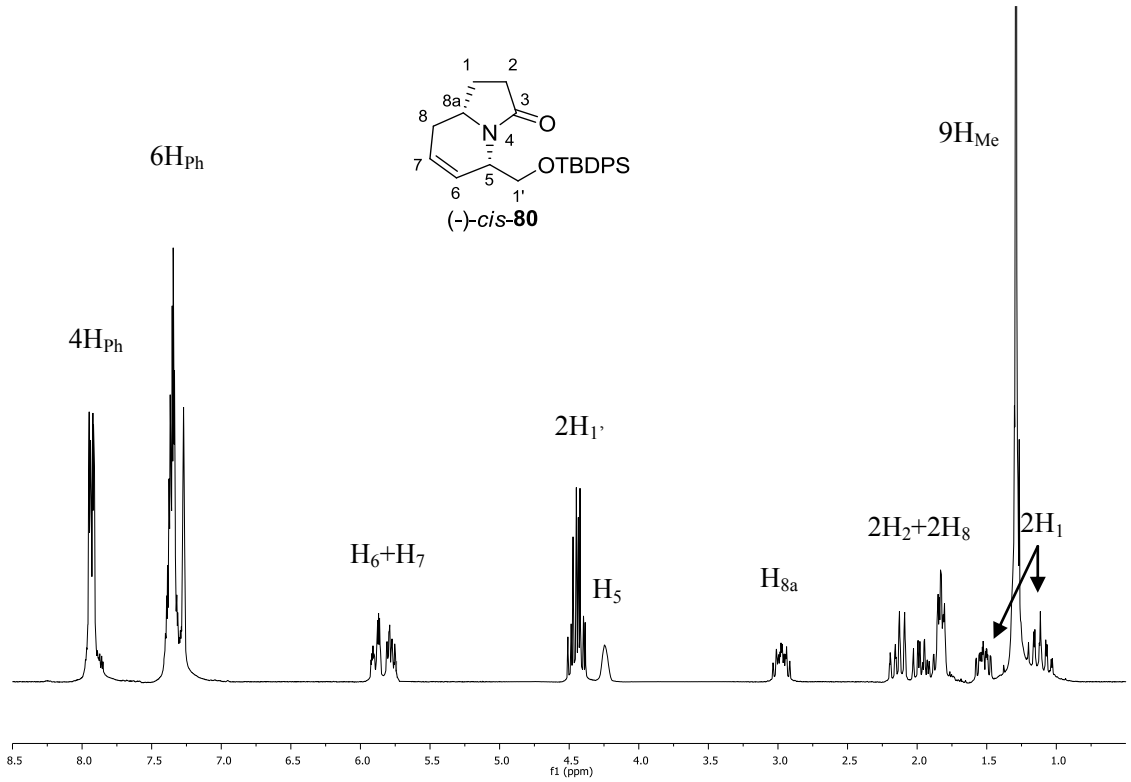
^{13}C NMR ($CDCl_3$, 90 MHz)



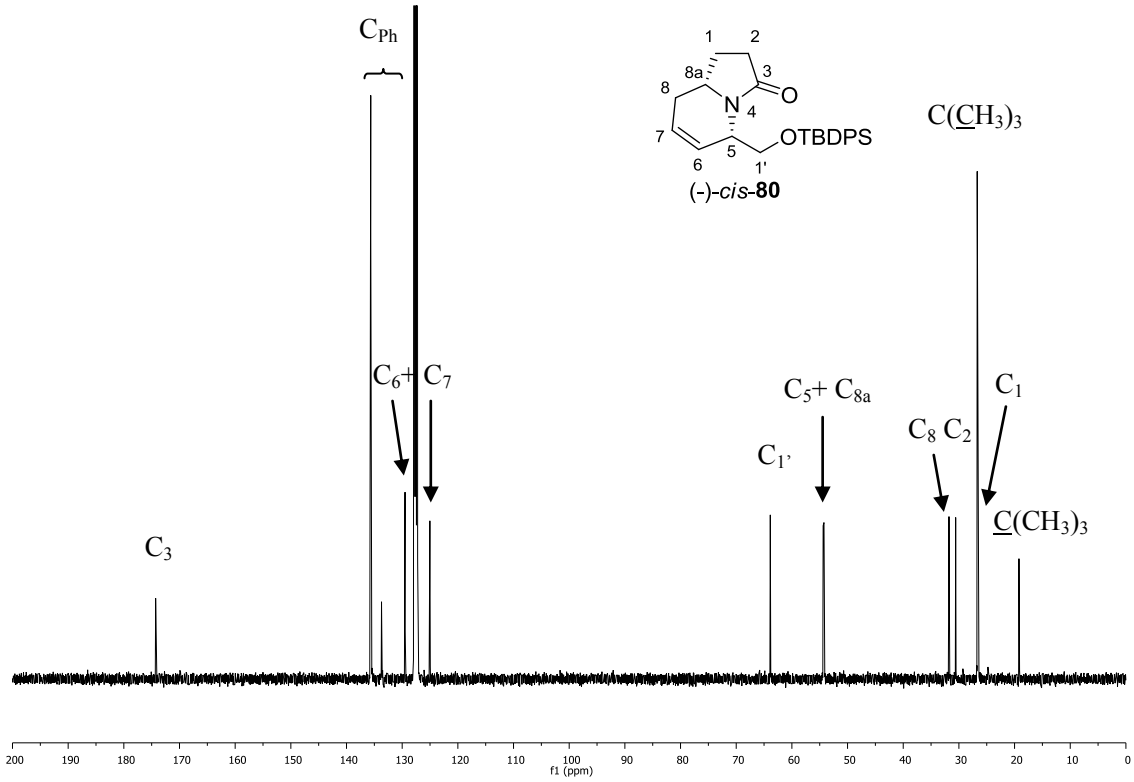
^{1}H NMR (C_6D_6, 360 MHz)



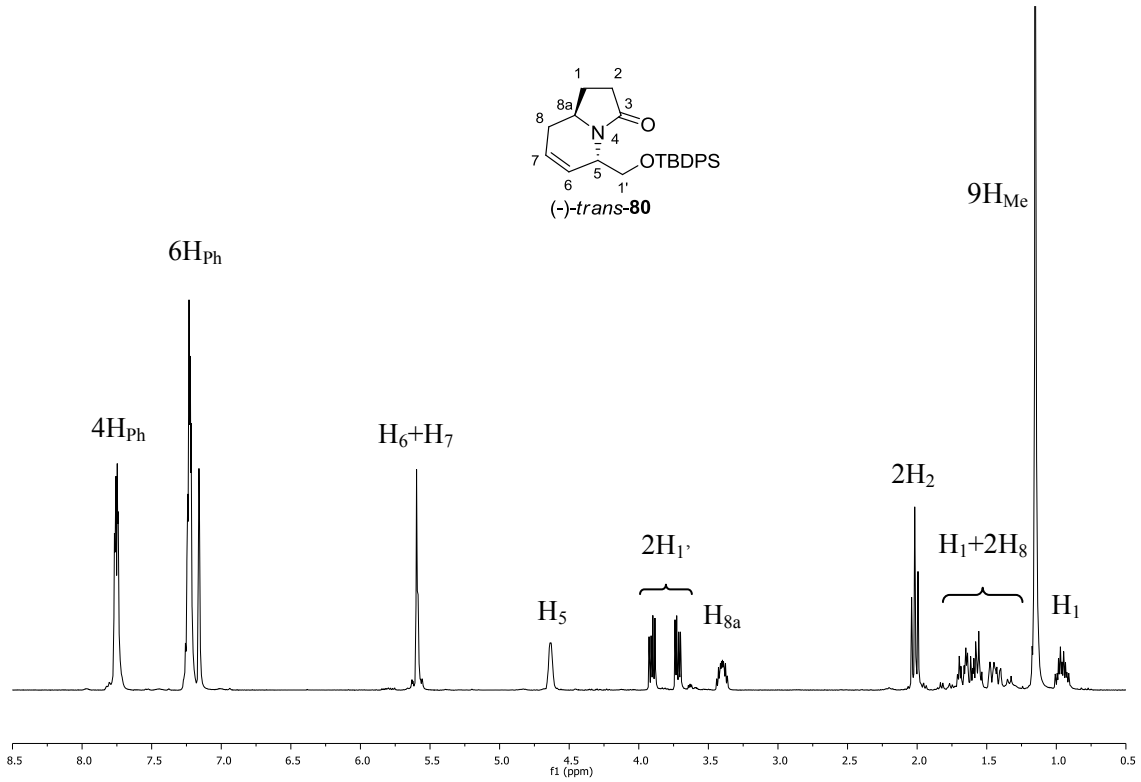
^{13}C NMR ($CDCl_3$, 90 MHz)



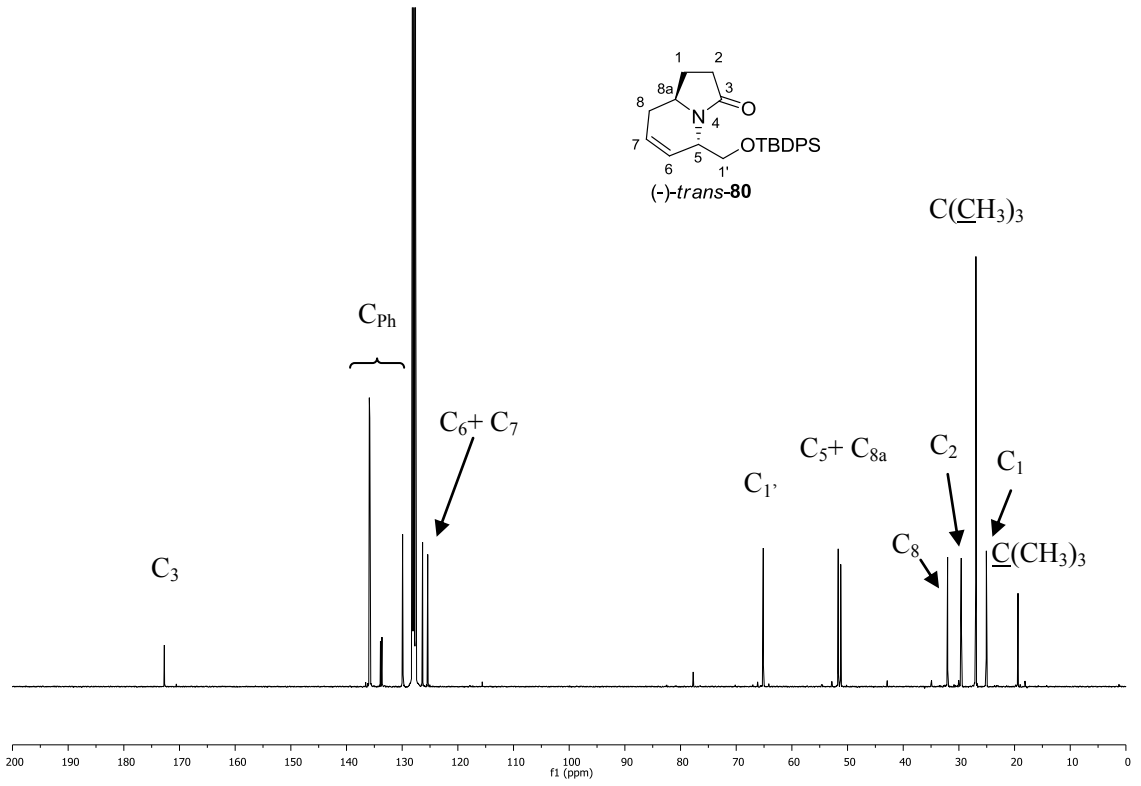
^{1}H NMR (C_6D_6, 250 MHz)



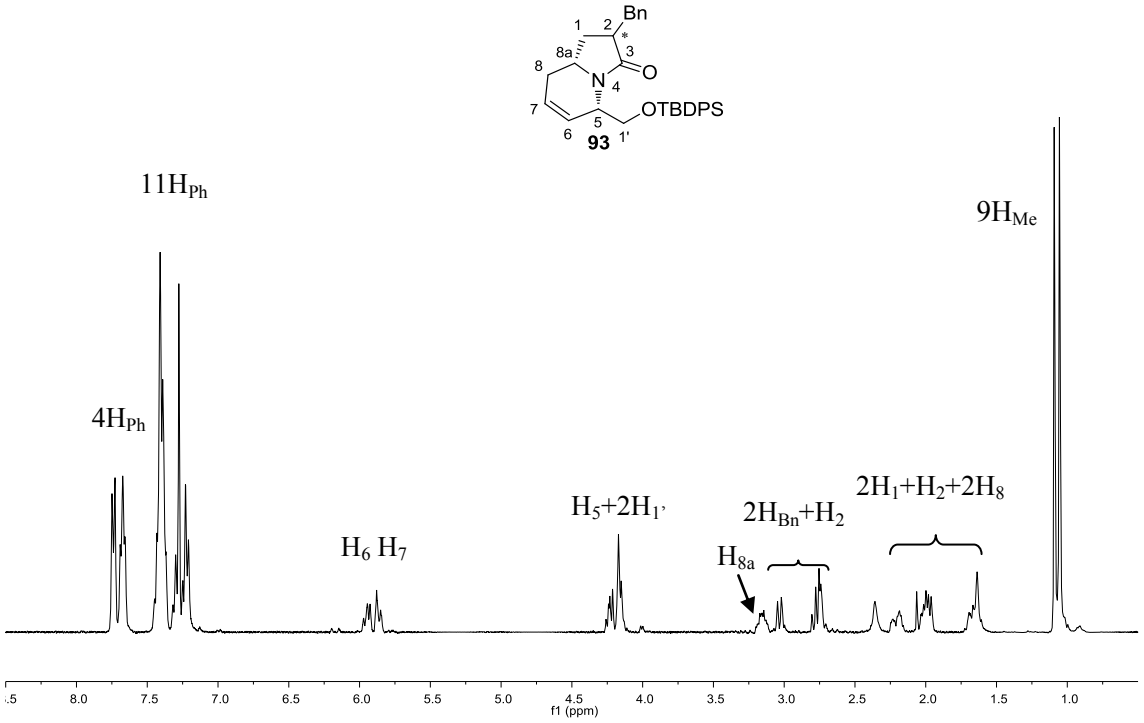
^{13}C NMR (C_6D_6, 101 MHz)



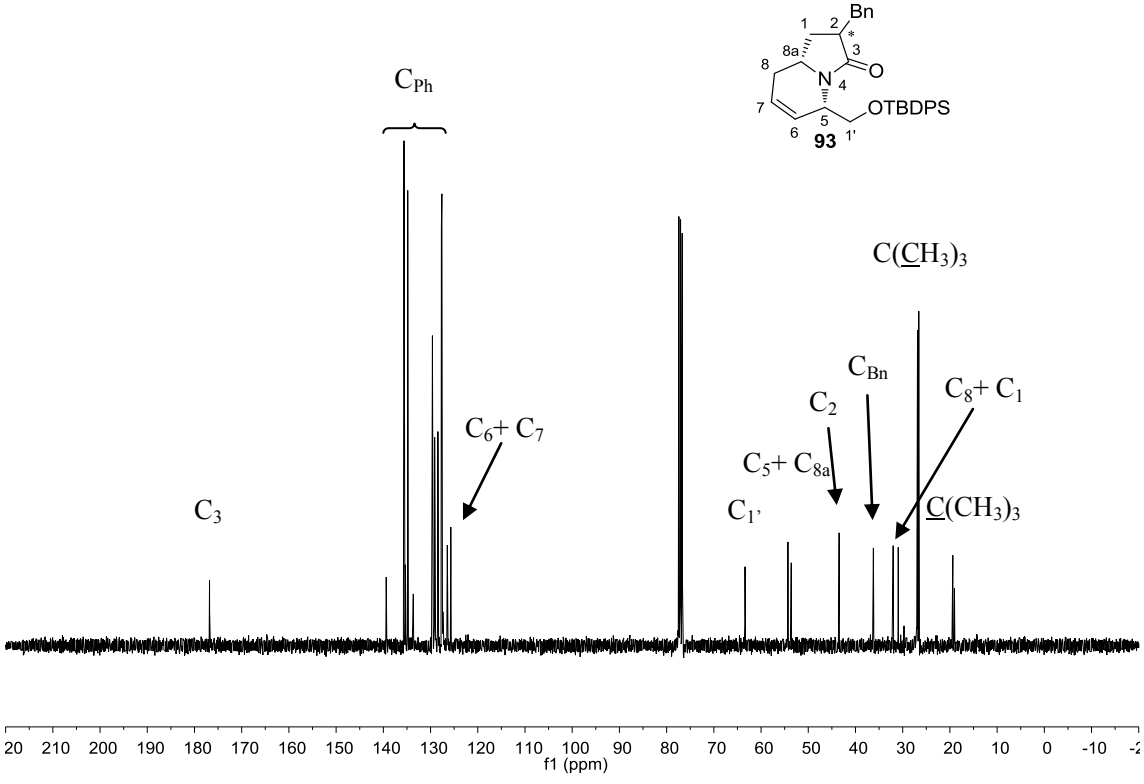
^{1}H NMR (C_6D_6, 400 MHz)



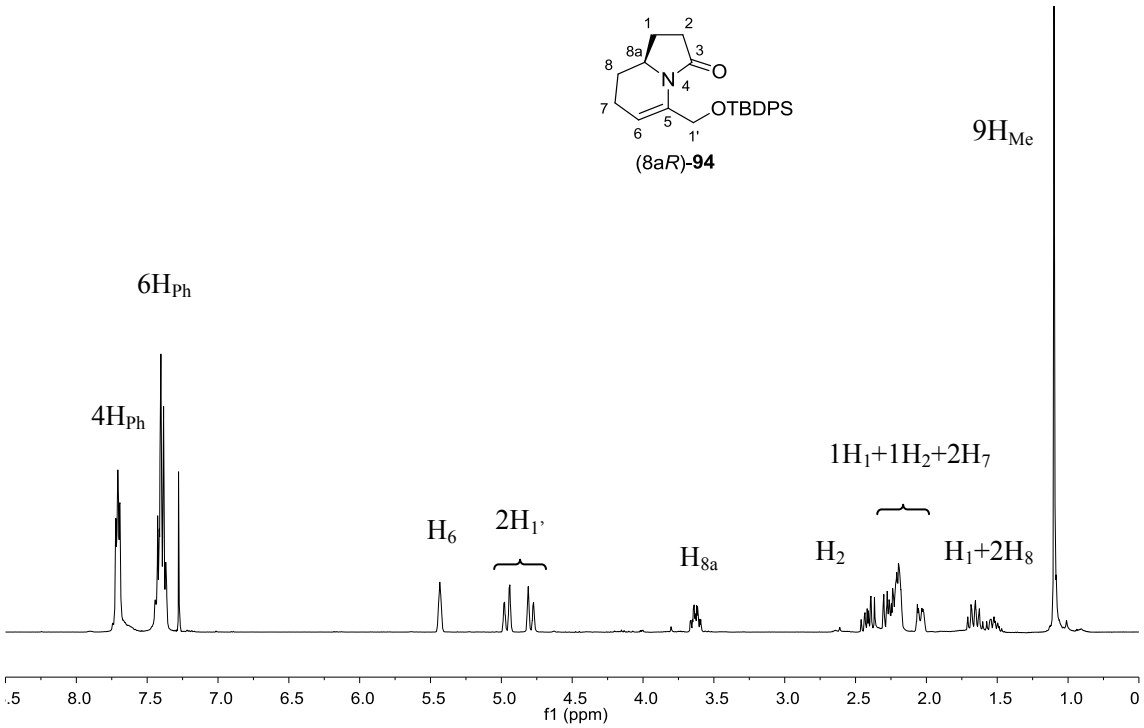
^{13}C NMR ($CDCl_3$, 101 MHz)



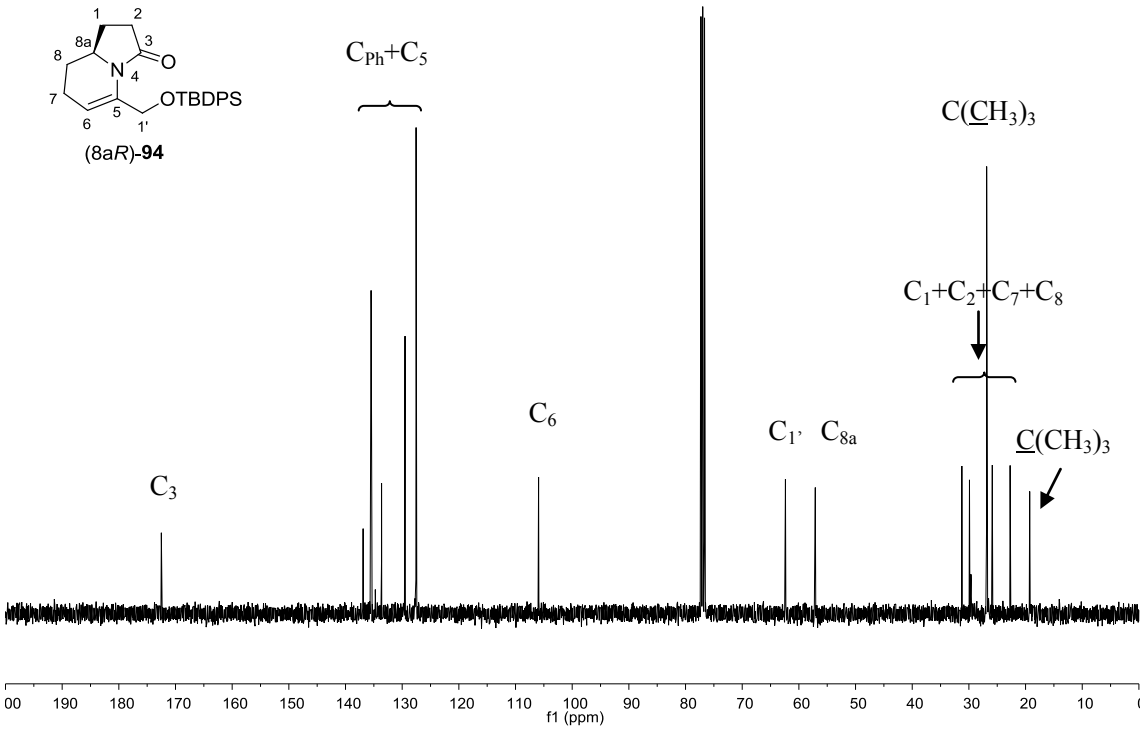
^{1}H NMR ($CDCl_3$, 250 MHz)



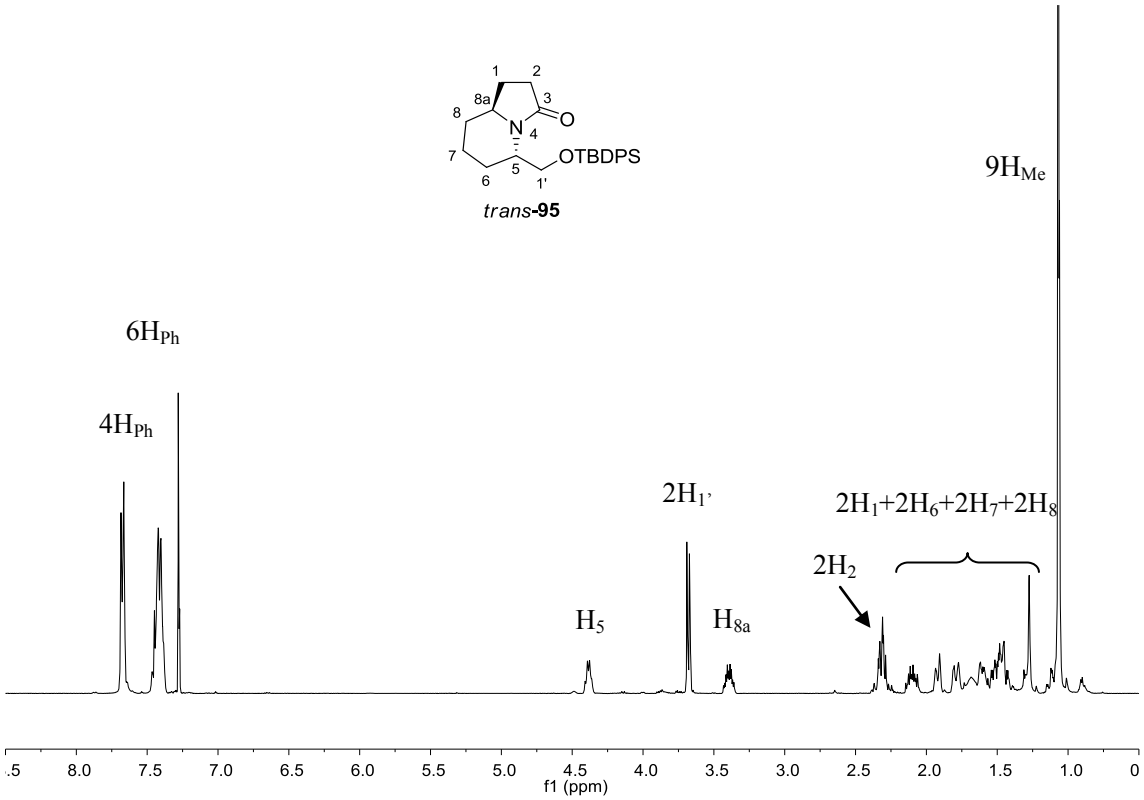
^{13}C NMR ($CDCl_3$, 60 MHz)



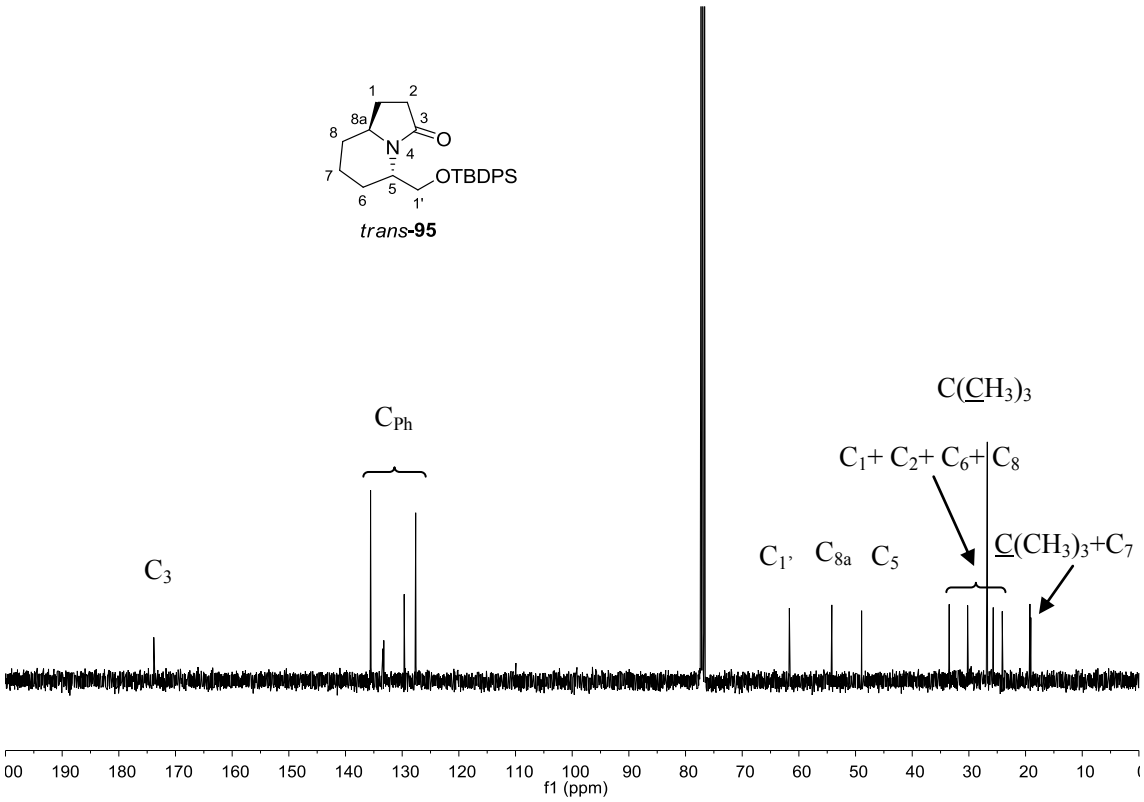
^{1}H NMR ($CDCl_3$, 400 MHz)



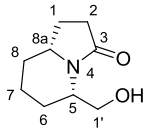
^{13}C NMR ($CDCl_3$, 101 MHz)



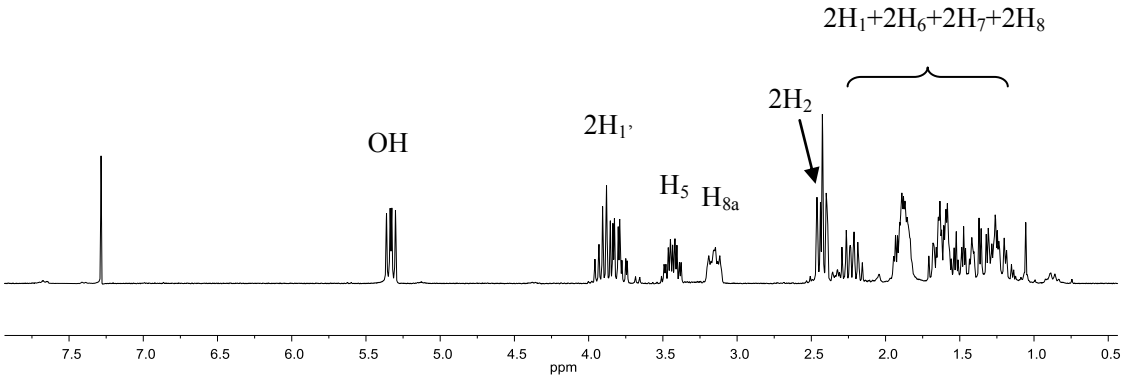
^{1}H NMR ($CDCl_3$, 400 MHz)



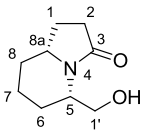
^{13}C NMR ($CDCl_3$, 101 MHz)



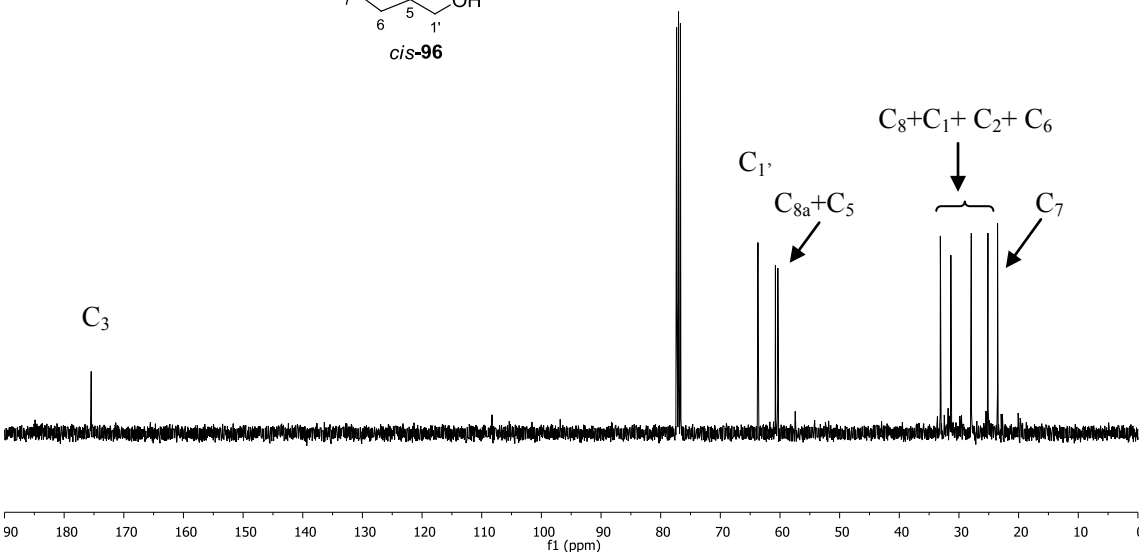
cis-**96**



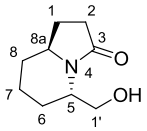
^{1}H NMR ($CDCl_3$, 250 MHz)



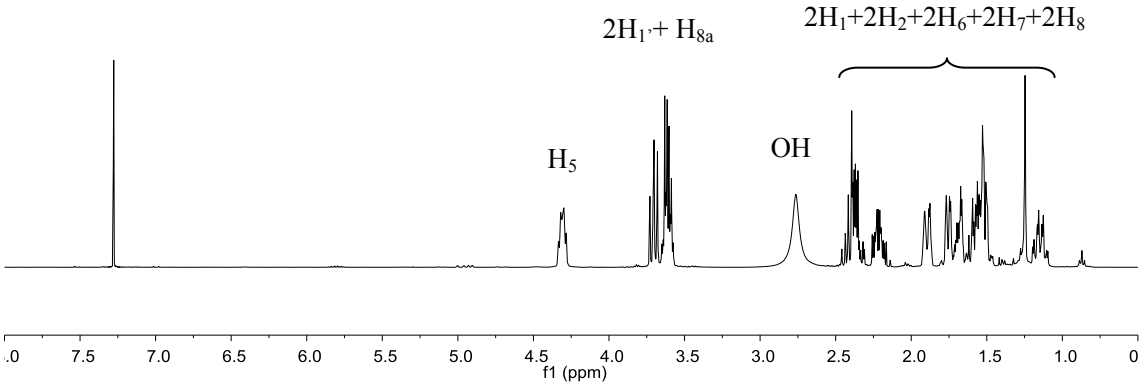
cis-**96**



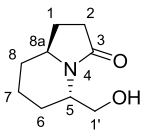
^{13}C NMR ($CDCl_3$, 101 MHz)



trans-**96**

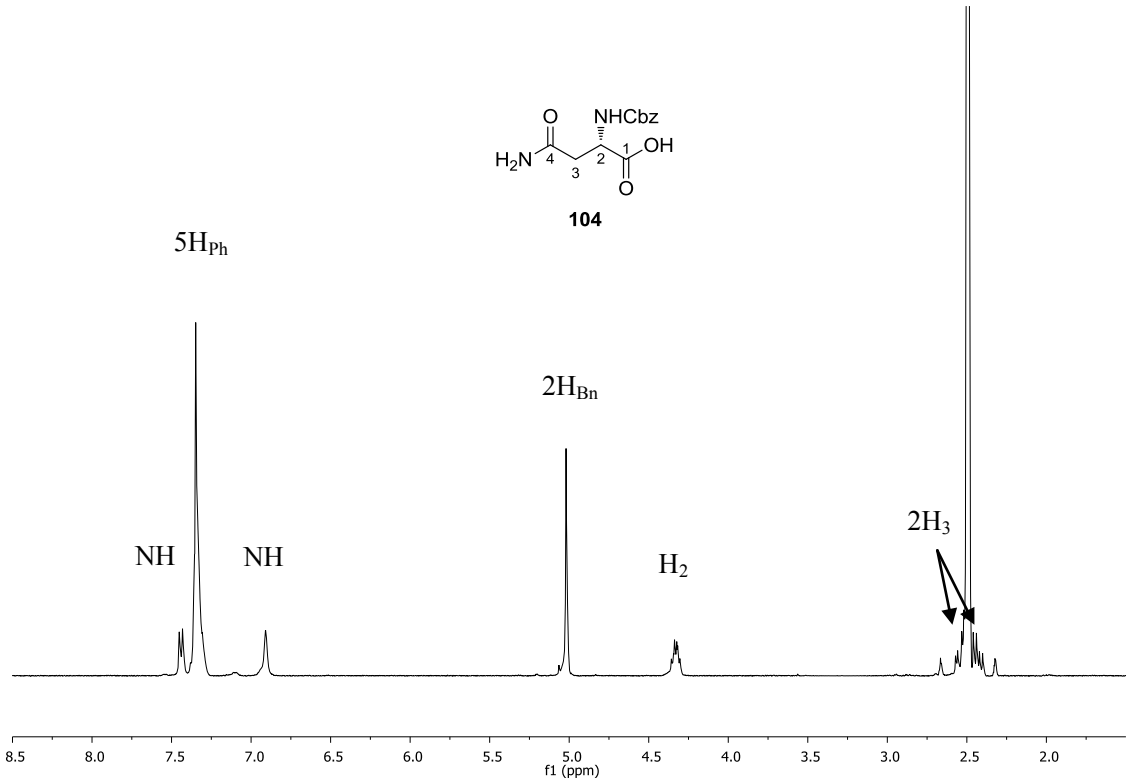


^{1}H NMR ($CDCl_3$, 400 MHz)

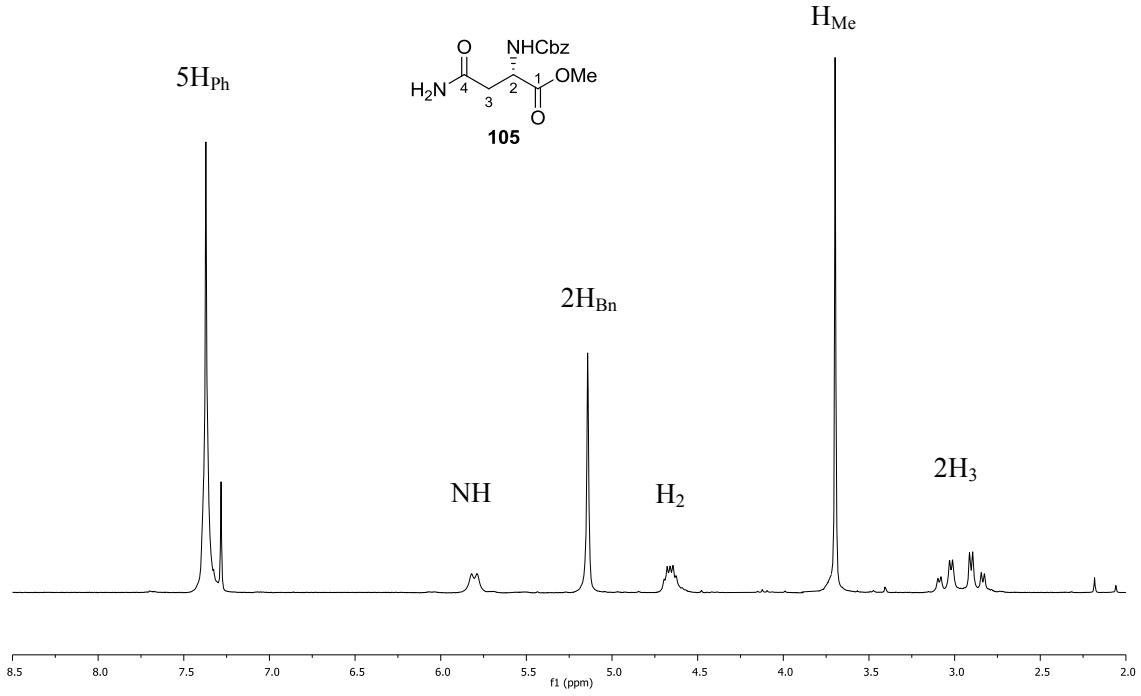


trans-**96**

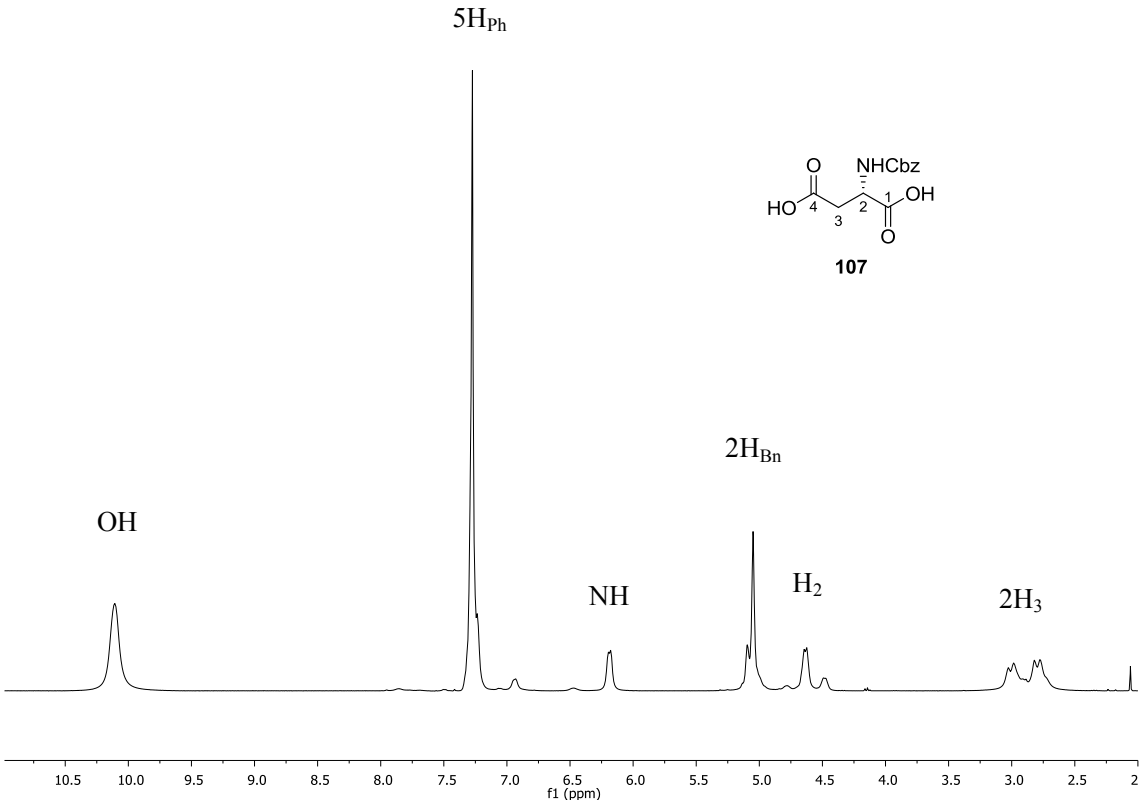
^{13}C NMR ($CDCl_3$, 101 MHz)



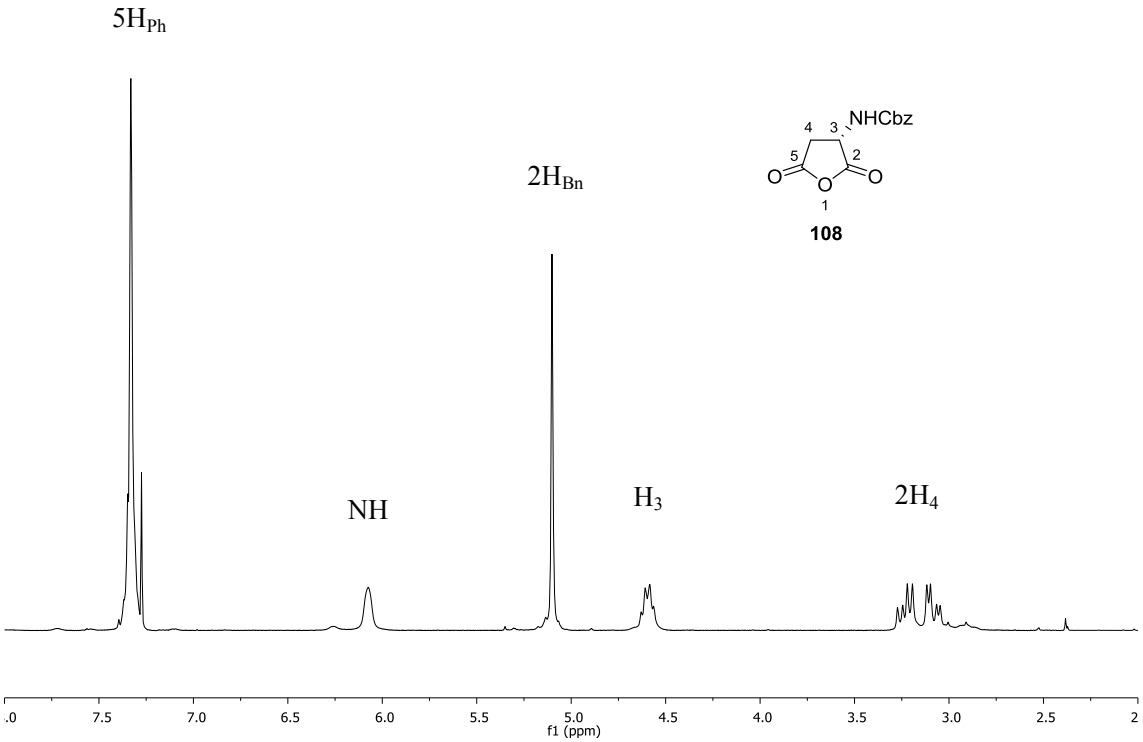
^{1}H NMR (DMSO-d_6, 400 MHz)



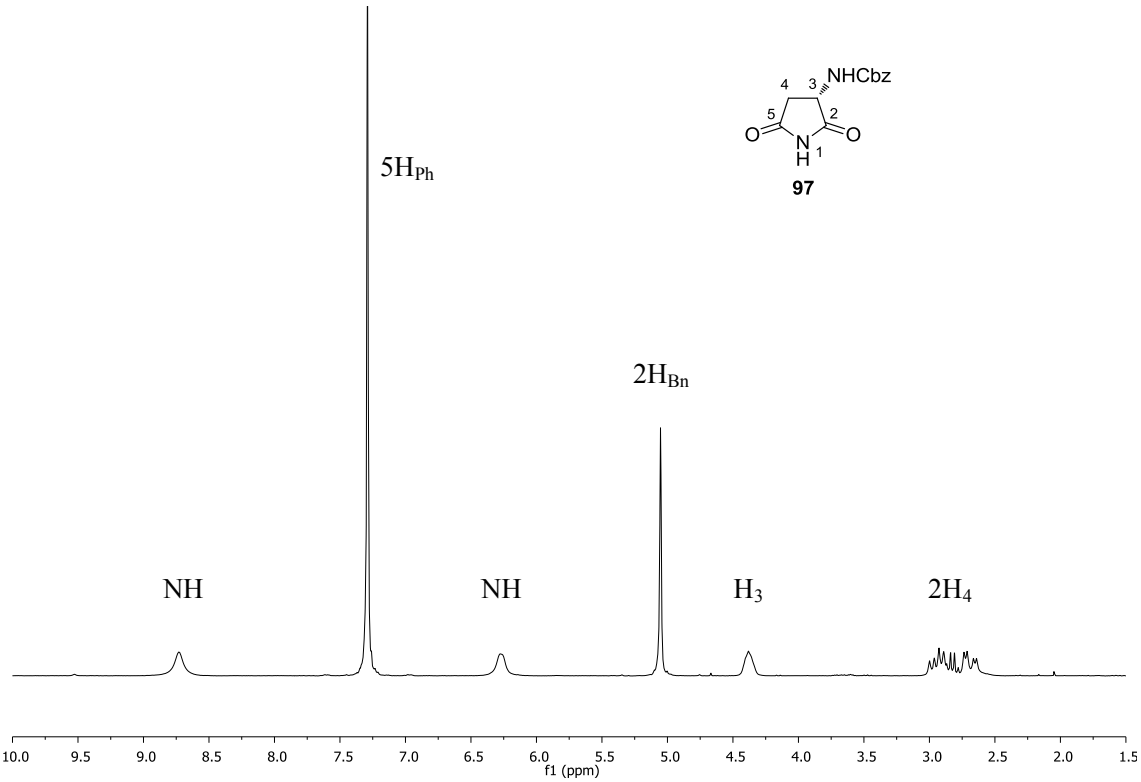
^{1}H NMR ($CDCl_3$, 250 MHz)



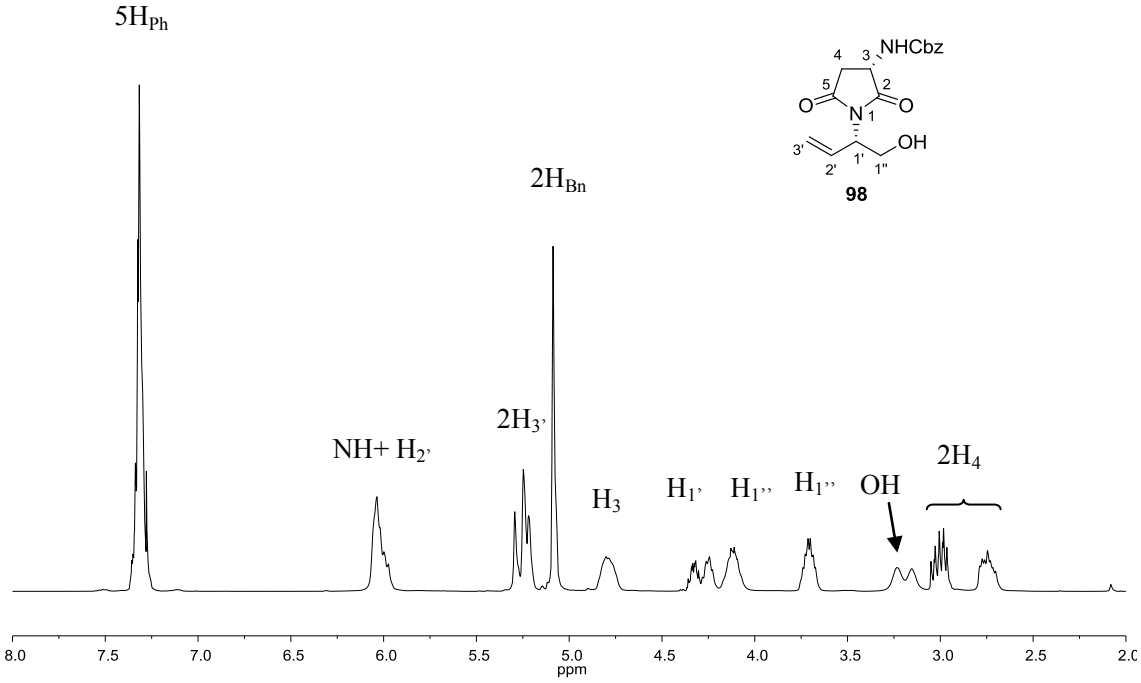
^{1}H NMR ($CDCl_3$, 360 MHz)



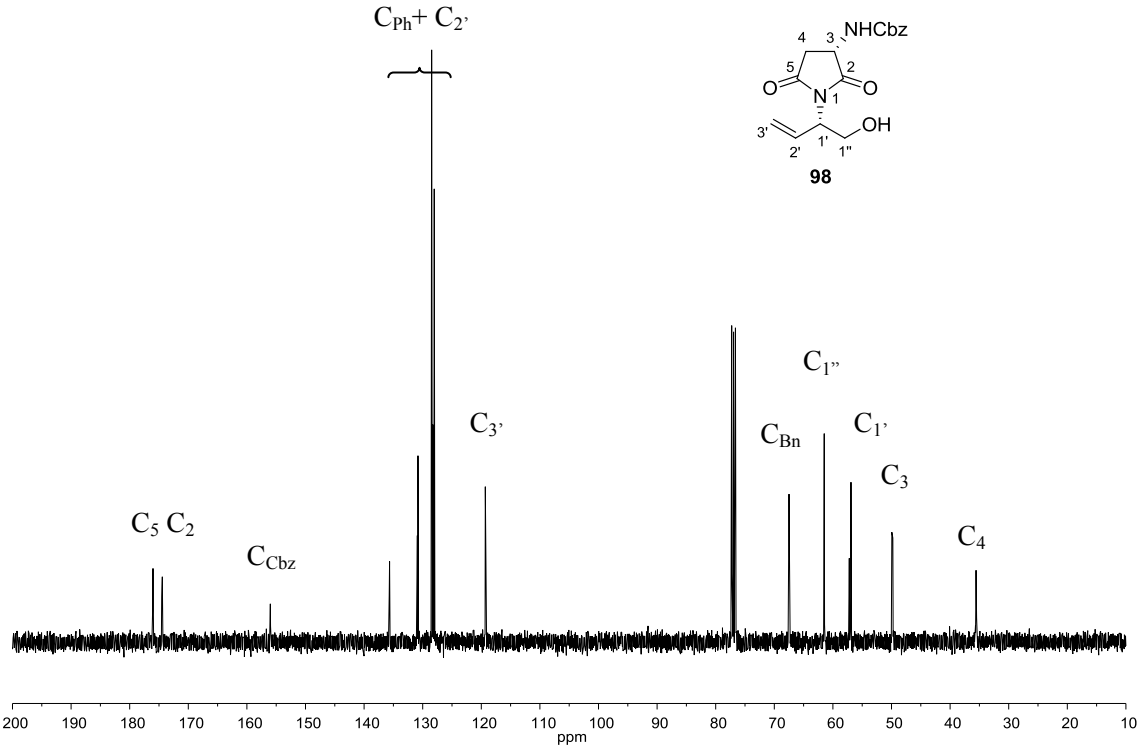
^{1}H NMR ($CDCl_3$, 360 MHz)



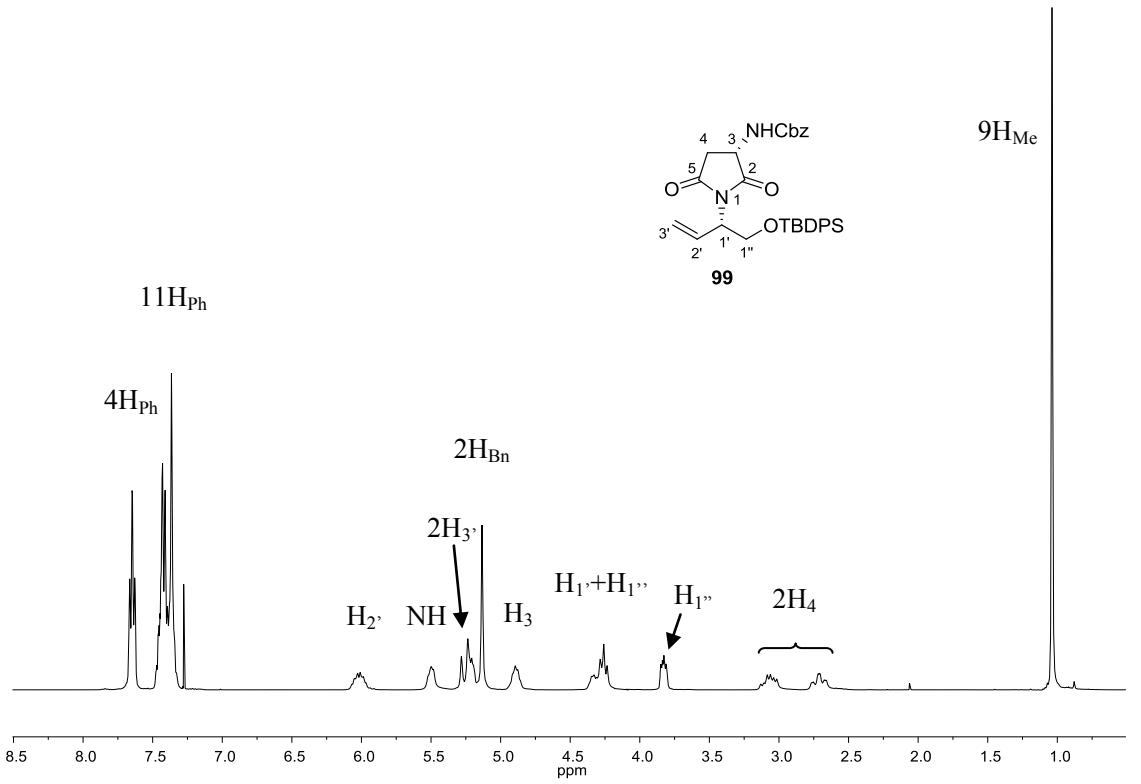
^{1}H NMR ($CDCl_3$, 250 MHz)



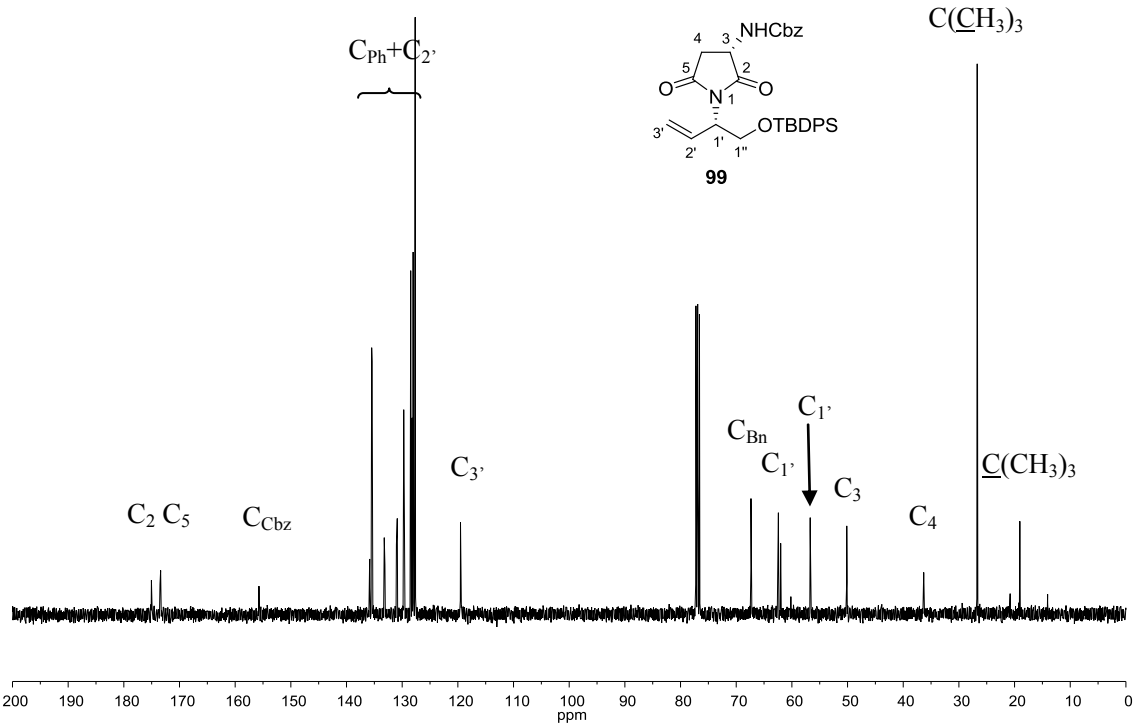
^{1}H NMR ($CDCl_3$, 400 MHz, 323K)



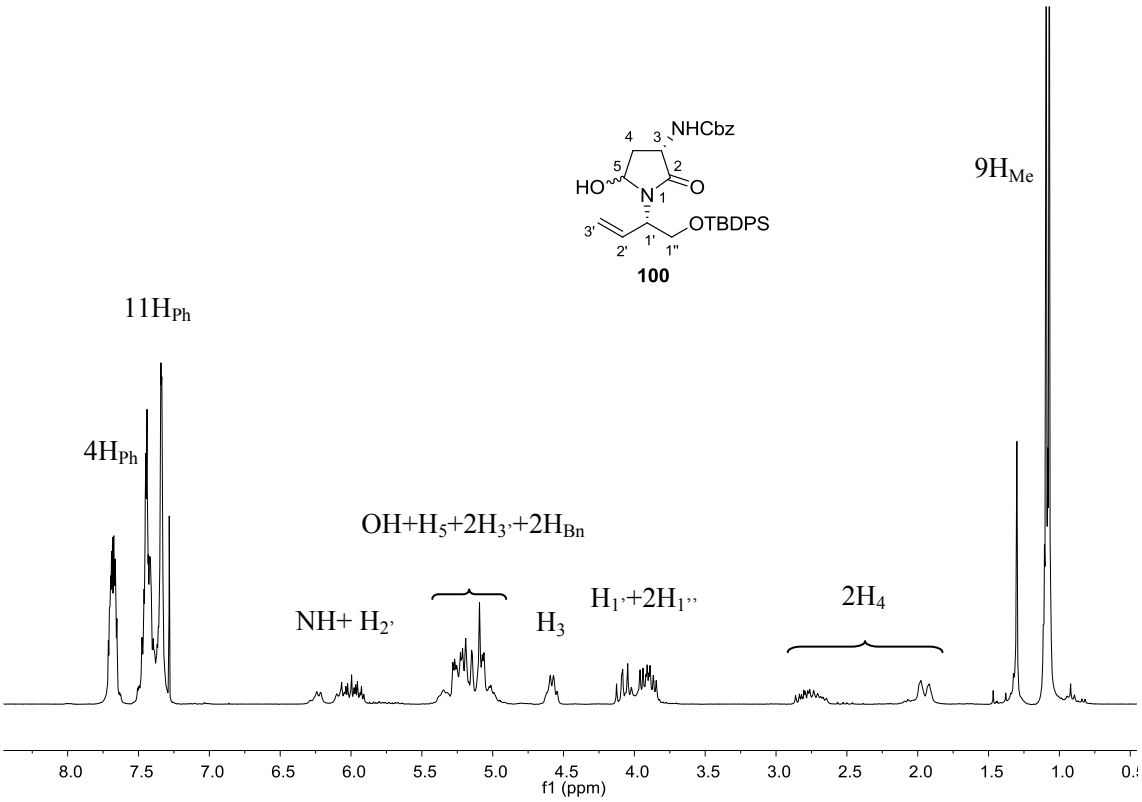
^{13}C NMR ($CDCl_3$, 101 MHz, 323K)



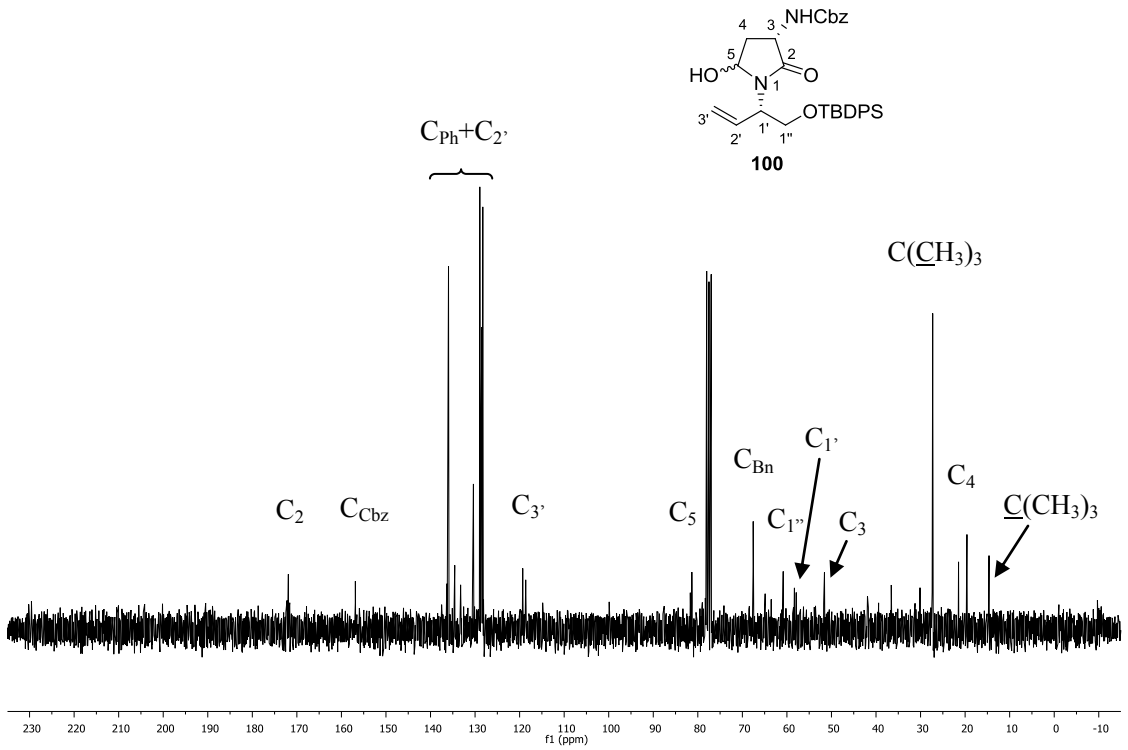
^{1}H NMR ($CDCl_3$, 400 MHz, 323K)



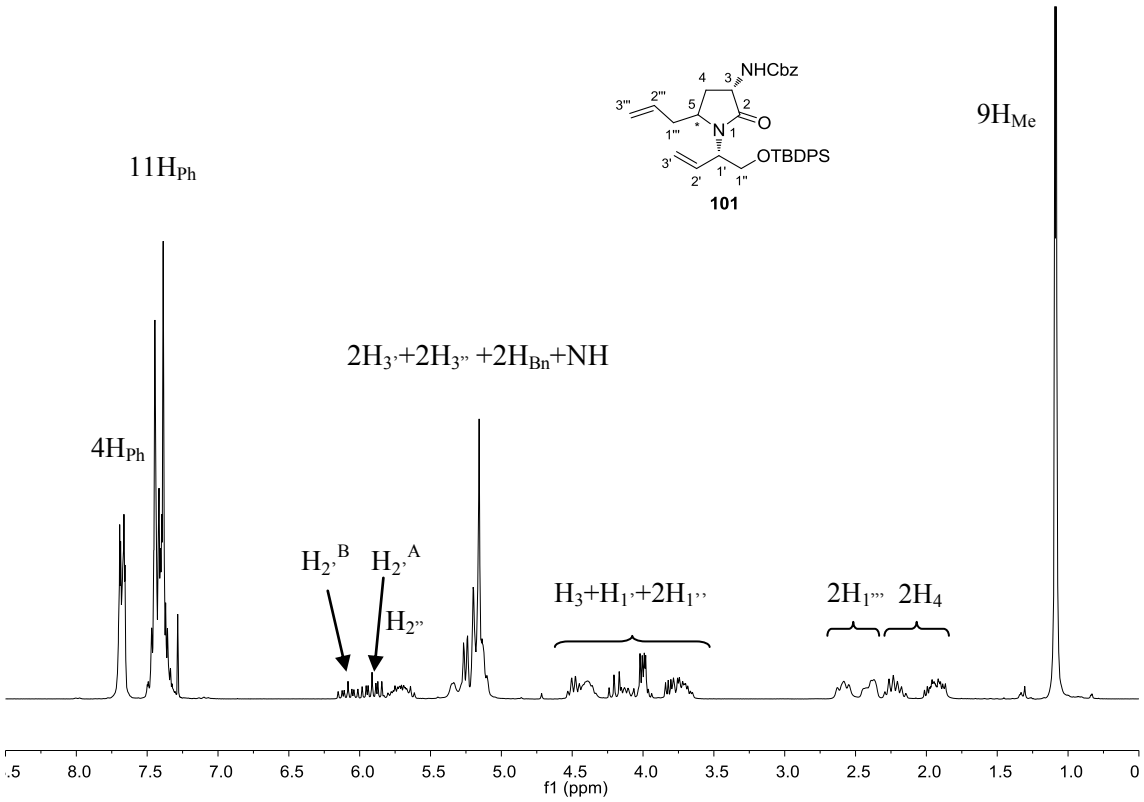
^{13}C NMR ($CDCl_3$, 101 MHz, 323K)



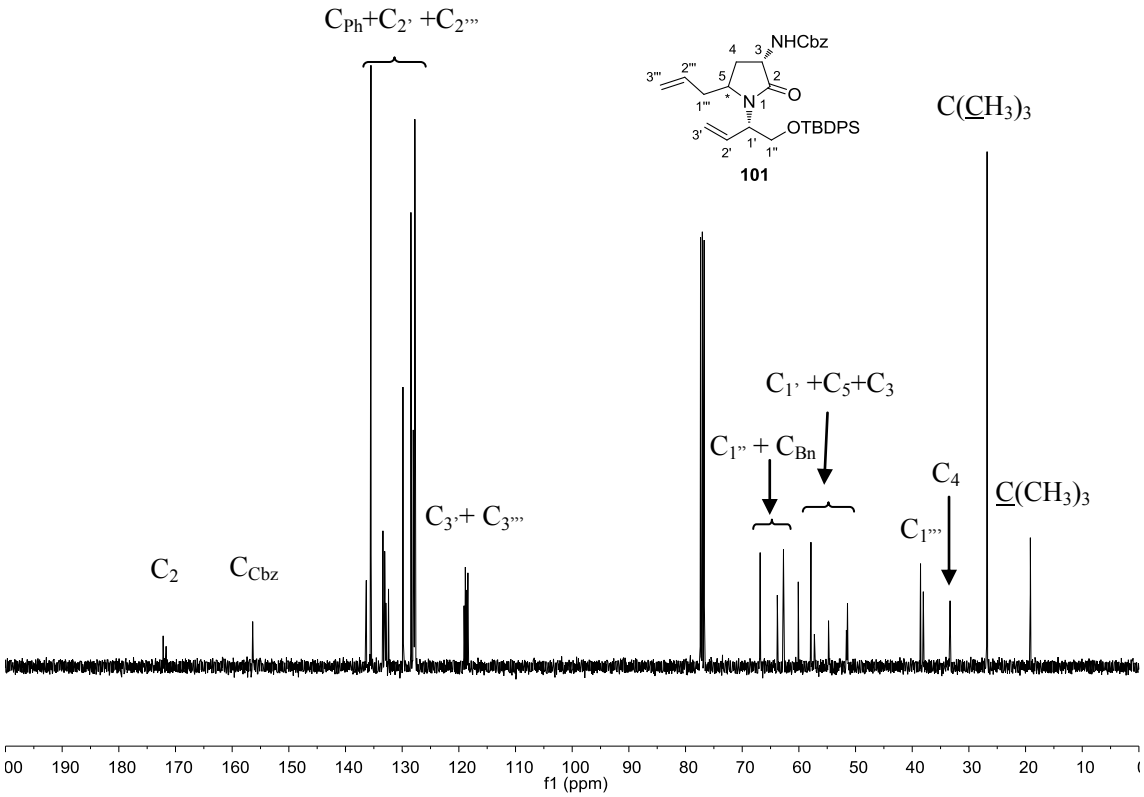
^{1}H NMR ($CDCl_3$, 250 MHz)



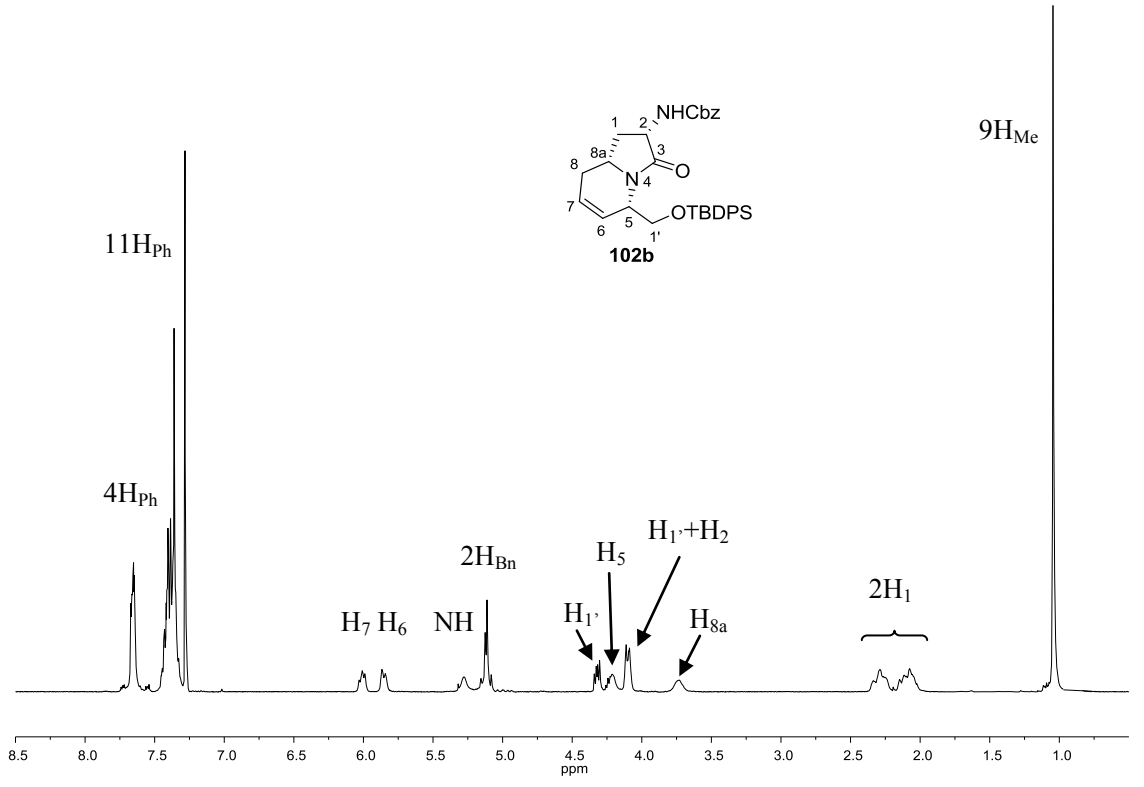
^{13}C NMR ($CDCl_3$, 60 MHz)



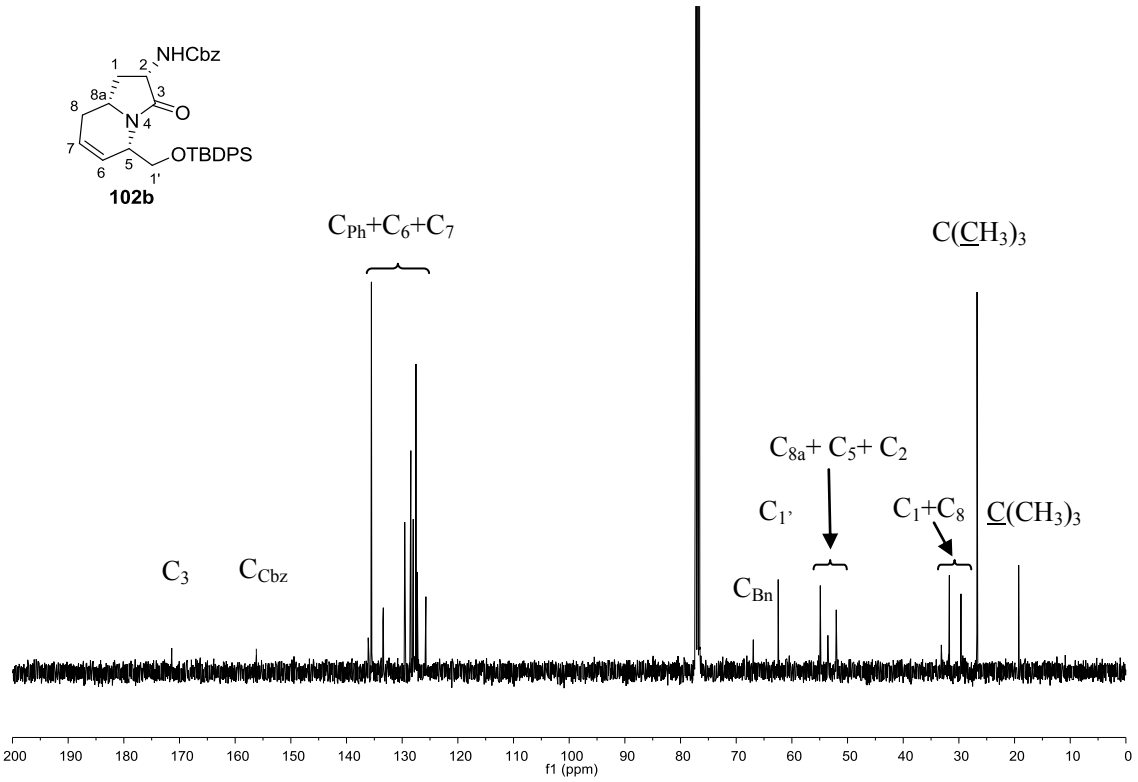
^{1}H NMR ($CDCl_3$, 250 MHz)



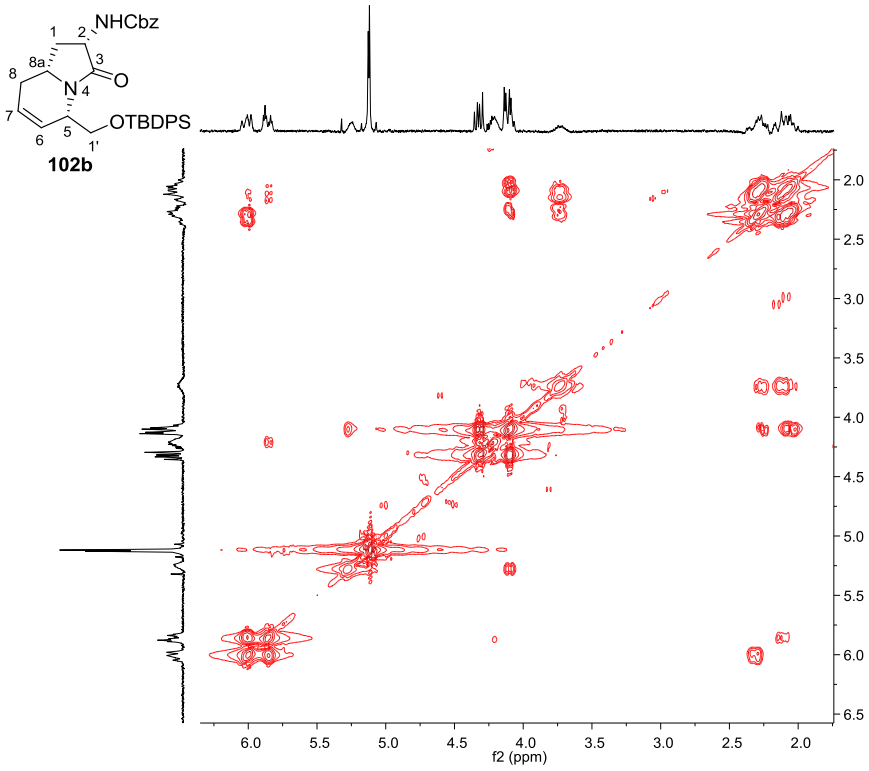
^{13}C NMR ($CDCl_3$, 101 MHz)



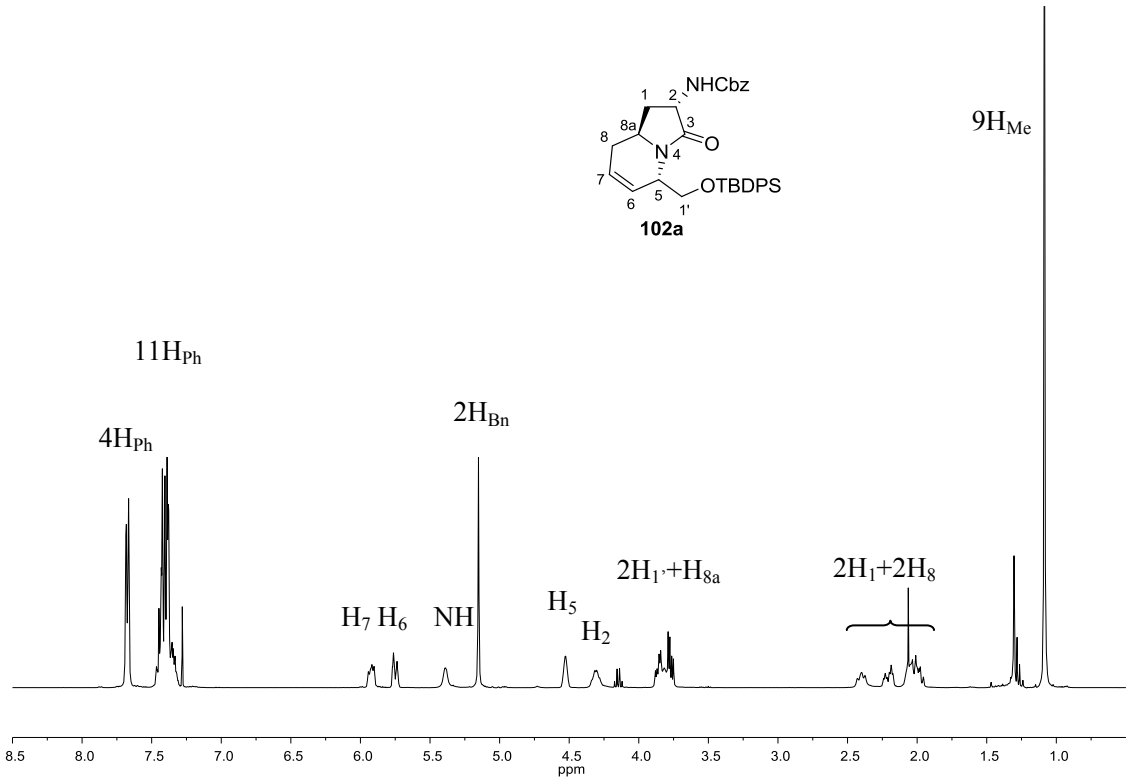
^{1}H NMR ($CDCl_3$, 400 MHz)



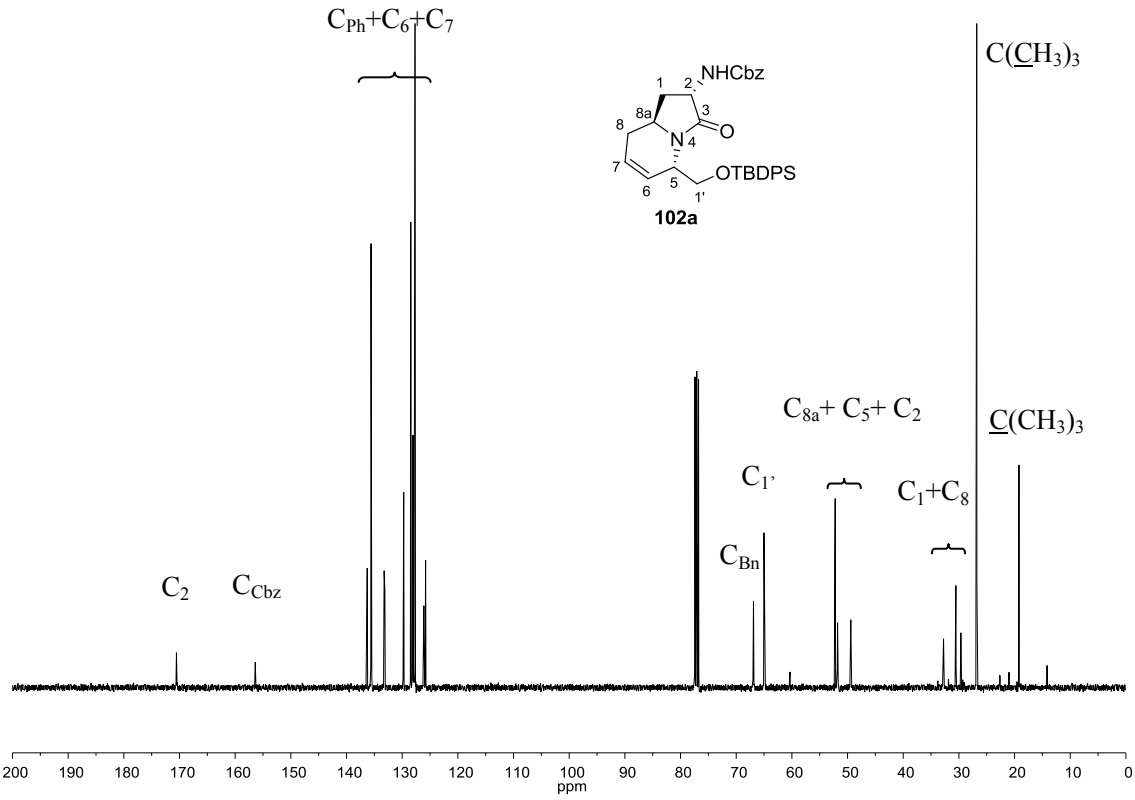
^{13}C NMR ($CDCl_3$, 101 MHz)



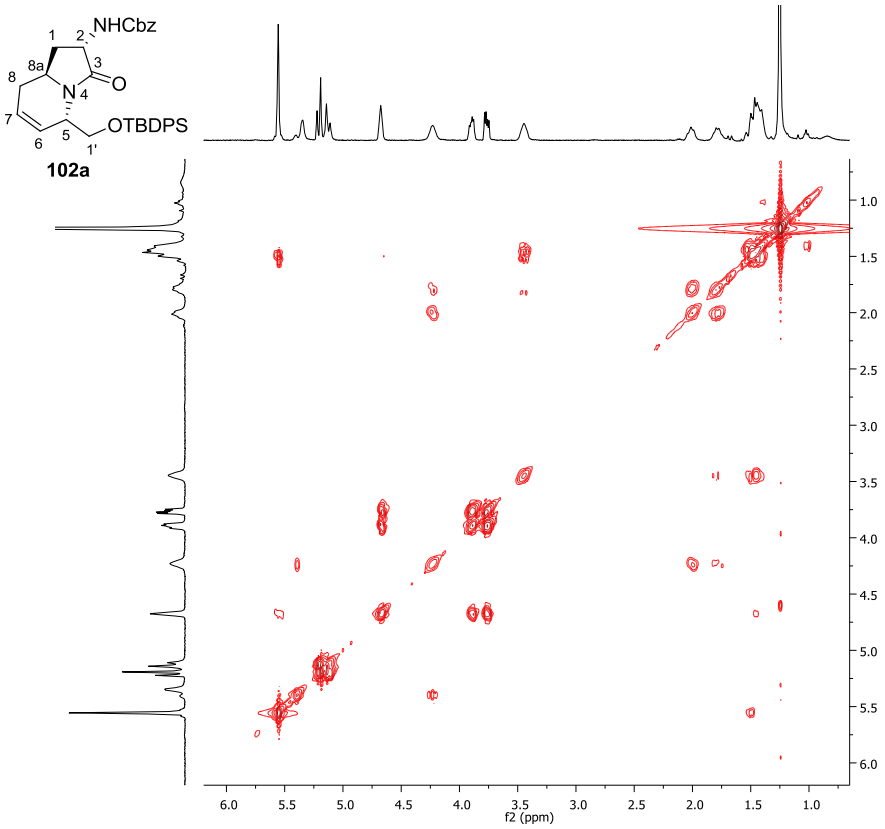
2D-COSY (C_6D_6, 400 MHz)



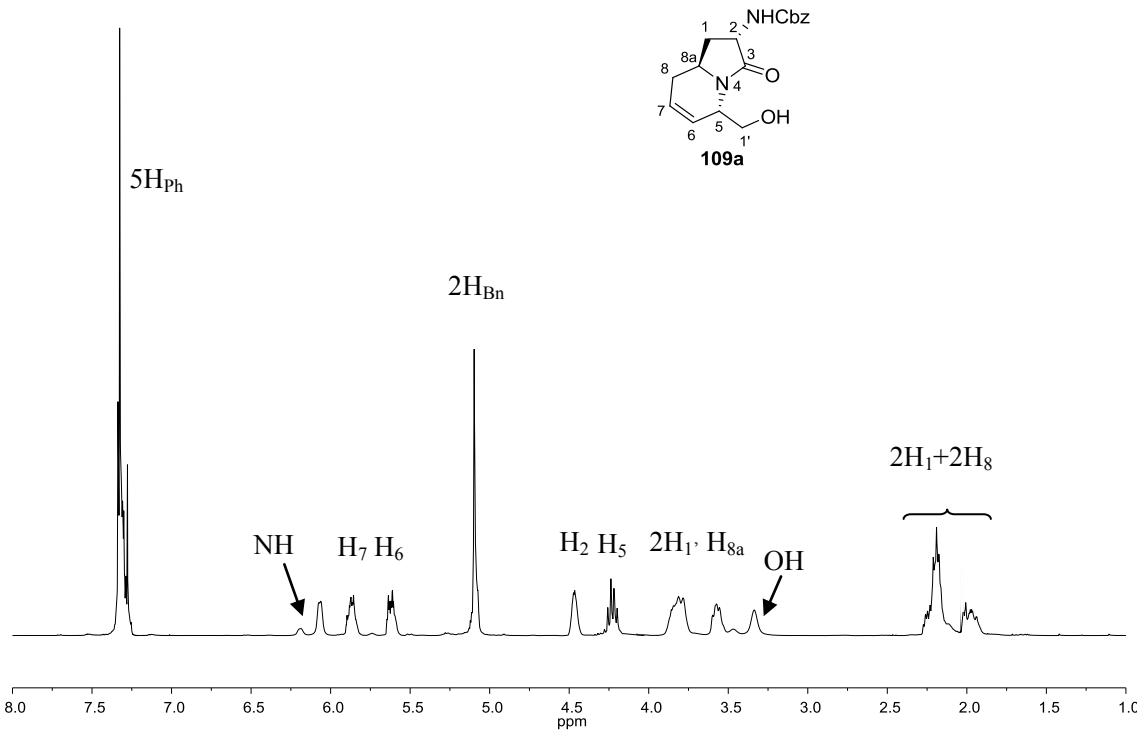
^{1}H NMR ($CDCl_3$, 400 MHz)



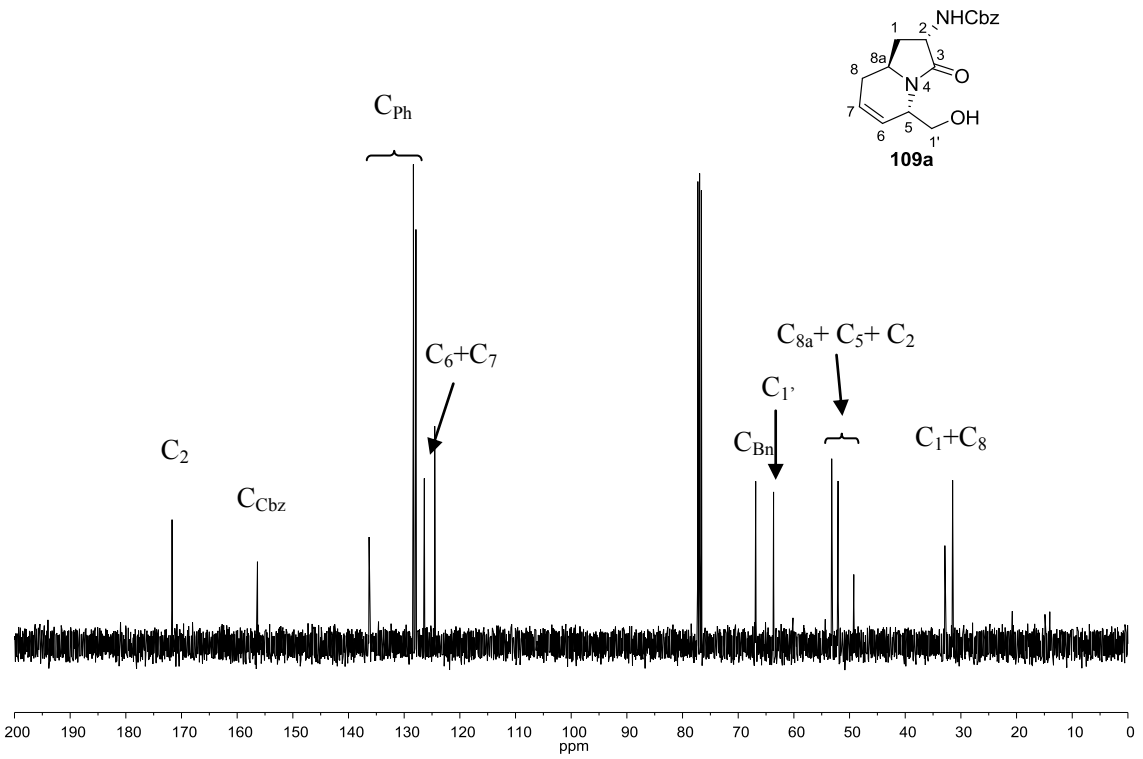
^{13}C NMR ($CDCl_3$, 101 MHz)



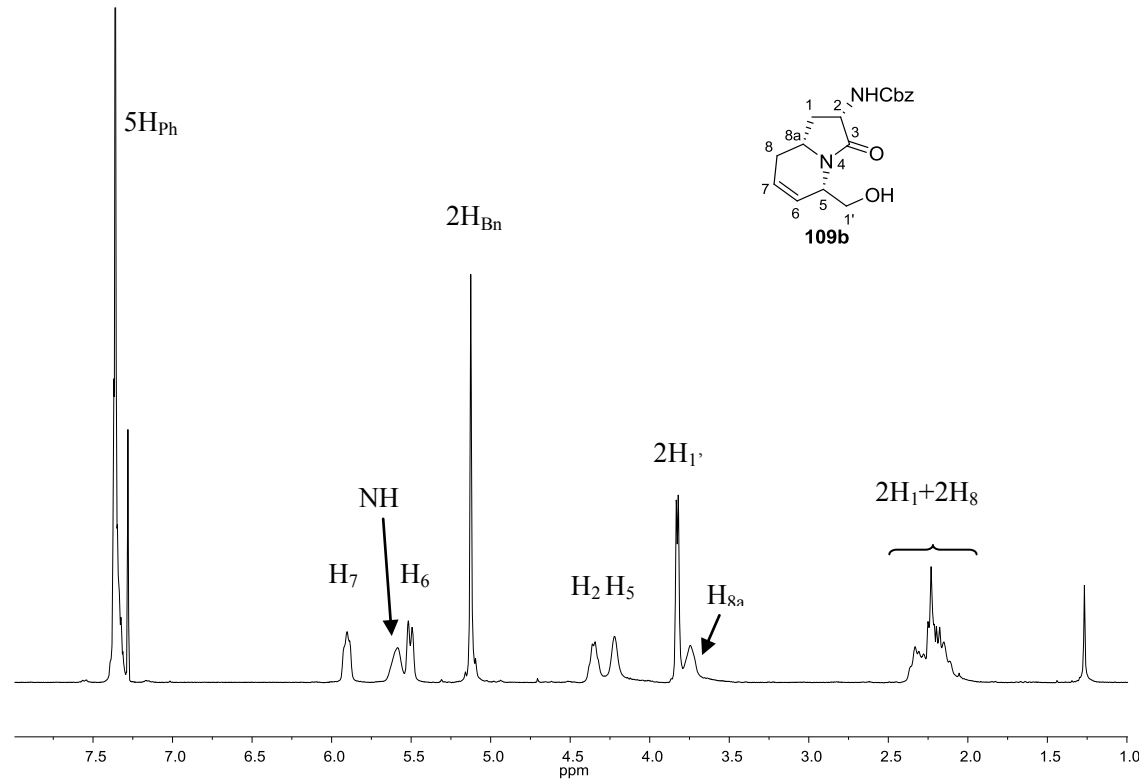
2D-COSY (C_6D_6, 400 MHz)



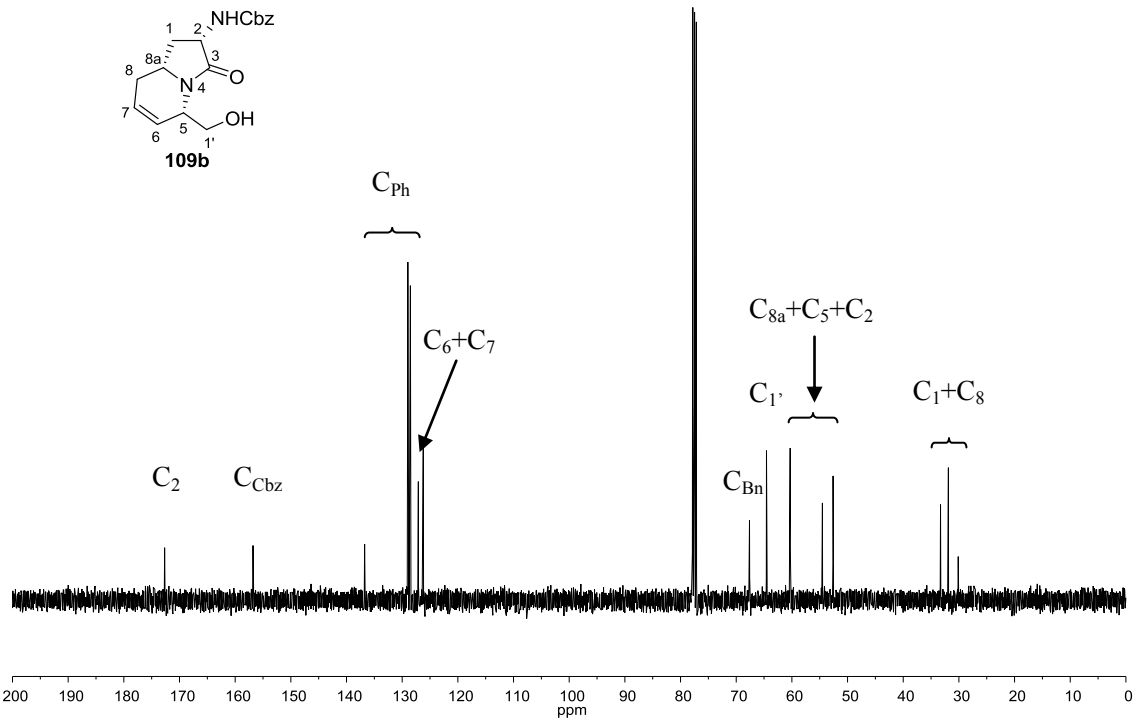
^{1}H NMR ($CDCl_3$, 400 MHz, 323K)



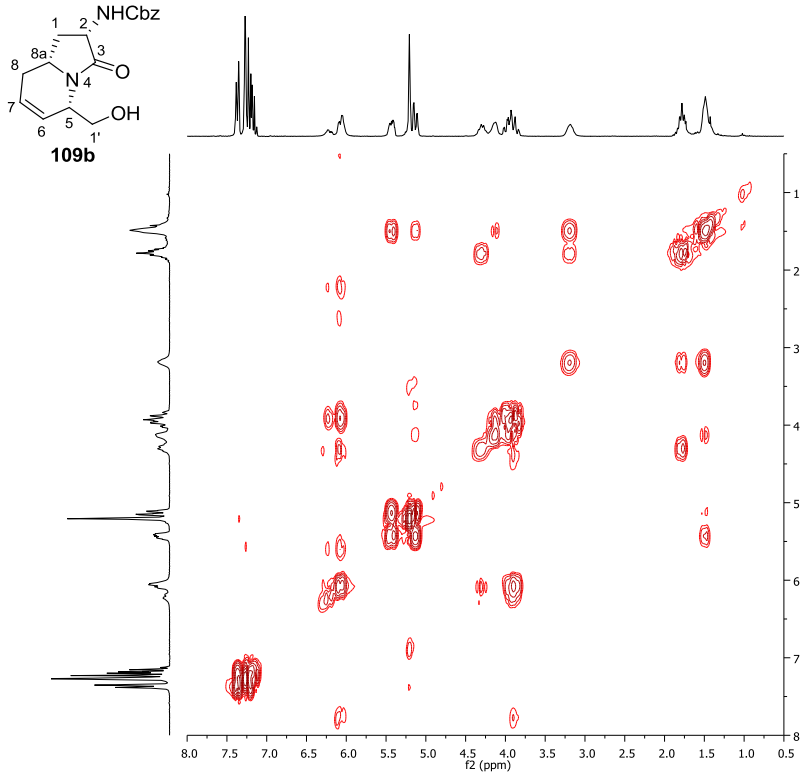
^{13}C NMR ($CDCl_3$, 101 MHz, 323K)



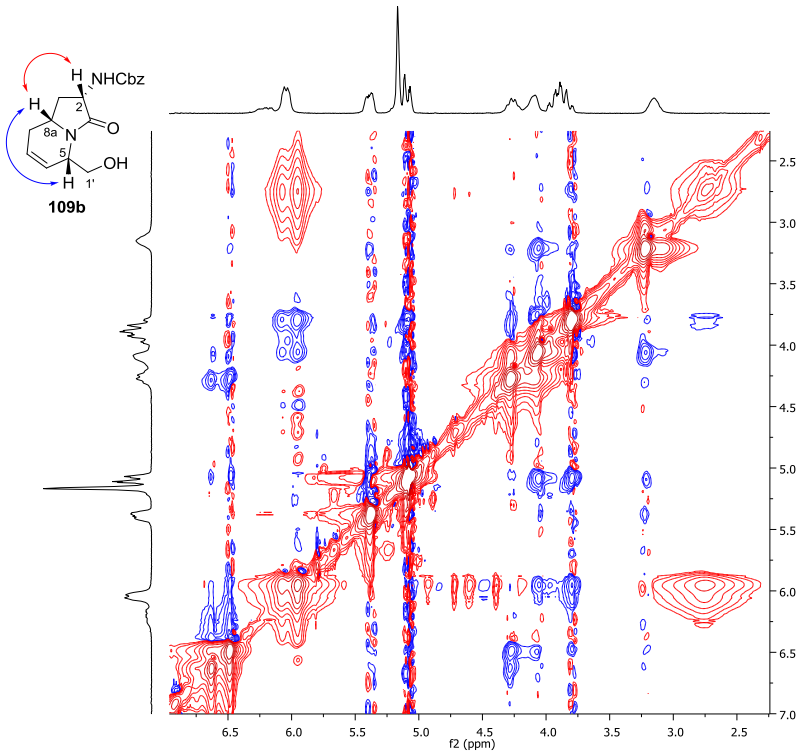
^{1}H NMR ($CDCl_3$, 400 MHz)



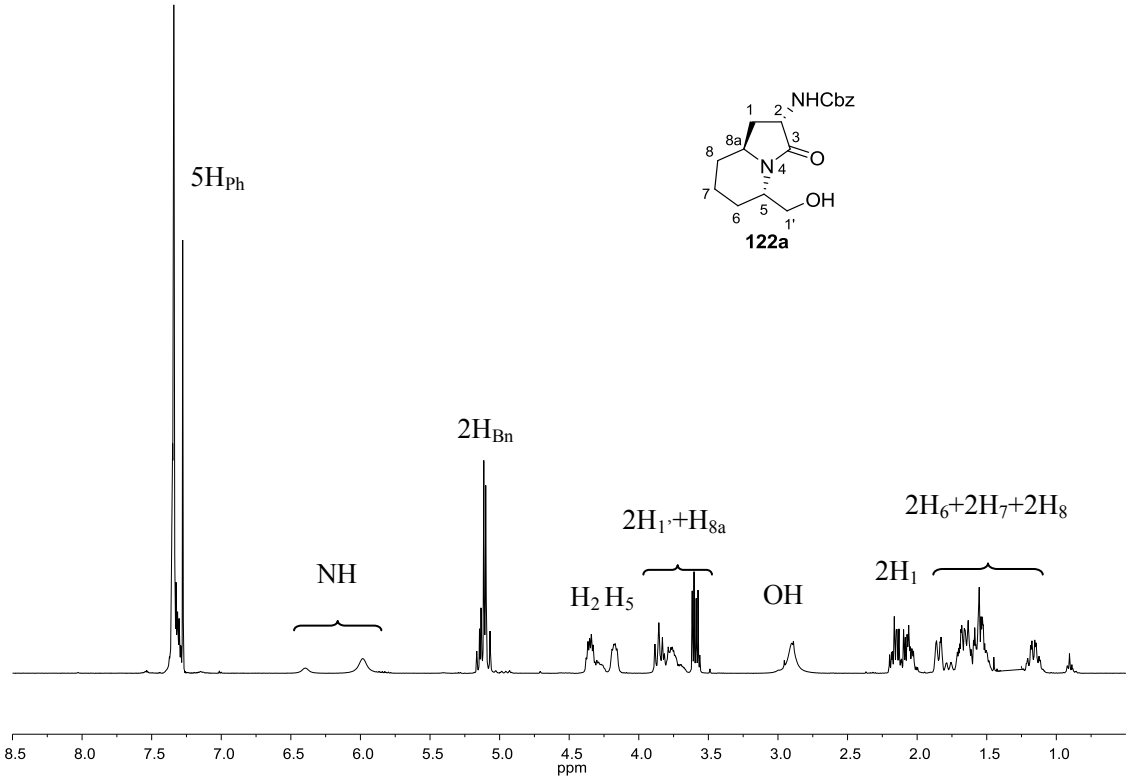
^{13}C NMR ($CDCl_3$, 101 MHz, 323K)



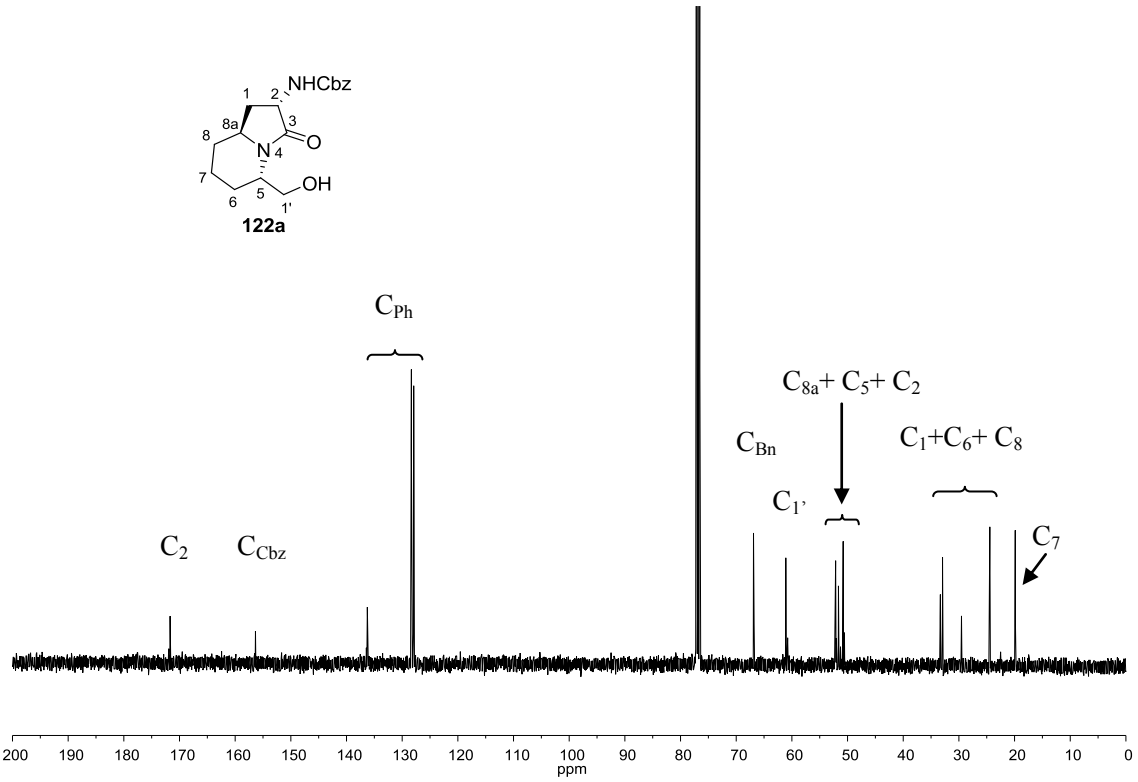
2D-COSY (C_6D_6, 400 MHz)



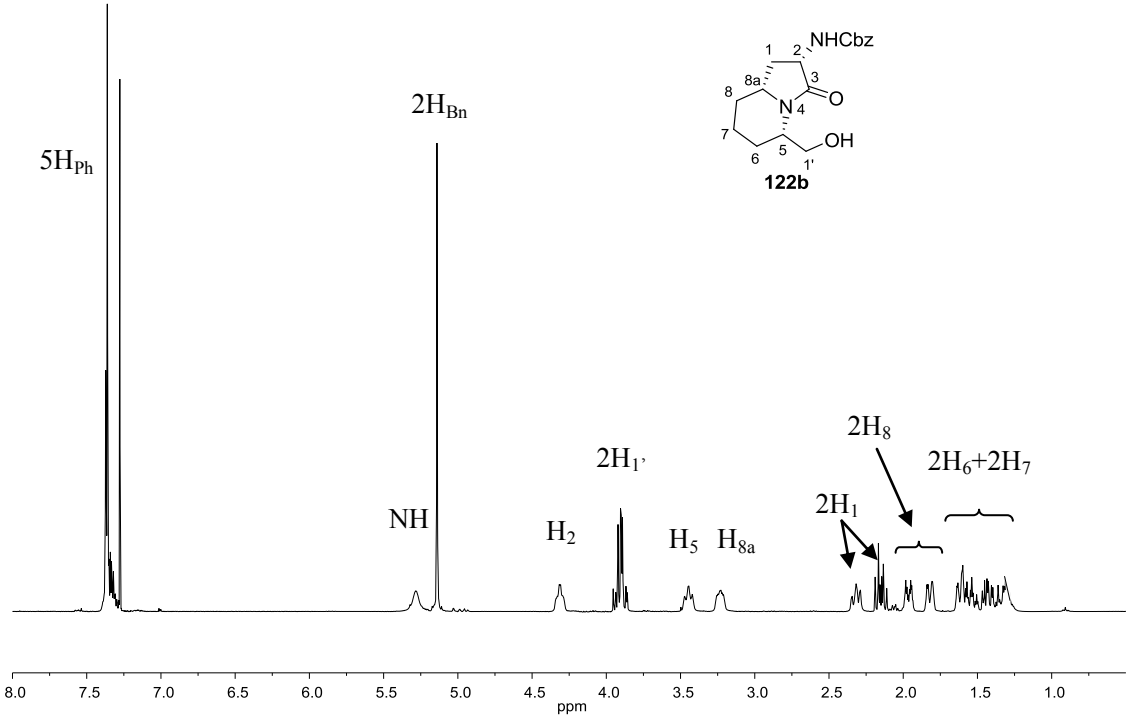
2D-NOESY (C_6D_6, 400 MHz)



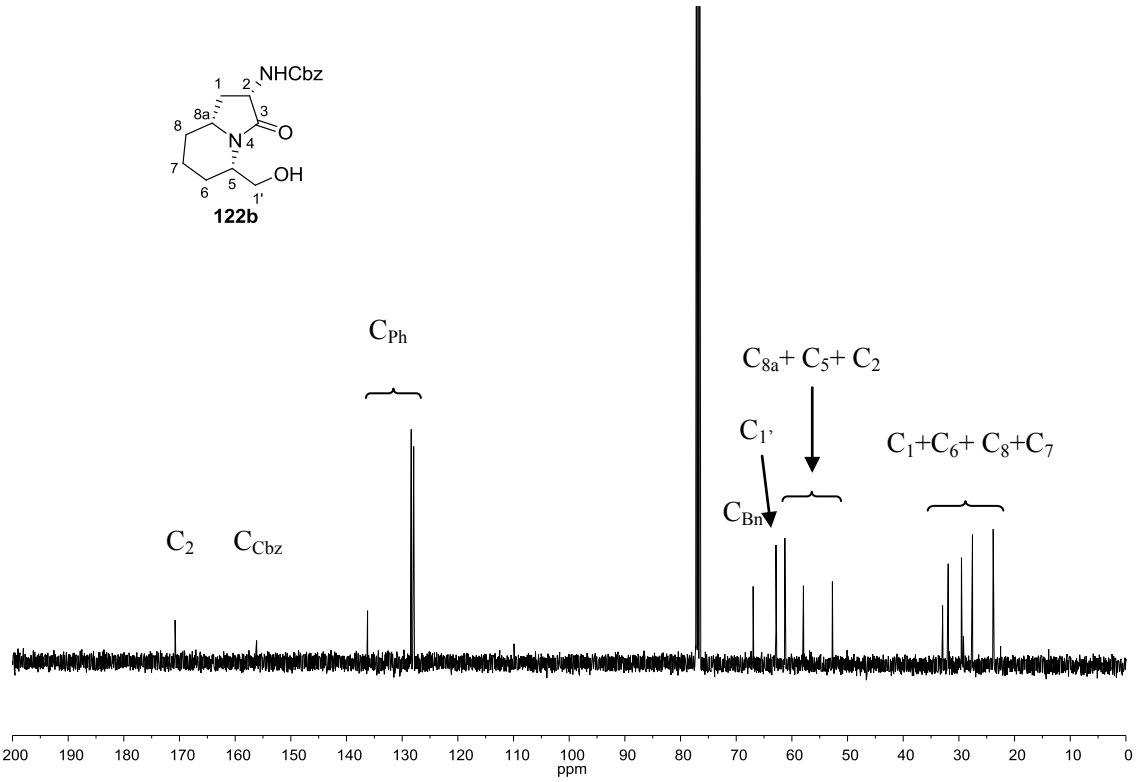
^{1}H NMR ($CDCl_3$, 400 MHz, 323K)



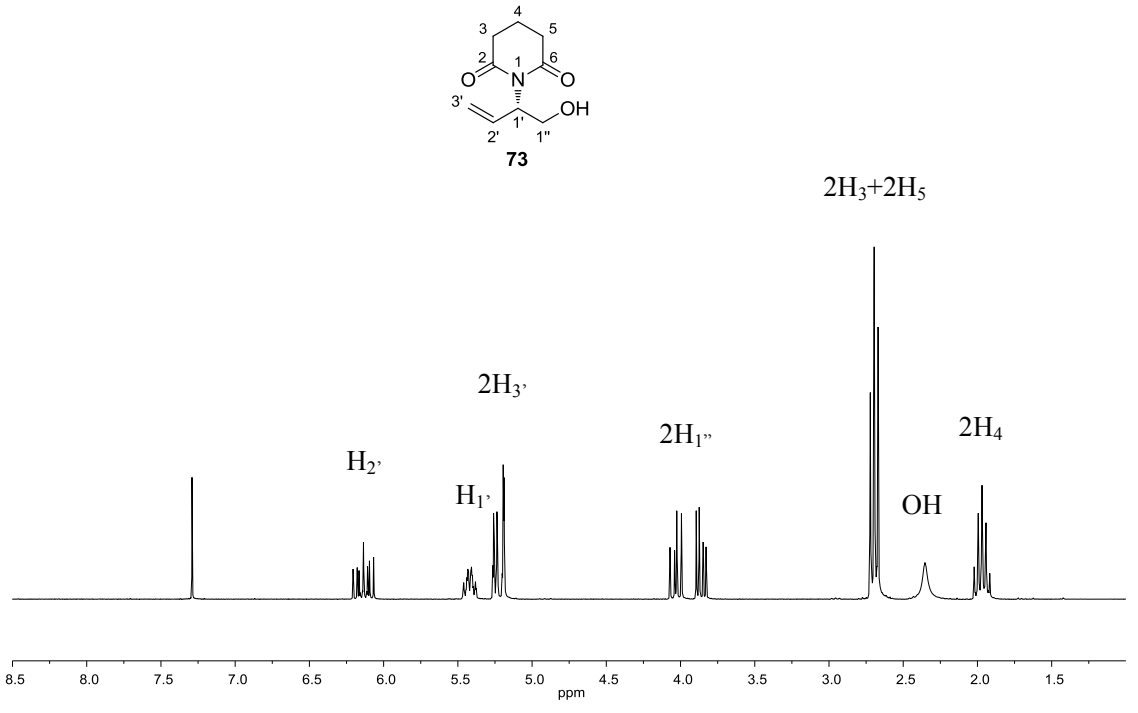
^{13}C NMR ($CDCl_3$, 101 MHz, 323K)



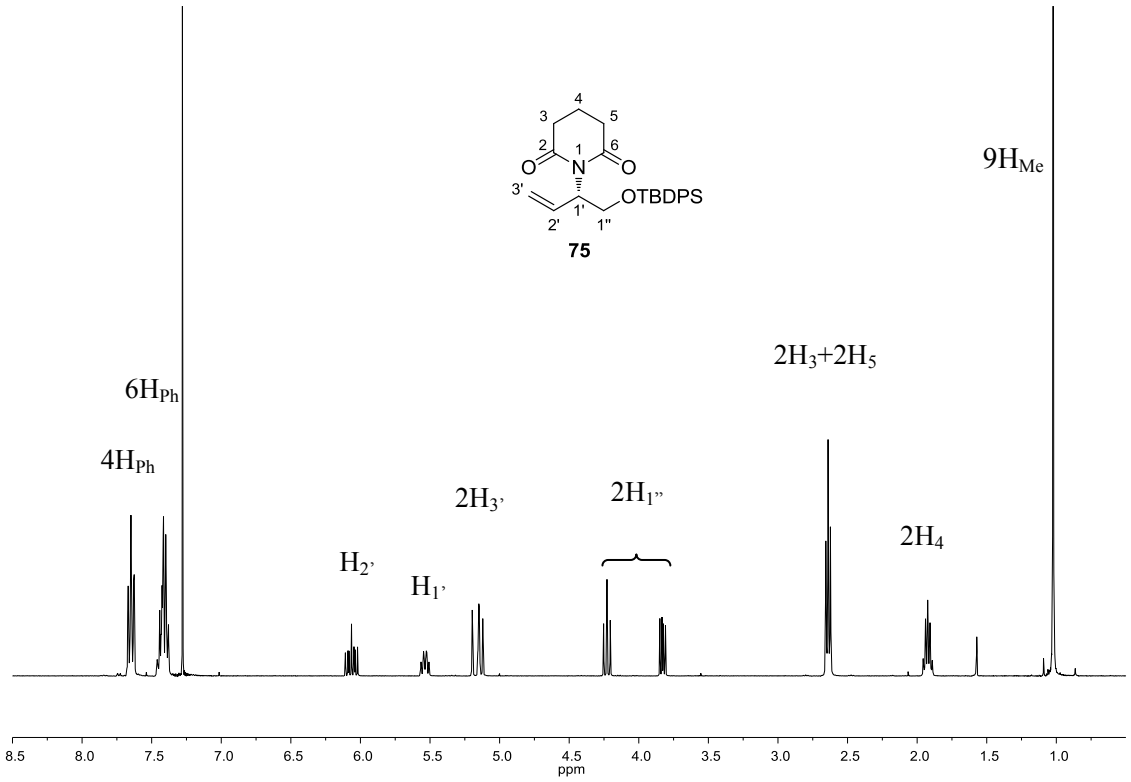
^{1}H NMR ($CDCl_3$, 400 MHz, 323K)



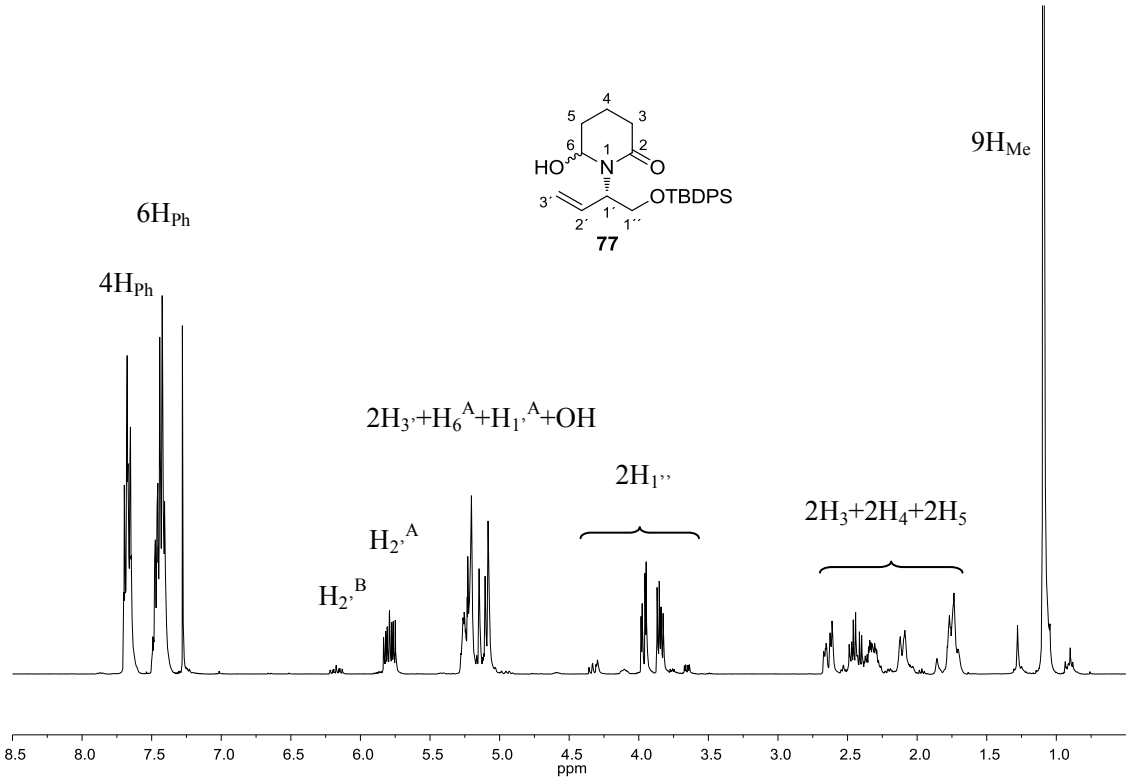
^{13}C NMR ($CDCl_3$, 101 MHz, 323K)



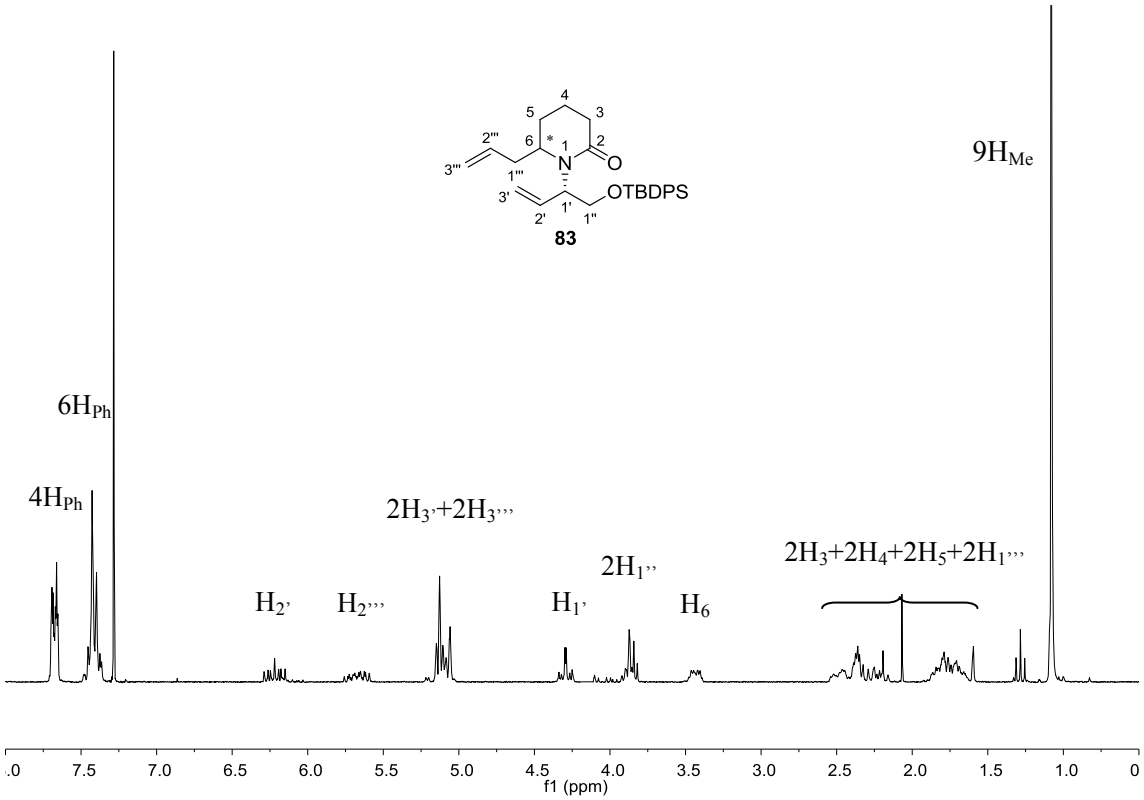
^{1}H NMR ($CDCl_3$, 250 MHz)



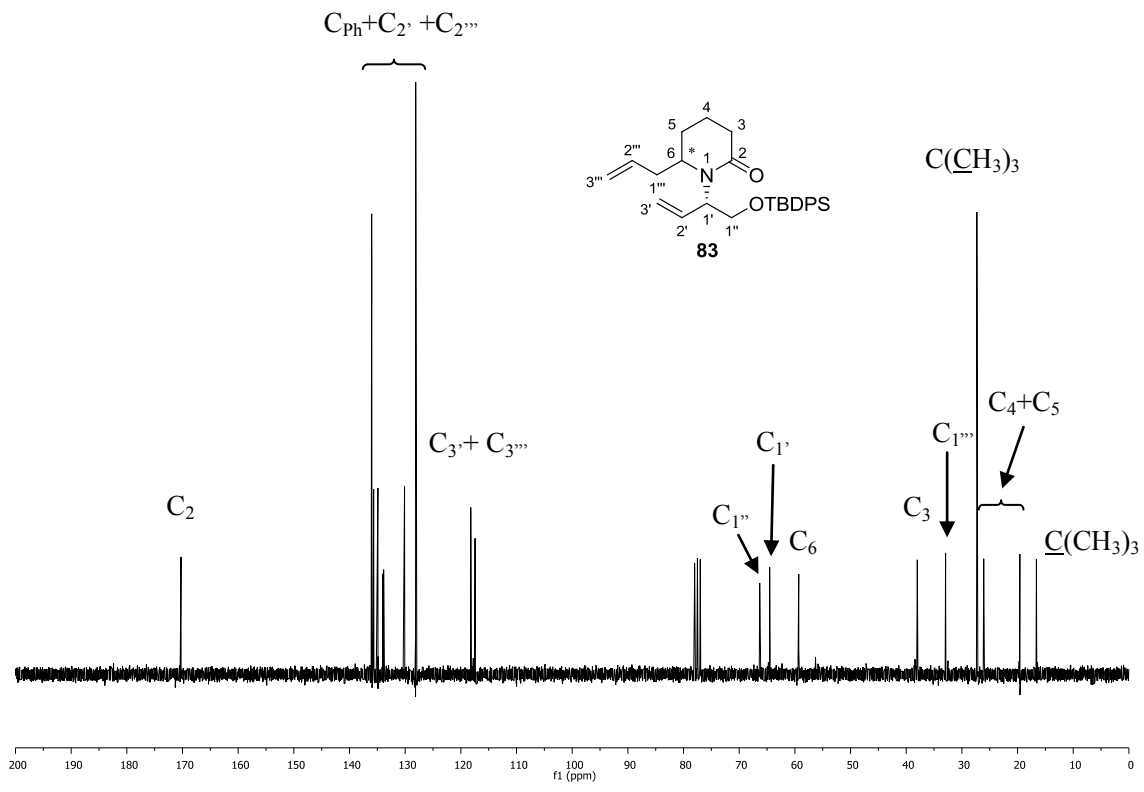
^{1}H NMR ($CDCl_3$, 400 MHz)



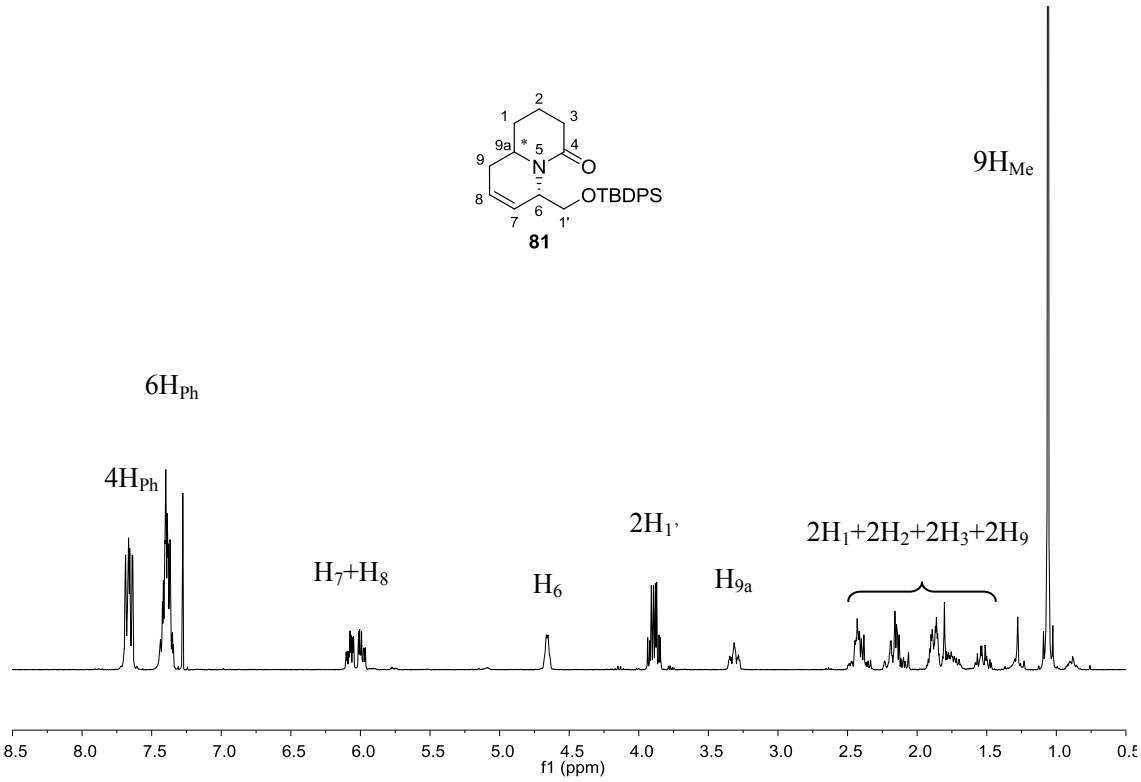
^{1}H NMR ($CDCl_3$, 400 MHz)



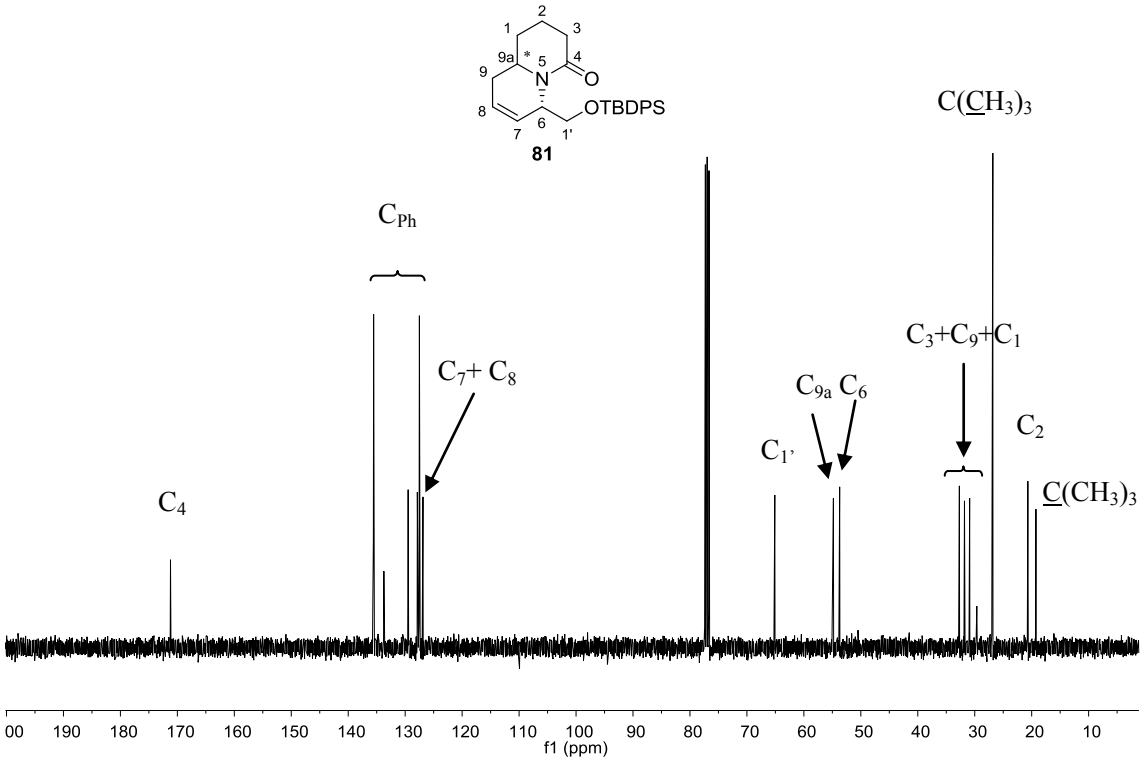
^{1}H NMR ($CDCl_3$, 250 MHz)



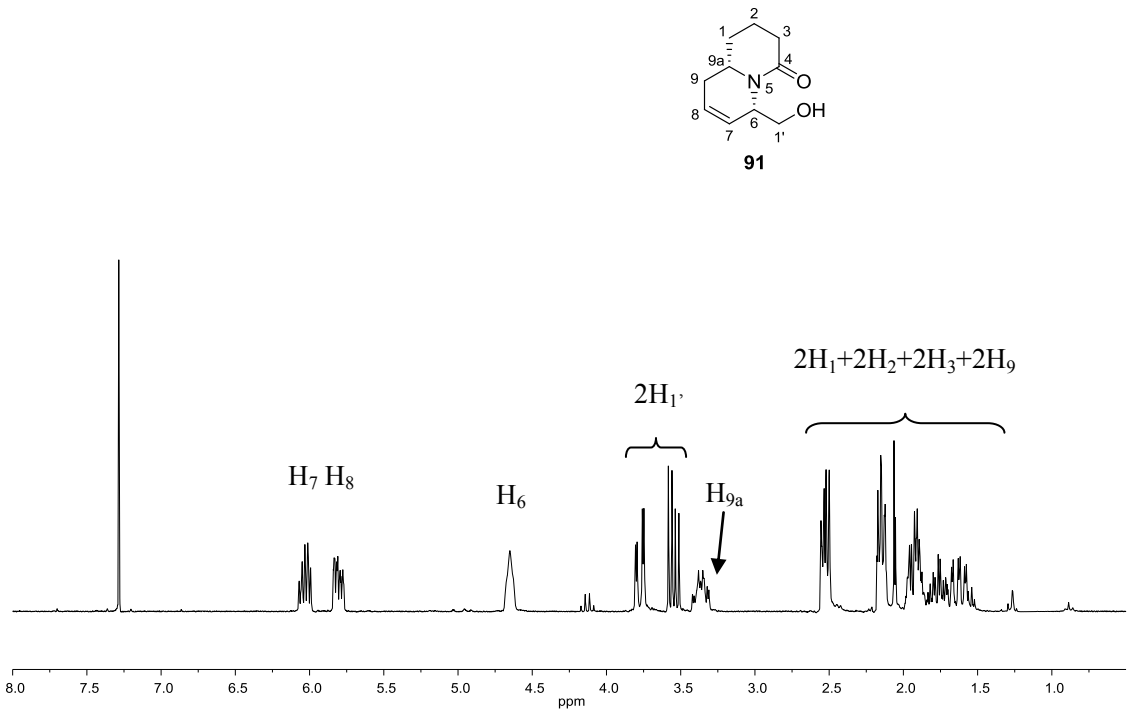
^{13}C NMR ($CDCl_3$, 63 MHz)



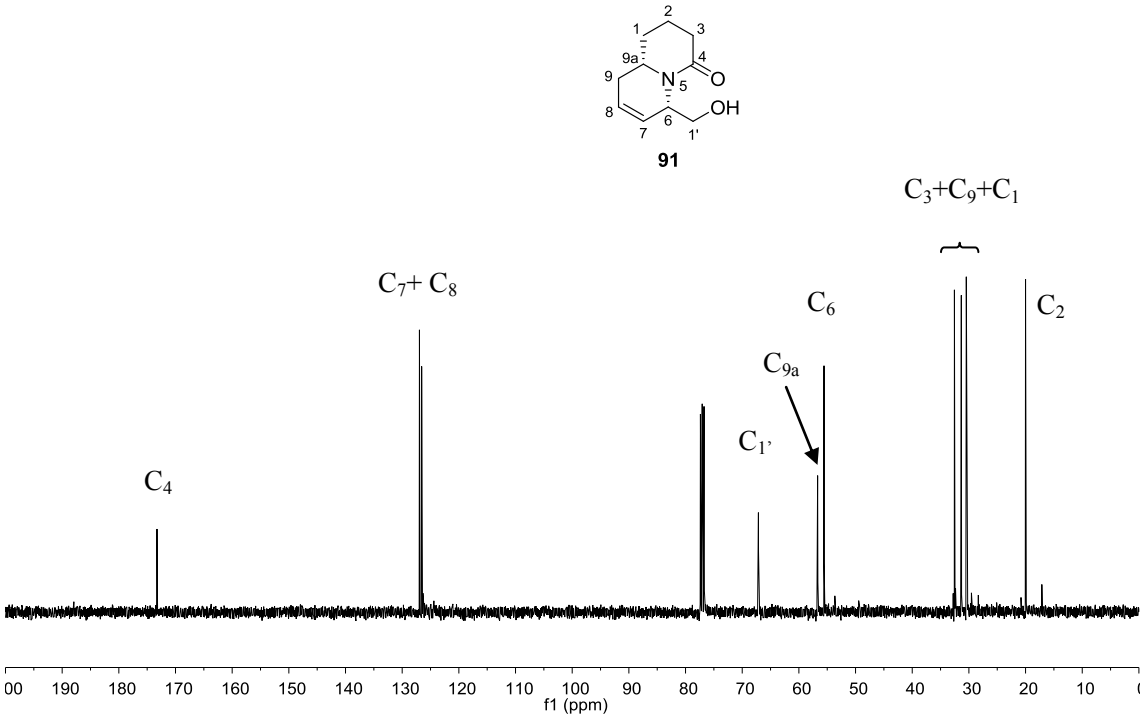
^{1}H NMR ($CDCl_3$, 400 MHz)



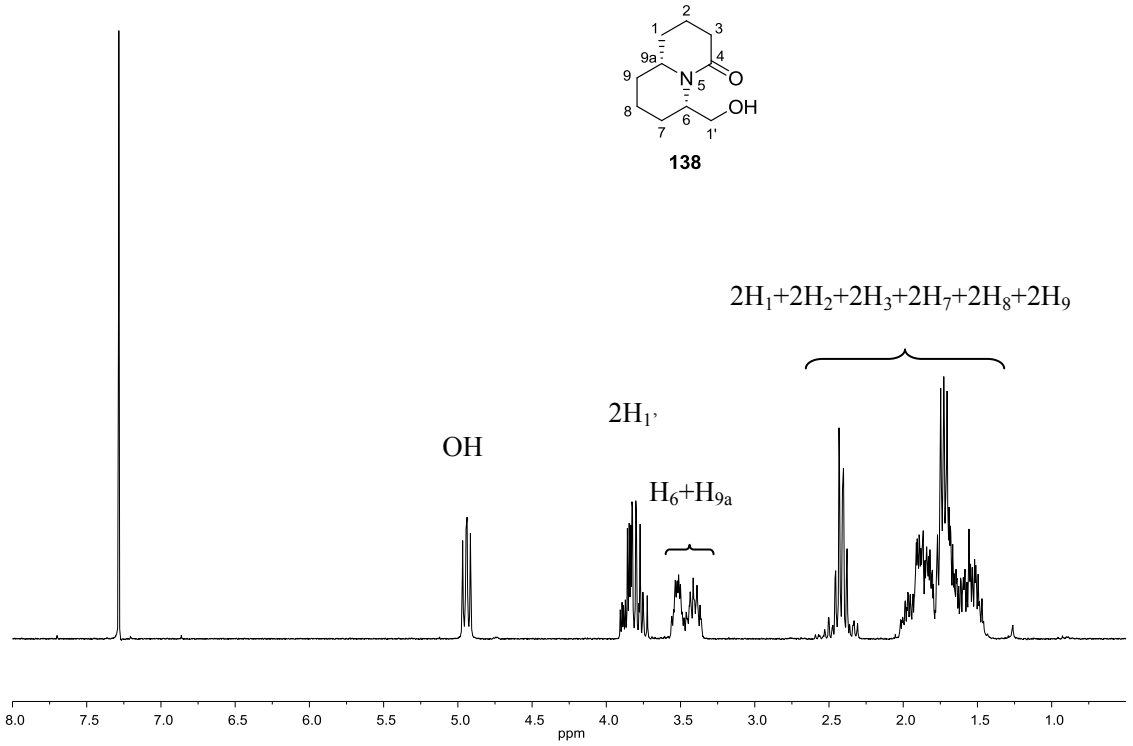
^{13}C NMR ($CDCl_3$, 101 MHz)



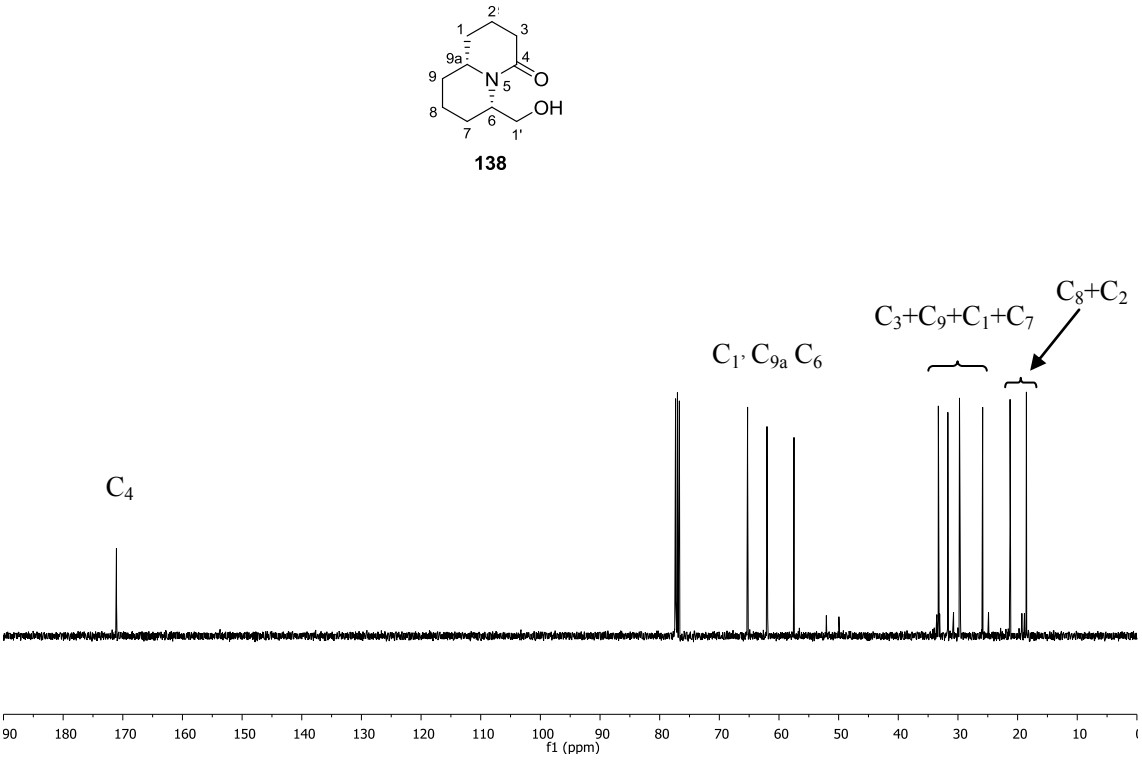
^{1}H NMR ($CDCl_3$, 250 MHz)



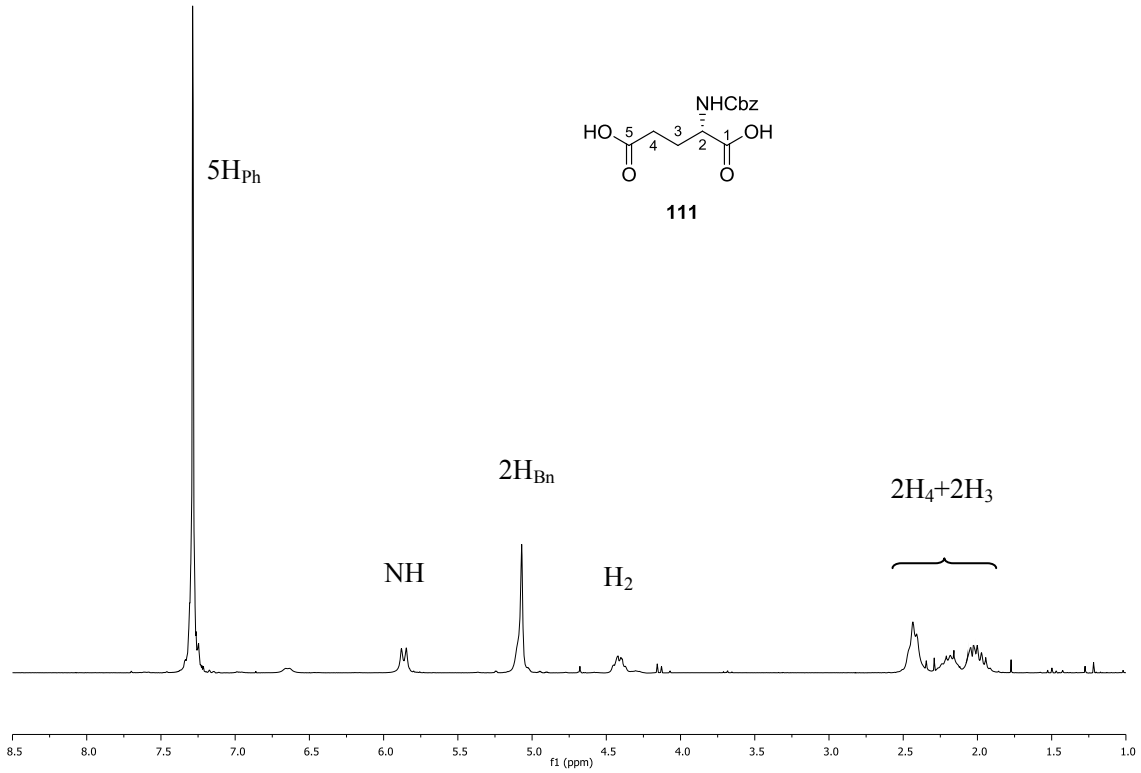
^{13}C NMR ($CDCl_3$, 101 MHz)



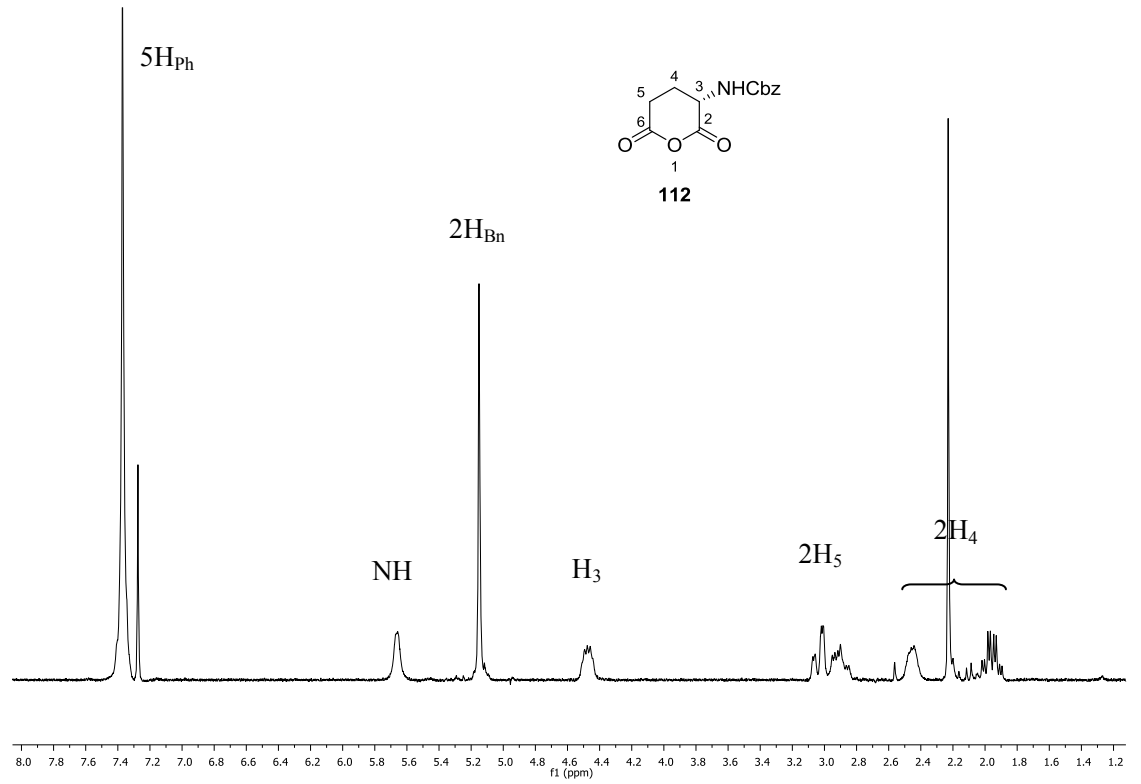
^{1}H NMR ($CDCl_3$, 250 MHz)



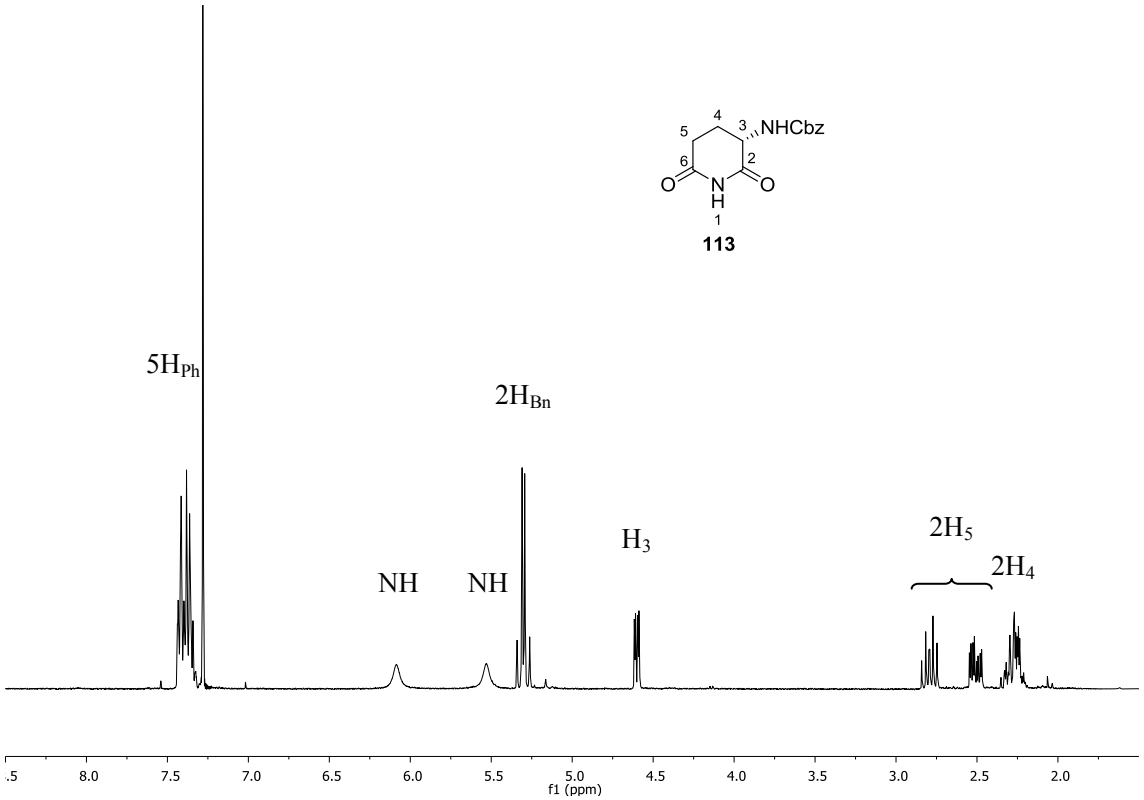
^{13}C NMR ($CDCl_3$, 101 MHz)



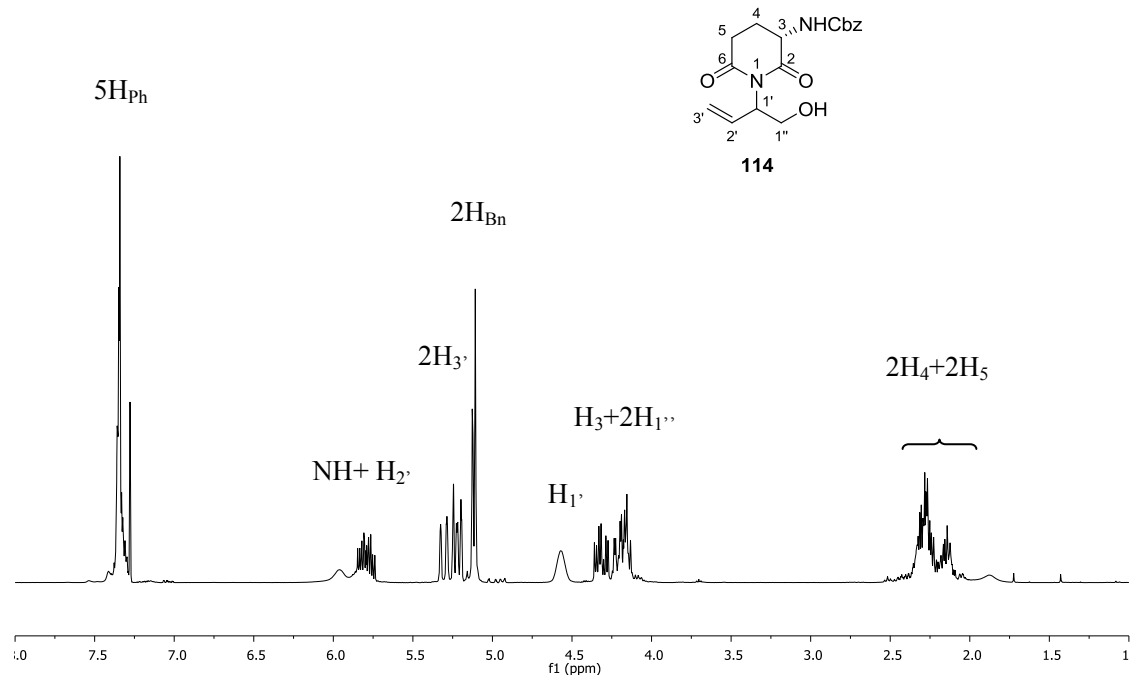
^{1}H NMR ($CDCl_3$, 250 MHz)



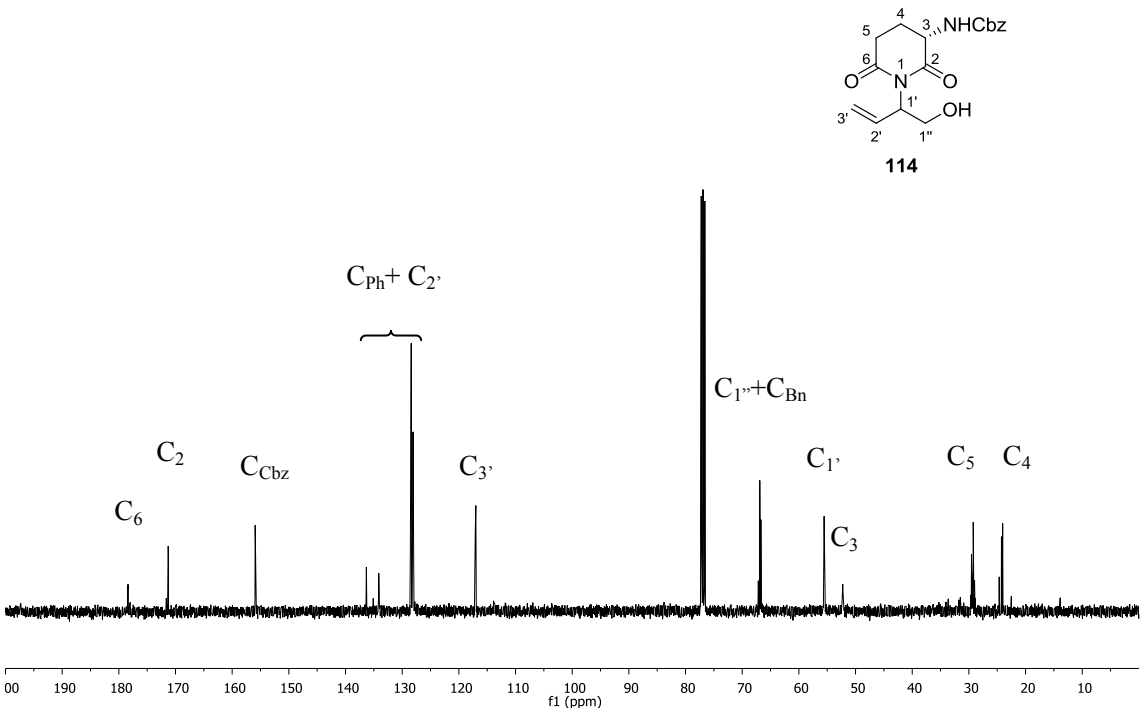
^{1}H NMR ($CDCl_3$, 250 MHz)



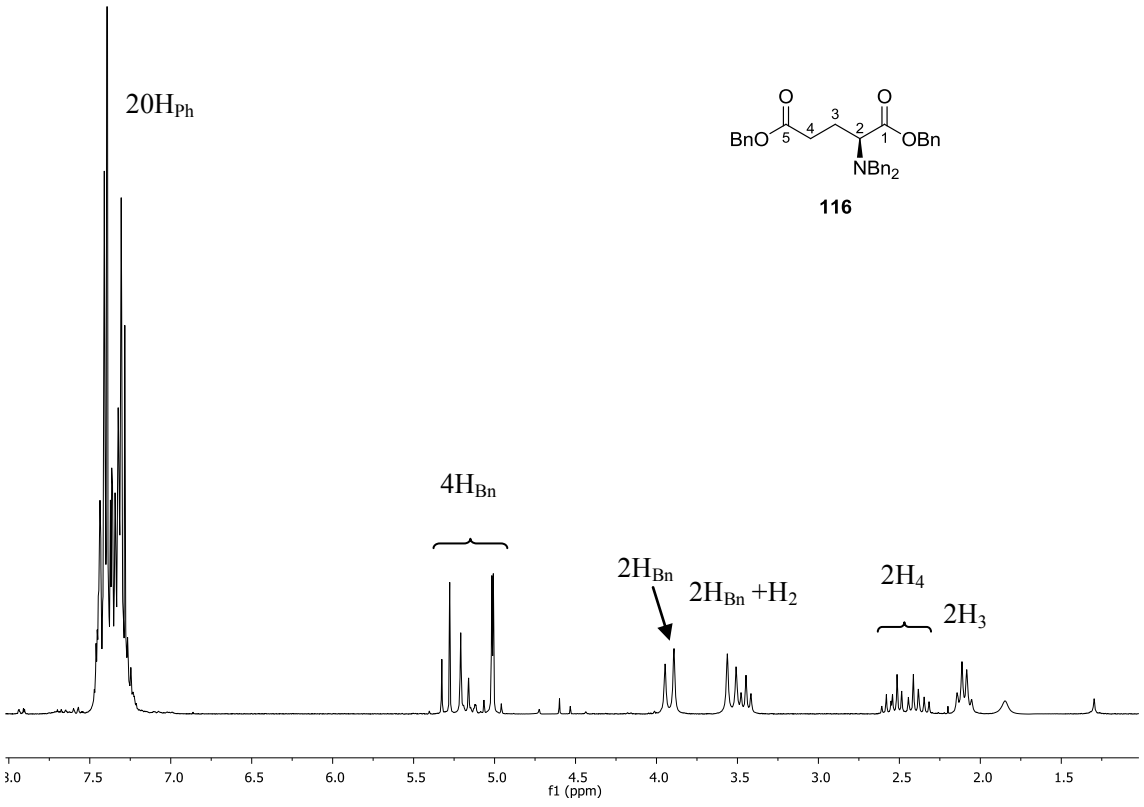
^{1}H NMR ($CDCl_3$, 400 MHz)



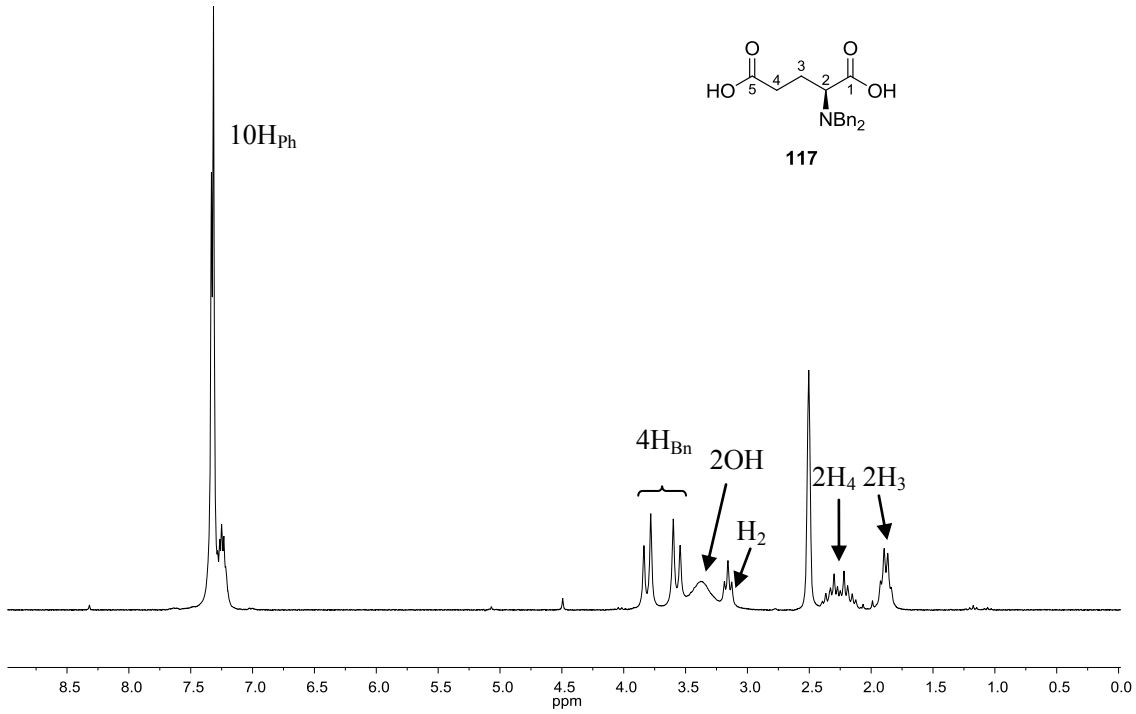
^{1}H NMR ($CDCl_3$, 400 MHz)



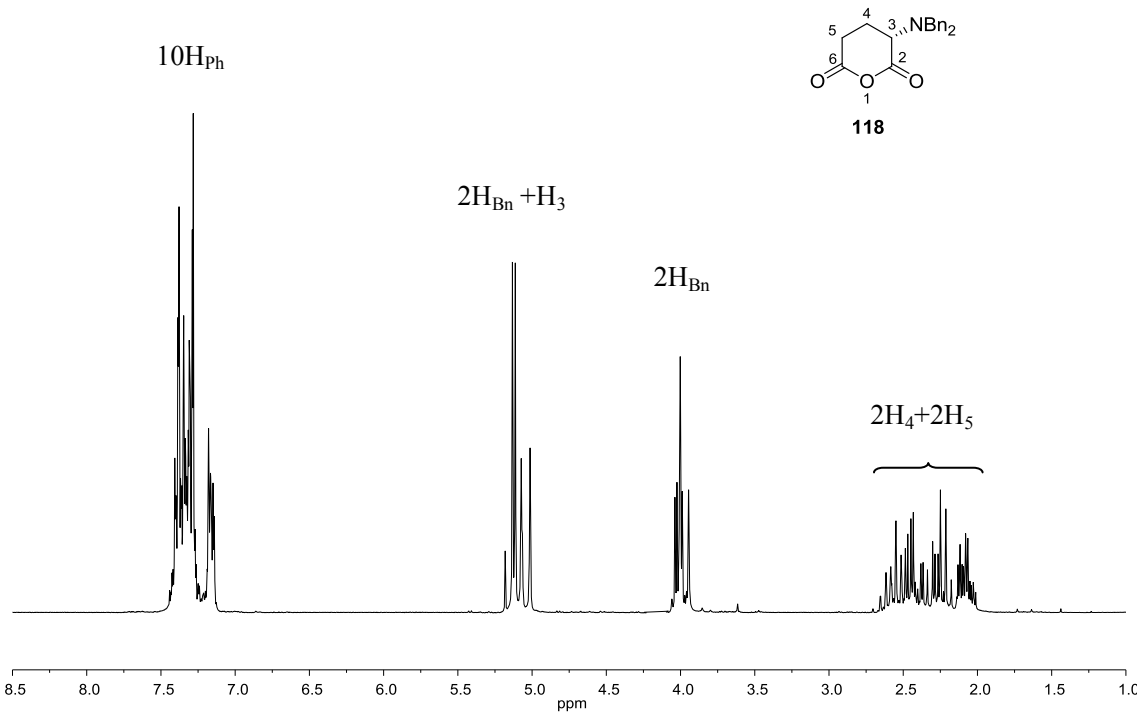
^{13}C NMR ($CDCl_3$, 101 MHz)



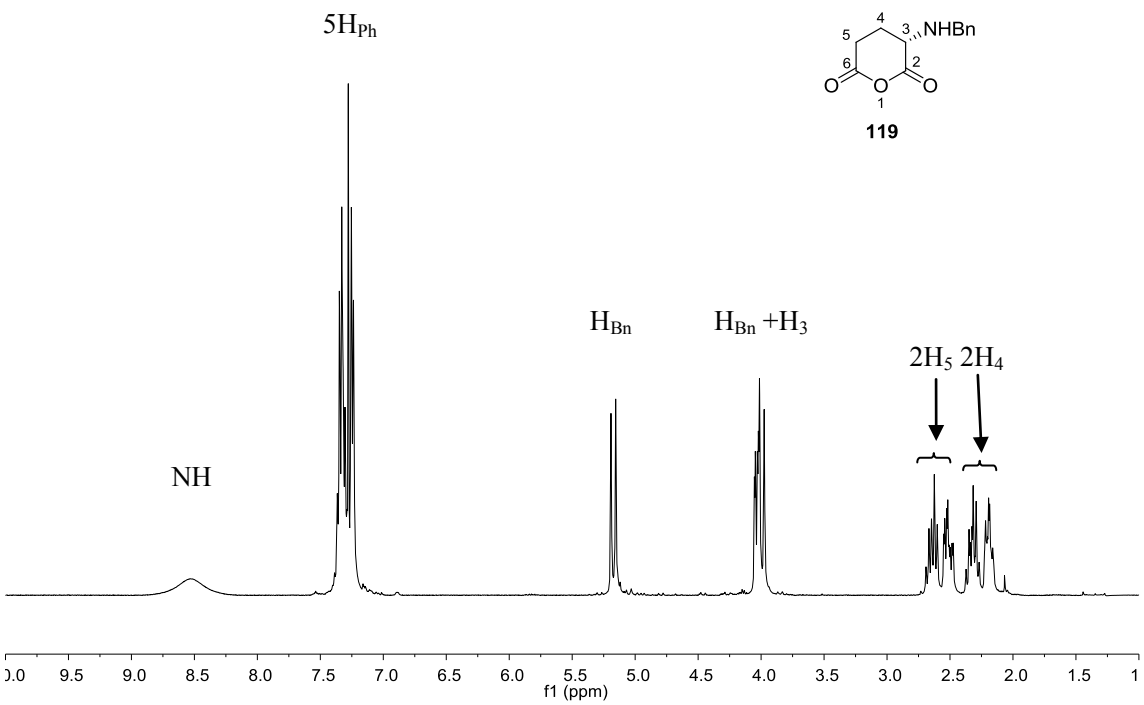
^{1}H NMR ($CDCl_3$, 250 MHz)



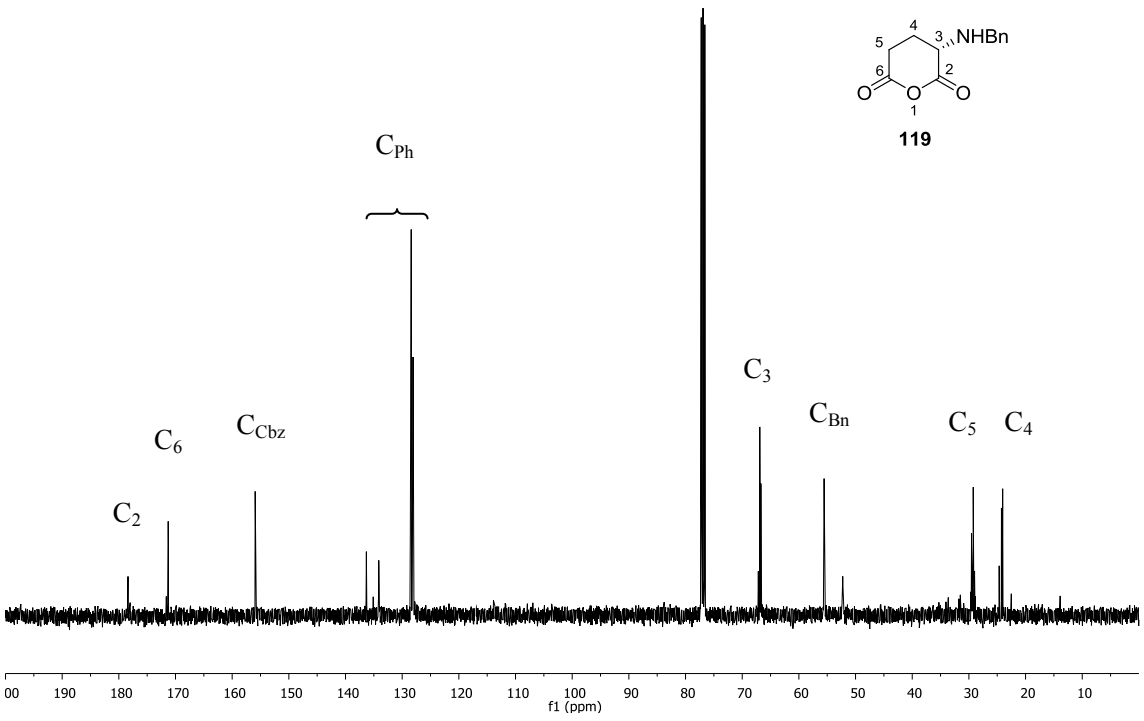
^{1}H NMR (DMSO-*d6*, 250 MHz)



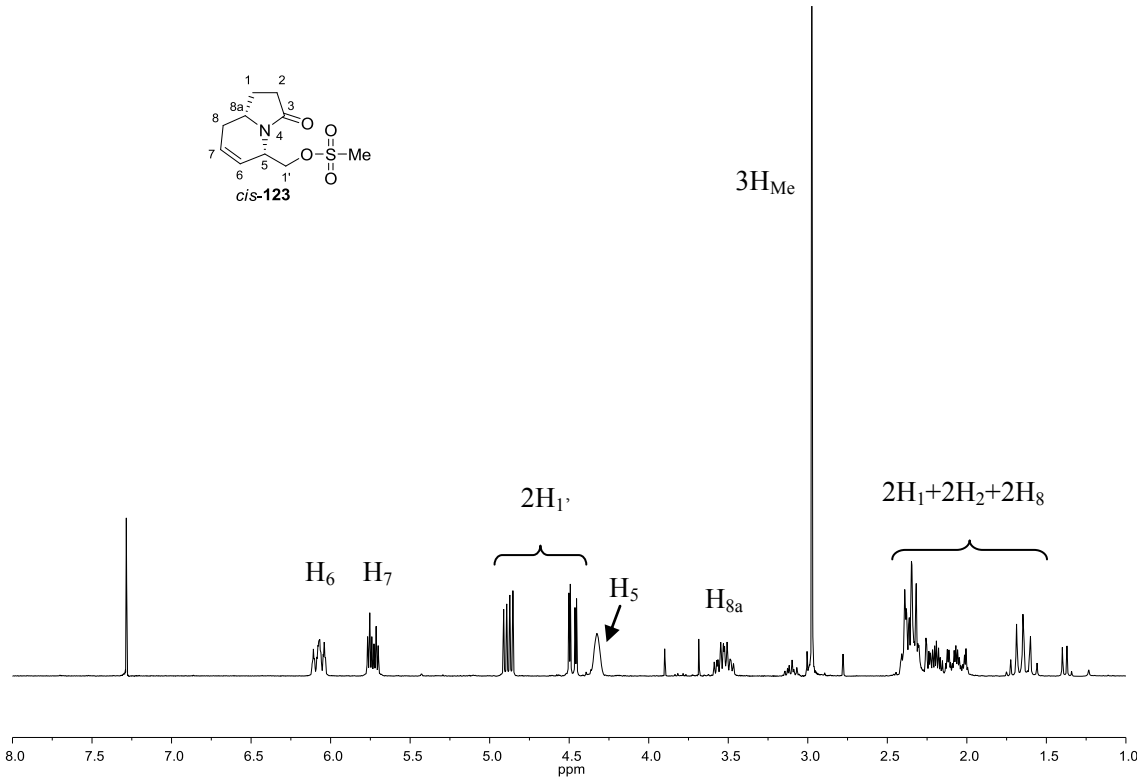
^{1}H NMR ($CDCl_3$, 250 MHz)



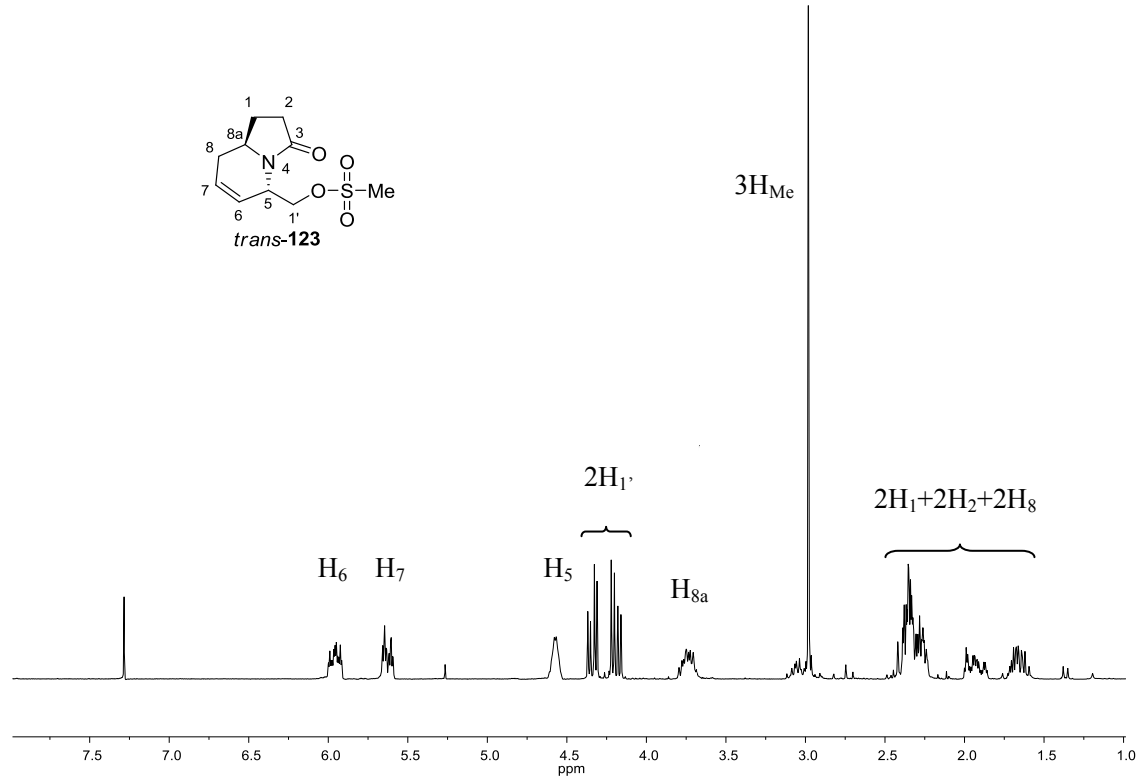
^{1}H NMR ($CDCl_3$, 400 MHz)



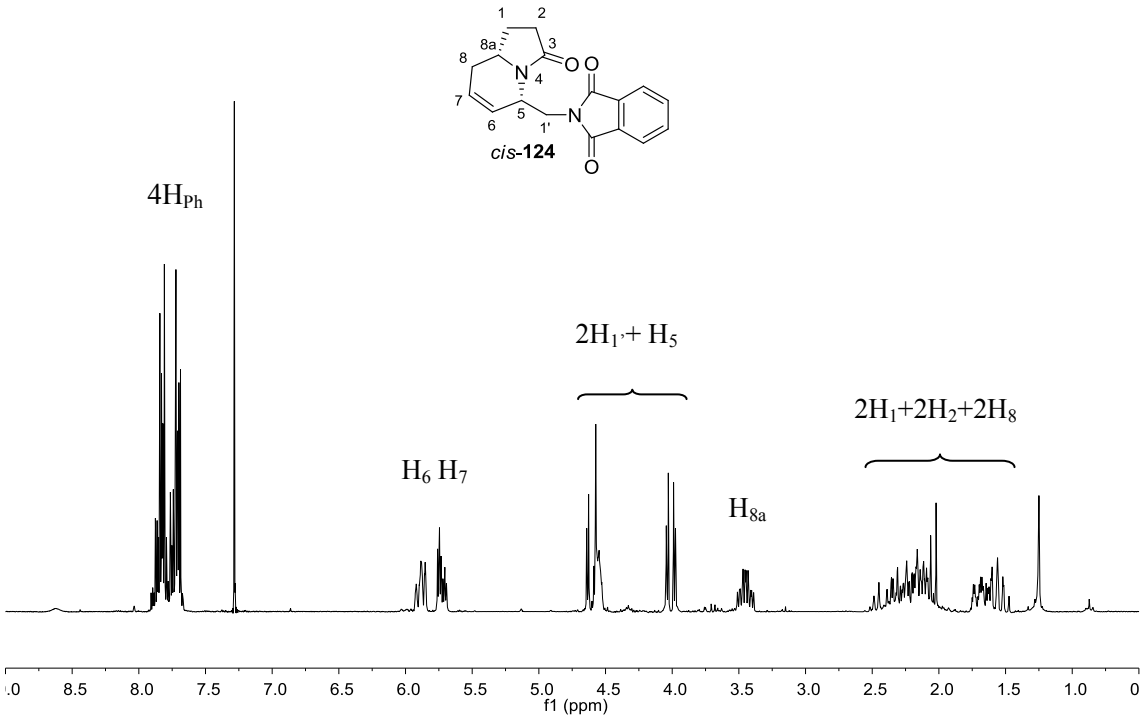
^{13}C NMR ($CDCl_3$, 101 MHz)



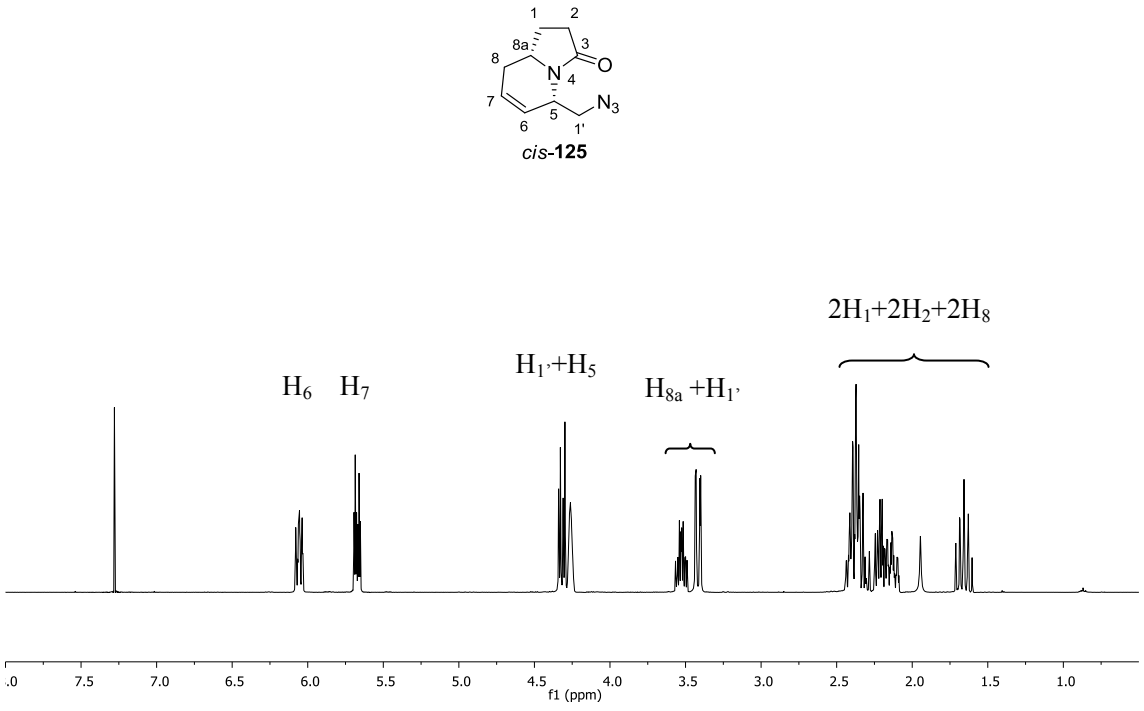
^{1}H NMR ($CDCl_3$, 250 MHz)



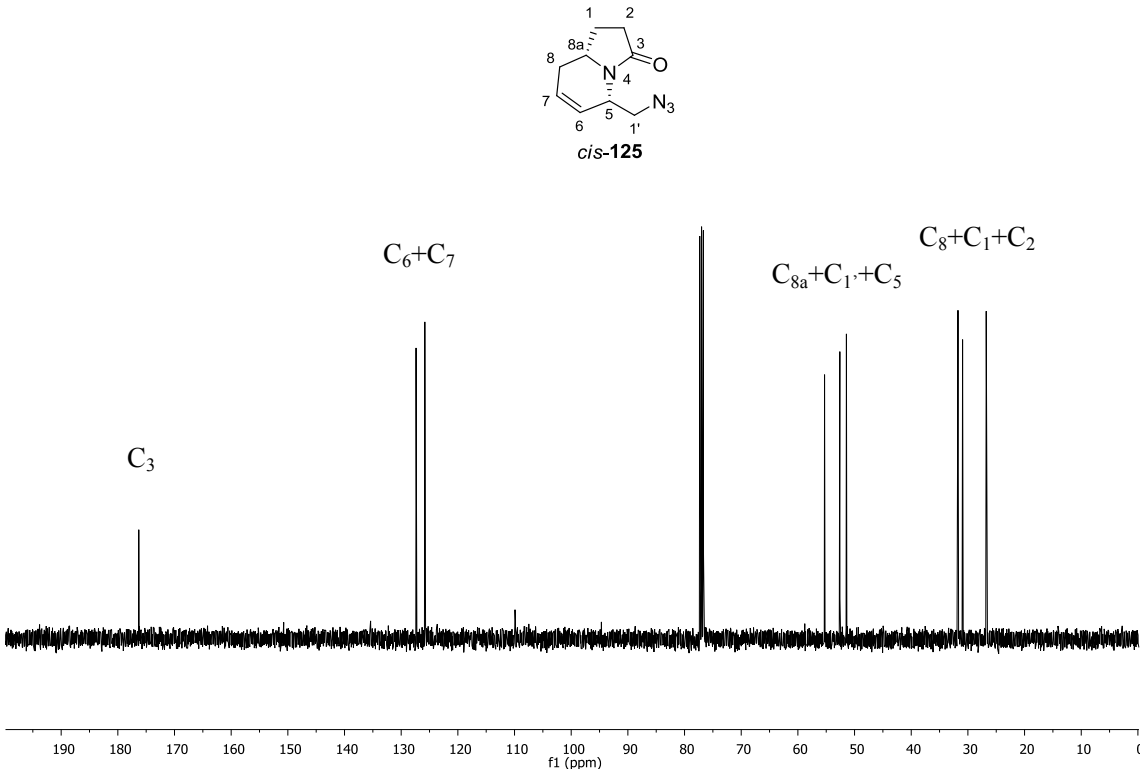
^{1}H NMR ($CDCl_3$, 250 MHz)



^{1}H NMR ($CDCl_3$, 250 MHz)

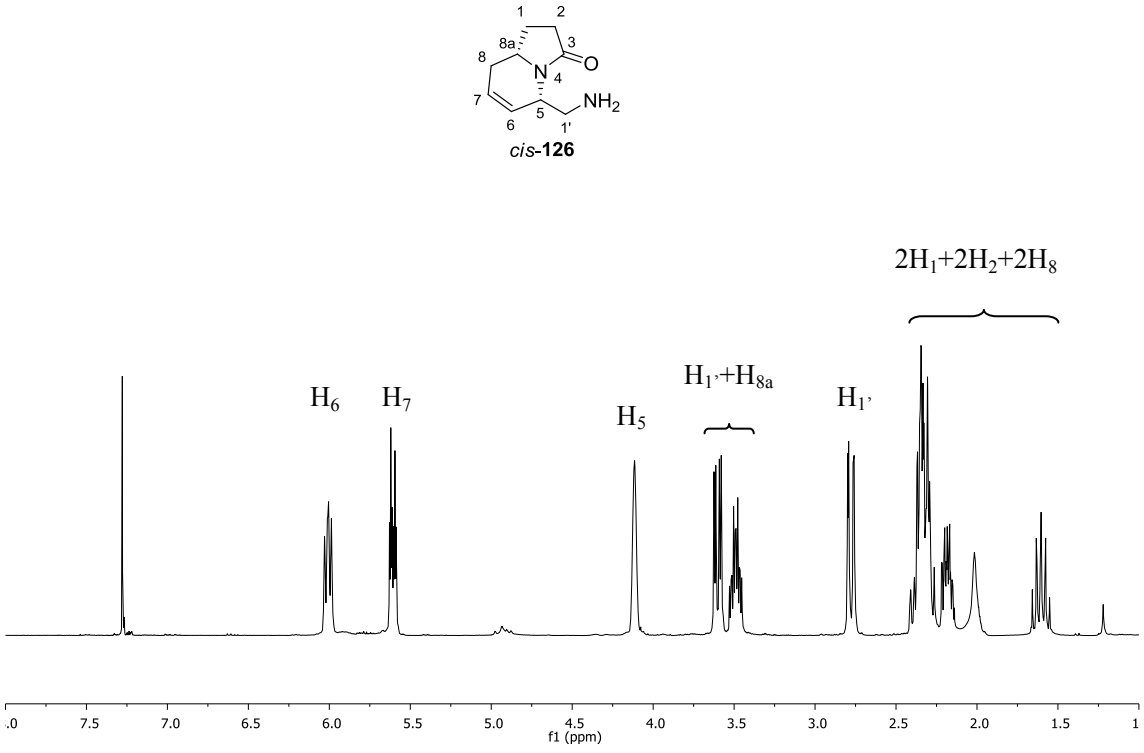


^{1}H NMR ($CDCl_3$, 400 MHz)



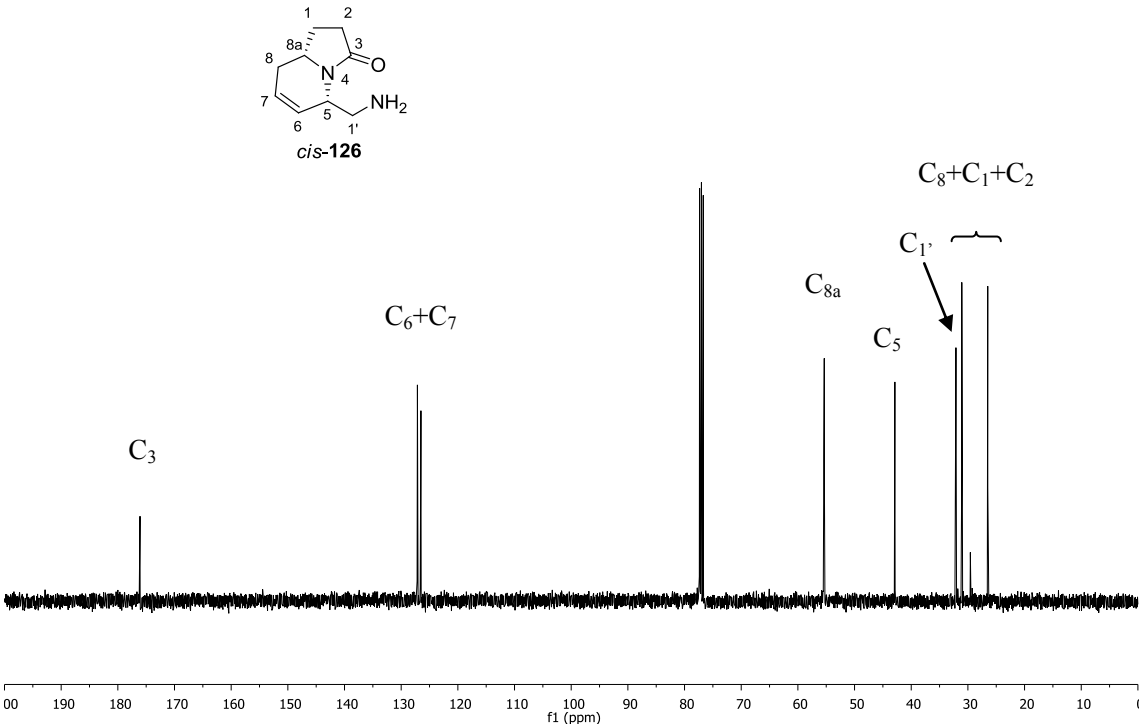
cis-**125**

^{13}C NMR ($CDCl_3$, 101 MHz)

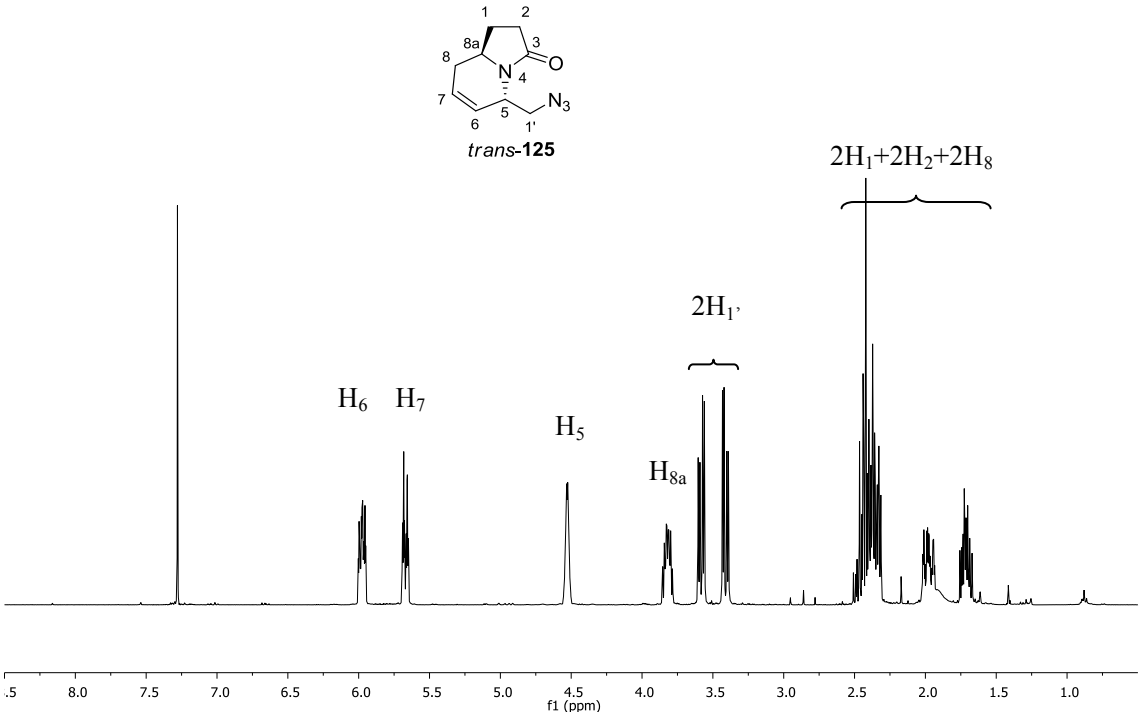


cis-**126**

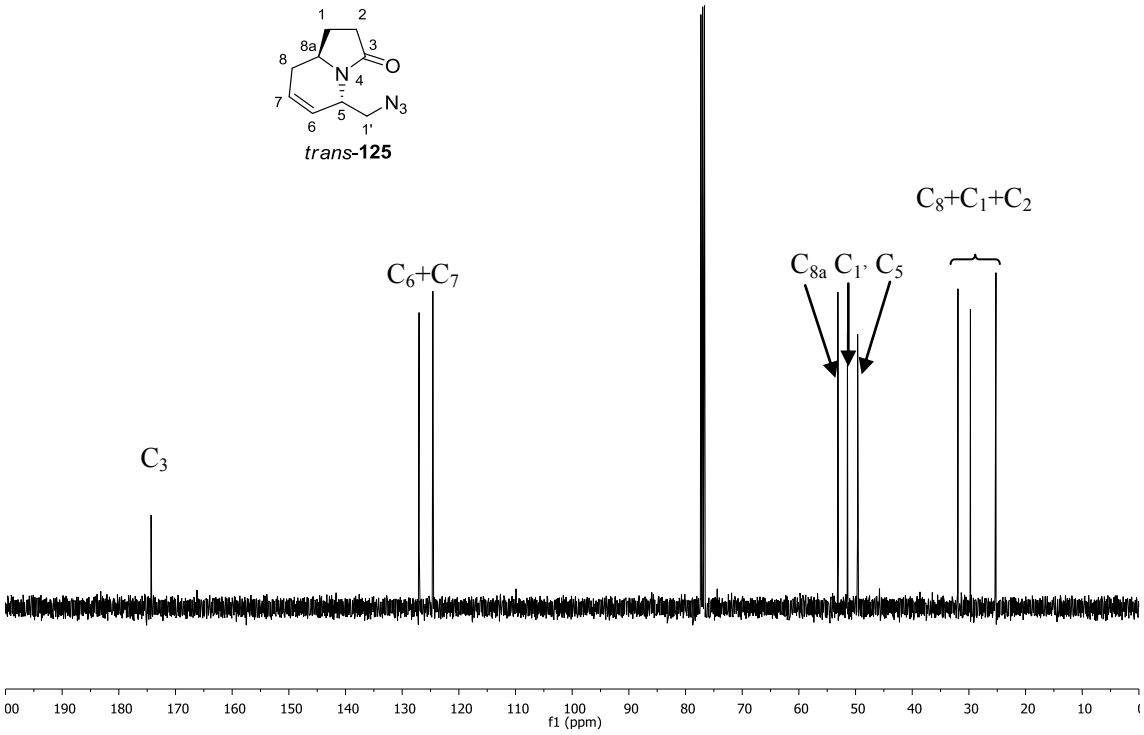
^{1}H NMR ($CDCl_3$, 400 MHz)



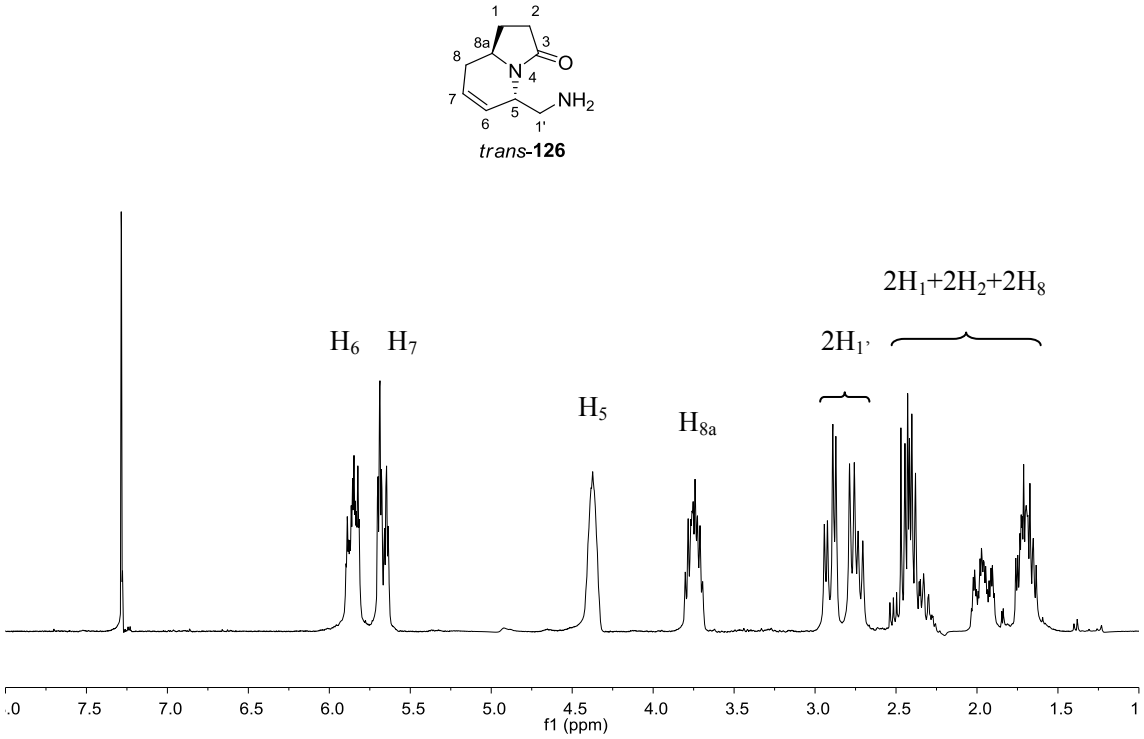
^{13}C NMR ($CDCl_3$, 101 MHz)



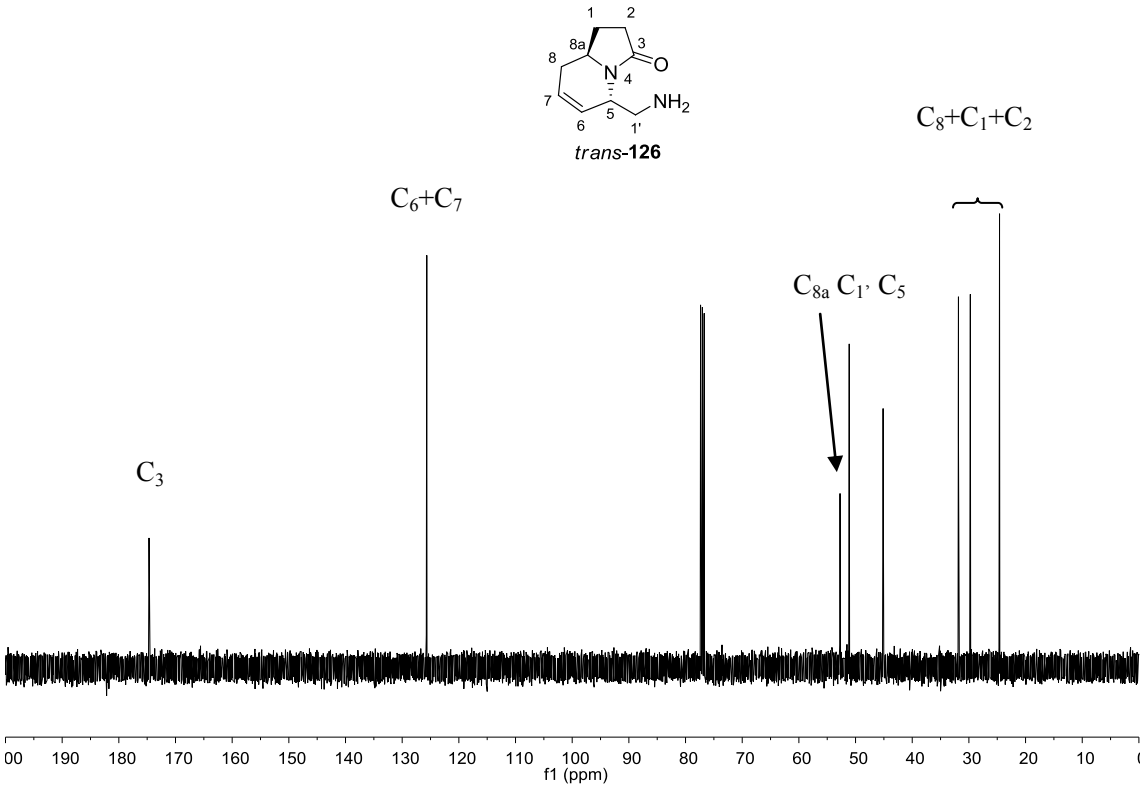
^{1}H NMR ($CDCl_3$, 400 MHz)



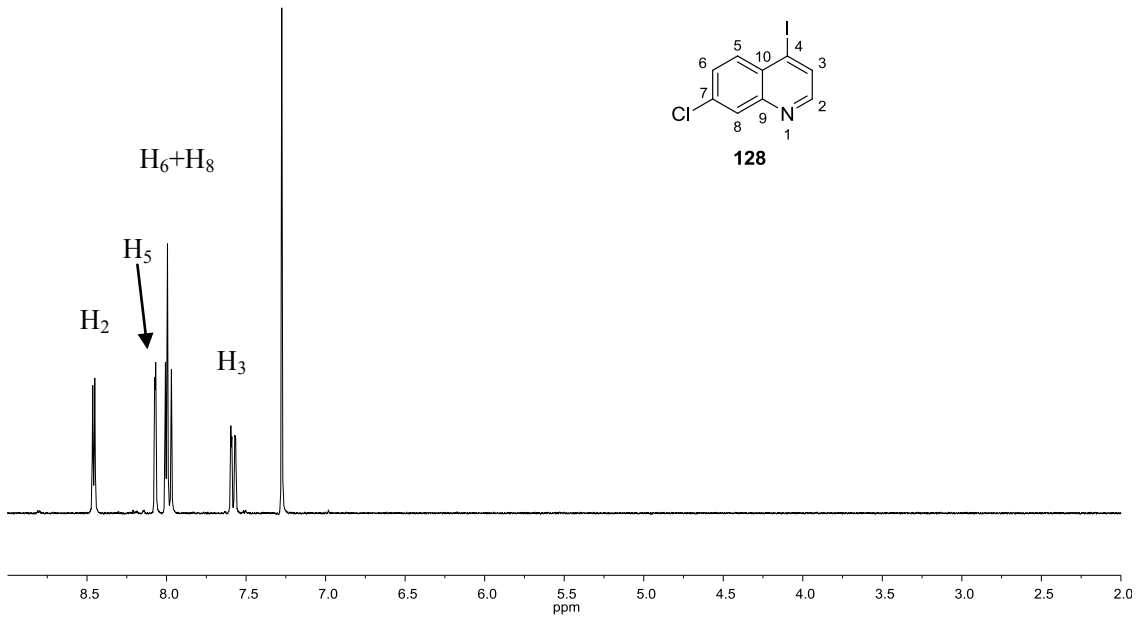
^{13}C NMR ($CDCl_3$, 101 MHz)



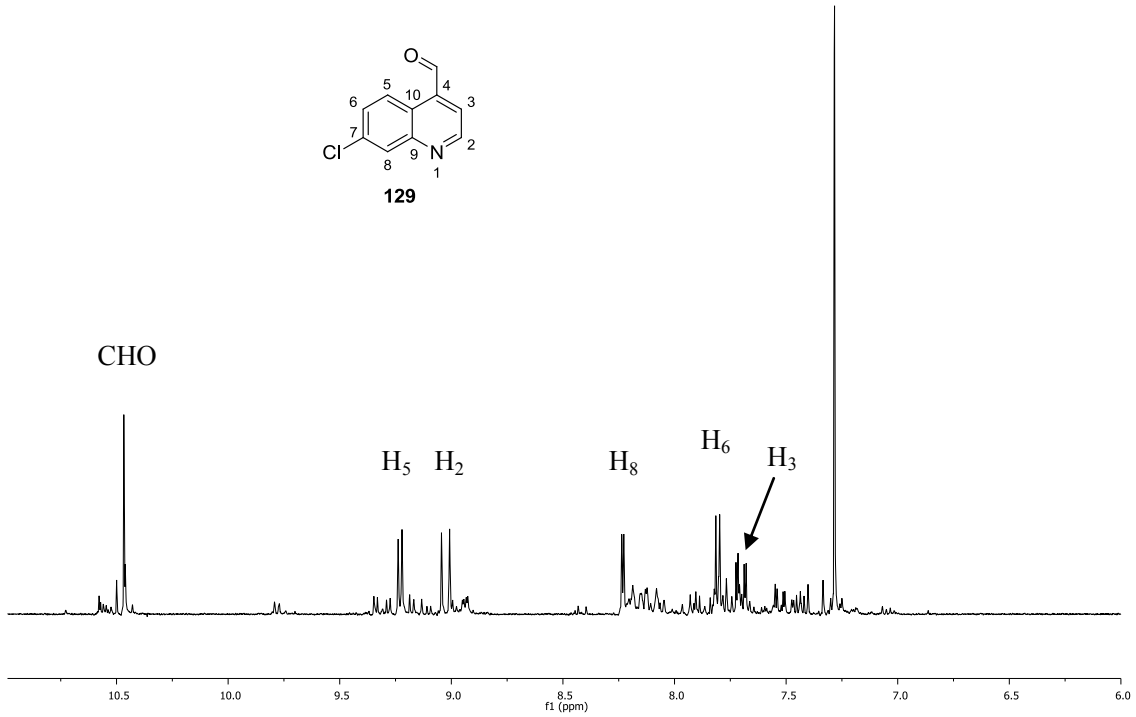
^{1}H NMR ($CDCl_3$, 250 MHz)



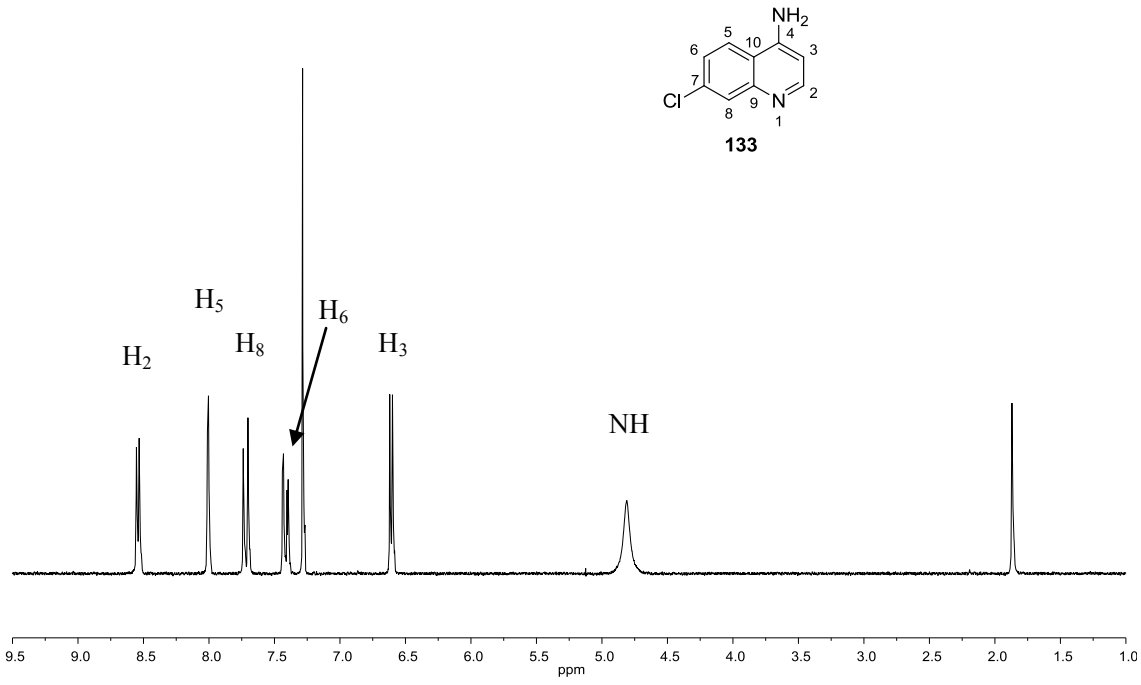
^{13}C NMR ($CDCl_3$, 101 MHz)



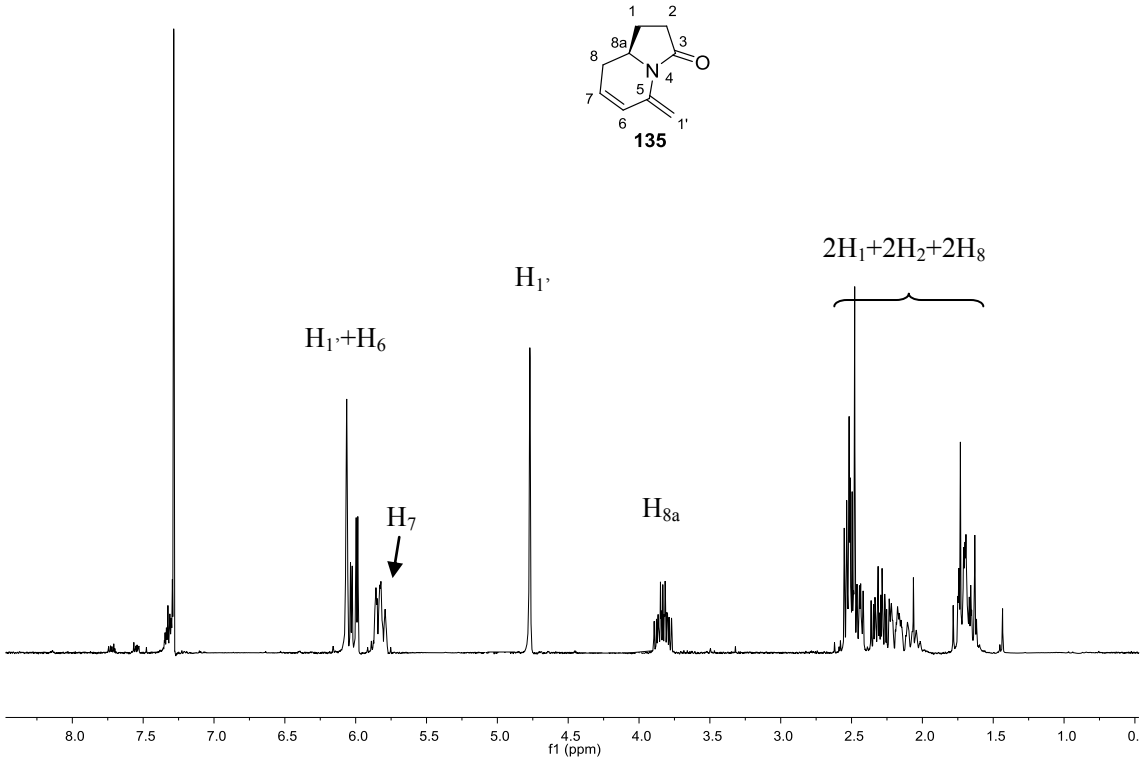
^{1}H NMR ($CDCl_3$, 360 MHz)



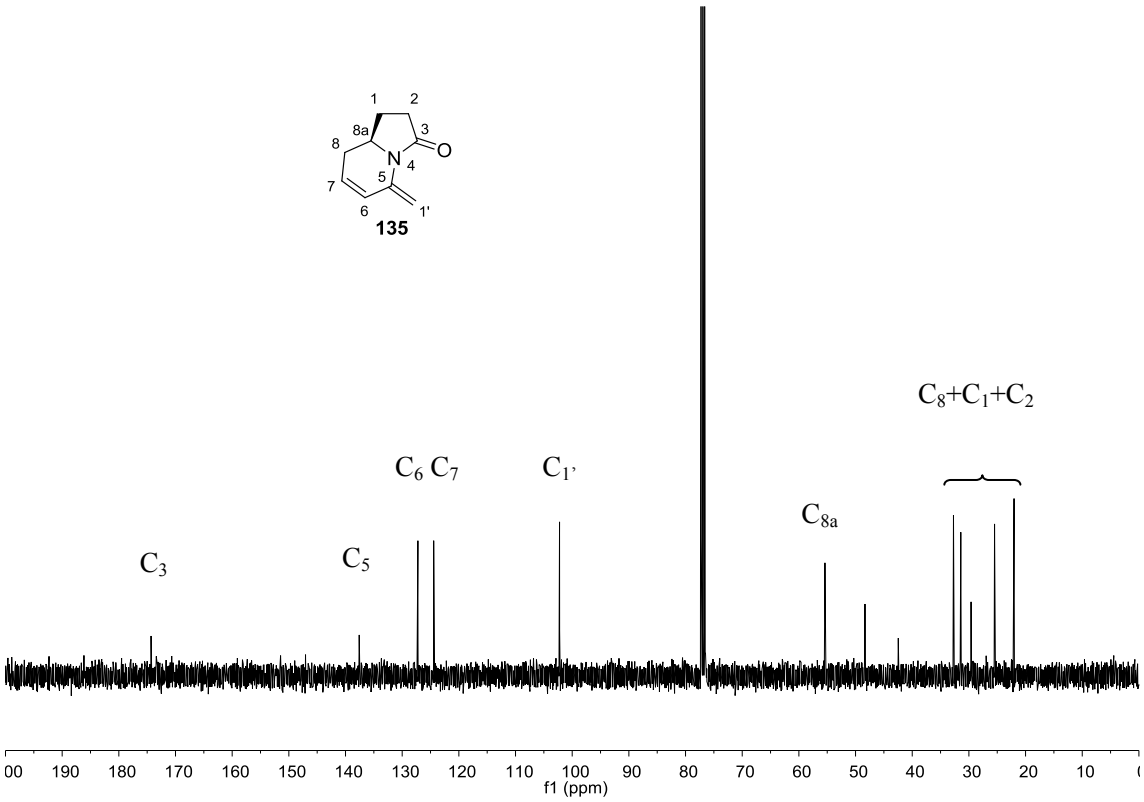
^{1}H NMR ($CDCl_3$, 250 MHz)



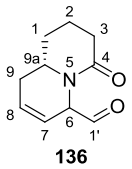
^{1}H NMR ($CDCl_3$, 360 MHz)



^{1}H NMR ($CDCl_3$, 250 MHz)



^{13}C NMR ($CDCl_3$, 101 MHz)



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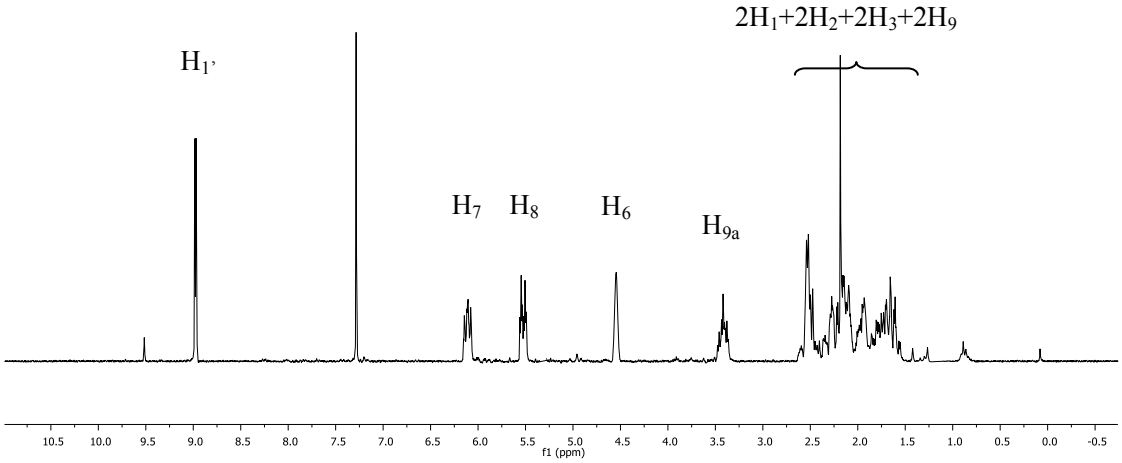
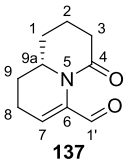


^{1}H NMR ($CDCl_3$, 250 MHz)



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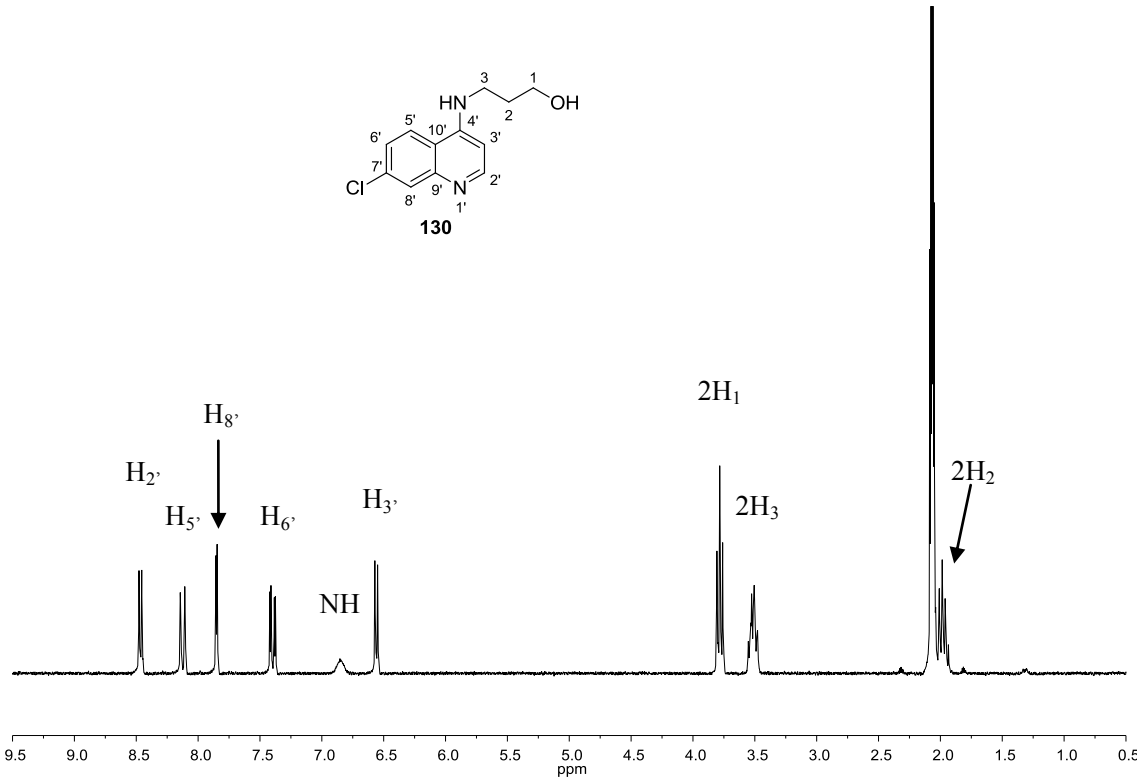
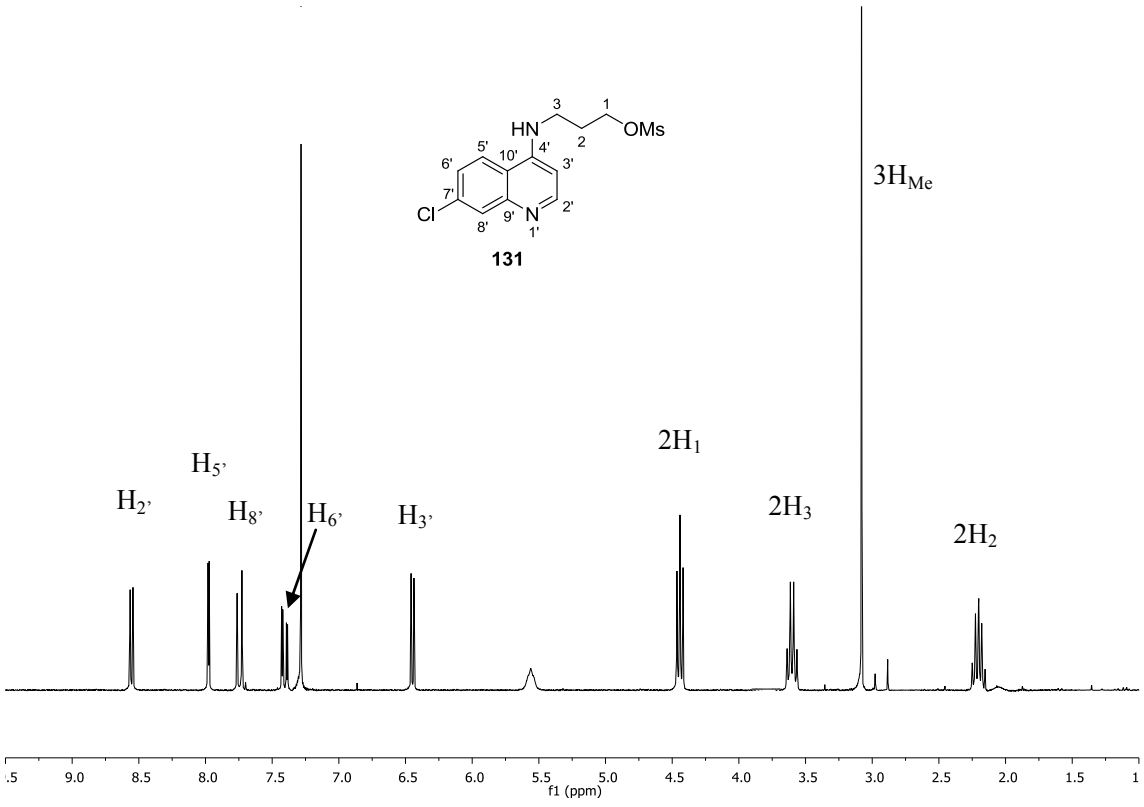
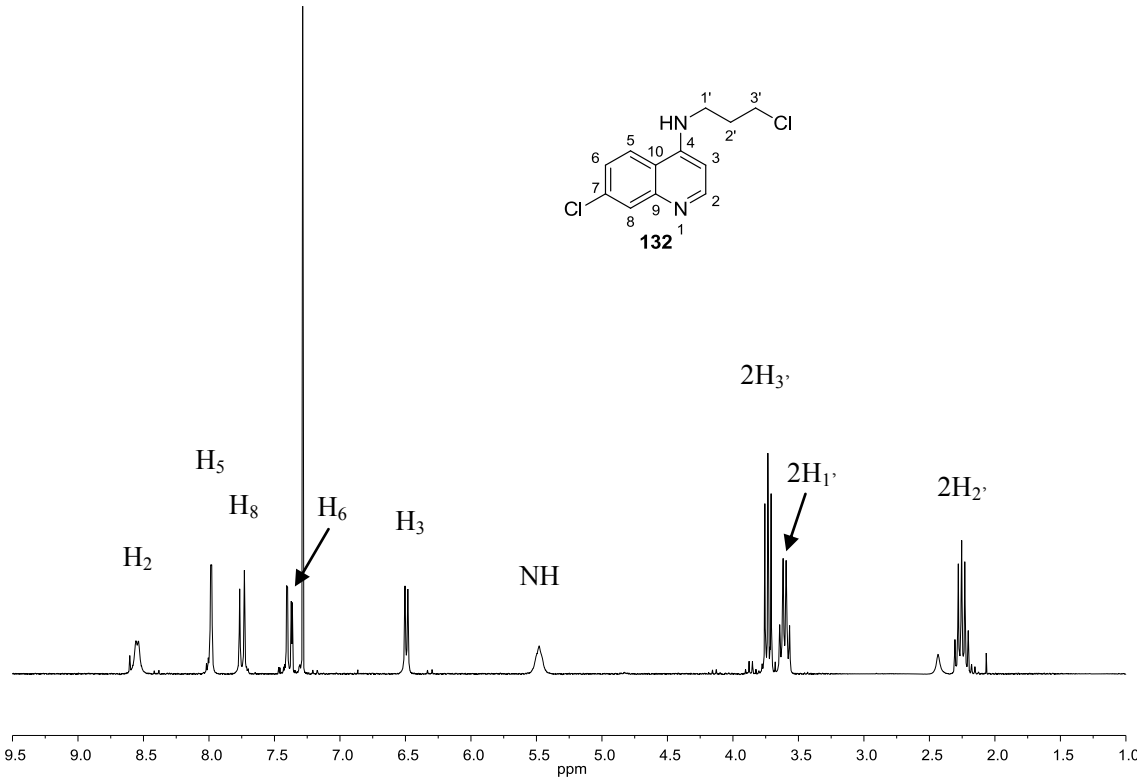
^{1}H NMR ($CDCl_3$, 250 MHz)



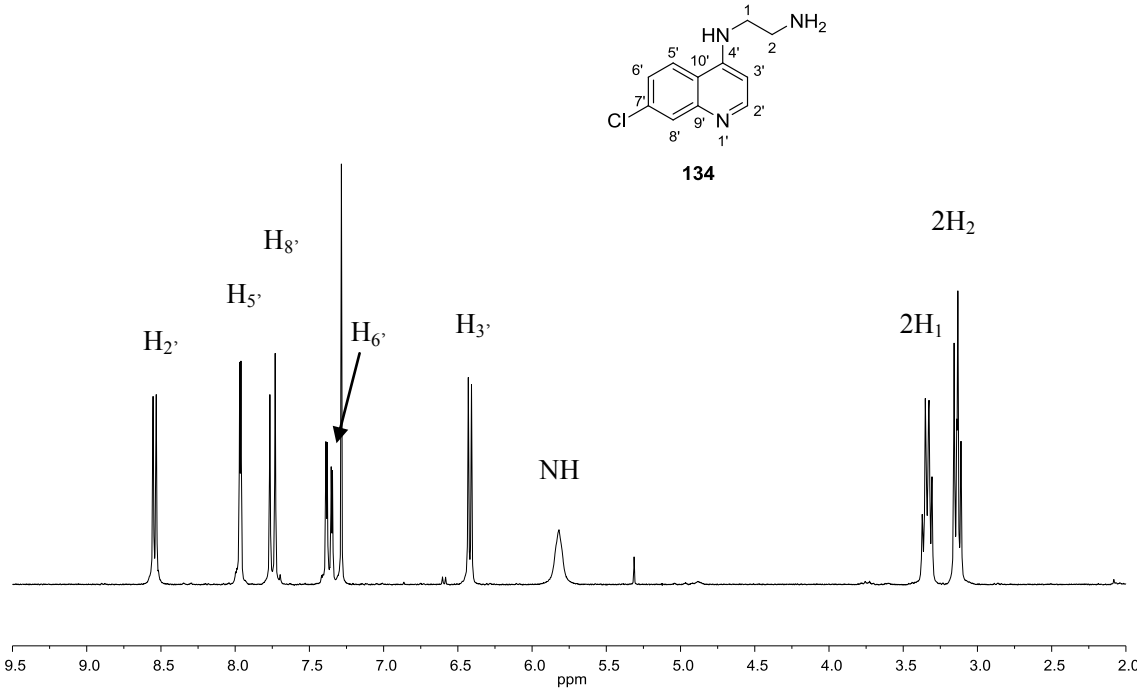
^{1}H NMR ($(CD_3)_2CO$, 250 MHz)



^{1}H NMR ($CDCl_3$, 250 MHz)



^{1}H NMR ($CDCl_3$, 250 MHz)



^{1}H NMR ($CDCl_3$, 250 MHz)