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Enantio- and Diastereoselective Cyclocondensation Reactions. Stereocontrolled Access to Azabicycles and Application to Natural Product Synthesis

Elena Ghirardi

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FACULTAT DE FARMÀCIA

DEPARTAMENT DE FARMACOLOGIA, TOXICOLOGIA I QUÍMICA TERAPÈUTICA

ENANTIO- AND DIASTEREOSELECTIVE CYCLOCONDENSATION REACTIONS. STEREOCONTROLLED ACCESS TO AZABICYCLES AND APPLICATION TO NATURAL PRODUCT SYNTHESIS

Elena Ghirardi

Barcelona, 2016

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PROGRAMA DE DOCTORAT:

ENANTIO- AND DIASTEREOSELECTIVE CYCLOCONDENSATION REACTIONS. STEREOCONTROLLED ACCESS TO AZABICYCLES AND APPLICATION TO NATURAL PRODUCT SYNTHESIS

Memòria presentada per Elena Ghirardi

per optar al títol de doctor per la universitat de Barcelona

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Barcelona, 2016

En primer lugar quisiera agradecer a la **Dra**. **Mercedes Amat Tusón**, directora de Tesis y Catedrática de Química Orgánica de la Facultat de Farmacia de la Universitat de Barcelona por aceptarme en su grupo de investigación confiando en mis capacidades y por su supervisión del trabajo y su aportación continua de conocimientos.

También quisiera agradecer a la **Dra. Rosa Griera Farrés**, directora de Tesis y profesora agregada de la Facultat de Farmacia de la Universitat de Barcelona, por su dedicación y su ayuda costante, además de su apoyo dentro y fuera del laboratorio.

Finalmente quiero agradecer al **Dr. Joan Bosch Cartes**, Catedrático de Química Orgánica de la Facultat de Farmacia de la Universitat de Barcelona por su confianza y sus valiosos consejos.

Financial support from the Spanish Ministry of Economy and Competitiveness (Project CTQ2012-35250) and Generalitat de Catalunya (2014SGR1189) is gratefully acknowledged. Thanks to the Ministry of Education, Culture and Sport (MECD, Spain) for the F.P.U. fellowship.

Publication

ENANTIO- AND DIASTEREOCONVERGENT CYCLOCONDENSATION REACTIONS: SYNTHESIS OF ENANTIOPURE *CIS*-DECAHYDROQUINOLINES. Amat, M.; Ghirardi, E.; Navío L.; Griera, R.; Llor, N.; Molins, E.; Bosch, J. *Chemistry, an European Journal* **2003**, *19*, 16044–16049.

Oral Communications

Highly stereoselective cyclocondensation reactions. Enantioselective synthesis of substituted *cis*-decahydroquinolines
Mercedes Amat, Nuria Llor, Laura Navío, Rosa Griera, Elena Ghirardi, Joan Bosch
San Sebastian, July 2012

Highly Stereoselective Cyclocondensation Reactions. Enantioselective Synthesis of Substituted cis-Decahydroquinolines
Mercedes Amat, Elena Ghirardi, Rosa Griera, Laura Navío, Nuria Llor, Joan Bosch
Granada, Juny 2013

Highly Stereoselective Cyclocondensation Reactions. Enantioselective Synthesis of Substituted *cis*-Octahydroindole Derivatives.
Elena Ghirardi, Mercedes Amat, Rosa Griera, Joan Bosch
Alicante, Juny 2014

Research Stay

From March 2015 until May 2015 I joined the group of Prof. Herzon Seth, at Yale University (CT). I focused my research on the synthesis of saccharides and linkers that will be used in the modulation of the anti-tumor activity of a potent metabolite.
This research stay was funded by the Ministry of Education, Culture and Sport (MECD, Spain).

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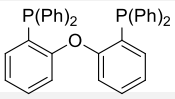
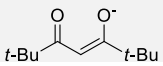
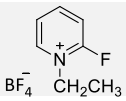
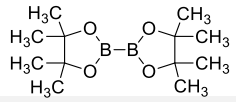
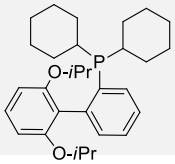
Symbols and abbreviations

9-BBN	9-Borabicyclo(3.3.1)nonane
anh	anhydrous
AI	Aminoindanol
Allyl-TMS	Allyltrimethylsilane
ax	Axial
Boc	*Tert*-butyloxycarbonyl
cat	Catalytic/catalyst
cis-DHQ	*cis*-decahydroquinoline
COD	Cyclooctadiene
conc	Concentrate
DIPEA	N,N-Diisopropylethylamine
DMAP	4-Dimethylaminopyridine
DMPU	*N, N*-dimethylpropyleneurea
DPEPhos	(Oxydi-2,1-phenylene)bis(diphenylphosphine) 
dpm	Dipivaloylmethanato 
DPPA	Diphenylphosphorylazide
dr	Diastereoisomeric ratio
eq	Equatorial
equiv.	Equivalents
EVK	Ethyl vinyl ketone
FEP	2-fluoro-1-ethyl pyridinium tetrafluoroborate 
HMPA	Hexamthylphosphoric triamide
Isob. acid	Isobutyric acid
LDA	Lithium diisopropyl amide
m-CPBA	*meta*-Chloroperbenzoic acid
mp	Melting point
MsCl	Mesyl chloride
MVK	Methyl vinyl ketone
MW	Micro-way
NMO	*N*-methylmorpholine-*N*-oxide
NMP	*N*-methylpyrrolidine

Pin-B-B-Pin	Bis(pinacolato)diboron	
PMB	4-Methoxybenzyl	
PMP	*para*-Methoxyphenyl	
PPA	Polyphosphoric acid	
PTSA	*para*-Toluensulfoni acid	
rac	racemic	
Red-Al	Sodium bis(2-methoxyethoxy)aluminiumhydride	
Phos	2-Dicyclohexylphosphino-2',6'-diisopropoxybiphenyl	
SEMCl	2-(Trimethylsilyl)ethoxymethyl chloride	
TBAF	Tetrabutyl-ammonium floride	
TBDMSCl	*tert*-Butyldimethylsilyl chloride	
TBDPS	*tert*-Butuldiphenylsilane	
TEMPO	(2,2,6,6-Tetramethylpiperidin-1-yl)oxyl	
TFA	Trifluoroacetic acid	
Tf_2O	Triflic anhydride	
TMG	1,1,3,3-Tetramethylguanidine	
TMSCl	Trimethyl silyl chloride	
TMSCN	Trimethylsilylcianide	
TPAP	tetrabutylammonium perruthenate	
Tos	Tosyl-	

CHAPTER 1. INTRODUCTION AND OBJECTIVES

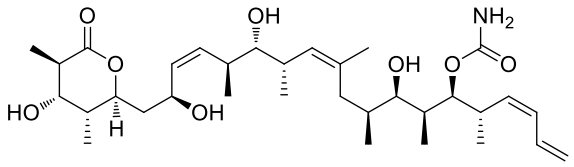
Natural product synthesis has played a central role in the evolution of organic chemistry and has been crucial in the development of modern drug discovery programs in the pharmaceutical industry. Biologically active natural products can be considered "privileged" scaffolds that have been evolutionarily selected for binding to particular domains of biological macromolecules.

The development of general methods for the total synthesis of natural products and other related biologically active compounds is a pivotal element in the evolution of organic synthesis.

In the last decade, our group has been developing a general methodology for the synthesis of enantiopure nitrogen-containing heterocycles, based on the use of chiral aminoalcohol-derived lactams as enantiomeric scaffolds. Over the years, the procedure has achieved a high degree of maturity and today constitutes a solid, versatile, and efficient tool for the enantioselective synthesis of complex alkaloids.

1.1. State of the art

Natural products have represented and still represent today an important part of our scientific culture: the nature, in one guise or another, has continued to influence the design of drug molecules. In the area of chemotherapy, over the time's frame from 1940s to 2010, of the 175 approved small molecules, 131 (74.8%) are synthetic, with 85 (48.6%) actually being either natural products or directly derived therefrom. In other areas, the influence of natural products is remarkable, with the anti-infective area being dependent on natural products and their structure.[1] This is because biologically active natural products are "privileged" scaffolds, since they have been evolutionarily selected for binding to particular domains of biological macromolecules.[2] Because of the natural selection process, these compounds possess a unique and vast chemical diversity, which permits optimal interactions with biological macromolecules. (+)-Discodermolide **I**, for example, a polyketide that was first isolated by Gunasekera in 1990 from the Caribbean deep-sea sponge *Discodermia dissolute,*[3] was reported to inhibit the proliferation of cancer cells by stabilizing microtubules and arresting the G_2/M stages of the cell cycle. It was considered a promising candidate for clinical development as a chemotherapeutic agent for the treatment of several neoplasias. Due to its significant antitumor activity, discodermolide attracted considerable interest from the pharmaceutical industry. However, a huge material supply problem limited the progression of discodermolide into clinical development, since it accounts for only 0.002 wt% of the dried rare *D. dissoluta* and it was not enough for clinical studies.[4]



I

Figure 1.1 (+)-discodermolide

As a result, synthetic chemists rose to the challenge of developing a scalable synthetic approach to the complex structure of **I**, culminating in the first total synthesis in 1993.[5] After that, several other total

[1] Newman, D. J.; Cragg, G. M. *J. Nat. Prod.* **2012**, *75*,311–335.
[2] a. Firn, R. D.; Jones, C. G. *Nat. Prod. Rep.* **2003**, *20*, 382–391; b. Bon, R. S.; Waldmsnn, H. *Acc. Chem. Res.* **2010**, *43*, 1103–1114; c. Hong, J. *Chem. Eur. J.* **2014**, *20*, 10204–20212; d. Trauner, D. *Nat. Prod. Rep.* **2014**, *31*, 411–413; e. Burke, M. D.; Schreiber, S. L. *Angew. Chem. Int. Ed.* **2004**, *43*, 46–58; f. Galloway, W. R. J. D.; Isidro-Llobet, A.; Spring, D. R. *Nat. Commun.* **2010**, *1*, 80.
[3] Gunasekera, S. P.; Gunasekera, M.; Longley, R. E.; Schulte, G. K. *J. Org. Chem.* **1990**, *55*, 4912–4915.
[4] Hong, J. *Chem. Eur. J.* **2014**, *20*, 10204–10212.
[5] Nerenberg, J. B.; Hung, D. T.; Somers, P. K.; Schreiber, S. L. *J. Am. Chem. Soc.* **1993**, *115*, 12621–12622.

syntheses and constructions of various fragments of discodermolide were reported.[6] Nevertheless, the interest of pharmaceutical industry in total synthesis of natural products has suffered a gradual decline in the last decades due to a number of factors: the lack of efficiency of chemical synthesis along with the development of combinatorial chemistry and the introduction of high-throughput screenings (HTS). Total synthesis of complex natural products has often resulted in unacceptably long and low-yielding unpractical sequences. The overall yield drops with the number of steps. Given an honest yield of 70% per step, the total yield drops to 14% after 5 steps and to 7% after 10 steps. After 20 steps sequence, which is no exceptional, an overall yield of 0.05% means that 99.5% of the initial materials has ended up as waste.[7] Thus, to improve the efficiency, chemists have to spend more time and energy to find appropriate methodologies, strategies, reagents and/or starting materials for practical and acceptable synthesis of relatively complex target molecules. However, the limited success of combinatorial chemistry and HTS, the considerable advances in automation of chromatographic and spectroscopic techniques and the advent of genome mining and metabolic engineering have reactivated the interest in natural products as valuable resources of drug discovery.

Natural product synthesis has represented and still represents, the most feasible way to obtain sufficient amounts of interesting natural products for biological tests, and to modify their structure for chemical probe development as displayed in the case of (+)-discodermolide. Semi-synthetic structural modification of natural products provides important structure-activity relationship data. These data enable subsequent computer-aided ligand optimization and the synthesis of analogs with improved pharmacological properties.[8] This is one of the reasons why natural product synthesis has been a flagship and a pivot of organic chemistry for more than six decades, starting from the contributions by Woodward and Corey, down to the latest achievements by Nicolau, Myers, Ley and many others.[7, 9] The synthesis of natural products has, therefore, constituted the main driving force behind the development of chemical transformations. Natural product synthesis henceforth provides a challenge to invent and to develop novel reaction and discover novel reactivity patterns.

However, before 1960s, the underlying incentive for natural product synthesis was to confirm their structures.[10] Such proposal was the result of a time-consuming process and intensive degradation studies of a given compound to the point that fragments of known constitution were obtained. Consequently, researchers of the era might have expected to solve their molecular puzzles after a few years of painstaking efforts; the assignment of absolute or relative configuration was, of course, essentially out of

[6] a. Smith, A. B.; Freeze, B. S. *Tetrahedron* **2007**, *64*, 261–298; b. Florence, G. J.; Gardner, N. M.; Paterson, I. *Nat. Prod. Rep.* **2008**, *25*, 342–375.

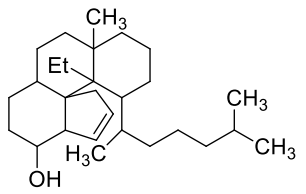
[7] Mulzer, J. *Nat. Prod. Rep.* **2014**, *31*, 595–603.

[8] Over, B.; Wetzel, S.; Grütter, C.; Nakai, Y.; Renner, S.; Rauh, D.; Waldmann, H. *Nat. Chem.* **2013**, *5*, 21–28.

[9] For representative examples: Nicolau, K. C.; Chen, J. S. *Classic in Total Synthesis III*, Wiley-VCH, Weinheim, **2011**, and earlier volumes of the series.

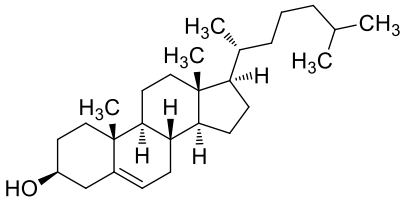
[10] Hoffmann, R. W. *Angew. Chem. Int. Ed.* **2013**, *52*, 123–130.

the question in most cases.[11] This intellectually difficult and physically tedious approach had its limitations and was often attended with errors. Thus, confirmation of the structure by total synthesis was needed. For example, during 1920s in Germany, Wieland and Windaus rose to the challenge and unravelled the key structural motif of several steroids, leading them to propose a number of architectures, such as structure **II** for cholesterol. Unfortunately, their proposal had a number of inaccuracies in terms of core structure-mistakes that were revealed in 1932 when Bernal obtained the first X-ray structure of a steroid.



II

Cholesterol proposed structure (1927)

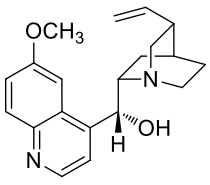


III

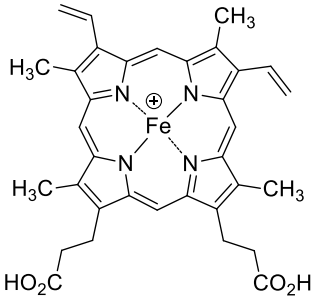
correct structure of cholesterol (1932)

Figure 1.2

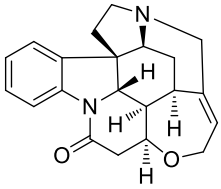
Remarkably, the near-exclusive use of chemical synthesis for structural elucidation did score a number of successes, such as the correct assignment for the natural products quinine, haemin prior to the start of World War II and strychnine in 1946.



quinine



haemin



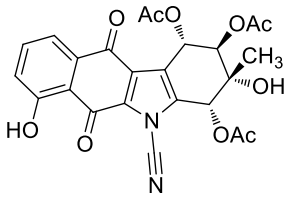
strychnine

Figure 1.3 Some natural products identified before 1960

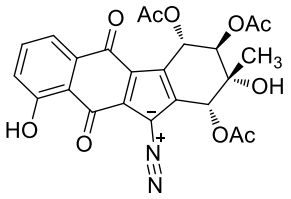
The development and evolution of more accurate, non-destructive methods, such as UV/vis spectroscopy (introduced in 1930s), IR spectroscopy (introduced in 1940s), mass spectroscopy (1950s), circular dichroism (CD) and, overall nuclear magnetic resonance (introduced in 1960s) changed drastically the approach to structure elucidation. Today, these methods have grown in both number and power to the extent that a researcher seeking to characterize a few milligrams of an unknown natural product would probably rely entirely on spectroscopic techniques. The benefits are clear: complex molecules can be tackled in far less time, even when the compounds are isolated in trace amounts. The number of errors reflects the fact that every method for structural assignment has its weakness, some of which cannot be

[11] Nicolau, K. C.; Snyder, S. A. *Angew. Chem. Int. Ed.* **2005**, *44*, 1012–1044.

resolved even if other tools for structural elucidation are also applied. For example, X-ray crystallography can lead to failure in the assignment of a structure, since it does not reveal the position of hydrogen atoms (those shown in any crystal structure have always been drawn). On the other hand, it is sometimes difficult to differentiate between NH groups and O atoms. X-Ray technique can also be inaccurate in the identification of functional groups devoid of hydrogen atoms. An example of this gap is the case of the longstanding incorrect structure proposal of kinamicyns, due to the assignment of a carbon atom instead of a nitrogen atom (a cyano rather that a diazo group, Figure 1.4).[12]



kinamicyn
Omura proposed structure 1973



kinamicyn
correct structure
Gould (1994)
Dmitrienko (1994)

Figure 1.4

NMR spectroscopy, too, only provides so much of the overall picture, especially in the case of molecules with insufficient hydrogen atoms, even though a number of powerful two-dimensional techniques, such as INEPT, HMBC, HMQC, and TOCSY can be applied. Moreover, the absolute configuration is not apparent in NMR spectra and it must be deduced, when no crystal is available, by comparison of the optical rotation of the isolated natural product with that of the synthesized compounds.[13]

Finally, despite the fact that modern strategies and methods in structural elucidation have experienced great improvements, errors can never be completely ruled out due to the deductive or indirect nature of these techniques. Since the comprehensive review "*Chasing Molecules That Were Never There: Misassigned Natural Products and the Role of Chemical Synthesis in Modern Structure Elucidation*" published by Nicolaou and Snyder in 2005,[11] many natural products have been described whose initial structural assignment turned out to be wrong. In many of these cases the ambiguity still awaits to be resolved. Therefore, a definitive structural proof of a natural product still necessitates its total synthesis.[13, 14]

[12] a. Ômura, S.; Nakagawa, A.; Yamada, H.; Hata, T.; Furusaki, A.; Watanabe, T. *Chem. Pharm. Bull.* **1973**, *21*, 931–940; b. Gould, S. J.; Tamayo, N.; Melville, C. R.; Cone, M. C. *J. Am. Chem. Soc.* **1994**, *116*, 2207–2208; c. Mithami, S.; Weeratunga, G.; Taylor, N. J.; Dmitrienko, G. I. *J. Am. Chem. Soc.* **1994**, *116*, 2209–2210.

[13] Maier, M. E. *Nat. Prod. Rep.* **2009**, *26*, 1105–1124.

[14] Li, J. W.-H.; Vederas, J. C. *Science* **2009**, *10*, 161–165.

1.2. Previous accomplishments of our research group

The main goal of our group during the last years is the search for new and general methodologies for the preparation of aza-heterocyclic derivatives in enantiopure form. The final aim is their application to the total synthesis of natural products. In early stages, we focused our interest on the development of procedures for the stereocontrolled preparation of polysubstituted piperidines, since more than 50% of the known alkaloids embody this heterocycle in their structure. To pursue this goal, chiral aminoalcohol-derived bicyclic lactams,[15] as precursors were employed; this approach fits in with the concept of "*enantiomeric scaffolding strategy*". This term, coined by L. S. Liebeskind,[16] defines a procedure in which a conceptually simple core molecule of high enantioputiry, bearing tactically versatile functionalization, is constructed; the residual functions enable the general elaboration of the core molecules in ways that allow the access to diverse families of molecules. At first, a variety of 1,2-aminoalcohols were analyzed as chiral inductors and we selected phenylglycinol due to its effectiveness, in terms of stereoselectivity and chemical yield, and commercial availability in both enantiomeric forms. On the other hand, (*R*)- and (*S*)-tryptophanol and (*S*)-(3,4-dimethoxyphenyl)alaninol have also been used in the context of the synthesis of some indole alkaloids and benzo[*a*]quinolizidines.

Oxazolopiperidone-based [17] bicyclic lactams are easily available in a single synthetic step by cyclocondensation of methyl 5-oxopentanoate and enantiopure aminoalcohols.[18] These enantiomeric scaffolds, identified as "first-generation oxazolopiperidone lactams" allow the regio- and stereocontrolled introduction of substituents at different positions of the piperidines ring, thanks to their tactical functionalization and conformational rigidity. The practical introduction of substituents in α position of the piperidine ring (C-6) was accomplished by α-amidoalkylation reactions,[19] or manipulation of the

[15] a. Romo, D.; Meyers, A. I. *Tetrahedron* **1991**, *47*, 9503–9569; b. Meyers, A. I.; Brengel, G. P. *Chem. Comm.* **1997**, 1–8; c. Groaning, M. D.; Meyers, A. I. *Tetrahedron*, **2000**, *56*, 9843–10100.

[16] Coombs, T. C.; Lee, M. D.; Wong, H.; Armstrong, M.; Cheng, B.; Chen, W.; Moretto, A. F.; Liebeskind, L. S. *J. Org. Chem.* **2008**, *73*, 882–888.

[17] a. Escolano, C.; Amat, M.; Bosch, J. *Chem. Eur. J.* **2006**, *12*, 8198–8207; b. Amat, M.; Pérez, M.; Bosch, J. *Synlett* **2011**, 143–160; c. Amat, M.; Llor, N.; Griera, R.; Pérez, M.; Bosch, J. *Nat. Prod. Comm.* **2011**, *6*, 515–526.

[18] For alternative procedures, see: a. Royer, J.; Husson, H. P. *Heterocycles* **1993**, 1493–1496; b. Terán, J. L.; Gnecco, D.; Galindo, A.; Juárez, J.; Bernès, S.; Enríquez, R. G. *Tetrahedron: Asymmetry* **2001**, *12*, 357–360; c. Airiau, E.; Spangenberg, T.; Girard, N.; Schoenfelder, A.; Salavdoru, J.; Taddei, M.; Mann, A. *Chem. Eur. J.* **2008**, *14*, 10938–10948; d. Tojino, M.; Otsuka, N.; Fukuyama, T.; Matsubara, H.; Ryu, I. *J. Am. Chem. Soc.* **2006**, *128*, 7712–7713.

[19] a. Amat, M.; Llor, N.; Bosch, J. *Tetrahedron Lett.* **1994**, *35*, 2223–2226; b. Amat, M.; Llor, N.; Hidalgo, J.; Hernández, A.; Bosch, J. *Tetrahedron Asymmetry* **1996**, *7*, 977–980; c. Amat, M.; Hidalgo, J.; Llor, N.; Bosch, J. *Tetrahedron Asymmetry*, **1998**, *9*, 2419–2422; d. Amat, M.; Llor, N.; Hidalgo, J.; Escolano, C. Bosch, J. *J. Org. Chem.* **2003**, *68*, 1919–1928; e. Amat. M.; Escolano, C.; Llor, N.; Huguet, M.; Pérez, M.; Bosch, J. *Tetrahedron Asymmetry* **2003**, *14*, 1679–1683.

carbonyl group. The stereoselective alkylation or dialkylation of the amide enolate [20] allows the introduction of substituents in β position. Finally, chiral unsaturated lactam derivatives permit the conjugated addition of organocuprates[21] and stabilized anions,[22] as well as Diels-Alder reaction,[23] with a high degree of stereoselectivity. A subsequent reductive removal of the chiral auxiliary, taking advantage of the benzylic character of the C-N bond provides access to enantiopure piperidines bearing a broad range of substitution patterns. In fact, in this processes, phenylglycinol acts as a chiral latent form of ammonia. Interestingly, both enantiomers of a target compound are accessible through the above methodology starting from (*R*)- or (*S*)-phenylglycinol.

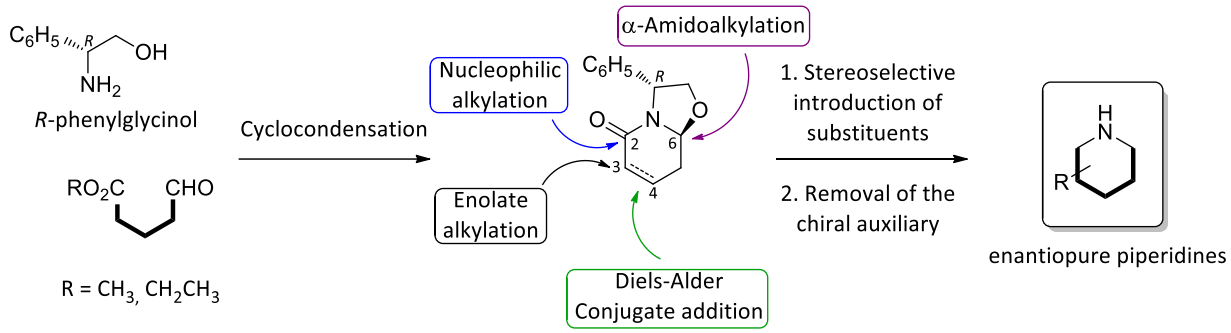


Figure 1.5 First-generation oxazolopiperidone lactams

Some enantiopure piperidines, indolizidine and quinolizidine alkaloids, as well as bioactive piperidine derivatives of relative complexity, synthesized in our laboratory following the general synthetic strategy, are depicted below.

[20] a. Amat, M.; Lozano, O.; Escolano, C.; Molins, E.; Bosch, J. *J. Org. Chem.* **2007**, *72*, 4431–4439; b. Amat, A.; Escolano, C.; Llor, N.; Lozano, O.; Gómez-Esqué, A.; Griera, R.; Bosch, J. *ARKIVOC* **2005**, *9*, 115–123.

[21] Amat, M.; Bosch, J.; Hidalgo, J.; Cantó, M.; Pérez, M.; Llor, N.; Molins, E.; Miravitlles, C.; Orozco, M.; Luque, F. J. *J. Org. Chem.* **2000**, *65*, 3074–3084.

[22] a. Amat, M.; Pérez, M.; Llor, N.; Bosch, J. *Org. Lett.* **2002**, *4*, 2787–2790; b. Amat, M.; Pérez, M.; Llor, N.; Martinelli, M.; Molins, E.; Bosch, J. *Chem. Comm.* **2004**, 1602–1603; c. Amat, M.; Pérez, M.; Llor, N.; Escolano, C.; Luque, F. J.; Molins, E.; Bosch, J. *J. Org. Chem.* **2004**, *69*, 8681–8693.

[23] Casamitjana, N.; Amat, M.; Llor, N.; Carreras, M.; Pujol, X.; Fernández, M. M.; López, V.; Molins. E.; Miravitlles, C.; Bosch, J. *Tetrahedron Asymmetry* **2003**, *14*, 2033–2039.

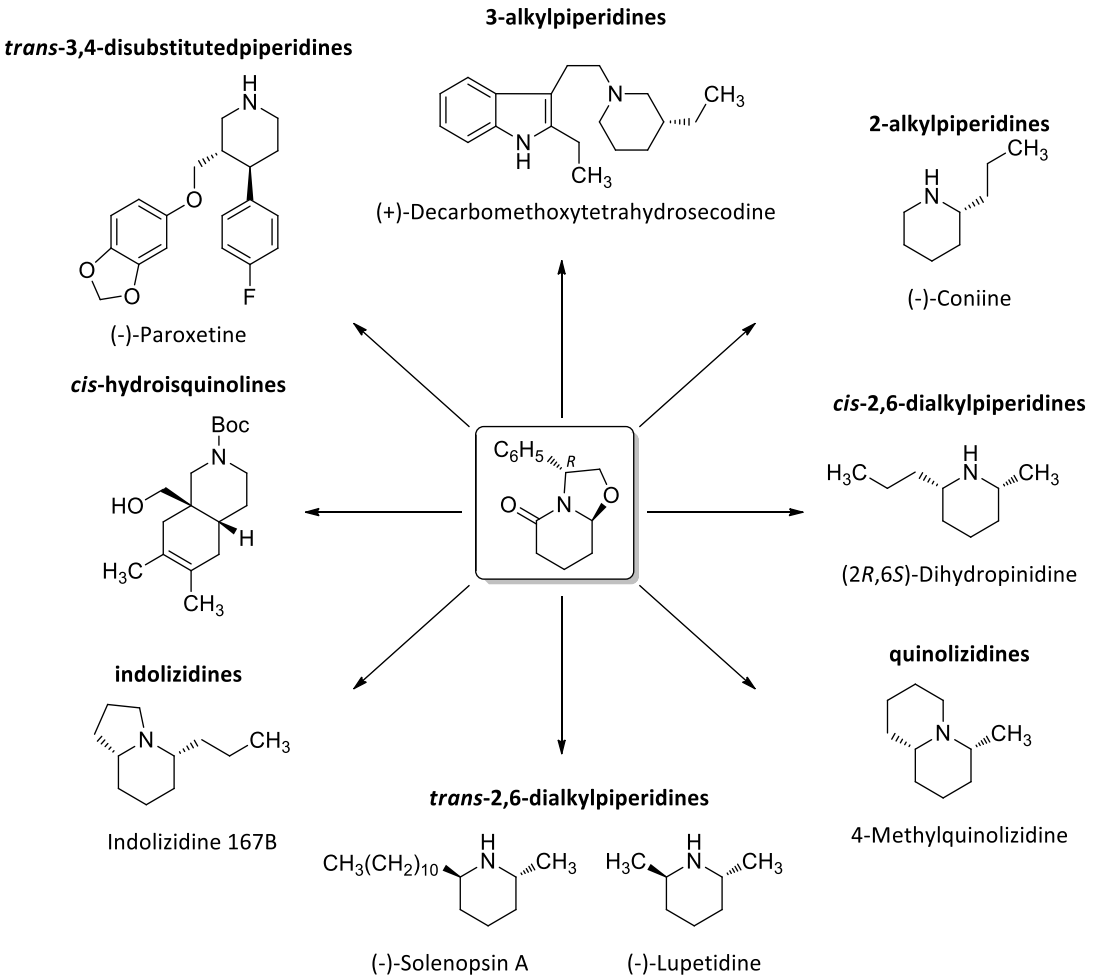


Figure 1.6 Enantiopure compounds from "First-generation oxazolopiperidone lactams"

Although these "first-generation oxazolopiperidone lactams" gave excellent results from a stereochemical point of view, access to enantiopure complex piperidines had two considerable drawbacks: 1) the step-by-step introduction of the substituents and 2) the unfeasible functionalization of piperidines C-5 position. Hence, a more straightforward procedure for the synthesis of enantiopure polysubstituted piperidines has been developed, involving the direct generation of chiral nonracemic oxazolopiperidone lactams that already incorporate carbon substituents at the β or γ position of the heterocyclic ring. In these cases, the preferred generation of one of the possible diastereoisomers of the corresponding bicyclic lactam during the cyclocondensation reaction, involves a dynamic kinetic resolution and/or the differentiation of the enantiotopic/diastereotopic acetate or propionate chains (Figure 1.7).[24]

[24] Amat, M.; Bassas, O.; Llor, N.; Cantó, M.; Pérez, M.; Molins, E.; Bosch, J. *Chem. Eur. J.* **2006**, *12*, 7872–7881.

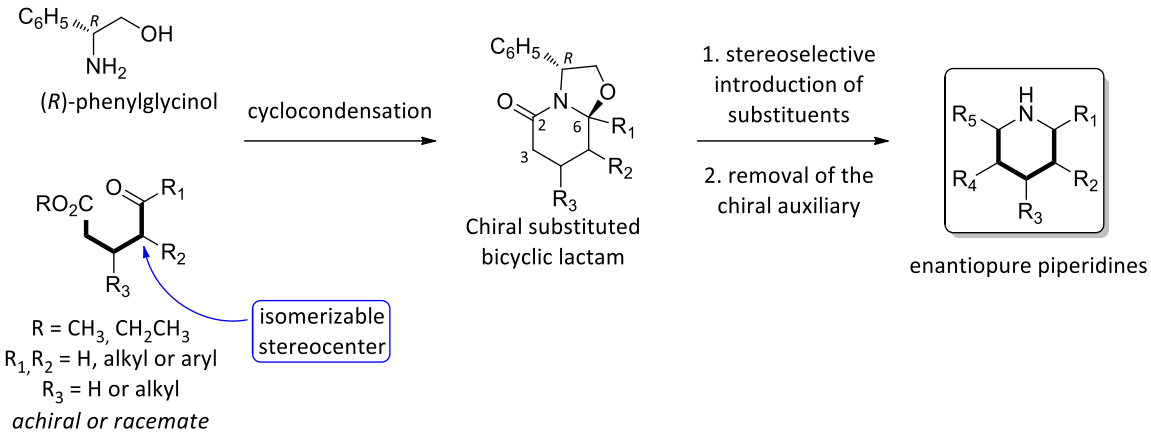


Figure 1.7 Second-generation oxazolopiperidone lactams

Starting from these refined scaffolds, classified as "second-generation oxazolopiperidone lactams", the scope of the methodology was significantly expanded with the synthesis of piperidine-containing structures of greater complexity than those obtained employing the first-generation lactams. The combination of the two strategies, that is the synthesis of mono- or dialkylated lactams by cyclocondensation reaction with subsequent introduction of substituents, by alkylation[25] or conjugate addition,[26] allowed the construction of a library of enantiopure piperidines and nitrogen-containing bicycles. Some of these compounds are displayed below.

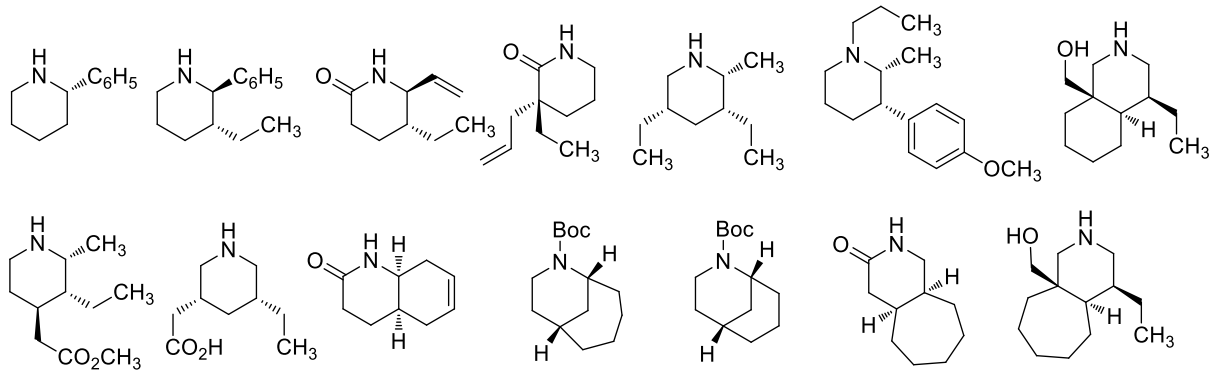


Figure 1.8 Enantiopure nitrogen-containing cycles

[25] a. Amat, M.; Escolano, C.; Lozano, O.; Llor, N.; Bosch, J. *Org. Lett*. **2003**, *5*, 3139–3142; b. Amat, M.; Escolano, C.; Lozano, O.; Gómez-Esqué, A.; Griera, R.; Molins, E.; Bosch, J. *J. Org. Chem.* **2006**, *71*, 3804–3815; c. Soteras, I.; Lozano, O.; Gómez-Esqué, A.; Escolano, C.; Orozco, M.; Amat, M.; Bosch, J.; Luque, F. J. *J. Am. Chem. Soc.* **2006**, *128*, 6581–6588.

[26] a. Amat, M.; Pérez, M.; Bosch, J.; Lago, E.; Molins, E. *Org. Lett.* **2001**, *3*, 611–614; b. Amat, M.; Llor, N.; Checa, B.; Pérez, M.; Bosch, J. *Tetrahedron Lett.* **2007**, *48*, 6722–6725; c. Amat, M.; Pérez, M.; Minaglia, A. T.; Peretto, B.; Bosch, J. *Tetrahedron* **2007**, *63*, 5839–5848; d. Amat, M.; Pérez, M.; Minaglia, A. T.; Bosch, J. *J. Org. Chem.* **2008**, *73*, 6920–6923; e. Amat, M.; Brunaccini, E.; Pérez, M.; Llor, N.; Bosch, J. *Org. Lett.* **2009**, *11*, 4370–4373; f. Amat, M.; Llor, N.; Checa, B.; Molins, E.; Bosch, J. *J. Org. Chem.* **2010**, *75*, 178–189; g. Amat, M.; Pérez, M.; Proto, S.; Gatti, T.; Bosch, J. *Chem. Eur. J.* **2010**, *16*, 9438–9441.

Our endeavors have subsequently focused on the application of this useful methodology in the area of targeted-oriented synthesis. Several alkaloids of increased complexity, belonging to a variety of structural types, were successfully elaborated involving the phenylglycinol-derived oxazolopiperidone lactams, with the ultimate aim of further demonstrating and validating the general synthetic utility of this enantiomeric scaffolding strategy. [27]

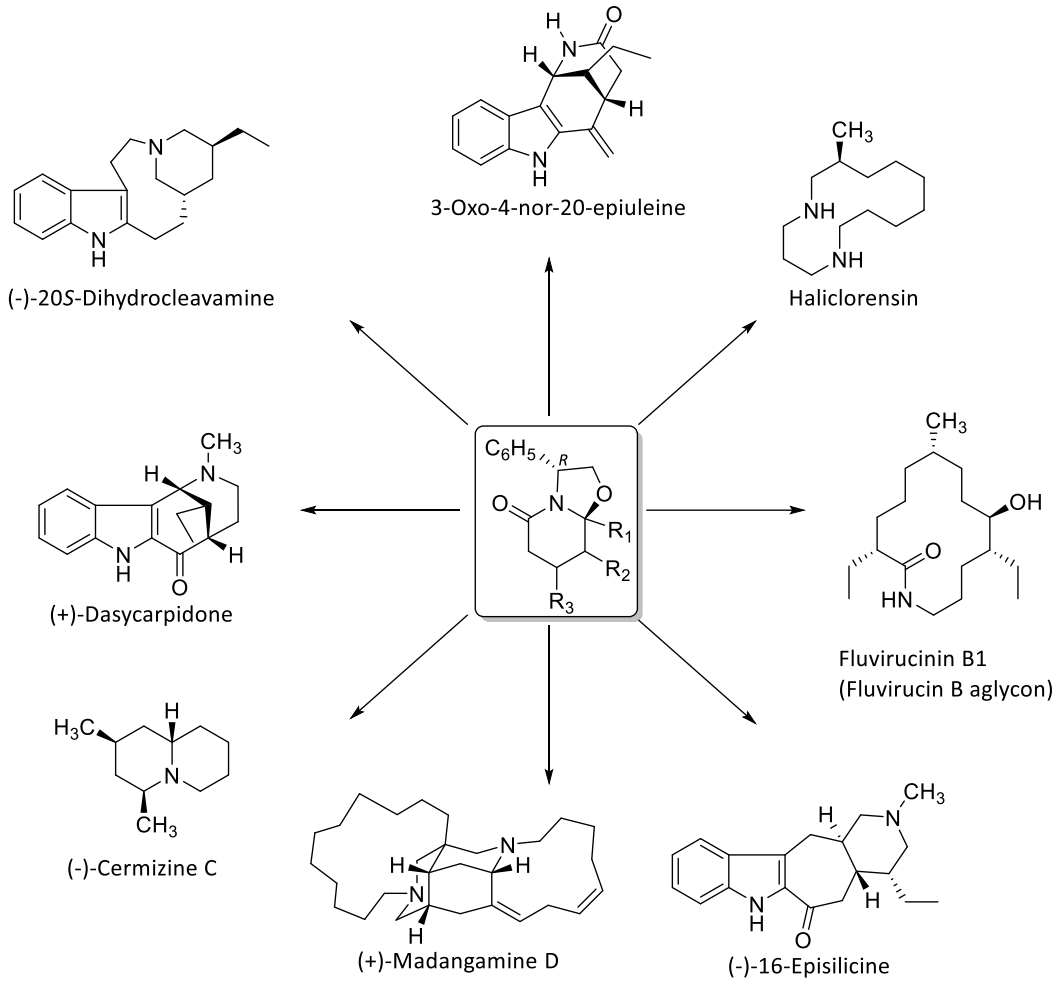


Figure 1.9 Representative compounds synthesized from phenylglycinol-derived oxazolopiperidone lactams

[27] a. Amat, M.; Griera, R.; Fabregat, R.; Molins, E.; Bosch, J. *Angew. Chem. Int. Ed.* **2008**, *47*, 3348–3351; b. Amat, M.; Griera, R.; Fabregat, R.; Bosch, J. *Tetrahedron: Asymmetry* **2008**, *19*, 1233–1236; c. Amat, M.; Fabregat, R.; Griera, R.; Bosch, J. *J. Org. Chem.* **2009**, *74*, 1794–1797; d. Amat, M.; Pinto, A.; Griera, R.; Bosch, J. *Chem. Comm.* **2013**, *49*, 11032–11034; e. Amat, M.; Guignard, G.; Llor, N.; Bosch, J. *J. Org. Chem.* **2014**, *79*, 2792–2802; f. Ballette, R.; Pérez, M.; Proto, S.; Amat, M.; Bosch, J. *Angew. Chem. Int. Ed.* **2014**, *53*, 6202–6205; g. Amat, M.; Pinto, A.; Griera, R.; Bosch, J. *Chem. Eur. J.* **2015**, *21*, 12804–12808.

On the other hand, (*S*)-tryptophanol and (*S*)-(3,4-dimethoxyphenyl)alaninol were tested as chiral inductors.[28] The functionalization already present in both α-positions of the piperidinic ring allows to carry out electrophilic substitution reactions on the aromatic ring, which lead to indolo[2,3-*a*]quinolizidine and benzo[*a*]quinolizidine derivatives. Remarkably, the 2-arylethyl moiety of these chiral inductors remains in the structure of final compounds.

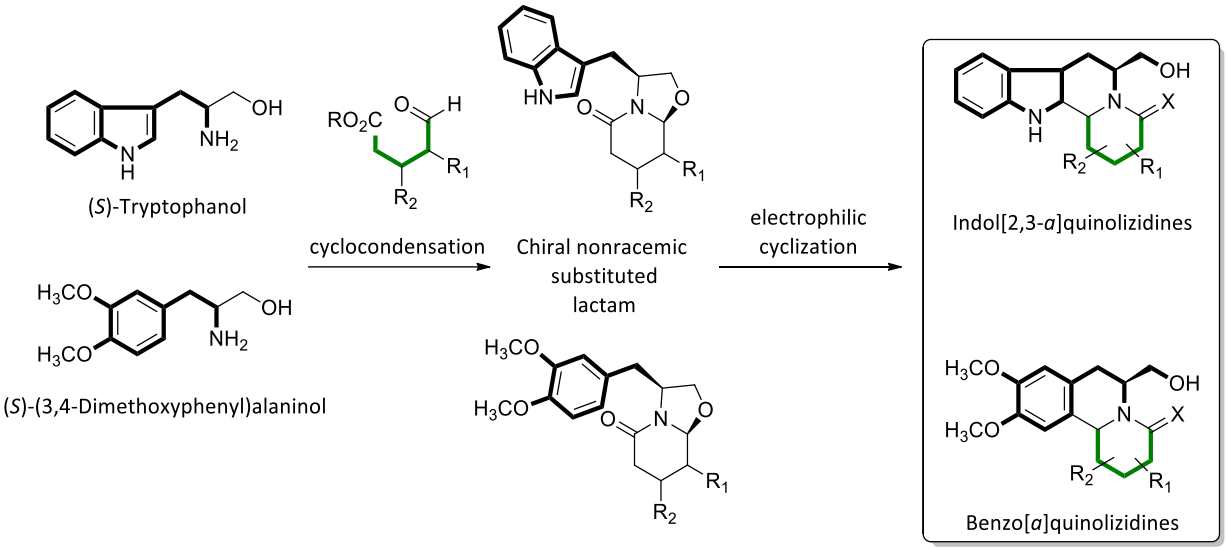


Figure 1.10. Synthesis of quinolizidine derivatives

Stereo- and regio-controlled synthesis of indol[2,3-*a*]quinolizidines can be carried out by using different reaction conditions from the same tryptophanol-derived lactam, thanks to the different reactivity of the two α positions of the piperidine ring: *route 1* intramolecular diastereodivergent α-amidoalkylation reaction (control of the configuration at C-12); *route 2* modified Bischler-Napieralsky type reaction, which enables the cyclization under neutral conditions on the carbonyl lactam. Therefore, starting from the same C-8 substituted lactam, we can synthesize regioisomeric indoloquinolizidines (Figure 1.11).

[28] a. Bassas, O.; Llor, N.; Santos, M. M. M.; Griera, R.; Molins, E.; Amat, M.; Bosch, J. *Org. Lett.* **2005**, *7*, 2817–2820; b. Amat, M.; Santos, M. M. M.; Bassas, O.; Llor, N.; Escolano, C.; Gómez-Esqué, A.; Molins, E.; Allin, S. M.; McKee, V.; Bosch, J. *J. Org. Chem.* **2007**, *72*, 5193–5201; c. Amat, M.; Santos, M. M. M.; Gómes, A. M.; Kokic, D.; Molins, E.; Bosch, J. *Org. Lett.* **2007**, *9*, 2907–2910; d. Amat, M.; Gómez-Esqué, A.; Escolano, C.; Santos, M. M. M.; Molins, E.; Bosch, J. *J. Org. Chem.* **2009**, *74*, 1205–1211.

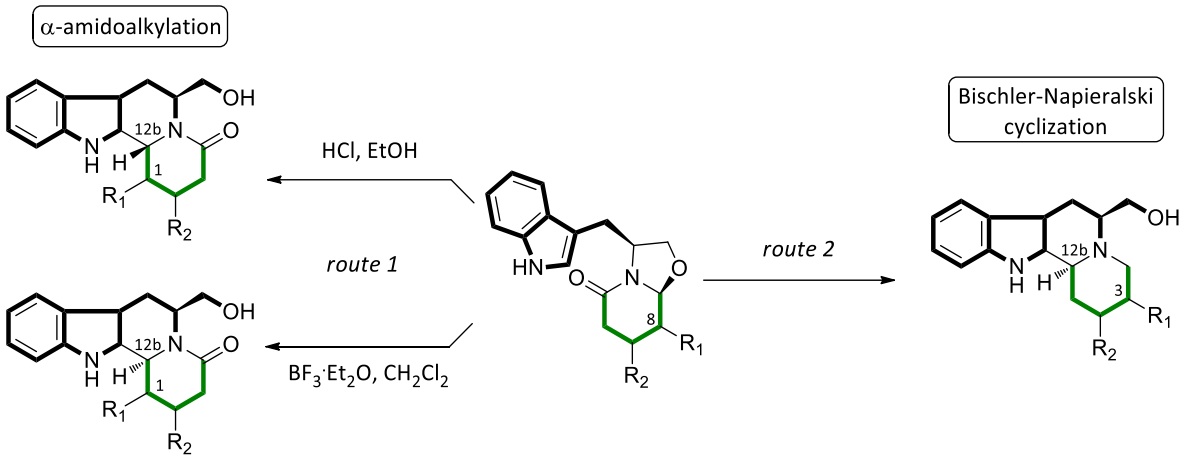


Figure 1.11 Electrophilic cyclization

This methodology has allowed to achieve the synthesis of compound **V**, a known precursor of (+)-dihydrocorynantheine[29] and (–)-dihydrocorynantheol (Figure 1.12).[30]

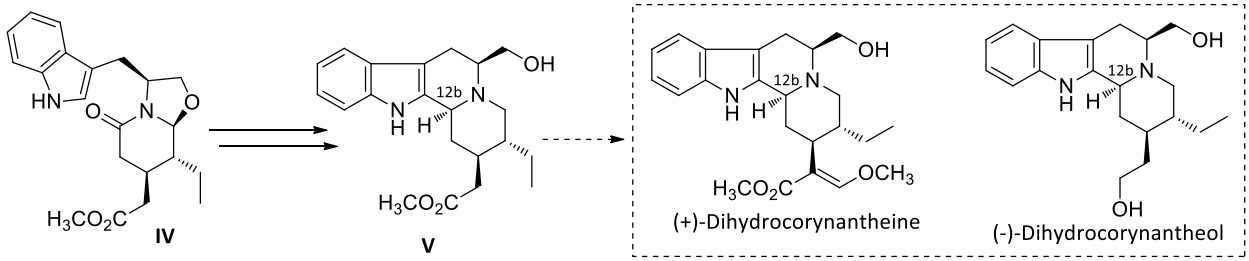


Figure 1.12. Formal synthesis of dihydrocorynantheine and (–)-dihydrocorynantheol

In order to gain access to the pentacyclic core of the yohimbine-type alkaloids, our group studied the stereoselectivity of base-catalyzed double Michael additions of α,β-unsaturated β-ketoesters (Nazarov-type reagents) to unsaturated indoloquinolizidine lactams **VI**. [31] The facial selectivity of the double Michael additions can be controlled by using either cesium carbonate or DBU and by appropriate selection of the indole-protecting group. This methodology has been used for the synthesis of the putative structure of the alkaloid nitraraine, for a diastereomer of the epiallo series and for the synthesis of 17a-carbaakuamigine.[32]

[29] a. Tietze, L. F.; Zhou, Y. *Angew. Chem. Int. Ed.* **1999**, *38*, 2045–2047; b. Weisbash, J. A.; Kirkpatrick, J. L.; Williams, K. R.; Anderson, E. L.; Yim, N. C.; Douglas, B. *Tetrahedron Lett.* **1965**, *6*, 3457–3463; c. Van Tamelen, E. E.; Hester, J. B. *J. Am. Chem. Soc.* **1969**, *91*, 7342–7349.

[30] a. Brown, R. T.; Jones, M. F.; Wingfield, M. *J. Chem. Soc., Chem. Comm.* **1984**, 847–848; b. Diez, A.; Vila, C.; Sinibaldi, M.-E.; Troin, Y.; Rubiralta, M. *Tetrahedron Lett.* **1993**, *34*, 733–736.

[31] Amat, M.; Arioli, F.; Pérez, M.; Molins, E.; Bosch, J. *Org. Lett.* **2013**, *15*, 2470–2473.

[32] Arioli, F.; Pérez, M.; Are, C.; Estarellas, C.; Luques, J. L.; Bosch, J.; Amat, M.; *Chem. Eur. J.* **2015**, *21*, 13382–13389.

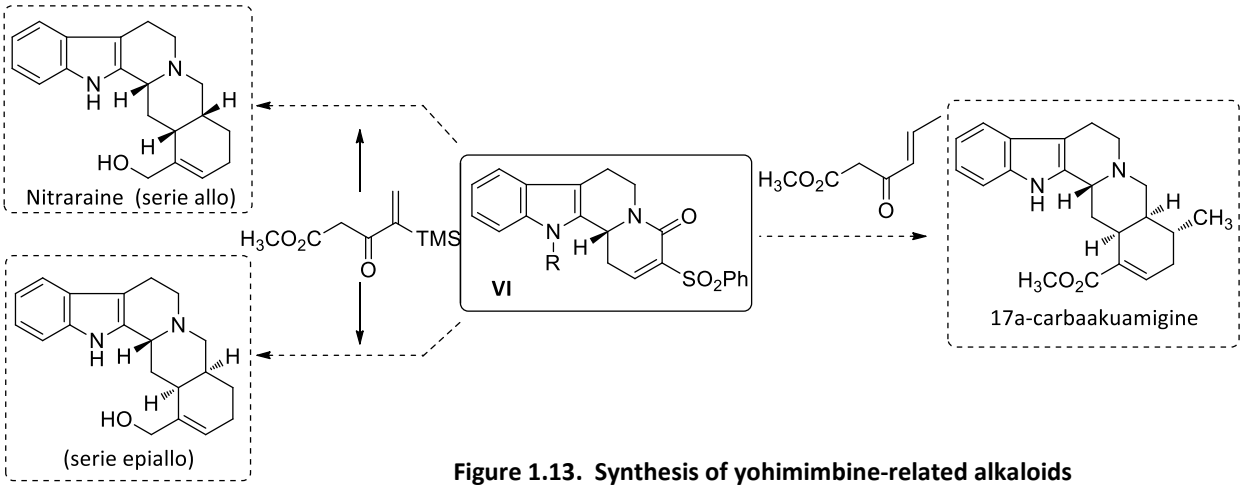


Figure 1.13. Synthesis of yohimimbine-related alkaloids

Furthermore, spiro[pyrrolidine-3,3'-indoline] and spiro[pyrrolidine-3,3'-oxindole] derivatives can be obtained from (*S*)-tryptophanol derived lactams. In particular, indole deactivated derivatives (Figure 1.14, Z = Tos or SO_2Ph), in the presence of titanium tetrachloride and triethylsilane, led to the corresponding spiroindolines. On the other hand, starting from 2-bromoindole derivatives the spirocyclization reaction, in the presence of TFA, conducted to the corresponding spirooxindoles.[33] In these processes, two new stereogenic centers, one of them quaternary, have been generated in high stereoselectivity.

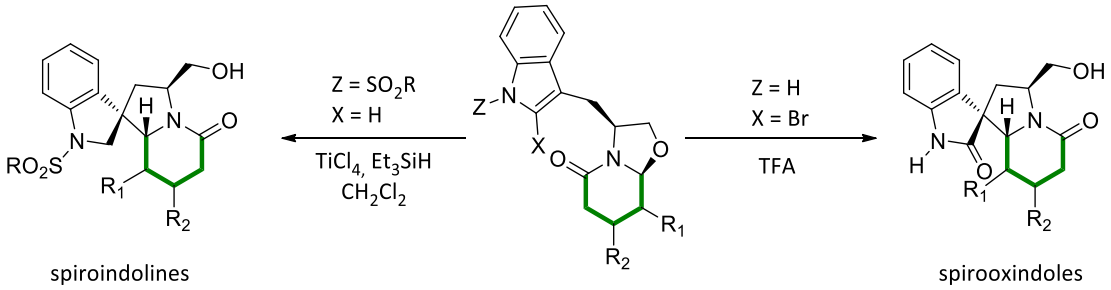


Figure 1.14 Synthesis of spiroindole derivatives

The synthetic utility of these spiroxindole derivatives demonstrated with the enantioselective formal synthesis of *ent*-isorhynchophylline and *ent*-rhynchophylline.[34]

[33] Amat, M.; Ramos, C.; Pérez, M.; Molins, E.; Florindo, P.; Santos, M. M. M.; Bosch, J. *Chem. Comm.* **2013**, *49*, 1954–1956.

[34] Ban, Y.; Seto, M.; Oishi, T. *Chem. Pharm. Bull.* **1975**, *23*, 2605–2613.

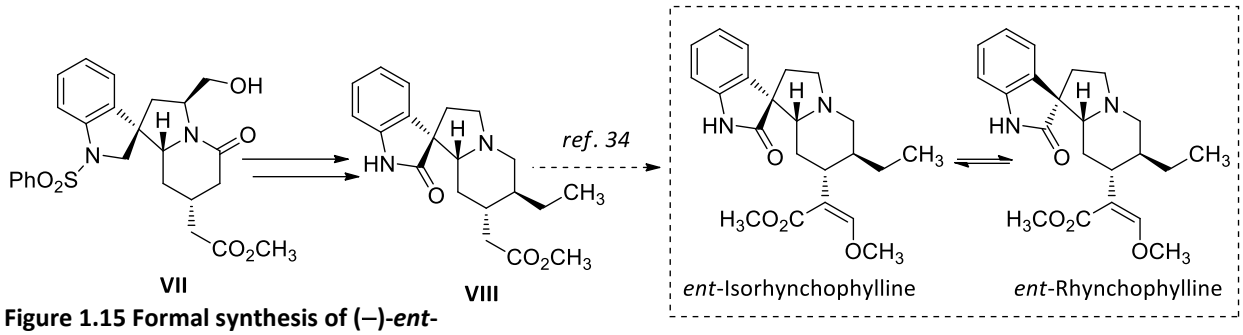


Figure 1.15 Formal synthesis of (–)-*ent*-isorhynchophylline

More recently, stereoselective cyclocondensation reactions from 2-substituted 6-oxo-1-cyclohexanepropionate derivatives and (*R*)-phenylglycinol leading to chiral unsaturated tricyclic lactams have been carried out.[35] Moreover, the subsequent catalytic hydrogenation of the alkene takes place in high stereoselectivity. Thus, C-8 substituted tricyclic lactams with three stereogenic centers of well-defined configuration can be generated in only two steps from achiral keto-esters and enantiopure aminoalcohols.

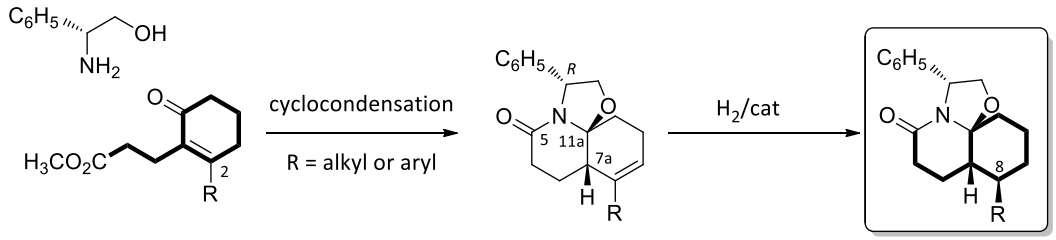


Figure 1.16. Chiral unsaturated tricyclic lactams C-8 substituted

Similarly, starting from analogous cyclohexenone derivatives substituted at the C-3 position, a variety of C-9 substituted chiral unsaturated tricyclic lactams have been prepared.[36]

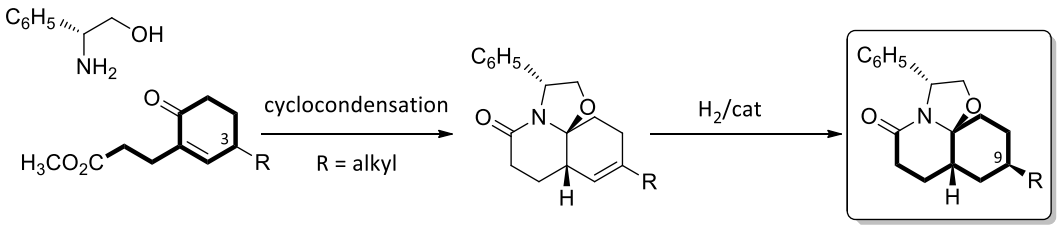


Figure 1.17. Chiral unsaturated tricyclic lactams C-9 substituted

[35] a. Fabregat, R. PhD Thesis, Barcelona **2009**; b. Amat, M.; Fabregat, R.; Griera, R.; Bosch, J. *J. Org. Chem.* **2009**, *74*, 1794–1797; c. Amat, M.; Griera, R.; Fabregat, R.; Molins, E.; Bosch, J. *Angew. Chem. Int. Ed.* **2008**, *47*, 3348–3351; d. Mercedes, A.; Fabregat, R.; Griera, R.; Florindo, P.; Molins, E.; Bosch, J. *J. Org. Chem.* **2010**, *75*, 3797–3805.

[36] Mercedes, A.; Navío, L.; Llor, N.; Molins, E.; Bosch, J. *Org. Lett.* **2012**, *14*, 210–213.

These chiral tricyclic lactams constitute excellent enantiomeric scaffolds for the synthesis of enantiopure decahydroquinoline derivatives as well as natural products bearing this structural unit. The synthetic value of this methodology was demonstrated with the synthesis of the decahydroquinoline alkaloid pumiliotoxin C[27a,d,g] and some members of the marine alkaloids lepadins.

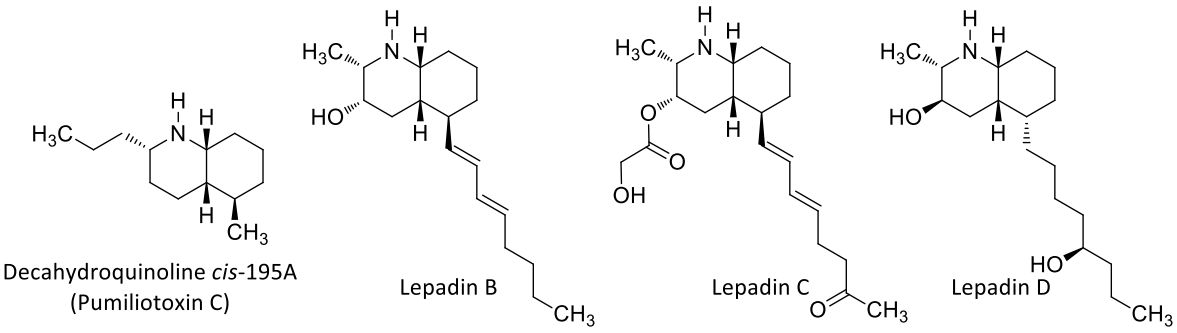


Figure 1.18. Decahydroquinoline alkaloids from tricyclic lactams

On the other hand, in previous work, the stereoselectivity of cyclocondensation reactions of a mixture of diastereoisomers of 4-substituted cyclohexanones having propionate chains at the 2 and 6 positions with (*R*)-phenylglycinol was explored.[37] In this reaction, a mixture of only two of the sixteen diastereoisomers that can be formed was observed, in a diastereomeric ratio of about 3:1. Thus, four stereogenic centers of well-defined configuration have been formed starting from mixtures of diastereomeric cyclohexanones. These lactams were converted into enantiopure 6-substituted *cis*-decahydroquinoline-8-propanols.

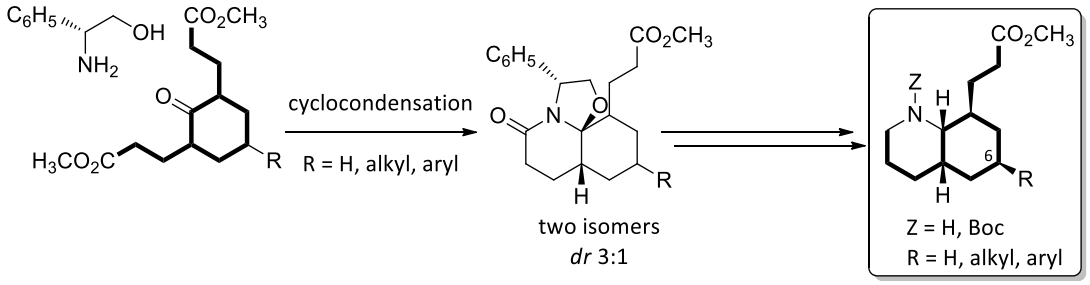


Figure 1.19. Enantiopure 6,8-disubstituted *cis*-decahydroquinolines from tricyclic lactams

[37] a. Laura Navío PhD thesis, Barcelona 2011; b. Amat, M.; Ghirardi, E.; Navío, L.; Griera, R.; Llor, N.; Molins, E.; Bosch, J. *Chem. Eur. J.* **2013**, *19*, 16044–16049.

1.3. Objectives of the Thesis

The main goal of the Thesis is to explore new cyclocondensation reactions of cycloalkanone derivatives, having ester chains, and enantiopure aminoalcohols, leading to chiral tricyclic lactams, in order to expand the potential of the methodology for the synthesis of functionalized optically active azabicycles of interest in natural product synthesis.

The specific goals of the work are:

a) The good results observed in the use of chiral unsaturated lactams as enantiomeric scaffolds for the synthesis of natural products containing *cis*-decahydroquinolines (see Figures 1.17 and 1.18), prompted us to undertake new cyclocondensation reactions of (*R*)-phenylglycinol and cyclopentenones (m = 1) or cyclohexenones (m = 2) bearing acetate (n = 1) or propionate chains (n = 2) at the 2-position. These reactions would lead to unsaturated tricyclic lactams with rings of different size. The final goal of this part of the work is to establish a new and efficient procedure for the synthesis of enantiopure octahydro-1*H*-cyclopenatl[*b*]pyridines (**a**), octahydrocyclopenta[*b*]pyrroles (**b**) and octahydro-1*H*-indoles (**d**).

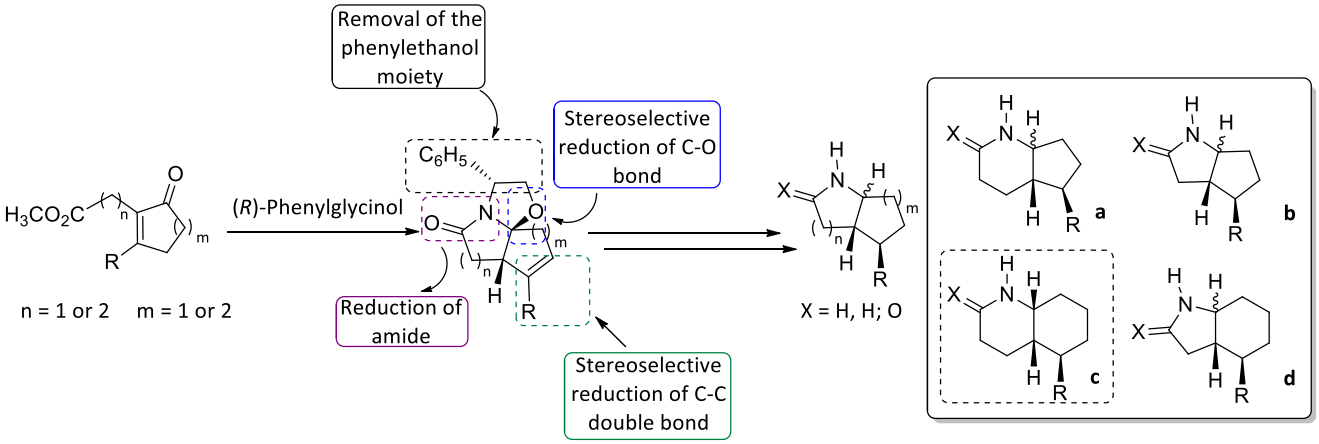


Figure 1.20

b) Phenylglycinol has demonstrated to be an excellent chiral inductor in most of the cyclocondensation reactions carried out using a great variety of oxo-ester derivatives. It is commercially available in both enantiomeric forms and the benzylic nature of the C-N bond allows the removal of the phenylethanol moiety of phenylglycinol under mild conditions at an appropriate stage of the synthesis. However, the moderate *d.r*. observed in the cyclocondensation of 4-substituted cyclohexanones having propionate chains at the 2 and 6 positions with (*R*)-phenylglycinol (see Figure 1.19) stimulated us in this work to evaluate other enantiopure amino-alcohols as chiral inductors in order to improve the efficiency of the process. With this goal in mind, we selected *cis*-aminoindanol which shares with phenylglycinol some

features (it is also commercially available in both enantiomeric forms and the nitrogen has a benzylic nature) but it is conformationally more rigid.

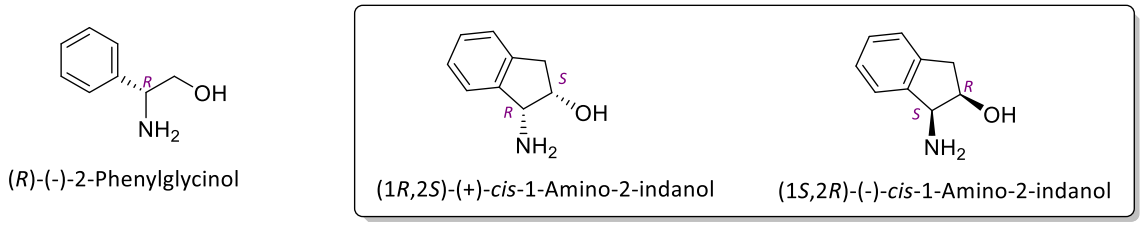


Figure 1.21

c) Inspired by the results observed in the cyclocondensation of cyclohexanones having propionate chains at the 2 and 6 positions with (*R*)-phenylglycinol (see Figure 1.19), we decided to explore new cyclocondensation reactions from 6-substituted cyclohexanones having a propionate (n = 2) or an acetate (n = 1) chain at C-2. In this way, a variety of C–11 and C–10 substituted tricyclic lactams (R = alkyl or aryl) could be stereoselectively obtained. The influence of the nature of the substituents and the use of propionate or acetate derivatives on the stereoselectivity of the cyclocondensation reactions will be analyzed. The final goal of this work is to establish an efficient procedure for the synthesis of enantiopure C-8 substituted decahydroquinolines and C-7 substituted octahydroindoles (Figure 1.22).

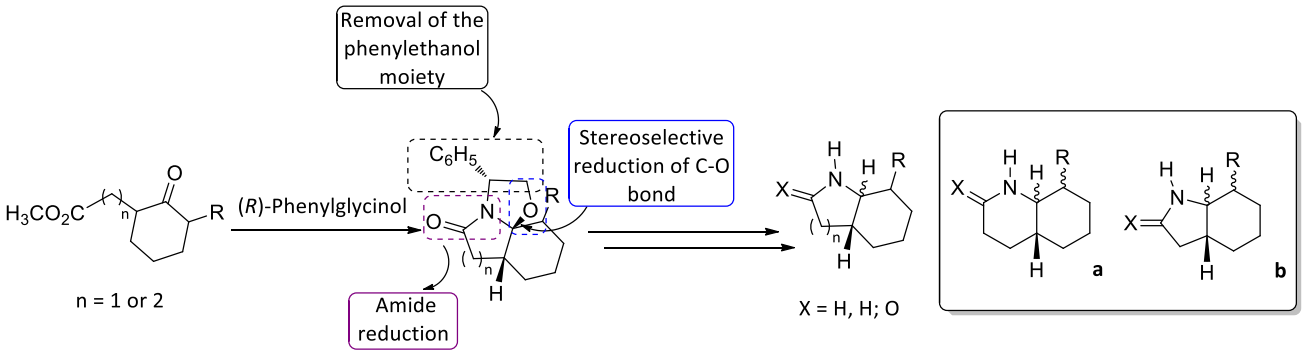


Figure 1.22

The study will allow us to evaluate the scope and limitations of our methodology for the enantioselective synthesis of azabicycles. In the event of obtaining good chemical and stereochemical results, a small library of decahydroquinolines, octahydroindoles, octahydro-1*H*-cyclopenta[*b*]pyridines and octahydrocyclopenta[*b*]pyrroles will be prepared.

CHAPTER 2. CYCLOCONDENSATION REACTIONS OF (*R*)-PHENYLGLYCINOL AND UNSATURATED CYCLIC KETOESTERS

2.1. Enantioselective synthesis of azabicycles from unsaturated lactams: previous work

In recent work,[35, 36] our group has described the stereoselective synthesis of tricyclic lactams, derived from (*R*)-phenylglycinol, as chiral scaffolds for the preparation of enantiopure C-5 and C-6 substituted *cis*-decahydroquinolines.[27a,b,c,d,37] The key steps of the overall process are i) a stereoselective cyclocondensation of (*R*)-phenylglycinol and cyclohexenonepropionate derivatives, substituted at C-2 or C-3, ii) the stereoselective reduction of the double bond on the resulting tricyclic lactam, taking advantage of the conformational rigidity of the tricyclic system, and iii) the removal of the phenylethanol moiety of the chiral inductor (Figure 2.1).

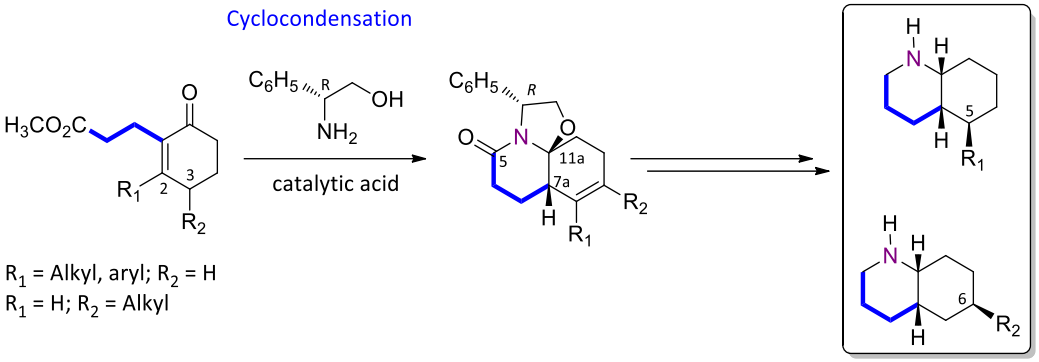


Figure 2.1 Cyclocondensation reaction of (*R*)-phenylglycinol and cyclohexenone derivatives

Under the reported conditions, achiral *δ*-oxo ester **I** led to the corresponding tricyclic *cis*-hydroquinoline lactam **IIa**, in which two stereocenters of well-defined absolute configuration have been formed, in a single step and the migration of the carbon-carbon double bond has occurred. Minor amounts (approximately 4:1) of diastereoisomer **IIb** at hydroquinoline ring fusion were also detected. This procedure, finally, allowed the construction of a library of tricyclic lactams (Figure 2.2). The size as well as the nature of the substituent does not affect the efficiency of the reaction, in terms of yield and stereoselectivity.

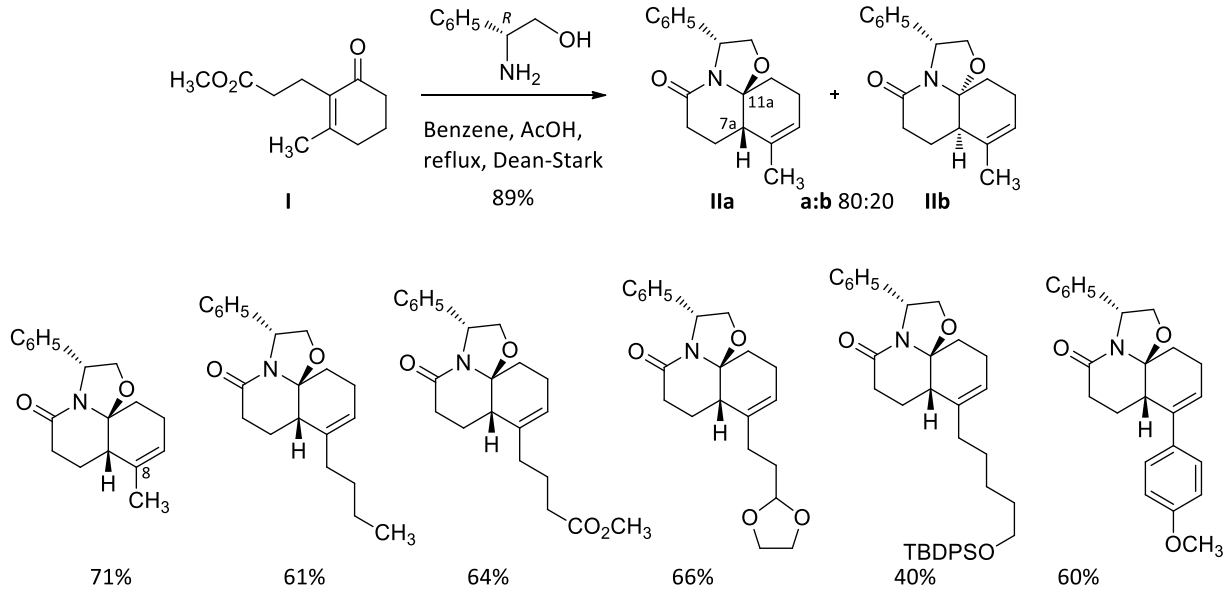


Figure 2.2

The stereoselective formation of these lactams involves the initial generation of en-imine **A**, which is in equilibrium *via* dienamine **B** with two diastereoisomeric imines **C** and four diastereoisomeric oxazolidines **D** (Figure 2.3).

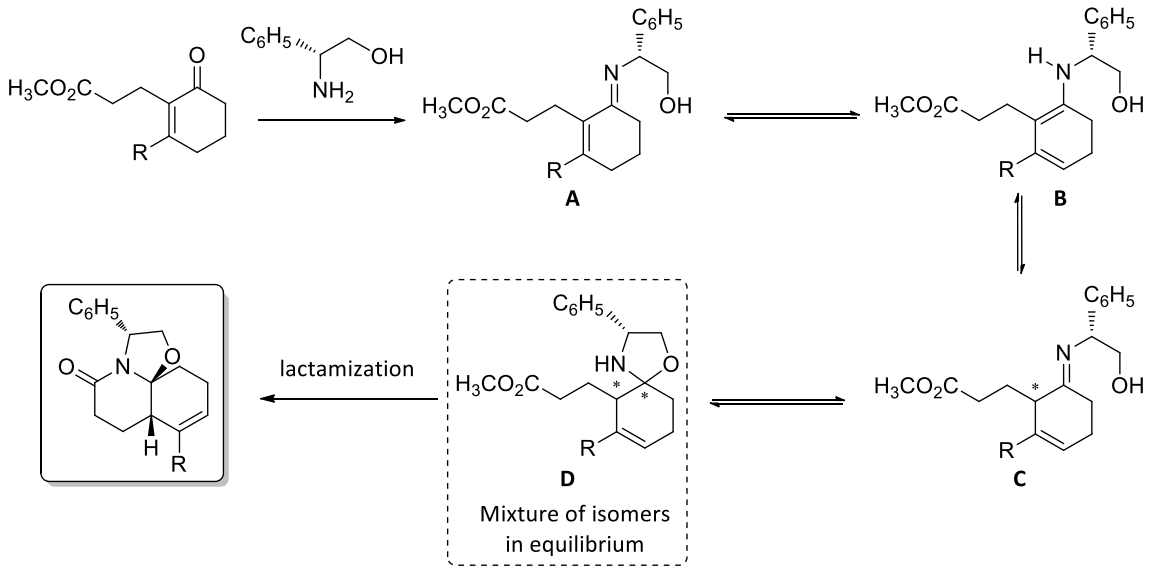


Figure 2.3 Proposed mechanism

The final irreversible lactamization occurs more rapidly from oxazolidine **D1** through a chairlike six-membered transition state in which the propionate chain avoids repulsive interaction with the substituent

at the carbocyclic ring ($A^{1,2}$ strain) and the C_6H_5 group. It should be noted that no lactams with *trans* ring fusion were detected by any chance. [38]

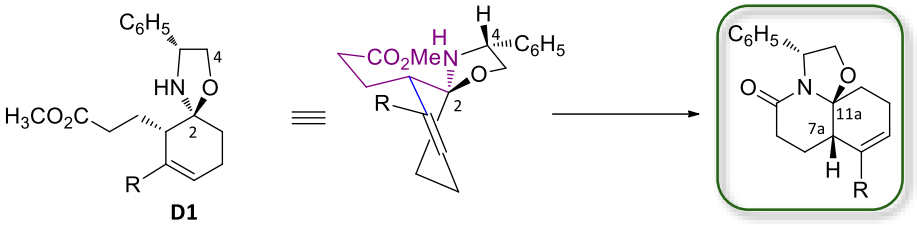
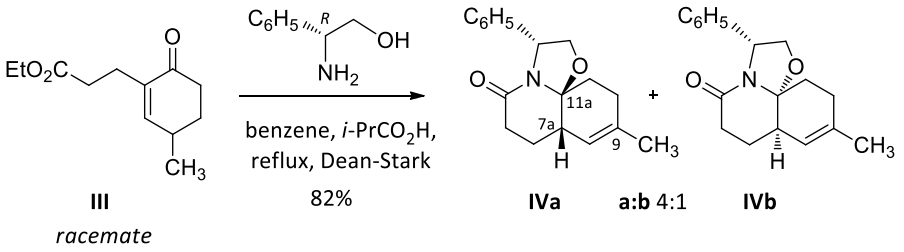


Figure 2.4 Lactamization from D1

Similarly, the cyclocondensation reaction of racemic cyclohexenone **III** and (*R*)-phenylglycinol led to lactams **IVa** and **IVb**, in a d.r. 4:1, with a substituent at C-9 and in which the migration of the carbon-carbon double bond has occurred.



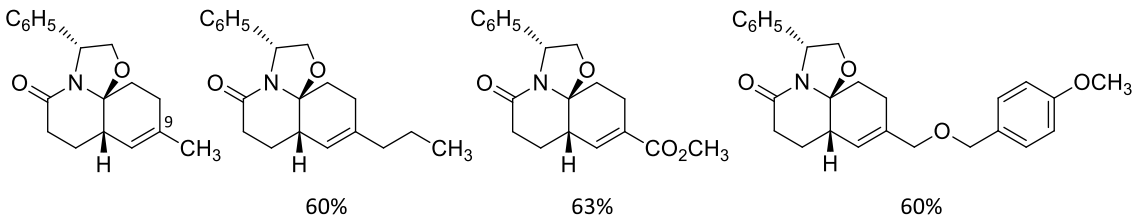


Figure 2.5 Cyclocondensation reaction starting from III

Catalytic hydrogenation of carbon-carbon double bond in lactams with substituent at C-8 gave the respective decahydroquinolines, in nearly quantitative yield. The reaction took place with high facial selectivity, with an uptake of hydrogen by the most accessible α-face. X-ray unambiguously of the C-8 methyl derivative unambiguously confirmed the absolute configuration. Reaction with alane of the resulting lactams brought about the opening of the oxazolidine ring, with retention of the configuration at C-8a and simultaneous reduction of lactam and ester carbonyl, when applicable. [39] Final hydrogenation led to enantiopure *cis*-decahydroquinoline derivatives (Figure 2.6).

[38] For the stereochemical outcome of related cyclocondensation reactions from γ-substituted δ-keto ester, see: a. Chapter 1 of the present Thesis; b. Amat, M.; Cantó M.; Llor, N..; Escolano, C.; Molins, E.; Bosch, J. *J. Org. Chem.* **2002**, *67*, 5343–5351; c. Amat, M.; Bassas, O.; Llor, N.; Cantó, M.; Perez, M.; Molins, E.; Bosch, J. *Chem.-Eur. J.* **2006**, *12*, 7872–7881.

[39] Fréville S.; Célérier, J. P.; Thuny, V. M.; Lhommet, G. *Tetrahedron Asymmetry* **1995**, *6*, 2651–2654.

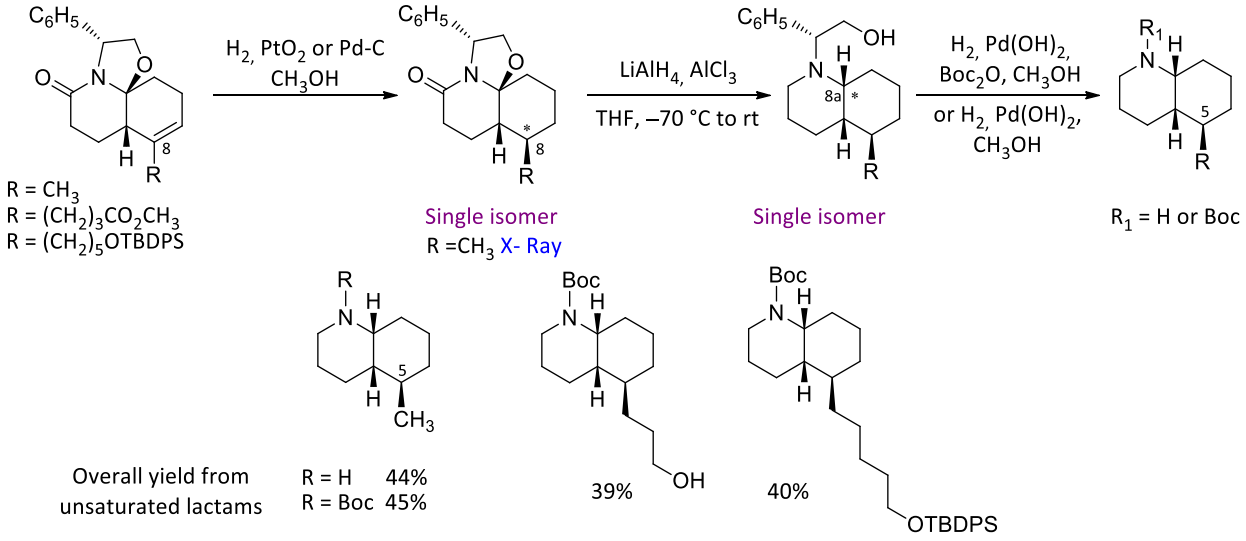


Figure 2.6 Synthesis of enantiopure C-5 alkyl *cis*-decahydroquinolines

In the same way, unsaturated lactams with a substituent at C-9, were converted into the corresponding *cis*-decahydroquinolines, with the generation of a new stereogenic center. The reduction of carbon-carbon double bond in this series is a little less stereoselective than in the previous work.

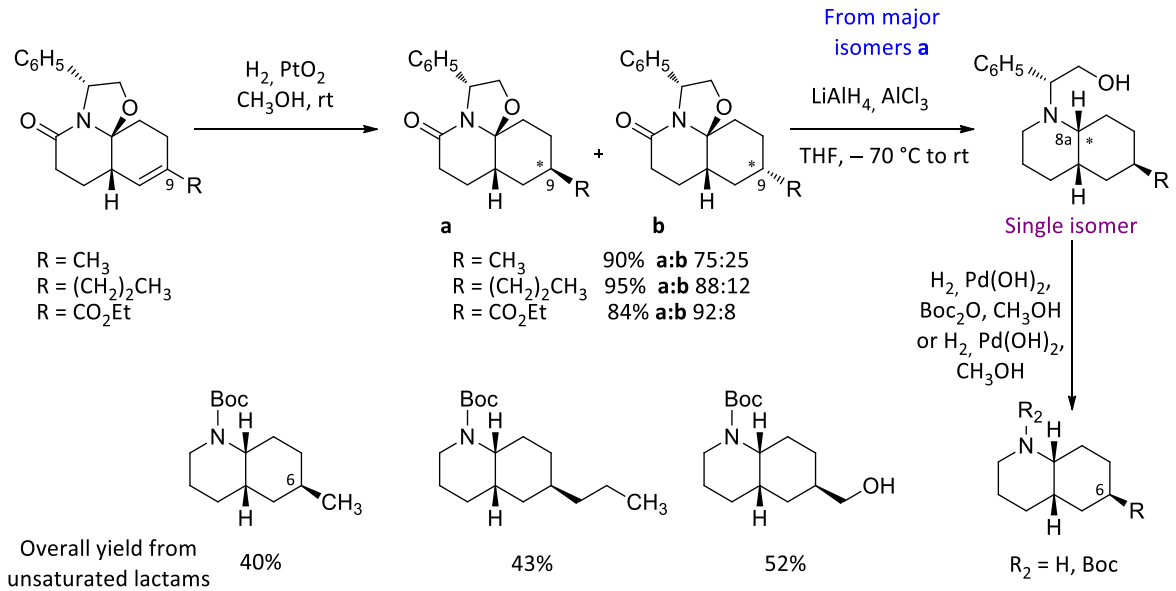


Figure 2.7 Synthesis of enantiopure C-6 alkyl *cis*-decahydroquinolines

2.1.1. Synthesis of active natural products

The usefulness of the methodology was demonstrated with the synthesis of active natural products which present a *cis*-decahydroquinoline core. In particular, manipulation of lactam carbonyl in **V**, whose thioamide was subjected to Eschenmoser sulfide contraction,[40] gave β-enamine ester **VI**. Subsequent transformations of the central core and of the acetate chain led to the isolation of amphibian alkaloid *cis*-195A (pumiliotoxin C), in which C-2 and C-5 are in relative *trans* disposition.[27a,35a]

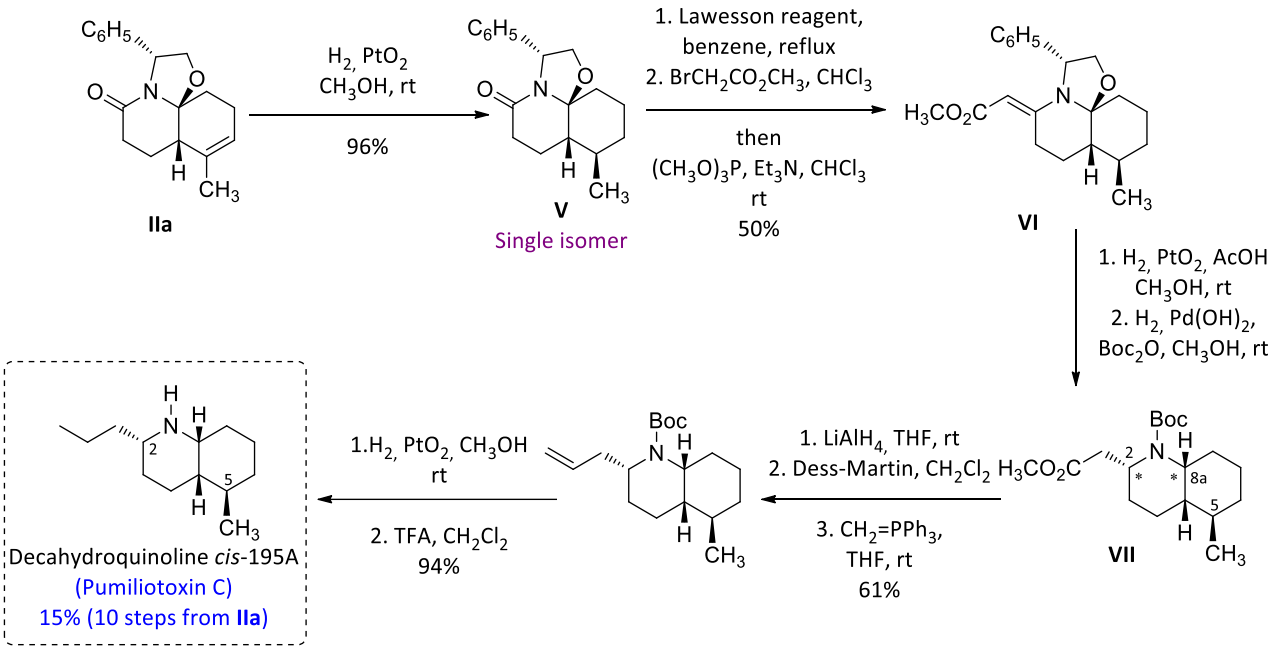


Figure 2.8 Synthesis of pumiliotoxin C

When unsaturated lactam **IIa** was subjected to Eschenmoser sulfide contraction conditions and the catalytic hydrogenation was performed starting from **VIII**, a dramatic change in the stereochemical outcome occurred. The resulting amine was identified as *ent*-2-*epi*-**VII**, with 2,8a-*trans*, 4a,5-*trans* and 4a,8a-*cis* relashionship.[35d] This result can be rationalized by considering that the hydrogenation of the double bond occurred with differing facial selectivity with respect to **IIa** and that the absolute configuration of the stereocenter generated at this step (C-5) determined the stereochemistry of the configurationally labile C-4a. In only five more steps, the synthesis of *ent*-2-*epi*-pumiliotoxin C was achieved.

[40] Shiozaki, K. In *Comprensive Organic Synthesis* **1991**, *2*, 865–872.

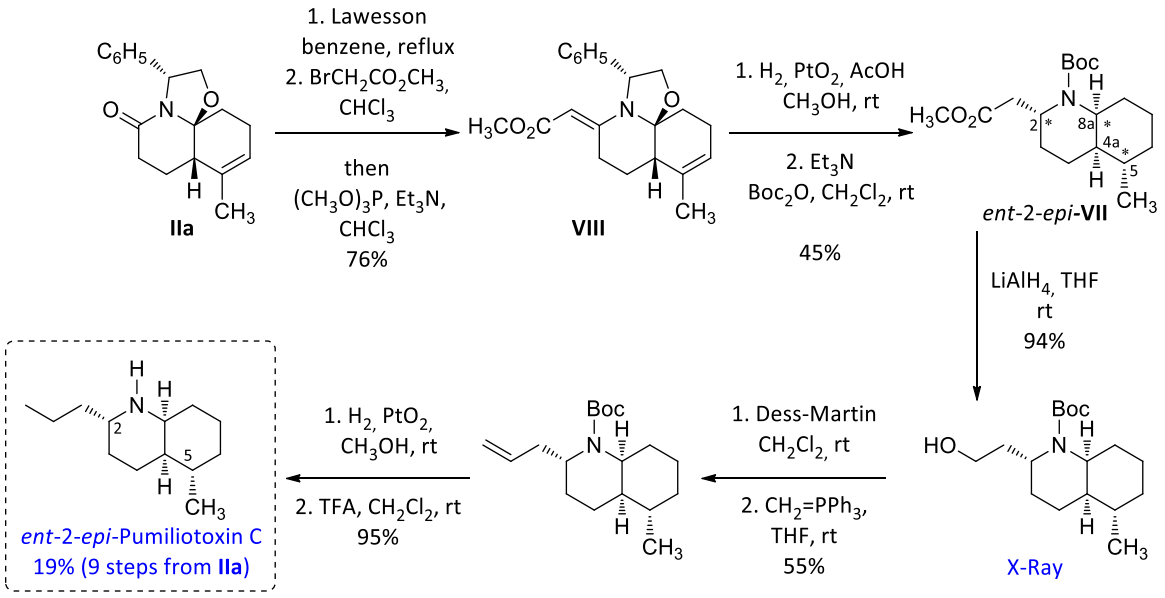


Figure 2.9 Synthesis of *ent*-2-*epi*-pumiliotoxin C

Alternatively, new enantiopure C-2 and C-3 substituted *cis*-decahydroquinolines could be prepared starting from C-8 substituted tricyclic lactams. Removal of the phenylethanol moiety of the chiral inductor in **IX** afforded the *N*-Boc protected *cis*-decahydroquinolinone **X**. Taking advantage of the carbonyl lactam of **X**, the stereoselective introduction of a methyl in C-2 and a hydroxyl group in C-3 should be possible leading to precursors for the synthesis of lepadins.[27d]

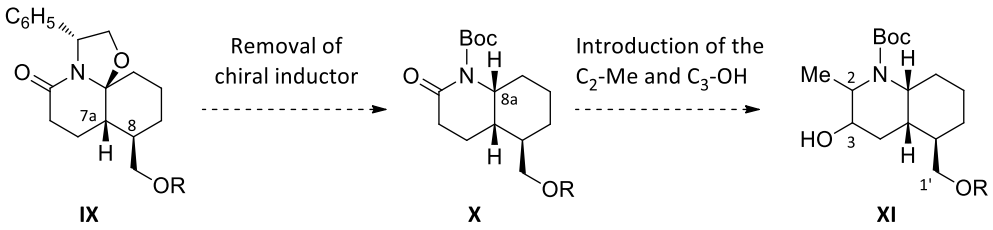


Figure 2.10 Introduction of substituents at C-2 and C-3

The cyclocondensation reaction of unsaturated ketone **XII** with (*R*)-phenylglycinol, followed by catalytic hydrogenation of the carbon-carbon double bond, afforded in 60% yield the tricyclic lactam **XIII**.

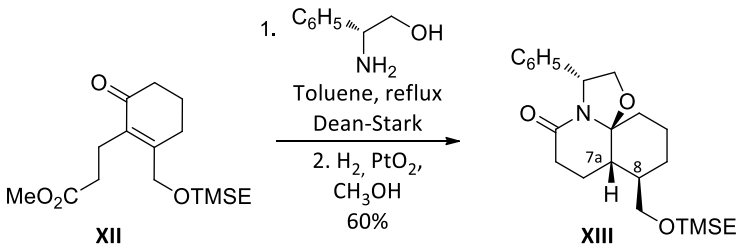


Figure 2.11

Alane reduction of **XIII** took place in very high stereoselectivity leading the corresponding *cis*-decahydroquinoline as a single isomer. The subsequent *N*-debenzylation and oxidation of the *N*-Boc derivative with ruthenium took place in excellent yields. A change of the protecting group during this sequence was necessary in order to avoid the ether (OTMSE) oxidation. The stereoselective introduction of a methyl at C-2 and an alcohol at C-3 was accomplished by reaction of the corresponding vinyltriflate with lithium dimethylcuprate[41] followed by hydroboration-oxidation.

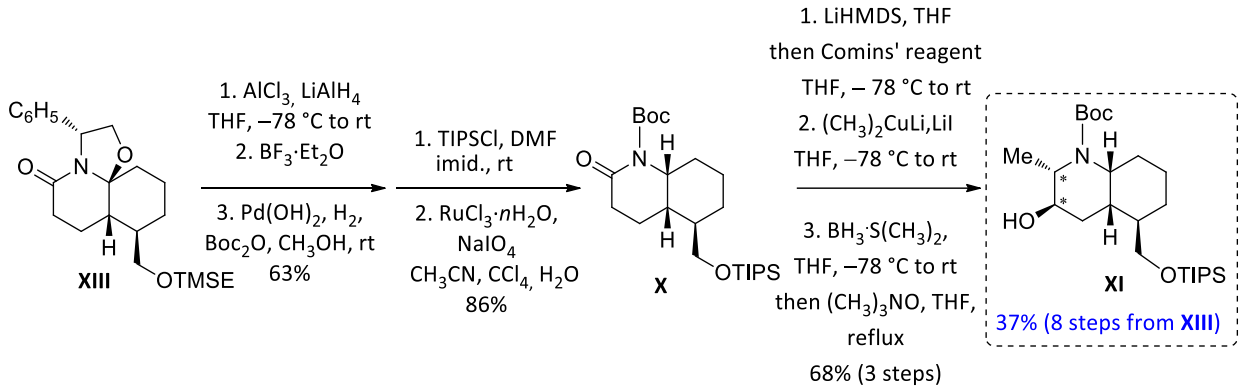


Figure 2.12

Compound **XI** is the common intermediate for the synthesis of lepadins A, B and C, in which the stereogenic center at C-3 had to be epimerized, and of lepadin D, in which the configuration at C-5 had to be inverted.

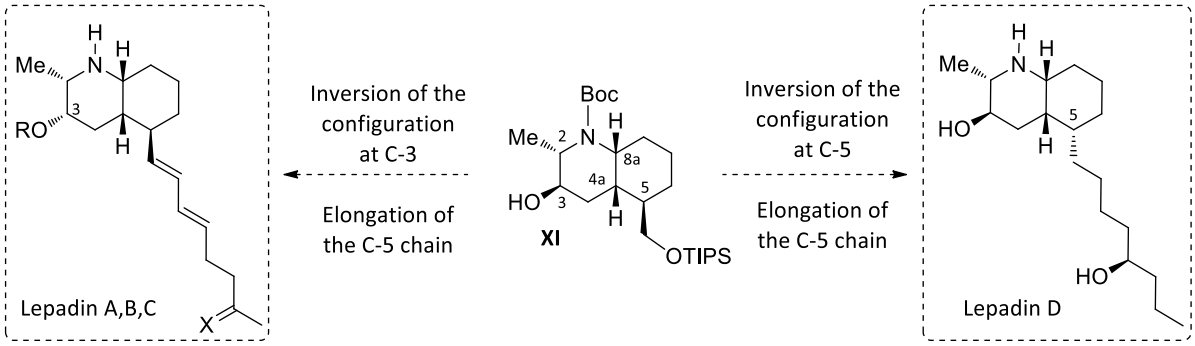


Figure 2.13

In particular, lepadin B was synthesized in four steps, starting from **XI**. The key steps are the inversion of configuration at C-3, *via* oxidation and reduction of the resulting ketone, and the elongation of the C-5

[41] a. Foti, C. J.; Comins, D. L. *J. Org. Chem.* **1995**, *60*, 2656–2657; b. Tsushima, K.; Hirade, T.; Hasegawa, H.; Murai, A. *Chem. Lett.* **1995**, 801.

chain, through Horner-Wadsworth-Emmons methodology, which ensure the required *E*,*E* stereochemistry. Lepadins A and C were previously obtained from intermediates **XIV** and **XV**.[42]

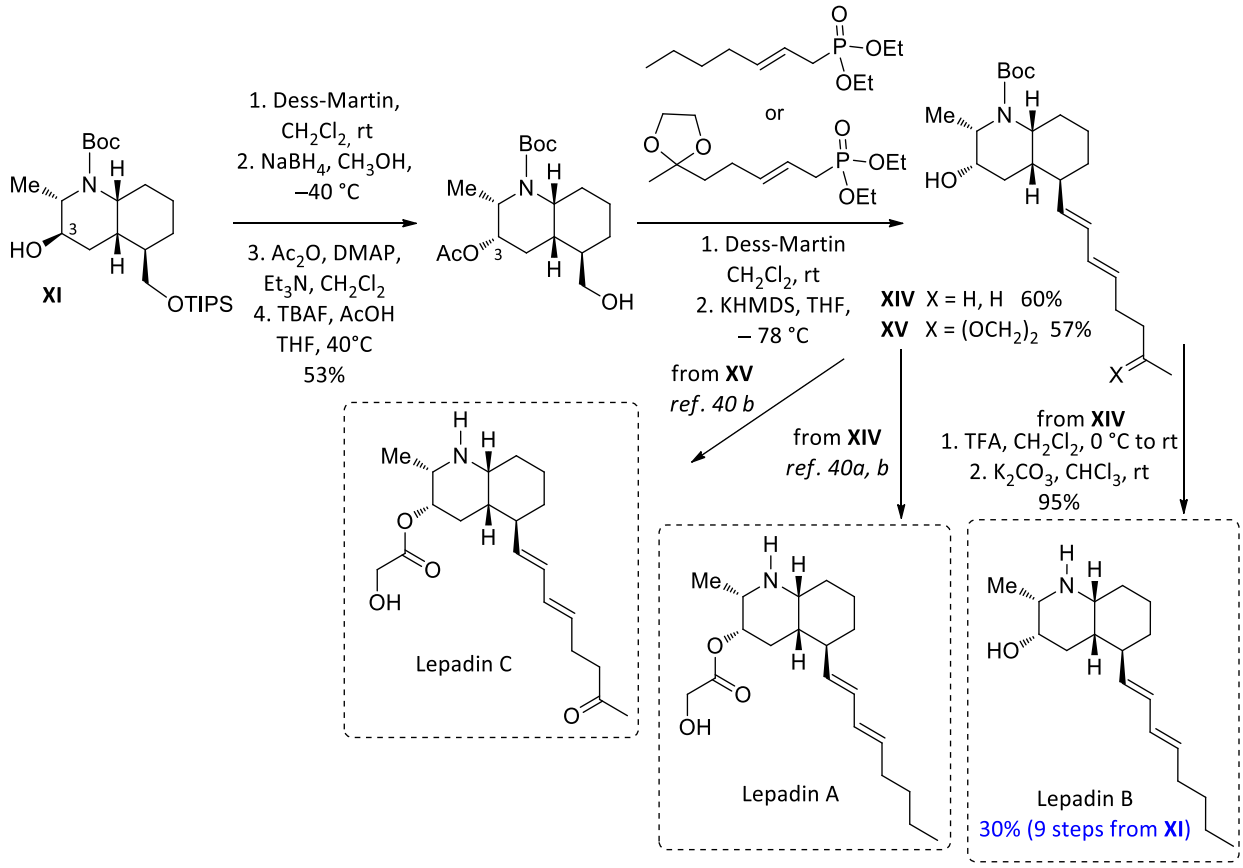


Figure 2.14 Synthesis of lepadin alkaloids

For the synthesis of lepadin D, the establishment of an exocyclic carbon-carbon double bond allowed the epimerization of C-5 stereocenter. The reduction of such double bond resulted to be completely stereoselective if no protecting groups at the nitrogen atom are present. After six additional steps, in which elongation of the chain at C-5 was performed, the total synthesis of lepadin D was then achieved.[27g]

[42] lepadin A was previously synthesized, see: a. Ozawa, T.; Aoyagi, S.; Kibayashy, C. *J. Org. Chem*. **2001**, *66*, 3338–3347; b. Pu, X.; Ma, D. *J. Org. Chem.* **2006**, *71*, 6562–6572 (Lepadin A and C).

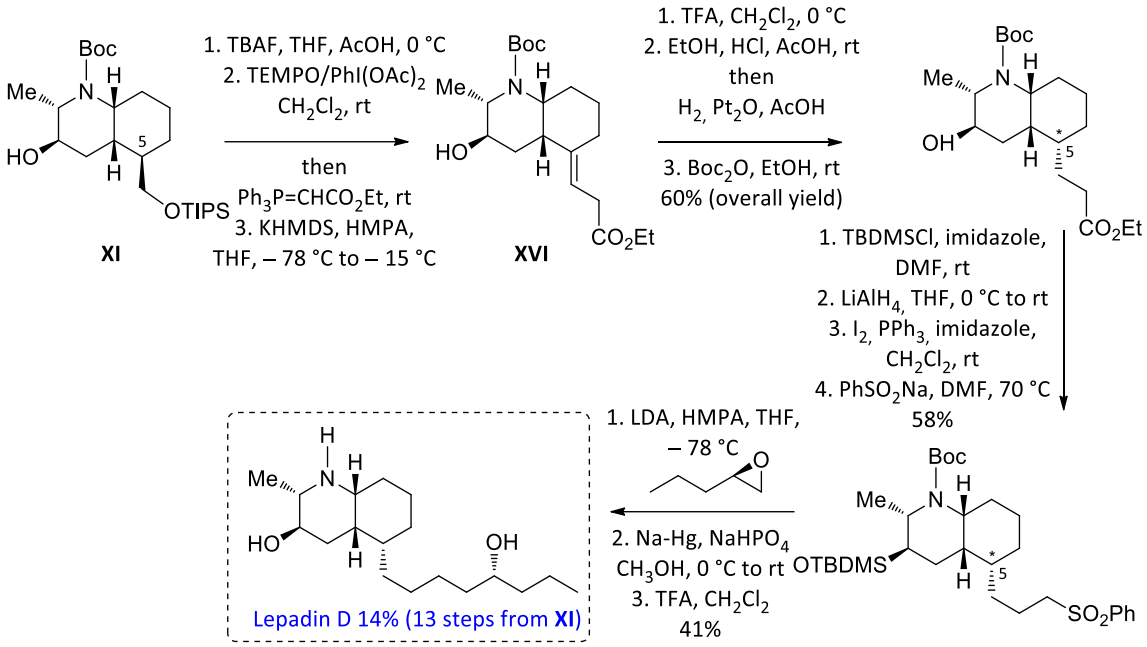


Figure 2.15 Synthesis of lepadin C

On the other hand, when ketoester **XVII** was condensed with (*S*)-tryptophanol, lactam **XVIII**, which can be considered a good precursor for the synthesis of tangutorine-type alkaloids, was obtained in good yield and stereoselectivity.

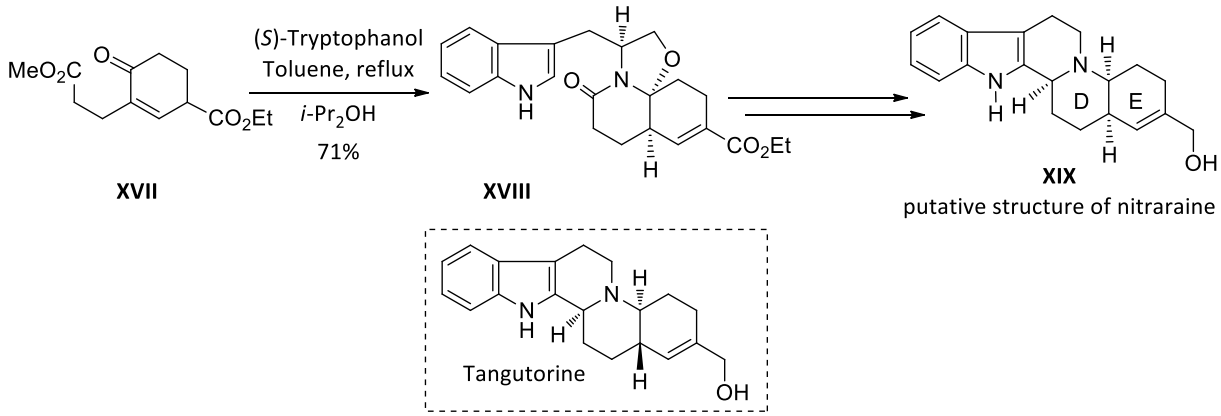


Figure 2.16

Compound **XIX** was prepared in the context of our studies on the structural elucidation of the indole alkaloid nitraraine. The original yohimbine-type pentacyclic structure proposed for this natural product was demonstrated by total synthesis to be wrong. More recently, on the base of biogenetic

considerations, Erwan Poupon[43] proposed the tangutorine-type structure **XIX**, which prompted us to undertake the total synthesis of the C-20 epimer of this alkaloid using our methodology.

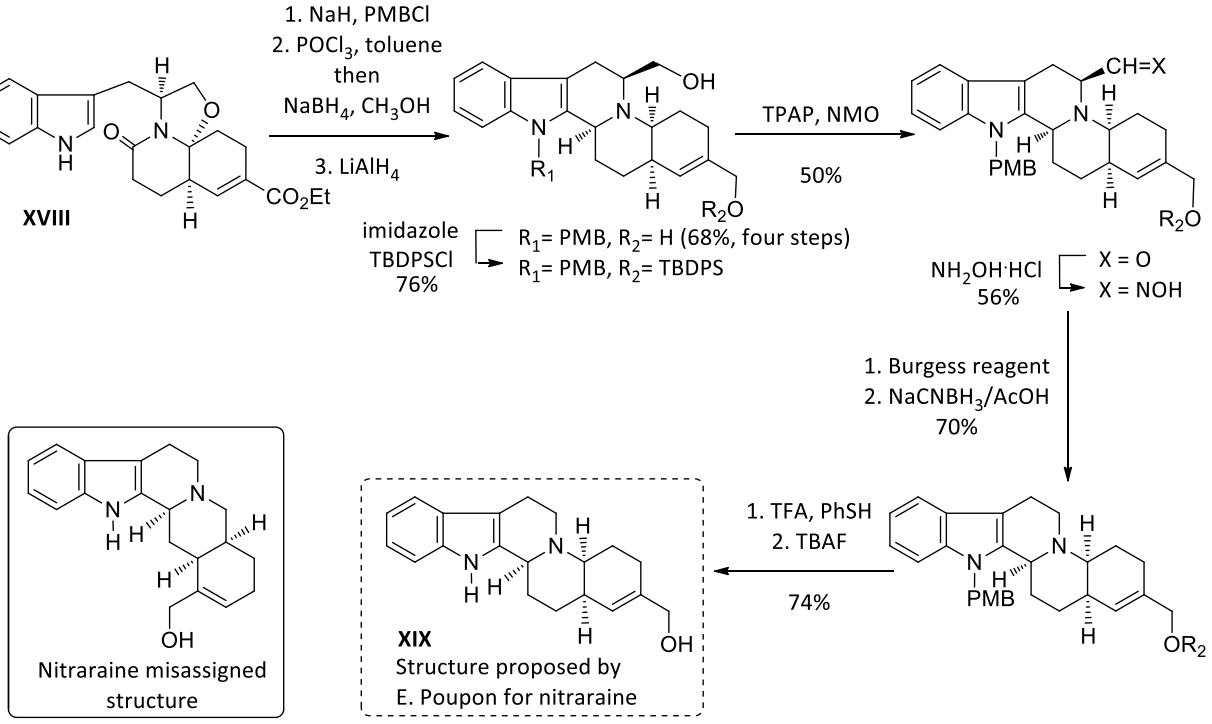


Figure 2.17

Unfortunately, the physical and spectroscopic data of **XIX** did not coincide with those described for the alkaloid nitraraine leaving unsolved the question about the structure of this natural product.

[43] a. Gravel, E.; Poupon, E. *Nat. Prod. Rep.* **2010**, *27*, 32–56; b. Salame, R.; Gravel, E.; Leblanc, K.; Poupon, E. *Org. Lett.* **2009**, *11*, 1891–1894.

2.2. Enantioselective synthesis of azabicycles from unsaturated lactams: present work.

Considering the good results obtained in previous works from chiral tricyclic lactams as enantiomeric scaffolds for the synthesis of C-5 and C-6 substituted *cis*-decahydroquinolines , we decided to expand the scope of our methodology by studying the stereoselective preparation of new unsaturated tricyclic lactams as precursors for the preparation of octahydro-1*H*-cyclopenta[*b*]pyridines and octahydro-1*H*-indoles substituted at the carbocyclic ring.

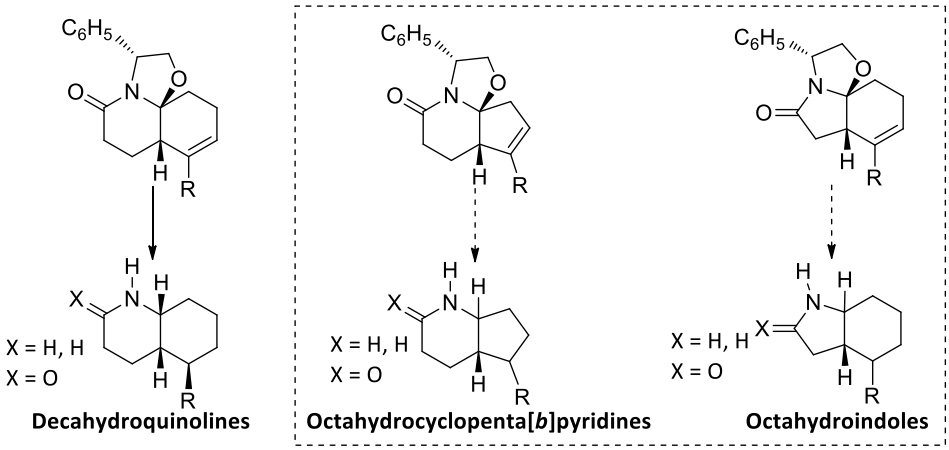


Figure 2.18

Octahydrocyclopenta[*b*]pyridines can be found in a few number of active natural products, such as streptazolin,[44] serratinine,[45] lycojaponicumin A[46] and aristolarin,[47] while the octahydroindole core can be frequently found in natural products isolated from species of *Amaryllidaceae*, *Scelentium*, *Stemona*, *Aeruginosins* and *Erythrina* alkaloids among the most representative families. Furthermore, perindopril, a potent drug for the treatment of hypertension and heart failure, presents a central octahydroindole structure.

[44] For synthesis of Streptazolin, see: a. Li, F.; Miller, M. J. *J. Org. Chem.* **2006**, *71*, 5221–5227; b. Kozikowski, A. P.; Park, P.-u. *J. Org. Chem.* **1990**, *55*, 4668–4682.

[45] For synthesis of Serratinine, see: Inubushi, Y.; Ishii, H.; Yasui, B.; HAshimoto, M.; Harayama, T. *Chem. Pharm. Bull.* **1968**, *16*, 82–91.

[46] For synthesis of Lycojaponicumins A, see: Krenske, E. H.; Patel, A.; Houk, K. N. *J. Am. Chem. Soc.* **2013**, *135*, 17638–17642.

[47] For synthesis of Aristolarin, see: Kyburz, R.; Schöpp, E.; Hesse, M. *Helvetica Chimica Acta* **1984**, *67*, 804–808.

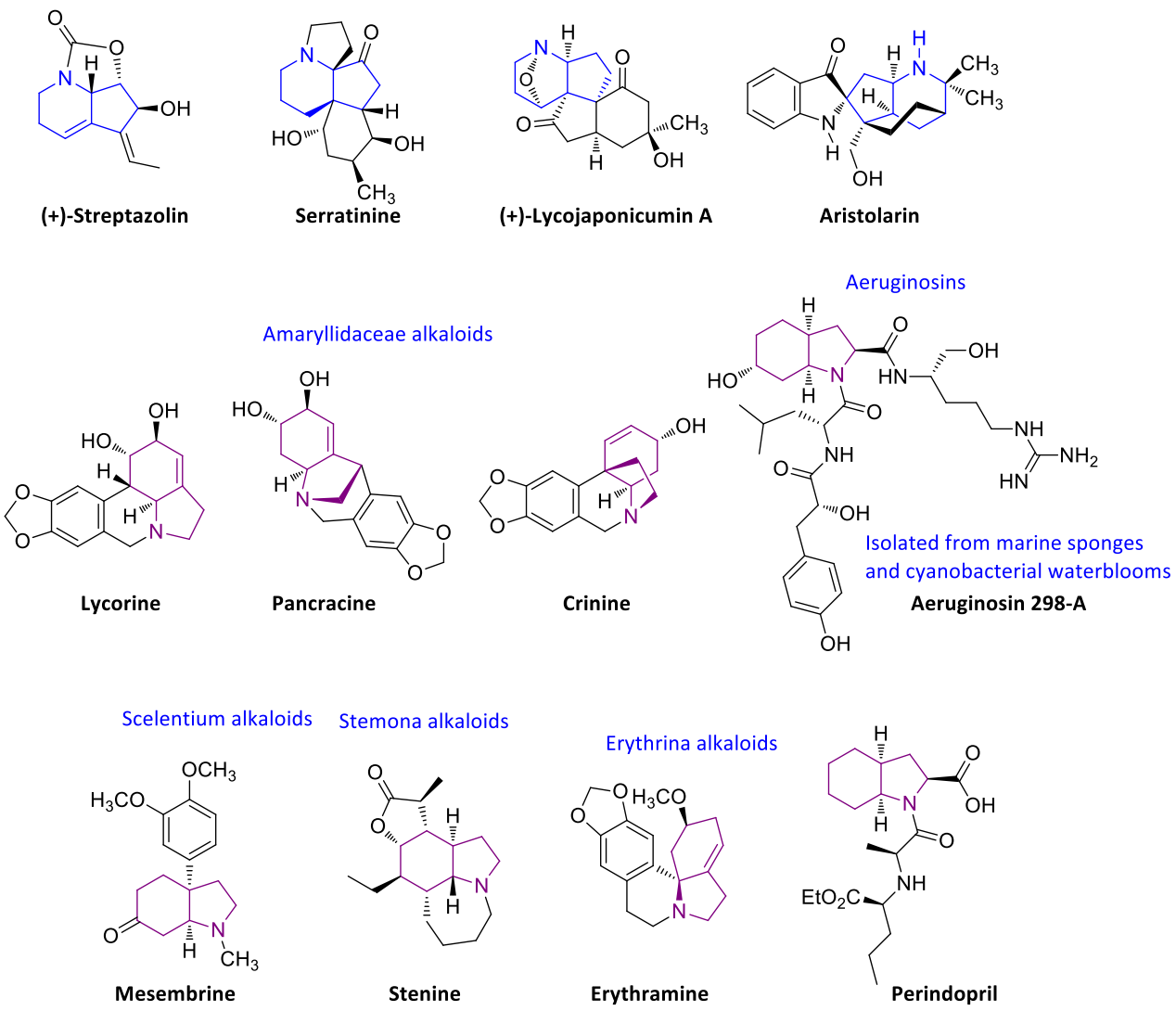


Figure 2.19 Octahydrocyclopenta[*b*]pyridine and octahydroindole alkaloids

2.2.1. Cyclocondensation reactions from 2-cyclopentenone-2-propionates and (*R*)-phenylglycinol.

As extension of the above-described work, the study on the cyclocondensation reaction of 2-oxo-cyclopentenpropionate derivatives and (*R*)-phenylglycinol was undertaken. The expected product was an unsaturated tricyclic lactam, with a five-membered carbocyclic ring and six-membered lactam ring. We then set out to study the stereoselective reduction of the carbon-carbon double bond and the removal of the chiral inductor, in order to synthesize C-5 alkyl octahydrocyclopentapyridines with three stereocenters with a well-defined configuration.

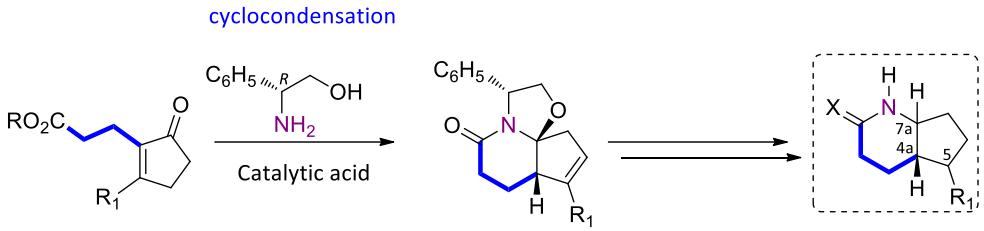


Figure 2.20 Synthetic plan

2.2.1.1. Preparation of starting materials

Since the required starting materials are not commercially available, an efficient procedure for their synthesis was first investigated. The devised synthetic procedure involved the introduction of the propionate chain on the carbocyclic ring by Michael addition of 1,3-cyclopentanedione to an acrylate ester followed by bromination of the dione and a cross-coupling reaction for the incorporation of alkyl substituents.

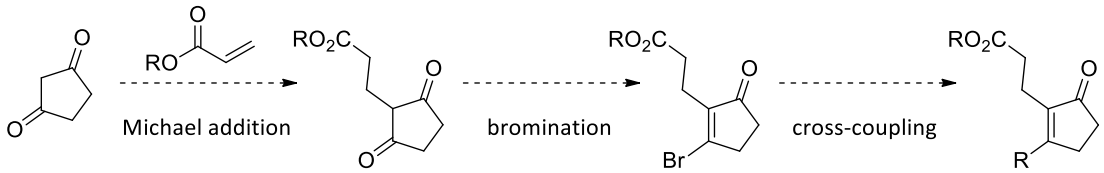


Figure 2.21 Approach to unsaturated ketoesters

Unfortunately, all attempts to introduce a propionate chain on **1** under the conditions described by Hamanaka[48], conducted to the target compound **2** in low yield (Figure 2.22).

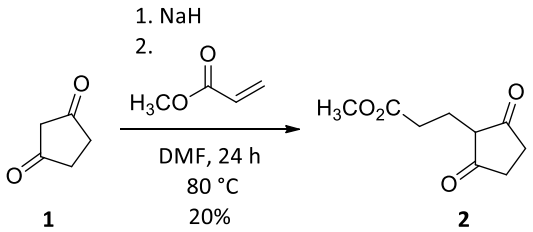


Figure 2.22

[48] Konno, M.; Nakae, T.; Sakuyama, S.; Imaki, K.; Nakai, H.; Hamanaka, N. *Synlett*, **1997**, 1472–1474.

In view of this disappointing result, a different methodology to access to the required 3-alkylcyclopentenone, was considered.[49] In particular, starting from 3-alkyl-2-cyclopentenones, the subsequent bromination at C-2,[50] followed by a cross-coupling,[51] should provide the required enones.

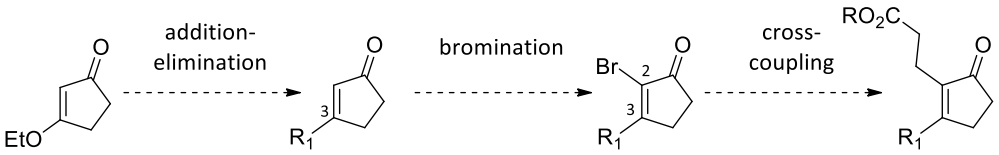
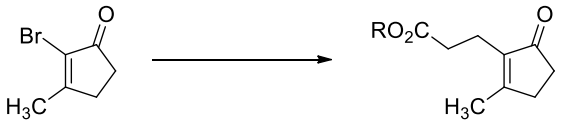


Figure 2.23 Alternative synthetic plan

In order to test the feasibility of our proposal the commercially available bromo enone **3** was employed.



3 **4**

Figure 2.24 Synthesis of compound 4

The introduction of the propionate chain could be accomplished by using a palladium-catalyzed coupling reaction. In particular, Molander and co-workers have reported a Suzuki-Miyaura-type cross-coupling reaction, using potassium alkyltrifluoroborates with various alkenyl bromides. This methodology provides an efficient procedure for sp^2-hybridized alkenyl bromides and sp^3-hybridized alkyl derivatives cross-coupling.[51, 52] Boron homoenolates can be prepared by a number of methods, including alkylation of halomethyl boronate species[53] as well as the 1,4-addition of diboron species to unsaturated ketones and esters.[54] Trifluoroborate **6** was prepared following the reported conditions,[54c] via conjugated addition of bis(pinacolate)-diboron to *t*-butyl acrylate, followed by treatment with KHF_2.[52, 53a]

[49] a. Rosini, G.; Ballini, R.; Sorrenti, P. *Tetrahedron*, **1983**, *39*, 4127–4132; b. Bunte, J. O.; Heilmann, E. K.; Hein, B.; Mattay, J. *Eur. J. Org. Chem.* **2004**, 3535–3550; c. Lemière, G.; Gandon, V.; Cariou, K.; Hours, A.; Fukuuyama, T.; Dhimane, A.-L.; Fensterbank, L.; Malacri, M. *J. Am. Chem. Soc.* **2009**, *131*, 2993–3006; d.Gao, M.; Thorpe, S. B.; Santos, W. L. *Org. Lett.* **2009**, *11*, 3478–3481; e. Mun, S.; Lee, J.-E.; Yun, J. **2006**, *8*, 4887–4889; f. Hiscox, W. C.; Metteson, D. S. *Journal of Organometallic Chemistry*, **2000**, *614–615*, 314–315; f. Ruprah, P. K.; Cros, J.-P.; Pease, J. E.; Whittingham, W. G.; Williams, J. M. J. *Eur. J. Org. Chem.* **2002**, 3145–3152.

[50] Jythi, D.; HariPrasad, S. *Synlett*, **2009**, *14*, 2309–2311.

[51] Molander, G. A.; Ham, J.; Seapy, D. G. *Tetrahedron*, **2007**, *63*, 768–775.

[52] Molander, G. A.; Petrillo, D. E. *Org. Lett.* **2008**, *10*, 1795–1798.

[53] a. Whiting, A. *Tetrahedron Lett.* **1991**, *32*, 1503–1506; b. Matteson, D. S.; Majundar, D. *J. Am. Chem. Soc.* **1980**, *102*, 7590–7591; c. Matteson, D. S.; Cheng, T.-C. *J. Org. Chem.* **1968**, *33*, 3055–3060.

[54] a. Lawson, Y. G.; Lesley, M. J. G.; Marder, T. B.; Norman, N. C.; Rice, C. R. *Chem. Commun.* **1997**, 2051–2052; b. Takajashi, K.; Ishiyama, T.; Miyaura, N. *Chem. Lett.* **2000**, 982–983; c. Mun, S.; Lee, J.-E.; Yun, J. *Org. Lett.* **2006**, *8*, 4887–4889.

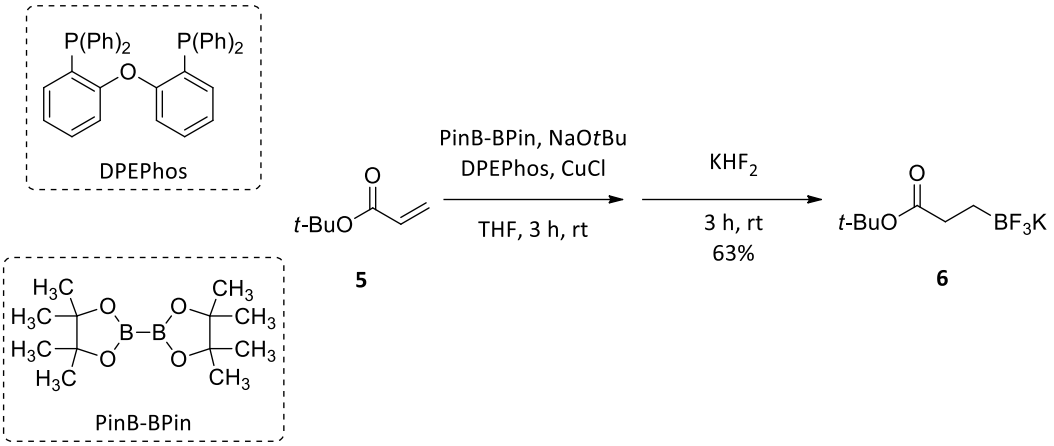
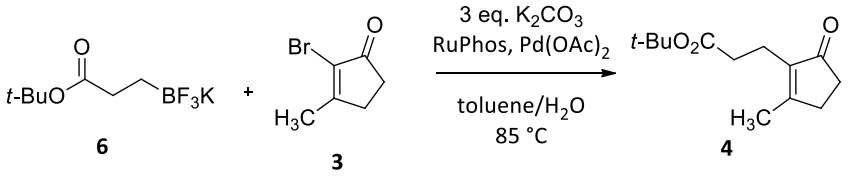


Figure 2.25 Synthesis of trifuoroborates 6

Cross-coupling between **3** and **6** was performed in the presence of $Pd(OAc)_2$, RuPhos and K_2CO_3 in toluene/water at 85 °C, and the influence of catalyst amount was tested (Table 2.1).



	equiv. $Pd(OAc)_2$	equiv. RuPhos	t	y%
1[52c]	0.026	0.05	19 h	41
2	0.026+0.051	0.05+0.1	38.5 h	55
3	0.037+0.012	0.075+0.025	37.5 h	90

Table 2.1 Coupling of trifluoroborates and bromolkenyl

We found that the portion-wise addition of catalysts promoted the reaction and after almost 38 h we got the desired product **4** in very good yield (entry 3).

Considering that ketoacid derivatives had been also described as cyclocondensation partners, **7** was prepared by hydrolysis of **4** in the presence of TFA.

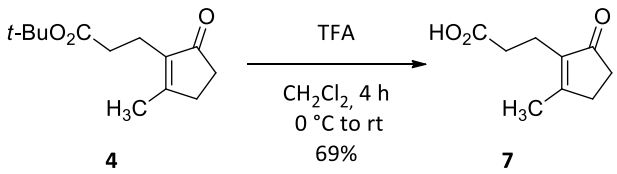


Figure 2.26 Hydrolysis of ester

2.2.1.2. Cyclocondensation reaction

At the sight of the excellent results obtained in previous studies, **4** and **7** were submitted to the reported cyclocondensation reaction conditions in refluxing benzene with a Dean–Stark apparatus. Acid activation was necessary when ketoester **4** are employed. After 48 h we observed the total consumption of the starting material **4**, but we could not obtain the tricyclic lactam **10**. Instead, we isolated the imine **8**. On the other hand, starting from acid **7**, the amide **9** was isolated

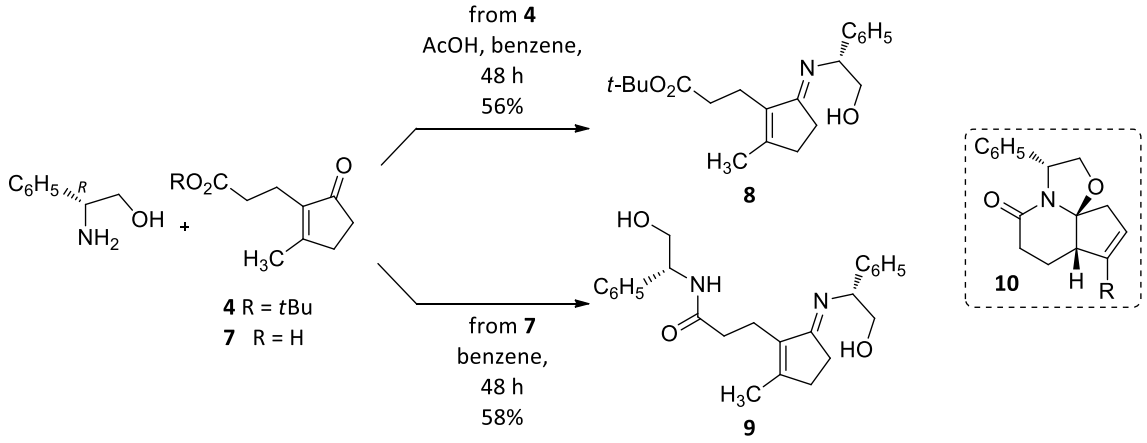


Figure 2.27 Reactions of (*R*)-phenylglycinol with ester 4 and acid 7

The disappointing outcome of this reaction can be accounted for by considering the proposed mechanism for cyclocondensation reaction of unsaturated oxoacid derivatives.

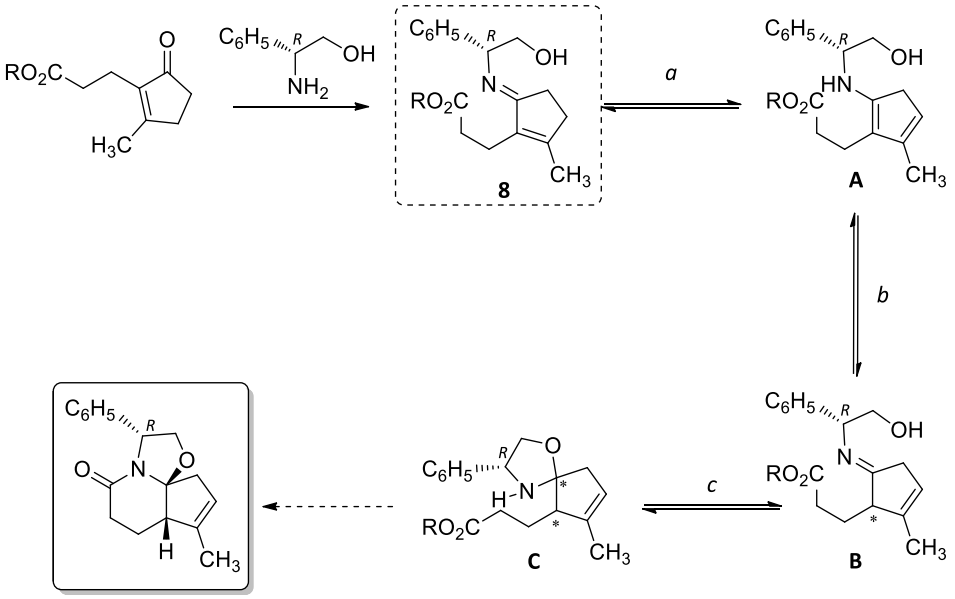


Figure 2.28 Proposed mechanism.

The initially formed conjugated imine **8** should be in equilibrium, via dienamine **A**, with two epimeric β,γ-unsaturated imines **B**. The addition of the hydroxyl group of the chiral inductor on the carbon of the imine **B**, would give rise to a mixture of four possible diastereoisomeric oxazolidines **C**. The irreversible and selective lactamization of one of the diastereomers of **C** under kinetic control should stereoselectively give one of the corresponding unsaturated lactams. The expected course of the reaction was interrupted, probably, because the isomerization of **8** to the dienamine **A** did not take place. In fact, it has been reported that isomerization of a double bond in five-membered carbocycles is more difficult than for six-membered ones (see Figure 2.3).[55]

2.2.2. Cyclocondensation reactions from 2-cyclohexanone-2-acetates and (*R*)-phenylglycinol.

The synthesis of enantiopure C-4 substituted octahydro-1*H*-indoles, starting from cyclohexenones with an acetate instead of a propionate chain, was then studied.

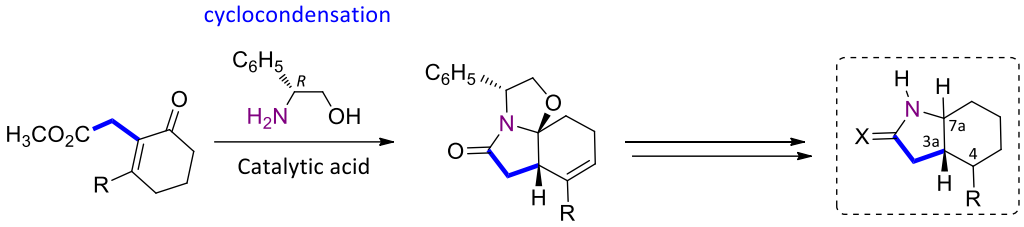


Figure 2.29 Synthetic plan

2.2.2.1. Preparation of starting materials

The alkylation of 1,3-cyclohexanedione with methyl bromoacetate was carried out following the conditions reported by Hamanaka.[56] It was found that maintaining **11** in refluxing methanol for 2 h, the alkylated methyl 2,6-dioxocyclohexaneacetate **12** could be obtained in acceptable yield, avoiding the formation of *O*-alkylated products **13** and **14**, which were isolated as traces.

[55] For stability of cyclic olefins, see: a. Herling, J.; Shabtai, J.; Gil-A. E. *J. Am. Chem. Soc.* **1965**, *87*, 4107–4110; b. Coppens, P.; Gil-Av.; E.; Herling, J.; Shabtai, J. *J. Am. Chem. Soc.* **1965**, *87*, 4111–4114.

[56] a. Konno, M.; Nakae, T.; Sakuyama, S.; Imaki, K.; Nakai, H.; Hamanaka, N. *Synlett* **1997**, 1472–1474; b. Sass, D. C.; de Oliveira, K. T.; Constantino, M. G. *Tetrahedron Lett.* **2008**, *49*, 5770–5772.

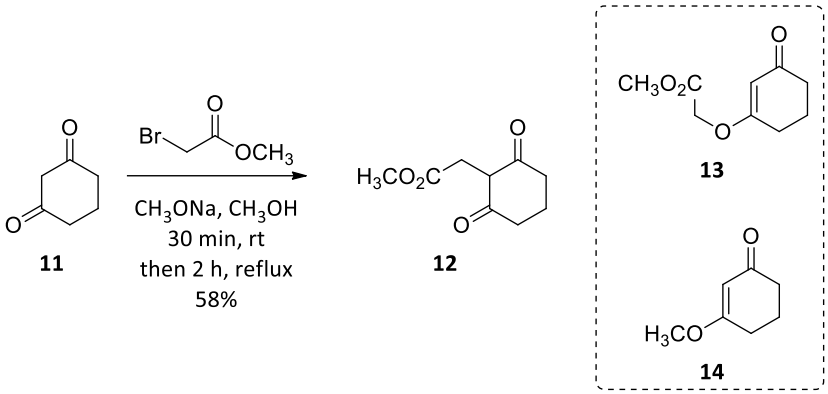


Figure 2.30 Alkylation of cyclohexanedione

Compound **12** was allowed to react with triphenylphosphine dibromide, adopting Piers and Nagakura's procedure.[57] In this way, the bromoenone **15** was obtained in quite good yield.

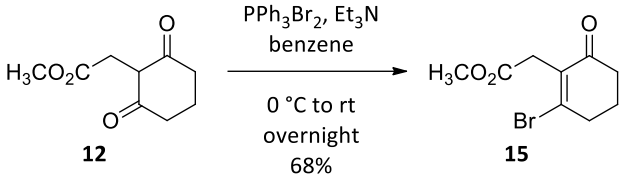


Figure 2.31 Synthesis of methyl 2-bromo-6-oxocyclohexeneacetate 15

The mechanism proposed for this reaction involves that the treatment of a 1,3-diketone with triphenylphosphine dibromide furnishes a phosponium salt, which suffers the conjugate addition of the bromide. Finally, the elimination of triphenylphosphine oxide provides β-bromo α,β-unsaturated ketone.

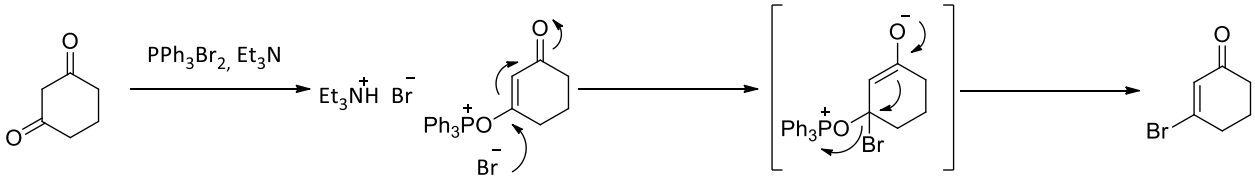


Figure 2.32 Mechanism of the formation of β-haloketones

The desired compound **16** was then prepared following the procedure described by Piers and Nagakura,[58] who reported the conjugate addition of lithium (phenyl)(alkyl) cuprates for the first time. Previous studies with more conventional cuprates, such as $(CH_3)_2CuLi$, provided a mixture of starting material, mono- and bis- alkylated ketones. Instead, the mixed cuprates permitted the effective control of the reaction. Under

[57] Piers, E.; Nagakura, I. *Synth. Commun.* **1975**, *5*, 193–199.

[58] a. Piers, E.; Nagakura, I. *J. Org. Chem.* **1975**, *40*, 2694–2696; b. Piers, E.; Grierson, J. R.; Lau, C. K.; Nagakura, I. *Can. J. Chem.* **1982**, *60*, 210–223; c. Piers, E; Nagakura, I.; Morton, H. E. *J. Org. Chem.* **1978**, *43*, 3630–3631; d. Piers, E.; Cheng, K. F.; Nagakura, I. *Can. J. Chem.* **1982**, *60*, 1256–1263; e. Piers, E.; Banville, J.; Lau, C. K.; Nagakura, I. *Can. J. Chem.* **1982**, *60*, 2965–2975.

this reaction conditions β-methylcyclohexenone **16** was prepared from **15** in moderate yield. The subsequent basic hydrolysis of **16** afforded the corresponding acid **17**.

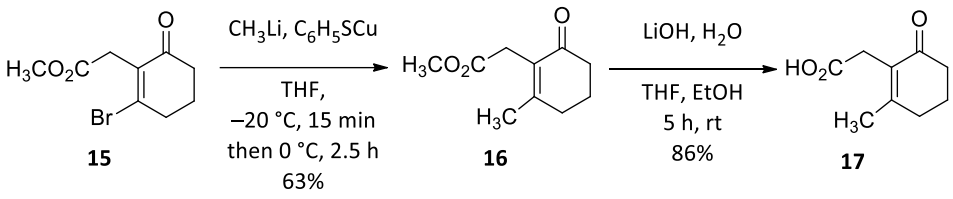


Figure 2.33 Synthesis of ester 16 and acid 17

2.2.2.2. Cyclocondensation reaction

Reaction of **16** with (*R*)-phenylglycinol in refluxing toluene or benzene with azeotropic removal of water with Dean–Stark apparatus, should provide a tricyclic lactam **19**, which presents a double bond on the carbocyclic ring. Unfortunately, in all trials either starting material or conjugate enamides **18** were isolated as an almost equimolar mixture of the two epimers at C-7a. Reaction with acid **17** provided similar results.

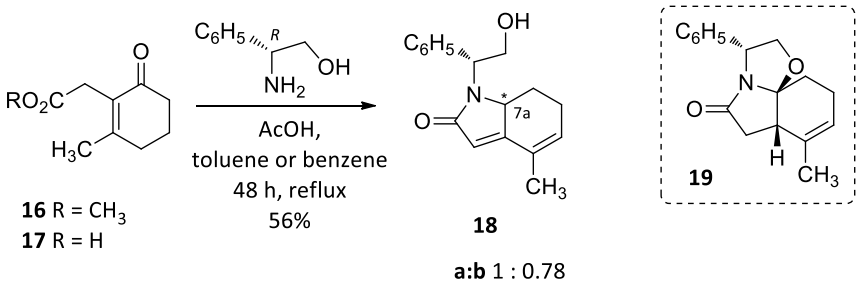


Figure 2.34 Cyclocondensation reaction

A detailed rationalization of this transformation is included in Chapter 4 of the present dissertation.

At the sight of these disappointing results, we decided to not go on with the study on the cyclocondensation reaction of cyclopentenonepropionate and cyclohexenoneacetate derivatives with (*R*)-phenylglycinol and to focus our attention on the synthesis of new azabicycles systems.

CHAPTER 3. ENANTIOSELECTIVE SYNTHESIS OF C-8 AND C-6,8 SUBSTITUTED *CIS*-DECAHYDROQUINOLINES

Cis- and *trans*-decahydroquinoline ring systems are the central structure of many naturally occurring biologically active alkaloids isolated from plants[59] and, mainly from terrestrial (amphibian, arthropods)[60] and marine (tunicates, flatworms)[61] organisms. Due to the wide range of biological activities and their ability to act as testing ground for new synthetic methods, decahydroquinolines have attracted considerable attention from organic chemists over the years.[62] However, the number of enantioselective synthesis is still limited.[63]

3.1. Enantioselective synthesis of *cis*-decahydroquinolines from saturated lactams: previous work.

In the context of the studies on the synthesis of enantiopure piperidine derivatives from chiral nonracemic lactams, our group reported the preparation of tricyclic lactam **IIIa** by dynamic kinetic resolution of racemic ester **I** or acid **II**. Minor amounts of isomer **IIIb** were isolated in both cases (Figure 3.1).[64] It is worth mentioning that only few examples of tricyclic lactams synthesized from cyclohexanone-based δ-ketoacid derivatives and (*R*)-phenylglycinol have been reported so far.

[59] a. Hemingway, S. R.; Phillipson J. D. *Proc. Phyt. Soc. Eur.* **1980**, *17*, 63–90; b. Blumenkopf, T. A.; Heathcock, C. H. *Alkaloids: Chemical and Biological Perspectives*, **1986**, Vol. 3 (Ed. S. W. Pelletier), Wiley, New York, pp. 185–240; c. Ma, X.; Gang, D. R. *Nat. Prod. Rep.* **2004**, *21*, 752–772.

[60] a. Spande, T. F.; Jain, P.; Garraffo, H. M.; Pannell, L. K.; Yeh, H. J. C.; Daly, J. W.; Fukumoto, S.; Imamura, K.; Tokuyama, T.; Torres, J. A.; Snelling, R. R.; Jones, T. H. *J. Nat. Prod.* **1999**, *62*, 5–21; b. Jones, T. H.; Gorman, J. S. T.; Snelling, R. R.; Delabie, J. H. C.; Blum, M. S.; Garraffo, H. H.; Jain, P.; Daly, J. W.; Spande, T. F. *J. Chem Ecol.* **1999**, *25*, 1179–1193; c. Daly, J. W.; Garraffo, H. M.; Jain, P.; Spande, T. F.; Snelling, R. R.; Jaramillo, C.; Rand, A. S. *J. Chem. Ecol.* **2000**, *26*, 73–85; For a recent review, see: d. Daly, J. W.; Spande, T. F.; Garraffo, H. M. *J. Nat. Prod.* **2005**, *68*, 1556–1575.

[61] a. Steffan, B. *Tetrahedron* **1991**, *47*, 8729–8732; b. Kubaneck, J.; Williams, D. D.; Dilip de Silva, E.; Allen, T.; Andersen, R. J. *Tetrahedron Lett.* **1995**, *56*, 6189–6192; c. Davis, R. A.; Carroll, A. R.; Quinn, R. J. *J. Nat. Prod.* **2002**, *65*, 454–457.

[62] a. Oppolzer, W.; Fröstl, W. *Helv. Chim. Acta* **1975**, *58*, 590–593; b. Overman, L. E.; Yokomatsu, T. *J. Org. Chem.* **1980**, *45*, 5229–5230; c. Brown, H. C.; Salunkhe, A. M. *Tetrahedron Lett.* **1993**, *34*, 1265–1268; d. Efange, S. M. N.; Khare, A. B.; Mach, R. H.; Parson, S. M. *J. Med. Chem.* **1999**, *42*, 2862–2869; e. Maldaner, A. O.; Pilli, R. A. *tetrahedron Lett.* **2000**, *41*, 7843–7846; f. Panda, M.; Phuan, P-W.; Kozlowski, M. C. *J. Org. Chem.* **2003**, *68*, 564–571; g. Gravier-Pelletier, C.; Maton, W.; Bertho, G.; Le Merrer, Y. *Tetrahedron* **2003**, *59*, 8721–8730; h. Mena, M.; Bonjoch, J. *Tetrahedron* **2005**, *61*, 8264–8270; i. Mena, M.; Bonjoch, J.; Pardo, D. G.; Cossy, J. *J. Org. Chem.* **2006**, *71*, 5930–5935; j. Ruiz, J. M.; Afonso, M. M.; Palenzuela, J. A. *Molecules* **2007**, *12*, 194–204; for a review, see: k. Kibayashi, C.; Aoyagi, S. *Studies in Natural Products Chemistry*; Atta-ur-Rahman, Ed. Elsevier: Amsterdam, **1997**; Vol. 19, pp 3–88.

[63] a. Heizbaum, M.; Fröhlich, R.; Glorius, F. *Adv. Synth. Catal.* **2010**, *352*, 357–362; b. Pham, V. C.; Jossany, A.; Grellier, P.; Sévenet, T.; Nguyen, V. H.; Bodo, B. *J. Org. Chem.* **2008**, *73*, 7565–7573.

[64] Amat, M.; Cantó, M.; Llor, N.; Ponzo, V.; Pérez, M.; Bosch, J. *Angew. Chem. Int. Ed.* **2002**, *41*, 335–338.

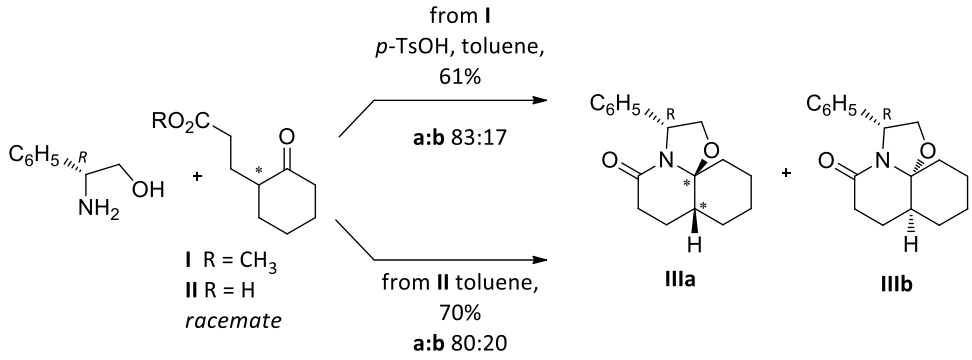


Figure 3.1

The stereochemical outcome of this reaction can be accounted for by considering that the mixture of four diastereomeric oxazolidines **C** formed initially is in equilibrium through the corresponding imines-enamines **A-B**.

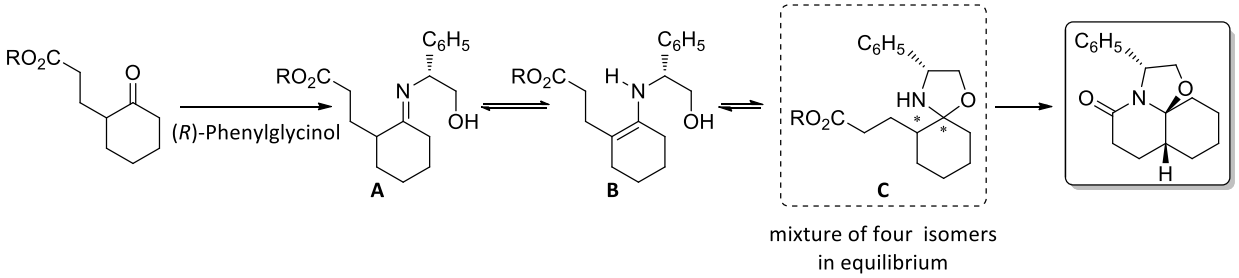


Figure 3.2 Proposed mechanism

The final irreversible lactamization takes place faster from diastereomer **C1** in which the configuration (*S*) at C-2 of the oxazolidine ring allows the approach of the carboxylate to the nitrogen atom for the less hindered face, opposite to the phenyl, and through a chair-like transition state, in which the C-C bond of the six-membered carbocyclic ring adopts an equatorial disposition. This approach leads to the predominant isomer **a**. The formation of the minor isomer **b** indicates that lactamization also takes place from the diastereoisomeric oxazolidine **C2**, in which the approach of carboxylate group to the nitrogen takes place from the more hindered face.

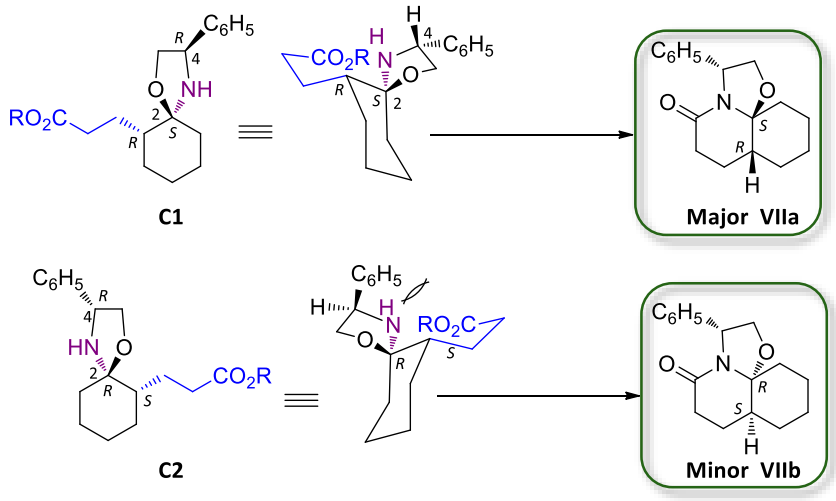


Figure 3.3 Lactamization of C1 and C2

Lactam **IIIa** was converted into the *cis*-decahydroquinoline **V**, by stereoselective alane reduction followed by catalytic hydrogenation.

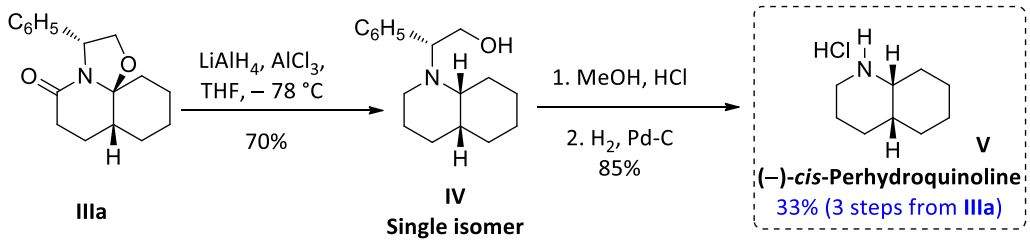


Figure 3.4 Synthesis of enantiopure *cis*-decahydroquinoline V

It is worth mentioning that, in 2013 Deprez and co-workers reported miniaturized conditions to prepare arrays of bicyclic and tricyclic lactams, using microwave irradiation. Water, or a mixture of ethanol and water, have been used as solvents to dispense reagents at low scale. Starting from acids **VI** and **VII** they obtained lactams **VIII** and **IX** in good yield as a mixture of isomers with a diastereoisomeric excess of 60%.[65]

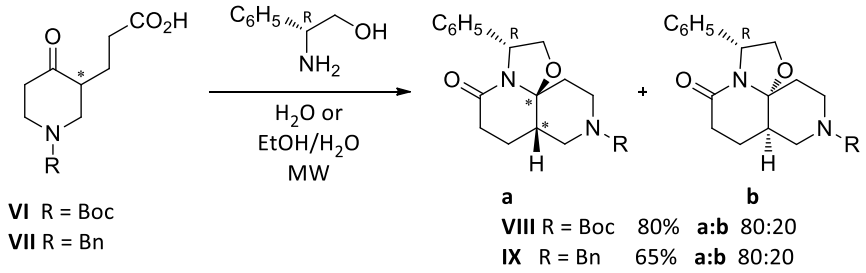


Figure 3.5 Deprez's tricyclic lactams

[65] Malaquin, S.; Jida, M.; Courtin, J.; Laconde, G.; Willand, N.; Deprez, B.; Deprez-Poulain, R. *Tetrahedron Lett.* **2013**, *54*, 562–567.

In conclusion, cyclocondensation reaction of (*R*)-phenylglycinol and saturated cyclohexanepropionate derivatives provides tricyclic lactams in comparable yield with respect to analogous unsaturated cyclohexanones (Chapter 2, Paragraph 2.1) leading to unsaturated tricyclic lactams.

3.2. Enantioselective synthesis of 8 and 6,8-substituted *cis*-decahydroquinolines from saturated lactams: present work.

The main objective of the work described in this Chapter is the study of a new procedure for the preparation of enantiopure 8 and 6,8-substituted *cis*-decahydroquinolines, for which few examples are reported. The key step would involve a cyclocondensation reaction starting from an isomeric mixture of cyclohexanone-2-propionate derivatives, bearing an additional substituent at C-3 or at C-3 and C-5, with (*R*)-phenylglycinol. In particular, dimethyl 2-oxo-1,3-cyclohexanonepropionate **A** exists as a mixture of three isomers: a *meso* form and two enantiomeric structures. When an additional substituent at C-5 is introduced (**B**), four isomers contribute to the mixture: two *meso* forms, with a pseudo-asymmetric center at C-4, and a pair of enantiomers in which C-5 is not a stereogenic center. Finally, in the case of 3-substituted 2-oxocyclohexanepropionate derivatives **C**, four stereoisomers, i.e. two racemate mixtures are possible (Figure 3.6).

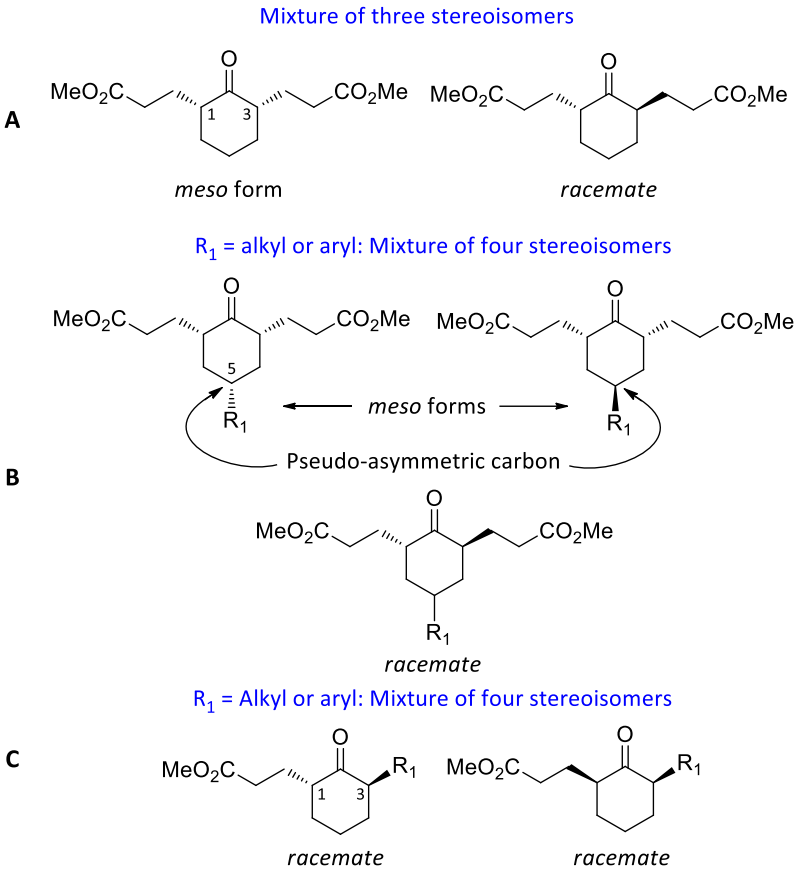


Figure 3.6

The hypothesis was that the cyclocondensation reaction of oxo-esters and aminoalcohols should lead to a mixture of diastereoisomeric oxazolidines that would be in equilibrium through the corresponding enamines. The lactamization key step would take place under kinetic control, selectively providing the isomer that is formed faster. The highly stereoconvergent process could open up a straightforward route to enantiopure decahydroquinolines that contain up to two substituents at the carbocyclic ring, with a well-defined configuration. In the case of simple ketodiester **A**, a desymmetrization reaction with differentiation of the two-enantiotopic propionate chains would occur from the *cis* (*meso*) isomer, whereas a dynamic kinetic resolution, with isomerization of the configurationally labile stereocenters would take place from the *trans* isomer (racemate). Lactamization step would give rise to one of the eight possible diastereoisomeric tricyclic lactams, and further transformations would provide C-8 propanol substituted decahydroquinolines. On the other hand, starting from ketones **B** the formation of one of the sixteen possible lactams was expected. Remarkably, an additional stereoselective step would occur in this series: the 5-substituted carbon would become a stereogenic center with a well-defined configuration. Finally, cyclocondensation of ketoacid derivatives **C**, would provide one of the eight possible lactams, in a process that would involve dynamic kinetic resolution with isomerization of the two configurationally labile stereocenters.

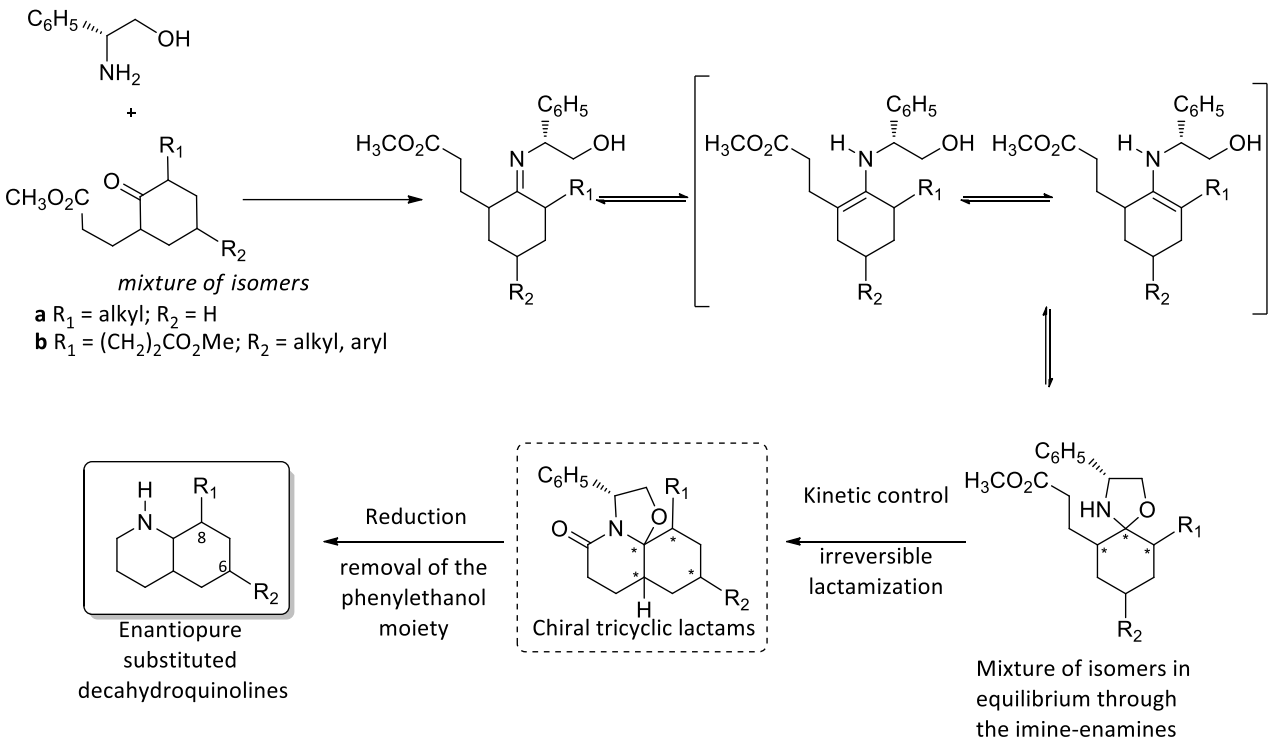


Figure 3.7 Expected mechanism

3.2.1. Previous accomplishments of our group: enantioselective synthesis of *cis*-decahydroquinoline-6-propanol derivatives from phenylglycinol-derived lactams

The cyclocondensation reaction of diester **20** with (*R*)-phenylglycinol in refluxing toluene, in the presence of isobutyric acid, provided a 76:24 mixture of tricyclic lactams **Xa** and **Xb**, respectively, in 86% yield.

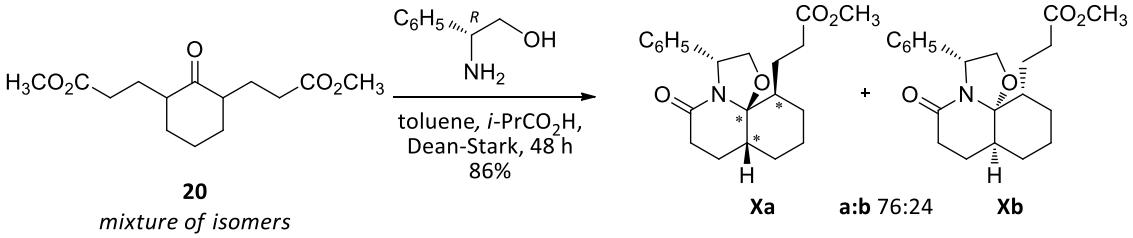


Figure 3.8 Cyclocondensation of 20

In the event of ketones **21**, **22** and **XI**, their cyclocondensation with (*R*)-phenylglycinol under the same conditions, gave rise to lactams **XII**-**XIV** as a mixture of two isomers, **a** and **b**, in good yield. It should be noted that one of the sixteen diastereomeric tricyclic lactams that can be formed is selectively isolated as the major component of the reaction mixture (Figure 3.9).

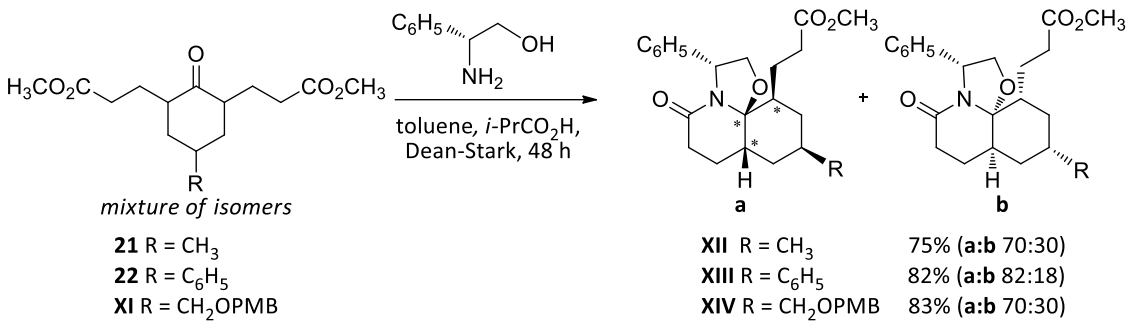


Figure 3.9 Cyclocondensation of 21, 22 and XI

The chiral auxiliary can be easily removed following a two-step procedure. A stereoselective alane reduction of the tricyclic lactam and a catalytic hydrogenation afforded enantiopure *cis*-decahydroquinolines with substituents at the C-6 and/or C-8 positions of the carbocyclic ring (Figure 3.10).

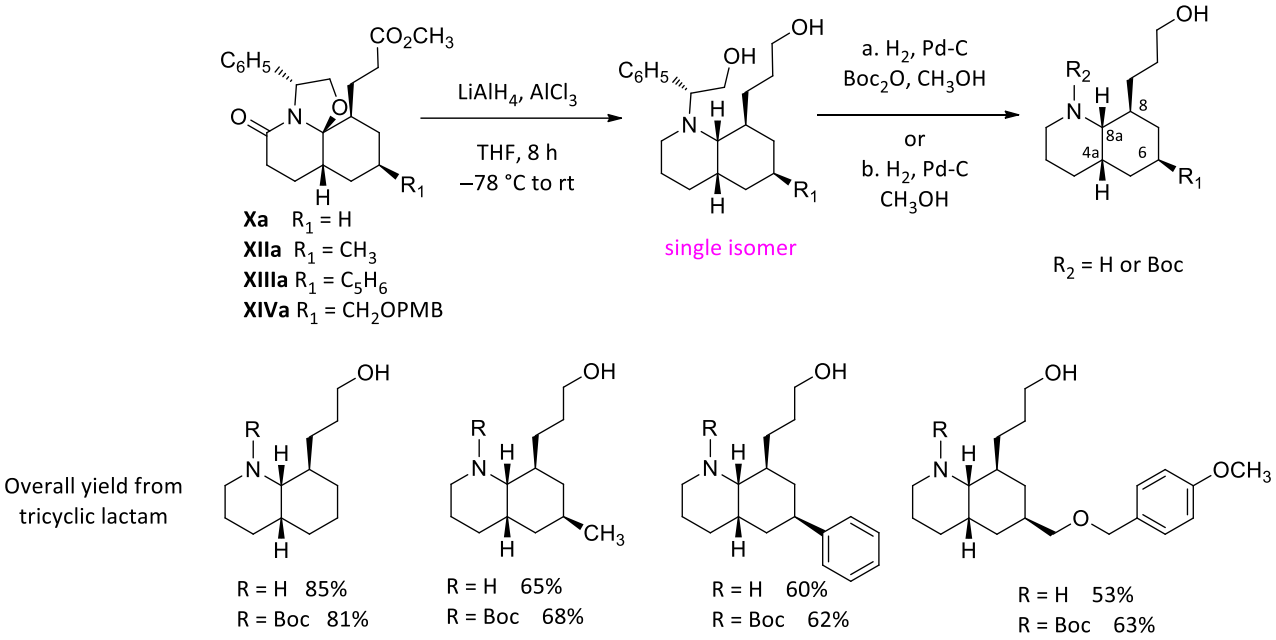
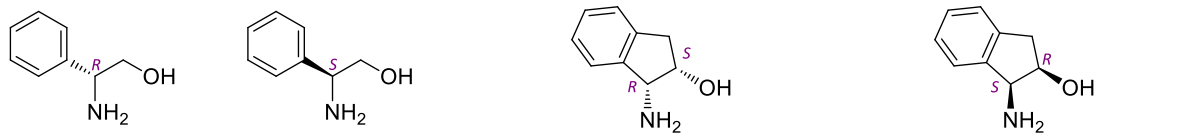


Figure 3.10 Synthesis of C-8 substituted and C-6,8 disubstituted *cis*-decahydroquinolines

This general method allows the straightforward (in only three or four synthetic steps) generation of enantiopure substituted *cis*-decahydroquinoline scaffolds from readily accessible δ-ketoesters.

3.2.2. Studies on the improvement of the procedure for the synthesis of saturated tricyclic lactams from cyclohexanone-2,6-dipropionic acid derivatives and enantiopure aminoalcohols

(*R*)-Phenylglycinol is the most used aminoalcohol in cyclocondensation reactions, affording bicyclic and tricyclic lactams with a high degree of stereoselection.[66] Phenylglycinol is commercially available in both enantiomeric forms and the benzylic nature of the C-N bond allows the removal of the phenylethanol moiety under mild conditions. Since *cis*-aminoindanol, among other chiral amino alcohols,[67] has demonstrated to be a good chiral inductor in stereoselective reactions, we decided to explore its potential. In addition, this aminoalcohol is also available in both enantiomeric forms and the presence of the benzylic function allows its easy removal. The condensed structure of aminoindanol, increases the rigidity of the structure with respect to the phenylglycinol. C*is*-(1*R*,2*S*)-aminoindanol and *cis*-(1*S*,2*R*)-aminoindanol can be finally considered conformationally rigid analogous of (*S*)-phenylglycinol and (*R*)-phenylglycinol respectively.



(*R*)-(-)-2-Phenylglycinol (*S*)-(+)-2-Phenylglycinol (1*R*,2*S*)-(+)-*cis*-1-Amino-2-indanol (1*S*,2*R*)-(-)-*cis*-1-Amino-2-indanol

Figure 3.11

3.2.2.1. Previous results on the use of cis-aminoindanol in cyclocondensation reactions with oxo-esters.

Cis-1-amino-2-indanol has been reported by Kibayashi to be an excellent chiral inductor in the reaction with 5-oxodecanoic acid. A mixture of epimeric lactams was obtained in good yield and stereoselection (92%, 12:1 *dr*).[68]

[66] a. Munchhof, M. J.; Meyers, A. I. *J. Org. Chem.* **1995**, *60*, 7084–7085; b. Meyers, A. I.; Anders, c. J.; Resek, J. E.; Woodal, C. C.; McLaughlin, M. A.; Lee, P. H.; Price, D. A. *Tetrahedron* **1999**, *55*, 8931–8952; c. A. Fréville, S.; Célérier, J. P.; Thuy, V. M.; Lhommet, G. *Tetrahedron Asymmetry* **1995**, *6*, 2651–2654; d. Yamazaki, N.; Ito, T.; Kibayashi, C. T*etrahedron Letters* **1999**, *40*, 739–742; e. Bahajaj, A. A.; Bailey, P. D.; Moore, M. H.; Morgan, K. M.; Vernon, J. M. *J. Chem Soc., Chemm. Commun.* **1994**, 2511–2512; f. Amat, M.; Cantó, M.; Llor, N.; Bosch, J. *Chem. Commun.* **2002**, 526–257.

[67] a. Yamazaki, N.; Dokoshi, W.; Kibayashi, C. *Org. Lett.* **2001**, *3*, 193–196; b. Yamazaki, N.; Ito, T.; Kibayashi, C. *Org. Lett.* **2000**, *2*, 465–467; c. Senanayake, C. H. *Aldrichimca Acta* **1998**, *31*, 3; d. Ghish, A. K.; Fidanze, S.; Senanayake, C. H. *Synthesis*, **1998**, 937–961.

[68] Yamazaki, N.; Ito, T.; Kibayashi, C. T*etrahedron Letters* **1999**, *40*, 739–742.

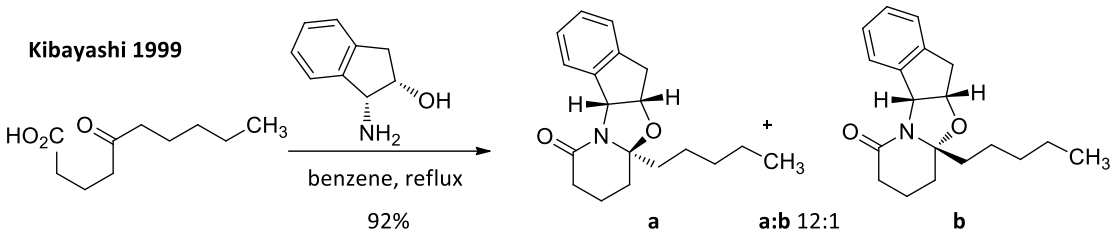


Figure 3.12 Kibayashi reported results

Our group also tested the efficiency of *cis*-aminoindanol, in the cyclocondensation of γ-ketoacids. In particular, reaction of this aminoalcohol with simple 5-oxohexanoic acid **XV** provided tetracyclic lactam **XVI**, as a 91:9 mixture of isomers **a** and **b**, in 99% yield. This excellent result improved considerably that obtained from phenylglycinol (58%, 75:25).[69] It is worth mentioning that the absolute configuration of the piperidine ring is opposite in the two runs, since *cis*-(1*S*,2*R*)-aminoindanol is the analogous of (*S*)-phenylglycinol (Figure 3.13).

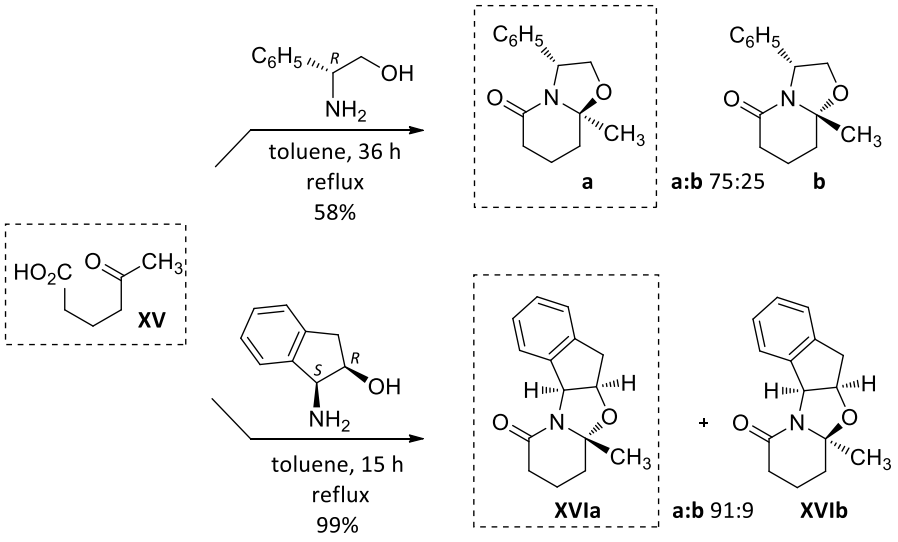


Figure 3.13

Similarly, cyclocondensation of racemic 4-alkyl-5-oxohexanoic acids **XVII** and **XIX** with aminoindanol took place with excellent chemical yields and even better stereoselectivity than when using phenylglycinol. Enantiopure tetracyclic lactam **XVIII** and **XX** were isolated in 61% and 77% yield respectively, thus making evident that dynamic kinetic resolution with epimerization of the stereocenter α to the ketone carbonyl had occurred to a considerable extent (Figure 3.14 and 3.15).

[69] Amat, M.; Bassas, O.; Llor, N.; Cantó, M.; Pérez, M.; Molins, E.; Bosch, J. *Chem. Eur. J.* **2006**, *12*, 7872–7881.

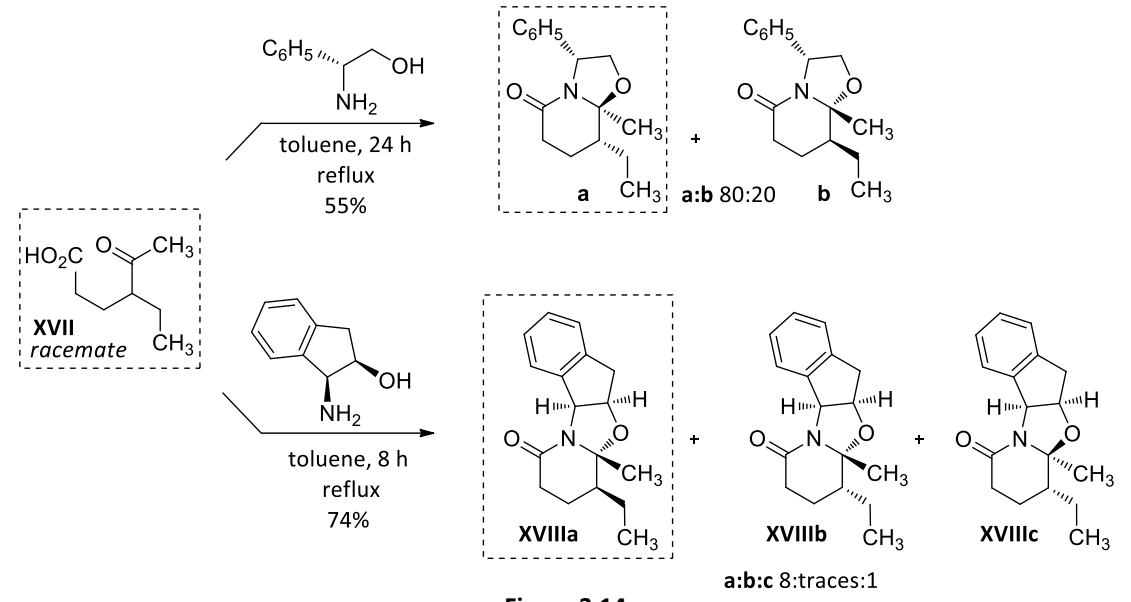


Figure 3.14

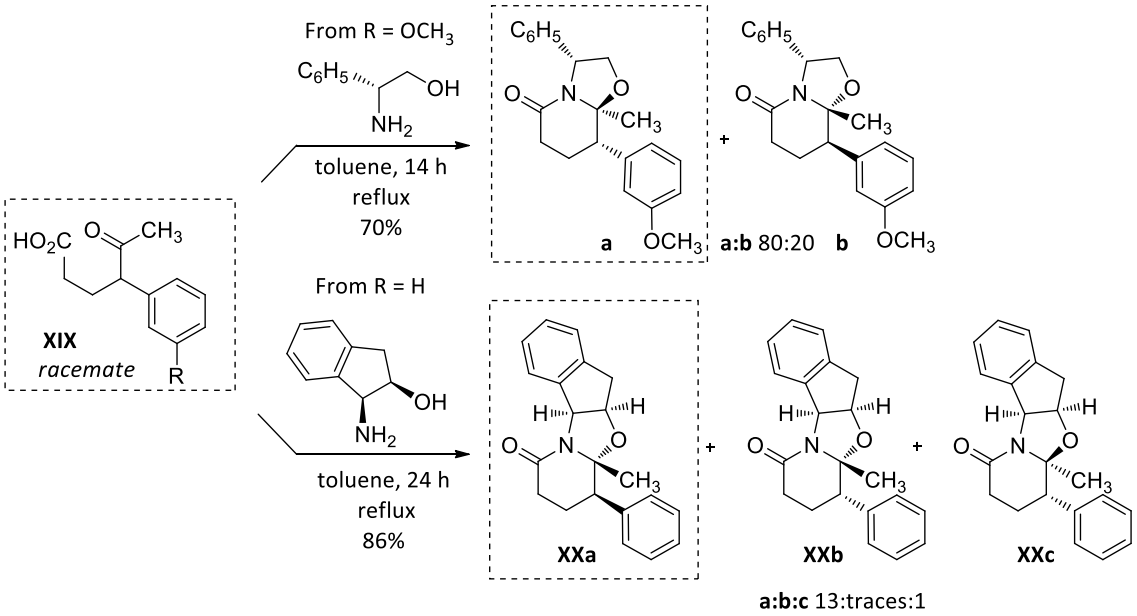


Figure 3.15

3.2.2.2. Present work

Ketoesters **20**-**22** were prepared, *via* enamine alkylation of the corresponding ketones **23**-**25**, as previously described.[70] These compounds were converted into the ketoacids **26**-**28**, by basic hydrolysis in the presence of lithium hydroxide, in water and tetrahydrofuran.

[70] Laura Navìo PhD Thesis, **2011**, Universitat de Barcelona

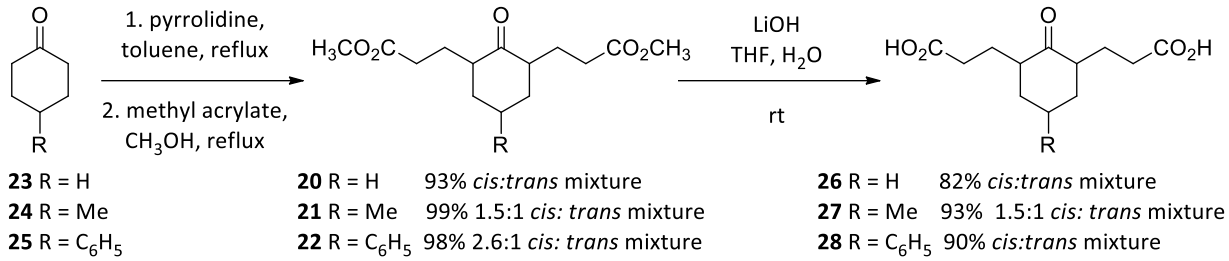


Figure 3.16 Preparation of ketoacids 26-28

Double alkylation in α and α' position of the pyrrolidine enamine of cyclohexanones **23-25** was accomplished by using a polar solvent such as methanol. Apolar solvents, such as dioxane, provide only monoalkylated compounds. The effect of the solvent may be rationalized taking into account that the transition state involves considerable charge separations and its energy should be lower in polar solvent, allowing the second attack. Furthermore, dynamic polar equilibrium should be favoured in polar and protic solvents.

At this point, with the necessary ketoacids **26-28** in hand, we went on testing the efficiency of the their cyclocondensation with *cis*-(1*S*,2*R*)-aminoindanol. Ketodiester **20** was reacted in refluxing toluene, in the presence of isobutyric acid and Dean–Stark apparatus, with aminoindanol. Compound **29** was isolated as inseparable mixture of isomers **a** and **b**, in 82% yield. Although the yield was comparable to that obtained with phenylglycinol, the diastereoisomeric ratio is higher and, noteworthy, the starting material was consumed in only 24 h. We observed that the sequential addition of chiral inductor (1.3 + 1.3 equiv.) to the reaction mixture positively affected the yield. *para*-Toluensulfonic acid caused the immediate precipitation of the chiral inductor as ammonium salt.

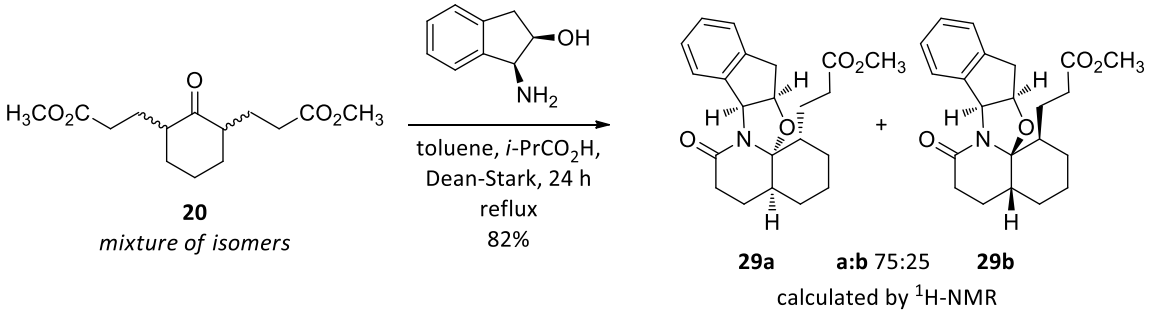


Figure 3.17 Cyclocondensation of ketodiester 20 with *cis*-aminoindanol

On the other hand, the ketoacid **26** reacted with aminoindanol in refluxing toluene, either in the presence of magnesium sulphate or with Dean–Stark apparatus. After 24 h a mixture of two isomers, **30a** and **30b**, in an about 70:30 ratio was isolated. Acids **30a** and **30b** were difficult to purify by column chromatography.

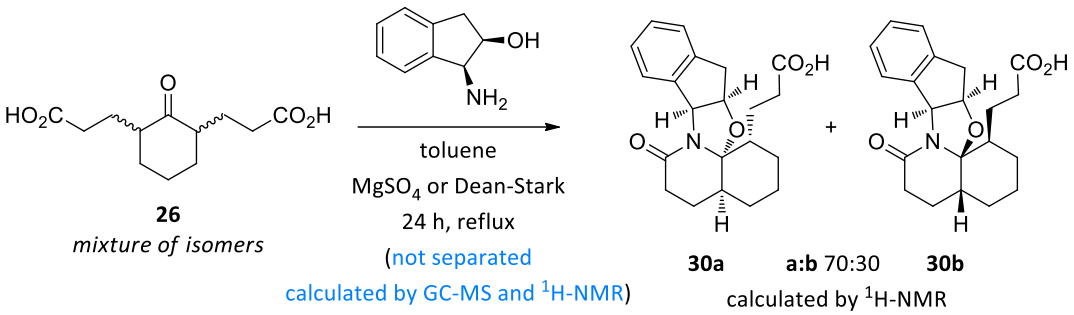


Figure 3.18 Cyclocondensation of 26 with *cis*-aminoindanol

The reaction of ketoester **21** with *cis*-aminoindanol was performed in refluxing toluene and in the presence of isobutyric acid in a Dean–Stark apparatus. After 24 h, a mixture of two lactams, **31a** and **31b**, in 67% of yield and 75:25 *dr* was obtained. Lactams **31a** and **31b** could not be separated by column chromatography and we decided to postpone its separation to the next step. On the other hand, cyclocondensation of oxoacid **27** with aminoindanol in refluxing toluene in the presence of $MgSO_4$ led, after 19 h, to lactams **32a** and **32b** in 60:40 *dr*. It is important to remember that in the correspondent phenylglycinol series, starting from **21**, the diastereoisomeric lactams were isolated in similar yield (75%), but in lower stereoisomeric ratio (70:30).

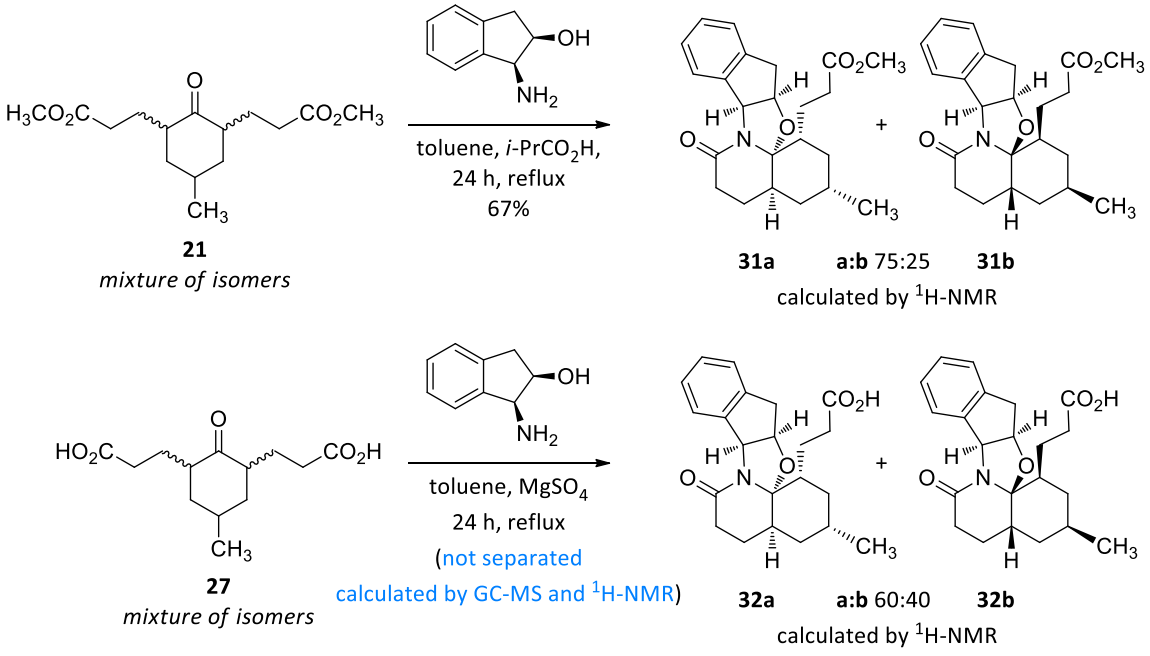


Figure 3.19 Cyclocondensation of 21 and 27 with *cis*-aminoindanol

Similarly, ketoacid **28** afforded lactams **33a** and **33b** as an inseparable 86:14 mixture.

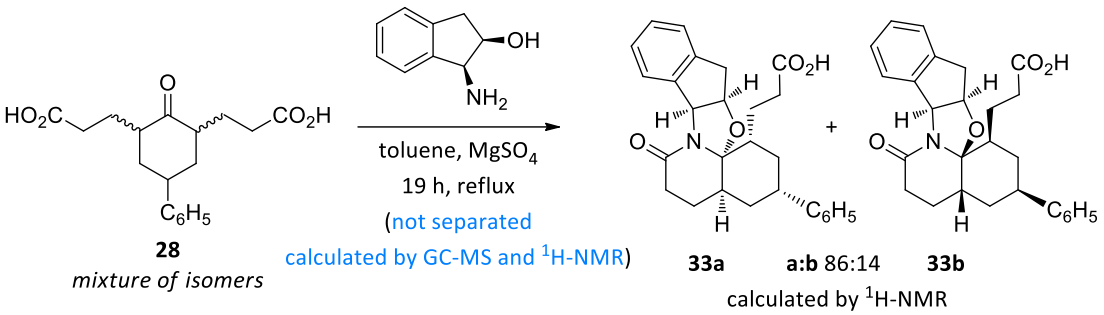


Figure 3.20 Cyclocondensation reaction of 28 with *cis*-aminoindanol

In conclusion, *cis*-aminoindanol constitutes a better chiral inductor in cyclocondensation reactions of cyclohexanone-2,6-dipropionate derivatives and aminoalcohols. The use of ketoesters instead of ketoacids provides better results.

3.2.3. Enantioselective synthesis of 8-substituted *cis*-decahydroquinolines

These good results encouraged us to expand the scope of this methodology by exploring cyclocondensation reactions of 6-alkyl-cyclohexanone-2-propionate derivatives and chiral aminoalcohols. The resulting lactams should provide an easy access to enantiopure 8-substituted *cis*-decahydroquinolines (Figure 3.21).

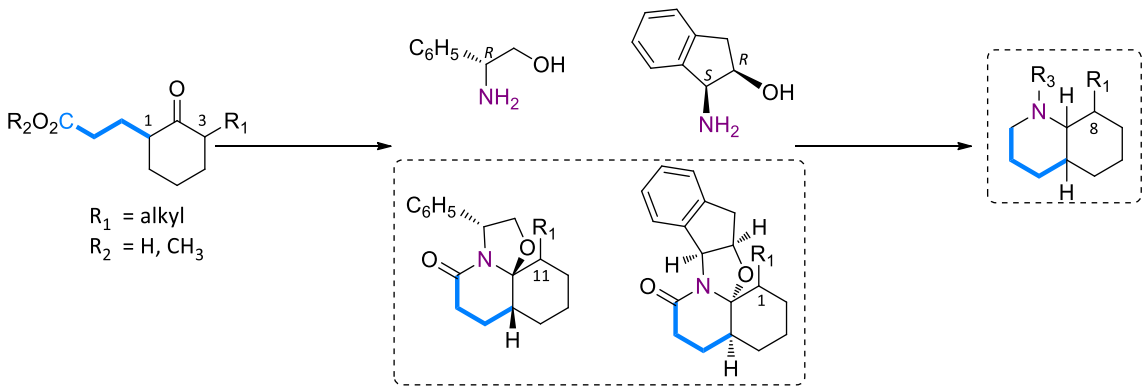


Figure 3.21 Synthetic plan

3.2.3.1. Synthesis of starting materials: preparation of 6-alkyl-cyclohexanone-2-propionate derivatives

Selective α-alkylation of carbonyl compounds, has been largely studied since constitutes an important process for carbon-carbon bond formation. This is a reaction between a nucleophile, an enolate[71,72] or an enamine,[73,74] and an appropriate alkylating agent. Silyl enol ethers are also precursors of enolate anions and represent a good alternative introduced by Stork in 1968.[75,76,77,78]

The formation of enamines was first described by Mannich and Davidson in 1936.[73c] Later Stork and co-workers disclosed the synthetic importance of these intermediates.[79] The alkylation of the pyrrolidine enamine of **34** with methyl acrylate was described by Hickmott[80] and Huffman[81] to provide ketoester **36**.

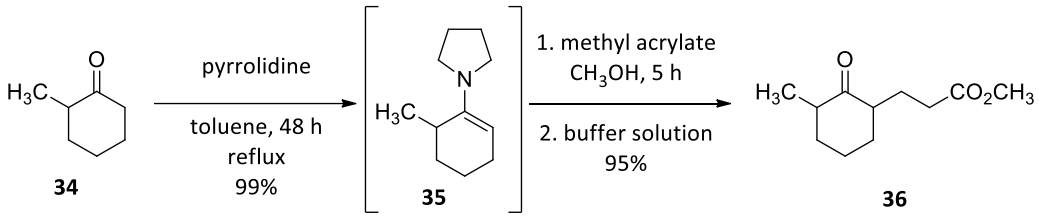


Figure 3.22

[71] a. Coates, R. M.; Hobbs, S. J. *J. Org. Chem.* **1984**, *49*, 140–152; b. Edwards, G. L.; Motherwell, W. B.; Powell, D. M.; Sandham, D. A. *Chem. Commun.* **1998**, 633–640; c. Marouka, K.; Sat, J.; Yamamoto, H. *J. Am. Chem. Soc.* **1992**, *114*, 4422–4423; d. Enholm, E. J.; Whitley, P. E.; Xie, Y. *J. Org. Chem.* **1996**, *61*, 5384–5390; e. Saito, S.; Ito, M.; Yamamoto, H. *J. Am. Chem. Soc.* **1997**, *119*, 611–612; f. Spino, C.; Beaulie, C.; Lafrenière, J. *J. Org. Chem.* **2000**, *65*, 7091–7097; g. Cerichelli, G.; Cerritelli, S.; Chiarini, M.; De Maria, P.; Fontana, A. *Chem. Eur. J.* **2002**, *8*, 5204–5210; h. Doyle, A. G.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2005**, *127*, 62–63; Nishimoto, J. Y.; Onishi, Y.; Yasuda, M.; Baba, A. *Angew. Chem. Int. Ed.* **2009**, *48*, 9131–9135.

[72] For synthesis of cinetic enolates: a. Carey, F. A.; Sundberg, R. J. *Advanced Organic Chemistry* **2007**, 1–62; b. d'Angelo, J. *Tetrahedron* **1976**, *32*, 2979–2990; c. Heatckock, C. H. *Modern Synthetic Methods* **1992**, *6*, 1.

[73] a. Nicewicz, D. A.; MacMillan, D. W. C. *Science*, **2008**, *322*, 77; b. Zhang, L.; Cui, L.; Li, X.; Li J.; Luo, S.; Cheng, J. P. *Eur. J. Org. Chem.* **2010**, 4876–4885; c. Mannich C.; Davidsen H. *Ber. Dtsch. Chem. Ges.* **1936**, *69B*, 2106; d. Stork, G.; Terrell, R.; Szmuszkovicz, J. *J. Am. Chem. Soc.* **1954**, 76, 2029–2030; e. Stork, G.; Landesman, H. K. *J. Am. Chem. Soc.* **1956**, *78*, 5128–5129; f. Storck, G.; Brizzolara, A.; Landesman, H.; Szmuskovicz, J.; Terrell, R. *J. Am. Chem. Soc.* **1963**, *85*, 207–222; g. For a convenient synthetic method: Heyl, F. W.; Herr, M. E. *J. Am. Chem. Soc.* **1953**, *75*, 1918–1920.

[74] Augustine, R. L. *Carbon-Carbon Bond Formation*, ed. Marcelo Dekker, New York, **1979**.

[75] Stork. G.; Hudrlik, P. F. *J. Am. Chem. Soc.* **1968**, *90*, 4462–4464.

[76] For the synthesis of enol silyl ether: a. House, H. O.; Czuba, L. J.; Gall, M.; Olmstead, H. D. *J. Org. Chem.* **1969**, *34*, 2324–2336; b. Fleming, I.; Paterson, I. *Synthesis*, **1979**, 736–737.

[77] For the synthesis of thermodynamic enol silyl ethers: a. 76b; b. House, H. O.; Czuba, L. J.; Gall, M.; Olmstead, H. D. *J. Org. Chem.* **1969**, *34*, 2324–2336.

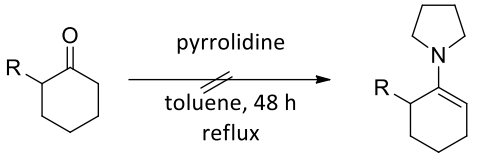
[78] Reactivity of enol silyl ethers with TBAF: Kuwajima, I.; Nakamura, E.; Shimizu, M. *J. Am. Chem. Soc.* **1982**, *104*, 1025–1030.

[79] Stork, G.; Brizzolara, A.; Landesman, H.; Szmuszkovicz, J.; Terrell, R. *J. Org. Chem.* **1963**, *85*, 207–222.

[80] Hickmott, P. W.; Firrell, N. F. *J. Chem. Soc. Perkin I*, **1978**, 340–347.

[81] Huffman, J. W.; Rowe, D.; Matthews, F. J. *J. Org. Chem.* **1982**, *47*, 1438–1445.

Unfortunately, all attempts to form enamines **39** and **40** from commercially available ketones **37** and **38** were unsuccessful and only starting materials were recovered (Figure 3.23). These evidences suggest that in the case of more hindered 2-alkylcyclohexanones the reaction is prevented.



37 R = Et
38 R = Bn

39 R = Et
40 R = Bn

Figure 3.23 Attempts enamine synthesis starting from 37 and 38

Since the use of enamine intermediates resulted to be not a general method for the introduction of a propionate chain on C-2 substituted cyclohexanones, a different procedure had to be found. In this context Mannich reaction, followed by addition of diethyl malonate, was explored. [82]

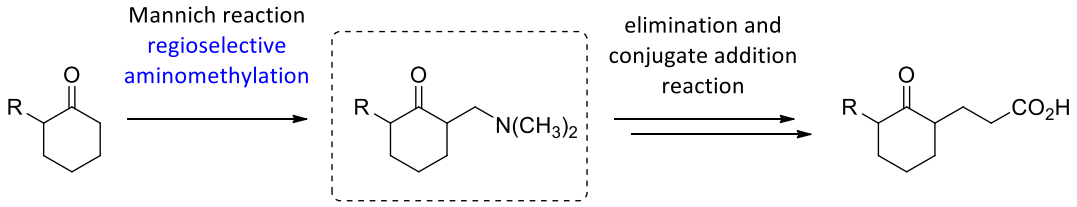


Figure 3.24 Approach to δ-ketoderivatives

In order to test the feasibility of the procedure, amine **41** was prepared following the conditions described by Tietze and Keuper.[83] Then, the β-aminoketone **41** was allowed to react with ethyl malonate and the resulting diester was subjected to hydrolysis and decarboxylation affording ketoacid **42** in 97% of overall yield. [84]

[82] a. Blicke, F. F. *Org. React.* **1942**, *1*, 303; b. Brewster, J. H.; Eliel, E. L. *Org. React.* **1953**, *7*, 99; c. Ahrend, M.; Westerman, B.; Risch, N. *Angew. Chem. Int. Ed.* **1998**, *37*, 1045–1070; d. Kurti, L.; Czakó, B. *Strategic Application of Named Reactions in Organic Synthesis* **2005**, *Ed. Elsevier,* 274–275; e. Schreiber, J.; Maag, H.; Haschimoto, N.; Eschenmoser, A. *Angew. Chem. Int. Ed. Engl.* **1971**, *10*, 330–331; f. Thompson, B. B. *J. Pharm. Sci.* **1968**, *57*, 715–733; g. Benkovic, S. J.; Benkovic, P. A.; Comfort, D. R. *J. Am. Chem. Soc.* **1969**, *91*, 1860–1861; h. Overman, L. E.; Ricca, D. J. *Comprehensive Organic Synthesis* (Eds.: Trost, B. M.; Fleming, I.), *2*, 1007–1046 (Pergamon, Oxford, **1991**).

[83] a. Kinast, G.; Tietze, L. F. *Angew. Chem.* **1976**, *88*, 261–262; b. Kinast, G.; Tietze, L.-F. *Angew. Chem. Int. Ed.* **1976**, *15*, 239; b. Keuper, R.; Risch, N. *Eur. J. Org. Chem.* **1988**, 2609–2615; c. Frank, R. L.; Pierle, R. C. *J. Am. Chem. Soc.* **1951**, *73*, 724–730.

[84] a. du Feu, E. D.; McQuillin, F. J.; Robinson, R. *J. Chem. Soc.* **1937**, 53–60 ; b. House, H. O.; Schellenbaum, M. *J. Org. Chem.* **1963**, *28*, 34–38.

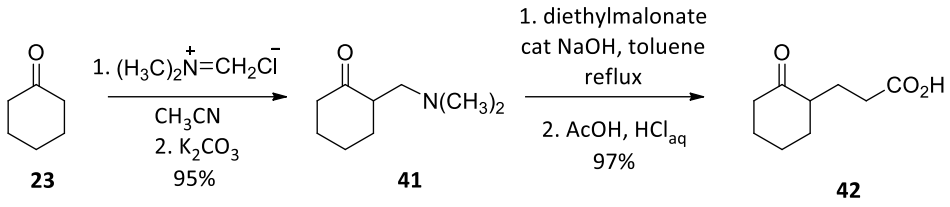


Figure 3.25 Mannich reaction on cyclohexanone 23

Relying on these good results, the sequence was applied to the synthesis of 2,6 substituted amines from commercial 2-alkylcyclohexanones. Unfortunately, the reaction of **34** and **37** with Eschenmoser's salt, in acetonitrile, provided a mixture of two products. In the case of **38** instead only 2,2'-disubstituted **47** was detected (Figure 3.26).

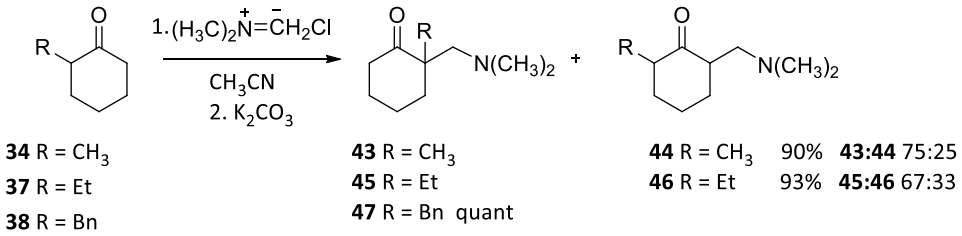


Figure 3.26 Mannich reaction of 34, 37 and 38

Mannich reaction of enol silyl ethers

The reaction of trimethylsilyl enol ether **XXI** with the Eschenmoser's salt has been reported by Danishefsky in 1976[85] to provide efficiently Mannich base **41**, after hydrolysis of the silyl enol ether with hydrochloric acid.

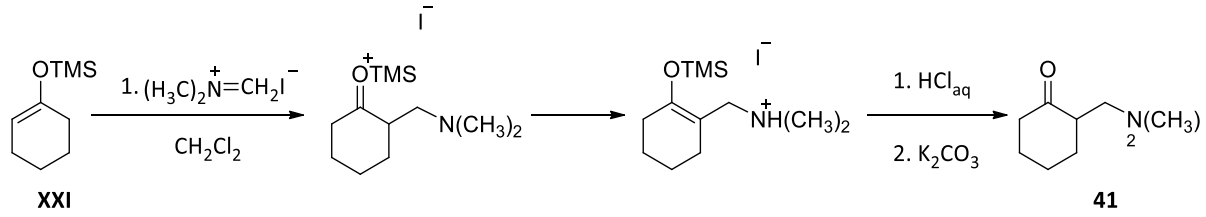


Figure 3.27 Danishefsky modification of Mannich reaction

Later on, in 1980,[86] the same authors described the synthesis of amines **43** and **44** from enol silyl ethers **XXII** and **48** respectively: the two silyl enol ethers react with the Eschenmoser's salt very fast, with no loss of regiospecificity.

[85] Danishefsky, S.; Kitahard, T.; McKee, R.; Schuda, P. F. *J. Am. Chem. Soc.* **1976**, 6715–6717.
[86] Danishefsky, S.; Prisbylla, M.; Lipisko, B. *Tetrahedron Letters* **1980**, *21*, 805–808.

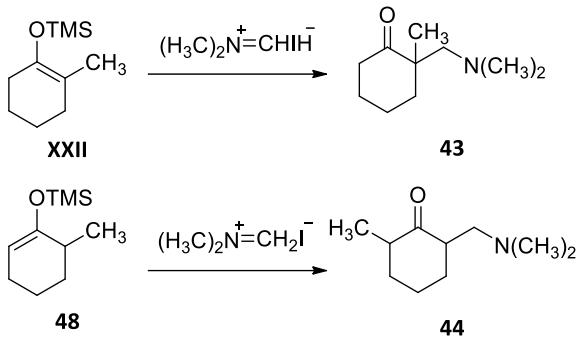


Figure 3.28 Danishefsky modification applied to asymmetric ketones

Following the reported conditions,[87] we regioselectively obtained the silyl enol ether **48**, which rapidly was made to react with the chloride of the Eschenmoser's salt to give the desired regioisomer **44** as mixture of stereoisomers. Notably, using the corresponding iodine salt the regioselectivity was not complete.

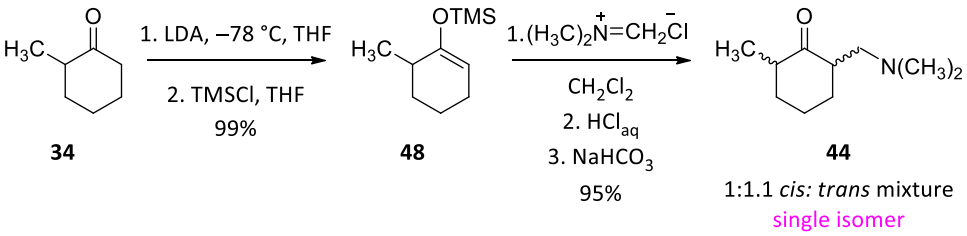


Figure 3.29 Synthesis of Mannich base 44

As expected, the reaction of the β-amino-ketone **44** with dimethyl malonate followed by a hydrolytic treatment of the reaction mixture gave the desired δ-ketoacid **49** in 86% overall yield. The mayor, and hence more stable, isomer was assigned to be *cis*, in which both substituents are equatorial.

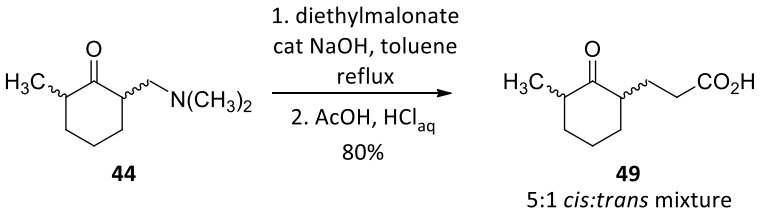
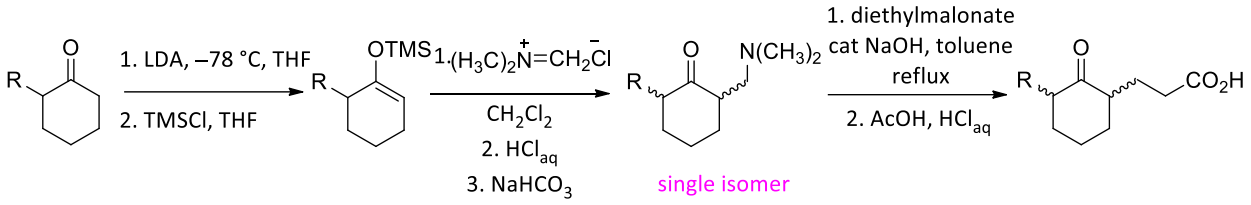


Figure 3.30 Synthesis of δ-ketoacid 49

In the same way, we obtained new δ-ketoacids **53**, which exhibits an ethyl substituent at C-6 of cyclohexanone, and **54**, with a 6-benzyl substituent, in very good yields as a mixture of two enantiomeric pairs.

[87] House, H. O.; Czuba, L. J.; Gall, M.; Olmstead, H. D. *J. Org. Chem.* **1969**, *34*, 2324–2336.



37 R = Et
38 R = Bn

50 R = Et 96%
51 R = Bn 99%

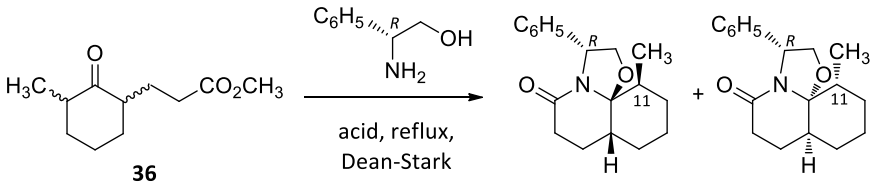
46 R = Et 98%
2:1 *cis:trans* mixture
52 R = Bn 90%
cis:trans mixture

53 R = Et 84%
2:1 *cis:trans* mixture
54 R = Bn 94%
3:1 *cis:trans* mixture

Figure 3.31 Synthesis of δ-ketoacids 53 and 54

3.2.3.2. Cyclocondensation reactions of 3-substituted 2-oxocyclohexanepropionate derivatives with (R)-phenylglycinol.

In order to explore the synthetic potential of our method, the reaction of 3-substituted 2-oxocyclohexanepropionate derivatives with (*R*)-phenylglycinol was studied. Ketoester **36** was first tested and the results are summarized in Table 3.1.



36
mixture of isomers

55a **55b**

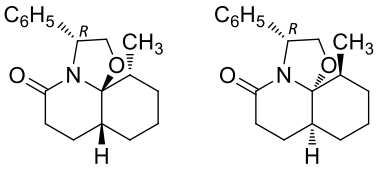
	equiv. PG	solvent	t[a]	add	y%	**a:b**
1	2.3	Toluene	48h	Isob. acid	15	-[b]
2	1.3+1.3	Toluene	24h	Isob. acid	60	66:34[c]
3	2.3	Toluene	48h	AcOH	41	68:32[c]
4	1.3 + 1.3	Toluene	48h	AcOH	61	67:33[c]
5	2.3	Toluene	48h	*p*-TsOH	10	-[b]
6	2.3	Benzene	48h	AcOH	38	75:25[c]
7	1.3+1.3	Benzene	48h	AcOH	57	75:25[c]
8	2.3	Benzene	48h	Isob. acid	10	-[b]
9	2.3	Benzene	48h	*p*-TsOH	15	-[b]

a. Evolution of reaction controlled by TLC; b. not separated (GC-MS); c. Calculated from isolated product, after chromatography column.

Table 3.1 Cyclocondensation reaction of ketoester 36 with (*R*)-phenylglycinol

The cyclocondensation reaction of **36** with (*R*)-phenylglycinol in refluxing toluene (0.1 M solution) in the presence of 1.5 equivalents of an acid (more than 1.5 equivalents of acid provoked a decrease of the yield)

using a Dean–Stark apparatus, provided isomers **55a** and **55b** (entry 1-5). In some runs, trace amounts of other two diastereosiomers, **55c** and **55d**, could be identified (Figure 3.32).

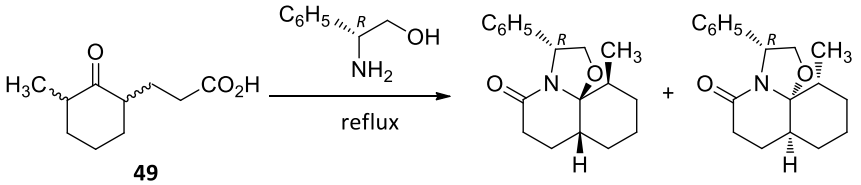


55c **55d**

Figure 3.32 Minor by-products in cyclocondensation

On the other hand, the stereoselectivity was improved when benzene was used, instead of toluene, although the chemical yields were similar. When *para*-toluensulfonic acid was employed, very low yields are obtained, probably because of its higher acidity that could provoke the protonation of the amine group of phenylglycinol. Isobutyric acid and acetic acid have a similar pK_a (4.86 and 4.76 respectively), but acetic acid is more effective. On the other hand, when phenylglycinol is added portionwise (1.3 +1.3 equiv.) the yield increased, although the stereoselectivity remained unchanged. The use of dichloromethane resulted in the recovery of starting material and the addition of FEP (2-fluoro-1-ethyl pyridinium tetrafluoroborate), that is described to be effective for the synthesis of peptides and to favor the lactamization process under mild condition,[88] was ineffective.

In order to compare the effect of using a keto-acid, instead of a keto-ester, in the cyclocondensation reaction, we subjected compound **49** to the conditions indicated in Table 3.2.



49
mixture of isomers

55a **55b**

	solvent	t[a]	add	y%	**a:b**
1	Toluene	48h	-	76	75:25[c]
2	Toluene	24h	$MgSO_4$[b]	89	67:33[c]
3	Benzene	48h	-	51	72:28[c]
4	Benzene	24h	$MgSO_4$	52	70:30[c]

a. Evolution of reaction controlled by NMR; b. 2 equivalents of magnesium sulphate; c. Calculated from isolated product, after column chromatography.

Table 3.2 Cyclocondensation reaction of ketoacid 49 with (*R*)-phenylglycinol

[88] a. Li, P.; Xu, J. C. *Tetrahedron*, **2000**, *56*, 8119–8131; b. Penhoat, M.; Bohn, P.; Dupas, G.; Papamicaël, C.; Marsais, F.; Levacher, V. *Tetrahedron Asymmetry* **2006**, *17*, 281–286; c. Penhoat, M.; Leleu, S.; Dupas, G.; Papamicaël, C.; Marsaia, F.; Levacher, V. *tetrahedron Letters* **2005**, *46*, 8385–8389; d. Bouet, A.; Oudeyer, S.; Dupas, G.; Marsais, F.; Levacher, V. *Tetrahedron Asymmetry* **2008**, *19*, 2396–2401.

The reaction was performed in a Dean–Stark apparatus or in the presence magnesium sulfate that acts as dehydrating agent. Starting from keto-acids, the addition of an acid was not necessary. Using toluene as a solvent resulted in higher yield and, surprisingly, similar stereoselectivity in comparison with benzene; albeit addition of magnesium sulphate decreased significantly the reaction time (from 48h to 24h), and entry 2, 4) and increased slightly the global yield, it negatively affected the ratio between the isomers. In addition, in these assays, we detected the formation of small amounts of isomers **55c** and **55d**. In previous runs, we used a 0.1 M solution of keto-acid in the corresponding solvent. We then decided to study the influence of concentration and we observed that for higher concentrations (0.2, 0.3, 0.5 M), **49** was scarcely soluble, while lower concentrations (0.08, 0.05 M) did not improve our previous results. MW irradiation has been reported to be an alternative to conventional heating, showing benefits in terms of yield and kinetics for many chemical transformations such as cyclocondensation reactions with amino-alcohols (84-97% yield).[89] Thus, the reaction in the absence of solvent or using toluene, benzene as well as other more suitable *medium* for MW, such as DMSO and chlorobenzene, was studied. In order to capture the water formed in the process, dehydrating agents ($MgSO_4$, Na_2SO_4 and montmorillonite[90]) were added. Finally, the influence of the reaction time was also evaluated. Despite in some runs we observed good results (64% yield, 75:25 *dr*, the best one), we could not reach the yields observed under the conventional reaction conditions indicated in Table 3.2. Finally, in 2013, Deprez reported good results in water-based (water or a water-ethanol mixture) cyclocondensation reactions.[91] However, when keto-acid **49** was subjected to conditions described by Deprez, the desired product was not formed probably because of the low solubility of our starting material in water.

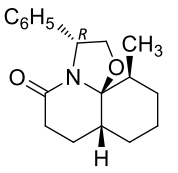
It could be concluded that the best conditions, which represent an optimal compromise between yield and stereoselectivity, are those reported in entry 1, Table 3.2, for which lactam **55a** was purely obtained in 57% of yield and its isomer **55b** was isolated in 19% of yield, starting from ketoacid **49**.

The absolute configuration of lactams **55a** and **55b** was unambiguously determined by X-ray crystallography, keeping in mind that pure (*R*)-phenylglycinol was used in the process.

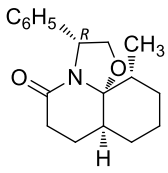
[89] Jida, M.; Deprez-Poulain, R.; Malaquin, S.; Roussel, P.; Agbossou-Niedercorn, F.; Deprez, B.; Laconde, G. *Green. Chem.* **2010**, *12*, 961–964.

[90] Montmorillonite is a very soft phyllosilicate. It is reported its use as catalyst and in micro-way assisted process is reported as a good dehydrating agent: montmorillonite swell in presence of water, which is trapped in the interlayer molecular spaces of this mineral.

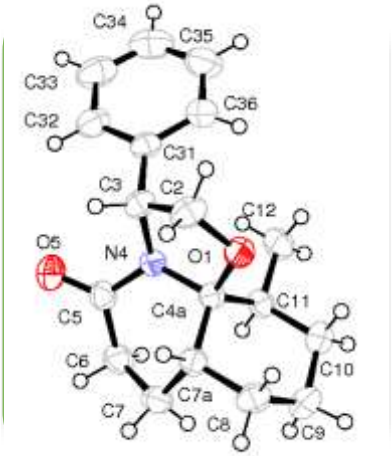
[91] Malaquin, S.; Jida, M.; Courtin, J.; Laconde, G.; Willand, N.; Deprez, B.; Poulain-Deprez, R. *Tetrahedron Letters* **2013**, *54*, 562–567.



55a



55b



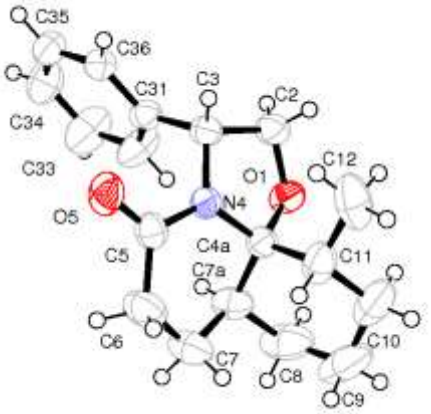
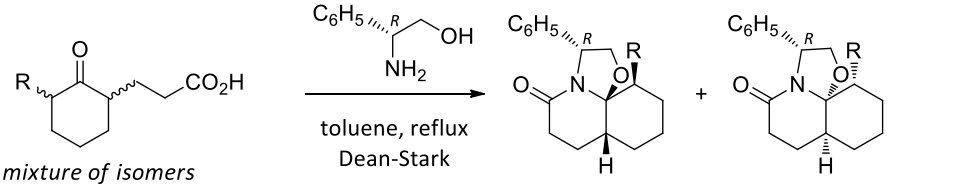


Figure 3.33 X-ray structure for lactam 55a and 55b

Next, the cyclocondensation reaction of acids **53** and **54**, with (*R*)-phenylglycinol was performed under the optimized reaction conditions.



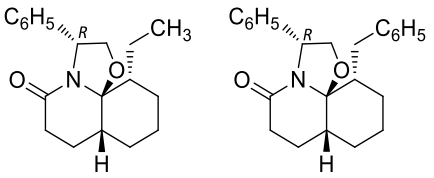
53 R = Et
54 R = Bn

56a R = Et **56b** 70% **a:b** 75:25
57a R = Bn **57b** 72% **a:b** 70:30

Figure 3.34 Cyclocondensation starting from 53 and 54

Starting from **53**, with an ethyl substituent at C-6 position, the reaction led to a mixture of diastereoisomeric lactams, **56a** and **56b** in 73:27 *ratio* in 70% global yield; small amounts of lactam **56c** (C-11 epimer of **56a**) were also detected. The reaction took place in 48 h, in refluxing toluene with removal of water with a Dean–Stark apparatus.

The benzyl group in ketoacid **54** did not affect the stereoselectivity and the chemical yield, with respect methyl group. We isolated lactams **57a** in 53% yield, and its stereoisomer **57b** in 21% yield; only traces of minor lactam **57c** (C-11 epimer of **57a**) were detected.



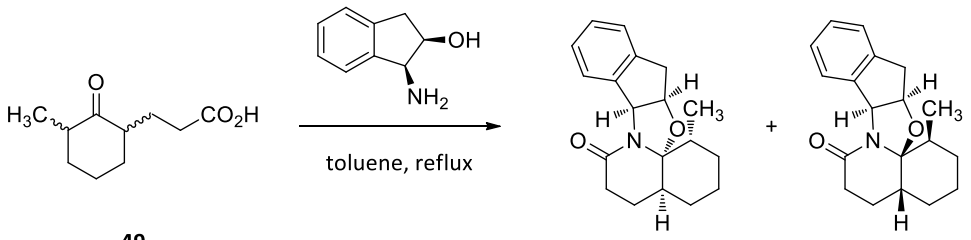
56c **57c**

Figure 3.35

The absolute configuration of the stereocenters of **56a**, **57a**, **56b** and **57b** was assigned by comparison of their spectroscopic data with those observed for **55a** and **55b**.

3.2.3.3. Cyclocondensation reactions of 6-substituted cyclohexanone-2-propionate derivatives with (1S,2R)-2-aminoindanol.

At this point, the stereoselectivity of cyclocondensation reaction of 6-substituted cyclohexanone-2-propionate derivatives with *cis*-aminoindanol as chiral inductor was explored.



49
mixture of isomers

58a **58b**

	t	add	y%	**a:b**[a]
1	48h	-	64	88:12
2	24h	$MgSO_4$	78	90:10

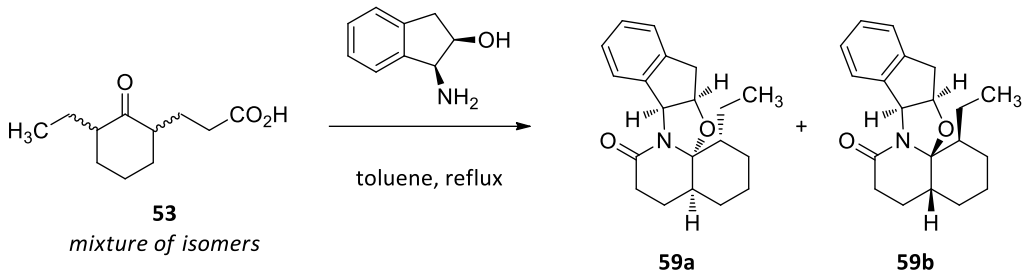
a. Calculated by ^{1}H-NMR.

Table 3.3 Cyclocondensation reaction with *cis*-aminoindanol

In entry 1, the reaction was carried out by heating a toluene solution of **49** with *cis*-aminoindanol in a Dean–Stark apparatus. Although the global yield was lower with respect to that obtained with phenylglycinol, the diastereoselectivity was higher (88:12 in this run, 74:26 when phenylglycinol was used). When magnesium sulfate was used to capture the water, instead of the Dean–Stark apparatus (entry 2), the time of reaction was drastically reduced (from 48h to 24h) and the chemical yield and the stereoselectivity were higher: we obtained a mixture of **58a** and **58b** in a 9:1 ratio, which represents a significant improvement.

It is worth mentioning that *trans*-aminoindanol, also commercially available, when subjected to a cyclocondensation reaction with keto-acid **49** under the optimized conditions afforded a mixture of diastereoisomers in low stereoselectivity.

Reaction of ketoacid **53** with *cis*-(1*S*,2*R*)-2-aminoindanol in a toluene solution containing magnesium sulfate, provided lactams **59a** and **59b** in only 24 h and in better yield and stereoselectivity (78% with 78:22 *dr*) than when using phenylglycinol.



53
mixture of isomers

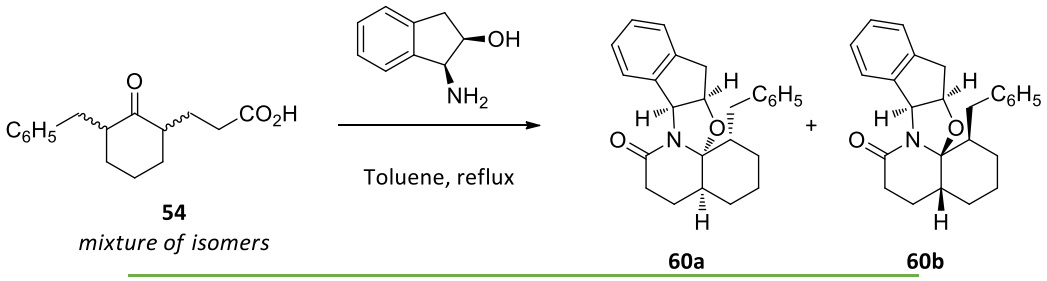
59a **59b**

	t	add	y%	**a:b**[a]
1	48h	-	62	75:25
2	24h	$MgSO_4$	78	78:22

a. Calculated by ^{1}H-NMR.

Table 3.4 Cyclocondensation of 53 with *cis*-aminoindanol

Finally, the reaction of **54** with *cis*-aminoindanol under the optimized conditions provided lactam **60a** in excellent yield and good stereoselectivity (95% of global yield, 85:15 *dr*),



54
mixture of isomers

60a **60b**

	t	add	y%	**a:b**[a]
1	48h	-	93	80:20
2	24h	$MgSO_4$	95	85:15

a. Calculated by ^{1}H-NMR.

Table 3.5 Cyclocondensation of 54 with *cis*-aminoindanol

In all the above cases, pure pentacyclic lactams could not be isolated, and mixtures of the two diastereoisomeric compounds were described. This drawback does not represent any problem under a synthetic point of view, since in the next step the major isomer could be efficiently separated.

In conclusion, the cyclocondensation of 6-substituted cyclohexanone-2-propionate derivatives **49**, **53** and **54** with phenylglycinol or *cis*-aminoindanol stereoselectively provided one isomer of the eight possible diastereoisomeric lactams (**55a**, **56a**, **57a**, **58a**, **59a**, and **60a**). In these essays, the use of *cis*-aminoindanol significantly improved the stereoselectivity and the chemical yield, with respect to reaction with (*R*)-phenylglycinol. On the other hand, changing phenylglycinol for *cis*-aminoindanol in the cyclocondensation reaction of 4-substituted cyclohexanone-2,6-dipropionate derivatives **20**, **21** and **28**, leading to **29a**, **31a**, or **32a**, also improved the stereoselectivity but in a lower extension (Figure 3.18 to 3.20).

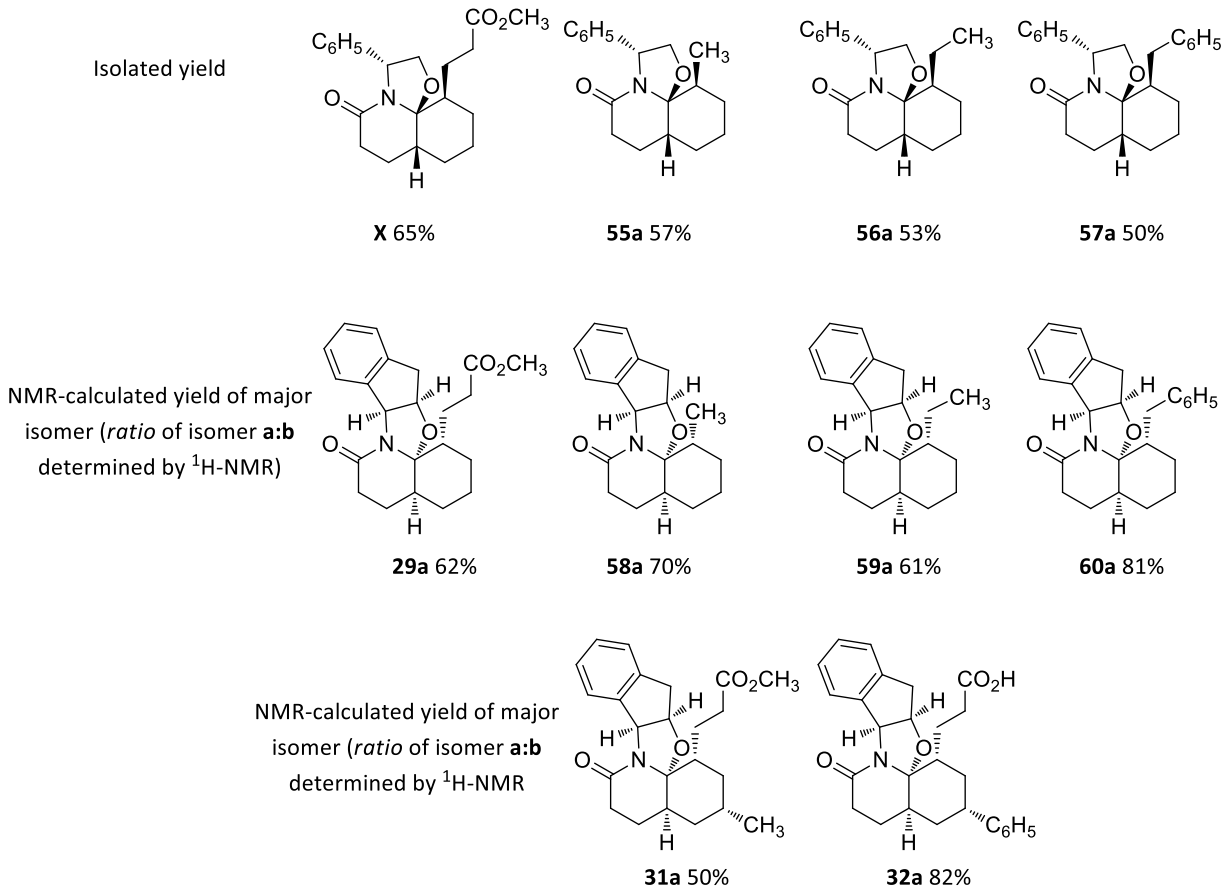


Figure 3.36 Major lactams resulted from cyclocondensation reactions

3.2.3.4. Mechanistic hypothesis.

The above procedure allows the preparation of enantiopure tricyclic or pentacyclic lactams starting from a mixture of stereoisomeric 6-substituted cyclohexanone-2-propionic acids and pure (*R*)-phenylglycinol or (1*S*,2*R*)-aminoindanol. In these reactions, initially, a mixture of eight diastereoisomeric oxazolidines, which are in equilibrium through the corresponding imine-enamines, may be formed. Consequently, the subsequent lactamization could lead to a mixture of eight diastereoisomeric lactams (Figure 3.37).[92,93] However, the lactamization step takes place under kinetic control, stereoselectively leading to the isomer which is formed faster.

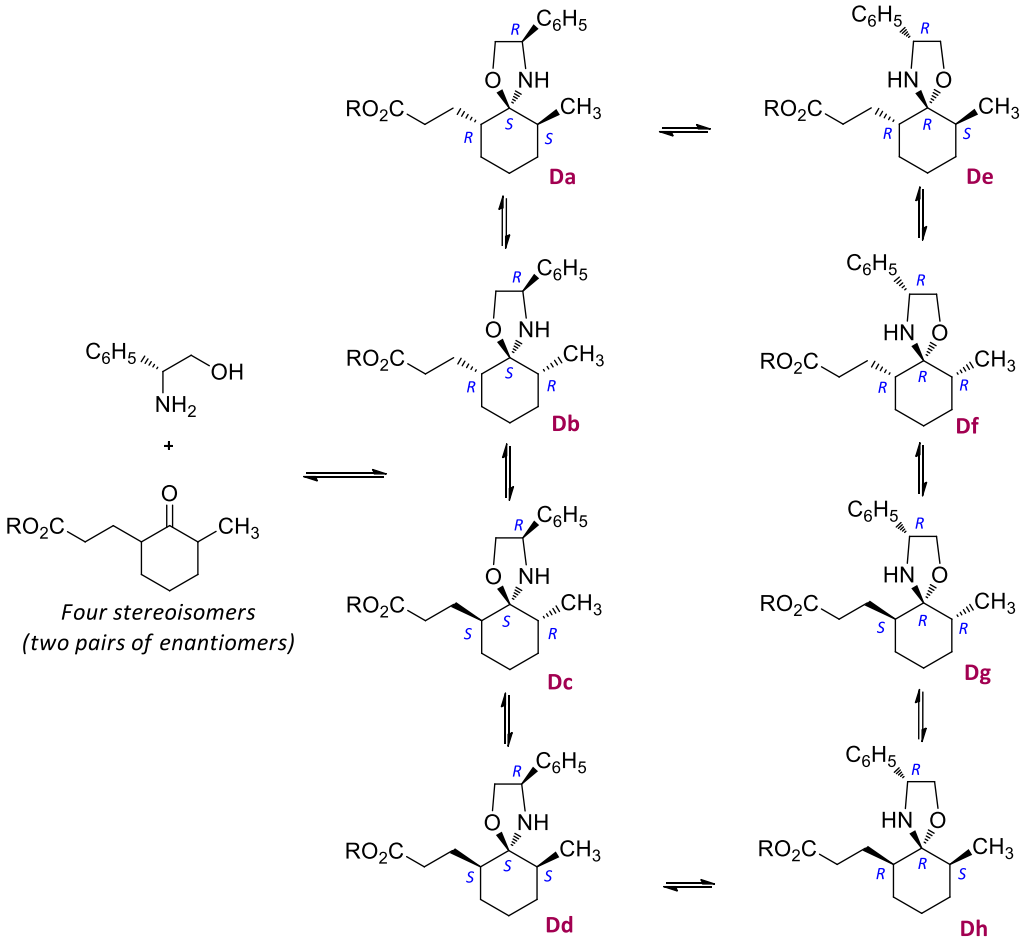


Figure 3.37 Eight possible diastereoisomeric oxazolidines

Thus, a dynamic kinetic resolution, through the isomerization of the configurationally labile stereocenters of the substrate takes place, stereoselectively leading to one isomer starting from a mixture of stereoisomers.

[92] In the case of 5-substituted-2-cyclohexanedipropionate derivatives, four or eight diastereoisomeric oxazolidine could be formed, and these structures had been already disclosed in Laura Navío PhD Thesis, **2011**, Barcelona.
[93] For the general complete proposed mechanism see Paragraph 3.2.1 of the present Thesis. Furthermore, these consideration can be applied to *cis*-aminoindanol series.

In order to rationalize the observed stereoselectivity, previous experimental results may be considered.[94] The reaction between (*R*)-phenylglycinol and racemic δ-oxo esters, with a labile stereocenter at C-4, led to bicyclic lactams in which the phenyl group and the substituents R_1 and R_2 are in a *cis* relative configuration. This result can be accounted for by considering that the lactamization of the diastereoisomeric oxazolidines occurred faster from the C-2 isomer of the oxazolidine ring that allows the approach of the carboxylate to the nitrogen from the less hindered face (opposite to the phenyl), *via* a chair-like transition state in which R_2 is equatorial (Figure 3.38).

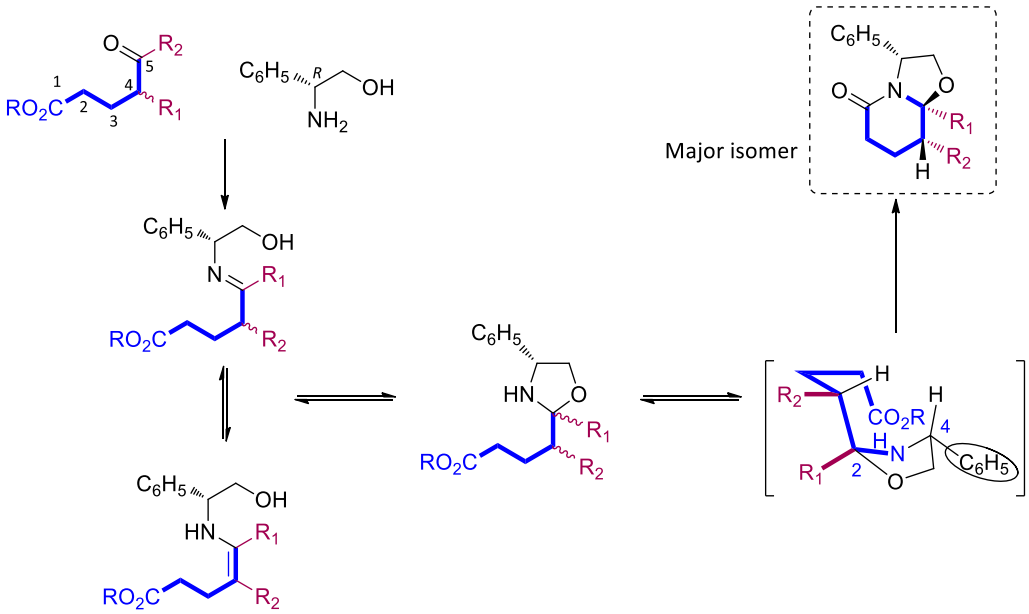


Figure 3.38

It is noteworthy that the formation of the *trans* isomers was never detected, due to the great annular tension in the final compound. Thus, if the C-O bond adopts a pseudo-axial valence (**E**), the oxazolidine ring would be highly strained due to the planarity and the conformational rigidity of the amide bond. Conformation **F** is not possible for geometrical reasons, as in *trans*-decaline systems. (Figure 4.39).

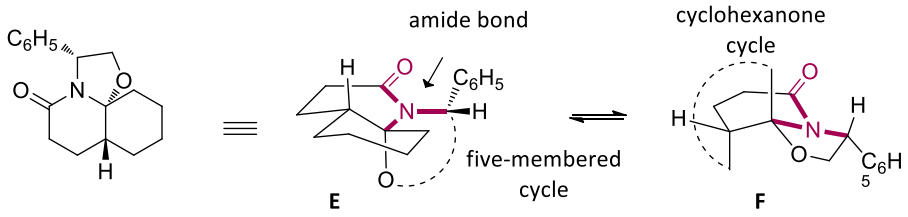


Figure 3.39 Tension in *trans*-decahydroquinolines

[94] a. Amat, M.; Llor, N.; Escolano, C.; Molins, E.; Bosch, J. *J. Org. Chem.* **2002**, *67*, 5343–5351; b. Bassas, O.; Llor, N.; Santos, M. M.; Griera, R.; Molins, E.; Amat, M.; Bosch, J. *Org. Lett.* **2005**, *7*, 2817–2820; c. Amat, M.; Bassas, O.; Pericàs, M. A.; Bosch, J. *Chem. Commun.* **2005**, 1327–1329.

In Figures 3.40 to 3.43 the transition state of the lactamization step leading to the eight possible isomeric lactams, through the corresponding oxazolidine is depicted.

Starting from oxazolidine **Da**, irreversible lactamization involves the approximation of the carboxylate from the less-hindered face, *anti* with respect to the phenyl group, and an equatorial disposition of the alkyl substituent (methyl in Figure 3.40), with respect to the cyclohexane ring, leading to lactam *cis*-A. However, in oxazolidine **Db** the methyl substituent on the carbocyclic ring is in axial position and, for this reason, is less favorable.

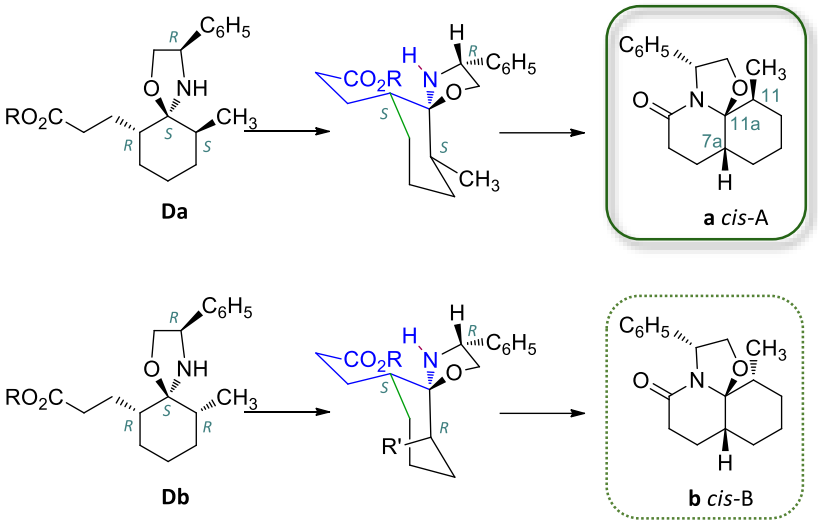


Figure 3.40

The formation of minor isomer *cis*-C can be explained through lactamization from the isomeric oxazolidine **Dg**, in which the alkyl substituent on the carbocyclic ring is in an equatorial position. However, in this case, the approximation of the carboxylate takes place from the more hindered face. Due to this fact, the reaction is slower than in the case of **Da** and isomer *cis*-C was isolated in lower yield.

Oxazolidine **Dh** leads to tricyclic lactam *cis*-D, through approximation of the carboxylate chain from the less favorable face as in **Dh**; furthermore the methyl substituent is in axial position and for this reason *cis*-D is isolated in traces amounts.

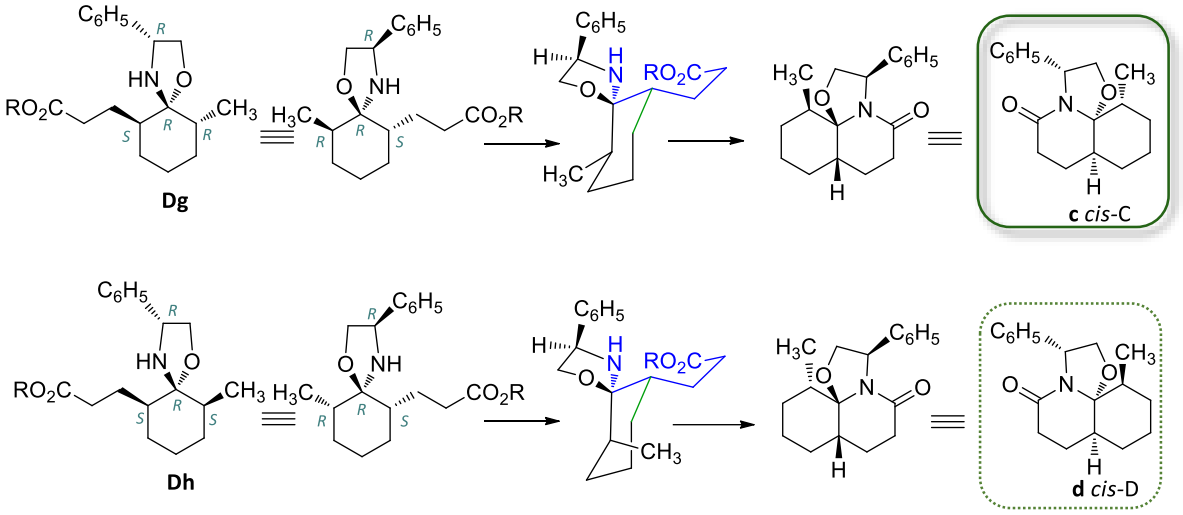


Figure 3.41

Finally, lactamization from the diastereoisomeric oxazolidines **De**, **Df**, **Dd** and **Dc** does not take place since *trans*-isomers would be formed.

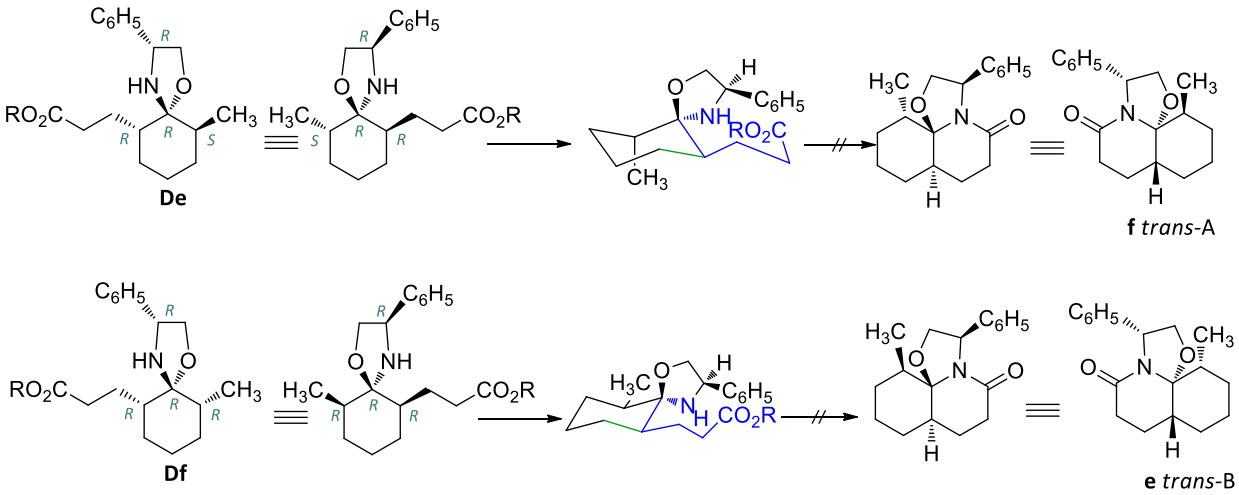


Figure 3.42

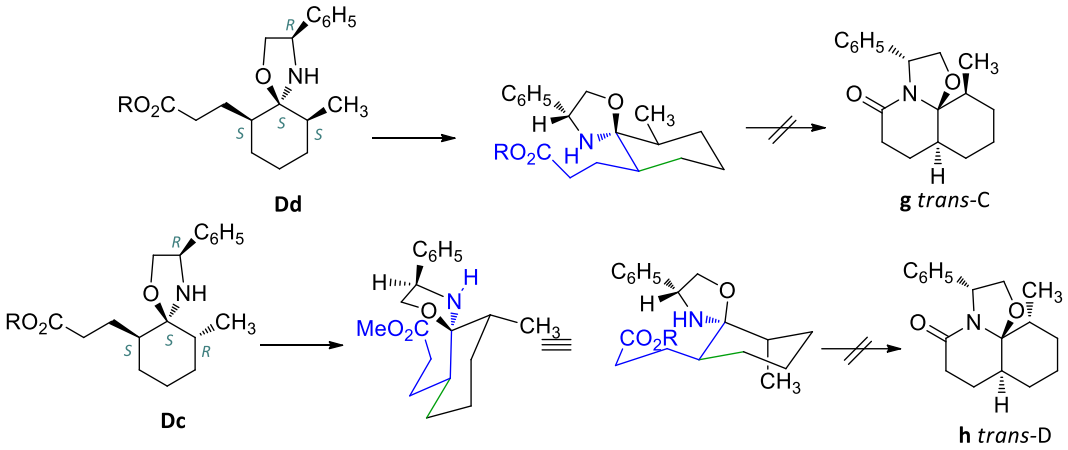


Figure 3.43

The higher rigidity of the oxazolidine ring and of the C-phenyl bond in *cis*-aminoindanol-derived lactams, in comparison with phenylglycinol-derived ones, play a crucial role in the greater selectivity observed for the first aminoalcohol. The oxazolidine ring in the phenylglycinol series, presents higher flexibility, which makes the lactamization step slower and less stereoselective. On the other hand, in the *cis*-aminoindanol series, the C-phenyl bond cannot rotate and the whole structure is more rigid, increasing thus the rate and the stereoselection of the lactamization.

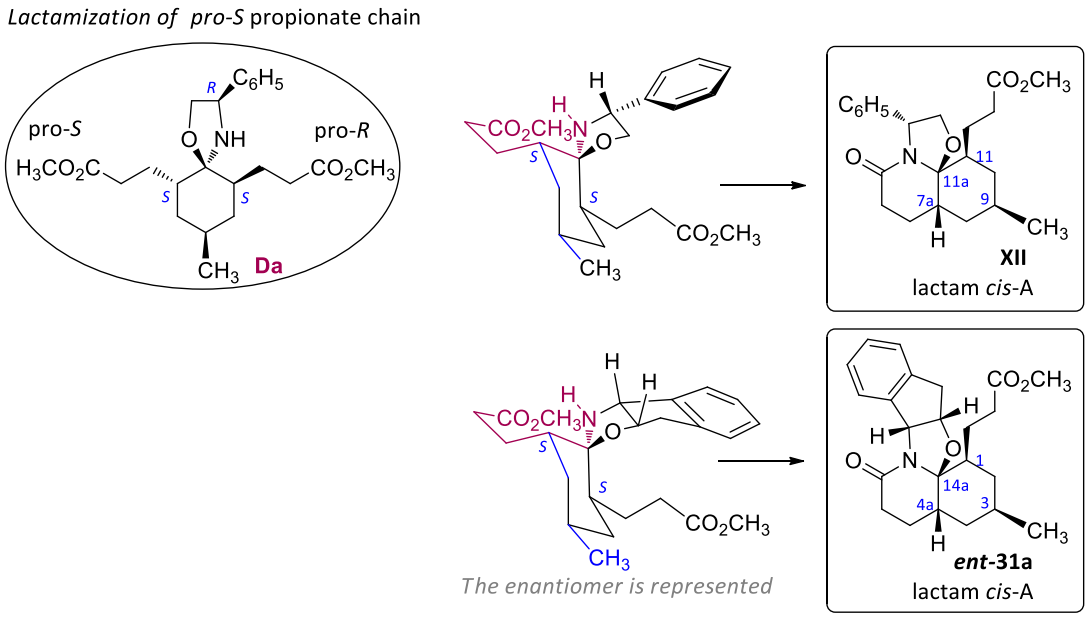


Figure 3.44

3.2.3.5. Enantioselective synthesis of cis-decahydroquinolines from tricyclic lactams.

The above described tricyclic and pentacyclic lactams are precursors of C-8 (and C-6,8) substituted *cis*-decahydroquinolines. The conversion required the stereoselective reductive cleavage of C-O oxazolidine bond, reduction of lactam carbonyl group and debenzylation (Figure 3.45).

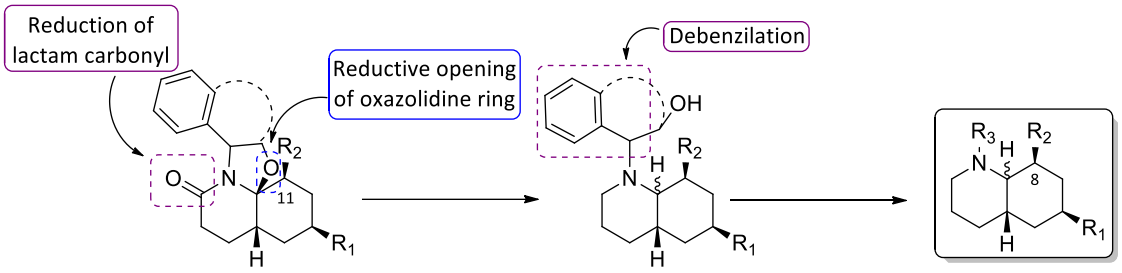
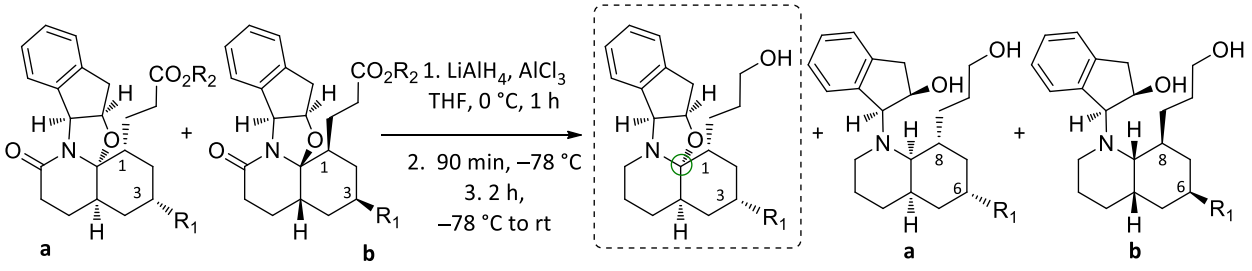


Figure 3.45 Approximation to 6,8-dialkyldecahydroquinolines

The key step is the reductive opening of the oxazolidine ring: it might have been expected that the presence of an alkyl chain next to the C-O bond to be reductively cleaved, could affect the stereoselectivity of the reaction.

Among the different boron and aluminum hydride derivatives ($LiAlH_4$, AlH_3, BH_3, Red-Al, 9-BBN), the mixture of $AlCl_3$ and $LiAlH_4$ in THF has been identified as the most efficient for the simultaneous reduction of amide group and the reductive opening of the oxazolidine ring in phenylglycinol lactam derivatives; in particular when these two reagents are mixed in anhydrous aprotic solvent (THF, Et_2O, etc.), AlH_3 (*alane*) is formed *in situ* and reduction takes place in good yield and stereoselectivity.

In order to complete the initial study (Paragraph 3.2.1. of present Thesis), isomeric lactams **29**, **31** and **32** were subjected to the reductive conditions: after almost 4 h, lactams **29** were totally converted into lactam **62a**, which was isolated as major isomer, and lactam **62b**, which was detected in trace amounts. However, under these conditions, the reduction of lactams **31** and **32** was not complete and amines **63** and **65**, in which only the amide and the ester carbonyls have been reduced, were found as the main products.



29 R_1 = H; R_2 = CH_3
31 R_1 = CH_3; R_2 = CH_3
32 R_1 = C_6H_5; R_2 = H

61 R_1 = H -
63 R_1 = CH_3 60%
65 R_1 = C_6H_5 55%

62 R_1 = H 64% (**b** traces)
64 R_1 = CH_3 (**a,b** traces)
66 R_1 = C_6H_5 (**a,b** traces)

Figure 3.46 Alane reduction of pentacyclic lactams 29, 31 and 32

The partial reduction of tricyclic phenylglycinol-derived lactams had been observed previously when a substituent is present at C-9 of the carbocyclic ring. Thus, in lactams **31** and **32** the ester and amide functions are more prone than oxazolidine ring to be reduced under these conditions. The unambiguous identification of oxazolidines **63** and **65** was possible thanks to ^{13}C-NMR spectrum, which shows of a quaternary carbon signal at 98 ppm (Figure 3.47).

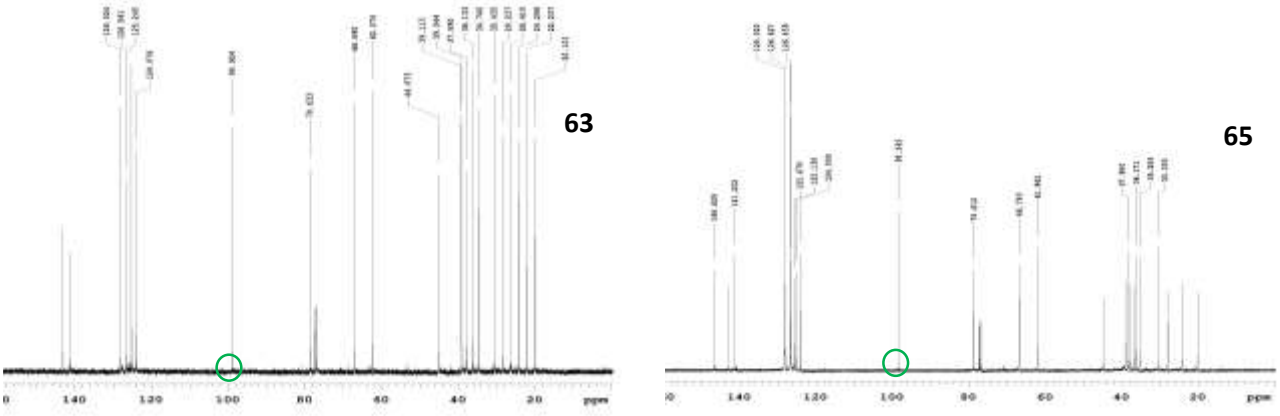
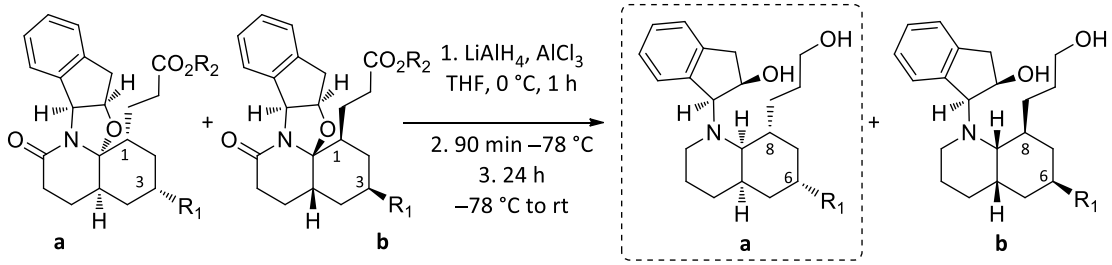


Figure 3.47 ^{13}C-NMR spectra for 63 and 65

When the reduction time of lactams **31** and **32** was extended to more than 24 h at room temperature *cis*-decahydroquinolines **64a** and **66a** were isolated, in comparable yield with respect to the observed in (*R*)-phenylglycinol series and no *trans*-isomers were observed. Once again, isomers **b** were not isolated, and the yield is referred to pure isolated amines **a**.



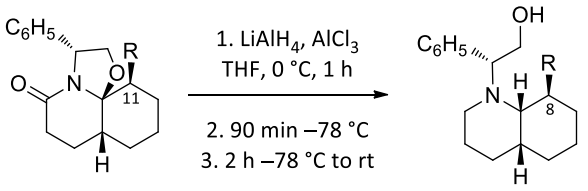
31 $R_1 = CH_3$; $R_2 = CH_3$
32 $R_1 = C_6H_5$; $R_2 = H$

64 $R_1 = CH_3$ 63% (**b** traces)
66 $R_1 = C_6H_5$ 60% (**b** traces)

Figure 3.48 Alane reduction of 1,3-disubstituted pentacyclic lactams: second attempt

Pure *cis*-decahydroquinolines were thus obtained, starting from a mixture of two inseparable isomeric pentacyclic lactams.

In the same way, pure lactams **55a**, **56a** and **57a** were subjected to reduction with alane and *cis*-decahydroquinolines **67**-**69** were isolated in good yield. No *trans*-isomers were observed, meaning that the close C-11 alkyl group did not affect the selective attack of the reductive agent.

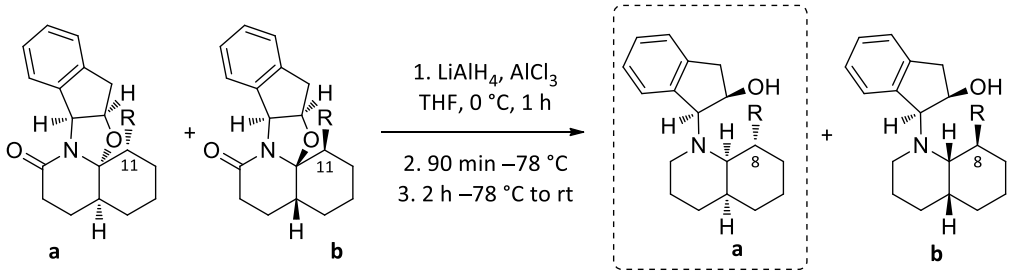


55a R = CH_3
56a R = Et
57a R = Bn

67 R = CH_3 80%
68 R = Et 60%
69 R = Bn 61%

Figure 3.49 Alane reduction of (*R*)-phenylglycinol derived lactams

Finally, pentacyclic lactams **58**-**60** (mixture of isomers **a** and **b**) derived from *cis*-(1*S*,2*R*)-2-aminoindanol, were subjected to reduction under the same reaction conditions. *Cis*-decahydroquinolines **70a-72a** were isolated in good yield and excellent stereoselectivity. No *trans*-isomers were detected. Remarkably, at this stage, we could easily separate the two diastereoisomers **a** and **b**, but isomers **b** were not characterized.



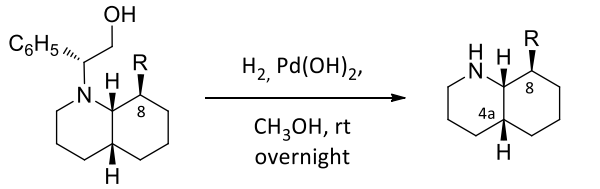
58 R = CH_3
59 R = Et
60 R = Bn

70a R = CH_3 84% (**b** traces)
71a R = Et 63% (**b** traces)*
72a R = Bn 67% (**b** traces)*
* not optimized results

Figure 3.50 Alane reduction of pentacyclic lactams

The chiral auxiliary residue was easily removed taking advantage of the benzylic character of the exocyclic carbon-nitrogen bond. Synthesis of *cis*-decahydroquinoline **73**, already described in literature,[95] allowed us to confirm the *cis*-fusion of decahydroquinoline systems and the relative configuration of the C-8, C-8a and C-4a, considering that C-4a and C-8, whose absolute configuration was confirmed by X-ray crystallography, were not involved in the two last steps. *Cis*-decahydroquinolines **74** and **75** were synthesized, in very good yield. The reaction took place overnight, under hydrogen atmosphere in methanol, catalyzed by palladium hydroxide. No column chromatography was needed, but simple basic treatment with potassium hydroxide solution led to pure amine.

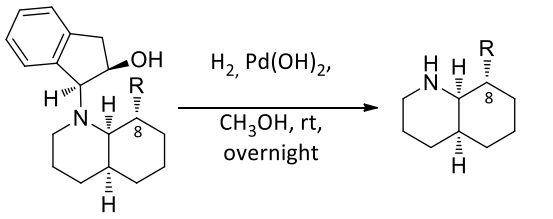
[95] a. Vierhapper, F. W.; Eliel, E. L. *J. Org. Chem.* **1977**, *42*, 51–62; b. Vierhapper, F. W.; Furst, G.; Lichter, R. L. *Organic Magnetic Resonance* **1981**, *17*, 127–130.



67 R = CH_3 **73** R = CH_3 82%
68 R = Et **74** R = Et 75%
69 R = Bn **75** R = Bn 89%

Figure 3.51 Synthesis of *cis*-decahydroquinoline 73-75

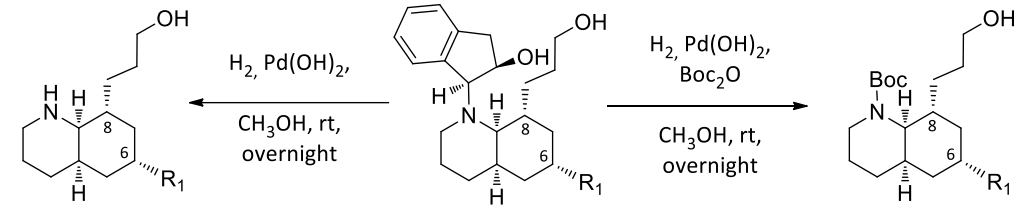
In the same way, pure *cis*-decahydroquinolines ***ent*-**73, **ent**-74, andent-**75** were obtained in good yield from **70a**, **71a**, and **72a**.



70a R = CH_3 ***ent*-73** R = CH_3 79%
71a R = Et ***ent*-74** R = Et 70%
72a R = Bn ***ent*-75** R = Bn 71%

Figure 3.52 Synthesis of *cis*-decahydroquinolines *ent*-73-75

Similarly, amines **62a**, **64a** and **66a** were converted into *cis*-decahydroquinolines **76**-**78** or to the *N*-protected bicycles **79**-**81**, in good to excellent yield. The absolute configuration was confirmed by comparison of the optical rotation power with that previously reported by our group.[37]



76 R_1 = H 69%
77 R_1 = CH_3 87%
78 R_1 = Bn 77%

62a R_1 = H
64a R_1 = CH_3
66a R_1 = Bn

79 R_1 = H 74%
80 R_1 = CH_3 75%
81 R_1 = Bn 81%

Figure 3.53 Synthesis of *cis*-decahydroquinolines 76-81

In conclusion tricyclic and pentacyclic lactams, prepared by cyclocondensation reaction of chiral aminoalcohol (phenylglycinol or *cis*-aminoindanol) and cyclohexanone based δ-ketoacid derivatives, are excellent precursors for the enantioselective synthesis of C-8 and C-6,8 substituted *cis*-decahydroquinolines, through a two steps synthetic sequence: simultaneous reduction of amide and oxazolidine ring and final debenzylation. Both, (*R*)-phenylglycinol and (1*S*-2*R*)-2-aminoindanol are commercial available as well as their enantiomers, which increases the synthetic potential of the methodology.

In Figure 3.54 all *cis*-decahydroquinolines synthesized in the present work are displayed, with overall yield from oxo-acid derivatives.

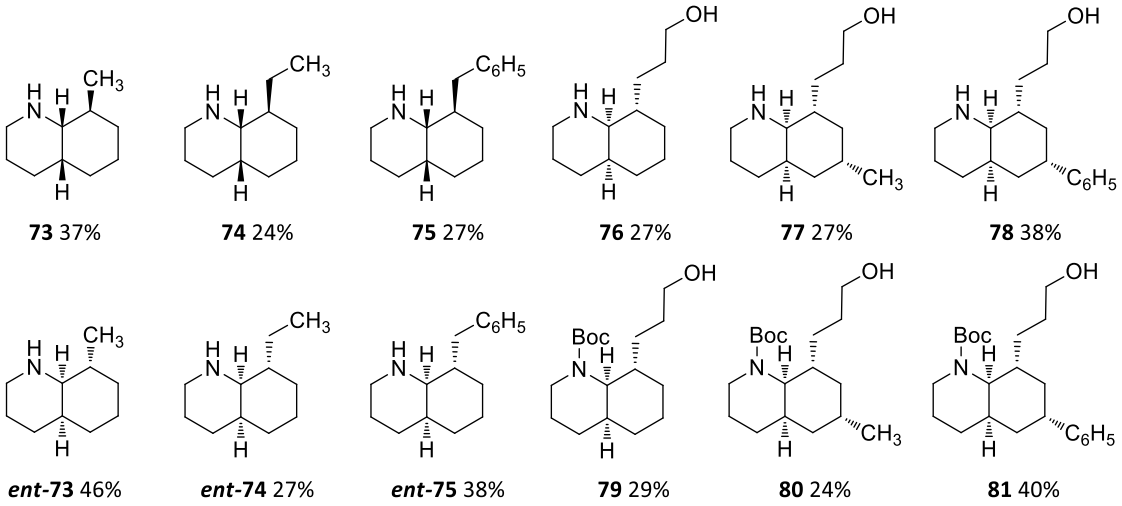


Figure 3.54 Synthesized *cis*-decahydroquinolines

3.3. Conformational studies

Cis-DHQs can exist in two conformational chair-like forms that are in equilibrium, in analogy with *cis*-decalins, which were largely studied in the sixties and seventies by Bastiansen and Hassel, using electron diffraction techniques.[96] In particular, c*is*-decalins have three steric interactions, as the gauche conformation of *n*-butane, which are not present in the more stable *trans*-compounds. Methyl substitution on *cis*-decalin produces steric interactions, shifting the balance between the two conformational forms.[97]

Starting from these observations, the conformational analysis of *cis*-DHQs was made. It has been reported that *cis*-DHQ, without substituents at the carbocyclic ring, can exist in two conformations, **G** and **H**, which differ in the ring and nitrogen inversion.[98]

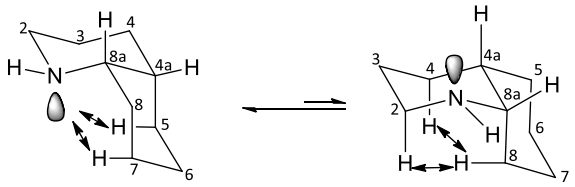


Figure 3.55 Conformational equilibrium in *cis*-decahydroquinolines

The ^{1}H-NMR and ^{13}C-NMR spectra for an unsubstituted *cis*-decahydroquinoline at 30 °C show broad signals due to a low conformational equilibrium, while at 55 °C a sharpening of the signals is observed. At low temperature (−74 °C), the spectra decoalesce into two sets of lines, which can be assigned to the two contributing conformations;[99] more precisely, the ^{13}C spectrum (−74 °C) gave the proportions of **G** and **H** as 93:7 respectively.[100] The strong preference for **G** is probably due to the equatorial disposition of the N-H bond, leading to the existence of two 1,4 hydrogen-lone pair interactions that are probably smaller than the corresponding 1,4 hydrogen-hydrogen interactions in conformation **H**. Another possible explication is the stronger stereoelectronic interaction in the *N*-in over the *N*-out conformer.[101]

The introduction of a substituent at C-8 involves a conformational equilibrium change because new factors come into play. In the case of a β-substituent, destabilizing 1,3 diaxial interactions between R and

[96] Bastiansen, O.; Hassel, O. *Nature (London)*, **1946**, *157*, 765-767.
[97] Dalling, D.K.; Grant, D.M.; Paul, E.G. *J. Amer. Chem. Soc.,* **1973**, *95*, 3718-3724.
[98] Booth, H.; Bostock, H. *Chem. Comm.,* **1967**, 177-178.
[99] a. Vierhapper, F.W.; Eliel, E.L. *J. Org. Chem.*, **1977**, *42*, 51-62; b. Brooth, H.; Griffiths, D.V. *J. Chem. Soc. Perkin Trans.2*, **1975**, 111-118.
[100] Brooth, H.; Griffith, D.V. *J. Chem. Soc. Perkin Trans.*, **1973**, *2*, 842.
[101] Pham, V.C.; Jossang, G.; Chiaroni, A.; Sévenet, T.; Nguyen, V.H.; Bodo, B. *Org. Lett.,* **2007**, *9*, 3531-3534.

C-4a and C-6 hydrogens in the *N*-in conformation exist whereas gauche interactions between R and the nitrogen in *N*-out conformation are present (Figure 3.56).

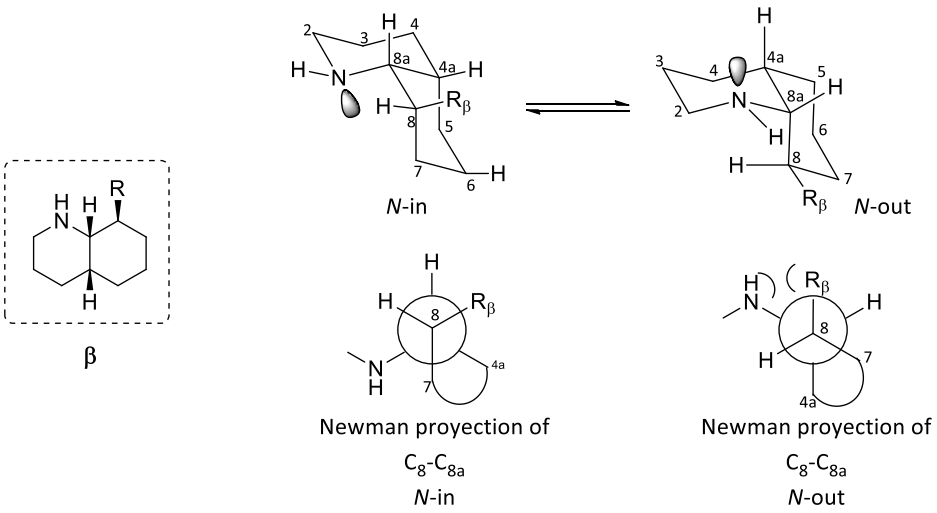


Figure 3.56 Conformation in C-8β substituted *cis*-decahydroquinolines

The ^{1}H and ^{13}C-NMR spectra of compound **76**, registered at room temperature, display broad signals which suggest a slow conformational equilibrium. These observations confirmed again the assigned absolute configuration of C-8, since in C-8 epimeric related compound more defined signals in the NMR spectra are observed.[102]

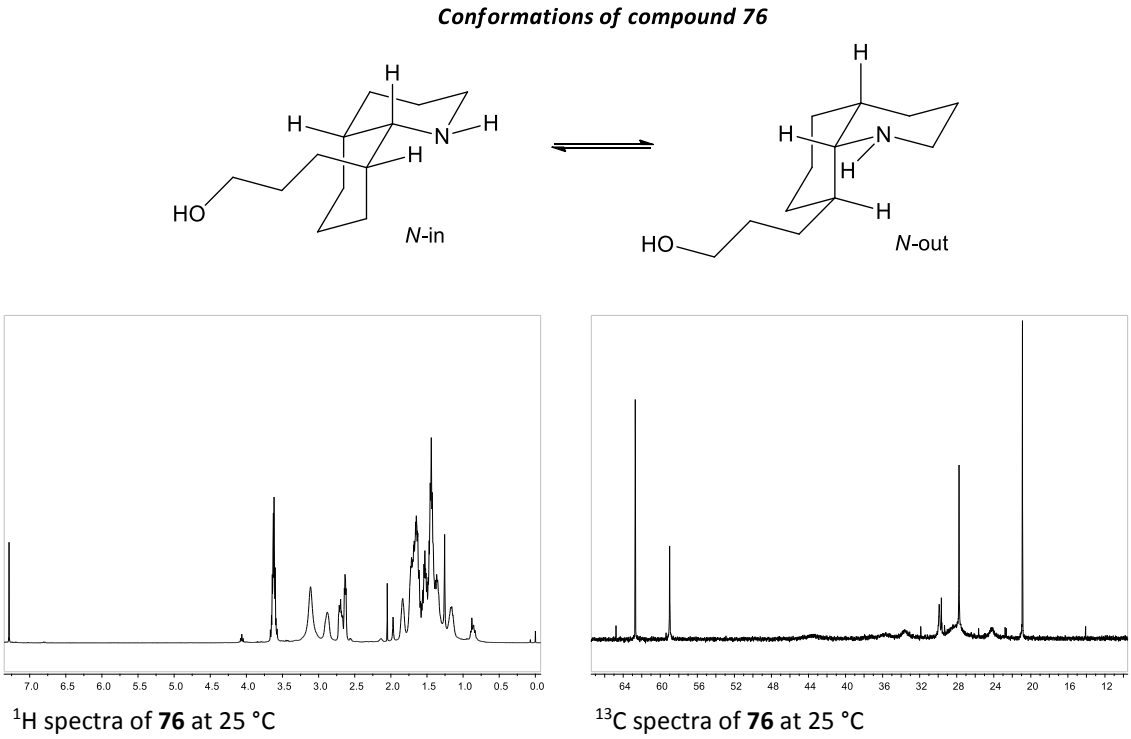
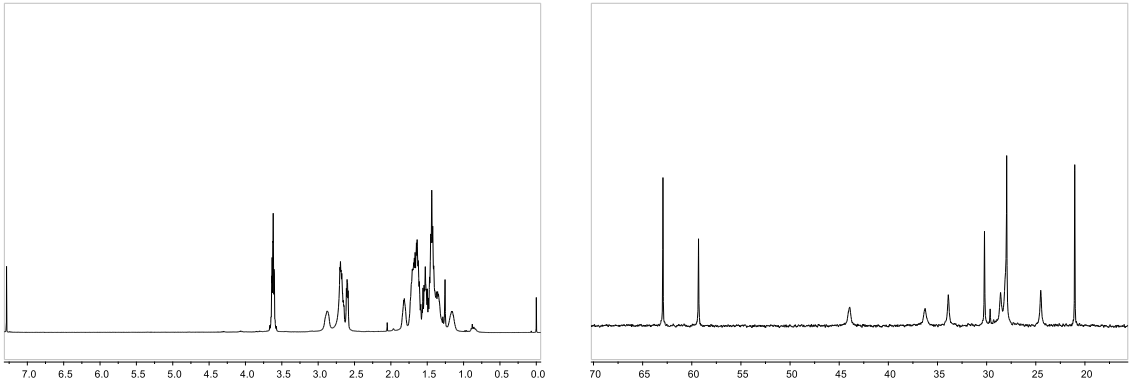


Figure 3.57

[102] Vierhapper, F. W.; Eliel, E. L. *J. Org. Chem.* **1977**, *42*, 51–62.

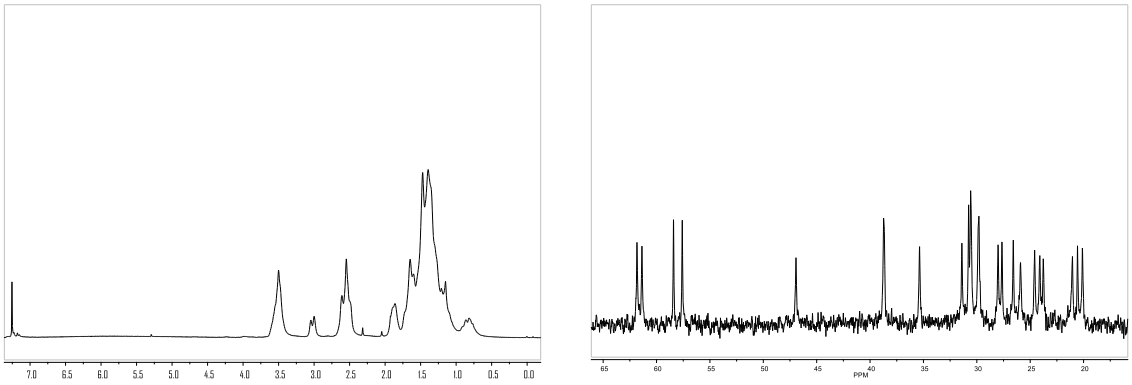
On the other hand, when the ^{1}H-NMR spectra of **76** was registered at 50 °C, more defined signals were identified. The increase of the temperature led to an increase of the interconversion rate between the two conformers, up to the coalescent temperature, above which only one signal for each carbon is evident in the ^{13}C-NMR spectra (Figure 3.58).



^{1}H spectra of **76** at 50 °C ^{13}C spectra of **76** at 50 °C

Figure 3.58

Finally, when the spectra were registered at low temperature (– 23 °C), a splitting of signals was observed in the ^{13}C-NMR, allowing the identification of the two conformers. Since the ^{1}H-NMR spectrum was not so defined, it was impossible to calculate the exact conformer population but the ^{13}C-NMR spectrum suggests that the two conformers exist in a similar rate.

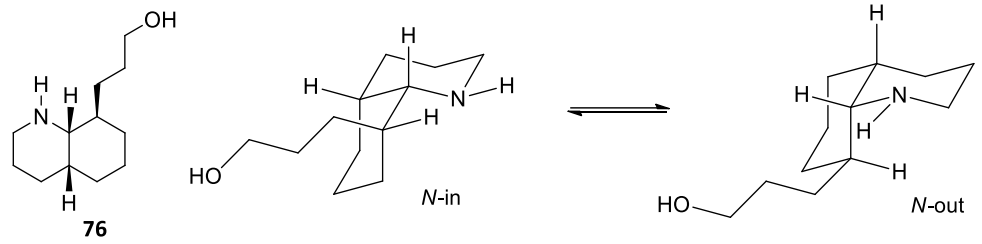


^{1}H spectra of **76** at –23 °C ^{13}C spectra of **76** at –23 °C

Figure 3.59

Full characterization of **76** was carried out by homo- and heterocorrelation experiments and by comparison of our results with those reported in the literature for related compounds. In Table 3.6 the signals for each conformation at –23 °C and those observed at 50 °C are reported. For the *N*-out conformation, signals at C-2 and C-4 are shifted at a higher field, due to the gauche effect of C_8-C_{8a} bond, which is axial with respect to the piperidine ring as well as for C-8 due to the axial disposition of C_4-C_{4a}

bond with respect to the carbocyclic ring. On the other hand, for the *N*-in conformation, signals for C-3 and C-7 are shifted at higher field, due to the steric compression of C_{4a}-C_5 bond, which is axial with respect to the piperidine ring, and of C_{8a}-N bond that adopts axial disposition with respect to the carbocyclic ring. Furthermore, C-4a is affected by the gauche effect of the hydroxypropyl substituent, shifting the corresponding signals to a higher field. The shifting to higher fields of C-6 in both conformations, can be ascribed to the hydroxypropyl group in *N*-in and to C_4-C_{4a} bond in *N*-out conformation.



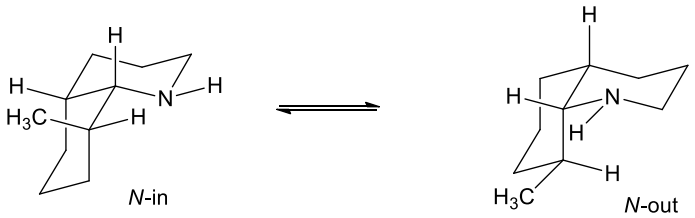
76

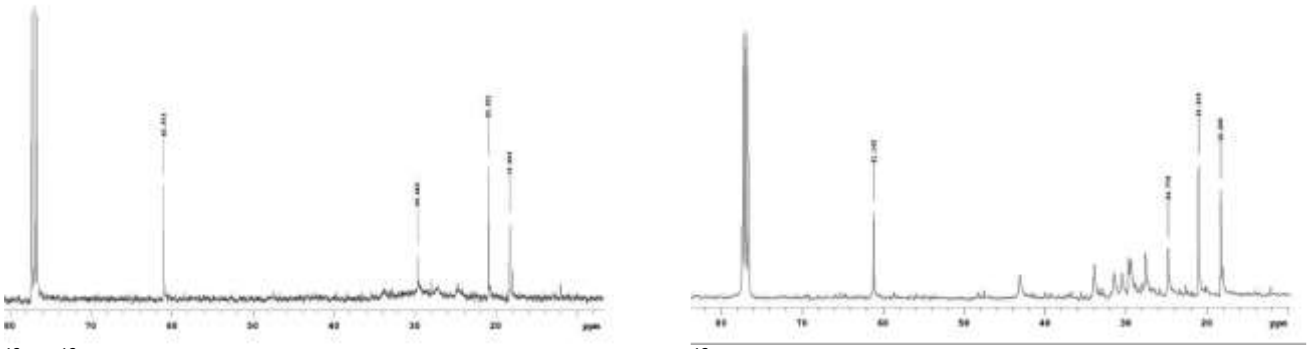
	T °C	2	3	4	4a	5	6	7	8	8a
N-in	−23	46.9	21.1	30.6	30.8	24.6	20.1	23.8	38.7	57.6
N-out	−23 [2]	38.7	25.9	24.1	35.4	30.6	20.6	31.4	29.8	58.4
76	50	44.0	24.5	27.7	33.9	29.7	21.0	30.2	36.3	59.3

Table 3.6

When the C-8 substituent is a methyl group (8β-CH_3, **73**), the mixture is conformationally heterogeneous: in fact, at room temperature, most of its signal are broad (Figure 3.60), however sharpening of the signals was observed when the NMR was recorded at 52 °C (only ^{13}C spectra are shown).

Conformations of compound 73





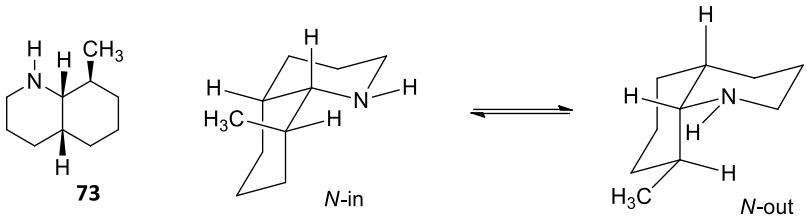
^{13}C ^{13}C-NMR spectrum of **73** at 25 °C

^{13}C-NMR spectrum of **73** at 52 °C

Figure 3.60

The signals observed in the ^{13}C-NMR spectra match with those reported in the literature for the same compound. Only moderate deviation of 0.1-0.3 ppm can be appreciated, probably attributable to the broadness of the signals and the little difference in the recording temperature (Table 3.6).

At −68 °C the spectrum revealed a major conformer (*N*-out, 59%) and a minor one (*N*-in, 41%), due to the stronger 1,3 diaxial interaction in *N*-in with respect to the gauche interaction in *N*-out.

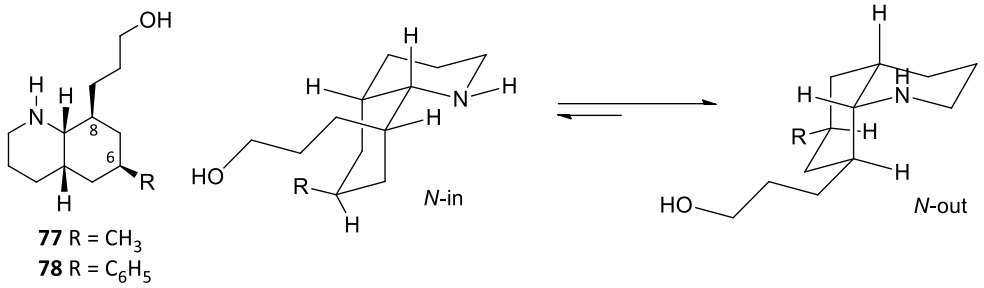


T °C		2	3	4	4a	5	6	7	8	8a	CH_3
30[1]		43.3	25.1	27.8	34.1	29.5	21.1	31.5	30.7	61.2	18.3
21[2]		[3]	[3]	27.9	[3]	29.6	20.9	[3]	[3]	61.0	18.3
55[1]		43.5	25.2	28.0	34.3	29.5	21.2	31.6	31.0	61.4	18.4
52[2]		43.1	24.8	27.6	34.0	29.4	21.0	31.4	30.5	61.2	18.2
−68[1]	**N-in**	47.8	21.5	30.4	30.1	25.2	20.4	26.2	34.9	60.4	17.5
−68[1]	**N-out**	39.0	26.8	24.8	35.7	32.1	21.0	34.5	26.6	60.6	18.8

1.Reported in the literature; 2. Our experimental data; 3. Not detected signal.

Table 3.7 ^{13}C-NMR data for 73

For the *cis*-decahydroquinolines **77** and **78**, bearing an additional substituent at C-6, the *N*-out conformation is favored, since the substituents are both in an equatorial position. In the ^{13}C-NMR spectrum of **78**, registered at 25 °C, well-defined signals were observed. On the contrary, **77** show low intensity signals for C-4, C-4a, C-5, C-7 and C-8a. On the other hand, the chemical shifts observed in the ^{13}C-NMR spectra registered at −23 °C correlate with those described at 25 °C, suggesting that the molecule adopts a preferential conformation.



77 R = CH_3
78 R = C_6H_5

T °C		2	3	4	4a	5	6	7	8	8a
25	**77**	40.5	26.8	25.6	-[1]	-[1]	-[1]	-[1]	26.8	-[1]
25[2]	**78**	39.5	27.3	25.5	37.1	39.4	38.4	39.8	31.9	58.2
−23	**77**	40.0	25.8	24.7	35.6	38.7	30.4	39.3	27.5	57.1
−23	**78**	39.2	26.1	24.8	36.0	38.6	38.0	38.9	31.0	57.3

1. Not detected signal.

Table 3.8

Conformational equilibrium of flexible biomolecules (*cis*-DHQ) is important for their biological properties, and for this reason, it is necessary to understand how a substituent in the ring framework can affect the equilibrium.

3.4. Formal synthesis of *Myrioneuron nutans* alkaloids

To illustrate the usefulness of our method, we decided to undertake the synthesis of some alkaloids isolated from the species *Myrioneuron nutans*. A *cis*-decahydroquinoline core with substituents at C-8 structurally characterizes these alkaloids. The decahydroquinoline, as main structural motif, is rare in natural products isolated from plants, and typical from some neotropical frogs[103] and ants.[104] Some decahydroquinoline alkaloids have been synthesized by our group.[35c,d]

3.4.1. Myrioneuron nutans alkaloids: brief introduction

Myrioneuron is a small genus distributed over the southeast of Asia and belonging to the Rubiaceae family, a large plant family known to biosynthesize a great variety of alkaloids with important pharmacological interests, such as quinine[105] and camptothecin.[106] *Myrioneuron nutans*, a small tree native in North-Viet Nam, was selected in the course of a screening program of plants for their cytotoxicity by Bodo's group, which in the early 2000s started to report new *cis*-DHQ alkaloids collected from dried and ground leaves of this particular plant.[107] More recently, Poupon has proposed that *Myrioneuron* alkaloids are closely related to *Nitraria* alkaloids, since the basic structure of some of them is very similar and, moreover, he has asserted that also their biosynthesis can be explained starting from the same intermediate.[108] This connection seems to be confirmed by the isolation of schoberine from both plant families, but the resulting questions of chemotaxonomy and evolutionary convergence remain unanswered.

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[103] a. Ozawa, T.; Aoyagi, S.; Kibayashi, C. *Org. Lett.* **2000**, *2*, 2955–2958; b. Kubanek, J.; Williams, D. E.; Dilip de Silva, E.; Allen, T.; Andersen, R. J. *Tetrahedron Lett.* **1995**, *36*, 6189–6191; c. Steffan, B. *Tetrahedron* **1958**, *47*, 8729–8732.

[104] a. Spande, T. F.; Jain, P.; Garraffo, H. M.; Pannell, L. K.; Yeh, H. J. C.; Daly, J. W.; Fukumoto, S.; Imamura, K.; Tokuyama, T.; Torres, J. A.; Snelling, R. R.; Jones, T. H. *J. Nat. Prod.* **1999**, *62*, 5–21.

[105] a. Woodward, R. B.; Doering, W. E. *J. Am. Chem. Soc.* **1945**, *67*, 860–874; b. Lyle, G. G.; Keefer, L. K. *Tetrahedron* **1967**, *23*, 3253–3256; c. Moreland, C. G.; Philip, A.; Caroll, F. I. *J. Org. Chem.* **1974**, *39*, 2413–2416; d. Bruneton, J. *Pharmacognosy Photochemistry Medicinal Plants*; Lavoisier-Technic and Documentation; London, Paris, New York, NY, 1995.

[106] a. Kitajima, M.; Masumoto, S.; Takayama, H.; Aimi, N. *Tetrahedron Lett.* **1997**, *38*, 4255–4258; b. Aimi, N.; Ueno, M.; Hoshino, H.; Sakai, S. I. *Tetrahedron Lett.* **1992**, *33*, 5403–5404; c. Aimi, N.; Nishimura, M.; Miwas, A.; Hoshino, H.; Sakai, S. I.; Haginiwa, J. *Tetrahedron Lett.* **2002**, *54*, 4991–5003.

[107] a. Pham, V. C.; Jossang, A.; Sévenet, T.; Nguyen, V. H.; Bodo, B. *Tetrahedron* **2007**, *63*, 11244–11249; b. Pham, V. C.; Jossang, A.; Sévenet, T.; Nguyen, V. H.: Bodo, B. *J. Org. Chem.* **2007**, *72*, 9826–9829; c. Pham, V. C.; Jossang, A.; Chiaroni, A.; Sévenet, T.; Nguyen, V. H.; Bodo, B. *Org. Lett.* **2007**, *18*, 3531–3534; d. Pham, V. C.; Jossang, A.; Grellier, P.; Sévenet, T.; Nguyen, V. H.; Bodo, B. *J. Org. Chem.* **2008**, *73*, 7565–7573; e. Pham, V. C.; Jossang, A.; Sévenet, T.; Nguyen, V. H.; Bodo, B. *Eur. J. Org. Chem.* **2009**, 1412–1416.

[108] Gravel, E.; Poupon, E. *Natural Product Reports* **2010**, *27*, 32–56.

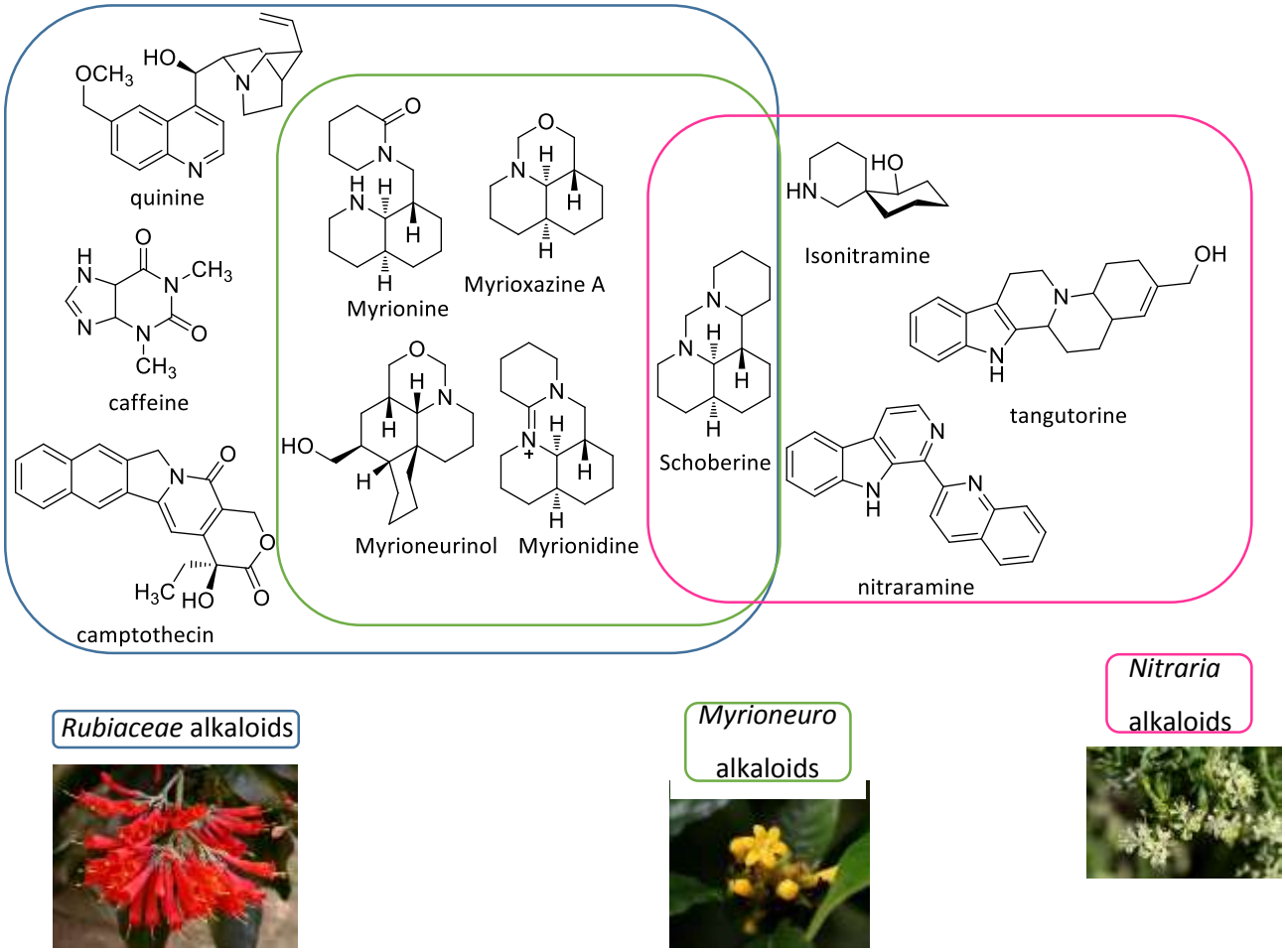


Figure 3.61 Representative alkaloids of Rubiaceae family and *Myrioneuron* and *Nitraria* genus

Cytotoxic activity against KB cell and *Plasmodium falcipaurum* (FcB1 strain, malaria) were studied for *Myrioneuron nutans* alkaloids isolated in enantiopure form. The results showed that most of these compounds were more active on *Plasmodium falcipaurum* (IC_{50} from 0.03 to 44) than on KB cell lines (IC_{50} 3 to > 100), indicating that the antiplasmodial activity could not be attributed to their cytotoxicity. It was found that the stereochemistry at C-8 and the iminium function play an important role in the bioactivity of myrionidine, since schoberine shows weaker cytotoxicity and antimalarial activity than this alkaloid.

3.4.2. Synthetic plan

Taking into account our experience in the synthesis of 8-alkyl-*cis*-DHQ, we planned to prepare enantiopure alcohol **82**, which was described by Bodo and co-workers to be a common intermediate for the synthesis of various *Mirioneuron nutans* alkaloids.[109] Other authors have reported the total synthesis of myrioxazine A and myrioneurinol, but in the racemic series.[110] Cyclocondensation of an appropriate ketoacid derivative with *cis*-(1*S*,2*R*)-2-aminoindanol should provide the corresponding pentacyclic lactam, with the correct stereochemistry. Deprotection of the alcohol moiety, reduction of carbonyl amide and oxazolidine ring and elimination of the benzylic residue by hydrogenation, should give rise to our target **82**.

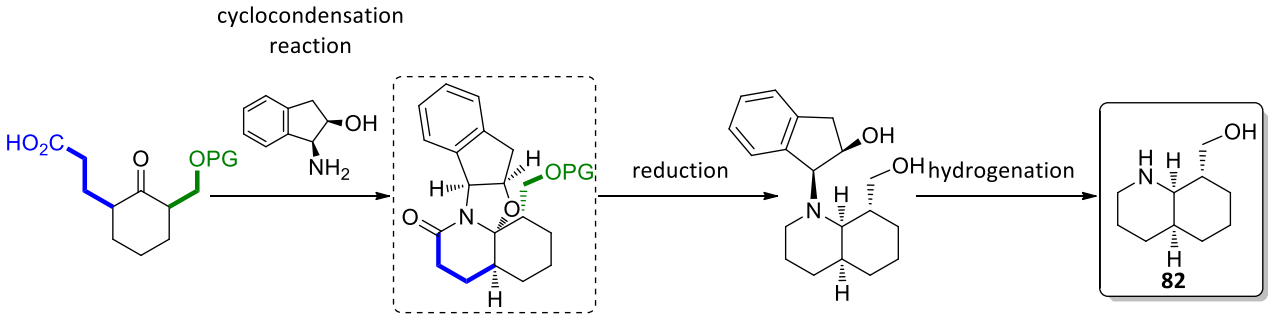


Figure 3.62 Proposed synthetic pathway for the enantiopure synthesis of 82

Starting from **82**, Bodo and co-workers described the synthesis of myrioxazine A, myrionine, myrionidine and schoberine, as displayed in Figure 3.63.

[109] a. Pham, V. C.; Jossang, A.; Chiaroni, A.; Sévenet, T.; Bodo, B. *Tetrahedron Lett.* **2002**, *43*, 7656–7568; b. Pham, V. C.; Jossang, A.; Grellier, P.; Sévenet, T.; Nguyen, V.H.; Bodo, B. *J. Org. Chem.* **2008**, *73*, 7565–7573.

[110] a. Nocket, A. J.; Weinreb, S. M. *Angew. Chem. Int. Ed.* **2014**, *53*, 1–5; b. Burrell, A. J. M.; Coldham, I.; Oram N. *Org. Lett.* **2009**, *7*, 1515–1518

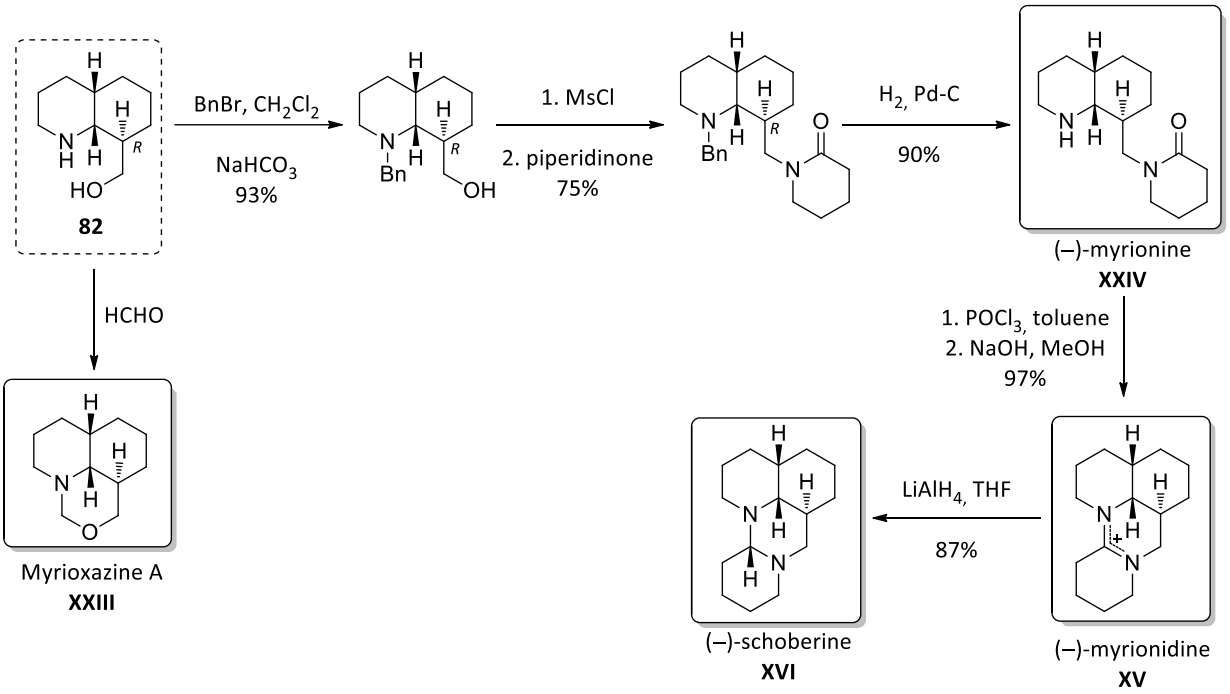


Figure 3.63

Cyclization of **82** with formaldehyde provided myrioxazine A. On the other hand, conversion of the hydroxymethyl group into its mesyl derivative on the N-benzyl-derivative of **82**, followed by N-alkylation of 2-piperidinone and benzyl deprotection afforded (–)-myrionine in 63% overall yield. Subsequent intramolecular cyclization of myrionine, carried out with $POCl_3$ in toluene, followed by treatment with NaOH in methanol gave (–)-myrionidine in good overall yield (97%). Reduction of the latter compound using $LiAlH_4$ in THF led to (–)-schoberine in 53% overall yield from **82**.

3.4.3. Synthesis of starting material

Initially we considered the reported 2-benzyloxymethyl cyclohexanone[111] as an excellent precursor for the synthesis of the required starting material. The propionate chain could be introduced as described above for compounds **49**, **53**, and **54**. Thus, starting from commercially available keto-ester **83**, we protected the ketone moiety with ethylene glycol and we converted the ester into the corresponding alcohol, by reaction with $LiAlH_4$. Subsequent protection of the alcohol with benzylbromide led to compound **86** in excellent yield. Unfortunately, acidic hydrolysis of the acetal **86** provided only a complex mixture of products.

[111] a. Nicolau, K. C.; Dai, W-M. *J. Am. Chem. Soc.* **1992**, *114*, 8908–8921; b. Heimann, J.; Schäfer, H. J.; Fröhlich, R.; Wibbeling, B. *Eur. J. Org. Chem.* **2003**, 2919–2932; c. Fukuzawa, A.; Sato, H.; Masumane, T. *Tetrahedron Lett.* **1987**, *28*, 4303–4306; d. *Tetrahedron* **1988**, *44*, 4259–4275.

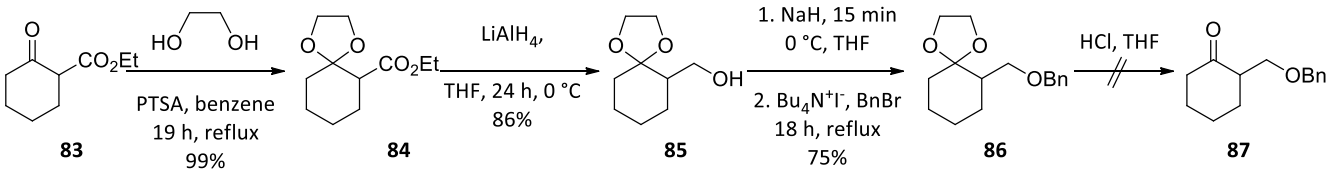


Figure 3.64 Synthesis of ketone 87

Probably, compound **87** rapidly decomposed by retro-Mannich reaction.[112] An alternative way for achieve the desired cyclohexanone-2-propionate derivative must be found.

3.4.4. Revised Synthetic plan

The introduction of a masked hydroxyl group, in particular a dimethyl phenyl silyl group, was considered a possible solution to overcome the above problem.[113] After the cyclocondensation reaction, the silyl group could be oxidized to an alcohol under the conditions described by Fleming.[114]

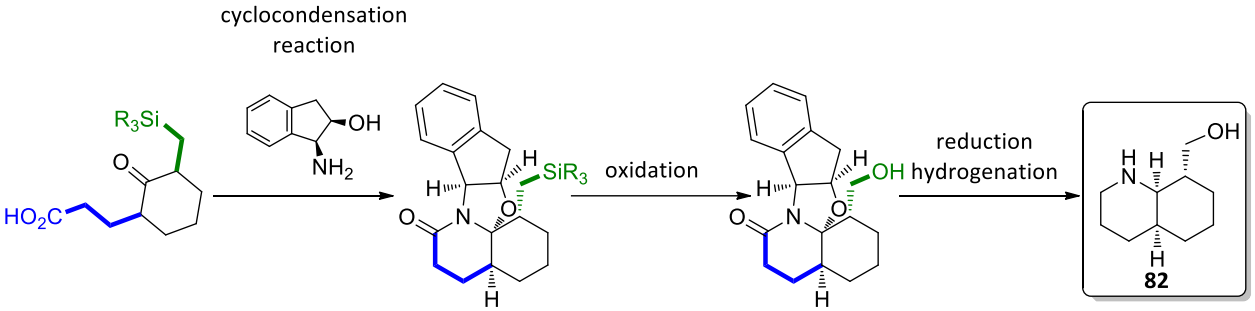


Figure 3.65 Revised approach to 82

3.4.5. Synthesis of acid 91

Direct alkylation of the lithium enolate of cyclohexanone,[115] with (iodomethyl)dimethylphenyl silane[116] did not afford the desired compound **89**. However, the reaction of imine **88** with (iodomethyl)dimethylphenyl silane,[117] followed by Mannich reaction from the enol silyl ether derivative

[112] a. Tramontini, M. *Synthesis*, **1973**, 703–774; b.Tramontini, M.; Angiolini, L. *Tetrahedron* **1990**, *46*, 1791–1837.
[113] Fleming, I.; Henning, R.; Parker, D. C.; Plaut, H. E.; Sanderson, P. E. J. *J. Chem. Soc. Perkin Trans. 1* **1995**, 317–337.
[114] Fleming, I.; Henning, R.; Plaut, H. *J. Chem. Soc. Chem. Commun.* **1984**, 29–31.
[115] Synthesized *via* enamine, controlling the single attack of the propionate chain; described in PhD thesis, Laura Navío, Barcelona **2011**.
[116] Prepared starting from (chloromethyl)dimethylphenyl silane with sodium iodide in acetone, as described in: Smitrovich, J. H.; Woerpel, K. A. *J. Am. Chem. Soc.* **1998**, *49*, 12998–12999.
[117] Flaming, I.; Goldhill, J. *J. Chem. Soc. Perkin Trans. 1* **1980**, 1493–1498.

of **89** and Michael addition of diethyl malonate on the resulting b-amino-ketone **90**, provided the acid **91** in good yield as a mixture of isomers.

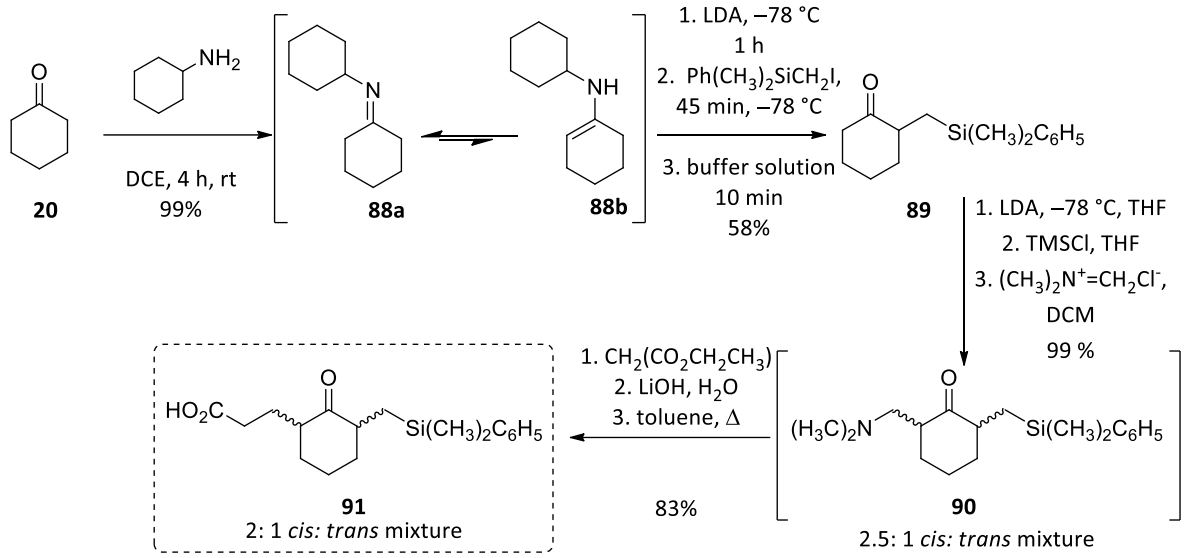


Figure 3.66 Synthesis of ketoacid 91

The decarboxylation step could not be performed under acidic conditions since the silyl group showed to be very sensitive. Consequently, we first hydrolyzed the ester functions in presence of lithium hydroxide and water in tetrahydrofuran and then, the decarboxylation was provoked by heating in refluxing toluene. We also tested dibenzylmalonate in the conjugate addition, since we could obtain the corresponding diacid by hydrogenation without affecting the silyl group. This sequence led to the desired ketoacid **91**, but in lower yield.

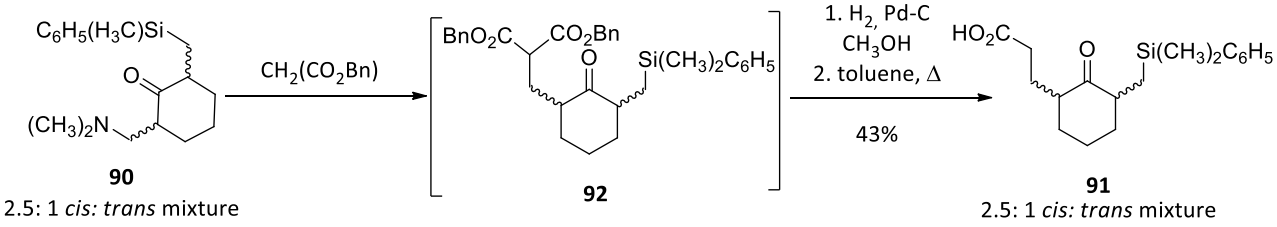


Figure 3.67 Alternative route for the synthesis of 91

3.4.6. Synthesis of 8-(hydroxymethyl)decahydroquinoline 82

With a method in hand for the preparation of keto-acid **91** we undertook its conversion into the target 8-hydroxymethyl-*cis*-decahydroquinoline **82** under the optimized conditions described in this Chapter for the synthesis of enantiopure 8-substituted *cis*-decahydroquinolines from (1*S*,2*R*)-1-aminoindanol-derived chiral lactams.

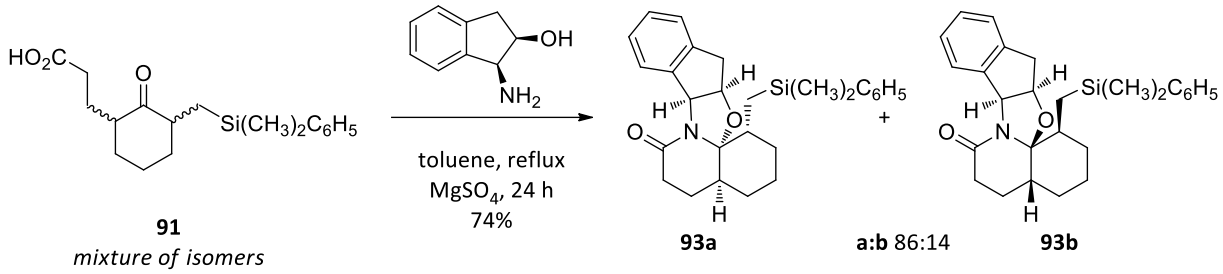


Figure 3.68 Synthesis of lactams 93

The cyclocondensation reaction was carried out in toluene and in presence of magnesium sulfate, affording isomers **93a** and **93b** as an inseparable mixture, in 74% yield and 86:14 *dr*. When a Dean–Stark apparatus was employed, lactams **93a**,**b** were isolated in lower yield.

The mixture of **93a,b** was treated with $HBF_4{\cdot}Et_2O$ in dichloromethane and then with *m*-CPBA in DMF to provoke the conversion of the (dimethyl)phenylsilyl group into an alcohol. At this stage, after separation of the two stereoisomers, pure alcohol **94** was obtained in good yield

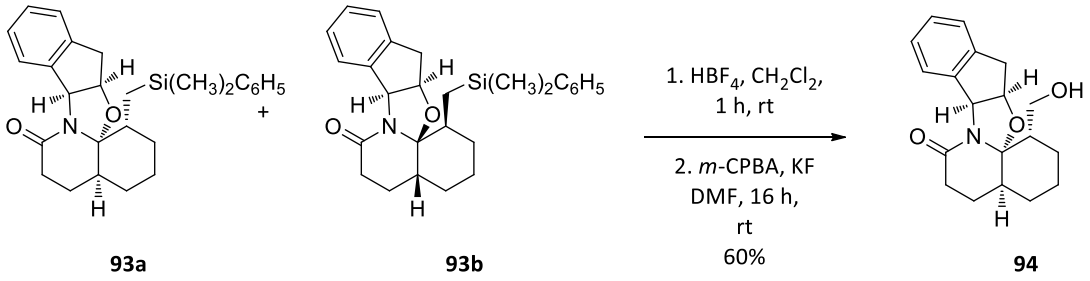


Figure 3.69 Oxidation of C-Si bond with Fleming-Tamao conditions

Tamao and Kumada described the conversion of (dimethyl)phenylsilyl groups into alcohols for the first time in 1983. They reported that silicon-carbon bonds could be cleaved by hydrogen peroxide, under basic conditions in the presence of bicarbonate salts, to afford the corresponding alcohols, provided that the silicon atom had at least one electron-withdrawing substituent.[118]

A year later, Fleming and co-workers discovered that the (dimethyl)phenylsilyl-carbon bond can be oxidatively cleaved in two steps to the corresponding alcohol with retention of configuration at the carbon to which the silicon is attached.[114] The two steps are: first, the protodesilylation of the phenyl ring using $HBF_4{\cdot}Et_2O$ or BF_3OAc complex and, second the treatment of the resulting silyl fluoride with a peracid, such as *meta*-chloroperbenzoic acid (*m*CPBA) and peracetic acid.

[118] Tamao, K.; Ishida, N.; Tanaka, T.; Kumada, M. *Organometallics* **1983**, *2*, 1694–1696.

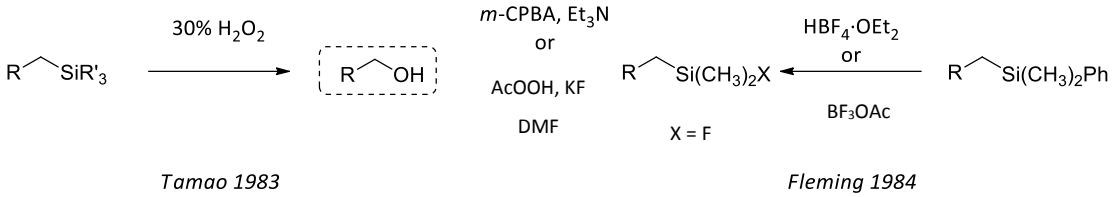


Figure 3.70 Oxidation of C-Si bond

The reduction of oxazolidine ring with simultaneous reduction of amide carbonyl with alane afforded the intermediate **95**, whose hydrogenation led to the target amino alcohol **82** in 66% yield.

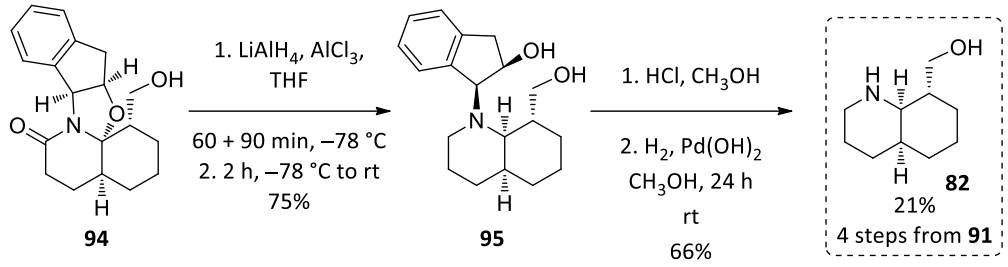


Figure 3.72 Synthesis of amino alcohol 82

The stereochemical identity of **82** was confirmed by comparison of its spectroscopic and optical rotation data with those described in the literature.[109] Thus, compound **82** was obtained in four steps in 21% overall yield from a stereoisomeric mixture of the 6-substituted cyclohexanone-2-propionate **91**, which represented a significant improvement with respect to the previous procedure reported by Bodo for the synthesis of aminoalcohol **82**. This alcohol is a known precursor of myrioxazine A, and also (–)-myrionine, (–)-myrionidine, (–)-schoberine and (+)-formylmyrionine and (–)-dihydroschoberine (Figure 3.72)

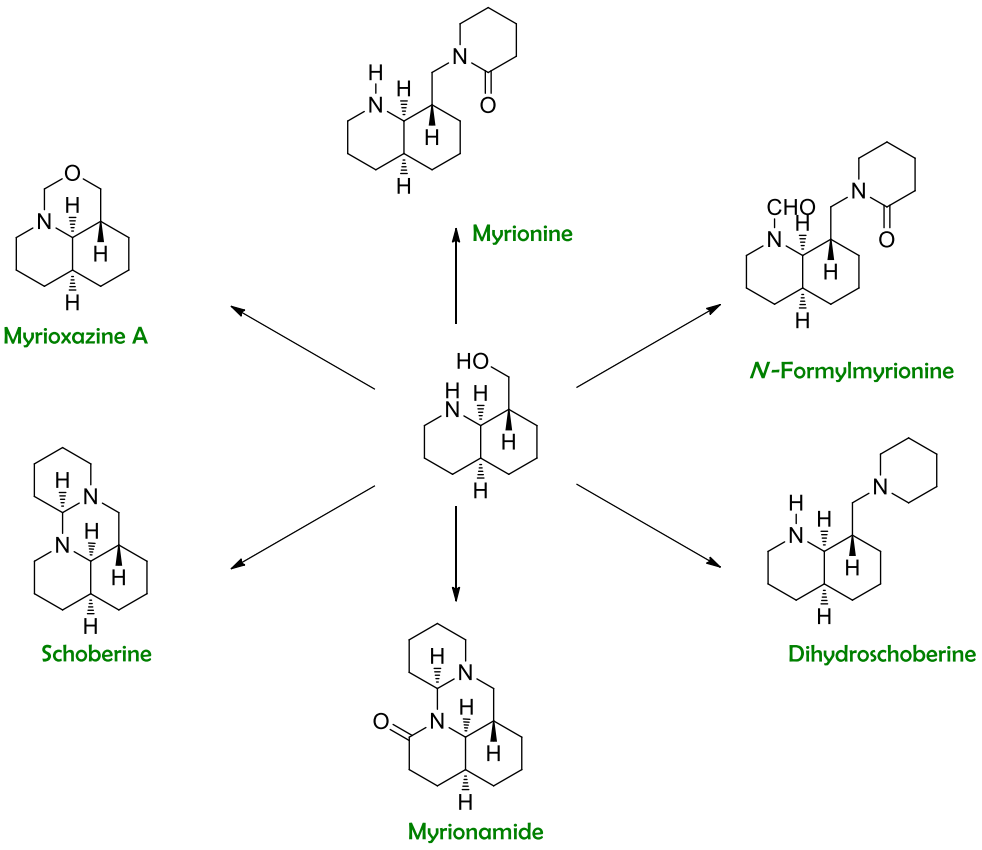

Myrionine
Myrioxazine A
N-Formylmyrionine
Schoberine
Dihydroschoberine
Myrionamide

Figure 3.72

CHAPTER 4. ENANTIOSELECTIVE SYNTHESIS OF SUBSTITUTED OCTAHYDROINDOLE DERIVATIVES

The scope of this chapter is the extension of our methodology to the synthesis of 7-alkyl *cis*-octahydroindoles and *cis*-octahydroindolones, starting from racemic cyclohexanone-1-acetate derivatives. The *cis*-octahydroindole skeleton is present in a number of natural products with biological activity (see paragraph 2.3. of present dissertation) and, for this reason, the development of a practical and efficient synthetic procedure is an important challenge for organic chemists.

4.1. Cyclocondensation reaction of 2-oxocyclohexane-based acetate derivatives

The cyclocondensation reaction of (*R*)-phenylglycinol and (1*S*,2*R*)-aminoindanol with 3-alkyl-2-oxo-cyclohexane-1-acetate derivatives **A**, **B** and **C** was considered. Starting from ketones **A** and **B**, we expected to control the formation of up to three stereocenters in only one-step. The resulting lactams will bring a substituent at C-10 and further simple transformations would finally provide enantiopure 7-substituted octahydroindoles and octahydroindolones. Moreover, in the case of **B**, the presence of a double bond would allow additional stereocontrolled manipulations, providing access to enantiopure 6,7-disubstitutes octahydroindoles and octahydroindolones. Finally, cyclocondensation reaction of **C** with chiral aminoalcohols, would give rise to only one of the sixteen possible lactams, in which four new stereogenic centers have been formed in a stereocontrolled way. In only two more steps, enantiopure C-5,7-disubstituted octahydroindoles and octahydroindolones could be obtained.

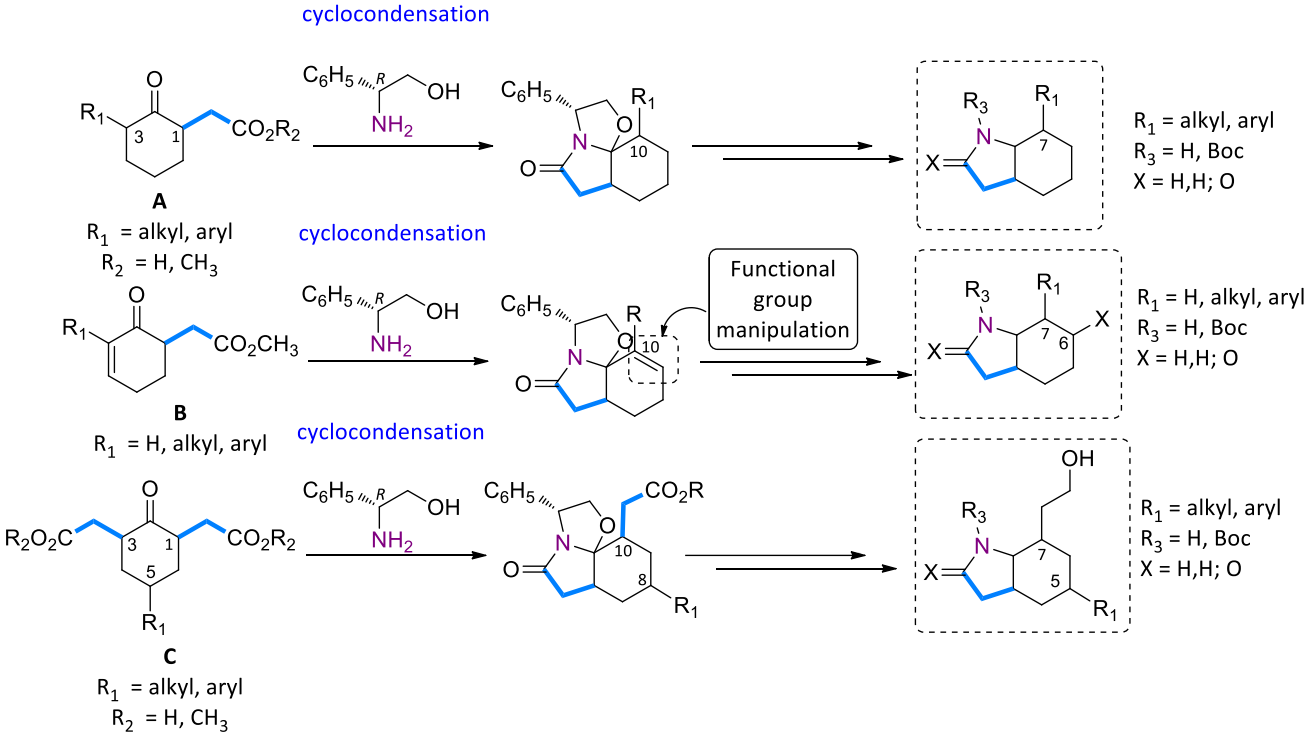


Figure 4.1 Synthetic plan

4.1.1. Previous works

Our research has firmly contributed to establish the synthetic usefulness of using enantiopure aminoalcohols as chiral inductors in the synthesis of nitrogen based compounds (piperidines, decahydroquinolines, etc.), but other groups have also displayed the potential of this methodology.[119,120,121] Among them, some groups have reported the cyclocondensation of simple 2-oxo-cyclohexaneacetic acid or a little more complex cyclohexanone-based acetate derivatives with (*R*)-phenylglycinol and other chiral aminoalcohols.[122] Remarkably, with this methodology Ennis synthesized an enantiopure diazacompound, using a 4-piperidinone-based acetic acid and phenylglycinol.[122f] Almost all runs were performed in refluxing toluene with removal of water by Dean–Stark apparatus or by addition of molecular sieves. More green microwaves technology have also been described to be successful, avoiding the use of organic solvents.[122b] Tricyclic lactams were isolated in good to excellent yield as single isomers. The absolute configuration of the octahydroindole core was controlled by the C-2 configuration of the aminoalcohol, while the presence of a chiral substituent at C-3 of aminoalcohol did not affect the stereoselection of the reaction. It is worth mentioning that in any case isomerizable substituents at the carbocyclic ring are present. Keto-acids are reported to be best partners of aminoalcohols in cyclocondensation reaction with respect to keto-esters, which normally require addition of acid. The reaction takes place in 18-24 h and the time increases with the complexity of starting materials, until 144 h.

[119]a. Meyers, A. I.; Romo, D. *Tetrahedron* **1991**, *47*, 9503–9569; b. Meyers, A. I.; Lefker, B. A. *Tetrahedron* **1987**, *43*, 5663–5676.

[120] Synthesis of pyrrolidines: a. Meyers, A. I.; Burgess, L. E. *J. Org. Chem.* **1991**, *56*, 2294–2296; b. Burgess, L. E.; Meyers, A. I. *J. Am. Chem. Soc.* **1991**, *113*, 9858–9859; c. Burgess, L. E.; Meyers, A. I. *J. Org. Chem.* **1992**, *57*, 1656–1662; d. Meyers, A. I.; Snyder, L. *J. Org. Chem.* **1992**, *57*, 3814–3819; e. Westrum, L. J.; Meyers, A. I. *Tetrahedron Lett.* **1994**, *35*, 973–976; f. Tschantz, M. A.; Burgess, L. E.; Meyers, A. I. *Org. Synth.* **1994**, *73*, 221–230; g. Bienz, S.; Busacca, C.; Meyers, A. I. *J. Am. Chem. Soc.* **1989**, *111*, 1905–1907.

[121] Synthesis of piperidines: a. Munchhof, M. J.; Meyers, A. I. *J. Org. Chem.* **1995**, *60*, 7084–7085.

[122] a. Ragan, J. A.; Claffey, M. C. *Heterocycles* **1995**, *41*, 57–70; b. Jida, M.; Deprez-Poulain, R.; Malaquin, S.; Roussel, P.; Agbossou-Niedercorn, F.; Deprez, B.; Laconde, G. *Green Chem.* **2010**, *12*, 961–964; c. Allin, S. M.; James, S. L.; Elsegood, M. R. J.; Martin, W. P. *J. Org. Chem.* **2002**, *67*, 9464–9467; d. Allin, S. M.; Towler, J. M. R.; Elsegood, M. R. J.; Saha, B.; Page, P. C. B. *Synthetic communications* **2012**, *42*, 872–882; e. Ennis, M .D.; Hoffman, R. L.; Ghazal, N. B.; Old, D. W.; Mooney, P. A. *J. Org. Chem.* **1996**, *61*, 5813–5817; f. Nieman, J. A.; Ennis, M. D. *Org. Lett.* **2000**, *10*, 1395–1397.

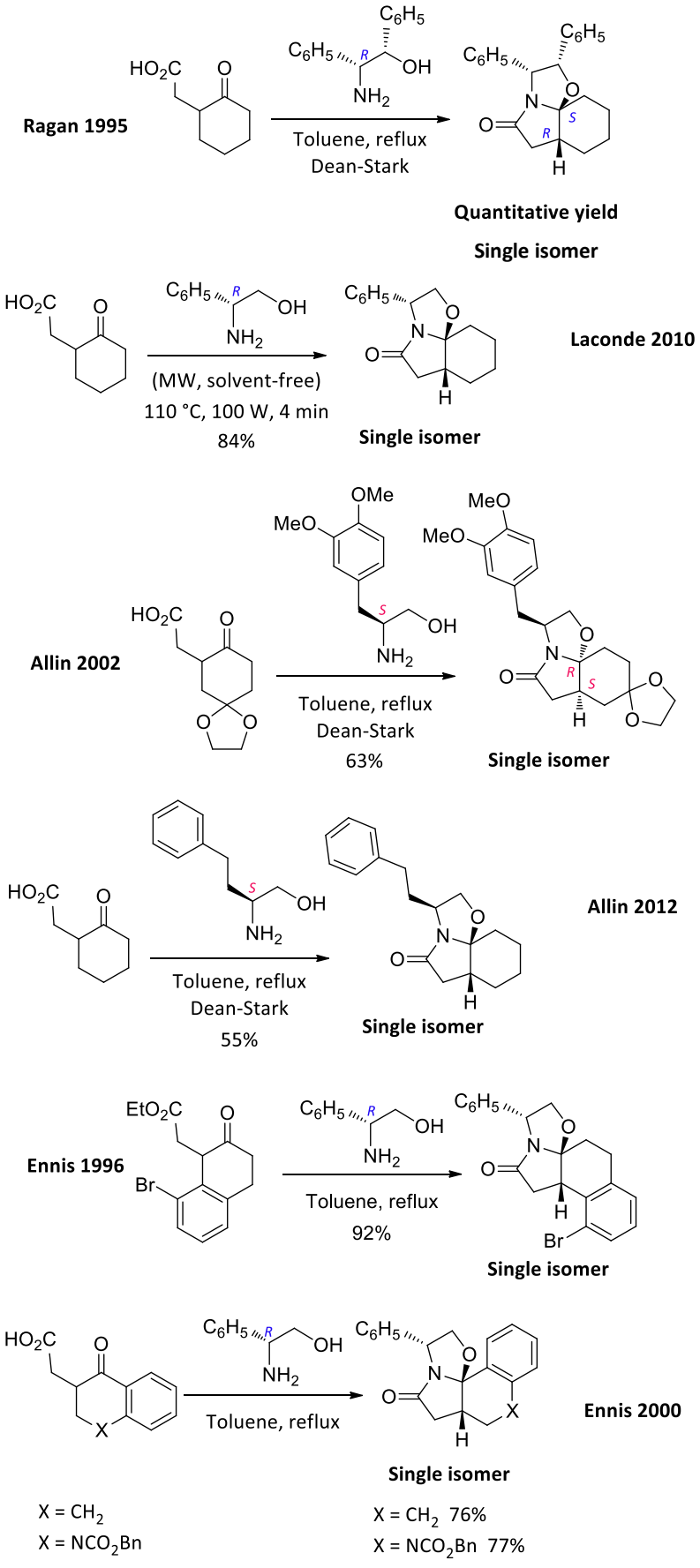


Figure 4.2 Previous studies on cyclocondensation reaction

Cyclocondensations of cyclopentanone-based acetate derivatives with phenylglycinol have been also reported and provided lactams bearing an octahydrocyclopenta[*b*]pyrroles unit. Even in these case no isomerizable substituents are presents and only one isomer has been obtained in very good yield. (Figure 4.3). [155a,b,e,123]

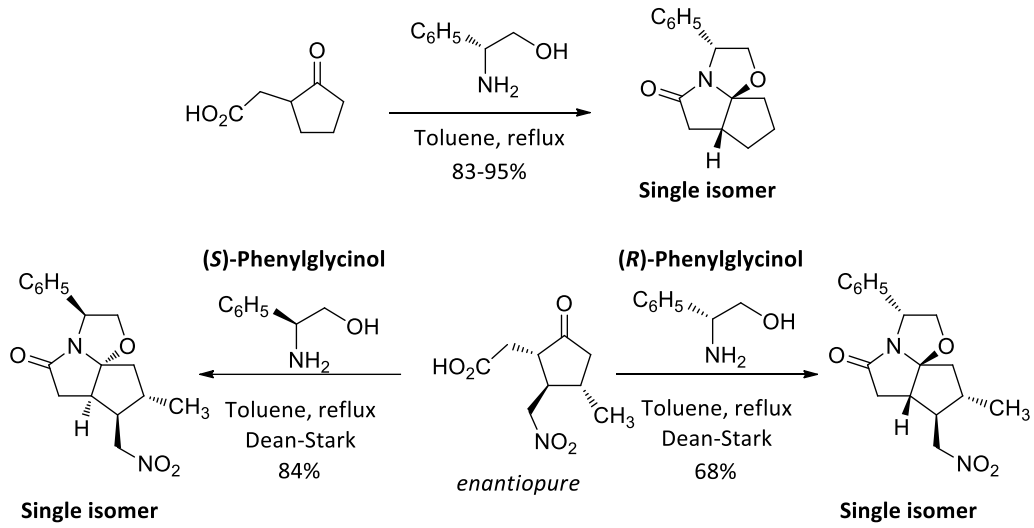


Figure 4.3

Even in the case of more complex aminoalcohols[155a,b,124] only one *cis* isomer was isolated and the yield seems to be dependent on the steric hindrance of the chiral inductor.

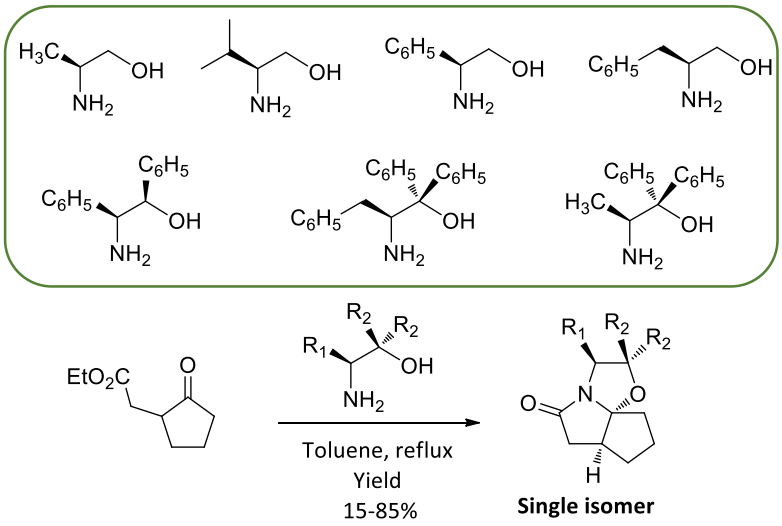


Figure 4.4

[123] Deprez-Polain, R.; Willand, N.; Boutillon, C.; Nowogrocki, G.; Azaroual, N.; Deprez, B. *Tetrahedron Lett.* **2004**, *45*, 5493–5496.

[124] Aurich, H. G.; Soeberdt, M. *Tetrahedron Lett.* **1998**, *39*, 2553–2554.

In conclusion we could deduce that the stereochemical outcome of the cyclocondensation process from cyclic 2-oxoacetate derivatives strongly depends on the configuration at C-2 of the chiral 2-amino alcohol and is highly stereoselective. The presence of an additional substituent at the chiral aminoalcohol as well as the size of the carbocyclic ring do not influence the final product configuration.[125]

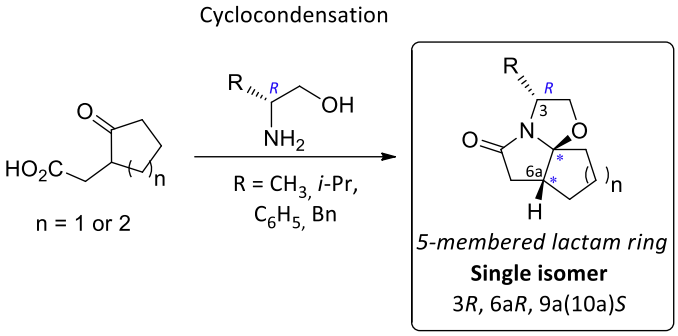


Figure 4.5

4.1.2. Present work

4.1.2.1. Preparation of starting materials

The required cyclohexanone-based acetate derivatives had to be synthesized, since they are not commercially available. Two different methodologies for the introduction of the acetate chain were applied, whether if simple cyclohexanone or already substituted cyclohexanones were employed. Compounds **97**-**100** were so obtained in good yield and complete regioselectivity by alkylation of the kinetic lithium enolate, derived from reaction of LDA and 2-substituted ketones **34**, **37**, **38** and **96**, with methyl bromoacetate in the presence of HMPA at low temperature. Acid **101** was obtained by basic hydrolysis of the corresponding ester.

[125] For other, no previously reported cyclocondensation reaction, see: a. Kossenjans, M.; Soeberdt, M.; Wallbaum, S.; Harms, K.; Martens, J.; Aurich, H. G. *J. Chem. Soc., Perkin Trans. 1*, **1999**, 2353–2365; b. Trauner, D.; Schwarz, J. B.; Danishefsky, S. J. *Angew. Chem. Int. Ed.* **1999**, *38*, 3542–3545; c. Allin, S. M.; Streetley, G. B.; Slater, M.; James, S. L.; Martin, W. P. *Tetrahedron Lett.* **2004**, *45*, 5493–5496; d. Moore, G.; Papamicaël, C.; Levacher, V.; Bourgignon, J.; Dupas, G. *Tetrahedron* **2004**, *60*, 4197–5204; e. Enders, D.; Niemeier, O.; Balensiefer, T. *Angew. Chem. Int. Ed.* **2006**, *118*, 1491–1495; f. Malaquin, S.; Jida, M.; Courtin, J.; Laconde, G.; Willand, N.; Deprez, B.; Deprez-Poulain, R. *Tetrahedron Lett.* **2013**, *54*, 562–567.

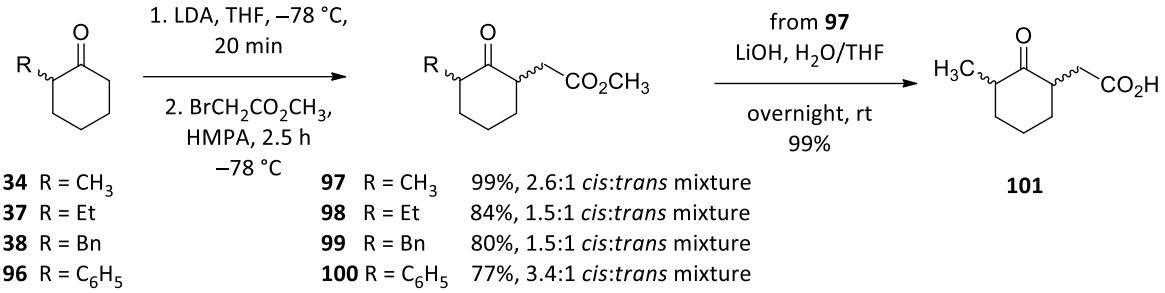


Figure 4.6 Synthesis of 2-oxocyclohexaneacetate derivatives *via* enolate

Ketones **104**[126] and **105** were easily prepared in excellent yield, using the same conditions, starting from commercially available cyclohexenones **102** and **103**.

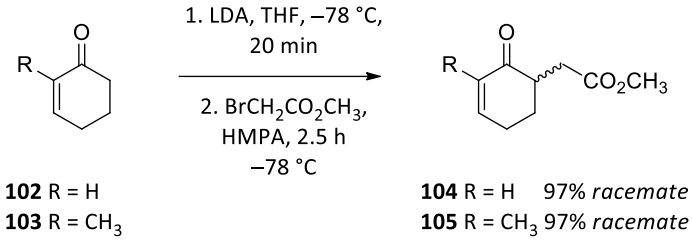


Figure 4.7 Synthesis of 2-oxocyclohexeneaceteta derivatives

On the other hand, methyl 2-oxocyclohexaneacetate **106** was synthesized by alkylation of the pyrrolidine-derived enamine of ketone **23** with methyl bromoacetate, in the presence of DIPEA, in refluxing acetonitrile.

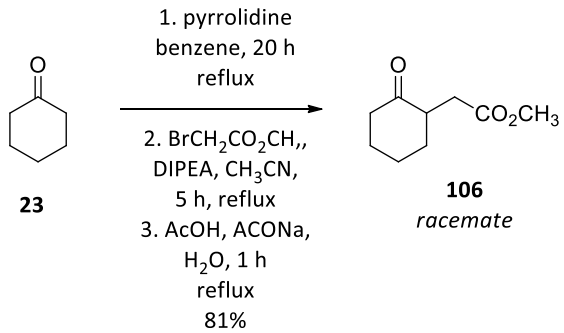


Figure 4.8 Synthesis of methyl 2-oxocyclohexaneacetate 106 *via* enamine

When the mixture of enamine and methyl bromoacetate was allowed to react 24 h instead of 5 h, keto-diester **107** was obtained in good yield. In the same conditions, ketones **24** and **25** provided diesters **108** and **109**, as a mixture of isomers (Figure 4.9).

[126] Previously described: Izawa, Y.; Zheng, C.; Stahl, S. S. *Angew. Chem. Int. Ed.* **2013**, *52*, 3672–3675.

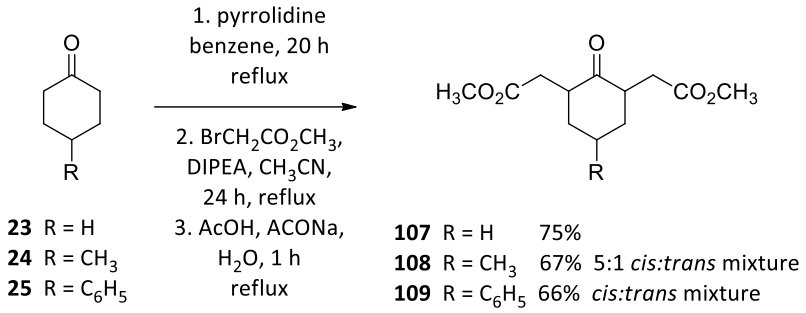
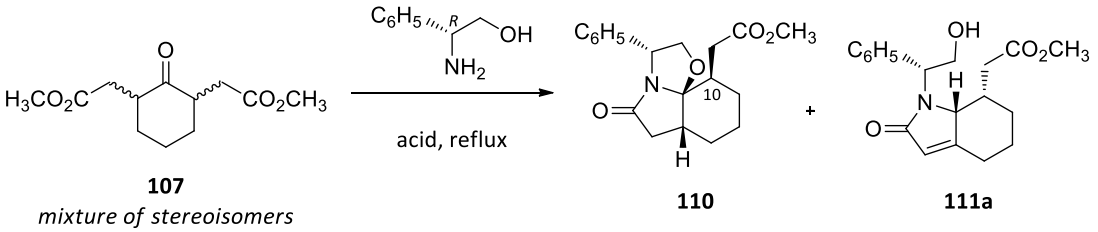


Figure 4.9

4.1.2.2. Cyclocondensation reaction of 2-oxocyclohexaneacetate derivatives

Keto-diester **107** was used as model for our initial study. The resulting enantiopure tricyclic lactam **110** exhibits an acetate chain at C-10, which could allow further functionalizations. Bicyclic enamide **111a** was also formed, in variable amounts. In both cases the new formed stereocenters have a well-defined configuration.



107
mixture of stereoisomers

110 **111a**

	equiv. PG	solvent	t	acid	y% (**110**)	**110**:**111a**[b]
1	2.6	Toluene	24h	*i*-PrCO$_2$H	50[a]	4:1
2	1.3+1.3	Toluene	48h	*i*-PrCO$_2$H	58[b]	4.1:1
3	1.5+1.5	Toluene	48h	AcOH	60[b]	5:1
4	1.5+1.5	Benzene	48h	*i*-PrCO$_2$H	52[b]	3:1
5	3	Benzene	48h	AcOH	50[b]	5.8:1
6	1.5+1.5	Benzene	48h	AcOH	62[a]	6.2:1[a]

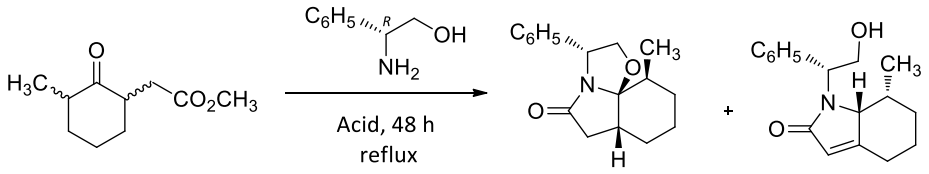
a. Isolated by flash chromatography; b. Calculated by GC-MS from filtrated crude.

Table 4.1 Cyclocondensation reaction of ketodiester 107 with (*R*)-phenylglycinol

The reaction was carried out initially in refluxing toluene (0.06 M solution) in the presence of acid (isobutyric or acetic acid, which were found to be the best catalyst in cyclocondensation of δ-oxoesters)[127], with azeotropic elimination of water with Dean–Stark apparatus. We obtained a 4:1 mixture of **110** and **111a** in good yield. Portionwise addition of phenylglycinol resulted in slightly improvement of the yield.

[127] See Chapter 3 of this Thesis.

At lower boiling point of the solvent used in the reaction (benzene instead of toluene was used), in the presence of acetic acid, resulted in an improvement of the yield of **110** and the formation of **111a** was limited. Reaction under microwave activation, dissolving the reagents in toluene or using neat conditions, did not afforded the expected lactam and complete recovering of starting materials was observed.
Then, ketoester **97** and ketoacid **101** in combination of (*R*)-phenylglycinol were allowed to react in various conditions.



97
mixture of stereoisomers

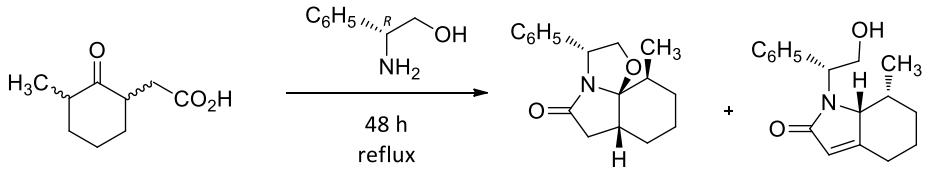
112a **113a**

	equiv. PG	solvent	add	y% (**112a**)[a]	**112a**:**113a**[b]
1	1.5+1.5	Toluene	*i*-$PrCO_2H$	45	4.5:1
2	4	Benzene	AcOH	66	7.5:1
3	1.5+1.5	Benzene	AcOH	75	9:1

a. Isolated by flash-chromatography b. Calculated by GC-MS from filtrated crude

Table 4.2 Cyclocondensation of ester 97

Starting from **97**, in benzene and acetic acid, with sequential addition of chiral inductor, furnished the best outcome: 75% of desired tricyclic lactam **112a**, in which three new stereogenic centers of well-defined configuration have been formed, and only 8% of unsaturated lactam **113a** were isolated. When the reaction was performed in dichloromethane, at low temperature (0 °C) with the addition of magnesium sulphate and copper triflate, the starting material did not evolve. The use of oxo-acid derivative **101** did not improve the chemical yield and the stereoselectivity with respect to keto-ester **97**, as displayed in Table 4.3.



101
mixture of stereoisomers

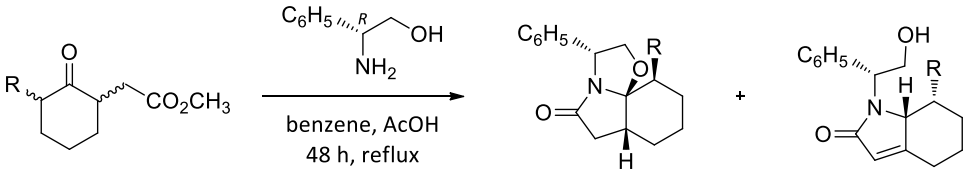
112a **113a**

	equiv. PG	solvent	y% (**112a**)[a]	**112a**:**113a**[b]
1	1.5+1.5	Toluene	45	5:1
2	1.5+1.5	Benzene	62	7.2:1

Table 4.3 Cyclocondensation reaction of acid 101

We thus concluded that the best conditions for this process require keto-esters and phenylglycinol in refluxing benzene and in the presence of acetic acid.

With this information in hand, we went on with the study of cyclocondensation reaction starting from ketoesters **98**-**100**. In every example, we observed the formation of only one tricyclic lactam **114**, **116** and **118** respectively and, in the case of alkyl substituents also unsaturated lactams **115a** and **117a** are also isolated, in relevant ratios.



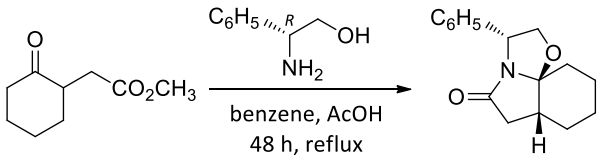
98 R = Et *mixture of isomers*
99 R = Bn *mixture of isomers*
100 R = C_6H_5 *mixture of isomers*

114 R = Et 57%
116 R = Bn 65%
118 R = C_6H_5 53%

115a 15%
117a 23%
-

Figure 4.10

Synthesis of the already described lactam **119** allowed us to compare the efficiency of our conditions with respect to those reported.[citas] The lactam **119** was isolated in 68% yield and the corresponding unsaturated compound was not detected, and we will further furnish an explanation.



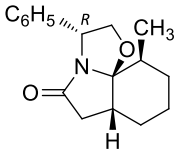
106
racemate

119

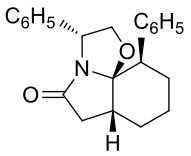
Figure 4.11

It is note-worthy that only cyclohexanone-2-acatate derivatives having alkyl substituents at the 6-position (**97**, **98** , **99** and **107**)provided unsaturated bicyclic lactams in the cyclocondensation reactions as by-products, whereas unsubstituted (**106**) or phenyl-substituted (**100**)starting materials afforded a single compound, the expected tricyclic lactam.

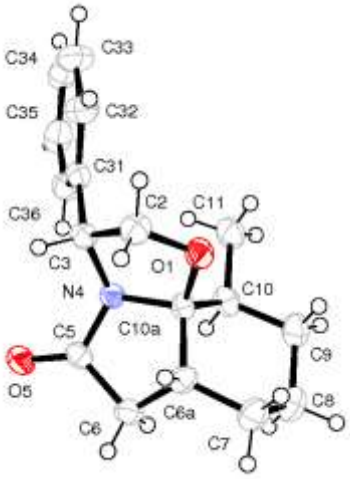
The absolute configuration of tricyclic lactams and unsaturated by-products was definitely determined by X-ray crystallography of **112a**, **118** and **113a**, keeping in mind that enantiopure (*R*)-phenylglycinol was used in the process. No *trans* isomers are formed in the process.



112a



118



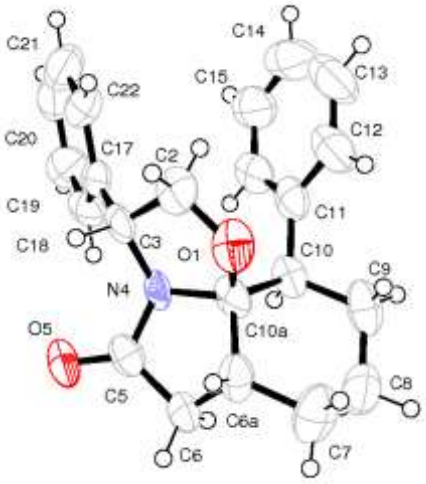
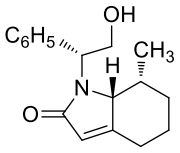


Figure 4.12 X-ray structure for lactam 112a and 118



113a

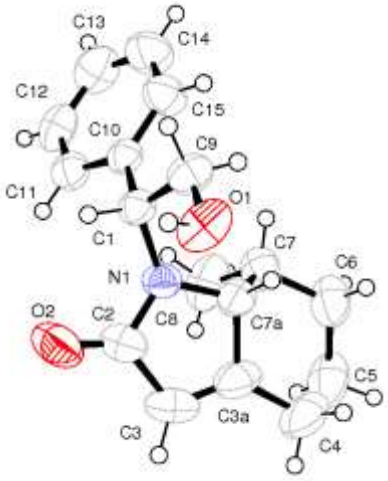


Figure 4.13 X-ray structure for lactam 113a

Finally, since (1*S*,2*R*)-2-aminoindanol gave better results than (*R*)-phenylglycinol in the series of decahydroquinolines, we applied the found conditions starting from ketoester **107** and *cis*-aminoindanol. Refluxing the reaction mixture in benzene for 48 h, in the presence of acetic acid, provided an inseparable mixture of two isomers, **120a** and **120b**, in 2.8:1 *ratio,* calculated by ^{1}H-NMR.

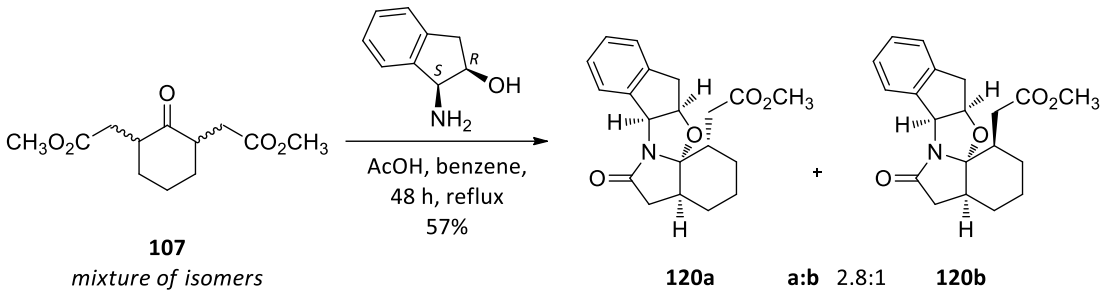


Figure 4.14 Cyclocondensation with (1*S*, 2*R*)-aminoindanol

Only few amounts of pure **120a** could be isolated, which allowed us to describe and identify this lactam as depicted in Figure 4.14. The structure of **120b** was assigned on the base of our proposed mechanism, which will be further explained. Since no improvement had been obtained with respect to phenylglycinol, we discarded the study of aminoindanol as chiral inductor in cyclocondensation reaction with 2-oxoacetate derivatives.

4.1.2.3. Cyclocondensation reaction of methyl 2-oxocyclohexeneacetate derivatives

Reaction of α,β-unsaturated ketones with (*R*)-phenylglycinol should result in the formation of lactams, which bring a carbon-carbon double bond at C_9-C_{10}. This functionalization could allow us further interesting modification of the carbocyclic ring. Initially, we tested the cyclocondensation on ketone **104** lacking an alkyl substituent at C-3. Unfortunately, a mixture of five products was observed. The proposed structures **121a**-**d** were deducted by studying the NMR spectra, with the aid of 2D homo- and heterocorrelation.

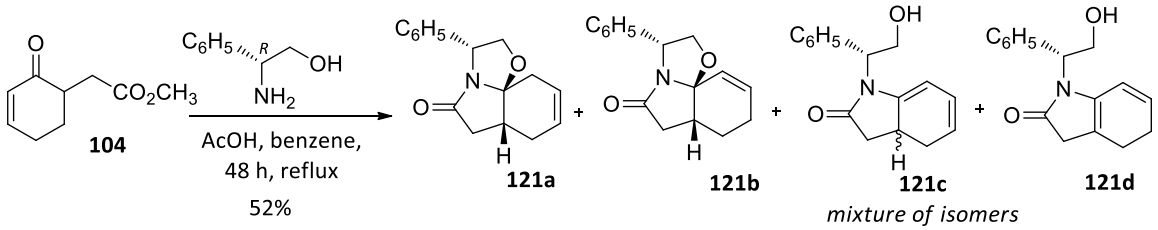
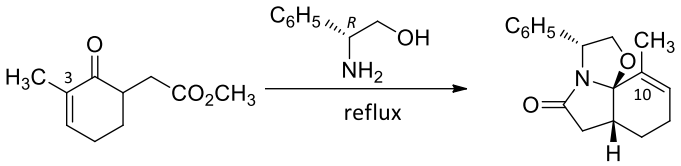


Figure 4.15 Cyclocondensation of 104

The presence of a substituent at C-3 in **105** avoided the formation of a chaotic mixture of products and only one lactam **122** of the four possible isomers was isolated, while the corresponding enamide was not detected. The best condition required refluxing toluene (benzene provided very poor yield), with acetic acid as catalyst.



105
racemate

122

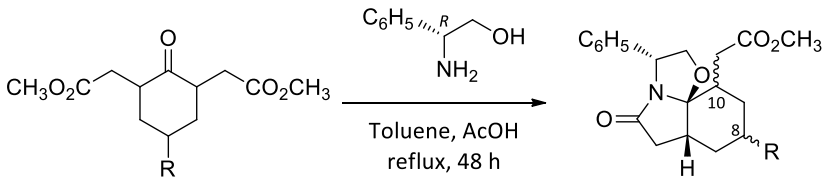
	equiv. PG	solvent	t	add	y%
1	1.5	Benzene	48h	AcOH	22
2	1.5+1.5	Benzene	72h	AcOH	16
3	1.5+1.5	Toluene	48h	AcOH	61
4	1.5	Toluene	24h	*p*TsOH	sm

Table 4.4 Cyclocondensation of 105

The absolute configuration was deducted on the basis of the already synthesized tricyclic lactams.

4.1.2.4. Cyclocondensation reaction of dimethyl-5-substituted-2-oxocyclohexanediacetate derivatives

In order to synthesize more complex tricyclic lactams exhibiting an acetate chain at C-10 and an additional substituent at C-8, the reaction of ketones **108** and **109** with phenylglycinol was studied using the best conditions found previously. Unfortunately an inseparable mixture of isomeric lactams, indicating lack of stereoselection, was obtained in both cases.



108 R = CH_3 *mixture of isomers*
109 R = C_6H_5 *mixture of isomers*

123 R = CH_3 56% 2.2:1:1
124 R = C_6H_5 60% 2:1.2:1

Figure 4.16 Cyclocondensation of keto-esters 108 and 109

In conclusion, in this section, seven new tricyclic lactams in which three stereogenic centers of well-defined configuration have been generated from mixture of racemic oxo-esters in a single step, are reported (Figure 4.17).

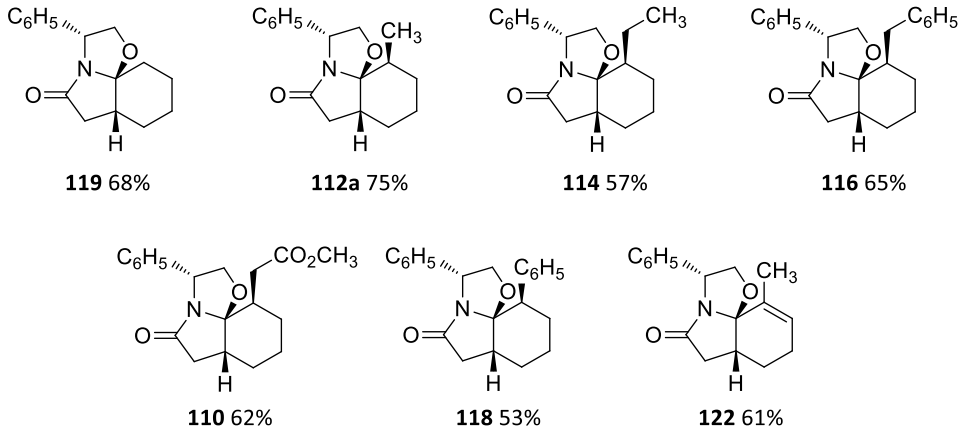


Figure 4.17

4.1.3. Proposed mechanism

The stereoselective formation of the C-10 substituted tricyclic lactams described in this section can be accounted for by considering that the initially formed imine **A** is in equilibrium, *via* enamines **B** and **C**, with up to eight diastereoisomeric oxazolidines **D** (Figure 4.18). Due to steric constraints, the subsequent irreversible lactamization lead to the isomer that is formed faster. A dynamic kinetic resolution, with epimerization of the two configurationally labile stereocenters in the substrate, takes place (from *trans* isomers of ketone **107**). .

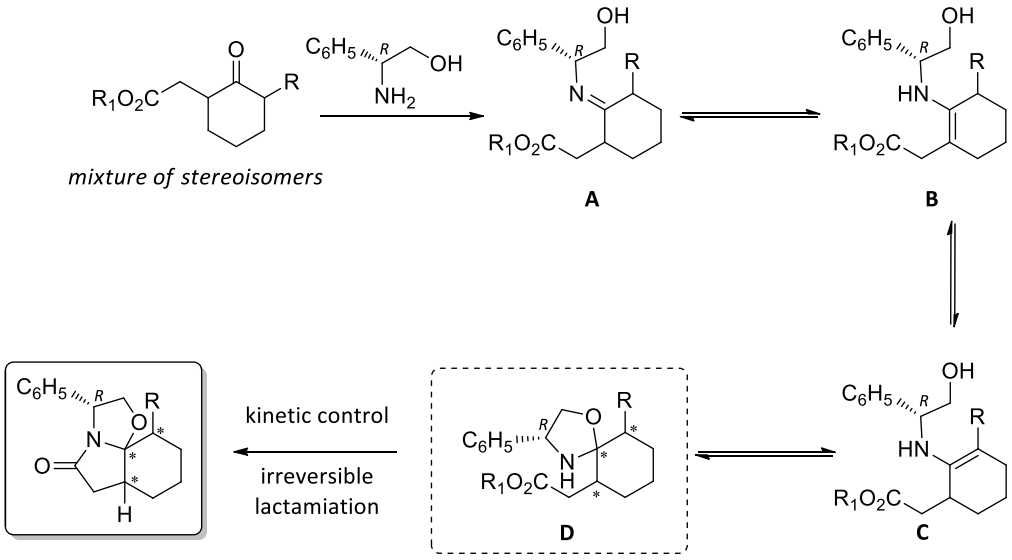


Figure 4.18 Proposed mechanism

In Figure 4.19 the eight possible diastereomeric tricyclic lactams that can be formed in the above reaction are depicted. Taking into account previous observations on the stereochemical outcome of cyclocondensation reactions of cyclohexanone-1-acetate derivatives with chiral aminoalcohols such as

phenylglycinol, only two isomers, **a** *cis*-A and **b** *cis*-B, should be formed. However, isomers **b** *cis*-B, epimers at C-10 with respect to lactams **a** *cis*-A, were not isolated.

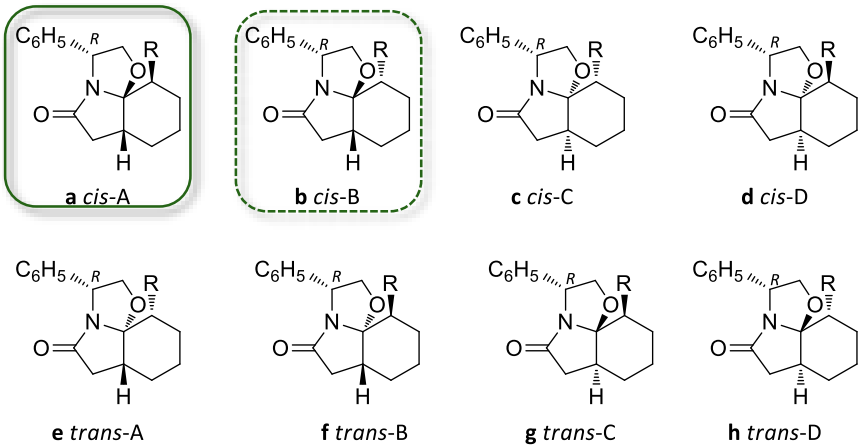


Figure 4.19 Eight possible diastereoisomeric lactams

Nevertheless, the observation that the stereogenic center next to the methyl in **113a**, whose stereochemical identity was unambiguously established by X-ray analysis, had the same configuration at this position than corresponding tricyclic lactam **b** *cis*-B (R = Me) made us to suspect that this compound was generated in the cyclocondensation reaction as a minor isomer but, under the reaction conditions, underwent a ring opening to give **113a**.

Figure 4.20

Formation of unsaturated bicyclic lactams **111a**, **113a**, **115a**, and **117a** can be accounted for by considering that the protonation of the oxygen atom of the oxazolidine ring under the acidic reaction conditions provokes the formation of an acyliminium salt (**E**) which is in equilibrium with the corresponding enamide (**F**). Stereoselective protonation from the less hindered face through the tautomeric enol form of the lactam (**G**) affords the observed unsaturated bicyclic lactams.

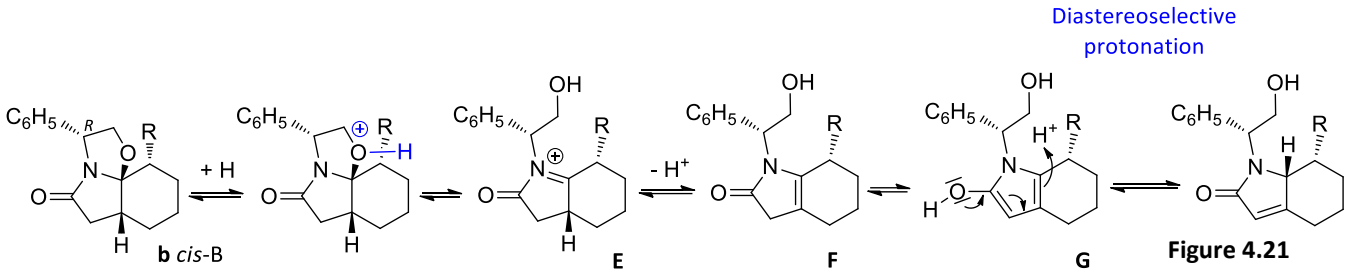


Figure 4.21

Proposed mechanism for the formation of unsaturated lactam

Thus, the observed results raise two questions: i) Why isomers **a** *cis*-A are formed in larger proportion with respect to isomers **b** *cis*-B?, and ii) Why minor isomers **b** *cis*-B undergo ring opening and major isomers **a** *cis*-A do not?.

As it has been mentioned before, the reaction of phenylglycinol and the oxo-ester generates a mixture of eight diastereomeric oxazolidines which are in equilibrium through the corresponding imine-enamines. The lactamization step takes place faster from the isomer at C-2 of the oxazolidine ring (corresponding to C-10a of the tricyclic lactam) that allow the approach of the carboxylate to the nitrogen atom from the less hindered face of the oxazolidine ring and from a conformation of the cyclohexane ring in which the acetate chain is axial (which defines the configuration of C-6a in the tricyclic lactam) affording a *cis* fusion. The major isomers **a** *cis*-A result from a transition state in which R_2 occupies an equatorial position on the cyclohexane ring. However, formation of the minor isomers **b** *cis*-B involves a transition state with strong destabilizing steric interactions between the acetate chain and R_2 in a 1,3-diaxial relative disposition on the carbocyclic ring.

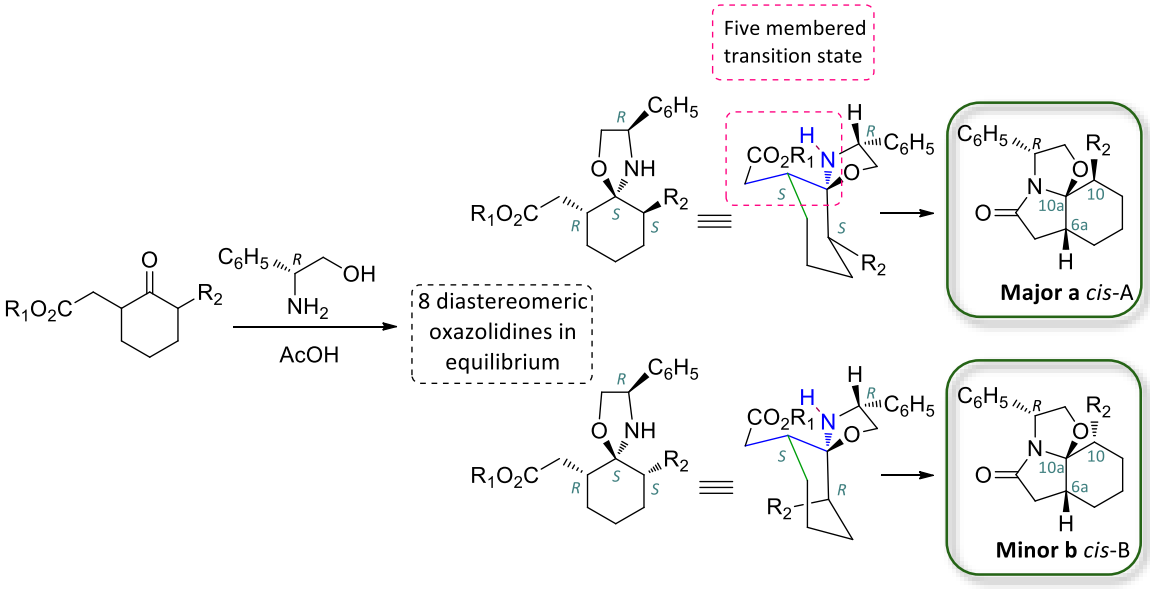


Figure 4.22 Lactamization from oxazolidines D1 and D2

On the other hand, in isomer **b** *cis*-B, due to the conformational rigidity of the tricyclic system, the substituent R holds near the methylene of the lactam ring provoking severe steric interactions. Ring opening of the tricyclic system releases this destabilizing factor leading to a bicyclic system.

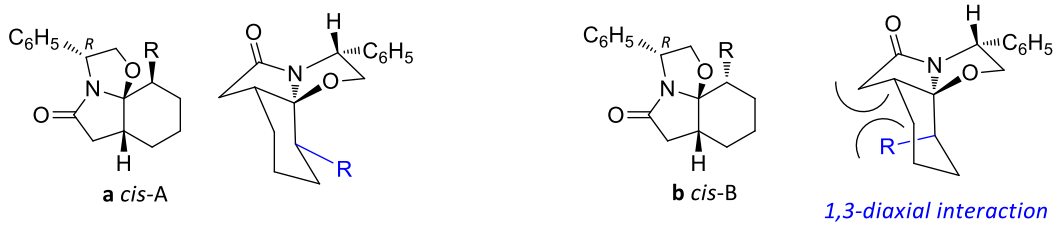


Figure 4.23

This hypothesis was confirmed when a mixture of C-10 epimeric lactams **122a** and **122b**[128] were subjected to the cyclocondensation reaction conditions. After heating a 0.06 M benzene solution for 48h in the presence of 1 equiv. of acetic acid, the complete conversion of isomer **122b** into the unsaturated lactam **113a** was observed whereas isomer **122a** remained unchanged. After this time, the addition of an excess of acetic acid and heating during a prolonged time led to the observation of small amounts of the unsaturated lactam resulting from ring opening of isomer **122a** to give **113b** (see later ring opening of lactam **122a**).

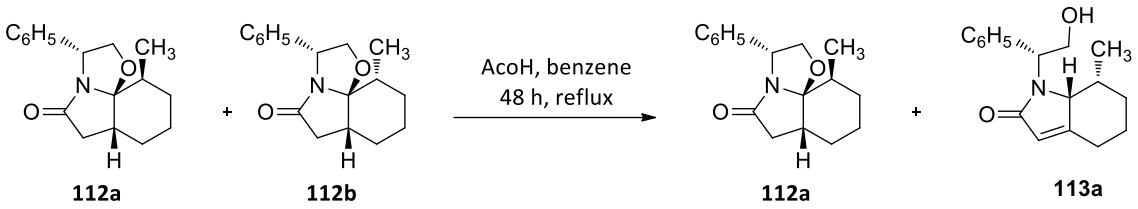


Figure 4.24 Evidence of the proposed mechanism

On the other hand, this hypothesis justifies the observation that the cyclocondensation of the unsubstituted cyclohexanone-1-acetate **106** with phenylglycinol does not afford unsaturated bicyclic derivatives, resulting from the ring opening of the oxazolidine ring of the tricyclic lactam **119**. Moreover, the major ratio of unsaturated bicyclic lactams **111a**, **113a**, **115a** and **117a** when the cyclocondensation reaction is carried out in toluene (bp 111 °C) with respect to benzene (bp 80 °C) are in agreement with the proposal mechanism.

It is worth mentioning that S. M. Allin reported that the treatment of the tricyclic lactam **I**, depicted in Figure 4.25, under acid conditions did not afford the expected tetracyclic compound **II**. Instead, the corresponding unsaturated bicyclic lactam **III**, whose structure was unambiguously assigned by X-ray analysis, was isolated in 80% yield.[122d]

[128] The obtaining of this mixture will be explained in Paragraph 4.4.1.

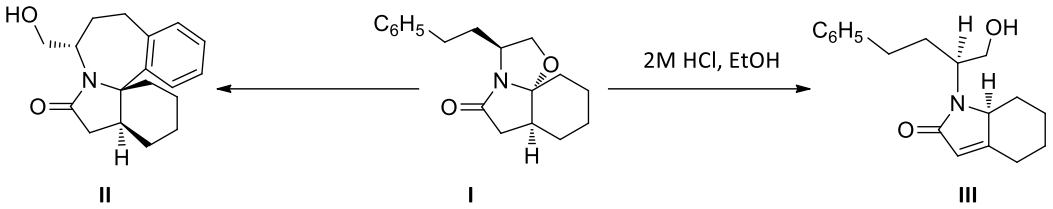
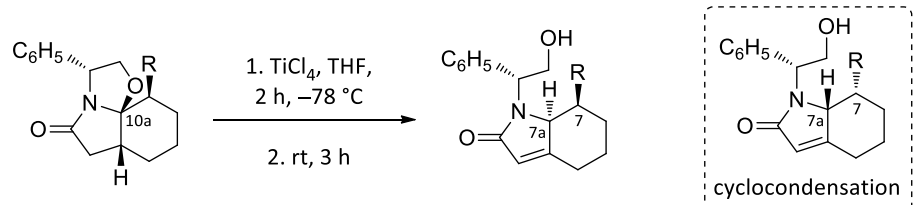


Figure 4.25 Reported reactivity by Allin

A final question remains to be considered: why in the cyclocondensation of the C-3 phenyl-substituted cyclohexanone-1-acetate **100** with phenylglycinol the formation of the corresponding unsaturated bicyclic lactam was not observed? The hypothesis is that due to the higher steric requirements of the phenyl substituent with respect to the alkyl counterparts, the difference of energy between the two transition states leading to **118** (**a** *cis*-A) or to the corresponding epimeric tricyclic lactam **b** *cis*-B is much higher and this isomer (**b**, R = C_6H_5) is not formed under the reaction conditions. As a result, the corresponding C-7 phenyl substituted unsaturated lactam was not observed.[129]

4.2. Reactivity of tricyclic lactams towards acids

Taking into account of the above considerations, the reactivity of lactams **a** *cis*-A under acidic conditions was investigated. In particular, it was found that titanium tetrachloride in THF promotes the conversion of tricyclic lactams into the corresponding unsaturated systems. The process is fast and clean. The yields are very good (up to 90%) and no hydrolysis of lactam or ester (in **110**) are observed. The most interesting aspect is that only one isomer is selectively formed, in which H-7 and H-7a adopt a *cis* relative disposition. The absolute configuration of these unsaturated lactams was deduced on the basis of NOE couplings and by comparison of their spectroscopic data with those of the analogs isolated in the cyclocondensation process.



112a R = CH_3
114 R = Et
116 R = Bn
110 R = $CH_2CO_2CH_3$

113b R = CH_3 70%
115b R = Et 61%
117b R = Bn 80%
111b R = $CH_2CO_2CH_3$ 90%

Figure 4.26 Formation of conjugated unsaturated lactam

[129] Smith, M. B.; Merch, J. *March's Advanced Organic Chemistry: Reactions, Mechanisms, and Structures,* Six ed.; Wiley Ed., NY, **2007**, 206–207.

When the phenyl-substituted lactam **118** was subjected to the same acidic conditions, the unexpected isomer **125**, in which H-7 and H-7a are in *trans* relative disposition, is formed. The structure was confirmed by conversion into the *cis*-octahydroindole **126a** (following the procedure that will be described later) which had been reported previously.[130]

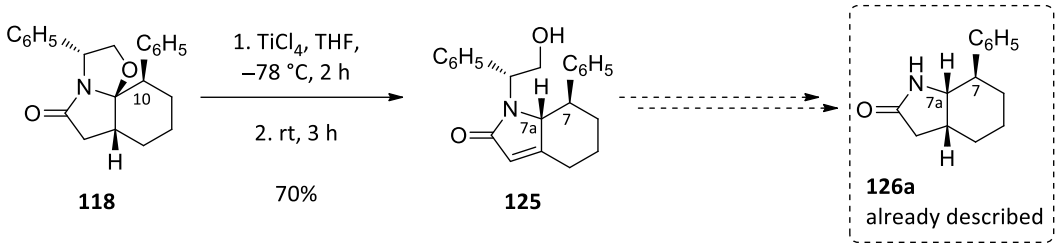


Figure 4.27 Synthesis and stereochemical determination of lactam 125

Other Lewis and protic acids as well as solvent combinations were tested (glacial acetic acid in refluxing toluene or THF; 2.6 M hydrochloric acid in ether or ethanol at room temperature or at reflux temperature; and, finally, $TiCl_4$ in dichloromethane), but in almost all runs the unsaturated lactams were not detected. Only when high concentrations of acetic acid or isobutyric acid in refluxing benzene or toluene were employed we observed the formation of the unsaturated lactam, but the reaction was very slow (more than 2:1 ratio of starting material: unsaturated lactam after 48 h, 6 equiv. of acid). Remarkably, when $TiCl_4$ is employed in combination with dichloromethane instead of tetrahydrofuran, no transformation is experimented.

Thus, once again, the C-10 alkyl substituted tricyclic lactams (**112a**, **114**, **116** and **110**) displayed a different behaviour with respect to the analogous phenyl derivative **118**. An inspection of the literature precedents on the stereoselectivity of similar protonation reactions of C-7 substituted hexahydroindolones, led us to identify only two examples, which are described below.

Treatment of the C-7a amino substituted hexahydroindolone, having a methyl substituent at the C-7 position, depicted in Figure 4.28, under acidic conditions stereoselectively afforded the corresponding unsaturated bicyclic lactam in which the hydrogens at C-7 and C-7a are *cis*. Only minor amounts of the *trans* isomer were observed.[131]

[130] Yasuhara, T.; Nishimura, K.; Osafune, E.; Muraoka, O.; Tomioka, K. *Chem. Pharm. Bull.* **2004**, *52*, 1109–1113 (racemic series).

[131] Endo, Y.; Shudo, K. *Heterocycles* **1992**, *33*, 91–95.

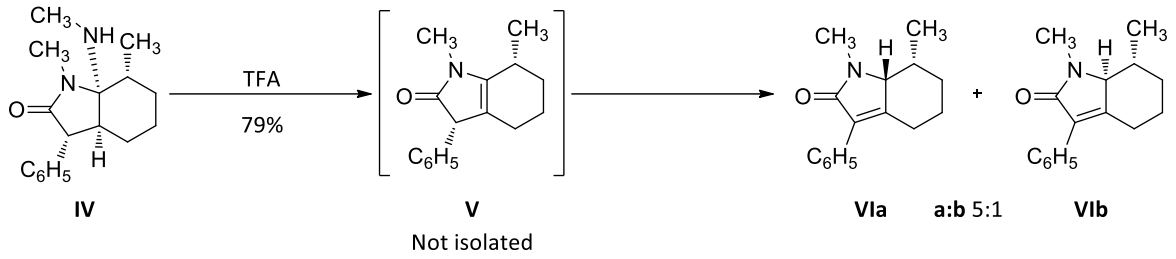


Figure 4.28

It is worth mentioning that in order to find further confirmation of the stereochemical outcome in the protonation of C-7 alkyl substituted hexahydroindolones, we subjected ketone **97** and enantiopure (2*S*)-2-methyl-benzylamine to the cyclocondensation reaction conditions. A mixture of two inseparable products **127a** and **127b** were identified. The *J* value of the doublet corresponding to the H-7a signal for **127a** and **127b** (*J* = 6.0 Hz and *J* = 5.6 Hz) is in agreement with a *cis* relative configuration of the H-7 and H-7a hydrogens.

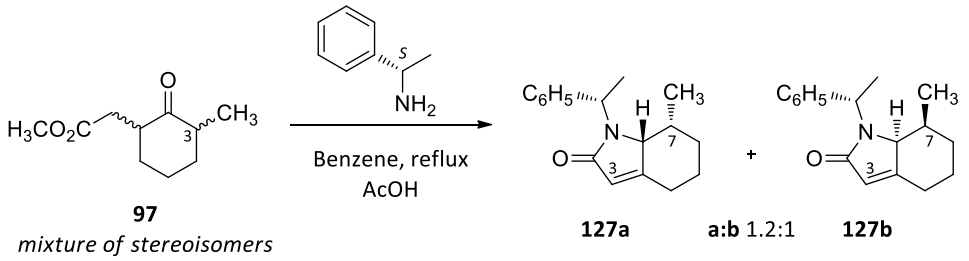


Figure 4.29 Study on the mechanism

On the other hand, when the oxime **VII**, depicted in Figure 4.30, was subjected to reduction with zinc dust in glacial acetic acid, a mixture of the hexahydroindolone enamide **VIII** and unsaturated lactam **IX** was observed.[132] This lactam **IX** is formed by stereoselective double bond isomerization from **VIII** through a mechanism similar to that depicted in Figure 4.21. The value of the coupling constant (*J* = 10 Hz) observed for the doublet attributable to the H-7a signal (δ = 3.81 ppm) is in agreement with an H-7 and H-7a *trans* relative configuration. Similarly, when cyclohexanone **X** was treated with benzylamine followed by heating of the reaction mixture with formic acid, the corresponding hexahydroindolone in which the hydrogens at C-7 and C-7a are *trans*, was stereoselectively isolated.

[132] Umezawa, R.; Hoshino, O.; Sawaki, S.; Sato, S.; Numano, N. *J. Org. Chem.* **1977**, *42*, 4272–4275.

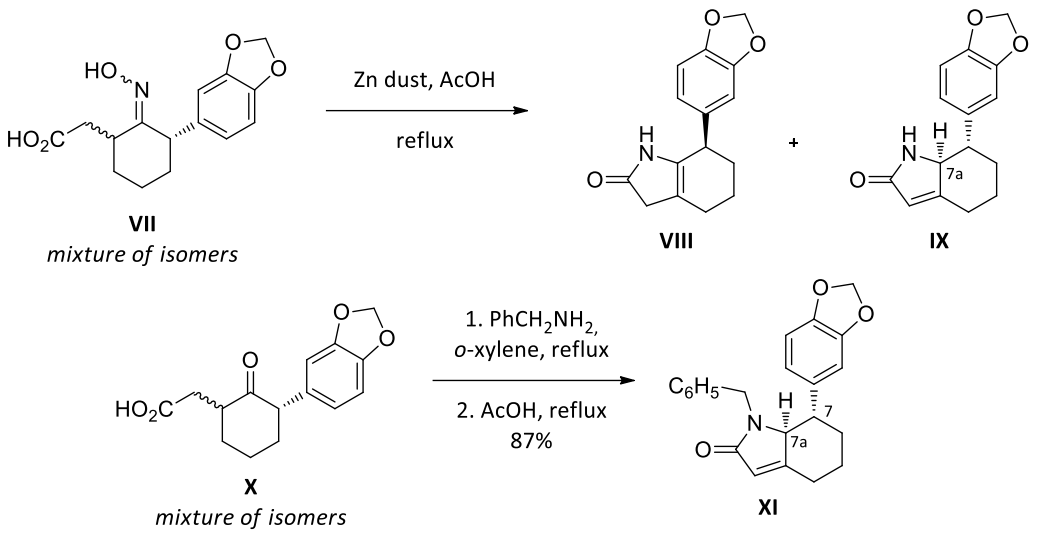


Figure 4.30 Previous reported example

The above results seem to confirm that the stereoselectivity in the protonation of the C-7a position in C-7 substituted hexahydro-2-indolones is determined by the nature of this substituent. Thus, when R_2 in an alkyl (Figure 4.31), H-7/H-7a *cis* isomers are stereoselectively formed. However, in compounds in which R_2 is a phenyl group only H-7/H-7a *trans* derivatives are isolated.

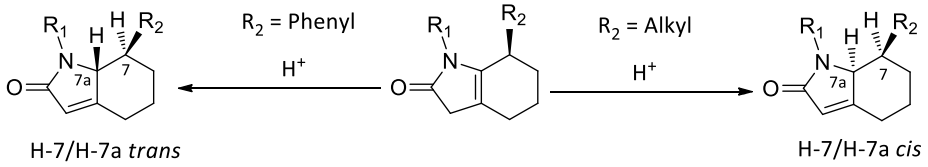


Figure 4.31

In Figure 4.32 a plausible mechanism for the ring opening of the oxazolidine ring tricyclic lactams **110**, **112a**, **114**, **116** and **118** leading to unsaturated bicyclic lactams is depicted. Coordination of the Lewis acid ($TiCl_4$) with the oxygen atom of the oxazolidine provokes the formation of an acyliminium salt which is in equilibrium with the corresponding enamine. Protonation of the resulting β-unsaturated lactam through the corresponding enolic form takes place from the less hindered face of the planar hydroxyl-pyrrole intermediate, stereoselectively affording the H-7/H-7a *cis* isomer. However, the resulting bicyclic unsaturated lactam is conformationally rigid and, in this *cis* isomer, the carbon substituent at the C-7 occupies an axial position. The different behaviour in the oxazolidine opening of the tricyclic lactam **118** (R = C_6H_5) under a stereochemical standpoint, could be rationalized by considering that when the substituent at C-7 position is bulky, such as a phenyl, an isomerization of the C-7a stereocenter takes place, affording the thermodynamically more stable C-7 isomer **125**, in which the phenyl is in an equatorial position.

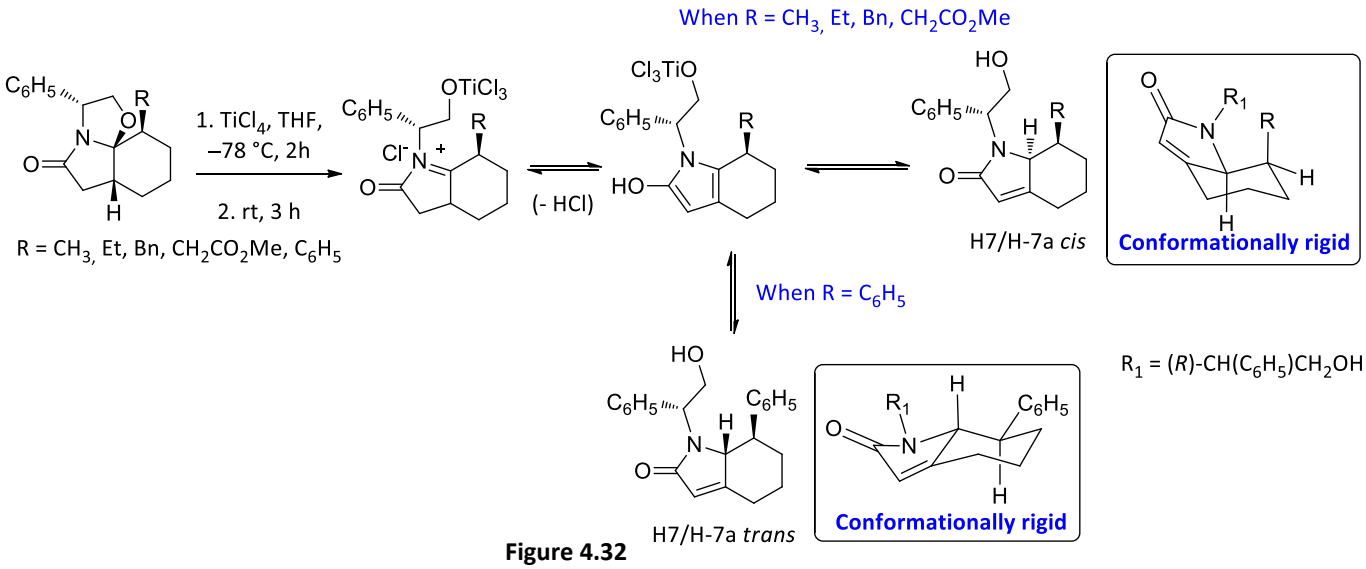

When R = CH3, Et, Bn, CH2CO2Me
1. TiCl4, THF, –78 °C, 2h
2. rt, 3 h
R = CH3, Et, Bn, CH2CO2Me, C6H5
(- HCl)
H7/H-7a cis
Conformationally rigid
When R = C6H5
H7/H-7a trans
Conformationally rigid
R1 = (R)-CH(C6H5)CH2OH

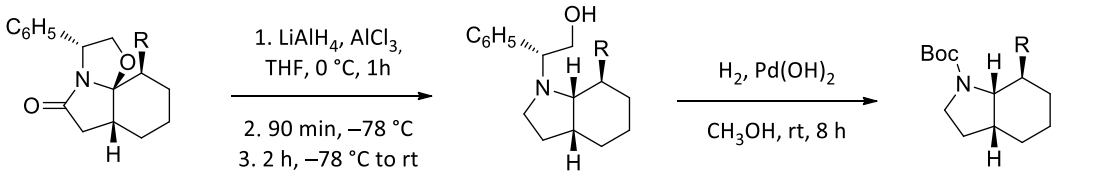
Figure 4.32

4.3. Synthesis of C-7 substituted octahydroindoles

Reductive opening of the oxazolidine ring and subsequent removal of the chiral inductor residue, should lead to the desired C-7 substituted *cis*-octahydroindole derivatives. On the other hand, adequate manipulation of the unsaturated conjugated bicyclic lactams would allow the preparation of stereoisomeric octahydroindolone derivatives.

4.3.1. Synthesis of c*is*-octahydroindolines C-7 *exo*-substituted

Cis-octahydroindoles **128**-**133** were prepared in good yield by reduction of the corresponding tricyclic lactams with alane at low temperature, as described in Paragraph 3.2.3. Even in these runs, no *trans* isomers were formed, meaning that the C-10 substituent as well as the ring size of lactam ring does not affect the stereoselection of the hydride attack. Finally, the chiral auxiliary was removed by taking advantage of the benzylic character of the exocyclic carbon-nitrogen bond. The reaction took place overnight, under hydrogen atmosphere in methanol, in the presence of palladium catalysis and di-*tert*-butyl bicarbonate. NMR spectra display complex signals, due to the presence of rotamers at nitrogen atom.



112a R = CH_3
114 R = Et
116 R = Bn
110 R = $CH_2CO_2CH_3$
118 R = C_6H_5
119 R = H

128 R = CH_3 82%
129 R = Et 67%
130 R = Bn 70%
131 R = $(CH_2)_2OH$ 76%
132 R = C_6H_5 76%
133 R = H 65%

134 R = CH_3 80%
135 R = Et 56%
136 R = Bn 73%
137 R = $(CH_2)_2OH$ 70%
138 R = C_6H_5 80%
139 R = H 79%

Figure 4.33 Synthesis of 7-substituted *cis*-octahydroindole

The stereoselectivity observed in the above reductions can be rationalized by considering that the alane, acting as a Lewis acid, weakens the C-O bond of the oxazolidine ring promoting the formation of an incipient iminium salt. Subsequent delivery of the hydride from the same face as the departing oxygen provides the *cis* isomer. Thus, the configuration of the new stereogenic center at C-7a of the octahydroindole is determined by that of the hemiaminal carbon of the oxazolidine ring.

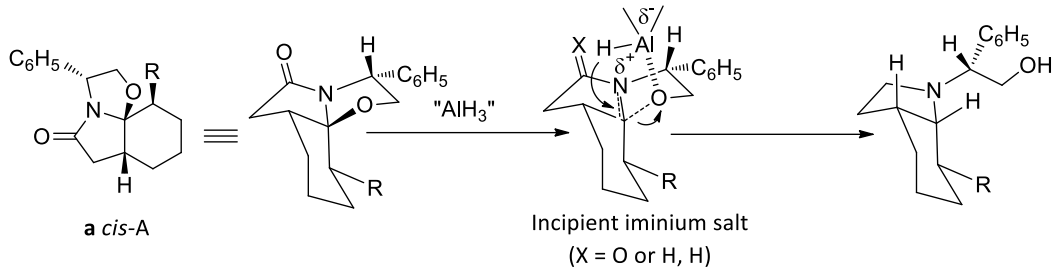


Figure 4.34 Mechanism for alane reduction

4.3.2. Synthesis of c*is*-octahydro-2-indolones C-7 *exo*-substituted

Chemo- and stereoselective reduction of the C-O bond of the oxazolidine ring of tricyclic lactams **112a**, **114**, **116**, **110**, and **119** followed by removal of the phenylethanol moiety of the chiral inductor would represent an efficient procedure for the synthesis of enantiopure C-7 substituted octahydro-2-indolones. Pioneering studies on the reductive opening of simple bicyclic phenylglycinol-derived lactams with triethylsilane in the presence of Lewis acids were performed by A. I. Meyers, [133] and later used by other authors for similar transformations.[122a, 122f, 125d, 134] The mechanism involves the formation of an acyliminium salt, promoted by coordination of the Lewis acid to the oxygen of the oxazolidine, and the subsequent silane reduction of the C=N bond. [135,136 137]

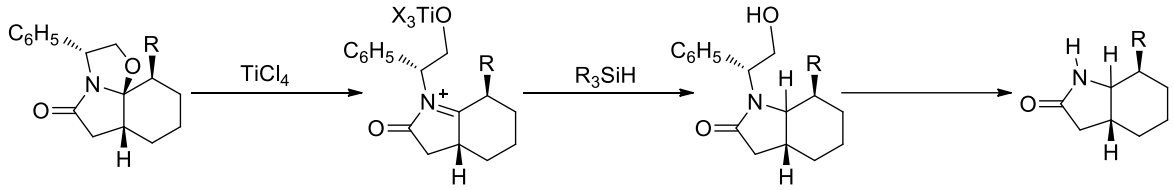


Figure 4.35 Mechanism for silane reduction

For instance, it has been reported that treatment of the lactam depicted in the following Figure 4.36 with triethylsilane and titanium tetrachloride in dichloromethane at low temperature, stereoselectively afforded the corresponding *cis* isomer of the resulting hexahydroindolone.[125d]

[133] Burgess, L. E.; Meyers, A. I. *J. Org. Chem.* **1992**, *57*, 1656–1662.
[134] Baussanne, I.; Chiaroni, A.; Royer, J. *Tetrahedron Asymmetry* **2001**, *12*, 1219–1224.
[135] Using trichlorosilane as reducing agent: a. Jisng, Y.; Liu, L.-X.; Yuan, W.-C.; Zhang, X.-M. *Synlett* **2012**, *23*, 1797–1800.
[136] For previous reported C-O cleavage in oxazolidines with silanes: a. Robl, J. A.; Cimarusti, M. P.; Simpkins, L. M.; Weller, H. N.; Pan, Y. Y.; Malley, M.; DiMarco, J. D. *J. Am. Chem. Soc.* **1994**, *116*, 2348–2355; b. Maier, M. E.; Evertz, K. *Tetrahedron Lett.* **1988**, *14*, 1677–1680.
[137] Reduction of electrophilic double bonds: Riant, O.; Mostefaï, Courmarcel, J. *Synthesis*, **2004**, *18*, 2943–2958.

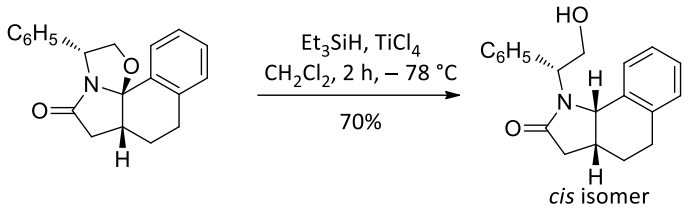
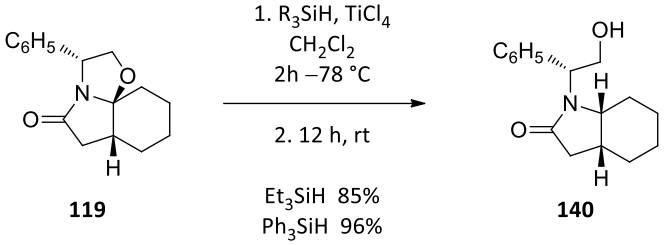


Figure 4.36

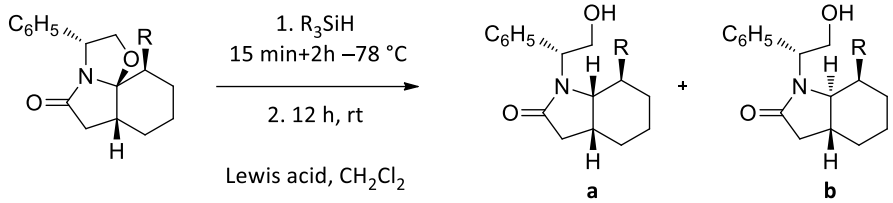
When these reaction conditions were applied to the reduction of unsubstituted tricyclic lactam **119**, the *cis* isomer of the corresponding octahydro-2-indolone **140** was isolated as a single isomer. The use of Ph_3SiH instead of Et_3SiH afforded an excellent 96% yield of the target compound **140**.



119 **140**

Figure 4.37 Reduction of lactam 119

Next, we applied the optimized conditions to the reduction of tricyclic lactams **112a**, **114**, **116**, **118** and **110**. In Tables 4.5-4.19 are reported the results obtained in the selective reductive opening of the oxazolidine ring in our tricyclic lactams. The procedure requires the addition of silane to a dichloromethane solution of tricyclic lactam, and then the slow addition of Lewis acid, at – 78 °C, which finally allows the fast evolution of the reaction. When THF was employed, in place of dichloromethane, dramatic changes in the reactivity were observed (as explained in Paragraph 4.2).



a **b**

112a R = CH_3
114 R = Et
116 R = Bn
118 R = C_6H_5
110 R = $CH_2CO_2CH_3$

141 R = CH_3
142 R = Et
143 R = Bn
144 R = C_6H_5
145 R = $CH_2CO_2CH_3$

Figure 4.38 General scheme for silane reduction

From **112a** R = CH_3

	silane	Lewis acid	y%	*dr* (NMR)
1	Et_3SiH	$TiCl_4$	67	93:7
2	Et_3SiH	$TiCl_4$ (1N sol. CH_2Cl_2)	-[a]	91:9
3	Et_3SiH	$BF_3{\cdot}Et_2O$	-[a]	90:10
4	Ph_3SiH	$TiCl_4$	87	100:0

a. no purified by chromatography column

Table 4.5

Initially we tested the efficiency of triethylsilane, in combination with titanium tetrachloride (pure or 1N dichloromethane solution) or trifluoroboroetherate on lactam **112a**. We found that variable amounts of *trans* isomer were obtained in all cases. On the other hand, when triphenylsilane was used, complete diastereoselection was accomplished (entry 4). The same excellent result was obtained with triphenylsilane starting from lactam **114** (Table 4.6).

From **114** R = Et

	silane	Lewis acid	y%	*dr* (NMR)
1	Et_3SiH	$TiCl_4$	61	92:8
2	Ph_3SiH	$TiCl_4$	79	100:0

Table 4.6

However, this was not a general trend: the use triphenylsilane with lactam **116** (Table 4.7) or **118** (Table 4.8), was not so effective. In particular, a 83:17 and 85:15 *cis*:*trans* isomeric mixture was obtained respectively. Reduction with triethylsilane (entries 2), instead, allowed the isolation of a single isomer, in good yields in both cases.

From **116** R = Bn

	silane	Lewis acid	y%	*dr* (NMR)
1	Et_3SiH	$TiCl_4$	60	100:0
2	Ph_3SiH	$TiCl_4$	62	83:17

Table 4.7

From **118** R = C_6H_5

	silane	Lewis acid	y%	*dr* (NMR)
1	Et_3SiH	$TiCl_4$	80	100:0
2	Ph_3SiH	$TiCl_4$	-[a]	85:15

a. not purified by chromathography column.

Table 4.8

On the other hand, lactam **110** reacted with triethylsilane, providing only the *cis* isomer in low yield (47%), in which neither the lactam nor the ester carbonyl were modified. Reduction with triphenylsilane led to complete decomposition the products.

From **110** R = $CH_2CO_2CH_3$

	silane	Lewis acid	y%	*dr* (NMR)	compound
1	Et_3SiH	$TiCl_4$	47	100:0	**144**
2	Ph_3SiH	$TiCl_4$	-[b]	-	**144**

b. decomposed

Table 4.9

Thus, although the reaction conditions have been optimized for every tricyclic lactam and excellent results have been obtained for each individual case, it is evident that the substituent at the C-7 position has an influence on the stereochemical outcome of the reaction and in some runs minor amounts of the C-7 isomer **b** are obtained. This observation can be accounted for by considering the mechanistic picture proposed by Meyers for the allylation of pyrrolidine-derived bicyclic lactams in the presence of a Lewis acid. A combination of the Felkin-Ahn model for nucleophilic addition to carbonyls with a stereogenic center in α-position, allylic 1,3-strain, and chelation effects are the factors governing the facial attack of the nuclophile to the acyliminium salt. From the initially formed acyliminium salt (**A**), a rotation of 180° (**B**) or 120° (**C**) around the exocyclic C-N would release the allylic strain between the alcoxytitanium or phenyl groups and the substituent (C-7/C-7a bond) on the electrophilic carbon on the iminium salt. On the other hand, in conformations **B** and **C** an opportunity for chelation involving the alkoxytitanium group and the amide carbonyl also emerges. As demonstrated by Meyers, the alcoxytitanium assumes the role of bulky group, with respect to the phenyl, and occupies the antiperiplanar position (conformation **C**). Hydride addition to the acyliminium salt from the less hindered β-face, opposite to the large alcoxytitanium group, furnishes the observed major *cis* **a** isomers. However, when a substituent (R) with an H-3a/H-7 *trans* relative configuration is present at the C-7 position of the intermediate iminium salt, this is rigidly holding in an axial position due to the lack of conformational flexibility of the bicyclic system.

As a consequence, the approach of the silane to the iminium salt is partially hindered by R, provoking an erosion in the diastereoselectivity of the reaction.

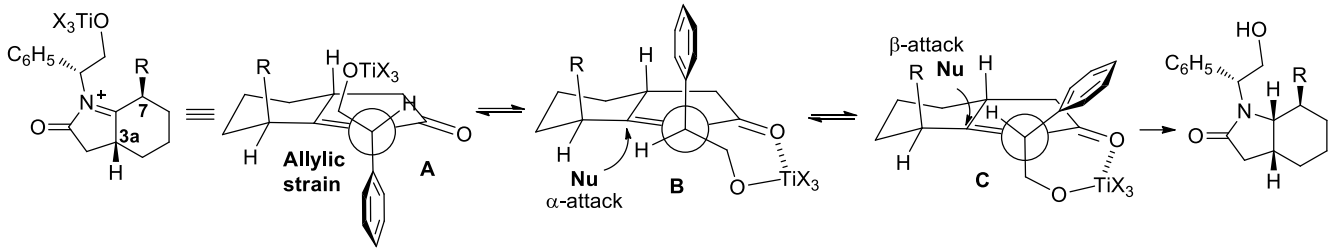


Figure 4.39

Thus, in this case, the stereoselectivity of this reaction is mainly governed by the configuration of the stereogenic center of the chiral inductor. Remarkably, when THF is employed, in place of dichloromethane, dramatic changes in the reactivity were observed (as explained in Paragraph 4.2). It is finally worth mentioning that all attempts to provoke a similar chemoselective reduction from the decahydroquinoline-based tricyclic lactams resulted in failure.

At this stage the chiral inductor had to be removed. Elimination of the phenylglycinol-based auxiliary takes advantage of the benzylic nature of the N-C bond and is generally accomplished using hydrogenolytic conditions (Pd or $Pd(OH)_2$, H_2 atmosphere or ammonium formate). Other methods require lead catalysis [$Pb(OAc)_4$] or oxidative cleavage, in the presence of sodium periodate.[138] The main important feature in those cases is that only the benzylic amine can be deprotected. In the case of amides other procedure must be exploited, and some example have been appeared in the literature. The fastest procedure is the reaction in presence of sodium or lithium and liquid ammonia (low temperature), initially described for bicyclic lactams by Meyers.[139] Other authors reported that, by reacting the alcohol with thionyl chloride or mesyl chloride, followed by basic elimination and then acid hydrolysis, removal of the chiral inductor can be completed.[140] Ennis in 1996 and Zuo in 2010 reported lithium hydroxide followed

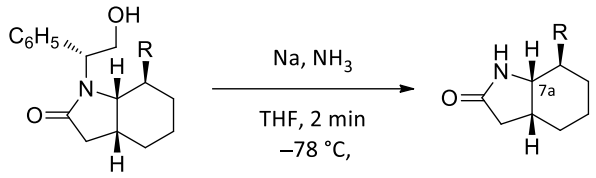
[138] For some examples: a. Andrés, J. M.; Herraiz-Sierra, I.; Pedrosa, R.; Pèrez-Encabo, A. *Eur. J. Org. Chem.* **2000**, *9*, 1719–1726 (mechanism); b. Lebeuf, R.; Robert, F.; Schenk, K.; Landais, Y. *Org. Lett.* **2006**, *8*, 4755–4758.

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

[140] a. Enders, D.; Reinhold, U. *Tetrahedron Asymmetry* **1997**, *12*, 1895–1946; b. Amat, M.; Arròniz, C.; Molins, E.; Escolano, C.; Bosch, J. *Org. Biomol. Chem.* **2011**, *9*, 2175–2184; c. Agani, C.; Couty, F.; Evano, G. *Tetrahedron Lett.* **1999**, *40*, 3709–3712; d. Nuzaw, v.; Beland, C.; Zammattig, F.; Villieras, J. *Tetrahedron Asymmetry* **1996**, *7*, 1835–1843; e. Chen, M.-D.; Zhou, X.; He, M.-Z.; Ruan, Y.-P.; Huang, P.-Q. *Tetrahedron* **2004**, *60*, 1651–1657; f. Fains, O.; Vernon, J. M. *Tetrahderon Lett.* **1997**, *47*, 8265–8266; g. Allin, S. M.; Northfiled, C. J.; Page, M. I.; Slawin, A. M. Z. *Tetrahedron Lett.* **1999**, *40*, 141–142; h. Hansen, J. D.; Newhouse, B. J.; Allen, S.; Anderson, A.; Eary, T.; Schiro, J.; Gaudino, J.; Laird, E.; Allen, A. C.; Chentry, D.; Eberhardt, C.; Burgess, L. E. *Tetrahedron Lett.* **2006**, *47*, 69–72.

by hydrochloridric acid in THF to be equally effective.[141] Finally, oxidative removal with CAN has been also described.[142]

We found that removal of the phenylglycinol residue, in the presence of sodium ammonia, at −78 °C is very efficient for our systems, and the desired bicyclic lactams were obtained in only 2 minute reaction. It is important to notice that in these conditions lactam carbonyl was not reduced, while ester carbonyl was.



141a R = CH_3
142a R = Et
143a R = Bn
145a R = $CH_2CO_2CH_3$
144a R = C_6H_5
140 R = H

146a R = CH_3 98%
147a R = Et 64%
148a R = Bn 66%
149a R = $(CH_2)_2OH$ 60%
126a R = C_6H_5 87%
150 R = H 70%

Figure 4.40 Elimination of chiral inductor in presence of sodium ammonia

The absolute configuration of carbon C-7a was confirmed by comparion of the spectroscopic data with those of lactams **126a** and **150**, previously described.[143,144] *Cis*-fusion assignment is also confirmed by $J_{3a\text{-}7a}$ value (between 7.2 Hz and 8 Hz), and *trans* relative disposition of H-7a and H-7 was settled by NOE experiments for lactam **146a** (1D, see supporting information), taking into account that C-7 does not take part in the above transformations.

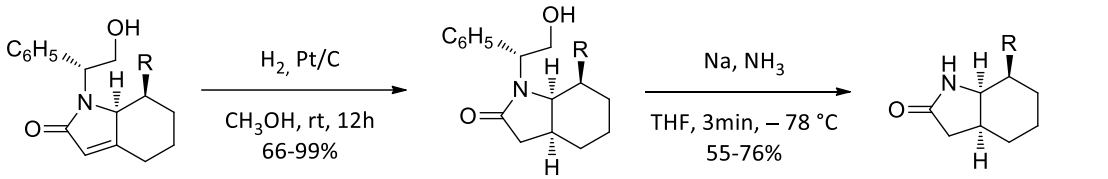
4.3.3. Synthesis of c*is*-octahydro-2-indolones C-7 *endo*-substituted

The activated carbon-carbon double bond present in the unsaturated lactams **113b**, **115b**, **117b** and **111b** is an useful functionality that allows the introduction of new substituents or the stereocontrolled generation of octahydroindole derivatives. In particular, the first modification that was considered was the selective reduction of such double bond. Various examples of reduction of α,β-unsaturated amide[145]

[141] a. Ennis, M. D.; Hoffman, R. L.; Ghazal, N. B.; Old, D. W.; Mooney, P. A. *J. Org. Chem.* **1996**, *61*, 5813–5817; b. Zuo, Z.; Xie, W.; Ma, D. *J. Am. Chem. Soc.* **2010**, *132*, 13226–13228.
[142] a. LAn, H.-Q.; Ye, J.-L.; Wang, A.-E.; Ruan, Y.-P.; Huang, P.-Q. *Chem. Eur. J.* **2011**, *17*, 958–968; b. Fujioka, H.; Hirose, H.; Ohba, Y.; Murai, K.; Nakahara, K.; Kita, Y. *Tetrahedron* **2007**, *63*, 625–637.
[143] Yasuhara, T.; Nishimura, K.; Osafune, E.; Muraoka, O.; Tomioka, K. *Chem. Pharm. Bull.* **2004**, *52*, 1109–1113.
[144] Ishibashi, H.; Fuke, Y.; Yamashita, T.; Ikeda, M. *Tetrahedron Asymmetry* **1996**, *7*, 2531–2538.
[145] As example, see: Koltunoc, K. Y.; Walspurger, S.; Sommer, T. *Eur. J. Org. Chem.* **2004**, 4039–4047.

and lactams[146] are reported in literature. On the other hand, various considerations were made on α,β unsaturated decalones: for these compounds catalytic hydrogenation, generally leads to formation of *cis*-decalines. On the other hand, reduction with lithium or sodium in ammonia, the *trans* isomer is preferentially formed.[147] In this field, other reducing agent were reported to complete the reaction, but with less stereoselectivity, such as silanes in combination with metals,[148] diimides[149] or sodium cyanoborohydride.[150] Considering all these reported results, different catalytic hydrogenation conditions were tested, in order to obtain *cis*-octahydroindolones.

Intermediate alcohols **141c**-**143c** and **145c** were obtained from the corresponding unsaturated lactams (described as intermediate compounds, as the NMR spectra present broad signals, and was difficult to make an accurate assignment). The best conditions imply the reaction of unsaturated lactams with hydrogen for 12 h at room temperature, in the presence of 50% of w/w platinum over carbon. No *trans* isomers were detected. The phenylethanol residue was definitely eliminated by reaction with sodium generated in liquid ammonia at −78 °C, providing C-7 *endo*-substituted *cis*-octahydroindolones **146b**-**149b**.



113b R = CH_3	**141c**	**146b** R = CH_3	75%
115b R = Et	**142c**	**147b** R = Et	61%
117b R = Bn	**143c**	**148b** R = Bn	48%
111b R = $CH_2CO_2CH_3$	**145c**	**149b** R = $(CH_2)_2OH$	50%

Figure 4.41 Catalytic hydrogenation and elimination of chiral inductor

The less expensive Pd catalysts ($Pd(OH)_2$ and Pd/C) were also investigated, but they resulted less effective (no complete reaction after more than 24 h). When platinum oxide was used in methanol, the

[146] As example, see: a. Aoun, R.; Renaud, J.-L.; Dixsieuf, P. H.; Bruneaun, C. *Angew. Chem. Int. Ed.* **2005**, *44*, 2021–2023; b. Maj, A. M.; Suisse, I.; Pinault, N.; Robert, N.; Agbossou-Niedercom, F. *Chem. Cat. Chem.* **2014**, *6*, 2621–2625; c. Metallinos, C.; Zaifman, J.; Van Belle, L.; Dodge, L.; Pilkington, M. *Organometallics* **2009**, *28*, 4534–4543; d. Mangaleswaran, S.; Argade, N. P. *Synthesis* **2004**, *10*, 1560–1562; d. *Eur. J. Org. Chem.* **2007**, *8*, 1294–1300.

[147] a. Stork, G.; Rosen, P.; Goldman, N. L. *J. Am. Chem. Soc.* **1961**, *81*, 2965–2966; b. Banerjee, D. K.; Chatterjee, S.; Bhattacharya, S. P. *J. Am. Chem. Soc.* **1955**, *77*, 408–410; c. van Eikeren, P. *J. Org. Chem.* **1980**, *45*, 4641–4645; d. Oritani, T.; Yamashita, K. *J. Org. Chem.* **1984**, *49*, 3689–3694; e. Stork, G.; Darling, S. D. *J. Am. Chem. Soc.* **1960**, *82*, 1512–1513.

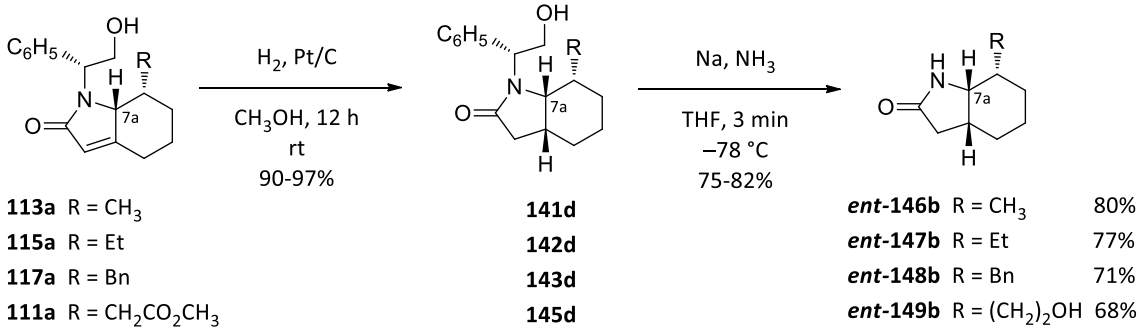
[148] a. Ito, H.; Ishizuka, T.; Arimoto, K.; Miura, K.; Hosomi, A. *Tetrahedron Lett.* **1997**, *38*, 8887–8890; b. Riant, O.; MostefaÏ, N.; Courmarcel, J. *Synthesis* **2004**, *18*, 2943–2958.

[149] A. Miller, C. E. *Journal of Chemical Education* **1965**, *42*, 254–259; b. Kroutil, J.; Trnka, T.; Černý, M. *Synthesis* **2004**, *3*, 446–450.

[150] Brodney, M. A.; Cole, M. L.; Freemont, J. A.; Kyi, S.; Junk, P. C.; Padwa, A.; Riches, A. G.; Ryan, J. H. *Tetrahedron Lett.* **2007**, *48*, 1939–1943.

hydrogenation was very fast (complete conversion of starting material in only 3 h), and even faster in acetic acid. The drawback in this case was the formation of a by-product, in which the catalyst has completely reduced the aromatic ring of the phenylglycinol moiety, avoiding the possibility of its simple and fast removal.

Unsaturated lactams **113a**, **115a**, **117a** and **111a**, by-products of the cyclocondensation reaction, were also submitted to the same above reported conditions. Catalytic hydrogenation, followed by elimination of the chiral inductor by reaction with alkali metal in liquid ammonia, led to enantiopure lactams ***ent*-146c**-***ent*-149c.**



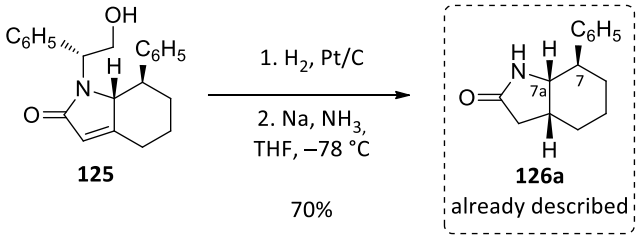
113a R = CH_3
115a R = Et
117a R = Bn
111a R = $CH_2CO_2CH_3$

141d
142d
143d
145d

***ent*-146b** R = CH_3 80%
***ent*-147b** R = Et 77%
***ent*-148b** R = Bn 71%
***ent*-149b** R = $(CH_2)_2OH$ 68%

Figure 4.42 Synthesis of *trans*-octahydroindolones, series *ent*-b

In the same conditions lactam **125** was converted into the already described lactam **126a**, confirming the absolute configuration.



125

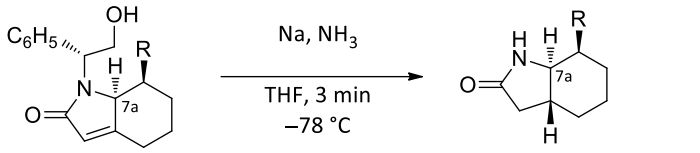
126a
already described

Figure 4.43

Finally, new C-7 substituted *cis*-octahydroindolones were synthesized. The absolute configuration of C-7 was determined by the cyclocondensation process, while those of C-3a and C-7a by choosing the right condition in the manipulation of the tricyclic lactams.

4.3.4. Synthesis of *trans*-octahydro-2-indolones C-7β substituted

At this point, the reduction of the conjugated carbon-carbon double bond in the presence of sodium ammonia was considered. Unsaturated lactams were directly subjected to reaction with sodium metal in ammonia: double bond reduction and phenylethanol residue removal took place at the same time. The reaction was carried out at −78 °C, and was completed in only 3 minutes. In this way C-7β-substituted *trans* octahydroindolones **146c**-**149c**, in which H-7 and H-7a are is relative *cis* disposition, were obtained in good overall yield and high stereoselectivity.



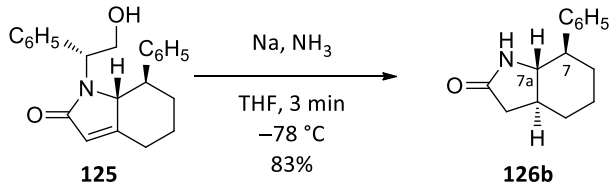
113b R = CH_3
115b R = Et
117b R = Bn
111b R = $CH_2CO_2CH_3$

146c R = CH_3 93%
147c R = Et 79%
148c R = Bn 77%*
149c R = $(CH_2)_2OH$ 60%*

*not optimized yields

Figure 4.44 Synthesis of *trans*-octahydroindolones

Reaction of **125** with sodium ammonia also provided *trans*-octahydroindolone **126b**, but with H-7 and H-7a in relative *trans* disposition. Relative configurations of **126b** were demonstrated unequivocally by comparing our spectroscopic data with those reported for the racemic series by Tomioka.[151]

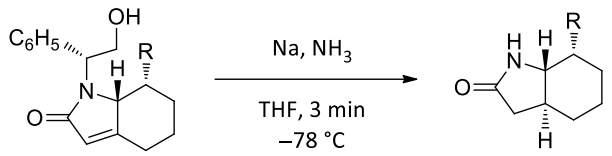


125 **126b**

Figure 4.45

Reaction of conjugated lactams with sodium in liquid ammonia provided *trans*-octahydroindoles, ***ent*-146c**-***ent*-149c**.

[151] Yasuhara, T.; Nishimura, K.; Osafune, E.; Muraoka, O.; Tomioka, K. *Chem. Pharm. Bull.* **2004**, *52*, 1109–1113.



113a R = CH_3
115a R = Et
117a R = Bn
111a R = $CH_2CO_2CH_3$

***ent*-146c** R = CH_3 90%
***ent*-147c** R = Et 68%*
***ent*-148c** R = Bn 62%*
***ent*-149c** R = $(CH_2)_2OH$ 61%*
* not optimized yield

Figure 4.46 Synthesis of *trans*-octahydroindolones, series *ent*-c

In conclusion, the potential of tricyclic lactams derived from (*R*)-phenylglycinol and cyclohexanone based γ-ketoester was revealed: choosing the correct conditions, C-7 substituted *cis* and *trans* octahydroindoles derivatives could be prepared with a high degree of stereoselection. In Figure 4.47, all octahydroindole-based products prepared in the present work are displayed. The indicate yield correspond to the overall process from oxo-ester and phenylglycinol (up to four steps).

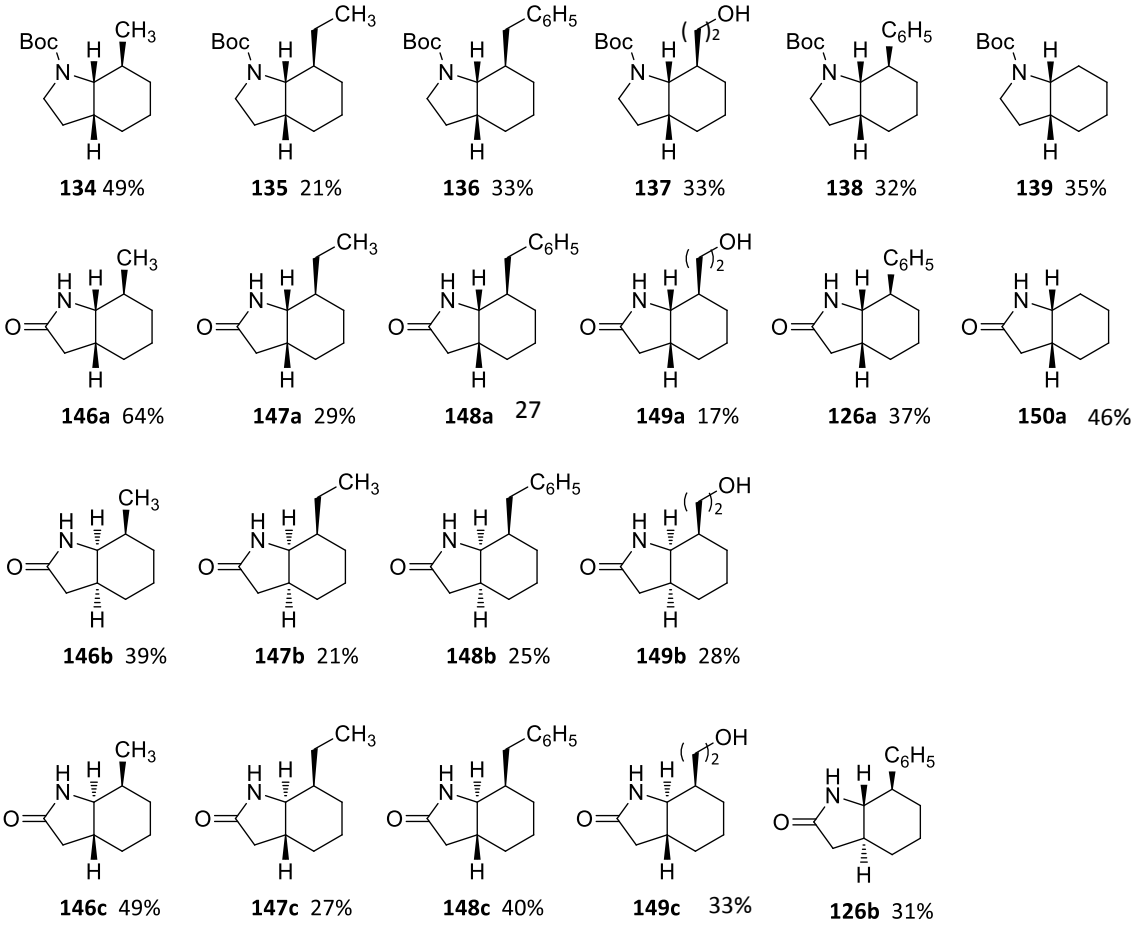


Figure 4.47 Octahydroindole-derivatives synthesized

4.4. Introduction of substituents on tricyclic lactams

The enhanced reactivity of these octahydroindole-based tricyclic lactams prepared in this work allows further modifications, which can disclose the access to more complicated structures. In the case of unsaturated structure **122**, selective hydrogenation, dihydroxylation, epoxidation, hydroboration-oxidation, etc. would give rise to new derivatives. Cleavage of the C-O oxazolidinic bond could allow the insertion of new substituents at C-7a position of octahydroindoles, by α-amidoalkylation reactions. Finally alkylation of amide enolate, could permit the insertion of a substituent at C-6 carbon of the tricyclic lactam.

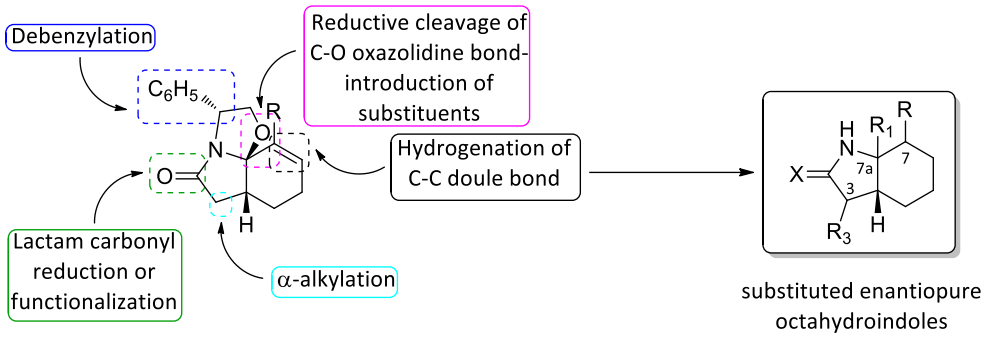
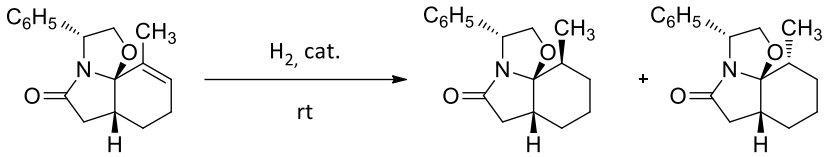


Figure 4.48 Approximation to polysubstituted octahydroindoles

4.4.1. Reduction of the C-C double bond

Starting from tricyclic lactam **122**, catalytic hydrogenation of the C-C double bond was performed, with the aim of obtaining lactam **112b**, epimer in C-10 of the already synthesized **112a**.



122 **112a** **112b**

	solvent	t	cat	y%	**112a:112b**
1	CH_3OH	18h	$Pd(OH)_2$	quant	100:0
2	CH_3OH	4h	PtO_2	quant	75:25
3	AcOH	3h	PtO_2	quant	45:55
4	AcOH	2h(400psi)	PtO_2	quant	45:55
5	AcOH+ CH_3OH	24h	PtO_2	quant	50:50
6	EtOH	24h	$Pd(OH)_2$	quant	100:0
7	THF	2h	$Mn(dpm)_3$	quant	60:40

Table 4.10

Palladium and platinum catalysts were tested in various solvents and, unfortunately, the formation of equimolar portion of the two possible lactams, or exclusively lactam **112a** were detected. At the sight of these disappointing results, we decided not to go on with this investigation.

4.4.2. α-amidoalkylation and synthesis of 7,7a-dialkyl *cis*-octahydroindolones

In 1976 Sakurai reported that allylsilanes react with a wide variety of aldehydes and ketones, in the presence of a stoichiometric quantities of $TiCl_4$, or other Lewis acids, such as $AlCl_3$ or $SnCl_4$.[152] The Lewis acid first activates the electrophilic carbon in presence of allyltrimethylsilane which then undergoes nucleophilic attack from electrons on the allylic silane. The silicon plays the key role in stabilizing the carbocation of carbon at the β-position.

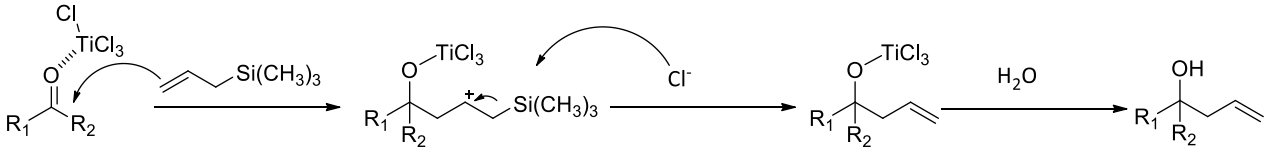
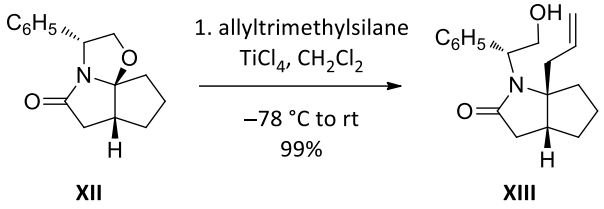


Figure 4.49 Sakurai reaction's mechanism

[152] a. Hosomi, A., Endo, M., Sakurai, H. *Chem. Lett.* **1976**, 941–942; b. Hosomi, A., Sakurai, H. *Tetrahedron Lett.* **1976**, 1295–1298.

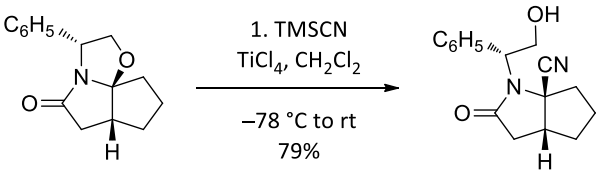
Although the most common substrates of the Hosomi-Sakurai reaction are ketones and aldehydes, a number or functional groups such as ketals and acetals are also used.[153] The stereoselective introduction of allyl substituents at the 2-position of nitrogen heterocycles from aminoalcohol-derived lactams using the Hosomi-Sakurai procedure was originally described by Meyers[154] and applied by Danishefsky for the preparation of a 6a-allyl substituted hexahydrocyclopenta-2-pyrrolone in the context of the total synthesis of (+)-halichlorine.[155] The reaction took place in very high yield and stereoselectivity.



XII **XIII**

Figure 4.50 Danishefsky's example of lactam allylation

On the other hand, the cyanation of aminoalcohol-derived lactams has also been reported fort the introduction of a nitrile at the α-position of the nitrogen heterocycles.[156] For instance, in 2003 D. Trauner reported the cyanation of the tricyclic lactam depicted in Figure 4.51 in excellent stereoselectivity and good chemical yield.[157]



XII **XIV**

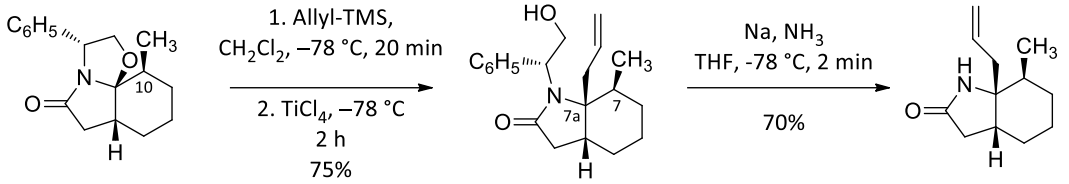
Figure 4.51 Trauner's lactam allylation

It is worth mentioning that these α-amidoalkylation reactions only take place in good yield when the size of the lactam ring in aminoalcohol-derived tricyclic lactams is five-membered but not from analogous derivatives bearing larger rings. The enhanced reactivity of the former is attributable to the higher angular strain which facilitates the generation of the intermediate acyliminium salt by opening of the oxazolidine ring. The mechanism of the above mentioned allylation and cyanation reactions is parallel to that depicted in Figure 4.39 for the chemoselective reduction of the tricyclic lactams prepared in this work

[153] Mukaiyama, T.; Murakami, M. *Synthesis* **1987**, 1043–1054.
[154] a. Meyers, A. I.; Burgess, L. E. *J. Org. Chem.* **1991**, *56*, 2294–2296; b. Burgess, L. E.; Meyers, A. I. *J. Am. Chem. Soc.* **1991**, *113*, 9858– 9589; c. Groaning, M. D.; Meyers, A. I. *Chem. Commun.* **2000**, 1027–1028.
[155] a. Trauner, D.; Danishefsky, S. J. *Tetrahedron Lett.* **1999**, *40*, 6513–6516; b. Trauner, D.; Schwarz, J. B.; Danishefsky, S. J. *Angew. Chem. Int. Ed.* **1999**, *38*, 3542–3545.
[156] Baussanne, I.; Chiaroni, A.; Royer, J. *Tetrahedron: Asymmetry* **2001**, *12*, 1219–1224.
[157] Dorsey, A. D.; Barbarow, J. E.; Trauner, D. *Org. Lett.* **2003**, *18*, 3237–3239.

with trialkylsilanes (Et_3SiH or Ph_3SiH). With these precedents in mind, we decided to explore the stereoselectivity in the introduction of an allyl and a cyano substituent by amidoalkylation reactions from our chiral tricyclic lactams in order to analyse the influence of the size of the carbocyclic ring, six membered in this case, and the substituent present at the next position of the electrophilic carbon of the intermediate acyliminium salt.

These are the unique examples of α-amidoalkylation in phenylglycinol tricyclic lactams, and in both cases, five-membered rings are present. We decide to test the reported conditions on lactam **112a**, with a C-10 methyl substituent. Allylation with allyltrimethylsilane in the presence of titanium tetrachloride, in dichloromethane, followed by elimination of phenylethanol moiety by rapid reaction with metallic sodium in liquid ammonia, led to lactam **152** as a single isomer. In this process a quaternary center is formed with complete stereoselectivity.

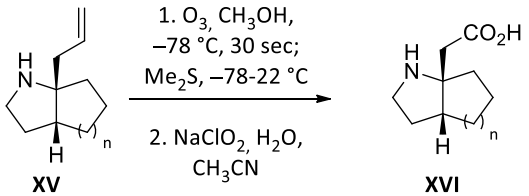


112a **151** **Single isomer** **152**

Figure 4.52 Synthesis of 7a-allyl-7-methyl-octahydro-2-indolone 152

The absolute configuration of lactam **152** was confirmed by NOE experiment and by comparison of spectroscopic data reported for similar compounds.[158]

The presence of allylic function in the α'-position of the amide, would enable the synthesis of β-amino acids, which are valuable building blocks in peptide-based drug design.[159] Replacement of proline with more rigid analogue, such as octahydroindole-2-acetic acid, has been exploited in several bradykinin B_2 antagonists, to improve both enzymatic stability and potency.[160] Moreover, proline-based catalysts have been shown to be powerful catalysts for a wide variety of transformations.[161]



XV **XVI** β-aminoacids

Figure 4.53 Overman's synthesis of β-aminoacids

[158] Aron, Z. D.; Overman, L. E. *Org. Lett.* **2005**, *7*, 913–916.
[159] Aron, Z. D.; Ito, T.; May, T. L.; Overman, L. E.; Wang, J. *J. Org. Chem.* **2013**, *78*, 9929–9948.
[160] Sayago, F. J.; Laborda, P.; Calaza, M. I.; Jiméenez, A. I.; Cativela, C. *J. Org. Chem.* **2011**, *76*, 2011–2028.
[161] For a review, see: Mukherjee, S.; Yang, J. W.; Hoffmann, S.; List, B. *Chem. Rev.* **2007**, *107*, 5471–5569.

On the other hand, when lactam **112a** was allowed to react with trimethylsilyl cyanide provided lactam **153** as a single isomer. Removal of the benzylic substituent on the nitrogen from **153** requires a multistep procedure since α-amino or amido-nitriles undergo rapid loss of hydrogen cyanide, in the presence of alkali metal, in a mixture of liquid ammonia and THF at low temperatures.[162] In fact, when **153** was treated with sodium in liquid ammonia, afforded a 9:1 mixture of **146a** and **146c** in 90% of yield. Oxidation with CAN resulted ineffective and only a complex mixture of products, along with a little amount of starting material (25%), was obtained. In a second attempt compound **153** was treated with thionyl chloride, and the resulting chloride was converted into the enamide **154** by treatment with DBU. Hydrolysis of enamide **154** with sulphuric acid provided the lactam **155** in good yield. Nitrile function was kept unchanged, although the use of strong acid, such as sulphuric acid, would suggest its conversion into acid. The strong absorption found at 2238.cm^{-1} in the IR spectra and a signal at 118.2 ppm in the ^{13}C-NMR, characteristic of a nitrile function, confirmed the structure of **155**.

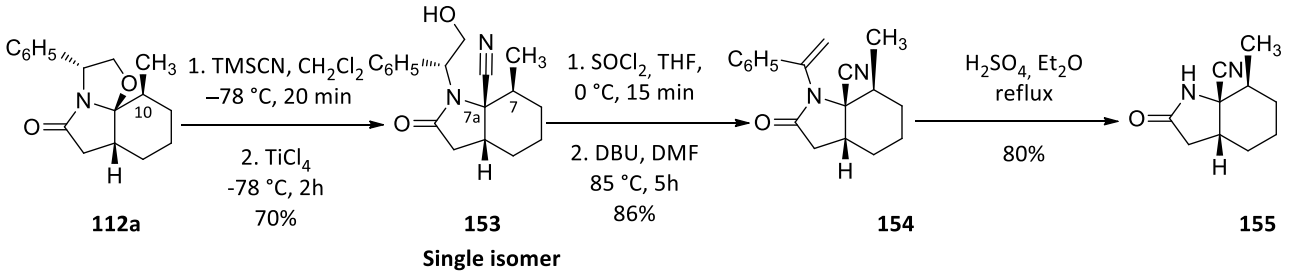


Figure 4.54 Synthesis of lactam 155

It is worth mentioning that the octahydro-2-indolone-7a-carbonitrike depicted in Figure 4.55 has been transformed into a variety of derivatives, increasing the synthetic value of **155** as a precursor of more complex compounds.[162d]

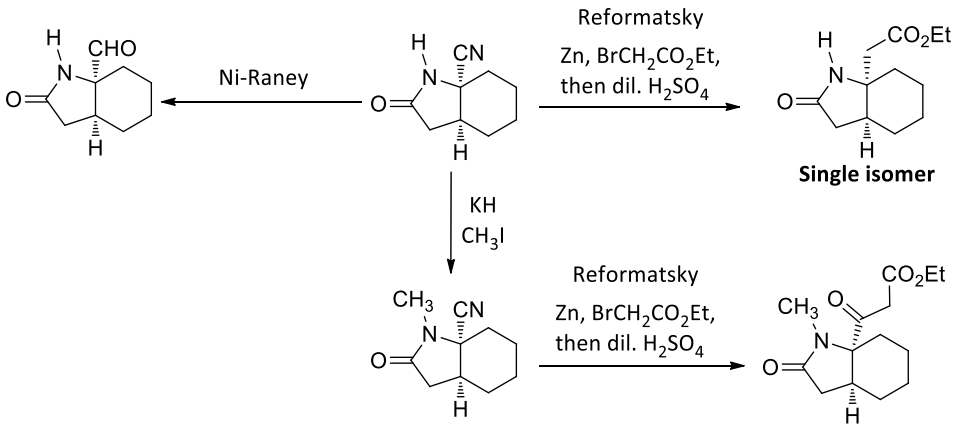


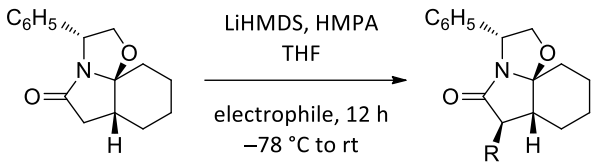
Figure 4.55 Tsuda's modifications of α-amidonitriles

[162] a. François, D.; Poupon, E.; Kunesch, N.; Husson, H.-P. *Eur. J. Org. Chem.* **2004**, 4823–4829; b. Arseniyadis, S.; Huang, P. Q.; Piveteau, D.; Husson, H.-P. *Tetrahedron* **1998**, *44*, 2457–2470; c. Bunnelle, W. H.; Shevlin, C. G. *Tetrahedron Lett.* **1989**, *30*, 4203–4206; d. Mohri, K.; Yoshida, Y.; Mataga, S.-I.; Hisatsune, Y.; Isobe, K.; Tsuda, Y. *Heterocycles* **1997**, *45*, 2405–2412.

Finally lactam **112a** was treated with ethyl and propyl magnesium bromide,[163] but unfortunately in all cases only starting material was collected.

4.4.3. α-alkylation of tricyclic lactam: introduction of substituent at C-3

The alkylation of the enolate of chiral lactams constitutes a procedure widely used by Meyers for the synthesis of complex molecules. Our group has also described the alkylation of phenylglycinol-derived oxazolopiperidone lactams, with quite good yield and stereoselectivity.[164] Initially the α alkylation of lactam **119**, with no substituent at C-10 carbon, was studied. Deprotonation with LiHMDS, at low temperature in anhydrous THF provided the lithium enolate, which reacted with an alkylating agent, in the presence of HMPA. In every run, only one alkylated product was isolated in good yield, as displayed in Table 4.11.



119

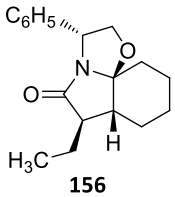
	alkylating agent	y%	compound
1	EtI	85%	**156** R = Et
2	Allylbromide	70%	**157** R = Allyl
3	Benzylbromide	65%	**158** R = Bn
4	$(Et_2O)_2CO$	56%	**159** R = CO_2Et

Table 4.11 α-alkylation of tricyclic lactam

The absolute configuration of the new stereogenic center of lactam **156** was determined by means of X-ray crystal analysis.

[163] a. Amat, M.; Escolano, C.; Gomez-Esqé, A.; Lozano, O.; Llor, N.; Griera, R.; Molins, E.; Bosch, J. *Tetrahedron Asymmetry* **2006**, *17*, 1581–1588; b. Escolano, C.; Amat, M.; Bosch, J. *Chem. Eur. J.* **2006**, *12*, 8198–8207; c. Amat, M.; Bassa, O.; Llor, N.; Cantó, M.; Pérez, M.; Molins, E.; Bosch, J. *Chem. Eur. J.* **2006**, *12*, 7872–7881.

[164] Amat, M.; Escolano, C.; Lozano, O.; Gómez-Esqué, A.; Griera, R.; Molins, E.; Bosch, J. *J. Org. Chem.* **2006**, *71*, 3804–3815.



156

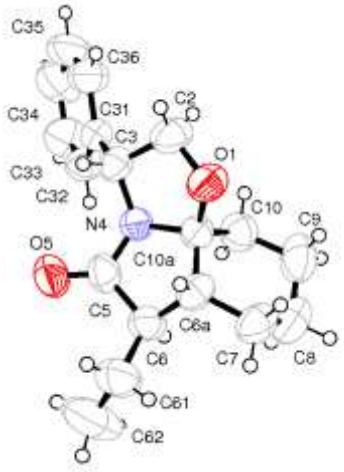
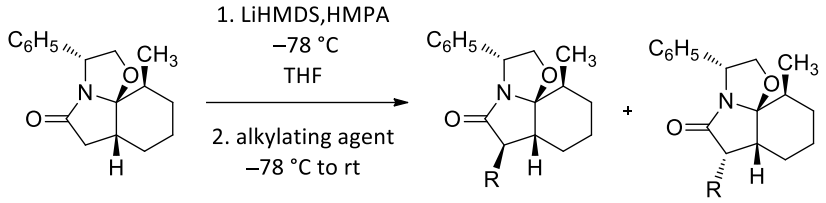


Figure 4.56 X-ray structure for lactam 156

With the aim to evaluate the influence of the C-10 substituent on the stereoselectivity of this reaction, lactam **112a** was subjected to the above mentioned reaction conditions with ethyliodide and allylbromide. A decrease in the stereoselectivity was observed and mixture of both C-6 epimers was detected. The absolute configuration of the new stereogenic center was confirmed by NOE experiment from **160**.

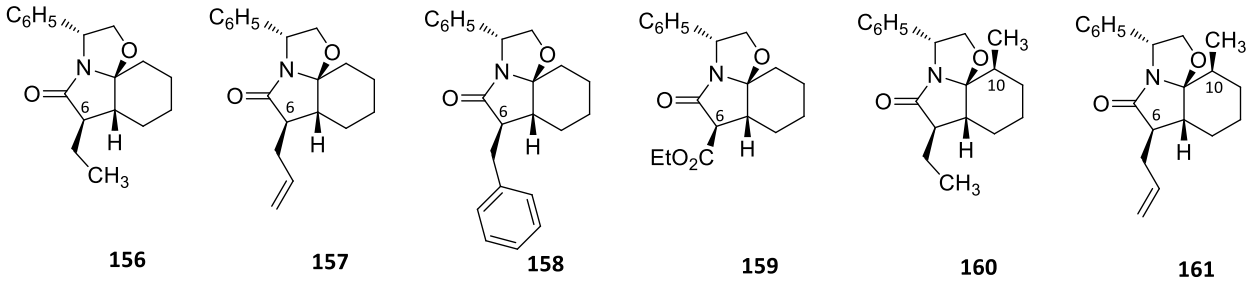


112a **a** **b**

	alkylating agent	t	y%	*dr* (NMR)	compound
1	EtI	1+12h	85%	7:1	**160**
2	Allylbromide	1+12h	70%	15:1	**161**

Table 4.12

In conclusion, high yield and good to excellent stereoselectivity was observed in the formation of six new C-6 substituted tricyclic lactams, which, in some cases, incorporate functional groups that would allow further modification and access to more complex octahydroindole-based structures.

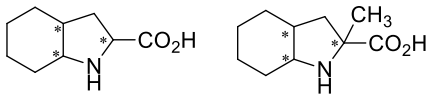


156 **157** **158** **159** **160** **161**

Figure 4.57 C-6 substituted tricyclic lactams

4.5. Approach to proline-based aminoacids

Proline analogues are of particular interest, due to the key role of proline in nucleating the secondary structure, and hence the function of peptides.[165] In particular, octahydroindoles-2-carboxylic acid (Oic) and its α-methylated counterpart [(αMe)Oic] hold considerable interest due to their well-suited structural features. Their bicyclic structures introduce a certain backbone rigidity when incorporated into peptides, similar to that induced by proline. This structural restriction may contribute not only to improve the resistance to degrading enzymes but also to enhance target binding and selectivity properties through the stabilization of specific secondary structural motifs. These properties may be particularly enhanced in the case of the α-methylated derivatives due to the quaternary character of the α-carbon atom.[166]



Oic (αMe)Oic

Figure 4.58 General structure of octahydroindoles-2-carboxylic acid (Oic) and its α-methyl derivative [(αMe)Oic]

At the same time, peptides that exhibit an increased bioavailability and/or binding abilities may be derived from these proline analogues, due to their lipophilicity and hydrophobic size. In particular Oic has found application in the elaboration of important drugs such as Perindopril, an angiotensin-converting enzyme (ACE) inhibitor, which is one of the top antihypertensive drugs on the market.[167] In addition, the Oic scaffold, containing additional functionalities, is found in the structure of aeruginosins.

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[165] a. Kay, B. K.; Williamson, M. P.; Sudol *FASEB J.* **2000**, *14*, 231–241; b. Vanhoof, G.; Goossens, F.; de Meester, I.; Henriks, D.; Scharpé, S. *FASEB J.* **1995**, *9*, 736–744; c. MacArthur, M. W.; Thornton, J. M. *J. Mol. Biol.* **1991**, *218*, 397–412.

[166] a. Cowell, S. M.; Lee, Y. S.; Cain, J. P.; Hruby, V. J. *Curr. Med. Chem.* **2004**, *11*, 2785–2798; b. Toniolo, C.; Crisma, M.; Formaggio, F.; Peggion, C. *Biopolymers* (*Pept. Sci.*) **2001**, *60*, 396–419; c. Venkatraman, J.; Shankaramma, S. C.; Balaran, P. *Chem. Rev.* **2001**, *101*, 3131–3152.

[167] a. Alfakih, K.; Hall, A. S. *Expert Opin. Pharmacother.* **2006**, *7*, 63–71; b. Hurst, M.; Jarvis, B. *Drugs* **2001**, *61*, 867–896; c. Todd, P. A.; Fitton, A. *Drugs* **1991**, *42*, 90–114.

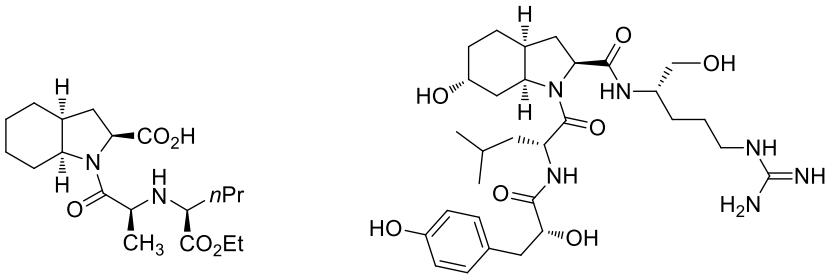


Figure 4.59 Some Oic-containing active compounds

Besides the attractiveness of Oic derivatives for drug generation, an additional interest of these compounds systems derives from their potential utility to carry out chemical transformations with induction of chirality. In fact, some Oic derivatives have already been used as chiral ligands or catalysts.[168] Accordingly, the development of new procedures for the synthesis of Oic derivatives in enantiopure form constitutes an area of interest for synthetic chemists.[169] Dubuffet and Lecouve have reported the transformation of cis-octahydro-2-indolones into cis-octahydroindole-2-carboxylic acids.[170]

Treatment of unsubstituted *cis*-octahydro-2-indolone with triflic anhydride followed by addition of lithium cyanide afforded a cyano-imine which was subsequently hydrolysed under acidic conditions. A final stereoselective catalytic hydrogenation of the C=N bond afforded the C-2/C-7a *cis* isomer of the corresponding α-amino-acid.

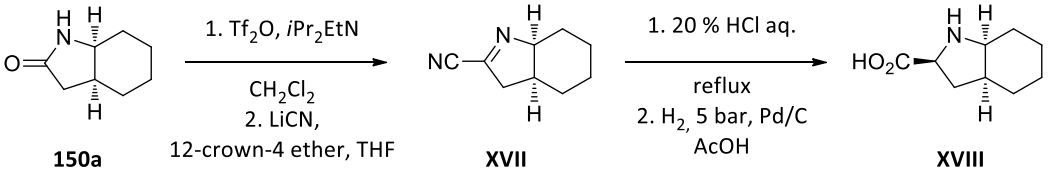


Figure 4.60

[168] a. Luo, R.-S.; Weng, J.; Ai, H.-B.; Lu, G.; Chan, A. S. C. *Adv. Synth. Catal.* **2009**, *351*, 2449–2459; b. Wu, Y.-Y.; Chai, Z.; Liu, X-Y.; Zhao, G.; Wang, S.-W.; *Eur. J. Org. Chem.* **2009**, 904–911; c. Liégault, B.; Tang, X.; Bruneau, C.; Renaud, J.-L. *Eur. J. Org. Chem.* **2008**, 934–940; d. Kim, Y. H. *Acc. Chem. Res.* **2001**, *34*, 955–962; e. Kim, Y. H.; Kim, S. H.; Park, D. H. *Tetrahedron Lett.* **1993**, *34*, 6063–6066.

[169] a. Sayago, F. J.; Laborda, P.; Calaza, M. I.; Jiménez, A. I.; Cativela, C. *Eur. J. Org. Chem.* **2011**, 2011–2028; b. Vincent, M.; Baliarda, J.; Marchand, B.; Remond, G. U.S. Pat. 4914214, **1990** (*Chem. Abstr.* **1989**, *111*, 115749); c. Pascard, C.; Guilhem, J.; Vincent, M.; Rémond, G.; Portevin, B.; Laubie, M. *J. Med. Chem.* **1991**, *34*, 663–669; d. Vincent, M.; Marchand, B.; Rémond, G.; Jaguelin-Guinamant, S.; Damien, G.; Portevin, B.; Baumal, J.-Y.; Volland, J.-P.; Bouchet, J.-P.; Lambert, P.H.; Serkiz, B.; Luitjen, W.; Laubie, M.; SChiavi, P. *Drug Des. Discovery* **1992**, *9*, 11–28; e. Kankan, R. N.M Rao, D. R. PCT Int. Appl. WO 2005100317, **2005** (*Chem. Abstr.* **2005**, *143*, 367597); f. Sayago, F. J.; Calaza, M. I.; Jiménez, A. I.; Cativela, C. *Tetrahedron* **2008**, *64*, 84–91; g. Dubuffet, T.; Lanlois, P. U.S. Pat. Appl. US 0167273, **2006** (*Chem. Abstr.* **2006**, *139*, 197771); h. Belvisi, L.; Colombo, L.; Colombo, M.; Di Giacomo, M.; Manzoni, L.; Vodopivec, B.; Scolastico, C. *Tetrahedron* **2001**, *57*, 6463–6473; i. Hanessian, S.; Margarita, R.; Hall, A.; Johnstone, S.; Tremblay, M.; Parlanti, L. *J. Am. Chem. Soc.* **2002**, *124*, 13342–13343; k. Barton, D. H. R.; Guilhem, J.; Hervé, Y.; Potier, P.; Thierry, J. *Tetrahedron Lett.* **1987**, *28*, 1413–1416; l. Sayago, F. J.; Calaza, M I.; Jiménez, A. I.; Cativela, C. *Tetrahedron: Asymmetry* **2008**, *19*, 2763–2766; m. Sayago, F. J.; Calaza, M .I.; Jiménez, A. I.; Cativela, C. *Tetrahedron* **2009**, *65*, 5174–5180.

[170] Dubuffet, T.; Lecouve, J.-P. Eur. Pat. Appl. EP 1354875, **2003**, (*Chem. Abstr.* **2003**, *139*, 308015).

However, for the conversion of the C-7 substituted *cis*-octahydro-2-indolones prepared in this work into Oic derivatives, we focused our attention in a procedure reported by B. Ganem based on the reduction of secondary amides to imines using Cp_2ZrHCl, the Schwartz's reagent, followed by cyanation with trimethylsilyl cyanide and final hydrolysis of the resulting aminonitrile. [171] This route is significantly shorter than previously reported similar transformations.[172]

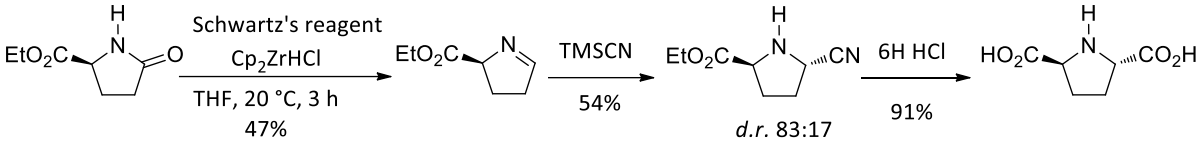


Figure 4.61 Partial reduction of amide with Schwartz's reagent

When ocahydro-2-indolones **164a** and**164b** were treated with the Schwartz's reagent, in THF at – 20 °C, followed by reaction with TMSCN in THF at room temperature, the α-amino-nitriles **162** and **163**, respectively, were isolated in good yields as mixtures of C-2 epimers. The intermediate imines are unstable and were allowed to react immediately. Compound **163** was hydrolyzed to the corresponding α-amino-acid in moderate yield. No attempts to isomerize the mixture of C-2 epimers of **164** through the corresponding esters were performed.[171b,173]

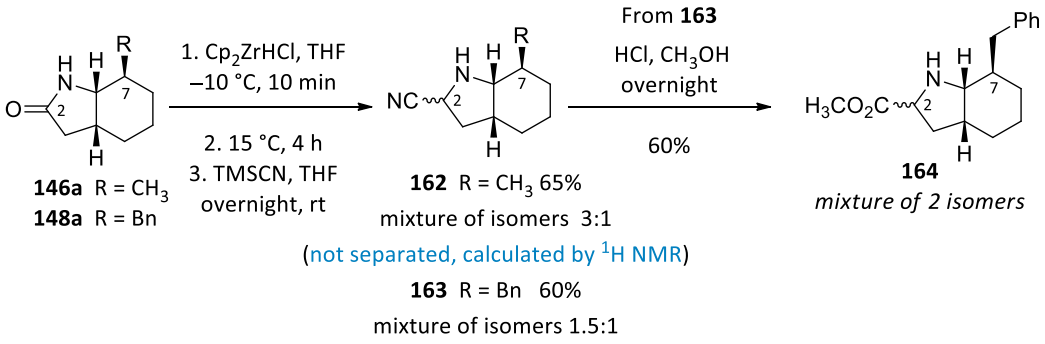


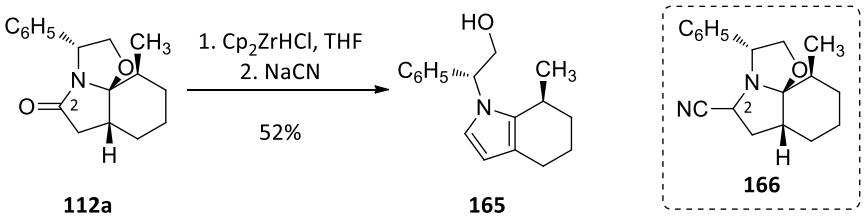
Figure 4.62 Cyanation reaction

When tricyclic lactam **112a** was subjected to the above reaction conditions pyrrole **165** was obtained in 52% yield as the only isolable product (Figure 4.63).

[171] a. Schedler, D. J. A.; Li, J.; Ganem, B. *J. Org. Chem.* **1996**, *61*, 4115–4119; b. Xia, Q.; Ganem, B. *Org. Lett.* **2001**, *3*, 485–487; Xia, Q.; Ganem, B. *Tetrahedron Lett.* **2002**, *43*, 1597–1598.

[172] For similar transformations of amides into aminonitriles, see: a. Corey, E. J.; Yuen, P.-W.; Hannon, F. J.; Wierda, D. A. *J. Org. Chem.* **1990**, *55*, 784–786; b. Langlois, N.; Rojas, A. *Tetrahedron* **1993**, *49*, 77–82; c. Durand, J.-O.; Larchevêque, M.; Petit, Y. *Tetrahedron Lett.* **1998**, *39*, 5743–5746.

[173] a. Takano, S.; Imabuchi, Y.; Ogasawara, K. *J. Chem. Soc. Chem. Commun.* **1988**, 1204–1206; b. Kuyama, H.; Nakada, T. *Tetrahedron Lett.* **1998**, *39*, 2171–2174.



112a **165** **166**

Figure 4.63

4.6. Lycorane-type alkaloids

Amaryllidaceae is a family of alkaloids that includes more than 200 compounds, isolated since 1987. The structure of most of these natural products has been determined and classified into eighteen types. The most representative compounds are shown in Figure 4.68: lycorine (lycorin- type), crinine (crinine- type), pancratistatin (isocarbostyril type), galanthamine (galanthamine- type), tazettine (tazettine- type), homolycorine (homolycorine- type), montanine (montanine- type), belladine (belladine- type), galanthindole (galanthindole- type), galasine (galasine- type), cripowellin A (cripowellin- type), cherylline (cherylline- type), Buflavine (buflavine- type), plicamine (plicamine- type), graciline (graciline- type), augustamine (augustamine- type), gracilamine (gracilamine- type), and hostasinine (hostasinine- type). Besides these structural types, there are mesembrine and cherylline (4-aryltetrahydroisoquinoline type), which belongs to the *Sceltium* alkaloids (Aizoaceae), but not ro the *Amaryllidaceae*.[174, 175, 176]

[174] a. Hoshino, O. *The Alkaloids*, Vol. 51, (Ed.: G. A. Cordell), Academic Press, San Diego, **1998**, 323–424; b. Prabhakar, S.; Travares, M. R. *Alkaloids: Chemical and Biological Perspectives*, Vol. 15, (Ed.: S. W. Pelletier), Elsevier Science Ltd., Oxford, **2001**, 433–572.

[175] Selected references for annual review on isolation and characterization of Amaryllidaceae and *Sceletium* alkaloids: a. Grundon, M. F. *Nat. Prod. Rep.* **1989**, *6*, 79–84; b. Lewis, J. R. *Nat. Prod. Rep.* **1990**, *7*, 549–556; c. Lewis, J. R. *Nat. Prod. Rep.* **1992**, 9, 183–191; d. Lewis, J. R. *Nat. Prod. Rep.* **1993**, *10*, 291–299; e. Lewis, J. R. *Nat. Prod. Rep.* **1994**, *11*, 329–332; f. Lewis, J. R. *Nat. Prod. Rep.* **1995**, *12*, 339–345; g. Lewis, J. R. *Nat. Prod. Rep.* **1996**, *13*, 171–176; h. Lewis, J. R. *Nat. Prod. Rep.* **1997**, *14*, 303–308; i. Jin, Z. *Nat. Prod. Rep.* **2007**, *24*, 886–905; l. Jin, Z. *Nat. Prod. Rep.* **2009**, *26*, 363–381; m. Jin, Z. *Nat. Prod. Rep.* **2011**, *28*, 1126–1142; n. Jin, Z. *Nat. Prod. Rep.* **2013**, *30*, 849–868.

[176] Other Lycorane-type alkaloids from *Zephyranthes citrina*: Herrera, M. R.; Machocho, A. K.; Brun, R.; Viladomat, F.; Codina, C.; Bastida, J. *Planta Med.* **2007**, *67*, 191–193.

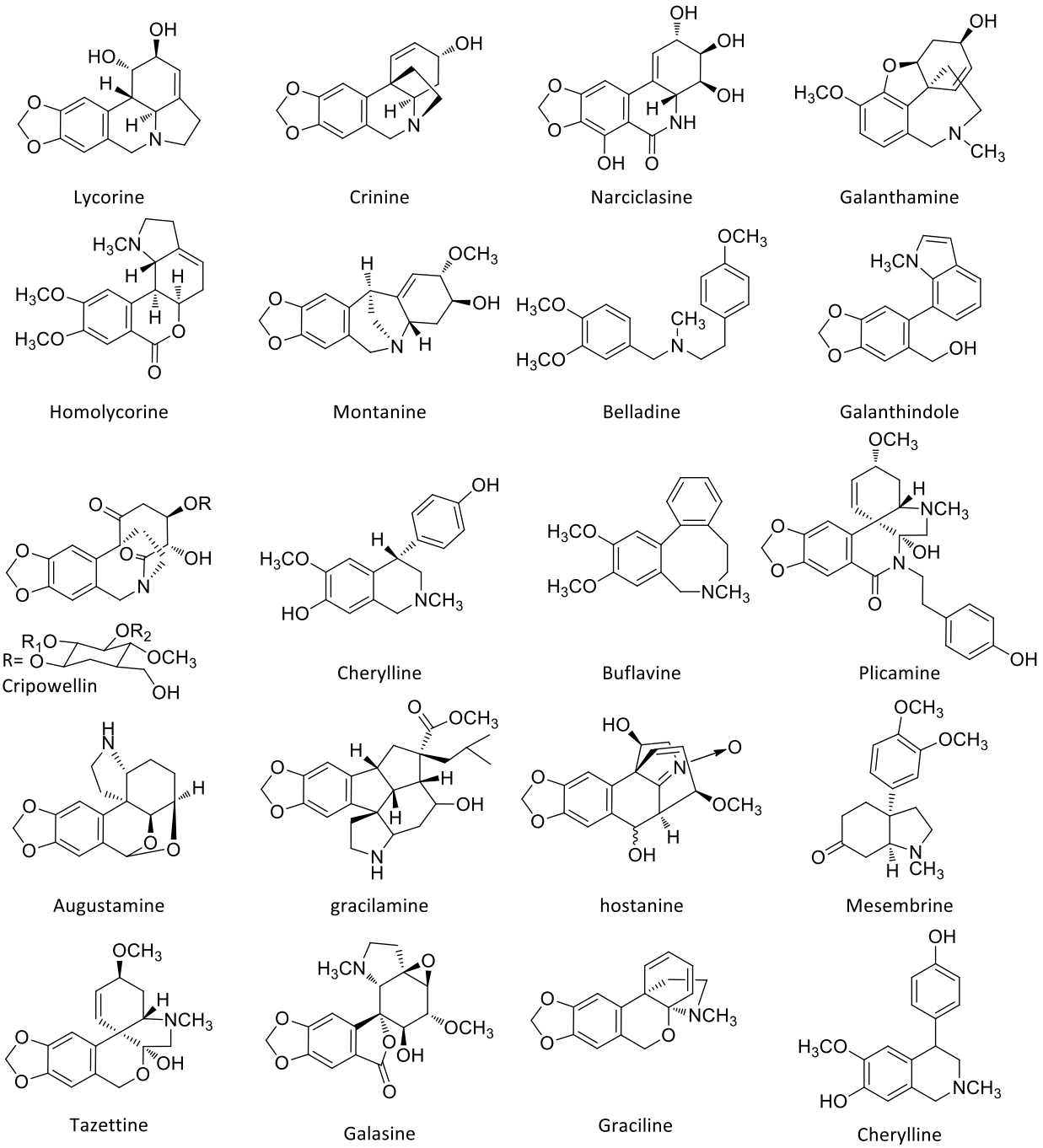


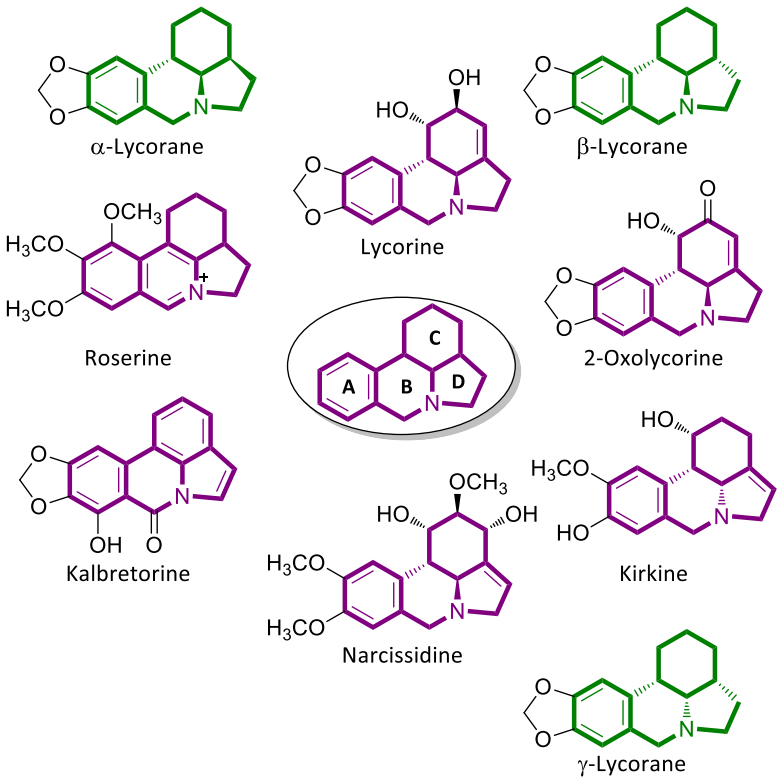
Figure 4.64 Amaryllidaceae type alkaloids

These naturally occurring products are potential drug candidates, which display biological properties, including analgesic, antiviral, and antineoplastic activities, as well as antifeedant activities and among them, highly oxygenated narciclasine (lycoricidine)-type has particularly attracted the attention of

biologists and pharmacologists for its antitumor activity.[177] Reviews that include these biological data have been published.[178]

In particular, we were interested in the lycorine-type alkaloids and related structures, which have a common ABCD tetracyclic pyrrolo[*d*,*e*]phenanthridine (galanthan) framework; most lycorine-type alkaloids have a *trans* B/C-ring junction (Figure 4.63). This class of alkaloids was predominant in *Crinium latifolium* and *Zephyranthes flava* whole plants.

Crinum latifolium



Zephyranthes flava

Figure 4.65 Representative Lycorine-type alkaloids

[177] a. Tanker, M.; Citoglu, G.; Gumusel, B.; Sener, B. *Int. J. Pharmacogn.* **1996**, *34*, 194–197; b. Gabrielsen, B.; Monath, T. P.; Huggins, J. W.; Kefauver, D. F.; Pettit, G. R.; Groszek, G. *J. Nat. Prod.* **1992**, *55*, 1569–1581; c. Ceriotti, G. *Nature* **1967**, *213*, 595–596; d. Jimenez, A.; Santos, A.; Alonso, G.; Vazquez, D. *Biochim. Biophys. Acta* **1976**, *425*, 342–348; e. Baez, A.; Vazuqez, D. *Biochim. Biophys. Acta* **1978**, *518*, 95–103; f. Numata, A.; Takemura, T.; Ohbayashi, H.; Katsuno, T.; Yamamoto, K.; Sato, K.; Kobayashi, S. *Chem. Pharm. Bull.* **1983**, *31*, 2146–2152; g. Singh, R. P.; Pant, N. C. *Experientia* **1980**, *36*, 550–552.

[178] a. Ruan, L. *Chem. Abstr.* **1988**, *110*, 91979; b. Polt, R. L. in *Organic Synthesis: theory and application* (Ed. T. Hudlicky), Vol. 3, **1996**, 109, JAIPress, Greenwich, CT.

Lycorine is the most representative compound, due to its broad spectrum of pharmacological properties,[179] including anticancer,[180] antiviral,[181] antiparasitic,[182] and anti-inflammatory activities,[183] as well as being phytotoxic in herbicide bioassays.[184] Compounds with tetracyclic core in green are not properly natural alkaloids, but are more precisely degradation products of some lycorine-type compounds.

4.6.1. α-Lycorane

4.6.1.1. Previous enantiopure synthesis

Due to their interesting biological activities and their unique tetracyclic structure, lycorine-type alkaloids have attracted numerous synthetic chemist.[185] However relatively few efficient approaches to their asymmetric synthesis have been reported so far.[186,187]

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[182] a. Campbell, W. E.; Nair, J. J.; Gammon, D. W.; Bastida, J.; Codina, C.; Viladomat, F.; Smith, P. J.; Albrecht, C. F. *Planta Med.* **1998**, *64*, 91–93; b. Campbell, W. E.; Nair, J. J.; Gammon, D. W.; Codina, C.; Bastida, J.; Viladomat, F.; Smith, P. J.; Albrecht, C. F. *Phytochemistry* **2000**, *53*, 587–591.

[183] Çitoğlu, G. S.; Acikara, Ö. B.; Yilmaz, B. S.; Özbek, H. *Fitoterapia* **2012**, *83*, 81–87.

[184] Schrader, K. K.; Andolfi, A.; Cantrell, C. L.; Cimmino, A.; Duke, S. O.; Osbrink, W.; Wedge, D. E.; Evidente, A. *Chem. Biodiversity* **2010**, *7*, 2261–2280.

[185] For review on the synthesis of *Amaryllidaceae* alkaloids: a. Oppolzer, W. *Pure Appl. Chem.* **1994**, *66*, 2127–2130; b. Prabhakar, S.; Tavares, M. R. in *Alkaloids: Chemical and Biological Perspective*, Vol. 15, (Ed.: S. W. Pelletier), Elsevier Science Ltd., Oxford, **2001**, 433–572; c. Banwell, M. G.; Gao, N.; Schwartz, B. D.; White, L. V. *Top. Curr. Chem.* **2012**, *309*, 163–202; d. Martin, S. F. in: *The Alkaloids*, Vol. 30, (Ed.: A. Brossi), Academic Press, New York, **1987**, 251–376; e. Hoshino, O. in: *The Alkaloids*, Vol. 31, (Ed.: G. A. Cordell), Academic Press, San Diego, **1998**, 323–424; f. Jin, Z. *Nat. Prod. Rep.* **2013**, *30*, 849–868.

[186] For selected examples on the enantioselective synthesis of Lycorane, see: a. Yoshizaki, H.; Satoh, H.; Sato, Y.; Nukui, S.; Shibasaki, M.; Mori, M. *J. Org. Chem.* **1995**, *60*, 2016–2021; b. Magnus, P.; Bailey, J. M.; Porter, M. J. *Tetrahedron*, **1999**, *55*, 13927–13936; c. Dong, L.; Xu, Y.-J.; Cun, L.-F.; Cui, X.; Mi, A.-Q.; Jiang, Y.-Z.; Gong, L.-Z. *Org. Lett*. **2005**, *7*, 4285–4288; d. Chapsal, B. D.; Hua, Z.; Ojima, I. *Org. Lett*. **2006**, *8*, 1395–1398; e. Chapsal, B. D.; Ojima, I. *Tetrahedron: Asymmetry* **2006**, *17*, 642–657; f. Dong, L.; Xu, Y.-J.; Yuan, W.-C.; Cui, X.; Cun, L.-F.; Gong, L.-Z. *Eur. J. Org. Chem.* **2006**, 4093–4105; g. Bor-Cherng, H.; Nimje, R. Y.; Wu, M.-F.; Sadani, A. A. *Eur. J. Org. Chem.* **2008**, 1449–1457; h. Rajkumar, S.; Shakland, K.; Brown, G. D.; Cobb, A. J. A. *Chem. Sci.* **2012**, *3*, 574–588; i. Wang, Y.; Luo, Y.-C.; zhang, H.-B.; Xu, P.-F. *Org. Biomol. Chem.* **2012**, *10*, 8211–8215; j. Li, G.; xie, J.-H.; Hou, J.; Zhu, S.-F.; Zhou, Q.-L. *Adv. Synth. Catal.* **2013**, *355*, 1597–1604; k. Meng, X.-L.; Liu, T.; Sun, Z.-W.; Wang, J.-C-; Peng, F.-Z.; Shao, Z.-H. *Org. Lett.* **2014**, *16*, 3044–3047; l. Sun, Z.; Zhou, M.; Li, X.; Meng, X.; Peng, F.; Zhang, H.; Shao, Z. *Chem. Eur. J.* **2014**, *20*, 6112–6119.

[187] For enantioselective synthesis of tetracyclic core of Lycorane alkaloids: a. Coya, E.; Sotomayor, N.; Lete, E. *Adv. Synth. Catal.* DOI: 10.1002/adsc.201500431; b. Bouaucheau, C.; Parlier, A.; Rudler, H. *J. Org. Chem*. **1997**, *62*, 7247–7259; c. Rajkumar, S.; Shankland, K.; Brown, G. D.; Bobb A. J. A. *Chem. Sci.* **2012**, *3*, 584–588.

In order to demonstrate the synthetic value of our methodology, the total synthesis of enantiopure α-lycorane was undertaken.

In 2008, Sadani proposed the first enantioselective formal synthesis of (–)-α-lycorane,[188] via an asymmetric organocatalytic domino reaction, starting from (*E*)-7-oxohept-2-enoate and a derivative of *trans*-nitrostyrene. Tandem Michael reactions were carried out one pot, in the presence of the Hayashi-Jorgensen catalyst, with excellent enantioselectivity (98%), but moderate diastereoselectivity and yield (2:1, 78%). The derived *tert*-butyl ester was converted into the intermediate **XXIV**, which had been reported to be a precursor of targeted lycorane.[189] The main drawback of this synthesis is that the required diastereoisomer is obtained in only 2:1 *dr*, while for its epimer *epi*-**XXIII** the authors described a highly diasteroselective approach by changing the configuration of the starting oxohept-2-enoate. The formyl group at C-4 and phenyl group at C-3 resulted *anti* in both **XXIII** and *epi*-**XXIII**.

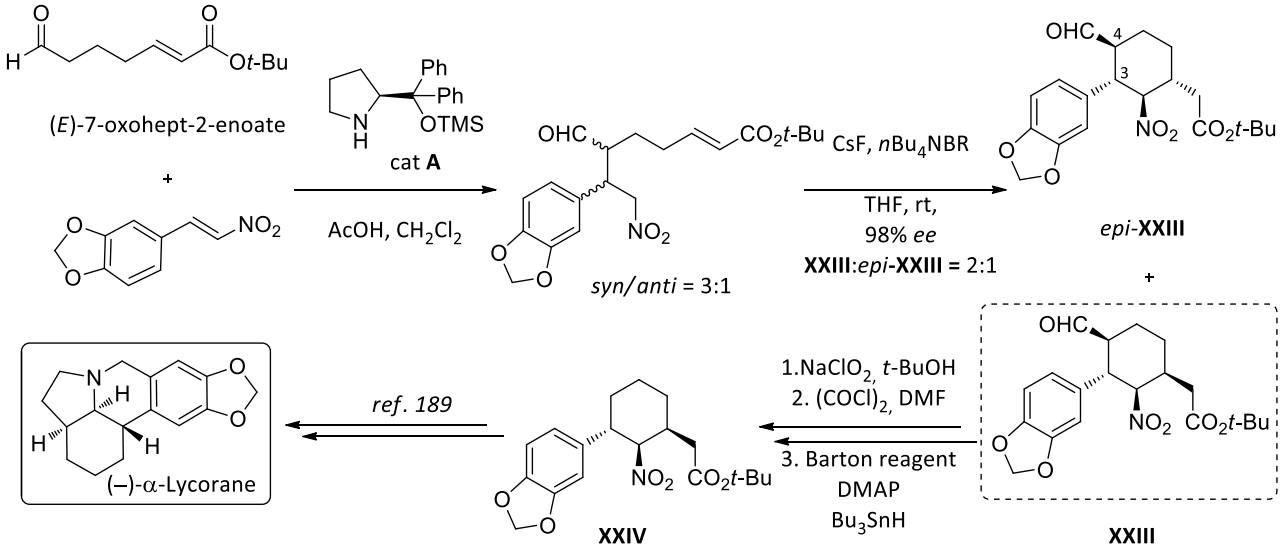

Figure 4.66 Sadani's synthesis of α-Lycorane

In a very similar way the synthetic developed by Xu[190] and Zhao[191] approach of (–)-α-lycorane, utilizes a bifunctional thiourea-catalyzed cascade Michael reaction. The desired product **XXVI** was obtained in excellent yield and stereoselectivity (90% *ee*, 12:1 *dr* in both cases) using 20 mol % **QT**. Reduction with nickel boride followed by cyclization successfully afforded products **XXVII**, which were converted into the lycorine-type tetracyclic core. The fact that the very low reactive malonate derivative can react with strong electron-donating nitro-olefin, is quite surprisingly and the thiourea based catalyst certainly plays an important role.[192]

[188] Hong, B.-C.; Nimje, R. Y.; Wu, M.-F.; Sadani, A. A. *Eur. J. Org. Chem.* **2008**, 1449–1457.
[189] Yasuhara, T.; Nishimura, K.; Yamashita, M.; Fukuyama, K.; Yamada, I.; Muropka, O.; Tomioka, K. *Org. Lett.* **2003**, *5*, 1123–1126.
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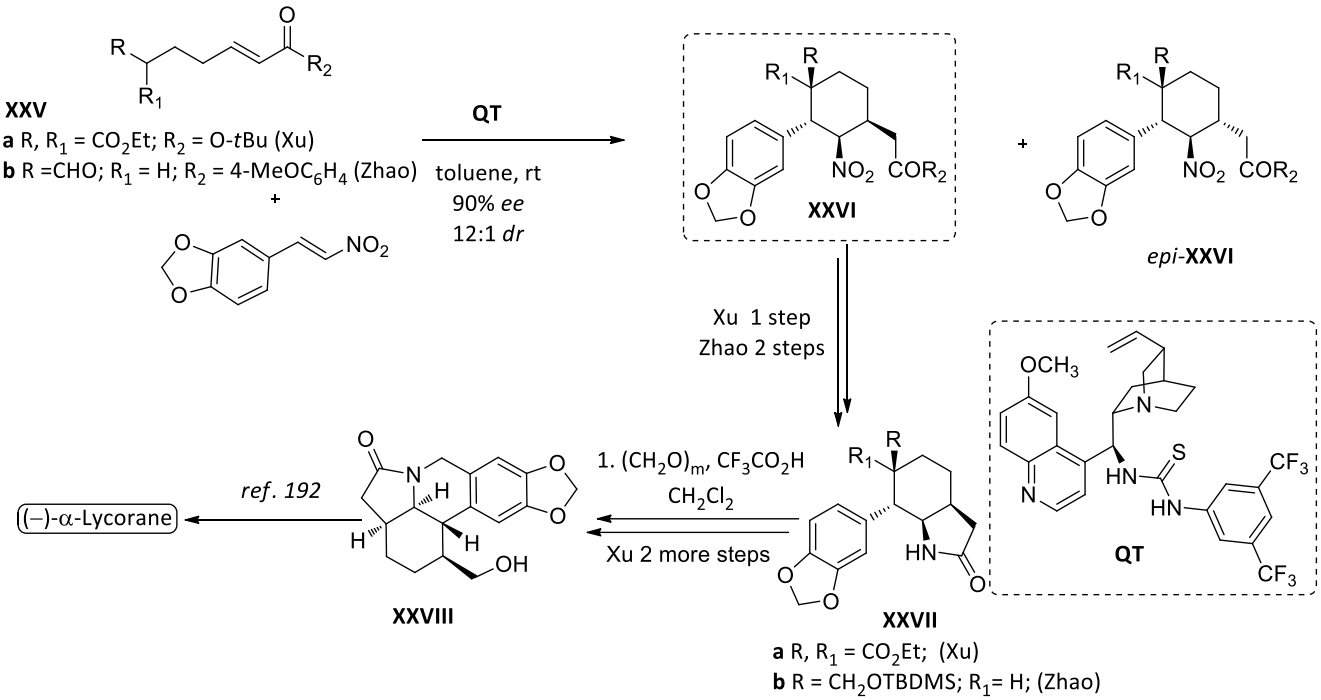


Figure 4.67 Xu and Zhao formal synthesis of α-Lycorane

In 2013 Zhou[193] reported the enantioselective synthesis of (–)-α-lycorane, through a procedure in which the asymmetric hydrogenation of racemic 2-arylcyclohexanone with a chiral spiro ruthenium catalyst was the key step. A Mitsunobo reaction, followed by catalytic hydrogenation of the resulting azide, afforded the primary amine with inversion of the configuration. Cyclization *via* Pictet–Spengler reaction and amine acylation with bromoacetyl chloride, followed by modified Umezawa's intramolecular nucleophilic cyclization afforded the tetracyclic compound **XXXIV**, as single isomer, which was finally converted in the targeted Lycorane, *via* modified Wolff-Kishner reduction (Figure 4.68).

[193] Li, Gang; Xie, J.-H.; Hou, J.; Zhu, S.-F.; Zhou, Q.-L. *Adv. Synth. Catal.* **2013**, *335*, 1597–1604.

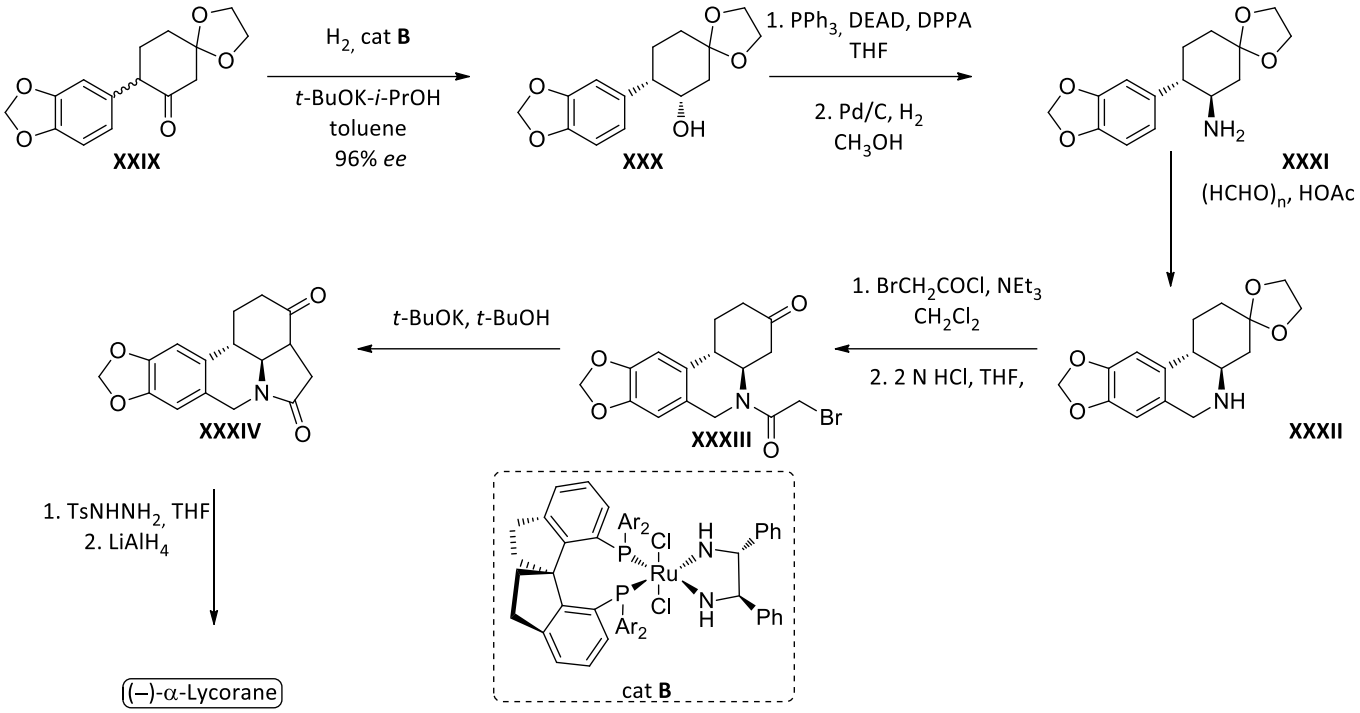


Figure 4.68 Zhou synthesis of α-Lycorane

Finally, in 2014 Zhi-Hui Shao, [194] reported the approach to this lycorine-type alkaloid by catalytic asymmetric conjugate addition of acetaldehyde to a nitrodienyne as most important step. Pinnick oxidation of the aldehyde **XXXVII**, followed by treatment with *para*-toluensulfonic acid led to **XXXVIII** that was converted into **XXXIX** after few modifications, in 93% *ee* and good yield. This compound had the same functionality of the already described compound **XXIV** and **XXVI**, and following Sadani's procedure, α-lycorane was synthesized.

[194] Sun, Z.; Zhou, M.; Li, X.; MEng, X.; Peng, F.; Zhang, H.; Shao, Z. ; Shao, Z. *Chem. Eur. J.* **2014**, *20*, 6112–6119.

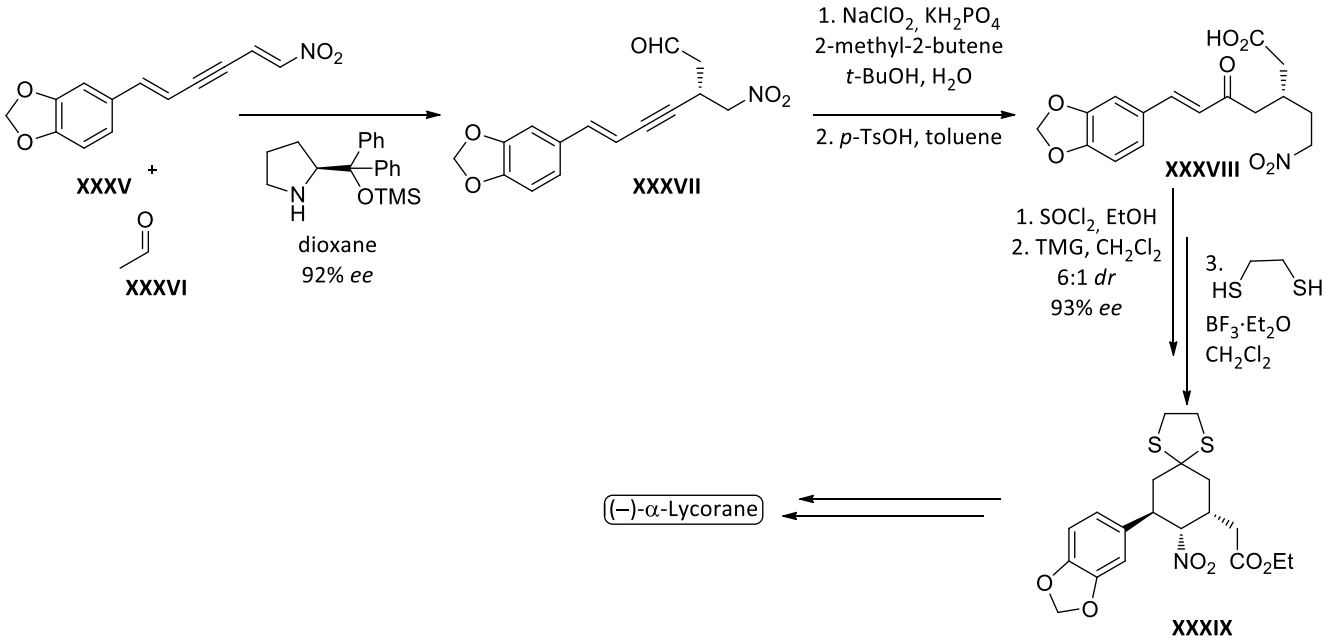


Figure 4.69 Shao's synthesis of α-Lycorane

4.6.1.2. Proposed synthetic plan

Our synthetic approach to (+)-α-lycorane is based on the synthetic methodology developed in this work for the synthesis of 7-substituted *cis*-octahydroindoles. Thus, starting from a 6-aryl cyclohexanone-2-acetate only three synthetic transformations are needed: i) a cyclocondensation with an enantiopure amino-alcohol, ii) the removal of the phenylethanol moiety of the chiral inductor, and iii) the closure of the B ring.

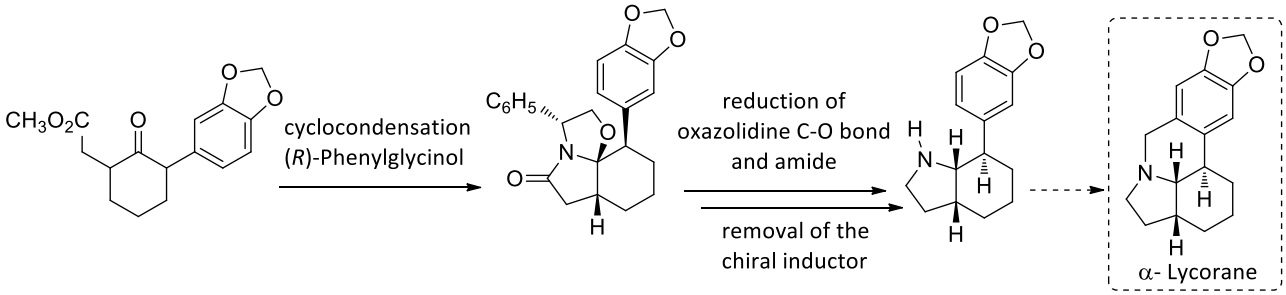


Figure 4.70 Synthesis of α-Lycorane

4.6.1.3. Enantioselective synthesis of (–)-α-Lycorane

The cyclohexanone **171** [195] was obtained as a mixture of isomers by following the reported procedure[196](Figure 4.75).

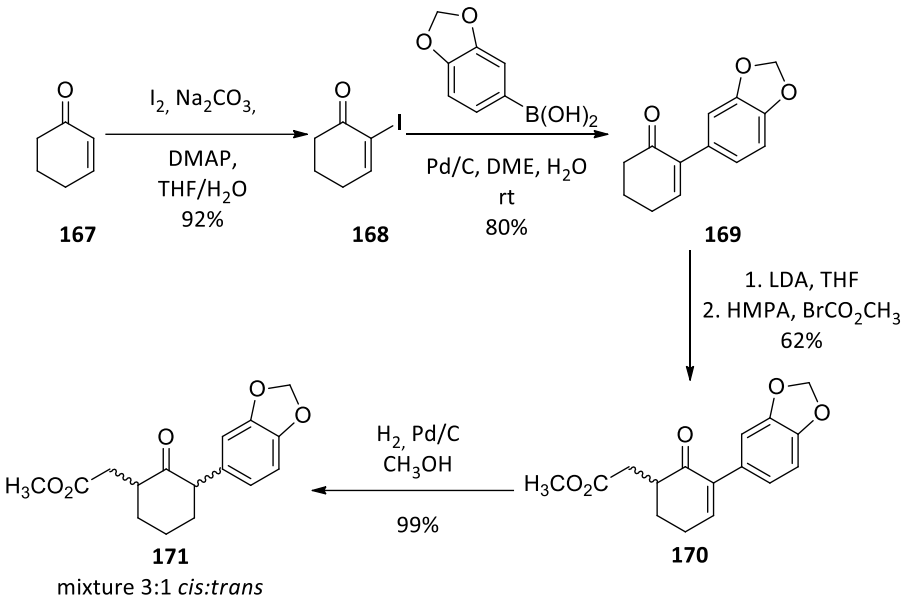


Figure 4.71 Synthesis of cyclohexanone 171

Reaction of **171** with (*R*)-phenylglycinol was performed under the optimized conditions (paragraph 4.1.2.2), in the presence of acetic acid. Lactam **172** was isolated in 54%, as a single isomer. Reduction of lactam carbonyl and simultaneous opening of oxazolidine ring led to *cis*-octahydroindole **173a** in 82% yield. The formation of the *trans* isomer (13%) was also detected and this isomer could not be separate at this stage. The mixture of the two octahydroindoles was subjected to hydrogenation, in order to eliminate the chiral inductor residue, and the resulting amine was protected with Boc. The desired pure compound **174** was obtained in 70% yield. Pictet-Spengler reaction with formaldehyde,[197] catalysed by hydrochloric acid, conducted to (+)-α-lycorane in very good yield. Thus, one of the most efficient procedures for the synthesis of α-lycorane has been reported: four steps and 35% of overall yield, from **171** (keeping in mind that previous enantioselective synthesis were reported to afford the alkaloids in up to 22% of overall yield). By changing the chiral inductor [(*S*)-phenylglycinol] the enantiomer (–)-α-lycorane could be synthesized.

[195] Its corresponding ethyl ester has been already described.
[196] Liu. C.; Xie, J.-H.; Li, Y.-L.; Chen, J.-Q.; Zhou, Q.-L. *Angew. Chem. Int. Ed.* **2013**, *52*, 593–596.
[197] Yang, S. H.; Song, C.-H.; Van, H. T. M.; Park, E.; Khadka, D. B.; Gong, E.-Y.; Lee, K.; Cho, W.-J. *J. Med. Chem.* **2013**, *56*, 3414–3418.

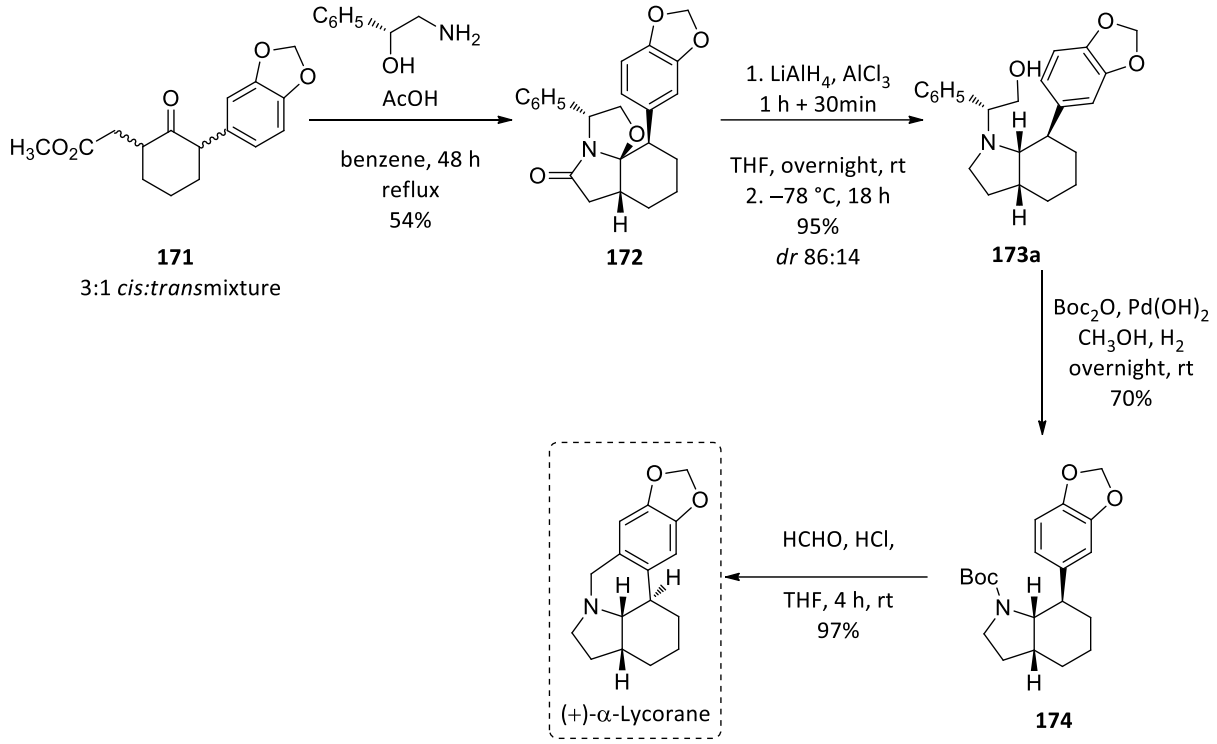


Figure 4.72 Enantioselective synthesis of (+)-α-Lycorane

CHAPTER 5. CONCLUSIONS

1. Cyclocondensation reactions of 2-oxocyclopentenepropionate derivatives **4** and **7** and 2-oxocyclohexeneacetate derivatives **16** and **17** were expected to provide unsaturated tricyclic lactams. In the first case, a five-membered carbocyclic ring and a six-membered lactam ring would be present, but conjugated imine **8** or **9** were isolated as unique products. The normal course of the reaction is avoided due to the difficult isomerization of double bonds in pentacyclic systems. In the second case a six-membered carbocyclic ring and a five-membered lactam ring would be formed, but a mixture of unsaturated conjugated bicyclic lactams **18** were obtained. The highly strained resulting tricyclic system was unstable and decomposed immediately, with the opening of the oxazolidine ring. Although our methodology resulted effective in the synthesis of unsaturated systems with six-membered lactam and carbocyclic rings, it has failed in the case of incipient or still present five-membered ring.
2. Reaction of (*R*)-phenylglycinol and (1*S*, 2*R*)- *cis*-1-amino-2-indanol with 3-substituted 2-oxocyclohexanepropionate derivatives **20**, **49**, **53** and **54** provided stereoselectively lactams **29a**, **55a**-**60a** , which led an alkyl substituent at the contiguous carbon to the oxazolidinic C-O bond. In only one step three new stereogenic centers were formed with a well-defined configuration, keeping in mind that the starting ketones were employed as mixture of isomers. Minor amounts of lactams **29b**, **55b**-**60b** were detected. This lactams are precursors of enantiopure C-8 alkyl *cis*-decahydroquinolines. *Cis*-aminoindanol provided better chemical yield and stereoselectivity than (*R*)-phenylglycinol.
3. Starting from an isomeric mixture of 2-oxopropionate derivatives **21** and **22**, aminoindanol derived pentacyclic lactams **31a** and **33a**, which exhibit a propionate chain and an alkyl substituent at the carbocyclic ring, were synthesized. In this case, four new stereogenic centres were stereoselectively formed, and minor amount lactams **31b** and **33b** were isolated. The chemical and stereochemical outcome of the reaction with *cis*-aminoindanol only slightly improved the already reported results obtained with (*R*)-phenylglycinol.
4. An efficient and straightforward methodology for the synthesis of enantiopure C-8 and C-6,8 substituted *cis*-decahydroquinolines was presented: in only three steps, that are cyclocondensation, alane reduction and debenzylation, the targeted azabicycles were obtained. The utility of this methodology was demonstrated by the synthesis of *cis*-decahydroquinoline **82**, which represents an advanced precursor for the preparation of *Myrioneuron alkaloids*. Our synthetic procedure greatly improved the previous results reported by Bodo for the synthesis of this alcohol.
5. Reaction of (*R*)-phenylglycinol and 3-alkyl-2-oxocyclohexaneacetate derivatives **97**-**100** and **107** provided with high yield and stereoselectivity tricyclic lactams **110**, **112a**, **114**, **116** and **118**, which incorporate an alkyl or aryl substituent at C-10.

6. Cyclocondensation reactions of ketones with an alkyl substituent at C-3, stereoselectively provided an additional minor exahydroindole by-product. The absolute configuration of these compounds **111a**, **113a**, **115a** and **117a** was confirmed by X-ray crystallography. In the case of any or aryl substituent at C-10 of the tricyclic lactam, no by products were detected. We demonstrated that these unsaturated products derived from the opening of the oxazolidine ring of the minor lactams, which are epimers at C-10 of the major lactams, in the presence of acids.
7. Stereoselective opening of oxazolidine ring of major lactams, in the presence of strong acids provided unsaturated compounds **111b**, **113b**, **115b** and **117b**, in which H-7 and H-7a resulted in *cis* relative disposition, as observed in the series **a**.
8. Acid opening of the oxazolidine ring in the lactam **118**, with an aryl substituent at C-10, provided the unsaturated compound **125**, in which H-7 and H-7a are in relative *trans* disposition. This different relative configuration can be accounted for by considering the structure rigidity of this system. The first kinetic protonation step led to a compound in which phenyl was in an unfavourable axial position. Equilibration occurred *via* activation of the lactam carbonyl and formation of an enenol intermediate. The further re-protonation led to the most stable conformer.
9. Major tricyclic lactams were converted into C-7 *exo* substituted *cis*-octahydroindoles, *via* reduction with alane and elimination of the chiral inductor in catalytic hydrogenation conditions.
10. C-7 *exo* substituted *cis*-octahydroindolones were obtained by reduction with silanes and elimination of the chiral inductor with sodium ammonia.
11. Exahydroindolones **111b**, **113b**, **115b** and **117b** were converted stereoselectively into the corresponding enantiopure C-7 *endo* substituted *cis*-octahydroindolones, by catalytic hydrogenation of the carbon-carbon double bond, followed by elimination of the chiral inductor through reaction with sodium radical, generated in liquid ammonia.
12. Changing the double bond reduction conditions, exahydroindolones **111b**, **113b**, **115b** and **117b** were transformed into the corresponding *trans*-octahydroindolones **146c**-**149c**. Sodium ammonia at low temperature allowed the reduction and the simultaneous removal of the phenylethanol moiety.
13. *Trans*-octahydroindole **126b** was obtained in the same reported conditions, starting from unsaturated bicyclic lactam **125**.
14. Tricyclic lactams synthesized from phenylglycinol and cyclohexanone-based acetate derivatives, represent excellent precursors of *cis* and *trans* octahydroindole derivatives. By the accurate choice of the reaction conditions, different structures could be obtained.

15. Studies on α-amidoalkylation have been realized and C-7, 7a disubstituted octahydroindoles **152** and **154** were obtained as single isomers, in good yield. The new introduced substituent is in *cis* relative disposition with respect the C-7 methyl group.
16. Alkylation of the amide enolate, generated by reaction of the tricyclic lactams **119** and **112a** with a strong base, provided C-6 and C-6, 10 substituted lactams **156**-**161** in good yield and good to excellent stereoselectivity.
17. In order to demonstrate the utility of this methodology, (+)-α-Lycorane was synthesized in only four steps, starting from easily available ketone **171**, in 35% of overall yield, which resulted an improvement with respect to previously reported synthesis.

CHAPTER 6. EXPERIMENTAL PART

6.1. General Experimental Procedures

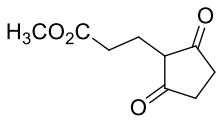
All air sensitive manipulations were carried out under a dry argon or nitrogen atmosphere. THF and toluene were carefully dried and distilled from sodium/benzophenone prior to use. CH_2Cl_2 was dried and distilled from CaH_2. Pyrrolidine was dried and distilled from KOH prior to use. Other solvents and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

Analytical thin-layers chromatography (TLC) was performed on SiO_2 (Merck silica gel 60 F_{254}) and the spots were located by exposure to UV light and/or with 1% aqueous $KMnO_4$ or 3% ethanolic anysaldehyde. Chromatography refers flash-column chromatography was carried out on SiO_2 (SDS silica gel 60 Å, 35-75 mm, 230-240 mesh ASTM) purchased from Merck. Drying of organic extracts during workup of reactions was performed over anhydrous $MgSO_4$ except where stated otherwise. Evaporation of solvent was accomplished with a rotator evaporator.

Instrumentation

Nuclear magnetic resonance spectra were recorded at 300 or 400 MHz (^{1}H NMR) and 75.4 or 100.6 (^{13}C NMR) at 25 °C in $CDCl_3$, unless otherwise noted. Chemical shifts are reported in part per million (ppm, δ scale) downfield from tetramethylsilane or relative to residuals ($CHCl_3$ 7.26 and 77.0 ppm; CD_2HOD 3.31 and 49.1 ppm) as an internal standard. Data are reported in the following manner: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, q = quarter, m = multiplet/or multiple resonance, br.s = broad signal), coupling constant (*J*) in hertz (Hz), integrated intensity, and assignment (when possible). Assignments and stereochemical determinations are given only when they are derived from definitive two-dimensional NMR experiments (*g*-HSQC-COSY). Specific optical rotator power was recorded in a Perkin-Elmer 241 polarimeter using a Na continue lamp. $[\alpha]_D$ values are given in 10^{-1} deg cm^2 g^{-1}. Melting points were determined in a capillary tube and are uncorrected. IR spectra were performed in a spectrophotometer Nicolet Avantar 320 FT-IR, and only noteworthy IR absorptions (cm^{-1}) are listed. Elemental analyses were performed using Elemental Microanalyst (model 1160, 1500, 1180 and 112) by *microanalysis center* of *Centre d'Investigaciò I Desenvolupament (C.I.D)* in Barcrelona. Mass spectra (MS, data are reported as *m/z* y (%) and High Resolution mass spectra (HMRS, data for $(M+H)^+$) were performed by *Centre Cientifics I Tecnologics de la Universitat de Barcelona*. *X-ray* analysis were performed using a difractometre Enraf-Nonius CA D4, using grafit monocromathic radiation Mo Kα by Dr. Elies Molins group from *Institut de Ciència de Materials de Barcelona* (ICMAB).

6.2. Experimental part- Chapter 2



Methyl 2,5-dioxocyclopentanepropionate (2)

A solution of 1,3-cyclopentanedione (200 mg, 1.98 mmol) in DMF (5 mL) was added dropwise at 0 °C to a suspension of NaH (60% dispersion in mineral oil, 95 mg, 2.38 mmol) in DMF (4 mL), and the mixture was stirred at 0 °C for 30 min. Then, methyl acrylate (0.21 mL, 2.31 mmol) was added, and the resulting mixture was stirred at 80 °C for 24 h. After cooling at room temperature, 2 N aqueous HCl (15 mL) was added and the mixture was extracted with EtOAc (2 x 10 mL). The combined organic extracts were washed with water, dried and concentrated to afford compound **2** (73 mg, 20%) as a brown solid (its enolic form is described).

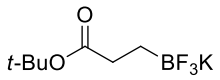
IR(NaCl): 1732, 1554 cm^{-1}.

mp: 137-139 °C.

^{1}H-RMN (300 MHz) δ: 2.38-2.43 (m, 2H), 2.48-2.54 (m, 7H), 3.73 (s, 3H, CH_3).

^{13}C-RMN (75.4 MHz) δ: 15.3 (CH_2), 30.2 (CH_2), 32.6 (CH_2), 52.5 (CH_3), 77.20 (C-1), 116.5 (C-2), 177.7 (*C*O_2, *C*O).

Anal. Calculated for [$C_9H_{12}O_4$]: C, 58.69%; H, 6.57%; found: C, 58.51%; H, 6.80%.



Potassium 2-(*tert*-butoxycarbonyl)ethyltrifluoroborate (6)[198]

A suspension of CuCl (9.0 mg, 0.09 mmol), sodium *tert*-butoxide (26.0 mg, 0.26 mmol), and DPEPhos (49.0 mg, 0.09 mmol) in THF (2.4 mL) was stirred for 30 min at room temperature. Then, a solution of bis(pinacolate)diboron (778 mg, 3.03 mmol) in THF (4.8 mL) was added dropwise via syringe. After 15 min, *tert*-butyl acrylate (0.44 mL, 2.97 mmol) and methanol (0.24 mL) were added sequentially *via* syringe. The mixture was stirred for 3 h at room temperature. The resulting slurry was filtered over Celite®, rinsing with ethyl acetate (8 mL). The filtrate was concentrated to afford an oil which was dissolved in acetonitrile (15 mL) and cooled to 0 °C. KHF_2 (928 mg, 11.88 mmol) in H_2O (2.6 mL) was added dropwise via syringe. The resulting mixture was stirred for 3 h, concentrated and then placed under high vacuum (0.001 Torr). The dried solids were triturated with hot acetone (3 x 8 mL) and filtered to remove inorganic salts. The resulting filtrate was concentrated to a minimal volume (~1 mL) and Et_2O (5 mL) was added to precipitate compound **6** as a white solid (444 mg, 63%).

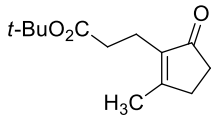
IR(NaCl): 1710 cm^{-1}.

mp: 148-150 °C.

^{1}H-RMN (300 MHz, CD_3OD) δ: 0.48-0.51 (m, 2H), 1.46 (s, 9H), 2.12-2.17 (m, 2H).

^{13}C-RMN (75.4 MHz, CD_3OD) δ: 29.3 (CH_3), 33.8 (CH_2), 81.2 (Cq), 180.2 (CO_2).

[198] Molander, G. A.; Petrillo, D. F. *Org. Lett.* **2008**, *10*, 1795–1798.



tert-Butyl 3-methyl-2-oxocyclopentenepropionate (4)

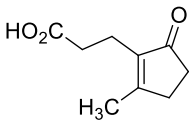
A suspension of **6** (344 mg, 1.46 mmol), 2-bromo-3-methyl-2-cyclopentenone (266 mg, 1.49 mmol), K_2CO_3 (622 mg, 4.46 mmol), $Pd(OAc)_2$ (14 mg, 0.05 mmol) and RuPhos (52.0 mg, 0.11 mmol) in degassed toluene (3.2 mL) and degassed H_2O (0.8 mL) was stirred at 85 °C for 18 h. Additional $Pd(OAc)_2$ (4.5 mg, 0.017 mmol) and RuPhos (17 mg, 0.37 mmol) were added and the stirring was continued for 19 h. Then, EtOAc (6 mL) and pH 7 buffer (6 mL) were added, and the layers were agitated and separated. The aqueous layer was extracted with additional EtOAc and the organic extracts were dried and concentrated. Flash-column chromatography (CH_2Cl_2) afforded the keto ester **4** (296 mg, 90%) as an oil.

IR (NaCl): 1728, 1700, 1649 cm^{-1}.

^{1}H-RMN (300 MHz) δ: 1.40 (s, 9H, [C(CH_3)$_3$]), 2.07 (s, 3H), 2.33-2.38 (m, 4H), 2.33-2.49 (m, 4H).

^{13}C-RMN (100.6 MHz) δ: 17.3 [C(CH_3)$_3$] , 18.8 (CH_2), 28.0 [C(CH_3)$_3$], 31.6 (CH_2), 33.4 (CH_2), 34.2 (CH_2), 80.1 (Cq), 138.8 (Cq), 171.2 (Cq), 172.3 (CO_2), 209.3 (CO).

HRMS calculated for $[C_{13}H_{20}O_3 + H]^+$: 225.1485; found: 225.1479.



3-Methyl-5-oxo-2-cyclopentenepropionic acid (7)

TFA (8.50 mL, 109 mmol) was added to a solution of the ester **4** (500 mg, 2.23 mmol) in CH_2Cl_2 (33 mL) at 0 °C, and the resulting solution was allowed to warm at room temperature and stirred for 4 h. Then, saturated aqueous Na_2CO_3 was added until pH~12 and the aqueous phase was washed with CH_2Cl_2, neutralized with HCl (6 N) and extracted with CH_2Cl_2. The organic extracts were dried and concentrated to afford the keto acid **7** (259 mg, 69%) as a yellow solid.

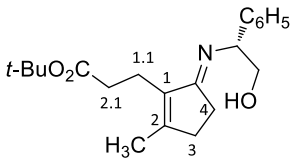
IR(NaCl): 2924, 1731, 1666, 1624 cm^{-1}.

mp: 83-85 °C.

^{1}H-RMN (300 MHz) δ: 2.09 (s, 3H), 2.36-2.39 (m, 2H), 2.50-2.53 (m, 6H).

^{13}C-RMN (75.4 MHz) δ: 17.2 (CH_3), 18.4 (CH_2), 31.7 (CH_2), 31.8 (CH_2), 34.1 (CH_2), 138.1 (Cq), 172.4 (Cq), 178.3 (*C*O_2), 209.9 (*C*O).

HRMS calculated for $[C_9H_{12}O_3 + H]^+$: 169.0859; found: 169.0862.



tert-butyl (_R_)-5-[_N_-(2-hydroxy-1-phenylethyl)imino]-2-methyl-1-cyclopentenepropionate (8)

(*R*)-Phenylglycinol (373 mg, 2.72 mmol) was added to a solution of keto ester **4** (202 mg, 0.9 mmol) and AcOH (160 μL, 2.77 mmol) in benzene (16 mL). The mixture was heated at reflux for 24 h with azeotropic elimination of H_2O produced by a Dean–Stark apparatus. The resulting mixture was cooled and concentrated to give an oil. Flash-column chromatography (1:1 hexane-AcOEt) afforded imine **8** (173 mg, 56%) as a yellow oil.

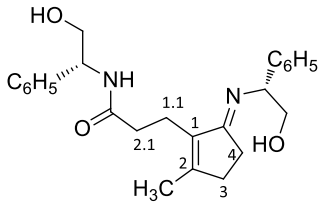
IR(NaCl): 3367, 2924, 2854, 1727, 1637 cm^{-1}.

^{1}H-RMN (400 MHz) δ: 1.42 (s, 9H, [C(*C*H_3)$_3$]), 1.93 (s, 3H, CH_3), 2.08-2.17 (m,1H, H-3), 2.36-2.53 (m, 4H, H-3.1, H-4, H-2.1), 2.58-2.63 (m, 3H, H-4, H-1.1), 2.79 (br.s, 1H, OH), 3.79-3.87 (m, 2H, C*H*$_2$O), 4.46-4.50 (m, 1H, C*H*N), 7.23-7.32 (m, 5H, H-Ar).

^{13}C-RMN (100.6 MHz) δ: 16.0 (CH_3), 20.1 (C-1.1), 27.3 (C-3), 28.1 [C(*C*H_3)$_3$], 33.8 (C-4), 33.9 (C-2.1), 67.3 (*C*HN), 68.5 (*C*H_2O), 80.1 [*C*(CH3)], 127.0 (C-Ar), 127.3 (2C-Ar), 128.3 (2C-Ar), 137.5 (C-1), 141.1 (C-*i*), 157.5 (C-2), 173.1 (*C*O_2), 181.0 (*C*N).

EM (CI) (M): 343.

HRMS calculated for $[C_{21}H_{29}NO_3 + H]^+$: 344.222; found: 344.2209.



_N_-[(1_R_)-2-hydroxy-1-phenylethyl]-5-{[(1_R_)-_N_-(2-hydroxy-1-phenylethyl)imino]}-2-methyl-1-cyclopentenepropionamide (9)

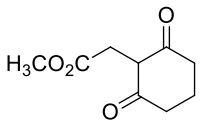
(*R*)-Phenylglycinol (423 mg, 3.08 mmol) was added to a solution of keto acid **7** (259 mg, 1.54 mmol) in toluene (24 mL). The mixture was heated at reflux for 48 h with azeotropic elimination of H_2O produced by a Dean–Stark apparatus. The resulting mixture was cooled and concentrated to give an oil. Flash-column chromatography (99:1 CH_2Cl_2–CH_3OH) afforded **9** (362 mg, 58%) as a yellow oil.

IR(NaCl): 3293, 3060, 3028, 2920, 2868, 1661, 1641 cm^{-1}.

^{1}H-RMN (300 MHz) δ: 1,.90 (s, 3H, CH_3), 2.17 (ddd, *J* = 3.3, 6.9 and 17.4 Hz, 2H, H-1.1), 2.36-2.39 (m, 2H, H-2.1), 2.50-2.63 (m, 1H, H-4), 2.73 (t, *J* = 7.4 Hz, 2H, H-3), 2.96-3.06 (m, 1H, H-4), 3.31 (br.s, 1H, OH), 3.48 (br.s, 1H, OH), 3.64-3.86 (m, 2H, C*H*$_2$O), 4.07 (t, *J* = 8.1 Hz, 1H, C*H*$_2$O), 4.46-4.50 (m, 1H, C*H*N), 4.53-4.56 (m, 1H, C*H*$_2$O), 5.10 (t, *J* = 8.9 Hz, 1H, C*H*N), 7.18-7.37 (m, 10H, H-Ar).

^{13}C-RMN (75.4 MHz) δ: 15.7 (CH_3), 21.1 (C-3), 26.2 (C-4), 27.1 (C-1.1), 33.9 (C-2.1), 67.7 (*C*HN), 68.7 (*C*H_2O), 69.1 (*C*HN), 74.4 (*C*H_2O), 126.4 (2C-Ar), 126.8 (C-Ar), 127.3 (2C-Ar), 127.4 (C-Ar), 128.2 (C-Ar), 128.5 (C-Ar), 128.6 (2C-Ar), 137.3 (C-1), 141.1 (C-*i*), 142.2 (C-*i*), 156.5 (C-2), 168.9 (*C*O), 179.9 (*C*N).

MS (CI) (M-OH): 390.2.



Methyl 2,6-dioxocyclohexaneacetate (12)

A solution of 1,3-cyclohexanedione (1.0 g, 8.65 mmol) in anhydrous CH_3OH (5 mL) was added dropwise at 0 °C to a suspension of CH_3ONa (590 mg, 10.4 mmol) in anhydrous CH_3OH (5 mL), and the mixture was stirred at 0 °C for 30 min. Then, methyl bromoacetate (1.0 mL, 10.4 mmol) was added, and the resulting mixture was stirred at reflux for 2 h. After cooling at room temperature, 2 N aqueous HCl (15 mL) was added and the mixture was extracted with EtOAc. The combined organic extracts were dried and concentrated. Flash-column chromatography (CH_2Cl_2) afforded compound **12** (917 mg, 58%) as a white solid (described as a mixture of ketonic and enolic forms). Little amounts of ketones **13** and **14** were isolated.

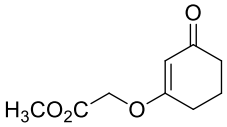
IR(NaCl): 1710, 1590 cm^{-1}.

mp: 122-125 °C.

^{1}H-RMN (300 MHz) δ: 1.83-1.89 (m, 1H keto), 1.91-1.99 (m, 2H enol), 2.22 (dq, *J* = 6.0 and 12.0 Hz, 1H keto), 2.45 (t, *J* = 6.5 Hz, 4H keto, 2H enol), 2.59-2.79 (m, 2H enol), 2.93 (d, *J* = 5.4 Hz, 2H keto), 3.50 (s, 2H enol), 3.68 (s, 3H keto), 3.74 (s, 3H enol), 3.79 (t, *J* = 5.4 Hz, 1H keto).

^{13}C-RMN (75.4 MHz) δ: 17.9 (CH_2 keto), 20.4 (CH_2 enol), 27.5 (CH_2 keto), 27.7 (CH_2 enol), 32.7 (CH_2 enol), 36.8 (CH_2 keto), 39.3 (CH_2 keto), 39.5 (CH_2 keto, CH_2 enol), 52.0 (CH_3 keto), 52.4 (CH_3 enol), 62.5 (CH keto), 108.7 (Cq enol), 172.5 (*C*O keto), 174.7 (*C*O enol), 187.2 (*C*-OH enol), 203.7 (*C*O keto, *C*O enol).

EM(IE) *m*/*e* (relative intensity, %): 184 (M^+, 11); 97 (33); 55 (100).



Methyl (3-oxycyclohex-1-enyloxy)acetate (13)

Little amounts of ketone **13** were also isolated, as yellow solid.

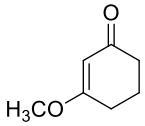
IR(NaCl): 1761, 1656, 1607 cm^{-1}.

mp: 54.5-57.5 °C.

^{1}H-RMN (300 MHz) δ: 1.97-2.07 (m, 2H), 2.36 (t, *J* = 6.6 Hz, 2H), 2.52 (t, *J* = 6.3 Hz, 2H), 3.80 (s, 3H), 4.50 (s, 2H), 5.25 (s, 1H).

^{13}C-RMN (75.4 MHz) δ: 20.9 (CH_2), 28.4 (CH_2), 36.4 (CH_2), 52.3 (CH_3), 64.4 (CH_2), 103.2 (CH), 167.2 (*C*O_2), 176.5 (*C*O), 199.2 (*C*O).

HRMS calculated for $[C_9H_{12}O_4 + H]^+$: 185.0808; found: 185.0812.



3-Methoxycyclohex-2-enone (14)

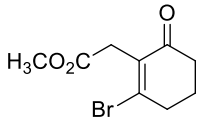
Little amounts of ketone **14** were also isolated, as yellow oil.

IR(NaCl): 1665, 1645, 1602 cm^{-1}.

^{1}H-RMN (300 MHz) δ: 1.85-1.92 (m, 2H), 2.25 (t, *J* = 6.6 Hz, 2H), 2.31 (t, *J* = 6.3 Hz, 2H), 3.60 (s, 3H), 5.28 (s, 1H).

^{13}C-RMN (75.4 MHz) δ: 21.0 (CH_2), 28.6 (CH_2), 36.5 (CH_2), 55.4 (CH_3), 102.0 (CH), 178.6 (*C*O), 199.6 (*C*O).

EM(IE) *m/e* (relative intensity, %): 126 (M^+, 94); 98 (100); 68 (99).



Methyl 2-bromo-6-oxocyclohexeneacetate (15)

Et_3N (5.9 ml, 42 mmol) and cyclohexanedione **12** (7 g, 38 mmol) were added to a stirred solution of triphenylphosphine dibromide (96%, 33.4 g, 76 mmol) in benzene (394 mL) at 0 °C. The mixture was stirred at room temperature overnight. Then, the solvent was evaporated and the resulting residue was chromatographed (CH_2Cl_2) to afford the title compound (6.34 g, 68%) as a white solid.

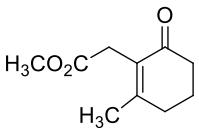
IR(ATR): 1737, 1678, 1625 cm^{-1}.

mp: 48-50 °C.

^1H NMR (300 MHz) δ: 2.04-2.10 (m, 2H), 2.49 (t, *J* = 6.8 Hz, 2H), 2.94 (t, *J* = 6.1 Hz, 2H), 3.51 (s, 2H), 3.66 (s, 3H).

^{13}C NMR (75.4 MHz) δ: 22.6 (CH_2), 35.1 (CH_2), 36.8 (CH_2), 37.5 (CH_2), 52.0 (CH_3), 134.4 (Cq-Br), 149.8 (Cq), 170.1 (*C*O_2), 194.2 (*C*O).

Anal. Calculated for [$C_9H_{11}BrO_3$]: C, 43.75%; H, 4.49%; Br, 32.34%. Found: C, 44.00%; H, 4.55%; Br, 32.06%.



Methyl 2-methyl-6-oxocyclohexeneacetate (16)

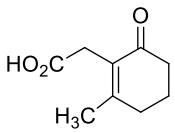
CH_3Li (5.1 mL, 1.6 M in Et_2O, 8.16 mmol) was added to a suspension of C_6H_5SCu (1.43 g, 8.11 mmol) in anhydrous THF (43 mL) at −20 °C, and the mixture was stirred at this temperature for 15 min. After cooling at −78 °C, a solution of bromo enone **15** (1 g, 4.05 mmol) in anhydrous THF (8 mL) was added, and the mixture was allowed to reach 0 °C, stirred for 2.5 h, and poured into saturated aqueous NH_4Cl. The aqueous layer was extracted with EtOAc (3 x 10 mL), and the organic extracts were dried and concentrated. Flash-column chromatography (8:2 hexane–EtOAc) afforded **16** (467 mg, 63%) as a yellow oil.

IR(ATR): 1736, 1663 cm^{-1}.

^1H NMR (300 MHz) δ: 1.91 (s, 3H), 1.90-1.94 (m, 2H), 2.37 (t, *J* = 6.5 Hz, 4H), 3.31 (s, 2H), 3.61 (s, 3H).

^{13}C NMR (75.4 MHz) δ: 21.5 (CH_3), 21.9 (CH_2), 30.4 (CH_2), 32.7 (CH_2), 37.0 (CH_2), 51.7 (CH_3), 129.1 (Cq), 158.4 (Cq), 171.7 (CO_2), 197.5 (*C*O).

HRMS calculated for $[C_{10}H_{14}O_3 + H]^+$: 183.1016; found: 183.1019.



2-Methyl-6-oxocyclohexeneacetic acid (17)

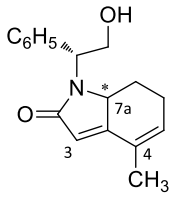
$LiOH \cdot H_2O$ (875 mg, 20.64 mmol) in H_2O (8.8 ml) was added to a solution of ester **16** (500 mg, 2.74 mmol) in THF (22 ml) and EtOH (25 ml), and the mixture was stirred at room temperature for 5 h. Then, the solvents were evaporated and the resulting residue was taken up in 2 N HCl (10 mL) and extracted with EtOAc (5 x 10 mL). The organic extracts were dried and concentrated to afford the acid **17** as an oil (395 mg, 86%).

IR(NaCl): 2929, 1709, 1659, 1629 cm^{-1}.

^{1}H-RMN (300 MHz, CD_3OD) δ: 1.98 (s, 3H), 2.07-2.18 (m, 2H), 2.38-2.48 (m, 4H), 3.33 (s, 2H), 5.06 (br s, 1H).

^{13}C-RMN (75.4 MHz, CD_3OD) δ: 22.6 (CH_3), 23.9 (CH_2), 32.2 (CH_2), 34.5 (CH_2), 38.9 (CH_2), 131.2 (Cq), 162.7 (Cq), 176.0 (*C*O_2), 201.3 (*C*O).

EM (CI) *m/e* (relative intensity,%): 186 ($M+NH_4^+$, 100); 169 ($M+H^+$, 78); 168 (M^+, 32).



1-[(1*R*)-2-Hydroxy-1-phenylethyl]-4-methyl-2-oxo-2,6,7,7a-tetrahydroindole (18)

(*R*)-Phenylglycinol (874 mg, 6.37 mmol) was added to a solution of keto ester **16** (387 mg, 2.12 mmol) and AcOH (368 μL, 6.37 mmol) in benzene (30 mL). The mixture was heated at reflux for 48 h with azeotropic elimination of H_2O produced by a Dean–Stark apparatus. The resulting mixture was cooled and concentrated to give an oil. Flash-column chromatography (6:4 CH_2Cl_2–AcOEt) afforded lactam **18a** (177 mg, 31%) as an oil and its C-7a epimer **18b** (142 mg, 25%) as an oil.

Spectroscopic and analytical data for compound **18a** (higher R_f)

IR(NaCl): 3361, 1656 cm^{-1}.

$[\alpha]^{22}_D$ – 37.4 (c, 0.9, $CHCl_3$).

^{1}H-RMN (300 MHz) δ: 1.34-1.48 (m, 1H, H-7), 1.89 (s, 3H, CH_3), 2.09-2.22 (m, 2H, H-6, H-7), 2.29-2.38 (m, 1H, H-6), 3.88 (ddd, *J* = 1.2, 4.6 and 13.2 Hz, 1H, H-7a), 4.08-4.13 (m, 1H, C*H*$_2$O), 4.26-4.35 (m, 1H, C*H*$_2$O), 4.71 (dd, *J* = 3.3 and 7.2 Hz, 1H, C*H*N), 4.87 (sa, 1H, OH), 5.80-5.81 (m, 1H, H-5), 5.84 (s, 1H, H-3), 7.23-7.37 (m, 5H, H-Ar).

^{13}C-RMN (75.4 MHz) δ: 17.7 (CH_3). 25.0 (C-6), 28.4 (C-7), 60.8 (C-7a), 60.9 (*C*HN), 64.1 (*C*H_2O), 115.5 (C-3), 127.0 (2C-*o*), 127.5 (2C-*p*), 128.1 (C-*i*), 128.6 (2C-*m*), 131.7 (C-5), 138.2 (C-4), 158.8 (C-3a), 173.5 (C-2).

HRMS calculated for $[C_{17}H_{19}NO_2 + H]^+$: 270.1489; found 270.1486.

Spectroscopic and analytical data for compound **18b** (lower R_f)

IR(NaCl): 3385, 1657 cm^{-1}.

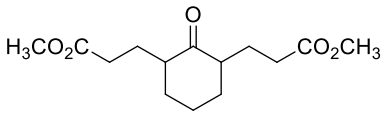
$[\alpha]^{22}_D$ – 9.2 (c, 0.9, $CHCl_3$).

^{1}H-RMN (300 MHz) δ: 1.21-1.35 (m, 2H, H-7, OH), 1.88 (s, 3H, CH_3), 1,99-2.09 (m, 1H, H-7), 2.13-2.31 (m, 2H, H-6), 3.96 (dd, *J* = 4.1 and 13.1 Hz, 1H, H-7a), 4.13 (dd, *J* = 4.2 and 11.7 Hz, 1H, C*H*$_2$O), 4.27 (dd, *J* = 7.5 and 11.7 Hz, 1H, C*H*$_2$O), 4.96 (dd, *J* = 4.2 and 7.5Hz, 1H, C*H*N), 5.79-5.81 (m, 1H, H-5), 5.84 (s, 1H, H-3), 7.23-7.37 (m, 5H, H-Ar).

^{13}C-RMN (75.4 MHz) δ: 17.8 (CH_3), 25.1 (C-6),29.5 (C-7), 60.7 (*C*HN), 62.8 (C-7a), 64.1 (*C*H_2O), 115.4 (C-3), 127.4 (2C-*o*), 127.5 (CH-*p*), 128.1 (C-*i*), 128.4 (2C-*m*),131.6 (C-5), 138.3 (C-4), 158.2 (C-3a), 173.4 (C-2).

HRMS calculated for $[C_{17}H_{19}NO_2 + H]^+$: 270.1489; found 270.1488.

6.3. Experimental part- Chapter 3



Dimethyl 2-oxo-1,3-cyclohexanedipropionate (20)[199]

A solution of cyclohexanone (850 mg, 8.6 mmol), pyrrolidine (1.41 mL, 17.2 mmol) in toluene (4 mL) was heated at reglux with azeotropic elimination of water, by Dean–Stark apparatus. After 20 h, the mixture was cooled and concentrated. Methyl acrylate (2.30 mL, 25.8 mmol) was slowly added to the above solution in CH_3OH (3 mL) and the mixture was heated at reflux for 5 h. Then, a buffer solution (3 mL, HOAc–H_2O–NaOAc 25 mL:25 mL:12.5 g), was added to the solution and the mixture was heated at reflux for 1 h. After cooling, the solvent was removed and the residue was dissolved in Et_2O (10 mL). The organic solution was washed with saturated aqueous Na_2CO_3 (3 x 10 mL), H_2O (3 x 10 mL) and brine (2 x 10 mL) and concentrated. Flash-column chromatography (1:1 hexane–EtOAc) afforded the keto diester **20** as a brown oil (2.16 g, 93%, *cis*:*trans* mixture).

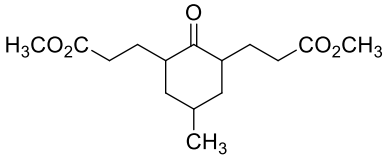
IR (film): 1707, 1737 cm^{-1}.

^{1}H NMR (400 MHz) δ: 1.28-1.39 (m, 4H, H-4, H-6), 1.52 (m, 4H, CH_2CH$_2$CO$_2$), 1.62-1.80 (m, 4H, CH_2CH$_2$CO$_2$, H-5), 1.80-2.18 (m, 8H, H-4, H-5, H-6, CH_2CH$_2$CO$_2$), 2.29-2.49 (m, 12H, H-1, H-3, CH_2CO$_2$), 3.66 (s, 12H, CH_3).

^{13}C NMR (100.6 MHz) δ: 20.6 and 24.5 (C-5), 25.3 and 25.6 (*C*H$_2$CH$_2$CO$_2$), 31.6 and 31.7 (*C*H$_2$CO$_2$), 33.1 and 35.4 (C-4, C-6), 48.1 and 50.1 (C-1, C-3), 51.5 and 51.6 (CH_3), 173.6 and 174.1 (CO_2), 212.7 and 214.6 (CO).

HMRS calculated for $[C_{14}H_{22}O_5 + H]^+$: 271.1467; found: 271.1536.

[199] Stork, G.; Brizzolara, A.; Landesman, H.; Szmuszkovicz, J.; Terrell, R. *J. Am. Chem. Soc.* **1963**, *85*, 207-222



Dimethyl 5-methyl-2-oxo-1,3-cyclohexanedipropionate (21)

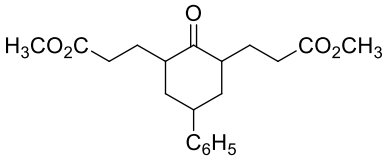
Operating as in the preparation of **20**, from a solution of pyrrolidine (2.93 mL, 35.6 mmol), 4-methylcyclohexanone **24** (2.2 g, 12.6 mmol) in toluene (6 mL), and methyl acrylate (4.0 mL, 44.5 mmol) in anhydrous CH_3OH (7 mL), compound **21** (5.0 g, 99%, 1.5:1 *cis*:*trans* mixture) was obtained after flash chromatography (9:1 to 7:3 hexane–EtOAc) as a yellow oil.

IR (film): 1708, 1737 cm^{-1}.

^1H NMR (400 MHz) δ: 0.95 (d, *J* = 6.8 Hz, 3H, CH_3), 1.09 (q, *J* = 12.8 Hz, 2H, H-4, H-6), 1.24 (d, *J* = 7.2 Hz, 3H, CH_3), 1.42-1.63 (m, 6H, C*H*$_2$CH$_2$CO$_2$, H-4, H-6), 1.78-1.93 (m, 3H, H-4, H-5, H-9), 1.96-2.24 (m, 7H, C*H*$_2$CH$_2$CO$_2$, H-4, H-5, H-6), 2.26-2.44 (m, 10H, C*H*$_2$CO$_2$, H-1, H-3), 2.51-2.62 (m, 2H, H-1, H-6), 3.65 (s, 12H, CH_3).

^{13}C NMR (100.6 MHz) δ: 18.0 and 21.1 (*C*H_3), 24.3 and 24.4 (*C*H_2CH$_2$CO$_2$), 26.6 and 26.9 (C-5), 31.3 and 31.5 (*C*H_2CO$_2$), 40.1 and 40.8 (CH_2), 44.5 and 49.6 (CH), 51.1 and 53.3 (O*C*H_3), 172.9 and 173.6 (*C*O_2), 212.8 and 214.7 (*C*O).

HMRS calculated for $[C_{15}H_{24}O_5 + H]^+$: 285.1624; found: 285.1693.



Dimethyl 2-oxo-5-phenyl-1,3-cyclohexanedipropionate (22)

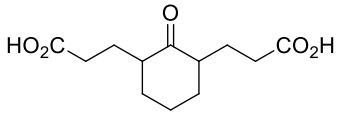
Operating as in the preparation of **20**, from a solution of pyrrolidine (2.1 mL, 25.3 mmol), 4-phenylcyclohexanone **25** (2.2 g, 12.6 mmol) in toluene (4 mL), and methyl acrylate (2.9 mL, 31.5 mmol) in anhydrous CH_3OH (5 mL), compound **22** (4.3 g, 98%, *cis*:*trans* mixture) was obtained after flash chromatography (9:1 to 6:4 hexane-EtOAc) as a yellow oil.

IR (film): 1707, 1736 cm^{-1}.

^1H NMR (400 MHz) δ: 1.52-1.69 (m, 4H, C*H*$_2$CH$_2$CO$_2$), 1.81-2.00 (m, 4H, C*H*$_2$CO$_2$), 2.03-2.14 (m, 4H, C*H*$_2$CH$_2$CO$_2$), 2.18-2.64 (m, 12H), 2.73-2.82 (m, 4H), 3.20-3.30 (m, 2H), 3.63 (s, 6H), 3.66 (s, 6H), 7.20-7.44 (m, 10H, H-Ar).

^{13}C NMR (100.6 MHz, selected signals) δ: 24.5 (*C*H$_2$CH$_2$CO$_2$), 31.5 and 31.7 (C-5), 35. and 38.1 (C-4), 45.7 (C-2, C-6), 51.4 (O*C*H$_3$), 126.2 and 126.6 (3C-Ar), 128.5 and 128.7 (2C-Ar) 142.0 (C-*i*), 173.1 and 173.8 (*C*O$_2$), 214.1 (*C*O).

HMRS calculated for $[C_{20}H_{26}O_5 + H]^+$: 347.1853; found: 347.1852.



2-Oxo-1,3-cyclohexanedipropionic acid (26)

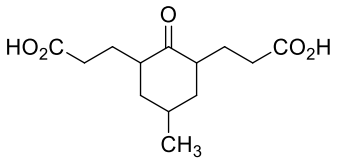
To a solution of aqueous LiOH solution (1M, 40 mL), and THF (40 mL) was added to keto ester **20** (644 mg, 2.38 mmol) and the mixture was stirred for 24 h at room temperature. The pH of the mixture was turn on acid with addition of an aqueous HCl solution (2N). The organic phase was taken up with EtOAc (20 mL) and concentrated affording the acid **26** as a white solid (473 mg, 82%, *cis*:*trans* mixture).

IR (film): 2933, 2862, 1707 cm^{-1}.

^{1}H NMR (400 MHz) δ: 1.21-1.25 (m, 1H), 1.48-1.53 (m, 1H), 1.60-1.68 (m, 2H), 1.75-1.82 (m, 2H), 1.93-2.16 (m, 4H), 2.27-2.35 (m, 1H), 2.41-2.49 (m, 3H), 2.54-2.59 (m, 1H).

^{13}C NMR (100.6 MHz) δ: 20.7 (CH_2), 24.3 (CH_2), 25.3 and 25.5 (CH_2), 29.4 and 31.4 (CH), 31.7 (CH_2), 33.9 (CH_2), 35.8 (CH_2), 47.8 (CH) 49.8 (CH), 179.6 and 179.7 (2*C*O_2), 213.2 and 215.6 (*C*O).

HMRS calculated for $[C_{12}H_{18}O_5 - H]^-$: 241.1083; found: 241.1081.



5-Methyl-2-oxo-1,3-cyclohexanedipropionic acid (27)

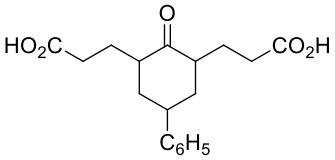
Operating as in the preparation of diacid **26**, from keto diester **21** (2 g, 7.04 mmol), aqueous LiOH solution (1M, 124 mL) and THF (117 mL), diacid **27** was obtained as a white solid (1.7 mg, 93%, 1.5:1 *cis:trans* mixture).

IR (film): 3047, 1708 cm^{-1}.

^{1}H NMR (400 MHz) δ: 0.96 (d, *J* = 5.6 Hz, 3H, CH_3), 0.98 (d, *J* = 5.6 Hz, 3H, CH_3), 1.11 (q, *J* = 12.8 Hz, 3H), 1.22-1.26 (m, 3H), 1.42-1.61 (m, 3H), 1.80-1.90 (m, 4H), 1.99-2.10 (m, 8H), 2.20-2.48 (m, 9H), 2.60 (br. s, 2H), 8.20 (br.s, 2H, OH).

^{13}C NMR (100.6 MHz) δ: 21.0 and 21.3 (*C*H_3), 24.2 and 26.9 (C-4, C-6), 29.4 and 31.8 (C-5), 31.5 and 31.9 (2*C*H_2CO_2), 31.6 (CH-1), 41.1, 42.2 and 43.3 (2*C*$H_2CH_2CO_2$), 48.7 and 49.9 (C-3), 179.5 and 178.4 (2*C*O_2), 213.3 and 213.7 (*C*O).

HMRS calculated for $2[C_{13}H_{20}O_5 - H]^-$: 511.2549; found: 511.2548.



2-Oxo-5-phenyl-1,3-cyclohexanedipropionic acid (28)

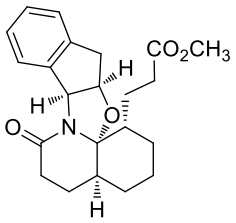
Operating as in the preparation of diacid **26**, from keto diester **22** (2.06 g, 5.97 mmol), aqueous LiOH solution (1M, 97 mL) and THF (99 mL), diacid **28** was obtained as a white solid (1.7 g, 90%, *cis:trans* mixture).

IR (film): 3028, 2930, 1709 cm^{-1}.

^{1}H NMR (400 MHz) δ: 1.50-1.69 (m, 3H), 2.02-2.14 (m, 3H), 2.21-2.27 (m, 1H), 2.31-2.48 (m, 4H), 2.60-2.67 (m, 3H), 3.17-3.28 (m, 1H), 7.19-7.31 (m, 5H).

^{13}C NMR (100.6 MHz) δ: 24.1 and 24.3 ($2CH_2$), 31.4 and 31.7 ($2CH_2$), 42.0 ($2CH_2$), 42.9 (2CH), 48.9 and 50.1 (CH), 126.5 (3C-Ar), 128.5 (2C-Ar), 143.9 and 144.1 (C-*i*), 177.9 and 179.1 ($2CO_2$), 212.4 and 214.9 (*C*O).

HMRS calculated for $[C_{18}H_{22}O_5 - H]^-$: 317.1394; found: 317.1402.



Methyl (1*S*,4a*S*,8a*S*,13a*R*,14a*S*)-7-oxo-1,2,3,4,4a,5,6,7,8,8a,13,13a,14a-dodecahydro-indeno[1',2':4,5]oxazolo[2,3-*j*]quinoline-1-propionate (29a)

(1*S*,2*R*)-(-)-*cis*-1-Amino-2-indanol (290 mg, 1.93 mmol) and isobutyric acid (335 µL, 3.61 mmol) were added to a solution of keto diester **20** (348 mg, 1.29 mmol) in toluene (20 mL). The mixture was heated at the reflux temperature for 19 h, with azeotropic elimination of water by a Dean-Stark system. Additional (1*S*,2*R*)-(-)-*cis*-1-amino-2-indanol (213 mg, 1.42 mmol) were added, and the stirring was continued for 5 h. After cooling, the mixture was concentrated under reduced pressure, and the resulting residue was dissolved in ethyl acetate (15 mL). The organic phase was washed with saturated aqueous sodium bicarbonate solution (2 x 10 mL) and concentrated. Flash-column chromatography (95:6 to 6:4 hexane–EtOAc) of the residue afforded a 3:1 mixture of inseparable lactams **29a** and **29b** (392 mg, 82 %).

Selected spectroscopic and analytical data, from the mixture, for compound **29a** (1*S*,4a*S*,8a*S*,13a*R*,14a*S*)

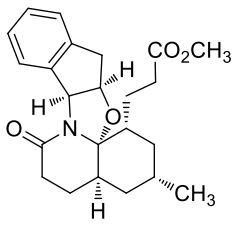
^{1}H NMR (400 MHz) δ: 3.51 (s, 3H, CO_2CH_3), 4.74 (m, 1H, H-13a), 5.87 (d, *J* = 5.6 Hz, 1H, H-8a), 7.16-7.25 (m, 3H, H-Ar), 7.45-7.50 (m, 1H, H-Ar).

^{13}C NMR (100.6 MHz) δ: 39.2 (CH), 51.3 (CH_3), 66.0 (CH), 77.7 (CH), 98.4 (CH), 171.4 (*C*O), 173.7 (CO_2).

Selected spectroscopic and analytical data, from the mixture, for compound **29b** (1*R*,4a*R*,8a*S*,13a*R*,14a*R*)

^{1}H NMR (400 MHz) δ: 3.68 (s, 3H, CO_2CH_3), 5.06 (m, 1H, H-13a), 5.76 (d, *J* = 5.6 Hz, 1H, H-8a), 7.16-7.25 (m, 3H, H-Ar), 8.04 (d, *J* = 6.8 Hz, 1H, H-Ar).

^{13}C NMR (100.6 MHz) δ: 41.3 (CH), 42.7 (CH), 51.7 (CH_3), 66.5 (CH), 81.1 (CH), 97.0 (CH), 169.9 (*C*O), 173.6 (CO_2).



Methyl (1*R*,3*R*,4a*R*,8a*S*,13a*R*,14a*S*)-3-Methyl-7-oxo-1,2,3,4,4a,5,6,7,8a,13,13a,14a-dodecahydro-indeno[1',2':4,5]oxazolo[2,3-*j*]quinoline-1-propionate (31a)

Operating as in the preparation of lactam **29a**, from oxo diester **21** (500 mg, 1.76 mmol), (1*S*,2*R*)-(-)-*cis*-1-amino-2-indanol (684 mg, 4.58 mmol), and isobutyric acid (458 µL, 4.9 mmol) in toluene (27 mL), a 3:1 mixture (calculated by ^{1}H NMR) of inseparable lactams **31a** and **31b** (451 mg, 67%) was obtained after flash-column chromatography (95:5 to 6:4 hexane–EtOAc).

Selected spectroscopic and analytical data, from the mixture, for compound **31a** (1*R*,3*R*,4a*R*,8a*S*,13a*R*,14a*S*)

^{1}H NMR (400 MHz) δ: 3.51 (s, 3H, CO_2CH_3), 4.74 (m, 1H, H-13a), 5.87 (d, *J*= 5.2 Hz, H-8a), 7.17-7.28 (m, 3H, H-Ar), 7.48 (d, *J*= 6.8 Hz, 1H, H-Ar).

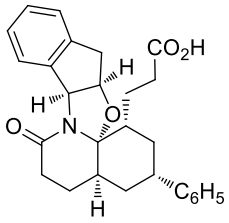
^{13}C NMR (100.6 MHz) δ: 38.7 (CH), 38.9 (CH), 51.2 (CH_3), 66.0 (CH), 77.7 (CH), 98.3 (Cq), 171.4 (*C*O), 173.7 (*C*O_2).

HMRS calculated for $[C_{23}H_{29}NO_4 + H]^+$: 384.2169; found: 384.2170.

Selected spectroscopic and analytical data, from the mixture, for compound **31b** (1*S*,3*S*,4a*S*,8a*S*,13a*R*,14a*R*)

^{1}H NMR (400 MHz) δ: 3.68 (s, 3H, CO_2CH_3), 5.06 (m, 1H, H-13a), 5.76 (d, *J*= 5.6 Hz, H-8a), 7.17-7.28 (m, 3H, H-Ar), 8.03 (d, *J*= 7.6 Hz, 1H, H-Ar).

^{13}C NMR (100.6 MHz) δ: 41.5 (CH), 42.4 (CH), 51.6 (CH_3), 66.4 (CH), 81.1 (CH), 96.8 (Cq), 169.7 (*C*O), 173.6 (*C*O_2).



(1*R*,3*R*,4a*R*,8a*S*,13a*R*,14a*S*)-7-Oxo-3-phenyl-1,2,3,4,4a,5,6,7,8a,13,13a,14a-dodecahydroindeno[1',2':4,5]oxazolo[2,3-*j*]quinoline-1-propanoic acid (33a)

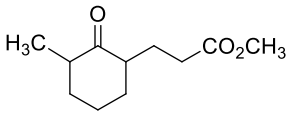
(1*S*,2*R*)-(-)-*cis*-1-Amino-2-indanol (808 mg, 5.42 mmol) and anhydrous $MgSO_4$ (1.30 g) were added to a solution of keto acid **28** (1.73 g, 5.42 mmol) in toluene (54 mL). The mixture was heated at the reflux temperature for 19 h. After cooling, the mixture was concentrated under reduced pressure, providing a crude 6:1 (calculated by ^{1}H NMR) mixture of lactams **33a** and **33b** (2.30 g).

Selected spectroscopic and analytical data, from the mixture, for compound **33a** (1*R*,3*R*,4a*R*,8a*S*,13a*R*,14a*S*)

^{1}H NMR (300 MHz) δ: 4.75 (t, *J* = 4.8 Hz, 1H, H-13a), 5.94 (d, *J* = 5.7 Hz, 1H, H-8a), 7.14-7.31 (m, 1H, H-Ar).

Selected spectroscopic and analytical data, from the mixture, for compound **33b** (1*S*,3*S*,4a*S*,8a*S*,13a*R*,14a*R*)

^{1}H NMR (300 MHz) δ: 4.69 (t, *J* = 5.1 Hz, 1H, H-13a), 5.83 (d, *J* = 6.0 Hz, 1H, H-8a), 8.14-8.17 (m, 1H, H-Ar).



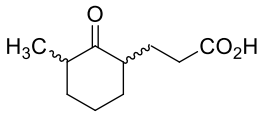
Methyl 3-(3-methyl-2-oxocyclohexyl)propionate ester (36)[200]

A solution of 2-methylcyclohexanone **34** (5.0 g, 44.6 mmol), pyrrolidine (7.3 mL, 89.3 mmol) in toluene (11 mL) was heated at reflux with azeotropic elimination of water, by Dean–Stark apparatus. After 16 h, the mixture was cooled and concentrated. Methyl acrylate (4.0 mL, 44.5 mmol) was added to the above residue in CH_3OH (14 mL) and the mixture was stirred at the reflux temperature for 5 h. The cold mixture was diluted with 3 mL of buffer solution (HOAc–H_2O– NaOAc 25 mL:25 mL:12.5 g) and heated at reflux for 1 h. Et_2O (15 mL) was added to the cooled mixture and was washed with aqueous HCl solution (2N, 2 x 10 mL) and brine (2 x 10 mL). The washed organic layer was dried and concentrated, and ther residue was purified by microdistillation (40 °C, 0 torr) to afford the keto ester **36** as a colorless oil (8.4 g, 95%, 3.2:1 *cis*:*trans* mixture).

^{1}H NMR (400 MHz) δ: 1.01 and 1.08 (d, *J* = 6.6 Hz, 6H, CH_3),1.32 (dq, *J* = 3 and 12 Hz, 4H), 1.49-1.56 (m, 3H), 1.61-1.70 (m, 6H), 2.00-2.18 (m, 5H), 2.21-2.45 (m, 6H), 3.66 (s, 6H, OC*H*$_3$).

^{13}C NMR (100.6 MHz) δ: 14.4 and 15.5 (*C*H_3), 20.5 and 24.7 (CH_2), 25.5 and 25.9 (CH_2), 31.7 (CH_2), 32.7 and 35.2 (CH_2), 34.8 and 37.4 (CH_2), 42.8 and 45.6 (CH), 48.0 and 49.7 (CH), 51.4 and 51.6 (O*C*H_3), 173.9 and 174.1 (*C*O_2), 213.4 and 216.0 (*C*O).

[200] House, H. O.; Schellenbaum, M. *J. Org. Chem.* **1963**, *28*, 34-38; House, H. O.; Roelofs, W. L.; Trost, B. M. *J. Org. Chem.* **1966**, *31*, 646-655.



(3-Methyl-2-oxocyclohexyl)propionic acid (49)[201]

A solution of LDA (4.5 mL of a 2.0 M solution in THF/heptanes/ethylbenzene, 8.92 mmol) was added dropwise to a solution of 2-methylcyclohexanone **34** (1.09 mL, 8.92 mmol) in THF (8 mL) at –78 °C, and the reaction mixture was stirred at –78 °C for 1 h. TMSCl (1.35 mL, 10.7 mmol) was added dropwise to the cold mixture, and the stirring was continued for an additional 15 min at –78 °C. The mixture was stirred at room temperature for 1 h and hexane (5 mL) was added; the resulting mixture was filtered over Celite®. The filtrate was concentrated to afford the silane **48** as a yellow oil (1.64 g, >99 %).

Spectroscopic and analytical data for compound **48**

^{1}H NMR (300 MHz) δ: 0.18 (s, 9H, Si(CH_3)$_3$), 1.03 (d, *J* = 6.4 Hz, 3H, CH_3), 1.03-1.05 (m, 2H), 1.54-1.70 (m, 1H), 1.75-1.88 (m, 1H), 1.94-2.00 (m, 2H), 2.07-2.15 (m, 1H), 4.80 (t, *J* = 4.4 Hz, 1H).

^{13}C NMR (75.4 MHz) δ: 0.34 (Si(*C*H_3)$_3$), 16.7 (*C*H_3), 20.3 (CH_2), 24.4 (CH_2), 31.6 (CH_2), 33.6 (CH_2), 103.5 (CH), 154.2 (Cq).

N,*N*-(dimethyl)methylamine chloride (832.2 mg, 8.90 mmol) was added to a solution of the above silane **48** in CH_2Cl_2 (10 mL) and the mixture was stirred until the complete dissolution of the salt at room temperature. Aqueous HCl solution (2N, 10 mL), was added and the stirring was continued for an additional 1 h. The mixture was poured into saturated aqueous $NaHCO_3$ (until pH = 10-12) and the stirring was continued for 15 min. The biphasic mixture was extracted with CH_2Cl_2 (3 x 10 mL). The combined organic extracts were dried and concentrated to afford the amine **44** (1.4 g, 95%, 1.1:1 *cis:trans* mixture).

[201] House, H. O.; Schellenbaum, M. *J. Org. Chem.* **1963**, *28*, 34-38; House, H. O.; Roelofs, W. L.; Trost, B. M. *J. Org. Chem.* **1966**, *31*, 646-655.

Spectroscopic and analytical data for compound **44**[202]

^{1}H NMR (400 MHz) δ: 0.97 (d, *J* = 6.4 Hz, 3H, C*H*$_3$), 1.02 (d, *J* = 6.8 Hz, 3H, C*H*$_3$), 1.25-1.45 (m, 3H), 1.64-1.98 (m, 9H), 2.17 (s, 6H, N(C*H*$_3$)$_2$), 2.19 (s, 6H, N(C*H*$_3$)$_2$), 2.23-2.28 (m, 2H), 2.51-2.56 (m, 2H), 2.63-2.72 (m, 4H).

^{13}C NMR (100.6 MHz) δ: 14.3 and 15.2 (CH_3), 20.5 and 25.4 (CH_2), 30.7 and 33.9 (CH_2), 35.7 and 37.4 (CH_2), 42.2 and 45.8 (CH), 45.6 and 45.9 (N(*C*H$_3$)$_2$), 47.7 and 49.1 (CH), 58.8 and 60.2 (CH_2), 213.5 and 215.4 (*C*O).

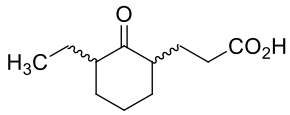
NaOH (110 mg, 2.76 mmol) and diethyl malonate (2.6 mL, 6.90 mmol) were added to a solution of amine **44** (1.2 mg, 6.90 mmol) in toluene (13 mL) and the mixture was heated at the reflux temperature for 24 h. Then, AcOH–HCl (2:1, 50 mL) was added to the mixture and the stirring was continued for 16 h at the reflux. The mixture was cooled over 30 min at room temperature and, aqueous NaOH solution (1N) was added (until pH = 10-12); the resulting biphasic mixture was extracted with EtOAc (3 x 20 mL). An aqueous HCl solution (2 N) was added to the combined aqueous phases (until pH = 2-3) and the organic residue was taken up with CH_2Cl_2 (3 x 15 mL); the combined organic extracts were concentrated to afford the acid **49** (1.0 g, 80%, 5:1 *cis:trans* mixture).

Spectroscopic and analytical data for compound **49**

^{1}H NMR (300 MHz) δ: 1.01 and 1.09 (d, *J* = 6.6 and 6.9 Hz, 3H, CH_3), 1.27-1.42 (m, 2H, C*H*$_2$CH$_2$CO$_2$), 1.47-2.17 (m, 6H, H-4, H-5, H-6), 2.31-2.61 (m, 4H, H-1, H-3, C*H*$_2$CO$_2$).

^{13}C NMR (75.4 MHz) δ: 14.5 and 15.8 (*C*H$_3$), 20.5 and 24.6 (C-5), 25.6 and 25.7 (C*H*$_2$CH$_2$CO$_2$), 31.9 (C*H*$_2$CO$_2$), 33.0 and 35.4 (C-6), 35.0 and 37.5 (C-4), 4.1 and 45.8 (C-1), 47.8 and 49.8 (C-3), 179.4 and 179.9 (*C*O$_2$), 213.8 and 216.3 (*C*O).

[202] Previously described: a. Schuda, P.F.; Ebner, C.B.; Morgan, T.M. *Tetrahedron Letters,* **1996**, *23*, 2567-2570; b. Matsumoto, K.; Hoshumor, S.; Otami, S.A.; Fujitsugi, O. *Synthetic Commun.* **1984**, *14*, 585-590; c. Miana, G.A.; Suitana, F. *Scientific Research* **1968**, *5*, 155-157



(3-Ethyl-2-oxocyclohexyl)propionic acid (53)

Operating as in the preparation of enol silyl ether **48**, from 2-ethylcyclohexane **37** (1 g, 7.93 mmol), LDA (4 mL of a 2.0 M solution in THF/heptanes/ethylbenzene, 7.93 mmol), TMSCl (1.2 mL, 9.51 mmol) and THF (8 mL), enol silyl ether **50** was obtained as a yellow oil (1.5 g, 96%).

Spectroscopic and analytical data for compound **50**

^{1}H NMR (400 MHz) δ: 0.18 [s, 9H, Si(C*H*$_3$)$_3$], 0.89 (t, *J* = 7.5 Hz, 3H, C*H*$_3$), 1.02-1.10 (m, 2H), 1.22-1.30 (m, 2H), 1.37-1.42 (m, 1H), 1.50-1.58 (m, 2H), 1.74-1.83 (m, 2H), 4.82 (dt, *J* = 1.2 and 3.9 Hz, 1H, H-2).

^{13}C NMR (100.6 MHz) δ: 0.34 [Si(*C*H$_3$)$_3$], 11.6 (*C*H$_3$-Et), 20.3 (*C*H$_2$-Et), 24.2 (CH$_2$), 24.9 (CH$_2$), 27.6 (CH$_2$), 40.3 (CH), 103.9 (CH), 153.5 (*C*O).

Operating as in the preparation of amine **44**, from **50** (3.1 g, 15.9 mmol), *N*,*N*-(dimethyl)methylamine chloride (1.5 g, 15.9 mmol) and CH_2Cl_2 (18 mL), amine **46** was obtained as a yellow oil (2.8 g, 98%, 2:1 *cis:trans* mixture).

Spectroscopic and analytical data for compound **46**

IR (film): 2933, 2818, 2766 cm^{-1}.

^{1}H NMR (300 MHz) δ: 0.88 (t, *J* = 7.5 Hz, 6H, C*H*$_3$), 1.16-1.44 (m, 4H), 1.50-2.00 (12H), 2.15-2.39 (m, 6H), 2.21 (s, 6H, N(C*H*$_3$)$_3$), 2.23 (s, 6H, N(C*H*$_3$)$_3$), 2.41-2.54 (m, 1H), 2.60-2.76 (m, 2H).

^{13}C NMR (75.4 MHz) δ: 11.3 and 11.3 (*C*H$_3$-Et), 20.3 and 21.6 (*C*H$_2$-Et), 22.6 and 25.0 (CH$_2$), 30.9 and 32.4 (CH$_2$), 33.8 and 34.6 (CH$_2$), 45.1 and 45.3 (N(*C*H$_3$)$_2$), 48.8 and 49.6 (CH), 52.3 and 53.1 (CH), 58.3 and 59.3 (CH$_2$), 212.2 and 214.2 (*C*O).

HMRS calculated for $[C_{11}H_{21}ON+H]^+$: 184.1696; found: 184.1696.

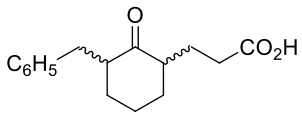
Operating as in the formation of acid **49**, from **46** (760 mg, 4.14 mmol), diethyl malonate (1.6 g, 4.14 mmol), NaOH (66.3 mg, 1.66 mmol) and toluene (8 mL), acid **53** was obtained as an oil (693 mg, 84%, 2:1 *cis:trans* mixture).

Spectroscopic and analytical data for compound **53**

^{1}H NMR (300 MHz) δ: 0.86-0.88 (t, *J* = 7.2 and 7.8 Hz, 3H, C*H*$_3$), 1.15-1.90 (m, 16H), 1.99-2.23 (m, 8H), 2.30-2.50 (m, 4H), 11.0 (br s, 2H, OH).

^{13}C NMR (75.4 MHz) δ: 11.7 (*C*H$_3$), 20.5 and 21.9 (*C*H$_2$CH$_3$), 23.6 and 24.3 (CH$_2$), 24.9 and 25.4 (CH$_2$), 31.6 and 31.7 (CH$_2$), 32.2 and 33.5 (CH$_2$), 34.9 and 35.4 (CH$_2$), 47.0 and 49.9 (CH), 51.2 and 52.7 (CH), 179.4 and 179.8 (CO$_2$), 213.4 and 216.0 (CO).

HMRS calculated for $[C_{11}H_{18}O_3 + H]^+$: 199.1300; found: 199.1298.



(3-Benzyl-2-oxocyclohexyl)propionic acid (54)

Operating as in the preparation of enol silyl ether **48**, from 2-benzylcyclohexanone **38** (976 μL, 5.30 mmol), LDA (2.65 mL of a 2.0 M solution in THF/heptanes/ethylbenzene, 5.30 mmol), TMSCl (809 μL, 6.37 mmol) and THF (6 mL), enol silyl ether **51** was obtained as a yellow oil (1.37 g, 99%).

Spectroscopic and analytical data for compound **51**

^{1}H NMR (400 MHz) δ: 0.22 [s, 9H, Si(C*H*$_3$)$_3$], 0.83-2.44 (m, 8H), 3.15 (dd, *J* = 3.6 and 13.2 Hz, 1H, H-1.1), 4.88 (dt, *J* = 1.2 and 4.0 Hz, 1H, H-2), 7.16-7.29 (m, 5H, H-Ar).

^{13}C NMR (100.6 MHz) δ: 0.38 [Si(*C*H$_3$)$_3$], 19.8 (CH$_2$), 24.2 (CH$_2$), 27.3 (CH$_2$), 38.5 (CH$_2$), 40.9 (CH), 104.4 (CH), 125.6 (C-Ar), 128.1 (2C-Ar), 129.1 (2C-Ar), 141.4 (C-*i*), 152.8 (*C*O).

Operating as in the preparation of amine **44**, from **51** (1.37 g, 5.27 mmol), *N*,*N*-(dimethyl)methylamine chloride (492 mg, 5.27 mmol) and CH_2Cl_2 (4 mL), amine **52** was obtained as a yellow oil (1.16 g, 90%, *cis:trans* mixture).

Spectroscopic and analytical data for compound **52**

IR (film): 2933, 2858, 2818, 2767 cm^{-1}.

^{1}H NMR (300 MHz) δ: 1.28-1.48 (m, 2H), 1.65-1.82 (m, 5H), 1.85-1.98 (m, 3H), 2.22 [s, 12H, N(C*H*$_3$)$_2$], 2.25-2.60 (m, 8H), 2.65-2.78 (m, 4H), 3.18 (dd, *J* = 4.8 and 13.8 Hz, 1H), 3.22 (dd, *J* = 4.5 and 13.5 Hz, 1H), 7.13-7.30 (m, 10H-Ar).

^{13}C NMR (75.4 MHz) δ: 20.5 and 21.0 (CH$_2$), 25.2 and 30.8 (CH$_2$), 32.5 and 34.1 (CH$_2$), 35.3 and 35.6 (CH$_2$), 45.5 and 45.8 [N(*C*H$_3$)$_2$], 47.2 and 48.1 (CH), 49.3 and 52.9 (CH), 58.8 and 60.0 (CH$_2$), 125.7 and 125.9 (C-Ar), 128.0 and 128.2 (2C-Ar), 128.9 and 129.0 (2C-Ar), 140.0 and 140.4 (C-*i*), 212.5 and 214.3 (*C*O).

HMRS calculated for [$C_{16}H_{23}NO$ + H]$^{+}$: 246.1852; found: 246.1853.

Operating as in the preparation of acid **49**, from **52** (1.16 g, 4.73 mmol), diethyl malonate (1.75 mL, 4.73 mmol), NaOH (75 mg, 1.87 mmol) and toluene (12 mL), acid **54** was obtained (1.16 g, 94%, 3:1 *cis:trans* mixture) as a yellow oil.

Spectroscopic and analytical data for compound **54**

IR (film): 2933, 2858, 2818, 2767 cm^{-1}.

^{1}H NMR (300 MHz) δ: 1.25-1.44 (m, 2H), 1.52-1.73 (m, 2H), 1.79-1.86 (m, 1H), 2.02-2.18 (m, 3H), 2.31-2.66 (m, 7H), 3.08 (dd, *J* = 5.4 and 13.2 Hz, 1H, C*H*$_2$Ph) and 3.21 (dd, *J* = 4.5 and 13.8 Hz, 1H, C*H*$_2$Ph), 7.13-7.30 (m, 5H).

^{13}C NMR (75.4 MHz) δ: 20.4 and 24.4 (CH_2), 25.3 (CH_2), 31.5 and 31.7 (CH_2), 33.2 and 34.7 (CH_2), 35.3 (CH_2), 35.4 and 36.2 (CH_2), 48.0 and 50.0 (CH), 50.6 and 52.8 (CH), 125.8 and 126.2 (C-Ar), 128.2 and 128.4 (2C-Ar), 128.9 and 129.1 (2C-Ar), 140.4 (C-*i*), 179.3 (*C*O_2), 212.8 (*C*O).

HMRS calculated for $[C_{16}H_{20}O_3 + H]^+$: 261.1491; found: 261.1493.

(3*R*,7a*R*,11*S*,11a*S*)-11-Methyl-5-oxo-3-phenyldecahydrooxazolo[2,3-*j*]quinoline (55a)

(*R*)-Phenylglycinol (236 mg, 1.73 mmol) was added to a solution of ketoacid **49** (212 mg, 1.15 mmol) in anhydrous toluene (12 mL). The mixture was heated at the reflux temperature for 48 h, with azeotropic elimination of water by Dean–Stark system. After cooling, the mixture was concentrated under reduced pressure, and the residue was dissolved in ethyl acetate (12 mL). The organic phase was washed with saturated aqueous sodium bicarbonate solution (2 x 10 mL) and concentrated. Flash column chromatography (99:1 to 7:3 hexane–EtOAc) of the residue afforded lactams **55a** (white solid, 187 mg, 57%) and **55b** (62 mg, 19%).

Spectroscopic and analytical data for compound **55a** (3*R*,7a*R*,11*S*,11a*S*)

IR (NaCl): 1657 cm^{-1}.

$[\alpha]^{22}_{D}$ – 203.3 (*c* 1.0, CH_3OH).

^{1}H NMR (400 MHz) δ: 0.54 (d, *J* = 6.6 Hz, 3H, C*H*$_3$), 1.34-1.47 (m, 1H, H-10), 1.49-1.58 (m, 4H, H-8, H-9, H-10), 1.76-1.80 (m, 2H, H-7, H-11), 1.83-2.00 (m, 3H, H-7a, H-7, H-8), 2.52-2.57 (m, 2H, H-6), 4.25 (dd, *J*= 5.7 and 6.6 Hz, 1H, H-2), 4.33 (dd, *J* = 3.3 and 6.6 Hz, 1H, H-2), 5.48 (dd, *J* = 5.7 ,3.3 Hz, 1H, H-3), 7.20-7.37 (m, 5H, H-Ar).

^{13}C NMR (100.6 MHz) δ: 16.4 (*C*H$_3$), 19.5 (C-7), 19.7 (C-9), 26.8 (C-8), 29.1 (C-6), 31.6 (C-10), 35.7 (C-11), 39.1 (C-7a), 59.2 (C-3), 68.4 (C-2), 98.5 (C-11a), 126.8 (2C-Ar), 127.0 (C-Ar), 128.2 (2C-Ar), 139.2 (C-*i*), 172.2 (*C*O).

Anal. Calcd for $C_{18}H_{23}NO_2$: C, 75.76; H, 8.12; N, 4.91. Found: C, 75.32; H, 8.03; N, 4.56.

Spectroscopic and analytical data for compound **55b** (3*R*,7a*S*,11*R*,11a*R*)

IR (NaCl): 1659 cm^{-1}.

$[\alpha]^{22}_D$ – 167.8 (*c* 1.0, CH_3OH).

^1H NMR (400 MHz) δ: 1.02 (d, *J* = 6.6 Hz, 3H, C*H*$_3$), 1.52-1.65 (m, 5H, H-8, H-9, H-10), 1.77-1.88 (m, 2H, H-7, H-11), 1.95-2.02 (m, 2H, H-7, H-8), 2.16-2.20 (m, 1H, H-7), 2.38-2.48 (m, 2H, H-6), 3.91 (dd, *J* = 4.2 and 8.7 Hz, 1H, H-2), 4.55 (dd, *J* = 7.8 and 8.7 Hz, 1H, H-2), 5.07 (dd, *J* = 4.2 and 8.7 Hz, 1H, H-3), 7.25-7.31 (m, 5H, H-Ar).

^{13}C NMR (100.6 MHz) δ: 16.4 (*C*H$_3$), 19.7 (C-9), 21.0 (C-7), 27.2 (C-8), 29.6 (C-6), 31.3 (C-10), 38.6 (C-11), 40.3 (C-7a), 61.8 (C-3), 74.9 (C-2), 97.0 (C-11a), 126.5 (2C-Ar), 127.3 (C-Ar), 128.5 (2C-Ar), 141.4 (C-*i*), 168.2 (*C*O).

HMRS calculated for $[C_{18}H_{23}NO_2 + H]^+$: 286.1802; found: 286.1805.

In some runs, traces amounts of lactams **55c** and **55d** were isolated.

Spectroscopic and analytical data for compound **55c** with higher R_f (3*R*,7a*R*,11*R*,11a*S*)

IR (NaCl): 1694 cm^{-1}.

$[\alpha]^{22}_D$ + 15.8 (*c* 1.0, CH_3OH).

^1H NMR (400 MHz) δ: 0.83 (d, *J* = 7.2 Hz, 3H, C*H*$_3$), 1.32-1.54 (m, 2H, H-7, H-9), 1.50-1.62 (m, 2H, H-10), 1.62-1.77 (m, 5H, H-7, H-8, H-9, H-11), 2.09-2.17 (m, 1H, H-7a), 2.45-2.65 (m, 2H, H-6), 4.13 (dd, *J* = 9.2, 6.4 Hz, 1H, H-2), 4.43 (dd, *J* = 8.4 and 9.2 Hz, 1H, H-2), 5.64 (dd, *J* = 6.4 and 8.4 Hz, 1H, H-3), 7.22-7.34 (m, 5H, H-Ar).

^{13}C NMR (100.6 MHz) δ: 14.0 (*C*H$_3$), 19.9 (C-10), 23.0 (C-7), 27.4 (C-9), 28.8 (C-8), 31.5 (C-11), 35.4 (C-6), 36.0 (C-7a), 58.9 (C-3), 66.7 (C-2), 98.1 (C-11a), 125.1 (2C-Ar), 126.8 (C-Ar), 128.3 (2C-Ar), 141.7 (C-*i*), 176.2 (*C*O).

HMRS calculated for $[C_{18}H_{23}NO_2 + H]^+$: 286.1802; found: 286.1805.

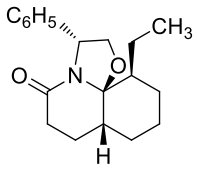
Spectroscopic and analytical data for compound **55d** with lower R_f (3*R*,7a*S*,11*S*,11a*R*)

IR (NaCl): 1637 cm^{-1}.

$[\alpha]^{22}_{D}$ – 100.4 (*c* 1.0, CH_3OH).

^{1}H NMR (400 MHz) δ: 1.15 (d, *J* = 9.0 Hz, 3H, C*H*$_3$), 1.38-1.49 (m, 1H, H-8), 1.58-1.71 (m, 4H, H-7, H-9, H-10), 1.81-1.89 (m, 2H, H-7a, H-9), 1.94-2.05 (m, 2H, H-8, H-11), 2.10-2.22 (m, 1H, H-7), 2.48-2.57 (m, 1H, H-6), 2.67 (ddd, *J* = 1.2, 9.2 and 10.4 Hz, 1H, H-6), 3.96 (t, *J* = 8.8 Hz, 1H, H-2), 4.43 (t, *J* = 8.8 Hz, 1H, H-2), 5.38 (t, *J* = 8.8 Hz, 1H, H-3), 7.22-7.34 (m, 5H, H-Ar).

^{13}C NMR (100.6 MHz) δ: 14.7 (C-10), 15.8 (*C*H$_3$), 22.1 (C-7), 28.1 (C-8), 28.4 (C-9), 30.4 (C-6), 33.8 (C-11), 39.7 (C-7a), 60.0 (C-3), 69.1 (C-2), 96.8 (C-11a), 126.1 (2C-Ar), 127.2 (C-Ar), 128.5 (2C-Ar), 140.0 (C-*i*), 171.2 (*C*O).



(3*R*,7a*R*,11*S*,11a*S*)-11-Ethyl-5-oxo-3-phenyldecahydrooxazolo[2,3-*j*]quinoline (56a)

Operating as in the preparation of lactam **55a**, from oxo acid **53** (1.39 g, 7.01 mmol) and (*R*)-phenylglycinol (1.44 g, 10.52 mmol) in anhydrous toluene (70 mL), lactams **56a** (white solid,1.10 g, 53%) and **56b** (370 mg, 17%, calculated by NMR) were obtained after flash-column chromatography (99:1 to 7:3 hexane–EtOAc).

Spectroscopic and analytical data for compound **56a** (3*R*,7a*R*,11*S*,11a*S*)

IR (NaCl): 1668 cm^{-1}.

$[\alpha]^{22}_{D}$ – 114.8 (*c* 1.0, CH_3OH).

^{1}H NMR (400 MHz) δ: 0.66 (t, *J* = 7.2 Hz, 3H, CH_3), 0.72-0.80 (m, 1H, C*H*$_2$$CH_3$), 1.17-1.27 (m, 1H, C*H*$_2$$CH_3$), 1.46-1.48 (m, 3H, H-8, H-10, H-11), 1.76-1.81 (m, 4H, H-7, H-8), 1.86-2.04 (m, 3H, H-7, H-7a, H-10), 2.51-2.56 (m, 2H, H-6), 4.20-4.29 (m, 2H, H-2), 5.45 (dd, *J* = 4.0 and 8.0 Hz, 1H, H-3), 7.36-7.23 (m, 5H, H-Ar).

^{13}C NMR (100.6 MHz) δ: 12.1 (*C*H_3), 19.4 (C-9), 19.6 (C-7), 22.4 (*C*$H_2$$CH_3$), 26.7 (C-10), 27.4 (C-8), 29.0 (C-6), 39.2 (C-7a), 42.9 (C-11), 59.4 (C-3), 68.2 (C-2), 99.0 (C-11a), 126.8 (2C-Ar), 127.0 (C-Ar), 128.1 (2C-Ar), 139.0 (C-*i*), 172.3 (*C*O).

HMRS calculated for $[C_{19}H_{25}NO_2 + H]^+$: 300.1958; found: 300.1959.

Spectroscopic and analytical data for compound **56b** (3*R*,7a*S*,11*R*,11a*R*), from spectrum of two isomer mixture

IR (NaCl): 1654 cm^{-1}.

^{1}H NMR (400 MHz) δ: 0.91 (t, *J* = 7.4 Hz, 3H, C*H*$_3$), 1.16-1.23 (m, 2H), 1.33-1.41 (m, 1H), 1.47-1.69 (m, 3H), 1.74-1.85 (m, 2H), 1.90-2,09 (m, 3H), 2.16-2.21 (m, 1H), 2.30-2.56 (m, 2H), 3.90 (dd, *J* = 3.4 and 9.0 Hz, 1H, H-2), 4.49 (t, *J* = 8.0 Hz, 1H, H-2), 5.06 (dd, *J* = 3.4 and 7.4 Hz, 1H, H-3), 7.21-7.34 (m, 5H, H-Ar).

^{13}C NMR (100.6 MHz) δ: 12.7 (*C*H$_3$), 19.8 (C-9), 20.9 (C-7), 22.8 (*C*H$_2$CH$_3$), 27.2 (C-8), 27.3 (C-10), 29.5 (C-6), 40.6 (C-11), 46.2 (C-7a), 62.1 (C-3), 74.4 (C-2), 97.2 (C-11a), 126.6 (2C-Ar), 127.4 (C-Ar), 128.5 (2C-Ar), 141.5 (C-*i*), 168.3 (*C*O).

In some runs, minor amounts of lactams **56c** were isolated.
Spectroscopic and analytical data for compound **56c** (3*R*,7a*R*,11*R*,11a*S*)

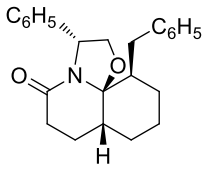
IR (NaCl): 1667 cm^{-1}.

$[\alpha]^{22}_{D}$ – 135.0 (*c* 1.0, CH_3OH).

^{1}H NMR (400 MHz) δ: 0.35 (t, *J* = 7.2 Hz, 3H, CH$_3$), 1.20-1.29 (m, 3H, H-7a, C*H*$_2$CH$_3$), 1.31-1.38 (m, 1H, H-8), 1.44-1.53 (m, 3H, H-8, H-9), 1.57-1.75 (m, 4H, H-7, H-10), 2,00 (tt, *J* = 12.4, 3.2 Hz, 1H, H-11), 2.39-2.48 (ddd, *J* = 2.8, 5.2 and 16.4 Hz, 1H, H-6), 2.57-2.63 (td, *J* = 1.4 and 16.4 Hz, 1H, H-6), 4.13 (m, 1H, H-2), 4.40 (m, 1H, H-2), 5.66 (dd, *J* = 4.0 and 8.0 Hz, 1H, H-3), 7.23-7.34 (m, 5H, H-Ar).

^{13}C NMR (100.6 MHz) δ: 12.1 (*C*H$_3$), 20.0 (*C*H$_2$CH$_3$), 20.0 (C-9), 22.8 (C-10), 23.1 (C-8), 28.5 (C-7), 35.3 (C-6), 36.8 (C-11), 39.5 (C-7a), 58.6 (C-3), 66.3 (C-2), 98.0 (C-11a), 125.1 (2C-Ar), 126.8 (C-Ar), 128.4 (2C-Ar), 141.8 (C-*i*), 176.0 (*C*O).

HMRS calculated for $[C_{19}H_{25}NO_2 + H]^+$: 300.1958; found: 300.1957.



(3*R*,7a*R*,11*R*,11a*R*)-11-Benzyl-5-oxo-3-phenyldecahydrooxazolo[2,3-*j*]quinoline (57a)

Operating as in the preparation of lactam **55a**, from oxo acid **54** (540 mg, 2.07 mmol) and (*R*)-phenylglycinol (425 g, 3.10 mmol) in anhydrous toluene (26 mL), lactams **57a** (colourless oil, 356 g, 50%) and **57b** (oil, 169 mg, 22%) were obtained after flash-column chromatography (99:1 to 7:3 hexane–EtOAc).

Spectroscopic and analytical data for compound **57a** (3*R*,7a*R*,11*R*,11a*R*)

IR (NaCl): 1659 cm^{-1}.

$[\alpha]^{22}_{D}$ – 53.6 (*c* 1.0, CH_3OH).

^{1}H NMR (400 MHz) δ: 11.25-1.55 (m, 6H, H-7, H-8, H-10), 1.75-1.95 (m, 5H, H-7a, H-9, H-11, CH_2Ph), 2.50 (dd, *J* = 12.8, 1.2 Hz, 1H, CH_2Ph), 2.60-2.65 (m, 2H, H-6), 4.28 (dd, *J* = 8.8, 7.2 Hz, 1H, H-2), 4.41 (dd, *J* = 4.0 and 8.8 Hz, 1H, H-2), 5.55 (dd, *J* = 4.0 and 7.2 Hz, 1H, H-3), 6.94 (d, *J* = 7.2 Hz, 2H, H-Ar), 7.10-7.31 (m, 6H, H-Ar), 7.43 (d, *J* = 7.2 Hz, 2H, H-Ar).

^{13}C NMR (100.6 MHz) δ: 19.2 (C-2), 19.4 (C-7), 26.7 (C-10), 27.5 (C-8), 29.1 (C-6), 36.4 (*C*H_2Ph), 38.9 (C-11), 43.4 (C-7a), 59.4 (C-3), 68.0 (C-2), 98.8 (C-11a), 125.6 (C-Ar), 126.8 (2C-Ar), 127.3 (C-Ar), 128.1 (2C-Ar), 128.3 (2C-Ar), 129.0 (2C-Ar), 139.0 (C-*i*), 141.0 (C-*i*), 172.4 (*C*O).

HMRS calculated for $[C_{24}H_{27}NO_2 + H]^+$: 362.2115; found: 362.2122.

Spectroscopic and analytical data for compound **57b** (3*R*,7a*S*,11*S*,11a*S*)

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

$[\alpha]^{22}_{D}$ – 140.2 (*c* 1.0, CH_3OH).

^{1}H NMR (400 MHz) δ: 1.39-1.63 (m, 5H, H-8, H-9, H-10), 1.80-1.95 (m, 3H, H-7, H-7a), 2.00-2.10 (m, 1H, H-8), 2.20-2.30 (m, 1H, H-11), 2.34-2.57 (m, 2H, H-6), 2.37 (t, *J* = 12.0 Hz, 1H, C*H*$_2$Ph), 3.00 (dd, *J* = 2.0 and 12.0 Hz, 1H, C*H*$_2$Ph), 3.99 (dd, *J* = 3.6 and 8.8 Hz, 1H, H-2), 4.61 (dd, *J* = 7.6 and 8.8 Hz, 1H, H-2), 5.15 (dd, *J* = 3.6 and 7.6 Hz, 1H, H-3), 7.10 (d, *J* = 6.8 Hz, 2H, H-Ar), 7.21-7.33 (m, 8H, H-Ar).

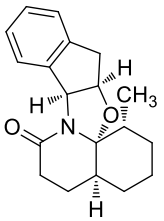
^{13}C NMR (100.6 MHz) δ: 19.6 (C-9), 20.7 (C-7), 27.1 (C-10), 27.3 (C-8), 29.6 (C-6), 36.8 (*C*H$_2$Ph), 40.6 (C-11), 46.5 (C-7a), 62.2 (C-2), 74.5 (C-3), 97.1 (C-11a), 126.1 (C-Ar), 126.7 (2C-Ar), 127.5 (C-Ar), 128.4 (2C-Ar), 128.6 (2C-Ar), 129.1 (2C-Ar), 140.3 (C-*i*), 141.3 (C-*i*), 168.3 (*C*O).

HMRS calculated for $[C_{24}H_{27}NO_2 + H]^+$: 362.2115; found: 362.2120.

In some runs, traces amounts of lactams **57c** were isolated.
Spectroscopic and analytical data for compound **57c** (3*R*,7a*R*,11*S*,11a*R*)

^{1}H NMR (400 MHz) δ: 1.10-1.14 (m, 1H, H-9), 1.49-1.83 (m, 8H, H-7, H-8, H-9, H-10, H-11), 2.17-2.25 (tt, *J* = 3.6 and 12.4 Hz, 1H, H-7a), 2.47-2.55 (m, 3H, H-6, C*H*$_2$Ph), 2.66 (tt, *J* = 3.2 and 16.8 Hz, 1H, C*H*$_2$Ph), 4.31 (dd, *J* = 6.4 and 8.4 Hz, 1H, H-2), 4.41 (t, *J* = 8.8 Hz, 1H, H-2), 5.74 (dd, *J* = 8.8 and 6.4 Hz, 1H, H-3), 6.18 (d, *J* = 6.4 Hz, 2H, H-Ar), 6.99-7.02 (m, 4H, H-Ar), 7.40-7.41 (m, 4H).

^{13}C NMR (100.6 MHz) δ: 19.9 (C-8), 22.5 (C-9), 23.2 (C-7), 28.9 (C-10), 33.1 (C-6), 35.4 (*C*H$_2$Ph), 36.9 (C-7a), 39.8 (C-11), 58.5 (C-3), 65.2 (C-2), 97.8 (C-11a), 125.7 (C-Ar), 126.0 (2C-Ar), 127.0 (C-Ar), 128.0 (2C-Ar), 128.7 (2C-Ar), 128.8 (2C-Ar), 140.2 (C-*i*), 141.4 (C-*i*), 176.2 (*C*O).



(1*R*,4a*S*,8a*S*,13a*R*,14a*R*)-1-Methyl-7-oxo-3-phenyl-1,2,3,4,4a,5,6,7,8a,13,13a,14a-dodecahydroindeno[1',2':4,5]oxazolo[2,3-*j*]quinoline (58a)

Operating as in the preparation of lactam **33a**, from oxo acid **49** (568 mg, 3.09 mmol) and (1*S*,2*R*)-(-)-*cis*-1-amino-2-indanol (691 g, 4.63 mmol) in anhydrous toluene (30 mL) containing anhydrous $MgSO_4$ (720 mg), a 9:1 (calculated by ^{1}H NMR) inseparable mixture of lactams **58a** and **58b** (715 mg, 78%) was obtained after flash-column chromatography (99:1 to 8:2 hexane–EtOAc).

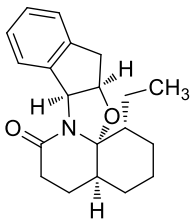
Spectroscopic and analytical data for compound **58a** (1*R*,4a*S*,8a*S*,13a*R*,14a*R*) from an enriched fraction

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

^{1}H NMR (400 MHz) δ: 0.04 (d, *J* = 6.4 Hz, 3H, *C*H$_3$), 1.26-1.59 (m, 6H, H-1, H-2, H-4, H-5), 1.77-1.92 (m, 4H, H-3, H-4a, H-5), 2.49-2.54 (m, 2H, H-6), 3.17 (d, *J* = 2.8 Hz, 2H, H-13), 4.74-4.77 (m, 1H, H-13a), 5.87 (d, *J* = 6.0 Hz, 1H, H-8a), 7.18-7.26 (m, 3H, H-Ar), 7.48 (dd, *J* = 2.0 and 5.6 Hz, 1H, H-Ar).

^{13}C NMR (100.6 MHz) δ: 14.2 (*C*H$_3$), 18.9 (C-3), 19.7 (C-2), 26.7 (C-5), 28.4 (C-6), 31.0 (C-4), 34.9 (C-1), 37.9 (C-13), 38.5 (C-4a), 65.9 (C-8a), 77.8 (C-13a), 98.2 (C-14a), 124.7 (C-Ar), 126.4 (C-Ar), 127.2 (C-Ar), 128.2 (C-Ar), 140.8 (C-*i*), 141.6 (C-*i*), 171.2 (*C*O).

HMRS calculated for $[C_{19}H_{23}NO_2 + H]^+$: 298.1802; found: 298.1799.



(1*R*,4a*S*,8a*S*,13a*R*,14a*R*)-1-Ethyl-7-oxo-1,2,3,4,4a,5,6,7,8a,13,13a,14a-dodecahydro-indeno[1',2':4,5]oxazolo[2,3-*j*]quinoline (59a)

Operating as in the preparation of lactam **33a**, from oxo acid **53** (430 mg, 2.17 mmol) and (1*S*,2*R*)-(-)-*cis*-1-amino-2-indanol (452 g, 3.02 mmol) in anhydrous toluene (20 mL) containing anhydrous $MgSO_4$ (260 mg), a 4:1 (calculated by ^{1}H NMR) inseparable mixture of lactams **59a** and **59b** (527 mg, 78%) and small amounts of pure **59a** were obtained after flash-column chromatography (99:1 to 8:2 hexane–EtOAc).

Spectroscopic and analytical data for compound **59a** (1*R*,4a*S*,8a*S*,13a*R*,14a*R*)

IR (film): 1635 cm^{-1}.

$[\alpha]^{22}_D$ + 84.7 (*c* 1.1, CH_3OH).

^{1}H NMR (400 MHz) δ: 0.20-0.28 (m, 1H, H-1.1), 0.46 (t, *J* = 7.2 Hz, 3H, H-2.1), 0.53-0.59 (m, 1H, C*H*$_2$CH$_3$), 1.13 (dt, *J* = 4.4 and 12.4 Hz, 1H, H-2), 1.24-1.30 (m, 1H, H-1), 1.43-1.50 (m, 2H, H-3), 1.50-1.54 (m, 1H, H-4), 1.61-1.65 (m, 1H, H-2), 1.70-1.85 (m, 3H, H-4a, H-5), 1.88-1.93 (m, 1H, H-4), 2.48-2.54 (m, 2H, H-6), 3.15 (d, *J* = 2.4 Hz, 2H, H-13), 4.74 (q, *J* = 2.8 Hz, 1H, H-13a), 5.86 (d, *J* = 5.6 Hz, 1H, H-8a), 7.21-7.26 (m, 3H, H-Ar), 7.48 (dd, *J* = 2.0 and 5.6 Hz, 1H, H-Ar).

^{13}C NMR (100.6 MHz) δ: 11.9 (*C*H$_3$), 18.9 (C-5), 19.7 (C-3), 20.4 (*C*H$_2$CH$_3$), 26.7 (C-4), 27.0 (C-2), 28.5 (C-6), 37.8 (C-13), 38.5 (C-4a), 41.8 (C-1), 66.1 (C-9), 77.6 (C-10), 98.8 (C-4a), 124.8 (C-Ar), 126.5 (C-Ar), 127.1 (C-Ar), 128.2 (C-Ar), 140.7 (C-*i*), 141.3 (C-*i*), 171.5 (*C*O).

HMRS calculated for $[C_{20}H_{25}NO_2 + H]^+$: 312.1958; found: 312.1958.

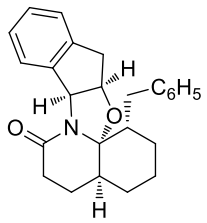
Spectroscopic and analytical data for compound **59b** (1*S*,4a*R*,8a*S*,13a*R*,14a*S*) from an enriched fraction

IR (film): 1652 cm^{-1}.

^{1}H NMR (400 MHz) δ: 0.92 (t, *J* = 7.2 Hz, 3H, CH_3), 1.22-2.08 (m, 12H, H-1, H-2, H-3, H-4, H-4a, H-5, CH_2CH_3), 2.48 (t, *J* = 7.6 Hz, 2H, H-6), 3.12 (d, *J* = 3.2 Hz, 2H, H-13), 5.03-5.06 (m, 1H, H-8a), 5.71 (d, *J* = 5.6 Hz, 1H, H-13a), 7.15-7.27 (m, 3H, H-Ar), 8.05 (d, *J* = 8.4 Hz, 1H, H-Ar).

^{13}C NMR (100.6 MHz) δ: 12.7 (CH_3), 19.7 (C-5), 20.4 (C-3), 23.3 (CH_2CH_3), 26.7 (C-4), 27.2 (C-2), 29.3 (C-6), 38.4 (C-13), 41.2 (C-4a), 45.5 (C-1), 66.5 (C-8a), 81.0 (C-13a), 97.3 (C-14a), 124.8 (C-Ar), 127.1 (C-Ar), 128.5 (C-Ar), 128.8 (C-Ar), 140.6 (C-*i*), 142.0 (C-*i*), 169.8 (*C*O).

HMRS calculated for $[C_{20}H_{25}NO_2 + H]^+$: 312.1958; found: 312.1953.



(1*S*,4a*S*,8a*S*,13a*R*,14a*S*)-1-Benzyl-7-oxo-1,2,3,4,4a,5,6,7,8a,13,13a,14a-dodecahydroindeno [1.1,2':4,5]oxazolo[2,3-*j*]quinoline (60a)

Operating as in the preparation of lactam **33a**, from oxo acid **54** (230 mg, 0.89 mmol) and (1*S*,2*R*)- (-)-*cis*-1-amino-2-indanol (200 g, 1.34 mmol) in anhydrous toluene (30 mL) containing anhydrous $MgSO_4$ (220 mg), a 5:1 (calculated by ^{1}H NMR) inseparable mixture of lactams **60a** and **60b** (315 mg, 95%) was obtained after flash-column chromatography (99:1 to 8:2 hexane–EtOAc).

Spectroscopic and analytical data for compound **60a** (1*S*,4a*S*,8a*S*,13a*R*,14a*S*) from enriched fraction

IR (film): 1653 cm^{-1}.

^{1}H NMR (400 MHz) δ: 1.16-1.42 (m, 5H, H-2, H-4, H-5, H-6), 1.48-1.53 (m, 1H, H-2), 1.61 (tt, *J* = 11.6, 2.8 Hz, 1H, H-4a), 1.76-1.83 (m, 2H, H-3), 1.89-2.03 (m, 3H, H-4, H-6, H-14a), 2.58-2.60 (m, 2H, H-1.1), 3.20-3.22 (m, 2H, H-13), 4.79 (dt, *J* = 5.6, 1.2 Hz, 1H, H-13a), 5.91 (d, *J* = 5.6 Hz, 1H, H-8a), 6.78-6.81 (m, 1H, H-Ar), 7.00-7.25 (m, 7H, H-Ar), 7.51-7.54 (m, 1H, H-Ar).

^{13}C NMR (100.6 MHz) δ: 18.7 (C-3), 19.4 (C-5), 26.6 (C-2), 27.0 (C-4), 28.5 (C-1.1), 34.4 (C-6), 37.6 (C-13), 38.3 (C-1), 42.2 (C-4a), 66.1 (C-8a), 77.7 (C-13a), 98.5 (C-14a), 124.8 (C-Ar), 125.3 (C-Ar), 126.2 (C-Ar), 127.4 (C-Ar), 127.9 (2C-Ar), 128.3 (C-Ar), 128.8 (2C-Ar), 140.5 (C-*i*), 141.2 (C-*i*), 141.2 (C-*i*), 171.4 (*C*O).

HMRS calculated for $[C_{25}H_{27}NO_2 + H]^+$: 374.2115; found: 374.2108.

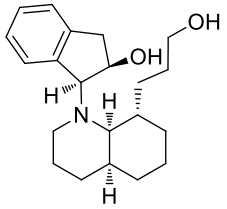
Spectroscopic and analytical data for compound **60b** (1*R*,4a*R*,8a*S*,13a*R*,14a*R*) from enriched fraction

IR (film): 1651 cm^{-1}.

^{1}H NMR (400 MHz) δ: 1.30-1.50 (m, 4H, H-3, H-4), 1.53-1.60 (m, 1H, H-4a), 1.63-1.88 (m, 5H, H-1, H-2, H-5), 2.40 (t, *J* = 11.6 Hz, 1H, C*H*$_2$Ph), 2.54-2.60 (m, 2H, H-6), 3.01 (dd, *J* = 2.4 and 11.6 Hz, 1H, H-1.1), 3.19 (d, *J* = 2.8 Hz, 2H, H-13), 5.15-5.18 (m, 1H, H-13a), 5.80 (d, *J* = 5.6 Hz, 1H, H-8a), 7.12 (d, *J* = 6.8 Hz, 1H, H-Ar), 7.19-7.30 (m, 7H, H-Ar), 8.07 (d, *J* = 7.2 Hz, 1H, H-Ar).

^{13}C NMR (100.6 MHz) δ: 19.4 (C-3), 20.2 (C-5), 26.7 (C-2), 27.2 (C-4), 29.4 (C-6), 37.2 (*C*H$_2$Ph), 38.4 (C-13), 41.4 (C-4a), 45.9 (C-1), 66.6 (C-8a), 81,2 (C-13a), 97.2 (C-14a), 124.8 (C-Ar), 126.1 (C-Ar), 127.2 (C-Ar), 128.4 (2C-Ar), 128.6 (C-Ar), 128.8 (C-Ar), 129.1 (2C-Ar), 140.4 (C-*i*), 140.6 (C-*i*), 141.9 (C-*i*), 169.8 (*C*O).

HMRS calculated for $[C_{25}H_{27}NO_2 + H]^+$: 374.2115; found: 374.2113.



(4a*S*,8*S*,8a*R*)-1-[(1*S*,2*R*)-2-Hydroxy-1-indanyl]-8-(3-hydroxypropyl)decahydroquinoline (62a)

$LiAlH_4$ (430 mg, 11.3 mmol) was slowly added to a suspension of $AlCl_3$ (467 mg, 3.5 mmol) in anhydrous THF (43 mL) at 0 °C. The mixture was stirred at 0 °C for 1 h and cooled to –78 °C; then a solution of a 3:1 mixture of lactams **29a** and **29b** (602 mg, 1.63 mmol) in anhydrous THF (6 mL), was added dropwise. The stirring was continued at –78 °C for 90 min and at room temperature for 90 min. Cold water (5 mL) was slowly added and the resulting mixture was filtered over Celite®, the filtrate was concentrated, and the residue was taken up with CH_2Cl_2 (12 mL). The organic solution was washed with brine (3 x 15 mL), dried and concentrated. Decahydroquinoline **62a** (345 mg, 64%) was obtained after flash-column (99:1 to 95:5 CH_2Cl_2–CH_3OH) as a colourless oil.

IR (film): 3385 cm^{-1}.

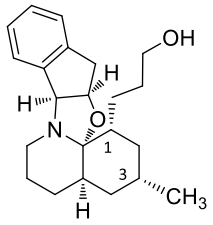
$[\alpha]^{22}_D$ + 7.44 (*c* 1.35, CH_3OH).

Several of the signals in the ^1H and ^{13}C spectra of **62a** were broad and il-defined, even not observed, thus indicating the existence of a slow conformational equilibrium.

^1H NMR (400 MHz) δ: 1.12-1.92 (m, 18H), 2.09 (br s, 1H), 2.27 (br s, 1H), 2.45 (br s, 1H), 2.70 (br s, 1H), 2.84 (dd, *J* = 16.4, 7.2 Hz, 1H), 3.23-3.26 (m, 1H), 3.66-3.71 (m, 1H), 4.41-4.43 (m, 1H), 7.17-7.27 (m, 4H, H-Ar), 7.28-7.42 (m, 1H).

^{13}C NMR (100.6 MHz) δ: 20.3, 20.5, 21.9, 28.1, 32.5, 34.0, 41.5, 62.9, 125.4 (C-Ar), 126.2 (C-Ar), 128.2 (C-Ar), 141.6 (C-*i*).

HMRS calculated for $[C_{21}H_{31}NO_2 + H]^+$: 330.2425; found: 330.2428.



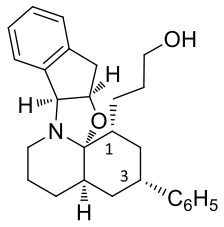
(1*R*,3*R*,4a*R*,8a*S*,13a*R*,14a*S*)-1-(3-Hydroxypropyl)-3-methyl-1,2,3,4,4a,5,6,7,8a,13,13a,14a-dodecahydro-indeno[1',2':4,5]oxazolo[2,3-*j*]quinoline (63)

Operating as in the preparation of **64a**, from $LiAlH_4$ (570 mg, 15 mmol) and $AlCl_3$ (1.22 g, 4.6 mmol) in anhydrous THF (58 mL) and a solution of a 3:1 mixture of lactams **31a** and **31b** (883 mg, 2.31 mmol) in anhydrous THF (3.5 mL), decahydroquinoline **63** (473 mg, 60%) was obtained after flash-column chromatography (9:1 hexane−EtOAc) as a colourless oil.

^{1}H NMR (400 MHz) δ: 0.86 (d, *J* = 6 Hz, 3H, CH_3), 0.97 (dd, *J* = 11.2 and 13.6 Hz, 2H), 1.22-1.40 (m, 4H), 1.50-1.62 (m, 4H), 1.64-1.74 (m, 3H), 1.81-1.93 (m, 2H), 2.20-2.25 (br. s, 1H, OH), 2.82 (dt, *J* = 3.2 and 13.6 Hz, 1H), 3.08-3.21 (m, 2H), 3.27 (dt, *J* = 2.0 and 14.8 Hz, 1H), 3.36 (dd, *J* = 5.6 and 7.2 Hz, 1H), 4.67 (d, *J* = 7.2 Hz, 1H), 4.98 (m, 2H), 7.14-7.30 (m, 4H, H-Ar).

^{13}C NMR (100.6 MHz) δ: 20.1 (C-6), 22.2 (CH_3), 24.3 (*C*$H_2CH_2CH_2OH$), 26.4 (C-3), 28.3 (C-5), 30.4 (*C*H_2CH_2OH), 34.8 (C-4a), 36.1 (C-1), 37.9 (C-4), 39.0 (C-2), 39.1 (C-13), 44.9 (C-7), 62.1 (*C*H_2OH), 66.9 (C-8a), 78.6 (C-13a), 98.9 (C-14a), 124.1 (C-Ar), 125.2 (C-Ar), 126.6 (C-Ar), 128.0 (C-Ar), 141.3 (C-*i*), 143.1 (C-*i*).

HMRS calculated for $[C_{22}H_{31}NO_2 + H]^+$: 342.2428; found: 342.2430.



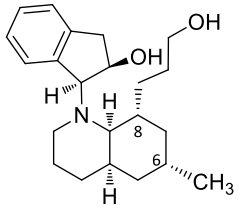
(1*R*,3*R*,4a*R*,8a*S*,13a*R*,14a*S*)-11-(3-Hydroxypropyl)-3-phenyl-1,2,3,4,4a,5,6,7,8a,13,13a,14a-dodecahydroindeno[1',2':4,5]oxazolo[2,3-*j*]quinoline (65)

Operating as in the preparation of **64a**, from $LiAlH_4$ (570 mg, 15 mmol) and $AlCl_3$ (1.22 g, 4.6 mmol) in anhydrous THF (58 mL) and a solution of a 6:1 mixture of lactams **32a** and **32b** (1.0 g, 2.31 mmol) in anhydrous THF (3.5 mL), decahydroquinoline **65** (513 mg, 55%) was obtained after flash-column chromatography (9:1 hexane–EtOAc) as a colourless oil.

^{1}H NMR (400 MHz) δ: 0.86-0.91 (m, 1H, C*H*$_2$CH$_2$CH$_2$OH), 1.18-1.64 (m, 6H, H-2, H-5, H-6, C*H*$_2$CH$_2$CH$_2$OH, C*H*$_2$CH$_2$OH), 1.77-1.89 (m, 4H, H-1, H-4, H-5), 1.97-2.00 (m, 2H, H-4a, H-6), 2.13 (dt, *J* = 5.2 and 13.2 Hz, 1H, H-2), 2.70-2.87 (m, 2H, H-3, H-7), 3.13-3.16 (m, 2H, H-13), 3.25 (br. s, 1H, OH), 3.31 (dd, *J* = 6 and 7.2 Hz, 3H, H-7, C*H*$_2$OH), 4.65 (d, *J* = 6.8 Hz, 1H, H-8a), 4.95-4.99 (m, 1H, H-13a), 7.11-7.28 (m, 9H, H-Ar).

^{13}C NMR (100.6 MHz) δ: 20.0 (C-6), 24.1 (*C*H$_2$CH$_2$CH$_2$OH), 27.9 (C-5), 30.4 (*C*H$_2$CH$_2$OH), 35.2 (C-1), 36.2 (C-4a), 36.8 (C-2), 37.8 (C-4), 38.0 (C-3), 38.9 (C-13), 44.7 (C-7), 61.9 (C-8a), 66.8 (*C*H$_2$OH), 78.6 (C-13a), 98.3 (C-14a), 124.0 (C-Ar), 125.1 (C-Ar), 125.7 (C-Ar), 126.5 (C-Ar), 126.6 (2C-Ar), 127.9 (C-Ar), 128.0 (2C-Ar), 141.2 (C-*i*), 142.9 (C-*i*), 146.6 (C-*i*).

HMRS calculated for $[C_{27}H_{33}NO_2 + H]^+$: 404.2584; found: 404.2590.



(4a*R*,6*R*,8*R*,8a*R*)-1-[(1*S*,2*R*)-2-Hydroxy-1-indanyl]-8-(3-hydroxypropyl)-6-methyldecahydroquinoline (64a)

$LiAlH_4$ (191 mg, 5.05 mmol) was slowly added to a suspension of $AlCl_3$ (208.0 mg, 1.56 mmol) in anhydrous THF (20 mL) at 0 °C. The mixture was stirred at 0 °C for 1 h and cooled to –78 °C; then a solution of a 3:1 mixture of lactams **31a** and **31b** (298 mg, 0.78 mmol) in anhydrous THF (3 mL), was added dropwise. The stirring was continued at –78 °C for 90 min and at room temperature for 24 h. Cold water (5 mL) was slowly added and the resulting mixture was filtered over Celite®, the filtrate was concentrated, and the residue was taken up with CH_2Cl_2 (10 mL). The organic solution was washed with brine (3 x 10 mL), dried and concentrated. Decahydroquinoline **64a** (170 mg, 63%) was obtained after flash-column chromatography (8:2 to 6:4 hexane–EtOAc) as a colourless oil.

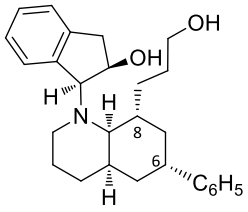
IR (film): 3347 cm^{-1}.

$[\alpha]^{22}_D$ – 23.2 (*c* 0.84, CH_3OH).

^{1}H NMR (400 MHz) δ: 0.75 (q, *J* = 12.0 Hz, 1H, H-7), 0.86 (d, *J* = 6.4 Hz, 3H, CH_3), 1.03-1.14 (m, 2H, H-3), 1.19-1.28 (m, 2H, H-5, C*H*$_2$CH$_2$O), 1.35-1.79 (m, 9H, H-4, H-5, H-6, H-7, C*H*$_2$CH$_2$CH$_2$OH, C*H*$_2$CH$_2$OH), 2.09-2.12 (m, 1H, H-8), 2.27-2.34 (m, 2H, H-2, H-4a), 2.53 (dd, *J* = 4.48 and 11.0 Hz, 1H, H-8a), 2.66-2.74 (m, 1H, H-2), 2.81 (dd, *J* = 7.6 and 16.0 Hz, 1H, C*H*$_2$CHOH), 3.14 (dd, *J* = 7.6 and 16.0 Hz, 1H, C*H*$_2$CHOH), 3.58-3.71 (m, 2H, C*H*$_2$OH), 4.15 (d, *J* = 7.2 Hz, 1H, C*H*N), 4.33 (q, *J* = 7.6 Hz, 1H, C*H*OH), 7.17-7.29 (m, 3H), 7.52-7.54 (m, 1H).

^{13}C NMR (100.6 MHz) δ: 22.5 (CH_3), 23.3 (C-3), 24.9 (*C*H$_2$CH$_2$CH$_2$OH), 26.5 (C-6), 28.7 (*C*H$_2$CH$_2$OH), 28.9 (C-4), 33.2 (C-8), 33.9 (C-4a), 40.8 (*C*H$_2$CHOH), 40.9 (C-7), 41.2 (C-5), 41.5 (C-2), 63.0 (CH_2O), 68.2 (C-8a), 71.0 (*C*HOH), 71.7 (*C*HN), 125.5 (C-Ar), 126.1 (C-Ar), 128.3 (C-Ar), 128.4 (C-Ar), 141.1 (C-*i*), 142.0 (C-*i*).

HMRS calculated for $[C_{22}H_{33}NO_2 + H]^+$: 344.2584; found: 344.2580.



(4a*R*,6*R*,8*R*,8a*R*)-1-[(1*S*,2*R*)-2-Hydroxy-1-indanyl]-8-(3-hydroxypropyl)-6-phenyldecahydroquinoline (66a)

Operating as in the preparation of decahydroquinoline **64a**, from $LiAlH_4$ (1.32 g, 34.7 mmol) and $AlCl_3$ (1.42 g, 10.7 mmol) in anhydrous THF (125 mL) and a solution of 6:1 crude mixture of lactams **32a** and **32b** (2.30 g, 5.3 mmol) in anhydrous THF (8 mL), decahydroquinoline **66a** (1.32 mg, 60%, overall yield from **28**) was obtained after flash-column chromatography (9:1 to 6:4 hexane–EtOAc) as a colourless oil.

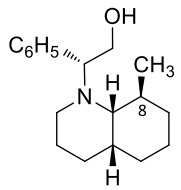
IR (film): 3206, 3358 cm^{-1}.

$[\alpha]^{22}_D$ – 5.1 (*c* 1.0, CH_3OH).

^{1}H NMR (400 MHz) δ: 1.11-2.01 (m, 12H, H-3, H-4, H-5, H-7, C*H*$_2$CH$_2$CH$_2$OH, C*H*$_2$CH$_2$OH), 2.24-2.30 (m, 1H, H-4a), 2.36-2.46 (m, 2H, H-2, H-8), 2.69-2.88 (m, 4H, H-2, H-6, H-8a, C*H*$_2$CHOH), 3.13-3.19 (m, 2H, C*H*$_2$CHOH, OH), 3.57-3.69 (m, 2H, C*H*$_2$OH), 4.22 (d, *J* = 7.2 Hz, 1H, C*H*N), 4.38 (q, *J* = 7.6 Hz, 1H, C*H*OH), 7.17-7.31 (m, 8H), 7.54-7.56 (m, 1H).

^{13}C NMR (100.6 MHz) δ: 23.1 (C-3), 24.5 (*C*H$_2$CH$_2$CH$_2$OH), 28.7 (*C*H$_2$CH$_2$OH), 28.9 (C-4), 33.6 (C-4a), 33.9 (C-8), 37.9 (C-6), 39.6 (C-5), 39.9 (C-7), 40.7 (*C*H$_2$CHOH), 41.5 (C-2), 62.7 (C*H*$_2$OH), 68.1 (C-8a), 71.0 (*C*HOH), 71.7 (*C*HN), 125.5 (C-Ar), 126.0 (C-Ar), 126.2 (C-Ar), 126.7 (2C-Ar), 128.2 (C-Ar), 128.3 (2C-Ar), 128.6 (C-Ar), 140.6 (C-Ar), 141.9 (C-Ar), 146.5 (C-Ar).

HMRS calculated for $[C_{27}H_{35}NO_2 + H]^+$: 406.2741; found: 406.2736.



(4a*R*,8*S*,8a*R*)-1-[(1*R*)-2-Hydroxy-1-phenylethyl]-8-methyldecahydroquinoline (67):

$LiAlH_4$ (130 mg, 3.42 mmol) was slowly added to a suspension of $AlCl_3$ (140 mg, 1.05 mmol) in anhydrous THF (14 mL) at 0 °C. The mixture was stirred at 0 °C for 1 h and cooled to –78 °C; then a solution of lactam **55a** (150 mg, 0.52 mmol) in anhydrous THF (3 mL), was added dropwise. The stirring was continued at –78 ºC for 90 min and at room temperature for 2 h. Cold water (5 mL) was slowly added and the resulting mixture was filtered over Celite®, the filtrate was concentrated, and the residue was taken up with CH_2Cl_2 (15 mL). The organic solution was washed with brine (2 x 10 mL), dried and concentrated. Decahydroquinoline **67** (114 mg, 80%) was obtained after flash-column chromatography (99:1 to 7:3 hexane–EtOAc) as white solid.

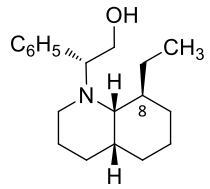
IR (film): 3348 cm^{-1}.

$[\alpha]^{22}_D$ + 0.75 (*c* 1.1, CH_3OH).

Several of the signals in the ^1H and ^{13}C NMR spectra of **67** at 25 °C were broad and ill-defined, even not observed, thus indicating the existence of a slow conformational equilibrium.

^1H NMR (400 MHz, broad signals) δ: 1.05 (d, *J* = 6.4 Hz, 3H, CH_3), 1.26-1.98 (m, 14H), 2.36-2.41 (m, 1H, H-2), 2.73-2.77 (m, 1H, H-2), 3.70-3.90 (m, 2H, C*H*N), 4.13-4.19 (m, 1H, CH_2OH), 7.27-7.32 (m, 5H, H-Ar).

^{13}C NMR (100.6 MHz, broad signals) δ: 20.7, 21.5, 28.8, 29.7, 30.7, 32.7, 47.2, 63.8, 127.5 (2C-Ar), 128.2 (C-Ar), 128.6 (2C-Ar).
HMRS calculated for $[C_{18}H_{27}NO + H]^+$: 274.2125; found: 274.2141.



(4a*R*,8*S*,8a*R*)-8-Ethyl-1-[(1*R*)-2-hydroxy-1-phenylethyl]decahydroquinoline (68)

Operating as in the preparation of decahydroquinoline **67**, from $LiAlH_4$ (82.4, 2.17 mmol) and $AlCl_3$ (89.3 mg, 0.67 mmol) in anhydrous THF (14 mL) and a solution of lactam **56a** (100 mg, 0.34 mmol) in anhydrous THF (3 mL), decahydroquinoline **68** (58 mg, 60%) was obtained after flash-column chromatography (99:1 to 7:3 hexane–EtOAc) as a colourless oil.

IR (film): 3504 cm^{-1}.

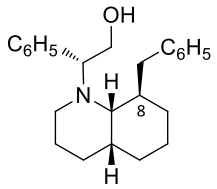
$[\alpha]^{22}_D$ – 1.06 (*c* 1.0, CH_3OH).

Several of the signals in the ^1H and ^{13}C NMR spectra of **68** at 25 °C were broad and ill-defined, even not observed, thus indicating the existence of a slow conformational equilibrium.

^1H NMR (400 MHz, 52 °C) δ: 0.95 (t, *J* = 7.6 Hz, 3H, CH_3), 1.16 (br. s, 1H), 1.26-1.50 (m, 8H), 1.62-1.83 (m, 4H), 1.93-1.96 (m, 1H), 2.13 (br. s, 2H), 2.47 (br. s, 1H), 2.79-2.82 (m, 1H), 3.69 (dd, *J* = 10.4, 5.5 Hz, 1H), 3.90 (t, *J* = 10.0 Hz, 1H), 4.21 (br. s, 1H), 7.24-7.33 (m, 5H, H-Ar).

^{13}C NMR (100.6 MHz, 52 °C) δ: 11.9 (CH_3), 20.8 (CH_2), 21.5 (CH_2), 24.7 (CH_2), 27.9, 29.7 (CH_2), 31.2 (CH), 35.5 (CH), 43.7 (CH_2), 62.2 (CH, CH_2), 127.5 (C-Ar), 128.3 (2C-Ar), 128.8 (2C-Ar).

HMRS calculated for $[C_{19}H_{29}NO + H]^+$: 288.2322; found: 288.2322.



(4a*R*,8*R*,8a*S*)-8-Benzyl-1-[(1*R*)-2-hydroxy-1-phenylethyl]decahydroquinoline (69)

Operating as in the preparation of decahydroquinoline **67**, from $LiAlH_4$ (259 mg, 6.84 mmol) and $AlCl_3$ (281.4 mg, 2.11 mmol) in anhydrous THF (26 mL) and a solution of lactam **57a** (380 mg, 1.05 mmol) in anhydrous THF (5 mL), decahydroquinoline **69** (224 mg, 61%) was obtained after flash-column chromatography (99:1 to 7:3 hexane–EtOAc) as a colourless oil.

IR (film): 3384 cm^{-1}.

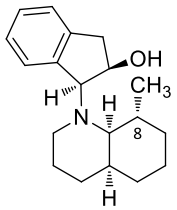
$[\alpha]^{22}_D$ – 19.2 (*c* 1.07, CH_3OH).

Several of the signals in the ^1H and ^{13}C NMR spectra of **69** at 25 °C were broad and ill-defined, even not observed, thus indicating the existence of a slow conformational equilibrium.

^1H NMR (400 MHz, 52 °C) δ: 1.20-1.95 (m, 9H), 2.10-2.23 (m, 3H), 2.30-2.80 (m, 4H), 2.90-3.00 (m, 1H), 3.19 (br. s, 1H), 3.70-3.80 (m, 1H), 3.93-3.97 (m, 1H), 4.22-4.24 (m, 1H), 7.12-7.31 (m, 10H, H-Ar).

^{13}C NMR (100.6 MHz, 52 °C, broad signals) δ: 20.8 (CH_2), 21.2 (CH_2), 29.6 (CH_2), 31.1 (CH), 36.7 (CH), 39.0 (CH_2), 61.8 (CH, CH_2), 125.8 (C-Ar), 127.6 (C-Ar), 128.4 (2C-Ar), 128.8 (2C-Ar), 129.3 (2C-Ar), 141.8 (C-*i*).

HMRS calculated for $[C_{24}H_{31}NO + H]^+$: 350.2478; found: 350.2488.



(4aS,8*R*,8a*S*)-1-[(1*S*,2*R*)-2-Hydroxy-1-indanyl]-8-methyldecahydroquinoline (70a)

Operating as in the preparation of decahydroquinoline **62a** from $LiAlH_4$ (166 mg, 4.36 mmol) and $AlCl_3$ (180 mg, 1.35 mmol) in anhydrous THF (17 mL) and a solution of the mixture 9:1 of lactams **58a** and **58b** (200 mg, 0.67 mmol) in anhydrous THF (6 mL), decahydroquinoline **70a** (162 mg, 84%) was obtained after flash-column chromatography (95:5 to 9:1 hexane–EtOAc) as a colourless oil.

IR (film): 3279 cm^{-1}.

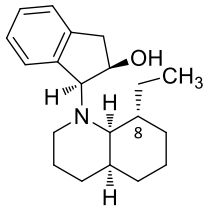
$[\alpha]^{22}_D$ – 3.4 (*c* 1.0, CH_3OH).

Several of the signals in the ^1H and ^{13}C NMR spectra of **70a** at 25 °C were broad and ill-defined, even not observed, thus indicating the existence of a slow conformational equilibrium.

^1H NMR (400 MHz, broad signals) δ: 1.10 (d, *J* = 6.8 Hz, 3H, CH_3), 1.15-1.50 (m, 10H), 1.69-1.74 (m, 3H), 2.15 (br. s, 1H), 2.34 (br. s, 1H), 2.52 (br. s, 1H), 2.83 (dd, *J* = 16.4, 4.4 Hz, 1H), 3.19-3.23 (m, 1H), 4.38-4.40 (m, 2H), 7.16-7.26 (m, 3H, H-Ar), 7.37 (br. s, 1H, H-Ar).

^{13}C NMR (100.6 MHz, broad signals) δ: 19.2, 20.6 (CH_2), 22.4, 32.5, 41.3 (CH_2), 70.3, 125.4 (C-Ar), 126.1 (C-Ar), 127.4 (C-Ar), 128.2 (C-Ar), 141.9 (C-*i*).

HMRS calculated for $[C_{19}H_{27}NO + H]^+$: 286.2165; found: 286.2165.



(4aS,8*R*,8a*S*)-8-Ethyl-1-[(1*S*,2*R*)-2-hydroxy-1-indanyl]decahydroquinoline (71a)

Operating as in the preparation of decahydroquinoline **62a**, from $LiAlH_4$ (241 mg, 6.4 mmol) and $AlCl_3$ (260 mg, 1.95 mmol) in anhydrous THF (25 mL) and a solution of the mixture 4:1 of lactams **59a** and **59b** (304 mg, 0.98 mmol) in anhydrous THF (10 mL), decahydroquinoline **71a** (184 mg, 63%) was obtained after flash-column chromatography (95:5 to 9:1 hexane–EtOAc) as a colourless oil.

IR (film): 3286 cm^{-1}.

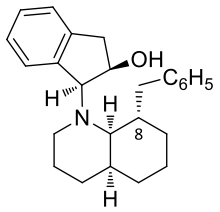
$[\alpha]^{22}_D$ + 15.36 (*c* 1.0, CH_3OH).

^{1}H NMR (400 MHz) δ: 0.99 (t, *J* = 7.6 Hz, 3H, CH_3), 1.17-1.68 (m, 12H), 1.87-2.18 (m, 4H), 2.43 (br s, 1H), 2.71 (br s, 1H), 2.85 (dd, *J* = 16.4, 7.6 Hz, 1H, C*H*$_2$CHOH), 3.25-3.30 (m, 1H, C*H*OH), 4.41-4.47 (m, 1H, C*H*N), 4.55 (br s, 1H, OH), 7.17-7.29 (m, 4H, H-Ar).

Several of the signals in the ^{13}C NMR spectrum of **71a** at 25 °C were broad and ill-defined, even not observed, thus indicating the existence of a slow conformational equilibrium.

^{13}C NMR (100.6 MHz) δ: 12.0 (CH_3), 20.6 (CH_2), 21.8 (CH_2), 24.4 (CH_2), 32.4 (CH), 36.1 (CH), 41.7 (CH_2), 69.6 (CH_2), 125.5 (C-Ar), 126.3 (C-Ar), 127.9 (C-Ar), 128.1 (C-Ar), 141.8 (C-*i*).

HMRS calculated for $[C_{20}H_{29}NO + H]^+$: 300.2322; found: 300.2326.



(4aS,8*S*,8a*R*)-8-Benzyl-1-[(1*S*,2*R*)-2-hydroxy-1-indanyl]decahydroquinoline (72a)

Operating as in the preparation of decahydroquinoline **62a**, from $LiAlH_4$ (110 mg, 2.9 mmol) and $AlCl_3$ (119 mg, 0.89 mmol) in anhydrous THF (11 mL) and a solution of the mixture 5:1 of lactams **60a** and **60b** (166 mg, 0.45 mmol) in anhydrous THF (10 mL), decahydroquinoline **72a** (109 mg, 67%) was obtained after flash-column chromatography (95:5 to 9:1 hexane–EtOAc) as a colourless oil.

IR (film): 3314 cm^{-1}.

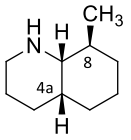
$[\alpha]^{22}_D$ + 37.14 (*c* 1.0, CH_3OH).

Several of the signals in the ^1H and ^{13}C NMR spectra of **72a** at 25 °C were broad and ill-defined, even not observed, thus indicating the existence of a slow conformational equilibrium.

^1H NMR (300 MHz, broad signals) δ: 1.20-2.03 (m, 9H), 2.15-2.19 (m, 1H), 2.49-3.00 (m, 5H), 2.85 (dd, *J* = 17.1, 6.6 Hz, 1H, C*H*$_2$Ph), 3.27 (dd, *J* = 15.6, 7.5 Hz, 1H, C*H*$_2$Ph), 4.40-4.51 (m, 4H), 7.06-7.36 (m, 9H, H-Ar).

^{13}C NMR (75.4 MHz) δ: 20.8, 31.9, 37.1, 38.3, 41.7, 69.1, 125.4 (C-Ar), 125.9 (C-Ar), 126.2 (C-Ar), 128.1 (C-Ar), 128.3 (C-Ar), 129.1 (C-Ar), 129.3 (C-Ar), 141.3 (C-*i*), 141.5 (C-*i*).

HMRS calculated for $[C_{25}H_{31}NO_3 + H]^+$: 362.2406; found: 362.2409.



(4a*R*,8*S*,8a*R*)-8-Methyldecahydroquinoline (73)

A solution of decahydroquinoline **67** (100 mg, 0.36 mmol) in CH_3OH (9 mL) was hydrogenated at rt for 8 h at atmospheric pressure in the presence of 40% $Pd(OH)_2$ (40 mg). The catalyst was removed by filtration and the solvent evaporated. The resulting oil was dissolved in EtOAc (10 mL) and extracted with aqueous HCl solution (1%, 3 x 10 mL). This aqueous layer was basified until pH = 10 with aqueous KPH (10 %) and extracted with Et_2O (5 x 10 mL). The organic extracts were dried and concentrated to afford *cis*-decahydroquinoline **73** (45 mg, 82%) as a colourless oil.

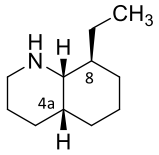
IR (film): 3425 cm^{-1}.

$[\alpha]^{22}_D$ + 13.2 (*c* 0.35, CH_3OH).

^1H NMR (400 MHz) δ: 0.95 (d, *J* = 7.2 Hz, 3H, CH_3), 1.05-1.10 (m, 1H), 1.39-1.48 (m, 4H), 1.62-1.73 (m, 3H), 1.86 (m, 2H), 2.35 (br. s, 2H), 2.47 (q, *J* = 4.0 Hz, 1H), 2.65-2.70 (m, 1H), 2.85 (br. s, 1H).

^{13}C NMR (100.6 MHz, 52 °C) δ: 18.3 (CH_3), 21.0 (CH_2), 24.8 (CH_2), 27.6 (CH_2), 29.4 (CH_2), 30.5 (CH), 31.4 (CH_2), 34.0 (CH), 43.1 (CH_2), 61.2 (CH).

HMRS calculated for $[C_{10}H_{19}N + H]^+$: 154.1590; found: 154.1591.



(4a*R*,8*S*,8a*R*)-8-Ethyldecahydroquinoline (74)

Operating as in the preparation of decahydroquinoline **73**, starting from **68** (142 mg, 0.49 mmol) in CH_3OH (3 mL), and 40% $Pd(OH)_2$ (57 mg), decahydroquinoline **74** (62 mg, 75%) was obtained as a colourless oil.

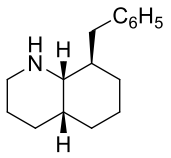
IR (film): 3338 cm^{-1}.

$[\alpha]^{22}_D$ – 15.4 (*c* 0.35, CH_3OH).

^1H NMR (400 MHz, 52 °C) δ: 0.91 (t, *J* = 7.2 Hz, 3H, CH_3), 1.16-1.22 (m, 1H), 1.27-1.39 (m, 3H), 1.43-1.55 (m, 5H), 1.62-1.67 (m, 2H), 1.67-1.78 (m, 2H), 1.81-1.90 (m, 1H), 2.67 (t, *J* = 8.8 Hz, 1H), 2.71-2.74 (m, 1H), 2.95-3.10 (m, 1H), 3.09 (br. s, 1H, NH).

^{13}C NMR (100.6 MHz, 52 °C) δ: 11.6 (CH_3), 20.9 (C-6), 23.4 (C-3), 24.2 (CH_2CH_3), 26.7 (C-4), 28.2 (C-5), 28.2 (C-7), 33.0 (C-8), 38.2 (C-4a), 44.1 (C-2), 59.2 (C-8a).

HMRS calculated for $[C_{11}H_{21}N + H]^+$: 168.1747; found: 168.1747.



(4a*R*,8*R*,8a*S*)-8-Benzyldecahydroquinoline (75)

Operating as in the preparation of decahydroquinoline **73**, starting from **69** (139 mg, 0.40 mmol) in CH_3OH (6 mL), and 40% $Pd(OH)_2$ (52 mg), decahydroquinoline **75** (81 mg, 89%) was obtained as a colourless oil.

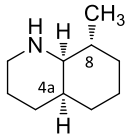
IR (film): 3317 cm^{-1}.

$[\alpha]^{22}_D$ + 11.6 (*c* 0.35, CH_3OH).

^{1}H NMR (400 MHz, 52 °C) δ: 1.07-1.13 (m, 1H, H-5), 1.21-1.30 (m, 2H, H-2), 1.36-1.50 (m, 4H, H-3, H-4, H-6), 1.60-1.75 (m, 3H, H-4, H-5, H-6), 1.87-1.92 (m, 1H, H-4a), 1.96-2.01 (m, 1H, H-8), 2.46 (dd, *J* = 13.4, 8.8 Hz, 1H, C*H*$_2$Ph), 2.62-2.69 (m, 2H, H-7, H-8a), 2.88 (dd, *J* = 13.4, 5.6 Hz, 1H, H-1.1), 2.97-2.92 (m, 1H, H-7), 7.12-7.14 (m, 3H, H-Ar), 7.23-7.27 (m, 2H, H-Ar).

^{13}C NMR (100.6 MHz) δ: 20.9 (C-6), 24.1 (C-4), 27.2 (C-5), 28.3 (C-3), 29.6 (C-2), 33.7 (C-8), 38.5 (*C*H$_2$Ph), 39.0 (C-4a), 44.3 (C-7), 59.3 (C-8a), 125.7 (C-Ar), 128.2 (2C-Ar), 129.1 (2C-Ar), 141.4 (C-*i*).

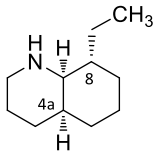
HMRS calculated for $[C_{16}H_{23}N + H]^+$: 230.1903; found: 230.1903.



(4a*R*,8*S*,8a*R*)-8-Methyldecahydroquinoline (*ent*-73)

Operating as in the preparation of decahydroquinoline **73**, starting from **70a** (80 mg, 0.28 mmol) in CH_3OH (7 mL), and 40% $Pd(OH)_2$ (32 mg), decahydroquinoline ***ent*-73** (34 mg, 79%) was obtained as a colourless oil.

$[\alpha]^{22}_D$ – 15.6 (*c* 0.35, CH_3OH).

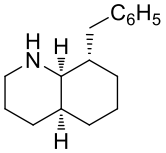


(4a*S*,8*R*,8a*S*)-8-Ethyldecahydroquinoline (*ent*-74)

Operating as in the preparation of decahydroquinoline **73**, starting from **71a** (51 mg, 0.17 mmol) in CH_3OH (3 mL), and 40% $Pd(OH)_2$ (20 mg), decahydroquinoline ***ent*-74** (20 mg, 70%) was obtained as a colourless oil.

$[\alpha]^{22}_D$ + 17.6 (*c* 1.0, CH_3OH).

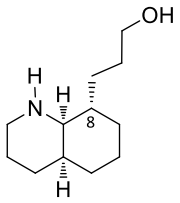
HMRS calculated for $[C_{11}H_{21}N + H]^+$: 168.1747; found: 168.1747.



(4a*S*,8*S*,8a*R*)-8-Benzyldecahydroquinoline (*ent*-75)

Operating as in the preparation of decahydroquinoline **73**, starting from **72a** (40 mg, 0.11 mmol) in CH_3OH (3 mL), and 40% $Pd(OH)_2$ (16 mg), decahydroquinoline ***ent*-75** (18 mg, 71%) was obtained as a yellow oil.

$[\alpha]^{22}_D$ – 12.6 (*c* 1.5, CH_3OH).



(4a*S*,8*R*,8a*S*)-8-(3-hydroxypropyl)decahydroquinoline (76)

Operating as in the preparation of decahydroquinoline **73**, starting from **62a** (128 mg, 0.39 mmol) in CH_3OH (9 mL) and 40% $Pd(OH)_2$ (51 mg), decahydroquinoline **76** (80 mg, 69%) was obtained as colourless oil.

IR (film): 3414 cm^{-1}.

$[\alpha]^{22}_D$ – 19.5 (*c* 1.03, $CHCl_3$).

^{1}H NMR (400 MHz) δ: 1.16 (br. s, 2 H), 1.26 (br. s, 2H), 1.34-1.46 (m, 4H), 1.48-1.56 (m, 2H), 1.59-1.69 (m, 5H), 1.79-1.82 (m, 1H), 2.50 (br. s, 2H), 2.58 (dd, *J*= 3.6 and 6.0 Hz, 1H), 2.63-2.69 (m, 2H), 3.61-3.63 (m, 2H).

Several of the signals in the ^{13}C NMR spectrum of **76** at 25 °C were broad and ill-defined, even not observed, thus indicating the existence of a slow conformational equilibrium.

^{13}C NMR (100.6 MHz) δ: 21.0 (CH_2), 24.4 (CH_2), 27.8 ($2CH_2$), 29.6 (CH_2), 30.1 (CH_2), 33.7 (CH), 35.9 (CH_2), 44.1 (CH_2), 59.1 (CH), 62.7 (CH_2).

Upon heating (50 °C) a sharpening of all signals was observed.

^{1}H NMR (400 MHz, 50 °C) δ: 1.14-1.18 (m, 1H), 1H.26-1.40 (m, 2H), 1.41-1.47 (m, 5H), 1.49-1.57 (m, 2H), 1.59-1.73 (m, 5H), 1.81-1.83 (m, 1H), 2.29 (br. s, 2H), 2.60 (dd, *J* = 4.0 and 6.0 Hz, 1H), 2.65-2.70 (m, 1H), 2.86-2.89 (m, 1H), 3.61-3.63 (td, *J* = 1.6 and 6.4 Hz, 2H).

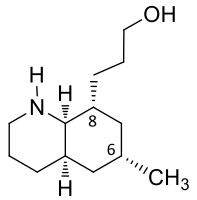
^{13}C NMR (100.6 MHz, 50 °C) δ: 21.0 (C-6), 24.5 (C-3), 27.7 (C-4), 28.0 (*C*$H_2CH_2CH_2OH$), 28.6 (*C*H_2CH_2OH), 29.7 (C-5), 30.2 (C-7), 33.9 (C-4a), 36.3 (C-8), 44.0 (C-2), 59.3 (C-8a), 62.9 (*C*H_2OH).

At a low temperature (– 23 ºC), the ^{13}C spectrum clearly showed two sets of sharp lines for each carbon, thus pointing out the presence of two conformers in approximately a 1:1 ratio.

^{1}H NMR (400 MHz, – 23 °C) δ: 0.75-0.90 (m, 1H), 1.15-1.65 (m, 16H), 1.86 (br. s, 1H), 2.50-2.61 (m, 2H), 3.00-3.10 (m, 1H), 3.50 (br. s, 2H).

^{13}C NMR (100.6 MHz, – 23 °C) δ: 20.1 and 20.6 (C-6), 21.1 and 25.9 (C-3), 23.8 and 31.4 (C-7), 24.1 and 30.6 (C-4), 24.6 and 30.6 (C-5), 26.6 and 28.0 (*C*$H_2CH_2CH_2OH$), 28.0 and 29.8 (*C*H_2CH_2OH), 29.8 and 38.7 (C-8), 30.8 and 35.4 (C-4a), 38.7 and 46.9 (C-2), 57.6 and 58.4 (C-8a), 61.4 and 61.8 (*C*H_2OH).

HMRS calculated for $[C_{12}H_{23}NO + H]^+$: 198.1852; found: 198.1853.



4a*R*,6*R*,8*R*,8a*R*)-8-(3-Hydroxypropyl)-6-methyldecahydroquinoline (77)

Operating as in the preparation of decahydroquinoline **73**, starting from **64a** (180 mg, 0.52 mmol) in CH_3OH (6 mL), and 40% $Pd(OH)_2$ (72 mg), decahydroquinoline **77** (96 mg, 87%) was obtained as a colourless oil.

IR (film): 3380, 2923 cm^{-1}.

$[\alpha]^{22}_D$ – 6.3 (*c* 0.95, $CHCl_3$).

^{1}H NMR (400 MHz) δ: 0.65-0.74 (m, 1H), 0.80-0.92 (m, 3H, CH_3), 1.16-1.33 (m, 3H), 1.42-1.52 (m, 3H), 1.60-1.79 (m, 6H), 1.87-2.11 (m, 2H), 2.90-3.12 (m, 4H), 3.62-3.66 (m, 2H), 4.78 (br. s, 1H, OH).

Several of the signals in the ^{13}C NMR spectrum of **77** at 25 °C were broad and ill-defined, even not observed, thus indicating the existence of a slow conformational equilibrium.

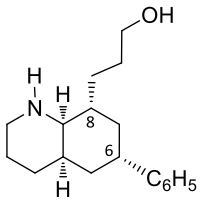
^{13}C NMR (100.6 MHz) δ: 22.4 (CH_3), 25.2 (C-4), 26.8 (C-3, C-8), 28.0 (*C*$H_2CH_2CH_2OH$), 28.3 (*C*H_2CH_2OH), 36.3 (C-4a), 39.1 (C-5), 40.3 (C-7), 40.5 (C-2), 58.1 (C-8a), 62.7 (*C*H_2OH).

At low temperature (– 23 °C) the spectra showed sharp lines.

^{1}H NMR (400 MHz, – 23 °C) δ: 0.68-0.72 (m, 2H), 0.84 (d, *J* = 6.6 Hz, 3H), 1.12-1.25 (m, 2H), 1.30-1.74 (m, 11H), 2.01 (br. s, 2H), 2.66-2.76 (m, 3H), 3.58-3.68 (m, 2H).

^{13}C NMR (100.6 MHz, – 23 °C) δ: 22.5 (CH_3), 24.7 (C-4), 25.8 (C-3), 26.5 (*C*$H_2CH_2CH_2OH$), 27.5 (C-8, *C*H_2CH_2OH), 30.4 (C-6), 35.6 (C-4a), 38.7 (C-5), 39.3 (C-7), 40.0 (C-2), 57.1 (C-8a), 62.0 (*C*H_2OH).

HMRS calculated for $[C_{13}H_{25}NO + H]^+$: 212.2009; found: 212.2006.



(4a*R*,6*R*,8*R*,8a*R*)-8-(3-Hydroxypropyl)-6-phenyldecahydroquinoline (78)

Operating as in the preparation of decahydroquinoline **73**, starting from **66a** (180 mg, 0.44 mmol) in CH_3OH (6 mL), and 40% $Pd(OH)_2$ (72 mg), decahydroquinoline **78** (93 mg, 77%) was obtained as a colourless oil.

IR (film): 3340, 2922 cm^{-1}.

$[\alpha]^{22}_D$ – 38.5 (*c* 1.0, $CHCl_3$).

^{1}H NMR (400 MHz) δ: 1.09-1.22 (m, 2H, H-5, C*H*$_2$CH$_2$CH$_2$OH), 1.40-1.50 (m, 3H, H-3, H-4, C*H*$_2$CH$_2$OH), 1.59-1.69 (m, 5H, H-4, H-7, C*H*$_2$CH$_2$CH$_2$OH, C*H*$_2$CH$_2$OH), 1.72-1.83 (m, 1H, H-3), 1.89 (dc, *J* = 3.2 and 12.8 Hz, 1H, H-5), 1.96-2.10 (m, 2H, H-4a, H-8), 2.60-2.74 (m, 6H, H-2, H-6, H-8a, NH, OH), 3.55 (dc, *J* = 10.8, 6.4 Hz, 2H, H-3.1), 7.08-7.13 (m, 3H, H-Ar), 7.19-7.23 (m, 2H, H-Ar).

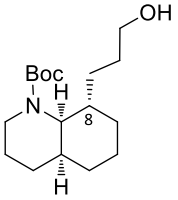
^{13}C NMR (100.6 MHz) δ: 25.5 (C-4), 27.3 (C-3), 28.2 (*C*H$_2$CH$_2$CH$_2$OH), 28.7 (*C*H$_2$CH$_2$OH), 31.9 (C-8), 37.1 (C-4a), 38.4 (C-6), 39.4 (C-5), 39.5 (C-2), 39.8 (C-7), 58.2 (C-8a), 62.7 (*C*H$_2$OH), 126.0 (C-Ar), 126.7 (C-Ar), 128.3 (C-Ar), 146.8 (C-*i*).

At a low temperature (– 23 °C) the spectrum did not show any significant changes.

^{1}H NMR (400 MHz, – 23 °C) δ: 1.12-1.28 (m, 3H), 1.30-1.74 (m, 8H), 1.80-1.88 (m, 2H), 1.98-2.19 (m, 2H), 2.52-2.78 (m, 4H), 3.48-3.68 (m, 2H), 4.65 (br. s, 1H), 7.10-7.32 (m, 5H).

^{13}C NMR (100.6 MHz, – 23 °C) δ: 24.8 (C-4), 26.1 (C-3), 27.7 (*C*H$_2$CH$_2$CH$_2$OH), 28.0 (*C*H$_2$CH$_2$OH), 31.0 (C-8), 36.0 (C-4a), 38.0 (C-6), 38.6 (C-5), 38.9 (C-7), 39.2 (C-2), 57.3 (C-8a), 62.0 (*C*H$_2$OH), 126.0 (C-Ar), 126.7 (C-Ar), 128.3 (C-Ar), 146.5 (C-*i*).

HMRS calculated for $[C_{18}H_{27}NO + H]^+$: 274.2165; found: 274.2173.



(4a*S*,8*S*,8a*R*)-1-(*tert*-Butoxycarbonyl)-8-(3-hydroxypropyl)decahydroquinoline (79)

A solution of decahydroquinoline **62a** (128 mg, 0.39 mmol) and Boc_2O (233 mg, 1.07 mmol)in CH_3OH (9 mL) was hydrogenated at rt for 8 h at atmospheric pressure in the presence of 40% $Pd(OH)_2$ (51 mg). The catalyst was removed by filtration and the solvent was evaporated. The resultin oil was chromatographed (95:5 hexane–EtOAc) to afford *cis*-decahydroquinoline **79** (86 mg, 74%) as a colorless oil.

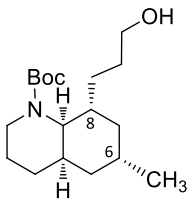
IR (film): 1687, 3443 cm^{-1}.

$[\alpha]^{22}_D$ + 13.3 (*c* 0.35, CH_3OH).

^{1}H NMR (400 MHz) δ: 1.00-1.10 (m, 2H, CH_2), 1.35-1.55 (m, 8H, H-3, H-6, C*H*$_2$CH$_2$CH$_2$OH, C*H*$_2$CH$_2$OH), 1.45 [s, 9H, $(CH_3)_3$], 1.61-1.86 (m, 7H, H-4a, H-6, H-8, *C*H$_2$CH$_2$CH$_2$OH, OH), 2.57-2.71 (m, 1H, H-2), 3.50-3.64 (m, 2H, C*H*$_2$OH), 3.74-4.07 (m, 2H, H-2, H-8a).

^{13}C NMR (100.6 MHz, 52 °C) δ: 20.9 (C-6), 24.8 (C-3), 26.2 (*C*H$_2$CH$_2$CH$_2$OH), 27.9 (C-4), 28.5 [$(CH_3)_3$], 29.6 (*C*H$_2$CH$_2$OH), 31.4 (C-5), 31.7 (C-7), 33.1 (C-4a), 35.9 (C-8), 38.0 and 39.2 (C-2), 56.6 and 58.6 (C-8a), 63.4 (*C*H$_2$OH), 79.1 [*C*$(CH_3)_3$], 155.4 (*C*O).

HMRS calculated for $[C_{17}H_{31}NO_3 + H]^+$: 298.2377; found: 298.2379.



(4a*R*,6*R*,8*R*,8a*R*)-1-(*tert*-Butoxycarbonyl)-8-(3-hydroxypropyl)-6-methyldecahydroquinoline (80)

Operating as in the preparation of decahydroquinoline **79**, from decahydroquinoline **64a** (180 mg, 0.52 mmol) in CH_3OH (7 mL), Boc_2O (137 mg, 0.63 mmol), and 40% $Pd(OH)_2$ (72 mg), decahydroquinoline **80** (122 mg, 75%) was obtained after flash-column chromatography (95:5 hexane–EtOAc) as a colourless oil.

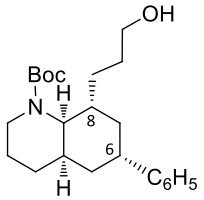
IR (film): 1690, 3412 cm^{-1}.

$[\alpha]^{22}_D$ + 12.3 (*c* 1.0, $CHCl_3$).

^{1}H NMR (400 MHz, 50 °C) δ: 0.60-0.79 (m, 1H, H-7), 0.86 (d, *J* = 6.4 Hz, 3H, CH_3), 1,00-1.29 (m, 1H, H-5), 1.38-1.51 (m, 7H, H-3, H-4, H-5, C*H*$_2$CH$_2$CH$_2$OH, C*H*$_2$CH$_2$OH), 1.45 [s, 9H, $(CH_3)_3$], 1.54-1.64 (m, 2H, H-6, C*H*$_2$CH$_2$CH$_2$OH), 1.65-1.76 (m, 2H, H-4, H-7), 1.81-1.88 (m, 3H, H-4a, H-8, OH), 2.55-2.70 (m, 1H, H-2), 3.53-3.63 (m, 2H, C*H*$_2$OH), 3.71-4.08 (m, 2H, H-2, H-8a).

^{13}C NMR (100.6 MHz, 50 °C) δ: 22.4 (CH_3), 25.6 (C-3), 26.0 and 26.3 (*C*H$_2$CH$_2$CH$_2$OH), 26.7 and 26.8 (C-6), 27.6 and 28.3 (C-4), 28.5 [$(CH_3)_3$], 29.4 and 29.8 (*C*H$_2$CH$_2$OH), 32.6 and 32.9 (C-4a), 36.0 and 36.3 (C-8), 38.0 and 39.3 (C-5), 40.1 and 40.3 (C-7), 40.5 and 40.6 (C-2), 56.4 and 58.4 (C-8a), 63.3 (*C*H$_2$OH), 79.1 [*C*$(CH_3)_3$], 155.4 (*C*O).

HMRS calculated for $[C_{13}H_{26}NO + H]^+$ (-Boc): 212.2009; found: 212.2006.



(4a*R*,6*R*,8*R*,8a*R*)-1-(*tert*-Butoxycarbonyl)-8-(3-hydroxypropyl)-6-phenyldecahydroquinoline (81)

Operating as in the preparation of decahydroquinoline **79**, from decahydroquinoline **66a** (180 mg, 0.45 mmol) in CH_3OH (7 mL), Boc_2O (116 mg, 0.53 mmol) and 40% $Pd(OH)_2$ (72 mg), decahydroquinoline **81** (135 mg, 81%) was obtained after flash-column chromatography (95:5 hexane–EtOAc) as a colourless oil.

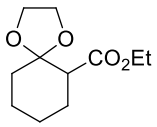
IR (film) 1685, 3441 cm^{-1}.

$[\alpha]^{22}_D$ + 5.7 (*c* 1.0, $CHCl_3$).

^{1}H NMR (400 MHz) δ: 1.10-1.34 (m, 3H, H-7, C*H*$_2$CH$_2$CH$_2$OH), 1.40-1.51 (m, 3H, H-3, H-4, C*H*$_2$CH$_2$OH), 1.48 [s, 9H, $(CH_3)_3$], 1.63-1.93 (m, 4H, C*H*$_2$CH$_2$OH, H-3, H-4, OH), 1.97-2.08 (m, 3H, H-4a, H-7, H-8), 2.61-2.81 (m, 3H, H-5, H-6), 3.51-3.64 (m, 2H, C*H*$_2$OH), 3.86-4.13 (m, 3H, H-2, H-8a), 7.18-7.22 (m, 3H, H-Ar), 7.27-7.31 (m, 2H, H-Ar).

^{13}C NMR (100.6 MHz) δ: 25.3 (C-3), 25.8 and 26.2 (C-4), 27.3 and 28.1 (*C*H$_2$CH$_2$CH$_2$OH), 28.4 and 28.5 [$(CH_3)_3$], 29.2 and 29.6 (*C*H$_2$CH$_2$OH), 32.8 and 33.2 (C-8), 35.9 and 36.2 (C-4a), 37.9 and 38.1 (C-5), 38.2 (C-6), 39.0 and 39.2 (C-7), 39.2 and 39.4 (C-2), 55.9 and 58.0 (C-8a), 63.1 (*C*H$_2$OH), 79.2 and 79.3 [*C*$(CH_3)_3$], 126.0 (C-Ar), 126.7 (C-Ar), 128.3 (2C-Ar), 146.5 (C-*i*), 155.3 and 155.4 (*C*O).

HMRS calculated for $[C_{23}H_{35}NO_3 + H]^+$: 374.2690; found: 374.2689.



2-Ethoxycarbonylcyclohexanone ethylene acetal (84)[203]

Ethylene glycol (655 μL, 11.8 mmol) was added to a solution of ethyl 2-oxocyclohexanecarboxylate (2 g, 11.8 mmol) and PTSA (223.5 mg, 1.17 mmol) in benzene (16 mL). The reaction mixture was stirred at the temperature of reflux for 19 h, with azeotropic elimination of water by Dean-Stark apparatus. The cooled mixture was diluted with Et_2O (15 mL) and washed with saturated aqueous $NaHCO_3$ solution (2 x 10 mL) and brine (2 x 10 mL). The organic layer was dried and concentrated to afford the ester **84** as a yellow oil (2.51 g, 99 %).

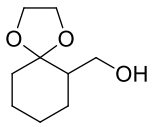
IR (film): 2937, 1732 cm^{-1}.

^1H NMR (300 MHz) δ: 1.26 (t, *J* = 6.0 Hz, 3H, CH_3), 1.43-1.52 (m, 1H), 1.58-1.72 (m, 4H), 1.80-1.97 (m, 3H), 2.65 (dd, *J* = 6.0 and 8.1 Hz, 1H, H-5), 3.87-3.97 (m, 4H, OCH_2CH_2O), 4.13 (q, *J* = 7.2 Hz, 2H, CO_2CH_2).

^{13}C NMR (75.4 MHz) δ: 13.8 (CH_3), 22.5 (CH_2), 23.0 (CH_2), 26.9 (CH_2), 34.2 (CH_2), 49.5 (CH), 59.7 (CH_2), 64.1 (CH_2), 64.5 (CH_2), 108.2 (Cq), 171.8 (CO_2).

HMRS calculated for $[C_{11}H_{18}O_4 + H]^+$: 215.1278; found: 215.1275.

[203] Schmid, G.H.; Rabai, J. Synthesis, *1988,* 332.

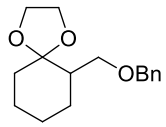


2-Hydroxymethylcyclohexanonethylene acetal (85)

$LiAlH_4$ (986 mg, 30 mmol) was slowly added to a solution of ester **84** (2.52 g, 11.8 mmol) in anhydrous THF (22 mL) at 0 °C, under inert atmosphere. The reaction mixture was allowed to react at room temperature for 24 h. The crude product mixture was cooled at 0 °C and brine (20 mL) was slowly added, until stop the hydrogen evolution. The mixture was heated at reflux temperature for 15 min. The cooled mixture was exctracted with Et_2O and the organic layer was concentrated to afford alcohol **85** (1.74 g, 86%) as a yellow oil.

^{1}H NMR (300 MHz) δ: 1.21-1.54 (m, 4H), 1.63-1.90 (m, 5H), 3.01 (br. S, 1H), 3.49-3.54 (m, 1H), 3.71-3.78 (m, 1H), 3.97-4.02 (m, 4H).

^{13}C NMR (75.4 MHz) δ: 23.3 (CH_2), 24.1 (CH_2), 26.7 (CH_2), 33.9 (CH_2), 45.5 (CH), 63.0 (CH_2), 63.9 (CH_2), 64.2 (CH_2), 111.2 (Cq).



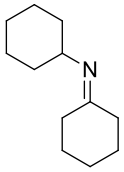
2-[(Benzyloxy)methyl]cyclohexanone ethylene acetal (86)

NaH (80 mg, 3.3 mmol) was slowly added to a solution of **85** (230 mg, 1.33 mmol) in anhydrous THF (5 mL) at 0 °C, under inert atmosphere, and the resulting suspension was stirred at this temperature for 15 min. Tetrabutyl ammonium iodide (15 mg, 0.04 mmol) and benzyl bromide (190.2 μL, 1.60 mmol) were added and the mixture was heated at reflux temperature for 18 h; then H_2O was slowly added to the cooled mixture until stops the evolution of hydrogen. The resulting mixture was extracted with Et_2O (4 x 10 mL) and the organic layer were dried and concentrated to afford the crude oil, which was purified by flash-column chromatography (7:3 hexane–EtOAc), affording compound **86** (266 mg, 75%) as a yellow oil.

IR (film): 2933, 2862 cm^{-1}.

^1H NMR (300 MHz) δ: 1.26-1.51 (m, 5H), 1.62-1.74 (m, 2H), 1.97-2.04 (m, 2H), 3.31 (t, *J* = 8.7 Hz, 1H, H-1.2), 3.71 (dd, *J* = 3.6 and 9.3 Hz, 1H), 3.88-4.00 (m, 4H, H-1.1), 4.00-4.55 (m, 2H), 7.26-7.42 (m, 5H).

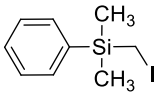
^{13}C NMR (75.4 MHz) δ: 23.8 (CH_2), 24.2 (CH_2), 27.8 (CH_2), 34.8 (CH_2), 44.8 (CH), 64.5 (CH_2), 64.6 (CH_2), 69.9 (CH_2), 73.1 (CH_2), 109.9 (Cq), 127.3 (C-Ar), 127.5 (C-Ar), 128.3 (C-Ar), 128.8 (C-Ar), 129.0 (C-Ar), 138.7 (C-*i*).



_N_-Cyclohexylidenecyclohexylamine (88)

Cyclohexylamine (2 g, 20.2 mmol) was added to a mixture of fresh distilled cyclohexanone (1.05 mL, 10.1 mmol) and PTSA (192.1 mg, 1.01 mmol) in fresh distilled DCE (31 mL), in presence of 4 Å molecular sieves (4 g), and the reaction mixture was allowed to react at room temperature for 4 h. The mixture was quenched with TEA (1 mL) and the resulting solution was washed with aqueous KOH (2N, 2 x 10 mL) and the organic layer concentrated, to afford the imine **88** (1.8 g, 99%) as a oil. The product is unstable and was immediately used for the next reaction.

^{1}H NMR (300 MHz) δ: 1.17-1.47 (m, 7H), 1.58-1.85 (m, 8H), 2.23-2.33 (m, 4H), 3.21-3.30 (m, 1H).



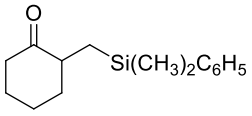
(Iodomethyl)dimethylphenylsilane[204]

To a solution of (chloromethyl)dimethylpenylsilane (3.0 mL, 17 mmol) in acetone (100 mL) sodium iodide (5.0 g, 33 mmol) was added. The reaction mixture was heated at reflux temperature for 24 h. The cooled reaction mixture was concentrated to afford a white solid which was partioned between H_2O (100 mL) and hexane (100 mL). The layers were separated and the aqueous layer was extracted with hexane (3 x 100 mL). The combined organic extacts were washed with brine (2x 50 mL), dried and concentrated. The residue was purified by microdistillation (80 °C, 0 torr) affording the desired product (4.4 g, 98 %) as a colorless liquid.

^{1}H NMR (300 MHz) δ: 0.67 (s, 6H, CH_3), 2.40 (s, 2H, CH_2), 7.70-7.80 (m, 2H, H-Ar), 7.61-7.62 (m, 3H, H-Ar).

^{13}C NMR (75.4 MHz) δ: -13.5 (*C*H_2I), -2.9 (2CH_3), 127.9 (2C-Ar), 129.5 (2C-Ar), 133.6 (C-Ar), 136.6 (C-*i*).

[204] Smitrovich, J.H.; Woerpel, k.A. *J. Am. Chem. Soc.* **1998**, *49*, 12998–12999.



2-(Dimethylphenylsilylmethyl)cyclohexanone (89)[205]

LDA (1.1 mL of a 2.0 M solution in THF/heptanes/ethylbenzene, 2.24 mmol) was added dropwise to a solution of imine **88** (400 mg, 2.24 mmol) in anhydrous THF (5 mL) at –78 °C, and the resulting mixture was stirred at this temperature for 1 h; then (iodomethyl)dimethylphenylsilane (740 mg, 2.7 mmol) was added dropwise to the cold mixture, and the stirring was continued for an additional 45 min. Et_2O (5 mL) was added, and the resulting mixture was washed with brine (2 x 5 mL). The product mixture was diluted with 5 mL of buffer solution (HOAc–H_2O– NaOAc 25 mL:25 mL:12.5 g) and the resulting mixture was stirred for 10 min. The separated organic layer was washed with aqueous brine solution (2 x 5 mL) and saturated aqueous $NaHCO_3$ (5 x 5 mL), dried and concentrated. The crude was purified by microdistillation (120 °C and then 144 °C, 2 Torr) affording the ketone **89** (320 mg, 58%) as a colorless oil.

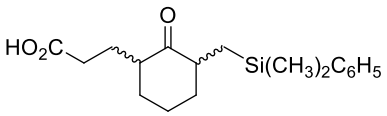
IR (film): 2925, 2832 cm^{-1}.

^{1}H NMR (400 MHz) δ: 0.29 (s, 6H, C*H*$_3$), 0.63 (dd, *J* = 7.2 and 15.0 Hz, 1H, C*H*$_2$Si),1.32-1.41 (m, 1H, H-5), 1.42 (d, *J* = 6 and 15.0 Hz, 1H, C*H*$_2$Si), 1.56-1.69 (m, 3H, H-3, H-4, H-5), 1.75-1.79 (m, 1H, H-4), 1.98-2.05 (m, 1H, H-5), 2.19-2.26 (m, 1H, H-6), 2.35-2.42 (m, 2H, H-2, H-6), 7.34-7.40 (m, 3H, H-Ar), 7.41-7.52 (m, 2H, H-Ar).

^{13}C NMR (100.6 MHz) δ: −2.46 (*C*H$_3$),–1.98 (CH$_3$), 15.5 (*C*H$_2$Si), 25.1 (C-4), 28.1 (C-3), 37.2 (C-5), 41.7 (C-6), 47.2 (C-2), 127.7 (2C-Ar), 128.8 (2C-Ar), 133.5 (C-Ar), 139.1 (C-*i*), 213.3 (*C*O).

HMRS calculated for $[C_{15}H_{22}OSi + NH_4]^+$: 264.1778; found: 264.1775.

[205] *J. Chem. Soc. Perkin Trans. II* **1980**, 1493-1498.



[3-(2-Dimethylphenylsilylmethyl)-2-oxocyclohexyl]propionic acid (91)

Operating as in the preparation of amine **44**, from ketone **89** (343 g, 1.39 mmol), LDA (695 μL of a 2.0 M solution in THF/heptanes/ethylbenzene, 1.39 mmol), TMSCl (210 μL, 1.7 mmol) and THF (2 mL), the corresponding silane was obtained as a yellow oil. Then, *N*,*N*-(dimethyl)methylamine chloride (130 mg, 1.39 mmol) was added to a solution of silane and CH_2Cl_2 (2 mL), and amine **90** was obtained as a yellow oil (475 g, 99%, 2.5:1 *cis:trans* mixture).

Spectroscopic and analytical data for compound **90**

IR (film): 2934, 2858, 1709 cm^{-1}.

^1H NMR (400 MHz) δ: 0.20 (s, 6H, SiC*H*$_3$), 0.21 (s, 6H, SiC*H*$_3$), 0.54 (dd, *J* = 7.6 and 15.2 Hz, 2H), 0.62 (dd, *J* = 6.4 and 14.8 Hz, 2H), 1.17 (t, *J* = 7.6 Hz, 2H), 1.22-1.46 (m, 1H), 1.27 (t, *J* = 7.2 and 14.8 Hz, 2H), 1.33-1.39 (m, 3H), 1.53-1.68 (m, 6H), 1.79-1.84 (m, 2H), 2.08 (s, 6H, NC*H*$_3$), 2.10 (s, 6H, NC*H*$_3$), 2.14 (dd, *J* = 7.2 and 12.0 Hz, 2H), 2.29-2.33 (m, 2H), 2.48-2.61 (m, 6H), 7.24-7.27 (m, 6H), 7.41-7.45 (m, 4H)

^{13}C NMR (100.6 MHz) δ: – 2.83 and – 2.54 (*C*H$_3$),– 2.47 and 1.94 (*C*H$_3$), 15.0 and 16.4 (CH_2), 20.6 and 25.5 (CH_2), 31.0 and 34.1 (CH), 37.0 and 38.6 (CH_2), 44.2 and 47.3 (CH), 45.4 and 45.7 (N*C*H$_3$), 47.8 and 49.0 (CH), 58.8 and 59.7 (CH_2), 125.4 (C-Ar), 127.6 (2C-Ar), 128.2 (2C-Ar), 128.7 (2C-Ar), 133.4 (2C-Ar), 139.2 (C-*i*), 213.1 and 214.9 (C-*i*).

HMRS calculated for $[C_{18}H_{29}NOSi+H]^+$: 304.2091; found: 304.2101.

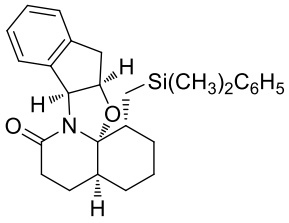
Operating as in the formation of acid **49**, from amine **90** (210 mg, 0.69 mmol), diethyl malonate (122 g, 0.76 mmol), NaOH (11.1 mg, 0.28 mmol) and toluene (2 mL), acid **91** was obtained as an oil (131 mg, 83%, 2:1 *cis:trans* mixture).

Spectroscopic and analytical data for acid **91**

^{1}H NMR (400 MHz) δ: 0.26 (d, *J* = 3.2 Hz, 6H, C*H*$_3$), 0.29 (d, *J* = 10 Hz, 6H, C*H*$_3$), 0.57 (d, *J* = 6 Hz, 1H), 0.60 (d, *J* = 6 Hz, 1H), 1.26-1.42 (m, 5H), 1.43-1.74 (m, 5H), 2.00-2.12 (m, 4H), 2.23-2.41 (m, 5H), 2.94 (d, *J* = 8.4 Hz, 2H), 3.04 (d, *J* = 12.8 Hz, 2H), 3.41 (s, 1H), 3.42 (s, 1H), 7.32-7.35 (m, 6H), 7.47 (m, 4 H), 9.25 (br. S, 2H, OH).

^{13}C NMR (100.6 MHz) δ: – 2.5 (*C*H$_3$),– 2.4 (*C*H$_3$),– 1.9 (*C*H$_3$),– 1.9 (*C*H$_3$), 15.2 (CH$_2$), 15.1 (CH$_2$), 24.5 (CH$_2$), 24.9 (CH$_2$), 25.4 (CH$_2$), 25.6 (CH$_2$), 31.5 (CH$_2$), 31.6 (CH$_2$), 35.5 (CH$_2$), 35.6 (CH$_2$), 39.0 (CH$_2$), 39.0 (CH$_2$), 47.7 (CH), 47.8 (CH), 49.8 (CH), 50.3 (CH), 127.7 (2C-Ar), 127.7 (2C-Ar), 127.8 (2C-Ar), 128.7 (C-Ar), 128.9 (2C-Ar), 133.5 (C-Ar), 138.5 (C-*i*), 139.2 (C-*i*), 179.0 (CO$_2$), 179.4 (*C*O$_2$), 213.5 (*C*O), 214.3 (*C*O).

HMRS calculated for $[C_{18}H_{26}NO_3Si+H]^+$: 320.1651; found: 320.1653



(1*R*,4a*S*,8a*S*,13a*R*,14a*R*)-1-[(Dimethylphenylsilyl)methyl]-7-oxo-3-phenyl-1,2,3,4,4a,5,6,7,8a,13,13a,14a-dodecahydroindenol[1',2':4,5]oxazolo-[2,3-j]quinolone (93a)

Operating as in the preparation of lactam **33a**, from oxoacid **91** (359 mg, 1.13 mmol) and (1*S*,2*R*)- (-)-*cis*-1-amino-2-indanol (252 g, 1.70 mmol) in anhydrous toluene (12 mL) containing anhydrous $MgSO_4$ (272 mg), a 6:1 (calculated by ^{1}H NMR) mixture of lactams **93a** and **93b** (360 mg, 74%) and small amount of pure **93a** were obtained after flash-column chromatography (1:1 hexane–CH_2Cl_2 to CH_2Cl_2).

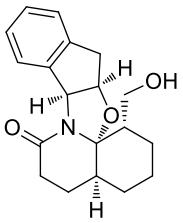
IR (NaCl): 1658, 1392 cm^{-1}.

$[\alpha]^{22}_D$ + 148.6 (*c* 0.33, CH_3OH).

^{1}H NMR (400 MHz) δ: –0.20 (dd, *J* = 10.8 and 14.8 Hz, 1H),– 0.09 (s, 3H, CH_3), 0.02 (d, *J* = 15.6 Hz), 0.04 (s, 3H), 0.32 (d, *J* = 13.6 Hz), 1.21-1.14 (m, 1H), 1.32-1.47 (m, 4H), 1.64-1.71 (m, 2H), 1.83-1.90 (m, 2H), 1.99-2.09 (m, 1H), 2.31-2.41 (m, 1H), 3.19 (d, *J* = 2.8 Hz, 2H), 4.75-4.78 (m, 1H), 5.87 (d, *J* = 5.6 Hz, 1H), 7.19-7.32 (m, 8H), 7.54 (d, *J* = 5.6 Hz).

^{13}C NMR (100.6 MHz) δ:– 2.6 (CH_3),– 2.2 (CH_3), 14.2 (*C*H_2Si), 18.8 (C-5), 19.8 (C-3), 26.6 (C-4), 28.2 (C-2), 30.7 (C-6), 36.1 (C-4a), 38.1 (C-13), 38.5 (C-1), 66.0 (C-8a), 77.7 (C-13a), 99.3 (C-9), 124.9 (C-Ar), 126.4 (C-Ar), 127.4 (C-Ar), 127.6 (C-Ar), 128.2 (C-Ar), 128.7 (C-Ar), 139.1 (C-*i*), 141.0 (C-*i*), 141.7 (C-*i*), 171.3 (*C*O).

HMRS calculated for $[C_{27}H_{33}NO_2Si + H]^+$: 432.2353; found: 432.2365.



(1*R*,4a*S*,8a*S*,13a*R*,14a*R*)-1-(Hydroxymethyl)-7-oxo-3-phenyl-1,2,3,4,4a,5,6,7,8a,13,13a,14a-dodecahydroindenol[1',2':4,5]oxazolo-[2,3-j]quinolone (94)

A solution of the 6:1 mixture of lactam **93a** and **93b** (110 mg, 0.26 mmol) and tetrafluoroboric acid diethyl ether complex (1 mL, 0.51 mmol), in anhydrous CH_2Cl_2 (2 mL) was stirred for 1 h. The mixture was concentrated and the residue was taken up with DMF (1 mL). Anhydrous potassium fluoride (61.4 mg, 1.05 mmol) and *meta*-chloroperbenzoic acid (217 mg, 0.88 mmol) were added and the pale yellow suspension was stirred for 16 h. The resulting mixture was filtered and concentrated. Flash-column chromatography on amine-functionalized silica gel (1:1 hexane–EtOAc) afforded lactam **94** (49 mg, 60%) as an oil.

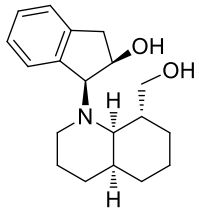
IR (film): 1658, 1392 cm^{-1}.

$[\alpha]^{22}_D$ + 148.6 (*c* 0.33, CH_3OH).

^{1}H NMR (400 MHz) δ : 1.40–1.45 (m, 2H, H-3, H-4), 1.50–1.55 (m, 2H, H-2, H-3), 1.62–1.70 (m, 2H, H-1, H-4), 1.80–1.93 (m, 4H, H-2, H-4a, H-5), 2.52–2.56 (m, 2H, H-6), 2.79 (dd, *J* = 4.8 and 11.6 Hz, 1H, C*H*$_2$OH), 2.89 (dd, *J* = 4.8 and 11.6 Hz, 1H, C*H*$_2$OH), 3.18 (d, *J* = 2.8 Hz, 2H, H-13), 4.74 (q, *J* = 2.8 Hz, 1H, H-13a), 5.88 (d, *J* = 5.2 Hz, 1H, H-8a), 7.26–7.30 (m, 3H, H-9, H-10, H-12), 7.52 ppm (d, *J* = 6.8 Hz, 1H, H-11).

^{13}C NMR (100.6 MHz) δ: 18.7 (C-5), 19.1 (C-3), 25.7 (C-4), 26.5 (C-2), 28.3 (C-6), 37.4 (C-13), 38.2 (C-4a), 42.3 (C-1),62.5 (*C*H$_2$OH), 65.9 (C-8a), 77.8 (C-13), 98.2 (C-14a), 125.4 (C-Ar), 126.0 (C-Ar), 127.8 (C-Ar), 128.8 (C-Ar), 140.2 (C-*i*), 140.8 (C-*i*), 171.8 (*C*O).

HMRS calculated for $[C_{19}H_{23}NO_3 + H]^+$: 314.1756; found: 314.1758.



(4a*S*,8*R*,8a*S*)-1-[(1*S*,2*R*)-2-Hydroxy-1-indanyl]-8-(hydroxymethyl)decahydroquinoline (95)

Operating as in the preparation of decahydroquinoline **62a**, from $LiAlH_4$ (30 mg, 0.80 mmol) and $AlCl_3$ (33 mg, 0.24 mmol) in anhydrous THF (3 mL) and a solution of lactams **94** (38 mg, 0.12 mmol) in anhydrous THF (1 mL), decahydroquinoline **95** (27 mg, 75%) was obtained after flash-column chromatography (from CH_2Cl_2 to 95:5 CH_2Cl_2–CH_3OH) as a colourless oil.

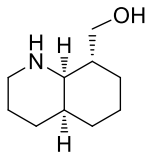
IR (NaCl) 3301 cm^{-1}.

$[\alpha]^{22}_D$ – 4.8 (*c* 0.9, CH_3OH).

Several of the signals in the ^1H and ^{13}C NMR spectrum of **95** at 25 °C were broad and ill-defined, even not observed, thus indicating the existence of a slow conformational equilibrium.

^1H NMR (400 MHz) δ: 0.99-1.73 (m, 11H), 2.13-2.23 (m, 3H), 2.70-2.80 (m, 2H), 2.83-2.89 (dd, *J* = 8.4 and 15.6 Hz, 1H), 3.00-3.07 (m, 2H), 3.58-3.60 (m, 1H), 3.70 (dd, *J* = 4.4 and 10.8 Hz, 1H), 4.27-4.34 (m, 2H), 7.10-7.20 (m, 3H), 7.37 (d, *J* = 6.8 Hz, 1H).

^{13}C NMR (100.6 MHz) δ: 20.2 (CH_2), 23.0 (CH_2), 29.7 (CH_2), 31.2 (CH), 39.6 (CH_2), 67.9 (CH_2), 125.4 (C-Ar), 126.3 (C-Ar), 127.3 (C-Ar), 128.4 (C-Ar), 140.2 (C-*i*), 142.5 (C-*i*).



(4a*S*,8*S*,8a*R*)-8-(Hydroxymethyl)decahydroquinoline (82)[206]

A solution of hydrochloride salt of compound **95** (41 mg, 0.11 mmol) in CH_3OH (3 mL), containing 40% $Pd(OH)_2$ (16 mg) was hydrogenated at room temperature for 24 h at atmospheric pressure. The catalyst was removed by filtration over Celite® and the filtrate was concentrated. The residue was taken up in Et_2O (5 mL), and the resulting solution was washed with aqueous NaOH (10%, 2 x 5 mL) and concentrated to afford *cis*-decahydroquinoline **82** (10 mg, 66%) as a colourless oil.

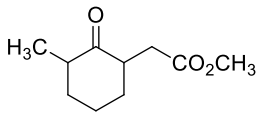
$[\alpha]^{22}_D$ – 2.0 (*c* 0.15, CH_3OH).

^{1}H NMR (400 MHz) δ: 0.74-0.90 (m, 1H), 1.34-1.48 (m, 6H), 1.54-1.57 (m, 1H), 1.70-1.77 (m, 3H), 2.10-2.20 (m, 1H), 2.54-2.70 (br. s, 2H), 2.76-2.84 (m, 3H), 3.50 (t, *J* = 10.4 Hz, 1H, C*H*$_2$OH), 3.61 (dd, *J* = 3.6 and 10.4 Hz, 1H, C*H*$_2$OH).

^{13}C NMR (100.6 MHz) δ: 20.0 (C-6), 25.1 (C-4), 27.8 (C-3), 28.4 (C-7), 31.4 (C-5), 33.4 (C-8), 37.5 (C-4a), 40.0 (C-2), 61.0 (C-8a), 70.7 (*C*H$_2$OH).

[206] a. Crabb, T.A.; Turner, C.H. *J. Chem. Soc. Perkin Trans. II* **1980**, 1778-1782; b. Burrell, A.J.M.; Coldhanm, J.; Oram, N. *Org. Lett*. **2009**, *11*, 1515-1518; c. Pham V.C.; Jossang, A.; Chiaroni, A.; Sévenet, T.; Bodo, B. *Tetrahedron Lett.* **2002**, *43*, 7565-7568.

6.4. Experimental part- Chapter 4



Methyl 3-methyl-2-oxocyclohexaneacetate (97)

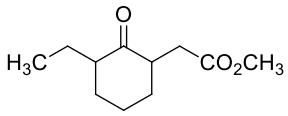
A solution of LDA (13.4 mL of a solution 2.0 M in THF/heptanes/ethylbenzene, 26.7 mmol) was added dropwise to a solution of **34** (3.3 mL, 26.7 mmol) in THF (18 mL) at −78 °C, and the mixture was stirred at this temperature for 20 min. Then, methyl bromoacetate (3.7 mL, 40.1 mmol) and HMPA (5.6 mL, 32.1 mmol) were added at −78 °C, and the stirring was continued at this temperature for 2.5 h. Saturated aqueous NH_4Cl solution (5 mL) was added, and the resulting mixture was extracted with EtOAc (3 x 15 mL). The combined organic extracts were washed with aqueous saturated NaCl solution (2 x 5 mL), dried and concentrated. Flash-column chromatography (hexane to 8:2 hexane–EtOAc) afforded ketoester **97** as a yellow oil (4.9 g, 99 %, 2.6:1 *cis:trans* mixture).

IR (film): 1739, 1711 cm^{-1}.

^1H NMR (400 MHz) δ: 1.02 (d, *J* = 6.4 Hz, 3H, CH_3), 1.21 (d, *J* = 7.6 Hz, 3H, CH_3), 1.30-1.46 (m, 4H, H-6, H-4), 1.74-1.90 (m, 4H, H-5), 2.09-2.18 (m, 6H, H-4, H-6, CH_2CO_2), 2.43-2.53 (m, 2H, H-3), 2.74-2.81 (m, 2H, CH_2CO_2), 2.85-2.93 (m, 2H, H-1), 3.67 (s, 3H, OCH_3), 3.70 (s, 3H, OCH_3).

^{13}C NMR (100.6 MHz) δ: 14.3 and 16.4 (CH_3), 19.8 and 25.1 (C-5), 32.9 and 34.1 (C-4), 33.3 and 34.6 (*C*H_2CO_2), 34.3 and 36.9 (C-6), 43.2 and 45.1 (C-3), 43.9 and 46.9 (C-7), 51.4 and 51.5 (O*C*H_3), 172.8 and 173.0 (*C*O_2), 212.2 and 214.5 (*C*O).

HMRS calculated for $[C_{10}H_{16}O_3 + H]^+$: 185.1172; found: 185.1171.



Methyl 3-ethyl-2-oxocyclohexaneacetate (98)

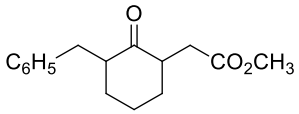
Operating as in the preparation of **97**, from ketone **37** (2.2 mL, 11.9 mmol), LDA (6.0 mL of a solution 2.0 M in THF/heptanes/ethylbenzene, 11.9 mmol), methyl bromoacetate (1.65 mL, 17.9 mmol) and HMPA (2.5 mL, 14.3 mmol) in THF (8 mL), keto ester **98** (1.98 g, 84%, 1.5: 1 *cis:trans* mixture) was obtained as an orange oil after flash-column chromatography (from hexane to 8:2 hexane–EtOAc).

IR (film): 1739, 1705 cm^{-1}.

^{1}H NMR (400 MHz) δ: 0.86-0.94 (m, 6H, C*H*$_3$), 1.16-1.93 (m, 12H), 2.04-2.64 (m, 8H), 2.72-2.81 (m, 2H), 2.84-2.90 (m, 1H), 2.97-3.05 (m, 1H), 3.67 (s, 6H, OC*H*$_3$).

^{13}C NMR (100.6 MHz) δ: 11.4 and 11.5 (CH_3), 20.2 and 21.7 (CH_2), 24.1 and 25.0 (CH_2), 31.4 and 33.4 (CH_2), 33.9 and 34.0 (CH_2), 34.2 and 34.7 (CH_2), 43.1 and 47.1 (CH), 51.2 and 51.7 (CH), 51.7 and 51.9 (O*C*H$_3$), 172.6 and 172.8 (*C*O$_2$), 211.7 and 213.9 (*C*O).

HRMS calculated for $[C_{11}H_{18}O_3 + H]^+$: 199.1329; found: 199.1326.



Methyl 3-benzyl-2-oxocyclohexaneacetate (99)

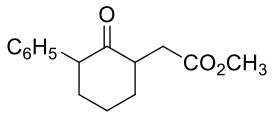
Operating as in the above preparation of **97**, from ketone **38** (1.5 g, 7.97 mmol), LDA (4.0 mL of a solution 2.0 M in THF/heptanes/ethylbenzene, 7.97 mmol), methyl bromoacetate (2.20 mL, 23.8 mmol) and HMPA (2.5 mL, 14.4 mmol) in THF (8 mL), keto ester **99** (1.66 g, 80%, 1.5:1 *cis:trans* mixture) was obtained as a yellow oil after flash-column chromatography (hexane to 8:2 hexane–EtOAc).

IR (film): 1701 cm^{-1}.

^{1}H NMR (400 MHz) δ: 1.24-2.44 (m, 8H), 2.57-3.27 (m, 4H), 3.66 and 3.68 (s, 3H, OC*H*$_3$), 7.13-7.31 (m, 5H).

^{13}C NMR (100.6 MHz) δ: 20.1 and 25.1 (CH_2), 30.2 and 33.2 (CH_2), 34.2 and 34.2 (CH_2), 34.4 and 34.9 (CH_2), 35.2 and 36.7 (CH_2), 44.0 and 47.3 (CH), 51.5 and 52.3 (O*C*H$_3$), 51.6 (CH), 125.9 and 126.4 (C-Ar), 128.3 and 128.3 (2C-Ar), 128.5 and 129.1 (2C-Ar), 139.0 and 140.3 (C-*i*), 172.8 and 173.1 (*C*O$_2$), 211.5 and 213.4 (*C*O).

HRMS calculated for $[C_{16}H_{20}O_3 + NH_4]^+$: 278.1751; found: 278.1751.



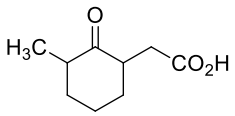
Methyl 2- oxo-3-phenylcyclohexaneacetate (100)[207]

Operating as in the preparation of **97**, from ketone **96** (2.0 g, 11.5 mmol), LDA (2.0 M in THF/heptanes/ethylbenzene, 5.7 mL, 11.5 mmol), methyl bromoacetate (1.6 mL, 17.2 mmol) and HMPA (2.4 mL, 13.8 mmol) in THF (7.8 mL), keto ester **100** (2.18 g, 77%, 3.4: 1 *cis:trans* mixture) was obtained as an colourless oil after flash chromatography (from hexane to 8:2 hexane–EtOAc).

^{1}H NMR (400 MHz) δ: 1.25-1.27 (m, 1H), 1.54 (dq, *J* = 4.4 and 12.4 Hz, 1H), 1.73-1.79 (m, 2H), 1.88-1.98 (m, 2H), 2.03-2.11 (m, 7H), 2.20 (dd, *J* = 6.0 and 16.8 Hz, 2H), 2.57-2.62 (m, 2H), 2.78 (dd, *J* = 8.0 and 16.8 Hz, 2H), 2.95-3.0 (m, 2H), 3.65 (s, 3H, C*H*$_3$), 3.8 (s, 3H, C*H*$_3$), 7.22-7.38 (m, 10H, H-Ar).

^{13}C NMR (100.6 MHz) δ: *cis* isomer 20.8 (CH_2), 30.5 (CH_2), 33.5 (CH_2), 34.3 (CH_2), 44.2 (CH), 51.5 (CH), 53.9 (CH), 126.7 (C-Ar), 127.1 (2C-Ar), 128.7 (2C-Ar), 137.4 (C-*i*), 172.5 (*C*O_2), 211. 7 (*C*O).

[207] Previously described: a. Krafft, M. E.; Cran, J. W. *Synlett* **2005**, *8*, 1263–1266; b. Johnson, C. J.; Adam, J. P.; Braun, M. P.; Senanayake, C. B. W.; Wovkulich, P. M.; Uskokovic, M. R. *Tetrahedron Lett.* **1992**, *33*, 917–918.



(3-Methyl-2-oxocyclohexyl)acetic acid (101)

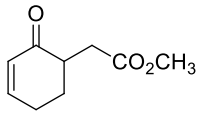
LiOH aqueous solution (1M, 40 mL) was added to a solution of ketoester **97** (700 mg, 3.8 mmol) in THF (40 mL) and the mixture was stirred overnight at room temperature. The pH of the mixture was turn on acid with addition of an aqueous HCl solution (2N). The organic phase was taken up in EtOAc (20 mL) and concentrated affording the acid **101** as a white solid (640 mg, 99%).

IR (film): 2933, 1701 cm^{-1}.

^{1}H NMR (400 MHz) δ: 1.03 (d, *J* = 6.8 Hz, 3H, C*H*$_3$), 1.31-147 (m, 3H), 1.74-1.90 (m, 3H), 2.09-2.24 (m, 3H), 2.43-2.52 (m, 1H), 2.81-2.90 (m, 1H).

^{13}C NMR (100.6 MHz) δ: 14.4 (*C*H_3), 25.2 (CH_2), 34.3 (CH_2), 34.6 (CH_2), 37.0 (CH_2), 45.3 (CH), 46.9 (CH), 178.4 (*C*O_2), 212.4 (*C*O).

HRMS calculated for $[C_9H_{15}O_3 + H]^+$: 171.1016; found: 171.1013.



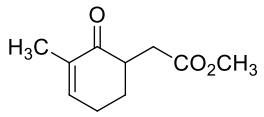
Methyl 2-oxo-3-cyclohexeneacetate (104)[208]

A solution of LDA (2.0 M in THF/heptanes/ethylbenzene, 5.2 mL, 10.4 mmol) was added dropwise to a solution of **102** (1.01 mL, 10.4 mmol) in THF (7 mL) at −78 °C, and the mixture was stirred at this temperature for 20 min. Then, methyl bromoacetate (1.44 mL, 15.6 mmol) and HMPA (2.2 mL, 12.5 mmol) were added at −78 °C, and the stirring was continued at this temperature for an additional 2.5 h. Saturated aqueous NH_4Cl solution (5 mL) was added, and the resulting mixture was extracted with EtOAc (3 x 15 mL). The combined organic extracts were washed with aqueous saturated NaCl solution (2 x 5 mL) and concentrated. Flash-column chromatography (hexane to 8:2 hexane–EtOAc) afforded keto ester **104** as a colorless oil (1.7 g, 97%).

^{1}H NMR (400 MHz) δ: 1.75-1.89 (m, 1H), 2.10-2.16 (m, 1H), 2.24-2.33 (m, 1H), 2.42-2.50 (m, 2H), 2.82-2.95 (m, 2H), 3.70 (s, 3H), 6.01-6.05 (m, 1H), 6.94-7.00 (m, 1H).

^{13}C NMR (100.6 MHz) δ: 25.9 (CH_2), 28.7 (CH_2), 34.3 (CH_2), 43.6 (CH), 51.7 (*C*H_3), 129.2 (CH), 149.9 (CH), 172.9 (*C*O_2), 199.4 (*C*O).

[208] Previously described: Izawa Y.; Zheng, C.; Stahl, S.S. *Angew. Chem. Int. Ed.* **2013**, *52*, 3672–3675.



Methyl 3-methyl-2-oxo-3-cyclohexeneacetate (105)

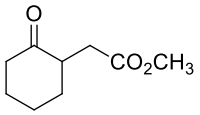
Operating as in the preparation of **104**, from ketone **103** (514 μL, 4.5 mmol), LDA (2.0 M in THF/heptanes/ethylbenzene, 2.04 mL, 4.5 mmol), methyl bromoacetate (750 μL, 6.75 mmol) and HMPA (850.8 μL, 5.4 mmol) in THF (3 mL), ketoester **105** (794 mg, 97%) was obtained as an orange oil after flash-column chromatography (from hexane to 8:2 hexane–EtOAc).

IR (NaCl): 2935, 2862, 1707 cm^{-1}.

^{1}H NMR (400 MHz) δ: 1.77-1.87 (m, 4H), 2.06-2.11 (m, 1H), 2.26-2.51 (m, 3H), 2.76-2.90 (m, 2H), 3.70 (s, 3H, C*H*$_3$), 6.72-6.74 (m, 1H).

^{13}C NMR (100.6 MHz) δ: 15.9 (*C*H_3), 25.6 (CH_2), 29.1 (CH_2), 34.6 (CH_2), 43.6 (CH), 51.5 (*C*H_3), 134.9 (CH), 144.8 (CH), 173.0 (*C*O_2), 199.8 (*C*O).

HRMS calculated for $[C_{10}H_{14}O_3 + H]^+$: 183.1016; found: 183.1019.



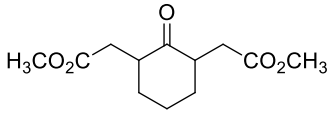
Methyl 2-oxo-cyclohexaneacetate (106)[209]

Pyrrolidine (3.4 mL, 40.8 mmol) was added to a solution of cyclohexanone (2.1 mL, 20.4 mmol) in toluene (68 mL). The mixture was heated at reflux with azeotropic elimination of water by a Dean-stark system. After 20 h, the mixture was cooled and concentrated, and the resulting residue was diluted with CH_3CN (10 mL). Methyl bromoacetate (4.7 mL, 51.0 mmol) and DIPEA (1.8 mL, 10.5 mmol) were added and the mixture was stirred at the reflux temperature for 5 h; then the mixture was cooled, 4 mL of buffer solution (HOAc–H_2O– NaOAc 25 mL:25 mL:12.5 g) were added, and the resulting mixture was heated at reflux for 1 h. The cooled mixture was diluted with Et_2O (15 mL) and the mixture was washed with aqueous HCl solution (2N, 2 x 10 mL) and brine (2 x 10 mL). The organic phase was dried and concentrated. The residue was purified by flash-column chromatography (9:1 hexane–acetone) afforded the ketoester **106** as a yellow oil (2.81 g, 81%).

^{1}H NMR (400 MHz) δ: 1.19-1.32 (m, 1H, H-6), 1.41-1.64 (m, 2H, H-4, H-5), 1.69-1.77 (m, 1H, H-5), 1.91-2.03 (m, 3H, H-2, H-4, H-6), 2.16-2.30 (m, 2H, H-3), 2.58-2.66 (m, 1H, C*H*$_2$CH$_3$), 2.66-2.76 (m, 1H, H-1), 3.51 (s, 3H, CO_2C*H*$_3$).

^{13}C NMR (100.6 MHz) δ: 24.8 (C-5), 27.4 (C-4), 33.5 (C-6), 33.8 (*C*H$_2$CO$_2$), 41.4 (C-3), 46.7 (C-1), 51.1 (*C*H$_3$), 172.5 (*C*O$_2$), 210.3 (*C*O).

[209] a. Already described in: Halloway, C.A.; Muratore, M.E.; Storer, I.R.; Dixon, D. J. *Org. Lett*. **2010**, *21*, 4720–4723; b. Yashikai, K.; Hayama, T.; Nishiura, K.; Yamada, K.; Tamioda, K. *J. Org. Chem.* **2005**, *70*, 681–683; c. Miura, K.; Fujisawa, N.; Saito, H.; Wang, D.; Hosomi, A. *Org. Lett*. **2001**, *16*, 2591–2594.



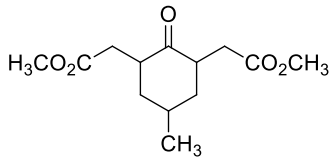
Dimethyl 2-oxo-1,3-cyclohexanediacetate (107)[210]

Pyrrolidine (3.5 mL, 42.1 mmol) was added to a solution of cyclohexanone (3.6 mL, 21.1 mmol) in benzene (70 mL). The reaction mixture was stirred for 20 h at the temperature of reflux, with azeotropic elimination of water. The product mixture was concentrated and diluted with anhydrous CH_3CN (10 mL). Methyl bromoacetate (4.9 mL, 52.8 mmol) and DIPEA (1.8 mL, 10.5 mmol) were added to the previous solution and the mixture was stirred at the reflux temperature for 24 h. The cold product mixture was diluted with 4 mL of buffer solution (HOAc–H_2O– NaOAc 25 mL:25 mL:12.5 g) and the resulting mixture was heated at reflux for 1 h. The cooled mixture was diluted with Et_2O (15 mL) and the diluted mixture was washed with aqueous HCl solution (2N, 2 x 10 mL) and brine (2 x 10 mL). The washed organic phase was concentrated. The residue was purified by flash-column chromatography (9:1 to 8:2 hexane–acetone) afforded the ketoester **107** as a yellow oil (3.83 g, 75%).

^{1}H NMR (400 MHz) δ: 1.35-1.49 (m, 2H, H-5), 1.78-1.92 (m, 2H, H-4, H-6), 2.14-2.22 (m, 4H, H-4, H-6, C*H*$_2$CO$_2$), 2.79 (dd, *J* = 6.6 and 16.5 Hz, 2H, C*H*$_2$CO$_2$), 2.95 (m, 2H, H-1, H-3), 3.67 (s, 6H, CH_3).

^{13}C NMR (100.6 MHz) δ: 24.8 (C-5), 33.8 (C-4, C-6), 34.3 (*C*H$_2$CO$_2$), 46.8 (C-1, C-3), 51.4 (2CH_3), 172.6 (2*C*O$_2$), 209.9 (*C*O).

[210] Already described in: Grieco, P.A.; Naguez, J.A., Masaki, Y.; Hiroi, K., Nishizama, M., Rosowsky, A., Oppenheim, S., Lazarus, H. *J. Med. Chem.* **1977***, 20*, 71−76.



Dimethyl 5-methyl-2-oxo-1,3-cyclohexanediacetate (108)

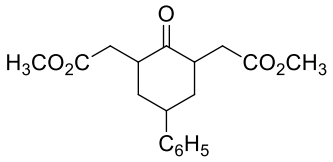
Operating as in the preparation of **107**, from a solution of pyrrolidine (2.3 mL, 26.8 mmol), 4-methylcyclohexanone **24** (1.64 mL, 13.37 mmol) in benzene (45 mL), and methyl bromoacetate (3.7 mL, 40 mmol) in anhydrous CH_3CN (6 mL), in presence of DIPEA (1.2 mL, 6.6 mmol) compound **108** (2.3 g, 67%, 5:1 *cis:trans* mixture) was obtained after flash chromatography (9:1 to 6:4 hexane–EtOAc) as a yellow oil.

IR (film): 1708, 1737 cm^{-1}.

^{1}H NMR (400 MHz, more significant signals) δ: 0.94-0.96 (m, 3H, C*H*$_3$), 1.10-1.23 (m, 2H, H-4, H-6), 1.28-1.30 (m, 3H, C*H*$_3$), 1.56-1.67 (m, 2H, H-4, H-6), 1.85-1.94 (m, 2H, H-4, H-6), 1.98-2.21 (m, 10H, H-5, H-4, H-6, C*H*$_2$CO$_2$), 2.67-2.76 (m, 4H, C*H*$_2$CO$_2$), 2.87-2.96 (m, 2H, H-1, H-3), 3.08-3.13 (m, 2H, H-1, H-3), 3.62 -3.65 (br. s 6H, OC*H*$_3$).

^{13}C NMR (100.6 MHz) δ: 17.8 and 21.3 (*C*H$_3$), 20.9 and 27.0 (C-5), 33.9 (*C*H$_2$CO$_2$), 40.1 and 42.9 (C-4, C-6), 41.9 and 45.8 (C-1, C-3), 51.6 and 52.3 (*C*H$_3$).

HMRS calculated for $[C_{13}H_{20}O_5 + H]^+$: 257.1384; found: 257.1386.



Dimethyl 2-oxo-5-phenyl-1,3-cyclohexanediacetate (109)

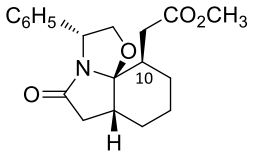
Operating as in the preparation of **107**, from a solution of pyrrolidine (1.44 mL, 17.24 mmol), 4-phenylcyclohexanone **25** (1.5 g, 8.62 mmol) in benzene (29 mL), and methyl bromoacetate (2.0 mL, 21.6 mmol) in anhydrous CH_3CN (4.5 mL), in presence of DIPEA (720 μL, 4.2 mmol) compound **109** (1.8 g, 66%, *cis:trans* mixture) was obtained after flash chromatography (8:2 hexane-EtOAc) as a yellow oil.

IR (film): 3028, 2930, 1709 cm^{-1}.

^1H NMR (400 MHz, broad signals) δ: 1.23-1.30 (m, 2H), 1.70-1.95 (m, 4H), 2.03-2.06 (m, 2H), 2.12-2.32 (m, 4H), 2.71-2.87 (m, 4H), 3.02-3.17 (m, 4H), 3.30 (br. s, 2H), 3.65-3.70 (m, 12H, OCH_3), 7.21-7.32 (m, 6H), 7.40-7.46 (m, 2H), 7.54-7.56 (m, 2H).

^{13}C NMR (100.6 MHz) δ: 33.8 and 34.0 ($2CH_2$), 35.4 and 37.4 ($2CH_2$), 35.7 and 37.7 (2CH), 42.6 and 43.3 (CH), 51.5 and 51.6 ($2OCH_3$), 126.3 (C-Ar), 126.6 (2C-Ar), 128.5 (C-Ar), 128.7 (2C-Ar), 141.2 (C-*i*), 142.1 (C-*i*), 172.5 ($2CO_2$), 210.0 (*C*O).

HMRS calculated for $[C_{18}H_{22}O_5 + H]^+$: 319.1540; found: 319544.



Methyl (3*R*,6a*R*,10*R*,10a*R*)-5-oxo-3-phenylperhydrooxazolo[2,3-*i*]indole-10-acetate (110)

(*R*)-Phenylglycinol (925 mg, 6.75 mmol) was added to a solution of ketodiester **107** (1.1 g, 4.5 mmol) and AcOH (500 μL, 6.75 mmol) in benzene (75 mL). The mixture was heated at the reflux temperature for 24 h, with azeotropic elimination of water by Dean–Stark system. Additional (*R*)-phenylglycinol (925 mg, 6.75 mmol) was then added and the stirring was continued for 24 h. After cooling, the mixture was concentrated, and the resulting residue was dissolved in ethyl acetate (15 mL). The organic phase was washed with saturated aqueous sodium bicarbonate solution (2 x 10 mL) and concentrated. Flash-column chromatography (hexane to 7:3 hexane–EtOAc) of the residue afforded lactam **110** (917 mg, 62%) as a colourless oil.

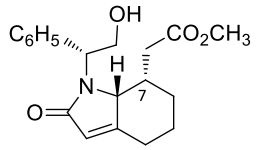
IR (film): 2931, 1732 cm^{-1}.

$[\alpha]^{22}_{D}$ – 108.7 (c 1.17, $CHCl_3$).

^{1}H NMR (400 MHz) δ: 1.24-1.32 (m, 1H, H-9), 1.51-1.69 (m, 4H, H-7, H-8 and H-9), 1.81-1.87 (m, 1H, H-7), 1.94 (dd, *J* = 10.0 and 15.6 Hz, 1H, C*H*$_2$CO$_2$), 2.06 (dd, *J* = 3.6 and 15.6 Hz, 1H, C*H*$_2$CO$_2$), 2.26-2.32 (m, 1H, H-10), 2.46-2.54 (m, 2H, H-6a, H-6), 2.74 (dd, *J* = 14.0 and 18.4 Hz, 1H, H-6), 3.55 (s, 3H, C*H*$_3$), 4.40-4.46 (m, 2H, H-2), 5.27 (t, *J* = 5.6 Hz, 1H, H-3), 7.26-7.37 (m, 5H, H-Ar).

^{13}C NMR (100.6 MHz) δ: 19.3 (C-8), 25.9 (C-7), 27.4 (C-9), 34.6 (*C*H$_2$CO$_2$), 38.2 (C-10), 38.6 (C-6), 42.2 (C-6a), 51.5 (O*C*H$_3$), 58.6 (C-3), 72.0 (C-2), 102.1 (C-10a), 125.8 (2C-Ar), 127.4 (C-Ar), 128.6 (2C-Ar), 139.5 (C-*i*), 173.2 (*C*O$_2$), 179.4 (*C*O).

HRMS calculated for $[C_{19}H_{23}NO_4 + H]^+$: 330.1700; found: 330.1700.



Methyl (7*S*,7a*R*)-1-[(1*R*)-2-hydroxy-1-phenylethyl]-2-oxo-2,4,5,6,7,7a-hexahydroindole -7-acetate (111a)

Amount of minor product **111a** (148 mg, 10%) was recovered, as a white solid by eluting the flash-column chromatography with EtOAc.

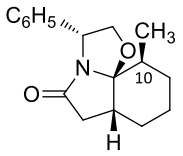
IR (film) 3340, 2921, 1735, 1665 cm^{-1}.

$[\alpha]^{22}_{D}$ –93.0 (c 1.0, $CHCl_3$).

^{1}H NMR (400 MHz) δ: 1.50-1.56 (m, 2H, H-4, H-5), 1.75-1.79 (m, 2H, H-4, H-5), 2.01 (dd, *J* = 9.2 and 16.4 Hz, 1H, C*H*$_2$CO$_2$), 2.12-2.17 (m, 1H, H-6), 2.21 (dd, *J* = 5.2 and 16.4 Hz, 1H, C*H*$_2$CO$_2$), 2.68-2.72 (m, 1H, H-6), 2.88-2.91 (m, 1H, H-7), 3.68 (s, 3H, OC*H*$_3$), 3.74 (d, *J* = 5.2 Hz, 1H, H-7a), 3.91-3.96 (m, 1H, C*H*$_2$OH), 4.25-4.32 (m, 1H, C*H*$_2$OH), 4.51 (dd, *J* = 3.6 and 8 Hz, 1H, C*H*N), 4.88 (t, *J* = 7.2 Hz, 1H, OH), 5.84 (s, 1H, H-3), 7.18-7.32 (m, 1H, H-Ar), 8.16-7.36 (m, 4H, H-Ar).

^{13}C NMR (100.6 MHz) δ: 20.9 (C-5), 26.6 (C-4), 27.6 (C-6), 29.1 (*C*H$_2$CO$_2$), 34.0 (C-7), 51.7 (*C*H$_3$), 61.9 (*C*HN), 64.2 (*C*H$_2$OH), 64.6 (C-7a), 120.3 (C-3), 126.9 (2C-Ar), 127.7 (C-Ar), 128.7 (2C-Ar), 138.1 (C-*i*), 160.2 (C-3a), 172.7 (*C*O$_2$), 173.6 (*C*O).

HRMS calculated for $[C_{19}H_{23}NO_4 + H]^+$: 330.1700; found: 330.1696.



(3*R*,6a*R*,10*S*,10a*S*)-10-Methyl-5-oxo-3-phenylperhydrooxazolo[2,3-*i*]indole (112a)

Operating as in the preparation of lactam **110**, from ketoester **97** (1.5 g, 8.15 mmol), (*R*)-phenylglycinol (3.4 g, 24.5 mmol) and AcOH (950 μL, 12.2 mmol) in benzene (136 mL), lactam **112a** (1.66 g, 75%) was obtained as a yellow solid after flash-column chromatography (hexane to 7:3 hexane–EtOAc).

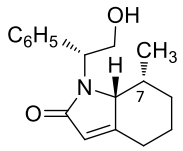
IR (film): 1712 cm^{-1}.

$[\alpha]^{22}_{D}$ – 116.7 (c 1.0, $CHCl_3$).

^{1}H NMR (400 MHz) δ: 0.67 (d, *J* = 6.4 Hz, 3H, C*H*$_3$), 1.25-1.34 (m. 1H, H-9), 1.46-1.65 (m, 4H, H-7, H-8, H-9), 1.80-1.92 (m, 2H, H-7, H-10), 2.45-2.53 (m, 2H, H-6, H-6a), 2.68-2.76 (m, 1H, H-6), 4.33 (dd, *J* = 5.6 and 8.4 Hz, 1H, H-2), 4.60 (t, *J* = 8.4 Hz, 1H, H-2), 5.24 (dd, *J* = 5.6 Hz and 8.4 Hz, 1H, H-3), 7.25-7.27 (m, 3H, H-Ar), 7.32-7.40 (m, 2H, H-Ar).

^{13}C NMR (100.6 MHz) δ: 15.5 (*C*H$_3$), 19.6 (C-8), 26.3 (C-7), 30.0 (C-9), 36.4 (C-10), 39.1 (C-6), 42.6 (C-6a), 58.3 (C-3), 73.6 (C-2), 102.9 (C-10a), 125.7 (2C-Ar), 127.2 (C-Ar), 128.5 (C2C-Ar), 140.0 (C-*i*), 179.7 (*C*O).

HRMS calculated for $[C_{17}H_{21}NO_2 + H]^+$: 272.1645; found: 272.1642.



(7*R*,7a*R*)-1-[(1*R*)-2-Hydroxy-1-phenylethyl]-7-methyl-2-oxo-2,4,5,6,7,7a-hexahydroindole (113a)

Amount of minor product **113a** (177 mg, 8%) was recovered, as a white solid by eluting the flash-column chromatography with EtOAc.

IR (film): 3338, 2937, 1661 cm^{-1}.

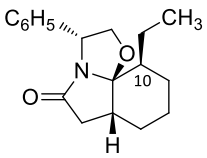
$[\alpha]^{22}_{D}$ –76.6 (c 1.06, $CHCl_3$).

mp: 69-71 °C

^{1}H NMR (400 MHz) δ: 0.73 (d, *J* = 7.2 Hz, 3H, CH_3), 1.49-1.75 (m, 4H, H-5, H-6), 2.09-2.17 (m, 1H, H-4), 2.43-2.48 (m, 1H, H-7), 2.66-2.68 (m, 1H, H-4), 3.68 (dd, *J* = 0.8 and 6 Hz, 1H, H-7a), 4.01 (dd, *J* = 3.2 and 12.4 Hz, 1H, C*H*$_2$OH), 4.26-4.31 (m, 1H, C*H*$_2$OH), 4.41 (dd, *J* = 3.2 and 7.6 Hz, 1H, C*H*N), 5.2 (br. s, 1H, OH), 5.83 (s, 1H, H-3), 7.19-7.21 (m, 1H, H-Ar), 7.27-7.37 (m, 4H, H-Ar).

^{13}C NMR (100.6 MHz) δ: 10.2 (CH_3), 21.0 (C-6), 27.9 (C-4), 29.2 (C-5), 32.1 (C-7), 62.2 (*C*HN), 64.6 (*C*H$_2$OH), 65.4 (C-7a), 120.2 (C-3), 127.0 (2C-Ar), 127.8 (C-Ar), 128.7 (2C-Ar), 138.4 (C-*i*), 160.4 (C-3a), 173.6 (*C*O).

HRMS calculated for $[C_{17}H_{21}NO_2 + H]^+$: 272.1645; found: 272.1646.



(3*R*,6a*R*,10*S*,10a*S*)-10-Ethyl-5-oxo-3-phenylperhydrooxazolo[2,3-*i*]indole (114)

Operating as in the preparation of lactam **110**, from ketoester **98** (1.9 g, 9.6 mmol), (*R*)-phenylglycinol (3.95 g, 28.8 mmol) and AcOH (1.1 mL, 14.3 mmol) in benzene (160 mL), lactam **114** (1.56 g, 57%) was obtained as a colourless oil after flash-column chromatography (hexane to 7:3 hexane–EtOAc).

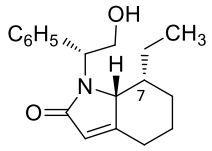
IR (film): 2931, 2873, 1713 cm^{-1}.

$[\alpha]^{22}_{D}$ – 123.0 (c 1.0, $CHCl_3$).

^{1}H NMR (400 MHz) δ: 0.70 (t, *J* = 7.2 Hz, 3H, C*H*$_3$), 0.93-1.02 (m, 1H, C*H*$_2$CH$_3$), 1.18-1.28 (m, 2H, H-9, C*H*$_2$CH$_3$), 1.46-1.53 (m, 1H, H-8), 1.55-1.66 (m, 3H, H-7, H-8, H-10), 1.71-1.81 (m, 1H, H-9), 1.82-1.89 (m, 1H, H-7), 2.46-2.49 (m, 1H, H-6a), 2.47 (dd, *J* = 7.2 and 18.0 Hz, 1H, H-6), 2.68 (dd, *J* = 13.6 and 18.0 Hz, 1H, H-6), 4.29 (dd, *J* = 6.0 and 8.8 Hz, 1H, H-2), 4.58 (t, *J* = 8.4 Hz, 1H, H-2), 5.24 (dt, *J* = 1.2 and 6.4 Hz, 1H, H-3), 7.23-7.36 (m, 5H, H-Ar).

^{13}C NMR (100.6 MHz) δ: 11.8 (*C*H$_3$), 19.8 (C-8), 21.2 (*C*H$_2$CH$_3$), 25.1 (C-9), 26.2 (C-7), 39.1 (C-6) 42.5 (C-6a), 43.0 (C-10), 58.6 (C-3), 73.3 (C-2), 103.3 (C-10a), 125.6 (2C-Ar), 127.1 (C-Ar), 128.4 (2C-Ar), 140 (C-*i*), 180.1 (*C*O).

HRMS calculated for $[C_{18}H_{23}NO_2 + H]^+$: 286.1802 ; found: 286.1795.



(7*R*,7a*R*)-7-Ethyl-1-[(1*R*)-2-hydroxy-1-phenylethyl]-2-oxo-2,4,5,6,7,7a-hexahydroindole (115a)

Amount of minor product **115a** (410.5 mg, 15%) was recovered, as a yellow solid by eluting the flash-column chromatography with EtOAc.

IR (film): 3338, 2938, 2873, 1661cm^{-1}.

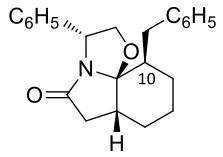
$[\alpha]^{22}_{D}$ –88.24 (c 1.31, $CHCl_3$).

mp: 80-82 °C.

^{1}H NMR (400 MHz) δ: 0.83 (t, *J* = 7.2 Hz, 3H, CH_3), 0.87-0.93 (m, 1H, C*H*$_2$CH$_3$), 1.18-1.54 (m, 4H, H-5, H-6, C*H*$_2$CH$_3$), 1.68 (d, *J* = 14 Hz, 1H, H-6), 2.08-2.18 (m, 2H, H-4, H-7), 2.66 (dd, *J* = 4.4 and 14 Hz, 1H, H-4), 3.72 (d, *J* = 6 Hz, 1H, H-7a), 4.01 (dd, *J* = 3.2 and 12 Hz, 1H, C*H*$_2$OH), 4.27 (t, *J* = 7.6 Hz, 1H, C*H*$_2$OH), 4.43-4.44 (m, 1H, C*H*N), 5.21 (br. s, 1H, OH), 5.78 (s, 1H, H-3), 7.16-7.36 (m, 5H, H-Ar).

^{13}C NMR (100.6 MHz) δ: 10.8 (CH_3), 15.1 (*C*H$_2$CH$_3$), 20.4 (C-5), 24.4 (C-6), 27.7 (C-4), 38.7 (C-7), 61.8 (*C*HN), 64.3 (*C*H$_2$OH), 65.8 (C-7a), 119.5 (C-3), 126.9 (2C-Ar), 127.6 (C-Ar), 128.6 (2C-Ar), 138.3 (C-*i*), 160.9 (C-3a), 173.6 (*C*O).

HRMS calculated for $[C_{18}H_{23}NO_2 + H]^+$: 286.1802; found: 286.1801.



(3*R*,6a*R*,10*R*,10a*S*)-10-Benzyl-5-oxo-3-phenylperhydrooxazolo[2,3-*i*]indole (116)

Operating as in the preparation of lactam **110**, from ketoester **99** (2.0 g, 7.2 mmol), (*R*)-phenylglycinol (3.0 g, 21.6 mmol) and AcOH (805 μL, 10.8 mmol) in benzene (120 mL), lactam **116** (1.64 g, 65%) was obtained as a colourless oil after flash-column chromatography (hexane to 7:3 hexane–EtOAc).

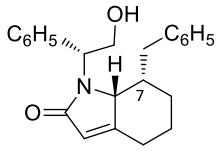
IR (film): 2928, 1713 cm^{-1}.

$[\alpha]^{22}_{D}$ – 197.4 (c 1.0, $CHCl_3$).

^{1}H NMR (400 MHz) δ: 1.10-1.22 (m, 1H, H-7), 1.26-1.39 (m, 1H, H-8), 1.50-1.68 (m, 3H, H-7, H-8, H-9), 1.79-1.86 (m, 1H, H-9), 1.91 (tt, *J* = 3.6 and 11.6 Hz, 1H, H-10), 2.09 (dd, *J* = 11.6 and 13.2 Hz, 1H, C*H*$_2$Ph), 2.45-2.50 (m, 2H, H-6, C*H*$_2$Ph), 2.53-2.60 (m, 1H, H-6a), 2.78 (dd, *J* = 12.0 and 15.2 Hz, 1H, H-6), 4.47 (dd, *J* = 4.8 and 8.4 Hz, 1H, H-2), 4.62 (t, *J* = 8.4 Hz, 1H, H-2), 5.32 (dd, *J* = 4.8 and 8.4 Hz, 1H, H-3), 6.93 (d, *J* = 6.8 Hz, 1H, H-Ar), 7.36-7.10 (m, 9H, H-Ar).

^{13}C NMR (100.6 MHz) δ: 19.7 (C-8), 25.7 (C-9), 25.9 (C-7), 35.3 (*C*H$_2$Ph), 38.9 (C-6), 44.0 (C-6a), 44.7 (C-10), 58.4 (C-3), 73.4 (C-2), 102.9 (C-10a), 125.7 (C-Ar), 125.8 (2C-Ar), 127.4 (C-Ar), 128.1 (2C-Ar), 128.6 (2C-Ar), 129.0 (2C-Ar), 139.8 (C-*i*), 140.6 (C-*i*), 179.4 (*C*O).

HRMS calculated for $[C_{23}H_{25}NO_2 + H]^+$:348.1958; found: 348.1961.



(7*S*,7a*R*)-7-Benzyl-1-[(1*R*)-2-hydroxy-1-phenylethyl]-2-oxo-2,4,5,6,7,7a-hexahydroindole (117a)

Amount of minor product **117** (580 mg, 23%) was recovered, as a white solid by eluting the flash-column chromatography with EtOAc.

IR (film): 3338, 2938, 2873, 1661 cm^{-1}.

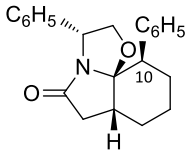
$[\alpha]^{22}_{D}$ –105.5 (c 1.05, $CHCl_3$).

mp: 101-102 °C.

^{1}H NMR (400 MHz) δ: 1.21-1.34 (m, 1H, H-4), 1.54-1.61 (m, 1H, H-4), 1.64-1.76 (m, 2H, H-5), 2.14-2.25 (m, 2H, H-6, C*H*$_2$Ph), 2.53-2.66 (m, 2H, H-7, C*H*$_2$Ph), 2.74-2.78 (m, 1H, H-6), 3.81 (dd, *J* = 1.2 and 4.8 Hz, 1H, H-7a), 3.97 (d, *J* = 11.6 Hz, 1H, C*H*$_2$OH), 4.25-4.28 (m, 1H, C*H*$_2$OH), 4.50 (dd, *J* = 3.2 and 7.6 Hz, 1H, C*H*N), 5.00-5.07 (m, 1H, OH), 5.89 (s, 1H, H-3), 7.09-7.40 (m, 10H, H-Ar).

^{13}C NMR (100.6 MHz) δ: 20.8 (C-5), 24.9 (C-4), 27.8 (C-6), 29.4 (*C*H$_2$Ph), 39.2 (C-7), 62.4 (*C*HN), 64.4 (*C*H$_2$OH), 65.6 (C-7a), 120.1 (C-3), 126.2 (2C-Ar), 127.1 (2C-Ar), 127.9 (C-Ar), 128.5 (2C-Ar), 128.8 (3C-Ar), 138.3 (C-*i*), 139.6 (C-*i*), 160.6 (C-3a), 173.7 (*C*O).

HRMS calculated for $[C_{23}H_{25}NO_2 + H]^+$: 348.1958; found: 348.1950.



(3*R*,6a*R*,10*R*,10a*R*)-5-Oxo-3,10-diphenylperhydrooxazolo[2,3-*i*]indole (118)

Operating as in the preparation of lactam **110**, from ketoester **100** (2.2 g, 8.4 mmol), (*R*)-phenylglycinol (3.4 g, 25.1 mmol) and AcOH (935 μL, 12.6 mmol) in benzene (140 mL), lactam **118** (1.48 g, 53%) was obtained as a white solid after flash-column chromatography (hexane to 7:3 hexane–EtOAc).

IR (film): 2926, 1710 cm^{-1}.

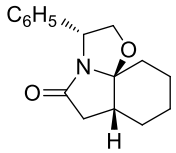
$[\alpha]^{22}_{D}$ –232.2 (c 2.9, $CHCl_3$).

mp = 130–132 .

^{1}H NMR (400 MHz) δ: 1.59-1.66 (m, 1H, H-8), 1.76-1.81 (m, 3H, H-7, H-8, H-9), 1.89-1.98 (m, 2H, H-7, H-9), 2.49 (dd, *J* = 7.2 and 15.2 Hz, 1H, H-6), 2.60-2.67 (m, 1H, H-3a), 2.94 (dd, *J* = 3.2 and 12.8 Hz, 1H, H-10), 3.00 (t, *J* = 15.2 Hz, 1H, H-6), 3.45 (dd, *J* = 7.2 and 8.4 Hz, 1H, H-2), 4.40 (t, *J* = 8.4 Hz, 1H, H-2), 4.92 (t, *J* = 7.2 Hz, 1H, H-3), 6.79-6.85 (m, 4H, H-Ar), 6.90-6.94 (m, 1H, H-Ar), 7.03-7.12 (m, 5H, H-Ar).

^{13}C NMR (100.6 MHz) δ: 21.2 (C-8), 25.3 (C-7), 29.8 (C-9), 39.6 (C-6), 46.6 (C-6a), 50.0 (C-10), 57.2 (C-3), 74.8 (C-2), 102.8 (C-10a), 126.1 (2C-Ar), 126.6 (C-Ar), 126.7 (C-Ar), 127.5 (2C-Ar), 127.9 (2C-Ar), 129.9 (2C-Ar), 138.9 (C-*i*), 139.3 (C-*i*), 178.1 (*C*O)

HRMS calculated for $[C_{22}H_{23}NO_2 + H]^+$: 334.1802; found: 334.1811.



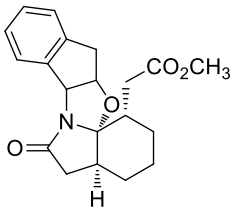
(3*R*,6a*R*,10a*S*)-5-Oxo-3-phenylperhydrooxazolo[2,3-*i*]indole (119)[211]

Operating as in the preparation of tricyclic lactam **110**, from ketoester **106** (670 mg, 3.94 mmol), (*R*)-phenylglycinol (1.61 g, 11.8 mmol), AcOH (442 μL, 5.9 mmol) in benzene (65 mL), lactam **119** (689 mg, 68 %) was obtained after flash-column chromatography (hexane to 7:3 hexane–EtOAc) as a white solid.

^{1}H NMR (400 MHz) δ: 1.41-1.64 (m, 5H), 1.68-1.75 (m, 1H), 1.81-1.91 (m, 2H), 2.43-2.56 (m, 2H), 2.71 (dd, *J* = 11.2 and 16.0 Hz, 1H), 4.13 (dd, *J* = 7.6 Hz, 1H), 4.58 (t, *J* = 7.6 Hz, 1H), 5.13 (t, *J* = 6.8 Hz, 1H), 7.24-7.35 (m, 5H, H-Ar).

^{13}C NMR (100.6 MHz) δ: 19.9 (C-8), 20.6 (C-7), 25.8 (C-9), 31.4 (C-10), 39.2 (C-6), 41.3 (C-6a), 57.6 (C-3), 73.8 (C-2), 100.3 (C-10a), 125.6 (2C-Ar), 127.4 (C-Ar), 128.6 (2C-Ar), 139.8 (C-*i*), 177.3 (*C*O).

[211] Mouhamad, J.; Deprez-Poulain, R.; Malaquin, S.; Roussel,P.; Agbossou-Niedercorn, F.; Deprez, B.; Laconde, G. *Green Chem.,* **2010**, 12, 961-964;



Methyl (1*S*,4a*S*,7a*S*,12a*R*,13a*S*)-6-oxo-1,2,3,4,4a,5,6,7a,12,12a,13a-dodecahydro-[1*H*]-indeno [1'2':4,5]oxazolo[2,3-*i*]indole-1-propionate (120a)

Operating as in the preparation of lactam **110** from ketodiester **107** (198 mg, 0.81 mmol), (1*S*,2*R*)-(–) -*cis*-1-amino-2-indanol (333 mg, 2.43 mmol) and AcOH (90 μL, 1.22 mmol) in benzene (14 mL), lactams **120** (158 mg, 57%) were obtained as a mixture of inseparable isomers after flash-column chromatography (hexane to 7:3 hexane–EtOAc). A small amount of **120a** was isolated.

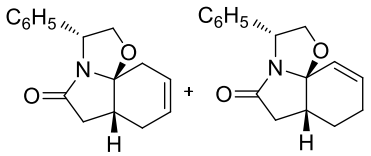
Spectroscopic and analytical data for compound **120a**

$[\alpha]^{22}_{D}$ – 125.2 (c 1.0, $CHCl_3$).

^{1}H NMR (400 MHz) δ: 1.14 (dq, *J* = 2.8 and 12.4 Hz, 1H, C*H*$_2$CO$_2$), 1.22 (dd, *J* = 2.8 and 15.6 Hz, 1H, H-2), 1.45-1.64 (m, 4H, H-2, H-3, C*H*$_2$CO$_2$), 1.69-1.78 (m, 2H, H-4), 2.06 (t, *J* = 12 Hz, 1H, H-1), 2.34 (dd, *J* = 7.6 and 15.6 Hz, 1H, H-5), 2.41-2.48 (m, 1H, H-4), 2.77 (t, *J* = 14.8 Hz, 1H, H-5), 3.15 (s, 2H, H-12), 3.48 (s, 3H, OC*H*$_3$), 4.85-4.87 (m, 1H, H-12a), 5.60 (d, *J* = 5.6 Hz, 1H, H-7a), 7.23-7.28 (m, 3H, H-8, H-9, H-11), 7.37 (d, *J* = 7.2 Hz, 1H, H-10).

^{13}C NMR (100.6 MHz) δ: 20.3 (C-3), 24.7 (C-4), 27.7 (*C*H$_2$CO$_2$), 33.1 (C-2), 37.4 (C-12), 38.2 (C-5), 38.9 (C-1), 45.6 (C-4a), 51.3 (O*C*H$_3$), 65.7 (C-7a), 82.4 (C-12a), 102.2 (C-13a), 125.3 (C-Ar), 125.8 (C-Ar), 127.7 (C-Ar), 128.8 (C-Ar), 140.1 (C-*i*), 141.1 (C-*i*), 173.6 (*C*O$_2$), 178.8 (*C*O).

HRMS calculated for $[C_{20}H_{23}NO_4 + H]^+$: 342.1700; found: 342.1700.



121a **121b**

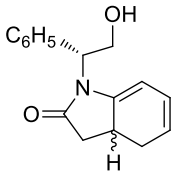
Mixture of product (121a and 121b)

(*R*)-Phenylglycinol (244 mg, 1.79 mmol) was added to a solution of ketoester **104** (215 mg, 1.19) mmol) and AcOH (90 μL, 1.2 mmol) in toluene (20 mL). The mixture was heated at the reflux temperature for 16 h, with azeotropic elimination of water by a Dean-Stark system. Additional (*R*)-Phenylglycinol (244 mg, 1.79 mmol) and AcOH (90 μL, 1.2 mmol) were added, and the stirring was continued for 8 h. After cooling, the mixture was concentrated, and the resulting residue was dissolved in ethyl acetate (15 mL). The organic phase was washed with saturated aqueous sodium bicarbonate solution (2 x 10 mL) and concentrated. Flash-column chromatography (hexane to 7:3 hexane-EtOAc) of the residue afforded lactam **121a**, **121b**, **121c** and **121d** (158 mg, 52%).

Selected spectroscopic data for compound **121a** (mayor isomer from enriched fraction)

^{1}H NMR (400 MHz) δ: 2.12-2.17 (m, 2H, H-7, H-10), 2.39 (d, *J* = 6.0 Hz, 1H, H-10), 2.45-2.42 (m, 1H, H-7), 2.56 (dd, *J* = 8.0 and 15.2 Hz, 1H, H-6), 2.68-2.82 (m, 2H, H-6, H-6a), 4.10-4.11 (m, 1H, H-2), 4.64 (q, *J* = 8.8 Hz, 1H, H-2), 5.19-5.25 (m, 1H, H-3), 5.89-5.94 (m, 1H, H-9), 6.05-6.10 (m, 1H, H-8), 7.21-7.36 (m, 5H, H-Ar).

^{13}C NMR (100.6 MHz) δ: 27.8 (C-7), 32.1 (C-10), 39.3 (C-6a), 40.7 (C-6), 57.2 (C-3), 72.8 (C-2), 103.0 (C-10a), 126.4 (C-9), 128.9 (C-8), 178.9 (*C*O).



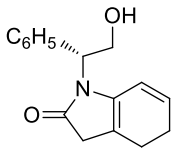
Mixture of epimers (121c)

From the above reaction mixture was isolated a mixture of two products **121c**; here we report a selection of signal for the two structure, albeit we cannot assign the signal to the exact structure.

Selected spectroscopic data for compounds **121c**

^{1}H NMR (400 MHz) δ: 1.94 (tq, *J* = 2.8 and 17.2 Hz, 2H, H-4, H-4), 2.26 (dq, *J* = 2.4 and 8.8 Hz, 2H, H-3, H-3), 2.42-2.50 (m, 2H, H-4, H-4), 2.69-2.81 (m, 2H, H-3a, H-3a), 2.81-2.89 (m, 2H, H-3, H-3), 4.15 (dd, *J* = 4.4 and 12.8 Hz, 2H, H-2.1, H-2.1), 4.35-4.40 (m, 2H, H-2.1, H-2.1), 4.93 (dd, *J* = 4.0 and 7.6 Hz, 1H, H1.1 (may)), 5.01 (dd, *J* = 4.4 and 8.4 Hz, 1H, H-1.1 (min)), 5.07 (dd, *J* = 2.0 and 5.2 Hz, 1H, H-7 (may)), 5.11 (dd, *J* = 2.0 and 5.2 Hz, 1H, H-7), 5.62-5.67 (m, 2H, H-5, H-5), 5.91-5.96 (m, 2H, H-6, H-6), 7.21-7.38 (m, 10H, H-Ar).

^{13}C NMR (100.6 MHz) δ: 29.2 (2C-4), 31.3 (C-3a (may)), 31.5 (C-3a (min)), 37.6 (C-3.2 (min)), 37.9 (C-3.2 (may)), 60.2 (C-1.1 (min)), 61.0 (C-1.1 (may)), 62.5 (C-2.1 (min)), 63.2 (C-2.1 (may)), 97.2 (2C-7), 120.5 (2C-5), 124.9 (2C-6), 142.9 (Cq (min)), 143.6 (Cq (may)), 177.3 (*C*O (may)), 177.4 (*C*O (min)).

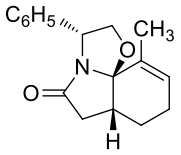


A small amount of compound **121d** was isolated.

Selected spectroscopic data from enriched mixture of products.

^{1}H NMR (400 MHz) δ: 1.75 (q, *J* = 6.0 Hz, 2H, H-2), 2.20-2.24 (m, 2H, H-5), 2.59-2.63 (m, 2H, H-3), 4.14 (dd, *J* = 3.6 and 12.0, 1H, C*H*$_2$OH), 4.21-4.33 (br. s, 1H, OH), 4.31-4.36 (m, 1H, C*H*$_2$OH), 4.97-5.00 (m, 1H, C*H*N), 5.51-5.54 (m, 1H, H-6), 5.80 (s, 1H, H-7), 7.18-7.37 (m, 5H, H-Ar).

^{13}C NMR (100.6 MHz) δ: 23.5 (C-4), 24.2 (C-3, C-5), 60.0 (*C*HN), 63.9 (*C*H$_2$OH), 113.0 (C-6), 115.8 (C-7), 126.7 (2C-Ar), 127.4 (C-Ar), 128.5 (2C-Ar), 138.1 (C-*i*), 139.9 (C-7a), 147.9 (C-3a), 171.8 (*C*O).



(3*R*,6a*R*,10a*S*)-10-Methyl-5-oxo-3-phenyl-2,3,5,6,6a,7,8,10a-octahydrooxazolo[2,3-*i*]indole (122)

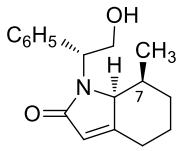
Operating as in the preparation of lactams **121**, from ketoester **105** (200 mg, 1.10 mmol), (*R*)-phenylglycinol (452 g, 3.30 mmol) and AcOH (125 μL, 1.65 mmol) in toluene (18 mL), lactam **122** (182 g, 61%) was obtained as a white solid after flash-column chromatography (hexane to 7:3 hexane–EtOAc).

IR (NaCl): 2927, 2355, 1715 cm^{-1}.

^{1}H NMR (400 MHz) δ: 1.21 (s, 3H, C*H*$_3$), 1.74 (dt, *J* = 2.8 and 14.0 Hz, 1H, H-7), 1.83-1.96 (m, 1H, H-7), 2.03-2.14 (m, 2H, H-8), 2.35 (dd, *J* = 6.4 and 14.8 Hz, 1H, H-6), 2.66-2.76 (m, 1H, H-6a), 2.77 (q, *J* = 14.8 Hz, 1H, H-6), 4.47 (t, *J* = 7.2 Hz, 1H, H-2), 4.63 (dd, *J* = 4.4 and 8.8 Hz, 1H, H-2), 5.35 (dd, *J* = 4.4 and 7.2 Hz, 1H, H-3), 5.67-5.68 (m, 1H, H-9), 7.25-7.36 (m, 5H, H-Ar).

^{13}C NMR (100.6 MHz) δ: 19.0 (*C*H$_3$), 20.3 (C-8), 21.1 (C-7), 36.2 (C-6), 44.5 (C-6a), 58.3 (C-3), 71.9 (C-2), 99.2 (C-10a), 126.4 (2C-Ar), 127.2 (C-Ar), 128.4 (2C-Ar), 128.7 (Cq), 132.9 (C-*i*), 139.2 (C-10), 178.5 (*C*O).

HRMS calculated for $[C_{17}H_{21}NO_2 + H]^+$: 272.1645; found: 272.1642 (without double bond, reductive conditions).



(7*S*,7a*S*)-1-[(1*R*)-2-Hydroxy-1-phenylethyl]-7-methyl-2-oxo-2,4,5,6,7,7a-hexahydroindole (113b)

$TiCl_4$ (933 μL, 8.12 mmol) was added dropwise to a stirred solution of lactam **112a** (1 g, 3.68 mmol) in anhydrous THF (18 mL) at –78 °C, and the stirring was continued at this temperature for 2 h, and for 3 h at room temperature. Then, the mixture was poured into saturated aqueous NH_4Cl, the organic phase was separated, and the aqueous phase was extracted with CH_2Cl_2. The combined organic extracts were dried, filtered, and concentrated. The resulting residue was chromatographed (AcOEt) to afford lactam **113b** (700 mg, 70%) as a white solid.

IR (film): 3323, 2928, 1664 cm^{-1}.

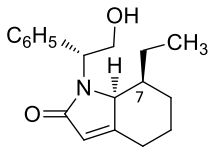
$[\alpha]^{22}_D$ +151.9 (c 0.99, $CHCl_3$).

mp = 129-130 °C

^{1}H NMR (400 MHz) δ: 0.46 (d, *J* = 6.8 Hz, 3H, C*H*$_3$), 1.49-1.66 (m, 4H, H-5, H-6), 2.11-2.18 (m, 1H, H-4), 2.37-2.41 (m, 1H, H-7), 2.61-2.65 (m, 1H, H-4), 3.79 (dd, *J* = 1.2 and 6 Hz, 1H, H-7a), 4.04 (dd, *J* = 5.0 and 11.0 Hz, 1H, C*H*$_2$OH), 4.12 (br. s, 1H, OH), 4.33 (dd, *J* = 8.6 and 11.0 Hz, 1H, C*H*$_2$OH), 4.88 (dd, *J* = 5.0 and 8.6 Hz, 1H, C*H*N), 5.75 (s, 1H, H-3), 7.25-7.41 (m, 5H, H-Ar).

^{13}C NMR (100.6 MHz) δ: 10.3 (*C*H$_3$), 19.8 (C-5), 27.7 (C-4), 29.3 (C-6), 33.2 (C-7), 60.9 (*C*HN), 63.4 (*C*H$_2$OHè), 67.9 (C-7a), 119.5 (C-3), 127.5 (C-Ar), 128.1 (2C-Ar), 128.3 (2C-Ar), 137.8 (C-*i*), 160.1 (C-3a), 174.0 (*C*O).

HRMS calculated for $[C_{17}H_{21}NO_2 + H]^+$: 272.1645; found: 272.1646.



(7*S*,7a*S*)-7-Ethyl-1-[(1*R*)-2-hydroxy-1-phenylethyl]-2-oxo-2,4,5,6,7,7a-hexahydroindole (115b)

Operating as in the preparation of **113b**, from lactam **114** (250 mg, 0.87 mmol) in THF (4 mL) and $TiCl_4$ (220 μL, 1.91 mmol), hexahydroindole **115b** (153 mg, 61%) was obtained as a colourless oil.

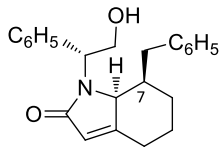
IR (film): 3367, 2938, 2872, 1660 cm^{-1}.

$[\alpha]^{22}_D$ +120.2 (c 1.01, $CHCl_3$).

^{1}H NMR (400 MHz) δ: 0.52 (t, *J* = 7.6 Hz, 3H, C*H*$_3$), 0.78-0.88 (m, 1H, C*H*$_2$CH$_3$), 0.95-1.01 (m, 1H, C*H*$_2$CH$_3$), 1.38 (tt, *J* = 3.6 and 13.6 Hz, 1H, H-4), 1.44-1.64 (m, 1H, H-5), 1.63-1.69 (m, 1H, H-5), 1.79-1.84 (m, 1H, H-4), 1.95-2.00 (m, 1H, H-7), 2.16-2.25 (m, 1H, H-6), 2.68 (dd, *J* = 5.2 and 14.8 Hz, 1H, H-6), 3.57 (br. s, 1H, OH), 3.81 (d, *J* = 5.6 Hz, 1H, H-7a), 4.07-4.12 (m, 1H, C*H*$_2$OH), 4.27-4.34 (m, 1H, C*H*$_2$OH), 4.86 (dd, *J* = 4.8 and 8.4 Hz, 1H, C*H*N), 5.70 (s, 1H, H-3), 7.28-7.42 (m, 5H, H-Ar).

^{13}C NMR (100.6 MHz) δ: 10.6 (*C*H$_3$), 14.9 (*C*H$_2$CH$_3$), 19.5 (C-5), 24.4 (C-4), 27.6 (C-6), 40.3 (C-7), 61.1 (*C*HN), 63.5 (*C*H$_2$OH), 68.5 (C-7a), 118.9 (C-3), 127.6 (C-Ar), 128.1 (2C-Ar), 128.4 (2C-Ar), 137.8 (C-*i*), 160.5 (C-3a), 173.9 (*C*O).

HRMS calculated for $[C_{18}H_{23}NO_2 + H]^+$: 286.1802; found: 286.1802.



(7*R*,7a*S*)-7-Benzyl-1-[(1*R*)-2-hydroxy-1-phenylethyl]-2-oxo-2,4,5,6,7,7a-hexahydroindole (117b)

Operating as in the above preparation of **113b**, from lactam **116** (255 mg, 0.73 mmol) in THF (4 mL) and $TiCl_4$ (185 μL, 1.61 mmol), octahydroindole **117b** (204 mg, 80%) was obtained as a white solid.

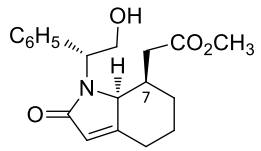
IR (film): 3278, 2935, 2856, 1661 cm^{-1}.

$[\alpha]^{22}_D$ +95.1 (c 1.0, $CHCl_3$).

^{1}H NMR (400 MHz) δ: 1.28-1.35 (m, 1H, H-4), 1.45-1.52 (m, 1H, H-4), 1.67-1.78 (m, 2H, H-5), 2.01 (t, *J* = 14.4 Hz, 1H, C*H*$_2$Ph), 2.13-2.31 (m, 1H, H-6), 2.34-2.340 (m, 2H, H-7, C*H*$_2$Ph), 2.75-2.80 (m, 1H, H-6), 3.99 (d, *J* = 5.2 Hz, 1H, H-7a), 4.12 (dd, *J* = 4.4 and 11.6 Hz, 1H, C*H*$_2$OH), 4.49 (dd, *J* = 7.8 and 11.6 Hz, 1H, C*H*$_2$OH), 4.83 (dd, *J* = 4.4 and 7.8 Hz, 1H, C*H*N), 5.85 (s, 1H, H-3), 6.59 (dd, *J* = 1.6 and 8.0 Hz, 1H, H-Ar), 7.08-7.15 (m, 3H, H-Ar), 7.33-7.51 (m, 6H, H-Ar).

^{13}C NMR (100.6 MHz) δ: 19.8 (C-5), 24.4 (C-4), 27.8 (C-6), 28.7 (*C*H$_2$Ph), 40.7 (C-7), 62.7 (*C*HN), 64.7 (*C*H$_2$OH), 69.5 (C-7a), 119.6 (C-3), 125.8 (C-Ar), 127.1 (C-Ar), 128.2 (2C-Ar), 128.3 (2C-Ar), 128.7 (2C-Ar), 128.8 (2C-Ar), 138.1 (C-*i*), 139.8 (C-*i*), 160.7 (C-3a), 160.3 (*C*O).

HRMS calculated for $[C_{23}H_{25}NO_2 + H]^+$: 348.1958; found: 348.1956.



Methyl (7*R*,7a*S*)-1-[(1*R*)-2-hydroxy-1-phenylethyl]-2-oxo-2,4,5,6,7,7a-hexahydroindole-7-acetate (111b)

Operating as in the above preparation of **113b**, from lactam **110** (134.4 mg, 0.41 mmol) in THF (2 mL) and $TiCl_4$ (104 μL, 0.90 mmol), octahydroindole **111b** (121 mg, 90%) was obtained as a colourless oil.

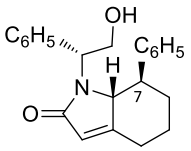
IR (film): 3391, 2943, 2862, 1734, 1668 cm^{-1}.

$[\alpha]^{22}_D$ +110.4 (c 0.48, $CHCl_3$).

^{1}H NMR (400 MHz) δ: 1.49-1.55 (m, 2H, H-4, H-5), 1.70-1.76 (m, 2H, H-4, H-5), 1.90 (dd, *J* = 11.2 and 16.2 Hz, 1H, C*H*$_2$CO$_2$), 2.14 (dd, *J* = 2.4 and 16.2 Hz, 1H, C*H*$_2$CO$_2$), 2.13-2.21 (m, 1H, H-6), 2.66-2.70 (m, 1H, H-6), 2.78-2.83 (m, 1H, H-7), 3.40-3.46 (m, 1H, OH), 3.55 (s, 3H, C*H*$_3$), 3.79 (d, *J* = 6Hz, 1H, H-7a), 4.05-4.10 (m, 1H, C*H*$_2$OH), 4.28-4.35 (m, 1H, C*H*$_2$OH), 5.00 (d, *J* = 1.8 and 8.8 Hz, 1H, C*H*N), 5.76 (s, 1H, H-3), 7.27-7.40 (m, 5H, H-Ar).

^{13}C NMR (100.6 MHz) δ: 19.9 (C-5), 25.9 (C-4), 26.9 (C-6), 27.6 (*C*H$_2$CO$_2$), 28.3 (*C*HN), 35.8 (C-7), 51.5 (*C*H$_3$), 63.6 (*C*H$_2$OH), 66.5 (C-7a), 119.5 (C-3), 127.9 (C-Ar), 128.1 (2C-Ar), 128.7 (2C-Ar), 137.3 (C-*i*), 159.9 (C-3a), 173.0 (*C*O$_2$), 173.9 (*C*O).

HRMS calculated for $[C_{19}H_{23}NNaO_4]^+$: 352.1519; found: 352.1525.

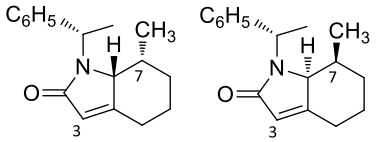


(7*S*,7a*S*)-1-[(1*R*)-2-hydroxy-1-phenylethyl]-2-oxo-7-phenyl-2,4,5,6,7,7a-hexahydroindole (125)

Operating as in the above preparation of **113b**, from lactam **118** (500 mg, 1.50 mmol) in THF (8 mL) and $TiCl_4$ (380 μL, 3.3 mmol), octahydroindole **125** (350 mg, 70%, calculated from crude ^{1}H NMR) was obtained as a colourless oil.

More significant spectroscopic data for compound **125** (from dirty fraction)

^{1}H NMR (400 MHz) δ: 1.43-1.52 (m, 2H), 1.57-1.68 (m, 2H), 1.85-1.92 (m, 2H), 2.41 (dd, *J* = 11.6 and 16. Hz, 1H), 2.52-2.59 (m, 1H), 2.67 (dd, *J* = 8.4 and 16.0 Hz, 1H), 3.57-3.60 (m, 1H), 3.73-3.83 (m, 2H), 5.15 (t, *J* = 6Hz, 1H, OH), 5.90 (s, 1H).



127a **127b**

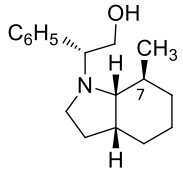
Mixture of compounds (127a/127b)

Operating as in the preparation of lactam **110**, starting from ketoester **97** (200 mg, 1.09 mmol) in benzene (18 mL), in the presence of (*S*)-(–)-α-methylbenzylamine (210.2 mg, 1.50 mmol) and AcOH (90 μL, 1.57 mmol), a mixture of 1.2:1 isomers **127** was obtained, after flash-column chromatography (hexane to 7:3 hexane–EtOAc).

Significant selected signals for **127a** and **127b**

^{1}H NMR (400 MHz) δ: 0.24 (d, *J* = 7.2 Hz, 3H, C*H*$_3$ min), 0.74 (d, *J* = 7.2 Hz, 3H, C*H*$_3$ maj), 1.97 (br. s, 1H, H-7 maj), 2.48-2.54 (m, 1H, H-7 min), 3.56 (d, *J* = 5.2 Hz, 1H, H-7a mai), 3.93 (d, *J* = 6Hz, 1H, H-7a min), 5.09-5.16 (m, 1H, H-3 min), 5.76 (s, 1H, H-3 maj).

^{13}C NMR (100.6 MHz) δ: 64.2 and 64.4 (C-7a), 119.5 and 120.1 (C-3), 159.4 and 159.8 (C-3a), 172.9 and 173.1(*C*O).



(3a*R*,7*S*,7a*R*)-1-[(1*R*)-2-Hydroxy-1-phenylethyl]-7-methyloctahydroindole (128)

$LiAlH_4$ (186 mg, 4.9 mmol) was slowly added to a suspension of and $AlCl_3$ (435 mg, 3.24 mmol) in anhydrous THF (20 mL) at 0 °C, and the mixture was stirred at the same temperature for 1 h and then cooled at − 78 °C. A solution of lactam **112a** (220 mg, 0.81 mmol) in anhydrous THF (10 mL) was added dropwise, and the stirring was continued at − 78 °C for 90 min and at room temperature for 2 h. Cold water (5 mL) was slowly added and the resulting mixture was filtered over Celite®, the filtrate was concentrated, and the residue was taken up with CH_2Cl_2 (15 mL). The organic solution was washed with brine (2 x 5 mL), dried and concentrated. Octahydroindole **128** (172 mg, 82%) was obtained as a colourless oil.

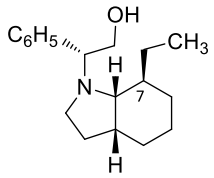
IR (film) 3495, 2926 cm^{-1}.

$[\alpha]^{22}_D$ –52.7 (c 1.0, $CHCl_3$).

^{1}H NMR (400 MHz) δ: 1.07 (d, *J* = 6.8 Hz, 3H, C*H*$_3$), 1.15-1.26 (m, 2H), 1.37-1.49 (m, 6H), 1.61-1.67 (m, 1H), 1.80-1.85 (m, 1H), 1.92-1.99 (m, 1H), 2.49 (t, *J* = 5.2 Hz, 1H), 2.52-2.58 (m, 1H), 2.92-2.97 (m, 1H), 3.66 (dd, *J* = 5.2 and 10.4 Hz, 1H), 3.96 (t, *J* = 10.0 Hz, 1H), 4.13 (dd, *J* = 5.2 Hz, 1H), 7.14-7.16 (m, 1H), 7.26-7.36 (m, 4H).

^{13}C NMR (100.6 MHz) δ: 19.2 (CH_3), 20.0 (CH_2), 28.3 (CH_2), 28.7 (CH_2), 29.2 (CH_2), 30.6 (CH), 35.5 (CH), 42.7 (CH_2), 61.2 (CH_2), 63.2 (CH), 65.3 (CH), 127.6 (C-Ar), 128.1 (2C-Ar), 129.0 (2C-Ar), 136.1 (C-*i*).

HRMS calculated for $[C_{17}H_{25}NO + H]^+$: 260.2009; found: 260.2008.



(3a*R*,7*S*,7a*R*)-7-Ethyl-1-[(1*R*)-2-hydroxy-1-phenylethyl]octahydroindole (129)

Operating as in the preparation of octahydroindole **128**, from $LiAlH_4$ (160 mg, 4.2 mmol) and $AlCl_3$ (374 mg, 2.8 mmol) in anhydrous THF (18 mL) and a solution of lactam **114** (200 mg, 0.70 mmol) in anhydrous THF (9 mL), octahydroindole **129** (128 mg, 67%) was obtained as a colourless oil.

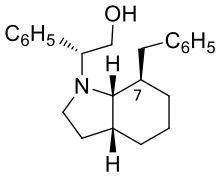
IR (film) 3505, 2925, 2857 cm^{-1}.

$[\alpha]^{22}_{D}$ –74.7 (c 1.0, $CHCl_3$).

^{1}H NMR (400 MHz) δ: 0.99 (t, *J* = 7.2 Hz, 3H, C*H*$_3$), 1.26-1.85 (m, 13H), 2.53-2.59 (m, 2H), 2.93-2.99 (m, 1H), 3.65 (dd, *J* = 4.4 and 9.6 Hz, 1H), 3.97 (t, *J* = 10.0 Hz, 1H), 4.07 (dd, *J* = 4.8 and 11.2 Hz, 1H), 7.14-7.16 (m, 1H), 7.16-7.36 (m, 4H).

^{13}C NMR (100.6 MHz) δ: 12.3 (*C*H$_3$), 19.9 (CH_2), 25.1 (CH_2), 25.3 (CH_2), 28.5 (CH_2), 28.8 (CH_2), 35.4 (CH), 36.7 (CH), 42.3 (CH_2), 61.1 (CH_2), 62.3 (CH), 63.3 (CH), 127.6 (C-Ar), 128.1 (2C-Ar), 129.1 (2C-Ar), 135.9 (C-*i*).

HRMS calculated for $[C_{18}H_{27}NO + H]^+$: 274.2165 ; found: 274.2168.



(3a*R*,7*R*,7a*R*)-7-Benzyl-1-[(1*R*)-2-hydroxy-1-phenylethyl]octahydroindole (130)

Operating as in the preparation of octahydroindole **128**, from $LiAlH_4$ (118 mg, 3.12 mmol) and $AlCl_3$ (277 mg, 2.08 mmol) in anhydrous THF (6 mL) and a solution of lactam **116** (180 mg, 0.52 mmol) in anhydrous THF (7 mL), octahydroindole **130** (122 mg, 70%) was obtained as a colourless oil.

IR (film): 3408, 2927, 2857 cm^{-1}.

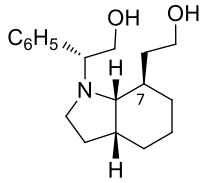
$[\alpha]^{22}_{D}$ –102.3 (c 1.0, $CHCl_3$).

Several of the signals in ^{1}H and ^{13}C NMR spectra of **130** at 25 °C were broad and ill-defined, even not observed.

^{1}H NMR (400 MHz) δ: 1.30-1.54 (m, 7H), 1.73 (m, 1H), 1.99-2.05 (m, 1H, H-3a), 2.24 (br. s, 1H, H-7), 2.56 (br. s, 2H, H-2), 2.61-2.66 (m, 2H, H-7a, C*H*$_2$Ph), 2.85 (dd, *J* = 8.4 and 12.8 Hz, 1H, C*H*$_2$Ph), 2.99 (br.s, 1H, OH), 3.59-3.62 (m, 1H, C*H*$_2$OH), 3.87-3.96 (m, 2H, C*H*N, C*H*$_2$OH), 6.67 (d, *J* = 7.2 Hz, 2H, H-Ar), 7.12-7.35 (m, 8H, H-Ar).

^{13}C NMR (100.6 MHz) δ: 19.9 (CH_2), 26.4 (CH_2), 28.2 (2CH_2), 29.0 (CH_2), 34.9 (C-3a), 36.9 (C-7), 39.4 (*C*H$_2$Ph), 42.2 (C-2), 60.8 (CH_2), 61.7 (*C*HN), 125.8 (2C-Ar), 128.0 (2C-Ar), 128.4 (2C-Ar), 129.0 (2C-Ar), 129.3 (2C-Ar), 141.4 (2C-*i*).

HRMS calculated for $[C_{23}H_{29}NO + H]^{+}$: 336.2322; found: 336.2318.



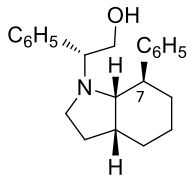
(3a*R*,7*R*,7a*S*)-7-(2-Hydroxyethyl)-1-[(1*R*)-2-hydroxy-1-phenylethyl]octahydroindole (131)

Operating as in the preparation of octahydroindole **128**, from $LiAlH_4$ (138 mg, 3.6 mmol) and $AlCl_3$ (324 mg, 2.44 mmol) in anhydrous THF (15 mL) and a solution of lactam **110** (199 mg, 0.60 mmol) in anhydrous THF (8 mL), octahydroindole **131** (133 mg, 76%) was obtained as a colourless oil.

^{1}H NMR (400 MHz) δ: 1.19-1.23 (m, 2H), 1.38-1.81 (m, 11H), 2.07-2.12 (m, 1H), 2.59-2.66 (m, 1H), 2.72-2.75 (m, 1H), 2.95-3.01 (m, 1H), 3.62 (dt, *J* = 4.4 and 10.4 Hz, 2H), 3.74-3.79 (m, 1H), 3.86-3.93 (m, 2H), 7.25-7.37 (m, 5H, H-Ar).

^{13}C NMR (100.6 MHz) δ: 20.5 (CH_2), 26.8 (CH_2), 27.8 (CH_2), 31.3 (CH_2), 35.4 (CH), 36.0 (CH), 38.4 (CH_2), 46.2 (CH_2), 61.8 (CH_2), 63.7 (CH_2), 66.9 (CH), 67.7 (CH), 127.7 (C-Ar), 128.4 (2C-Ar), 129.0 (2C-Ar), 137.9 (C-*i*).

HRMS calculated for $[C_{18}H_{27}NO_2 + H]^+$: 290.2115; found: 290.2117.



(3a*R*,7*R*,7a*S*)-1-[(1*R*)-2-Hydroxy-1-phenylethyl]-7-phenyloctahydroindole (132)

Operating as in the above preparation of **128**, from $LiAlH_4$ (1 M in THF, 9 mL, 9.0 mmol) and $AlCl_3$ (800 mg, 6.0 mmol) in THF (29 mL) and a solution of lactam **118** (500 mg, 1.50 mmol) in THF (19 mL), octahydroindole **132** (366 mg, 76%) was obtained as a colourless oil.

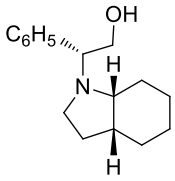
$[\alpha]^{22}_D$ –45.4 (c 1.03, $CHCl_3$).

Selected signals for compound **132**

^{1}H NMR (400 MHz) δ: 1.43-1.86 (m, 11H), 2.58-2.66 (m, 3H), 3.24-3.33 (m, 2H), 3.61 (t, *J* = 7.2 Hz, 1H), 7.03-7.04 (m, 2H, 2H), 7.05-7.37 (m, 8H).

^{13}C NMR (100.6 MHz) δ: 21.3, 26.9, 28.4, 32.5, 37.7, 48.3, 62.0 (CH), 66.5 (CH), 126.4 (C-Ar), 127.5 (C-Ar), 128.2 (2C-Ar), 128.6 (2C-Ar), 128.7 (2C-Ar).

HRMS calculated for $[C_{22}H_{27}NO + H]^+$: 322.2165; found: 322.2174.



(3a*R*,7a*R*)-1-[(1*R*)-2-Hydroxy-1-phenylethyl]octahydroindole (133)

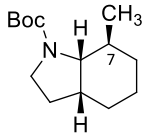
Operating as in the preparation of compound **128**, from $LiAlH_4$ (132 mg, 3.48 mmol) and $AlCl_3$ (310 mg, 2.3 mmol) in anhydrous THF (14 mL) and a solution of lactam **119** (150 mg, 0.58 mmol) in anhydrous THF (7 mL), octahydroindole **133** (93 mg, 65%) was obtained as a colourless oil.

$[\alpha]^{22}_D$ –75.4 (c 1.0, $CHCl_3$).

^{1}H NMR (400 MHz) δ: 1.22-1.63 (m, 10H), 1.83-2.01 (m, 2H), 2.54 (dt, *J* = 5.6 and 9.2 Hz, 1H), 2.69 (dd, *J* = 5.2 and 9.2 Hz, 1H), 2.92 (dt, *J* = 5.2 and 9.6 Hz, 1H), 3.69 (dd, *J* = 4.0 and 8.8 Hz, 1H), 3.90-3.99 (m, 2H), 7.17-7.36 (m, 5H, H-Ar).

^{13}C NMR (100.6 MHz) δ: 20.9 (CH_2), 24.1 (CH_2), 24.8 (CH_2), 28.2 (CH_2), 28.6 (CH_2), 37.3 (CH), 43.2 (CH_2), 57.8 (CH), 61.6 (CH), 61.7 (CH_2), 127.5 (C-Ar), 128.1 (2C-Ar), 129.0 (2C-Ar), 136.2 (C-*i*).

HRMS calculated for $[C_{16}H_{23}NO + H]^+$: 246.1852; found: 246.1850.



(3a*R*,7*S*,7a*R*)-1-(*tert*-Butoxycarbonyl)-7-methyloctahydroindole (134)

A solution of octahydroindole **128** (150 mg, 0.58 mmol) and Boc_2O (152 mg, 0.7 mmol) in CH_3OH (7 mL) was hydrogenated in the presence of 40% $Pd(OH)_2$ (60 mg) at room temperature for 8 h, at atmospheric pressure. The catalyst was removed by filtration and the solvent was evaporated. The resulting oil was purified, by flash-column chromatography (hexane to 7:3 hexane–EtOAc) to afford *cis*-octahydroindole **134** (110.7 mg, 80%) as a colourless oil.

IR (film): 2925, 1694 cm^{-1}.

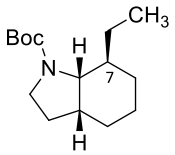
$[\alpha]^{22}_D$ –16.2 (c 1.0, $CHCl_3$).

Several of the signals in ^1H and ^{13}C NMR spectra of **134** at 25 °C were broad and ill-defined, even not observed.

^1H NMR (400 MHz) δ: 0.85-0.89 (m, 1H), 0.93-0.99 (m, 3H, C*H*$_3$), 1.26-1.74 (m, 7H), 1.46 [s, 9H, C(C*H*$_3$)], 1.88-1.93 (m, 1H), 2.18-2.21 (m, 1H), 3.31 (dt, *J* = 2.0 and 11.6 Hz, 1H), 3.36-3.40 (m, 1H), 3.45-3.49 (m, 1H).

^{13}C NMR (100.6 MHz) δ: 14.0 and 14.9 (CH_2), 20.2 and 20.7 (*C*H_3), 25.9 and 26.2 (CH), 26.9 (CH_2), 28.4 [C(*C*H_3)], 33.1 (CH), 34.1 and 34.5 (CH_2), 37.3 and 38.0 (CH_2), 44.3 and 45.0 (CH), 62.5 and 63.2 (CH_2), 78.4 and 78.8 [*C*(CH_3)], 155.2 (*C*O_2).

HRMS calculated for $[C_{14}H_{25}NO_2 + H]^+$: 240.1958; found: 240.1962.



(3a*R*,7*S*,7a*R*)-1-(*tert*-Butoxycarbonyl)-7-ethyloctahydroindole (135)

Operating as in the preparation of octahydroindole **134**, starting from **129** (184 mg, 0.67 mmol) Boc_2O (176 mg, 0.80 mmol) and 40% $Pd(OH)_2$ (74 mg) in CH_3OH (8 mL), octahydroindole **135** (95 mg, 56%) was obtained after flash-column chromatography (hexane to 7:3 hexane–EtOAc) as a colourless oil.

IR (film): 2928, 1694 cm^{-1}.

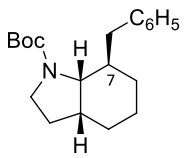
$[\alpha]^{22}_D$ –13.3 (c 1.0, $CHCl_3$).

Several of the signals in ^1H and ^{13}C NMR spectra of **135** at 25 °C were broad and ill-defined, even not observed.

^1H NMR (400 MHz) δ: 0.79-0.92 (m, 4H), 1.04-1.73 (m, 9H), 1.45 (s, 9H), 1.84-1.95 (m, 1H), 2.17-2.20 (m, 1H), 3.30 (dt, *J* = 2 and 11.2 Hz, 2H, H-2), 3.50 (m, 1H, H-7a).

^{13}C NMR (100.6 MHz) δ: 11.0 (CH_3), 20.7 (CH_2), 25.4 and 25.6 (CH_2), 26.1 and 26.3 (CH_2), 26.7 and 27.4 (CH), 28.5 [C(*C*H_3), CH_2], 37.7 and 38.1 (CH_2), 39.9 and 40.5 (CH), 44.4 and 45.1 (CH_2), 61.3 (CH), 78.6 [*C*(CH_3)], 155.5 (*C*O_2).

HRMS calculated for $[C_{15}H_{27}NO_2 + H]^+$: 254.2115; found: 254.2109.



(3a*R*,7*R*,7a*R*)-7-Benzyl-1-(*tert*-butoxycarbonyl)octahydroindole (136)

Operating as in the preparation of octahydroindole **134**, starting from **130** (169 mg, 0.50 mmol), Boc_2O (132 mg, 0.60 mmol) and 40% $Pd(OH)_2$ (68 mg) in CH_3OH (6 mL), octahydroindole **136** (116 mg, 73%) was obtained after flash-column chromatography (hexane to 7:3 hexane–EtOAc) as a colourless oil.

IR (film) 2928, 1692 cm^{-1}.

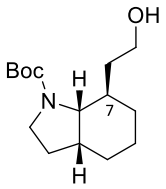
$[\alpha]^{22}_D$ –34.8 (c 1.0, $CHCl_3$).

Several of the signals in ^1H and ^{13}C NMR spectra of **136** at 25 °C were broad and ill-defined, even not observed.

^1H NMR (400 MHz) δ: 0.77-0.90 (m, 2H), 1.15-1.31 (m, 1H), 1.40-2.10 (m, 4H), 1.47 and 1.52 [s, 9H, C(CH_3)], 1.89-1.94 (m, 2H), 2.04-2.10 (m, 1H), 2.25 (m, 1H), 3.13-3.17 (m, 1H), 3.40-3.47 (m, 1H), 3.56-3.63 (m, 1H), 3.69 (br. s, 1H), 7.11-7.17 (m, 3H), 7.12-7.26 (m, 2H).

^{13}C NMR (100.6 MHz) δ: 20.4 and 20.6 (CH_2), 26.0 and 26.2 (CH_2), 27.4 (CH), 28.5 [C(*C*H_3)], 28.7 and 28.9 (CH_2), 37.6 and 38.2 (CH), 40.1 and 40.2 ($2CH_2$), 41.3 and 41.5 (CH), 44.5 and 45.1 (CH_2), 61.7 and 62.5 (CH), 78.8 and 79.3 (CH_3), 125.4 and 125.6 (C-Ar), 127.9 (C-Ar), 129.1 (3C-Ar), 141.2 and 141.6 (C-*i*), 155.4 and 155.7 (*C*O_2).

HRMS calculated for $[C_{20}H_{29}NO_2 + H]^+$: 316.2271; found: 316.2279.



(3a*R*,7*R*,7a*S*)-1-(*tert*-Butoxycarbonyl)-7-(2-hydroxyethyl)octathydroindole (137)

Operating as in the preparation of octahydroindole **134**, starting from **131** (254 mg, 0.88 mmol) Boc_2O (230 mg, 1.1 mmol) and 40% $Pd(OH)_2$ (102 mg) in CH_3OH (11 mL), octahydroindole **137** (165 mg, 70%) was obtained after flash-column chromatography (hexane to 7:3 hexane–EtOAc) as a colourless oil.

IR (film) 3437, 2926, 1688 cm^{-1}.

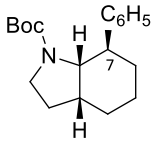
$[\alpha]^{22}_D$ –3.3 (c 0.16, $CHCl_3$).

Several of the signals in ^1H and ^{13}C NMR spectra of **137** at 25 °C were broad and ill-defined, even not observed.

^1H NMR (400 MHz) δ: 1.17-1.69 (m, 10H), 1.46 (s, 9H), 1.87-2.05 (m, 1H), 2.17-2.25 (m, 1H), 3.30-3.41 (m, 2H), 3.52 (br. s, 1H), 3.66-3.72 (m, 2H), 3.89-3.93 (m, 1H).

^{13}C NMR (100.6 MHz) δ: 20.9 (CH_2), 26.2 (CH_2), 26.8 (CH_2), 28.5 [C(*C*H_3)], 28.9 (CH_2), 34.5 (CH_2), 36.8 (CH), 37.6 (CH), 45.2 (CH_2), 60.1 (CH_2), 60.4 (CH), 79.3 [*C*(CH_3)], 156.0 (*C*O_2).

HRMS calculated for $[C_{15}H_{27}NO_3 + H]^+$: 270.2064; found: 270.2071.



(3a*R*,7*R*,7a*S*)-1-(*tert*-Butoxycarbonyl)-7-phenyloctahydroindole (138)

Operating as in the preparation of octahydroindole **134**, starting from **132** (368 mg, 1.15 mmol), Boc_2O (301 mg, 1.37 mmol) and 40% $Pd(OH)_2$ (147 mg), in CH_3OH (11 mL), octahydroindole **138** (277 mg, 80%) was obtained after flash-column chromatography (hexane to 7:3 hexane–EtOAc) as a colourless oil.

IR (film) 2926, 2888, 1687 cm^{-1}.

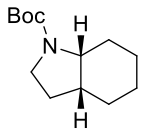
$[\alpha]^{22}_D$ + 22.0 (c 1.06, $CHCl_3$).

mp = 108-109 °C.

^{1}H NMR (400 MHz) δ: 0.98 [s, 9H, C(C*H*$_3$)], 1.48-1.70 (m, 3H, H-4, H-5), 1.72-1.89 (m, 4H, H-3, H-4, H-6), 2.01-2.16 (m, 1H, H-3), 2.32-2.43 (m, 2H, H-3a, H-7), 3.41 (t, *J* = 11.8 Hz, 1H, H-2), 3.53-3.60 (m, 1H, H-2), 3.85 (dd, *J* = 6.0 and 10.4 Hz, 1H, H-7a), 7.13-7.27 (m, 5H, H-Ar).

^{13}C NMR (100.6 MHz) δ: 21.0 (C-5), 25.8 (C-3), 26.2 (C-6), 27.8 [C(*C*H$_3$)], 31.5 (C-4), 38.4 (C-3a), 43.9 (C-2), 45.4 (C-7), 62.8 (C-7a), 78.5 [C(CH_3)], 125.9 (C-Ar), 127.8 (2C-Ar), 128.2 (2C-Ar), 144.5 (C-*i*), 154.6 (*C*O$_2$).

HRMS calculated for $[C_{19}H_{27}NO_2 + H]^+$: 302.2115; found: 302.2124.



(3a*R*,7a*R*)-1-(*tert*-Butoxycarbonyl)octahydroindole (139)[212]

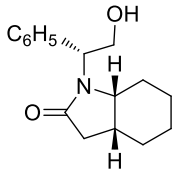
Operating as in the preparation of octahydroindole **133** (90 mg, 0.37 mmol), Boc_2O (96 mg, 0.44 mmol) and 40% $Pd(OH)_2$ (36 mg) in CH_3OH (5 mL) *cis*-octahydroindole **139** (71 mg, 79%) was obtained as a colorless oil, after flash-column chromatography (hexane to 8:2 hexane EtOAc).

Several of the signals in ^1H and ^{13}C NMR spectra of **139** at 25 °C were broad and ill-defined, even not observed.

^1H NMR (400 MHz) δ: 1.14-1.39 (m, 3H), 1.45 [s, 9H, C(CH_3)], 1.61-1.73 (m, 4H), 1.85-1.93 (m, 2H), 2.16-2.25 (m, 1H), 3.25-3.47 (m, 3H), 3.62-3.73 (m, 1H).

^{13}C NMR (100.6 MHz) δ: 20.9 and 21.1 (CH_2), 23.5 and 23.7 (CH_2), 26.1 and 26.3 (CH_2), 27.1 (CH_2) 27.4 (CH_2), 27.9 and 28.6 [C(*C*H_3)], 36.8 and 37.5 (CH), 44.8 and 45.2 (CH_2), 56.2 and 56.4 (CH), 78.6 (Cq), 129.0 (*C*O_2).

[212] Already described: Haya, L.; Sayago, F.; Mainar, A.M.; Cativela, C.; Urieta, J.S. *Physical Chemistry Chemical Physics*, **2011**, *13*, 17696-17703



(3a*R*,7a*R*)-1-[(1*R*)-2-Hydroxy-1-phenylethyl]-2-oxooctahydroindole (140)

Triphenylsilane (736 mg, 2.8 mmol) was added to a solution of **119** (330 mg, 1.28 mmol) in CH_2Cl_2 (6 mL) at − 78°C. The mixture was stirred at this temperature for 20 min and $TiCl_4$ (322 μL, 2.8 mmol) was then added dropwise, and the stirring was continued at the same temperature for 2 h. The solution was then warmed at room temperature and was allowed to react for 12 h. The mixture was poured into saturated aqueous NH_4Cl (6 mL), the organic phase was separated and the aqueous phase was extracted with CH_2Cl_2 (3 x 10 mL). The combined organic extracts were dried and concentrated. Flash-column chromatography (CH_2Cl_2 to 95:5 CH_2Cl_2–CH_3OH) afforded octahydroindolone **140** (319 mg, 96%) as a colourless oil.

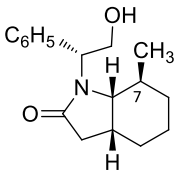
IR (film): 3368, 2931 2855, 1664 cm^{-1}.

$[\alpha]^{22}_D$ +23.0 (c 0.93, $CHCl_3$).

^{1}H NMR (400 MHz) δ: 1.12-1.19 (m, 1H, H-5), 1.38-1.49 (m, 4H, H-5, H-6, H-7), 1.54-1.57 (m, 2H, H-4), 1.66-1.72 (m, 1H, H-7), 2.33-2.42 (m, 3H, H-3, H-3a), 3.29-3.34 (m, 1H, H-7a), 3.93-3.99 (m, 1H, C*H*$_2$OH), 4.19-4.26 (m, 1H, C*H*$_2$OH), 4.49 (dd, *J* = 3.6 and 8.0 Hz, 1H, C*H*N), 4.82 (t, *J* = 6.8 Hz, 1H, OH), 7.24-7.36 (m, 5H, H-Ar).

^{13}C NMR (100.6 MHz) δ: 21.4 (C-6), 21.44 (C-5), 26.4 (C-4), 26.9 (C-7), 32.8 (C-3a), 36.7 (C-3), 58.1 (C-7a), 61.5 (*C*HN), 64.0 (*C*H$_2$OH), 125.1 (2C-Ar), 127.0 (C-Ar), 128.5 (2C-Ar), 137.6 (C-*i*), 176.7 (*C*O).

HRMS calculated for $[C_{16}H_{21}NO_2 + H]^+$: 260.1645; found: 260.1647.



(3a*R*,7*S*,7a*R*)-1-[(1*R*)-2-Hydroxy-1-phenylethyl]-7-methyl-2-oxooctahydroindole (141)

Operating as in the preparation of **140**, from **112a** (730 mg, 2.7 mmol), triphenylsilane (1.54 g, 5.9 mmol) and $TiCl_4$ (682 μL, 5.9 mmol) in CH_2Cl_2 (12 mL) octahydroindolone **141** (640 mg, 87%) was obtained after flash-column chromatography (CH_2Cl_2) as a colourless oil.

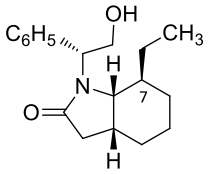
IR (film): 3450, 2928, 1666 cm^{-1}.

$[\alpha]^{22}_D$ +53.2 (c 1.0, $CHCl_3$).

^{1}H NMR (400 MHz) δ: 1.03 (d, *J* = 6.8 Hz, 3H, CH_3), 1.09 (t, *J* = 8.0 Hz, 1H, H-4), 1.40-1.42 (m, 1H, H-5), 1.47-1.51 (m, 4H, H-4, H-5, H-6), 1.86-189 (m, 1H, H-7), 2.36-2.42 (m, 3H, H-3, H-3a), 2.97 (t, *J* = 6.0 Hz, 1H, H-7a), 3.95-4.01 (m, 1H, C*H*$_2$OH), 4.23-4.30 (m, 1H, C*H*$_2$OH), 4.55 (dd, *J* = 3.2 and 8.0 Hz, 1H, C*H*N), 4.89 (t, *J* = 8.0 Hz, 1H, OH), 7.21-7.37 (m, 5H, H-Ar).

^{13}C NMR (100.6 MHz) δ: 19.2 (C-5), 19.7 (CH_3), 26.9 (C-6), 30.0 (C-4), 31.7 (C-7), 33.2 (C-3a), 37.6 (C-3), 64.4 (*C*HN), 64.9 (*C*H_2OH), 65.4 (C-7a), 127.0 (2C-Ar), 127.8 (C-Ar), 128.7 (2C-Ar), 137.7 (C-*i*), 177.6 (*C*O).

HRMS calculated for $[C_{17}H_{23}NO_2 + H]^+$: 274.1802; found: 274.1799.



(3a*R*,7*S*,7a*R*)-7-Ethyl-1-[(1*R*)-2-hydroxy-1-phenylethyl]-2-oxooctahydroindole (142)

Operating as in the preparation of **140**, from **114** (390 mg, 1.37 mmol), triphenylsilane (781 mg, 3.0 mmol) and $TiCl_4$ (345 μL, 3.0 mmol) in CH_2Cl_2 (6 mL), octahydroindolone **142** (311 mg, 79%) was obtained as a colourless oil after flash-column chromatography (CH_2Cl_2 to 9:1 CH_2Cl_2–CH_3OH).

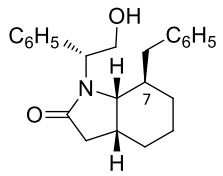
IR (film): 3367, 2932, 2865, 1667 cm^{-1}.

$[\alpha]^{22}_D$ +58.9 (c 1.12, $CHCl_3$).

^1H NMR (400 MHz) δ: 0.72 (t, *J* = 7.2 Hz, 3H, C*H*$_3$), 1.22-1.27 (m, 8H, H-4, H-5, H-6, H-1.2), 1.71 (br. s, 1H, H-7), 2.25 (dd, *J* = 4.8 and 15.6 Hz, 1H, H-3), 2.30-2.37 (m, 1H, H-3a), 2.46 (dd, *J* = 6.4 and 15.6 Hz, 1H, H-3), 3.16 (t, *J* = 5.2, 1H, H-7a), 4.00 (m, 1H, C*H*$_2$OH), 4.27 (dt, *J* = 8 and 12 Hz, 1H, C*H*$_2$OH), 4.44 (dd, *J* = 3.2 and 7.6 Hz, 1H, C*H*N), 4.81 (t, *J* = 8 Hz, 1H, OH), 7.14-7.40 (m, 5H, H-Ar).

^{13}C NMR (100.6 MHz) δ: 11.3 (CH_3), 18.7 (C-5), 24.4 (H-1.2), 25.2 (C-6), 27.4 (C-4), 32.0 (C-3a), 36.0 (C-7), 38.9 (C-3), 62.3 (C-7a), 63.4 (*C*H_2N), 64.8 (*C*H_2OH), 127.3 (2C-Ar), 127.8 (C-Ar), 128.7 (2C-Ar), 137.5 (C-*i*), 178.1 (*C*N).

HRMS calculated for $[C_{18}H_{25}NO_2 + H]^+$: 288.1958; found: 288.1960.



(3a*R*,7*R*,7a*R*)-7-Benzyl-1-[(1*R*)-2-hydroxy-1-phenylethyl]-2-oxooctahydroindole (143)

Operating as in the preparation of **140**, from **116** (140 mg, 0.4 mmol), triethylsilane (140 μL, 0.88 mmol) and $TiCl_4$ (97 μL, 0.88 mmol) in CH_2Cl_2 (2 mL), octahydroindolone **143** (87 mg, 62%) was obtained as a colourless oil after flash-column chromatography (CH_2Cl_2).

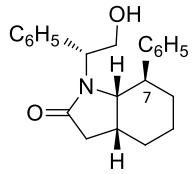
IR (film): 3340, 2930, 1667 cm^{-1}.

$[\alpha]^{22}_D$ +12.8 (c 1.0, $CHCl_3$).

^{1}H NMR (400 MHz) δ: 1.19-1.24 (m, 1H, H-4), 1.34-1.42 (m, 3H, H-4, H-5, H-6), 1.47-1.53 (m, 1H, H-5), 1.60-1.66 (m, 1H, H-6), 2.15-2.18 (m, 1H, H-3a), 2.20 (dd, *J* = 3.6 and 16 Hz, 1H, C*H*$_2$Ph), 2.36-2.39 (m, 1H, H-7), 2.52-2.44 (m, 2H, H-3, C*H*$_2$Ph), 2.65 (dd, *J* = 6.8 and 13.6 Hz, 1H, H-3), 3.23 (t, *J* = 4,0 Hz, 1H, H-7a), 3.99-4.03 (m, 1H, C*H*$_2$OH), 4.21-4.28 (m, 1H, C*H*$_2$OH), 4.47 (dd, *J* = 3.6 and 8.4 Hz, 1H, C*H*N), 4.65 (t, *J* = 7.2 Hz, 1H, OH), 6.91-6.93 (m, 1H, H-Ar), 7.11-7.32 (m, 9H, H-Ar).

^{13}C NMR (100.6 MHz) δ: 18.3 (C-5), 24.5 (C-4), 27.4 (C-6), 31.2 (C-7), 35.4 (C-3a), 37.8 (C-3), 39.2 (*C*H$_2$Ph), 62.0 (C-7a), 62.6 (*C*HN), 64.4 (*C*H$_2$OH), 126.0 (C-Ar), 127.2 (2C-Ar), 127.7 (C-Ar), 128.3 (2C-Ar), 128.5 (2C-Ar), 128.6 (2C-Ar), 137.2 (C-*i*), 139.5 (C-*i*), 178.2 (*C*O).

HRMS calculated for $[C_{23}H_{27}NO_2 + H]^+$: 350.2115; found: 350.2110.



(3a*R*,7*R*,7a*S*)-1-[(1*R*)-2-Hydroxy-1-phenylethyl]-7-phenyl-2-oxooctahydroindole (144)

Operating as in the preparation of **140**, from **118** (300 mg, 0.90 mmol), triethylsilane (316 μL, 1.98 mmol) and $TiCl_4$ (228 μL, 1.98 mmol) in CH_2Cl_2 (4 mL), octahydroindolone **144** (241 mg, 80%) was obtained as a colourless oil after flash-column chromatography (CH_2Cl_2).

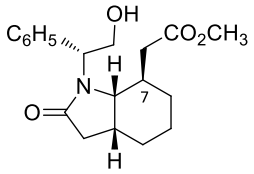
IR (NaCl): 3346, 2931, 1667 cm^{-1}.

$[\alpha]^{22}_D$ +68.72 (c 0.88, $CHCl_3$).

^{1}H NMR (400 MHz) δ: 1.34 (dq, *J* = 2.4 and 13.2 Hz, 1H, H-4), 1.48-1.60 (m, 2H, H-5, H-6), 1.62-1.69 (m, 1H, H-5), 1.73-1.78 (m, 1H, H-4), 1.81-1.85 (m, 1H, H-6), 2.36 (dd, *J* = 7.6 and 15.6 Hz, 1H, H-3), 2.57-2.63 (m, 1H, H-7a), 2.68 (td, *J* = 3.6 and 11.6 Hz, 1H, H-3a), 2.73 (t, *J* = 15.6 Hz, 1H, H-3), 3.31-3.35 (m, 2H, C*H*N, H-7), 3.58-3.63 (m, 1H, C*H*$_2$OH), 3.70-3.75 (m, 1H, C*H*$_2$OH), 5.03 (t, *J* = 6.4 Hz, 1H, OH), 6.76-6.80 (m, 2H, H-Ar), 7.16-7.40 (m, 8H, H-Ar).

^{13}C NMR (100.6 MHz) δ: 20.5 (C-5), 25.9 (C-6), 32.9 (C-4), 35.2 (C-3), 35.3 (C-7), 48.0 (C-3a), 64.4 (*C*H$_2$OH), 65.1 (C-7a), 65.4 (*C*HN), 127.0 (3C-Ar), 127.1 (C-Ar), 127.5 (C-Ar), 128.4 (3C-Ar), 129.0 (2C-Ar), 137.8 (C-*i*), 144.2 (C-*i*), 176.3 (*C*O).

HRMS calculated for $[C_{22}H_{25}NO_2 + H]^+$: 336.1958; found: 336.1959.



Methyl (3a*R*,7*R*,7a*S*)-1-[(1*R*)-2-Hydroxy-1-phenylethyl]-2-oxooctahydroindoline-7-acetate (145)

Operating as in the preparation of **140,** from **110** (299 mg, 0.91 mmol), triethylsilane (319 μL, 2.0 mmol) and $TiCl_4$ (220 μL, 2.0 mmol) in CH_2Cl_2 (4 mL), octahydroindolone **145** (141 mg, 47%) was obtained as a colorless oil after flash-column chromatography (CH_2Cl_2).

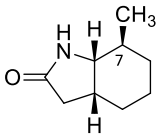
IR (film): 3345, 2933, 1735, 1667 cm^{-1}.

$[\alpha]^{22}_D$ +36.1 (c 1.0, $CHCl_3$).

^{1}H NMR (400 MHz) δ: 1.21 (dt, *J* = 1.6 and 6.8 Hz, 1H, H-6), 1.41 (br. s, 4H, H-4, H-5 H-6), 1.54-1.61 (m, 1H, H-4), 2.25 (dd, *J* = 4.8 and 15.6 Hz, 1H, C*H*$_2$CO$_2$), 2.28-2.40 (m, 4H, H-2, H-3a, H-7), 2.45 (dd, *J* = 6.8 and 15.6 Hz, 1H, C*H*$_2$CO$_2$), 3.30 (t, *J* = 4.4 Hz, 1H, H-7a), 3.55 (s, 3H, CH_3), 4.04 (dd, *J* = 4 and 12 Hz, 1H, C*H*$_2$OH), 4.35 (dt, *J* = 3.6 and 12 Hz, 1H, C*H*$_2$OH), 4.43-4.48 (m, 1H, OH), 4.62 (dd, *J* = 4 and 8 Hz, 1H, C*H*N), 7.24-7.36 (m, 5H, H-Ar).

^{13}C NMR (100.6 MHz) δ: 18.6 (C-5), 25.9 (C-6), 26.9 (C-4), 31.6 (C-7a), 31.8 (C-3a), 36.8 (C-2), 38.3 (*C*H$_2$Ph), 51.5 (CH_3), 61.4 (C-7a), 62.1 (*C*HN), 63.8 (*C*H$_2$OH), 127.2 (2C-Ar), 127.6 (C-Ar), 128.5 (2C-Ar), 137.4 (C-*i*), 172.2 (*C*O), 177.9 (*C*O$_2$).

HRMS calculated for $[C_{19}H_{25}NO_4 + H]^+$: 332.1856; found: 332.1848.



(3a*R*,7*S*,7a*R*)-7-Methyl-2-oxooctahydroindole (146a)

Into a three-necked, 100 mL round-bottomed flask equipped with a coldfinger condenser charged with dry-ice acetone were condensed 30 mL of NH_3 at –78 °C. Then, sodium metal was added in small portions until the blue colour persisted, and a solution of **141a** (320 mg, 1.17 mmol) in anhydrous THF (5 mL) was added slowly. After the mixture was stirred at –78 °C for 2 min, the reaction was quenched by addition of aqueous saturated NH_4Cl (10 mL). The stirring was continued at room temperature until NH_3 evaporates. The resulting mixture was extracted with CH_2Cl_2 (3 x 10 mL) and the combined organic extracts were dried and concentrated. Flash-column chromatography (7:3 hexane–EtOAc) afforded *cis*-octahydroindolone **146a** (176 mg, 98%) as a colourless oil.

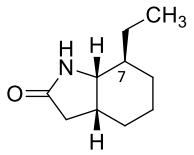
IR (film) 3212, 2924, 1692 cm^{-1}.

$[\alpha]^{22}_D$ +3.61 (c 1.04, $CHCl_3$).

^{1}H NMR (400 MHz) δ: 0.98 (d, *J* = 6.8 Hz, 3H, C*H*$_3$), 1.36-1.44 (m, 2H, H-5, H-7), 1.52-1.62 (m, 4H, H-4, H-5, H-6), 1.68-1.73 (m, 1H, H-4), 2.16 (dd, *J* = 8.4 and 16.4 Hz, 1H, H-3), 2.34 (dd, *J* = 10.8 and 16.4 Hz, 1H, H-3), 2.52-2.62 (m, 1H, H-3a), 3.03 (t, *J* = 7.2 Hz, 1H, H-7a).

^{13}C NMR (100.6 MHz) δ: 19.2 (*C*H$_3$), 20.4 (C-5), 26.3 (C-4), 30.6 (C-6), 34.4 (C-3), 34.5 (C-3a), 35.4 (C-7), 60.6 (C-7a), 178.8 (*C*O).

HRMS calculated for $[C_9H_{15}NO_2 + H]^+$: 154.1226; found: 154.1227.



(3a*R*,7*S*,7a*R*)-7-Ethyl-2-oxooctahydroindole (147a)

Operating as in the preparation of **146a**, from **142a** (156 mg, 0.54 mmol) in THF (6 mL), sodium in small portions, and liquid NH_3 (35 mL), octahydroindolone **147a** (58 mg, 64%) was obtained as a colorless oil after flash-column chromatography (95:5 hexane–AcOEt to AcOEt).

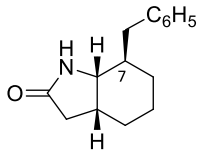
IR (film): 2961, 2931, 2859, 1689 cm^{-1}.

$[\alpha]^{22}_D$ +4.52 (c 0.75, $CHCl_3$).

^{1}H NMR (400 MHz) δ: 0.83-0.98 (m, 1H, H-6), 0.90 (t, *J* = 3.6 Hz, 3H, C*H*$_3$), 1.10-1.41 (m, 3H, H-4, H-5, H-7), 1.49-1.76 (m, 5H, H-4, H-5, H-6, C*H*$_2$CH$_3$), 2.16 (dd, *J* = 8.4 and 16.0 Hz, 1H, H-3), 2.23 (dd, *J* = 10.0 and 16.0 Hz, 1H, H-3), 2.52-2.60 (br. s, 1H, H-3a), 3.13 (t, *J* = 8.0 Hz, 1H, H-7a), 6.42 (br. s, 1H, NH).

^{13}C NMR (100.6 MHz) δ: 11.1 (CH$_3$), 20.2 (C-5), 25.8 (C-4), 26.4 (C-6), 26.6 (*C*H$_2$CH$_3$), 34.3 (C-3), 34.6 (C-3a), 41.7 (C-7), 58.8 (C-7a), 178.8 (*C*O).

HRMS calculated for $[C_{10}H_{17}NO + H]^+$: 168.1383; found: 168.1384.



(3a*R*,7*R*,7a*R*)-7-Benzyl-2-oxooctahydroindole (148a)

Operating as in the preparation of **146a**, from **143a** (350 mg, 1.0 mmol) in THF (6 mL), sodium in small portions, and liquid NH_3 (35 mL), octahydroindolone **148a** (152 mg, 66%) was obtained as a white solid after flash-column chromatography (99:1 to 97:3 CH_2Cl_2– CH_3OH).

IR (film): 3215, 2925, 1689 cm^{-1}.

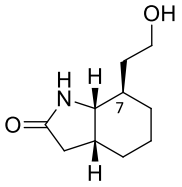
$[\alpha]^{22}_D$ + 9.77 (c 1.33, $CHCl_3$).

mp: 118-120 °C.

^{1}H NMR (400 MHz) δ: 0.85-0.94 (m, 1H, H-6), 1.22-1.31 (m, 2H, H-5, H-6), 1.48-1.68 (m, 4H, H-4, H-5, H-7), 2.15 (dd, *J* = 8.4 and 16.8 Hz, 1H, H-3), 2.22 (dd, *J* = 10.8 and 16.8 Hz, 1H, H-3), 2.39 (dd, *J* = 8.8 and 13.2 Hz, 1H, C*H*$_2$Ph), 2.53-2.59 (m, 1H, H-3a), 2.87 (dd, *J* = 4.4 and 13.2 Hz, 1H, C*H*$_2$Ph), 3.21 (t, *J* = 8.0 Hz, 1H, H-7a), 7.13-7.20 (m, 3H, H-Ar), 7.24-7.28 (m, 2H, H-Ar), 7.70 (br.s, 1H, NH).

^{13}C NMR (100.6 MHz) δ: 20.0 (C-5), 26.1 (C-4), 27.1 (C-6), 34.4 (C-3), 34.5 (C-3a), 39.8 (*C*H$_2$Ph), 42.4 (C-7), 58.5 (C-7a), 125.8 (C-Ar), 128.1 (2C-Ar), 129.0 (2C-Ar), 139.6 (C-*i*), 178.6 (*C*O).

HRMS calculated for $[C_{15}H_{19}NO + H]^+$: 230.1539; found: 230.1534.



(3a*R*,7*R*,7a*R*)-7-(2-Hydroxyethyl)-2-oxooctahydroindole (149a)

Operating as in the above preparation of **146a**, from **145a** (110 mg, 0.33 mmol) in THF (3 mL), sodium in small portions, and liquid NH_3 (35 mL), octahydroindolone **149a** (36 mg, 60%) was obtained as a colorless oil after flash-column chromatography (99:1 to 97:3 CH_2Cl_2–CH_3OH).

IR (film) 3264, 2933, 1687 cm^{-1}.

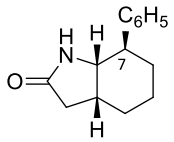
$[\alpha]^{22}_D$ +2.57 (c 1.5, $CHCl_3$).

Several of the signals in ^1H and ^{13}C NMR spectra of **149a** at 25 °C were broad and ill-defined, even not observed.

^1H NMR (400 MHz) δ: 0.88-0.99 (m, 1H), 1.37-1.68 (m, 9H, H-4, H-5, H-6, H-7, C*H*$_2$CH$_2$OH), 2.14-2.27 (m, 2H, H-3), 2.58 (br. s, 1H, H-3a), 3.18 (t, *J*= 8.0 Hz, 1H, H-7a), 3.60-3.66 (m, 1H, C*H*$_2$OH), 3.74-3.79 (m, 1H, C*H*$_2$OH).

^{13}C NMR (100.6 MHz) δ: 20.3 (C-5), 26.2 (C-6), 28.6 (C-4), 34.6 (C-3), 34.6 (C-3a), 37.4 (*C*H$_2$CH$_2$OH), 38.5 (C-7), 59.4 (C-7a), 60.4 (*C*H$_2$OH), 178.8 (*C*O).

HRMS calculated for $[C_{10}H_{17}NO_2 + H]^+$: 184.1332; found: 184.1329.



(3a*R*,7*R*,7a*S*)-7-Phenyl-2-oxooctahydroindole (126a)[213]

Operating as in the above preparation of **146a**, from **144a** (226 mg, 0.67 mmol) in THF (2 mL), sodium, and liquid NH_3 (~35 mL), octahydroindolone **126a** (127 mg, 87%) was obtained as a white solid after flash-column chromatography (7:3 to 1:1 hexane–EtOAc).

IR (film): 1685 cm^{-1}.

$[\alpha]^{22}_D$ +37.6 (c 0.5 $CHCl_3$).

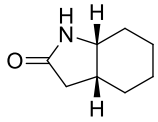
mp = 187-188 °C.

^{1}H NMR (400 MHz) δ: 1.46-1.56 (m, 2H), 1.71-1.89 (m, 4H), 2.21 (d, *J* = 8.8 and 16.4 Hz, 1H), 2.35-2.47 (m, 2H), 2.70-2.80 (m, 1H, H-7), 3.46 (dd, *J* = 7.2 and 9.6 Hz, 1H, H-7a), 5.59 (br.s, 1H, NH), 7.17-7.33 (m, 5H, H-Ar).

^{13}C NMR (100.6 MHz) δ: 21.1, 26.1, 30.3, 33.4, 34.9, 48.5. 59.8, 126.9, 127.5, 128.7, 143.1, 177.6.

HRMS calculated for $[C_{14}H_{17}NO + H]^+$: 216.1383; found: 216.1386.

[213] Already described: Yasuhara T.; Nishimura, K.; Osafumi, E.; Muraoka, O.; Tomioka, K. *Chem. Pharm. Bull.* **2004**, *52*, 1109-1113.



(3a*R*,7a*R*)-2-oxooctahydroindole (150)[214]

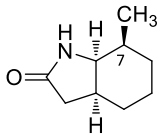
Operating as in the preparation of **146a**, from **140a** (240 mg, 0.93 mmol) in THF (5 mL), sodium in small portions, and liquid NH_3 (35 mL), octahydroindolone **150** (91 mg, 70%) was obtained as a white solid after flash-column chromatography (CH_2Cl_2).

^{1}H NMR (400 MHz) δ: 1.26-1.70 (m, 8H), 2.03-2.08 (m, 1H), 2.32-2.40 (m, 2H), 3.66-3.70 (m, 1H), 6.45 (br. s, 1H, NH).

^{13}C NMR (100.6 MHz) δ: 20.5 (C-5), 22.6 (C-6), 27.2 (C-7), 28.7 (C-4), 34.3 (C-3a), 37.9 (C-3), 53.3 (CH-7a), 180.0 (*C*O).

HRMS calculated for $[C_8H_{13}NO + H]^+$: 140.1070; found: 140.1072.

[214]Already described: *Tetrahedron Asymmetry* **1996**, *7*, 2531−2538.



(3a*S*,7*S*,7a*S*)-7-Methyl-5-oxooctahydroindole (146b)

A solution of **113b** (427 mg, 1.57 mmol) in CH_3OH (1 mL) containing Pt/C (214 mg) was stirred under hydrogen at room temperature for 12 h. The mixture was filtrated over Celite® and the solvent was evaporated affording the compound **141c** (390 mg, 91%) as colourless oil.

More significant spectroscopic data for compound **141c**

^{1}H NMR (400 MHz) δ: 0.93 (d, *J* = 7.2 Hz, 3H, C*H*$_3$), 1.25-1.65 (m, 6H), 1.99-2.04 (m, 1H), 2.24-2.41 (m, 3H), 3.35 (t, *J* = 6Hz, 1H), 3.73 (br. s, 1H, OH), 4.04 (dd, *J* = 5.6 and 11.2 Hz, 1H), 4.25 (t, *J* = 8.6 Hz, 1H), 5.02 (dd, *J* = 5.6 Hz and 8.6 Hz, 1H), 7.25-7.35 (m, 5H, H-Ar).

^{13}C NMR (100.6 MHz) δ: 16.0 (*C*H_3), 26.0 (2CH_2), 28.7 (CH_2), 32.4 (CH), 33.9 (CH), 37.8 (CH_2), 60.7 (CH), 62.0 (CH), 63.7 (CH_2), 127.8 (C-Ar), 128.0 (2C-Ar), 128.5 (2C-Ar), 137.3 (C-*i*), 177.6 (*C*O).

Into a three-necked, round-bottomed flask equipped with a coldfinger condenser charged with dry ice-acetone was condensed NH_3 (~30 mL) at –78 °C. Then, sodium metal was added in small portions until the dark blue colour persisted, and a solution of **141c** (360 mg, 1.31 mmol) in anhydrous THF (4 mL) was added slowly. After the mixture was stirred at –78 °C for 3 min the reaction was carefully quenched by addition of NH_4Cl. The stirring was continued at room temperature until NH_3 evaporates. The resulting solid mixture was partitioned between water and CH_2Cl_2. The aqueous phase was extracted with CH_2Cl_2 and the combined organic extracts were dried and concentrated. Flash-column chromatography (1:1 hexane–EtOAc) afforded octahydroindolone **146b** (165 mg, 82%) as a white solid.

Spectroscopic and analytical data for compound **146b**

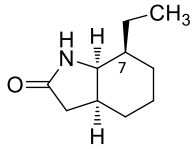
IR (film): 3204, 2924, 1701 cm^{-1}.

$[\alpha]^{22}_D$ – 18.5 (c 1.02, $CHCl_3$).

^{1}H NMR (400 MHz) δ: 0.99 (d, *J* = 7.2 Hz, 3H, *C*H_3), 1.09-1.29 (m, 2H, H-4, H-6), 1.43-1.48 (m, 1H, H-5), 1.61-71.71 (m, 4H, H-4, H-5, H-6, H-7), 1.95 (d, *J* = 16.4 Hz, 1H, H-3), 2.19-2.30 (m, 1H, H-3a), 2.49 (dd, *J* = 6.4 and 164 Hz, 1H, H-3), 3.68 (t, *J* = 4.4 Hz, 1H, H-7a), 5.42 (br. s, 1H, NH).

^{13}C NMR (100.6 MHz) δ: 19.2 (*C*H$_3$), 24.2 (C-5), 27.5 (C-4), 27.8 (C-6), 33.1 (C-7), 35.3 (C-3a), 40.0 (C-3), 58.5 (C-7a), 178.7 (*C*O).

HRMS calculated for [$C_9H_{15}NO$ + H]$^+$: 154.1226; found: 154.1223.



(3a*S*,7*S*,7a*S*)-7-Ethyl-5-oxooctahydroindole (147b)

Operating as in the preparation of **141c**, from **115b** (130 mg, 0.46 mmol) in CH_3OH (1 mL) and Pt/C (65 mg), lactam **142c** (110 mg, 84 %) was obtained**.**

More significant spectroscopic data for compound **142c**

^{1}H NMR (400 MHz) δ: 0.69 (t, *J* = 6.8 Hz, 3H, C*H*$_3$), 1.14-1.31 (m, 3H, H-1.2, H-5, H-4), 1.40-1.49 (m, 2H, H-1.2, H-5), 1.52-1.69 (m, 3H, H-4, H-6, H-7), 2.20-2.38 (m, 3H, H-3, H-3a), 3.44 (dd, *J* = 6.0 and 12.4 Hz, 1H, H-7a), 3.63 (br. s, 1H, OH), 4.00-4.05 (m, 1H, C*H*$_2$OH), 4.19-4.26 (m, 1H, C*H*$_2$OH), 4.88 (dd, *J* = 4.8 and 8.0 Hz, 1H, C*H*N), 7.27-7.35 (m, 5H, H-Ar).

^{13}C NMR (100.6 MHz) δ: 12.6 (*C*H$_3$), 16.8 (C-1.2), 21.2 (C-5), 24.2 (C-4), 26.3 (C-6), 34.2 (C-3a), 38.0 (C-3), 40.3 (C-7), 61.4 (C-1.1), 63.1 (C-7a), 64.2 (C-2.1), 127.8 (C-Ar), 128.1 (2C-Ar), 128.6 (2C-Ar), 137.5 (C-*i*), 177.9 (*C*O).

Operating as in the preparation of **146b**, from **142c** (98 mg, 0.34 mmol) in THF (2 mL), sodium, and liquid NH_3 (~35 mL), octahydroindolone **147b** (41 mg, 72%) was obtained as a colourless oil after flash chromatography (7:3 hexane–EtOAc to EtOAc).

Spectroscopic and analytical data for compound **147b**

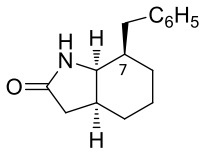
IR (film): 2928, 2856, 1701 cm^{-1}.

$[\alpha]^{22}_D$ –24.0 (c 1.00, $CHCl_3$).

^{1}H NMR (400 MHz) δ: 0.96 (t, *J* = 7.2 Hz, 3H, C*H*$_3$), 1.18-1.44 (m, 4H, H-6, H-7, C*H*$_2$CH$_3$), 1.55-1.58 (m, 2H, H-4), 1.61-1.84 (m, 3H, H-5, H-6), 1.94 (d, *J* = 16.2 Hz, 1H, H-3), 2.17-2.30 (m, 1H, H-3a), 2.49 (dd, *J* = 6 and 16.2 Hz, 1H, H-3), 3.77 (t, *J* = 4Hz, 1H, H-7a), 5.65 (br. s, 1H, N*H*).

^{13}C NMR (100.6 MHz) δ: 11.6 (*C*H$_3$), 24.2 (C-5), 25.7 (C-4), 26.6 (*C*H$_2$CH$_3$), 27.9 (C-6), 35.3 (C-3a), 39.9 (C-3), 40.0 (C-7), 56.7 (C-7a), 179.0 (*C*O).

HRMS calculated for $[C_{10}H_{17}NO + H]^+$: 168.1383; found: 168.1384.



(3a*S*,7*R*,7a*S*)-7-Benzyl-5-oxooctahydroindole (148b)

Operating as in the above preparation of **141c**, from **117b** (150 mg, 0.43 mmol) in CH_3OH (3 mL), Pt/C (75 mg), lactam **143c** (100 mg, 66 %) was obtained as a white solid. The crude product was directly employed in the next reaction, without further purification.

Operating as in the above preparation of **146b**, from **143c** (100 mg, 0.29 mmol) in THF (2 mL), sodium and liquid NH_3 (~35 mL), octahydroindolone **148b** (47 mg, 72%) was obtained as a colorless oil after flash chromatography (7:3 hexane–EtOAc to EtOAc).

Spectroscopic and analytical data for compound **148b**

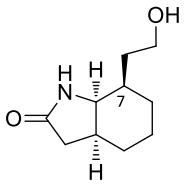
IR (film): 3220, 2928, 2854, 1695 cm^{-1}.

$[\alpha]^{22}_D$ –106.3 (c 1.0, $CHCl_3$).

^1H NMR (400 MHz) δ: 1.16-1.30 (m, 3H, H-4, H-5, H-6), 1.50-1.54 (m, 1H, H-4), 1.61-1.70 (m, 2H, H-5, H-6), 1.77-1.83 (m, 1H, H-3a), 1.93 (d, *J* = 16 Hz, 1H, C*H*$_2$Ph), 2.18-2.23 (m, 1H, H-7), 2.43 (dd, *J* = 6.8 and 16 Hz, 1H, C*H*$_2$Ph), 2.63 (t, *J* = 7.2 Hz, 2H, H-3), 3.61 (t, *J* = 4.4 Hz, 1H, H-7a), 6.58 (br. s, 1H, N*H*), 7.18-7.29 (m, 5H, H-Ar).

^{13}C NMR (100.6 MHz) δ: 24.2 (C-5), 25.8 (C-4), 27.8 (C-6), 35.3 (C-7), 40.0 (C-3), 40.1 (*C*H$_2$Ph), 40.8 (C-3a), 56.4 (C-7a), 126.1 (C-Ar), 128.4 (2C-Ar), 128.8 (2C-Ar), 139.6 (C-*i*), 179.3 (*C*O).

HRMS calculated for $[C_{15}H_{19}NO + H]^+$: 230.1539; found: 230.1539.



(3a*S*,7*R*,7a*S*)-7-(2-Hydroxyethyl)-5-oxooctahydroindole (149b)

Operating as in the above preparation of **141c**, from **111b** (103 mg, 0.31 mmol) in CH_3OH (2 mL) and Pt/C (50 mg), lactam **145c** (93 mg, 90 %) was obtained as a colourless oil, which was employed for the next reaction without further modifications.

More significant spectroscopic data for compound **145c**

^{1}H NMR (400 MHz) δ: 1.23-1.73 (m, 6H), 2.16-2.39 (m, 4H), 2.46-2.51 (m, 1H, H-7), 2.64 (d, *J* = 15.6 Hz, 1H), 3.42 (t, *J* = 6.4 Hz, 1H, H-7a), 3.52 (br. s, 1H, OH), 3.63 (s, 3H, C*H*$_3$), 4.87 (dd, *J* = 4.4 and 11.2 Hz, 1H, C*H*$_2$OH), 4.23 (t, *J* = 11.2 Hz, 1H, C*H*$_2$OH), 5.09 (dd, *J* = 4.4 and 11.2 Hz, 1H, C*H*N), 7.28-7.37 (m, 5H, H-Ar).

^{13}C NMR (100.6 MHz) δ: 15.6 (CH_2), 25.7 (CH_2), 25.8 (CH_2), 33.2 (CH_2), 33.7 (CH), 34.3 (CH), 37.0 (CH_2), 51.6 (*C*H$_3$), 59.9 (CH), 60.4 (CH), 63.5 (CH_2), 128.0 (3C-Ar), 128.7 (2C-Ar), 136.8 (C-*i*), 173.5 (*C*O$_2$), 177.3 (*C*O).

Operating as in the above preparation of **146b**, from **145c** (93 mg, 0.28 mmol) in THF (2 mL), sodium in small portions and liquid NH_3 (~35 mL), octahydroindolone **149b** (28 mg, 55%) was obtained as a colorless oil after flash chromatography (7:3 to 1:1 hexane-EtOAc).

Spectroscopic and analytical data for compound **149b**

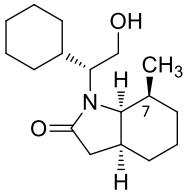
IR (film): 3406, 2925, 1676 cm^{-1}.

$[\alpha]^{22}_D$: −28.3 (c 0.25, $CHCl_3$).

^{1}H NMR (400 MHz) δ: 1.19-1.23 (m, 3H, H-4, H-5, H-6), 1.42-1.69 (m, 7H, H-4, H-5, H-6, H-7, OH, C*H*$_2$CH$_2$OH), 1.94 (d, *J* = 16.0 Hz, 1H, H-3), 2.20-2.31 (m, 1H, H-3a), 2.47 (dd, *J* = 2.2 and 16.0 Hz, 1H, H-3), 3.62-3.82 (m, 3H, H-7a, C*H*$_2$OH), 7.02 (br. s, 1H, *C*O).

^{13}C NMR (100.6 MHz) δ: 24.1 (C-5), 26.3 (C-4), 27.9 (C-6), 35.1 (C-7), 35.9 (C-3a), 36.5 (*C*H$_2$CH$_2$OH), 40.2 (C-3), 57.2 (C-7a), 60.2 (*C*H$_2$OH), 179.9 (*C*O).

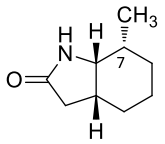
HRMS calculated for $[C_{10}H_{17}NO_2 + H]^+$: 184.1332; found: 184.1331.



When PtO_2 was used for hydrogenation, only the completely hydrogenated compound was isolated.

^{1}H NMR (400 MHz) δ: 0.84-0.96 (m, 2H), 1.02 (d, *J* = 7.2 Hz, 3H, C*H*$_3$), 1.05-1.98 (m, 15H), 2.07-2.14 (m, 1H), 2.17-2.37 (m, 3H), 2.58-2.62 (m, 1H, H-3a), 2.74-2.78 (m, 1H, C*H*N), 3.47 (t, *J* = 6.8 Hz, 1H, H-7a), 3.93 (br. s, 1H, C*H*$_2$OH), 5.63 (br. s, 1H, OH).

^{13}C NMR (100.6 MHz) δ: 15.9 (CH_2), 16.6 (CH_2), 25.7 (CH_2), 25.9 (CH_2), 26.1 (CH_2), 26.3 (CH_2), 28.6 (CH_2), 30.0 (CH_2), 30.5 (CH), 30.6 (CH_2), 33.0 (CH), 34.5 (CH), 35.9 (CH), 38.0 (CH_2), 62.2 (CH_2), 64.3 (CH), 65.6 (CH), 177.4 (*C*O).



(3a*R*,7*R*,7a*R*)-7-Methyl-5-oxooctahydroindole (*ent*-146b)

Operating as in the preparation of **141c**, from **113a** (229 mg, 0.84 mmol) in MeOH (3 mL) and Pt/C (110 mg), lactam **141d** (227 mg, 99%) was obtained and used without further purification.

More significant spectroscopic data for compound **141d**

Several of the signals in ^{1}H and ^{13}C NMR spectra of **141d** were broad and ill-defined, even not observed.

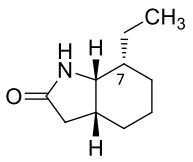
^{1}H NMR (400 MHz) δ: 1.02 (d, *J* = 7.2 Hz, 3H, C*H*$_3$), 1.26-1.39 (m, 2H, H-4, H-5), 1.46-1.71 (m, 4H, H-4, H-5, H-6), 2.32-2.41 (m, 2H, H-3, H-3a), 3.23 (t, *J* = 6.4 Hz, 1H, H-7a), 3.90 (d, *J* = 12.4 Hz, 1H, C*H*$_2$OH), 4.24-4.34 (m, 2H, C*H*N, C*H*$_2$OH), 5.02 (br. s, 1H, OH), 7.21-7.38 (m, 5H, H-Ar).

^{13}C NMR (100.6 MHz) δ: 15.0 (C-5), 15.1 (*C*H$_3$), 25.8 (C-6), 29.0 (C-4), 29.2 (C-7), 32.6 (C-3a), 38.2 (C-7a), 60.7 (C-7a), 63.8 (*C*HN), 64.7 (*C*H$_2$OH), 127.0 (2C-Ar), 128.0 (C-Ar), 128.8 (2C-Ar), 137.7 (C-*i*), 177.0 (*C*O).

HRMS calculated for [$C_{17}H_{23}NO_2$]: 274.1802; found: 274.1808.

Operating as in the preparation of **146b**, from **141d** (188.6 mg, 0.69 mmol) in THF (2 mL), sodium and liquid NH_3 (~35 mL), octahydroindolone ***ent*-146b** (85 mg, 81%) was obtained as a colourless oil after flash-column chromatography (7:3 hexane–EtOAc to EtOAc).

$[\alpha]^{22}_{D}$: + 22.01 (c 1.02, $CHCl_3$).



(3a*R*,7*R*,7a*R*)-7-Ethyl-5-oxooctahydroindole (*ent*-147b)

Operating as in the preparation of **141c**, from **115a** (100 mg, 0.35 mmol) in CH_3OH (1.5 mL), and Pt/C (50 mg), octahydroindolone **142d** (96 mg, 95%) was obtained as a yellow oil.

More significant spectroscopic data for compound **142d**

IR (film): 2930, 1662 cm^{-1}.

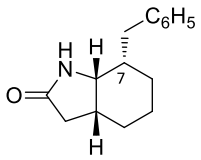
^1H NMR (400 MHz) δ: 0.87 (t, *J* = 7.2 Hz, 3H, C*H*$_3$), 1.08-1.15 (m, 1H, H-4), 1.22-1.33 (m, 2H, H-5, C*H*$_2$CH$_3$), 1.39-1.57 (m, 3H, H-5, H-6, C*H*$_2$CH$_3$), 1.61-1.75 (m, 3H, H-3a, H-4, H-6), 2.34-2.43 (m, 3H, H-3, H-7), 3.31 (t, *J* = 6.4 Hz, 1H, H-7a), 3.87-3.93 (m, 1H, C*H*$_2$OH), 4.21-4.27 (m, 1H, C*H*$_2$OH), 4.33 (d, *J* = 3.6 and 8.4 Hz, 1H, C*H*N), 4.96 (t, *J* = 7.2 Hz, 1H, OH), 7.22-7.38 (m, 5H, H-Ar).

^{13}C NMR (100.6 MHz) δ: 12.7 (*C*H$_3$), 15.4 (*C*H$_2$CH$_3$), 19.9 (C-5), 24.1 (C-4), 25.9 (C-6), 32.9 (C-7), 36.9 (C-3a), 38.3 (C-3), 61.4 (C-7a), 63.6 (*C*HN), 64.7 (*C*H$_2$OH), 127.1 (2C-Ar), 128.0 (C-Ar), 128.8 (2C-Ar), 137.6 (C-*i*), 177.3 (*C*O).

HRMS calculated for [$C_{18}H_{25}NO_2$]: 288.1958; found: 288.1950.

Operating as in the preparation of **146b**, from **142d** (86.3 mg, 0.30 mmol) in THF (2 mL), sodium and liquid NH_3 (~35 mL), octahydroindolone ***ent*-147b** (41 mg, 81%) was obtained as a colourless oil after flash-column chromatography (7:3 to 1:1 hexane–EtOAc).

$[\alpha]^{22}_D$ +24.0 (c 0.5, $CHCl_3$).



(3a*R*,7*S*,7a*R*)-7-Benzyl-5-oxooctahydroindole (*ent*-148b)

Operating as in the preparation of **141c**, from **117a** (110 mg, 0.32 mmol) in CH_3OH (1 mL), and Pt/C (55 mg), octahydroindolone **143d** (105 mg, 95%) was obtained as a yellow oil.

More significant spectroscopic data for compound **143d**

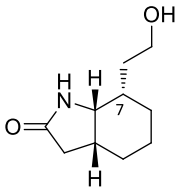
Several of the signals in ^1H and ^{13}C NMR spectra of **143d** were broad and ill-defined, even not observed.

^1H NMR (400 MHz) δ: 0.97-1.75 (m, 8H), 2.14-2.15 (m, 1H), 2.36-2.50 (m, 3H), 2.80-2.83 (m, 1H), 3.41-3.46 (m, 1H), 3.94 (dd, *J* = 3.2 and 12.2 Hz, 1H), 4.31 (dd, *J* = 8.8 and 12.2 Hz, 1H), 4.58 (br. s, 1H), 7.03-7.37 (m, 10H, H-Ar).

^{13}C NMR (100.6 MHz) δ: 15.1 (CH_2), 23.8 (CH_2), 25.7 (CH_2), 32.9 (CH), 33.5 (CH), 37.2 (CH), 37.9 (CH_2), 60.7 (CH), 64.1 (CH_2), 137.3 (C-*i*), 140.4 (C-*i*), 177.1 (*C*O).

Operating as in the above preparation of **146b**, from **143d** (105 mg, 0.30 mmol) in THF (2 mL), sodium in small portions and liquid NH_3 (~35 mL), octahydroindolone ***ent*-148b** (51 mg, 75%) was obtained as a colourless oil after flash chromatography (7:3 to 1:1 hexane−EtOAc).

$[\alpha]^{22}_D$ +108.5 (c 1.7, $CHCl_3$).



(3a*R*,7*S*,7a*R*)-7-(2-Hydroxyethyl)-5-oxooctahydroindole (*ent*-149b)

Operating as in the above preparation of **141c**, from **111a** (150 mg, 0.46 mmol) in CH_3OH (1.5 mL), and 50% Pt/C (75 mg), octahydroindolone **145d** (136 mg, 90%) was obtained as a yellow oil.

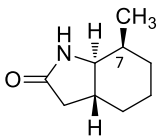
More significant spectroscopic data for compound **145d**

^{1}H NMR (400 MHz) δ: 1.23-1.70 (m, 6H, H-4, H-5, H-6), 2.23-2.51 (m, 5H, H-3a, H-3, C*H*$_2$CO$_2$), 2.54-2.60 (m, 1H, H-7), 3.37 (t, *J* = 6.8 Hz, 1H, H-7a), 3.67 (s, 3H, OC*H*$_3$), 3.85 (dd, *J* = 3.4 and 12.6 Hz, 1H, C*H*$_2$OH), 4.29 (dd, *J* = 8.8 and 12.6 Hz, 1H, C*H*$_2$OH), 4.39 (dd, *J* = 3.4 and 8.8 Hz, 1H, C*H*N), 4.60 (br. s, 1H, OH), 7.25-7.38 (m, 5H, H-Ar).

^{13}C NMR (100.6 MHz) δ: 15.2 (C-5), 25.5 (C-4), 25.8 (C-6), 31.4 (C-3a), 32.5 (C-7), 32.9 (*C*H$_2$CO$_2$), 37.6 (C-3), 51.7 (*C*H$_3$), 59.7 (C-7a), 63.3 (*C*HN), 64.2 (*C*H$_2$OH), 127.0 (2C-Ar), 128.0 (C-Ar), 128.8 (2C-Ar), 137.1 (C-*i*), 173.0 (*C*O$_2$), 176.8 (*C*O).

Operating as in the above preparation of **146b**, from **145d** (134 mg, 0.40 mmol) in THF (2 mL), sodium in small portions and liquid NH_3 (~35 mL), octahydroindolone ***ent*-149b** (57 mg, 76%) was obtained as a colorless oil after flash chromatography (7:3 to 1:1 hexane–EtOAc).

$[\alpha]^{22}_D$ +27.5 (c 1.0, $CHCl_3$).



(3a*R*,7*S*,7a*S*)-7-Methyl-5-oxooctahydroindole (146c)

Operating as in the above preparation of **146b**, from **113b** (109 mg, 0.40 mmol) in THF (2 mL), sodium in small portions and liquid NH_3 (~35 mL), octahydroindolone **146c** (57 mg, 93%) was obtained as a colourless oil after flash chromatography (7:3 hexane–EtOAc to EtOAc).

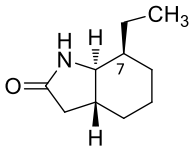
IR (film): 3276, 2928, 2856, 1686 cm^{-1}.

$[\alpha]^{22}_D$: +16.3 (c 0.47, $CHCl_3$).

^{1}H NMR (400 MHz) δ: 0.95 (d, *J* = 6.8 Hz, 3H, C*H*$_3$), 1.19-1.28 (m, 1H, H-4), 1.45-1.62 (m, 4H, H-5, H-6), 1.83 (d, *J* = 10.4 Hz, 1H, H-4), 1.93-2.08 (m, 2H, H-3, H-3a), 2.21-2.23 (m, 1H, H-7), 2.29 (dd, *J* = 4.4 and 13.6 Hz, 1H, H-3), 3.27 (dd, *J* = 4.0 and 10.4 Hz, 1H, H-7a), 6.12 (br. s, 1H, N*H*).

^{13}C NMR (100.6 MHz) δ: 11.0 (*C*H$_3$), 20.5 (C-5), 29.0 (C-4), 29.4 (C-7), 30.3 (C-6), 36.5 (C-3a), 37.9 (C-3), 63.6 (C-7a), 179.1 (*C*O).

HRMS calculated for $[C_9H_{15}NO + H]^+$: 154.1226; found: 154.1223.



(3a*R*,7*S*,7a*S*)-7-Ethyl-5-oxooctahydroindole (147c)

Operating as in the above preparation of **146b**, from **115b** (150 mg, 0.53 mmol) in THF (2 mL), sodium in small portions and liquid NH_3 (~35 mL), octahydroindolone **147c** (70 mg, 79%) was obtained as a colourless oil after flash chromatography (7:3 hexane–EtOAc to EtOAc).

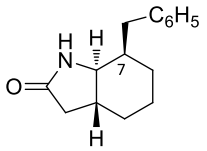
IR (film): 2928, 2856, 1701 cm^{-1}.

$[\alpha]^{22}_D$: +23.1 (c 0.83, $CHCl_3$).

^{1}H NMR (400 MHz) δ: 0.93 (t, *J* = 7.6 Hz, 3H, C*H*$_3$), 1.22-1.62 (m, 6H, H-4, H-5, H-6, C*H*$_2$CH$_3$), 1.80-1.90 (m, 3H, H-4, H-6, H-7), 1.94-2.05 (m, 2H, H-3, H-3a), 2.28 (dd, *J* = 5.2 and 13.6 Hz, 1H, H-3), 3.29 (dd, *J* = 4.4 and 10.4 Hz, 1H, H-7a), 5.42 (br. s, 1H, N*H*).

^{13}C NMR (100.6 MHz) δ: 12.6 (*C*H$_3$), 17.5 (C-5), 20.7 (*C*H$_2$CH$_3$), 26.8 (C-4), 29.1 (C-6), 37.4 (C-3a), 37.4 (C-3), 37.9 (C-7), 63.9 (C-7a), 178.7 (*C*O).

HRMS calculated for $[C_{10}H_{17}NO + H]^+$: 168.1383; found: 168.1379.



(3a*R*,7*R*,7a*S*)-7-Benzyl-5-oxooctahydroindole (148c)

Operating as in the above preparation of **146b**, from **117b** (50 mg, 0.14 mmol) in THF (3 mL), sodium in small portions and liquid NH_3 (~35 mL), octahydroindolone **148c** (25 mg, 77%) was obtained as a colorless oil after flash chromatography (7:3 to 1:1 hexane–EtOAc).

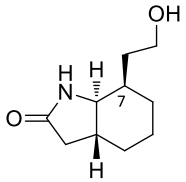
IR (film): 3238, 2928, 2856, 1691 cm^{-1}.

$[\alpha]^{22}_D$: +28.2 (c 0.2, $CHCl_3$).

^1H NMR (400 MHz) δ: 1.24-1.43 (m, 2H, H-4, H-5), 1.44-1.71 (m, 3H, H-4, H-5, H-6), 1.90-1.93 (m, 1H, H-6), 2.02 (t, *J* = 15.2 Hz, 1H, C*H*$_2$Ph), 2.14-2.32 (m, 2H, H-3a, H-7), 2.35 (dd, *J* = 6.4 and 15.2 Hz, 1H, C*H*$_2$Ph), 2.59 (dd, *J* = 10.4 and 13.8 Hz, 1H, H-3), 2.81 (dd, *J* = 4.0 and 13.8 Hz, 1H, H-3), 3.40 (dd, *J* = 4.4 and 10.8 Hz, 1H, H-7a), 5.44 (br. s, 1H, N*H*), 7.14-7.29 (m, 5H, H-Ar).

^{13}C NMR (100.6 MHz) δ: 20.7 (C-5), 26.9 (C-4), 29.1 (C-6), 31.5 (C-3), 37.5(C-7), 37.7 (C-3a), 37.8 (*C*H$_2$Ph), 63.5 (C-7a), 126.0 (2C-Ar), 128.5 (C-Ar), 129.0 (2C-Ar), 141.0 (C-*i*), 178.3 (*C*O).

HRMS calculated for $[C_{15}H_{19}NO + H]^+$: 230.1593; found: 230.1536.



(3a*R*,7*R*,7a*S*)-7-(2-Hydroxyethyl)-5-oxooctahydroindole (149c)

Operating as in the above preparation of **146b**, from **111b** (140 mg, 0.43 mmol) in THF (4 mL), sodium in small portions and liquid NH_3 (~35 mL), octahydroindolone **149c** (47 mg, 60%) was obtained as a colourless oil after flash chromatography (7:3 to 1:1 hexane–EtOAc).

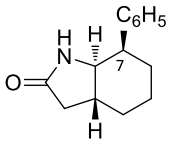
IR(film): 3260, 2926, 1681 cm^{-1}.

$[\alpha]^{22}_D$: + 5.30 (c 0.5, $CHCl_3$).

^{1}H NMR (400 MHz) δ: 1.21-1.30 (m, 2H), 1.38-1.62 (m, 4H), 1.69-1.77 (m, 2H), 1.82-1.85 (m, 1H), 1.94-2.04 (m, 2H), 2.23-2.30 (m, 2H), 3.30 (dd, *J* = 3.6 and 10.0 Hz, 1H), 3.58-3.63 (m, 1H), 3.72-3.77 (m, 1H), 6.40 (br. s, 1H, N*H*).

^{13}C NMR (100.6 MHz) δ: 20.9 (C-5), 28.2 (*C*$H_2$$CH_2$OH), 28.3 (C-4), 28.9 (C-6), 31.5 (C-7), 37.8 (C-3), 37.9 (C-3a), 61.1 (*C*H_2OH), 63.5 (C-7a), 178.8 (*C*O).

HRMS calculated for $[C_{10}H_{17}NO_2 + H]^+$: 184.1332; found: 184.1331.



(3a*S*,7*R*,7a*S*)-7-Phenyl-2-oxooctahydroindole (126b)[215]

Operating as in the above preparation of **146b**, from **125** (176 mg, 0.53 mmol) in THF (2 mL), sodium in small portions and liquid NH_3 (~35 mL), octahydroindolone **126b** (94 mg, 83%) was obtained as a white solid after flash chromatography (7:3 to 1:1 hexane-EtOAc).

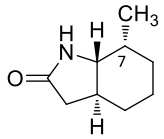
$[\alpha]^{22}_D$ + 153.6 (c 0.28, $CHCl_3$).

^{1}H NMR (400 MHz) δ: 1.38-1.69 (m, 2H), 1.93-2.17 (m, 6H), 2.39 (dd, *J* = 6.4 and 15.2 Hz, 1H), 2.64 (dt, *J* = 3.2 and 11.0 Hz, 1H), 3.25 (t, *J* = 11.0 Hz, 1H), 5.25 (br. s, 1H, NH), 7.18-7.35 (m, 5H, H-Ar).

^{13}C NMR (100.6 MHz) δ: 26.2 (CH_2), 28.2 (CH_2), 32.8 (CH_2), 38.0 (CH_2), 44.9 (CH), 48.8 (CH), 65.2 (CH), 126.9 (C-Ar), 127.1 (2C-Ar), 128.9 (2C-Ar), 142.3 (C-*i*), 177.7 (*C*O).

HRMS calculated for $[C_{14}H_{17}NO + H]^+$: 216.1383; found: 216.1382.

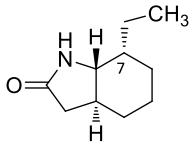
[215] Already described in racemic form: *Chem. Pharm. Bull.* **2004**, *52*, 1109–1113.



(3a*S*,7*R*,7a*R*)-7-Methyl-5-oxooctahydroindole (*ent*-146c)

Operating as in the above preparation of **146b**, from **113a** (100 mg, 0.37 mmol) in THF (2 mL), sodium in small portions and liquid NH_3 (~35 mL), octahydroindolone ***ent*-146c** (51 mg, 90%) was obtained as a white solid after flash chromatography (7:3 hexane–EtOAc to EtOAc).

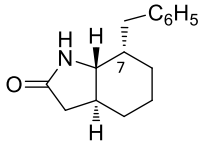
$[\alpha]^{22}_D$ –16.00 (c 0.5, $CHCl_3$).



(3a*S*,7*R*,7a*R*)-7-Ethyl-5-oxooctahydroindole (*ent*-147c)

Operating as in the above preparation of **146b**, from **115a** (70 mg, 0.25 mmol) in THF (2 mL), sodium, and liquid NH_3 (~35 mL), octahydroindolone ***ent*-147c**(28 mg, 68%) was obtained as a colourless oil after flash chromatography (7:3 hexane–EtOAc to EtOAc).

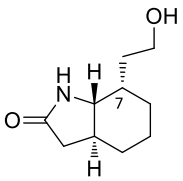
$[\alpha]^{22}_D$ –24.00 (c 1.0, $CHCl_3$).



(3a*S*,7*S*,7a*R*)-7-Benzyl-5-oxooctahydroindole (*ent*-148c)

Operating as in the above preparation of **146b**, from **117a** (100 mg, 0.29 mmol) in THF (2 mL), sodium in small portions and liquid NH_3 (~35 mL), octahydroindolone ***ent*-148c** (41 mg, 62%) was obtained as a colourless oil after flash chromatography (7:3 to 1:1 hexane–EtOAc).

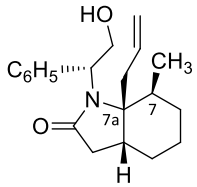
$[\alpha]^{22}_D$ –27.6 (c 0.2, $CHCl_3$).



(3a*S*,7*S*,7a*R*)-7-(2-Hydroxyethyl)-5-oxooctahydroindole (*ent*-149c)

Operating as in the above preparation of **146b**, from **111b** (94 mg, 0.29 mmol) in THF (2 mL), sodium in small portions and liquid NH_3 (~35 mL), octahydroindolone ***ent*-149c** (32 mg, 61%) was obtained as a colourless oil after flash chromatography (SiO_2, gradient from 7:3 to 1:1 hexane–EtOAc).

$[\alpha]^{22}_D$ –4.09 (c 0.66, $CHCl_3$).



(3a*R*,7*S*,7a*R*)-1-[(1*R*)-2-Hydroxy-1-phenylethyl]-7-methyl-2-oxo-7a-(2-propenyl) octahydroindole (151)

Trimethylallylsilane (403 μL, 2.52 mmol) was added at –78 °C to a solution of **112a** (311 mg, 1.15 mmol) in CH_2Cl_2 (5 mL), and the mixture was stirred for 20 min. Then, $TiCl_4$ (290 μL, 2.52 mmol) was added dropwise, and the stirring was continued at this temperature for 2 h. The mixture was poured into saturated aqueous NH_4Cl (5 mL), the organic phase was separated, and the aqueous phase was extracted with CH_2Cl_2. The combined organic extracts were dried and concentrated. Flash-column chromatography (CH_2Cl_2 to 95:5 CH_2Cl_2–CH_3OH) afforded octahydroindolone **151** (270 mg, 75%) as a white solid.

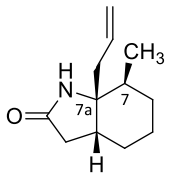
IR (film): 3366, 2930, 1662 cm^{-1}.

$[\alpha]^{22}_D$ +104.5 (c 1.02, $CHCl_3$).

^{1}H NMR (400 MHz) δ: 1.10 (d, *J* = 6.4 Hz, 3H, C*H*$_3$), 1.11-1.24 (m, 1H, H-6), 1.42-1.60 (m, 5H, H-4, H-5, H-6), 1.86-2.04 (m, 1H, H-7), 2.19-2.25 (m, 1H, C*H*$_2$CH), 2.28 (dd, *J* = 7.6 and 15.6 Hz, 1H, H-3), 2.39-2.53 (m, 2H, H-3a, C*H*$_2$CH), 2.56 (dd, *J* = 12.4 and 16.0 Hz, 1H, H-3), 4.09-4.29 (m, 2H, C*H*$_2$OH), 4.61-4.63 (m, 1H, C*H*N), 4.76-4.90 (m, 3H, C*H*=CH$_2$, C*H*$_2$=CH), 7.23-7.36 (m, 5H, H-Ar).

^{13}C NMR (100.6 MHz) δ: 16.6 (*C*H$_3$), 19.8 (C-5), 23.8 (C-4), 32.2 (C-6), 32.5 (*C*H$_2$CH), 33.9 (C-3), 37.0 (C-3a), 39.0 (C-7), 61.8(*C*HN), 66.1 (*C*H$_2$OH), 69.2 (C-7a), 118.3 (*C*H$_2$=CH), 127.3 (C-Ar), 127.6 (2C-Ar), 128.4 (2C-Ar), 132.8 (*C*H=CH$_2$), 138.9 (C-*i*), 177.6 (*C*O).

HRMS calculated for $[C_{20}H_{27}NO_2 + H]^+$: 314.2115; found: 314.2129.



(3a*R*,7*S*,7a*R*)-7-Methyl-5-oxo-7a-(2-propenyl)octahydroindole (152)

Into a three-necked, 100 mL, round-bottomed flask equipped with a cold-finger condenser charged with dry-ice acetone were condensed 30 mL of NH_3 at –78 °C. Then, sodium metal was added in small portions until the blue colour persisted, and a solution of **151** (198 mg, 0.63 mmol) in anhydrous THF (4 mL) was added slowly. After the mixture was stirred at –78 °C for 2 min and the reaction was quenched by addition of aqueous saturated NH_4Cl (5 mL). The stirring was continued at room temperature until NH_3 evaporates. The resulting mixture was extracted with CH_2Cl_2 and the combined organic extracts were dried and concentrated. Flash-column chromatography (7:3 hexane–EtOAc) afforded octahydroindolone **152** (85 mg, 70%) as a colourless oil.

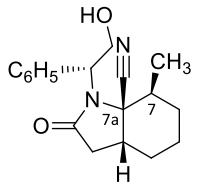
IR (film): 3158, 3077, 2921, 2857, 1702 cm^{-1}.

$[\alpha]^{22}_D$ +13.5 (c 0.6, $CHCl_3$).

^{1}H NMR (400 MHz) δ: 0.91 (d, *J* = 6.8 Hz, 3H, C*H*$_3$), 1.09 (dq, *J*= 3.2 and 12 Hz, 1H, H-6), 1.40-1.72 (m, 6H, H-4, H-5, H-6), 2.17 (dd, *J* = 7.6 and 15.6 Hz, 1H, H-3), 2.20 (dd, *J* = 8.8 and 14.8 Hz, 1H, C*H*$_2$CH), 2.31 (dd, *J* = 5.6 and 14.8 Hz, 1H, C*H*$_2$CH), 2.40 (dd, *J* = 15.6 Hz, 1H, H-3), 2.44-2.50 (m, 1H, H-3a), 5.09 (dd, *J* = 1.2 and 17.2 Hz, 1H, C*H*$_2$=CH), 5.14 (d, *J* = 10.0 Hz, 1H, C*H*$_2$=CH), 5.71-5.82 (m, 1H, C*H*=CH$_2$), 6.41 (br. s, 1H, N*H*).

^{13}C NMR (100.6 MHz) δ: 15.6 (CH_3), 20.8 (C-5), 24.1 (C-4), 29.8 (C-6), 33.6 (*C*H$_2$CH), 34.5 (C-3), 37.1 (C-3a), 39.1 (C-7), 62.2 (C-7a), 118.7 (*C*H$_2$=CH), 133.2 (*C*H=CH$_2$), 177.5 (*C*O).

HRMS calculated for $[C_{12}H_{19}NO + H]^+$: 194.1539; found: 194.1542.



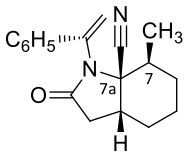
(3a*R*,7*S*,7a*R*)-7a-Ciano-1-[(1*R*)-2-hydroxy-1-phenylethyl]-7-methyl-5-oxooctahydroindole (153)

Trimethylsilyl cyanide (335 μL, 2.68 mmol) was added at –78 °C to a solution of **112a** (330 mg, 1.22 mmol) in anhydrous CH_2Cl_2 (5 mL), and the mixture was stirred for 20 min. Then, $TiCl_4$ (310 μL, 2.70 mmol) was added dropwise, and the stirring was continued at this temperature for 2 h. The mixture was poured into saturated aqueous NH_4Cl (5 mL), the organic phase was separated, and the aqueous phase was extracted with CH_2Cl_2. The combined organic extracts were dried and concentrated. Flash-column chromatography (CH_2Cl_2 to 95:5 CH_2Cl_2–CH_3OH) afforded octahydroindolone **153** (255 mg, 70%) as a yellow oil.

^{1}H NMR (400 MHz) δ: 1.32 (d, *J* = 6.8 Hz, 3H, C*H*$_3$), 1.38-1.49 (m, 1H), 1.54-1.69 (m, 3H), 1.71-1.83 (m, 1H), 2.02-2.17 (m, 2H), 2.47 (dd, J = 5.2 and 8.0 Hz, 2H), 2.73-2.80 (m, 1H), 3.66-3.70 (m, 1H, OH), 4.06-4.13 (m, 1H), 4.44-4.51 (m, 1H), 4.64 (dd, J = 4.8 and 7.6 Hz, 1H), 7.26-7.43 (m, 5H).

^{13}C NMR (100.6 MHz) δ: 18.5 (CH_3), 18.8 (CH_2), 25.0 (CH_2), 29.4 (CH_2), 34.7 (CH_2), 36.3 (CH), 39.9 (CH), 63.4 (CH), 64.0 (CH_2), 66.3 (C-7a), 116.9 (*C*N), 127.6 (2C-Ar), 128.0 (C-Ar), 128.5 (2C-Ar), 136.8 (C-*i*), 175.7 (*C*O).

HRMS calculated for $[C_{18}H_{22}N_2O_2 + H]^+$: 299.1754; found: 299.1761.



(3a*R*,7*S*,7a*R*)-7a-Ciano-7-methyl-5-oxo-1-(1-phenylethenyl)-octahydroindole (154)

$SOCl_2$ (81 μL, 1.12 mmol) was added to a cooled solution of **153** (166 mg, 0.56 mmol) in THF (5.6 mL) and the resulting mixture was stirred for 15 minutes at 0 °C. The solvent was evaporated, the resulting residue was dissolved in CH_2Cl_2 (5 mL), and the organic phase was washed with a aqueous saturated $NaHCO_3$ solution (3 x 5 mL). The organic layer was dried and concentrated. The resulting chloride was obtained as a red oil and used without further purification.

DBU (170 μL, 1.12 mmol) was added to a solution of the above chloride in DMF (2 mL) and the mixture was heated at 85 °C for 5 h. After cooling to room temperature, the mixture was poured into ice and water, and the resulting mixture was extracted with Et_2O (4 x 5 mL). The combined organic extracts were washed with aqueous saturated $NaHCO_3$ solution (2 x 5 mL), brine (3 x 5 mL) and water (2 x 5 mL), dried and concentrated. Flash-column chromatography (1:1 hexane–EtOAc) afforded octahydroindolone **154** (134 mg, 86%) as a yellow oil.

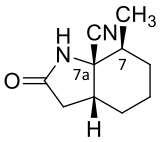
IR (film): 2933, 2856, 2237, 1717 cm^{-1}.

$[\alpha]^{22}_D$ +52.3 (c 1.0, $CHCl_3$).

^{1}H NMR (400 MHz) δ: 1.13 (d, *J* = 6.8 Hz, 3H), 1.22-1.27 (m, 2H), 1.39-1.56 (m, 4H), 1.80-1.85 (m, 1H), 2.12-2.17 (m, 1H), 2.36 (dd, *J* = 4.0 and 15.6 Hz, 1H), 2.73-2.79 (m, 2H), 5.50 (s, 1H), 5.82 (d, *J* = 0.8 Hz, 1H), 7.32-7.34 (m, 3H), 7.40-7.42 (m, 2H).

^{13}C NMR (100.6 MHz) δ: 17.3 (CH_3), 17.8 (CH_2), 26.7 (CH_2), 27.5 (CH_2), 32.7 (CH), 36.5 (CH_2), 37.9 (CH), 66.5 (q), 116.4 (CH_2), 118.8 (Cq), 126.4 (2C-Ar), 128.5 (2C-Ar), 129.0 (C-Ar), 136.0 (C-*i*), 141.9 (C-*i*), 174.3 (*C*O).

HRMS calculated for $[C_{18}H_{21}NO_2 + H]^+$: 281.1648; found: 281.1655.



(3a*R*,7*S*,7a*R*)-7a-Ciano-7-methyl-5-oxooctahydroindole (155)

Aqueous H_2SO_4 (5N, 21 mL) was added to a solution of **154** (324 mg, 1.16 mmol) in Et_2O (21 mL) and the resulting mixture was stirred at reflux temperature for 15 h. After cooling to room temperature the mixture was extracted with EtOAc (2 x 10 mL). The aqueous layer was basified to pH = 14 with aqueous 4N NaOH solution and extracted with EtOAc (5 x 10 mL). The organic extracts were dried and concentrated to afford **155** (165 mg, 80 %) as a yellow oil.

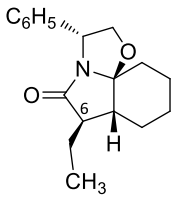
IR (film): 3064, 2937, 2853, 2238, 1683 cm^{-1}.

$[\alpha]^{22}_D$ – 20.9 (c 0.49, $CHCl_3$).

^{1}H NMR (400 MHz) δ: 1.18 (d, *J* = 6.8 Hz, 3H, C*H*$_3$), 1.20-1.29 (m, 1H, H-6), 1.38-1.49 (m, 1H, H-5), 1.61-1.72 (m, 3H, H-5, H-6, h-7), 1.79-1.84 (m, 2H, H-4), 2.34 (dd, *J* = 8 and 11.2 Hz, 2H, H-3), 2.88-2.96 (m, 1H, H-3a).

^{13}C NMR (100.6 MHz) δ: 16.7 (*C*H$_3$), 20.0 (C-5), 24.4 (C-4), 29.0 (C-6), 33.0 (C-3), 38.4 (C-7), 40.3 (C-3a), 60.7 (C-7a), 118.2 (*C*N), 176.3 (*C*O).

HRMS calculated for $[C_{10}H_{14}N_2O + H]^+$: 179.1179; found: 179.1181.



(3*R*,6*R*,6a*R*,10a*S*)-6-Ethyl-5-oxo-3-phenylperhydrooxazolo[2,3-*i*]indole (156)

LiHMDS (1N solution in THF, 780 μL, 0.78 mmol) was slowly added to a solution of lactam **119** (200 mg, 0.78 mmol) in anhydrous THF (1 mL), at −78 °C, and the mixture was stirred at this temperature for 1 h. Ethyl iodide (95 μL, 1.17 mmol) was added and the mixture was warmed to room temperature for 12 h. The mixture was poured into water, and extracted with CH_2Cl_2 (4 x 5 mL). The organic extracts were dried and concentrated. Flash-column chromatography (8:2 hexane−EtOAc) afforded octahydroindolone **156** (189 mg, 85%) as a colourless oil.

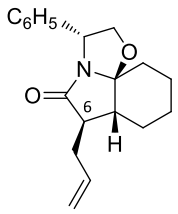
IR (film) 2933, 2860, 1710 cm^{-1}.

$[\alpha]^{22}_D$ – 99.8 (c 1.25, $CHCl_3$).

^{1}H NMR (400 MHz) δ: 1.03 (t, *J* = 7.6 Hz, 3H, C*H*$_3$), 1.42-1.49 (m, 1H, H-9), 1.58-1.72 (m, 7H, H-7, H-8, H-9, H-10, C*H*$_2$CH$_3$), 1.74-1.81 (m, 1H, H-7), 1.94 (d, *J* = 13.2 Hz, 1H, H-10), 2.10-2.13 (m, 1H, H-6a), 2.64-2.70 (m, 1H, H-6), 4.10 (t, *J* = 7.2 Hz, 1H, H-2), 4.54 (t, *J* = 7.2 Hz, 1H, H-2), 5.07 (t, *J* = 7.2 Hz, 1H, H-1), 7.22-7.33 (m, 5H, H-Ar).

^{13}C NMR (100.6 MHz) δ: 11.4 (CH$_3$), 19.8 (C-8), 20.6 (C-9), 21.2 (*C*H$_2$CH$_3$), 24.2 (C-7), 31.7 (C-10), 47.1 (C-6a), 49.4 (C-6), 57.2 (C-3), 73.8 (C-2), 98.3 (C-10a), 125.7 (2C-Ar), 127.3 (C-Ar), 128.6 (2C-Ar), 139.8 (C-*i*), 178.1 (*C*O).

HRMS calculated for $[C_{18}H_{23}NO_2 + H]^+$: 286.1802; found: 286.1805.



(3*R*,6*R*,6a*R*,10a*S*)-6-Allyl-5-oxo-3-phenylperhydrooxazolo[2,3-*i*]indole (157)

Operating as in the above preparation of **156**, from **119** (200 mg, 0.78 mmol), LiHMDS (1N solution in THF, 780 μL, 0.78 mmol) and allylbromide (100 μL, 1.17 mmol) in THF (1 mL), octahydroindolone **157** (162 mg, 70%) was obtained as a colourless oil after flash-column chromatography (8:2 hexane–EtOAc).

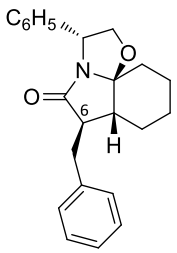
IR (film): 2933, 2861, 1711 cm^{-1}.

$[\alpha]^{22}_{D}$ – 140.4 (c 1.0, $CHCl_3$).

^{1}H NMR (400 MHz) δ: 1.42-1.46 (m, 2H, H-8, H-9), 1.57-1.79 (m, 5H, H-8, H-8, H-9, H-10), 1.94 (d, *J* = 14.4 Hz, 1H, H-10), 2.13-2.18 (m, 1H, H-6a), 2.32-2.39 (m, 1H, C*H*$_2$CH), 2.45-2.52 (m, 1H, C*H*$_2$CH), 2.79-2.85 (m, 1H, H-6), 4.10 (t, *J* = 8.8 Hz, 1H, H-2), 4.54 (t, *J* = 8.8 Hz, 1H, H-2), 5.04-5.11 (m, 3H, H-3, C*H*$_2$=CH), 5.81-5.92 (m, 1H, C*H*=CH$_2$), 7.22-7.33 (m, 5H, H-Ar).

^{13}C NMR (100.6 MHz) δ: 19.7 (C-8), 20.6 (C-9), 23.9 (C-7), 31.8 (C-10), 32.7 (*C*H$_2$CH), 47.3 (C-6), 47.9 (C-6a), 57.2 (C-3), 79.8 (C-2), 98.3 (C-10a), 117.0 (*C*H$_2$=CH), 125.7 (2C-Ar), 127.4 (C-Ar), 128.6 (2C-Ar), 135.5 (*C*H=CH$_2$), 139.7 (C-*i*), 177.3 (*C*O).

HRMS calculated for $[C_{19}H_{23}NO_2 + H]^+$: 298.1802; found: 298.1802.



(3*R*,6*R*,6a*R*,10a*S*)-5-Oxo-6-phenyl-3-phenylperhydrooxazolo[2,3-*i*]indole (158)

Operating as in the above preparation of **156**, from **119** (400 mg, 1.56 mmol), LiHMDS (1N solution in THF, 1.6 mL, 1.6 mmol) and benzyl bromide (276 μL, 2.33 mmol) in THF (1 mL), octahydroindolone **158** (351 mg, 65%) was obtained as a colourless oil after flash-column chromatography (8:2 hexane–EtOAc).

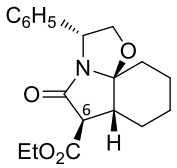
IR (film): 2930, 1716 cm^{-1}.

$[\alpha]^{22}{}_D$ –151.2 (c 1.0, $CHCl_3$).

^{1}H NMR (400 MHz) δ: 1.25-1.69 (m, 7H, H-7, H-8, H-9, H-10), 1.92 (dt, *J* = 3.6 and 13.4 Hz, 1H, H-10), 2.09-2.15 (m, 1H, H-6a), 2.79 (dd, *J* = 6.8 and 14.4 Hz, 1H, C*H*$_2$Ph), 3.05 (q, *J* = 6.8 Hz, 1H, H-6), 3.22 (dd, *J* = 5.6 and 14.4 Hz, 1H, C*H*$_2$Ph), 4.09 (dd, *J* = 7.2 and 92 Hz, 1H, H-2), 4.51 (t, *J* = 9.2 Hz, 1H, H-2), 5.10 (t, *J* = 7.2 Hz, 1H, H-3), 7.18-7.34 (m, 10H, H-Ar).

^{13}C NMR (100.6 MHz) δ: 19.7 (C-8), 20.4 (C-9), 24.2 (C-7), 31.6 (C-10), 34.9 (*C*H$_2$Ph), 47.7 (C-6a), 50.1 (C-6), 57.4 (C-3), 73.8 (C-2), 98.4 (C-10a), 125.7 (2C-Ar), 126.3 (C-Ar), 127.4 (2C-Ar), 128.4 (2C-Ar), 128.6 (C-Ar), 129.3 (2C-Ar), 139.4 (C-*i*), 139.7 (C-*i*), 177.6 (*C*O).

HRMS calculated for $[C_{23}H_{25}NO_2 + H]^+$: 348.1958; found: 348.1958.



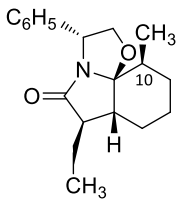
Ethyl (3*R*,6*R*,6a*R*,10a*S*)-5-oxo-6-(oxoethyl)-3-phenylperhydrooxazolo[2,3-*i*]indole-6-oxocarboxylate (159)

Operating as in the above preparation of **156**, from **119** (249 mg, 0.97 mmol), LiHMDS (1N solution in THF, 970 μL, 0.97 mmol) and diethyl carbonate (176 μL, 1.17 mmol) in THF (1 mL), octahydroindolone **159** (179 mg, 56%) was obtained as a colourless oil after flash-column chromatography (8:2 hexane–EtOAc).

^{1}H NMR (400 MHz) δ: 1.32 (t, *J* = 6 Hz, 3H, C*H*$_3$), 1.40-1.50 (m, 2H, H-8, H-9), 1.60-1.69 (m, 4H, H-7, H-8, H-9, H-10), 1.78-1.87 (m, 1H, H-7), 1.99-2.05 (m, 1H, H-10), 2.91 (dd, *J* = 5.2 and 12.4 Hz, 1H, H-6a), 3.79 (d, *J* = 13.2 Hz, 1H, H-6), 4.18-4.35 (m, 2H, H-2, C*H*$_2$CO$_2$), 4.60 (dd, *J* = 6.8 and 9.2 Hz, 1H, H-2), 5.12 (t, *J* = 6.8 Hz, 1H, H-3), 7.24-7.35 (m, 5H, H-Ar).

^{13}C NMR (100.6 MHz) δ: 14.1 (*C*H$_3$), 19.8 (C-8), 20.9 (C-9), 23.9 (C-7), 32.9 (C-10), 45.8 (C-6a), 55.4 (C-6), 57.5 (C-3), 61.5 (CO$_2$C*H*$_2$CH$_3$), 74.3 (C-2), 97.8 (C-10a), 125.8 (2C-Ar), 127.5 (C-Ar), 128.6 (2C-Ar), 138.9 (C-*i*), 168.2 (*C*O), 170.8 (*C*O$_2$).

HRMS calculated for [C$_{19}$H$_{23}$NO$_4$ + H]$^+$: 330.1700; found: 330.1694.



(3*R*,6*R*,6a*R*,10*S*,10a*S*)-6-Ethyl-10-methyl-5-oxo-3-phenylperhydrooxazolo[2,3-*i*]indole (160a)

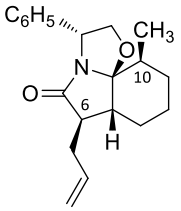
Operating as in the above preparation of **156**, from **112a** (108 mg, 0.40 mmol), LiHMDS (1N solution in THF, 400 μL, 0.4 mmol) and ethyl iodide (50 μL, 0.60 mmol) in THF (500 μL), octahydroindolone **160a** (91 mg, 77%) was obtained as an oil after flash-column chromatography (8:2 hexane–EtOAc). Minor amounts of **160b** were detected (9.4 mg, 8%).

Spectroscopic and analytical data for compound **160a**

^{1}H NMR (400 MHz) δ: 0.64 (d, *J* = 6.8 Hz, 3H, C*H*$_3$), 1.06 (t, *J* = 12 Hz, 3H, C*H*$_2$CH$_3$), 1.24-1.33 (m, 1H, H-9), 1.44-1.79 (m, 7H, H-7, H-8, H-9, C*H*$_2$CH$_3$), 1.86-1.92 (m, 1H, H-10), 2.18 (ddd, *J* = 2.8, 6.0 and 12.6 Hz, 1H, H-6a), 2.70-2.76 (q, *J* = 6.0 Hz, 1H, H-6), 4.37 (dd, *J* = 6.0 and 8.4 Hz, 1H, H-2), 4.60 (t, *J* = 8.4 Hz, 1H, H-2), 5.21 (dd, *J* = 6.0 and 8.4 Hz, 1H, H-3), 7.24-7.36 (m, 5H, H-Ar).

^{13}C NMR (100.6 MHz) δ: 11.5 (*C*H$_3$), 15.8 (*C*H$_3$), 20.1 (CH$_2$), 20.8 (CH$_2$), 24.0 (CH$_2$), 30.4 (CH$_2$), 37.9 (CH), 48.7 (CH), 49.3 (CH), 57.6 (CH), 73.9 (CH$_2$), 100.9 (Cq), 125.9 (2C-Ar), 127.1 (C-Ar), 128.4 (2C-Ar), 139.9 (C-*i*), 180.3 (*C*O).

HRMS calculated for [C$_{19}$H$_{25}$NO$_2$+ H]$^+$: 300.1964; found: 300.1962.



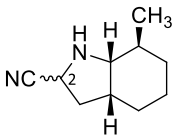
(3*R*,6*R*,6a*R*,10*S*,10a*S*)-6-Allyl-10-methyl-5-oxo-3-phenylperhydrooxazolo[2,3-*i*]indole (161a)

Operating as in the above preparation of **156**, from **112a** (100 mg, 0.38 mmol)), LiHMDS (1N solution in THF, 750 μL) and allyl bromide (50 μL, 0.60 mmol) in THF (500 μL), octahydroindolone **161** (81.2 mg, 70%) was obtained as 15:1 mixture of isomers after flash-column chromatography (8:2 hexane-EtOAc).

Spectroscopic and analytical data for compound **161a** (from enriched fraction)

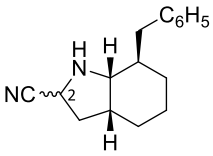
^{1}H NMR (400 MHz) δ: 0.55 (d, *J* = 6.8 Hz, 3H, C*H*$_3$), 1.15-1.23 (m, 1H, H-9), 1.34-1.60 (m, 3H, H-8, H-9), 1.65-1.67 (m, 2H, H-7), 1.72-1.81 (m, 1H, H-10), 2.08-2.15 (m, 1H, H-6a), 2.26-2.44 (m, 2H, C*H*$_2$CH), 2.77-2.83 (m, 1H, H-6), 4.29 (dd, *J* = 6.0 and 8.4 Hz, 1H, H-2), 4.51 (t, *J* = 8.4 Hz, 1H, H-2), 4.98-5.05 (m, 2H, C*H*$_2$=CH), 5.13 (t, *J* = 6.0 and 8.4 Hz, 1H, H-3), 5.77-5.87 (m, 1H, C*H*=CH$_2$), 7.09-7.27 (m, 5H, H-Ar).

^{13}C NMR (100.6 MHz) δ: 15.8 (*C*H$_3$), 20.1 (C-8), 23.8 (C-7), 30.4 (C-9), 32.3 (*C*H$_2$CH), 38.0 (C-10), 47.2 (C-6), 49.5 (C-6a), 57.7 (C-3), 73.8 (C-2), 101.0 (C-10a), 117.0 (*C*H$_2$=CH), 125.9 (2C-Ar), 127.1 (C-Ar), 128.4 (2C-Ar), 135.6 (*C*H=CH$_2$), 139.8 (C-*i*), 179.5 (*C*O).



Mixture of products (162)

A solution of lactam **146a** (200 mg, 1.30 mmol) in anhydrous THF (3.8 mL) was added dropwise to a suspension of $ZrCp_2HCl$ (505 mg, 1.96 mmol) in anhydrous THF (3.3 mL) at – 20 °C. After 10 min stirring, the mixture was gradually warmed to 15 °C and allowed to react for 4 h. Then TMSCN (325.3 mg, 2.6 mmol) was added dropwise and the reaction mixture was allowed to react overnight at room temperature. Saturated NH_4Cl (5 mL) was added and the organic product was extracted with CH_2Cl_2 (4 x 5 mL). We isolated an inseparable 3:1 mixture of isomers **162** (139 mg, 65%, calculated from ^{1}H-NMR and GC).



Mixture of products (163)

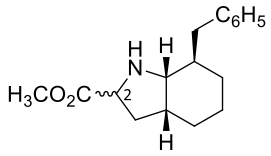
Operating as in the preparation of **162**, from lactam **148a** (200 mg, 0.87 mmol) in anhydrous THF (2.3 mL) and $ZrCp_2HCl$ (338 mg, 1.31 mmol) in anhydrous THF (1.5 mL) and TMSCN (218 μL, 1.75 mmol), we obtained a 1.5:1 inseparable mixture of isomers **163** (125 mg, 60%).

Selected spectroscopic data for **163** (mixture of 2 products)

IR (film): 2924, 2241 cm^{-1}.

^{1}H-NMR (400 MHz) δ: 0.88-1.01 (m, 2H), 1.26-1.40 (m, 2H), 1.43-1.74 (m, 8H), 2.00-2.12 (m, 4H), 2.18-2.31 (m, 4H), 2.38-2.44 (m, 2H), 2.77-2.84 (m, 2H), 2.99-3.04 (m, 2H), 4.01-4.07 (m, 2H), 7.13-7.30 (m, 10H).

^{13}C-NMR (100.6 MHz) δ: 20.1 and 20.2 (CH_2), 25.9 and 26.2 (CH_2), 27.2 and 28.4 (CH_2), 34.3 and 34.9 (CH_2), 36.3 and 36.6 (CH), 40.0 and 40.2 (CH_2), 40.5 and 40.6 (CH), 45.0 and 45.4 (CH), 62.0 and 63.0 (CH), 122.4 and 123.0 (CN), 125.8 and 126.0 (C-Ar), 128.2 and 128.3 (2C-Ar), 129.0 and 129.3 (2C-Ar), 140.4 and 140.7 (C-*i*).

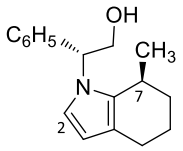


Mixture of compounds (164)

A solution of **163** (46 mg, 0.192 mmol) in CH_3OH (3 mL) was heated at the reflux temperature overnight, in the presence of HCl (6N sol. In CH_3OH, 3mL). Then, the resulting mixture was quenched with $NaHCO_3$ (until pH = 7) and the organic product was extracted with CH_2Cl_2 (3 x 5 mL) providing a mixture of epimers **164** (34 mg, 60%).

Selected spectroscopic data for **164** (mixture of epimers)

^{1}H-NMR (400 MHz) δ: 2.78-2.81 (m, 1H), 2.93-3.02 (m, 3H), 3.73 and 3.77 (s, 3H, CH_3), 3.88-3.92 (m, 2H), 7.17-7.28 (m, 10H).



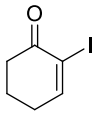
name (165)

Operating as in the preparation of **162**, from lactam **112a** (80 mg, 0.30 mmol) in THF (1 mL), $ZrCp_2HCl$ (174.1 mg, 0.44 mmol) in THF (747 μL) and TMSCN (75 μL, 0.60 mmol), we isolated compound **165** (40 mg, 52%) as a colourless oil, after flash-column chromatography (CH_2Cl_2 to 95:5 CH_2Cl_2:CH_3OH).

^{1}H-NMR (400 MHz) δ: 0.93 (d, *J* = 6.8 Hz, 3H, C*H*$_3$), 1.56-1.87 (m, 4H, H-5, H-6), 2.43-2.69 (m, 2H, H-4), 2.97-3.00 (m, 1H, H-7), 4.08-4.13 (m, 2H, C*H*$_2$OH), 5.30-5.33 (m, 1H, C*H*N), 6.06 (d, *J* = 3.0 Hz, 1H, H-3), 6.71 (d, *J* = 3.0 Hz, 1H, H-2), 7.73 (d, *J* = 9.2 Hz, 1H, H-Ar), 7.25-7.35 (m, 4H, H-Ar).

^{13}C-NMR (100.6 MHz) δ: 19.0 (C-5), 21.0 (*C*H$_3$), 23.5 (C-4), 26.0 (C-7), 31.5 (C-6), 60.0 (*C*H$_2$OH), 60.4 (*C*HN), 107.8 (C-3), 116.0 (C-2), 116.8 (C-3a), 126.6 (2C-Ar), 127.6 (C-Ar), 128.7 (2C-Ar), 133.8 (C-*i*), 139.0 (C-7a).

NRMS calculated for $[C_{17}H_{21}NO+H^+]^+$: 256.1701; found: 256.1705.



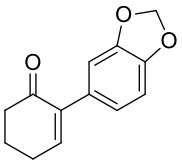
2-Iodo-2-cyclohexenone (168)[216]

To a solution of 2-cyclohexen-1-one (1.9 g, 20 mmol) in 1:1 THF–H_2O (100 mL) K_2CO_3 (3.3 g, 24 mmol), iodine (7.6 g, 30 mmol) and DMPA (488 mg, 4 mmol) successively was added, and the mixture was stirred at room temperature for 2 h. Then the mixture was diluted with EtOAc (200 mL) and washed with aqueous saturated Na_2CO_3 solution (4 x 100 mL) and aqueous HCl solution (0.1 N, 4 x 100 mL). The aqueous layers were extracted with EtOAc (3 x 100 mL) and the combined organic layers were dried and concentrated, affording cyclohexanone **168** (4.1 g, 92%) as a brown solid.

^{1}H NMR (400 MHz) δ: 2.06-2.13 (m, 2H), 2.43-2.47 (m, 2H), 2.67 (t, *J* = 6.4 Hz, 2H), 7.78 (t, *J* = 4 Hz, 1H, H-3).

^{13}C NMR (100.6 MHz) δ: 22.8 (CH_2), 29.9 (CH_2), 37.2 (CH_2), 103.8 (CH), 159.4 (Cq), 192.2 (*C*O).

[216] a. Previuosly described: Krafft, M.E.; Cran, J.W. *Synlett,* **2005**, *8*, 1263–1266. b. Johnson, C.J.; Adam, J. P.; Braun, M.P.; Senanayake, C.B.W.; Wovkulich, P.M.; Uskokovic, M.R. *Tetrahedron Lett.* **1992**, *33*, 917.



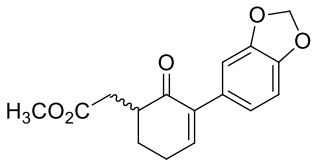
2-(3,4-Methylenedioxyphenyl)-2-cyclohexenone (169)[217]

To a solution of iodoenone **168** (2.0 g, 9.04 mmol) in DME–H_2O (1:1, 36 mL) were added Na_2CO_3 (1.9 g, 18.1 mmol) and 10% Pd/C (468 mg). The mixture was stirred at room temperature for 12 h to complete the reaction. The solution was filtered and the filtrate was extracted with Et_2O (2 x 20 mL). The organic layer was washed with aqueous NaOH solution (1N, 2 x 10 mL) and water (3 x 10 mL), dried and concentrated. The residue was purify by flash-column chromatography (9:1 to 8:2 hexane–EtOAc) to afford **169** as a white solid (1.56 g, 80%).

^{1}H NMR (400 MHz) δ: 2.06-2.12 (m, 2H), 2.50-2.60 (m, 4H), 5.94 (s, 2H), 6.74-6.86 (m, 3H), 6.96-6.99 (m, 1H).

^{13}C NMR (100.6 MHz) δ: 22.9 (CH_2), 26.6 (CH_2), 39.1 (CH_2), 101.0 (CH), 108.0 (CH_2), 109.4 (Cq), 122.1 (C-Ar), 130.5 (C-Ar), 139.9 (C-Ar), 147.1 (C-*i*), 147.2 (C-*i*), 147.3 (C-*i*), 198.1 (*C*O).

[217] Previously described: Chong L.; Xie, J:H:; Li, Y.L.; Chen, J.Q.; Zhou, Q.L. *Angew. Chem. Int. Ed.* **2013**, *52*, 593–596.

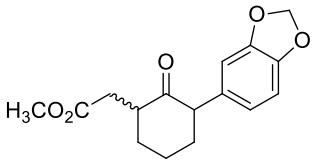


3-(3,4-methylenedioxyphenyl)-2-oxo-3-cyclohexaneacetate (170)[217]

A solution of LDA (2.0 M in THF/heptanes/ethylbenzene, 753 μL, 1.5 mmol) was added dropwise to a solution of **169** (325 mg, 1.51 mmol) in THF (2 mL) at −78 °C, and the mixture was stirred at this temperature for 30 min. Then, methyl bromoacetate (280 μL, 3.02 mmol) and HMPA (314 μL, 1.81 mmol) were added at −78 °C, and the stirring was continued at this temperature for an additional 2.5 h. Saturated aqueous NH_4Cl solution (5 mL) was added, and the resulting mixture was extracted with EtOAc (3 x 10 mL). The combined organic extracts were washed with aqueous saturated NaCl solution (2 x 5 mL), dried and concentrated. Column chromatography (hexane to 95:5 hexane–acetone) afforded keto ester **170** as a yellow solid (270 mg, 62%).

^{1}H NMR (400 MHz) δ: 1.88-2.00 (m, 1H), 2.13-2.20 (m, 1H), 2.35 (dd, *J* = 6.8 and 16.4 Hz, 1H, C*H*$_2$OH), 2.50-2.70 (m, 2H), 2.92 (dd, *J* = 6.0 and 16.4 Hz, 1H, C*H*$_2$OH), 2.99-3.06 (m, 1H), 3.71 (s, 3H, C*H*$_3$), 5.94 (s, 2H, C*H*$_2$O), 6.77, (dd, *J* = 0.8 and 14.8 Hz, 3H, H-Ar), 6.93-6.95 (m, 1H, H-3).

^{13}C NMR (100.6 MHz) δ: 26.1 (CH_2), 28.6 (CH_2), 34.5 (CH_2), 44.1 (CH), 51.5 (CH), 100.8 (CH_2), 107.7 (CH), 109.2 (CH), 121.9 (CH), 130.2 (C-*i*), 139.1 (C-*i*), 146.4 (C-Ar), 147.0 (Cq), 147.0 (C-*i*), 172.8 (*C*O$_2$), 198.1 (*C*O).

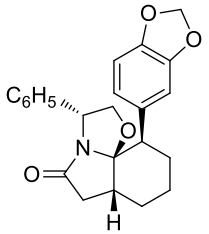


Methyl 3-(3,4-methylenedioxyphenyl)-2-oxocyclohexaneacetate (171)[217]

A solution of cyclohexanone **170** (370 mg, 1.28 mmol) in EtOH (4 mL) was hydrogenated at rt for 8 h at atmospheric pressure, in the presence of 10% Pd/C (66 mg). The catalyst was removed by filtration over Celite ® and the solvent was evaporated to afford ketone **171** (370 mg, 99%, 3:1 *cis*:*trans* mixture) as a colourless oil.

^{1}H NMR (400 MHz) δ: 1.42-1.60 (m, 1H), 1.72-1.77 (m, 1H), 1.84-2.08 (m, 3H), 2.17-2.34 (m, 4H), 2.46-2.52 (m, 2H), 2.72-2.81 (m, 2H), 2.96-3.08 (m, 1H), 3.59-3.72 (m, 2H), 3.64 (s, 3H, C*H*$_3$), 3.65 (s, 3H, C*H*$_3$), 5.90 (s, 2H, C*H*$_2$OH), 5.93 (s, 2H, C*H*$_2$OH), 6.55-6.57 (m, 2H), 6.62-6.63 (m, 2H), 6.72-6.80 (m, 4H).

^{13}C NMR (100.6 MHz) δ: 20.7 and 25.3 (CH_2), 30.6 and 34.2 (CH_2), 33.3 and 34.4 (CH_2), 36.3 and 37.7 (CH_2), 43.9 and 47.3 (CH), 51.4 and 53.4 (CH_3), 56.9 (CH), 100.7 and 100.8 (CH_2), 107.8 and 108.0 (CH), 108.2 and 108.3 (CH), 108.9 (C-Ar), 120.3 and 121.5 (C-Ar), 131.1 and 132.2 (C-*i*), 146.3 and 145.9 (C-*i*), 172.7 and 172.4 (*C*O$_2$), 209.3 and 211.6 (*C*O).



(3*R*,6a*R*,10*R*,10a*R*)-10-(3,4-methylenedioxyphenyl)-5-Oxo-3-phenylperhydrooxazolo[2,3-*i*]indole (172)

(*R*)-Phenylglycinol (287.0 g, 2.09 mmol) was added to a solution of ketoester **171** (270 mg, 0.9 mmol) and AcOH (310 μL, 4.18 mmol) in benzene (16 mL). The mixture was heated at the reflux temperature for 24 h, with azeotropic elimination of water by a Dean-Stark system. Additional (*R*)-Phenylglycinol (287 mg, 2.09 mmol) was added, and the stirring was continued for 24 h. After cooling, the mixture was concentrated, and the resulting residue was dissolved in ethyl acetate (15 mL). The organic phase was washed with saturated aqueous sodium bicarbonate solution (2 x 10 mL) and concentrated. Flash-column chromatography (hexane to 7:3 hexane–EtOAc) of the residue afforded lactam **172** (183 mg, 54%) as a colourless oil.

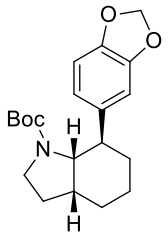
IR (film): 2920, 1713 cm^{-1}.

$[\alpha]^{22}_{D}$ –54.3 (c 1.03, $CHCl_3$).

^{1}H NMR (400 MHz) δ: 1.56-1.94 (m, 6H), 2.47 (dd, *J* = 7.2 and 15.2 Hz, 1H), 2.55-2.63 (m, 1H), 2.82 (dd, *J* = 3.2 and 12.8 Hz, 1H), 2.99 (t, *J* = 15.2 Hz, 1H), 3.80 (dd, *J* = 5.6 and 8.0 Hz, 1H), 4.37 (t, *J* = 8.4 Hz, 1H), 4.97 (t, *J* = 7.2 Hz, 1H), 5.67 (s, 1H), 5.78 (s, 1H), 6.23 (d, *J* = 7.6 Hz, 1H), 6.45 (dd, *J* = 1.2 and 7.6 Hz, 1H), 6.52 (s, 1H), 6.85-6.89 (m, 2H), 7.10-7.14 (m, 3H).

^{13}C NMR (100.6 MHz) δ: 21.1 (C-8), 24.9 (C-7), 29.8 (C-9), 39.1 (C-6), 46.0 (C-6a), 49.2 (C-10), 56.9 (C-3), 73.5 (C-2), 100.2 (*C*H_2O_2), 102.6 (C-10a), 107.0 (C-Ar), 110.1 (C-Ar), 122.9 (C-Ar), 125.9 (2C-Ar), 126.2 (C-Ar), 127.5 (2C-Ar), 132.9 (C-*i*), 138.8 (C-*i*), 145.9 (C-Ar), 146.4 (C-Ar), 177.7 (*C*ON).

HRMS calculated for $[C_{23}H_{23}NO_4 + H]^+$: 378.1700; found: 378.1702.



(3a*R*,7*R*,7a*S*)-7-1-(*tert*-butoxycarbonyl)-(3,4-methylenedioxyphenyl)-7-phenyloctahydroindole (174)

$LiAlH_4$ (100 mg, 2.61 mmol) was slowly added to a suspension of $AlCl_3$ (235 mg, 1.74 mmol) in THF (6 mL) at 0 °C. The mixture was stirred at the same temperature for 1 h and at –78 °C for 30 min. Then, a solution of lactam **118** (164 mg, 0.44 mmol) in THF (5 mL), was added dropwise. After the mixture was stirred at –78 °C for 1 h and at room temperature for 18 h, water was added. The resulting mixture was filtered over Celite®, the filtrate was concentrated and the residue was taken up with CH_2Cl_2. The organic solution was washed with brine, dried and concentrated affording the octahydroindole **173a** which was used without further purification in the next step.

A 0.08 M solution of the above crude and di-*tert*-butyl dicarbonate (107 mg, 0.49 mmol) in CH_3OH (5 mL) containing of $Pd(OH)_2$ (35 mg) was stirred under hydrogen at room temperature overnight. The catalyst was removed by filtration, and the solvent was evaporated. Flash chromatography (hexane to 7:3 hexane–EtOAc) afforded octahydroindole **174** (102 mg, 67% overall yield) as a colourless oil.

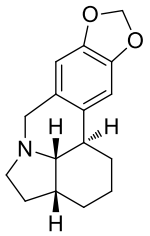
IR (film): 2928, 2856, 1691 cm^{-1}.

$[\alpha]^{22}_D$ + 45.4 (c 1.1, $CHCl_3$).

^{1}H NMR (400 MHz) δ: 1.09 [s, 9H, $C(CH_3)_3$], 1.45-1.87 (m, 7H, H-3, H-4, H-5, H-6), 1.97-2.08 (m, 1H, H-3), 2.33 (br. s, 2H, H-3a, H-7a), 3.40 (t, *J* = 19.6 Hz, 1H, H-2), 3.51-3.58 (m, 1H, H-2), 3.74 (dd, *J* = 6.4 and 10.8 Hz, 1H, H-7), 5.90 (s, 2H, CH_2O_2), 6.57 (d, *J* = 7.6 Hz, 1H, H-Ar), 6.67-6.70 (m, 2H, H-Ar).

^{13}C NMR (100.6 MHz) δ: 21.0 (C-5), 25.8 (C-6), 26.2 (C-3), 27.9 [$C(CH_3)_3$], 31.8 (C-4), 38.4 (C-3a), 43.9 (C-2), 45.2 (C-7a), 62.8 (C-7), 78.4 [$C(CH_3)_3$], 100.6 (CH_2O_2), 107.9 (C-Ar), 108.4 (C-Ar), 121.3 (C-Ar), 138.6 (C-*i*), 145.8 (C-*i*), 147.3 (C-*i*), 154.6 (CO_2N).

HRMS calculated for $[C_{40}H_{54}N_2O_8 + Na]^+$(2M+Na): 713.3772; found: 713.3773.



(+)-α-Lycorane

HCHO (60 μL, 0.73 mmol) was added to a solution of 18 (63 mg, 0.18 mmol) in 1N HCl (300 μL), and the mixture was allowed to react at room temperature for 4 h. Then, the resulting mixture was taken up with CH_2Cl_2 and the organic solution was washed with brine, dried and concentrated, affording (+)-α-Lycorane (45 mg, 97%) as a white crystal.

IR (film): 2926, 2888, 1687 cm^{-1}.

$[\alpha]^{22}_D$ + 30.0 (c 0.88, EtOH); + 38.0 (c 1.18, $CHCl_3$); {lit[218] *ent*: $[\alpha]^{22}_D$: + 31.0 (c 0.99, EtOH)}.

^{1}H NMR (400 MHz) δ: 1.12-1.26 (m, 1H, H-4), 1.56-1.93 (m, 6H, H-3, H-5, H-6), 2.20-2.26 (m, 1H, H-4), 2.35-2.44 (m, 2H, H-3a, H-7), 2.49 (dd, *J* = 6.4 and 10.0 Hz, 1H, H-7a), 2.81 (dt, *J* = 2.8 and 9.2 Hz, 1H, H-2), 3.10 (q, *J* = 8.4 Hz, 1H, H-2), 3.76 (d, *J* = 15.2 Hz, 1H, CH_2N), 4.12 (d, *J* = 15.2 Hz, 1H, CH_2N), 5.89 (s, 2H, CH_2O_2), 6.60 (s, 1H, H-Ar), 6.70 (s, 1H, H-Ar).

^{13}C NMR (100.6 MHz) δ: 20.7 (C-5), 24.8 (C-4), 26.0 (C-3), 27.8 (C-6), 33.8 (C-7), 36.8 (C-3a), 54.1 (C-2), 54.4 (*C*H_2N), 64.5 (C-7a), 100.6 (*C*H_2O_2), 104.4 (C-Ar), 106.9 (C-Ar), 128.5 (C-Ar), 134.8 (C-Ar), 145.3 (C-Ar), 146.1 (C-Ar).

HRMS calculated for $[C_{19}H_{27}NO_2 + H]^+$: 302.2115; found: 302.2124.

[218] Takeda, K.; Kotera, K.; Mizukami, S.; Kobayashi, M. *Chem. Pharm. Bull.* **1960**, *8*, 483– 489.