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Open-chain building blocks from chiral lactams. Enantioselective synthesis of macrocyclic nitrogen-containing natural products

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Memoria presentada por Guillaume Michel Pablo Guignard para optar al título de Doctor por la Universitat de Barcelona

Dirigida por:

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- Copies of the ^{1}H and ^{13}C spectra of all new compounds
- Crystallographic data for compounds **42** and **189**

Abbreviations

n-BuOH	: *n*-Butanol
MeOH	: Methanol
NaOH	: Sodium hydroxide
Boc_2O	: Di-*tert*-butyl dicarbonate
LiOH	: Lithium hydroxide
THF	: Tetrahydrofuran
EtOAc	: Ethyl acetate
Ts	: Tosyl
rt	: Room temperature
n-BuLi	: *n*-Butyl lithium
Et_20	: Diethyl ether
Red-Al	: Sodium bis(2-methoxyethoxy)aluminumhydride
EtOH	: Ethanol
LABs	: Lithium aminoborohydrides
CbzCl	: Benzyl chloroformate
$CHCl_3$	: Chloroform
LDA	: Lithium diisopropylamide
AcOH	: Acetic acid
Im	: Imidazole
Aq	: Aqueous
o/n	: Overnight
HTIB	: [Hydroxyl(tosyloxy)iodo]benzene
TBDPSCl	: *tert*-Butyldiphenylsilyl chloride
TBDMSCl	: *tert*-Butyldimethylsilyl chloride
TBHP	: *tert*-Butyl hydroperoxide
eq	: Equivalent(s)
m-CPBA	: 3-Chloroperbenzoic acid
PG	: Protecting group
Pyr	: Pyridine
DMAP	: 4-Dimethylaminopyridine
DMTMM	: 4-(4,6-Dimethoxy-1,3,5-triazin-2-yl)-4-methylmorpholinium chloride
TIPS	: Triisopropylsilyl
LiHMDS	: Lithium bis(trimethylsilyl)amide
KHMDS	: Potassium bis(trimethylsilyl)amide
p-TsOH	: 4-Toluenesulfonic acid
DEAD	: Diethyl azodicarboxylate
DMF	: Dimethyl formamide
MeCN	: Acetonitrile
TBAF	: Tetrabutylammonium fluoride
DMPU	: 1,3-Dimethyltetrahydropyrimidin-2(1*H*)-one
TFA	: Trifluoroacetic acid
DMSO	: Dimethylsulfoxide

DBU : 1,8-Diazabicyclo[5.4.0]undec-7-ene
EDCI : 3-(Ethyliminomethyleneamino)-*N*,*N*-dimethylpropan-1-amine
HOBT : Hydroxybenzotriazole

PUBLICATIONS

Access to enantiopure 4-substituted 1,5-aminoalcohols from phenylglycinol-derived δ-lactams: synthesis of *Haliclona* alkaloids.
Mercedes Amat,* Guillaume Guignard, Núria Llor, and Joan Bosch,* *J. Org. Chem.* 2014, *79*, 2792-2802.

A general methodology for the synthesis of enantiopure 1,5-aminoalcohols.
Guillaume Guignard, Núria Llor, Aina Urbina, Joan Bosch,* and Mercedes Amat,* *Eur*. *J. Org. Chem*. 2016, 693-703.

Enantioselective total synthesis of fluvirucinin B_1.
Guillaume Guignard, Núria Llor, Elies Molins, Joan Bosch,* and Mercedes Amat,* *Org. Lett*. 2016, *18*, 1788-1791.

Synthesis of fluvirucins and their aglycons, the fluvirucinins.
Mercedes Amat,* Núria Llor, Guillaume Guignard, and Joan Bosch,* *Synthesis* 2016, accepted.

CONTRIBUTIONS TO SCIENTIFIC MEETINGS

Oxazolopiperidone lactams as chiral building blocks for the enantioselective synthesis of aminoacid derivatives.
Mercedes Amat, Guillaume Guignard, Núria Llor, and Joan Bosch, Oral Communication, "Organic and medicinal chemistry workshop, synthesis of bioactive compounds", Lisboa, Portugal, June 2012.

Enantioselective synthesis of chiral 1,5-aminoalcohols from substituted oxazolopiperidones.
Mercedes Amat, Guillaume Guignard, Núria Llor, and Joan Bosch, Oral Communication, "XXXIV Reunión Bienal de la Real Sociedad Española de Química", Santander, Spain, September 2013.

Access to enantiopure 1,5-aminoalcohols from phenylglycinol-derived □-lactams.
Mercedes Amat, Guillaume Guignard, Núria Llor, and Joan Bosch, Oral Communication, "XXV Reunión Bienal de Química Orgánica de la Real Sociedad Española de Química", Alicante, Spain, June 2014.

Enantioselective synthesis of substituted 1,5-aminoalcohols from phenylglycinol-derived lactams**.**
Guillaume Guignard, Núria Llor, Joan Bosch, and Mercedes Amat, Poster, "BOSS XIV - 14th Belgian Organic Synthesis Symposium", Louvain-la-Neuve, Belgium, July 2014.

Access to enantiopure □-hydroxy acid derivatives from phenylglycinol-derived lactams**.**
Guillaume Guignard, Núria Llor, Aina Urbina, Joan Bosch, and Mercedes Amat, Oral Communication, "XXXV Reunión Bienal de la Real Sociedad Española de Química", La Coruña, Spain, July 2015.

Access to enantiopure 1,5-aminoalcohols: synthesis of *Haliclona* alkaloids.
Guillaume Guignard, Núria Llor, Aina Urbina, Joan Bosch, and Mercedes Amat, Poster, "XXXV Reunión Bienal de la Real Sociedad Española de Química", La Coruña, Spain, July 2015.

Synthesis of chiral linear-chain building blocks from phenylglycinol-derived lactams.
Núria Llor, Guillaume Guignard, Aina Urbina, Joan Bosch, and Mercedes Amat, Poster, "XXVI Reunión Bienal de Química Orgánica de la Real Sociedad Española de Química", Huelva, Spain, June 2016.

Chapter 1

INTRODUCTION

Natural product synthesis has played a central role in the evolution of organic chemistry and has been crucial for the development of modern drug discovery programs in the pharmaceutical industry. However, the justification for natural product synthesis has been constantly evolving over the last two centuries.[1] At the beginning, the chemical synthesis of natural products was the method of choice to confirm the structure of natural products assigned by degradation studies. In the last century, the advances in spectroscopic methods, high-resolution mass spectrometry, and X-ray crystallography have facilitated the expeditious structural assignment of highly complex molecules isolated from nature in milligram or even sub-milligram quantities. As a consequence, the synthesis of natural products was considered one of the main driving forces behind the development of chemical transformations, innovative concepts, strategies, and methodologies for complex molecule synthesis. In the 21st century, however, this justification for natural product synthesis is less accepted, so a reevaluation of the role of this activity is required.

Biologically active natural products can be considered as 'privileged' scaffolds that they have been evolutionarily selected for binding to particular domains of biological macromolecules.[2] As a result of the natural selection process, natural products possess a unique and vast chemical diversity with optimal interactions with biological macromolecules. Due to this diversity and specificity, natural products have proven to be by far the richest sources for new drug development. Of the 1,355 New Chemical Entities (NCEs) reported in the period

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

[2] (a) Firn, R. D.; Jones, C. G. *Nat. Prod. Rep.* **2003**, *20*, 382-391. (b) Bon, R. S.; Waldmann, H. *Acc. Chem. Res.* **2010**, *43*, 1103-1114. (c) Hong, J. *Chem. Eur. J.* **2014**, *20*, 10204-10212; d) Trauner, D. *Nat. Prod. Rep.* **2014**, *31*, 411-413.

1981–2010, 540 (40%) were either natural products or natural product derived.[3] In particular, 63 of the 99 (64%) small molecule anticancer drugs and 78 of the 104 (75%) antibiotics developed from 1981 to 2010 come from natural products.[3]

However, the interest of pharmaceutical industry in natural product chemistry has suffered a gradual decline in the last decades due to a number of factors: the development of combinatorial chemistry and introduction of high-throughput screening (HTS) against defined molecular targets; the challenges associated with isolation and purification of active principles from complex natural product extracts; the lack of novel entities in natural products; and last, the challenges involved in compound supply and the lack of adequate structural diversification strategies for preclinical and clinical studies. 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 (that is, searching a genome for DNA sequences that encode enzymes involved in the biosynthesis of particular products) and metabolic engineering (the practice of optimizing genetic and regulatory processes within cells to increase the production of a certain substance) have reactivated the interest in natural products as valuable resources for drug discovery.[4]

On the other hand, although the vast majority of natural products are derived from plants, in the last 50 years, research involving marine organisms has shown the great potential of these products as a source of new bioactive compounds.[5] Although most of these compounds show analogies with terrestrial metabolites, there are a few categories of products that seem to be structurally specific to marine species. Nevertheless, as a consequence of the limited amounts in which some natural products can be isolated, there is a huge material supply problem that limits the progression of natural products into clinical development, particularly those isolated from marine sources. Therefore, more selective, efficient and sophisticated synthetic methodologies are still needed to achieve the total synthesis of complex, challenging natural product targets, allowing the delivery of sufficient material for clinical studies.[6] Moreover, structural modifications that have the potential to enhance biological properties may not be accessible directly from the natural product. Semi-synthetic structural modifications of the natural products provide important structure-

[3] Newman, D. J.; Cragg, G. M. *J. Nat. Prod.* **2012**, *75*, 311-335.
[4] (a) Jesse, W.-H.; Vederas, J. C. *Science* **2009**, *325*, 161-165. (b) Molinski, T. F. *Org. Lett.* **2014**, *16*, 3849-3855.
[5] (a) Bhakuni, D. S.; Rawat, D. S. in *Bioactive Marine Natural Prodcts*; Springer: New York and Anamaya Publisher: New Delhi, India, 2005. (b) Molinski, T. F.; Dalisay, D. S.; Lievens, S. L.; Saludes, J. P. *Nat. Rev. Drug Discovery* **2009**, *8*, 69-85; c) Newman, D. J.; Cragg, G. M. *Mar. Drugs* **2014**, *12*, 255-278.
[6] (a) Jones, S. B.; Simmons, B.; Mastracchio, A.; MacMillan, D. W. C. *Nature* **2011**, *475*, 183-188. (b) McLeod, M. C.; Singh, G.; Plampin III J. N.; Rane, D.; Wang, J. L.; Day, V. W.; Aubé, J. *Nat. Chem.* **2014**, *6*, 133-140.

activity relationship data. These data enable subsequent computer-aided ligand optimization and the synthesis of analogs with improved pharmacological properties.[7] In addition to its crucial role in drug discovery, natural product synthesis has been used to respond to fascinating challenges posed by biology. Making biologically interesting natural products accessible in sufficient amounts and modifying the structure of natural products for chemical probe development have become additional objectives of synthetic chemists. Thus, natural product synthesis acquires a special role in chemical biology.

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. Typically, an X-ray structure of an organic compound is considered to be an ultimate proof of its structure. However, X-ray crystal diffraction usually does not reveal the positions of hydrogen atoms or reliably distinguish between oxygen atoms and NH groups. 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,[8] 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.[9] Therefore, a definitive structural proof of a natural product still necessitates its total synthesis.

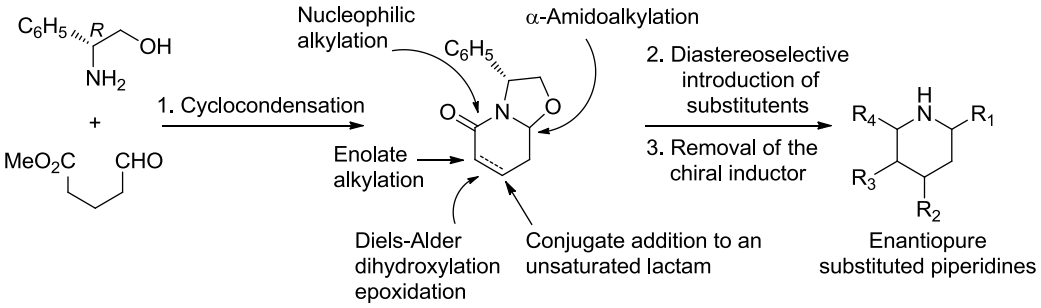
1.1. Synthetic background: oxazolopiperidone lactams

The main goal of the work we have been developing within our research group during the last years is the search for new and general methodologies for the preparation of aza-heterocyclic derivatives in enantiopure form, with the final aim of applying them to the total synthesis of natural products. In early stages, our group focused its 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 they explored the use of chiral aminoalcohol-derived bicyclic lactams as precursors of a variety of piperidine derivatives, an approach that fits in with the concept "*enantiomeric scaffolding strategy*". [10] This term, coined by

[7] Over, B.; Wetzel, S.; Grütter, C.; Nakai, Y.; Renner, S.; Rauh, D.; Waldmann, H. *Nat. Chem*. **2013**, *5*, 21-28.
[8] Nicolaou, K. C.; Snyder, S. A. *Angew. Chem. Int. Ed.* **2005**, *44*, 1012-1044.
[9] Maier, M. E. *Nat. Prod. Rep.* **2009**, *26*, 1105-1124.
[10] For reviews see: (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. Commun.* **2011**, *6*, 515-526. (d) Amat, M.; Pérez, M.; Bosch, J. *Chem. Eur. J.* **2011**, *17*, 7724-7732.

L. S. Liebeskind,[11] defines a procedure in which a conceptually simple core molecule of high enantiopurity, bearing tactically versatile functionality, is constructed, this resident functionality enabling the general elaboration of the core molecule in ways that allow access to diverse families of important molecules. Bicyclic lactams were originally developed by A. I. Meyers as chiral templates for the enantioselective synthesis of cycloalkenones and carboxylic acids containing quaternary stereocenters. In subsequent work, Meyers also reported some applications in the synthesis of simple α-substituted piperidine and tetrahydroquinoline alkaloids, as well as imino-sugars. This seminal work was summarized in three reviews.[12]

Chiral aminoalcohol-derived bicyclic lactams are easily available in a single synthetic step by cyclocondensation of δ-keto ester with an enantiopure amino alcohol, usually phenylglycinol.



Scheme 1.1

These enantiomeric scaffolds allow the regio- and stereocontrolled introduction of substituents at the different positions of the piperidine ring, thanks to their tactical functionalization (α-amidoalkylation[13], nucleophilic and enolate alkylation[14], conjugate addition to an unsaturated lactam[15] or Diels-Alder[16]

[11] 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.

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

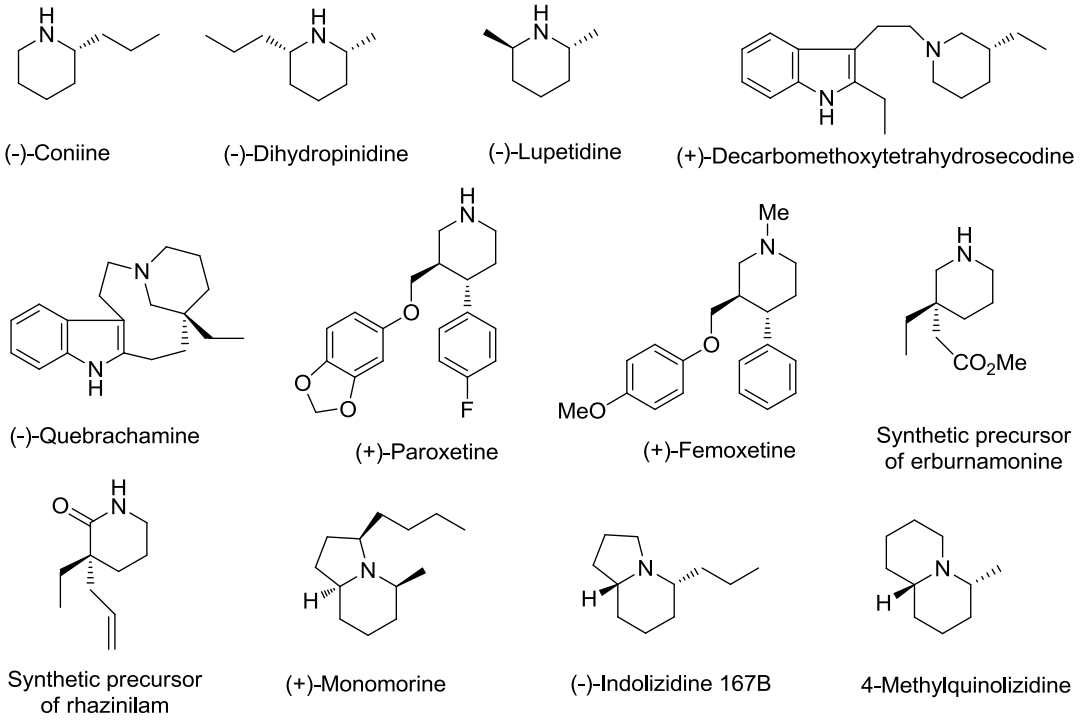
[13] (a) Amat, M.; Llor, N.; Bosch, J. *Tetrahedron Lett.* **1994**, *35*, 2223-2226. (b) Amat, M.; Llor, N.; Hidalgo, J.; Hernández, A.; Bosch, J. *Tetrahedron: Asymmetry* **1996**, *7*, 977-980. (c) Amat, M.; Hidalgo, J.; Llor, N.; Bosch, J. *Tetrahedron: Asymmetry* **1998**, *9*, 2419-2422. (d) Amat, 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.

[14] (a) Amat, M.; Escolano, C.; Llor, N.; Lozano, O.; Gómez-Esqué, A.; Griera, R.; Bosch, J. *ARKIVOC* **2005**, *IX*, 115-123. (b) Amat, M.; Escolano, C.; Lozano, O.; Gómez-Esqué, A.; Griera, R.; Molins, E.; Bosch, J. *J. Org. Chem.* **2006**, *71*, 3804-3815. (c) Amat, M.; Lozano, O.; Escolano, C.; Molins, E.; Bosch, J. *J. Org. Chem.* **2007**, *72*, 4431-4439.

[15] (a) Amat, M.; Bosch, J.; Hidalgo, J.; Cantó, M.; Pérez, M.; Llor, N.; Molins, E.; Miravitlles, C.; Orozco, M.; Luque, J. *J. Org. Chem.* **2000**, *65*, 3074-3084. (b) Amat, M.; Pérez, M.; Llor, N.; Bosch, J. *Org. Lett.* **2002**, *4*, 2787-2790. (c) Amat, M.; Pérez, M.; Llor, N.; Martinelli, M.; Molins, E.; Bosch, J. *Chem. Commun.* **2004**, 1602-1603. (d) Amat, M.; Pérez, M.; Llor, N.; Escolano, C.; Luque, F. J.; Molins, E.; Bosch, J. *J. Org. Chem.* **2004**, *69*, 8681-8693.

reactions) and conformational rigidity. 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 substitution pattern (Scheme 1.1). In fact, in this process phenylglycinol acts as chiral latent form of ammonia. Interestingly, as both enantiomers of phenylglycinol are commercially available, both enantiomers of a target compound are accessible through the above methodology.

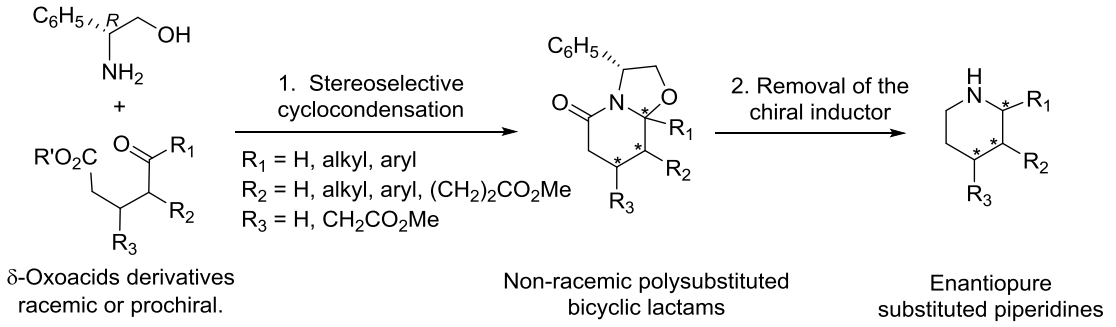
Some enantiopure piperidine, indolizidine and quinolizidine alkaloids, as well as bioactive piperidine derivatives of relative complexity, synthesized in our laboratory following the general synthetic strategy outlined in Scheme 1.1, are depicted below.



Scheme 1.2

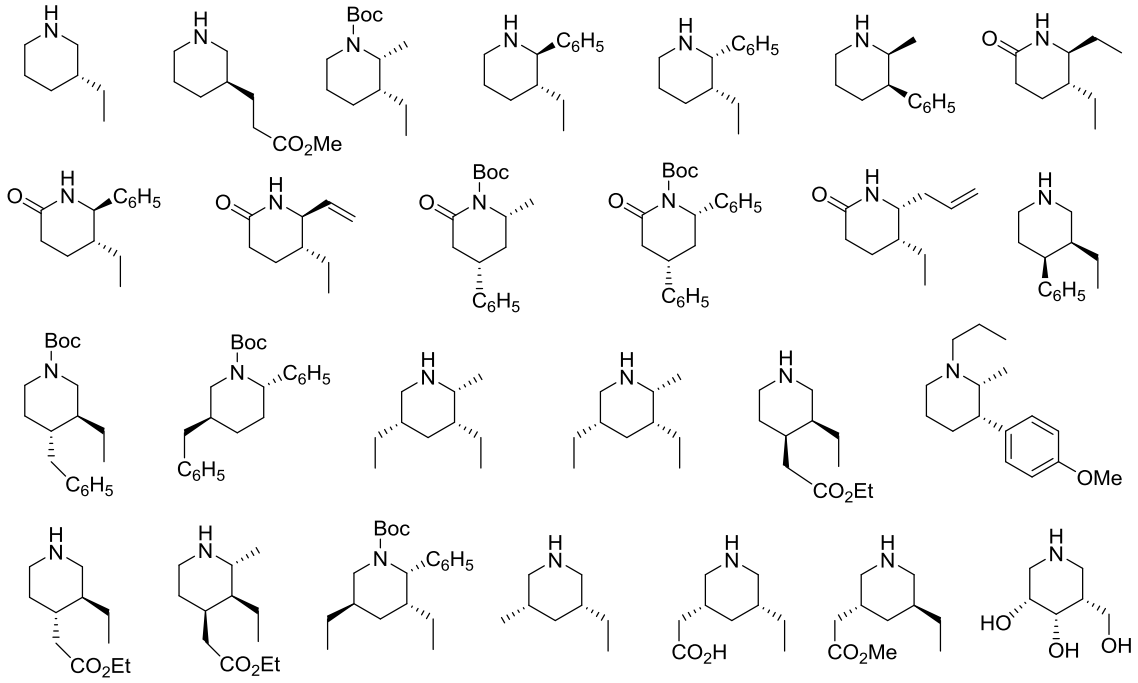
A more straightforward procedure for the synthesis of enantiopure polysubstituted piperidines has been developed, involving the direct generation of chiral nonracemic oxazolopiperidone lactams that already incorporate carbon substituents at the α,β or γ position of the heterocyclic ring.

[16] 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.



Scheme 1.3

The cyclocondensation between (*R*)-phenylglycinol and racemic γ-alkyl (or aryl)-δ-oxoacid derivatives or δ-keto diesters (racemic or prochiral) affords in good chemical yield one of the several possible enantiopure stereoisomers, in processes involving a dynamic kinetic resolution of the racemic substrate, and/or the differentiation of enantiotopic or diastereotopic esters groups. This represented an improvement in the efficiency of the methodology, since chiral bicylic lactams with substituents at the 3 and/or 4-position could now be generated in a single step. As a consequence of this substantial progress, an assorted enantiopure piperidine library could be successfully constructed.[17]

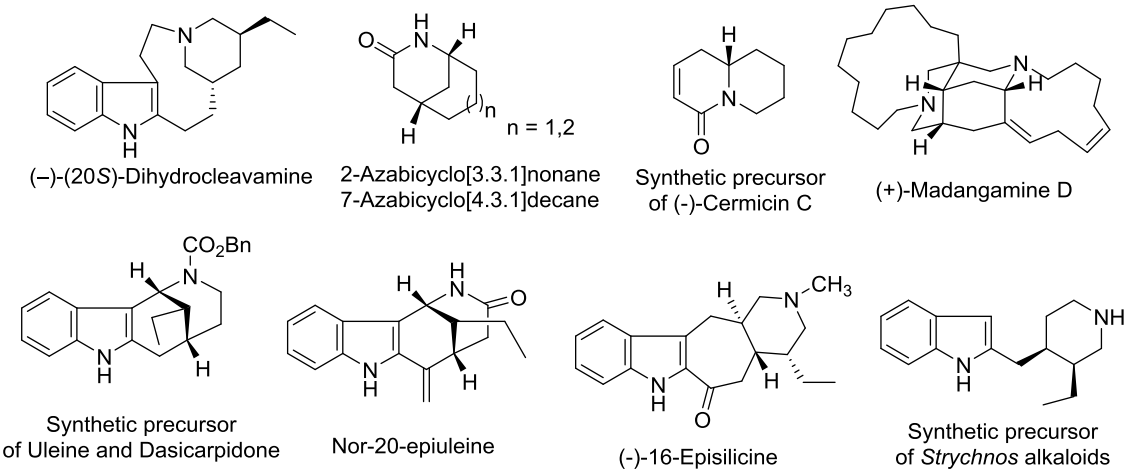


Scheme 1.4

It is worth emphasizing that this general methodology has been successfully employed to prepare some nitrogen-containing compounds of different levels or

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

complexity and substitution in enantiopure fashion and in relatively fewer steps.[18]

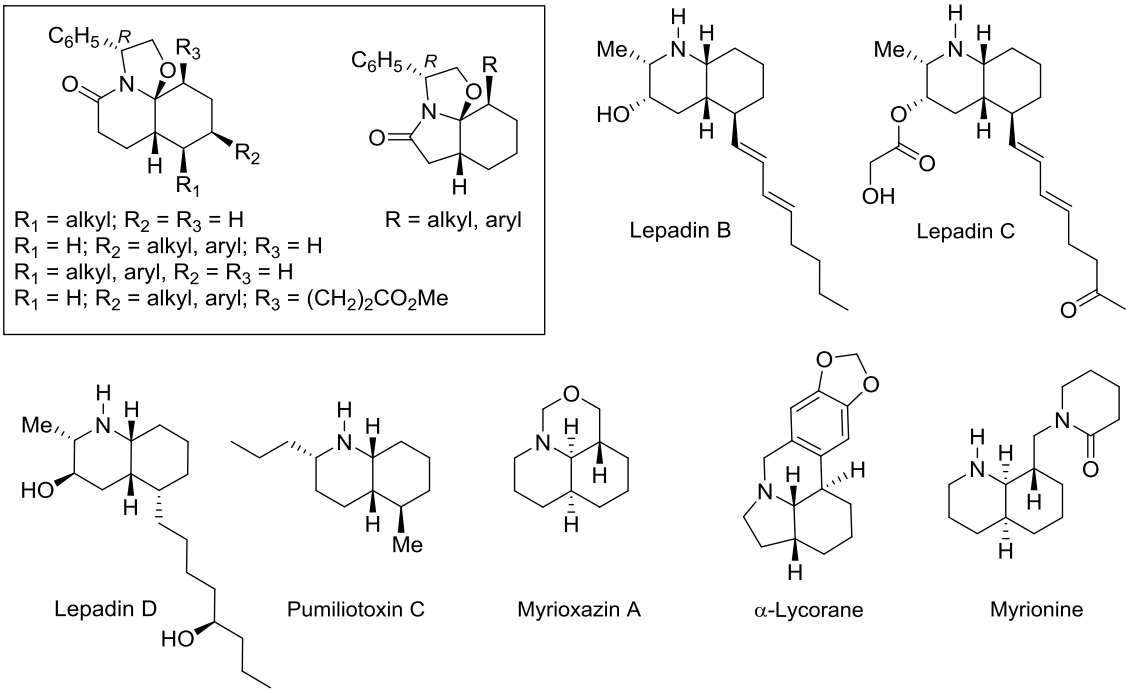


Scheme 1.5

More recently, our group has studied cyclocondensation reactions between (*R*)-phenylglycinol and mixtures of stereoisomers (racemates and mixtures of racemic diastereomers) derived from cyclohexanones or cyclohexenones bearing propionate or acetate chains at the 2-position, leading to tricyclic lactams (see Scheme 1.6). In most cases, we observed an excellent stereoselectivity in the generation of one of the possible diastereomers (up to 16, in some cases) of the corresponding tricyclic lactam with substituents at several positions of the carbocyclic ring. These tricyclic lactams can be easily transformed to enantiopure decahydroquinoline and octahydroindole derivatives, aza-bicycles present in many natural products of biological interest.[18h,18n,19]

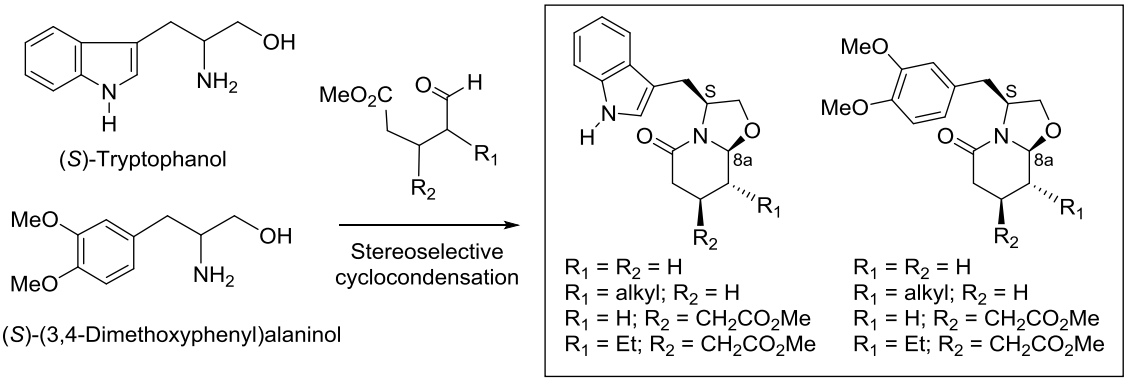
[18] (a) Amat, M.; Pérez, M.; Bosch, J.; Lago, E.; Molins, E. *Org. Lett.* **2001**, *3*, 611-614. (b) Amat, M.; Escolano, C.; Lozano, O.; Llor, N.; Bosch, J. *Org. Lett.* **2003**, *5*, 3139-3142. (c) Amat, M.; Llor, N.; Checa, B.; Pérez, M.; Bosch, J. *Tetrahedron Lett.* **2007**, *48*, 6722-6725. (d) Amat, M.; Pérez, M.; Minaglia, A. T.; Peretto, B.; Bosch, J. *Tetrahedron* **2007**, *63*, 5839-5848. (e) Amat, M.; Pérez, M.; Minaglia, A. T.; Bosch, J. *J. Org. Chem.* **2008**, *73*, 6920-6923. (f) Amat, M.; Griera, R.; Fabregat, R.; Molins, E.; Bosch, J. *Angew. Chem. Int. Ed.* **2008**, *47*, 3348-3351. (g) Amat, M.; Griera, R.; Fabregat, R.; Bosch, J. *Tetrahedron: Asymmetry* **2008**, *19*, 1233-1236. (h) Amat, M.; Brunaccini, E.; Pérez, M.; Llor, N.; Bosch, J. *Org. Lett.* **2009**, *11*, 4370-4373. (i) Amat, M.; Fabregat, R.; Griera, R.; Bosch, J. *J. Org. Chem.* **2009**, *74*, 1794-1797. (j) Amat, M.; Llor, N.; Checa, B.; Molins, E.; Bosch, J. *J. Org. Chem.* **2010**, *75*, 178-189. (k) Amat, M.; Pérez, M.; Proto, S.; Gatti, T.; Bosch, J. *Chem. Eur. J.* **2010**, *16*, 9438-9441. (l) Amat, M.; Pinto, A.; Griera, R.; Bosch, J. *Chem. Commun.* **2013**, *49*, 11032-11034. (m) Ballette, R.; Pérez, M.; Proto, S.; Amat, M.; Bosch, J. *Angew. Chem. Int. Ed.* **2014**, *53*, 6202-6205.

[19] (a) Amat, M.; Fabregat, R.; Griera, R.; Florindo, P.; Molins, E.; Bosch, J. *J. Org. Chem.* **2010**, *75*, 3797-3805. (b) Amat, M.; Ghirardi, E.; Navio, L.; Griera, R.; Llor, N.; Molins, E.; Bosch, J. *Chem. Eur. J.* **2013**, *19*, 16044-16049. (c) Amat, M.; Pinto, A.; Griera, R.; Bosch, J. *Chem. Eur. J.* **2015**, *21*, 12804-12808.



Scheme 1.6

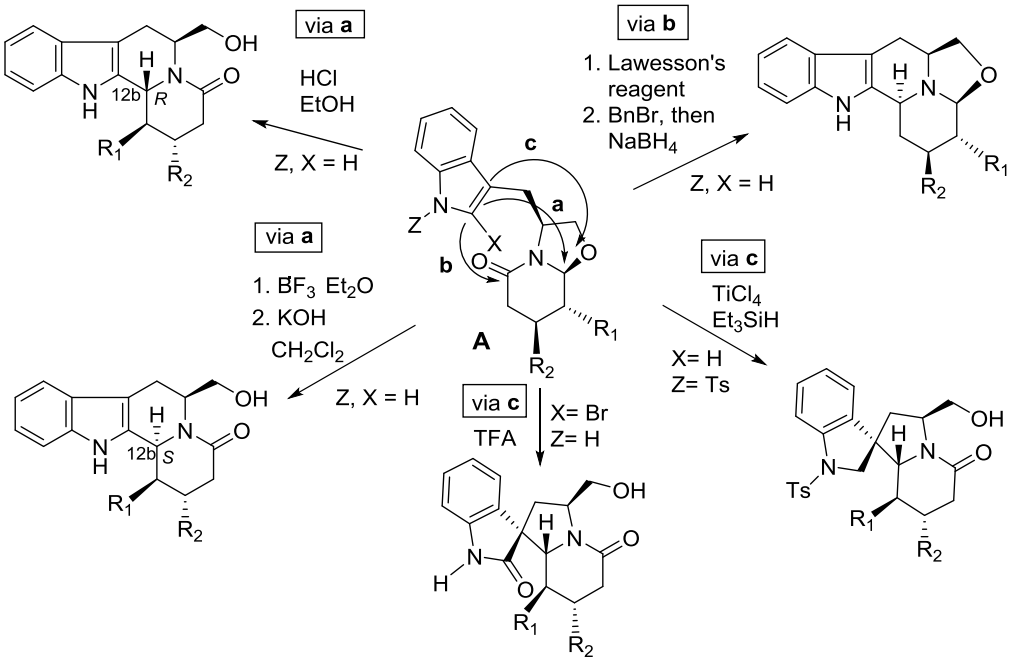
On the other hand, (*S*)-tryptophanol and (*S*)-3,4-(dimethoxyphenyl)alaninol have also been used in the context of the synthesis of some indolo[2,3-*a*]quinolizidine, benzo[*a*]quinolizidine and oxindole alkaloids.[20] Lactams derived from these alcohols are easily accessible in enantiopure form in a single synthetic step by a stereoselective cyclocondensation reaction between the aminoalcohol and an appropriate δ-oxo acid derivative.



Scheme 1.7

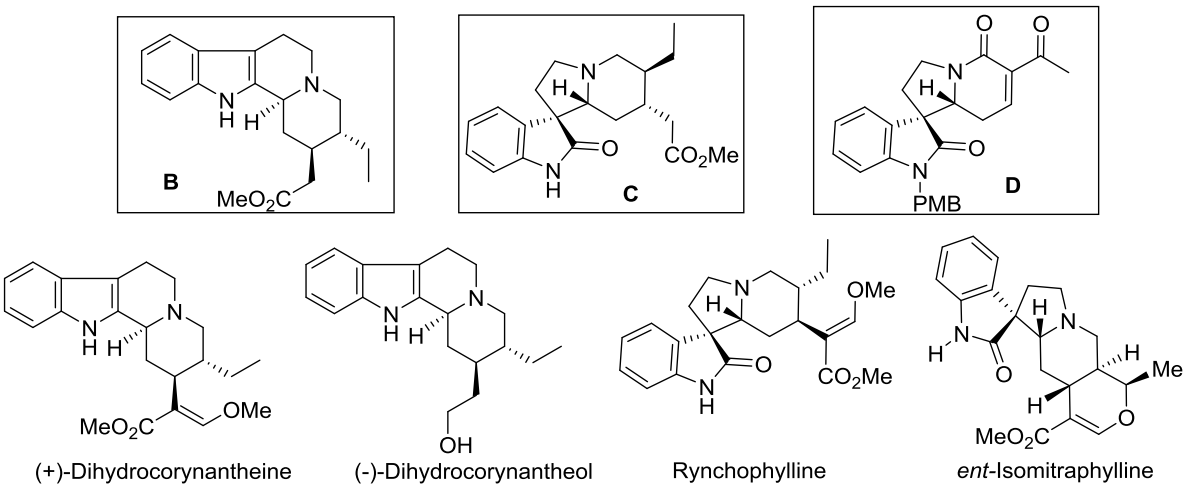
[20] (a) Bassas, O.; Llor, N.; Santos, M. M. M.; Griera, R.; Molins, E.; Amat, M.; Bosch, J. *Org. Lett.* **2005**, *7*, 2817-2820. (b) Amat, M.; Santos, M. M. M.; Bassas, O.; Llor, N.; Escolano, C.; Gómez-Esqué, A.; Molins, E.; Allin, S. M.; McKee, V.; Bosch, J. *J. Org. Chem.* **2007**, *72*, 5193-5201. (c) Amat, M.; Santos, M. M. M.; Gómez, A. M.; Jokic, 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. (e) Amat, M.; Ramos, C.; Pérez, M.; Molins, E.; Florindo, P.; Santos, M. M. M.; Bosch, J. *Chem. Commun*. **2013**, *49*, 1954-1956.

Taking advantage of the functionalization present in tryptophanol-derived oxazolopiperidone lactams **A** (Scheme 1.8), an electrophilic cyclization on the indole 2-position can involve either the hemiaminal ether carbon via an *N*-acyliminium cation (via **a**) or the lactam carbonyl via a Bischler−Napieralski-type reaction (via **b**), leading to regioisomeric indolo[2,3-*a*]quinolizidines (when $R_1 \neq H$). Additionally, by choosing the appropriate reaction conditions, an intramolecular α-amidoalkylation allows the stereocontrolled generation of C-12b epimeric derivatives. On the other hand, a Lewis acid/Et_3SiH-promoted cyclization on the indole 3-position from N_a-tosyl derivatives provides straightforward access to the spiro[indole-3,1'-indolizidine] framework present in a large number of alkaloids (via **c**). Our group has also studied spirocyclization reactions from 2-bromoindole-derived bicyclic lactams to obtain directly spirooxindoles with high stereoselectivity. These complementary types of cyclization are shown in Scheme 1.8.



Scheme 1.8

The usefulness of this methodology was demonstrated with the synthesis of tetracyclic ester **B**,[20d] (a known synthetic precursor of the alkaloids (+)-dihydrocorynantheine and (-)-dihydrocorynantheol), oxindole **C**,[20e] (synthetic precursor of *ent*-rynchophylline and *ent*-isorynchophylline) and α,β-unsaturated lactam **D** (synthetic precursor of *ent*-isomitraphylline and *ent*-isoformosanine).

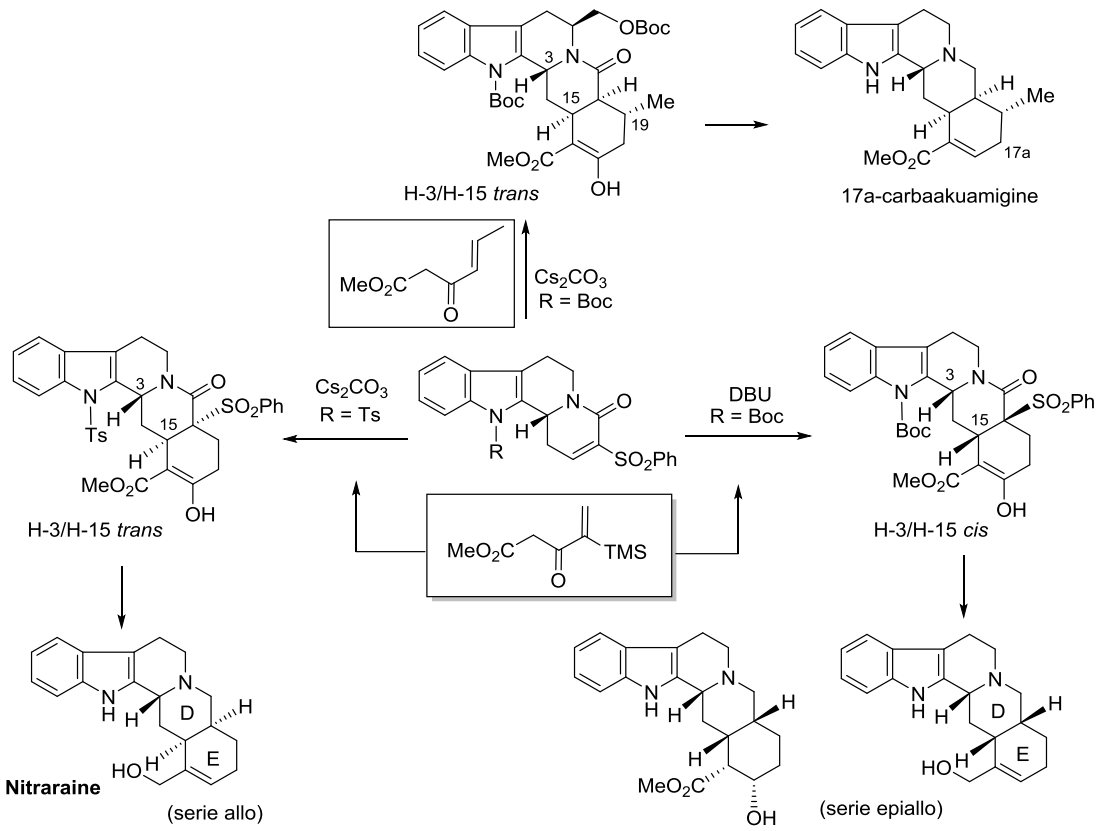


Scheme 1.9

Finally, our group has studied the facial selectivity of base-catalyzed double Michael addition reactions of γ,δ-unsaturared β-oxoesters (Nazarov-type reagents) with unsaturated indolo[2,3-*a*]quinolizidine lactams. When the appropriate base is chosen, N_{ind}-H and N_{ind}-Ts lactams react with a silylated Nazarov reagent to stereoselectively give yohimbine-type pentacyclic with a H-3/H-15 *trans* relationship (as in nitraraine), whereas N_{ind}-Boc lactams lead to H-3/H-15 *cis* derivatives.[21]

Taking into account the accessibility of enantiopure tryptophanol-derived indoloquinolizidine lactams and that the hydroxymethyl substituent of these lactams can be easily removed, the above methodology can provide access to pentacyclic derivatives both in the racemic series and in enantiopure form. The synthetic usefulness of pentacyclic Nazarov-derived adducts has been demonstrated by their conversion into allo and epiallo yohimbine-type targets.[22]

[21] Amat, M.; Arioli, F.; Pérez, M.; Molins, E.; Bosch, J. *Org. Lett.* **2013**, *15*, 2470-2473.
[22] Arioli, F.; Pérez, M.; Are, C.; M.; Estarellas, C.; Luque, J. L.; Bosch, J.; Amat, M. *Chem. Eur. J.* **2015**, *21*, 13382-13389.



Scheme 1.10

1.2. Objectives

Based on the previous experience of our group, we focused our attention on the use of phenylglycinol-derived bicyclic lactams as chiral building blocks for the preparation of versatile enantiopure open-chain intermediates with applicability in the synthesis of complex natural products or biologically active compounds.

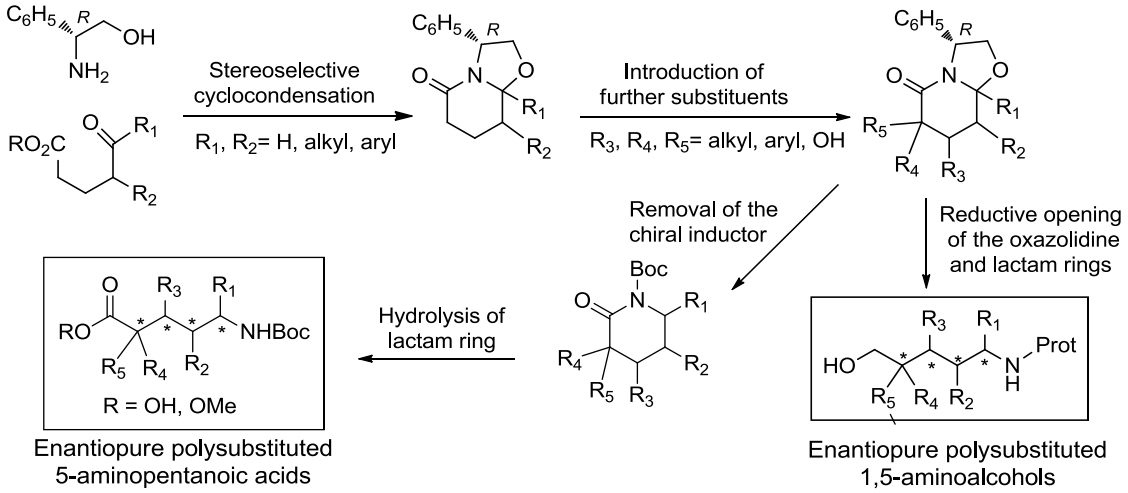
After the stereoselective introduction of substituents at different positions of the piperidine ring of the chiral lactams and the subsequent removal of the phenylethanol moiety of the chiral inductor, we initially planned to effect the hydrolytic cleavage of the lactam function to provide a variety of enantiopure substituted 5-aminopentanoic acids.

Additionally, we envisioned that the reductive cleavage of the oxazolidine and lactam rings would open a general synthetic entry to diversely substituted enantiopure 1,5-aminoalcohols.

In this way, we would access a variety of related enantiopure substituted and functionalized acyclic derivatives, taking advantage of the fact that the

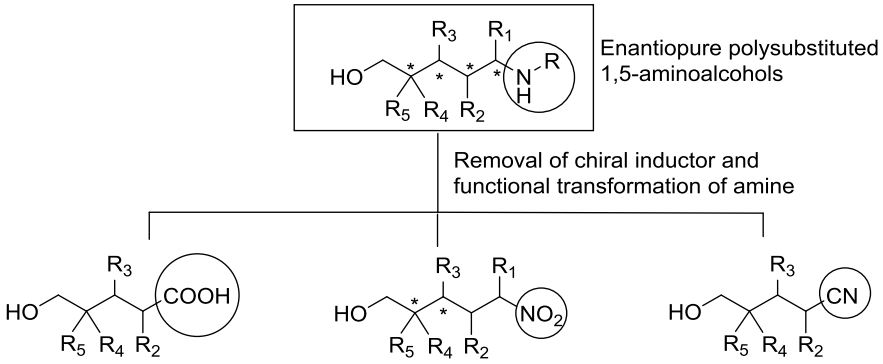
stereocontrolled generation of chiral centers is generally more efficient and easier to accomplish in conformationally rigid cyclic compounds than in acyclic compounds.

Chapter 2. Starting from diversely substituted phenylglycinol-derived bicyclic lactams, we report the preparation of a variety of substituted chiral amino acids and amino-alcohols with different substitution and stereochemical patterns and discuss the scope and limitations of the procedure.



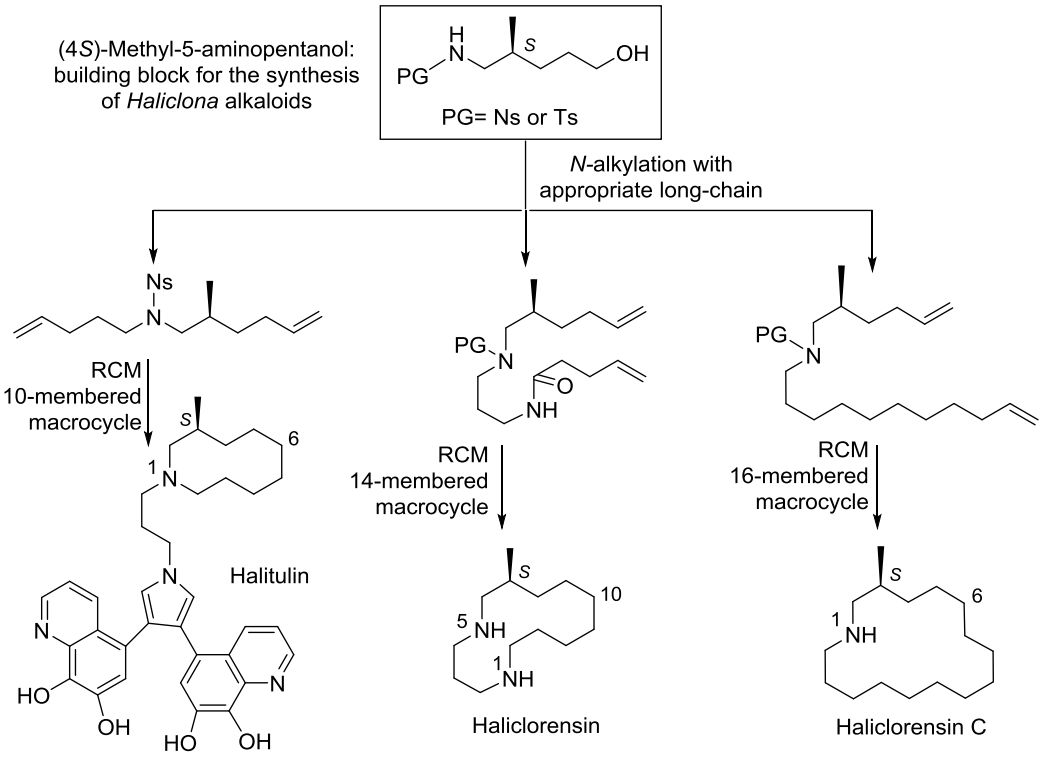
Scheme 1.11

To increase the synthetic value of the linear-chain enantiopure amino diols resulting from the above reductive ring opening reactions, we also planned to evaluate the feasibility of functional group transformations from the amino group, in order to access substituted enantiopure 1,5-nitroalcohols, 5-hydroxypentanoic acids, and 5-hydroxypentanenitriles.



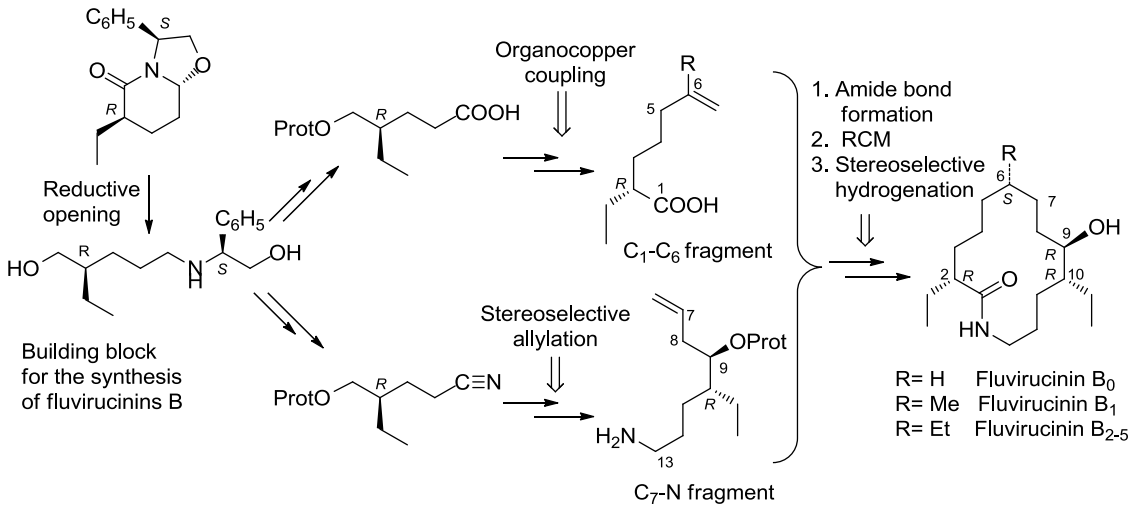
Scheme 1.12

Chapter 3. With the aim of demonstrating the usefulness of the above open-chain chiral building blocks, we planned to study their application to the synthesis of macrocyclic natural products. The synthesis of *Haliclona* alkaloids, such as haliclorensin, halitulin, and haliclorensin C, from 1,5-aminoalcohols would require the latter to be converted into appropriate long-chain secondary amino derivatives bearing two terminal alkene functionalities, which would allow the target azacyclic structures to be assembled using a ring-closing metathesis (RCM) reaction as the key step. (4*S*)-Methyl-5-aminopentanol was envisaged as the N_1-C_6 fragment of haliclorensin C and halitulin, and the fragment N_5-C_{10} of haliclorensin.



Scheme 1.13

We also planned to study the total synthesis of fluvirucinins B_0, B_1, and $B_{2\text{-}5}$. We envisioned a convergent synthesis from a common starting (*S*)-phenylglycinol-derived amino diol to access fragments C_1-C_6 and C_7-N of fluvirucinins B. The key steps would be an organocopper coupling, a stereoselective allylation, an RCM reaction (to form the required 14-membered ring), and a stereoselective hydrogenation. The starting enantiopure open-chain building blocks would be prepared in a straightforward manner from an appropriate phenylglycinol-derived lactam.


Reductive opening
Building block for the synthesis of fluvirucinins B
Organocopper coupling
C1-C6 fragment
Stereoselective allylation
C7-N fragment
1. Amide bond formation
2. RCM
3. Stereoselective hydrogenation
R= H Fluvirucinin B0
R= Me Fluvirucinin B1
R= Et Fluvirucinin B2-5

Scheme 1.14

Chapter 2

SYNTHESIS OF CHIRAL OPEN-CHAIN BUILDING BLOCKS FROM PHENYLGLYCINOL-DERIVED LACTAMS

2.1. Introduction

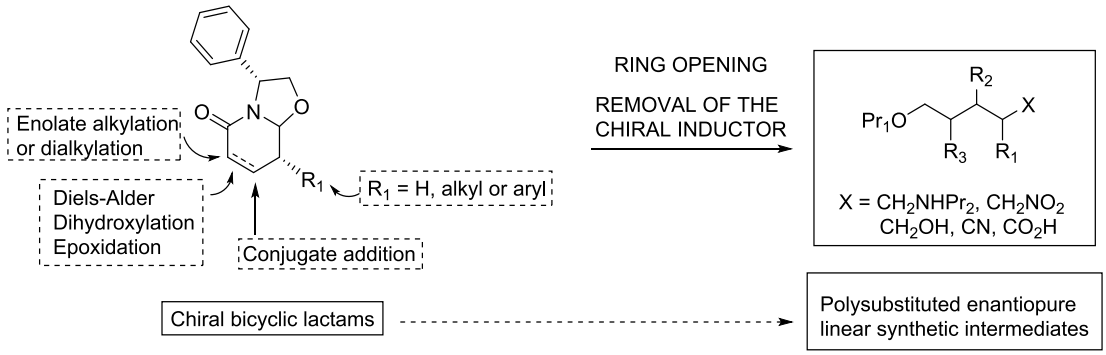
The stereocontrolled introduction of chiral centers into conformationally rigid cyclic systems is generally more efficient and easier to accomplish than into acyclic intermediates. This concept has often been used in the design of stereo- and enantioselective procedures for the synthesis of acyclic synthetic intermediates containing multiple chiral centers. The substituents are stereoselectively introduced into a cyclic enantiopure building block and then the ring is opened to yield a substituted linear-chain intermediate that maintains the stereochemical information.[23] However, traditionally, this approach to stereodefined acyclic intermediates has only been used for the synthesis of specific target compounds, but general methodologies providing access to a wide variety of synthetic targets have been scarcely developed.

As mentioned in Chapter 1, in previous work our group has explored the potential of chiral phenylglycinol-derived lactams, easily available from

[23] For a procedure for the piperidine ring-opening, see: (a) McCall, W. S.; Grillo, T. A.; Comins, D. L. *J. Org. Chem*. **2008**, *73*, 9744-9751. (b) McCall, W. S.; Comins, D. L. *Org. Lett*. **2009**, *11*, 2940-2942.

enantiopure aminoalcohols and oxo-acid derivatives, as enantiomeric scaffolds for the stereocontrolled construction of complex piperidine derivatives. As a result, we now have in hand flexible and versatile procedures for the generation of new stereocenters with a high degree of stereoselectivity and a predictable absolute and relative configuration at virtually all the carbon positions of the piperidine ring of these bicyclic lactams. Taking advantage of this experience, in this Thesis we will focus our attention on the preparation of versatile enantiopure linear intermediates with applicability in the synthesis of complex natural products or biologically active compounds. The general strategy involves the stereoselective introduction of substituents at the desired position of the piperidine ring of chiral bicyclic lactams using procedures previously developed in our group, the subsequent removal of the phenylethanol moiety of the chiral inductor, and the cleavage of the lactam function to lead to a variety of enantiopure 5-amino-alcohols, 5-nitro-alcohols, 1,5-diols, 5-hydroxy-esters or 5-hydroxy-nitriles, which constitute valuable chiral building blocks for the synthesis of natural products or biologically interesting compounds.

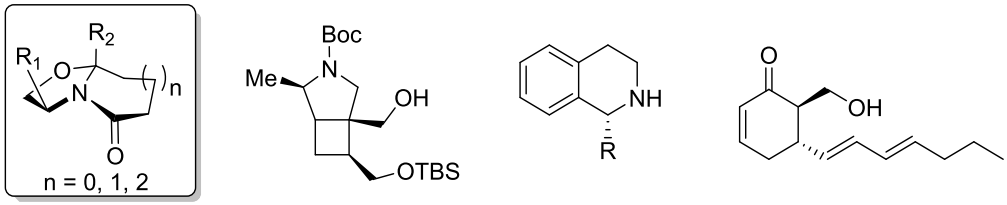
General strategy for the synthesis of substituted linear-chain intermediates from chiral bicyclic lactams



Scheme 2.1

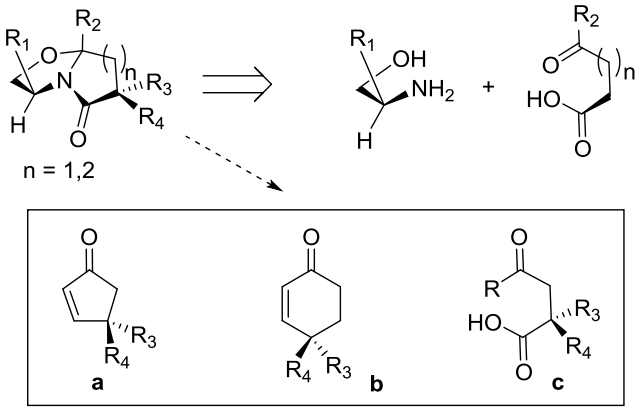
2.1.1. Precedents in the ring-opening of oxazolopiperidone lactams

A. I. Meyers, one of the pioneers in the field of chiral bicyclic lactams, has demonstrated that these structures are versatile building blocks for the asymmetric synthesis of a variety of natural and unnatural products.[12]



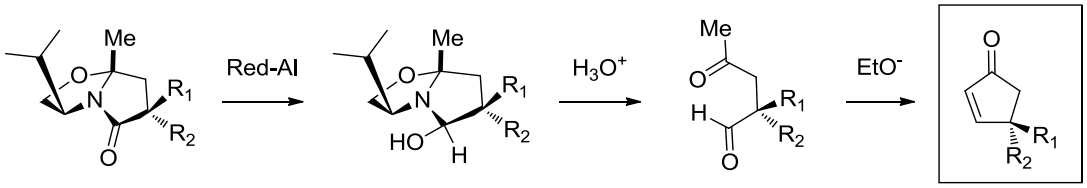
Scheme 2.2

He described the preparation of these lactams by condensation of an enantiomerically pure amino alcohol with a dicarbonyl compound, and demonstrated their utility in the synthesis of compounds containing quaternary stereocenters such as cyclopentenones **a**, cyclohexenones **b,** and carboxylic acids **c**.[24]



Scheme 2.3

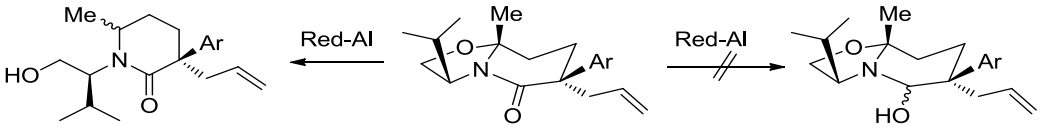
Enantiomerically pure 4,4-dialkylcyclopentenones are obtained from the corresponding dialkylated lactams by a three step sequence involving partial reduction of the lactam carbonyl, hydrolysis of the bicyclic system, and aldol cyclization. In this process, the initially formed enantiopure acyclic keto aldehyde undergoes intramolecular aldol cyclization to give cyclopentenone compounds with a quaternary stereocenter.



Scheme 2.4

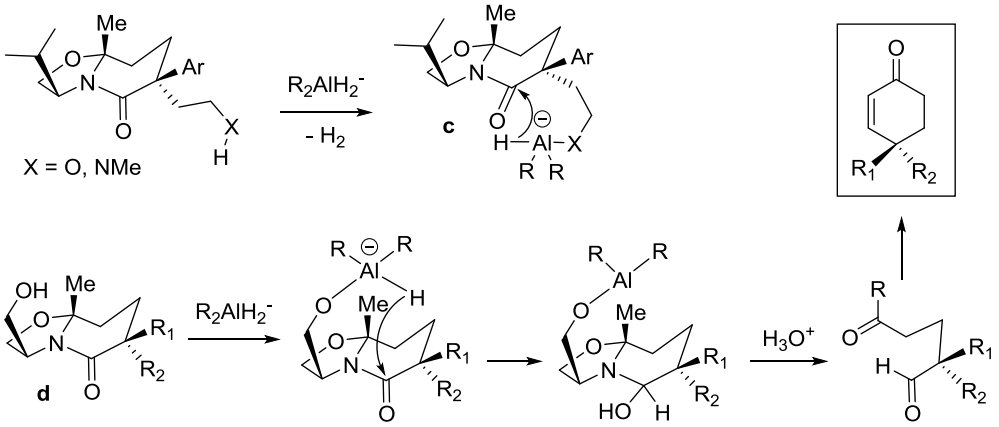
The homologous [4.3.0] bicyclic lactams exhibited different chemical properties in comparison to their [3.3.0] bicyclic lactam counterpart. Addition of hydride did not reduce the lactam carbonyl to the carbinolamine as in the [3.3.0] series but resulted, instead, in the reduction of the acetal center, leading to a piperidone as the major product.

[24] (a) Hughes, R. C.; Dvorak, C. A.; Meyers, A. I. *J. Org. Chem*. **2001**, *66*, 5545-5551. (b) Waterson, A. G.; Meyers, A. I. *J. Org. Chem*. **2000**, *65*, 7240-7243. (c) Arrington, M. P.; Meyers, A. I. *Chem. Commun*. **1999**, 1371-1372. (d) Degnan, A. P.; Meyers, A. I. *J. Am. Chem. Soc*. **1999**, *121*, 2762-2769. See also ref. 12.



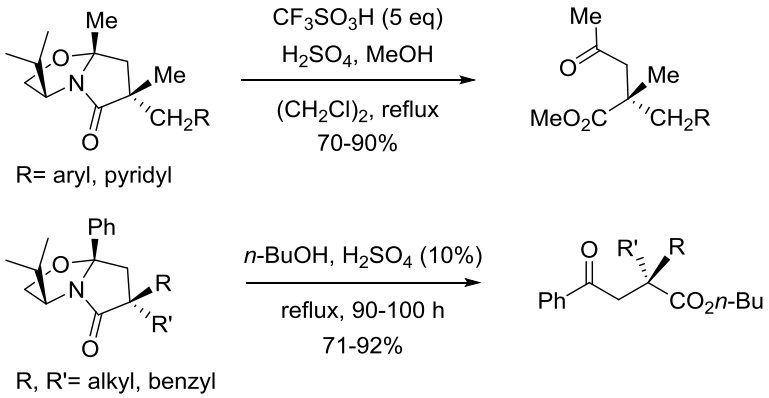
Scheme 2.5

In these oxazolopiperidone lactams the opening of the six-membered ring with concomitant removal of the auxiliary was possible only with lactams containing a β-amino or β-hydroxymethyl group on the side chain. This behavior was rationalized by assuming that the first equivalent of hydride removes the amine or alcohol proton resulting in an aluminium complex **c**, which serves as a "tether" to deliver hydride intramolecularly in a controlled fashion. It was further believed that if such a "tether" could be permanently incorporated into the chiral auxiliary of a bicyclic lactam **d**, this would also facilitate the delivery of hydride and the subsequent hydrolytic removal of the auxiliary. A subsequent *in situ* intramolecular aldol cyclization of the resulting acyclic keto aldehyde proceeds under the acidic conditions employed.[12]



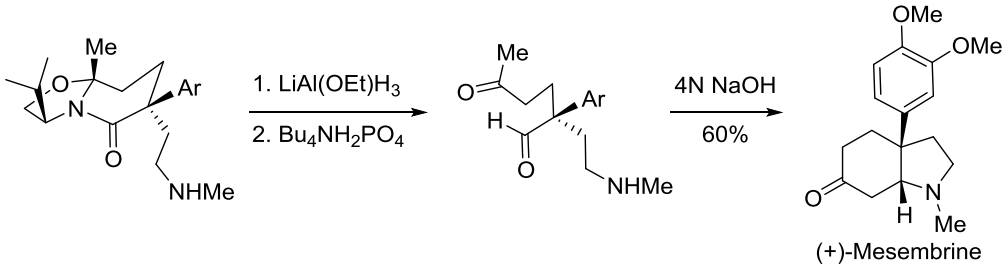
Scheme 2.6

In conclusion, Meyers, only for the specific case of angularly substituted lactams, described some precedents of cleavage, either by direct hydrolysis under acidic conditions to give δ-keto ester derivatives (only from [3.3.0] bicyclic lactams; Schemes 2.7) or by hydride attack to the lactam carbonyl, followed by hydrolysis of the resulting carbinolamine (from [3.3.0] and [4.3.0] bicyclic lactams, Schemes 2.4 and 2.6). In the latter cases, the initially formed 1,5-dicarbonyl derivatives undergo *in situ* aldolization to give corresponding cyclopentenones or cyclohexenones. In no cases are nitrogen-containing linear-chain products formed.



Scheme 2.7

In the example outlined Scheme 2.8, the reduction of the lactam carbonyl with lithium monoethoxy aluminium hydride followed by hydrolysis gave a ketoaldehyde precursor of (+)-mesembrine.[12a]



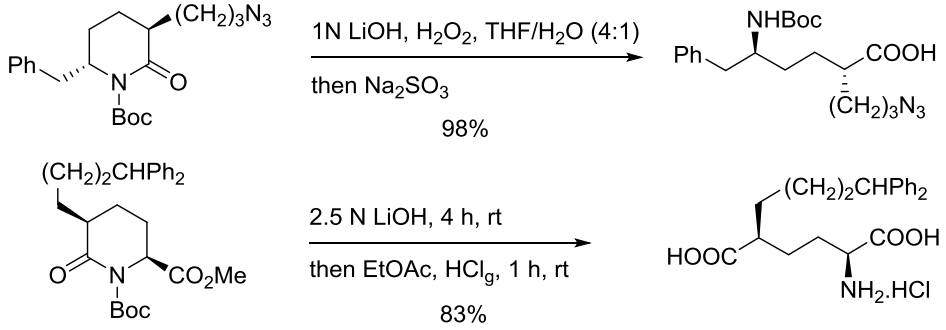
Scheme 2.8

2.2 Synthesis of enantiopure 4-substituted 5-aminopentanoic acid derivatives

2.2.1 Introduction

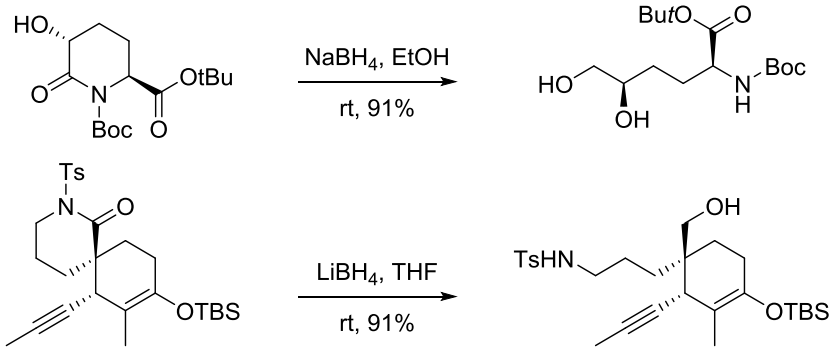
Several procedures have been employed for the ring opening of δ-lactams bearing an electron withdrawing group on the nitrogen atom. Although the direct acidic or alkaline hydrolysis requires somewhat drastic reaction conditions, *N*-Boc protected lactams undergo alkaline hydrolysis or methanolysis under mild conditions,[25] leading to the corresponding ω-amino acids or esters, respectively.

[25] a) Ezquerra, J.; Pedregal, C.; Escribano, A.; Carreño, M. C.; García Ruano, J. L. *Tetrahedron Lett.* **1995**, *36*, 3247-3250. b) Flynn, D. L.; Zelle, R. E.; Grieco, P. A. *J. Org. Chem*. **1983**, *48*, 2424-2426. c) Casimir, J. R.; Didierjean, C.; Aubry, A.; Rodriguez, M.; Briand, J.-P.; Guichard, G. *Org. Lett*. **2000**, *2*, 895-897. d) Kende, A. S.; Dong, H.-Q.; Mazur, A. W.; Ebetino, F. H. *Tetrahedron Lett*. **2001**, *42*, 6015-6018.



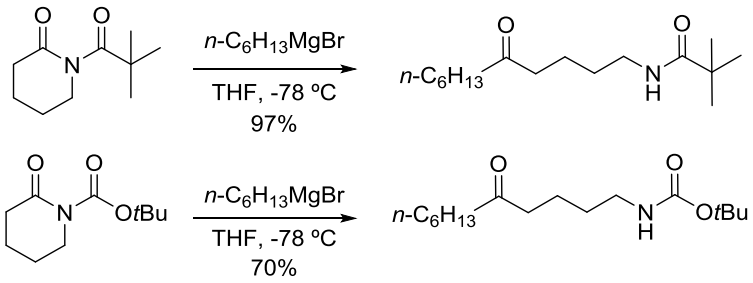
Scheme 2.9

There are also a few examples of the reductive cleavage of *N*-Boc and *N*-Ts piperidones using borohydride salts to give 1,5-aminoalcohols.[26]



Scheme 2.10

We can also found some examples of the ring-opening of *N*-acyl and *N*-alkoxycarbonyl δ-lactams with Grignard reagents, leading to δ-amino ketones. [27]

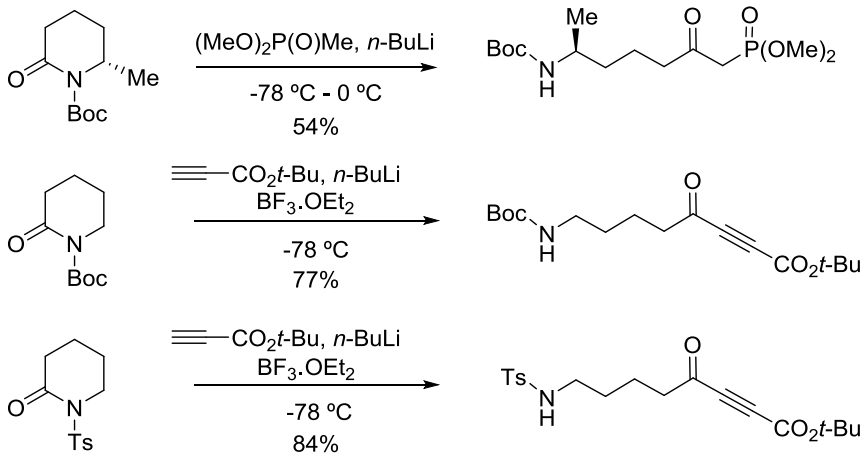


Scheme 2.11

Other carbon nucleophiles such as the phosphonate anion[28] and lithium *tert*-butyl propiolate[29] have also been used in δ-lactam hydrolysis, producing a Horner-Emmons reagent in the first example of Scheme 2.12.

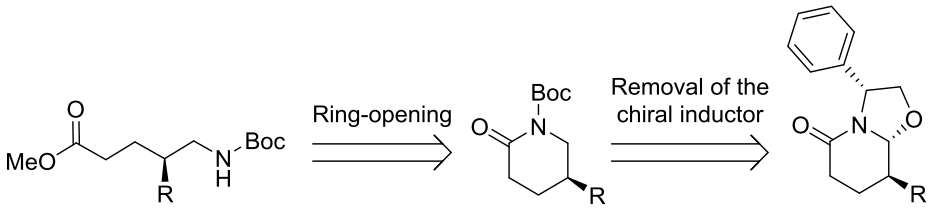
[26] a) Marin, J.; Violette, A.; Briand, J.-P.; Guichard, G. *Eur. J. Org. Chem*. **2004**, 3027-3039. b) Kong, K.; Moussa, Z.; Romo, D. *Org. Lett*. **2005**, *7*, 5127-5130. c) Didierjean, C.; Aubry, A.; Briand, J.-P.; Guichard, G. *J. Org. Chem.* **2002**, *67*, 8440-8449. d) See also: Wang, J.-J.; Wan-Ping, H. *J. Org. Chem.* **1999**, *64*, 5725-5727.

[27] (a) Giovannini, A.; Savoia, D.; Umani-Ronchi, A. *J. Org. Chem*. **1989**, *54*, 228-234.



Scheme 2.12

In this context, and with these precedents, we devised the preparation of enantiopure linear-chain amino acid derivatives by hydrolytic ring-opening of the *N*-Boc substituted 2-piperidones derived from chiral non-racemic C-8 substituted oxazolopiperidone lactams.

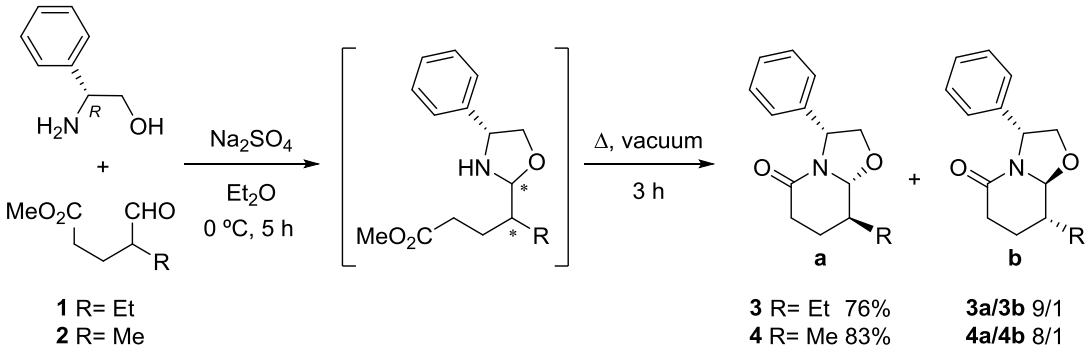


Scheme 2.13

2.2.2. Preparation of C-8 substituted lactams

Lactams **3a** and **4a** were prepared in good chemical yields and high stereoselectivity by cyclocondensation of racemic δ-oxoesters **1** and **2**, respectively, which bear an alkyl substituent at the epimerizable carbon α to the aldehyde carbonyl group, with an equimolecular amount of (*R*)-phenylglycinol, in a process that involves a dynamic kinetic resolution of the racemic substrate. The first step is the formation of a mixture of diastereoisomeric oxazolidines, which are in equilibrium with the corresponding imines-enamine, by reaction between the amino alcohol with the aldehyde. A final irreversible lactamization leads to the bicyclic lactams.

[28] Tchabanenko, K.; Adlington, R. M.; Cowley, A. R.; Baldwin, J. E. *Org. Lett.* **2005**, *7*, 585-588.
[29] Grant, T. N.; Benson, C. L.; West, F. G. *Org. Lett.* **2008**, *10*, 3985-3988.

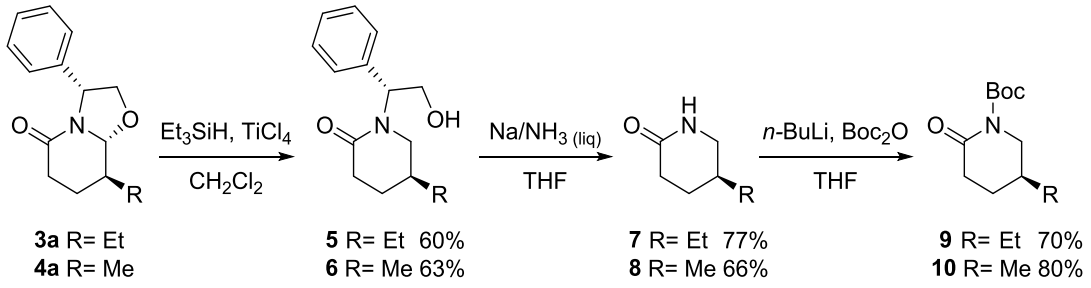


Scheme 2.14

Alternatively, lactam **4a** was also obtained in 74% yield and lower stereoselectivity (**4a**/**4b**: 3.1/1) by cyclocondensation of (*R*)-phenylglycinol with the aldehyde ester **2** in refluxing toluene with azeotropic removal of water. We obtained similar results working in microwave-assisted conditions (80%, **4a**/**4b**: 2.6/1).

2.2.3. Preparation of (*S*)-1-(*tert*-butoxycarbonyl)-5-substituted-2-piperidones

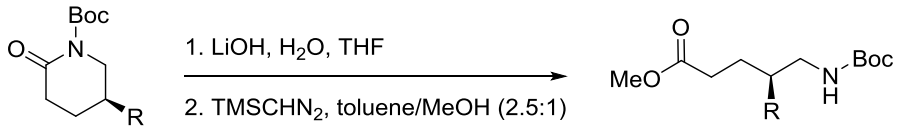
Enantiomerically pure (*S*)-1-(*tert*-butoxycarbonyl)-5-substituted-2-piperidones **9** and **10** were obtained from the corresponding bicyclic lactams **3a** and **4a**, respectively, by the three-step sequence outlined in Scheme 2.15. The removal of chiral auxiliary was accomplished by successive treatment with triethylsilane in the presence of $TiCl_4$, which brought about the reductive cleavage of the oxazolidine C–O bond, and sodium in liquid NH_3, which caused the cleavage of the benzylic C–N bond. The resulting *N*-unsubstituted 2-piperidones **7** and **8** were converted into the corresponding enantiopure *N*-Boc derivatives **9** and **10** in 70% and 80% yield, respectively.



Scheme 2.15

2.2.4. Preparation of 4-substituted 5-aminopentanoic acid derivatives

The synthesis of enantiopure linear-chain amino acid derivatives **11** and **12** was accomplished in excellent yields by alkaline hydrolytic opening of 2-piperidones **9** and **10**, using lithium hydroxide in aqueous THF at room temperature, followed by esterification of the resulting crude δ-amino acids with trimethylsilyldiazomethane. In this way, starting from lactams **3a** and **4a**, enantiopure esters **11** and **12** were synthesized in 5 steps with overall yields of 26% and 30%, respectively.



9 R= Et
10 R= Me

11 R= Et 80%
12 R= Me 90%

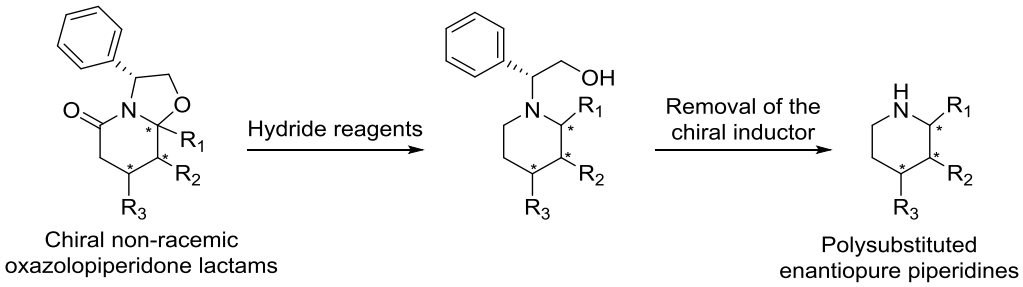
Scheme 2.16

Starting from racemic δ-oxoesters **1** and **2** and (*R*)-phenylglycinol, we synthesized enantiopure 4-substituted 5-aminopentanoic acid derivatives **11** and **12**, bearing a chiral center of defined configuration, in six steps. This overall process can be envisaged as a reductive amination of racemic aldehyde-esters **1** and **2** using a chiral latent form of ammonia, with concomitant dynamic kinetic resolution. Although the above sequence allows the preparation of enantiopure substituted open-chain scaffolds from phenylglycinol-derived lactams. we decided to explore alternative procedures for the ring opening of these lactams.

2.3. Ring opening of oxazolopiperidone lactams

2.3.1. Introduction

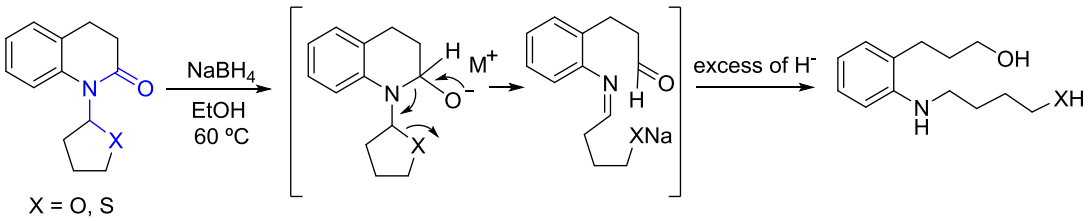
In previous work we have described[10] the use of boron- and aluminium-derived hydrides (BH_3, $LiAlH_4$, AlH_3, 9-BBN, or Red-Al) to reduce the lactam carbonyl with simultaneous reductive opening of the oxazolidine ring of diversely chiral non-racemic bicyclic lactams to give the respective piperidines.



Scheme 2.17

This methodology allowed us to synthesize a variety of enantiopure polysubstituted piperidines and some nitrogen-containing compounds of different levels of complexity and substitution (see Synthetic Background in Chapter 1). In no case did the reduction of oxazolopiperidone lactams under hydride reductive conditions afford ring-opening lactams.

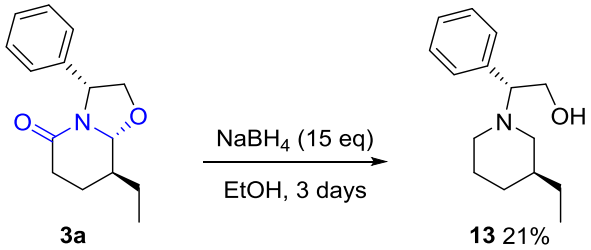
However, we found in the literature that treatment of 2-(tetrahydrofuranyl)- or 2-(tetrahydrothienyl)-3,4-dihydro-2(1*H*)-quinolinones[30] with $NaBH_4$ (or other hydride agents, such as $LiBH_4$, $LiAlH_4$ or L-selectride) gave fragmentation products in moderate yields (44-79%). The carbonyl group of the quinolinone is reduced by the hydride agent to form the intermediate shown in Scheme 2.18, which undergoes a 3-aza-Grob fragmentation. This transformation involved the successive ring opening of a six- and a five-membered ring, to give an imino aldehyde. An excess of hydride converts this intermediate to the saturated amino alcohol.



Scheme 2.18

The above reaction takes place on a substrate having a carbonyl-nitrogen-carbon-heteroatom (O or S) sequence that we can also be observed in our oxazolopiperidone lactams. We decided to apply the reductive conditions described Scheme 2.18 for the reduction of chiral bicyclic lactam **3a**, using a large excess of $NaBH_4$ (15 eq) in the presence of ethanol. After stirring for 3 days under these conditions, we only obtained piperidine **13** in 21% yield, with 77% of recovered starting material.

[30] (a) Hu, W.-P.; Wang, J.-J.; Tsai, P.-C. *J. Org. Chem.* **2000**, *65*, 4208-4209. (b) Marin, J.; Didierjean, C.; Aubry, A.; Briand, J.-P.; Guichard, G. *J. Org. Chem*. **2002**, *67*, 8440-8449. (c) Mitsunaga, S.; Ohbayashi, T.; Sugiyama, S.; Saitou, T.; Tadokoro, M.; Satoh, T. *Tetrahedron: Asymmetry* **2009**, *20*, 1697-1708.

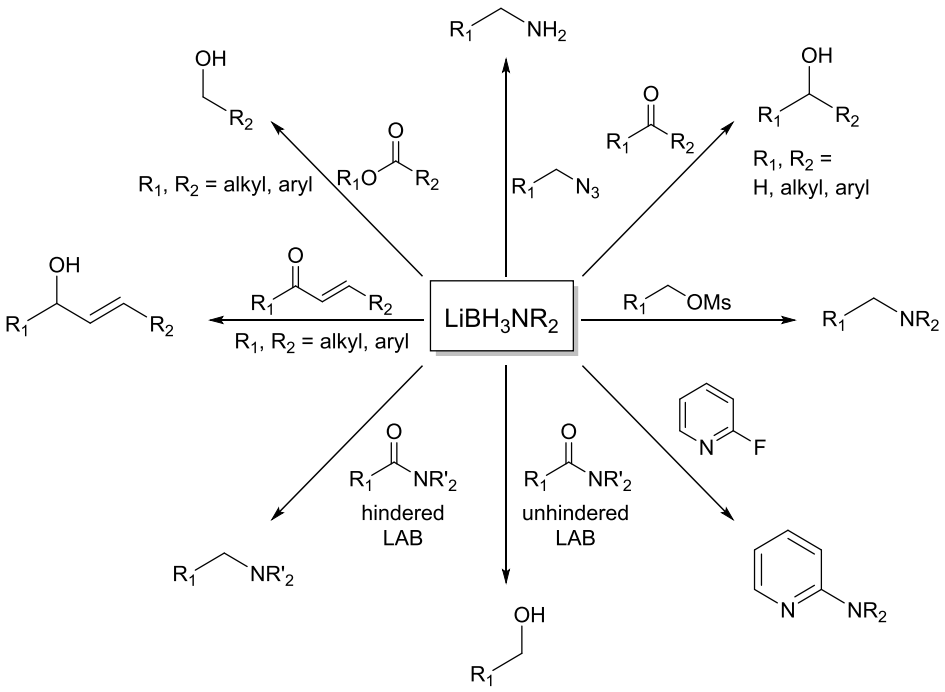


Scheme 2.19

As a consequence of this result we decided to focus our attention on another class of reducing agents, namely lithium aminoborohydrides (LABs), because we found in the literature some examples of the ring-opening of lactams using this kind of hydrides.

2.3.2. Lithium aminoborohydride (LAB) reagents

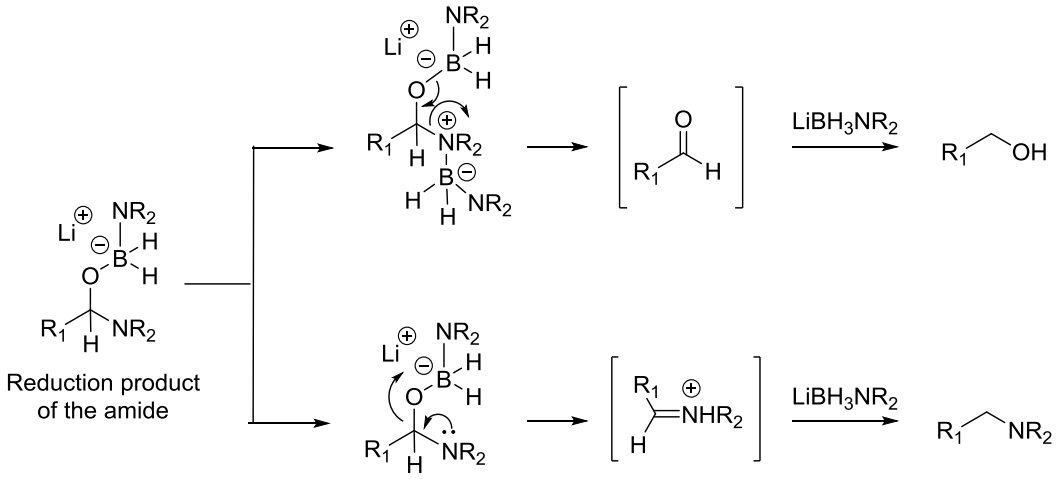
Lithium *N*,*N*-dialkylaminoborohydrides (LABs) were first reported by Singaram.[31] They are a new class of powerful, selective, and air-stable reducing agents. They can be used as solids or 1-2 M THF solutions, or can be easily generated by *in situ* deprotonation of the corresponding amine-borane complex using a lithiated base. LABs are capable of reducing a variety of functional groups, and their use as reducing agents has been the subject of several reviews.[31]



Scheme 2.20

[31] For a review on the use of lithium aminoborohydrides as reducing agents, see: (a) Pasumansky, L.; Singaram, B.; Goralski, C. T. *Aldrichimica Acta* **2005**, *38*, 62-66. (b) Pasumansky, L.; Goralski, C. T.; Singaram, B. *Org. Process Res. Dev*. **2006**, *10*, 959–970.

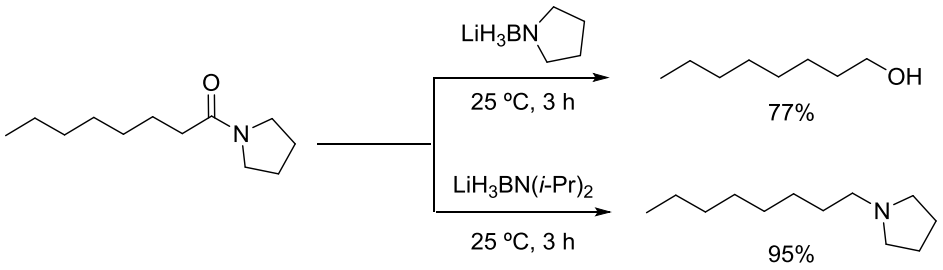
LAB reagents can perform a reagent-controlled reduction of amides to give either the corresponding alkanols or aminoalkanes. The selectivity of this reduction appears to involve a common intermediate resulting from the initial partial reduction product of the carbonyl lactam (Scheme 2.21). Then, two possible pathways can take place from this tetrahedral intermediate leading to the corresponding amine or alcohol. In the former, in sterically less demanding LABs, the boron moiety complexes the *N*-atom of the amide, thereby converting the amine to a good leaving group. Cleavage of the B-O bond and subsequent expulsion of the diaminodihydridoborohydride moiety leads to an aldehyde, which is furher reduced to the primary alcohol. In the case of sterically more demanding LABs, the nitrogen lone pair expels the lithium dihydridoaminoborinate to yield an iminium species, which is then rapidly reduced to the aminoalkane.[32]



Scheme 2.21

Lithium *N*,*N*-dialkylaminoborohydrides ($LiNR_2BH_3$) can reduce tertiary amides to either the corresponding alcohol or to an amine, depending on the steric environment of both the amide and the amine moiety of the reductant. For example, 1-pyrrolidinooctanamide can be reduced to 1-octanol in 77% yield by the lithium pyrrolidine-borane complex [$LiBH_3$(1-pyrrolidino)]. When the reduction was carried out with the significantly more sterically demanding lithium diisopropyl-borane complex ($LiBH_3N(i\text{-}Pr)_2$), 1-octylpyrrolidine was obtained in 95% yield.[33]

[32] Fisher, G. B.; Fuller, J. C.; Harrison, J.; Alvarez, S. G.; Burkhardt, E. R.; Goralski, C. T.; Singaram, B. *J. Org. Chem.* **1994**, *59*, 6378-6385.
[33] Fisher, G. B.; Fuller, J. C.; Harrison, J.; Goralski, C. T.; Singaram, B. *Tetrahedron Lett*. **1993**, *34*, 1091-1094.

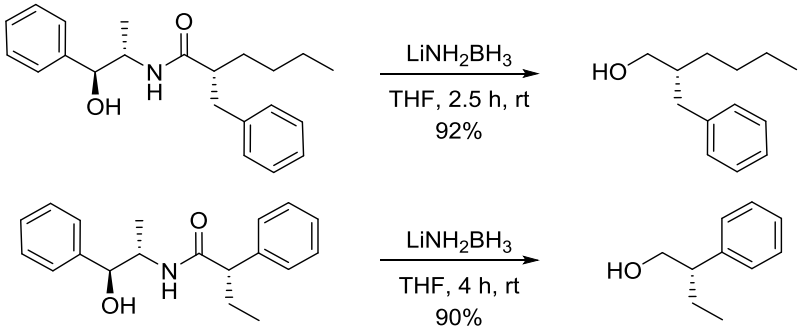


Scheme 2.22

On the other hand, the use of lithium *N*,*N*-dialkylaminoborohydrides ($LiNR_2BH_3$) results in the conversion of five- and six-membered *N*-alkyl lactams to the corresponding cyclic amines.[34]

For the reductive opening of oxazolopiperidone lactams, we selected lithium amidotrihydroborate ($LiNH_2BH_3$), which is an unhindered nucleophilic reducing agent that can be easily generated by *in situ* deprotonation of the commercially available $NH_3{\cdot}BH_3$ complex.[35] $LiNH_2BH_3$ was introduced by Myers[36] as the reagent of choice for the direct conversion of linear tertiary amides to the corresponding primary alcohols without epimerization of stereocenters α to the amide carbonyl.

Myers and co-workers described the reductive cleavage of acyclic amides, and he mentioned that the use of at least 4 molar equivalents of lithium amidotrihydroborate favoured the formation of the alcohol, while fewer equivalents increased the formation of the amine by-product. His work was illustrated with the use of $LiNH_2BH_3$ (4.0-4.5 eq) in the reduction of alkylated pseudoephedrine amides to primary alcohols (Scheme 2.23).[36]



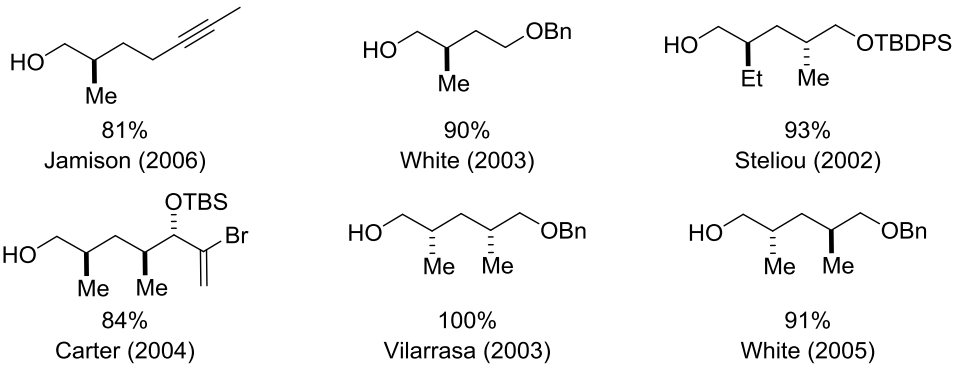
Scheme 2.23

[34] Flaniken, J. M.; Collins, C. J.; Lanz, M.; Singaram, B. *Org. Lett*. **1999**, *1*, 799-801. See also ref 31.

[35] For a one-pot procedure for the preparation of the ammonia-borane complex, see: Ramachandran, P. V.; Raju, B. C.; Gagare, P. D. *Org. Lett.* **2012**, *14*, 6119-6121.

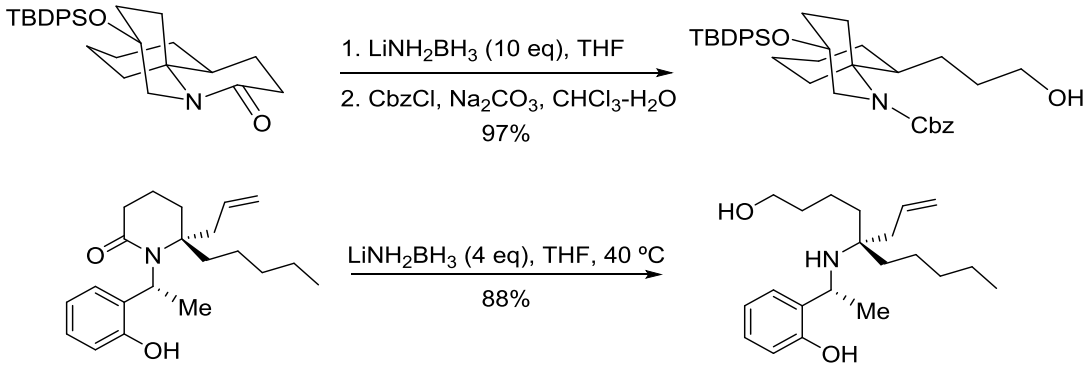
[36] a) Myers, A. G.; Yang, B. H.; Kopecky, D. J. *Tetrahedron Lett.* **1996**, *37*, 3623-3626. b) Myers, A. G.; Yang, B. H.; Chen, H.; McKinstry, L.; Kopecky, D. J.; Gleason, J. L. *J. Am. Chem. Soc*. **1997**, *119*, 6496-6511.

In summary, $LiNH_2BH_3$ has been extensively used for the direct reduction of linear-chain tertiary amides to primary alcohols,[37] and a variety of enantiopure linear primary alcohols have been prepared through the lithium amidotrihydroborate reduction protocol.



Scheme 2.24

Nevertheless, there are only two isolated examples reported by Kibayashi[38] of the $LiNH_2BH_3$ reductive ring-opening of δ-lactams to 1,5-amino alcohols (Scheme 2.25).



Scheme 2.25

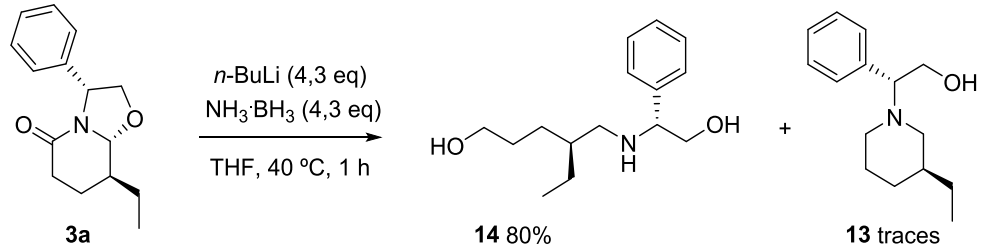
2.3.3. $LiNH_2BH_3$ for the reductive opening of oxazolopiperidone lactams

Considering the above results, we decided to reduce chiral oxazolopiperidone lactam **3a** using $LiNH_2BH_3$ as the reducing reagent. In this manner, chiral bicyclic lactam **3a** was directly converted into *N*-substituted 1,5-aminoalcohol **14**

[37] (a) For a review, see: Lund, A. In *Encyclopedia of Reagents for Organic Synthesis* (*EROS*); Paquette, L. A.; Fuchs, P. L.; Molander, G. A.; Crich, D. Eds.; Wiley, Chichester, 2009; pp. 6082-6083. b) For more recent work, see: Paterson, I.; Mühlthau, F. A.; Cordier, C. J.; Housden, M. P.; Burton, P. M.; Loiseleur, O. *Org. Lett.* **2009**, *11*, 353-356. See also ref 36.

[38] a) Abe, H.; Aoyagi, S.; Kibayashi, C. *J. Am. Chem. Soc.* **2000**, *122*, 4583-4592. b) Itoh, T.; Yamazaki, N.; Kibayashi, C. *Org. Lett.* **2002**, *4*, 2469-2472.

in 80% yield, in an unprecedented process involving the simultaneous reductive opening of the oxazolidine and lactam rings. We obtained only traces of the corresponding piperidine **13.** The best results were obtained when using an excess of 4.3 equiv of the $LiNH_2BH_3$ reagent (equimolecular solution of *n*-BuLi and borane-ammonia complex) with respect to lactam **3a**.



Scheme 2.26

This excellent result (Scheme 2.26) was obtained after optimization of the reaction conditions in order to apply them to the selective preparation of a series of enantiopure substituted 1,5-aminodiols and to minimize the undesired reduction of the carbonyl lactam leading to the piperidine compound.

In our initial studies we used LDA as the base to generate $LiNH_2BH_3$ reagent and we evaluate how many equivalents of $LiNH_2BH_3$ were necessary. The addition of enantiopure lactam **3a** to a solution of 2 equivalents of $LiNH_2BH_3$[36] afforded amino diol **14** in only 20% yield and piperidine **13** in 20% yield. The use of 4 molar equivalents of $LiNH_2BH_3$ gave the target aminoalcohol **14** in 44% yield and piperidine **13** in 10% yield.

Then, we studied the possible effect of the order of addition of the reagents. Thus, when a solution of lithium amidotrihydroborate (4 equivalents) was added to a solution of lactam **3a**, aminoalcohol **14** was obtained in 68% and piperidine **13** was formed in 13-15% yield.

Finally, in order to study the influence of the base, we prepared two equimolecular solutions of lithium amidotrihydroborate (4.3 equiv) using LDA or *n*-BuLi (4.3 equiv) as bases. In both cases, bicyclic lactam **3a** was directly converted into *N*-substituted 1,5-aminoalcohols **14** in 80% yield and with only traces of the piperidine **13** (Scheme 2.26). With these results we decided to continue our studies of reduction using BuLi as the base.

Wang and Hu[26d] reported in 1999 the $NaBH_4$-promoted amide bond cleavage of ether-protected aromatic five- and six-membered lactams to give saturated amino alcohols. After the initial reduction to a carbinolamine, a subsequent 3-aza-Grob fragmentation generates an imino aldehyde, which is *in situ* converted into the isolated amino alcohols (see also Scheme 2.18).

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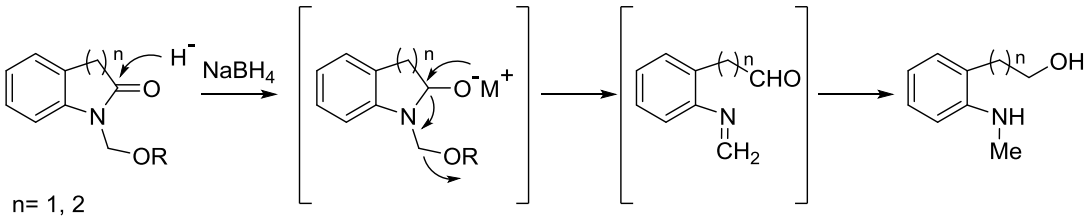
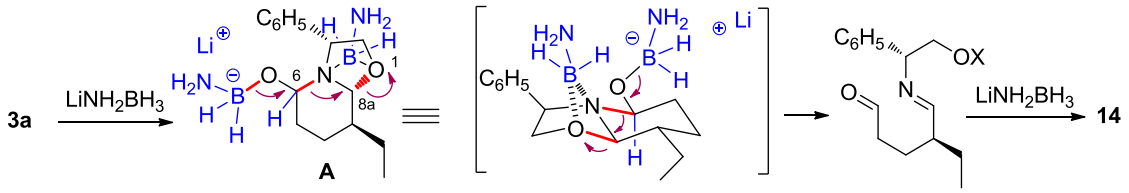


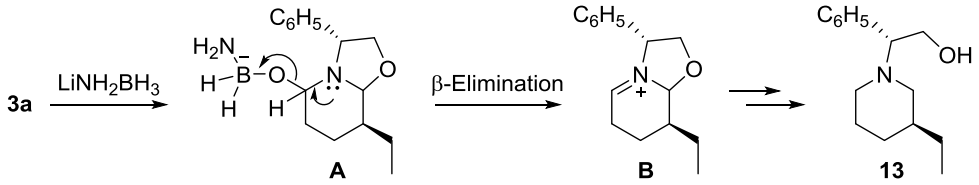
Scheme 2.27

Accordingly, the formation of aminodiol **14** can be rationalized by considering that the intermediate **A**, formed after the initial hydride attack to the lactam carbonyl, undergoes a Grob-type fragmentation[39] (Scheme 2.28) with cleavage of the B–O, C–N, and C–O bonds, which is facilitated by the complexation of borane species to the oxazolidine heteroatoms. A subsequent reduction of the resulting imino aldehyde would lead to **14**.



Scheme 2.28

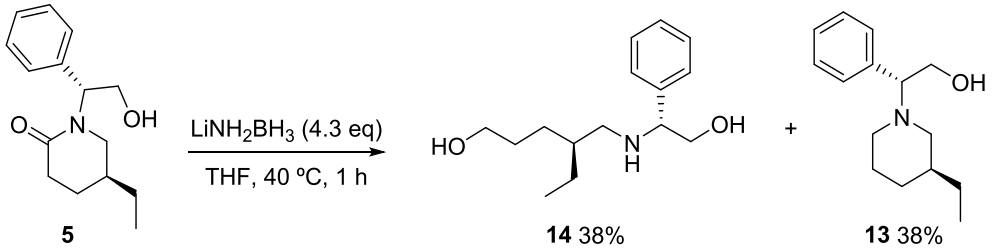
Alternatively, expulsion of lithium dihydridoamino-borinate from **A**, promoted by the nitrogen lone pair, would give a tetrahydropyridinium species **B** that would undergo further reduction to piperidine **13**.



Scheme 2.29

In agreement with the above concerted mechanism leading to aminodiol **14**, a similar $LiNH_2BH_3$ reduction of lactam **5**, which cannot undergo Grob fragmentation, gave (76% yield) a nearly equimolecular mixture of aminodiol **14** and the corresponding piperidine **13** (Scheme 2.30).

[39] For reviews, see: a) Grob, C. A.; Schiess, P. W. *Angew. Chem. Int. Ed*. **1967**, *6*, 1-15. b) Grob, C. A. *Angew. Chem. Int. Ed*. **1969**, *8*, 535-622. c) Deslongchamps, P. *Stereoelectronic Effects in Organic Chemistry* Pergamon Press, Oxford, **1983**, pp. 257-274. For related 3-aza-Grob fragmentations in the hydride reduction of lactams, see: d) Wang, J.-J.; Hu, W.-P. *J. Org. Chem.* **1999**, *64*, 5725-5727. e) Hu, W.-P., Wang, J.-J.; Tsai, P.-C. *J. Org. Chem*. **2000**, *65*, 4208-4209.



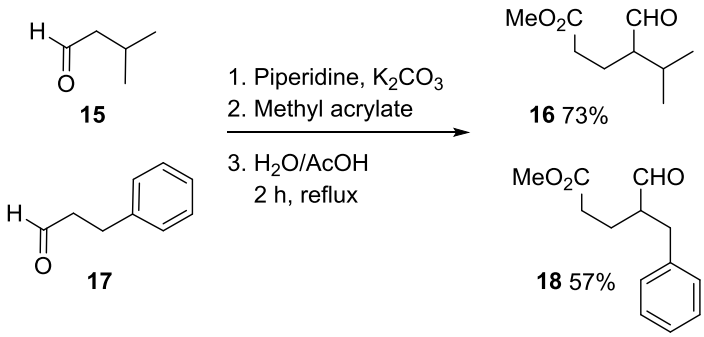
Scheme 2.30

These results encouraged us to prepare a variety of enantiopure oxazolopiperidone lactams bearing different substituents (H, alkyl, benzyl, phenyl, and protected hydroxy)[40] at the different positions of the piperidine ring, as potential building blocks for the synthesis of enantiopure substituted 1,5-aminoalcohols. All the lactams were prepared using procedures previously described within our research group for the regio- and stereocontrolled introduction of substituents at the different positions of the piperidine ring. In order to study the influence of the configuration of the C-8a stereogenic center of the bicyclic lactams during the double reductive ring-opening, in some of cases we prepared enantiopure substituted lactams with both 3-H/8a-H *cis* and 3-H/8a-H *trans* relative configuration.

2.3.4. Preparation of chiral bicyclic lactams

2.3.4.1. Preparation of 8-substituted oxazolopiperidone lactams

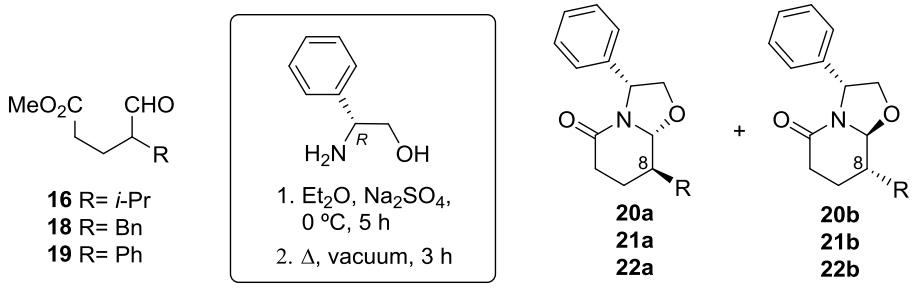
Enantiopure oxazolopiperidone lactams bearing different substituents (*iso*-propyl, benzyl, and phenyl) at the C-8 position of the piperidine ring were prepared following the procedure described for lactams **3a** and **4a** (see Scheme 2.14). The new racemic γ-substituted δ-oxoester derivatives **16** and **18** were prepared in 73% and 57% yield, respectively, by the three-step sequence outlined in Scheme 2.31.



Scheme 2.31

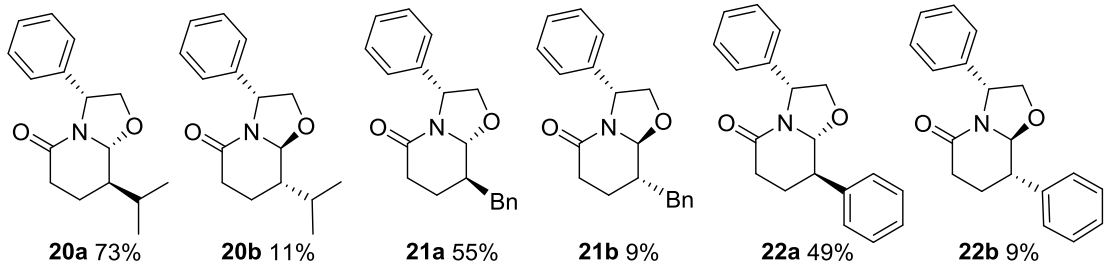
[40] See Introduction, *Synthetic background: oxazolopiperidone lactams*. See also ref 10.

Chiral non-racemic oxazolopiperidones **20a**-**22a**, substituted at the C-8 position of the piperidine ring, were stereoselectively prepared by cyclocondensation of the corresponding racemic δ-oxo esters, which bear a substituent at the epimerizable carbon α to the aldehyde carbonyl group, with (*R*)-phenylglycinol, in a process that involves a dynamic kinetic resolution of the racemic substrate.[41] Minor amounts (9-11%) of the corresponding 8,8a-diastereoisomeric oxazolopiperidones **20b**-**22b** were also isolated.



Scheme 2.32

The yields of enantiopure lactams **20**, **21** and **22**[42] are given in Scheme 2.33.



Scheme 2.33

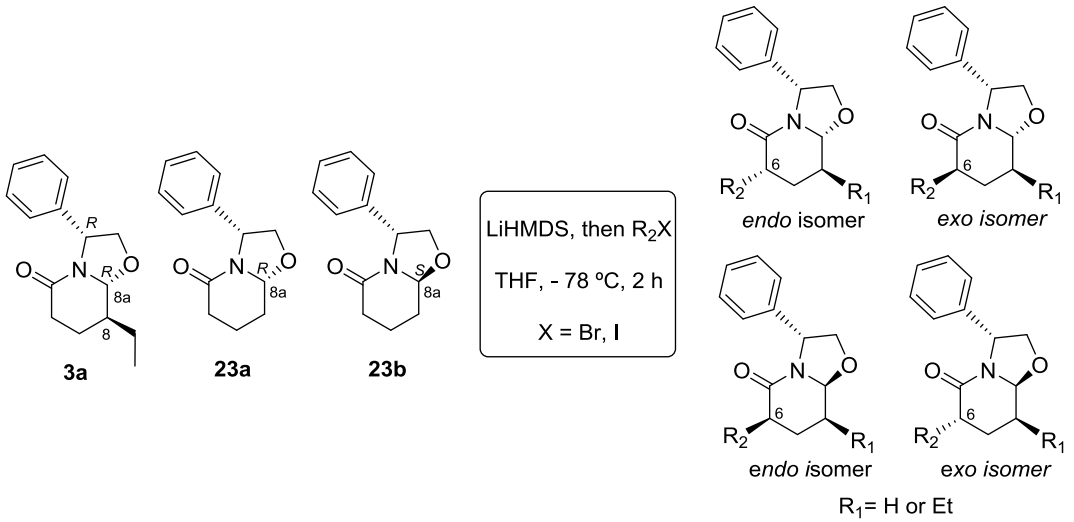
2.3.4.2. Preparation of 6- and 6,8-substituted oxazolopiperidone lactams

The enolate alkylation of the phenylglycinol-derived oxazolopiperidone lactams **3a**, **23a** and **23b**[15a] allowed the stereoselective introduction of alkyl and benzyl substituents at the β-position of the piperidine ring.[14b] For the C-8a unsubstituted lactams **23**, the stereochemical outcome of the alkylation

[41] For reviews, see: (a) Noyori, R.; Tokunaga, M.; Kitamura, M. *Bull. Chem. Soc. Jpn*. **1995**, *68*, 36–56. (b) Ward, R. S. *Tetrahedron: Asymmetry* **1995**, *6*, 1475–1490. (c) Caddick, S.; Jenkins, K. *Chem. Soc. Rev.* **1996**, *25*, 447–456. (d) Pellissier, H. *Tetrahedron* **2003**, *59*, 8291–8327. (e) Wolf, C. *Dynamic Stereochemistry of Chiral Compounds;* The Royal Society of Chemistry: Cambridge, 2008; Chapter 7.

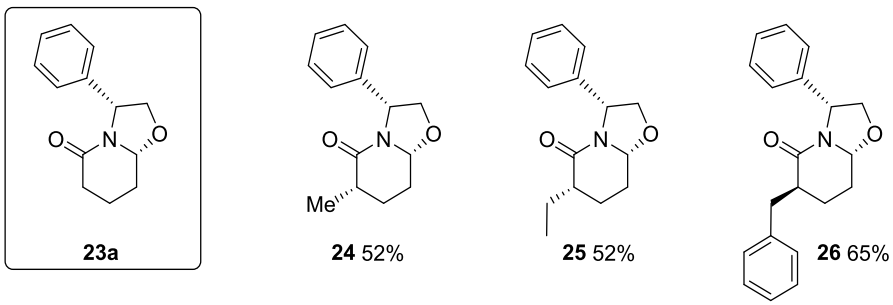
[42] For the synthesis of **22**, see: Amat, M.; Cantó, M.; Llor, N.; Escolano, C.; Molins, E.; Espinosa, E.; Bosch, J. *J. Org. Chem*. **2002**, *67*, 5343–5351.

depends on the relative configuration of the C-8a methine carbon.[43] The stereoselectivity is not affected by the presence or absence of an alkyl group at C-8.



Scheme 2.34

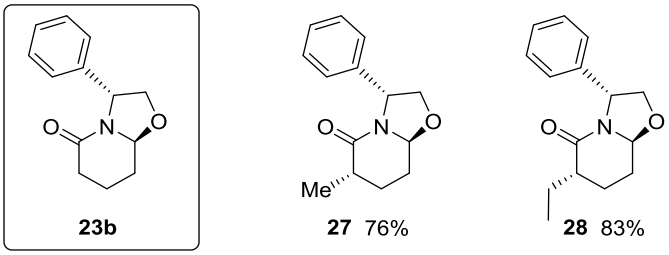
Alkylation of lactam **23a** (3-H/8a-H *cis* relative configuration) with methyl or ethyl iodide afforded the corresponding C-6-substituted lactams **24** and **25**, respectively, with preferential formation of the *endo* products (*endo*/*exo* ratio, 76:24 and 68:32, respectively).[14b] However, when treated with benzyl bromide the enolate of lactam **23a** afforded the corresponding *exo* isomer **26** in good stereoselectivity (*endo*/*exo* ratio, 8:92).[14b] The reversal of the π-facial diastereoselectivity observed in the benzyl bromide alkylation of the enolate of lactam **23a** was examined by means of theoretical calculations and attributed to the formation of a C-H**…**π bond between the enolate and the benzene ring of the incoming reagent.[44]



Scheme 2.35

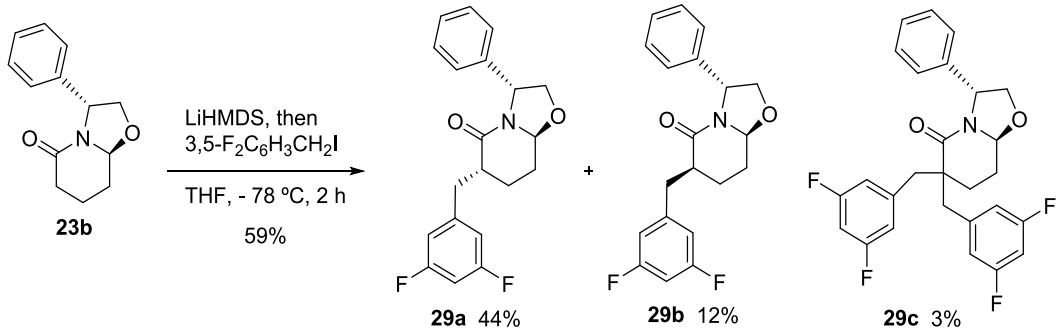
[43] Soteras, I.; Lozano, O.; Gómez-Esqué, A.; Escolano, C.; Orozco, M.; Amat, M.; Bosch, J.; Luque, F. J. *J. Am. Chem. Soc.* **2006**, *128*, 6581-6588.
[44] Soteras, I.; Lozano, O.; Escolano, C.; Orozco, M.; Amat, M.; Bosch, J.; Luque, F. *J. Org. Chem*. **2007**, *73*, 7756-7763.

Similarly, starting from chiral non-racemic lactam **23b** (3-H/8a-H *trans* relative configuration), enantiopure bicyclic lactams **27** and **28** were selectively obtained in high yields with preferential formation of the *exo* products (*endo*/*exo* ratio, 15:85 and 0:100, respectively).[14b]



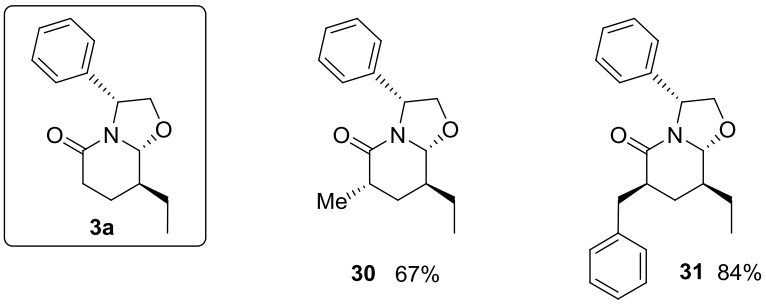
Scheme 2.36

Following this general procedure, we have prepared for the first time lactam **29a** in moderate yield and stereoselectivity (**29a**/**29b** ratio, 3.7:1). In this case, minor amounts of the dialkylated lactam **29c** were also formed.



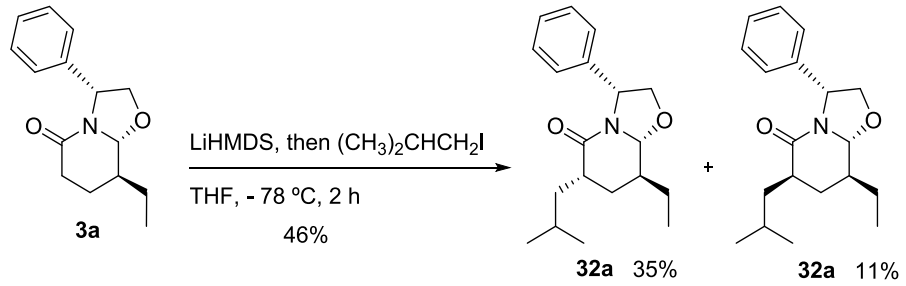
Scheme 2.37

On the other hand, the known enantiopure 6,8-disubstituted lactams **30** and **31** were prepared in high yields[14b] by alkylation of the C-8 ethyl-substituted oxazolopiperidone **3a** either with methyl iodide (*endo*/*exo* ratio, 71:29) or benzyl bromide (*endo*/*exo* ratio, 10:90). As observed in the preparation of the above 8-substituted series, the methyl substituent was introduced from the *endo* face whereas benzylation gave the *exo* isomer.[14b,44]



Scheme 2.38

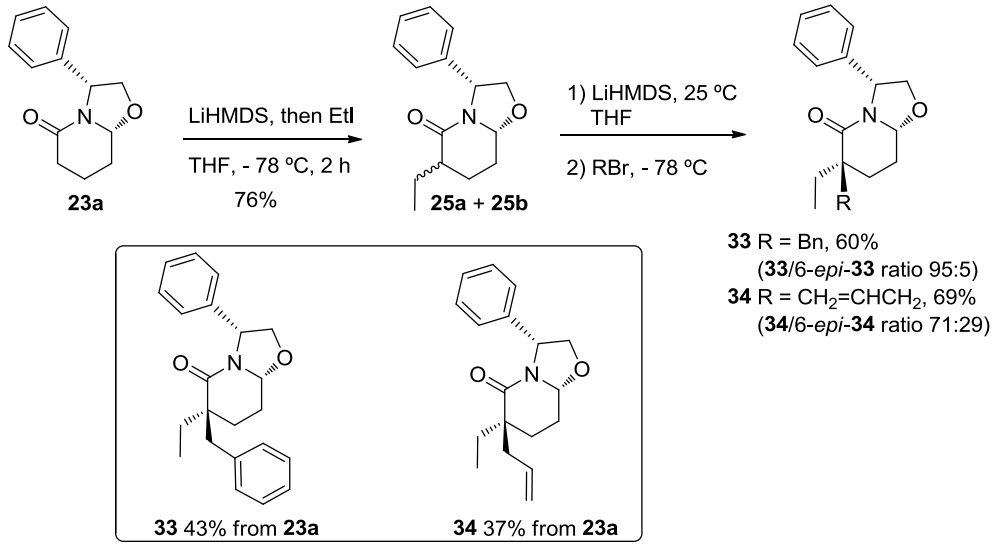
Finally, the new disubstituted lactam **32a,** bearing an isobutyl substituent at the C-3 position of the piperidine ring, was synthesized in moderate yield and stereoselectivity (**32a**/**32b** ratio, 3.2:1).



Scheme 2.39

2.3.4.3. Preparation of 6,6-disubstituted oxazolopiperidone lactams

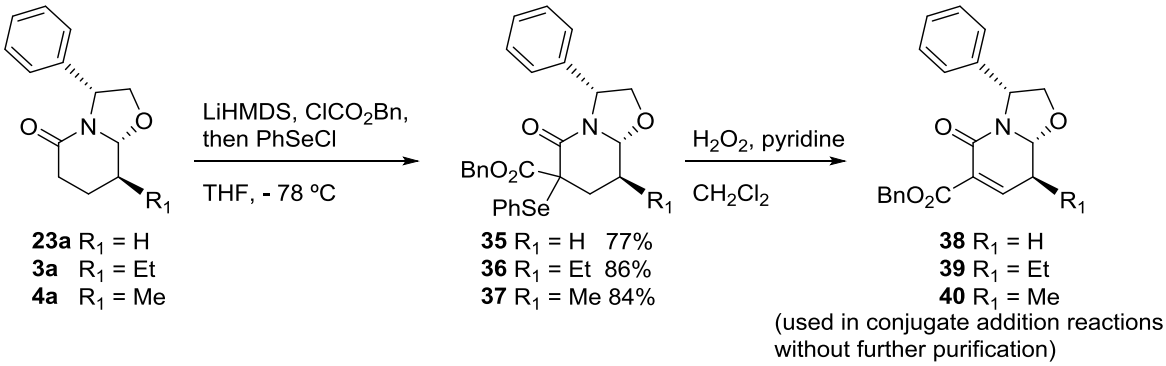
6,6-Disubstituted lactams **33** and **34** were synthesized using a described protocol for the stereoselective generation of a quaternary stereocenter at the α-position of the carbonyl function, by dialkylation of the ozazolopiperidone lactam **23a**.[14a] The introduction of the benzyl substituent from a diastereoisomeric mixture of monoalkylated lactams **25** afforded enantiopure **33** with very high stereoselectivity (95:5), resulting from an *exo* diastereofacial alkylation of the enolate, in 43% yield over two steps. Similarly, dialkylated compound **34** was obtained in 37% yield from **23a** with a moderate stereoselectivity, leading to a 71:29 mixture of isomers, in which the *exo*-allylated product predominated.



Scheme 2.40

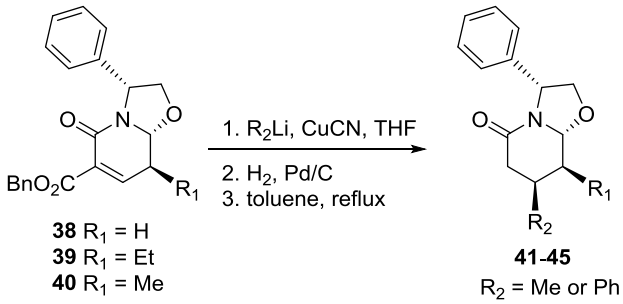
2.3.4.4. Preparation of 7- and 7,8-substituted oxazolopiperidone lactams

The introduction of an alkyl or aryl substituent at the C-4 position of the piperidine ring required the previous functionalization of this position, taking advantage of the lactam group.[15] Benzyloxycarbonylation of lactams **3a**, **4a**, and **23a**, followed by *in situ* selenation led to lactams **35**-**37**. Elimination of phenylsulfenic acid by way of the corresponding selenoxide afforded α,β-unsaturated lactams **38**-**40**.



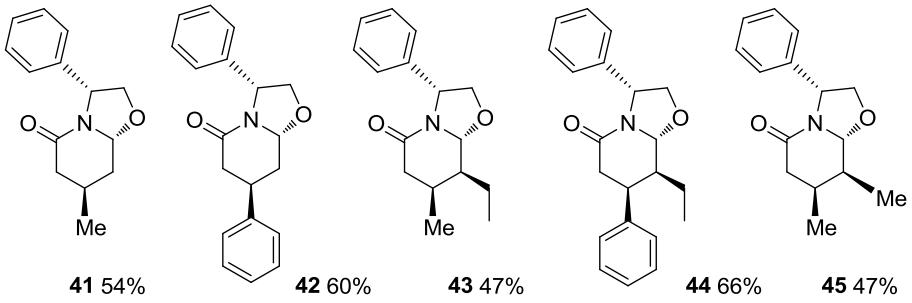
Scheme 2.41

The benzyloxycarbonyl group provides an additional and necessary activation towards the nucleophilic addition at the C-4 position of the piperidine ring. Thus, treatment of α,β-unsaturated lactams **38**-**40** with lithium cyanocuprates, followed by catalytic debenzylation and subsequent decarboxylation led to the corresponding enantiopure C-7 substituted oxazolopiperidone lactams **41**-**45**.



Scheme 2.42

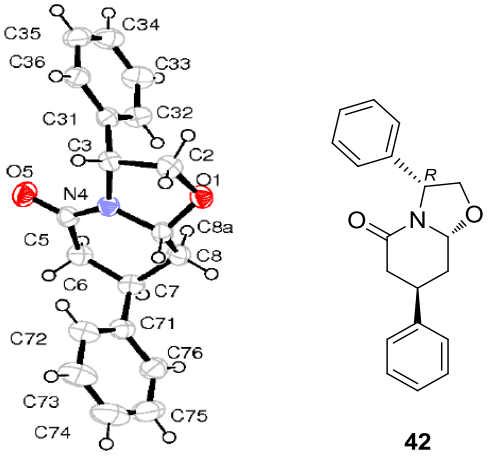
Using this methodology we have stereoselectively prepared 7-substituted lactams **41**[15a] and **42**, and 7,8-disubstituted lactams **43**,[18a] **44**,[18a] and **45** with the overall yields from lactams **35**-**37** indicated in Scheme 2.43.



41 54% **42** 60% **43** 47% **44** 66% **45** 47%

Scheme 2.43

The absolute configuration of **42** was unambiguously confirmed by X-ray crystallographic analysis (Scheme 2.44).



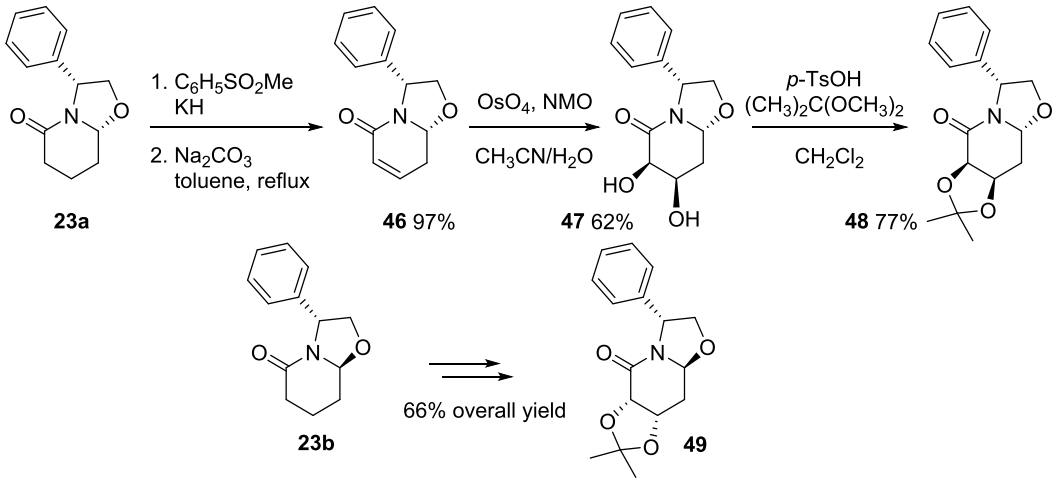
42

Scheme 2.44

2.3.4.5. Preparation of 6,7-disubstituted oxazolopiperidone lactams

Lactam **48**, which incorporates two protected hydroxy groups at positions 6 and 7, was prepared from lactam **23a** by the four-step sequence outlined in Scheme 2.45. Phenylsulfonylation of **23a** by treatment with a suspension of potassium hydride and methyl phenylsulfinate in anhydrous THF, followed by reflux in toluene in the presence of sodium carbonate gave α,β-unsaturated lactam **46**.[15d] Stereoselective dihydroxylation of **46** by treatment with a catalytic amount of osmium tetroxide and *N*-methylmorpholine-*N*-oxide in a mixture of acetonitrile-water, followed by protection of resulting diol **47** with 2,2-dimethoxypropane, afforded acetonide **48** in 48% overall yield from **46**. Similarly, acetonide **49**,[45] previously described by our research group, was synthesized in 66% yield starting from enantiopure lactam **23b**.

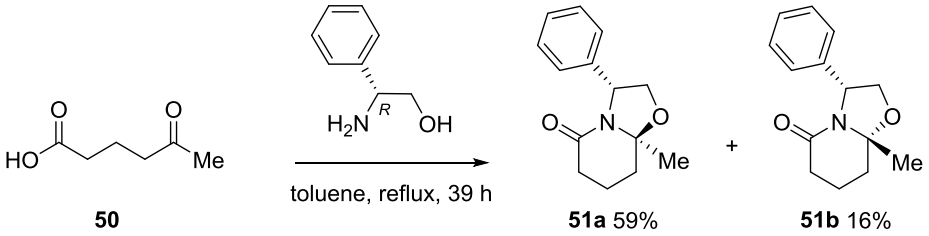
[45] Amat, M.; Llor, N.; Huguet, M.; Molins, E.; Espinosa, E.; Bosch, J. *Org. Lett.* **2001**, *3*, 3257-3260.



Scheme 2.45

2.3.4.6. Preparation of 8a-substituted oxazolopiperidone lactams

Lactams **51**[46] were directly obtained in 75% yield and with moderate stereoselectivity by cyclondensation of δ-keto acid **50** with (*R*)-phenylglycinol, thus installing a methyl group at the angular C-8a position.

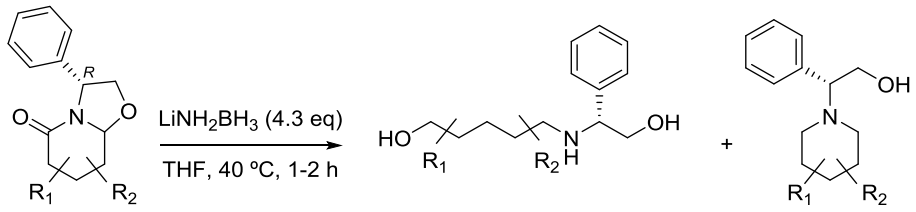


Scheme 2.46

2.3.5. Synthesis of enantiopure substituted 1,5-aminoalcohols

In this section we present the results obtained in the $LiNH_2BH_3$ reduction of all previously prepared chiral non-racemic oxazolopiperidone lactams, either with 3-H/8a-H *cis* or *trans* relative configuration. They include 6-, 7-, 8, and 8a-substituted as well as 6,6- 6,7- 6,8-, and 7,8-disubstituted derivatives, which differ not only in the position but also in the nature of the substituents and the configuration of stereocenters on the piperidine ring.

[46] (a) Fréville, S.; Célérier, J.-P.; Thuy, V. M.; Lhommet, G. *Tetrahedron Asymmetry* **1995**, *6*, 2651-2654. (b) Fréville, S.; Bonin, M.; Célérier, J.-P.; Husson, H.-P.; Lhommet, G.; Quirion, J.-C.; Thuy, V. M. *Tetrahedron* **1997**, *53*, 8447-8459.



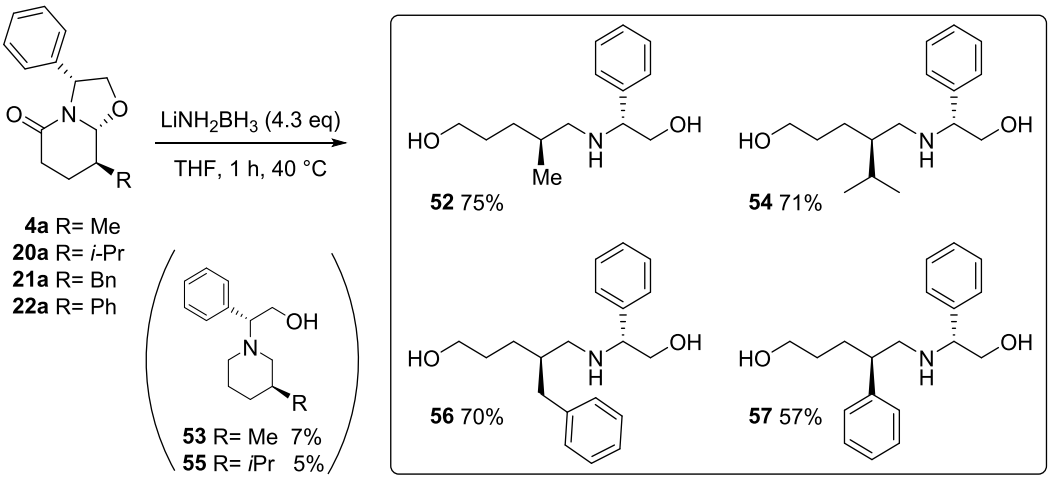
Scheme 2.47

In the optimized procedure, *n*-BuLi (4.3 eq) is added to a solution of solid borane-ammonia complex (4.3 eq) in THF at 0 ºC. Then, this mixture is transferred to a solution of enantiopure lactam in anhydrous THF and stirred at 40 ºC. As mentioned before, the corresponding substituted enantiopure 1,5-aminoalcohols were formed in good yields in an unprecedented process featuring the reductive opening of both the oxazolidine and lactam rings in a single synthetic step, through a stepwise sequence involving a 3-aza-Grob fragmentation[39] (see Scheme 2.28).

In all cases, the reduction afforded the corresponding linear-chain amino diol in good yields. Minor amounts of the corresponding *N*-(2-hydroxy-1-phenylethyl)piperidines were isolated in some cases as by-products.

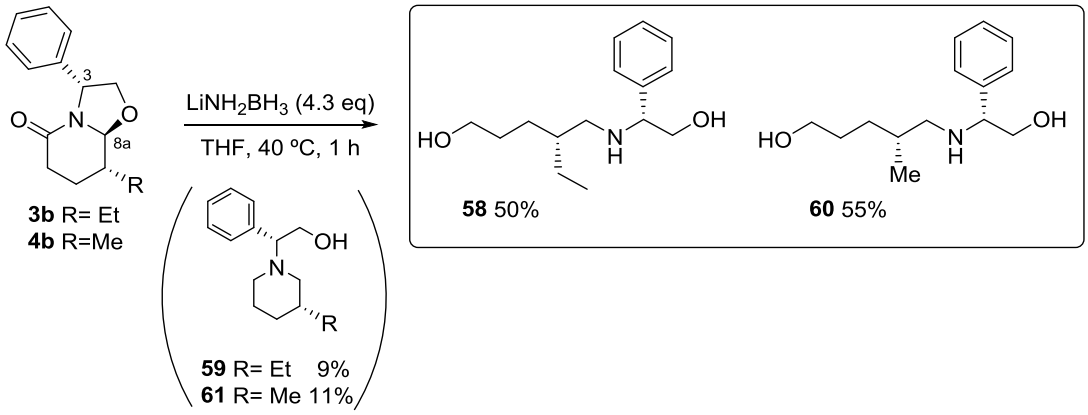
2.3.5.1. Reductive opening of 8-substituted oxazolopiperidone lactams

The reductive opening of C-8 substituted bicyclic lactams **4a**, **20a**, **21a** and **22a** under the above $LiNH_2BH_3$ conditions afforded the corresponding amino diols **52**, **54**, **56** and **57**, respectively, in the yields indicated in Scheme 2.48. Minor amounts of piperidines **53** and **55** were also obtained.



Scheme 2.48

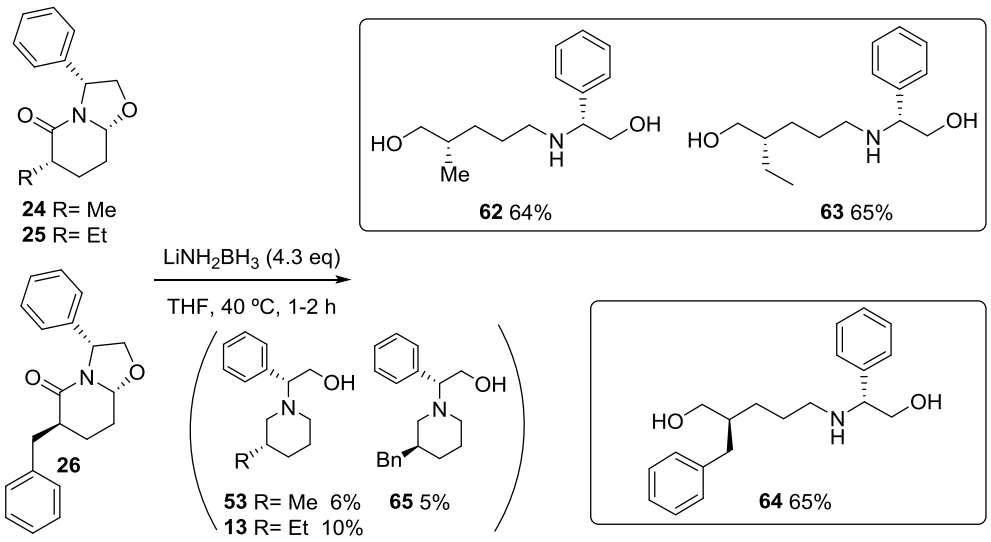
With the aim to study the influence of the configuration of the C-8a stereogenic center in the double reductive ring opening, we treated lactams **3b** and **4b**, with 3-H/8a-H *trans* relative configuration, under the same reductive conditions. We obtained the enantiopure linear-chain products **58** and **60** in 50% and 55% yield respectively, and we also observed a slight increase in the amount of the corresponding piperidines **59** and **61**.



Scheme 2.49

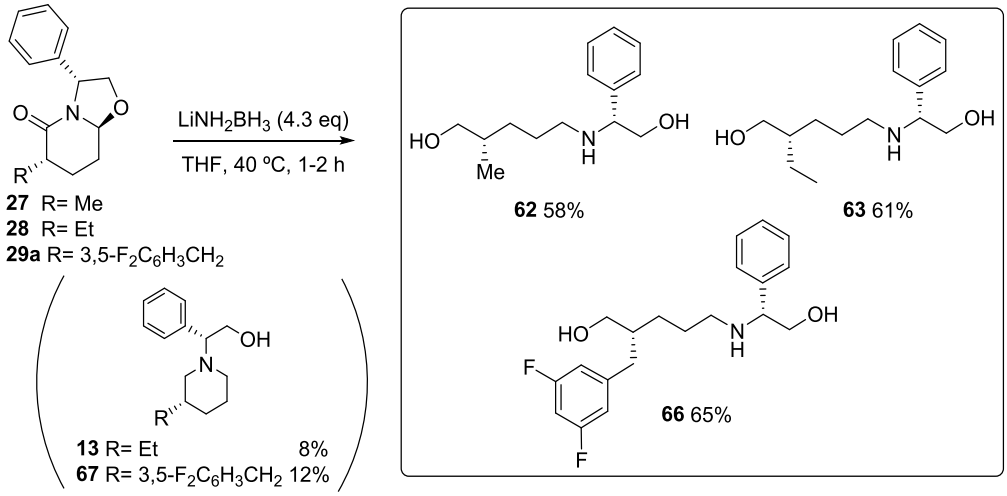
2.3.5.2. Reductive opening of 6-substituted oxazolopiperidone lactams

The reductive opening of enantiopure lactams **24a** and **25a** led to the corresponding aminodiols **62** and **63**, respectively, in good yield, with less than 10% of the corresponding piperidines **53** and **13**. Similar results were obtained starting from lactam **26b**, which possesses a C-6 configuration opposite to that of lactams **24a** and **25a**, affording enantiopure linear-chain derivative **64** in 65% yield. Trace amounts (5%) of 3-benzylpiperidine **65** were also isolated.



Scheme 2.50

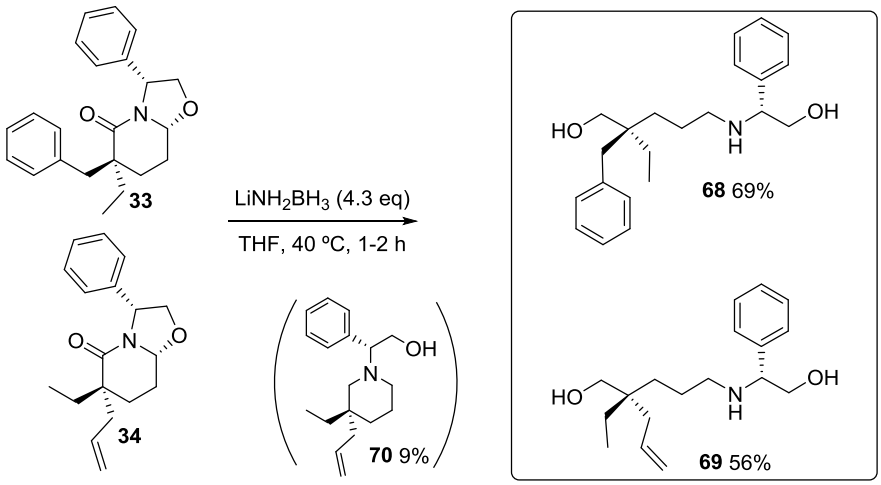
Similarly, the reductive ring opening of lactams **27a** and **28a**, with a 3-H/8a-H *trans* relative configuration, led to quite similar results, and amino diols **62** and **63** were obtained in 58% and 61% yields, respectively. Treatment of (3,5-difluoro)benzyl derivative **29a** under the usual $LiNH_2BH_3$ conditions afforded the corresponding amino diol **66** in 65% yield, accompanied by minor amounts of piperidine **67** (12%). It is worth mentioning that only one diastereomer, with no epimerization of the stereocenter at the α-position of the carbonyl group of the starting lactam, was obtained.



Scheme 2.51

2.3.5.3. Reductive opening of 6,6-disubstituted oxazolopiperidone lactams

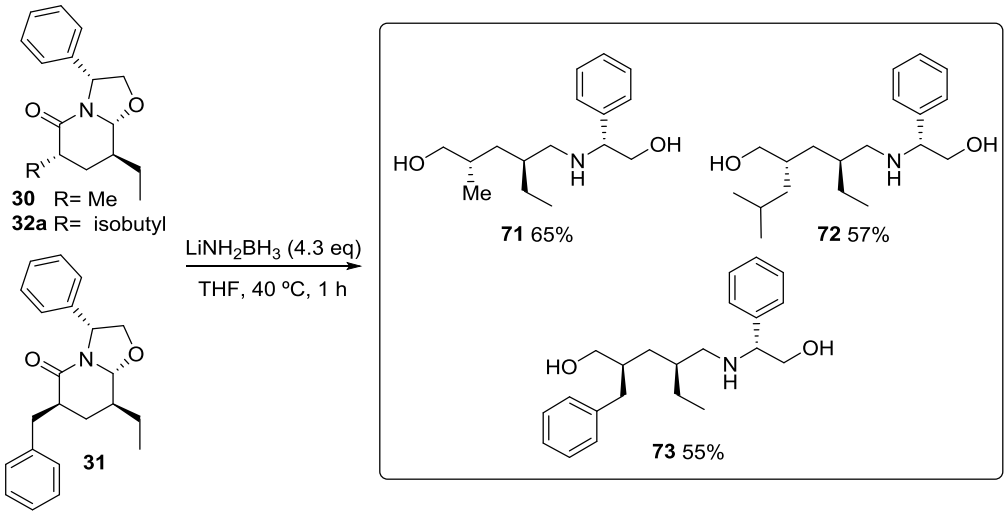
The stereocontrolled construction of chiral quaternary centers is a challenging issue in organic chemistry. Taking advantage of the procedure for the preparation of chiral lactams **33** and **34**, which bear a quaternary stereocenter at the C-3 position of the piperidine ring, we synthesized enantiopure 1,5-aminoalcohols **68** and **69** in good yields. Only minor amounts of piperidine **70** (8%) were observed in the case of the reduction of the allyl derivative **34**.



Scheme 2.52

2.3.5.4. Reductive opening of 6,8-disubstituted oxazolopiperidone lactams

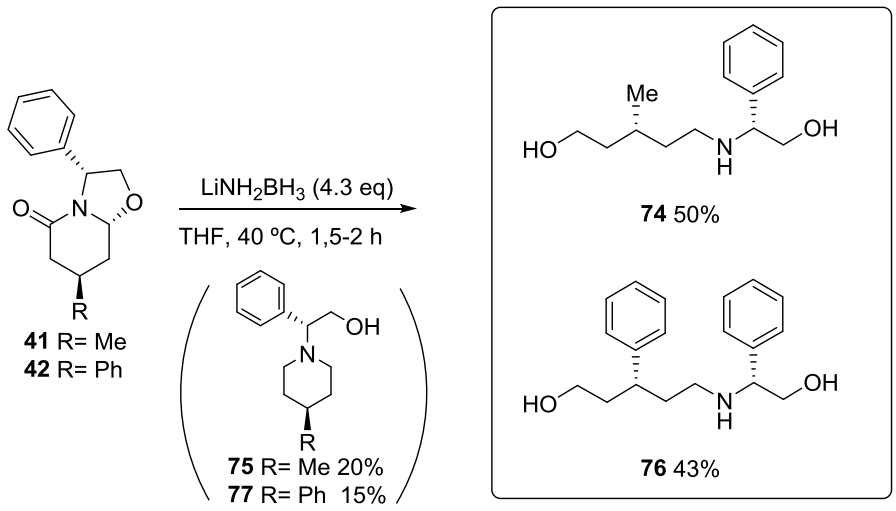
Lactams **30a**, **32a** and **31b** were directly converted into the respective enantiopure 2,4-disubstituted amino diols **71**-**73** in good chemical yield. In these series, the corresponding piperidine derivatives were not detected.



Scheme 2.53

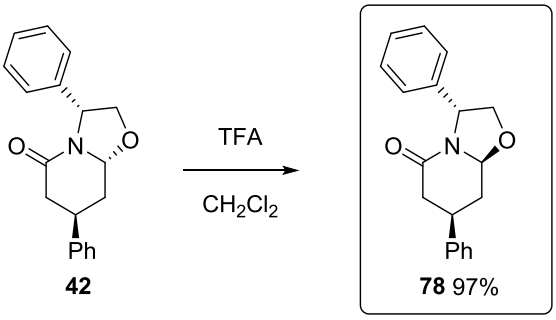
2.3.5.5. Reductive opening of 7-substituted oxazolopiperidone lactams

The $LiNH_2BH_3$ reduction of lactams **41** and **42**, which bear a methyl or phenyl substituent in a pseudoaxial bond, afforded the corresponding amino diols **74** and **76** in moderate yields. In this 7-substituted series, we observed an increased formation of the corresponding piperidines **75** (20%) and **77** (15%).



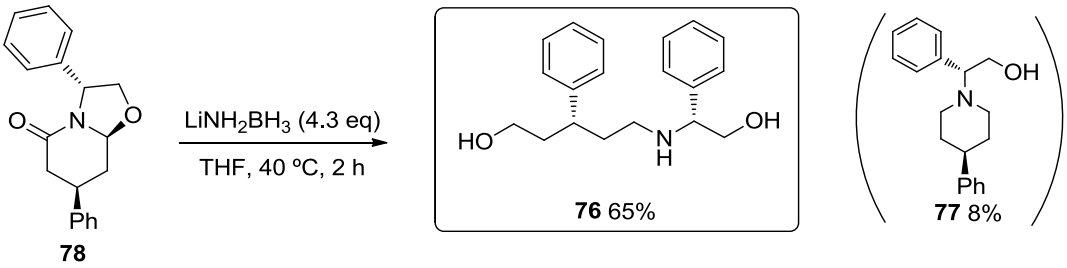
Scheme 2.54

In order to study the influence of the 3-H/8a-H *cis* or *trans* relative configuration on the amount of piperidine generated in the reductive ring-opening of the above 7-substituted lactams, we prepared lactam **78** (phenyl substituent in a pseudoequatorial bond) by equilibration under acidic conditions of the initially formed lactam **42**.



Scheme 2.55

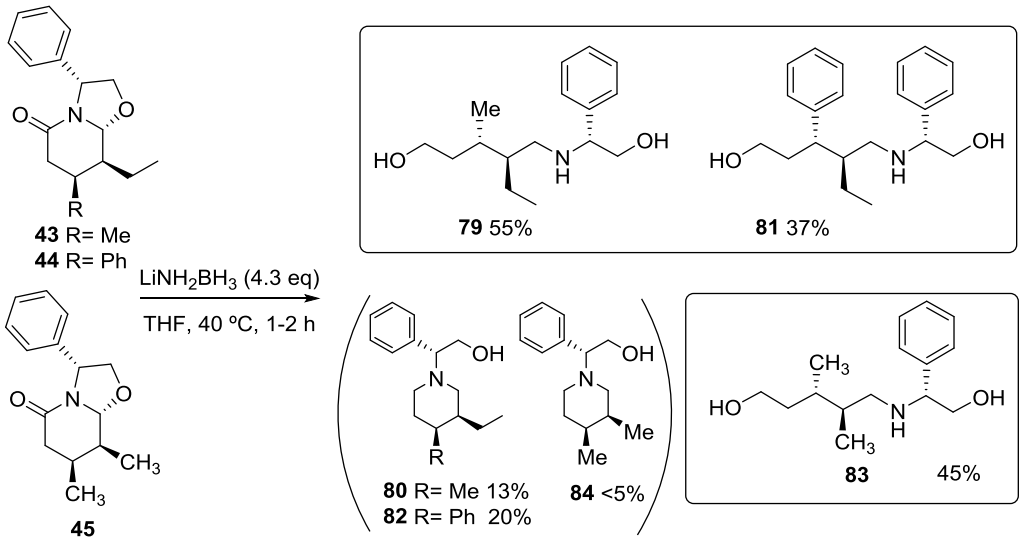
Treatment of lactam **78** under the usual $LiNH_2BH_3$ reduction conditions gave 1,5-aminoalcohol **76** in 65% yield, accompanied by only minor amounts (8%) of piperidine **77**.



Scheme 2.56

As has been seen in the reduction of tertiary amides with related $LiNR_2BH_3$ reagents[31-33] (see Scheme 2.22), the amount of the tertiary amine by-product formed in the above $LiNH_2BH_3$ reductions may also be related to the steric requirements of the lactam. Thus, the formation of piperidines **75** and **77** was more favored for the more sterically demanding lactams, for instance, in lactams **41** and **42**, which bear a C-7 axial subtituent.

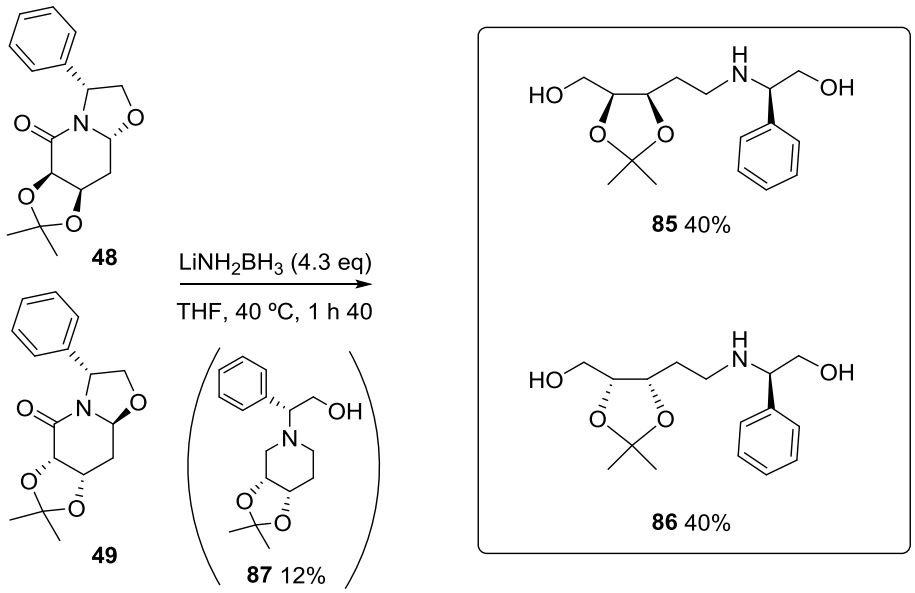
Following the same methodology, amino diols **79**, **81** and **83** were synthesized from 7,8-disubstituted lactams **43**, **44** and **45**.



Scheme 2.57

2.3.5.6. Reductive opening of 6,7-disubstituted oxazolopiperidone lactams

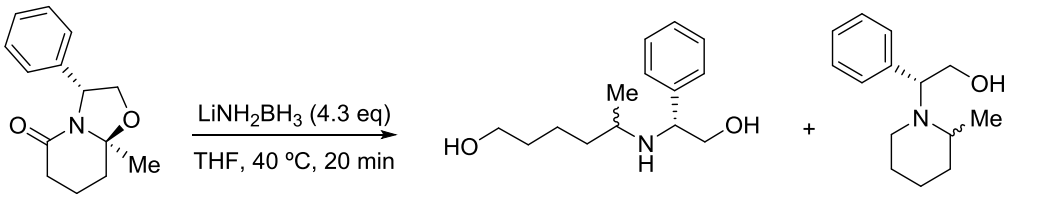
A similar reductive opening from the diastereoisomeric lactams **48** and **49** led to the corresponding enantiopure functionalized derivatives **85** and **86** in 40% yield. The formation of piperidine **87** was only observed starting from lactam **49** **(**3-H/8a-H *trans* relative configuration).



Scheme 2.58

2.3.5.7. Reductive opening of 8a-substituted oxazolopiperidone lactams

The reduction of the 8a-substituted lactam **51a** under $LiNH_2BH_3$ conditions led to nearly equimolecular epimeric mixtures of amino diol **88** and piperidine **89**. The epimerization of **88** can be explained by considering that the imino aldehyde formed after the Grob-type fragmentation (Scheme 2.28) is reduced without stereoselectivity affording a mixture of diastereoisomers at the α-position of the nitrogen.[47]



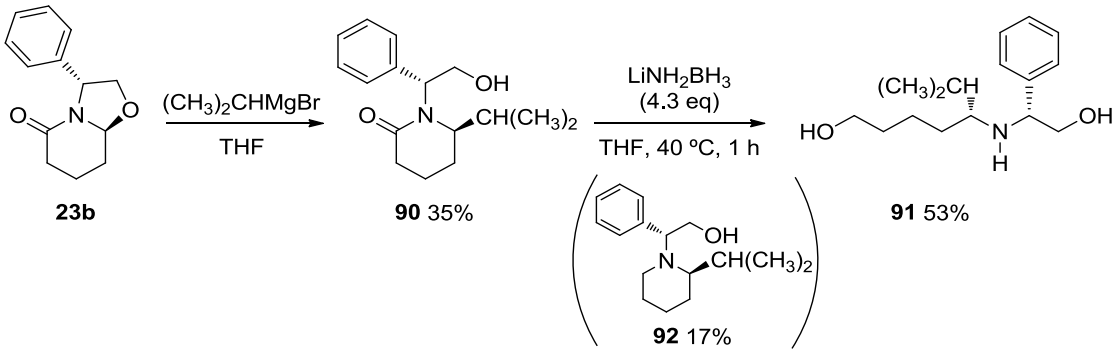
51a

88 50%
1:1 mixture of two diastereoisomers

89 16%
1:1 mixture of two diastereoisomers

Scheme 2.59

To circumvent this inconvenience, we studied the $LiNH_2BH_3$ reduction of the C-6 substituted piperidone **90**, which cannot undergo Grob fragmentation. This lactam was stereoselectively prepared by treatment of chiral oxazolopiperidone **23b** with a solution of isopropylmagnesium bromide in THF. The introduction of the substituent at the piperidine α-position by asymmetric α-amidoalkylation has been reported to occur with high stereoselectivity from **23b**.[13e,48] A subsequent reduction of **90** under $LiNH_2BH_3$ conditions afforded the enantiopure substituted open-chain amino diol **91** in 53% yield and piperidine **92** (17%).



23b

90 35%

91 53%

92 17%

Scheme 2.60

[47] For the reductive opening of the oxazolidine ring in phenylglycinol-derived 8a-substituted bicyclic δ-lactams, see: (a) Munchhof, M. J.; Meyers, A. I. *J. Org. Chem*. **1995**, *60*, 7084-7085. (b) Fréville, S.; Célérier, J. P.; Thuy, V. M.; Lhommet, G. *Tetrahedron: Asymmetry* **1995**, *6*, 2651-2654. (c) Amat, M.; Cantó, M.; Llor, N.; Bosch, J. *Chem. Commun*. **2002**, 526-527.

[48] Amat, M.; Escolano, C.; Gómez-Esqué, A.; Lozano, O.; Llor, N.; Griera, R.; Molins, E.; Bosch, J. *Tetrahedron: Asymmetry* **2006**, *17*, 1581-1588.

However, a limitation of this alternative synthesis for 5-substituted 1,5-aminoalcohol **91** is the low yield of the α-amidoalkylation reaction leading to the starting piperidone **90**.

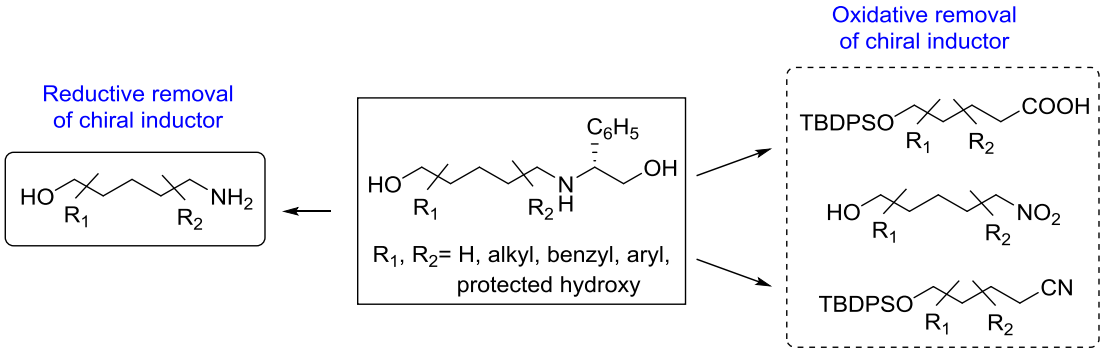
In summary, we have developed a straightforward and efficient procedure for the preparation of structurally diverse enantiopure *N*-substituted 1,5-aminodiols, bearing a variety of substitution patterns (alkyl, benzyl, aryl, protected hydroxyl), and stereochemistries. Starting from chiral non-racemic lactams, lithium amidotrihydroborate ($LiNH_2BH_3$) induces the reductive opening of both the oxazolidine and lactam rings in a single synthetic step. The only limitation encountered of the procedure is the reduction of 8a-substituted lactams, which led to the corresponding 1,5-aminoalcohol as an equimolecular epimeric mixture.

2.4. Removal of the chiral inductor

We planned to study the removal of the phenylethanol moiety of the amino diols prepared in this work using either reductive or oxidative conditions.

Reductive cleavage of the benzylic C-N bond of the amino diols by catalytic hydrogenation would afford enantiopure substituted 1,5-aminoalcohols.

Alternatively, we studied two sets of oxidative conditions (*m*-CPBA and I_2/aq. NH_3) to explore the feasibility of the conversion of the secondary amino group of our amino diols into other functionalities and, in this way, open access to a variety of enantiopure functionalized linear-chain building blocks such as 1,5-nitroalcohols, 5-hydroxypentanoic acids and 5-hydroxypentanenitriles.



Scheme 2.61

2.4.1. Reductive removal of the phenylethanol moiety

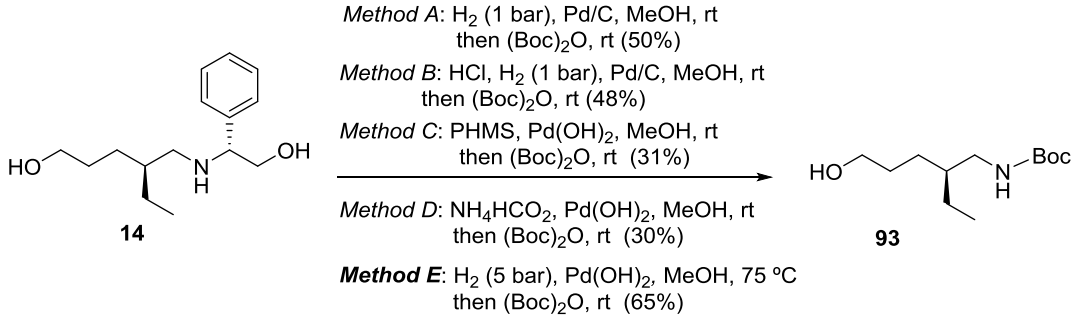
2.4.1.1. Preliminary studies

The chiral auxiliary could be easily removed under reductive conditions, taking advantage of the benzylic properties of the phenylethanol moiety. Catalytic hydrogenolysis is the most widely used procedure for the deprotection of *N*-benzyl-protected amines, and several experimental conditions were investigated, modifying both the hydrogen source and the transition metal.[49]

Initially, we performed the catalytic hydrogenation of aminopentanol **14** under mild conditions (1 pressure of hydrogen, MeOH, room temperature) using Pd/C as the catalyst. A subsequent protection of the resulting primary amine with Boc_2O provided *N*-Boc amino alcohol **93** in 50% yield in the best of cases.

In order to avoid the partial or total deactivation of the catalyst caused by the amine function of the 1,5-aminoalcohol, we also performed the catalytic hydrogenation using the hydrochloride of **14**. Unfortunately, we obtained similar results.

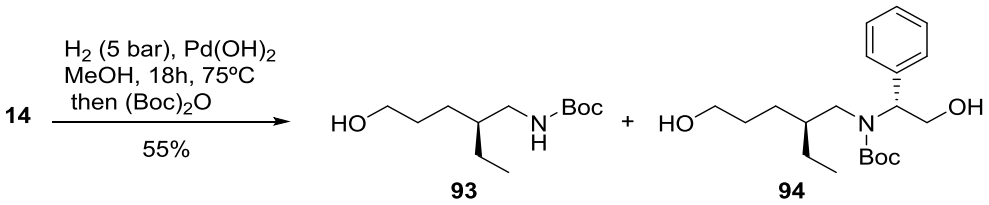
The use of polymethylhydrosiloxane (PMHS)[50] or ammonium formate[51] as the hydrogen donor in presence of $Pd(OH)_2$ did not improve the formation of the carbamate **93** (yield 30%). The best conditions were found using Pearlman's catalyst [$Pd(OH)_2$] in anhydrous methanol at 75 ºC for 18 hours under 5 bar pressure of hydrogen, followed by treatment of the crude with Boc_2O, Under these conditions 1,5-aminoalcohol **93** was obtained in 65% yield.



Scheme 2.62

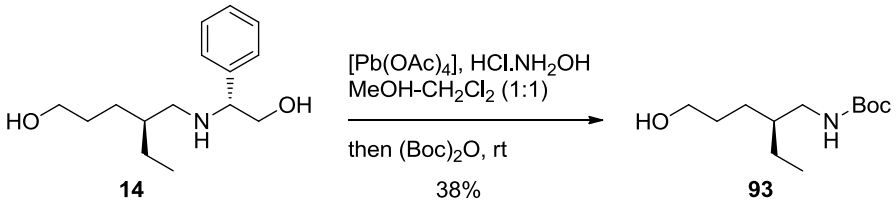
When the catalytic debenzylation of **14** was performed under the above conditions in the presence of Boc_2O, an equimolecular mixture of *N*-Boc amino alcohol **93** and *N*-Boc amino diol **94** was obtained.

[49] *Greene's Protective Groups in Organic Synthesis*, Wuts, P. G. M.; Greene, T. W.; Ed. Wiley-Interscience, A John Wiley & Sons, Inc.; New Jersey, 2007.
[50] Chandrasekhar, S.; Nagendra Babu, B.; Raji Reddy, Ch. *Tetrahedron Lett*. **2003**, *44*, 2057-2059.
[51] Ram, S.; Spicer, L. D. *Synthetic Commun*. **1987**, *17*, 415-418.



Scheme 2.63

An alternative procedure for the removal of the phenylethanol moiety, using oxidative conditions, did not improve the results either. Treatment of **14** with lead tetraacetate[52] in presence of hydroxylamine hydrochloride in a mixture 1:1 of MeOH-CH_2Cl_2, followed by protection of the resulting crude amine with Boc_2O, afforded the target *N*-Boc amino alcohol **93** in only 38% yield in the best of cases.

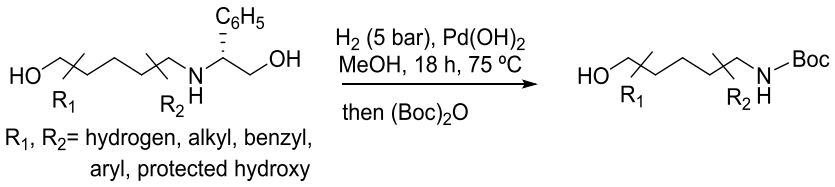


Scheme 2.64

2.4.1.2. Synthesis of enantiopure 1,5-aminoalcohols

The removal of the phenylethanol moiety present in the substituted 1,5-amino diols prepared in this work, using [$Pd(OH)_2$] in anhydrous methanol at 75 ºC for 18 hours under 5 bar pressure of hydrogen, followed by protection of the resulting crude primary amine with Boc_2O, led to a wide range of enantiopure *N*-Boc 5-aminopentanols **93**, **95**-**113**, bearing substituents at the 2-, 3-, 4-, 5-, 2,2-, 2,3-, 2,4-, and 3,4-positions with a well-defined configuration in their stereocenters (Table 2.1).

[52] (a) Roussi, G.; González Zamora, E.; Carbonnelle, A.-C.; Beugelmanws, R. *Heterocycles* **1999**, *51*, 2041-2063. (b) Yamauchi, T.; Higashiyama, K.; Kubo, H.; Ohmiya, S. *Tetrahedron: Asymmetry* **2000**, *11*, 3003-3015. (c) Stalker, R. A.; Munsch, T. E.; Tran, J. D.; Nie, X.; Warmuth, R.; Beatty, A.; Aakeröy, C. B. *Tetrahedron* **2002**, *58*, 4837-4849. (d) Delaye, P.-O.; Vasse, J.-L.; Szymoniak, J. *Org. Lett*. **2012**, *14*, 3004-3007; (e) Hajri, M.; Blondelle, C.; Martinez, A.; Vasse, J.-L., Szymoniak, J. *Tetrahedron Lett*. **2013**, *54*, 1029-1031.



Scheme 2.65

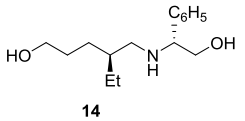
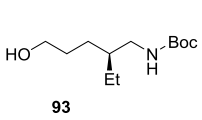
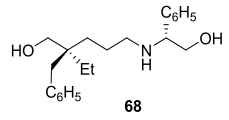
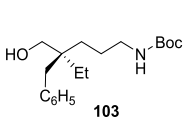
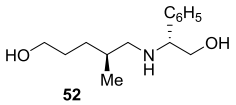
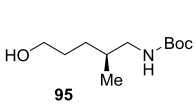
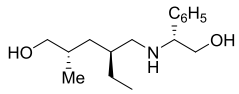
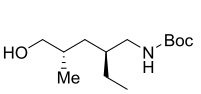
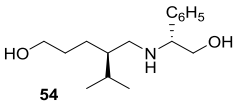
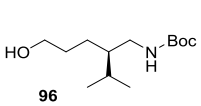
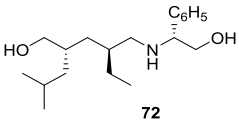
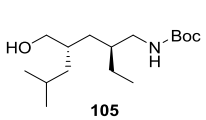
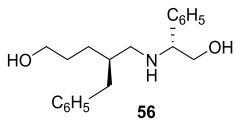
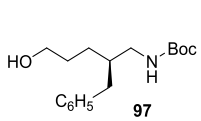
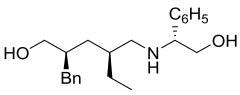
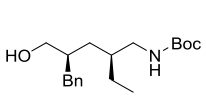
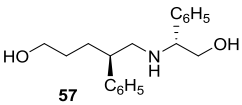
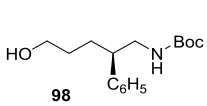
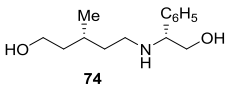
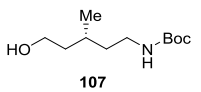
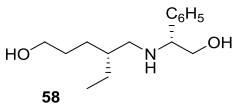
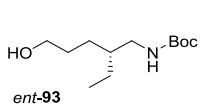
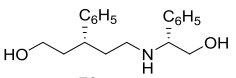
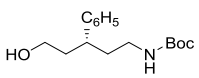
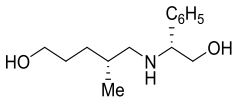
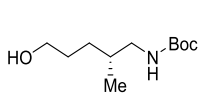
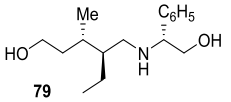
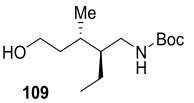
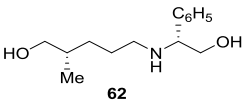
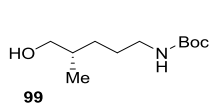
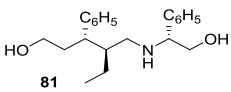
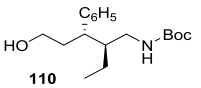
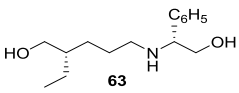
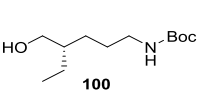
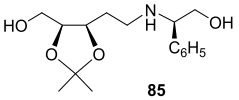
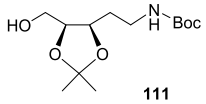
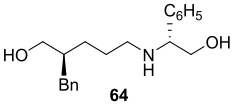
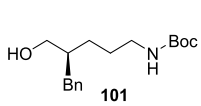
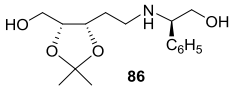
Aminodiol / *N*-Boc aminoalcohol, yield			Aminodiol / *N*-Boc aminoalcohol, yield		
 **14**	 **93**	65%	 **68**	 **103**	50%
 **52**	 **95**	70%	 **71**	 **104**	63%
 **54**	 **96**	50%	 **72**	 **105**	51%
 **56**	 **97**	51%	 **73**	 **106**	55%
 **57**	 **98**	53%	 **74**	 **107**	60%
 **58**	 ***ent*-93**	55%	 **76**	 **108**	50%
 **60**	 ***ent*-95**	57%	 **79**	 **109**	51%
 **62**	 **99**	48%	 **81**	 **110**	50%
 **63**	 **100**	55%	 **85**	 **111**	52%
 **64**	 **101**	60%	 **86**	**112**	60%
66	**102**	50%	**91**	**113**	49%

Table 2.1

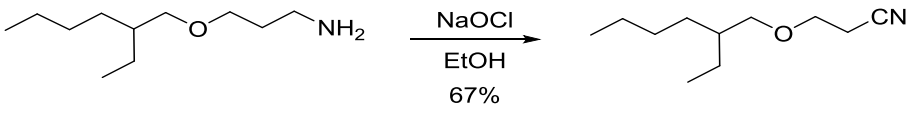
Our approach opens a general synthetic entry to diversely substituted enantiopure 5-amino-1-pentanols, functionalized nitrogen-containing building blocks that have been scarcely reported in the literature. As both enantiomers of phenylglycinol are commercially available, the methodology allows the preparation of these 5-aminopentanols in both enantiomeric series.

2.4.2. Oxidative removal of the chiral inductor

2.4.2.1. Oxidation of secondary amines into nitriles

Lots of synthetic conversions of amines using oxidative reagents have been described. In particular, procedures for the one-pot conversion of primary amines to the corresponding nitriles have been well-studied. Nitriles have considerable interest as an integral part of natural products and pharmaceuticals.[53] Moreover, the cyano group plays a crucial role in organic synthesis as it can be easily converted into a variety of functional groups, such as acids, amides, ketones, oximes and amines.[54] A common reaction for the preparation of nitrile derivatives is the nucleophilic substitution of alkyl halides by a cyano group, but in this case a carbon atom is added.[55] Due to the high toxicity of cyanide, other procedures using mild conditions, such as the dehydration of amides[56] and aldoximes,[57] have been developed.

Thus, in 1997, Yamazaki[58] described the oxidation of aliphatic primary amines having an α-methylene group using NaOCl in presence of ethanol.

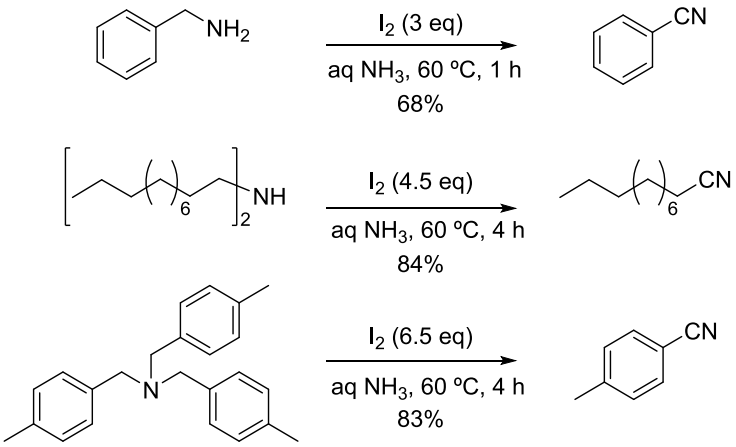


Scheme 2.66

[53] Friedrich, K.; Wallensfels, K. *The Chemistry of the Cyano Group*; Rappoport, Z.; Ed.; Wiley-Intersciences: New York, 1970, 67-122.
[54] Larock, R. C. *Comprehensive Organic Transformations*; VCH: New York, 1989, 819-995.
[55] (a) Kornblum, N.; Smiley, R. A.; Blackwood, R. K.; Iffland, D. C. *J. Am. Chem. Soc*. **1955**, *77*, 6269. (b) Ellis, G. P.; Rommey-Alexander, T. M. *Chem. Rev*. **1987**, *87*, 779.
[56] (a) Zhou, S.; Addis, D.; Das, S.; Junge, K.; Beller, M. *Chem. Commun*. **2009**, *45*, 4883-4885. (b) Zhou, S.; Junge, K.; Addis, D.; Das, S.; Beller, M. *Org. Lett*. **2009**, *11*, 2461-2464 (c) Sueoka, S.; Mitsudome, T.; Mizugaki, T.; Jitsukawa, K.; Kaneda, K. *Chem. Commun*. **2010**, *46*, 8243-8245. (d) Zhang, W.; Haskins, C. W.; Yang, Y.; Dai, M. *Org. Biomol. Chem*. **2014**, *12*, 9109-9112.
[57] (a) Song, Y.; Shen, D.; Zhang, Q.; Chen, B.; Xu, G. *Tetrahedron Lett*. **2014**, *55*, 639-641. (b) Yu, L.; Li, H.; Zhang, X.; Ye, J.; Liu, J.; Xu, Q.; Lautens, M. *Org. Lett*. **2014**, *16*, 1346-1349. (c) Zhang, X.; Sun, J.; Ding, Y.; Yu, L. *Org. Lett*. **2015**, *17*, 5840-5842.
[58] Yamazi, S. *Synth. Commun.* **1997**, *27*, 3559-3564.

One-pot preparative methods based in the use of ammonia combined with an appropriate oxidant allow the direct oxidative conversion of alcohols, aldehydes and amines into nitriles. The following systems[59] have been used for this purpose with good yields: $NH_3/O_2/CuCl_2{\cdot}H_2O/MeONa$, $NH_3/Pb(OAc)_4$, $NH_3/S_8/NaNO_2$, $NH_3/H_2O_2/CuCl$, NH_3/CAN, NH_3/NBS.

In this context, Togo et al.[60] described a direct, efficient, practical and less toxic oxidative conversion of primary alcohols and primary, secondary, and tertiary amines to the corresponding nitriles using molecular iodine in aq. NH_3 as the nitrogen source.

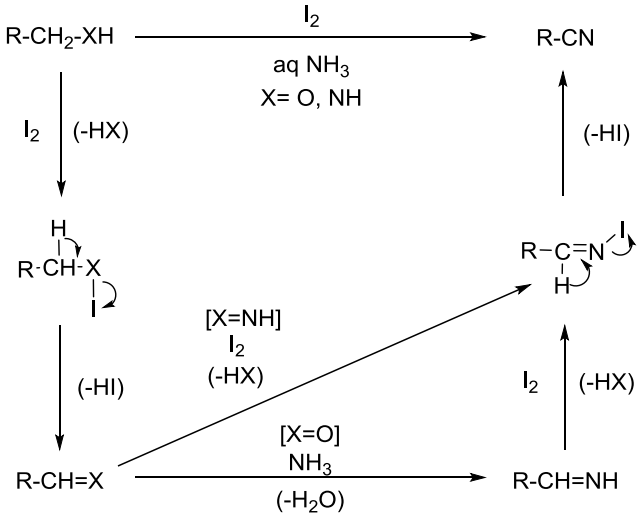


Scheme 2.67

A plausible reaction pathway for the conversion of primary alcohols and primary amines to the corresponding nitriles with molecular iodine is shown in Scheme 2.68. The initial *O*- or *N*-iodination of the alcohol or amine, followed by β-elimination of hydrogen iodide (HI) formed an aldehyde or aldimine, respectively. The aldehyde reacts with NH_3 to form an aldimine with loss of H_2O. A subsequent *N*-iodination of the aldimine followed by β-elimination of HI generates the corresponding nitrile.

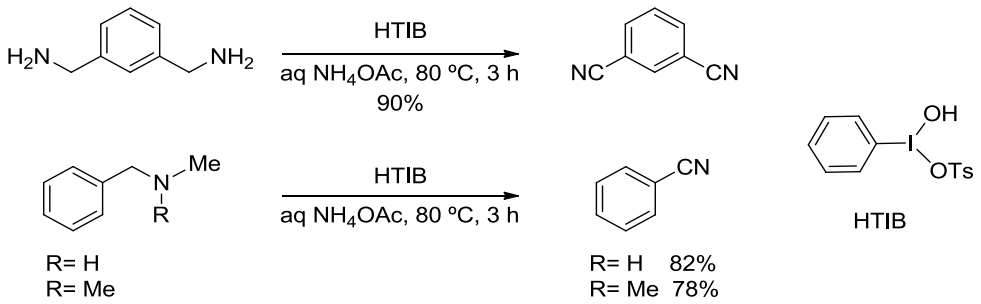
[59] (a) Brackman, W.; Smit, P. J. *J. Recl. Trav. Chim.* **1963**, *82*, 757-762. (b) Erman, M. B.; Snow, J. W.; Williams, M. J. *Tetrahedron Lett*. **2000**, *41*, 6749-6752. (c) Bandgar, B. P.; Makone, S. S. *Synlett* **2003**, 262-264. (d) Bandgar, B. P.; Makone, S. S. *Synth. Commun*. **2006**, *36*, 1347-1352. (e) Arote, N. D.; Bhalerao, D. S.; Akamanchi, K. G. *Tetrahedron Lett*. **2007**, *48*, 3651-3653. (f) Drouet, F.; Fontaine, P.; Masson, G.; Zhu, J. *Synthesis* **2009**, 1370-1374.

[60] (a) Mori, N.; Togo, H. *Synlett* **2005**, 1456-1458. (b) Iida, S.; Togo, H. *Tetrahedron* **2007**, *63*, 8274-8281.



Scheme 2.68

Similarly, Zhu and co-workers[61] described in 2010 a procedure for the direct oxidation of primary, secondary, and tertiary amines into the corresponding nitriles using the hypervalent iodine(III) reagent hydroxyl(tosyloxy)iodobenzene (HTIB; Koser's reagent) in combination with ammonium acetate as the nitrogen source.

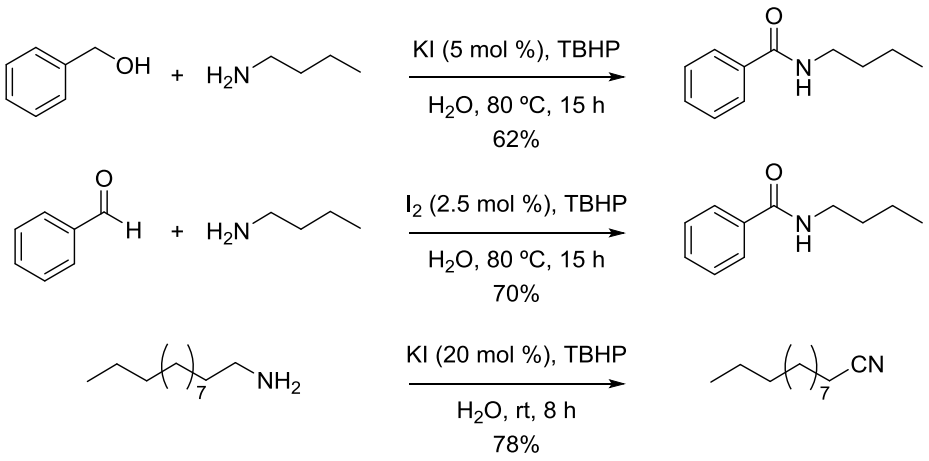


Scheme 2.69

Reddy and co-workers[62] related an effective procedure for the oxidative amidation of alcohols and aldehydes with primary amines using a catalytic amount of potassium iodide (or molecular iodine) in combination with *tert*-butyl hydroperoxide as an external oxidant. More recently,[62b] the same authors presented a catalytic oxidative conversion of alcohols, aldehydes and primary amines to the corresponding nitriles using the same reagents.

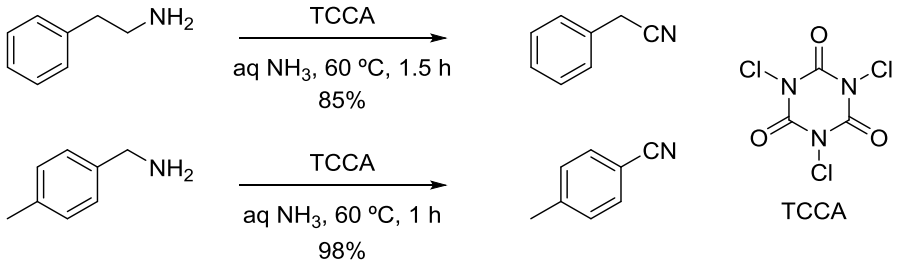
[61] Zhu, C.; Sun, C.; Wei, Y. *Synthesis* **2010**, 4235-4241.

[62] (a) Reddy, K. R.; Maheswari, C. U.; Venkateshwar, M.; Kantam, M. L. *Eur. J. Org. Chem.* **2008**, 3619-3622. (b) Reddy, K. R.; Maheswari, C. U.; Venkateshwar, M.; Prashanthi, S.; Kantam, M. L. *Tetrahedron Lett*. **2009**, *50*, 2050-2053.



Scheme 2.70

Also, treatment of primary amines with trichloroisocyanuric acid (TCCA) in aqueous ammonia gave the corresponding nitriles in good yields.[63]



Scheme 2.71

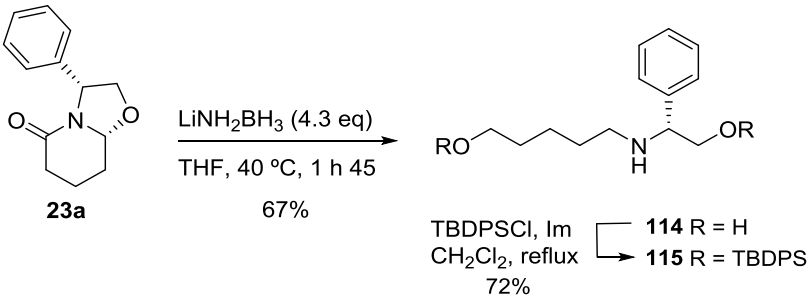
These results encouraged us to study the oxidation of the secondary amine function present in the enantiopure 1,5-amino diols previously synthesized. Taking into account that alcohols are also converted to nitriles under ammonia/oxidant conditions, it was necessary to protect both alcohol functions of the 1,5-aminodiol before treatment with the oxidative reagent. For our initial optimization studies, unsubstituted 1,5-aminodiol **114** was chosen as the model substrate.

2.4.2.1.1. Synthesis of 5-hydroxypentanitriles

The protected 1,5-aminoalcohol **115** was prepared following the two-step sequence outlined Scheme 2.72. Reductive ring opening of chiral lactam **23a** under $LiNH_2BH_3$ conditions afforded the corresponding enantiopure 1,5-aminoalcohol **114** in good yield (67%). A subsequent protection of both hydroxy

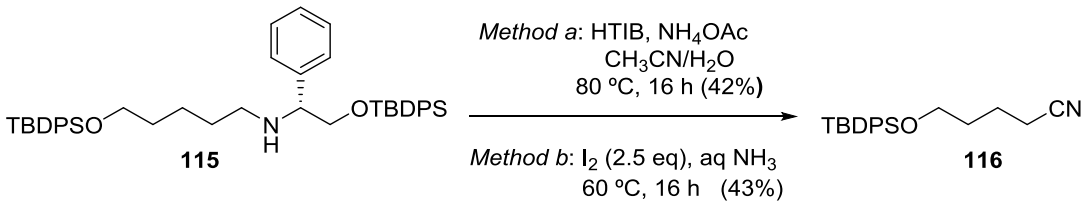
[63] Veisi, H. *Synthesis* **2010**, 2631-2635.

groups using *tert*-butyldiphenylsilyl chloride and imidazole in anhydrous dichloromethane led to **115** in 72% yield.



Scheme 2.72

Treatment of the secondary amine **115** with [hydroxyl(tosyloxy)iodo]benzene (HTIB) (2.5 eq) and ammonium acetate in a 4:1 mixture of acetonitrile-water at 80 ºC afforded the 5-hydroxypentanitrile derivative **116** in 42% yield. A similar result was obtained (43%) when the reaction was performed with molecular iodine (2.5 eq) in aqueous ammonia. In both cases, we recovered minor amounts of the starting material.

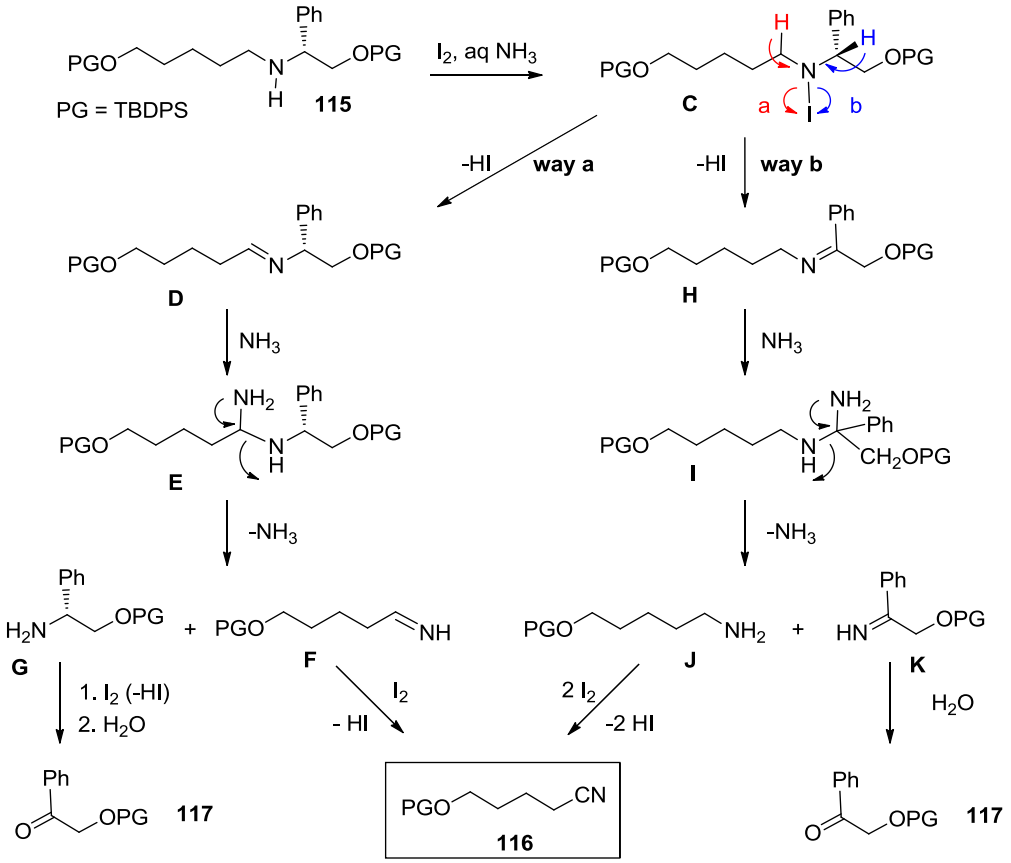


Scheme 2.73

The above moderate conversions can be explained by considering the low solubility of **115** in protic solvents. This problem was circumvented by dissolving **115** in THF, which is miscible in water. Moreover, according to the mechanism shown in Scheme 2.68 at least three equivalents of the oxidative reagent are necessary for the total conversion of secondary amine into the corresponding nitrile. We decided to pursue our optimization studies using I_2 in aqueous ammonia. The principal advantages of the use of molecular iodine are that it is a mild, cheap, and easily available oxidizing reagent, and it is useful because it is a solid and less toxic than other halogens. The best results were obtained when we used an excess of 8 equiv of molecular iodine in aqueous ammonia and THF at 60 ºC for 15 h. Under these conditions 5-hydroxypentanitrile **116** was isolated in good yield (70%).

The presumed reaction mechanism of the conversion of secondary amine **115** into nitrile **116** is outlined Scheme 2.74. Firstly, *N*-iodination of amine **115** would give iodoamine **C**. A β-elimination of hydrogen iodide (HI) from **C** can take place

by two different ways, *a* or *b*. In the way *a*, the less substituted and non-conjugated imine **D** would react with ammonia to form aminal **E**, which would decompose to an imine **F** and primary amine **G**. Following the same mechanism, *N*-iodination of imine **F** followed by β-elimination of HI would provide nitrile **116**. On the other hand, primary amine **G** would be converted to ketone **117** by a three-step sequence involving iodination, β-elimination of HI, and subsequent hydrolysis. Elimination of hydrogen iodide by the way *b* would give the conjugated imine **H**, which would react with ammonia to form **I**. A subsequent removal of the inductor would give amine **J**, the precursor of the target nitrile **116**, and imine **K**, which would be hydrolysed to would ketone **117**. In both cases, *a* and *b*, target nitrile **116** and ketone **117** would be obtained.

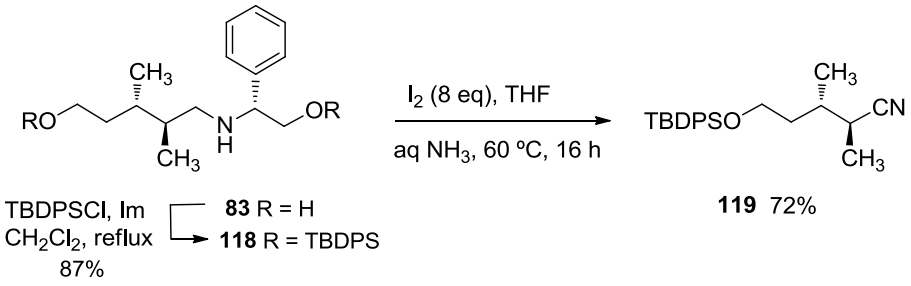


Scheme 2.74

2.4.2.1.2. Synthesis of 5-hydroxypentanenitriles from enantiopure amino diols

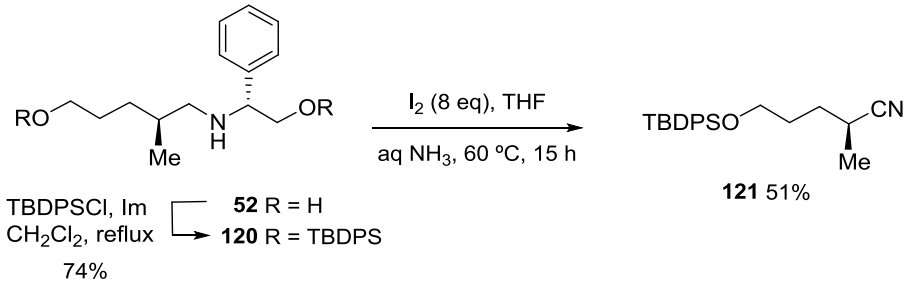
Nitrile **119** was obtained in good yield (72%) by protection of the two hydroxy groups of amino diol **83**, followed by oxidative cleavage of the phenylglycinol moiety with molecular iodine in aqueous ammonia. Interestingly, under these conditions, only one diastereoisomer was observed by NMR in the crude

reaction mixture. As no epimerization of the configurationally labile stereocenter α to the intermediate imine **D** occurs, it seems reasonable to postulate that imine **H** (most stable) was formed regioselectively.



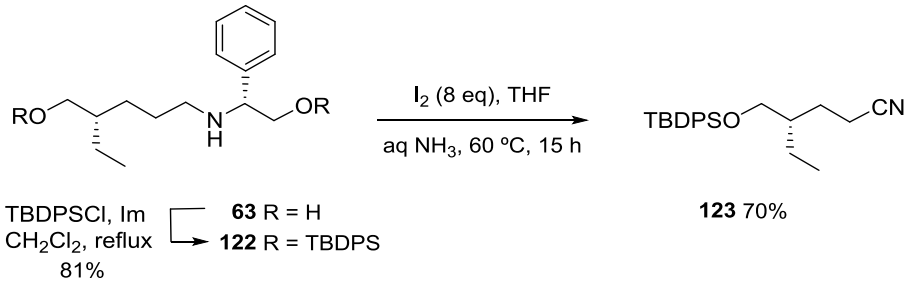
Scheme 2.75

Similarly, protection of both alcohol functions of amino diol **52** was performed in 74% yield. Oxidative cleavage of the phenylglycinol moiety of the *O*-protected amino diol **120** afforded the corresponding nitrile **121** in moderate yield (51%).



Scheme 2.76

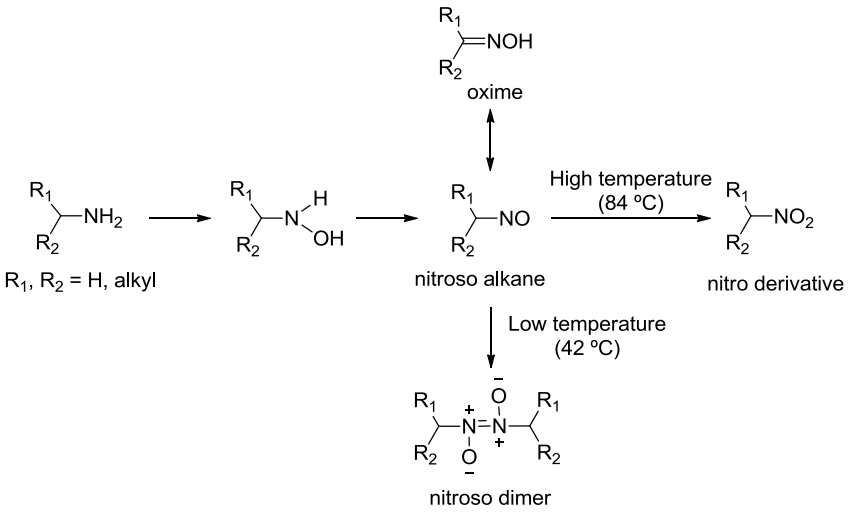
As an additional example, aminodiol **63** was protected as the silyl derivative **122** in excellent yield and then oxidized with molecular iodine in aqueous ammonia to give the corresponding nitrile **123** in 70% yield.



Scheme 2.77

2.4.2.2. Oxidation of amines with *m*-CPBA

m-Chloroperbenzoic acid has extensively been used for the conversion of aromatic and aliphatic primary amines into the corresponding nitro compounds[64] which constitute valuable synthetic intermediates.[65] These peroxy acid oxidations probably go by way of intermediate hydroxylamines and nitroso compounds (see Scheme 2.78). Hydroxylamines are postulated as intermediates in these oxidations, but they are rarely isolated or detected. Various side reactions can take place, the nature of which depends upon the reaction conditions. Aliphatic amines can give nitroso dimers, oximes (formed by acid-catalyzed rearrangement of the intermediate nitrosoalkane), or nitro derivatives. The peroxy acid must be used in excess to minimize the formation of the dimer of the intermediate nitroso compound. The proportion of both nitroso dimer and nitroalkane are temperature dependent. Indeed, formation of the nitroalkane is favoured when the reaction is carried out at elevated temperature.[66]



Scheme 2.78

2.4.2.2.1. *m*-CPBA oxidation of phenylglycinol-derived secondary amine 115

Taking into account that primary amines are oxidized to nitro derivatives by treatment with *m*-chloroperbenzoic acid, we decided to study this oxidation

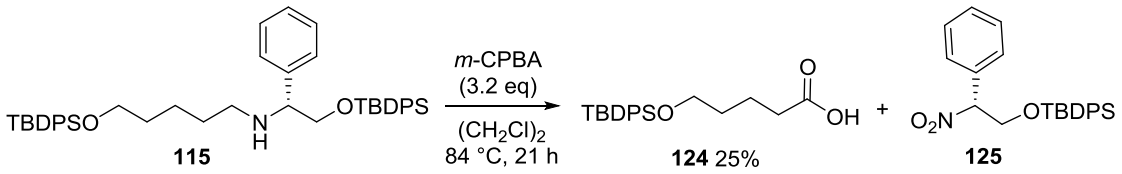
[64] Gilbert, K. E.; Borden, W. T. *J. Org. Chem.* **1979**, 44, 659-661.

[65] (a) Ono, N.; Kaji, A. *Synthesis* **1986**, 693-703. (b) Rosini, G.; Balini, R. *Synthesis* **1988**, 833-847. (c) Pereyre, M.; Quintard, J. P.; Rahm, A. Tin in *Organic Synthesis*, Butterworth, London, 1987, p. 106. (d) *Nitro Compounds; Recent Advances in Synthesis and Chemistry;* Feuer, H.; Nielsen, A. T. Eds.; VCH: New York, 1990. (e) Ono, N. *The Nitro Group in Organic Synthesis*; Feuer, H., Ed.; Wiley-VCH: New York, 2001. (f) Luzzio, F. A. *Tetrahedron* **2001**, *57*, 915-945.

[66] Gilchrist, T. L. in *Comprehensive Organic Synthesis*, vol .7; Ed. Trost, B.M.; Fleming, I.; Pergamon Press, Oxford, 1991, 736-737.

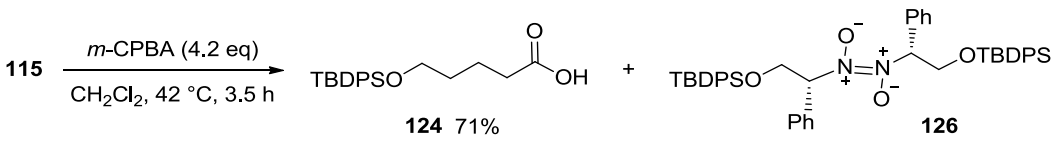
using several of the phenylglycinol-derived secondary amines previously prepared in this work. Given that alcohols are converted to carbonyl derivatives under these oxidative conditions, it was necessary to use the corresponding protected silyl derivatives.

Our first studies were performed with secondary amine **115**, which was treated with *m*-CPBA (3.2 eq) in refluxing 1,2-dichloroethane. After the reaction was quenched with aqueous sodium hydroxide to remove the excess of 3-chlorobenzoic acid generated in the process, flash chromatography provided carboxylic acid **124** (25%) and nitro compound **125**.



Scheme 2.79

This result made evident that, as expected, the amino group has undergone oxidation to a nitro group, but also that the oxidative cleavage of the CH_2-N (instead of the benzylic CH-N) bond has occurred.
In order to improve the formation of carboxylic acid **124** we decided to increase the amount of peroxy acid (4.2 equivalents) and to carry out the reaction at a lower temperature (reflux of dichloromethane). Operating under these conditions, carboxylic acid **124** was obtained in good yield (71%). As a consequence of operating at a lower temperature (see Scheme 2.81), we isolated the nitroso dimer **126** instead of nitrocompound **125**.



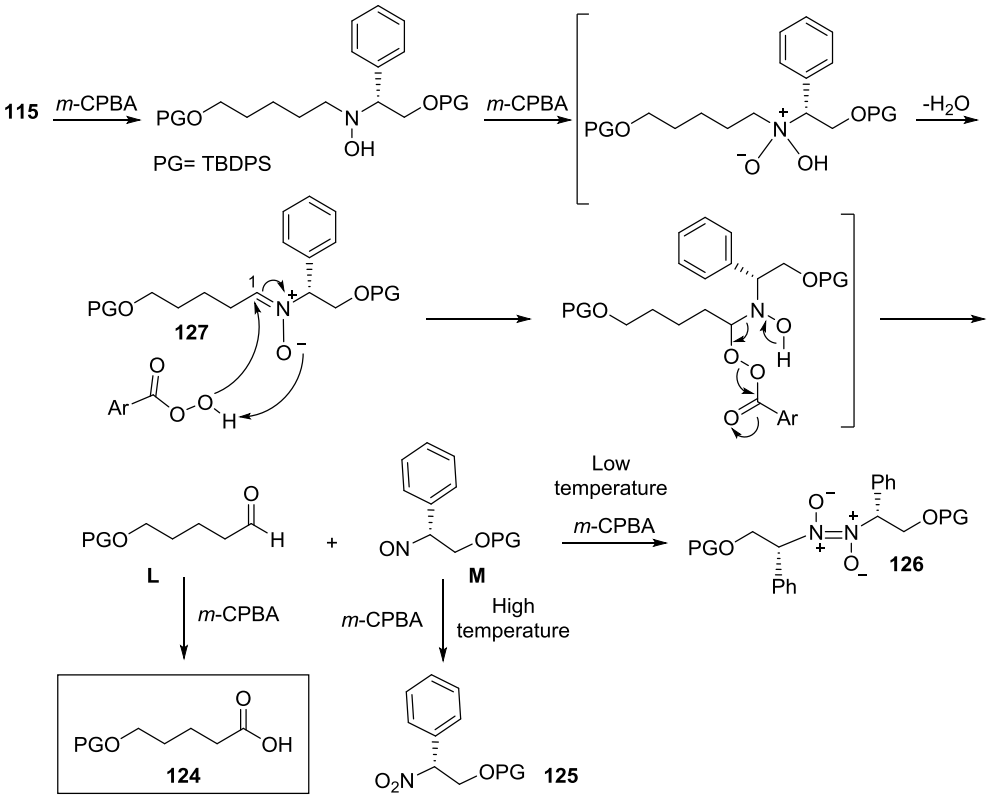
Scheme 2.80

2.4.2.2.2. Proposed mechanism

The formation of carboxylic acid **124** from secondary amine **115** can be accounted for by considering the initial generation of an hydroxylamine, which gives regioselectively the non-conjugated nitrone **127**[67] and their subsequent *m*-

[67] For the preparation of nitrones by oxidation of secondary amines, see: (a) Murahashi, S.-I.; Mitsui, H.; Shiota, T.; Tsuda, T.; Watanabe, S. *J. Org. Chem*. **1990**, *55*, 1736-1744. (b) Marcantoni, E.; Petrini, M.; Polimanti, O. *Tetrahedron Lett.* **1995**, *36*, 3561-3562. (c) Colonna, S.; Pironti, V.; Carrea, G.; Pasta, P.;

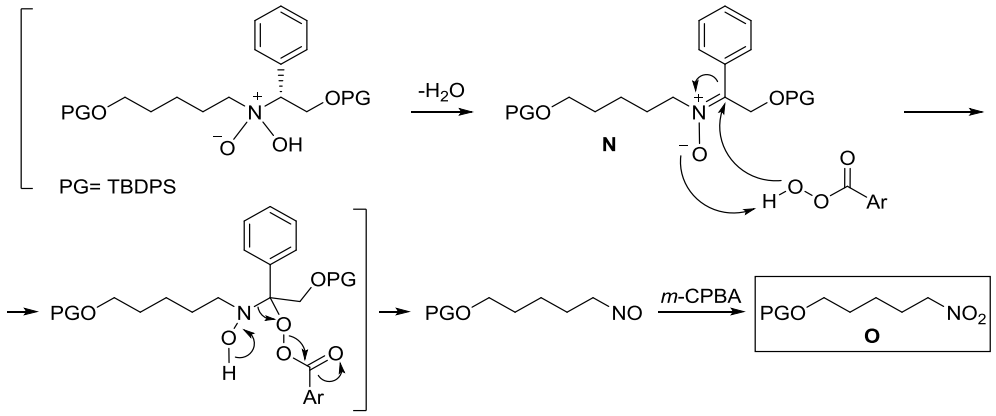
CPBA-promoted oxidative cleavage.[67e] Nucleophilic addition of the peracid to the nitrone **127**, followed by rearrangement of the generated intermediate led to aldehyde **L** and the nitroso derivative **M**. A subsequent oxidation afforded carboxylic acid **124** and the nitro compound **125** (at high temperature; 84 ºC) or the dimer **126** (at low temperature; 42 ºC).



Scheme 2.81

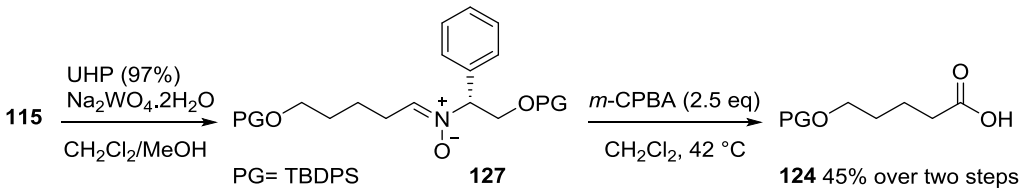
Interestingly, an alternative pathway involving the generation of the regioisomeric conjugated nitrone **N**, as outlined in Scheme 2.82, would afford the nitro derivative **O**, whose formation was never observed.

Zambianchi, F. *Tetrahedron* **2004**, *60*, 569-575. (d) Gella, C.; Ferrer, E.; Alibés, R.; Busqué, F.; de March, P.; Figueredo, M.; Font, J. *J. Org. Chem*. **2009**, *74*, 6365-6367. For peracid-promoted oxidative ring-opening of cyclic nitrones, see: (e) Bapat, J. B.; Durie, A. *Aust. J. Chem*. **1984**, *37*, 211-219.



Scheme 2.82

In support of the mechanism outlined in Scheme 2.81, nitrone **127**, prepared by Na_2WO_4/hydrogen peroxide-urea oxidation[67b] of the simple secondary amine **115**, was converted to hydroxypentanoic acid derivative **124** (45% from **115**) and dimer **126** by treatment with *m*-CPBA (2.5 equiv).

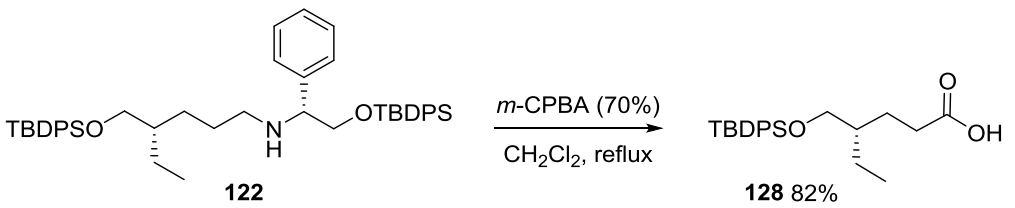


Scheme 2.83

2.4.2.2.3. Synthesis of enantiopure 5-hydroxypentanoic acid derivatives

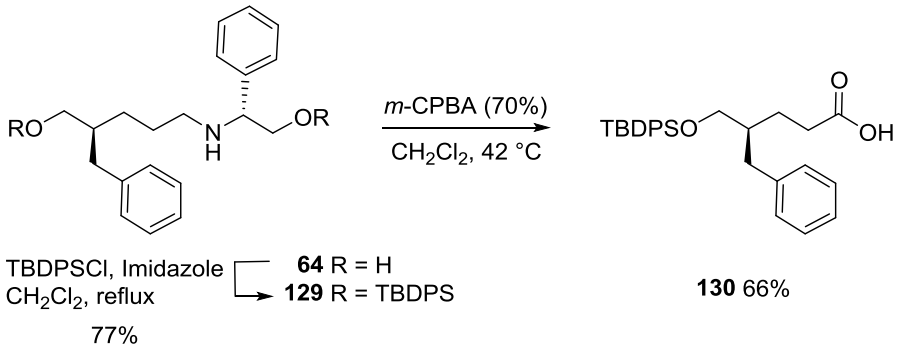
We then applied the above procedure to prepare a variety of enantiopure 5-hydroxypentanoic acid derivatives from the substituted amino diols previously prepared in this work.

Thus, treatment of the *O*-protected secondary amine **122** with an excess of *m*-CPBA in refluxing dichloromethane directly afforded carboxylic acid **128** in excellent yield (82%).



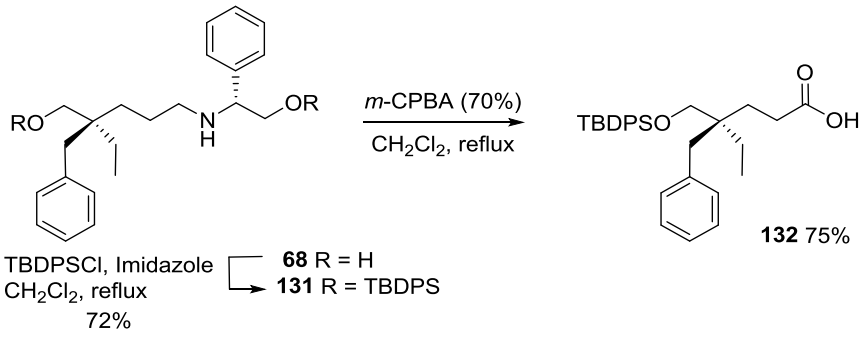
Scheme 2.84

Similarly, *O*-protected amino diol **129** was obtained in 77% yield from enantiopure 1,5-aminodiol **64**. Subsequent treatment of **129** under the above *m*-CPBA conditions afforded (*S*)-4-benzyl pentanoic acid derivative **130** in 66% yield.



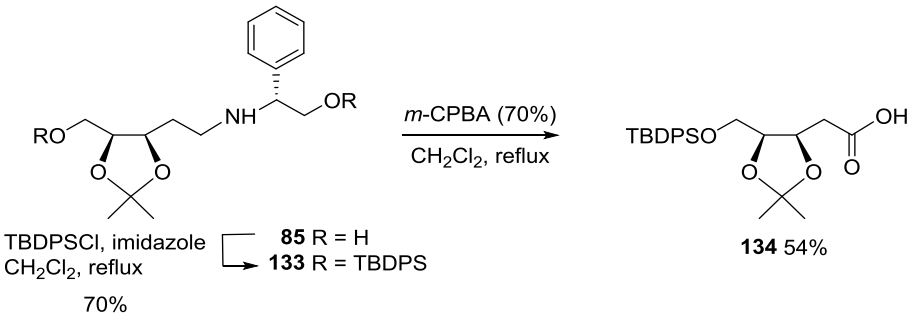
Scheme 2.85

The procedure allows the preparation of enantiopure *S*-hydroxypentanoic acid derivatives bearing a quaternary center. Thus, protection of enantiopure 1,5-aminoalcohol **68**, which bears a quaternary stereocenter at the C-2 position, was accomplished in 72% yield by using *tert*-butyldiphenylsilyl chloride and imidazole in anhydrous dichloromethane at reflux. Oxidation of the secondary amine **131** led to carboxylic acid **132** in good yield (75%).



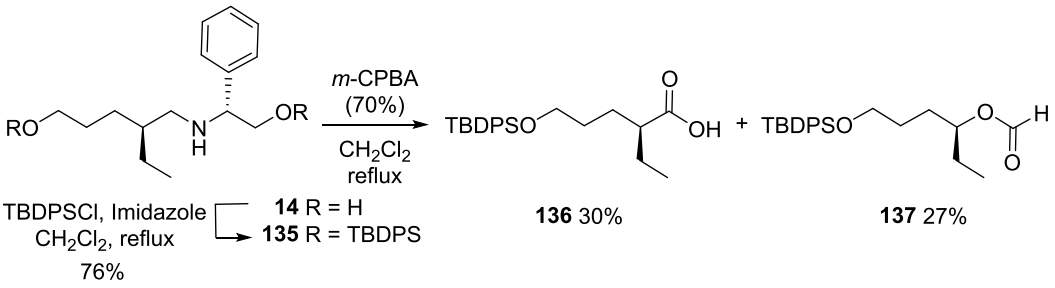
Scheme 2.86

To illustrate the usefulness of the procedure in the preparation of highly functionalized enantiopure derivatives, after protection of the two terminal hydroxy groups, secondary amine **85** was converted to the *O*-protected hydroxy acid **134** in moderate yield.



Scheme 2.87

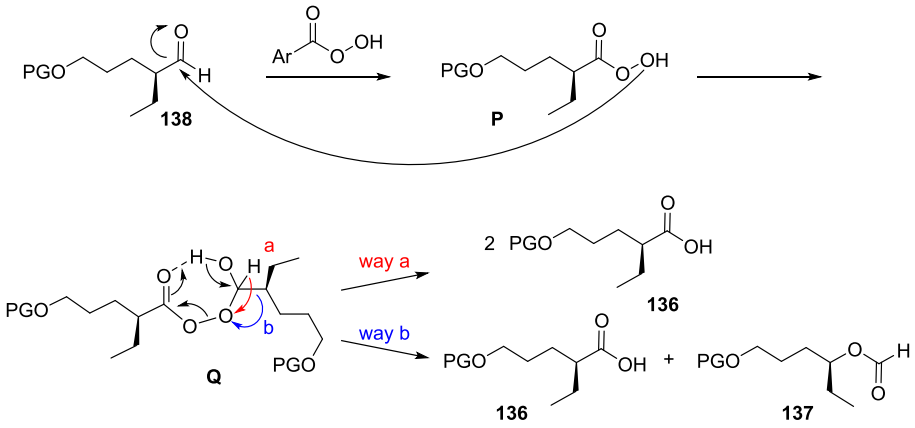
A limitation of the procedure was encountered in the oxidation of the silyl derivative **135**, which was prepared in 76% yield from enantiopure aminodiol **14**. In this case, the oxidative cleavage of β-substituted secondary amine **135** under *m*-CPBA conditions gave a mixture of carboxylic acid 1**36** and formate ester **137** in 30% and 27% isolated yields, respectively.



Scheme 2.88

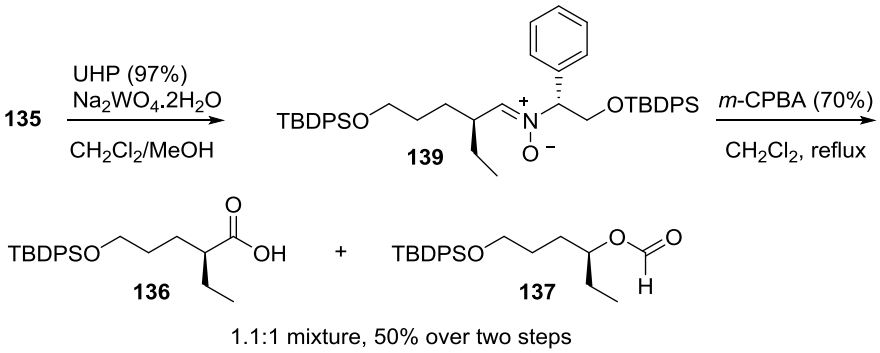
The formation of the formate ester **137** can be rationalized by a Baeyer-Villiger rearrangement involving a peroxy acid in the intermediate **Q.**[68] Indeed, as depicted in Scheme 2.90, nucleophilic addition of the peracid **P** on the carbonyl group of the *in situ* formed intermediate aldehyde **138** leads to a peroxy acid-aldehyde adduct **Q**. This adduct undergoes an acid-catalyzed rearrangement by migration of the aldehydic hydrogen, providing two molecules of carboxylic acid **136** (way *a*), or, alternatively, a rearrangement of the alkyl substituent giving acid **136** and formate ester **137** (way *b*). The presence of a substituent in α-position of the reacting aldehyde correlates with formate formation, and the favoured pathway depends on the ability of the R group bound to the aldehydic carbon to migrate.

[68] (a) Lehtinen, C.; Nevalainen, V.; Brunow, G. *Tetrahedron* **2000**, *56*, 9375-9382. (b) Marteau, C.; Ruyffelaere, F.; Aubry, J.-M.; Penverne, C.; Favier, D.; Nardello-Rataj, V. *Tetrahedron* **2013**, *69*, 2268-2275.



Scheme 2.89

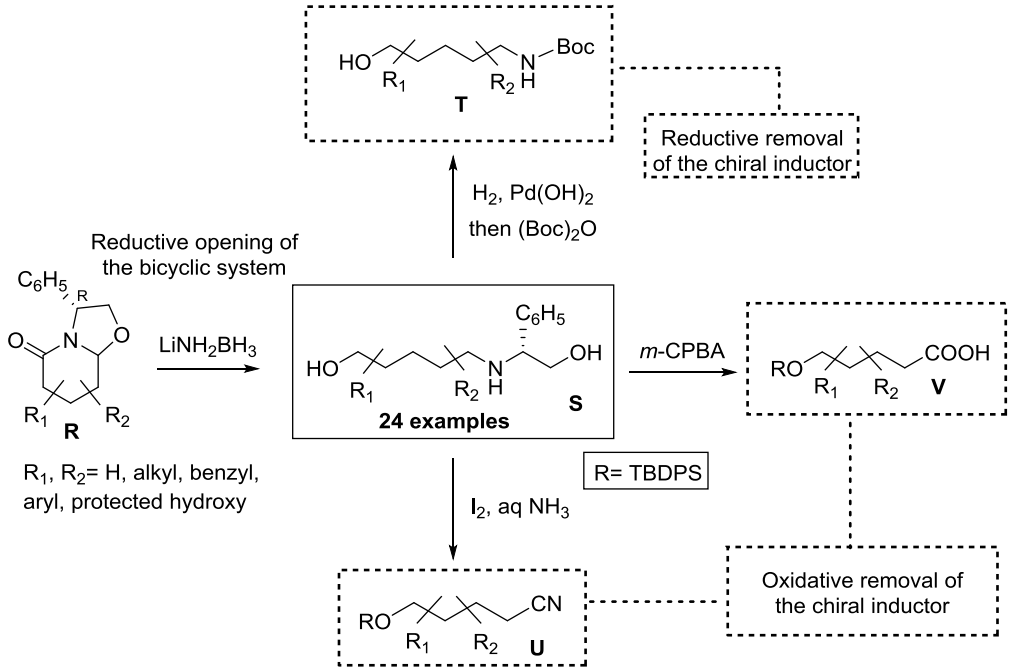
At this point, we decided to prepare nitrone **139** from secondary amine **135** following the methodology previously used for the preparation of the nitrone **127** (Scheme 2.84). In support of the above mechanism, nitrone **139** was converted to a nearly equimolecular mixture of hydroxypentanoic acid **136** and formate **137** by treatment with *m*-CPBA (2.5 equiv).



Scheme 2.90

In summary, we have described the straightforward conversion of a variety of (*R*)-phenylglycinol-derived oxazolopiperidone lactams **R** to open-chain enantiopure amino diols **S**, bearing a variety of substitution patterns (alkyl, benzyl, aryl, protected hydroxyl), and stereochemistries, by reduction with $LiNH_2BH_3$ in an unprecedented process involving the simultaneous reductive opening of the oxazolidine and lactam rings. The potential of these chiral building blocks was illustrated (see Scheme 2.91) with the preparation of enantiopure 5-amino-1-pentanols (**T**), 5-hydroxypentanenitriles (**U**), and 5-hydroxypentanoic acids (**V**). Chiral substituted-5-amino-1-pentanols **T** (see Table 2.1) were obtained by reductive removal of the phenylglycinol moiety present in amino diols **S**. Alternatively, amino diols **S** were converted to nitriles **U** by a I_2/NH_3 mediated oxidative cleavage of the secondary amino group. Finally, removal of the penylglycinol moiety present in **S** under oxidative

conditions, by an unprecedented *m*-CPBA-promoted transformation allowed us to obtain carboxylic acids **V**.



Scheme 2.91

Chapter 3

SYNTHESIS OF MACROCYCLIC NATURAL PRODUCTS FROM OPEN-CHAIN BUILDING BLOCKS

To demonstrate the synthetic value of the open-chain enantiopure building blocks described in Chapter 2 we used same of them as key scaffolds for the synthesis of several macrocyclic nitrogen compounds, such as *Haliclona* alkaloids and fluvirucinins B.

3.1. Marine alkaloids from *Haliclona* sponges

This introduction is focused on *Haliclona* alkaloids, and covers their isolation, characterization, biological activity, and synthesis. For a sake of clarity, the numbering of compounds in this section is independent of the rest of the Thesis.

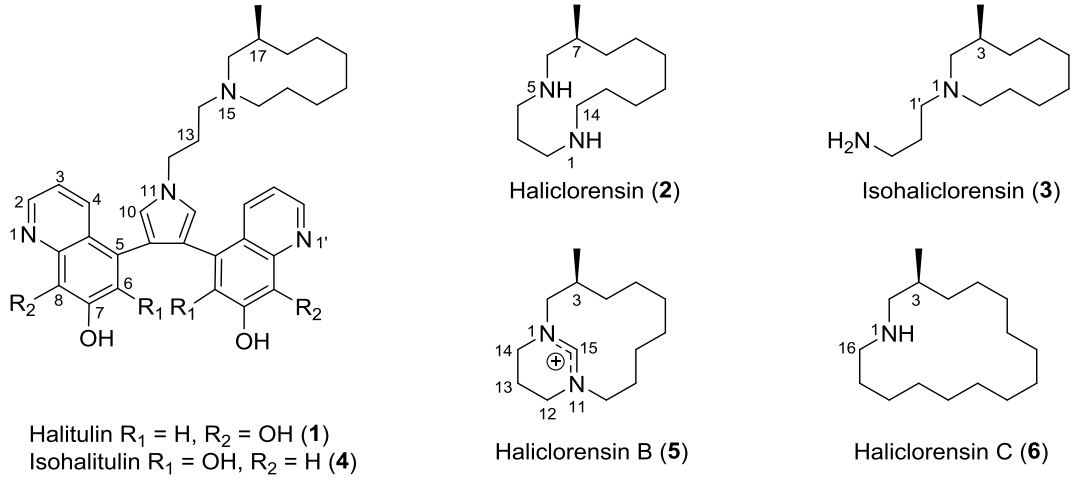
3.1.1. Introduction

Halitulin (**1**) and haliclorensin (**2**) are two unique alkaloids isolated by Kashman et al. in 1998 and 1999, respectively, from the marine sponge *Haliclona tulearensis* (class Demospongiae, order Haplosclerida, family Chalinidae, genus *Haliclona*) collected in Sodwana Bay, Durban, South Africa.[69] The significant cytotoxicity of haliclorensin against P-388 mouse leukemia cells and that of halitulin against several tumor cell lines has stimulated studies toward the total syntheses of both molecules. Steglich's [70] and Banwell's [71] syntheses of haliclorensin (**2**) allowed the revision of its structure, from **3** to **2**, and the initially assigned structure for haliclorensin was subsequently renamed isohaliclorensin (**3**). Furthermore, it was suggested that both compounds **2** and **3** (a precursor of halitulin, **1**) are originate from a common 1,11-diazabicyclo[8.4]tetradecane.[2]

On the other hand, two reports on the total synthesis of halitulin confirmed the previously assigned structure **1** and allowed the determination of its absolute (17*S*) configuration.[72] Together with halitulin and haliclorensin, an additional related compound was isolated from the same sponge.[69] Because this compound was isolated in minor amounts and was highly sensitive to light and air, its elucidation was not accomplished.

[69] (a) Koren-Goldshlager, G.; Kashman, Y.; Schleyer, M. *J. Nat. Prod*. **1998**, *61*, 282-284. (b) Kashman, Y.; Koren-Goldshlager, G.; Garcia Gravalos, M. D.; Schleyer, M. *Tetrahedron Lett*. **1999**, *40*, 997-1000.
[70] (a) Heinrich, M. R.; Steglich, W. *Tetrahedron Lett*. **2001**, *42*, 3287-3289. (b) Heinrich, M. R.; Kashman, Y.; Spiteller, P.; Steglich, W. *Tetrahedron* **2001**, *57*, 9973-9978.
[71] Banwell, M. G.; Bray, A. M.; Edwards, A. J.; Wong, D. J. *New J. Chem*. **2001**, *25*, 1347-1350.
[72] (a) Heinrich, M. R.; Steglich, W.; Banwell, M. G.; Kashman, Y. *Tetrahedron* **2003**, *59*, 9239-9247. (b) Zheng, J.-F.; Jin, L.-R.; Huang, P.-Q. *Org. Lett*. **2004**, *6*, 1139-1142.

More recently, in 2010,[73] the constituents of two Madagascan *Haliclona tulearensis* sponge specimens, collected in Salary Bay, ca. 100 km north of Tulear in Madagascar, were examined for the purpose of finding additional interesting metabolites and hopefully to once again isolate the above-mentioned sensitive compound and complete its elucidation. Three new alkaloids, designated isohalitulin (**4**) (the related unstable compound), haliclorensin B (**5**) and haliclorensin C (**6**) were identified. The $CHCl_3$-MeOH (2:1) extract of each frozen sample was subjected to solvent partitioning, i.e., aqueous MeOH against hexanes and $CHCl_3$. The $CHCl_3$ fraction of each extract was repeatedly chromatographed over a Sephadex LH-20 column. One sample of *Haliclona tulearensis* yielded isohalitulin (**4**) and the second sample yielded haliclorensins B (**5**) and C (**6**) as well as the known haliclorensin (**2**).



Scheme 3.1

On the grounds of common biogenetic precursors it was tentatively suggested that isohalitulin (**4**) and haliclorensins B (**5**) and C (**6**) have the same absolute configuration of the single stereogenic center (*S*) as determined for halitulin (**1**) and haliclorensin (**2**). Natural haliclorensin was shown to consist of a mixture of (*R*)- and (*S*)-enantiomers, with the (*S*)-enantiomer being predominant (1:3 ratio).[70b]

Obtaining different secondary metabolites from the two Salary Bay collections of *Haliclona tulearensis* and from a sample collected on the other side of the Mozambique Canal raises the question of the real source of the compounds, namely, the sponge or guest microorganisms.

[73] Isolation and tentative absolute configuration: Sorek, H.; Rudi, A.; Aknin, M.; Gaydou, E. M.; Kashman, Y. *J. Nat. Prod*. **2010**, *73*, 456-458.

Isohalitulin (**4**) and haliclorensins B (**5**) and C (**6**) were tested for toxicity to brine shrimp (*Artemia salina*)[74] and were found to be moderately active. Isohalitulin (**4**) showed a greater potency, with a LD_{50} value of 0.9 mM, while haliclorensins B (**5**) and C (**6**) had LD_{50} values of 2.2 and 2.1 mM, respectively.

3.1.2. Synthetic approaches

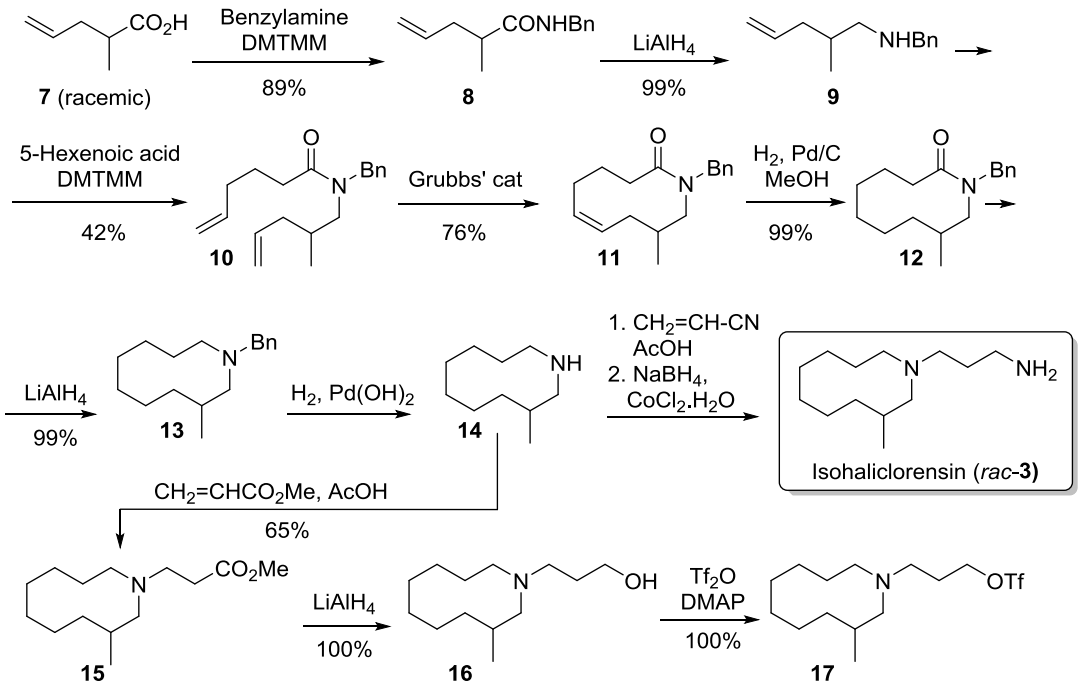
The synthesis of *Haliclona* alkaloids has been little explored. In fact, only total syntheses of halitulin (**1**) and haliclorensin (**2**) have been reported.

3.1.2.1. Banwell's approach to isohaliclorensin and halitulin

The first approach to halitulin was reported by Banwell in 2002 [75] and represented the synthesis of its tetra-*O*-methyl ether derivative. Two relevant aspects of the synthesis are the use of a ring-closing metathesis (RCM) reaction to assemble the azacyclodecane structure, and the preparation of 3,4-bis(7',8'-dimethoxyquinolin-5'-yl)pyrrole, before the coupling between both fragments. Banwell described in 2001[71] an unambiguous racemic synthesis of isohaliclorensin, concluding that the structure for haliclorensin had been incorrectly assigned. The closure of the 10-membered ring was efficiently accomplish (bond formed C_5-C_6) using the Grubbs' first generation catalyst from amino diene **10**, which was prepared by coupling between the *N*-benzylamine derivative **9** with 5-hexenoic acid. Catalytic hydrogenation of the resulting cyclic olefin **11**, followed by $LiAlH_4$ reduction of amide **12** and subsequent hydrogenolysis of the *N*-benzyl derivative **13** afforded 3-methylazacyclodecane **14**. The total synthesis of racemic isohaliclorensin (*rac*-**3**) was completed by treatment of secondary amine **14** with acrylonitrile, followed by reduction of the cyano group.[71]

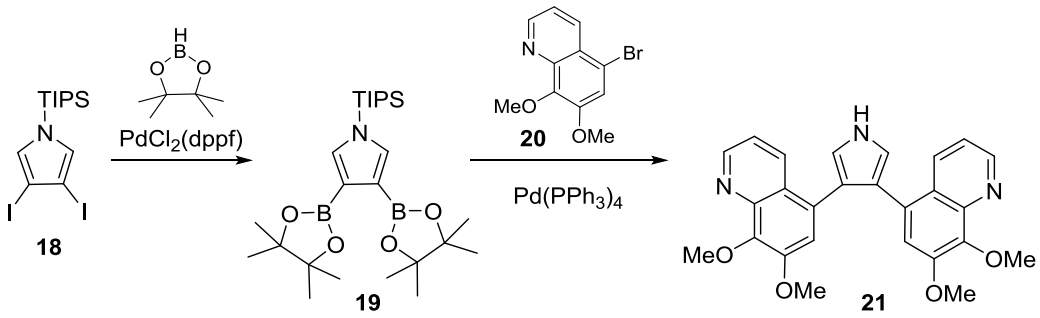
For the synthesis of halitulin, amine **14** was treated with methyl acrylate, and the resulting Michael addition product **15** was reduced with $LiAlH_4$ to give alcohol **16**, which was converted to triflate **17**.

[74] Meyer, B. N.; Ferrigni, N. R.; Putnam, J. E.; Jacobsen, L. B.; Nichols, D. E.; McLaughlin, J. C. *Planta Med*. **1982**, *45*, 31-34.
[75] Bandwell, M. G.; Bray, A. M.; Edwards, A. J.; Wong, D. J. *J. Chem. Soc., Perkin Trans*. 1 **2002**, 1340-1343.



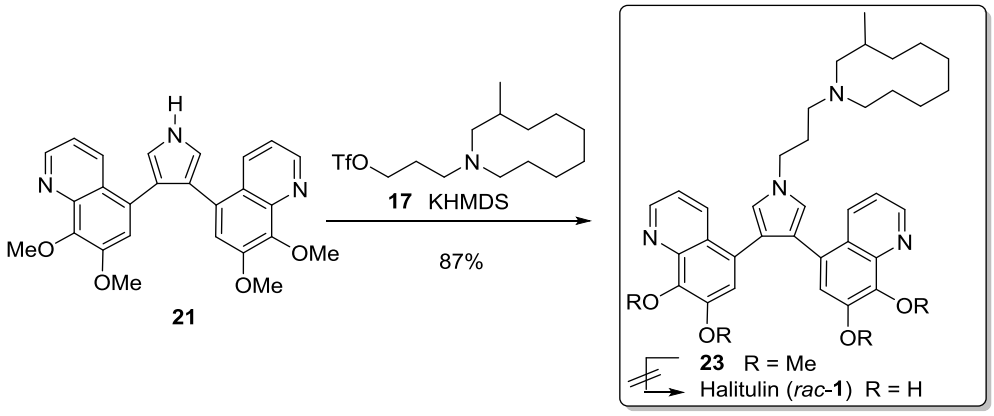
Scheme 3.2

On the other hand, 3,4-diiodopyrrole **18** was subjected to reaction with pinacolborane in the presence of $PdCl_2$(dppf) to give di-borolated derivative **19**. A Suzuki-Miyaura cross-coupling reaction of **19** with bromoquinoline **20** afforded compound **21**.



Scheme 3.3

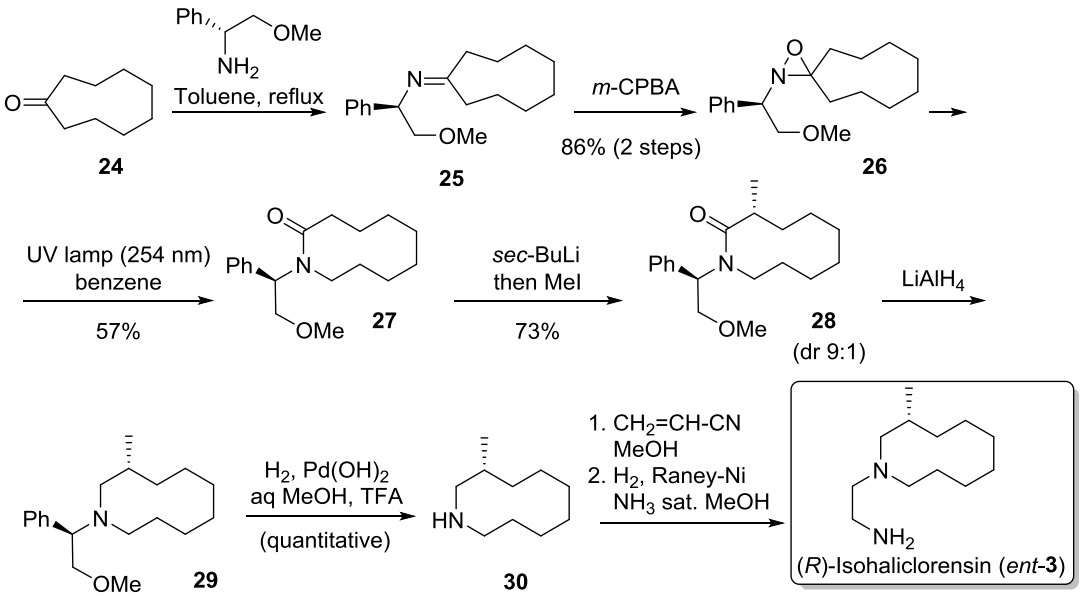
Being rather unstable, triflate **17** was immediately treated with the potassium salt of pyrrole **21** (generated by reacting compound **21** with KHMDS) affording tetra-*O*-methyl halitulin **23** in an excellent yield (87%). All attempts to effect the demethylation of compound **23** and thereby generate racemic halitulin *rac*-**1** were unsuccessful.



Scheme 3.4

3.1.2.2. Usuki's approach to (*R*)-isohaliclorensin

In 2001, Usuki reported[76] the asymmetric synthesis of (*R*)-isohaliclorensin (*ent*-**3**). The key steps were the photochemical ring-expansion of spirooxaziridine **26** to lactam **27** for the construction of the azacyclodecane moiety, and the 1,4-stereoiselective methylation of lactam **27**.



Scheme 3.5

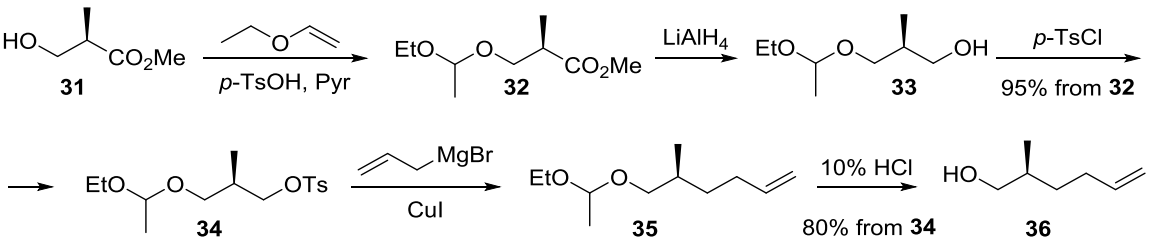
[76]Usuki, Y.; Hirakawa, H.; Goto, K.; Iio, H. *Tetrahedron: Asymmetry* **2001**, *12*, 3293-3296.

The required spirooxaziridine **26** was prepared as a single diastereomer by *m*-CPBA oxidation of the imine **25**, which was obtained by reaction of cyclononanone **24** and (*R*)-(-)-1-amino-1-phenyl-2-methoxyethane. Photolysis of **26** afforded the 10-membered lactam **27** in 57% yield. The subsequent methylation of **27** was accomplished by treatment with *sec*-BuLi, followed by addition of iodomethane to afford the product **28** as a 9:1 mixture of diastereomers. Secondary amine **30** was obtained by $LiAlH_4$ reduction of the amide **28** and subsequent hydrogenolysis using $Pd(OH)_2$ in presence of TFA to remove the chiral auxiliary. The total synthesis of isohaliclorensin (*ent*-**3**) was completed by addition of **30** to acrylonitrile, followed by subsequent reduction with Raney-Ni in methanol saturated with NH_3.

3.1.2.3. Steglich's approach to isohaliclorensin, halitulin and haliclorensin

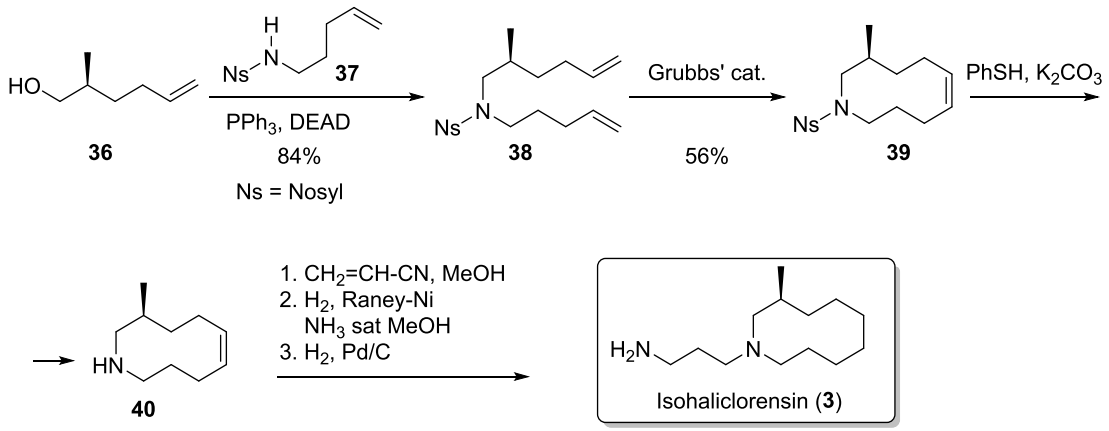
Steglich reported in 2001[70] the synthesis of (-)-(3*S*)-1-(3-aminopropyl)-3-methylazacyclodecane, the structure initially proposed for the marine alkaloid haliclorensin. However, the NMR and MS data of this compound differed considerably from the values given for haliclorensin.[69] The author proposed that the structure of the marine alkaloid haliclorensin was (*S*)-7-methyl-1,5-diazacyclotetradecane, and the initially assigned structure for haliclorensin was renamed isohaliclorensin (**3**).[70,71]

The strategy used for the synthesis of isohaliclorensin was quite similar to that of Banwell's synthesis, with the use of a ring-closing metathesis (RCM) reaction to generate the azacyclodecane ring system. A relevant aspect of the synthesis is the preparation of the enantiopure alcohol **36** in 5 steps from the (*R*)-Roche ester (**31**). Reduction of **32** with $LiAlH_4$ followed by *O*-tosylation, and treatment of the resulting tosylate with allylmagnesium bromide in the presence of CuI and subsequent hydrolysis afforded (2*S*)-2-methyl-5-hexenol (**36**).



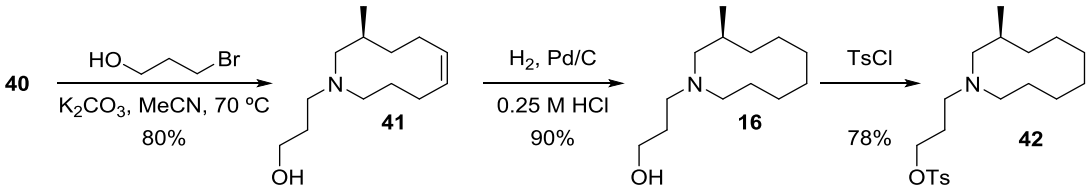
Scheme 3.6

Diene **38** was obtained by reaction of sulfonamide **37** with the enantiopure alcohol **36** under Mitsunobu conditions. Ring-closing metathesis of **38** followed by the removal of the nosyl group with PhSH[77] afforded the secondary cyclic amine **40**. The synthesis of isohaliclorensin (**3**) was completed by treatment of **40** with acrylonitrile in MeOH, subsequent hydrogenation over Raney-Ni in MeOH saturated with NH_3 and a final catalytic hydrogenation over Pd/C to remove the double bond.



Scheme 3.7

On the other hand, for the synthesis of halitulin (**1**), the tosylate moiety **42** was prepared in 3 steps from secondary amine **40**, by treatment with 3-bromo-1-propanol, followed by catalytic hydrogenation of **41** and subsequent tosylation of the saturated alcohol **16**.

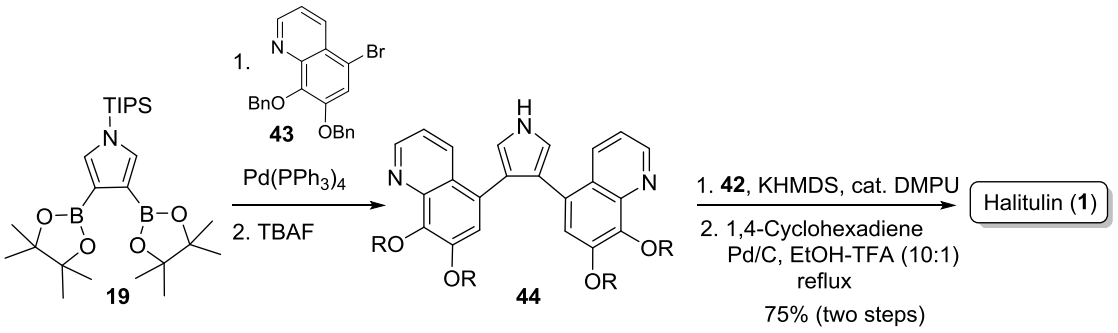


Scheme 3.8

The synthesis of the pyrrole subunit **44** was performed by Pd-catalyzed Suzuki-Miyaura coupling reaction of the pyrrole-3,4-diboronate **19** with the *O*,*O*-protected 5-bromoquinoline-7,8-diol **43**, following by treatment with TBAF. The synthesis of halitulin (**1**) was completed by alkylation of the potassium salt

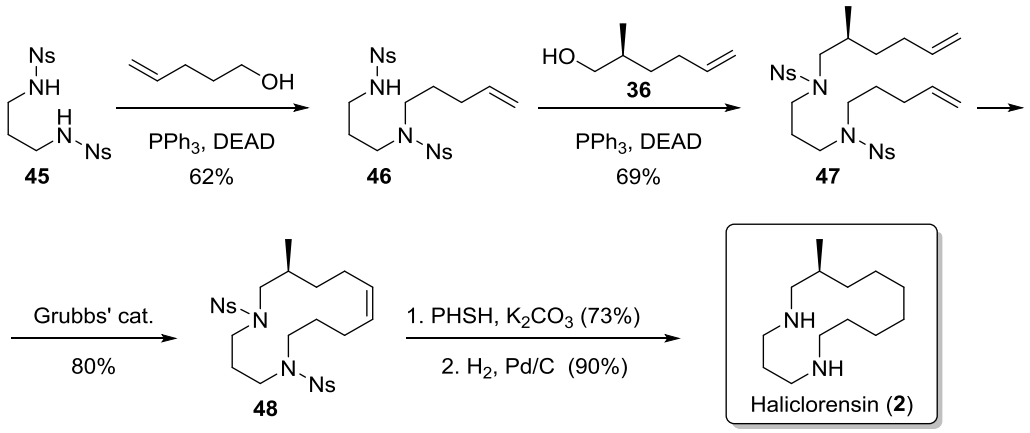
[77] Fukuyama, T.; Jow, C.-K.; Cheung, M. *Tetrahedron Lett*. **1995**, *36*, 6373-6374.

derived from **44** with tosylate **42**, followed by the removal of the benzyl groups by catalytic hydrogenation.



Scheme 3.9

Steglich and co-workers also reported[70] the synthesis of haliclorensin using the same intermediate (2*S*)-2-methyl-5-hexenol (**36)** used in the synthesis of isohaliclorensin, installing the C-7 stereogenic center. Successive couplings of bis-sulfonamide **45** under Mitsunobu conditions with 4-penten-1-ol and then with (2*S*)-2-methyl-5-hexenol **36** led to the protected diamine **47**. The formation of the 14-membered ring **48** was performed by ring closing metathesis of diene **47** using the Grubbs' catalyst. Finally, the total synthesis of haliclorensin (**2**) was accomplished by deprotection of the nosyl groups, followed by subsequent catalytic hydrogenation of the double bond.



Scheme 3.10

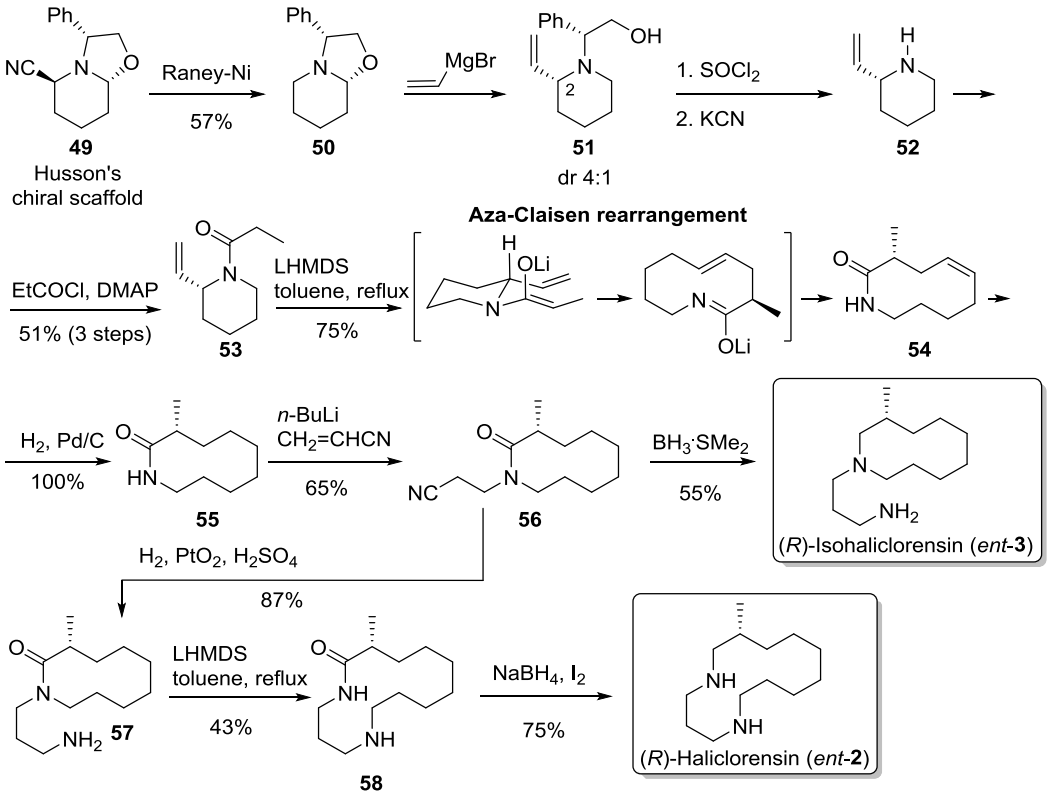
3.1.2.4. Huang's approach to isohaliclorensin and haliclorensin

Huang reported[72b] in 2004 an enantioselective synthesis of both isohaliclorensin and haliclorensin. Two relevant aspects of the synthesis are the use of ring-expansion reactions for the formation of the aza-macrocycle 10-membered ring system **54** of isohaliclorensin and the sequential ring-expansion reactions (aza-

Claisen rearrangement and Zip reaction) for the formation of the aza-macrocycle ring system **58** of haliclorensin.

Husson's chiral scaffold **49** was reduced to oxazolopiperidine **50** and then converted to the vinylated product **51** (dr 4:1). After removal of the phenylethanol moiety and acylation with propionyl chloride, the resulting (*R*)-*N*-propionyl-2-vinyl-piperidine **53** underwent a base-promoted aza-Claisen rearrangement, leading to the aza-10-membered ring system **54** in excellent yield. A subsequent catalytic hydrogenation gave azacyclodecanone **55**, which was converted to nitrile **56**. A final reduction of both the amide carbonyl and the cyano group with an excess of borane-dimethyl sulphide complex provided (*R*)-isohaliclorensin (*ent*-**3**).

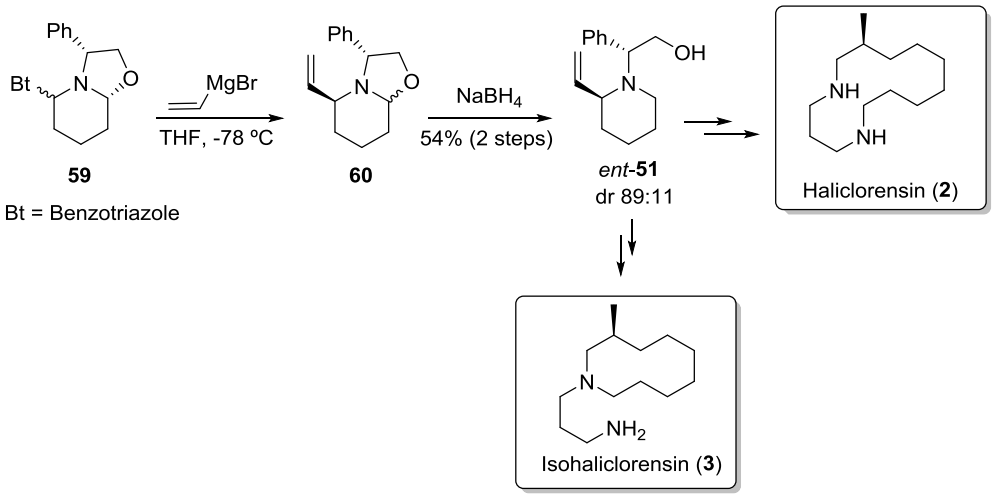
On the other hand, chemoselective reduction of the cyano group of **56** gave amino lactam **57**, which underwent a base-promoted ring-expansion to the 14-membered ring **58**. A final borane reduction completed the synthesis of (*R*)-haliclorensin (*ent*-**2**).



Scheme 3.11

Huang and co-workers also pursued the synthesis of the (*S*)-enantiomers of isohaliclorensin and haliclorensin. In this case, for the preparation of the enantiomer of **51** they started from Katritzky's chiral building block **59**. Thus, treatment of **59** with vinylmagnesium bromide followed by reduction of crude **60**

with $NaBH_4$ in EtOH provided alcohol *ent*-**51** as the major diastereoisomer, which was then converted to haliclorensin (**2**) and isohaliclorensin (**3**).



Scheme 3.12

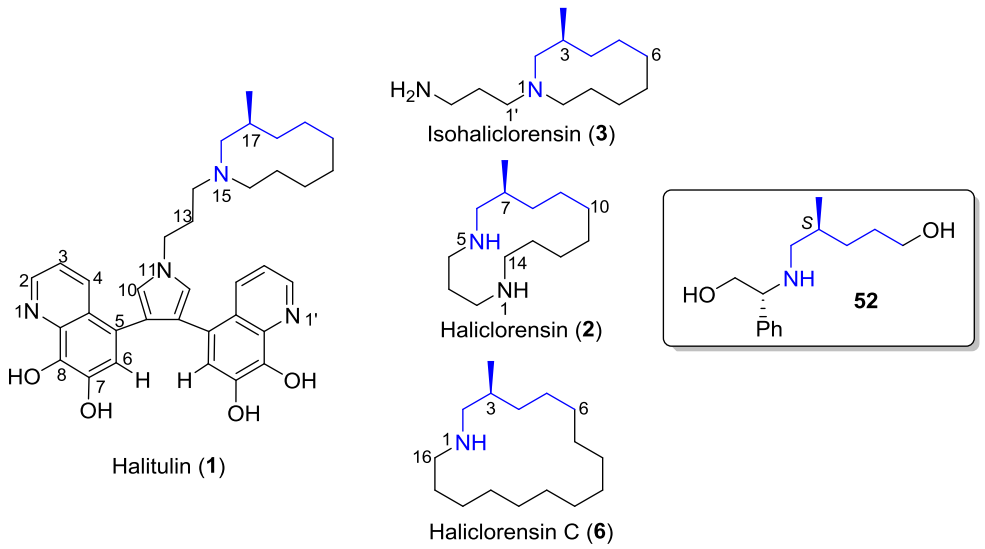
No total syntheses of isohalitulin, haliclorensin B and haliclorensin C had been described at the beginning of our studies.

3.1.3. Our studies in synthesis of *Haliclona* alkaloids

Taking into account that all *Haliclona* alkaloids possess the same substitution and stereochemical patterns (*S*-Me) at the β position to the nitrogen atom, we focused our attention on the total synthesis of haliclorensin and haliclorensin C, and the formal synthesis of halitulin and isohaliclorensin. The synthesis of these alkaloids was planned from the enantiopure amino alcohol **52**, previously described in Chapter 2, and would require the latter to be converted into appropriate long-chain secondary amino derivatives bearing two terminal alkene functionalities, which would allow the target azacyclic structures to be assembled using a ring-closing metathesis reaction as the key step.

Thus, the (*S*)-methyl-substituted amino diol **52** was envisaged as the precursor of the above four nitrogen-containing compounds.

For the sake of clarity, the carbon numbering used in this part of synthesis for the synthetic intermediates corresponds to that of the *Haliclona* alkaloid system.

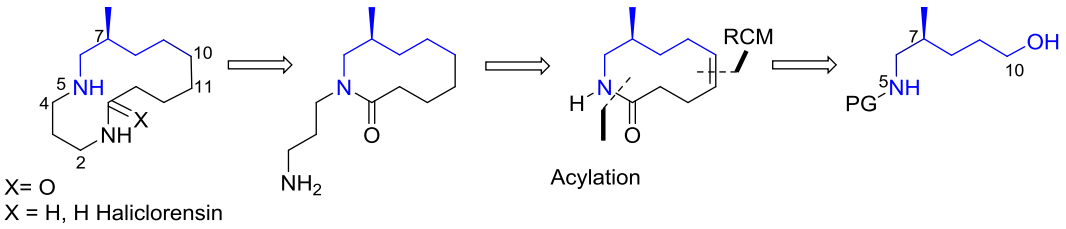


Scheme 3.13

3.1.4. Enantioselective total synthesis of (*S*)-haliclorensin

3.1.4.1. RCM-ring expansion approach

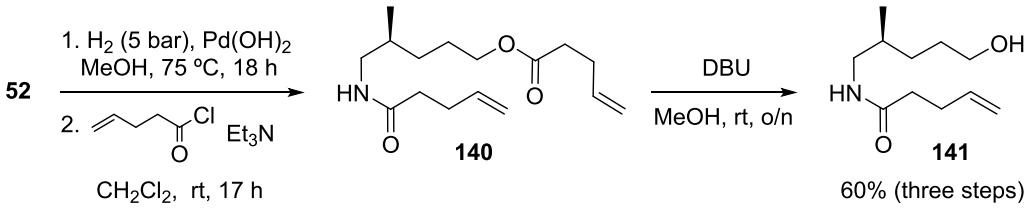
For the construction of the aza-macrocyle ring system of haliclorensin we envisioned the initial assembly of a 10-membered ring by a ring-closing metathesis reaction, and its subsequent expansion from an appropriate amino-lactam, as outlined in Scheme 3.14. It is described[72b] that the eight-membered lactam is the smallest which can be used for ring enlargement by three or four atoms.



Scheme 3.14

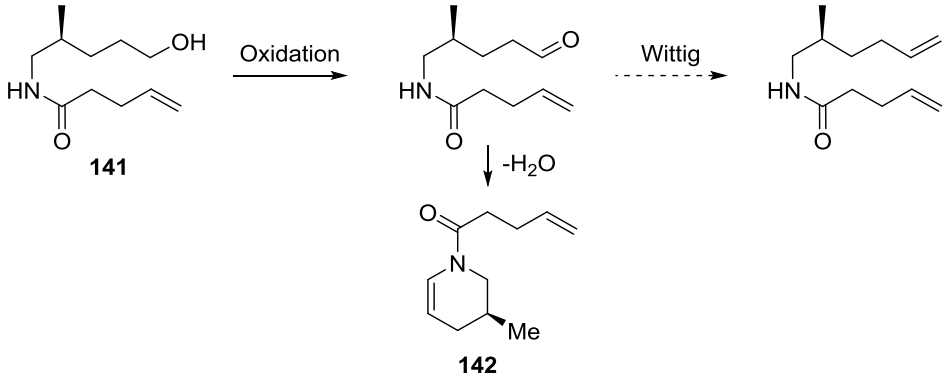
Hydrogenolysis of the phenylethanol moiety of amino diol **52**, followed by acylation of the resulting primary amine with 1 equivalent of 4-pentenoyl chloride in anhydrous dichloromethane gave a mixture of amide **141** and the diacylated product **140**. To prepare amide **141** we decided to use 3 equivalents of the acid chloride reagent to initially form the diacylated product **140**. A

subsequent selective hydrolysis of the ester function using DBU in methanol led to the target amide **141** in 60% yield over three steps.



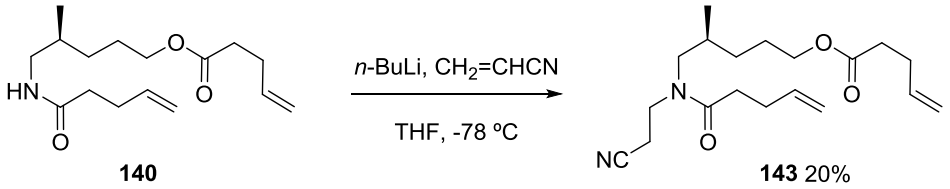
Scheme 3.15

Oxidation of alcohol **141** was carried out following different procedures (Dess-Martin reagent, IBX, Swern, PDC, Py·SO_3) but we never obtained the corresponding aldehyde. The cyclized derivative **142** was observed by NMR analysis instead.



Scheme 3.16

To avoid this undesirable cyclization we carried out the alkylation of the acylated amide **140** before performing the two-step oxidation/methylenation sequence. However, treatment of **140** with a solution of *n*-butyllithium in anhydrous THF at -78 ºC followed by alkylation of the resulting enolate with acrylonitrile led to the product **143** in only 20% yield in the best of cases.

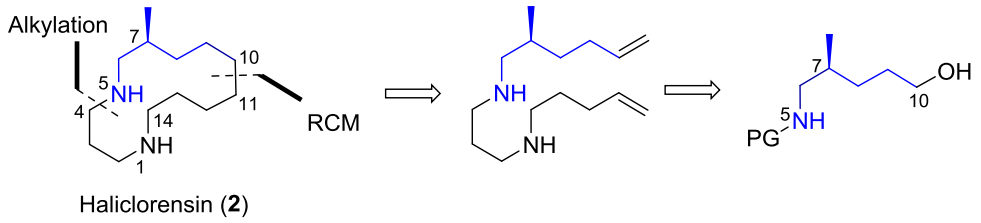


Scheme 3.17

These unsatisfying results led us to plan a new synthetic strategy.

3.1.4.2. *N*-Alkylation-RCM approach

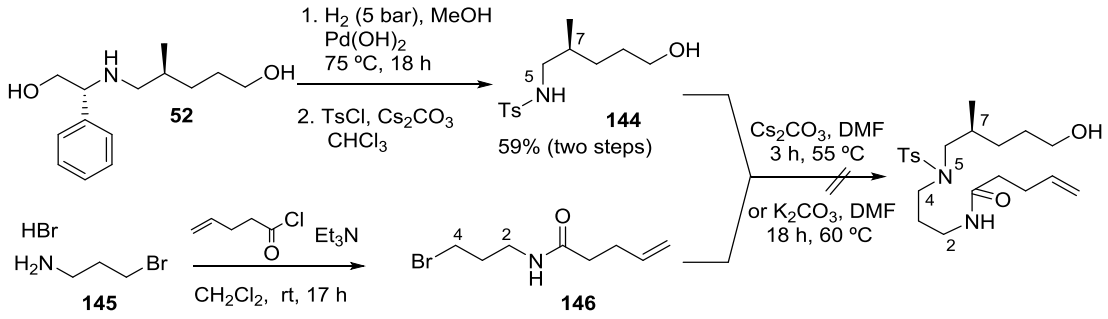
In this approach, *N*-alkylation of the starting aminoalcohol (bond formed N_5-C_4) and synthetic transformations followed by a final ring-closing metathesis reaction of the formed acyclic diene (bond formed C_{10}-C_{11}) would lead to the corresponding 14-membered diazacycle, as outlined in Scheme 3.18.



Scheme 3.18

3.1.4.3. *N*-alkylation (bond formed N_5-C_4)

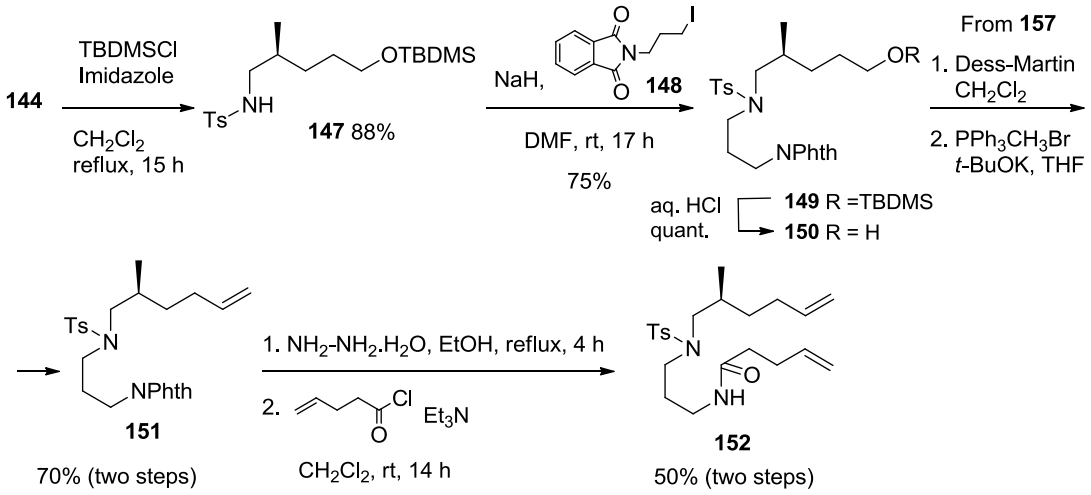
Amide **146** was prepared by treatment of 3-bromopropylamine hydrobromide **145** with 4-pentenoyl chloride, in a process previously described in the literature.[78] The conversion of enantiopure amino diol **52** into *N*-tosylamide **144** was performed in 59% yield by the two-step sequence outlined in Scheme 3.19. The formation of the N_5-C_4 bond of haliclorensin by alkylation of the tosylamide derivative **144** with *N*-(3-bromopropyl)amide **146** in anhydrous DMF, in presence of cesium carbonate or potassium carbonate was unsuccessful, and in all cases we recovered both starting materials.



Scheme 3.19

[78] (a) Reddy, D. N.; Prabhakaran, E. N. *J. Org. Chem.* **2011**, *76*, 680-683. (b) Clavé, G.; Bernardin, A.; Massonneau, M.; Renard, P.-Y.; Romieu, A. *Tetrahedron Lett.* **2006**, *47*, 6229-6233.

Satisfactorily, the formation of the N_5-C_4 bond was accomplished in 75% yield by alkylation of *N*-tosyl silyl derivative **147**, which was prepared by silylation of alcohol **144**, with iodide **148**.[79] The subsequent removal of the silyl protecting group gave alcohol **150** in 66% yield from secondary amine **144**. Then, alcohol **150** was converted to alkene **151** by a Dess-Martin oxidation/Wittig methylenation sequence in an excellent 70% yield. Hydrazinolysis of the phtalimido moiety of **151**, followed by acylation of the resulting primary amine with 4-pentenoyl chloride installed the two required terminal alkene functionalities, gaving **152** in 50% yield over two steps.

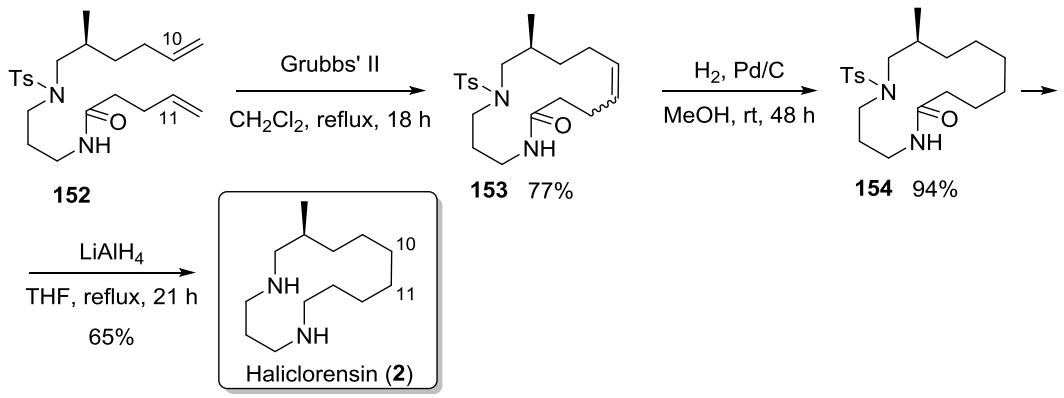


Scheme 3.20

3.1.4.4. Construction of the 14-membered macrocycle by a RCM reaction

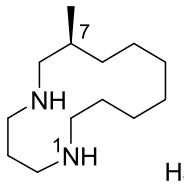
The formation of the C_{10}-C_{11} bond of the 14-membered diazacycle was performed by a ring-closing metathesis reaction. Enantiopure diene **152** was added into a solution of Grubb's II catalyst in refluxing anhydrous dichloromethane (0.2 mM), affording the target diazacyclotetradecane derivative **153** in excellent yield. The synthesis of haliclorensin (**2**) was completed by the two-step sequence outlined in Scheme 3.21. Catalytic hydrogenation of the carbon-carbon double bond of the diazacyclic structure **153** was performed in methanol using Pd/C (10%), affording **154** in high yield (94%). Subsequent treatment with $LiAlH_4$ in anhydrous THF brought about both the reductive removal of the tosyl group and the reduction of the lactam carbonyl, leading to the enantiopure haliclorensin.

[79] This iodide was quantitatively prepared by treatment of the corresponding bromide with sodium iodide: Majewski, M.; Ulaczyk-Lesanko, A.; Wang, F. *Can. J. Chem*. **2006**, *84*, 257-268.



Scheme 3.21

The ^{1}H-NMR spectroscopic data of our synthetic haliclorensin were coincident with those reported for natural product[69] and for previously synthesized haliclorensins.[70b,72b] In Table 3.1 the chemical shifts of ^{1}H NMR are compared with those described in the literature for the alkaloid haliclorensin.



Haliclorensin (**2**)

Reported in this work CD_3OD 400 MHz	Literature[69] DMSO 500 MHz	Literature[70b] CD_3OD 600 MHz,	Literature[72b] CD_3OD 500 MHz,
0.89 (d, 3H) *J* = 6.9 Hz	0.92 (d, 3H) *J* = 6.5 Hz	0.94 (d, 3H) *J* = 7.0 Hz	0.91 (d, 3H) *J* = 6.92 Hz
1.24-1.31 (m, 1H)	1.11 (m, 1H) 1.24 (m, 2H)	1.25-1.31 (m, 1H)	1.28-1.31 (m, 1H)
1.36-1.51 (m, 9H)	1.42 (m, 1H) 1.30-1.42 (m, 5H)	1.32-1.55 (m, 9H)	1.32-1.51 (m, 9H)
1.55-1.61 (m, 2H)	1.50 (m, 1H) 1.52 (m, 1H)	1.56-1.63 (m, 2H)	1.56-1.62 (m, 2H)
1.70-1.77 (m, 3H)	1.70 (m, 1H) 1.91 (m, 1H) 1.94 (m, 1H)	1.71-1.80 (m, 3H)	1.69-1.81 (m, 3H)
2.40 (dd, 1H) *J* = 11.8, 9.7 Hz	2.12 (quin, 1H) *J* = 7.0 Hz	2.42 (dd, 1H) *J* = 11.8, 9.7 Hz	2.45 (dd, 1H) *J* = 11.84, 9.69 Hz
2.55 (dd, 1H) *J* = 11.8, 3.8 Hz		2.57 (dd, 1H) *J* = 11.8, 3.8 Hz	2.57 (dd, 1H) *J* = 11.84, 3.69 Hz
2.58-2.63 (m, 1H)		2.64 (ddd, 1H) *J* = 11.1, 7.6, 3.5 Hz	2.70 (ddd, 1H) *J* = 11.45, 7.69, 4.00 Hz
2.64-2.68 (m, 2H)	2.67 (dd, 1H) *J* = 12.8, 6.9 Hz	2.66-2.70 (m, 2H)	2.72-2.76 (m, 2H)
2.71-2.73 (m, 2H)	2.84 (m, 1H)	2.72-2.75 (m, 2H)	2.77-2.86 (m, 2H)
2.82 (ddd, 1H) *J* =11.2, 6.8, 4.0 Hz	2.88 (m, 1H) 2.96 (m, 1H) 2.94 (m, 1H)	2.84 (ddd, 1H) *J* = 11.1, 7.0, 3.5 Hz	2.90 (ddd, 1H) *J* = 11.45, 7.08, 4.15 Hz
	3.03 (m, 2H) 3.09 (m, 1H)		

Table 3.1

The $[\alpha]^{22}_{D}$ value of our sample [-17.2 (*c* 0.5, MeOH)] was consistent with that of both the natural product[73] [-19 (*c* 0.57, MeOH)] and synthetic haliclorensins.[70b,72b]

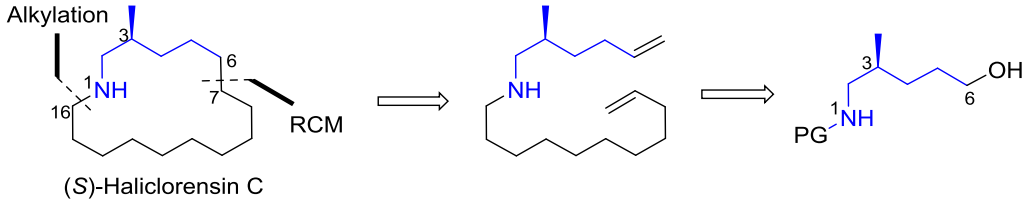
It should point, that the NMR spectra and specific rotation of haliclorensin are strongly pH dependent.[69,70b,73] In fact, a specific rotation of $[\alpha]^{22}_{D}$ – 2.2 (*c* 1.3, MeOH) was reported[69] in the first isolation of the alkaloid, from a sample whose NMR data indicate that it was at least partially protonated given that as the chemical shifts of the methylene groups adjacent to the nitrogen atoms are shifted (protons, downfield; carbons, upfield) with respect to the spectra of synthetic haliclorensin. An $[\alpha]_D$ value of – 8.5 has also been reported for the natural product, which, according to chiroptical measurements and GC-MS investigations, consisted of a 3:1 mixture of the (*S*)- and (*R*)-enantiomers.[70b]

3.1.5. Haliclorensin C. First total synthesis

3.1.5.1. Synthetic strategy

(*R*)-Phenylglycinol-derived amino diol **52** was also envisaged as a key intermediate for the synthesis of haliclorensin C.

We initially planned the introduction of the C_7-C_{16} linear-chain on the nitrogen of the aminoalcohol derived of **52**. Subsequent synthetic transformations and a ring-closing metathesis reaction from an appropriate long-chain secondary amino derivative bearing two terminal alkene functionalities would lead to the aza-macrocycle 16-membered ring system.

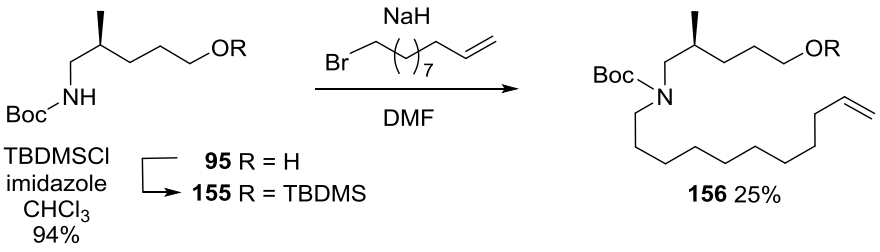


Scheme 3.22

3.1.5.1.1. Formation of the N_1-C_{16} bond by *N*-alkylation

(*S*)-3-Methyl-aminopentanol **95** was envisaged as the N_1-C_6 fragment of haliclorensin C. Treatment of alcohol **95** with *tert*-butyldimethylsilyl chloride in

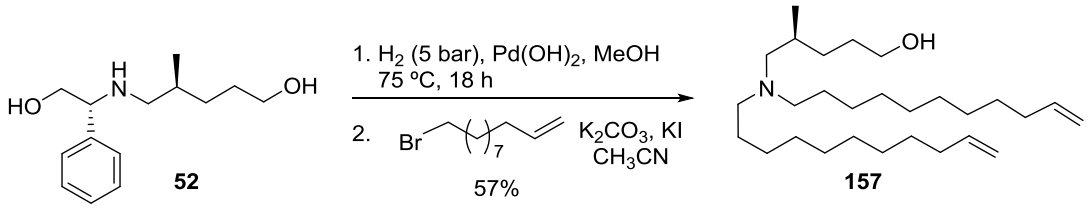
presence of imidazole in chloroform gave corresponding silyl derivative **155** in 94% yield. A subsequent alkylation[80] of the Boc-protected amine **155** with 10-undecenyl bromide and sodium hydride in anhydrous DMF afforded *N*-undecenyl amino derivative **156** in only 25% yield in the best of cases.



Scheme 3.23

Some examples[80c,d] are described in the literature about the monoalkylation of primary amines. For this reason, we decided to try the alkylation from the primary amine resulting from debenzylation of enantiopure amino diol **52**.

Treatment of **52** under hydrogenolysis conditions, followed by alkylation of the resulting primary amine with 1 equivalent of 10-undecenyl bromide in the presence of carbonate potassium in anhydrous acetonitrile led to the *N*,*N*-diundecenyl amino derivative **157** in 57% yield.



Scheme 3.24

Taking into account these unsatisfactory results and considering that we had an important batch of amino diol **14** (bearing an ethyl substituent at the β position of the amino group instead of methyl substituent our building block **52**), we

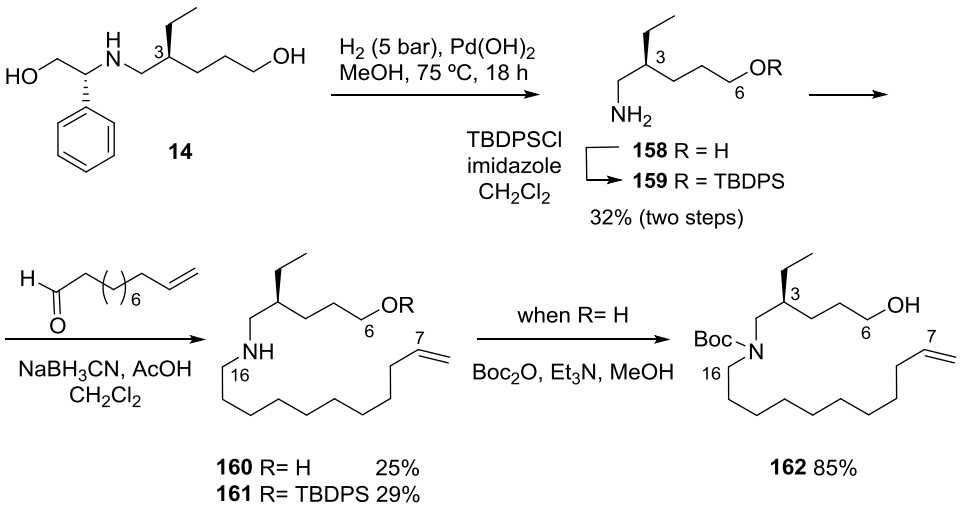
[80] (a) Liu, Y.; Maden, A.; Murray, W. V. *Tetrahedron* **2002**, *58*, 3159-3170. (b) Kan, T.; Fujiwara, A.; Kobayashi, H.; Fukuyama, T. *Tetrahedron* **2002**, *58*, 6267-6276. (c) Teodori, E.; Dei, S.; Garnier-Suillerot, A.; Gualtieri, F.; Manetti, D.; Martelli, C.; Romanelli, M. N.; Scapecchi, S.; Sudwan, P.; Salerno, M. *J. Med. Chem.* **2005**, *48*, 7426-7436. (d) Shieh, W.-C.; Chen, G.-P.; Xue, S.; McKenna, J.; Jiang, X.; Prasad, K.; Repic, O. *Org. Process Res. Dev*. **2007**, *11*, 711-715. (e) Molander, G. A.; Cadoret, F. *Tetrahedron Lett.* **2011**, *52*, 2199-2202. (f) Peng, L.; DeSouza, J.; Su, Z.; Novak, B. M.; Nevzorov, A. A.; Garland, E. R.; Melander, C. *Chem. Commun*. **2011**, *47*, 4896-4898.

decided to perform model studies for the total synthesis of haliclorensin C using this chiral building block.

3.1.5.1.2. Formation of the N_1-C_{16} bond by reductive amination

Hydrogenolysis of the phenylethanol moiety of amino diol **14**, followed by subsequent treatment of the resulting primary amine **158** with 10-undecenal, sodium cyanoborohydride, and acetic acid in anhydrous dichloromethane gave secondary amine **160** in only 25% yield. The alkylated product **160** was converted to the corresponding *N*-Boc derivative **162** in 85% yield.

The yield of the reductive amination was not improved (29% yield) starting form the silyl derivative **159**, which was prepared by silylation of **158** with *tert*-butyldiphenylsilyl chloride.

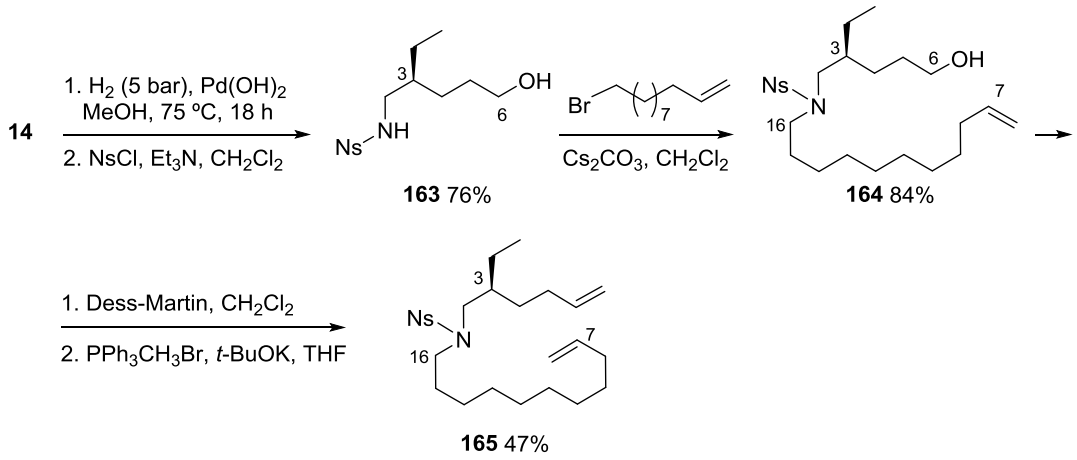


Scheme 3.25

As a consequence of low yields of the above sequence, we decided to explore another strategy.

3.1.5.1.3. Formation of the N_1-C_{16} bond by alkylation: Synthesis of dialkene 165

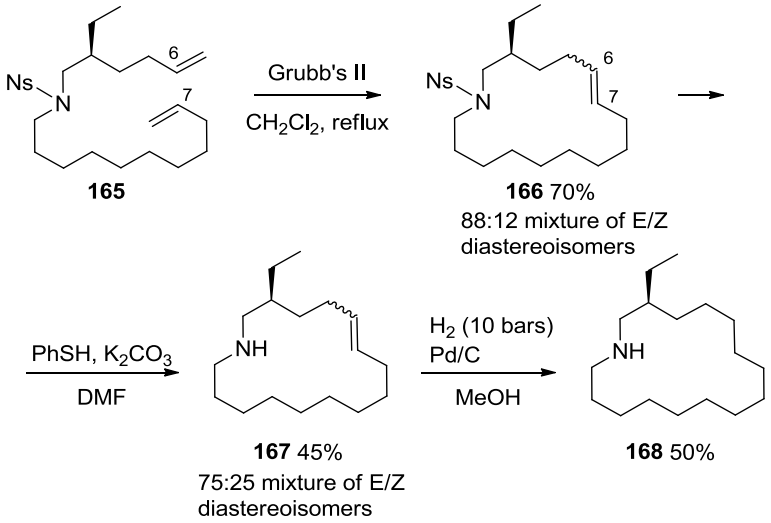
Alternatively, we decided to introduce the C_7-C_{16} fragment of haliclorensin C by alkylation of the amine **163** with 10-undecenyl bromide. Thus, reductive removal of the phenylethanol moiety of **14** and subsequent treatment with *o*-nitrobenzenesulfonyl chloride afforded the protected amine **163** in 76% yield. Alkylation of secondary amine **163** with 10-undecenyl bromide led to the *N*-protected secondary amine **164** in excellent yield (84%), which was converted to the *N*-hexenyl *N*-undecenyl amino derivative **165** by an oxidation/Wittig methylenation sequence. Oxidation of the alcohol function present in **164** using Dess-Martin reagent, followed by subsequent Wittig methylenation afforded the target diene **165** in 47% yield.



Scheme 3.26

3.1.5.1.4. Construction of the 16-membered macrocycle by a RCM: Synthesis of the ethyl analog of haliclorensin C

The formation of the C_6-C_7 bond of the 16-membered macrocycle **166** was performed by a ring closing metathesis reaction, by addition of diene **165** into a solution of Grubb's II catalyst in refluxing dichloromethane. The target azacyclic structure **166** was obtained in 70% yield as a 88:12 (calculated by GC-MS) mixture of *E*/*Z* diastereoisomers. When the cyclization was carried out under slow addition (0.08 ml/min) of diene **165**, the formation of dimers and oligomers was observed. Subsequent removal of the nosyl group of **166** with thiophenol and potassium carbonate in anhydrous dimethylformamide[77] afforded (*S*)-3-ethylazacyclo-6-hexadecene as a 75:25 (calculated by GC-MS) mixture of *E*/*Z* diastereoisomers **167** in 45% yield. Finally, catalytic hydrogenation using Pd/C (25%) led to (*S*)-3-ethylazacyclohexadecane **168** in 50% yield.



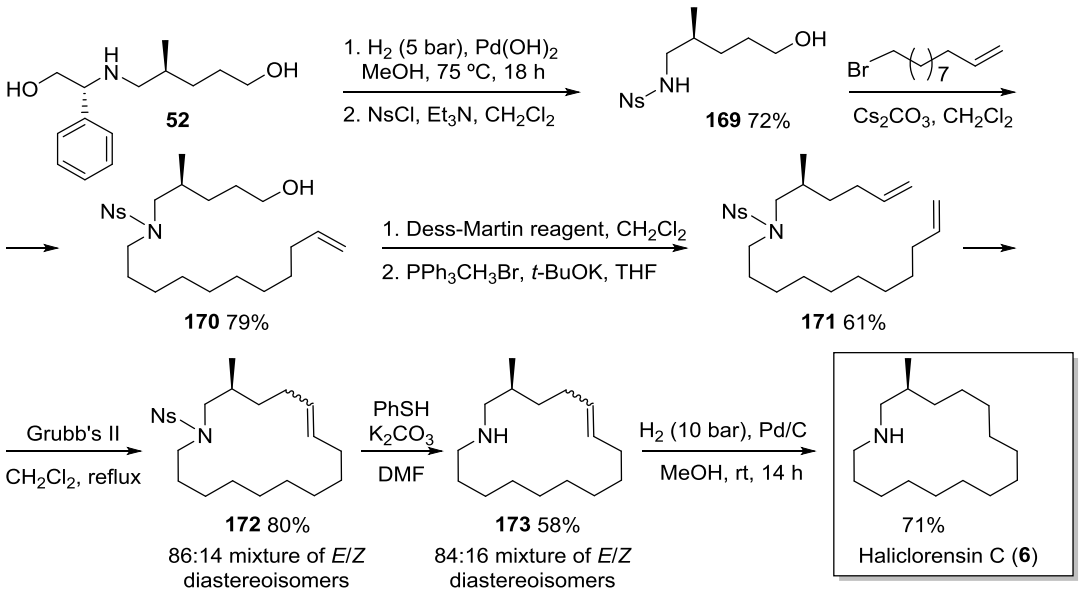
Scheme 3.27

The enantioselective synthesis of the ethyl analogue **168** of haliclorensin C was performed in 8 steps with an overall yield of 3% starting from enantiopure amino diol **14**.

3.1.6. First enantioselective total synthesis of (*S*)-haliclorensin C

The optimized synthetic procedure used for the synthesis of the ethyl analog of haliclorensin C **168** was applied to the synthesis of the alkaloid, starting from the enantiopure amino diol **52**, which bears the required (*S*)-methyl substituent.

Alcohol 52 was converted to *N*-*o*-nitrobenzenesulfonyl protected amine **169** in 72% yield. A subsequent alkylation of **169** with 10-undecenyl bromide afforded **170** in 79% yield. The conversion of alcohol **170** into *N*-hexenyl *N*-undecenyl amino derivative **171** was performed in 61% yield by a Dess-Martin oxidation/Wittig methylenation sequence. The 16-membered azacyclic structure **172** was synthesized in 80% yield by treatment of diene **171** with Grubb's II catalyst in refluxing dichloromethane (0.2 mM), affording a 86:14 mixture of *E*/*Z* diastereoisomers (calculated by GC-MS). Removal of *o*-nitrobenzenesulfonyl protecting group afforded in 58% yield secondary amine **173** as a 84:16 mixture (calculated by GC-MS) of *E*/*Z* diastereoisomers, which was hydrogenated to the target haliclorensin C (**6**).

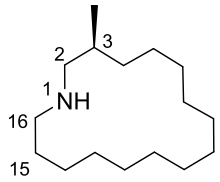


Scheme 3.28

The total synthesis of haliclorensin C (**6**) was performed in 8 steps with an overall yield of 11% starting from the enantiopure aminodiol **52**.

Although the ^{1}H and ^{13}C NMR data of our synthetic haliclorensin C did not coincide with those reported for the natural product,[73] the NMR spectra of the hydrochloride of our synthetic material matched the spectra reported for haliclorensin C. Unfortunaltely, haliclorensin C had been isolated[73] only in minute amounts (2 mg) and the ^{1}H and ^{13}C-NMR spectra included in the paper show considerable contamination. For this reason, the absolute configuration of haliclorensin C, tentatively proposed as *S*,[73] as determined for halitulin and haliclorensin, cannot be confirmed since the specific rotation of our synthetic material {$[\alpha]^{22}_{D}$ – 6.04 (c 0.85, MeOH)} was different from that reported[73] for the impure sample of the natural product {$[\alpha]^{22}_{D}$ + 53 (c 0.15, MeOH)}.

In the following Tables the chemical shift values observed in our ^{1}H NMR (Table 3.2) and ^{13}C NMR (Table 3.3) are compared with those described in the literature for natural haliclorensin C.



Haliclorensin C (**6**)

	Reported in this Thesis for haliclorensin C (4:1 $CDCl_3$-CD_3OD) 500 MHz	Reported in this Thesis for the hydrochloride (4:1 $CDCl_3$-CD_3OD) 400 MHz	Literature[73] (4:1 $CDCl_3$-CD_3OD) 500 MHz
CH_3	0.73 (d, *J* = 6.8 Hz, 3H)	1.06 (d, *J* = 6.8 Hz, 3H)	
H-4	1.08-1.22 (m, 1H)		
CH_2		1.26-1.40 (m, 22H)	
H-15	1.30-1.41 (m, 20H)	1.75 (m, 2H)	1.72 (m, 2H)
H-4, CH_2	1.42-1.56 (m, 3H)		
H-3	1.60-1.63 (m, 1H)	1.89 (m, 1H)	1.85 (m, 1H)
H-2	2.30 (dd, *J* = 11.8, 7.0 Hz, 1H) 2.36 (dd, *J* = 11.8, 5.2 Hz, 1H)	2.78-2.84 (m, 2H)	2.75 (m, 1H) 2.85 (m, 1H)
H-16	2.48-2.54 (m, 1H) 2.64-2.70 (m, 1H)	2.89-2.99 (m, 2H)	2.94 (m, 2H)

Table 3.2

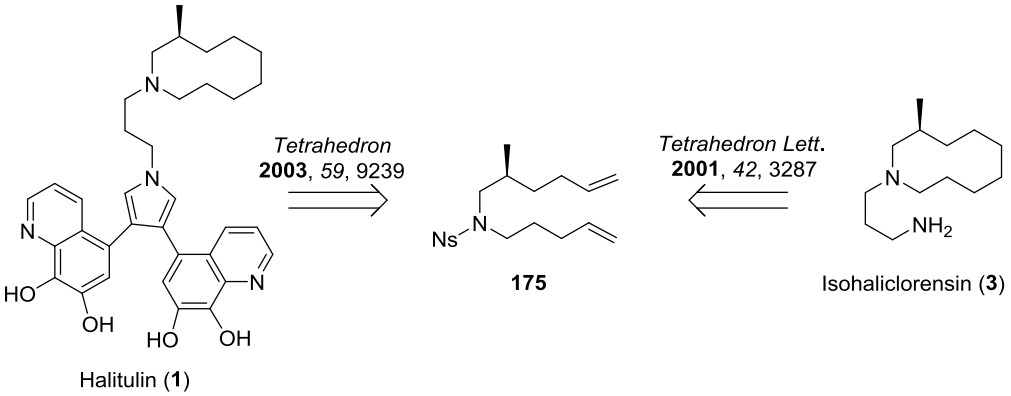
	Reported in this Thesis (4:1 $CDCl_3$-CD_3OD) 500 MHz	Reported in this Thesis for the hydrochloride (4:1 $CDCl_3$-CD_3OD) 400 MHz	Literature[73] (4:1 $CDCl_3$-CD_3OD) 500 MHz
CH_3	18.2	17.9	17.6
C-15	24.2	23.7	23.4
CH_2	24.9	24.7	10 peaks between δ 24.5 and 25.5
CH_2	26.0	24.9	
CH_2	26.1	26.2	
CH_2	26.1	26.3	
CH_2	26.2	26.4	
CH_2	26.3	26.5	
CH_2	26.4	26.6	
CH_2	26.5	26.7	
CH_2	27.0	26.8	
CH_2	27.0	27.1	
C-3	30.7	28.7	28.8
C-4	32.4	32.6	32.3
C-16	47.0	45.6	45.1
C-2	53.8	50.9	50.5

Table 3.3

3.1.7. Formal syntheses of halitulin and isohaliclorensin

Both the *Haliclona* alkaloid halitulin (**1**) and 1-(3-aminopropyl)-3-methylazacyclodecane (**3**) (also named isohaliclorensin; the structure initially

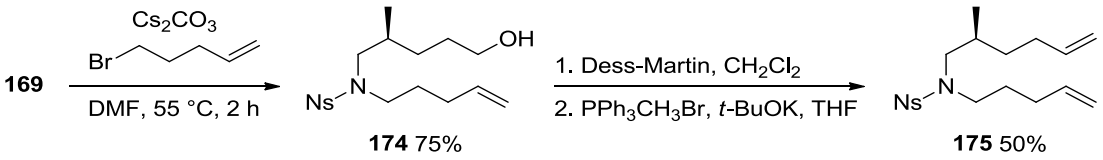
proposed for the marine alkaloid haliclorensin) have been synthesized from the enantiopur *N*-hexenyl *N*-pentenyl amino derivative **175**.[70a,72a] A ring-closing metathesis reaction was used for the construction of the azacyclodecane ring.



Scheme 3.29

We planned the synthesis of diene **175** starting from the enantiopure protected aminopentanol **169**, previously employed in the synthesis of haliclorensin C (**6**).

Alkylation of the protected amine **169** with 4-pentenyl bromide and cesium carbonate afforded amino alcohol **174** in excellent yield (75%). A subsequent oxidation of **174** under Dess-Martin conditions, followed by Wittig methylenation of the resulting aldehyde led to the target *N*-hexenyl *N*-pentenyl amino derivative **175** in 50% overall yield for the two steps.



Scheme 3.30

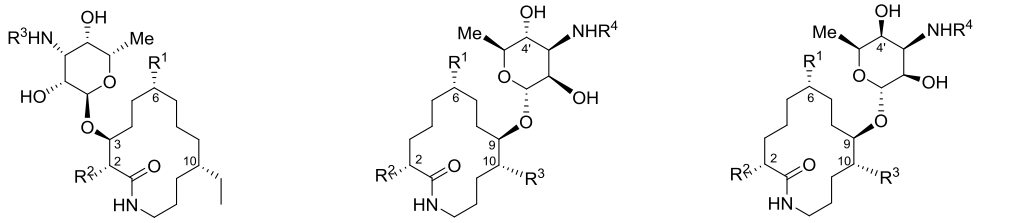
In summary, enantiopure 4-methyl-5-aminopentanol **52** has been demonstrated to be a useful starting building block in the enantioselective synthesis of the *Haliclona* alkaloids halicloresin C (first enantioselective total synthesis), haliclorensin and halitulin (formal), and also of the non-natural product isohaliclorensin (formal).

3.2. Fluvirucins and their aglycons, the fluvirucinins

This introduction gives an overview of fluvirucins, covering isolation, biological activities, biosynthesis, and total synthesis. The synthesis of fluvirucins and their aglycons, the fluvirucinins, is presented, paying special attention to the synthetic strategy and the stereochemical aspects. In order to facilitate the reading of this part, the numbering of compounds is independent to the rest of the memory.

3.2.1. Introduction

Fluvirucins are a family of naturally occurring glycosides structurally characterized by the presence of an amino sugar attached at the C-3 or C-9 position of a 14-membered macrocycle lactam aglycon. They also incorporate a methyl or ethyl substituent at C-2 (1*S*-hydroxyethyl in fluvirucin A_2), C-6 (absent in some members), and C-10 of the core lactam nucleus. The amino sugar moiety can be 3-amino-3,6-dideoxy-α-L-talopyranose, *e.g*. in fluvirucins A_1 and B_1, or its 4-epimer (L-mycosamine), *e.g*. in fluvirucin B_2, or an *N*-substituted derivative of either. The amino sugar moiety can be 3-amino-3,6-dideoxy-α-L-talopyranose, *e.g*. in fluvirucins A_1 and B_1, or its 4-epimer (L-mycosamine), *e.g*. in fluvirucin B_2, or an *N*-substituted derivative of either.



	R^1	R^2	R^3
Fluvirucin A_1	Me	Me	H
Fluvirucin A_2	Me	(*S*)CHOHMe	H
6-Desmethyl-*N*-methyl-fluvirucin A_1	H	Me	Me
N-Methylfluvirucin A_1	Me	Me	Me

	R^1	R^2	R^3	R^4
Sch 38511	Me	Me	Me	H
Sch 38512	Me	Et	Me	H
	H	Et	Et	H
Sch 38513	Me	Et	Et	H
Fluvirucin B_2 (Sch 38518)	Et	Et	Et	H
Fluvirucin B_4	Et	Et	Et	$CONH(CH_2)_2Ph$

4'-epi-Sch 38511[a]	
4'-epi-Sch 38512[a]	
Fluvirucin B_0	
Fluvirucin B_1 (Sch 38516)	
Fluvirucin B_3 (Sch 39185)	
Fluvirucin B_5	

[a] Tentatively assigned

Scheme 3.31

3.2.2. Isolation, biological activity, and biosynthesis

The first member of this family (Sch 38516) was reported in 1990 by scientists at Schering-Plough, who obtained it by extraction from the fermentation broth of

the actinomycete *Actinomadura vulgaris*.[81] Its structure was established by X-ray crystallographic analysis. In the following years, the same group reported the isolation of seven other glycosides (Sch 38511-38513, Sch 38518, and their C-4' epimers) produced by various species of *Actinomadura*.[82,83] (Scheme 3.31). All these compounds were found to exhibit antifungal activity against various strains of *Candida sp*. and dermatophytes.

Almost simultaneously, scientists at Bristol-Myers Squibb described seven macrolactam glycosides, named fluvirucins A_1, A_2, and B_1-B_5, from several actinomycete strains. These fluvirucins possess inhibitory activity against the influenza A virus, [84] which is partially retained in the corresponding fluvirucinins.[85b] Fluvirucin B_2 also acts as an inhibitor of phosphatidylinositol-specific phospholipase C. [85] The structures of some of these fluvirucins coincided with those previously reported by the Schering-Plough researchers.
More recently, researchers at Merck reported the isolation of fluvirucin B_0[86] and two new *N*-methyl derivatives of fluvirucin A_1 [87] from the actinomycete *Nonomuraea turkmerniaca*, all of which show anthelmintic activity.

By ^{13}C feeding experiments it was demonstrated that the aglycon moiety of fluvirucins is biosynthesized from acetate and propionate via a combination of polyketide and tricarboxylic acid mechanisms.[17b, 88] In this context, the identification and characterization of the putative polyketide synthase genes associated with fluvirucin B_1 aglycon biosynthesis in *Actinomadura vulgaris* has recently been reported.[89]

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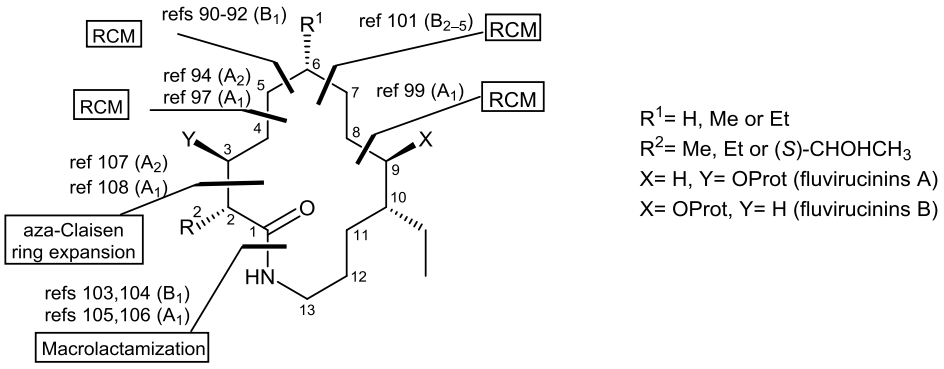
[81] Hegde V. R.; Patel, M. G.; Gullo, V. P.; Ganguly, A. K.; Sarre, O.; Puar, M. S.; McPhail, A. T. *J. Am. Chem. Soc.* **1990**, *112*, 6403-6405.
[82] (a) Hegde, V. R.; Patel, M. G.; Gullo, V. P.; Puar, M. S. *J. Chem. Soc., Chem. Commun*. **1991**, 810-812. (b) Hegde, V.; Patel, M.; Horan, A.; Gullo, V.; Marquez, J.; Gunnarsson, I.; Gentile, F.; Loebenberg, D.; King, A.; Puar, M.; Pramanik, B. *J. Antibiot.* **1992**, *45*, 624-632. (c) Cooper, R.; Truumees, I.; Yarborough, R.; Loebenberg, D.; Marquez, J.; Horan, A.; Patel, M.; Gullo, V.; Puar, M.; Pramanik, B. *J. Antibiot.* **1992**, *45*, 633-638.
[83] A macrolactam disaccharide (Sch 42729; α-D-Glc*p*-(1→2)-α-L-mycosamine)[83a] and a macrolactam trisaccharide (Sch 42282; β-D-Glc*p*-(1→4)-α-D-Glc*p*-(1→2)-α-L-mycosamine)[83b] bearing the same aglycon as Sch 38518 were also isolated: (a) Hegde, V. R.; Patel, M. G.; Gullo, V. P.; Horan, A. C.; King, A. H.; Gentile, F.; Wagman, G. H.; Puar, M. S.; Loebenberg, D. *J. Antibiot.* **1993**, *46*, 1109-1115. (b) Hegde, V. R.; Patel, M. G.; Horan, A. C.; King, A. H.; Gentile, F.; Puar, M. S.; Loebenberg, D. *J. Antibiot.* **1998**, *51*, 464-470.
[84] (a) Naruse, N.; Tenmyo, O.; Kawano, K.; Tomita, K.; Ohgusa, N.; Miyaki, T.; Konishi M.; Oki, T. *J. Antibiot.* **1991**, *44*, 733-740. (b) Naruse, N.; Tsuno, T.; Sawqada, Y.; Konishi, M.; Oki, T. *J. Antibiot.* **1991**, *44*, 741-755. (c) Naruse, N.; Konishi, M.; Oki, T.; Inouye, Y.; Kakisawa, H. *J. Antibiot.* **1991**, *44*, 756-761.
[85] Ui, H.; Imoto, M.; Umezawa, K. *J. Antibiot.* **1995**, *48*, 387-390.
[86] Ayers, S.; Zink, D. L.; Powell, J. S.; Brown, C. M.; Grund, A.; Genilloud, O.; Salazar, O.; Thompson, D.; Singh, S. B. *J. Antibiot.* **2008**, *61*, 59-62.
[87] Ayers, S.; Zink, D. L.; Mohn, K.; Powell, J. S.; Brown, C. M.; Murphy, T.; Grund, A.; Genilloud, O.; Salazar, O.; Thompson, D.; Singh, S. B. *J. Nat. Prod*. **2007**, *70*, 1371-1373.
[88] Puar, M. S.; Gullo, V.; Gunnarsson, I.; Hegde, V.; Patel, M.; Schwartz, J. *Bioorg. Med. Chem. Lett.* **1992**, *2*, 575-578.
[89] Lin, T.-Y.; Borketey, L. S.; Prasad, G.; Waters, S. A.; Schnarr, N. A. ACS *Synth. Biol.* **2013**, *21,* 635-642.

3.2.3 Synthetic approaches

The synthesis of fluvirucins has been little explored. In fact, only one total enantioselective synthesis of a member of this group, fluvirucin B_1, has been reported to date. In contrast, fluvirucinins have received considerable attention from the synthetic standpoint, which has resulted in enantioselective syntheses of fluvirucinins A_1, A_2, B_0, B_1, and $B_{2\text{-}5}$, the latter being the aglycon common to fluvirucins B_2, B_3, B_4, and B_5. Two key points in the synthesis of fluvirucins and fluvirucinins are the closure of a 14-membered lactam ring and the control of the configuration of its stereocenters.

As outlined in Figure 3.2, three main strategies have been used for the construction of the macrocyclic ring: a) an olefin ring-closing metathesis reaction (bond formed C_4-C_5, C_5-C_6, C_6-C_7 or C_8-C_9); b) a macrolactamization (bond formed N-C_1); and c) an amide-enolate-induced ring expansion via aza-Claisen rearrangement of a ten-membered 1-acyl-2-alkoxyvinyl-azacycle (bond formed C_2-C_3). For the sake of clarity, the carbon numbering used in this part for the synthetic intermediates corresponds to that of the fluvirucinin system. In addition, to facilitate its visualization, the fluvirucinin ring skeleton has been drawn with the same orientation throughout the introduction of fluvirucins and fluvirucinins, both in the A and B series.



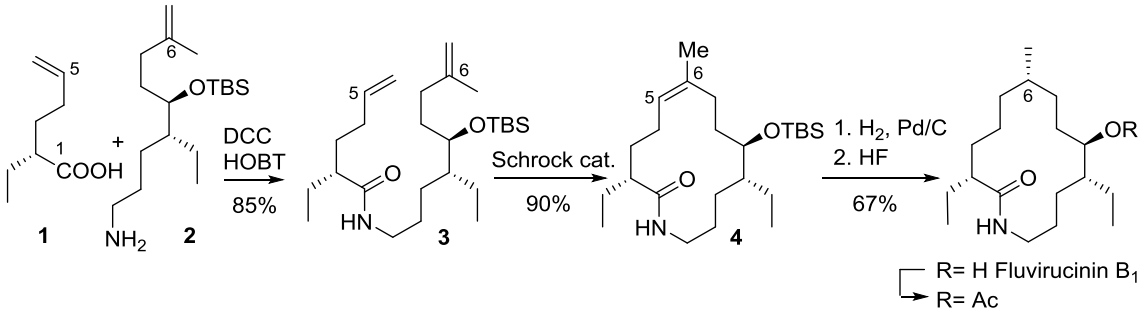
Scheme 3.32

For the sake of clarity, the carbon numbering for the synthetic intermediates corresponds to that of the fluvirucinin system. In addition, to facilitate the visualization, the fluvirucinin ring skeleton has been drawn with the same orientation throughout the chapter, both in the A and B series.

3.2.4. Closure of the 14-membered ring by RCM

3.2.4.1. Hoveyda's approach to fluvirucinin B_1 and fluvirucin B_1

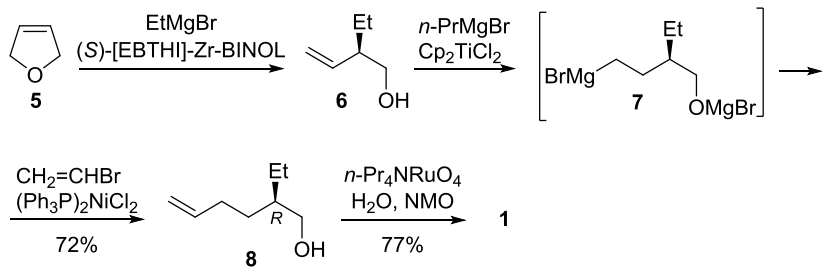
The first synthesis of a fluvirucinin was reported by Hoveyda in 1995.[90] Two relevant aspects of the synthesis are the use of a ring-closing metathesis (RCM) reaction to promote a stereoselective macrocyclization from a conformationally mobile acyclic diene and the use of macrocyclic stereocontrol to establish the remote stereochemistry at C-6 by catalytic hydrogenation. Thus, closure of the 14-membered ring was efficiently accomplished (bond formed C_5-C_6) under smooth conditions, using the Schrock Mo catalyst, from amido diene **3**, which was convergently prepared by coupling of acid **1** with amine **2** (Scheme 3.33). Catalytic hydrogenation of the resulting trisubstituted *Z* olefin **4** stereoselectively installed the C-6 stereogenic center to afford, after deprotection, fluvirucinin B_1, which was converted to the corresponding acetate.[90,91]



Scheme 3.33

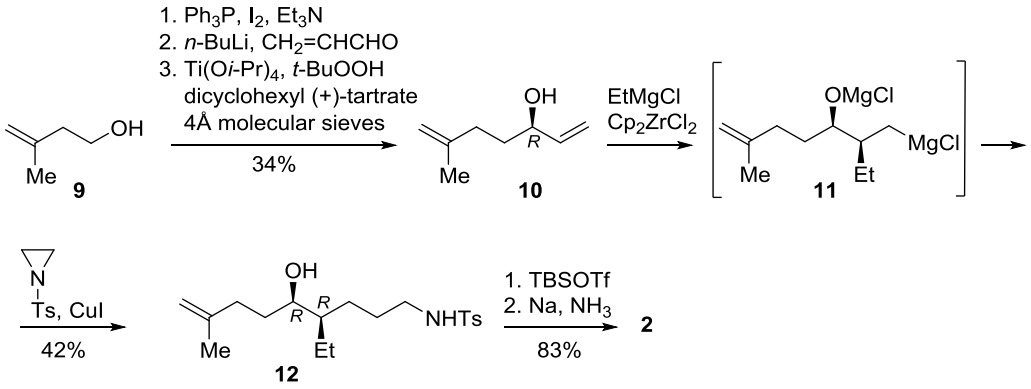
The required starting materials **1** and **2** (C_1-C_5 and C_6-N fragments, respectively, of fluvirucinin B_1), which incorporate the C-2, C-9, and C-10 stereogenic centers of fluvirucinin B_1, were prepared as outlined in Schemes 3.34 and 3.35.[90,91] Acid **1**, with the required *R* configuration, was prepared from dihydrofuran **5** via a sequence of three metal-catalyzed steps. An enantioselective Zr-catalyzed ethylmagnesation of **5** gave homoallylic alcohol **6**, which was subjected to a tandem Ti- and Ni-catalyzed hydrovinylation by hydromagnesation of the olefin, followed by an *in situ* cross-coupling reaction of the resulting Grignard reagent **7** with vinyl bromide. A Ru-catalyzed oxidation of the resulting alcohol **8** completed the synthesis of acid **1.**

[90] Houri, A. F.; Xu, Z.; Cogan, D. A.; Hoveyda, A. H. *J. Am. Chem. Soc*. **1995**, *117,* 2943-2944.
[91] Xu, Z.; Johannes, C. W.; Houri, A. F.; La, D. S.; Cogan, D. A.; Hofilena, G. E.; Hoveyda, A. H. *J. Am. Chem. Soc*. **1997**, *119,* 10302-10316.



Scheme 3.34

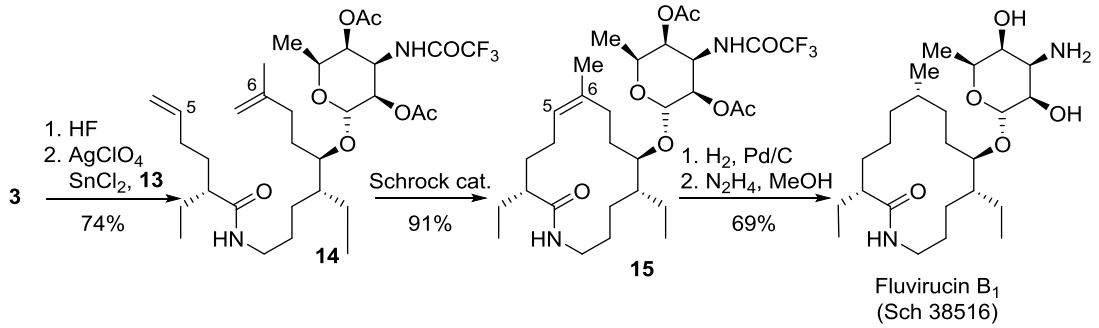
In turn, homoallylic alcohol **9** was converted to enantiopure allylic alcohol **10** (>99% ee) via kinetic Sharpless resolution of the corresponding racemate. A subsequent one-pot double alkylation of the monosubstituted olefin moiety of **10**, involving a diastereoselective Zr-catalyzed ethylmagnesation, and *in situ* trapping of the resulting alkylmagnesium halide intermediate **11** with tosyl aziridine, afforded **12** (97:3 dr). Final protection-deprotection steps led to amine **2** in 12% overall yield for the six-step procedure.



Scheme 3.35

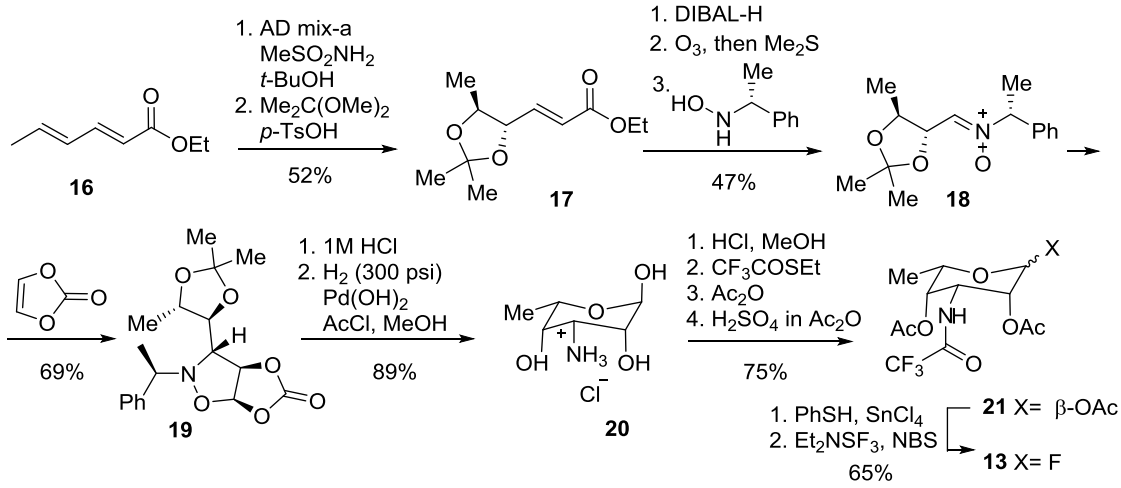
The same strategy was employed for the synthesis of fluvirucin B_1 (Sch 38516), which incorporates a novel carbohydrate moiety identified for the first time as part of a natural product. However, all attempts to glycosylate the deprotected alcohol derived from **4** with a variety of carbohydrate derivatives failed, probably due to the low solubility of the macrocyclic alcohol in organic solvents. This problem was circumvented using the more readily soluble alcohol resulting from deprotection of acyclic diene **3**, which underwent a stereoselective glycosylation with fluoroglycoside **13** to give **14** in excellent yield (Scheme 3.36). A subsequent RCM, followed by stereoselective hydrogenation of the resulting *Z*-unsaturated macrolactam **15** and deprotection of the sugar moiety, afforded fluvirucin B_1 (Sch 38516).[91,92] This synthesis was the first and, to date the only, synthesis of a member of the fluvirucin family.

[92] Xu, Z.; Johannes, C. W.; Salman, S. S.; Hoveyda, A. H. *J. Am. Chem. Soc*. **1996**, *118*, 10926-10927.



Scheme 3.36

The carbohydrate fragment (**20**) of fluvirucin B_1 was prepared from ethyl sorbate (**16**) as illustrated in Scheme 3.37. Key steps of the synthesis are a catalytic Sharpless asymmetric (80% ee) dihydroxylation of **16**, which ensured the optical purity, a diastereoselective dipolar [3+2] cycloaddition between (*R*)-α-methylbenzylamine-derived nitrone **18** and vinylene carbonate, and the removal of the protecting groups from the resulting cycloaddition product **19** by controlled acid hydrolysis and hydrogenolysis. The stereochemical identity of **20** was established through conversion to the corresponding *O*,*O*,*N*-triacetyl methyl glycoside, which proved identical to the material obtained from degradation of natural fluvirucin B_1. To perform the crucial glycosylation reaction, **20** was protected as an *O*,*O*-diacetyl-*N*-trifluoroacetyl derivative and then activated as a fluoroglycoside (**13**) via acetoxyglycoside **21** and a thioglycoside.[91-93]

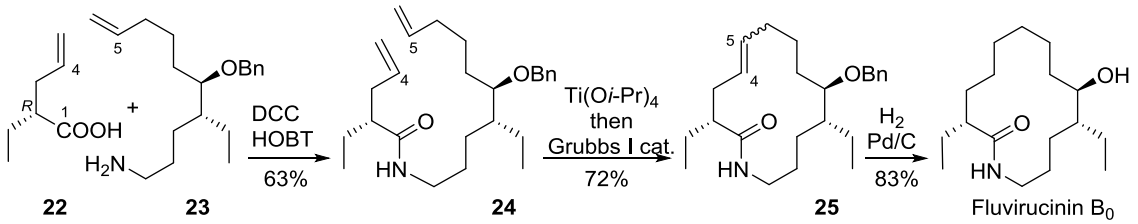


Scheme 3.37

[93] Xu, Z.; Johannes, C. W.; La, D. S.; Hofilena, G. E.; Hoveyda, A. H. *Tetrahedron* **1997**, *53*, 16377-16390.

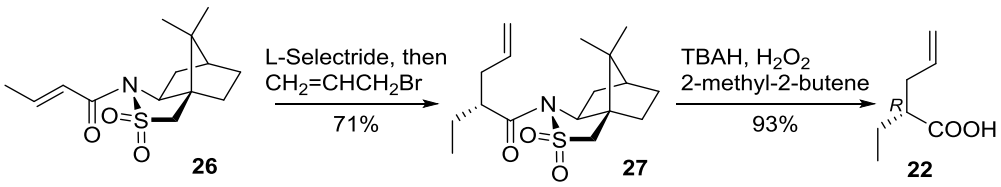
3.2.4.2. Bracher's approach to fluvirucinin B_0

In 2001, Bracher reported[94] the enantioselective synthesis of 6-nor-fluvirucinin B_1 before it was known that this nor derivative was the aglycon of fluvirucin B_0. The closure of the macrolactam ring was also effected by an RCM reaction, although, in this case, involving the formation of the C_4-C_5 bond.
The required amido diene **24**, which incorporates the three stereocenters of fluvirucinin B_0, was synthesized by coupling of acid **22** with amine **23** (C_1-C_4 and C_5-N fragments of fluvirucinin B_0). The RCM of **24** was satisfactorily performed with Grubbs catalyst, in the presence of Ti(O*i*-Pr)$_4$ to avoid the formation of an unproductive Ru-chelate with the γ,δ-unsaturated amide. A subsequent catalytic hydrogenation of the resulting diene **25** led to fluvirucinin B_0 (Scheme 3.38).



Scheme 3.38

Enantiopure acid **22** was prepared in two steps from Oppolzer's *N*-crotyl-(+)-camphorsultam **26**,[95] by conjugate hydride addition followed by trapping of the resulting enolate with allyl bromide and subsequent hydrolysis of *N*-acylsultam **27** (Scheme 3.39).

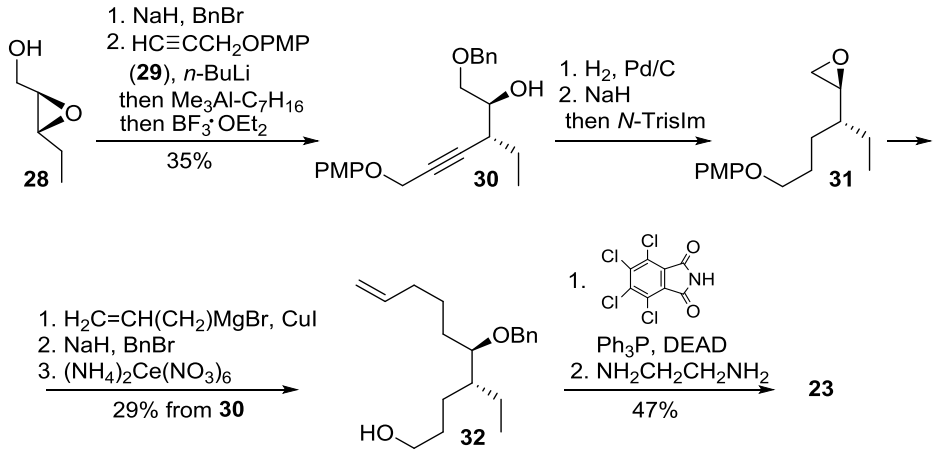


Scheme 3.39

In turn, amine **23** was obtained from epoxy alcohol **28**, which was accessible by Sharpless oxidation of the corresponding (*E*)-pentenol.[96] After protection of the hydroxy group, a regio- and stereoselective ring opening reaction with an

[94] Baltrusch, A. W.; Bracher, F. *Synlett* **2002**, 1724-1726.
[95] (a) Vandewalle, M.; Van der Eycken, J.; Oppolzer, W.; Vullioud, C. *Tetrahedron* **1986**, *42*, 4035-4043. (b) Thom, C.; Kocieński, P. *Synthesis* **1992**, 582-586.
[96] Honda, M.; Katsuki, T.; Yamaguchi, M. *Tetrahedron Lett*. **1984**, *25*, 3857-3860.

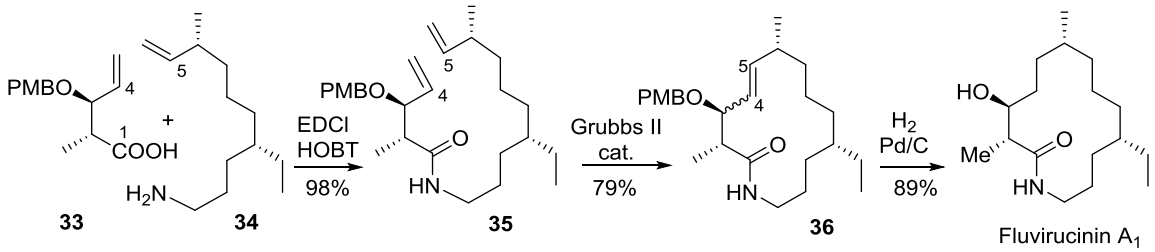
alkynyl alanate derived from **29** gave alcohol **30**, which was converted to saturated epoxide **31**. Regioselective opening of **31** with 3-butenylmagnesium bromide, followed by protection-deprotection steps and conversion of the primary alcohol function of **32** to a primary amino group, completed the synthesis of the amine half **23** (Scheme 3.40).[94]



Scheme 3.40

3.2.4.3. Radha Krishnas's approach to fluvirucinin A_1

In 2011, Radha Krishna reported[97] an enantioselective synthesis of fluvirucinin A_1 involving the same C_4-C_5 bond disconnection. Closure of the macrocyclic ring was also achieved by an RCM reaction, in this case from diene **35**, which was prepared in nearly quantitative yield by amidation between carboxylic acid **33** and amine **34** (C_1-C_4 and C_5-N fragments of fluvirucinin A_1). Hydrogenation of the resulting unsaturated macrolactam **36** (*Z*/*E* mixture) brought about both the reduction of the olefinic bond and the deprotection of the alcohol function to furnish fluvirucinin A_1 (Scheme 3.41).

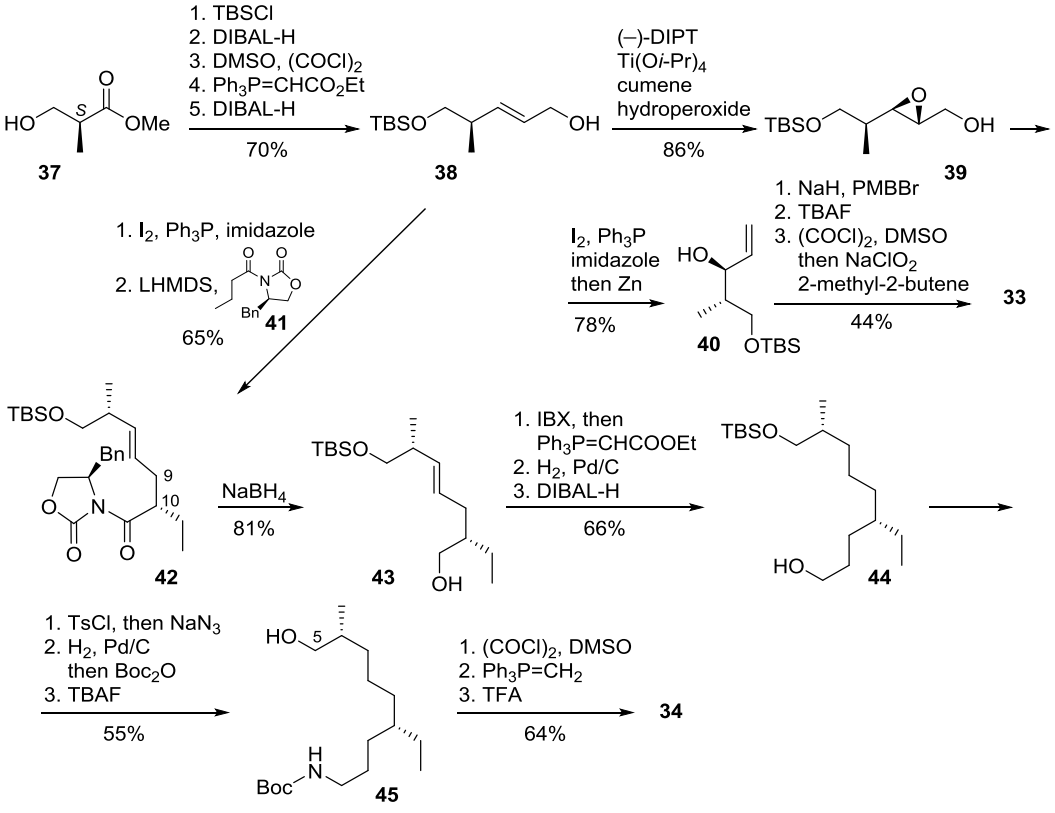


Scheme 3.41

[97] Radha Krishna, P. R.; Anitha, K. *Tetrahedron Lett.* **2011**, *52*, 4546-4549.

Both fragments, **33** and **34**, were accessed from a common intermediate **38** derived from (*S*)-Roche ester **37**, which provided the C-2 and C-6 stereogenic centers of fluvirucinin A_1. Conversion of ester **37** into allylic alcohol **38**[98] followed by Sharpless asymmetric epoxidation afforded epoxy alcohol **39**,[98b] which was converted to allylic alcohol **40** by Zn reduction of the corresponding iodide. Subsequent protecting-group interconversions and oxidation of the primary alcohol function afforded *O*-protected hydroxy acid **33** (Scheme 3.42).

The preparation of amino alkene **34** started with a highly diastereoselective (>95:5) Evans asymmetric alkylation of *N*-butyryl oxazolidinone **41** with the allylic iodide derived from **38**, which installed the C-10 stereogenic center of fluvirucinin A_1 (bond formed C_9-C_{10}). Reductive cleavage of the chiral auxiliary, followed by a two-carbon homologation of the resulting alcohol **43** gave alcohol **44**, which was converted to *N*-Boc amino alcohol **45**. A final Swern oxidation and one-carbon Wittig olefination completed the C_5-N fragment **34**.

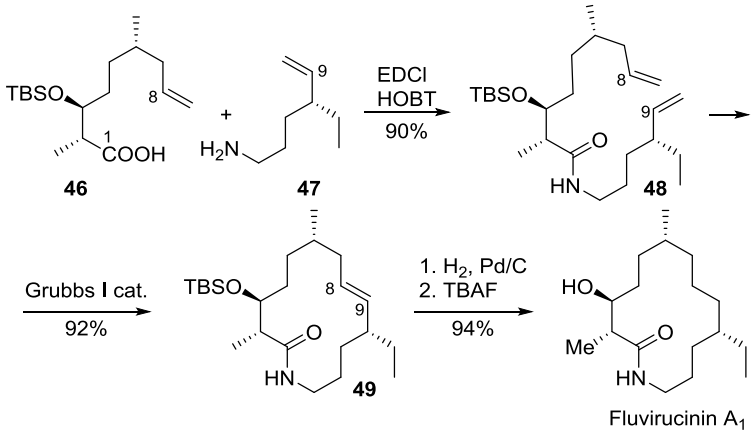


Scheme 3.42

[98] (a) Mendlik, M. T.; Cottard, M.; Rein, T.; Helquist, P. *Tetrahedron Lett.* **1997**, *38*, 6375-6378. (b) Fürstner, A.; Bouchez, L. C.; Funel, J.-A.; Liepins, V.; Porée, F.-H.; Gilmour, R.; Beaufils, F.; Laurich, D.; Tamiya, M. *Angew. Chem. Int. Ed*. **2007**, *46*, 9265-9270.

3.2.4.4. Negishi's approach to fluvirucinin A_1

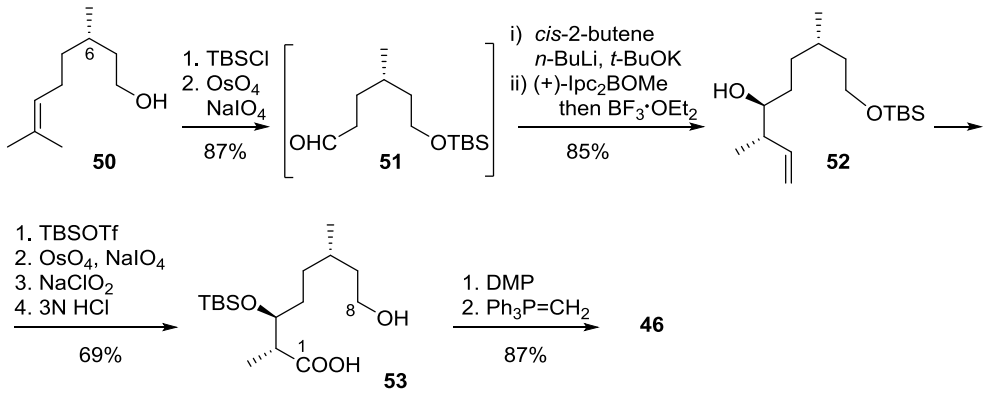
An alternative enantioselective synthesis of fluvirucinin A_1, also using an RCM reaction to promote the macrocyclization, was reported in 2008 by Negishi,[99] although, unlike other syntheses, in this approach the bond formed was C_8-C_9. The required diene **48** was prepared in excellent yield by amidation of acid **46** with amine **47** (C_1-C_8 and C_9-N fragments of fluvirucinin A_1), and the RCM was effected, also in excellent yield, using Grubbs I catalyst. Subsequent hydrogenation of the olefinic double bond and deprotection afforded fluvirucinin A_1 (Scheme 3.43).



Scheme 3.43

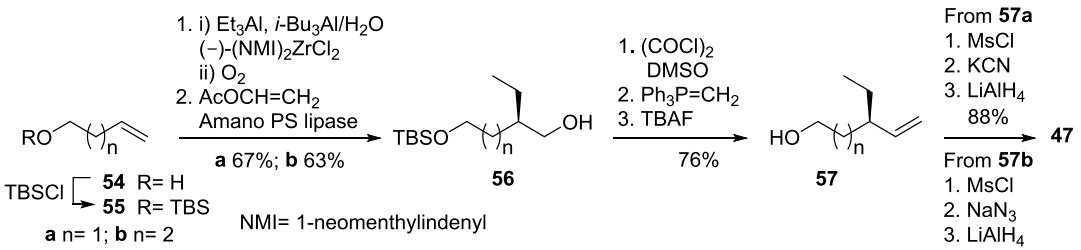
O-Protected hydroxy acid **46** was synthesized from (–)-(*S*)-β-citronellol (**50**), which provided the C-6 stereogenic center of the target macrocycle. The two other stereocenters of **46** were stereoselectively (dr ≥98%) generated by Brown crotylboration[100] of aldehyde **51**, which led to homoallylic alcohol **52** (Scheme 3.44). The synthesis of the C_1-C_8 fragment was completed by oxidative cleavage of the alkene moiety of **52**, protection-deprotection steps, and a one-carbon Wittig olefination of the aldehyde resulting from oxidation of alcohol **53**.

[99] Liang, B.; Negishi, E. *Org. Lett*. **2008**, 10, 193-195.
[100] Brown, H. C.; Bhat, K. S. *J. Am. Chem. Soc*. **1986**, *108*, 5919-5923.



Scheme 3.44

Amino alkene **47** was obtained by two alternative routes, both of them involving a Zr-catalyzed asymmetric carboalumination reaction followed by protection by lipase-catalyzed acetylation, starting from either 3-buten-1-ol (**54a**) or 4-penten-1-ol (**54b**). The resulting enantiomerically pure (≥ 98% ee) (*R*)-2-ethyl-1-alkanols **56a** and **56b**, containing the C-10 asymmetric center of fluvirucinin A, were converted to the C_9-N fragment **47** in six conventional steps, via alkenols **57a** and **57b**, as shown in Scheme 3.45.



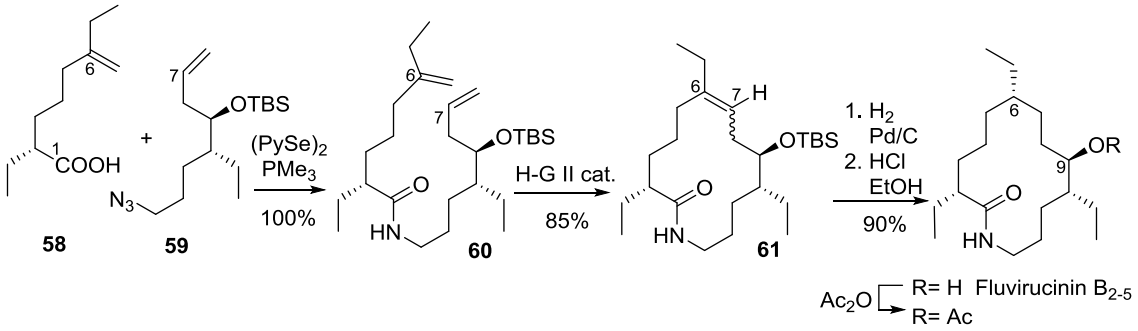
Scheme 3.45

3.2.4.5. The Vilarrasa-Urpí approach to fluvirucinin $B_{2\text{-}5}$

In 2009, Vilarrasa and Urpí reported the first and only, to date, enantioselective synthesis of fluvirucinin $B_{2\text{-}5}$, the aglycon common to fluvirucins B_2-B_5, via an RCM reaction involving the formation of the C_6-C_7 bond. [101] The macrocyclization was performed in the presence of Hoveyda-Grubbs II catalyst using diene **60** as the substrate, which was prepared by direct coupling of carboxylic acid **58** with azide **59** using the Staudinger-Vilarrasa reaction (Scheme 3.46).

[101] Llàcer, E.; Urpí, F.; Vilarrasa, J. *Org. Lett*. **2009**, *11*, 3198-3201.

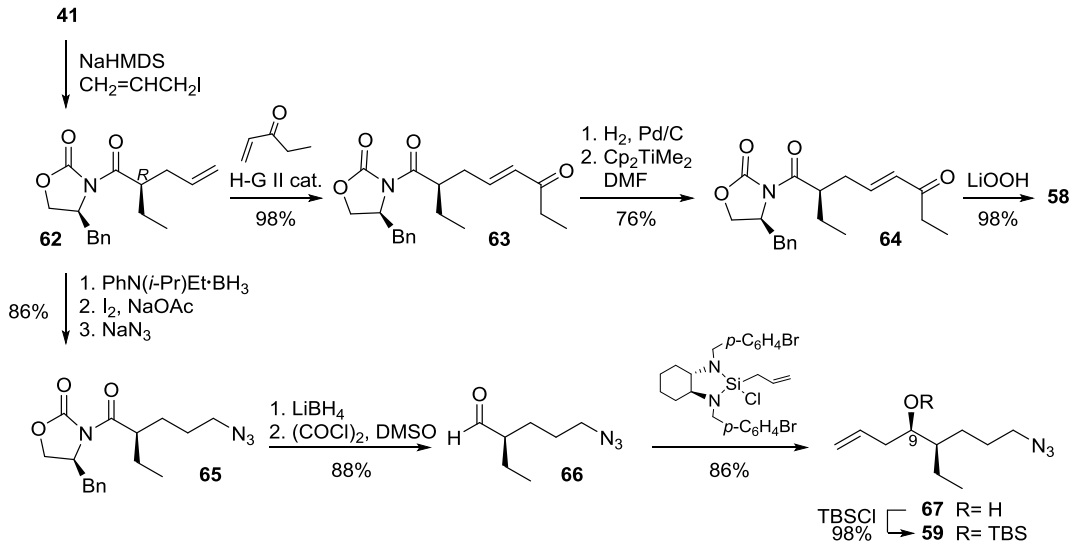
Hydrogenation of the trisubstituted double bond of the resulting unsaturated lactam **61** (1:1.2 mixture of *Z*/*E* isomers) stereoselectively installed the C-6 stereogenic center (9:1 dr). A subsequent hydrolysis afforded fluvirucinin $B_{2\text{-}5}$. The corresponding acetate was found to be identical to the reported acetylated aglycon derived from fluvirucin B_2 (Sch 38518).



Scheme 3.46

Both the ethyl-branched acid **58** and azide **59** (the C_1-C_6 and C_7-N fragments of fluvirucinin $B_{2\text{-}5}$) were stereoselectively prepared from the same starting material, the known[102] allylated *N*-acyloxazolidinone **62** (Scheme 3.47), which provided the C-2 and C-10 ethyl-substituted stereogenic centers of fluvirucinin $B_{2\text{-}5}$. Cross-methatesis of **62** with ethyl vinyl ketone, followed by hydrogenation of the resulting carbon-carbon double bond of enone **63** and selective Petasis ketone methylenation using DMF as a scavenger, afforded **64**. A final hydrolytic removal of the chiral auxiliary provided acid **58** in excellent overall yield. The conversion of **62** to azide **59** commenced with a one-pot hydroboration-iodination process, followed by replacement of the iodine atom by azide anion. After reductive removal of the auxiliary in **65** and oxidation of the resulting alcohol, a stereoselective (dr ≥ 98:2) allylation of aldehyde **66** using the (*S,S*)-Leighton reagent installed the C-9 stereogenic center to give *syn* alcohol **67**, which was protected as a TBS ether.

[102] Evans, D. A.; Rieger, D. L; Jones, T. K.; Kaldor, S. W. *J. Org. Chem.* **1990**, *55*, 6260-6268.



Scheme 3.47

3.2.5. Closure of the 14-membered ring by macrolactamization

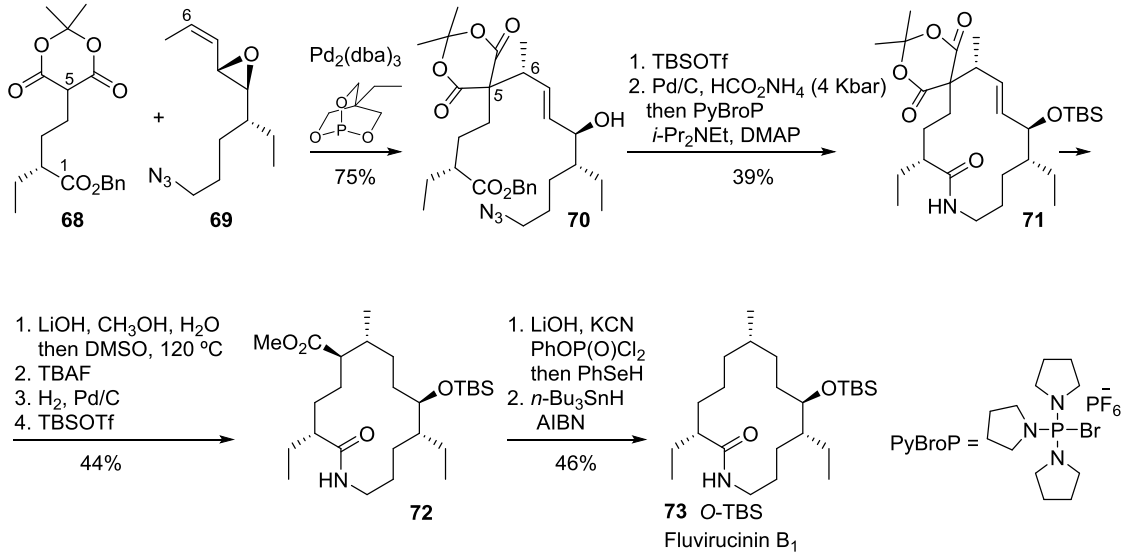
3.2.5.1. Trost's approach to fluvirucinin B_1

In 1997, Trost reported[103] a synthesis of fluvirucinin B_1 using a conceptually different approach, in which the macrocyclic ring was assembled by lactamization.

Starting from *N*-acyl imidazolidone **74**, two key intermediates, Meldrum's acid derivative **68** and epoxide **69** (C_1-C_5 and C_6-N fragments of fluvirucinin B_1) were synthesized in enantiopure form. Coupling of these two building blocks (bond formed C_5-C_6) by Pd-catalyzed addition of the pronucleophile **68** to alkenyl epoxide **69** occurred with complete transfer of chirality, via a π-allylpalladium species, thus creating the proper configuration at C-6. The resulting allylic alcohol **70**, which incorporates all stereogenic centers of fluvirucinin B_1, was obtained as a single diastereomer (Scheme 3.48). Then, simultaneous hydrogenolysis of the benzyl ester and azide functionalities and subsequent macrolactamization of the resulting amino acid took place under the reaction conditions depicted in Scheme 3.46 to give macrolactam **71**.

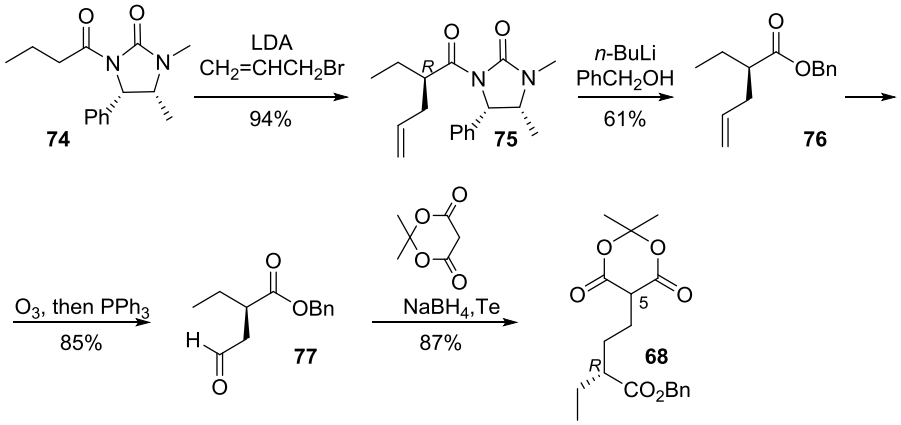
Once the macrocyclic ring system of fluvirucinin B_1 was assembled, the 1,3-dicarbonyl ester moiety was removed stepwise, by base-catalyzed hydrolysis-decarboxylation of **71** and, after hydrogenation of the olefinic bond, by radical decarbonylation of the acyl phenylselenide derived from ester **72**. The resulting *O*-silyl derivative **73** had previously been desilylated to fluvirucinin B_1.

[103] Trost, B. M.; Ceschi, M. A.; König, B. *Angew. Chem. Int. Ed. Engl.* **1997**, *36*, 1486-1489.



Scheme 3.48

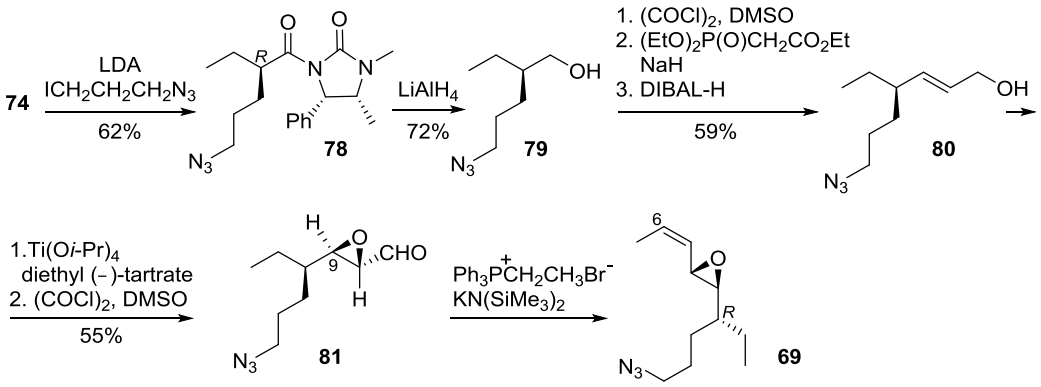
The synthesis of the key fragments **68** and **69** is outlined in Schemes 3.49 and 3.50. Stereoselective alkylation (de > 95%) of *N*-butyryl imidazolidinone **74**, followed by removal of the chiral auxiliary from imidazolidinone **75**, afforded ester **76**. After ozonolysis of the olefinic bond of **76**, the Meldrum's acid moiety was introduced on the resulting aldehyde **77** by reductive alkylation under Knoevenagel conditions to afford **68**.



Scheme 3.49

On the other hand, the synthesis of azide **69** started with a stereoselective alkylation of **74** (de ≥ 95%) leading to imidazolidinone **78**. Reductive removal of the chiral auxiliary followed by oxidation of the resulting alcohol **79** and a two-carbon homologation-reduction sequence gave allylic alcohol **80**. An asymmetric epoxidation afforded a single diastereomeric epoxide, thus defining

the C-9 absolute configuration. A subsequent oxidation and a stereoselective Wittig olefination (7:1 *Z*/*E* ratio) of the resulting aldehyde **81** gave the C_6-N fragment **69**.

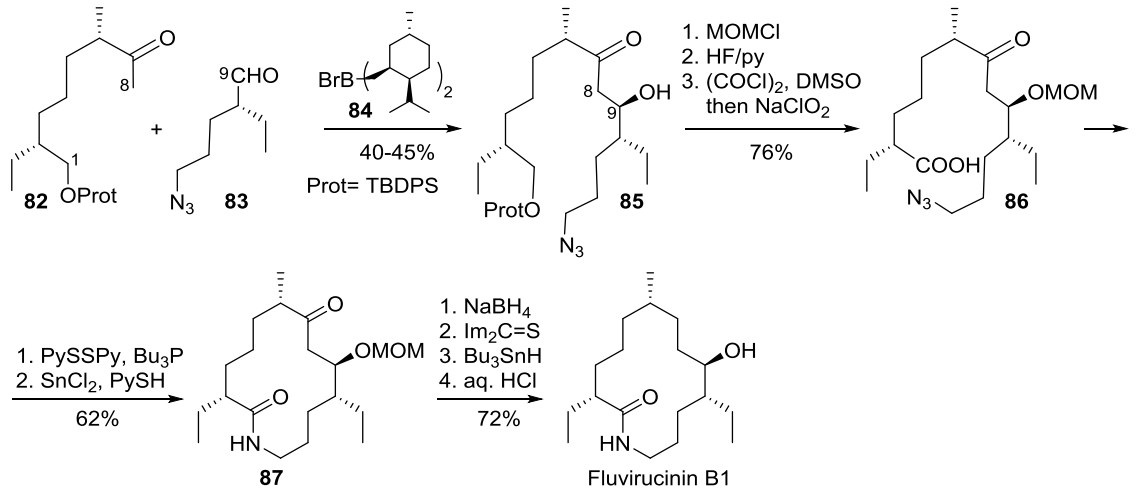


Scheme 3.50

3.2.5.2. The Vilarrasa-Urpí approach to fluvirucinin B_1

In 1999, Vilarrasa and Urpí published[104] an alternative synthesis of fluvirucinin B_1, also involving a lactamization reaction to construct the 14-membered ring. The crucial open-chain precursor **85** was prepared by a stereoselective aldol-like reaction (bond formed C_8-C_9) between aldehyde **83** and the boron enolate generated from ketone **82** and the menthone-derived boryl bromide **84** (Scheme 3.51). Alcohol **85** incorporates all carbon atoms of the target aglycon with the natural configuration in all stereocenters. After the subsequent conversion of *syn* alcohol **85** (20:1 *syn*/*anti* ratio) to ω-azido acid **86**, the macrolactamization to **87** was effected via a *S*-2-pyridyl ester by reduction of the azido group. A three-step reduction of the ketone carbonyl and deprotection of the alcohol function afforded fluvirucinin B_1. The spectroscopic data of the corresponding acetate matched those reported in the literature.

[104] Martín, M.; Mas, G.; Urpí, F.; Vilarrasa, J. *Angew. Chem. Int. Ed. Engl.* **1999**, *38*, 3086-3089.

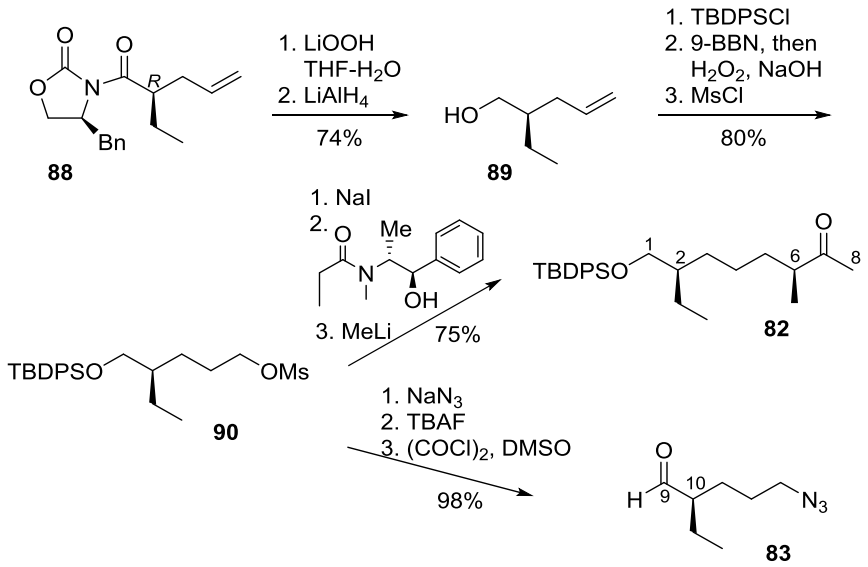


Scheme 3.51

Both ketone **82** and aldehyde **83** (C_1-C_8 and C_9-N fragments of fluvirucinin B_1) were synthesized from a common intermediate **90**, which provided the C-2 and C-10 ethyl-substituted stereocenters of the target aglycon. Compound **90** was accessible in five steps from the known Evans acyl oxazolidinone **88**, via alcohol **89**,[102] as outlined in Scheme 3.52.

The preparation of ketone **82** featured a diastereoselective alkylation of the *N*-propanoyl derivative of (-)-pseudoephedrine with the iodide derived from **90**, a process that installed the C-6 methyl-substituted stereocenter of fluvirucinin B_1. Removal of the chiral auxiliary with MeLi gave methyl ketone **82**.

In turn, azido aldehyde **83** was obtained from **90** in three conventional steps: introduction of the azido group, deprotection, and Swern oxidation.

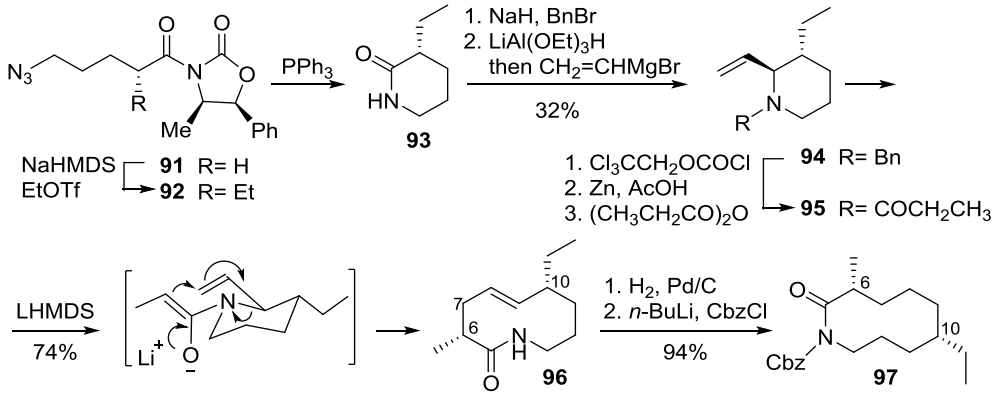


Scheme 3.52

3.2.5.3. Suh's approach to fluvirucinin A_1

The synthesis of fluvirucinin A_1 by Suh in 1999 was the first synthesis of a member of the fluvirucinin A series.[105] Before the final lactamization of amino acid **101** (Scheme 3.54), the key steps were a diastereoselective vinyl addition to a 2-piperidone derivative, an amide-enolate aza-Claisen rearrangement to generate the 10-membered lactam **96**, and the stereoselective condensation of an aldehyde with the boron enolate of *N*-propionyl oxazolidinone **99**.

The synthesis begins with the Evans asymmetric alkylation of *N*-acyl oxazolidinone **91**, to install the initial stereogenic center corresponding to C-10 of fluvirucinin A_1, and the conversion of the alkylated product **92** to 2-piperidone **93** (Scheme 3.53). The corresponding *N*-benzyl derivative was converted to *trans*-2,3-disubstituted piperidine **94** via a diastereoselective (95:5 *trans*/*cis* ratio) vinylation at the lactam carbonyl with the assistance of $LiAl(OEt)_3H$. Exchange of the benzyl group for propionyl gave amide **95**, which underwent a stereoselective amide-enolate-induced aza-Claisen rearrangement (bond formed C_6-C_7), leading to the ring-expanded lactam **96**, which possesses a new stereogenic center, corresponding to C-6 of fluvirucinin A_1. The reaction occurs via a *Z*-enolate in a chair-chair-like transition state bearing an equatorial ethyl substituent.

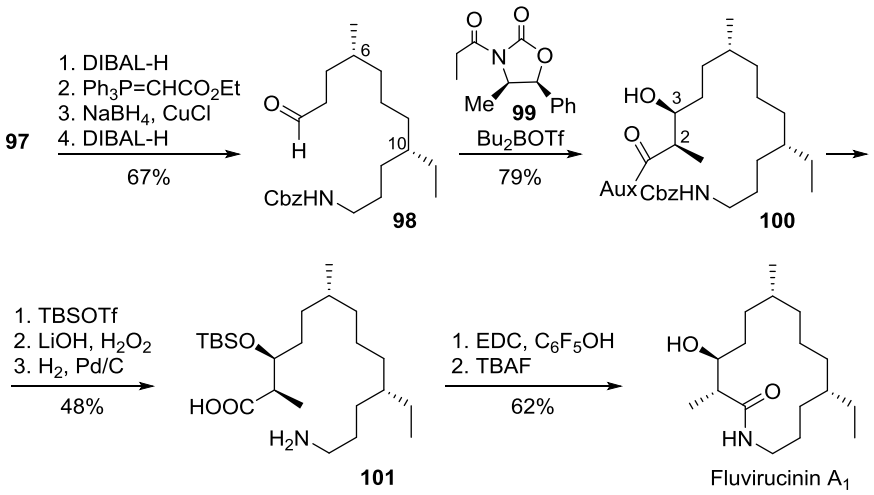


Scheme 3.53

After unsaturated lactam **96** was hydrogenated and *N*-protected, reductive ring-opening of lactam **97**, followed by a two-carbon Wittig olefination and two reduction steps, afforded saturated aldehyde **98** (Scheme 3.54). The two remaining stereocenters (C-2 and C-3) were stereoselectively introduced following the Evans protocol by an aldol-type reaction between aldehyde **98** and *N*-propionyl oxazolidinone **99**. Hydrolytic removal of the auxiliary and protecting-

[105] Suh, Y.-G.; Kim, S.-A.; Jung, J.-K.; Shin, D.-Y.; Min, K.-H.; Koo, B.-A.; Kim, H.-S. *Angew. Chem. Int. Ed. Engl.* **1999**, *38*, 3545-3547.

deprotecting steps converted the resulting alcohol **100** to amino acid **101**. A subsequent lactamization and deprotection provided synthetic fluvirucinin A_1, which was identical in all respects to the natural aglycon.



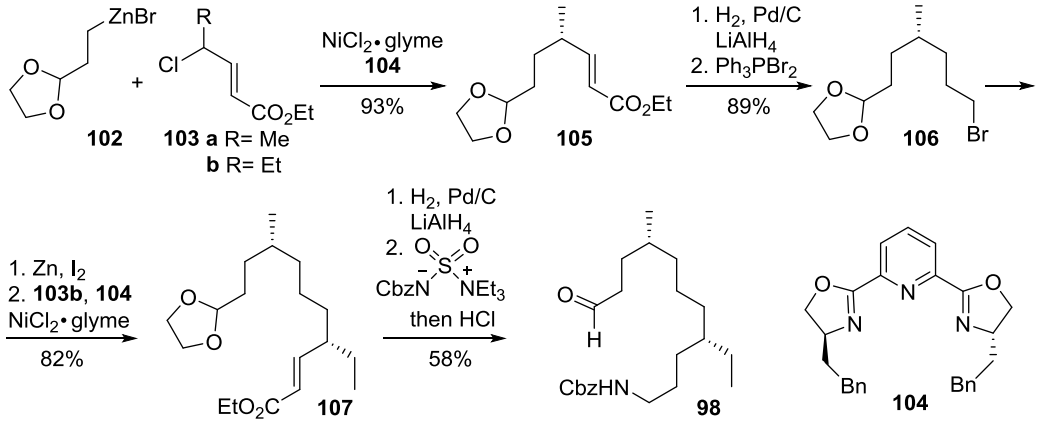
Scheme 3.54

3.2.5.4. Fu's approach to fluvirucinin A_1

In 2008, Fu reported[106] a formal total synthesis of fluvirucinin A_1, using two sequential Ni-catalyzed asymmetric $C(sp^3)$-$C(sp^3)$ Negishi cross-coupling reactions of allylic chlorides as the key steps.

The synthesis started from ethyl (*E*)-4-oxo-2-butenoate, which was converted in two steps to racemic secondary allylic chloride **103a** (Scheme 3.55). Nickel(II)-catalyzed cross-coupling of **103a** with alkylzinc reagent **102** in the presence of Pybox ligand **104** provided compound **105** in excellent yield and almost complete regio- (>20:1) and enantioselectivity (96% ee). After **105** was converted to bromide **106** and then to the corresponding alkylzinc derivative, a second nickel(II)-catalyzed asymmetric cross-coupling reaction with racemic allylic chloride **103b** generated unsaturated ester **107** in excellent diastero- (15:1 ratio) and enantioselectivity (>98 % ee). A subsequent reduction-amination sequence provided *N*-protected amino aldehyde **98**, an advanced intermediate in Suh's synthesis of fluvirucinin A_1.

[106] Son, S.; Fu, G. C. *J. Am. Chem. Soc*. **2008**, *130*, 2756-2757.



Scheme 3.55

3.2.6. Construction of the 14-membered ring by Aza-Claisen ring expansion

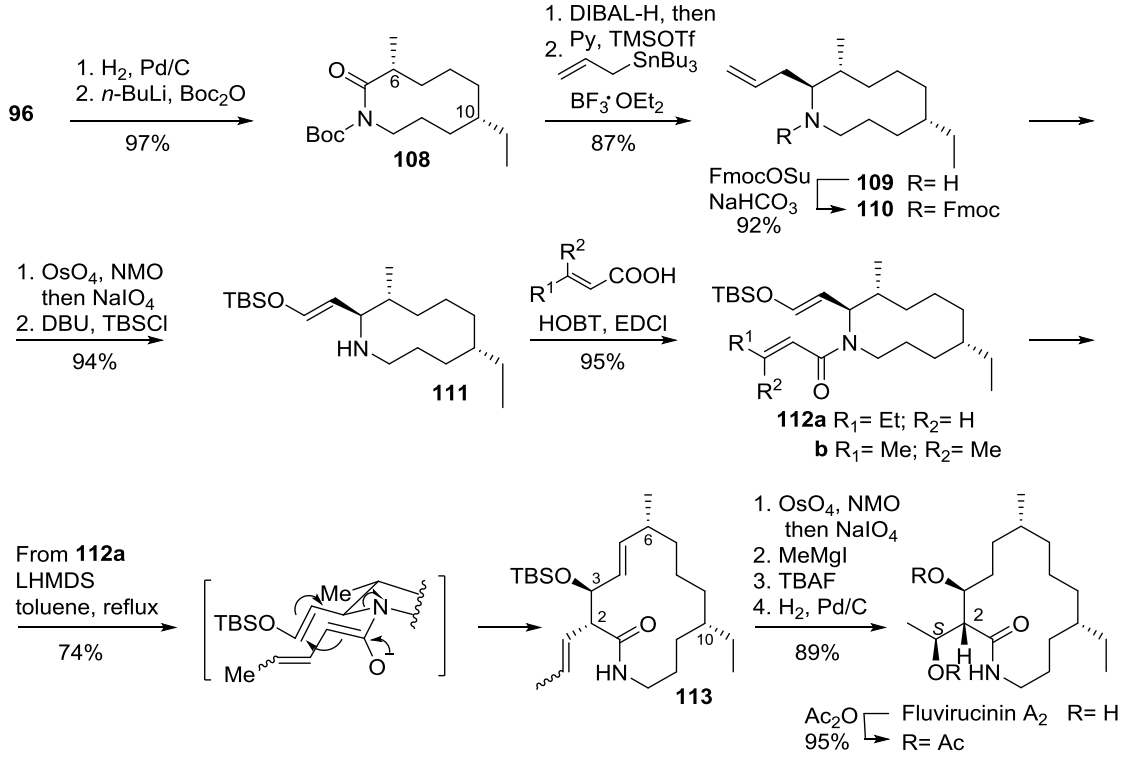
3.2.6.1. Suh's approach to Fluvirucinin A_2

In 2010, Suh contributed[107] the first total synthesis of fluvirucinin A_2 by an iterative lactam ring expansion via an amide-enolate-induced aza-Claisen rearrangement that provided the 14-membered lactam skeleton with the required absolute configuration at all ring stereogenic centers.

Ten-membered lactam **96**, an early intermediate in Suh's synthesis of fluvirucinin A_1, prepared by a first amide-enolate-induced aza-Claisen rearrangement (Scheme 3.53),[105] was converted to *N*-Boc saturated lactam **108** (Scheme 3.56). After partial reduction of the lactam carbonyl and trapping of the resulting *N*,*O*-hemiacetal as a silyl ether, a stereoselective amidoalkylation led to allyl azacycle **109**, which was protected as the Fmoc-derivative **110**. Oxidative cleavage of the allyl group to an aldehyde, followed by silylation stereoselectively afforded the required (*E*)-silyl enol ether **111** (*E*:*Z* > 10:1). The corresponding (*E*)-2-pentenamide **112a** underwent a regio- and stereoselective (dr > 10:1) vinylogous amide-enolate-induced aza-Claisen rearrangement, via a highly favorable transition state, leading to lactam **113** (bond formed C_2-C_3), with generation of the C-2 and C-3 stereogenic centers. Selective oxidation of the propenyl appendage of **113**, followed by stereoselective Grignard addition to the resulting aldehyde, left the (*S*)-1-hydroxyethyl chain at C-2. Deprotection of

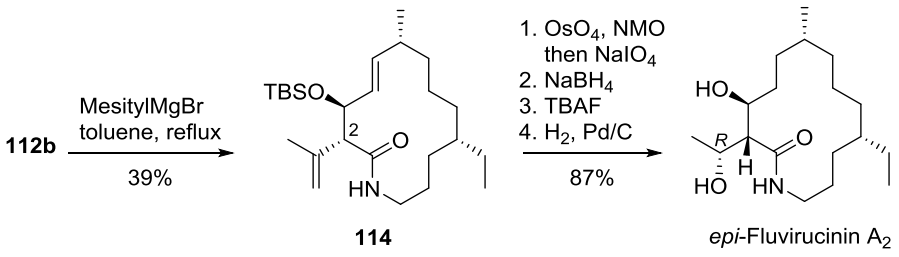
[107] Lee, Y.-S.; Jung, J.-W.; Kim, S.-H.; Jung, J.-K.; Paek, S.-M.; Kim, N.-J.; Chang, D.-J.; Lee, J.; Suh, Y.-G. *Org. Lett*. **2010**, *12*, 2040-2043.

the C-3 hydroxy group and hydrogenation of the olefinic double bond completed the synthesis of fluvirucinin A_2, whose diacetate exhibited spectral data identical to those of the diacetate derived from the natural aglycon.



Scheme 3.56

The stereoselectivity of the aza-Claisen rearrangement was dependent on the substitution at the unsaturated *N*-acyl moiety. Thus, starting from *N*-(3,3-dimethylacryloyl) derivative **112b**, the rearrangement was not stereoselective, leading to a 1:1 mixture of macrolactam **114** and its C-2 epimer, probably due to a non-selective formation of the *Z*-enolate (Scheme 3.57). Compound **114** was converted to *epi*-fluvirucinin A_2 by manipulation of the isopropenyl chain at C-2 and subsequent deprotection and hydrogenation steps. The *R* configuration of the 1-hydroxyethyl moiety was attained by stereoselective $NaBH_4$ reduction of a ketone generated by selective oxidative cleavage of the isopropenyl double bond.

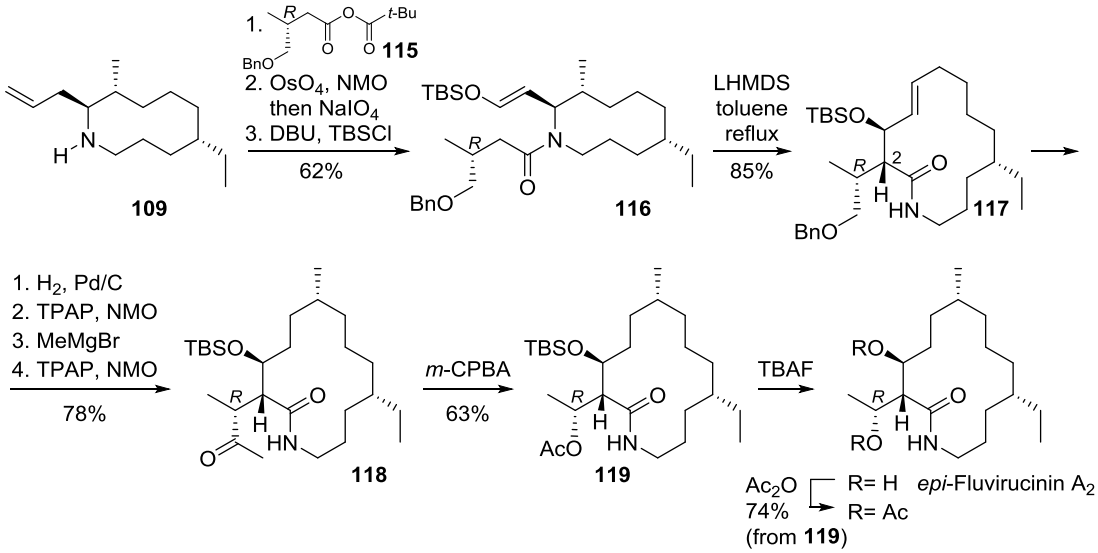


Scheme 3.57

The structures of the synthetic fluvirucinin A_2 and its *epi*-derivative were confirmed by an alternative synthesis of *epi*-fluvirucinin A_2 employing a Baeyer-Villiger oxidation to ensure the *R* configuration of the 1-hydroxyethyl chain.

After acylation of the ten-membered amine intermediate **109** with the *R* configurated mixed anhydride **115** and conversion of the allyl chain to an (*E*)-silyl enol ether, treatment of **116** under aza-Claisen rearrangement conditions afforded the 14-membered lactam **117** (Scheme 3.58). The (*R*)-benzyloxymethyl substituent in the C-2 chain of **117** was converted to (*R*)-acetyl in **118** and then to (*R*)-acetoxy in **119**, via a Baeyer-Villiger oxidation with retention of configuration.

The spectral data of *epi*-fluvirucinin A_2 prepared by this approach were identical to those of *epi*-fluvirucinin A_2 synthesized by the route depicted in Scheme 3.57.



Scheme 3.58

3.2.6.2. The Suh-Jung stereocontrolled approach to fluvirucinin A_1 and its C-3 epimer

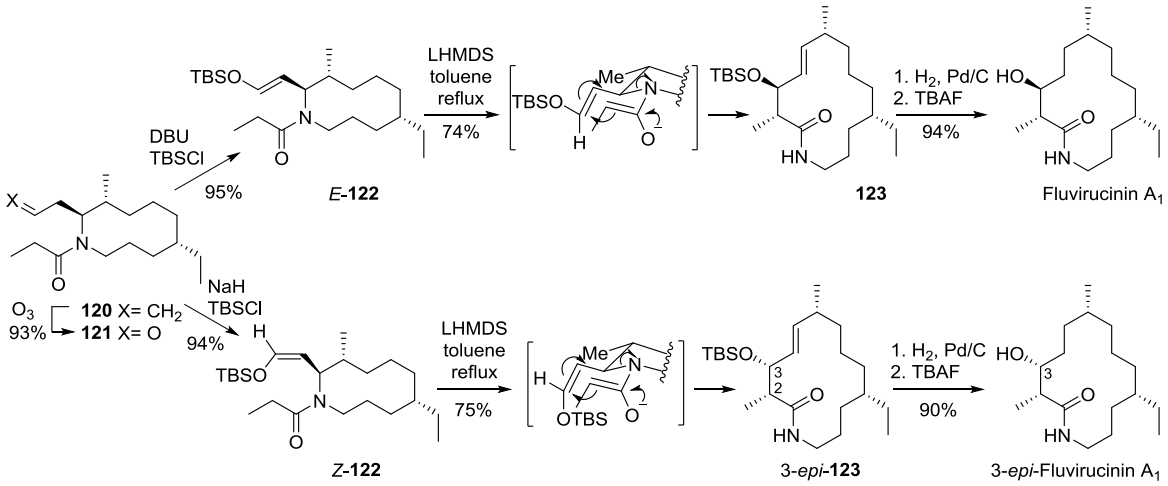
In the context of a systematic investigation of the aza-Claisen rearrangement-induced ring expansion of azacycles and its stereochemical outcome, in 2012 Suh and Jung reported[108] an alternative synthesis of fluvirucinin A_1. Based on a stereoselective (*E*)- and (*Z*)-silyl enol ether formation and the subsequent ring

[108] Suh, Y.-G.; Lee, Y.-S.; Kim, S.-H.; Jung, J.-K.; Yun, H.; Jang, J.; Kim, N.-J.; Jung, J.-W. *Org. Biomol. Chem*. **2012**, *10*, 561-568.

expansion of the resulting ten-membered 1-acyl-2-alkoxyvinyl azacycles, it provides stereocontrolled access to both fluvirucinin A_1 and its C-3 epimer.

The starting allyl azacycle **120** was stereoselectively prepared by the procedure outlined in Scheme 3.56, by amidoalkylation of the corresponding lactam.[107] Ozonolysis of **120** gave aldehyde **121**, which was then converted with almost complete stereoselectivity to either the (*E*)-silyl enol ether *E*-**122** or the *Z*-isomer *Z*-**122**, depending on the reaction conditions (Scheme 3.59).

These silyl enol ethers underwent stereospecific amide-enolate-induced aza-Claisen rearrangement (bond formed C_2-C_3), via the chair-like transition states depicted in Scheme 3.59, providing the respective C-3 isomeric 14-membered lactams **123** and 3-*epi*-**123**, which were then converted to fluvirucinin A_1 and its C-3 epimer.

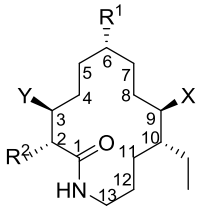


Scheme 3.59

Considerable work remains to be done on the synthesis of fluvirucins. To date, the only member of this family of natural products to have been synthesized is fluvirucin B_1, which incorporates 3-amino-3,6-dideoxy-α-L-talopyranose as the aminosugar moiety. No syntheses of fluvirucins bearing L-mycosamine as the carbohydrate fragment have been reported. In contrast, the synthesis of fluvirucinins has attracted considerable attention and a variety of strategies and procedures have been employed to assemble the macrocyclic ring system. Table 3.4 summarizes the synthetic strategies used for the construction of the 14-membered ring of fluvirucinins, showing the bond formed in the macrocyclization step in each synthesis. Except when the 14-membered ring is assembled by expansion of a 10-membered ring, the table also indicates the bond formed to complete the open-chain skeleton before the macrocyclization step, as well as the length of the two fragments used and the ring atoms they incorporate.

All the reported syntheses are enantioselective and most of them highly convergent, in many cases accessing both key intermediates from a single enantiopure building block. By an appropriate selection of the starting materials many of the strategies developed could be applied to the synthesis of other members of the fluvirucinin family.

Finally, it should be noted that the synthetic activity in this area has stimulated the development and extensive application of new synthetic methodologies such as RCM macrocyclizations, as well as the use of metal-catalyzed transformations in crucial synthetic steps.



R^1= H, Me or Et
R^2= Me, Et or (*S*)CHOHCH$_3$
X= H; Y= OH (fluvirucinins A)
X= OH; Y= H (fluvirucinins B)

Authors (Year)	Bond formed in the construction of the 14-membered ring	Bond formed and fragments used to complete the open-chain skeleton	Final target
Hoveyda[77-79] (1995,1996, 1997)	C_5—C_6	C_1—N: 5C (C_1—C_5) + 8C (C_6—N)	Fluvirucinin B_1; Fluvirucin B_1
Bracher[81] (2002)	C_4—C_5	C_1—N: 4C (C_1—C_4) + 9C (C_5—N)	Fluvirucinin B_0
Radha Krishna[84] (2011)	C_4—C_5	C_1—N: 4C (C_1—C_4) + 9C (C_6—N)	Fluvirucinin A_1
Negishi[86] (2008)	C_8—C_9	C_1—N: 8C (C_1—C_8) + 5C (C_9—N)	Fluvirucinin A_1
Vilarrasa—Urpí[88] (2009)	C_6—C_7	C_1—N: 6C (C_1—C_6) + 7C (C_7—N)	Fluvirucinin $B_{2\text{-}5}$
Trost[92] (1997)	C_1—N	C_5—C_6: 5C (C_1—C_5) + 8C (C_6—N)	Fluvirucinin B_1
Vilarrasa—Urpí[93] (1999)	C_1—N	C_8—C_9: 8C (C_1—C_8) + 5C (C_9—N)	Fluvirucinin B_1
Suh[94] (1999); Fu[95] (2008, formal)	C_1—N	C_2—C_3: 2C (C_1—C_2) + 11C (C_3—N)	Fluvirucinin A_1
Suh[96] (2010)	C_2—C_3	ten-membered ring expansion	Fluvirucinin A_2
Suh—Jung[97] (2012)	C_2—C_3	ten-membered ring expansion	Fluvirucinin A_1

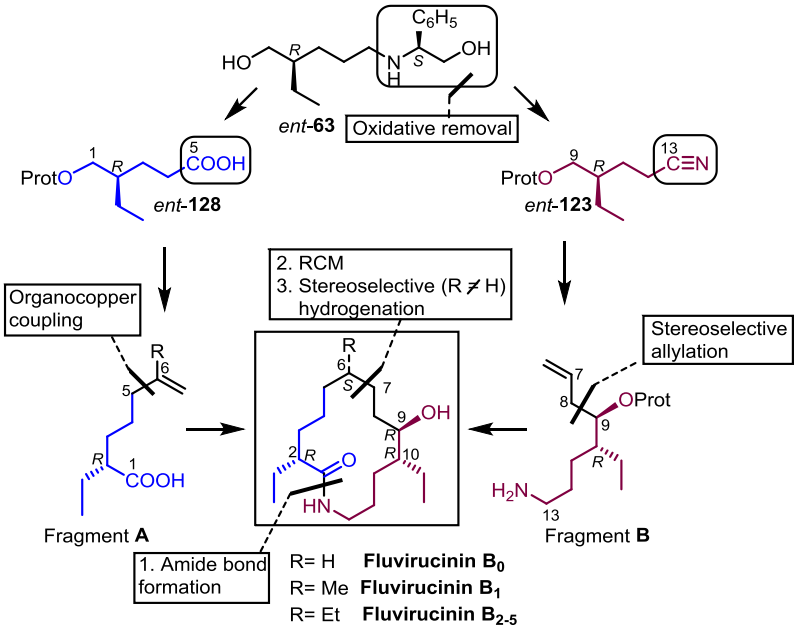
Table 3.4

3.2.7. Our synthetic strategy for the synthesis of fluvirucinin B_1

Taking into account that all fluvirucinins B possess the same substitution and stereochemical patterns at C-2 (*R*-Et), C-9 (*S*-OH), and C-10 (*R*-Et), differing only in the C-6 substituent (none in fluvirucinin B_0, 6*S*-Me in B_1, 6*S*-Et in $B_{2\text{-}5}$), we envisaged a unified synthetic strategy to these macrolactams in which the C-2 and C-10 ethyl substituents would come from a common enantiopure amino diol, *ent*-**63**, which is the enantiomer of the amino diol **63**, whose preparation has been reported in Chapter 2.

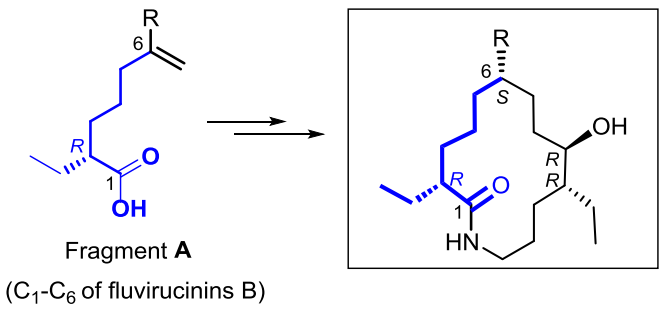
The required amino diol *ent*-**63** would be easily accessible by reductive opening of oxazolopiperidone *ent*-**28a** (*S*-phenylglycinol-derived, see Scheme 2.51, Chapter 2).

Oxidative removal of the chiral auxiliary of *ent*-**63** followed by synthetic transformations would lead to fragments **A** and **B** (Scheme 3.60). The enantioselective total synthesis of fluvirucinin B_1 would be accomplished by coupling of both enantiopure fragments followed by a ring-closing metathesis reaction to form the C_6-C_7 bond and subsequent stereoselective hydrogenation to install the (*S*)-methyl configuration at the C-6 position. Removal of the protecting group would lead to the aglycon fluvirucinin B_1.



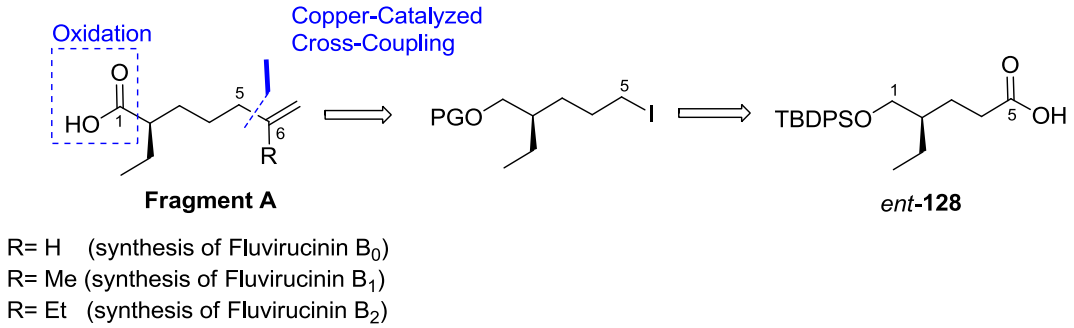
Scheme 3.60

3.2.7.1. Enantioselective synthesis of fragment A (C_1-C_6 of fluvirucinin B_1)



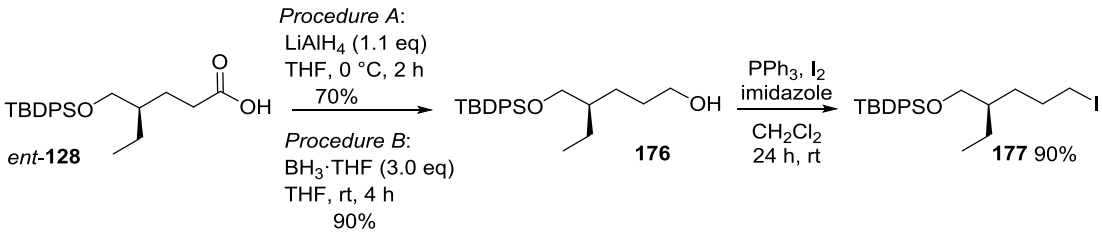
Scheme 3.61

The preparation of the fragment **A** (C_1-C_6) was envisioned starting from carboxylic acid *ent*-**128** (see compound **128** in chapter 2), prepared from enantiopure oxazolopiperidone lactam *ent*-**28a**. Later synthetic transformations would convert *ent*-**128** into the corresponding iodide derivative, which would undergo a copper-catalyzed cross-coupling with appropriate alkenyl Grignard reagents. Subsequent oxidation would lead to the formation of the fragment **A**.



Scheme 3.62

We started the preparation of the fragment **A** by the conversion of carboxylic acid *ent*-**128** to the iodide derivative **177**. We proposed a two-step sequence which involves the reduction of the acid to alcohol and the subsequent substitution of the hydroxy group by iodide. Treatment of acid *ent*-**128** with $LiAlH_4$ in anhydrous THF afforded primary alcohol **176** in 70% yield. Similar results were obtained using the borane-tetrahydrofuran complex as the reducing agent (72%). When the crude reaction mixture was treated with an alkaline mixture of potassium carbonate and diethyl ether, we recovered pure alcohol **176** in 90% yield. NMR spectroscopic and specific rotation of alcohol **176** matched those reported in the literature.[109] The conversion of primary alcohol **176** to iodide **177** used a direct procedure employing triphenylphosphine, molecular iodine and imidazole as the base. The best results were obtained when the reaction mixture was stirred for at least 15 h, leading to the alkyl iodide derivative **177** in 90% yield.

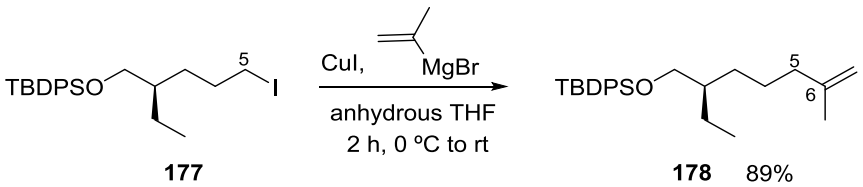


Scheme 3.63

[109] (a) Paquette, L. A.; Duan, M.; Konetzki, I.; Kempmann, C. *J. Am. Chem. Soc*. **2002**, *124*, 4257-4270. (b) Panek, J. S.; Jain, N. F. *J. Org. Chem*. **2001**, *66*, 2747-2756.

The key step for the preparation of fragment **A** was the conversion of iodide **177** to the corresponding alkene by an organometallic coupling. The mechanism for the substitution of halides using organocopper complexes is not very known and several postulations were made.[110]

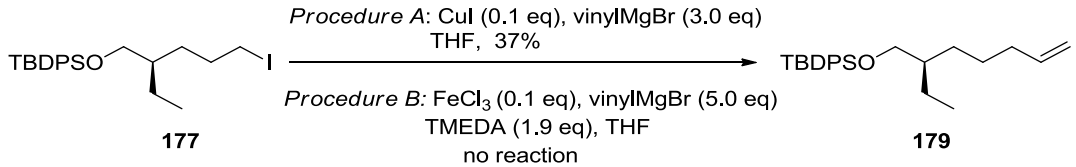
In our objective to prepare fluvirucinin B_1 (R= Me, see Scheme 3.60), a cross-coupling reaction with isopropenylmagnesium bromide in the presence of a catalytic amount of CuI[111] (bond formed C_5-C_6) provided the protected alcohol **178** in an excellent 89% yield.



177 **178** 89%

Scheme 3.64

In order to prepare also fluvirucinin B_0 (R= H) we applyed these optimized conditions using vinylmagnesium bromide[111a] instead isopropenylmagnesium bromide. We obtained the target alkene **179** in 37% yield the best of cases. A change of the reaction conditions (temperature or equivalents of cuprate) did not improve the reaction and usually we only recovered the starting material. We pursued our studies using vinylmagnesium bromide and iron trichloride in anhydrous THF in presence of tetramethylethylene diamine.[112] Unfortunately, under these conditions we never observed the formation of the target alkene **179**. With these results, we decided to continue our studies towards the synthesis of fluvirucinin B_1.



177 **179**

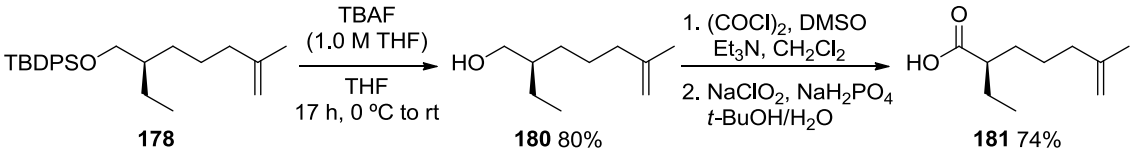
Scheme 3.65

[110] Lipshutz, B. H.; Sengupta, S. in *Organic reactions*: Paquette, L. A., Ed.; John Wiley & Sons, Inc: New York, 1992; Vol. 41, Chapter 2, pp 135-631.

[111] For copper-catalyzed couplings of alkenyl Grignard reagents with primary alkyl iodides, see: (a) Derguini-Boumechal, F.; Linstrumelle, G. *Tetrahedron Lett*. **1976**, 3225-3226. For more recent examples, see: (b) Takahashi, M.; Dodo, K.; Hashimoto, Y.; Shirai, R. *Tetrahedron Lett.* **2000**, *41*, 2111-2114. (c) Kochi, T.; Ellman, J. A. *J. Am. Chem. Soc.* **2004**, *126*, 15652-15653. (d) Terayama, N.; Yasui, E.; Mizukami, M.; Miyashita, M.; Nagumo, S. *Org. Lett*. **2014**, *16*, 2794-2797.

[112] For the use of iron catalysts, see: (a) Guérinot, A.; Reymond, S.; Cossy, J. *Angew. Chem. Int. Ed*. **2007**, *46*, 6521-6524. (b) Cahiez, G.; Duplais, C.; Moyeux, A. *Org. Lett*. **2007**, *9*, 3253-3254.

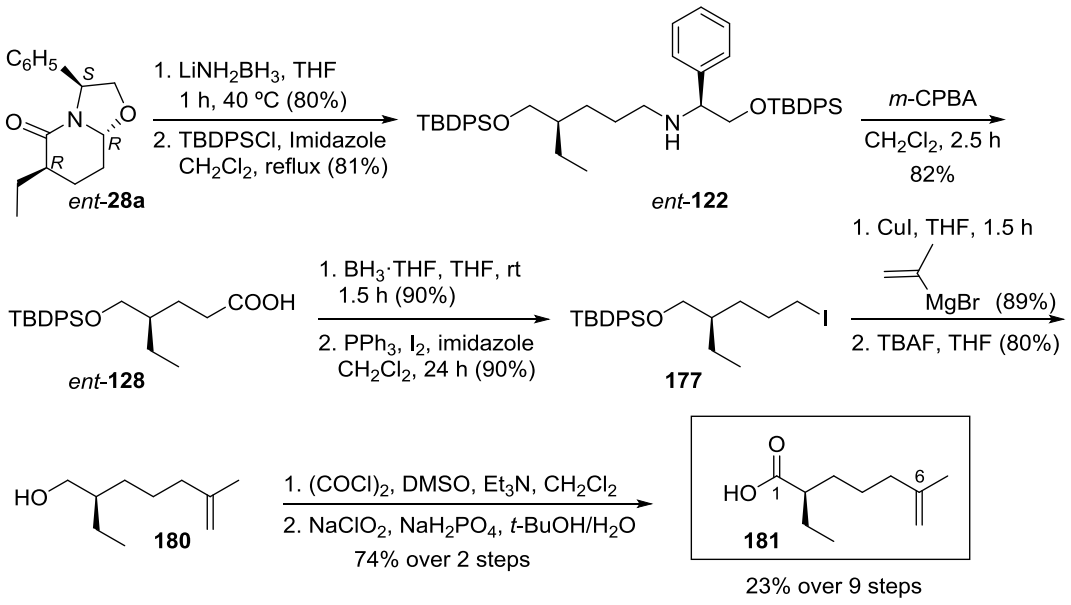
The preparation of the fragment **A** was completed by the three-step sequence outlined in Scheme 3.66. Deprotection of silyl derivative **178** with a solution of TBAF in anhydrous THF at room temperature afforded alcohol **180** in 80% yield. Treatment of this alcohol using Swern's conditions, followed by subsequent oxidation of the formed aldehyde afforded enantiopure carboxylic acid **181** in 74% yield.



178 **180** 80% **181** 74%

Scheme 3.66

The synthetic sequence to obtain carboxylic acid **181** (fragment **A** for the synthesis of fluvirucinin B_1) is illustrated in the following Scheme. Enantiopure carboxylic acid **181** was synthesized in 9 steps starting from chiral oxazolopiperidone lactam *ent*-**28a** in 23% overall yield.

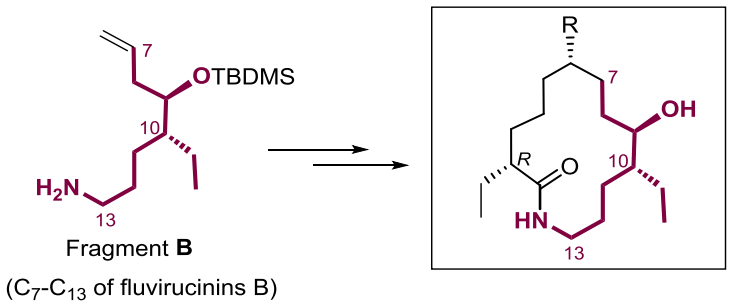


ent-**28a** *ent*-**122** *ent*-**128** **177** **180** **181**

23% over 9 steps

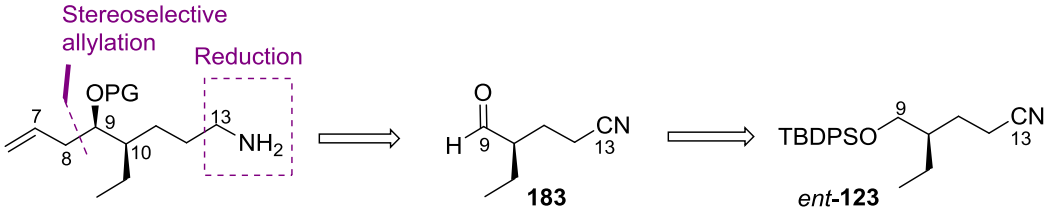
Scheme 3.67

3.2.7.2. Enantioselective synthesis of fragment B (C_7-C_{13} of fluvirucinins B)



Scheme 3.68

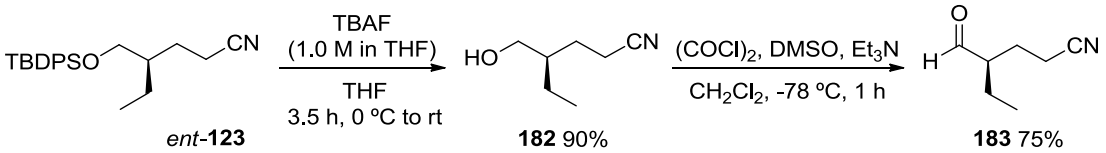
The preparation of the fragment **B** from nitrile derivative *ent*-**123** would require the generation of aldehyde **183** and the formation of the C_8-C_9 bond by stereoselective allylation of this aldehyde to install the (*R*)-hydroxy configuration at the C-9 position. The formation of the enantiopure nitrogen-containing fragment would be completed by subsequent protection of the secondary alcohol and reduction of the nitrile group to form the corresponding primary amine.



Scheme 3.25

Deprotection of silyl alcohol *ent*-**123** was performed with a solution of TBAF in anhydrous THF at room temperature, affording corresponding alcohol **182** in 80% yield.[113] The preparation of aldehyde **183** was accomplished by treatment of primary alcohol **182** with Swern's oxidation conditions in 75% yield. Purification by flash chromatography of the aldehyde was essential to have good yields in the next reaction.

[113] (a) White, J. D.; Hanselmann, R.; Jackson, R. W.; Porter, W. J.; Ohba, Y.; Tiller, T.; Wang, S. *J. Org. Chem*. **2001**, *66*, 5217-5231. (b) White, J. D.; Ohba, Y.; Porter, W. J.; Wang, S. *Tetrahedron Lett*. **1997**, *38*, 3167-3170.



ent-**123** **182** 90% **183** 75%

Scheme 3.70

The enantioselective allylation of aldehydes is an important asymmetric C-C bond forming reaction in organic chemistry, leading to products with a new stereocenter. Several chiral auxiliaries and metals have been described for this reaction to form pure homoallylic alcohols in high stereoselectivity. The principal chiral complexes used for enantioselective allylation are allylboranes [114], allylsilanes, [115] allyltitanium, [116] allylpalladium, [117] iridium, [118] and indium reagents.[119]

We focused our attention on the allylsilane derivatives, whose efficiency has been proven during the last decade by Leighton.[115] He has developed several chiral silicon-based reagents for the enantioselective allylation of aldehydes, ketones, and imines. Leighton demonstrated that chiral catalysts such as strained pseudoephedrine- and cyclohexanediamine-derived silacycles improved selectivities in the allylation and crotylation of aldehydes.[120] Both reagents can be prepared in high yield and purity and on a large scale. The strain associated with silacycle makes the silicon atom more Lewis acidic. Moreover, these reagents are moderately air-stable and reactions can occur at more usual temperatures (between -10 ºC and 0 ºC) contrary to boron reagents (between -100 ºC and -78 ºC and no air-stable).[121]

[114] (a) Jadhav, P. K.; Bhat, K. S.; Perumal, P. T.; Brown, H. C. *J. Org. Chem*. **1986**, *51*, 432-439. (b) Brown, H. C.; Bhat, K. S.; Randad, R. S*. J. Org. Chem.* **1989**, *54*, 1570-1576. (c) Enev, V. S.; Kaehlig, H.; Mulzer, J. *J. Am. Chem. Soc*. **2001**, *123*, 10764-10765. (d) Ramachandran, P. V. *Aldrichimica Acta* **2002**, *35*, 23-35. (e) Zhang, X.-S.; Da, S.-J.; Jiao, Y.; Li, H.-Z.; Xie, Z.-X.; Li, Y. *Chin. J. Chem*. **2008**, *26*, 1315-1322. (f) Nowrouzi, F.; Thadani, A. N.; Batey, R. A. *Org. Lett.* **2009**, *11*, 2631-2634.

[115] (a) Kinnaird, J. W. A.; Yee, N.; Kubota, K.; Wang, X.; Leighton, J. L. *J. Am. Chem. Soc.* **2002**, *124*, 7920-7921. (b) Kubota, K.; Leighton, J. L. *Angew. Chem. Int. Ed*. **2003**, 946-948. For synthetic applications, see: (c) Vintonyak, V. V.; Maier, M. E. *Org. Lett*. **2008**, *10*, 1239-1242. (d) Harsh, P.; O'Doherty, G. A. *Tetrahedron* **2009**, *65*, 5051-5055.

[116] (a) Hafner, A.; Duthaler, R. O.; Marti, R.; Rihs, G.; Rothe-Streit, P.; Schwarzenbach, F. *J. Am. Chem. Soc.* **1992**, *114*, 2321-2336. (b) Hoffman, T. J.; Kolleth, A.; Rigby, J. H.; Arseniyadis, S. *Org. Lett.* **2010**, *12*, 3348-3351. (c) Commandeur, M.; Commandeur, C.; Cossy, J. *Org. Lett*. **2011**, *13*, 6018-6021.

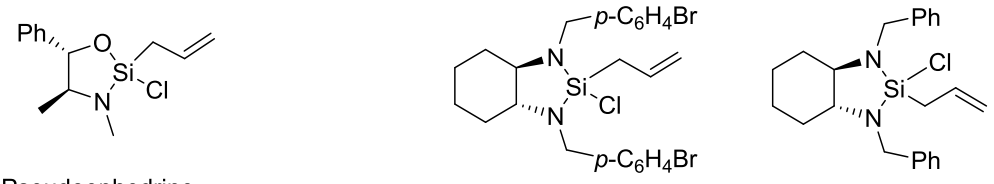
[117] Zanoni, G.; Pontiroli, A.; Marchetti, A.; Vidari, G. *Eur. J. Org. Chem*. **2007**, 3599-3611.

[118] (a) Kim, I. S.; Ngai, M.-Y.; Krische, M. J. *J. Am. Chem. Soc*. **2008**, *130*, 6340-6341. (b) Ngai, M.-Y.; Barchuk, A.; Krische, M. J. *J. Am. Chem. Soc*. **2008**, *130*, 14891-14899.

[119] Kargbo, R. B.; Cook, G. R. *Current Org. Chem*. **2007**, *11*, 1287-1309.

[120] Hackman, B. M.; Lombardi, P. J.; Leighton, J. L. *Org. Lett.* **2004**, *6*, 4375-4377.

[121] Racherla, U. S.; Brown, H. C. *J. Org. Chem*. **1991**, *56*, 401-404.

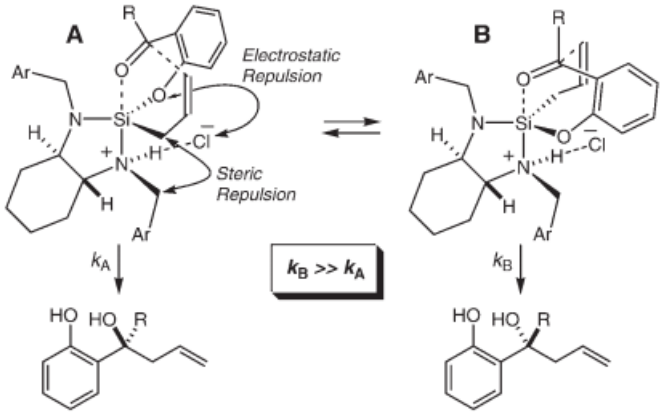


Pseudoephedrine-derived silacycle

Cyclohexanediamine-derived silacycles

Scheme 3.71

Leigthon et al. described[122] in 2006 a plausible mechanistic and stereochemical model of asymmetric ketone allylation of hydroxyacetophenone. Firstly, the phenol displaces the chloride from the silane, and HCl thus generated protonates one of the amino groups. Then, the ketone oxygen atom and the protonated amino group occupy apical positions on the trigonal bipyramidal intermediate. Only two such intermediates are possible (**A** and **B**; Scheme 3.72). In **A**, the indicated steric and electrostatic interactions may plausibly be posited, whereas in **B**, which correctly predicts the observed major enantiomer, no such interactions are present. A similar model could be envisioned for the stereoselective allylation or crotylation of aldehydes with the same *N*,*N*'-dialkylcyclohexanediamine silane reagent.



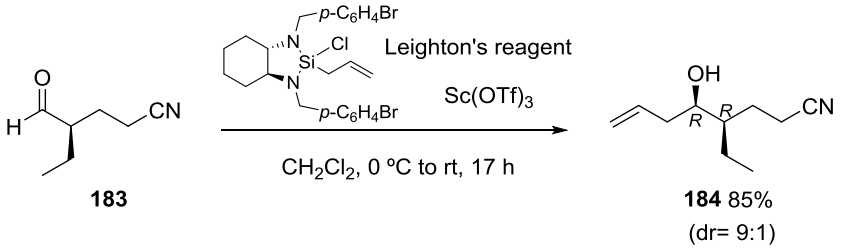
Scheme 3.72

When we applied the conditions described by Leighton and treated α-ethylsubstituted aldehyde **183** with the (*S*,*S*)-Leighton reagent in anhydrous dichloromethane at -20 ºC, we only recovered starting material. Similar results were obtained working between -10 ºC and 0 ºC. When the reaction mixture was stirred at room temperature, we observed complex signals by ^{1}H-NMR,

[122] Burns, N. Z.; Hackman, B. M.; Ng, P. Y.; Powelson, I. A.; Leighton, J. L. *Angew. Chem. Int. Ed*. **2006**, *45*, 3811-3813.

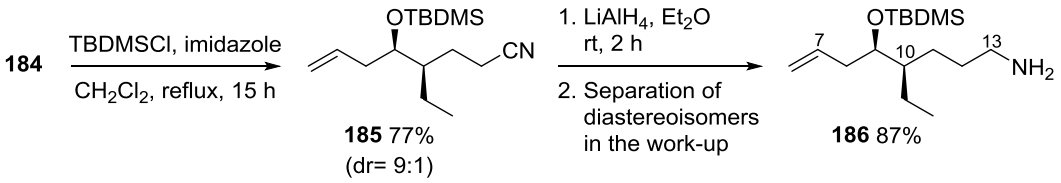
indicating a possible degradation of the reagent and/or lower diastereoselectivity of the allylation reaction.

More recently, Leighton and co-workers described an enantioselective aldehyde crotylation using *N*,*N*'-dialkylcyclohexanediamine silane reagents in the presence of scandium triflate as a Lewis acid.[123] Using these conditions, a stereoselective allylation installed the C-9 stereogenic center to give homoallylic *syn* alcohol **184** (bond formed C_8-C_9) in excellent yield (85%). Minor amounts (dr = 9:1) of the *anti*-adduct were detected by ^{1}H NMR.



Scheme 3.73

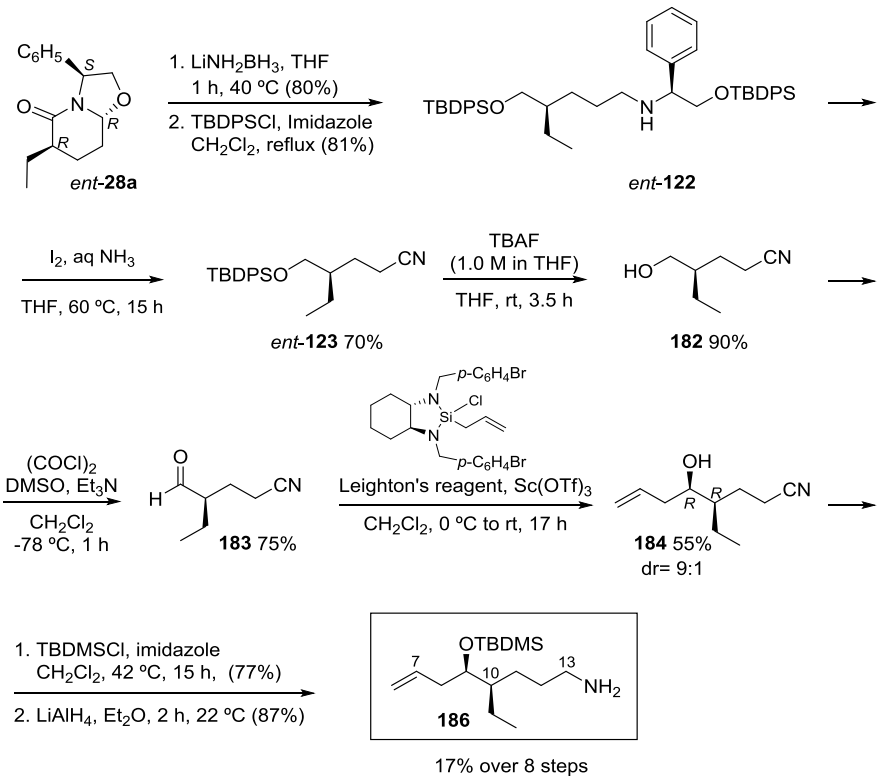
Secondary alcohol **184** was treated with *tert*-butyldimethylsilyl chloride and imidazole in refluxing anhydrous dichloromethane, giving silyl derivative **185** in 77% yield as a 9:1 mixture of diastereoisomers (calculated by ^{1}H NMR). Subsequent reduction of the cyano group with $LiAlH_4$ afforded enantiopure primary amine **186** (the C_7-N fragment of fluvirucinins B) in 87% yield. Purification of amine **186** afforded a single diastereomer.



Scheme 3.74

The synthetic sequence to obtain amine **184** (fragment **B** for the synthesis of fluvirucininins B) is illustrated in Scheme 3.75. Enantiopure amine **184** was synthesized in 8 steps starting from chiral oxazolopiperidone lactam *ent*-**28a** in 17% overall yield.

[123] For the use of $Sc(OTf)_3$ as a catalyst in enantioselective Leighton allylations, see: Kim, H.; Ho, S.; Leighton, J. L. *J. Am. Chem. Soc*. **2011**, *133*, 6517-6520. See also ref 102.

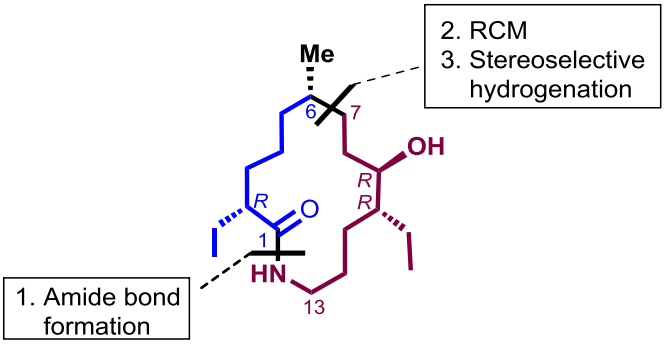


Scheme 3.75

3.2.8. First enantioselective total synthesis of fluvirucinin B_1

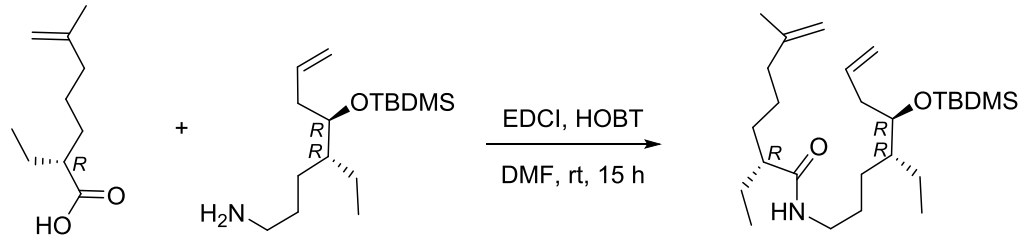
The accomplishment of the total synthesis of fluvirucinin B_1 was envisaged by the amide coupling of both enantiopure fragment **A** (C_1-C_6) and fragment **B** (N-C_7), followed by a ring-closing metathesis reaction to form the strategic C_6-C_7 bond in the key macrocyclization step. Stereoselective hydrogenation of the generated double bond would install the (*S*)-methyl configuration at the C-6 position, and subsequent removal of the protector group would lead to the target aglycon.

A similar macrocyclic stereocontrol in the synthesis of fluvirucinins was first observed by Hoveyda[91,92] in the hydrogenation of related macrocyclic olefins bearing a trisubstituted C_5-C_6 (instead of C_6-C_7) double bond.



Scheme 3.76

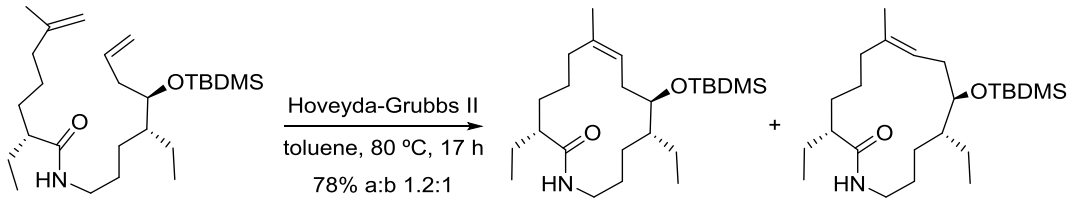
The coupling of both enantiopure fragments **181** and **186** was carried out using EDCI and HOBT in anhydrous DMF, affording the corresponding amide **187** in 79% yield.



181 **186** **187** 79%

Scheme 3.77

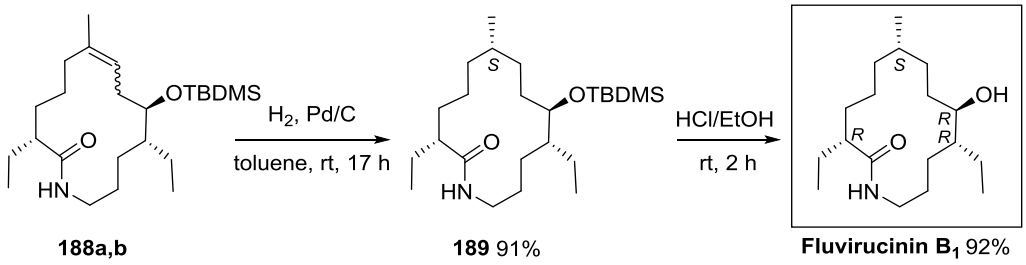
The azacyclotetradecanones *Z*-**188** and *E*-**188** were obtained as a 1.2:1 mixture of *Z*/*E* trisubstituted olefins in 78% yield by treatment of diene **187** with Hoveyda-Grubb's II catalyst in anhydrous toluene. Characterizations of both isomers *E* and *Z* were possible after efficient separation over silica gel.



187 *Z*-**188** 43% *E*-**188** 35%

Scheme 3.78

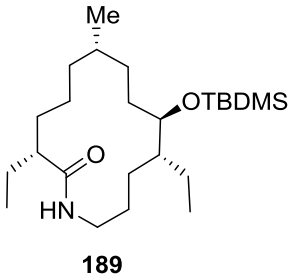
The stereoselective catalytic hydrogenation of both the 1.2:1 mixture of olefins *Z*-**188** and *E*-**188** or the pure *Z*-isomer *Z*-1**88** in anhydrous methanol using Pd/C installed the C-6 stereocenter of the macrocycle leading to the *O*-protected fluvirucinin derivative **189**. The NMR data of our silyl derivative **189** matched those reported in the literature[91,103] and its mp and absolute rotation were in good agreement with those previously reported.[103]



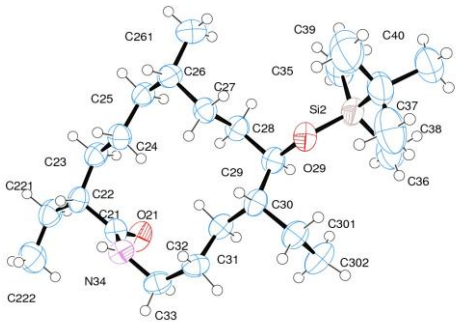
188a,b **189** 91% **Fluvirucinin B_1** 92%

Scheme 3.79

Additionally, the absolute configuration of **189** was unambiguously established by X-ray crystallographic analysis (Scheme 3.80). A final removal of the silyl protecting group completed the synthesis of fluvirucinin B_1, whose NMR data and [α] value are reported for the first time.

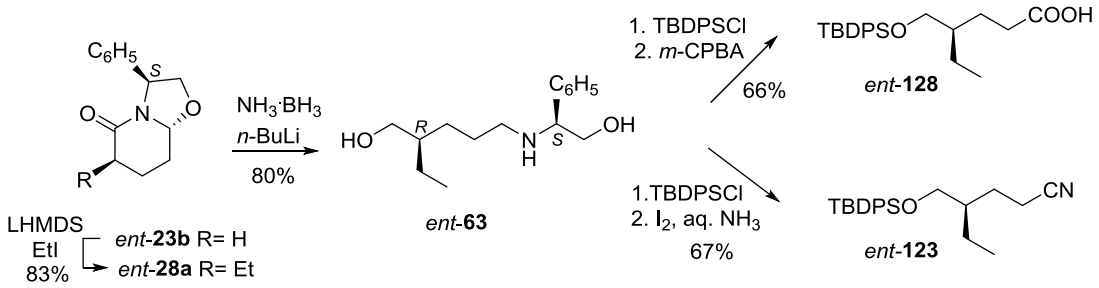


189



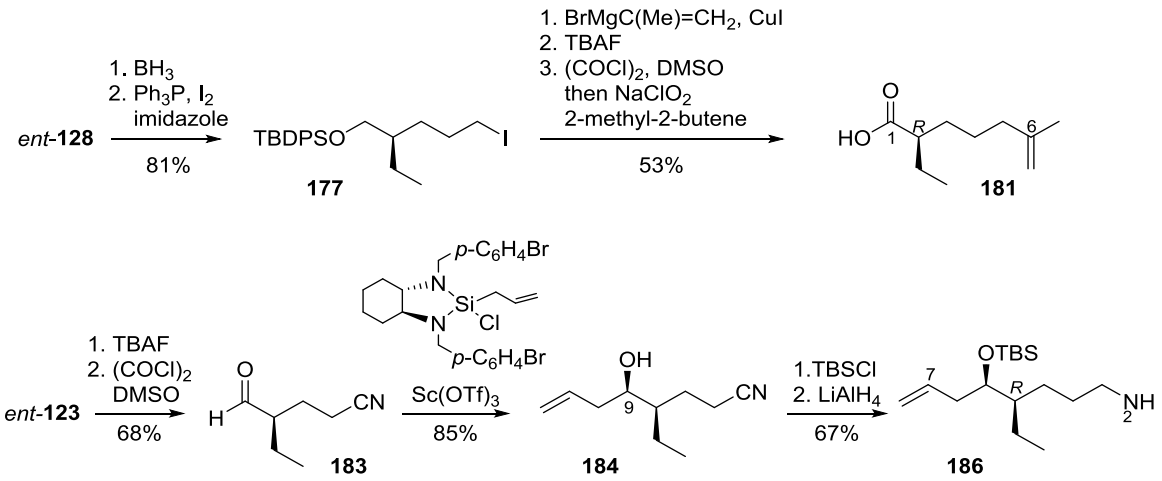
Scheme 3.80

The convergent synthetic sequence, reported in this present Thesis, to obtain fluvirucinin B_1 is summarized in Schemes 3.81-3.83 A distinctive feature of our synthesis is that the starting building blocks *ent*-**128** and *ent*-**123** have been prepared in a straightforward manner from a common phenylglycinol-derived lactam *ent*-**23a**.



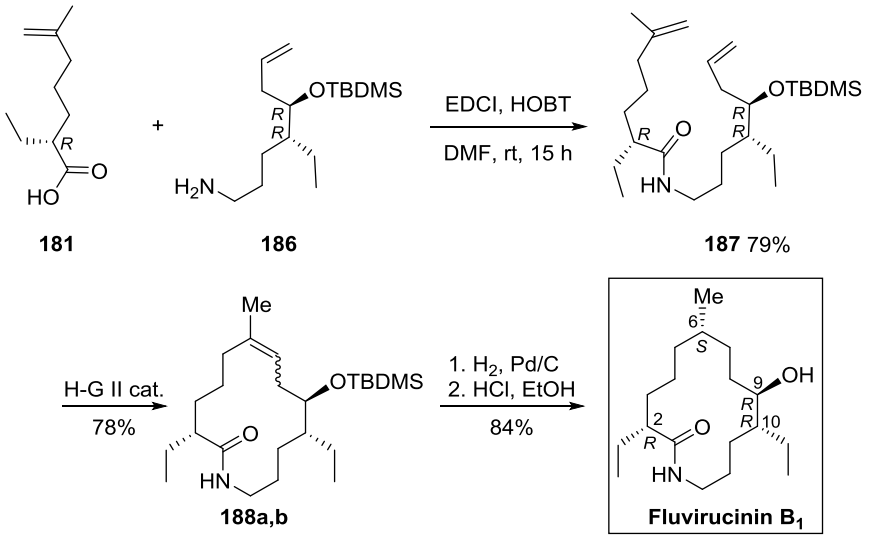
Scheme 3.81

From acid *ent*-**128** and nitrile *ent*-**123**, we synthesized carboxylic acid **181** and amine **186**, respectively, involving a Cu-catalyzed cross-coupling reaction and a stereoselective Leigthon allylation as the key steps.



Scheme 3.82

Finally, ring-closing metathesis from amino diene **187** followed by stereoselective hydrogenation of alkene **188** allowed us to describe enantioselective synthesis of fluvirucinin B_1.



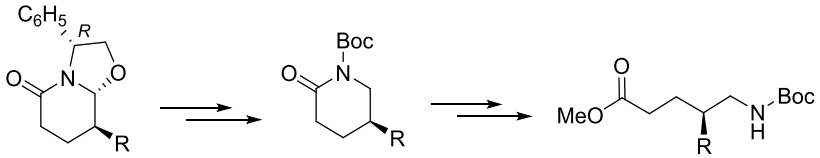
Scheme 3.83

The synthetic potential of the developed methodology in the present thesis (Chapter 2) is highlighted by the enantioselective syntheses of haliclorensin, halitulin (formal), haliclorensin C (the first enantioselective total synthesis) and fluvirucinin B_1 (Chapter 3).

Chapter 4

CONCLUSIONS

1. (*R*)-Phenylglycinol-derived oxazolopiperidone lactams can be converted to enantiopure open-chain amino ester scaffolds by alkaline hydrolysis of the *N*-Boc 2-piperidones resulting from the reductive cleavage of the oxazolidine ring.

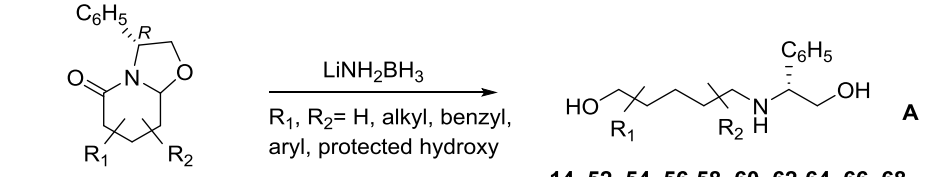


3a R= Et
4a R= Me

9 R= Et
10 R= Me

11 R= Et
12 R= Me

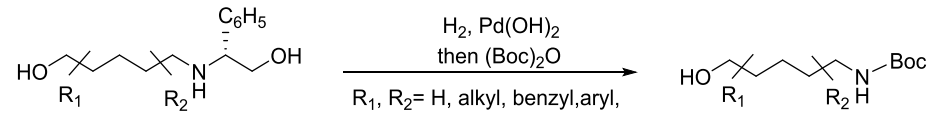
2. Lithium amidotrihydroborate ($LiNH_2BH_3$) reduction of diversely substituted (*R*)-phenylglycinol-derived oxazolopiperidone lactams brought about the reductive opening of both the oxazolidine and lactam rings, providing general access to structurally diverse enantiopure amino diols **A** bearing a variety of substitution patterns, substituents (alkyl, benzyl, aryl, protected hydroxy), and stereochemistries.



3, **4**, **20-34**, **41-45**, **48**, **49**

14, 52, **54**, **56-58**, **60, 62-64**, **66**, **68**, **69**, **71-74**, **76**, **79**, **81**, **83**, **85**, **86**

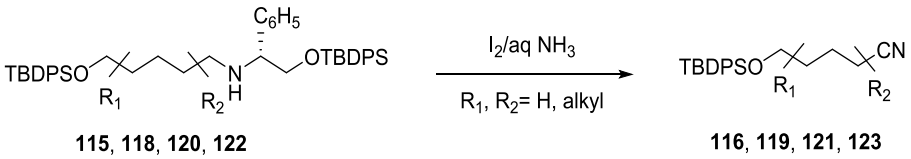
3. Reductive removal of the phenylethanol moiety present in the amino diols prepared by the above procedure, followed by treatment of the resulting primary amines with $(Boc)_2O$ provides a general synthetic entry to enantiopure *N*-Boc 5-aminopentanols bearing substitutents at the 2-, 3-, 4-, 2,2-, 2,3-, 2,4-, and 3,4- positions.



14, 52, **54**, **56-58**, **60, 62-64**, **66**, **68**, **69**, **71-74**, **76**, **79**, **81**, **83**, **85**, **86**

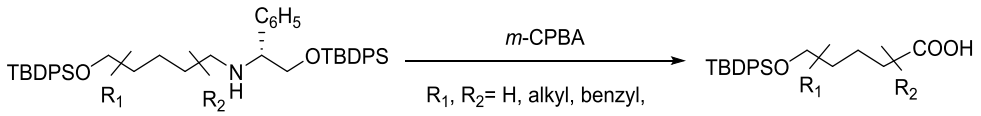
93-113, *ent*-**93**, *ent*-**95**

4. The oxidative removal of the phenylglycinol moiety of amino diols **A** (previously *O*-silylated) using the I_2/aq NH_3 system constitutes an excellent procedure for the straightforward preparation of enantiopure substituted 5-hydroxypentanenitrile derivatives.



115, **118**, **120**, **122** **116**, **119**, **121**, **123**

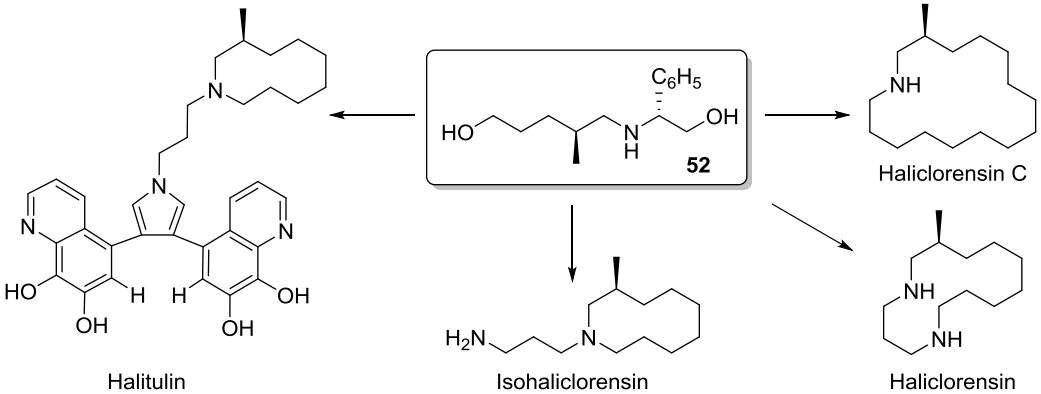
5. The *m*-CPBA-promoted oxidative removal of the phenylglycinol moiety of amino diols **A** (previously *O*-silylated) constitutes an excellent procedure for the straightforward preparation of enantiopure substituted 5-hydroxypentanoic acid derivatives.



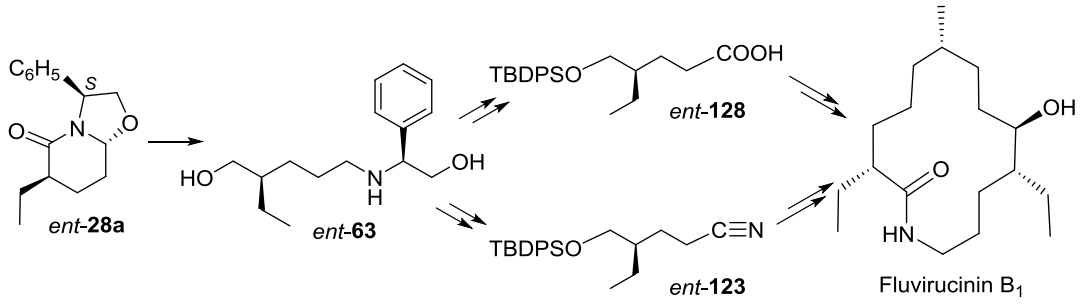
115, **122**, **129**, **131**, **133** **124**, **128**, **130**, **132**, **134**

6. As both enantiomers of phenylglycinol are commercially available, both enantiomers of a target 5-aminopentanol, 5-hydroxypentanoic acid, and 5-hydroxypentanenitrile are accessible through the above methodology.

7. The synthetic value of the open-chain amino diols **A** has been demonstrated with their use as key scaffolds for the enantioselective synthesis of the *Haliclona* alkaloids haliclorensin C (first total synthesis), haliclorensin (total), halitulin (formal), and isohaliclorensin (formal).



8. The synthetic value of the open-chain amino diols 5-hydroxypentanoic acids, and 5-hydroxypentanenitriles prepared from (*S*)-phenylglycinol-derived lactams has been demonstrated with their use as key scaffolds for the synthesis of the natural macrolactam fluvirucinin B_1.



9. The approach we have developed significantly expands the potential of phenylglycinol-derived δ-lactams, which have been converted for the first time to enantiopure open-chain building blocks.

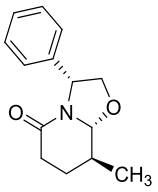
Chapter 5

EXPERIMENTAL DATA

General Procedures:

All air sensitive reactions were performed under a dry argon or nitrogen atmosphere with dry, freshly distilled solvents using standard procedures. Drying of organic extracts during the work-up of reactions was performed over anhydrous Na_2SO_4 or $MgSO_4$. Evaporation of solvent was accomphished with a rotatory evaporator. Thin-layer chromatography was done on SiO_2 (silica gel 60 F_{254}), and the spots were located by UV and either a 1% $KMnO_4$ solution or hexachloroplatinate reagent. Chromatography refers to flash column chromatography and was C-Arried out on SiO_2 (silica gel 60, 230-400 mesh). Melting points were determined in a capillary tube and are uncorrected. NMR spectra were recorded at 400 MHz (1H) and 100.6 MHz (13C), and chemical shifts are reported in δ values, in parts per million (ppm) relative to Me_4Si (0 ppm) or relative to residual chloroform (7.26 ppm, 77.0 ppm) or benzene (7.15 ppm, 128.0 ppm) as an internal standard. Data are reported in the following manner: chemical shift, multiplicity, 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 (HSQC-COSY). IR spectra were performed in a spectrophotometer Nicolet Avatar 320 FT-IR and only noteworthy IR absorptions (cm^{-1}) are listed. Optical rotation were measured on Perlin-Elmer 241 polarimeter. $[a]_D$ values are given in 10^{-1} deg cm^2 g^{-1}. High resolution mass spectra (HMRS) were performed by *Centres Científics i Tecnològics de la Universitat de Barcelona*.

(3*R*,8*S*,8a*R*)-8-Methyl-5-oxo-3-phenyl-2,3,6,7,8,8a-hexahydro-5*H*-oxazolo[3,2-α]pyridine (4a)



Method A: A mixture of racemic oxoester **2**[124] (565 mg, 3.92 mmol), (*R)*-phenylglycinol (537 mg, 3.92 mmol) and anhydrous Na_2SO_4 (2.17 g, 15.3 mmol) in Et_2O (10 mL) was stirred at 0 ºC for 5 h. The resulting suspension was filtered, and the filtrate was concentrated under reduced pressure. The residue was heated at 90 ºC for 5 h under vacuum (10-15 mm Hg). Column chromatography (SiO_2 previously washed with 7:3 hexane-Et_3N; gradient from 7:3 hexane-EtOAc to EtOAc) of the residue afforded lactam **4a** (670 mg, 74 %) and its **(3*R*,8*R*,8a*S*) diastereoisomer 4b** (85 mg, 9 %).

Method B: (*R*)-Phenylglycinol (1.97 g, 14.4 mmol) was added to a solution of racemic oxoester **2**[124] (1.9 g, 14.4 mmol) in anhydrous toluene (45 mL), and the mixture was heated at reflux for 25 h with azeotropic elimination of water produced by a Dean-Stark apparatus. The resulting mixture was cooled and concentrated under reduced pressure. The residue was dissolved in CH_2Cl_2 and washed with saturated aqueous $NaHCO_3$ solution. The combined organic extracts were dried, filtered, and concentrated to give an oil. Flash chromatography (SiO_2 previously washed with 7:3 hexane-Et_3N; gradient from 7:3 hexane-EtOAc to EtOAc) afforded lactam **4a** (1.70 g, 56 %) as a brown solid and its **(3*R*,8*R*,8a*S*) diastereoisomer 4b** (0.55 g, 18 %).

Method C: (*R*)-Phenylglycinol (190 mg, 1.39 mmol) and oxoester **2**[124] (200 mg, 1.39 mmol) in toluene (4.5 mL) were mixed in a capped 10 mL microwave vessel. The mixture was heated at 110 ºC (average effective ramp time = 5 min). The power was set at 100 W and the pressure at 218 psi for 10 min. The reaction mixture was then concentrated under reduced pressure and the crude product was dissolved in CH_2Cl_2 and washed with saturated aqueous $NaHCO_3$ solution. The organic phase was dried, filtered, and concentrated. Flash chromatography (SiO_2 previously washed with 7:3 hexane-Et_3N; gradient from 7:3 hexane-EtOAc to EtOAc) afforded lactam **4a** (185 mg, 58 %) and its (**3*R*,8*R*,8a*S*) diastereoisomer 4b** (70 mg, 22 %).

[124] (a) Shishido, Y.; Kibayashi, C. *J. Org. Chem*. **1992**, *57*, 2876-2883. (b) Oikawa, M.; Oikawa, H.; Ichichara, A. *Tetrahedron* **1995**, *51*, 6237-6254.

Spectroscopic data for **4a**

$[\alpha]^{22}_{D}$ –43.7 (*c* 1.0, MeOH).

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

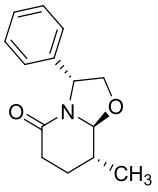
^{1}H NMR (400 MHz, $CDCl_3$, COSY, *g*-HSQC) δ 1.20 (d, *J* = 6.3 Hz, 3H, CH_3), 1.46-1.58 (m, 1H, H-7), 1.88-1.94 (m, 1H, H-7), 1.95-2.00 (m, 1H, H-8), 2.28-2.44 (m, 2H, H-6), 4.00 (dd, *J* = 8.8, 1.2 Hz, 1H, H-2), 4.13 (dd, *J* = 8.8, 6.4 Hz, 1H, H-2), 4.43 (d, *J* = 8.8 Hz, 1H, H-8a), 4.92 (d, *J* = 7.2 Hz, 1H, H-3), 7.21-7.40 (m, 5H, ArH).

^{13}C NMR (100.6 MHz, $CDCl_3$) δ 16.6 (CH_3), 26.9 (C-7), 31.4 (C-6), 34.5 (C-8), 59.1 (C-3), 73.7 (C-2), 93.5 (C-8a), 126.3 (C-*o*), 127.4 (C-*p*), 128.4 (C-*m*), 141.5 (C-*i*), 167.3 (CO).

HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{14}H_{18}NO_2$ 232.1332; found 232.1325.

Anal. Calcd for $C_{14}H_{17}NO_2$ C, 72.70; H, 7.41; N, 6.06; found C, 72.66; H, 7.20; N, 5.98.

Spectroscopic data for **(3*R*,8*R*,8a*S*)-8-methyl-5-oxo-3-phenyl-2,3,6,7,8,8a-hexahydro-5*H*-oxazolo [3,2-*α*]pyridine (4b)**



$[\alpha]^{22}_{D}$ –115.3 (*c* 1.0, MeOH).

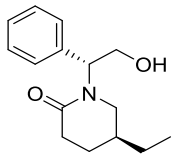
IR (film) 1658 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$, COSY, *g*-HSQC) δ 1.18 (d, *J* = 6.0 Hz, 3H, CH_3), 1.42-1.63 (m, 1H, H-7), 1.65-1.71 (m, 1H, H-8), 1.80-1.85 (m, 1H, H-7), 2.34-2.44 (m, 1H, H-6), 2.53 (dd, *J* = 18.0, 6.0 Hz, 1H, H-6), 3.75 (dd, *J* = 9.0, 7.8 Hz, 1H, H-2), 4.47 (dd, *J* = 9.0, 7.8 Hz, 1H, H-2), 4.60 (d, *J* = 8.0 Hz, 1H, H-8a), 5.25 (t, *J* = 7.8 Hz, 1H, H-3), 7.20-7.45 (m, 5H, ArH).

^{13}C NMR (100.6 MHz, $CDCl_3$) δ 17.1 (CH_3), 25.9 (C-7), 31.5 (C-6), 34.9 (C-8), 58.4 (C-3), 72.4 (C-2), 93.7 (C-8a), 126.1 (C-*o*), 127.5 (C-*p*), 128.7 (C-*m*), 139.5 (C-*i*), 168.7(CO).

Anal. Calcd for $C_{14}H_{17}NO_2$ C, 72.70; H, 7.41; N, 6.06; found C, 72.56; H, 7.35; N, 5.81.

(*S*)-5-Ethyl-[(1*R*)-2-hydroxy-1-phenylethyl]-2-piperidone (5)



Triethylsilane (0.51 mL, 4.77 mmol) and $TiCl_4$ (0.60 mL, 5.51 mmol) were added to a solution of lactam **3a** (500 mg, 2.12 mmol) in anhydrous CH_2Cl_2 (32 mL), and the mixture was stirred at 50 ºC for 24 h. Then, additional $TiCl_4$ (0.60 mL, 5.51 mmol) and triethylsilane (0.51 mL, 4.77 mmol) were added and the stirring was continued at 50 ºC for 24 h. The mixture was poured into saturated aqueous $NaHCO_3$ (100 mL). The aqueous phase was filtered over Celite® and extracted with CH_2Cl_2. The combined organic extracts were dried, filtered, and concentrated to give a residue, which was chromatographed (from 8:2 hexane-EtOAc to EtOAc) to afford **5**[125] (316 mg, 60 %) as a yellow oil.

Spectroscopic data for **5**

$[\alpha]^{22}_D$ –127.2 (*c* 0.9, EtOH); **$[\alpha]^{22}_D$** –73.5 (*c* 1.1, CH_2Cl_2); lit.[125] **$[\alpha]_D$** –74.2 (*c* 1.1, CH_2Cl_2).

IR (film) 3360, 1617 cm^{-1}.

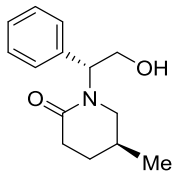
^{1}H NMR (400 MHz, $CDCl_3$, *g*-HSQC) δ 0.84 (t, *J* = 7.6 Hz, 3H, C*H*$_3$CH$_2$), 1.17-1.35 (m, 2H, CH$_3$C*H*$_2$), 1.37-1.49 (m, 1H, H-4), 1.50-1.60 (m, 1H, H-5), 1.88-1.93 (m, 1H, H-4), 2.44 (ddd, *J* = 18.0, 10.4, 7.2 Hz, 1H, H-3), 2.57 (ddd, *J* = 18.0, 6.0, 3.6 Hz, 1H, H-3), 2.90 (dd, *J* = 12.0, 9.6 Hz, 1H, H-6), 3.03 (ddd, *J* = 12.0, 5.0, 2.0 Hz, 1H, H-6), 4.05 (t, *J* = 10.4 Hz, 1H, CH$_2$O), 4.16 (dd, *J* = 11.6, 5.0 Hz, 1H, CH$_2$O), 5.86 (dd, *J* = 9.6, 5.0 Hz, 1H, CHN), 7.20-7.35 (m, 5H, ArH).

^{13}C NMR (100.6 MHz, $CDCl_3$) δ 11.4 (*C*H$_3$CH$_2$), 26.0 (CH$_3$*C*H$_2$), 26.5 (C-4), 31.8 (C-3), 35.6 (C-5), 48.3 (C-6), 58.2 (CHN), 61.2 (CH$_2$O), 127.5 (C-*o*), 127.6 (C-*p*), 128.6 (C-*m*), 137.1 (C-*i*), 171.8 (CO).

Anal. Calcd for $C_{15}H_{21}NO_2 \cdot 1/2\ H_2O$ C, 70.28; H, 8.65; N, 5.46; found C, 70.36; H, 8.37; N, 5.27.

[125] Castro, A.; Juárez, J.; Gnecco, D.; Terán, J. L.; Orea, L.; Bernès, S. *Synth. Commun.* **2006**, *36*, 935-942.

(*S*)-[(1*R*)-2-Hydroxy-1-phenylethyl]-5-methyl-2-piperidone (6)



Triethylsilane (0.52 mL, 3.24 mmol) and $TiCl_4$ (0.52 mL, 4.76 mmol) were added to a solution of lactam **4a** (500 mg, 2.16 mmol) in anhydrous CH_2Cl_2 (35 mL), and the mixture was stirred at 50 ºC for 24 h. Then, additional $TiCl_4$ (0.52 mL, 4.76 mmol) and triethylsilane (0.52 mL, 3.24 mmol) were added and the stirring was continued at 50 ºC for 24 h. The mixture was poured into saturated aqueous $NaHCO_3$ (100 mL). The aqueous phase was filtered over Celite® and extracted with CH_2Cl_2. The combined organic extracts were dried, filtered, and concentrated to give a residue, which was chromatographed (from 8:2 hexane-EtOAc to EtOAc) to afford **6**[125] (315 mg, 63 %) as a colorless oil.

Spectroscopic data for **6**

$[\alpha]^{22}_D$ –150.4 (*c* 0.1, MeOH); **$[\alpha]^{22}_D$** –88.3 (*c* 1.1, CH_2Cl_2); lit.[125] **$[\alpha]_D$** –86.8 (*c* 1.1, CH_2Cl_2).

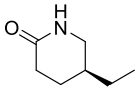
IR (film) 3372, 1616 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$, COSY, *g*-HSQC) δ 0.93 (d, *J* = 6.4 Hz, 3H, CH_3), 1.44-1.54 (m, 1H, H-4), 1.77-1.86 (m, 2H, H-4, H-5), 2.48 (ddd, *J* = 17.9, 11.4, 6.5 Hz, 1H, H-3), 2.59 (ddd, *J* = 17.9, 6.3, 2.9 Hz, 1H, H-3), 2.85 (dd, *J* = 11.8, 10.2 Hz, 1H, H-6), 2.98 (ddd, *J* = 11.8, 4.8, 2.1 Hz, 1H, H-6), 4.09 (dd, *J* = 11.4, 9.6 Hz, 1H, CH_2O), 4.17 (dd, *J* = 11.4, 5.1 Hz, 1H, CH_2O), 5.81 (dd, *J* = 9.6, 5.1 Hz, 1H, CHN), 7.17-7.38 (m, 5H, ArH).

^{13}C-NMR (100.6 MHz, $CDCl_3$) δ 18.6 (CH_3), 28.9 (C-5), 29.1 (C-4), 32.0 (C-3), 50.3 (C-6), 58.5 (CHN), 61.6 (CH_2O), 127.6 (C-*o*), 127.7 (C-*p*), 128.7 (C-*m*), 137.0 (C-*i*), 171.5 (CO).

HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{14}H_{20}NO_2$ 234.1489; found 234.1484.

(*S*)-5-Ethyl-2-piperidone (7)



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 ºC. A solution of **5** (300 mg, 1.21 mmol) in anhydrous THF (5 mL) was added, and the temperature was raised to –33 ºC. Sodium metal was added in small portions until the blue color persisted, and the mixture was stirred at –33 ºC for 3 minutes. The reaction was quenched by addition of solid NH_4Cl until the blue color disappeared, and then the mixture was stirred at room temperature for 5 h. CH_2Cl_2 was added, the solid was filtered, and the solvent was removed under reduced pressure. The resulting oil was chromatographed (from 8:2 hexane-EtOAc to 8:2 EtOAc-EtOH) to afford **7**[126] (119 mg, 77 %).

Spectroscopic data for **7**

$[\alpha]^{22}_{D}$ –58.3 (*c* 0.75, MeOH).

IR (film) 1665 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$, COSY, *g*-HSQC) δ 0.95 (t, *J* = 7.5 Hz, 3H, C*H*$_3$CH$_2$), 1.34-1.50 (m, 3H, CH$_3$C*H*$_2$, H-4), 1.62-1.78 (m, 1H, H-5), 1.87-1.98 (m, 1H, H-4), 2.25-2.50 (m, 2H, H-3), 2.94 (t, *J* = 12.0 Hz, 1H, H-6), 3.35 (m, 1H, H-6), 5.93 (br.s, 1H, NH).

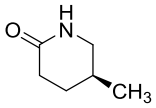
^{13}C NMR (75.4 MHz, $CDCl_3$) δ 11.4 (*C*H$_3$CH$_2$), 25.9 (CH$_3$*C*H$_2$), 26.6 (C-4), 30.7 (C-3), 34.7 (C-5), 47.3 (C-6), 172.7 (CO).

HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_7H_{14}NO$ 128.1070; found 128.1067.

Anal. Calcd for $C_7H_{13}NO \cdot 1/4\ H_2O$ C, 64.95; H, 10.54; N, 10.10; found C, 64.58; H, 10.18; N, 10.05.

[126] Fujii, T.; Yoshifuji, S.; Michishita, K.; Mitsukuchi, M.; Yoshida, K. *Chem. Pharm. Bull*. **1973**, 2695-2704.

(*S*)-5-Methyl-2-piperidone (8)



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 ºC. A solution of **6** (290 mg, 1.24 mmol) in anhydrous THF (5 mL) was added, and the temperature was raised to –33 ºC. Sodium metal was added in small portions until the blue color persisted, and the mixture was stirred at –33 ºC for 3 minutes. The reaction was quenched by addition of solid NH_4Cl until the blue color disappeared, and then the mixture was stirred at room temperature for 5 h. CH_2Cl_2 was added, the solid was filtered, and the solvent was removed under reduced pressure. The resulting oil was chromatographed (from 8:2 hexane-EtOAc to 8:2 EtOAc-EtOH) to afford **8**[127] (93 mg, 66 %).

Spectroscopic data for **8**

$[\alpha]^{22}_D$ –29.0 (*c* 0.55, MeOH); **$[\alpha]^{22}_D$** –80.0 (*c* 1.0, $CHCl_3$); lit.[127]

$[\alpha]^{23}_D$ –82.5 (*c* 1.0, $CHCl_3$).

IR (film) 3232, 1659 cm^{-1}.

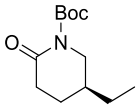
^{1}H NMR (300 MHz, $CDCl_3$, COSY, *g*-HSQC) δ 1.01 (d, *J* = 6.6 Hz, 3H, CH_3), 1.45-1.51 (m, 1H, H-4), 1.83-1.99 (m, 2H, H-4, H-5), 2.34 (ddd, *J* = 17.8, 10.8, 6.4 Hz, 1H, H-3), 2.43 (ddd, *J* = 17.8, 6.4, 3.5 Hz, 1H, H-3), 2.92 (t, *J* = 10.8 Hz, 1H, H-6), 3.26-3.33 (m, 1H, H-6), 6.10 (br.s, 1H, NH).

^{13}C NMR (75.4 MHz, $CDCl_3$) δ 18.2 (CH_3), 28.0 (C-5), 28.8 (C-4), 30.6 (C-3), 48.8 (C-6), 172.6 (CO).

HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_6H_{12}NO$ 114.0914; found 114.0913.

[127] Karanfil, A.; Balta, B.; Eskici, M. *Tetrahedron* **2012**, *68*, 10218-10229.

(*S*)-1-(*tert*-ButoxyC-Arbonyl)-5-ethyl-2-piperidone (9)



n-BuLi (1.6 M in hexanes, 0.88 mL, 1.4 mmol) was added at –78 ºC to a solution of lactam **7** (180 mg, 1.4 mmol) in anhydrous THF (3.8 mL), and the mixture was stirred at this temperature for 30 minutes. Then, a cooled (–78 ºC) solution of di-*tert*-butyl diC-Arbonate (309 mg, 1.4 mmol) in anhydrous THF (1.2 mL) was added, and the resulting mixture was stirred for 90 minutes at this temperature. Saturated aqueous NH_4Cl was added, and the resulting mixture was extracted with EtOAc. The combined organic extracts were dried and concentrated. The residue was chromatographed (from 9:1 hexane-EtOAc to 1:1 hexane-EtOAc) affording lactam **9** (221 mg, 70 %) as a colorless oil.

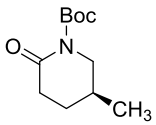
Spectroscopic data for **9**

^{1}H NMR (400 MHz, $CDCl_3$, COSY, *g*-HSQC) δ 0.96 (t, *J* = 7.5 Hz, 3H, CH_3CH_2), 1.30-1.46 (m, 3H, CH_3CH_2, H-4), 1.53 [s, 9H, $(CH_3)_3$], 1.68-1.77 (m, 1H, H-5), 1.89-1.98 (m, 1H, H-4), 2.45 (ddd, *J* = 17.3, 10.6, 6.4 Hz, 1H, H-3), 2.55 (ddd, *J* = 17.3, 6.4, 4.3 Hz, 1H, H-3), 3.17 (dd, *J* = 12.7, 10.1 Hz, 1H, H-6), 3.82 (ddd, *J* = 12.7, 4.8, 1.7 Hz, 1H, H-6).

^{13}C NMR (100.6 MHz, $CDCl_3$) δ 11.3 (CH_3CH_2), 26.2 (C-4), 26.3 (CH_3CH_2), 28.0 [$(CH_3)_3$], 34.1 (C-3), 35.2 (C-5), 50.9 (C-6), 82.8 [$C(CH_3)_3$], 152.8 (NCO), 171.5 (CO).

HRMS (ESI-TOF) m/z: $[M - tBu]^+$ Calcd for $C_8H_{12}NO_3$ 170.0812; found 170.0808.

(*S*)-1-(*tert*-ButoxyC-Arbonyl)-5-methyl-2-piperidone (10)



n-BuLi (1.6 M in hexanes, 0.55 mL, 0.88 mmol) was added at –78 ºC to a solution of lactam **8** (100 mg, 0.88 mmol) in anhydrous THF (2.5 mL), and the mixture was

stirred at this temperature for 30 minutes. Then, a cooled (–78 ºC) solution of di-*tert*-butyl diC-Arbonate (289 mg, 1.32 mmol) in anhydrous THF (1.2 mL) was added, and the resulting mixture was stirred for 90 minutes at this temperature. Saturated aqueous NH_4Cl was added, and the resulting mixture was extracted with EtOAc. The combined organic extracts were dried and concentrated. The residue was chromatographed (95:5 hexane-EtOAc) affording lactam **10** (150 mg, 80 %) as a colorless oil.

Spectroscopic data for **10**

$[\alpha]^{22}_{D}$ –19.5 (*c* 0.3, $CHCl_3$).

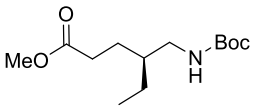
IR (film) 1770, 1715 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$, COSY, *g*-HSQC) δ 1.04 (d, *J* = 6.6 Hz, 3H, CH_3), 1.41-1.50 (m, 1H, H-4), 1.52 [s, 9H, $(CH_3)_3$], 1.84-1.92 (m, 1H, H-4), 1.93-2.03 (m, 1H, H-5), 2.47 (ddd, *J* = 17.4, 10.8, 6.5 Hz, 1H, H-3), 2.57 (ddd, *J* = 17.4, 6.5, 4.0 Hz, 1H, H-3), 3.11 (dd, *J* = 12.6, 10.4 Hz, 1H, H-6), 3.79 (ddd, *J* = 12.6, 4.8, 2.0 Hz, 1H, H-6).

^{13}C NMR (100.6 MHz, $CDCl_3$) δ 18.7 (CH_3), 28.0 [$(CH_3)_3$], 28.7 (C-4), 28.7 (C-5), 34.2 (C-3), 52.8 (C-6), 82.8 [*C*$(CH_3)_3$], 152.7 (NCO), 172.6 (CO).

HRMS (ESI-TOF) m/z: $[M + Na]^+$ Calcd for $C_{11}H_{19}NO_3Na$ 236.1257; found 236.1258.

Methyl (*S*)-5-[(*tert*-butoxyC-Arbonyl)amino]-4-ethylpentanoate (11)



A solution of LiOH (44.3 mg, 1.06 mmol) in water (1.1 mL) was added to a solution of lactam **9** (80 mg, 0.35 mmol) in THF (1.7 mL), and the mixture was stirred at room temperature for 4 h. THF was removed under reduced pressure, and the residue was dissolved in Et_2O. The organic extract was washed with aqueous 1 N HCl, dried, filtered, and concentrated to afford a C-Arboxylic acid (80 mg) as a colorless oil, which was used without purification in the next step:

^{1}H NMR (400 MHz, $CDCl_3$, COSY, *g*-HSQC) δ 0.90 (t, *J* = 7.5 Hz, 3H, C*H*$_3$CH$_2$), 1.25-1.36 (m, 2H, CH$_3$C*H*$_2$), 1.44 [s, 9H, $(CH_3)_3$], 1.43-1.48 (m, 1H, H-4), 1.55-1.67

(m, 2H, H-3), 2.30-2.42 (t, *J* = 7.6 Hz, 2H, H-2), 2.90-3.17 (m, 2H, H-5), 6.07 (br.s, 1H, NH).

^{13}C NMR (100.6 MHz, $CDCl_3$) δ 10.8 (CH_3CH_2), 24.0 (CH_3CH_2), 25.9 (C-3), 28.4 [$(CH_3)_3$], 31.3 (C-2), 39.3 (C-4), 42.9 (C-5), 79.3 [$C(CH_3)_3$], 156.2 (NCO), 179.0 (CO_2).

HRMS (ESI-TOF) m/z: $[M + Na]^+$ Calcd for $C_{12}H_{23}NO_4Na$ 268.1519; found 268.1519.

$TMSCHN_2$ (0.24 mL, 0.47 mmol) was added at 0 ºC to a solution of the above C-Arboxylic acid (80 mg) in toluene-methanol (2.5:1, 11 mL), and the mixture was stirred at this temperature for 1 h, quenched with some drops of AcOH, and concentrated under reduced pressure to afford pure ester **11** (73 mg, 80 %).

Spectroscopic data for **11**

$[\alpha]^{22}_D$ –8.4 (*c* 0.58, MeOH).

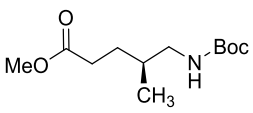
IR (film) 3371, 1740, 1715 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$, COSY, *g*-HSQC) δ 0.90 (t, *J* = 7.2 Hz, 3H, CH_3), 1.32 (m, 2H, CH_3CH_2), 1.44 [s, 9H, $(CH_3)_3$], 1.46 (m, 1H, H-4), 1.62 (m, 2H, H-3), 2.34 (t, *J* = 7.7 Hz, 2H, H-2), 3.02 (m, 1H, H-5), 3.09 (m, 1H, H-5), 3.70 (s, 3 H, CH_3O), 4.67 (br.s, 1H, NH).

^{13}C NMR (100.6 MHz, $CDCl_3$) δ 10.8 (CH_3), 23.9 (CH_3CH_2), 26.0 (C-3), 28.3 [$C(CH_3)_3$], 31.2 (C-2), 39.3 (C-4), 42.9 (C-5), 51.5 (CH_3O), 79.0 [$C(CH_3)_3$], 156.0 (NCO), 174.2 (CO_2).

HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{13}H_{26}NO_4$ 260.1856; found 260.1852.

Methyl (*S*)-5-[(*tert*-butoxyC-Arbonyl)amino]-4-methylpentanoate (12)



A solution of LiOH (50.2 mg, 1.20 mmol) in water (1.25 mL) was added to a solution of lactam **10** (85 mg, 0.40 mmol) in THF (1.9 mL), and the mixture was stirred at room temperature for 4 h. THF was removed under reduced pressure, and the

residue was dissolved in Et_2O. The organic extract was washed with aqueous 1 N HCl, dried, filtered, and concentrated to afford a C-Arboxylic acid (85 mg) as a colorless oil, which was used without purification in the next step:

^{1}H NMR (400 MHz, $CDCl_3$) δ 0.91 (d, *J* = 6.8 Hz, 3H, CH_3), 1.44 [s, 10H, $(CH_3)_3$, C*H*$_2$) 1.58-1.76 (m, 2H), 2.32-2.45 (m, 2H), 2.95-3.05 (m, 2H), 4.65 (br.s, 1H, NH).

HRMS (ESI-TOF) m/z: $[M - H]^+$ Calcd for $C_{11}H_{20}NO_4$ 230.1398; found 230.1397.

$TMSCHN_2$ (0.28 mL, 0.55 mmol) was added at 0 ºC to a solution of the above C-Arboxylic acid (85 mg) in toluene-methanol (2.5:1, 12.3 mL), and the mixture was stirred at this temperature for 1 h, quenched with some drops of AcOH, and concentrated under reduced pressure to afford pure ester **12** (88 mg, 90 %).

Spectroscopic data for **12**

$[\alpha]^{22}_D$ –5.45 (*c* 0.8, MeOH).

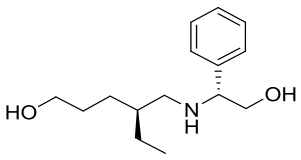
IR (film) 3375, 1735, 1715 cm^{-1};

^{1}H NMR (400 MHz, $CDCl_3$, COSY, *g*-HSQC) δ 0.85 (d, *J* = 6.6 Hz, 3H, CH_3), 1.38 [s, 10H, $(CH_3)_3$, H-3], 1.52-1.61 (m, 1H, H-4), 1.62-1.71 (m, 1H, H-3), 2.20-2.37 (m, 2H, H-5), 2.92-3.02 (m, 2H, H-2), 3.61 (s, 3H, CH_3O), 4.71 (br.s, 1H, NH).

^{13}C NMR (100.6 MHz, $CDCl_3$) δ 17.1 (CH_3), 28.3 [$(CH_3)_3$], 28.9 (C-3), 31.4 (C-5), 33.2 (C-4), 45.9 (C-2), 51.4 (CH_3O), 78.9 [*C*$(CH_3)_3$], 156.0 (NCO), 174.1 (CO_2).

HRMS (ESI-TOF) m/z: $[M + Na]^+$ Calcd for $C_{12}H_{23}NO_4Na$ 268.1519; found 268.1527.

(*S*)-4-Ethyl-5-{[(1*R*)-2-hydroxy-1-phenylethyl]amino}-1-pentanol (14)



n-BuLi (1.40 mL of a 2.5 M solution in hexanes, 3.51 mmol) was added to a solution of $NH_3{\cdot}BH_3$ (108 mg, 3.51 mmol) in anhydrous THF (2 mL) at 0 ºC, and the resulting mixture was stirred at this temperature for 10 min and at room temperature for 15 minutes. Then, this solution was added to a solution of **3a** (200 mg, 0.82 mmol) in

anhydrous THF (1 mL), and the stirring was continued at 40 ºC for 1 h. The reaction mixture was quenched with H_2O, and the resulting solution was extracted with Et_2O. The combined organic extracts were dried, filtered, and concentrated. Flash chromatography (from 8:2 hexane-EtOAc to 8:2 EtOAc-EtOH) of the residue gave aminoalcohol **14** (165 mg, 80 %) as a colorless oil.

Spectroscopic data for **14**

$[\alpha]^{22}_D$ –44.9 (*c* 0.16, MeOH).

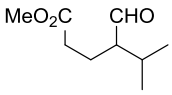
IR (film) 3330 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$, COSY, *g*-HSQC) δ 0.82 (t, *J* = 7.6 Hz, 3H, CH_3), 1.23-1.40 (m, 3H, H-3, CH_3CH_2), 1.42-1.50 (m, 4H, H-2, H-3, H-4), 2.40 (dd, *J* = 11.6, 6.4 Hz, 1H, H-5), 2.46 (dd, *J* = 11.6, 5.0 Hz, 1H, H-5), 3.41 (br.s, 3H, OH, NH), 3.57-3.64 (m, 3H, H-1, CH_2O), 3.71 (dd, *J* = 10.8, 4.0 Hz, 1H, CH_2O), 3.77 (dd, *J* = 8.8, 4.0 Hz, 1H, CHN), 7.24-7.38 (m, 5H, ArH).

^{13}C NMR (100.6 MHz, $CDCl_3$) δ 11.3 (CH_3), 24.9 (CH_3CH_2), 27.4 (C-3), 29.2 (C-2), 38.8 (C-4), 50.2 (C-5), 60.3 (C-1), 64.8 (CHN), 66.5 (CH_2O), 127.3 (C-*o*), 127.6 (C-*p*), 128.6 (C-*m*), 139.9 (C-*i*).

HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{15}H_{26}NO_2$ 252.1958; found 252.1947.

Methyl 4-Isopropyl-5-oxopentanoate (16)



Isovaleraldehyde **15** (7.54 mL, 69.7 mmol) was added dropwise to a cooled (0 ºC) mixture of piperidine (10.3 mL, 104.5 mmol) and K_2CO_3 (3.47 g, 25.1 mmol) and the mixture was stirred for 18 h at room temperature. Insoluble material was filtered through Celite®, and the filtrate was washed with Et_2O, dried, filtered, and concentrated in vacuum to remove the excess of piperidine. Methyl acrylate (7.64 mL, 84.8 mmol) was slowly added to a stirred solution of the resulting residue in anhydrous acetonitrile (21 mL) at 0 ºC. The mixture was stirred at reflux overnight. Glacial acetic acid (4.8 mL) and water (21 mL) were added, and the resulting solution was heated at reflux for 2 h. The mixture was allowed to cool to room temperature, the aqueous phase was saturated with NaCl, and the solution was extracted with

Et_2O. The combined organic extracts were dried, filtered, and concentrated to give an oil. Flash chromatography (8:2 hexane-Et_2O) afforded compound **16** (8.7 g, 73 %) as a colorless oil.

Spectroscopic data for **16**

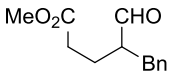
IR (film) 1738 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$, COSY, *g*-HSQC) δ 0.97 (d, *J* = 6.8 Hz, 3H, CHC*H*$_3$), 1.00 (d, *J* = 6.8 Hz, 3H, CHC*H*$_3$), 1.74-1.83 (m, 1H, H-3), 1.90-1.99 (m, 1H, H-3), 2.02-2.10 (m, 1H, C*H*Me_2), 2.12-2.18 (m, 1H, H-4), 2.25 (ddd, *J* = 16.1, 8.5, 7.4 Hz, 1H, H-2), 2.38 (ddd, *J* = 16.1, 8.9, 6.0 Hz, 1H, H-2), 3.67 (s, 3H, CH_3O), 9.65 (s, 1H, CHO).

^{13}C NMR (100.6 MHz, $CDCl_3$) δ 19.3 (CH_3), 19.9 (CH_3), 20.8 (C-3), 28.3 ($CHMe_2$), 31.8 (C-2), 51.3 (CH_3O), 57.3 (C-4), 173.3 (CO_2), 204.4 (CHO).

HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_9H_{17}O_3$ 173.1172; found 173.1168.

Methyl 4-Benzyl-5-oxopentanoate (18)



3-Phenylpropanal **17** (5.89 mL, 44.7 mmol) was added dropwise to a cooled (0 ºC) mixture of piperidine (6.61 mL, 67.1 mmol) and K_2CO_3 (2.23 g, 15.6 mmol) and the mixture was stirred for 18 h at room temperature. Insoluble material was filtered through Celite®, and the filtrate was washed with Et_2O, dried, filtered, and concentrated in vacuum to remove the excess of piperidine. Methyl acrylate (7.0 mL, 77.5 mmol) was slowly added to a stirred solution of the resulting residue in anhydrous acetonitrile (20 mL) at 0 ºC. The mixture was stirred at reflux overnight. Glacial acetic acid (5 mL) and water (20 mL) were added, and the resulting solution was heated at reflux for 2 h. The mixture was allowed to cool to room temperature, the aqueous phase was saturated with NaCl, and the solution was extracted with Et_2O. The combined organic extracts were dried, filtered, and concentrated to give an oil. Flash chromatography (from 95:5 hexane-Et_2O to 9:1 hexane-Et_2O) afforded compound **18** (5.8 g, 57 %) as a yellow oil.

Spectroscopic data for **18**

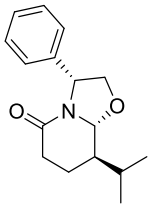
IR (film) 1732 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$, COSY, *g*-HSQC) δ 1.76-1.85 (m, 1H, H-3), 1.93-2.01 (m, 1H, H-3), 2.34 (m, 2H, H-2), 2.66-2.71 (m, 1H, H-4), 2.71-2.77 (m, 1H, CH_2Ar), 3.02 (dd, *J* = 13.4, 6.6 Hz, 1H, CH_2Ar), 3.65 (s, 3H, CH_3), 7.15-7.32 (m, 5H, ArH), 9.68 (d, *J* = 2.0 Hz, 1H, CHO).

^{13}C NMR (100.6 MHz, $CDCl_3$) δ 23.5 (C-3), 31.3 (C-2), 35.1 (CH_2Ar), 51.6 (CH_3), 52.4 (C-4), 126.5 (C-*p*), 128.6, 128.8 (C-*o*, C-*m*), 138.1 (C-*i*), 173.2 (CO_2), 203.5 (CHO).

HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{13}H_{17}O_3$ 221.1099; found 221.1089.

(3*R*,8*R*,8a*R*)-8-Isopropyl-5-oxo-3-phenyl-2,3,6,7,8,8a-hexahydro-5*H*-oxazolo[3,2-*a*]pyridine (20a)



Method A: A mixture of racemic oxoester **16** (1.07 g, 6.18 mmol), (*R)*-phenylglycinol (848 mg, 6.18 mmol) and anhydrous Na_2SO_4 (3.43 g, 24.1 mmol) in Et_2O (20 mL) was stirred at 0 ºC for 5 h. The resulting suspension was filtered, and the filtrate was concentrated under reduced pressure. The residue was heated at 90 ºC for 5 h under vacuum (10-15 mm Hg). Column chromatography (SiO_2 previously washed with 7:3 hexane-Et_3N; gradient from 7:3 hexane-EtOAc to EtOAc) of the residue afforded lactam **20a** (1.16 g, 73 %) and its **(3*R*,8*S*,8a*S*) diastereoisomer 20b** (180 mg, 11 %).

Method B: (*R*)-Phenylglycinol (867 mg, 6.32 mmol) was added to a solution of racemic oxoester **16** (1.09 g, 6.32 mmol) in anhydrous toluene (20 mL), and the mixture was heated at reflux for 25 h with azeotropic elimination of water produced by a Dean-Stark apparatus. The resulting mixture was cooled and concentrated under reduced pressure. The residue was dissolved in CH_2Cl_2 and washed with saturated aqueous $NaHCO_3$ solution. The combined organic extracts were dried, filtered, and concentrated to give an oil. Flash chromatography (SiO_2 previously washed with 7:3

hexane-Et_3N; gradient from 7:3 hexane-EtOAc to EtOAc) afforded lactam **20a** (1.06 g, 64 %) as a white solid and its **(3*R*,8*S*,8a*S*) diastereoisomer 20b** (230 mg, 14 %).

Spectroscopic data for **20a**

$[\alpha]^{22}_D$ –18.6 (*c* 1.2, MeOH).

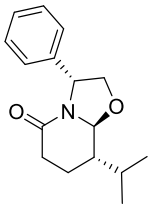
IR (film) 1658 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$, COSY, *g*-HSQC) δ 0.98 (d, *J* = 6.9 Hz, 3H, CH_3), 1.07 (d, *J* = 6.9 Hz, 3H, CH_3), 1.50-1.61 (m, 1H, H-7), 1.76-1.83 (m, 1H, H-8), 1.86-1.93 (m, 1H, H-7), 2.08-2.16 [m, 1H, C*H*$(CH_3)_2$], 2.30 (ddd, *J* = 17.9, 11.2, 6.8 Hz, 1H, H-6), 2.43 (ddd, *J* = 17.9, 6.8, 2.4 Hz, 1H, H-6), 4.01 (d, *J* = 9.0 Hz, 1H, H-2), 4.14 (dd, *J* = 9.0, 6.6 Hz, 1H, H-2), 4.67 (d, *J* = 9.2 Hz, 1H, H-8a), 4.92 (d, *J* = 6.6 Hz, 1H, H-3), 7.22-7.32 (m, 5H, ArH).

^{13}C NMR (100.6 MHz, $CDCl_3$) δ 17.7 (CH_3), 19.6 (C-7), 20.5 (CH_3), 27.7 [*C*H$(CH_3)_2$], 31.6 (C-6), 44.6 (C-8), 58.9 (C-3), 73.8 (C-2), 90.6 (C-8a), 126.3 (C-*o*), 127.4 (C-*p*), 128.5 (C-*m*), 141.6 (C-*i*), 167.3 (CO).

HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{16}H_{22}NO_2$ 260.1645; found 260.1640.

Spectroscopic data for **(3*R*,8*S*,8a*S*)-8-Isopropyl-5-oxo-3-phenyl-2,3,6,7,8,8a-hexahydro-5*H*-oxazolo[3,2-*a*]pyridine (20b)**



$[\alpha]^{22}_D$ –87.7 (*c* 1.2, MeOH).

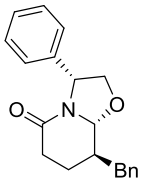
IR (film) 1666 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$, COSY, *g*-HSQC) δ 0.96 (dd, *J* = 6.9, 2.1 Hz, 3H, CH_3), 1.05 (dd, *J* = 6.9, 2.1 Hz, 3H, CH_3), 1.47-1.63 (m, 2H, H-7, H-8), 1.83-1.88 (m, 1H, H-7), 2.01-2.05 [m, 1H, C*H*$(CH_3)_2$], 2.30-2.39 (m, 1H, H-6), 2.59 (dm, *J* = 18.5 Hz, 1H, H-6), 3.74 (dt, *J* = 8.2, 2.1 Hz, 1H, H-2), 4.48 (dt, *J* = 8.2, 2.1 Hz, 1H, H-2), 4.80 (dd, *J* = 8.2, 2.1 Hz, 1H, H-8a), 5.26 (t, *J* = 7.8 Hz, 1H, H-3), 7.26-7.37 (m, 5H, ArH).

^{13}C NMR (100.6 MHz, $CDCl_3$) δ 18.0 (CH_3), 19.2 (C-7), 20.6 (CH_3), 28.1 [*C*H(CH_3)$_2$], 31.7 (C-6), 45.3 (C-8), 58.1 (C-3), 72.4 (C-2), 90.7 (C-8a), 126.1 (C-*o*), 127.5 (C-*p*), 128.8 (C-*m*), 139.7 (C-*i*), 169.1 (CO).

HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{16}H_{22}NO_2$ 260.1645; found 260.1639.

(3*R*,8*R*,8a*R*)-8-Benzyl-5-oxo-3-phenyl-2,3,6,7,8,8a-hexahydro-5*H*-oxazolo[3,2-*a*] pyridine (21a)



Method A: A mixture of racemic oxoester **18** (626 mg, 2.84 mmol), (*R)*-phenylglycinol (390 mg, 2.84 mmol) and anhydrous Na_2SO_4 (1.57 g, 11.1 mmol) in Et_2O (9 mL) was stirred at 0 ºC for 5 h. The resulting suspension was filtered, and the filtrate was concentrated under reduced pressure. The residue was heated at 90 ºC for 5 h under vacuum (10-15 mm Hg). Column chromatography (SiO_2 previously washed with 7:3 hexane-Et_3N; gradient from 7:3 hexane-EtOAc to EtOAc) of the residue afforded lactam **21a** (478 mg, 55 %) and its **(3*R*,8*S*,8a*S*) diastereoisomer 21b** (white solid, 80 mg, 9 %).

Method B: (*R*)-Phenylglycinol (391 mg, 2.85 mmol) was added to a solution of racemic oxoester **18** (627 mg, 2.85 mmol) in anhydrous toluene (9 mL), and the mixture was heated at reflux for 25 h with azeotropic elimination of water produced by a Dean-Stark apparatus. The resulting mixture was cooled and concentrated under reduced pressure. The residue was dissolved in CH_2Cl_2 and washed with saturated aqueous $NaHCO_3$ solution. The combined organic extracts were dried, filtered, and concentrated to give an oil. Flash chromatography (SiO_2 previously washed with 7:3 hexane-Et_3N; gradient from 7:3 hexane-EtOAc to EtOAc) afforded lactam **21a** (483 mg, 55 %) as a white solid and its **(3*R*,8*S*,8a*S*) diastereoisomer 21b** (white solid, 122 mg, 14 %).

Spectroscopic data for **21a**

$[\alpha]^{22}_{D}$ –144.8 (*c* 0.1, MeOH).

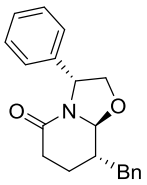
IR (film) 1658 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$, COSY, *g*-HSQC) δ 1.39-1.51 (m, 1H, H-7), 1.83-1.88 (m, 1H, H-7), 2.08-2.13 (m, 1H, H-8), 2.21 (ddd, *J* = 18.2, 11.6, 6.9 Hz, 1H, H-6), 2.36 (ddd, *J* = 18.2, 6.9, 1.8 Hz, 1H, H-6), 2.54 (dd, *J* = 13.5, 9.7 Hz, 1H, CH_2Ar), 3.27 (dd, *J* = 13.5, 3.5 Hz, 1H, CH_2Ar), 4.06 (dd, *J* = 9.0, 1.2 Hz, 1H, H-2), 4.18 (dd, *J* = 9.0, 6.4 Hz, 1H, H-2), 4.58 (d, *J* = 9.0 Hz, 1H, H-8a), 4.94 (d, *J* = 6.4 Hz, 1H, H-3), 7.23-7.35 (m, 10H, ArH).

^{13}C NMR (100.6 MHz, $CDCl_3$) δ 23.4 (C-7), 31.3 (C-6), 37.2 (CH_2Ar), 41.0 (C-8), 59.1 (C-3), 73.9 (C-2), 91.9 (C-8a), 126.3 (C-*o*), 126.5 (C-*p*), 127.5 (C-*p*), 128.5 and 129.2 (2C-*m*, C-*o*), 138.2 and 141.4 (2C-*i*), 167.2 (CO).

HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{20}H_{22}NO_2$ 308.1645; found 308.1645.

Spectroscopic data for **(3*R*,8*S*,8a*S*)-8-benzyl-5-oxo-3-phenyl-2,3,6,7,8,8a-hexahydro-5*H*-oxazolo[3,2-*a*]pyridine (21b)**



$[\alpha]^{22}_{D}$ –45.0 (*c* 0.15, MeOH).

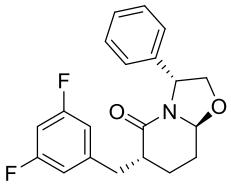
IR (film) 1659 cm-1.

^{1}H NMR (400 MHz, $CDCl_3$, COSY, *g*-HSQC) δ 1.43-1.55 (m, 1H, H-7), 1.79-1.90 (m, 2H, H-7, H-8), 2.26 (dd, *J* = 12.1, 6.6 Hz, 1H, H-6), 2.47-2.54 (m, 2H, H-6, CH_2Ar), 3.23 (dd, *J* = 13.5, 3.4 Hz, 1H, CH_2Ar), 3.81 (dd, *J* = 8.9, 7.8 Hz, 1H, H-2), 4.53 (dd, *J* = 8.9, 7.8 Hz, 1H, H-2), 4.76 (d, *J* = 8.4 Hz, 1H, H-8a), 5.28 (t, *J* = 7.8 Hz, 1H, H-3), 7.19-7.36 (m, 10H, ArH).

^{13}C NMR (100.6 MHz, $CDCl_3$) δ 22.4 (C-7), 31.4 (C-6), 37.7 (CH_2Ar), 41.6 (C-8), 58-5 (C-3), 72.5 (C-2), 92.1 (C-8a), 126.1 (C-*o*), 126.5 (C-*p*), 127.6 (C-*p*), 128.5 (C-*o*), 128.8, 129.4 (C-*m*), 138.4 and 139.5 (2C-*i*), 168.7 (CO).

HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{20}H_{22}NO_2$ 308.1645; found 308.1644.

(3*R*,6*R*,8a*S*)-6-(3,5-Difluorobenzyl)-5-oxo-3-phenyl-2,3,6,7,8,8a-hexahydro-5*H*-oxazolo[3,2-*a*] pyridine (29a)



LHMDS (4.5 mL, 4.49 mmol) was added to a solution of lactam **23b** (650 mg, 3.00 mmol) in anhydrous THF (34 mL), and the mixture was stirred at –78 ºC for 1 h. Then, 3,5-difluorobenzyl bromide (0.46 mL, 3.59 mmol) was added, and the mixture was stirred at –78 ºC for 8 h and at room temperature for 15 h. The reaction was quenched by the addition of NH_4Cl, and the resulting mixture was extracted with EtOAc. The combined organic extracts were dried, filtered, and concentrated. The resulting residue was chromatographed (from 9:1 hexane–EtOAc to EtOAc) to afford **29a** (450 mg, 44%) as a colorless oil, its 6*S* epimer **29b** (120 mg, 12%), and **29c** (40 mg, 3%).

Spectroscopic data for **29a**

$[\alpha]^{22}_D$ +12.4 (*c* 0.8, $CHCl_3$).

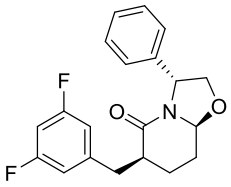
IR (film) 1649 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$, COSY, *g*-HSQC) δ 1.46-1.55 (m, 2H, H-7, H-8), 1.81-1.86 (m, 1H, H-7), 2.30-2.36 (m, 1H, H-8), 2.60-2.65 (m, 1H, H-6), 3.02-3.10 (m, 2H, CH_2Ar), 3.68 (dd, *J* = 9.0, 8.1 Hz, 1H, H-2), 4.49 (dd, *J* = 9.0, 8.1 Hz, 1H, H-2), 4.88 (m, 1H, H-8a), 5.24 (t, *J* = 8.1 Hz, 1H, H-3), 6.65-6.69 (m, 3H, F-ArH), 7.17-7.20 (m, 2H, ArH), 7.26-7.37 (m, 3H, ArH).

^{13}C NMR (75.4 MHz, $CDCl_3$) δ 22.1 (C-7), 27.9 (C-8), 37.5 (CH_2Ar), 43.0 (C-6), 58.5 (C-3), 72.9 (C-2), 88.7 (C-8a), 101.8 (F-Ar C-4, t, $J_{C\text{-}F}$ = 24.7 Hz), 112.2 (F-Ar C-2 and C-6, dd, $J_{C\text{-}F}$ = 16.7, 7.5 Hz), 125.7 (C-*o*), 127.5 (C-*p*), 128.8 (C-*m*), 139.2 (C-*i*), 142.7 (F-Ar C-1, t, $J_{C\text{-}F}$ = 9.2 Hz), 162.8 (F-Ar C-3 and C-5, dd, $J_{C\text{-}F}$ = 247.9, 13.2 Hz), 169.9 (CO).

HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{20}H_{20}F_2NO_2$ 344.1457; found 344.1454.

Spectroscopic data for **(3*R*,6*S*,8a*S*)-6-(3,5-difluorobenzyl)-5-oxo-3-phenyl-2,3,6,7,8,8a-hexahydro-5*H*-oxazolo[3,2-*a*]pyridine (29b)**



$[\alpha]^{22}_{D}$ –105.1 (*c* 0.55, $CHCl_3$).

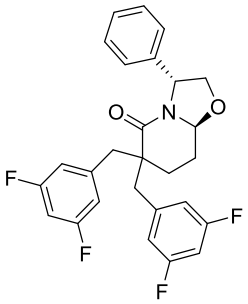
IR (film) 1724 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$, COSY, *g*-HSQC) δ 1.59-1.69 (m, 2H, H-7, H-8), 1.70-1.78 (m, 1H, H-7), 2.13-2.20 (m, 1H, H-8), 2.64 (m, 2H, H-6, CH_2Ar), 3.01 (m, 1H, CH_2Ar), 3.78 (dd, *J* = 9.0, 7.9 Hz, 1H, H-2), 4.77 (dd, *J* = 9.0, 7.9 Hz, 1H, H-2), 5.00 (m, 1H, H-8a), 5.28 (t, *J* = 7.9 Hz, 1H, H-3), 6.63 (m, 1H, F-ArH), 6.68-6.76 (m, 2H, F-ArH), 7.25-7.29 (m, 3H, ArH), 7.32-7.36 (m, 2H, ArH).

^{13}C NMR (100.6 MHz, $CDCl_3$) δ 20.4 (C-7), 25.2 (C-8), 36.7 (CH_2Ar), 41.4 (C-6), 58.4 (C-3), 72.3 (C-2), 88.2 (C-8a), 101.8 (F-Ar C-4, t, $J_{C\text{-}F}$ = 25.2 Hz), 111.8 (F-Ar C-2 and C-6, dd, $J_{C\text{-}F}$ = 17.9, 6.2 Hz), 126.2 (C-*o*), 127.6 (C-*p*), 128.7 (C-*m*), 139.4 (C-*i*), 143.7 (F-Ar C-1, t, $J_{C\text{-}F}$ = 9.3 Hz), 163.0 (F-Ar C-3 and C-5, dd, $J_{C\text{-}F}$ = 249.2, 13.3 Hz), 170.4 (CO).

HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{20}H_{20}F_2NO_2$ 344.1457; found 344.1454.

Spectroscopic data for **(3*R*,8a*S*)-6,6-bis(3,5-difluorobenzyl)-5-oxo-3-phenyl-2,3,6,7,8,8a-hexahydro-5*H*-oxazolo[3,2-*a*]pyridine (29c)**



$[\alpha]^{22}_{D}$ –29.6 (*c* 1.25, $CHCl_3$).

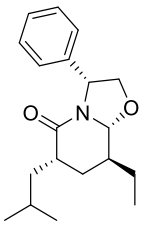
IR (film) 1636 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$, COSY, *g*-HSQC) δ 1.06-1.25 (m, 1H, H-7), 1.72-1.77 (m, 2H, H-7, H-8), 2.00-2.09 (m, 1H, H-8), 2.35 (d, *J* = 12.9 Hz, 1H, CH_2Ar), 2.78 (d, *J* = 13.3 Hz, 1H, CH_2Ar), 3.28 (d, *J* = 13.3 Hz, 1H, CH_2Ar), 3.33 (d, *J* = 12.9 Hz, 1H, CH_2Ar), 3.63 (dd, *J* = 9.2, 8.1 Hz, 1H, H-2), 4.37 (dd, *J* = 9.2, 8.1 Hz, 1H, H-2), 4.65 (dd, *J* = 9.0, 4.5 Hz, 1H, H-8a), 5.15 (t, *J* = 8.1 Hz, 1H, H-3), 6.47-6.51 (m, 2H, F-ArH), 6.67-6.77 (m, 1H, F-ArH), 7.05-7.09 (m, 2H, ArH), 7.31-7.44 (m, 3H, ArH).

^{13}C NMR (100.6 MHz, $CDCl_3$) δ 23.8 (C-7), 25.3 (C-8), 44.4 (CH_2Ar), 44.8 (CH_2Ar), 47.6 (C-6), 59.4 (C-3), 73.1 (C-2), 88.4 (C-8a), 102.3 (F-Ar C-4, t, $J_{C\text{-}F}$ = 24.9 Hz), 102.6 (F-Ar C-4, t, $J_{C\text{-}F}$ = 25.6 Hz), 113.2 (F-Ar C-2 and C-6, dd, $J_{C\text{-}F}$ = 17.9, 6.9 Hz), 113.6 (F-Ar C-2 and C-6, dd, $J_{C\text{-}F}$ = 17.9, 7.0 Hz), 126.1 (C-*o*), 127.7 (C-*p*), 128.9 (C-*m*), 138.8 (C-*i*), 140.6 (F-Ar C-1, t, $J_{C\text{-}F}$ = 8.5 Hz), 141.0 (F-Ar C-1, t, $J_{C\text{-}F}$ = 9.3 Hz), 162.5 (F-Ar C-3 and C-5, dd, $J_{C\text{-}F}$ = 248.5, 12.8 Hz), 162.9 (F-Ar C-3 and C-5, dd, $J_{C\text{-}F}$ = 249.2, 13.3 Hz), 171.1 (CO).

HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{27}H_{24}F_4NO_2$ 470.1738; found 470.1736.

(3*R*,6*S*,8*S*,8a*R*)-8-Ethyl-6-(isobutyl)-5-oxo-3-phenyl-2,3,6,7,8,8a-hexahydro-5*H*-oxazolo[3,2-*a*] pyridine (32a)



A solution of lactam **3a**[128] (739 mg, 3.0 mol) in anhydrous THF (5 mL) was added to a cooled (–78 ºC) solution of LHMDS (1M in THF, 4.52 mL, 4.52 mmol) in anhydrous THF (33 mL). After the solution was stirred at –78 ºC for 1h, 1-iodo-2-methylpropane (0.87 mL, 7.53 mmol) was added, and stirring was continued at –78 ºC for 6 h and at room temperature for an additional 12 h. The reaction was quenched by the addition of saturated aqueous NH_4Cl, and the resulting mixture was extracted with EtOAc. The combined organic extracts were dried, filtered, and concentrated to give an oil. Flash chromatography (from 8:2 to 1:1 hexane–EtOAc) afforded **32a** (320 mg, 35%) and its **6*R* epimer 32b** (95 mg, 11%).

[128] M. Amat, N. Llor, N. J. Hidalgo, J. Bosch, *Tetrahedron: Asymmetry* **1997**, *8*, 2237-2240.

Spectroscopic data for **32a**

$[\alpha]^{22}_{D}$ –29.4 (*c* 0.57, $CHCl_3$).

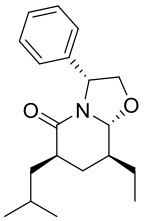
IR (film) 2955, 1657 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$, COSY, *g*-HSQC) δ 0.83 (d, *J* = 6.5 Hz, 3H, CH_3), 0.89 (d, *J* = 6.5 Hz, 3H, CH_3), 1.06 (t, *J* = 7.5 Hz, 3H, C*H*$_3$CH$_2$), 1.09-1.16 (m, 1H, H-7), 1.21-1.28 (m, 1H, H-8), 1.34-1.43 (m, 1H, CH_3C*H*$_2$), 1.64-1.74 (m, 1H, C*H*Me$_2$), 1.76-1.91 [m, 3H, CH_3C*H*$_2$, C*H*$_2$(CHMe$_2$)], 2.08-2.14 (ddd, *J* = 14.0, 7.0, 3.2 Hz, 1H, H-7), 2.22-2.30 (m, 1H, H-6), 4.00 (dd, *J* = 9.0, 1.1 Hz, 1H, CH_2O), 4.12 (dd, *J* = 9.0, 6.5 Hz, 1H, CH_2O), 4.50 (d, *J* = 8.8 Hz, 1H, H-8a), 4.85 (d, *J* = 6.5 Hz, 1H, CHN), 7.19-7.31 (m, 5H, ArH).

^{13}C NMR (100.6 MHz, $CDCl_3$) δ 10.9 (*C*H$_3$CH$_2$), 21.0 (CH_3), 23.5 (CH_3), 24.1 (CH_3*C*H$_2$), 25.0 (*C*HMe$_2$), 30.4 (C-7), 39.4 (C-6), 40.7 (C-8), 41.0 [*C*H$_2$(CHMe$_2$)], 59.3 (C-3), 73.7 (C-2), 92.3 (C-8a), 126.4 (C-*o*), 127.3 (C-*p*), 128.4 (C-*m*), 141.8 (C-*i*), 170.0 (CO).

HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{19}H_{28}NO_2$ 302.2115; found 302.2116.

Spectroscopic data for **(3*R*,6*R*,8*S*,8a*R*)-8-ethyl-6-(isobutyl)-5-oxo-3-phenyl-2,3,6,7,8,8a-hexahydro-5*H*-oxazolo[3,2-*a*]pyridine (32b)**



$[\alpha]^{22}_{D}$ +8.36 (*c* 1.1, $CHCl_3$).

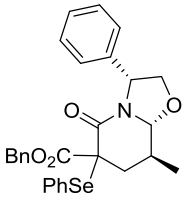
IR (film) 2956, 1659 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$, COSY, *g*-HSQC) δ 0.83 (d, *J* = 6.5 Hz, 3H, CH_3), 0.89 (d, *J* = 6.5 Hz, 3H, CH_3), 1.05 (t, *J* = 7.5 Hz, 3H, C*H*$_3$CH$_2$), 1.19-1.26 [m, 1H, C*H*$_2$(CHMe$_2$)], 1.32-1.43 (m, 1H, CH_3C*H*$_2$), 1.52-1.60 [m, 2H, H-7, C*H*$_2$(CHMe$_2$)], 1.61-1.68 (m, 1H, C*H*Me$_2$), 1.76-1.84 (m, 2H, CH_3C*H*$_2$, H-7), 1.87-1.96 (m, 1H, H-8), 2.30-2.36 (m, 1H, H-6), 4.01 (dd, *J* = 9.0, 1.1 Hz, 1H, CH_2O), 4.15 (dd, *J* = 9.0, 6.9 Hz, 1H, CH_2O), 4.54 (d, *J* = 8.7 Hz, 1H, H-8a), 4.89 (d, *J* = 5.9 Hz, 1H, CHN), 7.21-7.32 (m, 5H, ArH).

^{13}C NMR (100.6 MHz, $CDCl_3$) δ 11.0 (*C*H_3CH_2), 21.4 (CH_3), 23.1 (CH_3), 24.7 (CH_3*C*H_2), 25.5 (*C*HMe_2), 29.0 (C-7), 37.6 (C-8), 38.0 (C-6), 40.8 [*C*H_2(CHMe_2)], 58.5 (C-3), 73.9 (C-2), 92.3 (C-8a), 126.2 (C-*o*), 127.3 (C-*p*), 128.4 (C-*m*), 141.7 (C-*i*), 170.8 (CO).

HRMS (ESI-TOF) m/z: $[M + Na]^+$ Calcd for $C_{19}H_{27}NNaO_2$ 324.1934; found 324.1935.

(3*R*,8*S*,8a*R*)-6-(BenzyloxyC-Arbonyl)-8-methyl-5-oxo-3-phenyl-6-(phenylselanyl)-2,3,6,7,8,8a-hexahydro-5*H*-oxazolo[3,2-*a*]pyridine (37)



LHMDS (1M in THF, 28.6 mL, 28.6 mmol) was slowly added at –78 ºC to a solution of lactam **4a** (3 g, 12,8 mmol) in anhydrous THF (147 mL), and the resulting mixture was stirred for 45 min. Then, benzyl chloroformate (1,84 ml, 12,98 mmol) and, after 20 min of continuous stirring at –78 ºC, a solution of PhSeCl (3,22 g, 16,9 mmol) in anhydrous THF (30 mL) were sequentially added to the solution. The resulting mixture was stirred for 50 min, poured into 5% aqueous NH_4Cl, and the aqueous layer was extracted with EtOAc. The combined organic extracts were dried, filtered, and concentrated to give an oil. Flash chromatography (from 8:2 to 1:1 hexane–EtOAc) afforded lactam **37** (5.71 g, 84%), as a 7:3 mixture of C-6 epimers.

Spectroscopic data for major epimer of compound **37** (higher Rf)

IR (film) 1726, 1668 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$, COSY, *g*-HSQC) δ 1.01 (d, *J* = 6.4 Hz, 3H, CH_3), 1.88 (dd, *J* = 14.0, 12.7 Hz, 1H, H-7), 1.95-2.05 (m, 1H, H-8), 2.24 (dd, *J* = 14.0, 3.1 Hz H-7), 3.93 (d, *J* = 9.2 Hz, 1H, H-8a), 3.94 (dd, *J* = 8.8, 2.0Hz, 1H H-2), 3.99 (dd, *J* = 8.8, 7.0 Hz, 1H, H-2), 4.85 (dd, *J* = 7.0, 2.0 Hz, 1H, H-3), 5.02 (d, *J* = 12.4 Hz, 1H, CH_2), 5.07 (d, *J* = 12.4 Hz, 1H, CH_2), 7.14-7.60 (m,15H, ArH).

^{13}C NMR (100.6 MHz, $CDCl_3$) δ 15.9 (CH_3), 33.3 (C-8), 39.5 (C-7), 54.6 (C-6), 59.6 (C-3), 67.7 (CH_2), 73.9 (C-2), 93.1 (C-8a), 126.4 (C-Ar), 126.5 (C-Ar), 127.5 (C-Ar), 127.8 (C-Ar), 128 (C-Ar), 128.2 (C-Ar), 128.4 (C-Ar), 128.7 (C-Ar), 129.6 (C-Ar), 135.2 (C-*i*), 138.2 (C-Ar), 140.5 (C-*i*), 163.2 (CO), 170.3 (CO_2).

HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{28}H_{28}NO_4Se$ 522.1178; found 522.1186.

Spectroscopic data for minor epimer of compound **37** (lower Rf)

IR (film) 1726, 1668 cm^{-1}.

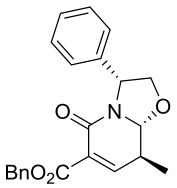
^{1}H NMR (400 MHz, $CDCl_3$, COSY, *g*-HSQC) δ 1.06 (d, *J* = 6.6 Hz, 3H, CH_3), 1.92 (dd, *J* = 15.4, 1H, H-7) 2.00 (dd, *J* = 15.4, 10.8, 1H, H-7), 2.30-2.43 (m, 1H, H-8), 4.06 (dd, *J* = 9.0, 1.4 Hz, 1H H-2), 4.09 (dd, *J* = 9.0, 6.6, 1H, H-2), 4.47 (d, *J* = 9.1 Hz, 1H, H-8a), 4.92 (dd, *J* = 6.5, 1.3 Hz, 1H, H-3), 5.15 (d, *J* = 12.3 Hz, 1H, CH_2), 5.20 (d, *J* = 12.3 Hz, 1H, CH_2), 7.10-7.19 (m,2H, ArH), 7.26-744 (m, 13H, ArH).

^{13}C NMR (100.6 MHz, $CDCl_3$) δ 16.0 (CH_3), 32.1 (C-8), 36.6 (C-7), 55.5 (C-6), 59.6 (C-3), 67.8 (CH_2), 76.7 (C-2), 92.9 (C-8a), 126.8 (C-Ar), 126.9 (C-Ar), 127.6 (C-Ar), 128.3 (C-Ar), 128.4 (C-Ar), 128.5 (C-Ar), 128.5 (C-Ar), 128.7 (C-Ar), 129.6 (C-Ar), 135.4 (C-i), 138.3 (C-Ar), 140.6 (C-Ar), 162.8 (CO), 170.3 (CO_2).

HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{28}H_{28}NO_4Se$ 522.1178; found 522.1174.

(3*R*,8*S*,8a*R*)-6-(BenzyloxyC-Arbonyl)-8-methyl-5-oxo-3-phenyl-2,3,8,8a-tetrahydro

-5*H*-oxazolo[3,2-*a*]pyridine (40)



Aqueous H_2O_2 (30%, 2.72 mL, 26.9 mmol) and pyridine (0.35 mL, 4.41 mmol) were added to a solution of the selenides **37** (2 g, 3.84 mmol) in CH_2Cl_2 (328 mL), and the resulting mixture was stirred at room temperature for 3 h. The reaction mixture was poured into distilled water, and the aqueous layer was extracted with CH_2Cl_2. The combined organic extracts were dried, filtered, and concentrated to give **40** as a colorless oil which was used in the next step without further purification.

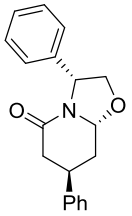
Spectroscopic data for **40**

^{1}H NMR (400 MHz, $CDCl_3$, COSY, *g*-HSQC) δ 1.36 (d, *J* = 7.2 Hz, 3H, CH_3), 2.93 (m, 1H, H-8), 4.19 (dd, *J* = 9.5, 1.6 Hz, 1H, H-2), 4.23 (dd, *J* = 9.5, 6.3 Hz, 1H, H-2), 4.77

(d, *J* = 10.6 Hz, 1H, H-8a), 5.07 (dd, *J* = 6.3, 1.7 Hz, 1H, H-3), 5.20 (d, *J* = 12.0 Hz, 2H, CH_2), 7.09 (d, *J* = 1.2 Hz, 1H, H-7), 7.26-7.40 (m, 10H, ArH).

^{13}C NMR (100.6 MHz, $CDCl_3$) δ 15.1 (CH_3), 36.8 (C-8), 58.3 (C-3), 67.1 (CH_2), 74.4 (C-2), 91.6 (C-8a), 126.8 (C-Ar), 127.7 (C-Ar), 128.2 (C-Ar), 128.3 (C-Ar), 128.5 (C-Ar), 129.4 (C-Ar), 135.5 (C-Ar), 140.4 (C-Ar), 157.4 (CO), 163.6 (CO_2).

(3*R*,7*R*,8a*R*)-3,7-Diphenyl-5-oxo-2,3,6,7,8,8a-hexahydro-5*H*-oxazolo[3,2-*a*] pyridine (42)



A solution of (3*R*,7*R*,8a*R*)-6-(benzyloxyC-Arbonyl)-5-oxo-3,7-diphenyl-2,3,6,7,8,8a-hexahydro-5*H*-oxazolo[3,2-*a*]pyridine[129] (1.15 g, 2.69 mmol) in anhydrous MeOH (100 mL) containing 10% Pd–C (115 mg) was stirred under hydrogen at 25 ºC for 17 h. The catalyst was removed by filtration and washed with hot MeOH. The combined organic solutions were concentrated to give an oil, which was dissolved in toluene (80 mL). The solution was heated to reflux for 3 h, cooled, and concentrated. The residue was chromatographed (1:1 hexane–EtOAc) to give pure compound **42** (630 mg, 80%).

Spectroscopic data for **42**

$[\alpha]^{22}_D$ –121.2 (*c* 1.1, $CHCl_3$).

IR (film) 1655, 1454 cm^{-1}.

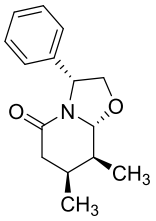
^{1}H NMR (400 MHz, $CDCl_3$, COSY, *g*-HSQC) δ 2.27 (ddd, *J* = 12.9, 9.6, 5.9 Hz, 1H, H-8), 2.52 (dt, *J* = 12.9, 5.0 Hz, 1H, H-8), 2.66 (d, *J* = 5.4 Hz, 2H, H-6), 3.52 (ddd, *J* = 9.6, 5.4, 5.0 Hz, 1H, H-7), 4.02 (dd, *J* = 9.0, 1.4 Hz, 1H, H-2), 4.11 (dd, *J* = 9.0, 6.8 Hz, 1H, H-2), 4.71 (dd, *J* = 9.3, 4.2 Hz, 1H, H-8a), 4.96 (t, *J* = 5.7, 1H, CHN), 7.22-7.37 (m, 10H, ArH).

[129] M. Amat, M. Pérez, J. Bosch, *Chem. Eur. J.* **2011**, *17*, 7724-7732.

^{13}C NMR (100.6 MHz, $CDCl_3$) δ 35.2 (C-7, C-8), 36.8 (C-6), 58.7 (C-3), 73.9 (C-2), 86.0 (C-8a), 126.4 (C-*o*), 126.8 (C-*o*), 126.9 (C-*p*), 127.6 (C-*p*), 128.6 (C-*m*), 128.8 (C-*m*), 141.3 (C-*i*), 143.0 (C-*i*), 167.1 (NCO).

HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{19}H_{20}NO_2$ 294.1489; found 294.1489.

(3*R*,7*S*,8*S*,8a*R*)-6,7-Dimethyl-5-oxo-3-phenyl-2,3,6,7,8,8a-hexahydro-5*H*-oxazolo[3,2-*a*]pyridine (45)



LiCl (651 mg, 15.3 mmol) was dried at 80 °C for 2 h under vacuum (10-15 mmHg) in a three-necked, 250 mL round-bottomed flask. Then, CuI (2.92 g, 15.3 mmol) and anhydrous THF (45 mL) were added under inert atmosphere at room temperature. The suspension was cooled at 0 ºC, methylmagnesiun bromide (5.12 mL of a 3 M solution in Et_2O, 15.3 mmol) and TMSCl (1.95 mL, 15.3 mmol) were added, and the mixture was stirred at 0 ºC for 10-15 min. Then, a solution of lactam **40** (1.39 g, 3.84 mmol) in anhydrous THF (20 mL) was added at –78 ºC and the resulting mixture reaction was stirred at this temperature for 24 h. The reaction was quenched by the addition of saturated aqueous NH_4Cl, and the resulting mixture was extracted with EtOAc. The combined organic extracts were dried, filtered, and concentrated to give a brown oil. Flash chromatography (from 7:3 to 1:1 hexane–EtOAc) afforded (3*R*,7*R*,8*S*,8a*R*)-6-(benzyloxyC-Arbonyl)-7,8-dimethyl-5-oxo-3-phenyl-2,3,6,7,8,8a-hexahydro-5*H*-oxazolo[3,2-*a*]pyridine (919 mg, 63%) as a 8:2 mixture of C-6 epimers.

Spectroscopic data for major epimer (from the mixture)

^{1}H NMR (400 MHz, $CDCl_3$, COSY, *g*-HSQC) δ 1.08 (d, *J* = 7.6 Hz, 3H, CH_3), 1.17 (d, *J* = 7.2 Hz, 3H, CH_3), 2.31-2.35 (m, 1H, H-7), 2.48-2.52 (m, 1H, H-8), 3.23 (d, *J* = 1.6 Hz, 1H, H-6), 3.98 (dd, *J* = 9.0, 1.5 Hz, 1H, H-2), 4.13 (dd , *J* = 9.0, 7.2 Hz, 1H, H-2), 4.56 (d, *J* = 10 Hz, 1H, H-8a), 4.91 (dd, *J* = 7.2, 1.5 Hz, 1H, H-3), 5.04 (d, *J* = 1.20 Hz, 1H, CH_2), 5.08 (d, *J* = 1.20 Hz, 1H, CH_2), 7.20-7.33 (m, 10H, ArH).

^{13}C NMR (100.6 MHz, $CDCl_3$) δ 13.5 (CH_3), 16.8 (C-8), 35.7 (C-7), 39.9 (C-8), 57.7 (C-6), 59.5 (C-3), 67.1 (CH_2), 73.7 (C-2), 92.4(C-8a), 126.4 (C-Ar), 127.4 (C-Ar), 127.9 (C-Ar), 128.1 (C-Ar), 128.3 (C-Ar), 128.4 (C-Ar), 135.4 (C-*i*), 140.6 (C-*i*), 162.4 (CO), 170.0 (CO_2).

A solution of a mixture of C-6 epimers of (3*R*,7*R*,8*S*,8a*R*)-6-(benzyloxyC-Arbonyl)-7,8-dimethyl-5-oxo-3-phenyl-2,3,6,7,8,8a-hexahydro-5*H*-oxazolo[3,2-*a*]pyridine (2.87 g, 7.57 mmol) in anhydrous MeOH (276 mL) containing 10% Pd–C (1.4 g) was hydrogenated at 25 ºC for 17 h. The catalyst was removed by filtration and washed with hot MeOH. The combined organic solutions were concentrated to give an oil, which was dissolved in toluene (100 mL). The solution was heated to reflux for 6 h, cooled, and concentrated. The residue was chromatographed (from 7:3 to 1:1 hexane–EtOAc) to give pure compound **45** (1.39 g, 75%).

Spectroscopic data for **45**

$[\alpha]^{22}_D$ –43.7 (*c* 1.0, MeOH).

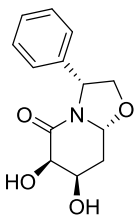
IR (film) 1656 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$, COSY, *g*-HSQC) δ 1.01 (d, *J* = 7.2 Hz, 3H, CH_3), 1.20 (d, *J* = 6.6 Hz, 3H, CH_3, 3H), 2.06-2.11 (m, 2H, H-7, H-8), 2.20 (dd, *J* = 17.6, 1.8 Hz, 1H, H-6), 2.50 (dd, *J* = 17.5, 6.1 Hz, 1H, H-6), 3.98 (dd, *J* = 9.0, 1.1 Hz, 1H, H-2), 4.11 (dd, *J* = 9.9, 6.8 Hz, 1H, H-2), 4.59 (d, *J* = 9.1 Hz, 1H, H-8a), 4.89 (d, *J* = 6.2 Hz, 1H, H-3), 7.18-7.36 (m, 5H, ArH).

^{13}C NMR (100.6 MHz, $CDCl_3$) δ 13.9 (CH_3), 14.5 (CH_3), 30.7 (C-7), 36.8 (C-8), 40.1 (C-6), 59.1 (C-3), 73.6 (C-2), 90.1 (C-8a), 126.1 (C-*m*), 127.2 (C-*p*), 128.53 (C-*o*), 141.5 (C-*i*), 167.0 (CO).

HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{15}H_{20}NO_2$ 246.1489; found 246.1493.

(3*R*,6*R*,7*R*,8a*R*)-6,7-dihydroxy-5-oxo-3-phenyl-2,3,6,7,8,8a-hexahydro-5*H*-oxazolo[3,2-*a*]pyridine (47)



To a solution of (3*R*,8a*R*)-5-oxo-3-phenyl-2,3,8,8a-tetrahydro-5*H*-oxazolo[3,2-*a*]pyridine **46**[129] (600 mg, 2.79 mmol) in CH_3CN (28 mL) and H_2O (0.1 mL) were added *N*-oxide-*N*-methylmorpholine (323 mg, 2.79 mmol) and OsO_4 (1.0 mL of a 2.5% in *t*-BuOH), and the mixture was stirred at room temperature for 17 h. The resulting solution was quenched with saturated aqueous $Na_2S_2O_5$ and stirred for an additional 1 h. The aqueous layer was extracted with EtOAc, and the combined organic extracts were dried, filtered, and concentrated. The resulting residue was chromatographed (8:2 EtOAc–EtOH), to give **47** (390 mg, 62%).

Spectroscopic data for **47**

$[\alpha]^{22}_D$ +9.31 (*c* 0.13, EtOH).

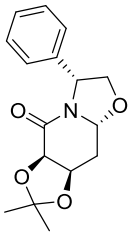
IR (film) 3416, 1654, 1469 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$, COSY, *g*-HSQC) δ 1.97-2.04 (m, 1H, H-8), 2.78 (dt, *J* = 13.3, 4.0 Hz, 1H, H-8), 2.84 (s, 1H, OH), 2.85 (s, 1H, OH), 3.93 (d, *J* = 3.2 Hz, 1H, H-6), 4.11 (dd, *J* = 9.0, 2.0 Hz, 1H, H-2), 4.27 (dd, *J* = 9.0, 7.5 Hz, 1H, H-2), 4.46 (m, 1H, H-7), 4.89 (dd, *J* = 7.5, 2.0 Hz, 1H, H-3), 5.21 (dd, *J* = 9.8, 4.0 Hz, 1H, H-8a), 7.26-7.32 (m, 5H, ArH).

^{13}C NMR (100.6 MHz, $CDCl_3$) δ 32.1 (C-8), 58.3 (C-3), 66.1 (C-7), 70.9 (C-6), 74.7 (C-2), 86.5 (C-8a), 126.6 (C-*o*), 127.9 (C-*p*), 128.6 (C-*m*), 140.5 (C-*i*), 167.8 (NCO).

HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{13}H_{16}NO_4$ 250.1074; found 250.1075.

(3*R*,6*R*,7*R*,8a*R*)-6,7-(Isopropylidenedioxy)-5-oxo-3-phenyl-2,3,6,7,8,8a-hexahydro-5*H*-oxazolo[3,2-*a*]pyridine (48)



p-Toluenesulfonic acid (39 mg, 0.22 mmol) and dimethoxypropane (1.07 mL, 8.74 mmol) were added to a solution of the above diol **47** (390 mg, 1.56 mmol) in CH_2Cl_2 (7.8 mL), and the mixture was stirred at room temperature overnight. Solid sodium acetate (2.9 g) was added, and the mixture was stirred for 20 minutes, poured into saturated aqueous $NaHCO_3$, and extracted with CH_2Cl_2. The combined organic

extracts were washed with saturated aqueous NaCl, dried, filtered, and concentrated. Flash chromatography (1:1 hexane−EtOAc) of the residue gave **48** (350 mg, 77%).

Spectroscopic data for **48**

$[\alpha]^{22}_{D}$ –48.2 (*c* 1.05, $CHCl_3$).

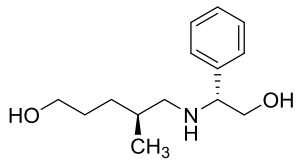
IR (film) 1664, 1448 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$, COSY, *g*-HSQC) δ 1.37 (s, 3H, CH_3), 1.48 (s, 3H, CH_3), 1.94 (ddd, *J* = 13.7, 10.1, 3.7 Hz, 1H, H-8), 2.71 (dt, *J* = 13.7, 2.6 Hz, 1H, H-8), 4.11 (dd, *J* = 9.1, 0.8 Hz, 1H, H-2), 4.23 (dd, *J* = 9.1, 6.5 Hz, 1H, H-2), 4.43 (d, *J* = 6.6 Hz, 1H, H-6), 4.67-4.70 (m, 1H, H-7), 4.98 (d, *J* = 6.5 Hz, 1H, H-3), 5.11 (dd, *J* = 10.1, 2.6 Hz, 1H, H-8a), 7.23-7.34 (m, 5H, ArH).

^{13}C NMR (100.6 MHz, $CDCl_3$) δ 23.5 (CH_3), 26.0 (CH_3), 33.6 (C-8), 58.6 (C-3), 71.4 (C-7), 73.8 (C-2), 74.5 (C-6), 84.4 (C-8a), 109.2 (*C*Me_2), 126.5 (C-*o*), 127.5 (C-*p*), 128.3 (C-*m*), 140.3 (C-*i*), 163.3 (NCO).

HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{16}H_{20}NO_4$ 290.1387; found 290.1391.

(*S*)-5-{[(1*R*)-2-Hydroxy-1-phenylethyl]amino}-4-methyl-1-pentanol (52)



n-BuLi (4.13 mL of a 2.5 M solution in hexanes, 10.3 mmol) was added to a solution of $NH_3{\cdot}BH_3$ (319 mg, 10.3 mmol) in anhydrous THF (9 mL) at 0 ºC, and the resulting mixture was stirred at this temperature for 10 min and at room temperature for 15 minutes. Then, this solution was added to a solution of **4a** (555 mg, 2.40 mmol) in anhydrous THF (4.5 mL), and the stirring was continued at 40 ºC for 1 h. The reaction mixture was quenched with H_2O, and the resulting solution was extracted with Et_2O. The combined organic extracts were dried, filtered, and concentrated. Flash chromatography (from 8:2 hexane-EtOAc to 8:2 EtOAc-EtOH) of the residue gave **53**[125] (40 mg, 7%) as a colorless oil, and aminoalcohol **52** (425 mg, 75 %).

Spectroscopic data for **52**

$[\alpha]^{22}_{D}$ –50.9 (*c* 0.68, MeOH).

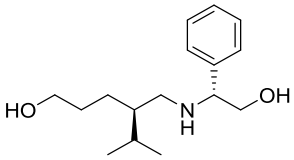
IR (film) 3314 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$, COSY, *g*-HSQC) δ 0.90 (d, *J* = 6.4 Hz, 3H, CH_3), 1.13-1.21 (m, 1H, H-2), 1.44-1.56 (m, 2H, H-2, H-3), 1.57-1.67 (m, 2H, H-3, H-4), 2.31 (br.s, 3H, OH, NH), 2.33 (dd, *J* = 11.7, 6.0 Hz, 1H, H-5), 2.43 (dd, *J* = 11.7, 7.0 Hz, 1H, H-5), 3.55 (dd, *J* = 10.6, 8.8 Hz, 1H, CH_2O), 3.61 (t, *J* = 6.0 Hz, 2H, H-1), 3.70 (dd, *J* = 10.6, 4.4 Hz, 1H, CH_2O), 3.75 (dd, *J* = 8.8, 4.4 Hz, 1H, CHN), 7.25-7.37 (m, 5H, ArH).

^{13}C NMR (100.6 MHz, $CDCl_3$) δ 18.6 (CH_3), 29.7 (C-3), 30.3 (C-2), 32.8 (C-4), 53.4 (C-5), 62.6 (C-1), 64.7 (CHN), 66.5 (CH_2O), 127.2 (C-*o*), 127.6 (C-*p*), 128.6 (C-*m*), 140.4 (C-*i*).

HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{14}H_{24}NO_2$ 238.1802; found 238.1799.

(*R*)-5-{[(1*R*)-2-Hydroxy-1-phenylethyl]amino}-4-isopropyl-1-pentanol (54)



n-BuLi (4.14 mL of a 1.6 M solution in hexanes, 6.6 mmol) was added to a solution of $NH_3{\cdot}BH_3$ (205 mg, 6.6 mmol) in anhydrous THF (6 mL) at 0 ºC, and the resulting mixture was stirred at this temperature for 10 min and at room temperature for 15 minutes. Then, this solution was added to a solution of **20a** (400 mg, 1.54 mmol) in anhydrous THF (3 mL), and the stirring was continued at 40 ºC for 1 h. The reaction mixture was quenched with H_2O, and the resulting solution was extracted with Et_2O. The combined organic extracts were dried, filtered, and concentrated. Flash chromatography (from 1:1 hexane-EtOAc to 8:2 EtOAc-EtOH) of the residue gave piperidine **55** (30 mg, 5 %), and aminoalcohol **54** (292 mg, 71 %) as a colorless oil.

Spectroscopic data for **54**

$[\alpha]^{22}_{D}$ –44.9 (*c* 0.65, MeOH).

IR (film) 3320 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$, COSY, *g*-HSQC) δ 0.78 (d, *J* = 6.8 Hz, 3H, CH_3), 0.82 (d, *J* = 6.8 Hz, 3H, CH_3), 1.31-1.41 (m, 3H, H-3, H-4), 1.45-1.52 (m, 1H, H-2), 1.54-1.61 (m, 1H, H-2),1.64-1.72 (m, 1H, C*H*CH_3), 2.31 (dd, *J* = 11.8, 4.2 Hz, 1H, H-5), 2.48 (dd, *J* = 11.8, 7.7 Hz, 1H, H-5), 3.54-3.65 (m, 3H, H-1, CH_2O), 3.68 (dd, *J* = 10.8, 4.0 Hz, 1H, CH_2O), 3.76 (dd, *J* = 9.1, 4.0 Hz, 1H, CHN), 7.24-7.35 (m, 5H, ArH).

^{13}C NMR (100.6 MHz, $CDCl_3$) δ 19.3 (CH_3), 19.4 (CH_3), 25.3 (C-3), 29.3 (*C*HCH_3), 30.2 (C-2), 43.2 (C-4), 48.8 (C-5), 61.8 (C-1), 64.9 (CHN), 66.5 (CH_2O), 127.3 (C-*o*), 127.5 (C-*p*), 128.5 (C-*m*), 140.1 (C-*i*).

HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{16}H_{28}NO_2$ 266.2115; found 266.2109.

Spectroscopic data for **55**

$[\alpha]^{22}_D$ –47.5 (*c* 0.25, MeOH).

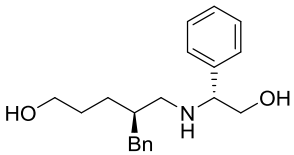
IR (film) 3406 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$, COSY, *g*-HSQC) δ 0.78-0.84 (m, 1H, H-4), 0.84 (d, *J* = 6.4 Hz, 3H, CH_3), 0.88 (d, *J* = 6.4 Hz, 3H, CH_3), 1.35-1.47 [m, 3H, H-3, H-5, C*H*$(CH_3)_2$], 1.60-1.70 (m, 3H, H-4, H-5, H-6), 2.03 (t, *J* = 10.5 Hz, 1H, H-2), 2.82 (br.m, 2H, H-2, H-6), 3.61 (dd, *J* = 10.3, 5.2 Hz, 1H, CH_2O), 3.70 (dd, *J* = 10.2, 5.2 Hz, 1H, CHN), 3.98 (t, *J* = 10.2 Hz, 1H, CH_2O), 7.17-7.19 (m, 2H, ArH), 7.30-7.37 (m, 3H, ArH).

^{13}C NMR (100.6 MHz, $CDCl_3$) δ 19.9 (CH_3), 20.3 (CH_3), 25.8 (C-5), 27.9 (C-4), 30.9 [*C*H$(CH_3)_2$], 43.3 (C-3), 46.6 (C-6), 57.1 (C-2), 59.9 (CH_2O), 70.3 (CHN), 127.7 (C-*p*), 128.0, 128.9 (C-*o*, C-*m*), 135.5 (C-*i*).

HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{16}H_{26}NO$ 248.2009; found 248.2005.

(*R*)-4-Benzyl-5-{[(1*R*)-2-hydroxy-1-phenylethyl]amino}-1-pentanol (56)



n-BuLi (2.83 mL of a 1.6 M solution in hexanes, 4.53 mmol) was added to a solution of $NH_3{\cdot}BH_3$ (140 mg, 4.53 mmol) in anhydrous THF (2.7 mL) at 0 ºC, and the resulting mixture was stirred at this temperature for 10 min and at room temperature for 15 minutes. Then, this solution was added to a solution of **21a** (324 mg, 1.05 mmol) in anhydrous THF (1.4 mL), and the stirring was continued at 40 ºC for 1 h. The

reaction mixture was quenched with H_2O, and the resulting solution was extracted with Et_2O. The combined organic extracts were dried, filtered, and concentrated. Flash chromatography (from 1:1 hexane-EtOAc to 8:2 EtOAc-EtOH) of the residue gave aminoalcohol **56** (233 mg, 70 %) as a colorless oil.

Spectroscopic data for **56**

$[\alpha]^{22}_D$ –35.8 (*c* 1.15, MeOH).

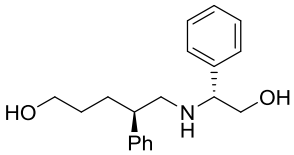
IR (film) 3331 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$, COSY, *g*-HSQC) δ 1.23-1.40 (m, 1H, H-3), 1.44-1.59 (m, 3H, H-3, H-2), 1.84 (br.s, 1H, H-4), 2.35-2.47 (m, 2H, H-5), 2.48-2.63 (m, 2H, CH_2Ar), 2.92 (br.s, 3H, OH, NH), 3.50-3.63 (m, 3H, H-1, CH_2O), 3.64-3.73 (m, 2H, CH_2O, CHN), 7.05-7.33 (m, 10H, ArH).

^{13}C NMR (100.6 MHz, $CDCl_3$) δ 27.8 (C-3), 29.3 (C-2), 39.2 (CH_2Ar), 39.6 (C-4), 50.1 (C-5), 62.4 (C-1), 64.8 (CHN), 66.5 (CH_2O), 125.8 (C-*p*), 127.3 (C-*m*), 127.6 (C-*p*), 128.2 (C-*m*), 128.5, 128.9 (C-*o*), 140.1, 140.5 (C-*i*).

HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{20}H_{28}NO_2$ 314.2115; found 314.2111.

(*R*)-5-{[(1*R*)-2-Hydroxy-1-phenylethyl]amino}-4-phenyl-1-pentanol (57)



n-BuLi (1.17 mL of a 2.5 M solution in hexanes, 2.93 mmol) was added to a solution of $NH_3{\cdot}BH_3$ (91 mg, 2.93 mmol) in anhydrous THF (3.3 mL) at 0 ºC, and the resulting mixture was stirred at this temperature for 10 min and at room temperature for 15 minutes. Then, this solution was added to a solution of **22a** (200 mg, 0.68 mmol) in anhydrous THF (1.7 mL), and the stirring was continued at 40 ºC for 1 h. The reaction mixture was quenched with H_2O, and the resulting solution was extracted with Et_2O. The combined organic extracts were dried, filtered, and concentrated. Flash chromatography (from 1:1 hexane-EtOAc to 8:2 EtOAc-EtOH) of the residue gave aminoalcohol **57** (116 mg, 57 %) as a colorless oil.

Spectroscopic data for **57**

$[\alpha]^{22}_{D}$ –48.1 (*c* 0.4, MeOH).

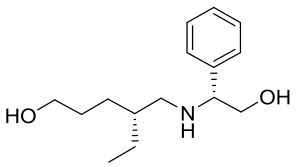
IR (film) 3323 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$, COSY, *g*-HSQC) δ 1.39-1.46 (m, 2H, H-3), 1.54-1.61 (m, 1H, H-2), 1.66 (br.s, 3H, OH, NH), 1.76-1.80 (m, 1H, H-2), 2.65-2.72 (m, 2H, H-4, H-5), 2.78-2.82 (m, 1H, H-5), 3.44 (dd, *J* = 10.2, 8.5 Hz, 1H, CH_2O), 3.56 (t, *J* = 6.4 Hz, 2H, H-1), 3.60-3.68 (m, 2H, CH_2O, CHN), 7.13-7.34 (m, 10H, ArH).

^{13}C NMR (100.6 MHz, $CDCl_3$) δ 30.1 (C-2), 30.5 (C-3), 46.0 (C-4), 53.3 (C-5), 62.7 (C-1), 64.8 (CHN), 66.4 (CH_2O), 126.5, 126.9 (C-*p*), 127.2, 127.7, 128.6, 128.6 (C-*o*, C-*m*), 140.4, 143.4 (C-*i*).

HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{19}H_{26}NO_2$ 300.1958; found 300.1952.

(*R*)-4-Ethyl-5-{[(1*R*)-2-hydroxy-1-phenylethyl]amino}-1-pentanol (58)



n-BuLi (2.77 mL of a 2.5 M solution in hexanes, 6.92 mmol) was added to a solution of $NH_3{\cdot}BH_3$ (214 mg, 6.92 mmol) in anhydrous THF (6 mL) at 0 ºC, and the resulting mixture was stirred at this temperature for 10 min and at room temperature for 15 minutes. Then, this solution was added to a solution of **3b** (395 mg, 1.61 mmol) in anhydrous THF (3 mL), and the stirring was continued at 40 ºC for 1 h. The reaction mixture was quenched with H_2O, and the resulting solution was extracted with Et_2O. The combined organic extracts were dried, filtered, and concentrated. Flash chromatography (from 8:2 hexane-EtOAc to 8:2 EtOAc-EtOH) of the residue gave piperidine **59**[60] (colorless oil, 35 mg, 9%) and aminoalcohol **58** (202 mg, 50 %) as a colorless oil.

Spectroscopic data for **58**

$[\alpha]^{22}_{D}$ –48.8 (*c* 0.7, $CHCl_3$).

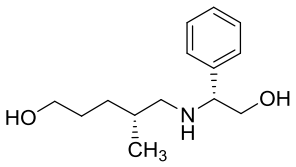
IR (film) 3329, 1453, 1058 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$, COSY, *g*-HSQC) δ 0.80 (t, *J* = 7.5 Hz, 3H, CH_3), 1.28-1.35 (m, 2H, CH_3CH_2), 1.36-1.43 (m, 2H, H-3), 1.43-1.54 (m, 3H, H-2, H-4), 2.36 (dd, *J* = 11.5, 6.0 Hz, 1H, H-5), 2.48 (dd, *J* = 11.5, 5.6 Hz, 1H, H-5), 3.29 (brs, 3H, 2OH, NH), 3.59 (masked, 1H, CH_2O), 3.60 (t, *J* = 6.4 Hz, 2H, H-1), 3.72-3.77 (m, 2H, CH_2O, CHN), 7.24-7.36 (m, 5H, ArH).

^{13}C NMR (100.6 MHz, $CDCl_3$) δ 10.8 (CH_3), 24.5 (CH_2CH_3), 27.4 (C-3), 29.2 (C-2), 39.4 (C-4), 50.4 (C-5), 62.5 (C-1), 65.2 (CHN), 66.4 (CH_2O), 127.2 (C-*o*), 127.5 (C-*p*), 128.5 (C-*m*), 140.5 (C-*i*).

HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{15}H_{26}NO_2$ 252.1958; found 252.1954.

(*R*)-5-{[(1*R*)-2-Hydroxy-1-phenylethyl]amino}-4-methyl-1-pentanol (60)



n-BuLi (2.98 mL of a 2.5 M solution in hexanes, 7.44 mmol) was added to a solution of $NH_3{\cdot}BH_3$ (230 mg, 7.44 mmol) in anhydrous THF (8 mL) at 0 ºC, and the resulting mixture was stirred at this temperature for 10 min and at room temperature for 15 minutes. Then, this solution was added to a solution of **4b** (400 mg, 1.73 mmol) in anhydrous THF (4 mL), and the stirring was continued at 40 ºC for 1 h. The reaction mixture was quenched with H_2O, and the resulting solution was extracted with Et_2O. The combined organic extracts were dried, filtered, and concentrated. Flash chromatography (from 8:2 hexane-EtOAc to 8:2 EtOAc-EtOH) of the residue gave piperidine **61**[57] (colorless oil, 35 mg, 11%), and aminoalcohol **60** (225 mg, 55 %) as a colorless oil.

Spectroscopic data for **60**

$[\alpha]^{22}_D$ –57.4 (*c* 0.9, MeOH).

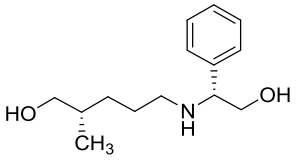
IR (film) 3328, 1492, 1453, 1056 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$, COSY, *g*-HSQC) δ 0.88 (d, *J* = 6.7 Hz, 3H, CH_3), 1.15-1.20 (m, 1H, H-2), 1.40-1.50 (m, 2H, H-2, H-3), 1.55-1.65 (m, 2H, H-3, H-4), 2.36 (m, 2H, H-5), 3.27 (brs, 3H, 2 OH, NH), 3.55-3.58 (m, 3H, H-1, CH_2O), 3.64 (m, 1H, CHN), 3.70 (m, 1H, CH_2O), 7.23-7.35 (m, 5H, ArH).

^{13}C NMR (100.6 MHz, $CDCl_3$) δ 18.0 (CH_3), 29.5 (C-3), 30.5 (C-2), 32.7 (C-4), 53.5 (C-5), 62.3 (C-1), 64.8 (CHN), 66.5 (C- CH_2OH), 127.3 (C-o), 127.7 (C-p), 128.4 (C-m), 140.3 (C-*ipso*).

HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{14}H_{24}NO_2$ 238.1802; found 238.1796.

(*S*)-5-{[(1*R*)-2-Hydroxy-1-phenylethyl]amino}-2-methyl-1-pentanol (62)



From lactam **23a**

n-BuLi (3.53 mL of a 2.5 M solution in hexanes, 8.84 mmol) was added to a solution of $NH_3{\cdot}BH_3$ (273 mg, 8.84 mmol) in anhydrous THF (11 mL) at 0 ºC, and the resulting mixture was stirred at this temperature for 10 min and at room temperature for 15 minutes. Then, this solution was added to a solution of **24** (475 mg, 2.05 mmol) in anhydrous THF (5.5 mL), and the stirring was continued at 40 ºC for 1 h. The reaction mixture was quenched with H_2O, and the resulting solution was extracted with Et_2O. The combined organic extracts were dried, filtered, and concentrated. Flash chromatography (from 8:2 hexane-EtOAc to 8:2 EtOAc-EtOH) of the residue gave piperidine **53** (colorless oil, 28 mg, 6%) and aminoalcohol **62** (314 mg, 64 %) as a colorless oil.

From lactam **23b**

Operating as above, from **27** (430 mg, 1.86 mmol), *n*-BuLi (3.2 mL of a 2.5 M solution in hexanes, 8.0 mmol), and $NH_3{\cdot}BH_3$ (247 mg, 8.0 mmol) in anhydrous THF (15 mL), aminoalcohol **62** (257 mg, 58%) was obtained after flash chromatography (from 8:2 hexane-EtOAc to 8:2 EtOAc-EtOH).

Spectroscopic data for **62**

$[\alpha]^{22}_{D}$ –50.7 (*c* 0.76, $CHCl_3$).

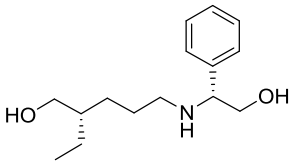
IR (film) 3330, 2927, 1454, 1040 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$, COSY, *g*-HSQC) δ 0.88 (d, *J* = 6.7 Hz, 3H, CH_3), 1.10-1.19 (m, 1H, H-3), 1.39-1.64 (m, 4H, H-2, H-3, H-4), 2.46-2.58 (m, 2H, H-5), 3.27 (brs, 3H, NH, OH), 3.43 (d, *J* = 6.0 Hz, 2H, H-1), 3.61 (dd, *J* = 10.9, 8.9 Hz, 1H, CH_2O), 3.72 (dd, *J*= 10.9, 4.2 Hz, 1H, CH_2O), 3.80 (dd, *J* = 8.9, 4.2 Hz, 1H, CHN), 7.25-7.37 (m, 5H, ArH).

^{13}C NMR (100.6 MHz, $CDCl_3$) δ 16.6 (CH_3), 26.6 (C-4), 30.4 (C-3), 35.3 (C-2), 47.2 (C-5), 64.7 (CHN), 66.2 (C- CH_2O), 67.5 (C-1), 127.3 (C-*o*), 127.7 (C-*p*), 128.6 (C-*m*), 139.7 (C-*i*).

HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{14}H_{24}NO_2$ 238.1802; found 238.1794.

(*S*)-2-Ethyl-5-{[(1*R*)-2-hydroxy-1-phenylethyl]amino}-1-pentanol (63)



From lactam **23a**

n-BuLi (1.68 mL of a 2.5 M solution in hexanes, 4.21 mmol) was added to a solution of $NH_3{\cdot}BH_3$ (130 mg, 4.21 mmol) in anhydrous THF (5 mL) at 0 ºC, and the resulting mixture was stirred at this temperature for 10 min and at room temperature for 15 minutes. Then, this solution was added to a solution of **25** (240 mg, 0.98 mmol) in anhydrous THF (2.5 mL), and the stirring was continued at 40 ºC for 2 h. The reaction mixture was quenched with H_2O, and the resulting solution was extracted with Et_2O. The combined organic extracts were dried, filtered, and concentrated. Flash chromatography (from 8:2 hexane-EtOAc to 8:2 EtOAc-EtOH) of the residue gave piperidine **13**[57] (colorless oil, 22 mg, 10%) and aminoalcohol **63** (159 mg, 65 %) as a colorless oil.

From lactam **23b**

Operating as above, from **28** (470 mg, 1.92 mmol), *n*-BuLi (3.3 mL of a 2.5 M solution in hexanes, 8.24 mmol), and $NH_3{\cdot}BH_3$ (254 mg, 8.24 mmol) in anhydrous THF (13.5

mL), piperidine **13** (37 mg, 8%) and aminoalcohol **63** (294 mg, 61%) were obtained after flash chromatography (from 8:2 hexane-EtOAc to 8:2 EtOAc-EtOH).

Spectroscopic data for **63**

$[\alpha]^{22}_{D}$ –63.9 (*c* 0.8, MeOH).

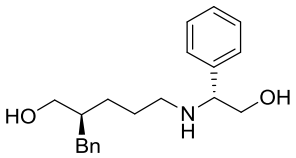
IR (film) 3300, 1454, 1037 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$, COSY, *g*-HSQC) δ 0.83 (t, *J* = 7.6 Hz, 3H, CH_3), 1.22-1.38 (m, 5H, CH_2CH_3, H-2, H-4), 1.48 (brs, 2H, H-3), 2.48 (m, 2H, H-5), 3.56-3.70 (m, 2H, H-1), 3.45 (dd, *J*= 10.9, 4.8 Hz, 1H, CH_2O), 3.49 (dd, *J* = 10.4, 3.6 Hz, 1H, CH_2O), 3.77 (dd, *J* = 4.8, 3.6 Hz, 1H, CHN), 7.23-7.30 (m, 5H, ArH).

^{13}C NMR (100.6 MHz, $CDCl_3$) δ 11.2 (CH_3CH_2), 23.5 (CH_3CH_2), 26.4 (C-3), 27.7 (C-4), 41.5 (C-2), 47.3 (C-5), 64.3 (C-1), 64.7 (CHN), 66.3 (CH_2O), 127.3 (C-*o*), 127.5 (C-*p*), 128.5 (C-*m*), 139.9 (C-*i*).

HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{15}H_{26}NO_2$ 252.1958; found 252.1955.

(*S*)-2-Benzyl-5-{[(1*R*)-2-hydroxy-1-phenylethyl]amino}-1-pentanol (64)



n-BuLi (2.54 mL of a 2.5 M solution in hexanes, 6.34 mmol) was added to a solution of $NH_3{\cdot}BH_3$ (196 mg, 6.34 mmol) in anhydrous THF (6 mL) at 0 ºC, and the resulting mixture was stirred at this temperature for 10 min and at room temperature for 15 minutes. Then, this solution was added to a solution of **26** (453 mg, 1.47 mmol) in anhydrous THF (3 mL), and the stirring was continued at 40 ºC for 2 h. The reaction mixture was quenched with H_2O, and the resulting solution was extracted with Et_2O. The combined organic extracts were dried, filtered, and concentrated. Flash chromatography (from 8:2 hexane-EtOAc to 8:2 EtOAc-EtOH) of the residue gave piperidine **65** (colorless oil, 23 mg, 5%) and aminoalcohol **64** (300 mg, 65 %) as a colorless oil.

Spectroscopic data for **64**

$[\alpha]^{22}_{D}$ –45.3 (*c* 1.0, $CHCl_3$).

IR (film) 3331, 1494, 1453 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$, COSY, *g*-HSQC) δ 1.30-1.37 (m, 1H, H-3), 1.37-1.48 (m, 1H, H-3), 1.48-1.57 (m, 2H, H-4), 1.77 (m, 1H, H-2), 2.52 (m, 2H, H-5), 2.55 (m, 1H, CH_2Ar), 2.63 (dd, *J* = 13.6, 7.5 Hz, 1H, CH_2Ar), 2.83 (brs, 3H, NH, OH), 3.47 (dd, *J* = 10.8, 5.3 Hz, 1H, H-1), 3.56 (dd, *J* = 10.8, 4.7 Hz, 1H, H-1), 3.59-3.62 (m, 1H, CH_2O), 3.69-3.73 (m, 1H, CH_2O), 3.76-3.78 (m, 1H, CHN), 7.13-7.19 (m, 3H, ArH), 7.24-7.37 (m, 7H, ArH).

^{13}C NMR (100.6 MHz, $CDCl_3$) δ 26.7 (C-4), 27.9 (C-3), 37.8 (CH_2Ar), 42.2 (C-2), 47.2 (C-5), 64.1 (C-1), 64.6 (CHN), 66.3 (CH_2O), 125.8 (C-*p*), 127.3 (C-*p*), 127.7 (C-*i*), 128.3 (C-Ar), 128.7 (C-Ar), 129.1 (C-Ar), 140.6 (C-*i*).

HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{20}H_{28}NO_2$ 314.2115; found 314.2106.

Spectroscopic data for **65**

$[\alpha]^{22}_{D}$ +2.1 (*c* 0.45, $CHCl_3$).

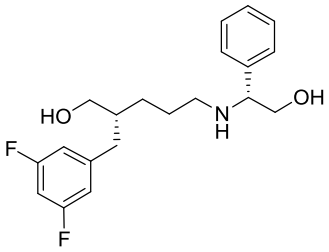
IR (film) 3386, 1453 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$, COSY, *g*-HSQC) δ 1.19-1.33 (m, 1H, H-4), 1.53-1.68 (m, 4H, H-2, H-4, H-5), 1.74-1.86 (m, 1H, H-3), 2.29-2.35 (m, 1H, H-2), 2.36 (dd, *J* = 13.5, 8.1 Hz, 1H, CH_2Ar), 2.56 (dd, *J* = 13.5, 6.5 Hz, 1H, CH_2Ar), 2.75 (m, 1H, H-6), 2.83 (m, 1H, H-6), 3.61 (dd, *J* = 10.3, 5.1 Hz, 1H, CH_2O), 3.74 (dd, *J* = 10.3, 5.1 Hz, 1H, CHN), 3.97 (t, *J* = 10.3 Hz, 1H, CH_2O), 7.09-7.38 (m, 10H, ArH).

^{13}C NMR (100.6 MHz, $CDCl_3$) δ 25.4 (C-5), 30.3 (C-4), 38.2 (C-3), 40.8 (CH_2Ar), 52.8 (C-6), 52.8 (C-2), 59.8 (CH_2O), 70.1 (CHN), 125.9 (C-*p*), 127.9 (C-*p*), 128.2 (C-*o*), 128.3 (C-*o*), 129.0 (C-*m*), 129.1 (C-*m*), 135.0 (C-*i*), 140.2 (C-*i*).

HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{20}H_{26}NO$ 296.2009; found 296.2010.

(*R*)-2-(3,5-Difluorobenzyl)-5-{[(1*R*)-2-hydroxy-1-phenylethyl]amino}-1-pentanol (66)



n-BuLi (2.26 mL of a 2.5 M solution in hexanes, 5.64 mmol) was added to a solution of $NH_3{\cdot}BH_3$ (174 mg, 5.64 mmol) in anhydrous THF (5 mL) at 0 ºC, and the resulting mixture was stirred at this temperature for 10 min and at room temperature for 15 minutes. Then, this solution was added to a solution of **29a** (450 mg, 1.31 mmol) in anhydrous THF (4.5 mL), and the stirring was continued at 40 ºC for 2 h. The reaction mixture was quenched with H_2O, and the resulting solution was extracted with Et_2O. The combined organic extracts were dried, filtered, and concentrated. Flash chromatography (from 8:2 hexane-EtOAc to 8:2 EtOAc-EtOH) of the residue gave piperidine **67** (colorless oil, 52 mg, 12%) and aminoalcohol **66** (299 mg, 65 %) as a colorless oil.

Spectroscopic data for **66**

$[\alpha]^{22}_{D}$ –33.9 (*c* 0.5, $CHCl_3$).

IR (film) 3353, 1625 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$, COSY, *g*-HSQC) δ 1.26-1.31 (m, 1H, H-3), 1.35-1.43 (m, 1H, H-3), 1.45-1.53 (m, 2H, H-4), 1.72 (brs, 1H, H-2), 2.51 (m, 3H, H-5, CH_2Ar), 2.65-2.70 (m, 1H, CH_2Ar), 3.44 (dd, *J* = 10.5, 5.2 Hz, 1H, H-2), 3.50 (dd, *J* = 10.5, 6.4 Hz, 1H, H-2), 3.63-3.74 (m, 4H, 2C*H*$_2$O), 3.80 (dd, *J* = 8.4, 3.7 Hz, 1H, CHN), 6.59-6.67 (m, 3H, F-ArH), 7.26-7.31 (m, 5H, ArH).

^{13}C NMR (100.6 MHz, $CDCl_3$) δ 26.3 (C-3), 27.7 (C-4), 37.4 (CH_2Ar, d, $J_{C\text{-}F}$ = 9.2 Hz), 41.7 (C-2, d, $J_{C\text{-}F}$ = 6.2 Hz), 47.0 (C-5), 63.2 (C-2), 64.7 (CHN), 66.1 (CH_2O), 101.3 (F-Ar C-4, t, $J_{C\text{-}F}$ = 24.9 Hz), 111.7 (F-Ar C-2 and C-6, dd, $J_{C\text{-}F}$ = 18.7, 6.2 Hz), 127.3 (CH-Ar), 127.8 (C-*p*), 128.7 (CH-Ar), 139.2 (C-*i*), 144.7 (F-Ar C-1, t, $J_{C\text{-}F}$ = 9.3 Hz), 162.8 (F-Ar C-3 and C-5, dd, $J_{C\text{-}F}$ = 247.7, 13.3 Hz).

HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{20}H_{26}F_2NO_2$ 350.1926; found 350.1926.

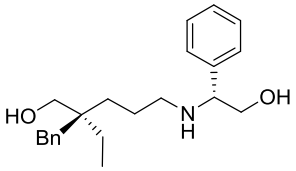
Spectroscopic data for **67:**

^{1}H NMR (400 MHz, $CDCl_3$, COSY, *g*-HSQC) δ 1.43-1.72 (m, 4H, H-4, H-5), 1.95-2.00 (m, 1H, H-3), 2.37-2.52 (m, 2H, H-2), 2.70-2.85 (m, 2H, H-6), 2.78-2.85 (m, 2H, CH_2Ar), 3.58-3.75 (m, 2H, CH_2O), 3.93-4.00 (m, 1H, NCH), 6.60-6.67 (m, 3H, F-ArH), 7.14-7.17 (dd, *J* = 7.9, 1.9 Hz, 2H, ArH), 7.36-7.37 (m, 3H, ArH).

^{13}C NMR (100.6 MHz, $CDCl_3$) δ 25.3 (C-5, d, J_{C-F} = 11.7 Hz), 30.4 (C-4, d, J_{C-F} = 29.7 Hz), 38.0 (C-3, d, J_{C-F} = 35.8 Hz), 40.5 (CH_2Ar), 46.9 (C-6), 52.7 (C-2, d, J_{C-F} = 11.7 Hz), 59.9 (CHAr, d, J_{C-F} = 3.1 Hz), 70.1 (CH_2O, d, J_{C-F} = 17.1 Hz), 101.4 (F-Ar C-4, dd, J_{C-F} = 24.8, 3.1 Hz), 111.7 (F-Ar C-2 and C-6, dd, J_{C-F} = 17.9, 6.9 Hz), 127.9 (C-*p*), 128.2 (CH-Ar), 128.9 (CH-Ar), 135.1 (C-*i*, d, J_{C-F} = 3.9 Hz), 144.3 (F-Ar C-1, d, J_{C-F} = 8.5 Hz), 162.9 (F-Ar C-3 and C-5, ddd, J_{C-F} = 247.6, 13.3, 3.9 Hz).

HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{20}H_{24}F_2NO$ 332.1820; found 332.1820.

(*S*)-2-Benzyl-5-[(*tert*-butoxyC-Arbonyl)amino]-2-ethyl-1-pentanol (68)



n-BuLi (1.83 mL of a 2.5 M solution in hexanes, 4.56 mmol) was added to a solution of $NH_3{\cdot}BH_3$ (141 mg, 4.56 mmol) in anhydrous THF (5 mL) at 0 ºC, and the resulting mixture was stirred at this temperature for 10 min and at room temperature for 15 minutes. Then, this solution was added to a solution of **33** (356 mg, 1.06 mmol) in anhydrous THF (2.5 mL), and the stirring was continued at 40 ºC for 1 h 30. The reaction mixture was quenched with H_2O, and the resulting solution was extracted with Et_2O. The combined organic extracts were dried, filtered, and concentrated. Flash chromatography (from EtOAc to 8:2 EtOAc-EtOH) of the residue gave aminoalcohol **68** (250 mg, 69 %) as a colorless oil.

Spectroscopic data for **68**

$[\alpha]^{22}_D$ –28.4 (*c* 0.96, $CHCl_3$).

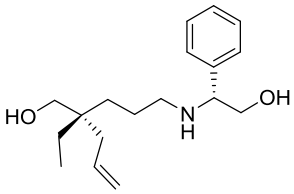
IR (film) 3384, 1601, 1494, 1452 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$, COSY, *g*-HSQC) δ 0.89 (t, *J* = 7.0 Hz, 3H, C*H*$_3$CH$_2$), 1.15-1.20 (m, 2H, H-3), 1.22-1.30 (m, 2H, H-4), 1.41-1.53 (m, 2H, CH$_2$CH$_3$), 2.45-2.49 (m, 2H, H-5), 2.52 (d, *J* = 13.2 Hz, 1H, CH$_2$Ph), 2.60 (d, *J* = 13.2 Hz, 1H, CH$_2$Ph), 3.28 (brs, 2H, H-1), 3.58 (dd, *J* = 11.0, 8.6, Hz, 1H, CH$_2$O), 3.72 (dd, *J* = 11.0, 4.4 Hz, 1H, CH$_2$O), 3.78 (dd, *J* = 8.6, 4.4 Hz, 1H, CHN), 7.16-7.37 (m, 10H, ArH).

^{13}C NMR (100.6 MHz, $CDCl_3$) δ 7.6 (*C*H$_3$CH$_2$), 23.2 (CH$_3$*C*H$_2$), 24.8 (C-3), 30.4 (C-4), 39.9 (CH$_2$Ar), 41.5 (C-2), 47.9 (C-5), 64.7 (CHN), 65.4 (C-1), 66.6 (CH$_2$O), 125.9 (C-*p*), 127.3 (C-*o*), 127.7 (C-*p*), 127.9 (C-*o*), 128.7 (C-*m*), 130.4 (C-*m*), 138.6 (C-*i*), 140.4 (C-*i*).

HRMS (ESI-TOF) m/z: [M + H]$^+$ Calcd for $C_{22}H_{32}NO_2$ 342.2428; found 342.2425.

(*S*)-2-Allyl-2-ethyl-5-{[(1*R*)-2-hydroxy-1-phenylethyl]amino}-2-ethyl-1-pentanol (69)



n-BuLi (2.4 mL of a 2.5 M solution in hexanes, 6.03 mmol) was added to a solution of $NH_3{\cdot}BH_3$ (186 mg, 6.03 mmol) in anhydrous THF (5.5 mL) at 0 ºC, and the resulting mixture was stirred at this temperature for 10 min and at room temperature for 15 minutes. Then, this solution was added to a solution of **34** (400 mg, 1.40 mmol) in anhydrous THF (2.5 mL), and the stirring was continued at 40 ºC for 2 h. The reaction mixture was quenched with H_2O, and the resulting solution was extracted with Et_2O. The combined organic extracts were dried, filtered, and concentrated. Flash chromatography (from 8:2 hexane-EtOAc to 8:2 EtOAc-EtOH) of the residue gave piperidine **70** (37 mg, 9%) and aminoalcohol **69** (227 mg, 56 %) as a colorless oil.

Spectroscopic data for **69**

$[\alpha]^{22}_D$ –34.3 (*c* 0.8, $CHCl_3$).

IR (film) 3331, 1454 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$, COSY, *g*-HSQC) δ 0.76 (t, *J*= 7.2 Hz, 3H, CH_3), 1.12-1.14 (m, 4H, CH_3CH_2, H-3), 1.40-1.45 (m, 2H, H-4), 1.89 (dd, *J* = 14.0, 7.6 Hz, 1H, CH_2=CHCH_2), 1.98 (dd, *J* = 14.0, 7.6 Hz, 1H, CH_2=CHCH_2), 2.44-2.49 (m, 2H, H-5), 3.30 (s, 1H, NH), 3.63-3.70 (m, 4H, H-1, CH_2O), 3.82 (dd, *J* = 8.4, 4.0 Hz, 1H, CHN), 4.16 (brs, 2H, OH), 4.99 (m, 2H, CH_2=CH), 5.68-5.78 (m, 1H, CH_2=C*H*), 7.30 (m, 5H, ArH).

^{13}C NMR (100.6 MHz, $CDCl_3$) δ 7.2 (CH_3CH_2), 22.4 (C-4), 25.3 (CH_3CH_2), 30.6 (C-3), 37.9 (CH_2=CHCH_2), 40.0 (C-2), 47.6 (C-5), 64.7 (CHN), 65.5 (CH_2O), 65.9 (C-1), 116.9 (CH_2=CH), 127.4 (C-*o*), 127.7 (C-*p*), 128.5 (C-*m*), 134.6 (CH_2=CH), 138.9 (C-i).

HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{18}H_{30}NO_2$ 292.2271; found 292.2266.

Spectroscopic data for **70**

$[\alpha]^{22}_D$ –19.5 (*c* 0.5, $CHCl_3$).

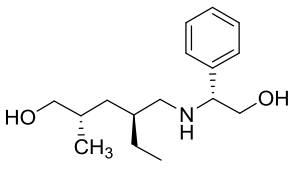
IR (film) 3440, 1637, 1452 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$, COSY, *g*-HSQC) δ 0.80 (t, *J* = 7.6 Hz, 3H, CH_3), 1.15-1.28 (m, 2H, CH_2), 1.31 (m, 2H, H-5), 1.60 (m, 2H, CH_2), 2.04-2.18 (m, 2H, H-4), 2.20 (m, 2H, H-2), 2.54 (brs, 2H, H-6), 3.59-3.66 (m, 2H, CHN, CH_2O), 3.99 (t, *J* = 9.6 Hz, CH_2O), 5.03 (m, 2H, CH_2=CH), 5.70-5.80 (m, 1H, CH_2=C*H*), 7.15-7.35 (m, 5H, ArH).

^{13}C NMR (100.6 MHz, $CDCl_3$) δ 7.15 (CH_3), 21.9 (CH_2), 28.3 (C-5), 33.4 (CH_2), 36.2 (C-3), 39.3 (C-4), 49.9 (C-6), 58.6 (C-2), 60.1 (CH_2O), 70.2 (CHN), 117.1 (CH_2=CH), 127.8 (C-*p*), 128.0 (C-*o*), 128.9 (C-*m*), 134.6 (CH_2=CH), 135.3 (C-*i*).

HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{18}H_{28}NO$ 274.2165; found 274.2161.

(2*S*,4*S*)-4-Ethyl-5-{[(1*R*)-2-hydroxy-1-phenylethyl]amino}-2-methyl-1-pentanol (71)



n-BuLi (3.48 mL of a 2.5 M solution in hexanes, 8.71 mmol) was added to a solution of $NH_3{\cdot}BH_3$ (269 mg, 8.71 mmol) in anhydrous THF (6 mL) at 0 ºC, and the resulting mixture was stirred at this temperature for 10 min and at room temperature for 15 minutes. Then, this solution was added to a solution of **30** (525 mg, 2.03 mmol) in anhydrous THF (3 mL), and the stirring was continued at 40 ºC for 1 h. The reaction mixture was quenched with H_2O, and the resulting solution was extracted with Et_2O. The combined organic extracts were dried, filtered, and concentrated. Flash chromatography (from 1:1 hexane-EtOAc to 8:2 EtOAc-EtOH) of the residue gave aminoalcohol **71** (349 mg, 65 %) as a colorless oil.

Spectroscopic data for **71**

$[\alpha]^{22}_D$ –64.7 (*c* 1.0, $CHCl_3$).

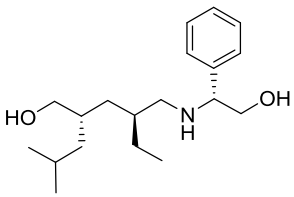
IR (film) 3319, 1454 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$, COSY, *g*-HSQC) δ 0.81 (t, *J* = 7.4 Hz, 3H, C*H*$_3$CH$_2$), 0.86 (d, *J* = 6.8 Hz, 3H, CH_3), 1.19-1.37 (m, 4H, H-3, CH_3CH_2), 1.47-1.55 (m, 1H, H-4), 1.70-1.77 (m, 1H, H-2), 2.29-2.34 (m, 1H, H-5), 2.47 (dd, *J* = 11.6, 4.5 Hz, 1H, H-5), 3.42 (m, 2H, H-1), 3.50-3.75 (brm, 3H, NH, OH), 3.58 (m, 1H, CH_2O), 3.68 (m, 1H, CH_2O), 3.75 (m, 1H, CHN), 7.24-7.35 (m, 5H ArH).

^{13}C NMR (100.6 MHz, $CDCl_3$) δ 11.0 (*C*H_3CH_2), 17.0 (CH_3), 25.6 (CH_3*C*H_2), 32.7 (C-2), 35.5 (C-3), 36.0 (C-4), 51.1 (C-5), 65.0 (CHN), 66.5 (CH_2O), 67.6 (C-1), 127.3 (C-*o*), 127.5 (C-*p*), 128.5 (C-*m*), 140.1 (C-*i*).

HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{16}H_{28}NO_2$ 266.2115; found 266.2113.

(2*S*,4*S*)-4-Ethyl-5-{[(1*R*)-2-hydroxy-1-phenylethyl]amino}-2-isobutyl-1-pentanol (72)



n-BuLi (2.5 mL of a 2.5 M solution in hexanes, 6.28 mmol) was added to a solution of $NH_3{\cdot}BH_3$ (194 mg, 6.28 mmol) in anhydrous THF (8.5 mL) at 0 ºC, and the resulting

mixture was stirred at this temperature for 10 min and at room temperature for 15 minutes. Then, this solution was added to a solution of **32a**(440 mg, 1.46 mmol) in anhydrous THF (4.5 mL), and the stirring was continued at 40 ºC for 1 h 15. The reaction mixture was quenched with H_2O, and the resulting solution was extracted with Et_2O. The combined organic extracts were dried, filtered, and concentrated. Flash chromatography (from 8:2 hexane-EtOAc to 8:2 EtOAc-EtOH) of the residue gave aminoalcohol **72** (254 mg, 57 %) as a colorless oil.

Spectroscopic data for **72**

$[\alpha]^{22}_D$ –40.4 (*c* 1.1, $CHCl_3$).

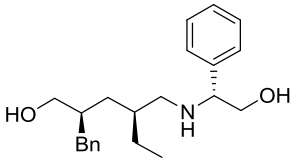
IR (film) 3330, 1454 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$, COSY, *g*-HSQC) δ 0.83 (t, *J* = 7.4 Hz, 3H, C*H*$_3$CH$_2$), 0.86 (d, *J* = 3.1 Hz, 3H, CH_3), 0.88 (d, *J* = 3.1 Hz, 3H, CH_3), 1.03-1.14 [m, 2H, H-3, C*H*$_2$CH(CH$_3$)$_2$], 1.19-1.30 [m, 3H, CH$_3$C*H*$_2$, C*H*$_2$CH(CH$_3$)$_2$], 1.39-1.45 (m, 2H, H-3, H-4), 1.54 (brm, 1H, H-2), 1.63 [sept, *J* = 6.7 Hz, 1H, C*H*(CH$_3$)$_2$], 2.23 (dd, *J* = 11.6, 7.7 Hz, 1H, H-5), 2.53 (dd, *J* = 11.6, 3.3 Hz, 1H, H-5), 3.00 (brm, 3H, NH, OH), 3.44 (dd, *J* = 11.1, 4.8 Hz, 1H, H-1), 3.58-3.63 (m, 1H, CH_2O), 3.69-3.73 (m, 2H, H-1, CH_2O), 3.76 (dd, *J* = 8.9, 3.8 Hz, 1H, CHN), 7.26-7.37 (m, 5H, ArH).

^{13}C NMR (100.6 MHz, $CDCl_3$) δ 11.4 (*C*H$_3$CH$_2$), 22.8 (CH_3), 22.9 (CH_3), 25.2 (CH), 26.7 (CH$_3$*C*H$_2$), 34.8 (C-3), 36.6 (C-2), 37.6 (C-4), 42.2 [C*H*$_2$CH(CH$_3$)$_2$], 51.6 (C-5), 64.5 (C-1), 65.0 (CHN), 66.7 (CH_2O), 127.4 (C-*o*), 127.5 (C-*p*), 128.5 (C-*m*), 140.2 (C-*i*).

HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{19}H_{34}NO_2$ 308.2584; found 308.2583.

(2*S*,4*S*)-2-Benzyl-5-{[(1*R*)-2-hydroxy-1-phenylethyl]amino}-4-ethyl-1-pentanol (73)



n-BuLi (2.69 mL of a 2.5 M solution in hexanes, 6.72 mmol) was added to a solution of $NH_3{\cdot}BH_3$ (207 mg, 6.72 mmol) in anhydrous THF (9 mL) at 0 ºC, and the resulting

mixture was stirred at this temperature for 10 min and at room temperature for 15 minutes. Then, this solution was added to a solution of **31** (524 mg, 1.56 mmol) in anhydrous THF (4.5 mL), and the stirring was continued at 40 ºC for 1 h. The reaction mixture was quenched with H_2O, and the resulting solution was extracted with Et_2O. The combined organic extracts were dried, filtered, and concentrated. Flash chromatography (from 7:3 hexane-EtOAc to 8:2 EtOAc-EtOH) of the residue gave aminoalcohol **73** (295 mg, 55 %) as a colorless oil.

Spectroscopic data for **73**

$[\alpha]^{22}_D$ –54.0 (*c* 0.38, $CHCl_3$).

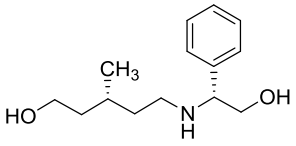
IR (film) 3338, 1494, 1453 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$, COSY, *g*-HSQC) δ 0.74 (t, *J* = 7.4 Hz, 3H, CH_3), 1.14-1.23 (m, 3H, H-3, CH_3CH_2), 1.35-1.40 (m, 1H, H-4), 1.44-1.51 (m, 1H, H-3), 1.73-1.80 (m, 1H, H-2), 2.23 (dd, *J* = 11.6, 8.2 Hz, 1H, H-5), 2.50 (dd, *J* = 11.6, 4.0 Hz, 1H, H-5), 2.53 (dd, *J* = 13.5, 6.8 Hz, 1H, CH_2Ar), 2.67 (dd, *J* = 13.5, 7.9 Hz, 1H, CH_2Ar), 2.99 (brs, 3H, NH, OH), 3.45 (dd, *J* = 11.5, 4.3 Hz, 1H, H-1), 3.58 (dd, *J* = 10.4, 9.2 Hz, 1H, CH_2O), 3.67 (dd, *J* = 11.5, 3.8 Hz, 1H, H-1), 3.68-3.69 (m, 1H, CH_2O), 3.71-3.76 (m, 1H, CHN), 7.15-7.19 (m, 3H, ArH), 7.24-7.37 (m, 7H, ArH).

^{13}C NMR (100.6 MHz, $CDCl_3$) δ 11.1 (CH_3), 26.4 (CH_3CH_2), 34.0 (C-3), 37.3 (C-4), 39.1 (CH_2Ar), 41.1 (C-2), 51.6 (C-5), 63.3 (C-1), 65.1 (CHN), 66.7 (CH_2O), 125.7 (C-Ar), 127.5 (C-*p*), 128.2 (C-Ar), 128.7 (C-*p*), 129.1 (C-Ar), 140.9 (C-*i*).

HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{22}H_{32}NO_2$ 342.2428; found 342.2424.

(*R*)-5-{[(1*R*)-2-Hydroxy-1-phenylethyl]amino}-3-methyl-1-pentanol (74)



n-BuLi (1.95 mL of a 2.5 M solution in hexanes, 4.87 mmol) was added to a solution of $NH_3{\cdot}BH_3$ (150 mg, 4.87 mmol) in anhydrous THF (4 mL) at 0 ºC, and the resulting mixture was stirred at this temperature for 10 min and at room temperature for 15 minutes. Then, this solution was added to a solution of **41** (262 mg, 1.14 mmol) in anhydrous THF (2 mL), and the stirring was continued at 40 ºC for 1 h 30. The

reaction mixture was quenched with H_2O, and the resulting solution was extracted with Et_2O. The combined organic extracts were dried, filtered, and concentrated. Flash chromatography (from 1:1 hexane-EtOAc to 8:2 EtOAc-EtOH) of the residue gave piperidine **75** (colorless oil, 49 mg, 20%) and aminoalcohol **74** (135 mg, 50 %) as a colorless oil.

Spectroscopic data for **74**

$[\alpha]^{22}_D$ –51.9 (*c* 0.84, $CHCl_3$).

IR (film) 3320, 1454 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$, COSY, *g*-HSQC) δ 0.86 (d, *J* = 6.6 Hz, 3H, CH_3), 1.28-1.42 (m, 2H, H-2, H-4), 1.46-1.59 (m, 2H, H-2, H-4), 1.64-1.72 (m, 1H, H-3), 2.44-2.51 (m, 1H, H-5), 2.56-2.63 (m, 1H, H-5), 3.48 (brs, 3H, NH, OH), 3.57-3.63 (m, 2H, H-1, CH_2O), 3.65-3.72 (m, 2H, H-1, CH_2O), 3.78 (dd, *J* = 8.9, 4.1 Hz, 1H, CHN), 7.24-7.35 (m, 5H, ArH).

^{13}C NMR (100.6 MHz, $CDCl_3$) δ 19.8 (CH_3), 27.2 (C-3), 36.5 (C-4), 39.4 (C-2), 44.8 (C-5), 60.1 (C-1), 64.9 (CHN), 66.3 (CH_2O), 127.2 (C-*o*), 127.6 (C-*p*), 128.5 (C-*m*), 139.9 (C-*i*).

HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{14}H_{24}NO_2$ 238.1802; found 238.1802.

Spectroscopic data for **75**

$[\alpha]^{22}_D$ –18.5 (*c* 2.4, $CHCl_3$).

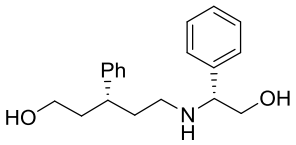
IR (film) 3414 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$, COSY, *g*-HSQC) δ 0.87 (d, *J* = 6.0 Hz, 3H, CH_3), 1.10-1.23 (m, 1H, H-4), 1.25-1.34 (m, 2H, H-3, H-5), 1.55-1.72 (m, 3H, H-3, H-5, H-2 or H-6), 2.29 (ddd, *J* = 11.3, 2.5 Hz, 1H, H-2 or H-6), 2.83 (m, 2H, H-2, H-6), 3.20 (brs, 1H, OH), 3.62 (dd, *J* = 10.1, 5.2 Hz, 1H, CH_2O), 3.70 (dd, *J* = 10.1, 5.2 Hz, 1H, CHN), 3.97 (t, *J* = 10.1 Hz, 1H, CH_2O), 7.17 (m, 2H, ArH), 7.28-7.36 (m, 3H, ArH).

^{13}C NMR (100.6 MHz, $CDCl_3$) δ 21.8 (CH_3), 30.8 (C-4), 34.6 and 34.9 (C-3 and C-5), 46.2 (C-2 or C-6), 52.8 (C-2 or C-6), 60.0 (CH_2O), 69.9 (CHN), 127.7 (C-*p*), 128.0 (C-o), 128.9 (C-*m*), 135.6 (C-*i*).

HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{14}H_{22}NO$ 220.1696; found 220.1700.

(*R*)-5-{[(1*R*)-2-Hydroxy-1-phenylethyl]amino}-3-phenyl-1-pentanol (76)



From lactam **42**

n-BuLi (1.41 mL of a 2.5 M solution in hexanes, 3.52 mmol) was added to a solution of $NH_3{\cdot}BH_3$ (109 mg, 3.52 mmol) in anhydrous THF (5 mL) at 0 ºC, and the resulting mixture was stirred at this temperature for 10 min and at room temperature for 15 minutes. Then, this solution was added to a solution of **42** (240 mg, 0.82 mmol) in anhydrous THF (2.5 mL), and the stirring was continued at 40 ºC for 2 h. The reaction mixture was quenched with H_2O, and the resulting solution was extracted with Et_2O. The combined organic extracts were dried, filtered, and concentrated. Flash chromatography (from 1:1 hexane-EtOAc to 8:2 EtOAc-EtOH) of the residue gave piperidine **77** (colorless oil, 35 mg, 15%) and aminoalcohol **76** (105 mg, 43 %) as a colorless oil.

From lactam **78**

Operating as above, from **78** (510 mg, 1.74 mmol), *n*-BuLi (3.0 mL of a 2.5 M solution in hexanes, 7.48 mmol), and $NH_3{\cdot}BH_3$ (231 mg, 7.48 mmol) in anhydrous THF (27 mL), piperidine **77** (40 mg, 8%) and aminoalcohol **76** (338 mg, 65%) were obtained after flash chromatography (from 1:1 hexane-EtOAc to 8:2 EtOAc-EtOH).

Spectroscopic data for **76**

$[\alpha]^{22}_D$ –40.9 (*c* 3.0, $CHCl_3$).

IR (film) 3321, 1452 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$, COSY, *g*-HSQC) δ 1.70-1.88 (m, 4H, H-2, H-4), 1.64-1.72 (m, 1H, H-3), 2.44-2.32-2.38 (m, 1H, H-5), 2.45-2.51 (m, 1H, H-5), 2.61 (brs, 3H, NH, OH), 2.80-2.87 (m, 1H, H-3), 3.39-3.46 (m, 1H, H-1), 3.48-3.54 (m, 2H, H-1, CH_2O), 3.62-3.66 (m, 2H, CH_2O, CHN), 7.13-7.31 (m, 10H, ArH).

^{13}C NMR (100.6 MHz, $CDCl_3$) δ 36.1 (C-4), 39.3 (C-2), 39.8 (C-3), 44.9 (C-5), 60.5 (C-1), 64.6 (CHN), 65.9 (CH_2O), 126.4 (C-*p*), 127.2 (C-*o*), 127.5 (C-*o*), 127.8 (C-*p*), 128.4 (C-*m*), 128.5 (C-*m*), 139.4 (C-*i*), 144.4 (C-*i*).

HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{19}H_{26}NO_2$ 300.1958; found 300.1957.

Spectroscopic data for **77**

$[\alpha]^{22}_D$ –6.4 (*c* 0.26, $CHCl_3$).

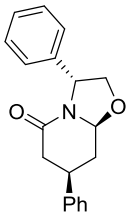
IR (film) 3417, 1601, 1493, 1451 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$, COSY, *g*-HSQC) δ 1.71 (dt, *J* = 12.4, 3.7 Hz, 1H, H-3 or H-5), 1.79-1.82 (m, 1H, H-4), 1.82-1.88 (m, 3H, H-3, H-5), 2.32-2.40 (m, 1H, H-2 or H-6), 2.42-2.48 (m, 1H, H-2 or H-6), 2.98-3.05 (m, 2H, H-2, H-6), 3.66 (dd, *J* = 10.4, 5.2 Hz, 1H, CH_2O), 3.76 (dd, *J* = 10.0, 5.2 Hz, 1H, CHN), 4.02 (t, *J* = 10.4 Hz, 1H, CH_2O), 7.16-7.39 (m, 10H, ArH).

^{13}C NMR (100.6 MHz, $CDCl_3$) δ 33.7 and 34.1 (C-3 and C-5), 42.6 (C-4), 46.4 and 53.5 (C-2 and C-6), 60.1 (CH_2O), 70.1 (CHN), 126.1 (C-*p*), 126.7 (C-*o*), 127.9 (C-*p*), 128.1 (C-*o*), 128.4 (C-*m*), 128.9 (C- *m*), 135.5 (C-*i*), 146.1 (C-*i*).

HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{19}H_{24}NO$ 282.1852; found 282.1851.

(3*R*,7*R*,8a*S*)-3,7-Diphenyl-5-oxo-2,3,6,7,8,8a-hexahydro-5*H*-oxazolo[3,2-*a*]pyridine (78)



TFA (1.6 mL, 20.4 mmol) was added to a solution of pure lactam **42** (630 mg, 2.15 mol) in anhydrous CH_2Cl_2 (66 mL), and the mixture was stirred at room temperature for 47 h. The resulting acidic solution was neutralized with a 2 N aqueous $NaHCO_3$ (25 mL). The organic phase was separated, and the aqueous layer was extracted with CH_2Cl_2. The combined organic solutions were dried and concentrated, and the residue was chromatographed (1:1 hexane–EtOAc) to give pure **78** (610 mg, 97%).

Spectroscopic data for **78**

$[\alpha]^{22}_{D}$ –58.2 (*c* 1.0, $CHCl_3$).

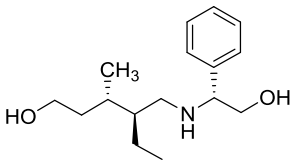
IR (film) 1647, 1454 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$, COSY, *g*-HSQC) δ 1.87 (ddd, *J* = 13.3, 12.4, 9.3 Hz, 1H, H-8), 2.47 (dd, *J* = 18.0, 12.0 Hz, 1H, H-6), 2.56 (dm, 1H, H-8), 2.84 (ddd, *J* = 18.0, 5.6, 1.72 Hz, 1H, H-6), 3.20 (m, 1H, H-7), 3.84 (dd, *J* = 9.0, 7.9 Hz, 1H, H-2), 4.56 (dd, *J* = 9.0, 7.9 Hz, 1H, H-2), 5.20 (dd, *J* = 9.3, 4.5 Hz, 1H, H-8a), 5.32 (t, *J* = 7.9, 1H, CHN), 7.21-7.37 (m, 10H, ArH).

^{13}C NMR (100.6 MHz, $CDCl_3$) δ 35.3 (C-7, C-8), 39.7 (C-6), 58.0 (C-3), 72.7 (C-2), 88.4 (C-8a), 126.1 (C-*o*), 126.4 (C-*o*), 127.0 (C-*p*), 127.6 (C-*p*), 128.7 (C-*m*), 128.8 (C-*m*), 139.3 (C-*i*), 142.4 (C-*i*), 168.1 (NCO).

HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{19}H_{20}NO_2$ 294.1489; found 294.1496.

(3*S*,4*S*)-4-Ethyl-5-{[(1*R*)-2-hydroxy-1-phenylethyl]amino}-3-methyl-1-pentanol (79)



n-BuLi (1.67 mL of a 2.5 M solution in hexanes, 4.18 mmol) was added to a solution of $NH_3{\cdot}BH_3$ (129 mg, 4.18 mmol) in anhydrous THF (6 mL) at 0 ºC, and the resulting mixture was stirred at this temperature for 10 min and at room temperature for 15 minutes. Then, this solution was added to a solution of **43** (252 mg, 0.97 mmol) in anhydrous THF (3 mL), and the stirring was continued at 40 ºC for 1 h. The reaction mixture was quenched with H_2O, and the resulting solution was extracted with Et_2O. The combined organic extracts were dried, filtered, and concentrated. Flash chromatography (from 8:2 hexane-EtOAc to 8:2 EtOAc-EtOH) of the residue gave piperidine **80** (32 mg, 13%) and aminoalcohol **79** (142 mg, 55 %) as a colorless oil.

Spectroscopic data for **79**

$[\alpha]^{22}_{D}$ –74.4 (*c* 0.7, $CHCl_3$).

IR (film) 3331, 1454 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$, COSY, *g*-HSQC) δ 0.83-0.87 (m, 6H, $2CH_3$), 1.16-1.22 (m, 1H, CH_3CH_2), 1.24-1.30 (m, 1H, H-2), 1.32-1.40 (m, 2H, H-4, CH_3CH_2), 1.48-1.57 (m, 1H, H-2), 1.82-1.88 (m, 1H, H-3), 2.35 (dd, *J* = 12.0, 5.3 Hz, 1H, H-5), 2.48 (dd, *J* = 12.0, 6.6 Hz, 1H, H-5), 2.54 (brs, 3H, NH, OH), 3.53-3.61 (m, 2H, H-1, CH_2O), 3.66-3.72 (m, 2H, H-1, CH_2O), 3.73-3.75 (m, 1H, CHN), 7.27-7.37 (m, 5H, ArH).

^{13}C NMR (100.6 MHz, $CDCl_3$) δ 12.5 (CH_3CH_2), 16.8 (CH_3), 22.3 (CH_3CH_2), 30.1 (C-3), 35.8 (C-2), 44.9 (C-4), 47.7 (C-5), 61.4 (C-1), 65.0 (CHN), 66.6 (CH_2O), 127.2 (C-*o*), 127.6 (C-*p*), 128.6 (C-*m*), 140.5 (C-*i*).

HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{16}H_{28}NO_2$ 266.2115; found 266.2117.

Spectroscopic data for **80**

$[\alpha]^{22}_D$ –22.3 (*c* 0.3, $CHCl_3$).

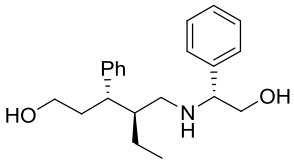
IR (film) 3330, 1454 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$, COSY, *g*-HSQC) δ 0.73 (d, *J* = 7.2 Hz, 3H, CH_3), 0.89 (t, *J* = 7.2 Hz, 3H, CH_3CH_2), 1.29 (m. 2H, CH_3CH_2), 1.43 (m, 1H, H-4), 1.51 (br.m, 1H, H-5), 1.58 (br.m, 1H, H-3), 1.70 (br.m, 1H, H- H-5), 2.17-2.48 (br.m, 4H, H-2 and H-6), 3.66 (m, 1H, CH_2O), 3.72 (m, NCH), 3.99 (t, J = 10.0 Hz, 1H, CH_2O), 7.18-7.37 (m, 5H, ArH).

^{13}C NMR (100.6 MHz, $CDCl_3$) δ 11.9 (CH_3CH_2), 14.1 (CH_3), 22.7 (CH_3CH_2), 28.4 (C-4), 31.5 (C-5), 41.2 (C-3), and 51.0 (C-2 and C-6), 60.1 (CH_2O), 70.2 (CHN), 127.9 (C-*p*), 128.0 (C-*o*), 129.0 (C-*m*), 135.4 (C-*i*).

HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{16}H_{26}NO$ 248.2009; found 248.2007.

(3*S*,4*S*)-4-Ethyl-5-{[(1*R*)-2-hydroxy-1-phenylethyl]amino}-3-phenyl-1-pentanol (81)



n-BuLi (1.0 mL of a 2.5 M solution in hexanes, 2.50 mmol) was added to a solution of $NH_3{\cdot}BH_3$ (77 mg, 2.50 mmol) in anhydrous THF (4 mL) at 0 ºC, and the resulting mixture was stirred at this temperature for 10 min and at room temperature for 15 minutes. Then, this solution was added to a solution of **44** (187 mg, 0.58 mmol) in

anhydrous THF (2 mL), and the stirring was continued at 40 ºC for 2 h. The reaction mixture was quenched with H_2O, and the resulting solution was extracted with Et_2O. The combined organic extracts were dried, filtered, and concentrated. Flash chromatography (from 7:3 hexane-EtOAc to 8:2 EtOAc-EtOH) of the residue gave piperidine **82**[130] (36 mg, 20%) and aminoalcohol **81** (71 mg, 37 %) as a colorless oil.

Spectroscopic data for **81**

$[\alpha]^{22}_D$ –87.9 (*c* 0.75, $CHCl_3$).

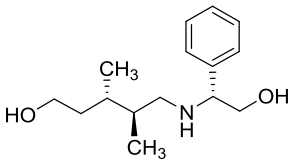
IR (film) 3332, 3061, 1453 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$, COSY, *g*-HSQC) δ 0.81 (t, *J* = 7.3 Hz, 3H, C*H*$_3$CH$_2$), 1.29-1.36 (m, 1H, CH$_3$C*H*$_2$), 1.51-1.57 (m, 1H, CH$_3$C*H*$_2$), 1.58-1.63 (m, 1H, H-4), 1.75-1.83 (m, 1H, H-2), 1.90-2.02 (brm, 4H, H-2, NH, OH), 2.20 (dd, *J* = 12.0, 5.0 Hz, 1H, H-5), 2.46 (dd, *J* = 12.0, 5.3 Hz, 1H, H-5), 2.85 (brm, 1H, H-3), 3.32-3.39 (m, 1H, H-1), 3.41-3.44 (m, 1H, CH$_2$O), 3.46-3.53 (m, 2H, H-1, CHN), 3.60 (dd, *J* = 10.3, 3.9 Hz, 1H, CH$_2$O), 7.13-7.31 (m, 10H, ArH).

^{13}C NMR (100.6 MHz, $CDCl_3$) δ 11.4 (*C*H$_3$CH$_2$), 22.1 (CH$_3$*C*H$_2$), 34.9 (C-2), 43.6 (C-3), 45.7 (C-4), 47.6 (C-5), 61.4 (C-1), 64.8 (CHN), 66.4 (CH$_2$O), 126.3 (C-*p*), 127.2 (C-*o*), 127.4 (C-*p*), 128.3 (C-*o*), 128.4 (C-*m*), 128.5 (C-*m*), 140.7 (C-*i*), 143.6 (C-*i*).

HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{21}H_{30}NO_2$ 328.2271; found 328.2269.

(3*S*,4*S*)-3,4-Dimethyl-5-{[(1*R*)-2-hydroxy-1-phenylethyl]amino}-1-pentanol (83)



n-BuLi (5.2 mL of a 2.5 M solution in hexanes, 13.0 mmol) was added to a solution of $NH_3{\cdot}BH_3$ (403 mg, 13.0 mmol) in anhydrous THF (5 mL) at 0 ºC, and the resulting mixture was stirred at this temperature for 10 min and at room temperature for 15 minutes. Then, this solution was added to a solution of **45** (744 mg, 3.03 mmol) in anhydrous THF (2.5 mL), and the stirring was continued at 40 ºC for 2 h. The reaction mixture was quenched with H_2O, and the resulting solution was extracted with Et_2O. The combined organic extracts were dried, filtered, and concentrated.

Flash chromatography (from 7:3 EtOAc-hexane to 9:1 EtOAc-EtOH) of the residue gave piperidine **84** (30 mg, 4%) and aminoalcohol **83** (346 mg, 45 %) as a colorless oil.

Spectroscopic data for **83**

$[\alpha]^{22}_{D}$ –87.9 (*c* 1.0, MeOH).

IR (film) 3340, 1454, 1055 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$, COSY, *g*-HSQC) δ 0.81 (d, *J* = 6.8 Hz, 3H, CH_3-C-4), 0.89 (d, *J* = 6.8 Hz, 3H, CH_3-C-3), 2.06-2.11 (m, 1H, H-2), 1.47-1.58 (m, 1H, H-2), 1.63-1.73 (m, 1H, H-4), 1.75-1.87 (m, 1H, H-3), 2.31 (dd, *J* = 11.9, 6.6 Hz, 1H, H-5), 2.51 (dd, *J* = 11.9, 7.7, 1H H-5), 3.28 (br.s, *J* = 9.0, 3H, OH, NH), 3.58 (m, 2H, H-1, CH_2-OH), 3.69 (m, 2H, H-1, CH_2-OH), 3.78 (dd, *J* = 8.7, 3.9 Hz, 1H, CH-Ar), 7.25-7.35 (m,5H, H-Ar).

^{13}C NMR (100.6 MHz, $CDCl_3$) δ 13.9 (CH_3-C-3), 17.7 (CH_3-C-4), 30.7 (C-3), 34.0 (C-2), 37.5 (C-4), 50.5 (C-5), 61.1 (C-1), 64.8 (CH-Ar), 66.4 (CH_2-OH), 127.3 (C-m), 127.6 (C-p), 128.6 (C-o), 139.9 (C-*i*).

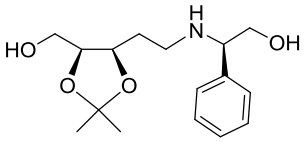
HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{15}H_{26}NO_2$ 252.1958; found 252.1953.

Spectroscopic data for **84**

^{1}H NMR (400 MHz, $CDCl_3$, COSY, *g*-HSQC) δ 0.78 (d, *J* = 6.2 Hz, 3H, CH_3), 0.93 (d, *J* = 7.1 Hz, 3H, CH_3) 1.48-1.55 (m, 4H, H-3, H-4 and H-5), 1.76 (m, 2H, H-6), 2.01 (m, 1H, H-2), 2.35 (brs, 1H, OH) 2.53-2.55 (m, 1H, H-2), 3.61 (dd, *J* = 10.4, 5.5 Hz, 1H, CH_2) 3.67 (dd, *J* = 10.4, 5.5Hz, 1H, CH), 3.69 (t, *J* = 10.4 Hz, 1H, CH_2), 7.15-7.18 (m, 2H, ArH), 7.28-7.36 (m, 3H, ArH).

^{13}C NMR (100.6 MHz, $CDCl_3$) δ 14.1 (CH_3), 14.7 (CH_3), 29.7 and 30.9 (C-3 and C-4), 32.7 (C-5), 40.3 (C-6), 53.5 (C-2), 60 (CH_2), 69.8 (CH), 127.7 (C-p), 128.1 (C-m), 128.9 (C-o), 135.6 (C-*i*).

(2*S*,3*R*)-5-{[(1*R*)-2-Hydroxy-1-phenylethyl]amino}-2,3-(isopropylidendioxi)-1-pentanol (85)



n-BuLi (1.46 mL of a 2.5 M solution in hexanes, 3.64 mmol) was added to a solution of $NH_3{\cdot}BH_3$ (112 mg, 3.64 mmol) in anhydrous THF (6 mL) at 0 ºC, and the resulting mixture was stirred at this temperature for 10 min and at room temperature for 15 minutes. Then, this solution was added to a solution of **48** (245 mg, 0.85 mmol) in anhydrous THF (2.5 mL), and the stirring was continued at 40 ºC for 1 h 40. The reaction mixture was quenched with H_2O, and the resulting solution was extracted with Et_2O. The combined organic extracts were dried, filtered, and concentrated. Flash chromatography (from 1:1 hexane-EtOAc to 8:2 EtOAc-EtOH) of the residue gave aminoalcohol **85** (100 mg, 40 %) as a colorless oil.

Spectroscopic data for **85**

$[\alpha]^{22}_D$ –38.3 (*c* 1.72, $CHCl_3$).

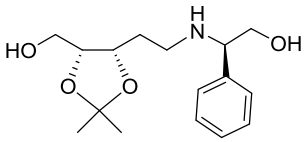
IR (film) 3359, 1454, 1044 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$, COSY, *g*-HSQC) δ 1.33 (s, 3H, CH_3), 1.43 (s, 3H, CH_3), 1.67-1.76 (m, 1H, H-4), 1.78-1.85 (m, 1H, H-4), 2.61-2.68 (m, 1H, H-5), 2.72-2.78 (m, 1H, H-5), 3.22 (brs, 3H, NH, OH), 3.55-3.63 (m, 3H, H-1, CH_2O), 3.71 (dd, *J* = 10.9, 4.1 Hz, 1H, CH_2O), 3.78 (dd, *J* = 8.5, 4.1 Hz, 1H, CHN), 4.11-4.15 (m, 1H, H-2), 4.17-4.22 (m, 1H, H-3), 7.27-7.37 (m, 5H, ArH).

^{13}C NMR (100.6 MHz, $CDCl_3$) δ 25.4 (CH_3), 28.1 (CH_3), 29.0 (C-4), 44.8 (C-5), 61.3 (C-1), 64.7 (CHN), 66.3 (CH_2O), 76.1 (C-3), 77.9 (C-2), 108.0 [*C*(CH_3)$_2$], 127.2 (C-*o*), 127.7 (C-*p*), 128.6 (C-*m*), 139.8 (C-*i*).

HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{16}H_{26}NO_4$ 296.1856; found 296.1848.

(2*R*,3*S*)-5-{[(1*R*)-2-hydroxy-1-phenylethyl]amino}-2,3-(isopropylidendioxi)-1-pentanol (86)



n-BuLi (2.50 mL of a 2.5 M solution in hexanes, 6.25 mmol) was added to a solution of $NH_3{\cdot}BH_3$ (193 mg, 6.25 mmol) in anhydrous THF (15 mL) at 0 ºC, and the resulting mixture was stirred at this temperature for 10 min and at room temperature for 15 minutes. Then, this solution was added to a solution of **49** (420 mg, 1.45 mmol) in anhydrous THF (7.5 mL), and the stirring was continued at 40 ºC for 1 h 30. The reaction mixture was quenched with H_2O, and the resulting solution was extracted with Et_2O. The combined organic extracts were dried, filtered, and concentrated. Flash chromatography (from 1:1 hexane-EtOAc to 8:2 EtOAc-EtOH) of the residue gave **87**[43] (50 mg, 12%) and aminoalcohol **86** (172 mg, 40 %) as a colorless oil.

Spectroscopic data for **86**

$[\alpha]^{22}_{D}$ –45.9 (*c* 2.35, $CHCl_3$).

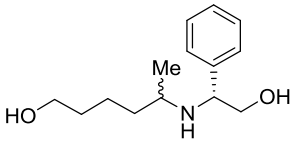
IR (film) 3404, 1493 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$, COSY, *g*-HSQC) δ 1.31 (s, 3H, CH_3), 1.41 (s, 3H, CH_3), 1.70-1.76 (m, 1H, H-4), 1.80-1.88 (m, 1H, H-4), 2.59-2.66 (m, 1H, H-5), 2.68-2.74 (m, 1H, H-5), 3.57-3.67 (m, 3H, H-1, CH_2O), 3.71 (dd, *J* = 11.0, 4.1 Hz, 1H, CH_2O), 3.82-3.90 (brm, 4H, CHN, OH, NH), 4.11-4.19 (m, 2H, H-2, H-3), 7.27-7.37 (m, 5H, ArH).

^{13}C NMR (100.6 MHz, $CDCl_3$) δ 25.3 (CH_3), 28.0 (CH_3), 28.9 (C-4), 44.5 (C-5), 61.1 (C-1), 64.8 (CHN), 66.1 (CH_2O), 75.7 (C-3), 77.7 (C-2), 108.0 [*C*(CH_3)$_2$], 127.4 (C-*o*), 127.9 (C-*p*), 128.7 (C-*m*), 138.8 (C-*i*).

HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{16}H_{26}NO_4$ 296.1856; found 296.1857.

(*S*)-5-{[(1*R*)-2-Hydroxy-1-phenylethyl]amino}-5-methyl-1-pentanol (88)



n-BuLi (2.43 mL of a 1.6 M solution in hexanes, 3.89 mmol) was added to a solution of $NH_3{\cdot}BH_3$ (120 mg, 3.89 mmol) in anhydrous THF (3 mL) at 0 ºC, and the resulting mixture was stirred at this temperature for 10 min and at room temperature for 15 minutes. Then, this solution was added to a solution of **51a** (209 mg, 0.90 mmol) in anhydrous THF (1.5 mL), and the stirring was continued at 40 ºC for 20 min. The reaction mixture was quenched with H_2O, and the resulting solution was extracted with Et_2O. The combined organic extracts were dried, filtered, and concentrated. Flash chromatography (from 1:1 hexane-EtOAc to 8:2 EtOAc-EtOH) of the residue gave piperidine **89**[130] (colorless oil, 32 mg, 16%) as a 1:1 mixture of C-2 epimers, and aminoalcohol **88** (colorless oil, 105 mg, 50 %) as a 1:1 mixture of C-5 epimers.

Spectroscopic data for **88**

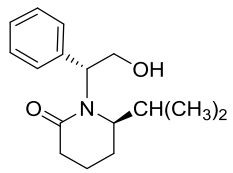
IR (film) 3350, 1453 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$, COSY, *g*-HSQC) δ 0.98 (d, *J* = 6.4 Hz, CH_3), 1.02 (d, *J* = 6.2 Hz, CH_3), 1.26-1.55 (m, H-2, H-3, H-4), 2.50-2.55 (m, H-5), 2.59-2.67 (m, H-5) 3.40 (brs, OH, NH), 3.51-3.74 (m, H-1, CH_2O), 3.87 (dd, *J* = 8.6, 4.3 Hz, 1H, CHN), 3.92 (dd, *J* = 8.5, 4.3 Hz, 1H, CHN), 7.24-7.35 (m, ArH).

^{13}C NMR (100.6 MHz, $CDCl_3$) δ 19.3, 21.2 (CH_3), 21.3, 21.8 (C-3), 32.3, 32.5 (C-2), 35.2, 37.1 (C-4), 49.6, 50.4 (C-5), 61.3, 62.1 (CHN), 61.8, 62.1 (CH_2O), 66.2, 66.4 (C-1), 126.6, 127.3 (C-*o*), 127.4, 127.6 (C- *p*), 128.6, 128.6 (C-*m*), 140.1, 140.7 (C-*i*).

HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{14}H_{24}NO_2$ 238.1802; found 238.1795.

(*R*)-1-[(1*R*)-2-Hydroxy-1-phenylethyl]-6-isopropyl-2-piperidone (90)



Isopropylmagnesium bromide (1.75 mL of a 2.9 M solution in 2-methyltetrahydrofuran, 5.07 mmol) was added to a cooled (0 °C) solution of **23b** (500 mg, 2.30 mmol) in anhydrous THF (3.5 mL), and the reaction mixture was stirred at

[130] H. Poerwono, K. Higashiyama, T. Yamauchi, H. Takahashi, *Heterocycles* **1997**, *46*, 385-400.

this temperature for 8 h, and at room temperature for an additional 12 h. The reaction was quenched by the addition of saturated aqueous NH_4Cl, and the resulting mixture was extracted with EtOAc. The combined organic extracts were dried, filtered, and concentrated to give an oil. Flash chromatography (from 8:2 hexane–EtOAc to EtOAc) afforded corresponding piperidone **90** (213 mg, 35%).

Spectroscopic data for **90**

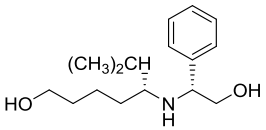
IR (film) 3363, 1633, 1455 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$, COSY, *g*-HSQC) δ 0.72 (d, *J* = 7.2 Hz, 3H, CH_3), 0.75 (d, *J* = 6.8 Hz, 3H, CH_3), 1.53-1.70 (m, 3H, H-4, H-5), 1.79-1.87 (m, 1H, H-4), 1.94-2.04 (m, 1H, C*H*$(CH_3)_2$), 2.30-2.38 (m, 1H, H-3), 2.48-2.55 (m, 1H, H-3), 3.16-3.20 (m, 1H, H-6), 3.73 (m, 1H, OH), 4.09 (dd, *J* = 10.8, 4.5, Hz, 1H, CH_2O), 4.29 (t, *J* = 10.8 Hz, 1H, CH_2O), 5.02 (dd, *J*= 8.0, 4.5 Hz, 1H, CHN), 7.23-7.33 (m, 5H, ArH).

^{13}C NMR (100.6 MHz, $CDCl_3$) δ 15.5 (CH_3), 18.5 (C-4), 19.2 (CH_3), 22.6 (C-5), 30.1 (*C*H$(CH_3)_2$), 33.1 (C-3), 62.8 (C-6), 64.6 (CH_2O), 65.2 (CHN), 127.3 (C-*p*), 128.2 (C-*o*), 128.2 (C-*m*), 137.3 (C-i), 174.3 (CO).

HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{16}H_{24}NO_2$ 262.1802; found 262.1792.

(*R*)-5-{[(1*R*)-2-Hydroxy-1-phenylethyl]amino}-5-isopropyl-1-pentanol (91)



n-BuLi (1.45 mL of a 2.5 M solution in hexanes, 3.62 mmol) was added to a solution of $NH_3{\cdot}BH_3$ (112 mg, 3.62 mmol) in anhydrous THF (4.5 mL) at 0 ºC, and the resulting mixture was stirred at this temperature for 10 min and at room temperature for 15 minutes. Then, this solution was added to a solution of **90** (220 mg, 0.84 mmol) in anhydrous THF (2.8 mL), and the stirring was continued at 40 ºC for 1 h 30. The reaction mixture was quenched with H_2O, and the resulting solution was extracted with Et_2O. The combined organic extracts were dried, filtered, and concentrated. Flash chromatography (from 1:1 hexane-EtOAc to 8:2 EtOAc-EtOH) of the residue gave piperidine **92** (35 mg, 17%) and aminoalcohol **91** (120 mg, 53 %) as a colorless oil.

Spectroscopic data for **91**

[α]$^{22}_{D}$ –79.9 (*c* 1.05, $CHCl_3$).

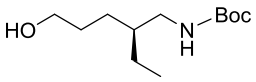
IR (film) 3344, 1454 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$, COSY, *g*-HSQC) δ 0.74 (d, *J* = 6.8 Hz, 3H, CH_3), 0.82 (d, *J* = 6.8 Hz, 3H, CH_3), 1.37-1.42 (m, 4H, H-2, H-3), 1.52-1.55 (m, 2H, H-4), 1.62-1-66 [m, 1H, C*H*$(CH_3)_2$], 2.22 (m, 1H, H-5), 2.74 (brs, 3H, OH, NH), 3.50 (dd, *J* = 12.0, 8.8 Hz, 1H, CH_2O), 3.63 (m, 3H, H-1, CH_2O), 3.81 (dd, *J* = 12.0, 8.8 Hz, 1H, CHN), 7.27-7.38 (m, 5H, ArH).

^{13}C NMR (100.6 MHz, $CDCl_3$) δ 18.3 (CH_3), 18.6 (CH_3), 21.6 (C-3), 29.7 (C-2), 30.2 [*C*H$(CH_3)_2$], 32.8 (C-4), 59.8 (C-5), 62.2 (CHN), 62.3 (C-1), 66.7 (CH_2O), 127.3 (C-*o*), 127.3 (C-*p*), 128.3 (C-*m*), 141.4 (C-*i*).

HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{16}H_{28}NO_2$ 266.2115; found 266.2111.

(*S*)-5-[(t*ert*-Butoxycarbonyl)amino]-4-ethyl-1-pentanol (93)



A solution of aminodiol **14** (325 mg, 1.29 mmol) in anhydrous MeOH (10 mL) containing 45% $Pd(OH)_2$ (146 mg) or 20% $Pd(OH)_2$ (65 mg) was hydrogenated at 75 °C for 22 h under 5 bar of pressure. Then, di-*tert*-butyldicarbonate (339 mg, 1.55 mmol) was added, and the mixture was stirred at room temperature for 24 h. The catalyst was removed by filtration and washed with hot MeOH. The combined organic solutions were concentrated to give an oil. Flash chromatography (from hexane-EtOAc 7:3 to hexane-EtOAc 1:1) afforded pure alcohol **93** (195 mg, 65 %) as a colorless oil.

Spectroscopic data for **93**

[α]$^{22}_{D}$ –3.3 (*c* 0.84, MeOH).

IR (film) 3348, 1692 cm^{-1}.

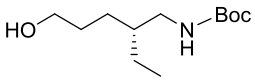
^{1}H NMR (400 MHz, $CDCl_3$, COSY, *g*-HSQC) δ 0.89 (t, *J* = 7.4 Hz, 3H, CH_3), 1.24-1.37 (m, 5H, CH_3CH_2, H-2, H-4), 1.44 [s, 9H, $(CH_3)_3$], 1.56-1.63 (m, 2H, H-3), 2.21

(br.s, 1H, OH), 3.03-3.15 (m, 2H, H-5), 3.64 (t, *J* = 6.3 Hz, 2H, H-1), 4.54 (br.s, 1H, NH).

^{13}C NMR (100.6 MHz, $CDCl_3$) δ 10.9 (CH_3), 24.1 (CH_3CH_2), 26.9 (C-2), 28.4 [$C(CH_3)_3$], 29.5 (C-3), 39.6 (C-4), 43.0 (C-5), 62.9 (C-1), 79.0 [$C(CH_3)_3$], 156.3 (NCO).

HRMS (ESI-TOF) m/z: [M – *t*Bu + 2H]$^+$ Calcd for $C_8H_{18}NO_3$ 176.1281; found 176.1279.

(*R*)-5-[(tert-Butoxycarbonyl)amino]-4-ethyl-1-pentanol (*ent*-93)

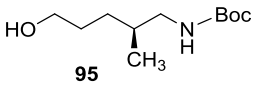


A solution of aminodiol **58** (105 mg, 0.42 mmol) in anhydrous MeOH (13 mL) containing 20% $Pd(OH)_2$ (21 mg) was hydrogenated at 75 °C for 22 h under 5 bars of pressure. Then, di-*tert*-butyldicarbonate (109 mg, 0.50 mmol) was added, and the mixture was stirred at room temperature for 24 h. The catalyst was removed by filtration and washed with hot MeOH. The combined organic solutions were concentrated to give an oil. Flash chromatography (from hexane-EtOAc 9:1 to hexane-EtOAc 8:2) afforded pure alcohol ***ent*-93** (53 mg, 55%) as a colorless oil.

Spectroscopic data for ***ent*-93**

$[\alpha]^{22}_D$ +2.8 (*c* 0.82, MeOH).

(*S*)-5-[(t*ert*-Butoxycarbonyl)amino]-4-methyl-1-pentanol (95)



95

A solution of aminodiol **52** (1.4 g, 5.9 mmol) in anhydrous MeOH (35 mL) containing 45% $Pd(OH)_2$ (630 mg) or 20% $Pd(OH)_2$ (280 mg) was hydrogenated at 75 °C for 22 h under 5 bar of pressure. Then, di-*tert*-butyldicarbonate (1.55 g, 7.08 mmol) was added, and the mixture was stirred at room temperature for 24 h. The catalyst was removed by filtration and washed with hot MeOH. The combined organic solutions

were concentrated to give an oil. Flash chromatography (8:2 hexane-EtOAc) afforded pure alcohol **95** (893 mg, 70 %) as a colorless oil.

Spectroscopic data for **95**

$[\alpha]^{22}_{D}$ –2.9 (*c* 1.0, MeOH).

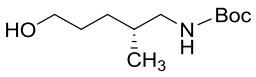
IR (film) 3355, 1692 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$, COSY, *g*-HSQC) δ 0.90 (d, *J* = 6.8 Hz, 3H, CH_3), 1.05-1.18 (m, 1H, H-3), 1.30-1.40 (m, 1H, H-3), 1.38 [s, 9H, $(CH_3)_3$], 1.45-1.57 (m, 3H, H-2, H-4), 2.60 (br.s, 1H, OH), 2.88 (ddd, *J* = 13.2, 6.4, 6.4 Hz, 1H, H-5), 2.99 (ddd, *J* = 13.2, 6.4, 6.4 Hz, 1H, H-5), 3.55 (t, *J* = 6.4 Hz, 2H, H-1), 4.77 (br.s, 1H, NH).

^{13}C NMR (100.6 MHz, $CDCl_3$) δ 17.4 (CH_3), 28.3 [C(CH_3)$_3$], 29.8 (C-3), 30.1 (C-2), 33.4 (C-4), 46.3 (C-5), 62.6 (C-1), 79.1 [C(CH_3)$_3$], 156.3 (CO).

HRMS (ESI-TOF) m/z: $[M - Boc + 2H]^+$ Calcd for $C_6H_{16}NO$ 118.1226; found 118.1227.

(*R*)-5-[(tert-Butoxycarbonyl)amino]-4-methyl-1-pentanol (*ent*-95)

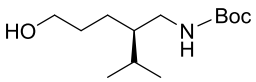


A solution of aminodiol **60** (190 mg, 0.80 mmol) in anhydrous MeOH (13 mL) containing 20% $Pd(OH)_2$ (38 mg) was hydrogenated at 75 °C for 22 h under 5 bars of pressure. Then, di-*tert*-butyldicarbonate (210 mg, 0.96 mmol) was added, and the mixture was stirred at room temperature for 24 h. The catalyst was removed by filtration and washed with hot MeOH. The combined organic solutions were concentrated to give an oil. Flash chromatography (from hexane-EtOAc 9:1 to hexane-EtOAc 1:1) afforded pure alcohol ***ent*-95** (100 mg, 57%) as a colorless oil.

Spectroscopic data for ***ent*-95**

$[\alpha]^{22}_{D}$ +2.25 (*c* 1.0, MeOH).

(*R*)-5-[(t*ert*-Butoxycarbonyl)amino]-4-isopropyl-1-pentanol (96)



A solution of aminodiol **54** (500 mg, 1.88 mmol) in anhydrous MeOH (12 mL) containing 45% $Pd(OH)_2$ (225 mg) or 20% $Pd(OH)_2$ (100 mg) was hydrogenated at 75 °C for 22 h under 5 bar of pressure. Then, di-*tert*-butyldicarbonate (493 mg, 2.26 mmol) was added, and the mixture was stirred at room temperature for 24 h. The catalyst was removed by filtration and washed with hot MeOH. The combined organic solutions were concentrated to give an oil. Flash chromatography (from hexane-EtOAc 8:2 to EtOAc) afforded pure alcohol **96** (208 mg, 45 %) as a colorless oil.

Spectroscopic data for **96**

$[\alpha]^{22}_D$ +2.5 (*c* 1.25, MeOH).

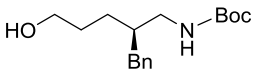
IR (film) 3347, 1693 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$, COSY, *g*-HSQC) δ 0.89 (d, *J* = 6.9 Hz, 6H, $2CH_3$), 1.24-1.33 (m, 3H, H-2, H-4), 1.44 [s, 9H, $(CH_3)_3$], 1.59-1.63 (m, 2H, H-3), 1.67-1.74 [m, 1H, C*H*$(CH_3)_2$], 3.06-3.17 (m, 2H, H-5), 3.64 (t, *J* = 6.4 Hz, 2H, H-1), 4.52 (br.s, 1H, NH).

^{13}C NMR (100.6 MHz, $CDCl_3$) δ 19.2 (CH_3), 19.5 (CH_3), 24.6 (C-3), 28.4 [*C*H$(CH_3)_2$, C(*C*$H_3)_3$], 30.5 (C-2), 41.4 (C-5), 44.3 (C-4), 62.9 (C-1), 79.1 [*C*$(CH_3)_3$], 156.2 (NCO).

HRMS (ESI-TOF) m/z: $[M - t\text{Bu} + 2H]^+$ Calcd for $C_9H_{20}NO_3$ 190.1438; found 190.1438.

(*R*)-4-Benzyl-5-[(t*ert*-butoxycarbonyl)amino]-1-pentanol (97)



A solution of aminodiol **56** (260 mg, 0.83 mmol) in anhydrous MeOH (10 mL) containing 45% $Pd(OH)_2$ (117 mg) or 20% $Pd(OH)_2$ (52 mg) was hydrogenated at 75

°C for 22 h under 5 bar of pressure. Then, di-*tert*-butyldicarbonate (217 mg, 1.0 mmol) was added, and the mixture was stirred at room temperature for 24 h. The catalyst was removed by filtration and washed with hot MeOH. The combined organic solutions were concentrated to give an oil. Flash chromatography (from hexane-EtOAc 8:2 to EtOAc) afforded pure alcohol **97** (123 mg, 51 %) as a colorless oil.

Spectroscopic data for **97**

$[\alpha]^{22}_{D}$ –1.9 (*c* 0.8, MeOH).

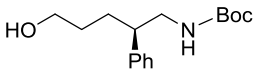
IR (film) 3348, 1689 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$, COSY, *g*-HSQC) δ 1.33-1.39 (m, 2H, H-3), 1.43 [s, 9H, $(CH_3)_3$], 1.54-1.68 (m, 2H, H-2), 1.82-1.86 (m, 1H, H-4), 2.04 (br.s., 1H, OH), 2.57 (d, *J* = 7.2 Hz, 2H, CH_2Ar), 3.09 (t, *J* = 5.6 Hz, 2H, H-5), 3.58 (t, *J* = 6.3 Hz, 2H, H-1), 4.62 (br.s, 1H, NH), 7.14-7.20 (m, 3H, ArH), 7.25-7.29 (m, 2H, ArH).

^{13}C NMR (100.6 MHz, $CDCl_3$) δ 27.2 (C-3), 28.3 [C(*C*$H_3)_3$], 29.5 (C-2), 38.6 (CH_2Ar), 40.4 (C-4), 43.2 (C-5), 62.7 (C-1), 79.2 [*C*$(CH_3)_3$], 126.0 (C-*p*), 128.3, 129.0 (C-*o*, C-*m*), 140.3 (C-*i*), 156.3 (NCO).

HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{17}H_{28}NO_3$ 294.2064; found 294.2063.

(*R*)-5-[(t*ert*-Butoxycarbonyl)amino]-4-phenyl-1-pentanol (98)



A solution of aminodiol **57** (193 mg, 0.65 mmol) in anhydrous MeOH (16 mL) containing 45% $Pd(OH)_2$ (86 mg) or 20% $Pd(OH)_2$ (38 mg) was hydrogenated at 75 °C for 22 h under 5 bar of pressure. Then, di-*tert*-butyldicarbonate (169 mg, 0.77 mmol) was added, and the mixture was stirred at room temperature for 24 h. The catalyst was removed by filtration and washed with hot MeOH. The combined organic solutions were concentrated to give an oil. Flash chromatography (from hexane-EtOAc 8:2 to hexane-EtOAc 1:1) afforded pure alcohol **98** (97 mg, 53 %) as a colorless oil.

Spectroscopic data for **98**

$[\alpha]^{22}_{D}$ +10.9 (*c* 0.65, MeOH).

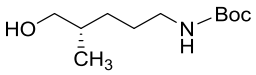
IR (film) 3363, 1693 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$, COSY, *g*-HSQC) δ 1.40 [s, 9H, $(CH_3)_3$], 1.43-1.49 (m, 2H, H-2), 1.57-1.67 (m, 1H, H-3), 1.73-1.80 (m, 1H, H-3), 2.76 (br.s, 1H, H-4), 3.18 (ddd, *J* = 13.6, 8.7, 4.9 Hz, 1H, H-5), 3.47-3.42 (m, 1H, H-5), 3.57 (t, *J* = 6.4 Hz, 2H, H-1), 4.43 (br.s, 1H, NH), 7.15-7.17 (m, 2H, ArH), 7.21-7.27 (m, 1H, H-*p*), 7.30-7.34 (m, 2H, ArH).

^{13}C NMR (100.6 MHz, $CDCl_3$) δ 28.3 [C(CH_3)$_3$], 29.6 (C-3), 30.4 (C-2), 45.9 (C-4), 46.2 (C-5), 62.6 (C-1), 79.2 [$C(CH_3)_3$], 126.7 (C-*p*), 127.8, 128.6 (C-*o*, C-*m*), 142.6 (C-*i*), 156.0 (NCO).

HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{16}H_{26}NO_3$ 280.1907; found 280.1905.

(*S*)-5-[(*tert*-Butoxycarbonyl)amino]-2-methyl-1-pentanol (99)



A solution of aminodiol **62** (250 mg, 1.05 mmol) in anhydrous MeOH (15 mL) containing 20% $Pd(OH)_2$ (50 mg) was hydrogenated at 75 °C for 22 h under 5 bars of pressure. Then, di-*tert*-butyldicarbonate (276 mg, 1.26 mmol) was added, and the mixture was stirred at room temperature for 24 h. The catalyst was removed by filtration and washed with hot MeOH. The combined organic solutions were concentrated to give an oil. Flash chromatography (8:2 hexane-EtOAc) afforded pure alcohol **99** (110 mg, 48%) as a colorless oil.

Spectroscopic data for **99**

$[\alpha]^{22}_{D}$ –3.9 (*c* 1.15, $CHCl_3$).

IR (film) 3356, 1689, 1454 cm^{-1}.

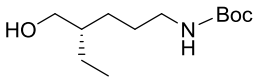
^{1}H NMR (400 MHz, $CDCl_3$, COSY, *g*-HSQC) δ 0.92 (d, *J* = 6.7 Hz, 3H, CH_3), 1.08-1.18 (m, 1H, H-3), 1.44 [s, masked signal, 10H, H-3, $(CH_3)_3$], 1.49-1.51 (m, 1H, H-4),

1.55-1.58 (m, 1H, H-4), 1.60-1.65 (m, 1H, H-2), 3.11 (m, 2H, H-5), 3.46 (m, 2H, H-1), 4.54 (brs, 1H, NH).

^{13}C NMR (100.6 MHz) δ 16.5 (CH_3), 27.4 (C-4), 28.3 [C(*C*H_3)$_3$], 30.0 (C-3), 35.3 (C-2), 40.6 (C-5), 67.8 (C-1), 79.0 [*C*(CH_3)$_3$], 156.1 (CO).

HRMS (ESI-TOF) m/z: [M + H]$^+$ Calcd for $C_{11}H_{24}NO_3$ 218.1751; found 218.1754.

(*S*)-5-[(*tert*-Butoxycarbonyl)amino]-2-ethyl-1-pentanol (100)



A solution of aminodiol **63** (250 mg, 1.00 mmol) in anhydrous MeOH (17 mL) containing 20% $Pd(OH)_2$ (50 mg) was hydrogenated at 75 °C for 22 h under 5 bars of pressure. Then, di-*tert*-butyldicarbonate (261 mg, 1.19 mmol) was added, and the mixture was stirred at room temperature for 18 h. The catalyst was removed by filtration and washed with hot MeOH. The combined organic solutions were concentrated to give an oil. Flash chromatography (8:2 hexane-EtOAc) afforded pure alcohol **100** (127 mg, 55%) as a colorless oil.

Spectroscopic data for **100**

[α]$^{22}_D$ +0.87 (*c* 1.75, $CHCl_3$).

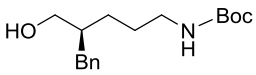
IR (film) 3449, 1670 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$, COSY, *g*-HSQC) δ 0.84 (t, *J* = 7.2 Hz, 3H, CH_3), 1.20-1.37 (m, 5H, C*H*$_2$$CH_3$, H-2, H-3), 1.39 [s, 9H, (CH_3)$_3$], 1.45-1.51 (m, 2H, H-4), 1.95 (brs. 1H, OH), 2.95-2.99 (m, 2H, H-5), 3.45 (dd, *J* = 10.0, 5.6 Hz, 1H, H-1), 3.49 (dd, *J* = 10.0, 4.8 Hz, 1H, H-1), 4.20 (brs, 1H, NH).

^{13}C NMR (100.6 MHz) δ 11.0 (CH_3), 23.3 (*C*$H_2$$CH_3$), 27.1 (C-4), 27.3 (C-3), 28.3 [C(*C*H_3)$_3$], 40.7 (C-5), 41.4 (C-2), 64.5 (C-1), 78.9 [*C*(CH_3)$_3$], 155.5 (CO).

HRMS (ESI-TOF) m/z: [M + Na]$^+$ Calcd for $C_{12}H_{25}NNaO_3$ 254.1727; found 254.1724.

(*S*)-2-Benzyl-5-[(*tert*-Butoxycarbonyl)amino]-1-pentanol (101)



A solution of aminodiol **64** (290 mg, 0.93 mmol) in anhydrous MeOH (15 mL) containing 20% $Pd(OH)_2$ (58 mg) was hydrogenated at 75 °C for 24 h under 5 bars of pressure. Then, di-*tert*-butyldicarbonate (242 mg, 1.11 mmol) was added, and the mixture was stirred at room temperature for 18 h. The catalyst was removed by filtration and washed with hot MeOH. The combined organic solutions were concentrated to give an oil. Flash chromatography (from CH_2Cl_2 to 8:2 CH_2Cl_2-Et_2O) afforded pure alcohol **101** (160 mg, 60%) as a colorless oil.

Spectroscopic data for **101**

$[\alpha]^{22}_D$ –7.3 (*c* 0.7, $CHCl_3$).

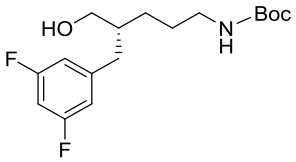
IR (film) 3349, 1693 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$, COSY, *g*-HSQC) δ 1.26-1.35 (m, 1H, H-3), 1.36-1.42 (m, 1H, H-3), 1.43 [s, 9H, $(CH_3)_3$], 1.49-1.59 (m, 2H, H-4), 1.76-1.86 (m, 1H, H-2), 1.91 (brs, 1H, OH), 2.59 (dd, *J* = 13.6, 6.8 Hz, 1H, CH_2Ar), 2.64 (dd, *J* = 13.6, 7.6 Hz, 1H, CH_2Ar), 3.02-3.14 (m, 2H, H-5), 3.49 (dd, *J* = 10.8, 5.3 Hz, 1H, H-1), 3.54 (dd, *J* = 10.8, 5.2 Hz, 1H, H-1), 4.59 (brs, 1H, NH), 7.16-7.20 (m, 3H, ArH), 7.25-7.29 (m, 3H, ArH).

^{13}C NMR (100.6 MHz, $CDCl_3$) δ 27.4 (C-4), 27.6 (C-3), 28.4 [C(CH_3)$_3$], 37.6 (CH_2Ar), 40.6 (C-5), 42.1 (C-2), 64.4 (C-1), 79.1 [C(CH_3)$_3$], 125.9 (C-*p*), 128.3 (C-*o*), 129.1 (C-*m*), 140.5 (C-*i*), 156.1 (CO).

HRMS (ESI-TOF) m/z: [M – Boc + H] $^+$ Calcd for $C_{12}H_{20}NO$ 194.1539; found 194.1536.

(*R*)-5-[(*tert*-Butoxycarbonyl)amino]-2-(3,5-difluorobenzyl)-1-pentanol (102)



A solution of aminodiol **66** (299 mg, 0.86 mmol) in anhydrous MeOH (15 mL) containing 20% $Pd(OH)_2$ (60 mg) was hydrogenated at 75 °C for 24 h under 5 bars of pressure. Then, di-*tert*-butyldicarbonate (225 mg, 1.03 mmol) was added, and the mixture was stirred at room temperature for 18 h. The catalyst was removed by filtration and washed with hot MeOH. The combined organic solutions were concentrated to give an oil. Flash chromatography (from CH_2Cl_2 to 8:2 CH_2Cl_2-Et_2O) afforded pure alcohol **102** (140 mg, 50%) as a colorless oil.

Spectroscopic data for **102**

$[\alpha]^{22}_D$ +1.65 (*c* 1.0, $CHCl_3$).

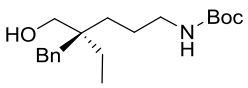
IR (film) 3362, 1685 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$, COSY, *g*-HSQC) δ 1.22-1.36 (m, 2H, H-3), 1.39 [s, 9H, $(CH_3)_3$], 1.40-1.55 (m, 2H, H-4), 1.73-1.80 (m, 1H, H-2), 2.50 (dd, *J* = 13.7, 7.2 Hz, 1H, CH_2Ar), 2.66 (dd, *J* = 13.7, 7.5 Hz, 1H, CH_2Ar), 3.03 (brm, 2H, H-5), 3.47 (m, 1H, H-2), 3.72 (m, 1H, H-2), 3.58 (t, *J* = 6.3 Hz, 2H, H-1), 4.75 (brs, 1H, NH), 6.59 (m, 1H, F-ArH), 6.65 (d, *J* = 6.0 Hz, 2H, F-ArH).

^{13}C NMR (100.6 MHz, $CDCl_3$) δ 27.3 (C-4), 27.4 (C-3), 28.3 [C(*C*$H_3)_3$], 37.3 (CH_2Ar, d, $J_{C\text{-}F}$ = 8.5 Hz), 40.5 (C-5), 41.7 (C-2), 65.2 (C-1), 79.2 [*C*$(CH_3)_3$], 101.2 (F-Ar C-4, t, $J_{C\text{-}F}$ = 25.7 Hz), 111.7 (F-Ar C-2 and C-6, dd, $J_{C\text{-}F}$ = 17.9, 6.2 Hz), 144.7 (F-Ar C-1, t, $J_{C\text{-}F}$ = 8.5 Hz), 156.2 (CO), 162.8 (F-Ar C-3 and C-5, dd, $J_{C\text{-}F}$ = 248.4, 13.2 Hz).

HRMS (ESI-TOF) m/z: $[M - t\text{Bu} + 2\ H]^+$ Calcd for $C_{13}H_{18}F_2NO_3$ 274.1249; found 274.1249.

(*S*)-2-Benzyl-5-[(*tert*-butoxycarbonyl)amino]-2-ethyl-1-pentanol (103)



A solution of aminodiol **68** (200 mg, 0.59 mmol) in anhydrous MeOH (16 mL) containing 20% $Pd(OH)_2$ (40 mg) was hydrogenated at 75 °C for 24 h under 5 bars of pressure. Then, di-*tert*-butyldicarbonate (141 mg, 0.64 mmol) was added, and the mixture was stirred at room temperature for 18 h. The catalyst was removed by filtration and washed with hot MeOH. The combined organic solutions were concentrated to give an oil. Flash chromatography (from CH_2Cl_2 to 8:2 CH_2Cl_2-Et_2O) afforded pure alcohol **103** (96 mg, 50%) as a colorless oil.

Spectroscopic data for **103**

$[\alpha]^{22}_{D}$ +8.1 (*c* 2.2, $CHCl_3$).

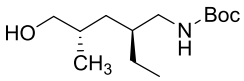
IR (film) 3365, 2935, 1689cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$, COSY, *g*-HSQC) δ 0.81 (t, *J* = 7.5 Hz, 3H, C*H*$_3$CH$_2$), 1.09-1.21 (m, 4H, H-3, CH$_3$C*H*$_2$), 1.37 [s, 9H, (CH$_3$)$_3$], 1.41-1.47 (m, 2H, H-4), 1.85 (brs, 1H, OH), 2.50 (brs, 2H, CH$_2$Ph), 2.97-3.05 (m, 2H, H-5), 3.21 (s, 2H, H-1), 4.63 (brs, 1H, NH), 7.10-7.13 (m, 3H, ArH), 7.17-7.21 (m, 2H, ArH).

^{13}C NMR (100.6 MHz, $CDCl_3$) δ 7.5 (*C*H$_3$CH$_2$), 23.7 (C-4), 25.2 (CH$_3$*C*H$_2$), 28.4 [C(*C*H$_3$)$_3$], 29.7 (C-3), 40.0 (CH$_2$Ph), 41.1 (C-5), 41.2 (C-2), 65.6 (C-1), 79.1 [*C*(CH$_3$)$_3$], 125.9 (C-*p*), 127.9 (C-*o*), 130.3 (C-*m*), 138.5 (C-*i*), 156.1 (CO).

HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{19}H_{32}NO_3$ 322.2377; found 322.2374.

(2*S*,4*S*)-5-[(*tert*-Butoxycarbonyl)amino]-4-ethyl-2-methyl-1-pentanol (104)



A solution of aminodiol **71** (365 mg, 1.38 mmol) in anhydrous MeOH (13 mL) containing 20% Pd(OH)$_2$ (75 mg) was hydrogenated at 75 °C for 24 h under 5 bars of pressure. Then, di-*tert*-butyldicarbonate (330 mg, 1.51 mmol) was added, and the mixture was stirred at room temperature for 18 h. The catalyst was removed by filtration and washed with hot MeOH. The combined organic solutions were concentrated to give an oil. Flash chromatography (from CH_2Cl_2 to 8:2 CH_2Cl_2-Et_2O) afforded pure alcohol **104** (213 mg, 63%) as a colorless oil.

Spectroscopic data for **104**

$[\alpha]^{22}_{D}$ –13.7 (*c* 1.41, $CHCl_3$).

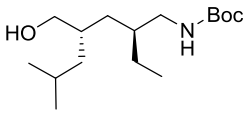
IR (film) 3346, 1689 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$, COSY, *g*-HSQC) δ 0.89 (t, *J* = 7.5 Hz, 3H, C*H*$_3$CH$_2$), 0.91 (d, *J* = 6.7 Hz, 3H, CH$_3$), 1.04 (ddd, *J* = 13.9, 8.3, 5.8 Hz, 1H, H-3), 1.24-1.37 (m, 3H, H-3, CH$_3$C*H*$_2$), 1.44 [s, 9H, (CH$_3$)$_3$], 1.53-1.58 (m, 1H, H-4), 1.69-1.78 (m, 1H, H-2), 3.05-3.09 (m, 2H, H-5), 3.41-3.52 (m, 2H, H-1), 4.57 (brs, 1H, NH).

^{13}C NMR (100.6 MHz, $CDCl_3$) δ 10.6 (*C*H_3CH_2), 16.9 (CH_3), 24.0 (CH_3*C*H_2), 28.4 [C(*C*H_3)$_3$], 33.0 (C-2), 35.2 (C-3), 36.9 (C-4), 43.8 (C-5), 68.4 (C-1), 79.0 [*C*(CH_3)$_3$], 156.2 (CO).

HRMS (ESI-TOF) m/z: [M – Boc + 2 H]$^+$ Calcd for $C_8H_{20}NO$ 146.1539; found 146.1541.

(2*S*,4*S*)-5-[(*tert*-Butoxycarbonyl)amino]-4-ethyl-2-isobutyl-1-pentanol (105)



A solution of aminodiol **72** (156 mg, 0.51 mmol) in anhydrous MeOH (17 mL) containing 20% $Pd(OH)_2$ (31 mg) was hydrogenated at 75 °C for 24 h under 5 bars of pressure. Then, di-*tert*-butyldicarbonate (122 mg, 0.56 mmol) was added, and the mixture was stirred at room temperature for 18 h. The catalyst was removed by filtration and washed with hot MeOH. The combined organic solutions were concentrated to give an oil. Flash chromatography (from CH_2Cl_2 to 8:2 CH_2Cl_2-Et_2O) afforded pure alcohol **105** (75 mg, 51%) as a colorless oil.

Spectroscopic data for **105**

$[\alpha]^{22}_D$ –2.5 (*c* 1.4, $CHCl_3$).

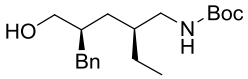
IR (film) 3354, 1691 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$, COSY, *g*-HSQC) δ 0.88-0.93 (m, 9H, 3CH_3), 1.03-1.10 [m, 2H, H-3, C*H*$_2$CH(CH_3)$_2$], 1.14-1.21 [m, 1H, C*H*$_2$CH(CH_3)$_2$], 1.27-1.35 (m, 2H, CH_3C*H*$_2$), 1.37-1.50 (m, 2H, H-3, H-4), 1.44 [s, 9H, (CH_3)$_3$], 1.60-1.70 [m, 2H, H-2, C*H*(CH_3)$_2$], 2.18 (brs, 1H, OH), 2.99 (dt, *J* = 13.7, 5.5 Hz, 1H, H-5), 3.20-3.28 (m, 1H, H-5), 3.36-3.40 (m, 1H, H-1), 3.60 (dd, *J* = 10.5, 3.9 Hz, 1H, H-1), 4.74 (brs, 1H, NH).

^{13}C NMR (100.6 MHz, $CDCl_3$) δ 11.0 (*C*H_3CH_2), 22.7 (CH_3), 23.2 (CH_3), 25.0 (CH_3*C*H_2), 25.4 (CH), 28.4 [C(*C*H_3)$_3$], 33.6 (C-3), 35.8 (C-2), 37.5 (C-4), 41.7 [C*H*$_2$CH(CH_3)$_2$], 43.0 (C-5), 65.7 (C-1), 79.1 [*C*(CH_3)$_3$], 156.6 (CO).

HRMS (ESI-TOF) m/z: [M + H]$^+$ Calcd for $C_{16}H_{34}NO_3$ 288.2533; found 288.2543.

(2*S*,4*S*)-2-Benzyl-5-[(*tert*-butoxycarbonyl)amino]-4-ethyl-1-pentanol (106)



A solution of aminodiol **73** (297 mg, 0.87 mmol) in anhydrous MeOH (20 mL) containing 20% $Pd(OH)_2$ (60 mg) was hydrogenated at 75 °C for 17 h under 5 bars of pressure. Then, di-*tert*-butyldicarbonate (209 mg, 0.96 mmol) was added, and the mixture was stirred at room temperature for 16 h. The catalyst was removed by filtration and washed with hot MeOH. The combined organic solutions were concentrated to give an oil. Flash chromatography (8:2 hexane-EtOAc) afforded pure alcohol **106** (157 mg, 55%) as a colorless oil.

Spectroscopic data for **106**

$[\alpha]^{22}_{D}$ –14.1 (*c* 1.4, $CHCl_3$).

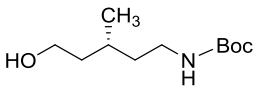
IR (film) 3360, 1685 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$, COSY, *g*-HSQC, 50ºC) δ 0.83 (t, *J* = 7.5 Hz, 3H, C*H*$_3$CH$_2$), 1.14-1.20 (m, 1H, H-3), 1.23-1.30 (m, 2H, CH$_3$C*H*$_2$), 1.38-1.50 (m, 2H, H-3, H-4), 1.43 [s, 9H, $(CH_3)_3$], 1.88-1.94 (m, 1H, H-2), 2.55-2.69 (CH_2Ar), 2.99 (dt, *J* = 5.6 Hz, 1H, H-5), 3.15 (brm, 1H, H-5), 3.44 (dd, *J* = 10.5, 5.5 Hz, 1H, H-1), 3.55 (dd, *J* = 10.5, 4.8 Hz, 1H, H-1), 4.53 (brs, 1H, NH), 7.15-7.19 (m, 3H, ArH), 7.24-7.28 (m, 2H, ArH).

^{13}C NMR (100.6 MHz, $CDCl_3$, 50ºC) δ 10.7 (*C*H$_3$CH$_2$), 24.9 (CH$_3$*C*H$_2$), 28.4 [C(*C*H$_3$)$_3$], 33.0 (C-3), 37.7 (C-4), 38.4 (CH_2Ar), 40.4 (C-2), 43.5 (C-5), 65.0 (C-1), 79.1 [*C*(CH$_3$)$_3$], 125.8 (C-*p*), 128.3 (C-*o*), 129.1 (C-*m*), 140.6 (C-*i*), 156.4 (CO).

HRMS (ESI-TOF) m/z: $[M + Na]^+$ Calcd for $C_{19}H_{31}NNaO_3$ 344.2196; found 344.2184.

(*R*)-5-[(*tert*-Butoxycarbonyl)amino]-3-methyl-1-pentanol (107)



A solution of aminodiol **74** (140 mg, 0.59 mmol) in anhydrous MeOH (16 mL) containing 20% $Pd(OH)_2$ (28 mg) was hydrogenated at 75 °C for 17 h under 5 bars of pressure. Then, di-*tert*-butyldicarbonate (142 mg, 0.65 mmol) was added, and the mixture was stirred at room temperature for 18 h. The catalyst was removed by filtration and washed with hot MeOH. The combined organic solutions were concentrated to give an oil. Flash chromatography (8:2 hexane-EtOAc) afforded pure alcohol **107** (77 mg, 60%) as a colorless oil.

Spectroscopic data for **107**

$[\alpha]^{22}_{D}$ +4.3 (*c* 0.44, $CHCl_3$).

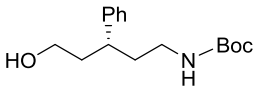
IR (film) 3349, 1686 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$, COSY, *g*-HSQC) δ 0.88 (d, *J* = 6.6 Hz, 3H, CH_3), 1.27-1.36 (m, 2H, H-2, H-4), 1.39 [s, 9H, $(CH_3)_3$], 1.43-1.50 (m, 1H, H-4), 1.54-1.66 (m, 2H, H-2, H-3), 2.41 (brs, 1H, OH), 3.01-3.10 (m, 1H, H-5), 3.12-3.20 (m, 1H, H-5), 3.57-3.68 (m, 2H, H-1), 4.70 (brs, 1H, NH).

^{13}C NMR (100.6 MHz, $CDCl_3$) δ 19.6 (CH_3), 26.8 (C-3), 28.3 [$C(CH_3)_3$], 37.1 (C-4), 38.3 (C-5), 39.3 (C-2), 60.4 (C-1), 79.0 [$C(CH_3)_3$], 156.2 (CO).

HRMS (ESI-TOF) m/z: $[M + Na]^+$ Calcd for $C_{11}H_{23}NNaO_3$ 240.1570; found: 240.1575.

(*R*)-5-[(*tert*-Butoxycarbonyl)amino]-3-phenyl-1-pentanol (108)



A solution of aminodiol **76** (48 mg, 0.16 mmol) in anhydrous MeOH (15 mL) containing 20% $Pd(OH)_2$ (9.6 mg) was hydrogenated at 75 °C for 17 h under 5 bars of pressure. Then, di-*tert*-butyldicarbonate (38 mg, 0.18 mmol) was added, and the mixture was stirred at room temperature for 18 h. The catalyst was removed by filtration and washed with hot MeOH. The combined organic solutions were concentrated to give an oil. Flash chromatography (8:2 hexane-EtOAc) afforded pure alcohol **108** (23 mg, 50%) as a colorless oil.

Spectroscopic data for **108**

$[\alpha]^{22}_{D}$ +14.3 (*c* 1.2, $CHCl_3$).

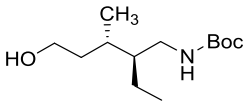
IR (film) 3350, 1689 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$, COSY, *g*-HSQC) δ 1.42 [s, 9H, $(CH_3)_3$], 1.49-1.57 (brs, 1H, OH), 1.71-1.89 (m, 3H, H-2, H-4), 1.91-1.98 (m, 1H, H-2), 2.78 (m, 1H, H-3), 2.93-3.06 (m, 2H, H-5), 3.40-3.47 (m, 1H, H-1), 3.51-3.57 (m, 1H, H-1), 4.47 (brs, 1H, NH).

^{13}C NMR (100.6 MHz, $CDCl_3$) δ 28.4 [$C(CH_3)_3$], 36.9 (C-4), 38.8 (C-5), 39.3 (C-2), 39.7 (C-3), 60.7 (C-1), 79.1 [$C(CH_3)_3$], 126.5 (C-*p*), 127.5 (C-*o*), 128.6 (C-*m*), 144.1 (C-*i*), 156.0 (CO).

HRMS (ESI-TOF) m/z: $[M + Na]^+$ Calcd for $C_{16}H_{25}NNaO_3$ 302.1727; found 302.1721.

(3*S*,4*S*)-5-[(*tert*-Butoxycarbonyl)amino]-4-ethyl-3-methyl-1-pentanol (109)



A solution of aminodiol **79** (101 mg, 0.38 mmol) in anhydrous MeOH (13 mL) containing 20% $Pd(OH)_2$ (20 mg) was hydrogenated at 75 °C for 24 h under 5 bars of pressure. Then, di-*tert*-butyldicarbonate (91 mg, 0.42 mmol) was added, and the mixture was stirred at room temperature for 18 h. The catalyst was removed by filtration and washed with hot MeOH. The combined organic solutions were concentrated to give an oil. Flash chromatography (from CH_2Cl_2 to 8:2 CH_2Cl_2-Et_2O) afforded pure alcohol **109** (47 mg, 51%) as a colorless oil.

Spectroscopic data for **109**

$[\alpha]^{22}_{D}$ –1.5 (*c* 2.6, $CHCl_3$).

IR (film) 3346, 1692 cm^{-1}.

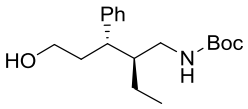
^{1}H NMR (400 MHz, $CDCl_3$, COSY, *g*-HSQC) δ 0.88-0.94 (m, 6H, $2CH_3$), 1.15-1.22 (m, 1H, CH_3CH_2), 1.26-1.40 (m, 3H, CH_3CH_2, H-2, H-4), 1.44 [s, 9H, $(CH_3)_3$], 1.66-1.75 (m, 1H, H-2), 1.81 (m, 1H, H-3), 2.05 (brs, 1H, OH), 2.96-3.02 (m, 1H, H-5),

3.14-3.19 (m, 1H, H-5), 3.58-3.64 (m, 1H, H-1), 3.71-3.76 (m, 1H, H-1), 4.66 (brs, 1H, NH).

^{13}C NMR (100.6 MHz, $CDCl_3$) δ 12.4 (CH_3CH_2), 16.4 (CH_3), 21.1 (CH_3CH_2), 28.4 [$C(CH_3)_3$], 28.8 (C-3), 35.6 (C-2), 41.0 (C-5), 45.9 (C-4), 61.1 (C-1), 79.2 [$C(CH_3)_3$], 156.5 (CO).

HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{13}H_{28}NO_3$ 246.2064; found 246.2067.

(3*S*,4*S*)-5-[(*tert*-Butoxycarbonyl)amino]-4-ethyl-3-phenyl-1-pentanol (110)



A solution of aminodiol **81**(110 mg, 0.34 mmol) in anhydrous MeOH (15 mL) containing 20% $Pd(OH)_2$ (22 mg) was hydrogenated at 75 °C for 24 h under 5 bars of pressure. Then, di-*tert*-butyldicarbonate (81 mg, 0.37 mmol) was added, and the mixture was stirred at room temperature for 18 h. The catalyst was removed by filtration and washed with hot MeOH. The combined organic solutions were concentrated to give an oil. Flash chromatography (from CH_2Cl_2 to 8:2 CH_2Cl_2-Et_2O) afforded pure alcohol **110** (52 mg, 50%) as a colorless oil.

Spectroscopic data for **110**

$[\alpha]^{22}_D$ +5.1 (*c* 0.6, $CHCl_3$).

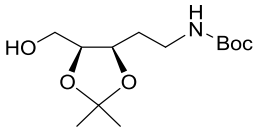
IR (film) 3350, 1694 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$, COSY, *g*-HSQC) δ 0.93 (t, *J* = 7.4 Hz, 3H, CH_3CH_2), 1.31-1.37 (m, 1H, CH_3CH_2), 1.41 [s, 9H, $(CH_3)_3$], 1.43-1.52 (m, 1H, CH_3CH_2), 1.62-1.68 (m, 2H, H-4, OH), 1.81-1.90 (m, 1H, H-2), 2.02-2.10 (m, 1H, H-2), 2.78 (brm, 1H, H-3), 2.82-2.87 (m, 1H, H-5), 3.09-3.15 (m, 1H, H-5), 3.32-3.38 (m, 1H, H-1), 3.49-3.55 (brm, 1H, H-1), 4.40 (brs, 1H, NH), 7.14-7.21 (m, 3H, ArH), 7.27-7.31 (m, 2H, ArH).

^{13}C NMR (100.6 MHz, $CDCl_3$) δ 11.2 (CH_3CH_2), 21.3 (CH_3CH_2), 28.4 [$C(CH_3)_3$], 34.5 (C-2), 41.2 (C-5), 42.7 (C-3), 45.8 (C-4), 61.0 (C-1), 79.0 [$C(CH_3)_3$], 126.4 (C-*p*), 128.2 (C-*o*), 128.4 (C-*m*), 142.9 (C-*i*), 156.2 (CO).

HRMS (ESI-TOF) m/z: $[M - Boc + 2\ H]^+$ Calcd for $C_{13}H_{22}NO$ 208.1696; found 208.1696.

(2*S*,3*R*)-5-[(*tert*-Butoxycarbonyl)amino]-2,3-(isopropylidendioxy)-1-pentanol (111)



A solution of aminodiol **85** (82 mg, 0.28 mmol) in anhydrous MeOH (14 mL) containing 20% $Pd(OH)_2$ (16 mg) was hydrogenated at 75 °C for 24 h under 5 bars of pressure. Then, di-*tert*-butyldicarbonate (67 mg, 0.31 mmol) was added, and the mixture was stirred at room temperature for 18 h. The catalyst was removed by filtration and washed with hot MeOH. The combined organic solutions were concentrated to give an oil. Flash chromatography (from CH_2Cl_2 to 8:2 CH_2Cl_2-Et_2O) afforded pure alcohol **111** (40 mg, 52%) as a colorless oil.

Spectroscopic data for **111**

$[\alpha]^{22}_D$ –4.18 (*c* 1.8, $CHCl_3$).

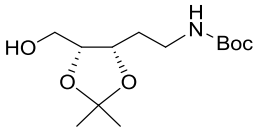
IR (film) 3368, 1695 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$, COSY, *g*-HSQC) δ 1.36 (s, 3H, CH_3), 1.44 [s, 9H, $(CH_3)_3$], 1.46 (s, 3H, CH_3), 1.66-1.75 (m, 2H, H-4), 2.23 (brs, 1H, OH), 3.18-3.34 (m, 2H, H-5), 3.62 (brm, 2H, H-1), 4.15-4.24 (m, 2H, H-2, H-3), 4.90 (brs, 1H, NH).

^{13}C NMR (100.6 MHz, $CDCl_3$) δ 25.3 (CH_3), 28.0 (CH_3), 28.4 [C(CH_3)$_3$], 28.9 (C-4), 44.5 (C-5), 61.1 (C-1), 64.8 (CHN), 66.1 (CH_2O), 75.7 (C-3), 77.7 (C-2), 79.5 [$C(CH_3)_3$], 108.0 [$C(CH_3)_2$], 127.4 (C-*o*), 127.9 (C-*p*), 128.7 (C-*m*), 138.8 (C-*i*).

HRMS (ESI-TOF) m/z: $[M + Na]^+$ Calcd for $C_{13}H_{25}NNaO_5$ 298.1625; found 298.1626.

(2*R*,3*S*)-5-[(*tert*-Butoxycarbonyl)amino]-2,3-(isopropylidendioxy)-1-pentanol (112)



A solution of aminodiol **86** (150 mg, 0.51 mmol) in anhydrous MeOH (13 mL) containing 20% $Pd(OH)_2$ (30 mg) was hydrogenated at 75 °C for 24 h under 5 bars of pressure. Then, di-*tert*-butyldicarbonate (122 mg, 0.56 mmol) was added, and the mixture was stirred at room temperature for 18 h. The catalyst was removed by filtration and washed with hot MeOH. The combined organic solutions were concentrated to give an oil. Flash chromatography (from CH_2Cl_2 to 8:2 CH_2Cl_2-Et_2O) afforded pure alcohol **112** (84 mg, 60%) as a colorless oil.

Spectroscopic data for **112**

$[\alpha]^{22}_D$ +4.00 (*c* 1.8, $CHCl_3$).

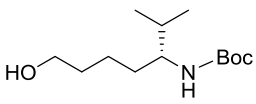
IR (film) 3368, 1695 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$, COSY, *g*-HSQC) δ 1.36 (s, 3H, CH_3), 1.44 [s, 9H, $(CH_3)_3$], 1.46 (s, 3H, CH_3), 1.66-1.75 (m, 2H, H-4), 2.23 (brs, 1H, OH), 3.18-3.34 (m, 2H, H-5), 3.62 (brm, 2H, H-1), 4.15-4.24 (m, 2H, H-2, H-3), 4.90 (brs, 1H, NH).

^{13}C NMR (100.6 MHz, $CDCl_3$) δ 25.3 (CH_3), 28.0 (CH_3), 28.4 [C(CH_3)$_3$], 28.9 (C-4), 44.5 (C-5), 61.1 (C-1), 64.8 (CHN), 66.1 (CH_2O), 75.7 (C-3), 77.7 (C-2), 79.5 [*C*(CH_3)$_3$], 108.0 [*C*(CH_3)$_2$], 127.4 (C-*o*), 127.9 (C-*p*), 128.7 (C-*m*), 138.8 (C-*i*).

HRMS (ESI-TOF) m/z: $[M + Na]^+$ Calcd for $C_{13}H_{25}NNaO_5$ 298.1625; found 298.1626.

(*R*)-5-[(*tert*-Butoxycarbonyl)amino]-5-isopropyl-1-pentanol (113)



A solution of aminodiol **91** (100 mg, 0.38 mmol) in anhydrous MeOH (15 mL) containing 20% $Pd(OH)_2$ (20 mg) was hydrogenated at 75 °C for 24 h under 5 bars of pressure. Then, di-*tert*-butyldicarbonate (99 mg, 0.45 mmol) was added, and the mixture was stirred at room temperature for 18 h. The catalyst was removed by filtration and washed with hot MeOH. The combined organic solutions were concentrated to give an oil. Flash chromatography (from CH_2Cl_2 to 8:2 CH_2Cl_2-Et_2O) afforded pure alcohol **113** (45 mg, 49%) as a colorless oil.

Spectroscopic data for **113**

$[\alpha]^{22}_D$ +2.95 (*c* 1.2, $CHCl_3$).

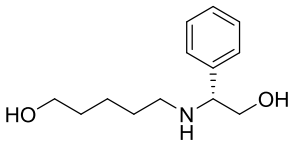
IR (film) 3334, 1682 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$, COSY, *g*-HSQC) δ 0.85 (d, *J* = 6.8 Hz, 3H, CH_3), 0.89 (d, *J*= 6.8 Hz, 3H, CH_3), 1.25-1.30 (m, 1H, H-4), 1.30-1.35 (m, 2H, H-3), 1.44 [s, 9H, $(CH_3)_3$], 1.48-1.60 (m, 3H, H-2, H-4), 1.62-1.71 (m, CH), 3.40-3.45 (m, 1H, H-5), 3.63 (dd, *J*= 1.6, 6.4 Hz, 2H, H-1), 4.36 (d, *J*= 9.2 Hz, 1H, NH).

^{13}C NMR (100.6 MHz, $CDCl_3$) δ 17.5 (CH_3), 19.1 (CH_3), 22.3 (C-3), 28.4 [C(CH_3)$_3$], 32.1 (C-4), 32.2 (CH), 32.5 (C-2), 55.3 (C-5), 62.5 (C-1), 78.2 [*C*(CH_3)$_3$], 156.2 (CO).

HRMS (ESI-TOF) m/z: $[M - Boc + 2 H]^+$ Calcd for $C_8H_{20}NO$ 146.1539; found 146.1536.

5-{[(1*R*)-2-Hidroxy-1-phenylethyl]amino}-1-pentanol (114)



n-BuLi (3.56 mL of a 2.5 M solution in hexanes, 8.9 mmol) was added to a solution of $NH_3{\cdot}BH_3$ (275 mg, 8.9 mmol) in anhydrous THF (10 mL) at 0 ºC, and the resulting mixture was stirred at this temperature for 10 min and at room temperature for 15 minutes. Then, this solution was added to a solution of **23a** (450 mg, 2.07 mmol) in anhydrous THF (5 mL), and the stirring was continued at 40 ºC for 1 h. The reaction mixture was quenched with H_2O, and the resulting solution was extracted with Et_2O. The combined organic extracts were dried, filtered, and concentrated. Flash

chromatography (from 1:1 hexane-EtOAc to 8:2 EtOAc-EtOH) of the residue gave aminoalcohol **114** (310 mg, 67 %) as a colorless oil.

Spectroscopic data for **114**

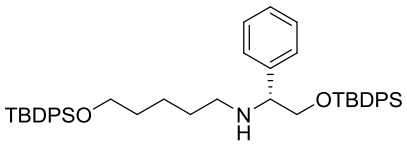
$[\alpha]^{22}_{D}$ –54.2 (*c* 1.25, $CHCl_3$).

^{1}H NMR (400 MHz, $CDCl_3$, COSY, *g*-HSQC) δ 1.37-1.43 (m, 2H, H-3), 1.47-1.58 (m, 4H, H-2, H-4), 2.46-2.60 (m, 2H, H-5), 3.45 (brs, 3H, OH, NH), 3.55 (dd, *J* = 10.5, 8.5 Hz, 1H, CH_2O), 3.62 (t, *J* = 6.4 Hz, 2H, H-1), 3.71 (dd, *J* = 10.5, 4.4 Hz, 1H, CH_2O), 3.76 (dd, *J* = 8.5, 4.4 Hz, 1H, CH), 7.26-7.30 (m, 3H, ArH), 7.33-7.37 (m, 2H, ArH).

^{13}C NMR (100.6 MHz, $CDCl_3$) δ 23.2 (C-3), 29.2 (C-4), 32.1 (C-2), 47.0 (C-5), 61.9 (C-1), 64.6 (CH), 66.4 (CH_2O), 127.3 (C-*o*), 127.5 (C-*p*), 128.5 (C-*m*), 140.1 (C-*i*).

HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{13}H_{22}NO_2$ 224.1645; found 224.1638.

(*R*)-5-[(*tert*-Butyldiphenylsilyl)oxy]-*N*-{2-[(*tert*-butyldiphenylsilyl)oxy]-1-phenylethyl}-1-pentanamine (115)



tert-Butyldiphenylsilyl chloride (1.1 mL, 4.24 mmol) and imidazole (289 mg, 4.24 mmol) were added to a solution of aminodiol **114** (430 mg, 1.93 mmol) in anhydrous CH_2Cl_2 (16 mL), and the mixture was heated at reflux for 17 h. Saturated aqueous NH_4Cl was added, and the mixture was extracted with CH_2Cl_2. The combined organic extracts were dried, filtered, and concentrated. The resulting residue was chromatographed (from hexane to 8:2 hexane–Et_2O) to afford pure compound **115** (890 mg, 72%) as a colorless oil.

Spectroscopic data for **115**

$[\alpha]^{22}_{D}$ –13.3 (*c* 1.3, $CHCl_3$).

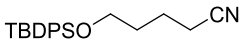
^{1}H NMR (400 MHz, $CDCl_3$) δ 1.10 [s, 9H, (CH_3)$_3$], 1.11 [s, 9H, (CH_3)$_3$], 1.46 (m, 2H, CH_2), 1.53 (m, 2H, CH_2), 1.63 (m, 2H, CH_2), 2.52 (m, 2H, H-1), 3.71 (t, *J* = 6.5 Hz,

2H, H-5), 3.74 (m, 2H, CH_2O), 3.83 (dd, *J* = 8.4, 4.0 Hz, 1H, CH), 7.30-7.32 (m, 4H, ArH), 7.39-7.46 (m, 13H, ArH), 7.66-7.74 (m, 8H, ArH).

^{13}C NMR (100.6 MHz, $CDCl_3$) δ 19.2 [*C*$(CH_3)_3$], 23.5 (C-3), 26.8, 26.9 [C(*C*$H_3)_3$], 30.0 (C-2), 32.5 (C-4), 47.6 (C-1), 63.9 and 65.1 (CH_2O), 68.9 (CH), 127.2 (C-Ar), 127.5 (C-Ar), 127.6 (C-Ar), 128.2 (C-Ar), 129.5 (C-Ar), 129.6 (C-Ar), 129.7 (C-Ar), 133.3 (C-*i*), 133.5 (C-*i*), 134.1 (C-*i*), 134.9 (C-*i*), 135.5 (C-Ar), 140.9 (C-*i*).

HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{45}H_{58}NO_2Si_2$ 700.4001; found 700.3996.

6-[(*tert*-Butyldiphenylsilyl)oxy]pentanenitrile (116)



Method A: HTIB (451 mg, 1.10 mmol) was added to a solution of **115** (309 mg, 0.44 mmol) and NH_4OAc (341 mg, 4.42 mmol) in acetonitrile-water (4:1, 2.5 mL), and the reaction mixture was stirred at 80 °C for 19 h. Saturated aqueous $NaHCO_3$ was added, and the mixture was extracted with EtOAc. The combined organic extracts were dried, filtered, and concentrated. The resulting residue was chromatographed (from hexane to 1:1 hexane–CH_2Cl_2) to afford pure nitrile **116** (70 mg, 42%) as a colorless oil.

Method B: 20% Aqueous solution of NH_3 (6 mL) and iodine (228 mg, 0.90 mmol) were added to a solution of amine **115** (70 mg, 0.10 mmol) in anhydrous THF (2 mL) at room temperature, and the resulting mixture was stirred at 60 ºC for 21 h. The mixture was washed with saturated aqueous Na_2SO_3 and extracted with Et_2O. The combined organic phases were dried, filtered, and concentrated to give an oil. Flash chromatography (from hexane to 6:4 hexane–CH_2Cl_2) afforded pure nitrile **116** (24 mg, 70%) as a yellow oil.

Spectroscopic data for **116**

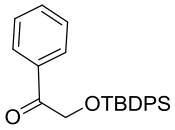
IR (film) 2247, 1428 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$) δ 1.05 [s, 9H, (C*H*$_3)_3$], 1.66-1.71 (m, 2H), 1.75-1.82 (m, 2H), 2.32 (t, *J* = 6.8 Hz, 2H, H-2), 3.67 (t, *J* = 6.0 Hz, 2H, H-5), 7.38-7.41 (m, 6H, ArH), 7.64-7.66 (m, 4H, ArH).

^{13}C NMR (100.6 MHz, $CDCl_3$) δ 16.8 (C-2), 19.2 [*C*$(CH_3)_3$], 22.2 (C-3), 26.8 [C(*C*$H_3)_3$], 31.2 (C-4), 62.6 (C-5), 119.7 (CN), 127.7 (C-*o*), 129.6 (C-*p*), 133.6 (C-*i*),135.5 (C-*m*).

HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{21}H_{28}NOSi$ 338.1935; found 338.1921.

2-[(*tert*-Butyldiphenylsilyl)oxy]-1-phenylethanone (117)



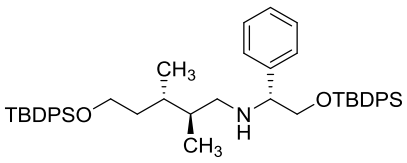
IR (film) 2929, 1707, 1113 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$) δ 1.10 [s, 9H, (C*H*$_3)_3$], 4.92 (s, 2H, CH_2), 7.36-7.45 (m, 9H, ArH), 7.69-7.73 (m, 4H, ArH), 7.80-7.83 (m, 2H, ArH).

^{13}C NMR (100.6 MHz, $CDCl_3$) δ 19.3 [*C*$(CH_3)_3$], 26.7 [C(*C*$H_3)_3$], 67.6 (CH_2), 127.8 (C-Ar), 128.5 (C-Ar), 129.9 (C-Ar), 132.9 (C-*i*), 133.2 (C-*i*), 135.6 (C-Ar), 196.7 (CO).

HRMS (ESI-TOF) m/z: $[M + Na]^+$ Calcd for $C_{24}H_{26}NaO_2Si$ 397.1594; found 397.1592.

(2*S*,3*S*)-5-[(*tert*-Butyldiphenylsilyl)oxy]-*N*-{(*R*)-2-[(*tert*-butyldiphenylsilyl)oxy]-1-phenylethyl}-2,3-dimethyl-1-pentanamine (118)



tert-Butyldiphenylsilyl chloride (0.75 mL, 2.89 mmol) and imidazole (197 mg, 2.89 mmol) were added to a solution of aminodiol **83** (346 mg, 1.38 mmol) in anhydrous CH_2Cl_2 (10 mL), and the mixture was heated at reflux for 17 h. Saturated aqueous NH_4Cl was added, and the mixture was extracted with CH_2Cl_2. The combined organic extracts were dried, filtered, and concentrated. The resulting residue was chromatographed (from hexane to 8:2 hexane–Et_2O) to afford pure compound **118** (872 mg, 87%) as a colorless oil.

Spectroscopic data for **118**

$[\alpha]^{22}_{D}$ –13.3 (*c* 1.33, MeOH).

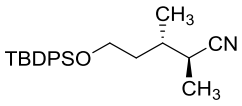
IR (film) 3071, 1111 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$) δ 0.82 (d, *J* = 6.8 Hz, 3H, CH_3), 0.93 (d, *J* = 6.8 Hz, 3H, CH_3), 1.07 [s, 18H, $(CH_3)_3$], 1.21-1.30 (m, 1H, H-4), 1.61-1.73 (m, 3H, H-2, H-3, H-4), 2.25-2.31 (m, 1H, H-1), 2.48 (dd, *J* = 11.2, 5.2 Hz, 1H, H-1), 3.64-3.79 (m, 5H, H-5, CH_2O, CHN), 7.28-7.42 (m, 21H, ArH), 7.68 (m, 4H, ArH).

^{13}C NMR (100.6 MHz, $CDCl_3$) δ 14.8 (CH_3), 17.1 (CH_3), 19.2 [*C*$(CH_3)_3$], 19.3 [*C*$(CH_3)_3$],26.8 [C(*C*$H_3)_3$], 26.9 [C(*C*$H_3)_3$], 32.3 (C-3), 35.3 (C-4), 38.6 (C-2), 51.6 (C-1), 62.7 and 65.7 (C-5 and CH_2O), 69.0 (CHN), 127.2 (C-Ar), 127.6 (C-Ar), 127.7 (C-Ar), 128.2(C-Ar), (C-Ar), 129.5 (C-Ar), 129.7 (C-Ar), 129.8 (C-Ar), 133.1(C-*i*), 133.5 (C-*i*), 134.2, (C-Ar), 134.9 (C-*i*), 135.6 (C-Ar).

HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{47}H_{62}NO_2Si_2$ 728.4314; found 728.4306.

(2*S*,3*S*)-5-[(*tert*-Butyldiphenylsilyl)oxy]-2,3-dimethylpentanenitrile (119)



20% Aqueous solution of NH_3 (27 mL) and iodine (1.55 g, 6.13 mmol) were added to a solution of amine **118** (557 mg, 0.77 mmol) in anhydrous THF (3 mL) at room temperature, and the resulting mixture was stirred at 60 ºC for 21 h. The mixture was washed with saturated aqueous Na_2SO_3 and extracted with Et_2O. The combined organic phases were dried, filtered, and concentrated to give an oil. Flash chromatography (from hexane to 6:4 hexane–CH_2Cl_2) afforded pure nitrile **119** (201 mg, 72%) as a yellow oil.

Spectroscopic data for **119**

$[\alpha]^{22}_{D}$ +4.94 (*c* 1.05, $CHCl_3$).

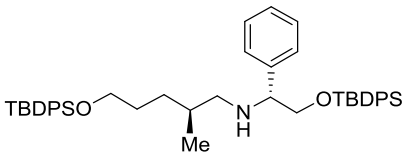
IR (film) 2237 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$) δ 1.00 (d, *J* = 6.7 Hz, 3H, CH_3), 1.05 [s, 9H, $(CH_3)_3$], 1.27 (d, *J* = 7.2 Hz, 3H, CH_3), 1.48-1.57 (m, 1H, H-4), 1.67-1.76 (m, 1H, H-4), 1.82-1.91 (m, 1H, H-3), 2.67 (dq, *J* = 7.2, 4.5 Hz, 1H, H-2), 3.67-3.76 (m, 2H, H-5), 7.36-7.46 (m, 6H, ArH), 7.63-7.66 (m, 4H, ArH).

^{13}C NMR (100.6 MHz, $CDCl_3$) δ 15.5 (CH_3), 16.0 (CH_3), 19.2 [*C*$(CH_3)_3$], 26.8 [C(*C*$H_3)_3$], 30.8 (C-2), 32.9 (C-3), 37.4 (C-4), 61.2 (C-5), 121.7 (CN), 127.7 (2C-*m*), 129.7 (C-*p*), 133.6 (2C-*i*), 135.5 (C-*o*), 135.7 (C-*o*).

HRMS (ESI-TOF) m/z: $[M + NH_4]^+$ Calcd for $C_{23}H_{35}N_2OSi$ 383.2513; found 383.2523.

(*S*)-5-[(*tert*-Butyldiphenylsilyl)oxy]-*N*-{(*R*)-2-[(*tert*-butyldiphenylsilyl)oxy]-1-phenylethyl}-2-methyl-1-pentanamine (120)



tert-Butyldiphenylsilyl chloride (0.94 mL, 3.62 mmol) and imidazole (246 mg, 3.62 mmol) were added to a solution of aminodiol **52** (390 mg, 1.64 mmol) in anhydrous CH_2Cl_2 (14 mL), and the mixture was heated at reflux for 14 h. Saturated aqueous NH_4Cl was added, and the mixture was extracted with CH_2Cl_2. The combined organic extracts were dried, filtered, and concentrated. The resulting residue was chromatographed (from hexane to 9:1 hexane–Et_2O) to afford pure compound **120** (860 mg, 74%) as a colorless oil.

Spectroscopic data for **120**

$[\alpha]^{22}_D$ –17.8 (*c* 1.0, $CHCl_3$).

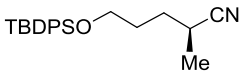
IR (film) 3070, 1112 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$, COSY, *g*-HSQC) δ 0.97 (d, *J* = 6.0 Hz, 3H, CH_3), 1.12 [s, 18H, $(CH_3)_3$], 1.22-1.29 (m, 1H, H-3), 1.49-1.68 (m, 4H, H-2, H-3, H-4), 2.33 (dd, *J* = 11.4, 6.8 Hz, 1H, H-1), 2.44 (dd, *J* = 11.4, 6.0 Hz, 1H, H-1), 3.68-3.77 (m, 4H, H-5, CH_2O), 3.81 (dd, *J* = 8.8, 4.0 Hz, 1H, CHN), 7.23-7.25 (m, 5H, ArH), 7.31-7.42 (m, 12H, ArH), 7.60-7.66 (m, 8H, ArH).

^{13}C NMR (100.6 MHz, $CDCl_3$) δ 18.2 (CH_3), 19.2 [*C*(CH_3)$_3$], 26.8 [C(*C*H_3)$_3$], 30.0 (C-4), 30.9 (C-3), 33.3 (C-2), 54.3 (C-1), 64.3 (C-5), 65.4 (CHN), 69.1 (CH_2O), 127.2 (C-Ar), 127.5 (C-Ar), 127.7 (C-Ar), 128.1 (C-Ar), 129.5 (C-Ar), 129.6 (C-Ar), 129.7 (C-Ar), 133.3 (C-*i*), 133.5 (C-*i*), 134.1 (C-*i*), 135.6 (C-Ar), 141.1 (C-*i*).

HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{46}H_{60}NO_2Si_2$ 714.4157; found 714.4154.

(*S*)-5-[(*tert*-Butyldiphenylsilyl)oxy]-2-methylpentanenitrile (121)



20% Aqueous solution of NH_3 (17 mL) and iodine (1.05 g, 4.12 mmol) were added to a solution of amine **120** (360 mg, 0.51 mmol) in anhydrous THF (5 mL) at room temperature, and the resulting mixture was stirred at 60 ºC for 13 h. The mixture was washed with saturated aqueous Na_2SO_3 and extracted with Et_2O. The combined organic phases were dried, filtered, and concentrated to give an oil. Flash chromatography (from hexane to 6:4 hexane–CH_2Cl_2) afforded pure nitrile **121** (92 mg, 51%) as a yellow oil.

Spectroscopic data for **121**

$[\alpha]^{22}_D$ +12.3 (*c* 1.3, $CHCl_3$).

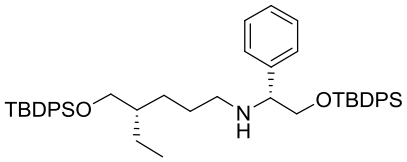
IR (film) 2239, 1428 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$, COSY, *g*-HSQC) δ 1.05 [s, 9H, (C*H*$_3$)$_3$], 1.29 (d, 3H, *J* = 7.2 Hz, CH_3), 1.62-1.76 (m, 4H, H-3, H-4), 2.58-2.64 (m, 1H, H-2), 3.69 (m, 1H, H-5), 7.37-7.46 (m, 6H, ArH), 7.63-7.67 (m, 4H, ArH).

^{13}C NMR (100.6 MHz, $CDCl_3$) δ 18.0 (CH_3), 19.2 [*C*(CH_3)$_3$], 25.2 (C-2), 26.8 [C(*C*H_3)$_3$], 29.7 and 30.7 (C-3, C-4), 62.9 (C-5), 122.9 (CN), 127.7 (C-*o*), 129.7 (C-*p*), 133.6 (C-*i*), 135.5 (C-*m*).

HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{22}H_{30}NOSi$ 352.2091; found 352.2107.

(*S*)-5-[(*tert*-Butyldiphenylsilyl)oxy]-*N*-{(*R*)-2-[(*tert*-butyldiphenylsilyl)oxy]-1-phenylethyl}-4-ethyl-1-pentanamine (122)



tert-Butyldiphenylsilyl chloride (9.1 mL, 34.8 mmol) and imidazole (3.39 g, 34.8 mmol) were added to a solution of aminodiol **63** (4.18 g, 16.6 mmol) in anhydrous CH_2Cl_2 (140 mL), and the mixture was heated at reflux for 17 h. Saturated aqueous NH_4Cl was added, and the mixture was extracted with CH_2Cl_2. The combined organic extracts were dried, filtered, and concentrated. The resulting residue was chromatographed (from hexane to 9:1 hexane–Et_2O) to afford pure compound **122** (9.7 g, 81%) as a colorless oil.

Spectroscopic data for **122**

$[\alpha]^{22}_D$ –3.55 (*c* 1.0, $CHCl_3$).

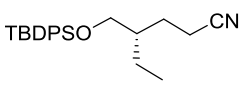
IR (film) 3070, 1112 cm^{-1};

^{1}H NMR (400 MHz, $CDCl_3$, COSY, *g*-HSQC) δ 0.82 (t, *J*= 7.2 Hz, 3H, C*H*$_3$CH$_2$), 1.05 [s, 18H, $(CH_3)_3$], 1.30-1.38 (m, 3H, H-2, CH_3CH_2), 1.38-1.48 (m, 4H, H-3, H-4, CH_3CH_2,), 1.90 (brs, 1H, NH), 2.39-2.49 (m, 2H, H-1), 3.53 (dd, *J* = 4.5, 2.0 Hz, 2H, H-5), 3.63-3.70 (m, 2H, CH_2O), 3.77 (dd, *J* = 8.1, 4.7 Hz, 1H, CHN), 7.19-7.26 (m, 5H, ArH), 7.32-7.44 (m, 12H, ArH), 7.60-7.67 (m, 8H, ArH).

^{13}C NMR (100.6 MHz, $CDCl_3$) δ 11.2 (CH_3CH_2), 19.2, 19.3 [$C(CH_3)_3$], 23.5 (CH_3CH_2), 26.8, 26.9 [$C(CH_3)_3$], 27.7 (C-3), 28.8 (C-2), 42.0 (C-4), 48.2 (C-1), 65.1 (CHN), 65.8 (C-5), 69.0 (CH_2O), 127.2 (C-Ar), 127.5 (C-Ar), 127.6 (C-Ar), 127.7 (C-Ar), 128.2 (C-Ar), 129.5 (C-Ar), 129.6 (C-Ar), 129.7 (C-Ar), 133.3 (C-*i*), 133.5 (C-*i*), 134.1 (C-*i*), 134.1 (C-*i*), 135.6 (C-Ar), 135.6 (C-Ar), 141.1 (C-*i*).

HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{47}H_{62}NO_2Si_2$ 728.4314; found 728.4314.

(*S*)-5-[(*tert*-Butyldiphenylsilyl)oxy]-4-ethylpentanenitrile (123)



20% Aqueous solution of NH_3 (6 mL) and iodine (228 mg, 0.90 mmol) were added to a solution of amine **122** (70 mg, 0.01 mmol) in anhydrous THF (2 mL) at room temperature, and the resulting mixture was stirred at 60 ºC for 21 h. The mixture was washed with saturated aqueous Na_2SO_3 and extracted with Et_2O. The combined organic phases were dried, filtered, and concentrated to give an oil. Flash chromatography (from hexane to 6:4 hexane–CH_2Cl_2) afforded pure nitrile **123** (25 mg, 70%) as a yellow oil.

Spectroscopic data for **123**

$[\alpha]^{22}_D$ +3.75 (*c* 0.5, $CHCl_3$).

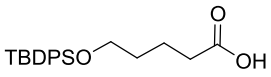
IR (film) 2960, 1471, 1427, 1112 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$, COSY, *g*-HSQC) δ 0.83 (t, *J* = 7.4 Hz, 3H, CH_3), 1.06 [s, 9H, $(CH_3)_3$], 1.27-1.43 (m, 2H, C*H*$_2$$CH_3$), 1.50-1.59 (m, 1H, H-4), 1.65-1.72 (m, 1H, H-3), 1.74-1.89 (m, 1H, H-3), 2.27-2.32 (m, 2H, H-2), 3.53 (dd, *J* = 10.4, 5.6 Hz, 1H, H-5), 3.59 (dd, *J* = 10.4, 4.4 Hz, 1H, H-5), 7.37-7.46 (m, 6H, ArH), 7.63-7.65 (m, 4H, ArH).

^{13}C NMR (100.6 MHz, $CDCl_3$) δ 11.2 (CH_3), 14.9 (C-2), 19.2 [*C*$(CH_3)_3$], 23.3 (CH_2), 26.9 [C(*C*$H_3)_3$], 27.1 (C-3), 41.1 (C-4), 64.9 (C-5), 120.0 (CN), 127.7 (C-*o*), 129.7 (C-*p*), 133.4 (C-*i*), 135.5 (C-*m*).

HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{23}H_{32}NOSi$ 366.2248; found 366.2240.

5-[(*tert*-Butyldiphenylsilyl)oxy]pentanoic acid (124)



A solution of amine **115** (285 mg, 0.41 mmol) in CH_2Cl_2 (1.5 mL) was added to a solution of *m*-chloroperbenzoic acid (70% of purity, 422 mg, 1.71 mmol) in CH_2Cl_2 (4 mL) at reflux temperature, and the resulting mixture was stirred at this temperature for 3 h. The reaction was quenched by addition of saturated aqueous $NaHCO_3$, and the mixture was extracted with CH_2Cl_2. The combined organic extracts were dried, filtered, and concentrated, and the resulting residue was chromatographed (from 1:1 hexane–CH_2Cl_2, CH_2Cl_2 to EtOAc) to afford the nitroso dimer **126** (70 mg) and C-Arboxylic acid **124** (yellow oil; 103 mg, 71%).

Spectroscopic data for **124**

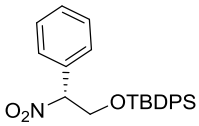
IR (film) 3071, 2931, 2858, 1709 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$, COSY, *g*-HSQC) δ 1.05 [s, 9H, $(CH_3)_3$], 1.57-1.64 (m, 2H, H-4), 1.70-1.78 (m, 2H, H-3), 2.35 (t, *J* = 7.6 Hz, 2H, H-2), 3.67 (t, *J* = 5.6 Hz, 2H, H-5), 7.35-7.43 (m, 6H, ArH), 7.65-7.67 (m, 4H, ArH).

^{13}C NMR (100.6 MHz, $CDCl_3$) δ 19.2 [*C*$(CH_3)_3$], 21.1 (C-3), 26.8 [C(*C*$H_3)_3$], 31.8 (C-4), 33.7 (C-2), 63.3 (C-5), 127.6 (C-*o*), 129.6 (C-*p*), 133.8 (C-*i*),135.5 (C-*m*).

HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{21}H_{29}O_3Si$ 357.1880; found 357.1886.

Spectroscopic data for nitro derivative **125**



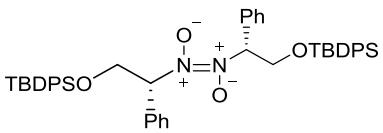
IR (film) 1557, 1113 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$, COSY, *g*-HSQC) δ 1.05 [s, 9H, $(CH_3)_3$], 3.88 (dd, *J* = 11.5, 3.6 Hz, 1H, CH_2), 4.62 (dd, *J* = 11.5, 10.0 Hz, 1H, CH_2), 5.61 (dd, *J* = 10.0, 3.6 Hz, 1H, CH), 7.32 (m, 3H, ArH), 7.38-7.42 (m. 8H, ArH), 7.64-7.66 (m, 4H, ArH).

^{13}C NMR (100.6 MHz, $CDCl_3$) δ 19.1 [*C*$(CH_3)_3$], 26.6 and 26.8 (1 solo, no 2) [C(*C*$H_3)_3$], 64.9 (CH_2), 92.6 (CH), 127.6 (C-Ar), 127.8 (C-Ar), 127.9 (C-Ar), 128.9 (C-Ar), 130.0 (C-*i*), 130.1 (C-*i*), 135.5 (C-Ar), 135.6 (C-Ar).

HRMS (ESI-TOF) m/z: $[M + NH_4]^+$ Calcd for $C_{24}H_{31}N_2O_3Si$ 423.2106; found 423.2098.

Spectroscopic data for dimer of nitroso compound **126**



IR (film) 3070, 2857, 1589, 1495, 1471, 1427, 1211, 1104 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$, COSY, *g*-HSQC) δ 1.00 [s, 9H, $(CH_3)_3$], 3.82 (dd, *J* = 10.8, 5.2 Hz, 1H, CH_2O), 4.50 (dd, *J* = 10.8, 8.6 Hz, 1H, CH_2O), 6.29 (dd, *J* = 8.6, 5.2 Hz, 1H, CHN), 7.00-7.02 (m, 2H, ArH), 7.11-7.14 (m, 2H, ArH), 7.18-7.23 (m, 1H, ArH), 7.30-7.41 (m, 6H, ArH), 7.54-7.57 (m, 2H, ArH), 7.67-7.69 (m, 2H, ArH).

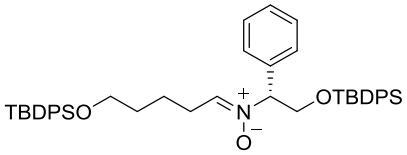
^{13}C NMR (100.6 MHz, $CDCl_3$) δ 19.1 [*C*$(C H_3)_3$], 26.7 [C$(CH_3)_3$], 63.8 (CH_2), 72.4 (CHN), 127.7 (C-Ar, 127.7(C-Ar), 127.8 (C-Ar), 128.3 (C-Ar), 128.5 (C-Ar), 129.7 (C-Ar), 129.7 (C-Ar), 132.2 (C-*i*), 132.9 (C-*i*), 133.0 (C-*i*), 135.5 (C-Ar), 135.6 (C-Ar).

HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{48}H_{55}N_2O_4Si_2$ 779.3695; found 779.3683.

From nitrone **127**

UHP (202 mg, 2.09 mmol) and $Na_2WO_4.2H_2O$ (8.7 mg, 0.026 mmol) were added at room temperature to a solution of amine **115** (365 mg, 0.52 mmol) in 1:1 CH_2Cl_2–methanol (3.4 mL), and the mixture was stirred at this temperature for 21 h. Solvents were removed under reduced pressure, and the crude residue was taken up with CH_2Cl_2. The resulting white solid was filtered, and the solvent was removed under reduced pressure to afford nitrone **127** (720 mg), which was used without purification in the next step.

Spectroscopic data for nitrone **127**

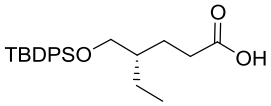


^{1}H NMR (400 MHz, $CDCl_3$, COSY, *g*-HSQC) δ 0.79 (m, 2H, H-3), 0.93 [s, 9H, $(CH_3)_3$], 0.96 [s, 9H, $(CH_3)_3$], 1.50 (brs, 2H, H-4), 2.40 (m, 1H, H-2), 2.47 (m, 1H, H-2), 3.58 (brs, 2H, H-5), 3.77 (dd, *J* = 10.4, 3.6 Hz, 1H, CHAr), 4.57 (t, *J* = 9.2 Hz, 1H, CH_2O), 4.65 (dd, *J* = 9.2 , 4.0 Hz, 1H, CH_2O), 6.75 (m. 1H, H-1), 7.20-7.40 (m, 17H, ArH), 7.55-7.65 (m, 8H, ArH).

^{13}C NMR (100.6 MHz, $CDCl_3$) δ 19.1 and 19.2 [*C*$(CH_3)_3$], 22.1 (C-3), 26.5 (C-2), 26.7 and 26.8 [C$(CH_3)_3$], 32.4 (C-4), 63.4 (C-5), 63.7 (CH), 79.6 (CH_2O), 127.6 (C-Ar), 127.7 (C-Ar), 127.8 (C-Ar), 127.9 (C-Ar), 128.4 (C-Ar), 128.7 (C-Ar),129.5 (C-Ar), 129.7 (C-Ar), 129.8 (C-Ar), 132.8 (C-*i*), 133.4 (C-*i*), 133.8 (C-*i*), 133.9 (C-*i*), 134.6 (C-*i*), 135.4 (C-Ar), 135.5 (C-Ar), 135.6 (C-Ar), 139.2 (C-1).

Operating as described in the preparation of **124**, from crude nitrone **127** (320 mg, 0.45 mmol) in CH_2Cl_2 (1.5 mL) and *m*-chloroperbenzoic acid (70% of purity, 276 mg, 1.12 mmol) in CH_2Cl_2 (4 mL), the nitroso dimer **126** (41 mg) and C-Arboxylic acid **124** (yellow oil; 84 mg, 45% from **115**) were obtained after flash chromatography (from 1:1 hexane–CH_2Cl_2, CH_2Cl_2 to EtOAc).

(*S*)-5-[(*tert*-Butyldiphenylsilyl)oxy]-4-ethylpentanoic acid (128)



A solution of amine **122** (2.15 g, 2.96 mmol) in CH_2Cl_2 (5 mL) was added to a solution of *m*-chloroperbenzoic acid (70% of purity, 3.06 g, 12.4 mmol) in CH_2Cl_2 (28 mL) at reflux temperature, and the resulting mixture was stirred at this temperature for 3 h. The reaction was quenched by addition of saturated aqueous $NaHCO_3$, and the mixture was extracted with CH_2Cl_2. The combined organic extracts were dried, filtered, and concentrated, and the resulting residue (350 mg) was chromatographed (from 1:1 hexane–CH_2Cl_2, CH_2Cl_2 to EtOAc) to afford the nitroso dimer **126** (420 mg) and C-Arboxylic acid **128** (yellow oil; 930 mg, 82%).

Spectroscopic data for **128**

$[\alpha]^{22}_D$ –1.96 (*c* 1.36, $CHCl_3$).

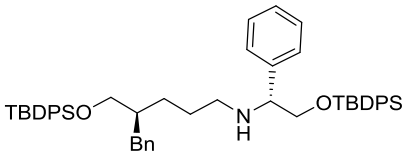
IR (film) 2960, 2931, 1709 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$, COSY, *g*-HSQC) δ 0.86 (t, *J* = 7.3 Hz, 3H, C*H*$_3$CH$_2$), 1.08 [s, 9H, $(CH_3)_3$], 1.32-1.45 (m, 2H, CH_3CH_2), 1.45-1.51 (m, 1H, H-4), 1.67-1.83 (m, 2H, H-3), 2.29-2.42 (m, 2H, H-2), 3.58 (dd, *J* = 10.2, 5.2 Hz, 1H, H-5), 3.59 (dd, *J* = 10.2, 5.2 Hz, 1H, H-5), 7.38-7.46 (m, 6H, ArH), 7.67-7.70 (m, 4H, ArH).

^{13}C NMR (100.6 MHz, $CDCl_3$) δ 11.2 (*C*H$_3$CH$_2$), 19.3 [*C*(CH$_3$)$_3$], 23.5 (CH$_3$*C*H$_2$), 25.9 (C-3), 26.9 [C(*C*H$_3$)$_3$], 31.7 (C-2), 41.5 (C-4), 65.3 (C-5), 127.6 (C-*o*), 129.6 (C-*p*), 133.8 (C-*i*), 133.8 (C-*i*), 135.6 (C-*m*), 180.4 (CO).

HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{23}H_{33}O_3Si$ 385.2193; found 385.2188.

(*S*)-4-Benzyl-5-[(*tert*-butyldiphenylsilyl)oxy]-*N*-{(*R*)-2-[(*tert*-butyldiphenylsilyl)oxy]-1-phenylethyl}-1-pentanamine (129)



tert-Butyldiphenylsilyl chloride (0.97 mL, 3.75 mmol) and imidazole (333 mg, 4.88 mmol) were added to a solution of aminodiol **64** (510 mg, 1.63 mmol) in anhydrous CH_2Cl_2 (15 mL), and the mixture was heated at reflux for 17 h. Saturated aqueous NH_4Cl was added, and the mixture was extracted with CH_2Cl_2. The combined organic extracts were dried, filtered, and concentrated. The resulting residue was chromatographed (96:4 hexane–EtOAc) to afford pure compound **129** (990 mg, 77%) as a colorless oil.

Spectroscopic data for **129**

$[\alpha]^{22}_D$ –13.3 (*c* 1.0, $CHCl_3$).

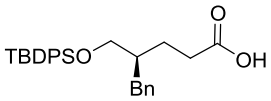
IR (film) 2930, 2857, 1428, 1112 cm^{-1};

^{1}H NMR (400 MHz, $CDCl_3$, COSY, *g*-HSQC) δ 0.96 [s, 9H, $(CH_3)_3$], 0.99 [s, 9H, $(CH_3)_3$], 1.25-1.34 (m, 4H, H-2, H-3), 1.58 (brs, 1H, NH), 1.65-1.72 (m, 1H, H-4), 2.29-2.33 (m, 2H, H-1), 2.48 (dd, *J* = 13.5, 6.8 Hz, 1H, CH_2Ar), 2.73 (dd, *J* = 13.5, 7.1 Hz, 1H, CH_2Ar), 3.41 (dd, *J* = 10.1, 5.4 Hz, 1H, H-5), 3.48 (dd, *J* = 10.1, 4.5 Hz, 1H, H-5), 3.53-3.61 (m, 2H, CH_2O), 3.63-3.68 (m, 1H, CHN), 7.02-7.18 (m, 12H, ArH), 7.24-7.33 (m, 12H, ArH), 7.51-7.57 (m, 6H, ArH).

^{13}C NMR (100.6 MHz, $CDCl_3$) δ 19.2 and 19.3 [*C*$(CH_3)_3$], 26.8 and 27.0 [C(*C*$H_3)_3$], 27.7 (C-3), 28.4 (C-2), 37.6 (CH_2Ar), 42.6 (C-4), 48.0 (C-1), 64.9 (C-5), 65.0 (CHN), 68.9 (CH_2O), 125.6 (C-Ar), 127.2 (C-Ar), 127.5 (C-Ar), 127.6 (C-Ar), 127.6 (C-Ar), 127.6 (C-Ar), 128.1 (C-Ar), 128.2 (C-Ar), 129.2 (C-Ar), 129.5 (C-Ar), 129.5 (C-Ar), 129.6 (C-Ar), 129.7 (C-Ar), 133.3 (C-*i*), 133.4 (C-*i*), 133.8 (C-*i*), 133.9 (C-*i*), 134.8 (C-Ar), 135.5 (C-Ar), 135.5 (C-Ar), 135.6 (C-Ar), 140.9 (C-*i*), 141.0 (C-*i*).

HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{52}H_{64}NO_2Si_2$ 790.4470; found 790.4465.

(*S*)-4-Benzyl-5-[(*tert*-butyldiphenylsilyl)oxy]pentanoic acid (130)



A solution of amine **129** (320 mg, 0.41 mmol) in CH_2Cl_2 (1.8 mL) was added to a solution of *m*-chloroperbenzoic acid (70% of purity, 420 mg, 1.70 mmol) in CH_2Cl_2 (4 mL) at reflux temperature, and the resulting mixture was stirred at this temperature for 3 h. The reaction was quenched by addition of saturated aqueous $NaHCO_3$, and the mixture was extracted with CH_2Cl_2. The combined organic extracts were dried, filtered, and concentrated, and the resulting residue was chromatographed (from 1:1 hexane–CH_2Cl_2, CH_2Cl_2 to EtOAc) to afford the nitroso dimer **126** (55 mg) and C-Arboxylic acid **130** (119 mg, 66%) as a yellow oil.

Spectroscopic data for **130**

$[\alpha]^{22}_D$ –6.91 (*c* 1.0, $CHCl_3$).

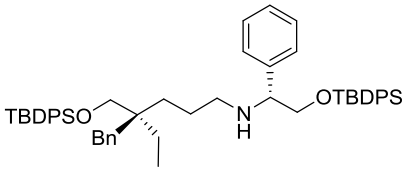
IR (film) 3069, 2930, 1708 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$, COSY, *g*-HSQC) δ 1.01 [s, 9H, $(CH_3)_3$], 1.59-1.70 (m, 2H, H-3), 1.72-1.76 (m, 1H, H-4), 2.12-2.27 (m, 2H, H-2), 2.51 (dd, *J* = 13.6, 6.6 Hz, 1H, CH_2Ar), 2.71 (dd, *J* = 13.6, 7.2 Hz, 1H, CH_2Ar), 3.46 (dd, *J* = 4.5, 1.2 Hz, 2H, H-5), 7.04-7.18 (m, 5H, ArH), 7.26-7.37 (m, 6H, ArH), 7.54-7.57 (m, 4H, ArH).

^{13}C NMR (100.6 MHz, $CDCl_3$) δ 19.3 [*C*$(CH_3)_3$], 25.9 (C-3), 26.9 [C(*C*$H_3)_3$], 31.7 (C-2), 37.5 (CH_2Ar), 41.9 (C-4), 64.6 (C-5), 125.8 (C-Ar), 127.6 (C-Ar), 127.7 (C-Ar), 128.2 (C-Ar), 129.1 (C-Ar), 129.6 (C-Ar), 129.6 (C-Ar), 133.5 (C-*i*), 133.6 (C-Ar), 135.6 (C-Ar), 140.3 (C-*i*), 180.0 (CO).

HRMS (ESI-TOF) m/z: $[M - H]^-$ Calcd for $C_{28}H_{33}O_3Si$ 445.2204; found 445.2194.

(*S*)-4-Benzyl-5-[(*tert*-butyldiphenylsilyl)oxy]-*N*-{(*R*)-2-[(*tert*-butyldiphenylsilyl)oxy]-1-phenylethyl}-4-ethyl-1-pentanamine (131)



tert-Butyldiphenylsilyl chloride (0.37 mL, 1.41 mmol) and imidazole (144 mg, 2.11 mmol) were added to a solution of aminodiol **68** (240 mg, 0.70 mmol) in anhydrous CH_2Cl_2 (6 mL), and the mixture was heated at reflux for 17 h. Saturated aqueous NH_4Cl was added, and the mixture was extracted with CH_2Cl_2. The combined organic extracts were dried, filtered, and concentrated. The resulting residue was chromatographed (from hexane to 95:5 hexane–EtOAc) to afford pure compound **131** (414 mg, 72%) as a colorless oil.

Spectroscopic data for **131**

$[\alpha]^{22}_D$ –5.67 (*c* 1.15, $CHCl_3$).

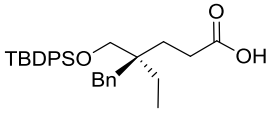
IR (film) 3070, 2930, 2857, 1471, 1428, 1112 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$, COSY, *g*-HSQC) δ 0.86 (t, *J* = 7.4 Hz, 3H, C*H*$_3$CH$_2$), 1.18 [s, 9H, (CH$_3$)$_3$], 1.19-1.26 (m, 2H, H-3), 1.27 [s, 9H, (CH$_3$)$_3$], 1.31-1.38 (m, 1H, H-2), 1.39-1.48 (m, 2H, H-2, C*H*$_2$CH$_3$), 1.53-1.64 (m, 1H, C*H*$_2$CH$_3$), 2.50-2.54 (m, 2H, H-1), 2.75 (d, *J* = 13.2 Hz, 1H, CH$_2$Ar), 2.81 (d, *J* = 13.2 Hz, 1H, CH$_2$Ar), 3.38 (d, *J* = 10.0 Hz, 1H, H-5), 3.42 (d, *J* = 10.0 Hz, 1H, H-5), 3.80-3.84 (m, 2H, CH$_2$O), 3.89 (dd, *J* = 8.0, 4.8 Hz, 1H, CHN), 7.34-7.40 (m, 10H, ArH), 7.44-7.56 (m, 12H, ArH), 7.72-7.76 (m, 4H, ArH), 7.78-7.81 (m, 4H, ArH).

^{13}C NMR (100.6 MHz, $CDCl_3$) δ 7.6 (*C*H$_3$CH$_2$), 19.2, 19.4 [*C*(CH$_3$)$_3$], 23.7 (CH$_3$*C*H$_2$), 25.4 (C-2), 26.9, 27.1 [C(*C*H$_3$)$_3$], 30.0 (C-3), 39.8 (CH$_2$Ar), 41.8 (C-1), 48.5 (C-4), 65.0 (CHN), 66.1 (C-5), 68.9 (CH$_2$O), 125.7 (C-Ar), 127.2 (C-Ar), 127.5 (C-Ar), 127.6 (C-Ar), 127.7 (C-Ar), 128.2 (C-Ar), 129.6 (C-Ar), 129.6 (C-Ar), 129.7 (C-Ar), 130.5 (C-Ar), 133.3 (C-*i*), 133.4 (C-*i*), 133.8 (C-*i*), 135.5 (C-Ar), 135.5 (C-Ar), 135.8 (C-Ar), 135.9 (C-Ar), 138.8 (C-*i*).

HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{54}H_{68}NO_2Si_2$ 818.4783; found 818.4773.

(*S*)-4-Benzyl-5-[(*tert*-butyldiphenylsilyl)oxy]-4-ethylpentanoic acid (132)



A solution of amine **131** (300 mg, 0.37 mmol) in CH_2Cl_2 (1.5 mL) was added to a solution of *m*-chloroperbenzoic acid (70% of purity, 380 mg, 1.54 mmol) in CH_2Cl_2

(3.5 mL) at reflux temperature, and the resulting mixture was stirred at this temperature for 3 h. The reaction was quenched by addition of saturated aqueous $NaHCO_3$, and the mixture was extracted with CH_2Cl_2. The combined organic extracts were dried, filtered, and concentrated, and the resulting residue was chromatographed (from 1:1 hexane–CH_2Cl_2, CH_2Cl_2 to EtOAc) to afford the nitroso dimer **126** (57 mg) and C-Arboxylic acid **132** (130 mg, 75%) as a yellow oil.

Spectroscopic data for **132**

$[\alpha]^{22}_D$ +2.52 (*c* 0.65, $CHCl_3$).

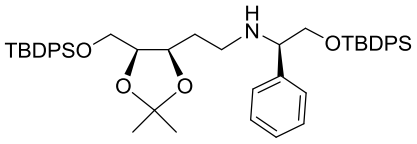
IR (film) 3074, 2933, 2861, 1707 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$, COSY, *g*-HSQC) δ 0.83 (t, *J* = 7.4 Hz, 3H, C*H*$_3$CH$_2$), 1.19 [s, 9H, $(CH_3)_3$], 1.22 (q, *J* = 7.4 Hz, 2H, CH_3CH_2), 1.54 (ddd, *J* = 14.0, 14.0, 5.0 Hz, 1H, H-3), 1.63 (ddd, *J* = 14.0, 14.0, 5.0 Hz, 1H, H-3), 2.06-2.14 (m, 1H, H-2), 2.18-2.27 (m, 1H, H-2), 2.66 (d, *J* = 13.0 Hz, 1H, CH_2Ar), 2.72 (d, *J* = 13.0 Hz, 1H, CH_2Ar), 3.29 (d, *J* = 10.3 Hz, 1H, H-5), 3.34 (d, *J* = 10.3 Hz, 1H, H-5), 7.18-7.25 (m, 5H, ArH), 7.40-7.49 (m, 6H, ArH), 7.69-7.72 (m, 4H, ArH).

^{13}C NMR (100.6 MHz, $CDCl_3$) δ 7.4 (*C*H$_3$CH$_2$), 19.4 [*C*(CH$_3$)$_3$], 24.7 (CH$_3$*C*H$_2$), 27.2 [C(*C*H$_3$)$_3$], 27.8 (C-3), 28.4 (C-2), 39.6 (CH_2Ar), 41.5 (C-4), 65.9 (C-5), 126.0 (C-*p*), 127.6 (C-Ar), 127.7 (C-Ar), 127.8 (C-Ar), 129.7 (C-*p*), 129.7 (C-*p*), 130.5 (C-Ar), 133.4 (C-*i*), 133.5 (C-*i*), 135.8 (C-Ar), 135.9 (C-Ar), 138.1 (C-*i*), 180.5 (CO).

HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{30}H_{39}O_3Si$ 475.2663; found 475.2667.

(3*R*,4*S*)-5-[(*tert*-Butyldiphenylsilyl)oxy]-*N*-{(*R*)-2-[(*tert*-butyldiphenylsilyl)oxy]-1-phenylethyl}-3,4-(isopropylidenedioxy)-1-pentanamine (133)



tert-Butyldiphenylsilyl chloride (0.17 mL, 0.64 mmol) and imidazole (22 mg, 0.97 mmol) were added to a solution of aminodiol **85** (95 mg, 0.32 mmol) in anhydrous CH_2Cl_2 (3.5 mL), and the mixture was heated at reflux for 17 h. Saturated aqueous NH_4Cl was added, and the mixture was extracted with CH_2Cl_2. The combined organic extracts were dried, filtered, and concentrated. The resulting residue was

chromatographed (from hexane to 95:5 hexane–EtOAc) to afford pure compound **133** (174 mg, 70%) as a colorless oil.

Spectroscopic data for **133**

$[\alpha]^{22}_D$ –4.32 (*c* 1.35, $CHCl_3$).

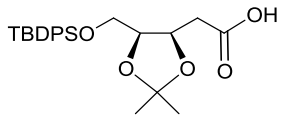
IR (film) 2930, 2857, 1428, 1112 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$, COSY, *g*-HSQC) δ 1.03 [s, 9H, $(CH_3)_3$], 1.04 [s, 9H, $(CH_3)_3$], 1.82 (brs, 2H, H-2), 2.67 (brs, 2H, H-1), 3.60 (dd, *J* = 10.5, 5.1 Hz, 1H, H-5), 3.65-3.73 (m, 3H, H-5, CH_2O), 3.79 (brs, 1H, CHN), 4.11-4.16 (m, 1H, H-4), 4.26-4.30 (m, 1H, H-3), 7.22-7.28 (m, 5H, ArH), 7.32-7.44 (m, 12H, ArH), 7.56-7.67 (m, 8H, ArH).

^{13}C NMR (100.6 MHz, $CDCl_3$) δ 19.1, 19.2 [*C*$(CH_3)_3$], 25.5 (CH_3), 26.8, 26.8 [C(*C*$H_3)_3$], 28.0 (CH_3), 29.6 (C-2), 45.2 (C-1), 62.5 (C-5), 64.5 (CHN), 67.8 (CH_2O), 76.5 (C-3), 77.7 (C-4), 108.3 (CMe_2), 127.6 (C-Ar), 127.7 (C-Ar), 127.7 (C-Ar), 127.8 (C-Ar), 128.4 (C-Ar), 129.6 (C-Ar), 129.7 (C-Ar), 132.8 (C-*i*), 133.0 (C-*i*), 133.1 (C-*i*), 133.2 (C-*i*), 135.5 (C-Ar).

HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{48}H_{62}NO_4Si_2$ 772.4212; found 772.4223.

(3*R*,4*S*)-5-[(*tert*-Butyldiphenylsilyl)oxy]3,4-(isopropylidenedioxy)pentanoic acid (134)



A solution of amine **133** (70 mg, 0.09 mmol) in CH_2Cl_2 (0.8 mL) was added to a solution of *m*-chloroperbenzoic acid (70% of purity, 94 mg, 0.38 mmol) in CH_2Cl_2 (1 mL) at reflux temperature, and the resulting mixture was stirred at this temperature for 3 h. The reaction was quenched by addition of saturated aqueous $NaHCO_3$, and the mixture was extracted with CH_2Cl_2. The combined organic extracts were dried, filtered, and concentrated, and the resulting residue was chromatographed (from 1:1 hexane–CH_2Cl_2, CH_2Cl_2 to EtOAc) to afford the nitroso dimer **126** (8 mg) and C-Arboxylic acid **134** (21 mg, 54%) as a yellow oil.

Spectroscopic data for **134**

$[\alpha]^{22}_{D}$ +2.93 (*c* 0.6, $CHCl_3$).

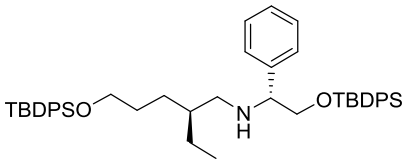
IR (film) 3071, 2931, 2858, 1714, 1112 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$, COSY, *g*-HSQC) δ 0.98 [s, 9H, $(CH_3)_3$], 1.27 (s, 3H, CH_3), 1.31 (s, 3H, CH_3), 2.61 (dd, *J* = 16.1, 9.1 Hz, 1H, H-2), 2.79 (dd, *J* = 16.1, 4.5 Hz, 1H, H-2), 3.58-3.65 (m, 2H, H-5), 4.18 (m, 1H, H-4), 4.60 (m, 1H, H-3), 7.29-7.39 (m, 6H, ArH), 7.57-7.60 (m, 4H, ArH).

^{13}C NMR (100.6 MHz, $CDCl_3$) δ 19.1 [*C*$(CH_3)_3$], 25.4 (CH_3), 26.8 [C(*C*$H_3)_3$], 27.9 (CH_3), 34.9 (C-2), 62.2 (C-5), 73.5 (C-3), 76.8 (C-4), 108.6 (CMe_2), 127.8 (C-*o*), 129.9 (C-*p*), 133.0 (C-*i*), 135.5 (C-*m*), 176.1 (CO).

HRMS (ESI-TOF) m/z: $[M - H]^-$ Calcd for $C_{24}H_{31}O_5Si$ 427.1946; found 427.1941.

(*S*)-5-[(*tert*-Butyldiphenylsilyl)oxy]-*N*-{(*R*)-2-[(*tert*-butyldiphenylsilyl)oxy]-1-phenylethyl}-2-ethyl-1-pentanamine (135)



tert-Butyldiphenylsilyl chloride (1.48 mL, 5.71 mmol) and imidazole (583 mg, 8.56 mmol) were added to a solution of **14** (720 mg, 2.85 mmol) in anhydrous CH_2Cl_2 (25 mL), and the mixture was heated at reflux for 18 h. Saturated aqueous NH_4Cl solution was added, and the mixture was extracted with CH_2Cl_2. The combined organic extracts were dried, filtered, and concentrated. The resulting residue was chromatographed (from hexane to 7:3 hexane-CH_2Cl_2) to afford pure compound **135** (1.59 g, 76%) as a colorless oil.

Spectroscopic data for **135**

$[\alpha]^{22}_{D}$ –14.9 (*c* 1.05, $CHCl_3$).

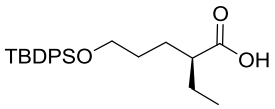
IR (film) 3070, 2858, 1589, 1472, 1428, 1104 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$, COSY, *g*-HSQC) δ 0.75 (t, *J* = 7.3 Hz, C*H*$_3$CH$_2$), 0.96 [s, 9H, (C*H*$_3$)$_3$], 0.97 [s, 9H, (C*H*$_3$)$_3$], 1.19-1.35 (m, 5H, CH$_3$C*H*$_2$, H-2, H-3), 1.42-1.49 (m, 2H, H-4), 2.27 (m, 2H, H-1), 3.52-3.61 (m, 4H, H-5, CH$_2$O), 3.65 (m, 1H, CHN), 7.10-7.17 (m, 5H, ArH), 7.24-7.35 (m, 12H, ArH), 7.54-7.60 (m, 8H, ArH).

^{13}C NMR (100.6 MHz, $CDCl_3$) δ 10.9 (*C*H$_3$CH$_2$), 19.2 [*C*(CH$_3$)$_3$], 24.4 (CH$_3$*C*H$_2$), 26.8, 26.9 [C(*C*H$_3$)$_3$], 27.7 (C-3), 29.8 (C-4), 39.5 (C-2), 50.7 (C-1), 64.3 (C-5), 65.5 (CHN), 69.1 (CH$_2$O), 127.1 (C-Ar), 127.6 (C-Ar), 127.7 (C-Ar), 128.1 (C-Ar), 129.5 (C-Ar), 129.6 (C-Ar), 129.7 (C-Ar), 133.3 (C-*i*), 133.5 (C-*i*), 134.1 (C-*i*), 135.6 (C-Ar), 141.1 (C-*i*).

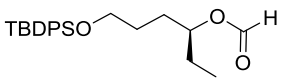
HRMS (ESI-TOF) m/z: M + H]$^+$ Calcd for $C_{47}H_{62}NO_2Si_2$ 728.4314; found 728.4304.

(*S*)-5-[(*tert*-Butyldiphenylsilyl)oxy]-2-ethylpentanoic acid (136)



A solution of amine **135** (420 mg, 0.58 mmol) in CH_2Cl_2 (1.5 ml) was added to a solution of *m*-cloroperbenzoic acid (70% of purity, 598 mg, 2.42 mmol) in CH_2Cl_2 (5 ml) at reflux temperature, and the resulting mixture was stirred at this temperature for 3 h. The reaction was quenched by addition of saturated aqueous $NaHCO_3$, and the mixture was extracted with CH_2Cl_2. The combined organic extracts were dried, filtered, and concentrated, and the resulting residue was chromatographed (from 1:1 hexane–CH_2Cl_2, CH_2Cl_2 to EtOAc) to afford the nitroso dimer **126** (40 mg), formiate **137** (60 mg, 27%) as a yellow oil, and C-Arboxylic acid **136** (66 mg, 30%) as a yellow oil.

Spectroscopic data for **137**



[α]$^{22}_D$ –8.6 (*c* 0.70, $CHCl_3$).

IR (film) 3070, 2857, 1717, 1184, 1112 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$, COSY, *g*-HSQC) δ 0.91 (t, *J* = 7.4 Hz, 3H, H-1), 1.06 [s, 9H, $(CH_3)_3$], 1.51-1.76 (m, 6H, H-2, H-4, H-5), 3.63-3.72 (m, 2H, H-6), 4.95 (quint, *J* = 6.0 Hz, 1H, H-3), 7.37-7.46 (m, 6H, ArH), 7.66-7.68 (m, 4H, ArH), 8.08 (s, 1H, OCHO).

^{13}C NMR (100.6 MHz, $CDCl_3$) δ 9.5 (C-1), 19.2 [*C*$(CH_3)_3$], 26.8 [C(*C*$H_3)_3$], 26.9 (C-2), 28.2 (C-5), 29.8 (C-4), 63.4 (C-6), 75.4 (C-3), 127.6 (C-*o*), 129.6 (C-*p*), 133.9 (C-*i*), 135.5 (C-*m*), 161.0 (CO).

HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{23}H_{33}O_3Si$ 385.2193; found 385.2203.

Spectroscopic data for **136**

$[\alpha]^{22}_D$ +4.00 (*c* 1.1, $CHCl_3$).

IR (film) 3071, 2931, 1699, 1110 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$, COSY, *g*-HSQC) δ 0.95 (dt, *J*= 7.4, 1.6 Hz, 3H, C*H*$_3$CH$_2$), 1.08 [s, 9H, $(CH_3)_3$], 1.54-1.74 (m, 6H, CH_3CH_2, H-3, H-4), 2.30-2.37 (m, 1H, H-2), 3.70 (m, 2H, H-5), 7.37-7.46 (m, 6H, ArH), 7.68-7.71 (m, 4H, ArH).

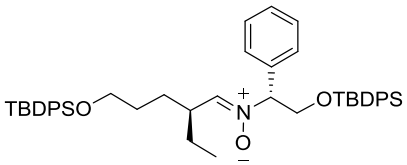
^{13}C NMR (100.6 MHz, $CDCl_3$) δ 11.7 (*C*H_3CH_2), 19.2 [*C*$(CH_3)_3$], 25.1 (CH_3*C*H_2), 26.9 [C(*C*$H_3)_3$], 27.9 (C-3), 30.2 (C-4), 46.7 (C-2), 63.6 (C-5), 127.6 (C-*o*), 129.6 (C-*p*), 133.9 (C-*i*), 135.6 (C-*m*), 182.7 (CO).

HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{23}H_{33}O_3Si$ 385.2193; found 385.2182.

From nitrone **139**

UHP (178 mg, 1.84 mmol) and $Na_2WO_4.2H_2O$ (15 mg, 0.046 mmol) were added at room temperature to a solution of amine **135** (365 mg, 0.52 mmol) in 1:1 CH_2Cl_2–methanol (3.2 mL), and the mixture was stirred at this temperature for 66 h. Solvents were removed under reduced pressure and the crude residue was taken up with CH_2Cl_2. The white solid was filtered and the solvent was removed under reduced pressure affording nitrone **139** (330 mg), which was used without purification in the next step.

Spectroscopic data for nitrone **139**

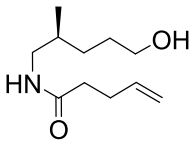


^{1}H NMR (400 MHz, $CDCl_3$) δ 0.95 (t, *J* = 7.6 Hz, 3H, CH_2CH_3), 1.02 [s, 9H, $(CH_3)_3$], 1.04 [s, 9H, $(CH_3)_3$], 1.36-1.59 (m, 6H), 3.05 (m, 1H), 3.54-3.67 (m, 2H), 3.81 (dd, *J* = 9.6, 2.4 Hz, 1H, CHAr), 4.57-4.75 (m, 2H, CH_2O), 6.75 (d, *J* = 8.0 Hz, 1H, H-1), 7.25-7.27 (m, 2H, ArH), 7.31-7.43 (m, 18H, ArH), 7.60-7.70 (m, 5H, ArH).

^{13}C NMR (100.6 MHz, $CDCl_3$) δ 11.7 (CH_3CH_2), 19.1, 19.2 [$C(CH_3)_3$], 24.8 (CH_2CH_3), 26.7, 26.8 [$C(CH_3)_3$], 27.7 (C-3), 30.1 (C-4), 37.3 (C-2), 63.7 (C-5), 63.8 (CH), 80.0 (CH_2O), 127.6 (C-Ar), 127.7 (C-Ar), 127.8 (C-Ar), 127.9 (C-Ar), 128.6 (C-Ar), 128.7 (C-Ar), 129.6 (C-Ar), 129.8 (C-Ar), 129.9 (C-Ar), 133.0 (C-*i*), 133.4 (C-*i*), 134.0 (C-*i*), 134.1 (C-*i*), 135.2 (C-*i*), 135.5 (C-Ar), 135.6 (C-Ar), 135.7 (C-Ar), 135.7 (C- Ar), 143.1 (C-1).

Operating as described in the preparation of **127**, from crude nitrone **139** (224 mg, 0.30 mmol) in CH_2Cl_2 (1.5 mL) and *m*-cloroperbenzoic acid (70% of purity, 186 mg, 0.76 mmol) in CH_2Cl_2 (3 mL), the nitroso dimer **126** (25 mg), formiate **137** (yellow oil, 42 mg, 24%) and C-Arboxylic acid **136** (46 mg, 26%) were obtained as yellow oils after flash chromatography (from 1:1 hexane–CH_2Cl_2, CH_2Cl_2 to EtOAc).

N-[(*S*)-5-Hydroxy-2-methylpentyl]-4-pentenamide (141)



A solution of aminodiol **52** (738 mg, 3.16 mmol) in anhydrous MeOH (30 mL) containing 20 % $Pd(OH)_2$ (150 mg) was hydrogenated at 68 °C for 18 h under 10 bar of pressure. The catalyst was removed by filtration and washed with hot MeOH. The combined organic solutions were concentrated, and the resulting residue was dissolved in CH_2Cl_2 (19 mL). 4-pentenoyl chloride (1.15 mL, 10.4 mmol) and Et_3N (1.46 mL, 10.4 mmol) were added at 0 ºC, and the mixture was allowed to react at room temperature for 17 h. The mixture was extracted with a 1.0 N aqueous HCl, and

the organic layer was dried, filtered and concentrated to give diene **140** which was used without purification in the next step:

IR (film) 3304, 1736, 1645 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$, COSY, *g*-HSQC) δ 0.90 (d, *J* = 6.7 Hz, 3H, CH_3), 1.10-1.20 (m, 1H, H-3), 1.34-1.43 (m, 1H, H-3), 1.55-1.75 (m, 3H, H-2, H-4), 2.25-2.29 (m, 2H, C*H*$_2$CO), 2.33-2.42 (m, 6H, C*H*$_2$CO, CH_2=CHC*H*$_2$), 3.07 (ddd, *J* = 13.3, 7.0, 6.1 Hz, 1H, H-5), 3.19 (dt, *J* = 13.3, 6.1 Hz, 1H, H-5), 4.05 (ddd, *J* = 6.7, 6.7, 1.1 Hz, 2H, H-2), 4.98-5.10 (m, 4H, C*H*$_2$=CH), 5.57 (br.s, 1H, NH), 5.76-5.87 (m, 2H, CH_2=C*H*).

^{13}C NMR (100.6 MHz, $CDCl_3$) δ 17.5 (*C*H_3), 26.1 (C-2), 28.9 (CH_2=CH*C*H_2), 29.7 (CH_2=CH*C*H_2), 30.5 (C-3), 33.0 (C-4), 33.5 (*C*H_2CO), 35.7 (*C*H_2CO), 42.5 (C-5), 64.4 (C-1), 115.4 (*C*H_2=CH), 115.6 (*C*H_2=CH), 136.6 (CH_2=*C*H), 137.1 (CH_2=*C*H), 172.3 (CO), 173.1 (CO).

HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{16}H_{28}NO_3$ 282.2064; found 282.2063.

DBU (9.47 mL, 63.3 mmol) was added to a solution of the above diene **140** in anhydrous methanol (50 mL), and the reaction mixture was stirred at room temperature for 15 h. Saturated aqueous NH_4Cl was added, and the resulting mixture was extracted with EtOAc. The extracts were dried, filtered, and concentrated. The residue was chromatographed (from 1:1 hexane-EtOAc to EtOAc) to give alcohol **141** (380 mg, 60%) as a yellow oil.

Spectroscopic data for **141**

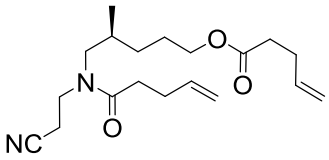
$[\alpha]^{22}_D$ –5.17 (*c* 1.0, MeOH).

^{1}H NMR (400 MHz, $CDCl_3$, COSY, *g*-HSQC) δ 0.91 (d, *J* = 6.7 Hz, 3H, CH_3), 1.15-1.25 (m, 1H, H-3), 1.38-1.47 (m, 1H, H-3), 1.50-1.56 (m, 1H, H-2), 1.56-1.70 (m, 2H, H-2 + H-4), 2.26-2.30 (m, 2H, C*H*$_2$CO), 2.36-2.42 (m, 2H, CH_2=CHC*H*$_2$), 3.07-3.13 (m, 1H, H-5), 3.17-3.24 (m, 1H, H-5), 3.64 (t, *J* = 6.4 Hz, 2H, H-1), 4.99-5.10 (m, 2H, C*H*$_2$=CH), 5.58 (br.s, 1H, NH), 5.83 (dddd, *J* = 16.8, 10.2, 10.2, 6.5 Hz, 1H, CH_2=C*H*).

^{13}C NMR (100.6 MHz, $CDCl_3$) δ 17.6 (*C*H_3), 29.6 (C-2), 29.6 (C-3), 30.1 (CH_2=CH*C*H_2), 32.9 (C-4), 35.7 (*C*H_2CO), 45.1 (C-5), 62.4 (C-1), 115.4 (*C*H_2=CH), 137.0 (CH_2=*C*H), 172.7 (CO).

HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{19}H_{22}NO_2$ 200.1645; found 200.1645.

(*R*)-5-(*N*-(2-cyanoethyl)pent-4-enamido)-4-methylpentyl 4-pentenoate (143)



To a solution of **140** (70 mg, 0.25 mmol) in anhydrous THF (2 mL) was added sodium hydride 95 % (10 mg, 0.38 mmol) at 0 ºC and the reaction mixture was stirred at this temperature for 1 h 15. Then, acrylonitrile (0.06 mL, 0.86 mmol) was added and the mixture was allowed to react at room temperature for 3 h. Additional acrylonitrile (0.06 mL, 0.86 mmol) was added and the reaction mixture was stirred at room temperature for an additional 18 h. The reaction was quenched by water, and the resulting mixture was extracted with dichloromethane. The combined organic extracts were dried, filtered and concentrated, and the resulting residue (120 mg) was chromatographed (from 9:1 hexane-EtOAc to 8:2 hexane-EtOAc) to give amide **143** (17 mg, 20%) as a yellow oil.

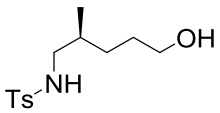
Spectroscopic data for **143**

^{1}H NMR (400 MHz, $CDCl_3$, COSY, *g*-HSQC) δ 0.93 (d, *J* = 6.6 Hz, 3H, CH_3), 1.12-1.80 (m, 7H, CH, $3CH_2$), 2.37-2.45 (m, 6H, CH_2CO, $2CH_2CH{=}CH_2$), 2.69 (dt, *J* = 6.4, 1.3 Hz, 2H, CH_2CO), 3.21 (dd, *J* = 14.9, 8.5 Hz, 1H, CH_2N), 3.33 (dd, *J* = 14.9, 6.6 Hz, 1H, CH_2N), 3.56 (t, *J* = 6.4 Hz, 2H, CH_2CH_2CN), 4.08 (t, *J* = 6.6 Hz, 2H, CH_2O), 5.00-5.09 (m, 4H, $CH_2{=}CH$), 5.78-5.90 (m, 2H, $CH_2{=}CH$).

^{13}C NMR (100.6 MHz, $CDCl_3$) δ 16.0 (CH_2), 17.2 (CH_3), 26.2 (C-2), 28.8 ($CH_2{=}CHCH_2$), 29.2 ($CH_2{=}CHCH_2$), 30.5 (C-3), 32.5 (CH_2CO), 32.9 (C-4), 33.5 (CH_2CO), 43.5 (C-5), 55.4 (CH_2N), 64.1 (C-1), 115.5 ($CH_2{=}CH$), 115.6 ($CH_2{=}CH$), 118.4 (CN), 136.6 ($CH_2{=}CH$), 137.1 ($CH_2{=}CH$), 173.0 (CO), 173.0 (CO).

HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{19}H_{31}N_2O_3$ 335.2329; found 335.2329.

(*S*)-4-Methyl-5-[(*p*-methylbenzenesulfonyl)amino]-1-pentanol (144)



A solution of aminodiol **52** (1.5 g, 6.32 mmol) in anhydrous MeOH (110 mL) containing 20 % $Pd(OH)_2$ (300 mg) was hydrogenated at 68 °C for 19 h under 11 bar of pressure. The catalyst was removed by filtration and washed with hot MeOH, and the combined organic solutions were concentrated. The resulting residue was dissolved in $CHCl_3$ (30 mL), and *p*-toluenesulfonyl chloride (1.33 g, 6.96 mmol) and Et_3N (1.06 mL, 7.56 mmol) were added. The mixture was allowed to react at room temperature for 15 h. The solvent was evaporated under reduced pressure, and the residue was chromatographed (from 9:1 hexane-EtOAc to EtOAc) to give alcohol **144** (1.01 g, 59 %) as a yellow oil.

Spectroscopic data for **144**

$[\alpha]^{22}_D$ +0.61 (*c* 0.8, MeOH).

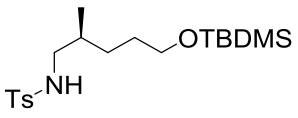
IR (film) 3507, 3286 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$, COSY, *g*-HSQC) δ 0.86 (d, *J* = 6.8 Hz, 3H, CH_3), 1.09-1.16 (m, 1H, H-3), 1.38-1.48 (m, 1H, H-3), 1.50-1.64 (m, 3H, H-2, H-4), 2.42 (s, 3H, CH_3Ts), 2.74 (dd, *J* = 12.5, 6.4 Hz, 1H, H-5), 2.79 (dd, *J* = 12.5, 6.8 Hz, 1H, H-5), 3.57 (t, *J* = 6.1 Hz, 2H, H-1), 5.32 (br.s, 1H, NH), 7.24 (d, *J* = 8.3 Hz, 2H, H-3Ts, H-5Ts), 7.74 (d, *J* = 8.3 Hz, 2H, H-2Ts, H-6Ts).

^{13}C NMR (100.6 MHz, $CDCl_3$) δ 17.4 (CH_3), 21.4 (CH_3Ts), 29.4 (C-3), 29.7 (C-2), 32.8 (C-4), 48.7 (C-5), 62.6 (C-1), 126.9 and 129.6 (CHTs), 136.9 (C-4Ts), 143.2 (C-1Ts).

HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{13}H_{22}NO_3S$ 272.1315; found 272.1317.

(*S*)-5-[(*tert*-Butyldimethylsilyl)oxy]-2-methyl-*N*-tosylpentanamine (147)



tert-Butyldimethylsilyl chloride (773 mg, 5.13 mmol) was added to a solution of alcohol **144** (870 mg, 3.20 mmol) and imidazole (349 mg, 5.13 mmol) in anhydrous CH_2Cl_2 (10 mL), and the mixture was heated at reflux for 15 h. The reaction was quenched by a saturated aqueous solution of NH_4Cl, and the mixture was extracted with CH_2Cl_2. The combined organic extracts were dried, filtered, and concentrated to

give an oil (1.2 g). Purification by flash chromatography (from 9:1 hexane-EtOAc to 1: 1 hexane-EtOAc) afforded pure compound **147** (1.09 g, 88 %) as a colorless oil.

Spectroscopic data for **147**

$[\alpha]^{22}_{D}$ –0.19 (*c* 1.02, MeOH).

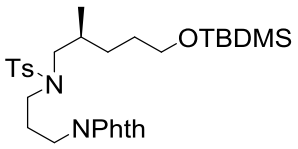
IR (film) 3564, 3282 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$, COSY, *g*-HSQC) δ – 0.01 (s, 6H, CH_3Si), 0.84 [s, 9H, $(CH_3)_3$], 0.86 (d, *J* = 6.0 Hz, 3H, CH_3), 1.07-1.09 (m, 1H, H-3), 1.28-1.45 (m, 3H, H-4, H-3), 1.52-1.59 (m, 1H, H-2), 2.39 (s, 3H, CH_3Ts), 2.69 (ddd, *J* = 12.5, 6.8, 6.8 Hz, 1H, H-1), 2.79 (ddd, *J* = 12.5, 5.6, 5.6 Hz, 1H, H-1), 3.50 (dt, *J* = 6.4, 1.5 Hz, 2H, H-5), 5.18 (br.s, 1H, NH), 7.26 (d, *J* = 8.4 Hz, 2H, H-3Ts, H-5Ts), 7.73 (d, *J* = 8.4 Hz, 2H, H-2Ts, H-6Ts).

^{13}C NMR (100.6 MHz, $CDCl_3$) δ – 5.4 ($2CH_3Si$), 17.4 (CH_3), 18.2 [$C(CH_3)_3$], 21.3 (CH_3Ts), 25.8 [$C(CH_3)_3$], 29.8 (C-3), 30.0 (C-4), 32.8 (C-2), 48.8 (C-1), 63.1 (C-5), 126.9 (C-HTs), 129.5 (C- HTs), 137.0 (C-4Ts), 143.0 (C-1Ts).

HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{19}H_{36}NO_3SSi$ 386.2180; found 386.217

(*S*)-5-[(*tert*-Butyldimethylsilyl)oxy]-2-methyl-*N*-[3-(phthalimido)propyl]-*N*-tosylpentanamine (149)



NaH (95 %, 136 mg, 5.39 mmol) was added to a solution of compound **147** (562 mg, 1.46 mmol) and 3-(phthalimido)propyl iodide **148**[132] (964 mg, 3.06 mmol) in anhydrous DMF (9 mL), and the mixture was stirred at room temperature for 17 h. The reaction was quenched by the addition of saturated aqueous NH_4Cl, and the aqueous layer was extracted with EtOAc. The combined organic extracts were dried, filtered, and concentrated. The resulting oil (1.03 g) was chromatographed (from 9:1 hexane-EtOAc to 8: 2 hexane-EtOAc) to give compound **149** (630 g, 75 %) as a colorless oil.

Spectroscopic data for **149**

$[\alpha]^{22}_{D}$ –4.61 (*c* 1.65, MeOH).

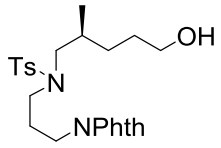
IR (film) 1773 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$, COSY, *g*-HSQC) δ 0.04 (s, 6H, CH_3Si), 0.88 [s, 9H, $(CH_3)_3$], 0.91 (d, *J* = 6.6 Hz, 3H, CH_3), 1.03-1.12 (m, 1H), 1.36-1.50 (m, 2H), 1.55-1.61 (m, 1H), 1.74 (m, 1H, H-4), 1.84-1.95 (m, 2H, C*H*$_2$$CH_2$N), 2.41 (s, 3H, CH_3Ts), 2.91 (d, *J* = 7.5 Hz, 2H, H-1), 3.12-3.17 (m, 2H, CH_2NTs), 3.56 (t, *J* = 6.5 Hz, 2H, H-5), 3.66 (t, *J* = 7.1 Hz, 2H, CH_2NPhth), 7.27 (d, *J* = 8.3 Hz, 2H, H-3Ts, H-5Ts), 7.64 (d, *J* = 8.3 Hz, 2H, H-2Ts, H-6Ts), 7.73 (dd, *J* = 5.4, 3.0 Hz, 2H, H-Phth), 7.84 (dd, *J* = 5.4, 3.0 Hz, 2H, H-Phth).

^{13}C NMR (100.6 MHz, $CDCl_3$) δ – 5.3 ($2CH_3Si$), 17.3 (CH_3), 18.2 [*C*$(CH_3)_3$], 21.5 (CH_3Ts), 25.9 [C(*C*$H_3)_3$], 27.9 (*C*$H_2$$CH_2$N), 30.1 (C-3), 30.3 (C-4), 31.9 (C-2), 35.6 (CH_2NPhth), 46.7 (CH_2NTs), 55.2 (C-1), 63.2 (C-5), 123.2 (CH-Phth), 127.1 (C-HTs), 129.6 (C-HTs), 131.9 (C-Phth), 133.9 (CH-Phth), 136.4 (C-4Ts), 143.1 (C-1Ts), 168.1 (CO).

HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{30}H_{45}N_2O_5SSi$ 573.2813; found 573.2813.

(*S*)-4-Methyl-5-{*N*-[3-(phthalimido)propyl]-*N*-tosylamino}-1-pentanol (150)



A solution of compound **149** (450 mg, 0.79 mol) in 1.0 N aqueous HCl (10 mL) was stirred at room temperature for 20 minutes. Then, the solution was concentrated to give alcohol **150** (360 mg, quantitative), which was used in the next step without purification.

Spectroscopic data for **150**

$[\alpha]^{22}_{D}$ –1.32 (*c* 1.12, MeOH).

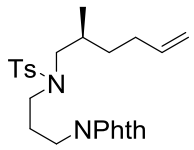
IR (film) 3542, 1770, 1716 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$, COSY, *g*-HSQC) δ 0.90 (d, *J* = 6.6 Hz, 3H, CH_3), 1.10-1.17 (m, 1H), 1.44-1.56 (m, 2H), 1.60-1.66 (m, 1H), 1.66-1.78 (m, 2H, H-4, OH), 1.89 (quint, *J* = 7.4 Hz, 2H, C*H*$_2$CH$_2$N), 2.40 (s, 3H, CH_3Ts), 2.85 (dd, *J* = 13.6, 7.5 Hz, 1H, H-5), 2.95 (dd, *J* = 13.6, 7.5 Hz, 1H, H-5), 3.14 (m, 2H, CH_2NTs), 3.62 (t, *J* = 6.2 Hz, 2H, H-1), 3.67 (t, *J* = 7.2 Hz, 2H, CH_2NPhth), 7.27 (d, *J* = 8.2 Hz, 2H, H-3Ts), 7.64 (d, *J* = 8.2 Hz, 2H, H-2Ts), 7.72 (m, 2H, H-Phth), 7.84 (m, 2H, H-Phth).

^{13}C NMR (100.6 MHz, $CDCl_3$) δ 17.4 (CH_3), 21.5 (CH_3Ts), 27.9 (*C*H_2CH$_2$N), 29.8 (CH_2), 30.1 (CH_2), 31.9 (CH), 35.8 (CH_2NPhth), 46.9 (CH_2NTs), 55.4 (C-5), 62.9 (C-1), 123.3 (CH-Phth), 127.2 (CHTs), 129.6 (CHTs), 131.9 (C-Phth), 134.0 (CH-Phth), 136.2 (C-4Ts), 143.2 (C-1Ts), 168.2 (CO).

HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{24}H_{31}N_2O_5S$ 459.1948; found 459.1941.

(*S*)-2-Methyl-*N*-[3-(phthalimido)propyl]-*N*-tosyl-5-hexenamine (151)



Dess–Martin reagent (220 mg, 0.52 mmol) was added to a solution of alcohol **150** (95 mg, 0.21 mmol) in anhydrous CH_2Cl_2 (2 mL), and the mixture was stirred at room temperature for 1.5 h. Then, saturated aqueous $Na_2S_2O_4$ (1 mL) and saturated aqueous $NaHCO_3$ (1 mL) were added, and the resulting mixture was stirred for 1 h. The aqueous layer was extracted with CH_2Cl_2, and the combined organic extracts were washed with brine, dried, filtered, and concentrated to give an aldehyde, which was used without purification in the next step:

^{1}H NMR (400 MHz, $CDCl_3$) δ 0.91 (d, *J* = 6.8 Hz, 3H, CH_3), 1.78-1.93 (m, 4H), 2.39-2.51 (m, 5H), 2.40 (s, 3H, CH_3Ts), 2.87 (dd, 1H, *J* = 13.6, 7.6 Hz, CH_2N), 2.98 (dd, *J* = 13.6, 7.2 Hz, 1H, CH_2N), 3.13-3.19 (m, 2H, CH_2N), 3.67 (t, *J* = 6.8 Hz, 2H, CH_2N), 7.27 (d, 2H, *J* = 8.2 Hz, H-Ts), 7.64 (d, *J* = 8.2 Hz, 2H, H-Ts), 7.75 (dd, *J* = 5.6, 3.2 Hz, 2H, H-Phth), 7.80 (dd, *J* = 5.6, 3.2 Hz, 2H, H-Phth), 9.75 (s, 1H, COH).

Then, from the above aldehyde (95 mg), *t*-BuOK (0.62 mL of a 1 M solution in THF, 0.62 mmol), and methyltriphenylphosphonium bromide (296 mg, 0.83 mmol) in anhydrous THF (5 mL), alkene **151** (66 mg, 70 %) was obtained as a colorless oil after flash chromatography (from 9:1 hexane-EtOAc to 85:15 hexane-EtOAc).

Spectroscopic data for **151**

$[\alpha]^{22}_{D}$ +2.71 (*c* 0.65, EtOH).

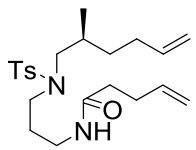
IR (film) 1772, 1712 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$, COSY, *g*-HSQC) δ 0.90 (d, *J* = 6.3 Hz, 3H, CH_3), 1.15 (m, 1H, H-3), 1.45 (m, 1H, H-3), 1.65 (m, 1H, H-2), 1.90 (m, 2H, C*H*$_2$CH_2N), 1.95 (m, 1H, H-4), 2.15 (m, 1H, H-4), 2.41 (s, 3H, CH_3Ts), 2.91 (m, 2H, H-1), 3.14 (m, 2H, CH_2NTs), 3.64 (m, 2H, CH_2NPhth), 4.86-4.99 (m, 2H, H-6), 5.73 (m, 1H, H-5), 7.26 (d, *J* = 8.2 Hz, 2H, H-3Ts, H-5Ts), 7.65 (d, *J* = 8.2 Hz, 2H, H-2Ts, H-6Ts), 7.72 (dd, *J* = 5.8, 3.3 Hz, 2H, H-Phth), 7.84 (dd, *J* = 5.8, 3.3 Hz, 2H, H-Phth).

^{13}C NMR (100.6 MHz, $CDCl_3$) δ 17.3 (CH_3), 21.4 (CH_3Ts), 27.9 (*C*H_2CH_2N), 31.0 (C-3), 31.5 (C-2), 33.4 (C-4), 35.8 (CH_2NPhth), 46.7 (CH_2NTs), 55.1 (C-1), 114.5 (C-6), 123.2 (CH-Phth), 127.2 (CHTs), 129.6 (CHTs), 132.2 (C-Phth), 133.9 (CH-Phth), 137.5 (C-4Ts), 138.5 (C-5), 143.1 (C-1Ts), 168.1 (CO).

HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{25}H_{31}N_2O_4S$ 455.1999; found 455.2024.

(*S*)-*N*-[3-(2-Methyl-*N*-tosyl-5-hexenylamino)propyl]-4-pentenamide (152)



A solution of hydrazine monohydrate (56 mg, 1.1 mmol) in ethanol (1.3 mL) was added to a solution of alkene **151** (506 mg, 1.1 mmol) in ethanol (4.5 mL), and the mixture was heated at reflux for 2.5 h. Insoluble material was removed by filtration, and the filtrate was concentrated to give the primary amine as a yellow oil (420 mg), which was used without purification in the next step:

^{1}H NMR (400 MHz, $CDCl_3$) δ 0.87 (d, *J* = 6.5 Hz, 3H, CH_3), 1.10-1.15 (m, 1H), 1.42-1.46 (m, 1H), 1.70-1.75 (m, 3H), 1.95-2.00 (m, 1H), 2.06-2.13 (m, 1H), 2.42 (s, 3H, CH_3Ts), 2.66 (br.s., 2H, NH_2), 2.80 (m, 2H, CH_2N), 2.87-2.90 (m, 2H, CH_2N), 3.12-3.19 (m, 2H, CH_2N), 4.91-5.00 (m, 2H, C*H*$_2$=CH), 5.70-5.75 (m, 1H, CH_2=C*H*), 7.20-7.30 (m, 2H, H-Ts), 7.60-7.70 (m, 2H, H-Ts).

4-Pentenoyl chloride (0.15 mL, 1.34 mmol) and Et_3N (0.2 mL, 1.45 mmol) were slowly added to a solution of the above amine in CH_2Cl_2 (3 mL), and the mixture was

stirred at room temperature for 2.5 h. The reaction was quenched with water, and the resulting mixture was extracted with CH_2Cl_2. The combined organic extracts were dried, filtered, and concentrated under vacuum to give an oil. Flash chromatography (from 9:1 hexane-EtOAc to 1:1 hexane-EtOAc) afforded dialkene **152** (224 mg, 50 %) as a colorless oil.

Spectroscopic data for **152**

$[\alpha]^{22}_D$ +1.9 (*c* 1.6, MeOH).

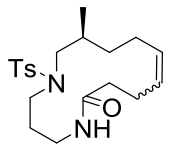
IR (film) 3305, 1644 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$, COSY, *g*-HSQC) δ 0.86 (d, *J* = 6.6 Hz, 3H, CH_3), 1.08-1.17 (m, 1H, CHC*H*$_2$), 1.40-1.49 (m, 1H, CHC*H*$_2$), 1.70-1.76 (m, 3H, C*H*$_2$CH$_2$N, CH), 1.92-2.00 (m, 1H, H-2), 2.07-2.16 (m, 1H, H-2), 2.28-2.31 (m, 2H, CH_2=CHC*H*$_2$), 2.38-2.41 (m, 2H, H-3), 2.43 (s, 3H, CH_3Ts), 2.84-2.95 (m, 2H, CHC*H*$_2$N), 3.10 (t, *J* = 6.7 Hz, 2H, TsNC*H*$_2$CH$_2$), 3.35 (m, 2H, C*H*$_2$NH), 4.93-5.10 (m, 4H, C*H*$_2$=CH), 5.73 (m, 1H, CH_2=C*H*), 5.84 (m, 1H, CH_2=C*H*), 6.36 (br.s, 1H, NH), 7.31 (d, *J* = 8.1 Hz, 2H, H-Ts), 7.66 (d, *J* = 8.1 Hz, 2H, H-Ts).

^{13}C NMR (100.6 MHz, $CDCl_3$) δ 17.2 (CH_3), 21.4 (CH_3Ts), 28.6 ($CH_2CH_2CH_2$), 29.5 (CH_2=CH*C*H$_2$), 30.8 (C-3), 31.4 (CH), 33.2 (*C*H$_2$CH$_2$CH=), 35.8 (C-2), 36.0 (CH_2NH), 46.8 (TsN*C*H$_2$CH$_2$), 55.9 (CH*C*H$_2$N), 114.6 (*C*H$_2$=CH), 115.3 (*C*H$_2$=CH), 127.0 (CH-Ts), 129.6 (CH-Ts), 135.9 (C-4Ts), 137.0 (CH_2=*C*H), 138.3 (CH_2=*C*H), 143.3 (C-1Ts), 172.4 (CO).

HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{22}H_{35}N_2O_3S$ 407.2363; found 407.2361.

(*S*)-13-Methyl-6-oxo-1-tosyl-1,5-diaza-9-cyclotetradecene (153)



A solution of **152** (101 mg, 0.25 mmol) in anhydrous CH_2Cl_2 (10 mL) was added to a solution of second-generation Grubbs catalyst (32 mg, 0.037 mmol) in CH_2Cl_2 (1.24 L) at reflux. The resulting mixture was stirred at reflux temperature for 14 h. The solvent was evaporated, and the resulting residue was chromatographed (from 8:2

hexane-EtOAc to 3:7 hexane-EtOAc) to yield a 91:9 (calculated by GC/MS) mixture of *E/Z* diastereoisomers **153** (72 mg, 77 %).

Spectroscopìc data for major diastereoisomer 153

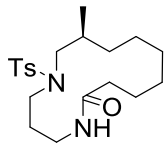
IR (film) 3300, 1647 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$, COSY, *g*-HSQC) δ 0.86 (d, *J* = 6.6 Hz, 3H, CH_3), 1.10-1.27 (m, 2H, H-4), 1.49-1.65 (m, 2H, H-3, H-13), 1.65-1.73 (m, 1H, H-13), 1.92-2.04 (m, 2H, C*H*$_2$CH=), 2.05-2.13 (m, 1H, H-9), 2.19-2.30 (m, 2H, C*H*$_2$CH=, H-9), 2.33-2.38 (m, 1H, C*H*$_2$CH=), 2.40 (s, 3H, CH_3Ts), 2.75 (dd, *J* = 12.6, 5.9 Hz, 1H, H-2), 2.86-2.90 (m, 1H, H-12), 2.95 (dd, *J* = 12.6, 9.1 Hz, 1H, H-2), 2.98-3.02 (m, 1H, H-14), 3.16-3.24 (m, 1H, H-12), 3.29-3.37 (m, 1H, H-14), 5.22-5.36 (m, 2H, C*H*=C*H*), 5.96 (br.s, 1H, NH), 7.26 (d, *J* = 8.2 Hz, 2H, H-3Ts, H-5Ts), 7.62 (d, *J* = 8.2 Hz, 2H, H-2Ts, H-6Ts).

^{13}C NMR (100.6 MHz, $CDCl_3$) δ 17.4 (CH_3), 21.4 (CH_3Ts), 26.9 (C-3), 28.0 (*C*H_2CH=), 28.3 (C-13), 28.9 (*C*H_2CH=), 32.0 (C-4), 36.2 (C-9), 36.4 (C-14), 44.8 (C-12), 53.5 (C-2), 127.0 (CH-Ts), 129.5 (CH=), 129.6 (CH-Ts), 131.7 (CH=), 136.5 (C-4Ts), 143.1 (C-1Ts), 172.4 (CO).

HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{20}H_{31}N_2O_3S$ 379.2053; found 379.2051.

(*S*)-13-Methyl-6-oxo-1-tosyl-1,5-diazacyclotetradecane (154)



A solution of alkene **153** (79 mg, 0.21 mmol) in anhydrous MeOH (7 mL) containing 10 % Pd-C (8 mg) was stirred under hydrogen at room temperature for 48 h. The catalyst was removed by filtration and washed with hot MeOH. The combined organic solutions were concentrated to give pure compound **154** (74 mg, 94 %) as a brown oil.

Spectroscopic data for **154**

$[\alpha]^{22}_D$ –12.7 (*c* 1.18, $CHCl_3$).

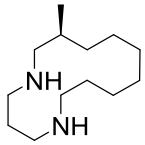
IR (film) 3410, 1643 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$, COSY, *g*-HSQC) δ 0.89 (d, *J* = 6.5 Hz, 3H, CH_3), 1.10-1.20 (m, 1H, 1H-CH_2), 1.22-1.35 (m, 6H, 3CH_2), 1.36-1.62 (m, 3H, CH_2, 1H-CH_2), 1.65-1.92 (m, 3H, H-3, CH_2), 2.10-2.27 (m, 2H, H-9), 2.42 (s, 3H, CH_3Ts), 2.76 (dd, *J* = 12.9, 5.5 Hz, 1H, H-2), 2.99 (dd, *J* = 12.9, 8.5 Hz, 1H, H-2), 2.95-2.98 (m, 1H, H-14), 3.07-3.14 (m, 2H, H-12), 3.42-3.54 (m, 1H, H-14), 6.10 (br.s, 1H, NH), 7.29 (d, *J* = 8.2 Hz, 2H, H-3Ts, H-5Ts), 7.65 (d, *J* = 8.2 Hz, 2H, H-2Ts, H-6Ts).

^{13}C NMR (100.6 MHz, $CDCl_3$) δ 17.1 (CH_3), 21.4 (CH_3Ts), 23.3 (CH_2), 24.3 (CH_2), 25.1 (CH_2), 25.8 (CH_2), 27.7 (C-3), 28.7 (CH_2), 30.9 (CH_2), 35.1 (C-9), 36.6 (C-14), 45.9 (C-12), 54.8 (C-2), 127.1 (CH-Ts), 129.6 (CH-Ts), 136.1 (C-4Ts), 143.2 (C-1Ts), 173.1 (CO).

HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{20}H_{33}N_2O_3S$ 381.2206; found 381.2207.

(*S*)-Haliclorensin



A solution of diazacycle **154** (74 mg, 0.19 mmol) in anhydrous THF (3.5 mL) was added to a suspension of $LiAlH_4$ (74 mg, 1.95 mmol) in anhydrous THF (4.5 mL) at 0 ºC, and the mixture was heated at reflux for 21 h. After cooling to room temperature, the reaction was quenched by water (7 mL), and the pH value was adjusted to 4 by adding 2 M aqueous HCl solution (2 mL). The mixture was extracted with Et_2O, and the aqueous phase was basified with a saturated aqueous solution of K_2CO_3 to reach pH 12. The solution was extracted with CH_2Cl_2, and the combined organic extracts were dried, filtered, and concentrated under vacuum to give a yellow oil. Flash chromatography (SiO_2 previously washed with 18:1:1 CH_2Cl_2-MeOH-NH_4OH; gradient from 19:1 CH_2Cl_2-MeOH to 17:3 CH_2Cl_2-MeOH) afforded **(*S*)-haliclorensin** (26 mg, 65 %) as a colorless oil.

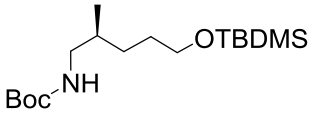
Spectroscopic data for **(*S*)-haliclorensin**

$[\alpha]^{22}_D$ –17.2 (*c* 0.5, MeOH); lit[69a] **$[\alpha]_D$** –2.2 (*c* 1.3, MeOH); lit[73] **$[\alpha]^{20}_D$** –19 (*c* 0.57, MeOH); lit[70] **$[\alpha]_D$** –18.5 (*c* 0.6, MeOH); lit[70] **$[\alpha]_D$** –8.5; lit[70] **$[\alpha]^{20}_D$** +7.0 (1M HCl); lit[72b] **$[\alpha]^{20}_D$** –18.2 (*c* 0.4, MeOH).

^{1}H NMR (400 MHz, CD_3OD, *g*-HSQC) δ 0.89 (d, *J* = 6.9 Hz, 3H, CH_3), 1.24-1.31 (m, 1H), 1.36-1.51 (m, 9H), 1.55-1.61 (m, 2H), 1.70-1.77 (m, 3H), 2.40 (dd, *J* = 11.8, 9.7 Hz, 1H), 2.55 (dd, *J* = 11.8, 3.8 Hz, 1H), 2.58-2.63 (m, 1H), 2.64-2.68 (m, 2H), 2.71-2.73 (m, 2H), 2.82 (ddd, *J* = 11.2, 6.8, 4.0 Hz, 1H).

^{13}C NMR (100.6 MHz, CD_3OD) δ 18.8 (CH_3), 22.0 (CH_2), 23.2 (CH_2), 24.7 (CH_2), 27.3 (CH_2), 27.7 (CH_2), 29.3 (CH_2), 30.5 (CH), 32.7 (CH_2), 47.5 (CH_2N), 49.8 (CH_2N), 50.5 (CH_2N), 55.6 (CH_2N).

(*S*)-2-Methyl-1-[(*tert*-butoxycarbonyl)amino]-5-[(*tert*-butyldimethylsilyl)oxy]pentanol (155)



tert-Butyldimethylsilyl chloride (263 mg, 1.74 mmol) was added to a solution of alcohol **95** (252 mg, 1.16 mmol) and imidazole (118 mg, 1.74 mmol) in anhydrous CH_2Cl_2 (10 mL), and the mixture was heated at reflux for 15 h. The reaction was quenched by a saturated aqueous solution of NH_4Cl, and the mixture was extracted with CH_2Cl_2. The combined organic extracts were dried, filtered, and concentrated to give protected alcohol **155** (300 mg, 94%).

Spectroscopic data for **155**

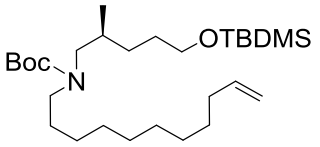
$[\alpha]^{22}_D$.

^{1}H NMR (400 MHz, $CDCl_3$, COSY, *g*-HSQC) δ 0.05 (s, 6H, CH_3Si), 0.89 (d, *J* = 6.8 Hz, 3H, CH_3), 0.89 [s, 9H, $(CH_3)_3$], 1.09-1.18 (m, 1H, H-3), 1.32-1.40 (m, 1H, H-3), 1.44 [s, 9H, $(CH_3)_3$], 1.48-1.61 (m, 3H, H-2, H-4), 2.89 (ddd, *J* = 13.0, 6.0, 6.0 Hz, 1H, H-1), 2.99 (ddd, *J* = 13.0, 6.0, 6.0 Hz, 1H, H-1), 3.59 (t, *J* = 6.4 Hz, 2H, H-5), 4.57 (br.s, 1H, NH).

^{13}C NMR (100.6 MHz, $CDCl_3$) δ –5.3 ($2CH_3Si$), 17.5 (CH_3), 18.3 [*C*$(CH_3)_3$], 25.9 [C(*C*$H_3)_3$], 28.4 [C(*C*$H_3)_3$], 30.1 (C-4), 30.3 (C-3), 33.4 (C-2), 46.5 (C-1), 63.3 (C-5), 79.0 [*C*$(CH_3)_3$], 156.1 (CO).

HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for

(*S*)-5-[(*tert*-Butyldimethylsilyl)oxy]-2-methyl-*N*-[undec-10-en-1yl]-*N*-[(t*ert*-butoxycarbonyl)] (156)



NaH (28 mg, 1.09 mmol) was added to a suspension of carbamate **155** (562 mg, 1.46 mmol) in anhydrous DMF (4 mL) at room temperature, and the resulting mixture was stirred at this temperature for 2 h. Then, 11-bromoundec-1-ene (0.18 mL, 1.09 mmol) was added and the stirring was continued at 75 ºC for 3 h 30. The mixture was poured into saturated aqueous $NaHCO_3$ and extracted with EtOAc. The combined organic extracts were dried, filtered, and concentrated. The resulting residue was chromatographed (95:5 hexane-EtOAc) to give alkene **156** (87 g, 25 %) as a yellow oil.

Spectroscopic data for **156**

$[\alpha]^{22}_{D}$ –2.2 (*c* 0.5, MeOH).

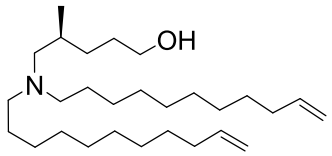
IR (film) 3354, 3077, 1708, 1641, 1463 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$, COSY, *g*-HSQC) δ 0.05 (s, 6H, CH_3Si), 0.89 (d, *J* = 6.8 Hz, 3H, CH_3), 0.89 [s, 9H, $(CH_3)_3$], 1.09-1.19 (m, 2H, CH_2), 1.23-1.39 (m, 16 H, CH_2), 1.44 [s, 9H, $(CH_3)_3$], 1.46-1.65 (m, 3 H, CH, CH_2), 2.00 (dd, *J* = 14.4, 6.8 Hz, $CH_2CH=CH_2$), 2.85-3.07 (m, 4H, CH_2N), 3.54 (t, *J* = 6.4 Hz, 2H, CH_2O), 4.86-4.97 (m, 2H, $CH_2=CH$), 5.71-5.81 (m,1H, $CH_2=CH$).

^{13}C NMR (100.6 MHz, $CDCl_3$) δ –5.3 ($2CH_3Si$), 17.5 [$C(CH_3)_3$], 18.3 (CH_3), 25.9 [$C(CH_3)_3$], 28.4 [$C(CH_3)_3$], 28.9 (CH_2), 29.1 (CH_2), 29.3 (CH_2), 29.4 (CH_2), 29.5 (CH_2), 30.1 (CH_2), 30.2 (CH_2), 30.3 (CH_2), 33.4 (CH), 33.8 ($CH_2CH=CH_2$), 46.5 (CH_2N), 46.8 (CH_2N), 63.3 (CH_2O), 78.9 [$C(CH_3)_3$], 114.1 ($CH_2=CH$), 139.2 ($CH_2=CH$), 156.1, 156.9 (CO).

HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for

(*S*)-5-(Di(undec-10-en-1-yl)amino)-4-methylpentan-1-ol (157)



A solution of aminodiol **52** (50 mg, 0.21 mmol) in anhydrous MeOH (10 mL) containing 20 % $Pd(OH)_2$ (10 mg) was hydrogenated at 68 °C for 18 h under 10 bar of pressure. The catalyst was removed by filtration and washed with hot MeOH. The combined organic solutions were concentrated, and the resulting residue was dissolved in anhydrous CH_3CN (1 mL). Then, 11-bromoundec-1-ene (0.05 mL, 0.23 mmol), K_2CO_3 (58 mg 0.42 mmol) and KI (77 mg, 0.46 mmol) were added and the stirring was continued at 60 ºC for 36 h. CH_2Cl_2 (2 mL) was added at room temperature and the organic phase was washed with 10% aqueous NaOH, dried, filtered, and concentrated to give an oil. Purification by flash chromatography (from 8:2 hexane-EtOAc to 1:1 hexane-EtOAc) afforded amine **157** (50 mg, 57 %) as a colorless oil.

Spectroscopic data for **157**

$[\alpha]^{22}_D$ +4.16 (*c* 0.95, MeOH).

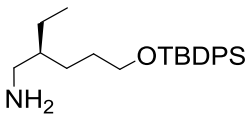
IR (film) cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$, COSY, *g*-HSQC) δ 1.06 (d, *J* = 6.8 Hz, 3H, CH_3), 1.24-1.39 (m, 24H, CH_2), 1.50-1.60 (m, 2H, CH_2), 1.65-1.75 (m, 6H, CH_2), 1.78-1.86 (m, 1H, CH), 2.01-2.05 (m, 4H, C*H*$_2$CH=CH_2), 2.69 (dd, *J* = 13.2, 5.6 Hz, 1H, CH_2N), 2.83 (dd, *J* = 13.2, 7.6 Hz, 1H, CH_2N), 2.88-2.98 (m, 4H, CH_2N), 3.65 (t, *J* = 6.0 Hz, 2H, CH_2O), 4.91-5.01 (m, 4H, C*H*$_2$=CH), 5.80 (m, 2H, CH_2=C*H*).

^{13}C NMR (100.6 MHz, $CDCl_3$) δ 18.5 (CH_3), 23.3 (CH_2), 26.8 (CH_2), 28.7 (CH_2), 28.8 (CH_2), 28.9 (CH_2), 29.0 (CH_2), 29.1 (CH_2), 29.2 (CH_2), 29.3 (CH_2), 30.9 (CH), 33.6 (*C*H_2CH=CH_2), 53.7 (CH_2N), 59.5 (CH_2N), 61.5 (CH_2O), 114.1 (*C*H_2=CH), 139.2 (CH_2=*C*H).

HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{28}H_{56}NO$ 422.4356; found 422.4358.

(*S*)-5-[(tert-Butyldimethylsilyl)oxy]-2-ethyl-1-pentanamine (159)



A solution of aminodiol **14** (241 mg, 0.96 mmol) in anhydrous MeOH (10 mL) containing 20 % $Pd(OH)_2$ (48 mg) was hydrogenated at 68 °C for 18 h under 10 bar of pressure. The catalyst was removed by filtration and washed with hot MeOH. The combined organic solutions were concentrated, and the resulting residue was dissolved in CH_2Cl_2 (3 mL). Imidazole (271 mg, 3.98 mmol) and TBDPSCl (1.093 g, 3.98 mmol) were added, and the mixture was allowed to react at room temperature for 12 h, and at 40 °C for 4 h. The reaction was quenched by the addition of saturated aqueous NH_4Cl, and the mixture was extracted with CH_2Cl_2. The combined organic extracts were dried, filtered, and concentrated to give an oil. Purification by flash chromatography (from 95:5 hexane-EtOAc to EtOAc) afforded pure amine **159** (115 mg, 32 %) as a yellow oil.

Spectroscopic data for **159**

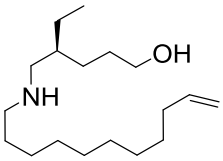
$[\alpha]^{22}_{D}$ –5.78 (*c* 0.32, $CHCl_3$).

^{1}H NMR (400 MHz, $CDCl_3$, COSY, *g*-HSQC) δ 0.88 (t, *J* = 7.4 Hz, 3H, CH_3CH$_2$), 1.04 [s, 9H, $(CH_3)_3$], 1.32-1.44 (m, 2H, H-3, CH_3CH_2), 1.45-1.58 (m, 4H, H-3, H-4, CH_3CH_2), 1.68-1.77 (m, 1H, H-2), 2.79 (dd, *J* = 7.8, 12.8 Hz, 1H, H-1), 2.89 (dd, *J* = 12.8, 5.4 Hz, 1H, H-1), 3.64 (t, *J* = 7.4 Hz, 2H, H-5), 7.34-7.43 (m, 6H, ArH), 7.63-7.66 (m, 2H, ArH), 7.70-7.73 (m, 2H, ArH).

^{13}C NMR (100.6 MHz, $CDCl_3$) δ 10.2 (CH_3CH_2), 19.3 [$C(CH_3)_3$], 23.6 (CH_2), 26.7 (CH_2), 27.0 [$C(CH_3)_3$], 29.2 (C-4), 37.5 (C-2), 42.7 (C-1), 63.9 (C-5), 127.8 (C-Ar), 127.8 (C-Ar), 129.7 (C-p), 129.7 (C-p), 134.0 (C-*i*), 134.9 (C-Ar), 135.4 (C-*i*), 135.7 (C-Ar).

HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for

(*S*)-4-Ethyl-5-(10-undecenylamino)-1-pentanol (160)



A solution of aminodiol **14** (370 mg, 1.47 mmol) in anhydrous MeOH (10 mL) containing 20 % $Pd(OH)_2$ (74 mg) was hydrogenated at 68 °C for 18 h under 10 bar of pressure. The catalyst was removed by filtration and washed with hot MeOH. The combined organic solutions were concentrated, and the resulting residue was dissolved in CH_2Cl_2 (1.3 mL). 10-Undecenal (0.58 mL, 2.94 mmol), $NaBH(AcO)_3$ (936 mg, 4.42 mmol) and AcOH (0.13 mL) were added, and the mixture was allowed to react at room temperature for 12 h. The mixture was poured into saturated aqueous $NaHCO_3$, and the organic layer was dried, filtered, and concentrated. The resulting residue was chromatographed (from 8:2 hexane-EtOAc to 8:2 EtOAc-MeOH) to give alkene **160** (104 mg, 25%) as a colorless oil.

Spectroscopic data for **160**

$[\alpha]^{22}_D$ –2.15 (*c* 0.3, MeOH).

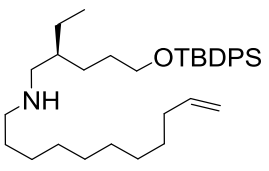
IR (film) 2926, 2855, 1461, 1061 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$, COSY, *g*-HSQC) δ 0.89 (t, *J* = 7.4 Hz, 3H, C*H*$_3$CH$_2$), 1.21-1.69 (m, 21H, H-4, 10CH$_2$), 1.99-2.05 (m, 2H, CH$_2$=CHC*H*$_2$), 2.56-2.61 (m, 1H, H-5), 2.66-2.75 (m, 3H, H-5, CH$_2$N), 3.62 (m, 2H, H-1), 4.43 (br.s, 1H, NH), 4.89-5.00 (m, 2H, C*H*$_2$=CH), 5.79 (dddd, *J* = 16.9, 10.2, 10.2, 6.7 Hz, 1H, CH$_2$=C*H*).

^{13}C NMR (100.6 MHz, $CDCl_3$) δ 11.0 (*C*H$_3$CH$_2$), 24.9 (CH$_2$), 27.1 (CH$_2$), 27.1 (CH$_2$), 28.3 (CH$_2$), 28.6 (CH$_2$), 28.9 (CH$_2$), 29.1 (CH$_2$), 29.3 (CH$_2$), 29.3 (CH$_2$), 29.5 (CH$_2$), 33.8 (CH$_2$=CH*C*H$_2$), 37.7 (C-4), 49.5 (CH$_2$N), 52.2 (C-5), 62.1 (C-1), 114.1 (*C*H$_2$=CH), 139.1 (CH$_2$=*C*H).

HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{18}H_{38}NO$ 284.2948; found 284.2939.

(*S*)-5-((tert-butyldimethylsilyl)oxy)-2-ethyl-propyl-*N*-(10-undec-10-en-1yl) (161)



10-Undecenal (0.48 mL, 0.24 mmol) was added to a suspension of aminodiol **159** (74 mg, 0.20 mmol) and $NaBH_3CN$ (25 mg, 0.40 mmol) in anhydrous CH_2Cl_2 (2.3 mL), and the reaction mixture was allowed to react at room temperature for 12 h. The

reaction was quenched by water, and the mixture was extracted with CH_2Cl_2. The combined organic extracts were dried, filtered, and concentrated. The resulting residue was chromatographed (from 98:2 hexane-EtOAc to EtOAc) to give alkene **161** (30 mg, 29%) as a colorless oil.

Spectroscopic data for **161**

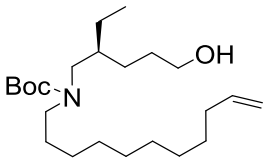
$[\alpha]^{22}_D$ –12.3 (*c* 0.225, MeOH).

^{1}H NMR (400 MHz, $CDCl_3$, COSY, *g*-HSQC) δ 0.90 (t, *J* = 7.4 Hz, 3H, C*H*$_3$CH$_2$), 1.05 [s, 9H, $(CH_3)_3$], 1.24-1.58 (m, 18H, 9CH_2), 1.65-1.77 (m, 3H, H-2, H-4), 2.01-2.06 (m, 2H, CH_2=CHC*H*$_2$), 2.81-2.84 (m, 2H, H-5), 2.88-2.96 (m, 2H, CH_2N), 3.66-3.70 (m, 2H, H-1), 4.91-5.01 (m, 2H, C*H*$_2$=CH), 5.80 (m, 1H, CH_2=C*H*), 7.32-7.55 (m, 6H, ArH), 7.63-7.67 (m, 4H, ArH).

^{13}C NMR (100.6 MHz, $CDCl_3$) δ 10.2 (*C*H$_3$CH$_2$), 19.3 [*C*$(CH_3)_3$], 23.1(CH_2), 23.7(CH_2), 25.8(CH_2), 26.7 (CH_2), 26.8 (CH_2), 27.0 [C(*C*H$_3$)$_3$], 29.0 (CH_2), 29.1 (CH_2), 29.2 (CH_2), 29.4 (CH_2), 29.8 (CH_2), 33.9 (CH_2=CH*C*H$_2$), 36.3 (C-4), 49.0 (CH_2N), 51.6 (C-5), 63.8 (C-1), 114.3 (*C*H$_2$=CH), 127.8 (C-o*), 129.8 (C-p), 133.9 (C-*ipso*), 135.6 (C-m*), 139.3 (CH_2=*C*H).

HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for

(*S*)-4-Ethyl-5-[*N*-(*tert*-butoxyC-Arbonyl)-*N*-(10-undecenyl)amino]-1-pentanol (162)



Et_3N (0.04 mL, 0.030 mmol) was added to a solution of **160** (82 mg, 0.29 mmol) and di-*tert*-butyl diC-Arbonate (69 mg, 0.31 mmol) in anhydrous MeOH (1.5 mL), and the reaction mixture was allowed to react at room temperature for 12 h. The reaction was quenched by water, and the organic layer was dried, filtered, and concentrated, to give pure amine **162** (95 mg, 85%), as a colorless oil.

Spectroscopic data for **162**

$[\alpha]^{22}_{D}$ –0.82 (*c* 0.6, MeOH).

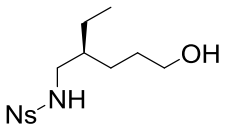
IR (film) 3453, 1694 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$, COSY, *g*-HSQC) δ 0.87 (t, *J* = 7.4 Hz, 3H, C*H*$_3$CH$_2$), 1.22-1.64 (m, 30H, C(CH$_3$)$_3$, H-4, 10CH$_2$), 2.00-2.05 (m, 2H, CH$_2$=CHC*H*$_2$), 3.00-3.07 (m, 1H, H-5), 3.08-3.18 (m, 3H, H-5, CH$_2$N), 3.54-3.64 (m, 2H, H-1), 4.89-5.00 (m, 2H, C*H*$_2$=CH), 5.79 (dddd, *J*= 16.9, 10.2, 10.2, 6.7 Hz, 1H, CH$_2$=C*H*).

^{13}C NMR (100.6 MHz, $CDCl_3$) δ 10.8 (*C*H$_3$CH$_2$), 26.9 (CH$_2$), 28.5 [C(*C*H$_3$)$_3$], 28.9 (CH$_2$), 29.0 (CH$_2$), 29.1 (CH$_2$), 29.3 (2CH$_2$), 29.4 (2CH$_2$), 29.5 (CH$_2$), 33.7 (CH$_2$=CH*C*H$_2$), 38.1 (C-4), 47.5 (CH$_2$N), 50.3 (C-5), 63.1 (C-1), 79.1 [*C*(CH$_3$)$_3$], 114.0 (*C*H$_2$=CH), 139.1 (CH$_2$=*C*H), 156.0 (N*C*O).

HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{23}H_{46}NO_3$ 384.3472; found 384.3466.

(*S*)-4-Ethyl-5-[(2-nitrobenzenesulfonyl)amino]-1-pentanol (163)



A solution of aminodiol **14** (1.15 g, 4.56 mmol) in anhydrous MeOH (25 mL) containing 20 % Pd(OH)$_2$ (230 mg) was hydrogenated at 68 °C for 18 h under 10 bar of pressure. The catalyst was removed by filtration and washed with hot MeOH. The combined organic solutions were concentrated, and the resulting residue was dissolved in anhydrous CH_2Cl_2 (16 mL). 2-Nitrobenzenesulfonyl chloride (1.12 g, 5.0 mmol) and Et_3N (0.7 mL, 5.0 mmol) were added, and the mixture was allowed to react at room temperature for 18 h. The solvent was removed under reduced pressure, and the residue was chromatographed (from 7:3 hexane-EtOAc to EtOAc) to give alcohol **163** (1.09 g, 76 %) as a colorless oil.

Spectroscopic data for **163**

$[\alpha]^{22}_{D}$ +0.95 (*c* 0.84, MeOH).

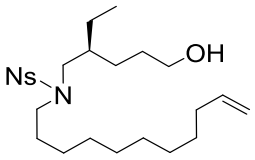
IR (film) 3348 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$, COSY, *g*-HSQC) δ 0.84 (t, *J* = 7.6 Hz, 3H, CH_3), 1.30-1.40 (m, 4H, H-3, CH_3CH_2), 1.47-1.54 (m, 3H, H-2, H-4), 1.65 (br.s, 1H, OH), 3.02 (dt, *J* = 6.1, 3.7 Hz, 2H, H-5), 3.60 (t, *J* = 6.4 Hz, 2H, H-1), 5.41 (t, *J* = 6.0 Hz, 1H, NH), 7.76 (m, 2H, H-5Ns, H-6Ns), 7.85 (m, 1H, H-4Ns), 8.13 (m, 1H, H-3Ns).

^{13}C NMR (100.6 MHz, $CDCl_3$) δ 10.7 (CH_3), 23.9 (CH_3CH_2), 26.9 (C-3), 29.3 (C-2), 33.1 (C-4), 46.2 (C-5), 62.8 (C-1), 125.3, 131.1 (C-3Ns, C-6Ns), 132.7 (C-4Ns), 133.5 (C-1Ns), 133.6 (C-5Ns), 148.0 (C-2Ns).

HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{13}H_{21}N_2O_5S$ 317.1166; found 317.1161.

(*S*)-4-Ethyl-5-[(2-nitrobenzenesulfonyl)amino]-5-(10-undecenyl)pentanol (164)



11-Bromo-1-undecene (0.80 mL, 3.65 mmol) was added to a suspension of alcohol **163** (1.05 g, 3.3 mmol) and Cs_2CO_3 (1.3 g, 3.98 mmol) in anhydrous DMF (25 mL), and the resulting mixture was stirred at 55 ºC for 3 h. The mixture was cooled to room temperature, poured into brine, and extracted with Et_2O. The combined organic extracts were dried, filtered, and concentrated to give an oil. Flash chromatography (7:3 hexane-EtOAc) afforded alkene **164** (1.30 g, 84%) as a colorless oil.

Spectroscopic data for **164**

$[\alpha]^{22}_D$ +1.82 (*c* 0.7, CH_2Cl_2).

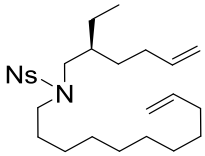
^{1}H NMR (400 MHz, $CDCl_3$, COSY, *g*-HSQC) δ 0.85 (t, *J* = 7.6 Hz, 3H, CH_3), 1.19-1.37 (m, 16H, $8CH_2$), 1.40-1.65 (m, 5H, H-4, CH_2, CH_2CH_3), 2.02 (m, 2H, CH_2=CHCH_2), 3.19-3.25 (m, 4H, H-5, CH_2N), 3.57 (t, *J* = 6.8 Hz, 2H, H-1), 4.95 (m, 2H, CH_2=CH), 5.80 (m, 1H, CH_2=C*H*), 7.62 (m, 1H, H-4Ns), 7.67 (m, 2H, C-5Ns, C-6Ns), 7.98 (m, 1H, H-3Ns).

^{13}C NMR (100.6 MHz, $CDCl_3$) δ 10.4 (CH_3), 23.2 (CH_2), 26.3 (CH_2), 26.6 (CH_2), 27.6 (CH_2), 28.8 (CH_2), 29.0 (CH_2), 29.1 (CH_2), 29.2 (CH_2), 29.3 (CH_2), 29.4 (CH_2), 33.6 (CH_2=CHCH_2), 36.5 (C-4), 47.1 (CH_2N), 50.7 (C-5), 62.8 (C-1), 114.0 (CH_2=CH),

123.3 (C-3Ns), 130.6 (C-6Ns), 131.4 (C-4Ns), 133.3 (C-5Ns), 133.4 (C-1Ns), 139.0 (CH_2=*C*H), 148.0 (C-2Ns).

HRMS (ESI-TOF) m/z: $[M + H]^+$ calcd for $C_{24}H_{41}N_2O_5S$ 469.2731; found 469.2731.

N-[2-Ethyl-5-hexenyl)-*N*-(2-nitrobenzenesulfonyl)-10-undecenamine (165)



Dess–Martin reagent (2.35 g, 5.55 mmol) was added to a solution of alcohol **164** (1.3 g, 2.77 mmol) in anhydrous CH_2Cl_2 (21 mL), and the mixture was stirred at room temperature for 1.5 h. Then, saturated aqueous $Na_2S_2O_4$ (0.75 mL) and saturated aqueous $NaHCO_3$ (0.75 mL) were added, and the resulting mixture was stirred for 1 h. The aqueous layer was extracted with CH_2Cl_2, and the combined organic extracts were washed with brine, dried, filtered, and concentrated to give an aldehyde, which was used without purification in the next step.

t-BuOK (13.8 mL of a 1 M solution in THF, 13.8 mmol) was added to a solution of methyltriphenylphosphonium bromide (6.92 g, 19.4 mmol) in anhydrous THF (70 mL) at room temperature, and the mixture was stirred for 1 h. Then, a solution of the above aldehyde in anhydrous THF (10 mL) was added via cannula, and the resulting mixture was stirred at room temperature for 3 h. Saturated aqueous NH_4Cl was added, and the resulting mixture was extracted with EtOAc. The extracts were dried, filtered, and concentrated. The residue was chromatographed (9:1 hexane-EtOAc) to give dialkene **165** (592 mg, 47 %) as a colorless oil.

Spectroscopic data for **165**

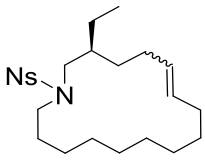
$[\alpha]^{22}_D$ +4.09 (*c* 2.1, MeOH).

^{1}H NMR (400 MHz, $CDCl_3$, COSY, *g*-HSQC) δ 0.84 (t, *J* = 7.5 Hz, 3H, CH_3), 1.14-1.39 (m, 16H, 8CH_2), 1.41-1.49 (m, 2H, CH_2), 1.54-1.64 (m, 1H, CH), 1.95-2.10 (m, 4H, CH_2=CHCH_2), 3.14-3.26 (m,4H, 2CH_2N), 4.91-5.02 (m, 4H, CH_2=CHCH_2), 5.74 (qt, *J* = 16.9, 10.0, 6.7, 6.7 Hz, 1H, CH_2=C*H*), 5.80 (qt, *J* = 16.9, 10.1, 6.7, 6.7 Hz, 1H, CH_2=C*H*), 7.59-7.62 (m, 1H, H-3Ns), 7.63-7.70 (m, 2H, H-5Ns, H-6Ns), 7.99-8.03 (m, 1H, H-4Ns).

^{13}C NMR (100.6 MHz, $CDCl_3$) δ 10.3 (CH_3), 23.2 (CH_2), 26.6 (CH_2), 27.5 (CH_2), 28.9 (CH_2), 29.0 (CH_2), 29.1 (CH_2), 29.3 (CH_2), 29.4 (CH_2), 29.5 (CH_2), 30.6 (CH_2=CH*C*H_2), 33.8 (CH_2=CH*C*H_2), 36.0 (CH), 47.0 (CH_2N), 50.7 (CH_2N), 114.1 (*C*H_2=CH), 114.7 (*C*H_2=CH), 124.1 (C-3Ns), 130.9 (C-6Ns), 131.4 (C-4Ns), 133.2 (C-5Ns), 133.9 (C-1Ns), 138.5 (CH_2=*C*H), 139.1 (CH_2=*C*H), 148.0 (C-2Ns).

HRMS (ESI-TOF) m/z: $[M + H]^+$ calcd for $C_{25}H_{41}N_2O_4S$ 465.2782; found 465.2776.

(*S*)-3-Ethyl-1-(2-nitrobenzenesulfonyl)azacyclohexadec-6-ene (166)



A solution of **165** (70 mg, 0.15 mmol) in anhydrous CH_2Cl_2 (15 mL) was added to a solution of second-generation Grubbs catalyst (19 mg, 0.15 mmol) in CH_2Cl_2 (750 mL) at reflux. The resulting mixture was stirred at reflux temperature for 14 h. The solvent was evaporated, and the resulting residue was chromatographed (95:5 hexane-EtOAc) to yield a 88:12 (calculated by GC/MS) mixture of *E/Z* diastereoisomers **166** (46 mg, 70 %).

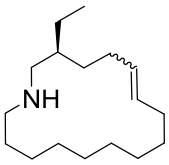
Spectroscopic data for major diastereoisomer **166**

^{1}H NMR (400 MHz, $CDCl_3$, COSY, *g*-HSQC) δ 0.83 (t, *J* = 7.5 Hz, 3H, CH_3), 1.00-1.11 (m, 1H, H-4), 1.18-1.44 (m, 17H, H-4, 8CH_2), 1.46-1.51 (m, 2H, CH_2), 1.67-1.80 (m, 1H, H-3), 1.97-2.19 (m, 4H, H-5, H-8), 3.07 (dd, *J* = 13.8, 7.5 Hz, H-2), 3.11-3.15 (m, 1H, H-16), 3.21-3.26 (m, 1H, H-16), 3.28 (dd, *J* = 13.8, 7.5 Hz, H-2), 5.25-5.41 (m, 2H, H-6, H-7), 7.57-7.62 (m, 1H, H-3Ns), 7.63-7.73 (m, 2H, H-5Ns, H-6Ns), 7.93-8.04 (m, 1H, H-4Ns).

^{13}C NMR (100.6 MHz, $CDCl_3$) δ 9.6 (CH_3), 21.9 (CH_2), 24.3 (CH_2), 25.7 (CH_2), 26.1 (CH_2), 26.1 (CH_2), 26.7 (CH_2), 26.7 (CH_2), 27.3 (CH_2), 28.8 (CH_2=CH*C*H_2), 29.6 (CH_2), 30.9 (CH_2=CH*C*H_2), 33.3 (C-3), 46.7 (C-16), 51.3 (C-2), 124.0 (C-3Ns), 130.2 (CH=), 130.7 (C-6Ns), 131.3 (C-4Ns), 131.4 (C-5Ns), 133.2 (CH=), 133.4 (C-1Ns), 148.1 (C-2Ns).

HRMS (ESI-TOF) m/z: $[M + H]^+$ calcd for $C_{23}H_{37}N_2O_4S$ 437.2469; found 437.2459.

(*S*)-3-Ethylazacyclohexadec-6-ene (167)



K_2CO_3 (82 mg, 0.59 mmol) and thiophenol (0.024 mL, 0.24 mmol) were added to a solution of **166** (86 mg, 0.20 mmol) in anhydrous DMF (4 mL), and the mixture was stirred at room temperature for 14 h. The reaction was quenched by the addition of aqueous 2 M NaOH, and the resulting mixture was extracted with CH_2Cl_2. The combined organic extracts were dried, filtered, and evaporated. The resulting residue was chromatographed (from 95:5 hexane-EtOAc to 8:2 EtOAc-Et_3N) to afford compound **167** (22 mg, 45 %) as a 75:25 (calculated by GC/MS) mixture of *E/Z* diastereoisomers as a brown oil.

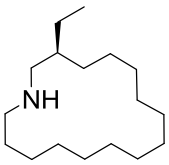
Spectroscopic data for major diastereoisomer **167**

^{1}H NMR (400 MHz, $CDCl_3$, COSY, *g*-HSQC) δ 0.87 (t, *J* = 7.5 Hz, 3H, CH_3), 1.25-1.44 (m, 16H, 8CH_2), 1.47-1.56 (m, 3H, CH_2), 1.94-2.12 (m, 4H, H-5, H-8), 2.41 (dd, *J* = 12.1, 7.5 Hz, 1H, H-2), 2.51-2.57 (dd, *J* = 12.0, 6.4 1H, H-16), 2.52-2.58 (dd, *J* = 12.1, 5.9 Hz, 1H, H-2), 2.62-2.68 (dd, *J* = 12.0, 5.7 Hz, 1H, H-16), 5.36-5.39 (m, 2H, H-6, H-7).

^{13}C NMR (100.6 MHz, $CDCl_3$) δ 10.8 (CH_3), 24.4 (CH_2), 25.2 (CH_2), 26.2 (CH_2), 26.3 (CH_2), 27.2 (CH_2), 27.3 (CH_2), 28.0 (CH_2), 28.2 (CH_2), 29.1 (CH_2=CH*C*H_2), 30.8 (CH_2), 31.8 (CH_2=CH*C*H_2), 36.9 (C-3), 47.6 (C-16), 52.3 (C-2), 130.8 (CH=), 130.9 (CH=).

HRMS (ESI-TOF) m/z: $[M + H]^+$ calcd for $C_{17}H_{34}N$ 252.2686; found 252.2689.

(*S*)-3-Ethylazacyclohexadecane (168)



A solution of alkene **167** (19 mg, 0.076 mmol) in anhydrous MeOH (10 mL) containing 25% Pd/C (5 mg) was hydrogenated at room temperature for 14 h under 10 bar of pressure. The catalyst was removed by filtration and washed with hot MeOH, and the combined organic solutions were concentrated. Flash chromatography (from 95:5 hexane-EtOAc to 8:2 EtOAc-Et_3N) of the residue gave **168** (8 mg, 50 %) as a brown oil.

Spectroscopic data for **168**

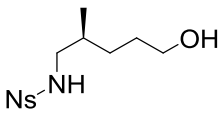
$[\alpha]^{22}_D$ –6.75 (*c* 0.15, MeOH).

^{1}H NMR (300 MHz, $CDCl_3$) δ 0.90 (t, *J* = 7.5 Hz, 3H, CH_3), 1.25-1.41 (m, 24H, $12CH_2$), 1.50-1.70 (m, 3H, H-3, CH_2), 2.40 (m, 2H, H-2), 2.60-2.85 (m, 2H, H-16).

^{13}C NMR (100.6 MHz, $CDCl_3$) δ 10.8 (CH_3), .24.8 (CH_2), 24.9 (CH_2), 25.0 (CH_2), 26.0 (CH_2), 26.1 (CH_2), 26.2 (CH_2), 26.3 (CH_2), 26.4 (CH_2), 26.5 (CH_2), 27.1 (CH_2), 27.4 (CH_2), 29.7 (CH_2), 29.8 (CH_2), 35.6 (C-3), 46.1 (C-16), 49.1 (C-2).

HRMS (ESI-TOF) m/z: $[M + H]^+$ calcd for $C_{17}H_{36}N$ 254.2842; found 254.2842.

(*S*)-4-Methyl-5-[(2-nitrobenzenesulfonyl)amino]-1-pentanol (169)



A solution of aminodiol **52** (1.36 g, 5.73 mmol) in anhydrous MeOH (35 mL) containing 20 % $Pd(OH)_2$ (272 mg) was hydrogenated at 68 °C for 18 h under 10 bar of pressure. The catalyst was removed by filtration and washed with hot MeOH. The combined organic solutions were concentrated, and the resulting residue was dissolved in anhydrous CH_2Cl_2 (19 mL). 2-Nitrobenzenesulfonyl chloride (1.4 g, 6.3 mmol) and Et_3N (0.88 mL, 6.3 mmol) were added, and the mixture was allowed to react at room temperature for 18 h. The solvent was removed under reduced pressure, and the residue was chromatographed (from 7:3 hexane-EtOAc to EtOAc) to give alcohol **169** (1.25 g, 72 %) as a colorless oil.

Spectroscopic data for **169**

$[\alpha]^{22}_{D}$ +2.66 (*c* 1.05, MeOH).

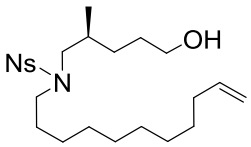
IR (film) 3349 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$, COSY, *g*-HSQC) δ 0.93 (d, *J* = 6.4 Hz, 3H, CH_3), 1.22-1.28 (m, 1H, H-3), 1.42-1.54 (m, 3H, H-3, H-2, OH), 1.55-1.62 (m, 1H, H-2), 1.64-1.74 (m, 1H, H-4), 2.92 (ddd, *J* = 13.2, 6.8, 6.8 Hz, 1H, H-5), 3.01 (ddd, *J* = 13.2, 6.8, 6.8 Hz, 1H, H-5), 3.61 (t, *J* = 6.4 Hz, 2H, H-1), 5.35 (t, *J* = 6.2 Hz, 1H, NH), 7.73-7.75 (m, 2H, H-5Ns, H-6Ns), 7.85 (m, 1H, H-4Ns), 8.12 (m, 1H, H-3Ns).

^{13}C NMR (100.6 MHz, $CDCl_3$) δ 17.4 (CH_3), 29.6 (C-2), 29.9 (C-3), 33.1 (C-4), 49.5 (C-5), 62.8 (C-1), 125.3, 131.1 (C-3Ns, C-6Ns), 132.7 (C-4Ns), 133.5 (C-1Ns), 133.7 (C-5Ns), 148.1 (C-2Ns).

HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{12}H_{19}N_2O_5S$ 303.1009; found 303.1008.

(*S*)-4-Methyl-5-[*N*-(2-nitrobenzenesulfonyl)-10-undecenylamino]-1-pentanol (170)



11-Bromo-1-undecene (0.10 mL, 0.44 mmol) was added to a suspension of alcohol **169** (110 mg, 0.36 mmol) and Cs_2CO_3 (154 mg, 0.47 mmol) in anhydrous DMF (2.5 mL), and the resulting mixture was stirred at 55 ºC for 3 h. The mixture was cooled to room temperature, poured into brine, and extracted with Et_2O. The combined organic extracts were dried, filtered, and concentrated to give an oil. Flash chromatography (7:3 hexane-EtOAc) afforded alkene **170** (130 mg, 79 %) as a colorless oil.

Spectroscopic data for **170**

$[\alpha]^{22}_{D}$ –10.2 (*c* 1.25, MeOH).

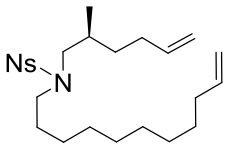
IR (film) 3334 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$, COSY, *g*-HSQC) δ 0.87 (d, *J* = 6.6 Hz, 3H, CH_3), 1.05-1.13 (m, 1H, H-3), 1.15-1.29 (m, 9H, H-3, 4CH_2), 1.32-1.38 (m, 2H, CH_2), 1.40-1.52 (m, 5H, CH_2), 1.58-1.67 (m, 1H, CH_2), 1.71-1.80 (m, 1H, H-4), 1.99-2.05 (m, 2H, CH_2=CHC*H*$_2$), 3.12 (dd, *J* = 14.2, 8.1 Hz, 1H, H-5), 3.20 (dd, *J* = 14.2, 7.1 Hz 1H, H-5), 3.18-3.32 (m, 2H, CH_2N), 3.61 (t, *J* = 6.4 Hz, 2H, H-1), 4.91-5.02 (m, 2H, C*H*$_2$=CH), 5.81 (qt, *J* = 17.0, 10.2, 6.7, 6.7 Hz, 1H, CH_2=C*H*), 7.60-7.70 (m, 3H, H-3Ns, H-5Ns, H-6Ns), 7.99-8.02 (m, 1H, H-4Ns).

^{13}C NMR (100.6 MHz, $CDCl_3$) δ 17.0 (CH_3), 26.6 (CH_2), 27.6 (CH_2), 28.9 (CH_2), 29.0 (CH_2), 29.1 (CH_2), 29.3 (CH_2), 29.4 (CH_2), 29.9 (CH_2), 29.9 (CH_2), 31.0 (C-4), 33.7 (CH_2=CH*C*H$_2$), 47.2 (CH_2N), 53.2 (C-5), 62.9 (C-1), 114.1 (*C*H$_2$=CH), 124.1 and 130.9 (C-3Ns, C-6Ns), 131.4 (C-4Ns), 133.2 (C-1Ns), 133.8 (C-5Ns), 139.1 (CH_2=*C*H), 148.0 (C-2Ns).

HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{23}H_{39}N_2O_5S$ 455.2574; found 455.2570.

N-[2-Methyl-5-hexenyl)-*N*-(2-nitrobenzenesulfonyl)-10-undecenamine (171)



Dess–Martin reagent (168 mg, 0.40 mmol) was added to a solution of alcohol **170** (90 mg, 0.20 mmol) in anhydrous CH_2Cl_2 (1.5 mL), and the mixture was stirred at room temperature for 1.5 h. Then, saturated aqueous $Na_2S_2O_4$ (0.75 mL) and saturated aqueous $NaHCO_3$ (0.75 mL) were added, and the resulting mixture was stirred for 1 h. The aqueous layer was extracted with CH_2Cl_2, and the combined organic extracts were washed with brine, dried, filtered, and concentrated to give an aldehyde, which was used without purification in the next step:

^{1}H NMR (300 MHz, $CDCl_3$) δ 0.88 (d, *J* = 8.8 Hz, 3H, CH_3), 1.12-1.29 (m, 9H), 1.31-1.51 (m, 6H), 1.73-1.84 (m, 2H), 1.99-2.07 (m, 2H, CH_2=CHC*H*$_2$), 2.37-2.58 (m, 2H, C*H*$_2$COH), 3.10-3.28 (m, 4H, 2CH_2N), 4.91-5.02 (m, 2H, C*H*$_2$=CH), 5.80 (qt, *J* = 16.9, 10.1, 6.7, 6.7 Hz, 1H, CH_2=C*H*), 7.60-7.70 (m, 3H, H-3Ns, H-5Ns, H-6Ns), 7.99-8.02 (m, 1H, H-4Ns), 9.76 (s, 1H, COH).

t-BuOK (0.99 mL of a 1 M solution in THF, 0.99 mmol) was added to a solution of methyltriphenylphosphonium bromide (497 mg, 1.38 mmol) in anhydrous THF (10 mL) at room temperature, and the mixture was stirred for 1 h. Then, a solution of the above aldehyde in anhydrous THF (10 mL) was added via cannula, and the resulting

mixture was stirred at room temperature for 3 h. Saturated aqueous NH_4Cl was added, and the resulting mixture was extracted with EtOAc. The extracts were dried, filtered, and concentrated. The residue was chromatographed (9:1 hexane-EtOAc) to give dialkene **171** (55 mg, 61 %) as a colorless oil.

Spectroscopic data for **171**

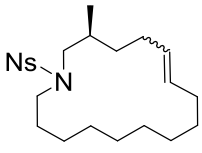
$[\alpha]^{22}_D$ –3.58 (*c* 0.9, MeOH).

^{1}H NMR (400 MHz, $CDCl_3$, COSY, *g*-HSQC) δ 0.85 (d, *J* = 6.6 Hz, 3H, CH_3), 1.09-1.30 (m, 11H, CH_2), 1.32-1.33 (m, 2H, CH_2), 1.41-1.50 (m, 3H, CH_2), 1.70-1.75 (m, 1H, CH), 1.95-2.06 (m, 3H, CH_2), 2.08-2.17 (m, 1H, CH_2), 3.12 (dd, *J* = 14.2, 8.3 Hz, 1H, CH_2N), 3.18 (dd, *J* = 14.2, 8.8 Hz, 1H, CH_2N), 3.13-3.21 (m, 2H, CH_2N), 4.91-5.02 (m, 4H, C*H*$_2$=CHCH_2), 5.74 (qt, *J* = 17.0, 10.1, 10.1, 6.7 Hz, 1H, CH_2=C*H*), 5.80 (qt, *J* = 17.3, 10.3, 10.3, 7.0 Hz, 1H, CH_2=C*H*), 7.59-7.62 (m, 1H, H-3Ns), 7.63-7.70 (m, 2H, H-5Ns, H-6Ns), 7.99-8.03 (m, 1H, H-4Ns).

^{13}C NMR (100.6 MHz, $CDCl_3$) δ 17.0 (CH_3), 26.6 (CH_2), 27.6 (CH_2), 28.9 (CH_2), 29.0 (CH_2), 29.1 (CH_2), 29.3 (CH_2), 29.4 (CH_2), 30.4 (CH), 31.1 (CH_2), 33.0 (CH_2=CH*C*H_2), 33.8 (CH_2=CH*C*H_2), 47.1 (C-1), 53.1 (CH_2N), 114.1 (*C*H_2=CH), 114.7 (*C*H_2=CH), 124.1 (C-3Ns), 130.9 (C-6Ns), 131.4 (C-4Ns), 133.2 (C-5Ns), 133.9 (C-1Ns), 138.4 (CH_2=*C*H), 139.1 (CH_2=*C*H), 148.0 (C-2Ns).

HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{24}H_{39}N_2O_4S$ 451.2625; found 451.2622.

(*S*)-3-Methyl-1-(2-nitrobenzenesulfonyl)azacyclohexadec-6-ene (172)



A solution of **171** (58 mg, 0.13 mmol) in anhydrous CH_2Cl_2 (10 mL) was added to a solution of second-generation Grubbs catalyst (16.4 mg, 0.02 mmol) in CH_2Cl_2 (650 mL) at reflux. The resulting mixture was stirred at reflux temperature for 14 h. The solvent was evaporated, and the resulting residue was chromatographed (95:5 hexane-EtOAc) to yield a 86:14 (calculated by GC/MS) mixture of *E/Z* diastereoisomers **172** (44 mg, 80 %).

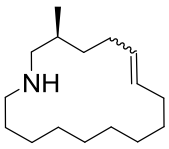
Spectroscopic data for major diastereoisomer **172**

^{1}H NMR (400 MHz, $CDCl_3$, COSY, *g*-HSQC) δ 0.84 (d, *J* = 6.6 Hz, 3H, CH_3), 1.06-1.18 (m, 1H, H-4), 1.19-1.59 (m, 15H, H-4, 7CH_2), 1.78-1.87 (m, 1H, H-3), 1.97-2.10 (m, 3H, H-5, H-8), 2.12-2.18 (m, 1H, H-8), 3.08 (dd, *J* = 13.9, 6.7 Hz, 1H, H-2), 3.14-3.24 (m, 3H, H-2, H-16), 5.26-5.45 (m, 2H, H-6, H-7), 7.59-7.62 (m, 1H, H-3Ns), 7.64-7.69 (m, 2H, H-5Ns, H-6Ns), 7.97-8.02 (m, 1H, H-4Ns).

^{13}C NMR (100.6 MHz, $CDCl_3$) δ 15.9 (CH_3), 24.4 (CH_2), 25.7 (CH_2), 26.2 (CH_2), 26.3 (CH_2), 26.8 (CH_2), 27.0 (CH_2), 27.4 (CH_2), 28.1 (C-3), 28.9 (*C*H_2CH=), 30.9 (*C*H_2CH=), 33.3 (C-4), 46.5 (C-16), 54.1 (C-2), 124.0 (C-3Ns), 130.0 (CH=), 130.8 (C-6Ns), 131.3 (CH=), 131.4 (C-4Ns), 133.1 (C-5Ns), 133.6 (C-1Ns), 148.1 (C-2Ns).

HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{22}H_{35}N_2O_4S$ 423.2312; found 423.2301.

(*S*)-3-Methylazacyclohexadec-6-ene (173)



K_2CO_3 (194 mg, 1.41 mmol) and thiophenol (0.058 mL, 0.56 mmol) were added to a solution of **172** (198 mg, 0.47 mmol) in anhydrous DMF (9 mL), and the mixture was stirred at room temperature for 14 h. The reaction was quenched by the addition of aqueous 2 M NaOH, and the resulting mixture was extracted with CH_2Cl_2. The combined organic extracts were dried, filtered, and evaporated. The resulting residue was chromatographed (from 95:5 hexane-EtOAc to 8:2 EtOAc-Et_3N) to afford compound **173** (64 mg, 58 %) as a 84:16 (calculated by GC/MS) mixture of *E/Z* diastereoisomers as a brown oil.

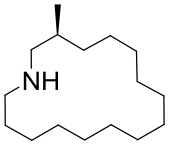
Spectroscopic data for major diastereoisomer **173**

^{1}H NMR (400 MHz, $CDCl_3$, COSY, *g*-HSQC) δ 0.87 (d, *J* = 6.6 Hz, 3H, CH_3), 1.14-1.22 (m, 1H, H-4), 1.24-1.54 (m, 15H, H-4, 7CH_2), 1.68-1.77 (m, 1H, H-3), 1.95-2.16 (m, 4H, H-5, H-8), 2.46 (m, 2H, H-2), 2.48-2.58 (m, 1H, H-16), 2.62-2.72 (m, 1H, H-16), 5.35-5.40 (m, 2H, H-6, H-7).

^{13}C NMR (100.6 MHz, $CDCl_3$) δ 17.8 (CH_3), 25.0 (CH_2), 26.0 (CH_2), 26.5 (CH_2), 27.3 (CH_2), 27.3 (CH_2), 27.6 (CH_2), 28.3 (CH_2), 29.2 (CH_2), 30.1 (C-3), 31.9 (*C*H_2CH=), 34.0 (*C*H_2CH=), 47.0 (C-16), 55.4 (C-2), 130.7 (CH=), 130.9 (CH=).

HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{16}H_{32}N$ 238.2529; found 238.2523.

(*S*)-Haliclorensin C



A solution of alkene **173** (46 mg, 0.19 mmol) in anhydrous MeOH (10 mL) containing 25% Pd/C (12 mg) was hydrogenated at room temperature for 14 h under 10 bar of pressure. The catalyst was removed by filtration and washed with hot MeOH, and the combined organic solutions were concentrated. Flash chromatography (from 95:5 hexane-EtOAc to 8:2 EtOAc-Et_3N) of the residue gave **(*S*)-haliclorensin C** (33 mg, 71 %) as a brown oil.

Spectroscopic data for **(*S*)-haliclorensin C**

$[\alpha]^{22}_D$ –6.04 (*c* 0.85, MeOH); lit[73] **$[\alpha]^{20}_D$** +53 (*c* 0.15, MeOH).

^{1}H NMR (500 MHz, 4:1 $CDCl_3$-CD_3OD, COSY, *g*-HSQC) δ 0.73 (d, *J* = 6.8 Hz, 3H, CH_3), 1.08-1.22 (m, 1H, H-4), 1.30-1.41 (m, 20H, 10CH_2), 1.42-1.56 (m, 3H, H-4, CH_2), 1.60-1.63 (m, 1H, H-3), 2.30 (dd, *J* = 11.8, 7.7 Hz, 1H, H-2), 2.36 (dd, *J* = 11.8, 5.2 Hz, 1H, H-2), 2.48-2.54 (m, 1H, H-16), 2.64-2.70 (m, 1H, H-16).

^{13}C NMR (125 MHz, 4:1 $CDCl_3$-CD_3OD) δ 18.2 (CH_3), 24.2 (CH_2), 24.9 (CH_2), 26.0 (CH_2), 26.1 (2CH_2), 26.2 (CH_2), 26.3 (CH_2), 26.4 (CH_2), 26.5 (CH_2), 27.0 (2CH_2), 30.7 (C-3), 32.4 (C-4), 47.0 (C-16), 53.8 (C-2).

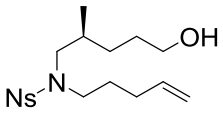
HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{16}H_{34}N$ 240.2686; found 240.2681.

Spectroscopic data for **(*S*)-haliclorensin C hydrochloride**

^{1}H NMR (400 MHz, 4:1 $CDCl_3$-CD_3OD, COSY, *g*-HSQC) δ 1.06 (d, *J* = 6.8 Hz, 3H, CH_3), 1.26-1.40 (m, 22H, 11CH_2), 1.75 (m, 2H, H-15), 1.89 (m, 1H, H-3), 2.78-2.84 (m, 2H, H-2), 2.89-2.99 (m, 2H, H-16).

^{13}C NMR (100.6 MHz, 4:1 $CDCl_3$-CD_3OD) δ 17.9 (CH_3), 23.7 (C-15), 24.7 (CH_2), 24.9 (CH_2), 26.2 (CH_2), 26.3 (CH_2), 26.4 (CH_2), 26.5 (CH_2), 26.6 (CH_2), 26.7 (CH_2), 26.8 (CH_2), 27.1 (CH_2), 28.7 (C-3), 32.6 (C-4), 45.6 (C-16), 50.9 (C-2).

(*S*)-4-Methyl-5-[*N*-(2-nitrobenzenesulfonyl)-4-pentenylamino]-1-pentanol (174)



5-Bromo-1-puntene (0.54 mL, 4.56 mmol) was added to a suspension of amine **169** (1.15 g, 3.80 mmol) and Cs_2CO_3 (1.61 g, 4.95 mmol) in anhydrous DMF (2.5 mL), and the resulting mixture was stirred at 55 ºC for 3 h. The mixture was cooled to room temperature, poured into brine, and extracted with Et_2O. The combined organic extracts were dried, filtered, and concentrated to give a yellow oil. Flash chromatography (from 7:3 hexane-EtOAc to 1:1 hexane-EtOAc) afforded alkene **174** (1.06 g, 75 %) as a colorless oil.

Spectroscopic data for **174**

$[\alpha]^{22}_{D}$ –13.4 (*c* 1.85, MeOH).

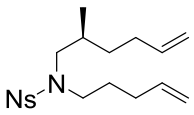
^{1}H NMR (400 MHz, $CDCl_3$, COSY, *g*-HSQC) δ 0.86 (d, *J* = 6.7 Hz, 3H, CH_3), 1.05-1.14 (m, 1H, H-3), 1.40-1.52 (m, 2H, H-2, H-3), 1.55-1.66 (m, 4H, H-2, CH_2, OH), 1.71-1.80 (m, 1H, H-4), 1.95-2.00 (m, 2H, CH_2=CHCH_2), 3.11 (dd, *J* = 14.2, 8.1 Hz, 1H, H-5), 3.20 (dd, *J* = 14.2, 7.1 Hz, 1H, H-5), 3.19-3.33 (m, 2H, CH_2N), 3.59 (t, *J* = 6.4 Hz, 2H, H-1), 4.93-4.99 (m, 2H, CH_2=CH), 5.69 (qt, *J* = 16.9, 10.2, 10.2, 6.6, Hz, 1H, CH_2=C*H*), 7.59-7.63 (H-3Ns), 7.64-7.71 (m, 2H, H-5Ns, H-6Ns), 7.97-8.02 (m, 1H, H-4Ns).

^{13}C NMR (100.6 MHz, $CDCl_3$) δ 17.0 (CH_3), 26.8 (CH_2), 29.8 (CH_2), 29.9 (CH_2), 30.6 (CH_2=CH*C*H_2), 31.1 (C-4), 46.8 (CH_2N), 53.5 (C-5), 62.9 (C-1), 115.4 (*C*H_2=CH),

124.1 (C-3Ns), 130.9 (C-6Ns), 131.5 (C-4Ns), 133.3 (C-5Ns), 133.6 (C-1Ns), 137.1 (CH_2=*C*H), 147.9 (C-2Ns).

HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{17}H_{27}N_2O_5S$ 371.1635; found 371.1635.

(*S*)-2-Methyl-*N*-(2-nitrobenzenesulfonyl)-*N*-(4-pentenyl)-5-hexenamine (175)



Dess–Martin reagent (1.49 g, 3.52 mmol) was added to a solution of alcohol **174** (355 mg, 1.0 mmol) in anhydrous CH_2Cl_2 (9 mL), and the mixture was stirred at room temperature for 1.5 h. Then, saturated aqueous $Na_2S_2O_4$ (0.75 mL) and saturated aqueous $NaHCO_3$ (0.75 mL) were added, and the resulting mixture was stirred for 1 h. The aqueous layer was extracted with CH_2Cl_2, and the combined organic extracts were washed with brine, dried, filtered, and concentrated to give an aldehyde, which was used without purification in the next step:

^{1}H NMR (300 MHz, $CDCl_3$) δ 0.88 (d, *J* = 6.6 Hz, 3H, CH_3), 1.33-1.39 (m, 1H), 1.53-1.63 (m, 2H), 1.74-1.83 (m, 2H), 1.95-2.02 (m, 2H), 2.40-2.52 (m, 2H, C*H*$_2$COH), 3.11-3.30 (m, 4H, 2CH_2N), 4.94-5.00 (m, 2H, C*H*$_2$=CH), 5.64-5.75 (m, 1H, CH_2=C*H*), 7.50-7.60 (m, 3H, H-3Ns, H-5Ns, H-6Ns), 7.99-8.00 (m, 1H, H-4Ns), 9.75 (s, 1H, COH).

t-BuOK (5.9 mL of a 1 M solution in THF, 5.9 mmol) was added to a solution of methyltriphenylphosphonium bromide (2.94 g, 8.22 mmol) in anhydrous THF (10 mL) at room temperature, and the mixture was stirred for 1 h. Then, a solution of the above aldehyde in anhydrous THF (60 mL) was added via cannula, and the resulting mixture was stirred at room temperature for 3 h. Saturated aqueous NH_4Cl was added, and the resulting mixture was extracted with EtOAc. The extracts were dried, filtered, and concentrated. The residue was chromatographed (9:1 hexane-EtOAc) to give dialkene **175** (175 mg, 50 %) as a colorless oil.

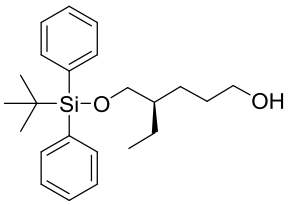
Spectroscopic data for **175**

$[\alpha]^{22}_D$ –12.0 (*c* 1.3, $CHCl_3$); lit[72a] **$[\alpha]^{22}_D$** –15.0 (*c* 1.3, $CHCl_3$).

^{1}H NMR (400 MHz, $CDCl_3$, COSY, *g*-HSQC) δ 0.85 (d, *J* = 6.6 Hz, 3H, CH_3), 1.09-1.18 (m, 1H), 1.41-1.50 (m, 1H), 1.53-1.65 (m, 2H), 1.70-1.79 (m, 1H), 1.95-2.02 (m, 3H, CH_2=CHC*H*$_2$, CH_2), 2.07-2.17 (m, 1H, CH_2=CHC*H*$_2$), 3.13 (dd, *J*= 14.2, 8.3 Hz, 2H, C-1), 3.19 (dd, *J*= 14.2, 7.2 Hz, 2H, C-1), 3.26 (m, 2H, CH_2N), 4.92-4.97 (m, 3H, C*H*$_2$=CHCH$_2$), 4.99-5.01 (m, 1H, C*H*$_2$=CHCH$_2$), 5.65-5.72 (m, 1H, CH_2=C*H*), 5.72-5.79 (m, 1H, CH_2=C*H*), 7.59-7.62 (m, 1H, H-3Ns), 7.65-7.68 (m, 2H, H-5Ns, H-6Ns), 7.99-8.02 (m, 1H, H-4Ns).

^{13}C NMR (100.6 MHz, $CDCl_3$) δ 16.9 (CH_3), 26.8 (CH_2), 30.4 (CH), 30.7 (CH_2), 30.9 (CH_2), 33.0 (CH_2), 46.7 (CH_2), 53.4 (CH_2), 114.7 (*C*H_2=CH), 115.4 (*C*H_2=CH), 124.1 (C-3Ns), 130.9 (C-6Ns), 131.4 (C-4Ns), 133.3 (C-5Ns), 133.7 (C-1Ns), 137.1 (CH_2=*C*H), 138.3 (CH_2=*C*H), 147.9 (C-2Ns).

(*R*)-5-[(*tert*-Butyldiphenylsilyl)oxy]-4-ethyl-1-pentanol (176)



BH_3-THF (3.83 mL of a 1.0 M solution in THF, 3.83 mmol) was added to a cooled (0 ºC) solution of *ent*-**128** (490 mg, 1.28 mmol) in anhydrous THF (15 mL), and the mixture was stirred at room temperature for 4 h. The reaction was quenched with 8 mL of a 1:1 H_2O–Et_2O mixture, poured into saturated aqueous K_2CO_3, and extracted with Et_2O. The combined organic extracts were dried, filtered, and concentrated. The resulting residue was purified by flash chromatography (85:15 hexane–EtOAc) to give the title alcohol **176** (423 mg, 90%) as a colorless oil.

Spectroscopic data for **176**

[α]$^{22}_D$ +2.12 (*c* 3.9, $CHCl_3$); Lit[110b] **[α]$^{23}_D$** +2.7 (*c* 0.05, $CHCl_3$); Lit[110a] (for the enantiomer) **[α]$^{22}_D$** –2.00 (*c* 3.9, $CHCl_3$).

IR (film) 3400, 2930, 1427, 1112 cm^{-1}.

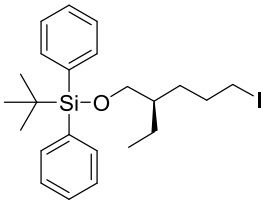
^{1}H NMR (400 MHz, $CDCl_3$, COSY, *g*-HSQC) δ 0.83 (t, *J* = 7.3 Hz, 3H, CH_3), 1.05 [s, 9H, $(CH_3)_3$], 1.30-1.37 (m, 2H, H-3, C*H*$_2$CH$_3$), 1.40-1.45 (m, 3H, H-3, H-4, C*H*$_2$CH$_3$),

1.46-1.51 (m, 2H, H-2), 1.55 (br.s, 1H, OH), 3.56 (d, *J* = 4.5 Hz, 2H, H-5), 3.59 (t, *J* = 6.5 Hz, 2H, H-1), 7.35-7.44 (m, 6H, ArH), 7.65-7.68 (m, 4H, ArH).

^{13}C NMR (100.6 MHz, $CDCl_3$) δ 11.2 (CH_3), 19.3 [*C*(CH_3)$_3$], 23.6 (CH_2), 26.6 [C(*C*H_3)$_3$], 26.9 (C-3), 30.1 (C-2), 41.8 (C-4), 63.3 (C-1), 64.3 (C-5), 127.5 (C-*o*), 129.5 (C-*p*), 133.9 (C-*i*), 135.6 (C-*m*).

HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{23}H_{35}O_2Si$ 371.2401; found 371.2416.

(*R*)-1-[(*tert*-Butyldiphenylsilyl)oxy]-2-ethyl-5-iodopentane (177)



Triphenylphosphine (300 mg, 1.13 mmol) and imidazole (80 mg, 1.13 mmol) were added to a solution of alcohol **176** (200 mg, 0.54 mmol) in anhydrous CH_2Cl_2 (7 mL) at room temperature. Then, iodine (290 mg, 1.13 mmol) was added at 0 °C, and the mixture was stirred at room temperature for 15 h. The solvent was evaporated under reduced pressure to afford a brown residue. Flash chromatography (from hexane to 95:5 hexane–CH_2Cl_2) of the residue gave iodide **177** (232 mg, 90%) as a colorless oil.

Spectroscopic data for **177**

$[\alpha]^{22}_D$ +1.47 (*c* 0.75, $CHCl_3$).

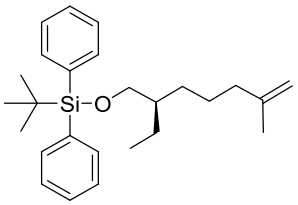
IR (film) 2929, 1111 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$, COSY, *g*-HSQC) δ 0.83 (t, *J* = 7.4 Hz, 3H, CH_3), 1.06 [s, 9H, (CH_3)$_3$], 1.30-1.51 (m, 5H, H-2, H-3, C*H*$_2$$CH_3$), 1.73-1.80 (quint, *J* = 7.5 Hz, 2H, H-4), 3.13 (t, *J* = 7.5 Hz, 2H, H-5), 3.51 (dd, *J* = 10.1, 4.5 Hz, 1H, H-1), 3.55 (dd, *J* = 10.1, 4.8 Hz, 1H, H-1), 7.36-7.45 (m, 6H, ArH), 7.64-7.67 (m, 4H, ArH).

^{13}C NMR (100.6 MHz, $CDCl_3$) δ 7.5 (C-5), 11.3 (CH_3), 19.3 [*C*(CH_3)$_3$], 23.6 (CH_2), 26.6 [C(*C*H_3)$_3$], 31.1 (C-4), 31.8 (C-3), 41.3 (C-2), 65.6 (C-1), 127.6 (C-*o*), 129.5 (C-*p*), 133.9 (C-*i*), 135.6 (C-*m*).

HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{23}H_{34}IOSi$ 481.1418; found 481.1425.

(*R*)-7-[(*tert*-Butyldiphenylsilyl)oxy]-6-ethyl-2-methyl-1-heptene (178)



Isopropenylmagnesium bromide (3.62 mL of a 0.5 M solution in THF, 1.81 mmol) was added at 0 ºC to a suspension of iodide **177** (290 mg, 0.60 mmol) and CuI (12.6 mg, 0.066 mmol) in anhydrous THF (3.5 mL), and the resulting mixture was stirred at room temperature for 2 h. Then, saturated aqueous NH_4Cl was added, and the mixture was extracted with EtOAc. The combined organic extracts were dried, filtered, and evaporated. The resulting residue was chromatographed (hexane) to afford alkene **178** (211 mg, 89%) as a colorless oil.

Spectroscopic data for **178**

$[\alpha]^{22}_D$ +0.66 (*c* 1.05, $CHCl_3$).

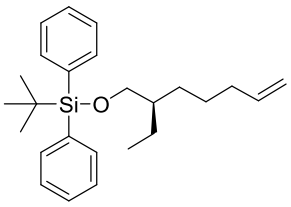
IR (film) 2927, 1425, 1113 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$, COSY, *g*-HSQC) δ 0.82 (t, *J* = 7.3 Hz, 3H, C*H*$_3$CH$_2$), 1.05 [s, 9H, $(CH_3)_3$], 1.25-1.33 (m, 1H, H-5), 1.35-1.47 (m, 6H, H-4, H-5, H-6, CH_3CH_2), 1.69 (s, 3H, CH_3), 1.95-1.98 (brt, *J* = 7.0 Hz, 2H, H-3), 3.54 (d, *J* = 4.9 Hz, 2H, H-7), 4.64-4.68 (m, 2H, H-1), 7.35-7.44 (m, 6H, ArH), 7.65-7.68 (m, 4H, ArH).

^{13}C NMR (100.6 MHz, $CDCl_3$) δ 11.3 (CH_3CH_2), 19.3 [$C(CH_3)_3$], 22.4 (CH_3), 23.6 (CH_3CH_2), 24.9 (C-4), 26.9 [$C(CH_3)_3$], 30.3 (C-5), 38.2 (C-3), 42.0 (C-6), 65.8 (C-7), 109.6 (C-1), 127.5 (C-*o*), 129.5 (C-*p*), 134.1 (C-*i*), 135.6 (C-*m*), 146.2 (C-2);

HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{26}H_{39}OSi$ 395.2765; found 395.2762.

(*R*)-7-[(*tert*-Butyldiphenylsilyl)oxy]-6-ethyl-1-heptene (179)



Vinylmagnesium bromide (0.8 ml of a 1.0 M in THF, 0.8 mmol) was added at 0 ºC to a suspension of iodide **177** (128 mg, 0.27 mmol) and CuI (5 mg, 0.027 mmol) in anhydrous THF (1.5 mL), and the resulting mixture was stirred at 0-15°C for 2 h. Then, saturated aqueous NH_4Cl was added, and the mixture was extracted with EtOAc. The combined organic extracts were dried, filtered, and evaporated. The resulting residue was chromatographed (Petroleum ether) to afford alkene **179** (37 mg, 37%) as a colorless oil.

Spectroscopic data for **179**

$[\alpha]^{22}_{D}$ +0.8 (*c* 0.95, $CHCl_3$).

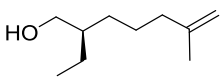
IR (film) 2960, 2930, 2858, 1428 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$, COSY, *g*-HSQC) δ 0.83 (t, *J* = 7.2 Hz, 3H, CH_3), 1.05 [s, 9H, $(CH_3)_3$], 1.29-1.37 (m, 4H, H-4, H-5, CH_3CH_2), 1.38-1.45 (m, 3H, H-5, CH_3CH_2), 2.00 (m, 2H, H-3), 3.54 (d, *J* = 4.6 Hz, 2H, H-7), 4.91-5.00 (m, 2H, H-1), 5.74-5.84 (H-2), 7.35-7.44 (m, 6H, ArH), 7.65-7.67 (m, 4H, ArH).

^{13}C NMR (100.6 MHz, $CDCl_3$) δ 11.2 (CH_3), 19.3 [$C(CH_3)_3$], 23.6 (CH_3CH_2), 26.2 (C-4), 26.9 [$C(CH_3)_3$], 30.1 (C-5), 34.2 (C-3), 42.0 (C-6), 65.8 (C-7), 114.2 (C-1), 127.5 (C-*o*), 129.5 (C-*p*), 134.1 (C-*i*), 135.6 (C-*m*), 139.1 (C-2).

HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{25}H_{37}OSi$ 381.2608; found 381.2624.

(*R*)-2-Ethyl-6-methyl-6-hepten-1-ol (180)



Tetrabutylammonium fluoride (3.83 mL of a 1.0 M solution in THF, 3.83 mmol) was added to a solution of **178** (378 mg, 0.96 mmol) in anhydrous THF (6 mL) at 0 ºC, and the mixture was stirred at room temperature for 17 h. The solvent was eliminated under reduced pressure and the crude residue was purified by flash chromatography (from hexane to 8:2 hexane–EtOAc) to give the title alcohol **180** (187 mg, 80%) as a colorless liquid.

Spectroscopic data for **180**

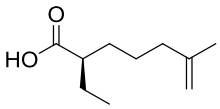
$[\alpha]^{22}_{D}$ –1.41 (*c* 0.7, $CHCl_3$).

IR (film) 3336, 1649, 1460 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$, COSY, *g*-HSQC) δ 0.90 (t, *J* = 7.3 Hz, 3H, CH_2CH_3), 1.26-1.32 (m, 2H, CH_3CH_2), 1.32-1.49 (m, 5H, H-2, H-3, H-4), 1.71 (s, 3H, CH_3), 2.01 (t, *J* = 7.5 Hz, 2H, H-5), 3.55 (d, *J* = 5.2 Hz, 2H, H-1), 4.67-4.70 (m, 2H, H-7).

^{13}C NMR (100.6 MHz, $CDCl_3$) δ 11.1 (CH_3CH_2), 22.3 (CH_3), 23.3 (CH_3CH_2), 24.8 (C-4), 30.0 (C-3), 38.1 (C-5), 41.9 (C-2), 65.2 (C-1), 109.8 (C-7), 146.0 (C-6).

(*R*) 2-Ethyl-6-methyl-6-heptenoic acid (181)



DMSO (0.46 mL, 6.47 mmol) was added to a cooled (–78 ºC) solution of oxalyl chloride (0.27 mL, 3.23 mmol) in anhydrous CH_2Cl_2 (16 mL), and the mixture was stirred at this temperature for 10 min. Then, a solution of the alcohol **180** (459 mg, 2.94 mmol) in CH_2Cl_2 (16 mL) was added, and the mixture was stirred at –78 ºC for 30 min. Triethylamine (2.05 mL, 14.7 mmol) was added and, after 40 min, the mixture was allowed to warm to room temperature and was washed with saturated $NaHCO_3$. The organic extract was dried, filtered, and concentrated, to give the corresponding aldehyde (460 mg) as a yellow oil, which was used without further purification:

^{1}H NMR (400 MHz, $CDCl_3$) δ 0.92 (t, *J* = 7.5 Hz, 3H, CH_3CH_2), 1.42-1.49 (m, 3H), 1.51-1.58 (m, 1H), 1.60-1.69 (m, 2H), 1.70 (s, 3H, CH_3), 2.02 (t, *J* = 7.0 Hz, 2H, H-5), 2.15-2.23 (m, 1H), 4.66-4.67 (m, 1H, H-7), 4.70-4.71 (m, 1H, H-7), 9.58 (d, *J* = 3.0 Hz, 1H, CHO).

A solution of $NaClO_2$ (3.19 g, 35.28 mmol) and NaH_2PO_4 (3.24 g, 27.0 mmol) in water (14 mL) was added to a solution of the above crude aldehyde (460 mg) and 2-methyl-2-butene (14.7 mL of a 2.0 M solution in THF, 29.4 mmol) in *t*-BuOH (28 mL), and the mixture was stirred at room temperature for 3 h. The reaction was quenched by addition of H_2O, and the aqueous layer was extracted with CH_2Cl_2. The combined organic extracts were dried, filtered, and concentrated. Flash chromatography (from 8:2 hexane–CH_2Cl_2 to CH_2Cl_2) of the residue gave C-Arboxylic acid **181** (370 mg, 74%) as a colorless liquid.

Spectroscopic data for **181**

$[\alpha]^{22}_D$ –6.87 (*c* 1.2, $CHCl_3$).

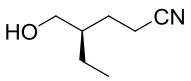
IR (film) 3074, 2938, 1707 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$, COSY, *g*-HSQC) δ 0.94 (t, *J* = 7.4 Hz, 3H, C*H*$_3$CH$_2$), 1.43-1.68 (m, 6H, CH$_3$C*H*$_2$, H-3, H-4), 1.70 (s, 3H, CH_3), 2.02 (brt, *J* = 7.0 Hz, 2H, H-5), 2.30 (m, 1H, H-2), 4.67 (br.s, 1H, H-7), 4.70 (br.s, 1H, H-7).

^{13}C NMR (100.6 MHz, $CDCl_3$) δ 11.7 (*C*H$_3$CH$_2$), 22.2 (CH_3), 25.2 (CH$_3$*C*H$_2$, C-4), 31.2 (C-3), 37.6 (C-5), 47.0 (C-2), 110.1 (C-7), 145.4 (C-6), 182.8 (CO).

HRMS (ESI-TOF) m/z: $[M - H]^-$ Calcd for $C_{10}H_{17}O_2$ 169.123; found 169.1228.

(*R*)-4-(Hydroxymethyl)hexanenitrile (182)



20% Aqueous solution of NH_3 (196 mL) and iodine (11.59 g, 45.7 mol) were added to a solution of amine *ent*-**122** (4.11 g, 5.65 mol) in anhydrous THF (10 mL) at room temperature, and the resulting mixture was stirred at 60 ºC for 21 h. The mixture was washed with a saturated aqueous Na_2SO_3 and extracted with Et_2O. The combined organic phases were dried, filtered, and concentrated to give crude *ent*-**123** as an oil, which was used without purification in the next step. An aliquot was chromatographed (from hexane to 6:4 hexane–CH_2Cl_2) to give pure *ent*-**123** {**$[\alpha]^{22}_D$** –4.00 (*c* 0.5, $CHCl_3$)}. Tetrabutylammonium fluoride (17.6 mL of a 1.0 M solution in THF, 17.6 mmol) was added to a solution of the above crude *ent*-**123** (2.06 g) in anhydrous THF (36 mL) at 0 ºC, and the mixture was stirred at room temperature for

3.5 h. The solvent was eliminated under reduced pressure and the crude residue was purified by flash chromatography (from 9:1 hexane–EtOAc to 1:1 hexane–EtOAc) to give nitrile derivative **182** (540 mg, 75% from *ent*-**122**) as a yellow oil.

Spectroscopic data for **182**

$[\alpha]^{22}_D$ –5.26 (*c* 1.25, $CHCl_3$); Lit[114a] **$[\alpha]^{22}_D$** –7.1 (*c* 0.97 in $CHCl_3$).

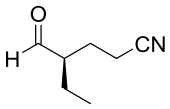
IR (film) 3440, 2247 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$, COSY, *g*-HSQC) δ 0.93 (t, *J* = 7.5 Hz, 3H, H-6), 1.32-1.45 (m, 2H, H-5), 1.52-1.62 (m, 1H, H-4), 1.65-1.83 (m, 2H, H-3), 2.05 (br.s, 1H, OH), 2.38-2.50 (m, 2H, H-2), 3.54 (dd, *J* = 10.9, 6.1 Hz, 1H, CH_2O), 3.65 (dd, *J* = 10.9, 4.6 Hz, 1H, CH_2O).

^{13}C NMR (100.6 MHz, $CDCl_3$) δ 11.0 (C-6), 15.0 (C-2), 23.1 (C-5), 26.8 (C-3), 40.8 (C-4), 64.1 (CH_2O), 120.1 (CN).

HRMS (ESI-TOF) m/z: $[M + NH_4]^+$ Calcd for $C_7H_{17}N_2O$ 145.1335; found 145.1337.

(*R*)-4-Formylhexanenitrile (183)



DMSO (0.25 mL, 3.55 mmol) was added to a cooled (–78 ºC) solution of oxalyl chloride (0.15 mL, 1.77 mmol) in hexane–EtOAc CH_2Cl_2 (7 mL), and the mixture was stirred at this temperature for 10 min. Then, a solution of alcohol **182** (205 mg, 1.61 mmol) in CH_2Cl_2 (7 mL) was slowly added, and the yellow mixture was stirred at –78 ºC for 30 min. Triethylamine (1.12 mL, 8.06 mmol) was added and, after 1 h, the mixture was allowed to warm to room temperature and washed with saturated $NaHCO_3$. The organic layer was dried, filtered, and concentrated, and the resulting residue was chromatographed (9:1 hexane–EtOAc) to afford aldehyde **183** (152 mg, 75%).

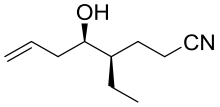
Spectroscopic data for **183**

$[\alpha]^{22}_{D}$ +9.1 (*c* 0.35, $CHCl_3$).

^{1}H NMR (400 MHz, $CDCl_3$, COSY, *g*-HSQC) δ 0.99 (t, *J* = 7.5 Hz, 3H, CH_3), 1.58-1.68 (m, 1H), 1.70-1.84 (m, 2H), 1.99-2.11 (m, 1H), 2.35-2.50 (m, 3H, H-4, H-2), 9.67 (s, 1H, CHO).

HRMS (ESI-TOF) m/z: $[M + NH_4]^+$ Calcd for $C_7H_{15}N_2O$ 143.1179; found 143.1181.

(4*R*,5*R*)-4-Ethyl-5-hydroxy-7-octenenitrile (184)



(*S*,*S*)-2-Allyl-1,3-bis-(4-bromobenzyl)-2-chlorooctahydro-2-1*H*-1,3,2-benzodiazasilole (Leighton reagent; 1.30 g, 2.30 mmol) and scandium triflate (49 mg, 0.096 mmol) were added to a solution of aldehyde **183** (240 mg, 1.92 mmol) in anhydrous CH_2Cl_2 (19 mL), and the resulting mixture was stirred at 0 ºC for 5 h, and at room temperature for 12 h. Then, a solution of tetrabutylammonium fluoride (1.9 mL, 1.9 mmol) was added, and the mixture was stirred at room temperature for 30 min. The solvent was evaporated, and the resulting residue was chromatographed (from 8:2 hexane–CH_2Cl_2 to CH_2Cl_2) to give alcohol **184** together with minor amounts of 5-*epi*-**184** (dr 9:1, 284 mg, 85% yield).

Spectroscopic data for **184**

IR (film) 3468, 2247 cm^{-1}.

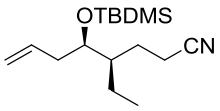
^{1}H NMR (400 MHz, $CDCl_3$, COSY, *g*-HSQC, from the mixture) δ 0.95 (t, *J* = 7.5 Hz, 3H, C*H*$_3$CH$_2$), 1.31-1.40 (m, 1H), 1.40-1.49 (m, 1H), 1.54-1.62 (m, 3H, 2H, OH), 1.62-1.71 (m, 1H), 2.09-2.18 (m, 1H), 2.25-2.31 (m, 1H), 2.45 (m, 2H, CH_2CN), 3.67-3.73 (m, 1H, H-5), 5.14-5.21 (m, 2H, H-8), 5.77-5.87 (m, 1H, H-7);

^{13}C NMR (100.6 MHz, $CDCl_3$, from the mixture) δ **184**: 11.6 (*C*H_3CH$_2$), 15.4 (CH_2CN), 21.4 (CH_2), 25.5 (CH_2), 37.9 (*C*H_2CH=CH$_2$), 43.3 (CH), 71.3 (CHOH), 118.3 (*C*H_2=CH), 120.0 (CN), 134.9 (C*H*$_2$=*C*H).

5-*epi*-**184**: 11.0 (*C*H_3CH_2), 15.2 (CH_2CN), 22.4 (CH_2), 24.9 (CH_2), 39.5 (*C*$H_2CH{=}CH_2$), 43.2 (CH), 71.4 (CHOH), 118.5 (*C*H_2=CH), 120.1 (CN), 134.6 (C*H*$_2$=*C*H).

HRMS (ESI-TOF) m/z: $[M + NH_4]^+$ Calcd for $C_{10}H_{21}N_2O$ 185.1648; found 185.1643.

(4*R*,5*R*)-5-[(*tert*-Butyldimethylsilyl)oxy]-4-ethyl-7-octenenitrile (185)



tert-Butyldimethylsilyl chloride (760 mg, 5.04 mmol) and imidazole (458 mg, 6.73 mmol) were added to a solution of the above mixture of epimeric alcohols **184** (281 mg, 1.68 mmol) in anhydrous CH_2Cl_2 (5 mL). The solution was stirred at reflux temperature for 15 h. Then, saturated aqueous NH_4Cl was added, and the mixture was extracted with CH_2Cl_2. The combined organic extracts were dried, filtered, and concentrated. Flash chromatography (from 9:1 hexane–EtOAc to 8:2 hexane-CH_2Cl_2) of the residue afforded the protected alcohol 185 (9:1 mixture of C-5 epimers; 365 mg, 77% yield) as a colorless oil.

Spectroscopic data for **185**

IR (film) 2959, 2246 cm^{-1}.

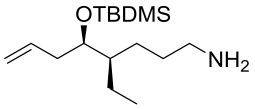
^{1}H NMR (400 MHz, $CDCl_3$, COSY, *g*-HSQC, from the mixture) δ 0.05 (s, 3H, CH_3Si), 0.06 (s, 3H, CH_3Si), 0.89 [s, 9H, $(CH_3)_3$], 0.94 (t, *J* = 7.4 Hz, 3H, C*H*$_3CH_2$), 1.29-1.36 (m, 2H, CH_2), 1.48-1.60 (m, 2H, H-4, CH_2), 1.82-1.90 (m, 1H, CH_2), 2.09-2.23 (m, 2H, H-6), 2.41 (t, *J* = 7.5 Hz, 2H, H-2), 3.72-3.77 (m, 1H, H-5), 5.02-5.08 (m, 2H, H-8), 5.73-5.83 (m, 1H, H-7).

^{13}C NMR (100.6 MHz, $CDCl_3$, from the mixture) δ **185*R*** (major epimer): –4.5 (CH_3Si), –4.4 (CH_3Si), 12.0 (*C*H_3CH_2), 15.8 (C-2), 18.0 [*C*$(CH_3)_3$], 22.7 (CH_2), 25.6 (CH_2), 25.8 [C(*C*$H_3)_3$], 37.3 (C-6), 44.4 (C-4), 73.4 (C-5), 116.9 (C-8), 119.9 (C-1), 135.6 (C-7).

185*S* (minor epimer): –4.8 (CH_3Si), –4 .2 (CH_3Si), 11.6 (*C*H_3CH_2), 15.3 (C-2), 18.0 [*C*$(CH_3)_3$], 22.6 (CH_2), 24.8 (CH_2), 25.8 [C(*C*$H_3)_3$], 39.5 (C-6), 42.6 (C-4), 72.8 (C-5), 117.2 (C-8), 120.2 (C-1), 134.6 (C-7).

HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{16}H_{32}NOSi$ 282.2248; found 282.2245.

(4*R*,5*R*)-5-[(*tert*-Butyldimethylsilyl)oxy]-4-ethyl-7-octenamine (186)



A solution of the above mixture of epimeric nitriles **185** (345 mg, 1.23 mmol) in anhydrous Et_2O (1.0 mL) was slowly added to a cooled (0 ºC) solution of $LiAlH_4$ (2.1 mL of a 1.0 M solution in THF, 2.09 mmol) in anhydrous Et_2O (1.0 mL), and the resulting mixture was stirred at room temperature for 2 h. After cooling to 0 ºC, H_2O (132 μL), 10% aqueous NaOH (250 μL), and H_2O (573 μL) were successively added. The insoluble white precipitate was removed by filtration and washed with Et_2O. The filtrate was dried, filtered, and concentrated to give pure amine **186** (305 mg, 87%) as a colorless oil.

Spectroscopic data for **186**

$[\alpha]^{22}_D$ +7.23 (*c* 1.0, MeOH).

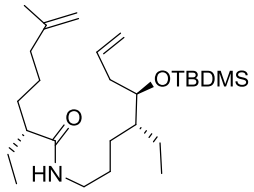
IR (film) 2957, 2930, 2858 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$, COSY, *g*-HSQC) δ 0.03 (s, 3H, CH_3Si), 0.04 (s, 3H, CH_3Si), 0.86-0.91 (m, 3H, CH_3CH_2), 0.88 [s, 9H, $(CH_3)_3$], 1.25-1.54 (m, 7H, H-2, H-3, H-4, CH_3CH_2), 2.11-2.22 (m, 2H, H-6), 2.67 (t, *J* = 7.0 Hz, 2H, H-1), 3.70-3.74 (m, 1H, H-5), 4.98-5.05 (m, 2H, H-8), 5.75-5.85 (dddd, *J* = 14.2, 10.3, 7.2, 7.2 Hz, 1H, H-7).

^{13}C NMR (100.6 MHz, $CDCl_3$) δ −4.7 (CH_3Si), −4.4 (CH_3Si), 12.1 (CH_3CH_2), 17.9 [$C(CH_3)_3$], 22.3 (CH_2), 25.7 [$C(CH_3)_3$], 26.3 (CH_2), 31.9 (CH_2), 37.8 (C-6), 42.5 (C-1), 44.7 (C-4), 73.4 (C-5), 116.1 (C-8), 136.1 (C-7).

HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{16}H_{36}NOSi$ 286.2561; found 286.2554.

(*R*)-*N*-{(4*R*,5*R*)-5-[(*tert*-Butyldimethylsilyl)oxy]-4-ethyl-7-octen-1-yl}-2-ethyl-6-methyl-6-heptenamide (187)



N-(3-Dimethylaminopropyl)-*N'*-ethylC-Arbodiimide hydrochloride (189 mg, 0.99 mmol) was added to a cooled solution (0 ºC) of amine **186** (268 mg, 0.94 mmol) and 1-hydroxybenzotriazole (159 mg, 1.17 mmol) in anhydrous DMF (5.5 mL), and the resulting mixture was stirred at 0 ºC for 10 min. Then, a solution of C-Arboxylic acid **181** (176 mg, 10.3 mmol) in anhydrous DMF (1.5 mL) was added, and the stirring was continued at room temperature for 15 h. The solvent was evaporated, the resulting residue was dissolved in Et_2O, and the solution was washed with H_2O. The organic layer was dried, filtered, and concentrated to give an oil. Flash chromatography (8:2 hexane–EtOAc) afforded amide **187** (325 mg, 79%) as a colorless oil.

Spectroscopic data for **187**

$[\alpha]^{22}_D$ +3.69 (*c* 2.05, $CHCl_3$).

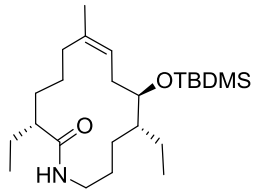
IR (film) 3297, 1641 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$, COSY, *g*-HSQC) δ 0.01 (s, 3H, CH_3Si), 0.01 (s, 3H, CH_3Si), 0.84-0.88 (m, 15H, 2C*H*$_3$CH$_2$, $(CH_3)_3$), 1.12-1.18 (m, 1H), 1.25-1.32 (m, 3H), 1.35-1.49 (m, 7H), 1.49-1.54 (m, 2H), 1.66 (s, 3H, CH_3), 1.88 (m, 1H), 1.96 (t, *J* = 7.0 Hz, 2H, C*H*$_2$CH$_2$=CH), 2.06-2.19 (m, 2H, C*H*$_2$CH$_2$=CH), 3.15-3.27 (m, 2H, CH_2N), 3.66-3.70 (m, 1H, CHO), 4.63 (br.d, *J* = 14.0 Hz, 2H, C*H*$_2$=CMe), 4.95-5.03 (m, 2H, C*H*$_2$=CH), 5.57 (br.t, *J* = 5.3 Hz, 1H, NH), 5.71-5.81 (m, 1H, CH_2=C*H*).

^{13}C NMR (100.6 MHz, $CDCl_3$) δ –4.5 (CH_3Si), –4.3 (CH_3Si), 12.1 (*C*H_3CH$_2$), 12.1 (*C*H_3CH$_2$), 18.0 [*C*$(CH_3)_3$], 22.2 (CH_3), 22.5 (CH_2), 25.6 (CH_2), 25.8 [C(*C*$H_3)_3$], 26.0 (CH_2), 26.6 (CH_2), 28.1 (CH_2), 32.3 (CH_2), 37.7 (*C*H_2CH=CH$_2$), 37.8 (*C*H_2CH=CH$_2$), 39.7 (CH_2NH), 44.7 (CH), 49.7 (CH), 73.5 (CHO), 109.9 (*C*H_2=CH), 116.3 (*C*H_2=CH), 136.1 (CH_2=*C*H), 145.5 (CH_2=*C*Me), 175.5 (CO).

HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{26}H_{52}NO_2Si$ 438.3762; found 438.3772.

_O_-[(_tert_-Butyldimethylsilyl)oxy]-6,7-didehydrofluvirucinin B_1 (188)



A solution of second-generation Hoveyda-Grubbs catalyst (40 mg, 0.063 mmol) in anhydrous toluene (32 mL) was added to a solution of **187** (138 mg, 0.32 mmol) and 1,4-benzoquinone (3.5 mg, 0.032 mmol) in anhydrous toluene (160 mL) at room temperature, and the resulting mixture was heated at 80 ºC for 17 h. The solvent was evaporated, and the resulting residue was chromatographed (from CH_2Cl_2 to 99:1 CH_2Cl_2–Et_2O) to yield lactam ***Z*-188** (56 mg, 43%) as a brown foam and its diastereoisomer ***E*-188** (45 mg, 35%) as a brown oil.

Spectroscopic data for ***Z*-188**

IR (film) 3292, 2959, 1641, 1549, 1462 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$, COSY, *g*-HSQC) δ 0.03 (s, 6H, $2SiCH_3$), 0.82 (t, *J* = 7.1 Hz, 3H, CH_3CH_2), 0.88-0.92 [m, 12H, CH_3CH_2, $(CH_3)_3$], 1.15-1.65 (m, 12H), 1.68 (s, 3H, CH_3), 1.69-1.90 (m, 2H), 1.95-2.08 (m, 2H), 2.20 (m, 2H), 2.98 (dm, *J* = 6.6 Hz, 1H, H-13), 3.58-3.68 (m, 2H, H-9, H-13), 5.19 (brt, *J* = 7.0 Hz, 1H, H-7), 5.62 (dd, *J* = 8.1, 3.7 Hz, 1H, NH).

^{13}C NMR (100.6 MHz, $CDCl_3$) δ –4.6 (CH_3Si), –4.2 (CH_3Si), 10.5 (CH_3CH_2), 12.3 (CH_3CH_2), 18.2 [$C(CH_3)_3$], 21.9 (CH_2), 24.0 (CH_3), 25.7 (CH_2), 26.0 [$C(CH_3)_3$], 26.7 (CH_2), 26.9 (CH_2), 27.5 (CH_2), 32.4 (C-5), 32.8 (C-8), 33.6 (CH_2), 39.1 (C-13), 43.9 (C-10), 49.7 (C-2), 74.0 (C-9), 120.6 (C-7), 136.3 (C-6), 175.5 (C-1).

HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{24}H_{48}NO_2Si$ 410.3449; found 410.3461.

Spectroscopic data for ***E*-188**

IR (film) 3292, 2959, 1641, 1549, 1462 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$, COSY, *g*-HSQC) δ 0.04 (s, 3H, CH_3Si), 0.06 (s, 3H, CH_3Si), 0.87-0.93 [m, 15H, $2CH_3CH_2$, $(CH_3)_3$], 1.20-1.24 (m, 1H), 1.30-1.50 (m, 8H), 1.52-1.58 (m, 3H), 1.60 (s, 3H, CH_3), 1.62-1.66 (m, 1H), 1.90-2.09 (m, 3H, H-2, H-5),

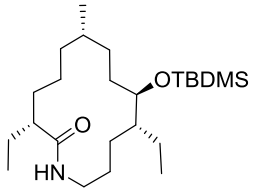
2.17-2.24 (m, 1H, H-8), 2.26-2.33 (m, 1H, H-8), 3.01 (m, 1H, H-13), 3.57-3.65 (m, 1H, H-13), 3.70 (ddd, *J* = 7.4, 4.3, 3.2 Hz, 1H, H-9), 5.27 (br.t, *J* = 7.0 Hz, 1H, H-7), 5.32 (br.s, 1H, NH).

^{13}C NMR (100.6 MHz, $CDCl_3$) δ −4.8 (CH_3Si), −4.4 (CH_3Si), 11.4 (CH_3CH_2), 12.4 (CH_3CH_2), 16.9 (CH_3), 18.1 [$C(CH_3)_3$], 22.1 (CH_2), 24.8 (CH_2), 25.0 (CH_2), 25.9 [$C(CH_3)_3$], 26.3 (CH_2), 27.4 (CH_2), 31.3 (CH_2), 33.2 (C-8), 37.4 (C-5), 39.7 (C-13), 43.6 (C-10), 48.3 (C-2), 73.3 (C-9), 121.1 (C-7), 135.7 (C-6), 175.6 (C-1).

HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{24}H_{48}NO_2Si$ 410.3449; found 410.3464.

***O*-[(*tert*-Butyldimethylsilyl)oxy]fluvirucinin B_1 (189):**

From *Z*-188:



A solution of ***Z*-188** (30 mg, 0.073 mmol) in anhydrous toluene (3 mL) containing Pd/C (26 mg) was hydrogenated at room temperature and atmospheric pressure for 17 h. The catalyst was removed by filtration over Celite®. The organic solution was concentrated, and the resulting oil was chromatographed (from CH_2Cl_2 to 98:2 CH_2Cl_2–Et_2O) and then crystallized (9:1 hexane–EtOAc) to give pure **189** (27 mg, 90%) as a white solid.

From a mixture of diastereoisomers *E*-*Z*:

Operating as above, from a 1.2:1 mixture of macrocycles ***Z*-188** - ***E*-188** (47 mg, 0.11 mmol) and Pd/C (41 mg) in anhydrous toluene (4.7 mL), compound **189** (43 mg, 91%) was obtained after flash chromatography (from CH_2Cl_2 to 98:2 CH_2Cl_2–Et_2O) and crystallization (9:1 hexane–EtOAc).

Spectroscopic data for **189**

mp 185-187 ºC [Lit[104] **mp** 187-188ºC].

$[\alpha]^{22}_D$ +17.0 (*c* 0.02, CH_2Cl_2); Lit[104] **$[\alpha]^{22}_D$** +12.0 (*c* 0.02, CH_2Cl_2).

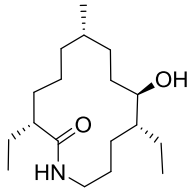
IR (film) 3297, 2928, 1642, 1552 cm^{-1}.

^{1}H NMR (400 MHz, C_6D_6, COSY, *g*-HSQC) δ 0.11 (s, 3H, CH_3Si), 0.12 (s, 3H, CH_3Si), 0.82 (t, *J* = 7.4 Hz, 3H, C*H*$_3$CH$_2$), 0.89 (t, *J* = 7.4 Hz, 3H, C*H*$_3$CH$_2$), 0.97 (d, *J* = 7.0 Hz, 3H, CH_3CH), 1.04 [s, 9H, $(CH_3)_3$], 1.19-1.41 (m, 9H), 1.43-1.56 (m, 6H), 1.58-1.73 (m, 4H), 1.77-1.88 (m, 2H), 2.47 (dm, *J* = 13.7 Hz, 1H, H-13), 3.52 (dt, *J* = 9.1, 3.4 Hz, 1H, H-9), 3.77 (m, 1H, H-13), 4.53 (dd, *J* = 9.0, 3.0 Hz, 1H, NH).

^{13}C NMR (100.6 MHz, C_6D_6) [92,104] δ –4.7 (CH_3Si), –3.7 (CH_3Si), 9.2 (*C*H$_3$CH$_2$), 12.5 (*C*H$_3$CH$_2$), 18.4 [*C*$(CH_3)_3$], 20.9 (CH_3), 21.1 (CH_2), 24.4 (CH_2), 25.2 (CH_2), 25.9 (CH_2), 26.2 [C(*C*H$_3$)$_3$], 26.3 (CH_2), 27.0 (CH_2), 28.5 (CH_2), 31.5 (C-6), 34.1 (CH_2), 34.8 (CH_2), 38.7 (CH_2), 42.9 (C-10), 50.9 (C-2), 73.1 (C-9), 174.8 (C-1).

HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{24}H_{50}NO_2Si$ 412.3605; found 412.3611.

Fluvirucinin B_1



A solution of **189** (9 mg, 0.022 mmol) in 1% HCl-EtOH (2 mL) was stirred at room temperature for 2 h. Then, the solution was concentrated to give **fluvirucinin B_1** (6 mg, 92%) as a white solid.

Spectroscopic data for **fluvirucinin B_1**

mp 236-238 ºC [Lit[85b] **mp** 235-245 ºC].

$[\alpha]^{22}_D$ +14.3 (*c* 0.175, 1:1 $CHCl_3$-CH_3OH).

IR (film) 3308, 2953, 2926, 2872, 2855, 1635 cm^{-1}.

^{1}H NMR (400 MHz, CD_3OD–$CDCl_3$, COSY, *g*-HSQC) δ 0.88 (t, *J* = 7.4 Hz, 3H, C*H*$_3$CH$_2$), 0.89 (t, *J* = 7.3 Hz, 3H, C*H*$_3$CH$_2$), 0.91 (d, *J* = 6.9 Hz, 3H, CH_3), 1.02-1.18 (m, 3H, CH_2, OH), 1.27-1.44 (m, 11H, 5CH_2, H-10), 1.52-1.73 (m, 7H, 3CH_2, H-6),

2.09-2.16 (m, 1H, H-2), 2.69 (m, 1H), 3.29-3.34 (masked, 1H, H-9), 3.75 (m, 1H), 7.88 (dd, *J* = 8.5, 4.1 Hz, 1H, NH).

^{13}C NMR (100.6 MHz, CD_3OD–$CDCl_3$) δ 11.7 (*C*H_3CH_2), 13.2 (*C*H_3CH_2), 22.2 (CH_3), 22.8 (CH_2), 23.8 (CH_2), 26.7 (CH_2), 26.8 (CH_2), 30.1 (CH_2), 31.1 (CH_2), 31.3 (CH_2), 32.9 (C-6), 34.5 (CH_2), 35.0 (CH_2), 40.4 (CH_2), 45.5 (C-10), 49.9 (masked, C-2), 75.0 (C-9), 178.9 (C-1).

HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{18}H_{36}NO_2$ 298.2741; found 298.274.