Università degli Studi di Firenze

DOTTORATO DI RICERCA IN
"*Scienze Chimiche*"

CICLO XXV

COORDINATORE Prof. Goti Andrea

Synthesis of Hydroxylated Pipecolic Acids and Conformationally Constrained Derivatives

Settore Scientifico Disciplinare CHIM/06

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Introduction

Chapter 1: Hydroxylated pipecolic acids in nature and in bioactive compounds

L-Pipecolic acids (Figure 1) are cyclic, naturally occurring nonproteinogenic α-amino acids which have been isolated from plants, fungi, microorganisms and human physiological fluids[1].

The simplest of them, (**1**, Figure 1) is the major product of the degradation of lysine in human brain[2a] and it accumulates in the body fluids causing pipecolic acidemia in subjects suffering from Zellweger syndrome, neonatal adrenoleukodystrophy, and infantile Refsum disease[2b,c].

L-pipecolic acid **1** is a component of a wide range of pharmacologically active compounds, such as for example, the immunosuppressive agents rapamycin[1c,3] (Figure 2) and FK506[1c,4] (Figure 2) the antitumor antibiotic sandramycin[5] (Figure 2) and the local anesthetic analogue ropivacaine[6] (Figure 2). Monohydroxy-substituted derivatives **2-7** (Figure 1a) are natural compounds which could be considered expanded hydroxyproline and serine analogues; they play an important role in medicinal chemistry as molecular scaffolds for the preparation of conformationally restricted peptides and pharmaceutically active substances or because they are essential structural components of naturally occurring compounds possessing noteworthy biological activity[1a-b].

So, 3-hydroxypipecolic acid **2** (Figure 1a) is embedded in the natural antitumor antibiotic tetrazomine[7] (Figure 2) and 4-hydroxypipecolic acid **4** (Figure 1a) is incorporated in the structures of the HIV-protease inhibitor palinavir[8] (Figure 3) and some antagonists of the cholecistokine hormone[9] (Figure 3). 4-Hydroxypipecolic acid **4** has also been used for the preparation of one of the most potent and selective *N*-methyl-D-aspartic acid (NMDA) receptor antagonists, CGS20281[10] (Figure 3) and LY272541[10] (Figure 3).

Naturally occurring 4-hydroxypipecolic acid derivatives form the largest subgroup of substituted pipecolic acids and include the cyclodepsipeptide antibiotic virginiamycin S1[11] (Figure 3), isolated from *Streptomyces virginiae*, serotonine receptor antagonist damipipecoline[12] (Figure 3) recently isolated from *Axinella damicornis* sponge, ovalin (Figure 3) from leguminose *Milletia ovolifolia* seeds[13], tumor necrosys factor α-converting enzyme inhibitor[14](Figure 3) and a sulphate compound possessing NMDA receptor agonistic activity[15] (Figure 3) from legume *Peltophorum africanum*. Pseudoconhydrine (Figure 3) is an example of natural compound embedding a reduced 5-hydroxypipecolic acid skeleton[16].

Pipecolic acids bearing two or three hydroxyl groups (**8-12**, Figure 1) are much less widespread in nature and were isolated from just a few sources. 4,5-Dihydroxypipecolic acid **8** was extracted from the leaves of *Derris elliptica*[17a], isomer **11** from *D. elliptica*[17a] and *Calliandra haematocephala*[17b], where it has a role in the specific resistance of plants to fungi[18], and compound **9** from the leaves of *Calliandra angustifolia* and the sap of *C. confusa*[19].

Figure 1a: *L*-series pipecolic acids

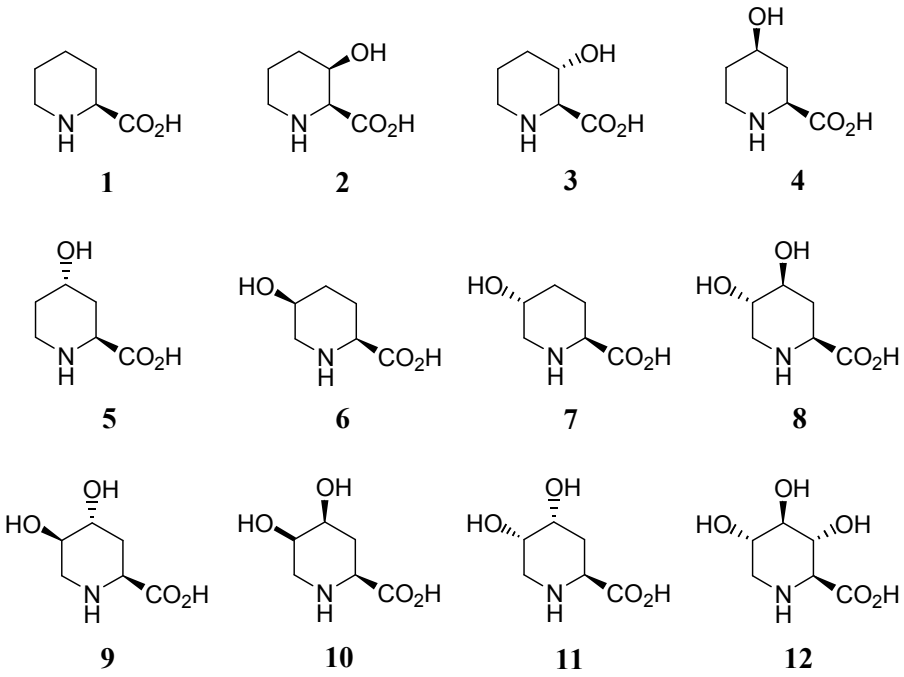


Figure 1b: *D*-series pipecolic acids

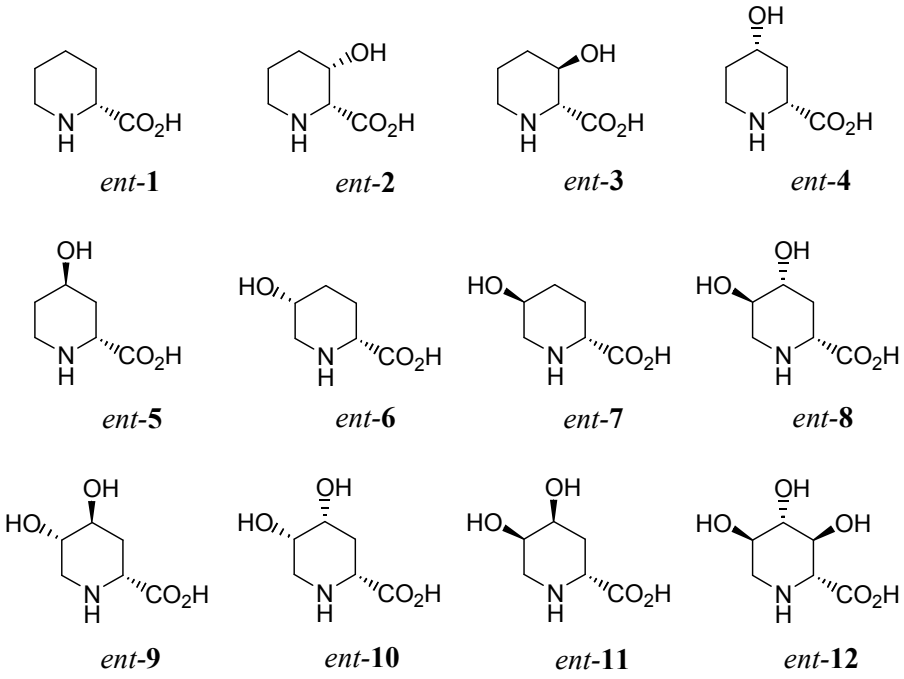


Figure 1: Natural (L-series) and non-natural (D-series) hydroxypipecolic acids

Cis,*cis* compound **10** has been detected by GC-MS in extracts from *Tetraberlinia polyfilla* together with **9** and isolated from the leaves of *C. pittieri*[20]. Similarly, compound **12** is the only trihydroxypipecolic acid known from natural sources as it has been isolated from the seeds of *Baphia racemosa*[21].

Figure 2

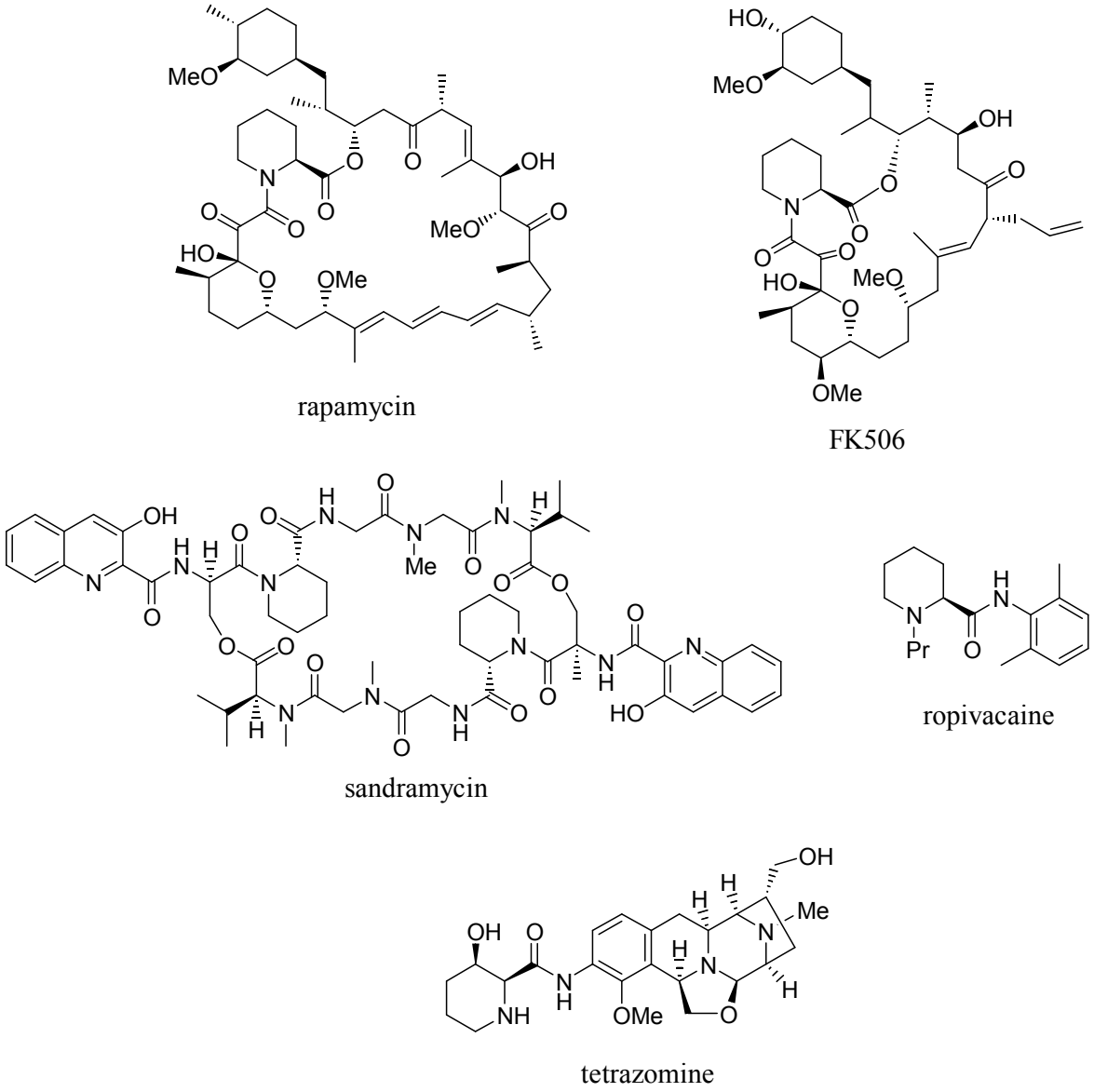
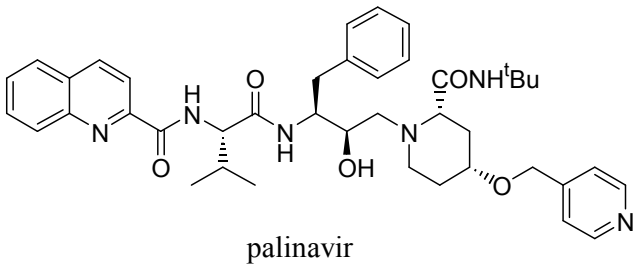
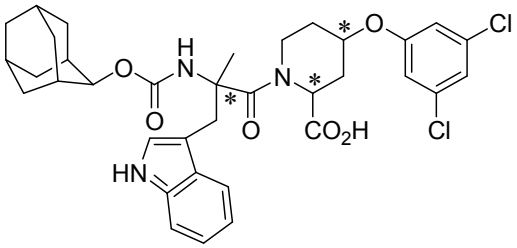


Figure 2: Bioactive compounds embedding pipecolic acids

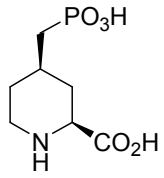
Figure 3



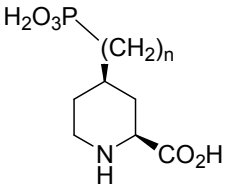
palinavir



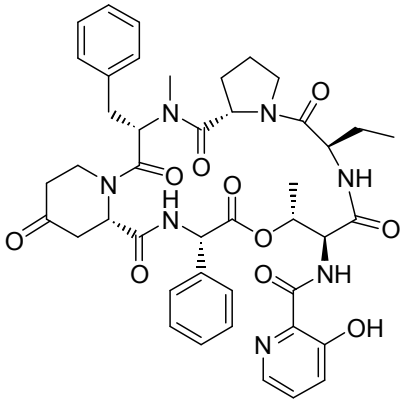
antagonist of cholecistokine ormone
(CCK-B antagonist)



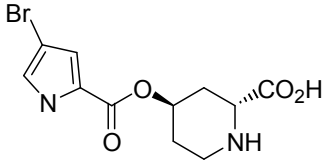
CGS20281



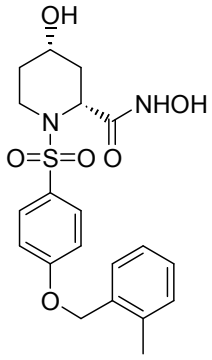
n = 1; LY272541
(CGS19755)
n = 3; LY257883



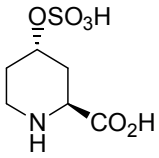
virginiamycin S1



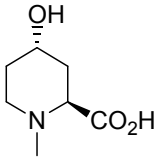
damipipecoline



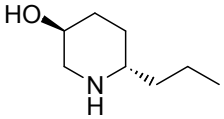
Tumor necrosys factor alfa-converting enzime inhibitor



NMDA receptor agonist



Ovalin



pseudoconhydrine

Figure 3: Bioactive compounds embedding pipecolic acids

Chapter 2: Previous syntheses of mono-hydroxypipecolic acids

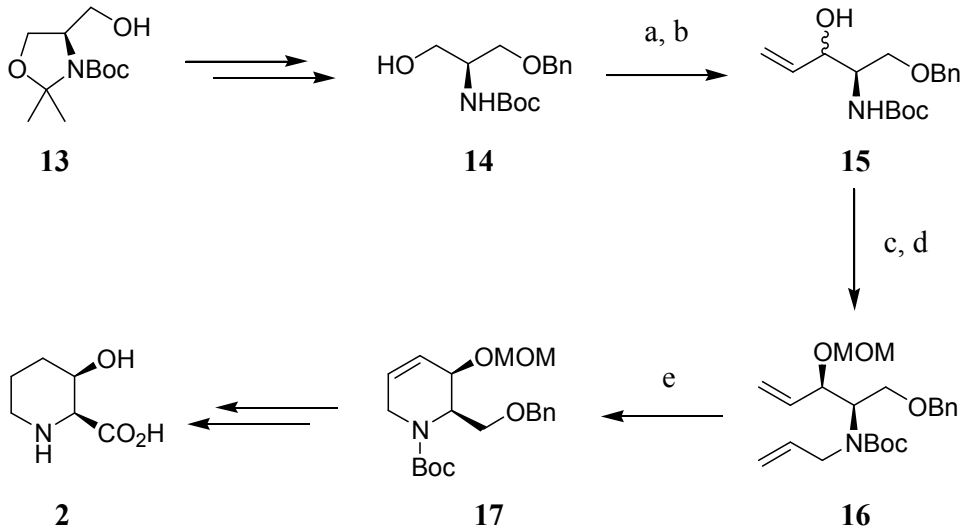
Because of their medicinal applications it is not surprising that there has been much interest in developing synthetic strategies to attain enantiopure 3-, 4-, and 5-hydroxypipecolic acids.

2.1 Synthesis from amino acids

The most common source for the starting materials for the asymmetric synthesis of pipecolic acid derivatives are linear proteinogenic α-amino acids. General strategies involve the functionalization of the side chain followed by cyclization reaction with the α-amino group.

L-pipecolic acid and 3-hydroxypipecolic acid have been prepared from hydroxyproline and serine derivatives, using a ring closing metathesis as the key step[22a,b]. The strategy involves the formation of an alkene side chain from an hydroxy group. Allylation of the α-amine followed by RCM reaction gives the pipecolic acid rings. For example, serine derivative **13** (Scheme 1) was converted in two steps into alcohol **14.**

Scheme 1



13 **14** **15** **16** **17** **2**

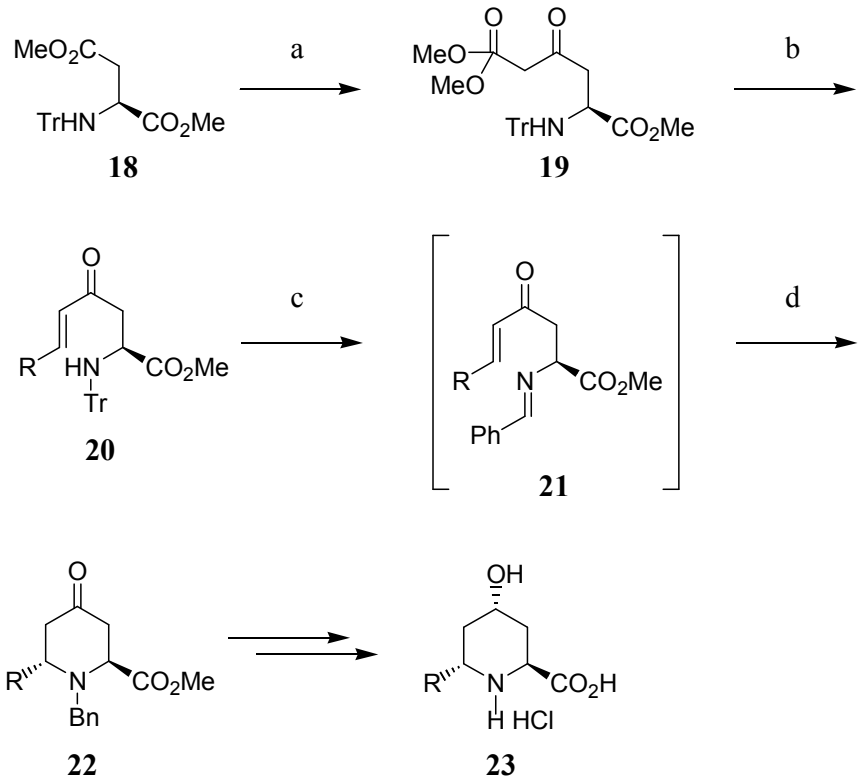
Schema 1: Reagents and conditions: (a) DMSO, $(COCl)_2$, Et_3N, CH_2Cl_2; (b) vinyl magnesium bromide, THF, 62% over two steps; (c) MOMCl, DIPEA, CH_2Cl_2, 82%; (d), NaH, allyl bromide, DMF, 90%; (e) Grubbs I catalyst, CH_2Cl_2, 84%

This was subject to Swern oxidation and the resulting aldehyde was treated with vinylmagnesium bromide to give an inseparable mixture of *syn*- and *anti*- allylic alcohols **15** in a 87:13 ratio, respectively. Protection of the secondary alcohol as methoxymethyl (MOM) ether

and allylation of the *tert*-butyloxycarbonyl (Boc)-derived amine gave the ring closing metathesis (RCM) precursor **16**, which at this stage could be separated from the minor *anti*-diastereoisomer. Reaction of diene **16** with Grubb's first generation catalyst gave dihydroxypiperidine **17** in 84% yield. Hydrogenation, oxidation of the resulting primary alcohol, followed by deprotection allowed the preparation of (2*S*,3*R*)-3-hydroxypipecolic acid **2** in good overall yield.

A one-pot imine reduction and conjugate addition has been used for the preparation of 6-substituted 2,6-*trans*-4-hydroxy-L-pipecolic acid[23]. Reaction of aspartic acid derivative **18** (Scheme 2) with the anion of dimethyl methylphosphonate gave corresponding ester **19** in 84% yield. This was used in a Horner-Wadsworth-Emmons reaction with various alkyl and aryl substituted aldehydes to give a series of E enones **20**. A four-steps, one pot reaction process involving removal of the trityl protecting group, formation of the imine **21** followed by chemoselective reduction and conjugate addition gave 4-oxo-*L*-pipecolic acid **22** in modest yield. Reduction of **22** and deprotection of the amine and carboxylic acid functional groups under standard conditions gave novel 6-substituted 4-hydroxy-pipecolic acid **23** in acceptable overall yield.

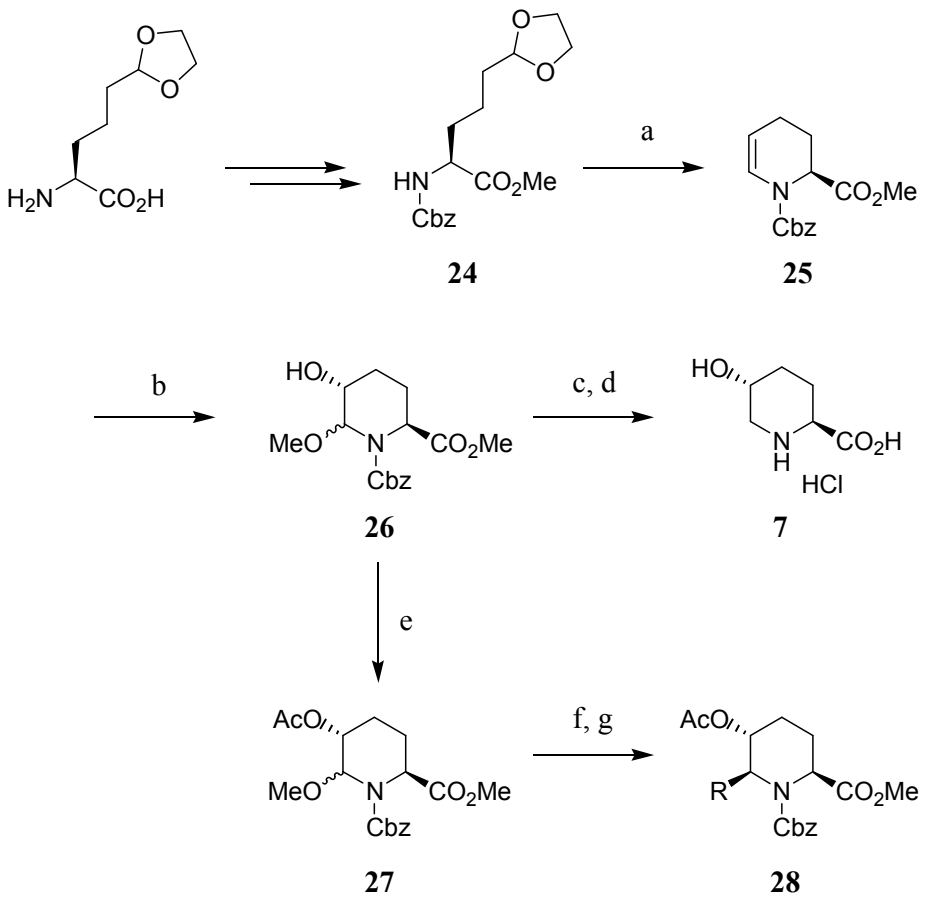
Scheme 2



Scheme 2: Reagents and conditions: (a) $(MeO)_2P(O)Me$, n-BuLi, THF, 84%; (b) RCHO, K_2CO_3, MeCN, 57-96%; (c) TFA, CH_2Cl_2 then PhCHO, Et_3N, 4 Å MS; (d), $NaBH_3CN$, 29-53% over four steps

An highly efficient and common strategy for preparing functionalized pipecolic acid ring system involved the use of inter- and intramolecular reaction of amides with various carbonyl species. For example, Blaauw and co-workers applied this strategy with good results for the synthesis of (2*S*,2*R*)-5-hydroxypipecolic acid **7** and 6-substituted derivatives[24] (Scheme 3).

Scheme 3



Scheme 3: Reagents and conditions: (a) TsOH, DMF, toluene, 98%; (b) Oxone®, $NaHCO_3$, MeOH, 98%; (c) H_2, Pd/C; (d) 6M HCl, 93% over two steps; (e) Ac_2O, Et_3N, DMAP, 99%; (f) TMS-R, Lewis acid, MeCN; (g) H_2, Pd/C, 82-92% over two steps

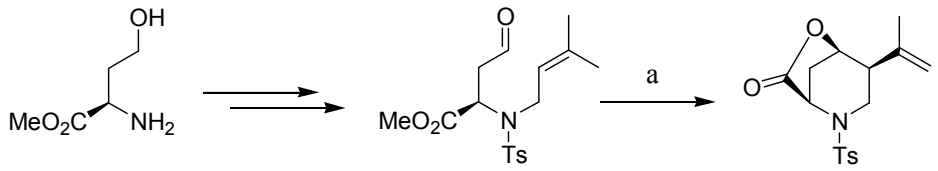
Upon treatment with *p*-toluensulphonic acid in refluxing toluene of acetal **24** (Scheme 3) a smooth cyclization-elimination reaction occurred, providing enamine **25** in 98% yield. Epoxidation of **25** in presence of methanol, the key step of the synthesis, resulted to give the *N*,*O*-aminal **26** in 98% yield and with 94:4 diastereoselectivity in favour of the 2*S*,5*R*-configurated product. Subsequent hydrogenation and hydrolysis of the methyl ester gave (2*S*,5*R*)-5-hydroxypipecolic acid **7** in high overall yield. *N*,*O*-aminal **26** proved to be a good precursor for the preparation of 6-substituted derivatives using N-acyliminium chemistry. After protection of the 5-hydroxy group, the N-acyliminium ion was formed by treatment with

$Sn(OTf)_2$ as a Lewis acid. In situ reaction with a series of silyl nucleophiles gave the 2,6-*cis*-substituted products **28** as single diastereoisomers in high yields. The formation of the 6*S*-configured products is due to nucleophilic attack to the N-acyliminium ion in a pseudoaxial fashion.

Ene-type reactions performed under acidic or Lewis acid conditions have been employed for the stereoselective synthesis of 4-hydroxypipecolic acids.

For example, aldehyde **29** (Scheme 4), synthesized in six steps from *L*-homoserine **30**, was subjected to a carbonyl-ene reaction in the presence of methylaluminum dichloride[25]. At room temperature this gave the *cis*,*cis* product which spontaneously lactonised to bicyclic pipecolic acid **31** in 79% yield.

Scheme 4

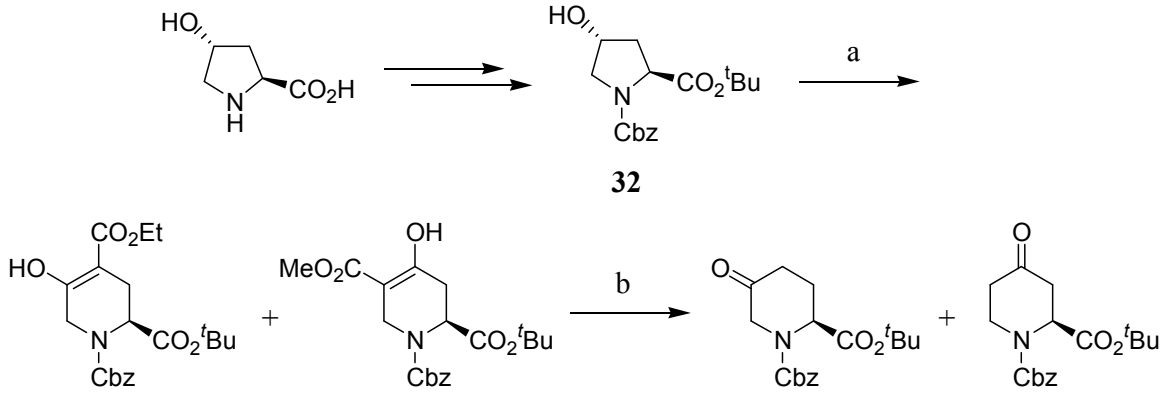


30 **29** **31**

Scheme 4: Reagents and conditions: (a) $MeAlCl_2$, 79%

Another strategy, in contrast to previous examples that used the cyclization of linear amino acids to form the pipecolic acid ring, involve ring expansion of cyclic amino acids[26] (Scheme 5).

Scheme 5



Scheme 5: Reagents and conditions: (a) ethyl diazoacetate, $BF_3{\cdot}OEt_2$, Et_2O, 90%; (b) NaCl, H_2O (cat.), DMSO, 75%

Hydroxy proline derivative **32** underwent a ring expansion reaction with ethyl diazoacetate in the presence of boron trifluoride-diethyl ether. The reaction gave a mixture of the two regioisomers **33** and **34**, which after decarboxylation reaction afforded the 5-oxo and 4-oxo derivatives **35** and **36**, which could be separated via FCC. $NaBH_4$ resulted as the better reducing agent to give C-4 and C-5 hydroxyl *cis* and *trans* derivatives with the highest yield and diastereoselectivity.

2.2 Synthesis from carbohydrates

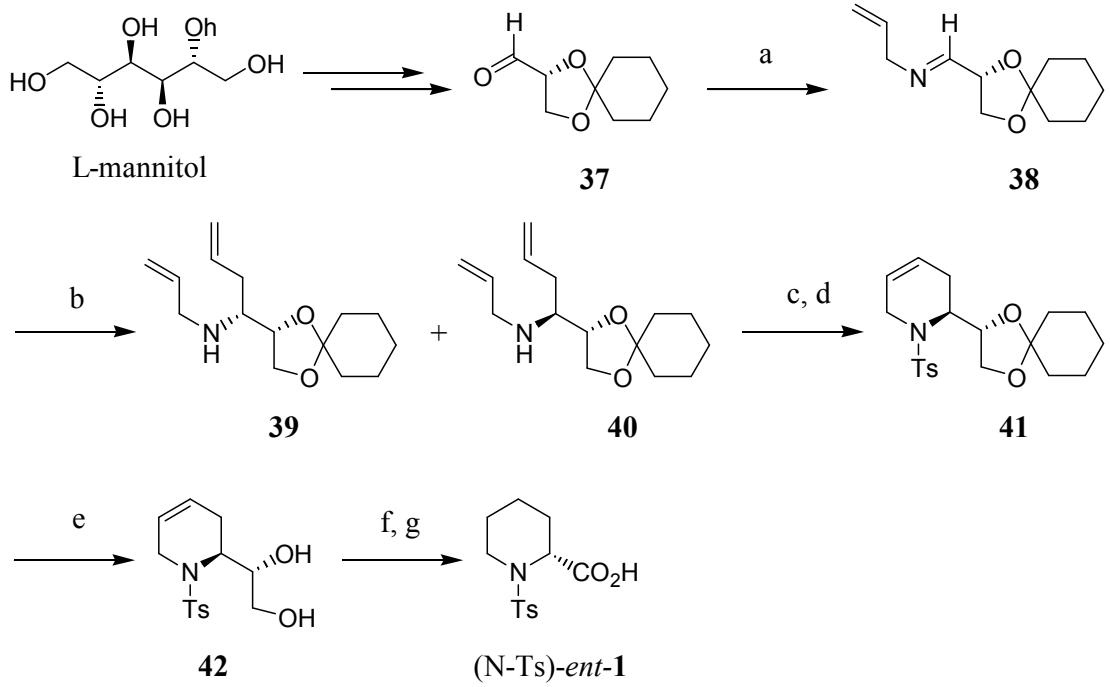
Carbohydrates have been used in combination with key ring forming reactions for the preparation of hydroxylated pipecolic acid derivatives, in similar fashion to amino acids.

The chirality of the pyranoside or furanoside motif is generally used to introduce new stereogenic centres before the key cyclization step, or used directly as a component of the pipecolic acid ring.

Carbohydrates have been converted into chiral dienes and utilized in RCM reactions[27a,b,c].

As an example, Chattopadhyay reported a stereodivergent route to both enantiomers of *N*-tosyl-protected L-pipecolic acids[27a] in which they use aldehyde **37**, prepared from D-mannytol[27c] as key building block (Scheme 6).

Scheme 6



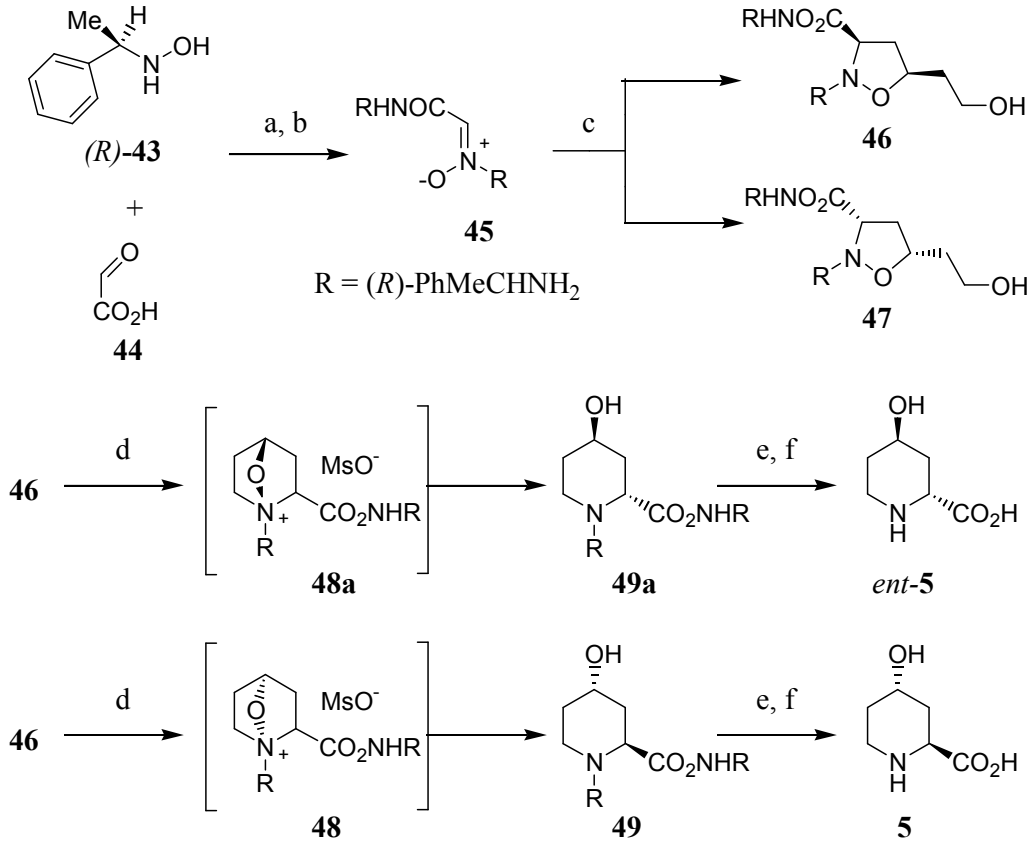
Scheme 6: Reagents and conditions: (a) allylamine, 4 Å MS, CH_2Cl_2, 91%; (b) allylzinc bromide, THF 66%; (c) TsCl, Et_3N, CH_2Cl_2, 91%; (d) Grubbs I catalyst, CH_2Cl_2, 89%; (e) 6 M HCl, 91% (f) H_2, Pd/C, EtOAc, 100%; (g) $NaIO_4$, $RuCl_3$ (cat.), CCl_4, MeCN, H_2O, 73%

Aldehyde **37** was allowed to react with allylamine under anhydrous conditions to give imine **38** which was treated with allylzinc bromide producing the addition products **39** and **40**, with **40** as the major product (19%-47%). The selectivity of the addition could be inverted using allylmagnesium bromide as nucleofile. Tosyl protection of product **40** was followed by RCM reaction with a first generation Grubb's catalyst which gave cyclic alkene **41** in good overall yield. Deprotection of the cyclohexylidene moiety in **41** led to the diol **42**, followed by hydrogenation and oxidative cleavage of the diol unit, to give *N*-tosyl-L-pipecolic acid (N-Ts)-*ent*-**1**. Starting from alkene **41**, the synthesis of 4,5-dihydroxylated compound was also described in the same report (see later for description of this route).

2.3 Chiral auxiliary based approaches

The main strategy in chiral auxiliary based approaches involves the use of a chiral amine source which eventually becomes the amine group of the pipecolic acid ring. For example, nitrone 1,3-dipolar cycloaddition was used for the synthesis of pipecolic acid derivatives[28].

Scheme 7



Scheme 7: Reagents and conditions: (a) Et_3N, 4 Å MS, CH_2Cl_2, 68% (b) DIC, HOBt, Et_2NPr_2, CH_2Cl_2, 52% (c) 1-buthenol, **46** 43%, **47** 43% (d) MsCl, Et_3N, CH_2Cl_2 (e) H_2, 10% Pd/C, MeOH (f) 6N HCl, *ent*-**5** 100% crude, **5** 54%

The condensation of chiral amine (1*R*)-1-phenylethylhydroxylamine **43** (Scheme 7) with glyoxylic acid **44**, followed by coupling with enantiopure amino acid produced nitrone **45**, which is entirely present in (Z) configuration. This selectivity is due to the strong hydrogen bond that stabilizes the nitrone. Treatment of **45** with 1-butenol led to 1,3-dipolar cycloaddition reaction, giving a 1:1 mixture of the isoxazolidines **46** and **47**, which were readly separated by chromatography on silica gel. Mesylation of isoxazolidines **46** and **47** led to the formation of epoxylated intermediates **48a** and **48** that spontaneously open in derivative **49a** and **49**, which were respectively converted into *trans*-4-hydroxypipecolic acids **5a** and **5**. Using a similar reaction sequence, starting from cyclic enantiopure nitrone, the synthesis of *cis*-4-hydroxypipecolic acid was also described[28].

2.4 Chiral synthons approaches

Chiral synthons were used for the synthesis of hydroxylated pipecolic acid derivatives.

Just as an example, for the synthesis of *cis* and *trans* 4-hydroxylated pipecolic acid **4** and *ent*-**5**, (3*S*)-4-ciano-3-hydroxybutanoate **50** (Scheme 8) from the chiral pool (ee 96%), was chosen as a starting material[29]. The configuration of the –OH group in the final molecule is maintained from the starting material[29b].

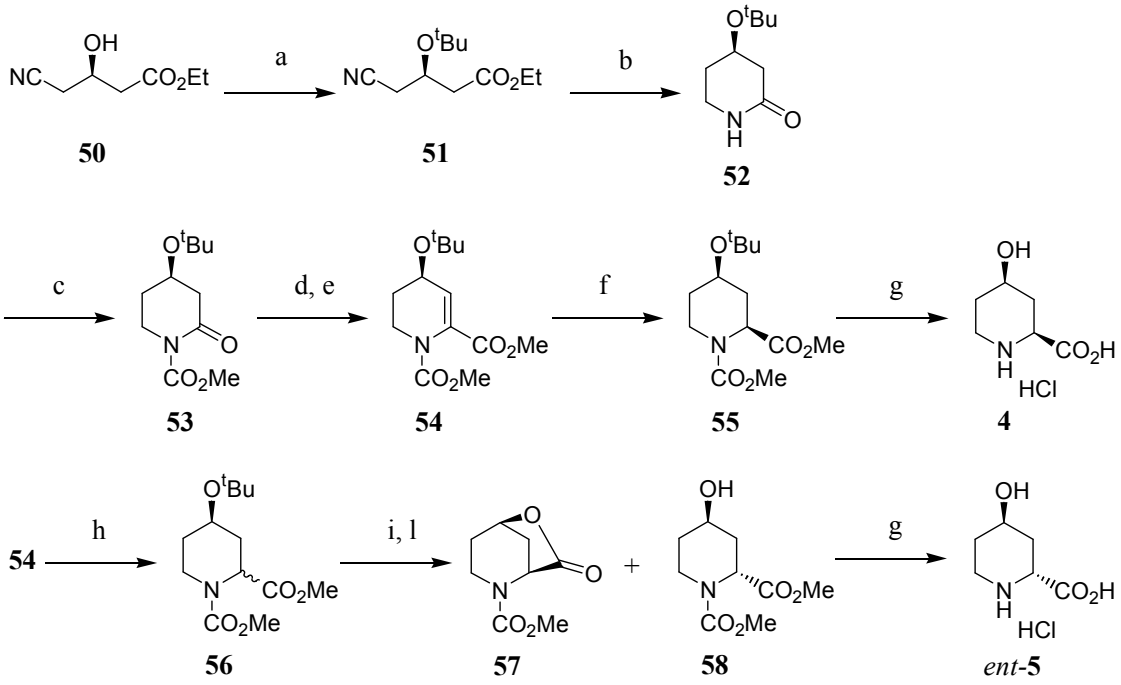
The hydroxyl-group in **50** was protected as *t*Bu using a novel procedure[30], which required the experimental conditions known to lead to the esterification of carboxylic acids, i.e. performing the reaction in *tert*-butyl acetate in the presence of a catalytic amount of $HClO_4$. So, by stirring a solution of the alcohol **50** in *tert*-butyl acetate at 25°C for 24 hours in the presence of acatalytic amount of perchloric acid, protected compound **51** was obtained in 94% yield after FCC. Compound **51** was involved in a Pt-catalyzed hydrogenation that gave lactam **52** in quantitative yield. Following protection of nitrogen as N-CO_2Me (**53**) the corresponding vinyl phosphate was prepared by treatment of **53** with KHMDS followed by addition of diphenyl chlorophosphate. Palladium-catalyzed methoxy-carbonylation of the phosphate in anhydrous DMF at 1 atm CO (balloon) finally gave the key ester intermediate **54** in 81% yield after chromatography.

The *cis* pipecolic derivative **55** was obtained by Pd-catalyzed hydrogenation of **54**. In that conditions, **55** was obtained in a 20:1 ratio whit the *trans* derivative[31]. Finally, exhaustive hydrolysis of **55** gave *cis* **4** in 66% overall yield from **50**.

For the synthesis of *trans* isomer, the unsaturated ester **54** was reduced with Super Hydride ($LiEt_3BH$). The reaction led to a 4:1 mixture of the desired *trans* and *cis* isomers, respectively. The two isomers were separated after deprotection of the -OH group and treatment of the

resulting alcohol mixture with PTSA in toluene at 100°C. In that condition, only the *cis* isomer lactonized (**57**), so the remaining *trans* **58** was isolated and finally converted in the desired *ent*-**5**.

Scheme 8



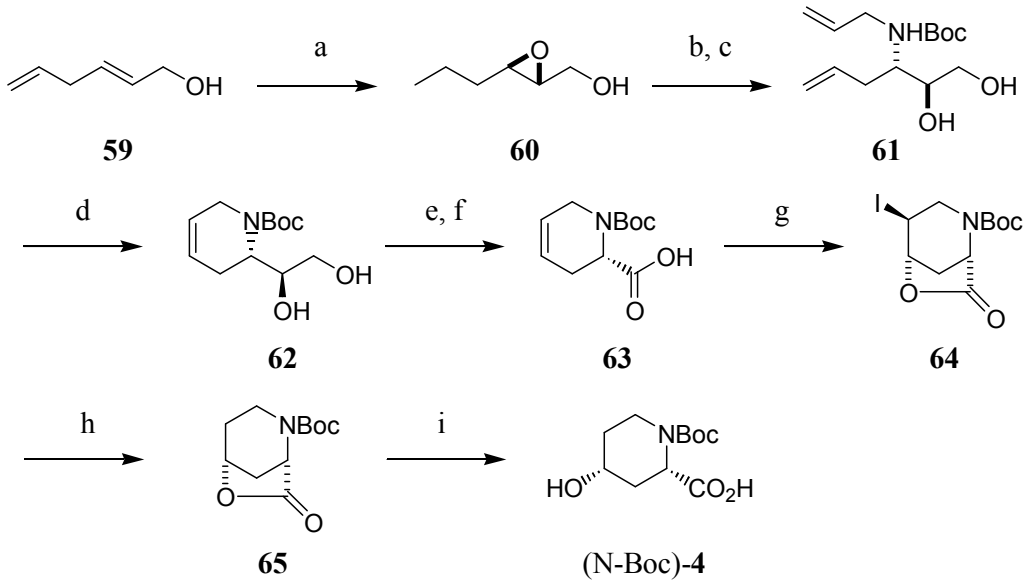
Scheme 8: Reagents and conditions: (a) t-BuOAc, $HClO_4$, 94% (b) H_2, PtO_2, MeOH, 100% (c) *n*-BuLi, MeOCOCl, THF, 88% (d) KHMDS, $(PhO)_2P(O)Cl$, THF, 99% (e) $Pd(OAC)_2$, Ph_3P, CO, MeOH, Et_3N, DMF, 81% (f) H_2, 10% Pd/C, $NaHCO_3$, MeOH, 100% (g) 2N HCl, 100% (h) $LiEt_3BH$, THF, *trans*/*cis* 4:1, 93% (i) $PTSA{\cdot}H_2O$, MeCN, 100% (l) PTSA, toluene, **58** 63% (g) 2N HCl, 100%

2.5 Catalytic Asymmetric Methods

Asymmetric cathalysis was involved in several processes for the synthesis of pipecolic acid derivatives.

Just as an example, for the synthesis of 4-hydroxypipecolic and 3-hydroxypipecolic Alegret used an epoxy-alcohol as source of chirality[32], a substrate obtained in good yield and 93% *ee* by asymmetric Sharpless epoxylation of diene alcohol **59** (Scheme 9) with (+)-diethyltartrate. The regioselective (10:1) C-3 ring opening of **60** by allylamine, followed by N-Boc protection gave diol **61** in *anti*-configuration. Ring closing metathesis of **61** lead to diol **62**, which was oxidized in a two-steps process to N-Boc protected baikjanin **63**. Iodolactamization in standard conditions lead to **64** in 98% yield. Iodide elimination to give **65** followed by lacton hydrolysis lead to desired (N-Boc)-**4**.

Scheme 9

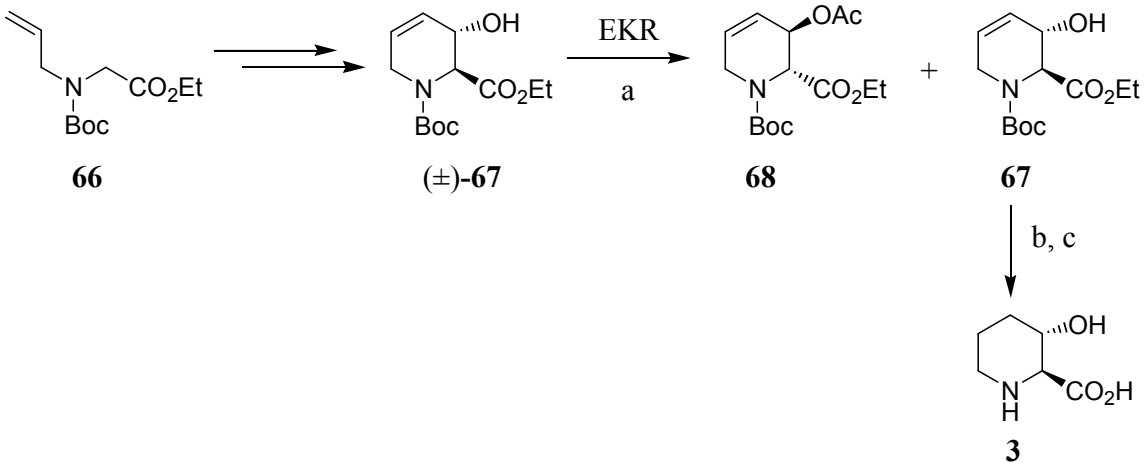


Scheme 9: Reagents and conditions: (a) t-Bu hydroperoxide, D-(-)-DIPT (cat) $Ti(O^iPr)_4$ (cat), 4 Å MS (b) allylamine, $LiClO_4$, 83% (c) Boc_2O, MeOH, 60% over two steps (d) Grubbs I catalyst, CH_2Cl_2, 70% (e) $NaIO_4$, THF/H_2O (f) $NaClO_2$, *t*BuOH/THF, 62-75% over two steps (g) I_2, KI, $NaHCO_3$, H_2O, CH_2Cl_2, 98% (h) Bu_3SnH, AIBN (cat), C_8H_8, 76% (i) NaOH, dioxane/H_2O 70%

2.6 Enzymatic kinetic resolution

Many hydrolytic enzymes have been used for the kinetic resolution of a variety of intermediates in the synthesis of enantio-enriched pipecolic acids, though the main class of enzymes used are lipases. For example, Takahata[33] report the enzymatic kinetic resolution of racemic *trans* substrate (±)-**67** (Scheme 10) obtained in two steps from allylglicine derivatives **66**.

Scheme 10



Scheme 10: Reagents and conditions: (a) lipase, vinyl acetate, *i*-Pr_2O, 47% for **68**, 47% for **67** (b) H_2, Pd/C, EtOAc 99% (c) 5 M HCl, 84%

The (2*S*, 3*S*)-**67** isomer was converted in acetate derivative **68** using *Bulkoldheria cepacia* lipase, immobilized on ceramic particles. Under the best conditions this process gave the acetate in 97% ee and the remaining alcohol with 99% ee.

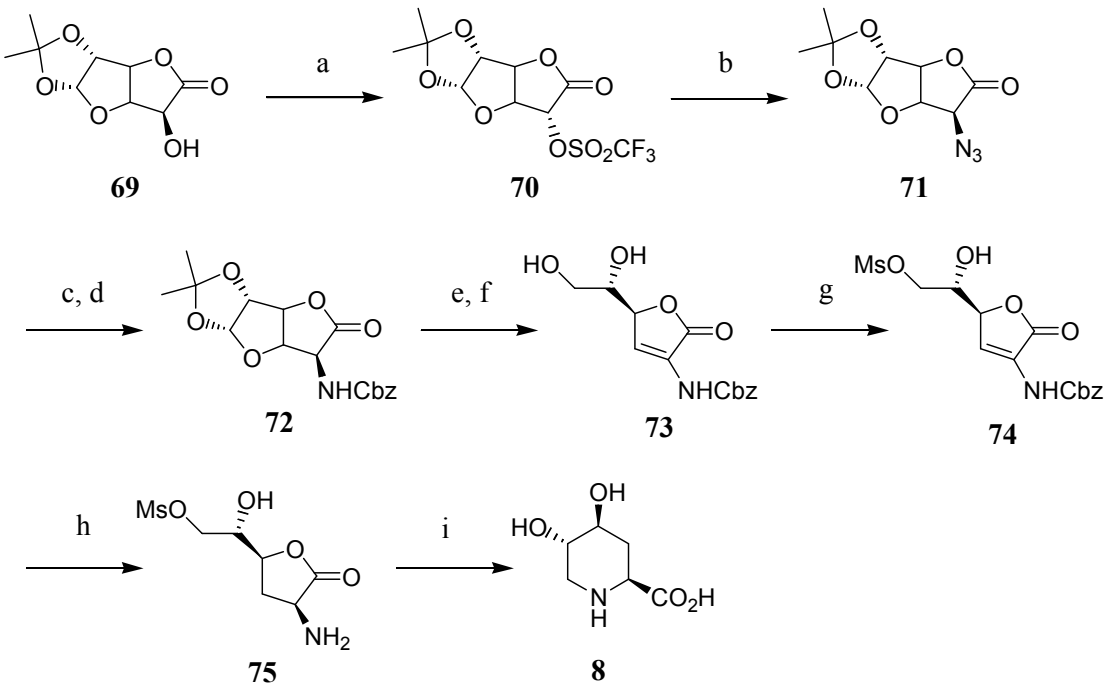
Chapter 3: Previous syntheses of 4,5-dihydroxylated pipecolic acids

Perhaps due to their scarcity in nature, only a limited number of total syntheses of dihydroxypipecolic acids have been described.

In 1976 Marlier report the synthesis of isomers **8**, **9**, **10** and **11**. Mixture of compounds **10** and **11** were obtained in by Marlier[17a] and later by Bleecker[19] through stereoselective *cis* dihydroxylation of the natural compound L-baikiain with OsO_4 in a *t*BuOH-H_2O_2. A tedious chromatographic separation procedure (included 8-day long eluition) and re-crystallization from Et_2OH-H_2O was required to separate and purify the two free acids, with an overall yield of 14% and 5% for **10** and **11**, respectively[17a]. To obtain the *trans* isomers **8** and **9**, N-Cbz protected L-baikiain was oxidized with H_2O_2 in HCO_2H. After N deprotection by hydrogenation on Pd/C the two isomers, obtained as a mixture, were isolated by the same chromatographic procedure as well for **10** and **11**, giving **8** and **9** with 15% and 14% overall yield.

In 1986 Fleet and co-workers reported the synthesis of 4,5 dihydroxy L-pipecolic acid **8 (**Figure 1**)** starting from isopropylidene derivative of D-glucoronolactone[34] **69** (Scheme 11).

Scheme 11



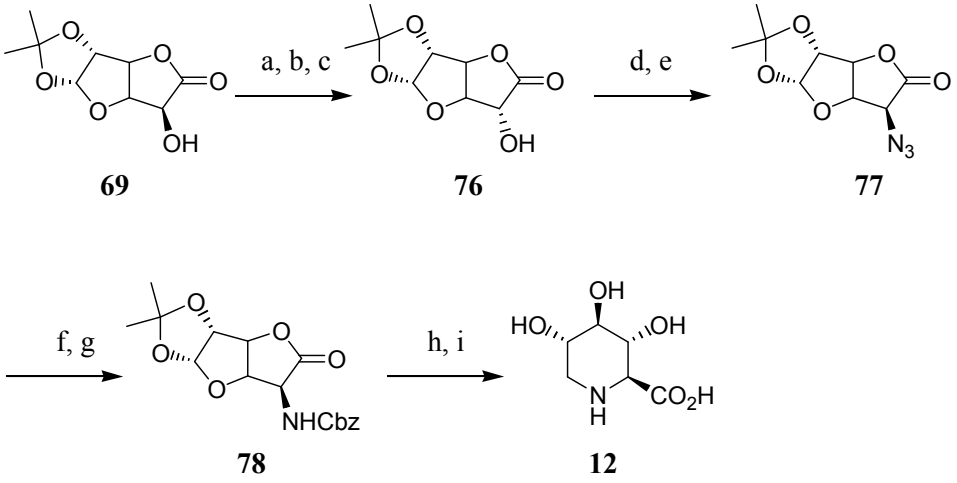
Scheme 11: Reagents and conditions: (a) $(CF_3SO_2)O$, pyridine, CH_2Cl_2 (b) NaN_3, DMF, 84% from **61** (c) H_2, Pd/C, EtOAc (d) Cbz-Cl, $NaHCO_3$, EtOAc/H_2O, 72% over two steps (e) MeONa/ MeOH (f) $NaBH_4$, MeOH, 91% over

two steps (g) $MeSO_2Cl$, pyridine, 80%, (h) H_2, Pd black, EtOAc, pyridine, quantitative yield (i) 0.1 M KOH, EtOH/H_2O 1:1, 82%

Reacting with $(CF_3SO_2)_2O$ in DCM in presence of pyridine, compound **69** gave the corresponding triflate **70** which was converted to the azide **71** with inversion of configuration in C-5. Palladium catalyzed hydrogenation followed by Cbz protection on the nitrogen atom gave compound **72**. Treatment of **72** with a base (MeONa) caused the anticipated fragmentation to give, after reaction with sodium borohydride, the unsaturated diol **73**. Compound **73** was selectivity protected on the primary –OH group as mesylate **74,** than reduced in a palladium black catalyzed hydrogenation to give a single diastereoisomer of aminomesilate **75**. The ring enclosure obtained by treatment with KOH gave dihydroxylated pipecolic acid **8**, which was purified by ion exchange chromatography.

In the same report[34], the synthesis of 3,4,5-trihydroxy derivative **12,** which was found to be a specific inhibitor of human liver β-D-glucuronidase[35], was also described (Scheme 12).

Scheme 12



69 **76** **77**

78 **12**

Scheme 12: Reagents and conditions: (a) $(CF_3SO_2)_2O$, pyridine, CH_2Cl_2 (b) Sodium trifluoroacetate (c) methanolysis 78% over three steps (d) $(CF_3SO_2)_2O$, pyridine, CH_2Cl_2 (e) NaN_3, DMF (f) H_2, Pd/C, EtOAc (g) Cbz-Cl, $NaHCO_3$, EtOAc/H_2O 44% from **60** (h) TFA/H_2O (i) H_2, palladium black, H_2O/ AcOH, 60% over two steps

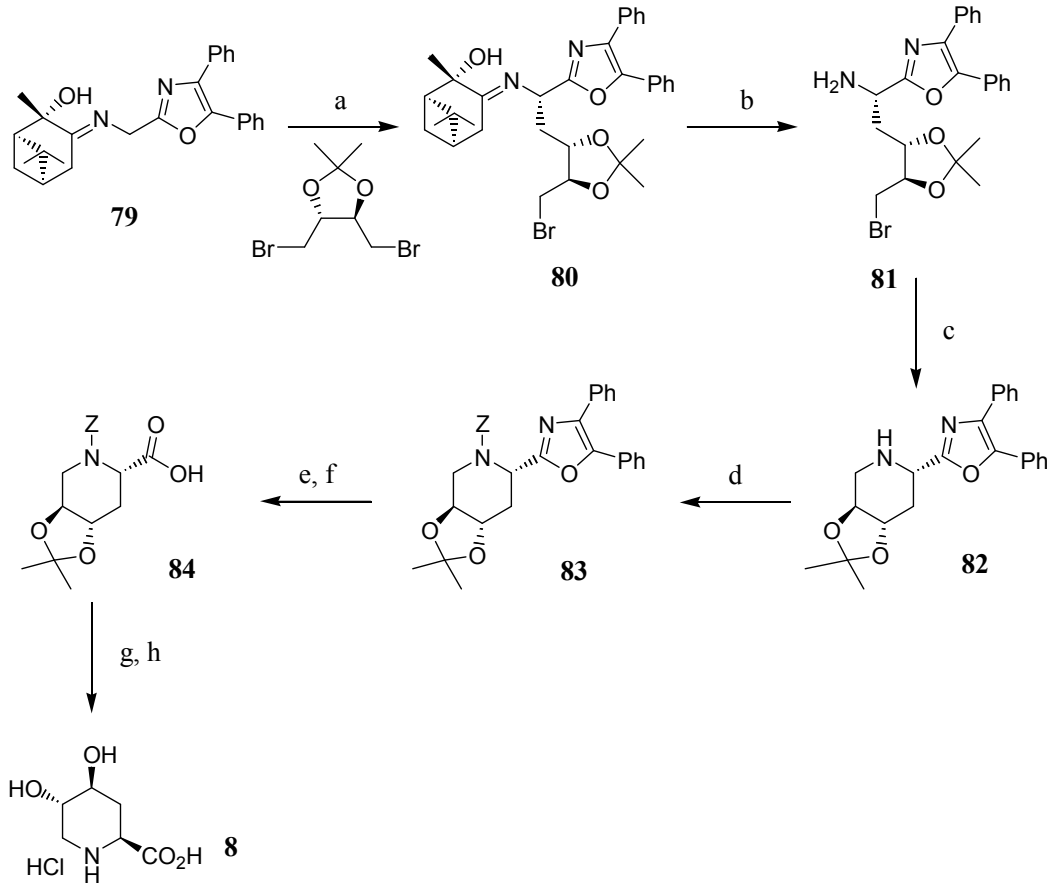
In order to maintain the overall retention of configuration of C-5, the stereochemistry of C5-OH group in **69** was inverted to give the epimeric compound **76** (Scheme 12).

Thus, alcohol **76** was converted in the corresponding gluco-azide **77**, then hydrogenated and protected on the nitrogen as Cbz, giving carbamate **78**. After removal of isopropylidene moiety by aqueous trifluoroacetic acid, the resulting lactol was involved in a catalytic hydrogenation on

palladium black, in aqueous acetic acid. In that conditions underwent intramolecular reductive amination and hydrolysis of the lactone, to give the trihydroxypipecolic acid **12**.

A total synthesis of 4,5-dihydroxypipecolic acid was developed by Thieme et al., based on the use of azomethine chiral auxiliaries and cyclization via nucleophylic bromide displacement[36].
The starting azomethines **79** (Scheme 13), treated with LDA and (4*R*,5*R*)-4,5-bis-(bromomethyl)-2,2-dimethyl-1,3-dioxolane gave the envisaged alkylation products **80** with high yield and stereoselectivity (95:5).
The configuration of the new stereogenic centre was governed by the configuration of the chiral auxiliary. In this case (*S*,*S*,*S)*-hydroxypinanone generates the (*R*) configuration in **80**. The chiral auxiliary in **80** was smoothly split off by hydrolysis in the presence of citric acid to afford 2-(α-aminoalkyl)-oxazole **81**.

Scheme 13

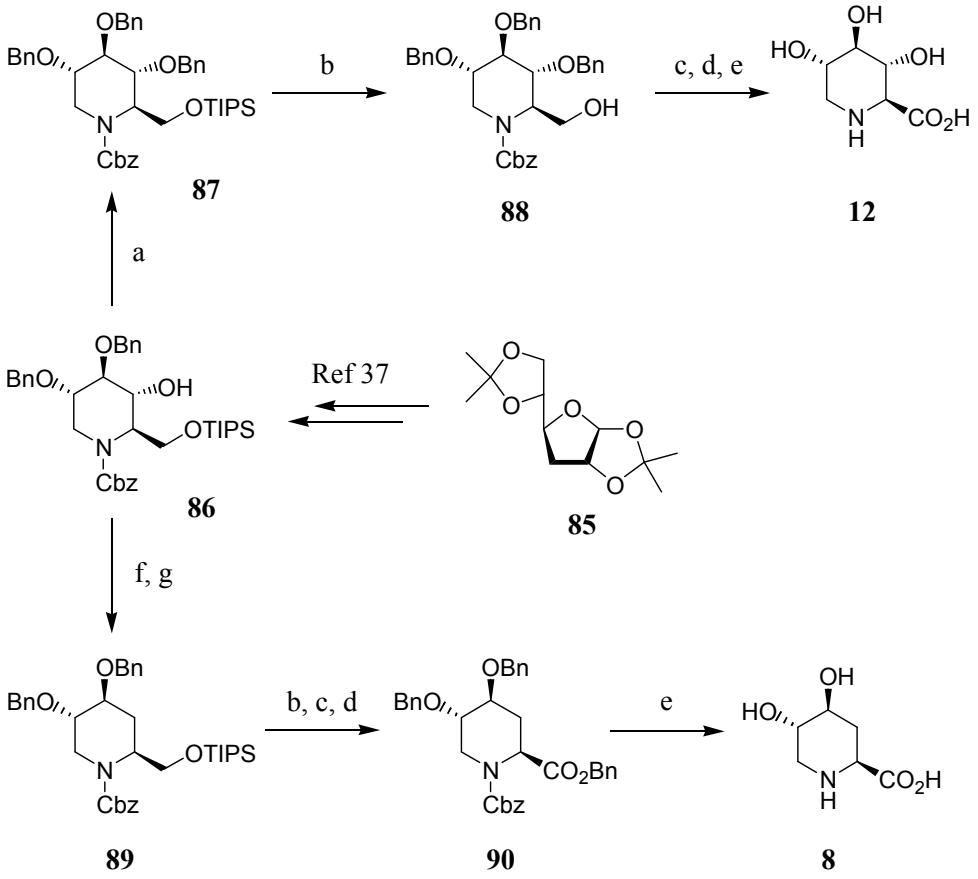


*Scheme 13: Reagents and conditions: (*a) LDA, (4R,5R)-4,5-bis-(bromomethyl)-2,2-dimethyl-1,3-dioxolane, THF, 62-85% (b) citric acid, H_2O/THF, 60-85% (c) Et_2OH, $NaHCO_3$ 71-88%, (d) Cbz-Cl, K_2CO_3 dioxane/H_2O, 97% (e) O_2, rose bengal, UV light, CH_2Cl_2 (f) dioxane/H_2O, 48% (g) H_2, Pd/C, MeOH (h) HCl, THF

Treatment of **81** with $NaHCO_3$ in ethanol induced the intramolecular cyclization, which afforded the optically active piperidine derivative **82** in 88% yield. Compound **82**, after protection as N-Cbz (**83**) reacted with oxygen under UV-light in the presence of Rose Bengal, for the cleavage of the C-C double bond of the oxazole ring, and following gave acid **84**. Finally enantiopure **8** was obtained as chlorohydrate after N-deprotection and exhaustive hydrolysis.

Starting from **85**, (Scheme 14) Kuzuhara and Takahashi, provided a seven-steps stereoselective synthesis of enantiopure 4-deoxynojirimycin derivative **86**[37], and they used it as a precursor for the synthesis of trihydroxylated **12**[38] and dihydroxylated **8**.
After benzylation of C3-OH in **86** that gave **87**, the silyl group in C-6 was removed, and the free primary –OH group in **88** was converted into a carbonyl function by Jones oxidation at room temperature, than converted in benzyl ester with BnBr and Cs_2CO_3. Finally, palladium catalyzed hydrogenation gave inhibitor **12** in good overall yield.

Scheme 14



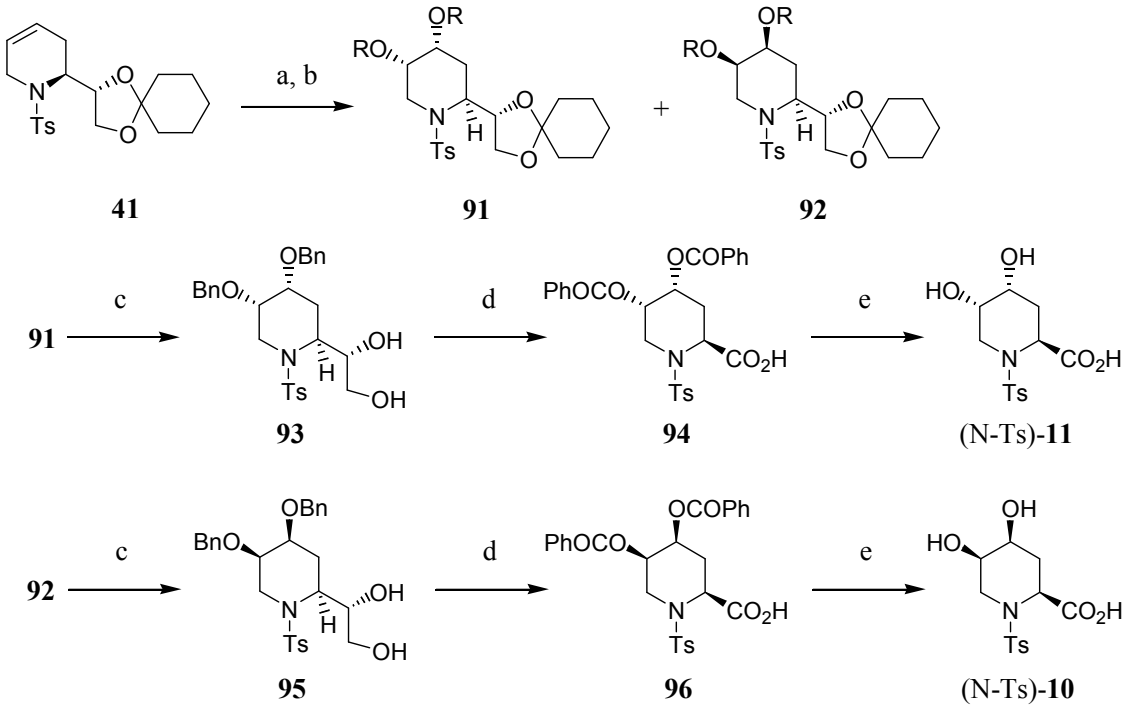
Scheme 14: Reagents and conditions: (a) NaH, BnBr, *n*-BuNI, DMF, 66% (b) *n*-BuNF, AcOH, THF, 98% (c) Jones Reagent (d) BnBr, Cs_2CO_3, DMF, 69% over two steps (e) H_2, 10% Pd/C, AcOH, EtOH, H_2O, 53% (f) PhOCSCl, pyridine/CH_2Cl_2 (g) Bu_3SnH, AIBN, toluene, 82% over two steps

The synthesis of dihydroxylated pipecolic acid **8** began with a deoxygenation reaction at C-3 position of **86**. This conversion was performed by converting the alcohol into a thiocarbonate derivative by the action of phenoxythiocarbonyl chloride, followed by deoxygenation *via* radical reaction with tributyltin hydride in the presence of azobis(isobutyronitryle) (AIBN) in toluene. With a similar strategies to as that from **87** to **12**, the compound **89** was finally converted into enantiopure derivative **8**.

More recently Chattopadhyay reported a stereodivergent route to *N*-tosyl-proteced L-pipecolic and *N*-tosyl-*4,5-cis* dihydroxylated derivatives[27] N-Ts-**11** and N-Ts-**10** (Scheme 15, Cfr Scheme 6).

Cyclic alkene **41** (Scheme 15) was subject to dihydroxylation with osmium tetroxide and *N*-methylmorpholine-*N*-oxide (NMO) to give a 1:1 mixture of *cis* dihydroxylated diastereoisomers, that were separated by column chromatography. Each diastereoisomer was protected as O-Bn to give **91** and **92**. The oxidation of the diol group in **91** and **92** with concomitant conversion of benyl group in benzoate gave pipecolic derivatives **94** and **96**, which finally were converted in the *N*-tosilated *cis* and *trans* derivatives (N-Ts)-**10** and (N-Ts)-**11**. However, no attempts of removing the N-Tosyl preotection were done.

Scheme 15



Scheme 15: Reagents and conditions: (a) OsO_4, NMO, acetone/H_20 4:1 (b) NaH, BnBr, THF/DMSO 10:1, **91** 31% over two steps, **92** 25% over two steps (c) 6N HCl, THF, **93** 81%, **95** 82%, (d) $NaIO_4$, $RuCl_3$ (cat), CCl_4/CHCN/H_2O (1:1:1.5) **94** 53%, **96** 59% (e) 1M KOH, MeOH, (N-Ts)-**11** 71%, (N-Ts)-**10** 68%

So, whereas a limited number of syntheses of compound **8** exist, in the end no practical and scalable syntheses of compounds **9**, **10** and **11** have instead been reported so far.

In general, the scarce attention towards polyhydroxylated pipecolic acids is surprising, because just as monohydroxylated pipecolic acids **2**-**7** have been used as frames around which to build biologically active compounds, polyhydroxypipecolic acids **8**-**11** could be exploited in a similar fashion, with the advantage that the presence of a further hydroxy group can either provide further interactions with the target protein's active site or be functionalized in order to attain higher potency and selectivity, as well as to modulate lipophilicity, a parameter that influences solubility, permeability through membranes, and clearance, i.e. biological processes relevant in drug discovery.

Chapter 4: Cyclopropanated amino acids as conformationally constrained molecular scaffold

The scope of pipecolic acids can be futher expanded by the introduction of conformational restrictions. In fact, the practice of constraining natural amino acids in their conformationally rigid analogues has been highly successful in the design and synthesis of peptidomimetics and other bioactive molecules, with improved selectivity and methabolic stability[39]. For example, a particular three-dimensional arrangement of the peptide side chains can be obtained by appropriately constraining, biasing or fixing the side chain conformers, in order to get a particular foldamer of the molecule. This approach requires a set of amino acids with particular steric constraints. Moreover the molecular rigidity that is attributed to cyclic molecules (like pipecolic acids), may be employed in reducing entropic costs that are associated with enzyme and receptor binding. In addition, the defined spatial arrangement of cyclic structures may be valuable in ascertaining information about the bioactive conformation, which can be used to modulate the binding properties, i. e. potency and selectivity.

On this ground, cyclic amino acid analogues containing a cyclopropane skeleton, including proline and pipecolic acids[40] (Figure 4), are of broad interest as biological probes, enzyme inhibitors and conformationally analogues of native amino acids[41], as the three membered ring introduces specific steric constraints into the amino acids, possibly leading to changes in peptide conformation and reactivity.

Figure 4

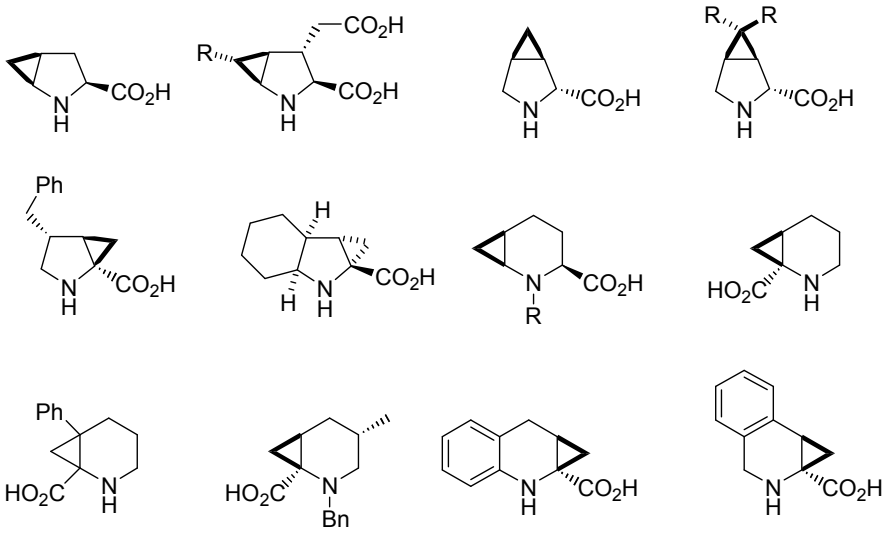


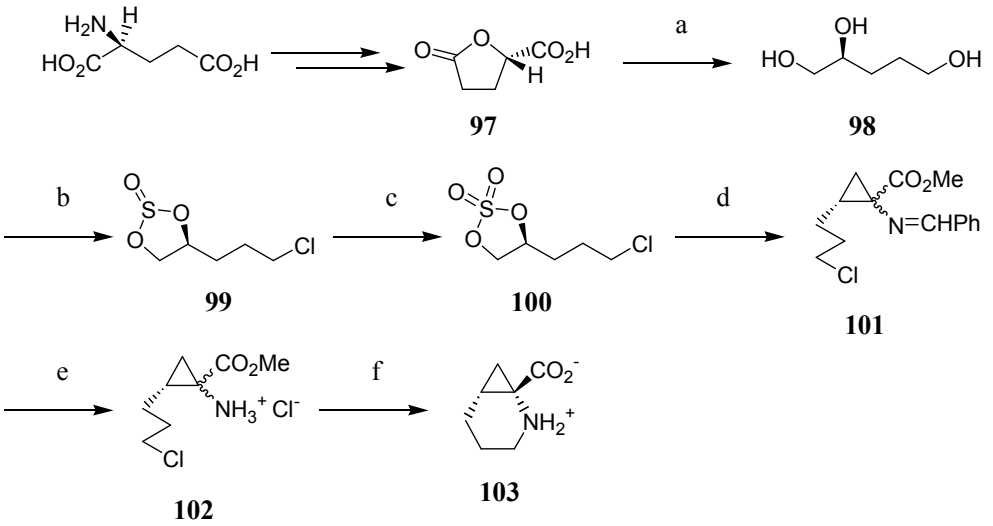
Figure 4: selected examples of cyclopropanated proline and pipecolic amino acids

In fact, the cyclopropane ring exibit a certain "unsatured character" which results in a restriction torsion angles about the Cα-C=O bond to small values, due to the conjugation of the carbonyl group with the ring[41]. More specifically, the 1-aminocyclopropane carboxylic acid residue has been shown to exhibit a marked preference for the conformational space $\Phi, \Psi = \pm 90°, 0°$ i.e. for the position *i* +2 of type I and type 2 β-turns[42], possibly leading to profound changes in the peptide conformation and reactivity.

4.1 Previous synthesis of 2,3-methanopipecolic acids

In literature are reported a variety of synthetic strategies for the synthesis of acyclic and five-membered 2,3–methano amino acids, while only few methods have been reported for the synthesis of 2,3-methanopipecolic acids.
In the first synthesis, described by Hercouet in 1996[43], lactone **97** (Scheme 16), obtained from *L*-glutammic acid[44] was converted to triol **98** by treatment with BMS in chloroform.

Scheme 16



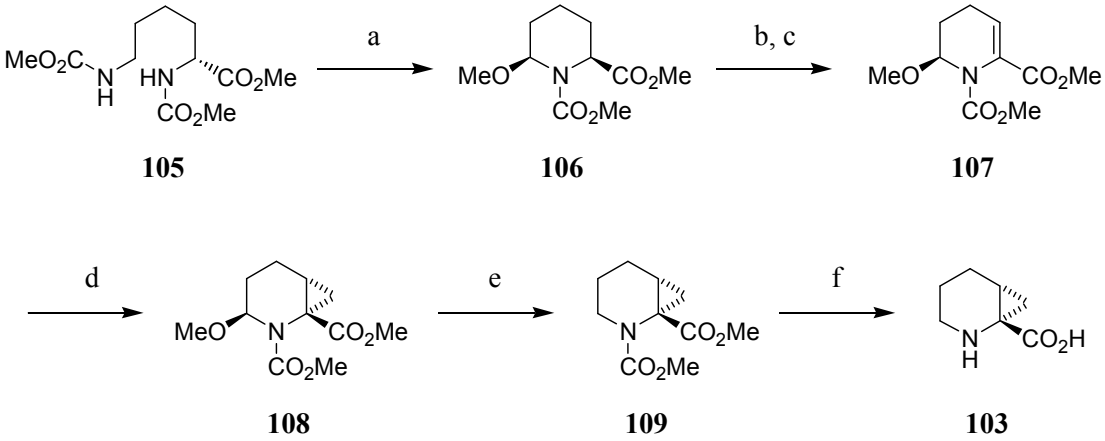
Scheme 16: Reagents and conditions: (a) $BH_3 \cdot Me_2S$, $CHCl_3$, MeOH, 78% (b) $SOCl_2$, CCl_4, 72% (c) $NaIO_4$, $RuCl_3 \cdot 3H_2O$ (cat), 96% (d) $PhCH{=}NCH_2CO_2Me$, NaH, DME, 99% (e) 1N/Et_2O HCl, 86% (f) 1NaOH, then 6N HCl, Dowex 50x8, 59%

Crude pentanetriol **98**, reacted with $SOCl_2$ in refluxing CCl_4 afforded cyclic sulfite **99**. This sulfite was oxidized to sulphate **100** via Sharpless reaction. Diastereospecific alkylation of methylbenzhylideneglycinate with **100** gave **101** as a single isomer with 99% yield. Product **101** was hydrolyzed to get the aminoester **102** as hydrochloride, that cyclised in basic conditions (NaOH) to the desired piperidine **103**, which was purified by ion exchange chromatography.

Following a different approach, Matsumura[45] report the synthesis of 2,3 methanopipecolic acid starting from *L*-Lysine derivative **105** (Scheme 17).

Cyclization of **105** to **106** occour via electrochemical anodic oxidation of **105** in methanol, followed by an acid-catalyzed cyclization, without isolation of the oxidation intermediate[46]. Treatment of **106** with KHMDS and diphenyldisulfide gave a phenylthiolated compound which was oxidized with *m*-CPBA to get 2,3-unsaturated derivative **107** in good overall yield and 88% ee. Cyclopropanation reaction was performed treating **107** with dimethylsulfoxonium methylide in DMSO. The reaction gave cyclopropanated **108** with very high facial selectivity (96:6% *de*). This selectivity could be explained in terms of steric and/or electrostatic repulsion between methoxy group of the molecule and dimetylsulfoxonium ylide. In fact, the ylide preferentially attack on the opposite face. The metoxy group in **108** was removed by reductive elimination with $NaBH_4$ in formic acid to get **109**, than the free acid **103** was obtained by hydrolysis with trimetylsilil iodide in $CHCl_3$.

Scheme 17



Scheme 17: Reagents and conditions: (a) anodic oxidation, MeOH, then H_2SO_4, 47% (b) KHMDS, PhSSPh, 90% (c) *m*-CPBA, 92% (d) Me_3SOI, NaH, DMSO, 73% (e) $NaBH_4$, HCO_2H, 75% (f) Me_3SiI, $CHCl_3$, 50%

Scope of the work

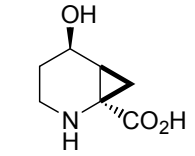
In the previous chapters we have described as the hydroxypipecolic acid scaffolds are emerging privileged structures involved in many important applications, in particular as constituents of pharmaceutically and biologically active compounds, as well as and conformational probes. Although an increasing number of works are devoted to the synthesis of mono- or polysubstituted pipecolic acid derivatives, the research of new synthetic routes to hydroxylated derivatives in enantiopure form remains a great centre of interest.

On this ground, the aim of this research work is the development of new methodologies for the synthesis of enantiopure mono- and dihydroxylated pipecolic acid derivatives (Figure 5). In particular, the work will be focus on several complementary approaches to the synthesis of 4-hydroxy-, 5-hydroxy- and 4,5-dihydroxypipecolic acids, in particular focusing, as for as it concerns the latter compounds, on the more neglected pipecolic acids **9-11** (Figure 2), and their enantiomers. Our approach will be based on the chemistry of lactam-derived enol phosphates developed in our lab, which we have recently shown to be suited to the preparation of enantiopure 4-hydroxypipecolic acids[29].

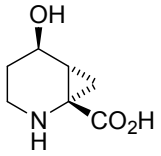
Moreover, with in mind the introduction of further constraints in hydroxypipecolic acids, we focused on the introduction of a cyclopropane ring in the position 2,3 of these molecules, in order to obtain mono- and dihydroxy methanopipecolic acid derivatives **110-113** and their enantiomers *ent*-**110-113** (Figure 5) as a new class of conformationally constrained amino acid analogues to be employed as conformational probes and in the discovery of new drugs.

For the above mentioned cyclopropanated derivatives, we envisage as a possible application the construction of RGD sequence-containing cyclopeptides, having in mind the synthesis of integrine ligands. This application is supported by preliminary calculation in MM2 which suggest the suitability of these scaffolds for building up cyclopeptides.

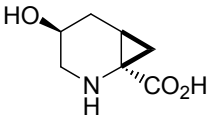
Figure 5



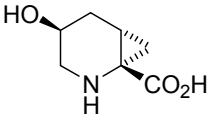
(1*R*,5*R*,6*S*)-**110**



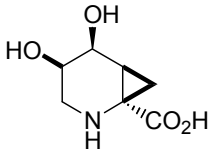
(1*S*,5*R*,6*R*)-**110**



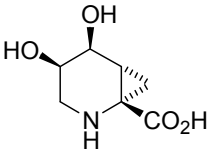
(1*R*,4*S*,6*S*)-**111**



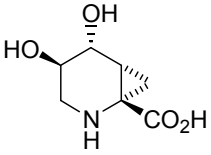
(1*S*,4*S*,6*R*)-**111**



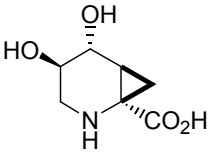
(1*R*,4*R*,5*S*,6*S*)-**112**



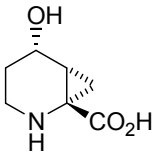
(1*S*,4*R*,5*S*,6*R*)-**112**



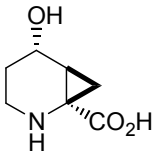
(1*S*,4*R*,5*R*,6*R*)-**113**



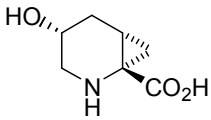
(1*R*,4*R*,5*R*,6*S*)-**113**



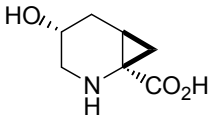
(1*S*,5*S*,6*R*)-*ent*-**110**



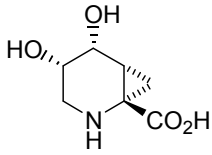
(1*R*,5*S*,6*S*)-*ent*-**110**



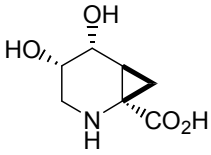
(1*S*,4*R*,6*R*)-*ent*-**111**



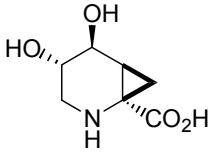
(1*R*,4*R*,6*S*)-*ent*-**111**



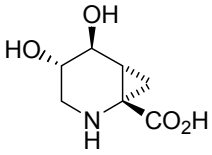
(1*S*,4*S*,5*R*,6*R*)-*ent*-**112**



(1*R*,4*S*,5*R*,6*S*)-*ent*-**112**



(1*R*,4*S*,5*S*,6*S*)-*ent*-**113**



(1*S*,4*S*,5*S*,6*R*)-*ent*-**113**

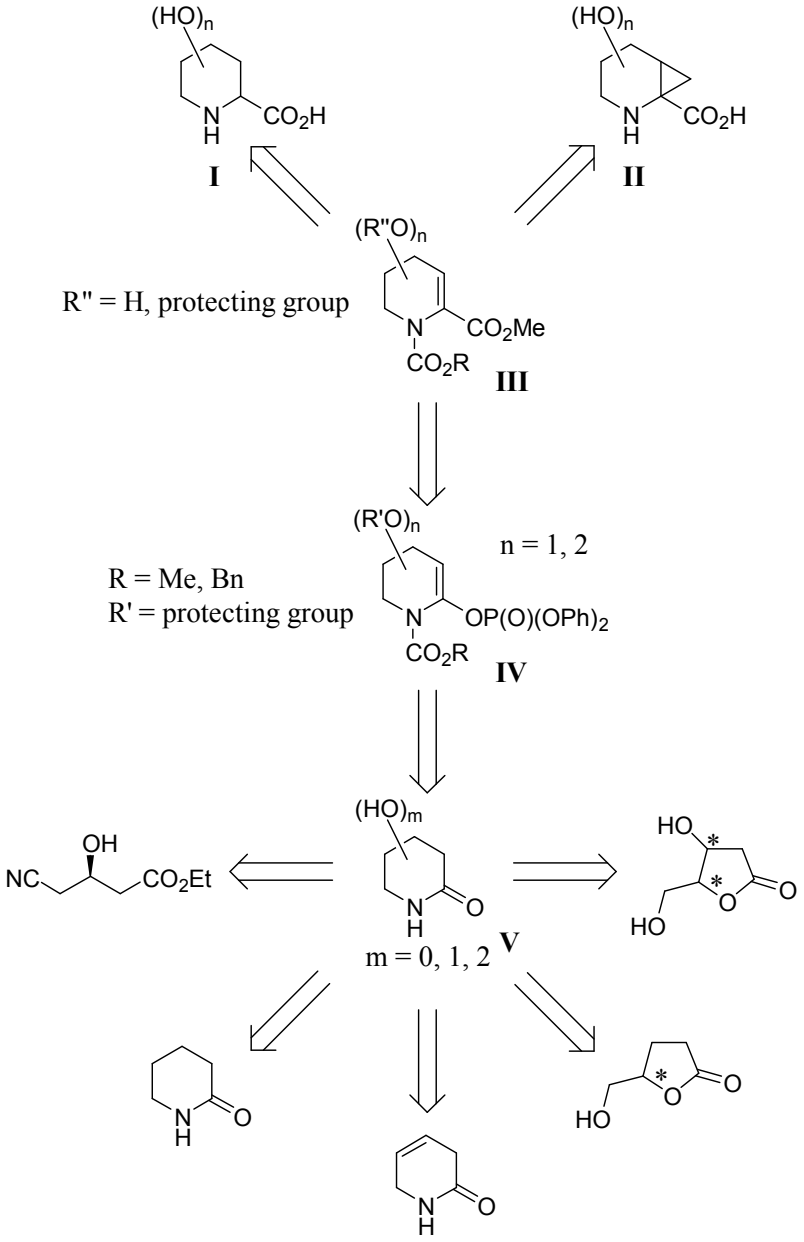
Figure 5: cyclopropanated hydroxypipecolic acid derivatives

Results and discussion

Chapter 1: General synthetic strategy

Our approach to the synthesis of hydroxypipecolic acids (**I**, Scheme 18), as well as their cyclopropanated derivatives (**II**), was based on the transformation of hydroxylated lactams (**V**) into enecarbamate esters (**III**) through a Pd-catalyzed methoxycarbonylation of the corresponding enol phosphates (**IV**)[47].

Scheme 18



Scheme 18: general synthetic pathway for hydroxylated pipecolic acids and their cyclopropanated analogues

Such enecarbamate esters were then converted into 4-hydroxypipecolic acids by exploiting the stereocontrol exerted by suitable OH group protections during the reduction step.

Stereocontrolled cyclopropanation reactions were developed and applied on the same enecarbamate ester precursors, in order to obtain 2,3-methanopipecolic derivatives with very high optical purity.

This methodology, of course, requires enantiopure hydroxylated lactams as starting material or, as an alternative, a racemate resolution at any stage of the synthesis. Both approaches were used by us during this research work for the synthesis of mono- and 4,5-dihydroxypipecolic acids[48,49] as well as their cyclopropanated derivatives[50], and various piperidine alkaloids such as glycosidase inhibitors fagomine[48] and 1-deoxymannojirimycin[51].

Chapter 2: Synthesis of 4-hydroxypipecolic derivatives

2.1 Sytnthesis of enecarbamate ester precursors from (3*R*)-4-ciano-3-hydroxybutanoate

In our laboratory, a synthetic route for the synthesis of 4-hydroxylpipecolic acids, which started from enantio-enriched precursor **54**, was previously developed. As shown in Scheme 8, the hydrogenation of lactam-derived precursor **54** on Pd/C lead to the formation of the *cis*-derivative **55** in a 20 : 1 ratio with the undesired *trans* isomer. In that case, stereocontrol of the reduction on the double bond was attributed to the *t*Bu.

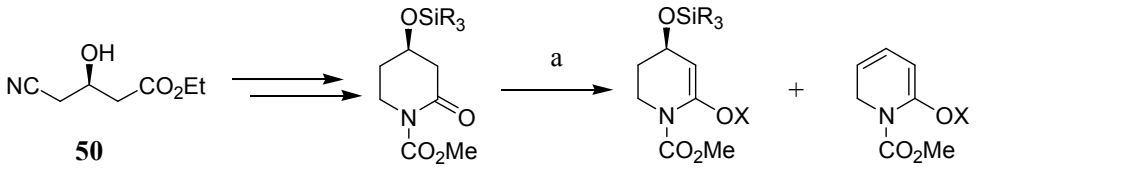
So, if such is the case, the use of a bulkier substituent (like a silyl group) on the hydroxy group should better directing the reduction towards the less hindered face of the double bond to furnish the target *cis* product with a higher facial selectivity than that obtained from **54**.

Unfortunately, as demonstred in a previus study[29a], 4-silyloxy-substituted lactams (obtained with a similar route from **50** as that reported for **55**, Scheme 19a**)**, appear unsuitable for the preparation of the corresponding vinyl triflates and/or phosphates.

In fact, the alkaline reaction conditions employed to generate phosphates or triflates (i.e treatment with KHMDS in THF at –78 °C), led to partial or complete elimination reaction products (Scheme 19a).

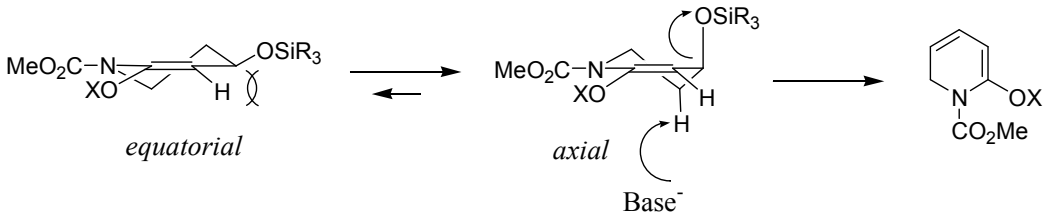
Scheme 19

a)



R_3Si = TIPS: 50% 50% X = Tf, $P(O)(OPh)_2$
R_3Si = TBDPS: 0% 100% X = Tf

b)



Scheme 19: Reagents and conditions: (a) KHMDS, $(PhO)_2P(O)Cl$ or $PhNTf_2$, THF, -78°C

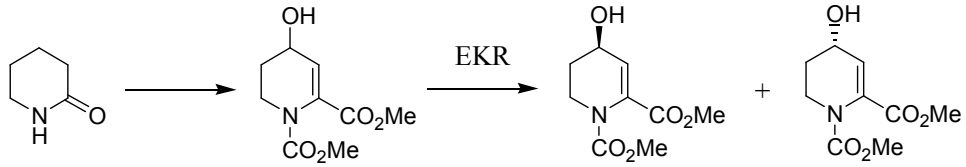
A possible reason for the particular tendency of enolates (or triflates) to give the elimination products is the strong $A^{(1,2)}$ strain generated between the olefinic proton on C-3 and the bulky equatorial silyloxy group after formation of the enolate (Scheme 19b). To reduce the strain, the 4-silyloxy group should adopt an axial orientation, but this could be prone to elimination by an E2 mechanism under the reaction conditions.

During my Ph-D, with the goal of establishing a general procedure for enantioselective synthesis of both enantiomers of 4-hydroxypiperidine derivatives, we worked on a different synthetic route to both antipodes of the 4-hydroxylated enecarbamate precursors. In this approach, the OH group and a suitable silyl protecting group will be inserted in a later stage of the synthesis, thus avoiding the problem of the elimination reaction.

2.2 Synthesis of enecarbamate ester precursors from δ-valerolactam[50]

According to the general synthetic strategy which requires enantiopure enecarbamate precursors, we thus envisaged a chemo-enzymatic approach that would enable us to prepare racemic **118** (Scheme 20) from commercial δ-valerolactam **114** in a short synthetic sequence, followed by a lipase-catalyzed kinetic resolution of **118** to obtain both (*R*)- and (*S*)- enantiomers in enantiopure or enantio-enriched form.

Scheme 20

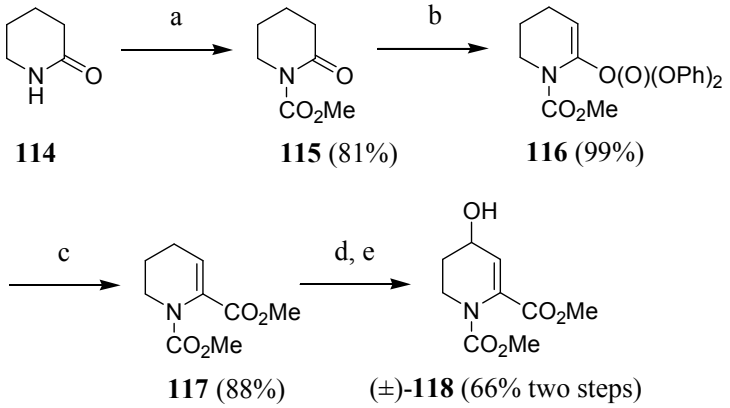


114 (±)-**118** (*R*)-**118** (*S*)-**118**

Scheme 20: synthesis of enantio-enriched enamide ester precursors by EKR of **118**

So, a four-step conversion of N-CO_2Me δ-valerolactam **115** into α,β-unsatured ester **117** (Scheme 21) was realized by Pd-catalyzed methoxycarbonylation of vinyl phosphate **116** whit the same approach as shown in Scheme 19, which provided **118** in 70% overall yield. Allylic oxidation of **117** was carried out with N-bromosuccinimide (NBS) in the presence of a catalytic amount of azobisisobutyronitrile (AIBN), followed by hydrolysis with $ZnCl_2$ in wet acetone (96%) which furnished (±)-**118** in 66% yield.

Scheme 21



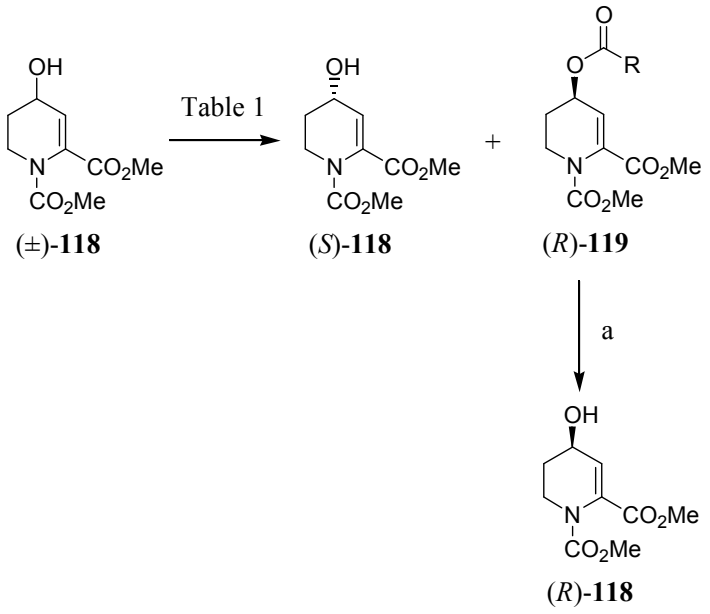
114 **115** (81%) **116** (99%)

117 (88%) (±)-**118** (66% two steps)

Scheme 21: Reagents and conditions: (a) *n*-BuLi, MeOCOCl, THF, -78°C (b) KHMDS, $(PhO)_2P(O)Cl$, THF, -78°C (c) $Pd(OAC)_2$, Ph_3P, CO, MeOH, Et_3N, DMF, 55°C, 3h (d) AIBN, NBS, $CCl_4/CHCl_3$ 9:1, reflux, 15 min (e) $ZnCl_2$, 96% aq. acetone, 25°C, 6h

With sufficient amounts of racemic (±)-**118**, we were ready to study the kinetic resolution of this alcohol by means of lipases in organic media (Scheme 22, Table 1).

Scheme 22



(±)-**118** (*S*)-**118** (*R*)-**119**

(*R*)-**118**

Scheme 22: Reagents and conditions: (a) MeONa, MeOH, 0°C, 3.5h

From the various commercially available lipases, we initially opted to use *Candida antarctica* lipase B (CAL-B) supported on acrylic resin (trade name Novozym 435), because it has been used on a few occasions, either immobilized or free in solution, for the resolution of carbacyclic allylic alcohols that structurally resemble compound **118**[52]. The enantiomeric ratio E ranged from 20 to 187 for substrate depending on the reaction conditions, thus allowing for an effective

resolution. For similar reasons, we employed *Bulkolderia cepacia* lipase[53] (immobilized on diatomaceous earth and commercialized with the name of lipase AMANO IM), which has previously been exploited for the kinetic resolution of alcohols such as 3-ethyl-, 3-bromo-, and 3-nitro-2-cyclohexen-1-ol[54] , with E values from 49 to higher than 100. As in the case of simple secondary[55] and cyclic allylic alcohols[56] the R enantiomer of **118** was preferentially acylated in all experiments (Table 1). With CAL-B, we initially screened various acyl donors in anhydrous acetonitrile which was the best solvent for some 2-cycloexen-1-ols[54a] and, more conventionally, in toluene[57]. In both solvents, the best results were obtained with 4-chlorophenyl butyrate (PCPB)[58] as the acyl donor.
Interestingly, we determined a low E value of about 20 when vinyl acetate was used (entries 1 and 5) which is almost identical to that measured for the kinetic resolution of seudenol catalyzed by free CAL-B[56b].

With 2,2,2-trifluoroethyl butyrate (TFEB), besides low E values, the reaction was slow and never reached 50% conversion (entries 2 and 6). With PCPB, we screened other solvents, and found that anhydrous THF was optimal (entry 10), which is in accordance with the observation that solvents with logP<2 are most suitable for polar substances[59]. In this case, by increasing the amount of enzyme and by using a 0.2 M subdtrate concentration, we eventually obtained an E value 135 that was only just suitable for effective kinetic resolution (entry 11). We also tested vinyl butyrate as the acyl donor under the same conditions, but found that the E value decreased (entry 12).

Better results were obtained with lipase PS-AMANO-IM, although higher enzyme to substrate ratio (mg/mmol) were required to reach acceptable conversion in reasonable times. The best result (entry 14) was obtained by carrying out the resolution in the presence of PCPB in THF at 0.8 M substrate concentration with 100 mg of lipase per mmol of (±)-**118** (E = 162). Under the same conditions with both vinyl acetate (entry 16) and vinyl butyrate (entry 17) this reaction was highly enantioselective, with measured E values of approximatively 160 and enantiomeric excesses for both enantiomers of **118** comparable to those of commercial ethyl (3*R*)- and (3*S*)-4-ciano-3-hydroxybutanoate (96% *ee*) previously employed for the preparation of enantiopure (*R*)- and (*S*)-**55** respectively (See Scheme 8). We thus applied the latter conditions to resolve a sufficient amount of **118** to proceed with the synthesis.
After chromatographic separation of (*R*)-**119** (45% yield, 95% ee) and (*S*)-**118**, pure (*R*)-**118** was obtained by hydrolysis of ester (*R*)-**119**.

Table 1

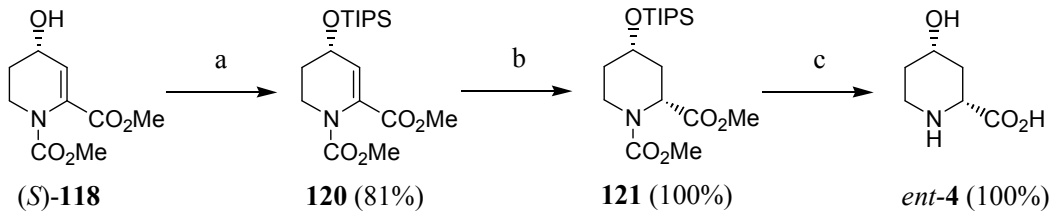
entry	Acylant reagent[a]	Solvent[b]	t (h)	c (%)[c]	(*R*)-**118** ee (%)[d]	(*S*)-**118** ee (%)[e]	E[f]
CALB[g]							
1	VA	CH_3CN	21	45	83	64	21
2	TFEB	CH_3CN	72	36[h]	90	-	31[i]
3	PCPB	CH_3CN	43	36[h]	94	-	54[i]
4[j]	PCPB	CH_3CN	18	54	84	99	59
5	VA	toluene	16	64	56	99	17
6	TFEB	toluene	28	37[h]	82	47	16
7[j]	PCPB	toluene	15	50	88	81	39
8	PCPB	CH_2Cl_2	72	12[h]	85	13	16
9	PCPB	acetone	72	35[h]	95	51	65
10[j]	PCPB	THF	23	47	94	84	92
11[k]	PCPB	THF	4.5	47	96	85	135
12[k,l]	VB[m]	THF	3	52	90	96	74
PS "Amano" IM[n]							
13	PCPB	THF	40	40[h]	97	65	130
14[o]	PCPB	THF	7	45	97	79	162
15	VA	THF	20	36[h]	94	54	56
16[o]	VA[p]	THF	9	45	97	80	163
17[l,o]	VB[p]	THF	6	49	96	93	168

[a] VA: vinyl acetate, TFEB: 2,2,2-trifluoroethyl butyrate, PCPB: 4-Chlorophenyl butyrate, VB: vinyl butyrate. [b] Anhydrous solvents were used. [c] Conversion determined by GLC and ^{1}H NMR. [d] Determined by ^{1}H-NMR analysis of the Mosher ester after hydrolysis. [e] Determined by ^{1}H NMR analysis of the Mosher ester. [f] E = enantiomeric ratio calculated as reported in ref [60] [g] Reaction carried out on 0.2-0.4 mmol of substrate at 30 °C, substrate concentration from 0.2 to 0.4 M, enzyme (mg)/substrate (mmol) ratio from 10 to 25, 2 equivalents of acylant reagent. [h] The reaction did not proceed further and it was stopped. [i] Calculated as $\ln[1-c(1+ee_p)]/\ln[1-c(1-ee_p)]$. [j] Substrate concentration = 0.8 M. [k] Enzyme (mg)/substrate (mmol) ratio = 200. [l] Molecular sieves (4Å, 130 mg/mmol) were used in this experiment. [m] 2.5 equivalents. [n] Reaction carried out on 0.2-0.4 mmol of substrate at 30 °C, substrate concentration = 0.8 M, enzyme (mg)/substrate (mmol) ratio = 20, 2 equivalents of acylant reagent. [o] Enzyme (mg) to substrate (mmol) ratio = 100. [p] 3.5 equivalents.

2.3 Synthesis of *cis* 4-hydroxypipecolic acid[48]

Now that the enantiopure precursor **118** was available, we could protect it with a large silyl group (TIPS, 81% yield) in order to obtain a higher selectivity for the subsequent Pd/C catalyzed hydrogenation to *cis* pipecolic acid. As previously reported for **4**[29b], the synthesis of *ent*-**4** was realized by hydrogenation of O-TIPS compound (*S*)-**120** (Scheme 23), which provided diastereopure (2*R*,4*S*)-*cis*-**121** in quantitative yield. In this case we managed to obtain a diastereomeric ratio higher than that previously obtained with the O-^{t}Bu protected compound (about 20 : 1, See Scheme 8) as we could not detect any trace of the *trans* compound in the ^{1}H-NMR spectrum of the crude reaction mixture. Exhaustive hydrolysis gave *ent*-**4** as its hydrochloride salt in 100% yield[61]. With a similar approach we synthesized the natural enantiomer of **4**.

Scheme 23



(*S*)-**118** **120** (81%) **121** (100%) *ent*-**4** (100%)

Scheme 23: Reagents and conditions: (a) TIPSCl, imidazole, DMF, 40°C, 5h (b) H_2, Pd/C, EtOAc, 25°C, 6h (c) 2N HCl, reflux

2.4 Two-step enzymatic kinetic resolution[50]

We considered that conformationally restricted amino acids, in order to be introduced in a peptide sequence, must have higher enantiomeric excesses than those so far obtained for alcohols (*R*)-**118** and (*S*)-**118** (See Scheme 22, Table 1) and efforts should consequently be made to obtain such synthetic intermediates in enantiopure form.

To this end, we first opted for a two-step lipase-catalyzed kinetic resolution of *N*-CO_2Me protected compound (±)-**118**. However, because of the widespread use of the Cbz group for N-protection in amino acids we also decided to study the enzymatic kinetic resolution of *N*-Cbz derivative (±)-**125** by various lipases and then to subject the products to the stereoselective cyclopropanation.

The two-steps kinetic resolution of (±)-**118** was realized by stopping the enzyme-catalyzed esterification of the alcohol, carried out under the best conditions we found (See Table 1), with a

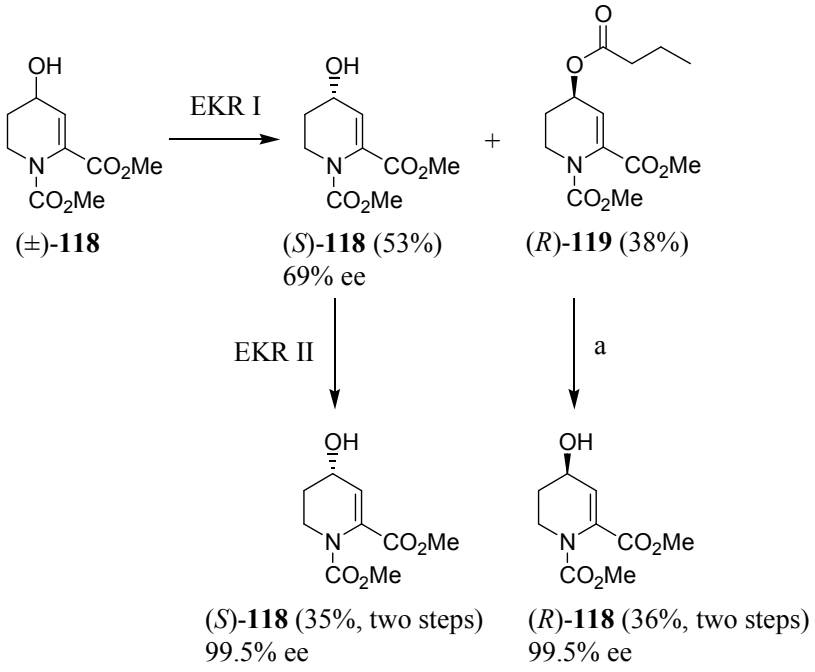
conversion around 40%. In this way, we should obtain the acylated product with high *ee* and only a little loss of material.

The resolution (Scheme 24) was realized by stopping the esterification of the alcohol, carried out in the presence of PS "AMANO" IM lipase and vinyl butyrate as the acylating agent in dried THF (i. e. the best conditions found for the standard kinetic resolution), with 42% conversion (determined by GC and NMR of the crude reaction mixture).

This allowed to obtain butyrate (*R*)- with very high enantiomeric purity (>99.5% *ee*, determined after hydrolysis) in a sufficient amount to proceed with the synthesis. The residual (S)-alcohol, obtained in 53% yield and 73% ee after chromatography, was subjected to the same EKR conditions, stopping the reaction after 22h when the conversion was 17%. After chromatography, enantiopure (*S*)-**118** was obtained in 35% yield over the two steps.

By this procedure, only a minimal amount of substrate was lost and both alcohols (*R*)-**118** and (*S*)-**118** were obtained with higher *ee* than by a single resolution.

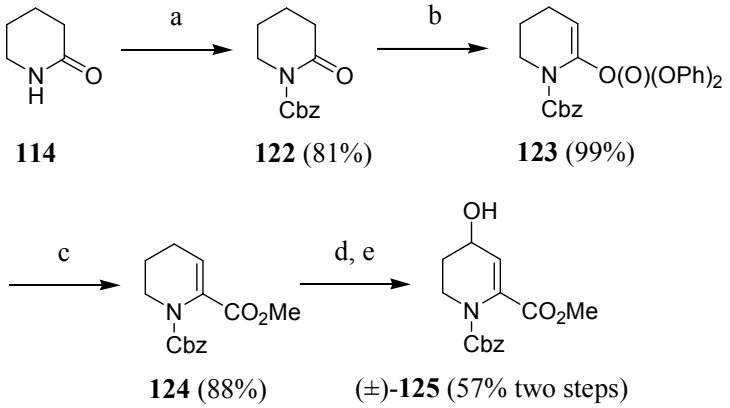
Scheme 24



Scheme 24: Reagents and conditions: (EKR I) vinyl butyrate, PS "AMANO" IM lipase, THF, 4Å MS, 30°C, 7h, 42% conversion (EKR II) vinyl butyrate, PS "AMANO" IM lipase, THF, 4Å MS, 30°C, 22h, 17% conversion (a) MeONa, MeOH, 0°C, 3.5h

Racemic *N*-Cbz-protected alcohol (±)-**125** (Scheme 25) was conveniently prepared by the same procedure reported for (±)-**118**.

Scheme 25



114 **122** (81%) **123** (99%)

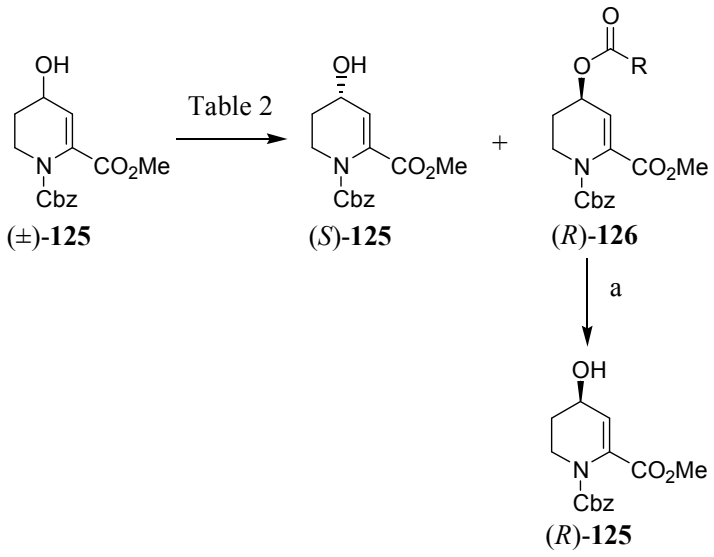
124 (88%) (±)-**125** (57% two steps)

Scheme 25: Reagents and conditions: (a) *n*-BuLi, MeOCOCl, THF, -78°C (b) KHMDS, $(PhO)_2P(O)Cl$, THF, -78°C (c) $Pd(OAC)_2$, Ph_3P, CO, MeOH, Et_3N, DMF, 58°C, 4h (d) AIBN, NBS, $CCl_4/CHCl_3$ 9:1, reflux, 15 min (e) $ZnCl_2$, 96% aq. acetone, 25°C, 6.5h

N-Cbz-protected δ-valerolactam **122** was quantitatively converted into the corresponding enol phosphate **123** and this subjected to Pd-catalyzed methoxycarbonylation to give **124** in 87% yield over two steps after chromatography. Allylic oxidation finally afforded (±)-**125** in 57% yield.

As for N-CO_2Me protected (±)-**118**, in order to determine the best conditions in terms of optical purity and yield of the products (see later for absolute configuration determination), a variety of lipases and solvents were applied to (±)-**125**. (Scheme 26, Tabella 2) Vinyl butyrate (VB, Tabella 2) and vinyl acetate (VA) were used as acylating reagents.

Scheme 26



(±)-**125** (*S*)-**125** (*R*)-**126** (*R*)-**125**

Scheme 26: Reagents and conditions: (a) MeONa, MeOH, 0°C, 3.5h

The kinetic resolution was carried out in the presence of various lipase at 30°C with an excess of either vinyl acetate or vinyl butyrate (3.5 eq) as the acylating reagent. Lipases from *Aspergillus niger*, *Candida rugosa*, *Candida antarctica* and Porcine Pancreatic lipase[62] were tested under various conditions in toluene and *tert*-butyl methyl ether (TBME) with vinyl acetate but the reaction were either very slow or did not take place at all.

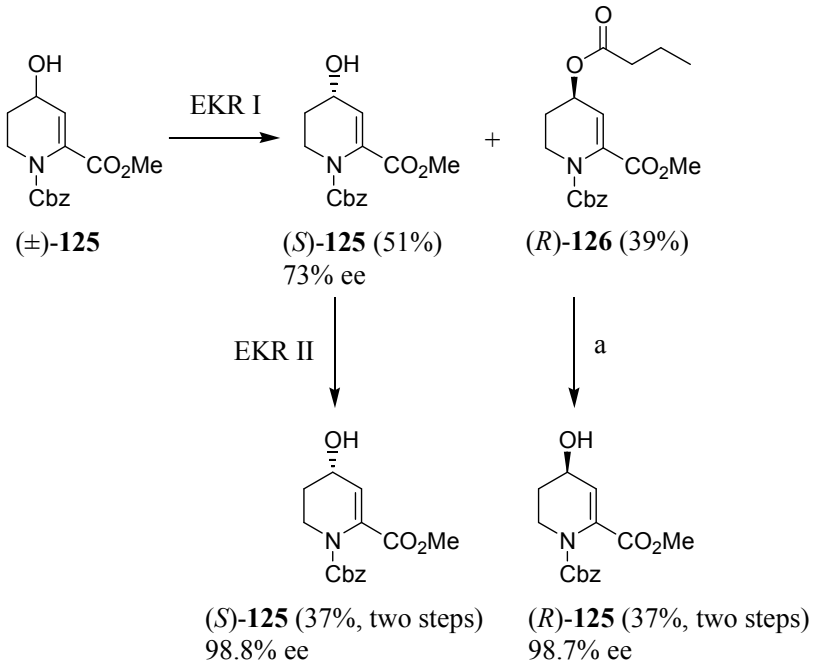
Table 2

entry	Acylant reagent[a]	Solvent[b]	t (h)	c (%)[c]	(*R*)-**125** ee (%)[d]	(*S*)-**125** ee (%)[e]
CALA[f]						
1	VB	THF	4	-	-	-
2	VA	Toluene	90	17[g]	-	-
3	VA	Toluene	7 d	38.5[g]	40	30
4	VA	TBME	7 d	48	31	30
CALB[f]						
5	VB	THF	4	52	85	94
6	VB	TBME	2.3	53	78	90
Amano[f]						
7	VB	TBME	3.6	54	91.4	99.5
8	VB	THF	72	49	94	89
PS-"SolGel"-AK						
9	VB	THF	4	-	-	-
ASN[f]						
10	VA	Toluene	4	-	-	-
CRL[f]						
11	VA	Toluene	96	6.5[g]	-	-
PPL[g]						
12	VA	Toluene	96	2.3[g]	-	-

Table 2: [a] VA: vinyl acetate, VB: vinyl butyrate. [b] Anhydrous solvents were used. [c] Conversion determined by GLC and ^{1}H-NMR. [d] Determined by HPLC analysis of (*R*)-**125** alcohol after hydrolysis. [e] Determined by HPLC analysis of (*S*)-**125** [f] Reaction carried out on 0.2-0.4 mmol of substrate at 30 °C, substrate concentration 0.8 M, enzyme (mg)/substrate (mmol) ratio = 100, 3.5 equivalents of acylant reagent, molecular sieves (4Å, 130 mg/mmol) [g] The reaction did not proceed further and it was stopped.

The best results were obtained with PS "AMANO" IM in TBME with vinyl butyrate (E > 200). We employed that condition for a two-step kinetic resolution of (±)-**125** (Scheme 27) carried out in a similar manner to that (±)-**118** resolution.

Scheme 27



Scheme 27: Reagents and conditions: (EKR I) vinyl butyrate, PS "AMANO" IM lipase, TBME, 4Å MS, 30°C, 1.9h, 44% conversion (EKR II) vinyl butyrate, PS "AMANO" IM lipase, THF, 4Å MS, 30°C, 1.4h, 16% conversion (a) MeONa, MeOH, O°C, 3.5h

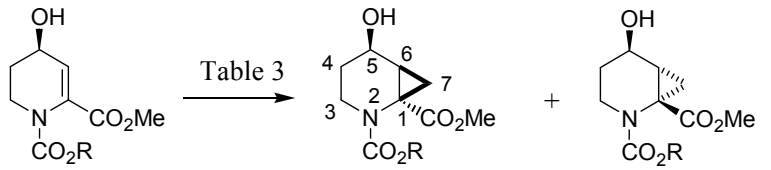
The first esterification reaction was stopped with 44% conversion (See Appendix 3) , and the remaining (*S*)-**125** (51% yield and 73% ee) was subject to a second reaction, interrupted with 16% conversion. This double step process gave the (*S*)-**125** with 37% yield and 98.8% *ee*, and (*R*)-**125** with 37% and 98.7% ee (See Appendix 2).

2.5 Synthesis of *cis* 4-hydroxy-cyclopropanated derivatives: OH-directed cyclopropanation

The OH-directed cyclopropanation of γ-hydroxy-α,β-unsaturated esters has been previously reported in a handful of cases, i.e. by samarium/mercury amalgam in conjunction with diiodomethane[63] and by the Furukawa modification of the Simmons–Smith reaction[64]. In both cases, the hydroxyl group exerted complete stereocontrol, so we explored the use of both Sm– and Zn-carbenoids for the cyclopropanation of enantiopure **118**, and the results are reported in Table 3. Disappointingly, the reaction under Molander's conditions[62b] (entry 1) although

reaching complete conversion after 5 h, provided the target compound in a mixture with various unidentified byproducts. Moreover, the stereoselectivity was very low, with the unexpected predominance of the *trans* compound (*trans*/*cis* ratio of about 1.3 : 1). Considering the highly oxophilic nature of samarium and the excellent stereoselectivity reported by Cossy[63a] we can only assume that the *N*-protecting group somehow competes with the OH group for the coordination of samarium and the delivery of the carbenoid onto the double bond. In support of this hypothesis, the *N*-Boc-directed cyclopropanation of allylic carbamates with Zn-carbenoids has recently been described by Davies[65].

Scheme 28



(*R*)-**118** R = Me
(*R*)-**125** R = Bn

(1*R*,5*R*,6*S*)-**127**
(1*R*,5*R*,6*S*)-**128**
cis

(1S,5*R*,6*R*)-**127**
(1*S*,5*R*,6*R*)-**128**
trans

Table 3

entry	R-OH[a]	Conditions	Conversion (%)[b]	*Cis* (%)[c]	*Trans* (%)[c]
1	**118**	$Sm/HgCl_2$, CH_2I_2, THF, -78°C→25°C, 5 h	100[d]	43	57
2	**118**	Et_2Zn, CH_2I_2, CH_2Cl_2, -12°C→25°C, 24 h	87	100 (60)[e]	-
3	**118**	Et_2Zn, CH_2I_2, TFA, CH_2Cl_2, -78°C→25°C, 24 h	72	100 (35)[e]	-
4	**118**	Et_2Zn, CH_2I_2, 2,4,6-trichlorphenol, CH_2Cl_2, -40°C→25°C, 4 h	100	100 (86)[e]	-
5	**125**	Et_2Zn, CH_2I_2, 2,4,6-trichlorphenol, CH_2Cl_2, -40°C→25°C, 3.5 h	100	100 (79)[e]	-

Table 3: [a] Reaction carried out on 0.2–0.9 mmol of substrate. [b] Reaction monitored by TLC. [c] Relative composition determined by 1H-NMR on the crude reaction mixture. [d] Starting material completely consumed but several unidentified products in the crude reaction mixture. [e] Yield after chromatography.

We tried the Simmons–Smith reaction under three different sets of conditions (entries 2–4): (1) with the Wittig–Furukawa reagent[66] $Zn(CH_2I)_2$ (2) with Charette's carbenoid[67] $Cl_3C_6H_2OZnCH_2I$ and (3) with Shi's carbenoid[68] $CF_3CO_2ZnCH_2I$.

In spite of the latter being one the most reactive carbenoids, the reaction did not reach complete conversion after 24 h (entry 3), as also observed for the reaction with the Wittig–Furukawa reagent (entry 2). Although in all cases we observed the formation of the expected *cis* product only, the best result in terms of cyclopropanation rate and yield after chromatography was obtained with Et_2Zn and CH_2I_2 in the presence of 2,4,6-trichlorophenol (entry 4). Under these conditions the reaction was complete in 4 h, providing the *cis* isomer (1*R*,5*R*,6*S*)-**127** in 86% yield.

These conditions were thus applied to *N*-Cbz protected alcohol (*R*)-**125** to give diastereopure cyclopropanated (1*R*,5*R*,6*S*)-**128** (entry 5) in good yield (79 %), as well as its enantiomer (*S*)-**125** to obtain (1*S*,5*S*,6*R*)-*ent*-**128** (73 %).

2.6 Synthesis of cyclopropanated *trans* derivatives

Having assessed our approach to the synthesis of the *cis*-cyclopropanated derivatives **127** and **128**, the preparation of both *trans* cyclopropanated isomers had to be developed as the next step of the study.

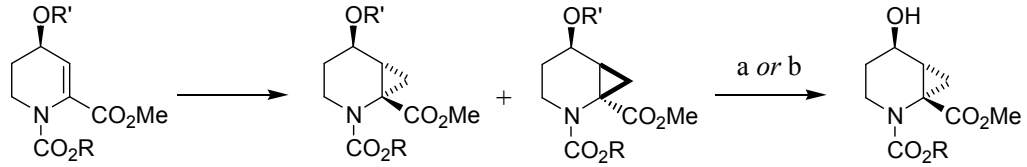
For the synthesis of these the *trans* isomers, we needed a bulky allylic protecting group that could direct the cyclopropanation onto the opposite face of the double bond.

For 4-OTBS-, OTIPS-, and O*t*Bu-protected derivatives of **118**, were already observed good to high facial selectivity in heterogeneous catalytic hydrogenation and hydroboration reactions[29,48], so we were confident that a similar selectivity could be obtained in cyclopropanation, either by exploiting Michael-type reactions of S-ylides or various carbenoids.

However, not only did *O*-protected derivative **129** (R = TBS, Scheme 29, Table 4), react very slowly with Charette's and Wittig–Furukawa's carbenoids (53–55% conversion after 20–44 h, entries 1–2) but the *cis* isomer still, albeit only slightly, prevailed. This could be explained by a weak coordination of the Zn-carbenoid to the oxygen atom in the 4-position.

In fact, when completely changing the reaction mechanism, i.e. using dimethylsulfoxonium methylide in DMSO at 25 °C, steric control by the 4-OR group took place, providing *trans* compounds **130**, **131** and **133** in an approximately 3.8–7 : 1 ratio with their *cis* isomers (entries 3–5) and in good yields (77–82%) after chromatography. This ratio could not be increased under different conditions, even when carrying out the reaction in DMF at –5 °C (entry 6).

Scheme 29



129 R = Me, R' = TBS
54 R = Me, R' = *t*Bu
132 R = Bn, R'= TBS

(1*S*,5*R*,6*R*)-**130**
(1*S*,5*R*,6*R*)-**131**
(1*S*,5*R*,6*R*)-**133**
trans

(1*R*,5*R*,6*S*)-**130**
(1*R*,5*R*,6*S*)-**131**
(1*R*,5*R*,6*S*)-**133**
cis

(1S,5*R*,6*R*)-**127** R = Me (69%)
(1*S*,5*R*,6*R*)-**128** R = Bn (73%)
trans

Scheme 29: Reagents and conditions: (a) 3N HCl, CH_3CN, 0°→25°C, 1h (b) MeONa, MeOH, 0°C

Table 4

entry	R-OH[a]	Conditions	Conversion (%)[b]	*Trans*/*Cis*[c]
1	**129**	Et_2Zn, CH_2I_2, CH_2Cl_2, -12°C→25°C, 24 h	53	1 : 1.2
2	**129**	Et_2Zn, CH_2I_2, 2,4,6-Trichlorphenol, CH_2Cl_2, -40°C→25°C, 44 h	55	1: 1.3
3	**129**	TMSOI[d], NaH, DMSO, 25°C, 2 h	100 (82)[e]	4.7 : 1
4	**54**	TMSOI[d], NaH, DMSO, 25°C, 1.5 h	100 (77)[e]	3.8 : 1
5	**132**	TMSOI[d], NaH, DMSO, 25°C, 2.2 h	100 (78)[e]	7 :1
6	**129**	TMSOI[d], NaH, DMF, -5°C, 24 h	93 (13)[e] [f]	3.1 : 1
7	**54**	TMSI[g], NaH, DMF, 25°C, 2 h	82 (14)[e] [f]	4.8 : 1
8	**54**	TMSI[g], NaH, DMSO, 25°C, 2 h	89 (5)[e] [f]	-
9	**129**	$TMSCHN_2$, $Pd(OAc)_2$, benzene, 30°C, 4 d	0	-

Table 4: [a] Reaction carried out on 0.5-1 mmol of substrate, monitored by TLC. [b] Determined by 1H NMR. [c] Relative composition determined by 1H NMR on the crude reaction mixture. [d] TMSOI = Trimethylsulfoxonium iodide. [e] Yield after chromatography. [f] Low yield due to a great extent of degradation of the starting material. [g] TMSI = Trimethylsulfonium iodide.

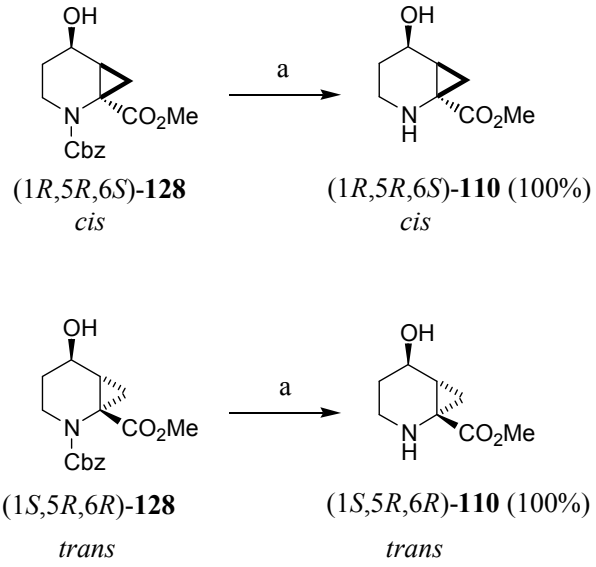
The facial selectivity was much the same (*trans*/*cis* ratio = 4.8 : 1) when we used dimethylsulfonium methylide for the *trans* cyclopropanation in DMF (entry 7) at room temperature; however, the isolated yield was very low (14% after chromatography) under these conditions (and even worse when carrying out the reaction in DMSO, entry 8) because of the formation of a large amount of polar byproducts, which were lost in the work up or during chromatography.

The Pd-catalyzed cyclopropanation (entry 9) carried out in the presence of trimethylsilyldiazomethane ($TMSCHN_2$), as reported for an electron-poor olefin[69], failed completely.

Despite the fact that the *trans* compounds were obtained in mixtures with their *cis* isomers, these could be easily separated by chromatography after OH deprotection (Scheme 29), which provided the enantiopure major *trans* compounds (1*S*,5*R*,6*R*)-**127** in 69 and 67% yield from (1*S*,5*R*,6*R*)-**130** and (1*S*,5*R*,6*R*)-**131**, respectively, and (1*S*,5*R*,6*R*)-**128** in 73% yield from (1*S*,5*R*,6*R*)-**133**. The best conditions were as usually applied to the synthesis of enantiomer (1*R*,5*S*,6*S*)-*ent*-**10** from (*S*)-**132**.

Finally, to obtain these amino acid analogues in a form suitable for peptide coupling, we carried out the N-deprotection on both enantiomers of compounds *cis* and *trans* **128** by hydrogenolysis (Scheme 30) at room temperature over 10% Pd/C, which provided free amino esters *cis* **110** and *trans* **110** both in quantitative yield[70].

Scheme 30

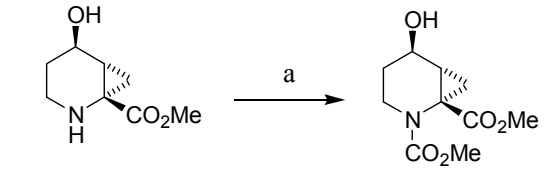


Scheme 30: Reagents and conditions: (a) H_2, 10% Pd/C, MeOH, 25°C, 3h

2.7 Determination of lipases enantiospecificity in EKR of racemic 4-hydroxylated N-Cbz protected enecarbamate esters

Compound *trans* (1*R*,5*S,*6*S)*-**110** was converted into the corresponding *N*-CO_2Me protected derivative (1*R*,5*S,*6*S*)-**127** (Scheme 31) whose positive optical rotation value is consistent to the stereospecificity of the lipase in the kinetic resolution of alcohol (±)-**125** (for *trans* (1*S*,5*R*,6*R*)-**127** obtained from (*R*)-**54** of known absolute configuration the $[\alpha]^{25}_{D}$ value is –4.43).

Scheme 31



(1*S*,5*R*,6*R*)-**110** (1*S*,5*R*,6*R*)-**127**

trans *trans*

Scheme 31: Reagents and conditions: (a) H_2, 10% Pd/C, MeOH, 25°C, 3h

2.8 *cis*/*trans* stereochemical assignement in 4-hydroxy-cyclopropanated derivatives

The relative *cis* and *trans* stereochemistry in compound **127** and **128** (Scheme 28) is easily assigned by the analysis of the coupling constants in the ^{1}H-NMR spectrum and by NOE studies. In *cis* compound 5-H resonates at 4.35 ppm with a J = 10.1 Hz consistent with its axial orientation. This is confirmed by a NOESY 1D experiment (mixing time 800 ms) which shows a correlation between 5-H and axial 3-H proton. In *trans* compound 5-H resonates at 4.28 ppm as a broad singlet due to its equatorial position, as confirmed by the lack of NOE correlation between 5-H and the protons at C3. In both isomers, the C-1 carbomethoxy group is axially oriented to remove the $A^{(1,3)}$ strain with the N-protecting group[71]. The ^{1}H-NMR spectra of compounds **130**, **131** and **133** (Scheme 29) are quite complex due to the presence in solution of rotamers for both *trans* and *cis* isomers. However, at least one set of signals allow for the identification of the two isomers and the determination of the ratio, i.e. 3-H axial proton which is always 0.4-0.5 ppm more downfield-shifted in the *trans* isomer. In this, moreover, the 5-H is always a broad singlet due to the lack of *trans* diaxal couplings.

Chapter 3: Synthesis of 4,5-dihydroxypipecolic acids

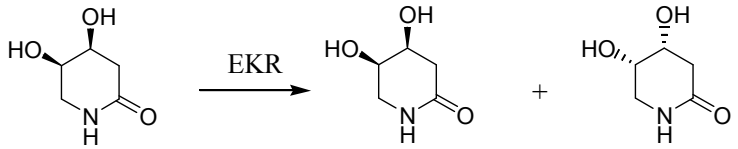
We started our study on 4,5-dihydroxylated pipecolic acids focusing on the 4,5-*cis*-dihydroxy compounds **10**, **11** and related enantiomers *ent*-**10** and *ent*-**11**.

According to the above strategy, for the synthesis of *cis* 4,5-dihydroxypipecolic acid **10** and **11**, *cis* 4,5-dihydroxylated lactam **137** would be required in enantipure form. Despite being a simple compound (and, in general, a potentially useful polyfunctionalized chiral synthon for diverse uses), the isolated enantiomers of the *cis* isomer **137** were unknown.

3.1 Synthesis of the *cis* 4,5-dihydroxypiridine precursors: EKR strategy

Encouraged by the good results obtained with 4-hydroxylated derivatives **118** and **125**, we envisaged a lipase-catalyzed kinetic resolution of 4,5-dihydroxylated precursors.
In 4-hydroxylated derivatives, the EKR was applied for the resolution of the enecarbamate substrates, but for the 4,5-dihydroxylated precursors we initially envisaged an enzymatic resolution at an "earlier" stage, i.e. on racemic 4,5-*cis*-dihydroxylated lactam **137** (Scheme 32).

Scheme 32

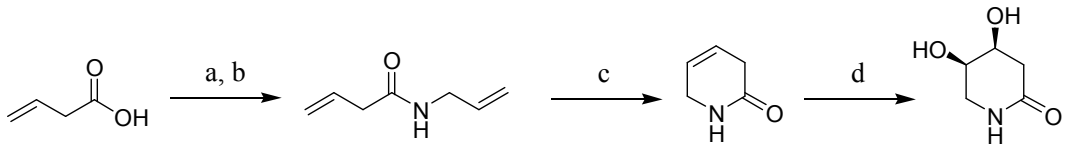


(±)-**137** (4*S*,5*R*)-**137** (4*R*,5*S*)-**137**

Scheme 32: EKR-based strategy for enhantiopure 4,5-cis-dihydroxylated lactams precursors

So, for the synthesis of the racemic 4,5-dihydroxylactam (±)-**137**, known unsaturated lactam **136** (Scheme 33), which can be prepared in a multigram scale by coupling of 3-buthenol (**134**) with allylamine and following RCM of the coupling product **135**[72], was chosen as the starting material.
In our laboratory were previously tried the Sharpless asymmetric dihyroxylation on lactam **136** by using both α and β AD-mix. However, despite testing several experiments procedures and, in particular, a most promising one reported for the corresponding unsatured lactone[73], it was never possible to obtain enantiomeric excesses higher than 14%[74].

Scheme 33



134 **135** (89%) **136** (70%) (±)-**137** (100%)

Scheme 33: Reagents and conditions: (a) ($COCl_2$), CH_2Cl_2, 25°C, 3 h (b) Grubbs I generation, CH_2Cl_2, reflux, 17 h (d) $KMnO_4$ (31mM), NaOH (50 mM), H_2O, 0°C, 1h

Among the various options for the dihydroxylation of **136** to give new lactam (±)-**137**, the addition of an aqueous solution of $KMnO_4$ to a vigorously stirred alkaline solution of the substrate in water at 0°C worked best in terms of product recovery and yield after work-up[75,76]. Reagents concentrations, pH, and addition rate were critical to avoid either overoxidation or migration of the double bond to give the corresponding α,β-unsaturated lactam.

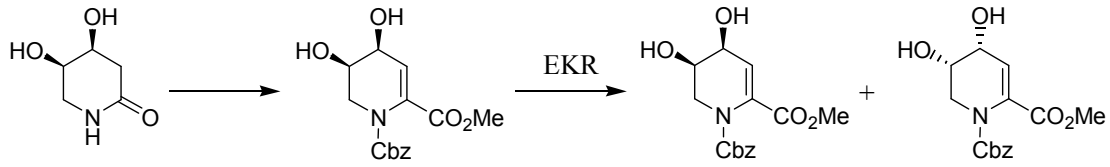
3.1.1 EKR attempts on racemic lactam 137

With a sufficient amount of (±)-**137**, we were ready for preliminary EKR studies.
The first problem was the scarce solubility of this substrates in the solvents used above for EKR. So, we carried out the experiments dissolving racemic **137** in THF, which seemed to be the best solvent of **137**. Three aliquots of substrate dissolved in THF (0.4 M) were reacted, respectively, in the presence of CAL-B, CAL-A and PS-AMANO-IM (100mg/mmol), with an excess of vinyl butyrate as acylant reagent. Unfortunately, probably due to the low solubility of the substrate in THF, in no cases we observed the conversion of the substrate to acylated products. Moreover, (±)-**137** was unsoluble also in dioxane and acetonitrile.

3.1.2 EKR application of 4,5-dihydroxylated enecarbamate derivative

Due to the failure of the enzymatic strategy on racemic lactam **137**, and envisaging a possible resolution in a "later" stage of the synthesis, we developed a synthetic route for the conversion of (±)-**137** in the corresponding enecarbamate derivative trough the enol-phosphates chemistry, which should be then subjected to the enzymatic resolution (Scheme 34).

Scheme 34



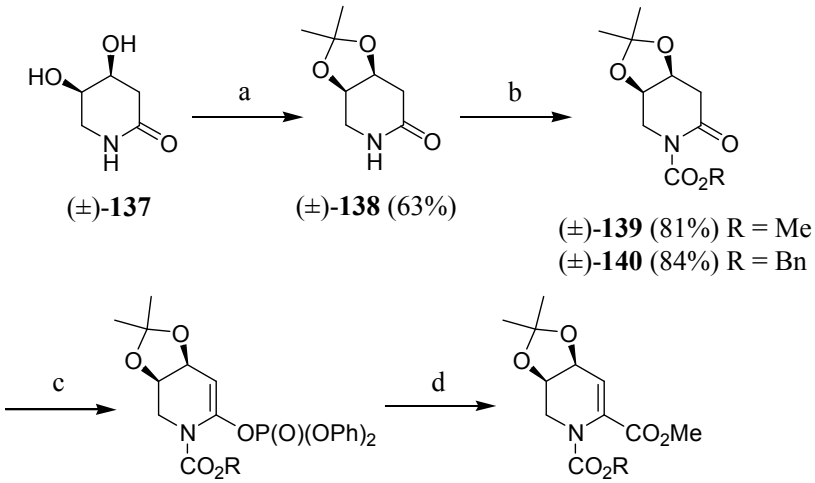
(±)-**137** (±)-**147** (4*S*,5*R*)-**147** (4*R*,5*S*)-**147**

Scheme 34: EKR-based strategy for enhantiopure 4,5-cis-dihydroxylated enamide precursors

This synthesis of the racemic enecarbamate precursor was previously developed for the N-Cbz derivative **147**. This was subjected to the enzimatic resolution, then applied also to the N-CO_2Me substrates **144**, previously employed in a diastereodivergent synthesis of alkaloid 1,4-dideoxymannojirimycin[51]. In Scheme 35 both routes where shown.

So, crude (±)-**137** was directly transformed into the isopropylidene-protected diol (±)-**138** which was obtained in 63% yield over two steps after chromatography, and then protected as *N*-CO_2Me or *N*-Cbz carbamates ((±)-**139** and (±)-**140**, 81% and 84% yield, respectively).

Scheme 35



(±)-**137**

(±)-**138** (63%)

(±)-**139** (81%) R = Me
(±)-**140** (84%) R = Bn

(±)-**141** (89%) R = Me
(±)-**142** (100%) R = Bn

(±)-**143** (69%) R = Me
(±)-**144** (72%) R = Bn

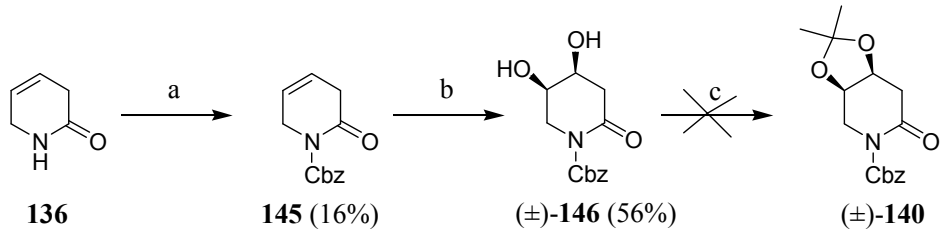
Scheme 35: Reagents and conditions: (a) 2,2-dimetoxypropane, *p*-TsOH, MeOH, 55°C, 1h (b) MeOCOCl or BnOCOCl, *n*-BuLi, THF, -78°C (c) KHMDS, $(PhO)_2P(O)Cl$, THF, -78°C (d) $Pd(OAC)_2$, Ph_3P, CO, MeOH, Et_3N, DMF, 60°C, 2.5h (R = Me) or 5h (R = Bn)

Quantitative generation of the corresponding enol phosphates (±)-**141** and (±)-**142** was accomplished by treatment of the lactams with KHMDS at -78°C in THF, followed by the addition of diphenylchlorophosphate. Pd-catalyzed metoxycarbonylation of the two phosphates was carried out according to the usual method, in anhydrous DMF and at 1 atm (CO balloon) and

finally gave the key ester intermediates (±)-**143** and (±)-**144** in 69 and 72% yield after two steps, respectively. In that conditions the *N*-Cbz phosphate reacted slowly than the *N*-CO_2Me protected. In fact, phosphate (±)-**142** was completely converted only after 5 h at 60°C, against the 2.5 h of the *N*-CO_2Me phosphate (±)-**141**.

During the synthesis we also tried to obtain isopropilidene-protected lactam **140** starting from diol **146** (Scheme 36), provided in scarce yield (16%) by N-Cbz protection of **136**. The following OH protection as isopropylidene (2,2-dimethoxypropane and catalytic *p*-TsOH, MeOH 55°C) failed, affording only unidentified polar degradation products.

Scheme 36

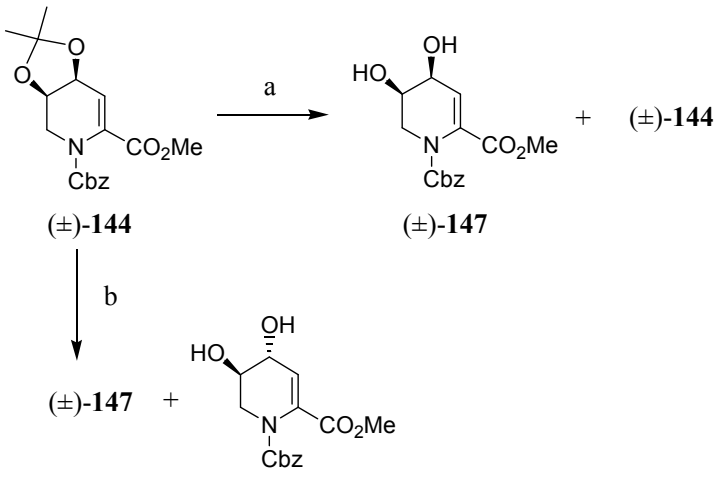


136 **145** (16%) (±)-**146** (56%) (±)-**140**

Scheme 36: Reagents and conditions: (a) *n*-BuLi, BnOCOCl, THF, -78°C (b) $KMnO_4$ (31mM), NaOH (50 mM), H_2O, 0°C, 1h (c) 2,2-dimetoxypropane, *p*-TsOH, MeOH, 55°C, 1h

In order to have the substrate ready for the enzymatic kinetic resolution, we performed the isopropylidene deprotection of (±)-**144** in a TFA/$CHCl_3$/H_2O 5 : 1 : 0.1 mixture (Scheme 37).

Scheme 37



(±)-**144** (±)-**147**

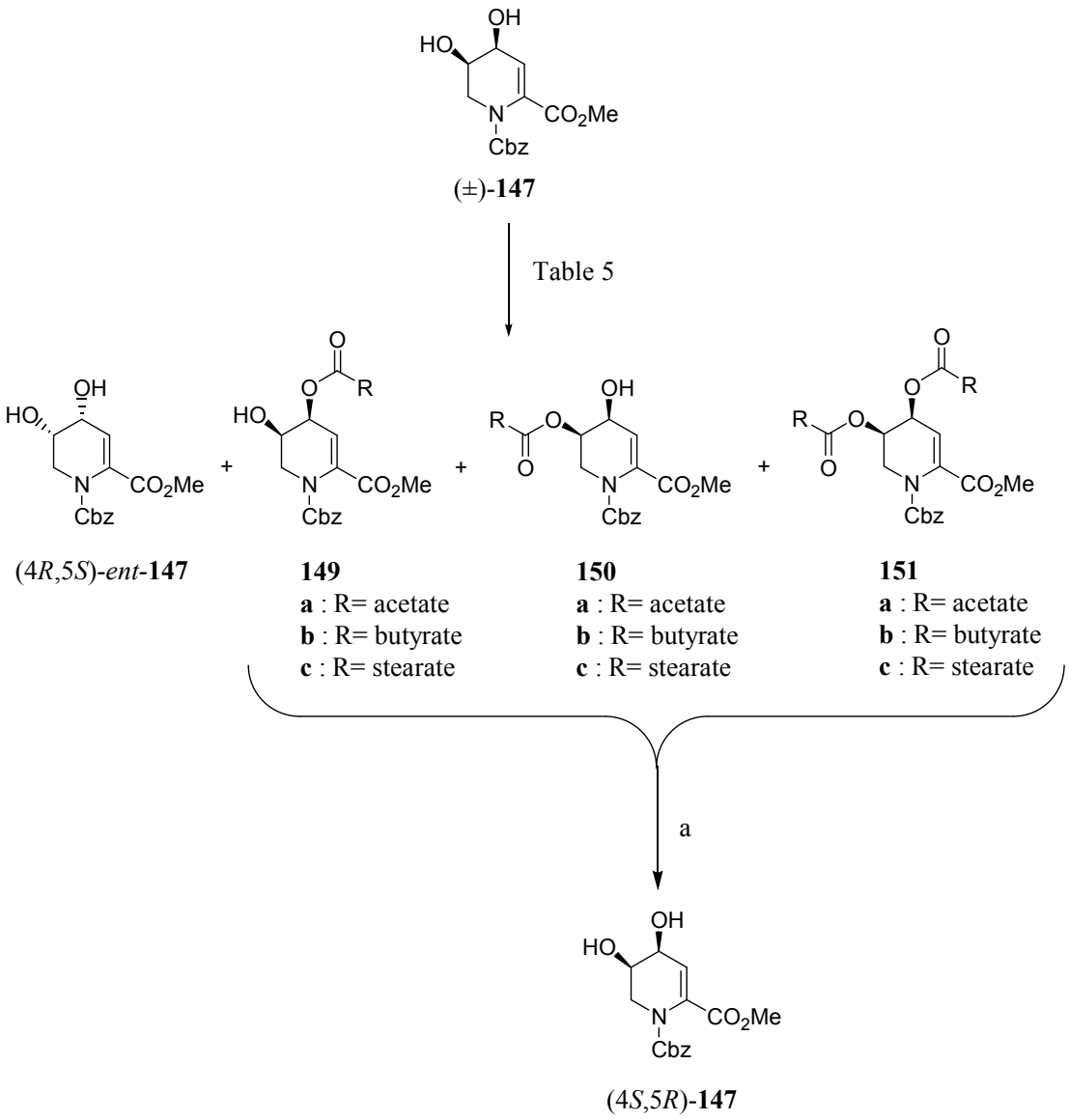
(±)-**147** + (±)-**148**

Scheme 37: Reagents and conditions: (a) TFA/$CHCl_3$/H_2O 5 : 1 : 0.1, 25°C, 11 min (b) TFA/$CHCl_3$/H_2O 5 : 1 : 0.1, 25°C, 0.5 h

Under these conditions, compound (±)-**144** reached complete conversion after 30 minutes, but the allylic hydroxyl group of the resulting *cis* alcohol **147** was prone to partial isomerisation due to the acid environment, forming also the undesired *trans* product (±)-**148**. Fortunately, this phenomena could be strongly limited by carrying out the reaction for shorter times (optimum 11 min, stopped with 66% conversion). In that way, we managed to obtain only the required compound **147** in a 2 : 1 mixture with the unreacted substrate. The two compounds could be isolated by flash column chromatography, and (±)-**144** subjected again to deprotection.

With a sufficient amount of racemic **147**, we were ready for EKR (Scheme 38, Table 5) experiments (see Appendix 6 for absolute configuration determination).

Scheme 38



Scheme 38: Reagents and conditions: (a) MeONa, MeOH, 0°C, 3.5h

The kinetic resolution was carried out in the presence of the three lipases that gave the best results for the resolution of the 4-hydroxylated alcohols, i.e. *Bulkorderia cepacia* lipase (PS-AMANO-IM) and *Candida antarctica* lipase B and A (CAL-B and CAL-A), with an excess of vinyl acetate, vinyl butyrate or vinyl stearate as the acylating reagent. As previously reported for the resolution of 4-hydroxylated compounds, the reactions were performed in various anhydrous solvents.

Table 5

entry	Acylant reagent[a]	Solvent[b]	t (h)	c (%)[c]	4/5 acylated ratio[c]	**151** (%)	**147** *ee* (%)	*ent*-**147** *ee* (%)	E[f]
CALA[g]									
1	VA	TBME	24	78	1.5 : 1	10	69[d]	n.d.	n.d
2	VB	TBME	5	46.8	1.7 : 1	1.1	1[d]	n.d.	n.d
CALB[g]									
3	VB	TBME	47	52	3 : 1	< 0.5	70[d]	76[d]	n.d
4	VB	THF	54	46	11 : 1	0.1	72[d] 57[e]	86[d] 72[e]	29 11
5	VB	Acetone	22	42	16 : 1	0.1	59[d] 51[e]	89[d] 79[e]	31 14
6	VB	Dioxane	70	53	11 : 1	-	69[e]	76[e]	15
7	VB	CH_3CN	21	39	15 : 1	-	42[e]	83[e]	16
8	VB	CH_2Cl_2	52	37	2.8 : 1	-	27[e]	74[e]	n.d
9	VB	Toluene	52	16	1.2 : 1	-	3[e]	45[e]	n.d
10	VS	THF	67	36	2 : 1	-	21[e]	n.d	n.d
"Amano"									
11[h]	VB	THF 0.8	24	52	1 : 1.3	2.7	67[d]	57[d]	n.d
12[g]	VB	TBME	21	66	0.7 : 1	3.4	83[d]	n.d.	n.d

Table 5: [a] VA: vinyl acetate, VB: vinyl butyrate, VS: vinyl stearate. [b] Anhydrous solvents were used. [c] Conversion determined by HPLC (column Acclaim 120 C18, see ref [77]) and 1H-NMR. [d] Determined by HPLC analysis (column Cyclobond I2000, see ref [78]). [e] Determined by HPLC analysis (column Lux Cellulose 4, see ref [79]). [f] Calculated as ln[1-c(1+eep)]/ln[1-c(1-eep)]. [g] Reaction carried out on 0.2-0.4 mmol of substrate at 30 °C, substrate concentration 0.2M, enzyme (mg)/substrate (mmol) ratio = 100, 3.5 equivalents of acylant reagent, molecular sieves (4Å, 130 mg/mmol). [h] Substrate concentration = 0.8 M

Because enzymes could acylate the hydroxy group at position 4, 5 or both (only in a few cases[80]), for each experiment we determined the regioselectivity of the enzymes and the enantiomeric excess of the acylated alcohols (after hydrolysis), as well as the *ee* of the unreacted diol. As in the case of simple 4-hydroxylate alcohols the (4*S,*5*R*) enantiomer of **147** was preferentially acylated in all experiments.
Each enzyme showed a proper regioselectivity. CAL-B (entries 3-10) preferentially acylated the OH-group in position 4, as well as CAL-A (entries 1 and 2), while using PS-AMANO-IM the 5-acylated isomer prevailed (entries 11 and 12).

Unfortunately, the ratio between the 4-acylated and 5-acylated regioisomers at a certain conversion rate was not stable during the time and could not be easily determined. In fact, we observed a time-related decrease of 4-acylated/5-acylated ratio when the products were in solution. We explained it as a spontaneous migration of the acyl group from oxygen in position 4 to position 5, as previously reported by Armesto et all. on quinic and shikimic acid derivatives[81]. This migration took place also during our efforts in chromatographyc separation of the regioisomers.

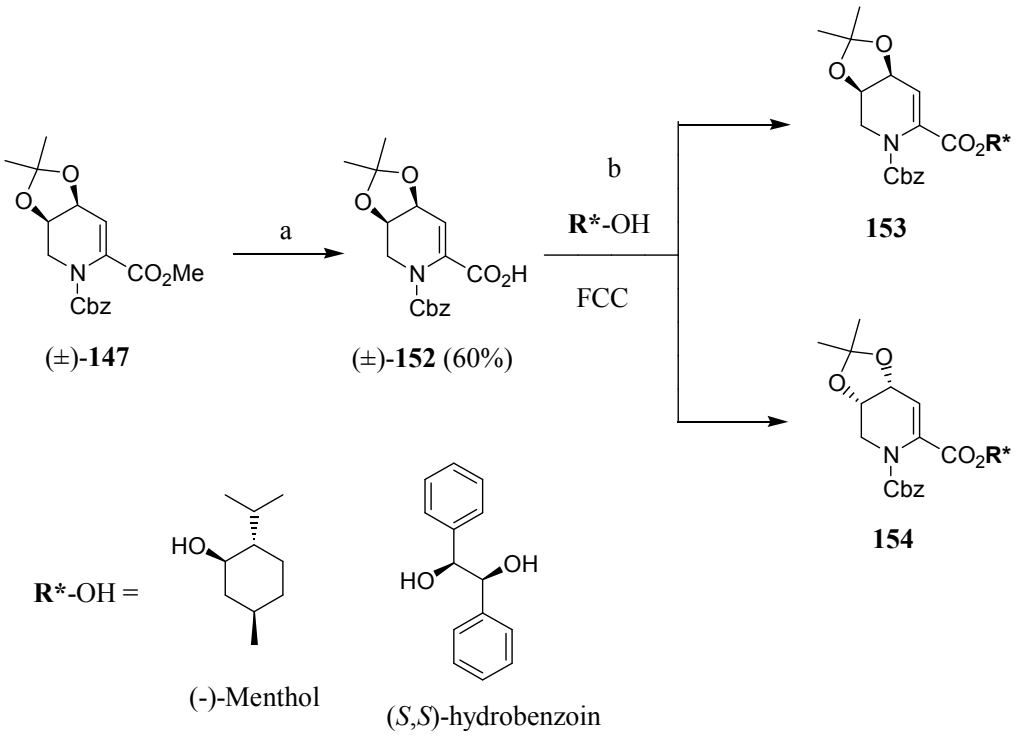
So, although the *ee* of 5-acylated compound formed by migration was necessarily the same of that of the original 4-acylated regioisomer, we were not able to determine the relative amount of 5-acylated isomer formed by direct action of the enzyme. Consequently, by measuring the *ee* of acylated products after hydrolysis (by HPLC), the enantioselectivity in position 5 or 4 could not be determined.

In order to minimize this problem, we focused on the most regioselective enzyme CAL-B (entry 3-10). Using vinyl butyrate as acylating agent, reaction time and enantiomeric excesses strongly depended on the employed solvent. In high-polarity solvents like acetone (entry 5), dioxane (entry 6) and acetonitrile (entry 7), reactions were faster and with an higher 4/5-acylated ratio with respect to what observed in low-polarity solvents (dichlormethane, toluene, entry 8 and 9).
The experiment carried out with vinyl stearate (VS) acylating agent lead to the worst results (entry 10).
Even under the best conditions we never managed to obtain products with sufficiently high *ee* (the enantiomeric ratio E was near 20 for the reaction performed in polar solvents), so this approach appeared unsuitable for the resolution of racemic **147** (although the results obtained in acetone and acetonitrile were promising and deserving further experiments).

3.2 Chemical resolution of racemic *cis*-4,5-dihydroxylated enecarbamate ester 147

Due to the failure of the enzymatic approach, we envisioned a chemical resolution of racemic **147** by esterification of racemic acid derivative **152** with enantiopure alcohols, having in mind a possible chromatographic separation of the two diastereoisomeric esters furnished by the reaction (Scheme 39). The experiments were carried out with enantiopure (-)-menthol and (*S*,*S*)-hydrobenzoin. Unfortunately, even though various eluition mixture were tested, diasteromeric esters **153** and **154** resulted as to be unseparable by flash column chromatography.

Scheme 39



Scheme 39: Reagents and conditions: (a) 1M LiOH, dioxane, 60°C, 21h (b) **R***-OH, DCC, DMAP, CH_2Cl_2, 0°C→25°C, 3 h (R-OH = menthol) or 21 h (R-OH = hydrobenzoin)

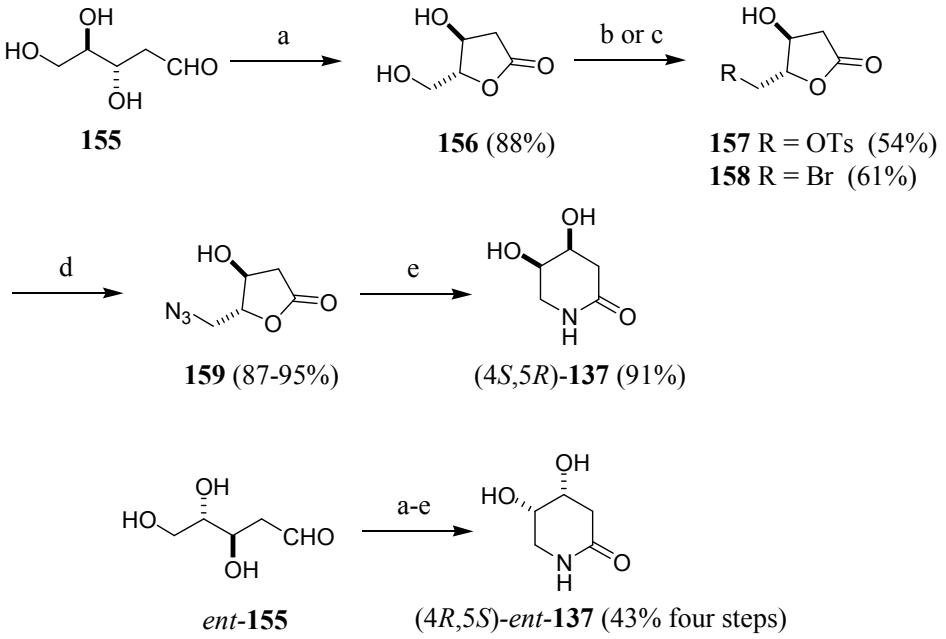
3.3 Synthesis of the *cis*-4,5-dihydroxylated precursors from enantiopure lactones

Due to the poor results of the enzymatic and chemical resolution of racemic **147**, we envisaged a completely different route to build our synthetic precursors in enantiopure form, starting from enantiopure hydroxylated lactones from the chiral pool.

For the synthesis of enantiopure **137** in enantiopure form, we envisaged a route which starts from enantiopure 2-deoxyribose **155**. Being both enantiomers of 2-deoxyribose commercially available, we realized the synthesis of enantiopure *cis* 4,5-dihydroxy δ-valerolactam **137**

(Scheme 40) from commercial 2-deoxy-D-ribose **155** , as well as the synthesis of its enantiomer *ent*-**137** from 2-deoxy-L-ribose *ent*-**155**.

Scheme 40



Scheme 40: Reagents and conditions: (a) Br_2, H_2O, 25 °C, 5 d; (b) TsCl, pyridine, -15 °C, 2 h, then 0 °C, 5 h; (c) $SOBr_2$, rt, 4.5 h; (d) NaN_3, CH_3CN, 18-C-6 or 15-C-5, reflux, 15-20 h; (e) H_2 (1 atm), 10% Pd/C, MeOH, 24h (f) 2,2-dimethoxypropane, *p*-TsOH, MeOH, 55 °C, 1 h; (g) CH_3OCOCl, *n*-BuLi, –78 °C; (h) $(PhO)_2POCl$, KHMDS, THF, –78 °C; (i) 10% $Pd(OAc)_2$, 20% Ph_3P, CO, MeOH, Et_3N, DMF, 75 °C, 1 h; (e) H_2 (1

To this end, 2-deoxy-D-ribose **155** was initially subjected to treatment with Br_2 in water for 5 days, which provided 2-deoxy-D-ribonolactone **156** in excellent yield (88%) after chromatography[82]. This compound proved stable in aprotic solvents, but in protic mediums such as methanol it slowly equilibrates to give a minor isomer which could be the corresponding six-membered lactone (i.e. the *cis*-4,5-dihydroxytetrahydropyran-2-one) or the intermediate aldonic acid, according to Han et al.[82a,b]. We found a ratio of about 2.5 : 1 in favor of the 2-deoxy-D-ribonolactone, a ratio which did not change after heating at 50 °C[83]. The (partial) conversion of **156** into the corresponding primary *O*-tosyl derivative **157** was realized as reported by treatment with TsCl in pyridine at -15 °C and then leaving at 0 °C for 5 h[84] conditions which furnished compound **157** in 54% yield after chromatography. This was the best yield we obtained under these conditions, as prolonging the reaction times to completely convert **156** into **157** led to the partial tosylation of the secondary OH group, too. Similarly, several attempts at selectively converting the primary hydroxy group into a mesylate (MsCl, Et_3N, in CH_2Cl_2 at -30 °C) always failed due to the concurrent mesylation of the secondary alcohol, followed by elimination of

methansulfonic acid during chromatography. Instead, bromination of compound **156** by treatment with thionyl bromide in anhydrous DMF at room temperature (4.5 h) occurred selectively at the primary position, but provided lactone (+)-**158** in 47% yield after chromatography. However, it was possible, after the work-up of the reaction, to recover an amount of unreacted starting material (31%) which was chromatographed and reacted again with $SOBr_2$ under the same conditions, thus providing bromolactone (+)-**158** in 61% total yield[85]. Transformation of both **157** and **158** into 2-deoxy-5-azido-D-ribonolactone **159** was accomplished by treatment with NaN_3 in refluxing acetonitrile and in the presence of 18-crown-6, which provided key intermediate **159** in 87% (from **157**) and 95% (from **158**).

Eventually, hydrogenation of **159** at atmospheric pressure (balloon) over 10% Pd/C gave pure dihydroxylated lactam (4*S*,5*R*)-**137** in 91% yield and whose 4,5-*cis* relative stereochemistry was confirmed by X-ray analysis (Figure 6). According to the same strategy, by converting 2-deoxy-L-ribose (*ent*-**155**) into the corresponding bromine (47% over two steps), and this into azide (97%), we were also able to prepare its enantiomer (4*R*,5*S*)-*ent*-**137** in 43% overall yield.

Figure 6

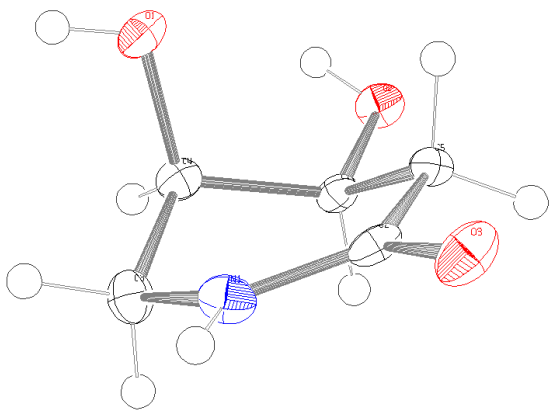


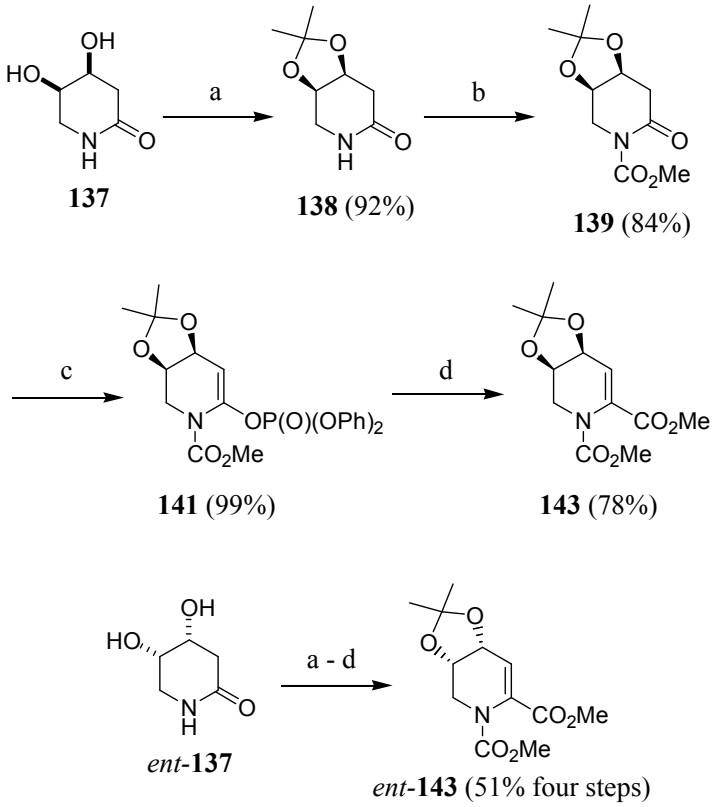
*Figure 6: X-ray of (4S,5R)-**137** nitrogen in blue, oxygen in red*

Lactam **137** was converted into enantiopure enecarbamate ester **143** according to the procedure we have disclosed for the synthesis of the corresponding racemic compound. Thus protection of (4*S*,5*R*)-**137** as the acetonide (–)-**138** (92%) (Scheme 41) , and then N-protection as carbamate (–)-**139** (84%) set the stage for the quantitative generation of the corresponding enol phosphate **141** by treatment of the lactam with KHMDS at –78 °C in THF followed by the addition of diphenylchlorophosphate.

Pd-catalyzed methoxycarbonylation of the phosphate in anhydrous DMF and at 1 atm (CO balloon) was carried out at 75° C in the presence of an excess of MeOH to give the key ester intermediates (+)-**143** in 78% yield after two steps.

Its enantiomer (-)-*ent*-**143** was prepared according to the same procedure starting from (4*R*,5*S*)-*ent*-**137**, with 51% overall yield.

Scheme 41



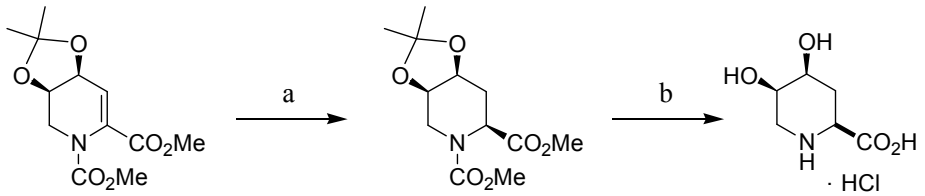
Scheme 41: Reagents and conditions: (a) 2,2-dimethoxypropane, *p*-TsOH, MeOH, 55 °C, 1 h; (b) CH_3OCOCl, *n*-BuLi, –78 °C; (c) $(PhO)_2POCl$, KHMDS, THF, –78 °C; (d) 10% $Pd(OAc)_2$, 20% Ph_3P, CO, MeOH, Et_3N, DMF, 75 °C, 1 h;

3.4 Synthesis of 4,5-*cis*-dihydroxypipecolic acid 10

To attain natural 4,5-*cis*-dihydroxypipecolic acid L-**10**, we subjected the enamine double bond of **143** to heterogeneous catalytic hydrogenation over 10% Pd/C at 1 atm, which gave *cis* ester (-)-**160** (Scheme 42) in quantitative yield and complete facial selectivity (by ^{1}H NMR).

Exhaustive deprotection in refluxing aqueous 4 N HCl eventually concluded the first total synthesis of free L-pipecolic acid **10** which was obtained in high 27% overall yield in 9 steps and of which we could measure the optical rotation so far unknown[17,19].

Scheme 42

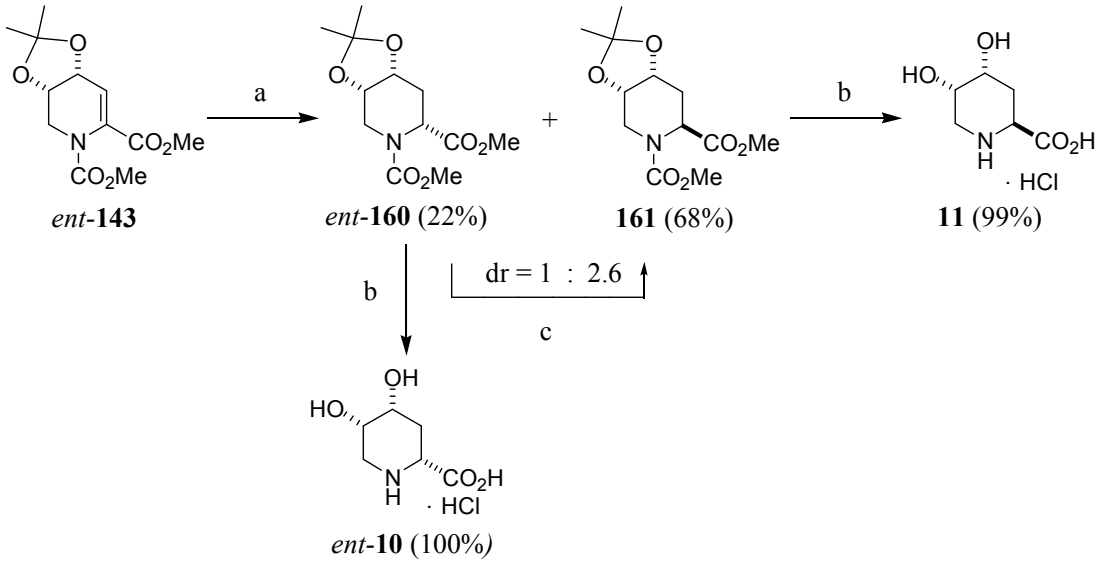


143 **160** (100%) **10** HCl (100%)

Scheme 42: Reagents and conditions: (e) H_2 (1 atm), 10% Pd/C, $NaHCO_3$, EtOAc, 4 h; 4N HCL, reflux 4 h

For the synthesis of the other 4,5-*cis* dihydroxylated pipecolic acid, that is compound **11**, the enamine substrate *ent*-**143** was subjected to a conjugate reduction by Super-Hydride ($LiEt_3BH$) at -10 °C (Scheme 43). After quenching the anion with a saturated $NaHCO_3$ solution, ^{1}H-NMR analysis of the crude reaction mixture revealed the formation of a 2.6 : 1 mixture between thermodynamically more stable ester (-)-**161** and *cis*,*cis* isomer *ent*-**160**. The two diastereoisomers were easily separated by chromatography, thus obtaining pure **161** in 68% yield and its minor isomer *ent*-**160** in 22% yield. On the basis of previous experience, the latter was subjected to epimerization by treatment with TBAF in THF[29a] which provided an approximately 1:1 mixture of the two compounds (**161** and *ent*-**160**) after 19 h at room temperature[86]. After another chromatography the total yield in target compound **161** was 78% over the two steps. Deprotection of **161** in refluxing 4N HCl eventually provided pure compound **11** in quantitative yield[87], and analogous treatment of *ent*-**160** provided the unnatural enantiomer of 2,4-*cis* 4,5-*cis* isomer *ent*-**10**.

Scheme 43



ent-**143** *ent*-**160** (22%) **161** (68%) **11** (99%)

ent-**10** (100%)

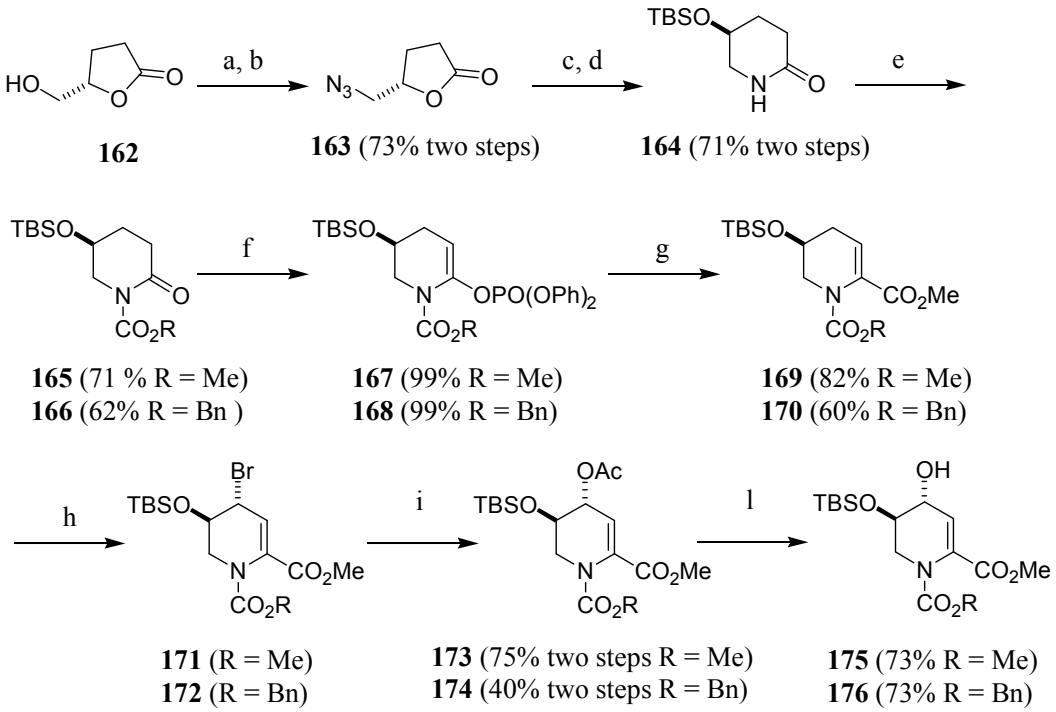
Scheme 43: Reagents and conditions: (a) $LiEt_3BH$, THF, -10 °C, 70 min; (b) 4N HCl, reflux, 24 h; (c) TBAF, THF, 0 °C → rt, 18 h

3.5 Synthesis of the *trans* 4,5-dihydroxypipecolic precursors from enantiopure lactones

For the synthesis of the 4,5-*trans* compound **9** we envisaged a route which starts from enantiopure 5-hydroxy-δ-valerolactam, whose synthesis has been reported by Herdeis from glutamic acid[88], and in which the required 4-OH group would be installed on the heterocyclic skeleton at a later stage of the synthesis, relying on the preferential axial attack in the key allylic bromination step and the possible *trans*-directing effect exerted by the bulky silyloxy group in compound **169** (Scheme 28)[89].

Having in mind to employ the resulting 4,5-*trans*-dihydroxylated enecarbamate as substrates for the synthesis of pipecolic acids as well as their cyclopropanated derivatives (which requires a N-protecting group removable by hydrogenation) we performed the synthesis of both *N*-CO_2Me protected and *N*-Cbz protected enecarbamate precursors **175** and **176**, respectively (Scheme 44).

Scheme 44



Scheme 44: Reagents and conditions: (a) MsCl, Et_3N, CH_2Cl_2, -30°C→25°C, 2h (b) NaN_3, 18-crown-6, MeCN, reflux, 10h (c) H_2, 10% Pd/C, MeOH, 25°C, 21h (d) TBSCl, imidazole, DMF, 38°C, Xh (e) MeOCOCl or BnOCOCl, *n*-BuLi, -78°C (f) KHMDS, $(PhO)_2P(O)Cl$, THF, -78°C (g) $Pd(OAC)_2$, Ph_3P, CO, MeOH, Et_3N, DMF, 70°C, 2.5h (h) AIBN, NBS, $CCl_4/CHCl_3$ 9:1, reflux, 1.5 h (i) Silver acetate, AcOH, 15 min, 25 °C; (l) MeONa, MeOH, 0 °C, 1 h

Their synthesis was realized starting from 5-OH protected lactam **164**, (Scheme 43) which was prepared from commercial (*S*)-(+)-γ-hydroxymethyl-γ-butyrolactone **162** as reported by

Herdeis[88], trough cyclization of azide **163** and silyl protection of the resulting alcohol. After N-protection as methyl carbamate or benzyl carbamate, compounds **165** and **166** were converted into the corresponding enol phosphates **167** and **168**, then into enecarbamate esters **169** and **170** (82% and 60% yield, respectively) as usual. The allylic bromination of both precursors was carried out by treatment with *N*-bromosuccinimide (NBS) in the presence of catalytic azobisisobutyronitrile (AIBN) in a refluxing mixture of $CCl_4/CHCl_3$[90].

Interestingly, whereas the reaction on the corresponding 5-unsubstituted enamide ester was complete in 15 min, under the same conditions thorough consumption of our substrates occurred only after 1.5 h.

On the other hand, we were glad to observe that allyl bromide **171** was obtained as a single *trans* diastereomer and with the two groups (Br and OTBS) axially oriented. This assignment was made on the basis of the very low coupling constant values (less than 4 Hz) of protons 4-H and 5-H of **171**, which resonates at 4.32 and 4.22 ppm almost as broad singlets, and the lack of nOe correlations between 6-H_{ax} and any of the two protons mentioned above. Our failed attempts to convert bromide **171** into a 4,5-*cis* diol derivative by a S_N2 displacement of the bromine with an *O*-nucleophile (e.g. with AcOK in anhydrous DCM in the presence of 18-crown-6 at 25 °C or with AcOLi in DMF at 45 °C) can be explained by the steric impediment exerted by the large, axially oriented, OTBS group. Instead, cationic processes were all successful to provide 4,5-*trans* diol derivative, in particular treatment of bromide with silver acetate (2 equiv.) in acetic acid furnished (-)-**173** with the highest yield (75% over two steps)[91].
Again, the *trans* stereochemical assignment of compound **173** is based on the analysis of the coupling constants in its ^{1}H-NMR spectrum: both 4-H (4.95 ppm) and 5-H (3-91 ppm) protons possess very low coupling constants (less than 3 Hz) which is in accordance with their equatorial position. Moreover, there is no nOe enhancement of 4-H and 5-H when selecting 6-H_{ax} in NOESY 1D experiments.
The *trans* selectivity in both radical and cationic processes to give **173** and **174**, respectively, can be only in part accounted for on the basis of steric reasons, as instead stereoelectronic effects could play a major role in stabilizing the transition state[89]. The axial introduction of the bromine on the half-chair conformation with the axial OTBS group at C-5 permits the maintenance of maximum π-overlap in the allylic radical during the reaction and, moreover, there could be a possible further stabilization by hyperconjugative delocalization of the forming Br-C σ-bond with the σ*orbital of C-OTBS bond (Figure 7).

Figure 7

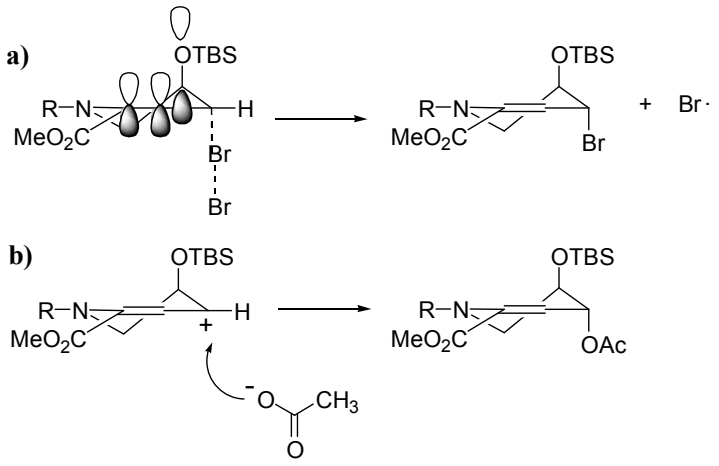


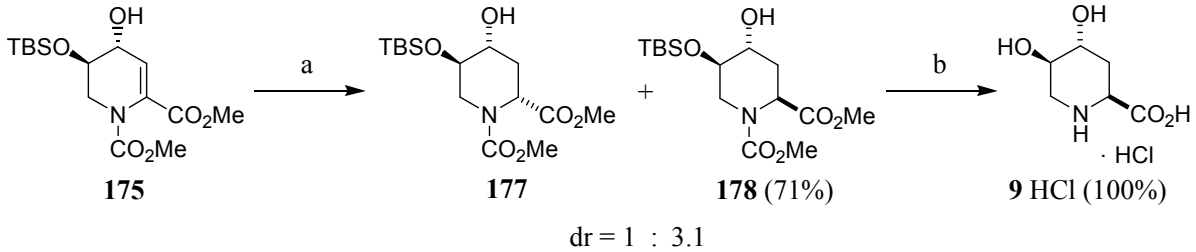
Figure 7: stereochemistry in the allylic oxidation (a) of compound **169** and SN_1 substitution (b) of **171**

The procedure with silver acetate in acetic acid was also applied on *trans* N-Cbz bromide **172**, providing **174** in 40% yield over two steps.
The acetyl group in **173** and **174** was following removed to give alcohols **175** and **176** (both with 73% yield).

3.6 Synthesis of 4,5-*trans*-dihydroxypipecolic acids

For the synthesis of the 4,5-*trans* compound **9**, the *N*-CO_2Me protected enecarbamate ester **175** was hydrogenated as usual yielding a 3.1 : 1 mixture (by ^{1}H-NMR) of 2,4-*trans*-4,5-*trans* compound (–)-**178** and 2,4-*cis*-4,5-*trans* isomer **177** (Scheme 45).

Scheme 45



175 **177** **178** (71%) **9** HCl (100%)

dr = 1 : 3.1

Scheme 45: Reagents and conditions: (a) H_2 (1 atm), 10% Pd/C, $NaHCO_3$, EtOAc, 20 h; (b) 4N HCl, reflux, 24 h

As expected, the effect of bulky silyloxy group was prevailing in dictating which face of the double bond would be adsorbed on the Pd-catalyst, although the stereoselectivity was lower than we had hoped. In any case, major isomer **178** was easily separated by chromatography (71% yield) and fully deprotected in refluxing aqueous 4 N HCl to give target pipecolic acid **9** in

quantitative yield. Unfortunately, it was not possible to isolate the minor isomer **177** if not in mixture with small amounts of **178**.

3.7 NOESY study on 4,5-dihydroxypipecolic acids

Because of the lack of high field NMR studies on these 4,5-dihydroxypipecolic acids, besides recording NMR spectra, we also performed NOESY 1D and 2D experiments to assess the spatial orientation of the three substituents on the piperidine ring. As shown in Figura 8, in all cases the carboxylic group at 2-position is equatorially oriented, as shown by the ever present nOe cross-peak between 2-H (axially oriented) and 6-H_{ax}, thus dictating the spatial orientation of the two hydroxyl groups. In compound **9**, the two protons at C-4 and C-5 resonate at 4.04 and 3.94 ppm almost as broad singlets with very low coupling constants (J < 3.5 Hz), consistent with their equatorial position.

Figure 8

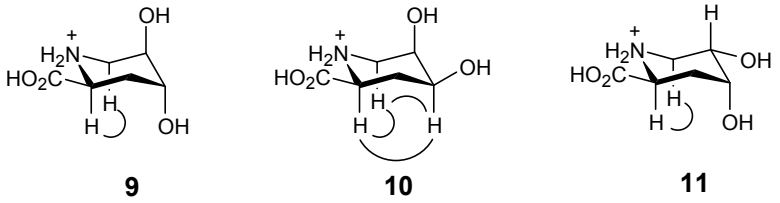


Figure 8: stereochemistry assignement by nOe

In compound **10**, a nOe correlation exists also between 2-H and 4-H, showing the equatorial orientation of the 4-OH group. In this compound, only 5-H appears as a broad singlet at 4.16 ppm consistent with the axial position of the 5-OH group. The reverse apply for compound **11**, for which we found a nOe correlation between 3-H_{ax} and 5-H, and it is the equatorially oriented 4-H (4.13 ppm) which has very low coupling constant values now. The equatorial orientation of 5-OH is further confirmed by the high value for the ^{3}J between 5-H and 6-H_{ax} (10 Hz), consistent with the axial orientation of 5-H.

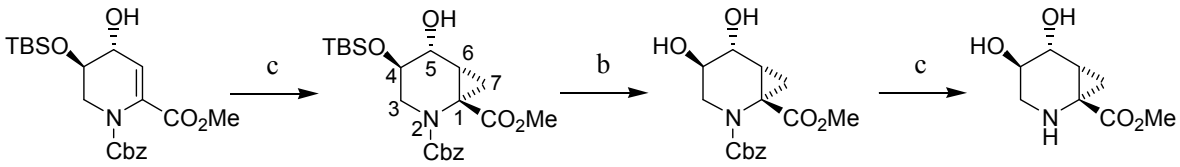
3.8 Synthesis of 4,5–dihydroxy-cyclopropanated derivatives

In a similar fashion to reported for 4-hydroxy-enecarbamates **118** and **125**, also the *N*-Cbz enecarbamate ester **176** was converted into the *cis* and *trans* cyclopropanated (whith respect to the orientation of the allylic OH group) derivatives, by exploiting the stereocontrol exerted by nude or bulky protected allylic OH group.

3.8.1 Synthesis of cyclopropanated derivatives: OH-directed cyclopropanation

The best strategies that were suitable to attain the 4-monohydroxy *cis* and *trans* cyclopropanated derivatives were applied to the enantiopure 4,5-dihydroxylated substrate **176**.
In particular, the OH-directed cyclopropanation by Charette's Zn-carbenoid (i. e. Et_2Zn and CH_2I_2 in the presence of 2,4,6-trichlorophenol) resulted as to be the better route to attain the *cis* product **179** (Scheme 46) with absolute diastereoselectivity (by ^{1}H-NMR) and very high yield after chromatography (95%).

Scheme 46



176 **179** (95%) **180** (73%) *cis*-**112** (99%)

Scheme 46: Reagents and conditions: (a) Et_2Zn, CH_2I_2, 2,4,6-trichlorphenol, CH_2Cl_2, -40°C→25°C, 22 h; (b) 3N HCl, CH_3CN, 0°C→25°C, 1 h; (c) H_2 (1 atm), 10% Pd/C, EtOAc, 20 h

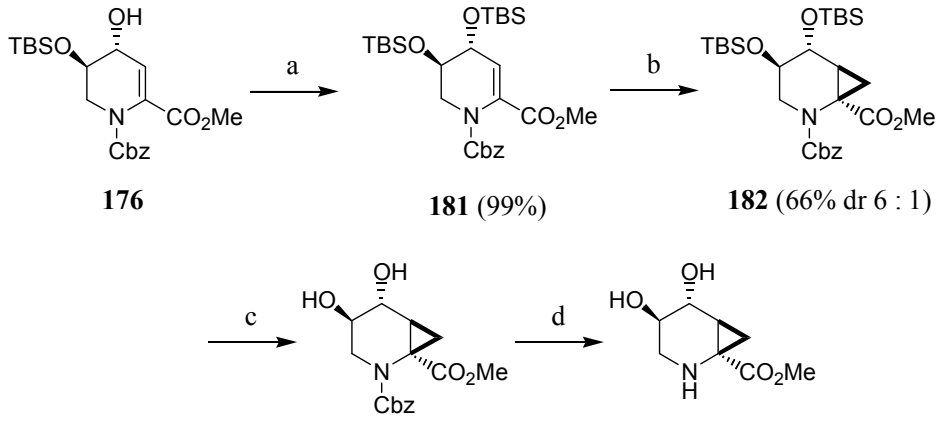
The attribution of the relative *cis* stereochemistry in compound **179** was easily assigned by NOE studies. In particular, NOESY 1D experiments (mixing time 800 ms) showed a correlation between 5-H and the axial 3-H proton, as well as a correlation between *endo* 7-H and 4-H, consistent with the proposed structure.

After removal of the TBS group with 3N HCl in ACN which gave intermediate **180** (73%), hydrogenation on Pd/C finally provided derivative *cis*-**112** in quantitative yield.

3.8.2 Synthesis of cyclopropanated derivatives: bulky group-directed cyclopropanation

For the synthesis of the *trans* derivative *trans*-**112**, we exploited the reaction of dimetilsulfoxonium methilyde on 4,5-disilyloxy-protected **181** (Scheme 47), obtained in 99% yield after TBS protection of the free hydroxy group in **176**. Reaction with ylide provided, just like the same reaction with the in 4-hydroxylated derivative, a mixture of the desired *trans* **182** and *cis* derivatives (66% yield), with a 6 : 1 ratio (by ^{1}H-NMR).
In this case, the attribution of *trans* stereochemistry was assigned by the lack of NOE correlation between 5-H and the protons at C3.

Scheme 47



176 **181** (99%) **182** (66% dr 6 : 1)

183 (44% dr 6 : 1) *trans*-**112** (83% dr 6 : 1)

Scheme 47: Reagents and conditions: (a) TBSCl, imidazole, DMF, 38°C, 2.5 h; (b) trimethylsulfoxonium iodide, NaH, DMSO, 25°C, 4 h; (c) 3N HCl, CH_3CN, CH_3CN, 0°C→25°C, 2 h; (d) H_2 (1 atm), 10% Pd/C, EtOAc, 20 h

Unfortunately, while *trans* 4-hydroxy-cyclopropanated derivative could be separated from the *cis* compound after hydrolysis of the silyloxy group, the two unprotected diastereoisomers **183** and **180** resulted unseparable by chromatography.

Despite this result, we continued the synthesis with deprotection of the nitrogen by hydrogenation on Pd/C which provided *trans*-**112** in 83% in a 6 : 1 diastereomeric ratio.

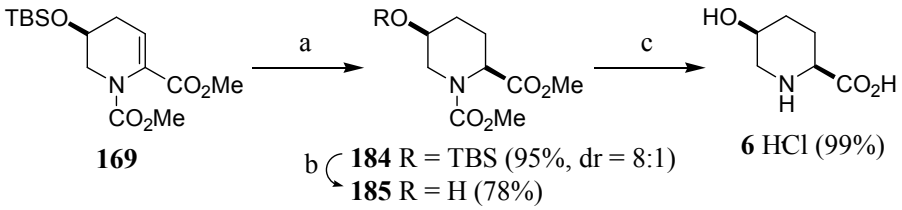
Chapter 4: synthesis of 5-hydroxylated pipecolic derivatives

4.1 Synthesis of 5-hydroxypipecolic acids[49]

Having assessed our approach to the synthesis of three of the four natural 4,5-dihydroxypipecolic acids **9-11**, we were tempted to exploit 5-silyloxy-protected compound **169** for the preparation of both *cis* and *trans* 5-hydroxypipecolic acid **6** and **7**, although the synthesis of these compounds has been already reported by a few authors in the past[92].

Thus, hydrogenation of **169** (Scheme 48) provided *cis* compound **184** (95% yield, stereochemical attribution based on nOe correlation between 3-H_{ax} and 5-H and a large ^{3}J value between 6-H_{ax} and 5-H in a compound with the 2-CO_2Me group axially-oriented – see infra) in a 8 : 1 ratio with its *trans* isomer.

Scheme 48



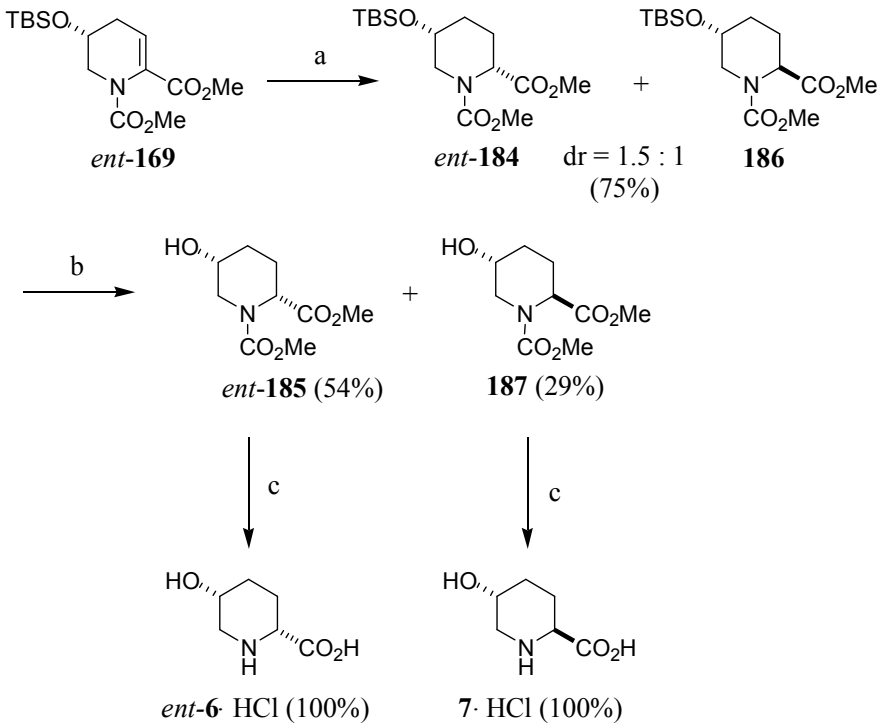
Scheme 48: Reagents and conditions: (a) H_2 (1 atm), 10% Pd/C, $NaHCO_3$, EtOAc, 20 h; (b) 3N HCl, CH_3CN, 25°C, 2h; (c) 4N HCl, reflux, 24 h

The facial selectivity of this experiment is much higher than we obtained for hydrogenation of **175** under the same conditions (See Scheme 35). This suggests a slight steric hindrance exerted by the 4-OH in **175**, as similarly observed when hydrogenating under the same conditions 4-hydroxy-substituted compounds[29a].

The minor diastereoisomer was removed from the mixture by chromatography after OH-deprotection to give diastereopure, known compound *cis* **185**[92g-h,93]. After N-deprotection in refluxing 4 N HCl, pure *cis* 5-hydroxypipecolic acid **6** was obtained in 43% overall yield from precursor **164**.

Conjugate reduction of the double bond in *ent*-**169** (Scheme 49) was as expected poorly stereoselective, providing the thermodynamically less stable *trans* isomer **186** in a 1 : 1.5 ratio with *cis* compound *ent*-**184**.

Scheme 49



Scheme 49: Reagents and conditions: (a) $LiEt_3BH$, THF, -10°C, 70 min (b) 3N HCl, CH_3CN, 0°C→25 °C, 2 h; (c) 4N HCl, reflux, 24 h;

This ratio is easily explained considering the forced axial orientation of the 2-CO_2Me group necessary to remove the $A^{(1,3)}$ strain with the N-protection[94]. In such a case, in *trans* compound **186** the 5-OTBS group is consequently axially oriented and thus less favored for the 1,3-diaxial repulsive interaction with 3-H. As above, deprotection gave free alcohols *ent*-**185** and **187** which, after chromatographic separation, were converted into *ent*-**6** (100%) and natural pipecolic acid **7** (100%).

4.2 Synthesis of *cis* 5-hydroxy-cyclopropanated derivatives

In addition to preparing 5-hydroxypipecolic acids, we tried to use the 5-hydroxylated substrates for the synthesis of cyclopropanated derivatives.

We thus investigated the application of the Zn-carbenoids previously applied to 4-mono and 4,5-dihydroxylated substrates, for OH-directed cyclopropanation of the homoallylic alcohol **188** (Scheme 42), obtained after OH deprotection on N-Cbz precursor **170**.

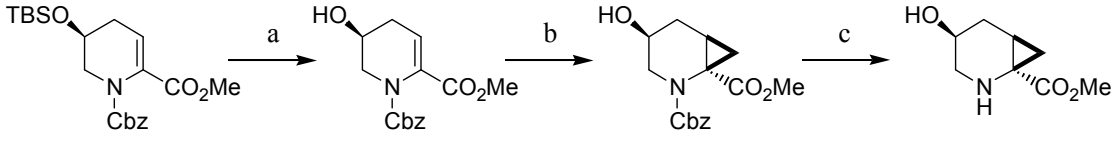
In the "mild" reaction conditions used above for **118** and **125** (-15°C or -40°C than room temperature), alcohol **188** reacted very slow either with Charette's and Furukawa's Zn-

carbenoids (<50% conversion, determined by 1H-NMR after, respectively, 96 an 72 h at room temperature).

Despite this low conversion rate, which could be explained by the not optimal spacial relationship between the homoallylic hydroxy group and the alkene[95], we were glad to observe that the hydroxy group still exerted complete stereocontrol, leading to the *cis* isomer **189** only (Scheme 50).

In order to reach the reaction to complete conversion in a shorter time[96] we first tried to increase the carbenoid concentration (3 eq of Et_2Zn and 6 eq of CH_2I_2, instead of 2 and 4, respectively), then to carry out the reaction in CH_2Cl_2 in refluxing conditions.

Scheme 50



170 **188** (83%) **189** (41%) *cis*-**111** (96%)

Scheme 50: Reagents and conditions: (a) 3N HCl, CH_3CN, 0°C → 25°C, 1.5 h; (b) Et_2Zn, CH_2I_2, CH_2Cl_2, -15°C → reflux, 16h,

In that conditions, the reaction was complete reached to complete conversion in 16 h, providing *cis*-**189** with complete diastereoselectivity, and in 41% yield after chromatography. Finally, the Cbz group was removed as usual, affording compound *cis* (*R*)-**111** in 96% yield.

Conclusion

In conclusion with this work we believe we have demonstrated the flexibility and easiness of our approach to the synthesis of polyhydroxylated pipecolic acids and their cyclopropanated derivatives based on the chemistry of lactam-derived enol phosphates. Starting from commercial, inexpensive material, in a few steps we were able to prepare all isomers of 4,5-dihydroxypipecolic acids and the simpler 4- hydroxy and 5-hydroxy derivatives. As a furher application of this chemistry, starting from the same common α,β-unsaturated enantiopure precursors we developed a methodology to attain their 2,3-cyclopropanated derivatives, which are a new kind of conformationally constrained hydroxypipecolic acids, potentially useful for the preparation of new drugs.

The synthesis of mono-hydroxylated and 4,5-dihydroxylated pipecolic acids, as well as their cyclopropanated derivatives, required the synthesis of enantiopure enecarbamate esters as substrates for the stereoselective elaboration of the double bond.

For the synthesis of 4-hydroxylated enecarbamate ester precursors **118** and **125** the key step in the process was the Pd-catalyzed methoxycarbonylation of racemic enol phosphates generated from elaboration of δ-valerolactam. Both enantiomers of the resulting 4-hydroxylated enecarbamate ester precursors **118** and **125** were obtained with high optical purity (*ee* 98.5 - 99.5%) by enantioselective enzymatic kinetic resolution of the corresponding racemic compounds.

Stereoselective hydrogenation on the O-silyl protected derivative, followed by exhaustive hydrolysis generate the *cis*-4-hydroxypipecolic acid *ent*-**4** with a higher *de* with respect to that previously obtained from O^{t}Bu-protected compounds[29a].
Enecarbamate substrates were also involved in cyclopropanation reactions, in which the stereochemical control was ensured by the 4-OH group itself, either free or protected. Charette's Zn-carbenoid for the OH-directed cyclopropanation and Michael-type addition of dimethylsulfoxonium methylide in DMSO for the synthesis of the *trans* products provided the 2,3-methanopipecolic acid derivatives with the highest yield and facial selectivity. The compounds so obtained are rigidified homoserine analogues which could find applications in medicinal chemistry as conformational probes and in drug discovery.

The synthesis of 4,5-*cis* 4,5-dihydroxypipecolic acids required the preparation from 2-deoxy-D-(and L) ribose of enantiopure *cis* 4,5-dihydroxy-δ-valerolactam **137**, which is a new compound and we believe useful as a starting material for the synthesis of other natural products. The key step in the process was the Pd-catalyzed methoxycarbonylation of the enol phosphate generated from **138**, which provided an enecarbamate ester easily converted by stereoselective reduction either to **10** or **11** (obtained in 27 and 17% yield, respectively, over ten steps).
Although in this work we did not specifically focused on the preparation of the unnatural enantiomers of **10** and **11**, we have in any case set the stage for their synthesis as we have prepared the enantiopure precursor **138** from both 2-deoxy-D- and L-ribose.

The synthesis of the 4,5-*trans* 4,5-dihydroxypipecolic acid was instead realized through a highly stereoselective allylic bromination of the enecarbamate ester obtained by methoxycarbonylation of the enol phosphate derived from a known 5-hydroxy-δ-valerolactam derivative. After substitution to give the 4-hydroxy-N-CO_2Me protected derivative **175**, the reduction of the double bond and subsequent hydrolysis provided target compound **9** (in 22% yield over 8 steps). As for 4,5-*cis* dihydroxypipecolic acids, unnatural enantiomers of **9** and **6-7** can be prepared by the same route as their precursor (*R*)-(-)-γ-hydroxymethyl-γ-butyrolactone is commercially available. As our approach allows the synthesis of several hundred mg of final compound, the potential of these 4,5-dihydroxypipecolic acids as conformationally constrained scaffolds in medicinal chemistry could now be assessed.

Moreover, starting from N-Cbz protected substrates **176** and **170**, we obtained their *cis* cyclopropanated derivatives in high optical purity employing Charette's and Furukawa's Zn-carbenoids for the OH-directed reaction of **176** and **170**, respectively, followed by N deprotection. Dimethylsulfoxonium methilyde in DMSO were employed for the synthesis of compound *trans*-**112** (even though this was obtained in a 6:1 ratio with the *cis* diastereoisomer).
As well as the 4-hydroxylated derivatives described above, the compounds so obtained are rigidified amino acid analogues which could find applications in medicinal chemistry as conformational probes and in drug discovery.

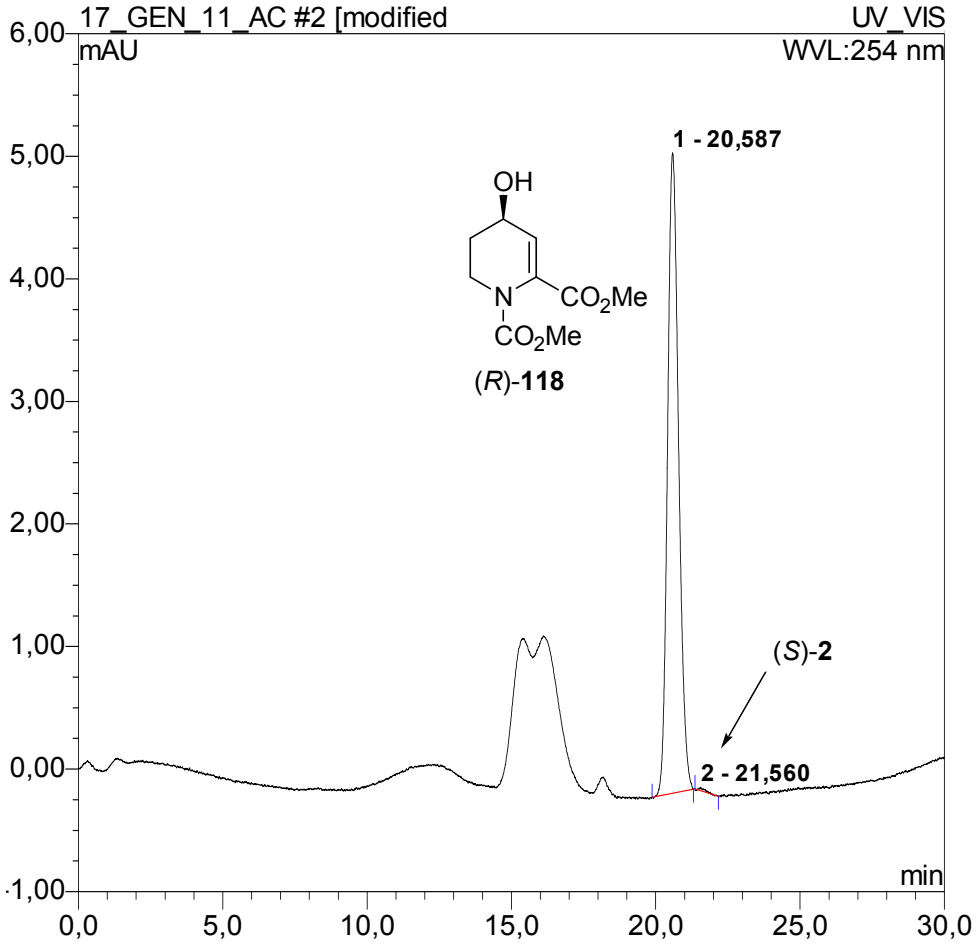
During my research work, besides the targets discussed above, their precursors, in racemic or enantiopure form, were also employed for the synthesis of alkaloids like fagomine[48] and 1-deoxymannojirimycin[51].

Appendix

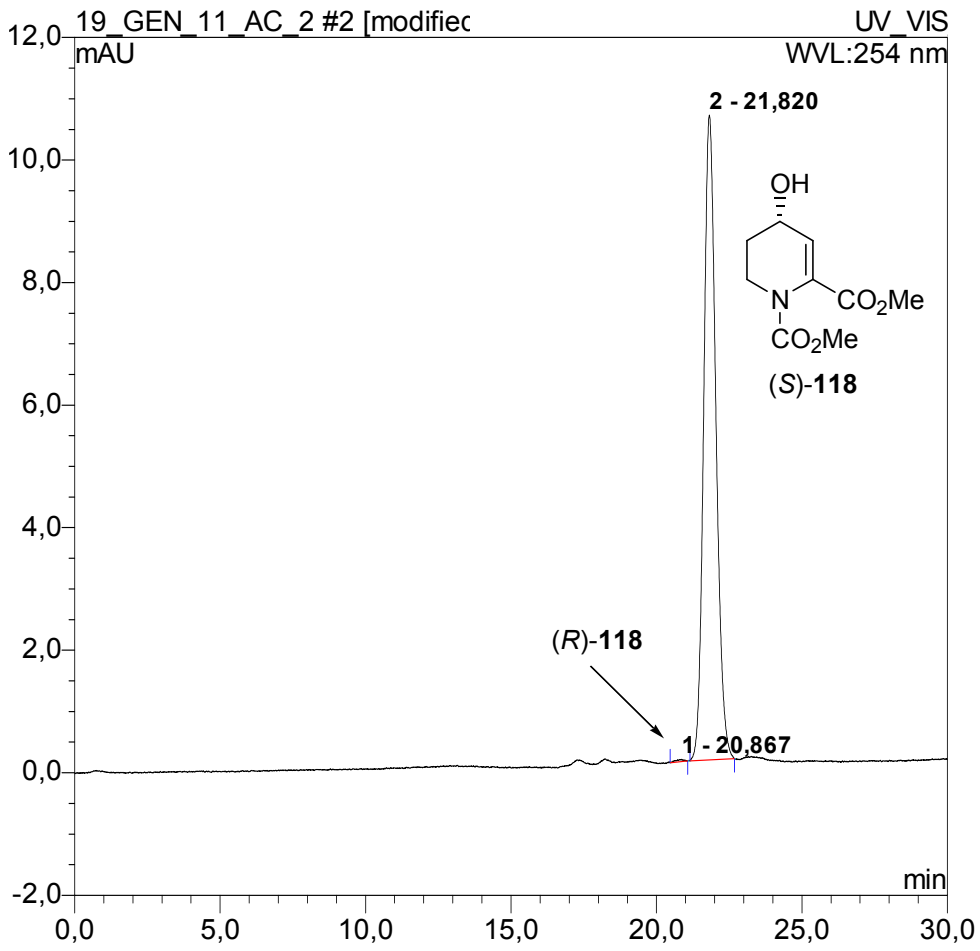
Appendix 1: Chiral HPLC analysis of alcohol 118

Substrate concentration = 1 mM in MeOH. V_{inj} = 0.1 µL. Eluant: MeOH-H_2O, 35:65, isocratic elution; flow = 0.2 mL/min. λ = 254 nm

Column: Cyclobond I 2000



No.	Ret.Time min	Peak Name	Height mAU	Area mAU*mim	Rel.Area %	Amount	Type
1	20,59	n.a.	5,225	2,310	99,76	n.a.	BMB*
2	21,56	n.a.	0,028	0,005	0,24	n.a.	BMB*



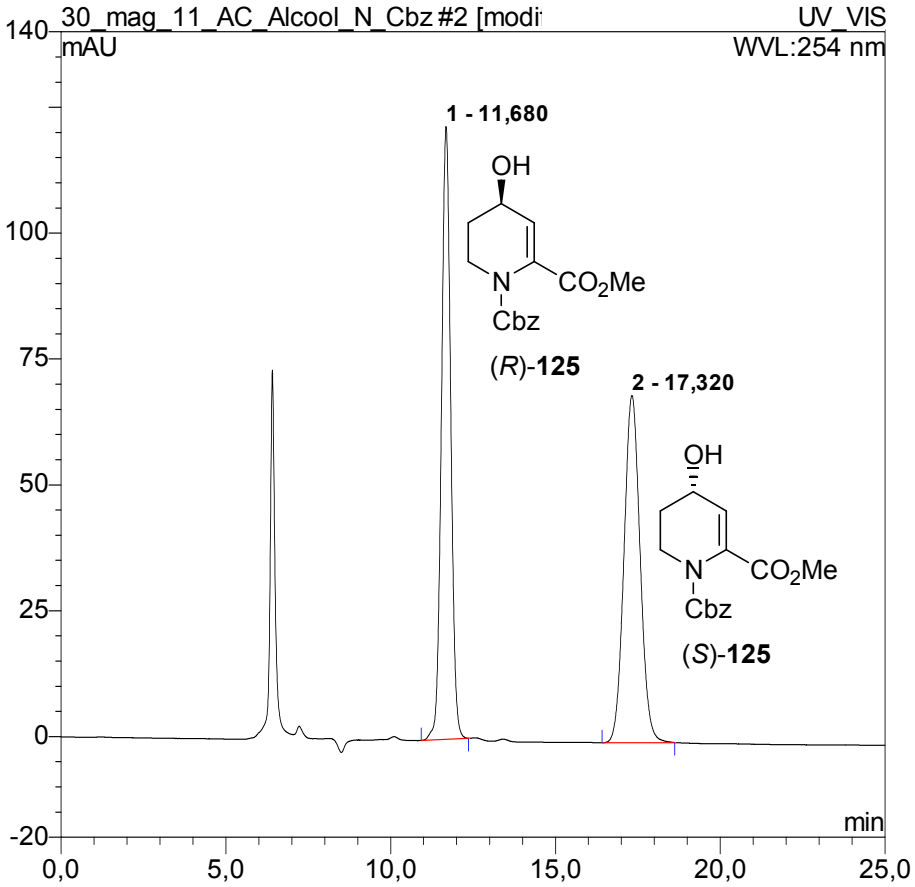
No.	Ret.Time min	Peak Name	Height mAU	Area mAU*min	Rel.Area %	Amount	Type
1	20,87	n.a.	0,040	0,012	0,23	n.a.	BMB*
2	21,82	n.a.	10,523	5,116	99,77	n.a.	BMB

Appendix 2: Chiral HPLC analysis of alcohol 125

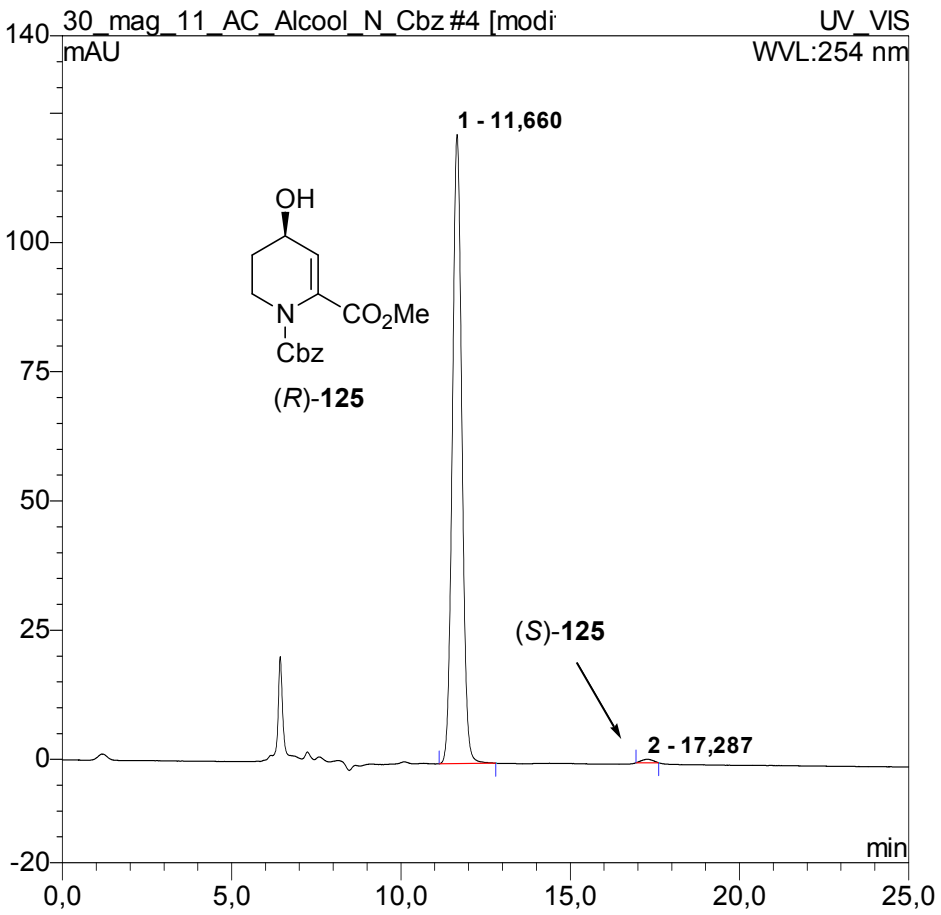
Substrate concentration = 5 mM in MeOH. V_{inj} = 2.0 µL. Eluant: Hexane-IPA, 40:60, isocratic elution; flow = 0.5 mL/min. λ = 254 nm

Column: Lux Cellulose-4

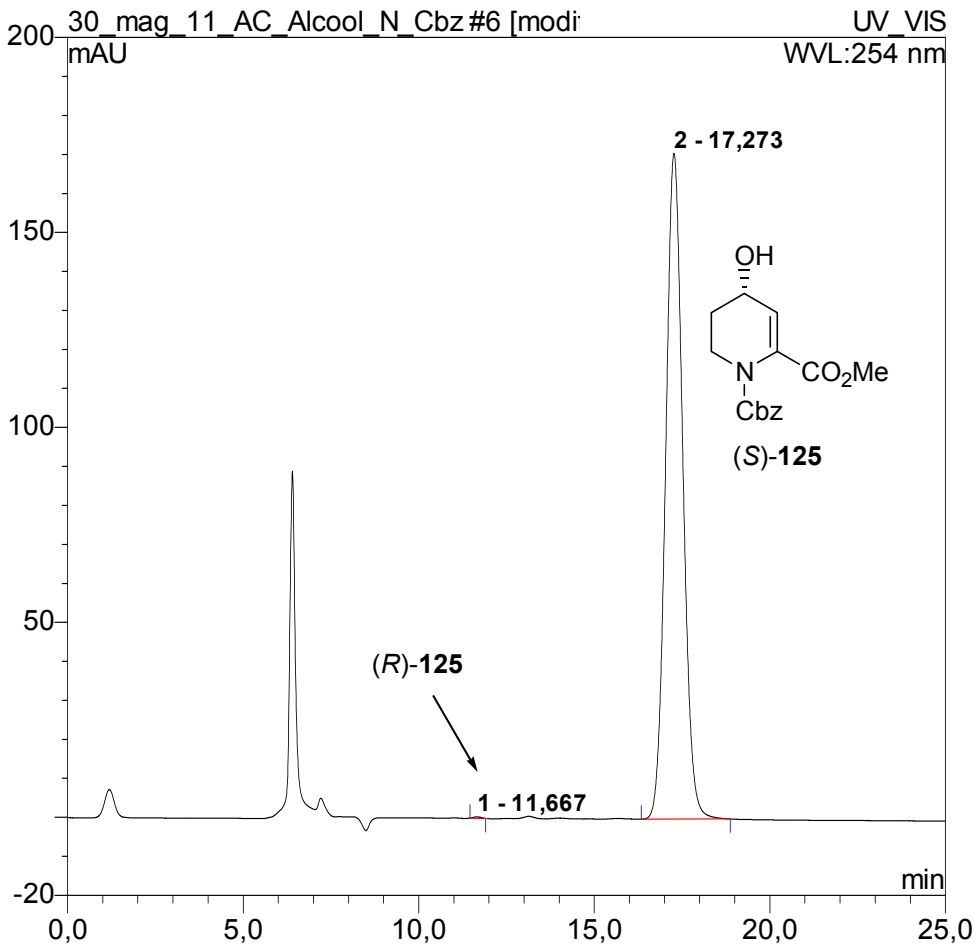
R_t = 11.68 min (*R*) and 17.32 min (*S*)



No.	Ret.Time min	Peak Name	Height mAU	Area mAU*min	Rel.Area %	Amount	Type
1	11,68	n.a.	121,741	39,847	50,47	n.a	BMB
2	17,32	n.a.	68,963	39,105	49,53	n.a.	BMB



No.	Ret.Time min	Peak Name	Height mAU	Area mAU*min	Rel.Area %	Amount	Type
1	11,66	n.a.	121,714	39,532	99,33	n.a.	BMB
2	17,29	n.a.	0,676	0,266	0,67	n.a.	BMB*



No.	Ret.Time min	Peak Name	Height mAU	Area mAU*min	Rel.Area %	Amount	Type
1	11,67	n.a.	0,341	0,086	0,09	n.a.	BMB*
2	17,27	n.a.	170,723	96,256	99,91	n.a.	BMB

Appendix 3: GLC control of the kinetic resolution of alcohol (±)-125

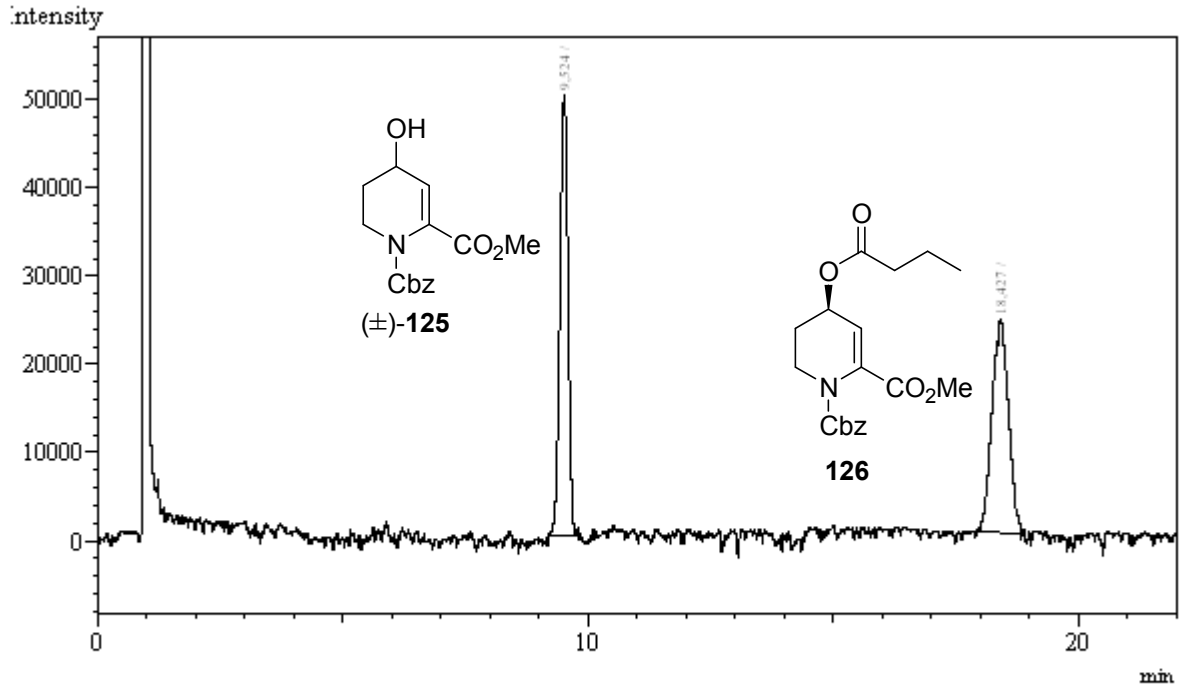
Column SBPTM-1 15 m × 0.53 mm (id), 3 μm film

Injector 250 °C

Detector (FID) 300 °C

Flow 2.34 mL/min

Column temperature 250 °C.



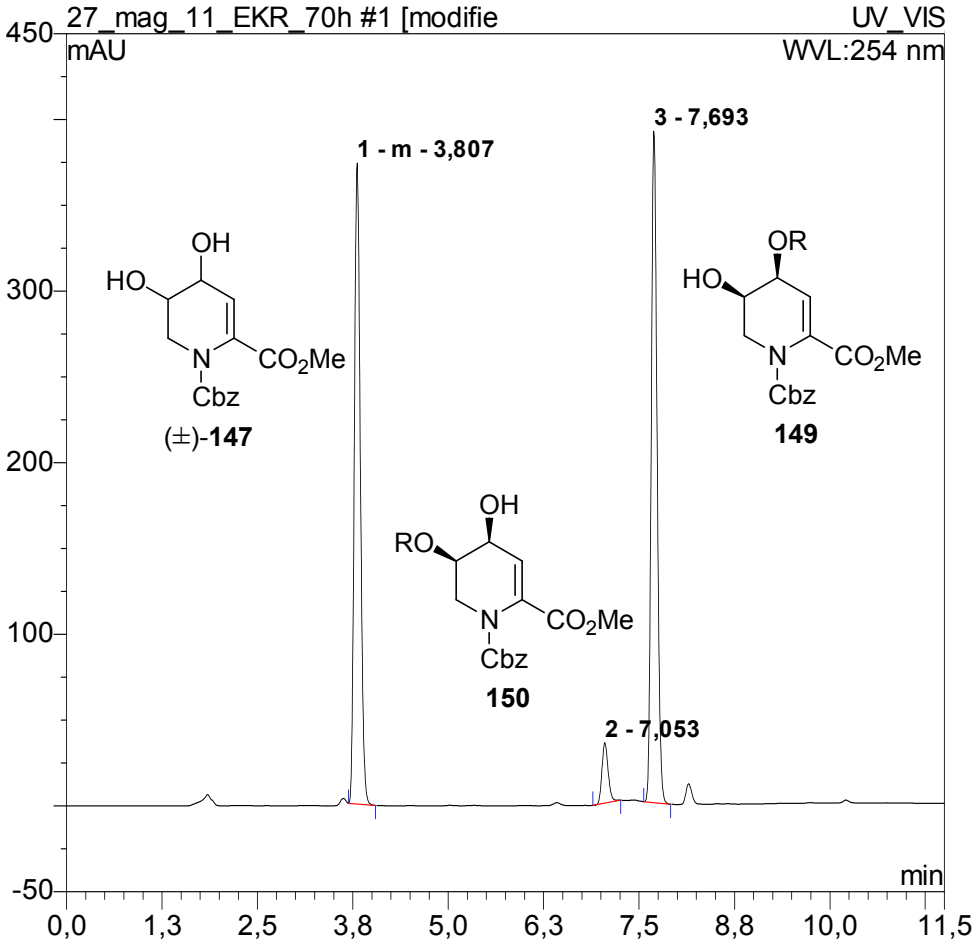
Peak#	Ret.Time	Area	Height	Area%
1	9,524	577907	49929	50,7927
2	18,427	559868	24091	49,2073
Total		1137775	74020	100,0000

Appendix 4: HPLC control of the kinetic resolution of diol (±)-147 (entry 6, 70h)

Substrate concentration = 5 mM in MeOH. Eluition program: from 55% ACN for 2.5' to 90% ACN for 3' in 3.5', then 55% ACN for 2.5' in 0'; λ=254

Column: Acclaim 120 C18

R_{t}-**147** = 3.81 min, $R_{t\text{-}5\text{-}butyrate}$ = 7.05 min, $R_{t\text{-}4\text{-}butyrate}$ = 7.69 min



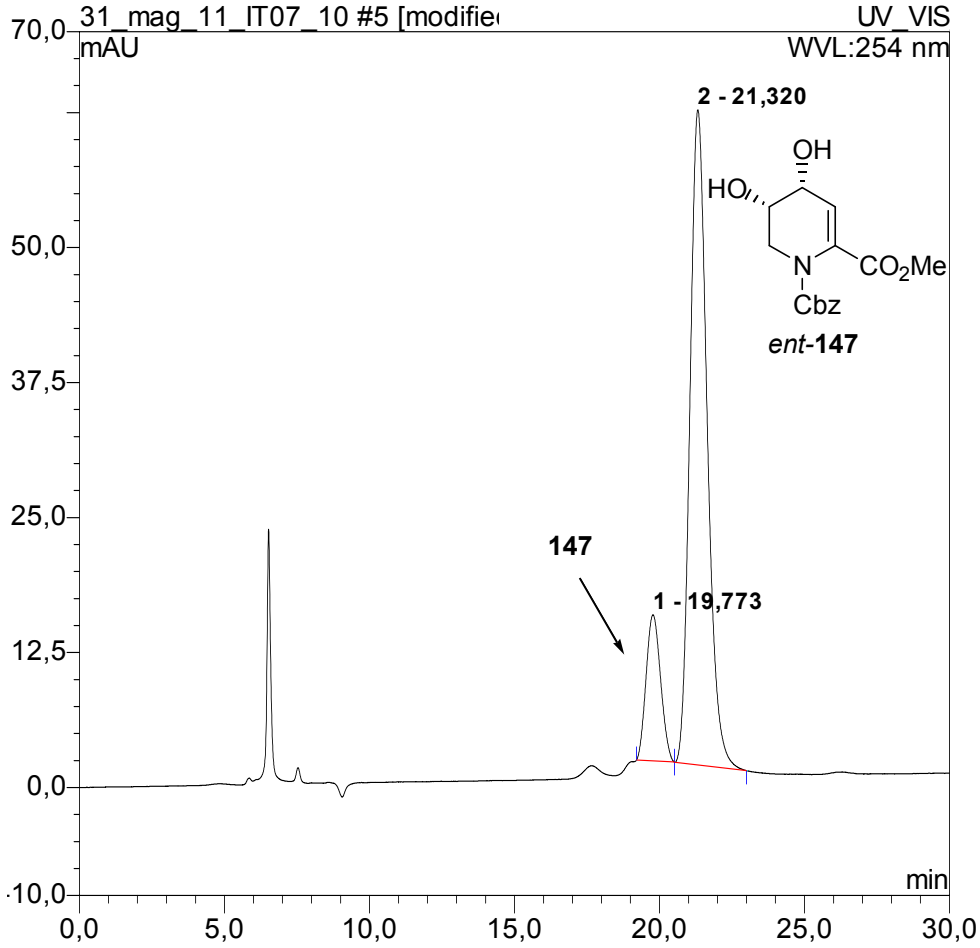
No.	Ret.Time min	Peak Name	Height mAU	Area mAU*min	Rel.Area %	Amount	Type
1	3,81	m	373,549	33,906	47,05	n.a.	BMB
2	7,05	n.a.	35,239	3,312	4,60	n.a.	BMB*
3	7,69	n.a.	391,517	34,847	48,35	n.a.	BMB
Total:			800,304	72,065	100,00	0,00	

Appendix 5: Chiral HPLC analysis of diol 147

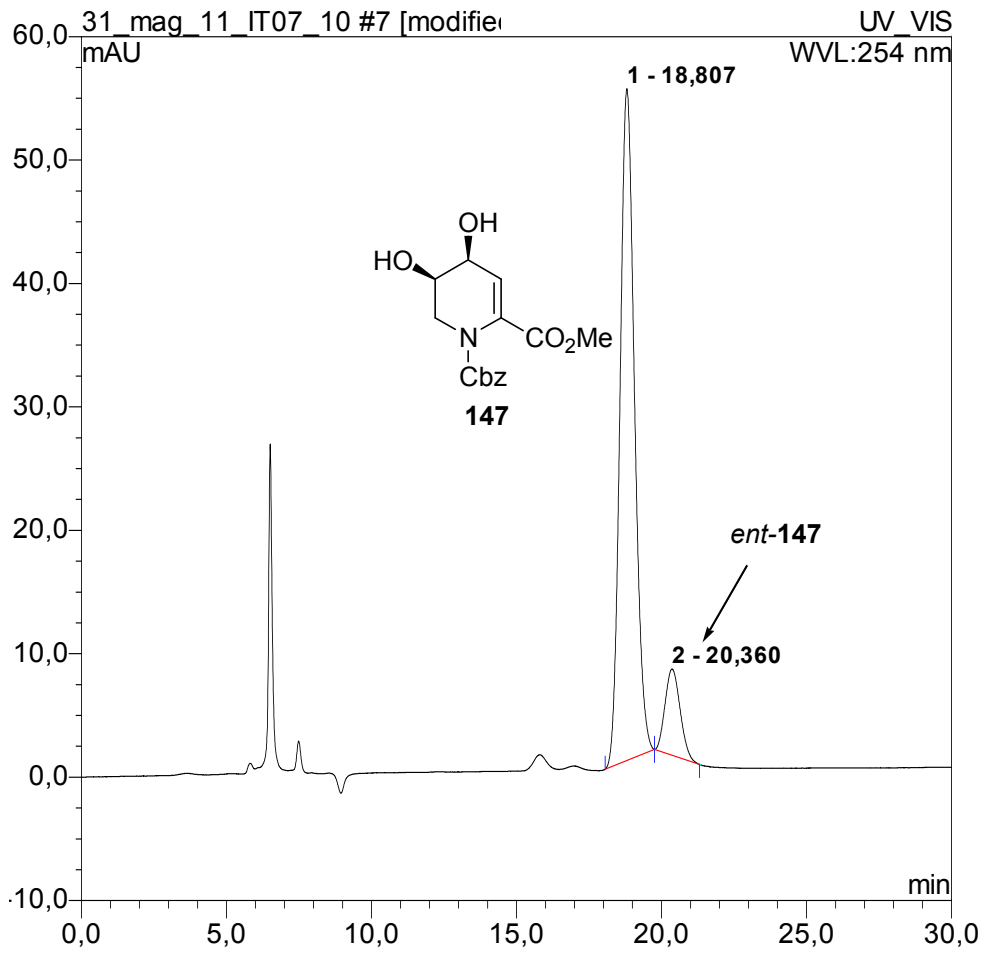
Substrate concentration = 5 mM in MeOH. Eluant: *n*-hexane/IPA 50:50; isocratic elution, λ=254

Column: Lux Cellulose 4

R_t **147** = 20.97, R_t *ent*-**147** = 22.97 min



No.	Ret.Time min	Peak Name	Height mAU	Area mAU*min	Rel.Area %	Amount	Type
1	19,77	n.a.	13,532	7,825	15,76	n.a.	BMB*
2	21,32	n.a.	60,671	41,832	84,24	n.a.	BMB*
Total:			74,203	49,657	100,00	0,000	



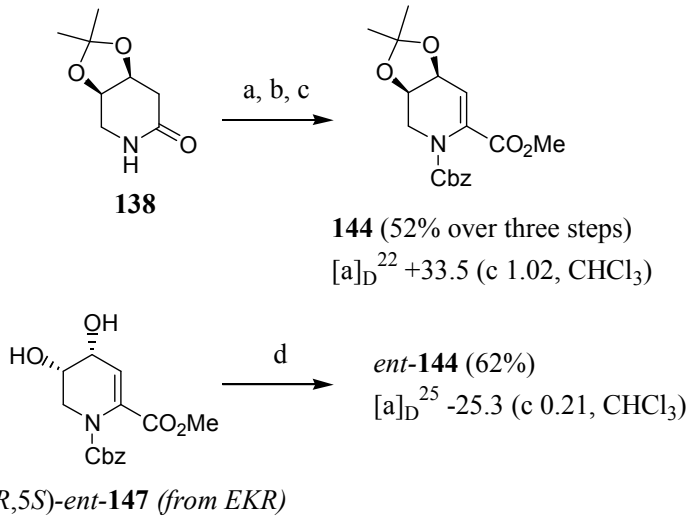
No.	Ret.Time min	Peak Name	Height mAU	Area mAU*min	Rel.Area %	Amount	Type
1	18,81	n.a.	54,436	31,447	88,15	n.a.	BMb*
2	20,36	n.a.	6,991	4,229	11,85	n.a.	bMB*
Total:			61,427	35,676	100,00	0,000	

Appendix 6: **Determination of lipases enantiospecificity in EKR of racemic *cis*-4,5-dihydroxylated enamide esters**

Since Scheme 40, both enantiomer of *cis*-lactam **137** were available, so we could determine the enantioselectivity of the lipases in the racemic resolution of **147** by assignement of the absolute configuration of the EKR products.

Diol (-)-**147**, directly obtained from the EKR (i.e the non-acylated isomer) was converted into the corresponding enamide ester (-)-**144** (Scheme 51) whose negative optical rotation value is consistent to the stereospecificity of the lipase in the kinetic resolution of diol (±)-**147** (for compound (4S,5R)-**144** obtained from enantiopure **138** of known absolute configuration the $[\alpha]^{22}_{D}$ value is +33.5).

Scheme 51



Scheme 51: Reagents and conditions: (a) BnOCOCl, *n*-BuLi, –78 °C; (b) $(PhO)_2POCl$, KHMDS, THF, –78 °C; (c) 10% $Pd(OAc)_2$, 20% Ph_3P, CO, MeOH, Et_3N, DMF, 75 °C, 1 h (d) 2,2-dimethoxypropane, *p*-TsOH, MeOH, 55 °C, 1.5 h

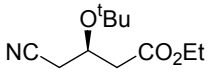
Experimental

General. Melting points are uncorrected. Chromatographic separations were performed under pressure on silica gel by flash-column techniques; R_f values refer to TLC carried out on 25-mm silica gel plates (Merck F_{254}), with the same eluent as indicated for the column chromatography. THF was distilled from Na/benzophenone. CH_2Cl_2 and *n*-hexane were distilled from CaH_2. Commercial anhydrous DMSO, DMF and MeOH were used. Commercial TBDME was used. CAL-B was purchased from Sigma-Aldrich and has a reported activity ≥ 10.000 U/g. Enzyme PS-AMANO-IM Lipase was a gift from Amano Enzyme Inc., and has a reported activity ≥ 500 U/g ^{1}H-NMR and ^{13}C-NMR spectra were recorded with a Mercury 400 instrument in $CDCl_3$ solution, unless otherwise stated. Solvent reference line were set at 7.26 ppm ($CDCl_3$), 4.79 ppm (D_2O) and 3.31 ppm (CD_3OD). Mass spectra were carried out by direct inlet on a LCQ FleetTM Ion Trap LC/MS system (Thermo Fisher Scientific) with an electrospray ionization (ESI) interface in the positive mode. Microanalyses were carried out with a Perkin-Elmer 2400/2 elemental analyser. Optical rotations were determined with a JASCO DIP-370 instrument. HPLC analyses were carried out on a Dionex Ultimate 3000 instrument.

HPLC column for monitoring enzymatic reactions on racemic **147** was Acclaim 120 C18, 250 x 4.60 nm, 5 μm; eluition program: from 55% ACN for 2.5' to 90% ACN for 3' in 3.5', then 55% ACN for 2.5' in 0'; λ=254, 223 nm; ($R_{t\text{-diol}}$ = 3.81 min, $R_{t\text{-5-butyrate}}$ = 7.05 min, $R_{t\text{-4-butyrate}}$ = 7.69 min, $R_{t\text{-4,5-dibutyrate}}$ = 10.23 min, $R_{t\text{-5-acetate}}$ = 4.99 min, $R_{t\text{-4-acetate}}$ = 5.55 min, $R_{t\text{-4,5-diacetate}}$ = 7.75 min).

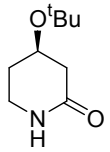
HPLC columns for calculate the enantiomeric ratio of diols were:

Lux Cellulose 4, 250 x 4.60 nm, 5 μm, eluition program: 50% IPA – 50% *n*-hexane, λ=254, 223 nm, (R_t **147** = 20.97, R_t *ent*-**147** = 22.97 min) and Cyclobond I2000, 250 x 4.60 nm, 5 μm, eluition program: 85% H_2O – 15% MeOH, λ=254, 223 nm, (R_t **147** = 20.09, R_t *ent*-**147** = 21.29 min).



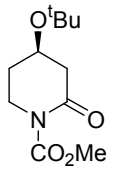
51

Ethyl (*R*)-3-*tert*-Butoxy-4-cyanobutanoate [(-)-**51**]. To a solution of (*R*)-**50** (1.257 g, 8.0 mmol) in *t*BuOAc (100 mL) was added dropwise $HClO_4$ (48 μL, 0.8 mmol) and the mixture was left at 25 °C under stirring. After 24 h, a saturated Na_2CO_3 aqueous solution (50 mL) was added, the mixture was extracted with EtOAc (3 × 30 mL) and the combined organic layers were washed with $NaHCO_3$ (satd) (50 mL) and dried over K_2CO_3. After filtration and evaporation of the solvent, compound **51** (1.65 g, 97%) was obtained as a pale yellow liquid which can directly be used in the next step. Chromatography (EtOAc-*n*-hexane, 1:3, R_f 0.3), gave **51** as a pale yellow oil (1.602 g, 94%). $[\alpha]^{20}_D$ = –9.0 (*c* 2.00, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 200 MHz) δ 4.15-4.03 (m, 1 H + 2 H), 2.62-2.54 (m, 4 H), 1.26-1.15 (m, 9 H + 3 H); ^{13}C NMR ($CDCl_3$, 50.33 MHz) δ 170.4 (s), 117.5 (s), 75.1 (s), 64.3 (d), 60.7 (t), 41.2 (t), 28.1 (q, 3 C), 25.4 (t), 14.1 (q); MS *m/z* (%) 198 (M^+ -15, 15), 140 (35), 112 (28), 57 (100). Anal. Calcd for $C_{11}H_{19}NO_3$: C, 61.95; H, 8.98; N, 6.57. Found: C, 61.98; H, 8.77; N, 6.28.



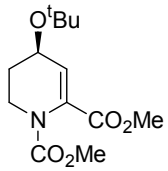
52

(*R*)-4-*tert*-Butoxypiperidin-2-one [(+)-**52**]. To a stirred solution of **51** (506 mg, 2.38 mmol), in MeOH (10 mL) was added PtO_2 (54 mg, 0.2 mmol) under N_2 atmosphere. The mixture was flushed with H_2 and then left under static pressure of H_2 (balloon) at 25 °C. After 48 h the reaction was complete (by TLC). The catalyst was filtered, washing with MeOH, and the solution was concentrated under vacuum, to give pure **52** (408 mg, 100%) as a white solid. The same reaction can be carried out in absolute EtOH, in which case is complete in 24 h. (+)-**52**: m.p.= 102.5-103.5 °C. $[\alpha]^{20}_D$ = +17.4 (*c* 0.35, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 5.78 (br s, 1 H), 3.96-3.89 (m, 1 H), 3.50-3.43 (m, 1 H), 3.34-3.20 (m, 1 H), 2.55 (dd, *J* = 17.6, 5.0 Hz, 1 H), 2.34 (dd, *J* = 17.6, 6.4 Hz, 1 H), 1.91-1.83 (m, 1 H), 1.79-1.71 (m, 1 H), 1.12 (s, 9 H); ^{13}C NMR ($CDCl_3$, 100.4 MHz) δ 171.6 (s), 74.0 (s), 64.0 (d), 40.7 (t), 38.4 (t), 30.2 (t), 28.3 (q, 3 C). MS *m/z* (%) 156 (M^+-15, 3), 115 (48), 98 (28), 87 (18), 72 (21), 59 (100). Anal. Calcd for $C_9H_{17}NO_2$: C, 63.13; H, 10.01; N, 8.18. Found: C, 63.03; H, 10.00; N, 8.09.



53

Methyl (*R*)-4-*tert*-Butoxy-2-oxopiperidine-1-carboxylate [(+)-**53**]. To a cooled (-78 °C) solution of lactam **52** (372 mg, 2.17 mmol) in anhydrous THF (9 mL) under N_2 atmosphere, was added dropwise a 1.6 M solution of *n*BuLi (1.49 mL, 2.39 mmol, 1.1 equiv) in hexane. After 40 min, methyl chloroformate (185 μL, 2.39 mmol, 1.1 equiv) was added dropwise, the cooling bath was removed, and the reaction mixture was allowed to warm to 0 °C. Stirring was continued for another 2 h and then a $NaHCO_3$ (satd) aqueous solution (6 mL) was slowly added, followed by water (15 mL). The mixture extracted with Et_2O (3 × 20 mL) and dried over Na_2SO_4. After filtration and evaporation of the solvent, **53** was obtained as a yellowish solid which was chromatographed (CH_2Cl_2-MeOH, 40:1, + 0.1% Et_3N, R_f 0.32) to give pure **53** (438 mg, 88%) as a white solid: m.p. = 55-56 °C. $[\alpha]^{20}_D$ = +15.5 (*c* 0.47, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 3.99-3.93 (m, 1 H), 3.89 (ddd, *J* = 12.8, 8.2, 4.7 Hz, 1 H), 3.86 (s, 3 H), 3.67 (ddd, *J* = 12.8, 7.3, 4.7 Hz, 1 H), 2.69 (dd, *J* = 16.8, 5.1 Hz, 1 H), 2.53 (dd, *J* = 16.8, 6.6 Hz, 1 H), 2.06-1.93 (m, 1 H), 1.86-1.76 (m, 1 H), 1.18 (s, 9 H); ^{13}C NMR ($CDCl_3$, 100.4 MHz) δ 169.9 (s), 154.8 (s), 74.2 (s), 63.7 (d), 53.9 (q), 43.8 (t), 42.7 (t), 31.2 (t), 28.2 (q, 3 C). MS *m/z* (%) 229 (M^+, 3), 173 (30), 156 (25), 102 (22), 88 (20), 57(100). Anal. Calcd for $C_{11}H_{19}NO_4$: C, 57.62; H, 8.35; N, 6.11. Found: C, 57.41; H, 8.13; N, 6.02.



54

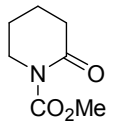
Dimethyl (*R*)-4-*tert*-Butoxy-5,6-dihydropyridine-1,2(4*H*)-dicarboxylate [(+)-**54**]. To a solution of KHMDS (4.7 mL of a 0.5 M solution in toluene, 2.35 mmol) in THF (12.5 mL), cooled at –78 °C and under nitrogen atmosphere, was added a solution of **53** (430 mg, 1.88 mmol) in THF (5 mL) and the resulting mixture was stirred for 1.5 h. Afterward a solution of $(PhO)_2P(O)Cl$ (487 μL, 2.35 mmol) in THF (4 mL) was added, leaving under stirring for 1 h at –78 °C before allowing the temperature to rise to 0 °C. Then, a 10% NaOH aqueous solution (38 mL) was added, the mixture was extracted with Et_2O (3 × 30 mL), washed with 10% NaOH (24 mL), and dried over anhydrous K_2CO_3 for 30 min. After filtration and evaporation of the solvent (without heating and leaving a small volume of solvent), the crude phosphate was chromatographed (EtOAc-*n*-hexane, 30:70, + 1% Et_3N, R_f 0.27) on a short layer of silica gel (3.5

cm of silica gel in a column with internal diameter of 3 cm) to give the phosphate (856 mg, 99%) as a pale yellow oil.

Phosphate: ^{1}H NMR ($CDCl_3$, 200 MHz) δ 7.32-7.17 (m, 10 H), 4.92 (br s, 1 H), 3.65-3.60 (m, 1 H), 3.52 (s, 3 H), 3.49-3.21 (m, 2 H), 1.82-1.64 (m, 2 H), 1.14 (s, 9 H); ^{13}C NMR ($CDCl_3$, 50.33 MHz) δ 154.1 (s), 150.4 (s), 141.1 (s), 129.7 (d, 4 C), 125.3 (d, 2 C), 120.1 (d, 4 C), 102.2 (d), 74.1 (s), 61.9 (d), 53.1 (q), 42.9 (t), 32.7 (t), 28.1 (q, 3 C).

Phosphate (856 mg, 1.86 mmol) was immediately dissolved in DMF (4.8 mL), $Pd(OAc)_2$ (42 mg, 0.186 mmol) and Ph_3P (97 mg, 0.372 mmol) were added and the solution was stirred 10 min under a CO atmosphere (balloon). Then Et_3N (516 μL, 3.72 mmol) and MeOH (3 mL, 74.4 mmol) were added and stirring was continued at 55 °C (external bath) for 3 h under static CO pressure. The solution was filtered through Celite, and the MeOH was evaporated. The residue was diluted with water (40 mL), extracted with Et_2O (3 × 40 mL) and dried over Na_2SO_4. After filtration and evaporation of the solvent, the oily residue was chromatographed (EtOAc-*n*-hexane, 1:2, +1% Et_3N, R_f 0.33) to give (+)-**54** (408 mg, 81%) as a thick pale yellow oil.

(+)-54. $[\alpha]^{23}_{D}$ = +157 (*c* 0.54, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 5.87 (d, *J* = 3.9 Hz, 1 H), 4.07-4.16 (m, 1 H), 3.97 (dt, *J* = 12.9, 4.3 Hz, 1 H), 3.76 (s, 3 H), 3.71 (s, 3 H), 3.28 (ddd, *J* = 12.9, 8.9, 4.7 Hz, 1 H), 1.89-1.81 (m, 2 H), 1.21 (s, 9 H); ^{13}C NMR ($CDCl_3$, 50.33 MHz) δ 164.7 (s), 153.8 (s), 132.3 (s), 122.5 (d), 74.1 (s), 60.6 (d), 52.8 (q), 51.8 (q), 40.5 (t), 32.4 (t), 27.8 (q, 3 C); MS *m/z* (%) 271 (M^+, 18), 198 (87), 183 (100), 94 (82), 80 (42), 57 (79). Anal. Calcd for $C_{13}H_{21}NO_5$: C, 57.55; H, 7.80; N, 5.16. Found: C, 57.41; H, 7.67; N, 5.01.

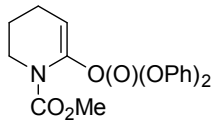


115

Methyl 2-oxopiperidine-1-carboxylate (**115**)

To a solution of methyl 2-oxopiperidine-1-carboxylate **114** (991 mg, 10 mmol) in THF (92 mL), cooled to -78 °C, *n*-BuLi (6.3 mL, 1.6 M solution in hexane, 10 mmol) was slowly added. The mixture was stirred at –78 °C for 15 min and then methyl chloroformate (850 μL, 11 mmol) was added drop-wise. After 10 min the solution was allowed to reach 0 °C, saturated aqueous $NaHCO_3$ (50 mL) was added and the organic layer was separated. The aqueous layer was extracted with CH_2Cl_2 (2 x 40 mL) and the combined organic extracts were dried over Na_2SO_4 and evaporated. The residue was purified by flash chromatography (*n*-hexane/EtOAc 1:1, R_f 0.27) to give **115** (1.30 g, 8.27 mmol, 83%) as a white solid.

115. ^{1}H NMR ($CDCl_3$, 400 MHz) δ = 3.84 (s, 3 H, OCH_3), 3.74–3.71 (m, 2 H, 6-H), 2.54–2.50 (m, 2 H, 3-H), 1.85–1.80 (m, 4 H, 4-H and 5-H) ppm. ^{13}C NMR ($CDCl_3$, 100.4 MHz) δ = 171.2 (s, CO), 155.0 (s, CO), 53.8 (q, OCH_3), 46.5 (t, C-6), 34.8 (t, C-3), 22.6 (t, C-4), 20.3 (t, C-5) ppm. ESI-MS *m/z* (%) = 158 (9) $[M + 1]^+$, 126 (100), 82 (49).



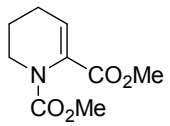
116

Methyl 6-[(diphenoxyphosphoryl)oxy]-3,4-dihydropyridine-1(2*H*)-carboxylate (116)

To a solution of KHMDS (20.8 mL of a 0.5 M solution in toluene, 10.38 mmol) in THF (54.8 mL), cooled at –78 °C and under nitrogen atmosphere, was added a solution of **115** (1.30 g, 8.3 mmol) in THF (21.7 mL) and the resulting mixture was stirred for 1.5 h. Afterward a solution of $(PhO)_2P(O)Cl$ (2.1 mL, 10.38 mmol) in THF (17.1 mL) was added, leaving under stirring for 1 h at –78 °C before allowing the temperature to rise to 0 °C. Then, a 10% NaOH aqueous solution (160 mL) was added, the mixture was extracted with Et_2O (3 × 130 mL), washed with 10% NaOH (100 mL) and water (100 mL), and dried over anhydrous K_2CO_3 for 1 hour. After filtration and evaporation of the solvent (without heating and leaving a small volume of solvent), the crude phosphate was chromatographed (EtOAc/*n*-hexane, 1:3, + 1% Et_3N, R_f 0.19) on a short layer of silica gel (4 cm of silica gel in a column with internal diameter of 4 cm) to give **116** (3.20 g, 99%) as a pale yellow oil.

116. ^{1}H NMR ($CDCl_3$, 400 MHz) δ = 7.37–7.32 (m, 4 H, CH_{arom}), 7.26–7.17 (m, 6 H, CH_{arom}), 5.10 (q, J = 2.9 Hz, 1 H, 3-H), 3.64–3.61 (m, 2 H, 6-H), 3.56 (s, 3 H, OCH_3), 2.18–2.04 (m, 2 H, 4-H), 1.76–1.69 (m, 2 H, 5-H) ppm. ^{13}C NMR ($CDCl_3$, 100.4 MHz) δ = 154.7 (s, CO), 150.5 (s, 2 C, C_{arom}), 140.0 (s, C-2), 129.8 (d, 4 C, C_{arom}), 125.5 (d, 2 C, C_{arom}), 120.1 (d, 4 C, C_{arom}), 100.4 (d, C-3), 53.1 (q, OCH_3), 45.7 (t, C-6), 22.6 (t, C-4), 21.6 (t, C-5) ppm. ESI-MS *m/z* (%) = 390 (6) $[M + 1]^+$, 346 (100), 265 (21).

$C_{19}H_{20}NO_6P$ (389) requires C 58.61; H 5.18; N 3.60. Found: C 58.34; H 5.00; N 3.27



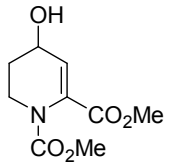
117

Dimethyl 5,6-dihydropyridine-1,2(4*H*)-dicarboxylate (117)

Phosphate **116** (2.87 g, 7.38 mmol) was immediately dissolved in DMF (19.4 mL), $Pd(OAc)_2$ (166 mg, 0.738 mmol) and Ph_3P (388 mg, 1.48 mmol) were added and the solution was stirred 10 min under a CO atmosphere (balloon). Then Et_3N (2.0 mL, 14.76 mmol) and MeOH (12.0 mL, 295.2 mmol) were added and stirring was continued at 55 °C (external bath) for 3 h under static CO pressure. The solution was diluted with water (200 mL), extracted with Et_2O (6 × 150 mL) and dried over Na_2SO_4. After filtration and evaporation of the solvent, the oily residue was chromatographed (EtOAc/*n*-hexane, 1:2, R_f 0.20) to give **117** (1.29 g, 88%) as a thick pale yellow oil.

117. ^{1}H NMR ($CDCl_3$, 200 MHz) δ = 6.04 (t, J = 4.0 Hz, 1 H, 3-H), 3.73 (s, 3 H, OCH_3), 3.67 (s, 3 H, OCH_3), 3.61–3.55 (m, 2 H, 6-H), 2.25–2.16 (m, 2 H, 4-H), 1.84–1.72 (m, 2 H, 5-H) ppm. ^{13}C NMR ($CDCl_3$, 50.33 MHz) δ = 164.9 (s, CO), 154.3 (s, CO), 132.2 (s, C-2), 122.8 (d, C-3), 53.1 (q, OCH_3), 52.0 (q, OCH_3), 43.6 (t, C-6), 22.9 (t, C-4), 22.7 (t, C-5) ppm. MS *m/z* (%) = 199 (29) $[M]^+$, 167 (11), 140 (30), 80 (20), 68 (29), 59 (100).

$C_9H_{13}NO_4$ (199) requires C 54.26; H 6.58; N 7.03. Found: C 54.29; H 6.33; N 6.86



(±)-**118**

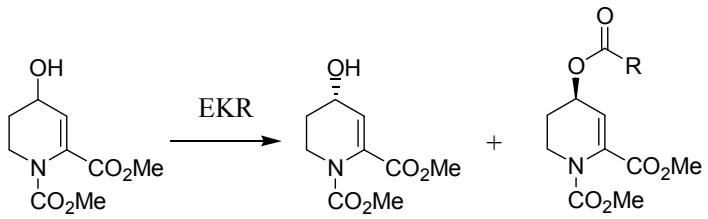
Dimethyl 4-Hydroxy-5,6-dihydropyridine-1,2(4*H*)-dicarboxylate [(±)-**118**]

A solution of **117** (1.29 g, 6.49 mmol), *N*-bromosuccinimide (1.47 g, 8.24 mmol) and a catalytic amount of azobisisobutyronitrile (90 mg, 0.55 mmol) in a 9:1 mixture of CCl_4 and $CHCl_3$ (224 mL) was refluxed with vigorous stirring for 15 min. After cooling, the reaction mixture was diluted with $CHCl_3$ (180 mL), washed with water (200 mL) and evaporated. The yellow oil thus obtained was dissolved in 96% aqueous acetone (113 mL) and $ZnCl_2$ (3.67 g, 26.93 mmol) was added to the solution portionwise over 4 h. After 6 h, the reaction mixture was diluted with $CHCl_3$ (130 mL), washed with water (300 mL), saturated aqueous $NaHCO_3$ (300 mL) and brine (300 mL) and dried over Na_2SO_4. After filtration and evaporation of the solvent, the crude product was chromatographed (EtOAc/*n*-hexane, 2:1, + 0.5% Et_3N, R_f 0.33) to give (±)-**118** (920 mg, 66%) as a thick pale yellow oil.

(±)-**118.** ^{1}H NMR ($CDCl_3$, 400 MHz) δ = 5.96 (dd, J = 3.9, 1.0 Hz, 1 H, 3-H), 4.31–4.27 (m, 1 H, 4-H), 4.05 (dt, J = 13.1, 4.1 Hz, 1 H, 6-H), 3.79 (s, 3 H, OCH_3), 3.73 (s, 3 H, OCH_3), 3.30 (ddd, J = 13.2, 9.2, 5.5 Hz, 1 H, 6-H'), 1.96–1.85 (m, 2 H, 5-H) ppm. ^{13}C NMR ($CDCl_3$, 100.4 MHz) δ = 165.1 (s, CO), 154.0 (s, CO), 133.6 (s, C-2), 120.4 (d, C-3), 61.2 (d, C-4), 53.4 (q,

OCH_3), 52.5 (q, OCH_3), 40.1 (t, C-6), 32.1 (t, C-5) ppm. MS *m/z* (%) = 215 (38) $[M]^+$, 183 (79), 155 (59), 127 (47), 114 (49), 97 (74), 59 (100).

$C_9H_{13}NO_5$ (215) requires C 50.23; H 6.09; N 6.51. Found: C 50.48; H 5.79; N 6.22.



(±)-**118** (*S*)-**118** (*R*)-**119**

Kinetic Resolution with PS "AMANO" IM lipase

Dimethyl (*R*)-4-(Butyryloxy)-5,6-dihydropyridine-1,2(4*H*)-dicarboxylate [(+)-**119**] and **(*S*)-4-Hydroxy-5,6-dihydropyridine-1,2(4*H*)-dicarboxylate** [(–)-**118**]

To a solution of (±)-**118** (538 mg, 2.5 mmol) in THF (3.1 mL) at 30 °C, was added lipase PS "AMANO" IM (250 mg) under N_2 atmosphere. After 20 minutes, vinyl butyrate (1.1 mL) was added and the reaction was left under vigorous stirring and monitored by GC. After 6.5 h, the conversion reached 50% and the reaction was stopped by filtration over a thin layer of celite. After evaporation, the crude product was chromatographed (EtOAc/*n*-hexane, 1:2) to give (*R*)-**119** (R_f 0.60, 321 mg, 45%, 95% ee) and (*S*)-**118** (R_f 0.15, 226 mg, 42%, 94% ee).

(*R*)-119 $[\alpha]^{25}_D$ = +206 (c 0.82, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 400 MHz) δ = 5.91 (d, *J* = 4.1 Hz, 1 H, 3-H), 5.31 (pseudo q, *J* = 3.9 Hz, 1 H, 4-H), 4.10 (dt, *J* = 13.1, 4.1 Hz, 1 H, 6-H), 3.79 (s, 3 H, OC*H*$_3$), 3.74 (s, 3 H, OC*H*$_3$), 3.28 (ddd, *J* = 13.1, 8.8, 6.2 Hz, 1 H, 6-H'), 2.27 (t, *J* = 7.0 Hz, 2 H, OC*H*$_2$), 1.94–1.98 (m, 2 H, 5-H), 1.60–1.68 (m, 2 H, C*H*$_2$), 0.94 (t, *J* = 7.3 Hz, 3 H, CH_3) ppm. ^{13}C NMR ($CDCl_3$, 100.4 MHz) δ = 172.7 (s, CO), 164.7 (s, CO), 153.9 (s, CO), 135.2 (s, C-2), 116.6 (d, C-3), 63.2 (d, C-4), 53.5 (q, OCH_3), 52.5 (q, OCH_3), 40.5 (t, C-6), 36.2 (t, $CH_2CH_2CH_2$), 29.3 (t, C-5), 18.4 (t, CH_2CH_3), 13.6 (q, CH_3). MS *m/z* (%) 286 (12) $[M + 1]^+$, 253 (21), 198 (59), 183 (77), 152 (58), 94 (100).

$C_{13}H_{19}NO_6$ (285) requires C 54.73; H 6.71; N 4.91. Found: C 54.58; H 6.93; N 5.12.

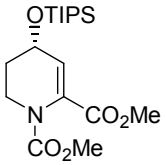
(*S*)-118. $[\alpha]^{25}_D$ = –132 (c 0.78, CHCl3). Spectroscopic data as reported above for racemic compound (±)-**118**.

Dimethyl (*R*)-4-Hydroxy-5,6-dihydropyridine-1,2(4*H*)-dicarboxylate [(+)-**118**]

To a solution of (+)-**119** (215 mg, 0.75 mmol) in dry MeOH (7.2 mL) cooled in an ice bath, MeONa (40.5 mg, 0.75 mmol) was added and it was stirred 5 h at 0 °C under N_2 atmosphere. Then glacial acetic acid (0.340 mL) was added and the MeOH was evaporated. The residue was

diluted with water (70 mL), extracted with EtOAc (4 × 70 mL) and dried over Na_2SO_4. After filtration and evaporation of the solvent, the crude product was chromatographed (EtOAc/*n*-hexane, 1:1, + 0.5% Et_3N, R_f 0.15) to give (*R*)-**118** (153 mg, 95%) as a thick pale yellow oil.

(*R*)-118. $[\alpha]^{25}_D$ = +134 (c 0.67, $CHCl_3$). Spectroscopic data as reported above for racemic compound (±)-**118**.

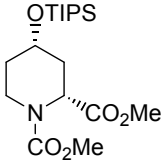


120

Dimethyl (S)-4-Triisopropylsilyloxy-5,6-dihydropyridine-1,2(4H)-dicarboxylate [(–)-120]

To a stirred solution of (*S*)-**118** (207 mg, 0.975 mmol) in anhydrous DMF (2.6 mL) were added imidazole (148 mg, 2.17 mmol) and TIPSCl (306 μL, 1.45 mmol) and it was stirred 5 h at 40 °C (external bath) under N2 atmosphere. After cooling to room temperature, water (25 mL) was added and the solution extracted with Et2O (4 × 25 mL). The combined organic layers were washed with brine (25 mL) and dried over Na2SO4. After filtration and evaporation of the solvent, the oily residue was chromatographed (EtOAc/n-hexane, 1:4, R_f 0.19) to give (*S*)-**120** (327 mg, 91%) as a thick colorless oil.

(*S*)-120. $[\alpha]^{20}_D$ = −125.2 (c 0.97, CHCl3). 1H NMR ($CDCl_3$, 400 MHz) δ = 5.92 (dd, J = 3.9, 0.8 Hz, 1 H, 3-H), 4.35 (pseudo q, J = 3.9 Hz. 1 H, 4-H), 3.98 (dt, *J* = 12.9, 4.1 Hz, 1 H, 6-H), 3.79 (s, 3 H, OCH3), 3.72 (s, 3 H, OCH3), 3.34 (ddd, *J* = 12.9, 10.3, 3.5 Hz, 1 H, 6-H'), 1.94–1.83 (m, 2 H, 5-H), 1.06 (s, 18 H + 3 H, TIPS) ppm. 13C NMR ($CDCl_3$, 100.4 MHz) δ = 165.3 (s, CO), 154.2 (s, CO), 132.4 (s, C-2), 122.2 (d, C-3), 62.0 (d, C-4), 53.3 (q, OCH_3), 52.3 (q, OCH_3), 40.3 (t, C-6), 33.2 (t, C-5), 18.0 (q, 6 C, CH_3 of TIPS), 12.2 (d, 3 C, CH of TIPS) ppm. ESI-MS m/z (%) = 394 (11) [M + 23]+, 296 (22), 220 (100), 62 (14). C18H33NO5Si (371) requires C 58.19; H 8.95; N 3.77. Found: C 57.86; H 8.98; N 3.83.

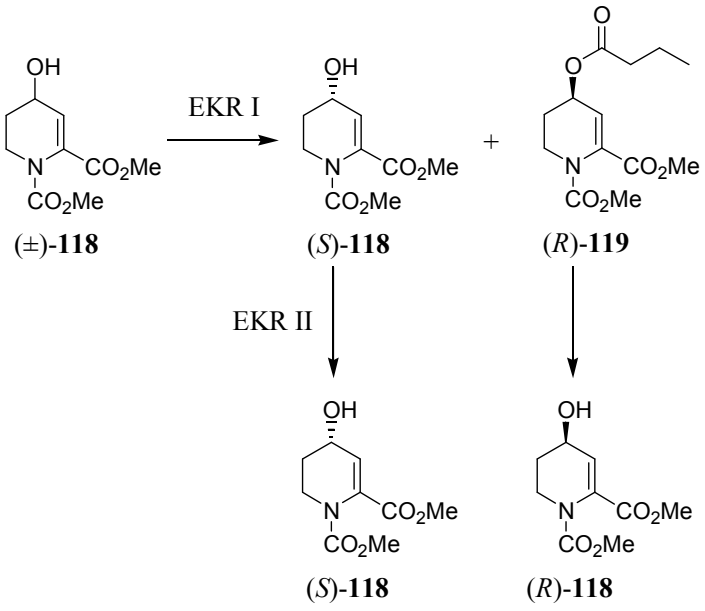


121

Dimethyl 4-Triisopropyloxypiperidine-1,2-dicarboxylate [(+)-**121**]: To a stirred suspension of $NaHCO_3$ (16 mg, 0.19 mmol) in anhydrous EtOAc (1.5 mL), Pd/C 10% (13.1 mg, 0.012 mmol) was added and it was stirred 30 min under a H_2 atmosphere (balloon). Then, a solution of (*S*)-**120** (26.2 mg, 0.077 mmol) in anhydrous EtOAc (680 μL) were added and it was stirred 6 h at room

temperature. The reaction was stopped by filtration over a thin layer of celite and the solvent was evaporated, to give (2*R*,4*S*)-**121** (26 mg, 100%) as a thick colorless oil.

121. $[\alpha]^{23}_{D}$ = +11.6 (c 1.06, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 400 MHz) δ = 4.80 (br d, *J* = 6.6 Hz, major rotamer, 2-H) and 4.64 (br d, *J* = 6.6 Hz, minor rotamer, 2-H), 4.19 (br quintet, *J* = 2.5 Hz, 1 H, 4-H), 3.96 (br d, *J* = 12.0 Hz, minor rotamer, 6-H_{eq}) and 3.83 (br d, *J* = 10.9 Hz, major rotamer, 6-H_{eq}), 3.72 and 3.69 (s, 3 H + 3 H, two rotamers, OCH_3), 3.56–3.44 (m, 1 H, 6-H_{ax}), 2.50–2.40 (br m, 1 H, 3-H_{eq}), 1.86 (br dd, *J* = 13.7, 7.2 Hz, 1 H, 3-H_{ax}), 1.78–1.55 (m, 2 H, 5-H), 1.04 (s, 18 H + 3 H, TIPS) ppm. ^{13}C NMR ($CDCl_3$, 100.4 MHz) δ = 171.9 (s, CO) 157.1 and 156.6 (s, two rotamers, CO), 63.8 (d, C-4), 52.8 (d, C-2), 51.9 (q, OCH_3), 51.2 and 50.9 (q, two rotamers, OCH_3), 35.9 and 35.7 (t, two rotamers, C-6), 33.9 and 33.8 (t, two rotamers, C-3), 32.4 and 32.2 (t, two rotamers, C-5), 18.0 and 17.9 (q, 6 C, CH_3 of TIPS), 12.2 (q, 3 C, CH of TIPS) ppm. ESI-MS *m/z* (%) = 374 (6) $[M + 1]^+$, 314 (100). $C_{18}H_{35}NO_5Si$ (373) requires C 57.87; H 9.44; N 3.75. Found: C 57.73; H 9.52; N 3.89.



Two-step lipase-catalyzed kinetic resolution of (±)-**118**:

Dimethyl (*R*)-4-(Butyryloxy)-5,6-dihydropyridine-1,2(4*H*)-dicarboxylate [(+)-119] and **(*S*)-4-Hydroxy-5,6-dihydropyridine-1,2(4*H*)-dicarboxylate [(–)-118**].

4 Å MS (153 mg) were added to a solution of (±)-**118** (253 mg, 1.18 mmol) in THF (1.5 mL) at 30 °C, followed by lipase PS "AMANO" IM (118 mg), under N_2 atmosphere. After 20 min, vinyl butyrate (523 μL, 4.12 mmol) was added and the reaction was left under vigorous stirring and monitored by GC. After 7 h, the conversion reached 42% and the reaction was stopped by filtration over a thin layer of Celite. After evaporation, the crude product was chromatographed (first with EtOAc-*n*-hexane, 1:2, then EtOAc-*n*-hexane, 2:1 to collect the alcohol) to give (*R*)-

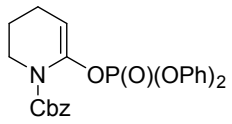
119 (R_f 0.60, 122 mg, 38%, 99.5% ee) and (*S*)-**118** (R_f 0.3, 134 mg, 53%, 69% ee). (*S*)-**118** was dissolved again in THF (0.8 mL) at 30 °C, 4 Å MS (80 mg) were added, followed by lipase PS "AMANO" IM (62 mg) under N_2 atmosphere. After 20 min, vinyl butyrate (236 μL, 1.86 mmol) was added and the reaction was left under stirring and monitored by GC. After 22 h, the conversion reached 17% and the reaction was stopped by filtration over a thin layer of celite. After evaporation, the crude product was chromatographed (EtOAc-*n*-hexane, 1:2) to give (*S*)-**118** (R_f 0.15, 226 mg, 89%, 99.5% ee).

(*R*)-**119.**[1b] $[\alpha]^{25}_D$ = +215.0 (c 0.78, $CHCl_3$). Spectroscopic data as reported above for (±)-**118**.

(*S*)-**118**.[1b] $[\alpha]^{25}_D$ = –139.7 (c 0.68, $CHCl_3$). Spectroscopic data as reported above for (±)-**118**.

Compound (*R*)-**119** was deprotected as reported above, giving (*R*)-**118** in 96% yield

(*R*)-**118**. $[\alpha]^{25}_D$ = +139.2 (c 0.71, $CHCl_3$). Spectroscopic data as reported above for (±)-**118**

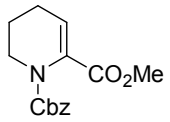


123

1-Benzyl 2-Methyl 5,6-Dihydropyridine-1,2(4*H*)-dicarboxylate (123)

To a solution of KHMDS (20.8 mL of a 0.5 M solution in toluene, 10.4 mmol) in THF (54 mL), cooled at –78 °C and under nitrogen atmosphere, was added a solution of *N*-Cbz-protected *δ*-valerolactam **122** (1.96 g, 8.39 mmol) in THF (20 mL) and the resulting mixture was stirred for 1.5 h. Afterward a solution of $(PhO)_2P(O)Cl$ (2.15 mL, 10.36 mmol) in THF (16.0 mL) was slowly added, leaving under stirring for 1 h at –78 °C before allowing the temperature to rise to 0 °C. Then, a 10% NaOH aqueous solution (165 mL) was added, the mixture was extracted with Et_2O (3 × 95 mL), the combined organic layers washed with 10% NaOH (60 mL) and dried over anhydrous K_2CO_3 for 30 min. After filtration and evaporation of the solvent (without heating and leaving a small volume of solvent), the crude phosphate was chromatographed (EtOAc-*n*-hexane, 1:2.5, + 1% Et_3N, R_f 0.25) on a short layer of silica gel (4.5 cm of silica gel in a column with internal diameter of 3 cm) to give the enol phosphate **123** as pale yellow oil (3.875 g, 99%).

123. ^{1}H NMR (400 MHz, $CDCl_3$): 7.38-7.26 (m, 10 H), 7.25-7.13 (m, 5 H), 5.14 (pseudo q, *J* = 3.9 Hz, 1 H, 3-H), 5.08 (s, 2 H, C*H*$_2$Ph), 3.70-3.61 (m, 2 H, 6-H), 2.24-2.11 (m, 2 H, 4-H), 1.81-1.69, 2 H, 5-H). ^{13}C NMR ($CDCl_3$, 100.4 MHz) δ = 154.0 (s, CO), 150.4 (s, 2 C), 139.9 (s, C-2), 135.9 (s), 129.7 (d, 4 C), 128.4 (d, 2C), 128.0 (d), 127.9 (d, 2 C), 125.4 (d, 2 C), 120.0 (d, 4 C), 100.5 (d, C-3), 67.8 (t, *C*H$_2$Ph), 45.7 (t, C-6), 22.6 (t, C-4), 21.6 (t, C-5) ppm. ESI-MS *m/z* (%): 953 (100) [$2M^+$ + 23], 488 (10) [M^+ + 23], 466 (8) [M^+ + 1].

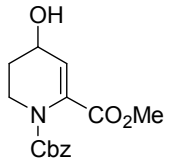


124

1-Benzyl 2-Methyl 5,6-Dihydropyridine-1,2(4*H*)-dicarboxylate (124)

Phosphate **123** was immediately dissolved in DMF (20 mL) and to the resulting solution were added $Pd(OAc)_2$ (189 mg, 0.84 mmol) and Ph_3P (439 mg, 1.67 mmol) under nitrogen atmosphere. The solution was stirred 10 min under a CO atmosphere (balloon), then Et_3N (2.3 mL, 16.7 mmol) and MeOH (7.0 mL, 335 mmol) were added and stirring was continued at 58 °C (external bath) for 4 h under static CO pressure and then left at room temperature overnight. The solution was diluted with water (150 mL), extracted with Et_2O (5 × 100 mL) and dried over Na_2SO_4. After filtration and evaporation of the solvent, the oily residue was chromatographed (EtOAc-*n*-hexane, 1:4, R_f 0.28) to give **124** (2.03 g, 88%) as a thick pale yellow oil.

124. ^{1}H NMR ($CDCl_3$, 400 MHz) δ = 7.40-7.28 (m, 5 H, *Ph*), 6.07 (t, J = 3.9 Hz, 1 H, 3-H), 5.14 (s, 2 H, CH_2Ph), 3.67-3.64 (m, 2 H, 6-H), 3.56 (br s, 3 H, OCH_3), 2.27-2.22 (m, 2 H, 4-H), 1.86-1.81 (m, 2 H, 5-H) ppm. ^{13}C NMR ($CDCl_3$, 100.4 MHz) δ = 165.1 (s, CO), 154.0 (s, CO), 135.8 (s), 132.4 (s, C-2), 128.5 (d, 2 C), 128.2 (d), 128.1 (d, 2 C), 123.1 (d, C-3), 68.0 (t, *C*H_2Ph), 51.9 (q, OCH_3), 43.7 (t, C-6), 22.9 (t, C-4), 22.7 (t, C-5) ppm. MS *m/z* (%) = 276 (2) $[M + 1]^+$, 232 (100). $C_{15}H_{17}NO_4$ (275.30) requires C 65.44; H 6.22; N 5.09. Found: C 65.27; H 6.11; N 5.01.



(±)-**125**

1-Benzyl 2-Methyl 4-Hydroxy-5,6-dihydropyridine-1,2(4*H*)-dicarboxylate (±)-125

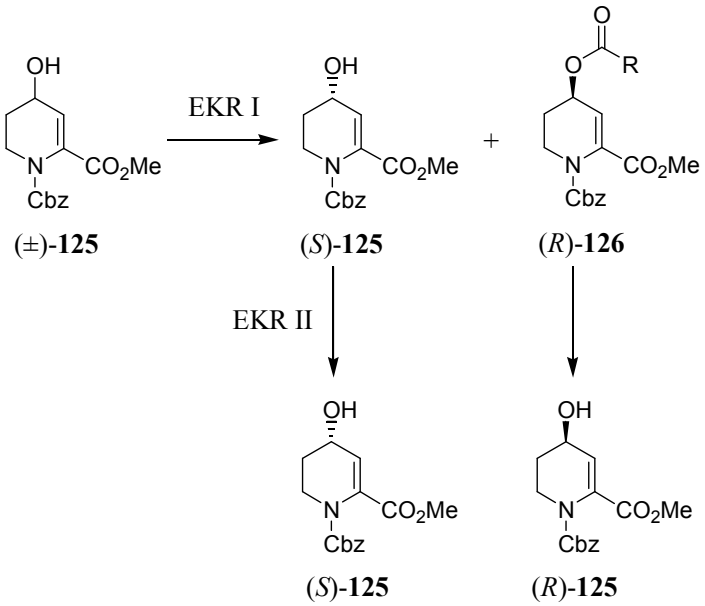
A solution of **124** (663 mg, 2.41 mmol), *N*-bromosuccinimide (545 mg, 3.06 mmol) and a catalytic amount of azobisisobutyronitrile (34 mg, 0.21 mmol) in a 9:1 mixture of anhydrous CCl_4 and $CHCl_3$ (83 mL) was refluxed with vigorous stirring for 15 min. After cooling, the reaction mixture was diluted with $CHCl_3$ (65 mL), washed with water (70 mL) and evaporated to give the 4-Br derivative as a yellow oil.

4-Br derivative. ^{1}H NMR ($CDCl_3$, 200 MHz) δ = 7.40-7.20 (m, 5 H, Ph), 6.04 (d, J = 4.4 Hz, 1 H, 3-H), 5.20 (part A of an AB system, J = 12.1 Hz, 1 H, CH_2Ph), 5.09 (part B of an AB system, J = 12.1 Hz, 1 H, CH_2Ph), 4.88-4.81 (m, 1 H, C*H*Br), 4.32-4.20 (m, 1 H, 6-H), 3.56 (s, 3 H, OCH_3), 3.65-3.20 (m, 1 H, 3-H'), 2.50-2.20 (m, 2 H, 5-H) ppm.

This oil was dissolved in 96% aqueous acetone (68 mL), six drops of water were added, and $ZnCl_2$ (1.362 g, 10 mmol) was added portionwise to the resulting solution over 4 h. After further 2.5 h, the reaction mixture was diluted with $CHCl_3$ (60 mL), washed with water (100 mL), saturated aqueous $NaHCO_3$ (100 mL) and brine (65 mL) and dried over Na_2SO_4. After filtration and evaporation of the solvent, the crude product was chromatographed (EtOAc-*n*-hexane, 2:1, R_f 0.40) to give (±)-**125** (399 mg, 57%) as a thick pale yellow oil.

(±)-**125.** ^{1}H NMR ($CDCl_3$, 400 MHz) δ = 7.40-7.30 (m, 5 H, *Ph*), 5.94 (dd, *J* = 3.9, 0.6 Hz, 1 H, 3-H), 5.18 (part A of an AB system, *J* = 12.1 Hz, 1 H, C*H*$_2$Ph), 5.09 (part B of an AB system, *J* = 12.1 Hz, 1 H, C*H*$_2$Ph), 4.31–4.27 (m, 1 H, 4-H), 4.08 (dt, *J* = 13.3, 4.3 Hz, 1 H, 6-H), 3.56 (br s, 3 H, OC*H*$_3$), 3.31 (ddd, *J* = 13.3, 9.4, 4.7 Hz, 1 H, 6-H'), 1.94–1.90 (m, 2 H, 5-H) ppm. ^{13}C NMR ($CDCl_3$, 100.4 MHz) δ = 165.0 (s, CO), 153.4 (s, CO), 135.4 (s), 133.6 (s, C-2), 128.5 (d, 2 C), 128.4 (d), 128.3 (d, 2 C), 120.7 (d, C-3), 68.3 (t, CH_2Ph), 61.3 (d, C-4), 52.2 (q, OCH_3), 40.2 (t, C-6), 32.2 (t, C-5) ppm. MS *m/z* (%) = 291 (1) $[M]^+$, 259 (100).

$C_{15}H_{17}NO_5$ (291.30) requires C 61.85; H 5.88; N 4.81. Found: C 62.01; H 5.68; N 4.57.



Lipase-catalyzed Kinetic Resolution of (±)-125:

1-Benzyl 2-Methyl (*S*)-4-Hydroxy-5,6-dihydropyridine-1,2(4*H*)-dicarboxylate [(–)-125] and 1-Benzyl 2-Methyl (*R*)-4-(Butyryloxy)-5,6-dihydropyridine-1,2(4*H*)-dicarboxylate [(+)-126]. 4 Å MS (78 mg) were added to a solution of (±)-**125** (176 mg, 0.604 mmol) in TBME (1.5 mL) at 30 °C, followed by lipase PS "AMANO" IM (60 mg), under N_2 atmosphere. After 20 min, vinyl butyrate (268 μL, 2.11 mmol) was added and the reaction was left under vigorous stirring and monitored by GC. After 1.7 h, the conversion reached 44% and the reaction was stopped by filtration over a thin layer of Celite. After evaporation, the crude product was chromatographed

(EtOAc–*n*-hexane, 1:2) to give (*R*)-**125** (R_f 0.54, 87 mg, 40%) and (*S*)-**126** (R_f 0.12, 90 mg, 51%, 73% ee). (*S*)-**125** was dissolved again in TBME (0.8 mL) at 30 °C, 4 Å MS (39 mg) were added followed by lipase PS "AMANO" IM (30 mg) under N_2 atmosphere. After 20 min, vinyl butyrate (132 μL) was added and the reaction was left under stirring and monitored by GC. After 2.2 h, the conversion reached 16% and the reaction was stopped by filtration over a thin layer of celite. After evaporation, the crude product was chromatographed to give (*S*)-**125** (65 mg, 37%, 99.8% ee).

(*S*)-**125**. $[\alpha]^{25}_D$ = –230.1 (c 0.50, $CHCl_3$). Spectroscopic data as reported above for (±)-**125**.

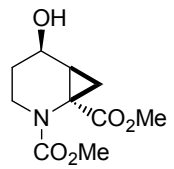
(*R*)-**126**. $[\alpha]^{25}_D$ = +189.9 (c 0.89, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 400 MHz) δ = 7.40-7.28 (m, 5 H, *Ph*), 5.90 (d, *J* = 4.3, Hz, 1 H, 3-H), 5.31 (pseudo q, *J* = 3.9 Hz, 1 H, 4-H), 5.19 (part A of an AB system, *J* = 12.1 Hz, 1 H, C*H*$_2$Ph), 5.10 (part B of an AB system, *J* = 12.1 Hz, 1 H, C*H*$_2$Ph), 4.17 (dt, *J* = 13.1, 4.1 Hz, 1 H, 6-H), 3.56 (br s, 3 H, OC*H*$_3$), 3.29 (ddd, *J* = 13.1, 9.4, 5.6 Hz, 1 H, 6-H'), 2.27 (t, *J* = 7.4 Hz, 2 H, COC*H*$_2$), 2.00–1.94 (m, 2 H, 5-H), 1.68-1.59 (m, 2 H, C*H*$_2$CH$_3$), 0.94 (t, *J* = 7.4 Hz, CH$_2$C*H*$_3$) ppm. ^{13}C NMR ($CDCl_3$, 100.4 MHz) δ = 172.6 (s, CO), 164.6 (s, CO), 153.3 (s, CO), 135.3 (s), 135.2 (s, C-2), 128.5 (d, 2 C), 128.4 (d), 128.3 (d, 2 C), 116.7 (d, C-3), 68.5 (t, CH_2Ph), 63.3 (d, C-4), 52.3 (q, OCH_3), 40.6 (t, C-6), 36.2 (t, CO*C*H$_2$), 29.3 (t, C-5), 18.4 (t, *C*H$_2$CH$_3$), 13.6 (q, CH$_2$*C*H$_3$) ppm. MS *m/z* (%) = 384 (12) $[M + 23]^+$, 296 (100), 162 (18).

$C_{19}H_{23}NO_6$ (361.39) requires C 63.15; H 6.41; N 3.88. Found: C 63.03; H 6.44; N 3.65.

1-Benzyl 2-Methyl (*R*)-4-Hydroxy-5,6-dihydropyridine-1,2(4*H*)-dicarboxylate [(+)-125]

To a solution of (*R*)-**126** (87 mg, 0.24 mmol) in dry MeOH (1 mL), cooled in an ice bath, was added MeONa (13 mg, 0.24 mmol), and the mixture stirred for 3.5 h at 0 °C under N_2 atmosphere. Then glacial acetic acid (14 μL) was added and the solvent was evaporated. The residue was diluted with water (20 mL), extracted with EtOAc (4 × 20 mL) and dried over Na_2SO_4. After filtration and evaporation of the solvent, the crude product was chromatographed (EtOAc-*n*-hexane, 1:1, R_f 0.24) to give (*R*)-**125** (66 mg, 95%, 98.7% ee) as a colorless oil.

(*R*)-125. $[\alpha]^{25}_D$ = +228.7 (c 0.54, $CHCl_3$). Spectroscopic data as reported above for (±)-**125**.



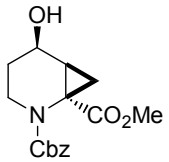
(1*R*,4*R*,5*S*)-*cis*-**127**

Dimethyl (1*R*,5*R*,6*S*)-5-Hydroxy-2-azabicyclo[4.1.0]heptane-1,2-dicarboxylate [*cis* (+)-127]

To a solution of 2,4,6-trichlorophenol (248 mg, 1.26 mmol) in anhydrous CH_2Cl_2 (12.6 mL), cooled to –40 °C, was added Et_2Zn (1.26 mL of a 1 M solution in hexane, 1.26 mmol) under nitrogen atmosphere. The mixture was left under stirring for 15 min, then CH_2I_2 (101 μL, 1.26 mmol) was added dropwise and, after another 15 min at –40 °C, a solution of alcohol (*R*)-**118** (136 mg, 0.63 mmol) in CH_2Cl_2 (0.8 mL) was added dropwise. The cooling bath was removed and reaction mixture was left under stirring for 4 h. The suspension was then cooled in a ice bath and a 10% solution of citric acid (5 mL) was added dropwise under vigorous stirring. The cooling bath was removed and when the solution became clear, the layers were separated, the aqueous layer extracted with CH_2Cl_2 (6 × 5 mL) and the combined organic layers washed with a 10% solution of Na_2CO_3 (2 × 40 mL) and dried over Na_2SO_4. After chromatography (Et_2O, R_f 0.12), compound (1*R*,5*R*,6*S*)-**127** (124 mg, 86%) was obtained as a colorless oil.

(1*R*,5*R*,6*S*)-127. $[\alpha]^{25}_D$ = +51.3 (c 0.93, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 400 MHz) (1.7:1 mixture of rotamers) δ = 4.35 (dt, *J* = 10.1, 6.2 Hz, 1 H, H-5), 4.02 (dt, *J* = 13.5, 3.9 Hz, 1 H, 3-H, major rotamer), 3.86 (dt, *J* = 14.0, 4.3 Hz, 1 H, 3-H, minor rotamer), 3.73 (s, 3 H, OCH_3, minor rotamer), 3.71 and 3.70 (s, 3 H + 3 H, OCH_3, both rotamers), 2.81 (td, *J* = 14.0, 1.8 Hz, 1 H, 3-H', minor rotamer), 2.73 (td, *J* = 13.5, 2.0 Hz, 1 H, 3-H', major rotamer), 2.05-1.89 (m, 2 H, 4-H and 6-H, and 1 H, minor rotamer), 1.87 (dd, *J* = 9.9, 5.3 Hz, 1 H, 7-H, major rotamer), 1.78 (br s, 1 H, OH), 1.27-1.16 (m, 1 H, 4-H', major rotamer, and 1 H, minor rotamer), 1.09 (dd, *J* = 7.6, 5.3 Hz, 1 H, 7-H', minor rotamer), 1.06 (dd, *J* = 7.6, 5.3 Hz, 1 H, 7-H', major rotamer) ppm. ^{13}C NMR ($CDCl_3$, 100.4 MHz) (mixture of rotamers) δ = 172.2 and 171.7 (s, CO), 156.9 and 156.3 (s, CO), 64.2 and 64.1 (d, C-5), 53.0 and 52.8 (q, OCH_3), 52.5 (q, OCH_3), 41.9 and 41.3 (s, C-1), 41.1 and 40.9 (t, C-3), 30.8 and 30.3 (d, C-6), 29.0 and 28.7 (t, C-4), 19.7 and 19.1 (t, C-7) ppm. MS *m/z* (%) = 230 (8) $[M + 1]^+$, 197 (100).

$C_{10}H_{15}NO_5$ (229.23) requires C 52.40; H 6.60; N 6.11. Found: C 52.09; H 6.72; N 5.98.



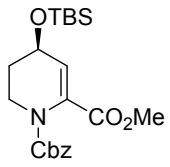
(1*R*,4*R*,6*S*)-*cis*-**128**

2-Benzyl 1-Methyl (1*R*,5*R*,6*S*)-5-Hydroxy-2-azabicyclo[4.1.0]heptane-1,2-dicarboxylate [*cis* (+)-128]

Prepared as reported above for *cis* (+)-**127** but the reaction was stopped after 3.5 h. Starting from (*R*)-**125** (47 mg, 0.16 mmol), compound **(**1*R*,5*R*,6*S*)-**128** (36 mg) was obtained after chromatography (Et_2O, R_f 0.24) as a colorless oil (72%).

(1*R*,5*R*,6*S*)-128. $[\alpha]^{25}_D$ = +31.2 (c 0.72, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 400 MHz) (2.4:1 mixture of rotamers) δ = 7.36-7.25 (m, 5 H, Ph), 5.26 (d, *J* = 12.5 Hz, 1 H, C*H*$_2$Ph, major rotamer), 5.15 (AB system, *J* = 12.5 Hz, 2 H, C*H*$_2$Ph, minor rotamer), 5.05 (d, *J* = 12.5 Hz, 1 H, C*H*$_2$Ph, major rotamer), 4.38-4.29 (m, 1 H, 5-H), 4.03 (dt, *J* = 13.5, 3.7 Hz, 1 H, 3-H, major rotamer), 3.91 (dt, *J* = 13.5, 3.7 Hz, 1 H, 3-H, minor rotamer), 3.69 (s, 3 H, OCH_3, minor rotamer), 3.51 (s, 3 H, OCH_3, major rotamer), 2.83 (td, *J* = 13.8, 1.8 Hz, 1 H, 3-H', minor rotamer), 2.74 (td, *J* = 14.2, 2.1 Hz, 1 H, 3-H', major rotamer), 2.12-2.00 (br, 1 H, O*H*), 2.06-1.90 (m, 2 H, 4-H and 6-H, and 1 H, minor rotamer), 1.87 (dd, *J* = 9.9, 5.1 Hz, 1 H, 7-H, major rotamer), 1.28-1.16 (m, 1 H, 4-H', major rotamer, and 1 H, minor rotamer), 1.07 (dd, *J* = 7.6, 5.1 Hz, 1 H, 7-H', minor rotamer), 1.08 (dd, *J* = 7.6, 5.1 Hz, 1 H, 7-H', major rotamer) ppm. ^{13}C NMR ($CDCl_3$, 100.4 MHz) (mixture of rotamers) δ = 172.1 and 171.7 (s, CO), 156.2 and 155.7 (s, CO), 136.5 (s, Ph), 128.5 and 128.4 (d, 2 C, Ph), 127.9 and 127.8 (d, Ph), 127.6 (d, 2 C), 67.4 and 67.3 (t, *C*H_2Ph), 64.1 and 63.1 (d, C-5), 52.5 and 52.3 (q, OCH_3), 41.9 and 41.4 (s, C-1), 41.2 and 41.0 (t, C-3), 30.7 and 30.3 (d, C-6), 29.0 and 28.7 (t, C-4), 19.7 and 19.1 (t, C-7) ppm. MS *m/z* (%) = 306 (100%) $[M + 1]^+$.

$C_{16}H_{19}NO_5$ (305.33) requires C 62.94; H 6.27; N 4.59. Found: C 62.66; H 6.12; N 4.27.



132

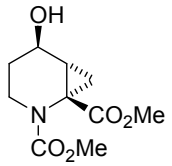
1-Benzyl 2-Methyl (*R*)-4-*tert*-Butyldimethylsilanyloxy-5,6-dihydropyridine-1,2(4*H*)-dicarboxylate [(+)-132]

To a stirred solution of (*R*)-**125** (62 mg, 0.21 mmol) in anhydrous DMF (0.7 mL) were added imidazole (43 mg, 0.63 mmol) and TBSCl (63 mg, 0.42 mmol) and it was stirred 2 h at 38 °C (external bath) under N_2 atmosphere. After cooling to room temperature, water (5 mL) was added and the solution extracted with Et_2O (5 × 4 mL). The combined organic layers were washed with brine (5 mL) and dried over Na_2SO_4. After filtration and evaporation of the solvent, the oily residue was chromatographed (EtOAc-*n*-hexane, 1:5, R_f 0.45) to give (*R*)-**132** (84 mg, 99%) as a thick colorless oil.

(*R*)-132. $[\alpha]^{20}_D$ = +126.0 (c 0.82, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 400 MHz) δ = 7.40-7.28 (m, 5 H, Ph), 5.85 (d, *J* = 3.7 Hz, 1 H, 3-H), 5.18 (part A of an AB system, *J* = 12.1 Hz, 1 H), 5.09 (part B of an AB system, *J* = 12.1 Hz, 1 H), 4.24 (pseudo q, *J* = 3.9 Hz. 1 H, 4-H), 4.02 (dt, *J* = 12.9, 4.5 Hz, 1 H, 6-H), 3.55 (br s, 3 H, OC*H*$_3$), 3.39-3.29 (m, 1 H, 6-H'), 1.90–1.81 (m, 2 H, 5-H),

0.88 (s, 9 H, TBS), 0.08 (s, 6 H TBS) ppm. ^{13}C NMR ($CDCl_3$, 100.4 MHz) δ = 165.2 (s, CO), 153.6 (s, CO), 135.6 (s, Ph), 132.5 (s, C-2), 128.5 (d, 2 C, Ph), 128.3 (d, Ph), 128.2 (d, 2 C, Ph), 122.6 (d, C-3), 68.2 (t, *C*H_2Ph), 62.0 (d, C-4), 52.1 (q, OCH_3), 40.4 (t, C-6), 33.1 (t, C-5), 25.8 (q, 3 C, TBS), 18.0 (s, TBS), –4.59 (q, TBS), –4.74 (q, TBS) ppm. MS *m/z* (%) = 405 (62) $[M]^+$, 361 (100).

$C_{21}H_{31}NO_5Si$ (405.56) requires C 62.19; H 7.70; N 3.45. Found: C 62.44; H 7.38; N 3.43.



trans-**127**

Dimethyl (1*S*,5*R*,6*R*)-5-Hydroxy-2-azabicyclo[4.1.0]heptane-1,2-dicarboxylate [*trans* (–)-127]

Cyclopropanation by dimethylsulfoxonium methylide of (*R*)-129. Dry DMSO (0.9 mL) was added to NaH (60% in weight in mineral oil, 24 mg, 0.6 mmol) previously washed with dry *n*-hexane (2 × 1.5 mL) under nitrogen atmosphere. To the resulting suspension was added trimethylsulfoxonium iodide (122 mg, 0.56 mmol) in three portions and the mixture was left 30 min under stirring at room temperature. After cooling with a water bath at 15 °C, a solution of (*R*)-**129** (122 mg, 0.37 mmol) in DMSO (500 μL) was added dropwise. The water bath was removed and the reaction mixture was left under stirring for 2 h. Water (12 mL) was added and the mixture extracted with Et_2O (7 × 9 mL), dried over Na_2SO_4, filtered and concentrated. Chromatography (EtOAc-*n*-hexane, 1:5, R_f 0.24) gave compound **130** (104 mg, 82%) as a 4.7:1 mixture of *trans* and *cis* isomers.

Trans isomer: ^{1}H NMR ($CDCl_3$, 400 MHz) (1.8:1 mixture of rotamers) δ = 4.12-4.09 (m, 1 H, 5-H), 3.78 (dt, *J* = 12.9, 4.2 Hz, 1 H, 3-H, major rotamer), 3.71 (s, 3 H, OCH_3, minor rotamer), 3.69 and 3.68 (s, 3 H + 3 H, OCH_3, both rotamers), 3.62 (dt, *J* = 12.3, 4.1 Hz, 1 H, 3-H, minor rotamer), 3.23 (ddd, *J* = 12.3, 10.7, 2.7 Hz, 1 H, 3-H', minor rotamer), 3.14 (ddd, *J* = 12.9, 10.9, 2.9 Hz, 1 H, 3-H', major rotamer), 1.91 (dd, *J* = 10.3, 5.5 Hz, 1 H, 7-H, minor rotamer), 1.85 (dd, *J* = 10.3, 5.3 Hz, 1 H, 7-H, major rotamer), 1.76-1.57 (m, 2 H, 6-H and 4-H), 1.51-1.39 (m, 1 H, 4-H'), 0.88 (s, 9 H, TBS), 0.73 (dd, *J* = 7.8, 5.5 Hz, 1 H, 7-H', minor rotamer), 0.70 (dd, *J* = 8.2, 5.5 Hz, 1 H, 7-H', major rotamer), 0.084 (s, 6 H, TBS) ppm.

The mixture of *trans* and *cis* **130** (79 mg, 0.22 mmol) was dissolved in acetonitrile (10 mL) and, after cooling at 0 °C, a 3 N solution of HCl (10 mL) was added dropwise. The cooling bath was removed and the mixture left under stirring 1 h. A satd solution of $NaHCO_3$ (20 mL) was slowly

added until pH 7, the aqueous layer extracted with EtOAc (6 × 20 mL) and the combined organic layers dried over Na_2SO_4, filtered and concentrated. Chromatography (Et_2O, R_f 0.23) gave (1*S*,5*R*,6*R*)-**127** (35 mg, 69%) as a colorless oil.

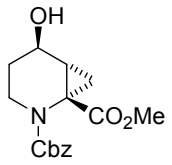
Cyclopropanation by dimethylsulfoxonium methylide of (*R*)-54. The reaction was carried out as reported above for (*R*)-**129**. Starting from (*R*)-**54** (87 mg, 0.32 mmol), chromatography (EtOAc-*n*-hexane, 1:4, R_f 0.22) of the crude reaction mixture gave compound **131** (70 mg, 77%) as a 3.8:1 mixture of *trans* and *cis* isomers.

Trans isomer: ^{1}H NMR ($CDCl_3$, 400 MHz) (2.3:1 mixture of rotamers) δ = 3.78-3.65 (s + m, 7 H, OCH_3 and 5-H), 3.28 (ddd, *J* = 12.5, 8.2, 4.3 Hz, 1 H, 3-H', minor rotamer), 3.21 (ddd, *J* = 12.9, 8.6, 4.3 Hz, 3-H', major rotamer), 1.92 (dd, *J* = 10.1, 5.5 Hz, 1 H, 7-H, minor rotamer), 1.85 (dd, *J* = 9.8, 5.1 Hz, 1 H, 7-H, major rotamer), 1.78-1.68 (m, 1 H, 6-H), 1.68-1.60 (m, 1 H, 4-H), 1.58-1.49 (m, 1 H, 4-H'), 1.21 (s, 9 H), 0.75 (dd, *J* = 7.8, 5.1 Hz, 1 H, 7-H', minor rotamer), 0.72 (dd, *J* = 7.8, 5.1 Hz, 1 H, 7-H', major rotamer) ppm.

The mixture of *trans* and *cis* **131** (70 mg, 0.25 mmol) was dissolved in acetonitrile (3.2 mL) and *p*TsOH·H_2O (58 mg, 0.3 mmol) was added under stirring at room temperature. After 21 h, another portion of *p*TsOH·H_2O (24 mg) was added and the mixture left under stirring for another 6 h. The mixture was filtered on a short layer of a Celite/$NaHCO_3$ (1:1) mixture and concentrated. Chromatography (Et_2O, R_f 0.23) gave *trans* (1*S*,5*R*,6*R*)-**127** (38 mg, 67%) as a colorless oil.

(1*S*,5*R*,6*R*)-(–)-127. $[\alpha]^{25}_D$ = –4.43 (c 0.47, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 400 MHz) (2:1 mixture of rotamers) δ = 4.28 (br s, 1 H, H-5), 3.86 (dt, *J* = 13.3, 3.9 Hz, 1 H, 3-H, major rotamer), 3.73 (s, 3 H, OCH_3, minor rotamer), 3.71 and 3.70 (s, 3 H + 3 H, OCH_3, both rotamers, and 1 H, 3-H, minor rotamer), 3.19 (td, *J* = 13.6, 2.1 Hz, 1 H, 3-H', minor rotamer), 3.09 (td, *J* = 13.3, 2.3 Hz, 1 H, 3-H', major rotamer), 1.97 (dd, *J* = 10.5, 5.5 Hz, 1 H, 7-H, minor rotamer), 1.93-1.87 (m, 1 H, 7-H, major rotamer, and 1 H, 6-H, minor rotamer), 1.87-1.67 (m, 1 H, 6-H, major rotamer, and 1 H, 4-H), 1.58-1.46 (m, 1 H, 4-H'), 0.78 (dd, *J* = 8.0, 5.5 Hz, 1 H, 7-H', minor rotamer), 0.75 (dd, *J* = 8.0, 5.3 Hz, 1 H, 7-H', major rotamer) ppm. ^{13}C NMR ($CDCl_3$, 100.4 MHz) (mixture of rotamers) δ = 172.5 (s, CO), 157.0 (s, CO), 63.2 and 63.1 (d, C-5), 52.9 and 52.8 (q, OCH_3), 52.5 (q, OCH_3), 39.0 and 38.6 (s, C-1), 36.5 and 35.9 (t, C-3), 31.1 and 31.0 (d, C-6), 30.9.0 and 30.8 (t, C-4), 20.5 and 20.0 (t, C-7) ppm. MS *m/z* (%) = 230 (9) $[M + 1]^+$, 211 (29), 197 (100), 80 (16).

$C_{10}H_{15}NO_5$ (229.23) requires C 52.40; H 6.60; N 6.11. Found: C 52.22; H 6.57; N 5.81.



trans-**128**

2-Benzyl 1-Methyl (1*S*,5*R*,6*R*)-5-Hydroxy-2-azabicyclo[4.1.0]heptane-1,2-dicarboxylate [*trans* (–)-128]

The reaction was carried out as reported above for (*R*)-**129**. Starting from (*R*)-**132** (78 mg, 0.19 mmol), chromatography (EtOAc-*n*-hexane, 1:6, R_f 0.22) of the crude reaction mixture gave compound **133** (62 mg, 78%) as a 7 : 1 mixture of *trans* and *cis* isomers.

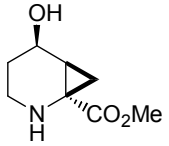
Trans isomer: ^{1}H NMR ($CDCl_3$, 400 MHz) (2.5:1 mixture of rotamers) δ = 7.37-7.26 (m, 5 H, Ph), 5.25 (part A of an AB system, *J* = 12.5 Hz, 1 H, major rotamer), 5.20 (part A of an AB system, *J* = 12.3 Hz, 1 H, minor rotamer), 5.14 (part B of an AB system, *J* = 12.3 Hz, 1 H, minor rotamer), 5.05 (part B of an AB system, *J* = 12.5 Hz, 1 H, major rotamer), 4.16-4.10 (m, 1 H, 5-H), 3.81 (dt, *J* = 12.9, 4.3 Hz, 1 H, 3-H, major rotamer), 3.71 (s, 3 H, OCH_3, minor rotamer), 3.53 (s, 3 H, OCH_3, major rotamers), 3.27 (ddd, *J* = 12.9, 10.5, 2.7 Hz, 1 H, 3-H', minor rotamer), 3.17 (ddd, *J* = 12.9, 10.9, 2.7 Hz, 1 H, 3-H', major rotamer), 1.94 (dd, *J* = 10.3, 5.7 Hz, 1 H, 7-H, minor rotamer), 1.87 (dd, *J* = 10.3, 5.7 Hz, 1 H, 7-H, major rotamer), 1.78-1.58 (m, 2 H, 6-H and 4-H), 1.52-1.40 (m, 1 H, 4-H'), 0.87 (s, 9 H), 0.76 (dd, *J* = 8.0, 5.7 Hz, 1 H, 7-H', minor rotamer), 0.72 (dd, *J* = 8.0, 5.7 Hz, 1 H, 7-H', major rotamer), 0.08 (s, 3 H, TBS, major rotamer), 0.07 (s, 3 H, TBS, major rotamer) ppm.

The mixture of *trans* and *cis* **133** was deprotected as reported above for compound **130**, obtaining after chromatography (Et_2O–*n*-hexane, 11:1, R_f 0.2) compound *trans* (–)-**128** (29 mg, 73%) as a colorless oil.

(1*S*,5*R*,6*R*)-(–)-128. $[\alpha]^{25}_D$ = –2.98 (c 1.01, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 400 MHz) (2.6:1 mixture of rotamers) δ = 7.37-7.26 (m, 5 H, Ph), 5.26 (part A of an AB system, *J* = 12.5 Hz, 1 H, major rotamer), 5.19 (part A of an AB system, *J* = 12.5 Hz, 1 H, minor rotamer), 5.14 (part B of an AB system, *J* = 12.5 Hz, 1 H, minor rotamer), 5.06 (part B of an AB system, *J* = 12.5 Hz, 1 H, major rotamer), 4.31–4.25 (m, 1 H, 5-H), 3.89 (dt, *J* = 13.2, 3.7 Hz, 1 H, 3-H, major rotamer), 3.77 (dt, *J* = 13.3, 3.7 Hz, 1 H, 3-H, minor rotamer), 3.71 (s, 3 H, OCH_3, minor rotamers), 3.53 (s, 3 H, OCH_3, major rotamers), 3.21 (td, *J* = 13.3, 2.1 Hz, 1 H, 3-H', minor rotamer), 3.11 (td, *J* = 13.2, 2.57 Hz, 1 H, 3-H', major rotamer), 1.98 (dd, *J* = 10.5, 5.5 Hz, 1 H, 7-H, minor rotamer), 1.92 (dd, *J* = 10.5, 5.5 Hz, 1 H, 7-H, major rotamer), 1.85-1.68 (m, 2 H, 6-H and 4-H), 1.59-1.48 (m, 1 H, 4-H'), 0.80 (dd, *J* = 8.0, 5.5 Hz, 1 H, 7-H', minor rotamer), 0.76 (dd, *J* = 8.0, 5.5 Hz, 1 H, 7-H', major rotamer) ppm. ^{13}C NMR ($CDCl_3$, 100.4 MHz) (mixture of rotamers) δ = 172.4 and

171.9 (s, CO), 156.2 (s, CO), 136.6 (s, Ph), 128.5 (d, 2 C, Ph), 127.9 (d, Ph), 127.6 (d, 2 C, Ph), 67.4 and 67.2 (t, *C*H_2Ph), 63.1 (d, C-5), 52.5 and 52.3 (q, OCH_3), 39.1 and 38.6 (s, C-1), 36.6 and 35.9 (t, C-3), 31.1 and 31.0 (d, C-6), 30.9 and 30.8 (t, C-4), 20.5 and 20.0 (t, C-7) ppm. MS/MS *m/z* (%) = 306 (9) [M + 1]+, 262 (100), 244 (6), 198 (9), 170 (9), 154 (8), 91 (2).

$C_{16}H_{19}NO_5$ (305.33) requires C 62.94; H 6.27; N 4.59. Found: C 62.73; H 6.11; N 4.19.



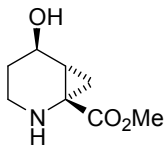
(1*R*,5*R*,6*S*)-*cis*-**110**

Methyl (1*R*,5*R*,6*S*)-5-Hydroxy-2-azabicyclo[4.1.0]heptane-1-carboxylate [*cis* (+)-110]

To a solution of alcohol (1*R*,5*R*,6*S*)-**128** (210 mg, 0.69 mmol) in ethyl acetate (19 mL) was added, under nitrogen atmosphere, 10% Pd/C (52 mg) and the resulting suspension stirred under an H_2 atmosphere (balloon) at room temperature for 3 h. After filtration over a Celite layer and evaporation of the solvent, pure amino ester *cis* (+)-**110** (118 mg) was obtained in quantitative yield as a colorless oil.

***cis*-110.** $[\alpha]^{25}_D$ = +80.9 (c 0.78, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 400 MHz) δ = 4.32-4.25 (m, 1 H, 5-H), 3.72 (s, 3 H, OCH_3), 2.84 (dt, *J* = 12.7, 4.1 Hz, 1 H, 3-H), 2.57 (td, *J* = 12.7, 2.3 Hz, 1 H, 3-H'), 2.10-2.03 (m, 1 H, 4-H), 1.90-1.76 (m, 3 H, 6-H, OH, and NH), 1.57 (dd, *J* = 9.8, 4.7 Hz, 1 H, 7-H), 1.24-1.13 (m, 1 H, 4-H'), 1.05 (dd, J = 7.4, 4.7 Hz, 1 H, 7-H') ppm. ^{13}C NMR ($CDCl_3$, 100.4 MHz) δ = 174.7 (s, CO), 64.6 (d, C-5), 52.5 (q, OCH_3), 42.6 (s, C-1), 41.7 (t, C-3), 31.4 (d, C-6), 28.1 (t, C-4), 21.8 (t, C-7) ppm. MS/MS *m/z* (%) = 172 (1%) $[M + 1]^+$, 154 (100), 122 (25), 94 (25).

$C_8H_{13}NO_3$ (171.19) requires C 56.13; H 7.65; N 8.18. Found: C 56.44; H 7.38; N 7.97



(1*S*,5*R*,6*R*)-*trans*-**110**

Methyl (1*S*,5*R*,6*R*)-5-Hydroxy-2-azabicyclo[4.1.0]heptane-1-carboxylate [*trans* (–)-110]

Reaction carried out as reported for *cis* (+)-**110**. Starting from (1*S*,5*R*,6*R*)-**128** (29 mg, 0.095 mmol), compound *trans* (–)-**110** (16.3 mg) was obtained in 100% yield as a colorless oil.

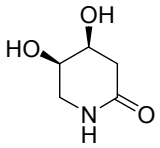
***trans*-110.** $[\alpha]^{25}_D$ = –21.8 (c 0.76, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 400 MHz) δ = 4.37-4.34 (br s, 1 H, 5-H), 3.71 (s, 3 H, OCH_3), 2.95 (td, *J* = 12.7, 3.1 Hz, 1 H, 3-H), 2.61 (dt, *J* = 12.7, 3.7 Hz, 1 H,

3-H'), 2.14-1.98 (m, 2 H, OH and NH), 1.83 (dd, J = 10.5, 7.8 Hz, 1 H, 7-H), 1.65-1.50 (m, 3 H, 6-H, 4-H and 4-H'), 0.74 (dd, J = 7.8, 4.7 Hz, 1 H, 7-H') ppm. ^{13}C NMR ($CDCl_3$, 100.4 MHz) δ = 175.0 (s, CO), 63.5 (d, C-5), 52.5 (q, OCH_3), 39.4 (s, C-1), 36.3 (t, C-3), 31.1 (d, C-6), 29.0 (t, C-4), 22.3 (t, C-7) ppm. MS/MS *m/z* (%) = 172 (3%) $[M + 1]^+$, 154 (100).

$C_8H_{13}NO_3$ (171.19) requires C 56.13; H 7.65; N 8.18. Found: C 56.38; H 7.44; N 8.01

Conversion of *trans* (1*R*,5*S*,6*S*)-110 into (1*R*,5*S*,6*S*)-127.

To a solution of *trans* (1*R*,5*S*,6*S*)-**110** (15 mg, 0.088 mmol) in dry CH_2Cl_2 (880 μL) cooled at 0 °C, were added dropwise Et_3N (16 μL, 0.114 mmol) and methyl chloroformate (9 μL, 0.114 mmol). The resulting mixture was stirred for 20 min before adding further Et_3N (16 μL, 0.114 mmol) and methyl chloroformate (9 μL, 0.114 mmol). The solution was then stirred at 25 °C for 1 h, then diluted with CH_2Cl_2 (3 mL), washed with brine (2.5 mL) and dried over Na_2SO_4. After evaporation of the solvent, the crude was dissolved in MeOH (200 μL) and K_2CO_3 (1 mg) was added leaving under stirring for 1 h. The solution was concentrated and chromatographed (Et_2O, R_f 0.24) to give compound *trans* (1*S*,5*R*,6*R*)-**127** (8 mg, 40%) as a colorless oil and $[\alpha]^{25}_D$ = +4.61 (c 0.41, $CHCl_3$).



(±)-**137**

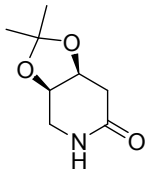
(±)-4,5-Dihydroxypiperidin-2-one [(±)-137].

A solution of 3,6-dihydro-1*H*-pyridin-2-one **136** (507 mg, 5.22 mmol) in MeOH (8 mL) was cooled in an ice bath and aqueous 50 mM NaOH (40 mL) was added, followed by aqueous 31 mM $KMnO_4$ (129 mL), that was added dropwise in 30'. The resulting brown solution was stirred for 10' and, after removal of the ice bath, MeOH was added (80 mL). After 30', the suspension was filtered through a Celite pad to remove the dark brown salts and the filtrate was concentrated, neutralized with 1 N HCl (5.5 mL) and concentrated *in vacuo* to give lactam **9** (680 mg) which was used in the next step without prior purification.

A sample of the crude reaction mixture was purified by flash chromatography (eluant: EtOAc-MeOH, 3:2; R_f 0.33) for the characterization, affording pure (±)-**137** as a white powder.

(±)-137. m.p. 144.0–144.9 °C. ^{1}H NMR (D_2O, 400 MHz) δ (ppm): 4.21–4.15 (m, 2 H, 4-H, 5-H), 3.46 (dd, J = 13.0, 4.3 Hz, 1 H, 6-H'), 3.37 (dd, J = 13.0, 5.1 Hz, 1 H, 6-H''), 2.68 (dd, J = 17.5, 5.5 Hz, 1 H, 3-H'), 2.50 (dd, J = 17.5, 7.8 Hz, 1 H, 3-H''). ^{13}C NMR (D_2O, 100.4 MHz) δ (ppm):

173.3 (s, C2), 66.0 (d, C4), 65.3 (d, C5), 43.6 (t, C6), 34.7 (t, C3). MS/MS (ESI) of $[M+1]^+$ *m/z* %: 132 (M^++1, 12), 114 (M^+-OH, 100), 96 (27). Anal. Calcd for $C_5H_9NO_3 \cdot 1/10H_2O$: C, 45.18; H, 6.98; N, 10.54. Found: C, 44.96, H, 6.46; N, 10.26.

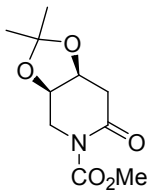


(±)-**138**

(±)-4,5-*O*-Isopropylidene-4,5-dihydroxypiperidin-3-one ((±)-138).

The crude lactam (±)-**137** was taken up into methanol (3 mL) and a catalytic amount of *p*-toluenesulfonic acid was added (169 mg, 0.89 mmol) followed by 2,2-dimethoxypropane (17.3 mL, 140 mmol). The mixture was warmed at 55°C for 1 h and, after cooling, diluted with MeOH (9 mL) and neutralized by K_2CO_3 (62 mg, 0.45 mmol). After filtration on a Celite pad and evaporation of the solvent, crude (±)-**138** was obtained as a yellow solid, which was purified by flash chromatography (eluant: CH_2Cl_2–MeOH, 20:1; R_f 0.17), affording pure (±)-**138** as a white powder (563 mg, 63% over two steps).

(±)-138. m.p. 137.2–138.3 °C. ^{1}H NMR (400 MHz) δ (ppm): 5.85 (br s, 1 H, NH), 4.69 (ddd, *J* = 7.2, 4.1, 2.7 Hz, 1 H, 4-H), 4.45-4.41 (m, 1 H, 5-H), 3.38 (ddd, *J* = 14.3, 5.9, 2.3 Hz, 1 H, 6-H'), 3.28 (dt, *J* = 14.3, 2.5 Hz, 1 H, 6-H''), 2.66 (ddd, *J* = 15.6, 2.7, 1.4 Hz, 1 H, 3-H'), 2.37 (dd, *J* = 15.6, 4.1 Hz, 1 H, 3-H''), 1.45 (s, 3 H, CH_3), 1.34 (s, 3 H, CH_3). ^{13}C NMR (100.4 MHz) δ (ppm): 171.2 (s, C2), 109.0 (s, $C(CH_3)_2$), 72.6 (d, C4), 72.3 (d, C5), 43.9 (t, C6), 36.4 (t, C3), 26.1 (q, CH_3), 24.1 (q, CH_3). MS/MS (ESI) of $[M+1]^+$ *m/z* %: 172 (M^++1, 13), 154 (1), 114 (100), 96 (27). Anal. Calcd for $C_8H_{13}NO_3 \cdot ⅛H_2O$: C, 55.40; H, 7.70; N, 8.08. Found: C, 55.86, H, 8.30; N, 8.30.



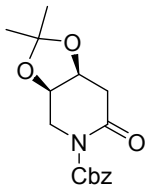
(±)-**139**

(±)-4,5-*O*-Isopropylidene-4,5-dihydroxy-2-oxopiperidine-1-carboxylic Acid Methyl Ester ((±)-139).

A solution of lactam (±)-**138** (888 mg, 5.19 mmol) in dry THF (52 mL) was cooled at –78 °C and a 1.6 M solution of *n*-BuLi (3.30 mL, 5.19 mmol) was slowly added, keeping the

temperature below –70°C during the addition. The mixture was stirred for 15 min and then methyl chloroformate (402 μL, 5.19 mmol) was added dropwise and, after 10 min, the cooling bath was removed and the temperature allowed to warm to 0 °C. Saturated $NaHCO_3$ (24 mL) and water (24 mL) were added and the product extracted with dichloromethane (3 × 20 mL). The combined organic extracts were dried over Na_2SO_4, filtered and evaporated *in vacuo* to give crude (±)-**139**. After purification by flash chromatography (eluant: *n*-hexane-EtOAc, 1:2; R_f 0.32) pure (±)-**139** was obtained as a white solid (998 mg, 84%).

(±)-139. m.p. 138.5–139.3 °C. ^{1}H NMR (400 MHz) δ (ppm): 4.64 (ddd, *J* = 7.6, 3.5, 2.7 Hz, 1 H, 4-H), 4.54-4.49 (m, 2 H, 5-H, 6-H'), 3.88 (s, 3 H, OCH_3), 3.30 (dd, *J* = 15.0, 2.3 Hz, 1 H, 6-H''), 2.85 (dd, *J* = 16.0, 2.7 Hz, 1 H, 3-H'), 2.49 (dd, *J* = 16.0, 3.5 Hz, 1 H, 3-H''), 1.38 (s, 3 H, CH_3), 1.32 (s, 3 H, CH_3). ^{13}C NMR (50.33 MHz) δ (ppm): 168.2 (s, C2), 154.0 (s, CO_2CH_3), 108.9 (s, $C(CH_3)_2$), 72.1 (d, C4), 71.5 (d, C5), 54.1 (q, OCH_3), 46.7 (t, C6), 39.3 (t, C3), 26.1 (q, CH_3), 24.2 (q, CH_3). MS/MS of $[M+1]^+$ *m/z* %: 230 (M^++1, 4), 171 (100), 139 (37). Anal. Calcd. for $C_{10}H_{15}NO_5$: C, 52.40; H, 6.60; N, 6.11. Found: C, 52.35, H, 6.47; N, 5.95.



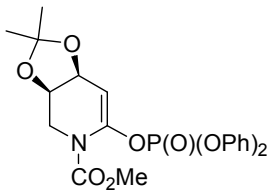
(±)-**140**

(±)-4,5-*O*-Isopropylidene-4,5-dihydroxy-2-oxopiperidine-1-carboxylic Acid Benzyl Ester ((±)-140).

Prepared as described for (±)-**139**, starting from (±)-**138** (1.09 g, 6.38 mmol) and benzyl chloroformate (1.0 mL, 7.0 mmol). After purification by flash chromatography (eluant: *n*-hexane-EtOAc, 1:1; R_f 0.22) pure (±)-**140** was obtained as a white solid (1.58 g, 81%).

(±)-**140**. m.p. 109.9–110.4 °C. ^{1}H NMR (400 MHz) δ (ppm): 7.45–7.41 (m, 2 H, Ph), 7.38–7.27 (m, 3 H, Ph), 5.32 (AB system, *J* = 12.5 Hz, 2 H, CH_2Ph), 4.64 (ddd, *J* = 7.6, 3.5, 2.7 Hz, 1 H, 4-H), 4.54-4.48 (m, 2 H, 5-H, 6-H'), 3.30 (dd, *J* = 14.6, 2.0 Hz, 1 H, 6-H''), 2.86 (dd, *J* = 15.8, 2.7 Hz, 1 H, 3-H'), 2.49 (dd, *J* = 15.8, 3.5 Hz, 1 H, 3-H''), 1.31 (s, 3 H, CH_3), 1.30 (s, 3 H, CH_3). ^{13}C NMR (100.4 MHz) δ (ppm): 168.3 (s, C2), 153.4 (s, NCO_2Bn), 135.4 (s, Ph), 128.5 (d, 2 C, Ph), 128.2 (d, Ph), 128.0 (d, 2 C, Ph), 109.1 (s, $C(CH_3)_2$), 72.2 (d, C4), 71.5 (d, C5), 68.6 (t, CH_2Ph), 46.7 (t, C6), 39.3 (t, C3), 26.0 (q, CH_3), 24.1 (q, CH_3). MS (ESI) *m/z* %: 633 ($[2M+Na]^+$, 100), 328 ($[M+Na]^+$, 12), 306 ($[M+1]^+$, 3). MS/MS of $[M+1]^+$ *m/z* %: 306 (9), 262

(100), 204 (4), 9 (16). Anal. Calcd. for $C_{16}H_{19}NO_5$: C, 62.94; H, 6.27; N, 4.59. Found: C, 63.10, H, 6.41; N, 4.49.

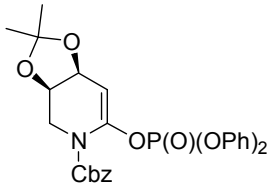


(±)-**141**

(±)-3,4-*O*-Isopropylidene-6-(diphenoxyphosphoryloxy)-3,4-dihydroxy-3,4-dihydro-2*H*-pyridine-1-carboxylic Acid Methyl Ester ((±)-141).

A solution of 0.5 M KHMDS in toluene (10.8 mL, 5.41 mmol) was diluted in anhydrous THF (42 mL) and cooled at –78°C. A solution of (±)-**139** (993 mg, 4.33 mmol) in anhydrous THF (15 mL) was then added dropwise, keeping the temperature below –70 °C, and the resulting mixture was stirred for 1.5 h. Diphenylchlorophosphate (1.1 mL, 5.41 mmol) was slowly added and, after 1 h, the mixture was allowed to warm at 0 °C. Aqueous 10% NaOH (100 mL) was slowly added and the product extracted with Et_2O (3 × 80 mL). The combined organic extracts were washed with 10% NaOH (60 mL) and dried over K_2CO_3 for 30 min. After filtration and evaporation of the solvent, the crude was purified over a short pad of silica gel, eluting with *n*-hexane-EtOAc, 2:1 buffered with 1% Et_3N (R_f 0.29), affording pure (±)-**141** as a colourless oil (1.77 g, 89%). This was used immediately for the next step.

(±)-141. ^{1}H NMR (400 MHz) δ (ppm): 7.38–7.32 (m, 4 H, Ph), 7.28–7.17 (m, 6 H, Ph), 5.33 (dd, *J* = 4.5, 2.7 Hz, 1 H, 5-H), 4.68 (ddd, *J* = 6.4, 4.5, 2.1 Hz, 1 H, 4-H), 4.30 (ddd, *J* = 6.4, 5.7, 3.1 Hz,1 H, 3-H), 3.81 (dd, *J* = 13.5, 5.7 Hz, 1 H, 2-H'), 3.68 (dd, *J* = 13.5, 3.1 Hz, 1 H, 2-H''), 3.58 (s, 3 H, OCH_3), 1.42 (s, 3 H, CH_3), 1.35 (s, 3 H, CH_3). ^{13}C NMR (50.33 MHz) δ (ppm): 154.6 (s, *C*O_2Me), 150.3 (s, C6), 143.5 (s, Ph), 143.4 (s, Ph), 129.8 (d, 4 C, Ph), 125.7 (d, 2 C, Ph), 120.1 (d, 2 C, Ph), 120.0 (d, 2 C, Ph), 109.9 (s, *C*$(CH_3)_2$), 99.8 (d, C5), 73.3 (d, C4), 70.7 (d, C3), 53.4 (q, OCH_3), 48.8 (t, C2), 27.5 (q, CH_3), 25.7 (q, CH_3).

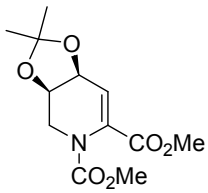


(±)-**142**

(±)-3,4-*O*-Isopropylidene-6-(diphenoxyphosphoryloxy)-3,4-dihydroxy-3,4-dihydro-2*H*-pyridine-1-carboxylic Acid Benzyl Ester ((±)-142).

Prepared as described for (±)-**141**, starting from (±)-**140** (1.57 g, 5.15 mmol) and affording, after purification over a short pad of silica gel (eluant: *n*-hexane-EtOAc, 2:1, 1% Et_3N; R_f 0.27), pure (±)-**142** as a colourless oil (2.77 g, 100%). This was used immediately for the next step.

(±)-142. ^{1}H NMR (400 MHz) δ (ppm): 7.35–7.29 (m, 10 H, Ph), 7.28–7.16 (m, 5 H, Ph), 5.35 (dd, *J* = 4.7, 2.6 Hz, 1 H, 5-H), 5.34 (d, *J* = 12.6 Hz, 1 H, C*H*$_2$Ph), 5.13 (d, *J* = 12.6 Hz, 1 H, C*H*$_2$Ph), 4.68 (ddd, *J* = 6.4, 4.7, 2.0 Hz, 1 H, 4-H), 4.31-4.27 (m, 1 H, 3-H), 3.93 (dd, *J* = 13.4, 5.3 Hz, 1 H, 2-H'), 3.64 (dd, *J* = 13.4, 2.9 Hz, 1 H, 2-H''), 1.32 (s, 6 H, CH_3). ^{13}C NMR (50.33 MHz) δ (ppm): 154.0 (s, *C*O_2Bn), 150.3 (s, C6), 143.9 (s, 2 C, OPh), 135.5 (s, CH_2*Ph*), 129.8 (d, 4 C, OPh), 128.4 (d, 2 C, CH_2*Ph*), 128.2 (d, 2 C, CH_2*Ph*), 128.1 (d, CH_2*Ph*), 125.6 (d, 2 C, OPh), 120.1 (d, 4 C, OPh), 110.0 (s, *C*$(CH_3)_2$), 100.1 (d, C5), 73.4 (d, C4), 70.8 (d, C3), 68.2 (t, *C*H_2Ph), 49.0 (t, C2), 27.5 (q, CH_3), 25.7 (q, CH_3). MS (ESI) *m/z* %: 560 ([M+Na]$^+$, 100), 537 (M^+, 98).



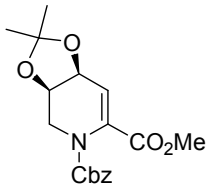
(±)-**143**

(±)-4,5-*O*-Isopropylidene-4,5-dihydroxy-5,6-dihydro-4*H*-pyridine-1,2-dicarboxylic Acid Dimethyl Ester ((±)-143).

In a round bottom flask was prepared a solution of phosphate (±)-**141** (1.77 g, 3.84 mmol), $Pd(OAc)_2$ (86 mg, 0.38 mmol) and Ph_3P (201 mg, 0.77 mmol) in anhydrous DMF (10 mL) under nitrogen atmosphere. The flask was flushed and saturated with carbon monoxide and, after 10 min, Et_3N (1.1 mL, 7.68 mmol) and anhydrous CH_3OH (6.2 mL, 154 mmol) were added. The mixture was saturated with CO (balloon) and heated at 60 °C (external bath) for 2.5 h. After cooling, water (103 mL) was added and the product extracted with Et_2O (4 × 100 mL). The combined organic extracted were dried over Na_2SO_4; after filtration and evaporation of the solvent, crude (±)-**143** was purified by flash chromatography (eluant: *n*-hexane-EtOAc, 2:1, 1% Et_3N; R_f 0.27), to afford pure (±)-**143** as a white solid (807 mg, 78%).

(±)-**143**. m.p. 112.0–113.0 °C. ^{1}H NMR (400 MHz) δ (ppm): 6.20 (d, *J* = 3.7, 1 H, 3-H), 4.58 (dd, *J* = 6.2, 3.7 Hz, 1 H, 4-H), 4.30 (ddd, *J* = 7.6, 6.2, 4.1 Hz, 1 H, 5-H), 3.95 (dd, *J* = 13.5, 4.1 Hz, 1 H, 6-H_{eq}), 3.80 (s, 3 H, OCH_3), 3.73 (s, 3 H, OCH_3), 3.36 (dd, *J* = 13.5, 7.6 Hz, 1 H, 6-H_{ax}), 1.43 (s, 3 H, CH_3), 1.38 (s, 3 H, CH_3). ^{13}C NMR (100.32 MHz) δ (ppm): 164.0 (s, *C*O_2Me), 154.4 (s, N*C*O_2Me), 134.5 (s, C2), 120.0 (d, C3), 109.7 (s, *C*$(CH_3)_2$), 72.5 (d, C4), 69.4 (d, C5),

53.5 (q, O*C*H_3), 52.5 (q, O*C*H_3), 46.2 (t, C6), 27.7 (q, *C*H_3), 25.7 (q, *C*H_3). MS (ESI) *m/z* %: 565 ([2M+Na]$^+$, 100), 294 ([M+Na]$^+$, 86), 272 ([M+1]$^+$, 7). Anal. Calcd. for $C_{12}H_{17}NO_6$: C, 53.13; H, 6.32; N, 5.16. Found: C, 53.44, H, 6.16; N, 4.95.

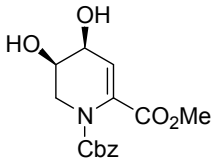


(±)-**144**

(±)-4,5-*O*-Isopropylidene-4,5-dihydroxy-5,6-dihydro-4*H*-pyridine-1,2-dicarboxylic Acid 1-Benzyl Ester 2-Methyl Ester ((±)-144).

Prepared as described for (±)-**143**, starting from phosphate (±)-**142** (2.77 g, 5.15 mmol) and heating at 60 °C for 5 h. After purification by flash chromatography (eluant: *n*-hexane-EtOAc, 3:1, 1% Et_3N; R_f 0.29), pure (±)-**144** was obtained as a white solid (1.28 g, 72%).

(±)-144. m.p. 87.5–89.0 °C. ^{1}H NMR (400 MHz) δ (ppm): 7.40–7.29 (m, 5 H, Ph), 6.18 (d, *J* = 3.5 Hz, 1 H, 3-H), 5.14 (AB system, *J* = 12.3 Hz, 2 H, C*H*$_2$Ph), 4.58 (dd, *J* = 6.1, 3.5 Hz, 1 H, 4-H), 4.32-4.27 (m, 1 H, 5-H), 3.97 (dd, *J* = 13.2, 3.8 Hz, 1 H, 6-H_{eq}), 3.64-3.56 (br s, 3 H, OCH_3), 3.41 (dd, *J* = 13.2, 7.6 Hz, 1 H, 6-H_{ax}), 1.40 (s, 3 H, CH_3), 1.37 (s, 3 H, CH_3). ^{13}C NMR (100.32 MHz) δ (ppm): 164.0 (s, *C*O_2Me), 153.8 (s, *C*O_2Bn), 135.5 (s, C2), 129.8 (s, Ph), 128.5 (d, 2 C, Ph), 128.3 (d, Ph), 128.2 (d, 2 C, Ph), 120.1 (d, C3), 109.7 (s, *C*$(CH_3)_2$), 72.5 (d, C4), 69.4 (d, C5), 68.3 (t, *C*H_2Ph), 52.3 (q, OCH_3), 46.3 (t, C6), 27.7 (q, CH_3), 25.7 (q, CH_3). MS (ESI) *m/z* %: 370 ([M+Na]$^+$, 78), 348 ([M+1]$^+$, 100). Anal. Calcd for $C_{18}H_{21}NO_6$: C, 62.24; H, 6.09; N, 4.03. Found: C, 62.27; H, 5.79; N, 4.26.



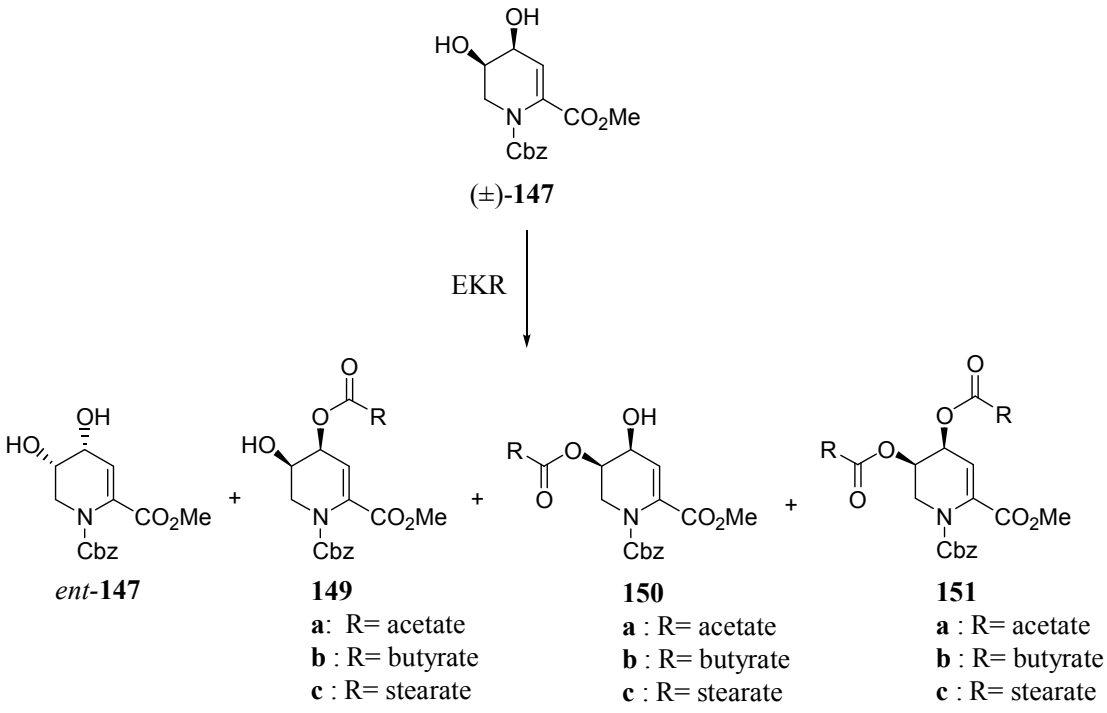
(±)-**147**

(±)-4,5-dihydroxy-5,6-dihydro-4H-pyridine-1,2-dicarboxylic Acid 1,2 1-Benzyl Ester 2-Methyl Ester ((±)-147).

To a solution of (±)-**144** (182 mg, 0.52 mmol) in $CHCl_3$ was added TFA (1 mL) then H_2O (100μL), and the mixture stirred for 11 min at room temperature. After cooling in an ice bath, the reaction mixture was added K_2CO_3 (1.11 g, 8.0 mmol) and stirred for 3 min. A saturated aqueous solution of $NHCO_3$ was added (10 mL). The aqueous phase was extracted with $CHCl_3$ (3 x 5 ml)

and the overall organic phases were dried on K_2CO_3. After filtration and evaporation of the solvent, the crude (±)-**147**, obtained as a 2 : 1 mixture with the unreacted substrate (±)-**144**, was chromatographed ($CHCl_3$-acetone, 2 : 1, R_f = 0.28) to give (±)-**147** (104 mg, 0.34 mmol, 65%) as a white gummy solid. Unreacted (±)-**144** was recovered (35 mg, 20% yield).

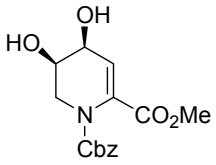
(±)-147. ^{1}H-NMR (400 MHz) δ (ppm): 7.38-7.30 (m, 5 H, Ph), 5.87 (d, *J* = 3.7 Hz, 1 H, 3-H), 5.15 (s, 2 H, C*H*$_2$Ph), 4.31-4.28 (m, 1 H, 4-H), 3.97-3.91 (m, 1 H, 5-H), 3.83-3.68 (m, 2 H, 6-H_{eq}), 3.56 (bs, 3 H, C*H*$_3$), 2.74 (dd, *J* = 5.86, 42.7 Hz, 2 H, 6-H_{ax}). ^{13}C NMR (100.32 MHz) δ (ppm) 164.7 (s, *C*OMe), 154.4 (s, *C*OBn), 135.3 (s, C-2), 133.3 (s, Ph), 128.4 (m, 4 C, Ph), 120.3 (s, C-3), 68.5 (s, C-4), 66.1 (s, C-5), 64.6 (s, *C*H$_2$Bn), 52.3 (s, O*C*H$_3$), 47.3 (s, C-6). MS (ESI) *m/z* (%): 308.50 (M^+ + 1), 330.33 (M^+ + 23)



General procedure for lipase-catalyzed Kinetic Resolution of (±)-147: (4*R*,5*S*)-4,5-dihydroxy-5,6-dihydro-4H-pyridine-1,2-dicarboxylic Acid 1,2 1-Benzyl Ester 2-Methyl Ester (*ent*-147) and (4*S*,5*R*)-4-acyloxy-5-hydroxy-5,6-dihydro-4H-pyridine-1,2-dicarboxylic Acid 1,2 1-Benzyl Ester 2-Methyl Ester (149) and (4*S*,5*R*)-4-hydroxy-5-acyloxy-5,6-dihydro-4H-pyridine-1,2-dicarboxylic Acid 1,2 1-Benzyl Ester 2-Methyl Ester (159) and (4*S*,5*R*)-4,5-diacyloxy-5,6-dihydro-4H-pyridine-1,2-dicarboxylic Acid 1,2 1-Benzyl Ester 2-Methyl Ester (151)

4 Å MS (130 mg/ mmol substrate) were added to a solution of (±)-**147** (176 mg, 0.604 mmol) in anhydrous solvent (1.5 mL) at 30 °C, followed by lipase (100 mg/mmol substrate), under N_2 atmosphere. After 20 min, acylating agent (3.5 eq) was added and the reaction was left under

vigorous stirring and monitored by HPLC. The reaction was stopped by filtration over a thin layer of Celite. After evaporation, the crude product was chromatographed (EtOAc–*n*-hexane, 1:2) to give *ent*-**147** (R_f = 0.15) (for *ee* obtained in each experiment, see Table 3), **149** ($R_{f\text{-}149b}$ = 0.45), **150** ($R_{f\text{-}\mathbf{150b}}$= 0.61, $R_{f\text{-}\mathbf{150c}}$= 0.66) and **151** ($R_{f\text{-}\mathbf{151c}}$= 0.86).

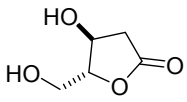


147

(4*S*,5*R*)-4,5-dihydroxy-5,6-dihydro-4H-pyridine-1,2-dicarboxylic Acid 1,2 1-Benzyl Ester 2-Methyl Ester (147)

To the solution of acylated **149**, **150** (and **151** when it is present) in dry MeOH (10 eq), cooled in an ice bath, was added MeONa (13 mg, 0.24 mmol), and the mixture stirred for 3.5 h at 0 °C under N_2 atmosphere. Then glacial acetic acid (14 μL) was added and the solvent was evaporated *in vaquo* without heating. The residue was diluted with water (20 mL), extracted with $CHCl_3$ (3 × 20 mL) and dried over K_2CO_3. After filtration and evaporation of the solvent, the crude **147** was obtained as a colorless oil.

147. Spectroscopic data as reported above for (±)-**147**. For *ee* obtained in each experiments, see Table 3



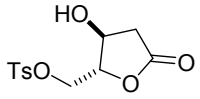
156

(4*S*,5*R*)-4-Hydroxy-5-(hydroxymethyl)dihydrofuran-2(3H)-one [(+)-(156)].

Bromine (4.0 mL, 78.0 mmol) was slowly added to a solution of 2-deoxy-D-ribose **155** (2.01 g, 15.0 mmol) in water (12 mL). The flask was then sealed and the red solution was stirred at room temperature for 5 days. After dilution with water (10 mL), Ag_2CO_3 was added until pH reached 7 (complete decolourization occurred). The suspension was filtered on a celite pad and the filtrate evaporated under vacuum. The residue was purified by flash chromatography (eluent: EtOAc-MeOH, 10:1; R_f 0.50) affording pure lactone **156** (1.74 g, 88%) as a colourless oil.[82a, 83]

156. $[\alpha]_D^{18}$ +3.05 (*c* 1.14, CH_3OH) [*lit.*[83] $[\alpha]_D^{25}$ +2.17 (*c* 0.6 , CH_3OH); *lit.*[97] $[\alpha]_D^{22}$ +3.50 (*c* 0.8, CH_3OH)]; $[\alpha]_D^{24}$ +19.2 (*c* 1.33, H_2O) [*lit.*[82a] $[\alpha]_D^{22}$ +19.9 (*c* 0.71, H_2O)]. ^{1}H NMR (d_6-DMSO, 400 MHz) δ (ppm): 5.52 (d, *J* = 0 4.1 Hz, 1 H, CHO*H*), 5.10 (t, *J* = 5.5 Hz, 1 H, CH_2OH), 4.33-4.27 (m, 2 H, 4-H and 5-H), 3.62-3.53 (m, 2 H, CH_2OH), 2.85 (dd, *J* = 17.6, 6.2

Hz, 1 H, 3-H), 2.26 (dd, *J* = 17.6, 2.1 Hz, 1 H, 3-H'); ^{1}H NMR (CD_3OD, 400 MHz) δ (ppm): 4.42 (dt, *J* = 6.6, 2.3 Hz, 1 H, 4-H), 4.36 (X part of an ABX system, m, 1 H, 5-H), 3.73 (AB part of an ABX system, *J* = 12.5, 3.3 Hz, 2 H, C*H*$_2$OH), 2.91 (dd, *J* = 18.0, 6.8 Hz, 1 H, 3-H), 2.37 (dd, *J* = 18.0, 2.5 Hz, 1 H, 3-H'). ^{13}C NMR (d_6-DMSO, 100.32 MHz) δ (ppm): 177.1 (s, CO), 89.2 (d, C5), 68.7 (d, C4), 61.7 (t, *C*H$_2$OH), 38.9 (t, C3);^{13}C NMR (CD_3OD, 100.32 MHz) δ (ppm): 178.6 (s, CO), 90.2 (d, C5), 69.7 (d, C4), 62.5 (t, *C*H$_2$OH), 39.2 (t, C3). MS (ESI) *m/z* %: 101 (19, M^+-31), 43 (100). $C_5H_8O_4$ (132.11): calcd C, 45.46; H, 6.10. Found: C, 45.35, H, 6.39.

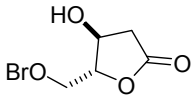


157

(2S,3S)-(3-Hydroxy-5-oxotetrahydrofuran-2-yl)methyl 4-Methylbenzenesulfonate [(+)-(157)].

A solution of lactone **156** (850 mg, 6.4 mmol) in freshly distilled pyridine (20 mL) was cooled at -15°C (external) and, after 15 min, TsCl (1.15 eq) was rapidly added and the mixture left under stirring at -15°C for 2 h and at 0 °C for 5 h. The solvent was then removed under vacuum and the residue taken up in water (20 mL); the product was extracted with EtOAc (4 x 20 mL) and the combined organic extracts washed with 0.5 M HCl (2 x 20 mL), water (20 mL) and dried over anhydrous Na_2SO_4. After filtration and evaporation of the solvent, crude **157** was obtained and purified by flash chromatography (eluent: *n*-hexane-EtOAc, 2:3; R_f 0.19), affording pure *O*-tosylate **157** as a white solid (990 mg, 54%).

157. M.p. 56.0-57.9 °C (*lit*.[84] 56-58 °C). $[\alpha]_D^{20}$ +36.5 (*c* 0.89, $CHCl_3$) [*lit*.[84] $[\alpha]_D^{20}$ +39.6 (*c* 5.3, CH_2Cl_2); *lit*.[98] $[\alpha]_D^{20}$ + 32.1 (*c* 3.2, CH_2Cl_2)]. ^{1}H NMR (400 MHz) δ (ppm): 7.76 (d, *J* = 8.2 Hz, 2 H, Ar), 7.37 (d, *J* = 8.4 Hz, 2 H, Ar), 4.62-4.58 (m, 1 H, 3-H), 4.51-4.48 (m, 1 H, 2-H), 4.29 (dd, *J* = 11.3, 3.3 Hz, 1 H, C*H*$_2$OTs), 4.16 (dd, *J* = 11.3, 3.5 Hz, 1 H, C*H*$_2$OTs), 2.90 (dd, *J* = 18.2, 7.2 Hz, 1 H, 4-H), 2.64 (br s, 1 H, O*H*), 2.53 (dd, *J* = 18.2, 3.7 Hz, 1 H, 4-H'), 2.46 (2, 3 H, CH_3). ^{13}C NMR (100.32 MHz) δ (ppm): 174.1 (s, CO), 145.7 (s, Ar), 131.8 (s, Ar), 130.2 (d, 2 C, Ar), 128.0 (d, 2 C, Ar), 83.6 (d, C2), 68.9 (d, C3), 67.8 (t, *C*H$_2$OTs), 37.7 (t, C4), 21.7 (q, CH_3). MS (ESI) *m/z* %: 286 ($[M]^+$, 100), 115 (6). $C_{12}H_{14}O_6S$ (286.30): calcd C, 50.34; H, 4.93. Found: C, 49.94, H, 5.06.

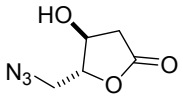


158

(4*S*,5*S*)-5-(Bromomethyl)-4-hydroxydihydrofuran-2(3*H*)-one [(+)-(158)].

A solution of lactone **156** (850 mg, 6.4 mmol) in anhydrous DMF (9.5 mL) was cooled at 0 °C and thionyl bromide (595 μL, 7.7 mmol) was dropwise added. After 2 min the cooling bath was removed and the orange solution left under stirring for 4.5 h. The reaction was quenched by adding anhydrous methanol (332 μL) and, after 10 min, water (95 mL). The product was extracted with EtOAc (4 x 80 mL) and the combined organic extracts were dried over anhydrous Na_2SO_4. After filtration and evaporation of the solvent, crude **158** was obtained and purified by flash chromatography (eluent: *n*-hexane-EtOAc, 1:1; R_f 0.25). Pure bromide **158** (587 mg, 47%) was so obtained as a colourless oil. The aqueous layer was concentrated under vacuum and the residue chromatographed (eluent: EtOAc, R_f 0.21) to give alcohol **156** (262 mg). This was treated again with $SOBr_2$ as reported above providing pure **158** (181 mg) in a total yield of 61%.

158. $[\alpha]_D^{26}$ +12.5 (*c* 1.22, EtOAc). ^{1}H NMR (400 MHz) δ (ppm): 4.63–4.58 (m, 1 H, 4-H), 4.58-4.53 (m, 1 H, 5-H), 3.61 (dd, *J* = 11.2, 3.9 Hz, 1 H, C*H*$_2$Br), 3.53 (dd, *J* = 11.2, 6.0 Hz, 1 H, C*H*$_2$Br), 2.99 (dd, *J* = 18.4, 7.2 Hz, 1 H, 3-H), 2.58 (dd, *J* = 18.4, 3.9 Hz, 1 H, 3-H'). ^{13}C NMR (100.32 MHz) δ (ppm): 175.7 (s, CO), 85.6 (d, C5), 70.1 (d, C4), 37.9 (t, *C*H$_2$Br), 31.5 (t, C3). MS (ESI) *m/z* %: 219 ([M+Na]$^+$, 45), 217 ([M+Na]$^+$, 47). $C_5H_7BrO_3$ (195.01): calcd C, 30.79; H, 3.62. Found: C, 30.85, H, 3.93



159

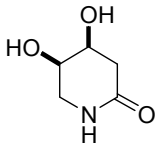
(4*S*,5*R*)-5-Azidomethyl-4-hydroxydihydrofuran-2-one [(+)-(159)].

From tosylate 157. Tosylate **157** (825 mg, 2.88 mmol) was dissolved into anhydrous acetonitrile (12.5 mL) under nitrogen atmosphere; 18-crown-6 ether (152 mg, 0.58 mmol) and NaN_3 (280 mg, 1.5 eq) were rapidly added to this solution and the mixture was heated under reflux. After 7 h a further amount of NaN_3 (0.2 eq) was added and the suspension refluxed until completion (in all 15 h). After cooling at room temperature, the suspension was filtered on a Celite pad and the filtrate concentrated under vacuum. The residue was purified by flash chromatography (eluent: *n*-hexane-EtOAc, 2:3; R_f 0.23), affording pure azide **159** (401 mg, 87%) as a colourless oil.

From bromide 158. Bromide **158** (580 mg, 2.97 mmol) was dissolved into anhydrous acetonitrile (13 mL) under nitrogen atmosphere; 15-crown-5 ether (118 μL, 0.59 mmol) and

NaN_3 (387 mg, 2.0 eq) were rapidly added to this solution and the mixture was heated under reflux. After 8 h a further amount of NaN_3 (0.5 eq) was added and the suspension refluxed until completion (20 h; TLC monitoring). After cooling at room temperature, the suspension was filtered on a mixed silica gel-celite pad and the filtrate concentrated under *vacuum*. Azide **159** (443 mg, 95%) was so obtained as a colourless oil and no further purifications were required.

159. $[\alpha]_D^{25}$ +100.5 (*c* 0.39, $CHCl_3$). ^{1}H NMR (400 MHz) δ (ppm): 4.51–4.45 (m, 2 H, 4-H, 5-H), 3.64 (AB part of an ABX system, *J* = 13.3, 3.9 Hz, 2 H, C*H*$_2$N$_3$), 2.96 (dd, *J* = 18.2, 6.8 Hz, 1 H, 3-H), 2.55 (dd, *J* = 18.2, 3.9 Hz, 1 H, 3-H'). ^{13}C NMR (100.32 MHz) δ (ppm): 175.8 (s, CO), 85.5 (d, C5), 69.0 (d, C4), 51.8 (t, *C*H$_2$N$_3$), 37.8 (t, C3). MS/MS (ESI of $[M + 1]^+$): *m/z* (%) = 158 ($[M^+$+1], 100). $C_5H_7N_3O_3$ (157.13): calcd C, 38.22; H, 4.49; N, 26.74. Found: C, 37.96, H, 4.72; N, 26.56.

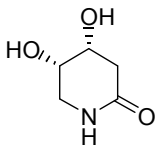


137

(4*S*,5*R*)-4,5-Dihydroxypiperidin-2-one (+)-137)

Azide **159** (840 mg, 5.35 mmol) was dissolved into anhydrous methanol (35 mL) under nitrogen atmosphere. Then, 10% Pd/C catalyst (3% mol) was added and the reaction flask flushed first with N_2 and then with hydrogen and left under hydrogen atmosphere (balloon) at room temperature for 24 h. The suspension was filtered on a Celite pad and the filtrate concentrated under vacuum, affording pure lactam **137** as a white solid (638 mg, 91%) with spectroscopic data identical to those of the racemic compound (EJOC 2012).

137. M.p. 160.9-162.0 °C. $[\alpha]_D^{23}$ +17.8 (*c* 0.62, CH_3OH). Spectoscopic data as reported for the racemic compound (±)-**137**

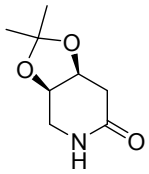


ent-**137**

(4*S*,5*R*)-4,5-Dihydroxypiperidin-2-one (*ent*-137)

Prepared as reported above for (+)-**137**. Starting from 2-deoxy-L-ribose (*ent*-**155**) (700 mg, 5.22 mmol) pure lactone *ent*-**137** (545 mg, 79%) was obtained as a colourless oil.

***ent*-137**. $[\alpha]_D^{23}$ (*c* 1.04, H_2O). Analytical and spectroscopic data as reported above.

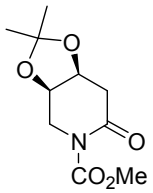


138

(3a*R*,7a*S*)-2,2-Dimethyltetrahydro[1,3]dioxolo[4,5-c]pyridin-6(3a*H*)-one [(–)-(138)].

Lactam (4*S*,5*R*)-**137** (630 mg, 4.80 mmol) was dissolved in anhydrous methanol (4.3 mL) and a catalytic amount of *p*-toluenesulfonic acid was added (183 mg, 0.96 mmol) followed by 2,2-dimethoxypropane (10.6 mL, 86 mmol). The mixture was warmed at 55°C for 2.5 h and, after cooling, diluted with MeOH (4.5 mL) and neutralized by K_2CO_3 (73 mg, 0.53 mmol). After filtration on a Celite pad and evaporation of the solvent, crude **138** was obtained and purified by flash chromatography (eluent: CH_2Cl_2–MeOH, 20:1; R_f 0.18), affording pure **138** as a white powder (756 mg, 92%) with spectroscopic data identical to those of the racemic compound.

(-)-138. M.p. 118.2-119.2 °C. $[\alpha]_D^{24}$ –121.9 (*c* 0.75, $CHCl_3$). Analytical and spectroscopic data as reported above for the racemic compound (±)-**138**

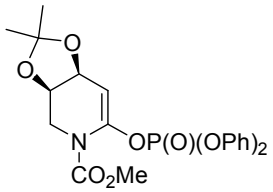


139

(3a*R*,7a*S*)-Methyl 2,2-Dimethyl-6-oxotetrahydro[1,3]dioxolo[4,5-c]pyridine-5(4*H*)-carboxylate [(–)-(139)].

A solution of lactam **138** (750 mg, 4.38 mmol) in dry THF (44 mL) was cooled at –78 °C and a 1.6 M solution of *n*-BuLi (2.74 mL, 4.38 mmol) was slowly added, keeping the temperature below –70°C during the addition. The mixture was stirred for 15 min and then methyl chloroformate (338 μL, 4.38 mmol) was added dropwise; after 10 min, the cooling bath was removed and the temperature allowed to warm to 0 °C. Saturated $NaHCO_3$ (20 mL) and water (20 mL) were added and the product extracted with dichloromethane (4 × 15 mL). The combined organic extracts were dried over Na_2SO_4, filtered and evaporated *in vacuo* to give crude **139**. After purification by flash chromatography (eluent: *n*-hexane-EtOAc, 1:2; R_f 0.32) pure **139** was obtained as a white solid (843 mg, 84%) with spectroscopic data identical to those of the racemic compound.

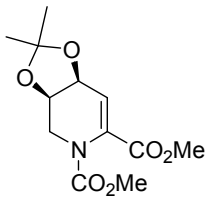
139. M.p. 70.2-72.1 °C. $[\alpha]_D^{24}$ –63.9 (*c* 0.91, $CHCl_3$). Spectoscopic data as reported above for racemic (±)-**139**.



141

(3a*R*,7a*S*)-Methyl 6-(Diphenoxyphosphoryloxy)-2,2-dimethyl-3a,7a-dihydro-4*H*-[1,3]dioxolo[4,5-c]pyridine-5(4*H*)-carboxylate (141).

Prepared as reported above for the racemic compound, starting from enantiopure **139** (840 mg, 3.66 mmol), affording pure **141** as a colourless oil (1.68 g, 99%). This was used immediately for the next step. Spectroscopic data identical to those of the racemic compound.

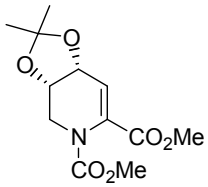


143

(3a*R*,7a*S*)-Dimethyl 2,2-Dimethyl-3a,7a-dihydro[1,3]dioxolo[4,5-c]pyridine-5,6(4*H*)-dicarboxylate [(+)-(143)].

In a round bottom flask was prepared a solution of phosphate **141** (1.68 g, 3.64 mmol), $Pd(OAc)_2$ (82 mg, 0.36 mmol) and Ph_3P (191 mg, 0.73 mmol) in anhydrous DMF (8.6 mL) under nitrogen atmosphere. The flask was flushed and saturated with carbon monoxide and, after 10 min, Et_3N (1.0 mL, 7.28 mmol) and anhydrous CH_3OH (5.9 mL, 146 mmol) were added. The mixture was saturated with CO (balloon) and heated at 75°C (external bath) for 1 h. After cooling, water (86 mL) was added and the product extracted with Et_2O (4 × 50 mL). The combined organic extracted were dried over Na_2SO_4; after filtration and evaporation of the solvent, crude **143** was purified by flash chromatography (eluant: *n*-hexane-EtOAc, 2:1, 1% Et_3N; R_f 0.27), to afford pure **143** as a thick colourless oil (770 mg, 78%) and with spectroscopic data identical to those of the racemic compound.

143. $[\alpha]_D^{26}$ +40.0 (*c* 1.12, $CHCl_3$).



ent-**143**

(3a*S*,7a*R*)-Dimethyl 2,2-Dimethyl-3a,7a-dihydro[1,3]dioxolo[4,5-c]pyridine-5,6(4*H*)-dicarboxylate [(–)-*ent*-25]

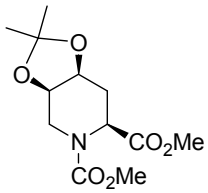
Prepared as reported for (+)-**143**, in two steps, starting from (+)-**137** (227 mg, 0.99 mmol) and affording pure (–)-**143** (185 mg, 69%) as colourless oil.

***ent*-143.** $[\alpha]_D^{25}$ –39.3 (*c* 0.78, $CHCl_3$). Analytical and spectroscopic data as reported above.

Attribution of absolute configuration of diol 147 from EKR (Scheme 38)

Conversion of enantiopure lactam 138 in enamide ester 144: Prepared as reported for (±)-**144** starting from enantiopure **138**, affording enantiopure **144** in 52% yield over 3 steps, with spectroscopic data identical to those racemic compound and $[\alpha]_D^{22}$ +33.5 (*c* 1.02, $CHCl_3$).

Conversion of diol *ent*-147 (directly obtained from EKR) in enamide ester *ent*-144: prepared as reported above for **138**, starting from *ent*-**147**, affording after chromatography (*n*-hexane-EtOAc 1:1, R_f = 0.22) pure *ent*-144 in 62% yield and $[\alpha]_D^{26}$ -25.3 (*c* 0.21, $CHCl_3$).



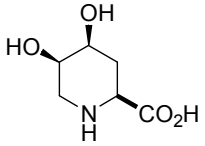
160

(3a*R*,6*S*,7a*S*)-Dimethyl 2,2-dimethyltetrahydro[1,3]dioxolo[4,5-c]pyridine-5,6(4*H*)-dicarboxylate [(–)-(160)].

A suspension of $NaHCO_3$ (155 mg, 1.84 mmol, 2.5 eq) and 10% Pd/C (126 mg, 0.12 mmol, 0.16 eq) in EtOAc (19.4 mL) was flushed with H_2 and vigorously stirred under H_2 atmosphere for 30 min. A solution of **143** (200 mg, 0.74 mmol) in EtOAc (1.7 mL mL) was then added and the resulting mixture flushed with H_2 and stirred under H_2 (balloon) at room temperature for 4 h. After filtration on a Celite pad, the filtrate was concentrated under *vacuum* to give pure **160** as a colourless oil (195 mg, 97%) with spectroscopic data identical to those of the racemic compound.

160. $[\alpha]_D^{25}$ –7.1 (*c* 0.93, $CHCl_3$). ^{1}H NMR (400 MHz) (1.3:1 mixture of rotamers) δ (ppm): 4.54 (t, *J* = 6.4 Hz, 1 H, 2-H, major), 4.40 (t, *J* = 6.8 Hz, 1 H, 2-H, minor), 4.29–4.15 (m, 2 H, 4-H, 5-

H, both rotamers + 1 H, 6-H_{eq} minor), 3.99 (dd, *J* = 13.9, 6.2 Hz, 1 H, 6-H_{eq}, major), 3.74 (s, 3 H, CO_2CH_3), 3.72 (s, 3 H, NCO_2CH_3, major), 3.68 (s, 3 H, NCO_2CH_3, minor), 3.33 (dd, *J* = 13.9, 8.2 Hz, 1 H, 6-H_{ax}, major), 3.26 (dd, *J* = 13.7, 8.2 Hz, 1 H, 6-H_{ax}, minor), 2.38–2.16 (m, 2 H, 3-H', 3-H''), 1.43 (s, 3 H, CH_3), 1.32 (s, 3 H, CH_3). $C_{12}H_{19}NO_6$ (273.28): calcd C, 51.06; H, 7.14; N, 4.96. Found: C, 50.92; H, 7.18; N, 4.72.



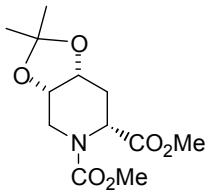
10 HCl

(2*S*,4*S*,5*R*)-4,5-Dihydroxypipecolic Acid [(–)-10·HCl].

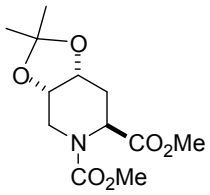
A 25 mM solution of compound **160** (187 mg, 0.68 mmol) in aqueous 4 N HCl was heated under reflux for 24 h. After cooling, the solvent was concentrated under vacuum. The residue was triturated with cold diethyl ether and then dried under vacuum until constant weight. Pure acid (–)-**10** was so obtained as hydrochloride (135 mg, quantitative).

White solid.

(–)-**10.** M.p. 167 °C (dec.). $[\alpha]_D^{24}$ –29.0 (*c* 0.54, H_2O); $[\alpha]_D^{28}$ –25.3 (*c* 0.54, 2N HCl). ^{1}H NMR (400 MHz, D_2O) δ (ppm): 4.15 (br s, 1 H, 5-H), 4.10 (dd, *J* = 12.1, 3.7 Hz, 1 H, 2-H), 4.04 (ddd, *J* = 10.9, 4.3, 2.9 Hz, 1 H, 4-H), 3.51 (dd, *J* = 13.5, 3.9 Hz, 1 H, 6-H_{eq}), 3.25 (dd, *J* = 13.9, 1.8 Hz, 1 H, 6-H_{ax}), 2.36 (dt, *J* = 13.7, 4.1 Hz, 1 H, 3-H_{eq}), 2.19-2.10 (m, 1 H, 3-H_{ax}). ^{13}C NMR (100.4 MHz, D_2O) δ (ppm): 170.5 (s, CO), 66.7 (d, C-5), 64.4 (d, C-4), 55.3 (d, C-2), 46.7 (t, C-6), 27.6 (t, C-3); MS/MS (ESI of $[M + 1]^+$): *m/z* (%) = 162 ($[M^+$+1], 2), 144 (53), 116 (100), 98 (25). $C_6H_{13}NO_4Cl$ (197.62): calcd C, 36.47; H, 6.63; N, 7.12. Found: C, 36.38; H,6.85; N, 7.03



ent-**160**



161

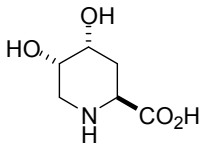
(3a*S*,6*R*,7a*R*)-Dimethyl 2,2-dimethyltetrahydro[1,3]dioxolo[4,5-c]pyridine-5,6(4*H*)-dicarboxylate [(+)-*ent*-(160)] and (3a*S*,6*S*,7a*R*)-Dimethyl 2,2-dimethyltetrahydro[1,3]dioxolo[4,5-c]pyridine-5,6(4*H*)-dicarboxylate [(–)-161]

A solution of (–)-*ent*-**143** (185 mg, 0.68 mmol) in anhydrous THF (2.5 mL) was cooled at –10 °C and Super-Hydride (1 M solution in THF, 820 μL, 0.82 mmol) was slowly added. After 70 min, the temperature was raised to 0 °C and the mixture stirred for 5 min, before being cooled

again at –10 °C and quenched by satd $NaHCO_3$ solution (8 mL). The product was extracted with CH_2Cl_2 (5 x 15 mL); the combined organic extracts were washed once with water (25 mL) and dried over anhydrous Na_2SO_4. After filtration and evaporation of the solvent, the crude 2.6 : 1 mixture of **161** and *ent*-**160** was obtained. The two diastereoisomers were separated by flash chromatography (eluent: *n*-hexane-EtOAc, 2:1), affording pure **161** (126 mg, 68%) and *ent*-**160** (41 mg, 22%) both as a thick colourless oil.

(+)-e*nt*-160. $[\alpha]_D^{25}$ +8.0 (*c* 0.64, $CHCl_3$).

(–)-161. $[\alpha]_D^{27}$ –113.4 (*c* 0.96, $CHCl_3$). ^{1}H NMR (400 MHz) (1.4:1 mixture of rotamers) δ (ppm): 4.52 (dd, *J* = 11.9, 5.7 Hz, 1 H, 2-H, major), 4.47-4.42 [m, 2 H, 2-H (minor) and 4-H (both rotamers)], 4.31 (dm, *J* = 8.0 Hz, 1 H, 5-H, minor), 4.28 (dm, *J* = 7.8 Hz, 1 H, 5-H, major), 4.20 (dd, *J* = 14.6, 2.0 Hz,1 H, 6-H_{eq} minor), 4.07 (dd, *J* = 15.0, 2.0 Hz, 1 H, 6-H_{eq}, major), 3.72 (s, 3 H, CO_2CH_3, major), 3.71 (s, 3 H, CO_2CH_3, minor), 3.70 (s, 3 H, NCO_2CH_3, major), 3.67 (s, 3 H, NCO_2CH_3, minor), 3.14 (dd, *J* = 15.0, 2.0 Hz, 1 H, 6-H_{ax}, major), 3.09 (dd, *J* = 14.6, 1.8 Hz, 1 H, 6-H_{ax}, minor), 2.38–2.28 (m, 1 H, 3-H), 1.78–1.69 (m, 1 H, 3-H'), 1.37 (s, 3 H, CH_3), 1.30 (s, 3 H, CH_3). ^{13}C NMR (100.4 MHz) δ (ppm): ^{13}C NMR (100.4 MHz) (mixture of rotamers) δ (ppm): 173.1 (s, CO_2Me), 156.7 and 156.3 (s, NCO_2Me), 108.5 and 108.4 (s, $C(CH_3)_2$), 72.6 and 72.5 (d, C-4), 69.7 (d, C-5), 52.9 and 52.8 (d, C-2), 52.2 (q, OCH_3), 50.9 and 50.8 (q, OCH_3), 42.4 and 42.1 (t, C-6), 27.9 and 27.6 (t, C-3), 26.2 and 26.1 (q, CH_3), 24.2 and 24.1 (q, CH_3). MS/MS (ESI of $[M + 1]^+$): *m/z* (%) = 274 ($[M^+ + 1]$, 3), 242 (45), 216 (100), 214 (22), 184 (7), 156 (5). $C_{12}H_{19}NO_6$ (273.28): calcd C, 51.06; H, 7.14; N, 4.96. Found: C, 50.88; H, 7.28; N, 4.80



11 HCl

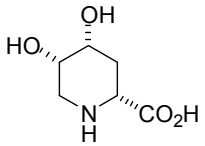
(2*S*,4*R*,5*S*)-4,5-Dihydroxypipecolic Acid [(–)-11·HCl].

Prepared as reported for (–)-**10**, starting from **161** (145 mg, 0.53 mmol) and obtaining pure (–)-**11** as hydrochloride (104 mg, 99%).

White solid.

11. Mp = 253 °C (dec.); $[\alpha]_D^{25}$ –10.7 (*c* 0.53, 2N HCl); ^{1}H NMR (400 MHz, D_2O) δ (ppm): 4.20 (dd, *J* = 10.9, 3.9 Hz, 1 H, 2-H), 4.13–3.99 (br m, 1 H, 4-H), 3.98 (ddd, *J* = 9.8, 4.1, 2.7 Hz, 1 H, 5-H), 3.33 (dd, *J* = 12.5, 4.3 Hz, 1 H, 6-H_{eq}), 3.19 (dd, *J* = 12.5, 10.0 Hz, 1 H, 6-H_{ax}), 2.39 (ddd, *J* = 15.0, 5.9, 4.1 Hz, 1 H, 3-H_{eq}), 2.11-2.04 (ddd, *J* = 15.0, 11.0, 2.5 Hz, 1 H, 3-H_{ax}). ^{13}C

NMR (100.4 MHz, D_2O) δ (ppm): 171.1 (s, CO), 66.7 (d, C-5), 64.6 (d, C-4), 51.7 (d, C-2), 42.3 (t, C-6), 29.8 (t, C-3); MS/MS (ESI of $[M + 1]^+$): *m/z* (%) = 162 ($[M^+$+1], 21), 144 (100), 116 (25), 98 (69). $C_6H_{13}NO_4Cl$ (197.62): calcd C, 36.47; H, 6.63; N, 7.12. Found: C, 36.34; H, 6.88; N, 6.99.

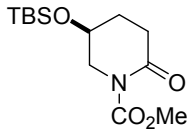


ent-**10**

(2*R*,4*R*,5*S*)-4,5-Dihydroxypipecolic Acid [(+)-*ent*-10·HCl]

Prepared as reported for (–)-**10**, starting from *ent*-**160** (18 mg, 0.065 mmol) and obtaining pure (+)-*ent*-**10** as hydrochloride (13 mg, quantitative).

(+)-*ent*-10. $[\alpha]_D^{24}$ +26.1 (*c* 0.65, 2N HCl)

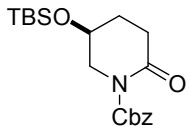


165

(5*S*)-Methyl 5-(*tert*-Butyldimethylsilanyloxy)-2-oxopiperidine-1-carboxylate [(+)-(165)]

Prepared as reported for (–)-**115**, starting from **164** (2.22 g, 9.68 mmol) and affording, after purification by flash chromatography (*n*-hexane-EtOAc, 2:1; R_f 0.25), pure (+)-**165** (1.98 g, 71%) as a white solid.

(+)-165. M.p. 64.1–65.0 °C (*lit.*[92g] m.p. 68 °C). $[\alpha]_D^{21}$ +17.2 (*c* 1.07, $CHCl_3$) {*lit.*[92g] $[\alpha]_D^{20}$ +10.9 (*c* 1.0. MeOH)}. ^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm): 4.20–4.15 (m, 1 H, 5-H), 3.86 (s, 3 H, OC*H*$_3$), 3.75 (ddd, *J* = 13.3, 4.7, 1.6 Hz, 1 H, 6-H), 3.68 (dd, *J* = 13.3, 3.7 Hz, 1 H, 6-H'), 2.75 (ddd, *J* = 17.4, 9.6, 6.8 Hz, 1 H, 3-H), 2.46 (dt, *J* = 17.4, 6.0 Hz, 1 H, 3-H'), 2.05–1.92 (m, 1 H, 4-H), 1.90–1.81 (m, 1 H, 4-H), 0.87 [s, 9 H, SiC$(CH_3)_3$], 0.08 [s, 6 H, Si$(CH_3)_2$]. ^{13}C NMR ($CDCl_3$, 100.4 MHz) δ (ppm): 170.8 (s, *C*O), 154.9 (s, N*C*O_2Me), 64.1 (d, C-5), 53.9 (q, OC*H*$_3$), 52.9 (t, C-6), 30.8 (t, C-3), 28.6 (t, C-4), 25.6 [(q, 3 C, SiC(*C*$H_3)_3$], 17.8 [(s, Si*C*$(CH_3)_3$], –4.9 [(q, 2 C, Si$(CH_3)_2$]. MS/MS (ESI of $[M + 1]^+$) *m/z* (%): 288 ($[M^+ + 1]$, 19), 256 (65), 156 (86), 147 (27), 114 (100). $C_{13}H_{25}NO_4Si$ (287.49): calcd C, 54.32; H, 8.77; N, 4.87. Found: C, 54.26; H, 8.50; N, 4.88.

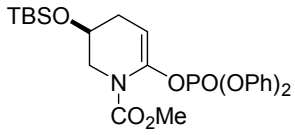


166

(5S)-Benzyl 5-(tert-Butyldimethylsilanyloxy)-2-oxopiperidine-1-carboxylate [(+)-(166)]

Prepared as described for (±)-**139**, starting from **164** (2.22 g, 9.68 mmol) and benzyl chloroformate, and affording, after purification by flash chromatography (*n*-hexane-EtOAc, 4:1; R_f 0.21), pure (+)-**166** (1.98 g, 71%) as a white solid.

(+)-166. M.p. 35.6–36.8 °C. $[\alpha]_D^{23}$ +12.4 (*c* 0.80, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm): 7.44-7.41 (m, 2H, Ph), 7.38-7.29 (m, 3 H, Ph), 5.29 (s, 2 H, CH_2Bn), 4.19-4.15 (m, 1 H, 5-H), 3.75 (ddd, *J* = 13.3, 4.7, 1.6 Hz, 1 H, 6-H), 3.68 (dd, *J* = 13.3, 3.7 Hz, 1 H, 6-H'), 2.76 (ddd, *J* = 17.2, 9.4, 6.6 Hz, 1 H, 3-H), 2.46 (ddd, *J* = 17.2, 6.2, 5.7 Hz, 1 H, 3-H'), 2.00-1.92 (m, 1 H, 4-H), 1.90-1.82 (m, 1 H, 4-H'), 0.86 [s, 9 H, $SiC(CH_3)_3$], 0.07 [s, 3 H, $Si(CH_3)_2$], 0.06 [s, 3 H, $Si(CH_3)_2$]. ^{13}C NMR ($CDCl_3$, 100.4 MHz) δ (ppm): 170.7 (s, *C*O), 154.1 (s, N*C*O_2Bn), 135.5 (s, C_{arom}), 128.2 (d, 2 C, C_{arom}), 128.2 (d, 2 C, C_{arom}), 68.5 (s, *C*H_2Ph), 64.2 (s, C-5), 52.9 (s, C-6), 30.9 (s, C-3), 28.9 (s, C-4), 25.6 (s, [(s, 3 C, $SiC(CH_3)_3$]), 18.0 [(s, $SiC(CH_3)_3$], -4.9 [(d, 2 C, $Si(CH_3)_2$]. MS/MS (ESI of $[M + 23]^+$) *m/z* (%): 386 $[M + 23]^+$, 37), 342 (100). $C_{19}H_{29}NO_4Si$ (363.52): calcd C, 62.78; H, 8.04; N, 3.85. Found: C, 62.40; H, 7.67; N, 3.98.



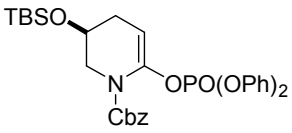
167

(3*S*)-Methyl 6-[(diphenoxyphosphoryl)oxy]-3-(*tert*-butyldimethylsilanyloxy)-3,4-dihydropyridine-1(2*H*)-carboxylate (167)

Prepared as reported for **123**, starting from **165** (1.97 g, 6.85 mmol) and affording, after purification by chromatography (EtOAc-*n*-hexane, 1:3, + 1% Et_3N; R_f 0.55), phosphate **167** (3.52 g, 99%) as a pale yellow oil which was immediately used in the next step.

167. ^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm): 7.37–7.32 (m, 4 H, CH_{arom}), 7.28–7.13 (m, 6 H, CH_{arom}), 5.04 (q, *J* = 3.1 Hz, 1 H, 3-H), 4.04–3.99 (m, 1 H, 5-H), 3.76 (dd, *J* = 12.5, 5.6 Hz, 1 H, 6-H), 3.55 (s, 3 H, OCH_3), 3.40 (dd, *J* = 12.5, 2.1 Hz, 1 H, 6-H'), 2.36 (dq, *J* = 18.1, 4.3 Hz, 1 H, 4-H), 2.06 (dq, J = 18.1, 3.5 Hz, 1 H, 4-H'), 0.86 [s, 9 H, $SiC(CH_3)_3$], 0.06 [s, 3 H, $Si(CH_3)_2$], 0.05 [s, 3 H, $Si(CH_3)_2$]. ^{13}C NMR ($CDCl_3$, 100.4 MHz) δ (ppm): 155.3 (s, CO), 150.5 (s, 2 C, C_{arom}), 139.6 (s, C-2), 129.8 (d, 4 C, C_{arom}), 125.5 (d, 2 C, C_{arom}), 120.1 (d, 4 C, C_{arom}), 98.2 (d, C-3), 64.7 (d, C-5), 53.0 (q, OCH_3), 51.4 (t, C-6), 32.0 (t, C-4), 25.6 [(q, 3 C, $SiC(CH_3)_3$], 18.0

[(s, Si*C*$(CH_3)_3$], –5.00 [(q, 2 C, Si$(CH_3)_2$]. MS/MS (ESI of $[M + 1]^+$) *m/z* (%): 520 ($[M^+ + 1]$, 11), 476 (100), 379 (10), 344 (8).

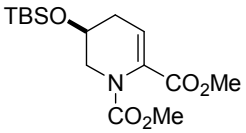


168

(3*S*)-Benzyl 6-[(diphenoxyphosphoryl)oxy]-3-(*tert*-butyldimethylsilanyloxy)-3,4-dihydropyridine-1(2*H*)-carboxylate (168)

Prepared as reported for **123**, starting from **166** (1.97 g, 6.85 mmol) and affording, after purification by chromatography (EtOAc-*n*-hexane, 1:4, + 1% Et_3N; R_f 0.22), phosphate **168** (3.52 g, 99%) as a pale yellow oil which was immediately used in the next step.

168. ^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm): 7.36-7.23 (m, 10 H, Ph), 7.19-7.15 (m, 5 H, Ph), 5.06 (AB system, 2 H, *CH*$_2$Bn), 4.04-3.99 (m, 1 H, 5-H), 3.76 (dd, *J* = 12.7, 6.1 Hz, 1 H, 6-H), 3.44 (dd, *J* = 12.7, 2.1 Hz, 1 H, 6-H'), 2.38 (dq, *J* = 18.2, 4.3 Hz, 1 H, 4-H), 2.07 (dq, *J* = 18.2, 3.9 Hz, 1 H, 4-H'), 0.85 [s, 9 H, SiC$(CH_3)_3$], 0.05 [s, 3 H, Si$(CH_3)_2$], 0.04 [s, 3 H, Si$(CH_3)_2$]. ^{13}C NMR ($CDCl_3$, 100.4 MHz) δ (ppm): 154.6 (s, CO), 150.3 (d, N*C*OBn), 139.5 (d, C-2), 135.8 (s, C_{arom}), 129.7 (s), 128.4 (s), 128.0 (s, 2 C, C_{arom}), 125.2 (d, 2 C, C_{arom}), 120.1 (t, 4-C, C_{arom}), 98.5 (d, C-3), 67.9 (s, *C*H_2Bn), 64.7 (s, C-5), 51.5 (s, C-6), 32.0 (s, C-4), 25.7 [(s, 3 C, SiC(*C*$H_3)_3$], 18.0 [(s, Si*C*$(CH_3)_3$], -5.0 [(s, 2 C, Si$(CH_3)_2$]. MS/MS (ESI of $[M + 1]^+$) *m/z* (%): 596 ($[M^+ + 1]$, 100), 499 (50), 272 (80).



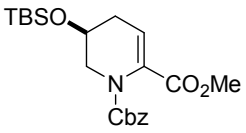
169

(5*S*)-Dimethyl 5-(*tert*-Butyldimethylsilanyloxy)-5,6-dihydropyridine-1,2(4*H*)-dicarboxylate [(+)-169]

Prepared as reported for **124**, starting from phosphate **167** (3.52 g, 6.77 mmol) and affording, after purification by chromatography (EtOAc-*n*-hexane, 1:4; R_f 0.27), pure **169** (1.83 g, 82%) as a thick pale yellow oil.

169. $[\alpha]_D^{19}$ +5.27 (*c* 0.99, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm): 6.06 (t, *J* = 3.9 Hz, 1 H, 3-H), 4.06–4.02 (m, 1 H, 5-H), 3.77 (s, 3 H, OC*H*$_3$), 3.70 (s, 3 H, OC*H*$_3$), 3.59 (dd, *J* = 12.7, 6.2 Hz, 1 H, 6-H), 3.52 (dd, *J* = 12.7, 2.7 Hz, 1 H, 6-H'), 2.44 (ddd, *J* = 19.3, 5.5, 3.7 Hz, 1 H, 4-H), 2.13 (dt, *J* = 19.3, 4.3 Hz, 1 H, 4-H'), 0.86 [s, 9 H, SiC$(CH_3)_3$], 0.07 [s, 6 H, Si$(CH_3)_2$]. ^{13}C NMR

($CDCl_3$, 100.4 MHz) δ (ppm): 164.7 (s, CO), 155.2 (s, NCO), 132.1 (s, C-2), 121.4 (d, C-3), 64.5 (d, C-5), 53.1 (q, OCH_3), 52.1 (q, OCH_3), 49.7 (t, C-6), 33.2 (t, C-4), 25.6 [(q, 3 C, $SiC(CH_3)_3$], 18.0 [(s, $SiC(CH_3)_3$], –5.00 [(q, 2 C, $Si(CH_3)_2$]. MS *m/z* (%): 329 (M^+, 100), 298 (7). $C_{15}H_{27}NO_5Si$ (329.46): calcd C 54.68; H 8.26; N 4.25. Found: C 54.87; H 8.27; N 4.13.

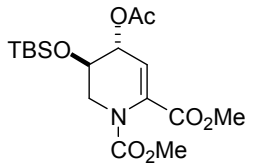


170

(5*S*)-1-Benzyl 2-methyl 5-(*tert*-Butyldimethylsilanyloxy)-5,6-dihydropyridine-1,2(4*H*)-dicarboxylate [(+)-170]

In a round bottom flask was prepared a solution of phosphate **168** (1.68 g, 3.25 mmol), $Pd(OAc)_2$ (73 mg, 0.33 mmol) and Ph_3P (170 mg, 0.65 mmol) in anhydrous DMF (7.7 mL) under nitrogen atmosphere. The flask was flushed and saturated with carbon monoxide and, after 10 min, Et_3N (0.9 mL, 6.5 mmol) and anhydrous CH_3OH (5.9 mL, 146 mmol) were added. The mixture was saturated with CO (balloon) and heated at 60°C (external bath) for 8 h. After cooling, water (80 mL) was added and the product extracted with Et_2O (4 × 50 mL). The combined organic extracted were dried over Na_2SO_4; after filtration and evaporation of the solvent, crude **170** was purified by flash chromatography (eluant: *n*-hexane-EtOAc, 6:1, R_f 0.11), to afford pure **170** as a thick colourless oil (800 mg, 60%) and with spectroscopic data identical to those of the racemic compound.

170: $[\alpha]_D^{21}$ -10.6 (*c* 1.16, $CHCl_3$). ^1H NMR ($CDCl_3$, 400 MHz) δ (ppm): 7.37-7.29 (m, 5 H, Ph), 6.04 (t, *J* = 3.9 Hz, 1 H, 3-H), 5.12 (AB system, 2 H, CH_2Bn), 4.05-4.02 (m, 1 H, 5-H), 3.60 (m, 2 H, 6-H + 6 H'), 3.54 (m, 3 H, OCH_3), 2.45 (ddd, *J* = 19.3, 5.5, 3.7 Hz, 1 H, 4-H), 2.14 (dt, *J* = 19.3, 4.1 Hz, 1 H, 4-H'), 0.86 [s, 9 H, $SiC(CH_3)_3$], 0.06 [s, 6 H, $Si(CH_3)_2$]. ^{13}C NMR ($CDCl_3$, 100.4 MHz) δ (ppm): 164.7 (s, CO), 154.6 (s, NCO), 135.8 (s, C_{arom}), 132.0 (s, C-2), 128.3 (t, 4 C, C_{arom}), 121.5 (s, C-3), 68.0 (s, CH_2Bn), 64.6 (s, C-5), 51.9 (s, C-5), 49.8 (s, C-6), 33.3 (s, C-4), 25.7 [(s, 3 C, $SiC(CH_3)_3$], 18.0 [(s, $SiC(CH_3)_3$], -4.9 [(q, 2 C, $Si(CH_3)_2$]. MS (ESI) *m/z* (%): 428 ([M^+ + 23], 33) 406 ([M^+ + 1], 66).



173

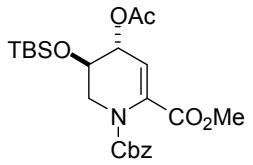
(4*R*,5*R*)-Dimethyl 4-Acetyloxy-5-(*tert*-Butyldimethylsilanyloxy)-5,6-dihydropyridine-1,2(4*H*)-dicarboxylate [(–)-173]

A solution of **169** (906 mg, 2.75 mmol), *N*-bromosuccinimide (622 mg, 3.49 mmol) and a catalytic amount of AIBN (77 mg, 0.47 mmol) in a 9:1 mixture of CCl_4 and $CHCl_3$ (99 mL) was refluxed under vigorous stirring for 1.5 h. After cooling, the mixture was diluted with $CHCl_3$ (80 mL), washed with water (90 mL) and concentrated under *vacuum* to give crude bromide **171** as a yellow oil that was immediately used for the next step without further purification.

(–)-171. ^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm): 6.09 (dd, *J* = 4.3, 1.0 Hz, 1 H, 3-H), 4.33–4.30 (m, 1 H, 4-H), 4.27-4.24 (m, 1 H, 5-H), 4.11(dd, *J* = 12.1, 4.14.7 Hz, 1 H, 6-H), 3.80 (s, 3 H, OC*H*$_3$), 3.70 (s, 3 H, OCH_3), 3.53 (d, *J* = 12.1, Hz, 1 H, 6-H'), 0.83 [s, 9 H, $SiC(CH_3)_3$], 0.08 [s, 6 H, $Si(CH_3)_2$]

Silver acetate (688 g, 4.13 mmol) was added to a solution of **171** (898 mg, 2.20 mmol) in glacial CH_3CO_2H (115 mL) and the resulting mixture stirred at room temperature for 15 min. The suspension was then filtered on a celite pad and the filtrate diluted with Et_2O (300 mL), washed with satd $NaHCO_3$ to neutralization (6 x 150 mL) and dried over anhydrous Na_2SO_4. After filtration and evaporation of the solvent, crude **173** was obtained and purified by flash chromatography (EtOAc-*n*-hexane, 1:4, R_f 0.30), affording pure **173** (1.03 g, 75% over two steps) as a thick pale yellow oil.

(–)-**173**. $[\alpha]_D^{25}$ –149.6 (*c* 1.06, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm): 5.90 (dd, *J* = 4.1, 1.4 Hz, 1 H, 3-H), 4.96–4.94 (m, 1 H, 4-H), 4.08 (dd, *J* = 13.3, 4.5 Hz, 1 H, 6-H), 3.91-3.89 (m, 1 H, 5-H), 3.79 (s, 3 H, OC*H*$_3$), 3.71 (s, 3 H, OC*H*$_3$), 3.19 (dd, *J* = 13.3, 1.4 Hz, 1 H, 6-H'), 2.06 (s, 3 H, CH_3CO), 0.83 [s, 9 H, $SiC(CH_3)_3$], 0.11 [s, 3 H, $Si(CH_3)_2$], 0.07 [s, 3 H, $Si(CH_3)_2$]. ^{13}C NMR ($CDCl_3$, 100.4 MHz) δ (ppm): 169.5 (s, CH_3*C*O), 164.4 (s, CO), 155.0 (s, NCO), 135.1 (s, C-2), 115.4 (d, C-3), 67.9 (d, C-4), 67.3 (d, C-5), 53.3 (q, OCH_3), 52.4 (q, OCH_3), 47.0 (t, C-6), 25.4 [(q, 3 C, $SiC(CH_3)_3$], 20.9 (q, CH_3CO), 17.7 [(s, $SiC(CH_3)_3$], –5.0 [(q, 1 C, $Si(CH_3)_2$], –5.3 [(q, 1 C, $Si(CH_3)_2$]. MS/MS (ESI of $[M + 23]^+$) *m/z* (%): 410 ($[M^+ + 23]$, 12), 350 (8), 328 (83), 296 (41), 292 (100). $C_{17}H_{29}NO_7Si$ (387.50): calcd C 52.69; H 7.54; N 3.61. Found: C 52.83; H 7.87; N 3.43

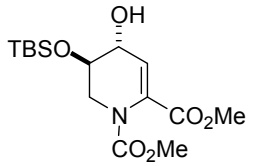


174

(4*R*,5*R*)-1-Benzil 2-Methyl 4-Acetyloxy-5-(*tert*-Butyldimethylsilanyloxy)-5,6-dihydropyridine-1,2(4*H*)-dicarboxylate [(+)-174]

Prepared as reported for (-)-**173**, starting from **170** (262 mg, 0.65 mmol) and affording, after purification by chromatography (EtOAc-*n*-hexane, 1:10; R_f 0.27), pure **174** (1.83 g, 82%) as a thick pale yellow oil.

(+)-174. $[\alpha]_D^{23}$ +103.7 (*c* 0.82, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm): 7.37-7.28 (m, 5 H, Ph), 5.87 (dd, *J* = 4.1, 1.4, 1 H, 3-H), 5.13 (AB system, 2 H, *CH*$_2$Bn), 4.97-4.95 (m, 1 H, 4-H), 4.12-4.09 (m, 1 H, 6-H_{eq}), 3.93-3.90 (m, 1 H, 5-H), 3.53 (br s, 3 H, CO_2*CH*$_3$), 3.21 (d, *J* = 13.3, 1 H, 6-H_{ax}), 2.06 (s, 3 H, O*CH*$_3$), 0.83 [s, 9 H, $SiC(CH_3)_3$], 0.10 [s, 3 H, $Si(CH_3)_2$], 0.06 [s, 3 H, $Si(CH_3)_2$]. ^{13}C NMR ($CDCl_3$, 100.4 MHz) δ (ppm): 169.5 (s, CH_3*C*O), 164.5 (s, CO), 154.4 (s, NCO), 135.3 (s, C_{arom}), 135.1 (s, C-2), 128.4 (d, 4 C, C_{arom}), 115.4 (s, C-3), 68.4 (s, *C*H_2Bn), 68.1 (s, C-4), 67.4 (s, C-5), 52.2 (OCH_3), 47.1 (s, C-6), 25.5 [(s, 3 C, $SiC(CH_3)_3$], 21.0 (s, *C*H_3CO), 17.8 [(s, $SiC(CH_3)_3$], -5.0 [(s, 1 C, $Si(CH_3)_2$], -5.2 [(s, 1 C, $Si(CH_3)_2$]. MS/MS (ESI of $[M + 23]^+$) *m/z* (%): 486 ($[M^+ + 23]$, 50), 360 (100), 29 (53).



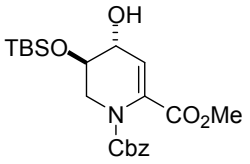
175

(4*R*,5*R*)-Dimethyl 5-(*tert*-Butyldimethylsilanyloxy)-4-hydroxy-5,6-dihydropyridine-1,2(4*H*)-dicarboxylate [(–)-175]

A solution of **173** (1.03 g, 2.66 mmol) in anhydrous MeOH (29 mL) was cooled at 0 °C and MeONa (144 mg, 2.66 mmol) was rapidly added. The mixture was stirred at 0 °C for 1 h, acidified by addition of glacial acetic acid (380 μL, 6.65 mmol) and the solvent removed under *vacuum* without heating. The residue was diluted with water (260 mL) and the product extracted with Et_2O (5 × 110 mL); the combined organic extracts were dried over Na_2SO_4. After filtration and evaporation of the solvent, crude **175** was obtained and purified by chromatography (EtOAc-*n*-hexane, 1:2; R_f 0.20) to give pure **175** (670 mg, 73%) as a thick colourless oil.

175. $[\alpha]_D^{21}$ –111.4 (*c* 1.13, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm): 5.96 (dd, *J* = 3.9, 1.2 Hz, 1 H, 3-H), 3.99 (dd, *J* = 12.9, 4.5 Hz, 1 H, 6-H_{eq}), 3.92–3.89 (m, 1 H, 4-H), 3.88–3.86 (m, 1

H, 5-H), 3.79 (s, 3 H, OCH_3), 3.70 (s, 3 H, OCH_3), 3.24 (dd, J = 12.9, 1.4 Hz, 1 H, 6-H'), 0.84 [s, 9 H, SiC$(CH_3)_3$], 0.09 [s, 3 H, Si$(CH_3)_2$], 0.07 [s, 3 H, Si$(CH_3)_2$]. ^{13}C NMR ($CDCl_3$, 100.4 MHz) δ (ppm): 164.8 (s, CO), 155.1 (s, NCO), 133.5 (s, C-2), 119.2 (d, C-3), 69.9 (d, C-4), 67.1 (d, C-5), 53.2 (q, OCH_3), 52.4 (q, OCH_3), 46.4 (t, C-6), 25.5 [(q, 3 C, SiC($CH_3)_3$], 17.9 [(s, Si$C(CH_3)_3$], –5.0 [(q, 1 C, Si$(CH_3)_2$], –5.1 [(q, 1 C, Si$(CH_3)_2$]. MS/MS (ESI of $[M + 1]^+$) *m/z* (%): 346 ($[M^+ + 1]$, 21), 328 (47), 314 (100), 296 (17). $C_{15}H_{27}NO_6Si$ (345.46): calcd C 52.15; H 7.88; N 4.05. Found: C 52.08; H 8.05; N 3.95

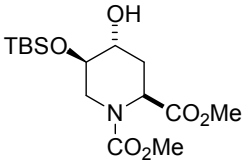


176

(4*R*,5*R*)-1-Benzil 2-Methyl 5-(*tert*-Butyldimethylsilanyloxy)-4-hydroxy-5,6-dihydropyridine-1,2(4*H*)-dicarboxylate [(–)-176]

Prepared as reported for **175**, starting from **174** (262 mg, 0.65 mmol) and affording, after purification by chromatography (EtOAc-*n*-hexane, 1:10; R_f 0.27), pure **176** (1.83 g, 82%) as a thick pale yellow oil

176. $[\alpha]_D^{20}$ -110.1 (*c* 1.15, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm): 7.37-7.29 (m, 5 H, Ph), 5.93 (dd, J = 3.7, 1.2, 1H, 3-H), 5.12 (AB system, 2 H, CH_2Bn), 4.02 (dd, J = 12.7, 9.2, 1 H, 6-H_{eq}) 3.91-3.89 (m, 2 H, 4-H + 5-H), 3.53 (br s, 3 H, OCH_3), 3.27 (d, J = 12.9, 1 H, 6-H_{ax}), 0.84 [s, 9 H, SiC$(CH_3)_3$], 0.08 [s, 3 H, Si$(CH_3)_2$], 0.06 [s, 3 H, Si$(CH_3)_2$]. ^{13}C NMR ($CDCl_3$, 100.4 MHz) δ (ppm): 164.8 (s, CO), 154.4 (s, NCO), 135.4 (s, C_{arom}), 133.5 (s, C-2), 128.4 (t, 4 C, C_{arom}), 119.2 (s, C-3), 69.9 (s, CH_2Bn), 68.3 (s, C-4), 67.3 (s, C-5), 52.2 (s, OCH_3), 46.5 (s, C-6), 25.6 [(s, 3 C, SiC($CH_3)_3$], 17.9 [(s, Si$C(CH_3)_3$], -5.0 [(s, 2 C, Si$(CH_3)_2$]. MS (ESI) *m/z* (%): 444 $[M + 23]^+$, 32), 421 ($[M]^+$, 10), 378 (5).



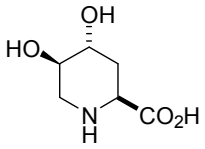
178

(2*S*,4*R*,5*R*)-Dimethyl 5-(*tert*-Butyldimethylsilyloxy)-4-hydroxypiperidine-1,2-dicarboxylate [(–)-178]

Prepared as reported for (–)-**160**, starting from **175** (650 mg, 1.88 mmol) and leaving the mixture under stirring and hydrogen atmosphere for 24 h. After filtration on a celite pad and removal of

the solvent under *vacuum*, a crude 3:1 mixture of **178** and **177** was obtained. The major diastereoisomer **178** (346 mg, 53%) was obtained in pure form by flash chromatography (eluent: *n*-hexane-Et_2O, 2:3; R_f 0.25), as a thick colourless oil. The fraction containing the mixture of both isomers **178** and **177** was further chromatographed to give another amount of pure **178** (117 mg; overall yield 71%).

178. $[\alpha]_D^{25}$ –39.6 (*c* 0.95, MeOH). ^{1}H NMR (400 MHz) (1.1:1 mixture of rotamers) δ (ppm): 5.01 (d, *J* = 6.2 Hz, 1 H, 2-H, major), 4.85 (d, *J* = 6.2 Hz, 1 H, 2-H, minor), 4.21 (dd, *J* = 13.0, 3.9 Hz, 1 H, 6-H_{eq}, minor), 4.03 (dd, *J* = 13.8, 3.5 Hz, 1 H, 6-H_{eq}, major), 3.75 and 3.70 (s, 6 H, CO_2CH_3 and NCO_2CH_3, both rotamers), 3.41–3.35 (m, 2 H, 4-H and 5-H), 2.85 (dd, *J* = 13.8, 10.1 Hz, 1 H, 6-H_{ax}, major), 2.77 (dd, *J* = 13.0, 10.1 Hz, 1 H, 6-H_{ax}, minor), 2.53–2.47 (m, 1 H, 3-H_{eq}), 2.33 (dd, *J* = 14.6, 1.2 Hz, 1 H, OH), 1.74–1.66 (m, 1 H, 3-H_{ax}), 0.90 [s, 9 H, $SiC(CH_3)_3$], 0.12 [s, 6 H, $Si(CH_3)_2$]. ^{13}C NMR (100.4 MHz) δ (ppm): ^{13}C NMR (100.4 MHz) (mixture of rotamers) δ (ppm): 171.2 and 171.1 (s, CO_2Me), 156.4 and 155.9 (s, NCO_2Me), 73.2 and 73.1 (d, C-4), 71.4 (d, C-5), 53.9 and 53.7 (d, C-2), 53.2 and 53.1 (q, OCH_3), 52.6 and 52.5 (q, OCH_3), 46.2 and 46.1 (t, C-6), 32.0 and 31.7 (t, C-3), 25.7 [(q, 3 C, $SiC(CH_3)_3$], 18.0 [(s, $SiC(CH_3)_3$], –4.5 [(q, 1 C, $Si(CH_3)_2$], –4.7 [(q, 1 C, $Si(CH_3)_2$]. MS/MS (ESI of $[M + 1]^+$) *m/z* (%): 348 ($[M^+ + 1]$, 27), 316 (100), 288 (72). $C_{15}H_{29}NO_6Si$ (347.48): calcd C, 51.85; H, 8.41; N, 4.03. Found: C, 51.51; H, 8.60; N, 4.35.

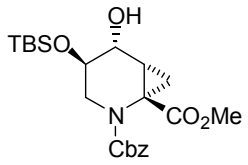


9 HCl

(2*S*,4*R*,5*R*)-4,5-Dihydroxypipecolic Acid [(–)-9·HCl]

Prepared as reported for (–)-**10**, starting from **178** (410 mg, 1.18 mmol) and obtaining pure (–)-**9** as hydrochloride (233 mg, quantitative).

(–)-9. M.p. 252 °C (dec.); $[\alpha]_D^{21}$ –18.2 (*c* 0.57, 2N HCl); ^{1}H NMR (400 MHz, D_2O) δ (ppm): 4.17 (dd, *J* = 11.5, 4.1 Hz, 1 H, 2-H), 4.06–4.01 (br m, 1 H, 4-H), 3.97–3.92 (br m, 1 H, 5-H), 3.43 (dd, *J* = 13.5, 2.0 Hz, 1 H, 6-H_{eq}), 3.30 (dd, *J* = 13.5, 3.5 Hz, 1 H, 6-H_{ax}), 2.32–2.17 (m, 2 H, 3-H). ^{13}C NMR (100.4 MHz, D_2O) δ (ppm): 174.2 (s, CO), 67.4 (d, C-4), 67.1 (d, C-5), 54.8 (d, C-2), 47.0 (t, C-6), 30.3 (t, C-3). MS/MS (ESI of $[M + 1]^+$) *m/z* (%): 162 ($[M^+ + 1]$, 7), 144 (16), 126 (5), 116 (100), 98 (19). $C_6H_{13}NO_4Cl$ (197.62): calcd C, 36.47; H, 6.63; N, 7.12. Found: C, 36.26; H, 6.85; N, 7.00.



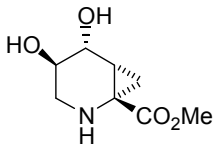
cis-**179**

2-Benzyl 1-Methyl (1*S*,4*R*,5*R*,6*R*)-4-(*tert*-Butyldimethylsilanyloxy)-5-hydroxy-2-azabicyclo[4.1.0]heptane-1,2-dicarboxylate [(–)-179]

To a solution of 2,4,6-trichlorophenol (33 mg, 0.167 mmol) in anhydrous CH_2Cl_2 (1.9 mL), cooled to –40 °C, was added Et_2Zn (167 μL of a 1 M solution in hexane, 0.167 mmol) under nitrogen atmosphere. The mixture was left under stirring for 15 min, then CH_2I_2 (101 μL, 1.26 mmol) was added dropwise and, after another 15 min at –40 °C, a solution of alcohol **176** (35 mg, 0.083 mmol) in CH_2Cl_2 (300 μL) was added dropwise. The cooling bath was removed and reaction mixture was left under stirring for 22 h. The suspension was then cooled in a ice bath and a 10% solution of citric acid (3 mL) was added dropwise under vigorous stirring. The cooling bath was removed and when the solution became clear, the layers were separated, the aqueous layer extracted with CH_2Cl_2 (4 × 3 mL) and the combined organic layers washed with a 10% solution of Na_2CO_3 (2 × 3 mL) and dried over Na_2SO_4. After filtration and evaporation of the solvent, crude *cis*-**179** was obtained and purified by chromatography (*n*-exane-EtOAc 5:2, R_f 0.18), to give compound *cis*-**179** (23 mg, 95%) as a colorless oil.

179. $[\alpha]_D^{24}$ –27.3 (*c* 0.88, $CHCl_3$); ^{1}H NMR (400 MHz, 1.7:1 mixture of rotamers) δ (ppm): 7.36-7.29 (m, 5 H, Ph), 5.29 (part A of an AB system, *J* = 12.5, 1 H, C*H*$_2$Bn, major), 5.21 (part A of an AB system, *J* = 12.3, 1 H, *CH*$_2$Bn, minor), 5.11 (part B of an AB system, *J* = 12.5, 1 H, *CH*$_2$Bn, minor), 5.04 (part B of an AB system, *J* = 12.5, 1 H, C*H*$_2$Bn, major), 4.07-4.04 (m, 1 H, 5-H both rotamers), 3.96 (dd, *J* =12.3, 4.0, 1 H, 3-H, major), 3.82 (dd, *J* = 12.3, 4.1, 1 H, 3-H, minor rotamer), 3.70 (s, 3 H, OCH_3, minor), 3.51 (s, 3 H, OCH_3, major), 3.39-3.33 (m, 1 H, 4-H, major) 3.32-3.26 (m, 1 H, 4-H, minor), 2.75 (dd, *J* = 12.9, 9.8, 1 H, 3-H', minor), 2.72 (dd, *J* = 12.9, 9.8, 1 H, 3-H', major), 2.10-2.01 (m, 2 H, 6-H + OH), 1.95 (dd, *J* = 10.1, 5.5, 1 H, 7-H_{exo}, minor), 1.89 (dd, *J* = 10.1, 5.5, 1 H, 7-H_{exo}, major), 1.12-1.08 (m, 1 H, 7-H_{endo}, both rotamers), 0.88 [s, 9 H, $SiC(CH_3)_3$, major], 0.84 [s, 9 H, $SiC(CH_3)_3$ minor], 0.11 [s, 3 H, $Si(CH_3)_2$, major], 0.10 [s, 3 H, $Si(CH_3)_2$, major], 0.03 [s, 3 H, $Si(CH_3)_2$, minor], -0.01 [s, 3 H, $Si(CH_3)_2$ minor]. ^{13}C NMR (100.4 MHz, $CHCl_3$) (mixture of rotamers) δ (ppm): 171.9 and 171.3 (s, CO), 156.0 and 155.5 (s, NCO), 136.4 and 136.1 (s, 1 H, C_{arom}), 128.4 and 128.2 (t, 2 C, C_{arom}), 72.1 and 71.9 (s, *C*H_2Bn), 70.1 and 70.9 (s, C-5), 67.6 and 67.4 (s, C-4), 52.6 and 52.4 (s, OCH_3), 47.5 and 47.0 (s, C-1), 41.8 and 41.0 (s, C-3), 29.1 and 28.7 (s, C-6), 25.6 [(d, 3 C, $SiC(CH_3)_3$], 21.2 and 20.8 (s, C-7), 17.9 [(s, $SiC(CH_3)_3$], -4.6 and -4.7 and -4.8 [(s, 2 C, $Si(CH_3)_2$].

MS (ESI) *m/z* (%): 436 ([M^+ + 1], 100)



cis-**112**

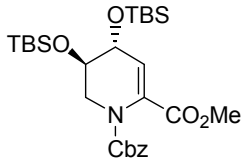
1-Methyl (1*S*,4*R*,5*R*,6*R*)-4,5-Dihydroxy-2-azabicyclo[4.1.0]heptane-1-carboxylate (*cis*-112)

Compound *cis* **179** (26 mg, 0.06 mmol) was dissolved in acetonitrile (2.7 mL) and, after cooling at 0 °C, a 3 N solution of HCl (2.7 mL) was added dropwise. The cooling bath was removed and the mixture left under stirring 1 h. A satd solution of $NaHCO_3$ (20 mL) was slowly added until pH 7, the aqueous layer extracted with EtOAc (6 × 20 mL) and the combined organic layers dried over Na_2SO_4, filtered and concentrated. Chromatography (Et_2O, R_f 0.23) gave diol **180** (14 mg, 73%) as a colorless oil.

180. ^{1}H NMR (400 MHz, mixture of rotamers) δ (ppm): 7.36-7.28 (m, 5 H, Ph), 5.25 (part A of an AB system, *J* = 12.6 Hz, 1 H, C*H*$_2$Bn, major), 5.19 (part A of an AB system, *J* = 12.3 Hz, 1 H, C*H*$_2$Bn, minor), 5.12 (part B of an AB system, *J* = 12.3 Hz, 1 H, C*H*$_2$Bn, minor), 5.04 (part B of an AB system, *J* = 12.6 Hz, 1 H, C*H*$_2$Bn, major), 4.07-3.95 (br, 2 H, 5-H + 3-H, both rotamers), 3.70 (s, 3 H, OCH_3, minor), 3.53 (s, 3 H, OCH_3, major), 3.33-3.29 (m, 1 H, 4-H, both rotamers), 2.83-2.66 (m, 1 H, 3-H', both rotamers), 2.11-2.02 (m, 1 H, 6-H), 1.98-1.87 (m, 1 H, 7-H_{exo}, both rotamers), 1.10-1.06 (m, 1 H, 7-H_{endo}, both rotamers).

To a solution of alcohol **180** (14 mg, 0.04 mmol) in ethyl acetate (1.5 mL) was added, under nitrogen atmosphere, 10% Pd/C (7 mg) and the resulting suspension stirred under an H_2 atmosphere (balloon) at room temperature for 4.5 h. After filtration over a Celite layer and evaporation of the solvent, pure *cis* (+)-**112** (118 mg) was obtained in quantitative yield as a colorless oil

***cis*-112.** $[\alpha]_D^{21}$ –60.1 (*c* 0.96, $CHCl_3$); ^{1}H NMR (400 MHz) δ (ppm): 4.02-3.99 (br, 1 H, 3-H), 3.72 (s, 3 H, OCH_3), 3.68-3.38 (br, 1 H, 3-H'), 3.08-2.85 (br, 3 H, OH, NH), 2.56-2.50 (m, 1 H, 5-H), 2.18-2.11 (m, 1 H, 7-H), 1.57 (dd, *J* = 10.2, 4.9 Hz, 1 H, 7-H), 1.13-1.10 (m, 1 H, 7-H'). ^{13}C NMR (100.4 MHz, $CHCl_3$) δ (ppm): 174.2 (s, CO), 71.7 (s, C-4), 71.0 (s, C-5), 48.0 (s, OCH_3), 42.9 (s, C-1), 29.7 (s, C-3) 28.3 (s, C-6), 22.7 (s, C-7). MS (ESI) *m/z* (%): 188 ([M^+ + 1], 100)



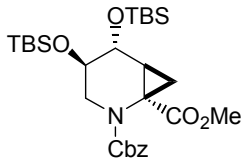
181

(4*R*,5*R*)-2-Benzyl 1-Methyl 4,5-Bis-(*tert*butyldimethylsilanoxy)-5,6-dihydropyridine 1,2(*4H*)-dicarboxylate (181)

To a stirred solution of **176** (55 mg, 0.13 mmol) in anhydrous DMF (0.6 mL) were added imidazole (27 mg, 0.39 mmol) and TBSCl (39 mg, 0.26 mmol) and it was stirred 2.5 h at 38 °C (external bath) under N_2 atmosphere. After cooling to room temperature, water (5 mL) was added and the solution extracted with Et_2O (5 × 6 mL). The combined organic layers dried over Na_2SO_4. After filtration and evaporation of the solvent, the crude **181** was chromatographed (EtOAc-*n*-hexane, 1:8, R_f 0.41) to give **181** (72 mg, 99%) as a white solid.

181. M.p. 96.0-97.1°C; $[\alpha]_D^{21}$ –146.3 (*c* 1,12 $CHCl_3$); ^{1}H NMR (400 MHz, $CHCl_3$) δ (ppm): 7.36-7.28 (m, 5 H, Ph) 5.82 (dd, *J* = 4.1, 1.4 Hz, 1 H, 3-H), 5.14-5.04 (m, 2 H, CH_2Ph), 4.14-4.12 (m, 1 H, 6-H_{eq}), 3.80-3.79 (m, 2 H, 4-H + 5-H), 3.50 (br s, 3 H, OCH_3), 3.15 (d, *J* = 13.1 Hz, 1 H, 6-H_{ax}), 0.87 [s, 9 H, $SiC(CH_3)_3$], 0.83 [s, 9 H, $SiC(CH_3)_3$], 0.10 [s, 3 H, $Si(CH_3)_2$], 0.09 [s, 3 H, $Si(CH_3)_2$], 0.06 [s, 3 H, $Si(CH_3)_2$], 0.04 [s, 3 H, $Si(CH_3)_2$]. ^{13}C NMR (100.4 MHz, $CHCl_3$) δ (ppm): 164.8 (s, CO), 154.4 (s, NCO), 135.2 (s, C_{arom}), 132.1 (s, C-2), 128.4 (t, 4 C, C_{arom}), 120.4 (s, C-3), 70.0 (s, CH_2Bn), 67.8 (s, C-4), 66.5 (s, C-5), 51.9 (s, OCH_3), 45.7 (s, C-6), 25.5 [(s, 3 C, $SiC(CH_3)_3$], 25.3 [(s, 3 C, $SiC(CH_3)_3$], 17.7 [(s, $SiC(CH_3)_3$], 17.6 [(s, $SiC(CH_3)_3$] -4.7 [(s, 1 C, $Si(CH_3)_2$], -4.9 [(s, 1 C, $Si(CH_3)_2$], -5.1 [(s, 1 C, $Si(CH_3)_2$], -5.2 [(s, 1 C, $Si(CH_3)_2$]. MS/MS (ESI of [M^+ + 23]) *m/z* (%): 360 (100), 228 (89).

$C_{27}H_{45}NO_6Si_2$ (535.82) calcd C, 60.52; H, 8.47; N, 2.61. Found C, 60.31; H, 8.32, N, 3.00



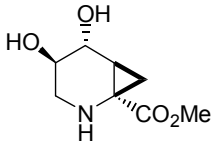
182 (dr 6 : 1)

2-Benzyl 1-Methyl (1*R*,4*R*,5*R*,6*S*)-4,5-Bis-(*tert*-Butyldimethylsilanyloxy)-2-azabicyclo[4.1.0]heptane-1,2-dicarboxylate [(–)-182]

Cyclopropanation by dimethylsulfoxonium methylide of 181. Dry DMSO (0.7 mL) was added to NaH (60% in weight in mineral oil, 8 mg, 0.19 mmol) previously washed with dry *n*-hexane (2 × 1 mL) under nitrogen atmosphere. To the resulting suspension was added trimethylsulfoxonium iodide (38 mg, 0.17 mmol) in three portions and the mixture was left 40

min under stirring at room temperature. After cooling with a water bath at 15 °C, a solution of **181** (62 mg, 0.12 mmol) in DMSO-DMF 1:1 (400 μL) was added dropwise. The water bath was removed and the reaction mixture was left under stirring for 4 h. Water (6 mL) was added and the mixture extracted with Et_2O (7 × 5 mL), dried over Na_2SO_4, filtered and concentrated. Chromatography (EtOAc-*n*-hexane, 1:10, R_f 0.10) gave compound **183** (43 mg, 82%) as a 6:1 mixture of *trans* and *cis* isomers.

183. ^{1}H NMR ($CDCl_3$, 400 MHz, *trans* isomer, 1.7:1 mixture of rotamers) δ (ppm): 7.37-7.27 (m, 5 H, Ph), 5.28 (part A of an AB system, J = 12.5 Hz, 1 H, CH_2Ph, minor rotamer), 5.23 (part A of an AB system, J = 12.7 Hz, 1 H, CH_2Ph, major rotamer), 5.05 (part B of an AB system, J = 12.5 Hz, 1 H, CH_2Ph, major rotamer), 4.98 (part B of an AB system, J = 12.3, 1 H, CH_2Ph, minor rotamer) 3.92 (s + dd, 13.1, 3.1 Hz, 2 H, 5-H, both rotamers + 3-H, major), 3.71 (s, 3 H, OCH_3, minor), 3.56 (s, 3 H, OCH_3, major), 3.22 (d, J = 13.1 Hz, 1 H, 3-H', minor), 3.10 (d, J = 13.1 Hz, 1 H, 3-H', major), 1.81 (dd, J = 10.5, 4.5 Hz, 1 H, 7-H_{exo}, minor), 1.72 (dd, J = 10.7, 4.3, 1 H, 7-H_{exo}, major), 1.42-1.37 (m, 1 H, 7-H_{endo}, both rotamers), 0.88 [s, 9 H, $SiC(CH_3)_3$, major], 0.87 [s, 9 H, $SiC(CH_3)_3$, minor], 0.81 [s, 9 H, $SiC(CH_3)_3$, major], 0.79 [s, 9 H, $SiC(CH_3)_3$, minor], 0.10 [s, 3 H, $Si(CH_3)_2$ major], 0.08 [s, 3 H, $Si(CH_3)_2$, both rotamers], 0.07 [s, 3 H, $Si(CH_3)_2$, major], 0.05 [s, 3 H, $Si(CH_3)_2$, major], 0.04 [s, 3 H, $Si(CH_3)_2$, major], 0.01 [s, 3 H, $Si(CH_3)_2$, minor], -0.08 [s, 3 H, $Si(CH_3)_2$, monor].



ent-**116** (dr 6 : 1)

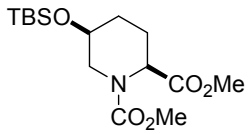
1-Methyl (1*R*,4*R*,5*R*,6S)-4,5-Dihydroxy-2-azabicyclo[4.1.0]heptane-1-carboxylate

The mixture of *trans* and *cis* **182** (79 mg, 0.22 mmol) was treated as reported for **180**, affording, after chromatography (EtOAc, R_f 0.27), diol **183** as a 6 : 1 mixture with the *cis* isomer (10 mg, 44%) as a white solid.

183. ^{1}H NMR (200 MHz, $CDCl_3$) (*trans* isomer, mixture or rotamers δ (ppm) : 7.36-7.28 (m, 5 H, Ph), 5.12 (AB system, 2 H, CH_2Bn) 3.94-3.70 (m, 2 H, 5-H + 3-H), 3.70 (s, 3 H, OCH_3, minor), 3.53 (s, 3 H, OCH_3, major), 3.34-3.28 (m, 1 H, 3-H', both rotamers), 2.33 (br s, 2 H, OH), 1.94 (dd, J = 10.4, 4.9 Hz, 1 H, 7-H, minor), 1.85 (dd, J = 10.4, 4.7 Hz, 1 H, 7-H, major), 1.79-1.70 (m, 1 H, 6-H', both rotamers), 1.30-1.23 (m, 1 H, 7-H', both rotamers).

Diol **183** was treated as reported for *cis*-**112**, affording pure *ent*-**116** in 83% yield (6:1 ratio with the *cis* isomer) as a pale yellow oil.

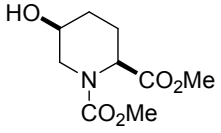
***ent*-116**.^{1}H NMR (400 MHz, $CDCl_3$) (*trans* isomer) δ (ppm): 4.02-4.01 (br, 1 H, 5-H), 3.72 (s, 3 H, OCH_3), 3.62-3.60 (br, 1 H, 3-H), 3.03 (dd, *J* = 12.7, 2.3 Hz, 1 H, 4-H), 2.67 (dd, *J* = 12.7, 4.9 Hz, 1 H, 3-H'), 2.43-2.42 (br, 3 H, NH, OH), 1.62-1.67 (m, 1 H, 6-H), 1.53 (dd, *J* = 10.7, 4.7 Hz, 1 H, 7-H').



184

(2*S*,5*S*)-Dimethyl 5-(*tert*-Butyldimethylsilanyloxy)piperidine-1,2-dicarboxylate [(–)-184].
Prepared as reported for (–)-**160**, starting from **169** (920 mg, 2.79 mmol) and leaving the mixture under stirring and hydrogen atmosphere for 21 h. After filtration on a celite pad and removal of the solvent under *vacuum*, the so obtained crude **184** was purified by flash chromatography (eluent: *n*-hexane-EtOAc, 6:1; R_f 0.24), affording pure **184** (878 mg, 95%) as a colourless oil, in mixture with a small amount of the *trans* diastereoisomer.

184. $[\alpha]_D^{30}$ –24.5 (*c* 0.74, MeOH) {*lit.*[92g] $[\alpha]_D^{20}$ –15.4 (*c* 1.0, MeOH)} ^{1}H NMR (400 MHz) (1.3:1 mixture of rotamers, dr 8:1) δ (ppm): 4.88 (d, *J* = 4.4 Hz, 1 H, 2-H, major), 4.72 (d, *J* = 5.1 Hz, 1 H, 2-H, minor), 4.17 (dd, *J* = 12.9, 4.9 Hz, 1 H, 6-H_{eq}, minor), 3.99 (dd, *J* = 12.9, 4.9 Hz, 1 H, 6-H_{eq}, major), 3.74 and 3.70 (s, 6 H, CO_2CH_3 and NCO_2CH_3, both rotamers), 3.60–3.51 (m, 1 H, 5-H), 2.75 (dd, *J* = 12.9, 10.5 Hz, 1 H, 6-H_{ax}, major), 2.67 (dd, *J* = 12.9, 10.5 Hz, 1 H, 6-H_{ax}, minor), 2.31–2.23 (m, 1 H, 3-H_{eq}), 1.88–1.81 (m, 1 H, 4-H_{eq}), 1.74–1.62 (m, 1 H, 3-H_{ax}), 1.31–1.19 (m, 1 H, 4-H_{ax}), 0.87 [s, 9 H, $SiC(CH_3)_3$], 0.07 [s, 3 H, $Si(CH_3)_2$], 0.06 [s, 3 H, $Si(CH_3)_2$] ppm. ^{13}C NMR (100.4 MHz) δ (ppm): ^{13}C NMR (100.4 MHz) (mixture of rotamers) δ (ppm): 171.6 (s, CO_2Me), 156.7 and 156.2 (s, NCO_2Me), 67.4.2 and 67.2 (d, C-5), 53.7 and 53.4 (d, C-2), 53.1 (q, OCH_3), 52.4 and 52.3 (q, OCH_3), 48.5 and 48.3 (t, C-6), 31.1 and 31.0 (t, C-3), 25.8 [(q, 3 C, $SiC(CH_3)_3$], 25.4 and 25.0 (C-4), 18.1 [(s, $SiC(CH_3)_3$], –4.7 [(q, 2 C, $Si(CH_3)_2$]. MS (ESI) *m/z* (%): 332 ([M^+ + 1], 100). $C_{15}H_{29}NO_5Si$ (331.48): calcd C, 54.35; H, 8.82; N, 4.23. Found: C, 54.19; H, 9.02; N, 3.99.

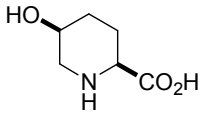


185

(2*S*,5*S*)-Dimethyl 5-Hydroxypiperidine-1,2-dicarboxylate [(–)-185].
A solution of compound **169** (878 mg, 2.65 mmol) in acetonitrile (80 mL) was cooled at 0 °C and aqueous 3 N HCl was dropwise added (80 mL). After 10 min the ice bath was removed and

the mixture was left under stirring at room temperature for 2 h. Satd $NaHCO_3$ solution was then slowly added until complete neutralization and the product extracted with EtOAc (5 x 160 mL). The combined organic extracts were dried over anhydrous Na_2SO_4. After filtration and evaporation of the solvent, crude **185** was obtained and purified by flash chromatography (eluent: *n*-hexane-EtOAc, 2:3; R_f 0.35), affording pure compound **185** as a single diasteroisomer (448 mg, 78%). Colourless oil.

185. $[\alpha]_D^{24}$ –40.3 (*c* 0.42, MeOH) {*lit.*[92g] $[\alpha]_D^{20}$ –24.1 (*c* 1.0, MeOH)}. ^{1}H NMR (400 MHz) (1.3:1 mixture of rotamers) δ (ppm): 4.88 (d, *J* = 5.5 Hz, 1 H, 2-H, major), 4.73 (d, *J* = 4.9 Hz, 1 H, 2-H, minor), 4.27 (br d, *J* = 12.3 Hz, 1 H, 6-H_{eq}, minor), 4.13 (br d, *J* = 12.5 Hz, 1 H, 6-H_{eq}, major), 3.74 (s, 3 H, CO_2CH_3), 3.73 and 3.69 (s, 3 H, NCO_2CH_3), 3.67–3.59 (m, 1 H, 5-H), 2.20 (br t, *J* = 11.9, 1 H, 6-H_{ax}, major), 2.71 (br t, *J* = 11.7, 1 H, 6-H_{ax}, minor), 2.29 (br d, *J* = 14.1 Hz, 1 H, 3-H_{eq}), 2.01–1.93 (m, 2 H, OH and 4-H_{eq}), 1.77–1.68 (m, 1 H, 3-H_{ax}), 1.28–1.18 (m, 1 H, 4-H_{ax})

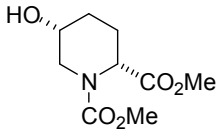


6 HCl

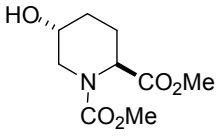
(2*S*,5*S*)-5-Hydroxypipecolic Acid [(–)-6·HCl]

Prepared as reported for (–)-**10**, starting from (–)-**185** (100 mg, 0.46 mmol) and obtaining pure (–)-**6** as hydrochloride (83 mg, 99%).

(–)-6. $[\alpha]_D^{23}$ –20.8 (*c* 1.6, H_2O) {*lit.*[92g] $[\alpha]_D^{20}$ –21.9 (*c* 1.0, H_2O)}. ^{1}H NMR (400 MHz, D_2O) δ (ppm): 4.22 (br s, 1 H, 5-H_{eq}), 4.02 (dd, *J* = 11.7, 3.7 Hz, 1 H, 2-H_{ax}), 3.38 (dt, *J* = 13.5, 1.9 Hz, 1 H, 6-H_{eq}), 3.25 (dd, *J* = 13.5, 1.6 Hz, 1 H, 6-H_{ax}), 2.22-1.83 (m, 4 H, 3-H and 4-H)



ent-**185**



187

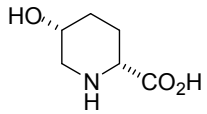
(2*R*,5*R*)-Dimethyl 5-Hydroxypiperidine-1,2-dicarboxylate [(+)-*ent*-185] and (2*S*,5*R*)-Dimethyl 5-Hydroxypiperidine-1,2-dicarboxylate [(–)-187]

Reduction of *ent*-**169** (520 mg, 1.58 mmol) was performed as reported for 169 affording, after chromatographic purification, a 1.5:1 mixture of *ent*-**184** and **186** (392 mg, 75%).

Removal of the *O*-silyl group was performed on the mixture as reported above for (–)-**185**, affording, after chromatographic separation, pure *ent*-**185** (138 mg, 54%) and (–)-**187** (74 mg, 29%), both as colourless oil.

***Ent*-185**. $[\alpha]_D^{23}$ +39.1 (*c* 0.91, MeOH).

187. R_f 0.21. $[\alpha]_D^{24}$ –49.1 (*c* 0.58, MeOH). ^{1}H NMR (400 MHz) (1.2:1 mixture of rotamers) δ (ppm): 4.98 (br d, *J* = 4.7 Hz, 1 H, 2-H, major), 4.85 (br s, 1 H, 2-H, minor), 4.15 (br d, *J* = 14.4 Hz, 1 H, 6-H_{eq}, minor), 4.03 (br, 1 H, 5-H_{eq}), 3.98 (br d, *J* = 13.7 Hz, 1 H, 6-H_{eq}, major), 3.74 (s, 3 H, CO_2CH_3), 3.73 and 3.71 (s, 3 H, NCO_2CH_3), 3.26 (br d, *J* = 13.7, 1 H, 6-H_{ax}, major), 3.17 (br d, *J* = 14.4, 1 H, 6-H_{ax}, minor), 2.25–2.12 (m, 1 H, 3-H), 2.10–1.95 (m, 1 H, 4-H), 1.85–1.63 (m, 2 H, OH and 4-H'), 1.58–1.45 (m, 1 H, 3-H').

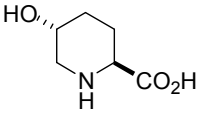


ent-**6**·HCl (100%)

(2*R*,5*R*)-5-Hydroxypipecolic Acid [(+)-*ent*-6·HCl]

Prepared as reported for (–)-**10**, starting from *ent*-**185** (138 mg, 0.64 mmol) and obtaining pure (+)-*ent*-**6** as hydrochloride (115 mg, quantitative).

(+)-*ent*-6. $[\alpha]_D^{24}$ +21.2 (*c* 1.1, H_2O). Spectroscopic data identical to those of (–)-**6**

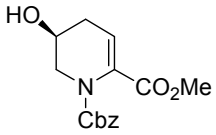


7·HCl

(2*S*,5*R*)-5-Hydroxypipecolic Acid [(–)-7·HCl]

Prepared as reported for (–)-**10**, starting from **187** (74 mg, 0.34 mmol) and obtaining pure (–)-**7** as hydrochloride (62 mg, quantitative).

$[\alpha]_D^{23}$ –9.5 (*c* 0.59, H_2O) {*lit.*[99] $[\alpha]_D^{20}$ –9.7 (*c* 0.9, H_2O); *lit.*[92g] for (2*R*,5*S*) $[\alpha]_D^{20}$ +8.6 (*c* 1.0, H_2O)}. ^{1}H NMR (400 MHz, D_2O) δ (ppm): 4.05–3.98 (m, 2 H, 2-H and 5-H), 3.54 (dd, *J* = 12.5, 4.1 Hz, 1 H, 6-H_{eq}), 2.94 (dd, *J* = 12.5, 9.4 Hz, 1 H, 6-H_{ax}), 2.46–2.38 (m, 1 H, 3-H), 2.18–2.11 (m, 1 H, 4-H), 1.96–1-85 (m, 1 H, 3-H'), 1.72-1.62 (m, 4-H') ppm

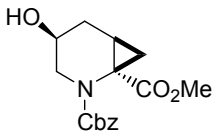


188

1-Benzyl 2-Methyl (*S*)-5-Hydroxy-5,6-dihydropyridine-1,2(4*H*)-dicarboxylate [(–)-188]

Prepared as reported for **180**, starting from **170** (100 mg, 0.25 mmol). After purification by flash chromatography (eluant: *n*-hexane-EtOAc, 1:1; R_f 0.17) pure **188** was obtained as a white solid (60 mg, 83%).

188. M.p. 87.8 - 89.2 °C; $[\alpha]_D^{25}$ –14.6 (*c* 0.65, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 7.38-7.29 (m, 5 H, Ph), 6.06 (t, *J* = 3.9 Hz, 1 H, 3-H), 5.19 (part A of an AB system, *J* = 12.2 Hz, 1 H, C*H*$_2$Bn), 5.12 (part B of an AB system, *J* = 12.2, 1 H, C*H*$_2$Bn), 4.18-4.17 (m, 1 H, 5-H), 3.82 (dd, *J* = 13.1, 6.1 Hz, 1 H, 6-H), 3.59-3.55 (m, 4 H, 6-H' + OCH_3), 2.54 (ddd, *J* = 9.6, 5.7, 3.71 Hz, 1-H, 4-H), 2.22 (dt, *J* = 19.9, 4.1 Hz, 1-H, 4-H'). ^{13}C NMR (100.4 MHz, $CDCl_3$) δ (ppm): 164.5 (s, CO), 154.9 (s, NCO), 135.7 (s, C_{arom}), 132.1 (s, C-2), 128.5 (s, 2 C, C_{arom}), 128.3 (s, 2 C, C_{arom}), 128.2 (s, C_{arom}), 121.0 (s, C-3), 68.2 (s, *C*H$_2$Bn), 64.1 (s, C-5), 52.0 (s, OCH_3), 49.4 (s, C-6), 32.1 (C-4). MS (ESI) *m/z* (%): 292 ([M^+ + 1], 28), 248 (12). $C_{15}H_{17}NO_5$ (291.30) calcd C, 61.85; H, 5.88; N, 4.81; found C, 62.11; H, 5.62; N, 4.62

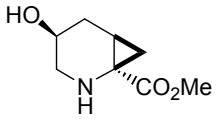


cis-**189**

2-Benzyl 1-Methyl (1*R*,4*S*,6*S*)-4-Hydroxy-2-azabicyclo[4.1.0]heptane-1,2dicarboxylate [(+)-*cis*-188]

To a solution of **188** (44 mg, 0.15 mmol) in anhydrous CH_2Cl_2 (1.5 mL), cooled to –15 °C, Et_2Zn (450 μL of a 1 M solution in hexane, 0.45 mmol) then CH_2I_2 (72 μL, 0.90 mmol) were added dropwise under N_2 atmosphere. The cooling bath was removed and reaction mixture was left under stirring for 1 h at room temperature, then refluxed for 18h. The suspension was then cooled in a ice bath and a 10% solution of citric acid (4 mL) was added dropwise under vigorous stirring. The cooling bath was removed and when the solution became clear, the layers were separated, the aqueous layer extracted with CH_2Cl_2 (3 × 4 mL) and the combined organic layers were dried over Na_2SO_4. After filtration and evaporation of the solvent, crude *cis*-**189** was purified by chromatography (*n*-hexane/EtOAn, 1 : 1; R_f 0.21), which give compound *cis*-**189** (19 mg, 41%) was obtained as a colorless oil.

cis-**189.** $[\alpha]_D^{25}$ +22.7 (*c* 0.92, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) (2.8:1 mixture of rotamers) δ (ppm): 7.36-7.25 (m, 5 H, Ph), 5.26 (part A of an AB system, *J* = 12.5 Hz, 1 H, C*H*$_2$Bn), 5.09 (part B of an AB system, *J* = 12.5 Hz, 1 H, C*H*$_2$Bn), 4.64-3.88 (m, 2 H, 4-H, both rotamers + 3-H, major rotamer), 3.85 (dd, *J* = 12.3, 4.1, 1 H, 6-H, minor rotamer), 3.69 (s, 3 H, OCH_3, minor), 3.55 (s, 3 H, OCH_3, major), 3.07 (dd, *J* = 13.7, 2.5, 1 H, 3-H', minor), 2.91-2.71 (m, 1 H, 3-H', major), 2.16-1.91 (m, 2 H, 5-H + 7-H, both rotamers), 1.85 (dd, *J* = 10.2, 4.7 Hz, 1 H, 6-H, both rotamers), 1.72-1.60 (m, 1 H, 5-H', both rotamers), 1.28-1.20 (m, 1 H, 7-H', both rotamers). ^{13}C NMR (100.4 MHz, $CDCl_3$) (mixture of rotamers) δ (ppm): 172.9 and 172.5 (s), 157.7 and 156.6 (s), 136.7 and 136.6 (s), 128.3 and 127.8 (q), 67.3 (s), 64.9 (s), 52.4 and 52.2 (s), 47.4 and 46.8 (s), 38.7 and 38.4 (s), 28.8 and 27.9 (s), 24.0 and 23.7 (s), 22.5 and 22.2 (s). MS/MS (ESI of $[M + 1]^+$) *m/z* (%): 306 ($[M + 1]^+$, 3), 262 (100).



cis-**111**

1-Methyl-(1*R*,4*S*,6*S*)-4-Hydroxy-2-azabicyclo[4.1.0]heptane 1-carboxylate [(+)-*cis*-111]

Prepared as reported for (+)-*cis*-**110**, starting from *cis*-**189** (17 mg, 0.06 mmol) and obtaining pure (+)-*cis*-**111** as a pale yellow oil (10 mg, 96%).

***cis*-111.** $[\alpha]_D^{24}$ +91.0 (*c* 0.91, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ (ppm): 3.88-3.85 (m, 1 H, 4-H), 3.71 (s, 3 H, OCH_3), 2.83 (ddd, *J* = 12.7, 3.9, 1.4 Hz, 1 H, 3-H), 2.69-2.65 (m, 3 H, 3-H' + OH + NH), 2.10-1.98 (m, 2 H, 5-H + 7-H), 1.64-1.54 (m, 5-H' + 6-H), 1.15 (dd, *J* = 7.03, 3.5 Hz, 1 H, 7-H'). ^{13}C NMR (100.4 MHz, $CDCl_3$) δ (ppm): 175.4 (s, CO), 64.0 (s), 52.4 (s), 47.5 (s), 39.5 (s), 28.7 (s), 26.1 (s), 19.6 (s). MS (ESI) *m/z* (%) 172 ($[M]^+$, 100)

Ringraziamenti

Impruneta, 20/12/2012

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Andrea Casini

References

[1] Most recent reviews: (a) Alastair A. Cant, Andrew Sutherland, *Synthesis* **2012**, 1935; (b) C. Kadouri-Puchot, S. Comesse, *Amino Acids* **2005**, *29*, 101. (c) M. He. *J. Ind. Microbiol. Biotechnol*. **2006**, *33*, 401

[2] (a) Bernasconi, R.; Jones, R.S.G.; Bittiger, H.; Olpe, H.R.; Heid, J.; Martin, P. Klein, M.; Loo, P.; Braunwalder, A.; Shmutz, M.; *J. Neur. Transm*. **1986**, *67*, 175 (b) C. Tranchant, P. Aubourg, M. Mohr, F. Rocchiccioli, C. Zaenker, J. M. Warter. *Neurology* **1993**, *43*, 2044. (c) S. Brul, A. Westerveld, A. Strijland, R. J. A. Wanders, A. W. Schram, H. S. A. Heymans, R. B. H. Schutgens, H. Van Den Bosch, J. M. Tager. *J. Clin. Invest.* **1988**, *81*, 1710.

[3] (a) D. C. Swindells, P. S. White, J. A. Findlay. *Can. J. Chem*. **1978**, *56*, 2491. (b) A. B. Smith III, K. J. Hale, L. M. Laakso, K. Chen, A. Riéra. *Tetrahedron Lett*. **1989**, *30*, 6963. (c) A. B. Smith III, S. M. Condon, J. A. McCauley, J. L. Leazer Jr, J. W. Leahy, R. E. Maleczka Jr. *J. Am. Chem. Soc*. **1997**, *119*, 962. (d) A. B. Smith III, C. M. Adams. *Acc. Chem. Res*. **2004**, *37*, 365.

[4] (a) H. Tanaka, A. Kuroda, H. Marusawa, H. Hatanaka, T. Kino, T. Goto, M. Hashimoto, T. Taga, *J. Am. Chem. Soc*. **1987**, *109*, 5031. (b) D. Romo, S. D. Meyer, D. D. Johnson, S. L. Schreiber. *J. Am. Chem. Soc*. **1993**, *115*, 7906. (c) R. E. Ireland, J. L. Gleason, L. D. Gregnas, T. K. Highsmith, *J. Org. Chem*. **1996**, *61*, 6856.

[5] D. L. Boger, J.-H. Chen, K. W. Saionz. *J. Am. Chem. Soc*. **1996**, *118*, 1629.

[6] E. Pacella, S. Collini, F. Pacella, D. C. Piraino, V. Santamaria, R. A. De Blasi. *Eur. Rev. Med. Pharmacol. Sci*. **2010**, *14*, 539.

[7] (a) K. Suzuki, T. Sato, M. Morioka, K. Nagai, K. Abe, H. Yamaguchi, T. Sato, O. Takeshi, K. Susaki, *J. Antibiot.* **1991**, *44*, 479. (b) J. D. Scott, T. N. Tippie, R. M. Williams. *Tetrahedron Lett*. **1998**, *39*, 3659.

[8] a) P. C. Anderson, F. Soucy, C. Yoakim, P. Lavallée, P. L. Beaulieu (Bio-Mega/Boehringer Ingelheim Research), Patent U.S. 5,614,533, 1997; b) D. Lamarre, G. Croteau, E. Wardrop, L. Bourgon, D. Thibeault, C. Clouette, M. Vaillancourt, E. Cohen, C. Pargellis, C. Yoakim, P. C. Anderson. *Antimicrob. Agents Chemother*. **1997**, *41*, 965.

[9] B. Bellier, S. D. Nasimiento, H. Meudal, E. Gincel, B. P. Roques, C. Garbay. *Bioorg. Med. Chem. Lett*. **1998**, *8*, 1419.

[10] a) P. L. Ornstein, D. D. Schoepp, M. B. Arnold, J. D. Leander, D. Lodge, J. W. Paschal, T. Elzey. *J. Med. Chem*. **1991**, *34*, 90; b) S. J. Hays, T. C. Malone, G. Johnson. *J. Org. Chem*. **1991**, *56*, 4084.

[11] a) C. Cocito. *Microbiol. Rev*. **1979**, *43*, 145; b) H. Vanderhaeghe, G. Janssen, F. Compernolle. *Tetrahedron Lett*. **1971**, *12*, 2687.

[12] A. Aiello, E. Fattorusso, A. Giordano, M. Menna, W. E. G. Müller, S. Perovic´-Ottstadt, H. C. Schröder. *Bioorg. Med. Chem*. **2007**, *15*, 5877.

[13] R. K. Gupta, M. Krishnamurti. *Phytochemistry* **1979**, *18*, 2021.

[14] Letavic, M.A.; Axt, M. Z.; Barberia, J. T.; Carty, T. J.; Danley, D. E.; Geoghenan, K. F.; Halim, N. S.; Hoth, L. R.; Kamath, A. V.; Laird, E. R.; Lopresti-Morrow, L. L.; McClure, K. F.; Mitchell, P. G.; Natarajan, V.; Moe, M. C.; Pandit, J.; Reeves, L.; Schulthe, G. K.; Snow, S. L.; Sweenwy, F. J.; Tan, D. H.; Yu, C. H. *Bioorg. Med. Chem. Lett*. **2002**, *12*, 1287

[15] S. V. Evans, T. K. Shing, R. T. Aplin, L. E. Fellows, G. W. J. Fleet, *Phytochemistry* **1985**, *24*, 2593.

[16] R. W. Bates, K. Sivarajan, B. F. Straub. *J. Org. Chem*. **2011**, *76*, 6844.

[17] (a) M. Merlier, G. Dardenne, J. Casimir, *Phytochemistry* **1976**, *15*, 183. (b) Merlier M., Dardenne, G.; Casimir, J. *Phytochemistry* **1972**, *11*, 2597.

[18] Brenner, S. A.; Romeo, J. T. *Appl. Envir. Microb*. **1986**, *51*, 690

[19] A. B. Bleecker, J. T. Romeo. *Phytochemistry* **1981**, *20*, 1845.

[20] (a) G. C. Kite, J. J. Wieringa. *Biochem. Syst. Ecol*. **2003**, *31*, 279. (b) A. B. Bleecker, J. T. Romeo, *Phytochemistry* **1983**, *22*, 1025.

[21] K. S. Manning, D. G. Lynn, J. Shabanowitz, L. E. Fellows, M. Singh, B. D. Schrire. *J. Chem. Soc. Chem. Commun*. **1985**, 127.

[22] (a) Chang, M.Y.; Kung, Y.H.; Wu, T.C. *Heterocycles* **2006**, 68, 2365 (b) Chattopadhyay, S.K.; Roy, S. P.; Saha, T. *Sythesis* **2011**, 2664.

[23] Fowler, L.S.; Thomas, L.H.; Ellis, D.; Sutherland, A. *Chem. Commun.* **2011**, *47*, 6569.

[24] Botman, P. N. M.; Dommerholt, F. J.; de Gelter, R.; Broxterman, Q. B; Schoemaker, H.E.; Rutjes, F.P.J.T.; Blaaw, R.H. *Org. Lett*. **2004**, *6*, 4941

[25] Cariou, C. A. M.; Kariuki, B. M.; Snaith, J. S. *Org. Biomol. Chem*. **2008**, *6*, 3337

[26] Jung, J.-C.; Avery, M.. A. *Tetrahedron: Asymmetry* **2006**, *17*, 2479

[27] Chattopadhyay, S. K.; Biswas, T.; Biswas, T.; *Tetrahedron Lett*. **2008**, *49*, 1365 (b) van den Broek, S. A. M. W.; Rensen, P. G. W.; van Delft, F. L.; Rutjes, F. P. J. T. *Eur. J. Org. Chem*. **2010**, 5906 (c) Chattopadhyay, A.; Mamdapur, V. R. *J. Org. Chem*. **1995**, *60* 585

[28] (a) Cordero, F. M.; Fantini, P.; Brandi, A. *Synlett* **2006**, 3251 (b) Cordero, F. M.; Bonollo, S.; Machetti, F.; Brandi, A.; *Eur. J. Org. Chem* **2006**, 3235

[29] (a) Occhiato, E. G.; Scarpi, D.; Guarna, A.; *Eur. J. Org. Chem*. **2008**, 524 (b) Occhiato, E. G.; Scarpi, D.; Guarna, A.; Tabasso, S.; Deagostino, A.; Prandi, C.; *Synthesis* **2009**, 21, 3611

[30] Barge, A.; Occhiato, E. G.; Prandi, C.; Scarpi, D.; Tabasso, S.; Venturello, P.; *Synlett* **2010**, 812

[31] The furher studies for the enhancement of this *de* will be discussed in this work (Results and discussion)

[32] Alegret, C.; Santacana, F.; Riera, A. *J.Org. Chem*. **2007**, *72*, 7688, (b) Alegret, C.; Ginesta, X.; Riera, A. *Eur. J. Org. Chem*. **2008**, 1789

[33] (a) Ohara, C.; Takahashi, R.; Miyagawa, T.; Yoshimura, Y.; Kato, A.; Adachi, I.; Takahata, H. *Bioorg. Med. Chem. Lett*. **2008**, *18*, 1810. (b) Yoshimura, Y.; Ohara, C.; Imahori, T.; Saito, Y.; Kato, A.; Miyauchi, S.; Adachi, I.; Takahata, H. *Bioorg. Med. Chem*. **2008**, *16*, 8273

[34] B. P. Bashyal, H.-F. Chow, G. W. J. Fleet. *Tetrahedron Lett*. **1986**, *27*, 2305.

[35] Michela I. Simone, Raquel G. Soengas, Sarah F. Jenkinson, Emma L. Evinson, Robert J. Nash, George W. J. Fleet. *Tethahedron: Asymmetry* **2012**, *23*, 401

[36] Thieme, M.; Vieira, E.; Liebscher, J.; *Synthesis* **2000**, 2051.

[37] Takahashi, S.; Kuzuhara, H.; *Chemical Letters* **1994**, *11*, 2119

[38] Takahashi, S.; Kuzuhara, H.; *Biosci. Biotech. Biochem*. **1995**, *59*, 762

[39] Hruby, V. J.; Al-Obeidi, F.; Kazmierer, W.; *Biochem. J*. **1990**, *268*, 249

[40] For previous recent syntheses (a) Hanessian. S.; Auzzas. L.; *Acc. Chem. Res*. **2008**, *41*, 4619 (b) Brackmann, N.; Colombo, C.; Cabrele, A de Meijere, *Eur. J. Org. Chem*. **2006**, 4440; (c) Szakonyi, Z. Fulop, D.; Tourwé, D.; De Kimpe, N.; *J. Org. Chem* **2002**, *67*, 2192 (d) Matsumura, Y.; Inoue, M.; Nakamura, Y.; Talib, I. L.; Maki, T.; Onomura, O.; *Tetrahedron Lett*. **2000**, *41*, 4619 (e) Czombos, J.; Aelterman, W.; Tkachev, A.; Martins, J. C.; Tourwé, D.; Pèter, A.; Tòth, G.; Fulop, F.; De Kimpe, N.; *J. Org. Chem*. **2000**, *65*, 5469 (f) Lorthiois, E.; Marek, I.; Normant, J. F. *J.Org. Chem*. **1998**, *63*, 566 (g) Ezquerra, J.; Escribano, A.; Rubio, A.; Remuinan, M. J.; Vaquero, J.

J.; *Tetrahedron: Asymmetry* **1996**, *7*, 2613 (h) Hercouet, A.; Bessières, B.; Le Corre, M.; Toupet, L.; *Tetrahedron Lett*. **1996**, *37*, 4529

[41] Stammer, C. H.; *Tetrahedron* **1990**, *46*, 2231

[42] (a) Bruncko, M.; Crich, D.; *J. Org. Chem*. **1994**, *59*, 4239 (b) Toniolo, C.; Crisma, M.; Formaggio, F.; Benedetti, E.; Santini, A.; Iacovino, R.; Saviano, M.; Di Blasio, B.; Pedone, C.; Kamphuis, J.; *Biopolymers* **1997**, *40*, 519 (c) Burges, K.; Ke, C.-Y.; *J. Org. Chem*. **1996**, *61*, 8627

[43] Hercouet, A.; Bessières, B.; Le Corre, M.; Toupet, L. *Tetrahedron Lett.* **1996**, *37*, 4529.

[44] (a) Gringore, O. H.; Rouessac, F. P.; *Organic Syntheses*, **1985**, *63*, 121 (b) Larcheveque, M.; Lalande, J.; *Tetrahedron* **1984**, *40*, 1061

[45] Matsumura, Y.; Inoue, M.; Nakamura, Y.; Talib, I.L.; Maki, T.; Onomura, O.; *Tetrahedron Lett*. **2000**, *41*, 1241

[46] Shono, T.; Matsumura, Y.; Tsubata, K.; Uchida, K.; *J. Org. Chem*. **1986**, *51*, 2590

[47] Most recent reviews on carbonylative and other Pd-catalyzed reactions of lactam-derived enol phosphate: (a) Sellars, J. D.; Steel, P. G.; *Chem. Soc. Rev*. **2011**, *40*, 5170. (b) Occhiato, E. G.; Scarpi, D.; Prandi, C.; *Heterocycles* **2010**, *80*, 697

[48] Bartali, L.; Casini, A.; Guarna, A.; Occhiato, E. G.; Scarpi, D.; *Eur. J. Org. Chem*. **2010**, 5831

[49] Scarpi, D.; Bartali, L.; Casini, A.; Occhiato, E. G.; *Eur. J. Org. Chem*. **2012**, accepted

[50] Occhiato, E. G.; Casini, A.; Guarna, A.; Scarpi, D.; *Eur. J. Org. Chem*. **2011**, 6544

[51] Scarpi, D.; Bartali, L.; Casini, A.; Guarna, A.; Occhiato, E. G.; *Eur. J. Org. Chem*. **2012**, 2597

[52] (a) Akai, S.; Tanimoto, K.; Kita, Y.; *Angew. Chem. Int. Ed*. **2004**, *43*, 1407 (b) Roticci, D.; Norin, T.; Hult, K.; Carrea, G.; *Tetrahedron: Asimmetry* **1995**, *6*, 3023

[53] Hagiwara. H.; Nakano, T.; Uda, H.; *Bull. Chem. Soc. Jpn*. **1993**, *66*, 3110

[54] (a) Doussot, J.; Guy, R.; Garreau, R.; Falguières, A.; Ferroud, C.; *Tetrahedron: Asymmetry* **2000**, *11*, 2259; (b) Carrea, G.; Danieli, B.; Palmisano, G.; Riva, S.; Santagostino, M.; *Tetrahedron: Asymmetry* **1992**, *3*, 775

[55] (a) Persson, B. A.; Larsson, A. L. E.; Le Ray, M.; Bäckvall, J-E.; *J. Am. Chem. Soc*. **1999**, *121*, 1645 (b) Kim, M.-J.; Chung, Y. I.; Choi,, Y. K.; Lee, H. K.; Kim, D.; Park, J.; *J. Am. Chem. Soc.* **2003**, *125*, 11494, and references cited therein

[56] (a) Akai, S.; Tanimoto, K.; Kita, Y.; *Angew. Chem. Int. Ed*. 2004, 43, 1407 (b) Roticci, D.; Norin, T.; Hult, K.; *Org. Lett*. **2000**, *2*, 1373 (c) Orrenius, C.; Norin, T.; Hult, K.; Carrea, G.; *Tetrahedron: Asymmetry* **1995**, **6**, 3023

[57] Toluene was used in the lipase-mediated kinetic resolution of 5-hydroxy-5,6-dihydro-2(1H)-pyridones. In our case, the results were poorer with this solvent than with more polar ones, see: Gòmez, R.; Alcudia, A.; Liebeskind, L. S.; *Org. Lett* **2001**, *3*, 3381. Furhermore, alcohol **118** was insoluble in hexane so the conditions reported for seudenol by Roticci et al. could not be applied.

[58] PCPB was prepared as reported: Fransson, A.-B. L.; Xu, Y.; Leijondahl, K.; Bäckvall, J.-E.; *J. Org. Chem*. **2006**, *71*, 6309

[59] Armesto, N.; Ferrero, M.; Fernàndez, S.; Gotor, V.; *J. Org. Chem*. **2002**, 67, 4978 and references cited therein

[60] The enantioselectivity in an enzymatic kinetic resolution process is expressed by the enantiomeric ratio, E, which is the ratio between the specificity constants (k_{cat}/K_M) of the enzyme for the competing R and S enantiomers: $E = (k_{cat}/K_M)_R/(k_{cat}/K_M)_S$. E was calculated using the formula $E = \ln[(1 - ee_s)/(1 + ee_s/ee_p)]/\ln[(1 + ee_s)/(1 + ee_s/ee_p)]$. J. L. L. Rakels, A. J. J. Straathof, J. Heijnen, *J. Enzyme Microb. Technol*. **1993**, *15*, 1051

[61] Synthesis of *trans* pipecolic acid was the topic of another thesis work

[62] Lipases from *Candida antarctica* CAL-B and CAL-A, and PS "AMANO" lipase were equilibrated with a saturated aqueous LiCl (water activity aw = 0.11) for at least 48 h before use. *Aspergillus niger* lipase, porcine pancreatic lipase and *Candida rugosa* lipase were equilibrated with MgCl2·6H2O (aw = 0.38). (a) G. V. Chowdary, S. G. Prapulla. *Process Biochemistry* **2002**, *38*, 393. (b) C. Orrenius, T. Norin, K. Hult, G. Carrea. *Tetrahedron: Asymmetry* **1995**, *6*, 3023. (c) S. H. Krishna, M. Persson, U. T. Bornsheuer. *Tetrahedron: Asymmetry* **2002**, *13*, 2693.

[63] J. Cossy, N. Furet, S. BouzBouz, *Tetrahedron* **1995**, *43*, 11751. For a review on substrate-directable chemical reactions including cyclopropanation reactions, see: A. H. Hoveyda, D. A. Evans, G. C. Fu, *Chem. Rev.* **1993**, *93*, 1307. (b) G. Molander, L. Harring, *J. Org. Chem.* **1989**, *54*, 3525

[64] J.-C. Poupon, R. Lopez, J. Prunet, J.-P. Ferezou, *J. Org. Chem.* **2002**, *67*, 2118

[65] K. Csatayova, S. G. Davies, J. A. Lee, K. B. Ling, P. M. Roberts, *Tetrahedron* **2010**, *66*, 8420

[66] J. Furukawa, N. Kawabata, J. Nishimura, *Tetrahedron* **1968**, *24*, 53.

[67] A. B. Charette, S. Francoeur, J. Martel, N. Wilb, *Angew. Chem.* **2000**, *112*, 4713; *Angew. Chem. Int. Ed.* **2000**, *39*, 4539.

[68] Yang, Z.; Lorenz, C. J.; Shi, Y.; *Tetrahedron Lett.* **1998**, *39*, 8621

[69] A. C. Glass, B. B. Morris, L. N. Zakharov, S.-Y. Liu, *Org. Lett.* **2008**, *10*, 4855.

[70] To demonstrate the suitability of the procedure to prepare sufficient amounts of compound for medicinal chemistry studies, we prepared, as an example, ca. 120 mg of cis (+)-**110** in a single run from racemic **125**

[71] D. L. Comins, S. P. Joseph, in: *Advances in Nitrogen Heterocycles* (Eds.: C. J. Moody), JAI Press, Greenwich, CT, **1996**, vol. 2, pp. 251–294

[72] Arrayàs, R. M.; Alcudia, A.; Liebskind, L. S.; *Org. Lett* **2001**, *3*, 3381

[73] Andreana, P. R.; McLellan, J. S.; Chen, Y.; Wang, P. G.; Org. Lett. **2002**, *4*, 3875

[74] Unpublished data

[75] J. E. Taylor, D. Williams, D. Edwards, D. Otonnaa, D. Samanich, *Can. J. Chem.* **1984**, *62*, 11.

[76] We experienced problems in product recovery from the reaction mixture when we carried out a standard dihydroxylation by catalytic OsO_4 in the presence of NMO in acetone/water

[77] HPLC column for monitoring enzymatic reactions was Acclaim 120 C18, 250 x 4.60 nm, 5 μm; eluition program: from 55% ACN for 2.5' to 90% ACN for 3' in 3.5', then 55% ACN for 2.5' in 0'; R_t-diol = 3.81 min, R_t-5-butyrate = 7.05 min, R_t-4-butyrate = 7.69 min, R_t-4,5-dibutyrate = 10.23 min, R_t-5-acetate = 4.99 min, R_t-4-acetate = 5.55 min, R_t-4,5-diacetate = 7.75 min

[78] Cyclobond I2000, 250 x 4.60 nm, 5 μm, eluition program: H_2O–MeOH 85:15, isocratic eluition, flow = 0.7 ml/min, λ=254, 223 nm, (R_t **147** = 20.09, R_t *ent*-**147** = 21.29 min).

[79] Lux Cellulose 4, 250 x 4.60 nm, 5 μm, eluition program: IPA – *n*-hexane 50:50, isocratic eluition, flow = 0.5 ml/min, λ=254, 223 nm, (R_t **147** = 20.97, R_t *ent*-**147** = 22.97 min)

[80] We found that enantiomeric excess of diols obtained from the hydrolysis of diacylated products were similar to those obtained from hydrolysis of monoacylated derivatives.

[81] Armesto N.; Ferrero M.; Fernández S.; Gotor V.; *J. Org. Chem.* **2003**, *68*, 5784-5787

[82] (a) Han, S.-Y.; Joullié, M. M.; Petasis, N. A.; Bigorra, J.; Corbera, J.; Font, J.; Ortuño, R. M.; *Tetrahedron*, **1993**, *49*, 349. (b) Han, S.-Y.; Joullié, M. M.; Fokin, V. V.; Petasis, N. A.; *Tetrahedron: Asymmetry* **1994**, *5*, 2535. (c) Song, J.; Hollingsworth, R. I.; *Tetrahedron: Asymmetry* **2001**, *12*, 387.

[83] We observed this by recording the spectrum of **156** in CD_3OD. The signals associated to the minor isomer are the following: ^{1}H NMR (CD_3OD, 400 MHz) δ = 3.98 (ddd, *J* = 9.4, 7.0, 3.3 Hz, 1 H), 3.71 (dd, *J* = 11.3, 3.9 Hz, 1 H),

3.57 (dd, *J* = 11.3, 6.0 Hz, 1 H), 3.49-3.43 (m, 1 H), 2.75 (dd, J = 15.4, 3.3 Hz, 1 H), 2.42 (dd, *J* = 15.4, 9.4 Hz, 1 H) ppm, which seems more consistent with the structure of the pyran-2-one derivative. Our ^{1}H and ^{13}C NMR spectra of compound **156**, recorded both in CD_3OD and d_6-DMSO, are identical to those reported in literature. See P. O. Miranda, F. Estévaz, J. Quintana, C. I. Garcia, I. Brouard, J. I. Padrón, J. P. Pivel, J. Bermejo. *J. Med. Chem*. **2004**, *47*, 292.

[84] J. Cardellah, J. Font, R. M. Ortuño, *J. Heterocyclic Chem*. **1984**, *21*, 327

[85] (a) V. Bouchez, I. Stasik, D. Beaupére, R. Uzan, *Carbohydr. Res.* **1997**, *300*, 139; (b) V. Bouchez, I. Stasik, D. Beaupére, R. Uzan, *Tetrahedron Lett.* **1997**, *38*, 7733.

[86] The basicity of the fluoride anion seems sufficient for a slow epimerization to occur in these compounds. Epimerization of a very similar compound has been also carried out by treatment with LiHMDS in THF, but we did not try this procedure. I. Ojima, M. Tzamarioudaki, M. Eguchi, *J. Org. Chem.* **1995**, *60*, 7078

[87] As in the case of compound **10**, also the optical rotation of **11** has not been measured from the compound isolated from *Derris elliptica* (ref. [17a]) and *Calliandra haematocephala* (ref. [17b]), nor for synthetic compound (ref. [17a])

[88] Herdeis, C.; *Synthesis* **1986**, 232

[89] W. Nerinckx, P. J. De Clercq, C. Couwenhoven, W. R. M. Overbeek, S. J. Halkes, *Tetrahedron* **1991**, *47*, 9419

[90] K. Mochida, T. Hirata, *Chem. Pharm. Bull*. **1988**, *36*, 3642

[91] Tokoroyama, T.; Koike, H.; Hirotsu, K.; Ezaki, Y. *Tetrahedron* **1982**, *38*, 2559.

[92] (a) C. Klein, W. Huettel, *Adv. Synth. Cat.* **2011**, *353*, 1375; (b) M. A. Wijdeven, F. L. Van Delft, F. P. J. T. Rutjes, *Tetrahedron* **2010**, *66*, 5623; (c) P. M. N. Botman, F. J. Dommerholt, R. de Gelder, Q. B. Broxterman, H. E. Schoemaker, F. P. J. T. Rutjes, R. H. Blaauw, *Org. Lett*. **2004**, *6*, 4941; (d) T. Shibasaki, W. Sakurai, A. Hasegawa, Y. Uosaki; H. Mori, M. Yoshida, A. Ozaki, *Tetrahedron Lett*. **1999**, *40*, 5227; (e) D. R. Adams, P. D. Bailey, I. D. Collier, J. D. Heffernan, S. Stokes, *J. Chem. Soc., Chem. Commun*. **1996**, 349; (f) S. Hoarau, J. L. Fauchere, L. Pappalardo, M. L. Roumestant, P. Viallefont, *Tetrahedron: Asymmetry*, **1996**, *7*, 2585; (g) C. Herdeis, E. Heller, *Tetrahedron: Asymmetry* **1993**, *4*, 2085; (h) C. Herdeis, W. Engel, *Tetrahedron: Asymmetry* **1991**, *2*, 945. (i) P. D. Bailey, J. S. Bryans, *Tetrahedron Lett.* **1988**, *29*, *2231*; (j) R. E. A. Callens, M. J. O. Anteunis, F. Reyniers, *Bull. Soc. Chim. Belges*; **1982**, *91*, 713.

[93] In ref. **92g** there is an erroneous attribution of chemical shifts to 5-H and 6-H_{eq} for compound **185** which resonate at 3.67–3.59 (5-H) and at 4.27 (6-H_{eq}, minor rotamer) and 4.13 (6-H_{eq}, major rotamer), respectively. Also, the reported optical rotation value ($[\alpha]_D^{20}$ = –24.1 in MeOH), is significantly lower than the value found by us ($[\alpha]_D^{24}$ = –40.3 in the same solvent).

[94] D. L. Comins, S. P. Joseph, in: *Advances in Nitrogen Heterocycles* (Ed.: C. J. Moody), JAI Press, Greenwich, CT, **1996**, vol. 2, p. 251–294.

[95] For recent review: Lebel, H.; Marcoux, J.-F.; Molinaro, C.; Charette, A. B.; *Chem. Rev*. **2003**, *103*, 977-1050

[96] By the way, our attempts to isolate cyclopropanated product from the unreacted substrate, fall

[97] J. Kitajima, T. Ishikawa, Y. Tanaka, Y. Ida, *Chem. Pharm. Bull*. **1999**, *47*, 988

[98] B. Moelholm Malle, I. Lundt, R. H. Furneaux, *J. Carbohydrate Chem*. **2000**, *19*, 573

[99] S. –I. Hatanaka, S. Kaneko, *Phytochemistry* **1977**, *16*, 1041