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Ready Access to Stereodefined β-Hydroxy-γ-amino Acids. Enantioselective Synthesis of Fully Protected Cyclohexylstatine.

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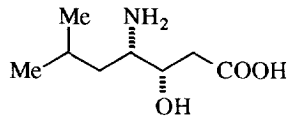
Abstract: A convenient entry to enantiopure *syn* or *anti* β-hydroxy-γ-amino acids is described. The starting compounds for the synthesis, *anti* 3-amino-1,2-diols, are readily available in high enantiomeric purity through catalytic asymmetric epoxidation of an allylic alcohol and titanium-promoted oxirane opening. After adequate protection of the nitrogen, a stereodivergent sequence leads to both *anti* and *syn* *N*-Boc-aminoalkyl epoxides. Subsequent regioselective ring-opening with cyanide, protection of the resulting secondary alcohol and nitrile to carboxyl conversion afford, in good yields, protected β-hydroxy-γ-amino acids belonging to either the *anti (erythro)* or *syn (threo)* series. This methodology has been applied to the enantioselective preparation of cyclohexylstatine, a key component of several aspartyl protease inhibitors, in fully protected form.

Introduction

The structural class of β-hydroxy-γ-amino acids has in recent years been the object of much attention, especially in connection with the development of new pharmaceutics based on protease inhibitors.[1] Statine, *(3S,4S)*-4-amino-3-hydroxy-6-methylheptanoic acid (**1**), is an essential component of pepstatine, a natural hexapeptide antibiotic which acts as an inhibitor of aspartic acid proteases such as renin, pepsin and cathepsin D.[2] The low selectivity of pepstatine has induced the development of more specific synthetic analogs; in particular, the substitution of the isobutyl moiety of statine by the more lipophilic cyclohexylmethyl substituent has led to the widely used analog cyclohexylstatine (**2**), a key component of renin inhibitors.[3] The inhibitory activity of these compounds is due to their ability to mimic the tetrahedral intermediate in the enzymatic hydrolysis of the peptide bond, and the *syn (threo)* relative configuration of the amino and hydroxyl groups found in statine and its analogs appears to be necessary for the inhibitor to attain a conformation suitable for interaction with the enzyme. On the other hand, there are several examples of biologically active β-hydroxy-γ-amino acids belonging to the diastereomeric *anti (erythro)* series: Isostatine, *(3S,4R,5S)*-4-amino-3-hydroxy-5-methylheptanoic acid (**3**), is a component of didemnins A, B and C, antiviral cytotoxic cyclodepsipeptides isolated from a Caribbean tunicate;[4] dolaisoleuine (**4**) is found in dolastatin 10, an antineoplastic pentapeptide also of marine origin;[5] and *(2S,3S,4R)*-4-amino-3-hydroxy-2-methylpentanoic acid (**5**), is the amino acid

linker of bleomycin B_2, the main constituent of the powerful carcinostatic blenoxane.[6] It is worth noting that even simple β-hydroxy-γ-amino acids such as *(R)*-GABOB (**6**) or *(R)*-carnitine (**7**) are also interesting from the therapeutical point of view.[7]



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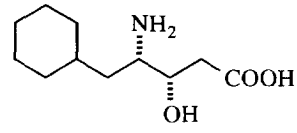

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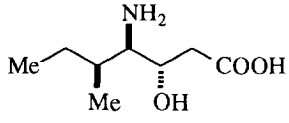

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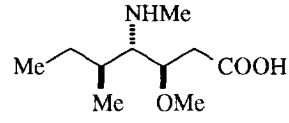

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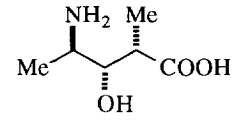

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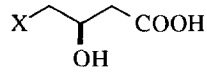
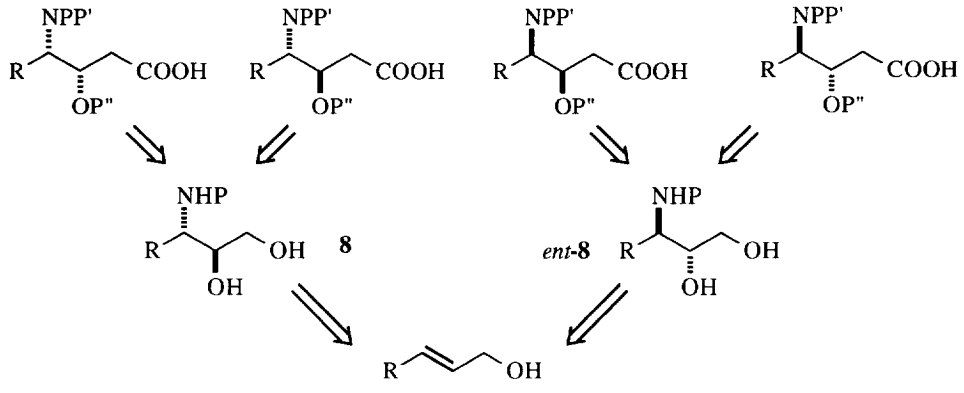


6 ($X=NH_2$)
7 ($X=NMe_3^+Cl^-$)

The biological activity of these and other β-hydroxy-γ-amino acids has fostered the development, both in academia and in pharmaceutical companies, of numerous synthetic approaches. In a very schematic way, the synthetic strategies described in the literature can be summarized as follows: (i) aldol condensations of achiral[3,5,8] or chiral[6,9] ester enolates and protected α-amino aldehydes; (ii) allylation[10] or vinylation[11] reactions of protected α-amino aldehydes, followed by oxidative transformation of the olefinic moiety; (iii) acylation of ester enolates with active α-amino acid derivatives, followed by reduction of the resulting γ-amino-β-keto esters;[12] (iv) stereoselective reduction of tetramic acids,[13] obtained from α-acylamino acid derivatives; (v) stereocontrolled elaboration of 2-oxazolidinones;[14] and (vi) miscellaneous methods, including hetero Diels-Alder reactions of α-amino aldehydes,[15] and the use of chiral aziridines[16] or azidoalkyl epoxides[17] as starting products. Most of these methodologies, however, suffer from one or more of the following drawbacks: they are either not totally stereoselective, applicable only to the synthesis of *syn* or *anti* diastereomers, or are limited by the structures available for the aminoacid-derived starting materials.

We present in this paper a broad scope, stereodivergent and enantioselective approach which allows the synthesis of any of the four possible stereoisomers of a given β-hydroxy-γ-amino acid in fully protected form, ultimately arising from a single allylic alcohol of *(E)* configuration (Scheme 1). This approach relies on the ready availabilty of *anti N*-protected-3-amino-1,2-diols of general structure **8** in high enantiomeric excess. In effect, research in our laboratory has demonstrated that these amino diols can be easily secured from an *(E)*-allyl alcohol by means of an efficient three-step sequence consisting of: (i) Sharpless catalytic asymmetric epoxidation,[18] (ii) nucleophilic opening of the resulting epoxy alcohol,[19,20] and (iii) eventual change of the nitrogen-protecting group. In the past few years, we have also shown that amino diols **8** are very versatile

chiral starting materials allowing the enantioselective preparation of azetidinols,[21] aziridines,[21] *N*-Boc-α-amino acids,[22] allyl amines,[23] *N*-Boc-β-amino acids,[23] and both *anti*[24,25] and *syn*[24] α-hydroxy-β-amino acids.

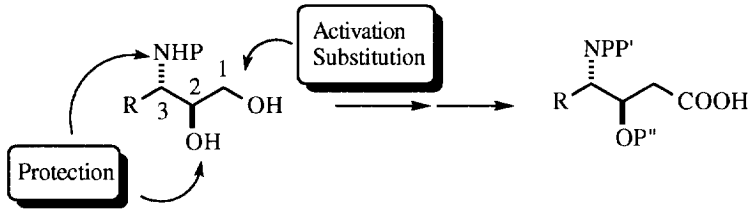


Scheme 1

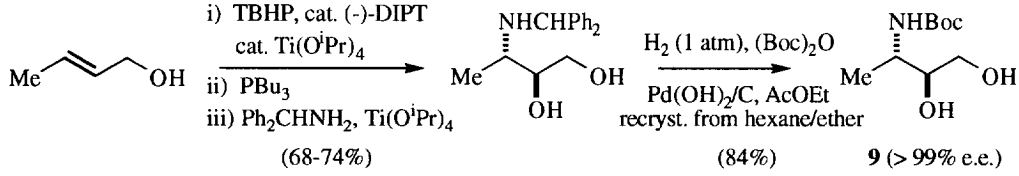
Results and Discussion

A. Enantioselective Synthesis of Protected *anti* β-Hydroxy-γ-amino Acids

The obtention of *anti* β-hydroxy-γ-amino acids from 3-amino-1,2-alkanediols **8** reduces essentially, barring changes in the protecting groups, to the introduction of an hydroxycarbonyl synthon at C-1, following the selective activation of this position.

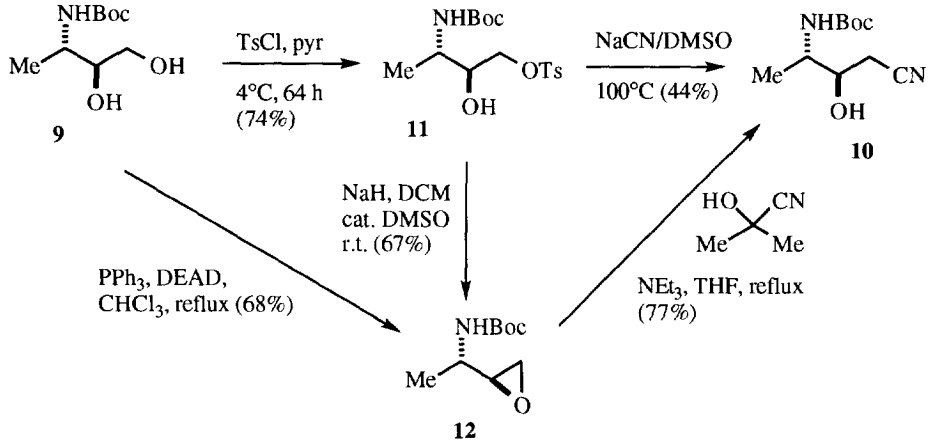


In order to test the methodology for this transformation, we chose as starting material *(2S,3S)-N*-Boc-3-amino-1,2-butanediol (**9**), which is prepared in multigram amounts and with an optical purity greater than 99%[22a] by means of the following two-step sequence, which we have previously described[20,24] (Scheme 2):



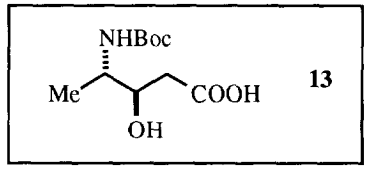
Scheme 2

After some experimentation, we found that **9** could be converted into the key hydroxy nitrile intermediate **10** in two different ways (Scheme 3): In the first route, the treatment of **9** with 1.1 equivalents of tosyl chloride in pyridine gave in 74% yield the *p*-toluenesulfonate **11**, which without further purification and after exposure to sodium cyanide in DMSO[26] afforded **10** in moderate yields. Better results were obtained however by means of epoxide **12** (obtained either from **11** by reaction with sodium hydride[27] or directly from **9** through an intramolecular Mitsunobu reaction[28]), which underwent smoothly the desired regioselective oxirane opening when subjected to the action of acetone cyanhoydrin in basic medium.[29] It is worth noting that the epoxide opening protocol described by Crotti and co-workers[30] (KCN-$LiClO_4$ in refluxing acetonitrile) was not effective in this case, and gave a mixture of unidentified products.

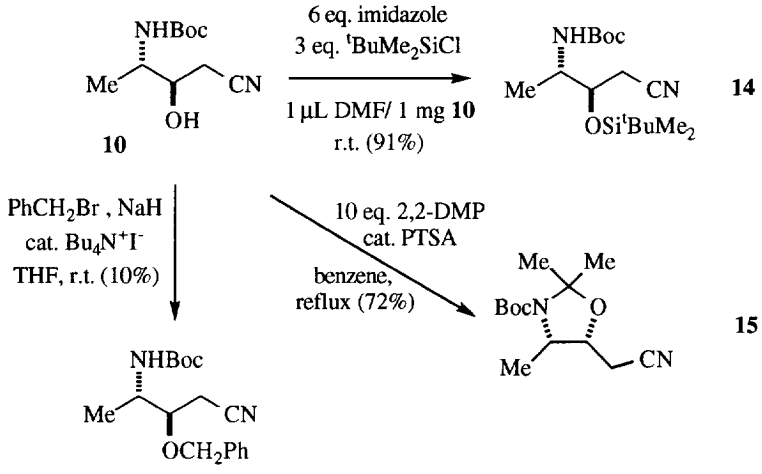


Scheme 3

With the requisite hydroxy nitrile **10** in hand, we devoted some time to the hydrolysis of the cyano group, which proved to be more troublesome than anticipated. In effect, when **10** was heated to reflux in a 30% aqueous KOH solution containing hydrogen peroxide, 4-oxopentanoic acid was obtained as the sole reaction product, and the use of a variety of known procedures for mild nitrile hydrolysis[31] led either to the production of complex mixtures or to the recovery of starting material. Finally, *(3R,4S)*-4-(*tert*-butoxycarbonylamino)-3-hydroxypentanoic acid (**13**) was obtained by refluxing **10** with 25% aqueous NaOH solution in methanol, in a disappointing 26% yield.

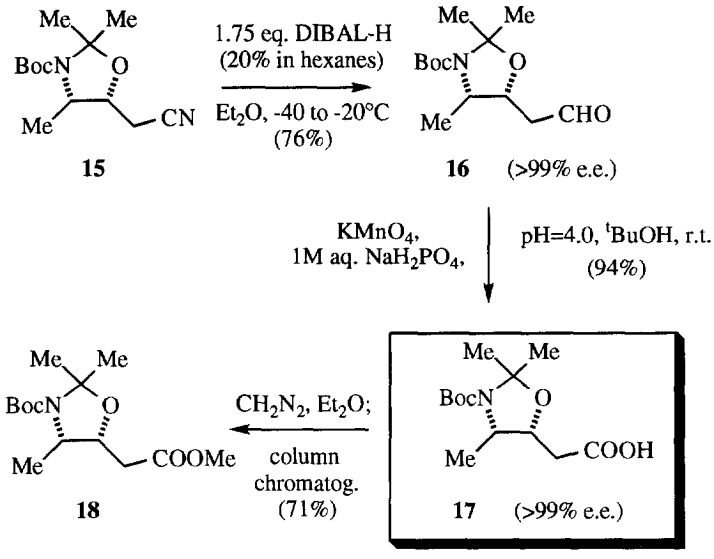


At the light of these results, we decided to invert the order of synthetic operations and protect before hydrolysis the secondary hydroxyl group in **10**. Screening of several experimental conditions led us to discover that **10** could be efficiently converted both to the *t*-butyldimethylsilyl derivative **14**[32] and to the *cis*-*N*-Boc-oxazolidine **15**,[33] through modification of the usual protection protocols (Scheme 4). On the other hand, the derivatisation of the alcohol as benzyl ether was much more inefficient, probably due to the acidity of the neighbouring NH group.



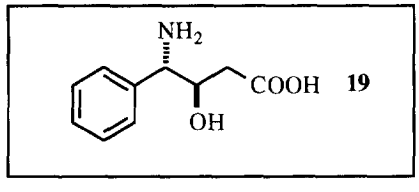
Scheme 4

For the remaining steps of the conversion of **10** into a fully protected *anti* β-hydroxy-γ-amino acid, oxazolidine **15** proved to be more adequate than silyl ether **14**. Since the exposure of both **14** and **15** to the conditions that had effected the hydrolysis of **10** to the hydroxy acid **13** resulted only in the formation of 4-oxopentanoic acid, we resorted to the use of non-hydrolytic conditions to effect the required nitrile to carboxyl conversion (Scheme 5). To this end, an ethereal solution of **15** was treated with excess diisobutyl aluminum hydride in hexanes,[34] to give, after hydrolysis, a 76% yield of the aldehyde **16** in enantiomerically pure form according to chiral HPLC analysis (>99% e.e., Chiralcel® OD-R column, methanol/ 0.5M $NaClO_4$ mixtures); when **14** was submitted to the same reaction conditions, no aldehyde could be isolated from the resulting complex mixture of products, and the use of stoichiometric amounts of hydride led only to the recovery of unreacted **14**. Once again, the acidity of the unprotected carbamate moiety can be invoked to explain these results. Finally, the oxidation of **16** was accomplished by means of the methodology developed by Masamune and co-workers,[35] which involves the use of potassium permanganate in buffered (pH 4) aqueous *tert*-butyl alcohol. Under these mild conditions, *(4S,5R)*-3-(*tert*-butoxycarbonyl)-5-carboxymethyl-2,2,4-trimethyl-1,3-oxazolidine (**17**) was obtained in 94% yield. Since it is known that the reaction conditions involved in the procedure of Masamune do not affect the stereochemical integrity of aldehydes, even when a chiral center α to carbonyl is present in their structures,[35] it is assumed that the stereochemical purity of **17** will be that of the precursor aldehyde, i.e., > 99% d.e. and e.e. Although this product is essentially pure according to its spectral data, further purification can be more conveniently effected by column chromatography of the methyl ester **18**.



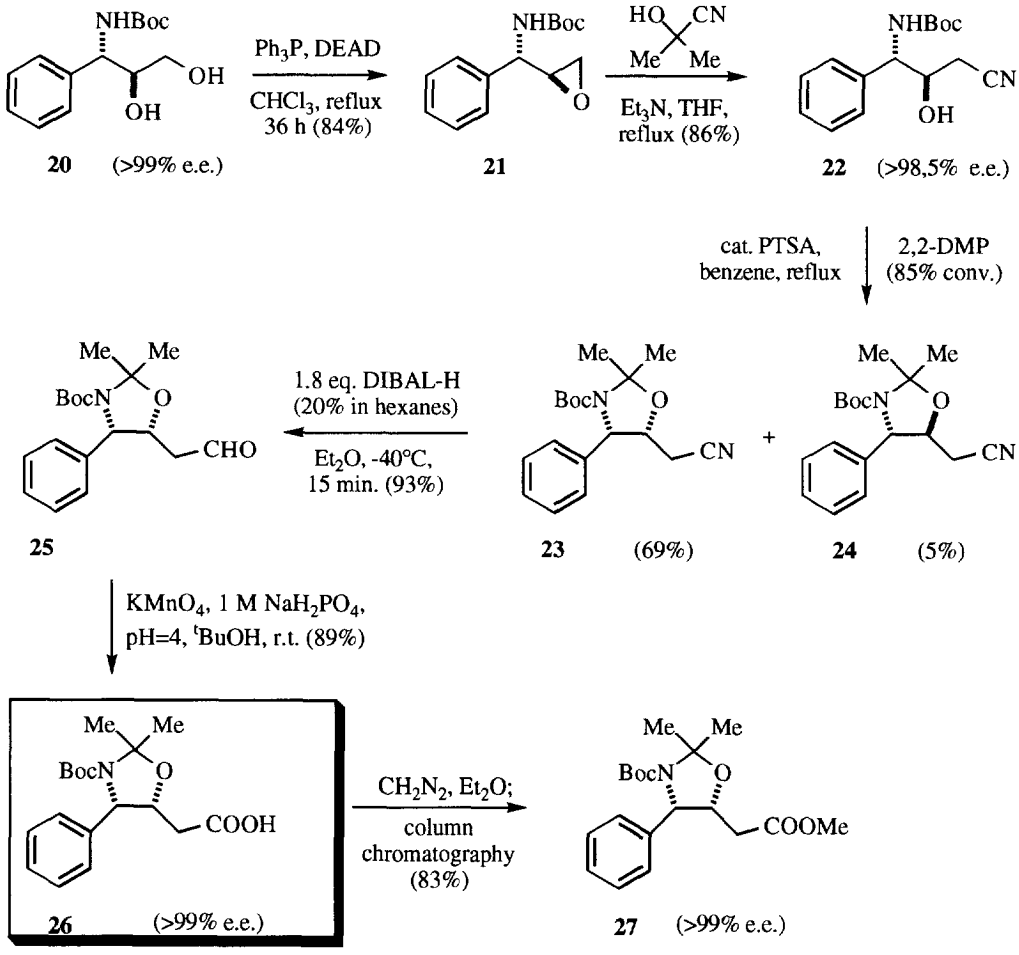
Scheme 5

The five-step conversion of amino diol **9** into **17** which takes place *via* the intermediates **12**, **10**, **15** and **16** discloses a potentially general route to fully protected *anti* β-hydroxy-γ-amino acids, the stereochemical integrity of the starting *N*-Boc-3-amino-1,2-diol (> 99% e.e. in the present instance) being preserved along the whole sequence. In order to test the applicability of our method, we set out to synthesize a protected derivative of *(3R,4S)*-4-amino-3-hydroxy-4-phenylbutanoic acid (**19**), a potentially active γ-aminoacid which had not been previously obtained in stereochemically pure form.[36]



The starting product for this application was *enantiomerically pure (2S,3S)*-3-(*tert*-butoxycarbonylamino)-3-phenylpropane-1,2-diol (**20**).[22a,25] The initial step of the sequence (Scheme 6) involved an intramolecular Mitsunobu reaction on **20**, that led to the epoxide **21**.[28] This compound was then regioselectively opened under the conditions previously developed for **10**, to afford hydroxy nitrile **22** in an excellent 86% yield. The stereochemical purity of **22** was > 98.5%, according to DSC analysis. Due to the steric bulk of the phenyl residue, somewhat harsher reaction conditions (three successive benzene distillations from a mixture containing excess 2,2-dimethoxypropane and catalytic amounts of *p*-toluenesulfonic acid) had to be employed for the formation of *cis*-oxazolidine **23**, which could finally be isolated in a satisfactory 69% yield (based on reacted starting material). Interestingly enough, even under these conditions epimerisation

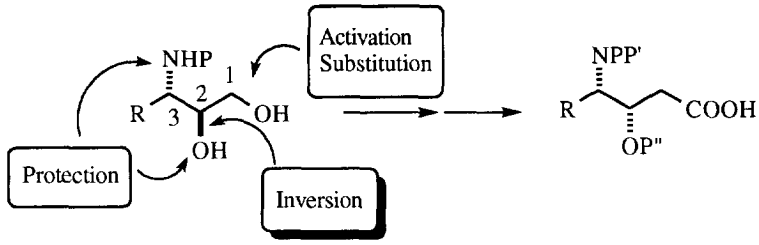
occurred to a very limited extent, and the thermodinamically more stable *trans*-oxazolidine **24** was isolated in only 5% yield. The remaining steps of the synthetic sequence took place uneventfully. The reduction of **23** with DIBAL-H was very fast and almost quantitative, and the oxidation of the resulting aldehyde **25** with $KMnO_4$ gave an 89% yield of the acid **26**, whose esterification with ethereal diazomethane produced, after column chromatography, an 83% yield of the methyl ester **27** in high enantiomeric and diastereomeric purity according to both HPLC analysis (>99% e.e., Chiralcel® OD-R column, methanol/ 0.5M $NaClO_4$ mixtures) and DSC measurements. Thus, the stereochemical purity is conserved along the whole sequence from **20** to **27**.



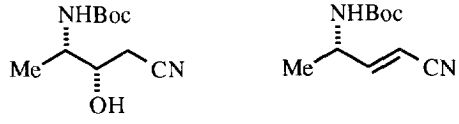
Scheme 6

B. Enantioselective Synthesis of Protected *syn* β-Hydroxy-γ-amino Acids

In principle, the methodology described in the previous section should also be applicable to the preparation of *syn* β-hydroxy-γ-amino acids, provided that a configuration inversion at the C-2 position of **8** is included in the sequence.

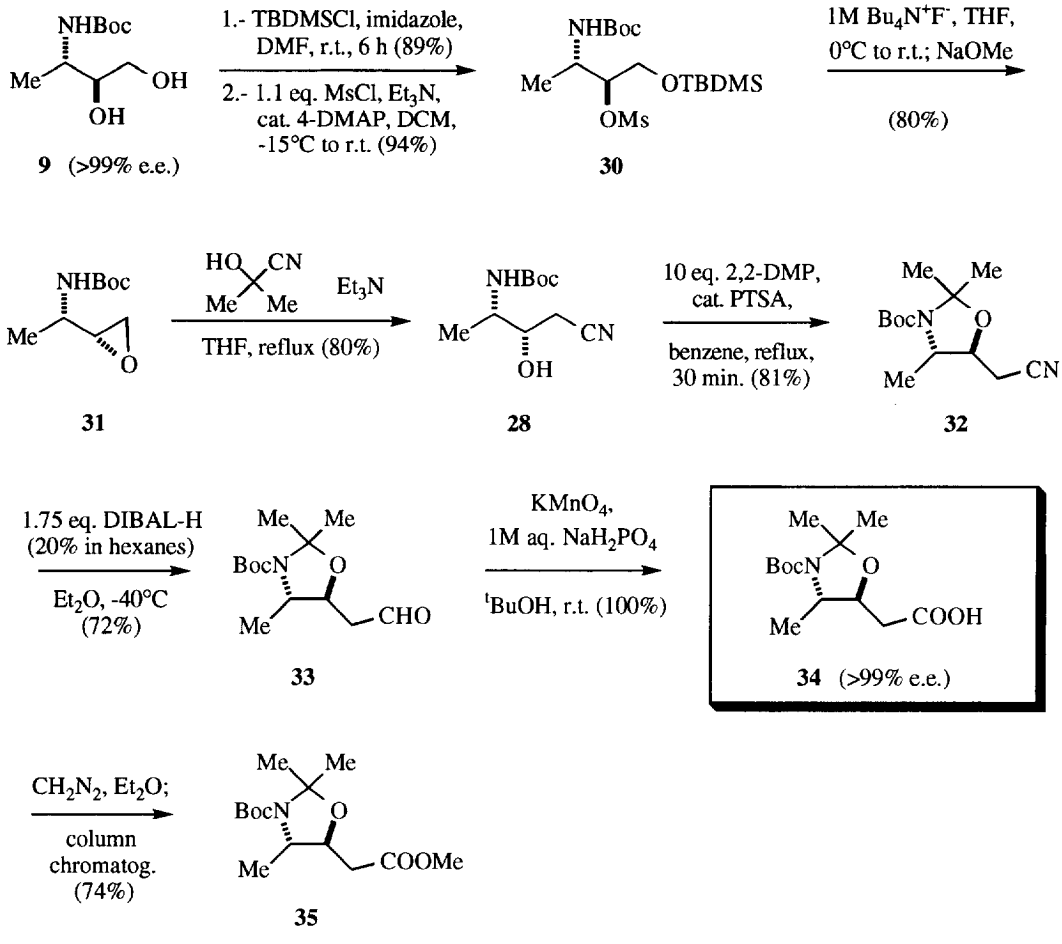


As before, the methodology set-up was effected on the *N*-Boc-amino diol **9**. In our first approach, the attempted Mitsunobu inversion (using either benzoic[37] or *p*-nitrobenzoic acids[38]) on **10** gave none of the desired *syn*-hydroxy nitrile **28**, leading instead to product mixtures which contained substantial amounts of the α,β-unsaturated nitrile **29**.



28 **29**

We were pleased to find however that these initial difficulties could be easily overcome by performing the required inversion at an earlier stage of the sequence (Scheme 7). To this end, the primary hydroxyl of **9** was protected as a *tert*-butyldimethylsilyl ether;[25] subsequent mesylation of the secondary hydroxyl gave in almost quantitative yields the activated derivative **30**, which was treated first with tetrabutylammonium fluoride and then with sodium methoxide to afford the *N*-Boc-aminoalkyl epoxide **31**, *with complete inversion of configuration at C-2*.[28] From this key intermediate, **28** could be readily secured by exposure to acetone cyanohydrin/triethylamine in refluxing THF, as described above for the epimeric epoxide **12**. The subsequent simultaneous protection of the carbamate and hydroxyl groups effected by acid-catalysed treatment of **28** with 2,2-dimethoxypropane was facilitated by virtue of the much more stable (with respect to **15**) *trans* configuration of the oxazolidine **32**, which was obtained in 81% yield after 30 min. in refluxing benzene *and without any solvent distillation.* The same methodology previously used in the *anti* series (DIBAL-H reduction followed by permanganate oxidation at controlled pH) allowed the obtention of the fully protected *anti*-4-amino-3-hydroxypentanoic acid (**34**) in 72% overall yield from **32**. Although no direct measurement of the enantiomeric purity of **34** has been performed, the similarity of reaction conditions suffered along the sequence by the different intermediates with those involved in the synthesis of **17** from **12**, fully supports the idea that **34** is obtained in homochiral (> 99% e.e.) form.



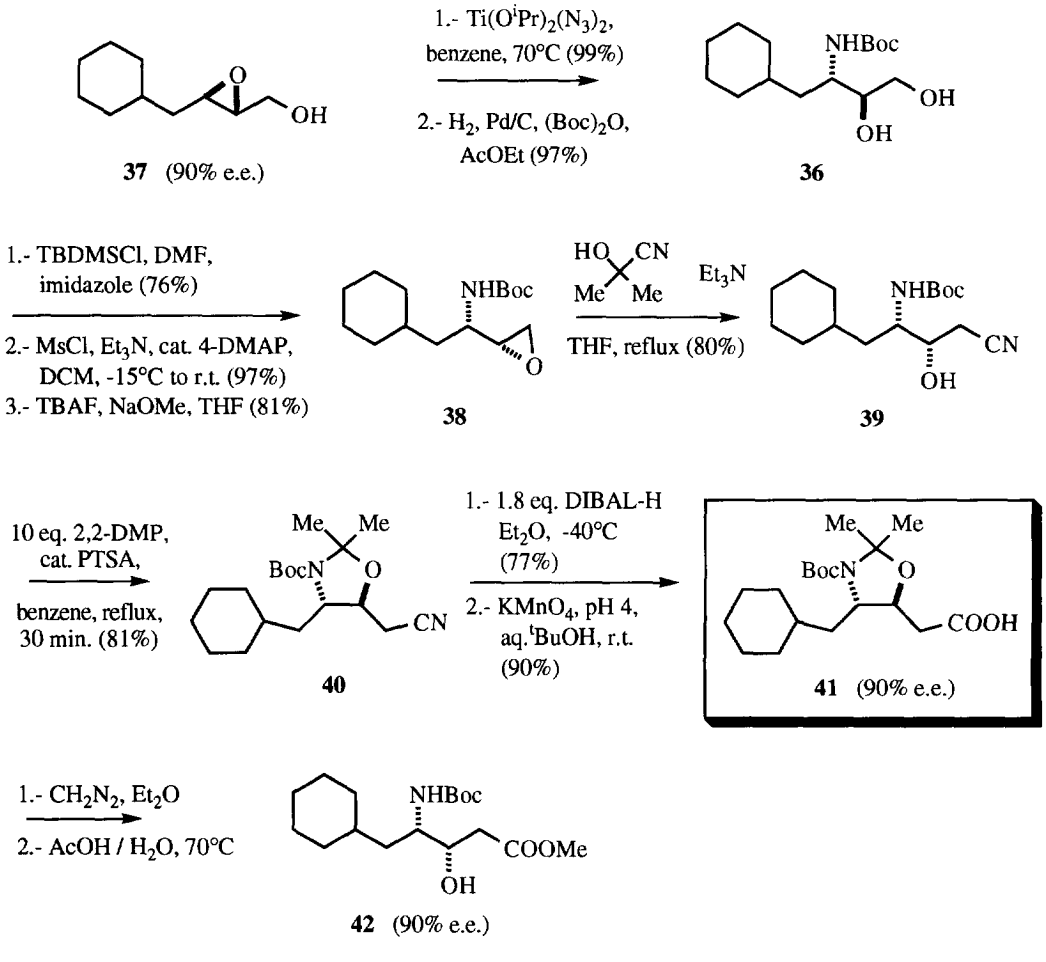
Scheme 7

A final assessment of the versatility of the present methodology was provided by a highly stereoselective synthesis of fully protected *(3S,4S)*-cyclohexylstatine **2**, an interesting β-hydroxy-γ-amino acid whose enhanced lipophilic character (with respect to statine **1**) imparts desirable biological activity to a number of renin inhibitors.[3]

The requisite *(2S,3S)-N*-Boc-3-amino-4-cyclohexylbutane-1,2-diol (**36**) was efficiently (98% yield) obtained from the known[28] epoxy alcohol **37** (90% e.e.) *via* regioselective ring opening with titanium diazidodiisopropoxide[39] and catalytic hydrogenation in the presence of di-*tert*-butyl dicarbonate[40] (Scheme 8). Applying the same conditions developed for the model compound **9** (silylation of the primary alcohol, mesylation and base-induced deprotection-cyclization), this diol was successfully converted into the *syn-N*-Boc-amino epoxide **38**. The oxirane ring of **38** was opened by cyanide anion to give the *(3S,4S)-N*-Boc-hydroxy nitrile **39** in 80% yield. As observed for **32**, the formation of the *trans*-oxazolidine **40** was very facile, and an 81% yield of diastereomerically pure compound was obtained after chromatographic

purification. Although the DIBAL-H mediated reduction of the nitrile **40** took place with good yields (77%), the resulting aldehyde was not very stable, and was directly oxidized to afford the *(4S,5S)*-3-(*tert*-butoxycarbonyl-5-carboxymethyl-4-cyclohexylmethyl-2,2-dimethyl-1,3-oxazolidine (**41**) in 90% yield. This compound, obtained as a white crystalline solid, is the *N*-Boc-*N,O*-oxazolidine-protected form of cyclohexylstatine **2**.

In order to test the stereochemical purity of **41**, this compound was converted into the known[41] hydroxyester **42** in 69% overall yield by esterification with diazomethane followed by oxazolidine hydrolysis with aqueous acetic acid. A comparison of the specific rotation of **42** with that of the homochiral compound[41] revealed that the enantiomeric purity of **41** was 90%. Once again, it is demonstrated that *N*-Boc-3-amino-1,2-diols can be converted into β-hydroxy-γ-amino acids without any loss in stereochemical purity.



Scheme 8

In summary, we have developed an efficient method for the highly enantioselective synthesis of β-hydroxy-γ-amino acids, having either *syn* or *anti* relative configuration, starting from readily available allylic alcohols, and whose key steps involve catalytic Sharpless epoxidation (as the sole source of chirality),[18] regioselective epoxy alcohol opening with an ammonia surrogate,[20] stereodivergent conversion of the resulting amino diols to *N*-Boc-aminoalkyl epoxides[28] and nucleophilic attack to the less substituted oxirane position by cyanide anion. Due to its generality, this synthetic protocol should be applicable to the obtention of a wide variety of β-hydroxy-γ-amino acids.

Experimental

Melting points were determined in open ended capillary tubes on a Büchi-Tottoli apparatus or on a Reichert-Thermovar Köfler apparatus and are uncorrected. Infrared spectra were measured with a Perkin-Elmer 681 or with a Nicolet FT-IR 510 spectrometer using film NaCl or KBr pellet techniques. ^{1}H and ^{13}C NMR spectra were recorded in $CDCl_3$, on a Varian Gemini-200 or on a Varian Unity-300 spectrometer with tetramethylsilane or chloroform as an internal standard. Chemical shifts are expressed in δ (PPM) units downfield by TMS. The multiplicity in ^{13}C NMR spectra was determined by means of DEPT techniques. Mass spectra were recorded at 70 eV ionizing voltage on a Hewlett-Packard 5890 apparatus. Ammonia was used generally for chemical ionization (CI). MS spectra are presented as *m/z* (% rel. int.). Optical rotations were measured with a Perkin-Elmer 241 MC automatic polarimeter. Elemental analyses were performed by the"Servei d'Anàlisis Elementals del CSIC de Barcelona". DSC measurements were performed on a Mettler DSC30 instrument at the "Servei de Calorimetria de Reacció i Anàlisi Tèrmica. Divisió III. Universitat de Barcelona". THF and diethyl ether used in the reactions were dried by distillation over metallic sodium and benzophenone, dichloromethane, chloroform, DMF and DMSO were distilled over calcium hydride and benzene over metallic sodium. All reactions were carried out in oven-dried glassware under an atmosphere of pre-purified nitrogen. The course of all of the reactions described could be conveniently monitored by TLC (Merck DC-Alufolien KIESELGEL 60 F_{254}). Silicagel (J. T. Baker, 70-230 mesh) was used for column chromatography, separations being performed on triethylamine-pretreated silicagel (2.5% v/v), eluting (unless otherwise stated) with hexane/ethyl acetate mixtures of increasing polarity. HPLC analyses were performed with a Chiralcel® OD-R column, eluting with methanol / 0.5M sodium perchlorate mixtures, on a Hewlett-Packard HPLC1050 instrument.

Obtainment of the *anti*-hydroxynitrile 10

A. *Via* tosylate 11

***(2S,3S)*-3-(*tert*-Butoxycarbonylamino)-2-hydroxybutyl *p*-Toluenesulfonate, 11:** To a cooled (-15°C) solution of *(2S,3S)*-3-(*tert*-butoxycarbonylamino)butane-1,2-diol **9**[24] (0.20 g, 0.97 mmol) in dry pyridine (1.4 mL), *p*-toluenesulfonyl chloride (0.204 g, 1.07 mmol) was added portionwise over 10 minutes. The resulting mixture was kept at 4°C for 64 hours; water (3 mL) and dichloromethane (3 mL) were subsequently added. The phases were separated and the aqueous one extracted with additional (2x5 mL) dichloromethane. The combined organic phases were successively washed with aqueous 2 M hydrochloric acid (until acid pH), saturated aqueous $NaHCO_3$ and water, dried over anhydrous $MgSO_4$ and stripped of solvents at reduced pressure, to give 0.26 g (74% yield) of tosylate **11**, pure enough to be used in the

following step. This product could be further purified, but with low material recovery, by column chromatography. Colourless oil. IR (NaCl film): 3400(br), 3070, 2980, 2930, 2880, 1700 (br), 1600, 1520, 1370, 1250, 1170, 1100, 825 cm^{-1}; ^1H NMR (200 MHz): 1.12 (3H, d, J=7 Hz), 1.41 (9H, s), 2.45 (3H, s), 3.5-4.1 (4H+OH, m), 4.8 (1H, br d), 7.35 (2H, d, J= 10 Hz), 7.8 (2H, d, J = 10 Hz); ^{13}C NMR (50 MHz): 15.7 (CH_3), 21.6 (CH_3), 28.2 ($3CH_3$), 48.5 (CH), 71.2 (CH_2), 72.2 (CH), 79.9 (Cq), 127.9 (CH), 129.9 (CH), 132.3 (Cq), 141.5 (Cq), 156.0 (Cq); MS (CI): 360 ($[M+1]^+$, 6%); $[\alpha]^{23}_D$ = -8.0 (c=2.72, $CHCl_3$).

Preparation of hydroxynitrile 10 from 11: To a hot (90°C), stirred suspension of sodium cyanide (30 mg, 0.6 mmol) in anhydrous DMSO (0.2 mL), a solution of tosylate **11** (0.20 g, 0.56 mmol) in DMSO (0.5 mL) was added. The resulting mixture was heated for one hour at 100°C, slowly cooled to room temperature and poured into water (5 mL). Extraction with ether gave, after washing with brine, drying over $MgSO_4$ and elimination of the solvent, 84 mg of an oil which was purified by column chromatography, to afford 45 mg (44% yield) of hydroxynitrile **10** (see below).

B. *Via* epoxide 12.

***(S)*-1-[*(S)*-1-(*tert*-Butoxycarbonylamino)ethyl]oxirane 12.**

i) From the tosylate 11: To a suspension of sodium hydride (0.56 mmol, from 17 mg of a 80% mixture with paraffin and washing with anhydrous hexane) in dry dichloromethane (1 mL) were added a solution of tosylate **11** (0.20 g, 0.56 mmol) in dichloromethane (4 mL) and two drops of DMSO. After stirring for 4 hours at room temperature, some drops of methanol were added to remove any trace of unreacted hydride, and the mixture was poured into water (5 mL). The aqueous phase was extracted with ether, and the organic extract was dried over anhydrous $MgSO_4$. Elimination of the solvents at reduced pressure and purification of the crude product by column chromatography gave 70 mg (67% yield) of **12** as a colourless oil.

ii) *From the aminodiol 9:* To a solution of aminodiol **9** (0.10 g, 0.49 mmol) and triphenylphosphine (0.13 g, 0.51 mmol) in anhydrous chloroform (4 mL) was added a solution of diethyl azodicarboxylate (90 mg, 0.51 mmol) in chloroform (0.2 mL). The mixture was heated under reflux for 65 hours, cooled to room temperature and stripped of the solvent at reduced pressure. Purification of the crude product by column chromatography gave 62 mg (68% yield) of **12** as a colourless oil.

Oxirane **12**, prepared according to either of these procedures, showed identical spectroscopic data and exhibited, within the limits of experimental error, coincident values for specific rotation. IR (NaCl film): 3350(br), 3040, 2980, 2930, 2880, 1700 (br), 1530, 1395, 1365, 1250, 840 cm^{-1}; ^1H NMR (200 MHz): 1.15 (3H, d, J=7 Hz), 1.45 (9H, s), 2.72 (1H, m), 2.77 (1H, m), 2.94 (1H, m), 3.65 (1H, br s), 4.6 (1H, br s); ^{13}C NMR (50 MHz): 16.4 (CH_3), 28.3 ($3CH_3$), 46.2 (CH_2), 49.0 (CH), 54.6 (CH), 80.0 (Cq), 155.0 (Cq); MS (CI): 188 ($[M+1]^+$, 16%), 205 ($[M+18]^+$, 100%); $[\alpha]^{23}_D$ = -13.8 (c=1.98, $CHCl_3$).

***(3R,4S)*-4-(*tert*-Butoxycarbonylamino)-3-hydroxypentanenitrile 10:** A solution of the oxirane **12** (1.36 g, 7.27 mmol), 2-hydroxy-2-methylpropanenitrile (0.74 g, 8.66 mmol) and triethylamine (1.21 mL, 8.66 mmol) in anhydrous THF (2.9 mL) was heated under reflux over 22 hours, poured into water and extracted with ether. The organic phase was washed first with brine and then with water, dried over

anhydrous $MgSO_4$ and stripped of solvents at reduced pressure, to give 1.38 g of a crude product which was purified by column chromatography to afford 1.20 g (77% yield) of hydroxynitrile **10**, identical in all respects to the product obtained from tosylate **11**. White solid. mp 113-114°C; IR (KBr): 3420(br), 3370, 3000, 2980, 2960, 2940, 2860, 2250, 1680, 1520, 1450, 1390, 1365, 1240, 1160, 1040 cm^{-1}; ^1H NMR (200 MHz): 1.19 (3H, d, J=7 Hz), 1.45 (9H, s), 2.52 (2H, d, J = 6.6 Hz), 3.80 (1H, m), 3.94 (1OH, br s), 4.12 (1H, m), 4.71 (1H, br d); ^{13}C NMR (50 MHz): 15.9 (CH_3), 22.0 (CH_2), 28.3 ($3CH_3$), 50.9 (CH), 71.3 (CH), 80.7 (Cq), 117.9 (Cq), 156.6 (Cq); MS (CI): 215 ($[M+1]^+$, 17%), 232 ($[M+18]^+$, 100%), 249 ($[M+35]^+$, 2%), 176 ($[M+18-C_4H_8]^+$, 30%); $[\alpha]^{23}_D$ = -18.5 (c=2.14, $CHCl_3$); Anal. calcd for $C_{10}H_{18}N_2O_3$: C, 56.06%; H, 8.47%; N, 13.07%. Found: C, 56.27%; H, 8.36%; N, 12.89%.

***(3R,4S)*-4-(*tert*-Butoxycarbonylamino)-3-hydroxypentanoic Acid 13:** A suspension of hydroxynitrile **10** (50 mg, 0.23 mmol) in 25% aqueous NaOH (1.5 mL) and methanol (5 mL) was heated to reflux for 24 hours, after which time no NH_3 evolution was detected. The resulting mixture was cooled to 0°C, acidified (pH=5) with cool (0°C) 1 M aqueous HCl, concentrated *in vacuo* and thoroughly extracted with ethyl acetate. The combined extracts were washed with brine, dried over anhydrous $MgSO_4$ and stripped of solvents at reduced pressure, to afford 14 mg (26% yield) of a colourless oil whose spectral characteristics coincided with those expected for the acid **13**. IR (NaCl film): 3380(br), 2980, 2940, 2860,1710 (br), 1520, 1450, 1395, 1370 cm^{-1}; ^1H NMR (200 MHz): 1.15 (3H, d, J=7 Hz), 1.44 (9H, s), 2.60 (2H, m), 3.75 (1H, br s), 4.00 (1H, br s), 4.83 (1H, br s); MS (CI): 234 ($[M+1]^+$, 81%), 251 ($[M+18]^+$, 100%), 195 ($[M+18-C_4H_8]^+$, 37%), 178 ($[M+1-C_4H_8]^+$, 7%).

***(3R,4S)*-3-(*tert*-Butyldimethylsilyloxy)-4-(*tert*-butoxycarbonylamino)pentanenitrile 14:** A mixture of hydroxynitrile **10** (50 mg, 0.23 mmol), *tert*-butyldimethylsilyl chloride (0.105 g, 0.70 mmol), imidazole (95 mg, 1.40 mmol) and dry DMF (50 μL) was stirred at room temperature for 7 hours, diluted with dichloromethane and poured into water. The organic phase was washed with saturated aqueous ammonium chloride and dried over $MgSO_4$. The solvents were eliminated at reduced pressure to give 0.13 g of a crude product, which was purified by column chromatography, affording 70 mg (91% yield) of the nitrile **14**. Colourless oil. IR (NaCl film): 3360(br), 2980, 2960, 2940, 2880, 2860, 2250, 1700 (br), 1500, 1460, 1390, 1360, 1250, 1170, 1050 cm^{-1}; ^1H NMR (200 MHz): 0.11 (3H, s), 0.16 (3H, s), 0.92 (9H, s), 1.13 (3H, d, J=7 Hz), 1.45 (9H, s), 2.47 (2H, d, J = 6 Hz), 3.70 (1H, m), 4.06 (1H, m), 4.50 (1H, br d); ^{13}C NMR (50 MHz): -4.8 (CH_3), -4.6 (CH_3), 14.1 (CH_3), 18.0 (Cq), 23.5 (CH_2), 25.7 ($3CH_3$), 28.3 ($3CH_3$), 50.4 (CH), 70.3 (CH), 79.6 (Cq), 117.4 (Cq), 154.9 (Cq); MS (CI): 329 ($[M+1]^+$, 42%), 346 ($[M+18]^+$, 100%), 290 ($[M+18-C_4H_8]^+$, 33%), 273 ($[M+1-C_4H_8]^+$, 12%); $[\alpha]^{23}_D$ = -22.4 (c=3.20, $CHCl_3$).

***(4S,5R)*-3-(*tert*-Butoxycarbonyl)-5-cyanomethyl-2,2,4-trimethyl-1,3-oxazolidine 15:** A mixture of hydroxynitrile **10** (0.20 g, 0.93 mmol), 2,2-dimethoxypropane (1.14 mL, 9.33 mmol), *p*-toluenesulfonic acid monohydrate (3 mg, 0.016 mmol) and anhydrous benzene (3.2 mL) was heated to reflux until the starting material disappeared (45 minutes). After cooling to room temperature and diluting with ether (5 mL) the resulting solution was washed successively with aqueous saturated $NaHCO_3$ solution and brine. Drying of the organic phase over anhydrous $MgSO_4$ and elimination of the solvents at reduced pressure gave a crude product (0.19 g) which was purified by column chromatography. In this way 0.17 g (72% yield) of the

oxazolidine **15** was obtained as a colourless oil. IR (NaCl film): 2970, 2920, 2890, 2250, 1690 (br), 1530, 1480, 1460, 1390, 1110 cm^{-1}; ^1H NMR (200 MHz): 1.17 (3H, d, J=6 Hz), 1.48 (9H, s), 1.53 (3H, br s), 1.59 (3H, br s), 2.54 (1H, dd, J = 15 Hz, J' = 5 Hz), 2.70 (1H, br d, J = 15 Hz), 4.10 (1H, br s), 4.30 (1H, m); ^{13}C NMR (50 MHz): 13.5* (CH_3), 14.1 (CH_3), 18.3 (CH_2), 23.9 (CH_2), 25.1* (CH_3), 27.1* (CH_3), 28.0 (CH_3), 28.3 ($3CH_3$), 54.6 (CH), 71.5 (CH), 80.0 (Cq), 93.5 (Cq), 116.4 (Cq), 150.5 (br, Cq) (the signals with an asterisk correspond to the minor rotamer of the *N*-Boc group); MS (CI): 255 ($[M+1]^+$, 95%), 272 ($[M+18]^+$, 100%), 289 ($[M+35]^+$, 1%), 216 ($[M+18-C_4H_8]^+$, 30%); $[\alpha]^{23}_D$ = -9.55 (c=3.92, $CHCl_3$).

***(4S,5R)*-3-(*tert*-Butoxycarbonyl)-5-formylmethyl-2,2,4-trimethyl-1,3-oxazolidine 16:** To a cold (-40°C) solution of the nitrile **15** (45 mg, 0.18 mmol) in anhydrous diethyl ether (1.5 mL) were added 0.31 mL (0.31 mmol) of a 20% solution of DIBAL-H in hexanes. The mixture was stirred at -40°C for 45 minutes, at -20°C for another 45 minute period, treated with ethyl acetate (1.5 mL) and then allowed to warm up to room temperature. A saturated aqueous solution of of sodium potassium tartrate (1.5 mL) was then added, followed by vigorous stirring during 2 hours. The resulting mixture was diluted with ether (5 mL), and the organic phase was washed with brine and dried over anhydrous $MgSO_4$. Evaporation of the solvents and purification of the crude product (45 mg) by column chromatography afforded 35 mg (76% yield) of the desired aldehyde **16**. Colourless oil. IR (NaCl film): 2980, 2930, 2720, 1730, 1695 (br), 1450, 1390, 1365, 1070 cm^{-1}; ^1H NMR (200 MHz): 1.08 (3H, m), 1.48 (9H, s), 1.52 (3H, br s), 1.60 (3H, br s), 2.63 (1H, dd, J = 17 Hz, J' = 4 Hz), 2.85 (1H, br d, J = 17 Hz), 4.10 (1H, m), 4.49 (1H, m), 9.82 (1H, m); ^{13}C NMR (50 MHz): 14.1* (CH_3), 14.7 (CH_3), 23.8 (CH_3), 25.0* (CH_3), 27.2* (CH_3), 28.1 (CH_3), 28.5 ($3CH_3$), 43.6* (CH_2), 43.8 (CH_2), 54.8 (CH), 70.8* (CH), 71.0 (CH), 79.5 (Cq), 80.1* (Cq), 92.6 (Cq), 150.5 (br, Cq), 199.4 (Cq) (the signals with an asterisk correspond to the minor rotamer of the *N*-Boc group); MS (CI): 258 ($[M+1]^+$, 100%), 275 ($[M+18]^+$, 26%), 219 ($[M+18-C_4H_8]^+$, 15%), 174 ($[M+1-C_4H_8-CO]^+$, 23%), 158 ($[M+1-C_5H_8O_2]^+$, 53%); $[\alpha]^{23}_D$ = +2.90 (c=1.49, $CHCl_3$).

***(4S,5R)*-3-(*tert*-Butoxycarbonyl)-5-carboxymethyl-2,2,4-trimethyl-1,3-oxazolidine 17:** To a vigorously stirred mixture of aldehyde **16** (40 mg, 0.155 mmol), *tert*-butyl alcohol (0.9 mL) and 5% aqueous NaH_2PO_4 (0.6 mL), at room temperature, a 1 M aqueous solution of $KMnO_4$ (0.9 mL, 0.9 mmol) was added dropwise. The excess permanganate was destroyed by addition of aqueous Na_2SO_3 solution, and the solution was cooled to 0°C and acidified (pH 4-5) with precooled 10% aqueous HCl, until the colloidal precipitate of MnO_2 redissolved. The aqueous phase was thoroughly extracted with ethyl acetate, and the combined organic extracts washed with brine, dried over anhydrous $MgSO_4$ and stripped of solvents at reduced pressure, to give 40 mg (94%) of the acid **17**. Colourless oil. IR (NaCl film): 3600-2500, 2985, 2940, 1720, 1700 (br), 1480, 1450, 1390 (br), 1365, 1070, 960 cm^{-1}; ^1H NMR (200 MHz): 1.11 (3H, br s), 1.48 (9H, s), 1.54 (3H, br s), 1.59 (3H, br s), 2.57 (1H, dd, J = 16 Hz, J' = 4 Hz), 2.75 (1H, br d, J = 16 Hz), 4.00, 4.15* (1H, br s), 4.43 (1H, m), 8.20 (1COOH, br s) (the signal with asterisk corresponds to a rotamer of the *N*-Boc group); ^{13}C NMR (50 MHz): 13.8, (CH_3), 14.6* (CH_3), 23.8 (CH_3), 24.9* (CH_3), 27.2* (CH_3), 28.1 (CH_3), 28.4 ($3CH_3$), 43.3 (CH_2), 54.8 (CH), 72.05 (CH), 79.5 (Cq), 80.2* (Cq), 92.5 (Cq), 92.9* (Cq), 151.5 (br, Cq), 175.0 (Cq), 175.5* (Cq) (the signals with an asterisk correspond to a rotamer of the *N*-Boc group); MS (CI): 274 ($[M+1]^+$, 100%), 291 ($[M+18]^+$, 13%), 218 ($[M+1-C_4H_8]^+$, 6%), 174 ($[M+1-C_5H_8O_2]^+$, 55%), 158 ($[M-C_5H_{10}NO_2]^+$, 18%); $[\alpha]^{23}_D$ = -2.80 (c=1.89, $CHCl_3$). A

portion (20 mg) of this product was treated with an excess of ethereal diazomethane to give, after purification by column chromatography, 15 mg (71% yield) of the methyl ester **18**. Colourless oil. IR (NaCl film): 2980, 2920, 2850, 1740, 1695 (br), 1450, 1435, 1390, 1360, 1060 cm^{-1}; ^1H NMR (200 MHz): 1.09 (3H, m), 1.48 (9H, s), 1.53 (3H, br s), 1.58 (3H, br s), 2.54 (1H, dd, J = 17 Hz, J' = 4 Hz), 2.72 (1H, br d, J = 17 Hz), 3,72 (3H, s), 4.00, 4.10* (1H, br s), 4.44 (1H, m) (the signal with asterisk corresponds to a rotamer of the *N*-Boc group).

***(S)*-1-[*(S)*-1-(*tert*-Butoxycarbonylamino)-1-phenylmethyl]oxirane 21:** A stirred mixture of *N*-Boc-amino diol **20**[22a] (0.50 g, 1.87 mmol), triphenylphosphine (0.52 g, 1.96 mmol) and diethyl azodicarboxylate (0.34 g, 1.96 mmol) in dry chloroform (16 mL) was heated under reflux for 36 h; after elimination of the solvent at reduced pressure, the crude residue was purified by column chromatography, to give 0.39 g (84% yield) of the epoxide **21**. White solid. mp. 90-91°C. IR (KBr): 3380, 3040, 3000, 2950, 1695, 1530, 1250, 750, 700 cm^{-1}. ^1H NMR (200 MHz): 1.42 (9H, s), 2.50 (1H, dd, J=4.8 Hz, J'=2.6 Hz), 2.75 (1H, dd, J=4.8 Hz, J'=3.9 Hz), 3.25 (1H, m), 4.71 (1H, br s), 5.20 (1 NH, br d), 7.32 (5H, m). ^{13}C NMR (50 MHz): 28.3 ($3CH_3$), 45.8 (CH_2), 53.8 (CH), 55.4 (CH), 79.9 (Cq), 127.1 (2CH), 127.9 (CH), 128.6 (2CH), 137.9 (Cq), 155.1 (Cq). MS (CI): 250 ([M+1]$^+$, 33%), 267 ([M+18]$^+$, 100%), 284 ([M+35]$^+$, 4%); $[\alpha]_D^{23}$ = +22.4 (c=2.74, $CHCl_3$); Anal. calcd for $C_{14}H_{19}NO_3$: C, 67.45%; H, 7.68%; N, 5.62%. Found: C, 67.49%; H, 7.65%; N, 5.59%.

***(3R,4S)*-4-(*tert*-Butoxycarbonylamino)-4-phenyl-3-hydroxybutanenitrile 22:** Following the same procedure used for the preparation of **10**, and starting from 0.39 g (1.56 mmol) of the oxirane **21**, 0.37 g (86% yield) of hydroxynitrile **22** were obtained. White solid. mp. 156-157°C. IR (KBr): 3380 (br), 3060, 3030, 3010, 2980, 2920, 2250, 1685, 1510, 1455, 1390, 1365, 1240, 1010, 750, 700 cm^{-1}. ^1H NMR (200 MHz): 1.42 (9H, s), 2.45 (2H, m), 3.22 (1 OH, br s), 4.25 (1H, m), 4.73 (1H, br s), 5.30 (1 NH, br s), 7.36 (5H, m). ^{13}C NMR (50 MHz): 22.8 (CH_2), 28.3 ($3CH_3$), 59.0 (CH), 70.5 (CH), 80.7 (Cq), 117.6 (Cq), 127.6 (2CH), 128.6 (CH), 129.1 (2CH), 136.9 (Cq), 155.7 (Cq). MS (CI): 277 ([M+1]$^+$, 33%), 294 ([M+18]$^+$, 100%), 238 ([M+18-C_4H_8]$^+$, 60%); $[\alpha]_D^{23}$ = +37.3 (c=1.86, $CHCl_3$); Anal. calcd for $C_{15}H_{20}N_2O_3$: C, 65.20%; H, 7.30%; N, 10.14%. Found: C, 64.80%; H, 7.35%; N, 9.67%.

***(4S,5R)*-3-(*tert*-Butoxycarbonyl)-5-cyanomethyl-4-phenyl-2,2-dimethyl-1,3-oxazolidine 23:** A mixture of the hydroxynitrile **22** (80 mg, 0.29 mmol), 2,2-dimethoxypropane (0.30 g, 2.90 mmol), *p*-toluenesulfonic acid monohydrate (1 mg, 0.005 mmol) and dry benzene (1.5 mL) was heated to reflux for 30 minutes, after which time 1 mL of solvent was distilled off. Additional 2,2-dimethoxypropane (0.30 g, 2.90 mmol) and benzene (1.5 mL) were added, and the reaction mixture was heated under reflux for two hours. The whole process was repeated twice, and the reaction mixture was allowed to cool down to room temperature. Work up as described for **15**, followed by column chromatography eluting with hexane/diethyl ether mixtures led to the recovery of 12 mg of starting material and to the isolation of 4 mg (5%, based on 85% conversion) of the *trans*-oxazolidine **24**, and 54 mg (69% yield, based on 85% conversion) of the *cis*-oxazolidine **23** as a colourless oil. Spectral data for **23**: IR (NaCl film): 3070, 3040, 2980, 2940, 2260, 1700 (br), 1480, 1455, 1380, 1365, 770, 710 cm^{-1}; ^1H NMR (200 MHz): 1.43 (9H, s), 1.63 (3H, s), 1.87 (3H, s), 2.02 (1H, dd, J = 16.7 Hz, J' = 5 Hz), 2.25 (1H, br d, J = 16.7 Hz), 4.61 (1H, m), 4.90, 5.00* (1H, br s), 7.30 (m, 5H) (the

signal with an asterisk corresponds to the minor rotamer of the *N*-Boc group); ^{13}C NMR (50 MHz): 19.9 (CH_2), 23.4 (CH_3), 24.5* (CH_3), 26.2 (CH_3), 27.0* (CH_3), 28.0 ($3CH_3$), 63.8 (CH), 72.7 (CH), 80.0 (Cq), 94.5 (Cq), 116.6 (Cq), 127.6 (2CH), 128.2 (CH), 128.5 (2CH), 137.9 (Cq), 150.5 (br, Cq) (the signals with an asterisk correspond to the minor rotamer of the *N*-Boc group); MS (CI): 317 ($[M+1]^+$, 27%), 334 ($[M+18]^+$, 100%), 351 ($[M+35]^+$, 2%), 278 ($[M+18-C_4H_8]^+$, 15%); $[\alpha]^{23}_D$ = +1.82 (c=2.82, $CHCl_3$).

***(4S,5R)*-3-(*tert*-Butoxycarbonyl)-5-methoxycarbonylmethyl-4-phenyl-2,2-dimethyl-1,3-oxazolidine 27:** Following the same procedure used for the preparation of **16**, starting from 85 mg (0.27 mmol) of the nitrile **24**, and stirring the reaction mixture at -40°C for 15 minutes, 80 mg (93% yield) of the crude aldehyde **25** were obtained after work-up . Colourless oil. IR (NaCl film): 3080,2980, 2940, 2860, 2720, 1695 (br), 1600, 1480, 1450, 1375, 1360, 1250, 1095, 770, 710 cm^{-1}; ^1H NMR (200 MHz): 1.43 (9H, s), 1.63 (3H, s), 1.86 (3H, s), 2.20 (1H, m), 2.55 (1H, br d, J = 17 Hz), 4.40 (1H, m), 4.80, (1H, m), 7.27 (m, 5H). Without further purification, this product was submitted to the oxidation conditions described for **17** to afford 75 mg (89% yield) of the crude acid **26**. Selected spectral data: ^1H NMR (200 MHz): 1.44 (9H, s), 1.62 (3H, s), 1.86 (3H, s), 2.10 (1H, br d, J = 17.5 Hz,), 2.38 (1H, br d, J = 17.5 Hz), 4.75 (1H, m), 4.88, 5.10* (1H, br s), 7.29 (m, 5H) (the signal with an asterisk corresponds to the minor rotamer of the *N*-Boc group); ^{13}C NMR (50 MHz): 23.2 (CH_3), 24.3* (CH_3), 26.2 (CH_3), 27.1* (CH_3), 28.1 ($3CH_3$), 28.3* ($3CH_3$), 35.5 (CH_2), 63.9 (CH), 72.9 (CH), 79.9 (Cq), 80.6* (Cq), 93.6 (Cq), 127.6 (2CH), 127.7 (CH), 128.2 (2CH), 139.0 (Cq), 151.8 (Cq), 175.5 (Cq) (the signals with an asterisk correspond to the minor rotamer of the *N*-Boc group). Finally, treatment of **26** (65 mg, 0.19 mmol) with an excess of ethereal diazomethane and subsequent purification by column chromatography afforded 55 mg (83% yield) of pure methyl ester **27**. White solid. mp 101-102°C. IR (KBr): 3060, 2990, 2930, 1740, 1685 (br), 1510, 1460, 1400, 1370, 1100, 765, 710 cm^{-1}; ^1H NMR (200 MHz): 1.44 (9H, s), 1.63 (3H, s), 1.86 (3H, s), 2.05 (1H, br d, J = 17 Hz), 2.37 (1H, br d, J = 17 Hz), 3.60 (3H, s), 4.77 (1H, m), 4.88, 5.00* (1H, br s), 7.27 (m, 5H) (the signal with an asterisk corresponds to the minor rotamer of the *N*-Boc group); ^{13}C NMR (50 MHz): 23.2 (CH_3), 24.3* (CH_3), 26.2 (CH_3), 27.1* (CH_3), 28.1 ($3CH_3$), 28.4* ($3CH_3$), 35.3 (CH_2), 51.7 (CH_3), 63.9 (CH), 73.1 (CH), 79.6 (Cq), 93.6 (Cq), 116.6 (Cq), 127.5 (2CH), 127.7 (CH), 128.0 (2CH), 150.5 (br, Cq), 171.0 (Cq) (the signals with an asterisk correspond to the minor rotamer of the *N*-Boc group); MS (CI): 350 ($[M+1]^+$, 47%), 367 ($[M+18]^+$, 100%), 384 ($[M+35]^+$, 4%), 311 ($[M+18-C_4H_8]^+$, 3%); 294 ($[M+1-C_4H_8]^+$, 2%);$[\alpha]^{23}_D$ = -14.1 (c=1.46, $CHCl_3$); Anal. calcd for $C_{19}H_{27}NO_5$: C, 65.31%; H, 7.79%; N, 4.01%. Found: C, 65.27%; H, 7.89%; N, 3.93%.

***(1S,2S)*-1-(*tert*-Butyldimethylsilyloxymethyl)-2-(*tert*-butoxycarbonylamino)propyl Methanesulfonate 30:** To a cold (-15°C) solution of *(2S,3S)*-1-(*tert*-butyldimethylsilyloxy)-3-(*tert*-butoxycarbonylamino)-2-butanol[25] (1.205 g, 3.77 mmol), triethylamine (0.420 g, 4.15 mmol) and 4-dimethylaminopyridine (23 mg, 0.19 mmol) in anhydrous dichloromethane (3.6 mL) a solution of methanesulfonyl chloride (0.475 g, 4.15 mmol) in dry dichloromethane (0.9 mL) was added dropwise. The mixture was slowly warmed to room temperature, stirred for 24 hours, diluted with dichloromethane (10 mL) and successively washed with cold (0°C) 10% aqueous HCl, saturated aqueous $NaHCO_3$ and water. Drying over $MgSO_4$ and elimination of the solvent at reduced pressure gave a crude product (1.56 g) which, upon column chromatography, afforded 1.41 g (94% yield) of the mesylate **30** as a colourless oil. IR (NaCl film):

3400(br), 2990, 2970, 2940, 2900, 2870, 1720 (br), 1520, 1400, 1375, 1260, 1180 cm^{-1}; ^1H NMR (200 MHz): 0.09 (3H, s), 0.10 (3H, s), 0.91 (9H, s), 1.18 (3H, d, J=6 Hz), 1.44 (9H, s), 3.09 (3H, s), 3.82 (2H, m), 3.98 (1H, m), 4.71 (1H, m); ^{13}C NMR (50 MHz): -5.7 ($2CH_3$), 15.4 (CH_3), 18.0 (Cq), 25.7 ($3CH_3$), 28.2 ($3CH_3$), 38.4 (CH_3), 46.8 (CH), 63.1 (CH_2), 79.3 (Cq), 84.1 (CH), 155.1 (Cq); MS (CI): 284 ([M+1-$C_6H_{14}Si$]$^+$, 4%), 301 ([M+18-$C_6H_{14}Si$]$^+$, 46%), 245 ([M+18-$C_6H_{14}Si$-C_4H_8]$^+$, 26%), 149 ([M+18-$C_6H_{14}Si$-C_4H_8-CH_4SO_3]$^+$, 100%); $[\alpha]^{23}_D$ = -15.1 (c=2.19, $CHCl_3$).

***(R)*-1-[*(S)*-1-(*tert*-Butoxycarbonylamino)ethyl]oxirane 31:** To a cold (0°C) solution of the mesylate **30** (1.12 g, 2.82 mmol) in anhydrous THF (10 mL), 5.12 mL (5.63 mmol) of a 1.1 M THF solution of tetrabutylammonium fluoride (containing 5% water) were added dropwise. The resulting mixture was stirred for 30 minutes at room temperature, and solid sodium methoxide (0.18 g, 3.10 mmol) was added in one portion. Stirring was continued for 2 hours, after which time the reaction mixture was poured into water (25 mL) and extracted with ether. Washing with brine, drying over $MgSO_4$ and elimination of the solvents *in vacuo* gave 0.78 g of an oil which was purified by column chromatography to afford 0.42 g (80% yield) of the epoxide **31**. Colourless oil. IR (NaCl film): 3340(br), 3050, 2980, 2930, 2880, 1710 (br), 1525, 1395, 1370, 1250, 905 cm^{-1}; ^1H NMR (200 MHz): 1.26 (3H, d, J=7 Hz), 1.44 (9H, s), 2.61 (1H, m), 2.74 (1H, m), 2.98 (1H, m), 4.00 (1H, m), 4.45 (1H, br s); ^{13}C NMR (50 MHz): 18.4 (CH_3), 28.2 ($3CH_3$), 44.3 (CH_2), 44.9 (CH), 54.4 (CH), 79.3 (Cq), 155.3 (Cq); MS (CI): 188 ([M+1]$^+$, 85%), 100%), 149 ([M+18-C_4H_8]$^+$, 100%); 132 ([M+1-C_4H_8]$^+$, 77%); $[\alpha]^{23}_D$ = -7.2 (c=1.06, $CHCl_3$).

***(3S,4S)*-4-(*tert*-Butoxycarbonylamino)-3-hydroxypentanenitrile 28:** Following the same procedure used for the preparation of **10** from the oxirane **12**, 0.425 g (2.27 mmol) of **31** gave 0.39 g (80% yield) of the nitrile **28**. White solid. mp 70-72°C; IR (KBr): 3420(br), 2985, 2960, 2260, 1690 (br), 1520, 1450, 1390, 1365, 1250, 1170, 1060 cm^{-1}; ^1H NMR (200 MHz): 1.24 (3H, d, J=7 Hz), 1.45 (9H, s), 2.56 (2H, d, J = 6 Hz), 3.72 (1H, m), 3.91 (1H, m), 4.20 (1 OH, br s), 4.98 (1H, br d); ^{13}C NMR (50 MHz): 17.7 (CH_3), 23.4 (CH_2), 28.2 ($3CH_3$), 49.8 (CH), 70.3 (CH), 80.0 (Cq), 118.1 (Cq), 156.2 (Cq); MS (CI): 215 ([M+1]$^+$, 28%), 159 ([M+1-C_4H_8]$^+$, 100%), 115 ([M+1-$C_5H_8O_2$]$^+$, 39%); $[\alpha]^{23}_D$ = -22.2 (c=2.41, $CHCl_3$); Anal. calcd. for $C_{10}H_{18}N_2O_3$: C, 56.06%; H, 8.47%; N, 13.07%. Found: C, 56.05%; H, 8.54%; N, 13.02%.

***(4S,5S)*-3-(*tert*-Butoxycarbonyl)-5-cyanomethyl-2,2,4-trimethyl-1,3-oxazolidine 32:** A mixture of hydroxynitrile **28** (0.16 g, 0.75 mmol), 2,2-dimethoxypropane (0.92 mL, 7.47 mmol), *p*-toluenesulfonic acid monohydrate (2 mg, 0.011 mmol) and anhydrous benzene (2.6 mL) was heated under reflux for 30 minutes. Work-up and purification in the conditions described above for **15** gave 0.16 g (81% yield) of the oxazolidine **32** as a colourless oil. IR (NaCl film): 2980, 2945, 2880, 2265, 1700 (br), 1530, 1470, 1450, 1390, 1100 cm^{-1}; ^1H NMR (200 MHz): 1.37 (3H, d, J=6 Hz), 1.48 (9H, s), 1.52 (3H, s), 1.61 (3H, s), 2.66 (2H, d, J = 6 Hz), 3.74 (1H, m), 3.98 (1H, q, J = 6 Hz); ^{13}C NMR (50 MHz): 19.6* (CH_3), 22.6 (CH_2), 27.3* ($2CH_3$), 28.3 ($3CH_3$), 57.4* (CH), 76.7* (CH), 80.2 (Cq), 95.0 (Cq), 116.4 (Cq), 151.7 (Cq) (the signals with an asterisk correspond are broad and correspond to a rotamer mixture of the *N*-Boc group); MS (CI): 255 ([M+1]$^+$, 50%), 272 ([M+18]$^+$, 100%), 289 ([M+35]$^+$, 1%), 216 ([M+18-C_4H_8]$^+$, 68%), 199 ([M+1-C_4H_8]$^+$, 8%); $[\alpha]^{23}_D$ = +8.70 (c=3.27, $CHCl_3$).

***(4S,5S)*-3-(*tert*-Butoxycarbonyl)-5-formylmethyl-2,2,4-trimethyl-1,3-oxazolidine 33:** To a cold (-40°C) solution of the nitrile **32** (0.145 g, 0.57 mmol) in anhydrous diethyl ether (4.3 mL) was added 1.0 mL (1.0 mmol) of a 20% solution of DIBAL-H in hexanes. The mixture was stirred at -40°C for 15 minutes, treated with ethyl acetate (5 mL) and allowed to warm up to room temperature. Work up and purification in the conditions described above for **16** afforded 105 mg (72% yield) of the desired aldehyde **33**. Colourless oil. IR (NaCl film): 2980, 2940, 2740, 1735, 1695 (br), 1480, 1460, 1390, 1350, 1075 cm^{-1}; ^1H NMR (200 MHz): 1.36 (3H, m), 1.48 (9H, s), 1.51 (3H, s), 1.58 (3H, s), 2.70 (2H, m), 3.60 (1H, m), 4.20 (1H, m), 9.82 (1H, m); ^{13}C NMR (50 MHz): 18.7* (CH_3), 26.6* ($2CH_3$), 28.5 ($3CH_3$), 47.2 (CH_2), 57.8* (CH), 76.2* (CH), 79.8 (Cq), 94.8 (Cq), 151.9 (Cq), 199.9 (Cq) (the signals with an asterisk are broad and correspond to a rotamer mixture of the *N*-Boc group); MS (CI): 258 ($[M+1]^+$, 20%), 275 ($[M+18]^+$, 30%), 219 ($[M+18-C_4H_8]^+$, 16%), 158 ($[M+18-C_5H_{11}NO_2]^+$, 14%).

***(4S,5S)*-3-(*tert*-Butoxycarbonyl)-5-carboxymethyl-2,2,4-trimethyl-1,3-oxazolidine 34:** Oxidation of **33** (90 mg, 0.35 mmol) using the conditions described above for **17** gave 70 mg (99% yield) of the acid **34**. Colourless oil. IR (NaCl film): 3600-2500, 2970, 2920, 1730 (sh), 1700 (br), 1480, 1450, 1390 (br), 1360, 1070, 960 cm^{-1}; ^1H NMR (200 MHz): 1.34 (3H, d, J = 6.4 Hz), 1.48 (9H, s), 1.52 (3H, br s), 1.60 (3H, br s), 2.66 (2H, d, J = 6.3 Hz), 3.70 (1H, br s), 4.17 (1H, m), 9.20 (1COOH, br s); ^{13}C NMR (50 MHz): 19.1* (CH_3), 27.3* ($2CH_3$), 28.9 ($3CH_3$), 39.3 (CH_2), 57.7*/58.1* (CH), 77.9* (CH), 80.3 (Cq), 94.5 (Cq), 152.0 (Cq), 175.5 (Cq) (the signals with an asterisk are broad and correspond to a rotamer mixture of the *N*-Boc group); MS (CI): 274 ($[M+1]^+$, 100%), 291 ($[M+18]^+$, 95%), 235 ($[M+18-C_4H_8]^+$, 67%), 218 ($[M+1-C_4H_8]^+$, 17%), 174 ($[M+1-C_5H_8O_2]^+$, 55%); $[\alpha]^{23}_D$ = +4.0 (c=4.5, $CHCl_3$). Treatment of this product with an excess of ethereal diazomethane produced, after purification by column chromatography, 70 mg (74% yield) of the methyl ester **35**. Colourless oil. IR (NaCl film): 2970, 2920, 2840, 1740, 1695 (br), 1450, 1435, 1385, 1355, 1070 cm^{-1}; ^1H NMR (200 MHz): 1.22 (3H, d, J = 6.2 Hz), 1.48 (9H, s), 1.52 (3H, br s), 1.57 (3H, br s), 2.61 (2H, d, J = 6.5 Hz), 3.70 (1H, br s), 3.72 (3H, s), 4.16 (1H, m). ^{13}C NMR (50 MHz): 19.2* (CH_3), 27.5* ($2CH_3$), 28.7 ($3CH_3$), 39.3 (CH_2), 52.1 (CH_3), 58.1* (CH), 77.9* (CH), 80.2 (Cq), 94.5* (Cq), 152.0* (Cq), 171.3 (Cq) (the signals with an asterisk are broad and correspond to a rotamer mixture of the *N*-Boc group); MS (CI): 288 ($[M+1]^+$, 41%), 305 ($[M+18]^+$, 61%), 249 ($[M+18-C_4H_8]^+$, 67%), 232 ($[M+1-C_4H_8]^+$, 17%).

***(2S,3S)*-3-(*tert*-Butoxycarbonylamino)-4-cyclohexylbutane-1,2-diol 36.**

1.- *(2S,3S)*-3-Azido-4-cyclohexylbutane-1,2-diol: To a vigorously stirred, hot (75 °C) suspension of titanium diazidodiisopropoxide[39b] (1.76 g, 7.05 mmol) in anhydrous benzene (30 mL), under argon athmosphere, a solution of *(2R,3R)*-3-cyclohexyl-2,3-epoxy-1-butanol **37**[28] (1.0 g, 5.87 mmol) in benzene (30 mL) was added *via* cannula. Stirring was continued for 5-10 minutes, and the reaction mixture was allowed to cool down to room temperature. After elimination of the solvent *in vacuo*, the residue was taken up in a mixture of diethyl ether (115 mL) and 5% aqueous sulfuric acid (45 mL). The aqueous phase was extracted with dichloromethane (2x30 mL), and the combined organic extracts dried over anhydrous $MgSO_4$. The solvents were stripped off and the solid residue recrystallized from hexane to give 1.24 g (99% yield) of the title compound. IR (NaCl film): 3360 (br), 2920, 2840, 2100, 1440, 1250, 1040 cm^{-1}. ^1H NMR (200 MHz): 0.80-1.80 (13H, m), 2.10 (1 OH, br s), 2.68 (1 OH, br s), 3.60-3.70 (4H, m); ^{13}C NMR (50

MHz): 26.0 (CH_2), 26.2 (CH_2), 26.4 (CH_2), 32.3 (CH_2), 34.1 (CH_2), 34.4 (CH), 38.2 (CH_2), 62.0 (CH), 63.0 (CH_2), 74.0 (CH); MS (CI): 214 ($[M+1]^+$, 5%), 231 ($[M+18]^+$, 100%), 248 ($[M+35]^+$, 10%); $[\alpha]^{23}_D$ = -1.36 (c=1.84, $CHCl_3$); Anal. calcd. for $C_{10}H_{19}N_3O_2$: C, 56.32%; H, 8.98%; N, 19.70%. Found: C, 56.44%; H, 9.05%; N, 19.74%.

2.- Hydrogenation and protection of the amino group: To a stirred suspension of 10% Pd/C (0.11 g) in dry ethyl acetate (1.9 mL), under a hydrogen athmosphere, a solution of *(2S,3S)*-3-azido-4-cyclohexylbutane-1,2-diol (1.07 g, 5.01 mmol) and di-*tert*-butyl dicarbonate (1.42 g, 6.52 mmol) in ethyl acetate (11 mL) was added *via* cannula. After stirring for 18 hours at room temperature, the reaction mixture was filtered through Celite®, which was subsequently washed thoroughly with dichloromethane. Elimination of the solvents at reduced pressure gave a crude product (1.94 g), which was purified by column chromatography, to give 1.4 g (97% yield) of pure *N*-Boc-aminodiol **36**. White solid. mp 65-68°C. IR (KBr): 3330 (br), 2980, 2920, 2840, 1685 (br), 1535, 1450, 1390, 1370, 1250, 1180, 1060 cm^{-1}. ^1H NMR (200 MHz): 0.80-1.80 (13H, m), 1.45 (9H, s), 3.2-3.8 (4H + 2 OH, m), 4.52 (1H, br d); ^{13}C NMR (50 MHz): 26.0 (CH_2), 26.3 (CH_2), 26.4 (CH_2), 28.3 ($3CH_3$), 32.1 ($2CH_2$), 34.2 (CH), 38.9 (CH_2), 49.9 (CH), 62.9 (CH_2), 74.9 (CH), 80.0 (Cq), 157.5 (Cq); MS (EI): 170 ($[C_{10}H_{20}NO]^+$, 100%), 126 ($[C_8H_{16}N]^+$, 90%), 109 ($[C_8H_{13}]^+$, 16%); $[\alpha]^{23}_D$ = -24.4 (c=1.59, $CHCl_3$); Anal. calcd. for $C_{15}H_{29}NO_4$: C, 62.74%; H, 10.10%; N, 4.88%. Found: C, 62.76%; H, 10.32%; N, 4.63%.

***(R)*-1-[*(S)*-1-(*tert*-Butoxycarbonylamino)-2-cyclohexylethyl]oxirane 38.**

1.- *(2S,3S)*-1-(*tert*-Butyldimethylsilyloxy)-3-(*tert*-butoxycarbonylamino)-4-cyclohexyl-2-butanol: To a stirred solution of aminodiol **36** (1.40 g, 4.87 mmol) and imidazole (0.73 g, 10.72 mmol) in dry DMF (25 mL), a solution of 0.81 g (5.36 mmol) of *tert*-butyldimethylsilyl chloride in DMF (4.7 mL) was added. Stirring was continued at room temperature for 24 hours, after which time the reaction mixture was poured into water and thoroughly extracted with dichloromethane. The organic extracts were washed with aqueous saturated ammonium chloride, dried over $MgSO_4$ and submitted to vacuum distillation (1 mm Hg) yielding a crude product (2.3 g) which was purified by column chromatography to give 1.49 g (76% yield) of the title compound as a colourless oil. IR (NaCl film): 3400 (br), 2900, 2840, 1680 (br), 1535, 1490, 1380, 1350, 1240, 1150, 1100, 820, 760 cm^{-1}. ^1H NMR (200 MHz): 0.08 (6H, s), 0.91 (9H, s), 1.10-1.90 (13H, m), 1.44 (9H, s), 3.00 (1 OH, br s), 3.65-3.81 (4H, m), 4.99 (1H, br d); ^{13}C NMR (50 MHz): -5.6 ($2CH_3$), 18.0 (Cq), 25.8 ($3CH_3$), 26.1 (CH_2), 26.3 (CH_2), 26.5 (CH_2), 28.3 ($3CH_3$), 32.4 (CH_2), 34.1 (CH), 34.2 (CH_2), 38.5 (CH_2), 50.7 (CH), 64.4 (CH_2), 73.5 (CH), 78.9 (Cq), 156.1 (Cq); MS (EI): 170 ($[C_{10}H_{20}NO]^+$, 100%), 126 ($[C_8H_{16}N]^+$, 91%); $[\alpha]^{23}_D$ = -17.6 (c=1.10, $CHCl_3$).

2.- *(1S,2S)*-1-(*tert*-Butyldimethylsilyloxymethyl)-2-(*tert*-butoxycarbinylamino)-3-cyclohexylpropyl Methanesulfonate: To a cold (-15°C) solution of *(2S,3S)*-1-(*tert*-butyldimethylsilyloxy)-3-(*tert*-butoxycarbonylamino)-4-cyclohexyl-2-butanol (1.29 g, 3.21 mmol), triethylamine (0.36 g, 3.52 mmol) and 4-dimethylaminopyridine (20 mg, 0.16 mmol) in anhydrous dichloromethane (3.4 mL), a solution of methanesulfonyl chloride (0.40 g, 3.52 mmol) in dichloromethane (0.8 mL) was added dropwise. The mixture was slowly warmed to room temperature, stirred for 4 hours, diluted with dichloromethane (10 mL) and successively washed with cold (0°C) 10% aqueous HCl, saturated aqueous $NaHCO_3$ and water. Drying over $MgSO_4$ and elimination of the solvent at reduced pressure gave a crude product (1.52 g) which, upon

column chromatography, afforded 1.49 g (97% yield) of the title compound as a colourless oil. IR (NaCl film): 3400 (br), 3260, 3140, 2930, 2860, 1710 (br), 1510, 1390, 1370, 1250, 1170 cm^{-1}. ^1H NMR (200 MHz): 0.09 (6H, s), 0.10 (9H, s), 1.10-1.90 (13H, m), 1.44 (9H, s), 3.08 (3H, s), 3.80-4.40 (3H, m), 4.70 (1H, m), 5.01 (1H, br d); ^{13}C NMR (50 MHz): -5.6 ($2CH_3$), 18.0 (Cq), 25.7 ($3CH_3$), 26.0 (CH_2), 26.2 (CH_2), 26.4 (CH_2), 28.2 ($3CH_3$), 32.2 (CH_2), 33.8 (CH), 34.0 (CH_2), 37.6 (CH_2), 38.6 (CH_3), 48.8 (CH), 63.3 (CH_2), 79.3 (Cq), 84.0 (CH), 155.6 (Cq); MS (CI): 480 ($[M+1]^+$, 22%), 497 ($[M+18]^+$, 62%), 441 ($[M+18-C_6H_{14}Si]^+$, 98%), 170 ($[C_{10}H_{20}NO]^+$, 100%); $[\alpha]^{23}_D$ = -15.2 (c=2.03, $CHCl_3$).

3.- Desilylation-cyclization: The same conditions described above for the preparation of **31** gave, starting from 110 mg (0.23 mmol) of *(1S,2S)*-1-(*tert*-butyldimethylsilyloxymethyl)-2-(*tert*-butoxycarbonylamino)-3-cyclohexylpropyl methanesulfonate, 50 mg (81% yield) of the *syn* epoxide **38**. Colourless oil. IR (NaCl film): 3340 (br), 3050, 2980, 2920, 2860, 1710 (br), 1515, 1450, 1395, 1370, 1250, 1175, 880 cm^{-1}. ^1H NMR (200 MHz): 0.80-1.90 (13H, m), 1.43 (9H, s), 2.60 (1H, m), 2.72 (1H, m), 2.98 (1H, m), 4.01 (1H, m), 4.33 (1H, br d); ^{13}C NMR (50 MHz): 26.1 (CH_2), 26.3 (CH_2), 26.4 (CH_2), 28.3 ($3CH_3$), 32.7 (CH_2), 33.7 (CH_2), 34.0 (CH), 40.9 (CH_2), 44.4 (CH_2), 46.4 (CH), 54.0 (CH), 79.4 (Cq), 155.6 (Cq); MS (CI): 270 ($[M+1]^+$, 38%), 287 ($[M+18]^+$, 100%), 304 ($[M+35]^+$, 3%), 231 ($[M+18-C_4H_8]^+$, 13%); $[\alpha]^{23}_D$ = -12.5 (c=2.03, $CHCl_3$).

***(3S,4S)*-4-(*tert*-Butoxycarbonylamino)-5-cyclohexyl-3-hydroxypentanenitrile 39:** Following the same procedure used for the preparation of **10** from the oxirane **12**, 0.58 g (2.15 mmol) of **38** produced 0.51 g (80% yield) of the nitrile **39**. Colourless oil. IR (NaCl film): 3400 (br), 2980, 2930, 2860, 2270, 1690 (br), 1515, 1455, 1395, 1370, 1255, 1170 cm^{-1}. ^1H NMR (200 MHz): 0.80-1.90 (13H, m), 1.45 (9H, s), 2.57 (2H, m), 3.65 (1H, m), 3.93 (1H, m), 4.23 (1 OH, br s), 4.76 (1H, br d); ^{13}C NMR (50 MHz): 23.7 (CH_2), 26.1 (CH_2), 26.2 (CH_2), 26.4 (CH_2), 28.3 ($3CH_3$), 32.7 (CH_2), 33.7 (CH_2), 34.1 (CH), 39.3 (CH_2), 51.6 (CH), 69.7 (CH), 80.0 (Cq), 118.2 (Cq), 156.5 (Cq); MS (CI): 297 ($[M+1]^+$, 38%), 314 ($[M+18]^+$, 100%), 331 ($[M+35]^+$, 1%), 258 ($[M+18-C_4H_8]^+$, 5%); $[\alpha]^{23}_D$ = -32.4 (c=2.68, $CHCl_3$).

***(4S,5S)*-3-(*tert*-Butoxycarbonyl)-5-cyanomethyl-4-cyclohexylmethyl-2,2-dimethyl-1,3-oxazolidine 40:** Under the same conditions described above for the preparation of **32**, hydroxynitrile **39** (0.445 g, 1.50 mmol) gave 0.41 g (81% yield) of pure oxazolidine **40**. White solid. mp 93-94°C. IR (KBr): 2980, 2930, 2850, 2250, 1700 (br), 1480, 1450, 1395, 1365, 1095 cm^{-1}. ^1H NMR (200 MHz): 0.80-1.90 (13H, m), 1.49 (9H, s), 1.52 (3H, br s), 1.62 (3H, br s), 2.64 (2H, d, J = 6.6 Hz), 3.84 (1H, br s), 4.16 (1H, td, J = 6.7 Hz, J' = 2 Hz); ^{13}C NMR (50 MHz): 24.6 (CH_2), 25.9 (CH_2), 26.2 (CH_2), 26.3 (CH_2), 27.9* (CH_3), 28.4 ($3CH_3$), 29.0* (CH_3), 32.2 (CH_2), 34.3 (CH_2), 35.1 (CH), 41.6* (CH_2), 60.0 (CH), 76.0 (CH), 80.3 (Cq), 94.8 (Cq), 116.7 (Cq), 151.4 (Cq) (the signals with an asterisk are broad and correspond to a rotamer mixture of the *N*-Boc group); MS (CI): 337 ($[M+1]^+$, 26%), 354 ($[M+18]^+$, 100%), 298 ($[M+18-C_4H_8]^+$, 89%), 281 ($[M+1-C_4H_8]^+$, 13%); $[\alpha]^{23}_D$ = +8.13 (c=1.35, $CHCl_3$); Anal. calcd. for $C_{19}H_{32}N_2O_3$: C, 67.82%; H, 9.59%; N, 8.33%. Found: C, 67.88%; H, 9.63%; N, 8.31%.

***(4S,5S)*-3-(*tert*-Butoxycarbonyl)-5-carboxymethyl-4-cyclohexylmethyl-2,2-dimethyl-1,3-oxazolidine 41:** Reduction of **40** (0.29 g, 0.86 mmol) using the conditions described above for the

preparation of **33** gave 0.23 g (77%) of *(4S,5S)*-3-(*tert*-butoxycarbonyl)-4-cyclohexylmethyl-5-formylmethyl-2,2-dimethyl-1,3-oxazolidine as a colourless oil. Selected spectral data: IR (NaCl film): 2980, 2940, 2860, 2740, 1740, 1700 (br), 1480, 1450, 1395, 1370, 1100 cm^{-1}. ^1H NMR (200 MHz): 0.80-1.90 (13H, m), 1.48 (9H, s), 1.51 (3H, br s), 1.60 (3H, br s), 2.66-2.73 (2H, AB part of ABXY system, J_{AB} = 17.7 Hz), 3.72 (1H, br s), 4.40 (1H, td, J = 6.2 Hz, J' = 2.4 Hz), 9.80 (1H, m); ^{13}C NMR (50 MHz): 26.1 (CH_2), 26.3 (CH_2), 26.5 (CH_2), 27.8* (CH_3), 28.5 ($3CH_3$), 29.0* (CH_3), 32.3 (CH_2), 34.5 (CH_2), 35.0 (CH), 42.0* (CH_2), 49.5 (CH_2), 60.4 (CH), 75.3 (CH), 80.0 (Cq), 151.7 (Cq), 200.2 (CH) (the signals with an asterisk are broad and correspond to a rotamer mixture of the *N*-Boc group); MS (CI-CH_4): 340 ($[M+1]^+$, 77%), 356 ($[M+17]^+$, 11%), 284 ($[M+1-C_4H_8]^+$, 100%), 296 ($[M+1-C_2H_4O]^+$, 33%); $[\alpha]^{23}_D$ = +1.55 (c=2.16, $CHCl_3$). Without further purification, this aldehyde was oxidised under the conditions previously used for the obtention of **17**, **26** and **34** to give 0.35 g of a crude product which upon recrystallization from hexane afforded pure acid **41** (0.21 g, 90% yield). White solid. mp 108-109°C. IR (KBr): 3280 (br), 2990, 2940, 2860, 1730 (sh), 1710 (br), 1485, 1450, 1390, 1370, 1090, 950 cm^{-1}. ^1H NMR (200 MHz): 0.80-1.90 (13H, m), 1.48 (9H, s), 1.52 (3H, br s), 1.61 (3H, br s), 2.62-2.72 (2H, AB part of ABX system, J_{AB} = 16 Hz), 3.78 (1H, br s), 4.33 (1H, m); ^{13}C NMR (50 MHz): 26.0 (CH_2), 26.3 (CH_2), 26.5 (CH_2), 28.5 ($3CH_3$), 29.1* ($2CH_3$), 32.2 (CH_2), 34.4 (CH_2), 35.0 (CH), 40.6 (CH_2), 41.8* (CH_2), 60.3 (CH), 76.4 (CH), 80.0 (Cq), 94.0 (Cq), 151.6 (Cq), 176.2 (Cq) (the signals with an asterisk are broad and correspond to a rotamer mixture of the *N*-Boc group); MS (CI): 356 ($[M+1]^+$, 49%), 373 ($[M+18]^+$, 100%), 317 ($[M+18-C_4H_8]^+$, 9%), 300 ($[M+1-C_4H_8]^+$, 2%); $[\alpha]^{23}_D$ = +4.86 (c=2.10, $CHCl_3$); Anal. calcd. for $C_{19}H_{33}NO_5$: C, 64.20%; H, 9.36%; N, 3.94%. Found: C, 64.12%; H, 9.48%; N, 4.00%.

Methyl *(3S,4S)*-4-*tert*-Butoxycarbonylamino-5-cyclohexylmethyl-3-hydroxypentanoate 42: The acid **41** (0.032 g, 0.09 mmol) was treated at room temperature with a solution of diazomethane in diethyl ether until the yellow colour of the diazomethane solution subsisted for several minutes. The solution was then concentrated in vacuo and the residue purified by column chromatography on triethylamine-pretreated silicagel (2.5% v/v), eluting with hexane/ethyl acetate mixtures of increasing polarity, to afford 0.026 g of the methyl ester of the starting acid as a white solid. To this ester, 0.7 mL of 85% aqueous acetic acid were added, and the mixture heated at 70°C for 40 min. After cooling down to room temperature, ethyl acetate (3 mL) was added and the resulting solution washed with saturated aq. $NaHCO_3$ (3 mL). The organic phase was dried over $MgSO_4$ and concentrated in vacuo, and the residue purified by column chromatography on triethylamine-pretreated silicagel (2.5% v/v), eluting with hexane/ethyl acetate mixtures of increasing polarity, to afford 0.020 g (69% yield) of the known hydroxyester **42**[41] as an oil which slowly crystallised on standing. $[\alpha]^{23}_D$ = -33.1 (c=0.9, CH_3OH). (lit.[41] for 100% e.e.: $[\alpha]^{23}_D$ = -36.5 (c=0.7-1.26, CH_3OH)).

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