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Highly convergent stereoselective synthesis of chiral key intermediates in the synthesis of Palinavir from imines derived from L-glyceraldehyde

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Abstract—Imines derived from *O*-protected (*S*)-glyceraldehyde are valuable intermediates in the synthesis of different kinds of amino acids. We have developed a highly convergent and stereoselective method to obtain (2*S*,3*S*)-*N*-*tert*-butoxycarbonyl-1-phenyl-3,4-epoxy-2-butylamine and (2*S*,4*R*)-*N*-*tert*-butoxycarbonyl-4-hydroxypipecolic acid *tert*-butylamide, which are key intermediates in the synthesis of Palinavir, that consist in the treatment of the appropriate imine with benzylmagnesium bromide and Danishefsky's diene, respectively, and subsequent transformation of the obtained adducts into the desired compounds. The reaction of *N*-benzylimine derived from (*S*)-2,3-di-*O*-benzylglyceraldehyde with benzylmagnesium bromide is completely diastereoselective at low temperature. Hetero Diels–Alder reaction of imine derived from (*S*)-2,3-di-*O*-benzylglyceraldehyde and (*R*)-*N*-α-methylbenzylamine is completely diastereoselective at low temperature in the presence of ZnI_2. © 2002 Published by Elsevier Science Ltd.

1. Introduction

The synthesis of enantiomerically pure chiral compounds represents a major challenge in organic chemistry. Among the different approaches developed to this end, the use of naturally occurring compounds provides an enormous range and diversity of possible starting materials. To be of use in asymmetric synthesis these compounds should be cheap and readily available, preferably in both enantiomeric forms. In this context carbohydrates,[1] sugars and polyhydroxylated compounds, in general, and (*R*)- and (*S*)-glyceraldehyde derivatives, which are easily available from D-mannitol and L-ascorbic acid or L-mannonic γ-lactone, respectively, are particularly important building blocks.[1a,2]

The synthesis of amino acids in their enantiomerically pure form has been a major subject of study in our group for many years. In the course of our work aimed at the development of new versatile synthetic methodologies for the asymmetric synthesis of different kinds of amino acids, we have shown that imines derived from *O*-protected D-glyceraldehyde can act as synthetic precursors in the synthesis of amino acids,[3] α-amino-β-hydroxy acids[4] and α-hydroxy-β-amino acids[5] through the addition of nucleophiles to the C=N bond, and pipecolic acid derivatives[6] by hetero Diels–Alder cycloaddition with activated dienes.

Palinavir (**1**) (Fig. 1) is a highly potent peptidomimetic-based inhibitor of human immunodeficiency virus protease (HIVPr) inhibitor and viral replication in vitro with a favourable pharmacological profile.[7] Whereas the 3-amino-2-propanol-hydroxypipecolic acid segment of this compound seems to be fundamental to mimic the transition state for the cleavage of the phenylalanine–proline peptide bond and modulate the overall physicochemical properties of this inhibitor while maintaining antiviral properties, substitution of the quinaldic-valine fragment leads to structurally simpler hydroxyethylamine-based HIV protease inhibitors.[8]

In the synthesis of the right-hand side of this compound developed by Beaulieu et al.[9] compound **4** was prepared by coupling the chiral α-amino epoxide **2**, obtained in 28–35% overall yield from *N*,*N*-dibenzylalaninol on a kg scale,[9c] with enantiomerically pure 4-hydroxypipecolic acid

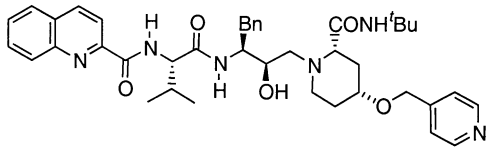

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Figure 1. Structure of Palinavir.

Keywords: asymmetric synthesis; addition reactions; cycloadditions; Grignard reagents.

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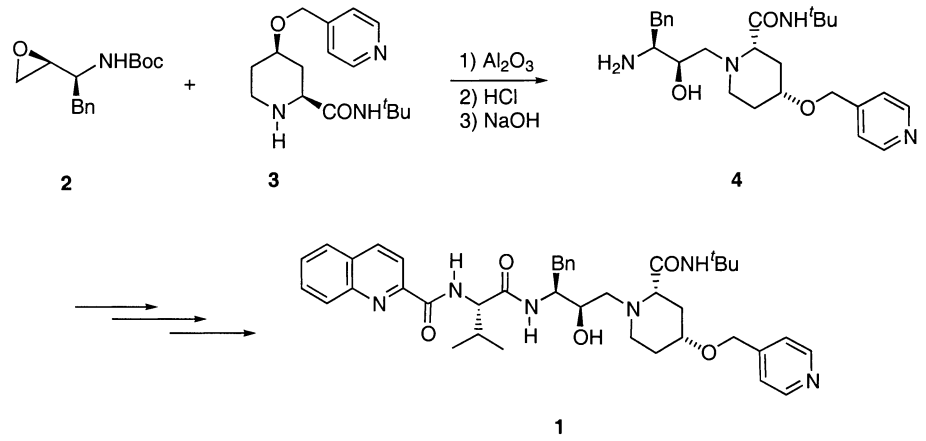


Scheme 1. Beaulieu synthesis of the right-handed segment of Palinavir: (a) Al_2O_3; (b) HCl; (c) NaOH.

amide **3**, obtained in ca. 20% overall yield on a kg scale from 3-buten-1-ol[9c,10] or aspartic acid derivatives[11] (Scheme 1).

A variety of approaches towards the stereoselective synthesis of *syn* and *anti* α-amino epoxides have been reported. The synthesis of *syn* derivatives can be performed by epoxidation of *N*-protected-α-amino aldehydes by sulfoxonium ylides,[12] reduction of α-*N*,*N*-dibenzylamino-α′-chloroketones followed by cyclisation[13] or epoxidation of allylamines.[14] Epoxidation of *N*,*N*-diprotected-α-amino aldehydes by sulfoxonium ylides,[15] stereoselective reduction of α-*N*-acylamino-α′-chloroketones and subsequent cyclisation,[14d,16] condensation of dihalomethanes with *N*,*N*-dibenzylamino-α-amino aldehydes[7a,9c,13,17] or reductive amination of ketoepoxides[18] allows the synthesis of *anti* epoxides. Finally, the appropriate regioselective activation of one hydroxy group in 3-amino-1,2-diols allows the synthesis of epoxides of *syn* and *anti* configuration.[4c,19]

Asymmetric syntheses of pipecolic acid and derivatives have recently been reviewed.[20] Enantiomerically pure *cis* and *trans* 4-hydroxypipecolic acid derivatives have been obtained by different procedures. Apart from chemical or enzymatic resolution of compounds obtained by hydrogenation of pyridine derivatives[21] or resolution of the racemic lactone obtained by intramolecular iminium ion cyclisation of homoallylic amines,[9c,10] several asymmetric syntheses of these compounds have been described. In this context diastereoselective reduction of 4-oxopipecolic acid derivatives with the appropriate reducing agent usually affords the corresponding 4-hydroxy derivative of *cis* or *trans* configuration.[11,22] From *cis* 4-hydroxypipecolic acid derivatives *trans* compounds have been obtained by Mitsunobu inversion.[22b,d] *N*-Acyliminium ions have proven to be appropriate precursors of 4-hydroxypipecolic acid derivatives,[23] and both enantiomers of *cis*-4-hydroxypipecolic acid have been prepared using L-lysine, D-glucosamine, D-gluconoheptono-1,4-lactone, or (*R*)- or (*S*)-glycidol as the chiral source.[24] Finally, δ-amino β-keto esters have been recently used as chiral building blocks for the synthesis of the four stereoisomers of 4-hydroxypipecolic acid.[25]

Since Sato et al. first reported that *N*-substituted 2,3-*O*-isopropylidene-D-glyceraldimines add organometallic reagents asymmetrically,[26] the addition of organometallic reagents to the C–N double bond of a chiral imine has proven to be a useful strategy to the stereoselective synthesis of amines.[27] On the other hand the aza-Diels–Alder reaction between a chiral imine and an activated diene is one of the most powerful methodologies for the construction of piperidine derivatives.[28]

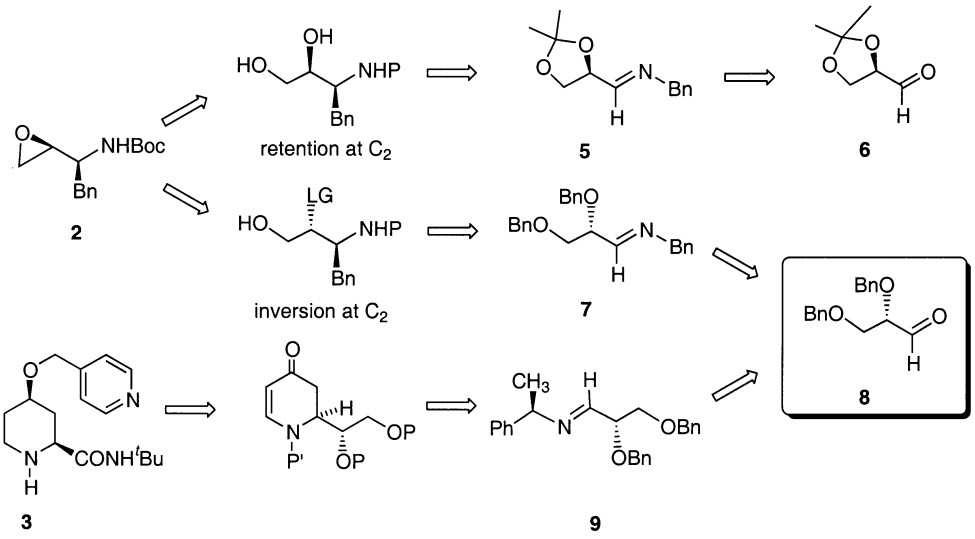
Taking into account that glyceraldimines add organometallic reagents[3,4c,5,26,29] and behave as dienophiles in the aza-Diels–Alder reaction[6] in this paper we have studied the stereoselective synthesis of both chiral fragments of chiral intermediate **4**, using imines derived from glyceraldehyde as synthetic precursors.

2. Results and discussion

2.1. Retrosynthetic analysis

The retrosynthetic analysis of compounds **2** and **3** suggested that both chiral fragments could be obtained in enantiomerically pure form starting from imines derived from glyceraldehyde with the appropriate configuration at C_2, as shown in Scheme 2.

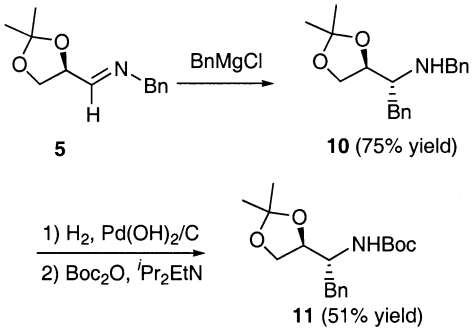
Fragment **2** could be obtained from the *N*-benzylimines derived from *O*-protected glyceraldehyde by nucleophilic addition of a benzylmagnesium halide and subsequent cyclisation of the amino alcohol. According to our previously described results on the addition of methylmagnesium,[5] phenylmagnesium[3a,4c] and vinylmagnesium[3b] bromides to imines derived from *O*-protected glyceraldehyde, organometallic addition to *N*-benzylimines derived from (*R*)-2,3-di-*O*-isopropylideneglyceraldehyde would afford the corresponding aminodiols with *S* configuration at the newly formed stereogenic carbon, whereas organometallic addition to *N*-benzylimines derived from (*R*)-2,3-di-*O*-benzylglyceraldehyde would provide aminodiols of *R* configuration at the same stereogenic carbon. In order to obtain (2*S*,3*S*)-*N*-*tert*-butoxycarbonyl-1-phenyl-3,4-epoxy-2-butylamine (**2**), the *anti* aminoepoxide with the desired absolute configuration, (*R*)-2,3-di-*O*-isopropylideneglyceraldehyde or (*S*)-2,3-di-*O*-benzylglyceraldehyde could be used as starting materials. Nevertheless, when we tested



Scheme 2. Retrosynthetic steps to epoxide **2** and 4-hydroxypipecolic acid derivative **3** from glyceraldehyde derivatives.

the addition of commercially available benzylmagnesium chloride with the imine **5**, derived from (*R*)-2,3-di-*O*-isopropylideneglyceraldehyde, under the usual conditions, the corresponding amine **10** of *R* configuration at the newly formed stereogenic carbon was obtained (Scheme 3). This result is in contrast to our previously described findings regarding the reversal of the stereochemical course of the addition of phenylmagnesium and vinylmagnesium bromides to *N*-benzylimines derived from glyceraldehyde depending on the *O*-protecting group.[3,4c] The absolute configuration of the newly formed stereogenic carbon was unambiguously established after N-debenzylation/Boc-protection of compound **10** to afford Boc derivative **11** and X-ray analysis of this product. For this reason imine **5** was definitively rejected as a starting material for our synthetic proposal.

The 4-hydroxypipecolic acid derivative would be the result of a hetero Diels–Alder reaction between Danishefsky's diene and *N*-benzylimines derived from 2,3-di-*O*-benzylglyceraldehyde or 2,3-di-*O*-isopropylideneglyceraldehyde followed by subsequent manipulation of the substituents on the piperidone ring. In a previous paper we described that hetero Diels–Alder reactions of *N*-benzylimines derived from *O*-protected (*R*)-glyceraldehyde preferentially provide the corresponding piperidones of 2*R* configuration and that the best results are obtained when (*R*)-2,3-di-*O*-benzylglyceraldehyde is used as the starting material. Moreover, when the imine derived from α-methylbenzylamine of the appropriate configuration is combined with the di-*O*-benzylderivative of glyceraldehyde, the subsequent cycloaddition reaction occurs with complete diastereoselectivity.[6b] In this case (*S*)-2,3-di-*O*-benzylglyceraldehyde and (*R*)-α-methylbenzylamine must be chosen in order to construct the skeleton of the 4-hydroxypipecolic acid of *S* configuration at C_2.



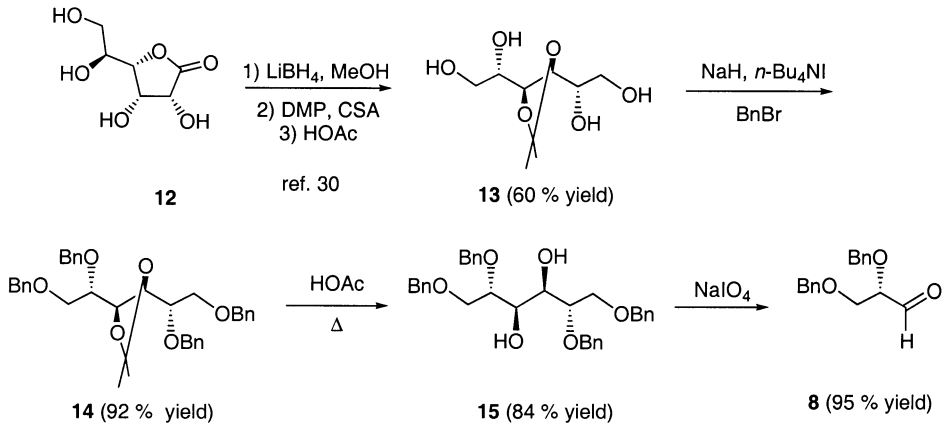
Scheme 3. Asymmetric benzylmagnesiumchloride addition to imine **5**.

Taking into account these considerations we decided to use (*S*)-2,3-di-*O*-benzylglyceraldehyde as the starting material to develop a convergent stereoselective synthesis for both key intermediates in the synthesis of compound **4**.

2.2. Synthesis of (*S*)-2,3-di-*O*-benzylglyceraldehyde

(*S*)-2,3-Di-*O*-benzylglyceraldehyde was obtained from commercially available L-mannonic γ-lactone (**12**) by the route shown in Scheme 4. Reduction of L-mannonic γ-lactone (**12**) with lithium borohydride in dry methanol gave L-mannitol, which was converted into the corresponding triacetonide using 2,2-dimethoxypropane in dry acetone containing camphorsulfonic acid. The product of this reaction was then partially hydrolysed to the monoacetonide **13** according to a recently described procedure.[30]

From compound **13** (*S*)-2,3-di-*O*-benzylglyceraldehyde (**8**) was obtained by similar procedures to those described for the synthesis of enantiomeric (*R*)-2,3-di-*O*-benzylglyceraldehyde.[31] Benzylation of 3,4-*O*-isopropylidene-L-mannitol (**13**) with benzyl bromide in the presence of sodium hydride and tetrabutylammonium iodide afforded 1,2,5,6-tetra-*O*-benzyl-3,4-*O*-isopropylidene-L-mannitol (**14**), which was hydrolysed in an acidic medium to give 1,2,5,6-tetra-*O*-benzyl-L-mannitol (**15**). Heterogeneous sodium periodate glycol cleavage of **15** gave the desired product (*S*)-2,3-di-*O*-benzylglyceraldehyde (**8**), from which *N*-benzylimines **7** and **9** were obtained according to our previously described procedures for ent-**7**[5] and ent-**9**,[6b] respectively.



Scheme 4. Synthesis of (*S*)-2,3-di-*O*-benzyl-L-glyceraldehyde.

2.3. Synthesis of (2*S*,3*S*)-*N*-*tert*-butoxycarbonyl-1-phenyl-3,4-epoxy-2-butylamine

Addition of imine **7** to commercially available benzylmagnesium chloride under standard conditions,[3,4c,5] gave the corresponding amine **16** of 1*S*,2*R* configuration together with a large amount of a by-product that was isolated and fully characterised as olefin **17** on the basis of its analytical and spectroscopic data (Scheme 5). The formation of this by-product clearly results from an elimination/nucleophilic addition process that competes with the pure imine nucleophilic addition.

On using benzylmagnesium bromide as the organometallic reagent and carrying out the reaction at low temperature (−30°C), the elimination reaction was avoided and amine **16** was obtained as a single diastereoisomer in 68% isolated yield. Attempts to perform a one-step synthesis of N-Boc amino diol **19** by hydrogenolysis of amine **16** in the presence of di-*tert*-butyldicarbonate at atmospheric pressure afforded a mixture of compounds. From this mixture the N-Boc derivative of the starting compound, which is inert to hydrogenation even at high pressure and temperature, and compound **18** were isolated. On the other hand, hydrogenolysis of the N-debenzylated intermediate was extremely difficult unless N-Boc protection had previously been performed. We therefore performed a three-step procedure involving selective benzylamine hydrogenolysis of compound **16** by hydrogenation, catalysed by palladium hydroxide on charcoal, at atmospheric pressure for 12 h. This step was followed by N-Boc protection with di-*tert*-butyldicarbonate and extensive hydrogenolysis of the resulting compound for 2 h.

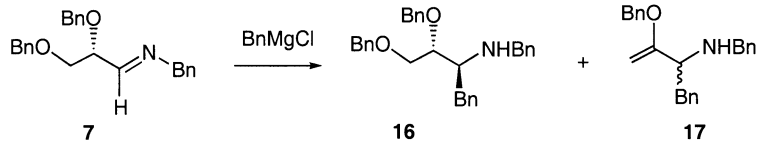
From compound **19** epoxide **2** has been obtained according to a slight modificaton of Samuelsson previously described procedure[19g] for the synthesis of this compound, i.e. the primary alcohol group in compound **19** was selectively protected in 95% yield by treatment with *tert*-butyldimethylsilyl chloride/imidazole in DMF, which allowed the mesylation of the secondary hydroxyl group by the action of methanesulfonyl chloride in a basic medium to give compound **21**. Subsequent treatment of compound **21** with TBAF in THF led to the corresponding alkoxide, which immediately cyclised in situ with concomitant stereochemical inversion to afford the desired epoxide **2** in 67% yield (Scheme 6).

In this way the required intermediate **2** to the synthesis of Palinavir was obtained stereoselectively from chiral imine **8** in six steps and ca. 26% overall yield.

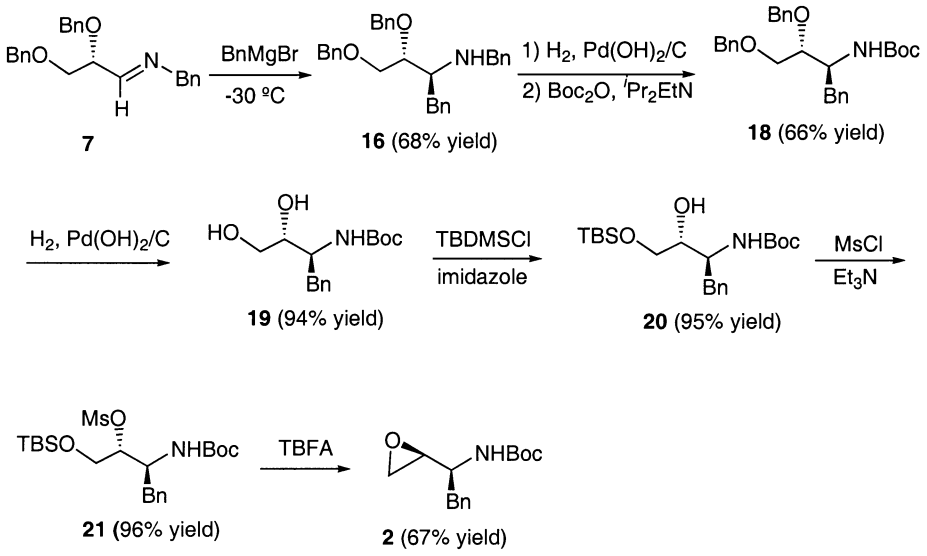
The excellent agreement of the specific rotation measured for compound **2**, $[\alpha]^{D}_{25}=+6.6$ (*c* 1.1, $CHCl_3$) or, $[\alpha]^{D}_{25}=-9.0$ (*c* 1.1, CH_3OH), with the previously described values[7a] for the same compound allowed us to further confirm the stereochemistry and enantiomeric purity of the compound obtained.

2.4. Synthesis of (2*S*,4*R*)-*N*-*tert*-butoxycarbonyl-4-hydroxypipecolic acid *tert*-butylamide

In a previous detailed study we assessed the reactions of imines obtained from (*R*)-2,3-di-*O*-benzylglyceraldehyde and benzylamines with 1-methoxy-3-trimethylsilyloxybuta-1,3-diene (Danishefsky's diene) in the presence of a Lewis acid. We concluded that at low temperature using acetonitrile as solvent, ZnI_2 as the Lewis acid and (*S*)-α-methylbenzylamine as the chiral auxiliary to achieve double stereodifferentiation, the reaction takes place with complete control of stereochemistry to give enaminone *ent*-**22**, which is a potential scaffold for useful synthetic transformations.



Scheme 5. Asymmetric benzylmagnesiumchloride addition to imine **7**.

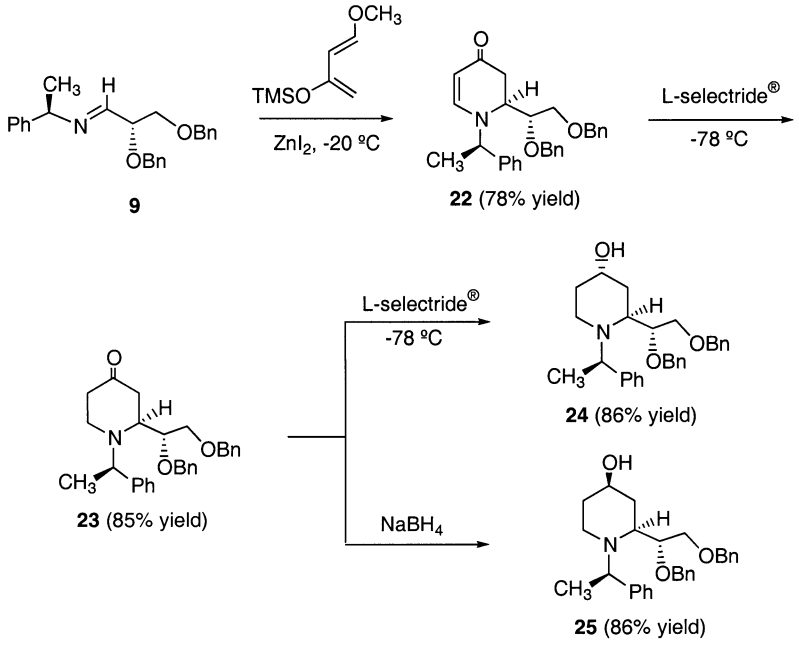


Scheme 6. Synthesis of chiral epoxide **2**.

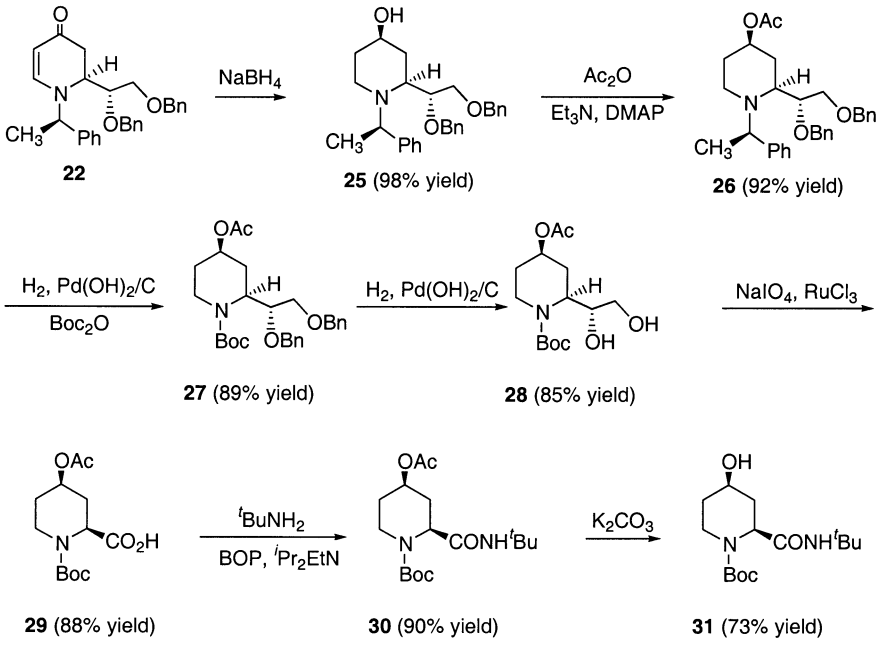
The synthetic scheme designed for the synthesis of (2*S*,4*R*)-*N*-*tert*-butoxycarbonyl-4-hydroxypipecolic acid thus started with the reaction between imine **9**, derived from (*S*)-2,3-di-*O*-benzylglyceraldehyde and (*R*)-α-methylbenzylamine (matched pair), and Danishefsky's diene. On using acetonitrile as the solvent at −20°C and in the presence of ZnI_2, the reaction afforded enaminone **22** of *S* configuration at C_2 as a single diasteroisomer in 73% yield. Selective reduction of enaminone **22** with L-selectride® in THF at −78°C gave the 4-piperidinone **23**. Although in some cases it has been reported[11,22c] that 4-oxopipecolic acid derivatives are reduced to *cis* 4-hydroxypipecolic acid derivatives using L- or K-selectride® as reducing agents, the reaction of 4-piperidinone **23** with L-selectride® afforded the corresponding 4-hydroxy compound **24** of *trans* configuration as a single diastereoisomer. This behaviour is in accordance with previously reported studies on the reduction of 2,6-disubstituted-4-oxo-piperidines.[32] Alternatively, upon treatment of 4-piperidinone **23** with sodium borohydride *cis* 4-hydroxy derivative **25** was obtained with total diastereoselectivity (Scheme 7).

Once the stereochemistry of the carbonyl reduction step had been determined, the one-step reduction of enamidone **22** to *cis* 4-hydroxy derivative **25** with sodium borohydride was tested. The simultaneous reduction of the double bond moiety and the carbonyl group was successfully achieved to yield the desired compound in 98% yield.

Compound **25** was then acetylated and converted into the N-Boc derivative **27** by selective hydrogenolytic N-debenzylation in the presence of di-*tert*-butyldicarbonate.



Scheme 7. Reaction of chiral imine **9** with Danishefsky's diene and subsequent reduction of cycloadduct **22**.



Scheme 8. Synthesis of 4-hydroxypipecolic acid derivative **31**.

Subsequent removal of the O-benzyl groups by hydrogenolysis using palladium hydroxide as a catalyst gave the corresponding diol **28**. Oxidative cleavage of the 1,2-diol moiety by treatment with excess sodium periodate in the presence of ruthenium trichloride afforded orthogonally protected (2*S*,4*R*)-4-hydroxypipecolic acid **29**, which was coupled efficiently with *tert*-butylamine using the coupling reagent BOP to yield the corresponding *tert*-butylamide **30**. Finally, basic hydrolysis of the acetyl group cleanly afforded (2*S*,4*R*)-*N*-*tert*-butoxycarbonyl-4-hydroxypipecolic acid *tert*-butylamide (**31**) according to Scheme 8.

In this way the required intermediate **32** for the synthesis of Palinavir was constructed stereoselectively from chiral imine **8** in eight steps and about 31% overall yield.

Comparison of the specific rotation of compound **31**, $[\alpha]^{D}_{25}=-64.4$ (*c* 1.03, CH_3OH), with the known value[20] for (2*S*,4*R*)-*N*-*tert*-butoxycarbonyl-4-hydroxypipecolic acid *tert*-butylamide allowed us to further confirm the stereochemistry and enantiomeric purity of the compound obtained.

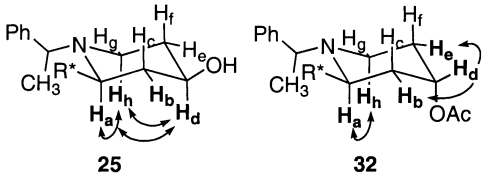
Although this route can be judged unsuitable for scale-up it should be amenable to the preparation of other substituted pipecolic acids as stereoisomeric compounds of **32**.

2.5. Structural assignments

A detailed study of the ^{1}H NMR spectral data of compounds **24** and **25**, produced in the reduction of 4-piperidinone **23** with L-selectride® or sodium borohydride, respectively, allowed complete structural assignments to be made.

The signals of the ^{1}H NMR spectrum of compound **25** can be assigned by a DQF-COSY spectrum. The complete assignment of the diastereotopic protons (axial vs equatorial) and of the relative configuration at C_4 with respect to the known configuration at C_2 is possible by nOe difference experiments. Intraresidue Nuclear Overhauser enhancements are observed between proton H_a at about 2.75 ppm and H_d at about 3.51 ppm which indicate the proximity of these nuclei and its 1,3-diaxial disposition proving the *cis* stereochemistry of compound **25**.

The assignment of the *trans* configuration for diastereomeric compound **24** follows by elimination and it is also consistent with the nuclear Overhauser enhancements observed for the acetylated compound **32**. Acetilation was necessary to obtain and ^{1}H NMR spectrum in which the signal due to H_d appeared well resolved as a lone multiplet. Representative nuclear Overhauser enhancements are collected in Fig. 2.



saturation	% nOe	saturation	% nOe
2.75 ppm (H_a)	8.8 (H_d)	3.12 ppm (H_a)	11 (H_h)
	5.8 (H_h)		
	5.5 (H_b)	5.05 ppm (H_d)	9 (H_b+H_e)
3.51 ppm (H_d)	5.7 (H_a)		
2.09 ppm (H_h)	9.5 (H_a)		
	11.8 (H_d)		

Figure 2. Determination of the relative configuration of products **25** and **32** derived from reduction of piperidone **23** by means of nOe measurements.

3. Conclusion

We have designed convenient and completely stereoselective processes for the synthesis of (2*S*,3*S*)-*N*-*tert*-butoxycarbonyl-1-phenyl-3,4-epoxy-2-butylamine and (2*S*,4*R*)-4-hydroxypipecolic acid *tert*-butylamide, key intermediates in the synthesis of the right-handed segment of Palinavir, from the common starting material (*S*)-2,3-di-*O*-benzylglyceraldehyde. The stereoselective synthesis of (2*S*,3*S*)-*N*-*tert*-butoxycarbonyl-1-phenyl-3,4-epoxy-2-butylamine is based on a low temperature benzylmagnesium bromide addition to the *N*-benzylimine derived from *O*-protected (*S*)-glyceraldehyde which confers a high versatility to this methodology as the use of the imine with the appropriate absolute configuration and the right choice of the conditions to perform the cyclisation would allow the synthesis of any diastereoisomer of the epoxide. Moreover by changing the organometallic reagent it would be possible to obtain key intermediates to the synthesis of new analogues of hydroxyethylamine-based HIV protease inhibitors with different side chains which is important to optimise the aqueous solubility and antiviral activity.[33]

4. Experimental

4.1. General procedures

Melting points were determined in open capillaries using a Büchi capillary melting point apparatus and are not corrected. Infrared spectra were recorded on a Perkin–Elmer 1600FT spectrophotometer as neat liquids or as nujol dispersions, and prominent peaks are expressed in cm^{-1}. NMR spectra were recorded on Varian Unity-300 or Bruker ARX-300 instruments operating at 300 MHz for ^1H NMR and at 75 MHz for ^{13}C NMR. The chemical shifts (δ) are reported in parts per million and the coupling constants (J) in Hertz. The following abbreviations are used: s, singlet; d, doublet; t, triplet; m, multiplet; bs, broad signal; bd, broad doublet; dd, doublet of doublets, ddd, doublet of doublet of doublets. The ^1H and ^{13}C NMR spectra of N-Boc protected compounds were not conclusive at room temperature due to the presence of a dynamic equilibrium between rotamers caused by the restricted rotation of the nitrogen–carbon bond of the urethane group. In order to overcome this problem NMR spectra of these compounds were acquired at 333 K. Optical rotations were measured on a Perkin–Elmer 241-C polarimeter at 25°C with concentrations given in g $100\,mL^{-1}$. Elemental analyses were performed using a Perkin–Elmer 200 C,H,N,S elemental analyser. Electron impact mass spectra were obtained on a high resolution VG-autospec spectrometer.

4.2. Materials

Tetrahydrofuran (THF) and diethyl ether were distilled from sodium benzophenone ketyl. Chloroform and dichloromethane were distilled from P_2O_5. Dimethylformamide was dried for two days with 3 Å molecular sieves. Acetonitrile was distilled from anhydrous $CaCl_2$. Whenever possible the reactions were monitored by TLC. TLC was performed on precoated silica gel polyester plates and products were visualised using UV light (254 nm) and anisaldehyde/sulphuric acid/ethanol (2:1:100). Column chromatography was performed using silica gel (Kiesegel 60). Chemicals for reactions were used as purchased from The Aldrich Chemical Co. Compounds **7** and **9** were synthesised from (*S*)-2,3-di-*O*-benzylglyceraldehyde according to our previously described procedures for *ent*-**7**[5] and *ent*-**9**,[4c] respectively. 3,4-*O*-Isopropylidene-L-mannitol (**13**) was obtained from L-manonic-γ-lactone according to the literature procedure.[30] Benzylmagnesium bromide (ca. 0.8 M solution in diethyl ether) was prepared according to Brown's procedure.[34]

4.2.1. (2*S*,3*R*)-3-Benzylamino-1,2-di-*O*-isopropylidene-4-phenyl-1,2-butanediol (10). A solution of chiral imine **5** (1.1 g, 5 mmol) in diethyl ether (20 mL) was added dropwise over 30 min to a stirred solution of benzylmagnesium chloride (1 M solution in diethyl ether, 10.5 mL, 10.5 mmol) at −20°C under argon. After being stirred for 15 h at room temperature, the reaction mixture was poured into saturated aqueous NH_4Cl (30 mL), the organic layer separated and the aqueous layer extracted with diethyl ether (3×10 mL). The combined organic layers were dried over anhydrous $MgSO_4$, filtered and concentrated in vacuo. Purification of the residue by flash chromatography eluting with diethyl ether/hexane 1:1 afforded 1.17 g (75%) of (2*S*,3*R*)-3-benzylamino-1,2-di-*O*-isopropylidene-4-phenyl-1,2-butanediol (**10**) as a yellowish oil. $[\alpha]^D_{25}=+0.8$ (*c* 1, $CHCl_3$); IR (neat) 3405 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.32 (s, 3H), 1.39 (s, 3H), 1.90 (brs, 1H), 2.68–2.78 (m, 2H), 2.81–2.88 (m, 1H), 3.67 (dd, J=8, 7 Hz, 1H), 3.75 (d, J=13.2 Hz, 1H), 3.83 (dd, J=8, 6.5 Hz, 1H), 3.86 (d, J=13.2 Hz, 1H), 4.04–4.11 (m, 1H), 7.15–7.30 (m, 10H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 25.2, 26.6, 37.3, 51.6, 60.0, 66.5, 77.6, 108.8, 126.3, 126.8, 128.1, 128.3, 128.5, 129.3, 138.7, 140.4; HRMS (FAB+): m/z=312.1970 (MH^+ calcd for $C_{20}H_{26}NO_2$: 312.1963).

4.2.2. (2*S*,3*R*)-3-*tert*-Butoxycarbonylamino-1,2-di-*O*-isopropylidene-4-phenyl-1,2-butanediol (11). To a stirred suspension of 20% $Pd(OH)_2$/C (250 mg) in absolute ethanol (10 mL) under H_2 at 1 atm, was added a solution of (2*S*,3*R*)-3-benzylamino-1,2-di-*O*-isopropylidene-4-phenyl-1,2-butanediol (**10**) (935 mg, 3 mmol) in absolute ethanol (10 mL). The reaction was vigorously stirred at room temperature overnight, filtered and the solvent evaporated in vacuo. The obtained residue, diisopropylethylamine (45 mg, 0.35 mmol) and di-*tert*-butyl dicarbonate (1.31 g, 6 mmol) were dissolved in dry THF (25 mL). After being stirred at 60°C for 2 h the reaction mixture was concentrated in vacuo to afford a crude product, which was purified by flash chromatography eluting first with diethyl ether/hexane (1:7) and then with diethyl ether/hexane (1:5) to give (2*S*,3*R*)-3-*tert*-butoxycarbonylamino-1,2-di-*O*-isopropylidene-4-phenyl-1,2-butanediol (**11**) (491 mg, 51%) as a white solid. Mp=91°C (lit.[35] mp 89–90°C); $[\alpha]^D_{25}=+38.3$ (*c* 1, $CHCl_3$) {lit.[35] $[\alpha]^D_{20}=+35.8$ (*c* 1.5, $CHCl_3$)}; IR (Nujol) 3400, 1695 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.31 (s, 3H), 1.39 (s, 9H), 1.44 (s, 3H), 2.82 (dd, J=13.8, 8.1 Hz, 1H), 2.89 (dd, J=13.8, 7 Hz, 1H), 3.64 (dd, J=8.1, 6.9 Hz, 1H), 3.80–3.90 (m, 1H), 3.87 (dd, J=8.1, 6.9 Hz, 1H), 4.07 (ddd, J=6.9, 6.9, 2.1 Hz, 1H), 4.68 (bd, J=7.8 Hz, 1H), 7.15–7.30 (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 25.0, 26.4, 28.4, 39.7, 52.5, 66.4, 75.7, 79.4, 109.1, 126.5,

128.5, 129.5, 138.2, 155.8; Elemental analysis calcd (%) for $C_{18}H_{27}NO_4$: C, 67.26; H, 8.47; N, 4.35; found: C, 67.56; H, 8.53; N, 4.41.

4.2.3. 1,2,5,6-Tetra-*O*-benzyl-3,4-*O*-isopropylidene-L-mannitol (14). To a cooled (0°C) solution of 3,4-*O*-isopropylidene-L-mannitol (**13**) (7.75 g, 35 mmol) in dry THF (100 mL) under an atmosphere of argon was added NaH (60% dispersion in mineral oil, 7.37 g, 175 mmol), tetrabutylammonium iodide (12.95 g, 35 mmol) and benzyl bromide (59.85 g, 350 mmol). After stirring at room temperature overnight, the reaction mixture was partitioned between water (50 mL) and diethyl ether (100 mL). The organic layer was separated and the aqueous layer extracted with diethyl ether (3×30 mL). The combined organic layers were dried over anhydrous $MgSO_4$, filtered and concentrated in vacuo. The residue was purified by flash chromatography on a silica gel column. Elution first with hexanes and then with diethyl ether/hexanes (1:4) gave 18.7 g (92% yield) of 1,2,5,6-tetra-*O*-benzyl-3,4-*O*-isopropylidene-L-mannitol (**14**) as a colourless oil. $[\alpha]^{D}_{25}=-12.2$ (*c* 0.95, $CHCl_3$); IR (neat) 1096 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.33 (s, 3H), 3.56–3.63 (m, 1H), 3.70–3.78 (m, 2H), 4.15–4.17 (m, 1H), 4.45 (s, 2H), 4.55 (d, *J*=11.7 Hz, 1H), 4.71 (d, *J*=11.7 Hz, 1H), 7.24–7.29 (m, 10H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 27.1, 70.6, 72.7, 73.3, 78.5, 79.2, 109.7, 127.5, 127.5, 127.5, 127.8, 128.2, 128.3, 138.3, 138.5; HRMS (FAB+): *m*/*z*=583.3041 (MH^+ calcd for $C_{37}H_{43}O_6$: 583.3059).

4.2.4. 1,2,5,6-Tetra-*O*-benzyl-L-mannitol (15). 1,2,5,6-Tetra-*O*-benzyl-3,4-*O*-isopropylidene-L-mannitol (**14**) (17.5 g, 30 mmol) was dissolved in 70% acetic acid (80 mL) and the resulting solution stirred at 100°C for 2 h. The solution was carefully concentrated in vacuo and the residue obtained was dissolved in diethyl ether (60 mL) and washed with saturated aqueous $NaHCO_3$ (30 mL). The organic layer was separated, dried over $MgSO_4$ and the solvent evaporated in vacuo. Purification of the residue by filtration through a silica gel pad, eluting with diethyl ether/hexanes (1:1), gave 13.7 g (84% yield) of 1,2,5,6-tetra-*O*-benzyl-L-mannitol (**15**) as a colourless oil. $[\alpha]^{D}_{25}=+12.7$ (*c* 1.02, $CHCl_3$) {lit.[36] for enantiomer of **15** $[\alpha]^{D}_{20}=-12.4$ (*c* 0.83, $CHCl_3$)}; IR (neat) 3450, 1092 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 3.02 (d, *J*=6 Hz, 1H), 3.62–3.79 (m, 3H), 3.95 (d, *J*=6 Hz, 1H), 4.53 (s, 2H), 4.57 (d, *J*=11.7 Hz, 1H), 4.71 (d, *J*=11.7 Hz, 1H), 7.24–7.29 (m, 10H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 69.9, 70.2, 73.0, 73.5, 79.2, 127.6, 127.7, 127.7, 127.9, 128.4, 138.0, 138.1; HRMS (FAB+): *m*/*z*=543.2762 (MH^+ calcd for $C_{34}H_{39}O_6$: 543.2746).

4.2.5. (*S*)-2,3-Di-*O*-benzyl-L-glyceraldehyde (8). To a solution of 1,2,5,6-tetra-*O*-benzyl-L-mannitol (**15**) (2.9 g, 5.35 mmol) in methanol (30 mL) was added solid $NaIO_4$ (1.37 g, 6.4 mmol) with vigorous stirring. After being stirred at room temperature for 24 h the reaction mixture was filtered and the solid washed with diethyl ether (3×30 mL). The combined organic filtrates were evaporated in vacuo and the residue was dissolved in diethyl ether, filtered and evaporated in vacuo to afford 1.37 g (95% yield) of (*S*)-2,3-di-*O*-benzyl-L-glyceraldehyde (**8**) as a thick oil, which was used without further purification. An analytically pure sample of the aldehyde was obtained by purification of the residue by flash chromatography (diethyl ether/hexanes, 1:1). $[\alpha]^{D}_{25}=-37.6$ (*c* 1.10, $CHCl_3$); IR (neat) 1734 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 3.76 (dd, *J*=10.8, 5.2 Hz, 1H), 3.78 (dd, *J*=10.8, 4.5 Hz, 1H), 3.97 (ddd, *J*=5.2, 4.5, 0.6 Hz, 1H), 4.52 (d, *J*=12.3 Hz, 1H), 4.56 (d, *J*=12.3 Hz, 1H), 4.68 (d, *J*=11.7 Hz, 1H), 4.73 (d, *J*=11.7 Hz, 1H), 7.20–7.40 (m, 10H), 9.70 (d, *J*=0.6 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 69.1, 72.7, 73.6, 82.7, 127.7, 127.8, 128.0, 128.1, 128.4, 128.5, 137.1, 137.5, 202.1; HRMS (FAB+): *m*/*z*=271.1340 (MH^+ calcd for $C_{17}H_{19}O_3$: 271.1334).

4.2.6. (1*S*,2*R*)-*N*-Benzyl-2,3-dibenzyloxy-1-benzyl-1-propylamine (16). A solution of chiral imine **7** (1.25 g, 3.5 mmol) in diethyl ether (5 mL) was added dropwise over 30 min to a stirred solution of benzylmagnesium bromide (0.8 M solution in diethyl ether, 9.14 mL, 7.3 mmol) in diethyl ether (60 mL) at −30°C under argon. After being stirred overnight at −30°C, the reaction mixture was poured into saturated aqueous NH_4Cl (30 mL), the organic layer was separated and the aqueous layer extracted with diethyl ether (2×30 mL). The combined organic layers were dried over anhydrous $MgSO_4$, filtered and concentrated in vacuo. Purification of the residue by flash chromatography, eluting with diethyl ether, afforded 1.1 g (68%) of (1*S*,2*R*)-*N*-benzyl-2,3-dibenzyloxy-1-benzyl-1-propylamine (**16**) as a yellowish oil. $[\alpha]^{D}_{25}=+6.0$ (*c* 1, $CHCl_3$); IR (neat) 3083 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 2.75–2.92 (m, 2H), 2.94–3.02 (m, 1H), 3.60–3.68 (m, 1H), 3.70–3.80 (m, 4H), 4.44 (d, *J*=11.9 Hz, 1H), 4.49 (d, *J*=11.9 Hz, 1H), 4.54 (d, *J*=11.8 Hz, 1H), 4.77 (d, *J*=11.8 Hz, 1H), 7.05–7.40 (m, 20H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 36.9, 51.8, 59.9, 71.6, 72.7, 73.4, 78.7, 126.0, 126.8, 127.5, 127.7, 127.8, 128.2, 128.2, 128.3, 128.4, 129.2, 138.4, 139.0, 139.8, 140.7; HRMS (FAB+): *m*/*z*=452.2596 (MH^+ calcd for $C_{31}H_{34}NO_2$: 452.2589).

4.2.7. (1*S*,2*R*)-*N*-*tert*-Butoxycarbonyl-2,3-dibenzyloxy-1-benzyl-1-propylamine (18). To a stirred suspension of 20% $Pd(OH)_2/C$ (150 mg) in absolute ethanol (10 mL) under H_2 at 1 atm, was added a solution of (1*S*,2*R*)-*N*-benzyl-2,3-dibenzyloxy-1-benzyl-1-propylamine (**16**) (780 mg, 1.75 mmol) in absolute ethanol (6 mL). The reaction was vigorously stirred at room temperature overnight, filtered and the solvent evaporated in vacuo. The obtained residue, diisopropylethylamine (26 mg, 0.2 mmol) and di-*tert*-butyl dicarbonate (765 mg, 3.5 mmol) were dissolved in dry THF (15 mL). After being stirred at 60°C for 2 h the reaction mixture was concentrated in vacuo to afford a crude product, which was purified by flash chromatography eluting first with diethyl ether/hexane (1:7) and then with diethyl ether/hexane (1:5) to give (1*S*,2*R*)-*N*-*tert*-butoxycarbonyl-2,3-dibenzyloxy-1-benzyl-1-propylamine (**18**) (525 mg, 66%) as a colourless oil. $[\alpha]^{D}_{25}=-9.9$ (*c* 1, $CHCl_3$); IR (neat) 3440, 1713 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.37 (s, 9H), 2.78–2.86 (m, 2H), 3.50–3.67 (m, 3H), 4.01–4.08 (m, 1H), 4.42 (d, *J*=12 Hz, 1H), 4.50 (d, *J*=12 Hz, 1H), 4.53 (d, *J*=11.7 Hz, 1H), 4.74 (d, *J*=11.7 Hz, 1H), 4.85 (brs, 1H), 7.10–7.40 (m, 15H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 28.4, 39.0, 53.5, 71.6, 73.1, 73.6, 77.5, 79.1, 126.3, 127.6, 127.7, 127.8, 128.0, 128.4, 128.4, 129.4, 138.4, 138.6, 155.6; HRMS (FAB+): *m*/*z*=461.2559 (M^+ calcd for $C_{29}H_{35}NO_4$: 461.2566).

4.2.8. (2*R*,3*S*)-3-*tert*-Butoxycarbonylamino-4-phenyl-1,2-butanediol (19). A solution of (1*S*,2*R*)-*N*-*tert*-butoxycarbonyl-2,3-dibenzyloxy-1-benzyl-1-propylamine (**18**) (230 mg, 0.5 mmol) in methanol (5 mL) was hydrogenated with 20 wt% $Pd(OH)_2$ (75 mg) catalyst at room temperature and hydrogen at atmospheric pressure for 5 h. When the reaction was complete the catalyst was removed by filtration and the filtrate evaporated to dryness. The resulting crude material was purified by filtration through a silica gel pad, eluting with diethyl ether, to give 132 mg (94% yield) of (2*R*,3*S*)-3-*tert*-butoxycarbonylamino-4-phenyl-1,2-butanediol (**19**) as a white solid. Mp 80°C (lit.[37] mp 88.5–90.5°C); $[\alpha]^{D}_{25}=-36.0$ (*c* 1, $CHCl_3$) {lit.[37] $[\alpha]^{D}_{20}=-36.8$ (*c* 1, $CHCl_3$)}; IR (Nujol) 3370, 1691 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.38 (s, 9H), 2.89 (d, *J*=7.8 Hz, 2H), 3.46–3.61 (m, 2H), 3.62–3.70 (m, 1H), 3.83–3.95 (m, 1H), 4.76 (bd, *J*=8.7 Hz, 1H), 7.15–7.30 (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 28.3, 38.5, 53.0, 64.3, 72.0, 80.0, 126.5, 128.6, 129.2, 138.1, 156.7; Elemental analysis calcd (%) for $C_{15}H_{23}NO_4$: C, 64.04; H, 8.24; N, 4.98; found: C, 64.12; H, 8.27; N, 5.03.

4.2.9. (2*R*,3*S*)-3-*tert*-Butoxycarbonylamino-1-*tert*-butyldimethylsilyloxy-4-phenyl-2-butanol (20). A solution of (2*R*,3*S*)-3-*tert*-butoxycarbonylamino-4-phenyl-1,2-butanediol (**19**) (380 mg, 1.35 mmol), *tert*-butyldimethylsilylchloride (225 mg, 1.5 mmol) and imidazole (204 mg, 3 mmol) in dry dimethylformamide (7 mL) was stirred at room temperature for 24 h. The mixture was diluted with diethyl ether (25 mL) and washed with saturated aqueous NH_4Cl (12 mL). The organic layer was treated with water, the organic layer separated and the aqueous layer extracted with diethyl ether (3×15 mL). The combined organic layers were dried over anhydrous $MgSO_4$, filtered and concentrated in vacuo. The crude product was purified by flash chromatography on a silica gel column. Successive elution with diethyl ether/hexanes (1:5), diethyl ether/hexanes (1:3) and diethyl ether/hexanes (1:1) gave 507 mg (95% yield) of (2*R*,3*S*)-3-*tert*-butoxycarbonylamino-1-*tert*-butyldimethylsilyloxy-4-phenyl-2-butanol (**20**) as a white solid. Mp 83°C; $[\alpha]^{D}_{25}=-24.0$ (*c* 1, $CHCl_3$); IR (nujol) 3357, 1668 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.02 (s, 3H), 0.03 (s, 3H), 0.87 (s, 9H), 1.38 (s, 9H), 2.56 (bs, 1H), 2.90 (d, *J*=8 Hz, 1H), 3.47–3.59 (m, 2H), 3.60–3.65 (m, 1H), 3.72–3.80 (m, 1H), 4.96 (bd, *J*=9 Hz, 1H), 7.15–7.25 (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$) δ −5.5, −5.4, 18.3, 25.9, 28.4, 39.0, 53.8, 65.1, 71.4, 79.3, 126.3, 128.4, 129.5, 138.6, 155.9; Elemental analysis calcd (%) for $C_{21}H_{37}NO_4Si$: C, 63.76; H, 9.43; N, 3.54; found: C, 63.82; H, 9.37; N, 3.51.

4.2.10. (2*S*,3*R*)-*N*-*tert*-Butoxycarbonyl-4-*tert*-butyldimethylsilyloxy-3-mesyloxy-1-phenyl-2-butylamine (21). A solution of methanesulfonyl chloride (170 mg, 1.5 mmol) in dry dichloromethane (1 mL) was added dropwise to a solution of (2*R*,3*S*)-3-*tert*-butoxycarbonylamino-1-*tert*-butyldimethylsilyloxy-4-phenyl-2-butanol (**20**) (500 mg, 1.27 mmol) and triethylamine (150 mg, 1.5 mmol) in dry dichloromethane (10 mL) at 0°C under argon. The solution was allowed to warm up to room temperature and, after stirring for 1 h, the reaction mixture was partitioned between water (5 mL) and dichloromethane (5 mL). The organic layer was separated and the aqueous layer extracted with diethyl ether (3×15 mL). The combined organic layers were dried over anhydrous $MgSO_4$, filtered and concentrated in vacuo. The residue was purified by flash chromatography on a silica gel column. Elution with diethyl ether/hexanes (1:1) gave 575 mg (96% yield) of (2*S*,3*R*)-*N*-*tert*-butoxycarbonyl-4-*tert*-butyldimethylsilyloxy-3-mesyloxy-1-phenyl-2-butylamine (**21**) as an oil. $[\alpha]^{D}_{25}=-35.0$ (*c* 1, $CHCl_3$); IR (neat) 3378, 1710 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.03 (s, 3H), 0.05 (s, 3H), 0.88 (s, 9H), 1.35 (s, 9H), 2.83 (dd, *J*=14.1, 7.8 Hz, 1H), 2.93 (dd, *J*=14.1, 6.7 Hz, 1H), 3.06 (s, 3H), 3.80 (dd, *J*=11.5, 5.3 Hz, 1H), 3.84 (dd, *J*=11.5, 6.5 Hz, 1H), 4.09–4.18 (m, 1H), 4.64 (bs, 1H), 4.66–4.71 (m, 1H), 7.15–7.30 (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$) δ −5.6, −5.5, 18.3, 25.9, 28.3, 38.6, 38.9, 52.6, 63.4, 79.8, 83.6, 126.7, 128.4, 129.4, 137.4, 155.3; HRMS (FAB+): *m*/*z*=473.2278 (M^+ calcd for $C_{22}H_{39}NO_6SSi$: 473.2267).

4.2.11. (2*S*,3*S*)-*N*-*tert*-Butoxycarbonyl-1-phenyl-3,4-epoxy-2-butylamine (2). A 1 M solution of tetrabutylammonium fluoride in THF (1.3 mL, 1.3 mmol) was added dropwise to a solution of (2*S*,3*R*)-*N*-*tert*-butoxycarbonyl-4-*tert*-butyldimethylsilyloxy-3-mesyloxy-1-phenyl-2-butylamine (**21**) (310 mg, 0.65 mmol) in dry THF (6 mL) at 0°C. The solution was then warmed up to room temperature and stirred overnight. The reaction mixture was partitioned between water (3 mL) and diethyl ether (5 mL). The organic layer was separated and the aqueous layer extracted with diethyl ether (3×10 mL). The combined organic layers were dried over anhydrous $MgSO_4$, filtered and concentrated in vacuo. The residue was purified by flash chromatography on a silica gel column. Elution first with diethyl ether/hexanes (1:5) and then with diethyl ether/hexanes (1:1) gave 115 mg (67% yield) of (2*S*,3*S*)-*N*-*tert*-butoxycarbonyl-1-phenyl-3,4-epoxy-2-butylamine (**2**) as a pale yellow solid. Mp 123°C (lit.[7a] mp 122–124.5°C); $[\alpha]^{D}_{25}=+6.6$ (*c* 1.1, $CHCl_3$) {lit.[7a] $[\alpha]^{D}=+6.9$ (*c* 1, $CHCl_3$)}; $[\alpha]^{D}_{25}=-9.0$ (*c* 1.1, CH_3OH) {lit.[7a] $[\alpha]^{D}=-8.6$ (*c* 1, CH_3OH)}; IR (nujol) 3374, 1677 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.37 (s, 9H), 2.70 (dd, *J*=4.9, 2.6 Hz, 1H), 2.74 (dd, *J*=4.9, 3.9 Hz, 1H), 2.83 (dd, *J*=14.1, 7.5 Hz, 1H), 2.86–2.94 (m, 1H), 2.96 (dd, *J*=14.1, 5.2 Hz, 1H), 3.58–3.76 (m, 1H), 4.36 (brs, 1H), 7.18–7.30 (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 28.2, 37.7, 46.4, 52.9, 53.2, 79.6, 126.6, 128.4, 129.3, 136.9, 155.2; Elemental analysis calcd (%) for $C_{15}H_{21}NO_3$: C, 68.41; H, 8.04; N, 5.32; found: C, 68.38; H, 8.09; N, 5.21.

4.2.12. (*S*)-*N*-[(*R*)-α-Methylbenzyl]-2-[(*R*)-1,2-dibenzyloxyethyl]-5,6-dihydro-4-pyridone (22). To a suspension of ZnI_2 (2.25 g, 7 mmol) in dry acetonitrile (30 mL), cooled under argon at −20°C, was added a solution of the crude imine **9** (2.60 g, 7 mmol) in dry acetonitrile (6 mL) and the mixture was stirred for 10 min. Danishefsky's diene (1.8 g, 2 mL, 10.5 mmol) was then added in one portion by syringe and the reaction was stirred overnight at −20°C. The resulting dark yellow solution was partitioned between saturated aqueous $NaHCO_3$ (30 mL) and dichloromethane (30 mL). The organic layer was separated and the aqueous layer extracted with dichloromethane (3×20 mL). The combined organic phases were washed with 1N HCl and brine, dried over $MgSO_4$ and the solvent evaporated in vacuo. The resulting dark-coloured oil was purified by filtration through a silica gel pad (diethyl ether followed by ethyl acetate as

eluents) to yield 2.4 g (78% yield) of (*S*)-*N*-[(*R*)-α-methylbenzyl]-2-[(*R*)-1,2-dibenzyloxyethyl]-5,6-dihydro-4-pyridone (**22**) as a yellowish oil. $[\alpha]^{D}_{25}=-96.0$ (*c* 1, $CHCl_3$) {lit.[6b] for the enantiomer of **22** $[\alpha]^{D}_{20}=+84.0$ (*c* 1, $CHCl_3$)}; IR (neat) 1640, 1584 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.57 (d, *J*=6.9 Hz, 3H), 2.36 (bd, *J*=17.1 Hz, 1H), 2.73 (dd, *J*=16.8, 6.6 Hz, 1H), 3.50 (dd, *J*=11.1, 3.3 Hz, 1H), 3.73 (dd, *J*=11.1, 1.8 Hz, 1H), 3.98–4.10 (m, 2H), 4.47 (d, *J*=11.7 Hz, 1H), 4.48 (d, *J*=12 Hz, 1H), 4.54 (d, *J*=12 Hz, 1H), 4.65 (d, *J*=11.7 Hz, 1H), 4.72 (q, *J*=6.9 Hz, 1H), 4.77 (dd, *J*=7.4, 1.2 Hz, 1H), 6.71 (d, *J*=7.4 Hz, 1H), 7.20–7.40 (m, 15H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 20.2, 37.3, 56.7, 62.7, 67.7, 72.2, 73.5, 76.4, 97.5, 127.8, 127.8, 127.8, 127.9, 128.0, 128.3, 128.4, 128.8, 137.8, 138.0, 139.2, 149.8, 190.4; HRMS (EI): *m*/*z*=441.2291 (M^+ calcd for $C_{29}H_{31}NO_3$: 441.2303).

4.2.13. (*S*)-*N*-[(*R*)-α-Methylbenzyl]-2-[(*R*)-1,2-dibenzyloxyethyl]-4-piperidone (23). L-Selectride® (1 M, 6 mL, 6 mmol) was added dropwise to a solution of (*S*)-*N*-[(*R*)-α-methylbenzyl]-2-[(*R*)-1,2-dibenzyloxyethyl]-5,6-dihydro-4-pyridone (**22**) (2.3 g, 5.2 mmol) in dry THF (35 mL) at −78°C under an argon atmosphere. After being stirred for 72 h at that temperature, the reaction mixture was quenched with saturated aqueous NH_4Cl (15 mL) and partitioned between water (30 mL) and diethyl ether (30 mL). The organic layer was separated and the aqueous layer extracted with diethyl ether (3×20 mL). The combined organic phases were washed with brine, dried over $MgSO_4$ and the solvent evaporated in vacuo. The crude product was purified by silica gel column chromatography eluting first with diethyl ether/hexanes (1:3) and then with diethyl ether/hexanes (3:2) to yield 1.98 g (85% yield) of (*S*)-*N*-[(*R*)-α-methylbenzyl]-2-[(*R*)-1,2-dibenzyloxyethyl]-4-piperidone (**23**) as a colourless oil. $[\alpha]^{D}_{25}=-1.0$ (*c* 1, $CHCl_3$) {lit.[6b] for the enantiomer of **23** $[\alpha]^{D}_{20}=+0.8$ (*c* 1, $CHCl_3$)}; IR (neat) 1712 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.35 (d, *J*=6.6 Hz, 3H), 2.10–2.19 (m, 2H), 2.33 (ddd, *J*=16.6, 9.9, 6.6 Hz, 1H), 2.60 (dd, *J*=15, 6.6 Hz, 1H), 3.08–3.18 (m, 1H), 3.23–3.28 (m, 1H), 3.35 (ddd, *J*=13.8, 9.9, 4.2 Hz, 1H), 3.54–3.62 (m, 1H), 3.65–3.70 (m, 2H), 4.00 (q, *J*=6.6 Hz, 1H), 4.45 (d, *J*=12 Hz, 1H), 4.50 (d, *J*=12 Hz, 1H), 4.55 (d, *J*=11.4 Hz, 1H), 4.63 (d, *J*=11.4 Hz, 1H), 7.10–7.40 (m, 15H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 19.2, 38.0, 40.1, 43.4, 58.5, 58.7, 71.8, 73.4, 73.5, 81.2, 127.1, 127.2, 127.4, 127.5, 127.6, 128.1, 128.2, 128.3, 128.4, 138.2, 138.3, 145.2, 209.0; HRMS (FAB+): *m*/*z*=444.2551 (MH^+ calcd for $C_{29}H_{34}NO_3$: 444.2538).

4.2.14. (2*S*,4*S*)-*N*-[(*R*)-α-Methylbenzyl]-2-[(*R*)-1,2-dibenzyloxyethyl]-4-hydroxypiperidine (24). L-Selectride® (1 M, 0.75 mL, 0.75 mmol) was added dropwise to a solution of (*S*)-*N*-[(*R*)-α-methylbenzyl]-2-[(*R*)-1,2-dibenzyloxyethyl]-4-piperidone (**23**) (288 mg, 0.65 mmol) in dry THF (10 mL) at −78°C under an argon atmosphere. After being stirred for 1 h at that temperature, the reaction mixture was quenched with saturated aqueous NH_4Cl (5 mL) and partitioned between water (5 mL) and diethyl ether (15 mL). The organic layer was separated and the aqueous layer extracted with diethyl ether (3×15 mL). The combined organic phases were washed with brine, dried over $MgSO_4$ and the solvent evaporated in vacuo. The crude product was purified by filtration through a silica gel pad, eluting first with diethyl ether/hexanes (1:1) and then with diethyl ether/hexanes (3:1) to yield 250 mg (86% yield) of (2*S*,4*S*)-*N*-[(*R*)-α-methylbenzyl]-2-[(*R*)-1,2-dibenzyloxyethyl]-4-hydroxypiperidine (**24**) as a pale yellow oil. $[\alpha]^{D}_{25}=+8.7$ (*c* 1, $CHCl_3$); IR (neat) 3400 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.25 (d, *J*=6.6 Hz, 3H), 1.38–1.61 (m, 3H), 1.85–1.94 (m, 1H), 2.40 (ddd, *J*=12.3, 6, 3.9 Hz, 1H), 2.62 (ddd, *J*=12.3, 9, 3.6 Hz, 1H), 3.11–3.20 (m, 1H), 3.62 (dd, *J*=10.5, 6.9 Hz, 1H), 3.85 (dd, *J*=10.5, 2.1 Hz, 1H), 3.95–4.15 (m, 3H), 4.47 (d, *J*=12 Hz, 1H), 4.55 (d, *J*=12 Hz, 1H), 4.66 (d, *J*=11.7 Hz, 1H), 4.79 (d, *J*=11.7 Hz, 1H), 7.16–7.40 (m, 15H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 13.5, 32.2, 33.4, 40.1, 54.2, 56.2, 65.4, 71.5, 72.8, 73.4, 78.6, 126.5, 127.5, 127.5, 127.6, 127.7, 128.0, 128.3, 128.3, 128.4, 138.4, 139.0, 145.0; HRMS (FAB+): *m*/*z*=446.2682 (MH^+ calcd for $C_{29}H_{36}NO_3$: 446.2695).

4.2.15. (2*S*,4*R*)-*N*-[(*R*)-α-Methylbenzyl]-2-[(*R*)-1,2-dibenzyloxyethyl]-4-hydroxypiperidine (25). *Method A*. A solution of sodium borohydride (160 mg, 4.2 mmol) in 4% aqueous sodium hydroxide (35 mL) was added dropwise to a solution of (*S*)-*N*-[(*R*)-α-methylbenzyl]-2-[(*R*)-1,2-dibenzyloxyethyl]-4-piperidone (**23**) (1.55 g, 3.5 mmol) in THF (35 mL) at 0°C. After being stirred for 30 min at that temperature, the reaction mixture was extracted with dichloromethane (3×15 mL). The combined organic phases were washed with brine, dried over $MgSO_4$ and the solvent evaporated in vacuo. The crude product was purified by filtration through a silica gel pad, eluting with diethyl ether/hexanes (3:1) to yield 1.34 g (86% yield) of (2*S*,4*R*)-*N*-[(*R*)-α-methylbenzyl]-2-[(*R*)-1,2-dibenzyloxyethyl]-4-hydroxypiperidine (**25**) as a colourless oil.

Method B. Sodium borohydride (1.73 g, 45.5 mmol) was added to a solution of (*S*)-*N*-[(*R*)-α-methylbenzyl]-2-[(*R*)-1,2-dibenzyloxyethyl]-5,6-dihydro-4-pyridone (**22**) (2 g, 4.55 mmol) in ethanol (100 mL). After being stirred for 16 h at room temperature, the reaction mixture was neutralised with 1N hydrochloric acid and concentrated in vacuo. The resulting solution was extracted with dichloromethane (3×25 mL), the combined organic phases were dried over $MgSO_4$ and the solvent evaporated in vacuo. The crude product was purified by filtration through a silica gel pad, eluting with ethyl acetate to yield 1.98 g (98% yield) of (2*S*,4*R*)-*N*-[(*R*)-α-methylbenzyl]-2-[(*R*)-1,2-dibenzyloxyethyl]-4-hydroxypiperidine (**25**) as a colourless oil.

$[\alpha]^{D}_{25}=-0.7$ (*c* 0.95, $CHCl_3$); IR (neat) 3403 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.11–1.30 (m, 2H), 1.16 (d, *J*=6.9 Hz, 3H), 1.57–1.75 (m, 1H), 2.08 (ddd, *J*=11.7, 11.7, 2.4 Hz, 1H), 2.30 (dddd, *J*=12, 4.5, 2.4, 2.4 Hz, 1H), 2.43 (ddd, *J*=11.7, 3.9, 3.9 Hz, 1H), 2.75 (ddd, *J*=10.5, 4.5, 2.7 Hz, 1H), 3.45–3.60 (m, 1H), 3.68 (dd, *J*=10.5, 7.5 Hz, 1H), 3.99 (dd, *J*=10.5, 1.2 Hz, 1H), 4.03–4.14 (m, 2H), 4.47 (d, *J*=12 Hz, 1H), 4.60 (d, *J*=12 Hz, 1H), 4.70 (d, *J*=11.7 Hz, 1H), 4.84 (d, *J*=11.7 Hz, 1H), 7.18–7.40 (m, 15H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 9.1, 34.5, 35.1, 42.6, 54.1, 57.3, 69.4, 71.3, 72.7, 73.5, 77.7, 126.5, 127.4, 127.5, 127.6, 127.6, 127.7, 128.0, 128.3, 128.3, 128.4, 138.2, 138.8, 143.9; HRMS (FAB+): *m*/*z*=446.2687 (MH^+ calcd for $C_{29}H_{36}NO_3$: 446.2695).

4.2.16. (2*S*,4*R*)-*N*-[(*R*)-α-Methylbenzyl]-2-[(*R*)-1,2-dibenzyloxyethyl]-4-acetyloxypiperidine (26). A solution of (2*S*,4*R*)-*N*-[(*R*)-α-methylbenzyl]-2-[(*R*)-1,2-dibenzyloxyethyl]-4-hydroxypiperidine (**25**), (1.35 g, 3 mmol) triethylamine (365 mg, 3.6 mmol), dimethylaminopyridine (20 mg, 0.16 mmol) and acetic anhydride (335 mg, 3.3 mmol) in dry dichloromethane (45 mL) was stirred at room temperature for 2 h under an argon atmosphere. The reaction mixture was then concentrated in vacuo and the residue purified by filtration through a silica gel pad, eluting with diethyl ether/hexanes (1:2) to yield 1.36 g (92% yield) of (2*S*,4*R*)-*N*-[(*R*)-α-methylbenzyl]-2-[(*R*)-1,2-dibenzyloxyethyl]-4-acetyloxypiperidine (**26**) as a colourless oil. $[\alpha]^{D}_{25}=-4.8$ (*c* 1, $CHCl_3$); IR (neat) 1733 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.15 (d, *J*=6.9 Hz, 3H), 1.18–1.32 (m, 2H), 1.71–1.77 (m, 1H), 1.98 (s, 3H), 2.08 (ddd, *J*=12, 12, 2.4 Hz, 1H), 2.30 (dddd, *J*=12, 4.5, 2.4, 2.4 Hz, 1H), 2.39 (ddd, *J*=12, 3.9, 3.9 Hz, 1H), 2.81 (ddd, *J*=11.4, 4.5, 2.4 Hz, 1H), 3.66 (dd, *J*=10.5, 7.8 Hz, 1H), 4.00–4.14 (m, 3H), 4.49 (d, *J*=12.3 Hz, 1H), 4.55–4.67 (m, 1H), 4.60 (d, *J*=12.3 Hz, 1H), 4.70 (d, *J*=12 Hz, 1H), 4.80 (d, *J*=12 Hz, 1H), 7.18–7.40 (m, 15H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 8.2, 21.3, 31.5, 31.7, 42.7, 53.7, 57.3, 71.0, 72.0, 72.7, 73.5, 77.2, 126.5, 127.4, 127.5, 127.5, 127.6, 127.8, 128.0, 128.3, 128.4, 138.3, 138.8, 143.5, 170.4; HRMS (FAB+): *m*/*z*=488.2805 (MH^+ calcd for $C_{31}H_{38}NO_4$: 488.2800).

4.2.17. (2*S*,4*R*)-*N*-*tert*-Butoxycarbonyl-2-[(*R*)-1,2-dibenzyloxyethyl]-4-acetyloxypiperidine (27). A solution of (2*S*,4*R*)-*N*-[(*R*)-α-methylbenzyl]-2-[(*R*)-1,2-dibenzyloxyethyl]-4-acetyloxypiperidine (**26**) (1.2 g, 2.5 mmol) and di-*tert*-butyl dicarbonate (1.66 g, 7.6 mmol) in absolute ethanol (15 mL) was added to a stirred suspension of 20% $Pd(OH)_2$/C (300 mg) in absolute ethanol (5 mL) and the mixture was hydrogenated with H_2 at 1 atm by shaking at room temperature for 2 h. After completion the reaction mixture was filtered and concentrated in vacuo to afford a crude product which was purified by flash chromatography eluting first with diethyl ether/hexane (1:4) and then with diethyl ether/hexane (1:1) to give (2*S*,4*R*)-*N*-*tert*-butoxycarbonyl-2-[(*R*)-1,2-dibenzyloxyethyl]-4-acetyloxypiperidine (**27**) (1.07 g, 89%) as a colourless oil. $[\alpha]^{D}_{25}=+14.1$ (*c* 0.76, $CHCl_3$); IR (neat) 1735, 1693 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.41 (s, 9H), 1.61–1.22 (m, 2H), 1.80 (ddd, *J*=15, 6.6, 3.3 Hz, 1H), 1.91 (s, 3H), 1.89–1.94 (m, 1H), 2.78 (ddd, *J*=15, 10.4, 3.9 Hz, 1H), 3.56 (dd, *J*=10.8, 4.8 Hz, 1H), 3.64 (dd, *J*=10.8, 3.3 Hz, 1H), 3.83–3.94 (m, 1H), 4.03 (ddd, *J*=9.6, 4.8. 3.3 Hz, 1H), 4.42 (ddd, *J*=9.6, 6.6, 2.4 Hz, 1H), 4.50 (d, *J*=12 Hz, 1H), 4.53 (d, *J*=12 Hz, 1H), 4.55 (d, *J*=12 Hz, 1H), 4.70 (d, *J*=12 Hz, 1H), 4.98–5.06 (m, 1H), 7.18–7.35 (m, 10H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 21.2, 28.5, 29.3, 29.7, 34.8, 51.3, 67.6, 71.3, 72.3, 73.6, 79.5, 127.5, 127.6, 127.7, 128.2, 128.2, 128.4, 138.4, 138.9, 155.4, 169.8; HRMS (FAB+): *m*/*z*=484.2689 (MH^+ calcd for $C_{28}H_{38}NO_6$: 484.2699).

4.2.18. (2*S*,4*R*)-*N*-*tert*-Butoxycarbonyl-2-[(*R*)-1,2-dihydroxyethyl]-4-acetyloxypiperidine (28). A solution of (2*S*,4*R*)-*N*-*tert*-butoxycarbonyl-2-[(*R*)-1,2-dibenzyloxyethyl]-4-acetyloxypiperidine (**27**) (965 mg, 2 mmol) in ethanol (20 mL) was hydrogenated with 20 wt% $Pd(OH)_2$ (300 mg) as catalyst at room temperature and atmospheric pressure for 2 h. When the reaction was complete the catalyst was removed by filtration and the solid washed with ethyl acetate (3×20 mL). The combined organic extracts were evaporated to dryness and the resulting crude material was purified by filtration through a silica gel pad, eluting with ethyl acetate to give (2*S*,4*R*)-*N*-*tert*-butoxycarbonyl-2-[(*R*)-1,2-dihydroxyethyl]-4-acetyloxypiperidine (**28**) (515 mg, 85%) as a colourless oil. $[\alpha]^{D}_{25}=-45.0$ (*c* 0.93, $CHCl_3$); IR (neat) 3465, 1735, 1663 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.46 (s, 9H), 1.71–1.80 (m, 2H), 1.86–1.92 (m, 2H), 2.03 (s, 3H), 2.41 (bs, 1H), 2.91 (bs, 1H), 3.24 (ddd, *J*=14.1, 10.2, 5.4 Hz, 1H), 3.52 (ddd, *J*=10.8, 5.6, 5.6 Hz, 1H), 3.67 (ddd, *J*=10.8, 6.6, 4.2 Hz, 1H), 3.89 (ddd, *J*=13.5, 3.9, 3.9 Hz, 1H), 4.01–4.10 (m, 1H), 4.42 (ddd, *J*=8.7, 4.5, 4.5 Hz, 1H), 5.06–5.10 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 21.1, 28.4, 29.3, 29.9, 36.3, 51.9, 64.1, 67.3, 72.6, 80.8, 156.7, 169.7; HRMS (FAB+): *m*/*z*=304.1753 (MH^+ calcd for $C_{14}H_{26}NO_6$: 304.1760).

4.2.19. (2*S*,4*R*)-*N*-*tert*-Butoxycarbonyl-4-acetyloxypipecolic acid (29). Small portions of $NaIO_4$ (1.5 g, 7 mmol) were added to a stirred solution of (2*S*,4*R*)-*N*-*tert*-butoxycarbonyl-2-[(*R*)-1,2-dihydroxyethyl]-4-acetyloxypiperidine (**28**) (532 mg, 1.75 mmol) in acetonitrile/carbon tetrachloride/water (2:2:3, 50 mL). After being vigorously stirred for 5 min following completion of the addition, the mixture was treated with $RuCl_3 \cdot H_2O$ (16.6 mg, 0.08 mmol) and stirring was continued for 2 h. Dichloromethane (20 mL) was then added, the organic phase was separated and the aqueous phase extracted with dichloromethane (3×10 mL). The combined organic extracts were dried over $MgSO_4$ and the solvent evaporated to dryness. The resulting crude material was purified by silica gel column chromatography eluting with diethyl ether/hexanes (2:1) to give (2*S*,4*R*)-*N*-*tert*-butoxycarbonyl-4-acetyloxypipecolic acid (**29**) (443 mg, 88%) as a pale yellow oil. $[\alpha]^{D}_{25}=-8.9$ (*c* 1, $CHCl_3$); IR (neat) 3500–2800, 1742, 1695 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.44 (s, 9H), 1.68 (dddd, *J*=12.6, 11.7, 4.6, 2.2 Hz, 1H), 1.78–1.85 (m, 1H), 1.90 (ddd, *J*=14.3, 7.2, 2.7 Hz, 1H), 1.95 (s, 3H), 2.55 (dddd, *J*=14.3, 3.8, 2.1, 2.1 Hz, 1H), 3.25–3.35 (m, 1H), 3.85–3.92 (m, 1H), 4.75–4.93 (m, 1H), 5.04–5.09 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 20.8, 28.4, 28.8, 30.5, 36.3, 51.0, 66.2, 80.5, 155.6, 169.8, 175.8; HRMS (FAB+): *m*/*z*=288.1453 (MH^+ calcd for $C_{13}H_{22}NO_6$: 288.1447).

4.2.20. (2*S*,4*R*)-*N*-*tert*-Butoxycarbonyl-4-acetyloxypipecolic acid *tert*-butylamide (30). To a stirred solution of (2*S*,4*R*)-*N*-*tert*-butoxycarbonyl-4-acetyloxypipecolic acid (**29**) (496 mg, 1.72 mmol) in acetonitrile/dimethylformamide (10:1, 5.5 mL) at 0°C under an argon atmosphere was added *tert*-butylamine (190 mg, 2.6 mmol), benzotriazol-1-yl-oxy(tridimethylamino)phosphonium hexafluorophosphate (BOP reagent) (840 mg, 1.9 mmol) and diisopropylethylamine (665 mg, 5.15 mmol). After additional stirring at room temperature for 1.5 h, the reaction mixture was filtered and the solvent evaporated in vacuo. The resulting crude material was purified by silica gel column chromatography eluting with ethyl acetate to give (2*S*,4*R*)-*N*-*tert*-butoxycarbonyl-4-acetyloxypipecolic acid *tert*-butylamide (**30**) (535 mg, 90%) as a white solid. Mp

112–115°C; $[\alpha]^{D}_{25}=-7.5$ (*c* 0.91, CH_3OH); IR (nujol) 3422, 3323, 1742, 1688, 1677 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.18 (s, 9H), 1.41 (s, 9H), 1.56–1.78 (m, 3H), 1.91 (s, 3H), 2.66 (dddd, *J*=14.7, 3.6, 1.8, 1.8 Hz, 1H), 3.08 (ddd, *J*=13.8, 10.7, 4.8 Hz, 1H), 3.85–3.95 (m, 1H), 4.45–4.53 (m, 1H), 4.95 (dddd, *J*=3.6, 3.4, 3.4, 3.4 Hz, 1H), 5.67 (brs, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 21.1, 28.1, 28.2, 28.8, 28.9, 36.3, 50.9, 53.3, 66.0, 80.8, 155.1, 169.3, 170.1; Elemental analysis calcd (%) for $C_{17}H_{30}N_2O_5$: C, 59.63; H, 8.83; N, 8.18; found: C, 59.38; H, 8.95; N, 8.08.

4.2.21. (2*S*,4*R*)-*N*-*tert*-Butoxycarbonyl-4-hydroxypipecolic acid *tert*-butylamide (31). To a stirred solution of (2*S*,4*R*)-*N*-*tert*-butoxycarbonyl-4-acetyloxypipecolic acid (**30**) (531 mg, 1.55 mmol) in methanol (10 mL) was added a 1 M aqueous solution of K_2CO_3 (4.65 mL). After stirring at room temperature for 2 h, the reaction mixture was concentrated in vacuo and extracted with ethyl acetate (3×10 mL). The combined organic extracts were dried over $MgSO_4$ and the solvent evaporated to dryness. The resulting crude material was purified by silica gel column chromatography eluting with ethyl acetate/hexanes (1:1) to give (2*S*,4*R*)-*N*-*tert*-butoxycarbonyl-4-hydroxypipecolic acid *tert*-butylamide (**31**) (340 mg, 73%) as a white solid. Mp 131–132°C (lit.[10] mp 131–133°C); $[\alpha]^{D}_{25}=-64.4$ (*c* 1.03, CH_3OH) {lit.[10] $[\alpha]^{D}_{25}=-64.9$ (*c* 1.03, CH_3OH)}; IR (nujol) 3343, 1673, 1646 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.31 (s, 9H), 1.47 (s, 9H), 1.56 (dddd, *J*=13.5, 13.1, 5.3, 3.2 Hz, 1H), 1.67–1.76 (m, 1H), 1.79 (ddd, *J*=15, 6.9, 3.6 Hz, 1H), 2.20–2.28 (m, 1H), 3.14 (ddd, *J*=13.1, 13.1, 2.7 Hz, 1H), 3.76–3.85 (m, 1H), 3.96–4.33 (m, 1H), 4.64–4.69 (m, 1H), 5.42 (brs, 1H), 6.52 (brs, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 28.4, 28.7, 30.8, 32.5, 35.9, 51.4, 53.9, 61.7, 80.9, 156.2, 172.7; Elemental analysis calcd (%) for $C_{15}H_{28}N_2O_4$: C, 59.98; H, 9.40; N, 9.33; found: C, 59.88; H, 9.35; N, 9.26.

4.2.22. (2*S*,4*S*)-*N*-[(*R*)-α-Methylbenzyl]-2-[(*R*)-1,2-dibenzyloxyethyl]-4-acetyloxypiperidine (32). A solution of (2*S*,4*S*)-*N*-[(*R*)-α-methylbenzyl]-2-[(*R*)-1,2-dibenzyloxyethyl]-4-hydroxypiperidine (**24**) (225 mg, 0.5 mmol), triethylamine (61 mg, 0.6 mmol), dimethylaminopyridine (3.3 mg, 0.026 mmol) and acetic anhydride (56 mg, 0.55 mmol) in dry dichloromethane (7.5 mL) was stirred at room temperature for 2 h under an argon atmosphere. Then the reaction mixture was concentrated in vacuo and the residue purified by filtration through a silica gel pad, eluting with diethyl ether/hexanes (1:2), to yield 235 mg (96% yield) of (2*S*,4*S*)-*N*-[(*R*)-α-methylbenzyl]-2-[(*R*)-1,2-dibenzyloxyethyl]-4-acetyloxypiperidine (**32**) as a yellowish oil. $[\alpha]^{D}_{25}=+7.5$ (*c* 1, $CHCl_3$); IR (neat) 1735 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.24 (d, *J*=6.6 Hz, 3H), 1.49–1.60 (m, 2H), 1.96–2.07 (m, 2H), 2.03 (s, 3H), 2.40–2.57 (m, 2H), 3.08–3.17 (m, 1H), 3.62 (dd, *J*=10.8, 6.9 Hz, 1H), 3.87 (dd, *J*=10.8, 1.8 Hz, 1H), 3.92–4.10 (m, 2H), 4.47 (d, *J*=12 Hz, 1H), 4.55 (d, *J*=12 Hz, 1H), 4.70 (d, *J*=12 Hz, 1H), 4.79 (d, *J*=12 Hz, 1H), 5.02–5.10 (m, 1H), 7.18–7.40 (m, 15H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 8.2, 21.4, 29.2, 30.3, 40.5, 54.7, 56.3, 68.8, 71.2, 72.8, 73.4, 78.5, 126.5, 127.4, 127.5, 127.6, 127.8, 128.0, 128.2, 128.3, 128.3, 138.3, 138.9, 145.0, 170.4; HRMS (FAB+): *m*/*z*=488.2815 (MH^+ calcd for $C_{31}H_{38}NO_4$: 488.2800).

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