Asymmetric synthesis of (2*R*,4*R*,5*S*)-tetrahydropseudodistomin and stereoisomers by cycloaddition of nitrone to vinylglycinol[1]

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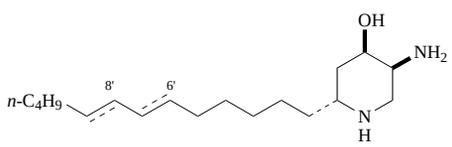
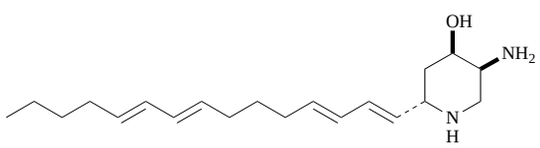
Cycloaddition of the nitrone, derived from tetradecanal, to vinylglycinol provides an asymmetric synthesis of both (2*R*,4*R*,5*S*)-tetrahydropseudodistomin and all the stereoisomers of the racemic tetrahydropseudodistomins.

Introduction

Pseudodistomins A **1** and B **2** are isomeric piperidine alkaloids which were isolated from the Okinawan tunicate *Pseudodistoma kanoko* and shown to have *in vitro* antitumour activity against L1210 and L5178Y leukemia cells and to inhibit calmodulin-activated brain phosphodiesterase.[2] Their structures were confirmed based on their degradation studies[3,4] and recent synthesis[3,5] of the acetates of racemic **1** and **2** and tetrahydropseudodistomin **3**.[6–8] In 1995,[9] pseudodistomin C **4** was isolated



1 (+)-Pseudodistomin A : 6'-*trans* , 8'-*cis*
2 (+)-Pseudodistomin B : 6'-*trans* , 8'-*trans*
3 (2*R*,4*R*,5*S*)-Tetrahydropseudodistomin : 6',8'-saturated



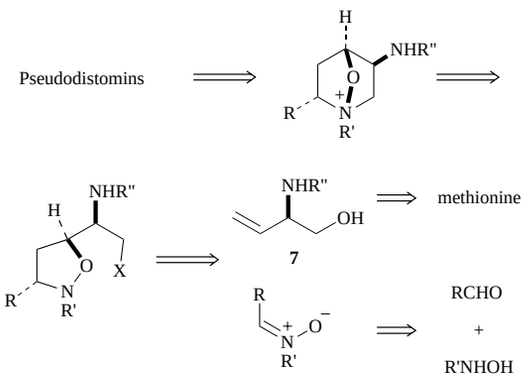
4 (+)-Pseudodistomin C

from the same tunicate and shown to have cytotoxicity against L1210 and human epidermoid carcinoma KB cells *in vitro*. The structure of the alkaloid **4** was unambiguously established by asymmetric total synthesis.[10] Because of the limited availability from natural sources of these compounds and in order to establish the relationship between their unique structures and biological activity, we have investigated a convenient procedure for the synthesis of pseudodistomins and related compounds on a large scale.

We now report in detail a new asymmetric synthesis of (2*R*,4*R*,5*S*)-tetrahydropseudodistomin **3** in only eight steps from D-methionine ester by a route involving two key reactions: cycloaddition of a nitrone to the vinylglycinol leading to the formation of the isoxazolidines and their ring transformation to the corresponding 2-substituted 5-aminopiperidin-4-ols (see Scheme 1).

Results and discussion

Nitrone cycloaddition is known as an attractive reaction for the construction of 1,3-amino alcohol systems widely found in natural products.[11] In general, the intramolecular cycloaddition of nitrones to olefins proceeds more stereoselectively than the

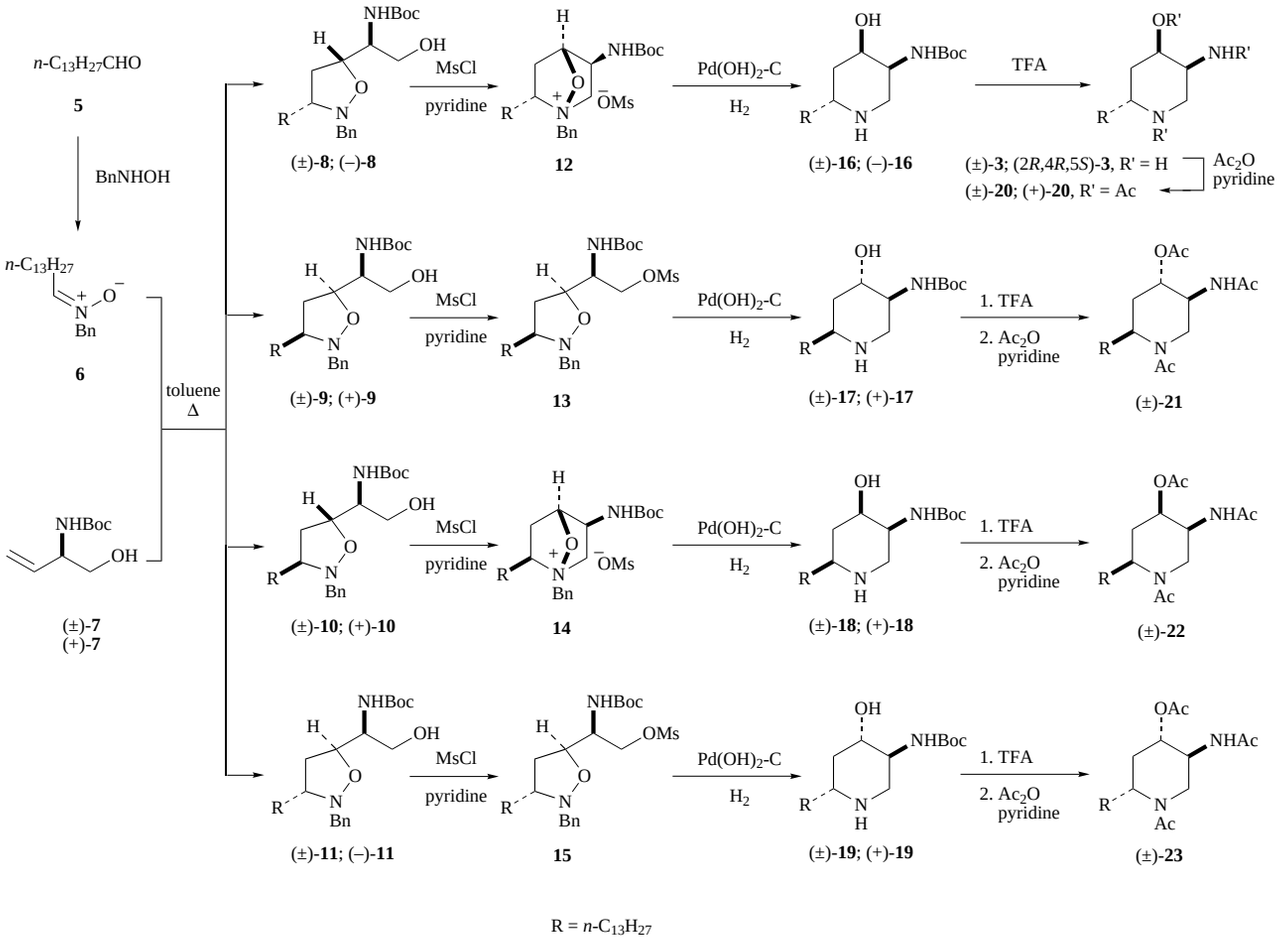


Scheme 1

intermolecular reactions. However, recently intermolecular cycloadditions of nitrones to chiral olefins have been systematically investigated and successfully applied to natural product synthesis.[12] Additionally, our recent work[13] has shown that *C*,*N*-dialkyl nitrone cycloaddition to either homoallyl alcohols or allyl alcohols proceeded smoothly to afford isoxazolidines which were effectively converted into substituted piperidines.

With a practical synthesis of pseudodistomins as a target, we chose the known[14] vinylglycinol **7** as a dipolarophile (see Scheme 1). As a preliminary experiment, we first investigated the cycloaddition of the nitrone **6** to (±)-*N*-*tert*-butoxycarbonyl (*N*-Boc)vinylglycinol **7**. The nitrone **6** was prepared by condensation of the tetradecanal **5** and *N*-benzylhydroxylamine[15] according to the literature.[16] Formation of a single geometrical isomer of the nitrone **6** was indicated by ^{1}H NMR (in $CDCl_3$ and C_6D_6) and ^{13}C NMR spectral results. Comparison of the ^{1}H NMR signals at δ 6.62 in $CDCl_3$ and δ 6.04 in C_6D_6 arising from the olefinic hydrogen with those of the known *Z*-(δ 6.68–6.95 in $CDCl_3$ and δ 5.90–6.22 in C_6D_6)[17] and *E*-nitrones (δ 6.85 in $CDCl_3$ and δ 6.31 in C_6D_6)[17] suggested that the nitrone **6** has a *Z*-configuration.

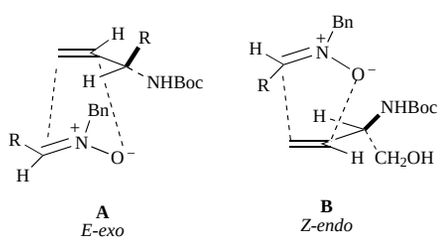
Cycloaddition of the nitrone **6** to (±)-vinylglycinol **7** (refluxing toluene for 64 h) gave a 2:3:3:5 mixture of four adducts (±)-**8**–(±)-**11** in 80% yield which was separated by repeated medium-pressure liquid chromatography (MPLC). The stereostructures of the adducts (±)-**8**–(±)-**11** were tentatively deduced from ^{1}H NMR spectral results, particularly a ^{1}H-^{1}H nuclear Overhauser effect spectroscopic (NOESY) experiment. This showed cross peaks between 3-H and one proton of 4-H_2, and 5-H and the same proton of 4-H_2 in the *cis*-isomers **8** and **9**; also between 3-H and one proton of 4-H_2, and 5-H and the other proton of 4-H_2 in the *trans*-isomers **10** and **11**, respectively. However, the relative configuration between 5-H and 1″-H could not be deduced from the spectral data. Therefore, the stereostructures of all the adducts were unambiguously



Scheme 2

confirmed from the structures of the easily assignable piperidine derivatives which were readily prepared by ring transformation of the isoxazolidines. Upon treatment with methanesulfonyl chloride (MsCl) in pyridine, the adducts (±)-**9** and (±)-**11** gave the corresponding mesylates (±)-**13** and (±)-**15** while the most non-polar adduct (±)-**8** and the third one (±)-**10** gave the bicyclic compounds (±)-**12** and (±)-**14** as a result of concomitant ring formation. Treatment of two mesylates (±)-**13** and (±)-**15** with hydrogen in the presence of Pearlman catalyst smoothly underwent a three-step reaction sequence involving cleavage of the *N*–*O* bond, debenzylation and *N*-alkylation to give the respective piperidinols (±)-**17** and (±)-**19** in 62–80% yields. Similarly, the two quaternary salts (±)-**12** and (±)-**14** were converted into the piperidinols (±)-**16** and (±)-**18** in 68–83% yield. Careful ^{1}H NMR spectral analyses of (±)-**16**–(±)-**19** and the before-mentioned cycloadducts (±)-**8**–(±)-**11** firmly established the stereostructures of the four isomeric piperidines (±)-**16**–(±)-**19** as shown. Thus, it was demonstrated that in the cycloaddition of the nitrone **6** to the vinylglycinol **7**, slightly more of the 1″,5-*threo* adducts (±)-**9** and (±)-**11** were obtained than the 1″,5-*erythro* adducts (±)-**8** and (±)-**10**. Of these isoxazolidines the *cis-erythro* isomer (±)-**8** is the desired cycloadduct for the synthesis of pseudodistomins. The observed stereoselectivity in this work is in accord with that observed in the previously reported cycloaddition of nitrones to substituted allylamines.[18]

Next, we investigated possible interconversions between the four cycloadducts (±)-**8**–(±)-**11** and also between the *E*- and *Z*-isomers of the starting nitrone **6** to explain plausibly the nitrone cycloaddition pathway. There was no thermal interconversions between the four adducts (±)-**8**–(±)-**11** even in refluxing toluene, thus indicating that the cycloaddition proceeded irreversibly under the reaction conditions to give the

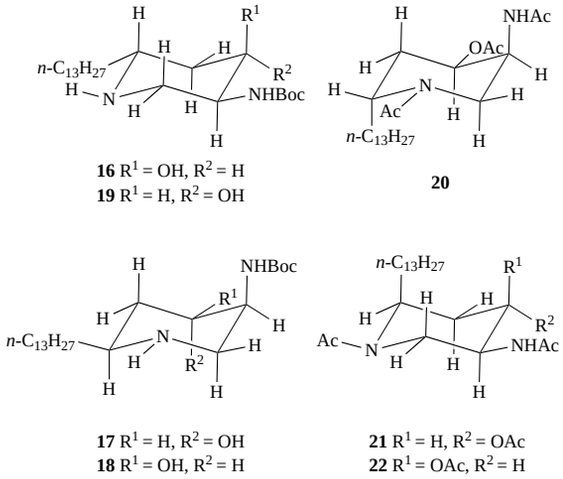


A *E-exo* **B** *Z-endo*

Fig. 1

kinetically controlled products (±)-**8**–(±)-**11**. No isomerisation of the nitrone **6** was also observed even after 32 h in refluxing toluene. Benz *et al*.[18] studied the cycloaddition of *C*,*N*-dialkylnitrone to substituted allylamine and explained the generation of the preferred diastereoisomer by an *E-exo* transition state **A** as a result of thermal equilibration between the ground state *Z*-nitrone and the *E*-isomer under the reaction conditions. However, since in our case no isomerisation of the *Z*-nitrone **6** to *E*-nitrone was observed under the reaction condition, the *Z-endo* transition state **B** is responsible for the generation of the major isomer **11** as shown in Fig. 1.

As mentioned before, we obtained two different types of products in the mesylation of the *threo*- and *erythro*- cycloadducts (±)-**8**–(±)-**11** depending upon their stereostructures. This interesting behaviour may be explained as follows: conformation **C** of the mesylate which would be transiently formed from the *erythro*-adducts **8** and **10** would be favourable for cyclisation to the bicyclic products **12** and **14**. On the other hand, the mesylate prepared from the *threo*-adducts **9** and **11** would preferably exist in the conformation **E** which is not suitable for cyclisation. A further conformation **D** would be less stable because of steric repulsion between the R^2 group at the



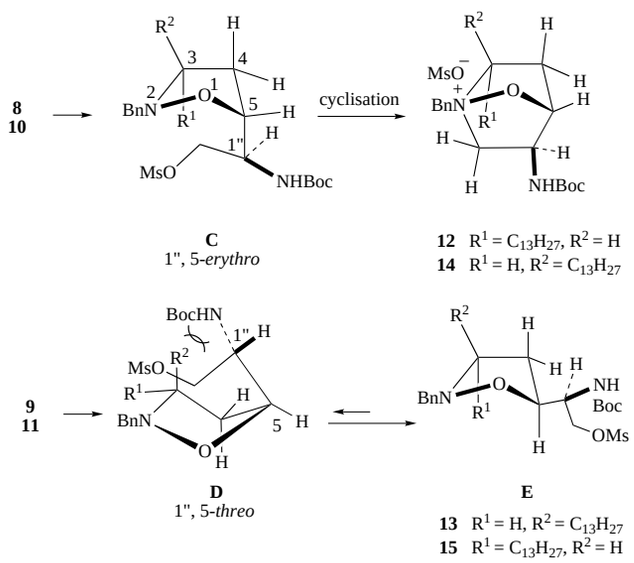
16 R^1 = OH, R^2 = H
19 R^1 = H, R^2 = OH

20

17 R^1 = H, R^2 = OH
18 R^1 = OH, R^2 = H

21 R^1 = H, R^2 = OAc
22 R^1 = OAc, R^2 = H

Fig. 2



C
1", 5-*erythro*

12 $R^1 = C_{13}H_{27}$, R^2 = H
14 R^1 = H, $R^2 = C_{13}H_{27}$

D
1", 5-*threo*

E

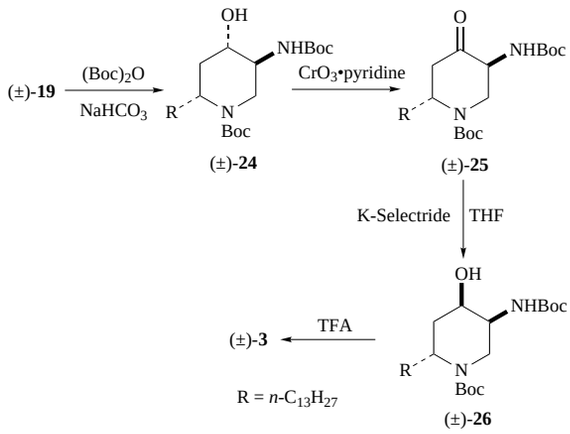
13 R^1 = H, $R^2 = C_{13}H_{27}$
15 $R^1 = C_{13}H_{27}$, R^2 = H

Scheme 3

3-position and the carbamate group on the side chain. Thus, the *threo*-mesylates (±)-**13** and (±)-**15** would exist preferentially in the conformation **E**, whilst the *erythro*-mesylates **C** formed *in situ* from **8** and **10** would undergo smooth cyclisation to give the quaternary salts (±)-**12** and (±)-**14** under the conditions of reaction and/or the following work-up.

For the synthesis of tetrahydropseudodistomin and the related stereoisomers, the piperidinols (±)-**16**–(±)-**19** were then converted into the acetates (±)-**20**–(±)-**23**. Deprotection of the *N*-Boc group in the piperidinols (±)-**16**–(±)-**19** with trifluoroacetic acid (TFA) gave the amino alcohols in quantitative yields which were characterised as their corresponding acetates (±)-**20**–(±)-**23**, of which (±)-**20** was identical with the authentic acetate[2,6–8] upon comparison of their respective spectral data. Furthermore, the piperidinol (±)-**19**, prepared from the major cycloadduct (±)-**11** was effectively converted into (±)-tetrahydropseudodistomin **3** by applying Natsume's method.[6] The piperidinol (±)-**19** was treated with $(Boc)_2O$ to give the dicarbamate (±)-**24** (80%). Oxidation of (±)-**24** with chromium(VI) trioxide–pyridine gave the ketone (±)-**25** which was then stereoselectively reduced with K-Selectride to furnish the piperidinols (±)-**26** (82%). Removal of the *N*-Boc group in (±)-**26** with TFA gave (±)-tetrahydropseudodistomin **3**.

Having accomplished the synthesis of four isomeric 2,4,5-trisubstituted piperidines (±)-**16**–(±)-**19** and 1,2,4,5-tetrasubstituted piperidines (±)-**20**–(±)-**23**, we turned our attention to a conformational analysis of these piperidines in $CDCl_3$ solution by ^{1}H NMR spectral analysis. Of the eight piperidines



Scheme 4

(±)-**16**–(±)-**23**, isomer (±)-**23** exhibited such broad signals because of slowly interconverting conformations that conformational analysis was unsuccessful. The two tetrasubstituted piperidines (±)-**21** and (±)-**22** were found to be a mixture of two rotational isomers around the tertiary amide groups [*N*(1)-acetyl groups] [(±)-**21**, 3:1; (±)-**22**, 2:1]. Similar rotational isomers have been reported[2] for the tetraacetyl compound **20** (4:1) which was prepared from natural pseudodistomins A and B. Careful analyses of the ^{1}H NMR spectra, particularly comparisons of the coupling constants of the ring protons in all the isomers, have disclosed the following characteristic conformational features. Most of the tri- and tetra-substituted piperidines **16**–**22** exist in a chair conformation except for isomer **23** which exhibited very broad ^{1}H NMR signals as mentioned before. The four trisubstituted piperidines (±)-**16**–(±)-**19** have an equatorial alkyl side chain at the 2 position regardless of the configurations of the 4- and 5-substituents. On the other hand, the *N*(1)-acetyl tetrasubstituted piperidines (±)-**20**–(±)-**22** have an axial alkyl side chain at the 2 position, which is understandable since the alternative chair conformation suffers from a steric interaction between the *N*(1)-acetyl group and the alkyl side chain at the 2 position. The Knapp group[8] has reported along similar lines for a conformational analysis of tetrahydropseudodistomin acetate **20**.

Synthesis of (2*R*,4*R*,5*S*)-tetrahydropseudodistomin

The new synthetic method described in this study was successfully applied to the asymmetric synthesis of (2*R*,4*R*,5*S*)-tetrahydropseudodistomin **3**. The known[14] chiral (+)-vinylglycinol **7** was readily prepared from D-methionine. Cycloaddition of the nitrone **6** to the (+)-vinylglycinol **7** gave four chiral adducts **8**–**11** in 79% combined yield, of which the most non-polar adduct (−)-**8** was converted into the target compound. Mesylation of (−)-**8** gave a bicyclic compound which was successively subjected to catalytic hydrogenolysis and deprotection to afford the desired (2*R*,4*R*,5*S*)-tetrahydropseudodistomin **3** in 67% overall yield from (−)-**8**. Acylation of the piperidinol (2*R*,4*R*,5*S*)-**3** with acetic anhydride–pyridine gave the acetate (+)-**20**, mp 82–84 °C (Et_2O), $[\alpha]_D$ +70 (*c* 0.6, MeOH) {lit.[2] $[\alpha]_D$ +33 (*c* 1, MeOH); lit.[8] $[\alpha]_D$ +36.9 (*c* 0.8, MeOH)} which was identical with an authentic sample upon comparison of the IR, ^{1}H and ^{13}C NMR spectra. Our asymmetric synthesis provides the fully characterised crystalline (+)-tetrahydropseudodistomin acetate **20** for the first time. Similarly, other chiral cycloadducts (+)-**9**, (+)-**10** and (−)-**11** were converted into the respective chiral piperidinols, (+)-**17**, (+)-**18** and (+)-**19**, whose spectral data were identical with those of the corresponding racemic compounds.

In conclusion, a combination of nitrone cycloaddition to the vinylglycinol and ring transformation of the resulting cycloadducts to piperidines has provided a general method for the

asymmetric synthesis of tetrahydropseudodistomin and related compounds.

Experimental

^{1}H NMR spectra were measured using Varian Gemini-200 (200 MHz), Gemini-300 (300 MHz) and VXR-500 (500 MHz) instruments and ^{13}C NMR spectra were measured with a VXR-500 (125 MHz) machine for solutions in deuteriochloroform unless otherwise stated (tetramethylsilane was used as the internal reference); *J* values are given in Hz. IR spectra were measured with a Perkin-Elmer 1600 FTIR instrument for solutions in chloroform unless otherwise stated and mass spectra were taken with Hitachi M-4100 instruments. Optical rotations were measured on a Jasco DIP-370 digital polarimeter and are given in units of 10^{-1} deg cm^2 g^{-1}. Mps were determined with Kofler-type hot-stage apparatus and are uncorrected. All reactions were carried out under nitrogen and the extracts from the reaction mixtures were washed with water, dried over anhydrous sodium sulfate and evaporated under reduced pressure. TLC was performed on pre-coated silica gel 60F-254 (0.2 mm thick, Merck) and preparative TLC (PLC) on pre-coated silica gel 60F-254 (0.25 mm thick, Merck), with UV detection at 254 and 300 nm. MPLC was undertaken on a 530-4-10V apparatus (Yamazen) with Lobar größe B (310-25, LiChroprep Si60, Merck) as column adsorbent. Flash column chromatography (FCC) was performed on Merck Kieselgel 60 (230–400 mesh) as column adsorbent. Ether refers to diethyl ether. All products described in this paper were found to be homogeneous by TLC, MPLC and ^{1}H NMR spectra.

(*Z*)-*N*-Tetradecylidenebenzylamine N-oxide 6

N-Benzylhydroxylamine[15] (277 mg, 2.81 mmol) was added to a stirred mixture of tetradecanal **5** (598 mg, 2.81 mmol) and molecular sieves 4 Å (1.58 g) in toluene (16 cm^3) and the mixture was stirred at room temperature for 2 h. After the molecular sieves had been filtered off, the filtrate was evaporated to give a solid which was recrystallised from hexane to afford the nitrone **6** (390 mg, 55%) as needles, mp 105–106 °C; ν_{max}/cm^{-1} 1601 (C=N); δ_H(500 MHz) 7.42–7.35 (5 H, m, ArH), 6.62 (1 H, t, *J* 6, 1-H), 4.89 (2 H, s, CH_2Ph), 2.48 (2 H, br q, *J* 6, 2-H$_2$), 1.48 (2 H, br quint., *J* 6, 3-H$_2$), 1.34–1.22 (20 H, m, 4–13-H$_2$) and 0.88 (3 H, t, *J* 7, 13-Me); δ_H(200 MHz; C_6D_6) 6.04 (1 H, t, *J* 6, 1-H) and 4.43 (2 H, s, CH_2Ph); δ_C(75 MHz) 139.6 (d, C-1), 133.0 (s, Ph), 129.2, 129.2, 128.9, 128.9 and 128.9 (each d, Ph), 69.2 (t, *C*H$_2$Ph), 31.9 (t, C-12), 29.7, 29.7, 29.7, 29.6, 29.5, 29.5, 29.4 and 29.3 (each t, C-4–C-11), 26.8 (t, C-2 or C-3), 25.6 (t, C-2 or C-3), 22.7 (t, C-13) and 14.1 (q, C-14) (Found: C, 79.15; H, 11.2; N, 4.4. $C_{21}H_{35}NO$ requires C, 79.4; H, 11.1; N, 4.4%). The crude nitrone **6** was used for the following cycloaddition without purification.

Cycloaddition of the nitrone 6 to (±)-*N*-Boc-vinylglycinol 7

N-Benzylhydroxylamine (1.13 g, 9.16 mmol) was added to a stirred mixture of tetradecanal **5** (2.18 g, 10.3 mmol) and molecular sieves 4 Å (4.8 g) in toluene (20 cm^3). After being stirred at room temperature for 3 h, the reaction mixture was filtered. To the filtrate was added a solution of (±)-*N*-Boc-vinylglycinol[14] **7** (1.2 g, 6.4 mmol) in toluene (28 cm^3), and the mixture was refluxed for 94 h. After this, it was concentrated by evaporation of the solvent and the residue was subjected to FCC [ethyl acetate–hexane (1:2)] to give the adducts (±)-**8** (0.43 g, 13%), (±)-**9** (0.56 g, 17%), (±)-**10** (0.62 g, 19%) and (±)-**11** (1.02 g, 31%).

(±)-[3α,5α(*S)]-2-Benzyl-5-(1-*tert*-butoxycarbonylamino-2-hydroxyethyl)-3-tridecylisoxazolidine 8**

Crystals; mp 67–68 °C (from hexane); ν_{max}/cm^{-1} 3650–3050 (NH, OH) and 1700 (NHCO$_2$); δ_H(500 MHz) 7.38–7.25 (5 H, m, ArH), 5.33 (1 H, br d, *J* 8, N*H*Boc), 4.33 (1 H, br dt, *J* 8 and 4.5, 5-H), 4.15 and 3.75 (2 H, ABq, *J* 14, CH_2Ph), 3.90 (1 H, br d, *J* 11, 2″-H), 3.53–3.44 (2 H, m, 1″-H and 2″-H), 2.79 (1 H, qd, *J* 8 and 4, 3-H), 2.58 (1H, dt, *J* 12.5 and 8, 4-H), 1.86 (1 H, ddd, *J* 12.5, 8 and 5, 4-H), 1.65–1.23 (24 H, m, 1′–12′-H$_2$), 1.42 (9 H, s, Bu^t) and 0.88 (3 H, t, *J* 7, 12′-Me) (Found: C, 71.1; H, 10.3; N, 5.5. $C_{30}H_{52}N_2O_4$ requires C, 71.4; H, 10.4; N, 5.55%).

(±)-[3β,5β(*S)]-2-Benzyl-5-(1-*tert*-butoxycarbonylamino-2-hydroxyethyl)-3-tridecylisoxazolidine 9**

Needles; mp 47–48 °C (from hexane); ν_{max}/cm^{-1} 3650–3050 (NH, OH) and 1700 (NHCO$_2$); δ_H(500 MHz) 7.38–7.24 (5 H, m, ArH), 5.54 (1 H, br d, *J* 8, N*H*Boc), 4.36 (1 H, ddd, *J* 8, 6 and 2, 5-H), 3.98 and 3.76 (2 H, ABq, *J* 13, CH_2Ph), 3.79–3.64 (2 H, m, 2″-H$_2$), 3.60 (1 H, m, 1″-H), 2.85 (1 H, br q, *J* 8, 3-H), 2.55 (1 H, dt, *J* 12 and 8, 4-H), 1.87 (1 H, br dt, *J* 12 and 7, 4-H), 1.75–1.20 (24 H, m, 1′–12′-H$_2$), 1.44 (9 H, s, Bu^t) and 0.88 (3 H, t, *J* 7, 12′-Me) (Found: C, 71.3; H, 10.5; N, 5.45. $C_{30}H_{52}N_2O_4$ requires C, 71.4; H, 10.4; N, 5.55%).

(±)-[3β,5α(*S)]-2-Benzyl-5-(1-*tert*-butoxycarbonylamino-2-hydroxyethyl)-3-tridecylisoxazolidine 10**

Crystals; mp 67–69 °C (from hexane); ν_{max}/cm^{-1} 3600–3100 (NH, OH) and 1702 (NHCO$_2$); δ_H(200 MHz) 7.35–7.23 (5 H, m, ArH), 5.04 (1 H, br d, *J* 7, N*H*Boc), 4.09 (1 H, m, 5-H), 4.02 and 3.83 (2 H, ABq, *J* 13.5, CH_2Ph), 3.83–3.54 (3 H, m, 1″-H, 2″-H$_2$), 2.87 (1 H, br, 3-H), 2.32 (1 H, dt, *J* 12 and 7, 4-H), 2.08 (1 H, dt, *J* 12 and 7, 4-H), 1.80–1.10 (24 H, m, 1′–12′-H$_2$), 1.44 (9 H, s, Bu^t) and 0.88 (3 H, t, *J* 6, 12′-Me) (Found: C, 71.1; H, 10.6; N, 5.4. $C_{30}H_{52}N_2O_4$ requires C, 71.4; H, 10.4; N, 5.55%).

(±)-[3α,5β(*S)]-2-Benzyl-5-(1-*tert*-butoxycarbonylamino-2-hydroxyethyl)-3-tridecylisoxazolidine 11**

Crystals; mp 45–46 °C (from hexane); ν_{max}/cm^{-1} 3600–3000 (NH, OH) and 1702 (NHCO$_2$); δ_H(200 MHz) 7.37–7.23 (5 H, m, ArH), 4.98 (1 H, br d, *J* 8, N*H*Boc), 4.22 (1 H, br t, *J* 6.5, 5-H), 4.03 and 3.81 (2 H, ABq, *J* 13, CH_2Ph), 3.75–3.56 (3 H, m, 1″-H and 2″-H$_2$), 2.74 (1 H, br, 3-H), 2.24 (1 H, dt, *J* 12 and 7, 4-H), 2.00 (1 H, br dt, *J* 12 and 7, 4-H), 1.62–1.40 (24 H, m, 1′–12′-H$_2$), 1.46 (9 H, s, Bu^t) and 0.88 (3 H, t, *J* 7, 12′-Me) (Found: C, 71.1; H, 10.5; N, 5.4. $C_{30}H_{52}N_2O_4$ requires C, 71.4; H, 10.4; N, 5.55%).

(±)-(2α,4β,5β)-5-*tert*-Butoxycarbonylamino-2-tridecylpiperidin-4-ol 16

To a solution of the isoxazolidine **8** (206 mg, 0.41 mmol) in pyridine (1.0 cm^3), MsCl (138 mg, 1.2 mmol) was added at 0 °C and the mixture was stirred at the same temperature for 5 h. After this, the mixture was diluted with water with ice-cooling and extracted with methylene dichloride. The extract was washed with saturated aqueous sodium hydrogen carbonate, dried and evaporated to give a quaternary salt **12** which was characterised from the ^{1}H NMR spectrum of the crude product; δ_H(200 MHz) 7.66 (1 H, br d, *J* 6, N*H*Boc), 7.62–7.32 (5 H, m, ArH), 5.68 and 5.36 (2 H, ABq, *J* 14, CH_2Ph), 5.03 (1 H, br d, *J* 6, 2-H), 4.56 (2 H, m, 6-H$_2$), 4.31 (1 H, br q, *J* 6, 4-H), 3.39 (1 H, m, 5-H), 2.84 (3 H, s, OMs), 2.47 (1 H, m, 3-H), 2.12 (1 H, m, 3-H), 1.70–1.10 (24 H, m, 1′–12′-H$_2$), 1.44 (9 H, s, Bu^t) and 0.88 (3 H, t, *J* 6, 12′-Me). A solution of the crude product **12** in methanol (10 cm^3) was catalytically hydrogenated over 20% palladium hydroxide on carbon (100 mg) under hydrogen at atmospheric pressure and room temperature for 24 h. The catalyst was filtered off and the filtrate was concentrated to give a residue which was made alkaline with 1 M aqueous sodium hydroxide with ice-cooling and then extracted with methylene dichloride. The extract was washed with brine, dried and evaporated to give a residue which was recrystallised from methanol to give the piperidinol **16** (136 mg, 83%) as crystals, mp 163–164 °C; ν_{max}/cm^{-1} 1707 (NHCO$_2$); δ_H(500 MHz) 4.93 (1 H, br d, *J* 8, N*H*Boc), 4.09 (1 H, br q, *J* 3, 4-H), 3.58 (1 H, m, 5-H), 2.97 (1 H, dd, *J* 11 and 5, 6-H^{eq}), 2.81 (1 H, m, 2-H), 2.76 (1 H,

t, *J* 11, 6-H^{ax}), 1.85 (1 H, ddd, *J* 13, 4 and 3, 3-H^{eq}), 1.44 (9 H, s, Bu^t), 1.41–1.22 (25 H, m, 3-H^{ax} and 1′–12′-H$_2$) and 0.88 (3 H, t, *J* 6, 12′-Me) (Found: C, 68.8; H, 11.7; N, 7.1. $C_{23}H_{46}N_2O_3$ requires C, 69.3; H, 11.6; N, 7.0%).

(±)-(2β,4α,5β)-5-*tert*-Butoxycarbonylamino-2-tridecylpiperidin-4-ol 17

According to the procedure described above, treatment of the isoxazolidine **9** (206 mg, 0.41 mmol) with MsCl (94 mg, 0.82 mmol) in pyridine (2.5 cm^3) gave the mesylate **13**; δ_H(200 MHz) 4.34 (1 H, br t, *J* 7, 5-H), 4.19–3.62 (5 H, m, C*H*$_2$Ph, 1″-H and 2″-H$_2$) and 2.82 (3 H, s, Ms). A solution of the crude product **13** in methanol (15 cm^3) was catalytically hydrogenated over 20% palladium hydroxide on carbon (100 mg) under hydrogen at atmospheric pressure and room temperature for 24 h. The crude product was purified by FCC [ethyl acetate–hexane (2:1) and ethyl acetate–hexane (4:1)] to give the piperidinol **17** (131 mg, 80%) as crystals, mp 51.5–53 °C (from ether); ν_{max}/cm^{-1} 1696 (NHCO$_2$); δ_H(200 MHz) 5.52 (1 H, br s, N*H*Boc), 3.93 (1 H, br q, *J* 3, 4-H), 3.55 (1 H, m, 5-H), 3.24 (1 H, br d, *J* 12, 6-H^{eq}), 2.86 (1 H, m, 2-H), 2.77 (1 H, br dd, *J* 12 and 2.5, 6-H^{ax}), 1.68–1.19 (26 H, m, 3-H$_2$ and 1′–12′-H$_2$), 1.44 (9 H, s, Bu^t) and 0.88 (3 H, t, *J* 6, 12′-Me) (Found: C, 66.7; H, 11.4; N, 6.7. $C_{23}H_{46}N_2O_3$·4/5H$_2$O requires C, 66.9; H, 11.6; N, 6.8%).

(±)-(2β,4β,5β)-5-*tert*-Butoxycarbonylamino-2-tridecylpiperidin-4-ol 18

According to the procedure described above, treatment of a solution of the isoxazolidine **10** (286 mg, 0.567 mmol) with MsCl (130 mg, 1.13 mmol) in pyridine (3 cm^3) gave the quaternary salt **14**; δ_H(200 MHz) 7.71 (1 H, br d, *J* 5, N*H*Boc), 5.70 and 4.87 (2 H, ABq, *J* 13, C*H*$_2$Ph), 5.04 (1 H, br d, *J* 6, 2-H), 5.02–4.62 (2 H, m, 6-H$_2$) and 2.83 (3 H, s, OMs). A solution of the crude product **14** in methanol (21 cm^3) was catalytically hydrogenated over 20% palladium hydroxide on carbon (56 mg) under hydrogen at atmospheric pressure and room temperature for 24 h. The crude product was purified by PLC [methylene dichloride–methanol (9:1)] to give **18** (154 mg, 68%) as crystals, mp 98–99 °C (from hexane); ν_{max}(Nujol)/cm^{-1} 1700 (NHCO$_2$); δ_H(500 MHz) 5.45 (1 H, br s, N*H*Boc), 3.92 (1 H, br, 5-H), 3.73 (1 H, br dt, *J* 12 and 4, 4-H), 3.00 (1 H, dd, *J* 12 and 3, 6-H^{eq}), 2.78 (1 H, br d, *J* 12, 6-H^{ax}), 2.47 (1 H, dtd, *J* 11.5, 6 and 2.5, 2-H), 1.79 (1 H, m, 3-H^{eq}), 1.46 (9 H, s, Bu^t), 1.36 (1 H, m, 3-H^{ax}), 1.33–1.22 (24 H, m, 1′–12′-H$_2$) and 0.88 (3 H, t, *J* 7, 12′-Me) (Found: C, 69.1; H, 11.65; N, 6.9. $C_{23}H_{46}N_2O_3$ requires C, 69.3; H, 11.6; N. 7.0%).

(±)-(2α,4α,5β)-5-*tert*-Butoxycarbonylamino-2-tridecylpiperidin-4-ol 19

According to the procedure described above, treatment of the isoxazolidine **11** (489 mg, 0.97 mmol) with MsCl (222 mg, 1.94 mmol) in pyridine (4 cm^3) gave the mesylate **15**; δ_H(200 MHz) 4.28–3.70 (6 H, m, 5-H, C*H*$_2$Ph, 1″-H and 2″-H$_2$) and 2.81 (3 H, s, Ms). A solution of the crude product **15** in methanol (36 cm^3) was catalytically hydrogenated over 20% palladium hydroxide on carbon (94 mg) under hydrogen at atmospheric pressure and room temperature for 24 h. Recrystallisation of the crude product from ethyl acetate gave **19** (239 mg, 62%) as crystals, mp 154.5–155.5 °C; ν_{max}(Nujol)/cm^{-1} 1684 (NHCO$_2$); δ_H(500 MHz) 4.49 (1 H, br s, N*H*Boc), 3.40 (1 H, br td, *J* 10 and 4, 4-H), 3.34 (1 H, m, 5-H), 3.24 (1 H, dd, *J* 12 and 4.5, 6-H^{eq}), 2.51 (1 H, m, 2-H), 2.37 (1 H, dd, *J* 12 and 11, 6-H^{ax}), 2.08 (1 H, br ddd, *J* 12.5, 4.5 and 2, 3-H^{eq}), 1.45 (9 H, s, Bu^t), 1.42–1.18 (25 H, m, 3-H^{ax} and 1′–12′-H$_2$) and 0.88 (3 H, t, *J* 7, 12′-Me) (Found: C, 68.7; H, 11.55; N, 7.0. $C_{23}H_{46}N_2O_3$·1/5H$_2$O requires C, 68.7; H, 11.6; N, 7.0%).

(±)-(2α,4β,5β)-5-Amino-2-tridecylpiperidin-4-ol [(±)-tetrahydropseudodistomin] 3

To a solution of **16** (35 mg, 0.088 mmol) in methylene dichloride (6.6 cm^3), TFA (6.6 cm^3) was added dropwise, and the mixture was stirred at room temperature for 3 h. After this it was concentrated by solvent evaporation to give a residue which was made alkaline with saturated aqueous sodium hydrogen carbonate with ice-cooling and extracted with methylene dichloride. The organic layer was dried and evaporated to give (±)-tetrahydropseudodistomin **3** (26 mg) as amorphous solid; δ_H(200 MHz) 3.85 (1 H, br d, *J* 2.5, 4-H), 2.97–2.66 (4 H, m, 2-H, 5-H and 6-H$_2$), 1.93 (1 H, br dt, *J* 14 and 3, 3-H^{eq}), 1.40–1.05 (25 H, m, 3-H^{ax} and 1′–12′-H$_2$) and 0.88 (3 H, t, *J* 6, 12′-Me).

(±)-(2α,4β,5β)-5-Acetamido-4-acetoxy-1-acetyl-2-tridecylpiperidine 20

A mixture of (±)-tetrahydropseudodistomin **3** (26 mg, 0.088 mmol) and acetic anhydride (0.30 cm^3, 3.2 mmol) in pyridine (0.8 cm^3) was stirred at room temperature for 12 h. The solution was concentrated to give a residue which was triturated with saturated aqueous sodium hydrogen carbonate and extracted with methylene dichloride. The extract was dried and evaporated to give the residue which was purified by PLC [methylene dichloride–methanol (92:8)] to give **20** (20 mg, 54%) as crystals, mp 114–115 °C (from ether) (Found: C, 67.1; H, 10.4; N, 6.5. $C_{24}H_{44}N_2O_4$·1/3 H$_2$O requires C, 66.95; H, 10.5; N, 6.5%). The IR and ^{1}H and ^{13}C NMR spectra of **20** were found to be identical with those of tetrahydropseudodistomin acetate **20**[2] obtained from natural pseudodistomins A **1** and B **2**.

(±)-(2β,4α,5β)-5-Acetamido-4-acetoxy-1-acetyl-2-tridecylpiperidine 21

According to the procedure described above, treatment of the piperidinol **17** (131 mg, 0.329 mmol) with TFA (1.3 cm^3, 16.45 mmol) in methylene dichloride (9 cm^3) gave the crude diamine which was acetylated with acetic anhydride (1.04 cm^3, 10.2 mmol) in pyridine (2.5 cm^3) to afford the crude acetamide which without purification was purified by PLC [ethyl acetate–methanol (9:1)] to give **21** (78 mg, 56%) as an oil; ν_{max}/cm^{-1} 1727 (OCO), 1675 (NHCO) and 1634 (NCO); δ_H(500 MHz) 6.08 (3/4 H, br d, *J* 6.5, N*H*Ac), 5.65 (1/4 H, br d, *J* 7, N*H*Ac), 5.06 (1 H, br td, *J* 11 and 5, 4-H), 4.90 (3/4 H, br q, *J* 6, 2-H), 4.82 (1/4 H, br dd, *J* 13.5 and 5, 6-H^{eq}), 4.09 (3/4 H, br dd, *J* 13 and 5, 6-H^{eq}), 3.96 (1/4 H, br, 2-H), 3.85 (1/4 H, br, 5-H), 3.72 (3/4 H, m, 5-H), 2.83 (3/4 H, dd, *J* 14 and 11, 6-H^{ax}), 2.48 (1/4 H, br t, *J* 12.5, 6-H^{ax}), 2.17, 2.09 and 1.96 (each 3 H, s, Ac × 3), 1.93–1.15 (26 H, m, 3-H$_2$, and 1′–12′-H$_2$) and 0.88 (3 H t, *J* 7, 12′-Me) (Found: M$^+$, 424.3297. $C_{24}H_{44}N_2O_4$ requires *M*, 424.3298).

(±)-(2β,4β,5β)-5-Acetamido-4-acetoxy-1-acetyl-2-tridecylpiperidine 22

According to the procedure described above, treatment of **18** (76 mg, 0.19 mmol) with TFA (0.74 cm^3, 9.5 mmol) in methylene dichloride (5 cm^3) gave the crude diamine which was acetylated with acetic anhydride (0.62 cm^3, 6.1 mmol) in pyridine (1.5 cm^3) to afford the crude acetamide which was purified by PLC [methylene dichloride–methanol (92:8)] to give **22** as crystals (70 mg, 87%), mp 62–63 °C (from hexane); ν_{max}/cm^{-1} 1742 (OCO), 1687 (NHCO) and 1632 (NCO); δ_H(500 MHz) 5.83 (2/3 H, br d, *J* 5, N*H*Ac), 5.59 (1/3 H, br, N*H*Ac), 5.08 (1 H, br s, 4-H), 4.74 (2/3 H, br q, *J* 6, 2-H), 4.62 (1/3 H, m, 6-H^{eq}), 4.07 (1/3 H, br, 5-H), 3.98 (2/3 H, br, 5-H), 3.82 (1/3 H, br, 2-H), 3.79 (2/3 H, br d, *J* 13, 6-H^{eq}), 3.19 (2/3 H, br t, *J* 12, 6-H^{ax}), 2.73 (1/3 H, br t, *J* 11, 6-H^{ax}), 2.17, 2.15 and 2.01 (each 3 H, s, Ac × 3), 1.92–1.14 (26 H, m, 3-H$_2$ and 1′–12′-H$_2$) and 0.88 (3 H, t, *J* 7, 12′-Me) (Found: C, 67.6; H, 10.5; N, 6.6. $C_{24}H_{44}N_2O_4$ requires C, 67.9; H, 10.45; N, 6.6%).

(±)-(2α,4α,5β)-5-Acetamido-4-acetoxy-1-acetyl-2-tridecylpiperidine 23

According to the procedure described above, treatment of **19** (139 mg, 0.35 mmol) with TFA (1.35 cm^3, 17.5 mmol) in

methylene dichloride (22 cm^3) gave the crude diamine which was acetylated with acetic anhydride (0.67 cm^3, 7.0 mmol) in pyridine (1.7 cm^3) to afford the crude acetamide which was purified by PLC [ethyl acetate–methanol (92:8)] to give **23** as crystals (49 mg, 33%), mp 83.5–84.5 °C (from ether); ν_{max}/cm^{-1} 1737 (OCO), 1673 (NHCO) and 1631 (NCO); δ_H(200 MHz) 6.35 (1/2 H, m, N*H*Ac), 5.95 (1/2 H, m, N*H*Ac), 5.10–3.20 (5 H, br, 2-H, 4-H, 5-H and 6-H_2), 2.08, 2.08 and 2.00 (each 3 H, s, Ac × 3), 2.00–1.15 (26 H, m, 3-H_2 and 1′–12′-H_2) and 0.88 (3 H, t, *J* 6, 12′-Me) (Found: C, 67.6; H, 10.4; N, 6.5. $C_{24}H_{44}N_2O_4$ requires C, 67.9; H, 10.45; N, 6.6%). ^{1}H NMR spectrum exhibited a broad signal pattern due to the presence of rotational isomers around the tertiary amides group.

tert-Butyl (±)-(2α,4α,5β)-5-*tert*-butoxycarbonylamino-4-hydroxy-2-tridecylpiperidine-1-carboxylate 24

To a solution of **19** (30 mg, 0.075 mmol) in methylene dichloride (10 cm^3), an aqueous solution (0.73 cm^3) containing sodium hydrogen carbonate (6 mg, 0.075 mmol) was added, followed by a solution of $(Boc)_2O$ (16 mg, 0.075 mmol) in methylene dichloride (6 cm^3), added dropwise at room temperature. The mixture was refluxed for 21.5 h, after which it was treated with saturated aqueous sodium hydrogen carbonate and extracted with methylene dichloride. The extract was washed, dried and evaporated to give the residue which was purified by PLC [methylene dichloride–methanol (97:3)] to give **24** as an oil (30 mg, 80%); ν_{max}/cm^{-1} 3600–3100 (NH, OH) and 1681 ($NHCO_2$, NCO_2); δ_H(200 MHz) 5.16 (1 H, br d, *J* 6, N*H*Boc), 4.01 (1 H, br quint, *J* 7, 2-H), 3.87–3.74 (2 H, m, 4-H, 6-H^{eq}), 3.53 (1 H, m, 5-H), 3.33 (1 H, dd, *J* 14.5 and 4, 6-H^{ax}), 1.97 (1 H, ddd, *J* 14.5, 7 and 4, 3-H^{eq}), 1.85–1.12 (25 H, m, 3-H^{ax} and 1′–12′-H), 1.47 and 1.43 (each 9 H, s, Bu^t × 2) and 0.88 (3 H, t, *J* 6, 12′-Me) (Found: M^+, 498.4040. $C_{28}H_{54}N_2O_5$ requires *M*, 498.4030).

tert-Butyl (±)-(2α,5β)-5-*tert*-butoxycarbonylamino-4-oxo-2-tridecylpiperidine-1-carboxylate 25

To a solution of pyridine (155 mg, 1.96 mmol) in methylene dichloride (2 cm^3) was added chromium(VI) trioxide (98 mg, 0.98 mmol) in small portions, and the mixture was stirred at room temperature for 15 min. After this, the solution was treated dropwise with a solution of **24** (81 mg, 0.16 mmol) in methylene dichloride (1 cm^3) at room temperature and then stirred at room temperature for 1.5 h. The mixture was then concentrated by solvent removal to give a residue which was diluted with ether. After filtration of the resulting solution through Celite, the filtrate was evaporated to give the unstable ketone **25** (81 mg) as an oil; δ_H(200 MHz) 5.28 (1 H, br s, N*H*Boc), 4.36 (1 H, m, 2-H or 5-H), 4.16 (1 H, br, 2-H or 5-H), 3.96 (1 H, br dd, *J* 14 and 4, 6-H^{eq}), 3.68 (1 H, br d, *J* 14, 6-H^{ax}), 2.88 (1 H, br dd, *J* 14 and 7, 3-H^{eq}), 2.36 (1 H, br d, *J* 14, 3-H^{ax}), 1.78–1.20 (24 H, m, 1′–12′-H_2), 1.48 and 1.44 (each 9 H, s, Bu^t × 2) and 0.88 (3 H, t, *J* 6, 12′-Me). Product **25** was used for the following reaction without further purification.

Reduction of the ketone 25 with K-Selectride

To a solution of the crude ketone **25** (81 mg, 0.16 mmol) in THF (7 cm^3), K-Selectride (1.0 M in THF; 0.37 cm^3, 0.37 mmol) was added dropwise at −78 °C and the mixture was stirred at −78 °C for 25 min. After this, saturated aqueous ammonium chloride was added to the mixture which was then extracted with methylene dichloride. The extract was washed, dried and evaporated to give a residue which was purified by PLC [ethyl acetate–hexane (1:2)] to give **26** (67 mg, 82%) and the epimer **24** (6 mg, 7%). The ^{1}H NMR spectrum of **24** was identical with that of **24** prepared from **19**.

tert-Butyl (±)-(2α,4β,5β)-5-*tert*-butoxycarbonylamino-4-hydroxy-2-tridecylpiperidine-1-carboxylate 26

Crystals; mp 50–52 °C (from hexane); ν_{max}/cm^{-1} 1685 ($NHCO_2$, NCO_2); δ_H(200 MHz) 4.94 (1 H, br d, *J* 6, N*H*Boc), 4.28 (1 H, m, 2-H), 4.12 (1 H, br dd, *J* 14 and 1, 6-H^{eq}), 4.06–3.83 (2 H, m, 4-H and 5-H), 2.99 (1 H, dd, *J* 14 and 2, 6-H^{ax}), 1.60–1.10 (26 H, m, 3-H_2 and 1′–12′-H_2), 1.47 and 1.45 (each 9 H, s, Bu^t × 2) and 0.88 (3 H, t, *J* 6, 12′-Me) (Found: M^+, 498.4043. $C_{28}H_{54}N_2O_5$ requires *M*, 498.4030). Deprotection of **26** (33 mg, 0.066 mmol) with TFA (0.25 cm^3, 3.3 mmol) in methylene dichloride (4 cm^3) gave the alcohol **3** (19 mg). ^{1}H NMR spectra of **3** was identical with that of **3** prepared from **16**.

Cycloaddition of the nitrone 6 to (+)-*N*-Boc-vinylglycinol 7

According to the procedure described for cycloaddition of (±)-*N*-Boc-vinylglycinol, a solution of (+)-*N*-Boc-vinylglycinol **7** {[α]$_D$ +29 (*c* 1.1, chloroform), lit.[14a] [α]$_D$ +29 (*c* 1.6, chloroform), lit.[14b] [α]$_D$ +29 (*c* 2.1, chloroform)} (2.6 g, 13.9 mmol) and the nitrone **6**, prepared from tetradecanal **5** (2.23 g, 18.1 mmol) and *N*-benzylhydroxylamine (4.82 g, 22.7 mmol), in toluene (40 cm^3) was refluxed for 94 h to give a mixture of the adducts (−)-**8** (0.98 g, 14%), (+)-**9** (1.30 g, 19%), (+)-**10** (1.35 g, 19%) and (−)-**11** (1.86 g, 27%).

(−)-[3*R*,5*R*(*S*)]-2-Benzyl-5-(1-*tert*-butoxycarbonylamino-2-hydroxyethyl)-3-tridecylisoxazolidine 8. *Crystals*; mp 64–65 °C (from hexane); [α]$_D$ −52 (*c* 0.7, methanol) (Found: C, 71.4; H, 10.4; N 5.4. $C_{30}H_{52}N_2O_4$ requires C, 71.4; H, 10.4; N, 5.55%). The ^{1}H NMR spectrum of (−)-**8** was identical with that of (±)-**8**.

(+)-[3*S*,5*S*(*S*)]-2-Benzyl-5-(1-*tert*-butoxycarbonylamino-2-hydroxyethyl)-3-tridecylisoxazolidine 9. *Needles*; mp 49–51 °C (from hexane); [α]$_D$ +21 (*c* 0.9, methanol) (Found: C, 71.15; H, 10.55; N, 5.5. $C_{30}H_{52}N_2O_4$ requires C, 71.4; H, 10.4; N, 5.55%). ^{1}H NMR spectrum of (+)-**9** was identical with that of (±)-**9**.

(+)-[3*S*,5*R*(*S*)]-2-Benzyl-5-(1-*tert*-butoxycarbonylamino-2-hydroxyethyl)-3-tridecylisoxazolidine 10. *Crystals*; mp 59–60 °C (from hexane); [α]$_D$ +42 (*c* 0.8, methanol) (Found: C, 71.35; H, 10.5; N, 5.5. $C_{30}H_{52}N_2O_4$ requires C, 71.4; H, 10.4; N, 5.55%). The ^{1}H NMR spectrum of (+)-**10** was identical with that of (±)-**10**.

(−)-[3*R*,5*S*(*S*)]-2-Benzyl-5-(1-*tert*-butoxycarbonylamino-2-hydroxyethyl)-3-tridecylisoxazolidine 11. *Crystals*; mp 41–42 °C (from hexane); [α]$_D$ −61 (*c* 1.0, methanol) (Found: C, 71.3; H, 10.3; N, 5.55. $C_{30}H_{52}N_2O_4$ requires C, 71.4; H, 10.4; N, 5.55%) (Found: M^+, 504.3933. $C_{30}H_{52}N_2O_4$ requires *M*, 504.3925). The ^{1}H NMR spectrum of (−)-**11** was identical with that of (±)-**11**.

(−)-(2*R*,4*R*,5*S*)-5-*tert*-Butoxycarbonylamino-2-tridecylpiperidin-4-ol 16

According to the procedure described for the ring transformation of (±)-**8**, (−)-**8** (410 mg, 0.811 mmol) was treated with MsCl (276 mg, 2.41 mmol) in pyridine (1.4 cm^3) to give the quaternary salt, which was catalytically hydrogenated over 20% palladium hydroxide on carbon (80 mg) in methanol (30 cm^3) to afford **16** (229 mg, 71%) as crystals, mp 105–107 °C (from ethyl acetate); [α]$_D$ −27 (*c* 0.5, methanol) (Found: C, 68.9; H, 11.6; N, 7.0. $C_{23}H_{46}N_2O_3 \cdot 1/10H_2O$ requires C, 69.0; H, 11.6; N, 6.9%). The ^{1}H NMR spectrum of (−)-**16** was identical with that of (±)-**16**.

(+)-(2*R*,4*R*,5*S*)-5-Acetamido-4-acetoxy-1-acetyl-2-tridecylpiperidine 20

According to the procedure described for synthesis of (±)-**3**, (−)-**16** (60 mg, 0.15 mmol) was treated with TFA (861 mg, 7.55 mmol) in methylene dichloride (8.0 cm^3) to give (2*R*,4*R*,5*S*)-**3** (42 mg, 94%). Treatment of **3** with acetic anhydride (0.48 cm^3, 4.7 mmol) in pyridine (1.2 cm^3) gave the (+)-acetamide **20** (35 mg, 57%) as crystals, mp 82–84 °C (from ether); [α]$_D$ +70 (*c* 0.6, methanol) {lit.,[2] [α]$_D$ +33 (*c* 1, methanol), lit.,[8] [α]$_D$ +36.9 (*c* 0.8, methanol)} (Found: C, 67.7; H, 10.6; N, 6.5. $C_{24}H_{44}N_2O_4$ requires C, 67.9; H, 10.45; N, 6.6%). The ^{1}H NMR spectra of (2*R*,4*R*,5*S*)-**3** and (+)-**20** were identical with those of (±)-**3** and (±)-**20**, respectively.

(+)-(2*S*,4*S*,5*S*)-5-*tert*-Butoxycarbonylamino-2-tridecylpiperidin-4-ol 17

According to the procedure described for ring transformation of the racemic **9**, (+)-**9** (511 mg, 1.01 mmol) was treated with MsCl (232 mg, 2.02 mmol) in pyridine (1.8 cm^3) to give the mesylate, which was catalytically hydrogenated over 20% palladium hydroxide on carbon (102 mg) in methanol (38 cm^3) to afford (+)-**17** (282 mg, 70%) as an oil, $[\alpha]_D$ +17 (*c* 2.0, methanol) (Found: M^+, 398.3522. $C_{23}H_{46}N_2O_3$ requires *M*, 398.3506). The ^1H NMR spectrum of (+)-**17** was identical with that of (±)-**17**.

(+)-(2*S*,4*R*,5*S*)-5-*tert*-Butoxycarbonylamino-2-tridecylpiperidin-4-ol 18

According to the procedure described for ring transformation of the racemic **10**, (+)-**10** (402 mg, 0.796 mmol) was treated with MsCl (183 mg, 1.60 mmol) in pyridine (1.4 cm^3) to give the quaternary salt, which was catalytically hydrogenated over 20% palladium hydroxide on carbon (202 mg) in methanol (29 cm^3) to afford (+)-**18** (202 mg, 64%) as crystals, mp 57–58 °C (from hexane); $[\alpha]_D$ +38 (*c* 1.0, methanol) (Found: C, 68.4; H, 11.8; N, 6.9. $C_{23}H_{46}N_2O_3 \cdot 1/3H_2O$ requires C, 68.3; H, 11.6; N, 6.9%). The ^1H NMR spectrum of (+)-**18** was identical with that of (±)-**18**.

(+)-(2*R*,4*S*,5*S*)-5-*tert*-Butoxycarbonylamino-2-tridecylpiperidin-4-ol 19

According to the procedure described for ring transformation of the racemic **11**, (−)-**11** (262 mg, 0.52 mmol) was treated with MsCl (119 mg, 1.04 mmol) in pyridine (0.92 cm^3) to give the mesylate, which was catalytically hydrogenated over 20% palladium hydroxide on carbon (52 mg) in methanol (20 cm^3) to afford (+)-**19** (128 mg, 62%) as crystals, mp 169–170 °C (from methanol); $[\alpha]_D$ +4 (*c* 0.9, methanol) (Found: C, 68.8; H, 11.8; N, 7.1. $C_{23}H_{46}N_2O_3 \cdot 1/5H_2O$ requires C, 68.7; H, 11.6; N, 7.0%). The ^1H NMR spectrum of (+)-**19** was identical with that of (±)-**19**.

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