Asymmetric synthesis of *N*,*O*,*O*,*O*-tetra-acetyl D-*lyxo*-phytosphingosine, jaspine B (pachastrissamine), 2-*epi*-jaspine B, and deoxoprosophylline *via* lithium amide conjugate addition†

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The highly diastereoselective *anti*-aminohydroxylation of (*E*)-γ-tri-*iso*-propylsilyloxy-α,β-unsaturated esters, *via* conjugate addition of lithium (*S*)-*N*-benzyl-*N*-(α-methylbenzyl)amide and subsequent *in situ* enolate oxidation with (+)-(camphorsulfonyl)oxaziridine, has been used as the key step in the asymmetric synthesis of *N*,*O*,*O*,*O*-tetra-acetyl D-*lyxo*-phytosphingosine (20% yield over 7 steps), the anhydrophytosphingosine jaspine B (10% yield over 9 steps), 2-*epi*-jaspine B (14% yield over 9 steps), and the *Prosopis* alkaloid deoxoprosophylline (26% yield over 7 steps).

Introduction

The phytosphingosines are a sub-class of the sphingoid bases that consist of a 1,3,4-trihydroxy-2-amino unit at the head of a long hydrocarbon chain. By far the most abundant phytosphingosine is D-*ribo*-phytosphingosine **1**, with 18 carbon atoms in the hydrocarbon chain, although smaller amounts of other chain lengths have been detected (Fig. 1). Sphingolipids are essential components of eukaryotic cells[1] and phytosphingolipids exhibit important physiological properties.[2,3] As such, there has been much interest in their synthesis, and this was the subject of a review in 2002.[4] The majority of routes to this molecular class are enantiospecific, utilising starting materials from the chiral pool;[5] in comparison asymmetric routes are relatively rare.[6]

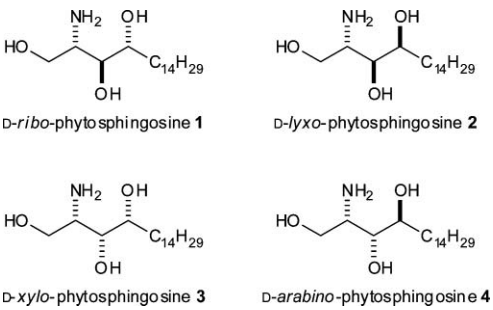

Fig. 1 Diastereoisomers of C_{18} phytosphingosine **1**–**4**.

Recent studies on the marine sponge *Pachastrissa* sp. by Higa and co-workers[7] led to the isolation of a cyclic anhydrophytosphingosine, which they named pachastrissamine **6**. Shortly after, in an independent study, Debitus and co-workers reported the isolation of two anhydrophytosphingosines from the marine sponge *Jaspis* sp.,[8] which they named jaspine A **5** and B **6**; pachastrissamine and jaspine B being identical (Fig. 2). To date, eleven enantiospecific syntheses of jaspine B **6** have been reported,[9–15] utilizing L-serine,[9] D-xylose,[10] (*R*)-glycidol,[11] D-*ribo*-phytosphingosine,[12] D-glucose,[13] D-galactose,[14] and D-tartaric acid[15] as the sources of chirality. Three asymmetric syntheses of jaspine B **6** have also been disclosed:[16,17] in addition to the procedure communicated by us (employing lithium amide conjugate addition),[16] two other strategies have been reported which both employ the Sharpless asymmetric dihydroxylation reaction.[17] Two syntheses of 'truncated' analogues (bearing C_5 and C_8 side-chains), based upon manipulation of L-xylose,[18] and Sharpless asymmetric epoxidation,[19] have also appeared.

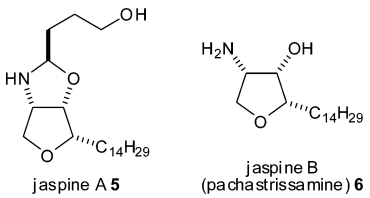

Fig. 2 Jaspine A **5** and jaspine B (pachastrissamine) **6**.

Previous investigations from this laboratory have demonstrated that the conjugate addition of homochiral, secondary lithium amides (derived from α-methylbenzylamine)[20] to α,β-unsaturated esters and *in situ* enolate oxidation with (camphorsulfonyl)oxaziridine (CSO) represents an efficient entry to *anti*-α-hydroxy-β-amino esters.[21] This methodology has been used as the key step in a number of natural product syntheses[22] and was applied by us as described in the preceding manuscript to the asymmetric synthesis of the sphingoid bases sphinganine and sphingosine.[23] In this manuscript we report the further application of this versatile methodology to encompass the asymmetric syntheses of the *N*,*O*,*O*,*O*-tetra-acetyl derivative of D-*lyxo*-phytosphingosine **2**, jaspine B (pachastrissamine) **6** and

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2-*epi*-jaspine B **7**, as well as its extension to the asymmetric synthesis of the *Prosopis* alkaloid deoxoprosophylline. Part of this work has been communicated previously.[16]

Results and discussion

Retrosynthetic analysis of jaspine B **6** and 2-*epi*-jaspine B **7** proceeded *via* initial disconnection of either endocyclic O–C bond of the THF skeleton to give a protected phytosphingosine **8** (with either the D-*lyxo*- or D-*ribo*-configuration). It was anticipated that phytosphingosine derivative **8** could result from diastereoselective addition of an organometallic reagent to aldehyde **9**. In turn, aldehyde **9** could be derived from *anti*-α-hydroxy-β-amino ester **10** (Fig. 3).

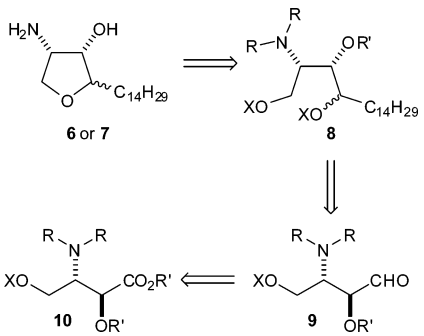


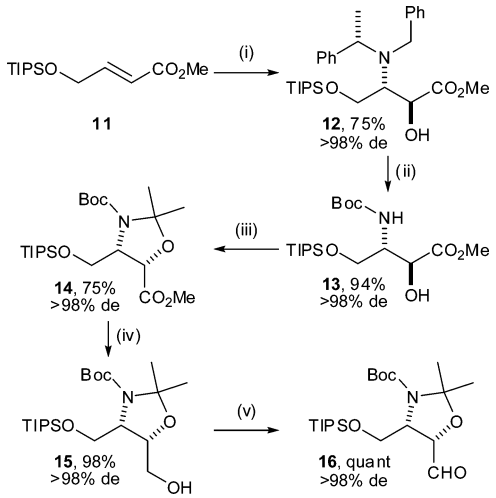
Fig. 3 Retrosynthetic analysis of jaspine B **6** and 2-*epi*-jaspine B **7**.

It was therefore envisaged that the development of an efficient asymmetric route to either D-*lyxo*- or D-*ribo*-phytosphingosine **1** or **2**, coupled with subsequent ring closure, would facilitate an entry to jaspine B **6** and 2-*epi*-jaspine B **7**.

Asymmetric synthesis of *N*,*O*,*O*,*O*-tetra-acetyl D-*lyxo*-phytosphingosine

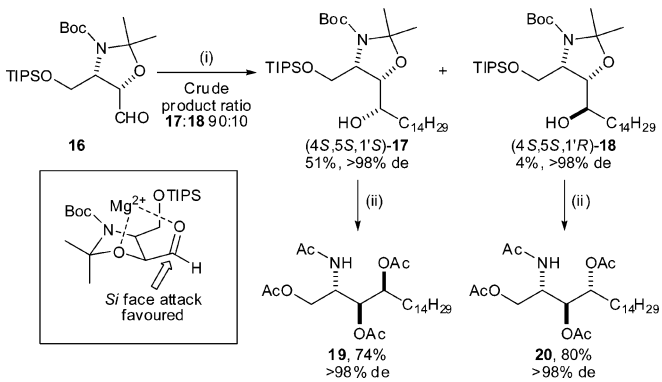
Aldehyde **16** was reported by us in the preceding manuscript as an intermediate in the synthesis of sphinganine and sphingosine,[23] and therefore its utility in the proposed synthesis of D-*lyxo*- or D-*ribo*-phytosphingosine was examined. Conjugate addition of lithium (*S*)-*N*-benzyl-*N*-(α-methylbenzyl)amide to γ-tri-*iso*-propylsilyloxy-α,β-unsaturated ester **11** and enolate oxidation with (+)-CSO[21] gave α-hydroxy-β-amino ester **12** which, after protecting group manipulation, furnished oxazolidine ester **14**. Reduction of **14** with DIBAL-H, followed by re-oxidation with IBX, gave aldehyde **16** which was used immediately (Scheme 1).[16,23]

Aldehyde **16** was treated with a solution of tetradecylmagnesium bromide in THF (prepared from 1-bromotetradecane and magnesium turnings in the presence of iodine). It was found that an excess of Grignard reagent (5 eq, based on 1-bromotetradecane) was required to drive the addition reaction to completion, giving a chromatographically separable 90 : 10[24] mixture of alcohols (4*S*,5*S*,1′*S*)-**17** and (4*S*,5*S*,1′*R*)-**18**, isolated in 51 and 4% yield respectively, and in >98% de in both cases. The configurations of the newly formed C(1′)-stereocentres within alcohols **17** and **18** could not be assigned *a priori*; they were established *via* conversion to the corresponding *N*,*O*,*O*,*O*-tetra-acetyl phytosphingosines **19** and **20**. Global hydrolysis of the protecting groups within the major diastereoisomeric alcohol (4*S*,5*S*,1′*S*)-**17** was achieved



Scheme 1 *Reagents and conditions:* (i) lithium (*S*)-*N*-benzyl-*N*-(α-methylbenzyl)amide, THF, −78 °C, 2 h, then (+)-CSO, −78 °C to rt, 12 h; (ii) H_2 (5 atm), $Pd(OH)_2$/C, Boc_2O, EtOAc, rt, 12 h; (iii) 2,2-dimethoxypropane, $BF_3{\cdot}Et_2O$, acetone, reflux, 12 h; (iv) DIBAL-H, DCM, 0 °C, 6 h; (v) IBX, DMSO, rt, 12 h.

upon treatment with HCl in MeOH–H_2O, with subsequent acetylation giving *N*,*O*,*O*,*O*-tetra-acetyl D-*lyxo*-phytosphingosine **19** with spectroscopic properties in excellent agreement with those previously reported {$[\alpha]_D^{21}$ −3.1 (*c* 0.7 in $CHCl_3$); lit.[25] $[\alpha]_D^{22}$ −3.1 (*c* 1.1 in $CHCl_3$)}. Analogous treatment of the minor diastereoisomeric alcohol (4*S*,5*S*,1′*R*)-**18** gave *N*,*O*,*O*,*O*-tetra-acetyl D-*ribo*-phytosphingosine **20** {$[\alpha]_D^{22}$ +18.2 (*c* 1.0 in $CHCl_3$); lit.[25] $[\alpha]_D^{22}$ +21.9 (*c* 1.1 in $CHCl_3$)}. The preferential addition of tetradecylmagnesium bromide to the *Si* face of aldehyde **16**, giving alcohol (4*S*,5*S*,1′*S*)-**17** as the major diastereoisomeric product, is therefore consistent with the 1,2-addition reaction proceeding *via* a chelated Cram model[26] (Scheme 2).

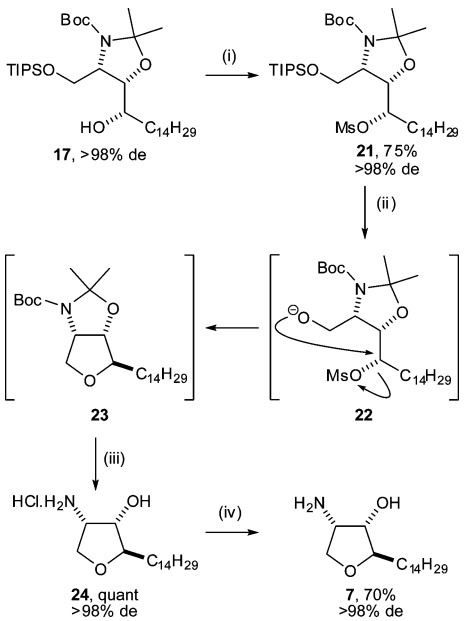


Scheme 2 *Reagents and conditions:* (i) $C_{14}H_{29}MgBr$, THF, 0 °C to rt, 6 h; (ii) HCl (3 M, aq), MeOH, 50 °C, 3 h, then Ac_2O, DMAP, pyridine, rt, 12 h.

Asymmetric synthesis of jaspine B and 2-*epi*-jaspine B

With samples of epimeric alcohols **17** and **18** in hand their conversion to jaspine B **6** and 2-*epi*-jaspine B **7** was investigated. It was anticipated that activation of the C(1′)-hydroxyl within the major diastereoisomeric alcohol (4*S*,5*S*,1′*S*)-**17** as a leaving group, followed by sequential desilylation and S_N2-type ring closure

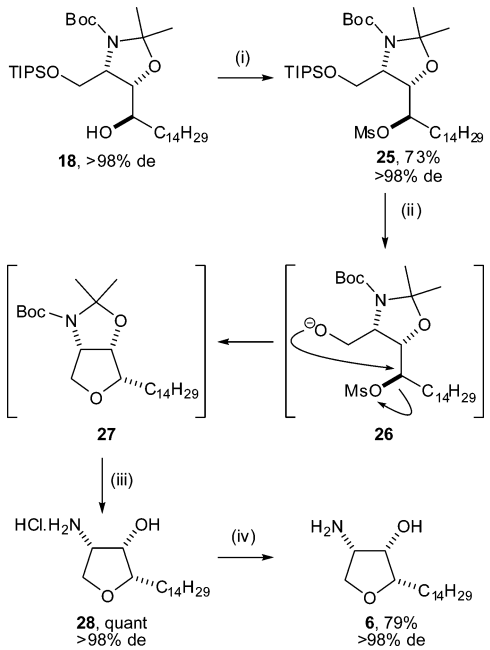
would give the tetrahydrofuran skeleton. Subsequent deprotection would then furnish **7**.[27] Thus, mesylation of alcohol (4*S*,5*S*,1′*S*)-**17** gave mesylate **21** in 75% yield. Subsequent desilylation of **21** with TBAF was followed by *in situ* cyclisation of the resultant primary oxyanion species **22**, giving tetrahydrofuran **23**. Tetrahydrofuran **23** proved inseparable by chromatography from the silicon-containing by-products formed in the desilylation reaction and therefore acidic hydrolysis was undertaken, giving **24** in quantitative yield and >98% de from **21**. Subsequent basification and recrystallisation gave **7** in 70% yield (14% overall yield in 10 steps from γ-tri-*iso*-propylsilyloxy-α,β-unsaturated ester **11**) and >98% de, with spectroscopic data in excellent agreement with that of the literature {$[\alpha]_D^{24}$ +16.4 (*c* 0.85 in MeOH); lit.[12a] $[\alpha]_D^{22}$ +15.0 (*c* 1.0 in MeOH)} (Scheme 3).



Scheme 3 *Reagents and conditions:* (i) MsCl, DMAP, Et_3N, DCM, 0 °C, 3 h; (ii) TBAF, THF, rt, 30 min; (iii) HCl (3 M, aq), MeOH, 50 °C, 3 h; (iv) KOH (2 M, aq), then recrystallisation.

Following the successful synthesis of **7** from the major diastereoisomeric alcohol (4*S*,5*S*,1′*S*)-**17** resulting from addition of tetradecylmagnesium bromide to aldehyde **16**, it was predicted that a similar sequence of reactions applied to the minor diastereoisomeric alcohol (4*S*,5*S*,1′*R*)-**18** would give jaspine B **6**. In accordance with this hypothesis, mesylation of (4*S*,5*S*,1′*R*)-**18** gave mesylate **25**, with subsequent desilylation upon treatment with TBAF accompanied by cyclisation to **27**. Hydrolysis of **27**, basification and recrystallisation gave jaspine B **6** as a white solid, in 58% overall yield from alcohol **18** (Scheme 4).

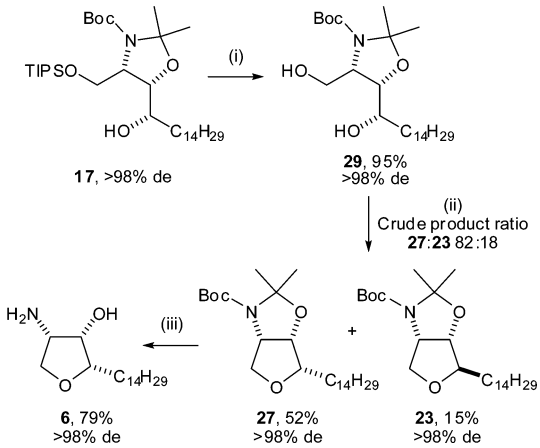
The overall yield of jaspine B **6** from γ-tri-*iso*-propylsilyloxy-α,β-unsaturated ester **11**, however, was unacceptably low (1.1%) due to the use of alcohol (4*S*,5*S*,1′*R*)-**18** (the minor diastereoisomer resulting from Grignard addition to aldehyde **16**, isolated yield 4%) in the synthesis. An alternative approach to the natural product from the major diastereoisomeric alcohol (4*S*,5*S*,1′*S*)-**17** was therefore envisaged. It was proposed that desilylation of (4*S*,5*S*,1′*S*)-**17** would give the corresponding diol **29**, which could be selectively activated at the primary hydroxyl group, with subsequent ring closure giving tetrahydrofuran **27**. Thus,



Scheme 4 *Reagents and conditions:* (i) MsCl, DMAP, pyridine, 0 °C to rt, 12 h; (ii) TBAF, THF, rt, 30 min; (iii) HCl (3 M, aq), MeOH, 50 °C, 3 h; (iv) KOH (2 M, aq), then recrystallisation.

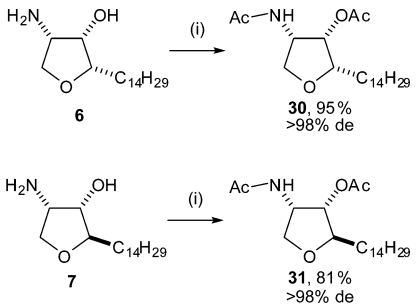
desilylation of (4*S*,5*S*,1′*S*)-**17** with TBAF gave diol **29** in 95% isolated yield. Attempted selective mesylation of the primary hydroxyl group of diol **29** under a variety of conditions was unsuccessful due to competing mesylation of the secondary hydroxyl group, forming a mixture of mono- and dimesylated species. Competitive mesylation of the secondary hydroxyl group could not be prevented even at −78 °C and employing a sub-stoichiometric amount of mesyl chloride (0.5 eq). It was therefore proposed that treatment of diol **29** with a more bulky activating agent would increase the selectivity for activation of the primary over the secondary hydroxyl. Unfortunately, treatment of diol **29** with triphenylphosphine and *N*-iodosuccinimide gave a complex mixture of products, whilst attempted tosylation at room temperature returned only starting material, even after extended reaction times (5 days) and in the presence of a stoichiometric amount of DMAP. At reflux in pyridine, however, a mixture of tetrahydrofurans **27** and **23**, resulting from tosylation of the primary and secondary hydroxyl groups, respectively, and *in situ* cyclisation, was observed. The effect of reaction temperature on the formation of these two diastereoisomers was therefore investigated, and revealed that no tosylated or cyclised products appeared until above 60 °C; however, at this temperature both **27** and **23** were observed. Optimum conditions for the selective formation of tetrahydrofuran **27** from diol **29** were heating at 80 °C with 3 equivalents of tosyl chloride and catalytic DMAP for 8 hours, which gave quantitative conversion to an 82 : 18 mixture of **27** : **23**, with subsequent chromatographic separation giving **27** in 52% yield and >98% de, and **23** in 15% yield and >98% de. Subsequent global deprotection of **27** and recrystallisation gave jaspine B **6** in an improved 10% overall yield in 9 steps from γ-tri-*iso*-propylsilyloxy-α,β-unsaturated ester **11** (Scheme 5).

The samples of jaspine B **6** prepared independently from both alcohols (4*S*,5*S*,1′*S*)-**17** and (4*S*,5*S*,1′*R*)-**18** (Scheme 4 and



Scheme 5 *Reagents and conditions:* (i) TBAF, THF, rt, 30 min; (ii) TsCl, DMAP, pyridine, reflux, 8 h; (iii) HCl (3M, aq), MeOH, 50 °C, 3 h, then KOH (2M, aq), then recrystallisation.

Scheme 5) were identical by ^{1}H NMR and displayed physical and spectroscopic properties in excellent agreement with those originally reported for the natural product by Higa *et al.* {$[\alpha]_D^{23}$ +17.5 (*c* 0.3 in EtOH); lit.[7] $[\alpha]_D^{25}$ +18.0 (*c* 0.1 in EtOH)}. In order to further confirm the relative stereochemistry of our samples of jaspine B **6** and 2-*epi*-jaspine B **7**, both were derivatised to the corresponding *N*,*O*-diacetates **30** and **31** upon treatment with Ac_2O and DMAP in pyridine (Scheme 6). The spectroscopic properties of **30** and **31** were in excellent agreement with those of the literature {**30** $[\alpha]_D^{23}$ −26.4 (*c* 0.5 in $CHCl_3$); lit.[12a] $[\alpha]_D^{25}$ −22.6 (*c* 1.0 in $CHCl_3$); **31** $[\alpha]_D^{21}$ −14.6 (*c* 0.5 in $CHCl_3$); lit.[12a] $[\alpha]_D^{22}$ −15.4 (*c* 1.0 in $CHCl_3$)}.



Scheme 6 *Reagents and conditions:* (i) Ac_2O, DMAP, pyridine, rt, 12 h.

^{1}H NMR NOE analyses conducted on these samples were in accordance with the original data reported by Higa[7] and Debitus.[8] For *N*,*O*-diacetyl jaspine B **30**, a series of enhancements between C(2)*H*, C(3)*H*, C(4)*H*, and C(5)H_A, suggested that they all occupy the same face of the tetrahydrofuran ring (Fig. 4) whilst in *N*,*O*-diacetyl-2-*epi*-jaspine B **31** a series of strong enhancements between C(3)*H*, C(4)*H* and C(1′)H_2 suggest that these protons occupy the same face of the tetrahydrofuran core. Other NOE enhancements to C(5)H_2 served to confirm this assignment (Fig. 5).

Subsequent recrystallisation of *N*,*O*-diacetyl jaspine B **30** from $CHCl_3$–heptane gave colourless prisms which proved suitable for single crystal X-ray structural analysis.[28] This unambiguously confirmed the all *cis* relationship of the substituents around the ring. An extended data collection using Cu-Kα radiation allowed determination of a Flack parameter[29] for the structure of −0.04(15), which satisfies the criterion for a reliable assignment

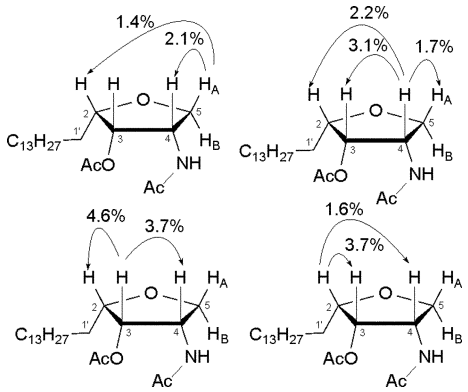


Fig. 4 Selected ^{1}H NMR NOE enhancements for *N*,*O*-diacetyl jaspine B **30**.

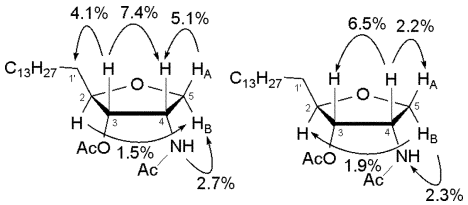


Fig. 5 Selected ^{1}H NMR NOE enhancements for *N*,*O*-diacetyl-2-*epi*-jaspine B **31**.

of absolute configuration of a material known to be homochiral,[29] and allowed the reported absolute (2*S*,3*S*,4*S*)-configuration of the natural product (originally determined by Higa *et al.*[7] using the Mosher method)[30] to be confirmed unambiguously.

Asymmetric synthesis of deoxoprosophylline

In order to further demonstrate the versatility of this lithium amide methodology for the synthesis of natural products containing an amino diol motif, application to the synthesis of the *Prosopis* alkaloid deoxoprosophylline **32** was examined. The *Prosopis* alkaloids, isolated from *Prosopis africana* Taub.,[31] possess a polar head group and a hydrophobic tail and are therefore often considered as cyclic analogues of the sphingoid bases.[32] These polysubstituted piperidine alkaloids[33] exhibit a range of useful pharmacological properties, such as anesthetic, analgesic and antibiotic activity.[34] There has thus been considerable synthetic interest in this subgroup of piperidine alkaloids and several syntheses producing the natural products in both racemic and homochiral forms have appeared in the literature.[35,36]

Retrosynthetic analysis of deoxoprosophylline **32** revealed that disconnection of the N(1)–C(6) bond gave ketone **33**. Functional group manipulation and further disconnection across the double bond of **34** gave aldehyde **9**, an intermediate in the retrosynthesis of jaspine B **6** (*vide supra*, Fig. 3). In the forward direction, it was anticipated that hydrogenation of the alkene within **34** and hydrogenolysis of the *N*-benzyl-*N*-α-methylbenzyl protecting groups could be achieved in one pot to liberate the corresponding primary amine, which was expected to undergo spontaneous cyclisation to the corresponding imine,[37] with subsequent *in situ* imine reduction giving deoxoprosophylline **32** (Fig. 6).

The synthesis of deoxoprosophylline **32** therefore began with *N*-benzyl-*N*-α-methylbenzyl protected α-hydroxy-β-amino ester **36**,[23]

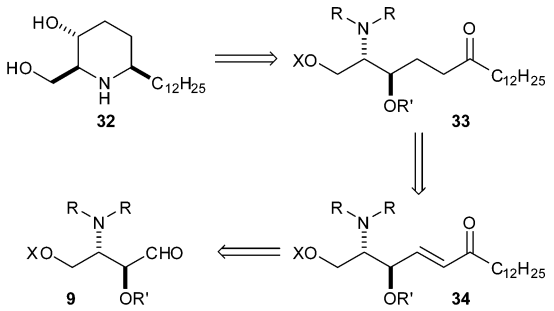
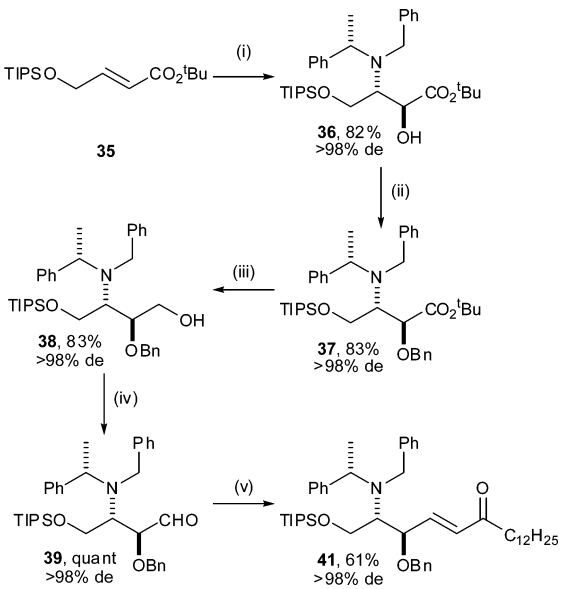


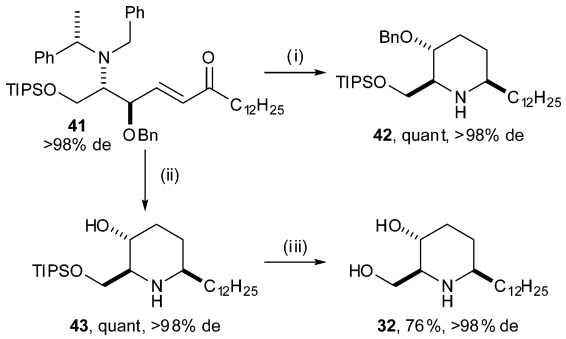
Fig. 6 Retrosynthetic analysis of deoxoprosophylline **32**.

prepared *via* the conjugate addition of lithium (*S*)-*N*-benzyl-*N*-(α-methylbenzyl)amide to γ-tri-*iso*-propylsilyloxy-α,β-unsaturated ester **35** and *in situ* enolate oxidation with (+)-CSO.[21] Attempted protection of the hydroxyl group within **36** with either TBDMSCl or TIPSCl was unsuccessful and returned starting material in both cases. *O*-Benzyl protection was therefore investigated, and benzylation of **36** was achieved upon treatment with NaH, 15-crown-5 and BnBr, giving **37** in 83% yield and >98% de. Subsequent reduction of **37** with DIBAL-H gave alcohol **38** in 83% yield and >98% de, with re-oxidation with IBX giving aldehyde **39** in quantitative yield and >98% de.[38] Wadsworth–Emmons olefination of aldehyde **39** was effected utilizing the lithium anion of dimethyl 2-oxotetradecylphosphonate **40**, giving (*E*)-**41** ($J_{4,5}$ = 16.2 Hz) as a single diastereoisomer, isolated in 61% yield and >98% de after chromatography (Scheme 7).



Scheme 7 *Reagents and conditions:* (i) lithium (*S*)-*N*-benzyl-*N*-(α-methylbenzyl)amide, THF, −78 °C, 2 h, then (+)-CSO, −78 °C to rt, 12 h; (ii) NaH, THF, 0 °C to rt, 1 h, then 15-crown-5, BnBr, 12 h, rt; (iii) DIBAL-H, DCM, 0 °C, 18 h; (iv) IBX, DMSO, rt, 18 h; (v) BuLi, $(MeO)_2P(O)CH_2COC_{12}H_{25}$ **40**, THF, −78 °C, 30 min, then **39**, THF, −78 °C to rt, 12.5 h.

With **41** in hand, tandem hydrogenation and hydrogenolysis, and concomitant cyclisation, was next probed. Treatment of **41** with Pd/C under 5 atmospheres pressure of hydrogen for 24 h gave incomplete debenzylation, although returned **42** as a single diastereoisomer in quantitative yield. Over 48 h, however, and employing acetic acid as co-solvent, complete conversion to a single diastereoisomer of piperidine **43** was observed, with subsequent desilylation and recrystallisation furnishing deoxoprosophylline **32** in >98% de and 26% overall yield in 7 steps from **35**, with spectroscopic properties in excellent agreement with those of the literature {$[\alpha]_D^{22}$ +13.5 (*c* 0.3 in $CHCl_3$); lit. for enantiomer[35a] $[\alpha]_D$ −14.0 (*c* 0.2 in $CHCl_3$); lit.[35k] $[\alpha]_D^{20}$ +13.0 (*c* 0.2 in $CHCl_3$)} (Scheme 8).



Scheme 8 *Reagents and conditions:* (i) Pd/C, H_2 (5 atm), EtOAc, 24 h; (ii) Pd/C, H_2 (5 atm), EtOAc–AcOH (1 : 1), 48 h; (iii) TBAF, THF, rt, 12 h.

Conclusion

In conclusion, the highly diastereoselective *anti*-amino-hydroxylation of readily available α,β-unsaturated esters, *via* conjugate addition of lithium (*S*)-*N*-benzyl-*N*-(α-methylbenzyl)amide and *in situ* enolate oxidation with (+)-CSO, has been used as the key step for asymmetric synthesis of *N*,*O*,*O*,*O*-tetra-acetyl D-*lyxo*-phytosphingosine, the anhydrophytosphingosine jaspine B (pachastrissamine) and 2-*epi*-jaspine B, and the *Prosopis* alkaloid deoxoprosophylline. This synthetic strategy should be widely applicable to the generation of homologues of these natural product families with different side chain lengths and substituents.

Experimental

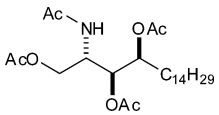
General experimental

All reactions involving organometallic or other moisture-sensitive reagents were carried out under a nitrogen or argon atmosphere using standard vacuum line techniques and glassware that was flame dried and cooled under nitrogen before use. Solvents were dried according to the procedure outlined by Grubbs and co-workers.[39] Water was purified by an Elix® UV-10 system. All other solvents were used as supplied (analytical or HPLC grade) without prior purification. Organic layers were dried over $MgSO_4$. Thin layer chromatography was performed on aluminium plates coated with 60 F_{254} silica. Plates were visualised using UV light (254 nm), iodine, 1% aq $KMnO_4$, or 10% ethanolic phosphomolybdic acid. Flash column chromatography was performed on Kieselgel 60 silica.

Melting points were recorded on a Gallenkamp Hot Stage apparatus and are uncorrected. Optical rotations were recorded on a Perkin-Elmer 241 polarimeter with a water-jacketed 10 cm cell. Specific rotations are reported in 10^{-1} deg cm^2 g^{-1} and concentrations in g 100 mL^{-1}. IR spectra were recorded on Bruker Tensor 27 FT-IR spectrometer as either a thin film on NaCl plates

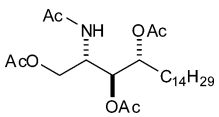
(film) or a KBr disc (KBr), as stated. Selected characteristic peaks are reported in cm^{-1}. NMR spectra were recorded on Bruker Avance spectrometers in the deuterated solvent stated. Spectra were recorded at rt unless otherwise stated. The field was locked by external referencing to the relevant deuteron resonance. Low-resolution mass spectra were recorded on either a VG MassLab 20–250 or a Micromass Platform 1 spectrometer. The ion [M + 59]$^+$ refers to [M + MeCN + NH_4]$^+$. Accurate mass measurements were run on either a Bruker Micro TOF internally calibrated with polyalanine, or a Micromass GCT instrument fitted with a Scientific Glass Instruments BPX5 column (15 m × 0.25 mm) using amyl acetate as a lock mass.

(2*S*,3*S*,4*S*)-1,3,4-Triacetoxy-2-acetamido-octadecane [*N*,*O*,*O*,*O*-tetra-acetyl D-*lyxo*-phytosphingosine] 19



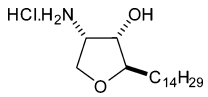
A solution of **17** (100 mg, 0.16 mmol) in 3 M aq HCl (1 mL) and MeOH (5 mL) was heated at 50 °C for 3 h. Removal of the solvent *in vacuo* gave a white solid which was redissolved in pyridine (5 mL). Ac_2O (80 mg, 0.85 mmol) and DMAP (5 mg, cat.) were added and the solution was stirred at rt for 12 h. The reaction mixture was then diluted with Et_2O (10 mL) and extracted with H_2O (10 mL). The aqueous layer was separated and extracted with Et_2O (10 mL). The combined organic layers were washed sequentially with sat aq $CuSO_4$ (10 mL), H_2O (10 mL) and brine (10 mL), then dried and concentrated *in vacuo* to give **19** as a pale yellow oil (58 mg, 74%, >98% de); $[\alpha]_D^{21}$ −3.1 (*c* 0.7 in $CHCl_3$); {lit.[25] $[\alpha]_D^{22}$ −3.1 (*c* 1.1 in $CHCl_3$); ν_{max} (film) 2918 (C–H), 1736 (C=O), 1683 (C=O); δ_H (500 MHz, $CDCl_3$) 0.93 (3H, t *J* 6.6, C(18)H_3), 1.21–1.34 (24H, m, C(6)–C(17)H_2), 1.48–1.60 (2H, m, C(5)H_2), 2.03 (3H, s, CO*Me*), 2.12 (3H, s, CO*Me*), 2.14 (3H, s, CO*Me*), 2.18 (3H, s, CO*Me*), 4.00 (1H, dd *J* 11.7, 2.7, C(1)H_A), 4.29 (1H, dd *J* 11.7, 4.2, C(1)H_B), 4.57–4.61 (1H, m, C(2)*H*), 5.14–5.15 (2H, m, C(3)*H*, C(4)*H*), 5.80–5.82 (1H, br d *J* 9.7, N*H*); δ_C (125 MHz, $CDCl_3$) 14.5 (*C*(18)), 20.8 (CO*Me*), 20.9 (CO*Me*), 21.3 (CO*Me*), 22.7 (*C*(17)), 23.3 (CO*Me*), 25.2, 25.9, 28.0, 29.4, 29.5, 29.6, 29.7, 30.9, 31.8, 32.4, 32.6 (*C*(5)–*C*(16)), 47.3 (*C*(2)), 63.1 (*C*(1)), 71.7 (*C*(3)), 73.0 (*C*(4)), 169.8 (*C*OMe), 170.4 (*C*OMe), 170.8 (*C*OMe), 171.2 (*C*OMe); *m*/*z* (ESI$^+$) 508 ([M + Na]$^+$, 100%), 486 (40); HRMS (ESI$^+$) $C_{26}H_{48}NO_7^+$ ([M + H]$^+$) requires 486.3431; found 486.3439.

(2*S*,3*S*,4*R*)-1,3,4-Triacetoxy-2-acetamido-octadecane [*N*,*O*,*O*,*O*-tetra-acetyl D-*ribo*-phytosphingosine] 20



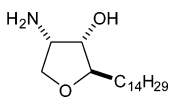
A solution of **18** (77 mg, 0.12 mmol) in 3 M aq HCl (1 mL) and MeOH (5 mL) was heated at 50 °C for 3 h. Removal of the solvent *in vacuo* gave a white solid which was redissolved in pyridine (5 mL). Ac_2O (80 mg, 0.85 mmol) and DMAP (5 mg, cat.) were added and the solution was stirred at rt for 12 h. The reaction mixture was then diluted with Et_2O (10 mL) and extracted with H_2O (10 mL). The aqueous layer was separated and extracted with Et_2O (10 mL). The combined organic layers were washed sequentially with sat aq $CuSO_4$ (10 mL), H_2O (10 mL) and brine (10 mL), then dried and concentrated *in vacuo* to give **20** as gum (45 mg, 80%, >98% de); $[\alpha]_D^{22}$ +18.2 (*c* 1.0 in $CHCl_3$); {lit.[25] $[\alpha]_D^{22}$ +21.9 (*c* 1.1 in $CHCl_3$)}; ν_{max} (KBr) 2915 (C–H), 1734 (C=O), 1683 (C=O); δ_H (400 MHz, $CDCl_3$) 0.88 (3H, t *J* 7.0, C(18)H_3), 1.24–1.31 (24H, m, C(6)–C(17)H_2), 1.60–1.67 (2H, m, C(5)H_2), 2.03 (3H, s, CO*Me*), 2.05 (6H, s, 2 × CO*Me*), 2.08 (3H, s, CO*Me*), 4.00 (1H, dd *J* 11.6, 2.9, C(1)H_A), 4.29 (1H, dd *J* 11.6, 4.7, C(1)H_B), 4.44–4.50 (1H, m, C(2)*H*), 4.93 (1H, dt *J* 9.7, 3.1, C(4)*H*), 5.1 (1H, dd *J* 8.3, 3.1, C(3)*H*), 6.01 (1H, br d *J* 9.4, N*H*); δ_C (100 MHz, $CDCl_3$) 14.1 (*C*(18)), 20.8 (CO*Me*), 20.9 (CO*Me*), 21.0 (CO*Me*), 22.7 (*C*(17)), 23.3 (CO*Me*), 25.5, 28.1, 29.3, 29.4, 29.5, 29.6, 29.6, 29.6, 29.7, 29.8, 29.9, 31.9 (*C*(5)–*C*(16)), 47.6 (*C*(2)), 62.8 (*C*(1)), 71.9 (*C*(3)), 73.0 (*C*(4)), 169.7 (*C*OMe), 170.1 (*C*OMe), 170.8 (*C*OMe), 171.2 (*C*OMe); *m*/*z* (ESI$^+$) 508 ([M + Na]$^+$, 100%), 486 (25); HRMS (ESI$^+$) $C_{26}H_{48}NO_7^+$ ([M + H]$^+$) requires 486.3431; found 486.3436.

(2*R*,3*S*,4*S*)-2-Tetradecyl-4-amino-tetrahydrofuran-3-ol hydrochloride 24



TBAF (1 M in THF, 1.4 mL, 1.4 mmol) was added to a stirred solution of **21** (236 mg, 0.34 mmol) in THF (10 mL) at rt and stirring was continued for 12 h. H_2O (10 mL) was then added, the organic layer was separated and the aqueous layer was extracted with Et_2O (10 mL). The combined organic layers were washed sequentially with H_2O (20 mL) and brine (20 mL) before being dried and concentrated *in vacuo*. The residue was dissolved in MeOH (10 mL), 3 M aq HCl (1 mL) was added and the solution was heated at 50 °C for 3 h. The reaction mixture was then allowed to cool to rt and the solvents were removed *in vacuo* to give **24** as a white solid (115 mg, quant, >98% de); mp 93–95 °C; $[\alpha]_D^{21}$ +15.5 (*c* 0.9 in MeOH); ν_{max} (KBr) 2917 (C–H), 3302 (O–H), 3060 (N–H); δ_H (500 MHz, MeOH-d_4) 0.93 (3H, t *J* 6.4, C(14′)H_3), 1.26–1.46 (20H, m, (C(4′)H_2-C(13′)H_2), 1.46–1.68 (6H, m, C(1′)H_2-C(3′)H_2), 3.70–3.77 (3H, m, C(2)*H*, C(4)*H*, C(5)H_A), 4.04–4.06 (1H, m, C(3)*H*), 4.16–4.19 (1H, m, C(5)H_B); δ_C (125 MHz, MeOH-d_4) 13.1 (*C*(14′)), 22.7, 25.5, 29.1, 29.16, 29.17, 29.28, 29.33, 29.39, 29.42, 29.45, 31.5, 31.7, 32.7 (*C*(1′)–*C*(13′)), 52.3 (*C*(2)), 68.0 (*C*(5)), 73.0 (*C*(4)), 83.8 (*C*(3)); *m*/*z* (CI$^+$) 300 ([M − Cl]$^+$, 100%); HRMS (CI$^+$) $C_{18}H_{38}NO_2^+$ ([M − Cl]$^+$) requires 300.2903; found 300.2902.

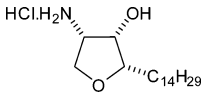
(2*R*,3*S*,4*S*)-2-Tetradecyl-4-amino-tetrahydrofuran-3-ol 7



2 M aq KOH (5 mL) and DCM (5 mL) were added to **24** (31 mg, 0.09 mmol) and the mixture was stirred for 1 min. The organic layer was separated and the aqueous layer was extracted with DCM (3 × 5 mL). The combined organic extracts were dried and concentrated *in vacuo*. Recrystallisation of the residue from $CHCl_3$–heptane (1 : 1) gave **7** as a white solid (20 mg, 70%, >98% de); mp

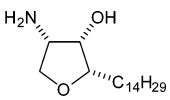
106–108 °C ($CHCl_3$–heptane); $[\alpha]_D^{24}$ +16.4 (*c* 0.85 in MeOH); {lit.[12a] $[\alpha]_D^{22}$ +15.0 (*c* 1.0 in MeOH)}; ν_{max} 2918 (C–H); δ_H (400 MHz, $CDCl_3$) 0.88 (3H, t *J* 6.7, C(14′)H_3), 1.26–1.35 (24H, m, C(2′)–C(13′)H_2), 1.37–1.49 (1H, m, C(1′)H_A), 1.50–1.64 (1H, m, C(1′)H_B), 2.08 (1H, br s, O*H*), 3.37–3.47 (1H, m, C(5)H_A), 3.46–3.49 (1H, m, C(4)*H*), 3.60–3.64 (2H, m, C(2)*H*, C(3)*H*), 4.11–4.15 (1H, m, C(5)H_B); δ_C (100 MHz, $CDCl_3$) 14.1 (*C*(14′)), 22.7, 25.9, 29.4, 29.6, 29.61, 29.67, 31.9, 33.8 (*C*(1′)–*C*(13′)), 52.6 (*C*(4)), 73.2 (*C*(5)), 74.8 (*C*(2)), 85.3 (*C*(3)); *m*/*z* (ESI$^+$) 300 ([M + H]$^+$, 100%); HRMS (ESI$^+$) $C_{18}H_{38}NO_2^+$ ([M + H]$^+$) requires 300.2903; found 300.2902.

(2*S*,3*S*,4*S*)-2-Tetradecyl-4-amino-tetrahydrofuran-3-ol hydrochloride 28



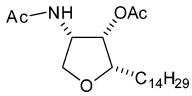
TBAF (1 M in THF, 1.9 mL, 1.9 mmol) was added to a stirred solution of **25** (325 mg, 0.47 mmol) in THF (10 mL) at rt and stirring was continued for 12 h. H_2O (10 mL) was then added, the organic layer was separated and the aqueous layer was extracted with Et_2O (10 mL). The combined organic layers were washed sequentially with H_2O (20 mL) and brine (20 mL) before being dried and concentrated *in vacuo*. The residue was dissolved in MeOH (10 mL), 3 M aq HCl (1 mL) was added and the solution was heated at 50 °C for 3 h. The reaction mixture was then allowed to cool to rt and the solvents were removed *in vacuo* to give **28** as a white solid (157 mg, quant, >98% de); mp 148–150 °C; $[\alpha]_D^{23}$ +2.6 (*c* 0.38 in MeOH); ν_{max} (film) 3396 (O–H), 2923 (C–H); δ_H (400 MHz, MeOH-d_4) 0.91 (3H, t, *J* 6.6, C(14′)H_3), 1.20–1.60 (24H, m, C(2′)–C(13′)H_2), 1.62–1.80 (2H, m, C(1′)H_2), 3.73 (1H, ddd, *J* 10.0, 7.6, 3.6, C(2)*H*), 3.83 (1H, app q, *J* 4.0, C(5)H_A), 3.88–3.96 (2H, m, C(4)*H*, C(5)H_B), 4.28 (1H, dd, *J* 5.2, 3.6, C(2)*H*); δ_C (100 MHz, MeOH-d_4) 13.5, 22.8, 26.2, 28.7, 29.5, 29.7, 29.8, 29.9, 32.1, 53.4, 68.0, 69.9, 83.4; *m*/*z* (ESI$^+$) 300 ([M − Cl]$^+$, 100%).

(2*S*,3*S*,4*S*)-2-Tetradecyl-4-amino-tetrahydrofuran-3-ol [jaspine B (pachastrissamine)] 6



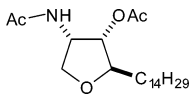
2 M aq KOH (5 mL) and DCM (5 mL) were added to **28** (157 mg, 0.47 mmol) and the mixture stirred for 1 min. The organic layer was separated and the aqueous layer was extracted with DCM (3 × 5 mL). The combined organic extracts were dried and concentrated *in vacuo*. Recrystallisation of the residue from Et_2O–heptane (1 : 1) gave **6** as a white solid (110 mg, 79%, >98% de); mp 90–92 °C (Et_2O–heptane); $[\alpha]_D^{23}$ +17.5 (*c* 0.3 in EtOH); {lit.[7] $[\alpha]_D^{25}$ +18.0 (*c* 0.1 in EtOH)}; ν_{max} (KBr) 3340 (N–H), 3074 (O–H), 2921 (C–H), 2849 (C–H); δ_H (400 MHz, $CDCl_3$) 0.87 (3H, t, *J* 6.7, C(14′)H_3), 1.18–1.50 (24H, m, C(2′)H_2-C(13′)H_2), 1.55–1.70 (2H, m, C(1′)H_2), 3.50 (1H, dd, *J* 8.4, 7.2, C(5)H_A), 3.61–3.69 (1H, m, C(4)*H*), 3.74 (1H, td, *J* 7.2, 4.0, C(2)*H*), 3.87 (1H, t, *J* 4.0, C(3)*H*), 3.91 (1H, t, *J* 7.7, C(5)H_B); δ_C (100 MHz, $CDCl_3$) 14.1, 22.7, 26.3, 29.3, 29.4, 29.5, 29.6, 29.7, 29.8, 31.9, 54.4, 71.8, 72.4, 83.1; *m*/*z* (ESI$^+$) 300 ([M + H]$^+$, 100%); HRMS (ESI$^+$) $C_{18}H_{38}NO_2^+$ ([M + H]$^+$) requires 300.2897; found 300.2900.

(2*S*,3*S*,4*S*)-2-Tetradecyl-3-acetoxy-4-acetamido-tetrahydrofuran [*N*,*O*-diacetyl-jaspine B] 30



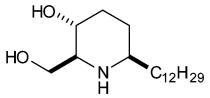
Ac_2O (1 mL) and DMAP (2 mg) were added sequentially to a stirred solution of **6** (67 mg, 0.22 mmol) in pyridine (5 mL) at rt. After 12 h the reaction mixture was quenched with H_2O (2 mL). The reaction mixture was then diluted with H_2O (10 mL) and extracted with Et_2O (3 × 10 mL). The combined organic extracts were washed sequentially with sat aq $CuSO_4$ solution (2 × 20 mL), H_2O (20 mL) and brine (20 mL), then dried and concentrated *in vacuo* to give **30** as a white solid (80 mg, 95%, >98% de); mp 100–102 °C (Et_2O–heptane); $[\alpha]_D^{23}$ −26.4 (*c* 0.5 in $CHCl_3$); {lit.[12a] $[\alpha]_D^{25}$ −22.6 (*c* 1.0 in $CHCl_3$)}; ν_{max} (KBr) 3295 (N–H), 2921 (C–H), 1733 (C=O), 1653 (C=O); δ_H (400 MHz, $CDCl_3$) 0.88 (3H, t, *J* 6.0, C(14′)H_3), 1.20–1.32 (24H, m, C(2′)–C(13′)H_2), 1.35–1.57 (2H, m, C(1′)H_2), 2.00 (3H, s, CO*Me*), 2.19 (3H, s, CO*Me*), 3.60 (1H, t, *J* 8.1, C(5)H_A), 3.91 (1H, ddd, *J* 7.6, 5.2, 3.6, C(2)*H*), 4.10 (1H, t, *J* 8.1, C(5)H_B), 4.82 (1H, ddd, *J* 13.2, 7.6, 5.6, C(4)*H*), 5.38 (1H, dd, *J* 5.6, 3.6, C(3)*H*), 5.60 (1H, br d, *J* 7.9, N*H*); δ_C (100 MHz, $CDCl_3$) 14.1 (*C*(14′)), 20.8 (CO*Me*), 22.7 (*C*(13′)), 23.2 (CO*Me*), 26.0, 28.4, 28.5, 29.2, 29.3, 29.4, 29.5, 29.6, 29.7, 31.9 (*C*(1′)–C(12′)), 51.3 (*C*(4)), 69.8 (*C*(5)), 73.5 (*C*(3)), 81.2 (*C*(2)), 169.9 (*C*OMe), 170.0 (*C*OMe); *m*/*z* (ESI$^+$) 442 ([M + 59]$^+$, 100%); HRMS (ESI$^+$) $C_{22}H_{41}NNaO_4^+$ ([M + Na]$^+$) requires 406.2933; found 406.2929.

(2*R*,3*S*,4*S*)-2-Tetradecyl-3-acetoxy-4-acetamido-tetrahydrofuran 31



Ac_2O (1 mL) and DMAP (5 mg) were added sequentially to a stirred solution of **7** (25 mg, 0.08 mmol) in pyridine (5 mL) at rt. After 12 h the reaction mixture was quenched with H_2O (2 mL). The reaction mixture was then diluted with H_2O (10 mL) and extracted with Et_2O (3 × 10 mL). The combined organic extracts were washed sequentially with sat aq $CuSO_4$ solution (2 × 20 mL), H_2O (20 mL) and brine (20 mL), then dried and concentrated *in vacuo* to give **31** as a white solid (23 mg, 81%, >98% de); mp 65–67 °C; $[\alpha]_D^{21}$ −14.6 (*c* 0.5 in $CHCl_3$); {lit.[12a] $[\alpha]_D^{22}$ −15.4 (*c* 1.0 in $CHCl_3$)}; ν_{max} (KBr) 2915 (C–H), 1730 (C=O), 1685 (C=O); δ_H (500 MHz, $CDCl_3$) 0.93 (3H, t, *J* 7.1, C(14′)H_3), 1.26–1.35 (24H, m, C(2′)H_2–C(13′)H_2), 1.34–1.68 (2H, m, C(1′)H_2), 2.06 (3H, s, CO*Me*), 2.18 (3H, s, CO*Me*), 3.55–3.58 (1H, m, C(5)H_A), 3.90–3.93 (1H, m, C(2)*H*), 4.21–4.24 (1H, m, C(5)H_B), 4.67–4.73 (1H, m, C(4)*H*), 4.95–4.97 (1H, m, C(3)*H*), 5.69 (1H, d *J* 8.2, N*H*); δ_C (125 MHz, $CDCl_3$) 14.2 (*C*(14′)), 21.1 (CO*Me*), 22.8 (*C*(13′)), 23.2 (CO*Me*), 25.6, 29.4, 29.51, 29.55, 29.60, 29.65, 29.67, 29.70, 29.72, 29.80, 32.0, 33.6 (*C*(1′)*C*(12′)), 49.9 (*C*(4)), 69.9 (*C*(5)), 77.1 (*C*(3)), 84.2 (*C*(2)); *m*/*z* (ESI$^+$) 442 ([M + 59]$^+$, 100%); HRMS (ESI$^+$) $C_{22}H_{42}NO_4^+$ ([M + H]$^+$) requires 384.2114; found 384.3112.

(2*R*,3*S*,6*S*)-2-Hydroxymethyl-6-dodecylpiperidin-3-ol [deoxoprosophylline] 32



TBAF (1 M in THF, 0.16 mL, 0.16 mmol) was added to a stirred solution of **43** (50 mg, 0.11 mmol) in THF (5 mL) at rt and the resultant solution was stirred for 12 h. The mixture was then diluted with Et_2O (10 mL) and H_2O (10 mL). The organic layer was separated and the aqueous layer was extracted with Et_2O (3 × 10 mL). The combined organic extracts were successively washed with H_2O (10 mL) and brine (10 mL) before being dried and concentrated *in vacuo.* Recrystallization from acetone gave **32** as a white solid (25 mg, 76%, >98% de); mp 84–85 °C; {lit.[35a] mp 90–91 °C; lit.[35k] mp 83 °C}; $[a]_D^{22}$ +13.5 (*c* 0.3 in $CHCl_3$); {lit.[35a] for enantiomer $[a]_D$ −14.0 (*c* 0.2 in $CHCl_3$); lit.[35k] $[a]_D^{20}$ −13.0 (*c* 0.2 in $CHCl_3$)}; ν_{max} (KBr) 3267 (O–H); δ_H (400 MHz, $CDCl_3$) 0.89 (3H, t, *J* 6.9, C(12′)H_3), 1.20–1.32 (24H, m, C(1′)H_2–C(11′)H_2, C(4)H_A, C(5)H_A), 1.66–1.79 (1H, m, C(5)H_B), 1.96–2.2 (1H, m, C(4)H_B), 2.40–2.70 (2H, m, C(2)*H*, C(6)*H*), 3.39–3.53 (1H, ddd, *J* 10.9, 9.1, 4.7, C(3)*H*), 3.71 (1H, dd, *J* 10.8, 5.2, C(2)C$H_A$$H_B$OH), 3.85 (1H, dd, *J* 10.8, 4.8, C(2)C$H_A$$H_B$OH); δ_C (100 MHz, $CDCl_3$) 14.1, 22.6, 26.2, 29.3, 29.6, 29.8, 31.2, 31.9, 34.0, 36.6, 55.9, 63.2, 65.0, 70.1.

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