Asymmetric synthesis of vicinal amino alcohols: xestoaminol C, sphinganine and sphingosine†

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The highly diastereoselective *anti*-aminohydroxylation of 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*-diacetyl xestoaminol C (41% yield over 8 steps), *N*,*O*,*O*-triacetyl sphinganine (30% yield over 8 steps) and *N*,*O*,*O*-triacetyl sphingosine (30% yield over 7 steps).

Introduction

The vicinal amino alcohol motif is a recurring structural component in a diverse range of biologically active natural products and synthetic molecules.[1] Numerous biologically active long-chain vicinal amino alcohols such as xestoaminols A **1** and C **2**,[2] and obscuraminol A **3**[3] have been isolated from marine sources, whilst the sphingoid bases sphinganine **4**, phytosphingosine **5** and sphingosine **6** are ubiquitous components of biomolecules that occur in eukaryotic cells (Fig. 1).[4] The varied biological activity of these compounds has ensured that a variety of methods for the synthesis of vicinal amino alcohols have been developed,[1] with the sphingoid bases in particular receiving considerable attention.[5] The majority of these routes use starting materials derived from the chiral pool,[6] although asymmetric routes, for instance based upon Sharpless asymmetric dihydroxylation or epoxidation, or asymmetric aldol reaction, have also received some attention.[7]

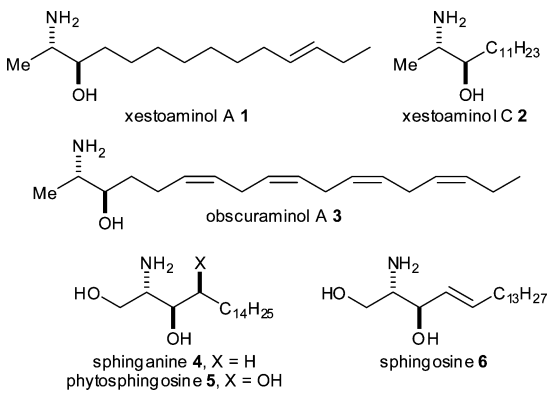

Fig. 1 Structures of xestoaminols A **1** and C **2**, obscuraminol A **3**, sphinganine **4**, phytosphingosine **5** and sphingosine **6**.

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Previous investigations from within this laboratory have demonstrated that the tandem conjugate addition of a homochiral, secondary lithium amide (derived from α-methylbenzylamine)[8] and *in situ* enolate oxidation with (camphorsulfonyl)oxaziridine (CSO) represents an efficient entry to *anti*-α-hydroxy-β-amino esters.[9] This methodology has been utilised as the key synthetic strategy for a number of natural product syntheses,[10] and we delineate herein the application of this useful transformation to the asymmetric synthesis of the *N*,*O*-diacetyl derivative of xestoaminol C **2**, and the *N*,*O*,*O*-triacetyl derivatives of sphinganine **4** and sphingosine **6**. Part of this work has been communicated previously.[11]

Results and discussion

Asymmetric synthesis of *N*,*O*-diacetyl xestoaminol C

Our initial synthetic target for the development of a general strategy towards the synthesis of saturated, long chain, vicinal amino alcohols was xestoaminol C **2**. This simple vicinal amino alcohol was first reported as being isolated from the Fijian sponge *Xestospongia* sp. in 1990 and shown to display reverse transcriptase inhibition.[2] It was subsequently isolated from the tunicate *Pseudodistoma obscurum*[3] and one enantiospecific synthesis, employing L-alanine as the source of chirality, has been reported to date.[12]

Based on retrosynthetic analysis of xestoaminol C **2**, it was proposed that the alkyl chain could be introduced *via* olefination of the functionalised aldehyde **8**. Aldehyde **8** would be available from ester **9** which, in turn, results from *anti*-aminohydroxylation of an α,β-unsaturated ester. A synthetic strategy reliant on *N*- and *O*-benzyl protection was therefore initially pursued in order to facilitate global, hydrogenolytic deprotection of **7** to the natural product (Fig. 2).

Aminohydroxylation of *tert*-butyl crotonate upon sequential treatment with lithium (*S*)-*N*-benzyl-*N*-(α-methylbenzyl)amide and (+)-CSO[9] gave the known *anti*-α-hydroxy-β-amino ester **10** in >98% de,[13] with chromatographic purification giving **10**[9] in 77% yield and >98% de. Benzylation of **10** was accomplished upon treatment with BnBr, 15-crown-5 and NaH, giving **11** in 88% yield. Transformation of ester **11** to the corresponding aldehyde **13** was achieved *via* reduction with $LiAlH_4$ to give alcohol **12** in 91% yield,

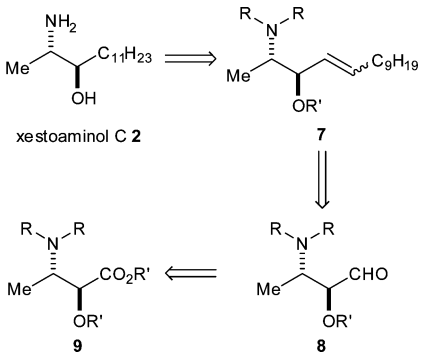
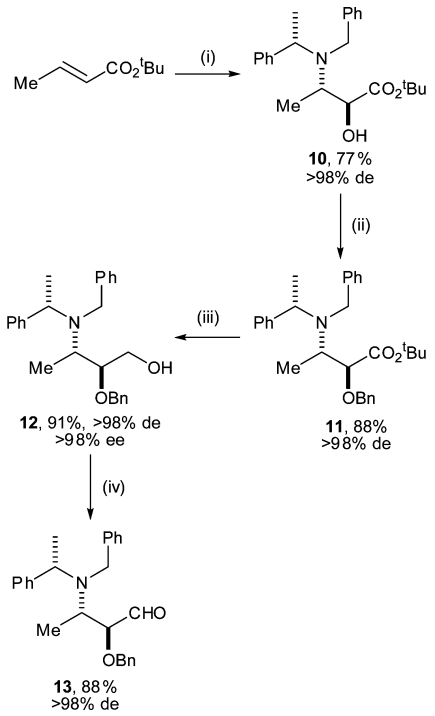


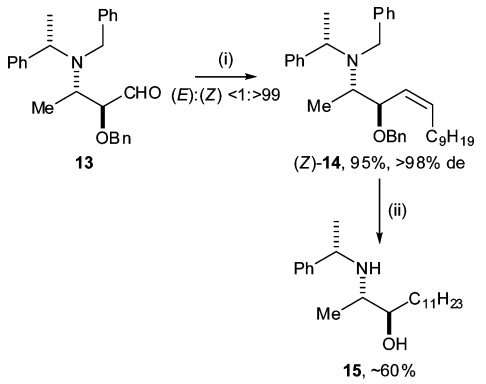
Fig. 2 Retrosynthetic analysis of xestoaminol C **2**.

>98% de and >98% ee,[14] with subsequent Swern oxidation of **12** giving aldehyde **13** in 88% yield and >98% de (Scheme 1).[15]



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) NaH, 15-crown-5, BnBr, THF, 0 °C to rt, 12 h; (iii) $LiAlH_4$, THF, 0 °C to rt, 6 h; (iv) DMSO, $(ClCO)_2$, Et_3N, DCM, −78 °C to rt, 1 h.

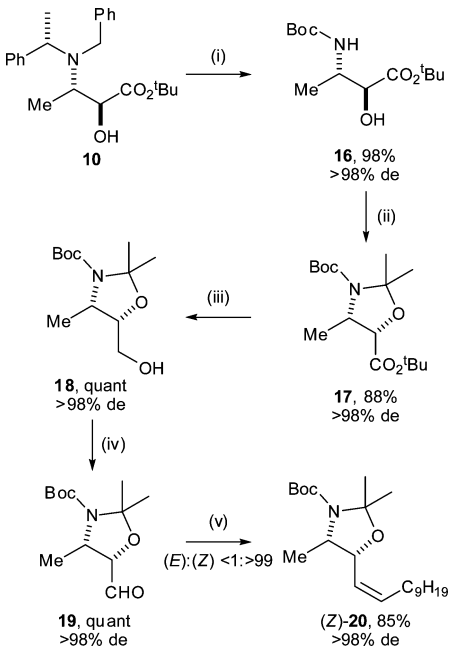
Attention was then turned to the installation of the alkyl chain *via* Wittig olefination of aldehyde **13**. However, treatment of aldehyde **13** with the ylide derived from (1-decyl)triphenylphosphonium bromide in THF[16] returned only starting material, even when a large excess of reagent (5 eq) was employed. Hypothesising that the low reactivity of the ylide might be due to its lipophilic nature disfavouring reaction in a polar solvent, the reaction was attempted in a mixture of THF–hexane (1 : 1) giving 83% conversion to (*Z*)-alkene **14** ($J_{4,5}$ = 10.9 Hz) as the sole diastereoisomer, which was isolated in 56% yield. Reaction optimisation led to a superior experimental protocol whereby deprotonation of (1-decyl)triphenylphosphonium bromide in THF prior to the addition of hexane, and the subsequent addition of aldehyde **13** in THF, gave complete conversion and furnished (*Z*)-**14** in 95% yield. With construction of the skeletal framework complete, global deprotection of (*Z*)-**14** to give xestoaminol C **2** was investigated. Hydrogenolysis of (*Z*)-**14** in MeOH–H_2O–AcOH (40 : 4 : 1)[8,17] returned *N*-α-methylbenzyl protected **15** contaminated with unknown impurities. Attempted cleavage of the *N*-α-methylbenzyl protecting group from **15** under a range of more forcing hydrogenolysis conditions gave, in each case, a low mass return of a complex mixture of unidentifiable products (Scheme 2).



Scheme 2 *Reagents and conditions:* (i) $C_{10}H_{21}PPh_3^+Br^-$, BuLi, THF–hexane (1 : 1), −78 °C to rt, 12 h; (ii) H_2 (1 atm), $Pd(OH)_2/C$, MeOH–H_2O–AcOH (40 : 4 : 1), rt, 6 h.

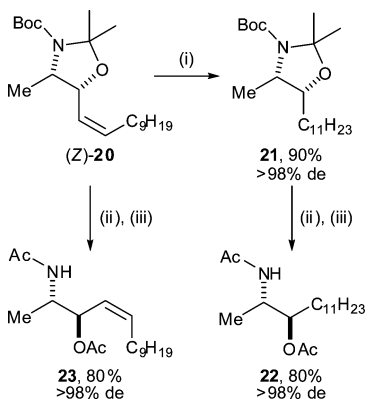
Following the recalcitrance of the *N*-α-methylbenzyl group to hydrogenolysis, and in order for this methodology to be compatible for the preparation of unsaturated vicinal amino alcohols, it was proposed that removal of the *N*-benzyl-*N*-α-methylbenzyl protecting groups at an earlier juncture in the synthesis would be advantageous, and an alternative protecting group strategy was envisaged. An *N*-Boc-*N*,*O*-acetal protecting group strategy, to enable global hydrolysis, was therefore pursued. *N*-Debenzylation of *anti*-α-hydroxy-β-amino ester **10** and concomitant *N*-Boc protection gave **16**[10f] in 98% yield and >98% de, with subsequent *N*,*O*-acetal protection being achieved upon treatment of **16** with 2,2-dimethoxypropane and $BF_3{\cdot}Et_2O$ in acetone,[18] giving oxazolidine **17** in 88% isolated yield and >98% de. Reduction of **17** with $LiAlH_4$ at 0 °C gave alcohol **18** in quantitative yield. Oxidation of **18** using a Swern protocol gave a sample of aldehyde **19** contaminated with unidentified side-products; treatment with IBX in DMSO,[19] however, afforded **19** in quantitative yield.[20] Wittig olefination of aldehyde **19** gave olefin (*Z*)-**20** as a single diastereoisomer ($J_{4,5}$ = 7.6 Hz) which was isolated in 85% yield and >98% de (Scheme 3).

With *N*-Boc-*N*,*O*-acetal protected (*Z*)-**20** in hand, deprotection to enable completion of the synthesis of xestoaminol C **2** was investigated. Thus, catalytic hydrogenation with Pd/C furnished **21** in 90% yield and >98% de, with subsequent removal of the *N*-Boc and *N*,*O*-acetal protecting groups within **21** being achieved under acidic conditions,[21] giving a crude reaction mixture from which xestoaminol C **2** was isolated as its *N*,*O*-diacetyl derivative **22** in 80% yield and >98% de, in order that comparison with literature data could be made. The spectroscopic properties of **22** were entirely consistent with those previously reported {$[\alpha]_D^{22}$ −22.7 (*c* 0.6 in MeOH); lit.[3] $[\alpha]_D^{24}$ −21.8 (*c* 0.4 in MeOH); lit.[12] $[\alpha]_D^{24}$ −22.1 (*c* 0.2 in MeOH)}. The applicability of this strategy for the preparation of unsaturated derivatives was next demonstrated by



Scheme 3 *Reagents and conditions:* (i) H_2 (5 atm), $Pd(OH)_2/C$, Boc_2O, EtOAc, rt, 12 h; (ii) 2,2-dimethoxypropane, $BF_3{\cdot}Et_2O$, acetone, rt, 12 h; (iii) $LiAlH_4$, THF, 0 °C, 6 h; (iv) IBX, DMSO, rt, 12 h; (v) $C_{10}H_{21}PPh_3^+Br^-$, BuLi, THF–hexane (1 : 1), −78 °C to rt, 12 h.

global hydrolysis of (*Z*)-**20**, followed by acetylation, giving **23** in 80% yield and >98% de (Scheme 4).



Scheme 4 *Reagents and conditions:* (i) H_2 (1 atm), Pd/C, EtOAc, rt, 6 h; (ii) HCl (3 M, aq), MeOH, 50 °C, 3 h; (iii) Ac_2O, DMAP, pyridine, rt, 12 h.

Asymmetric synthesis of *N*,*O*,*O*-triacetyl sphinganine and *N*,*O*,*O*-triacetyl sphingosine

With an efficient asymmetric synthesis of *N*,*O*-diacetyl xestoaminol C **22** complete, the successful *N*-Boc-*N*,*O*-acetal protecting group strategy was applied to the synthesis of sphinganine **4** and sphingosine **6**. Retrosynthetic analysis revealed that aminohydroxylation of a suitably γ-*O*-protected-α,β-unsaturated ester would give access to aldehyde **24** from which both sphingoid bases could be derived (Fig. 3). Previous investigations from this laboratory have demonstrated that tandem conjugate addition and enolate functionalisation of γ-*tert*-butyldimethylsilyloxy-α,β-unsaturated ester **26** with lithium (*S*)-*N*-benzyl-*N*-(α-methylbenzyl)amide and (+)-CSO proceeds efficiently to generate the corresponding α-hydroxy-β-amino-γ-*tert*-butyldimethylsilyloxy ester.[22] As the proposed strategy toward the synthesis of sphinganine **4** and sphingosine **6** required several deprotection and functional group interconversion steps, a range of γ-*O*-silyl protecting groups were screened for their suitability in the synthetic sequence.

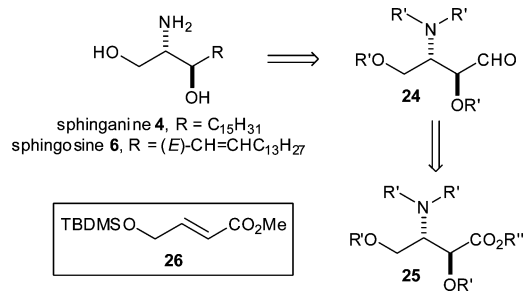
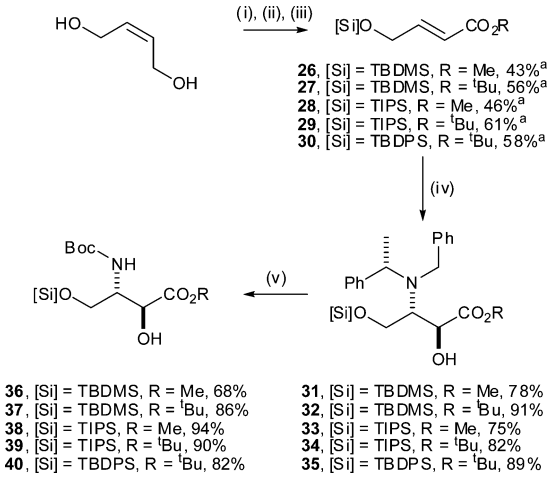


Fig. 3 Retrosynthetic analysis of sphinganine **4** and sphingosine **6**.

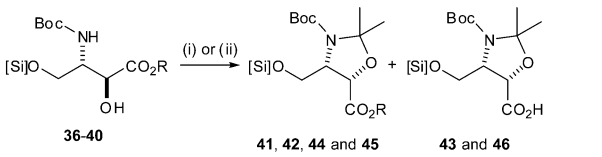
Thus, γ-silyloxy-α,β-unsaturated esters **26–30** were prepared from *cis*-but-2-ene-1,4-diol,[22] in >98% de in each case. Subsequent conjugate addition of lithium (*S*)-*N*-benzyl-*N*-(α-methylbenzyl)amide to **26–30** and enolate oxidation with (+)-CSO proceeded in >98% de in each case[13] to generate the corresponding (2*S*,3*S*,α*S*)-α-hydroxy-β-amino-γ-silyloxy esters **31–35** which were isolated in good yield (75–91%), and in >98% de in each case. The relative and absolute configurations within **31–35** were assigned by analogy to the well-established stereochemical outcome resulting from the conjugate addition and enolate oxidation reaction.[9,10,22] Subsequent hydrogenolysis of **31–35** and *in situ* carbamate protection gave **36–40** in 68–94% yield and in >98% de in each case (Scheme 5).



Scheme 5 *Reagents and conditions:* (i) [Si]Cl, imidazole, DMAP, DCM, rt, 12 h; (ii) O_3, DCM, −78 °C, 30 min, then DMS, rt, 12 h; (iii) $(EtO)_2P(O)CH_2CO_2R$, $^iPr_2NEt$, LiCl, MeCN, 48 h; (iv) lithium (*S*)-*N*-benzyl-*N*-(α-methylbenzyl)amide, THF, −78 °C, 2 h, then (+)-CSO, −78 °C to rt, 12 h; (v) H_2 (5 atm), $Pd(OH)_2/C$, Boc_2O, EtOAc, rt, 12 h. [[a] Yield over 3 steps from *cis*-but-2-ene-1,4-diol. All compounds **26–40** were isolated as single diastereoisomers (>98% de).]

With **36–40** in hand *N*,*O*-acetal formation was investigated utilising the conditions applied successfully to **16** in the synthesis

of xestoaminol C **2** (*vide supra*, Scheme 3). However, treatment of γ-*O*-TBDPS *tert*-butyl ester **40** with 2,2-dimethoxypropane and $BF_3{\cdot}Et_2O$ in acetone returned a complex mixture of products whilst under the same conditions γ-*O*-TBDMS and γ-*O*-TIPS *tert*-butyl esters **37** and **39** gave, in both cases, a mixture of two products, identified as the corresponding oxazolidine esters **42** and **45** and the oxazolidine acids **43** and **46**; the latter presumably arising from Lewis acid catalysed ester hydrolysis. The ratio of these two products was found to depend markedly upon reaction concentration although the formation of the undesired acid products was minimised by performing the reactions at high dilution with a minimal amount of Lewis acid catalyst, enabling the isolation of **42** and **45** in 52 and 75% yield respectively. Application of this protocol to γ-*O*-TBDMS and γ-*O*-TIPS methyl esters **36** and **38** meanwhile gave incomplete conversion (~50% in both cases) to the corresponding oxazolidines **41** and **44**, although no trace of ester hydrolysis was observed. Further experimentation with γ-*O*-TIPS methyl ester **38** demonstrated that the reaction could be driven to approximately 80% conversion upon heating giving oxazolidine ester **44** in 75% isolated yield and returned starting material **38** (20%), which could be recycled (Scheme 6).

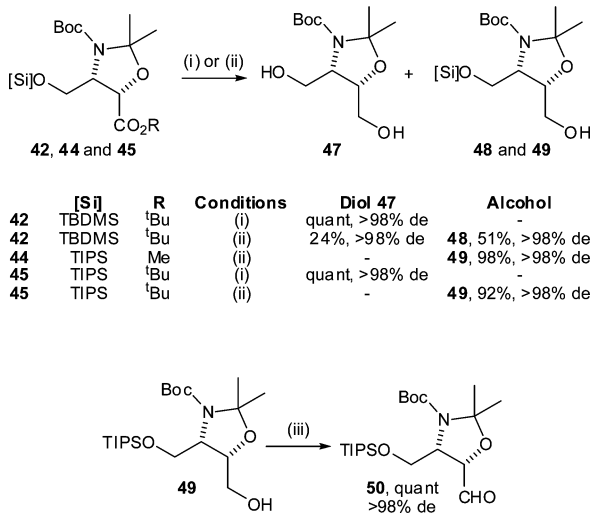


	[Si]	R	Conditions	Conversion %	Oxazolidine ester	Oxazolidine acid
36	TBDMS	Me	(i)	50	**41**, 48%, >98% de	-
37	TBDMS	^{t}Bu	(i)	100	**42**, 52%, >98% de	**43**, 20%, >98% de
38	TIPS	Me	(ii)	80	**44**, 75%, >98% de	-
39	TIPS	^{t}Bu	(i)	100	**45**, 75%, >98% de	**46**, 25%, >98% de

Scheme 6 *Reagents and conditions*: (i) 2,2-dimethoxypropane, $BF_3{\cdot}Et_2O$, acetone, rt, 12 h; (ii) 2,2-dimethoxypropane, $BF_3{\cdot}Et_2O$, acetone, 50 °C, 12 h.

Attention next turned to the conversion of oxazolidine esters **42**, **44** and **45** to the corresponding aldehydes *via* a two step protocol. However, treatment of both *O*-TBDMS and *O*-TIPS oxazolidine *tert*-butyl esters **42** and **45** with $LiAlH_4$ at 0 °C resulted in reduction of the ester and concomitant desilylation, giving diol **47** as the sole product in both cases. In an attempt to reduce the *tert*-butyl ester without promoting desilylation the reactions were performed at −78 °C but returned only starting material in both cases. The use of DIBAL-H to effect ester reduction was next probed and although treatment of *O*-TBDMS oxazolidine ester **42** with DIBAL-H at 0 °C gave a mixture of diol **47** and *O*-TBDMS alcohol **48** contaminated with unidentifiable by-products, reduction of *O*-TIPS oxazolidine esters **44** and **45** gave *O*-TIPS alcohol **49** as the sole product in both cases, with no trace of desilylation being observed. Re-oxidation of **49** with IBX[19] gave aldehyde **50** in quantitative yield (Scheme 7).

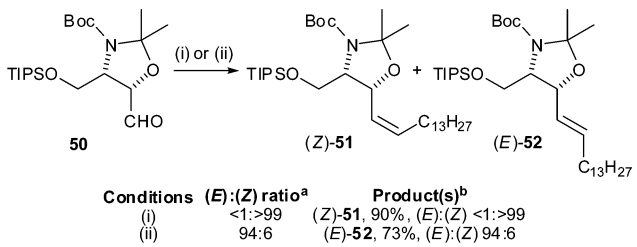
With an efficient preparation of aldehyde **50** in hand, investigations focused upon olefination to install the long alkyl chain present in the targets sphinganine **4** and sphingosine **6**. Under the optimum conditions utilised in the synthesis of xestoaminol C **2**, Wittig olefination of aldehyde **50** with the ylide derived from (1-tetradecyl)triphenylphosphonium bromide gave (*Z*)-**51** ($J_{4,5}$ = 7.2 Hz) as the sole reaction product in 90% isolated yield after chromatography. In order to facilitate the preparation



	[Si]	R	Conditions	Diol 47	Alcohol
42	TBDMS	^{t}Bu	(i)	quant, >98% de	-
42	TBDMS	^{t}Bu	(ii)	24%, >98% de	**48**, 51%, >98% de
44	TIPS	Me	(ii)	-	**49**, 98%, >98% de
45	TIPS	^{t}Bu	(i)	quant, >98% de	-
45	TIPS	^{t}Bu	(ii)	-	**49**, 92%, >98% de

Scheme 7 *Reagents and conditions*: (i) $LiAlH_4$, THF, 0 °C, 6 h; (ii) DIBAL-H, DCM, 0 °C, 6 h; (iii) IBX, DMSO, rt, 12 h.

of sphingosine **6** an alternative strategy for the stereoselective preparation of the corresponding (*E*)-alkene isomer **52** was next probed. The Schlosser modification of the Wittig reaction is frequently employed to generate the (*E*)-alkene product from the reaction of a non-stabilised ylide[23] although recent studies by Kim *et al.* have shown that high (*E*) selectivity is observed simply by addition of excess of methanol to the reaction medium at low temperature.[24] Following this protocol, olefination of aldehyde **50** followed by quenching with methanol gave an (*E*) : (*Z*) ratio of 94 : 6, with chromatography giving (*E*)-**52** in 73% yield and 88% de [(*E*) : (*Z*) 94 : 6] (Scheme 8).

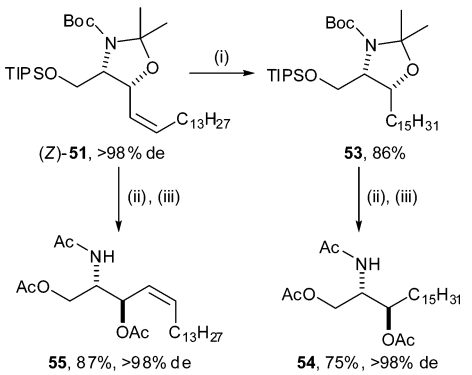


Conditions	(*E*):(*Z*) ratio[a]	Product(s)[b]
(i)	<1:>99	(*Z*)-**51**, 90%, (*E*):(*Z*) <1:>99
(ii)	94:6	(*E*)-**52**, 73%, (*E*):(*Z*) 94:6

Scheme 8 *Reagents and conditions:* (i) $C_{14}H_{29}PPh_3{}^+Br^-$, BuLi, THF–hexane (1 : 1), −78 °C to rt, 12 h; (ii) $C_{14}H_{29}PPh_3{}^+Br^-$, BuLi, THF–hexane (1 : 2), −78 °C, 2 h, then MeOH, −78 °C to rt, 12 h. [[a] Crude; [b] purified].

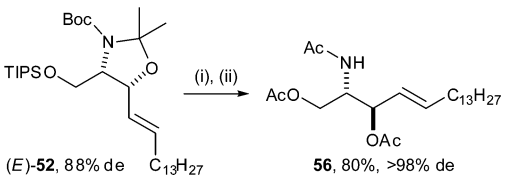
The synthesis of sphinganine **4** was completed through hydrogenation of (*Z*)-**51** to give **53** in 86% yield and >98% de, with subsequent global hydrolytic deprotection and acetylation of the crude mixture giving *N*,*O*,*O*-triacetyl sphinganine **54** in 75% isolated yield and >98% de with spectroscopic properties in excellent agreement with those of the literature {$[\alpha]_D^{22}$ +18.4 (*c* 0.3 in $CHCl_3$); lit.[25] $[\alpha]_D^{22}$ +19.2 (*c* 1.0 in $CHCl_3$); lit.[26] $[\alpha]_D^{24}$ +17.2 (*c* 0.2 in $CHCl_3$)}. In addition, sequential hydrolysis of (*Z*)-**51** and acetylation gave *N*,*O*,*O*-triacetyl (*Z*)-sphingosine **55** in 87% isolated yield and >98% de, with spectroscopic properties in agreement with those of the literature {$[\alpha]_D^{22}$ +6.6 (*c* 0.9 in $CHCl_3$); lit.[27] $[\alpha]_D^{24}$ +4.3 (*c* 0.9 in $CHCl_3$)} (Scheme 9).

Meanwhile, hydrolysis of the protecting groups within (*E*)-**52** and acetylation, followed by purification by chromatography and recrystallisation, gave *N*,*O*,*O*-triacetyl sphingosine **56** in 80%



Scheme 9 *Reagents and conditions:* (i) H_2 (1 atm), Pd/C, EtOAc, rt, 6 h; (ii) HCl (3 M, aq), MeOH, 50 °C, 3 h; (iii) Ac_2O, DMAP, pyridine, rt, 12 h.

isolated yield and >98% de, with spectroscopic properties in excellent agreement with those in the literature {$[\alpha]_D^{20}$ −12.0 (*c* 1.0 in $CHCl_3$); lit.[28] $[\alpha]_D^{24}$ −11.4 (*c* 1.2 in $CHCl_3$)} (Scheme 10).



Scheme 10 *Reagents and conditions:* (i) HCl (3 M, aq), MeOH, 50 °C, 3 h; (ii) Ac_2O, DMAP, pyridine, rt, 12 h.

Conclusion

In conclusion, the highly diastereoselective *anti*-aminohydroxylation of readily available α,β-unsaturated esters, *via* the 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 the asymmetric synthesis of a range of long chain vicinal amino alcohols, including the *N*,*O*-diacetyl derivative of xestoaminol C and the *N*,*O*,*O*-triacetyl derivatives of sphinganine and sphingosine, in good overall yield. The further application of this methodology to the asymmetric synthesis of *N*,*O*,*O*,*O*-tetra-acetyl D-*lyxo*-phytosphingosine, the anhydrophytosphingosine jaspine B and its C(2)-epimer, and the *Prosopis* alkaloid deoxoprosophylline is reported in the following manuscript.

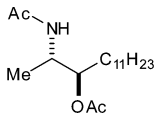
Experimental

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.[29] 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.

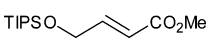
Elemental analyses were recorded by the microanalysis service of the Inorganic Chemistry Laboratory, University of Oxford, UK. Melting points were recorded on a Gallenkamp Hot Stage apparatus and are uncorrected. Optical rotations were recorded on a Perkin-Elmer 241 polarimeter with a water-jacketed 10 cm cell. Specific rotations are reported in 10^{-1} deg cm^2 g^{-1} and concentrations in g/100 mL. 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. Accurate mass measurements were run on either a Bruker MicroTOF, and were 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*R*)-2-Acetamido-3-acetoxy-tetradecane [*N*,*O*-diacetyl xestoaminol C] 22



3 M aq HCl (1 mL) was added to a solution of **21** (50 mg, 0.14 mmol) in MeOH (10 mL) and heated at 50 °C for 3 h. The reaction mixture was concentrated *in vacuo.* The residue was dissolved in pyridine (10 mL) and Ac_2O (0.06 mL, 0.68 mmol) and DMAP (2 mg) were added sequentially. The reaction mixture was stirred for 12 h before being quenched with H_2O (2 mL). The reaction mixture was diluted with H_2O (10 mL) and Et_2O (10 mL) and the layers were separated. The aqueous layer was extracted with Et_2O (2 × 10 mL). The combined organic layers were washed sequentially with sat aq $CuSO_4$ (2 × 10 mL), H_2O (10 mL) and brine (10 mL), dried and concentrated *in vacuo.* Purification *via* flash column chromatography (eluent 30–40 °C petrol–EtOAc, 1 : 1) gave **22** as white solid (34 mg, 80%, >98% de); R_f 0.18 (30–40 °C petrol–EtOAc, 1 : 1); mp 51–53 °C (30–40 °C petrol–EtOAc); $[\alpha]_D^{22}$ −22.7 (*c* 0.6 in MeOH); {lit.[3] $[\alpha]_D^{24}$ −21.8 (*c* 0.4 in MeOH), lit.[12] $[\alpha]_D^{24}$ −22.1 (*c* 0.2 in MeOH)}; ν_{max} (KBr) 3354, 2980, 2935, 1791, 1755, 1714, 1519; δ_H (400 MHz, $CDCl_3$) 0.87 (3H, t, *J* 6.8, C(14)H_3), 1.08 (3H, d, *J* 6.8, C(1)H_3), 1.20–1.37 (18H, m, C(5)H_2-C(13)H_2), 1.43–1.62 (2H, m, C(4)H_2), 1.94 (3H, s, CO*Me*), 2.08 (3H, s, CO*Me*), 4.10–4.19 (1H, m, C(2)*H*), 4.80–4.86 (1H, ddd, *J* 8.5, 5.1, 3.4, C(3)*H*), 5.90 (1H, br d, *J* 8.2, N*H*); δ_C (125 MHz, $CHCl_3$) 14.1, 14.8, 21.1, 22.7, 23.5, 25.6, 29.31, 29.34, 29.4, 29.5, 29.6, 31.3, 31.9, 47.5, 77.0, 169.3, 171.6; *m*/*z* (ESI$^+$) 336 ([M + Na]$^+$, 100%); HRMS (ESI$^+$) $C_{18}H_{35}NNaO_3^+$ ([M + Na]$^+$) requires 336.2509; found 336.2502.

Methyl (*E*)-4-tri-*iso*-propylsilyloxy-but-2-enoate 28



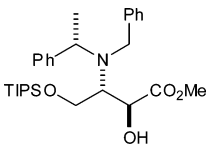
TIPSCl (4.86 mL, 22.7 mmol) was added in one portion to a stirred solution of but-2-ene-1,4-diol (0.93 mL, 11.4 mmol), imidazole

(2.33 g, 34.1 mmol) and DMAP (30 mg) in DCM (30 mL) at rt. After stirring for 12 h, the reaction mixture was concentrated *in vacuo.* The residue was dissolved in Et_2O (30 mL) and washed with 1 M aq HCl (30 mL), dried and concentrated *in vacuo* to give 1,4-bis-(tri-*iso*-propylsilyloxy)but-2-ene as a colourless oil (4.41 g, 97%) that was used without purification; δ_H (400 MHz, $CDCl_3$) 1.02–1.12 (42H, m, 2 × Si(C*H*Me_2)$_3$), 4.29–4.33 (4H, m, C(1)H_2, C(4)H_2), 5.30–5.33 (2H, m, C(2)*H*, C(3)*H*).

O_3 was bubbled through a stirred solution of 1,4-bis-(tri-*iso*-propylsilyloxy)but-2-ene (4.41 g, 11.0 mmol) in DCM (30 mL) at −78 °C until the solution turned blue. O_2 was then bubbled through the solution until it turned colourless. DMS (30 mL) was added dropwise *via* syringe and the reaction mixture stirred for 12 h. The reaction mixture was concentrated *in vacuo.* The residue was redissolved in Et_2O (30 mL) and washed with H_2O (30 mL), dried and concentrated *in vacuo* to give (tri-*iso*-propylsilyloxy)acetaldehyde as a colourless oil (4.38 g, 92%) that was used without purification; δ_H (400 MHz, $CDCl_3$) 1.02–1.10 (21H, m, Si(C*H*Me_2)$_3$), 4.25 (2H, d, *J* 1.0, CH_2), 9.73 (1H, t, *J* 1.0, C*H*O).

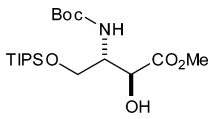
Methyl diethylphosphonoacetate (4.97 g, 23.6 mmol), LiCl (5.54 g, 132 mmol) and $^iPr_2NEt$ (3.76 mL, 21.6 mmol) were added to a stirred solution of (tri-*iso*-propylsilyloxy)acetaldehyde (4.25 g, 19.7 mmol) in MeCN (50 mL). The reaction mixture was stirred for 48 h and then quenched by addition of H_2O (5 mL). The organic layer was separated and the aqueous layer was extracted with EtOAc (40 mL). The combined organic extracts were dried and concentrated *in vacuo.* Purification *via* flash column chromatography (eluent 30–40 °C petrol–Et_2O, 30 : 1) gave **28** as a colourless oil (2.79 g, 52%, >98% de); R_f 0.14 (30–40 °C petrol–Et_2O, 30 : 1); ν_{max} (film) 1728 (C=O), 1663 (C=C); δ_H (400 MHz, $CDCl_3$) 1.04–1.09 (21H, m, Si(C*H*Me_2)$_3$), 3.75 (3H, s, O*Me*), 4.38 (2H, dd, *J* 3.1, 2.4, C(4)H_2), 6.18 (1H, dt, *J* 15.4, 2.4, C(2)*H*), 7.02 (1H, dt, *J* 15.4, 3.1, C(3)*H*); δ_C (100 MHz, $CDCl_3$) 11.9 (Si(*C*HMe$_2$)$_3$), 17.9 (Si(CH*Me*$_2$)$_3$), 51.5 (O*Me*), 62.4 (*C*(4)), 119.0 (*C*(2)), 147.8 (*C*(3)), 167.2 (*C*(1)); *m*/*z* (ESI$^+$) 273 ([M + H]$^+$, 100%); HRMS (ESI$^+$) $C_{14}H_{29}O_3Si^+$ ([M + H]$^+$) requires 273.1886; found 273.1880.

Methyl (2*S*,3*S*,α*S*)-2-hydroxy-3-[*N*-benzyl-*N*-(α-methyl-benzyl)amino]-4-tri-*iso*-propylsilyloxy-butanoate 33



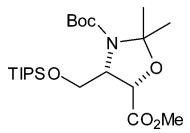
BuLi (2.5 M in hexanes, 8.14 mL, 11.4 mmol) was added dropwise *via* syringe to a stirred solution of (*S*)-*N*-benzyl-*N*-(α-methylbenzyl)amine (2.48 g, 11.8 mmol) in THF (50 mL) at −78 °C. After stirring for 30 min a solution of **28** (2.0 g, 7.35 mmol) in THF (20 mL) at −78 °C was added dropwise *via* cannula. After stirring for a further 2 h at −78 °C the reaction mixture was quenched with (+)-CSO (3.37 g, 14.7 mmol) and allowed to warm to rt over 12 h. Sat aq NH_4Cl (5 mL) was added and the mixture was stirred for 5 min before being concentrated *in vacuo.* The residue was partitioned between DCM (50 mL) and 10% aq citric acid (10 mL). The organic layer was separated and the aqueous layer was extracted with DCM (2 × 50 mL). The combined organic extracts were washed sequentially with sat aq $NaHCO_3$ (50 mL) and brine (50 mL), dried and concentrated *in vacuo.* The residue was dissolved in Et_2O (50 mL), the insoluble CSO residues were filtered off, and the filter cake was washed with Et_2O (2 × 20 mL). The filtrate was concentrated *in vacuo* and the process was repeated. Purification *via* flash column chromatography (eluent 30–40 °C petrol–Et_2O, 20 : 1) gave **33** as a colourless oil (2.75 g, 75%, >98% de); R_f 0.18 (30–40 °C petrol–Et_2O, 20 : 1); $C_{29}H_{45}NO_4Si$ requires C, 69.7; H, 9.1; N, 2.8%; found C, 69.6; H, 9.1; N, 2.8%; $[\alpha]_D^{22}$ +37.0 (*c* 2.3 in $CHCl_3$); ν_{max} (film) 3515 (O–H), 1737 (C=O); δ_H (400 MHz, $CDCl_3$) 1.02–1.06 (21H, m, Si(C*H*Me_2)$_3$), 1.36 (3H, d, *J* 6.8, C(α)*Me*), 3.03 (1H, d, *J* 6.2, O*H*), 3.55–3.61 (1H, m, C(3)*H*), 3.67 (3H, s, O*Me*), 3.82 (1H, d, *J* 15.0, NCH_A), 3.79–3.85 (1H, m, C(4)H_A), 3.93–4.02 (2H, m, C(4)H_B, C(α)*H*), 4.05–4.10 (1H, m, C(2)*H*), 4.14 (1H, d, *J* 15.0, NCH_B), 7.20–7.46 (10H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 11.9 (Si(*C*HMe$_2$)$_3$), 17.9 (Si(CH*Me*$_2$)$_3$), 18.1 (C(α)*Me*), 51.4 (N*C*H$_2$), 52.1 (O*Me*), 58.0 (*C*(α)), 60.1 (*C*(3)), 62.2 (*C*(4)), 71.0 (*C*(2)), 126.6, 127.0 (*p-Ph*), 127.9, 128.1, 128.2, 128.3 (*o-Ph*, *m-Ph*), 141.7, 143.1 (*i-Ph*), 174.7 (*C*(1)); *m*/*z* (ESI$^+$) 522 ([M + Na]$^+$, 28%), 500 (100); HRMS (ESI$^+$) $C_{29}H_{46}NO_4Si^+$ ([M + H]$^+$) requires 500.3196; found 500.3194.

Methyl (2*S*,3*S*)-2-hydroxy-3-[*N*-(*tert*-butoxycarbonyl)amino]-4-tri-*iso*-propylsilyloxy-butanoate 38



Pearlman's catalyst (1.25 g, 25% w/w) was added to a vigorously stirred solution of **33** (5.0 g, 10.0 mmol) and Boc_2O (2.4 g, 11.0 mmol) in EtOAc (50 mL) and the mixture was placed under H_2 (5 atm). Stirring continued for 12 h, after which time the reaction mixture was filtered through Celite (eluent EtOAc) and concentrated *in vacuo.* Purification *via* flash column chromatography (eluent 30–40 °C petrol–Et_2O, 10 : 1; then 30–40 °C petrol–Et_2O, 1 : 1) gave **38** as a colourless oil (3.81 g, 94%, >98% de); R_f 0.08 (30–40 °C petrol–Et_2O, 10 : 1); $C_{19}H_{39}NO_6Si$ requires C, 56.3; H, 9.7; N, 3.45%; found C, 56.2; H, 9.7; N, 3.5%; $[\alpha]_D^{21}$ +17.3 (*c* 0.4 in $CHCl_3$); ν_{max} (film) 3453 (O–H), 1732 (C=O), 1720 (C=O); δ_H (400 MHz, $CDCl_3$) 1.01–1.09 (21H, m, Si(C*H*Me_2)$_3$), 1.45 (9H, s, CMe_3), 3.54 (1H, br s, O*H*), 3.74–3.91 (2H, m, C(4)H_2), 3.78 (3H, s, O*Me*), 3.95–4.05 (1H, m, C(3)*H*), 4.26–4.34 (1H, m, C(2)*H*), 5.19 (1H, d *J* 8.5, N*H*); δ_C (100 MHz, $CDCl_3$) 11.8 (Si(*C*HMe$_2$)$_3$), 17.8 (Si(CH*Me*$_2$)$_3$), 28.3 (C*Me*$_3$), 52.5 (O*Me*), 53.5 (*C*(3)), 62.9 (*C*(4)), 72.1 (*C*(2)), 79.7 (*C*Me$_3$), 155.4 (N*C*O), 173.1 (*C*(1)); *m*/*z* (ESI$^+$) 428 ([M + Na]$^+$, 44%), 406 (100); HRMS (ESI$^+$) $C_{19}H_{40}NO_6Si^+$ ([M + H]$^+$) requires 406.2625; found 406.2615.

(4*S*,5*S*)-2,2-Dimethyl-*N*(3)-*tert*-butoxycarbonyl-4-tri-*iso*-propylsilyloxymethyl-5-methoxycarbonyl-oxazolidine 44

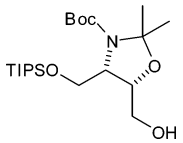


$BF_3{\cdot}Et_2O$ (1 M in Et_2O) was added dropwise to a stirred solution of **38** (1.10 g, 2.72 mmol) and 2,2-dimethoxypropane (10 mL) in

acetone (20 mL) until a permanent colour change from colourless to dark orange was observed. After stirring at 50 °C for 12 h the reaction mixture was allowed to cool to rt and Et_3N was added dropwise until pH 7 was achieved. The reaction mixture was then concentrated *in vacuo.* Purification *via* flash column chromatography (eluent 30–40 °C petrol–Et_2O, 10 : 1; then 30–40 °C petrol–Et_2O, 2 : 1) gave **44** as a colourless oil (first to elute, 907 mg, 75%, >98% de) and unreacted **38** as a colourless oil (second to elute, 218 mg, 20%, >98% de).

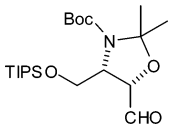
Data for **44**: R_f 0.53 (30–40 °C petrol–Et_2O, 2 : 1); $[\alpha]_D^{22}$ +15.2 (*c* 1.8 in $CHCl_3$); ν_{max} (film) 1739 (C=O), 1699 (C=O); δ_H (400 MHz, $CDCl_3$) 1.01–1.10 (21H, m, Si(C*H*Me_2)$_3$), 1.47 (9H, s, CMe_3), 1.50–1.57 (3H, m, C(2)Me_A), 1.63–1.69 (3H, m, C(2)Me_B), 3.70–3.98 (2H, m, C(4)CH_2), 3.77 (3H, s, O*Me*), 4.12–4.29 (1H, m, C(4)*H*), 4.62–4.69 (1H, m, C(5)*H*); δ_H (500 MHz, DMSO-d_6, 363 K) 1.02–1.10 (21H, m, Si(C*H*Me_2)$_3$), 1.45 (9H, s, CMe_3), 1.50 (3H, s, C(2)Me_A), 1.56 (3H, s, C(2)Me_B), 3.70 (3H, s, O*Me*), 3.73 (1H, dd, *J* 10.1, 3.0, C(4)CH_A), 3.84 (1H, dd, *J* 10.1, 6.7, C(4)CH_B), 4.12 (1H, dt, *J* 6.3, 3.0, C(4)*H*), 4.76 (1H, d, C(5)*H*); δ_C (125 MHz, DMSO-d_6, 363 K) 12.4 (Si(*C*HMe$_2$)$_3$), 18.6 (Si(CH*Me*$_2$)$_3$), 25.1 (C(2)Me_A), 27.6 (C(2)Me_B), 28.9 (CMe_3), 52.2 (O*Me*), 60.7 (C(4)*C*H$_2$), 61.3 (*C*(4)), 74.0 (*C*(5)), 80.6 (*C*Me$_3$), 94.1 (*C*(2)), 151.8 (N*C*O), 168.5 (*C*O$_2$Me); *m/z* (ESI$^+$) 468 ([M + Na]$^+$, 54%), 446 (100); HRMS (ESI$^+$) $C_{22}H_{44}NO_6Si^+$ ([M + H]$^+$) requires 446.2938; found 446.2934.

(4*S*,5*S*)-2,2-Dimethyl-*N*(3)-*tert*-butoxycarbonyl-4-tri-*iso*-propylsilyloxymethyl-5-hydroxymethyl-oxazolidine 49



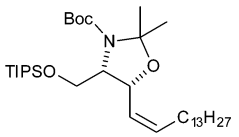
DIBAL-H (1 M in DCM, 5.38 mL, 5.38 mmol) was added dropwise *via* syringe to a stirred solution of **44** (1.2 g, 2.69 mmol) in DCM (20 mL) at 0 °C. After stirring for 6 h, the reaction mixture was quenched with sat aq NH_4Cl (0.5 mL), filtered through Celite (eluent DCM) and concentrated *in vacuo* to give **49** as a colourless oil (1.1 g, 98%, >98% de) that was used without purification. Purification of an aliquot *via* flash column chromatography (eluent 30–40 °C petrol–Et_2O, 2 : 1) gave an analytical sample; R_f 0.09 (30–40 °C petrol–Et_2O, 2 : 1); $[\alpha]_D^{22}$ +9.8 (*c* 0.8 in $CHCl_3$); ν_{max} (film) 3495 (O–H), 1700 (C=O); δ_H (400 MHz, $CDCl_3$) 1.04–1.44 (21H, m, Si(C*H*Me_2)$_3$), 1.44–1.57 (15H, m, C(2)Me_2, CMe_3), 3.09–3.33 (1H, br m, O*H*), 3.67–3.82 (2H, m, C(5)CH_2), 3.84–3.92 (2H, m, C(4)CH_2), 3.98–4.16 (1H, m, C(4)*H*), 4.25–4.33 (1H, m, C(5)*H*); δ_H (500 MHz, DMSO-d_6, 363 K) 1.05–1.12 (21H, m, Si(C*H*Me_2)$_3$), 1.45 (9H, s, CMe_3), 1.48 (3H, s, C(2)Me_A), 1.50 (3H, s, C(2)Me_B), 3.72–3.91 (4H, m, C(4)CH_2, C(5)CH_2), 4.12–4.22 (1H, m, C(4)*H*), 4.35 (1H, app t, *J* 5.8, C(5)*H*); δ_C (125 MHz, DMSO-d_6, 363 K) 12.5 (Si(*C*HMe$_2$)$_3$), 18.7 (Si(CH*Me*$_2$)$_3$), 29.0 (CMe_3), 32.2 (C(2)Me_2), 60.2 (*C*(4)), 60.7 (C(4)*C*H$_2$, C(5)*C*H$_2$), 79.8 (*C*(5)), 80.8 (*C*Me$_3$), 93.1 (*C*(2)), 152.0 (N*C*O); *m/z* (ESI$^+$) 440 ([M + Na]$^+$, 14%), 418 (100); HRMS (ESI$^+$) $C_{21}H_{44}NO_5Si^+$ ([M + H]$^+$) requires 418.2989; found 418.2997.

(4*S*,5*S*)-2,2-Dimethyl-*N*(3)-*tert*-butoxycarbonyl-4-tri-*iso*-propylsilyloxymethyl-5-carbonylmethyl-oxazolidine 50



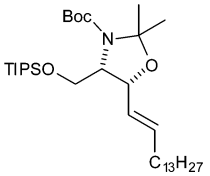
IBX (2.21 g, 7.89 mmol) was added to a solution of **49** (1.10 g, 2.63 mmol) in DMSO (20 mL) at rt and stirred for 12 h. The reaction mixture was diluted with Et_2O (20 mL), washed with H_2O (5 × 20 mL), dried and concentrated *in vacuo* to give **50** as a colourless oil (1.09 g, quant, >98% de) that was used without purification; δ_H (400 MHz, $CDCl_3$) 1.00–1.10 (21H, m, Si(C*H*Me_2)$_3$), 1.43–1.57 (12H, m, C(2)Me_A, CMe_3), 1.63–1.69 (3H, m, C(2)Me_B), 3.67–3.97 (2H, m, C(4)CH_2), 4.20–4.36 (1H, m, C(4)*H*), 4.44–4.54 (1H, m, C(5)*H*), 9.72–9.82 (1H, m, C*H*O).

(4*S*,5*R*,1′*Z*)-2,2-Dimethyl-*N*(3)-*tert*-butoxycarbonyl-4-tri-*iso*-propylsiloxymethyl-5-pentadec-1′-en-1′-yl-oxazolidine (*Z*)-51



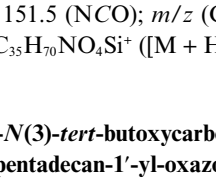
BuLi (2.5 M in hexanes, 2.1 mL, 5.29 mmol) was added dropwise *via* syringe to a stirred solution of (1-tetradecyl)triphenylphosphonium bromide (3.25 g, 6.01 mmol) in THF (60 mL) at −78 °C. After 30 min hexane (75 mL) was added, followed by the dropwise addition of a solution of **50** (500 mg, 1.20 mmol) in THF (15 mL) *via* cannula. The reaction mixture was allowed to warm to rt over 12 h and quenched with sat aq NH_4Cl (10 mL). Brine (100 mL) was added, the organic layer was separated, and the aqueous layer was extracted with Et_2O (3 × 50 mL). The combined organic extracts were dried and concentrated *in vacuo.* Purification *via* flash column chromatography (eluent 30–40 °C petrol–Et_2O, 200 : 1; increased to 30–40 °C petrol–Et_2O, 10 : 1) gave (*Z*)-**51** as a colourless oil (645 mg, 90%, >98% de); R_f 0.16 (30–40 °C petrol–Et_2O, 10 : 1); $[\alpha]_D^{22}$ −7.8 (*c* 1.7 in $CHCl_3$); ν_{max} (film) 2926 (C–H), 1702 (C=O); δ_H (400 MHz, $CDCl_3$) 0.89–0.91 (3H, m, C(15′)H_3), 1.02–1.09 (21H, m, Si(C*H*Me_2)$_3$), 1.20–1.65 (37H, m, C(2)Me_2, C(4′)H_2-C(14′)H_2, CMe_3), 1.99–2.20 (2H, m, C(3′)H_2), 3.64 (1H, dd, *J* 10.2, 2.0, C(4)CH_A), 3.71–3.93 (1H, m, C(4)*H*), 4.00 (1H, dd, *J* 10.2, 4.6, C(4)CH_B), 4.88–4.95 (1H, m, C(5)*H*), 5.62–5.77 (2H, m, C(1′)*H*, C(2′)*H*); δ_H (500 MHz, PhMe-d_8, 363 K) 0.92 (3H, t, *J* 6.9, C(15′)H_3), 1.08–1.20 (21H, m, Si(C*H*Me_2)$_3$), 1.27–1.46 (22H, m, C(4′)H_2-C(14′)H_2), 1.47 (9H, s, CMe_3), 1.62 (3H, s, C(2)Me_A), 1.70 (3H, s, C(2)Me_B), 2.04–2.20 (2H, m, C(3′)H_2), 3.86 (1H, dd, *J* 9.8, 2.5, C(4)CH_A), 4.01 (1H, br s, C(4)*H*), 4.12 (1H, dd, *J* 9.8, 6.4, C(4)CH_B), 4.96–4.99 (1H, m, C(5)*H*), 5.62–5.67 (1H, m, C(2′)*H*), 5.91–5.96 (1H, m, C(1′)*H*); δ_C (125 MHz, PhMe-d_8, 363 K) 12.2 (Si(*C*HMe$_2$)$_3$), 13.6 (*C*(15′)), 17.9 (Si(CH*Me*$_2$)$_3$), 22.5, 27.8, 28.2, 29.15, 29.23, 29.5, 29.55, 29.59, 29.61, 29.64, 29.7, 31.9 (C(2)Me_2, *C*(3′)-*C*(14′), CMe_3), 61.3 (*C*(4)) 61.8 (C(4)*C*H$_2$), 72.3 (*C*(5)), 79.0 (*C*Me$_3$), 92.0 (*C*(2)), 125.7 (*C*(2′)), 133.9 (*C*(1′)), 151.5 (N*C*O); *m/z* (CI$^+$) 596.5 ([M + H]$^+$, 100%); HRMS (CI$^+$) $C_{35}H_{70}NO_4Si^+$ ([M + H]$^+$) requires 596.5074; found 596.5054.

(4*S*,5*R*,1′*E*)-2,2-Dimethyl-*N*(3)-*tert*-butoxycarbonyl-4-tri-*iso*-propylsiloxymethyl-5-pentadec-1′-en-1′-yl-oxazolidine (*E*)-52



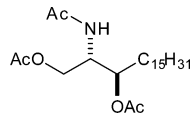
BuLi (2.5 M in hexanes, 2.1 mL, 5.29 mmol) was added dropwise *via* syringe to a stirred solution of (1-tetradecyl)triphenylphosphonium bromide (3.25 g, 6.01 mmol) in THF (60 mL) at −78 °C. After 30 min hexane (75 mL) was added, followed by the dropwise addition of a solution of **50** (500 mg, 1.20 mmol) in THF (15 mL) *via* cannula. The reaction mixture was stirred at −78 °C for 2 h before the addition of MeOH (50 mL). The reaction mixture was allowed to warm to rt over a further 12 h and quenched with sat aq NH_4Cl (10 mL). Brine (100 mL) was added, the organic layer was separated, and the aqueous layer was extracted with Et_2O (3 × 50 mL). The combined organic extracts were dried and concentrated *in vacuo.* Purification *via* flash column chromatography (eluent 30–40 °C petrol–Et_2O, 10 : 1) gave (*E*)-**52** as a colourless oil (523 mg, 73%, (*E*) : (*Z*) 94 : 6); R_f 0.16 (30–40 °C petrol–Et_2O, 10 : 1); $[\alpha]_D^{20}$ +3.5 (*c* 2.2 in $CHCl_3$); ν_{max} (film) 2926 (C–H), 1703 (C=O); δ_H (400 MHz, $CDCl_3$) 0.95–0.99 (3H, m, C(15′)H_3), 1.10–1.23 (21H, m, Si(CHMe_2)$_3$), 1.31–1.72 (37H, m, C(2)Me_2, C(4′)H_2-C(14′)H_2, CMe_3), 2.10–2.19 (2H, m, C(3′)H_2), 3.70–3.78 (1H, m, C(4)CH_A), 3.84–4.12 (2H, m, C(4)H, C(4)CH_B), 4.59–4.64 (1H, m, C(5)H), 5.80–5.96 (2H, m, C(1′)H, C(2′)H); δ_H (500 MHz, PhMe-d_8, 363 K) 0.92 (3H, t, *J* 6.9, C(15′)H_3), 1.11–1.18 (21H, m, Si(CHMe_2)$_3$), 1.26–1.50 (31H, m, C(4′)H_2-C(14′)H_2, CMe_3), 1.58 (3H, s, C(2)Me_A), 1.68 (3H, s, C(2)Me_B), 2.10–2.14 (2H, m, C(3′)H_2), 3.80–3.86 (1H, m, C(4)CH_A), 3.93 (1H, br s, C(4)H), 4.04 (1H, dd, *J* 9.8, 7.6, C(4)CH_B), 4.50–4.52 (1H, m, C(5)H), 5.77–5.85 (1H, m, C(2′)H), 5.87–5.93 (1H, m, C(1′)H); δ_C (125 MHz, PhMe-d_8, 363 K) 12.2 (Si(CHMe$_2$)$_3$), 13.6 (*C*(15′)), 17.9 (Si(CHMe_2)$_3$), 22.5, 24.1, 27.3, 28.1, 29.2, 29.27, 29.30, 29.53, 29.57, 29.61, 29.7, 31.9 (C(2)Me_2, *C*(3′)-*C*(14′), CMe_3), 61.3 (*C*(4)), 62.0 (C(4)*C*H$_2$), 77.2 (*C*(5)), 79.0 (*C*Me$_3$), 92.4 (*C*(2)), 125.7 (*C*(2′)), 134.1 (*C*(1′)), 151.5 (N*C*O); *m*/*z* (CI$^+$) 596.5 ([M + H]$^+$, 100%); HRMS (CI$^+$) $C_{35}H_{70}NO_4Si^+$ ([M + H]$^+$) requires 596.5074; found 596.5084.

(4*S*,5*R*)-2,2-Dimethyl-*N*(3)-*tert*-butoxycarbonyl-4-tri-*iso*-propylsiloxymethyl-5-pentadecan-1′-yl-oxazolidine 53



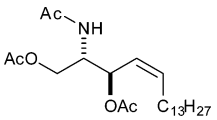
Pd/C (5 mg, 10% w/w) was added to a stirred solution of (*Z*)-**51** (50 mg, 0.08 mmol) in EtOAc (5 mL) at rt. The reaction mixture was stirred under H_2 (1 atm) for 6 h. The reaction mixture was filtered through Celite (eluent EtOAc) and concentrated *in vacuo.* Purification *via* flash column chromatography (eluent 30–40 °C petrol–Et_2O, 2 : 1) gave **53** as a colourless oil (43 mg, 86%, >98% de); R_f 0.8 (30–40 °C petrol–Et_2O, 2 : 1); $[\alpha]_D^{17}$ +10.0 (*c* 2.2 in $CHCl_3$); ν_{max} (film) 2925 (C–H), 1702 (C=O); δ_H (400 MHz, $CDCl_3$) 0.85–0.91 (3H, m, C(15′)H_3), 1.02–1.12 (21H, m, Si(CHMe_2)$_3$), 1.20–1.37 (26H, m, C(2′)H_2-C(14′)H_2), 1.45–1.54 (15H, m, C(2)Me_2, CMe_3), 1.55–1.85 (2H, m, C(1′)H_2), 3.59–3.89 (3H, m, C(4)H, C(4)H_2), 4.00–4.06 (1H, m, C(5)H); δ_H (500 MHz, PhMe-d_8, 363 K) 0.88–1.68 (65H, m, C(2)Me_2, C(2′)-C(13′)H_2, C(14′)H_3, CMe_3, Si(CHMe_2)$_3$), 1.80–1.92 (2H, m, C(1′)H_2), 3.78–4.05 (4H, m, C(4)HCH_2, C(5)H); δ_C (125 MHz, PhMe-d_8, 363 K) 12.2, 13.5, 17.8, 22.5, 23.9, 26.8, 27.4, 28.0, 28.1, 29.2, 29.3, 29.6, 29.7, 31.8, 61.2, 76.7, 78.9, 92.0, 151.5; *m*/*z* (ESI$^+$) 598.5 ([M + H]$^+$, 100%); HRMS (ESI$^+$) $C_{35}H_{72}NO_4Si^+$ ([M + H]$^+$) requires 598.5231; found 598.5252.

(2*S*,3*R*)-1,3-Diacetoxy-2-acetamido-octadecane [*N*,*O*-diacetyl sphinganine] 54



3 M aq HCl (1 mL) was added to a solution of **53** (30 mg, 0.05 mmol) in MeOH (10 mL) and heated at 50 °C for 3 h. The reaction mixture was concentrated *in vacuo.* The residue was dissolved in pyridine (10 mL) and Ac_2O (0.1 mL, excess) and DMAP (2 mg) were added sequentially. The reaction mixture was stirred for 12 h before being quenched with H_2O (2 mL). The reaction mixture was diluted with H_2O (10 mL) and Et_2O (10 mL) and the layers were separated. The aqueous layer was extracted with Et_2O (2 × 10 mL). The combined organic layers were washed sequentially with sat aq $CuSO_4$ (2 × 10 mL), H_2O (10 mL) and brine (10 mL), dried and concentrated *in vacuo.* Recrystallisation from $CHCl_3$–pentane (1 : 1) gave **54** as a white solid (11 mg, 75%, >98% de); mp 83–85 °C ($CHCl_3$–pentane); $[\alpha]_D^{22}$ +18.4 (*c* 0.25 in $CHCl_3$); {lit.[25] $[\alpha]_D^{22}$ +19.2 (*c* 1.0 in $CHCl_3$); lit.[26] $[\alpha]_D^{24}$ +17.2 (*c* 0.2 in $CHCl_3$)}; ν_{max} (KBr) 3306, 2912, 2853, 1732, 1649, 1545, 1232; δ_H (400 MHz, $CDCl_3$) 0.87 (3H, t, *J* 6.7, C(18)H_3), 1.21–1.38 (22H, m, C(7)H_2-C(17)H_2), 1.52–1.70 (2H, m, C(6)H_2), 2.01 (3H, s, COMe), 2.07 (3H, s, COMe), 2.08 (3H, s, COMe), 4.07 (1H, dd, *J* 11.6, 3.9, C(1)H_A), 4.26 (1H, dd, *J* 11.6, 6.1, C(1)H_B), 4.34–4.45 (1H, m, C(2)H), 4.88–4.95 (1H, m, C(3)H), 5.85 (1H, d, *J* 8.9 NH); δ_C (100 MHz, $CDCl_3$) 14.1, 20.8, 21.0, 22.7, 23.3, 25.3, 29.3, 29.4, 29.5, 29.60, 29.63, 29.7, 31.5, 31.9, 50.5, 62.6, 73.9, 169.8, 170.9, 171.0; *m*/*z* (ESI$^+$) 450 ([M + Na]$^+$, 100%); HRMS (ESI$^+$) $C_{24}H_{45}NNaO_5^+$ ([M + Na]$^+$) requires 450.3190; found 450.3180.

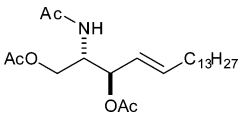
(2*S*,3*R*,4*Z*)-1,3-Diacetoxy-2-acetamido-octadec-4-ene [*N*,*O*,*O*-triacetyl-(*Z*)-sphingosine] 55



3 M aq HCl (1 mL) was added to a solution of (*Z*)-**51** (30 mg, 0.05 mmol) in MeOH (10 mL) and heated at 50 °C for 3 h. The reaction mixture was concentrated *in vacuo.* The residue was dissolved in pyridine (10 mL) and Ac_2O (0.1 mL, excess) and DMAP (2 mg) were added sequentially. The reaction mixture was stirred for 12 h before being quenched with H_2O (2 mL). The reaction mixture was diluted with H_2O (10 mL) and Et_2O (10 mL) and the layers were separated. The aqueous layer was extracted with Et_2O (2 × 10 mL). The combined organic layers were washed

sequentially with sat aq $CuSO_4$ (2 × 10 mL), H_2O (10 mL) and brine (10 mL), dried and concentrated *in vacuo.* Recrystallisation from $CHCl_3$–pentane (1 : 1) gave **55** as a white solid (13 mg, 87%, >98% de); mp 83–85 °C ($CHCl_3$–pentane); $[\alpha]_D^{22}$ +6.6 (*c* 0.9 in $CHCl_3$); {lit.[27] $[\alpha]_D^{24}$ +4.3 (*c* 0.9 in $CHCl_3$)}; ν_{max} (KBr) 3336, 2926, 2851, 1734, 1655, 1539, 1236; δ_H (400 MHz, $CDCl_3$) 0.88 (3H, t, *J* 6.8, C(18)H_3), 1.14–1.43 (22H, m, C(7)H_2-C(17)H_2), 1.99 (3H, s, CO*Me*), 2.05 (3H, s, CO*Me*), 2.08 (3H, s, CO*Me*), 2.00–2.27 (2H, m, C(6)H_2), 4.04 (1H, dd, *J* 11.6, 3.9, C(1)H_A), 4.34 (1H, dd, *J* 11.6, 6.5, C(1)H_B), 4.39–4.47 (1H, m, C(2)*H*), 5.28–5.36 (1H, m, C(3)*H*), 5.60–5.73 (2H, m, C(4)*H*, C(5)*H*); δ_C (125 MHz, $CDCl_3$) 14.1, 20.8, 21.1, 22.7, 23.4, 28.0, 29.3, 29.35, 29.42, 29.5, 29.6, 29.64, 29.66, 29.67, 31.9, 51.1, 62.6, 69.6, 77.2, 123.8, 137.0, 169.8, 170.0, 171.0; *m/z* (ESI$^+$) 448 ([M + Na]$^+$, 100%); HRMS (ESI$^+$) $C_{24}H_{43}NNaO_5^+$ ([M + Na]$^+$) requires 448.3033; found 448.3030.

(2*S*,3*R*,4*E*)-1,3-Diacetoxy-2-acetamido-octadec-4-ene [*N*,*O*,*O*-triacetyl sphingosine] 56



3 M aq HCl (1 mL) was added to a solution of (*E*)-**52** (50 mg, 0.05 mmol, (*E*) : (*Z*) 94 : 6) in MeOH (10 mL) and heated at 50 °C for 3 h. The reaction mixture was concentrated *in vacuo.* The residue was dissolved in pyridine (10 mL) and Ac_2O (0.1 mL, excess) and DMAP (2 mg) were added sequentially. The reaction mixture was stirred for 12 h before being quenched with H_2O (2 mL). The reaction mixture was diluted with H_2O (10 mL) and Et_2O (10 mL) and the layers were separated. The aqueous layer was extracted with Et_2O (2 × 10 mL). The combined organic layers were washed sequentially with sat aq $CuSO_4$ (2 × 10 mL), H_2O (10 mL) and brine (10 mL), dried and concentrated *in vacuo.* Recrystallisation from $CHCl_3$–pentane (1 : 1) gave **56** as a white solid (29 mg, 80%, >98% de); mp 99–101 °C ($CHCl_3$–pentane); $[\alpha]_D^{20}$ −12.0 (*c* 1.0 in $CHCl_3$); {lit.[28] $[\alpha]_D^{24}$ −13.0 (*c* 1.6 in $CHCl_3$)}; ν_{max} (KBr) 3287, 2919, 2850, 1734, 1656, 1552, 1232; δ_H (400 MHz, $CDCl_3$) 0.88 (3H, t, *J* 6.8, C(18)H_3), 1.19–1.40 (22H, m, C(7)-C(17)H_2), 1.95–2.09 (2H, m, C(6)H_2) overlapping 1.99 (3H, s, CO*Me*) and 2.07 (6H, s, 2 × CO*Me*), 4.04 (1H, dd, *J* 11.6, 4.1, C(1)H_A), 4.30 (1H, dd, *J* 11.6, 6.1, C(1)H_B), 4.39–4.48 (1H, m, C(2)*H*), 5.26–5.28 (1H, m, C(3)*H*), 5.39 (1H, dd, *J* 15.4, 7.5, C(4)*H*), 5.68 (1H, d, *J* 9.2, N*H*), 5.79 (1H, dd, *J* 15.4, 6.8, C(5)*H*); δ_C (100 MHz, $CDCl_3$) 14.1, 20.8, 21.1, 22.7, 23.4, 28.9, 29.2, 29.3, 29.4, 29.6, 29.7, 31.9, 32.3, 50.6, 60.4, 62.6, 73.8, 124.1, 137.5, 169.7, 170.0, 171.0; *m/z* (ESI$^+$) 448 ([M + Na]$^+$, 100%); HRMS (ESI$^+$) $C_{24}H_{43}NNaO_5^+$ ([M + Na]$^+$) requires 448.3033; found 448.3023.

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