

Asymmetric Syntheses of 3-Deoxy-3-aminosphingoid Bases:
Approaches Based on Parallel Kinetic Resolution and Double Asymmetric Induction

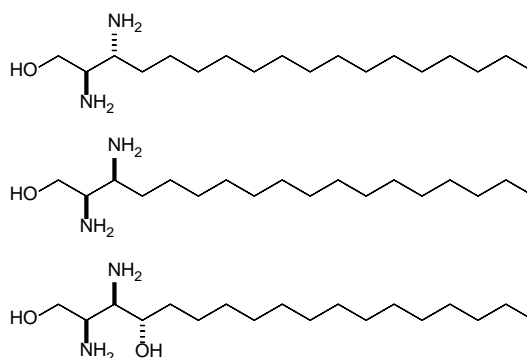
Kristína Csatayová,[†] Stephen G. Davies,^{*} Ai M. Fletcher, Thomas R. Fowler,

Matthew S. Kennedy, Paul M. Roberts, and James E. Thomson

Department of Chemistry, Chemistry Research Laboratory,

University of Oxford, Mansfield Road, Oxford OX1 3TA, U.K.

steve.davies@chem.ox.ac.uk



The asymmetric syntheses of a range of *N*- and *O*-protected 3-deoxy-3-aminosphingoid bases have been achieved using two complementary approaches. DL-Serine was converted to a racemic *N,N*-dibenzyl-protected γ -amino- α,β -unsaturated ester which was resolved using a parallel kinetic resolution (PKR) strategy upon reaction with a pseudoenantiomeric mixture of lithium (*R*)-*N*-benzyl-*N*-(α -methylbenzyl)amide and lithium (*S*)-*N*-3,4-dimethoxybenzyl-*N*-(α -methylbenzyl)amide, giving the corresponding enantio- and diastereoisomerically pure β,γ -diamino esters. Alternatively, elaboration of L-serine gave the corresponding enantiopure *N,N*-dibenzyl-protected γ -amino- α,β -unsaturated ester, and doubly diastereoselective conjugate addition of the antipodes of lithium *N*-benzyl-*N*-(α -methylbenzyl)amide was found to proceed under the dominant stereocontrol of the lithium amide reagent in both cases, thus augmenting the accessible range of β,γ -diamino esters. Both of these protocols were expanded to include in situ oxidation of the enolate formed upon conjugate addition, giving access to the corresponding α -hydroxy- β,γ -diamino esters. Elaboration of these β,γ -diamino and α -hydroxy- β,γ -diamino esters gave the protected forms of the 3-deoxy-3-aminosphingoid base targets.

Introduction

The sphingoid bases, of which sphinganine **1**, sphingosine **2** and phytosphingosine **3** (Figure 1) are the archetypal members of the various sub-classes, form the backbone of sphingolipids, which are essential components of all eukaryotic cells. The sphingoid bases and their derivatives (ceramides, sphingolipids) play varied and important roles in cell structure, cell signalling, and even cell death. As such, there has been much interest in their synthesis¹ and in the synthesis of analogues² (Figure 1).

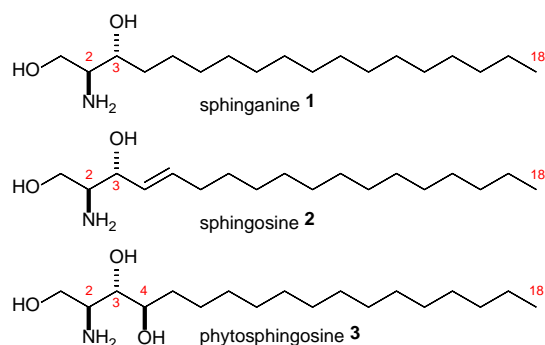
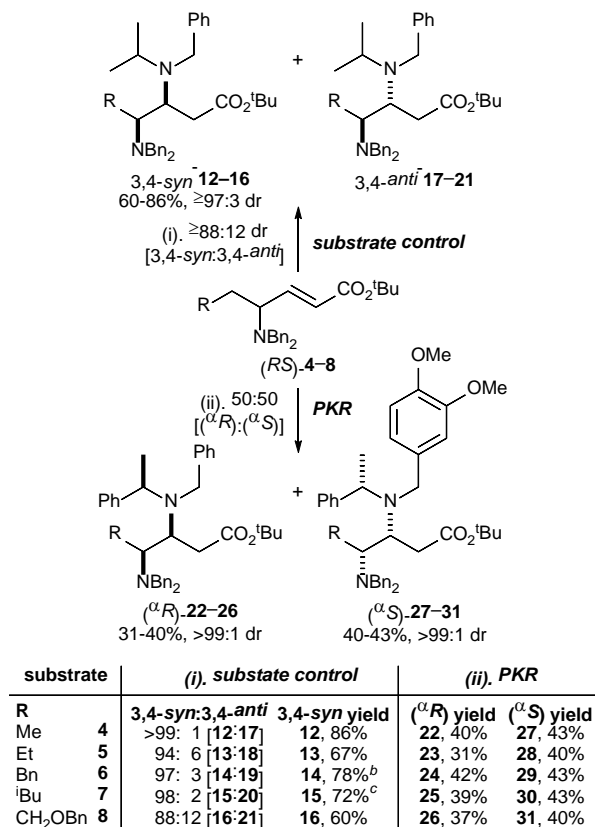


FIGURE 1. Structures of the archetypal sphingoid bases: sphinganine **1**, sphingosine **2** and phytosphingosine **3**.

We have previously investigated the parallel kinetic resolution (PKR) of a range of racemic *N,N*-dibenzyl-protected γ -amino- α,β -unsaturated esters (*RS*)-**4–8** (derived from the corresponding racemic α -amino acids) using the conjugate addition of a 50:50 pseudoenantiomeric mixture of lithium (*R*)-*N*-benzyl-*N*-(α -methylbenzyl)amide **10** and lithium (*S*)-*N*-3,4-dimethoxybenzyl-*N*-(α -methylbenzyl)amide **11**.³ The key features of the PKR protocol are as follows: (i) the chiral α,β -unsaturated esters (*RS*)-**4–8** exhibit a preference for the formation of the corresponding 3,4-*syn* products **12–16** upon conjugate addition of achiral lithium *N*-benzyl-*N*-isopropylamide **9** and (ii) this substrate control, when combined with the known diastereoselectivity elicited by lithium amides (*R*)-**10** and (*S*)-**11** (reagent control)⁴ leads to high levels of enantioselectivity and hence efficient PKR. For example, PKR of the α,β -unsaturated ester (*RS*)-**8**, derived from DL-serine, gave a 50:50 mixture of the corresponding enantiopure β,γ -diamino esters **26** and **31**, and chromatographic separation gave **26** in 37% yield and **31** in 40% yield, as single diastereoisomers in both cases³ (Scheme 1).

SCHEME 1^a



^aReagents and conditions: (i) lithium *N*-benzyl-*N*-isopropylamide **9**, THF, -78 °C, 2 h; (ii) lithium (*R*)-*N*-benzyl-*N*-(α -methylbenzyl)amide **10**, lithium (*S*)-*N*-3,4-dimethoxybenzyl-*N*-(α -methylbenzyl)amide **11**, THF, -78 °C, 2 h. ^b97:3 dr [14:19]. ^c98:2 dr [15:20].

We proposed that this PKR protocol could be utilised as the key step in the synthesis of a range of 3-deoxy-3-aminosphingoid bases via elaboration of a suitable enantiopure β,γ -diamino ester **33** (X = H), derived from DL-serine. Alternatively, enantiopure **33** (X = H) could also be accessed via an approach based upon double asymmetric induction,⁵ involving the conjugate addition of an enantiopure lithium amide to the corresponding enantiopure *N*- and *O*-protected α,β -unsaturated ester **32**, derived from L-serine. Further, if an electrophilic oxygen source was used (rather than a proton) as a quenching agent for the intermediate enolate(s) formed upon conjugate addition to *N,N*-dibenzyl-protected γ -amino- α,β -unsaturated ester **32** in either of these approaches, then the complementary series of enantiopure α -hydroxy- β,γ -diamino esters **33** (X = OH) would also be accessible.⁶⁻⁹ It was proposed that chemoselective *O*-deprotection of **33** (X = H, OH) with *in situ* cyclisation would furnish the corresponding lactone **34**. Reduction of **34** was anticipated to yield the corresponding lactol **35**, and elaboration of **35** via Wittig olefination would give **36**. Tandem hydrogenation/hydrogenolysis of **36** would then give the corresponding 3-deoxy-3-aminosphingoid base **37** (Figure 2). This approach avoids the stoichiometric formation of a potentially unstable β -amino aldehyde intermediate (the lactol **35** acting as a masked form of this species). We delineate herein the results of our investigations within this area.

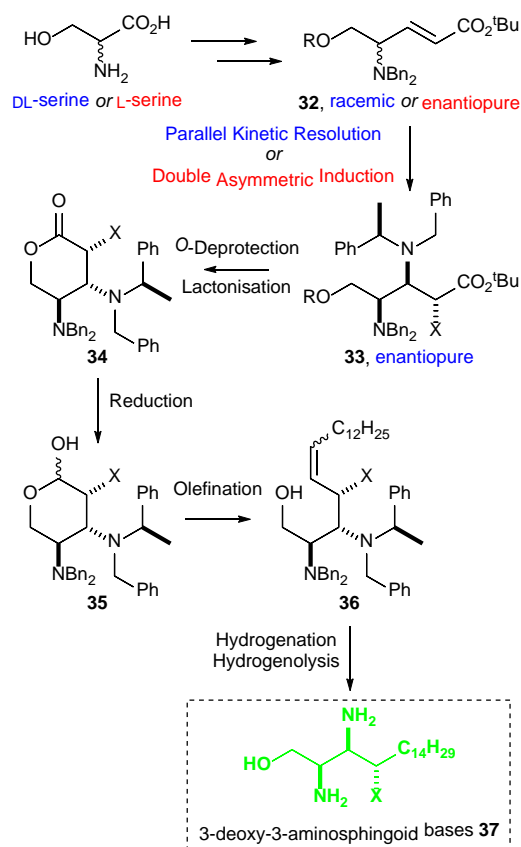


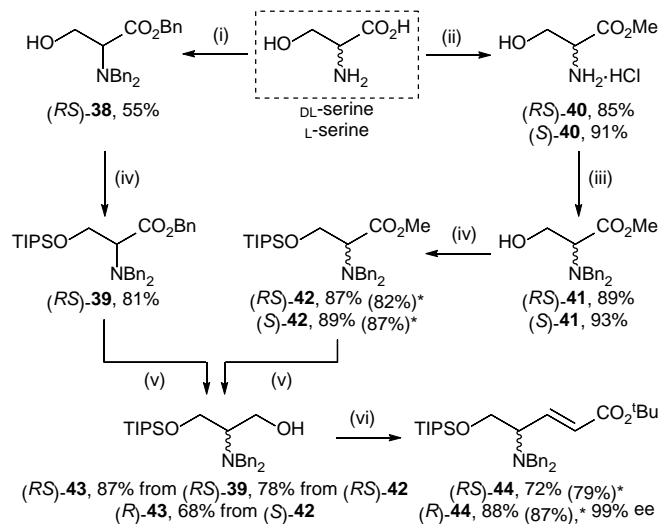
FIGURE 2. Enantiopure β,γ -diamino esters or α -hydroxy- β,γ -diamino esters **33** ($X = H$ or OH), derived from (i) DL-serine using PKR, or (ii) L-serine using double asymmetric induction, as precursors to 3-deoxy-3-aminosphingoid bases **37** ($X = H$ or OH).

Results and Discussion

Although we have already evaluated racemic *N,N,O*-tribenzyl-protected α,β -unsaturated ester (*RS*)-**8** in the PKR reaction manifold,³ this was synthesised from *O*-benzyl DL-serine which is a relatively high-cost starting material, meaning that its applicability for larger-scale synthesis is limited. In addition, the global *N*- and *O*-benzyl protection of the corresponding enantiopure β,γ -diamino esters **26** and **31** (Scheme 1) was not anticipated to be ideal for the proposed chemoselective *O*-debenzylation step in the synthesis. Therefore, it was resolved to pursue the synthesis of an orthogonally *N,O*-protected α,β -unsaturated ester starting from DL-serine: this material is inexpensive, readily available in multigram quantities, and obviously allows the incorporation of orthogonal *N*- and *O*-protecting groups. Based upon our previous approach to racemic *N,N*-dibenzyl-protected γ -amino- α,β -unsaturated esters (*RS*)-**4–8**,³ treatment of DL-serine with BnBr and K₂CO₃ gave (*RS*)-**38** in 55% yield. *O*-Silyl protection of (*RS*)-**38** was then readily achieved by treatment with TIPSCl and imidazole, which proceeded to give (*RS*)-**39** in 81% isolated yield. Reduction of (*RS*)-**39** by treatment with DIBAL-H gave alcohol (*RS*)-**43** in 87% yield. Swern oxidation of (*RS*)-**43** to the corresponding aldehyde was followed by *in situ* Wittig olefination upon addition of Ph₃P=CH₂CO₂^tBu to give racemic α,β -unsaturated ester (*RS*)-**44** in >99:1 dr [*E*]:[*Z*] ratio]. ¹H NMR ³*J* coupling constant analysis showed a diagnostic value of ³*J* = 15.8 Hz between C(2)*H* and C(3)*H* olefinic protons, enabling confident

assignment of the expected (*E*)-geometry for the newly formed carbon-carbon double bond within (*RS*)-**44**. Purification gave (*RS*)-**44** in 72% yield, representing an overall yield of 28% from DL-serine. Hulme *et al.* have reported a strategy for the preparation of an analogue of **43** bearing an *O*-TBDPS rather than *O*-TIPS group.¹⁰ Following this protocol, methyl ester hydrochloride salt (*RS*)-**40** was formed upon treatment of DL-serine with AcCl in MeOH, in 85% yield. Treatment of (*RS*)-**40** with BnBr and K₂CO₃ gave (*RS*)-**41** in 89% yield. *O*-Silyl protection of (*RS*)-**41** by treatment with TIPSCl and imidazole proceeded to give (*RS*)-**42** in 87% yield. This procedure could be telescoped [i.e., omitting purification of intermediates (*RS*)-**40** and (*RS*)-**41**], which allowed isolation of (*RS*)-**42** in 82% overall yield from DL-serine. Reduction of (*RS*)-**42** with DIBAL-H gave alcohol (*RS*)-**43** in 78% isolated yield, which could be elaborated to (*RS*)-**44** as before. However, when alcohol (*RS*)-**43** was subjected (without prior purification) to the one pot Swern/Wittig reaction, racemic α,β -unsaturated ester (*RS*)-**44** was isolated in 79% yield and >99:1 dr [(*E*):(*Z*) ratio] over the two steps from (*RS*)-**42**. Thus, the route via methyl ester (*RS*)-**42** was higher yielding than the route via benzyl ester (*RS*)-**39**, despite the involvement of an additional synthetic step in the former case: (*RS*)-**44** was prepared from DL-serine in 65% overall yield in five steps (with two chromatographic purifications) via methyl ester (*RS*)-**42**, compared to only 28% overall yield in four steps (with four chromatographic purifications) via benzyl ester (*RS*)-**39**. The optimum route enabled routine synthesis of >15 g batch quantities of (*RS*)-**44**. As enantiopure **44** was required to evaluate the effects of double asymmetric induction, a sample of (*R*)-**44** was prepared via an analogous procedure but starting from L-serine. This synthesis could be run without purification of intermediates (*S*)-**40**, (*S*)-**41** and (*R*)-**43**, giving α,β -unsaturated ester (*R*)-**44** in 76% overall yield and >99:1 dr [(*E*):(*Z*) ratio] in five steps (with two chromatographic purifications) from L-serine. Chiral HPLC analyses of (*RS*)-**44** and (*R*)-**44** allowed the enantiomeric purity of the sample of (*R*)-**44** to be determined as 99% ee¹¹ (Scheme 2).

SCHEME 2^a



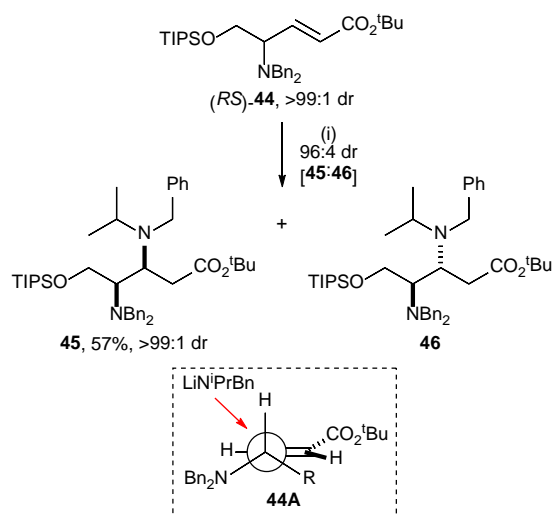
^aReagents and conditions: (i) BnBr, K₂CO₃, H₂O, reflux, 18 h; (ii) AcCl, MeOH, reflux, 3 h; (iii) BnBr, K₂CO₃, MeCN, rt, 24 h; (iv) imidazole, TIPSCl, DMF, rt, 18 h; (v) DIBAL-H, PhMe, -78 °C, 1 h; (vi) (COCl)₂, DMSO, Et₃N, CH₂Cl₂, -78 °C, 1 h; (vii)

Ph₃P=CHCO₂¹Bu, CH₂Cl₂, rt, 18 h. * Yields in parentheses are for telescoped processes (i.e., over three steps from serine for the synthesis of **42**, and over two steps from **42** for the synthesis of **44**, without purification of any intermediates).

Our standard procedure¹² for evaluating the suitability of a racemic α,β -unsaturated ester to undergo PKR using a pseudoenantiomeric mixture of lithium amides **10** and **11** involves first independently evaluating both the inherent levels of substrate control and the extent of recognition between the enantiomers of the substrate and reagent. The inherent substrate control is assessed upon conjugate addition of (achiral) lithium *N*-benzyl-*N*-isopropylamide **9** to the racemic α,β -unsaturated ester, with high levels of substrate control being manifested in high diastereoselectivity upon conjugate addition. The extent of enantiorecognition is then quantified by conducting a mutual kinetic resolution (MKR), i.e., the addition of racemic lithium *N*-benzyl-*N*-(α -methylbenzyl)amide **10** to the racemic α,β -unsaturated ester. This approach eliminates the effect of mass action and readily allows quantification of the stereoselectivity factor, *E*, from the reaction diastereoselectivity, obtained by peak integration of the ¹H NMR spectrum of the crude reaction mixture.¹³ Systems for which *E* \geq 10 can be expected to result in highly efficient PKR upon treatment with a 50:50 pseudoenantiomeric mixture of lithium amides **10** and **11**. This approach was implemented for racemic α,β -unsaturated ester (*RS*)-**44**.

Addition of lithium amide **9** to racemic α,β -unsaturated ester (*RS*)-**44** in THF at -78 °C gave a 96:4 mixture of the racemic, diastereoisomeric $\beta\gamma$ -diamino esters **45** and **46**, as established by ¹H NMR spectroscopic analysis of the crude reaction mixture. From this result, it is evident that (*RS*)-**44** shows very high levels of diastereocontrol upon conjugate addition of lithium amide **9**. Following purification, **45** was isolated in 57% yield as a single diastereoisomer, along with an impure sample of **46** in <5% yield. The relative (*RS*,*SR*)- and (*RS*,*RS*)-configurations of **45** and **46**, respectively, were assigned by analogy to those of the corresponding *O*-benzyl-protected analogues **16** and **21**, of known relative configuration:³ the ¹H NMR chemical shifts and ³*J* coupling constant values associated with the C(2)*H*₂ protons of **16** and **45**, and those of **21** and **46**, displayed close parity.¹⁴ We have previously proposed a simplistic model to account for the diastereocontrol elicited by chiral α,β -unsaturated esters **4–8** upon conjugate addition of lithium amide **9**.³ This model is similar to the Felkin-Ahn model, whereby the configuration of the allylic stereocentre controls the stereochemical outcome of the reaction, with the lithium amide **9** approaching the double bond from the least hindered face. Based upon the observed solid-state conformation of (*RS*)-**4** (derived from DL-alanine), a reactive conformation was proposed whereby the C(4)-hydrogen atom is at 90° to the plane defined by the double bond, and the bulky C(4)-*N,N*-dibenzylamino group is in the less crowded “outside” position.³ In the case of **44**, this corresponds to conformation **44A**: approach of lithium amide **9** would then be predicted to occur over the hydrogen atom, leading to the 3,4-*syn* diastereoisomer **45** as the major product (Scheme 3).

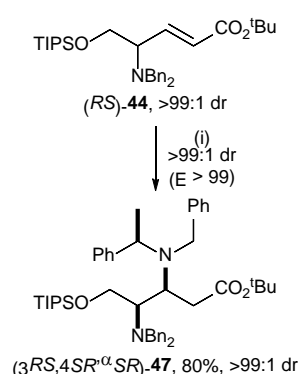
SCHEME 3^a



^aReagents and conditions: (i) lithium *N*-benzyl-*N*-isopropylamide **9**, THF, −78 °C, 2 h. R = CH₂OTIPS.

MKR of racemic lithium amide (*RS*)-**10** and racemic α,β -unsaturated ester (*RS*)-**44** was next attempted. In the event, addition of (*RS*)-**10** to (*RS*)-**44** gave a racemic β,γ -diamino ester **47** as a single diastereoisomer, indicating a very high level of enantiorecognition ($E > 99$),¹³ with chromatographic purification giving **47** in 80% yield. The relative (3*RS*,4*SR*, α *SR*)-configuration of **47** was initially assigned by analogy to the outcomes of MKR of the racemic *N,N*-dibenzyl-protected γ -amino- α,β -unsaturated esters (*RS*)-**4–8** with lithium amide (*RS*)-**10**, and later unambiguously confirmed by single crystal X-ray diffraction analysis of a derivative. The very high level of enantiorecognition observed in this MKR is consistent with the high level and sense of diastereocontrol shown by the substrate (*RS*)-**44** upon conjugate addition of achiral lithium amide **9**, as well as with the known diastereoselectivity elicited by chiral lithium amide **10** in its conjugate addition reactions to a range (>250 examples) of achiral α,β -unsaturated esters⁴ (Scheme 4).

SCHEME 4^a

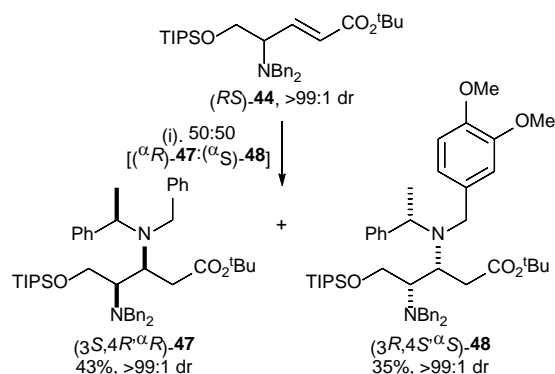


^aReagents and conditions: (i) lithium (*RS*)-*N*-benzyl-*N*-(α -methylbenzyl)amide (*RS*)-**10**, THF, −78 °C, 2 h.

Following the successful MKR, reaction of an equimolar mixture of lithium amides (*R*)-**10** and (*S*)-**11** with racemic α,β -unsaturated ester (*RS*)-**44** gave a 50:50 mixture of only two enantiopure β,γ -diamino esters, **47** and **48**, demonstrating efficient PKR. The difference in polarity between the phenyl group within **47** and the 3,4-dimethoxyphenyl group within **48** afforded good chromatographic separation, and **47** was isolated in 43% yield, whilst **48** was isolated in 35% yield. As expected, the ¹H and ¹³C NMR spectra of this

enantiopure sample of **47** proved to be identical to those for the racemic sample of **47** produced in the MKR of (*RS*)-**44** using lithium amide (*RS*)-**10**. Thus, the absolute (*3S,4R,αR*)-configuration of the enantiopure sample of **47** was confidently assigned from the known (*R*)-configuration of the α -methylbenzyl stereogenic centre derived from the lithium amide reagent (*R*)-**10**. The absolute (*3R,4S,αS*)-configuration was therefore assigned to **48** on the basis that it is pseudoenantiomeric to (*3S,4R,αR*)-**47** (Scheme 5).

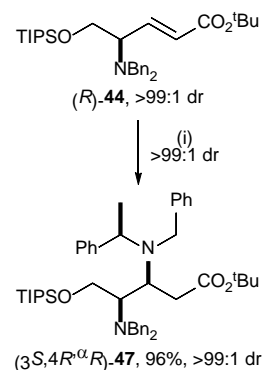
SCHEME 5^a



^aReagents and conditions: (i) lithium (*R*)-*N*-benzyl-*N*-(α -methylbenzyl)amide (*R*)-**10**, lithium (*S*)-*N*-benzyl-*N*-(α -methyl-3,4-dimethoxybenzyl)amide (*S*)-**11**, THF, -78°C , 2 h.

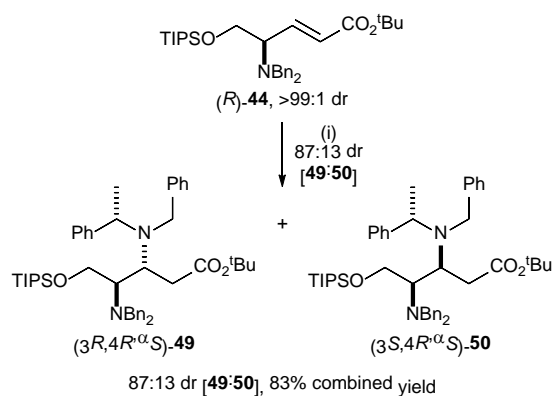
Attention now turned to evaluating double asymmetric induction,⁵ utilising the conjugate addition of the antipodes of lithium amide **10** to enantiopure α,β -unsaturated ester (*R*)-**44**, as an alternative method to access enantiopure β,γ -diamino esters, including **47**. The sense of substrate control elicited by (*RS*)-**44** upon conjugate addition of lithium amide **9** suggested that reaction of enantiopure lithium amide (*R*)-**10** with enantiopure α,β -unsaturated ester (*R*)-**44** would constitute the “matched” pairing⁵ and give enantiopure β,γ -diamino ester (*3S,4R,αR*)-**47** with high diastereoselectivity. In the event, addition of 1.6 equiv of lithium amide (*R*)-**10** to (*R*)-**44** gave 93% conversion to **47** as a single diastereoisomer. When 2.0 equiv of lithium amide (*R*)-**10** were used, quantitative conversion was achieved and **47** was isolated in 96% yield as a single diastereoisomer after chromatography. As expected, the ^1H and ^{13}C NMR spectroscopic data for this enantiopure sample of **47** were identical to those of the racemic sample isolated from the MKR reaction, and the enantiopure sample isolated from the PKR reaction; the signs and magnitudes of the specific rotations of both of the enantiopure samples of **47** (obtained by PKR and by double asymmetric induction) were identical (Scheme 6).

SCHEME 6^a



^aReagents and conditions: (i) lithium (*R*)-*N*-benzyl-*N*-(α -methylbenzyl)amide (*R*)-**10**, THF, -78°C , 2 h.

The reaction of enantiopure lithium amide (*S*)-**10** with enantiopure α,β -unsaturated ester (*R*)-**44** was expected to be the “mismatched” pairing,⁵ and hence expected to proceed with lower levels of diastereoselectivity, and at a slower rate, than the corresponding reaction of the “matched” pairing.⁵ Given the enantiopurities of both (*S*)-**10** (i.e., >99% ee) and (*R*)-**44** (i.e., 99% ee), it was anticipated that the “mismatched” reaction would form a maximum of two possible conjugate addition products: the C(3)-epimers **49** and **50** (both in enantiopure form). Prior to conducting the experiment, however, it was not possible to predict the identity of the major diastereoisomer, as this would be governed by the dominant stereocontrolling factor: either the diastereocontrol of the lithium amide reagent (*S*)-**10** (which was predicted to favour **49**), or the diastereocontrol of the α,β -unsaturated ester substrate (*R*)-**44** (which was predicted to favour **50**). In the event, addition of 1.6 equiv of lithium amide (*S*)-**10** to (*R*)-**44** resulted 85% conversion to an 87:13 mixture of **49** and **50**, respectively. When 2.0 equiv of lithium amide (*S*)-**10** were used, quantitative conversion was achieved and an 87:13 mixture of **49** and **50** was isolated in 83% combined yield after chromatography (Scheme 7). The absolute configuration of the newly formed C(3)-stereogenic centre of **49** was subsequently established unambiguously following single crystal X-ray diffraction analysis of a derivative, and thence **50** was assigned as the C(3)-epimer of **49**. The reduced level (and opposite sense) of diastereoselectivity, coupled with the reduced conversion, displayed in the conjugate addition 1.6 equiv of lithium amide (*S*)-**10** to (*R*)-**44** (85% conversion, 87:13 dr) as compared to the conjugate addition of 1.6 equiv of lithium amide (*R*)-**10** to (*R*)-**44** (93% conversion, >99:1 dr) validated the prediction that the former pairing is “mismatched” (and the latter “matched”).⁵ The production of **49** as the major diastereoisomeric product of this reaction shows that the dominant stereocontrolling element is the lithium amide reagent (*S*)-**10** and, therefore, the deployment of this double asymmetric induction strategy allows the diastereodivergent preparation of either the 3,4-*syn*- or 3,4-*anti*-configured β,γ -diamino esters **47** or **49**, respectively.

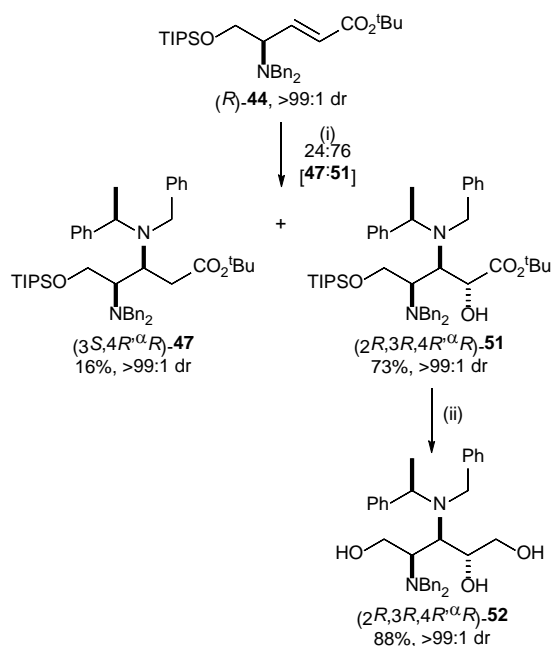
SCHEME 7^a

^aReagents and conditions: (i) lithium (S)-N-benzyl-N-(α-methylbenzyl)amide (S)-10, THF, −78 °C, 2 h.

With confirmation that the combination of enantiopure lithium amide (R)-10 with enantiopure α,β-unsaturated ester (R)-44 constitutes the “matched” pairing,⁵ incorporation of an *in situ* enolate oxidation using camphorsulfonyloxaziridine (CSO)^{6–9} was next investigated. First, the addition of lithium amide (R)-10 to (R)-44 was carried out at an overall concentration of 0.08 M w.r.t. 44, and was followed by addition of (–)-CSO. This produced a complex mixture of products, containing enantiopure β,γ-diamino ester 47 and enantiopure β,γ-diamino 51 in an approximately 50:50 ratio, as determined by ¹H NMR spectroscopic analysis. However, the complexity of the crude reaction mixture precluded assessment of the diastereoisomeric purity of both 47 and 51. Purification by column chromatography gave 47 in 37% yield and 51 in 40% yield, as single diastereoisomers in both cases. Treatment of 51 with LiAlH₄ resulted in concomitant reduction of the ester functionality and removal of the *O*-silyl protecting group to give the corresponding triol 52 in 88% yield (Scheme 8). The relative configuration within 52 was established unambiguously by single crystal X-ray diffraction analysis (Figure 3),¹⁵ with the absolute (2R,3R,4R,αR)-configuration following from the known (R)-configuration of the α-methylbenzyl stereogenic center; in addition the determination of a Flack *x* parameter^{16,17} for the structure of −0.1(3) was consistent with this assignment. This analysis also allowed the absolute (2R,3R,4R,αR)-configuration of 51 to be unambiguously assigned, as well as the absolute (3S,4R,αR)-configuration of 47 since both 47 and 51 arise from the same intermediate enolate. In an attempt to increase the proportion of α-hydroxy-β,γ-diamino ester 51 over β,γ-diamino ester 47 in the crude reaction mixture, the concentration of the reaction was increased by reducing the total volume of solvent. This strategy proved successful: increasing the overall concentration gave product ratios with increased proportions of α-hydroxy-β-amino ester 51. At an overall concentration of 1.25 M w.r.t. 44, the product ratio of 47:51 was determined to be 24:76 by ¹H NMR spectroscopic analysis. Purification gave β,γ-diamino ester 47 in 16% yield and α-hydroxy-β,γ-diamino ester 51 in 73% yield. The efficacy of (+)-CSO in effecting the enolate oxidation was also assessed under these optimised conditions: in this case, however, analysis of the ¹H NMR spectrum of the crude reaction mixture indicated the presence of

47 only. This result suggests that there are significant levels of enantiorecognition between the intermediate enolate [derived from conjugate addition of lithium amide (*R*)-**10** to α,β -unsaturated ester (*R*)-**44**] and the enantiomers of CSO^{6,7,18} (Scheme 8).

SCHEME 8^a



^aReagents and conditions: (i) lithium (*R*)-*N*-benzyl-*N*-(α -methylbenzyl)amide (*R*)-**10**, THF, $-78\text{ }^{\circ}\text{C}$, 2 h, then (-)-CSO, $-78\text{ }^{\circ}\text{C}$ to rt, 18 h; (ii) LiAlH_4 , THF, rt, 18 h.

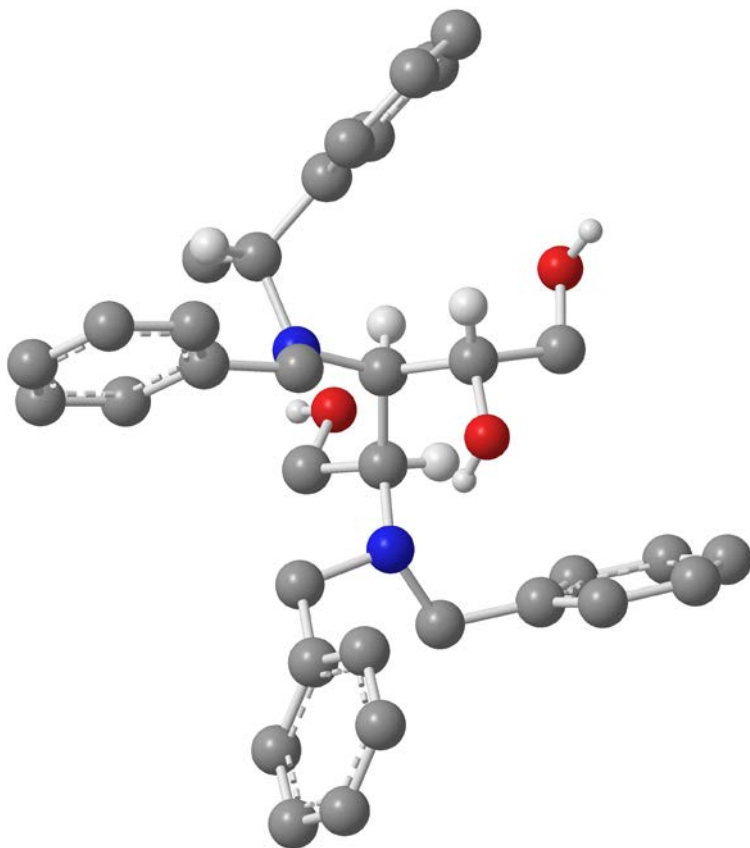
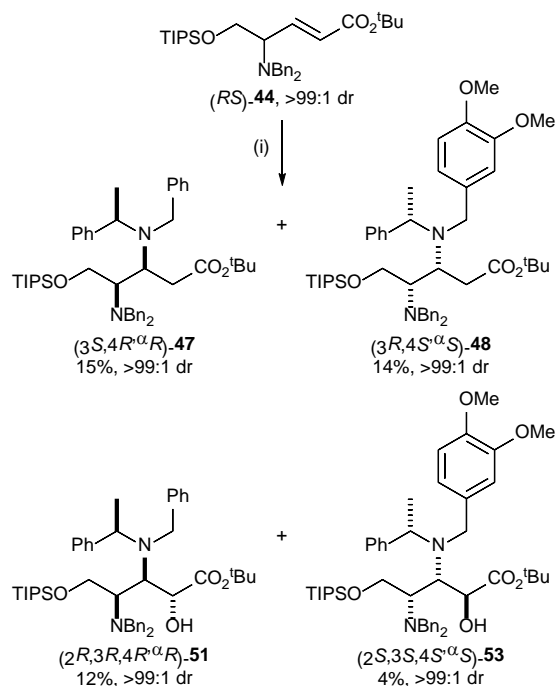


FIGURE 3. Chem3D representation of the X-ray crystal structure of **52** (selected H atoms are omitted for clarity).

The possibility of incorporating enolate oxidation into the PKR procedure was next briefly evaluated. As significant enantiorecognition was observed when quenching the intermediate enolate derived from

conjugate addition of enantiopure lithium amide (*R*)-**10** to enantiopure α,β -unsaturated ester (*R*)-**44** with the antipodes of CSO, an equimolar mixture of (–)-CSO and (+)-CSO was used as the quenching agent for the PKR procedure: the intermediate enolates that must be present, *viz.* that derived from conjugate addition of lithium amide (*R*)-**10** to (*R*)-**44** and that derived from conjugate addition of lithium amide (*S*)-**11** to (*S*)-**44**, are pseudoenantiomeric and should thus show complementary reactivity with the enantiomers of CSO. Conjugate addition of lithium amides (*R*)-**10** and (*S*)-**11** to (*RS*)-**44** at an overall concentration of 1.25 M w.r.t. **44** followed by addition of (–)-CSO and (+)-CSO gave a complex mixture of products. Substantial peak overlap in the ^1H NMR spectrum of the crude reaction mixture, coupled with the presence of CSO residues, enabled no information regarding product distribution or diastereoisomeric ratios to be gleaned. Chromatographic purification of this mixture allowed isolation of the enantiopure β,γ -diamino esters **47** and **48** (the result of enolate protonation) in 15% and 14% yields, respectively, along with enantiopure α -hydroxy- β,γ -diamino esters **51** and **53** (the result of enolate oxidation) in 12% and 4% yields, respectively. The absolute (2*S*,3*S*,4*S*, α *S*)-configuration was assigned to **53** on the basis that it is pseudoenantiomeric to **51**. Although the isolated yields of α -hydroxy- β,γ -diamino esters **51** and **53** were rather low, these results suggest that the combination of PKR with enolate oxidation may prove useful in future scenarios (Scheme 9).

SCHEME 9^a

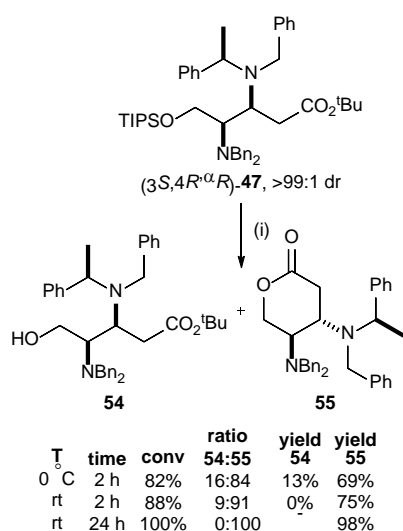


^aReagents and conditions: (i) lithium (*R*)-*N*-benzyl-*N*-(α -methylbenzyl)amide (*R*)-**10**, lithium (*S*)-*N*-benzyl-*N*-(α -methyl-3,4-dimethoxybenzyl)amide (*S*)-**11**, THF, $-78\text{ }^{\circ}\text{C}$, 2 h, then (–)-CSO, (+)-CSO, $-78\text{ }^{\circ}\text{C}$ to rt, 18 h.

With efficient routes to enantiopure β,γ -diamino esters **47** and **49**, and enantiopure α -hydroxy- β,γ -diamino ester **51** in place, their elaboration to the corresponding 3-deoxy-3-aminosphingoid bases was

explored, with one of the key steps being *O*-desilylation followed by lactonisation. Treatment of enantiopure β -amino ester **47** with TBAF at 0 °C for 2 h gave 82% conversion to a 16:84 mixture of β,γ -diamino- δ -hydroxy ester **54** and lactone **55**, respectively. This was an encouraging result, as it showed that lactone **55** was forming *in situ*; presumably, following *O*-silyl deprotection, the basicity of the reaction mixture provides conditions which promote lactonisation of **54**. Purification of the crude reaction mixture gave **47** in 9% yield, **54** in 13% yield and >99:1 dr, and **55** in 69% yield and >99:1 dr. Optimisation of the reaction conditions led to complete *O*-desilylation and lactonisation as indicated by the presence of only **55** in ^1H NMR spectrum of the crude reaction mixture; in this case purification by chromatography gave **55** in 98% yield. ^1H NMR 3J coupling constant analysis of **55** was consistent with a half-chair conformation being adopted in solution, in which both of the bulky amino moieties adopt pseudoaxial positions, presumably to minimise 1,2-strain (Scheme 10).

SCHEME 10^a

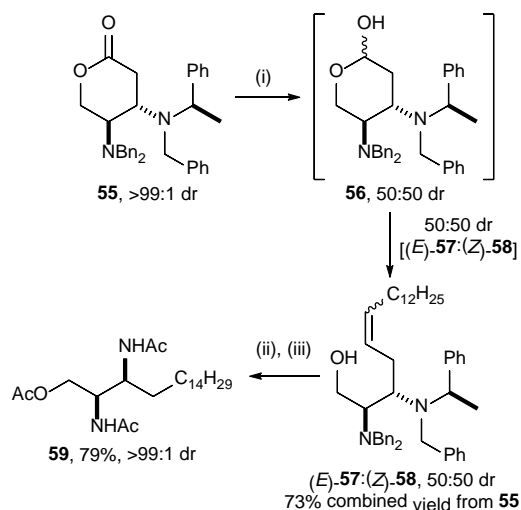


^aReagents and conditions: (i) TBAF, THF, temperature, time (see table).

A one-pot DIBAL-H reduction and Wittig olefination was next attempted on lactone **55**. The choice of solvent proved critical for the success of this process: the optimum protocol involved treatment of **55** in PhMe (2 volumes)¹⁹ with DIBAL-H, followed by the addition of an excess (5 equiv) of the ylide derived from deprotonation of $[\text{C}_{13}\text{H}_{27}\text{PPh}_3]^+[\text{Br}]^-$ in THF (1 volume)¹⁹ which produced an ~50:50 mixture of two compounds, **57** and **58**, with chromatography giving an ~50:50 mixture of **57** and **58** in 73% combined yield. Peak overlap in the ^1H NMR spectrum of the purified mixture of **57** and **58** precluded 3J coupling constant analysis, although the ^{13}C NMR chemical shifts of the allylic carbon atoms [C(4) and C(7)] of both **57** and **58** were consistent with the presence of olefin isomers: the chemical shift values associated with these carbons of **57** were ~5 ppm higher than the corresponding resonances for **58**, consistent with the so-called γ -effect²⁰ and hence signifying that **57** is the (*E*)-isomer and **58** is the (*Z*)-isomer. The importance of reaction solvent on the outcome of the two-step reduction/olefination reaction is underscored by the following

observations: (1) Phosphonium salt $[C_{13}H_{27}PPh_3]^+[Br]^-$ is insoluble in PhMe. (2) Attempted reduction of lactone **55** to lactol **56** using DIBAL-H in THF gave only 36% conversion (to a 50:50 mixture of anomers) after 1 h, which were isolated in 36% combined yield after chromatography. Use of PhMe gave complete conversion to **56** (50:50 mixture of anomers) within the same time period, allowing isolation of lactols **56** in 85% combined yield after chromatography. (3) Treatment of a solution of lactols **56** (50:50 mixture of anomers) in THF with BuLi, followed by the addition of a solution of the ylide derived from $[C_{13}H_{27}PPh_3]^+[Br]^-$ in THF, returned only starting material **56**, phosphonium salt and unidentified species; chromatographic purification gave only returned lactols **56** in 40% yield (i.e., PhMe is required as a co-solvent to promote efficient olefination). With an efficient preparation of olefins (*E*)-**57** and (*Z*)-**58** developed, their elaboration to the target 3-deoxy-3-aminosphingoid base was investigated. Treatment of the mixture of (*E*)-**57** and (*Z*)-**58** with H_2 (5 atm) in the presence of Pearlman's catalyst $[Pd(OH)_2/C]$ in 1.25 M methanolic HCl gave a white bulk that produced an intractable 1H NMR spectrum. However, peracetylation of the crude reaction mixture and purification by recrystallization gave 3-deoxy-3-aminosphingoid base derivative **59** in 79% yield [from the 50:50 mixture of (*E*)-**57** and (*Z*)-**58**]. The convergence of the 50:50 mixture of (*E*)-**57** and (*Z*)-**58** into a single compound **59** in 79% yield lends further support to their assignment as olefin isomers. The overall yield of **59** was 41% in ten steps from L-serine, or 16% (out of a theoretical maximum of 50%) in ten steps from DL-serine (Scheme 11).

SCHEME 11^a

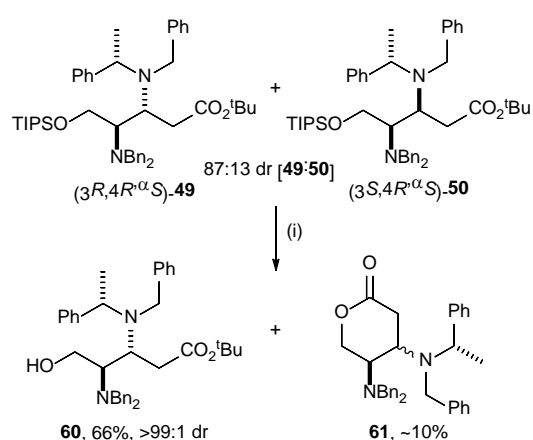


^aReagents and conditions: (i) DIBAL-H, PhMe, $-78\text{ }^\circ\text{C}$, 1 h, then $[C_{13}H_{27}PPh_3]^+[Br]^-$, BuLi, $80\text{ }^\circ\text{C}$, 1 h; (ii) H_2 , $[Pd(OH)_2/C]$, HCl/MeOH (1.25 M), rt, 72 h; (iii) Ac_2O , DMAP, pyridine, rt, 72 h.

Elaboration of the diastereoisomeric, enantiopure β,γ -diamino ester **49** to the corresponding 3-deoxy-3-aminosphingoid base was next explored. Treatment of an 87:13 mixture of **49** and **50** with TBAF followed by chromatography²¹ gave δ -hydroxy ester **60** in 66% isolated yield and an impure sample of lactone **61** [of unknown configuration at C(3)] in ~10% isolated yield (Scheme 12).²¹ The relative configuration within **60** was unambiguously established by single crystal X-ray diffraction analysis (Figure 4),¹⁵ with the absolute

(3*R*,4*R*, α *S*)-configuration following from the known (*S*)-configuration of the α -methylbenzyl stereocenter; in addition the determination of a Flack x parameter^{16,17} for the structure of +0.08(15) was consistent with this assignment. This analysis allowed both the relative and absolute configurations of both **49** and **50** to be assigned unambiguously. In addition, treatment of **60** with TIPSCl gave a sample of **49** as a single diastereoisomer (albeit in only 19% isolated yield), thus confirming the homochirality of these two species. Lactonisation of δ -hydroxy ester **60** was attempted under a range of conditions but in each case failed. The obduracy of **60** to undergo lactonisation (in contrast to its diastereoisomer **54**) may be due to the large 1,2-torsional strain that would unavoidably be experienced between the bulky amino moieties in the cyclic product (Scheme 12).

SCHEME 12^a



^aReagents and conditions: (i) TBAF, THF, rt, 24 h.

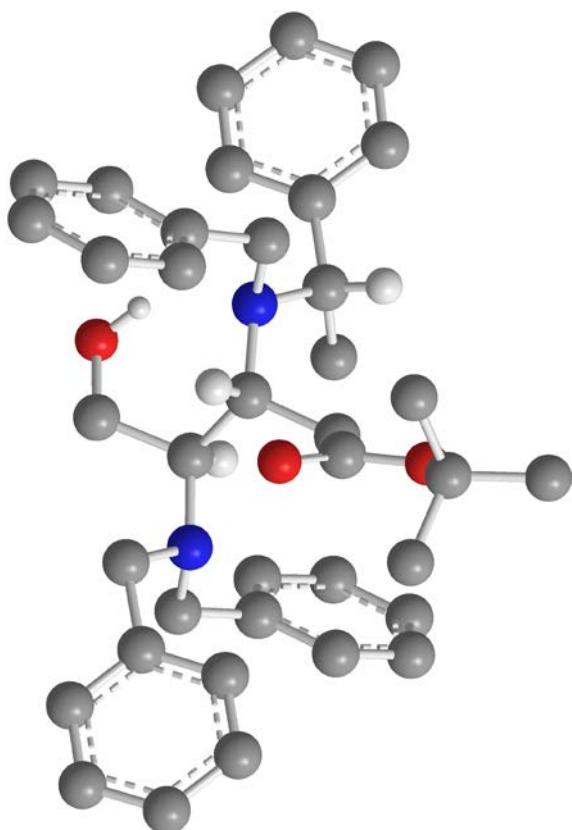
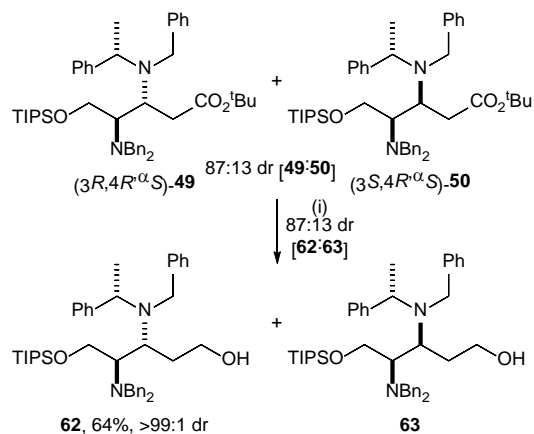


FIGURE 4. Chem3D representation of the X-ray crystal structure of **60** (selected H atoms are omitted for clarity).

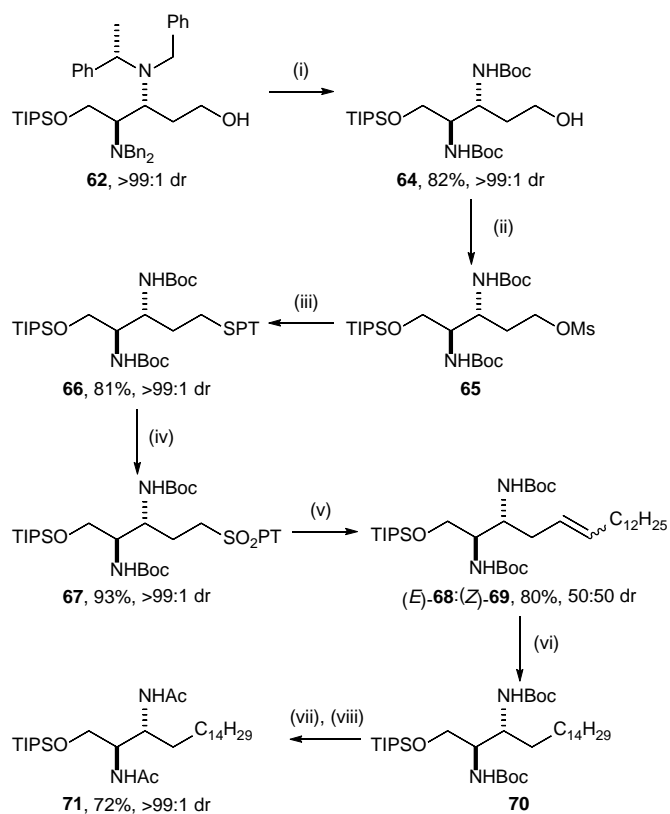
With lactonisation proving difficult, the possibility of effecting the chain elongation on an open chain system was next considered. Reduction of an 87:13 mixture of **49** and **50** gave an 87:13 mixture of the corresponding primary alcohol epimers **62** and **63**, from which the major diastereoisomer **62** was isolated in 64% yield after chromatography, although **63** was not isolated (Scheme 13). Attempted oxidation of **62** under a range of conditions resulted in extensive decomposition, consistent with the anticipated instability of the corresponding β -amino aldehyde. Hydrogenolysis of **62** in the presence of Boc₂O gave the bis-*N*-Boc-protected analogue **64** in 82% yield, which similarly resulted in formation of a complex mixture of products upon its attempted oxidation under a range of conditions. The possibility of converting either **62** or **64** into the nucleophilic rather than electrophilic component for an ensuing Julia-Kociński olefination²² was therefore assessed. Mitsunobu reaction of **62** with *N*(1)-phenyl-1*H*-tetrazole-5-thiol (PTSH) gave a mixture of unidentifiable products, presumably the result of participation of the amino groups. In contrast, Mitsunobu reaction of **64** with PTSH proceeded to give sulfide **66** in 60% isolated yield. However, it proved more efficacious to proceed via the corresponding mesylate **65**, which upon treatment with PTSH in the presence of K₂CO₃ provided sulfide **66** in an improved 81% yield (from **64**). Subsequent oxidation of **66** with H₂O₂ in the presence of ammonium molybdate gave sulfone **67** in 93% yield. Julia-Kociński olefination²² of tridecanal using sulfone **67** gave a 50:50 mixture of two compounds, **68** and **69**, which were isolated in 80% combined yield. Overlapping of peaks in the ¹H NMR spectra of both the crude and isolated products again frustrated ³*J* coupling constant analysis to establish that **68** and **69** were indeed related as olefin isomers; however, the ¹³C NMR chemical shifts of the allylic carbon atoms [C(4) and C(7)] of both **68** and **69** were consistent with this assignment (γ -effect),²⁰ with **68** being assigned as the (*E*)-isomer and **69** as the (*Z*)-isomer. Hydrogenation of the 50:50 mixture of (*E*)-**68** and (*Z*)-**69** gave a single compound **70**; treatment of **70** with TFA in CH₂Cl₂ effected removal of the *N*-Boc groups and was followed by *N*-acetylation, for ease of purification, giving 3-deoxy-3-aminosphingoid base derivative **71** in 72% yield [from the 50:50 mixture of (*E*)-**68** and (*Z*)-**69**]. Again, the convergence of the 50:50 mixture of (*E*)-**68** and (*Z*)-**69** into a single compound **71** in 72% yield provides further support to their assignment as olefin isomers. The overall yield of **71** was 14% in fourteen steps from L-serine (Scheme 14).

SCHEME 13^a



^aReagents and conditions: (i) LiAlH_4 , THF, rt, 18 h.

SCHEME 14^a

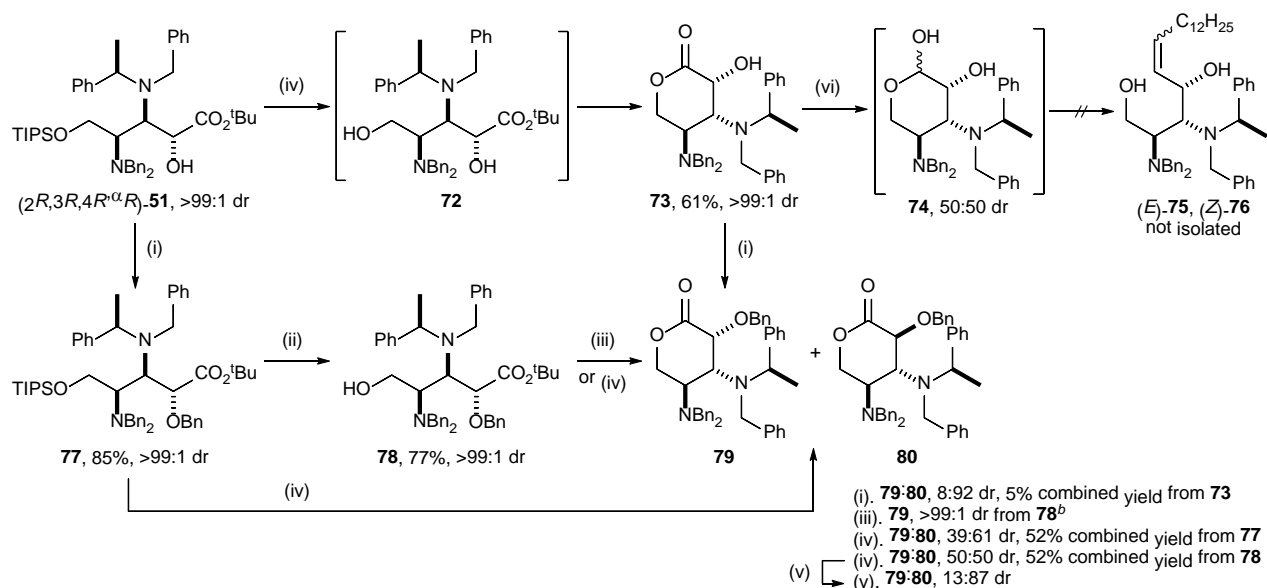


^aReagents and conditions: (i) H_2 , $\text{Pd}(\text{OH})_2/\text{C}$, Boc_2O , MeOH, rt, 72 h; (ii) MsCl , Et_3N , DMAP, CH_2Cl_2 , rt, 3 h; (iii) PTSH, K_2CO_3 , acetone, 67 °C, 2.5 h; (iv) H_2O_2 (30% aq), $(\text{NH}_4)_2\text{Mo}_7\text{O}_{24} \cdot 4\text{H}_2\text{O}$, EtOH, rt, 18 h; (v) LiHMDS , tridecanal, THF, rt, 18 h; (vi) H_2 , Pd/C , MeOH, rt, 3 h; (vii) TFA, CH_2Cl_2 , rt, 18 h; (viii) Ac_2O , DMAP, pyridine, rt, 24 h.

Finally, the elaboration of enantiopure α -hydroxy- β,γ -diamino ester **51** was considered. Under the conditions successfully employed for the one-pot *O*-desilylation/lactonisation of **47**, treatment of **51** with TBAF gave 87% conversion to the corresponding lactone **73** (the intermediate α,δ -dihydroxy- β,γ -diamino ester **72** was not observed). Increasing the amount of TBAF resulted in >95% conversion to **73** which was isolated in 61% yield after chromatography. In this case ^1H NMR 3J coupling constant analysis did not edify a likely conformational preference for **73**. Although reduction of **73** with DIBAL-H gave a 50:50 mixture of the corresponding lactols **74**, attempted Wittig reaction of **74** or attempted one-pot DIBAL-H/Wittig reaction of lactone **73** (under the optimised conditions used for the conversion of **55** into olefins **57** and **58**, and under

other conditions) resulted in incomplete consumption of starting material to form complex mixtures of products. An *O*-protecting group strategy was therefore implemented. *O*-Benzylation of **51** upon treatment with NaH and then BnBr, gave **77** in 85% yield. Subsequent treatment of **77** with TBAF gave a 39:61 mixture of diastereoisomeric lactones **79** and **80** which were isolated in 52% combined yield. Alternative protocols for *O*-desilylation and lactonisation were investigated and whilst treatment of **77** with TBAF buffered with AcOH returned only starting material, exposure of **77** to HF·pyridine gave δ -hydroxy ester **78** in 77% yield. Treatment of **78** with 40% aq HBF₄ for 48 h gave a somewhat complex mixture containing starting material **78** and lactone **79** as major components, with only a trace amount of lactone **80** being observed. Purification gave **78** in 30% yield and a 50:50 mixture of **78** and **79** in 34% combined calculated yield. In contrast, treatment of **78** with TBAF gave a 50:50 mixture of lactones **79** and **80**, which were isolated in 52% combined yield. Resubjection of the 50:50 mixture of **79** and **80** to these reaction conditions for a further 4 days gave a 13:87 mixture of lactones **79** and **80**. Taken together, these results are consistent with *O*-desilylation of **77** under basic conditions being followed by lactonisation of the resultant δ -hydroxy ester **78**, and then epimerisation of the initially formed lactone **79** into **80**. It is on the basis of this mechanistic postulate that the configurations of both **79** and **80** were assigned. Although it is apparent that cyclisation of **78** under acidic conditions did not result in competing epimerisation, this condition set is ineffective at promoting complete lactonisation. Attempted *O*-benzylation of lactone **73** proved similarly inefficacious at providing lactone **79**: treatment of **73** with NaH and BnBr resulted in incomplete consumption of starting material to form of a complex mixture of products, with exhaustive chromatographic purification giving recovered **73** in 21% yield and an 8:92 mixture of lactones **79** and **80** in 5% combined yield (Scheme 15).

SCHEME 15^a

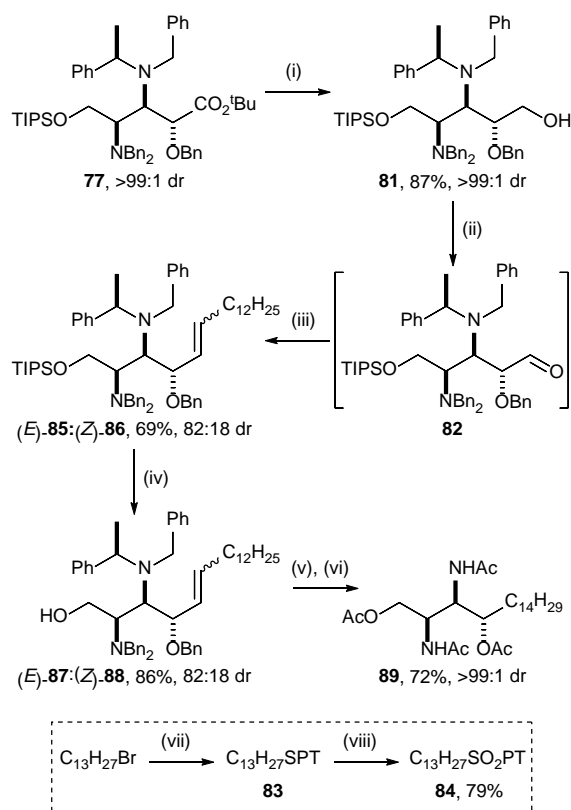


Reagents and conditions: (i) NaH, THF, 0 °C, 30 min, then BnBr, 0 °C to rt, 24 h; (ii) HF·pyridine, THF, rt, 18 h; (iii) HBF₄ (40% aq), CH₂Cl₂, rt, 48 h; (iv) TBAF, THF, rt, 24 h; (v) TBAF, THF, rt, 4 days; (vi) DIBAL-H, PhMe, -78 °C, 1 h. **79** was isolated as a 50:50 mixture with unreacted starting material **78** from this reaction, in 34% combined calculated yield.

With the lactonisation route again proving troublesome, the possibility of effecting the elaboration of **51** into the corresponding 3-deoxy-3-aminosphingoid base via an open chain form was investigated; in this instance however the synthesis would involve the intermediacy of an α -oxy- β -amino aldehyde, which are much less susceptible to retro-conjugate addition than their α -unsubstituted counterparts. Treatment of **77** with DIBAL-H gave alcohol **81** in 87% yield, with oxidation with IBX giving complete conversion to aldehyde **82**. Purification of aldehyde **82** was not attempted, and it was instead immediately subjected to Wittig olefination using the ylide derived from [C₁₃H₂₇PPh₃]⁺[Br]⁻ under the optimised conditions employed for the conversion of **55** into olefins (*E*)-**57** and (*Z*)-**58**, which resulted in formation of a complex mixture of products. When the reaction was run using THF as the solvent alone, a similarly complex mixture was formed although this time a 90:10 ratio of olefin (*Z*)-**86** (³*J* = 10.6 Hz) to starting material **82** was evident. It was again not possible to accurately assess the reaction diastereoselectivity due to peak overlap and the complexity of the ¹H NMR spectrum of the crude reaction mixture. Chromatography gave an impure sample of (*Z*)-**86** in ~35% isolated yield and >95:5 dr. In contrast, Julia-Kociński olefination²² of aldehyde **82** using sulfone **84** [prepared via *S*-alkylation of PTSH with 1-bromotridecane and then *S*-oxidation of the intermediate sulfide **83**] delivered an 82:18 mixture of (*E*)-**85** and (*Z*)-**86** in 69% combined yield. Peak overlap in the ¹H NMR spectrum did not allow ³*J* coupling constant analysis for the major component, although the known olefin geometry of (*Z*)-**86** allowed its assignment as (*E*)-**85**; the ¹³C NMR chemical shifts of the allylic carbon atoms [C(4) and C(7)] of both (*E*)-**85** and (*Z*)-**86** were consistent with these assignments (γ -effect).²⁰ Treatment of the 82:18 mixture of (*E*)-**85** and (*Z*)-**86** with TBAF over 18 h resulted in incomplete conversion to an 82:18 mixture of the corresponding *O*-desilylated compounds (*E*)-**87** and (*Z*)-**88**, from which an 82:18 mixture of starting materials (*E*)-**85** and (*Z*)-**86** were isolated in 21% combined yield, an 82:18 mixture of (*E*)-**87** and (*Z*)-**88** in 68% combined yield. Although complete *O*-desilylation of (*E*)-**85** and (*Z*)-**86** was observed after a reaction time of 84 h (giving an 82:18 mixture of (*E*)-**87** and (*Z*)-**88** in 61% combined yield), use of HF·pyridine effected complete *O*-desilylation of (*E*)-**85** and (*Z*)-**86** within 18 h to give an 82:18 mixture of (*E*)-**87** and (*Z*)-**88** in 86% combined yield. Sufficient resonance dispersion in the ¹H NMR spectrum of this mixture allowed ³*J* coupling constant analysis of the major product (*E*)-**87**, which displayed ³*J* = 15.7 Hz between the olefinic protons, consistent with the (*E*)-olefin geometry. A TOCSY experiment allowed decoupling of the allylic protons in the minor isomer (*Z*)-**88** and revealed ³*J* = 10.9 Hz between the olefinic protons, consistent with the (*Z*)-olefin geometry. Once again, the ¹³C NMR chemical shifts of the allylic carbon atoms [C(4) and C(7)] of both (*E*)-**87** and (*Z*)-**88** were consistent with

these assignments (γ -effect).²⁰ Ensuing hydrogenolysis of the 82:18 mixture of (*E*)-**87** and (*Z*)-**88**, and then peracetylation of the crude reaction mixture (for ease of purification) gave 3-deoxy-3-aminosphingoid base derivative **89** in 72% yield and >99:1 dr. The overall yield of **89** was 15% in thirteen steps from L-serine, or 3% (out of a theoretical maximum of 50%) in thirteen steps from DL-serine. The major difference contributing to the superior efficiency of the former over the latter route reflects the differing proficiencies of the enolate oxidation steps (Scheme 16).

SCHEME 16^a



^aReagents and conditions: (i) DIBAL-H, PhMe, -78°C to rt, 18 h; (ii) IBX, DMSO, rt, 18 h; (iii) **84**, LiHMDS, THF, rt, 18 h; (iv) HF-pyridine, THF, rt, 18 h; (v) H_2 , $\text{Pd}(\text{OH})_2/\text{C}$, HCl (1.25 M in MeOH), rt, 72 h; (vi) Ac_2O , DMAP, pyridine, rt, 72 h; (vii) K_2CO_3 , PTSH, acetone, 65°C , 2.5 h; (viii) H_2O_2 (30% aq), $(\text{NH}_4)_2\text{Mo}_7\text{O}_{24}\cdot 4\text{H}_2\text{O}$, EtOH, rt, 18 h.

Conclusion

In conclusion, the asymmetric syntheses of a range of *N*- and *O*-protected 3-deoxy-3-aminosphingoid bases have been achieved from DL-serine and/or L-serine. The approach from DL-serine relies on the parallel kinetic resolution of a racemic *N,N*-dibenzyl-protected γ -amino- α,β -unsaturated ester upon conjugate addition of a pseudoenantiomeric mixture of lithium (*R*)-*N*-benzyl-*N*-(α -methylbenzyl)amide and lithium (*S*)-*N*-3,4-dimethoxybenzyl-*N*-(α -methylbenzyl)amide, giving the corresponding enantio- and diastereoisomerically pure β,γ -diamino esters. The approach from L-serine relies on the doubly diastereoselective conjugate additions of the antipodes of lithium *N*-benzyl-*N*-(α -methylbenzyl)amide to the same *N,N*-dibenzyl-protected γ -amino- α,β -unsaturated ester but in enantiomerically pure form; in both cases

the conjugate addition reactions proceed under the dominant stereocontrol of the lithium amide reagents to give the corresponding enantiomerically pure β,γ -diamino esters. The incorporation of an enolate oxidation (rather than protonation) into both of these protocols allows access to the corresponding α -hydroxy- β,γ -diamino esters. The β,γ -diamino esters and α -hydroxy- β,γ -diamino esters were then elaborated using the ester functionality as a synthetic handle to give protected forms of the corresponding 3-deoxy-3-aminosphingoid bases.

Experimental Section

General Experimental Details. Reactions involving moisture-sensitive reagents were carried out under a nitrogen 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.²³ Organic layers were dried over MgSO_4 . Flash column chromatography was performed on Kieselgel 60 silica.

Melting points are uncorrected. Specific rotations are reported in $10^{-1} \text{ deg cm}^2 \text{ g}^{-1}$ and concentrations in g/100 mL. IR spectra were recorded using an ATR module. Selected characteristic peaks are reported in cm^{-1} . NMR spectra were recorded in the deuterated solvent stated. The field was locked by external referencing to the relevant deuteron resonance. ^1H – ^1H COSY and ^1H – ^{13}C HMQC analyses were used to establish atom connectivity. Accurate mass measurements were run on a MicroTOF instrument internally calibrated with polyalanine.

X-ray Crystal Structure Determination.¹⁵ Data were collected using graphite monochromated $\text{Cu-K}\alpha$ radiation using standard procedures at 150 K. The structures were solved by direct methods (SIR92); all non-hydrogen atoms were refined with anisotropic thermal parameters. Hydrogen atoms were added at idealised positions. The structures were refined using CRYSTALS.²⁴

Benzyl (*RS*)-2-(*N,N*-dibenzylamino)-3-hydroxypropanoate (*RS*)-38. K_2CO_3 (78.9 g, 572 mmol) and BnBr (67.9 mL, 572 mmol) were added sequentially to a stirred solution of DL-serine (20.0 g, 190 mmol) in H_2O (300 mL) and the resultant solution was stirred at reflux for 18 h. The resultant solution was allowed to cool to rt and then extracted with Et_2O ($3 \times 300 \text{ mL}$). The combined organics were washed with brine (500 mL), dried and concentrated in vacuo. Vacuum distillation gave (*RS*)-38 as a pale yellow oil (39.6 g, 55%);²⁵ δ_{H} (400 MHz, CDCl_3) 2.15–2.79 (1H, br s, OH), 3.57–3.69 (1H, m, $\text{C}(3)H_{\text{A}}$) overlapping 3.64 (2H, d, J 13.5, $\text{N}(\text{CH}_\text{A}\text{H}_\text{B}\text{Ph})_2$), 3.72–3.84 (2H, m, $\text{C}(2)H$, $\text{C}(3)H_{\text{B}}$), 3.89 (2H, d, J 13.5, $\text{N}(\text{CH}_\text{A}\text{H}_\text{B}\text{Ph})_2$), 5.23 (1H, d, J 12.2, $\text{OCH}_\text{A}\text{H}_\text{B}\text{Ph}$), 5.30 (1H, d, J 12.2, $\text{OCH}_\text{A}\text{H}_\text{B}\text{Ph}$), 7.22–7.44 (15H, m, Ph).

Benzyl (RS)-2-(N,N-dibenzylamino)-3-(triisopropylsilyloxy)propanoate (RS)-39. TIPSCl (1.03 g, 5.33 mmol) and imidazole (726 mg, 10.7 mmol) were added sequentially to a stirred solution of (RS)-**38** (1.00 g, 2.67 mmol) in DMF (10 mL) and the resultant solution was stirred at rt for 18 h. Brine (10 mL) was added and the aqueous layer was extracted with CH₂Cl₂ (3 × 30 mL). The combined organics were dried and concentrated in vacuo. Purification via flash column chromatography (eluent 30–40 °C petroleum ether/EtOAc, 30:1) gave (RS)-**39** as a colourless oil (1.15 g, 81%); ν_{\max} 1734 (C=O); δ_{H} (500 MHz, CDCl₃) 0.95–1.05 (21H, m, Si(CHMe₂)₃), 3.60 (1H, app t, *J* 6.3, C(2)*H*), 3.67 (2H, d, *J* 14.2, N(CH_AH_BPh)₂), 3.94 (2H, d, *J* 14.2, N(CH_AH_BPh)₂) overlapping 3.95–3.99 (1H, m, C(3)*H_A*), 4.12 (1H, dd, *J* 10.7, 6.6, C(3)*H_B*), 5.14 (1H, d, *J* 12.3, OCH_AH_BPh), 5.29 (1H, d, *J* 12.3, OCH_AH_BPh), 7.19–7.43 (15H, m, *Ph*); δ_{C} (125 MHz, CDCl₃) 11.9 (Si(CHMe₂)₃), 17.9 (Si(CHMe₂)₃), 55.5 (N(CH₂Ph)₂), 63.2 (C(2)), 63.4 (C(3)), 66.0 (OCH₂Ph), 126.8, 126.9 (*p-Ph*), 128.2, 128.4, 128.5, 128.7 (*o,m-Ph*), 136.1, 139.8 (*i-Ph*), 171.4 (C(1)); *m/z* (ESI⁺) 554 ([M+Na]⁺, 96%), 532 ([M+H]⁺, 100%); HRMS (ESI⁺) C₃₃H₄₆NO₃Si⁺ ([M+H]⁺) requires 532.3241; found 524.3241.

Methyl (RS)-2-amino-3-hydroxypropanoate hydrochloride (RS)-40. AcCl (2.03 mL, 28.6 mmol) was added dropwise to stirred MeOH (12 mL) at 0 °C and the resultant solution was stirred at 0 °C for 15 min. DL-Serine (1.00 g, 9.52 mmol) was added portionwise and the resultant solution was stirred at reflux for 3 h, then allowed to cool to rt and concentrated in vacuo. Recrystallization (MeOH) gave (RS)-**40** as a white solid (1.26 g, 85%);⁹ mp 130–132 °C; δ_{H} (400 MHz, D₂O) 3.70 (3H, s, *OMe*), 3.83 (1H, dd, *J* 12.7, 3.5, C(3)*H_A*), 3.95 (1H, dd, *J* 12.7, 4.1, C(3)*H_B*), 4.13 (1H, app t, *J* 3.8, C(2)*H*).

Methyl (S)-2-amino-3-hydroxypropanoate hydrochloride (S)-40. AcCl (2.03 mL, 28.6 mmol) was added dropwise to stirred MeOH (12 mL) at 0 °C and the resultant solution was stirred at 0 °C for 15 min. L-Serine (1.00 g, 9.52 mmol) was added portionwise and the resultant solution was stirred at reflux for 3 h, then allowed to cool to rt and concentrated in vacuo. Recrystallization (MeOH) gave (S)-**40** as a white solid (1.34 g, 91%);⁹ mp 164–166 °C; [α]_D²⁰ +4.2 (*c* 1.0 in MeOH).

Methyl (RS)-2-(N,N-dibenzylamino)-3-hydroxypropanoate (RS)-41. K₂CO₃ (2.89 g, 20.9 mmol) and BnBr (1.24 mL, 10.4 mmol) were added sequentially to a stirred solution of (RS)-**40** (650 mg, 4.18 mmol) in MeCN (8 mL) and the resultant solution was stirred at rt for 24 h. H₂O (10 mL) was added and the aqueous layer was extracted with EtOAc (3 × 10 mL). The combined organics were dried and concentrated in vacuo. Purification via flash column chromatography (eluent 30–40 °C petroleum ether/EtOAc, 8:1) gave (RS)-**41** as a colourless oil (1.11 g, 89%);⁹ δ_{H} (400 MHz, CDCl₃) 2.58 (1H, br s, *OH*), 3.59 (1H, dd, *J* 15.1, 7.6, C(3)*H_A*), 3.69 (2H, d, *J* 13.4, N(CH_AH_BPh)₂), 3.68–3.79 (2H, m, C(2)*H*, C(3)*H_B*), 3.80 (3H, s, *OMe*), 3.91 (2H, d, *J* 13.4, N(CH_AH_BPh)₂), 7.20–7.39 (10H, m, *Ph*).

Methyl (S)-2-(N,N-dibenzylamino)-3-hydroxypropanoate (S)-41. K₂CO₃ (2.89 g, 20.9 mmol) and BnBr (1.24 mL, 10.4 mmol) were added sequentially to a stirred solution of (S)-**40** (650 mg, 4.18 mmol) in MeCN (8 mL) and the resultant solution was stirred at rt for 24 h. H₂O (10 mL) was added and the aqueous layer was extracted with EtOAc (3 × 10 mL). The combined organics were dried and concentrated in vacuo. Purification via flash column chromatography (eluent 30–40 °C petroleum ether/EtOAc, 8:1) gave (S)-**41** as a colourless oil (1.16 g, 93%);⁹ [α]_D²⁰ –167.1 (*c* 1.0 in CHCl₃).

Methyl (RS)-2-(N,N-dibenzylamino)-3-(triisopropylsilyloxy)propanoate (RS)-42. *Method A.* From (RS)-**41**. TIPSCl (644 mg, 3.34 mmol) and imidazole (455 mg, 6.68 mmol) were added sequentially to a stirred solution of (RS)-**41** (500 mg, 1.67 mmol) in DMF (10 mL) and the resultant solution was stirred at rt for 18 h. Brine (5 mL) was added and the aqueous layer was extracted with CH₂Cl₂ (3 × 15 mL). The combined organics were dried and concentrated in vacuo. Purification via flash column chromatography (eluent 30–40 °C petroleum ether/EtOAc, 30:1) gave (RS)-**42** as a colourless oil (661 mg, 87%); ν_{\max} 1738 (C=O); δ_{H} (400 MHz, CDCl₃) 0.95–1.07 (21H, m, Si(CHMe₂)₃), 3.57 (1H, app t, *J* 6.0, C(2)*H*), 3.70 (2H, d, *J* 14.2, N(CH_AH_BPh)₂), 3.75 (3H, s, OMe), 3.93–4.01 (3H, m, N(CH_AH_BPh)₂, C(3)*H_A*), 4.10 (1H, dd, *J* 9.9, 6.5, C(3)*H_B*), 7.19–7.43 (10H, m, *Ph*); δ_{C} (100 MHz, CDCl₃) 11.9 (Si(CHMe₂)₃), 17.9 (Si(CHMe₂)₃), 51.1 (OMe), 55.5 (N(CH₂Ph)₂), 63.3 (C(2), C(3)), 126.9 (*p-Ph*), 128.2, 128.7 (*o,m-Ph*), 139.9 (*i-Ph*), 172.1 C(1); *m/z* (ESI⁺) 478 ([M+Na]⁺, 100%), 456 ([M+H]⁺, 98%); HRMS (ESI⁺) C₂₇H₄₂NO₃Si⁺ ([M+H]⁺) requires 456.2928; found 456.2925.

Method B. Telescoped Procedure from DL-Serine. Step 1. AcCl (7.1 mL, 99.9 mmol) was added dropwise to stirred MeOH (40 mL) at 0 °C and the resultant solution was stirred at 0 °C for 15 min. DL-Serine (3.50 g, 33.3 mmol) was added portionwise and the resultant solution was stirred at reflux for 3 h, then allowed to cool to rt and concentrated in vacuo to give (RS)-**40** as a white solid (5.29 g).

Step 2. K₂CO₃ (23.0 g, 166 mmol) and BnBr (9.89 mL, 83.3 mmol) were added sequentially to a stirred solution of the residue (RS)-**40** (5.29 g) from the previous step in MeCN (80 mL) and the resultant solution was stirred at rt for 24 h. H₂O (100 mL) was added and the aqueous layer was extracted with EtOAc (3 × 100 mL). The combined organics were dried and concentrated in vacuo to give (RS)-**41** as a yellow oil (11.2 g).

Step 3. TIPSCl (12.8 g, 66.6 mmol) and imidazole (9.07 g, 133 mmol) were added sequentially to a stirred solution of the residue (RS)-**41** (11.2 g) from the previous step in DMF (30 mL) and the resultant solution was stirred at rt for 18 h. Brine (60 mL) was added and the aqueous layer was extracted with CH₂Cl₂ (3 × 300 mL). The combined organics were dried and concentrated in vacuo. Purification via flash

column chromatography (eluent 30–40 °C petroleum ether/EtOAc, 30:1) gave (*RS*)-**42** as a colourless oil (12.4 g, 82%).

Methyl (*S*)-2-(*N,N*-dibenzylamino)-3-(triisopropylsilyloxy)propanoate (*S*)-42. *Method A.* From (*S*)-**41**. TIPSCl (644 mg, 3.34 mmol) and imidazole (455 mg, 6.68 mmol) were added sequentially to a stirred solution of (*S*)-**41** (500 mg, 1.67 mmol) in DMF (10 mL) and the resultant solution was stirred at rt for 18 h. Brine (10 mL) was added and the aqueous layer was extracted with CH₂Cl₂ (3 × 15 mL). The combined organics were dried and concentrated in vacuo. Purification via flash column chromatography (eluent 30–40 °C petroleum ether/EtOAc, 30:1) gave (*S*)-**42** as a colourless oil (676 mg, 89%); [α]_D²⁰ –44.2 (*c* 1.0 in CHCl₃).

Method B. Telescoped Procedure from L-Serine. Step 1. AcCl (10.1 mL, 143 mmol) was added dropwise to stirred MeOH (60 mL) at 0 °C and the resultant solution was stirred at 0 °C for 15 min. L-Serine (5.00 g, 47.6 mmol) was added portionwise and the resultant solution was stirred at reflux for 3 h, then allowed to cool to rt and concentrated in vacuo to give (*S*)-**40** as a white solid (7.21 g).

Step 2. K₂CO₃ (32.9 g, 238 mmol) and BnBr (14.1 mL, 119 mmol) were added sequentially to a stirred solution of the residue (*S*)-**40** (7.21 g) from the previous step in MeCN (120 mL) and the resultant solution was stirred at rt for 24 h. H₂O (150 mL) was added and the aqueous layer was extracted with EtOAc (3 × 300 mL). The combined organics were dried and concentrated in vacuo to give (*S*)-**41** as a yellow oil (27.8 g).

Step 3. TIPSCl (18.3 g, 94.9 mmol) and imidazole (12.9 g, 189 mmol) were added sequentially to a stirred solution of the residue (*S*)-**41** (27.8 g) from the previous step in DMF (140 mL) and the resultant solution was stirred at rt for 18 h. Brine (200 mL) was added and the aqueous layer was extracted with CH₂Cl₂ (3 × 300 mL). The combined organics were dried and concentrated in vacuo. Purification via flash column chromatography (eluent 30–40 °C petroleum ether/EtOAc, 30:1) gave (*S*)-**42** as a colourless oil (18.8 g, 87%); [α]_D²⁰ –43.1 (*c* 1.0 in CHCl₃).

(*RS*)-2-(*N,N*-Dibenzylamino)-3-(triisopropylsilyloxy)propan-1-ol (*RS*)-43. *Method A.* From (*RS*)-**39**. DIBAL-H (1.0 M in PhMe, 2.35 mL, 2.35 mmol) was added dropwise to a stirred solution of (*RS*)-**39** (500 mg, 0.940 mmol) in PhMe (2 mL) at –78 °C and the resultant solution was stirred at –78 °C for 1 h. MeOH (1 mL) was added dropwise and the resultant solution was allowed to warm to rt, then diluted with CH₂Cl₂ (15 mL) and satd aq Rochelle salt (15 mL). The resultant biphasic mixture was stirred vigorously at rt for 18 h and then the aqueous layer was extracted with CH₂Cl₂ (3 × 15 mL). The combined organics were dried and concentrated in vacuo. Purification via flash column chromatography (eluent 30–40 °C petroleum ether/Et₂O, 20:1) gave (*RS*)-**43** as a colourless oil (350 mg, 87%); ν_{max} 3451 (O–H); δ_{H} (500 MHz, CDCl₃)

1.05–1.17 (21H, m, Si(CHMe₂)₃), 2.93 (1H, br s, OH), 3.03 (1H, m, C(2)H), 3.57–3.65 (2H, m, C(1)H₂), 3.68 (2H, d, *J* 13.6, N(CH_AH_BPh)₂), 3.83 (1H, dd, *J* 10.4, 6.3, C(3)H_A), 3.91 (2H, d, *J* 13.6, N(CH_AH_BPh)₂), 3.97 (1H, dd, 10.4, 6.0, C(3)H_B), 7.22–7.34 (10H, m, *Ph*); δ_C (125 MHz, CDCl₃) 11.7 (Si(CHMe₂)₃), 17.7 (Si(CHMe₂)₃), 54.1 (N(CH₂Ph)₂), 59.8 (C(1)), 60.0 (C(2)), 61.5 (C(3)), 127.1 (*p-Ph*), 128.4, 128.9 (*o,m-Ph*), 139.9 (*i-Ph*); *m/z* (ESI⁺) 450 ([M+Na]⁺, 100%), 428 ([M+H]⁺, 98%); HRMS (ESI⁺) C₂₆H₄₂NO₂Si⁺ ([M+H]⁺) requires 428.2979; found 428.2975.

Method B. From (RS)-42. DIBAL-H (1.0 M in PhMe, 1.65 mL, 1.65 mmol) was added dropwise to a stirred solution of (RS)-42 (300 mg, 0.658 mmol) in PhMe (2 mL) at –78 °C and the resultant solution was stirred at –78 °C for 1 h. MeOH (1 mL) was added dropwise and the resultant solution was allowed to warm to rt, then diluted with CH₂Cl₂ (15 mL) and satd aq Rochelle salt (15 mL). The resultant biphasic mixture was stirred vigorously at rt for 18 h and then the aqueous layer was extracted with CH₂Cl₂ (3 × 15 mL). The combined organics were dried and concentrated in vacuo. Purification via flash column chromatography (eluent 30–40 °C petroleum ether/Et₂O, 20:1) gave (RS)-43 as a colourless oil (221 mg, 78%).

(R)-2-(N,N-Dibenzylamino)-3-(triisopropylsilyloxy)propan-1-ol (R)-43. DIBAL-H (1.0 M in PhMe, 1.10 mL, 1.10 mmol) was added dropwise to a stirred solution of (S)-42 (200 mg, 0.439 mmol) in PhMe (2 mL) at –78 °C and the resultant solution was stirred at –78 °C for 1 h. MeOH (1 mL) was added dropwise and the resultant solution was allowed to warm to rt, then diluted with CH₂Cl₂ (15 mL) and satd aq Rochelle salt (15 mL). The resultant biphasic mixture was stirred vigorously at rt for 18 h and then the aqueous layer was extracted with CH₂Cl₂ (3 × 15 mL). The combined organics were dried and concentrated in vacuo. Purification via flash column chromatography (eluent 30–40 °C petroleum ether/Et₂O, 20:1) gave (R)-43 as a colourless oil (128 mg, 68%); [α]_D²⁰ –50.2 (*c* 1.0 in CHCl₃).

tert-Butyl (RS,E)-4-(N,N-dibenzylamino)-5-(triisopropylsilyloxy)pent-2-enoate (RS)-44. Method A. From (RS)-43. A solution of DMSO (97 μL, 1.37 mmol) in CH₂Cl₂ (5 mL) at –78 °C was added dropwise to a stirred solution of (COCl)₂ (108 μL, 1.26 mmol) in CH₂Cl₂ (5 mL) at –78 °C, and the resultant solution was stirred at –78 °C for 10 min. A solution of (RS)-43 (450 mg, 1.05 mmol) in CH₂Cl₂ (5 mL) at –78 °C was then added dropwise via cannula and the resultant solution was stirred at –78 °C for 1 h. Et₃N (293 μL, 2.10 mmol) was then added dropwise and the resultant solution was allowed to warm to rt. Ph₃P=CHCO₂^tBu (395 mg, 1.05 mmol) was then added and the resultant solution was stirred at rt for 18 h. The resultant solution was washed with satd aq Na₂CO₃ (20 mL) and the aqueous layer was extracted with CH₂Cl₂ (3 × 25 mL). The combined organics were dried and concentrated in vacuo. Purification via flash column chromatography (eluent 30–40 °C petroleum ether/Et₂O, 30:1) gave (RS)-44 as a pale yellow oil (395 mg, 72%, >99:1 dr [(E):(Z) ratio]); ν_{max} 1714 (C=O), 1650 (C=C); δ_H (500 MHz, CDCl₃) 1.00–1.06 (21H, m,

Si(CHMe₂)₃), 1.51 (9H, s, CMe₃), 3.42 (1H, m, C(4)H), 3.64 (2H, d, *J* 13.9, N(CH_AH_BPh)₂) 3.82–3.91 (3H, m, C(5)H_A, N(CH_AH_BPh)₂), 3.94–3.99 (1H, dd, *J* 10.1, 6.9, C(5)H_B), 5.95 (1H, dd, *J* 15.8, 1.3, C(2)H), 6.97 (1H, dd, *J* 15.8, 6.9, C(3)H), 7.19–7.41 (10H, m, *Ph*); δ_C (125 MHz, CDCl₃) 28.1 (CMe₃), 54.7 (N(CH₂Ph)₂), 60.7 (C(4)), 64.0 (C(5)), 80.3 (CMe₃), 126.8 (*p-Ph*), 128.2, 128.5 (*o,m-Ph*), 140.0 (*i-Ph*) 125.6 (C(2)), 144.7 (C(3)), 165.7 (C(1)); *m/z* (ESI⁺) 546 ([M+Na]⁺, 15%), 524 ([M+H]⁺, 100%); HRMS (ESI⁺) C₃₂H₅₀NO₃Si⁺ ([M+H]⁺) requires 524.3554; found 524.3556.

Method B. Telescoped Procedure from (RS)-42. *Step 1.* DIBAL-H (1.0 M in PhMe, 68.1 mL, 68.1 mmol) was added dropwise to a stirred solution of (RS)-42 (12.4 g, 27.2 mmol) in PhMe (80 mL) at –78 °C and the resultant solution was stirred at –78 °C for 1 h. MeOH (40 mL) was added dropwise and the resultant solution was allowed to warm to rt, then diluted with CH₂Cl₂ (300 mL) and satd aq Rochelle salt (300 mL). The resultant biphasic mixture was stirred vigorously at rt for 18 h and then the aqueous layer was extracted with CH₂Cl₂ (3 × 300 mL). The combined organics were dried and concentrated in vacuo to give (RS)-43 as a colourless oil (11.4 g).

Step 2. A solution of DMSO (2.51 mL, 35.4 mmol) in CH₂Cl₂ (10 mL) at –78 °C was added dropwise to a stirred solution of (COCl)₂ (2.80 mL, 32.7 mmol) in CH₂Cl₂ (100 mL) at –78 °C, and the resultant solution was stirred at –78 °C for 10 min. A solution of the residue (RS)-43 (11.4 g) from the previous step in CH₂Cl₂ (50 mL) at –78 °C was then added dropwise via cannula and the resultant solution was stirred at –78 °C for 1 h. Et₃N (7.59 mL, 54.4 mmol) was then added dropwise and the resultant solution was allowed to warm to rt. Ph₃P=CHCO₂^tBu (10.2 g, 27.2 mmol) was then added and the resultant solution was stirred at rt for 18 h. The resultant solution was washed with satd aq Na₂CO₃ (200 mL) and the aqueous layer was extracted with CH₂Cl₂ (3 × 300 mL). The combined organics were dried and concentrated in vacuo. Purification via flash column chromatography (eluent 30–40 °C petroleum ether/Et₂O, 30:1) gave (RS)-44 as a pale yellow oil (11.2 g, 79%, >99:1 dr [(*E*):(*Z*) ratio]).

tert-Butyl (R,E)-4-(N,N-dibenzylamino)-5-(triisopropylsilyloxy)pent-2-enoate (R)-44. *Method A. From (R)-43.* A solution of DMSO (21.6 μL, 0.304 mmol) in CH₂Cl₂ (1 mL) at –78 °C was added dropwise to a stirred solution of (COCl)₂ (24.1 μL, 0.281 mmol) in CH₂Cl₂ (1 mL) at –78 °C, and the resultant solution was stirred at –78 °C for 10 min. A solution of (R)-43 (100 mg, 0.233 mmol) in CH₂Cl₂ (1 mL) at –78 °C was then added dropwise via cannula and the resultant solution was stirred at –78 °C for 1 h. Et₃N (65.2 μL, 0.468 mmol) was then added dropwise and the resultant solution was allowed to warm to rt. Ph₃P=CHCO₂^tBu (88.0 mg, 0.233 mmol) was then added and the resultant solution was stirred at rt for 18 h. The resultant solution was washed with satd aq Na₂CO₃ (2 mL) and the aqueous layer was extracted with CH₂Cl₂ (3 × 5 mL). The combined organics were dried and concentrated in vacuo. Purification via flash

column chromatography (eluent 30–40 °C petroleum ether/Et₂O, 30:1) gave (*R*)-**44** as a pale yellow oil (106 mg, 88%, >99:1 dr [(*E*):(*Z*) ratio]); [α]_D²⁰ –16.0 (*c* 1.0 in CHCl₃).

Method B. Telescoped Procedure from (S)-42. Step 1. DIBAL-H (1.0 M in PhMe, 103 mL, 103 mmol) was added dropwise to a stirred solution of (*S*)-**42** (18.8 g, 41.3 mmol) in PhMe (80 mL) at –78 °C and the resultant solution was stirred at –78 °C for 1 h. MeOH (40 mL) was added dropwise and the resultant solution was allowed to warm to rt, then diluted with CH₂Cl₂ (300 mL) and satd aq Rochelle salt (300 mL). The resultant biphasic mixture was stirred vigorously at rt for 18 h and then the aqueous layer was extracted with CH₂Cl₂ (3 × 300 mL). The combined organics were dried and concentrated in vacuo to give (*R*)-**43** as a colourless oil (17.6 g).

Step 2. A solution of DMSO (3.81 mL, 53.6 mmol) in CH₂Cl₂ (20 mL) at –78 °C was added dropwise to a stirred solution of (COCl)₂ (4.25 mL, 49.5 mmol) in CH₂Cl₂ (100 mL) at –78 °C, and the resultant solution was stirred at –78 °C for 10 min. A solution of the residue (*R*)-**43** (17.6 g) from the previous step in CH₂Cl₂ (50 mL) at –78 °C was then added dropwise via cannula and the resultant solution was stirred at –78 °C for 1 h. Et₃N (11.5 mL, 82.5 mmol) was then added dropwise and the resultant solution was allowed to warm to rt. Ph₃P=CHCO₂^tBu (15.5 g, 41.3 mmol) was then added and the resultant solution was stirred at rt for 18 h. The resultant solution was washed with satd aq Na₂CO₃ (200 mL) and the aqueous layer was extracted with CH₂Cl₂ (3 × 300 mL). The combined organics were dried and concentrated in vacuo. Purification via flash column chromatography (eluent 30–40 °C petroleum ether/Et₂O, 30:1) gave (*R*)-**44** as a pale yellow oil (18.7 g, 87%, >99:1 dr [(*E*):(*Z*) ratio], 99% ee); [α]_D²⁰ –28.0 (*c* 1.0 in CHCl₃).

(*RS*)-**44** was analysed by chiral HPLC, giving complete resolution of enantiomers (Chiralpak AD-H; mobile phase hexane; flow rate 1.0 mL/min; (*S*)-**44** *t*_R = 7.78 min; (*R*)-**44** *t*_R = 8.76 min). The sample of (*R*)-**44** was thence assessed to be 99% ee.

***tert*-Butyl (RS,SR)-3-(*N*-benzyl-*N*-isopropylamino)-4-(*N,N*-dibenzylamino)-5-(triisopropylsilyloxy)pentanoate 45.** *Substrate Control.* BuLi (2.2 M in hexanes, 0.34 mL, 0.75 mmol) was added dropwise to a stirred solution of *N*-benzyl-*N*-isopropylamine (114 mg, 0.764 mmol) in THF (3 mL) at –78 °C and the resultant solution was stirred at –78 °C for 30 min. A solution of (*RS*)-**44** (200 mg, 0.382 mmol, >99:1 dr [(*E*):(*Z*) ratio]) in THF (1.5 mL) at –78 °C was added dropwise via cannula and the resultant solution was stirred at –78 °C for 2 h. Satd aq NH₄Cl (1 mL) was then added and the resultant solution was allowed to warm to rt and then concentrated in vacuo. The residue was suspended in 10% aq citric acid (10 mL) and extracted with CH₂Cl₂ (3 × 25 mL). The combined organics were washed sequentially with satd aq NaHCO₃ (10 mL) and brine (10 mL), then dried and concentrated in vacuo to give a 96:4 mixture of **45** and **46**, respectively. Purification via flash column chromatography (eluent 30–40 °C petroleum ether/EtOAc,

20:1) gave an impure sample of **46** as a colourless oil (5 mg, <5%); ν_{\max} 1723 (C=O); δ_{H} (500 MHz, CDCl_3) 0.94 (3H, d, J 6.0, NCHMe_A), 1.01 (3H, d, J 6.6, NCHMe_B), 1.15–1.24 (21H, m, $\text{Si}(\text{CHMe}_2)_3$), 1.47 (9H, s, CMe_3), 2.09 (1H, dd, J 16.7, 6.3, $\text{C}(2)H_A$), 2.62–2.73 (1H, m, NCHMe_2), 2.81 (1H, m, $\text{C}(4)H$), 3.10 (1H, dd, J 16.7, 3.2, $\text{C}(2)H_B$), 3.18–3.36 (2H, m, $\text{C}(3)H$, $\text{NCH}_A\text{H}_B\text{Ph}$), 3.40 (1H, d, J 14.5, $\text{NCH}_A\text{H}_B\text{Ph}$), 3.70–3.96 (5H, m, $\text{C}(5)H_A$, $\text{N}(\text{CH}_2\text{Ph})_2$), 4.25–4.39 (1H, m, $\text{C}(5)H_B$), 7.16–7.30 (15H, m, Ph); δ_{C} (125 MHz, CDCl_3) 12.0 ($\text{Si}(\text{CHMe}_2)_3$), 18.1 (NCHMe_A), 18.3 ($\text{Si}(\text{CHMe}_2)_3$), 22.5 (NCHMe_B), 28.2 (CMe_3), 34.6 ($\text{C}(2)$), 48.3 (NCHMe_2), 50.0 (NCH_2Ph), 53.8 ($\text{C}(3)$), 54.6 ($\text{N}(\text{CH}_2\text{Ph})_2$), 59.8 ($\text{C}(4)$), 65.6 ($\text{C}(5)$), 80.0 (CMe_3), 126.4, 126.5 ($p\text{-Ph}$), 127.9, 127.9, 128.7, 129.6 ($o,m\text{-Ph}$), 140.6, 141.2 ($i\text{-Ph}$), 173.9 ($\text{C}(1)$); m/z (ESI^+) 695 ($[\text{M}+\text{Na}]^+$, 36%), 673 ($[\text{M}+\text{H}]^+$, 100%); HRMS (ESI^+) $\text{C}_{42}\text{H}_{65}\text{N}_2\text{O}_3\text{Si}^+$ ($[\text{M}+\text{H}]^+$) requires 673.4759; found 673.4761. Further elution gave **45** as a colourless oil (145 mg, 57%, >99:1 dr); ν_{\max} 1724 (C=O); δ_{H} (500 MHz, CDCl_3) 0.94 (3H, d, J 6.6, NCHMe_A) overlapping 0.96 (3H, d, J 6.6, NCHMe_B), 1.11–1.24 (21H, m, $\text{Si}(\text{CHMe}_2)_3$), 1.44 (9H, s, CMe_3), 2.51 (1H, dd, J 15.8, 4.7, $\text{C}(2)H_A$), 2.71 (1H, dd, J 15.8, 6.9, $\text{C}(2)H_B$), 2.91 (1H, septet, J 6.6, NCHMe_2), 3.00 (1H, m, $\text{C}(4)H$), 3.52 (1H, d, J 15.0, $\text{NCH}_A\text{H}_B\text{Ph}$) overlapping 3.54–3.59 (1H, m, $\text{C}(3)H$), 3.64 (2H, d, J 14.0, $\text{N}(\text{CH}_A\text{H}_B\text{Ph})_2$), 3.71 (1H, d, J 15.0, $\text{NCH}_A\text{H}_B\text{Ph}$), 3.84 (2H, d, J 14.0, $\text{N}(\text{CH}_A\text{H}_B\text{Ph})_2$), 3.92 (1H, dd, J 10.4, 6.9, $\text{C}(5)H_A$), 4.12 (1H, dd, J 10.4, 6.9, $\text{C}(5)H_B$), 7.17–7.33 (15H, m, Ph); δ_{C} (125 MHz, CDCl_3) 12.0 ($\text{Si}(\text{CHMe}_2)_3$), 18.2, 18.3 ($\text{Si}(\text{CHMe}_2)_3$, NCHMe_A), 22.0 (NCHMe_B), 28.1 (CMe_3), 34.9 ($\text{C}(2)$), 49.0 (NCHMe_2), 50.4 (NCH_2Ph), 55.4 ($\text{N}(\text{CH}_2\text{Ph})_2$), 56.5 ($\text{C}(3)$), 62.1 ($\text{C}(5)$), 63.8 ($\text{C}(4)$), 80.1 (CMe_3), 126.0, 126.5 ($p\text{-Ph}$), 127.8, 128.0, 128.2, 128.9 ($o,m\text{-Ph}$), 140.5, 141.5 ($i\text{-Ph}$), 172.8 ($\text{C}(1)$); m/z (ESI^+) 695 ($[\text{M}+\text{Na}]^+$, 13%), 673 ($[\text{M}+\text{H}]^+$, 100%); HRMS (ESI^+) $\text{C}_{42}\text{H}_{65}\text{N}_2\text{O}_3\text{Si}^+$ ($[\text{M}+\text{H}]^+$) requires 673.4759; found 673.4758.

tert-Butyl (3*RS*,4*SR*, α *SR*)-3-[*N*-benzyl-*N*-(α -methylbenzyl)amino]-4-(*N,N*-dibenzylamino)-5-(triisopropylsilyloxy)pentanoate (3*RS*,4*SR*, α *SR*)-47. *Mutual Kinetic Resolution.* BuLi (2.2 M in hexanes, 0.34 mL, 0.75 mmol) was added dropwise to a stirred solution of (*RS*)-*N*-benzyl-*N*-(α -methylbenzyl)amine (161 mg, 0.764 mmol) in THF (3 mL) at -78°C and the resultant solution was stirred at -78°C for 30 min. A solution of (*RS*)-**44** (200 mg, 0.382 mmol, >99:1 dr [$(E):(Z)$ ratio]) in THF (1.5 mL) at -78°C was added dropwise via cannula and the resultant solution was stirred at -78°C for 2 h. Satd aq NH_4Cl (1 mL) was then added and the resultant solution was allowed to warm to rt and then concentrated in vacuo. The residue was suspended in 10% aq citric acid (10 mL) and extracted with CH_2Cl_2 (3×25 mL). The combined organics were washed sequentially with satd aq NaHCO_3 (10 mL) and brine (10 mL), then dried and concentrated in vacuo. Purification via flash column chromatography (eluent $30\text{--}40^\circ\text{C}$ petroleum ether/ EtOAc , 25:1) gave (*3RS*,4*SR*, α *SR*)-**47** as a colourless oil (223 mg, 80%, >99:1 dr); $\text{C}_{47}\text{H}_{66}\text{N}_2\text{O}_3\text{Si}$ requires C, 76.8; H, 9.05; N, 3.8%; found C, 76.9; H, 9.0; N, 3.9%; ν_{\max} 1721 (C=O); δ_{H} (500 MHz, CDCl_3) 1.00–1.17 (21H, m,

Si(CHMe₂)₃), 1.30–1.36 (12H, m, C(α)Me, CMe₃), 1.78 (1H, dd, *J* 16.4, 2.5, C(2)H_A), 2.55 (1H, dd, *J* 16.4, 8.8, C(2)H_B), 2.96–3.01 (1H, m, C(4)H), 3.39 (1H, d, *J* 15.8, NCH_AH_BPh), 3.57 (2H, d, *J* 13.9, N(CH_AH_BPh)₂), 3.63–3.72 (2H, m, C(3)H, C(α)H), 3.85–3.95 (4H, m, C(5)H_A, NCH_AH_BPh, N(CH_AH_BPh)₂), 4.17 (1H, dd, *J* 10.4, 5.7, C(5)H_B), 6.91–6.95 (2H, m, *Ph*), 7.05–7.12 (3H, m, *Ph*), 7.18–7.31 (15H, m, *Ph*); δ_C (125 MHz, CDCl₃) 11.9 (Si(CHMe₂)₃), 18.2 (Si(CHMe₂)₃), 20.6 (C(α)Me), 28.0 (CMe₃), 33.3 (C(2)), 51.4 (NCH₂Ph), 55.3 (N(CH₂Ph)₂), 56.4 (C(3)), 58.4 (C(α)), 61.3 (C(5)), 64.6 (C(4)), 79.9 (CMe₃), 125.8, 126.6, 126.8, 127.5, 127.9, 127.9, 128.0, 128.3, 129.0 (*o,m,p-Ph*), 140.5, 141.5, 142.7 (*i-Ph*), 172.4 (C(1)); *m/z* (ESI⁺) 757 ([M+Na]⁺, 100%), 735 ([M+H]⁺, 100%); HRMS (ESI⁺) C₄₇H₆₇N₂O₃Si⁺ ([M+H]⁺) requires 735.4915; found 735.4909.

***tert*-Butyl (3*S*,4*R*,α*R*)-3-[*N*-benzyl-*N*-(α-methylbenzyl)amino]-4-(*N,N*-dibenzylamino)-5-(triisopropylsilyloxy)pentanoate (3*S*,4*R*,α*R*)-47 and *tert*-butyl (3*R*,4*S*,α*S*)-3-[*N*-3',4'-dimethoxybenzyl-*N*-(α-methylbenzyl)amino]-4-(*N,N*-dibenzylamino)-5-(triisopropylsilyloxy)pentanoate (3*R*,4*S*,α*S*)-48.**

Parallel Kinetic Resolution. BuLi (2.2 M in hexanes, 0.34 mL, 0.75 mmol) was added dropwise to a stirred solution of (*R*)-*N*-benzyl-*N*-(α-methylbenzyl)amine (80.7 mg, 0.382 mmol, >99% ee) and (*S*)-*N*-3,4-dimethoxybenzyl-*N*-(α-methylbenzyl)amine (104 mg, 0.382 mmol, >99% ee) in THF (3 mL) at –78 °C and the resultant solution was stirred at –78 °C for 30 min. A solution of (*RS*)-**44** (200 mg, 0.382 mmol, >99:1 dr [(*E*):(*Z*) ratio]) in THF (1.5 mL) at –78 °C was added dropwise via cannula and the resultant solution was stirred at –78 °C for 2 h. Satd aq NH₄Cl (1 mL) was then added and the resultant solution was allowed to warm to rt and then concentrated in vacuo. The residue was suspended in 10% aq citric acid (10 mL) and extracted with CH₂Cl₂ (3 × 25 mL). The combined organics were washed sequentially with satd aq NaHCO₃ (10 mL) and brine (10 mL), then dried and concentrated in vacuo to give a 50:50 mixture of (3*S*,4*R*,α*R*)-**47** and (3*R*,4*S*,α*S*)-**48**. Purification via flash column chromatography (eluent 30–40 °C petroleum ether/EtOAc, 25:1; increased to 30–40 °C petroleum ether/EtOAc, 5:1) gave (3*S*,4*R*,α*R*)-**47** as a colourless oil (121 mg, 43%, >99:1 dr); [α]_D²⁰ –0.7 (*c* 1.0 in CHCl₃). Further elution gave (3*R*,4*S*,α*S*)-**48** as a colourless oil (106 mg, 35%, >99:1 dr); C₄₉H₇₀N₂O₅Si requires C, 74.0; H, 8.9; N, 3.5%; found C, 73.9; H, 8.9; N, 3.6%; [α]_D²⁰ +3.0 (*c* 1.0 in CHCl₃); ν_{max} 1723 (C=O); δ_H (500 MHz, CDCl₃) 1.05–1.19 (21H, m, Si(CHMe₂)₃), 1.31 (9H, s, CMe₃), 1.38 (3H, d, *J* 6.9, C(α)Me), 1.72 (1H, dd, *J* 16.4, 8.2, C(2)H_A), 2.46 (1H, dd, *J* 16.4, 8.2, C(2)H_B), 3.01 (1H, m, C(4)H), 3.41 (1H, d, *J* 15.8, NCH_AH_BAr), 3.60–3.73 (4H, m, C(3)H, C(α)H, N(CH_AH_BPh)₂) overlapping 3.71 (3H, s, OMe), 3.78–3.94 (4H, m, C(5)H_A, NCH_AH_BAr, N(CH_AH_BPh)₂) overlapping 3.83 (3H, s, OMe), 4.21 (1H, dd, *J* 10.4, 6.9, C(5)H_B), 6.54–6.58 (2H, m, *Ar*), 6.63 (1H, d, *J* 7.9, *Ar*), 7.15–7.31 (15H, m, *Ph*); δ_C (125 MHz, CDCl₃) 12.0 (Si(CHMe₂)₃), 18.2 (Si(CHMe₂)₃), 19.8 (C(α)Me), 28.0 (CMe₃), 33.6 (C(2)), 50.9 (NCH₂Ar), 55.4, 55.6, 55.7 (C(α), OMe), 55.8 (N(CH₂Ph)₂), 58.1 (C(3)), 62.5 (C(5)), 63.5

(C(4)), 79.8 (CMe₃), 110.6, 110.8, 119.5, 126.5, 126.8, 127.9, 128.0, 128.3, 128.8 (C(2'), C(5'), C(6'), *o,m,p*-Ph), 133.7, 140.4, 142.5, 147.1, 148.5 (C(1'), C(3'), C(4'), *i*-Ph), 172.1 (C(1)); *m/z* (ESI⁺) 817 ([M+Na]⁺, 72%), 795 ([M+H]⁺, 100%); HRMS (ESI⁺) C₄₉H₇₁N₂O₅Si⁺ ([M+H]⁺) requires 795.5127; found 795.5128.

***tert*-Butyl (3*S*,4*R*, α *R*)-3-[*N*-benzyl-*N*-(α -methylbenzyl)amino]-4-(*N,N*-dibenzylamino)-5-triisopropylsilyloxy)pentanoate (3*S*,4*R*, α *R*)-47.** Doubly Diastereoselective “Matched” Reaction. BuLi (2.2 M in hexanes, 0.34 mL, 0.75 mmol) was added dropwise to a stirred solution of (*R*)-*N*-benzyl-*N*-(α -methylbenzyl)amine (161 mg, 0.764 mmol, >99% ee) in THF (3 mL) at –78 °C and the resultant solution was stirred at –78 °C for 30 min. A solution of (*R*)-**44** (200 mg, 0.382 mmol, >99:1 dr [(*E*):(*Z*) ratio]) in THF (1.5 mL) at –78 °C was added dropwise via cannula and the resultant solution was stirred at –78 °C for 2 h. Satd aq NH₄Cl (1 mL) was then added and the resultant solution was allowed to warm to rt and then concentrated in vacuo. The residue was suspended in 10% aq citric acid (10 mL) and extracted with CH₂Cl₂ (3 × 25 mL). The combined organics were washed sequentially with satd aq NaHCO₃ (10 mL) and brine (10 mL), then dried and concentrated in vacuo. Purification via flash column chromatography (eluent 30–40 °C petroleum ether/EtOAc, 25:1) gave (3*S*,4*R*, α *R*)-**47** as a colourless oil (267 mg, 96%, >99:1 dr); [α]_D²⁰ –0.9 (*c* 1.0 in CHCl₃).

***tert*-Butyl (3*R*,4*R*, α *S*)-3-[*N*-benzyl-*N*-(α -methylbenzyl)amino]-4-(*N,N*-dibenzylamino)-5-triisopropylsilyloxy)pentanoate (3*R*,4*R*, α *S*)-49.** Method A. Doubly Diastereoselective “Mismatched” Reaction. BuLi (2.2 M in hexanes, 0.34 mL, 0.75 mmol) was added dropwise to a stirred solution of (*S*)-*N*-benzyl-*N*-(α -methylbenzyl)amine (161 mg, 0.764 mmol, >99% ee) in THF (3 mL) at –78 °C and the resultant solution was stirred at –78 °C for 30 min. A solution of (*R*)-**44** (200 mg, 0.382 mmol, >99:1 dr [(*E*):(*Z*) ratio]) in THF (1.5 mL) at –78 °C was added dropwise via cannula and the resultant solution was stirred at –78 °C for 2 h. Satd aq NH₄Cl (1 mL) was then added and the resultant solution was allowed to warm to rt and then concentrated in vacuo. The residue was suspended in 10% aq citric acid (10 mL) and extracted with CH₂Cl₂ (3 × 25 mL). The combined organics were washed sequentially with satd aq NaHCO₃ (10 mL) and brine (10 mL), then dried and concentrated in vacuo to give an 87:13 mixture of (3*R*,4*R*, α *S*)-**49** and (3*S*,4*R*, α *S*)-**50**, respectively. Purification via flash column chromatography (eluent 30–40 °C petroleum ether/EtOAc, 25:1) gave an 87:13 mixture of (3*R*,4*R*, α *S*)-**49** and (3*S*,4*R*, α *S*)-**50**, respectively, as a colourless oil (231 mg, 83%). Data for (3*S*,4*R*, α *S*)-**50**: δ _H (400 MHz, CDCl₃) [selected data] 2.57 (1H, dd, *J* 16.1, 3.5, C(2)*H*_A), 2.81 (1H, dd, *J* 16.1, 8.7, C(2)*H*_B).

Method B. From **60**. TIPSCl (41 μ L, 0.190 mmol), imidazole (23.6 mg, 0.346 mmol) and DMAP (2.1 mg, 0.017 mmol) were added sequentially to a stirred solution of **60** (100 mg, 0.173 mmol, >99:1 dr) in CH₂Cl₂ (2 mL) at rt, and the resultant solution was stirred at rt for 18 h then concentrated in vacuo. The

residue was partitioned between Et₂O (5 mL) and 1 M aq HCl (2 mL), and the aqueous layer was extracted with Et₂O (3 × 3 mL). The combined organics were washed with satd aq NaHCO₃ (5 mL), then dried and concentrated in vacuo. Purification via flash column chromatography (eluent 30–40 °C/EtOAc, 20:1) gave (3*R*,4*R*, α *S*)-**49** as a pale yellow viscous oil (24 mg, 19%, >99:1 dr); [α]_D²² –7.8 (*c* 1.0 in CHCl₃); ν_{\max} 1724 (C=O); δ_{H} (400 MHz, CDCl₃) 1.18 (3H, d, *J* 7.0, C(α)*Me*), 1.19–1.30 (21H, m, Si(CHMe₂)₃), 1.42 (9H, s, CMe₃), 1.78–1.90 (1H, m, C(2)*H*_A), 2.71 (1H, dd, *J* 17.0, 5.0, C(2)*H*_B), 2.94–3.03 (1H, m, C(4)*H*), 3.06–3.21 (1H, m, NCH_AH_BPh), 3.29 (1H, d, *J* 15.0, NCH_AH_BPh), 3.36–3.43 (1H, m, C(3)*H*), 3.67 (1H, q, *J* 7.0, C(α)*H*), 3.71–3.79 (2H, m, N(CH_AH_BPh)₂), 3.83–3.97 (3H, m, C(5)*H*_A, N(CH_AH_BPh)₂), 4.50 (1H, dd, *J* 10.7, 3.8, C(5)*H*_B), 7.12–7.34 (20H, m, *Ph*); δ_{C} (125 MHz, CDCl₃) 12.0 (Si(CHMe₂)₃), 18.3 (Si(CHMe₂)₃), 21.6 (C(α)*Me*), 28.2 (CMe₃), 33.2 (C(2)), 52.0 (NCH₂Ph), 53.9 (C(3)), 54.9 (N(CH₂Ph)₂), 59.8 (C(α)), 60.5 (C(4)), 65.8 (C(5)), 79.9 (CMe₃), 126.4, 126.5, 126.8 (*p-Ph*), 127.9, 128.0, 128.2, 128.4, 128.8, 129.8 (*o,m-Ph*), 140.4, 140.6, 141.4 (*i-Ph*), 173.4 (C(1)); *m/z* (ESI⁺) 757 ([M+Na]⁺, 18%), 735 ([M+H]⁺, 100%); HRMS (ESI⁺) C₄₇H₆₇N₂O₃Si⁺ ([M+H]⁺) requires 735.4915; found 735.4917.

tert-Butyl (2*R*,3*R*,4*R*, α *R*)-2-hydroxy-3-[*N*-benzyl-*N*-(α -methylbenzyl)amino]-4-(*N,N*-dibenzylamino)-5-(triisopropylsilyloxy)pentanoate **51.** Doubly Diastereoselective “Matched” Reaction with *in situ* Enolate Oxidation. BuLi (2.2 M in hexanes, 0.34 mL, 0.75 mmol) was added dropwise to a stirred solution of (*R*)-*N*-benzyl-*N*-(α -methylbenzyl)amine (161 mg, 0.764 mmol, >99% ee) in THF (1 mL) at –78 °C and the resultant solution was stirred at –78 °C for 30 min. A solution of (*R*)-**44** (200 mg, 0.382 mmol, >99:1 dr [(*E*):(*Z*) ratio]) in THF (1 mL) at –78 °C was added dropwise via cannula and the resultant solution was stirred at –78 °C for 2 h. (–)-CSO (175 mg, 0.764 mmol) was then added and the resultant solution was allowed to warm to rt over 18 h, then concentrated in vacuo. The residue was suspended in 10% aq citric acid (10 mL) and extracted with CH₂Cl₂ (3 × 25 mL). The combined organics were washed sequentially with satd aq NaHCO₃ (10 mL) and brine (10 mL), then dried and concentrated in vacuo to give a 24:76 mixture of (3*S*,4*R*, α *R*)-**47** and (2*R*,3*R*,4*R*, α *R*)-**51**, respectively. Purification via flash column chromatography (eluent 30–40 °C petroleum ether/EtOAc, 20:1; increased to 30–40 °C petroleum ether/EtOAc, 5:1) gave (3*S*,4*R*, α *R*)-**47** as a colourless oil (46 mg, 16%, >99:1 dr); [α]_D²⁰ –0.9 (*c* 1.0 in CHCl₃). Further elution gave (2*R*,3*R*,4*R*, α *R*)-**51** as a colourless oil (210 mg, 73%, >99:1 dr); C₄₇H₆₆N₂O₄Si requires C, 75.15; H, 8.9; N, 3.7%; found C, 75.05; H, 8.8; N, 3.8%; [α]_D²⁰ –13.1 (*c* 1.0 in CHCl₃); ν_{\max} 3021 (O–H), 1735 (C=O); δ_{H} (500 MHz, CDCl₃) 1.10–1.23 (21H, m, Si(CHMe₂)₃), 1.38 (3H, d, *J* 7.7, C(α)*Me*) overlapping 1.40 (9H, s, CMe₃), 3.40 (1H, m, C(4)*H*), 3.72 (1H, dd, *J* 4.6, 1.7 C(3)*H*) overlapping 3.75 (2H, d, *J* 14.0, N(CH_AH_BPh)₂), 3.80–3.82 (1H, m, C(2)*H*), 3.87 (1H, d, *J* 16.4, NCH_AH_BPh), 3.95 (1H, q, *J* 7.7, C(α)*H*), 4.00 (2H, d, *J* 14.0, N(CH_AH_BPh)₂) overlapping 4.06 (1H, *J* 10.6, 7.1, C(5)*H*_A), 4.21 (1H, *J* 10.6,

6.3, C(5)*H_B*), 4.48 (1H, d, *J* 16.4, NCH_AH_BPh), 6.37 (1H, br d, *J* 6.1, OH), 7.00–7.28 (20H, m, *Ph*); δ_{C} (125 MHz, CDCl₃) 12.0 (Si(CHMe₂)₃), 18.2 (Si(CHMe₂)₃), 20.8 (C(α)Me), 28.1 (CMe₃), 53.5 (NCH₂Ph), 56.1 (N(CH₂Ph)₂), 57.4 (C(3)), 58.5 (C(α)), 62.1 (C(5)), 64.7 (C(4)), 73.7 (C(2)), 81.2 (CMe₃), 126.0, 126.8, 127.1, 127.3, 128.0, 128.1, 128.2, 128.6, 129.0 (*o,m,p-Ph*) 138.7, 141.2, 141.6 (*i-Ph*), 173.2 (C(1)); *m/z* (ESI⁺) 773 ([M+Na]⁺, 27%), 751 ([M+H]⁺, 100%); HRMS (ESI⁺) C₄₇H₆₇N₂O₄Si⁺ ([M+H]⁺) requires 751.4865; found 751.4863.

(2*R*,3*R*,4*R*, α *R*)-3-[*N*-Benzyl-*N*-(α -methylbenzyl)amino]-4-(*N,N*-dibenzylamino)pentan-1,2,5-triol 52. LiAlH₄ (1.0 M in THF, 2.0 mL, 2.0 mmol) was added to a stirred solution of **51** (500 mg, 0.666 mmol) in THF (5 mL) at –78 °C and the resultant solution was stirred at rt for 18 h, then cooled to 0 °C. 2.0 M aq NaOH (5 mL) was added and the resultant biphasic mixture was stirred at rt for 2 h, before being filtered through Celite® (eluent EtOAc) and concentrated *in vacuo*. Purification via flash column chromatography (eluent CHCl₃/*i*PrOH, 20:1) gave **52** as a pale yellow solid (309 mg, 88%, >99:1 dr); mp 80–83 °C; $[\alpha]_{\text{D}}^{22}$ +29.2 (*c* 1.0 in CHCl₃); ν_{max} 3390 (O–H); δ_{H} (500 MHz, CDCl₃) 1.43 (3H, d, *J* 7.1, C(α)Me), 2.44 (1H, app t, *J* 9.4, C(1)*H_A*), 2.78 (1H, app d, *J* 7.6, C(1)*H_B*), 3.09–3.17 (2H, m, C(3)*H*, C(2)*H*), 3.22–3.27 (1H, m, C(4)*H*), 3.60 (2H, d, *J* 13.7, N(CH_AH_BPh)₂), 3.82 (1H, br s, OH), 3.91 (1H, q, *J* 7.1, C(α)*H*), 4.03 (1H, d, *J* 16.1, NCH_AH_BPh), 4.09–4.17 (3H, m, C(5)*H_A*, N(CH_AH_BPh)₂), 4.32 (1H, dd, *J* 11.2, 5.0, C(5)*H_B*), 4.62 (1H, d, *J* 16.1, NCH_AH_BPh), 7.16–7.39 (20H, m, *Ph*); δ_{C} (125 MHz, CDCl₃) 19.5 (C(α)Me), 53.4 (NCH₂Ph), 56.0 (C(3)), 56.2 (N(CH₂Ph)₂), 58.2 (C(α)), 59.6 (C(5)), 60.5 (C(4)), 65.0 (C(1)), 72.8 (C(2)), 126.7, 127.4, 127.5, 127.8, 128.2, 128.3, 128.4, 128.5, 129.3 (*o,m,p-Ph*), 137.8, 139.8, 140.7 (*i-Ph*); *m/z* (ESI⁺) 525 ([M+H]⁺, 100%); HRMS (ESI⁺) C₃₄H₄₁N₂O₃⁺ ([M+H]⁺) requires 525.3112; found 525.3107.

***tert*-Butyl (2*R*,3*R*,4*R*, α *R*)-2-hydroxy-3-[*N*-benzyl-*N*-(α -methylbenzyl)amino]-4-(*N,N*-dibenzylamino)-5-(triisopropylsilyloxy)pentanoate 51 and *tert*-butyl (2*S*,3*S*,4*S*, α *S*)-3-[*N*-3',4'-dimethoxybenzyl-*N*-(α -methylbenzyl)amino]-4-(*N,N*-dibenzylamino)-5-**

(triisopropylsilyloxy)pentanoate 53. *Parallel Kinetic Resolution with in situ Enolate Oxidation.* BuLi (2.2 M in hexanes, 0.34 mL, 0.75 mmol) was added dropwise to a stirred solution of (*R*)-*N*-benzyl-*N*-(α -methylbenzyl)amine (80.7 mg, 0.382 mmol, >99% ee) and (*S*)-*N*-3,4-dimethoxybenzyl-*N*-(α -methylbenzyl)amine (104 mg, 0.382 mmol, >99% ee) in THF (1 mL) at –78 °C and the resultant solution was stirred at –78 °C for 30 min. A solution of (*RS*)-**44** (200 mg, 0.382 mmol, >99:1 dr [(*E*):(*Z*) ratio]) in THF (1 mL) at –78 °C was added dropwise via cannula and the resultant solution was stirred at –78 °C for 2 h. (–)-CSO (87 mg, 0.38 mmol) and (+)-CSO (87 mg, 0.38 mmol) were then added and the resultant solution was allowed to warm to rt over 18 h, then concentrated *in vacuo*. The residue was suspended in 10% aq

citric acid (10 mL) and extracted with CH₂Cl₂ (3 × 25 mL). The combined organics were washed sequentially with satd aq NaHCO₃ (10 mL) and brine (10 mL), then dried and concentrated in vacuo. Purification via flash column chromatography (eluent 30–40 °C petroleum ether/EtOAc, 25:1; increased to 30–40 °C petroleum ether/EtOAc, 5:1) gave (3*S*,4*R*, α *R*)-**47** as a colourless oil (42 mg, 15%, >99:1 dr); [α]_D²⁵ –0.7 (*c* 1.0 in CHCl₃). Further elution gave (2*R*,3*R*,4*R*, α *R*)-**51** as a yellow oil (34 mg, 12%, >99:1 dr); [α]_D²⁵ –13.6 (*c* 1.0 in CHCl₃). Further elution gave (3*R*,4*S*, α *S*)-**48** as a colourless oil (42 mg, 14%, >99:1 dr); [α]_D²⁵ +3.4 (*c* 1.0 in CHCl₃). Further elution gave (2*S*,3*S*,4*S*, α *S*)-**53** as a colourless oil (12 mg, 4%, >99:1 dr); [α]_D²⁵ +24.9 (*c* 1.0 in CHCl₃); ν_{\max} 3514 (O–H), 1722 (C=O); δ_{H} (500 MHz, CDCl₃) 1.15–1.22 (21H, m, Si(CHMe₂)₃), 1.30 (3H, d, *J* 6.7, C(α)Me), 1.51 (9H, s, CMe₃), 2.96 (1H, d, *J* 15.3, NCH_AH_BAr), 3.21 (1H, br s, OH), 3.59–3.64 (1H, m, C(4)*H*), 3.76 (3H, s, OMe), 3.79 (3H, s, OMe), 3.89–3.91 (3H, m, NCH_AH_BAr, N(CH_AH_BPh)₂), 3.99 (1H, dd, *J* 6.4, 3.3, C(3)*H*), 4.05 (1H, q, *J* 6.7, C(α)*H*), 4.11 (2H, d, *J* 14.0, N(CH_AH_BPh)₂), 4.20 (1H, dd, *J* 11.4, 6.2, C(5)*H*_A), 4.38 (1H, dd, *J* 11.4, 3.1, C(5)*H*_B), 4.40–4.42 (1H, m, C(2)*H*), 6.11 (1H, dd, *J* 8.3, 1.7, C(6')*H*), 6.42–6.48 (2H, m, C(2')*H*, C(5')*H*), 6.92–6.98 (5H, m, *Ph*), 7.27–7.31 (2H, m, *Ph*), 7.37 (4H, t, *J* 7.6, *Ph*), 7.48 (4H, d, *J* 7.4, *Ph*); δ_{C} (125 MHz, CDCl₃) 12.2 (Si(CHMe₂)₃), 18.3 (Si(CHMe₂)₃), 22.0 (C(α)Me), 28.1 (CMe₃), 53.9 (NCH₂Ar), 55.6 (N(CH₂Ph)₂), 55.7, 55.9 (OMe), 59.0 (C(4)), 59.4 (C(3)), 61.5 (C(5)), 62.7 (C(α)), 74.1 (C(2)), 82.3 (CMe₃), 110.3 (C(5')), 111.4 (C(2')), 119.6 (C(6')), 126.4, 127.0, 127.3, 128.3, 128.4, 129.7 (*o,m,p-Ph*), 135.3 (C(1')), 140.0, 145.1 (*i-Ph*), 146.6 (C(4')), 148.1 (C(3')), 174.1 (C(1)); *m/z* (ESI⁺) 812 ([M+H]⁺, 100%), 755 (17%); HRMS (ESI⁺) C₄₉H₇₁N₂O₆Si⁺ ([M+H]⁺) requires 811.5076; found 811.5067.

tert-Butyl (3*S*,4*R*, α *R*)-3-[*N*-benzyl-*N*-(α -methylbenzyl)amino]-4-(*N,N*-dibenzylamino)-5-hydroxypentanoate **54 and (3*S*,4*R*, α *R*)-3-[*N*-benzyl-*N*-(α -methylbenzyl)amino]-4-(*N,N*-dibenzylamino)-5-pentanolactone **55**.** *Method A.* TBAF (1.0 M in THF, 0.41 mL, 0.41 mmol) was added to a stirred solution of (3*S*,4*R*, α *R*)-**47** (200 mg, 0.272 mmol, >99:1 dr) in THF (2 mL) at 0 °C and the resultant solution was stirred at 0 °C for 2 h. Et₂O (1 mL) and H₂O (1 mL) were added and the aqueous layer was extracted with Et₂O (3 × 25 mL). The combined organics were washed with satd aq NaHCO₃ (25 mL), then dried and concentrated in vacuo to give 82% conversion to a 16:84 mixture of **54** and **55**, respectively. Purification via flash column chromatography (eluent 30–40 °C petroleum ether/EtOAc, 20:1; increased to 30–40 °C petroleum ether/EtOAc, 5:1) gave (3*S*,4*R*, α *R*)-**47** as a colourless oil (18 mg, 9%, >99:1 dr); [α]_D²⁰ –1.4 (*c* 1.0 in CHCl₃). Further elution gave **54** as a colourless oil (20 mg, 13% >99:1 dr); [α]_D²⁰ –26.7 (*c* 1.0 in CHCl₃); ν_{\max} 3427 (O–H), 1721 (C=O); δ_{H} (500 MHz, CDCl₃) 1.38 (9H, s, CMe₃), 1.63 (3H, d, *J* 6.9, C(α)Me), 1.86 (1H, dd, *J* 16.7, 2.4, C(2)*H*_A), 1.94 (1H, dd, *J* 16.7, 8.8, C(2)*H*_B), 3.07 (1H, m, C(4)*H*), 3.22 (1H, br s, OH), 3.44 (1H, dd, *J* 10.9, 8.7, C(5)*H*_A), 3.55 (1H, d, *J* 15.0, NCH_AH_BPh) overlapping 3.54–3.59

(1H, m, C(5)*H_B*), 3.69 (2H, d, *J* 13.9, N(CH_A*H_B*Ph)₂), 3.78 (2H, d, *J* 13.9, N(CH_A*H_B*Ph)₂), 3.90 (1H, m, C(3)*H*), 4.04 (1H, q, *J* 6.9, C(α)*H*) overlapping 4.04 (1H, d, *J* 15.0, NCH_A*H_B*Ph), 7.16–7.40 (20H, m, *Ph*); δ_C (125 MHz, CDCl₃) 21.1 (C(α)*Me*), 28.0 (*CMe*₃), 34.5 (C(2)), 51.0 (NCH₂Ph), 53.0 (C(3)), 54.1 (N(CH₂Ph)₂), 57.5 (C(α)), 58.8 (C(5)), 62.5 (C(4)), 80.7 (*CMe*₃), 125.3, 126.8, 127.2 (*p-Ph*), 126.9, 128.2, 128.3, 128.7, 128.9, 129.0 (*o,m-Ph*), 139.9, 140.1, 142.5 (*i-Ph*), 172.2 (C(1)); *m/z* (ESI⁺) 579 ([M+H]⁺, 100%); HRMS (ESI⁺) C₃₈H₄₇N₂O₃⁺ ([M+H]⁺) requires 579.3581; found 579.3584. Further elution gave **55** as a white foam (94 mg, 69%, >99:1 dr); [α]_D²⁰ –60.7 (*c* 1.0 in CHCl₃); ν_{max} 1748 (C=O); δ_H (500 MHz, CDCl₃) 1.37 (3H, d, *J* 6.9, C(α)*Me*), 2.15 (1H, dd, *J* 15.1, 6.5, C(2)*H_A*), 2.23 (1H, dd, *J* 15.1, 9.0, C(2)*H_B*), 3.27 (1H, m, C(4)*H*), 3.47 (2H, d, *J* 13.9, N(CH_A*H_B*Ph)₂), 3.56 (1H, d, *J* 14.3, NCH_A*H_B*Ph), 3.59–3.65 (1H, m, C(3)*H*) overlapping 3.62 (1H, d, *J* 14.3, NCH_A*H_B*Ph), 3.82 (1H, q, *J* 6.9, C(α)*H*) overlapping 3.84 (2H, d, *J* 13.9, N(CH_A*H_B*Ph)₂), 4.15 (1H, dd, *J* 12.3, 4.4, C(5)*H_A*), 4.43 (1H, dd, *J* 12.3, 4.7, C(5)*H_B*), 7.00–7.46 (20H, m, *Ph*); δ_C (125 MHz, CDCl₃) 20.4 (C(α)*Me*), 31.8 (C(2)), 50.9 (NCH₂Ph), 53.8 (C(3)), 54.9 (N(CH₂Ph)₂), 57.9 (C(4)), 58.1 (C(α)), 65.5 (C(5)), 126.8, 127.3, 127.5, 127.6, 128.2, 128.4, 128.4, 128.6, 129.0 (*o,m,p-Ph*), 139.1, 140.2, 142.7 (*i-Ph*), 172.9 (C(1)); *m/z* (ESI⁺) 527 ([M+Na]⁺, 20%), 505 ([M+H]⁺, 100%); HRMS (ESI⁺) C₃₄H₃₆N₂NaO₂⁺ ([M+Na]⁺) requires 527.2669; found 527.2663.

Method B. TBAF (1.0 M in THF, 3.24 mL, 3.24 mmol) was added to a stirred solution of (3*S*,4*R*,α*R*)-**47** (1.59 g, 2.16 mmol, >99:1 dr) in THF (15 mL) at 0 °C and the resultant solution was stirred at rt for 24 h. Et₂O (15 mL) and H₂O (15 mL) were added and the aqueous layer was extracted with Et₂O (3 × 50 mL). The combined organics were washed with satd aq NaHCO₃ (100 mL), then dried and concentrated in vacuo to give **55**. Purification via flash column chromatography (eluent 30–40 °C petroleum ether/EtOAc, 5:1) gave **55** as a pale yellow oil (1.07 g, 98%, >99:1 dr); [α]_D²⁰ –55.1 (*c* 1.0 in CHCl₃).

(2*R*,3*S*,α*R*,*E*)-2-(*N,N*-Dibenzylamino)-3-[*N*-benzyl-*N*-(α-methylbenzyl)amino]octadec-5-en-1-ol **57 and (2*R*,3*S*,α*R*,*Z*)-2-(*N,N*-dibenzylamino)-3-[*N*-benzyl-*N*-(α-methylbenzyl)amino]octadec-5-en-1-ol **58**.** DIBAL-H (1.0 M in PhMe, 2.82 mL, 2.82 mmol) was added to a stirred solution of **55** (1.36 g, 2.69 mmol, >99:1 dr) in PhMe (13 mL) at –78 °C and the resultant mixture was stirred at –78 °C for 1 h. Meanwhile, BuLi (2.2 M in hexanes, 1.78 mL, 3.91 mmol) was added dropwise to a stirred solution of [C₁₃H₂₇PPh₃]⁺[Br][–] (2.12 g, 4.03 mmol) in THF (6.5 mL) at 0 °C and the resultant solution was stirred at 0 °C for 30 min. The ‘lactol’ solution was then added dropwise via cannula and the resultant solution was stirred at 80 °C for 1 h. The resultant solution was allowed to cool to rt, then H₂O (5 mL) and brine (5 mL) were added sequentially and the aqueous layer was extracted with EtOAc (3 × 10 mL). The combined organics were washed with satd aq NaHCO₃ (30 mL), then dried and concentrated in vacuo. Purification via flash column chromatography (eluent 30–40 °C petroleum ether/EtOAc, 12:1) gave an ~50:50 mixture of **57**

and **58** as a colourless viscous oil (1.32 g, 73%); ν_{\max} 3457 (O–H); δ_{H} (400 MHz, CDCl_3) 0.88–0.97 (6H, m, C(18) H_3), 1.20–1.35 (40H, m, C(8) H_2 –C(17) H_2), 1.44 (3H, d, J 7.3, C(α) Me), 1.48 (3H, d, J 6.9, C(α) Me), 1.84–1.94 (4H, m, C(7) H_2), 1.97–2.06 (4H, m, C(4) H_2), 3.09 (2H, br s, OH), 3.15–3.28 (4H, m, C(2) H , C(3) H), 3.46–3.73 (14H, m, C(1) H_2 , $\text{NCH}_2\text{H}_2\text{Ph}$, $\text{N}(\text{CH}_2\text{Ph})_2$), 3.98–4.15 (4H, m, C(α) H , $\text{NCH}_2\text{H}_2\text{Ph}$), 5.01–5.18 (2H, m, C(5) H), 5.20–5.34 (2H, m, C(6) H), 7.14–7.40 (40H, m, Ph); δ_{C} (100 MHz, CDCl_3) 14.2 (C(18)), 21.0, 21.4 (C(α) Me), 22.7 (C(17)), 25.6 (C(4) [**58**]), 27.8 (C(7) [**58**]), 29.3, 29.4, 29.7, 29.7 (C(8)–C(16)), 30.5 (C(4) [**57**]), 31.9 (C(8)–C(16)), 32.7 (C(7) [**57**]), 51.2, 51.3, 53.7, 54.2, 57.6, 58.4, 59.5, 59.8, 63.3 (C(1)–C(3), C(α), NCH_2Ph , $\text{N}(\text{CH}_2\text{Ph})_2$), 126.6, 126.7, 127.0, 127.0, 127.1, 128.2, 128.2, 128.3, 128.3, 128.3, 128.4, 128.4, 128.7 (*o,m,p-Ph*), 128.8, 128.9 (C(5)), 128.9, 129.0 (*o,m,p-Ph*), 130.6, 132.1 (C(6)), 139.9, 140.0, 141.1, 141.1, 144.1, 144.4 (*i-Ph*); m/z (ESI⁺) 673.5 ([M+H]⁺, 72%); HRMS (ESI⁺) $\text{C}_{47}\text{H}_{65}\text{N}_2\text{O}^+$ ([M+H]⁺) requires 673.5091; found 673.5083.

(2R,3S)-2,3-Diacetamidooctadecan-1-yl acetate 59. *Step 1.* $\text{Pd}(\text{OH})_2/\text{C}$ (50% w/w of substrate, 100 mg) was added to a vigorously stirred solution of a 50:50 mixture of **57** and **58** (200 mg, 0.297 mmol) in degassed HCl (1.25 M in MeOH, 3 mL) at rt and the resultant suspension was stirred under H_2 (5 atm) at rt for 72 h, then filtered through Celite[®] (eluent MeOH) and concentrated in vacuo.

Step 2. Ac_2O (225 μL , 2.38 mmol) and DMAP (3.6 mg, 0.030 mmol) were added sequentially to a stirred solution of the residue from the previous step in pyridine (838 μL , 10.4 mmol) at rt, and the resultant solution was stirred at rt for 72 h. EtOAc (5 mL) was added, the resultant solution was washed with satd aq CuSO_4 (5 mL), and the aqueous layer was extracted with EtOAc (3 \times 5 mL). The combined organics were washed with satd aq NaHCO_3 (3 \times 10 mL) and the combined aqueous layers were then extracted with EtOAc (3 \times 10 mL). The combined organics were dried and concentrated in vacuo. Recrystallisation (CH_2Cl_2 /30–40 °C petroleum ether) gave **59** as a pale orange solid (101 mg, 79%, >99:1 dr); mp 115–116 °C; $[\alpha]_{\text{D}}^{22}$ –16.0 (c 1.0 in CHCl_3); ν_{\max} 3282 (N–H), 1737 (C=O ester), 1645 (C=O amide); δ_{H} (500 MHz, CDCl_3) 0.88 (3H, t, J 7.0, C(18) H_3), 1.20–1.33 (26H, m, C(5) H_2 –C(17) H_2), 1.36–1.45 (1H, m, C(4) H_A), 1.56–1.64 (1H, m, C(4) H_B), 1.97 (3H, s, COMe), 1.98 (3H, s, COMe), 2.10 (3H, s, COMe), 3.97 (1H, ddd, J 18.0, 9.0, 3.6, C(3) H), 4.05–4.11 (1H, m, C(2) H), 4.14 (1H, dd, J 11.7, 3.6, C(1) H_A), 4.20 (1H, dd, J 11.7, 5.0, C(1) H_B), 5.91 (1H, d, J 9.1, NHAc), 6.46 (1H, d, J 8.5, NHAc); δ_{C} (125 MHz, CDCl_3) 14.1 (C(18)), 20.8 (COMe), 22.7 (C(17)), 23.2, 23.2 (COMe), 29.3, 29.4, 29.5, 29.5, 29.6, 29.6, 29.6, 29.7 (C(5)–C(16)), 31.5 (C(4)), 31.9 (C(5)–C(16)), 50.4 (C(3)), 52.6 (C(2)), 63.7 (C(1)), 170.9, 171.0, 171.2 (COMe); m/z (ESI⁺) 449 ([M+Na]⁺, 65%), 427 ([M+H]⁺, 100%); HRMS (ESI⁺) $\text{C}_{24}\text{H}_{46}\text{N}_2\text{NaO}_4^+$ ([M+Na]⁺) requires 449.3350; found 449.3338.

tert-Butyl**(3*R*,4*R*, α *S*)-3-[*N*-benzyl-*N*-(α -methylbenzyl)amino]-4-(*N,N*-dibenzylamino)-5-**

hydroxypentanoate 60. TBAF (1.0 M in THF, 1.02 mL, 1.02 mmol) was added to a stirred solution of an 87:13 mixture of **49** and **50** (500 mg, 0.680 mmol) in THF (12 mL) at 0 °C and the resultant solution was stirred at rt for 24 h. Et₂O (5 mL) and H₂O (5 mL) were added and the aqueous layer was extracted with Et₂O (3 × 10 mL). The combined organics were washed with satd aq NaHCO₃ (30 mL), then dried and concentrated in vacuo. Purification via flash column chromatography (eluent 30–40 °C petroleum ether/EtOAc, 5:1) gave **60** as a pale yellow oil (260 mg, 66%, >99:1 dr); [α]_D²² –26.4 (*c* 1.0 in CHCl₃); ν_{\max} 3424 (O–H), 1724 (C=O); δ_{H} (500 MHz, MeOH-*d*₄) 1.16 (3H, d, *J* 6.8, C(α)*Me*), 1.41 (9H, s, *CMe*₃), 1.94–2.03 (1H, m, C(2)*H*_A), 2.74 (1H, dd, *J* 16.5, 3.0, C(2)*H*_B), 2.86–2.93 (1H, m, C(4)*H*), 3.26–3.31 (2H, m, NCH₂Ph), 3.54 (2H, d, *J* 11.7, N(CH_AH_BPh)₂), 3.62–3.72 (3H, m, C(3)*H*, N(CH_AH_BPh)₂), 3.73 (1H, q, *J* 6.8, C(α)*H*), 3.80–3.87 (1H, m, C(5)*H*_A), 3.90–4.05 (1H, m, C(5)*H*_B), 7.15–7.30 (20H, m, *Ph*); δ_{C} (125 MHz, MeOH-*d*₄) 22.4 (C(α)*Me*), 28.7 (*CMe*₃), 34.3 (C(2)), 53.7 (NCH₂Ph), 55.6 (N(CH₂Ph)₂), 56.6 (C(3)), 61.3 (C(5)), 61.5 (C(4)), 63.1 (C(α)), 81.7 (*CMe*₃), 128.0, 128.1, 128.4, 129.2, 129.3, 129.6, 130.0, 130.0, 130.8 (*o,m,p-Ph*), 141.5, 142.0, 145.5 (*i-Ph*), 175.2 (C(1)); *m/z* (ESI⁺) 579 ([*M*+*H*]⁺, 100%); HRMS (ESI⁺) C₃₈H₄₇N₂O₃⁺ ([*M*+*H*]⁺) requires 579.3581; found 579.3572. Further elution gave an impure sample of **61** as a colourless oil (37 mg, ~10%); ν_{\max} 1748 (C=O); δ_{H} (400 MHz, CDCl₃) 1.38 (3H, d, *J* 6.9, C(α)*Me*), 2.72 (1H, dd, *J* 15.3, 6.6, C(2)*H*_A), 2.82 (1H, dd, *J* 15.3, 8.5, C(2)*H*_B), 3.25 (1H, app q, *J* 4.9, C(4)*H*), 3.28 (2H, d, *J* 13.7, N(CH_AH_BPh)₂), 3.50 (2H, d, *J* 13.7, N(CH_AH_BPh)₂), 3.53–3.56 (1H, m, C(3)*H*), 3.59 (1H, d, *J* 13.6, NCH_AH_BPh), 3.65 (1H, d, *J* 13.6, NCH_AH_BPh), 3.90 (1H, q, *J* 6.9, C(α)*H*), 4.12–4.17 (1H, dd, *J* 12.4, 4.9, C(5)*H*_A), 4.43 (1H, dd, *J* 12.4, 4.9, C(5)*H*_B), 6.95–7.05 (5H, m, *Ph*), 7.20–7.43 (15H, m, *Ph*); δ_{C} (100 MHz, CDCl₃) 14.9 (C(α)*Me*), 34.4 (C(2)), 50.4 (NCH₂Ph), 53.3 (C(3)), 54.7 (N(CH₂Ph)₂), 56.5 (C(α)), 58.1 (C(4)), 66.0 (C(5)), 127.0, 127.1, 128.2, 128.2, 128.2, 128.3, 128.8, 129.0, 129.0 (*o,m,p-Ph*), 139.1, 139.5, 143.4 (*i-Ph*), 173.1 (C(1)); *m/z* (ESI⁺) 505 ([*M*+*H*]⁺, 100%); HRMS (ESI⁺) C₃₄H₃₇N₂O₂⁺ ([*M*+*H*]⁺) requires 505.2850; found 505.2846.

(3*R*,4*R*, α *S*)-3-[*N*-Benzyl-*N*-(α -methylbenzyl)amino]-4-(*N,N*-dibenzylamino)-5-

(triisopropylsilyloxy)pentan-1-ol 62. LiAlH₄ (1.0 M in THF, 1.1 mL, 1.1 mmol) was added to a stirred solution of an 87:13 mixture of **49** and **50** (200 mg, 0.272 mmol) in THF (13 mL) at –78 °C and the resultant solution was stirred at rt for 18 h. The resultant solution was cooled to 0 °C, 1 M aq NaOH (1 mL) was added and the resultant biphasic mixture was stirred at 67 °C for 1 h, then filtered through Celite® (eluent EtOAc), dried and concentrated in vacuo to give an 87:13 mixture of **62** and **63**, respectively. Purification via flash column chromatography (30–40 °C petroleum ether/EtOAc, 5:1) gave **62** as a colourless oil (115 mg, 64%, >99:1 dr); [α]_D²² +24.8 (*c* 1.0 in CHCl₃); ν_{\max} 3410 (O–H); δ_{H} (400 MHz, benzene-*d*₆) 1.13 (3H, d,

J 6.8, C(α)Me), 1.22–1.28 (21H, m, Si(CHMe₂)₃), 1.50–1.57 (1H, m, C(2)H_A), 1.60–1.67 (1H, m, C(2)H_B), 2.24 (1H, br s, OH), 2.82–2.88 (1H, m, C(3)H), 3.26–3.34 (1H, m, C(4)H), 3.35–3.42 (1H, m, NCH_AH_BPh), 3.45–3.55 (3H, m, C(1)H₂, NCH_AH_BPh), 3.66 (1H, q, *J* 6.8, C(α)H), 3.80–3.88 (2H, m, N(CH_AH_BPh)₂), 3.93–4.13 (3H, m, C(5)H_A, N(CH_AH_BPh)₂), 4.58 (1H, dd, *J* 10.9, 3.9, C(5)H_B), 7.05–7.09 (4H, m, *Ph*), 7.17–7.27 (10H, m, *Ph*), 7.34 (2H, d, *J* 7.3, *Ph*), 7.49 (4H, d, *J* 7.3, *Ph*); δ_{C} (100 MHz, benzene-*d*₆) 12.8 (Si(CHMe₂)₃), 18.9 (Si(CHMe₂)₃), 23.0 (C(α)Me), 32.4 (C(2)), 53.2 (NCH₂Ph), 55.9 (N(CH₂Ph)₂), 56.3 (C(1)), 56.9 (C(3)), 61.3 (C(α)), 62.5 (C(4)), 66.3 (C(5)), 127.2, 127.6, 127.8–129.5, 131.0 (*o,m,p-Ph*), 140.7, 142.7, 146.4 (*i-Ph*); *m/z* (ESI⁺) 665 ([M+H]⁺, 100%); HRMS (ESI⁺) C₄₃H₆₁N₂O₂Si⁺ ([M+H]⁺) requires 665.4497; found 665.4492.

(2*R*,3*R*)-1-Triisopropylsilyloxy-2,3-di-(*N*-*tert*-butoxycarbonylamino)pentan-5-ol 64. Boc₂O (985 mg, 4.51 mmol) and Pd(OH)₂/C (40% w/w of substrate, 400 mg) were added sequentially to a vigorously stirred solution of **62** (1.00 g, 1.50 mmol, >99:1 dr) in degassed MeOH (5 mL) at rt and the resultant suspension was stirred under H₂ (5 atm) at rt for 72 h, then filtered through Celite[®] (eluent MeOH) and concentrated in vacuo. Purification via flash column chromatography (eluent 30–40 °C petroleum ether/Et₂O, 3:1; increased to 30–40 °C petroleum ether/Et₂O, 1:1) gave **64** as a pale yellow oil (606 mg, 82%, >99:1 dr); [α]_D²² +19.8 (*c* 1.0 in CHCl₃); ν_{max} 3355 (N–H, O–H), 1684 (C=O); δ_{H} (400 MHz, CDCl₃) 1.02–1.19 (21H, m, Si(CHMe₂)₃), 1.40–1.50 (19H, m, C(4)H_A, CMe₃), 1.77–1.87 (1H, m, C(4)H_B), 3.56–3.74 (3H, m, C(2)H, C(5)H₂), 3.88 (1H, d, *J* 13.0, C(1)H_A), 3.93–4.04 (3H, m, C(1)H_B, C(3)H), 5.12 (1H, d, *J* 8.5, NH), 5.94 (1H, d, *J* 9.2, NH); δ_{C} (100 MHz, CDCl₃) 11.7 (Si(CHMe₂)₃), 17.9 (Si(CHMe₂)₃), 28.3, 28.4 (CMe₃), 36.3 (C(4)), 50.0 (C(3)), 53.1 (C(2)), 58.4 (C(5)), 63.5 (C(1)), 79.7, 79.8 (CMe₃), 155.4, 157.5 (NCO); *m/z* (ESI⁺) 513 ([M+Na]⁺, 100%); HRMS (ESI⁺) C₂₄H₅₀N₂NaO₆Si⁺ ([M+Na]⁺) requires 513.3330; found 513.3341.

(2*R*,3*R*)-1-Triisopropylsilyloxy-2,3-di-(*N*-*tert*-butoxycarbonylamino)-5-(1'-phenyl-1*H*-tetrazol-5'-ylthio)pentane 66. *Method A. Mitsunobu Reaction.* DEAD (42 μ L, 0.265 mmol), PPh₃ (64.1 mg, 0.245 mmol) and PTSH (182 mg, 1.02 mmol) were added sequentially to a stirred solution of **64** (100 mg, 0.204 mmol, >99:1 dr) in THF (1.5 mL) at 0 °C and the resultant solution was stirred at rt for 18 h. The resultant solution was diluted with EtOAc (2 mL), washed sequentially with brine (2 mL) and H₂O (2 mL), then dried and concentrated in vacuo. Purification via flash column chromatography (eluent CHCl₃/^{*i*}PrOH, 30:1) gave **66** as a colourless oil (80 mg, 60%, >99:1 dr); [α]_D²² +25.9 (*c* 1.0 in CHCl₃); ν_{max} 3357 (N–H), 1687 (C=O); δ_{H} (400 MHz, CDCl₃) 1.10–1.15 (21H, m, Si(CHMe₂)₃), 1.43 (18H, s, CMe₃), 1.96–2.07 (1H, m, C(4)H_A), 2.10–2.27 (1H, m, C(4)H_B), 3.26–3.35 (1H, m, C(5)H_A), 3.55–3.70 (2H, m, C(2)H, C(5)H_B), 3.85 (1H, app d, *J* 10.6, C(1)H_A), 3.99 (1H, dd, *J* 10.6, 2.1, C(1)H_B), 4.01–4.06 (1H, m, C(3)H), 5.11 (1H, d, *J* 8.5, NH),

5.75 (1H, d, *J* 9.5, NH), 7.50–7.62 (5H, m, *Ph*); δ_{C} (100 MHz, CDCl₃) 11.7 (Si(CHMe₂)₃), 18.0 (Si(CHMe₂)₃), 28.3, 28.3 (CMe₃), 30.3 (C(5)), 33.7 (C(4)), 52.2 (C(2)), 52.7 (C(3)), 63.5 (C(1)), 79.3, 79.6 (CMe₃), 123.9, 129.8, 130.0 (*o,m,p-Ph*), 133.7 (*i-Ph*), 154.4 (C(5')), 155.4, 156.3 (NCO); *m/z* (ESI⁺) 673 ([M+Na]⁺, 100%), 651 ([M+H]⁺, 47%); HRMS (ESI⁺) C₃₁H₅₅N₆O₅SSi⁺ ([M+H]⁺) requires 651.3718; found 651.3716.

Method B. Mesylation/displacement. Step 1. Et₃N (606 μ L, 4.35 mmol), MsCl (135 μ L, 1.74 mmol) and DMAP (10.6 mg, 0.087 mmol) were added sequentially to a stirred solution of **64** (427 mg, 0.870 mmol, >99:1 dr) in CH₂Cl₂ (26 mL) at rt and the resultant solution was stirred at rt for 3 h. H₂O (15 mL) was added and the aqueous layer was extracted with CH₂Cl₂ (3 \times 10 mL). The combined organics were washed sequentially with 1 M aq HCl (50 mL), satd aq NaHCO₃ (50 mL) and brine (50 mL), then dried and concentrated in vacuo to give **65** as a colourless oil (450 mg).

Step 2. PTSH (171 mg, 0.957 mmol) and K₂CO₃ (240 mg, 1.74 mmol) were added sequentially to a stirred solution of the residue **65** (450 mg) from the previous step in acetone (8 mL) at rt and the resultant solution was stirred at 67 °C for 2.5 h, then allowed to cool rt and filtered. CH₂Cl₂ (10 mL) and H₂O (10 mL) were added, and the aqueous layer was extracted with CH₂Cl₂ (3 \times 10 mL). The combined organics were washed with H₂O (3 \times 25 mL), then dried and concentrated in vacuo. Purification via flash column chromatography (eluent 30–40 °C petroleum ether/EtOAc, 6:1) gave **66** as a pale yellow oil (458 mg, 81%, >99:1 dr).

(2R,3R)-1-Triisopropylsilyloxy-2,3-di-(N-tert-butoxycarbonylamino)-5-(1'-phenyl-1H-tetrazol-5'-ylsulfonyl)pentane 67. A solution of **66** (383 mg, 0.588 mmol, >99:1 dr) in EtOH (10 mL) was added dropwise to a stirred solution of (NH₄)₂Mo₇O₂₄·4H₂O (146 mg, 0.118 mmol) in 30% aq H₂O₂ (1.00 mL, 8.86 mmol) at 0°C and the resultant solution was stirred at rt for 18 h. Brine (10 mL) was added and the aqueous layer was extracted with EtOAc (3 \times 20 mL). The combined organics were dried and concentrated in vacuo. Purification via flash column chromatography (eluent 30–40 °C petroleum ether/EtOAc, 5:1) gave **67** as a white solid (374 mg, 93%, >99:1 dr); mp 95–97 °C; [α]_D²² –1.2 (*c* 1.0 in CHCl₃); ν_{max} 3355 (N–H), 1684 (C=O), 1164 (S=O); δ_{H} (400 MHz, CDCl₃) 1.00–1.18 (21H, m, Si(CHMe₂)₃), 1.41–1.46 (18H, m, CMe₃), 2.04–2.15 (1H, m, C(4)*H*_A), 2.19–2.30 (1H, m, C(4)*H*_B), 3.64–3.72 (1H, m, C(2)*H*), 3.76–3.91 (3H, m, C(1)*H*_A, C(5)*H*₂), 3.91–4.01 (2H, m, C(1)*H*_B, C(3)*H*), 5.07 (1H, d, *J* 8.4, NH), 5.66 (1H, d, *J* 9.0, NH), 7.50–7.65 (5H, m, *Ph*); δ_{C} (100 MHz, CDCl₃) 11.7 (Si(CHMe₂)₃), 18.0 (Si(CHMe₂)₃), 28.3 (CMe₃), 29.7 (C(4)), 51.8 (C(3)), 53.1 (C(2)), 53.8 (C(5)), 63.3 (C(1)), 79.8, 80.0 (CMe₃), 125.1, 129.7, 131.4 (*o,m,p-Ph*), 133.0 (*i-Ph*), 153.3, 155.5, 156.1 (C(5'), NCO); *m/z* (ESI⁺) 705 ([M+Na]⁺, 100%), 683 (27%), 527 (66%); HRMS (ESI⁺) C₃₁H₅₄N₆NaO₇SSi⁺ ([M+Na]⁺) requires 705.3436; found 705.3442.

(2R,3R,E)-1-Triisopropylsiloxy-2,3-di-(N-tert-butoxycarbonylamino)octadec-5-ene 68 and (2R,3R,Z)-1-triisopropylsiloxy-2,3-di-(N-tert-butoxycarbonylamino)octadec-5-ene 69. Tridecanal (139 μ L, 0.584 mmol) and LiHMDS (1.0 M in THF, 2.36 mL, 2.36 mmol) were added sequentially to a stirred solution of **67** (400 mg, 0.614 mmol, >99:1 dr) in THF (2 mL) at $-10\text{ }^{\circ}\text{C}$ and the resultant solution was stirred at rt for 18 h. The resultant solution was cooled to $0\text{ }^{\circ}\text{C}$ and then satd aq NH_4Cl (1 mL) and brine (5 mL) were added sequentially. The aqueous layer was extracted with Et_2O ($3 \times 5\text{ mL}$) and then the combined organics were dried and concentrated in vacuo to give a 50:50 mixture of **68** and **69**. Purification via flash column chromatography (eluent $30\text{--}40\text{ }^{\circ}\text{C}$ petroleum ether/ Et_2O , 10:1) gave a 50:50 mixture of **68** and **69** as a colourless oil (291 mg, 80%); ν_{max} 3365 (N–H), 1687 (C=O); δ_{H} (500 MHz, CDCl_3) 0.85–0.90 (6H, m, $\text{C}(18)\text{H}_3$), 1.03–1.14 (42H, m, $\text{Si}(\text{CHMe}_2)_3$), 1.21–1.31 (40H, m, $\text{C}(8)\text{H}_2\text{--C}(17)\text{H}_2$), 1.39–1.47 (36H, m, CMe_3), 1.92–1.98 (2H, m, $\text{C}(7)\text{H}_2$ [**68**]), 1.98–2.05 (2H, m, $\text{C}(7)\text{H}_2$ [**69**]), 2.17–2.27 (2H, m, $\text{C}(4)\text{H}_A$), 2.29–2.43 (2H, m, $\text{C}(4)\text{H}_B$), 3.62–3.68 (2H, m, $\text{C}(2)\text{H}$), 3.76–3.69 (4H, m, $\text{C}(1)\text{H}_A$, $\text{C}(3)\text{H}$), 3.93–3.99 (2H, m, $\text{C}(1)\text{H}_B$), 5.09–5.14 (2H, m, NH), 5.32–5.40 (2H, m, $\text{C}(5)\text{H}$), 5.43–5.51 (2H, m, $\text{C}(6)\text{H}$), 5.54–5.64 (2H, m, NH); δ_{C} (125 MHz, CDCl_3) 11.7 ($\text{Si}(\text{CHMe}_2)_3$), 14.1 ($\text{C}(18)$), 18.0, 18.0 ($\text{Si}(\text{CHMe}_2)_3$), 22.7 ($\text{C}(17)$), 27.6 ($\text{C}(7)$ [**69**]), 28.4, 28.4 (CMe_3), 29.2, 29.3, 29.4, 29.5, 29.6, 29.6, 29.7, 30.3 ($\text{C}(8)\text{--C}(16)$), 31.2 ($\text{C}(4)$ [**69**]), 31.9 ($\text{C}(8)\text{--C}(16)$), 32.6 ($\text{C}(7)$ [**68**]), 36.7 ($\text{C}(4)$ [**68**]), 51.5, 51.6 ($\text{C}(2)$), 53.1, 53.4 ($\text{C}(3)$), 63.2, 63.3 ($\text{C}(1)$), 124.8 ($\text{C}(5)$ [**69**]), 125.4 ($\text{C}(5)$ [**68**]), 132.7 ($\text{C}(6)$ [**69**]), 134.0 ($\text{C}(6)$ [**68**]), 155.3, 155.9 (NCO); m/z (ESI^+) 677 ($[\text{M}+\text{Na}]^+$, 100%), 499 (59%); HRMS (ESI^+) $\text{C}_{37}\text{H}_{74}\text{N}_2\text{NaO}_5\text{Si}^+$ ($[\text{M}+\text{Na}]^+$) requires 677.5259; found 677.5250.

(2R,3R)-1-Triisopropylsilyloxy-2,3-diacetamidooctadecane 71. *Step 1.* Pd/C (20% w/w of substrate, 12 mg) was added to a vigorously stirred suspension of a 50:50 mixture of **68** and **69** (59 mg, 0.090 mmol) in degassed MeOH (1.5 mL) at rt. The resultant suspension was stirred under H_2 (5 atm) at rt for 3 h, then filtered through Celite® (eluent MeOH) and concentrated in vacuo to give **70** as a pale yellow viscous oil (53 mg).

Step 2. TFA (69 μ L, 0.90 mmol) was added to a stirred solution of the residue **70** from the previous step (53 mg) in CH_2Cl_2 (1.5 mL) at rt and the resultant solution was stirred at rt for 18 h, then concentrated in vacuo to give a pale yellow oil (93 mg).

Step 3. Ac_2O (0.13 mL, 1.4 mmol) was added to a stirred solution of the residue from the previous step (93 mg) and DMAP (1 mg, 9 μ mol) in pyridine (0.25 mL, 3.2 mmol) at rt, and the resultant solution was stirred at rt for 24 h. EtOAc (10 mL) was added, the resultant solution was washed with satd aq CuSO_4 ($2 \times 5\text{ mL}$), and the aqueous layer was extracted with EtOAc ($2 \times 5\text{ mL}$). The combined organics were washed with satd aq NaHCO_3 (15 mL), then dried and concentrated in vacuo. Purification via flash column

chromatography (eluent CHCl₃/iPrOH/35% aq NH₄OH, 90:3:1) gave **71** as a white solid (35 mg, 72%, >99:1 dr); mp 146–149 °C; [α]_D²² +45.7 (c 1.0 in CHCl₃); ν_{\max} 3270 (N–H), 1643 (C=O); δ_{H} (500 MHz, CDCl₃) 0.89 (3H, t, *J* 7.0, C(18)H₃), 1.06–1.14 (21H, m, Si(CHMe₂)₃), 1.22–1.33 (26H, m, C(5)H₂–C(17)H₂), 1.46–1.56 (2H, m, C(4)H₂), 1.99 (3H, s, COMe), 2.00 (3H, s, COMe), 3.85 (1H, dd, *J* 10.4, 3.9, C(1)H_A), 3.93–3.99 (2H, m, C(1)H_B, C(2)H), 4.06–4.13 (1H, m, C(3)H), 6.16 (1H, d, *J* 7.6, NH), 6.50 (1H, d, *J* 9.2, NH); δ_{C} (125 MHz, CDCl₃) 11.7 (Si(CHMe₂)₃), 14.1 (C(18)), 17.9 (Si(CHMe₂)₃), 22.7 (C(17)), 26.2, 29.3, 29.4, 29.5, 29.5, 29.6–29.7, 32.0 (C(5)–C(16)), 23.4, 23.5 (COMe), 33.2 (C(4)), 52.1 (C(2)), 52.3 (C(3)), 63.1 (C(1)), 169.9 (COMe), 170.3 (COMe); *m/z* (ESI⁺) 541 ([M+H]⁺, 100%); HRMS (ESI⁺) C₃₁H₆₅N₂O₃Si⁺ ([M+H]⁺) requires 541.4759; found 541.4753.

(2*R*,3*R*,4*R*, α *R*)-2-Hydroxy-3-[*N*-benzyl-*N*-(α -methylbenzyl)amino]-4-(*N,N*-dibenzylamino)-5-pentanolactone 73. TBAF (1.0 M in THF, 10.6 mL, 10.6 mmol) was added to a stirred solution of (2*R*,3*R*,4*R*, α *R*)-**51** (3.96 g, 5.28 mmol, >99:1 dr) in THF (80 mL) at 0 °C and the resultant solution was stirred at rt for 24 h. Et₂O (40 mL) and H₂O (40 mL) were added and the aqueous layer was extracted with Et₂O (3 × 200 mL). The combined organics were washed with satd aq NaHCO₃ (150 mL), then dried and concentrated in vacuo. Purification via flash column chromatography (eluent 30–40 °C petroleum ether/EtOAc, 20:1; increased to 30–40 °C petroleum ether/EtOAc, 5:1) gave **73** as a white foam (1.67 g, 61%, >99:1 dr); C₃₄H₃₆N₂O₃ requires C, 78.4; H, 7.0; N, 5.4%; found C, 78.4; H, 6.95; N, 5.4%; [α]_D²⁰ –14.3 (c 1.0 in CHCl₃); ν_{\max} 3477 (O–H), 1744 (C=O); δ_{H} (400 MHz, CDCl₃) 1.24 (3H, d, *J* 6.8, C(α)Me), 3.29–3.40 (2H, m, C(3)H, C(4)H) overlapping 3.34 (2H, d, *J* 12.9, N(CH_AH_BPh)₂), 3.67–3.76 (2H, m, NCH₂Ph) overlapping 3.73 (2H, d, *J* 12.9, N(CH_AH_BPh)₂), 3.93 (1H, dd, *J* 13.0, 3.3, C(5)H_A), 4.24 (1H, q, *J* 6.8, C(α)H), 4.34 (1H, d, *J* 10.9, C(2)H), 4.67 (1H, app d, *J* 13.0, C(5)H_B) 7.01–7.42 (20H, m, *Ph*); δ_{C} (100 MHz, CDCl₃) 20.3 (C(α)Me), 51.1 (NCH₂Ph), 54.7 (N(CH₂Ph)₂), 56.7 (C(3)), 61.0 (C(α)), 62.6 (C(4)), 63.9 (C(5)), 68.4 (C(2)), 126.8, 127.1, 127.4, 128.0, 128.1, 128.4, 128.4, 129.2 (*o,m,p-Ph*), 138.7, 140.8, 145.0 (*i-Ph*), 174.5 (C(1)); *m/z* (ESI⁺) 543 ([M+Na]⁺, 40%), 521 ([M+H]⁺, 100%); HRMS (ESI⁺) C₃₄H₃₇N₂O₃⁺ ([M+H]⁺) requires 521.2799; found 521.2780.

***tert*-Butyl (2*R*,3*R*,4*R*, α *R*)-2-benzyloxy-3-[*N*-benzyl-*N*-(α -methylbenzyl)amino]-4-(*N,N*-dibenzylamino)-5-(triisopropylsilyloxy)pentanoate 77.** NaH (60% dispersion in mineral oil, 82 mg, 2.06 mmol) was added to a stirred solution of (2*R*,3*R*,4*R*, α *R*)-**51** (910 mg, 1.21 mmol, >99:1 dr) in THF (10 mL) at 0 °C and the resultant solution was stirred at 0 °C for 30 min. BnBr (288 μ L, 2.42 mmol) was then added and the resultant solution was stirred at rt for 24 h. Satd aq NH₄Cl (2 mL) was then added and the organic layer was washed sequentially with brine (15 mL) and H₂O (15 mL). The combined aqueous layers were extracted with Et₂O (3 × 25 mL), then the combined organics were dried and concentrated in vacuo.

Purification via flash column chromatography (eluent 30–40 °C petroleum ether, neat; increased to 30–40 °C petroleum ether/EtOAc, 20:1) gave **77** as a pale yellow oil (863 mg, 85%, >99:1 dr); $[\alpha]_{\text{D}}^{22} +20.4$ (*c* 1.0 in CHCl₃); ν_{max} 1735 (C=O); δ_{H} (400 MHz, CDCl₃) 0.97–1.12 (21H, m, Si(CHMe₂)₃), 1.37 (3H, d, *J* 6.7, C(α)Me), 1.52 (9H, s, CMe₃), 3.53–3.63 (2H, m, C(4)H, C(α)H), 3.67 (1H, d, *J* 15.3, NCH_AH_BPh), 3.73–3.80 (2H, m, C(2)H, NCH_AH_BPh), 3.81–3.89 (3H, m, C(3)H, N(CH_AH_BPh)₂), 3.93–4.02 (3H, m, OCH_AH_BPh, N(CH_AH_BPh)₂), 4.02–4.12 (2H, m, C(5)H₂), 4.52 (1H, d, *J* 10.6, OCH_AH_BPh), 6.98–7.13 (10H, m, *Ph*), 7.19–7.32 (11H, m, *Ph*), 7.36–7.42 (4H, m, *Ph*); δ_{C} (100 MHz, CDCl₃) 11.9 (Si(CHMe₂)₃), 18.2 (Si(CHMe₂)₃), 21.5 (C(α)Me), 28.1 (CMe₃), 53.0 (NCH₂Ph), 55.0 (N(CH₂Ph)₂), 59.1 (C(α)), 61.2 (C(4)), 61.8 (C(3)), 62.5 (C(5)), 72.0 (OCH₂Ph), 80.6 (C(2)), 81.6 (CMe₃), 125.8, 126.4, 126.6, 127.4, 127.6, 127.8, 127.8, 128.1, 128.3, 128.4, 129.7, 129.7 (*o,m,p-Ph*), 137.7, 141.0, 141.5, 143.9 (*i-Ph*), 171.3 (C(1)); *m/z* (ESI⁺) 841 ([M+H]⁺, 100%); HRMS (ESI⁺) C₅₄H₇₃N₂O₄Si⁺ ([M+H]⁺) requires 841.5334; found 841.5336.

tert-Butyl (2R,3R,4R, α R)-2-benzyloxy-3-[N-benzyl-N-(α -methylbenzyl)amino]-4-(N,N-dibenzylamino)-5-hydroxypentanoate **78.** HF (70% in pyridine, 463 μ L, 17.8 mmol) was added to a stirred solution of **77** (500 mg, 0.594 mmol, >99:1 dr) in THF (10 mL) at 0 °C and the resultant mixture was stirred at rt for 18 h. Satd aq NaHCO₃ (10 mL) was added and the aqueous layer was extracted with EtOAc (3 \times 15 mL), then the combined organics were dried and concentrated in vacuo. Purification via flash column chromatography (eluent 30–40 °C petroleum ether/EtOAc, 8:1) gave **78** as a colourless oil (313 mg, 77%, >99:1 dr); $[\alpha]_{\text{D}}^{22} +2.6$ (*c* 1.0 in CHCl₃); ν_{max} 3527 (O–H), 1734 (C=O); δ_{H} (400 MHz, CDCl₃) 1.50 (9H, s, CMe₃), 1.62 (3H, d, *J* 7.1, C(α)Me), 3.24 (1H, br s, OH), 3.39–3.47 (2H, m, C(4)H, C(5)H_A), 3.58–3.65 (2H, m, C(2)H, NCH_AH_BPh), 3.66–3.76 (4H, m, C(5)H_B, N(CH_AH_BPh)₂, OCH_AH_BPh), 3.84 (2H, d, *J* 13.4, N(CH_AH_BPh)₂), 4.02 (1H, app d, *J* 7.2, C(3)H), 4.10 (1H, q, *J* 7.1, C(α)H), 4.40 (1H, d, *J* 15.7, NCH_AH_BPh), 4.53 (1H, d, *J* 11.0, OCH_AH_BPh), 7.13–7.40 (25H, m, *Ph*); δ_{C} (100 MHz, CDCl₃) 21.5 (C(α)Me), 28.1 (CMe₃), 51.9 (NCH₂Ph), 54.4 (N(CH₂Ph)₂), 57.7 (C(α)), 58.9 (C(5)), 59.3 (C(3)), 60.9 (C(4)), 72.4 (OCH₂Ph), 79.1 (C(2)), 82.3 (CMe₃), 126.6, 126.9, 127.1, 127.5, 127.5, 128.1, 128.2, 128.2, 128.3, 128.3, 128.5, 129.2 (*o,m,p-Ph*), 137.7, 140.1, 140.5, 142.5 (*i-Ph*), 171.6 (C(1)); *m/z* (ESI⁺) 685 ([M+H]⁺, 100%); HRMS (ESI⁺) C₄₅H₅₃N₂O₄⁺ ([M+H]⁺) requires 685.4000; found 685.3994.

(2R,3R,4R, α R)-2-Benzyloxy-3-[N-benzyl-N-(α -methylbenzyl)amino]-4-(N,N-dibenzylamino)-5-pentanolactone **79 and (2S,3R,4R, α R)-2-benzyloxy-3-[N-benzyl-N-(α -methylbenzyl)amino]-4-(N,N-dibenzylamino)-5-pentanolactone **80**.** *Method A.* NaH (60% dispersion in mineral oil, 20 mg, 0.50 mmol) was added to a stirred solution of **73** (238 mg, 0.457 mmol, >99:1 dr) in THF (5 mL) at 0 °C and the resultant solution was stirred at 0 °C for 30 min. BnBr (109 μ L, 0.914 mmol) was then added and the resultant solution was stirred at rt for 24 h. Satd aq NH₄Cl (2 mL) was then added and the organic layer was

washed sequentially with brine (10 mL) and H₂O (10 mL). The combined aqueous layers were extracted with Et₂O (3 × 15 mL), and the combined organics were dried and concentrated in vacuo. Purification via flash column chromatography (eluent 30–40 °C petroleum ether/EtOAc, 5:1) gave **73** as a colourless viscous oil (49 mg, 21%, >99:1 dr). Exhaustive chromatography of the residue gave an 8:92 mixture of **79** and **80** as a colourless oil (13 mg, 5%); ν_{max} 1753 (C=O); δ_{H} (400 MHz, acetone-*d*₆) 1.08 (3H, d, *J* 7.0, C(α)Me), 3.31 (1H, app q, *J* 4.3, C(4)*H*), 3.47 (2H, d, *J* 13.7, N(CH_AH_BPh)₂), 3.54 (1H, dd, *J* 8.1, 4.3, C(3)*H*), 3.66 (2H, d, *J* 13.7, N(CH_AH_BPh)₂), 3.69 (1H, d, *J* 14.6, NCH_AH_BPh), 3.80 (1H, d, *J* 14.6, NCH_AH_BPh), 4.19 (1H, d, *J* 10.8, OCH_AH_BPh), 4.26 (1H, q, *J* 7.0, C(α)*H*), 4.37 (1H, d, *J* 8.1, C(2)*H*), 4.45 (1H, dd, *J* 12.5, 4.1, C(5)*H*_A), 4.73 (1H, d, *J* 10.8, OCH_AH_BPh), 4.73–4.79 (1H, m, C(5)*H*_B), 7.00–7.50 (25H, m, *Ph*); δ_{C} (125 MHz, acetone-*d*₆) 22.6 (C(α)Me), 52.1 (NCH₂Ph), 55.3 (N(CH₂Ph)₂), 59.5 (C(4)), 60.8 (C(α)), 62.1 (C(3)), 65.0 (C(5)), 73.1 (OCH₂Ph), 77.5 (C(2)), 127.4, 127.9, 128.0, 128.7, 129.1, 129.2, 129.4, 130.1 (*o,m,p-Ph*), 139.0, 140.5, 142.6, 145.9 (*i-Ph*), 172.1 (C(1)); *m/z* (ESI⁺) 611 ([M+H]⁺, 100%), HRMS (ESI⁺) C₄₁H₄₃N₂O₃⁺ ([M+H]⁺) requires 611.3268; found 611.3267.

Method B. HBF₄ (48% aq, 48 μ L, 0.37 mmol) was added to a stirred solution of **78** (50 mg, 73 μ mol, >99:1 dr) in CH₂Cl₂ (0.3 mL) at rt and the resultant solution was stirred at rt for 48 h. CHCl₃/*i*PrOH (3:1 v/v, 3 mL) was then added and the resultant solution was washed with satd aq NaHCO₃ (2 mL), then dried and concentrated in vacuo. Purification via flash column chromatography (eluent 30–40 °C petroleum ether/EtOAc, 5:1) gave **78** as a colourless oil (15 mg, 30%, >99:1 dr). Further elution gave a 50:50 mixture of **78** and **79** as a colourless oil (16 mg, 34% [calculated]). Data for **79**: δ_{H} (400 MHz, CDCl₃) [selected peaks] 1.18 (3H, d, *J* 6.9, C(α)Me), 3.39–3.46 (3H, m, C(4)*H*, N(CH_AH_BPh)₂), 3.58–3.65 (1H, m, C(3)*H*), 3.70 (2H, d, *J* 13.9, N(CH_AH_BPh)₂), 3.76 (1H, d, *J* 4.7, C(2)*H*), 3.90 (2H, app s, NCH₂Ph), 4.17–4.25 (2H, m, C(5)*H*_A, C(α)*H*), 4.36 (1H, d, *J* 11.6, OCH_AH_BPh), 4.49–4.57 (1H, m, C(5)*H*_B), 4.71 (1H, d, *J* 11.6, OCH_AH_BPh); δ_{C} (100 MHz, CDCl₃) [selected peaks] 20.6 (C(α)Me), 52.2 (NCH₂Ph), 54.6 (N(CH₂Ph)₂), 56.9 (C(4)), 57.2 (C(3)), 59.7 (C(α)), 65.5 (C(5)), 72.7 (OCH₂Ph), 77.7 (C(2)).

Method C. TBAF (1.0 M in THF, 0.24 mL, 0.24 mmol) was added to a stirred solution of **77** (100 mg, 0.119 mmol, >99:1 dr) in THF (2 mL) at 0 °C and the resultant solution was stirred at rt for 24 h. Et₂O (2 mL) and H₂O (2 mL) were added, and the aqueous layer was extracted with Et₂O (3 × 5 mL). The combined organics were washed with satd aq NaHCO₃ (15 mL), then dried and concentrated in vacuo to give a 39:61 mixture of **79** and **80**, respectively. Purification via flash column chromatography (eluent 30–40 °C petroleum ether/EtOAc, 5:1) gave a 39:61 mixture of **79** and **80** as a colourless oil (38 mg, 52%).

Method D. TBAF (1.0 M in THF, 0.15 mL, 0.15 mmol) was added to a stirred solution of **78** (50 mg, 0.073 mmol, >99:1 dr) in THF (1.5 mL) at 0 °C and the resultant solution was stirred at rt for 24 h. Et₂O (1

mL) and H₂O (1 mL) were added, and the aqueous layer was extracted with Et₂O (3 × 3 mL). The combined organics were washed with satd aq NaHCO₃ (10 mL), then dried and concentrated in vacuo to give a 50:50 mixture of **79** and **80**. Purification via flash column chromatography (eluent 30–40 °C petroleum ether/EtOAc, 5:1) gave a 50:50 mixture of **79** and **80** as a colourless oil (23 mg, 52%).

(2R,3R,4R,αR)-2-Benzyloxy-3-[N-benzyl-N-(α-methylbenzyl)amino]-4-(N,N-dibenzylamino)-5-(triisopropylsilyloxy)pentan-1-ol 81. DIBAL-H (1.0 M in PhMe, 11.8 mL, 11.8 mmol) was added to a stirred solution of **77** (1.66 g, 1.97 mmol, >99:1 dr) in PhMe (33 mL) at –78 °C and the resultant solution was stirred at rt for 18 h. The resultant solution was cooled to 0 °C and satd aq NH₄Cl (10 mL) and satd aq Rochelle salt (20 mL) were added sequentially. The resultant biphasic mixture was stirred at rt for 18 h, then filtered through Celite® (eluent EtOAc), dried and concentrated in vacuo. Purification via flash column chromatography (eluent 30–40 °C petroleum ether/EtOAc, 10:1) gave **81** as colourless oil (1.32 g, 87%, >99:1 dr); [α]_D²² +15.4 (*c* 1.0 in CHCl₃); ν_{max} 3420 (O–H); δ_H (400 MHz, CDCl₃) 0.95 (3H, d, *J* 6.9, C(α)*Me*), 1.04–1.17 (21H, m, Si(CHMe₂)₃), 1.61 (1H, br s, OH), 3.24–3.29 (1H, m, C(2)*H*), 3.33 (1H, dd, *J* 6.6, 3.5, C(3)*H*), 3.44–3.61 (5H, m, C(1)*H*₂, C(4)*H*, C(α)*H*, NCH_AH_BPh), 3.72 (2H, d, *J* 13.0, N(CH_AH_BPh)₂), 3.74 (1H, d, *J* 14.8, NCH_AH_BPh), 3.98 (1H, dd, *J* 10.7, 3.8, C(5)*H*_A), 4.15 (2H, d, *J* 13.0, N(CH_AH_BPh)₂), 4.20 (1H, d, *J* 11.1, OCH_AH_BPh), 4.41 (1H, dd, *J* 10.7, 8.0, C(5)*H*_B), 4.60 (1H, d, *J* 11.1, OCH_AH_BPh), 6.97 (2H, m, *Ph*), 7.15–7.21 (8H, m, *Ph*), 7.23–7.30 (7H, m, *Ph*), 7.35 (4H, t, *J* 7.4, *Ph*), 7.44 (4H, d, *J* 7.0, *Ph*); δ_C (100 MHz, CDCl₃) 12.0 (Si(CHMe₂)₃), 18.2 (C(α)*Me*), 18.3 (Si(CHMe₂)₃), 52.4 (NCH₂Ph), 55.6 (N(CH₂Ph)₂), 57.7 (C(α)), 62.0 (C(5)), 62.3 (C(1)), 63.1 (C(3)), 63.3 (C(4)), 71.1 (OCH₂Ph), 79.5 (C(2)), 126.5, 126.8, 127.0, 127.5, 127.5, 128.0, 128.1, 128.1, 128.1, 128.3, 128.3, 130.0 (*o,m,p-Ph*), 137.9, 140.3, 140.4, 143.1 (*i-Ph*); *m/z* (ESI⁺) 771 ([M+H]⁺, 100%); HRMS (ESI⁺) C₅₀H₆₇N₂O₃Si⁺ ([M+H]⁺) requires 771.4915; found 771.4907

1-(1'-Phenyl-1*H*-tetrazol-5'-ylsulfonyl)tridecane 84. *Step 1.* K₂CO₃ (2.07 g, 15.0 mmol) and PTSH (1.47 g, 8.23 mmol) were added sequentially to a stirred solution of 1-bromotridecane (1.97 g, 7.48 mmol) in acetone (30 mL) and the resultant solution was stirred at 65 °C for 2.5 h. The resultant solution was allowed to cool to rt, then filtered and concentrated in vacuo. The residue was partitioned between CH₂Cl₂ (20 mL) and H₂O (20 mL) and the aqueous layer was extracted with CH₂Cl₂ (3 × 20 mL). The combined organics were washed with H₂O (50 mL), then dried and concentrated in vacuo to give **83** as a white solid (2.40 g); δ_H (400 MHz, CDCl₃) 0.89 (3H, t, *J* 6.9, C(13)*H*₃), 1.20–1.35 (18H, m, C(4)*H*₂–C(12)*H*₂), 1.40–1.49 (2H, m, C(3)*H*₂), 1.82 (2H, app quintet, *J* 7.4, C(2)*H*₂), 3.40 (2H, t, *J* 7.4, C(1)*H*₂), 7.51–7.62 (5H, m, *Ph*).

Step 2. A solution of the residue **83** (2.40 g) from the previous step in EtOH (100 mL) was added dropwise to a stirred solution of (NH₄)₂Mo₇O₂₄·4H₂O (1.85 g, 1.50 mmol) in 30% aq H₂O₂ (11.5 mL, 112

mmol) at 0 °C and the resultant solution was stirred at rt for 18 h. Brine (100 mL) was added and the aqueous layer was extracted with EtOAc (3 × 150 mL). The combined organics were dried and concentrated in vacuo. The residue was suspended in MeOH (30 mL) and the resultant suspension was stirred at rt until complete dissolution occurred (~1 h), then the resultant solution was cooled to 0 °C and stirred at 0 °C for 1 h during which time a precipitate formed. The precipitate of **84** was then collected by filtration, the filtrate was concentrated in vacuo and the above process was repeated twice to give **84** as a white solid (2.33 g, 79%); mp 50–52 °C; ν_{max} 1339 (S=O), 1151 (S=O); δ_{H} (400 MHz, CDCl₃) 0.88 (3H, t, *J* 6.7, C(13)*H*₃), 1.20–1.28 (18H, m, C(4)*H*₂–C(12)*H*₂), 1.44–1.54 (2H, m, C(3)*H*₂), 1.89–2.01 (2H, m, C(2)*H*₂), 3.68–3.77 (2H, m, C(1)*H*₂), 7.55–7.73 (5H, m, *Ph*); δ_{C} (100 MHz, CDCl₃) 14.1 (C(13)), 21.9 (C(2)), 22.6, 29.1, 29.3, 29.4, 29.5, 29.6 (C(4)–C(12)), 28.1 (C(3)), 56.0 (C(1)), 125.0, 129.7, 131.4 (*o,m,p-Ph*), 133.0 (*i-Ph*), 153.4 (C(5')); *m/z* (ESI⁺) 415 ([M+Na]⁺, 100%); HRMS (ESI⁺) C₂₀H₃₂O₂N₄NaS⁺ ([M+Na]⁺) requires 415.2138; found 415.2142.

(2*R*,3*R*,4*S*, α *R*,*E*)-1-(Triisopropylsilyloxy)-2-(*N,N*-dibenzylamino)-3-[*N*-benzyl-*N*-(α -methylbenzyl)amino]-4-benzyloxyoctadec-5-ene **85 and (2*R*,3*R*,4*S*, α *R*,*Z*)-1-(triisopropylsilyloxy)-2-(*N,N*-dibenzylamino)-3-[*N*-benzyl-*N*-(α -methylbenzyl)amino]-4-benzyloxyoctadec-5-ene **86**. Method A. Wittig Olefination. Step 1. IBX (54 mg, 0.19 mmol) was added to a stirred solution of **81** (50 mg, 65 μ mol, >99:1 dr) in DMSO (1 mL) at rt and the resultant solution was stirred at rt for 18 h. Et₂O (2 mL) was added and the resultant solution was washed with H₂O (5 × 2 mL), then dried and concentrated in vacuo to give **82** as a yellow oil (41 mg).**

Step 2. BuLi (2.2 M in hexanes, 88 μ L, 0.19 mmol) was added dropwise to a stirred solution of [C₁₃H₂₇PPh₃]⁺[Br][−] (0.10 g, 0.19 mmol) in THF (1.2 mL) at 0 °C and the resultant solution was stirred at 0 °C for 30 min. A solution of the residue **82** (41 mg) from the previous step in THF (1.2 mL) at 0 °C was then added dropwise via cannula and the resultant solution was stirred at 75 °C for 2 h. The resultant solution was allowed to cool to rt, then H₂O (1 mL) and brine (1 mL) were added sequentially and the aqueous layer was extracted with EtOAc (3 × 5 mL). The combined organics were washed with satd aq NaHCO₃ (10 mL) then dried and concentrated in vacuo. Purification via flash column chromatography (eluent 30–40 °C petroleum ether/Et₂O, 50:1) gave an impure sample of **86** as a colourless oil (24 mg, ~90% purity, ~35%, >95:5 dr [(*E*):(*Z*) ratio]); ν_{max} 1602 (C=C); δ_{H} (500 MHz, CDCl₃) 0.87 (3H, t, *J* 6.9, C(18)*H*₃), 1.01–1.12 (24H, m, C(α)*Me*, Si(*CHMe*₂)₃), 1.22–1.31 (20H, m, C(8)*H*₂–C(17)*H*₂), 1.84–1.93 (1H, m, C(7)*H*_A), 1.97–2.06 (1H, m, C(7)*H*_B), 3.20 (1H, dd, *J* 6.9, 3.8, C(3)*H*), 3.54 (2H, d, *J* 13.9, (N(*CH*_A*H*_BPh)₂), 3.49–3.56 (1H, m C(2)*H*), 3.69 (1H, d, *J* 15.3, N*CH*_A*H*_BPh), 3.79 (1H, d, *J* 11.2, O*CH*_A*H*_BPh), 3.92 (1H, q, *J* 6.8, C(α)*H*), 3.93–4.00 (3H, m, N(*CH*_A*H*_BPh)₂, N*CH*_A*H*_BPh), 4.16 (1H, dd, *J* 10.6, 6.0, C(1)*H*_A), 4.21 (1H, dd, *J* 10.6, 5.8, C(1)*H*_B),

4.31–4.38 (2H, m, C(4)*H*, OCH_AH_BPh), 5.23 (1H, app t, *J* 10.6, C(5)*H*), 5.49–5.56 (1H, m, C(6)*H*), 7.00–7.28 (25H, m, *Ph*); δ_{C} (125 MHz, CDCl₃) 12.0 (Si(CHMe₂)₃), 14.1 (C(18)), 18.2 (Si(CHMe₂)₃), 20.3 (C(α)Me), 22.7 (C(17)), 29.4, 29.5, 29.6, 29.6, 29.7, 31.9 (C(8)–C(16)), 27.9 (C(7)), 51.8 (NCH₂Ph), 55.1 (N(CH₂Ph)₂), 58.3 (C(α)), 61.1 (C(1)), 62.9 (C(2)), 64.6 (C(3)), 69.2 (OCH₂Ph), 74.7 (C(4)), 125.9, 126.3, 126.5, 126.9, 127.2, 127.7, 127.7, 127.9, 128.0, 128.0, 128.4, 128.4 (*o,m,p*-Ph), 129.4 (C(5)), 133.6 (C(6)), 138.8, 141.0, 142.1, 145.3 (*i*-Ph); *m/z* (ESI⁺) 937 (100%), 936 ([M+H]⁺, 56%), 833 (70%); HRMS (ESI⁺) C₆₃H₉₁N₂O₂Si⁺ ([M+H]⁺) requires 935.6844; found 935.6833.

Method B. Julia Olefination. Step 1. IBX (406 mg, 1.45 mmol) was added to a stirred solution of **81** (372 mg, 0.482 mmol) in DMSO (7.5 mL) at rt and the resultant solution was stirred at rt for 18 h. Et₂O (20 mL) was added and the resultant solution was washed with H₂O (5 × 30 mL), then dried and concentrated in vacuo to give **82** as a yellow oil (325 mg).

Step 2. LiHMDS (1.0 M in THF, 0.88 mL, 0.88 mmol) was added dropwise via syringe to a stirred solution of the residue **82** (325 mg) from the previous step and **84** (172 mg, 0.439 mmol) in THF (1.5 mL) at –10 °C, and the resultant solution was stirred at rt for 18 h. The resultant solution was cooled to 0 °C and then satd aq NH₄Cl (1 mL) and brine (3 mL) were added sequentially. The aqueous layer was extracted with Et₂O (3 × 5 mL) and the combined organics were dried and concentrated in vacuo to give an 82:18 mixture of **85** and **86**, respectively. Purification via flash column chromatography (eluent 30–40 °C petroleum ether/Et₂O, 40:1) gave an 82:18 mixture of **85** and **86** as a pale yellow oil (312 mg, 69%). Data for mixture: ν_{max} 1603 (C=C); *m/z* (ESI⁺) 937 (100%), 936 ([M+H]⁺, 67%), 833 (50%); HRMS (ESI⁺) C₆₃H₉₁N₂O₂Si⁺ ([M+H]⁺) requires 935.6844; found 935.6816. Data for **85**: δ_{H} (400 MHz, CDCl₃) 0.87–0.93 (3H, m, C(18)*H*₃), 1.05–1.17 (24H, m, C(α)Me, Si(CHMe₂)₃), 1.27–1.38 (20H, m, C(8)*H*₂–C(17)*H*₂), 1.83–2.07 (4H, m, C(7)*H*₂), 3.17–3.26 (1H, m, C(3)*H*), 3.49–3.60 (3H, m, C(2)*H*, N(CH_AH_BPh)₂), 3.63–3.76 (1H, m, NCH_AH_BPh), 3.78–3.84 (1H, m, OCH_AH_BPh), 3.91–3.99 (2H, m, C(α)*H*, NCH_AH_BPh), 3.99–4.04 (2H, m, N(CH_AH_BPh)₂), 4.19 (1H, dd, *J* 10.4, 5.8, C(1)*H*_A), 4.25 (1H, dd, *J* 10.4, 5.8, C(1)*H*_B), 4.30–4.42 (2H, m, C(4)*H*, OCH_AH_BPh), 5.15–5.32 (1H, m, C(5)*H*), 5.52–5.60 (1H, m, C(6)*H*), 7.08–7.40 (25H, m, *Ph*); δ_{C} (100 MHz, CDCl₃) 12.0 (Si(CHMe₂)₃), 14.2 (C(18)), 18.3 (Si(CHMe₂)₃), 19.1 (C(α)Me), 22.7 (C(17)), 29.3, 29.4, 29.5, 29.6, 29.6, 29.8, 30.3, 30.9, 32.0 (C(8)–C(16)), 32.3 (C(7)), 51.8 (NCH₂Ph), 55.3 (N(CH₂Ph)₂), 57.4 (C(α)), 61.7 (C(1)), 63.5 (C(2)), 64.2 (C(3)), 69.5 (OCH₂Ph), 81.6 (C(4)), 126.1, 126.3, 126.4, 127.0, 127.4, 127.7, 127.8, 127.9, 128.0, 128.2, 128.3 (*o,m,p*-Ph), 130.3 (C(5)), 134.2 (C(6)), 138.9, 141.2, 141.7, 144.4 (*i*-Ph);

(**2R,3R,4S, α R,E**)-2-(*N,N*-Dibenzylamino)-3-[*N*-benzyl-*N*-(α -methylbenzyl)amino]-4-(benzyloxy)octadec-5-en-1-ol **87** and (**2R,3R,4S, α R,Z**)-2-(*N,N*-dibenzylamino)-3-[*N*-benzyl-*N*-(α -

methylbenzyl)amino]-4-(benzyloxy)octadec-5-en-1-ol 88. *Method A.* TBAF (1.0 M in THF, 0.42 mL, 0.42 mmol) was added to a stirred solution of an 82:18 mixture of **85** and **86** (195 mg, 0.207 mmol) in THF (4 mL) at 0 °C and the resultant solution was stirred at rt for 18 h. Et₂O (2 mL) and H₂O (2 mL) were added and the aqueous layer was extracted with Et₂O (3 × 5 mL). The combined organics were washed with satd aq NaHCO₃ (15 mL), then dried and concentrated in vacuo. Purification via flash column chromatography (eluent 30–40 °C petroleum ether/Et₂O, 30:1; increased to 30–40 °C petroleum ether/Et₂O, 5:1) gave an 82:18 mixture of **85** and **86** as a pale yellow oil (40 mg, 21%). Further elution gave an 82:18 mixture of **87** and **88** as a colourless oil (111 mg, 68%). Data for mixture: ν_{\max} 3453 (O–H), 1602 (C=C); m/z (ESI⁺) 780 ([M+1+H]⁺, 100%), 779 ([M+H]⁺, 98%); HRMS (ESI⁺) C₅₄H₇₁N₂O₂⁺ ([M+H]⁺) requires 779.5510; found 779.5498. Data for **87**: δ_H (500 MHz, CDCl₃) 0.89 (3H, t, *J* 6.9, C(18)H₃), 1.24–1.30 (20H, m, C(8)H₂–C(17)H₂), 1.33 (3H, d, *J* 7.0, C(α)Me), 1.91–2.06 (2H, m, C(7)H₂), 3.26 (1H, dd, *J* 6.2, 3.4, C(3)H), 3.41 (1H, app q, *J* 6.0, C(2)H), 3.57 (2H, d, *J* 14.0, N(CH_AH_BPh)₂), 3.64–3.83 (7H, m, C(1)H₂, C(4)H, N(CH_AH_BPh)₂, NCH_AH_BPh, OCH_AH_BPh), 3.96 (1H, q, *J* 7.0, C(α)H), 4.25 (1H, d, *J* 15.4, NCH_AH_BPh), 4.33 (1H, d, *J* 11.2, OCH_AH_BPh), 5.30 (1H, dd, *J* 15.7, 7.7, C(5)H), 5.36–5.44 (1H, m, C(6)H), 7.11–7.36 (25H, m, *Ph*); δ_C (125 MHz, CDCl₃) 14.2 (C(18)), 21.7 (C(α)Me), 22.7 (C(17)), 29.2, 29.3, 29.4, 29.5, 29.6, 29.7, 30.3, 31.9 (C(8)–C(16)), 32.4 (C(7)), 52.0 (NCH₂Ph), 54.5 (N(CH₂Ph)₂), 58.1 (C(α)), 60.0 (C(1)), 62.8 (C(3)), 62.9 (C(2)), 69.8 (OCH₂Ph), 80.3 (C(4)), 125.5, 126.5, 126.8, 127.5, 127.7, 128.0, 128.2, 128.3, 128.3, 128.5, 129.2 (*o,m,p-Ph*), 129.8 (C(5)), 134.5 (C(6)), 138.0, 140.3, 141.4, 144.4 (*i-Ph*). Data for **88**: δ_H (500 MHz, CDCl₃) [selected peaks] 0.86–0.93 (3H, m, C(18)H₃), 1.24–1.30 (20H, m, C(8)H₂–C(17)H₂), 1.98–2.06 (1H, m, C(7)H_A), 1.96–1.98 (1H, m, C(7)H_B), 3.16 (1H, dd, *J* 6.2, 3.2, C(3)H), 3.39–3.50 (3H, m, C(2)H, N(CH_AH_BPh)₂), 3.55–3.61 (1H, m, OCH_AH_BPh), 3.65–3.85 (2H, m, N(CH_AH_BPh)₂), 4.02 (1H, q, *J* 7.2, C(α)H), 4.30 (1H, d, *J* 11.2, OCH_AH_BPh), 4.40 (1H, dd, *J* 10.0, 3.0, C(4)H), 5.35–5.45 (1H, m, C(5)H), 5.53–5.63 (1H, m, C(6)H); δ_C (125 MHz, CDCl₃) [selected peaks] 14.2 (C(18)), 22.7 (C(17)), 27.9 (C(7)), 54.2 (N(CH₂Ph)₂), 58.5 (C(α)), 62.2 (C(2)), 63.7 (C(3)), 69.6 (OCH₂Ph), 75.5 (C(4)), 129.5 (C(5)), 134.2 (C(6)).

Method B. HF (70% in pyridine, 172 μ L, 6.64 mmol) was added to a stirred solution of an 82:18 mixture of **85** and **86** (207 mg, 0.221 mmol) in THF (4 mL) at 0 °C and the resultant mixture was stirred at rt for 18 h. Satd aq NaHCO₃ (10 mL) was added and the aqueous layer was extracted with EtOAc (3 × 15 mL), then the combined organics were dried and concentrated in vacuo. Purification via flash column chromatography (eluent 30–40 °C petroleum ether/EtOAc/35% aq NH₄OH, 90:10:1) gave an 82:18 mixture of **87** and **88** as a colourless oil (149 mg, 86%).

(2R,3R,4S)-2,3-Diacetamidooctadecan-1,4-diyl diacetate 89. *Step 1.* Pd(OH)₂/C (50% w/w of substrate, 122 mg) was added to a vigorously stirred solution of an 82:18 mixture of **87** and **88** (243 mg, 0.312 mmol) in degassed HCl (1.25 M in MeOH, 3 mL) at rt and the resultant suspension was stirred under H₂ (5 atm) at rt for 72 h, then filtered through Celite[®] (eluent MeOH) and concentrated in vacuo.

Step 2. Ac₂O (590 μ L, 6.24 mmol) and DMAP (3.8 mg, 0.031 mmol) were added sequentially to a stirred solution of the residue from the previous step in pyridine (879 μ L, 10.9 mmol) at rt, and the resultant solution was stirred at rt for 72 h. EtOAc (5 mL) was added, the resultant solution was washed with satd aq CuSO₄ (10 mL), and the aqueous layer was extracted with EtOAc (3 \times 20 mL). The combined organics were washed with satd aq NaHCO₃ (3 \times 50 mL) and the combined aqueous layers were then extracted with EtOAc (3 \times 50 mL). The combined organics were dried and concentrated in vacuo. Purification via flash column chromatography (eluent PhMe/*i*PrOH, 4:1) gave **89** as pale orange solid (109 mg, 72%, >99:1 dr); mp 73–75 °C; [α]_D²² –28.9 (*c* 1.0 in CHCl₃); ν_{\max} 3292 (N–H), 1740 (C=O, ester), 1657 (C=O, amide); δ_{H} (400 MHz, CDCl₃) 0.87 (3H, t, *J* 6.8, C(18)H₃), 1.18–1.33 (24H, m, C(6)H₂–C(17)H₂), 1.53–1.61 (2H, m, C(5)H₂), 1.95 (3H, s, COMe), 1.99 (3H, s, COMe), 2.05 (3H, s, COMe), 2.09 (3H, s, COMe), 4.08–4.27 (4H, m, C(1)H₂, C(2)H, C(3)H), 4.91 (1H, app q, *J* 5.9, C(4)H), 6.47–6.62 (2H, m, NH); δ_{C} (100 MHz, CDCl₃) 14.1 (C(18)), 20.8, 21.0 (COMe), 22.6 (C(17)), 23.2, 23.2 (COMe), 25.4, 29.3, 29.4, 29.5, 29.5, 29.6, 29.6, 29.6, 30.2, 31.9 (C(5)–C(16)), 49.2 (C(2)), 52.4 (C(3)), 63.4 (C(1)), 72.6 (C(4)), 171.0 (COMe); *m/z* (ESI⁺) 507 ([M+Na]⁺, 100%); HRMS (ESI⁺) C₂₆H₄₈N₂NaO₆⁺ ([M+Na]⁺) requires 507.3405; found 507.3398.

Supporting Information Available: Copies of ¹H and ¹³C NMR spectra, and crystallographic information file (for structures CCDC 1533117 and CCDC 1533118). This material is available free of charge via the Internet at <http://pubs.acs.org>.

[†] Deceased (26th July 2015).

References and Notes

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