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Asymmetric syntheses of methyl *N*-Boc-2-deoxy-2-amino-L-erythroside, methyl *N*-Boc-2-deoxy-2-amino-D-threoside and methyl *N*-Boc-2,3-dideoxy-3-amino-L-arabinopyranoside

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ABSTRACT

The asymmetric syntheses of methyl *N*-Boc-2-deoxy-2-amino-L-erythroside and methyl *N*-Boc-2-deoxy-2-amino-D-threoside have been achieved from sorbic acid, in six and eight steps, and in 35 and 13% overall yield, respectively. Diastereoselective aminohydroxylation of *tert*-butyl sorbate gives access to two diastereoisomeric α-hydroxy-β-amino-γ,δ-unsaturated esters. Reduction of the ester functionality and ozonolysis of the double bond gives the corresponding aldehyde, which exists exclusively in the ring-closed (furanose) form. An alternative synthesis of methyl *N*-Boc-2-deoxy-2-amino-L-erythroside was also developed, reliant on aminohydroxylation of an α,β-unsaturated ester bearing an acetal functionality at the γ-position, and this synthesis proceeded in five steps and 54% overall yield from acrolein diethyl acetal. This approach was extended to permit the synthesis of methyl *N*-Boc-2,3-dideoxy-3-amino-L-arabinopyranoside in six steps and 58% overall yield from ethyl 3,3-diethoxypropanote.

1. Introduction

Amino sugar moieties (analogues of monosaccharides in which one of the hydroxyl functionalities has been formally exchanged for an amino functionality) are prevalent as the glycosidic fragments in both naturally occurring and synthetic molecules with highly desirable biological activity, for example, antibacterial, antiviral and anticancer.[1] As such, there have been significant efforts from the synthetic community directed towards the development of efficient approaches to this class of compound.[2] Within this area, we have explored the oxidative functionalisation of the olefin within a range of alkyl 3-[*N*-benzyl-*N*-(α-methylbenzyl)amino]hex-4-enoates as an efficient method for the preparation of a range of amino hexoses.[3–6] The requisite substrates for these studies are readily accessible via our conjugate addition methodology, using either antipode of lithium *N*-benzyl-*N*-(α-methylbenzyl)amide as an enantiopure ammonia equivalent.[7] Subsequently, for example, treatment of **1** with OsO_4 under Upjohn conditions[8] proceeded under steric control to give diol **2**, which upon lactonisation, reduction and deprotection gave L-ristosamine, isolated as its *N*,*O*-diacetyl protected methyl glycoside **4**. Meanwhile, diastereoselective ammonium-directed epoxidation[9–12] of **5** gave epoxide **6**, which upon regioselective ring-opening, lactonisation, reduction and deprotection gave D-3-*epi*-daunosamine, isolated as its *N*,*O*-diacetyl protected methyl glycoside **10** (Scheme 1).[6]

We envisaged that this concept could be adapted to enable the preparation of the 2-deoxy-2-aminotetroses (2-deoxy-2-amino-L-erythrose **19** and 2-deoxy-2-amino-D-threose **20**) using ozonolysis (rather than dihydroxylation or epoxidation) of the C=C bond. Thus, it was anticipated that reduction of the ester functionality within either the *anti*- or *syn*-diastereoisomer of an alkyl 2-hydroxy-3-[*N*-benzyl-*N*-(α-methylbenzyl)amino]hex-4-enoate **12** would permit subsequent oxidative cleavage of the C=C bond within **13** to give the corresponding aldehyde **17**, which should undergo spontaneous cyclisation to the corresponding furanoside **18**. Alternatively, we anticipated a complementary synthetic approach to these compounds involving conjugate addition of enantiopure lithium *N*-benzyl-*N*-(α-methylbenzyl)amide to an α,β-unsaturated ester **14** (bearing an acetal functionality at the γ-position), with enolate oxidation using CSO as one of the key steps to give access to the *anti*- and *syn*-α-hydroxy-β-amino ester diastereoisomers **15**, with subsequent hydrolysis giving the corresponding furanoside **18** directly (Fig. 1). We report herein the results of our investigations into the development of these two approaches, which culminate in the formation of 2-deoxy-2-amino-L-erythrose **19** and 2-deoxy-2-amino-D-threose **20** in

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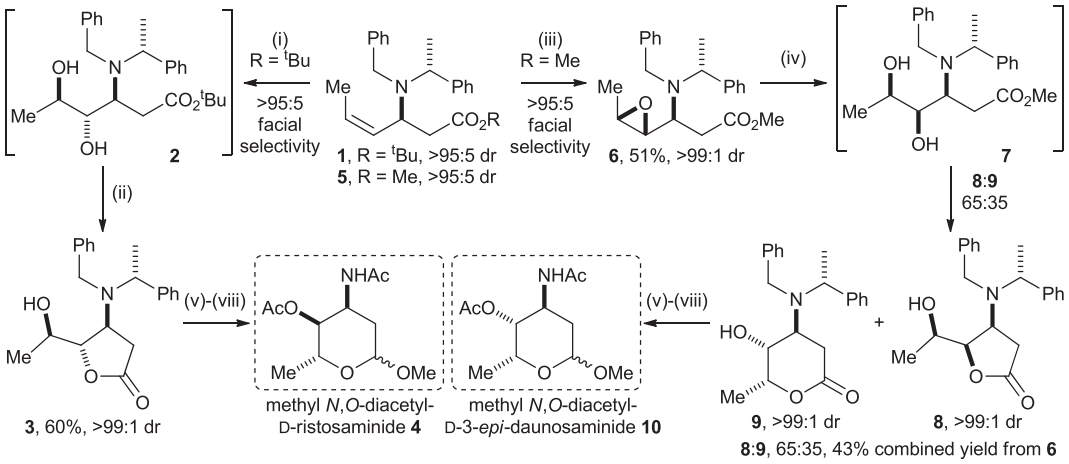


Scheme 1. Reagents and conditions: (i) OsO_4, NMO, THF, H_2O, rt, 16 h; (ii) F_3CCO_2H, CH_2Cl_2, rt, 12 h; (iii) F_3CCO_2H, F_3CCO_3H, CH_2Cl_2, rt, 16 h; (iv) H_2SO_4 (concd aq), 1,4-dioxane, H_2O, rt, 12 h; (v) Boc_2O, H_2, $Pd(OH)_2/C$, MeOH, rt, 48 h; (vi) DIBAL-H, CH_2Cl_2, −78 °C, 30 min; (vii) HCl, MeOH, rt, 16 h; (viii) Ac_2O, pyridine, DMAP, rt, 12 h.

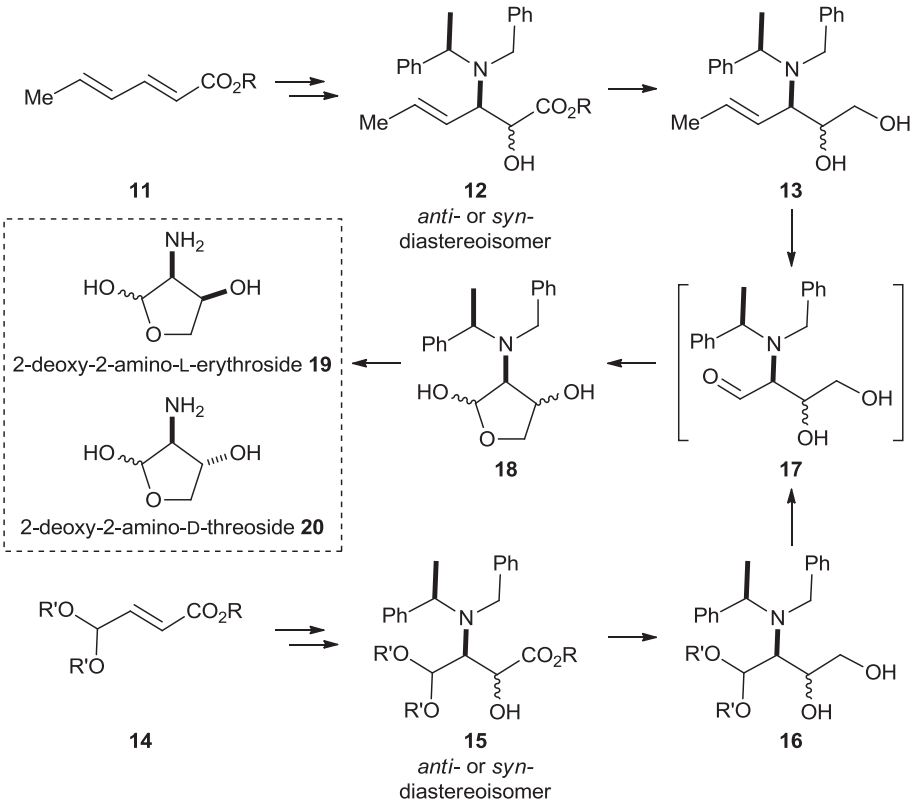
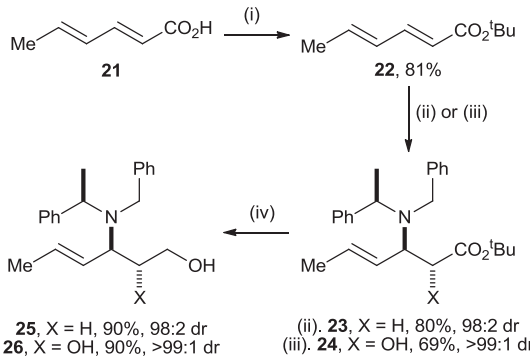


Fig. 1. Proposed synthesis of the 2-deoxy-2-aminotetroses 2-deoxy-2-amino-L-erythrose **19** and 2-deoxy-2-amino-D-threose **20**.

protected form.[13] The extension of this methodology to enable an asymmetric synthesis of 2,3-dideoxy-3-amino-L-arabinose in protected form is also delineated.

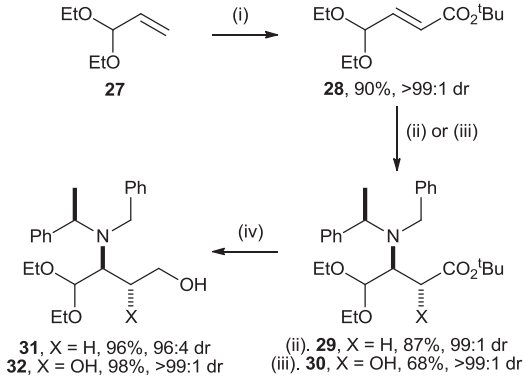
2. Results and discussion

The requisite α-hydroxy-β-amino ester substrates for these investigations were first prepared. Esterification of commercially available sorbic acid **21** was achieved under standard conditions (isobutylene/H_2SO_4)[14] to give *tert*-butyl sorbate **22** in 81% yield. Conjugate addition of lithium (*R*)-*N*-benzyl-*N*-(α-methylbenzyl)-amide to **22** and either in situ enolate protonation [using NH_4Cl (satd aq)][7] or oxidation [using (−)-camphorsulfonyloxaziridine, (−)-CSO][7,15] gave the known β-amino ester (3*S*,α*R*)-**23**[3–5,16,17] and the known *anti*-α-hydroxy-β-amino ester (*R*,*R*,*R*)-**24**[4,18] in 80% isolated yield and 98:2 dr, and 69% isolated yield and >99:1 dr, respectively. Reduction of the ester functionalities within both **23** and **24** using $LiAlH_4$ delivered the corresponding primary alcohols **25**[16] and **26**[18] in 90% isolated yield in both cases, and in 98:2 dr and >99:1 dr, respectively (Scheme 2).



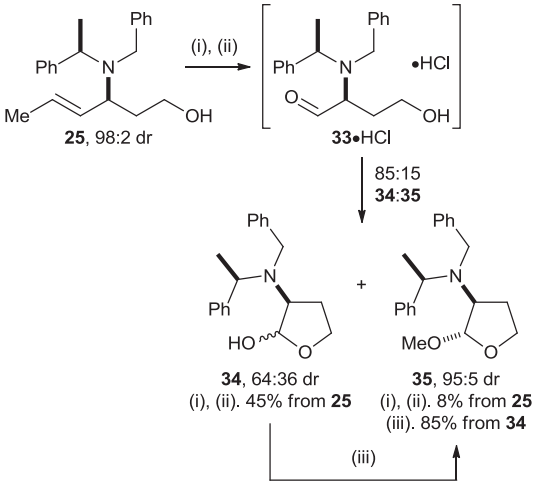
Scheme 2. Reagents and conditions: (i) isobutylene, H_2SO_4 (concd aq), CH_2Cl_2, 0 °C, 1 h, then rt, 48 h; (ii) lithium (*R*)-*N*-benzyl-*N*-(α-methylbenzyl)amide, THF, −78 °C, 2 h, then NH_4Cl (satd aq), −78 °C to rt, 15 min; (iii) lithium (*R*)-*N*-benzyl-*N*-(α-methylbenzyl)amide, THF, −78 °C, 2 h, then (−)-CSO, −78 °C to rt, 12 h; (iv) $LiAlH_4$, THF, 0 °C to rt, 16 h.

Cross-metathesis of acrolein diethyl acetal **27** with *tert*-butyl acrylate gave **28** ($^3J_{2,3}$=15.9 Hz) as a single diastereoisomer, which was isolated in 90% yield. Conjugate addition of lithium (*R*)-*N*-benzyl-*N*-(α-methylbenzyl)amide to **28** proceeded to give β-amino ester **29** in 99:1 dr, which was isolated in 87% yield. The amino-hydroxylation of **28** was performed, which gave α-hydroxy-β-amino ester **30** in 68% isolated yield and >99:1 dr. The absolute (3*S*,α*R*)-configuration within **29** and the absolute (2*R*,3*S*,α*R*)-configuration within **30** were assigned from the established stereochemical outcomes of these hydroamination[7,19] and amino-hydroxylation[7,15] reactions applied to a range of achiral α,β-unsaturated esters. Reduction of **29** and **30** using $LiAlH_4$ gave the corresponding primary alcohols **31** and **32** in 96 and 98% isolated yield, and in 96:4 dr and >99:1 dr, respectively (Scheme 3).



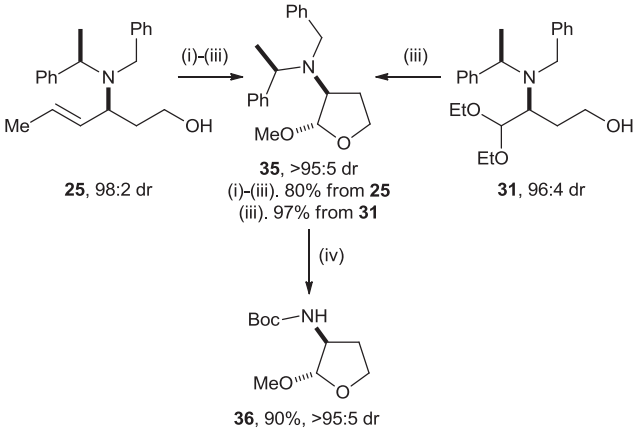
Scheme 3. Reagents and conditions: (i) *tert*-butyl acrylate, Hoveyda−Grubbs II, CH_2Cl_2, reflux, 22 h; (ii) lithium (*R*)-*N*-benzyl-*N*-(α-methylbenzyl)amide, THF, −78 °C, 2 h, then NH_4Cl (satd aq), −78 °C to rt, 15 min; (iii) lithium (*R*)-*N*-benzyl-*N*-(α-methylbenzyl)-amide, THF, −78 °C, 2 h, then (−)-CSO, −78 °C to rt, 12 h; (iv) $LiAlH_4$, THF, 0 °C to rt, 16 h.

The behaviour of substrates **25** and **31** (lacking the hydroxyl group) towards the proposed oxidation and hydrolysis procedures, respectively, was examined to delineate efficient experimental protocols. Ozonolysis of **25** was investigated first. In order to prevent competing oxidation of the nitrogen atom, **25** was initially converted to the corresponding HCl salt upon treatment with 2.0 M HCl in Et_2O, and a solution of **25**·HCl in MeOH was then subjected to O_3 then Me_2S to give an 85:15 mixture of furanoside **34** (64:36 anomeric mixture) and the corresponding methyl glycoside **35** (95:5 anomeric mixture). Purification allowed isolation of **34** in 45% yield and **35** in 8% yield. Methyl glycoside **35** presumably arises from interception of the intermediate aldehyde **33**·HCl and/or furanoside **34**·HCl by the methanol solvent. Heating **34** (64:36 anomeric mixture) with HCl in MeOH at 50 °C for 16 h gave complete conversion to methyl glycoside **35** (95:5 anomeric mixture), which was isolated in 85% yield. The relative configuration at the anomeric stereocentre within methyl glycoside **35** was assigned on the basis of ^{1}H NMR NOE analysis (Scheme 4).



Scheme 4. Reagents and conditions: (i) HCl (2.0 M in Et_2O), rt, 5 min, then evaporate solvent; (ii) O_3, CH_2Cl_2, MeOH, −78 °C, then Me_2S, −78 °C to rt, 16 h; (iii) HCl (1.25 M in MeOH), MeOH, 50 °C, 16 h.

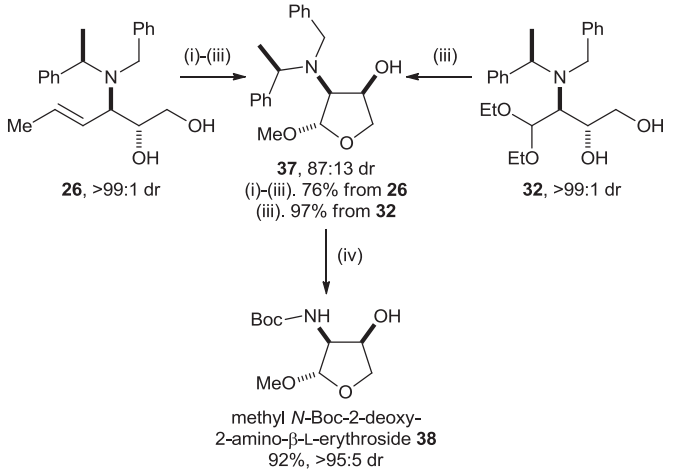
In order to access methyl glycoside **35** from **25** directly, the crude reaction mixture from the ozonolysis reaction was treated with HCl in MeOH, which allowed isolation of **35** in 80% yield (>95:5 anomeric mixture), representing an overall yield of 47% in five steps from sorbic acid **21**. However, heating **31** with HCl in MeOH gave **35** in 97% isolated yield, representing an overall yield of 73% in four steps from acrolein diethyl acetal **27**. Attempted hydrogenolysis of **35** (>95:5 anomeric mixture) in the presence of $Pd(OH)_2$/C followed by filtration of the crude reaction mixture through Celite® resulted in only low mass return of a species, which produced a broad and unintelligible ^{1}H NMR spectrum. However, repetition of the hydrogenolysis experiment but in the presence of Boc_2O gave the corresponding *N*-Boc protected methyl glycoside **36** (>95:5 anomeric mixture) in 90% yield (Scheme 5).



Scheme 5. Reagents and conditions: (i) HCl (2.0 M in Et_2O), rt, 5 min, then evaporate solvent; (ii) O_3, CH_2Cl_2, MeOH, −78 °C, then Me_2S, −78 °C to rt, 16 h; (iii) HCl (1.25 M in MeOH), 50 °C, 16 h; (iv) Boc_2O, H_2 (5 atm), $Pd(OH)_2$/C, MeOH, 24 h, rt.

These conditions were next applied to the synthesis of 2-deoxy-2-amino-L-erythrose **19** (in protected form). This amino sugar has previously been isolated from *Agaricus biosporus* (the common mushroom).[13,20] Reaction of **26** under the optimised conditions for

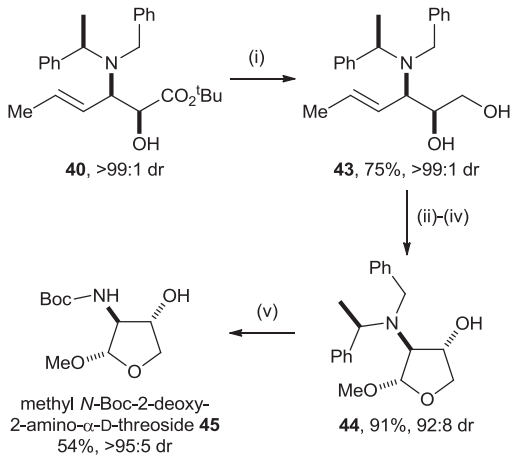
ozonolysis and methyl glycoside formation delivered **37** (87:13 anomeric mixture), which was isolated in 76% yield. Meanwhile, methanolysis of **32** gave **37** (87:13 anomeric mixture) in 97% yield. Subsequent hydrogenolysis of **37** in the presence of Boc_2O gave methyl *N*-Boc-2-deoxy-2-amino-β-L-erythroside **38** (87:13 anomeric mixture), which was isolated in 92% yield (>95:5 anomeric mixture). The relative configurations at the anomeric stereocentres within methyl glycosides **37** and **38** were assigned on the basis of ^{1}H NMR NOE analyses (Scheme 6).



Scheme 6. Reagents and conditions: (i) HCl (2.0 M in Et_2O), rt, 5 min, then evaporate solvent; (ii) O_3, CH_2Cl_2, MeOH, −78 °C, then Me_2S, −78 °C to rt, 16 h; (iii) HCl (1.25 M in MeOH), 50 °C, 16 h; (iv) Boc_2O, H_2 (5 atm), $Pd(OH)_2$/C, MeOH, 24 h, rt.

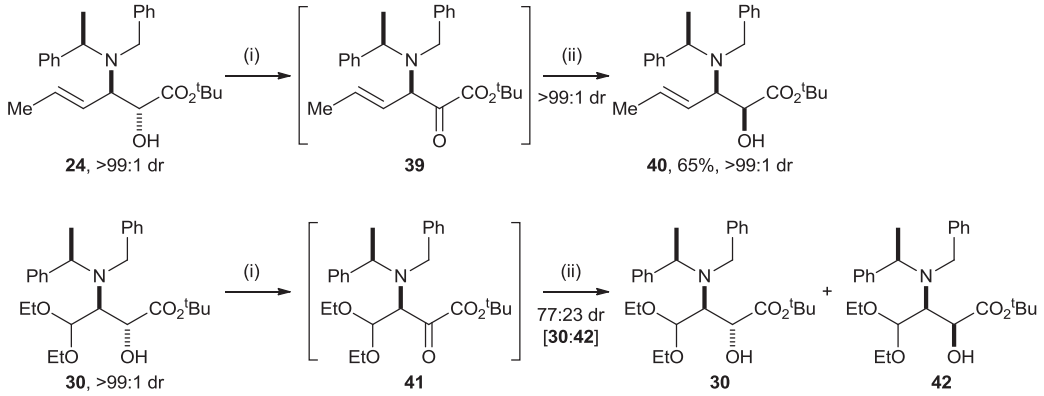
With an efficient synthesis of **38** (a protected form of 2-deoxy-2-amino-L-erythrose **19**) in hand, investigations turned towards the development of a synthesis of the diastereoisomer, 2-deoxy-2-amino-D-threose **20**. An oxidation/diastereoselective reduction protocol was investigated to effect epimerisation of the hydroxyl-bearing stereocentre within *anti*-α-hydroxy-β-amino ester **24**.[21,22] Following our previously reported protocol,[21,22] Swern oxidation of **24** gave complete conversion to the corresponding ketone **39**, with treatment of **39** with $NaBH_4$ in MeOH at −20 °C giving *syn*-α-hydroxy-β-amino ester **40** in >99:1 dr and 65% isolated yield. Interestingly, under identical conditions, Swern oxidation of **30** proceeded to give ketone **41** in complete conversion, although subsequent reduction with $NaBH_4$ gave a 77:23 mixture of **30** and **42**, respectively. A brief screen of a range of reducing agents [DIBAL-H, $LiAlH_4$, $LiBH_4$, $LiAl(O^tBu)_3H$] resulted in analogous diastereoselectivity, and *anti*-α-hydroxy-β-amino ester **30** was formed either preferentially or exclusively [82:18 dr using DIBAL-H; >99:1 dr using $LiAlH_4$,[23] $LiBH_4$ and $LiAl(O^tBu)_3H$] (Scheme 7).

Reduction of *syn*-α-hydroxy-β-amino ester **40** with $LiAlH_4$ gave primary alcohol **43** in 75% yield and >99:1 dr, with ozonolysis and methanolysis giving methyl glycoside **44** (92:8 anomeric mixture) in 91% yield. Subsequent hydrogenolysis of **44** in the presence of Boc_2O gave methyl *N*-Boc-2-deoxy-2-amino-α-D-threoside **45** (92:8 anomeric mixture), which was isolated in 54% yield (>95:5 anomeric mixture). The relative configurations at the anomeric stereocentres within methyl glycosides **44** and **45** were assigned on the basis of ^{1}H NMR NOE analyses (Scheme 8).



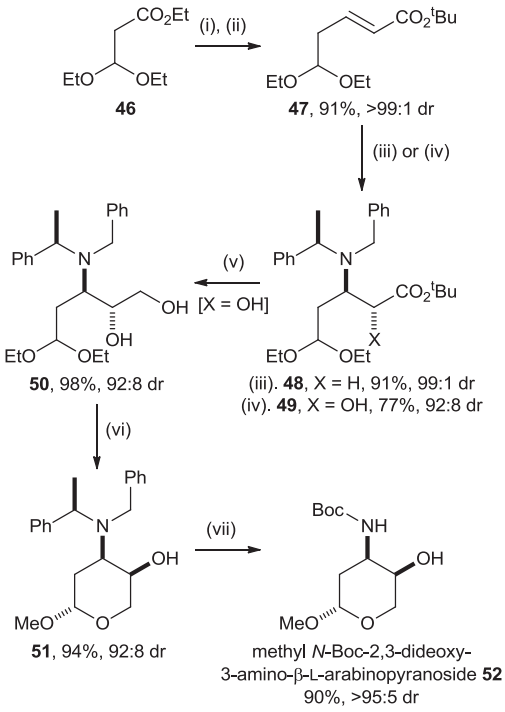
Scheme 8. Reagents and conditions: (i) $LiAlH_4$, THF, 0 °C to rt, 16 h; (ii) HCl (2.0 M in Et_2O), rt, 5 min, then evaporate solvent; (iii) O_3, CH_2Cl_2, MeOH, −78 °C, then Me_2S, −78 °C to rt, 16 h; (iv) HCl (1.25 M in MeOH), 50 °C, 16 h; (v) Boc_2O, H_2 (5 atm), $Pd(OH)_2$/C, MeOH, 24 h, rt.

This methodology was next extended to facilitate the asymmetric synthesis of a representative 2,3-dideoxy-3-aminopentose. Reduction of ethyl 3,3-diethoxypropanoate **46** with DIBAL-H gave the corresponding aldehyde, which was olefinated using $Ph_3P{=}CHCO_2{}^tBu$ to give α,β-unsaturated ester **47** ($^3J_{2,3}$=15.7 Hz) in 91% yield and >99:1 dr. Conjugate addition of lithium (*R*)-*N*-benzyl-*N*-(α-methylbenzyl)amide to **47** gave β-amino ester **48** in 99:1 dr, isolated in 91% yield. The absolute (*R*,*R*)-configuration within **48** was assigned from the well-established stereochemical outcome of this type of conjugate addition reaction.[7,19] Aminohydroxylation of **47** upon conjugate addition of lithium (*R*)-*N*-benzyl-*N*-(α-methylbenzyl)amide followed by in situ enolate oxidation using (−)-CSO gave α-hydroxy-β-amino ester **49** in 77% yield and 92:8 dr. The absolute (*R*,*R*,*R*)-configuration within **49** was assigned by analogy to the well-established stereochemical outcome of this amino-hydroxylation procedure.[7,15] Given that the lithium amide exerts



Scheme 7. Reagents and conditions: (i) $(COCl)_2$, DMSO, CH_2Cl_2, −78 °C, 35 min, then Et_3N, −78 °C to rt, 30 min; (ii) $NaBH_4$, MeOH, −20 °C, 2 h.

total control upon formation of the C(3)-stereogenic centre within **48**, and that **48** and **49** are formed from protonation or oxidation, respectively, of the same intermediate lithium β-amino enolate, the minor diastereoisomer resulting from the aminohydroxylation reaction was assigned as being epimeric at C(2). Reduction of **49** with $LiAlH_4$ gave primary alcohol **50** in 98% yield and 92:8 dr, and methanolysis of **50** gave methyl glycoside **51** in 94% yield and 92:8 dr. The identical diastereoisomeric ratios of the primary alcohol starting material **50** and methyl glycoside product **51** of this transformation indicate that the anomeric stereocentre is formed with total control for both the major and minor diastereoisomers in this system. The relative configuration at the anomeric stereocentre within the major diastereoisomer **51** was assigned with the aid of ^{1}H NMR ^3J coupling constant analysis. Subsequent hydrogenolysis of **51** in the presence of Boc_2O gave methyl *N*-Boc-2,3-dideoxy-3-amino-β-L-arabinopyranoside **52** in 90% yield and >95:5 dr (Scheme 9).



Scheme 9. Reagents and conditions: (i) DIBAL-H, CH_2Cl_2, −78 °C, 50 min; (ii) $Ph_3P{=}CHCO_2{}^tBu$, rt, 16 h; (iii) lithium (*R*)-*N*-benzyl-*N*-(α-methylbenzyl)amide, THF, −78 °C, 2 h, then NH_4Cl (satd aq), −78 °C to rt, 15 min; (iv) lithium (*R*)-*N*-benzyl-*N*-(α-methylbenzyl)amide, THF, −78 °C, 2 h, then (−)-CSO, −78 °C to rt, 12 h; (v) $LiAlH_4$, THF, 0 °C to rt, 16 h; (vi) HCl (1.25 M in MeOH), 50 °C, 16 h; (vii) Boc_2O, H_2 (5 atm), $Pd(OH)_2$/C, MeOH, 24 h, rt.

3. Conclusion

In conclusion, efficient asymmetric syntheses of the diastereoisomeric 2-deoxy-2-aminotetroses and a representative 2,3-dideoxy-3-aminopentose (in protected form) have been rapidly achieved from α-hydroxy-β-amino esters (readily prepared using our diastereoselective procedure for aminohydroxylation of an α,β-unsaturated ester) bearing either a γ,δ-C=C bond or an acetal functionality at the γ-position. In both cases these functionalities can be used to generate an aldehyde functional group, via either ozonolysis in the former case or hydrolysis in the latter case. Thus, methyl *N*-Boc-2-deoxy-2-amino-β-L-erythroside and methyl *N*-Boc-2-deoxy-2-amino-α-D-threoside were both prepared from sorbic acid, employing ozonolysis of the γ,δ-C=C bond, in six and eight steps, and in 35 and 13% overall yield, respectively. Methyl *N*-Boc-2-deoxy-2-amino-β-L-erythroside was also prepared from acrolein diethyl acetal, employing hydrolysis of the acetal functionality, in five steps and 54% overall yield. This approach also proved amenable to the synthesis of methyl *N*-Boc-2,3-dideoxy-3-amino-β-L-arabinopyranoside from ethyl 3,3-diethoxypropanote, in six steps and 58% overall yield.

4. Experimental section

4.1. General experimental details

All reactions involving organometallic or other moisture-sensitive reagents were carried out under a nitrogen or argon atmosphere using standard vacuum line techniques and glassware that was flame dried and cooled under nitrogen before use. Solvents were dried according to the procedure outlined by Grubbs and co-workers.[24] Water was purified by an Elix® UV-10 system. Organic layers were dried over $MgSO_4$. Thin layer chromatography was performed on aluminium plates coated with 60 F_{254} silica. Plates were visualised using UV light (254 nm), iodine, 1% aq $KMnO_4$, or 10% ethanolic phosphomolybdic acid. Flash column chromatography was performed on Kieselgel 60 silica or on an automated flash column chromatography platform.

Melting points are uncorrected. Specific rotations are reported in 10^{-1} deg cm^2 g^{-1} and concentrations in g/100 mL. IR spectra were recorded as a thin film on NaCl plates (film), as a KBr disc (KBr), or using an ATR module (ATR), as stated. 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. ^{1}H–^{1}H COSY and ^{1}H–^{13}C HSQC analyses were used to establish atom connectivity.

4.2. *tert*-Butyl (*E*,*E*)-hexa-2,4-dienoate [*tert*-butyl sorbate] 22

Condensed isobutylene (60 mL) at −78 °C was added to a stirred solution of sorbic acid **21** (10.0 g, 89.3 mmol) and concd aq H_2SO_4 (1.00 mL) in CH_2Cl_2 (200 mL) at 0 °C and the resultant mixture was stirred at 0 °C for 1 h. The reaction mixture was then allowed to warm to rt and stirred at rt for 48 h. The reaction mixture was washed with satd aq $NaHCO_3$ (5×100 mL) and the combined aqueous washings were extracted with CH_2Cl_2 (2×100 mL). The combined organic extracts were washed with brine (100 mL), then dried and concentrated in vacuo to give **22** as a colourless oil (12.0 g, 81%);[3–5,16,17] δ_H (400 MHz, $CDCl_3$) 1.44 (9H, s, C*Me*$_3$), 1.80 (3H, d, *J* 6.0, C(6)*H*$_3$), 5.66 (1H, d, *J* 15.4, C(2)*H*), 6.01–6.16 (2H, m, C(4)*H*, C(5)*H*), 7.14 (1H, dd, *J* 15.4, 10.2, C(3)*H*).

4.3. *tert*-Butyl (3*S*,α*R*,*E*)-3-[*N*-benzyl-*N*-(α-methylbenzyl) amino]hex-4-enoate 23

n-BuLi (2.5 M in hexanes, 15.0 mL, 37.5 mmol) was added dropwise to a stirred solution of (*R*)-*N*-benzyl-*N*-(α-methylbenzyl)-amine (8.04 g, 38.1 mmol) in THF (120 mL) at −78 °C, and the resultant mixture was stirred at −78 °C for 30 min. A solution of **22** (4.00 g, 23.8 mmol) in THF (80 mL) was then added via cannula and the resultant mixture was stirred at −78 °C for 2 h. Satd aq NH_4Cl (20 mL) was then added and the reaction mixture was allowed to warm to rt over 15 min, then partitioned between Et_2O (100 mL) and H_2O (100 mL). The aqueous layer was extracted with Et_2O (3×100 mL) and the combined organic extracts were washed sequentially with 10% aq citric acid (500 mL), satd aq $NaHCO_3$ (500 mL) and brine (500 mL), then dried and concentrated in vacuo. Purification via flash column chromatography (eluent 30–40 °C petrol/Et_2O, 20:1) gave **23** as a pale yellow oil (7.22 g, 80%, 98:2 dr);[3–5,16,17] $[\alpha]_D^{25}$ −22.2 (*c* 2.0 in $CHCl_3$); {lit. $[\alpha]_D^{24}$ −23.3 (*c* 2.04 in $CHCl_3$)}; δ_H (400 MHz, $CDCl_3$) 1.37 (9H, s, C*Me*$_3$), 1.38 (3H, d, *J* 6.8,

C(α)*Me*), 1.70 (3H, d, *J* 4.6, C(6)H_3), 2.22 (1H, dd, *J* 14.2, 9.2, C(2)H_A), 2.35 (1H, dd, *J* 14.2, 5.5, C(2)H_B), 3.66 (2H, app s, NCH_2Ph), 3.73–3.78 (1H, m, C(3)*H*), 4.01 (1H, q, *J* 6.8, C(α)*H*), 5.52–5.54 (2H, m, C(4)*H*, C(5)*H*), 7.17–7.39 (10H, m, *Ph*).

4.4. *tert*-Butyl (*R*,*R*,*R*,*E*)-2-hydroxy-3-[*N*-benzyl-*N*-(α-methylbenzyl)amino]hex-4-enoate 24

n-BuLi (2.5 M in hexanes, 9.22 mL, 23.1 mmol) was added dropwise to a stirred solution of (*R*)-*N*-benzyl-*N*-(α-methylbenzyl) amine (5.03 g, 23.8 mmol) in THF (60 mL) at −78 °C, and the resultant mixture was stirred at −78 °C for 30 min. A solution of **22** (2.50 g, 14.9 mmol) in THF (30 mL) was then added via cannula and the resultant mixture was stirred at −78 °C for 2 h. (−)-CSO (5.80 g, 25.3 mmol) was then added and the reaction mixture was allowed to warm to rt over 12 h. Satd aq NH_4Cl (10 mL) was then added, and the resultant mixture was concentrated in vacuo. The residue was dissolved in CH_2Cl_2 (200 mL) and the resultant solution was washed sequentially with 10% aq citric acid (200 mL), satd aq $NaHCO_3$ (200 mL) and brine (200 mL), then dried and concentrated in vacuo. Purification via flash column chromatography (eluent 30–40 °C petrol/Et_2O, 20:1) gave **24** as a pale yellow oil (4.06 g, 69%, >99:1 dr);[4,18] $[\alpha]_D^{25}$ −63.1 (*c* 1.0 in $CHCl_3$); {lit. $[\alpha]_D^{25}$ −62.6 (*c* 1.0 in $CHCl_3$)}; δ_H (400 MHz, $CDCl_3$) 1.34 (9H, s, C*Me*$_3$), 1.37 (3H, d, *J* 6.8, C(α)*Me*), 1.71 (3H, d, *J* 6.3, C(6)H_3), 2.94 (1H, br s, O*H*), 3.54 (1H, dd, *J* 9.1, 2.6, C(3)*H*), 3.76 (1H, d, *J* 14.4, NCH_AH$_B$Ph), 3.97 (1H, d, *J* 14.4, NCH$_A$$H_B$Ph), 4.08 (1H, br s, C(2)*H*), 4.23 (1H, q, *J* 6.8, C(α)*H*), 5.55 (1H, dq, *J* 15.4, 6.3, C(5)*H*), 5.66–5.72 (1H, m, C(4)*H*), 7.19–7.42 (10H, m, *Ph*).

4.5. (3*S*,α*R*,*E*)-3-[*N*-Benzyl-*N*-(α-methylbenzyl)amino]hex-4-en-1-ol 25

$LiAlH_4$ (1.0 M in THF, 7.65 mL, 7.65 mmol) was added to a stirred solution of **23** (2.90 g, 7.65 mmol, 98:2 dr) in THF (30 mL) at 0 °C, and the resultant mixture was stirred at rt for 16 h. The reaction mixture was then cooled to 0 °C and lumps of ice (~2 g), and then 2.0 M aq NaOH solution (15 mL), were added cautiously with vigorous stirring being maintained throughout. The resultant mixture was then allowed to warm to rt over 15 min, diluted with EtOAc (90 mL), and the resultant mixture was stirred for 30 min before being filtered through Celite® (eluent EtOAc). The filtrate was then dried and concentrated in vacuo. Purification via flash column chromatography (eluent 30–40 °C petrol/Et_2O, 2:1) gave **25** as a colourless oil (2.14 g, 90%, 98:2 dr);[16] $[\alpha]_D^{25}$ −65.6 (*c* 2.7 in $CHCl_3$); {lit.[16] $[\alpha]_D^{24}$ −62.3 (*c* 2.73 in $CHCl_3$)}; δ_H (400 MHz, $CDCl_3$) 1.40–1.47 (1H, m, C(2)H_A), 1.42 (3H, d, *J* 7.0, C(α)*Me*), 1.75 (3H, d, *J* 5.9, C(6)H_3), 1.81–1.90 (1H, m, C(2)H_B), 2.73 (1H, br s, O*H*), 3.28–3.41 and 3.55–3.60 (3H, m, C(1)H_2, C(3)*H*), 3.64 (1H, d, *J* 13.7, NCH_AH$_B$Ph), 3.90 (1H, d, *J* 13.7, NCH$_A$$H_B$Ph), 4.06 (1H, q, *J* 7.0, C(α)*H*), 5.55 (1H, dq, *J* 15.0, 5.9, C(5)*H*), 5.67 (1H, dd, *J* 15.0, 9.1, C(4)*H*), 7.22–7.37 (10H, m, *Ph*).

4.6. (*R*,*R*,*R*,*E*)-3-[*N*-Benzyl-*N*-(α-methylbenzyl)amino]hex-4-en-1,2-diol 26

$LiAlH_4$ (1.0 M in THF, 3.80 mL, 3.80 mmol) was added to a stirred solution of **24** (1.50 g, 3.80 mmol, >99:1 dr) in THF (15 mL) at 0 °C, and the resultant mixture was stirred at rt for 16 h. The reaction mixture was then cooled to 0 °C and lumps of ice (~1 g), and then 2.0 M aq NaOH solution (8 mL), were added cautiously with vigorous stirring being maintained throughout. The resultant mixture was then allowed to warm to rt over 15 min, diluted with EtOAc (45 mL) and the resultant mixture was stirred for a further 30 min before being filtered through Celite® (eluent EtOAc). The filtrate was dried and concentrated in vacuo. Purification via flash column chromatography (eluent 30–40 °C petrol/Et_2O, 2:1) gave **26** as a colourless oil (1.10 g, 90%, >99:1 dr);[18] $[\alpha]_D^{25}$ −49.4 (*c* 1.0 in $CHCl_3$); {lit.[18] $[\alpha]_D^{22}$ −48.7 (*c* 1.0 in $CHCl_3$)}; δ_H (400 MHz, $CDCl_3$) 1.42 (3H, d, *J* 6.7, C(α)*Me*), 1.83 (3H, d, *J* 4.8, C(6)H_3), 3.20 (1H, br s, C(3)*H*), 3.44 (2H, app d, *J* 5.0, C(1)H_2), 3.60 (1H, ddd, *J* 9.9, 5.4, 4.5, C(2)*H*), 3.62 (1H, br s, O*H*), 3.70 (1H, d, *J* 13.7, NCH_AH$_B$Ph), 3.93 (1H, d, *J* 13.7, NCH$_A$$H_B$Ph), 4.04–4.13 (1H, m, C(α)*H*), 5.67–5.79 (2H, m, C(5)*H*, C(4)*H*), 7.26–7.36 (10H, m, *Ph*).

4.7. *tert*-Butyl (*E*)-4,4-diethoxybut-2-enoate 28

Hoveyda–Grubbs II catalyst (482 mg, 0.77 mmol) was added to a degassed solution of acrolein diethyl acetal **27** (1.00 g, 7.68 mmol) and *tert*-butyl acrylate (3.37 mL, 23.0 mmol) in CH_2Cl_2 (38 mL) and the resultant mixture was heated at reflux for 22 h. The reaction mixture was then concentrated in vacuo. Purification via flash column chromatography (eluent 30–40 °C petrol/Et_2O, 35:1) gave **28** as a colourless oil (1.59 g, 90%, >99:1 dr); ν_{max} (ATR) 1716 (C=O), 1664 (C=C); δ_H (400 MHz, $CDCl_3$) 1.23 (6H, t, *J* 7.2, O(CH_2*Me*)$_2$), 1.49 (9H, s, C*Me*$_3$), 3.49–3.56 (2H, m, O(CH_AH$_B$Me)$_2$), 3.62–3.69 (2H, m, O(CH$_A$$H_B$Me)$_2$), 5.03 (1H, dd, *J* 4.4, 1.4, C(4)*H*), 6.05 (1H, dd, *J* 15.9, 1.4, C(2)*H*), 6.72 (1H, dd, *J* 15.9, 4.4, C(3)*H*); δ_C (100 MHz, $CDCl_3$) 15.1 (O(CH_2*Me*)$_2$), 27.9 (C*Me*$_3$), 61.2 (O(CH_2Me)$_2$), 80.6 (*C*Me$_3$), 99.2 (*C*(4)), 125.7 (*C*(2)), 142.2 (*C*(3)), 165.2 (*C*(1)); *m*/*z* (ESI$^+$) 253 ([M+Na]$^+$, 100%); HRMS (ESI$^+$) $C_{12}H_{22}NaO_4^+$ ([M+Na]$^+$) requires 253.1410; found 253.1401.

4.8. *tert*-Butyl (3*S*,α*R*)-3-[*N*-benzyl-*N*-(α-methylbenzyl) amino]-4,4-diethoxybutanoate 29

n-BuLi (2.5 M in hexanes, 0.35 mL, 0.86 mmol) was added dropwise to a stirred solution of (*R*)-*N*-benzyl-*N*-(α-methylbenzyl) amine (188 mg, 0.89 mmol) in THF (5 mL) at −78 °C, and the resultant mixture was stirred at −78 °C for 30 min. A solution of **28** (128 mg, 0.56 mmol, >99:1 dr) in THF (5 mL) was then added via cannula and the resultant mixture was stirred at −78 °C for 2 h. Satd aq NH_4Cl (5 mL) was then added and the resultant mixture was allowed to warm to rt over 15 min, then partitioned between Et_2O (10 mL) and H_2O (10 mL). The aqueous layer was extracted with Et_2O (3×25 mL) and the combined organic extracts were washed sequentially with 10% aq citric acid (50 mL), satd aq $NaHCO_3$ (50 mL) and brine (50 mL), then dried and concentrated in vacuo. Purification via flash column chromatography (eluent 30–40 °C petrol/Et_2O, 15:1) gave **29** as a colourless oil (214 mg, 87%, 99:1 dr); $[\alpha]_D^{25}$ −33.6 (*c* 1.0 in $CHCl_3$); ν_{max} (ATR) 1724 (C=O); δ_H (400 MHz, $CDCl_3$) 1.12 (3H, t, *J* 7.1, OCH$_2$*Me*), 1.22 (3H, t, *J* 7.1, OCH$_2$*Me*), 1.41 (3H, d, *J* 7.1, C(α)*Me*), 1.46 (9H, s, C*Me*$_3$), 1.99 (1H, dd, *J* 15.7, 4.3, C(2)H_A), 2.33 (1H, dd, *J* 15.7, 7.8, C(2)H_B), 3.42–3.58 (3H, m, OCH_2Me, OCH_AH$_B$Me), 3.63 (1H, d, *J* 14.9, NCH_AH$_B$Ph), 3.72–3.80 (2H, m, C(3)*H*, OCH$_A$$H_B$Me), 3.93 (1H, q, *J* 7.1, C(α)*H*), 3.99 (1H, d, *J* 14.9, NCH$_A$$H_B$Ph), 4.45 (1H, d, *J* 4.8, C(4)*H*), 7.22–7.44 (10H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 15.1, 15.4 (C(OCH$_2$*Me*)$_2$), 19.9 (C(α)*Me*), 28.1 (C*Me*$_3$), 33.5 (*C*(2)), 51.2 (NCH$_2$Ph), 55.0 (*C*(3)), 58.6 (*C*(α)), 62.7, 63.8 (C(OCH$_2$Me)$_2$), 79.7 (*C*Me$_3$), 105.8 (*C*(4)), 126.4, 126.8, 127.9, 128.0, 128.1, 128.2 (*o*,*m*,*p*-*Ph*), 141.9, 143.2 (*i*-*Ph*), 171.8 (*C*(1)); *m*/*z* (ESI$^+$) 442 ([M+H]$^+$, 100%); HRMS (ESI$^+$) $C_{27}H_{40}NaO_4^+$ ([M+H]$^+$) requires 442.2952; found 442.2948.

4.9. *tert*-Butyl (2*R*,3*S*,α*R*)-2-hydroxy-3-[*N*-benzyl-*N*-(α-methylbenzyl)amino]-4,4-diethoxybutanoate 30

n-BuLi (2.5 M in hexanes, 0.96 mL, 2.40 mmol) was added dropwise to a stirred solution of (*R*)-*N*-benzyl-*N*-(α-methylbenzyl) amine (524 mg, 2.48 mmol) in THF (10 mL) at −78 °C, and the resultant mixture was stirred at −78 °C for 30 min. A solution of **28** (357 mg, 1.55 mmol, >99:1 dr) in THF (8 mL) was then added via

cannula and the resultant mixture was stirred at −78 °C for 2 h. (−)-CSO (605 mg, 2.64 mmol) was then added and the reaction mixture was allowed to warm to rt over 12 h. Satd aq NH_4Cl (5 mL) was then added, and the resultant mixture was concentrated in vacuo. The residue was dissolved in CH_2Cl_2 (20 mL) and the resultant solution was washed sequentially with 10% aq citric acid (20 mL), satd aq $NaHCO_3$ (20 mL) and brine (20 mL), then dried and concentrated in vacuo. Purification via flash column chromatography (eluent 30–40 °C petrol/Et_2O, 20:1) gave **30** as a colourless solid (482 mg, 68%, >99:1 dr); mp 51–52 °C; $[\alpha]_D^{25}$ −41.2 (*c* 1.0 in $CHCl_3$); ν_{max} (ATR) 1724 (C=O); δ_H (400 MHz, $CDCl_3$) 1.13 (3H, t, *J* 7.1, OCH_2Me), 1.35 (3H, t, *J* 7.1, OCH_2Me), 1.44 (3H, d, *J* 6.8, C(α)*Me*), 1.49 (9H, s, CMe_3), 3.12 (1H, d, *J* 4.0, O*H*), 3.47–3.77 (6H, m, C(2)*H*, C(3)*H*, $C(OCH_2Me)_2$), 3.80 (1H, d, *J* 15.6, NCH_AH_BPh), 4.08 (1H, q, *J* 6.8, C(α)*H*), 4.37 (1H, d, *J* 15.6, NCH_AH_BPh), 4.71 (1H, d, *J* 8.1, C(4)*H*), 7.22–7.53 (10H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 15.1, 15.6 ($C(OCH_2Me)_2$), 19.3 (C(α)*Me*), 28.0 (CMe_3), 51.7 (NCH_2Ph), 57.6 (*C*(α)), 60.1 (*C*(3)), 62.5, 65.1 ($C(OCH_2Me)_2$), 71.5 (*C*(2)), 82.0 (CMe_3), 102.0 (*C*(4)), 126.4, 126.9, 127.9, 128.0, 128.1, 128.2 (*o*,*m*,*p*-*Ph*), 141.9, 142.5 (*i*-*Ph*), 173.7 (*C*(1)); *m*/*z* (ESI^+) 458 ($[M+H]^+$, 100%); HRMS (ESI^+) $C_{27}H_{39}NNaO_5^+$ ($[M+Na]^+$) requires 480.2720; found 480.2728.

4.10. (3*S*,α*R*)-3-[*N*-Benzyl-*N*-(α-methylbenzyl)amino]-4,4-diethoxybutan-1-ol 31

$LiAlH_4$ (1.0 M in THF, 2.72 mL, 2.72 mmol) was added to a solution of **29** (1.00 g, 2.27 mmol, >99:1 dr) in THF (10 mL) at 0 °C, and the resultant mixture was stirred at rt for 16 h. The reaction mixture was then cooled to 0 °C and lumps of ice (~1 g), and then 2.0 M aq NaOH solution (6 mL), were added cautiously with vigorous stirring being maintained throughout. The resultant mixture was then allowed to warm to rt over 15 min, diluted with EtOAc (30 mL), and the resultant mixture was stirred for a further 30 min before being filtered through Celite® (eluent EtOAc). The filtrate was then dried and concentrated in vacuo. Purification via flash column chromatography (eluent 30–40 °C petrol/Et_2O, 2:1) gave **31** as a colourless oil (808 mg, 96%, 96:4 dr); $[\alpha]_D^{25}$ −28.8 (*c* 1.0 in $CHCl_3$); ν_{max} (ATR) 3427 (O–H); δ_H (400 MHz, $CDCl_3$) 1.16 (3H, t, *J* 7.1, OCH_2Me), 1.24 (3H, t, *J* 7.1, OCH_2Me), 1.39 (3H, d, *J* 6.8, C(α)*Me*), 1.50–1.58 (1H, m, C(2)H_A), 1.74–1.82 (1H, m, C(2)H_B), 2.57 (1H, br s, O*H*), 2.99–3.03 (1H, m, C(3)*H*), 3.45–3.53 (2H, m, C(1)H_2), 3.61–3.68 (2H, m, $O(CH_AH_BMe)_2$), 3.75–3.82 (2H, m, $O(CH_AH_BMe)_2$), 3.86 (1H, d, *J* 14.6, NCH_AH_BPh), 3.98 (1H, d, *J* 14.6, NCH_AH_BPh), 4.03 (1H, q, *J* 6.8, C(α)*H*), 4.59 (1H, d, *J* 3.5, C(4)*H*), 7.23–7.39 (10H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 15.2, 15.4 ($C(OCH_2Me)_2$), 18.2 (C(α)*Me*), 29.0 (*C*(2)), 51.0 (NCH_2Ph), 57.3, 57.6 (*C*(3), *C*(α)), 61.6 (*C*(1)), 63.7, 63.9 ($C(OCH_2Me)_2$), 106.3 (*C*(4)), 126.6, 126.9, 127.7, 128.2, 128.4 (*o*,*m*,*p*-*Ph*), 141.8, 144.2 (*i*-*Ph*); *m*/*z* (ESI^+) 394 ($[M+Na]^+$, 19%), 372 ($[M+H]^+$, 100%); HRMS (ESI^+) $C_{23}H_{33}NNaO_3^+$ ($[M+Na]^+$) requires 394.2353; found 394.2350.

4.11. (2*R*,3*S*,α*R*)-3-[*N*-Benzyl-*N*-(α-methylbenzyl)amino]-4,4-diethoxybutan-1,2-diol 32

$LiAlH_4$ (1.0 M in THF, 0.36 mL, 0.36 mmol) was added to a solution **30** (164 mg, 0.36 mmol, >99:1 dr) in THF (4 mL) at 0 °C, and the resultant mixture was stirred at rt for 16 h. The reaction mixture was then cooled to 0 °C and lumps of ice (~1 g), and then 2.0 M aq NaOH solution (3 mL), were added cautiously with vigorous stirring being maintained throughout. The resultant mixture was then allowed to warm to rt over 15 min, diluted with EtOAc (10 mL), and the resultant mixture was stirred for a further 30 min before being filtered through Celite® (eluent EtOAc). The filtrate was then dried and concentrated in vacuo. Purification via flash column chromatography (eluent 30–40 °C petrol/Et_2O, 1:2) gave **32** as a colourless oil (137 mg, 98%, >99:1 dr); $[\alpha]_D^{25}$ −39.3 (*c* 1.0 in $CHCl_3$); ν_{max} (ATR) 3424 (O–H); δ_H (400 MHz, $CDCl_3$) 1.12–1.18 (6H, m, $C(OCH_2Me)_2$), 1.31 (3H, d, *J* 6.9, C(α)*Me*), 2.87 (1H, dd, *J* 7.6, 2.5, C(3)*H*), 3.22 (1H, dd, *J* 11.4, 6.1, C(1)H_A), 3.39 (1H, dd, *J* 11.4, 3.7, C(1)H_B), 3.44–3.83 (4H, m, $C(OCH_2Me)_2$), 3.84–3.87 (1H, m, C(2)*H*), 3.90 (1H, d, *J* 14.4, NCH_AH_BPh), 3.98 (1H, d, *J* 14.4, NCH_AH_BPh), 4.02 (1H, q, *J* 6.9, C(α)*H*), 4.71 (1H, d, *J* 2.5, C(4)*H*), 7.14–7.29 (10H, m, *Ph*); δ_C (400 MHz, $CDCl_3$) 15.3, 15.4 ($C(OCH_2Me)_2$), 16.7 (C(α)*Me*), 51.7 (NCH_2Ph), 57.7 (*C*(α)), 59.1 (*C*(3)), 64.5, 64.6 ($C(OCH_2Me)_2$), 65.1 (*C*(1)), 71.1 (*C*(2)), 106.1 (*C*(4)), 126.9, 127.2, 127.9, 128.3, 128.4, 128.6 (*o*,*m*,*p*-*Ph*), 141.2, 143.7 (*i*-*Ph*); *m*/*z* (ESI^+) 388 ($[M+H]^+$, 100%); HRMS (ESI^+) $C_{23}H_{33}NNaO_4^+$ ($[M+Na]^+$) requires 410.2302; found 410.2295.

4.12. (2*R*,3*S*,α*R*)- and (2*S*,3*S*,α*R*)-3-[*N*-Benzyl-*N*-(α-methylbenzyl)amino]tetrahydrofuran-2-ol 34, and (2*S*,3*S*,α*R*)-2-methoxy-3-[*N*-benzyl-*N*-(α-methylbenzyl)amino]tetrahydrofuran 35

HCl (2.0 M in Et_2O, 6.50 mL, 13.0 mmol) was added to a stirred solution of **25** (570 mg, 1.84 mmol, 98:2 dr) in Et_2O (14 mL) and the resultant mixture was stirred at rt for 5 min, then concentrated in vacuo. The residue of **25**·HCl was dissolved in CH_2Cl_2/MeOH (v/v, 1:1, 80 mL), the resultant solution was cooled to −78 °C, and O_3 was bubbled through the solution until it turned blue. O_2 was then bubbled through the solution until it turned colourless, after which Me_2S (5 mL) was added dropwise. The reaction mixture was allowed to warm to rt over 16 h, then concentrated in vacuo. The residue was dissolved in CH_2Cl_2 (50 mL) and the resultant solution was washed with satd aq $NaHCO_3$ (30 mL), then dried and concentrated in vacuo to give an 85:15 mixture of **34** (64:36 dr) and **35** (95:5 dr). Purification via flash column chromatography (eluent 30–40 °C petrol/Et_2O, 2:1) gave **34** as a colourless oil (247 mg, 45%, 64:36 dr); ν_{max} (ATR) 3394 (O–H); *m*/*z* (ESI^+) 320 ($[M+Na]^+$, 92%), 298 ($[M+H]^+$, 69%); HRMS (ESI^+) $C_{19}H_{24}NO_2^+$ ($[M+H]^+$) requires 298.1802; found 298.1790. Data for major anomer:[25] δ_H (400 MHz, $CDCl_3$) 1.48 (3H, d, *J* 6.8, C(α)*Me*), 1.59–1.77 (1H, m, C(4)H_A),* 1.89–1.97 (1H, m, C(4)H_B), 3.50–3.99 (6H, m, C(3)*H*, C(5)H_2, C(α)*H*, NCH_2Ph),* 5.51 (1H, d, *J* 1.8, C(2)*H*), 7.27–7.50 (10H, m, *Ph*);* δ_C (100 MHz, $CDCl_3$) 15.9 (C(α)*Me*), 29.1 (*C*(4)), 50.8 (NCH_2Ph), 57.5 (*C*(α)), 65.5 (*C*(3)), 66.4 (*C*(5)), 100.8 (*C*(2)), 126.7–128.5 (*o*,*m*,*p*-*Ph*),* 141.3, 143.4 (*i*-*Ph*). Data for minor anomer:[26] δ_H (400 MHz, $CDCl_3$) 1.53 (3H, d, *J* 7.1, C(α)*Me*), 1.59–1.77 (2H, m, C(4)H_2),* 3.50–3.99 (5H, m, C(3)*H*, C(5)H_2, NCH_2Ph),* 4.17 (1H, q, *J* 7.1, C(α)*H*), 5.37 (1H, d, *J* 4.3, C(2)*H*), 7.27–7.50 (10H, m, *Ph*);* δ_C (100 MHz, $CDCl_3$) 13.5 (C(α)*Me*), 26.9 (*C*(4)), 52.9 (NCH_2Ph), 57.2 (*C*(α)),63.1 (*C*(3)), 65.9 (*C*(5)), 96.5 (*C*(2)), 126.7–128.5 (*o*,*m*,*p*-*Ph*),* 140.6, 142.2 (*i*-*Ph*). Further elution gave **35** as a colourless oil (46 mg, 8%, 95:5 dr); $[\alpha]_D^{25}$ −55.7 (*c* 2.0 in $CHCl_3$); ν_{max} (ATR) 1097, 1041; δ_H (500 MHz, $CDCl_3$) 1.41 (3H, d, *J* 6.9, C(α)*Me*), 1.63–1.70 (1H, m, C(4)H_A), 1.84–1.90 (1H, m, C(4)H_B), 3.32 (3H, s, O*Me*), 3.47–3.51 (1H, m, C(3)*H*), 3.66–3.71 (1H, m, C(5)H_A), 3.79 (2H, app d, *J* 15.1, NCH_2Ph), 3.85–3.91 (2H, m, C(5)H_B, C(α)*H*), 4.93 (1H, d, *J* 2.0, C(2)*H*), 7.21–7.44 (10H, m, *Ph*); δ_C (500 MHz, $CDCl_3$) 15.5 (C(α)*Me*), 29.2 (*C*(4)), 50.6 (NCH_2Ph), 54.7 (O*Me*), 57.5 (*C*(α)), 64.6 (*C*(3)), 66.0 (*C*(5)), 107.2 (*C*(2)), 126.8, 127.7, 128.0, 128.1, 128.2 (*o*,*m*,*p*-*Ph*), 141.4, 143.3 (*i*-*Ph*); *m*/*z* (ESI^+) 312 ($[M+H]^+$, 81%); HRMS (ESI^+) $C_{20}H_{26}NO_2^+$ ($[M+H]^+$) requires 312.1958; found 312.1955.

4.13. (2*S*,3*S*,α*R*)-2-Methoxy-3-[*N*-benzyl-*N*-(α-methylbenzyl)amino]tetrahydrofuran 35

Method A: *Step 1*: HCl (2.0 M in Et_2O, 3.40 mL, 6.80 mmol) was added to a stirred solution of **25** (298 mg, 0.96 mmol, 98:2 dr) in Et_2O (10 mL) and the resultant mixture was stirred at rt for 5 min, then concentrated in vacuo. The residue of **25**·HCl was dissolved in CH_2Cl_2/MeOH (v/v, 1:1, 40 mL), the resultant solution was cooled to

−78 °C, and O_3 was bubbled through the solution until it turned blue. O_2 was then bubbled through the solution until it turned colourless, after which Me_2S (3 mL) was added dropwise. The reaction mixture was allowed to warm to rt over 16 h, then concentrated in vacuo. The residue was dissolved in CH_2Cl_2 (25 mL) and the resultant solution was washed with satd aq $NaHCO_3$ (15 mL), dried and concentrated in vacuo to give an 85:15 mixture of **34** (64:36 dr) and **35** (95:5 dr).

Step 2: HCl (1.25 M in MeOH, 2.00 mL, 2.50 mmol) was added to a stirred solution of the residue of **34** and **35** (179 mg) in MeOH (5 mL), and the resultant mixture was heated at 50 °C for 16 h, before being allowed to cool to rt and concentrated in vacuo. The residue was dissolved in CH_2Cl_2 (5 mL) and the resultant solution was washed with satd aq $NaHCO_3$ (5 mL), then dried and concentrated in vacuo. Purification via flash column chromatography (eluent 30–40 °C petrol/Et_2O, 15:1) gave **35** as a colourless oil (149 mg, 80%, >95:5 dr); $[\alpha]_D^{25}$ −56.4 (*c* 2.0 in $CHCl_3$).

Method B: HCl (1.25 M in MeOH, 0.26 mL, 0.32 mmol) was added to a stirred solution of **31** (30 mg, 0.08 mmol, 96:4 dr) in MeOH (1.6 mL), and the resultant mixture was heated at 50 °C for 16 h, before being allowed to cool to rt and concentrated in vacuo. The residue was dissolved in CH_2Cl_2 (3 mL) and the resultant solution was washed with satd aq $NaHCO_3$ (3 mL), then dried and concentrated in vacuo. Purification via flash column chromatography (eluent 30–40 °C petrol/Et_2O, 15:1) gave **35** as a colourless oil (24 mg, 97%, >95:5 dr); $[\alpha]_D^{25}$ −58.9 (*c* 2.0 in $CHCl_3$).

Method C: HCl (1.25 M in MeOH, 2.00 mL, 2.50 mmol) was added to a stirred solution of **34** (200 mg, 0.67 mmol, 64:36 dr) in MeOH (3 mL), and the resultant mixture was heated at 50 °C for 16 h, before being allowed to cool to rt and concentrated in vacuo. The residue was dissolved in CH_2Cl_2 (4 mL) and the resultant solution was washed with satd aq $NaHCO_3$ (4 mL), then dried and concentrated in vacuo. Purification via flash column chromatography (eluent 30–40 °C petrol/Et_2O, 15:1) gave **35** as a colourless oil (178 mg, 85%, 95:5 dr); $[\alpha]_D^{25}$ −56.7 (*c* 2.0 in $CHCl_3$).

4.14. *tert*-Butyl (*S*,*S*)-(2-methoxytetrahydrofuran-3-yl)carbamate 36

A stirred solution of **35** (200 mg, 0.64 mmol, >95:5 dr) and Boc_2O (435 mg, 1.28 mmol) in MeOH (2 mL) was purged with N_2 for 15 min. After this time, $Pd(OH)_2/C$ (50% w/w of **35**, 100 mg) was added and the resultant suspension was placed under H_2 (5 atm), and stirring was continued for 24 h. The resultant suspension was filtered through Celite® (eluent MeOH) and the filtrate was concentrated in vacuo. Purification via flash column chromatography (eluent 30–40 °C petrol/EtOAc, 10:1) gave **36** as a colourless oil (125 mg, 90%, >95:5 dr); $[\alpha]_D^{25}$ −34.8 (*c* 2.1 in $CHCl_3$); ν_{max} (ATR) 3329 (N–H), 1690 (C=O); δ_H (500 MHz, $CDCl_3$) 1.44 (9H, s, C*Me*$_3$), 1.66–1.72 (1H, m, C(4)*H*$_A$), 2.32–2.39 (1H, m, C(4)*H*$_B$), 3.32 (3H, s, O*Me*), 3.90–4.00 (2H, m, C(5)*H*$_2$), 4.08 (1H, br s, C(3)*H*), 4.62 (1H, br s, N*H*), 4.78 (1H, m, C(2)*H*); δ_C (125 MHz, $CDCl_3$) 28.3 (C*Me*$_3$), 30.2 (*C*(4)), 54.4 (O*Me*), 55.8 (*C*(3)), 65.7 (*C*(5)), 79.6 (*C*Me$_3$), 107.8 (*C*(2)), 155.0 (N*C*O); *m*/*z* (ESI$^+$) 240 ([M+Na]$^+$, 100%); HRMS (ESI$^+$) $C_{10}H_{19}NNaO_4^+$ ([M+Na]$^+$) requires 240.1206; found 240.1214.

4.15. (2*S*,3*S*,4*R*,α*R*)-2-Methoxy-3-[*N*-benzyl-*N*-(α-methylbenzyl)amino]tetrahydrofuran-4-ol 37

Method A: *Step 1*: HCl (2.0 M in Et_2O, 3.77 mL, 7.53 mmol) was added to a stirred solution of **26** (350 mg, 1.08 mmol, >99:1 dr) in Et_2O (10 mL) and the resultant mixture was stirred at rt for 5 min, then concentrated in vacuo. The residue of **26**·HCl was dissolved in CH_2Cl_2/MeOH (v/v, 1:1, 40 mL), the resultant solution was cooled to −78 °C, and O_3 was bubbled through the solution until it turned blue. O_2 was then bubbled through the solution until it turned colourless, after which Me_2S (3 mL) was added dropwise. The reaction mixture was allowed to warm to rt over 16 h, then concentrated in vacuo. The residue was dissolved in CH_2Cl_2 (25 mL) and the resultant solution was washed with satd aq $NaHCO_3$ (15 mL), then dried and concentrated in vacuo.

Step 2: HCl (1.25 M in MeOH, 6.00 mL, 7.50 mmol) was added to a stirred solution of the residue from the previous step in MeOH (5 mL), and the resultant mixture was heated at 50 °C for 16 h, before being allowed to cool to rt and concentrated in vacuo. The residue was dissolved in CH_2Cl_2 (5 mL) and the resultant solution was washed with satd aq $NaHCO_3$ (5 mL), then dried and concentrated in vacuo. Purification via flash column chromatography (eluent 30–40 °C petrol/Et_2O, 4:1) gave **37** as a colourless oil (268 mg, 76%, 87:13 dr); ν_{max} (ATR) 3440 (O–H); *m*/*z* (ESI$^+$) 350 ([M+Na]$^+$, 100%), 328 ([M+H]$^+$, 94%); HRMS (ESI$^+$) $C_{20}H_{26}NO_3^+$ ([M+H]$^+$) requires 328.1907; found 328.1900. Data for major anomer: δ_H (400 MHz, $CDCl_3$) 1.43 (3H, d, *J* 6.8, C(α)*Me*), 3.30 (1H, dd, *J* 5.6, 2.1, C(3)*H*), 3.32 (3H, s, O*Me*), 3.83–3.97 (5H, m, C(4)*H*, C(5)*H*$_2$, NC*H*$_2$Ph),* 4.12 (1H, q, *J* 6.8, C(α)*H*), 5.12 (1H, d, *J* 2.2, C(2)*H*), 7.24–7.44 (10H, m, *Ph*);* δ_C (100 MHz, $CDCl_3$) 12.7 (C(α)*Me*), 51.9 (NC*H*$_2$Ph), 55.1 (O*Me*), 56.3 (*C*(α)), 66.6 (*C*(3)), 69.8, 73.1 (*C*(4), *C*(5)), 104.8 (*C*(2)), 127.3, 127.4, 127.8, 128.4, 128.7 (*o*,*m*,*p*-*Ph*), 139.6, 141.8 (*i*-*Ph*). Data for minor anomer: δ_H (400 MHz, $CDCl_3$) 1.48 (3H, d, *J* 7.0, C(α)*Me*), 3.00–3.02 (1H, m, C(3)*H*), 3.17 (3H, s, O*Me*), 3.83–3.97 (5H, m, C(4)*H*, C(5)*H*$_2$, NC*H*$_2$Ph),* 4.43 (1H, q, *J* 7.0, C(α)*H*), 4.81 (1H, d, *J* 3.9, C(2)*H*), 7.24–7.44 (10H, m, *Ph*);* δ_C (100 MHz, $CDCl_3$) 15.2 (C(α)*Me*), 53.3 (NC*H*$_2$Ph), 54.8 (O*Me*), 57.6 (*C*(α)), 68.7 (*C*(3)), 69.6, 75.3 (*C*(4), *C*(5)), 103.7 (*C*(2)), 126.8, 127.1, 128.0, 128.2, 128.3 (*o*,*m*,*p*-*Ph*), 141.3, 142.0 (*i*-*Ph*).

Method B: HCl (1.25 M in MeOH, 0.72 mL, 0.90 mmol) was added to a stirred solution of **32** (87 mg, 0.22 mmol, >99:1 dr) in MeOH (4 mL), and the resultant mixture was heated at 50 °C for 16 h, before being allowed to cool to rt and concentrated in vacuo. The residue was dissolved in CH_2Cl_2 (4 mL) and the resultant solution was washed with satd aq $NaHCO_3$ (3 mL), dried and concentrated in vacuo. Purification via flash column chromatography (eluent 30–40 °C petrol/Et_2O, 4:1) gave **37** as a colourless oil (70 mg, 97%, 87:13 dr).

4.16. *tert*-Butyl (2*S*,3*S*,4*R*)-(2-methoxy-4-hydroxytetrahydrofuran-3-yl)carbamate [methyl *N*-Boc-2-deoxy-2-amino-β-L-erythroside] 38

A stirred solution of **37** (209 mg, 0.64 mmol, 87:13 dr) and Boc_2O (435 mg, 1.28 mmol) in MeOH (2 mL) was purged with N_2 for 15 min. After this time, $Pd(OH)_2/C$ (50% w/w of **37**, 105 mg) was added and the resultant suspension was placed under H_2 (5 atm), and stirring was continued for 24 h. The resultant suspension was filtered through Celite® (eluent MeOH) and the filtrate was concentrated in vacuo. Purification via flash column chromatography (eluent 30–40 °C petrol/EtOAc, 10:1) gave **38** as a colourless oil (137 mg, 92%, >95:5 dr); $[\alpha]_D^{25}$ −31.8 (*c* 2.0 in $CHCl_3$); ν_{max} (ATR) 3442 (O–H), 3329 (N–H), 1688 (C=O); δ_H (500 MHz, $CDCl_3$) 1.39 (9H, s, C*Me*$_3$), 3.51 (3H, s, O*Me*), 3.58 (1H, br s, O*H*), 3.59–4.22 (3H, m, C(4)*H*, C(5)*H*$_2$), 4.33 (1H, dd, *J* 5.8, 2.3, C(3)*H*), 5.71 (1H, d, *J* 2.3, C(2)*H*), 8.01 (1H, br s, N*H*); δ_C (125 MHz, $CDCl_3$) 28.3 (C*Me*$_3$), 54.8 (O*Me*), 67.9 (*C*(3)), 69.0 (*C*(4)), 71.3 (*C*(5)), 79.6 (*C*Me$_3$), 114.2 (*C*(2)), 155.7 (N*C*O); *m*/*z* (ESI$^+$) 256 ([M+Na]$^+$, 100%); HRMS (ESI$^+$) $C_{10}H_{19}NNaO_5^+$ ([M+Na]$^+$) requires 256.1155; found 256.1158.

4.17. *tert*-Butyl (2*S*,3*R*,α*R*,*E*)-2-hydroxy-3-[*N*-benzyl-*N*-(α-methylbenzyl)amino]hex-4-enoate 40

Step 1: DMSO (575 μL, 8.10 mmol) was added dropwise to a stirred solution of $(COCl)_2$ (685 μL, 8.10 mmol) in CH_2Cl_2 (50 mL) at −78 °C and the resultant mixture was stirred at −78 °C for 5 min.

A solution of **24** (1.60 g, 4.05 mmol, >99:1 dr) in CH_2Cl_2 (50 mL) was then added via cannula and the reaction mixture was stirred at −78 °C for 30 min. Et_3N (2.3 mL, 16.20 mmol) was then added and stirring was continued at −78 °C for 10 min. The reaction mixture was then allowed to warm to rt over 20 min. H_2O (25 mL) was then added and the resultant mixture was extracted with CH_2Cl_2 (3×30 mL). The combined organic extracts were then dried and concentrated in vacuo to give **39** as a yellow oil (1.60 g); δ_H (200 MHz, $CDCl_3$) 1.38 (3H, d, *J* 6.9, C(α)*Me*), 1.47 (9H, s, C*Me*$_3$), 1.74 (3H, d, *J* 4.9, C(6)*H*$_3$), 3.85 (2H, A_2, NC*H*$_2$Ph), 4.01 (1H, q, *J* 6.9, C(α)*H*), 4.58 (1H, d, *J* 7.4, C(3)*H*), 5.51–5.75 (2H, m, C(4)*H*, C(5)*H*), 7.15–7.45 (10H, m, *Ph*).

Step 2: $NaBH_4$ (152 mg, 4.00 mmol) was added portionwise to a stirred solution of the residue of **39** (1.60 g) in MeOH (8 mL) at −20 °C and the resultant mixture was stirred at −20 °C for 2 h. The reaction mixture was then allowed to warm to rt and concentrated in vacuo. The residue was partitioned between H_2O (20 mL) and Et_2O (20 mL), and the aqueous layer was extracted with Et_2O (3×20 mL). The combined organic extracts were then dried and concentrated in vacuo. Purification via flash column chromatography (eluent 30–40 °C petrol/Et_2O, 20:1) gave **40** as a colourless oil (2.14 g, 65%, >99:1 dr); $[\alpha]_D^{25}$ −73.0 (*c* 1.0 in $CHCl_3$); ν_{max} (ATR) 3496 (O–H), 1728 (C=O); δ_H (500 MHz, $CDCl_3$) 1.36 (9H, s, C*Me*$_3$), 1.46 (3H, d, *J* 6.9, C(α)*Me*), 1.76 (3H, d, *J* 4.4, C(6)*H*$_3$), 3.33 (1H, dd, *J* 9.4, 4.4, C(3)*H*), 3.66 (1H, d, *J* 13.6, NC*H*$_A$H$_B$Ph), 3.75 (1H, d, *J* 9.4, C(2)*H*), 3.86 (1H, d, *J* 13.6, NCH$_A$*H*$_B$Ph), 4.08 (1H, q, *J* 6.9, C(α)*H*), 5.62–5.63 (2H, m, C(4)*H*, C(5)*H*), 7.24–7.32 (10H, m, *Ph*); δ_C (125 MHz, $CDCl_3$) 14.4 (C(α)*Me*), 18.2 (*C*(6)), 27.9 (C*Me*$_3$), 50.2 (NCH$_2$Ph), 56.3 (*C*(α)), 62.7 (*C*(3)), 71.7 (*C*(2)), 81.1 (*C*Me$_3$), 126.7, 127.2, 127.3, 127.8, 128.4, 128.6, 129.1, 131.3 (*C*(4), *C*(5), *o*,*m*,*p*-*Ph*), 139.5, 143.7 (*i*-*Ph*), 171.5 (*C*(1)); *m*/*z* (ESI$^+$) 396 ([M+H]$^+$, 100%); HRMS (ESI$^+$) $C_{25}H_{34}NO_3^+$ ([M+H]$^+$) requires 396.2533; found 396.2529.

4.18. *tert*-Butyl (2*S*,3*S*,α*R*)-2-hydroxy-3-[*N*-benzyl-*N*-(α-methylbenzyl)amino]-4,4-diethoxybutanoate 42

Step 1: DMSO (125 μL, 1.79 mmol) was added dropwise to a stirred solution of $(COCl)_2$ (152 μL, 1.79 mmol) in CH_2Cl_2 (6 mL) at −78 °C and the resultant mixture was stirred at −78 °C for 5 min. A solution of **30** (410 mg, 0.90 mmol) in CH_2Cl_2 (6 mL) was then added via cannula and the reaction mixture was stirred at −78 °C for 30 min. Et_3N (520 μL, 3.59 mmol) was then added and stirring was continued at −78 °C for 10 min. The reaction mixture was then allowed to warm to rt over 20 min. H_2O (5 mL) was then added and the resultant mixture was extracted with CH_2Cl_2 (3×10 mL). The combined organic extracts were then dried and concentrated in vacuo to give **41** as a yellow oil (400 mg); δ_H (200 MHz, $CDCl_3$) 1.08 (3H, t, *J* 7.1, OCH$_2$*Me*), 1.30 (3H, t, *J* 7.1, OCH$_2$*Me*), 1.41 (3H, d, *J* 6.9, C(α)*Me*), 1.49 (9H, s, C*Me*$_3$), 3.35–3.80 (4H, m, (OC*H*$_2$Me)$_2$), 3.93–4.22 (3H, m, NC*H*$_2$Ph, C(α)*H*), 4.64 (1H, d, *J* 7.3, C(3)*H*), 4.80 (1H, d, *J* 7.3, C(4)*H*), 7.11–7.42 (10H, m, *Ph*).

Step 2: $NaBH_4$ (34 mg, 0.90 mmol) was added to a stirred solution of the residue **41** (400 mg) in MeOH (8 mL) at −20 °C and the resultant mixture was stirred at −20 °C for 2 h. The reaction mixture was then allowed to warm to rt and concentrated in vacuo. The residue was partitioned between H_2O (20 mL) and Et_2O (20 mL), and the aqueous layer was extracted with Et_2O (3×20 mL). The combined organic extracts were then dried and concentrated in vacuo to give a 77:23 mixture of **30** and **42**, respectively. Data for **42**: δ_H (400 MHz, $CDCl_3$) 1.14 (3H, t, *J* 7.1, OCH$_2$*Me*), 1.21 (3H, t, *J* 7.1, OCH$_2$*Me*), 1.36 (9H, s, C*Me*$_3$), 1.38 (3H, d, *J* 6.9, C(α)*Me*), 3.35 (1H, t, *J* 6.1, C(3)*H*), 3.42 (1H, dq, *J* 8.8, 7.1, C(OC*H*$_A$H$_B$Me)$_A$), 3.54 (1H, dq, *J* 9.3, 7.1, C(OC*H*$_A$H$_B$Me)$_B$), 3.64–3.70 (2H, m, C(OCH$_A$*H*$_B$Me)$_2$), 3.83 (1H, d, *J* 14.2, NC*H*$_A$H$_B$Ph), 3.96 (1H, d, *J* 14.2, NCH$_A$*H*$_B$Ph), 4.05 (1H, d, *J* 5.4, C(2)*H*), 4.22 (1H, q, *J* 6.9, C(α)*H*), 4.72 (1H, d, *J* 6.4, C(4)*H*), 7.04–7.23 (10H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 15.4, 15.5 (C(OCH$_2$*Me*)$_2$) 18.7 (C(α)*Me*), 28.0 (C*Me*$_3$), 52.1 (NCH$_2$Ph), 59.5 (*C*(α)), 61.0 (*C*(3)), 63.5, 64.3 (C(OCH$_2$Me)$_2$), 71.4 (*C*(2)), 81.6 (*C*Me$_3$), 103.8 (*C*(4)), 126.6, 126.8, 128.0, 128.9 (*o*,*m*,*p*-*Ph*), 141.0, 144.4 (*i*-*Ph*), 172.6 (*C*(1)).

4.19. (2*S*,3*R*,α*R*,*E*)-3-[*N*-Benzyl-*N*-(α-methylbenzyl)amino]-hex-4-en-1,2-diol 43

$LiAlH_4$ (1.0 M in THF, 2.53 mL, 2.53 mmol) was added to a solution **40** (1.00 g, 2.53 mmol, >99:1 dr) in THF (10 mL) at 0 °C, and the resultant mixture was allowed to warm to rt and stirred at rt for 16 h. The reaction mixture was then cooled to 0 °C and lumps of ice (~1 g), and then 2.0 M aq NaOH solution (5 mL), were added cautiously with vigorous stirring being maintained throughout. The resultant mixture was then allowed to warm to rt over 15 min, diluted with EtOAc (30 mL) and the resultant mixture was stirred for a further 30 min before being filtered through Celite® (eluent EtOAc). The filtrate was then dried and concentrated in vacuo. Purification via flash column chromatography (eluent 30–40 °C petrol/Et_2O, 2:1) gave **43** as a colourless oil (0.62 g, 75%, >99:1 dr); $[\alpha]_D^{25}$ −43.0 (*c* 1.3 in $CHCl_3$); ν_{max} (ATR) 3410 (O–H); δ_H (400 MHz, $CDCl_3$) 1.37 (3H, d, *J* 6.9, C(α)*Me*), 1.71 (3H, dd, *J* 6.5, 1.6, C(6)*H*$_3$), 3.16 (2H, m, C(1)*H*$_A$, C(3)*H*), 3.40 (1H, dt, *J* 9.5, 3.0, C(2)*H*), 3.53 (1H, app dd, *J* 11.4, 3.0, C(1)*H*$_B$), 3.57 (1H, d, *J* 13.3, NC*H*$_A$H$_B$Ph), 3.81 (1H, d, *J* 13.3, NCH$_A$*H*$_B$Ph), 3.98 (1H, q, *J* 6.9, C(α)*H*), 5.48 (1H, ddd, *J* 15.2, 9.5, 1.6, C(4)*H*), 5.66 (1H, dq, *J* 15.2, 6.5, C(5)*H*), 7.13–7.29 (10H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 13.6 (C(α)*Me*), 18.4 (*C*(6)), 50.4 (NCH$_2$Ph), 55.9 (*C*(α)), 59.7 (*C*(3)), 62.7 (*C*(1)), 69.2 (*C*(2)), 127.2, 127.3, 127.4, 127.9, 128.4, 128.6, 129.2, 131.9 (*C*(4), *C*(5), *o*,*m*,*p*-*Ph*), 139.4, 143.4 (*i*-*Ph*); *m*/*z* (ESI$^+$) 326 ([M+H]$^+$, 100%); HRMS (ESI$^+$) $C_{21}H_{28}NO_2^+$ ([M+H]$^+$) requires 326.2115; found 326.2118.

4.20. (2*S*,3*S*,4*S*,α*R*)-2-Methoxy-3-[*N*-benzyl-*N*-(α-methylbenzyl)amino]tetrahydrofuran-4-ol 44

Step 1: HCl (2.0 M in Et_2O, 6.45 mL, 12.9 mmol) was added to a stirred solution of **43** (600 mg, 1.85 mmol, >99:1 dr) in Et_2O (5 mL) and the resultant mixture was stirred at rt for 5 min, then concentrated in vacuo. The residue of **43**·HCl was dissolved in CH_2Cl_2/MeOH (v/v, 1:1, 80 mL), the resultant solution was cooled to −78 °C, and O_3 was bubbled through the solution until it turned blue. O_2 was then bubbled through the solution until it turned colourless, after which Me_2S (6 mL) was added dropwise. The resultant solution reaction was allowed to warm to rt over 16 h, then concentrated in vacuo. The residue was dissolved in CH_2Cl_2 (40 mL) and the resultant solution was washed with satd aq $NaHCO_3$ (20 mL), then dried and concentrated in vacuo.

Step 2: HCl (1.25 M in MeOH, 5.2 mL, 6.50 mmol) was added to a stirred solution of the residue from the previous step in MeOH (10 mL), and the resultant mixture was heated at 50 °C for 16 h, before being allowed to cool to rt and concentrated in vacuo. The residue was dissolved in CH_2Cl_2 (5 mL) and the resultant solution was washed with satd aq $NaHCO_3$ (5 mL), then dried and concentrated in vacuo. Purification via flash column chromatography (eluent 30–40 °C petrol/Et_2O, 10:1) gave **44** as a colourless oil (493 mg, 91%, 92:8 dr); $[\alpha]_D^{25}$ +10.3 (*c* 0.6 in $CHCl_3$); ν_{max} (ATR) 3430 (O–H); δ_H (400 MHz, $CDCl_3$) 1.35 (3H, d, *J* 6.8, C(α)*Me*), 3.26 (1H, app dd, *J* 3.8, 1.0, C(3)*H*), 3.29 (3H, s, O*Me*), 3.52 (1H, dd, *J* 9.3, 6.4, C(5)*H*$_A$), 3.74 (2H, A_2, NC*H*$_2$Ph), 3.88 (2H, m, C(4)*H*, C(5)*H*$_B$), 4.00 (1H, q, *J* 6.8, C(α)*H*), 4.86 (1H, d, *J* 1.0, C(2)*H*), 7.14–7.37 (10H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 14.3 (C(α)*Me*), 51.4 (NCH$_2$Ph), 55.0 (O*Me*), 57.1 (*C*(4)), 71.8 (*C*(5)), 72.3 (*C*(3)), 74.6 (*C*(α)), 106.3 (*C*(2)), 126.7, 127.0, 127.7, 127.9, 128.1, 128.3 (*o*,*m*,*p*-*Ph*), 140.7, 143.4 (*i*-*Ph*); *m*/*z* (ESI$^+$) 328 ([M+H]$^+$, 100%); HRMS (ESI$^+$) $C_{20}H_{26}NO_3^+$ ([M+H]$^+$) requires 328.1907; found 328.1911.

4.21. *tert*-Butyl (*S,S,S*)-(2-methoxy-4-hydroxytetrahydrofuran-3-yl)carbamate [methyl *N*-Boc-2-deoxy-2-amino-α-D-threoside] 45

A stirred solution of **44** (190 mg, 0.58 mmol, 92:8 dr) and Boc_2O (253 mg, 1.16 mmol) in MeOH (1.8 mL) was purged with N_2 for 15 min. After this time, $Pd(OH)_2/C$ (50% w/w of **44**, 95 mg) was added and the resultant suspension was placed under H_2 (5 atm), and stirring was continued for 24 h. The resultant suspension was filtered through Celite® (eluent MeOH) and the filtrate was concentrated in vacuo. Purification via flash column chromatography (eluent 30–40 °C petrol/EtOAc, 4:1) gave **45** as a colourless oil (72 mg, 54%, >95:5 dr); $[\alpha]_D^{25}$ +45.0 (*c* 0.4 in $CHCl_3$); ν_{max} (ATR) 3309 (O–H), 1682 (C=O); δ_H (500 MHz, $CDCl_3$) 1.38 (9H, s, CMe_3), 3.32 (3H, s, O*Me*), 3.34 (1H, br s, O*H*), 3.82 (1H, dd, *J* 9.8, 3.4, C(5)H_A), 3.90 (1H, d, *J* 6.0, C(4)*H*), 4.06 (1H, br s, C(3)*H*), 4.14 (1H, dd, *J* 9.8, 6.0, C(5)H_B), 4.58 (1H, br s, N*H*), 4.76 (1H, app s, C(2)*H*); δ_C (125 MHz, $CDCl_3$) 27.3 (CMe_3), 54.0 (O*Me*), 62.0 (*C*(4)), 72.9 (*C*(5)), 75.0 (*C*(3)), 79.4 (*C*Me$_3$), 106.4 (*C*(2)), 154.4 (NCO); *m*/*z* (ESI$^+$) 489 ([2M+Na]$^+$, 100%), 256 ([M+Na]$^+$, 55%); HRMS (ESI$^+$) $C_{10}H_{19}NNaO_5^+$ ([M+Na]$^+$) requires 256.1155; found 256.1155.

4.22. *tert*-Butyl (*E*)-5,5-diethoxypent-2-enoate 47

DIBAL-H (1.0 M in PhMe, 23.7 mL, 23.7 mmol) was added dropwise to a stirred solution of ethyl 3,3-diethoxypropanoate **46** (3.00 g, 15.8 mmol) in CH_2Cl_2 (160 mL) at −78 °C. The resultant solution was stirred at −78 °C for 50 min, then MeOH (40 mL) was added and the resultant solution was allowed to warm to rt over 15 min. Celite® (~50 g) and H_2O (50 mL) were added, the resultant mixture was stirred vigorously for 15 min and then filtered. $Ph_3P{=}CHCO_2{}^tBu$ (5.93 g, 15.8 mmol) was added to the filtrate, and the resultant mixture was stirred at rt for 16 h, then concentrated in vacuo. Purification via flash column chromatography (eluent 30–40 °C petrol/Et_2O, 7:1) gave **47** as a colourless oil (3.50 g, 91%, >99:1 dr); ν_{max} (ATR) 1714 (C=O), 1655 (C=C); δ_H (400 MHz, $CDCl_3$) 1.20 (6H, t, *J* 7.1, C(OCH$_2$*Me*)$_2$), 1.47 (9H, s, CMe_3), 2.48–2.52 (2H, m, C(4)H_2), 3.47–3.54 (2H, m, OCH_2Me), 3.61–3.69 (2H, m, OCH_2Me), 4.55–4.58 (1H, m, C(5)*H*), 5.82 (1H, d, *J* 15.7, C(2)*H*), 6.80 (1H, dt, *J* 15.7, 7.1, C(3)*H*); δ_C (100 MHz, $CDCl_3$) 15.2 (C(OCH$_2$*Me*)$_2$), 28.1 (CMe_3), 36.8 (*C*(4)), 61.2 (C(OCH$_2$Me)$_2$), 80.1 (*C*Me$_3$), 101.4 (*C*(5)), 125.4 (*C*(2)), 142.2 (*C*(3)), 165.7 (*C*(1)); *m*/*z* (ESI$^+$) 267 ([M+Na]$^+$, 100%); HRMS (ESI$^+$) $C_{13}H_{24}NaO_4^+$ ([M+Na]$^+$) requires 267.1567; found 267.1570.

4.23. *tert*-Butyl (*R,R*)-3-[*N*-benzyl-*N*-(α-methylbenzyl)amino]-5,5-diethoxypentanoate 48

n-BuLi (2.5 M in hexanes, 1.90 mL, 4.82 mmol) was added dropwise to a stirred solution of (*R*)-*N*-benzyl-*N*-(α-methylbenzyl) amine (1.05 g, 4.98 mmol) in THF (25 mL) at −78 °C, and the resultant mixture was stirred at −78 °C for 30 min. A solution of **47** (865 mg, 3.11 mmol, >99:1 dr) in THF (10 mL) was then added via cannula and the resultant mixture was stirred at −78 °C for 2 h. Satd aq NH_4Cl (20 mL) was then added and the resultant mixture was allowed to warm to rt over 15 min, then partitioned between Et_2O (100 mL) and H_2O (100 mL). The aqueous layer was extracted with Et_2O (3×100 mL) and the combined organic extracts were washed sequentially with 10% aq citric acid (500 mL), satd aq $NaHCO_3$ (500 mL) and brine (500 mL), then dried and concentrated in vacuo. Purification via flash column chromatography (eluent 30–40 °C petrol/Et_2O, 10:1) gave **48** as a colourless oil (1.29 g, 91%, 99:1 dr); $[\alpha]_D^{25}$ −42.2 (*c* 1.0 in $CHCl_3$); ν_{max} (ATR) 1722 (C=O); δ_H (400 MHz, $CDCl_3$) 1.17–1.25 (6H, m, C(OCH$_2$*Me*)$_2$), 1.37 (3H, d, *J* 7.1, C(α)*Me*), 1.42 (9H, s, CMe_3), 1.64–1.70 (1H, m, C(4)H_A), 1.73–1.79 (1H, m, C(4)H_B), 1.89–1.91 (2H, m, C(2)H_2), 3.35–3.42 (1H, m, OCH_AH$_B$Me), 3.47–3.62 (4H, m, C(3)*H*, OCH_2Me, NCH_AH$_B$Ph), 3.67–3.75 (1H, m, OCH$_A$$H_B$Me), 3.78–3.85 (2H, m, C(α)*H*, NCH$_A$$H_B$Ph), 4.87 (1H, dd, *J* 8.1, 3.0, C(5)*H*), 7.23–7.44 (10H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 15.2, 15.4 (C(OCH$_2$*Me*)$_2$), 19.9 (C(α)*Me*), 28.0 (CMe_3), 37.1 (*C*(4)), 37.8 (*C*(2)), 50.0 (NCH$_2$), 50.5 (*C*(3)), 58.0 (*C*(α)), 60.4, 61.0 (C(OCH$_2$Me)$_2$), 80.1 (*C*Me$_3$), 100.9 (*C*(5)), 126.7, 127.0, 128.0, 128.1, 128.2, 128.3 (*o*,*m*,*p*-*Ph*), 141.5, 142.4 (*i*-*Ph*), 171.7 (*C*(1)); *m*/*z* (ESI$^+$) 456 ([M+H]$^+$, 100%); HRMS (ESI$^+$) $C_{28}H_{41}NNaO_4^+$ ([M+Na]$^+$) requires 478.2928; found 478.2931.

4.24. *tert*-Butyl (*R,R,R*)-2-hydroxy-3-[*N*-benzyl-*N*-(α-methylbenzyl)amino]-5,5-diethoxypentanoate 49

n-BuLi (2.5 M in hexanes, 7.80 mL, 19.5 mmol) was added dropwise to a stirred solution of (*R*)-*N*-benzyl-*N*-(α-methylbenzyl) amine (4.26 g, 20.1 mmol) in THF (60 mL) at −78 °C, and the resultant mixture was stirred at −78 °C for 30 min. A solution of **47** (3.50 g, 12.6 mmol, >99:1 dr) in THF (50 mL) was then added via cannula and the resultant mixture was stirred at −78 °C for 2 h. (−)-CSO (4.90 g, 21.4 mmol) was then added and the reaction mixture was allowed to warm to rt over 12 h. Satd aq NH_4Cl (10 mL) was then added, and the resultant mixture was concentrated in vacuo. The residue was dissolved in CH_2Cl_2 (200 mL) and the resultant solution was washed sequentially with 10% aq citric acid (200 mL), satd aq $NaHCO_3$ (200 mL) and brine (200 mL), then dried and concentrated in vacuo. Purification via flash column chromatography (eluent 30–40 °C petrol/Et_2O, 8:1) gave **49** as a colourless oil (4.57 g, 77%, 92:8 dr); $[\alpha]_D^{25}$ −33.6 (*c* 1.0 in $CHCl_3$); ν_{max} (ATR) 3495 (O–H), 1719 (C=O); δ_H (400 MHz, $CDCl_3$) 1.05–1.12 (6H, m, C(OCH$_2$*Me*)$_2$), 1.24 (3H, d, *J* 6.9, C(α)*Me*), 1.27–1.32 (1H, m, C(4)H_A), 1.40 (9H, s, CMe_3), 1.76–1.83 (1H, m, C(4)H_B), 2.88 (1H, d, *J* 5.6, O*H*), 3.21–3.50 (4H, m, C(3)*H*, OCH_2Me, OCH_AH$_B$Me), 3.58 (1H, d, *J* 15.7, NCH_AH$_B$Ph), 3.62–3.70 (2H, m, C(2)*H*, OCH$_A$$H_B$Me), 3.84 (1H, q, *J* 6.9, C(α)*H*), 4.27 (1H, d, *J* 15.7, NCH$_A$$H_B$Ph), 4.75 (1H, dd, *J* 8.3, 2.5, C(5)*H*), 7.14–7.40 (10H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 15.4, 15.5 (C(OCH$_2$*Me*)$_2$), 19.7 (C(α)*Me*), 27.9 (CMe_3), 32.3 (*C*(4)), 50.9 (NCH$_2$Ph), 55.4 (*C*(3)), 58.3 (*C*(α)), 60.3, 62.3 (C(OCH$_2$Me)$_2$), 71.1 (*C*(2)), 82.7 (*C*Me$_3$), 101.6 (*C*(5)), 126.5, 127.1, 128.0, 128.1, 128.2, 128.3 (*o*,*m*,*p*-*Ph*), 142.4, 142.6 (*i*-*Ph*), 174.3 (*C*(1)); *m*/*z* (ESI$^+$) 472 ([M+H]$^+$, 100%); HRMS (ESI$^+$) $C_{28}H_{42}NO_5^+$ ([M+H]$^+$) requires 472.3057; found 472.3066.

4.25. (*R,R,R*)-3-[*N*-Benzyl-*N*-(α-methylbenzyl)amino]-5,5-diethoxypentane-1,2-diol 50

$LiAlH_4$ (1.0 M in THF, 1.78 mL, 1.78 mmol) was added to a solution **49** (840 mg, 1.78 mmol, 92:8 dr) in THF (20 mL) at 0 °C, and the resultant mixture was stirred at rt for 16 h. The reaction mixture was then cooled to 0 °C and lumps of ice (~1 g), and then 2.0 M aq NaOH solution (8 mL), were added cautiously with vigorous stirring being maintained throughout. The resultant mixture was then allowed to warm to rt over 15 min, diluted with EtOAc (30 mL) and the resultant mixture was stirred for a further 30 min before being filtered through Celite® (eluent EtOAc). The filtrate was then dried and concentrated in vacuo. Purification via flash column chromatography (eluent 30–40 °C petrol/Et_2O, 1:2) gave **50** as a colourless oil (699 mg, 98%, 92:8 dr); $[\alpha]_D^{25}$ −41.4 (*c* 1.0 in $CHCl_3$); ν_{max} (ATR) 3417 (O–H); δ_H (400 MHz, $CDCl_3$) 1.22 (3H, t, *J* 7.1, OCH$_2$*Me*), 1.27 (3H, t, *J* 7.1, OCH$_2$*Me*), 1.43 (3H, d, *J* 6.8, C(α)*Me*), 1.95–2.02 (1H, m, C(4)H_A), 2.09–2.14 (1H, m, C(4)H_B), 2.97 (1H, br s, C(3)*H*), 3.28 (1H, dd, *J* 11.0, 5.8, C(1)H_A), 3.38 (1H, dd, *J* 11.0, 4.0, C(1)H_B), 3.47–3.58 (3H, m, C(2)*H*, O(CH_AH$_B$Me)$_2$), 3.69–3.93 (5H, m, C(α)*H*, O(CH$_A$$H_B$Me)$_2$, NC$H_2$Ph), 4.71–4.74 (1H, m, C(5)*H*), 7.25–7.41 (10H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 14.0 (C(α)*Me*), 15.2, 15.4 (C(OCH$_2$*Me*)$_2$), 34.2 (*C*(4)), 51.5 (NCH$_2$), 53.4 (*C*(3)), 57.3 (*C*(α)), 62.2, 63.1 (C(OCH$_2$Me)$_2$), 65.2 (*C*(1)), 72.9 (*C*(2)), 102.9 (*C*(5)), 127.1, 127.2,

128.2, 128.3, 128.4, 128.8 (*o*,*m*,*p*-*Ph*), 140.5, 143.6 (*i*-*Ph*); *m*/*z* (ESI^+) 402 ($[M+H]^+$, 100%); HRMS (ESI^+) $C_{24}H_{36}NO_4^+$ ($[M+H]^+$) requires 402.2639; found 402.2641.

4.26. (2*S*,4*R*,5*R*,α*R*)-2-Methoxy-4-[*N*-benzyl-*N*-(α-methylbenzyl)amino]tetrahydro-2*H*-pyran-5-ol 51

HCl (1.25 M in MeOH, 8.78 mL, 11.0 mmol) was added to a stirred solution of **50** (1.10 g, 2.74 mmol, 92:8 dr) in MeOH (30 mL), and the resultant mixture was heated at 50 °C for 16 h, before being allowed to cool to rt and concentrated in vacuo. The residue was dissolved in CH_2Cl_2 (15 mL) and the resultant solution was washed with satd aq $NaHCO_3$ (10 mL), then dried and concentrated in vacuo. Purification via flash column chromatography (eluent 30–40 °C petrol/Et_2O, 1:1) gave **51** as a colourless oil (878 mg, 94%, 92:8 dr); $[\alpha]_D^{25}$ −37.8 (*c* 2.0 in $CHCl_3$); ν_{max} (ATR) 3419 (O–H); δ_H (400 MHz, $CDCl_3$) 1.48 (3H, d, *J* 6.8, C(α)*Me*), 1.82 (1H, dd, *J* 12.6, 4.3, C(3)H_A), 2.03 (1H, td, *J* 12.6, 3.5, C(3)H_B), 2.64 (1H, br s, O*H*), 3.25 (1H, dt, *J* 12.6, 3.8, C(4)*H*), 3.34 (3H, s, O*Me*), 3.51 (1H, br s, C(5)*H*), 3.60–3.70 (3H, m, C(6)H_2, NCH_AH$_B$Ph), 3.91 (1H, d, *J* 15.4, NCH$_A$$H_B$Ph), 4.26 (1H, q, *J* 6.8, C(α)*H*), 4.77 (1H, d, *J* 2.0, C(2)*H*), 7.17–7.48 (10H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 13.9 (C(α)*Me*), 30.1 (*C*(3)), 51.8 (NCH_2Ph), 54.8 (O*Me*), 54.9 (*C*(4)), 55.5 (*C*(α)), 62.3 (*C*(6)), 66.1 (*C*(5)), 98.3 (*C*(2)), 126.8, 127.0, 127.3, 128.0, 128.3, 128.4 (*o*,*m*,*p*-*Ph*), 142.3, 142.9 (*i*-*Ph*); *m*/*z* (ESI^+) 342 ($[M+H]^+$, 100%); HRMS (ESI^+) $C_{21}H_{28}NO_3^+$ ($[M+H]^+$) requires 342.2064; found 342.2056.

4.27. *tert*-Butyl (2*S*,4*R*,5*R*)-(2-methoxy-5-hydroxytetrahydro-2*H*-pyran-4-yl)carbamate [methyl *N*-Boc-2,3-dideoxy-3-amino-β-L-arabinopyranoside] 52

A stirred solution of **51** (218 mg, 0.64 mmol, 92:8 dr) and Boc_2O (435 mg, 1.28 mmol) in MeOH (2 mL) was purged with N_2 for 15 min. After this time, $Pd(OH)_2$/C (50% w/w of **51**, 109 mg) was added and the resultant suspension was placed under H_2 (5 atm), and stirring was continued for 24 h. The resultant suspension was filtered through Celite® (eluent MeOH) and the filtrate was concentrated in vacuo. Purification via flash column chromatography (eluent 30–40 °C petrol/EtOAc, 11:1) gave **52** as a colourless oil (142 mg, 90%, >95:5 dr); $[\alpha]_D^{25}$ −23.8 (*c* 2.0 in $CHCl_3$); ν_{max} (ATR) 3441 (O–H), 3328 (N–H), 1687 (C=O); δ_H (500 MHz, $CDCl_3$) 1.39 (3H, d, *J* 6.8, C(α)*Me*), 1.83–2.08 (3H, m, C(3)H_2), 3.51 (3H, s, O*Me*), 3.58–3.86 (5H, m, C(4)*H*, C(5)*H*, C(6)H_2, O*H*), 4.97 (1H, d, *J* 2.3, C(2)*H*), 8.01 (1H, br s, N*H*); δ_C (125 MHz, $CDCl_3$) 28.3 (CMe_3), 32.4 (*C*(3)), 53.2 (*C*(4)), 54.9 (O*Me*), 66.1 (*C*(5)), 67.5 (*C*(6)), 79.6 (CMe_3), 112.7 (*C*(2)), 155.7 (NCO); *m*/*z* (ESI^+) 270 ($[M+Na]^+$, 100%); HRMS (ESI^+) $C_{11}H_{21}NNaO_5^+$ ($[M+Na]^+$) requires 270.1312; found 270.1311.

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