A flexible and efficient synthesis of the pyrrolidine α-glycosidase inhibitor 1,4-dideoxy-1,4-imino-D-arabinitol (DAB-1)

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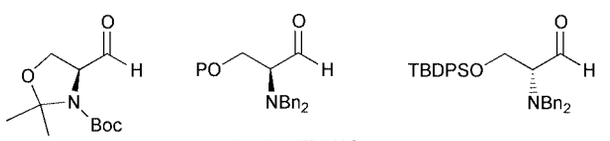
Received (in Cambridge, UK) 5th April 2000, Accepted 12th April 2000
Published on the Web 23rd May 2000

The α-glucosidase inhibitor 1,4-dideoxy-1,4-imino-D-arabinitol (DAB-1) **8** is synthesised in ten steps from D-serine with an overall yield of 49%; the key step of this synthesis makes use of the readily prepared serine-derived α-dibenzylamino aldehyde **3** in a highly diastereoselective glycolate aldol reaction.

Introduction

The use of serine-derived aldehydes in synthesis[1] has been hampered by their reactivity and susceptibility to epimerisation. The development of the Garner aldehyde **1** has helped to



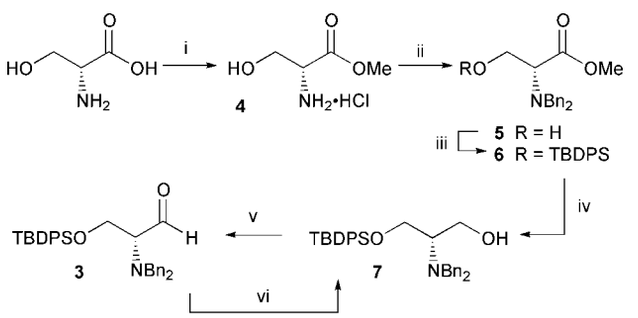
Serine-derived aldehydes.

overcome these problems,[2] but the diastereoselectivity displayed in the reactions of *N*-Boc-protected aldehydes is often poor.[3] We, like others, have been attracted to the highly *anti* diastereoselective nucleophilic addition reactions that *N*,*N*-dibenzyl-α-amino aldehydes have been shown to undergo[4] and the more recent reports of *syn* diastereoselective additions of dialkylzinc reagents to the same aldehydes.[5] These *N*,*N*-dibenzyl-α-amino aldehydes have also been shown to have a greater configurational stability than their benzyloxycarbonyl- or *tert*-butoxycarbonyl-protected counterparts, making them more widely applicable to synthesis.

Early reports of a *tert*-butyldimethylsilyl (TBDMS)-protected aldehyde **2a** largely remained unnoticed due to a lack of experimental detail,[6] and the benzyl-protected aldehyde **2b**[7] lacks the orthogonal nature of protecting groups required to make it truly useful. The methoxymethyl-protected aldehyde **2c** was used in studies directed towards the addition of dialkylzinc reagents to *N*,*N*-dibenzyl-α-amino aldehydes.[5] However, it is the recent publication of reports making use of **2a** in the synthesis of γ-hydroxy-β-amino alcohols[8] and *N*,*N*-dibenzylsphingosines[9] that has prompted us to report our own success in this area with the synthesis of the *tert*-butyldiphenylsilyl (TBDPS)-protected aldehyde **3**.

Results and discussion

D-Serine may be readily converted to its methyl ester hydrochloride salt **4** (98%)[10] which is subsequently *N*,*N*-dibenzyl-protected under non-aqueous conditions to give **5** in good yield (95%, Scheme 1). The TBDPS protecting group was chosen as a suitable orthogonal protecting group, not least due to the stability it exhibits in subsequent manipulations to give aldehyde



Scheme 1 *Reagents, conditions and yields*: i) CH_3COCl, MeOH, reflux, 3 h, 98%; ii) K_2CO_3, BnBr, CH_3CN, rt, 24 h, 95%; iii) TBDPSCl, imidazole, DMF, rt, 18 h, 100%; iv) DIBAL-H, $PhCH_3$, −78 °C, 30 min, 93%; v) $(COCl)_2$, DMSO, CH_2Cl_2, −78 °C, 1 h; Et_3N, 100%; vi) DIBAL-H, $PhCH_3$, −78 °C, 5 min, 90%.

3.† Treatment of **5** with the silyl chloride in the presence of imidazole resulted in a quantitative conversion to protected α-amino ester **6**. A range of reduction/oxidation protocols for the production of aldehyde **3** was investigated. However, the most efficient method was found to involve a two-step DIBAL-H reduction–Swern oxidation procedure.

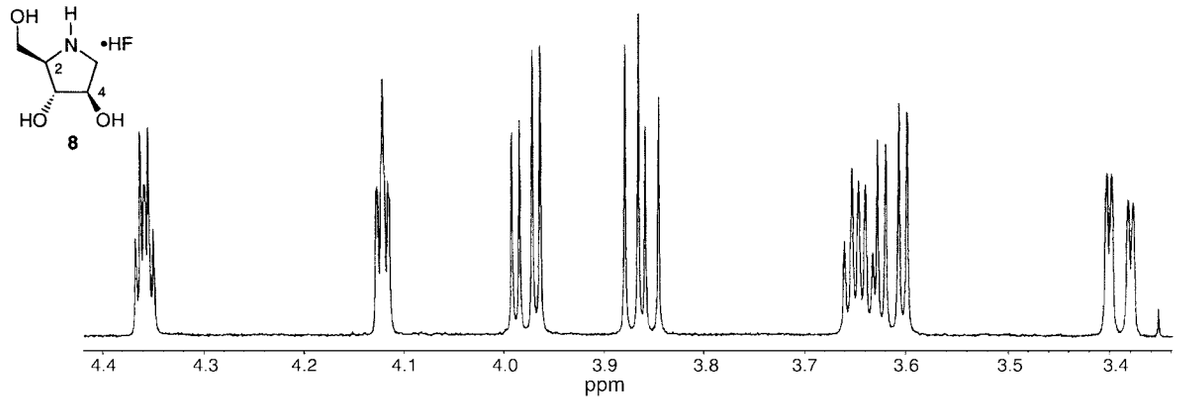
The optical purity of alcohol **7** was confirmed by chiral HPLC using a Chiracel OD column (solvent; 5% propan-2-ol in hexane). Reassuringly, when compared with traces for the racemic alcohol, this showed that there was no appreciable racemisation of alcohol **7** even on storage (−20 °C) for up to a month (material >98% ee). The most probable route for such racemisation might involve silyl group migration from the C(1) to C(3) alcohol.[11] Samples of the Swern oxidation product aldehyde **3** were subjected to the usual work-up procedure and then treated with DIBAL-H to regenerate alcohol **7** in order to check the enantiopurity. This was also confirmed by chiral HPLC to be >98% ee. Thus aldehyde **3** could be produced with high optical purity in 5 steps and an overall yield of 86% from D-serine.

With a convenient preparation of aldehyde **3** in hand we wished to demonstrate its applicability in synthesis. The polyhydroxylated pyrrolidines are exciting targets due to the range of biological activities they exhibit[12] including action as glycosidase inhibitors,[13] and as potential anti-HIV candidates.[14]

† We, as others,[8,9] have found that the use of aluminium reducing agents ($LiAlH_4$ or DIBAL-H) gave rise to deleterious silyl deprotection when the TBDMS protecting group was employed.

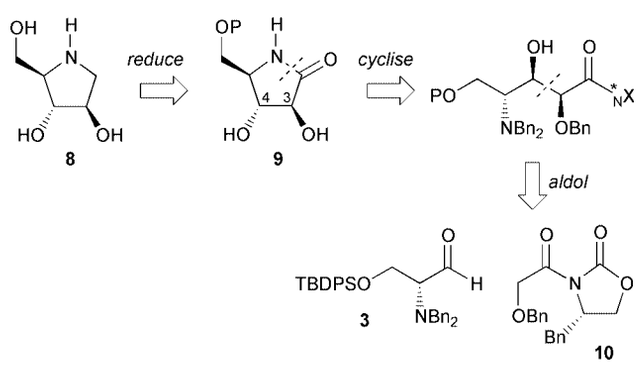
DOI: 10.1039/b002707n

Table 1 ^{1}H NMR spectral data for **8**·HCl (D_2O; 400 MHz)[16a] and **8**·HF (D_2O; 600 MHz)



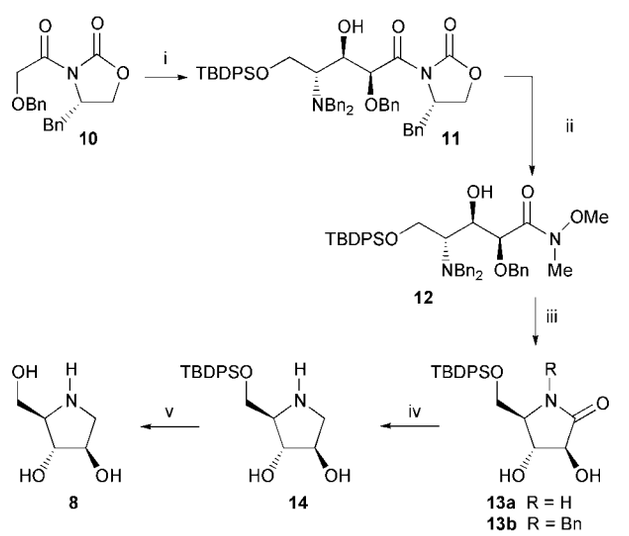
	C(5)H_2		C(4)H	C(3)H	C(2)H	C(2)CH_2OH	
8·HCl ppm (Hz)	**3.37** (12.7, 2.6)	**3.58** (12.7, 4.6)	**4.34** (4.6, 2.6)	**4.10** (4.1, 2.5)	**3.62** (8.4, 4.6, 4.1)	**3.84** (12.3, 8.4)	**3.96** (12.3, 4.6)
8·HF ppm (Hz)	**3.38** (12.6, 2.7)	**3.61** (12.6, 5.0)	**4.36** (5.0, 2.7)	**4.12** (3.7)	**3.65** (8.2, 4.2)	**3.86** (12.2, 8.2)	**3.98** (12.2, 4.6)

There have been a number of recent approaches towards their synthesis, utilising both carbohydrate and non-carbohydrate precursors.[12,15] Our approach towards the synthesis of 1,4-dideoxy-1,4-imino-D-arabinitol (DAB-1) **8** (Scheme 2),[16] identified the C(3)–C(4) bond of the intermediate pyrrolidin-2-one **9** as a key disconnection, allowing a *syn* diastereoselective glycolate aldol reaction with serine-derived aldehyde **3** to set the desired stereochemistry. It was anticipated that a diastereoselective synthesis of **9** would require 'matched' stereoselectivity of the two chiral components; the boron enolate derived from the glycolate Evans' oxazolidinone **10**[17] and the aldehyde **3**.



Scheme 2 Retrosynthetic analysis of DAB-1.

The glycolate derivative of Evans' oxazolidinone, compound **10**, was prepared using the literature procedure from benzyloxyacetyl chloride and 4-benzyloxazolidin-2-one.[18] Formation of the *Z*-boron enolate (Bu_2BOTf, Et_3N, CH_2Cl_2) and reaction with aldehyde **3** gave the desired *syn* aldol adduct **11** in excellent yield as a single diastereomer (82%, Scheme 3). This was cleanly converted to Weinreb amide **12** without protection of the secondary hydroxy group. Hydrogenation using Pearlman's catalyst [$Pd(OH)_2$, H_2] was effective in removing the benzyl protecting groups from both the hydroxy and the amino groups, and *in situ* cyclisation gave pyrrolidinone **13a** (≡**9**) in 71% yield. Interception of the hydrogenation reaction before its completion revealed that deprotection of the *N*-benzyl protecting groups was complete within the first 2–3 h of reaction. However, removal of the *O*-benzyl group was more sluggish and usually required 24–72 h to reach completion. Examination of the coupling constants displayed in the 600 MHz ^{1}H NMR spectrum of pyrrolidinone **13a** confirmed the predicted stereochemistry; C(3)–C(4) *J* 7.3 Hz from the *syn* aldol, with C(4)–C(5) *J* 7.3 Hz due to Felkin–Anh selectivity exhibited by aldehyde **3**. In an attempt to reduce the number of synthetic steps to DAB-1 **8**, the direct reduction of aldol adduct **11** to give pyrrolidinone **13a** was investigated. Although a quantitative recovery of material was achieved, it was found to be a 1 : 1 mixture of the desired pyrrolidinone **13a** and its benzyl-protected counterpart **13b**. Isolated **13b** was found to be extremely resistant to subsequent deprotection under a range of conditions. Thus conversion to the pyrrolidinone **13a** *via* the Weinreb amide **12** became the method of choice.



Scheme 3 *Reagents, conditions and yields:* i) Et_3N, *n*-Bu_2BOTf, CH_2Cl_2, −78 ⟶ 0 °C, 3 h; **3**, CH_2Cl_2, −78 ⟶ 0 °C, 2.5 h, 82%; ii) (MeO)NHMe·HCl, Me_3Al, THF, −30 °C; **11**, THF, 0 °C, 2 h, 100%; iii) $Pd(OH)_2$, H_2 (1 atm), MeOH, 72 h, 71%; iv) BH_3·THF, THF, reflux, 18 h, 100%; v) HF (48% aq.), CH_3CN, rt, 15 min; $MeOSiMe_3$; Dowex OH^-, 100%.

Reduction of the lactam by heating to reflux a THF solution of **13a** and borane[15h] gave the protected polyhydroxylated pyrrolidine **14** in quantitative yield. Finally, silyl deprotection made use of an aqueous solution of HF in acetonitrile. Excess of fluoride was removed at the end of the procedure by reaction with methoxytrimethylsilane and separation of the resultant fluorosilane by evaporation,[19] a protocol that has recently found considerable use in the synthesis of oligosaccharides. Purification was then achieved simply by trituration of the resultant solid with ethyl acetate to give the hydrofluoride salt of DAB-1 **8** as a single diastereomer in 10 steps and 49% overall yield from D-serine. The hydrofluoride salt was found to give ^{1}H NMR data in good agreement with those reported for the hydrochloride salt (Table 1), and an optical rotation of similar

magnitude: **8**·HF $[\alpha]_D$ +26.3 (*c* 0.30, H_2O), *cf.* **8**·HCl $[\alpha]_D$ +37.9 (*c* 0.53, H_2O).[20] ‡

A small quantity of the hydrofluoride salt was converted to the free base **8** (Dowex OH^-) to allow spectral comparison. Again the ^1H and ^{13}C NMR data were in good agreement with those reported in the literature.[16b] It was noted that chemical shifts in the ^1H NMR spectrum of the natural product showed significant concentration and pH dependence. Synthetic DAB-1 **8** prepared by this route was found to have a specific optical rotation of $[\alpha]_D$ +8.2 (*c* 0.25, H_2O), *cf.* $[\alpha]_D$ +7.8 (*c* 0.46, H_2O).[20]

Conclusions

The synthesis of DAB-1 **8** has served to illustrate the utility of the *tert*-butyldiphenylsilyl-protected aldehyde **3** in aldol-type reactions. The synthesis has great potential for the development of analogues of the natural product through the judicious choice of aldol coupling partners and further studies are underway in this area.

Experimental

General

All reactions involving air- or water-sensitive reagents were carried out under an atmosphere of argon using flame- or oven-dried glassware. Unless otherwise noted, starting materials and reagents were obtained from commercial suppliers and were used without further purification. THF was distilled from Na–benzophenone ketyl immediately prior to use. Toluene, CH_2Cl_2, Et_3N, and DMF were distilled from calcium hydride. Anhydrous methanol and acetonitrile were used as supplied by Aldrich. Unless otherwise indicated, organic extracts were dried over anhydrous magnesium sulfate and concentrated under reduced pressure using a rotary evaporator. Purification by flash column chromatography was carried out using Merck Kieselgel 60 silica gel as the stationary phase. Chiral HPLC was performed using a Waters instrument equipped with a UV detector and a Chiracel OD column (internal diameter 4.6 mm). All solvents for use in HPLC analysis were vacuum filtered and degassed prior to use, and a standard flow rate of 0.5 cm^3 min^{-1} was used. IR spectra were measured on a Biorad FTS-7 or Perkin-Elmer Paragon 1000 FT-IR spectrometer as thin films unless otherwise stated. ^1H and ^{13}C NMR spectra were measured on a Varian Gemini 200, Bruker AC250, Bruker AM250 or Varian Inova 600 spectrometer; *J*-values are in Hz. Mps were determined on a Gallenkamp Electrothermal Melting Point apparatus and are uncorrected. Optical rotations were measured on an AA-1000 polarimeter with a path length of 1.0 dm, at the sodium D-line, at room temperature. Elemental analysis was carried on a Perkin-Elmer 2400 CHN Elemental Analyser. Fast atom bombardment (FAB) mass spectra were obtained using a Kratos MS50TC mass spectrometer at The University of Edinburgh.

Methyl (2*R*)-2-amino-3-hydroxypropanoate hydrochloride 4

Acetyl chloride (56.1 g, 50.8 cm^3, 0.715 mol) was added dropwise to methanol (300 cm^3) at 0 °C. The mixture was stirred for *ca.* 15 min and D-serine (25.0 g, 0.238 mol) was then added portionwise to the solution. The resulting mixture was heated to reflux and held at reflux for 3 h. Concentration under reduced pressure provided hydrochloride salt **4** (36.2 g, 98%) as a solid. Recrystallisation from methanol provided an analytical sample; mp 164–166 °C (Aldrich 163–166 °C); $[\alpha]_D$ –4.0 (*c* 4.0, EtOH); δ_H (200 MHz; D_2O) 4.13 (1H, t, *J* 3.8), 3.95 (1H, dd, *J* 12.7, 4.1), 3.83 (1H, dd, *J* 12.7, 3.5), 3.70 (3H, s); δ_C (50.3 MHz; D_2O) 168.6, 58.8, 54.3, 53.3 (Found: C, 30.57; H, 6.33; N, 8.79. Calc. for $C_4H_9NO_3$·HCl: C, 30.87; H, 6.43; N, 9.00%).

‡ Specific optical rotations $[\alpha]_D$ are given in units of 10^{-1} deg cm^2 g^{-1}.

Methyl (2*R*)-2-dibenzylamino-3-hydroxypropanoate 5

To a solution of D-serine methyl ester hydrochloride **4** (15.0 g, 96.5 mmol) in acetonitrile (240 cm^3) was added potassium carbonate (66.6 g, 0.483 mol) followed by benzyl bromide (41.1 g, 28.6 cm^3, 0.240 mol). The mixture was stirred for 24 h. Water (300 cm^3) was added and the aqueous phase was extracted with EtOAc (3 × 300 cm^3). The combined organic extracts were dried, and concentrated under reduced pressure. The residue was chromatographed on silica gel [hexane–EtOAc (4:1)] to give methyl ester **5** (27.5 g, 95%) as an oil; $[\alpha]_D$ +146.5 (*c* 0.96, $CHCl_3$); ν_{max} (neat)/cm^{-1} 3455, 1731, 1601, 1585, 1494; δ_H (200 MHz; $CDCl_3$) 7.39–7.21 (10H, m), 3.92 (2H, d, *J* 13.4) 3.80 (3H, s), 3.80–3.69 (2H, m), 3.69 (2H, d, *J* 13.4), 3.59 (1H, dd, *J* 15.0, 7.5), 2.58 (1H, br s); δ_C (50.3 MHz; $CDCl_3$) 171.1, 138.6, 128.9, 128.4, 127.3, 61.6, 59.2, 54.6, 51.2; *m*/*z* (FAB) 299 (M^+, 59%), 268 (100), 240 (96), 181 (41), 92 (41); HRMS (FAB) (Found: M^+, 299.1576. $C_{18}H_{21}NO_3$ requires *m*/*z*, 299.1521).

Methyl (2*R*)-3-(*tert*-butyldiphenylsiloxy)-2-(dibenzylamino)-propanoate 6

To a solution of ester **5** (11.4 g, 37.8 mmol) and *tert*-butyldiphenylsilyl chloride (TBDPSCl) (20.8 g, 19.7 cm^3, 75.6 mmol) in DMF (60 cm^3) was added imidazole (10.5 g, 151 mmol). The mixture was stirred for 18 h. Brine (150 cm^3) was added and the aqueous phase was extracted with CH_2Cl_2 (3 × 150 cm^3). The combined organics were dried, and concentrated under reduced pressure. The residue was chromatographed on silica gel [hexane–EtOAc (15:1)] to give the benzyl-protected methyl ester **6** (20.4 g, 100%) as an oil; $[\alpha]_D$ +30.9 (*c* 2.2 $CHCl_3$); ν_{max} (neat)/cm^{-1} 1734, 1592; δ_H (200 MHz; $CDCl_3$) 7.67–7.22 (20H, m), 4.06 (1H, dd, *J* 10.2, 6.2), 4.03 (2H, d, *J* 14.3), 4.00 (1H, dd, *J* 10.2, 6.2), 3.77 (2H, d, *J* 14.3), 3.76 (3H, s), 3.70 (1H, t, *J* 6.2), 1.05 (9H, s); δ_C (62.8 MHz; $CDCl_3$) 171.8, 139.6, 135.4, 133.0, 129.5, 128.5, 128.1, 127.5, 126.8, 63.2, 62.8, 55.3, 51.0, 26.5, 19.0; *m*/*z* (FAB) 537 (M^+, 100%), 478 (40), 268 (35), 135 (25); HRMS (FAB) (Found: M^+, 537.2721. $C_{34}H_{39}NO_3Si$ requires *m*/*z*, 537.2699).

(2*S*)-3-(*tert*-Butyldiphenylsiloxy)-2-(dibenzylamino)propan-1-ol 7

To a solution of ester **6** (3.0 g, 5.6 mmol) in anhydrous toluene (20 cm^3) at −78 °C was added diisobutylaluminium hydride (DIBAL-H) [14.0 cm^3 (1.0 M in toluene), 14.0 mmol]. The mixture was stirred at −78 °C for 30 min then quenched by dropwise addition of methanol (≈10 cm^3). The resulting mixture was allowed to warm to room temperature and diluted with CH_2Cl_2 (100 cm^3). Saturated aq. sodium potassium tartrate (75 cm^3) was added and the biphasic mixture was stirred vigorously for 3 h by which time two clear phases were apparent. The organic phase was separated and the aqueous phase was extracted with CH_2Cl_2 (3 × 100 cm^3). The combined organics were dried, and concentrated under reduced pressure. The residue was chromatographed on silica gel [hexane–EtOAc (5:1)] to give alcohol **7** (2.64 g, 93%) as an oil; $[\alpha]_D$ −58.4 (*c* 1.15, $CHCl_3$); ν_{max} (neat)/cm^{-1} 3451, 1593; δ_H (200 MHz; $CDCl_3$) 7.74–7.19 (20H, m), 3.90 (1H, dd, *J* 10.7, 6.0), 3.88 (2H, d, *J* 13.4), 3.75 (1H, dd, *J* 10.7, 6.0), 3.61 (2H, d, *J* 13.4), 3.58 (2H, d, *J* 7.5), 3.10 (1H, dt, *J* 7.4, 6.0), 2.92 (1H, br s), 1.10 (9H, s); δ_C (62.8 MHz; $CDCl_3$) 139.4, 135.5, 132.9, 129.8, 129.7, 128.8, 128.3, 127.7, 61.3, 59.9, 59.4, 53.9, 26.7, 19.0; *m*/*z* (FAB) 510 ($[M + H]^+$, 91%), 480 (92), 240 (99), 197 (100), 77 (50); HRMS (FAB) (Found: $[M + H]^+$, 510.2829. $C_{33}H_{40}NO_2Si$ requires *m*/*z*, 510.2828).

***Via* reduction of aldehyde 3.** To a solution of aldehyde **3** (see below), (78.0 mg, 0.15 mmol) in toluene (1.0 cm^3) at −78 °C was added DIBAL-H [0.21 cm^3 (1.0 M in toluene), 0.21 mmol]. The

mixture was stirred at −78 °C for 5 min, then quenched by sequential addition of water (50 mm^3), aq. sodium hydroxide (50 mm^3; 1 M), and water (1 cm^3). The resulting mixture was allowed to warm to room temperature and was extracted with CH_2Cl_2 (3 × 2 cm^3). The combined extracts were dried, and concentrated under reduced pressure. The residue was chromatographed on silica gel [hexane–EtOAc (5:1)] to give alcohol **7** (70 mg, 90%) as a colourless oil, HPLC (*S* enantiomer) t_R = 5.2 min, (*R* enantiomer) t_R = 6.2 min [hexane–propan-2-ol (19:1)], >98% ee.

(2*R*)-3-(*tert*-Butyldiphenylsiloxy)-2-(dibenzylamino)propanal 3

To a solution of oxalyl chloride (0.45 g, 0.31 cm^3, 3.6 mmol) in CH_2Cl_2 (15 cm^3) at −78 °C was added dropwise a solution of DMSO (0.57 g, 0.43 cm^3, 4.5 mmol) in CH_2Cl_2 (0.5 cm^3). The mixture was stirred for *ca.* 5 min whereupon it became cloudy. A solution of alcohol **7** (1.57 g, 3.08 mmol) in CH_2Cl_2 (5.0 cm^3) at −78 °C was introduced *via* cannula. The resulting clear solution was stirred at −78 °C for 1 h. Triethylamine (1.20 g, 1.63 cm^3, 11.7 mmol) was added and the resulting cloudy solution was allowed to warm to room temperature. Water (10 cm^3) was added, producing two clear phases. The organic phase was separated and the aqueous phase was extracted with CH_2Cl_2 (3 × 10 cm^3). The combined organics were washed sequentially with 1% HCl (20 cm^3), water (20 cm^3), saturated aq. sodium bicarbonate (20 cm^3) and brine (20 cm^3), then dried, and concentrated under reduced pressure to give aldehyde **3** (1.56 g, 100%) as an oil which was used in the aldol reaction without further purification, ν_{max} (neat)/cm^{-1} 3068, 2711, 1731, 1601, 1588, 1494; δ_H (200 MHz; $CDCl_3$) 9.80 (1H, s), 7.76–7.26 (20H, m), 4.16 (1H, dd, *J* 11.0, 5.7), 4.09 (1H, dd, *J* 11.0, 5.7), 3.98 (2H, d, *J* 13.9), 3.90 (1H, d, *J* 13.9), 3.52 (1H, t, *J* 5.7); δ_C (50.3 MHz; $CDCl_3$) 202.8, 139.3, 135.6, 135.5, 132.8, 132.7, 129.8, 128.6, 128.3, 127.7, 127.1, 67.8, 60.5, 55.6, 26.7, 19.9.

(2′*S*,3′*R*,4*S*,4′*R*)-4-Benzyl-3-[2′-Benzyloxy-5′-(*tert*-butyldiphenylsiloxy)-4′-dibenzylamino-3′-hydroxypentanoyl]-oxazolidin-2-one 11

To a solution of the glycolate equivalent **10**[18] (3.42 g, 10.5 mmol) in CH_2Cl_2 (57 cm^3) at −78 °C was added triethylamine (1.39 g, 1.91 cm^3, 13.7 mmol) followed by dropwise addition of dibutylboron triflate (1.0 M in CH_2Cl_2; 12.8 cm^3, 12.8 mmol). The solution was stirred at −78 °C for 45 min, then allowed to warm to 0 °C over 30 min and stirred at 0 °C for 1.25 h. The solution was then recooled to −78 °C and a −78 °C solution of aldehyde **3** (1.47 g, 2.89 mmol) in CH_2Cl_2 (7.5 cm^3) was added dropwise *via* cannula. The reaction mixture was stirred at −78 °C for 1 h, allowed to warm to 0 °C over a period of 30 min and stirred for a further 1 h at 0 °C. The reaction was quenched by the addition of methanol (40 cm^3) followed by pH 7 phosphate buffer (25 cm^3). Hydrogen peroxide (30% aq. solution; 10 cm^3) in methanol (10 cm^3) was added dropwise to the solution and the mixture was stirred and warmed to room temperature over *ca.* 1 h. The organic phase was separated and the aqueous phase was extracted with CH_2Cl_2 (3 × 75 cm^3); the combined organic phase was dried, and concentrated under reduced pressure. The residue was chromatographed on silica gel [hexane–EtOAc (3.5:1)] to give aldol adduct **11** (1.98 g, 82%) as a solid, mp 62–63 °C; $[\alpha]_D$ +14.5 (*c* 0.87, $CHCl_3$); ν_{max} (neat)/cm^{-1} 3559, 1781, 1706; δ_H (600 MHz; $CDCl_3$) 7.74–7.13 (30H, m), 5.41 (1H, d, *J* 2.6), 4.47 (1H, dddd, *J* 10.1, 7.1, 3.2, 2.1), 4.26 (1H, d, *J* 11.0), 4.26–4.24 (1H, m), 4.11 (1H, dd, *J* 9.1, 2.1), 4.08–4.05 (3H, m), 4.06 (1H, d, *J* 11.0), 3.86 (2H, d, *J* 13.8), 3.61 (2H, d, *J* 13.8), 3.29 (1H, q, *J* 5.4), 3.22 (1H, dd, *J* 13.4, 3.2), 3.05 (1H, br d, *J* 8.1), 2.58 (1H, dd, *J* 13.4, 10.1), 1.04 (9H, s); δ_C (62.8 MHz; $CDCl_3$) 171.1, 152.9, 139.9, 137.2, 135.7, 135.6, 135.2, 133.0, 132.8, 129.6, 129.3, 129.0, 128.8, 128.3, 128.0, 127.6, 127.6, 127.2, 126.7, 78.3, 72.5, 72.1, 66.6, 61.3, 59.6, 55.8, 54.6, 37.2, 26.7, 18.9; *m*/*z* (FAB) 833 ([M + H]$^+$, 100%), 478 (15); HRMS (FAB) (Found: [M + H]$^+$, 833.3954. $C_{52}H_{57}N_2O_6Si$ requires *m*/*z*, 833.3985).

(2*S*,3*R*,4*R*)-2-Benzyloxy-5-(*tert*-butyldiphenylsiloxy)-4-dibenzylamino-3-hydroxy-*N*-methoxy-*N*-methylpentanamide 12

To a suspension of dry *N*,*O*-dimethylhydroxylamine hydrochloride (4.20 g, 43.0 mmol) in THF (7.5 cm^3) at −30 °C was added trimethylaluminium [21.5 cm^3 (2 M in toluene), 43.0 mmol]. The solution was allowed to warm to room temperature over *ca.* 15 min, after which time a clear solution remained. The solution was recooled to −30 °C and a −30 °C solution of the aldol adduct **11** (1.43 g, 1.72 mmol) in THF (5 cm^3) was added dropwise *via* cannula. The mixture was warmed to 0 °C and stirred at 0 °C for 2 h. The reaction mixture was then cannulated into a rapidly stirred biphasic mixture of CH_2Cl_2 (50 cm^3) and saturated aq. sodium potassium tartrate (50 cm^3) and stirred for 5 h whereupon two clear phases were observed. The organic phase was separated and the aqueous phase was extracted with CH_2Cl_2 (3 × 50 cm^3). The combined organics were dried, and concentrated under reduced pressure. The residue was chromatographed on silica gel [hexane–EtOAc (4:1)] to give amide **12** (1.23 g, 100%) as a solid, mp 42–43 °C; $[\alpha]_D$ −30.4 (*c* 1.1, $CHCl_3$); ν_{max} (neat)/cm^{-1} 3458, 1664, 1597; δ_H (600 MHz; $CDCl_3$) 7.74–7.16 (25H, m), 4.62 (1H, br s), 4.36 (1H, d, *J* 10.7), 4.20 (1H, td, *J* 7.8, 2.1), 4.10 (1H, dd, *J* 11.0, 4.5), 4.07 (1H, dd, *J* 11.0, 5.6), 3.93 (1H, d, *J* 10.7), 3.89 (2H, d, *J* 14.0), 3.72 (2H, d, *J* 14.0), 3.40 (3H, s), 3.20 (1H, ddd, *J* 7.8, 5.6, 4.5), 3.15 (3H, s), 2.75 (1H, br d, *J* 6.8), 1.08 (9H, s); δ_C (62.8 MHz; $CDCl_3$) 171.4, 140.0, 137.5, 135.7, 135.6, 133.3, 133.0, 129.6, 128.7, 128.1, 127.9, 127.9, 127.6, 127.5, 127.4, 126.7, 75.2, 71.4, 70.9, 60.9, 60.8, 59.3, 54.8, 32.1, 26.7, 18.9; *m*/*z* (FAB) 717 ([M + H]$^+$, 30%), 639 (11), 478 (100), 278 (37), 135 (77), 91 (92); HRMS (FAB) (Found: [M + H]$^+$, 717.3728. $C_{44}H_{53}N_2O_5Si$ requires *m*/*z*, 717.3724).

(3*S*,4*R*,5*R*)-5-(*tert*-Butyldiphenylsiloxymethyl)-3,4-dihydroxypyrrolidin-2-one 13a

A solution of the Weinreb amide **12** (1.00 g, 1.40 mmol) and Pearlman's catalyst [1.00 g; 20% $Pd(OH)_2$/C] in methanol (10 cm^3) was exposed to a hydrogen atmosphere (1 atm) and stirred vigorously for 72 h. The mixture was then filtered through a pad of Celite and concentrated under reduced pressure. The residue was chromatographed on silica gel [hexane–EtOAc (2:3)] to give pyrrolidinone **13a** (0.383 g, 71%) as a foam; $[\alpha]_D$ +11.5 (*c* 1.1, $CHCl_3$); ν_{max} (neat)/cm^{-1} 3424, 1720; δ_H (600 MHz; $CDCl_3$) 7.61–7.25 (10H, m), 6.15 (1H, br s), 4.67 (1H, br s), 4.28 (1H, d, *J* 7.7), 3.98 (1H, br t, *J* 7.3), 3.88 (1H, dd, *J* 10.7, 3.5), 3.79 (1H, br s), 3.61 (1H, dd, *J* 10.7, 7.3), 3.51 (1H, td, *J* 7.3, 3.5), 1.03 (9H, s); δ_C (50.2 MHz; $CDCl_3$) 174.2, 135.5, 132.6, 130.0, 127.9, 75.7, 64.4, 58.0, 26.6, 19.0; *m*/*z* (FAB) 386 ([M + H]$^+$, 15%), 307 (40), 154 (100), 107 (75), 77 (61); HRMS (FAB) (Found: [M + H]$^+$, 386.1776. $C_{21}H_{28}NO_4Si$ requires *m*/*z*, 386.1787).

(2*R*,3*R*,4*R*)-2-(*tert*-Butyldiphenylsiloxymethyl)-3,4-dihydroxypyrrolidine 14

To a solution of the pyrrolidinone **13a** (160 mg, 0.415 mmol) in THF (2.0 cm^3) at 0 °C was added BH_3·THF [6.23 cm^3 (1 M solution), 6.23 mmol]. After *ca.* 10 min the mixture was heated to reflux and held at reflux for 18 h. The solution was cooled to 0 °C and methanol (≈8 cm^3) was cautiously added to destroy any remaining borane. The solution was then concentrated under reduced pressure. The residue was chromatographed on silica gel [hexane–EtOAc (1:1)] to give the pyrrolidine **14** (154 mg, 100%) as a solid, mp 150 °C; $[\alpha]_D$ −8.1 (*c* 0.99, MeOH); ν_{max} (neat)/cm^{-1} 3542, 3489, 3350, 3180; δ_H (600 MHz; CD_3OD)

7.73–7.70 (4H, m), 7.45–7.39 (6H, m), 5.22 (1H, br s), 4.20 (1H, br dt, *J* 4.9, 1.6), 4.08 (1H, dd, *J* 10.6, 4.9), 4.03 (1H, dt, *J* 4.4, 1.8), 3.85 (1H, dd, *J* 10.6, 2.7), 3.17–3.12 (1H, m), 3.07–3.02 (1H, m), 2.79–2.75 (1H, m), 1.07 (9H, s); δ_C (50.3 MHz; CD_3OD) 134.9, 132.2, 129.2, 127.1, 78.5, 75.1, 73.1, 59.8, 59.0, 25.4, 18.3; *m*/*z* (FAB) 372 ($[M + H]^+$, 100%), 198 (4), 49 (6); HRMS (FAB) (Found: $[M + H]^+$, 372.1995. $C_{21}H_{30}NO_3Si$ requires *m*/*z*, 372.1995).

(2*R*,3*R*,4*R*)-3,4-Dihydroxy-2-(hydroxymethyl)pyrrolidine hydrofluoride 8·HF

To a solution of the silyl-protected pyrrolidine **14** (19 mg, 0.051 mmol) in acetonitrile (0.75 cm^3) was added hydrofluoric acid [0.141 cm^3 (48% solution in water), ~5 equiv.]. The mixture was stirred for 15 min before being concentrated under reduced pressure. The residue was treated with methoxytrimethylsilane (2.0 cm^3) and re-concentrated. This process was repeated twice. The residue obtained was triturated with EtOAc (3 × 1.0 cm^3) to give the hydrofluoride salt of DAB-1 **8**·HF (8 mg, 100%) as a tacky solid; $[\alpha]_D$ +26.3 (*c* 0.30, H_2O); δ_H (600 MHz; D_2O) 4.36 (1H, dt, *J* 5.0, 2.7), 4.12 (1H, br t, *J* 3.7), 3.98 (1H, dd, *J* 12.2, 4.6), 3.86 (1H, dd, *J* 12.2, 8.2), 3.65 (1H, dt, *J* 8.2, 4.2), 3.61 (1H, dd, *J* 12.6, 5.0), 3.38 (1H, dd, *J* 12.6, 2.7); δ_C (62.9 MHz; D_2O), 75.5, 74.2, 66.6, 58.9, 49.9; *m*/*z* (FAB) 134 ($[M + H]^+$, 30%), 116 (26), 102 (47), 91 (21); HRMS (FAB) (Found: $[M + H]^+$, 134.0817. $C_5H_{12}NO_3$ requires *m*/*z*, 134.0817).

1,4-Dideoxy-1,4-imino-D-arabinitol (DAB-1) 8

A small amount of the HF salt was subjected to ion-exchange chromatography [Dowex OH^-; prepared by treatment of Dowex 1-X2 with 1 M aq. NaOH, followed by flushing with water until the eluent returned to pH 7] eluting with water to give the free base **8** as a viscous oil in quantitative yield; $[\alpha]_D$ +8.2 (*c* 0.25, H_2O) {lit.,[20] $[\alpha]_D$ +7.8 (*c* 0.46, H_2O)}; δ_H (600 MHz; D_2O) 4.16 (1H, dt, *J* 5.8, 3.9), 3.85 (1H, dd, *J* 5.5, 3.9), 3.75 (1H, dd, *J* 11.5, 4.8), 3.67 (1H, dd, *J* 11.5, 6.4), 3.12 (1H, dd, *J* 12.2, 5.8), 2.99 (1H, br q, *J* 5.5), 2.84 (1H, dd, *J* 12.2, 3.9); δ_C (62.9 MHz; D_2O), 79.0, 77.4, 65.0, 62.0, 50.4. ^1H and ^{13}C NMR data are in good agreement with the literature.[16b,20]

Acknowledgements

We thank the EPSRC (GR/96309957 to C. H. M.), The University of Edinburgh (summer project studentship to D. K. H.) and Pfizer for support. We also thank Dr C. M. Hewage for running 600 MHz spectra.

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