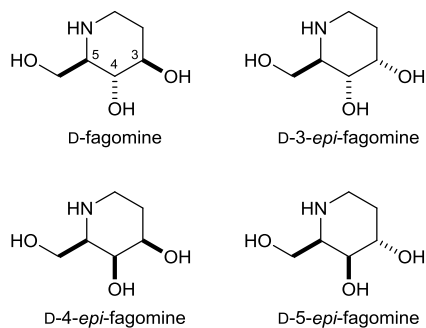


Asymmetric synthesis of D-fagomine and its diastereoisomers

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Abstract

A divergent strategy for the asymmetric syntheses of D-fagomine and three of its diastereoisomers has been developed. The diastereoselective conjugate addition of an enantiopure lithium amide to an α,β -unsaturated ester was used as the key step to install the correct configuration required for the C(5)-stereogenic centre within the targets. In situ enolate oxidation generated the corresponding *anti*- α -hydroxy- β -amino ester, which possessed the correct configuration required for the C(4)-stereogenic centre within both D-fagomine and D-3-*epi*-fagomine. Subsequent epimerisation of this key *anti*- α -hydroxy- β -amino ester upon oxidation and diastereoselective reduction gave the corresponding *syn*- α -hydroxy- β -amino ester, which possessed the correct configuration required for the C(4)-stereogenic centre within both D-4-*epi*-fagomine and D-5-*epi*-fagomine. Elaboration of both α -hydroxy- β -amino esters upon reduction to the corresponding aldehydes followed by aldol reaction generated the requisite C(3)-stereogenic centres within the target compounds, then cyclisation and deprotection gave the enantiopure iminosugars in good overall yields, as single diastereoisomers (>99:1 dr).

Key words: D-fagomine, D-3-*epi*-fagomine, D-4-*epi*-fagomine, D-5-*epi*-fagomine, asymmetric synthesis, lithium amide

Dedicated to Professor Léon Ghosez in recognition of his major achievements in chemistry.

1. Introduction

D-Fagomine (1,2,5-trideoxy-1,5-imino-D-*arabino*-hexitol) **1** is a piperidine iminosugar which was first isolated from Japanese buckwheat, *Fagopyrum esculentum*, in 1974 by Koyama and Sagamura,¹ and has more recently been isolated from a number of members of the *Morus* genus,^{2,3} *Xanthocercis zambesiaca*,⁴ and the Moreton Bay chestnut *Castanospermum australe*.⁵ Its diastereoisomers, D-3-*epi*-fagomine (1,2,5-trideoxy-1,5-imino-D-*ribo*-hexitol) **2** and L-5-*epi*-fagomine (1,2,5-trideoxy-1,5-imino-L-*xylo*-hexitol) *ent*-**4**

have also been isolated from Nature,^{3,4,6,7} and this class of hydroxylated piperidines has been commonly targeted in total syntheses.^{3,8} D-Fagomine **1**, along with other iminosugars including D-3-*epi*-fagomine **2**, have been reported to show antihyperglycemic effects in streptozotocin-induced diabetic mice.⁹ The inhibitory effects of D-fagomine **1** against α -glucosidase and β -galactosidases have been reported, although D-3-*epi*-fagomine **2** was found to be more potent against these enzymes. Additionally, L-5-*epi*-fagomine *ent*-**4** showed no significant inhibitory effects against any of the glycosidases used in the study.⁴ The synthetic analogue D-4-*epi*-fagomine **3** has been shown to inhibit some α -galactosidases although its inhibitory potency was reduced over 6000-fold when compared to its 2-hydroxylated analogue, D-1-deoxygalactonojirimycin.¹⁰ Given the important biological activity of these compounds, we sought to develop a common strategy for the asymmetric synthesis of all of the eight stereoisomers of fagomine (Fig. 1). It was envisaged that our diastereoselective aminohydroxylation methodology¹¹ could be used to install the configuration required for the C(4) and C(5) stereogenic centres within these iminosugars, and that further elaboration of the resultant α -hydroxy- β -amino esters via conversion to the corresponding aldehyde and ensuing aldol reaction would set the configuration required for the C(3) stereogenic centres within the target iminosugars, which could then be revealed upon cyclisation and deprotection. Our initial studies in this area, targeting all D-configured members of this family, are reported herein.

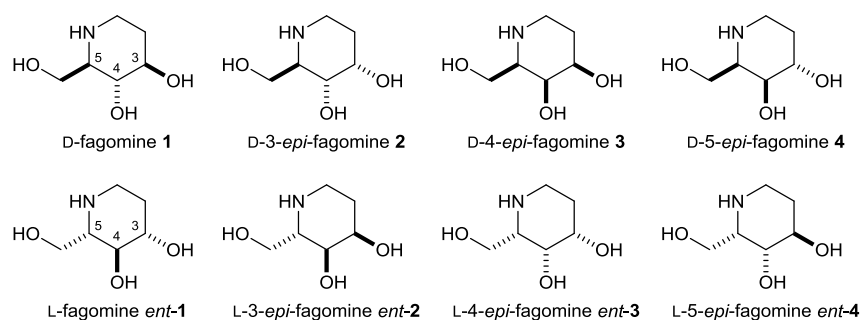
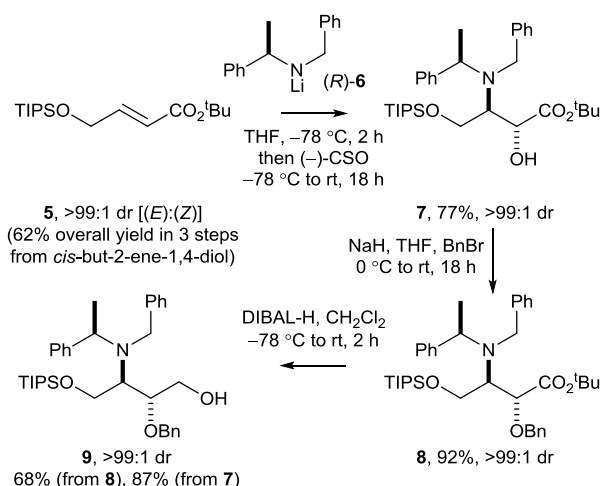


Fig. 1. The eight stereoisomers of fagomine.

2. Results and Discussion

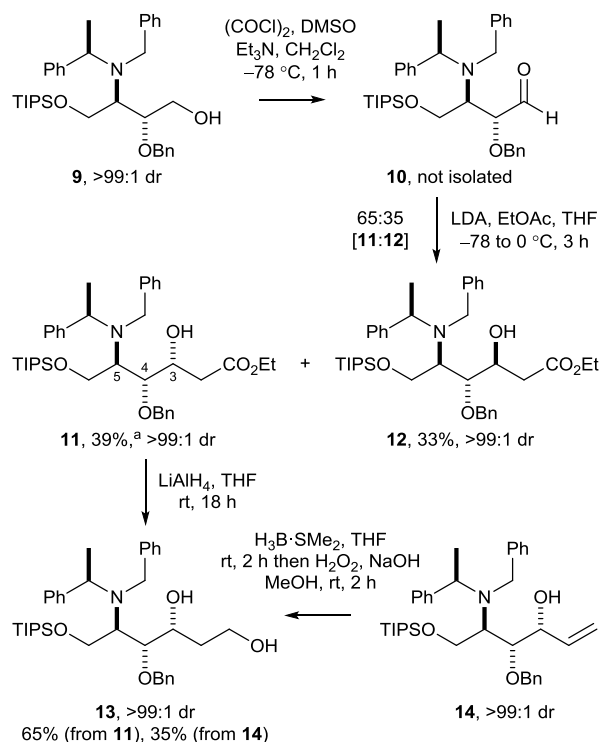
Amino alcohol **9** was prepared according to our established procedure.^{12,13} Conjugate addition of enantiopure lithium amide¹¹ (*R*)-**6** to α,β -unsaturated ester **5** (which was prepared in 62% overall yield in 3 steps from *cis*-but-2-ene-1,4-diol) followed by oxidation of the intermediate lithium (*Z*)- β -amino enolate¹⁴ with (–)-camphorsulfonyloxaziridine [(–)-CSO] gave *anti*- α -hydroxy- β -amino ester **7** in 77% yield and >99:1 dr. *O*-Benzoylation of **7** was achieved in 92% yield and subsequent reduction of the ester moiety within **8** upon treatment with DIBAL-H gave the corresponding alcohol **9** in 68% yield as a single diastereoisomer (>99:1 dr). However, a superior overall yield was obtained upon sequential *O*-benzylation of **7** and

immediate reduction of **8** (i.e., avoiding the purification of **8**), which gave **9** in 87% yield (from **7**) and >99:1 dr (Scheme 1).



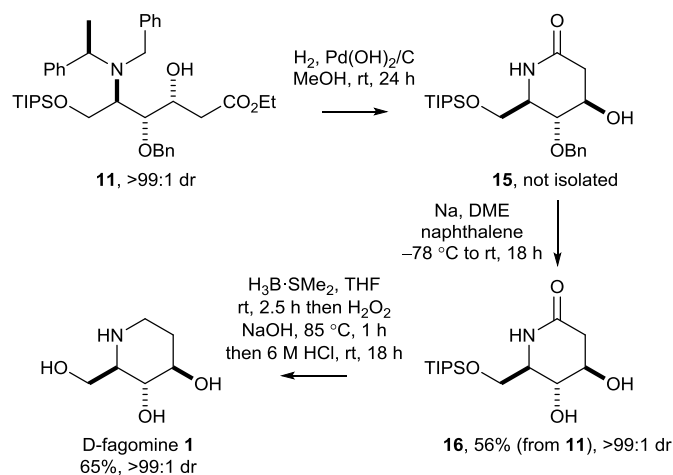
Scheme 1.

Oxidation of the primary hydroxyl functionality within **9**,¹⁵ followed by aldol reaction of the resultant aldehyde **10** with the lithium enolate derived from ethyl acetate, gave a 65:35 mixture of aldol products **11** and **12**, respectively. Purification of the crude reaction mixture via flash column chromatography gave the major diastereoisomer **11** in 39% yield and >99:1 dr; the minor diastereoisomer **12** was also isolated in 33% yield and >99:1 dr, in addition to a mixed fraction comprising a 74:26 mixture of **11** and **12**, respectively, in 12% combined yield. The configurations of **11** and **12** were established upon chemical correlation of the major diastereoisomer **11** to the known unsaturated amino alcohol **14**,¹² which was synthesised in 51% yield and >99:1 dr upon addition of vinylmagnesium bromide to aldehyde **10**.¹⁶ Hydroboration of the olefin within **14** gave diol **13** in 35% yield (unoptimised) and >99:1 dr, and reduction of the ester moiety within **11** (>99:1 dr) upon treatment with LiAlH₄ also gave **13** as a single diastereoisomer in 65% yield (Scheme 2). The spectroscopic data and specific rotations for these two samples of **13** were in complete accord, securing the configuration of **11**. The configuration of its C(3)-epimer **12** was confirmed upon chemical correlation to D-3-*epi*-fagomine **2** (vide infra).



Scheme 2. ^a 74:26 mixture [**11**:**12**] was also isolated in 12% combined yield.

Elaboration of the major diastereoisomeric product **11** to D-fagomine **1** was achieved via hydrogenolysis in the presence of Pearlman's catalyst $[\text{Pd}(\text{OH})_2/\text{C}]$, which effected complete *N*-debenzylation and cyclisation to the corresponding lactam **15**,¹⁷ although the *O*-benzyl protecting group was not removed under these conditions. Various attempts to remove this *O*-benzyl protecting group were evaluated with the most efficacious being reduction with sodium naphthalide, which gave **16** in 56% isolated yield (from **11**) as a single diastereoisomer (Scheme 3). The relative configuration of **16** was unambiguously confirmed via X-ray diffraction analysis (Fig. 2),¹⁸ and the assigned absolute (*R,R,R*)-configuration of **16** was confirmed upon refinement of a Flack *x* parameter¹⁹ of $-0.02(6)$ for the structure **16**,²⁰ which satisfies the criteria for a reliable assignment of absolute configuration of a material known to be enantiopure. Subsequent reduction of the amide functionality within **16** upon reduction with BH_3 followed by *O*-desilylation under acidic conditions gave D-fagomine **1** in 65% yield and >99:1 dr after chromatographic purification (Scheme 3). The spectroscopic data, melting point and specific rotation of this sample of **1** {mp $170\text{--}173^\circ\text{C}$; $[\alpha]_{\text{D}}^{25} +14.9$ (*c* 1.0 in H_2O)} were in good agreement with literature values {lit.⁵ mp $184\text{--}185^\circ\text{C}$; lit.¹ mp $186\text{--}188^\circ\text{C}$; lit.^{2,3} $[\alpha]_{\text{D}} +19.5$ (*c* 1.0 in H_2O); lit.⁵ $[\alpha]_{\text{D}}^{20} +24.7$ (*c* 0.4 in H_2O); lit.^{21,22} $[\alpha]_{\text{D}}^{20} +21.6$ (*c* 0.36 in H_2O); lit.²³ $[\alpha]_{\text{D}}^{20} +17.9$ (*c* 0.78 in H_2O)}, which confirmed both the identity of this sample of **1** and also the assigned configurations of the synthetic precursors **11**, **15** and **16**.



Scheme 3.

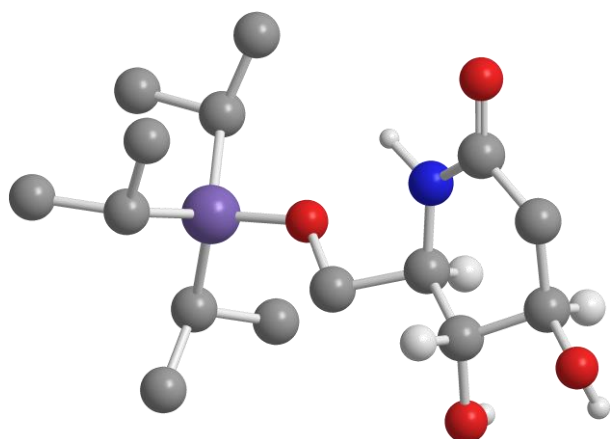
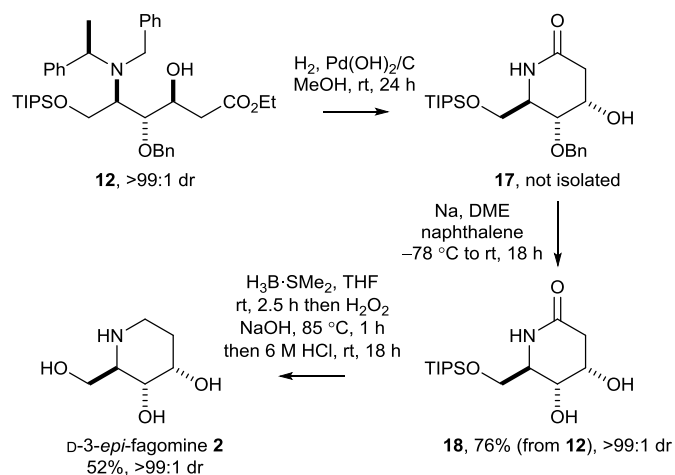


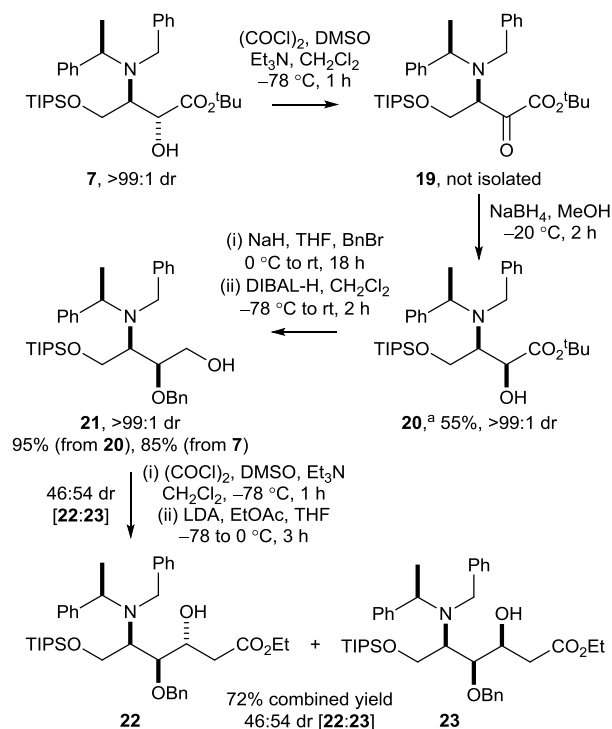
Fig. 2. X-ray crystal structure of (*R,R,R*)-**16** (selected H atoms have been omitted for clarity).

Similarly, D-3-*epi*-fagomine **2** was produced upon elaboration of the epimeric precursor **12**. Hydrogenolysis of **12** effected *N*-debenzylation and cyclisation to give lactam **17**, and treatment of **17** with sodium naphthalide gave **18** in 76% yield (from **12**) and >99:1 dr. Reduction of **18** with BH_3 and *O*-desilylation then gave D-3-*epi*-fagomine **2** in 52% yield as a single diastereoisomer (Scheme 4). The spectroscopic data, melting point and specific rotation of this sample of **2** {mp 188–191 °C; $[\alpha]_{\text{D}}^{25} +62.8$ (*c* 1.0 in H_2O)} were in good agreement with literature values {lit.^{8d} mp 220–222 °C; lit.^{3,4,6} $[\alpha]_{\text{D}}$ +69.0 (*c* 0.5 in H_2O); lit.^{8d} $[\alpha]_{\text{D}}^{26} +74.4$ (*c* 0.95 in H_2O)}, which confirmed both the identity of this sample of **2** and also the assigned configurations of the synthetic precursors **12**, **17** and **18**.



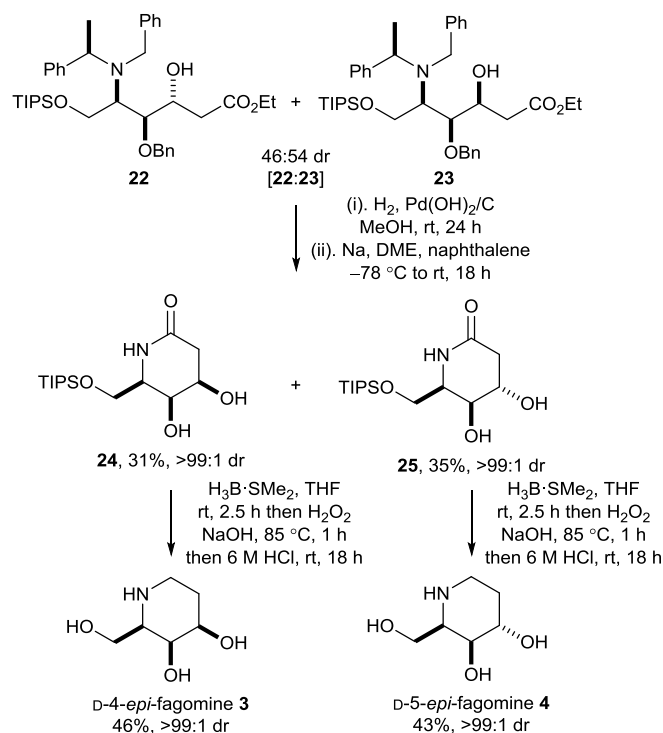
Scheme 4.

The two remaining D-configured diastereoisomers, D-4-*epi*-fagomine **3** and D-5-*epi*-fagomine **4**, were targeted next via preparation of the epimeric *syn*- α -hydroxy- β -amino ester **20** following an oxidation/diastereoselective reduction protocol²⁴ and elaboration via an analogous strategy. Swern oxidation of **7** gave the intermediate ketone **19**, and reduction of **19** with NaBH₄ in MeOH at -20°C gave a 93:7 mixture of *syn*-**20** and *anti*-**7**, respectively, from which **20** was isolated in 55% yield and >99:1 dr. *O*-Benzoylation of **20** and subsequent reduction of the ester moiety upon treatment with DIBAL-H gave **21** in 95% yield as a single diastereoisomer. However, a superior overall yield was obtained upon sequential oxidation of alcohol **7**, diastereoselective reduction of ketone **19**, *O*-benzoylation of **20**, and subsequent ester reduction (i.e., avoiding the purification of intermediate **20**), which gave **21** as a single diastereoisomer (>99:1 dr) in 85% overall yield (from **7**). Oxidation of the primary hydroxyl functionality within **21**, followed by aldol reaction of the resultant aldehyde with the lithium enolate derived from ethyl acetate, gave a 46:54 mixture of aldol products **22** and **23**, respectively. Purification of the crude reaction mixture via flash column chromatography gave an inseparable 46:54 mixture of diastereoisomers **22** and **23**, respectively, in 72% combined yield (Scheme 5).



Scheme 5. ^a 88:12 mixture [20:7] was also isolated in 32% combined yield.

Treatment of the 46:54 mixture of **22** and **23**, respectively, under hydrogenolytic conditions promoted N-debenzylation and cyclisation to an ~40:60 mixture of the epimeric lactams **24** and **25**.²⁵ Purification of this mixture via flash column chromatography gave **24** in 31% yield and >99:1 dr, and **25** in 35% yield and >99:1 dr (Scheme 6). The relative configuration of **25** was unambiguously established via X-ray diffraction analysis (Fig. 3),^{18,20} and the assigned absolute (4*S*,5*S*,6*R*)-configuration of **25** was confirmed upon refinement of a Flack *x* parameter¹⁹ of +0.10(8); this analysis therefore also secured the configuration of the epimer **24**, and the synthetic precursors **20**, **21** and **23**. In both cases, reduction of the amide functionalities within **24** and **25** was followed by *O*-desilylation under acidic conditions to give D-4-*epi*-fagomine **3** {[α]_D²⁵ +13.9 (*c* 1.0 in CHCl₃)} and D-5-*epi*-fagomine **4** {[α]_D²⁵ +8.0 (*c* 1.0 in H₂O)}, respectively, as single diastereoisomers (>99:1 dr) in 46 and 43% yield (Scheme 6). The spectroscopic data and specific rotations of these samples of **3** and **4** were in good agreement with literature values²⁶ {for D-4-*epi*-fagomine **3**: lit.^{8b} [α]_D²⁵ +11.7 (*c* 1.8 in H₂O); lit.^{8g} [α]_D²⁵ +10.4 (*c* 1.4 in H₂O); lit.^{8d} [α]_D²² +10.2 (*c* 1.42 in H₂O); lit.³ [α]_D +19.0 (*c* 0.46 in H₂O); for D-5-*epi*-fagomine **4**: lit.^{8d} [α]_D²⁵ +13.4 (*c* 0.32 in H₂O); lit.²⁷ [α]_D²⁵ +12.1 (*c* 0.33 in H₂O)}, which confirmed both the identities of these samples of **3** and **4** and also the assigned configurations of the synthetic precursors **20–25**.



Scheme 6.

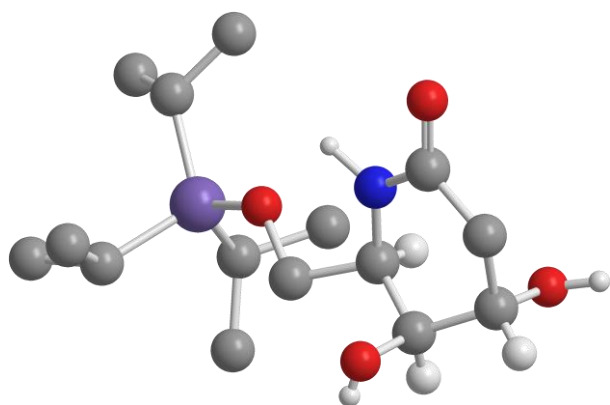


Fig. 3. X-ray crystal structure of (4S,5S,6R)-**25** (selected H atoms have been omitted for clarity).

3. Conclusion

In conclusion, a divergent strategy for the asymmetric syntheses of D-fagomine, D-3-*epi*-fagomine, D-4-*epi*-fagomine and D-5-*epi*-fagomine has been developed. The diastereoselective aminohydroxylation of an α,β -unsaturated ester upon conjugate addition of lithium (*R*)-*N*-benzyl-*N*-(α -methylbenzyl)amide followed by in situ enolate oxidation with (–)-camphorsulfonyloxaziridine gave an enantiopure *anti*- α -hydroxy- β -amino ester [with the correct configuration required for the C(4) and C(5) stereogenic centres within D-fagomine and D-3-*epi*-fagomine], and epimerisation of this substrate gave the corresponding *syn*- α -hydroxy- β -amino ester [with the correct configuration required for the C(4) and C(5) stereogenic centres within D-4-*epi*-fagomine and D-5-*epi*-fagomine]. Elaboration of both of these α -hydroxy- β -amino esters upon reduction to the corresponding aldehydes followed by aldol reaction with the lithium enolate derived

from ethyl acetate generated the C(3) stereogenic centres within the target iminosugars. Finally, cyclisation and deprotection gave the enantiopure iminosugars in good overall yields, as single diastereoisomers in each case. This strategy is also applicable to the asymmetric syntheses of the L-configured antipodes, by employing lithium (*S*)-*N*-benzyl-*N*-(α -methylbenzyl)amide and (+)-camphorsulfonyloxaziridine in the initial aminohydroxylation step. The syntheses of L-fagomine, L-3-*epi*-fagomine, L-4-*epi*-fagomine and L-5-*epi*-fagomine are ongoing within our laboratory, and the complete set of eight stereoisomers will consequently be subjected to biological evaluation.

4. Experimental Section

4.1. General experimental details

All reactions involving organometallic or other moisture-sensitive reagents were carried out under a nitrogen atmosphere using standard vacuum line techniques and glassware that was flame dried and cooled under nitrogen before use. Solvents were dried according to the procedure outlined by Grubbs and co-workers.²⁸ BuLi was purchased as a solution in hexanes and titrated against diphenylacetic acid before use. All other reagents were used as supplied without prior purification. Organic layers were dried over Na₂SO₄. Thin layer chromatography was performed on aluminium plates coated with 60 F₂₅₄ silica. Plates were visualised using UV light (254 nm), 1% aq KMnO₄ or Dragendorff's reagent. Flash column chromatography was performed on Kieselgel 60 silica. Melting points are uncorrected. Specific rotations are reported in 10⁻¹ deg cm² g⁻¹ and concentrations in g/100 mL. IR spectra were recorded using an ATR module. Selected characteristic peaks are reported in cm⁻¹. NMR spectra were recorded in the deuterated solvent stated. Spectra were recorded at rt unless otherwise stated. The field was locked by external referencing to the relevant deuteron resonance. ¹H-¹H COSY, ¹H-¹³C HMQC, and ¹H-¹³C HMBC analyses were used to establish atom connectivity. Accurate mass measurements were run on a TOF spectrometer internally calibrated with polyalanine.

4.2. *tert*-Butyl (*E*)-4-(triisopropylsilyloxy)but-2-enoate 5

Step 1: TIPSCl (61.2 mL, 286 mmol) was added to a stirred solution of *cis*-2-butene-1,4-diol (12.0 g, 136 mmol), imidazole (27.8 g, 409 mmol) and DMAP (50 mg, cat.) in CH₂Cl₂ (300 mL) at rt, and the resultant mixture was stirred at rt for 18 h then concentrated in vacuo. The residue was dissolved in Et₂O (400 mL) and the resultant solution was washed with 1.0 M aq HCl (200 mL), then dried and concentrated in vacuo.

Step 2: O₃ was bubbled through a stirred, degassed solution of the residue from the previous step in CH₂Cl₂ (500 mL) at -78 °C until a blue colouration was apparent, then the reaction mixture was purged with O₂ until

it became colourless. Me₂S (10 mL) was added dropwise and the resultant mixture was allowed to warm to rt over 18 h. The reaction mixture was concentrated in vacuo, the residue was dissolved in Et₂O (300 mL) and the resultant solution was washed with H₂O (200 mL), then dried and concentrated in vacuo.

Step 3: LiCl (69.2 g, 1.63 mol), *tert*-butyl diethylphosphonoacetate (82.2 g, 326 mmol) and ⁱPr₂NEt (52.1 mL, 299 mmol) were added to a stirred solution of the residue from the previous step in MeCN (500 mL) and the resultant mixture was stirred at rt for 72 h, then H₂O (300 mL) was added. The aqueous layer was extracted with EtOAc (3 × 300 mL) and the combined organic extracts were dried and concentrated in vacuo. Purification via flash column chromatography (eluent 30–40 °C petroleum ether/Et₂O, 50:1) gave **5** as colourless oil (52.7 g, 62%, >95:5 dr);²⁹ δ_H (400 MHz, CDCl₃) 1.04–1.10 (21H, m, Si(CHMe₂)₃), 1.50 (9H, s, CMe₃), 4.41 (2H, dd, *J* 3.4, 2.3, C(4)H₂), 6.06 (1H, dt, *J* 15.4, 2.3, C(2)H), 6.90 (1H, dt, *J* 15.4, 3.4, C(3)H).

4.3. *tert*-Butyl (*R,R,R*)-2-hydroxy-3-[*N*-benzyl-*N*-(*α*-methylbenzyl)amino]-4-(triisopropylsilyloxy)butanoate **7**

BuLi (2.2 M in hexanes, 46.1 mL, 101 mmol) was added dropwise to a stirred solution of (*R*)-*N*-benzyl-*N*-(*α*-methylbenzyl)amine (22.1 g, 105 mmol, >99:1 er) in THF (170 mL) at –78 °C and the resultant mixture was stirred at –78 °C for 30 min. A solution of **5** (20.6 g, 65.4 mmol, >95:5 dr) in THF (170 mL) was then added and the resultant mixture was stirred at –78 °C for 2 h. (–)-CSO (30.0 g, 131 mmol) was added then the resultant mixture was allowed to warm to rt over 18 h. Satd aq NH₄Cl (30 mL) was added and the reaction mixture was stirred at rt for 5 min, then concentrated in vacuo. The residue was partitioned between CH₂Cl₂ (400 mL) and 10% aq citric acid (400 mL), and the aqueous layer was extracted with CH₂Cl₂ (3 × 200 mL). The combined organic layers were washed sequentially with satd aq NaHCO₃ (300 mL) and brine (300 mL), then dried and concentrated in vacuo. The residue was dissolved in Et₂O (200 mL), filtered and the filtrate was concentrated in vacuo to give a complex mixture. Purification via flash column chromatography (eluent 30–40 °C petroleum ether/Et₂O, 30:1) gave **7** as a colourless viscous oil (27.9 g, 77%, >95:5 dr);¹³ [α]_D²⁵ –35.7 (*c* 1.0 in CHCl₃); {lit.¹³ for *ent*-**7**: [α]_D²⁰ +37.4 (*c* 1.1 in CHCl₃)}; δ_H (400 MHz, CDCl₃) 1.02–1.10 (21H, m, Si(CHMe₂)₃), 1.35 (1H, d, *J* 7.1, C(α)Me), 1.42 (9H, s, CMe₃), 3.03 (1H, d, *J* 6.6, OH), 3.49–3.54 (1H, m, C(3)H), 3.80 (1H, d, *J* 15.0, NCH_AH_BPh), 3.84–3.89 (2H, m, C(4)H₂), 3.99 (1H, dd, *J* 6.6, 1.7, C(2)H), 4.02 (1H, q, *J* 7.1, C(α)H), 4.20 (1H, d, *J* 15.0, NCH_AH_BPh), 7.21–7.47 (10H, m, *Ph*).

4.4. *tert*-Butyl (*R,R,R*)-2-benzyloxy-3-[*N*-benzyl-*N*-(α -methylbenzyl)amino]-4-(triisopropylsilyloxy)butanoate **8**

A solution of **7** (13.1 g, 24.2 mmol, >95:5 dr) in THF (290 mL) was added to a stirred solution of NaH (60% in mineral oil, 1.93 g, 48.4 mmol) in THF (290 mL) at 0 °C and the resultant mixture was stirred at 0 °C for 1 h. BnBr (5.76 mL, 48.4 mmol) was added and the resultant mixture was allowed to warm to rt over 18 h then satd aq NH₄Cl (50 mL) and Et₂O (300 mL) were added. The resultant mixture was washed with brine (300 mL) and the aqueous layers were extracted with Et₂O (3 × 200 mL) then the combined organic layers were dried and concentrated in vacuo. Purification via flash column chromatography (eluent 30–40 °C petroleum ether/Et₂O, 1:0 to 30:1) gave **8** as a colourless viscous oil (14.0 g, 92%, >95:5 dr);¹³ [α]_D²⁵ +24.1 (*c* 1.0 in CHCl₃); {lit.¹³ for *ent*-**8** [α]_D²⁵ –33.1 (*c* 0.7 in CHCl₃); δ _H (400 MHz, CDCl₃) 1.04 (21H, m, Si(CHMe₂)₃), 1.35 (3H, d, *J* 6.9, C(α)Me), 1.42 (9H, s, CMe₃), 3.48–3.53 (1H, m, C(3)H), 3.65 (1H, d, *J* 15.2, NCH_AH_BPh), 3.75 (1H, d, *J* 2.7, C(2)H), 3.83 (1H, dd, *J* 11.0, 3.7, C(4)H_A), 3.94–4.06 (2H, m, C(4)H_B, C(α)H), 4.18 (1H, d, *J* 11.2, OCH_AH_BPh), 4.26 (1H, d, *J* 15.2, NCH_AH_BPh), 4.54 (1H, d, *J* 11.2, OCH_AH_BPh), 7.17–7.31 (11H, m, *Ph*), 7.36 (2H, d, *J* 7.1, *Ph*), 7.44 (2H, d, *J* 7.3, *Ph*).

4.5. (*R,R,R*)-2-Benzyloxy-3-[*N*-benzyl-*N*-(α -methylbenzyl)amino]-4-(triisopropylsilyloxy)butan-1-ol **9**

Method A: DIBAL-H (1.0 M in CH₂Cl₂, 29.9 mL, 29.9 mmol) was added to a stirred solution of **8** (4.72 g, 7.47 mmol, >95:5 dr) in CH₂Cl₂ (125 mL) at –78 °C then stirred at rt for 2 h. Satd aq NH₄Cl (30 mL) was added and the resultant mixture was filtered through Celite[®] (eluent CH₂Cl₂) then dried and concentrated in vacuo. Purification via flash column chromatography (eluent 30–40 °C petroleum ether/EtOAc, 15:1) gave **9** as a pale yellow viscous oil (2.78 g, 68%, >95:5 dr);¹³ [α]_D²⁵ +18.1 (*c* 1.0 in CHCl₃); {lit.¹³ for *ent*-**9**: [α]_D²⁰ –9.5 (*c* 4.0 in CHCl₃)}; δ _H (400 MHz, CDCl₃) 1.05–1.18 (21H, m, Si(CHMe₂)₃), 1.43 (3H, d, *J* 6.9, C(α)Me), 3.03 (1H, br s, OH), 3.18 (1H, q, *J* 5.7, C(3)H), 3.41–3.50 (3H, m, C(1)H₂, C(2)H), 3.94–4.09 (4H, m, C(4)H_A, C(α)H, NCH₂Ph), 4.16 (1H, dd, *J* 10.2, 5.2, C(4)H_B), 4.36 (1H, d, *J* 11.5, OCH_AH_BPh), 4.55 (1H, d, *J* 11.5, OCH_AH_BPh), 7.22–7.33 (15H, m, *Ph*).

Method B – Step 1: A solution of **7** (15.0 g, 27.6 mmol, >95:5 dr) in THF (250 mL) was added to a stirred solution of NaH (60% in mineral oil, 2.21 g, 55.2 mmol) in THF (250 mL) at 0 °C and the resultant mixture was stirred at 0 °C for 1 h. BnBr (6.56 mL, 55.2 mmol) was added and the resultant mixture was allowed to warm to rt over 18 h then satd aq NH₄Cl (50 mL) and Et₂O (300 mL) were added. The resultant mixture was washed with brine (300 mL) and the aqueous layers were extracted with Et₂O (3 × 200 mL) then the combined organic layers were dried and concentrated in vacuo to give **8**.

Method B – Step 2: DIBAL-H (1.0 M in CH₂Cl₂, 110 mL, 110 mmol) was added to a stirred solution of the residue of **8** from the previous step in CH₂Cl₂ (500 mL) at –78 °C then stirred at rt for 2 h. Satd aq NH₄Cl (30 mL) and satd aq Rochelle salt (100 mL) were added at 0 °C and the resultant mixture was allowed to warm to rt over 18 h, then filtered through Celite® (eluent CH₂Cl₂), dried and concentrated in vacuo. Purification via flash column chromatography (eluent 30–40 °C petroleum ether/EtOAc, 15:1) gave **9** as a pale yellow viscous oil (13.4 g, 87% from **7**, >95:5 dr).

4.6. Ethyl (*R,R,R,R*)-3-hydroxy-4-benzyloxy-5-[*N*-benzyl-*N*-(α -methylbenzyl)amino]-6-(triisopropylsilyloxy)hexanoate **11 and ethyl (3*S*,4*R*,5*R*, α *R*)-3-hydroxy-4-benzyloxy-5-[*N*-benzyl-*N*-(α -methylbenzyl)amino]-6-(triisopropylsilyloxy)hexanoate **12****

Step 1: DMSO (0.76 mL, 10.7 mmol) was added to a stirred solution of (COCl)₂ (0.45 mL, 5.34 mmol) in CH₂Cl₂ (15 mL) at –78 °C and the resultant mixture was allowed to stir at –78 °C for 10 min then **9** (1.50 g, 2.67 mmol, >95:5 dr) in CH₂Cl₂ (15 mL) was added at –78 °C. The resultant mixture was allowed to stir at –78 °C for 1 h then Et₃N (2.23 mL, 16.0 mmol) was added and the resultant mixture was allowed to stir at –78 °C for 20 min then at rt for 20 min. The organic layer was washed with H₂O (2 × 15 mL) then the combined aqueous layers were extracted with CH₂Cl₂ (2 × 15 mL) then the combined organic layers were dried and concentrated in vacuo to give **10** as a pale yellow viscous oil; [α]_D²⁵ +30.2 (*c* 1.0 in CHCl₃); ν_{\max} (ATR) 2866 (C–H), 1728 (C=O); δ_{H} (400 MHz, CDCl₃) 1.01–1.10 (21H, m, Si(CHMe₂)₃), 1.38 (3H, d, *J* 7.0, C(α)Me), 3.46–3.52 (1H, m, C(3)H), 3.55 (1H, dd, *J* 4.2, 2.5, C(2)H), 3.77 (1H, d, *J* 14.7, NCH_AH_BPh), 3.81–3.91 (2H, m, C(4)H_A, C(α)H), 4.06 (1H, dd, *J* 9.6, 7.6, C(4)H_B), 4.12 (1H, d, *J* 14.7, NCH_AH_BPh), 4.34 (1H, d, *J* 11.3, OCH_AH_BPh), 4.48 (1H, d, *J* 11.3, OCH_AH_BPh), 7.20–7.38 (15H, m, *Ph*), 9.19 (1H, d, *J* 2.5, C(1)H); δ_{C} (100 MHz, CDCl₃) 11.9 (Si(CHMe₂)₃), 17.1 (C(α)Me), 18.0 (Si(CHMe₂)₃), 51.9 (NCH₂Ph), 57.1 (C(α)), 59.6 (C(3)), 62.0 (C(4)), 72.6 (OCH₂Ph), 83.2 (C(2)), 126.7, 127.1, 127.8, 128.1, 128.2, 128.2, 128.3, 128.3, 128.4 (*o,m,p-Ph*), 137.2, 141.2, 142.2 (*i-Ph*), 202.9 (C(1)); *m/z* (ESI⁺) 592 ([M+CH₅O]⁺, 100%); HRMS (ESI⁺) C₃₆H₅₄NO₄Si⁺ ([M+ CH₅O]⁺) requires 592.3817; found 592.3807.

Step 2: BuLi (2.2 M in hexanes, 1.70 mL, 3.74 mmol) was added to a stirred solution of ⁱPr₂NH (0.52 mL, 3.74 mmol) in THF (5 mL) at –78 °C and the resultant mixture was stirred at –78 °C for 20 min then EtOAc (0.37 mL, 3.74 mmol) was added at –78 °C and the resultant mixture was stirred at –78 °C for 30 min. A solution of the residue of **10** from the previous step in THF (10 mL) was added at –78 °C and the resultant mixture was allowed to stir at –78 °C for 1 h then at 0 °C for 2 h before satd aq NH₄Cl (2 mL) and Et₂O (10 mL) was added. The aqueous layer was extracted with Et₂O (3 × 10 mL) then the combined organic layers

were washed with brine (25 mL) then were dried and concentrated in vacuo to give a ~65:35 mixture of **11** and **12**, respectively. Purification via flash column chromatography (eluent 30–40 °C petroleum ether/EtOAc, 10:1) gave **12** as a pale yellow viscous oil (566 mg, 33% from **9**, >95:5 dr); $[\alpha]_{\text{D}}^{25} +8.8$ (*c* 1.0 in CHCl₃); ν_{max} (ATR) 3519 (broad, O–H), 1731 (C=O); δ_{H} (500 MHz, CDCl₃) 1.08–1.20 (21H, m, Si(CHMe₂)₃), 1.28 (3H, t, *J* 7.2, OCH₂CH₃), 1.48 (3H, d, *J* 6.9, C(α)Me), 1.79 (1H, dd, *J* 16.3, 3.6, C(2)*H*_A), 2.22 (1H, dd, *J* 16.3, 8.9, C(2)*H*_B), 3.04–3.08 (1H, m, C(5)*H*), 3.61 (1H, dd, *J* 7.2, 3.4, C(4)*H*), 3.99 (1H, d, *J* 14.1, NCH_AH_BPh), 4.03 (1H, d, *J* 14.1, NCH_AH_BPh), 4.06 (1H, dd, *J* 10.1, 6.6, C(6)*H*_A), 4.09–4.16 (3H, m, OCH₂CH₃, C(α)*H*), 4.18–4.23 (2H, m, C(6)*H*_B, OH), 4.28–4.33 (1H, m, C(3)*H*), 4.48 (1H, d, *J* 11.5, OCH_AH_BPh), 4.76 (1H, d, *J* 11.5, OCH_AH_BPh), 7.21–7.38 (15H, m, *Ph*); δ_{C} (125 MHz, CDCl₃) 12.0 (Si(CHMe₂)₃), 14.1 (OCH₂CH₃), 17.1 (C(α)Me), 18.1 (Si(CHMe₂)₃), 36.4 (C(2)), 51.8 (NCH₂Ph), 57.7 (C(α)), 59.0 (C(5)), 60.3 (OCH₂CH₃), 62.5 (C(6)), 69.3 (C(3)), 73.0 (OCH₂Ph), 81.3 (C(4)), 126.7, 126.8, 127.3, 127.5, 127.9, 128.1, 128.2, 128.2, 129.0 (*o,m,p-Ph*), 138.5, 140.9, 144.6 (*i-Ph*), 173.0 (C(1)); *m/z* (ESI⁺) 648 ([M+H]⁺, 100%); HRMS (ESI⁺) C₃₉H₅₈NO₅Si⁺ ([M+H]⁺) requires 648.4079; found 648.4062. Further elution gave a 74:26 mixture of **11** and **12**, respectively, as a pale yellow viscous oil (210 mg, 12% from **9**). Further elution gave **11** as a pale yellow viscous oil (675 mg, 39% from **9**, >95:5 dr); $[\alpha]_{\text{D}}^{25} +13.1$ (*c* 1.0 in CHCl₃); ν_{max} (ATR) 3505 (O–H), 1735 (C=O); δ_{H} (500 MHz, CDCl₃) 1.08–1.18 (21H, m, Si(CHMe₂)₃), 1.28 (3H, t, *J* 14.3, OCH₂CH₃), 1.50 (3H, d, *J* 6.9, C(α)Me), 1.89 (1H, dd, *J* 15.4, 9.5, C(2)*H*_A), 2.08 (1H, dd, *J* 15.4, 3.9, C(2)*H*_B), 3.36–3.43 (2H, m, C(4)*H*, C(5)*H*), 3.72 (1H, br s, OH), 4.01 (1H, d, *J* 14.3, NCH_AH_BPh), 4.09 (1H, d, *J* 14.3, NCH_AH_BPh), 4.10–4.18 (5H, m, C(6)*H*₂, C(α)*H*, OCH₂CH₃), 4.43 (1H, d, *J* 11.4, OCH_AH_BPh), 4.44–4.48 (1H, br s, C(3)*H*), 4.51 (1H, d, *J* 11.4, OCH_AH_BPh), 7.20–7.38 (15H, m, *Ph*); δ_{C} (125 MHz, CDCl₃) 12.1 (Si(CHMe₂)₃), 14.2 (OCH₂CH₃), 17.6 (C(α)Me), 18.2 (Si(CHMe₂)₃), 38.3 (C(2)), 52.2 (NCH₂Ph), 58.7 (C(5)), 59.0 (C(α)), 60.2 (OCH₂CH₃), 62.7 (C(6)), 68.4 (C(3)), 73.6 (OCH₂Ph), 78.9 (C(4)), 127.0, 127.1, 127.5, 127.6, 128.1, 128.2, 128.4, 128.4, 129.1 (*o,m,p-Ph*), 138.0, 140.7, 144.6 (*i-Ph*), 172.1 (C(1)); *m/z* (ESI⁺) 648 ([M+H]⁺, 100%); HRMS (ESI⁺) C₃₉H₅₈NO₅Si⁺ ([M+H]⁺) requires 648.4079; found 648.4070.

4.7. (R,R,R,R)-4-Benzyloxy-5-[N-benzyl-N-(α -methylbenzyl)amino]-6-(triisopropylsilyloxy)hexa-1,3-diol **13**

Method A:³⁰ BH₃·SMe₂ (2.0 M in THF, 0.26 mL, 0.527 mmol) was added to a stirred solution of **14** (100 mg, 0.170 mmol, >95:5 dr) in THF (1.6 mL) at 0 °C and the resultant mixture was stirred at rt for 2 h then cooled to 0 °C and MeOH/THF (1:1, 1.8 mL), 3 M aq NaOH (1.73 mL) and 30% aq H₂O₂ (0.58 mL, 5.10 mmol)

were added sequentially and the resultant mixture was left to stir at rt for 2 h. EtOAc (5 mL) and H₂O (5 mL) were added and the aqueous layer was extracted with EtOAc (3 × 5 mL) then the combined organic layers were dried and concentrated in vacuo. Purification via flash column chromatography (eluent 30–40 °C petroleum ether/EtOAc, 15:1 increased to 2:1) gave **13** as a colourless viscous oil (36 mg, 35%, >95:5 dr); $[\alpha]_D^{25} +19.1$ (*c* 1.0 in CHCl₃); ν_{\max} (ATR) 3407 (O–H); δ_H (500 MHz, CDCl₃) 1.08–1.15 (21H, m, Si(CHMe₂)₃), 1.19–1.28 (2H, m, C(2)H₂), 1.48 (3H, d, *J* 6.9, C(α)Me), 2.63 (1H, br s, OH), 3.31–3.35 (2H, m, C(4)H, C(5)H), 3.50–3.65 (2H, m, C(1)H₂), 3.76 (1H, br s, OH), 3.97–4.16 (6H, m, C(3)H, C(6)H₂, C(α)H, NCH₂Ph), 4.46 (1H, d, *J* 11.4, OCH_AH_BPh), 4.52 (1H, d, *J* 11.4, OCH_AH_BPh), 7.21–7.35 (15H, m, Ph); δ_C (125 MHz, CDCl₃) 12.0 (Si(CHMe₂)₃), 17.5 (C(α)Me), 18.1 (Si(CHMe₂)₃), 34.7 (C(2)), 52.1 (NCH₂Ph), 58.7 (C(α)), 58.9 (C(5)), 62.1 (C(1)), 62.7 (C(6)), 72.0 (C(3)), 73.9 (OCH₂Ph), 80.3 (C(4)), 127.0, 127.0, 127.6, 128.0, 128.3, 128.4, 129.1 (*o,m,p*-Ph), 138.1, 140.7, 144.5 (*i*-Ph); *m/z* (ESI⁺) 606 ([M+H]⁺, 100%); HRMS (ESI⁺) C₃₇H₅₆NO₄Si⁺ ([M+H]⁺) requires 606.3973; found 606.3972.

Method B: LiAlH₄ was added to a stirred solution of **11** (100 mg, 0.154 mmol, >95:5 dr) in THF at 0 °C and allowed to warm to rt over 18 h then 2.0 M aq NaOH (2 mL) was added and the resultant mixture was stirred at rt for 2 h then filtered and concentrated in vacuo. Purification via flash column chromatography (eluent 40–60 °C petroleum ether/EtOAc/35% aq NH₄OH, 66:33:1) gave **13** as a colourless viscous oil (61 mg, 65%, >95:5 dr).

4.8. (R,R,R,R)-1-(Triisopropylsilyloxy)-2-[N-benzyl-N-(α-methylbenzyl)amino]-3-benzyloxyhex-5-en-4-ol **14**

Vinylmagnesium bromide (1.0 M in THF, 0.54 mL, 0.54 mmol) was added to **10** (250 mg, 0.447 mmol, >95:5 dr) in THF (5 mL) at 0 °C and allowed to warm to rt over 18 h then cooled to 0 °C and satd aq NH₄Cl (1 mL) was added and the resultant mixture was concentrated in vacuo. The residue was partitioned between EtOAc (10 mL) and H₂O (10 mL) and the aqueous layer was extracted with EtOAc (3 × 10 mL) then the combined organic layers were washed with brine (25 mL) then dried and concentrated in vacuo to give **14** in 70:30 dr. Purification via flash column chromatography (eluent 30–40 °C petroleum ether/EtOAc, 25:1) gave **14** as a colourless viscous oil (133 mg, 51%, >95:5 dr);^{12,17} $[\alpha]_D^{25} +38.2$ (*c* 1.0 in CHCl₃); {lit.¹² $[\alpha]_D^{20} +36.5$ (*c* 1.0 in CHCl₃)}; δ_H (400 MHz, CDCl₃) 1.06–1.15 (21H, m, Si(CHMe₂)₃), 1.39 (3H, d, *J* 6.8, C(α)Me), 3.18 (1H, d, *J* 6.9, OH), 3.22 (1H, dd, *J* 7.8, 2.4, C(3)H), 3.43 (1H, app dt, *J* 7.8, 4.8, C(2)H), 3.96 (2H, app s, NCH₂Ph), 4.02 (1H, dd, *J* 10.4, 7.8, C(1)H_A), 4.06–4.18 (2H, m, C(1)H_B, C(α)H), 4.29 (1H, d, *J* 11.3, OCH_AH_BPh), 4.46 (1H, br s, C(4)H), 4.51 (1H, d, *J* 11.3, OCH_AH_BPh), 5.03 (1H, app dt, *J* 10.5, 1.8,

C(6)*H*_A), 5.23 (1H, app dt, *J* 17.2, 1.8, C(6)*H*_B), 5.58 (1H, ddd, *J* 17.2, 10.5, 4.7, C(5)*H*), 7.15–7.41 (15H, m, *Ph*).

4.9. (*R,R,R*)-4,5-Dihydroxy-6-(triisopropylsilyloxymethyl)piperidin-2-one **16**

Step 1: Pd(OH)₂/C (160 mg, 20 mol%) was added to a vigorously stirred solution of **11** (802 mg, 1.24 mmol, >95:5 dr) in degassed MeOH (10 mL). The reaction mixture was stirred under H₂ (1 atm) for 24 h then filtered through Celite (eluent MeOH) and concentrated in vacuo.

Step 2: Na (285 mg, 12.4 mmol) was added to a stirred solution of naphthalene (1.91 g, 14.9 mmol) in DME (14 mL) at rt and stirred at rt for 2 h then cooled to –78 °C. The residue from the previous step was dissolved in DME (33 mL) and added at –78 °C and the resultant mixture was allowed to warm to rt over 18 h. Satd aq NH₄Cl (5 mL) was added and the aqueous layer was extracted with Et₂O (3 × 25 mL). The combined organic layers were washed with brine (40 mL) then dried and concentrated in vacuo. Purification via flash column chromatography (eluent CHCl₃/*i*PrOH/35% aq NH₄OH, 78:12:1) to give **16** as an off-white solid (220 mg, 56% from **11**, >95:5 dr); mp 109–111 °C; [α]_D²⁵ +16.1 (*c* 1.0 in CHCl₃); ν_{\max} (ATR) 3398 (O–H, N–H), 1651 (C=O); δ_{H} (500 MHz, CDCl₃, 18.9 mM)³¹ 1.04–1.09 (21H, m, Si(CHMe₂)₃), 2.37 (1H, dd, *J* 17.4, 11.0, C(3)*H*_A), 2.68 (1H, d, *J* 3.5, OH), 2.82 (1H, dd, *J* 17.4, 5.7, C(3)*H*_B), 3.09 (1H, d, *J* 2.7, OH), 3.36 (1H, app td, *J* 8.5, 4.5, C(6)*H*), 3.47 (1H, td, *J* 9.1, 2.5, C(5)*H*), 3.67 (1H, dd, *J* 9.7, 8.2, C(1')*H*_A), 3.89–3.96 (1H, m, C(4)*H*), 4.04 (1H, dd, *J* 9.7, 4.5, C(1')*H*_B), 5.95 (1H, br s, NH); δ_{C} (125 MHz, CDCl₃, 18.9 mM)³¹ 11.8 (Si(CHMe₂)₃), 17.9 (Si(CHMe₂)₃), 37.8 (C(3)), 56.3 (C(6)), 65.6 (C(1')), 69.0 (C(4)), 72.5 (C(5)), 169.3 (C(2)); δ_{H} (500 MHz, CDCl₃, 139 mM)³¹ 1.00–1.16 (21H, m, Si(CHMe₂)₃), 2.34 (1H, dd, *J* 17.5, 10.8, C(3)*H*_A), 2.78 (1H, dd, *J* 17.5, 6.0, C(3)*H*_B), 3.31–3.36 (1H, m, C(6)*H*), 3.42 (1H, t, *J* 9.0, C(5)*H*), 3.63 (1H, dd, *J* 9.6, 8.5, C(1')*H*_A), 3.83 (1H, q, *J* 8.6, C(4)*H*), 4.06 (1H, dd, *J* 9.8, 3.9, C(1')*H*_B), 6.25 (1H, br s, NH); δ_{C} (125 MHz, CDCl₃, 139 mM)³¹ 11.7 (Si(CHMe₂)₃), 17.9 (Si(CHMe₂)₃), 37.7 (C(3)), 56.7 (C(6)), 65.2 (C(1')), 68.8 (C(4)), 71.9 (C(5)), 170.3 (C(2)); *m/z* (ESI⁺) 318 ([M+H]⁺, 100%), 340 ([M+Na]⁺, 63%); HRMS (ESI⁺) C₁₅H₃₂NO₄Si⁺ ([M+H]⁺) requires 318.2095; found 318.2096.

4.9.1. X-ray crystal structure determination for **16**

Data were collected using an Oxford Diffraction SuperNova diffractometer with graphite monochromated Cu-K α radiation using standard procedures at 250 K. The structures were solved by direct methods (SIR92); all non-hydrogen atoms were refined with anisotropic thermal parameters. Hydrogen atoms were added at idealised positions. The structures were refined using CRYSTALS.^{18,32}

X-ray crystal structure data for **16** [C₁₅H₃₁NO₄Si]: $M = 317.50$, monoclinic, space group $P 2_1$, $a = 14.0713(7)$ Å, $b = 8.2150(4)$ Å, $c = 16.8488(8)$ Å, $\beta = 107.330(5)^\circ$, $V = 1859.23(17)$ Å³, $Z = 4$, $\mu = 1.232$ mm⁻¹, colourless prism, crystal dimensions = $0.12 \times 0.13 \times 0.25$ mm³. A total of 7686 unique reflections were measured for $4 < \theta < 76$ and 7655 reflections were used in the refinement. The final parameters were $wR_2 = 0.257$ and $R_1 = 0.096$ [$I > 3.0\sigma(I)$], with Flack enantiopole = $-0.02(6)$.¹⁹

4.10. 1,2,5-Trideoxy-1,5-imino-D-arabino-hexitol [D-fagomine] **1**

BH₃·SMe₂ (2.0 M in THF, 1.10 mL, 2.20 mmol) was added to a solution of **16** (100 mg, 0.315 mmol, >95:5 dr) in THF (6 mL) at 0 °C and stirred at 0 °C for 30 min then warmed to rt over 2 h then 3 M aq NaOH (2 mL) and 30% aq H₂O₂ (2 mL) were added and the resultant mixture was heated at 85 °C for 1 h then cooled to 0 °C. 6 M HCl (5 mL) was added and the resultant mixture was allowed to warm to rt over 18 h then the volatiles were removed in vacuo and the aqueous layer subjected to ion exchange chromatography (DOWEX 50WX8-200, eluent 1.0 M aq NH₄OH). Purification via flash column chromatography (eluent CH₂Cl₂/MeOH/35% aq NH₄OH, 25:25:1) gave D-fagomine **1** as a white solid (30 mg, 65%, >95:5 dr); mp 170–173 °C; {lit.⁵ mp 184–185 °C, lit.¹ mp 186–188 °C}; $[\alpha]_D^{25} +14.9$ (c 1.0 in H₂O); {lit.^{2,3} $[\alpha]_D +19.5$ (c 1.0 in H₂O); lit.⁵ $[\alpha]_D^{20} +24.7$ (c 0.4 in H₂O); lit.^{21,22} $[\alpha]_D^{20} +21.6$ (c 0.36 in H₂O); lit.²³ $[\alpha]_D^{20} +17.9$ (c 0.78 in H₂O)}; δ_H (400 MHz, D₂O)³³ 1.40–1.52 (1H, m, C(2)*H*_A), 1.97–2.04 (1H, m, C(2)*H*_B), 2.56 (1H, ddd, J 9.7, 6.7, 3.0, C(5)*H*), 2.63 (1H, td, J 12.8, 2.6, C(1)*H*_A), 3.00–3.07 (1H, m, C(1)*H*_B), 3.19 (1H, t, J 9.7, C(4)*H*), 3.55 (1H, ddd, J 11.5, 9.0, 5.0, C(3)*H*), 3.65 (1H, dd, J 11.6, 6.7, C(6)*H*_A), 3.86 (1H, dd, J 11.6, 3.0, C(6)*H*_B); δ_C (100 MHz, D₂O)³³ 35.5 (C(2)), 45.4 (C(1)), 63.7 (C(5)), 64.5 (C(6)), 76.0 (C(4)), 76.1 (C(3)); m/z (ESI⁺) 148 ([M+H]⁺, 100%); HRMS (ESI⁺) C₆H₁₄NO₃⁺ ([M+H]⁺) requires 148.0968; found 148.0968. A sample of **1** was dissolved in CHCl₃/*i*PrOH (3:1) and 2.0 M aq NaOH, and the aqueous layer was extracted with CHCl₃/*i*PrOH (3:1), then the combined organic extracts were concentrated in vacuo to give **1** as a white solid. The ¹H and ¹³C NMR spectroscopic data for this sample were identical to those reported above.

4.11. (4*S*,5*R*,6*R*)-4,5-Dihydroxy-6-(triisopropylsilyloxymethyl)piperidin-2-one **18**

Step 1: Pd(OH)₂/C (20 mg, 20 mol%) was added to a vigorously stirred solution of **12** (100 mg, 0.154 mmol, >95:5 dr) in degassed MeOH (2 mL). The reaction mixture was stirred under H₂ (1 atm) for 24 h then filtered through Celite (eluent MeOH) and concentrated in vacuo.

Step 2: Na (35 mg, 1.5 mmol) was added to a stirred solution of naphthalene (237 mg, 1.85 mmol) in DME (2 mL) at rt and stirred at rt for 2 h then cooled to $-78\text{ }^{\circ}\text{C}$. The residue from the previous step was dissolved in DME (4 mL) and added at $-78\text{ }^{\circ}\text{C}$ and the resultant mixture was allowed to warm to rt over 18 h. Satd aq NH_4Cl (5 mL) was added and the aqueous layer was extracted with Et_2O ($3 \times 5\text{ mL}$). The combined organic layers were washed with brine (10 mL) then dried and concentrated in vacuo. Purification via flash column chromatography (eluent $\text{CHCl}_3/\text{iPrOH}/35\%\text{ aq NH}_4\text{OH}$, 86:14:1) gave **18** as a pale orange solid (37 mg, 76%, >95:5 dr); mp $50\text{--}53\text{ }^{\circ}\text{C}$; $[\alpha]_{\text{D}}^{25} +31.7$ ($c\text{ }1.0$ in CHCl_3); ν_{max} (ATR) 3399 (O–H, N–H), 1651 (C=O); δ_{H} (500 MHz, CDCl_3 , 18.9 mM)³¹ 1.05–1.11 (21H, m, $\text{Si}(\text{CHMe}_2)_3$), 2.57 (1H, dd, J 18.1, 4.1, C(3) H_{A}), 2.63 (1H, dd, J 18.1, 3.2, C(3) H_{B}), 3.02 (1H, br s, OH), 3.23 (1H, br s, OH), 3.63–3.75 (3H, m, C(5) H , C(6) H , C(1') H_{A}), 3.97 (1H, dd, J 9.6, 5.2, C(1') H_{B}), 4.18 (1H, dd, J 5.9, 3.5, C(4) H), 5.98 (1H, br s, NH); δ_{C} (125 MHz, CDCl_3 , 18.9 mM)³¹ 11.7 ($\text{Si}(\text{CHMe}_2)_3$), 17.9 ($\text{Si}(\text{CHMe}_2)_3$), 36.9 (C(3)), 54.3 (C(6)), 66.0 (C(1')), 67.4 (C(4)), 69.7 (C(5)), 169.5 (C(2)); δ_{H} (500 MHz, CDCl_3 , 139 mM)³¹ 1.03–1.09 (21H, m, $\text{Si}(\text{CHMe}_2)_3$), 2.53 (1H, dd, J 17.9, 3.9, C(3) H_{A}), 2.59 (1H, dd, J 17.9, 3.5, C(3) H_{B}), 3.58–3.72 (3H, m, C(5) H , C(6) H , C(1') H_{A}), 3.83 (1H, br s, OH), 3.97 (1H, dd, J 9.6, 4.4, C(1') H_{B}), 4.05 (1H, br s, OH), 4.11–4.16 (1H, m, C(4) H), 6.29 (1H, brs, NH); δ_{C} (125 MHz, CDCl_3 , 18.9 mM)³¹ 11.7 ($\text{Si}(\text{CHMe}_2)_3$), 17.9 ($\text{Si}(\text{CHMe}_2)_3$), 37.0 (C(3)), 54.9 (C(6)), 65.4 (C(1')), 67.1 (C(4)), 69.0 (C(5)), 170.4 (C(2)); δ_{H} (400 MHz, acetone- d_6) 1.06–1.11 (21H, m, $\text{Si}(\text{CHMe}_2)_3$), 2.35 (1H, dd, J 17.2, 4.5, C(3) H_{A}), 2.45 (1H, dd, J 17.2, 4.1, C(3) H_{B}), 3.56–3.62 (1H, m, C(6) H), 3.80 (1H, obsc dd, J 9.9, 6.0, C(1') H_{A}), 3.81–3.84 (1H, m, C(5) H), 4.00 (1H, dd, J 9.9, 4.2, C(1') H_{B}), 4.09–4.14 (1H, m, C(4) H), 4.19 (1H, d, J 5.9, OH), 4.26 (1H, d, J 3.6, OH), 6.32 (1H, br s, NH); δ_{C} (125 MHz, acetone- d_6) 12.6 ($\text{Si}(\text{CHMe}_2)_3$), 18.3 ($\text{Si}(\text{CHMe}_2)_3$), 38.1 (C(3)), 56.6 (C(6)), 65.8 (C(1')), 68.1 (C(4)), 68.8 (C(5)), 169.9 (C(2)); m/z (ESI⁺) 318 ([M+H]⁺, 100%), 340 ([M+Na]⁺, 25%); HRMS (ESI⁺) $\text{C}_{15}\text{H}_{32}\text{NO}_4\text{Si}^+$ ([M+H]⁺) requires 318.2095; found 318.2096.

4.12. 1,2,5-Trideoxy-1,5-imino-D-ribo-hexitol [D-3-*epi*-fagomine] **2**

$\text{BH}_3\cdot\text{SMe}_2$ (2.0 M in THF, 1.66 mL, 3.31 mmol) was added to a solution of **18** (150 mg, 0.472 mmol, >95:5 dr) in THF (6 mL) at $0\text{ }^{\circ}\text{C}$ and stirred at $0\text{ }^{\circ}\text{C}$ for 30 min then warmed to rt over 2 h then 3 M aq NaOH (2 mL) and 30% aq H_2O_2 (2 mL) were added and the resultant mixture was heated at $85\text{ }^{\circ}\text{C}$ for 1 h then cooled to $0\text{ }^{\circ}\text{C}$. 6 M HCl (5 mL) was added and the resultant mixture was allowed to warm to rt over 18 h then the volatiles were removed in vacuo and the aqueous layer subjected to ion exchange chromatography (DOWEX 50WX8-200, eluent 1.0 M aq NH_4OH). Purification via flash column chromatography (eluent $\text{CH}_2\text{Cl}_2/\text{MeOH}/35\%\text{ aq NH}_4\text{OH}$, 25:25:1) gave D-3-*epi*-fagomine **2** as a white solid (36 mg, 52%, >95:5 dr);

mp 188–191 °C; {lit.^{8d} mp 220–222 °C}; $[\alpha]_{\text{D}}^{25} +62.8$ (*c* 1.0 in H₂O); {lit.^{3,4,6} $[\alpha]_{\text{D}} +69.0$ (*c* 0.5 in H₂O); lit.^{8d} $[\alpha]_{\text{D}}^{26} +74.4$ (*c* 0.95 in H₂O)}; δ_{H} (400 MHz, D₂O)³³ 1.67–1.77 (1H, m, C(2)*H*_A), 1.80–1.88 (1H, m, C(2)*H*_B), 2.73–2.91 (3H, m, C(1)*H*₂, C(5)*H*), 3.47 (1H, dd, *J* 10.1, 3.0, C(4)*H*), 3.62 (1H, dd, *J* 11.5, 6.6, C(6)*H*_A), 3.82 (1H, dd, *J* 11.5, 3.2, C(6)*H*_B), 4.09 (1H, app q, *J* 3.1, C(3)*H*); δ_{C} (100 MHz, D₂O)³³ 33.8 (C(2)), 41.2 (C(1)), 58.6 (C(5)), 64.9 (C(6)), 70.7 (C(3)), 72.4 (C(4)); *m/z* (ESI⁺) 148 ([M+H]⁺, 100%); HRMS (ESI⁺) C₆H₁₄NO₃⁺ ([M+H]⁺) requires 148.0968; found 148.0968. A sample of **2** was dissolved in CHCl₃/*i*PrOH (3:1) and 2.0 M aq NaOH, and the aqueous layer was extracted with CHCl₃/*i*PrOH (3:1), then the combined organic extracts were concentrated in vacuo to give **2** as a white solid. The ¹H and ¹³C NMR spectroscopic data for this sample were identical to those reported above.

4.13. *tert*-Butyl (2*S*,3*R*, α *R*)-2-hydroxy-3-[*N*-benzyl-*N*-(α -methylbenzyl)amino]-4-(triisopropylsilyloxy)butanoate **20**

Step 1: DMSO (2.62 mL, 36.9 mmol) was added to a stirred solution of (COCl)₂ (1.56 mL, 18.5 mmol) in CH₂Cl₂ (23 mL) at –78 °C and the resultant mixture was allowed to stir at –78 °C for 10 min then **7** (5.00 g, 9.23 mmol, >95:5 dr) in CH₂Cl₂ (23 mL) was added at –78 °C. The resultant mixture was allowed to stir at –78 °C for 1 h then Et₃N (7.72 mL, 55.4 mmol) was added and the resultant mixture was allowed to stir at –78 °C for 20 min then at rt for 20 min. The organic layer was washed with H₂O (2 × 20 mL) then the combined aqueous layers were extracted with CH₂Cl₂ (2 × 20 mL) then the combined organic layers were dried and concentrated in vacuo to give **19** (>95% conversion) as a yellow viscous oil.

Step 2: NaBH₄ (349 mg, 9.23 mmol) was added to a stirred solution of the residue of **19** in MeOH (307 mL) at –20 °C and the resultant mixture was stirred at –20 °C for 2 h then concentrated in vacuo to give a 93:7 mixture of **20** and **7**, respectively. Purification via flash column chromatography (eluent 30–40 °C petroleum ether/Et₂O, 25:1) gave a 88:12 mixture of **20** and **7**, respectively, as pale yellow viscous oil (1.58 g, 32%, 88:12 dr). Further elution gave **20** as a pale yellow viscous oil (2.76 g, 55%, >95:5 dr); $[\alpha]_{\text{D}}^{25} -26.5$ (*c* 1.0 in CHCl₃); ν_{max} (ATR) 3510 (O–H), 1723 (C=O); δ_{H} (400 MHz, CDCl₃) 1.06–1.14 (21H, m, Si(CHMe₂)₃), 1.41 (9H, s, CMe₃), 1.46 (3H, d, *J* 7.0, C(α)Me), 3.29 (1H, q, *J* 6.4, C(3)*H*), 3.74 (1H, d, *J* 3.4, OH), 3.86–3.99 (4H, m, C(2)*H*, C(4)*H*₂, NCH_AH_BPh), 4.04 (1H, d, *J* 13.9, NCH_AH_BPh), 4.18 (1H, q, *J* 7.0, C(α)*H*), 7.18–7.32 (10H, m, *Ph*); δ_{C} (100 MHz, CDCl₃) 11.9 (Si(CHMe₂)₃), 17.4 (C(α)Me), 18.1 (Si(CHMe₂)₃), 27.9 (CMe₃), 51.0 (NCH₂Ph), 58.8 (C(α)), 61.5 (C(3)), 61.7 (C(4)), 70.1 (C(2)), 81.5 (CMe₃), 126.8, 126.9, 127.9, 128.2, 128.7 (*o,m,p-Ph*), 140.7, 143.7 (*i-Ph*), 172.9 (C(1)); *m/z* (ESI⁺) 542 ([M+H]⁺, 100%); HRMS (ESI⁺) C₃₂H₅₂NO₄Si⁺ ([M+H]⁺) requires 542.3660; found 542.3650.

4.14. (2*S*,3*R*,*aR*)-2-Benzoyloxy-3-[*N*-benzyl-*N*-(α -methylbenzyl)amino]-4-(triisopropylsilyloxy)butan-1-ol **21**

Method A – Step 1: A solution of **20** (2.76 g, 5.09 mmol, >95:5 dr) in THF (45 mL) was added to a stirred suspension of NaH (60% in mineral oil, 408 mg, 10.2 mmol) in THF (45 mL) at 0 °C and the resultant mixture was stirred at 0 °C for 1 h. BnBr (1.21 mL, 10.2 mmol) was added and the resultant mixture was allowed to warm to rt over 18 h then satd aq NH₄Cl (10 mL) and Et₂O (50 mL) were added. The resultant mixture was washed with brine (300 mL) and the aqueous layers were extracted with Et₂O (3 × 50 mL) then the combined organic layers were dried and concentrated in vacuo.

Method A – Step 2: DIBAL-H (1.0 M in CH₂Cl₂, 20.4 mL, 20.4 mmol) was added to a stirred solution of the residue from the previous step in CH₂Cl₂ (80 mL) at –78 °C then stirred at rt for 2 h. Satd aq NH₄Cl (10 mL) was added and the resultant mixture was filtered through Celite® (eluent CH₂Cl₂) then dried and concentrated in vacuo. Purification via flash column chromatography (eluent 30–40 °C petroleum ether/EtOAc, 12:1) gave **21** as a pale yellow viscous oil (2.73 g, 95% from **20**, >95:5 dr); [α]_D²⁵ –9.1 (*c* 1.0 in CHCl₃); ν_{max} (ATR) 3591 (O–H); δ_{H} (400 MHz, CDCl₃) 1.04–1.18 (21H, m, Si(CHMe₂)₃), 1.44 (3H, d, *J* 6.9, C(α)Me), 2.39 (1H, br s, OH), 2.95–3.01 (1H, m, C(3)H), 3.20–3.29 (1H, m, C(1)H_A), 3.56–3.63 (2H, m, C(1)H_B, C(2)H), 3.72 (1H, d, *J* 13.2, NCH_AH_BPh), 4.05 (1H, dd, *J* 9.5, 5.1, C(4)H_A), 4.09–4.16 (1H, m, C(4)H_B), 4.19 (1H, q, *J* 6.9, C(α)H), 4.35 (1H, d, *J* 13.2, NCH_AH_BPh), 4.43 (1H, d, *J* 11.7, OCH_AH_BPh), 4.61 (1H, d, *J* 11.7, OCH_AH_BPh), 7.21–7.39 (15H, m, *Ph*); δ_{C} (100 MHz, CDCl₃) 12.0 (Si(CHMe₂)₃), 13.7 (C(α)Me), 18.1 (Si(CHMe₂)₃), 52.0 (NCH₂Ph), 56.4 (C(α)), 59.3 (C(3)), 61.3 (C(4)), 61.9 (C(1)), 72.3 (OCH₂Ph), 79.6 (C(2)), 126.9, 127.2, 127.3, 128.1, 128.2, 128.3, 129.4 (*o,m,p-Ph*), 139.0, 141.0, 143.9, (*i-Ph*); *m/z* (ESI⁺) 562 ([M+H]⁺, 100%); HRMS (ESI⁺) C₃₅H₅₂NO₃Si⁺ ([M+H]⁺) requires 562.3711; found 562.3709.

Method B – Step 1: DMSO (14.1 mL, 199 mmol) was added to a stirred solution of (COCl)₂ (8.42 mL, 99.5 mmol) in CH₂Cl₂ (125 mL) at –78 °C and the resultant mixture was allowed to stir at –78 °C for 10 min then **7** (27.0 g, 49.8 mmol, >95:5 dr) in CH₂Cl₂ (125 mL) was added at –78 °C. The resultant mixture was allowed to stir at –78 °C for 1 h then Et₃N (41.7 mL, 299 mmol) was added and the resultant mixture was allowed to stir at –78 °C for 20 min then at rt for 20 min. The organic layer was washed with H₂O (2 × 150 mL) then the combined aqueous layers were extracted with CH₂Cl₂ (2 × 200 mL) then the combined organic layers were dried and concentrated in vacuo to give **19** (>95% conversion) as a yellow viscous oil.

Method B – Step 2: NaBH₄ (1.88 g, 49.8 mmol) was added to a stirred solution of the residue of **19** in MeOH (1.60 L) at –20 °C and the resultant mixture was stirred at –20 °C for 2 h then concentrated in vacuo to give **20**.

Method B – Step 3: A solution of the residue of **20** from the previous in THF (300 mL) was added to a stirred suspension of NaH (60% in mineral oil, 3.98 g, 99.6 mmol) in THF (300 mL) at 0 °C and the resultant mixture was stirred at 0 °C for 1 h. BnBr (11.9 mL, 99.6 mmol) was added and the resultant mixture was allowed to warm to rt over 18 h then satd aq NH₄Cl (20 mL) and Et₂O (100 mL) were added. The resultant mixture was washed with brine (100 mL) and the aqueous layers were extracted with Et₂O (3 × 150 mL) then the combined organic layers were dried and concentrated in vacuo.

Method B – Step 4: DIBAL-H (1.0 M in CH₂Cl₂, 200 mL, 200 mmol) was added to a stirred solution of the residue from the previous step in CH₂Cl₂ (600 mL) at –78 °C then stirred at rt for 2 h. Satd aq NH₄Cl (50 mL) was added and the resultant mixture was filtered through Celite® (eluent CH₂Cl₂) then dried and concentrated in vacuo. Purification via flash column chromatography (eluent 30–40 °C petroleum ether/EtOAc, 12:1) gave **21** as a pale yellow viscous oil (23.9 g, 85% from **7**, >95:5 dr).

4.15. Ethyl (3*R*,4*S*,5*R*, α *R*)-3-hydroxy-4-benzyloxy-5-[*N*-benzyl-*N*-(α -methylbenzyl)amino]-6-(triisoproylsilyloxy)hexanoate **22 and ethyl (3*S*,4*S*,5*R*, α *R*)-3-hydroxy-4-benzyloxy-5-[*N*-benzyl-*N*-(α -methylbenzyl)amino]-6-(triisoproylsilyloxy)hexanoate **23****

Step 1: DMSO (0.51 mL, 7.12 mmol) was added to a stirred solution of (COCl)₂ (0.30 mL, 3.56 mmol) in CH₂Cl₂ (10 mL) at –78 °C and the resultant mixture was allowed to stir at –78 °C for 10 min then **21** (1.00 g, 1.78 mmol, >95:5 dr) in CH₂Cl₂ (10 mL) was added at –78 °C. The resultant mixture was allowed to stir at –78 °C for 1 h then Et₃N (1.49 mL, 10.7 mmol) was added and the resultant mixture was allowed to stir at –78 °C for 20 min then at rt for 20 min. The organic layer was washed with H₂O (2 × 15 mL) then the combined aqueous layers were extracted with CH₂Cl₂ (2 × 15 mL) then the combined organic layers were dried and concentrated in vacuo.

Step 2: BuLi (2.2 M in hexanes, 1.13 mL, 2.49 mmol) was added to a stirred solution of ⁱPr₂NH (0.35 mL, 2.49 mmol) in THF (5 mL) at –78 °C and the resultant mixture was stirred at –78 °C for 20 min then EtOAc (0.24 mL, 2.49 mmol) was added at –78 °C and the resultant mixture was stirred at –78 °C for 30 min. A solution of the residue from the previous step in THF (5 mL) was added at –78 °C and the resultant mixture was allowed to stir at –78 °C for 1 h then at 0 °C for 2 h before satd aq NH₄Cl (2 mL) and Et₂O (10 mL) was added. The aqueous layer was extracted with Et₂O (3 × 10 mL) then the combined organic layers were

washed with brine (25 mL) then were dried and concentrated in vacuo to give a 46:54 mixture of **22** and **23**, respectively. Purification via flash column chromatography (eluent 30–40 °C petroleum ether/acetone, 10:1) gave a 46:54 mixture of **22** and **23**, respectively, as a colourless viscous oil (902 mg, 72%, 54:46 dr). Data for mixture: ν_{\max} (ATR) 3587 (O–H), 1733 (C=O); m/z (ESI⁺) 648 ([M+H]⁺, 100%); HRMS (ESI⁺) C₃₉H₅₈NO₅Si⁺ ([M+H]⁺) requires 648.4079; found 648.4076. Data for **22**: δ_{H} (400 MHz, CDCl₃) 1.07–1.16 (21H, m, Si(CHMe₂)₃), 1.20–1.26 (3H, m, OCH₂CH₃), 1.40–1.46 (3H, m, C(α)Me), 1.87 (1H, dd, *J* 15.7, 8.8, C(2)*H*_A), 2.11 (1H, dd, *J* 15.7, 4.4, C(2)*H*_B), 3.07–3.13 (1H, m, C(5)*H*), 3.55 (1H, dd, *J* 5.9, 2.5, C(4)*H*), 3.61–3.68 (1H, m, NCH_AH_BPh), 4.00–4.30 (5H, m, C(6)*H*₂, C(α)*H*, OCH₂CH₃), 4.31–4.37 (1H, m, C(3)*H*), 4.46–4.53 (1H, m, NCH_AH_BPh), 4.57 (1H, d, *J* 11.7, OCH_AH_BPh), 4.69 (1H, d, *J* 11.7, OCH_AH_BPh), 7.19–7.42 (15H, m, *Ph*); δ_{C} (100 MHz, CDCl₃) [selected data] 12.0 (Si(CHMe₂)₃), 14.2 (OCH₂Me), 18.2 (Si(CHMe₂)₃), 38.7 (C(2)), 52.0 (NCH₂Ph), 55.6 (C(α)), 57.8 (C(5)), 60.9 (C(6)), 68.2 (C(3)), 73.6 (OCH₂Ph), 81.0 (C(4)). Data for **23**: δ_{H} (400 MHz, CDCl₃) 1.07–1.16 (21H, m, Si(CHMe₂)₃), 1.20–1.26 (3H, m, OCH₂CH₃), 1.40–1.46 (3H, m, C(α)Me), 1.99 (1H, dd, *J* 15.4, 5.0, C(2)*H*_A), 2.24 (1H, dd, *J* 15.4, 8.3, C(2)*H*_B), 3.02 (1H, td, *J* 6.8, 3.4, C(5)*H*), 3.50 (1H, t, *J* 3.4, C(4)*H*), 3.74 (1H, d, *J* 13.4, NCH_AH_BPh), 3.84–3.91 (1H, m, C(3)*H*), 4.00–4.30 (5H, m, C(6)*H*₂, C(α)*H*, OCH₂CH₃), 4.41 (1H, d, *J* 13.4, NCH_AH_BPh), 4.46–4.53 (1H, m, OCH_AH_BPh), 4.63 (1H, d, *J* 11.6, OCH_AH_BPh), 7.19–7.42 (15H, m, *Ph*); δ_{C} (100 MHz, CDCl₃) [selected data] 12.0 (Si(CHMe₂)₃), 14.2 (OCH₂CH₃), 18.2 (Si(CHMe₂)₃), 38.9 (C(2)), 51.9 (NCH₂Ph), 55.6 (C(α)), 60.0 (C(5)), 60.9 (C(6)), 69.8 (C(3)), 75.2 (OCH₂Ph), 81.0 (C(4)).

4.16. (4*R*,5*S*,6*R*)-4,5-Dihydroxy-6-(triisopropylsilyloxymethyl)piperidin-2-one **24 and (4*S*,5*S*,6*R*)-4,5-dihydroxy-6-(triisopropylsilyloxymethyl)piperidin-2-one **25****

Step 1: Pd(OH)₂/C (100 mg, 20 mol%) was added to a vigorously stirred solution of a 46:54 mixture of **22** and **23**, respectively, (500 mg, 0.772 mmol, 54:46 dr) in degassed MeOH (4 mL). The reaction mixture was stirred under H₂ (5 atm) for 24 h then filtered through Celite (eluent MeOH) and concentrated in vacuo.

Step 2: Na (177 mg, 7.72 mmol) was added to a stirred solution of naphthalene (1.19 g, 9.26 mmol) in THF (10 mL) at rt and stirred at rt for 2 h, then cooled to –78 °C. The residue from the previous step was dissolved in THF (10 mL) and added at –78 °C and the resultant mixture was allowed to warm to 0 °C over 3 h. Satd aq NH₄Cl (10 mL) was added and the aqueous layer was extracted with Et₂O (3 × 20 mL). The combined organic layers were washed with brine (25 mL) then dried and concentrated in vacuo. Purification via flash column chromatography (eluent CHCl₃/*i*PrOH/35% aq NH₄OH, 89:11:1) to give **24** as colourless viscous oil (76 mg, 31%, >95:5 dr); $[\alpha]_{\text{D}}^{25}$ +27.1 (*c* 1.0 in CHCl₃); ν_{\max} (ATR) 3402 (O–H), 1646 (C=O); δ_{H}

(500 MHz, CDCl₃, 18.9 mM)³¹ 1.04–1.18 (21H, m, Si(CHMe₂)₃), 2.61 (1H, dd, *J* 17.2, 10.2, C(3)H_A), 2.67 (1H, dd, *J* 17.2, 6.6, C(3)H_B), 2.79 (1H, br s, OH), 2.98 (1H, br s, OH), 3.50–3.55 (1H, m, C(6)H), 3.91 (1H, dd, *J* 10.1, 4.4, C(1')H_A), 3.91 (1H, dd, *J* 10.1, 8.0, C(1')H_B), 4.04–4.12 (2H, m, C(4)H, C(5)H), 5.95 (1H, br s, NH); δ_C (125 MHz, CDCl₃, 18.9 mM)³¹ 11.8 (Si(CHMe₂)₃), 17.9 (Si(CHMe₂)₃), 35.5 (C(3)), 55.2 (C(6)), 63.9 (C(1')), 67.7 (C(4)), 67.7 (C(5)), 170.3 (C(2)); δ_H (500 MHz, CDCl₃, 139 mM)³¹ 1.01–1.14 (21H, m, Si(CHMe₂)₃), 2.55–2.67 (2H, m, C(3)H₂), 3.47–3.52 (1H, m, C(6)H), 3.79 (1H, br s, OH), 3.85–3.91 (2H, m, C(1')H₂), 4.00–4.07 (2H, m, C(4)H, C(5)H), 4.19 (1H, br s, OH), 5.95 (1H, br s, NH); δ_C (125 MHz, CDCl₃, 18.9 mM)³¹ 11.8 (Si(CHMe₂)₃), 17.9 (Si(CHMe₂)₃), 35.3 (C(3)), 55.7 (C(6)), 63.8 (C(1')), 67.3 (C(5)), 67.6 (C(4)), 171.2 (C(2)); *m/z* (ESI⁺) 318 ([M+H]⁺, 100%), 340 ([M+Na]⁺, 74%); HRMS (ESI⁺) C₁₅H₃₂NO₄Si⁺ ([M+H]⁺) requires 318.2095; found 318.2088. Further elution gave **25** as a pale orange solid (85 mg, 35%, >95:5 dr); mp 140–141 °C; [α]_D²⁵ +29.4 (*c* 1.0 in CHCl₃); ν_{max} (ATR) 3398 (O–H), 1644 (C=O); δ_H (500 MHz, CDCl₃, 18.9 mM)³¹ 1.04–1.11 (21H, m, Si(CHMe₂)₃), 2.39 (1H, dd, *J* 17.9, 3.4, C(3)H_A), 2.80 (1H, brs, OH), 2.86 (1H, dd, *J* 17.9, 4.6, C(3)H_B), 3.49 (1H, br s, OH), 3.78–3.82 (1H, m, C(6)H), 3.92–3.99 (2H, m, C(1')H₂), 3.99–4.03 (1H, m, C(5)H), 4.15–4.20 (1H, m, C(4)H), 5.93 (1H, br s, NH); δ_C (125 MHz, CDCl₃, 18.9 mM)³¹ 11.7 (Si(CHMe₂)₃), 17.9 (Si(CHMe₂)₃), 36.1 (C(3)), 52.9 (C(6)), 64.5 (C(1')), 67.1 (C(4)), 69.1 (C(5)), 170.8 (C(2)); δ_H (500 MHz, CDCl₃, 139 mM)³¹ 1.00–1.19 (21H, m, Si(CHMe₂)₃), 2.35 (1H, d, *J* 17.5, C(3)H_A), 2.81 (1H, d, *J* 17.5, C(3)H_B), 3.75–3.80 (1H, m, C(6)H), 3.89–3.98 (3H, m, C(5)H, C(1')H₂), 4.09–4.14 (1H, m, C(4)H), 4.17 (1H, br s, OH), 4.23 (1H, br s, OH), 6.28 (1H, br s, NH); δ_C (125 MHz, CDCl₃, 139 mM)³¹ 11.7 (Si(CHMe₂)₃), 17.9 (Si(CHMe₂)₃), 35.8 (C(3)), 53.3 (C(6)), 64.2 (C(1')), 66.9 (C(4)), 68.1 (C(5)), 171.6 (C(2)); *m/z* (ESI⁺) 318 ([M+H]⁺, 72%), 340 ([M+Na]⁺, 100%); HRMS (ESI⁺) C₁₅H₃₂NO₄Si⁺ ([M+H]⁺) requires 318.2095; found 318.2090.

4.16.1. X-ray crystal structure determination for **25**

Data were collected using an Oxford Diffraction SuperNova diffractometer with graphite monochromated Cu-Kα radiation using standard procedures at 250 K. The structures were solved by direct methods (SIR92); all non-hydrogen atoms were refined with anisotropic thermal parameters. Hydrogen atoms were added at idealised positions. The structures were refined using CRYSTALS.^{18,32}

X-ray crystal structure data for **25** [C₁₅H₃₁NO₄Si]: *M* = 317.50, orthorhombic, space group *P* 2₁ 2₁ 2, *a* = 32.2727(12) Å, *b* = 11.3243(4) Å, *c* = 10.2112(4) Å, *V* = 3731.8(2) Å³, *Z* = 8, μ = 1.228 mm⁻¹, colourless block, crystal dimensions = 0.14 × 0.16 × 0.21 mm³. A total of 6959 unique reflections were

measured for $4 < \theta < 76$ and 6933 reflections were used in the refinement. The final parameters were $wR_2 = 0.277$ and $R_1 = 0.105$ [$I > 3.0\sigma(I)$], with Flack enantiopole = +0.10(8).¹⁹

4.17. 1,2,5-Trideoxy-1,5-imino-D-lyxo-hexitol [D-4-*epi*-fagomine] **3**

BH₃·SMe₂ (2.0 M in THF, 1.14 mL, 2.27 mmol) was added to a solution of **24** (103 mg, 0.324 mmol, >95:5 dr) in THF (4 mL) at 0 °C and stirred at 0 °C for 30 min then warmed to rt over 2 h then 3 M aq NaOH (2 mL) and 30% aq H₂O₂ (2 mL) were added and the resultant mixture was heated at 85 °C for 1 h then cooled to 0 °C. 6 M aq HCl (5 mL) was added and the resultant mixture was allowed to warm to rt over 18 h then the volatiles were removed in vacuo and the aqueous layer subjected to ion exchange chromatography (DOWEX 50WX8-200, eluent 1.0 M aq NH₄OH). Purification via flash column chromatography (eluent CH₂Cl₂/MeOH/35% aq NH₄OH, 50:50:1) gave D-4-*epi*-fagomine **3** as a colourless viscous oil (22 mg, 46%, >95:5 dr); $[\alpha]_D^{25} +13.9$ (c 1.0 in CHCl₃); {lit.^{8b} $[\alpha]_D^{25} +11.7$ (c 1.8 in H₂O); lit.^{8g} $[\alpha]_D^{25} +10.4$ (c 1.5 in H₂O); lit.^{8d} $[\alpha]_D^{22} +10.2$ (c 1.42 in H₂O); lit.³ $[\alpha]_D +19$ (c 0.46 in H₂O)}; δ_H (400 MHz, D₂O)³³ 1.92–2.10 (2H, m, C(2)*H*₂), 3.08 (1H, td, J 13.2, 3.9, C(1)*H*_A), 3.34 (1H, ddd, J 8.5, 5.1, 1.2, C(5)*H*), 3.47 (1H, ddd, J 13.2, 4.6, 2.4, C(1)*H*_B), 3.79–3.94 (3H, m, C(3)*H*, C(6)*H*₂), 4.08–4.10 (1H, m, C(4)*H*); δ_C (100 MHz, D₂O)³³ 27.0 (C(2)), 45.2 (C(1)), 62.4 (C(6)), 63.0 (C(5)), 68.9 (C(4)), 70.4 (C(3)); m/z (ESI⁺) 148 ([M+H]⁺, 100%); HRMS (ESI⁺) C₆H₁₄NO₃⁺ ([M+H]⁺) requires 148.0968; found 148.0969. A sample of **3** was dissolved in CHCl₃/PrOH (3:1) and 2.0 M aq NaOH, and the aqueous layer was extracted with CHCl₃/PrOH (3:1), then the combined organic extracts were concentrated in vacuo to give **3** as a colourless viscous oil; δ_H (400 MHz, D₂O) 1.64–1.72 (2H, m, C(2)*H*₂), 2.56 (1H, td, J 12.5, 4.3, C(1)*H*_A), 2.65–2.71 (1H, m, C(5)*H*), 3.00–3.08 (1H, m, C(1)*H*_B), 3.60–3.66 (2H, m, C(6)*H*₂), 3.70–3.76 (1H, m, C(3)*H*), 3.88–3.92 (1H, m, C(4)*H*); δ_C (100 MHz, D₂O) 30.5 (C(2)), 45.7 (C(1)), 61.7 (C(5)), 64.7 (C(6)), 70.6 (C(4)), 72.9 (C(3)).

4.18. 1,2,5-Trideoxy-1,5-imino-D-xylo-hexitol [D-5-*epi*-fagomine] **4**

BH₃·SMe₂ (2.0 M in THF, 1.38 mL, 2.76 mmol) was added to a solution of **25** (125 mg, 0.394 mmol, >95:5 dr) in THF (4 mL) at 0 °C and stirred at 0 °C for 30 min then warmed to rt over 2 h then 3 M aq NaOH (2 mL) and 30% aq H₂O₂ (2 mL) were added and the resultant mixture was heated at 85 °C for 1 h then cooled to 0 °C. 6 M aq HCl (5 mL) was added and the resultant mixture was allowed to warm to rt over 18 h then the volatiles were removed in vacuo and the aqueous layer subjected to ion exchange chromatography (DOWEX 50WX8-200, eluent 1.0 M aq NH₄OH). Purification via flash column chromatography (eluent CH₂Cl₂/MeOH/35% aq NH₄OH, 25:25:1) gave D-5-*epi*-fagomine **4** as colourless viscous oil (25 mg, 43%,

>95:5 dr); $[\alpha]_{\text{D}}^{25} +8.0$ (c 1.0 in H_2O); {lit.^{8d} $[\alpha]_{\text{D}}^{25} +13.4$ (c 0.32 in H_2O); lit.²⁷ $[\alpha]_{\text{D}}^{25} +12.1$ (c 0.33 in H_2O)}; δ_{H} (400 MHz, D_2O)³³ 1.81–1.89 (1H, m, C(2) H_{A}), 2.15–2.28 (1H, m, C(2) H_{B}), 3.21–3.32 (2H, m, C(1) H_2), 3.51–3.59 (1H, m, C(5) H), 3.81 (1H, dd, J 12.2, 8.7, C(6) H_{A}), 3.87 (1H, dd, J 12.2, 5.0, C(6) H_{B}), 3.93–3.97 (1H, m, C(4) H), 4.01–4.07 (1H, m, C(3) H); δ_{C} (100 MHz, D_2O)³³ 26.5 (C(2)), 41.7 (C(1)), 58.7 (C(5)), 62.4 (C(6)), 67.7 (C(3)), 68.7 (C(4)); m/z (ESI⁺) 148 ($[\text{M}+\text{H}]^+$, 100%); HRMS (ESI⁺) $\text{C}_6\text{H}_{14}\text{NO}_3^+$ ($[\text{M}+\text{H}]^+$) requires 148.0968; found 148.0967. A sample of **4** was dissolved in $\text{CHCl}_3/i\text{PrOH}$ (3:1) and 2.0 M aq NaOH, and the aqueous layer was extracted with $\text{CHCl}_3/i\text{PrOH}$ (3:1), then the combined organic extracts were concentrated in vacuo to give **4** as a colourless viscous oil; δ_{H} (400 MHz, D_2O) 1.58 (1H, dq, J 14.1, 4.2, C(2) H_{A}), 1.91–2.01 (1H, m, C(2) H_{B}), 2.81–2.88 (2H, m, C(1) H_2), 3.10 (1H, td, J 6.7, 2.6, C(5) H), 3.62–3.69 (2H, m, C(6) H_2), 3.69–3.73 (1H, m, C(4) H), 3.90 (1H, app q, J 4.3, C(3) H); δ_{C} (100 MHz, D_2O) 30.6 (C(2)), 41.4 (C(1)), 58.1 (C(5)), 63.5 (C(1')), 70.5 (C(4)), 71.5 (C(3)).

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