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Efficient and Stereodivergent Syntheses of D- and L-Fagomines and Their Analogues

Nitee Kumari,[a] B. Gopal Reddy,[a] and Yashwant D. Vankar*[a]

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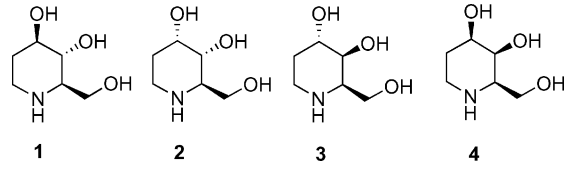
The syntheses of D- and L-fagomines **1**, **4**, **5** and **6** and their isomers from starting D-glycals have been achieved. The syntheses involve elaboration of common amino alcohol precursors obtained from 2-deoxy-1-amino sugar derivatives. The key steps in the syntheses are intramolecular reductive amination and intramolecular N-heterocyclization.

Introduction

Polyhydroxyated piperidines (azasugars) containing a nitrogen atom in place of the ring oxygen atom of a sugar moiety have been a subject of great synthetic interest because of their remarkable biological activity as glycosidase inhibitors.[1,2] Since glycosidases are involved in numerous fundamental biological processes, azasugars have been shown to be effective therapeutic agents for the treatment of a wide range of diseases, including diabetes,[3] viral infection,[4] tumour metastasis[5] and lysosomal storage disorder.[6] In addition, some azasugars have also been reported to inhibit enzymes such as glycosyltransferases,[7] glycogen phosphorylases,[8] a sugar nucleotide mutase,[9] nucleoside processing enzyme[10] and metalloproteinases.[11] These important developments in the fields of bio-organic and medicinal chemistry, with direct potential for therapeutic applications, have led to many synthetic approaches towards naturally occurring azasugars and structurally modified analogues.[1,2]

1,2-Dideoxy-azasugars represent a small but an important class of glycosidase inhibitors.[12] Fagomine (**1**, Scheme 1), a member of this family, was isolated from the seeds of Japanese buckwheat *Fagopyrum esculentum australe* Moench[13] and also from the seeds of *Castanospermum australe* (Leguminosae).[14] Recently, isomers of fagomine such as **2** and **3** have been isolated from the leaves and roots of the legume *Xanthocersis zambesiaca*.[1e,15]

Further, fagomine (**1**) has been reported to have a potent antihyperglycemic effect in streptozocin-induced diabetic mice and in potentiation of glucose-induced insulin secretion.[16] Another recent report[17] also found 4-*epi*-fagomine (**4**) to be a potent glycosidase inhibitor, particularly for mammalian α-glucosidase and ß-galactosidase, as well as for lysosomal α-galactosidase A in Fabry lymphoblasts.



Scheme 1.

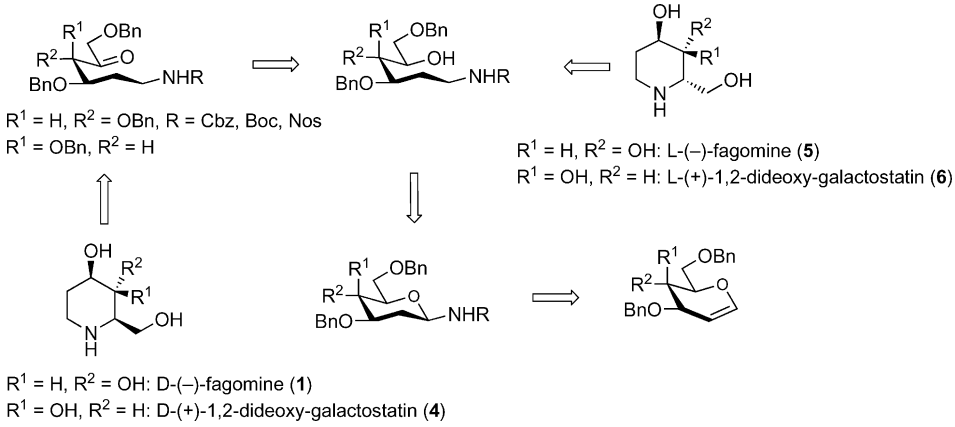
Several syntheses of D-fagomine (**1**), both from carbohydrate[18] and from non-carbohydrate precursors,[19] have been reported in the literature. However, syntheses of fagomine isomers such as **2** and **3** have been reported much more rarely.[19f] Most synthetic efforts have been directed towards the synthesis of fagomines possessing the naturally occurring D configuration; only Shipman and co-workers were able to produce the L-configured fagomine diastereomer as a by-product,[18d] whereas Passacantilli and co-workers[20] reported the synthesis of 1,2-dideoxy-L-azasugars from D-glycal derivatives.

In continuation of our efforts directed towards the synthesis of new glycosidase inhibitors from carbohydrate derivatives,[21] here we report short and efficient syntheses of D- and L-fagomines and their epimers by two methodologies newly developed in our laboratory[22,23] for the preparation of 2-deoxy-1-amino sugar derivatives from D-glycals.

Results and Discussion

The two approaches towards fagomines and their analogues are based on the introduction of amino functionalities into D-glycals, followed by ring-opening to cleave the C–O bonds, and finally cyclizations to make C–N bonds. Our retrosynthetic analysis is outlined in Scheme 2.

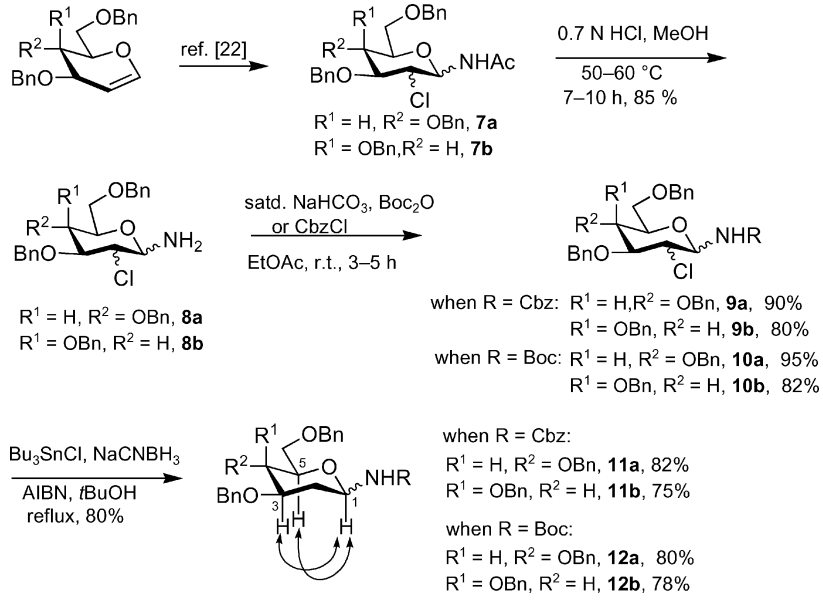
[a] Department of Chemistry, Indian Institute of Technology Kanpur,
Kanpur 208016, India
Fax: +91-512-259-7436
E-mail: vankar@iitk.ac.in



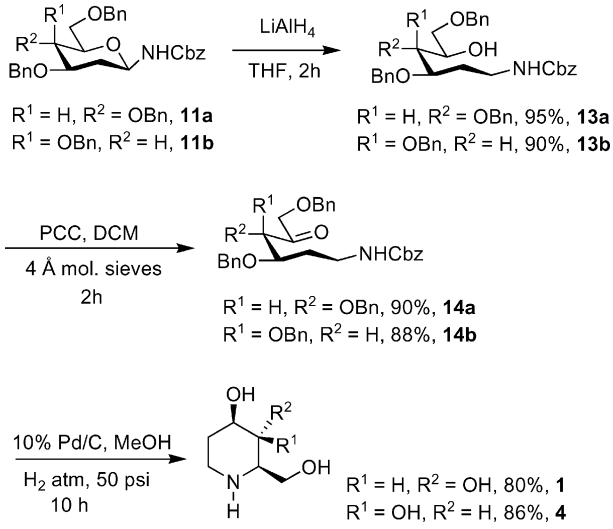
Scheme 2.

In the first approach, we introduced amino groups as described in a recent report[22] from our laboratory to make vicinal chloroacetamide sugar derivatives from D-glycals. 3,4,6-Tri-*O*-benzyl-D-glucal, on treatment with silver nitrate/oxalyl chloride in acetonitrile, thus gave a diastereomeric mixture (1:1) of the corresponding chloroactamide derivative **7a** (Scheme 3) in 80% yield, whereas in the case of 3,4,6-tri-*O*-benzyl-D-galactal the product **7b** was formed in 15:1 diastereomeric ratio, also in 80% yield. The amide functionalities in chloroacetamides **7a** and **7b** were unmasked to provide the corresponding free amines **8a** and **8b**, respectively, under mild acidic conditions as described in our reported procedure.[22] The resulting crude amines were protected as benzyl carbamates **9a** and **9b**, which after dechlorination under radical conditions[24] afforded the 2-deoxy-1-amino sugar derivatives **11a** and **11b**, respectively (Scheme 3). Interestingly, **11b** was found to exist in only one anomeric form (β-anomer), whereas **11a** was found to be a 1:1 anomeric mixture. The formation of **11a** as an anomeric mixture did not matter, because the reduction with $LiAlH_4$ in the next step led to the loss of the asymmetric centre. Thus, reduction of these 2-deoxy-1-amino sugar derivatives **11a** and **11b** with $LiAlH_4$ gave the ring-opened amino alcohols **13a** and **13b** (Scheme 4), respectively. Oxidation of the free hydroxy groups in **13a** and **13b** with pyridinium chlorochromate (PCC) in CH_2Cl_2 easily provided the desired ketones **14a** and **14b** in 90% and 88% yields, respectively. Reductive amination and debenzylation of ketones **14a** and **14b** under H_2 (50 psi) in MeOH in the presence of Pd/C (10%) afforded the desired fagomine (**1**, 80:20 diastereomeric ratio) and 4-*epi*-fagomine (**4**, 85:25 diastereomeric ratio), respectively, each in a single step.

For the synthesis of L-fagomine (**5**) and 4-*epi*-L-fagomine (**6**), the free amines in **8a** and **8b** were protected as *tert*-butyl carbamates to give **10a** and **10b** (Scheme 3), followed by radical dechlorination to form 2-deoxy-1-amino derivatives **12a** and **12b**, respectively. These amino compounds **12a** and **12b**, under ring-opening reaction conditions similar



Scheme 3.



Scheme 4.

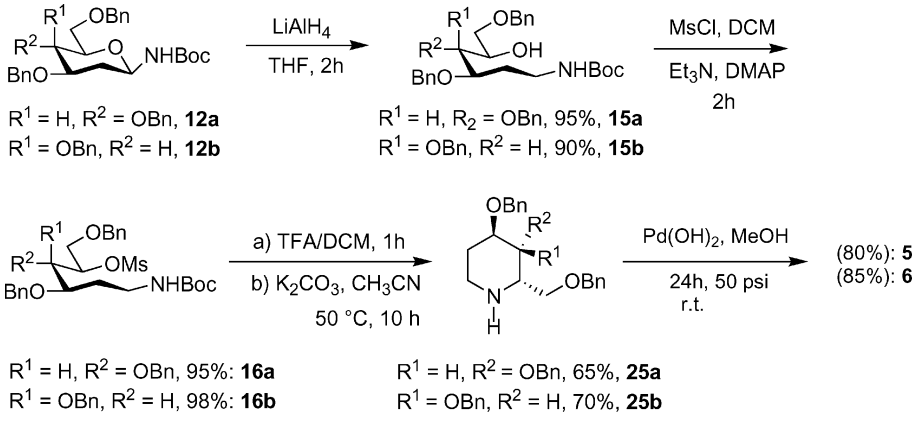
to those used in the cases of **11a** and **11b**, gave amino alcohols **15a** and **15b** (Scheme 5), respectively, upon treatment with $LiAlH_4$. The free hydroxy groups of amino alcohols **15a** and **15b** were mesylated with $MsCl/Et_3N$, followed by intramolecular N-heterocyclization. This was accomplished by the removal of their Boc groups in CF_3COOH/dichloromethane, followed by K_2CO_3-induced intramolecular S_N2 cyclization,[25] leading to the targets **25a** and **25b** (Scheme 5). The spectroscopic data for compounds **25a** and **25b** were in accordance with the literature data.[20] The removal of the benzyl ethers in **25a** and **25b** was carried out with $Pd(OH)_2$ in MeOH to afford fully deprotected L-fagomine (**5**) and 4-*epi*-L-fagomine (**6**) in 80% and 85% yields, respectively.

In our second approach directed towards the synthesis of **1** and **4**, we again followed a methodology developed in our laboratory for easy access to 2-deoxy-1-azido sugars from D-glycals,[23] using $TMSONO_2$ and $TMSN_3$ in acetonitrile for the synthesis of **17a** and **17b** (Scheme 6). Reduction of the azido sugars **17a** and **17b** with $LiAlH_4$ (2 equiv.) in ether at reflux afforded the corresponding amino alcohols **18a** and **18b**, respectively. The primary $–NH_2$ groups were protected as –NHNos moieties to give **19a** and **19b**, which was followed by benzylation with BnBr in the presence of K_2CO_3 as a base to give tertiary amines **20a** and **20b**, respectively.

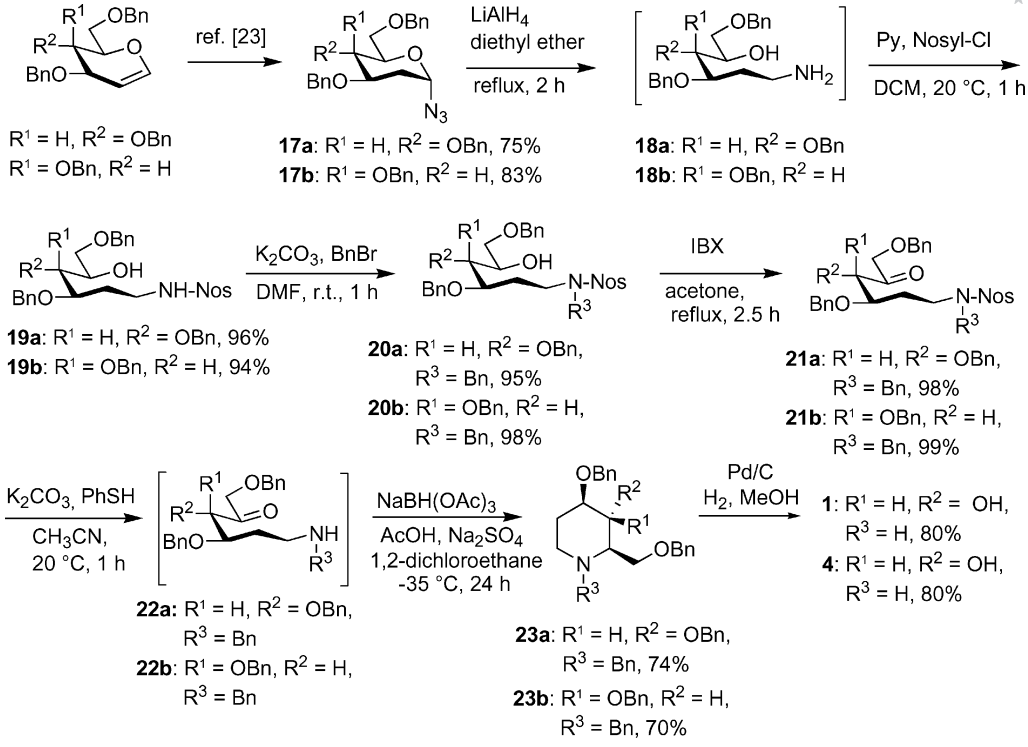
Oxidation of the free hydroxy groups in **20a** and **20b** with IBX gave the corresponding ketones **21a** and **21b** in 99% and 85% yields, respectively. Removal of the nosyl groups in **21a** and **21b** with $PhSH/K_2CO_3$ in acetonitrile[26] gave the secondary amines **22a** and **22b**, which were unstable on silica gel columns, so we proceeded further without purification. Intramolecular reductive amination of the crude amino ketones **22a** and **22b** with $NaBH(OAc)_3$ afforded the corresponding cyclized products **23a** and **23b**, respectively, as single stereoisomers. Finally, removal of the benzyl groups in **23a** and **23b** by hydrogenolysis with 20% $Pd(OH)_2/C$ in THF under H_2 pressure at room temperature afforded fagomine (**1**) and 3-*epi*-fagomine (**4**), respectively. The spectroscopic data for **1** and **4** were found to be in agreement with the reported data.[19]

We have also synthesized L-fagomine (**5**) and 4-*epi*-L-fagomine (**6**) from compounds **19a** and **19b**, respectively, via intermediates **25a** and **25b** as shown in Scheme 7. Thus, **19a** and **19b** were treated with PPh_3 and diisopropyl azadicarboxylate (DIAD) for intramolecular S_N2-type cyclization, under typical Mitsunobu conditions, to afford the cyclized products **24a** and **24b**, respectively, in good yields. Removal of the nosyl groups was carried out with $PhSH/K_2CO_3$ to give **25a** and **25b**, respectively.

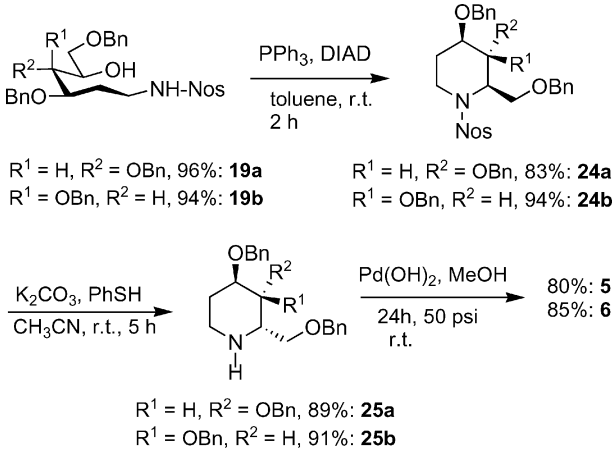
The inhibitory activities of fagomine isomers **5** and **6** were tested against a few glycosidases,[27] and the results are shown in Table 1. Compound **5** was found to show moderate inhibition of β-glucosidase, α-galactosidase and β-galactosidase, whereas it showed no inhibition of α-glucosidase and α-mannosidase. On the other hand, compound **6** showed no inhibition of α-glucosidase, β-glucosidase and α-mannosidase, but reasonable inhibition of α-galactosidase and β-galactosidase at 0.8 mM concentration.



Scheme 5.



Scheme 6.



Scheme 7.

Table 1. IC_{50} values for compounds **5** and **6**.

Enzymes	**5**	**6**
α-Glucosidase (rice)	NI[a]	NI[a]
β-Glucosidase (almonds)	5.8 mM	NI[a]
α-Galactosidase (coffee beans)	0.6 mM	0.9 mM
β-Galactosidase (bovine liver)	0.67 mM	0.77 mM
α-Mannosidase (jack beans)	NI[a]	NI[a]

[a] NI: no inhibition at <1.0 mM concentration; inhibition studies were carried out at optimal pH of the enzymes and at 37 °C.

Conclusions

In conclusion, we have developed two synthetic strategies for fagomine and its analogues involving the use of 2-deoxy-1-amino sugar derivatives obtained from D-glycals by methods developed in our laboratory for choloroamidation and hydroazidation. A concise sequence of ring-opening and cyclization reactions then allowed us to prepare both D- and L-fagomine and their analogues in few steps. The strategy based on hydroazidation of glycals is more efficient for the synthesis of D-fagomine and its derivatives, whereas the strategy based on choloroamidation of glycals is more effective for the synthesis of L-fagomine and derivatives.

Experimental Section

General: Infrared spectra were recorded on a Bruker FT/IR Vector 22 spectrophotometer. ^1H and ^{13}C NMR spectra were recorded on JEOL LA-400 and JEOL ECX-500 spectrometers in $CDCl_3$ with tetramethylsilane as the internal standard. The mass spectra were recorded on a Waters HAB213 Q Tof Premier Micromass spectrometer and a Microscopic II triple Quadrupole mass spectrometer. Rotation values were recorded on an Autopol II automatic polarimeter at the wavelength of the sodium D-line (589 nm) at 25 °C. Column chromatography was performed on silica gel (100–200 mesh), and thin-layer chromatography (TLC) was performed on silica gel plates made with grade G silica gel obtained from s.d.fine-chem Ltd., Mumbai. Melting points were determined with a Fischer–John melting point apparatus. All solvents and common reagents were purified by established procedures.

Starting Material: All starting materials **7a**, **7b**, **8a**, **8b**, **17a** and **17b** were prepared by the reported procedures.[22,23]

Benzyl (4*S*,5*R*,6*R*)-4,5-Bis(benzyloxy)-6-(benzyloxymethyl)-3-chloro-tetrahydro-2*H*-pyran-2-ylcarbamate (9a): Benzyl chloroformate (CbzCl) (0.54 g, 3.19 mmol) and saturated aq. $NaHCO_3$ solution (5 mL) were added at room temperature to a mixture of chloroamine **8a** (1 g, 2.13 mmol) and EtOAc (7 mL). The reaction mixture was stirred for 2.5–3 h until the reaction was complete (TLC monitoring). The organic layer was separated, and the aqueous layer was extracted with more EtOAc (2 × 10 mL). Conventional workup, followed by column chromatographic purification, gave a 1:1 mixture of two diastereomers; yield 90% (1.16 g), liquid, R_f = 0.50 (hexane/ethyl acetate, 8:2). ^{1}H NMR (500 MHz, $CDCl_3$, 1:1 mixture of diastereomers): δ = 7.13–7.41 (m, 20 H) 6.01–6.03 (d, J = 9.5 Hz, 1 H, NHCbz, isomer A), 5.80–5.81 (d, J = 8.5 Hz, 1 H, NHCbz, isomer B), 5.25–5.27 (d, J = 10 Hz, 1 H, 1-H, isomer A), 4.45–5.19 (m, 13 H, 6 × CH_2Ph, both isomers, 1-H, isomer B), 4.36 (br. s, 1 H, 6′-H, isomer A), 3.98–4.01 (t, J = 9 Hz, 1 H, 5-H, isomer A), 3.65–3.85 (8 H, 2-H, 3-H, 6-H, isomer B, 2-H, 3-H, 5-H, 6-H, 6′-H, isomer A), 3.55–3.61 (m, 2 H, 4-H, both isomers) ppm. ^{13}C NMR (100 MHz, $CDCl_3$, mixture of diastereomers): δ = 156.2 (N–C=O), 138.1, 137.9, 137.3, 135.9 (C^{quat}, Ph), 128.49, 128.47, 128.44, 128.40, 128.32,128.29, 128.24, 128.13, 127.95, 127.91, 127.89, 127.86, 127.80, 127.72, 127.69, 127.65,127.62, 127.5 (Ph), 85.9, 82.8, 80.7, 78.2, 76.7, 76.5, 76.1, 75.2, 74.9, 73.5, 73.2, 71.2, 68.4, 67.9, 67.3, 67.2, 61.7, 61.1 ppm. IR (CH_2Cl_2): $\tilde{\nu}_{max}$ = 1731, 3327 cm^{-1}. MS/ESI: [M + Na]$^+$ calcd. 624.2129; found 624.2131.

Benzyl (2*R*,3*R*,4*S*,5S,6*R*)-4,5-Bis(benzyloxy)-6-(benzyloxymethyl)-3-chloro-tetrahydro-2*H*-pyran-2-ylcarbamate (9b): The same experimental procedure as used to obtain compound **9a** from **8a** was followed; yield 80% (1.03 g), viscous liquid, R_f = 0.50 (hexane/ethyl acetate, 8:2), $[\alpha]_D^{25}$ = +20.8 (c = 1.88, CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.23–7.39 (m, 20 H), 5.65 (d, J = 9.8 Hz, 1 H), 5.13 (s, 2 H), 5.003 (t, J = 9.52 Hz, 1 H, 1-H), 4.84 (d, J = 11.5 Hz, 1 H), 4.66 (d, J = 11.0 Hz, 2 H), 4.61 (d, J = 11.0 Hz, 1 H), 4.34–4.43 (q, J = 11.9 Hz, 2 H), 4.11 (t, J = 9.8 Hz, 1 H, 2-H), 3.97 (br. s, 1 H, 4-H), 3.68–3.72 (m, 1 H, 6′-H), 3.51–3.54 (m, 3 H, 3-H, 5-H, 6-H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 155.5 (N–C=O), 138.13, 137.7, 137.48, 136.01 (C^{quat}, Ph), 128.43, 128.27, 128.24, 128.1, 127.95, 127.89, 127.81, 127.71, 127.56, 127.0 (Ph), 83.1, 74.9, 74.8, 73.4, 73.2, 67.8, 67.2, 65.2, 59.8 ppm. IR (CH_2Cl_2): $\tilde{\nu}_{max}$ = 1725, 3345 cm^{-1}. MS/ESI: [M + Na]$^+$ calcd. 624.2129; found 624.2130.

Benzyl (4*R*,5*S*,6*R*)-4,5-Bis(benzyloxy)-6-(benzyloxymethyl)tetrahydro-2*H*-pyran-2-ylcarbamate (11a): Tributyltin chloride (35.1 mg, 0.11 mmol), sodium cyanoborohydride (60.9 mg, 0.82 mmol) and AIBN (5 mg) were added to a solution of the chloro derivative **9a** (500 mg, 0.83 mmol) in *t*BuOH (10 mL) in a dry, round-bottomed flask. The suspension was heated at reflux for 2 h, and after completion of the reaction (TLC monitoring) the reaction mixture was concentrated in vacuo, water was added, and extraction was carried out with EtOAc (3 × 10 mL). The organic layer was then washed with NH_4OH solution (2%) followed by brine. The organic layer was dried with anhydrous sodium sulfate and concentrated in vacuo to provide crude dechlorinated product, which was purified by column chromatography; yield 82%, liquid R_f = 0.50 (hexane/ethyl acetate, 8:2). ^{1}H NMR (500 MHz, $CDCl_3$, 1:1 mixture of diastereomers): δ = 7.32–7.16 (m, 20 H), 5.50 (d, J = 9.5 Hz, 1 H, NHCbz, isomer A), 5.45 (d, J = 8.5 Hz, 1 H, NHCbz, isomer B), 5.14 (br. s, 4 H), 5.02–5.07 (br., 1 H, 1-H, isomer A), 4.58–4.65 (m, 13 H, 6 × CH_2Ph, both isomers, 1-H, isomer B), 3.84–4.17 (m, 4 H, both isomers), 3.54–3.73 (m, 6 H, both isomers), 1.95–2.00 (m, 4 H, both isomers) ppm. ^{13}C NMR (100 MHz, $CDCl_3$, mixture of diastereomers): δ = 156.0 (N–C=O), 138.1, 137.9, 137.2, 136.8 (C^{quat}, Ph), 128.49, 128.47, 128.44, 128.40, 128.32,128.29, 128.24, 128.13, 127.95, 127.91, 127.89, 127.86, 127.80, 127.72, 127.69, 127.65,127.62, 127.5 (Ph), 85.9, 82.8, 80.7, 78.2, 76.7, 76.5, 76.1, 75.2, 74.9, 73.5, 73.2, 71.2, 68.4, 67.9, 67.3, 67.2, 61.7, 61.1, 33.1 ppm. IR (CH_2Cl_2): $\tilde{\nu}_{max}$ = 1726, 3343 cm^{-1}. MS/ESI: [M + Na]$^+$ calcd. 590.2519; found 590.2513.

Benzyl (2*R*,4*R*,5*R*,6*R*)-4,5-Bis(benzyloxy)-6-(benzyloxymethyl)-tetrahydro-2*H*-pyran-2-ylcarbamate (11b): The same experimental procedure as used for converting compound **9a** to give compound **11a** was followed; yield 75% (353 mg), viscous liquid, R_f = 0.50 (hexane/ethyl acetate, 8:2), $[\alpha]_D^{25}$ = –18.2 (c = 61, CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.25–7.37 (m, 20 H), 5.46 (d, J = 9.8 Hz, 1 H), 5.04–5.14 (q, J = 12.2 Hz, 2 H), 4.95–5.03 (m, 1 H), 4.90 (d, J = 11.7 Hz, 1 H), 4.53–4.64 (m, 3 H), 4.38–4.45 (q, J = 11.7 Hz, 2 H), 3.89 (br. s, 1 H), 3.56–3.63 (m, 4 H), 1.97–2.01 (m, 2 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 155.2 (N–C=O), 138.78, 138.12, 137.99, 136.15 (C^{quat}, Ph), 128.47, 128.37, 128.19, 127.9, 127.7, 127.5, 127.3 (Ph), 78.7, 77.6, 75.2, 74.5, 73.5, 71.6, 70.4, 68.5, 66.9, 32.6 ppm. IR (CH_2Cl_2: $\tilde{\nu}_{max}$ = 1725, 3345 cm^{-1}. MS/ESI: [M + Na]$^+$ calcd. 590.2519; found 590.2512.

Benzyl (3*R*,4*R*)-3,4,6-Tris(benzyloxy)-5-hydroxyhexylcarbamate (13a): A solution of compound **11a** (300 mg, 0. 53 mmol) in THF (3 mL) was added dropwise at 0 °C to a suspension of $LiAlH_4$ (40.3 mg, 1.06 mmol) in dry THF (5 mL). The reaction mixture was stirred for 2 h at room temperature. The reaction mixture was cooled to 0 °C and quenched with EtOAc and water, followed by NaOH (1 N). The resulting white precipitate was removed by filtration through a celite pad, and the filtrate was extracted with ethyl acetate (2 × 50 mL). The organic layer was washed with brine and dried with Na_2SO_4, and the solvent was removed to provide the ring-opened product, which was purified by column chromatography; yield 95%, viscous liquid R_f = 0.50 (hexane/ethyl acetate, 6:4), $[\alpha]_D^{25}$ = +26.9 (c = 1.05, CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.21–7.36 (m, 20 H), 5.06 (s, 2 H) 4.43–4.69 (m, 7 H), 3.96 (m, 1 H), 3.65–3.67 (m, 4 H), 3.14–3.17 (m, 3 H), 1.77–1.84 (m, 2 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 156.2 (N–C=O), 138.03, 137.93, 137.49, 136.63 (C^{quat}, Ph) 128.50, 12845, 128.40, 128.15, 128.02, 127.88, 127.72, 126.93 (Ph), 73.6, 73.5, 72.7, 71.1, 70.7, 66.5, 65.8, 38.2, 30.1 ppm. IR (CH_2Cl_2): $\tilde{\nu}_{max}$ = 1715, 3425 cm^{-1}. MS/ESI: [M + Na]$^+$ calcd. 592.2675; found 592.2670.

Benzyl (3*R*,4*S*)-3,4,6-Ttris(benzyloxy)-5-hydroxyhexylcarbamate (13b): The same experimental procedure as used for converting compound **11a** to **13a** was followed; yield 90% (363 mg), viscous liquid R_f = 0.50 (hexane/ethyl acetate, 6:4), $[\alpha]_D^{25}$ = +26.9 (c = 1.05, CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.19–7.28 (m, 20 H), 5.02 (s, 2 H) 4.44–4.69 (m, 7 H), 3.96 (br. s, 1 H), 3.65 (m, 2 H), 3.45–3.47 (m, 2 H), 3.19 (m ppm. 2 H), 2.23 (br. s, 1 H), 1.75–1.77 (m, 2 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 156.3, 137.9 (m), 128.1 (m), 77.8, 74.02, 73.5, 72.5, 70.9, 69.8, 66.5, 38.2,30.6 ppm. IR (CH_2Cl_2): $\tilde{\nu}_{max}$ = 1710, 3420 cm^{-1}. MS/ESI: [M + Na]$^+$ calcd. 592.2675; found 592.2669.

Benzyl (3*R*,4*S*)-3,4,6-Tris(benzyloxy)-5-oxohexylcarbamate (14a): Pyridinium chlorochromate (400 mg, 1.8 mmol) was added to a stirred mixture of compound **13a** (500 mg, 0.88 mmol) and molecular sieves (4 Å, 100 mg) in CH_2Cl_2 (10 mL), in an ice/salt bath. Dichloromethane was then poured into the mixture after it had been stirred for 10 h at room temperature. The resulting mixture was filtered through celite, and the solvent was evaporated. The residue was purified by column chromatography; yield 90% (448 mg), viscous liquid, R_f = 0.50 (hexane/ethyl acetate, 9:1), $[\alpha]_D^{25}$ = –13.3 (c = 00.30, CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.21–7.36 (m, 20 H), 5.06 (s, 2 H), 4.39–4.64 (m, 7 H), 4.27 (s, 2

H), 4.05–4.06 (d, J = 3.68 Hz, 1 H), 3.96 (m, 1 H), 3.65 (m, 1 H), 3.08–3.11 (m, 2 H), 1.73–1.75 (m, 2 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 207.9, 156.2, 137.34, 137.1, 136.67 (C^{quat}, Ph), 128.6, 128.5, 128.41, 128.03, 127.9 (Ph), 83.7, 73.5, 74.4, 73.8, 73.4, 72.8, 66.7, 37.7, 30.5 ppm. IR (CH_2Cl_2): $\tilde{\nu}_{max}$ = 1723, 3350 cm^{-1}. MS/ESI: [M + Na]$^+$ calcd. 590.2519; found 590.2517.

Benzyl (3*R*,4*R*)-3,4,6-Tris(benzyloxy)-5-oxohexylcarbamate (14b): The same experimental procedure as used for converting compound **13a** to **14a** was followed; yield 88% (438 mg), viscous liquid, R_f = 0.50 (hexane/ethyl acetate, 9:1), $[\alpha]_D^{25}$ = +15.0 (c = 1, CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.26–7.36 (m, 20 H), 5.06 (s, 2 H), 4.76–4.79 (m, 1 H), 4.45–4.61 (m, 6 H), 4.31 (s, 2 H), 4.17 (d, J = 3.44 Hz, 1 H), 3.85–3.88 (m, 1 H), 3.17–3.28 (m, 2 H), 1.59–1.88 (m, 2 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 207.5, 161.2, 137.5, 137.42, 136.8 (C^{quat}, Ph) 128.55, 128.46, 128.15, 128.00 (Ph), 83.7, 78.2, 74.2, 73.3, 73.2, 72.5, 66.5, 37.8, 30.5 ppm. IR (CH_2Cl_2): $\tilde{\nu}_{max}$ = 1723, 3350 cm^{-1}. MS/ESI: [M + Na]$^+$ calcd. 590.2519; found 590.2514.

(2*R*,3*R*,4*R*)-2-(Hydroxymethyl)piperidine-3,4-diol (1): Pd/C (10%, 150 mg) was added to a solution of the oxidized product **14a** (300 mg, 0.53 mmol) in MeOH (50 mL). The reaction mixture was shaken under hydrogen (50 psi) for 24 h at room temperature. After removal of the catalyst by filtration through neutralized and deactivated Al_2O_3, the solvent was evaporated under reduced pressure. D-Fagomine (**1**) was afforded as a mixture of two diastereoisomers in a ratio of 80:20.

(2*R*,3*S*,4*R*)-2-(Hydroxymethyl)piperidine-3,4-diol (4): The same experimental procedure as used for converting compound **14a** into **1** was followed. The product was obtained as a mixture of two diastereoisomers in a ratio of 85:15.

***tert*-Butyl (4*S*,5*R*,6*R*)-4,5-Bis(benzyloxy)-6-(benzyloxymethyl)-3-chlorotetrahydro-2*H*-pyran-2-ylcarbamate (10a):** Boc_2O (1.1 g, 5.05 mmol) and saturated aq. $NaHCO_3$ solution (10 mL) were added at room temperature to a solution of a mixture of chloroamines **8a** (2 g, 4.23 mmol in 15 mL EtOAc). The reaction mixture was stirred for 2.5–3 h to complete the reaction (TLC monitoring). The organic layer was separated, and the aqueous layer was extracted with more EtOAc (2 × 10 mL). Conventional workup followed by column chromatographic purification gave a 1:1 mixture of two diastereomers; yield 90% (2.18 g), liquid, R_f = 0.50 (hexane/ethyl acetate, 8:2). ^{1}H NMR (500 MHz, $CDCl_3$, 1:1 mixture of diastereomers): δ = 7.13–7.41 (m, 15 H, Ar-H), 5.72–5.74 (d, J = 10 Hz, 1 H, 1-H, isomer A), 5.35–5.364 (d, J = 9.5 Hz, 1 H, 1-H, isomer B), 5.17–5.18 (d, J = 10 Hz, 1 H, 1-H, isomer A), 4.47–4.99 (m, 13 H, 6 × OCH_2Ph, both isomers, 1-H, isomer B), 4.37–4.38 (d, J = 2.5 Hz, 1 H, 6-H, isomer B), 3.98–4.01 (t, J = 9 Hz, 1 H, 5-H, isomer B), 3.65–3.85 (m, 8 H, 2-H, 3-H, 6′-H, isomer A, 2-H, 3-H, 5-H, 6-H, 6′-H, isomer B), 3.53–3.58 (m, 2 H, 4-H, both isomers), 1.50 (s, 9 H, *tert*-butyl, isomer B), 1.48 (s, 9 H, *tert*-butyl, isomer A) ppm. ^{13}C NMR (100 MHz, $CDCl_3$, 1:1 mixture of diastereomers): δ = 154.6, 154.2 (N–C=O), 138.15, 137.88, 137.3 (C^{quat}, Ph), 128.46, 128.3, 128.27, 128.23, 128.19, 127.94, 127.92, 127.86, 127.79, 127.7,127.61, 127.45 (Ph), 86.1, 80.7, 78.2, 77.2, 76.5, 76.1, 75.2, 74.9, 73.5, 73.4, 73.2, 71.2, 68.5, 68.1, 61.5, 61.2, 28.2 ppm. IR (CH_2Cl_2): $\tilde{\nu}_{max}$ = 1726, 3343 cm^{-1}. MS/ESI: [M + Na]$^+$ calcd.; 590.2285; found 590.2288.

***tert*-Butyl (2*R*,3*R*,4*S*,5S,6*R*)-4,5-Bis(benzyloxy)-6-(benzyloxymethyl)-3-chlorotetrahydro-2*H*-pyran-2-ylcarbamate (10b):** The same experimental procedure as used for **10a** from **8a** was followed; yield 80% (1.95 g), liquid, R_f = 0.50 (hexane/ethyl acetate, 8:2), $[\alpha]_D^{25}$ = +48.9 (c = 1.125, CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.25–7.45 (m, 15 H), 5.28–5.29 (d, J = 9.6 Hz, 1 H), 4.39–5.22 (m, 7 H), 4.04 (t, J = 9.5 Hz, 1 H), 3.97 (m, 1 H), 3.68–3.72 (m, 1 H), 3.54–3.58 (m, 3 H), 1.40 (s, 9 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 154.6, 138.21, 137.71, 137.47 (C^{quat}, Ph), 128.43, 128.21, 127.98, 127.93, 127.8, 127.7 (Ph), 83.2, 82.8, 80.5, 74.8, 73.4, 73.1, 67.7, 59.9, 28.2 ppm. IR (CH_2Cl_2): $\tilde{\nu}_{max}$ = 1725, 3345 cm^{-1}. MS/ESI: [M + Na]$^+$ calcd. 590.2285; found 590.2288.

***tert*-Butyl (4*R*,5*S*,6*R*)-4,5-Bis(benzyloxy)-6-(benzyloxymethyl)tetrahydro-2*H*-pyran-2-ylcarbamate (12a):** The same experimental procedure as used for **11a** from **9a** was followed; yield 80%, 182 mg, liquid, R_f = 0.50 (hexane/ethyl acetate, 8:2), ^{1}H NMR (500 MHz, $CDCl_3$) (1:1 mixture of diastereomers) δ = 7.16–7.32 (m, 15 H, Ar-H), 5.25 (br., 1 H), 4.94 (br., 1 H), 4.86 (d, J = 9.5 Hz, 1 H), 4.34–4.66 (m, 13 H), 4.17 (br., 1 H), 3.84–4.05 (m, 3 H), 3.46–3.73 (m, 5 H), 2.23–2.26 (m, 2 H), 1.95 (m, 2 H), 1.44 (s, 9 H, *tert*-butyl), 1.42 (s, 9 H, *tert*-butyl) ppm. ^{13}C NMR (100 MHz, $CDCl_3$, 1:1 mixture of diastereomers): δ = 154.6, 154.2 (N–C=O), 138.15, 137.88, 137.3 (C^{quat}, Ph), 128.46, 128.3, 128.27, 128.23, 128.19, 127.94, 127.92, 127.86, 127.79, 127.7,127.61, 127.45 (Ph), 86.1, 80.7, 78.2, 77.2, 76.5, 76.1, 75.2, 74.9, 73.5, 73.4, 73.2, 71.2, 68.5, 68.1, 61.5, 61.2, 33.3, 28.2 ppm. IR (CH_2Cl_2): $\tilde{\nu}_{max}$ = 1726, 3343 cm^{-1}. MS/ESI: [M + Na]$^+$ calcd. 556.2675; found 556.2677.

***tert*-Butyl (2*R*,4*R*,5*R*,6*R*)-4,5-Bis(benzyloxy)-6-(benzyloxymethyl)-tetrahydro-2*H*-pyran-2-ylcarbamate (12b):** The same experimental procedure as used for **11a** from **9a** was followed; yield 78%, viscous liquid, R_f = 0.50 (hexane/ethyl acetate, 8:2), $[\alpha]_D^{25}$ = –11.4 (c = 3.5, CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.25–7.33 (m, 15 H), 5.17–5.19 (d, J = 10.6 Hz, 1 H), 4.39–4.92 (m, 7 H), 3.89 (br. s, 1 H), 3.57–3.63 (m, 4 H), 1.95–1.99 (m, 2 H) 1.42 (s, 9 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 154.5, 138.86, 138.16, 138.02 (C^{quat}, Ph), 128.46, 128.36, 128.16, 127.9, 127.69, 127.46, 127.3 (Ph), 80.2, 78.4, 77.7, 75.1, 74.4, 73.4, 71.7, 70.4, 68.5, 32.7, 28.3 ppm. IR (CH_2Cl_2): $\tilde{\nu}_{max}$ = 1718, 3340 cm^{-1}. MS/ESI: [M + Na]$^+$ calcd. 556.2675; found 556.2675.

***tert*-Butyl (3*R*,4*R*)-3,4,5-Tris(benzyloxy)-5-hydroxyhexylcarbamate (15a):** The same experimental procedure as used for **13a** from **11a** was followed; yield 95% (384 mg), viscous liquid, R_f = 0.50 (hexane/ethyl acetate, 6:4), $[\alpha]_D^{25}$ = +19.2 (c = 1.04, CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.24–7.35 (m, 15 H), 4.46–4.68 (m, 7 H), 3.96–3.98 (m, 1 H), 3.65–3.83 (m, 4 H), 3.11–3.18 (m. 3 H), 1.74–1.82 (m, 2 H), 1.43 (s, 9 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 155.9, 138.05, 137.97, 137.54 (C^{quat}, Ph), 128.48, 128.38, 128.14, 128.02, 127.88, 127.68 (Ph), 79.2, 73.6, 73.5, 72.7, 71.1, 70.8, 37.8, 29.7, 28.4 ppm. IR (CH_2Cl_2): $\tilde{\nu}_{max}$ = 3306, 1730, 1533 cm^{-1}. MS/ESI: [M + Na]$^+$ calcd. 558.2832; found 558.2834.

***tert*-Butyl(3*R*,4*S*)-3,4,6-tris(benzyloxy)-5-hydroxyhexylcarbamate (15b):** The same experimental procedure as used for **13a** from **11a** was followed; yield 90% (364 mg), R_f = 0.3 (hexane/ethyl acetate, 6:4), $[\alpha]_D^{25}$ = +2.2 (c = 1.35, CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.25–7.33 (m, 15 H), 4.47–4.76 (m, 7 H), 3.92–3.96 (dt, J = 5.7, 3.4 Hz, 1 H), 3.68–3.73 (m, 2 H, 3-H), 3.52 (m, 2 H), 3.18 (t, J = 6.5 Hz, 2 H), 2.61 (br. s, 1 H), 1.77–1.82 (dd, J = 12.4, 6.36 Hz, 2 H), 1.42 (s, 9 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 156.3, 137.9, 137.64, 137.5 (C^{quat}, Ph) 127.8–127.4 (m, Ph), 78.0, 77.9, 73.9, 73.4, 72.5, 70.9, 69.9, 37.8, 30.7, 28.4 ppm. IR (CH_2Cl_2): $\tilde{\nu}_{max}$ = 3440, 1705 cm^{-1}. MS/ESI: [M + Na]$^+$ calcd. 558.2832; found 558.2834.

(3*S*,4*R*)-1,3,4-Tris(benzyloxy)-6-(*tert*-butoxycarbonylamino)hexan-2-yl Methanesulfonate (16a): Alcohol **15a** (200 mg, 0.37 mmol) was dissolved in dry DCM (2 mL), and the mixture was cooled to 0 °C with an ice bath. Triethylamine (74.7 mg, 0.74 mmol) and 4-(dimethylamino)pyridine (0.2 mmol) were added, followed by slow addition of MsCl (63.3 mg, 0.56 mmol). The reaction mixture was

stirred for 1 h at 0 °C to complete the reaction (TLC monitoring) and was then quenched by addition of saturated aq. $NaHCO_3$ solution (10 mL), and the mixture was extracted with CH_2Cl_2 (3 × 25 mL). The organic layer was washed with brine and dried with anhydrous sodium sulfate. Concentration of the organic layer on a rotary evaporator gave a crude product, which was purified through column chromatography; yield 95% (217 mg), viscous liquid, R_f = 0.50 (hexane/ethyl acetate, 6:4), $[\alpha]_D^{25}$ = +28.6 (*c* = 00.35, CH_2Cl_2). ^1H NMR (400 MHz, $CDCl_3$): δ = 7.26–7.37 (m, 15 H), 4.98–4.99 (m, 1 H), 4.42–4.77 (m, 7 H), 3.83–3.95 (m, 3 H), 3.53–3.56 (m, 1 H), 3.07–3.10 (m, 2 H), 3.01 (s, 3 H), 1.51–1.75 (m, 2 H), 1.43 (s, 9 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 155.8, 137.7, 137.65 (C^{quat}, Ph), 127.93–128.49 (m, Ph), 82.9, 79.9, 74.3, 73.4, 72.7, 69.0, 38.4, 37.6, 30.6, 28.4 ppm. IR (CH_2Cl_2): $\tilde{\nu}_{max}$ = 3424, 1710, 1362 cm^{-1}. MSESI: $[M + Na]^+$ calcd. 636.2607; found 636.2600.

(3*R*,4*R*)-1,3,4-Tris(benzyloxy)-6-(*tert*-butoxycarbonylamino)hexan-2-yl Methanesulfonate (16b): The same experimental procedure as used for **16a** from **15a** was followed; yield 98% (198 mg). R_f = 0.4 (hexane/ethyl acetate, 7:3), $[\alpha]_D^{25}$ = +8.6 (*c* = 2.68, CH_2Cl_2). ^1H NMR (400 MHz, $CDCl_3$): δ = 7.25–7.33 (m, 15 H), 4.79–4.82 (m, 2 H), 4.44–4.63 (m, 6 H), 3.95–3.97 (m, 1 H), 3.67–3.71 (m, 3 H), 3.18 (m, 2 H), 2.89 (s, 3 H), 1.77–1.82 (m, 2 H), 1.41 (s, 9 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 155.9, 137.79, 137.72, 137.21 (C^{quat}, Ph), 128.44, 127.99, 127.87 (Ph), 81.6, 79.2, 78.9, 78.4, 74.4, 73.5, 71.9, 69.4, 38.4, 37.4, 30.1, 28.4 ppm. IR (CH_2Cl_2): $\tilde{\nu}_{max}$ = 3425, 1711 cm^{-1}. $MSES^+$: $[M + H]^+$ calcd. 614.2788; found 614.2786.

(2*S*,3*R*,4*R*)-3,4-Bis(benzyloxy)-2-(benzyloxymethyl)piperidine (25a): Trifluoroacetic acid (0.08 mL, 1.05 mmol) was added dropwise over 5 min, with stirring at 0 °C, to a solution of mesylate **16a** (253 mg, 0.41 mmol) in dry DCM (4 mL). The reaction mixture was then immediately warmed to room temperature and was stirred for 45 min, after which it was again cooled to 0 °C and diluted with CH_2Cl_2 (10 mL). K_2CO_3 solution (2 M, 5 mL) was added carefully. This mixture was partitioned, and the aqueous phase was extracted with DCM (5 mL × 4). The combined organic phase was dried with anhydrous K_2CO_3 and was filtered through celite. The solvents were removed on a rotary evaporator. The residues were then dissolved in CH_3CN (15 mL), and K_2CO_3 (283 mg, 2.05 mmol) was added in two portions over 2 h. After the mixture had been stirred for 12 h it was gradually heated up to 70 °C over 3 h. The consumption of primary amine was confirmed by TLC, and the mixture was filtered through celite and concentrated in vacuo to give the crude cyclized product, which was purified by column chromatography; yield 65% (111 mg), viscous liquid, (over two steps) R_f = 0.30 (hexane/ethyl acetate 2:8), $[\alpha]_D^{25}$ = –11.75 (*c* = 1.7, CH_2Cl_2). ^1H NMR (400 MHz, $CDCl_3$): δ = 7.10–7.29 (m, 15 H), 5.01 (br., 1 H), 4.41–4.63 (m, 6 H), 3.43–3.67 (m, 5 H, 3-H), 2.95–3.02 (m, 2 H), 1.70–1.99 (m, 2 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 138.21, 137.93 (C^{quat}, Ph), 128.37, 128.32, 128.01, 127.76, 127.63, 127.4 (Ph), 82.9, 73.3, 72.8, 72.5, 71.4, 70.9, 69.4, 54.1, 39.8, 29.6, 25.1 ppm. IR (CH_2Cl_2): $\tilde{\nu}_{max}$ = 3424, 1710, 1362 cm^{-1}. MS/ESI: $[M + H]^+$ calcd. 418.2382; found 418.2383.

(2*S*,3*S*,4*R*)-3,4-Bis(benzyloxy)-2-(benzyloxymethyl)piperidine (25b): The same experimental procedure as for procuring compound **25a** from **16a** was followed; yield 70% (120 mg), (over two steps), viscous liquid, R_f = 0.30 (hexane/ethyl acetate 2:8), $[\alpha]_D^{25}$ = –46.75 (*c* = 1.6, CH_2Cl_2). ^1H NMR (400 MHz, $CDCl_3$): δ = 7.23–7.37 (m, 15 H), 4.34–4.68 (m, 6 H), 3.95 (br. s, 1 H), 3.73 (m, 1 H) 3.60 (m, 1 H), 3.34–3.38 (m, 2 H), 2.76 –3.02 (m, 3 H), 1.45–1.98 (m, 2 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 138.89, 138.3, 131.33 (C^{quat}, Ph), 128.29, 128.25, 128.00, 127.75, 127.58, 127.38 (Ph), 78.1, 73.5, 73.4, 71.4, 71.1, 70.9, 70.7, 54.7, 39.7, 29.5 ppm. IR (CH_2Cl_2): $\tilde{\nu}_{max}$ = 3340, 1685, 1100 cm^{-1}. MSESI: $[M + H]^+$ calcd. 418.2382; found 418.2383.

(2*R*,3*R*,4*R*)-6-Amino-1,3,4-tris(benzyloxy)hexan-2-ol (18a): A solution of compound **17a** (200 mg, 0.435 mmol) in diethyl ether (3 mL) was added dropwise at 0 °C to a suspension of $LiAlH_4$ (41 mg, 1.10 mmol) in dry ether (5 mL). The reaction mixture was slowly brought to room temperature and was then heated at reflux for 2 h. The reaction mixture was cooled to 0 °C and quenched with EtOAc and water, followed by NaOH (1 N). The resulting white precipitate was removed by filtration through a celite pad and the filtrate was extracted with ethyl acetate (2 × 50 mL). The organic layer was washed with brine and dried with Na_2SO_4, and the solvent was removed to provide the crude amino alcohol **18a**, which was subjected to subsequent reaction without any further purification.

(2*R*,3*S*,4*R*)-6-Amino-1,3,4-tris(benzyloxy)hexan-2-ol (18b): The same experimental procedure as used for **18a** from **17a** was followed.

4-Nitro-*N*-[(3*R*,4*R*)-3,4,6-tris(benzyloxy)-5-oxohexyl]benzenesulfonamide (19a): Pyridine (41 μL, 0.506 mmol) and *p*-nitrobenzenesulfonyl chloride (111 mg, 0.505 mmol) were added at 20 °C to a stirred solution of amino alcohol **18a** (200 mg, 0.459 mmol) in CH_2Cl_2 (4 mL). The mixture was stirred for 1 h and extracted with CH_2Cl_2 (2 × 15 mL), and the organic layer was washed with water and brine and dried with anhydrous Na_2SO_4. The concentrated crude product was purified by column chromatography to give compound **19a**; yield 96% (259 mg), viscous liquid, (over two steps), $[\alpha]_D^{25}$ = +23.0 (*c* = 1, CH_2Cl_2). ^1H NMR (400 MHz, $CDCl_3$): δ = 8.19–8.22 (m, 2 H), 7.80–7.83 (m, 2 H), 7.19–7.36 (m, 15), 4.90 (t, *J* = 6.1 Hz, 1 H), 4.38–4.63 (m, 6 H), 3.90 (br. s, 1 H), 3.58–3.73 (m, 4 H), 3.04 (br. s, 1 H), 2.88–3.00 (m, 2 H), 1.72–1.86 (m, 2 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 149.7, 145.7, 137.79, 137.65, 137.37 (C^{quat}, Ph), 128.58, 128.46, 128.40, 12832, 128.16, 128.07, 128.05, 127.97, 127.89, 127.79 (Ph), 77.7, 76.6, 73.7, 73.4, 72.6, 70.9, 70.5, 40.4, 30.1 ppm. IR (CH_2Cl_2): $\tilde{\nu}_{max}$ = 3286, 1730, 1529 cm^{-1}. MS ES$^+$: *m*/*z* = 643 $[M + Na]^+$. $C_{33}H_{36}N_2O_8S$ {643.20 $[M + Na]^+$}: C 63.85, H 5.85, N 4.51, S 5.17; found C 63.90, H 5.91, N 4.55, S 5.09.

4-Nitro-*N*-[(3*R*,4*S*)-3,4,6-tris(benzyloxy)-5-hydroxyhexyl]benzenesulfonamide (19b): The same experimental procedure as used for **19a** from **18a** was followed; yield 94% (253 mg, over two steps), viscous liquid, $[\alpha]_D^{25}$ = –1.5 (*c* = 2, CH_2Cl_2). ^1H NMR (400 MHz, $CDCl_3$): δ = 8.20–8.23 (m, 2 H), 7.80–7.83 (m, 2 H), 7.22–7.35 (m, 15 H), 5.12–5.17 (dd, *J* = 15.4, 4.9 Hz, 1 H), 4.38–4.70 (m, 6 H), 3.81 (d, *J* = 3.4 Hz, 1 H), 3.68–3.72 (m, 2 H), 3.45–3.51 (m, 2 H), 3.00–3.12 (m, 1 H), 2.29–2.99 (m, 1 H), 2.27 (br. s, 1 H), 1.79–1.84 (br. dd, *J* = 12.4, 6.1 Hz, 2 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 149.7, 145.7, 137.59, 137.51 (C^{quat}, Ph), 128.66, 128.49, 128.45, 128.11, 128.03, 127.93, 127.9, 124.19 (Ph), 78.6, 78.1, 74.3, 73.4, 72.1, 70.9, 69.9, 40.4, 30.0 ppm. IR (CH_2Cl_2): $\tilde{\nu}_{max}$ = 3306, 1730, 1533 cm^{-1}. MS ES$^+$: *m*/*z* = 643 $[M + Na]^+$. $C_{33}H_{36}N_2O_8S$ {643.20 $[M + Na]^+$}: C 63.85, H 5.85, N 4.51, S 5.17; found C 63.89, H 5.88, N 4.57, S, 5.21.

***N*-Benzyl-4-nitro-*N*-[(3*R*,4*R*)-3,4,6-tris(benzyloxy)-5-hydroxyhexyl]-benzenesulfonamide (20a):** K_2CO_3 (167 mg, 1.209 mmol) and benzyl bromide (53 μL, 0.445 mmol) were added at 20 °C to a stirred solution of sulfonamide **19a** (250 mg, 0.403 mmol) in DMF (4 mL). The mixture was stirred for a further 1 h and after completion of the reaction it was extracted with diethyl ether (2 × 20 mL), washed with water and brine, and dried with Na_2SO_4. The organic layer

was concentrated to provide a crude product, which was purified by column chromatography to give compound **19a**; yield 95%, 271 mg, viscous liquid, $[\alpha]_D^{25}$ = +12.0 (*c* = 1, CH_2Cl_2). ^1H NMR (400 MHz, $CDCl_3$): δ = 8.18–8.21 (m, 2 H, Ar-H), 7.81–7.83 (m, 2 H, Ar-H), 7.16–7.36 (m, 20 H, Ar-H), 4.24–4.57 (m, 8 H, 4 × CH_2Ph), 3.82 (br. s, 1 H, 1′-H), 3.51–3.61 (m, 4 H, 6-H, 6′-H, 3-H, 4-H), 3.14 (br. t, *J* = 7.5 Hz, 2 H, –OH and 5-H), 2.96 (br. s, 1 H, 1-H), 1.61–1.78 (m, 2 H, 2-H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 149.7, 145.6, 137.93, 137.89, 137.62, 135.33 (C^{quat}, Ph), 128.69, 128.37, 128.33, 128.17, 128.12, 127.95, 127.86, 127.81, 127.73, 124.21 (Ph), 77.6, 76.6, 73.47, 73.43, 72.3, 70.9, 70.4, 51.8, 45.1, 29.0 ppm. IR (CH_2Cl_2): $\tilde{\nu}_{max}$ = 3452, 1747, 1530 cm^{-1}. MS ES$^+$: *m*/*z* = 733 [M + Na]$^+$. $C_{40}H_{42}N_2O_8S$ {733.25[M + Na]$^+$}: C 67.59, H 5.96, N 3.94, S 4.51; found C 67.62, H 5.91, N 3.99, S 4.53.

***N*-Benzyl-4-nitro-*N*-[(3*R*,4*S*)-3,4,6-tris(benzyloxy)-5-hydroxyhexyl]-benzenesulfonamide (20b):** The same experimental procedure as used for converting **19a** to **20a** was followed; yield 98% (280 mg), viscous liquid, $[\alpha]_D^{25}$ = –4.34 (*c* = 1.1, CH_2Cl_2). ^1H NMR (400 MHz, $CDCl_3$): δ = 8.19–8.22 (m, 2 H) ppm. 7.83–7.87 (m, 2 H), 7.19–7.7.34 (m, 20 H), 4.12–4.62 (m, 8 H), 3.73–3.77 (m, 1 H), 3.51–3.6 (m, 2 H), 3.41–3.47 (br. d, *J* = 5.36 Hz, 1 H), 3.20–3.30 (m, 2 H), 2.67 (br. s, 1 H), 1.70–1.77 (m, 2 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 149.7, 145.5, 137.88, 135.51 (C^{quat}, Ph), 128.74, 128.42, 128.35, 128.25, 128.15, 127.89, 127.84, 127.80, 124.25 (Ph), 78.8, 74.0, 73.4, 72.1, 70.9, 69.7, 52.1, 45.2, 29.5 ppm. IR (CH_2Cl_2): $\tilde{\nu}_{max}$ = 3309, 1746, 1532 cm^{-1}. MS ES$^+$: *m*/*z* = 733 [M + Na]$^+$. $C_{40}H_{42}N_2O_8S$ {733.25 [M + Na]$^+$}: C 67.59, H 5.96, N 3.94, S 4.51; found C 67.64, H 5.99, N 3.98, S 4.54.

***N*-Benzyl-4-nitro-*N*-[(3*R*,4*S*)-3,4,6-tris(benzyloxy)-5-oxohexyl]benzenesulfonamide (21a):** IBX (1-hydroxy-1,2-benziodoxol-3(1*H*)-one 1-oxide, 2-iodoxybenzoic acid, 283 mg, 1.014 mmol) was added at room temperature to a stirred solution of alcohol **20a** (240 mg, 0.338 mmol) in acetone (4 mL). The mixture was heated at reflux at 80 °C for 2.5 h, and after completion of reaction (TLC monitoring) it was cooled to room temperature and filtered through a sintered funnel. Evaporation of the filtrate gave a crude product, which was purified by column chromatography to give compound **21a**; yield 98%, 234 mg, viscous liquid, $[\alpha]_D^{25}$ = –13.0 (*c* = 1, CH_2Cl_2). ^1H NMR (400 MHz, $CDCl_3$): δ = 8.19–8.21 (m, 2 H), 7.80–7.82 (m, 2 H), 7.12–7.32 (m, 20 H), 4.18–4.53 (m, 10 H), 3.95 (d, *J* = 4.1 Hz, 1 H), 3.66–3.69 (dd, *J* = 10.4, 5.3 Hz, 1 H), 3.10–3.15 (m, 2 H), 1.57–1.75 (m, 2 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 207.3, 149.7, 145.3, 137.3, 137.0, 136.6, 135.3, (C^{quat}, Ph), 128.7, 128.47, 128.38, 128.29, 128.25, 128.14, 128.11, 127.89, 127.84, 127.77, 124.2 (Ph), 83.5, 76.6, 74.1, 73.5, 73.2, 72.2, 52.1, 44.8, 29.2 ppm. IR (CH_2Cl_2): $\tilde{\nu}_{max}$ = 1730, 1529 cm^{-1}. MS ES$^+$: *m*/*z* = 731 [M + Na]$^+$. $C_{40}H_{40}N_2O_8S$ {731.24 [M + Na]$^+$}: C 67.78, H 5.69, N 3.95, S 4.52; found C 67.85, H 5.77, N 3.93, S 4.55.

***N*-Benzyl-4-nitro-*N*-[(3*R*,4*R*)-3,4,6-tris(benzyloxy)-5-oxohexyl]benzenesulfonamide (21b):** The same experimental procedure as used for **21a** was followed; yield 99% (236 mg), viscous liquid, $[\alpha]_D^{25}$ = –5.7 (*c* = 0.70, CH_2Cl_2). ^1H NMR (400 MHz, $CDCl_3$): δ = 8.22–8.24 (m, 2 H), 7.8–7.87 (m, 2 H), 7.16–7.34 (m, 20 H), 4.15–4.52 (m, 8 H), 4.01–4.02 (d, *J* = 3.6 Hz, 1 H), 3.70–3.72 (m, 1 H), 2.20–2.24 (m, 2 H), 1.60–1.74 (m, 2 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 207.4, 149.7, 145.5, 137.5, 137.0, 136.9, 135.4, (C^{quat}, Ph), 128.77, 128.54, 128.48, 128.40, 128.38, 128.26, 128.18, 128.15, 127.98, 127.88, 127.82, 127.79 (Ph), 83.5, 74.1, 73.3, 73.1, 72.1, 52.1, 44.8, 29.1 ppm. IR (CH_2Cl_2): $\tilde{\nu}_{max}$ = 1729, 1530 cm^{-1}. MS ES$^+$: *m*/*z* = 731 [M + Na]$^+$. $C_{40}H_{40}N_2O_8S$ {731.24 [M + Na]$^+$}: C 67.78, H 5.69, N 3.95, S 4.52; found C 67.83, H 5.73, N 3.99, S 4.54.

(2*S*,3*R*,4*R*)-1-Benzyl-3,4-bis(benzyloxy)-2-(benzyloxymethyl)piperidine (23a): K_2CO_3 (116 mg, 0.846 mmol) and thiophenol (35 μL, 0.338 mmol) were added at 23 °C to a stirred solution of compound **21a** (200 mg, 0.282 mmol) in dry CH_3CN (4 mL). The reaction mixture was stirred for 5 h, and after completion of the reaction the mixture was extracted with ethyl acetate (2 × 15 mL). The organic phase was washed with water and brine, dried with anhydrous Na_2SO_4 and concentrated under reduced pressure (avoiding heating) to give the unstable amino derivative **22a**. The amino derivative was subjected to subsequent reaction without any further purification. Amino derivative **22a** was hence dissolved in 1,2-dichloroethane (3 mL), the reaction mixture was cooled to –35 °C, and anhydrous Na_2SO_4 (134 mg, 1.12 mmol), glacial acetic acid (97 μL, 1.70 mmol) and $NaBH(OAc)_3$ (90 mg, 0.423 mmol) were added. The stirring was continued for 24 h at the same temperature, and the suspension was filtered, the solvent was evaporated, and the residue was purified by chromatotron (ethyl acetate/hexane/0.2% Et_3N) to give compound **23a**; yield 74% (106 mg), oil (over two steps), $[\alpha]_D^{25}$ = –10.0 (*c* = 0.6, CH_2Cl_2). ^1H NMR (400 MHz, $CDCl_3$): δ = 7.19–7.36 (m, 20 H), 4.93 (d, *J* = 11.0 Hz, 1 H), 4.56–4.66 (q, *J* = 11.7 Hz, 2 H), 4.52 (d, *J* = 11.0 Hz, 1 H), 4.47 (br. s, 2 H), 4.11 (br. d, *J* = 13.4 Hz, 1 H), 3.77–3.84 (m, 2 H), 3.42–3.48 (ddd, *J* = 13.2, 8.3, 4.8 Hz, 1 H), 3.35 (br. d, *J* = 13.4 Hz, 1 H), 2.80 (br. d, *J* = 11.9 Hz, 1 H), 2.41 (br. d, *J* = 8.3 Hz, 1 H), 1.93–2.03 (m, 2 H), 1.59–1.60 (m, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 138.91, 138.2 (C^{quat}, Ph), 129.13, 128.32, 128.28, 128.12, 128.00, 127.96, 127.62, 127.53, 127.46, 127.4, 126.84 (Ph), 82.0, 79.1, 74.9, 73.2, 71.1, 67.2, 65.1, 57.1, 49.2, 28.6 ppm. MS ES$^+$: *m*/*z* = 508 [M + H]$^+$; $C_{34}H_{37}NO_3$ {508.28 [M + H]$^+$}: C 80.44, H 7.35, N 2.76; found C 80.48, H 7.41, N 2.78.

(2*S*,3*S*,4*R*)-3,4-Bis(benzyloxy)-2-(benzyloxymethyl)-1-benzylpiperidine (23b): The same experimental procedure as used for the synthesis of **23a** from **21a** was followed; yield 70% (100 mg), oil, $[\alpha]_D^{25}$ = –5.33 (*c* = 0.75, CH_2Cl_2). ^1H NMR (400 MHz, $CDCl_3$): δ = 7.21–7.34 (20 H), 4.94 (d, *J* = 11.0 Hz, 1 H), 4.56–4.67 (q, *J* = 11.9 Hz, 2 H), 4.51 (d, *J* = 11.0 Hz, 1 H), 4.48 (br. s, 2 H), 4.10 (d, *J* = 13.6 Hz, 1 H), 3.77–3.84 (m, 2 H), 3.60 (t, *J* = 8.8 Hz, 1 H), 3.39–3.48 (m, 1 H), 3.33 (d, *J* = 13.6 Hz, 1 H), 2.77–2.82 (dt, *J* = 11.7, 7.3, 3.4 Hz, 1 H), 2.37–2.41 (dt, *J* = 9.0, 5.6, 3.0 Hz, 1 H), 1.93–2.03 (m, 2 H, 2′-H), 1.51–1.61 (m, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 138.89, 138.20 (C^{quat}, Ph), 129.1, 128.32, 128.29, 128.12, 128.00, 127.96, 127.62, 127.53, 127.46, 127.4, 126.81 (Ph), 82.02, 79.11, 76.61, 74.9, 73.22, 71.18, 67.26, 65.14, 57.18, 49.26, 28.67 ppm. MS ES$^+$: *m*/*z* = 508 [M + H]$^+$; $C_{34}H_{37}NO_3$ {508.28 [M + H]$^+$}: C 80.44, H 7.35, N 2.76; found C 80.46, H 7.39, N 2.73.

(2*R*,3*R*,4*R*)-2-(Hydroxymethyl)piperidine-3,4-diol (1): Pd/C (10%, 150 mg) was added to a solution of **23a** (300 mg, 0.53 mmol) in MeOH (50 mL). The reaction mixture was shaken under hydrogen (50 psi) for 24 h at room temperature. After removal of the catalyst by filtration through neutralized and deactivated Al_2O_3, the solvent was evaporated under reduced pressure. D-Fagomine (**1**) was afforded as a pale brown solid; yield 80% (62 mg), $[\alpha]_D^{25}$ = +20.4 (*c* = 1.0 in H_2O), ^1H NMR (400 MHz, D_2O): δ = 3.76 (dd, *J* = 11.8, 3.0 Hz, 1 H), 3.73 (dd, *J* = 11.8, 6.5 Hz, 1 H), 3.56 (ddd, *J* = 11.5, 9.0, 5.0 Hz, 1 H), 3.35 (t, *J* = 9.5 Hz, 1 H), 3.25–3.27 (m, 1 H), 2.89–2.96 (m, 2 H), 2.01 (m, 1 H), 1.53–1.43 (m, 1 H) ppm. ^{13}C NMR (125 MHz, D_2O): δ = 70.8, 69.9, 60.2, 58.1, 41.9, 28.9 ppm.

(2*R*,3*S*,4*R*)-2-(Hydroxymethyl)piperidine-3,4-diol (4): The same procedure as used for converting **23a** to **1** was followed; yield 86% (67 mg), $[\alpha]_D^{25}$ = +10.4 (*c* = 1.4 in H_2O), ^1H NMR (500 MHz, D_2O): δ = 3.90 (s, 1 H, 3-H), 3.69–3.77 (m, 2 H), 3.58–3.61 (m, 1 H), 3.01

(m, 1 H), 2.85–2.89 (m, 1 H), 2.67–2.75 (m, 2 H), 2.51 (m, 1 H), 1.63–1.84 (m, 2 H) ppm. ^{13}C NMR (125 MHz, D_2O): δ = 69.3, 68.7, 62.8, 59.9, 46.8, 25.6 ppm.

(2*S*,3*R*,4*R*)-3,4-Bis(benzyloxy)-2-(benzyloxymethyl)-1-(4-nitrophenylsulfonyl)piperidine (24a): PPh_3 (101 mg, 0.386 mmol) and diisopropyl azodicarboxylate (76 μL, 0.386 mmol) were added at room temperature to a stirred solution of compound **19a** (200 mg, 0.322 mmol) in dry toluene (3 mL). The reaction mixture was stirred for a further 2 h and after completion of reaction (TLC monitoring), solvent was evaporated and the crude product was purified by column chromatography to give compound **24a**; yield 83% (161 mg), viscous liquid, $[\alpha]_D^{25}$ = –11.76 (*c* = 0.85, CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 17.84–8.03 (m, 4 H), 7.11–7.36 (m, 15 H), 4.59–4.78 (m, 4 H), 4.48–4.52 (br. dd, *J* = 10.5, 6.1 Hz, 1 H), 4.32–4.35 (2 × d, *J* = 11.7 Hz, 2 H), 3.75–3.82 (dd, *J* = 13.8, 4.8 Hz, 1 H), 3.64–3.73 (m, 3 H), 3.53–3.57 (dd, *J* = 9.5, 6.1 Hz, 1 H), 3.05–3.12 (dt, *J* = 13.6, 2.6 Hz, 1 H), 1.97–2.04 (m, 1 H), 1.48–1.57 (m, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 149.5, 146.7, 138.4, 137.9, 137.4 (C^{quat}, Ph), 128.49, 128.39, 128.36, 128.22, 127.91, 127.84, 127.69, 127.59, 127.52, 123.86 (Ph), 80.1, 76.2, 73.3, 73.2, 72.4, 66.0, 55.7, 40.0, 31.1 ppm. IR (CH_2Cl_2): $\tilde{\nu}_{max}$ = 1722, 1529 cm^{-1}. MS: ES$^+$: *m*/*z* = 620 [M + NH_4]$^+$; $C_{33}H_{34}N_2O_7S$ {620.24 [M + NH_4]$^+$}: C 65.76, H 5.69, N 4.65, S 5.32; found C 65.80, H 5.73, N 4.68, S 5.34.

(2*S*,3*S*,4*R*)-3,4-Bis(benzyloxy)-2-(benzyloxymethyl)-1-(4-nitrophenylsulfonyl)piperidine (24b): The same procedure as used for **24a** was followed. Viscous liquid; yield 94%, (176 mg), $[\alpha]_D^{25}$ = +59.13 (*c* = 1.15, CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.21–7.93 (19 H), 4.48–4.62 (br. dd, *J* = 11.0, 4.6 Hz, 1 H), 4.40–4.49 (m, 6 H), 3.95 (br. d, *J* = 2.2 Hz, 1 H), 3.74 (br. d, *J* = 14.4 Hz, 1 H), 3.53–3.67 (m, 3 H, 3-H), 3.16–3.24 (br. dt, *J* = 14.3, 3.0 Hz, 1 H), 1.71–1.78 (m, 1 H), 1.61 (br. d, *J* = 8.8 Hz, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 149.4, 146.3, 138.0, 137.8, 137.4 (C^{quat}, Ph), 128.51, 128.41, 128.39, 128.32, 128.11, 127.98, 127.94, 127.65, 127.32, 123.631 (Ph), 74.4, 73.4, 72.8, 72.6, 70.3, 69.0, 57.6, 41.5, 24.8 ppm. IR (CH_2Cl_2): $\tilde{\nu}_{max}$ = 1743, 1529 cm^{-1}. MS ES$^+$: *m*/*z* = 620 [M + NH_4]$^+$; $C_{33}H_{34}N_2O_7S$ {620.24 [M + NH_4]$^+$}: C 65.76, H 5.69, N 4.65, S 5.32; found C 65.78, H 5.75, N 4.69, S 5.35.

(2S,3*R*,4*R*)-3,4-Bis(benzyloxy)-2-(benzyloxymethyl)piperidine (25a): K_2CO_3 (170 mg, 1.21 mmol) and benzyl bromide (55 μL, 0.46 mmol) were added at 20 °C to a stirred solution of sulfonamide **24a** (250 mg, 0.415 mmol) in DMF (4 mL). The mixture was stirred for a further 1 h and after completion of the reaction it was extracted with diethyl ether (2 × 20 mL) and washed with water and brine, and dried with Na_2SO_4. The organic layer was concentrated to provide a crude product, which was purified by column chromatography to give compound **25a**; yield 89% (154 mg).

(2S,3*S*,4*R*)-3,4-Bis(benzyloxy)-2-(benzyloxymethyl)piperidine (25b): The same experimental procedure as used for **25b** from **24a** was followed; yield 91% (157 mg).

(2*S*,3*R*,4*R*)-2-(Hydroxymethyl)piperidine-3,4-diol (5): $Pd(OH)_2$ (150 mg) was added to a solution of **25a** (150 mg, 1.02 mmol) in MeOH (20 mL). The reaction mixture was shaken under hydrogen (50 psi) for 24 h at room temperature. After removal of the catalyst by filtration through neutralized and deactivated Al_2O_3, the solvent was evaporated under reduced pressure. L-Fagomine (**5**) was afforded as a pale brown solid; yield 80% (42 mg), $[\alpha]_D^{25}$ = +20.0 (*c* = 0.5 in MeOH), ^{1}H NMR (500 MHz, D_2O): δ = 3.87 (dd, *J* = 12.5, 3.2 Hz, 1 H), 3.73 (dd, *J* = 12.6, 5.6 Hz, 1 H), 3.65 (ddd, *J* = 11.5, 9.0,5.0 Hz, 1 H), 3.33 (t, *J* = 6.5 Hz, 1 H), 3.18–3.16 (m, 1 H), 3.07–3.02 (m, 2 H), 2.074–1.97 (m, 1 H), 1.64–1.62 (m, 1 H) ppm. ^{13}C NMR (125 MHz, D_2O): δ = 70.9, 69.8, 60.0, 57.8, 41.8, 28.9 ppm.

(2*S*,3*S*,4*R*)-2-(Hydroxymethyl)piperidine-3,4-diol (6): The same procedure as used for **5** was followed; yield 85% (46 mg), $[\alpha]_D^{25}$ = –8.0 (*c* = 0.5 in MeOH). ^{1}H NMR (500 MHz, D_2O): δ = 3.96 (ddd, *J* = 5.1, 4.5, 2.5 Hz, 1 H), 3.80 (dd, *J* = 12.6, 5.6 Hz, 1 H), 3.78 (dd, *J* = 11.5, 5.0 Hz, 1 H), 3.72 (dd, *J* = 11.5, 5.0 Hz, 1 H), 3.56 (m, 1 H), 3.18–3.16 (m, 1 H), 3.05–3.01 (m, 1 H), 1.82–1.67 (m, 2 H) ppm. ^{13}C NMR (125 MHz, D_2O): δ = 70.3, 67.9, 60.8, 57.8, 38.8, 28.9 ppm.

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