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(3*S*,4*R*,5*R*)-3-(2-Hydroxyethyl)piperidine-3,4,5-triol as an isofagomine analogue: synthesis and glycosidase inhibition study

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ABSTRACT

The synthesis of (3*S*,4*R*,5*R*)-3-(2-hydroxyethyl)piperidine-3,4,5-triol **10** has been described from D-glucose. The base promoted cyclization for the construction of the piperdine framework is the key step of the synthesis.

1. Introduction

Azasugars (or iminosugars) are sugar-mimics with a nitrogen in place of the ring oxygen, and have attracted a great deal of attention as inhibitors of carbohydrate processing enzymes such as glycosidases and glycosyl transferases.[1] Since the discovery of 1-deoxynojirimycin **1** (DNJ), a potent α-glucosidase inhibitor, research efforts have been directed toward the synthesis and biological evaluation of naturally occurring and synthetic azasugars.[2] In view of their promising inhibition profile, azasugars are now finding clinical applications as antidiabetic,[3] anticancer,[4] anti-HIV,[5] and therapeutic agents for some genetic disorders.[6] *N*-Butyl-DNJ (Miglustat) **2** and *N*-hydroxyethyl-DNJ (Miglitol) **3** have already been approved for the treatment of type I Gaucher's disease and type II diabetes, respectively. *Galacto*-DNJ **4** has demonstrated inhibition of lysosomal α-galactosidase and is currently in phase B clinical trials for the treatment of Fabry's disease (Fig. 1).[7] The search for anomer selective β-glycosidase inhibitors has led to a new class of sugar-mimics, 1-*N*-iminosugars or 1-azasugars with a nitrogen atom at the anomeric position. The representative 1-*N*-azasugar isofagomine **5** was first designed by Bols et al.[8] as an apparent transition state analog mimicking the carbocationic form of the oxycarbenium-like transition state in which the positive charge resides at the anomeric carbon. Isofagomine has been found to be a selective and very strong inhibitor of β-glucosidase [K_i = 0.11 μM, sweet almonds][8,9] and its 2-hydroxy analog noeuromycin **6** shows β-glucosidase inhibition in the nanomolar range.[10] Similarly, isogalactofagomine **7** was found to be a selective and potent inhibitor for β-galactosidases [K_i = 0.004 μM, *Aspergillus oryzae*].[11] Due to the pronounced and selective inhibition activities of isofagomine and its congeners, there has been an increased interest toward the synthesis of such 1-*N*-iminosugars.[12] Dhavale et al.[13] have reported the synthesis of piperidine **8** with a hydroxyethyl chain at C-4, which was found to be specific and potent inhibitor against β-glucosidase. Similarly, Takahata et al.[14] have reported the synthesis of homoisofagomine **9**.

Continuing our interest toward the design, synthesis, and biological evaluation of natural and unnatural azasugars and hybrid molecules as glycosidase inhibitors,[15] we have synthesized (3*S*,4*R*,5*R*)-3-(2-hydroxyethyl)piperidine-3,4,5-triol **10** from readily available and inexpensive D-glucose. The design was conceived from the view that a pendant hydroxyethyl substituent at C-3 along with the hydroxyl group may impart selective and/or improved inhibition, as has been observed in the literature.[13,16]

2. Results and discussion

The synthesis emanated from diol **14** (Scheme 1), which was obtained from D-glucose in four steps by following the literature procedures.[17–19] The regioselective protection of the primary alcohol in **14** as trityl ether provided **15** in 90% yield. Dihydroxylation of **15** with OsO_4–NMO followed by sodium periodate oxidation afforded the corresponding aldehyde, which upon sodium borohydride reduction furnished diol **16** in 80% yield. Protection of both the hydroxyl groups in **16** as benzyl ethers using sodium hydride and benzyl bromide provided **17** in excellent yield. Detritylation in **17** using $HClO_4{\cdot}SiO_2$, a procedure developed in our laboratory,[20] gave alcohol **18** in 92% yield. Mesylation of the primary alcohol followed by nucleophilic displacement with sodium azide in DMF furnished the azido compound **20** in good yield. The IR spectrum of **20** showed a strong absorption peak at 2101 cm^{-1}, confirming the presence of an azide group. Cleavage of the 1,2-acetonide functionality in **20** using TFA–H_2O (1:1) followed by sodium periodate oxidation afforded the desired aldehyde **21** in 88% yield. Compound **21**, in its ^1H NMR spectrum, showed characteristic peaks at δ 8.17 for the –OCHO group and at δ 9.38 for the –CHO group. Similarly, in the ^{13}C NMR spectrum of **21**, an oxycarbonyl signal appeared at δ 159.2 while the carbonyl signal of the –CHO appeared downfield at δ 199.5. Its

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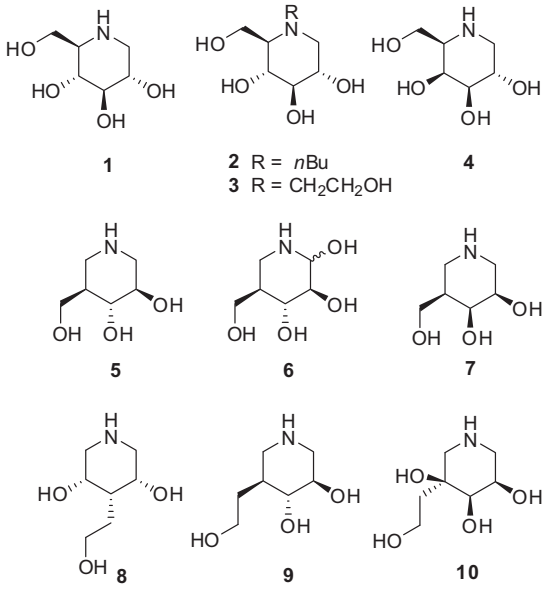
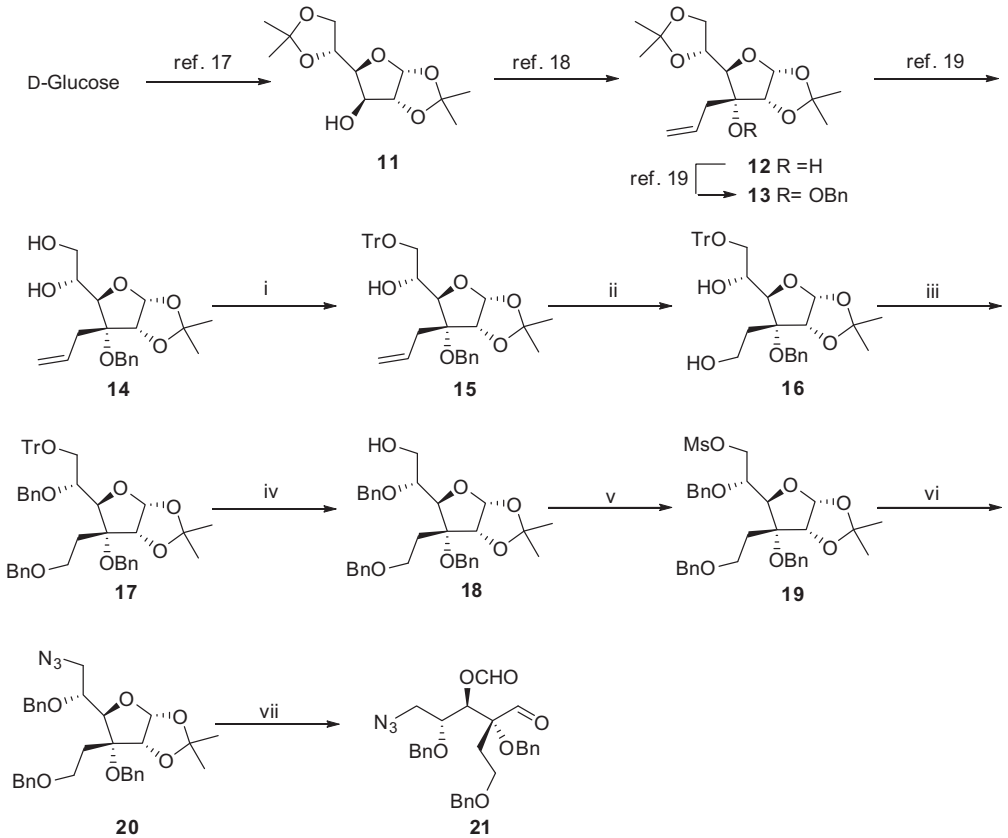


Figure 1. DNJ, isofagomine and its derivatives.

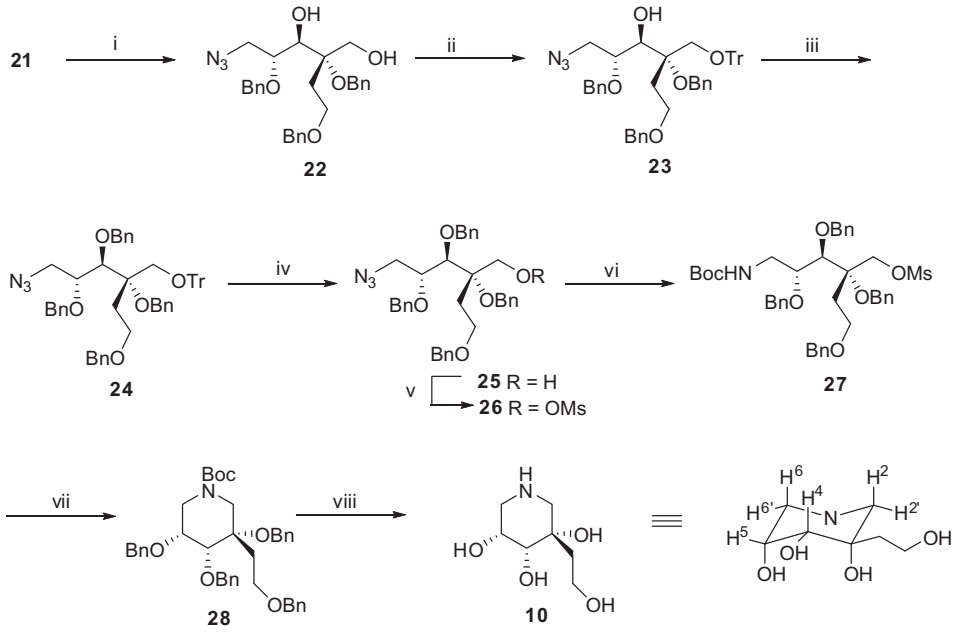
IR spectrum also showed strong absorption peaks at 2105 and 1736 cm^{-1} for the azide and carbonyl groups, respectively. The azido aldehyde **21** thus obtained was now ready for cyclization. However, the one pot reaction[21] of azide reduction, reductive amination, and debenzylation using 20% $Pd(OH)_2/C$ under hydrogenation condition in methanol was unsuccessful in giving the desired product. This reaction was not clean, and led to the formation of a mixture of products. Next, the treatment of azide **21** with $Pd/CaCO_3$[22] in MeOH in the presence of H_2 (1 atm) at room temperature followed by reductive amination with sodium cyanoborohydride gave the cyclized product albeit in poor yield.

Hence, we explored a different pathway and instead of performing the direct cyclization, we attempted the base promoted cyclization for obtaining the desired piperidine framework. Thus, reduction of aldehyde **21** with sodium borohydride in methanol furnished the diol **22** in 83% yield (Scheme 2). The disappearance of the corresponding –OCHO and the –CHO group signals in the ^1H and ^{13}C NMR spectrum of **21** and presence of characteristic absorptions at 3433 cm^{-1} for –OH and 2100 cm^{-1} for an azide group in its IR spectrum indicated its azido alcohol structure. Regioselective protection of the primary alcohol in **22** as a trityl ether and secondary alcohol as benzyl ether gave compound **24**. However, trityl cleavage in **24** employing $HClO_4{\cdot}SiO_2$ was unsuccessful and whole starting material was recovered back from the reaction. Thereby, detritylation in **24** was carried out by using TFA/CH_2Cl_2 which gave the alcohol **25** without affecting the azide moiety. The IR spectrum of **25** showed a broad peak at 3442 cm^{-1} for –OH stretching and a strong absorption peak at 2099 cm^{-1} for the azide group. The reaction of the hydroxyl group with methanesulfonyl chloride, Et_3N, and a catalytic amount of DMAP furnished the mesylated derivative **26**.

The next step of the synthesis was the formation of the piperidine ring. For this, azide **26** was reduced to the corresponding amine using Ph_3P in $THF–H_2O$ (9:1) at room temperature. However, cyclization of the crude amine with Et_3N in refluxing methanol followed by Boc protection provided the cyclized compound **28**



Scheme 1. Reagents and conditions: (i) TrCl, Et_3N, CH_2Cl_2, 0 °C to rt, overnight, 90%; (ii) (a) OsO_4, NMO, acetone/water/*t*BuOH (1:1:0.5), rt, 12 h; (b) $NaIO_4$, $MeOH/H_2O$ (9:1), 0 °C, 30 min; (c) $NaBH_4$, MeOH, 0 °C to rt, 2 h, 80% (over three steps); (iii) NaH, BnBr, DMF, 0 °C to rt, overnight, 96%; (iv) $HClO_4{\cdot}SiO_2$, MeOH, rt, 3 h, 92%; (v) MsCl, Et_3N, CH_2Cl_2, 0 °C, 1 h, 95%; (vi) NaN_3, DMF, 120 °C, 3 h, 85%; (vii) (a) TFA/H_2O (1:1), rt, 1 h; (b) $NaIO_4$, $MeOH/H_2O$ (9:1), 0 °C to rt, 8 h, 88%.



Scheme 2. Reagents and conditions: (i) $NaBH_4$, MeOH, 0 °C to rt, overnight, 83%; (ii) TrCl, Et_3N, CH_2Cl_2, 12 h, 77%; (iii) NaH, BnBr, DMF, 0 °C, 2 h, 97%; (iv) TFA, CH_2Cl_2, 0 °C, 30 min, 81%; (v) MsCl, Et_3N, CH_2Cl_2, 0 °C, 1 h, 97%; (vi) (a) Ph_3P, THF/H_2O (9:1), rt, 8 h; (b) Boc_2O, $NaHCO_3$, EtOAc, 0 °C to rt, overnight, 81%; (vii) NaH, THF, reflux, 4 h, 75%; (viii) (a) $Pd(OH)_2/C$, H_2, 20 psi, rt, 12 h; (b) 6 M HCl, MeOH, rt, 12 h; (c) Dowex OH^- quantitative yield.

in poor yield (25%) along with an unidentifiable product. Cyclization using K_2CO_3/CH_3CN[23] instead of Et_3N/MeOH[24] did not lead to any significant improvements in the yield of **28**. Consequently, we changed the reaction sequence to obtain the desired piperidine. The reduction of the azide in **26** with Ph_3P provided the corresponding free amine, which upon treatment with di-*tert*-butylpyrocarbonate afforded the Boc protected amine **27** in 81% yield over two steps. Reaction of amine **27** with *t*BuOK (2 equiv) in THF provided the cyclized product **28** in only 15% yield along with recovered starting material. Increasing the base equivalents led to the formation of side products. Treatment of the amine **27** with NaH (2 equiv) in THF under refluxing conditions produced the desired Boc protected piperidine **28** in 75% yield. The ^1H NMR spectrum of compound **28** showed a broadening of the signals indicating that it was a mixture of rotamers. However, the diappearence of signals corresponding to the $-SO_2CH_3$ protons confirmed the cyclization. Cyclization was further confirmed from the mass spectrum HRMS $[M+H]^+$ peak at 638.3482 [expected 638.3481]. Finally, deprotection of the benzyl groups with 20% $Pd(OH)_2/C–H_2$ in methanol at 20 psi followed by treatment with 6 M HCl allowed the removal of the NHBoc protecting group, which after passing through a basic Dowex column afforded the fully deprotected compound **10** in almost quantitative yield. Compound **10** was well characterized by ^1H, ^{13}C NMR, as well as by mass spectrometry studies. In the ^1H NMR spectrum of **10**, the appearance of two broad doublets at δ 2.95 and 2.77 ($J_{6a,6e}$ = 13.7 Hz) corresponding to protons H-6 and H-6′ suggested that H-5 is equatorially oriented and bisects the H-6 protons (dihedral angle ~55°). The H-5 proton also appeared as broad singlet at δ 3.87 thus indicating the $^2C_5$ conformation in **10**. The inhibitory activity of compound **10** was tested against four commercially available glycosidases at millimolar concentration. However it was only active against β-galactosidase (*Aspergillus oryzae*) with IC_{50} = 5.0 mM.[25]

3. Conclusions

In conclusion, we have reported the synthesis of the 1-*N*-iminosugar **10** from inexpensive and readily available D-glucose. Compound **10** was a very weak galactosidase inhibitor [IC_{50} = 5.0 mM]. It is expected that further structural modifications may lead to improved inhibitions.

4. Experimental

Infrared spectra were recorded with a Bruker FT/IR Vector 22 spectrometer. ^1H and ^{13}C NMR spectra were recorded with a JEOL LA-400 (400 and 100 MHz, respectively) or JEOL ECX-500 spectrometer (500 and 125 MHz, respectively) in solutions of $CDCl_3$ using tetramethylsilane as the internal standard. Chemical shifts are reported in ppm downfield to tetramethylsilane. Coupling constants are reported in Hz and splitting patterns are expressed as s (singlet), d (doublet), dd (doublet of doublets), m (multiplet), and br s (broad singlet). The mass spectra were recorded with a Waters HAB 213 Q Tof Premier Micromass. Optical rotations were recorded with 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) using hexane and ethyl acetate as eluents. Thin-layer chromatography (TLC) was performed on silica gel plates made by using grade G silica gel obtained from s.d.fine-chem Ltd, Mumbai, or on Merck silica gel precoated on plastic plates. All solvents and common reagents were purified by established procedures.

4.1. General procedure (A): Tritylation of the primary alcohol

To a stirred solution of diol (1 mmol) in CH_2Cl_2 (10 mL) at 0 °C were added Et_3N (3 mmol), TrCl (1.2 mmol), and a catalytic amount of DMAP. The reaction mixture was stirred for 8–10 h at room temperature and then usual work-up by CH_2Cl_2 and water gave a crude product, which was purified by column chromatography to give the pure tritylated compounds.

4.2. General procedure (B): Benzylation of the alcohol

At first, 60% suspension of NaH in paraffin oil (1.2 mmol) was added portionwise to a stirred solution of the alcohol (1 mmol)

in DMF (10 mL) at 0 °C. After 30 min, benzyl bromide (1.2 mmol) was added dropwise at 0 °C and the reaction mixture was stirred for 2–4 h at room temperature. Excess NaH was quenched by pouring the reaction mixture onto ice and then extracted with diethyl ether (30 mL) followed by washing with water and brine solution. The organic layer was dried with anhydrous Na_2SO_4, concentrated in vacuo and the crude product, purified by column chromatography to give benzylated products.

4.3. General procedure (C): Mesylation of the primary alcohol

To a stirred solution of alcohol (1 mmol) in CH_2Cl_2 (10 mL) at 0 °C were added Et_3N (1.5 mmol), followed by the slow addition of methanesulfonyl chloride (1.2 mmol) and a catalytic amount of DMAP. The reaction mixture was stirred for 1 h at 0 °C (TLC monitoring) and then quenched by the addition of saturated $NaHCO_3$ solution (10 mL). The mixture was extracted with CH_2Cl_2 (2×25 mL). The combined organic layer was washed with water and brine and dried over anhydrous Na_2SO_4. Concentration of the organic layer on a rotary evaporator gave a crude product which was purified by column chromatography.

4.4. (*R*)-1-((3a*R*,5*R*,6*R*,6a*R*)-6-Allyl-6-(benzyloxy)-2,2-dimethyltetrahydrofuro[2,3-*d*][1,3]dioxol-5-yl)-2-(trityloxy)ethanol 15

Diol **14** (1 g, 2.85 mmol) was tritylated using general procedure (A) to give **15** (1.522 g, 90%) as a colorless thick liquid. R_f = 0.5 (hexane/EtOAc, 9:1). $[\alpha]_D^{25} = +5.9$ (*c* 1.0, CH_2Cl_2). IR (neat) ν_{max}: 3524, 2983, 1089 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 7.48–7.46 (m, 6H, Ar*H*), 7.40–7.18 (m, 14H, Ar*H*), 6.00–5.93 (m, 1H, –C*H*=CH$_2$), 5.59 (d, 1H, *J* = 3.68 Hz), 5.18–5.12 (m, 2H, –CH=C*H*$_2$), 4.74 (s, 2H, –OC*H*$_2$Ph), 4.48 (d, 1H, *J* = 3.8 Hz), 4.31 (d, 1H, *J* = 9.2 Hz), 3.92 (br s, 1H), 3.34 (dd, 1H, *J* = 9.7, 2.4 Hz), 3.29 (dd, 1H, *J* = 9.7, 5.1 Hz), 2.70 (d, 1H, *J* = 3.6 Hz), 2.65 (dd, 1H, *J* = 14.6, 7.8 Hz), 2.55 (dd, 1H, *J* = 14.6, 6.6 Hz), 1.57 (s, 3H, –C(C*H*$_3$)$_2$), 1.33 (s, 3H, –C(C*H*$_3$)$_2$) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ 144.0, 138.5, 132.5, 128.7, 128.2, 127.7, 127.3, 126.8, 118.7, 112.6, 103.8, 86.4, 84.5, 82.1, 78.5, 69.0, 67.4, 65.4, 35.8, 26.7, 26.6 ppm. HRMS (ESI): calcd for $C_{38}H_{40}O_6$ $[M+Na]^+$ 615.2723; found $[M+Na]^+$ 615.2723.

4.5. (*R*)-1-((3a*R*,5*R*,6*R*,6a*R*)-6-(Benzyloxy)-6-(2-hydroxy-ethyl)-2,2-dimethyltetrahydrofuro[2,3-*d*][1,3]dioxol-5-yl)-2-(trityloxy)ethanol 16

At first, NMO (0.388 g, 3.29 mmol) and OsO_4 (25 mg/mL solution in *t*BuOH, 0.05 mL, 0.005 mmol) were added to a stirred solution of compound **15** (1.5 g, 2.53 mmol) in acetone/water/*t*BuOH (10 mL, 1:1:0.5) at room temperature. The reaction mixture was stirred for 12 h and then treated with $Na_2S_2O_5$ (0.623 g, 3.29 mmol). The reaction mixture was stirred for a further 30 min and then extracted with ethyl acetate (2×50 mL). The combined organic extracts were washed with water and brine. Evaporation of the organic layer followed by filtration through a short column gave the diol which was taken in MeOH/H_2O (9:1, 15 mL) and cooled to 0 °C. $NaIO_4$ (1.082 g, 5.06 mmol) was added to it and stirred the reaction mixture for 30 min at room temperature. The reaction was quenched by the addition of water and the reaction mixture was concentrated under reduced pressure. The residue obtained was extracted with ethyl acetate (2×50 mL) and the combined organic layers were washed with brine and concentrated. The crude aldehyde was subjected to further reaction. The aldehyde was dissolved in methanol and cooled to 0 °C. Next, $NaBH_4$ (1.082 g, 5.06 mmol) was added and the reaction mixture was stirred for 2 h. The reaction was quenched by the addition of a saturated NH_4Cl solution and the reaction mixture was concentrated under high vacuum to remove the methanol. The aqueous phase was extracted with ethyl acetate and the combined organic extracts were washed with water and brine and dried with anhydrous Na_2SO_4. Purification through column chromatography furnished the pure compound **16** (1.2 g, 80%) as a colorless liquid. R_f = 0.5 (hexane/EtOAc, 1:1). $[\alpha]_D^{25} = +3.8$ (*c* 1.5, CH_2Cl_2). IR (neat) ν_{max}: 3400, 2927, 1073, 1020 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 7.48–7.42 (m, 6H, Ar*H*), 7.38–7.18 (m, 14H, Ar*H*), 5.61 (d, 1H, *J* = 3.6 Hz), 4.78 (s, 2H, –OC*H*$_2$Ph), 4.54 (d, 1H, *J* = 3.6 Hz), 4.40 (d, 1H, *J* = 9.2 Hz), 3.83–3.79 (m, 3H), 3.36–3.29 (m, 2H), 2.80 (br s, 1H, –O*H*), 2.60 (br s, 1H, –O*H*), 2.10–2.03 (m, 1H), 1.89–1.84 (m, 1H), 1.56 (s, 3H, –C(C*H*$_3$)$_2$), 1.33 (s, 3H, –C(C*H*$_3$)$_2$) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ 144.0, 138.6, 128.8, 128.6, 128.4, 128.0, 127.9, 127.6, 127.1, 127.0, 112.9, 103.5, 86.7, 84.7, 83.5, 69.3, 67.6, 65.5, 58.4, 33.5, 26.9, 26.7 ppm. HRMS (ESI): calcd for $C_{37}H_{40}O_7$ $[M+Na]^+$ 619.2672; found $[M+H]^+$ 619.2678.

4.6. (3a*R*,5*R*,6*R*,6a*R*)-6-(Benzyloxy)-5-((*R*)-1-(benzyloxy)-2-(trityloxy)ethyl)-6-(2-benzyloxy)ethyl)-2,2-dimethyltetrahydrofuro[2,3-*d*][1,3]dioxole 17

Diol **16** (1.2 g, 2.0 mmol) was benzylated with NaH (0.192 g, 4.8 mmol) and benzyl bromide (0.57 mL, 4.8 mmol) using general procedure (B) to give **17** (1.50 g, 96%) as a colorless thick liquid. R_f = 0.7 (hexane/EtOAc, 4:1). $[\alpha]_D^{25} = +3.8$ (*c* 1.5, CH_2Cl_2). IR (neat) ν_{max}: 2985, 1077, 1027 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 7.47–7.45 (m, 6H, Ar*H*), 7.30–7.19 (m, 24H, Ar*H*), 5.61 (d, 1H, *J* = 3.1 Hz), 4.78–4.69 (m, 3H), 4.65 (d, 1H, *J* = 3.1 Hz), 4.51 (d, 1H, *J* = 7.0 Hz), 4.46 (d, 1H, *J* = 11.4 Hz, –OC*H*$_2$Ph), 4.34 (s, 2H, –OC*H*$_2$Ph), 3.80 (br s, 1H), 3.65–3.58 (m, 2H), 3.42 (br s, 2H), 2.13–2.09 (m, 1H), 1.90–1.87 (m, 1H), 1.55 (s, 3H, –C(C*H*$_3$)$_2$), 1.30 (s, 3H, –C(C*H*$_3$)$_2$) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ 144.0, 139.1, 138.5, 138.1, 128.7, 128.4, 128.3, 128.0, 127.9, 127.6, 127.5, 127.2, 127.1, 126.8, 112.2, 103.1, 86.5, 83.7, 83.3, 78.0, 72.9, 72.2, 67.0, 65.9, 63.6, 31.7, 26.7, 26.4 ppm. HRMS (ESI): calcd for $C_{51}H_{52}O_7$ $[M+H]^+$ 799.3611; found $[M+H]^+$ 799.3618.

4.7. (*R*)-2-(Benzyloxy)-2-((3a*R*,5*R*,6*R*,6a*R*)-6-(benzyloxy)-6-(2-(benzyloxy)ethyl)-2,2 dimethyltetrahydrofuro-[2,3-*d*][1,3]dioxol-5-yl)ethanol 18

To a stirred solution of compound **17** (1.50 g, 1.93 mmol) in anhydrous methanol (10 mL) was added $HClO_4{\cdot}SiO_2$ (1.5 g) and the reaction mixture was stirred at room temperature for 3 h. The reaction mixture was then filtered, washed with methanol, and then the combined organic extracts were concentrated under vacuum. Purification through silica gel chromatography afforded the pure alcohol **18** (0.950 g, 92%) as a colorless liquid. R_f = 0.5 (hexane/EtOAc, 7:3). $[\alpha]_D^{25} = +40.2$ (*c* 1.0 CH_2Cl_2). IR (neat) ν_{max}: 3440, 2933, 1590, 1166, 1026 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 7.34–7.16 (m, 15H, Ar*H*), 5.69 (d, 1H, *J* = 3.6 Hz), 4.78–4.70 (m, 3H), 4.64–4.56 (ABq, 2H, *J* = 11.4 Hz, –OC*H*$_2$Ph), 4.46 (s, 3H, –OC*H*$_2$Ph), 3.84–3.76 (m, 3H), 3.74–3.65 (m, 2H), 2.46 (br s, 1H), 2.26–2.19 (m, 1H), 2.12–2.07 (m, 1H), 1.55 (s, 3H, –C(C*H*$_3$)$_2$), 1.33 (s, 3H, –C(C*H*$_3$)$_2$) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ 138.2, 137.9, 128.3, 128.2, 128.1, 127.6, 127.6, 127.5, 127.4, 127.3, 112.4, 103.4, 83.9, 82.6, 80.2, 73.0, 72.2, 67.2, 65.9, 61.8, 32.1, 26.7, 26.4 ppm. HRMS (ESI): calcd for $C_{32}H_{38}O_7$ $[M+Na]^+$ 557.2516; $[M+NH_4]^+$ 557.2961 found $[M+Na]^+$ 557.2518; $[M+NH_4]^+$ 557.2968.

4.8. (*R*)-2-(Benzyloxy)-2-((3a*R*,5*R*,6*R*,6a*R*)-6-(benzyloxy)-6-(2-(benzyloxy)ethyl)-2,2-dimethyltetrahydro-furo[2,3-*d*][1,3] dioxol-5-yl)ethyl methanesulfonate 19

Alcohol **18** (0.900 g, 1.68 mmol) was converted into the mesylate following general procedure (C) to give compound **19**

(0.980 g, 95%) as a colorless liquid. R_f = 0.6 (hexane/EtOAc, 7:3). $[\alpha]_D^{25} = +30.2$ (*c* 1.0, CH_2Cl_2). IR (neat) ν_{max}: 2934, 1496, 1357, 1175, 1027 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 7.34–7.17 (m, 15H, Ar*H*), 5.66 (d, 1H, *J* = 3.4 Hz), 4.76–4.68 (m, 4H), 4.58 (dd, 1H, *J* = 11.2, 2.4 Hz), 4.53 (d, 1H, *J* = 11.2 Hz), 4.41 (s, 2H, –OCH_2Ph), 4.38–4.32 (m, 2H), 3.93–3.90 (m, 1H), 3.72–3.68 (m, 1H), 3.67–3.61 (m, 1H), 2.91 (s, 3H, –SO_2CH_3), 2.16–2.11 (m, 1H), 1.98–1.93 (m, 1H), 1.57 (s, 3H, –C(CH_3)$_2$), 1.32 (s, 3H, –C(CH_3)$_2$) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ 138.8, 138.0, 137.4, 128.5, 128.3, 128.2, 127.8, 127.5, 127.3, 112.7, 103.4, 83.8, 83.0, 77.9, 75.4, 73.2, 72.5, 69.7, 67.4, 65.7, 37.8, 32.0, 26.9, 26.5 ppm. HRMS (ESI): calcd for $C_{33}H_{40}O_9S$ $[M+Na]^+$ 635.2291; found $[M+Na]^+$ 635.2293.

4.9. (3a*R*,5*R*,6*R*,6a*R*)-5-((*R*)-2-Azido-1-(benzyloxy)ethyl)-6-(benzyloxy)-6-(2-(benzyloxy)ethyl)-2,2-dimethyltetrahydrofuro[2,3-*d*][1,3]dioxole 20

To a stirred solution of mesylate **19** (0.900 g, 1.46 mmol) in dry DMF (10 mL) was added NaN_3 (6 mmol). This heterogeneous mixture was stirred at 120 °C for 3 h, cooled to room temperature, water (10 mL) was added, and extracted with diethyl ether (3 × 10 mL). The combined organic layer was washed with brine solution and dried over Na_2SO_4. Solvent removal under reduced pressure gave a residue, which upon purification through column chromatography gave azide **20** (0.700 g, 85%) as a viscous liquid. R_f = 0.7 (hexane/EtOAc, 4:1). $[\alpha]_D^{25} = +34.4$ (*c* 1.8, CH_2Cl_2). IR (neat) ν_{max}: 2933, 2101, 1166, 1026 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 7.34–7.16 (m, 15H, Ar*H*), 5.65 (d, 1H, *J* = 3.6 Hz), 4.77–4.66 (m, 4H), 4.55 (d, 1H, *J* = 11.0 Hz), 4.39 (s, 3H), 3.80 (td, 1H, *J* = 6.6, 2.9 Hz), 3.71–3.56 (m, 3H), 3.49 (dd, 1H, *J* = 13.4, 6.0 Hz), 2.18–2.11 (m, 1H), 1.98–1.92 (m, 1H), 1.58 (s, 3H, –C(CH_3)$_2$), 1.32 (s, 3H, –C(CH_3)$_2$) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ 137.1, 136.2, 135.7, 126.6, 126.4, 126.3, 126.1, 125.9, 125.8, 125.6, 125.3, 110.8, 101.4, 81.9, 81.3, 77.0, 74.8, 71.3, 70.7, 65.4, 63.9, 50.1, 30.2, 25.0, 24.7 ppm. HRMS (ESI): calcd for $C_{32}H_{37}N_3O_6$ $[M+Na]^+$ 582.2580; found $[M+H]^+$ 582.2581.

4.10. (2*R*,3*R*,4*R*)-1-Azido-2,4,6-tris(benzyloxy)-4-formylhexan-3-yl formate 21

A solution of azide **20** (0.500 g, 0.89 mmol) in TFA–water (2 mL, 1:1) was stirred for 1 h at room temperature. The reaction mixture was then cooled to 0 °C, diluted with CH_2Cl_2 (5 mL), and quenched by the careful addition of saturated K_2CO_3 solution. This mixture was partitioned and the aqueous phase was extracted with CH_2Cl_2 (20 × 2 mL). The combined organic extracts were washed with water and brine, dried with anhydrous Na_2SO_4, and the solvents were removed. The crude product was dissolved in MeOH/H_2O (9:1, 5 mL) and cooled to 0 °C. Next, $NaIO_4$ (0.285 g, 1.34 mmol) was added and stirred for 8 h at room temperature. Water was added to the reaction mixture and the solvent was evaporated in vacuo. The residue was extracted with ethyl acetate (20 × 2 mL) and the combined organic layers were washed with brine and concentrated. Purification through column chromatography furnished the pure compound **21** (0.406 g, 88%) as a colorless liquid. R_f = 0.7 (hexane/EtOAc, 7:3). $[\alpha]_D^{25} = +13.0$ (*c* 0.4, CH_2Cl_2). IR (neat) ν_{max}: 2923, 2105, 1736, 1595, 1364, 1129, 1025 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 9.38 (s, 1H, –C*H*O), 8.17 (s, 1H, –OC*H*O), 7.41–7.18 (m, 15H, Ar*H*), 5.59 (d, 1H, *J* = 8.7 Hz), 4.77–4.71 (ABq, 2H, *J* = 11.7 Hz, –OCH_2Ph), 4.59–4.51 (ABq, 2H, *J* = 11.0 Hz, –OCH_2Ph), 4.44–4.36 (ABq, 2H, *J* = 11.9 Hz, –OCH_2Ph), 3.81–3.76 (m, 1H), 3.56–3.50 (m, 2H), 3.41 (dd, 1H, *J* = 13.4, 3.1 Hz), 3.14 (dd, 1H, *J* = 13.4, 4.6 Hz), 2.27–2.11 (m, 2H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ 199.5, 159.2, 137.6, 137.5, 136.6, 128.6, 128.5, 128.4, 128.1, 128.0, 127.8, 127.7, 127.1, 83.8, 76.4, 76.2, 73.3, 72.8, 66.0, 64.2, 50.6, 31.1 ppm. HRMS (ESI): calcd for $C_{29}H_{31}N_3O_6$[M+Na]$^+$ 540.2111; found $[M+Na]^+$ 540.2115.

4.11. (2*R*,3*R*,4*R*)-5-Azido-2,4-bis(benzyloxy)-2-(2-(benzyloxy)ethyl) pentane-1,3-diol 22

At first, sodium borohydride (0.015 g, 0.39 mmol) was added to a stirred solution of aldehyde **21** (0.400 g, 0.77 mmol) in methanol (5 mL) and cooled to 0 °C. The reaction mixture was stirred overnight and then quenched by the addition of saturated NH_4Cl solution (2 mL). The reaction mixture was concentrated under high vacuum to remove methanol. The aqueous phase was extracted with ethyl acetate (20 × 2 mL) and the combined organic extracts were washed with water and brine and dried with anhydrous Na_2SO_4. Purification through column chromatography furnished the diol **22** (0.316 g, 83%) as a colorless liquid. R_f = 0.6 (hexane/EtOAc, 7:3). $[\alpha]_D^{25} = +20.0$ (*c* 0.1, CH_2Cl_2). IR (neat) ν_{max}: 3433, 2918, 2100, 1591, 1065, 1027 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ 7.38–7.25 (m, 15H, Ar*H*), 4.68 (d, 1H, *J* = 11.0 Hz, –OCH_2Ph), 4.61–4.56 (ABq, 2H, *J* = 11.0 Hz, –OCH_2Ph), 4.53 (d, 1H, *J* = 11.0 Hz, –OCH_2Ph), 4.51 (s, 2H, –OCH_2Ph), 3.94 (s, 2H), 3.76–3.59 (m, 5H), 3.55 (dd, 1H, *J* = 13.3, 2.7 Hz), 3.18 (br s, 1H), 3.13 (s, 1H), 2.38–2.29 (m, 1H), 2.19–2.05 (m, 1H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ 138.5, 137.3, 137.2, 128.4, 128.1, 127.9, 127.8, 127.5, 127.3, 80.4, 78.1, 73.4, 72.5, 71.9, 65.6, 64.8, 64.6, 50.9, 30.7 ppm. HRMS (ESI): calcd for $C_{28}H_{33}N_3O_5$[M+H]$^+$ 492.2498; found $[M+H]^+$ 492.2495.

4.12. (2*R*,3*R*,4*R*)-1-Azido-2,4,6-tris(benzyloxy)-4-(trityloxymethyl) hexan-3-diol 23

Following the general procedure (A) for the tritylation gave the compound **23** (0.345 g, 77%) as a colorless liquid. R_f = 0.5 (hexane/EtOAc, 9:1). $[\alpha]_D^{25} = +9.0$ (*c* 0.7, CH_2Cl_2). IR (neat) ν_{max}: 3428, 2923, 2100, 1595, 1450, 1056, 1028 cm^{-1}.^1H NMR (500 MHz, $CDCl_3$): δ 7.44–7.38 (m, 10H, Ar*H*), 7.34–7.25 (m, 16H, Ar*H*), 7.20–7.19 (m, 2H, Ar*H*), 7.05–7.03 (m, 2H, Ar*H*), 4.82–4.77 (ABq, 2H, *J* = 11.4 Hz, –OCH_2Ph), 4.44 (d, 1H, *J* = 10.5 Hz, –OCH_2Ph), 4.35–4.29 (ABq, 2H, *J* = 11.9 Hz, –OCH_2Ph), 4.10 (d, 1H, *J* = 10.5 Hz, –OCH_2Ph), 3.79–3.77 (m, 1H,), 3.72–3.69 (m, 1H), 3.60 (dd, 1H, *J* = 13.3, 2.7 Hz), 3.57–3.49 (m, 3H), 3.47 (d, 1H, *J* = 10.5 Hz), 3.39–3.36 (m, 1H), 3.27 (d, 1H, *J* = 10.5 Hz), 2.46–2.41 (m, 1H), 2.39–2.34 (m, 1H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ 143.6, 139.4, 137.9, 137.6, 128.9, 128.6, 128.5, 128.4, 128.1, 127.9, 127.8, 127.7, 127.4, 127.3, 127.2, 87.1, 81.0, 78.8, 73.8, 73.3, 72.0, 66.5, 66.2, 65.1, 51.6, 30.8 ppm. HRMS (ESI): calcd for $C_{47}H_{47}N_3O_5$ $[M+Na]^+$ 756.3414; found $[M+Na]^+$ 756.3414.

4.13. (2*R*,3*R*,4*R*)-1-Azido-2,3,4,6-tetra(benzyloxy)-4-(trityloxymethyl)hexane 24

Following general procedure for benzylation (B) gave the compound **24** (0.325 g, 96.7%) as a colorless liquid. R_f = 0.6 (hexane/EtOAc, 9:1). $[\alpha]_D^{25} = +16.3$ (*c* 1.0, CH_2Cl_2). IR (neat) ν_{max}: 2920, 2099, 1592, 1451, 1088, 1028 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ 7.44–7.42 (m, 6H, Ar*H*), 7.35–7.23 (m, 29H, Ar*H*), 4.88 (d, 1H, *J* = 11.4 Hz, –OCH_2Ph), 4.66–4.57 (m, 3H, –OCH_2Ph), 4.50–4.45 (ABq, 2H, *J* = 11.5 Hz, –OCH_2Ph), 4.36 (s, 2H, –OCH_2Ph), 4.10 (d, 1H, *J* = 2.7 Hz), 3.94–3.93 (m, 1H,), 3.56–3.52 (m, 2H), 3.49–3.40 (m, 3H), 3.19 (d, 1H, *J* = 10.1 Hz), 2.50–2.44 (m, 1H), 2.36–2.30 (m, 1H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ 143.5, 139.2, 138.5, 138.4, 138.1, 129.0, 128.6, 128.5, 128.4, 128.1, 128.0, 127.9, 127.8, 127.7, 127.5, 127.3, 127.2, 87.0, 82.5, 80.5, 80.1, 75.0, 73.1, 72.4, 66.1, 65.6, 64.8, 52.3, 31.1 ppm. HRMS (ESI): calcd for $C_{54}H_{53}N_3O_5$ $[M+Na]^+$ 846.3883; found $[M+Na]^+$ 846.3888.

4.14. (2*R*,3*R*,4*R*)-5-Azido-2,3,4-tris(benzyloxy)-2-(2-(benzyloxy) ethyl)pentan-1-diol 25

Trifluoroacetic acid (0.05 mL, 0.72 mmol) was added dropwise to a solution of compound **24** (0.300 g, 0.36 mmol) cooled to 0 °C, then stirred at the same temperature for 30 min, diluted with CH_2Cl_2 (5 mL), and quenched by the careful addition of saturated K_2CO_3 solution. This mixture was partitioned and the aqueous phase was extracted with CH_2Cl_2 (20 × 2 mL). The combined organic extracts were washed with water and brine, dried with anhydrous Na_2SO_4, and concentrated under reduced pressure. Purification through column chromatography gave alcohol **25** (0.170 g, 80.5%) as a colorless liquid. R_f = 0.6 (hexane/EtOAc, 4:1). $[\alpha]_D^{25} = +12.2$ (*c* 0.5, CH_2Cl_2). IR (neat) ν_{max}: 3442, 2923, 2868, 2099, 1453, 1092, 1066, 1027 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 7.37–7.21 (m, 20H, Ar*H*), 4.84 (d, 1H, *J* = 11.2 Hz, –OC*H*$_2$Ph), 4.65–4.53 (m, 5H, –OC*H*$_2$Ph), 4.47–4.40 (ABq, 2H, *J* = 11.7 Hz, –OC*H*$_2$Ph), 4.02–3.99 (m, 1H), 3.94 (d, 1H, *J* = 2.7 Hz), 3.69–3.68 (br s, 2H), 3.60–3.53 (m, 3H), 3.52–3.47 (m, 1H), 3.19 (br s, 1H), 2.19–2.17 (m, 1H), 2.11–2.08 (m, 1H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ 138.9, 138.2, 137.9, 137.6, 128.7, 128.6, 128.5, 128.1, 128.0, 127.9, 127.5, 127.3, 82.2, 80.6, 79.9, 75.2, 73.5, 72.4, 65.8, 65.3, 64.8, 52.3, 30.9 ppm. HRMS (ESI): calcd for $C_{35}H_{39}N_3O_5$ $[M+H]^+$ 582.2968; found $[M+H]^+$ 582.2966.

4.15. (2*R*,3*R*,4*R*)-5-Azido-2,3,4-tris(benzyloxy)-2-(2-(benzyloxy) ethyl)pentyl methanesulfonate 26

Alcohol **25** (0.150 g, 0.25 mmol) was mesylated following general procedure (C) to give compound **26** (0.165 g, 97%) as a colorless liquid. R_f = 0.5 (hexane/EtOAc, 4:1). $[\alpha]_D^{25} = +11.2$ (*c* 0.9, CH_2Cl_2). IR (neat) ν_{max}: 2918, 2100, 1360, 1177, 1097, 1027 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ 7.35–7.26 (m, 20H, Ar*H*), 4.81 (d, 1H, *J* = 11.4 Hz, –OC*H*$_2$Ph), 4.67–4.60 (m, 4H, –OC*H*$_2$Ph), 4.56 (d, 1H, *J* = 11.0 Hz, –OC*H*$_2$Ph), 4.44 (br s, 2H, –OC*H*$_2$Ph), 4.42–4.36 (ABq, 2H, *J* = 11.0 Hz, –OC*H*$_2$Ph), 4.01 (m, 1H), 3.96 (d, 1H, *J* = 4.1 Hz), 3.67–3.59 (m, 2H), 3.55 (dd, 1H, *J* = 13.7, 2.7 Hz), 3.51 (dd, 1H, *J* = 13.3, 6.4 Hz), 2.71 (s, 3H, –SO_2CH_3), 2.33–2.27 (m, 1H), 2.21–2.15 (m, 1H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ 138.2, 138.0, 137.9, 137.5, 128.6, 128.5, 128.3, 128.1, 128.0, 127.9, 127.7, 127.4, 81.1, 79.4, 79.3, 75.3, 73.3, 72.6, 70.1, 65.7, 65.3, 51.9, 36.9, 30.6 ppm. HRMS (ESI): calcd for $C_{36}H_{41}N_3O_7S$ $[M+H]^+$ 660.2743; found $[M+H]^+$ 660.2742.

4.16. (2*R*,3*R*,4*R*)-2,3,4-Tris(benzyloxy)-2-(2-(benzyloxy)ethyl)-5-(*tert*-butoxycarbonyl-amino)pentyl methanesulfonate 27

To a stirred solution of azide **26** (0.150 g, 0.22 mmol) in THF/H_2O (9:1, 2 mL) was added Ph_3P (0.078 g, 0.3 mmol). The reaction mixture was stirred for 8 h at room temperature. Concentration under reduced pressure afforded the crude amine, which was taken in ethyl acetate (3 mL) and cooled to 0 °C. Next, saturated $NaHCO_3$ solution (2 mL) was added followed by Boc_2O (0.1 mL, 0.44 mmol). The reaction mixture was stirred overnight, after which it was extracted with ethyl acetate, washed with water and brine, and dried over Na_2SO_4. Solvent evaporation followed by purification through column chromatography gave the Boc protected amine **27** (0.134 g, 80.7%) as a colorless liquid. R_f = 0.4 (hexane/EtOAc, 4:1). $[\alpha]_D^{25} = +16.8$ (*c* 0.4, CH_2Cl_2). IR (neat) ν_{max}: 3434, 2931, 1710, 1363, 1176, 1027 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 7.33–7.24 (m, 20H, Ar*H*), 4.84–4.81 (m, 2H, –OC*H*$_2$Ph, –N*H*Boc), 4.66–4.58 (m, 3H), 4.55 (d, 1H, *J* = 11.4 Hz, –OC*H*$_2$Ph), 4.48–4.41 (m, 5H), 3.97 (d, 1H, *J* = 2.7 Hz), 3.89 (m, 1H), 3.67 (m, 2H), 3.54 (m, 1H), 3.37 (m, 1H), 2.72 (s, 3H, –SO_2CH_3), 2.30–2.23 (m, 2H), 1.39 (s, 9H, –C(*CH*$_3$)$_3$) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ 156.0, 138.3, 138.1, 138.0, 128.5, 128.4, 128.3, 128.3, 128.1, 128.0, 127.8, 127.6, 127.4, 81.7, 79.2, 79.1, 78.3, 75.2, 73.3, 71.9, 70.1, 65.2, 41.2, 36.9, 31.1, 28.4 ppm. HRMS (ESI): calcd for $C_{41}H_{51}NO_9S$ $[M+H]^+$ 734.3363; found $[M+H]^+$ 734.3366.

4.17. (3*S*,4*R*,5*R*)-*tert*-Butyl 3,4,5-tris(benzyloxy)-3-(2-(benzyloxy) ethyl)piperidine-1-carboxylate 28

At first, NaH (60% suspension in mineral oil, 0.014 g, 0.34 mmol) was added portionwise to a stirred solution of the mesylate **27** (0.125 g, 0.17 mmol) in THF (5 mL) at 0 °C. The reaction mixture was refluxed for 4 h. Excess NaH was quenched by pouring the reaction mixture into ice and then extracted with ethyl acetate (2 × 15 mL) followed by washing with water and brine solution. The organic layer was dried with anhydrous Na_2SO_4, and concentrated in vacuo. Purification through column chromatography gave piperidine **28** (0.081 g, 75%) as a colorless liquid. R_f = 0.6 (hexane/EtOAc, 4:1). $[\alpha]_D^{25} = -5.0$ (*c* 0.4, CH_2Cl_2). IR (neat) ν_{max}: 2926, 1693, 1495, 1454, 1391, 1050, 1027 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$, rotamer ratio approximately 1:1): δ 7.42–7.32 (m, 40H, Ar*H*), 5.03 (br s, 1H, –OC*H*$_2$Ph), 4.90 (br s, 1H, –OC*H*$_2$Ph), 4.85 (br s, 1H, –OC*H*$_2$Ph), 4.76 (br s, 1H, –OC*H*$_2$Ph), 4.65 (br s, 1H, –OC*H*$_2$Ph), 4.55–4.49 (m, 10H, –OC*H*$_2$Ph), 4.46 (br s, 1H, –OC*H*$_2$Ph), 4.13 (br s, 1H), 4.07 (br s, 1H), 3.99 (br s, 1H), 3.88 (br s, 1H), 3.77 (br s, 4H), 3.72 (br s, 4H), 3.39 (br s, 2H), 3.28 (br s, 2H), 2.08–2.04 (m, 4H), 1.50 (s, 18H, –C(*CH*$_3$)$_3$) ppm. ^{13}C NMR (125 MHz, $CDCl_3$, rotamer ratio approximately 1:1): δ 155.1, 154.9, 139.6, 139.4, 139.0, 138.7, 138.5, 138.2, 128.6, 128.5, 128.4, 128.2, 128.1, 128.0, 127.8, 127.6, 127.4, 127.3, 80.1, 78.8, 78.5, 78.1, 75.0, 74.9, 74.6, 74.4, 73.5, 71.3, 70.9, 65.6, 63.9, 46.5, 45.8, 43.1, 41.8, 31.2, 28.5 ppm. HRMS (ESI): calcd for $C_{40}H_{47}NO_6$ $[M+H]^+$ 638.3481; found $[M+H]^+$ 638.3482.

4.18. (3*S*,4*R*,5*R*)-3-(2-Hydroxyethyl)piperidine-3,4,5-triol 10

A solution of **28** (0.075 g, 0.12 mmol) in methanol (10 mL) was stirred under H_2 (20 psi) in the presence of 20% $Pd(OH)_2/C$ (25 mg) for 12 h. After completion of the reaction, the reaction mixture was filtered through a pad of Celite and the filtrate was concentrated. The residue was dissolved in methanol (1.5 mL), after which was added 6 M aqueous HCl (1.5 mL) and stirred at room temperature for 12 h. The reaction mixture was passed through a Dowex (50X) basic resin column and concentrated under reduced pressure to give piperidine **10** (0.020 g, quantitative yield). R_f = 0.3 (EtOAc/MeOH, 7:3). $[\alpha]_D^{25} = -12.5$ (*c* 0.5, MeOH). ^1H NMR (500 MHz, $CDCl_3$): δ 3.87 (br s, 1H, H-5), 3.61 (t, 2H, *J* = 6.9 Hz, H-8, H-8′), 3.53 (d, 1H, *J* = 2.3 Hz, H-4), 2.95 (d, 1H, *J* = 13.7 Hz, H-6), 2.87 (d, 1H, *J* = 13.7 Hz, H-2), 2.77 (d, 1H, *J* = 13.7 Hz, H-6′), 2.66 (d, 1H, *J* = 13.7 Hz, H-2′), 1.81–1.76 (m, 1H, H-7), 1.71–1.65 (m, 1H, H-7′) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ 72.9, 70.4, 67.9, 56.5, 51.0, 47.6, 37.5 ppm. HRMS (ESI): calcd for $C_7H_{15}NO_4$ $[M+H]^+$ 178.1079; found $[M+H]^+$ 178.1079.

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