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Note

Practical synthesis of (−)-1-amino-1-deoxy-*myo*-inositol from achiral precursors

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Abstract—A new synthesis of enantiomerically pure 1-amino-1-deoxy-*myo*-inositol is reported. The route described employs *p*-benzoquinone, an achiral compound, as the starting material to give conduritol B tetraacetate in three steps. Kinetic resolution of this compound using a palladium catalyst with a chiral ligand allows access to a conduritol B tetraester in high enantiomeric excess. This compound is transformed into tetrabenzyl conduritol B epoxide, which is regioselectively opened with azide to give the key azidocyclitol. Final transformation into (−)-1-amino-1-deoxy-*myo*-inositol hydrochloride is achieved in four synthetic steps. This sequence allows the synthesis of this compound in high enantiomeric purity in a semi-preparative scale.

Keywords: Aminoinositol; Conduritol B; *myo*-Inositol; Aminoconduritol; Enantiomer; Kinetic resolution

Carbohydrates and their derivatives in which one or more hydroxyl groups are replaced by amino functions represent a remarkable class of compounds whose chemistry and biology has received intense scrutiny.[1] Phosphatidylinositol (PI) and phosphorylated inositol derivatives, which are among carbohydrate-related compounds, play a crucial role in biology and are involved in important cell processes.[2] To mention only a few examples, they are involved in the release of Ca^{2+}, and can affect glycosidase activity or display antibiotic activity.[3] The relevance of inositol and their derivatives in cell function and regulation makes them very attractive compounds for research.

The synthesis of molecules in which one or more inositol hydroxyl groups are modified or removed would make possible not only a deeper study of their structure–activity relationships but also more thorough research in the field of aminoglycoside antibiotics.[4] The large number of inositol analogues[3,5–10] reported to date clearly indicates the increasing importance of research activities in this field. Moreover, recent work in our laboratory on aminocyclitol derivatives as glycolipid mimetics has resulted in the discovery of several new glucocerebrosidase enzyme inhibitors.[11,12] In this context, the preparation of 1-amino-1-deoxy-*myo*-inositol (−)-**1** having the natural *myo*-inositol configuration to obtain new analogues for biological assays was necessary.

Two syntheses of this compound have been previously described in the literature. The approach of Iinuma et al.[13] starts with (−)-D-*chiro*-inositol, which is selectively oxidized with O_2 and catalytic platinum black to L-*myo*-inosose,[14] followed by a two-step transformation into amine (−)-**1** via the corresponding oxime; this route gives the product in 15% overall yield from inositol. In an approach published by the Altenbach group,[10] *p*-benzoquinone is transformed into 2,3-dibromocyclohex-5-ene-1,4-diol diacetate, which is subjected to a kinetic resolution in a multigram scale with porcine pancreatic lipase to give a mixture of the corresponding

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1*R*,2*S*,3*S*,4*R*-diol and its enantiomeric 1*S*,2*R*,3*R*,4*S* diacetate. This compound can be separated and purified by crystallization in 26% yield from *p*-benzoquinone over three steps.[15,16] Enantiomerically pure (1*S*,2*R*,3*R*,4*S*)-1,4-diacetoxy-2,3-dibromocyclohex-5-ene is next converted into aminociclitol (−)-**1** in eight steps in 19% overall yield (4.9% yield from *p*-benzoquinone).[10]

Here, we report the synthesis of enantiomerically pure (−)-1-amino-1-deoxy-*myo*-inositol ((−)-**1**) hydrochloride by a new 12-step synthetic sequence in 5% overall yield starting from *p*-benzoquinone. The enantiodiscriminating step of this synthesis involves the resolution of racemic conduritol B tetracetate (±)-**2** using the palladium-catalyzed kinetic resolution previously developed by Trost and Hembre.[17] This catalytic asymmetric reaction is currently used in our group for the preparation of the enantiomers of conduritol B from (±)-**2**.

The proposed retrosynthetic analysis (Scheme 1) involves the regioselective nucleophilic attack of azide nucleophile on epoxide (+)-**6** to give azidoalcohol (+)-**7**, which can be transformed into the desired final compound (−)-**1** after *O*-benzyl deprotection. Preparation of epoxide (+)-**6** would be straightforward by introducing the protecting *O*-benzyl groups in epoxide (+)-**5**, which, in turn, could be obtained from conduritol B (+)-**4** derived from tetraester (+)-**3**. This compound can be obtained enantiomerically pure through the kinetic resolution of conduritol B tetraacetate (±)-**2** using a chiral palladium catalyst, as described by Trost and co-workers.[17,18]

The advantages of this approach are manifold, because (1) it makes possible the synthesis of enantiomerically pure products using achiral starting materials; (2) the compound responsible for the enantiodiscriminating step can be used in catalytic amounts; (3) both enantiomers are available through this approach, and (4) it opens the way to *myo*-inositol analogues by coupling the amino group with different functionalities to obtain new molecules for biological studies, a goal which is currently underway in our research group.

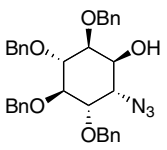
The synthetic sequence started with *p*-benzoquinone, which was converted in three steps into racemic conduritol B tetraacetate (±)-**2** in 90% yield following a reported procedure (Scheme 2).[18,19] When tetraacetate (±)-**2** was subjected to palladium-catalyzed kinetic resolution[18] using chiral diphosphine (*S*,*S*)-**8**, the (+)-enantiomer of **2** was converted to pivalate (+)-**3**, whereas the (−)-**2** enantiomer of the tetraacetate remained unreacted. A slight modification of Trost's original procedure was introduced, which consisted of the in situ preparation of the catalyst precursor, bis(π-allyl)-palladium dichloride, by reacting allyltrimethylsilane and $PdCl_2(CH_3CN)_2$ in acetonitrile.[20] This modification gave, in our hands, more reproducible results by eliminating the problems associated to the manipulation of this sensitive compound.

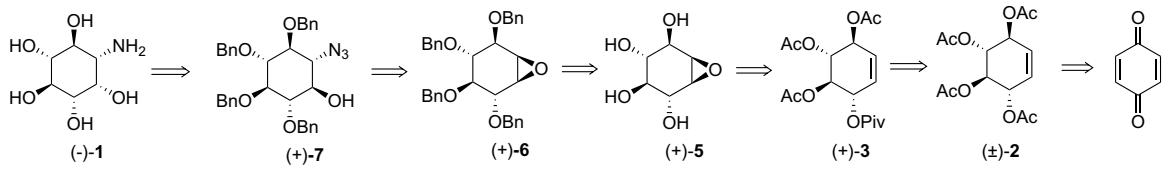
According to Trost et al.,[21] kinetic resolution using this ligand results from the different rates at which the enantiomers of tetraacetate (±)-**2** form the chiral π-allylpalladium complex with chiral diphosphine (*S*,*S*)-**8**, the key intermediate of the transformation, and also from the different reactivity of the allylic pivalate ester compared with the corresponding allylic acetates. In our hands, the reaction worked nicely on a multigram scale and the progress of the reaction could be monitored by HPLC. After chromatographic separation of the product pivalate, (+)-**3** was isolated by column chromatography in 43% yield from unreacted tetraacetate (−)-**2**. The enantiomeric purity of the product was checked by chiral HPLC. The enantiomeric excesses determined for pivalate (+)-**3** and confirmed at a later stage for epoxide (+)-**6** were found to be always higher than 96%.

The transformation of pivalate (+)-**3** into amine (−)-**11** (Scheme 3) was achieved by introducing minor changes to the procedure described by Serrano et al.,[22] which was used to synthesize **11** in racemic form. The sequence initially involved the deprotection of hydroxyl groups in (+)-**3** using Zemplen conditions to give (+)-**4** in 99% isolated yield. Epoxidation of this tetraol with MCPBA afforded (+)-**5** in 88% yield, followed by protection of the hydroxyl groups as benzyl ethers furnishing compound (+)-**6** in 65% isolated yield. Epoxide opening of (+)-**6** with $NaN_3/LiClO_4$ gave the desired regioisomer (+)-**7** in 61% yield.[†]

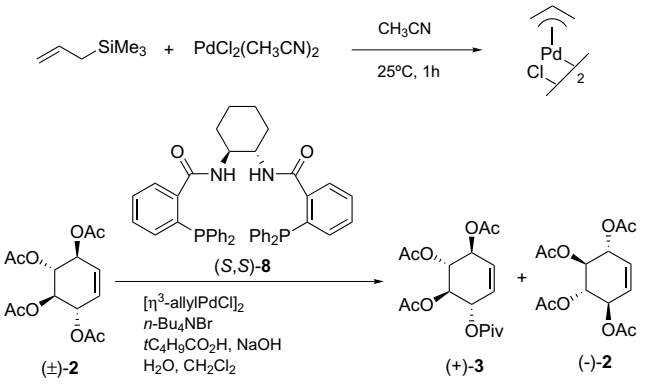
The free hydroxyl group in cyclitol azide (+)-**7** was transformed into its mesylate (+)-**9** in 88% yield and this compound was used to perform the stereochemical inversion to azidocylitol (+)-**10**. Following our previous procedure,[22] the inversion was attempted by heating (+)-**9** in DMF in a sealed tube at 140 °C for prolonged times. Whereas this reaction performed well in some cases, in others we observed a slow transformation, recovering, in part, the unreacted starting mesylate. After conducting different optimization experiments, we discovered that the presence of traces of water in the reaction media was essential for this transformation. This is in contrast with our previous report,[22] where it was claimed that this reaction was independent of the water content. The only explanation found for this apparent contradiction is the working scale. Thus, because our former experiments were carried out at less than 0.2 mmol scale, some adventitious water could have been present in the reaction media, making the

[†] This reaction was accompanied with minor amounts of the regioisomer (below), which could be removed by column chromatography.





Scheme 1. Retrosynthetic analysis of (−)-1-amino-1-deoxy-*myo*-inositol.



Scheme 2. Kinetic resolution of conduritol B tetraacetate.

addition of extra amounts of water unnecessary to accomplish this transformation. In any case, when (+)-**9** was heated in DMF containing 2% water, we were able to isolate (+)-**10** with consistent yields around 70%.

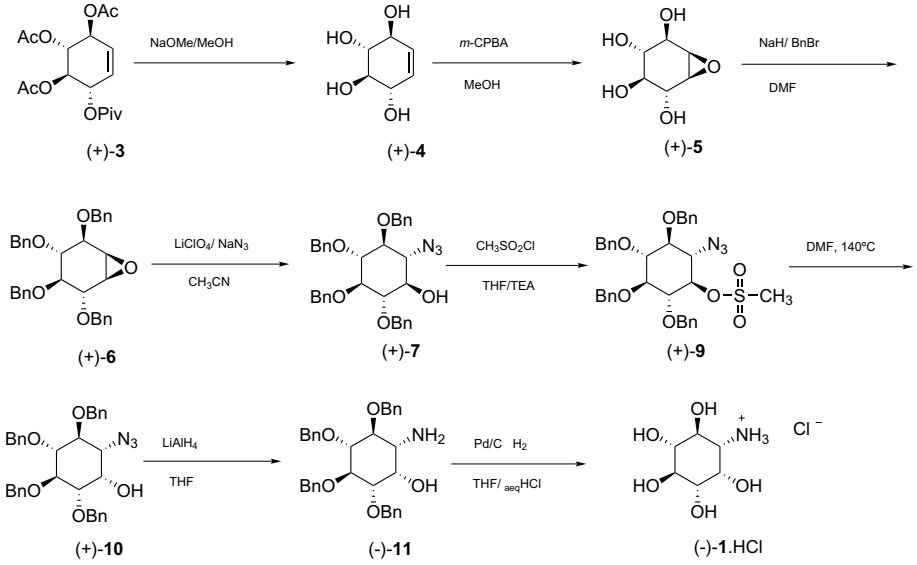
The next step was the reduction of the azido group with $LiAlH_4$ in THF, which proceeded to give the product in 70% isolated yield. Once the tetra-*O*-benzylated amine (−)-**11** was obtained, deprotection of the hydroxyl groups to complete the synthesis of the desired amino inositol analogue (−)-**1** was attempted. Hydrogenolysis using Pd/C at 1 atm in different solvents gave poor results due to the low reactivity of the starting material. However, we finally succeeded in using this catalyst in a mixture of THF and aqueous concentrated HCl (~99:1 v/v) as the solvent under hydrogen pressure (3 atm). Under these conditions, pure hydrochloride (−)-**1** was obtained in 96% isolated yield after a simple filtration of the heterogeneous palladium catalyst (Scheme 3).

In summary, a new procedure for the synthesis of an inositol analogue where the 1-hydroxyl group present in natural *myo*-inositol is replaced with an amino group is reported. This procedure is currently employed in our group to obtain (−)-1-amino-1-deoxy-*myo*-inositol hydrochloride starting from *p*-benzoquinone in semi-preparative scale.

1. Experimental

1.1. General methods

Solvents were distilled prior to use and dried by standard methods. FT-IR spectra are reported in ν, cm^{-1}. ^1H and ^{13}C NMR spectra were obtained in $CDCl_3$, CD_3OD, or D_2O solutions at 500 or 300 MHz (for ^1H) and 125, 100, or 75 MHz (for ^{13}C). Signal assignment was based on 2D NMR experiments (COSY, HMQC). Melting points were uncorrected. Chemical shifts were



Scheme 3. Synthesis of (−)-1-amino-1-deoxy-*myo*-inositol hydrochloride from conduritol B tetraester (+)-**3**.

reported in delta (δ units, parts per million (ppm) relative to the singlet at 7.24 ppm of $CDCl_3$ for ^1H and in ppm relative to the center line of a triplet at 77.0 ppm of $CDCl_3$ for ^{13}C. The ESIMS spectra were recorded on a Waters LCT Premier Mass spectrometer.

1.2. (+)-(1*S*,2*R*,3*R*,4*S*)-1-Pivaloxy-2,3,4-triacetoxy-5-cyclohexene (3)

In a Schlenk flask under nitrogen atmosphere, 198 mg (0.76 mmol) of $PdCl_2(CH_3CN)_2$ was suspended in 10 mL of dry CH_3CN. Allyltrimethylsilane in CH_3CN (0.5 M, 1.52 mL, 0.76 mmol) was added via a syringe and the reaction mixture was stirred at 25 °C for 2 h. The solvent was removed in vacuo and the subsequent kinetic resolution of conduritol B was made assuming that the reaction of the synthesis of (η^3-allyl)-palladium dichloride had been quantitative.

Independently, a mixture of (±)-1,2,3,4-tetra-*O*-acetylconduritol B (±)-**2** (12 g, 38.2 mmol), (*S*,*S*)-ligand **8** (1.57 g, 2.28 mmol), tetrahexylammonium bromide (3.32 g, 7.64 mmol) and pivalic acid (3.12 g, 30.6 mmol) was degassed by evacuating and purging with argon (3×). Under nitrogen, dry CH_2Cl_2 (60 mL) was added and the mixture was stirred until the solution was complete. The liquid was transferred via a canuula to the Schlenk flask containing the catalyst (0.76 mmol) under argon. Finally 40 mL of 0.5 M NaOH, previously degassed, was added via a syringe. The reaction mixture was stirred at 30 °C monitoring the disappearance of (+)-**2** tetraacetate by HPLC (OL244 chiral column, 0.46 × 12.5 cm eluting with 90:10 heptane/isopropanol, 0.7 mL/min); (+)-(1*S*,2*R*,3*R*,4*S*)-1-pivaloxy-2,3,4-triacetoxy-5-cyclohexene $t_R = 4.54$ min, (−)-(1*R*,2*S*,3*S*,4*R*)-1,2,3,4-tetraacetoxy-5-cyclohexene $t_R = 5.67$ min, (+)-(1*S*,2*R*,3*R*,4*S*)-1,2,3,4-tetraacetoxy-5-cyclohexene $t_R = 6.62$ min). When the transformation of (+)-**2** into (+)-**3** was finished (8–12 h are usually required), the reaction mixture was washed with 20% aq K_2CO_3 (60 mL) and the aqueous layer extracted with diethyl ether (2 × 40 mL). The combined organic layers were dried over $MgSO_4$, filtered through a plug of silica to remove the catalyst and concentrated in vacuo to give a white solid (13.1 g). The crude product obtained was filtrated through a plug of silica eluting with hexanes/EtOAc (4:1) to afford pivalate (+)-**3** (5.92 g, 17.3 mmol, 43% yield, ee >96%) and unreacted tetracetate (−)-**2** (5.75 g, 18 mmol, 48% yield, 90% ee). Compound (+)-**3**: mp = 93 °C; (lit.[18] mp = 110 °C); $[\alpha]_D$ +132.0 (*c* 1.1, $CHCl_3$); IR (*v*, film): 2980, 1758, 1369, 1215, 1150, 1032, 964; ^1H NMR (δ, 500 MHz): 1.18 (s, 9H), 2.02 (s, 3H), 2.04 (s, 3H), 2.07 (s, 3H), 5.53–5.41 (m, 2H), 5.55–5.52 (m, 2H), 5.70 (s, 2H); ^{13}C NMR (δ, 125 MHz): 20.5, 20.6, 20.8, 26.8, 26.8, 26.8, 38.7, 70.9, 71.2, 71.2, 71.6, 127.1, 127.6, 169.6, 169.9, 170.2, 177.7; ESIMS: *m*/*z* calcd for $C_{17}H_{24}O_8Na$: 379.1369 $[M+Na]^+$. Found: 379.1367; HPLC: Chiralpak® IA (0.46 × 25 cm) eluting with heptane/^{i}PrOH (90:10), 0.7 mL/min, $\lambda = 254$;nm; t_R (+)-**3** = 7.9 min, t_R (−)-**3** = 8.5 min.

1.3. (+)-(1*S*,2*R*,3*R*,4*S*)-5-Cyclohexene-1,2,3,4-tetraol (4)

Na (35 mg) was dissolved in anhydrous MeOH (180 mL) in a three-necked round bottomed flask under a nitrogen atmosphere. Pivalate (+)-**3** (6.1 g, 17.8 mmol) was added and the reaction mixture was stirred at room temperature for 24 h. After 24 h the solvent was removed in vacuo and the residue was dried on a vacuum pump. The solid was then dissolved in MeOH (80 mL) and neutralized with 1 N HCl. The solvent was removed furnishing product **4** as a white solid (2.78 g; 17.8 mmol, 99%). Mp = 175–177 °C (lit.[23] mp = 172–173); $[\alpha]_D$ +164.5 (*c* 1.1, MeOH); lit.[23] $[\alpha]_D$ +183 (*c* 1.1, MeOH); IR(KBr, *v*): 3294, 2904, 2859, 1458, 1374, 1035; ^1H NMR (δ, 500 MHz): 3.42–3.48 (m, 2H), 4.14–4.20 (m, 2H), 5.61 (s, 2H); ^{13}C NMR (δ, 125 MHz): 70.0, 75.5, 129.2; ESIMS: *m*/*z* calcd for $C_6H_{10}O_4Na$: 169.0478 $[M+Na]^+$. Found: 169.0478.

1.4. (+)-(1*R*,2*R*,3*S*,4*S*,5*R*,6*S*)-2,3,4,5-Tetraol-7-oxabicyclo[4.1.0]heptane (5)

(+)-(1*S*,2*R*,3*R*,4*S*)-5-Cyclohexene-1,2,3,4-tetraol **4** (1.6 g, 11.1 mmol) was dissolved in MeOH (150 mL), MCPBA (10.0 g, 45 mmol) was added and the reaction mixture was stirred at room temperature overnight. The solvent was removed in vacuo and the residue was triturated with CH_2Cl_2 to dissolve excess MCPBA and 3-chlorobenzoic acid. The remaining white solid was washed with CH_2Cl_2 and dried at vacuum to give essentially pure (+)-**5** (1.46 g, 9.8 mmol, 88%). Mp = 155–157 °C (lit.[24] mp = 158–160 °C); $[\alpha]_D$ +57.3 (*c* 0.5, H_2O); lit.[24] $[\alpha]_D$ +66 (*c* 0.6, H_2O); IR (KBr, *v*): 3362, 1408, 1346, 1268, 1101, 1046, 1016, 939, 849, 812, 719; ^1H NMR (δ, 500 MHz): 3.14–3.17 (m, 3H), 3.35–3.36 (m, 1H), 3.66–3.68 (m, 1H), 3.82–3.84 (m, 1H); ^{13}C NMR (δ, 125 MHz): 56.7, 57.4, 70.5, 70.7, 71.5, 74.9; ESIMS: *m*/*z* calcd for $C_6H_{10}O_5Na$: 185.0426 $[M+Na]^+$. Found: 186.0429.

1.5. (+)-(1*S*,2*R*,3*S*,4*S*,5*R*,6*R*)-2,3,4,5-Tetrakisbenzyloxy-7-oxabicyclo[4.1.0]heptane (6)

Sodium hydride (2.4 g, 60% dispersion in mineral oil, 99.9 mmol) was placed in a three-necked round bottomed flask under nitrogen atmosphere and the hydride was washed several times with pentane to remove the mineral oil. In another flask under nitrogen atmosphere, epoxide (+)-**5** (1.8 g, 11.1 mmol) was dissolved in anhydrous DMF (60 mL) and was then transferred via a canuula to the flask containing the hydride. The mixture

was stirred at 30 °C for 30 min, BnBr (13.2 mL, 111 mmol) was then added dropwise and the reaction mixture was stirred at 30 °C overnight. Then the solvent was removed in vacuo, the residue was dissolved in water and the aqueous layer was extracted with diethyl oxide. The organic layer was washed with brine, dried over Na_2SO_4 and concentrated to give a yellow oil (11 g), which was purified by flash chromatography using a mixture of hexane/EtOAc (5:1). Product (+)-**6** was obtained as a white solid (4.0 g, 7.6 mmol, 68%). Mp 103–105 °C (lit.[25] mp 103–105 °C); $[\alpha]_D$ +32.9 (*c* 1.2, $CHCl_3$) (lit.[25] $[\alpha]_D$ +33 (*c* 1.2, $CHCl_3$); IR (film, *v*): 3028, 2867, 1491, 1450, 1370, 1088, 851, 690; ^{1}H NMR (δ, 500 MHz, D_2O): 3.22 (d, $J = 3.9$ Hz, 1H), 3.34–3.35 (m, 1H), 3.48–3.52 (m, 1H), 3.48–3.52 (m, 1H), 3.63–3.66 (m, 1H), 3.91–3.93 (m, 2H), 4.72–4.88 (m, 8H), 7.28–7.42 (m, 20H); ^{13}C NMR (δ, 75 MHz, $CDCl_3$): 53.9, 55.2, 73.0, 73.2, 75.5, 75.9, 79.0, 79.2, 79.3, 83.4, 127.5–128.5, 137.6, 138.2, 138.5, 138.5; ESIMS: *m*/*z* calcd for $C_{34}H_{35}O_5$: 523.2484 $[M+H]^+$. Found: 523.2489; HPLC: Chiralpak® IA (0.46 × 25 cm) eluting with heptane/^{i}PrOH (90:10), 0.7 mL/min, $\lambda = 254$ nm; t_R (+)-**6** = 17.2 min, t_R (−)-**6** = 16.1 min.

1.6. (+)-(1*R*,2*R*,3*S*,4*R*,5*R*,6*S*)-2-Azido-3,4,5,6-tetrakis-benzyloxycyclohexanol (7)

A 2 N solution of $LiClO_4$ in anhydrous CH_3CN (150 mL) was added dropwise under nitrogen to the starting epoxide (+)-**6** (5.0 g, 9.57 mmol). NaN_3 (6.2 g, 95.7 mmol) was added next and the reaction mixture was stirred at reflux. After 24 h the mixture was cooled to 0 °C, quenched by the addition of water (150 mL) and extracted with CH_2Cl_2 (3 × 100 mL). The combined organic layers were washed with brine, dried over Na_2SO_4, and concentrated to give a brown oil. Azidoalcohol (+)-**7** (5.8 g, 5.8 mmol, 61%) was isolated as a white solid after flash column chromatography on silica eluting with hexane/EtOAc (6:1). Mp = 91–93 °C; $[\alpha]_D$ +15 (*c* 1.0, $CHCl_3$); IR (film, *v*): 3344, 2907, 2108, 1455, 1359, 1133, 1058, 739, 697; ^{1}H NMR (δ, 500 MHz, $CDCl_3$): 2.61 (br s, 1H), 3.42–3.47 (m, 4H), 3.54–3.58 (m, 1H), 3.62–3.65 (m, 1H), 4.79–4.98 (m, 8H), 7.33–7.38 (m, 5H); ^{13}C NMR (δ, 100 MHz, $CDCl_3$): 66.5, 72.8, 75.8, 76.0, 76.0, 76.0, 81.2, 82.6, 82.8, 83.6, 127.8–128.8, 137.8, 138.2, 138.2, 138.3; ESIMS: *m*/*z* calcd for $C_{34}H_{35}N_3O_5Na$: 588.2474 $[M+Na]^+$. Found: 588.2489.

1.7. (+)-(1*R*,2*S*,3*S*,4*R*,5*S*,6*R*)-(2-Azido-3,4,5,6-tetrakis-benzyloxy)cyclohexyl methanesulfonate (9)

MsCl (0.43 mL, 4.29 mmol) was added over a solution of azidoalcohol (+)-**7** (2.2 g, 3.9 mmol) in anhydrous THF (40 mL) and TEA (1.7 mL) under nitrogen atmosphere. The mixture was stirred at room temperature, after 26 h the solvent was removed in vacuo, the residue was taken in Et_2O (40 mL), filtered and the solid was washed several times with Et_2O. The filtrate and washings were concentrated to give the crude azidomesilate, which was purified by chromatography on silica eluting with hexane/EtOAc (5.5:1) to afford compound (+)-**9** as a colorless oil (2.2 g, 3.2 mmol, 81%). $[\alpha]_D$ +27.3 (*c* 1, $CHCl_3$); IR (film, *v*, cm^{-1}): 2928, 2856, 2111, 1456, 1358, 1177, 1063, 953, 821, 742, 698; ^{1}H NMR (δ, 500 MHz, $CDCl_3$): 3.06 (s, 3H), 3.49 (t, $J = 9.3$ Hz, 1H), 3.57–3.66 (m, 4H), 4.45 (t, $J = 9.7$ Hz, 1H), 4.85–4.94 (m, 8H), 7.28–7.38 (m, 5H); ^{13}C NMR (δ, 100 MHz, $CDCl_3$): 39.2, 64.6, 75.8, 75.9, 76.0, 76.1, 80.2, 80.6, 80.7, 82.0, 82.9; ESIMS: *m*/*z* calcd for $C_{35}H_{37}O_7NaS$: 666.2250 $[M+Na]^+$. Found: 666.2250.

1.8. (+)-(1*S*,2*R*,3*S*,4*R*,5*R*,6*S*)-2-Azido-3,4,5,6-tetrakis-benzyloxycyclohexanol (10)

Mesylate (+)-**9** (6.1 g, 9.5 mmol) was treated with DMF (75 mL) and water (1.5 mL) in a sealed tube at 140 °C for 96 h. The solvent was then removed in vacuo to give a brown oil that was purified by silica column chromatography eluting with hexane/EtOAc (6:1). Azidoalcohol (+)-**10** was obtained as a white solid (3.6 g, 6.5 mmol, 68%). Mp = 111–114 °C; $[\alpha]_D$ +19.5 (*c* 1, $CHCl_3$); IR (film, *v*): 3030, 3007, 2103, 1494, 1453, 1358, 1067, 736, 697; ^{1}H NMR (δ, 500 MHz, $CDCl_3$): 2.51 (br s, 1H), 3.35–3.37 (dd, 1H, $J = 9.5$, 2.4 Hz), 3.47–3.49 (dd, 1H, $J = 9.5$, 2.4 Hz), 3.54 (t, 1H, $J = 9.5$ Hz), 3.96 (t, 1H, $J = 9.5$ Hz), 4.03 (t, 1H, $J = 9.8$ Hz), 4.20 (t, 1H, $J = 2.4$ Hz), 4.70–4.94 (m, 8H), 7.31–7.37 (m, 5H); ^{13}C NMR (δ, 100 MHz, $CDCl_3$): 61.7, 68.1, 72.8, 76.1, 76.2, 76.2, 78.7, 80.6, 81.4, 83.8, 127.9–128.6, 137.2, 137.7, 138.3, 138.4, 159.9; ESIMS: *m*/*z* calcd for $C_{34}H_{35}N_3O_5Na$: 588.2474 $[M+Na]^+$. Found: 588.2499.

1.9. (−)-(1*S*,2*R*,3*S*,4*R*,5*R*,6*S*)-2-Amino-3,4,5,6-tetra-kisbenzyloxycyclohexanol (11)

A solution of azidoalcohol (+)-**10** (3.5 g, 6.2 mmol) in anhydrous THF (80 mL) was added dropwise under nitrogen over a solution of $LiAlH_4$ (470 mg, 12 mmol) in anhydrous THF (50 mL) at 0 °C. After stirring for 90 min at this temperature, the reaction was quenched by adding EtOAc (10 mL) and, 5 min later, water (10 mL). The solvent was then removed in vacuo and the residue was suspended in water. The aqueous layer was extracted with CH_2Cl_2 (3 × 100 mL) and the combined organic layers were washed with brine, dried over Na_2SO_4, and concentrated to give the crude aminoalcohol that was purified by silica flash chromatography. Elution with CH_2Cl_2–MeOH–TEA (99:1:0.7) afforded pure aminoalcohol (−)-**11** as a white solid (2.32 g, 4,3 mmol, 70%). Mp = 158–161 °C; $[\alpha]_D$ −21.5 (*c* 1,

$CHCl_3$); IR (film, ν): 3030, 2923, 1453, 1357, 1074, 734, 696; ^{1}H NMR (δ, 500 MHz, $CDCl_3$): 2.14 (br s, 1H), 2.62–2.66 (m, 1H), 3.48 (dd, 1H, $J = 9.5$, 2.5 Hz), 3.51 (t, 1H, $J = 9.5$ Hz), 3.63 (t, 1H, $J = 9.5$ Hz), 3.98 (t, 1H, $J = 9.5$ Hz), 4.11 (t, 1H, $J = 2.5$ Hz), 4.65–5.03 (m, 8H), 7.30–7.37 (m, 20H); ^{13}C NMR (δ, 75 MHz, $CDCl_3$): 53.8, 69.4, 72.6, 75.6, 75.7, 75.8, 81.4, 81.9, 82.1, 84.7, 127.5–128.5, 137.9, 138.5, 138.6, 138.7; ESIMS: m/z calcd for $C_{34}H_{38}NO_5$: 540.2750 $[M+H]^+$. Found: 540.2748.

1.10. (−)-1-Amino-1-deoxy-*myo*-inositol hydrochloride (1)

In a glass pressure flask, aminoalcohol (−)-**11** (800 mg, 1.5 mmol) was dissolved in a mixture of THF (45 mL) and concentrated HCl (0.5 mL). Pd/C (600 mg, 5–10% Pd on activated C, water-wet) was then added. The flask was repeatedly filled and evacuated with hydrogen and vigorously stirred at room temperature for 24 h under H_2 (3 atm). After this period, the reaction mixture was filtered through a plug of Celite to separate the catalyst, and the filter was washed three times with THF/MeOH (1:1). The filtrate and combined washings were concentrated to give compound (−)-**1** as hydrochloride salt (301 mg, 1.4 mmol, 94%). Mp = 188–190 (dec); $[\alpha]_D$ −4.3 (c 0.4, H_2O); IR (KBr, ν): 3380, 3061, 2906, 2470, 1570, 1495, 1123, 1034, 709; ^{1}H NMR (δ, 500 MHz, D_2O): 3.27 (dd, 1H, $J = 10.7$ Hz, $J =$ 2.4 Hz), 3.32 (t, 1H, $J = 9.3$ Hz), 3.55 (d, 1H, $J = 9.8$ Hz, $J = 2.9$ Hz), 3.60 (t, 1H, $J =$ 9.5 Hz), 3.71 (t, 1H, $J = 10.0$ Hz), 4.16 (t, 1H, $J = 2.6$ Hz); ^{13}C NMR (125 MHz, D_2O): 53.7, 68.5, 69.3, 71.6, 72.0, 74.7; Calcd elemental analysis for $C_6H_{14}ClNO_5$: C, 33.42; H, 6.54; Cl, 16.44; N, 6.50. Found: C, 33.21; H, 6.79; Cl, 16.20; N, 6.26; ESIMS: m/z calcd for $C_6H_{14}NO_5$: 180.0872 $[M+H]^+$. Found: 180.0866.

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