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Asymmetric Synthesis of Nabscessin A from Inositol and D-Camphor

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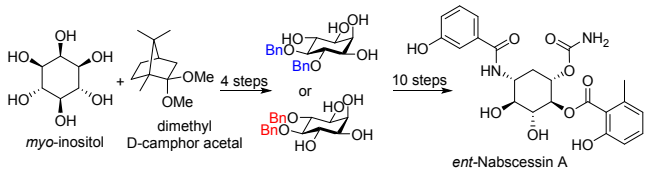


ABSTRACT. Enantiomer of nabscessin A (**1**), an aminocyclitol amide with antimicrobial activity, was synthesized from *myo*-inositol and dimethyl D-camphor acetal in 14 steps. Formal synthesis of natural nabscessin A was also achieved through the new approach to access both enantiomers of 4,5-di-*O*-benzyl-*myo*-inositol, derived from the same set of starting materials. This synthesis features utilizations of the existing framework of *myo*-inositol and a regioselective esterification.

Introduction

Nabscessins A-C are a family of aminocyclitol amides recently isolated from metabolites of a pathogenic actinomycete, *Nocardia abscessus* IFM 10029^T (Figure 1).[1-2] Preliminary study on

nabscessins A and B showed that they possess antimicrobial activity against *Cryptococcus neoformans*.[1] These compounds are structural isomers and only differ in the linkage of the 2-hydroxy-6-methylbenzoyl group to the aminocyclitol, 2-deoxy-*scyllo*-inosamine (DOIA), which is also present in a group of aminoglycoside antibiotics, inosamycins.[3-4] DOIA is also the biosynthetic precursor to 2-deoxystreptamine (DOS),[5-6] the aglycon of related and clinically important antibiotics, including gentamicin, kanamycin and neomycin, etc.[7-13]

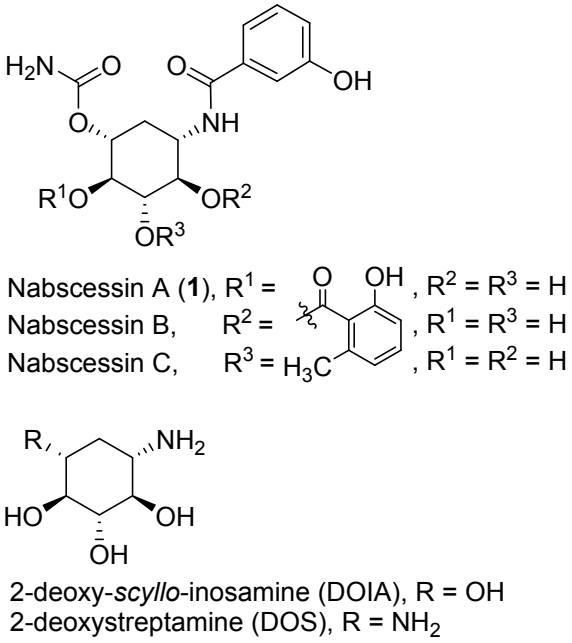


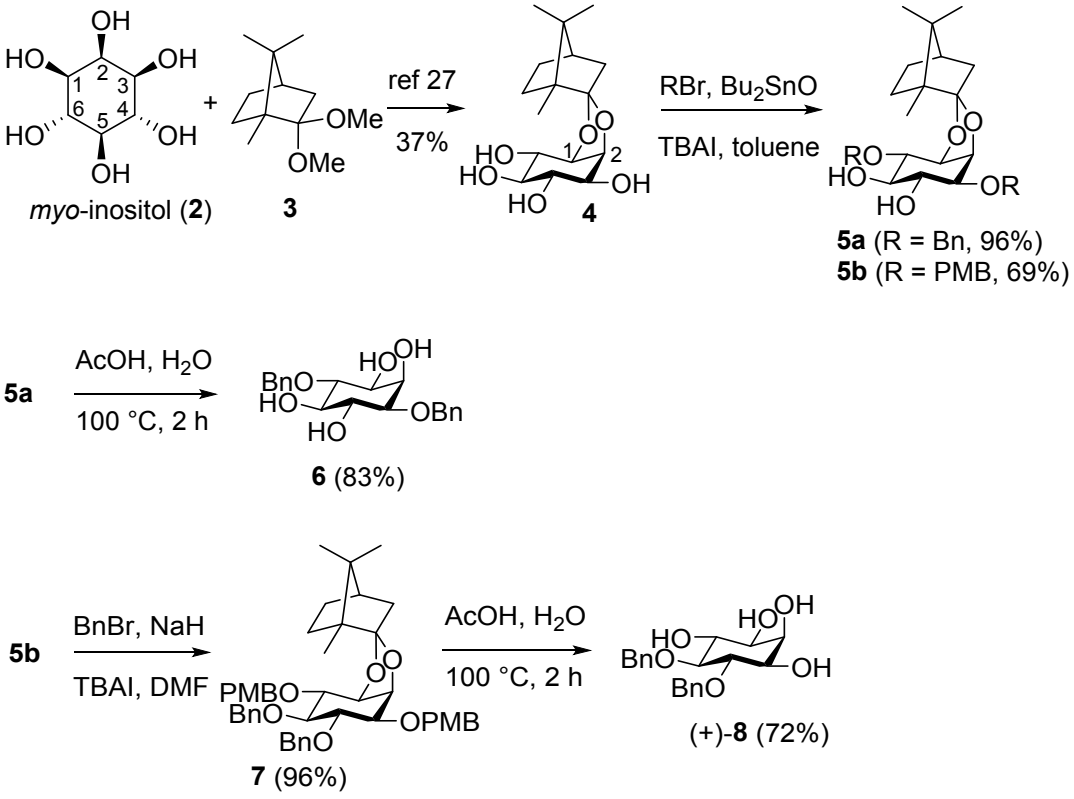
Figure 1. Structures of nabscessins A-C and aminocyclitols.

Thus, synthesis and functional group transformations of 2-deoxy-*scyllo*-inosamine are essential to prepare nabscessins. In this regard, the six-membered carbocycle of DOIA and its derivatives were either adopted from natural materials[14-19] or constructed by chemical methods,[20-21] such as ring-closing metathesis (RCM).[22-23] For example, Banwell's group reported synthesis of nabscessin B, in which the key carbocycle, 1,2-diacetal-γ-hydroxy-cyclohexenone, was derived from L-tartaric acid in six steps and 14 more steps were required to achieve nabscessin B.[23] Here, we report our approach to access nabscessin A *via* inexpensive, natural D-camphor and

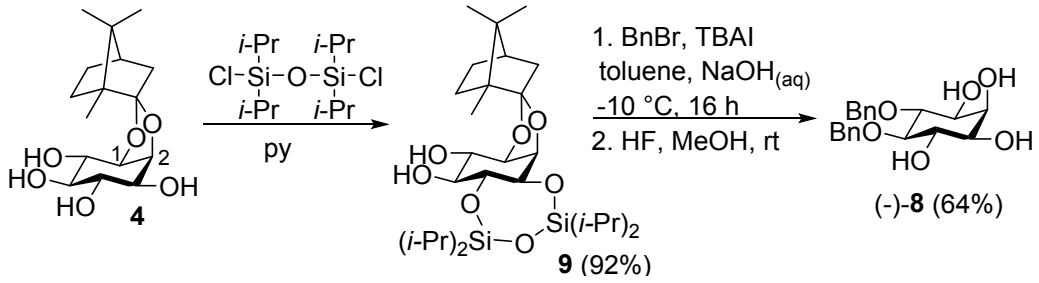
myo-inositol (**2**), the most abundant cyclitol occurring in nature.[24-26] In addition to saving effort to form the carbocycle by using **2**, this pair of starting materials also makes it possible to prepare both enantiomers of nabscessin A.

Results and discussion

Desymmetrization of meso *myo*-inositol was achieved with dimethyl D-camphor acetal (**3**) to give 1,2-camphor acetal **4** according to the procedures reported by Bruzik's and Konradsson's groups (Scheme 1).[27-28] The obtained compound **4**, collected from recrystallization, was diastereomerically pure (see ^{1}H and ^{13}C NMR in Supporting Information) and applied in the following synthesis. We were glad to find that the reaction of compound **4**, dibutyltin oxide and benzyl/4-methoxybenzyl bromides provided di-benzylated compounds **5a/5b**. The regiochemistry of the dibenzylation reactions was established by hydrolyzing the 1,2-camphor acetal of **5a** to yield the known L-3,6-Di-*O*-benzyl-*myo*-inositol (**6**).[29] The regioselectivity observed here is the same as that noticed in the corresponding reaction of 1,2-acetonide protected *myo*-inositol.[30] Further benzylations of **5b** and acid hydrolysis to remove the camphor acetal and PMB groups afforded (+)-4,5-di-*O*-benzyl-*myo*-inositol **8**, which was prepared asymmetrically for the first time.[31] On the other hand, the enantiomer (-)-**8** was also synthesized from **4** through the following sequence: protection of the two hydroxyl groups at C-3 and C-4 to form the known silyl ether **9**,[28] dibenzylations under a phase-transfer condition[32] and following hydrolysis (Scheme 2). The phase-transfer condition and low temperature (-10 °C) were required to keep the silyl-protecting group intact during the dibenzylations.



Scheme 1. Synthesis of (+)-4,5-di-*O*-benzyl-*myo*-inositol (**8**).



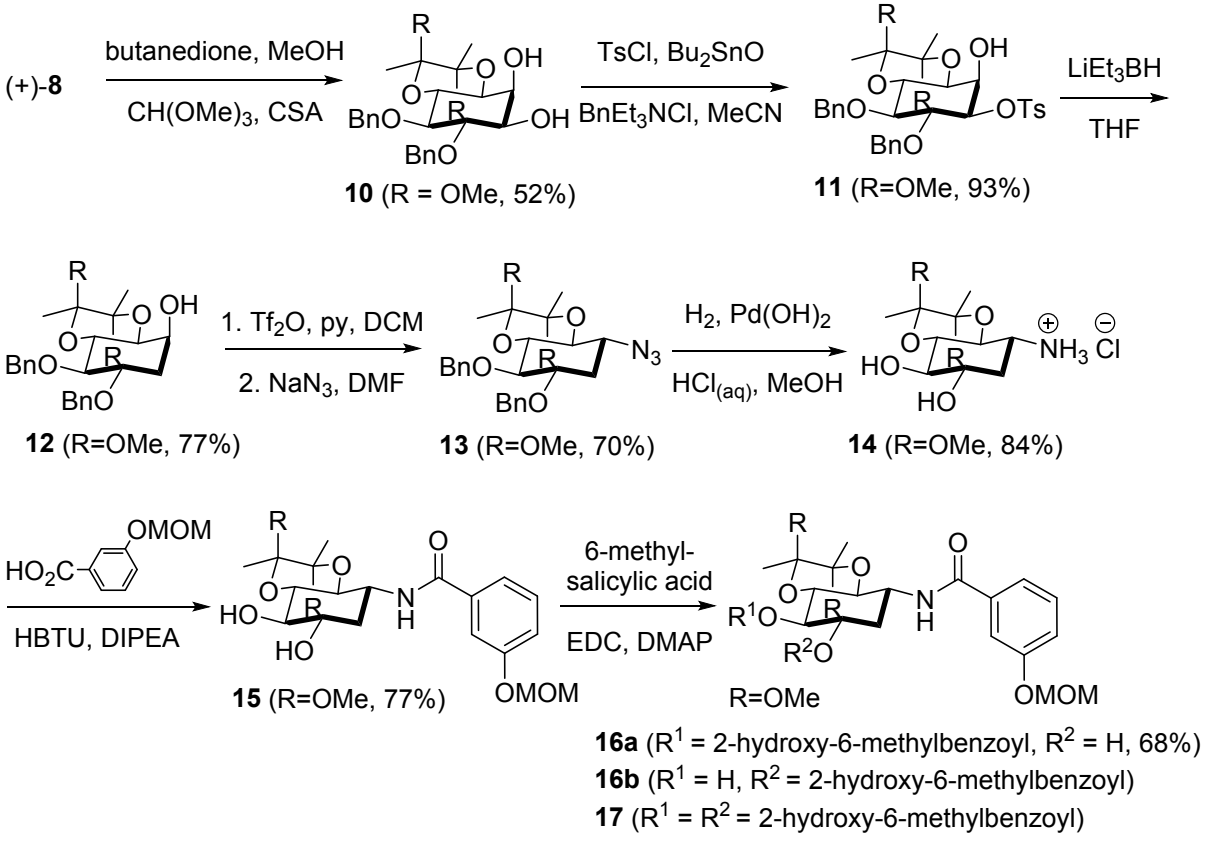
Scheme 2. Synthesis of (-)-4,5-di-*O*-benzyl-*myo*-inositol (**8**).

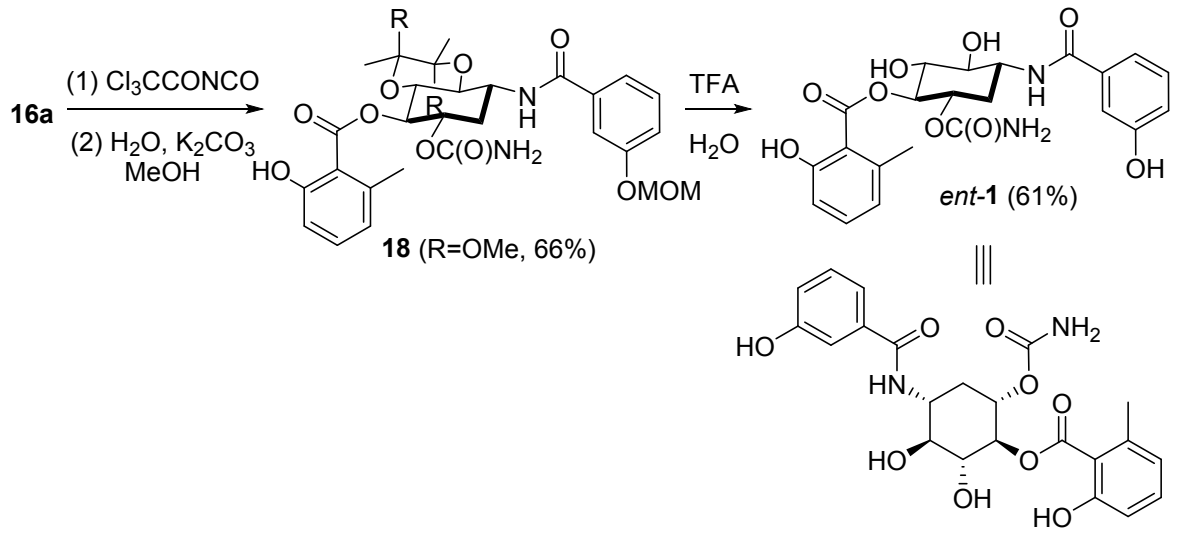
Compound (+)-**8** was chosen to continue the synthesis because its preparation is more efficient and convenient than that of (-)-**8**. The vicinal, *trans*-diol of (+)-**8** was protected by butanedione to yield diacetal **10**.[33] The stereoselective deoxygenation of *myo*-inositol monotosylates, developed by Yu and Spencer,[34] was applied to convert **10** to tosylate **11** and the following reduction with lithium triethylborohydride to yield deoxy-inositol **12**. The axial hydroxyl group

was transformed to a triflate and replaced with an azido group to form **13** in 70% yield over the two steps. Palladium catalyzed hydrogenation and hydrogenolysis of azide **13** generated amino-diol **14**, which was coupled with 3-(methoxymethoxy)benzoic acid to form amide **15**, assisted by *N,N,N',N'*-tetramethyl-*O*-(1*H*-benzotriazol-1-yl)uronium hexafluorophosphate (HBTU) and *N,N*-diisopropylethylamine (DIPEA). The selective esterification between **15** and 6-methylsalicyclic acid by various carbodiimides was critical (Table 1).[35-37] Mixtures of monoesters **16a**, **16b** and diester **17** were produced by DCC and DIC (entries 1 and 2, Table 1). To identify regioisomers **16a** and **16b**, the two compounds were separated by column chromatography and analyzed by NMR. The proton of the *O*-methine (C*H*-OR^2) was resolved according to its adjacent couplings to the methylene group, but no coupling with the amide proton, in their respective ^{1}H-^{1}H COSY spectrum (Supporting Information). The compound with a more downfielded C*H*-OR^2 (δ 5.23 *versus* 3.63) was assigned as **16b** for its attachment to the acyl group. We found that the *N*-(3-(dimethylamino)propyl)-*N'*-ethylcarbodiimide (EDC) or its hydrochloride salt provided the product free of **16b**, and 68% yield of **16a** was harvested when the reaction was conducted at 10 °C for 48 h (entry 3–5, Table 1). All the screened carbodiimides providing **16a** as the major product indicated that the hydroxyl group neighboring to the diacetals of **15** is more reactive in the esterification. This may be attributed to the hydrogen-bonding interaction between diacetals and carbodiimide-activated 6-methylsalicylic acid. The dimethylamino group of EDC, which should be protonated during the reaction, increased the interaction to give a better selectivity. This conjecture is supported by the result that the regioselectivity imposed by EDC diminished when a base, DBU, was added to trap protons (entry 6). A carbamate group was then installed by the addition of 2,2,2-trichloroacetyl isocyanate to **16a** and treatment of potassium carbonate in

methanol to yield **18**.[38] Removal of the diacetals and methoxymethyl group with aqueous trifluoroacetic acid (TFA) gave *ent*-nabscessin A (*ent*-**1**) in 61% yield.

The NMR and mass spectroscopic data of *ent*-**1** were consistent with the reported natural nabscessin A, and the specific rotation of synthetic *ent*-**1** was opposite to that of reported, natural nabscessin A, $[\alpha]_D$ +10.7 (*c* 0.13, MeOH) and −10.8 (*c* 1.0, MeOH), respectively.[1] With our access to both enantiomerically pure building blocks (+)-**8** and (-)-**8** (Scheme 1 and 2), the procedure shown in Scheme 3 is also applicable to prepare natural nabscessin A. Therefore, nabscessin A was synthesized for the first time in 14 steps.





Scheme 3. Synthesis of *ent*-nabscessin A.

Table 1. Regioselective esterification of **15**.[a]

entry	coupling reagent	yield of esters (%)[b]		
		16a	**16b**	**17**
1	DCC	50	33	6
2	DIC	49	30	8
3	EDC	51	-	12
4	EDC · HCl	58	-	12
5[c]	EDC	68	-	9
6[d]	EDC	33	16	31

[a]Reaction condition: **15** (1.0 equiv), 6-methylsalicyclic acid (1.2 equiv) and coupling reagent (1.5 equiv) in CH_2Cl_2, rt, 16 h. [b]Isolated yields. [c]10 °C, 48 h. [d]Adding DBU (3.0 equiv).
DCC = *N,N*'-dicyclohexyl-carbodiimide, DIC = *N,N*'-diisopropyl-carbodiimide, EDC = *N*-(3-dimethylaminopropyl)-*N'*-ethylcarbodiimide, DBU = 1,8-diazabicyclo[5.4.0]undec-7-ene.

In summary, we report an asymmetric synthesis of nabscessin A, where we utilized the carbocycle of *myo*-inositol, natural camphor to achieve desymmetrization and prepare both

enantiomers of key intermediate **8,** and a regioselective esterification. The chemistry of inositol accumulated by previous researchers was also essential in utilizing the oxygenated carbocycle. This approach should be applicable to prepare other aminocyclitol-related natural products.

Experimental Section

General information: Dichloromethane and toluene were dried over calcium hydride and distilled prior to use. Tetrahydrofuran and diethyl ether were dried over sodium, monitored with benzophenone ketyl radicals and distilled prior to use. DMF was dried over molecular sieves (3 Å). TLC was conducted using pre-coated silica gel 60 F_{254} plates containing a fluorescent indicator; purification by chromatography was conducted using silica gel (230–400 mesh). Chemical shifts for ^{1}H-NMR and $^{13}C\{^{1}H\}$ NMR spectra are reported in δ units (parts per million) with reference to residual solvent peaks. All spectra were obtained at 25 °C. The multiplicities are abbreviated as follows: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, dd = doublet of doublets, td = triplet of doublets. High-resolution mass spectrometry (HRMS) data were recorded on a JMS-700 quadrupole mass spectrometer. D-camphor *myo*-inositol acetal (**4**) was prepared according to the literature procedure.[27]

(1'*R*,2*R*,3a*R*,4*S*,4'*R*,5*R*,6*R*,7*S*,7a*S*)-4,7-Bis(benzyloxy)-1',7',7'-trimethylhexahydrospiro[benzo[d][1,3]dioxole-2,2'-bicyclo[2.2.1]heptane]-5,6-diol (**5a**). A reaction flask containing compound **4** (408.2 mg, 1.30 mmol), dibutyltin oxide (808.1 mg, 3.25 mmol), methanol (2.5 mL) and toluene (2.6 mL) was heated to reflux for 3 h in an oil bath (130 °C). The reaction mixture was concentrated, added with toluene (10 mL) and concentrated under a vacuum for 1 h to remove the solvents. The residue was diluted with toluene (5.1 mL), added with benzyl bromide (340 μL, 488.6 mg, 2.86 mmol) and tetrabutylammonium iodide (527.6 mg, 1.43 mmol), and heated to reflux for another 16 h in an oil bath (130 °C). The solvent was removed under a vacuum, and the crude product was purified with column chromatography (SiO_2, EtOAc/hexanes, 1:1, R_f 0.38) to give **5a** as a light-yellow liquid (618.3 mg, 1.25 mmol,

96%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.38–7.25 (m, 10H), 4.95 (d, *J* = 11.5 Hz, 1H), 4.73–4.64 (m, 3H), 4.31 (t, *J* = 5.0 Hz, 1H), 3.96 (t, *J* = 6.0 Hz, 1H), 3.85 (t, *J* = 9.5 Hz, 1H), 3.56 (dd, *J* = 9.5 Hz, *J* = 4.5 Hz, 1H), 3.47–3.37 (m, 2H), 2.81 (br, 1H), 2.76 (br, 1H), 1.96–1.91 (m, 1H), 1.89–1.85 (m, 1H), 1.74–1.69 (m, 2H), 1.46 (d, *J* = 13.0 Hz, 1H), 1.41–1.35 (m, 1H), 1.25–1.20 (m, 1H), 1.04 (s, 3H), 0.86 (s, 3H), 0.79 (s, 3H); $^{13}C\{^1H\}$ NMR ($CDCl_3$, 126 MHz) δ 138.3, 137.9, 128.53, 128.46, 128.1, 128.0, 127.9, 127.8, 118.1, 83.1, 77.5, 73.4, 73.2, 72.8, 71.7, 71.2, 51.6, 48.1, 45.3, 45.2, 29.7, 27.1, 20.5, 10.0; $[\alpha]_D^{20}$ -18.3 (*c* 1.1, $CHCl_3$); HRMS-ESI m/z calcd for $[M+H]^+$ ($C_{30}H_{39}O_6$) 495.2741, found 495.2722.

(1'*R*,2*R*,3a*R*,4*S*,4'*R*,5*R*,6*R*,7*S*,7a*S*)-4,7-Bis((4-methoxybenzyl)oxy)-1',7',7'-trimethylhexahydrospiro[benzo[d][1,3]dioxole-2,2'-bicyclo[2.2.1]heptane]-5,6-diol (5b). A reaction flask containing compound **4** (1.20 g, 3.82 mmol), dibutyltin oxide (2.38 g, 9.54 mmol), methanol (7.5 mL) and toluene (7.5 mL) was heated to reflux for 3 h in an oil bath (130 °C). The reaction mixture was concentrated, diluted with toluene (15 mL) and concentrated under a vacuum for 1 h to remove the solvents. The residue was diluted with toluene (15 mL), added with 4-methoxybenzyl bromide (1.69 g, 8.40 mmol) and tetrabutylammonium iodide (1.55 g, 4.21 mmol), and heated to reflux for another 16 h in an oil bath (130 °C). The solvent was removed under a vacuum, and the crude product was purified with column chromatography (SiO_2, EtOAc/hexanes, 1:1, R_f 0.33) to give **5b** as a light-yellow liquid (1.46 g, 2.64 mmol, 69%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.28–7.26 (m, 4H); 6.86 (d, *J* = 8.5 Hz, 4H), 4.87 (d, *J* = 11.5 Hz, 1H), 4.65 (d, *J* = 11.5 Hz, 1H), 4.55 (d, *J* = 11.0 Hz, 1H), 4.57 (d, *J* = 11.0 Hz, 1H), 4.30 (t, *J* = 5.0 Hz, 1H), 3.93 (t, *J* = 6.5 Hz, 1H), 3.81 (t, *J* = 9.5 Hz, 1H), 3.78 (s, 3H), 3.77 (s, 3H), 3.53 (dd, *J* = 9.5 Hz, *J* = 5.0 Hz, 1H), 3.42 (dd, *J* = 9.5 Hz, *J* = 6.5 Hz, 1H), 3.36 (t, *J* = 10.0 Hz, 1H), 2.74 (br, 1H), 2.68 (br, 1H), 1.96–1.92 (m, 1H), 1.89–1.85 (m, 1H), 1.74–1.72 (m, 2H), 1.47 (d, *J* = 13.0 Hz, 1H), 1.41–1.36 (m, 1H), 1.25–1.20 (m, 1H), 1.04 (s, 3H), 0.85 (s, 3H), 0.80 (s, 3H); $^{13}C\{^1H\}$ NMR ($CDCl_3$, 126 MHz) δ 159.5, 159.3, 130.5, 129.9, 129.7, 129.5, 118.0, 114.0, 113.9, 82.9, 77.1, 76.4, 73.3, 72.9, 72.8, 71.22, 71.18, 55.3, 51.6, 48.1, 45.3, 45.2, 29.7, 27.1, 20.5, 20.4, 10.1; $[\alpha]_D^{20}$ -9.1 (*c* 1.79, $CHCl_3$); HRMS-ESI m/z calcd for $[M+H]^+$ ($C_{32}H_{43}O_8$) 555.2952, found 555.2928.

L-3,6-Di-*O*-benzyl-*myo*-inositol (**6**). A reaction mixture of compound **5a** (500.0 mg, 1.0 mmol), acetic acid (28 mL) and water (7 mL) was heated in an oil bath (100 °C) for 2 h and

concentrated. The crude product was recrystallized in ethyl acetate to give **6** as a colorless solid (300.1 mg, 0.83 mmol, 83%). Mp 172.0–174.5 °C; $[\alpha]_D^{20}$ -5.5 (*c* 0.45, DMSO); ^{1}H NMR (500 MHz , $(CD_3)_2SO$) δ 7.46–7.10 (m, 10H), 4.84 (d, *J* = 4.9 Hz, 1H), 4.81–4.73 (m, 5H), 4.66–4.63 (m, 2H), 4.56 (d, *J* = 12.0 Hz, 1H), 3.97 (br, 1H), 3.63–3.58 (m, 1H), 3.44 (t, *J* = 9.0 Hz, 1H), 3.31–3.28 (m, 1H), 3.16–3.10 (m, 2H); ^{13}C{^{1}H} NMR (126 MHz, $(CD_3)_2SO$) δ 139.9, 139.3, 127.9, 127.8, 127.6, 127.5, 127.4, 127.0, 126.9, 81.8, 79.7, 75.0, 73.5, 72.2, 71.4, 70.7, 69.7. The spectroscopic data were consistent with the reported values.[29]

(1'*R*,2*R*,3a*R*,4*S*,4'*R*,5*R*,6*R*,7*S*,7a*S*)-5,6-Bis(benzyloxy)-4,7-bis((4-methoxybenzyl)oxy)-1',7',7'-trimethylhexahydrospiro[benzo[d][1,3]dioxole-2,2'-bicyclo[2.2.1]heptane] (7). Sodium hydride (60 % dispersion in mineral oil, 807.7 mg, 20.2 mmol) was added to a solution of **5b** (1.40 g, 2.52 mmol), tetrabutylammonium iodide (93.2 mg, 0.25 mmol) and *N,N*-dimethylformamide (DMF, 25.2 mL) at 0 °C. The reaction mixture was stirred for 15 min, added with benzyl bromide (901 μL, 1.30 g, 7.57 mmol) at 0 °C, stirred for another 16 h at rt, quenched with water (20 mL) at 0 °C and extracted with ethyl acetate (40 mL, 20 mL × 2). The combined organic layers were washed with saturated $NaCl_{(aq)}$ (20 mL × 3), dried over sodium sulfate, filtered and concentrated. The crude product was purified with column chromatography (SiO_2, EtOAc/hexanes, 1:5, R_f 0.39) to give **6** as a light-yellow liquid (1.80 g, 2.45 mmol, 96%). ^{1}H NMR (500 MHz , $CDCl_3$) δ 7.30–7.27 (m, 14H), 6.85 (ddd, *J* = 6.5 Hz, *J* = 6.5 Hz, *J* = 2.5 Hz, 4H), 4.84–4.61 (m, 8H), 4.28 (dd, *J* = 6.5 Hz, *J* = 4.5 Hz, 1H), 3.94 (t, *J* = 6.5 Hz, 1H), 3.80 (s, 3H), 3.79 (s, 3H), 3.74 (dd, *J* = 9.5 Hz, *J* = 4.5 Hz, 1H), 3.70 (dd, 9.5 Hz, *J* = 6.5 Hz, 1H), 1.49 (d, *J* = 15.0 Hz, 1H), 1.42–1.36 (m, 1H), 1.25 (m, 1H), 1.09 (s, 3H), 0.88 (s, 3H), 0.86 (s, 3H); ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ 159.2, 138.8, 131.0, 130.6, 129.6, 129.4, 128.0, 127.5, 117.6, 113.8, 113.8, 83.0, 82.1, 80.8, 76.3, 75.2, 75.0, 73.7, 72.0, 55.3, 51.6, 48.0, 45.2, 45.0, 29.8, 27.1, 20.7, 20.4, 10.2; $[\alpha]_D^{20}$ +2.7 (*c* 0.87, $CHCl_3$); HRMS-ESI m/z calcd for $[M+H]^+$ ($C_{46}H_{55}O_8$) 735.3891, found 735.3868.

(1*R*,2*R*,3*S*,4*R*,5*S*,6*S*)-5,6-Bis(benzyloxy)cyclohexane-1,2,3,4-tetraol (+)-8. A reaction mixture of compound **7** (862.0 mg, 1.17 mmol), acetic acid (36 mL) and water (4 mL) was heated in an oil bath (100 °C) for 2 h and concentrated. The residue was added with methanol (2 mL), stirred and concentrated to remove the solvents. The light yellow, viscous liquid was further washed with diethyl ether (15 mL × 3), and the residue was concentrated to dryness to

give **(+)-8** as a colorless solid (305.5 mg, 0.85 mmol, 72%). Mp 154.5–156.0 °C; ^{1}H NMR (500 MHz, $(CD_3)_2SO$) δ 7.33–7.21 (m, 10H), 4.85–4.79 (m, 2H), 4.72–4.66 (m, 2H), 4.54 (d, *J* = 5.5 Hz, 1H), 3.72 (d, *J* = 2.5 Hz, 1H), 3.61 (ddd, *J* = 9.5 Hz, *J* = 9.5 Hz, *J* = 5.5 Hz, 1H), 3.56 (t, *J* = 9.5 Hz, 1H), 3.23–3.21 (m, 1H), 3.18 (t, *J* = 9.5 Hz, 1H); ^{13}C{^{1}H} NMR (126 MHz, $(CD_3)_2SO$) δ 140.0, 140.0, 128.4, 128.4, 127.9, 127.9, 127.8, 127.8, 127.5, 127.5, 84.1, 82.2, 74.5, 73.5, 73.4, 72.3, 72.2; $[\alpha]_D^{20}$ +34.3 (*c* 0.25, DMSO); HRMS-ESI m/z calcd for $[M+H]^+$ ($C_{20}H_{25}O_6$) 361.1646, found 361.1649.

(1*R*,2*R*,4*R*,6'*S*,7'*S*,7a'*R*,10a'*R*,10b'*R*)-2',2',4',4'-Tetraisopropyl-1,7,7-trimethylhexahydrospiro[bicyclo[2.2.1]heptane-2,9'-[1,3]dioxolo[4',5':3,4]benzo[1,2-*f*][1,3,5,2,4]trioxadisilepine]-6',7'-diol (**9**). 1,3-Dichloro-1,1,3,3-tetraisopropyldisoxane (296.5 μL, 292.2 mg, 0.99 mmol) was added to a solution of **4** (242.7 mg, 0.77 mmol) and pyridine (4.9 mL) at –30 ℃. The reaction mixture was slowly warmed up to rt, stirred for another 16 h at rt, diluted with ethyl acetate (15 mL) and washed with water (15 mL × 3). The organic layer was washed with saturated $NaCl_{(aq)}$ (15 mL), dried over sodium sulfate, filtered and concentrated. The crude product was purified with column chromatography (SiO_2, EtOAc/hexanes, 1:3, R_f 0.36) to give **9** as a colorless liquid (394.1 mg, 0.71 mmol, 92%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.20 (t, *J* = 5.0 Hz, 1H), 3.91 (dd, *J* = 9.0 Hz, *J* = 4.5 Hz, 1H), 3.82 (t, *J* = 7.0 Hz, 1H), 3.78 (t, *J* = 9.5 Hz, 1H), 3.57 (dd, *J* = 10.5 Hz, *J* = 7.0 Hz, 1H), 3.25 (t, *J* = 9.5 Hz, 1H), 2.64 (br, 2H), 1.93–2.01 (m, 2H), 1.66–1.69 (m, 2H), 1.47 (d, *J* = 12.5 Hz, 1H), 1.34–1.39 (m, 1H), 1.18–1.23 (m, 1H), 0.96–1.08 (m, 31H), 0.83 (s, 3H), 0.80 (s, 3H); ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ 117.6, 76.6, 75.8, 75.7, 75.5, 73.6, 73.4, 51.4, 48.0, 45.4, 45.2, 29.4, 27.1, 20.5, 20.2, 17.6, 17.37, 17.31, 17.3, 17.2, 17.1, 17.0, 13.0, 12.7, 12.2; $[\alpha]_D^{20}$ +9.0 (*c* 1.05, $CHCl_3$); HRMS-ESI m/z calcd for $[M+H]^+$ ($C_{28}H_{53}O_7Si_2$) 557.3324, found 557.3309.

(1*S*,2*R*,3*S*,4*S*,5*R*,6*R*)-5,6-Bis(benzyloxy)cyclohexane-1,2,3,4-tetraol (-)-8. A mixture of tetrabutylammonium iodide (37.9 mg, 0.103 mmol), benzyl bromide (352 μL, 506.8 mg, 2.96 mmol) and sodium hydroxide (0.55 mL, w/w 50% in water) was cooled to -10 ℃ and added with a solution of **9** (44.0 mg, 0.079 mmol) in toluene (0.55 mL). The reaction mixture was stirred at -10 ℃ for 16 h, diluted with diethyl ether (5 mL) and washed with water (1 mL × 4). The organic layer was washed with saturated $NaCl_{(aq)}$ (2 mL), dried over sodium sulfate, filtered and concentrated to give the benzylated intermediate (123.4 mg). The intermediate was redissolved

in methanol (0.5 mL) and added with hydrofluoric acid (40% wt in H_2O, 73 μL, 33.5 mg, 1.67 mmol). The reaction mixture was stirred at rt for 3 h and concentrated. The crude product was purified with column chromatography (SiO_2, EtOAc, R_f 0.31) to give **(-)-8** as a colorless solid (18.2 mg, 0.051 mmol, 64%).^{1}H NMR (500 MHz, $(CD_3)_2SO$) δ 7.33–7.22 (m, 10H), 4.86–4.77 (m, 2H), 4.70–4.65 (m, 2H), 4.51 (d, J = 9.5 Hz, 1H), 3.73–3.72 (m, 1H), 3.65–3.59 (m, 1H), 3.52–3.51 (m, 1H), 3.42 (br, 4H), 3.23-3.13 (m, 2H); $[\alpha]_D^{20}$ -34.6 (*c* 0.23, DMSO); HRMS-ESI m/z calcd for $[M+H]^+$ ($C_{20}H_{25}O_6$) 361.1646, found 361.1639.

(2*R*,3*R*,4a*S*,5*S*,6*R*,7*S*,8*R*,8a*S*)-7,8-Bis(benzyloxy)-2,3-dimethoxy-2,3-dimethyloctahydrobenzo[b][1,4]dioxine-5,6-diol (10). A reaction mixture of **(+)-8 (**582.0 mg, 1.61 mmol), 2,3-butanedione (157 μL, 154.4 mg, 1.78 mmol), trimethyl orthoformate (751 μL, 728.3 mg, 1.58 mol), camphorsulfonic acid (18.7 mg, 0.08 mmol) and methanol (7.5 mL) was heated in an oil bath (90 ℃) for 16 h, quenched with triethylamine (43 μL) and concentrated. The crude product was purified with column chromatography (SiO_2, EtOAc/hexanes, 1:1, R_f 0.50) to give **10** as a light-yellow liquid (397.3 mg, 0.84 mmol, 52%). ^{1}H NMR (500 MHz , $CDCl_3$) δ 7.36–7.26 (m, 10H), 4.99 (d, J = 11.0 Hz, 1H), 4.94 (d, J = 11.0 Hz, 1H), 4.76 (d, J = 11.0 Hz, 1H), 4.69 (d, J = 11.0 Hz, 1H), 4.15 (t, J = 11.0 Hz, 1H), 4.09 (s, 1H), 3.76 (t, J = 9.3 Hz, 1H), 3.59–3.52 (m, 3H), 3.28 (s, 3H), 3.25 (s, 3H), 2.59 (br, 1H), 2.51 (br, 1H), 1.33 (s, 3H), 1.32 (s, 3H); ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ 138.8, 138.6, 128.6, 128.3, 128.0, 127.9, 127.8, 127.6, 100.0, 99.2, 81.9, 81.0, 75.8, 75.5, 72.1, 69.9, 69.7, 68.3, 48.1, 47.9, 17.9, 17.6; $[\alpha]_D^{20}$ -17.5 (*c* 0.36, $CHCl_3$); HRMS-ESI m/z calcd for $[M+H]^+$ ($C_{26}H_{35}O_8$) 475.2326, found 475.2373.

(2*R*,3*R*,4a*S*,5*R*,6*R*,7*R*,8*R*,8a*S*)-7,8-Bis(benzyloxy)-5-hydroxy-2,3-dimethoxy-2,3-dimethyloctahydrobenzo[b][1,4]dioxin-6-yl 4-methylbenzenesulfonate (11). A reaction mixture of **10** (338.5 mg, 0.71 mmol), dibutyltin oxide (353.5 mg, 1.42 mmol), benzyltriethylammonium chloride (193.6 mg, 0.85 mmol), 4-toluenesulfonyl chloride (162.1 mg, 0.85 mmol) and acetonitrile (21.6 mL) was heated to reflux for 16 h in an oil bath (90 °C) and concentrated. The crude product was purified with column chromatography (SiO_2, EtOAc/hexanes, 1:3, R_f 0.48) to give **11** as a white solid (415.1 mg, 0.66 mmol, 93%). Mp 189.5–193.0 ℃; ^{1}H NMR (500 MHz , $CDCl_3$) δ 7.74 (d, J = 8.0 Hz, 2H), 7.25–7.23 (m, 8H), 7.11 (d, J = 8.0 Hz, 2H), 7.07–7.05 (m, 2H), 4.89 (d, J = 11.0 Hz, 1H), 4.67 (d, J = 11.0 Hz, 2H), 4.51–4.47 (m, 2H), 4.35 (d, J = 2.5 Hz, 1H), 4.13 (t, J = 9.5 Hz, 1H), 3.92 (t, J = 9.5 Hz, 1H),

3.56 (dd, J = 11.0 Hz, J = 2.5 Hz, 1H), 3.52 (t, J = 9.5 Hz, 1H), 3.26 (s, 6H), 2.53 (br, 1H), 2.33 (s, 3H), 1.32 (s, 3H), 1.32 (s, 3H); $^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$) δ 144.8, 138.5, 138.2, 133.7, 129.7, 129.7, 128.3, 128.2, 128.1, 127.8, 127.6, 127.5, 127.4, 100.0, 99.2, 81.5, 80.7, 80.0, 75.7, 69.6, 68.7, 67.5, 48.3, 47.9, 21.6, 17.8, 17.6; $[\alpha]_D^{20}$ -3.9 (c 0.34, $CHCl_3$); HRMS-ESI m/z calcd for $[M+H]^+$ ($C_{33}H_{41}O_{10}S$) 629.2415, found 629.2359.

(2*R*,3*R*,4a*S*,5*S*,7*S*,8*R*,8a*S*)-7,8-Bis(benzyloxy)-2,3-dimethoxy-2,3-dimethyloctahydrobenzo[b][1,4]dioxin-5-ol (12). Lithium triethylborohydride (1 *M* in THF, 3.1 mL, 3.1 mmol) was added to a solution of **11 (**195.4 mg, 0.31 mmol) and THF (1.2 mL) at 0 °C. The reaction mixture was heated to reflux for 24 h in an oil bath (85 °C), quenched with water (2 mL) at 0 °C, concentrated to remove THF and extracted with ethyl acetate (5 mL × 3). The combined organic layers were washed with saturated $NaCl_{(aq)}$ (5 mL), dried with sodium sulfate, filtered and concentrated. The crude product was purified with column chromatography (SiO_2, EtOAc/hexanes, 1:1, R_f 0.32) to give **12** as a colorless liquid (109.5 mg, 0.24 mmol, 77%). ^1H NMR (500 MHz, $CDCl_3$) δ 7.39–7.24 (m, 10H), 4.95 (d, J = 11.0 Hz, 1H), 4.81 (d, J = 11.0 Hz, 1H), 4.72 (d, J = 11.5 Hz, 1H), 4.63 (d, J = 11.5 Hz, 1H), 4.06 (t, J = 10.0 Hz, 1H), 4.00 (dd, J = 5.0 Hz, J = 3.0 Hz, 1H), 3.88 (ddd, J = 11.5 Hz, J = 9.5 Hz, J = 5.0 Hz, 1H), 3.59 (dd, J = 10.0 Hz, J = 2.5 Hz, 1H), 3.55 (t, J = 9.5 Hz, 1H), 3.27 (s, 3H), 3.25 (s, 3H), 2.32 (ddd, J = 14.0 Hz, J = 5.0 Hz, J = 2.5 Hz, 1H), 1.47 (ddd, J = 15.0 Hz, J = 11.5 Hz, J = 2.5 Hz, 1H), 1.34 (s, 3H), 1.31 (s, 3H); $^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$) δ 139.3, 138.9, 128.3, 128.2, 127.9, 127.8, 127.5, 127.4, 99.9, 99.9, 99.2, 83.1, 75.4, 73.4, 71.1, 69.5, 66.9, 48.0, 47.8, 33.6, 17.9, 17.6; $[\alpha]_D^{20}$ -5.6 (c 0.69, $CHCl_3$); HRMS-ESI m/z calcd for $[M+H]^+$ ($C_{26}H_{35}O_7$) 459.2377, found 459.2340.

(2*R*,3*R*,4a*R*,5*R*,6*S*,8*R*,8a*S*)-8-Azido-5,6-bis(benzyloxy)-2,3-dimethoxy-2,3-dimethyloctahydrobenzo[b][1,4]dioxine (13). Trifluoromethanesulfonic anhydride (41 μL, 69.0 mg, 0.25 mmol) was added to a solution of **12 (**74.8 mg, 0.16 mmol), pyridine (105 μL, 103.2 mg, 1.31 mmol) and dichloromethane (4.9 mL) at 0 °C. The reaction mixture was stirred at 0 ℃ for 3 h, concentrated, added with anhydrous DMF (6.2 mL) and sodium azide (160.0 mg, 1.63 mmol), stirred at rt for another 2 h, quenched with water (10 mL) and extracted with ethyl acetate (20 mL, 10 mL × 2). The combined organic layers were washed with saturated $NaCl_{(aq)}$ (10 mL), dried with sodium sulfate, filtered and concentrated. The crude product was purified

with column chromatography (SiO_2, EtOAc/hexanes, 1:5, R_f 0.66) to give **13** as a colorless liquid (54.2 mg, 0.11 mmol, 70%). ^{1}H NMR (500 MHz , $CDCl_3$) δ 7.36–7.25 (m, 10H), 4.91 (d, *J* = 11.0 Hz, 1H), 4.78 (d, *J* = 11.0 Hz, 1H), 4.67 (d, *J* = 11.0 Hz, 1H), 4.61 (d, *J* = 11.0 Hz, 1H), 3.64–3.59 (m, 2H), 3.53 (t, *J* = 9.1 Hz, 1H), 3.46–3.42 (m, 2H), 3.34 (s, 3H), 3.28 (s, 3H), 2.21 (ddd, *J* = 9.0 Hz, *J* = 9.0 Hz, *J* = 4.5 Hz, 1H), 1.39 (t, *J* = 11.5 Hz, 1H), 1.35 (s, 3H), 1.33 (s, 3H); ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ 138.9, 138.3, 128.4, 128.3, 128.0, 127.7, 127.6, 99.7, 99.4, 82.1, 77.5, 75.6, 73.2, 72.8, 71.7, 56.7, 48.1, 48.0, 33.3, 33.3, 17.7, 17.6; $[\alpha]_D^{20}$ -1.3 (*c* 0.55, $CHCl_3$); HRMS-ESI m/z calcd for $[M+Na]^+$ ($C_{26}H_{33}N_3O_6Na$) 506.2262, found 506.2230.

(2*R*,3*R*,4a*S*,5*R*,7*S*,8*R*,8a*S*)-7,8-Dihydroxy-2,3-dimethoxy-2,3-dimethyloctahydrobenzo[*b*][1,4]dioxin-5-aminium (**14**). A reaction suspension of **13 (**40.1 mg, 0.083 mmol), palladium on carbon (10% wt, 26.5 mg, 0.025 mmol), methanol (5.5 mL) and $HCl_{(aq)}$ (1*N*, 170 μL, 0.166 mmol) was stirred at rt for 8 h under an atmosphere of hydrogen (1 atm) and filtered through a pad of celite. The filtrate was concentrated to give compound **14** (21.9 mg, 0.070 mmol, 84%) as a colorless of solid. Mp >220 ℃ (decomposed); ^{1}H NMR (500 MHz , CD_3OD) δ 3.81 (dd, *J* = 10.5 Hz, *J* = 6.0 Hz, 1H), 3.52–3.50 (m, 1H), 3.45 (d, *J* = 5.5 Hz, 2H), 3.36 (s, 3H), 3.31 (s, 3H), 3.28 (br, 1H), 2.81–2.76 (m, 1H), 2.12 (ddd, *J* = 8.5 Hz, *J* = 8.5 Hz, *J* = 4.0 Hz, 1H), 1.34 (s, 3H), 1.33 (s, 3H); ^{13}C{^{1}H} NMR (126 MHz, CD_3OD) δ 99.2, 99.1, 98.2, 74.7, 73.6, 72.4, 71.3, 70.3, 65.5, 37.4, 16.6, 16.6; HRMS-ESI m/z calcd for $[M]^+$ ($C_{12}H_{24}NO_6$) 278.1598, found 278.1592.

***N*-((2*R*,3*R*,4a*S*,5*R*,7*S*,8*R*,8a*S*)-7,8-Dihydroxy-2,3-dimethoxy-2,3-dimethyloctahydrobenzo[*b*][1, 4]dioxin-5-yl)-3-(methoxymethoxy)benzamide** (**15**). A solution of **14 (**40.1 mg, 0.081 mmol), *N,N*-diisopropylethylamine (DIPEA, 18.4 μL, 13.6 mg, 0.106 mmol) in THF (2.2 mL) was added to the mixture of 3-(methoxymethoxy)benzoic acid (19.2 mg, 0.106 mmol), DIPEA (18.4 μL, 13.6 mg, 0.106 mmol), HBTU (43.1 mg, 0.114 mmol) and THF (2.2 mL) at rt. The reaction mixture was stirred at rt for 16 h, concentrated, added with water (15 mL) and extracted with ethyl acetate (10 mL × 3). The combined organic layers were washed with saturated $NaCl_{(aq)}$ (10 mL), dried over sodium sulfate, filtered and concentrated. The crude product was purified with column chromatography (SiO_2, EtOAc, R_f 0.35) to give **15** as a colorless liquid (27.6 mg, 0.063 mmol, 77%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.39 (s, 1H), 7.31 (t, *J* = 6.5 Hz, 1H), 7.25–7.20 (m, 1H), 7.09 (t, *J* = 6.5 Hz, 1H), 6.65 (br, 1H), 5.09 (dd, *J* = 10.5

Hz, J = 7.5 Hz, 2H), 4.06–4.05 (m, 1H), 3.71–3.70 (m, 2H), 3.54–3.52 (m, 2H), 3.39 (s, 3H), 3.24 (s, 6H), 2.42–2.41 (m, 1H), 1.54 (dd, J = 24.0 Hz, J = 12.0 Hz, 1H), 1.29 (s, 3H), 1.24 (s, 3H); $^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$) δ 167.5, 157.4, 136.0, 129.7, 120.3, 119.6, 114.8, 99.6, 99.4, 94.4, 74.7, 71.2, 70.4, 70.1, 56.1, 48.0, 47.9, 47.6, 35.5, 17.7, 17.6; $[\alpha]_D^{20}$ -21.1 (*c* 0.58, $CHCl_3$); HRMS-ESI m/z calcd for $[M+H]^+$ ($C_{12}H_{24}NO_6$) 278.1598, found 278.1593.

(2*R*,3*R*,4a*R*,5*R*,6*S*,8*R*,8a*S*)-6-Hydroxy-2,3-dimethoxy-8-(3-(methoxymethoxy)benzamido)-2,3-dimethyloctahydrobenzo[*b*][1,4]dioxin-5-yl 2-hydroxy-6-methylbenzoate (16a). *N*-(3-Dimethylaminopropyl)-*N'*-ethylcarbodiimide (12.0 μL, 10.6 mg, 0.068 mmol) was added to a solution of 2-hydroxy-6-methylbenzoic acid (7.6 mg, 0.050 mmol), 4-(dimethylamino)pyridine (DMAP, 0.60 mg, 0.0046 mmol) and dichloromethane (2.2 mL) at 0 °C. The reaction mixture was stirred at 0 °C for 15 min, added with a solution of **15** (20.1 mg, 0.046 mmol) in dichloromethane (2.2 mL) dropwise at 0 °C, stirred at 10 °C for 48 h and concentrated. The crude product was purified with column chromatography (SiO_2, EtOAc/hexanes, 3:2, R_f 0.55) to give **16a** as a colorless liquid (17.8 mg, 0.031 mmol, 68%). ^1H NMR (500 MHz , $CDCl_3$) δ 10.75 (br, 1H), 7.40 (s, 1H), 7.32–7.26 (m, 3H), 7.14 (d, J = 7.0 Hz, 1H), 6.81 (d, J = 8.0 Hz, 1H), 6.70 (d, J = 7.0 Hz, 1H), 6.27 (br, 1H), 5.31 (t, J = 9.5 Hz, 1H), 5.16 (s, 2H), 4.05–4.03 (m, 1H), 4.08–4.07 (m, 1H), 3.94–3.93 (m, 1H), 3.87–3.80 (m, 1H), 3.44 (s, 3H), 3.27 (s, 3H), 3.17 (s, 3H), 2.65–2.64 (m, 1H), 2.55 (s, 3H), 1.39–1.37 (m, 1H), 1.26 (s, 3H), 1.25 (s, 3H); $^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$) δ 171.1, 167.5, 162.0, 157.5, 140.9, 136.0, 134.1, 129.8, 122.9, 120.1, 119.7, 115.7, 114.8, 113.1, 99.7, 99.6, 94.5, 70.5, 69.4, 69.2, 56.1, 49.3, 48.1, 48.0, 47.6, 36.4, 23.7, 17.6, 17.5; $[\alpha]_D^{20}$ -13.4 (*c* 1.08, $CHCl_3$); HRMS-ESI m/z calcd for $[M+H]^+$ ($C_{29}H_{38}NO_{11}$) 576.2439, found 576.2434. Compound **17** (2.8 mg, 0.0039 mmol, 9%) was also isolated after column chromatography (SiO_2, EtOAc/hexanes, 3:2, R_f 0.68) ^1H NMR (500 MHz , $CDCl_3$) δ 10.95 (br, 1H), 10.92 (br, 1H), 7.40 (br, 2H), 7.35–7.31 (m, 2H), 7.23 (dd, 16.5 Hz, J = 7.5 Hz, 2H), 7.16 (dt, J = 7.0 Hz, J = 2.5 Hz, 1H), 6.77 (dd, J = 12.5 Hz, J = 8.5 Hz, 1H), 6.65 (dd, J = 12.5 Hz, J = 7.5 Hz, 1H), 6.09 (br, 1H), 5.77 (t, J = 10.0 Hz, 1H), 5.55–5.49 (m, 1H), 5.18 (s, 2H), 4.07–4.04 (m, 1H), 4.01 (t, J = 9.5 Hz, 1H), 3.94 (t, J = 9.5 Hz, 1H), 3.45 (s, 3H), 3.27 (s, 3H), 3.14 (s, 3H), 2.91 (dt, J = 12.5 Hz, J = 4.5 Hz, 1H), 2.48 (s, 3H), 2.44 (s, 3H), 1.95 (dd, J = 24.5 Hz, J = 12.5 Hz, 1H), 1.28 (s, 3H), 1.25 (s, 3H); $^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$) δ 170.6, 170.5, 167.5, 163.1, 162.8, 157.6, 141.5, 141.0, 135.9, 134.7, 134.5, 129.9, 123.1, 120.1, 119.8, 115.7, 115.7, 114.6, 111.9, 111.5, 99.8, 99.7, 94.5, 73.1, 70.7, 69.7,

56.1, 48.1, 47.9, 36.6, 29.7, 24.7, 24.2, 24.0, 23.3, 17.6, 17.5; HRMS-ESI m/z calcd for $[M+H]^+$ ($C_{38}H_{47}NO_{13}$) 725.3042, found 725.2910.

Compound **16b** (6.9 mg, 0.012 mmol, 33%) was also isolated as a colorless liquid from the corresponding reaction of **15** (16.3 mg, 0.037 mmol), 2-hydroxy-6-methylbenzoic acid (6.7 mg, 0.044 mmol), DCC (11.4 mg, 0.055 mmol) and DMAP (0.4 mg, 0.0012 mmol) after column chromatography (SiO_2, EtOAc/hexanes, 3:2, R_f 0.46). ^{1}H NMR (500 MHz, $CDCl_3$) δ 10.95 (br, 1H), 7.38 (s, 1H), 7.34–7.27 (m, 3H), 7.15 (d, J = 6.5 Hz, 1H), 6.82 (d, J = 8.5 Hz, 1H), 6.69 (d, J = 7.5 Hz, 1H), 6.06 (br, 1H), 5.21–5.26 (m, 1H), 5.17 (s, 2H), 3.98–3.89 (m, 3H), 3.62 (t, J = 9.5 Hz, 1H), 3.45 (s, 3H), 3.28 (s, 3H), 3.26 (s, 3H), 2.77 (m, 1H), 2.52 (s, 3H), 1.93 (dd, J = 24.5 Hz, J = 12.0 Hz, 1H), 1.33 (s, 3H), 1.30 (s, 3H); ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ 17.6, 23.9, 29.7, 31.2, 38.2, 48.1, 48.4, 56.1, 59.6, 69.2, 71.4, 72.6, 72.8, 94.5, 99.5, 112.4, 114.7, 115.7, 119.7, 120.0, 123.0, 129.8, 134.3, 136.1, 141.3, 157.5, 162.7, 167.5, 170.7; HRMS-ESI m/z calcd for $[M+H]^+$ ($C_{29}H_{38}NO_{11}$) 576.2439, found 576.2413.

(2*R*,3*R*,4a*R*,5*R*,6*S*,8*R*,8a*S*)-6-(Carbamoyloxy)-2,3-dimethoxy-8-(3-(methoxymethoxy)benzamido)-2,3-dimethyloctahydrobenzo[*b*][1,4]dioxin-5-yl 2-hydroxy-6-methylbenzoate (**18**). Trichloroacetyl isocyanate (2.62 μL, 4.14 mg, 0.022 mmol) was added to a solution of **17** (11.5 mg, 0.019 mmol) and dichloromethane (0.5 mL) at 0 °C. The reaction mixture was warmed up to rt, stirred for 3 h, added with methanol (0.5 mL) and $K_2CO_{3(aq)}$ (0.1 *M*, 0.5 mL), stirred for another 2 h at rt, concentrated to remove methanol and extracted with dichloromethane (10 mL x 3). The combined organic layers were washed with saturated $NaCl_{(aq)}$ (10 mL), dried over sodium sulfate, filtered and concentrated. The crude product was purified with column chromatography (SiO_2, EtOAc/hexanes, 3:2, R_f 0.48) to give **18** as a colorless liquid (7.8 mg, 0.012 mmol, 66%). ^{1}H NMR (500 MHz , $CDCl_3$) δ 11.04 (br, 1H), 7.39 (s, 1H), 7.34–7.21 (m, 2H), 7.24–7.22 (m, 2H), 7.15–7.14 (m, 1H), 6.79 (d, J = 7.5 Hz, 1H), 6.66 (d, J = 7.5 Hz, 1H), 6.12 (br, 1H), 5.34–5.29 (m, 1H), 5.21 (t, J = 10.0 Hz, 1H), 5.17 (s, 2H), 4.66 (br, 2H), 4.03–4.02 (m, 1H), 3.89 (t, J = 10.0 Hz, 1H), 3.75 (t, J = 10.0 Hz, 1H), 3.44 (s, 3H), 3.24 (s, 3H), 3.23 (s, 3H), 2.83–2.80 (m, 1H), 2.49 (s, 3H), 1.81 (dd, J = 24.5 Hz, J = 12.0 Hz, 1H), 1.27 (s, 3H); ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ 170.7, 167.4, 163.0, 157.5, 155.5, 141.8, 136.0, 134.5, 129.8, 123.2, 119.7, 115.6, 114.7, 111.9, 99.5, 94.5, 73.3, 70.8, 69.8, 69.5, 59.5, 56.1,

47.9, 47.8, 38.2, 32.9, 31.2, 29.7, 24.1, 17.5; $[\alpha]_D^{20}$ -10.9 (*c* 0.37, $CHCl_3$); HRMS-ESI m/z calcd for $[M+H]^+$ ($C_{30}H_{39}N_2O_{12}$) 619.2498, found 619.2472.

(1*S*,2*R*,3*S*,4*R*,6*S*)-6-(Carbamoyloxy)-2,3-dihydroxy-4-(3-hydroxybenzamido)cyclohexyl 2-hydroxy-6-methylbenzoate (*ent*-1). A reaction mixture of **18** (6.3 mg, 0.0102 mmol), trifluoroacetic acid, (0.9 mL) and water (0.1 mL) was stirred at rt for 19 h and concentrated. The crude product was purified with column chromatography (SiO_2, $CHCl_3$/methanol, 4:1, R_f 0.53) to give ***ent*-1** as a colorless solid (2.9 mg, 0.0062 mmol, 61%). Mp 205.5–208.0 ℃; IR (neat) 3340, 1722, 1591, 1062 cm^{-1}; ^1H NMR (500 MHz , $(CD_3)_2CO$) δ 10.72 (br, 1H), 8.64 (br, 1H), 7.67 (br, 1H), 7.40 (s, 1H), 7.38 (d, *J* = 7.5 Hz, 1H), 7.32 (t, *J* = 7.5 Hz, 1H), 7.28 (t, *J* = 7.5 Hz, 1H), 7.00 (d, *J* = 8.0 Hz, 1H), 6.82–6.78 (m, 2H), 6.03 (br, 1H), 5.34 (t, *J* = 9.5 Hz, 1H), 5.10–5.05 (m, 1H), 4.77 (br, 1H), 4.60 (br, 1H), 4.20–4.15 (m, 1H), 3.84 (t, *J* = 9.5 Hz, 1H), 3.76 (t, *J* = 9.5 Hz, 1H), 2.58 (s, 3H), 2.49–2.45 (m, 1H), 1.79 (dd, *J* = 24.5 Hz, *J* = 12.0 Hz, 1H); $^{13}C\{^1H\}$ NMR (126 MHz, $(CD_3)_2CO$) δ 170.7, 168.2, 161.2, 158.4, 157.0, 141.4, 137.0, 134.1, 130.1, 123.4, 119.1, 118.9, 115.8, 115.2, 77.4, 75.5, 74.7, 70.5, 50.1, 34.0, 22.9; $[\alpha]_D^{20}$ +10.7 (*c* 0.13, MeOH); HRMS-ESI m/z calcd for $[M+H]^+$ ($C_{22}H_{25}N_2O_9$) 461.1555, found 461.1555.

Supporting Information. ^1H and $^{13}C\{^1H\}$ NMR spectra for compounds **4**, **6, 8**, ***ent*-1** and all the new compounds.

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References

1. Hara, S.; Ishikawa, N.; Hara, Y.; Nehira, T.; Sakai, K.; Gonoi, T.; Ishibashi, M. Nabscessins A and B, Aminocyclitol Derivatives from Nocardia abscessus IFM 10029T. *J. Nat. Prod.* **2017,** *80*, 565-568.
2. Hara, S.; Hara, Y.; Arai, M. A.; Kusuya, Y.; Takahashi, H.; Yaguchi, T.; Ishibashi, M. Isolation of Nabscessin C from *Nocardia abscessus* IFM 10029^T and a Study on Biosynthetic Pathway for Nabscessins. *Chem. Pharm. Bull.* **2018,** *66*, 976-982.
3. Tsunakawa, M.; Hanada, M.; Tsukiura, H.; Tomita, K.; Tomatsu, K.; Hoshiya, T.; Miyaki, T.; Konishi, M.; Kawaguchi, H. Inosamycin, a Complex of New Aminoglycoside Antibiotics I. Production, Isolation and Properties. *J. Antibiot.* **1985,** *38*, 1302-1312.
4. Tsunakawa, M.; Hanada, M.; Tsukiura, H.; Konishi, M.; Kawaguchi, H. Inosamycin, a Complex of New Aminoglycoside Antibiotics II. Structure Determination. *J. Antibiot.* **1985,** *38*, 1313-1321.
5. Yokoyama, K.; Ohmori, D.; Kudo, F.; Eguchi, T. Mechanistic Study on the Reaction of a Radical SAM Dehydrogenase BtrN by Electron Paramagnetic Resonance Spectroscopy. *Biochemistry* **2008,** *47*, 8950-8960.

6. Kakinuma, K.; Ogawa, Y.; Sasaki, T.; Seto, H.; Otake, N. Stereochemistry of ribostamycin biosynthesis. Application of hydrogen-2 NMR spectroscopy. *J. Am. Chem. Soc.* **1981,** *103*, 5614-5616.
7. Rinehart, K. L., Jr. ; Stroshane, R. M. BIOSYNTHESIS OF AMINOCYCLITOL ANTIBIOTICS. *J. Antibiot.* **1976,** *29*, 319-.
8. Edson, R. S.; Terrell, C. L. The Aminoglycosides. *Mayo Clin. Proc.* **1999,** *74*, 519-528.
9. Hotta, K.; Kondo, S. Kanamycin and its derivative, arbekacin: significance and impact. *J. Antibiot.* **2018,** *71*, 417-424.
10. Chang, C. W. T.; Takemoto, J. Y. Antifungal amphiphilic aminoglycosides. *MedChemComm* **2014,** *5*, 1048-1057.
11. Park, S. R.; Park, J. W.; Ban, Y. H.; Sohng, J. K.; Yoon, Y. J. 2-Deoxystreptamine-containing aminoglycoside antibiotics: Recent advances in the characterization and manipulation of their biosynthetic pathways. *Nat. Prod. Rep.* **2013,** *30*, 11-20.
12. Sasseville, D. Neomycin. *Dermatitis* **2010,** *21*, 3-7.
13. Böttger, E. C.; Crich, D. Aminoglycosides: Time for the Resurrection of a Neglected Class of Antibacterials? *ACS Infect. Dis.* **2020,** *6*, 168-172.
14. Igarasgi, K.; Honma, T.; Fujiwara, T.; Kondo, E. SYNTHESIS OF (1D)-1,3,5,2,4- AND (1L)-l ,2,4,3,5-5-AMINOCYCLOHEXANETETROLS. *J. Antibiot.* **1981,** *34*, 288-291.
15. Kim, S.-C.; Lee, S.-C.; Cheong, C.-S. Synthetic Study toward a Protected 2-Deoxystreptamine. *Bull. Korean Chem. Soc.* **2004,** *25*, 1578-1580.
16. Yu, J.; Spencer, J. B. Convenient synthesis of 2-deoxy-scyllo-inosose and 2-deoxy-scyllo-inosamine: two key intermediates on the biosynthetic pathway to aminoglycoside antibiotics. *Tetrahedron Lett.* **2001,** *42*, 4219-4221.
17. Wacharasindhu, S.; Worawalai, W.; Rungprom, W.; Phuwapraisirisan, P. (+)-proto-Quercitol, a natural versatile chiral building block for the synthesis of the α-glucosidase inhibitors, 5-amino-1,2,3,4-cyclohexanetetrols. *Tetrahedron Lett.* **2009,** *50*, 2189-2192.
18. Worawalai, W.; Sompornpisut, P.; Wacharasindhu, S.; Phuwapraisirisan, P. Voglibose-inspired synthesis of new potent α-glucosidase inhibitors N-1,3-dihydroxypropylaminocyclitols. *Carbohydr. Res.* **2016,** *429*, 155-162.

19. Ogawa, S.; Asada, M.; Ooki, Y.; Mori, M.; Itoh, M.; Korenaga, T. Design and synthesis of glycosidase inhibitor 5-amino-1,2,3,4-cyclohexanetetrol derivatives from (−)-vibo-quercitol. *Bioorg. Med. Chem.* **2005,** *13*, 4306-4314.
20. Marco-Contelles, J.; Pozuelo, C.; Jimeno, M. L.; Martinez, L.; Martinez-Grau, A. 6-Exo free radical cyclization of acyclic carbohydrate intermediates: a new synthetic route to enantiomerically pure polyhydroxylated cyclohexane derivatives. *J. Org. Chem.* **1992,** *57*, 2625-2631.
21. Baer, H. H.; Siemsen, L.; Astles, D. J. Chemical synthesis of 3-amino-2,3-dideoxy-d-myo-inositol (an intermediate in the biosynthesis of 2-deoxystreptamine) and its d-epi stereoisomer. *Carbohydr. Res.* **1986,** *156*, 247-255.
22. Alegret, C.; Benet-Buchholz, J.; Riera, A. Stereodivergent Syntheses of Conduramines and Aminocyclitols. *Org. Lett.* **2006,** *8*, 3069-3072.
23. Ma, X.; Yan, Q.; Banwell, M. G.; Ward, J. S. A Total Synthesis of the Antifungal Deoxyaminocyclitol Nabscessin B from l-(+)-Tartaric Acid. *Org. Lett.* **2018,** *20*, 142-145.
24. Ogawa, S.; Ohishi, Y.; Asada, M.; Tomoda, A.; Takahashi, A.; Ooki, Y.; Mori, M.; Itoh, M.; Korenaga, T. Convenient synthesis of (+)-valiolamine and (−)-1-epi-valiolamine from (−)-vibo-quercitol. *Org. Biomol. Chem.* **2004,** *2*, 884-889.
25. Duchek, J.; Adams, D. R.; Hudlicky, T. Chemoenzymatic Synthesis of Inositols, Conduritols, and Cyclitol Analogues. *Chem. Rev.* **2011,** *111*, 4223-4258.
26. Sureshan, K. M.; Shashidhar, M. S.; Praveen, T.; Das, T. Regioselective Protection and Deprotection of Inositol Hydroxyl Groups. *Chem. Rev.* **2003,** *103*, 4477-4504.
27. Hederos, M.; Konradsson, P. Synthesis of the Core Tetrasaccharide of Trypanosoma cruzi Glycoinositolphospholipids: Manp(α 1 → 6)-Manp(α 1 → 4)-6-(2-aminoethylphosphonic acid)-GlcNp(α 1→6)-myo-Ins-1-PO4. *J. Org. Chem.* **2005,** *70*, 7196-7207.
28. Bruzik, K. S.; Tsai, M. D. Efficient and systematic syntheses of enantiomerically pure and regiospecifically protected myo-inositols. *J. Am. Chem. Soc.* **1992,** *114*, 6361-6374.
29. J. Mills, S.; V. L. Potter, B. Synthesis of the enantiomers of myo-inositol 1,2,4,5-tetrakisphosphate, a regioisomer of myo-inositol 1,3,4,5-tetrakisphosphate. *J. Chem. Soc., Perkin Trans. 1* **1997**, 1279-1286.

30. Simas, A. B. C.; Pais, K. C.; da Silva, A. A. T. A More Convenient and General Procedure for O-Monobenzylation of Diols via Stannylenes: A Critical Reevaluation of the Bu2SnO Method. *J. Org. Chem.* **2003,** *68*, 5426-5428.
31. Ley, S. V.; Parra, M.; Redgrave, A. J.; Sternfeld, F. Microbial oxidation in synthesis: preparation of myo-inositol phosphates and related cyclitol derivatives from benzene. *Tetrahedron* **1990,** *46*, 4995-5026.
32. Ichikawa, Y.; Manaka, A.; Kuzuhara, H. Discrimination between the 2,3- and the 2′,3′-hydroxyl groups of maltose and cellobiose through their specific protection. *Carbohydr. Res.* **1985,** *138*, 55-64.
33. Riley, A. M.; Correa, V.; Mahon, M. F.; Taylor, C. W.; Potter, B. V. L. Bicyclic Analogues of d-myo-Inositol 1,4,5-Trisphosphate Related to Adenophostin A: Synthesis and Biological Activity. *J. Med. Chem.* **2001,** *44*, 2108-2117.
34. Yu, J.; Spencer, J. B. Stereoselective Deoxygenation of myo-Inositol Monotosylates with Lithium Triethylborohydride. *J. Org. Chem.* **1996,** *61*, 3234-3235.
35. Valeur, E.; Bradley, M. Amide bond formation: beyond the myth of coupling reagents. *Chem. Soc. Rev.* **2009,** *38*, 606-631.
36. Montalbetti, C. A. G. N.; Falque, V. Amide bond formation and peptide coupling. *Tetrahedron* **2005,** *61*, 10827-10852.
37. Dhaon, M. K.; Olsen, R. K.; Ramasamy, K. Esterification of N-protected .alpha.-amino acids with alcohol/carbodiimide/4-(dimethylamino)pyridine. Racemization of aspartic and glutamic acid derivatives. *J. Org. Chem.* **1982,** *47*, 1962-1965.
38. Kočovský, P. Carbamates : A method of synthesis and some syntehtic applications. *Tetrahedron Lett.* **1986,** *27*, 5521-5524.