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Synthesis of the Aminocyclitol Units of (−)-Hygromycin A and Methoxyhygromycin from *myo*-Inositol

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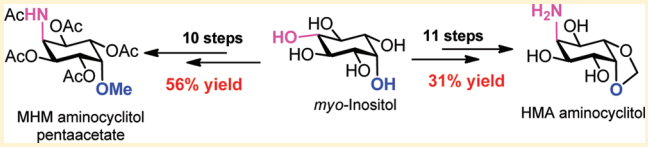
Supporting Information

ABSTRACT: Concise and efficient syntheses of the aminocyclitol cores of hygromycin A (HMA) and methoxyhygromycin (MHM) have been achieved starting from readily available *myo*-inositol. Reductive cleavage of *myo*-inositol orthoformate to the corresponding 1,3-acetal, stereospecific introduction of the amino group via the azide, and resolution of a *racemic* cyclitol derivative as its diastereomeric mandelate esters are the key steps in the synthesis. Synthesis of the aminocyclitol core of hygromycin A involved chromatography in half of the total number of steps, and the aminocyclitol core of methoxyhygromycin involved only one chromatography.

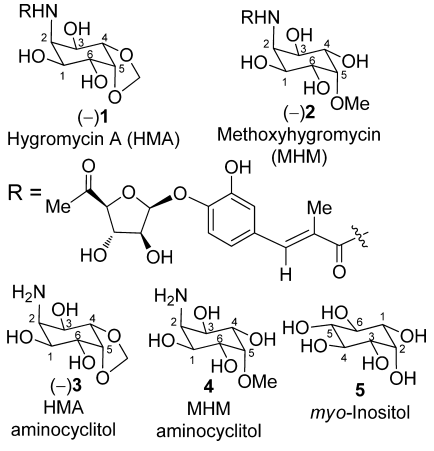


There has been an upsurge in interest in the chemistry of *myo*-inositol and its derivatives/analogues because of the involvement of phosphoinositols in cellular signal transduction mechanisms and anchoring of certain proteins to cell membranes.[1−3] Synthetic methodologies and techniques have been developed in the recent past for the synthesis of inositol derivatives useful in the study of the inositol cycle, starting from the most abundantly available isomer, *myo*-inositol.[4] Some of these methods have also been used for the synthesis of natural products and their analogs.[5] 1,2-Acetal derivatives of *myo*-inositol (acetals of vicinal hydroxyl groups) have been frequently used as early intermediates for the synthesis of various classes of compounds mentioned above, although the acetalization of *myo*-inositol often leads to the formation of all possible isomeric acetals, which have to be separated. In contrast, the 1,3-bridged acetals of *myo*-inositol can be prepared as single products in good yields via reductive cleavage of *O*-protected orthoester derivatives of *myo*-inositol.[6,7] 1,3-Bridged acetals provide opportunities for new selective reactions (of the inositol hydroxyl groups) since conformation of the two six-membered rings in these acetals can deviate from the normal chair conformation.[8−10] Hence, 1,3-acetals of *myo*-inositol derivatives have the potential to emerge as useful intermediates for the preparation of biologically relevant cyclitol derivatives and natural products containing the cyclitol moiety. We herein delineate the synthesis of aminocyclitol moieties of hygromycin A (**1**, Chart 1), methoxyhygromycin (**2**), and the unnatural enantiomer of the former aminocyclitol, from *myo*-inositol (**5**) via its 1,3-bridged acetals.

The aminocyclitol unit of **1** has previously been synthesized by Trost[11] and Donohoe,[12,13] and a formal synthesis was reported by Arjona.[14] The aminocyclitol **4** was synthesized from *myo*-inositol (**5**) by Chida et al.;[15] biosynthesis of the aminocyclitol (−)-**3** has also been investigated.[16]

Aminocyclitols are a diverse class of compounds with interesting biological properties.[17−20] There have been

Chart 1. Structure of Hygromycin A (HMA), Methoxyhygromycin (MHM), and Their Aminocyclitol Units



continuous efforts in the recent past to obtain naturally occurring aminocyclitols as well as their synthetic analogues with enhanced or more selective biological profiles that could be useful in the intervention of cellular processes.[21,22] For instance, certain aminocyclitol derivatives have been shown to be potential candidates for the development of therapeutic agents,[23] as enzyme inhibitors with diverse biomedical applications,[24,25] and also as molecular tools for the investigation of the *myo*-inositol cycle and related cellular processes.[26−28] Hygromycin A (**1**), in addition to being a broad-spectrum antibiotic,[29,30] functions as a peptidyl transferase inhibitor,[31] a hemagglutination inactivator, and an effective agent for the control of swine dysentery.[32,33] A series

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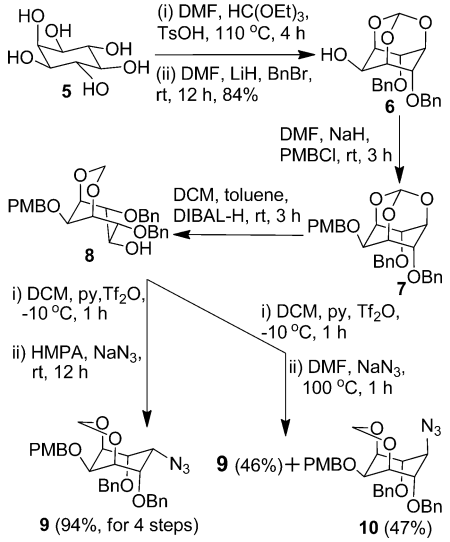
of synthetic modifications and structure activity relationship studies on (−)-**1** revealed that the aminocyclitol moiety in hygromycin A is critical for the antibacterial activity, while the fucofuranose moiety can be replaced with an allyl group or hydrogen.[16,33−35] Methoxyhygromycin (**2**), an analogue of hygromycin A, has been shown to possess herbicidal activity.[16,32,36]

A comparison of the structure of the aminocyclitol (−)**3** and *myo*-inositol (**5**) reveals that the relative orientation of all the substituents on the carbocylic ring, except the C5-substituent, is the same in both molecules. To convert **5** to (−)-**3**, (a) the C5-hydroxyl group must be converted to an amino group with inversion of configuration at the C5-carbon, (b) the C2 and C3-hydroxyl groups must be converted to the corresponding methylidene acetal, and (c) the *myo*-inositol derivative must be resolved or desymmetrized to obtain one enantiomer of the aminocyclitol unit of HMA. Key reactions in our synthetic approach to achieve these changes in *myo*-inositol were (i) one-pot conversion of *myo*-inositol to 4,6-di-*O*-benzyl orthoformate **6**, (ii) regioselective cleavage of the orthoformate in **7**, (iii) stereospecific introduction of the azido group at C5, and (iv) the resolution of the *racemic*-alcohol **13** as its mandelate esters.

Our synthesis began with a one-pot conversion of the commercially available *myo*-inositol (**5**) to the dibenzyl ether **6** (Scheme 1).[37] The C-2 hydroxyl group in **6** was protected as

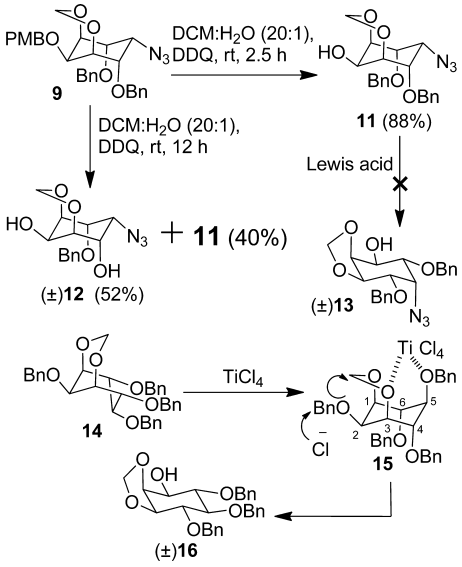
Scheme 1. Synthesis of the Azido Cyclitol 9



the PMB ether **7**, and the crude **7** was subjected to regioselective cleavage[6,7] by DIBAL-H to obtain the alcohol **8**. The high preference observed for the cleavage of the C5−O bond is due to the preferential complexation of the C5-oxygen atom of **7** with aluminum (in DIBAL-H). The steric bulk of the reducing agent precludes complexation of aluminum with C1 and C3 oxygen atoms of **7**. The free hydroxyl group in **8** was converted to the corresponding triflate by treatment with triflic anhydride in dichloromethane/pyridine at −10 °C. Nucleophilic displacement of the triflate by the azide[8] in HMPA gave the desired azide **9** in 94% yield (over four steps, **6**−**9**); the azide **9** was isolated by crystallization. We initially used DMF as a solvent for the substitution of the triflate (of **8**) by the azide ion.[8] This reaction did not proceed at ambient temperature; the reaction did proceed at 100 °C but gave a mixture of isomeric azides **9** and **10**, separable by chromatography. Configuration of the azides **9** and **10** was established unambiguously by single-crystal X-ray diffraction analysis. The observed difference in product formation in DMF and HMPA could be due to the difference in the temperature at which the reaction takes place. Better facility of the nucleophilic substitution reaction in HMPA (dielectric constant = 30) as compared to DMF (dielectric constant = 38) due to solvation of the cation by HMPA is well precedented in the literature.[38] However, further experimental and perhaps theoretical investigations are necessary to understand the effect of the solvent on the selectivity of this nucleophilic substitution reaction in this conformationally flexible bicyclic derivative **8**.[10]

Our initial attempts to cleave the PMB ether in **9** with DDQ resulted in the concomitant cleavage of one of the benzyl ethers as well (Scheme 2).[39] However, we could achieve the exclusive

Scheme 2. PMB Ether Cleavage in 9 and the Attempted Isomerization of the 1,3-Acetal to the Corresponding 1,2-Acetal



cleavage of the PMB ether by carrying out the reaction of **9** with DDQ under controlled conditions. The structures of the benzyl ethers **11** and (±)-**12** were established by single-crystal X-ray diffraction analysis.

Our attempts to isomerize the 1,3-methylidene acetal in **9** and **11** in the presence of Lewis acids ($TiCl_4$, $ZnCl_2$, $MgBr_2$, $BF_3{\cdot}OEt_2$)[6,40−42] to the corresponding 1,2-methylidene acetal (±)-**13**, failed.[43] This isomerization initially appeared feasible since the inositol ring in the acetals **9** and **11** is locked in a relatively less stable "axial rich" conformation compared to the acetal (±)-**13**, which exists in the relatively stable "equatorial rich" conformation. In addition, the 1,3-acetal **14** on treatment with a stoichiometric quantity of titanium tetrachloride is known to give the 1,2-acetal (±)-**16** (Scheme 2).[6,44] The conversion of **14** to (±)-**16** appears to require the chelation of titanium with three axially oriented oxygen atoms of the cyclitol. Perhaps the isomerization of **9** or **11** to the corresponding acetal did not proceed because of the absence of a suitably oriented oxygen atom at the C5-position of the inositol ring in **9** and **11** to aid the chelation of the Lewis acid (see **15**).

The PMB group and the 4,6-methylidene acetal in **9** were cleaved with concd HCl to obtain the triol **17** (Scheme 3).

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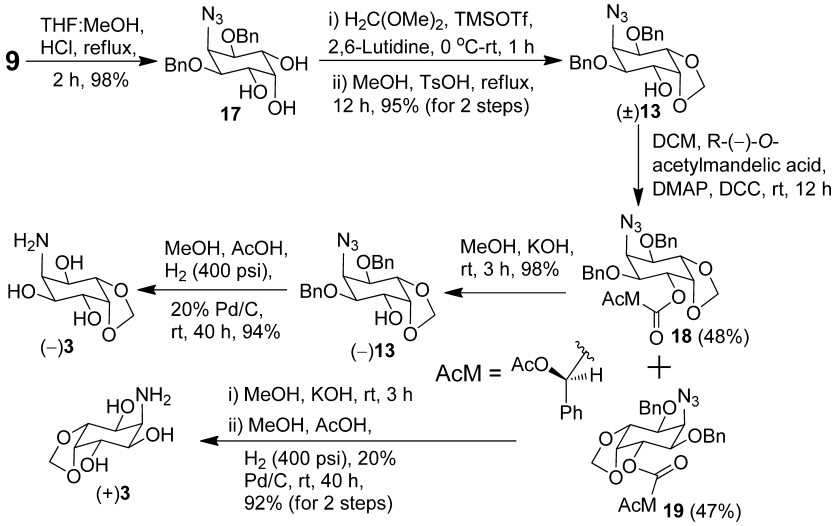
Scheme 3. Synthesis of the Aminocyclitol Unit of HMA and Its Enantiomer from 9

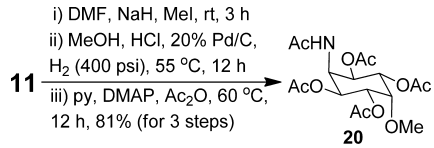


Treatment of the triol **17** with TMSOTf/lutidine in dimethoxymethane gave the methoxymethyl ether of (±)-**13**; the methoxymethyl ether could be cleaved in refluxing methanol in the presence of catalytic amount of TsOH without disturbing the *cis*-acetal to obtain the *racemic* alcohol **13** exclusively.[11,45] In our initial attempts, we observed that **17** could be converted to the desired 1,2-methylidene acetal (±)-**13** by using $POCl_3$ and DMSO,[46] but the yield obtained was very low (20%). Hence, we opted for the conversion of **17** to (±)-**13** via the MOM ether.

To synthesize the enantiomeric aminocyclitol of HMA, the *racemic*-alcohol **13** was *O*-acylated with (*R*)-(−)-*O*-acetylmandelic acid in the presence of DCC. The diasteriomeric esters **18** (48%) and **19** (47%) were separated by flash column chromatography. The structure and the relative configuration of **18** were confirmed by single-crystal X-ray diffraction analysis. The mandelate ester in **18** was hydrolyzed with methanolic KOH at room temperature to obtain (−)**13**. Finally, cleavage of the two benzyl ethers and reduction of the azide to the corresponding amine was carried out by catalytic hydrogenolysis in the presence of Pd/C in methanol−acetic acid to afford the amino cyclitol (−)-**3**. Similarly, we also converted **19** to the unnatural isomer (+)-**3**. The 11-step synthetic sequence starting from *myo*-inositol described so far, provided the aminocyclitol (−)-**3** as well as its enantiomer, in 31% overall yield (see the Supporting Information for comparison with previous literature reports). It is pertinent to note that none of the synthetic steps during the conversion of **5** to **9** involved chromatography, and the latter six steps (except the separation of **18** and **19**) resulted in the formation of a single product, which was isolated by chromatography. We also prepared the *racemic* amino cyclitol unit of HMA by reduction of the azide and cleavage of the benzyl ethers in *racemic* **13**. This was done in order to optimize the reaction conditions before the resolution of *racemic* **13** and preparation of the optically pure aminocyclitol (−)-**3**.

The synthesis of the aminocyclitol unit of methoxyhygromycin began with the methylation of the C2-hydroxyl group of the alcohol **11** (Scheme 4). Deprotection of all the hydroxyl groups as well as reduction of the azide to the amine was accomplished in a single step, and the aminocyclitol unit of MHM was isolated as its pentaacetate **20**. The structure of **20**

Scheme 4. Synthesis of the Aminocyclitol Unit of MHM



was established by single-crystal X-ray diffraction analysis. This synthetic sequence involved 10 steps, in four pots, and the overall yield of **20** was 56%.

To conclude, new syntheses from *myo*-inositol of the key aminocyclitol portion of hygromycin A as well as methoxyhygromycin are reported. During the synthesis of the former, only five column chromatographic purifications were necessary (out of a total of 11 steps), while the synthesis of the latter required only one column chromatographic purification and all the intermediates were purified by crystallization. These syntheses represent the highest yielding routes reported for the aminocyclitols (−)-**3** and **4** and illustrate the advantages of using inositol-1,3-acetals as early intermediates in syntheses starting from *myo*-inositol.

EXPERIMENTAL SECTION

General Experimental Methods. All of the solvents were purified according to the literature procedures[47] before use. A 60% dispersion of sodium hydride in mineral oil was used for *O*-alkylation reactions. Workup implies washing of the organic layer successively with water, dilute HCl (~2%), water, saturated sodium bicarbonate solution, water, followed by brine. Column chromatographic separations were carried out on silica gel (60−120 mesh or 230−400 mesh) or neutral alumina with a solvent system as mentioned in individual procedures. The compounds previously reported in the literature were characterized by comparison of their melting points and/or ^{1}H NMR spectra with reported data. All the racemic derivatives of *myo*-inositol (numbered with the prefix (±)) are represented in schemes by one of the enantiomers without numbering of the inositol ring carbon atoms.

4,6-Di-*O*-benzyl-*myo*-inositol 1,3,5-Orthoformate (6). *myo*-Inositol (**5**, 11.36 g, 63.10 mmol), triethyl orthoformate (16.00 mL, 96.78 mmol), and *p*-toluenesulfonic acid (1.08 g, 6.31 mmol) in dry DMF (100 mL) were heated at 110 °C for 4 h. The clear solution obtained was allowed to cool to room temperature, and dry triethylamine (1.2 mL) was added. The reaction mixture was concentrated under reduced pressure to afford a gummy solid which

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was dissolved in dry DMF (500 mL) and stirred after the addition of lithium hydride (2.00 g, 252.4 mmol) at ambient temperature for 1 h. To the thick slurry formed was added benzyl bromide (16.5 mL, 138.82 mmol) and the mixture stirred for 12 h. Ice was added to the reaction mixture, which was stirred for 2 h; solvents were removed under reduced pressure, and the residue was worked up with ethyl acetate and dried over anhyd sodium sulfate. The solvent was removed under reduced pressure, and the crude product was crystallized from hot 30% ethyl acetate in light petroleum to afford the crystalline dibenzyl ether **6** (19.63 g, 84%): mp 123−124 °C (lit.[48] mp 124−125 °C).

2-*O*-(4-Methoxybenzyl)-4,6-di-*O*-benzyl-*myo*-inositol 1,3,5-Orthoformate (7). To a solution of the dibenzyl ether **6** (14.81 g, 40.00 mmol) in dry DMF (100 mL) was added sodium hydride (1.92 g, 48.00 mmol) and the mixture stirred for 10 min. *p*-Methoxybenzyl chloride (6.00 mL, 44.00 mmol) was then added dropwise, and the reaction mixture was stirred for 3 h. Excess sodium hydride was quenched by the addition of ice-cold water. The solvent was evaporated under reduced pressure, and the residue was worked up with ethyl acetate and dried over anhyd sodium sulfate. The solvent was removed under reduced pressure to afford the **7** (19.60 g) as a gum, which was used for the next reaction without purification.

A small quantity of the crude **7** was purified by column chromatography (eluent: 15% ethyl acetate in light petroleum) to afford **7** as a gummy liquid: TLC R_f = 0.3 in 15% ethyl acetate/light petroleum; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 7.15−7.32 (m, 12H), 6.80−6.85 (m, 2H), 5.52 (d, J = 1.2 Hz, 1H), 4.59 (s, 2H), 4.54 (q, J = 11.4 Hz, 4H), 4.40−4.42 (m, 1H), 4.29−4.37 (m, 2H), 4.22−4.28 (m, 2H), 4.01−4.06 (m, 1H), 3.76 (s, 3H) ppm; ^{13}C NMR ($CDCl_3$, 50.3 MHz) δ 159.2, 137.5, 129.7, 128.3, 127.7, 127.4, 113.7, 103.1, 73.9, 71.4, 71.1, 70.5, 68.0, 66.5, 55.1. Anal. Calcd for $C_{29}H_{30}O_7$ (490.54): C, 71.00; H, 6.16. Found: C, 71.26; H, 6.10.

1,3-*O*-Methylidene-2-*O*-(4-methoxybenzyl)-4,6-di-*O*-benzyl-*myo*-inositol (8). A 1 M solution of DIBAL-H in toluene (100.0 mL, 100.00 mmol) was added dropwise over a period of 15 min to a solution of the crude **7** (19.58 g) in dry dichloromethane (250 mL) at 0 °C and then stirred at room temperature for 3 h. The reaction mixture was poured into a stirred solution of sodium potassium tartarate (240 g in 400 mL water) and saturated solution of ammonium chloride (400 mL) and stirred for 12 h. The mixture was extracted with dichloromethane (2 × 400 mL), washed with brine, and dried over anhyd sodium sulfate. The solvent was removed under reduced pressure to obtain the alcohol **8** (19.73 g) as a gummy liquid which was used for next reaction without purification. A small quantity of the crude **8** was purified by column chromatography (eluent: 15% ethyl acetate in light petroleum): TLC R_f = 0.3 in 15% ethyl acetate/light petroleum; IR (neat) $\bar{\nu}$ 3510−3570 cm^{-1}; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 7.15−7.35 (m, 12H), 6.7−6.85 (m, 2H), 5.55 (d, J = 4.9 Hz, 1H), 4.69 (d, J = 4.9 Hz, 1H), 4.50−4.66 (m, 6H), 4.39−4.46 (m, 2H), 4.27−4.32 (m, 1H), 3.90−4.07 (m, 3H), 3.77 (s, 3H), 3.00 (d, J = 9.9 Hz, 1H) ppm; ^{13}C NMR ($CDCl_3$, 50.3 MHz) δ 159.2, 137.8, 129.5, 128.2, 127.5, 127.3, 113.7, 85.5, 81.0, 72.5, 71.9, 70.1, 69.4, 69.3, 55.1 ppm. Anal. Calcd for $C_{29}H_{32}O_7$ (492.56): C, 70.71; H, 6.55. Found: C, 70.32; H, 6.65.

1,3-Di-*O*-benzyl-2-azido-2-deoxy-4,6-*O*-methylidene-5-*O*-(4-methoxybenzyl)-*neo*-inositol (9). To a cooled (−10 °C) solution of crude **8** (12.40 g, ∼25.0 mmol) in dry pyridine (15 mL) and dry dichloromethane (50 mL) was added triflic anhydride (3.26 mL, 30.00 mmol) dropwise over a period of 15 min. The temperature of the reaction mixture was then allowed to rise to room temperature, and stirring was continued for 1 h. The solvents were removed under reduced pressure, and the residue was worked up with dichloromethane and dried over anhyd sodium sulfate. The solvent was removed under reduced pressure to afford the crude triflate (15.7 g) as a gum which was used in the next step.

To a solution of the crude triflate (15.0 g) in HMPA (30 mL) was added sodium azide (3.90 g, 60.00 mmol) and the reaction mixture stirred for 12 h at room temperature. The reaction mixture was poured into cold water and extracted with diethyl ether (3 × 100 mL). The ether extract was washed with brine and dried over anhyd sodium sulfate. The solvent was removed under reduced pressure to obtain the crude product, which was purified by crystallization (hot 10% ethyl acetate in light petroleum) to afford the azide **9** (11.67 g, 94% for four steps) as a colorless solid: TLC R_f = 0.5 in 30% ethyl acetate/light petroleum; mp 81−82 °C; IR (Nujol) $\bar{\nu}$ 2110 cm^{-1}; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 7.28−7.37 (m, 10H), 7.13−7.20 (m, 2H), 6.72−6.82 (m, 2H), 5.46 (d, J = 4.6 Hz, 1H), 4.67 (q, J = 11.9 Hz, 4H), 4.52 (brs, 1H), 4.41 (s, 2H), 4.37−4.39 (m, 1H), 4.21−4.26 (m, 2H), 4.05 (t, J = 4.2 Hz, 2H), 3.74 (s, 3H), 3.69−3.73 (m, 1H) ppm; ^{13}C NMR ($CDCl_3$, 50.3 MHz) δ 159.2, 137.7, 129.5, 129.4, 128.3, 127.7, 127.6, 113.8, 85.4, 80.2, 73.4, 70.4, 70.2, 68.8, 55.1, 53.7 ppm. Anal. Calcd for $C_{29}H_{31}N_3O_6$ (517.57): C, 67.30; H, 6.04; N, 8.12. Found: C, 67.07; H, 6.36; N, 8.32%.

Reaction of the Triflate of 8 with Sodium Azide in DMF. A mixture of the crude triflate (0.62 g, ∼1.0 mmol; prepared from alcohol **8**), sodium azide (0.33 g, 2.14 mmol), and DMF (10 mL) was stirred at 100 °C for 1 h in an atmosphere of argon. The solvent was evaporated under reduced pressure, and the residue worked up with ethyl acetate and dried over anhydrous sodium sulfate. The solvent was removed under reduced pressure, and the products were separated by column chromatography to obtain **9** (0.238 g, 46%; eluent: 10% ethyl acetate in light petroleum) and **10** (0.243 g, 47%; eluent: 15% ethyl acetate in light petroleum) as colorless solids.

Data for 10: TLC R_f = 0.4 in 30% ethyl acetate/light petroleum; mp 61−62 °C (crystals from hot 10% ethyl acetate in light petroleum); IR (neat) $\bar{\nu}$ 2104 cm^{-1}; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 7.28−7.45 (m, 12H), 6.82−6.90 (m, 2H), 5.23 (d, J = 5.2 Hz, 1H), 4.74 (d, J = 5.1 Hz, 1H), 4.60−4.71 (m, 4H), 4.58 (s, 2H), 4.25 (brs, 2H), 3.87 (t, J = 1.8 Hz, 1H), 3.78−3.83 (m, 2H), 3.79 (s, 3H), 3.56 (t, J = 7.0 Hz, 1H) ppm; ^{13}C NMR ($CDCl_3$, 50.3 MHz) δ 159.4, 137.1, 129.5, 128.4, 127.9, 113.9, 85.5, 81.1, 71.9, 71.7, 70.6, 69.6, 63.5, 55.2 ppm. Anal. Calcd for $C_{29}H_{31}N_3O_6$ (517.57): C, 67.30; H, 6.04; N, 8.12. Found: C, 67.25; H, 6.01; N, 8.02.

1,3-Di-*O*-benzyl-2-azido-2-deoxy-4,6-*O*-methylidene-*neo*-inositol (11). To a solution of **9** (3.10 g, 6.00 mmol) in dichloromethane (40 mL) and water (2 mL) was added DDQ (3.40 g, 15.00 mmol) and the mixture stirred for 2.5 h at room temperature. The reaction mixture was diluted with dichloromethane (100 mL) and washed with satd $NaHCO_3$ solution and water followed by brine and dried over anhyd sodium sulfate. The solvent was evaporated under reduced pressure to obtain a gum which was purified by column chromatography (eluent: 20% ethyl acetate in light petroleum) to afford **11** (2.10 g, 88%) as a colorless solid: TLC R_f = 0.3 in 20% ethyl acetate/light petroleum; mp 55.5−57 °C (crystals from hot 20% ethyl acetate in light petroleum); IR (Nujol) $\bar{\nu}$ 3200−3650, 2108 cm^{-1}; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 7.27−7.43 (m, 10H), 5.48 (d, J = 4.6 Hz, 1H), 4.83 (d, J = 11.8 Hz, 2H), 4.56−4.69 (m, 4H), 4.14−4.21 (m, 2H), 4.07 (t, J = 4.2 Hz, 2H), 3.76 (t, J = Ins H, 3.9 Hz, 1H), 2.07 (s, 1H) ppm; ^{13}C NMR ($CDCl_3$, 50.3 MHz) δ 137.6, 128.3, 127.8, 127.7, 85.2, 79.9, 73.5, 72.6, 62.7, 53.7 ppm. Anal. Calcd for $C_{21}H_{23}N_3O_5$ (397.42): C, 63.46; H, 5.83; N, 10.57. Found: C, 63.80; H, 5.45; N, 10.96.

***rac*-1-*O*-Benzyl-2-azido-2-deoxy-4,6-*O*-methylidene-*neo*-inositol [(±)-12].** To a solution of **9** (1.03 g, 2.00 mmol) in dichloromethane (30 mL) and water (1.5 mL) was added DDQ (1.1 g, 5.00 mmol), and the mixture was stirred for 12 h at room temperature. The reaction mixture was diluted with dichloromethane (50 mL), washed with satd $NaHCO_3$ solution and water followed by brine, and dried over anhyd sodium sulfate. The solvent was evaporated under reduced pressure to obtain a gum which was purified by column chromatography to afford **11** (0.32 g, 40%; eluent: 15% ethyl acetate in light petroleum) and (±)-**12** (0.41 g, 52%; eluent: 30% ethyl acetate in light petroleum) as colorless solids. Data for (±)-**12**: TLC R_f = 0.3 in 30% ethyl acetate/light petroleum; mp 107−108 °C (crystals from hot 50% ethyl acetate in light petroleum); IR (Nujol) $\bar{\nu}$ 3200−3500, 2109 cm^{-1}; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 7.27−7.45 (m, 5H), 5.57 (d, J = 4.6 Hz, 1H), 4.79 (d, J = 11.5 Hz, 1H), 4.51−4.68 (m, 3H), 4.16−4.33 (m, 4H), 4.04−4.12 (m, 1H), 2.89 (d, J = 6.6 Hz, 1H), 2.39 (d, J = 4.2 Hz, 1H) ppm; ^{13}C NMR ($CDCl_3$+CD_3OD, 50.3 MHz) δ 136.8, 128.3, 127.9, 85.0, 79.4, 74.7,

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73.8, 72.3, 72.2, 60.9, 54.7 ppm. Anal. Calcd for $C_{14}H_{17}N_3O_5$ (307.30): C, 54.72; H, 5.58; N, 13.67. Found: C, 54.84; H, 5.59; N, 13.30.

1,3-Di-*O*-benzyl-2-azido-2-deoxy-*neo*-inositol (17). A mixture of **9** (9.31 g, 18.00 mmol), THF−methanol (25 mL + 75 mL), and concd HCl (10 mL) was refluxed for 2 h. The solvents were removed under reduced pressure to obtain a solid which was purified by column chromatography (eluent: 50% ethyl acetate in light petroleum) to afford **17** (6.80 g, 98%) as a colorless solid: TLC R_f = 0.3 in 50% ethyl acetate/light petroleum; mp 106−107.5 °C; IR (Nujol) $\bar{\nu}$ 3350−3430, 2099 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ 7.30−7.45 (m, 10H), 4.63 (q, J = 11.6 Hz, 4H), 4.14 (t, J = 2.9 Hz, 1H), 4.00 (t, J = 3.0 Hz, 1H), 3.84 (dd, J_1 = 3.0 Hz, J_2 = 9.7 Hz, 2H), 3.67 (dd, J_1 = 3.2 Hz, J_2 = 9.6 Hz, 2H), 2.56 (brs, 3H) ppm; ^{13}C NMR (CD_3OD, 50.3 MHz) δ 139.6, 129.4, 129.1, 128.8, 78.5, 73.7, 73.4, 71.0, 62.4 ppm. Anal. Calcd for $C_{20}H_{23}N_3O_5$ (385.41): C, 62.33; H, 6.01; N, 10.90. Found: C, 62.22; H, 6.42; N, 11.18.

***rac*-1,3-Di-*O*-benzyl-2-azido-2-deoxy-4,5-*O*-methylidene-*neo*-inositol [(±)-13].** To a cooled (0 °C) solution of **17** (1.93 g, 5.00 mmol) in dimethoxymethane (20 mL) were added 2,6-lutidine (1.40 mL, 12.00 mmol) and trimethylsilyl trifluoromethanesulfonate (TMSOTf, 3.60 mL, 20.00 mmol). The reaction mixture was allowed to warm to ambient temperature, and stirring was continued for 1 h. The reaction mixture was quenched by solid sodium bicarbonate, and the solvents were removed under reduced pressure. The crude reaction mixture was dissolved in ethyl acetate, washed successively with water and saturated sodium bicarbonate solution followed by brine, and dried over anhyd sodium sulfate. The solvent was removed under reduced pressure to afford a gum (2.20 g; TLC R_f = 0.3 in 15% ethyl acetate/light petroleum) which was used in the next step without purification.

To a solution of the crude gum (2.20 g) in dichloromethane (15 mL) were added methanol (25 mL), water (2 mL), and *p*-toluenesulfonic acid (0.10 g, 0.53 mmol), and the mixture refluxed for 12 h. After neutralization with solid Na_2CO_3 and filtration, the residue was concentrated under reduced pressure. Purification of the residue by column chromatography (eluent: 40% ethyl acetate in light petroleum) gave (±)-**13** (1.89 g, 95%, two steps) as a gum: TLC R_f = 0.3 in 40% ethyl acetate/light petroleum; IR (neat) $\bar{\nu}$ 3300−3600, 2102 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ 7.27−7.45 (m, 10H), 5.09 (s, 1H), 4.96 (s, 1H), 4.60−4.79 (m, 4H), 4.35 (dd, J_1 = 5.2 Hz, J_2 = 7.6 Hz, 1H), 4.12−4.26 (m, 2H), 3.95 (t, J_1 = 3.0 Hz, 1H), 3.62 (dd, J_1 = 2.7 Hz, J_2 = 9.0 Hz, 1H), 3.40 (dd, J_1 = 3.0 Hz, J_2 = 7.7 Hz, 1H), 2.57 (brs, 1H) ppm; ^{13}C NMR ($CDCl_3$, 50.3 MHz) δ 137.5, 137.3, 128.6, 128.4, 128.1, 127.9, 127.8, 127.76, 127.6, 94.8, 77.7, 77.2, 76.5, 76.0, 72.7, 72.0, 68.1, 61.1 ppm. Anal. Calcd for $C_{21}H_{23}N_3O_5$ (397.42): C, 63.46; H, 5.83; N, 10.57. Found: C, 63.26; H, 5.88; N, 10.38.

Reaction of the Triol 17 with $POCl_3$ in DMSO.[46] To a solution of **17** (0.50 g, 1.3 mmol) in dry DMSO (7 mL) was added $POCl_3$ (0.2 mL, 2.2 mmol) and the mixture stirred at 65 °C for 3 h. The reaction mixture was then diluted with water and extracted with dichloromethane (3 × 100 mL). After the usual workup, the crude **13** was purified by column chromatography (eluent: 40% ethyl acetate in light petroleum) to obtain (±)-**13** (0.10 g, 20%) as a gum.

1L-1,3-Di-*O*-benzyl-2-azido-2-deoxy-4,5-*O*-methylidene-6-[(*R*)-(−)-*O*-(acetylmandeloyl)]-*neo*-inositol (18) and 1D-1,3-Di-*O*-benzyl-2-azido-2-deoxy-4,5-*O*-methylidene-6-[(*R*)-(−)-*O*-(acetylmandeloyl)]-*neo*-inositol (19). To a solution of (±)-**13** (0.84 g, 2.12 mmol) in dry dichloromethane (15 mL) were added (*R*)-(−)-*O*-acetylmandelic acid (0.62 g, 3.18 mmol), DCC (0.52 g, 2.52 mmol), and DMAP (0.02 g, 0.21 mmol), and the mixture was stirred at room temperature for 12 h. The solvent was removed under reduced pressure to obtain a gum which was purified by flash column chromatography to afford **18** (0.58 g, 48%; eluent: 10 to 15% ethyl acetate in light petroleum) as a solid and **19** (0.57 g, 47%; eluent: 15 to 20% ethyl acetate in light petroleum) as a gummy liquid. Data for **18**: TLC R_f = 0.5 in 25% ethyl acetate/light petroleum; mp 106−107.5 °C (crystals from hot 10% chloroform in *n*-hexane); $[\alpha]_D^{25}$ −36 (c = 1.0, $CHCl_3$); IR ($CHCl_3$) $\bar{\nu}$ 2106, 1755, 1748 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ 7.27−7.50 (m, 15H), 5.98 (s, 1H), 5.49 (dd, J_1 = 4.3 Hz, J_2 = 9.4 Hz, 1H), 4.88 (s, 1H), 4.75 (s, 1H), 4.48−4.70 (m, 4H), 4.30 (dd, J_1 = 4.9 Hz, J_2 = 7.4 Hz, 1H), 4.05 (t, J = 4.6 Hz, 1H), 3.85 (t, J = 3.0 Hz, 1H), 3.76 (dd, J_1 = 3.1 Hz, J_2 = 9.4 Hz, 1H), 3.3 (dd, J_1 = 2.9 Hz, J_2 = 7.5 Hz, 1H), 2.19 (s, 3H) ppm; ^{13}C NMR ($CDCl_3$, 50.3 MHz) δ 170.1, 168.0, 137.4, 133.2, 129.1, 128.6, 128.5, 128.4, 128.0, 127.9, 127.86, 127.7, 127.4, 94.8, 75.2, 74.9, 74.4, 74.2, 72.9, 71.9, 71.3, 61.8, 20.6 ppm. Anal. Calcd for $C_{31}H_{31}N_3O_8$ (573.59): C, 64.91; H, 5.45; N, 7.33. Found: C, 65.01; H, 5.68; N, 7.00.

Data for 19: TLC R_f = 0.45 in 25% ethyl acetate/light petroleum; $[\alpha]_D^{25}$ +30 (c = 1.0, $CHCl_3$); IR ($CHCl_3$) $\bar{\nu}$ 2106, 1751, 1744 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ 7.26−7.55 (m, 13H), 6.97−7.07 (m, 2H), 6.03 (s, 1H), 5.46 (dd, J_1 = 4.1 Hz, J_2 = 9.8 Hz, 1H), 5.06 (s, 1H), 4.97 (s, 1H), 4.62 (q, J = 12.2 Hz, 2H), 4.35 (dd, J_1 = 5.0 Hz, J_2 = 12.4 Hz, 1H), 4.24 (t, J = 4.5 Hz, 1H), 4.02 (q, J = 12.3 Hz, 2H), 3.70 (t, J = 3.1 Hz, 1H), 3.62 (dd, J_1 = 3.0 Hz, J_2 = 10.2 Hz, 1H), 3.30 (dd, J_1 = 2.9 Hz, J_2 = 8.5 Hz, 1H), 2.19 (s, 3H) ppm; ^{13}C NMR ($CDCl_3$, 50.3 MHz) δ 170.2, 168.0, 137.3, 137.2, 133.3, 129.3, 128.7, 128.5, 128.4, 128.0, 127.8, 127.7, 127.6, 127.5, 94.9, 77.0, 75.2, 74.6, 74.4, 74.2, 72.7, 71.8, 71.5, 61.9, 20.6 ppm; HRMS (ES^+) calcd for $C_{31}H_{31}N_3O_8Na$ [M + Na]$^+$ 596.2009, found 596.2047.

1L-1,3-Di-*O*-benzyl-2-azido-2-deoxy-4,5-*O*-methylidene-*neo*-inositol [(−)-13]. To a solution of the ester **18** (0.57 g, 1.00 mmol) in methanol (10 mL) was added KOH (0.28 g, 5.00 mmol) and the mixture stirred for 3 h at room temperature. The solvents were removed under reduced pressure, and the residue was dissolved in ethyl acetate, washed with water and brine, and dried over anhyd sodium sulfate. Solvent was removed under reduced pressure to obtain the crude alcohol which was purified by column chromatography (eluent: 40% ethyl acetate/light petroleum) to obtain (−)-**13** as a gum (0.39 g, 98%): TLC R_f = 0.3 in 40% ethyl acetate/light petroleum; $[\alpha]_D^{25}$ −32 (c = 1.0 in $CHCl_3$); IR (neat) $\bar{\nu}$ 3320−3600, 2103 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ 7.27−7.45 (m, 10H), 5.09 (s, 1H), 4.96 (s, 1H), 4.60−4.79 (m, 4H), 4.32−4.8 (dd, J_1 = 5.2 Hz, J_2 = 7.6 Hz, 1H) 4.13−4.26 (m, 2H), 3.95 (t, J_1 = 3.0 Hz, 1H), 3.59−3.365 (dd, J_1 = 2.7 Hz, J_2 = 9.0 Hz, 1H), 3.37−3.42 (dd, J_1 = 3.0 Hz, J_2 = 7.7 Hz, 1H), 2.57 (brs, 1H) ppm; ^{13}C NMR ($CDCl_3$, 50.3 MHz) δ 137.5, 137.3, 128.6, 128.4, 128.1, 127.9, 127.8, 127.76, 127.6, 94.8, 77.7, 77.2, 76.5, 76.0, 72.7, 72.0, 68.1, 61.1 ppm; HRMS (ES^+) calcd for $C_{21}H_{24}N_3O_5$ [M + H]$^+$ 398.1716, found 398.1715.

1L-2-Amino-2-deoxy-4,5-*O*-methylidene-*neo*-inositol [(−)-3]. The azide (−)**13** (0.36 g, 0.91 mmol) was hydrogenolyzed in a mixture of methanol (6 mL) and acetic acid (0.1 mL) in the presence of 20% Pd/C (0.09 g) at 400 psi at rt for 40 h in a Parr reactor. The catalyst was filtered using a short bed of Celite, and the catalyst was washed with methanol (2 × 25 mL) and distilled water (2 × 10 mL) successively. The combined filtrate was evaporated under reduced pressure and the residue coevaporated with triethylamine (2 × 5 mL) to obtain the crude amine which was purified by column chromatography [neutral alumina; eluent: MeOH/$CHCl_3$/NH_4OH (10:10:0.1)] to isolate (−)**3** as a colorless amorphous solid (0.163 g, 94%): $[\alpha]_D^{25}$ −29 (c = 1.1, H_2O) [lit.[49] $[\alpha]_D^{22}$ −33 (c = 1.97, H_2O)]; mp 150−157 °C (lit.[50] mp 151−156 °C).

1D-2-Amino-2-deoxy-4,5-*O*-methylidene-*neo*-inositol [(+)-3]. To a solution of the ester **19** (0.57 g, 1.00 mmol) in methanol (10 mL) was added KOH (0.28 g, 5.00 mmol) and the mixture stirred for 3 h at room temperature. The solvents were removed under reduced pressure, and the residue was dissolved in ethyl acetate, washed with water and brine, and dried over anhyd sodium sulfate. Solvent was removed under reduced pressure to obtain the crude alcohol (0.40 g) as a gummy liquid which was used in the next reaction without purification.

The crude product (0.40 g) was hydrogenolyzed in a mixture of methanol (6 mL) and acetic acid (0.1 mL) in the presence of 20% Pd/C (0.10 g) at 400 psi at rt for 40 h in a Parr reactor. The catalyst was filtered using a short bed of Celite, and the catalyst was washed with methanol (2 × 25 mL) and distilled water (2 × 10 mL) successively. The combined filtrate was evaporated under reduced pressure and the residue coevaporated with triethylamine (2 × 5 mL) to obtain the crude amine which was purified by column chromatography [neutral alumina; eluent: MeOH/$CHCl_3$/NH_4OH (10:10:0.1)] to obtain (+)-**3** as a colorless amorphous solid (0.176 g, 92%): $[\alpha]_D^{25}$ +30 (c =

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1.2, H_2O); mp 153−159 °C; ^1H NMR (D_2O, 500 MHz; with acetone as internal reference at δ 2.08 ppm): 5.07 (s, 1H), 4.83 (s, 1H), 4.17 (dd, J_1 = 4.9 Hz, J_2 = 7.7 Hz, 1H), 4.06 (t, J = 4.6, 1H), 4.01 (dd, J_1 = 4.2 Hz, J_2 = 9.7 Hz, 1H), 3.73 (dd, J_1 = 3.7 Hz, J_2 = 9.8 Hz, 1H), 3.60 (dd, J_1 = 3.1 Hz, J_2 = 7.7 Hz, 1H), 3.26 (t, J = 3.1 Hz, 1H) ppm; ^{13}C NMR (D_2O, 125.76 MHz) δ 95.5, 76.8, 76.2, 70.5, 67.74, 67.70, 50.9 ppm; HRMS (ES^+) calcd for $C_7H_{14}NO_5$ $[M + H]^+$ 192.0872, found 192.0881.

1,3,4,6-Tetra-*O*-acetyl-2-acetylamino-2-deoxy-5-*O*-methyl-*neo*-inositol (20). To a solution of the alcohol **11** (0.40 g, 1.01 mmol) in dry DMF (5 mL) was added sodium hydride (0.05 g, 1.25 mmol) and the mixture stirred for 10 min. Methyl iodide (0.1 mL, 1.6 mmol) was then added dropwise, and the reaction mixture was stirred for 3 h. Excess sodium hydride was quenched by the addition of ice-cold water. The solvent was evaporated under reduced pressure, and the residue was worked up with ethyl acetate and dried over anhyd sodium sulfate. The solvent was removed under reduced pressure to obtain the corresponding methyl ether (0.405 g) as a gum, which was used for the next reaction without purification.

One-pot deprotection of benzyl groups, 1,3-*O*-methylidene acetal, and reduction of the azide was carried out by hydrogenation in a mixture of methanol (7 mL) and concd HCl (1 mL) in the presence of 20% Pd/C (0.10 g) at 400 psi at 55 °C for 12 h in a Parr reactor. The catalyst was filtered using a short bed of Celite, and the catalyst was washed with methanol (2 × 25 mL) and distilled water (2 × 10 mL) successively. The combined filtrate was evaporated under reduced pressure and the residue coevaporated with triethyl amine (2 × 5 mL) to obtain the crude amine (0.095 g) as a dirty white solid. The crude amine was acetylated with acetic anhydride (2.0 mL) and DMAP (0.01 g) in dry pyridine (5 mL) at 60 °C for 12 h. The solvents were removed under reduced pressure, and the residue obtained was worked up with dichloromethane and dried over anhyd sodium sulfate. The solvent was evaporated, and the crude acetate was purified by crystallization from a mixture of hot ethyl acetate/light petroleum (4:1) to obtain colorless crystals of **20** (0.33 g, 81% for three steps): TLC R_f = 0.3 in ethyl acetate; mp 159−162 °C; IR ($CHCl_3$) $\bar{\nu}$ 3379, 1747, 1720, 1684 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 6.47 (d, J = 9.8 Hz, 1H), 5.44 (dd, J_1 = 5.5 Hz, J_2 = 11.0 Hz, 2H), 5.17 (dd, J_1 = 2.5 Hz, J_2 = 11.0 Hz, 2H), 4.95−5.04 (m, 1H), 3.93 (t, J = 2.6 Hz, 1H), 3.52 (s, 3H), 2.12 (s, 6H), 2.06 (s, 3H), 2.01 (s, 6H) ppm; ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 170.9, 169.5, 76.5, 70.1, 67.1, 61.5, 47.0, 23.1, 20.9, 20.7 ppm. Anal. Calcd for $C_{17}H_{25}NO_{10}$ (403.38): C, 50.62; H, 6.25; N, 3.47. Found: C, 51.01; H, 6.26; N, 3.19.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

[Crystallographic data for **9**−**12**, **18**, and **20** and copies of ^1H and ^{13}C NMR spectra for all new compounds appearing in the schemes. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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