Synthetic Study toward a Protected 2-Deoxystreptamine

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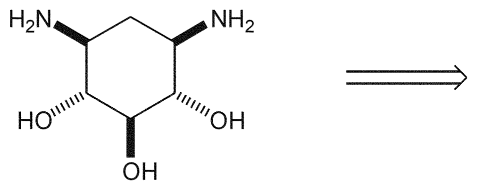
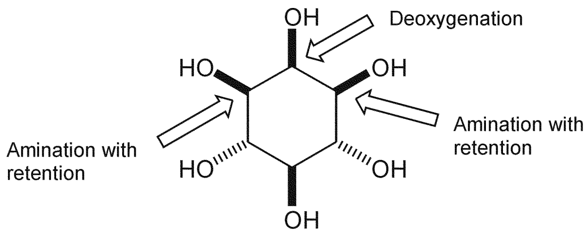
2-Deoxystreptamine (**1**) is a key component of aminoglycoside antibiotics such as Streptomycin, Neomycins, Kanamycins, Gentamycins and Sisomycins which are still clinically useful.[1,2] The structure and configuration were established to be a 1,3-diamino-4,5,6-cyclohexanetriol with all-*trans* configuration.[3] Despite numerous research interests in this area, only several chemical synthetic methods are known.[4]

Here we described the first synthetic approach of the protected 2-deoxystreptamine from *myo*-inositol.



2-Deoxystreptamine (**1**)



myo-Inositol

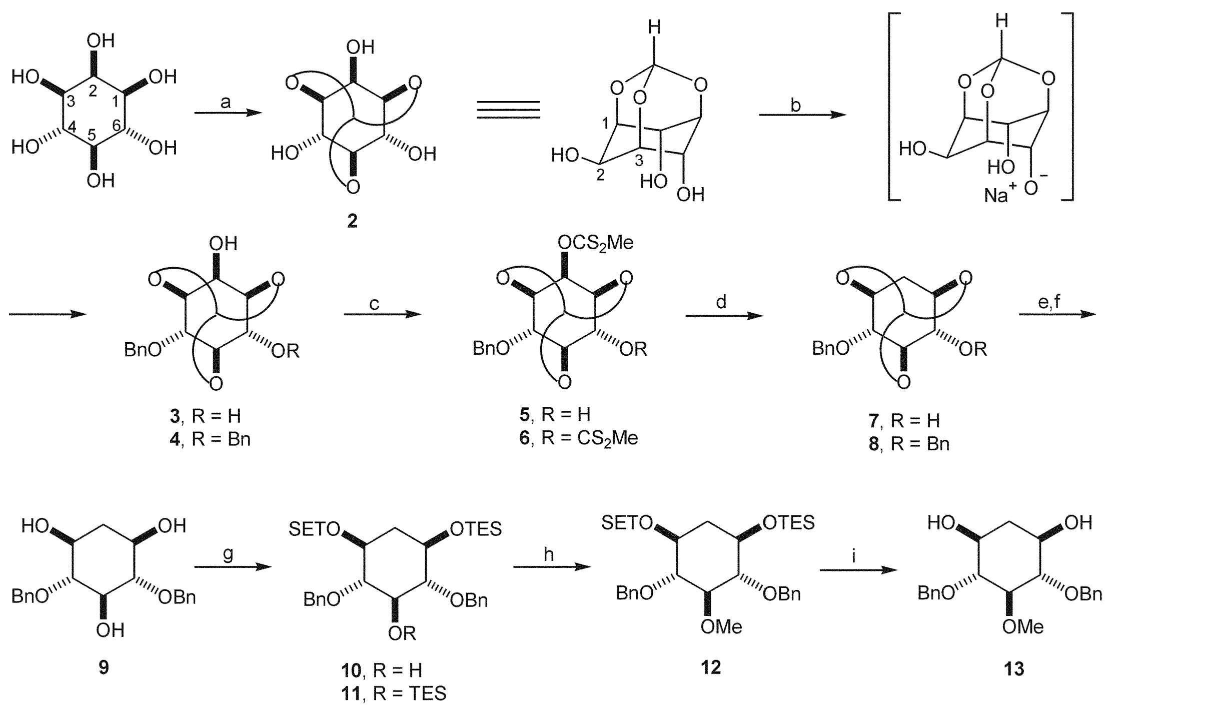
Reaction of *myo*-inositol with triethyl orthoformate in the presence of acid catalyst gave inositol orthoformate **2** whose synthesis and structure was reported.[5] It provides simultaneous protection of three hydroxyl groups at C-1,3,5 and results in inversion of the axial/equatorial relationship of the remaining free hydroxyl groups (Scheme 1). Selective monobenzylation at C-4 in **2** was carried out with NaH in DMF in high yield, together with a trace of the 4,6-dibenzyl ether **4**.[6] This high regioselectivity and degree of monobenzylation are presumably due to internal coordination in an intermediate anion.[6] Radical induced cleavage method was employed to deoxygenate the OH group at C-2 position. The less hindered equatorial C-2 hydroxyl group in **3** was selectively converted to xanthate ester compound **5**, which was smoothly cleaved to **7**. The remaining C-6 position was subsequently protected with benzyl ether to afford **8**. Hydrolysis of masking orthoformate group with aqueous HCl provides 2-deoxy-4,6-*O*-dibenzyl-*myo*-inositol (**9**). Triols such as **9** are selectively protected and masking of intermediate **10** with methyl ether affords **12**. Fluoride-assisted removal of silyl groups at C-1,3 afforded diol compound **13**.

Introduction of amine function with the requisite configuration at C-1,3 positions was carried out oxidation, oxime formation and reduction of oxime to amine sequences. Oxidation of **13** with PCC delivers monoketone compound which accompanies oxime formation with hydroxylamine in pyridine. Reduction of oxime **14** with $LiAlH_4$ to amine compounds **15**, **16** proceeded at a moderate pace and gave satisfactory yield with an isomer ratio greater than 95 : 5 with 84% yield. The successful outcome of this diastereoselectivity has been attributed to thermodynamically controlled reduction of oxime. If a chair conformation were favored for the reduction products **15**, **16** from **14**, the required isomer **16** with an equatorial amine substituent should be favored over **15** with that substituent axial (Scheme 2). Subsequent protection of resulting amine function in **16** with Boc group furnishes **17**. Introduction of another amine function at C-3 position was accomplished by reiteration of above procedure with high stereoselectivity (92 : 8). Finally, protection of amine **19** with Boc group provides the target protected 2-deoxystreptamine **21**.

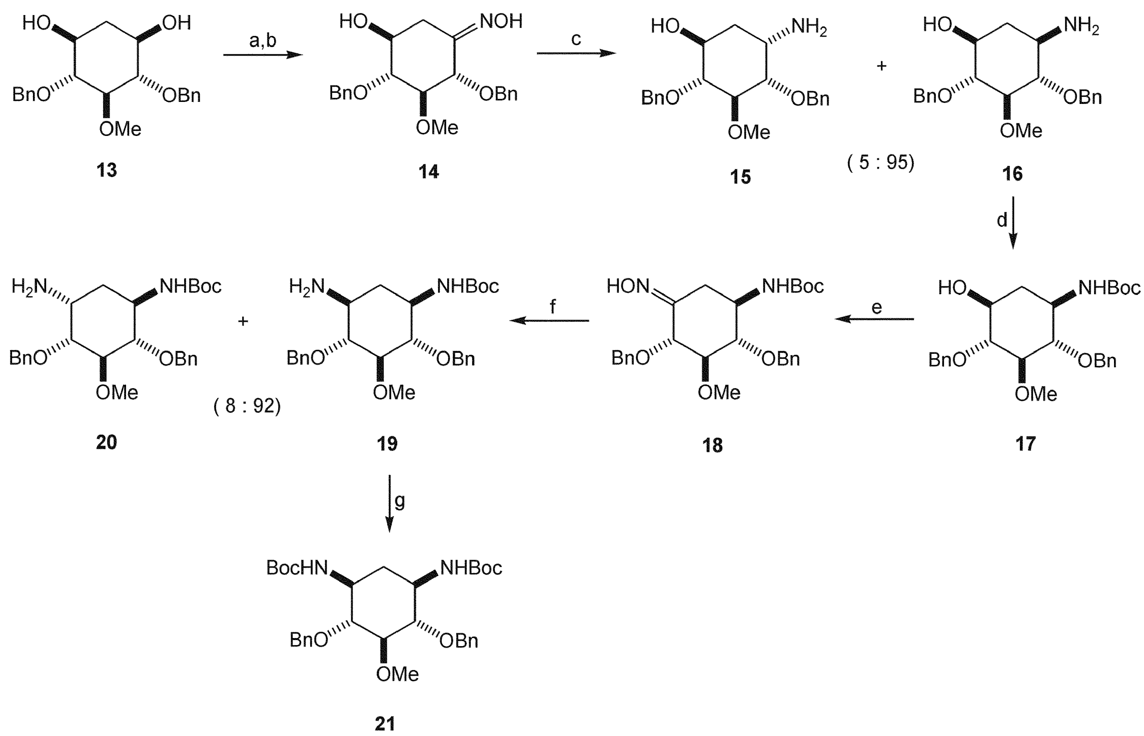
Stereochemical characterization of the target product **21** was accomplished by ^1H and ^{13}C NMR spectra. That the target **21** was the symmetrical isomer was readily apparent from the overlap of magnetic resonances corresponding to the equivalent hydrogens and carbons in its ^1H NMR and ^{13}C NMR spectra.[8] Although several synthesis of the 2-deoxystreptamine were reported previously, the present synthesis of **21** is the first synthetic approach from *myo*-inositol as a starting material and, most importantly, generates the high stereoselectivity at C-1,3.

Experimental Section

(±) 1,2-Dideoxy-1-amino-4,6-*O*-dibenzyl-5-*O*-methyl-*myo*-inositol (16). To a stirred solution of oxime **14** (600 mg, 1.62 mmol) in freshly distilled THF (10.0 mL) was added 95% $LiAlH_4$ (260 mg, 6.48 mmol) at room temperature. The resulting mixture was refluxed for 2 h. After the



Scheme 1[7]. Reagents and conditions: (a) $HC(OEt)_3$, *p*-TsOH (cat.), DMF, 80%; (b) NaH (1.1 eq.), BnBr (1.1 eq.), DMF, 25 °C, 85% (**3** : **4** 8 : 1); (c) NaH (1.1 eq.), CS_2 (1.1 eq.), MeI, reflux, 85% (**5** : **6** – 8 : 1); (d) $(n\text{-}Bu)_3SnH$, AIBN, toluene, reflux, 90%; (e) NaH (1.2 eq.), BnBr (1.2 eq.), DMF; (f) aq. HCl, two steps 93%; (g) TESCl (2.2 eq.), pyridine, 85% (**10** : **11** = 7 : 1); (h) NaH (1.2 eq.), MeI (1.2 eq.), DMF, 94%; (i) $(n\text{-}Bu)_4NF$, THF, 100%.



Scheme 2[7]. Reagents and Conditions: (a) PCC, CH_2Cl_2, rt; (b) $H_2NOH{\cdot}HCl$, pyridine, two steps 85%; (c) $LiAlH_4$, THF, reflux, 84%; (d) $(Boc)_2O$, Et_3N, 100%; (e) same as (a) and (b), 80%; (f) same as (c), 80%; (g) same as (d), 100%.

reaction mixture was cooled to room temperature, excess hydride was destroyed with H_2O (1.0 mL) and diluted with EtOAc (25.0 mL). The solution was filtered with a cake of florisil and concentrated under reduced pressure to afford crude product. This crude product was purified by column chromatography with 10% CH_2Cl_2 in ethanol to give **16** (462 mg): ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.40 (m, 2H), 3.19 (m, 1H), 3.41 (m, 1H), 3.48 (m, 1H), 3.65 (m, 1H), 3.66 (s, 3H), 4.02 (m, 1H), 4.68 (m, 3H), 5.00 (d, 1H, J = 11.4 Hz), 7.35 (m, 10H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 34.01, 46.70, 61.95, 68.01, 72.11, 75.50, 83.01, 83.04, 86.45, 128.63, 128.74, 128.80, 128.91, 129.46, 129.51, 139.38, 139.50; Anal. Calcd for $C_{21}H_{27}NO_4$: C, 70.56; H, 7.61; N, 3.92. Found: C, 70.47; H, 7.58; N, 3.91.

(±) 1,2-Dideoxy-1-*N*-Boc-4,6-*O*-dibenzyl-5-*O*-methyl-myo-inositol (17). Di-*tert*-butyl dicarbonate (135 mg, 0.62 mmol) in THF (1.5 mL) was added dropwise over 10 min. to a stirred solution of freshly distilled THF (2.6 mL), amine compound **16** (148 mg, 0.414 mmol) and Et_3N (0.36 mL) at room temperature under N_2. This resulting mixture was stirred at room temperature for 3 h and quenched with H_2O (0.5 mL). The solution was extracted with EtOAc (2 × 10.0 mL) and organic layer was rinsed with brine, dried over anhydrous $MgSO_4$, filtered and concentrated under reduced pressure to give crude product. This crude product was purified by column chromatograph with 20% EtOAc in hexane to give compound **17** (187 mg): ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.39 (s, 9H), 1.44 (m, 2H), 3.23 (dd, 1H, J = 8.4 & 10.5 Hz), 3.32 (m, 1H), 3.52 (m, 1H), 3.62 (s, 3H), 3.73 (m, 1H), 4.15 (m, 1H), 4.55 (d, 1H, J = 11.4 Hz), 4.64 (d, 1H, J = 11.4 Hz), 4.68 (d, 1H, J = 11.4 Hz), 4.93 (d, 1H, J = 11.4 Hz), 7.35 (m, 10H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 29.35, 32.09, 46.00, 60.50, 61.78, 68.00, 71.80, 75.02, 80.10, 83.59, 84.50, 128.74, 128.77, 128.80, 128.91, 129.46, 129.51, 139.21, 139.39, 156.38; Anal. Calcd for $C_{26}H_{35}NO_6$: C, 68.25; H, 7.71; N, 3.06. Found: C, 69.07; H, 7.78; N, 3.09.

(±) 1-*N*-Boc-4,6-*O*-dibenzyl-5-*O*-methyl-2-deoxystreptamine (19). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.40 (s, 9H), 1.70 (m, 2H), 3.25 (m, 1H), 3.26 (s, 3H), 3.50 (m, 3H), 4.10 (m, 1H), 4.63 (m, 4H), 4.55 (d, 1H, J = 11.4 Hz), 7.31 (m, 10H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 29.02, 29.96, 41.74, 48.90, 68.39, 72.32, 72.63, 73.02, 77.25, 77.69, 127.77, 128.77, 128.00, 128.11, 128.52, 128.64, 128.90, 138.49, 138.87, 155.68; Anal. Calcd for $C_{26}H_{36}N_2O_5$: C, 68.40; H, 7.95; N, 6.14. Found: C, 68.77; H, 7.89; N, 6.19.

(±) 1,3-Di-*N,N'*-Boc-4,6-*O*-dibenzyl-5-*O*-methyl-2-deoxystreptamine (21). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.42 (s, 18H), 1.60 (m, 2H), 3.25 (s, 3H), 3.57 (m, 1H), 3.64 (m, 2H), 3.89 (m, 2H), 4.50 (d, 2H, J = 11.4 Hz), 4.62 (d, 2H, J = 11.7 Hz), 7.30 (m, 10H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 28.30, 29.01, 47.74, 58.45, 72.11, 76.90, 77.56, 79.61, 128.10, 128.25, 128.70, 138.51, 156.38; Anal. Calcd for $C_{31}H_{44}N_2O_7$: C, 66.88; H, 7.97; N, 5.03. Found: C, 66.67; H, 7.87; N, 5.09.

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7. All compounds are drawn as their absolute configuration but are racemic mixtures.
8. See the nmr data of compound **21** in experimental section.