Synthetic Study toward a Protected 2-Deoxystreptamine

Seok-Chan Kim,* Seung-Chul Lee, and Chan-Seong Cheong†

Department of Bio & Nano Chemistry, Kookmin University, Seoul 136-702, Korea
†Life Science Division, Korea Institute of Science and Technology, P.O. Box 131, Cheongryang, Seoul 136-650, Korea
Received July 1, 2004

Key Words: 2-Deoxystreptamine, myo-Inositol, Stereoselective synthesis

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.

![Diagram of 2-Deoxystreptamine (1)](image)

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.

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-mylo-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 LiAlH₄ 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.

Stereocchemical characterization of the target product 21 was accomplished by ¹H and ¹³C 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 ¹³C 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-mylo-inositol (16). To a stirred solution of oxime 14 (600 mg, 1.62 mmol) in freshly distilled THF (10.0 mL) was added 95% LiAlH₄ (260 mg, 6.48 mmol) at room temperature. The resulting mixture was refluxed for 2 h. After the...
reaction mixture was cooled to room temperature, excess hydride was destroyed with H2O (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% CH2Cl2 in ethanol to give 16 (462
mg): 1H NMR (CDCl$_3$, 300 MHz) $\delta$ 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); 13C NMR (CDCl$_3$, 75 MHz) $\delta$ 34.01, 46.70, 61.95, 68.01, 72.11, 75.50, 83.01, 83.04, 86.45, 128.63, 128.74, 128.80, 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-myoinositol (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$_3$N (0.36 mL) at room temperature under N$_2$. This resulting mixture was stirred at room temperature for 3 h and quenched with H$_2$O (0.5 mL). The solution was extracted with EtOAc ($\times$ 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): 1H NMR (CDCl$_3$, 300 MHz) $\delta$ 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), 4.67 (d, 1H, $J$ = 11.4 Hz), 7.35 (m, 10H); 13C NMR (CDCl$_3$, 75 MHz) $\delta$ 29.35, 31.90, 46.00, 46.80, 50.70, 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). 1H NMR (CDCl$_3$, 300 MHz) $\delta$ 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); 13C NMR (CDCl$_3$, 75 MHz) $\delta$ 28.30, 29.96, 47.74, 48.90, 68.39, 72.32, 72.63, 73.07, 77.25, 77.69, 127.77, 128.77, 128.80, 128.81, 128.85, 128.89, 138.49, 138.87, 155.68; Anal. Calcd for C$_{31}$H$_{44}$NO$_7$: C, 68.77; H, 7.89; N, 6.19.

Acknowledgment. We would like to thank Korea Institute of Science and Technology for financial support of this work.

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