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# An Efficient Synthesis of Protected 2-Deoxy-Streptamine and Analogues

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**Abstract**. Protected 2-deoxy-streptamine **13** and a variety of analogues **9**, **10**, **12**, and **14** were synthesized, starting with the intermediate 2L-2,3,5/3-2,3,4-tri-O-benzyl-1-*syn*-O-oximino-2,3,4,5-cyclohexanetetrol **2**, derived from D-glucose. 

Since the discovery of the first aminoglycoside antibiotic, streptomycin,[1] in 1944 by Waksman, numerous aminoglycosides have been described. The most important and clinically useful antibiotics such as neomycin, kanamycin, gentamycin and sisomycin contain 2-deoxy-streptamine **1** (Scheme 1) as the aminocyclitol subunit.[2] Despite intensive research interest in this area, only streptamine, 2-deoxy-streptamine and 2,5-dideoxy-streptamine are readily available. However, 2-deoxy-streptamine and 2,5-dideoxy-streptamine are not suitable for total chemical synthesis. They are *meso* compounds, and in order to avoid formation of complex diastereomeric mixtures on glycosylation, properly protected derivatives must be prepared in enantiomerically pure forms.

In this communication we wish to report the synthesis of protected 2-deoxy-streptamine **13** and the analogues **9**, **10**, **12**, and **14**.

The oxime **2** was elaborated from D-glucose *via* carbohydrate-inosose Ferrier rearrangement as previously described.[3,4] The reduction of **2** with $LiAlH_4$ into the corresponding amine as described in the literature[4] was unsuccessful. Speculating that the low reactivity of the oxime **2** towards $LiAlH_4$ reduction could be overcome through the protection of oximino group, compound **2** was treated with benzyl chloride in the presence of NaH in DMF. This reaction afforded regioselectively the derivative **3** {mp 82-84°C; $[\alpha]_D^{20}$ -16 (c=1.0; $CHCl_3$)( in 91% yield (Scheme 1). The *syn* configuration of **2** and **3** was determined from the $^1H$ and $^{13}C$ NMR spectrum and by comparison with data from the literature.[5] The reduction of **3** with $LiAlH_4$ gave a mixture of the epimeric amines **4** and **5** along with the benzylhydroxylamine **6**[6] in 90% yield (proportion 1.9.1). The compound **6** could be quantitatively deprotected to the amine **5** using $NaBH_4$ and $NiCl_2$ in methanol.[7]

Acetylation of **4** and **5** with acetic anhydride in methanol led to the N-acylated amines **7** {oil, $[\alpha]_D^{20}$ -5; (c=2.7; $CH_2Cl_2$)} and **8** {mp 194-196°C; $[\alpha]_D^{20}$ +36 (c=1.1; $CHCl_3$)} in 90% yield. Substitution of the hydroxyl groups of **7** and **8** was performed using DAST in methylene chloride[8], and the expected fluorinated analogues **9**[9] and **10**[10] were both obtained in 70% yield

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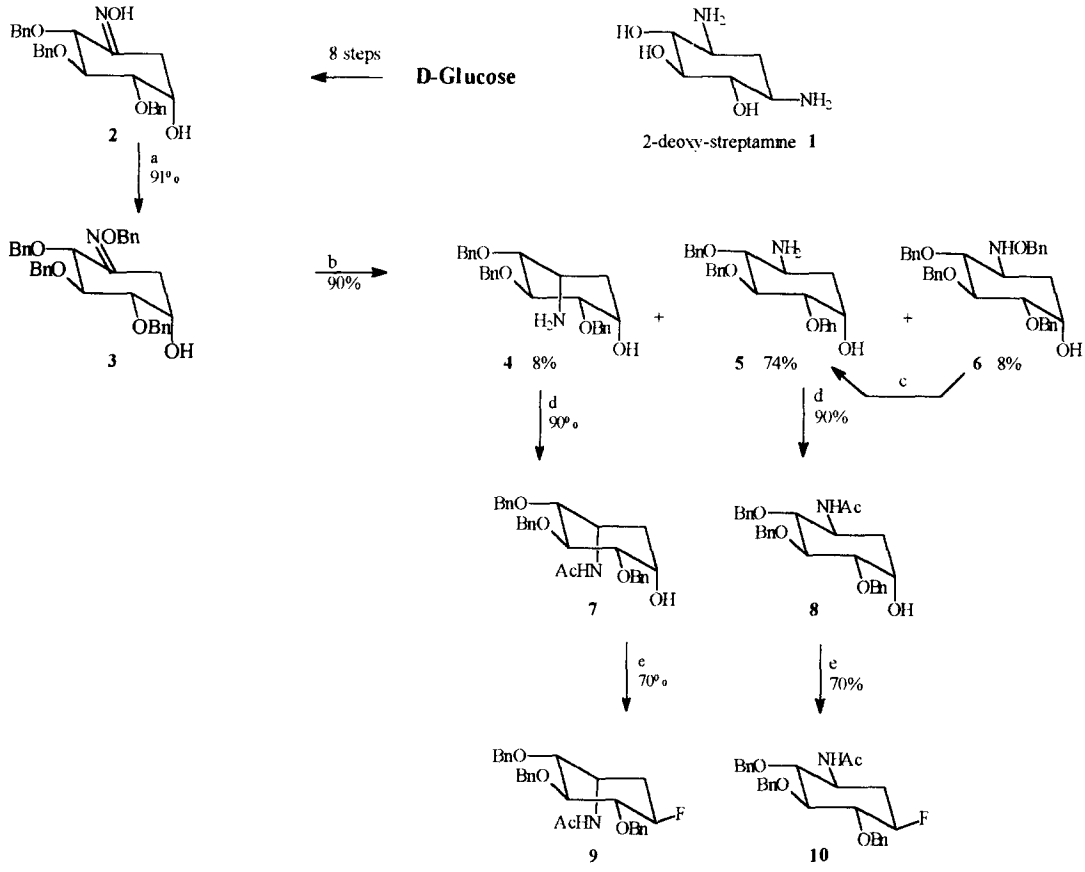
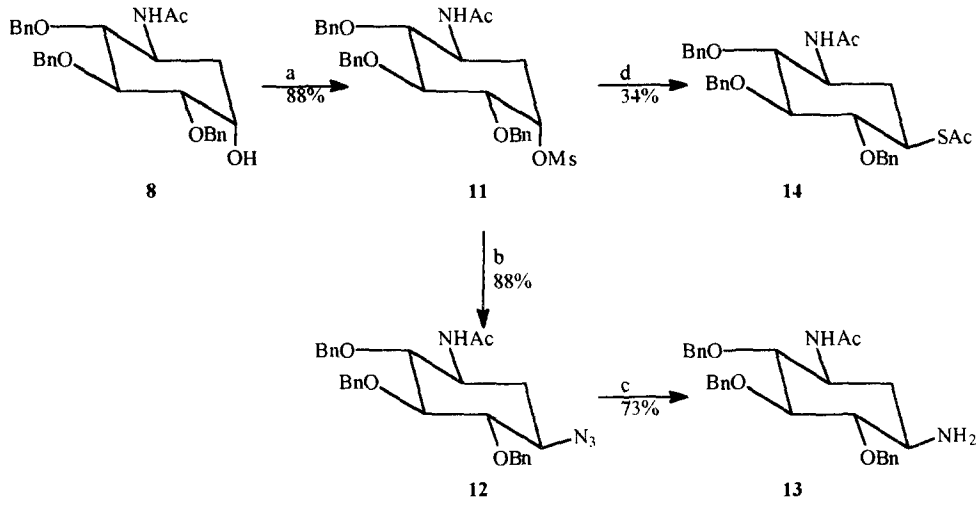



a) $PhCH_2Cl$, NaH, DMF, 0°C-100°C, 24h; b) $LiAlH_4$, THF, reflux, 12h; c) $NaBH_4$, $NiCl_2$, MeOH, -10°C, 4h; d) $Ac_2O$, MeOH, 0°C-r.t., 8h; c) DAST, $CH_2Cl_2$, 0°C- r.t., 4h

Scheme 1

Compound **8** was converted to the mesylate **11**[11]{mp 175-177°C; $[\alpha]_D^{20}$ +75 (c=0.7; $CHCl_3$)} in 88% yield (Scheme 2) by treatment with methanesulfonyl choride in pyridine. Treatment of **11** with sodium azide in DMSO gave the compound **12**[12] in 88% yield. The latter was reduced by triphenylphosphine in THF giving the target compound **13** {dec.220-227°C; $[\alpha]_D^{20}$ +22 (c=2.3; $CH_2Cl_2$)} in 73% yield. Reaction of the mesylate **11** with potassium thioacetate in DMF afforded the desired compound **14**[13] in 34% yield. Optimization of this reaction is under investigation The structures of all new compounds were unequivocally established by $^1H$, cosy $^1H$ x $^1H$ and $^{13}C$ NMR analysis.




a) MsCl, Pyr., 0°C- r.t., 12h; b) $NaN_3$, DMSO, 100°C, 48h; c) $PPh_3$, THF/$H_2O$, 0°C- r.t., 24h;
d) KSAc, DMF, 100°C, 48h.

Scheme 2

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(6) **6**, caracterized as hydrochloride form, dec 172-174°C, $[\alpha]_D^{20}$ +33 (c=0.5; $CHCl_3$),
MS (E.I):m/z=540 $(M+H)^+$
$^1$HNMR (400MHz; $CDCl_3$): δ 1.80 (m, 1H, H6a), 2.60 (m, 1H, H6e, $J_{6a\text{-}6e}$=12.7Hz), 3.35 (s, 1H, H4), 3.80 (s, 3H, H1, H2, H3), 4.05 (s, 1H, H-5), 4.50-4.90 (m, 6H, $\underline{CH_2}$Ph), 5.20 (dd, 2H, NO$\underline{CH_2}$Ph), 7.0-7.4 (m, 20H, Ph) ; $^{13}$CNMR (100,6MHz; $CDCl_3$): δ 28.02 (C6), 58.13 (C1), 65.41 (C4), 77.72 (C3), 82.53 and 82.71 (C2 and C4).

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(9) **9**, mp 73-75°C; $[\alpha]_D^{20}$ -6 (c=1 3, $CH_2Cl_2$)

$^1$HNMR (400 MHz; $C_6D_6$). δ 0.67 (m, 1H, H6a), 0.95 (s, 3H, $CH_3$), 1.85 (m, 1H, H6e), 2.62 (dd, 1H, H2, $J_{2-1}$=4.7 Hz, $J_{2-3}$=9 0 Hz), 2 77 (m, 1H, H4), 2.98 (t, 1H, H3, $J_{3-4}$=8.5 Hz), 3.90 (m, 1H, H1), 4 08 (m, 1H, H5, $J_{5-F}$=49 Hz, $J_{5-4}$=8.5 Hz, $J_{5-6e}$=3.5 Hz, $J_{5-6a}$=9.8 Hz), 3.63-4.26 (m, 6H, $\underline{CH_2}$Ph), 5.20 (d,1H, NH, $J_{NH-1}$ = 6.9Hz), 6 44-6.73 (m, 15H, Ph) ; $^{13}$CNMR (100.6 MHz, $CDCl_3$): δ 23,28 ($CH_3$), 30.48 and 30.68 (C6), 44 23 and 44 36 (C1), 79.33 (C2), 80.03 and 80.13 (C3), 82.84 and 83.01 (C4), 90.35 and 92.11 (C5, $J_{C5-F}$=177 Hz), 170,74 (C=O)

(10) **10**, mp 169-171°C; $[\alpha]_D^{20}$ +20 (c=0.4; $CHCl_3$)

$^1$HNMR (400 MHz; $CDCl_3$): δ 1 44 (m, 1H, H6a, $J_{6a-6e}$=12 Hz), 2.49 (m, 1H, H6e), 3.35 (dd, 1H, H2, $J_{2-3}$=8.6 Hz, $J_{2-1}$=10 Hz), 3.55 (t, 1H, H3, $J_{3-4}$=8.6 Hz), 3.60 (m, 1H, H4, $J_{4-5}$=8.5 Hz), 3.74 (m, 1H, H1), 4.60 (m, 1H, H5, $J_{5-f}$=49 Hz, $J_{5-6a}$=9.3 Hz), 4.60-4.92 (m, 7H, $\underline{CH_2}$Ph and NH), 7.25-7.40 (m, 15H, Ph) , $^{13}$CNMR (100.6 MHz, $CDCl_3$): δ 23.34 ($CH_3$), 33.03 and 33.22 (C6), 47.05 and 47 21 (C1), 80.89 (C2), 82.81 and 82.93 (C3), 83 78 and 83.93 (C4), 90.51 and 92.30 (C5, $J_{C5-F}$=179 Hz), 169.88 (C=O).

(11) **11**, mp 175-177°C; $[\alpha]_D^{20}$ +75 (c=0 7; $CHCl_3$)

$^1$HNMR (400MHz; $CDCl_3$): δ 1.72 (dt, 1H, H6a), 1.75 (s, 1H, $\underline{CH_3}$CONH), 2.42 (dt, 1H, H6e, $J_{6e-6a}$=14.6 Hz, $J_{6e-1}$=$J_{6e-5}$=4.3 Hz), 3.07 (s, 3H, $\underline{CH_3}SO_3R$), 3.53 (dd, 1H, H4, $J_{4-3}$=9.2 Hz, $J_{4-5}$=2.9 Hz), 3.57 (dd, 1H, H2, $J_{2-1}$=10 Hz, $J_{2-3}$=9.0 Hz), 3.85 (t, 1H, H3), 3.88 (m, 1H, H1), 4.60-4.93 (m, 6H, $\underline{CH_2}$Ph), 5 13 (m, 1H, H5), 5.20 (d, 1H, NH), 7.27-7.38 (m, 15H, Ph) ; $^{13}$CNMR (100.6 MHz, $CDCl_3$): δ 23.47 ($\underline{CH_3}$CO), 31.56 (C6), 39.33 ($\underline{CH_3}SO_3R$), 48.39 (C1), 76.72, 80.20, 80.65 and 81 81 (C2, C3, C4 and C5), 170.26 (C=O).

(12) **12**, mp 211-213°C; $[\alpha]_D^{20}$ +63 (c=0 9; $CHCl_3$)

$^1$HNMR (400MHz; $C_6D_6$): δ 0,58 (q, 1H, H6a, $J_{6a-6e}$=13Hz), 1.68 (dt, 1H, H6e, $J_{6e-5}$=$J_{6e-1}$=4.5 Hz), 1.86 (s, 3H, $CH_3$), 2.53 (m, 1H, H5, $J_{5-4}$=9.8 Hz), 2.73 (dd, 1H, H2, $J_{2-1}$=10.2 Hz, $J_{2-3}$=9.3 Hz), 2.88 (t, 1H, H4, $J_{4-3}$=9.4 Hz), 3.01 (t, 1H, H3), 3.46 (m, 1H, H1), 3.98 (d, 1H, NH, $J_{NH-1}$=7.2 Hz), 4.17-4.57 (m, 6H, $\underline{CH_2}$Ph), 6.70-7.10 (m, 15H, Ph) ; $^{13}$CNMR (100.6 MHz; $CDCl_3$): δ23.32 ($CH_3$), 33.10 (C6), 48.80 (C1), 60.77 (C5), 81.21 (C2), 84.55 and 84.95 (C3 and C4), 169.97 (C=O).

(13) **14**, dec. 204-206°C; $[\alpha]_D^{20}$ +30 (c=1.4; $CHCl_3$)

$^1$HNMR (400MHz; $CDCl_3$): δ 1.50 (q, 1H, H6a), 1 71 (s, 3H, $CH_3CON$), 2.24 (s, 3H, $CH_3COS$), 2.35 (dt, 1H, H6e, $J_{6e-6a}$=13.0 Hz), 3.40 (dd, 1H, H2, $J_{2-1}$=10 Hz, $J_{2-3}$=9.1 Hz), 3.50 (m, 2H, H4 and H5, $J_{4-3}$=$J_{4-5}$=9.0 Hz), 3.64 (t, 1H, H3), 3.75 (m, 1H, H1), 4.60-4.93 (m, 6H, $\underline{CH_2}$Ph), 4.95 (d, 1H, NH, $J_{NH-1}$=7.0 Hz), 7.25-7.37 (m, 15H, Ph) ; $^{13}$CNMR (100.6 MHz; $CDCl_3$): δ 23.40 ($\underline{CH_3}$CONH), 30.72 ($\underline{CH_3}$COS), 33.90 (C6), 43.43 (C5), 50.80 (C1), 81.27, 82.30 and 86.43 (C2, C3 and C4), 169.85 (HNC=O), 194.35 (SC=O).