SYNTHESIS OF α-LINKED 2′,3′-DIDEOXY-2′-FLUORO-PSEUDO-DISACCHARIDES RELATED TO AMINOCYCLITOL-GLYCOSIDE ANTIBIOTICS

Sir:

It has recently been shown[1] that the removal of the 2′-amino or 2′-hydroxyl groups in the aminocyclitol-glycoside antibiotics does not seriously alter the effectiveness of the natural products. Obviously the 2′-deoxy analogues must be less stable than the parent aminocyclitol-glycoside antibiotics; this would reduce their potential clinical use.

We have therefore synthesized and report here the stereocontrolled preparation of α-linked 2′, 3′-dideoxy-2′-fluoro-cyclitol and -aminocyclitol pseudo-disaccharides related to the crucial repeating units of aminocyclitol-glycoside antibiotics.

The sequence used here employs an acid-catalysed addition of 2-deoxy-2-fluoro-glycal[2] (**A**) to an alcohol (scheme), followed by regiospecific hydrogenation from the β-face of the resultant α-linked unsaturated glycoside (**B**), leading to 2′,3′-dideoxy-2′-fluoro α-glycoside (**C**), having the desired D-*ribo*-configuration. As far as we are aware, such 2′,3′-dideoxy-2′-fluoro-pseudo-saccharides have not been reported in the literature to date.

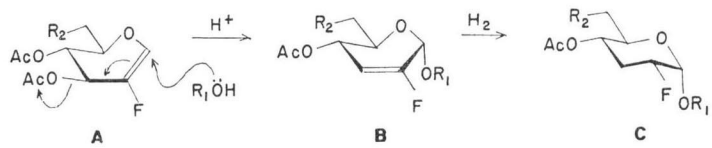
86% yield. The major component **4** (58%), mp 198~199°C, $[\alpha]_D$ +31° (*c* 1.09, $CHCl_3$) (^1H nmr; $J_{1'\sim3'}=0.5$ Hz, $J_{4'\sim5'}=9$Hz) was isolated by a single crystallisation from alcohol. The minor, amorphous product **6** (28%) showed; $[\alpha]_D$ +23° (*c* 1.8, $CHCl_3$) (^1H nmr, $J_{1'\sim3'}=0.5$ Hz, $J_{4'\sim5'}=3$ Hz).

The α-glycoside **4** was regiospecifically hydrogenated in quantitative yield, in ethyl acetate in the presence of a 10% palladium on carbon catalyst and a trace of glacial acetic acid, to compound **8**, mp 160~162°C; $[\alpha]_D$ +41° (*c* 1.37, $CHCl_3$). Reduction occurred exclusively from the β-face of the α-glycoside **4**. Azidolysis of **8**, using sodium azide in N, N-dimethyl-formamide at 110°C for 1 hour, gave a mixture of three products (78%), which were separated by chromatography on silica gel. The major component was identified as the diazide **12**, $[\alpha]_D$ +62° (*c* 2, $CHCl_3$) (^1H nmr: $J_{1'\sim2'}=4$ Hz, $J_{2'\sim3'_e}=5$ Hz, $J_{2'\sim3'_a}=11$ Hz, $J_{4'\sim5'}=11$ Hz).

The minor, unsaturated components, formed by elimination of toluene-*p*-sulphonic acid in **8**, were not examined further.

De-esterification of **12**, followed by reduction [Pt; methanol - water (1 : 1)], gave 5-*O*-(2′,3′-dideoxy-2′-fluoro-α-D-*ribo*-hexopyranose)-2,6-dideoxystreptamine **13**, isolated as its crystalline sulphate, mp 237~239°C, $[\alpha]_D=+60°$ (*c* 1.24, H_2O).

Scheme.



R_1 = Cyclitol or Aminocyclitol

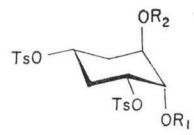
R_2 = OAc , OTs

A similar approach has been reported recently[3,4] for the synthesis of α-linked 3′-deoxy-cyclitol and -aminocyclitol glycosides, thus illustrating the versatility of our synthetic scheme. Acid catalysed rearrangement of cyclic vinyl ether systems (glycals) leading to unsaturated glycosides has been extensively studied[5].

Addition of compound **3** to a solution of **1**[3,4] (1 equiv.) in dichloroethane containing a catalytic amount of boron trifluoride-etherate at −15 °C, over 5 hours, gave a mixture of 2 products in

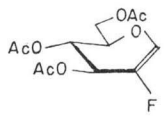
Similarly, in the natural 4-O series, the reaction of **3** with the compound **2**[3,4] resulted in a mixture of the stereoisomers **5** and **7**, according* to ^1H and ^{13}C nmr data; reduction of the olefins (*in situ*) furnished the oily major compound **9** (63%), $[\alpha]_D=+80°$ (*c* 1.1, $CHCl_3$) and the syrupy minor β-glycoside **11**, $[\alpha]_D=+27°$ (*c* 2, $CHCl_3$). Treatment of the α-glycoside **9** with tetra-*n*-butyl-ammonium fluoride in tetrahydrofuran afforded the oily **10** in quantitative yield, $[\alpha]_D$ +62.5° (*c* 1, $CHCl_3$).

* Satisfactory mass and ^{13}C nmr spectra were obtained for all new compounds.



1 R_1 = Bz ; R_2 = H

2 R_1 = H ; R_2 = -SiMe2Bu^t



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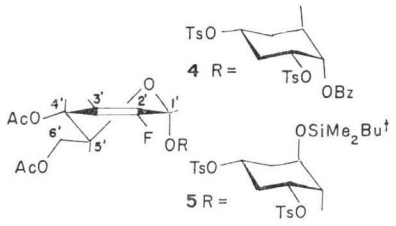
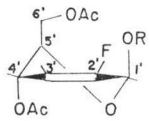
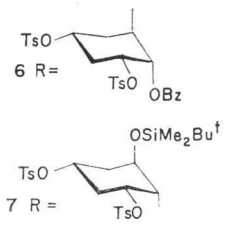


4 R =

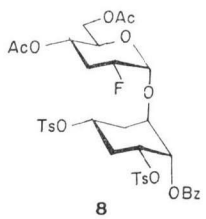
5 R =





6 R =

7 R =



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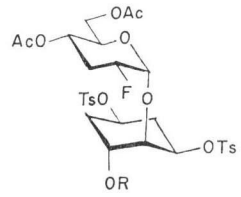
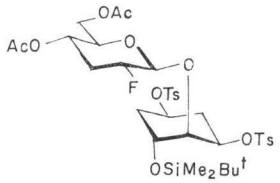


9 R = SiMe$_2$Bu^t

10 R = H



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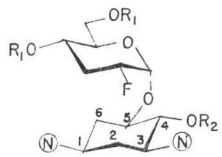
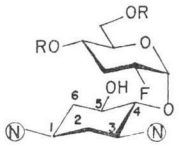


12 Ⓝ = N_3 ; R_1 = Ac ; R_2 = Bz

13 Ⓝ = NH_2 ; R_1 = R_2 = H



14 Ⓝ = N_3 ; R = Ac

15 Ⓝ = NH_2 ; R = H

Ts = p-MeC$_6$H$_4$SO$_2$- ; Ac = MeCO- ; Bz = PhCO-

Azidolysis of **10** yielded the syrupy **14**, $[\alpha]_D$ +90° (*c* 0.93, $CHCl_3$). ^{1}H nmr: $J_{1'\sim2'}$ = 3.7 Hz, $J_{2'\sim3'_e}$ = 5.6 Hz, $J_{2'\sim3'_a}$ = 12.5 Hz, $J_{4'\sim5'}$ = 8.7 Hz). Deacetylation of the latter, followed by catalytic hydrogenation gave the pseudo-disaccharide, 4-*O*-(2′,3′-dideoxy-2′-fluoro-α-D-*ribo*-hexopyranosyl)-2,6-dideoxy-streptamine **15**, readily characterized as its sulphate, mp 206~208°C, $[\alpha]_D$ +43°, (*c* 1, H_2O).

We anticipate that these products will be valuable precursors for the total and mutasynthesis[6,7] of 2′,3′-dideoxy-2′-fluoro aminocyclitol glycoside antibiotics.

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References

1) WRIGHT, J. J. & P. LEE: Synthesis and conformational properties of novel 2′-unsubstituted aminoglycoside antibiotics of the gentamicin-sisomicin class. Abstracts IXth International

Symposium on Carbohydrate Chemistry, London, p. 151, April, 1978

2) ADAMSON, J.; A. B. FOSTER & J. H. WESTWOOD: 2-Deoxy-2,2-difluoro-D-arabino-hexose ("2,2-difluoroglucose). Carbohyd. Res. 18: 345~347, 1971

3) GERO, S. D.; J. CLEOPHAX, A. ROLLAND, A. SEPULCHRE, D. MERCIER, L. CASTELLANOS & N. ROLLAND: Total synthesis of α-linked cyclitol and aminocyclitol glycosides by acid catalysed procedures. Abstracts IXth International Symposium on Carbohydrate Chemistry. London, p. 81. April, 1978

4) CLEOPHAX, J.; DO KHAC DUC, J. M. DELAUMENY, S. D. GERO & A. ROLLAND: Synthesis of α-linked 3'-deoxy-cyclitol and amino-cyclitol glucosides. J. Chem. Soc., Chem. Comm. 1978: 771~773, 1978

5) FERRIER, R. J.: Unsaturated sugars. Adv. Carbohyd. Chem. Biochem. 24: 199~266, 1969

6) RINEHART, Jr., K. L.: Mutasynthesis of new antibiotics. Pure & Appl. Chem. 49: 1361~1384, 1977

7) TAKEDA, K.; A. KINUMAKI, T. FURUMAI, T. YAMAGUCHI, S. OHSHIMA & Y. ITO: Mutational biosynthesis of butirosin analogs. J. Antibiotics 31: 247~249, 1978