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Note

Reaction of 2-deoxy-6-*O*-[2,3-dideoxy-4,6-*O*-isopropylidene-2,3-(*N*-tosylepimino)-α-D-mannopyranosyl]-4,5-*O*-isopropylidene-1,3-di-*N*-tosylstreptamine with potassium hydrogenfluoride

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In a previous paper[1] we reported a new method for preparing the 2-amino-2,3-dideoxy-3-fluoro-α-D-glucopyranosyl structure by ring-opening of 2,3-dideoxy-2,3-(*N*-tosylepimino)-α-D-allopyranosides by potassium hydrogenfluoride (KHF_2) in *N*,*N*-dimethylformamide (DMF). As these epimines are readily prepared from 2-amino-2-deoxy-D-glucopyranosides, the whole reaction may be considered as a method for introducintg fluorine at C-3 with no net inversion. The present paper describes an attempt to introduce fluorine at C-2 of the 3-amino-3-deoxy-D-glucopyranosyl structure through a 2,3-dideoxy-2,3-(*N*-tosylepimino)-α-D-mannopyranosyl derivative, and is an extension of the previous study. This synthetic route, when successful, may be applied to the synthesis of 2″-deoxy-2″-fluorokanamycins from kanamycin; such 2″-deoxy-2″-fluorokanamycins are expected to show activity, by their lack of an OH-2″ group, against resistant bacteria[2,3] producing 2″-*O*-adenylylating enzymes. Further, this introduction of fluorine may lower the basicity of the NH_2-3″ group of kanamycin, and decrease the toxicity[4] of this antibiotic.

The tri-*N*-tosyl derivative[5] **1** of 6-*O*-(3-amino-3-deoxy-α-D-glucopyranosyl)-2-deoxystreptamine[6], a component of kanamycin, was treated with 2,2-dimethoxypropane in an acidic medium to give the 4,5:4′,6′-isopropylidene acetal **2**. Sulfonylation of **2** with benzylsulfonyl chloride then gave the 2′-*O*-sulfonyl derivative **3**. Treatment of **3** with methanolic sodium hydroxide gave the 2′,3′-*N*-tosylepimine **4**. The structure of **4** was confirmed by its ^{1}H-NMR spectrum: the H-2′ and H-3′ signals appeared as an AB quartet with $J_{1',2'} = J_{3',4'} \sim 0$ and $J_{2',3'}$ 4.5 Hz; the pattern closely resembled that of 2,3-anhydro-6-deoxy-α-D-mannopyranoside[7]

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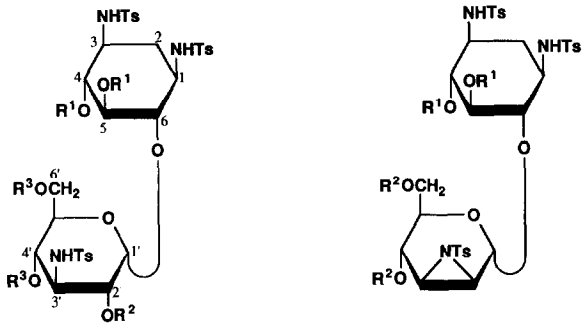
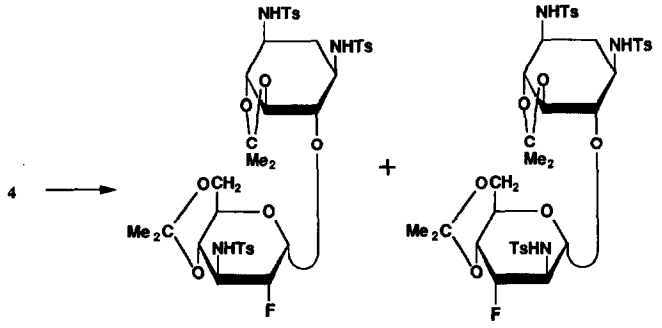
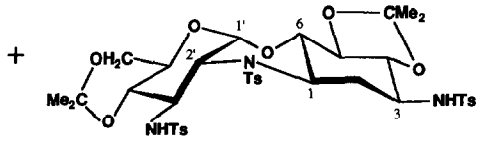


1 $R^1 = R^2 = R^3 = H$
2 $R^1R^1 = R^3R^3 = CMe_2$, $R^2 = H$
3 $R^1R^1 = R^3R^3 = CMe_2$, $R^2 = SO_2CH_2Ph$
4 $R^1R^1 = R^2R^2 = CMe_2$
5 $R^1 = R^2 = H$

or 2,3-dideoxy-2,3-epimino-α-D-mannopyranoside[8]. The lack of one of the three resonances of N*H*Ts displayed by **3** also supported the structure. Deprotection of **4** gave **5**.

Compound **4** was treated with KHF_2 in DMF at 150° as previously reported[1]. After 36 h, three compounds (**6**, **7** and **8**) were produced, along with some minor products Compound **6**, isolated in only 5.6% yield, was the desired 2-deoxy-6-*O*-(2, 3-dideoxy-2-fluoro-4, 6-*O*-isopropylidene-3-tosylamido-α-D-glucopyranosyl)-4, 5-





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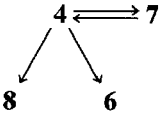
O-isopropylidene-1,3-di-*N*-tosylstreptamine, as proved by the ^{1}H- and ^{19}F-NMR spectra (large $J_{2',3'}$, $J_{3',4'}$ and $J_{4',5'}$ values and $J_{2',F}$ 47 Hz). Another minor product, isolated in 3.6% yield, was 2-deoxy-6-*O*-(2,3-dideoxy-3-fluoro-4,6-*O*-isopropylidene-2-tosylamido-α-D-altropyranosyl)-4,5-*O*-isopropylidene-1,3-di-*N*-tosylstreptamine (**7**), as proved by the ^{1}H- and ^{19}F-NMR spectra (small $J_{1',2'}$, $J_{2',3'}$, and $J_{3',4'}$ values, and $J_{3',F}$ 50 Hz). The major product, isolated in 34% yield and containing no fluorine was determined to be 6-*O*-(2',3'-dideoxy-4',6'-*O*-isopropylidene-3'-tosylamido-α-D-glucopyranosyl)-1,2,3-trideoxy-4,5-*O*-isopropylidene-3-tosylamidoinositol-1,2'-*N*-tosylepimine (**8**). The large couplings of $J_{1,2ax}$, $J_{2ax,3}$, $J_{4,5}$, $J_{5,6}$, $J_{2',3'}$, $J_{3',4'}$, and $J_{4',5'}$, confirmed by the ^{1}H-shift-correlated 2D spectrum, indicated that the fundamental structure of **1** is retained in **8**. The observation of two, but not three, signals for N*H*Ts's (at C-3 and C-3', but not at C-1) also supported the structure. Compound **8** is evidently produced by attack of the *N*HTs-1 of **4** to the C-2' under *N*-tosylepimine-ring opening under catalysis of the fluoride ion. In a shorter 15-h reaction, **7** and **8** were produced as the two major products. Since **8** is considered to be one of the final products, and was not converted into any other product, comparison of the product-yields of short- and long-time reactions suggests that **7** was produced first, together with **8**, and **7** was gradually converted into the thermodynamically more stable **6** and **8** possibly through **4**. To ascertain the mechanism, further experiments were carried out to determine the change of product ratio (**6**:**7**) with time, starting from **4** (and also **7**); this was done by measuring the strengths of the fluorine signals of the product mixture in their ^{19}F-NMR spectra on the samples obtained after minimum purification-procedures required for the measurements. Estimation of the yields of **8** from the ^{1}H-NMR spectra of the reaction mixtures was unsuccessful because of overlapping of the signals with those of **4**, **6**, **7**, and several by-products. The results (from **4**) obtained (see Experimental) supported our assumption. Likewise, **7** was treated similarly for 36 h, whereupon **7** mostly disappeared (checked by the ^{19}F-NMR spectrum) and **6** became the major product (the ratio of **6**:**7** was 4.5:1). These results strongly suggest that the reaction system involves a mixture of reversible and concurrent reactions, as shown:



In conclusion, this experiment failed to give the 3-amino-2,3-dideoxy-2-fluoro-D-glucopyranosyl structure in acceptable yield, but another reversible system[1] involving an *N*-tosylepimine is clarified.

EXPERIMENTAL

General. — General procedures are the same with those reported[1]. HPLC was performed on SSC-ODS-922 (Sensyu Scientific Co.).

*2-Deoxy-6-*O*-(3-deoxy-4,6-*O*-isopropylidene-3-tosylamido-α-*D*-glucopyranosyl)-4,5-*O*-isopropylidene-1,3-di-*N*-tosylstreptamine* (**2**). — A solution of **1** (2.86 g) in 1:15 DMF–CH_2Cl_2 (150 mL) was refluxed for 30 min in a flask connected to a Soxhlet apparatus containing 5A molecular sieves. After the addition of 2,2-dimethoxypropane (9 mL) and anhyd TsOH (0.35 g), refluxing was continued for 30 min. The solution was poured, under vigorous stirring, into aq $NaHCO_3$ (satd, 1 L), and the whole mixture was extracted with $CHCl_3$. The extracts were concentrated to a residue that was chromatographed (20:1 $CHCl_3$–MeOH) to give **2** as a solid, 2.21 g (70%), $[\alpha]_D^{21}$ + 46° (*c* 1, $CHCl_3$); ^{1}H-NMR (pyridine-d_5): δ 1.18, 1.24, 1.27, and 1.29 (each s, 3 H, isopropylidene × 2), 2.20 (3 H) and 2.29 (6 H) [each s, Ts(*Me*) × 3], 4.04 (dd, 1 H, $J_{1',2'}$ 3.5 and $J_{2',3'}$ 10 Hz, H-2′), and 5.48 (d, 1 H, H-1′).

Anal. Calcd for $C_{39}H_{51}N_3O_{13}S_3$: C, 54.09; H, 5.94; N, 4.85; S, 11.11. Found: C, 53.75; H, 5.74; N, 5.10; S, 11.10.

*6-*O*-(2-*O*-Benzylsulfonyl-3-deoxy-4,6-*O*-isopropylidene-3-tosylamido-α-*D*-glucopyranosyl)-2-deoxy-4,5-*O*-isopropylidene-1,3-di-*N*-tosylstreptamine* (**3**). — A solution of **2** (2.30 g) and benzylsulfonyl chloride (3.2 g) in pyridine (60 mL) was kept for 2 h at −20°. Water (1.5 mL) was added an the solution was concentrated. The residue was extracted with $CHCl_3$ and the solution was washed with aq. $NaHCO_3$ (satd), and concentrated. The residue was chromatographed (5:1 $CHCl_3$–acetone) to give **3** as a solid, 2.20 g (92%), $[\alpha]_D^{21}$ + 17° (*c* 1, $CHCl_3$); ^{1}H-NMR (pyridine-d_5): δ 1.24, (6 H), 1.28 (3 H), and 1.35 (3 H) (each s, isopropylidene × 2), 2.21 (3 H) and 2.29 (6 H) [each s, Ts(*Me*) × 3], 3.84 (t, 1 H, H-4′), 4.64 (q, 1 H, H-3′), 4.89 (1 H) and 5.41 (1 H) (each d, *J* 14 Hz, CH_2Ph), 5.15 (dd, 1 H, H-2′), 5.76 (d, 1 H, H-1′), 8.11 (d, 1 H, *J* 10 Hz, NH-1 or 3), 9.60 (d, 1 H, *J* 7 Hz, NH-3 or 1), and 9.83 (d, 1 H, NH-3′); $J_{1',2'}$ 3.5, and $J_{2',3'} = J_{3',4'} = J_{4',5'} = J_{3'NH}$ 10 Hz.

Anal. Calcd for $C_{46}H_{57}N_3O_{15}S_4$: C, 54.15; H, 5.63; N, 4.12; S, 12.57. Found: C, 53.92, H, 5.39; N, 4.06; S, 12.85.

*2-Deoxy-6-*O*-(2,3-dideoxy-4,6-*O*-isopropylidene-2,3-*N*-tosylepimino-α-*D*-mannopyranosyl)-4,5-*O*-isopropylidene-1,3-di-*N*-tosylstreptamine* (**4**). — Compound **3** (1.98 g) dissolved in 0.5 M NaOMe in MeOH (40 mL) was kept for 4 h at 50°. Evaporation followed by addition of aq 5% $KHSO_4$ (55 mL) gave a precipitate, which was extracted with $CHCl_3$. The organic solution was washed with water, dried (Na_2SO_4), and concentrated. The residue was recrystalized from ether, 1.19 g (72%), mp 242–244°, $[\alpha]_D^{21}$ + 39° (*c* 1, $CHCl_3$); ^{1}H-NMR (pyridine-d_5): δ 1.27, 1.28, 1.30, and 1.45 (each s, 3 H, isopropylidene × 2), 2.20, 2.22, and 2.33 [each s, 3 H, Ts(*Me*) × 3], 3.49 (d, 1 H, H-2′ or 3′) and 3.62 (d, 1 H, H-3′ or 2′) (both signals form an ABq system), 5.73 (s, 1 H, H-1′) 9.35 (br, 1 H, NH-1 or 3), and 9.70 (br, 1 H, NH-3 or 1); $J_{1',2'} = J_{3',4'}$ 0 and $J_{2',3'}$ 4.5 Hz.

Anal. Calcd for $C_{39}H_{49}N_3O_{12}S_3$: C, 55.24; H, 5.82; N, 4.96; S, 11.34. Found: C, 55.00; H, 5.65; N, 4.87; S, 11.42.

*2-Deoxy-6-*O*-(2,3-dideoxy-2,3-*N*-tosylepimino-α-*D*-mannopyranosyl)-1,3-di-*N*-tosylstreptamine* (**5**). — A solution of **4** (240 mg) in aq 80% AcOH (5 mL) was heated for 10 min at 80°. Evaporation followed by column chromatography (10:2:1

$CHCl_3$–MeOH–H_2O, the lower layer) of the residue gave **5** as a solid, 155 mg (71%), $[\alpha]_D^{21}$ + 60° (*c* 1, MeOH); ^{1}H-NMR (pyridine-d_5): δ 2.20 (6 H) and 2.33 (3 H) [each s, Ts(*Me*) × 3], 3.62 (d, 1 H, H-3′ or 2′), 3.90 (d, 1 H, H-2′ or 3′), and 5.88 (s, 1 H, H-1′).

Anal. Calcd for $C_{33}H_{41}N_3O_{12}S_3 \cdot 0.5\ H_2O$: C, 51.02; H, 5.45; N, 5.41; S, 12.38. Found: C, 51.04, H, 5.51; N, 5.64; S, 12.60.

Reaction of **4** *with potassium hydrogenfluoride. — (i) 36-Hour reaction.* A mixture of **4** (291 mg) and KHF_2 (140 mg) in DMF (6 mL) was heated for 36 h at 150°. TLC (30:5:1 $CHCl_3$–butanone–MeOH) of the solution showed five clear spots of R_F 0.15 (**6**), 0.2 (**7**), 0.24, 0.3 (the 3′-hydroxyl analog of **7**?), and 0.9 (**8**) (cf. **4**: R_F 0.65). After cooling, the solution was poured into an aq $NaHCO_3$ (satd, 30 mL) and the whole mixture was extracted with $CHCl_3$. Concentration of the organic solution gave a mixture of products, which were separated by column chromatography (30:3:1 $CHCl_3$–butanone–MeOH) and subsequent HPLC (7:3 MeOH–H_2O; applied only for the products having R_F 0.15–0.3) to give solids of **6** 16.3 mg (5.6%), **7**, 10.6 mg (3.6%), and **8**, 105 mg (34%).

Compound **6** had $[\alpha]_D^{24}$ + 29° (*c* 1.2, $CHCl_3$); ^{1}H-NMR (pyridine-d_5): δ 1.24 (6 H), 1.26 (3 H), and 1.28 (3 H) (each s, isopropylidene × 2), 1.98 (q, 1 H, H-2*ax*), 2.21 (3 H) and 2.26 (6 H) [each s, Ts(*Me*) × 3], 2.80 (dt, 1 H, H-2*eq*), 3.54 (t, 1 H, H-5), 3.70 (t, 1 H, H-4 or 6), 3.7–3.9 (4 H, H-1,3,4′,6′a), 3.97 (dd, 1 H, H-6′b), 4.23 (t, 1 H, H-6 or 4), 4.29 (dt, 1 H, H-5′), 4.57 (quintet, 1 H, H-3′), 4.77 (ddd, 1 H, H-2′), 5.81 (d, 1 H, H-1′), 8.75 (d, 1 H, *J* 8 Hz, NH-1 or 3; disappeared on deuteration), 9.62 (d, 1 H, *J* 9.5 Hz, NH-3 or 1; disappeared on deuteration), and 9.69 (d, 1 H, NH-3′; disappeared on deuteration); $J_{1,2ax} = J_{2ax,2eq} = J_{2ax,3}$ 13 $J_{1,2eq} = J_{2eq,3}$ 5, $J_{3,4} = J_{4,5} = J_{5,6} = J_{6,1}$ 10, $J_{1',2'}$ 4, $J_{2',3'} = J_{3',4'} = J_{3',NH} = J_{4',5'} = J_{5',6'a} = J_{6'a,6'b}$ 10, $J_{5',6'b}$ 5, $J_{1',F}$ 0, $J_{2',F}$ 47, and $J_{3',F}$ 10 Hz. ^{19}F-NMR (pyridine-d_5): δ −183.48 (dd, F-2′); mass spectrum: Calcd for $C_{39}H_{50}FN_3O_{12}S_3$: mol wt 868.1, Found: *m/z* 868 $(M + H)^+$ and 890 $(M - Na)^+$.

Compound **7** had $[\alpha]_D^{23}$ + 30° (*c* 0.7, $CHCl_3$); ^{1}H-NMR (pyridine-d_5): δ 1.19, 1.21, 12.6, and 1.45 (each s, 3 H, isopropylidene × 2), 1.83 (q, 1 H, H-2*ax*); 2.09, 2.24, and 2.29 [each s, 3H, Ts(*Me*) × 3], 2.58 (dt, 1 H, H-2*eq*), 3.58–4.12 (5 H, H-1,3,4,5,6), 3.77 (t, 1 H, H-6′a), 4.06 (dd, 1 H, H-6′b), 4.40 (dd, 1 H, H-4′), 4.69 (unresolved narrow m, 1 H, H-2′), 4.87 (dt, 1 H, H-5′), 5.31 (d, 1 H, H-3′), 5.59 (s, 1 H, H-1′), 9.01 and 9.54 (each unresolved m, 1 H, NH-1 and 3; disappeared on deuteration), and 9.98 (unresolved m, 1 H, NH-2′; disappeared on deuteration); $J_{1,2ax} = J_{2ax,2eq} = J_{2ax,3}$ 13, $J_{1,2eq} = J_{2eq,3}$ 4, $J_{1',2'} = J_{2',3'} = 0$. $J_{4',5'} = J_{5',6'a} = J_{6'a,6'b}$ ~ 11, $J_{5',6'b}$ 5, $J_{3',F}$ 50, and $J_{4',F}$ 29 Hz. ^{19}F-NMR (pyridine-d_5): δ −199.49 (ddd, F-3′), $J_{2',F}$ 9 Hz; mass spectrum: Calcd for $C_{39}H_{50}FN_3O_{12}S_3$: mol wt 868.1, Found: *m/z* 868 $(M + H)^+$ and 890 $(M + Na)^+$.

Compound **8** had $[\alpha]_D^{22}$ + 27° (*c* 1, $CHCl_3$); ^{1}H-NMR (pyridine-d_5): δ 0.97, 1.27, 137, and 1.39 (each s, 3 H, isopropylidene × 2), 2.16, 2.27, and 2.28 [each s, 3 H, Ts(*Me*) × 3], 2.23 (1 H, H-2*eq*), 2.53 (q, 1 H, H-2*ax*), 3.70 (t, 1 H, H-4), 3.81 (t, 1 H, H-6′a), 3.82 (t, 1 H, H-4′), 3.86 (dd, 1 H, H-6′b), 3.96 (t, 1 H, H-5), 4.06 (dt, 1

H, H-5′), 4.16 (m, 1 H, H-3), 4.19 (ddd, 1 H, H-1), 4.53 (q, 1 H, H-3′), 4.61 (t, 1 H, H-6), 4.82 (dd, 1 H, H-2′), 5.52 (d, 1 H, H-1′), 9.47 (d, *J* 8 Hz, NH-3), and 9.91 (d, *J* 9.5 Hz, NH-3′); $J_{1,2ax} = J_{2ax,2eq} = J_{2ax,3}$ 13, $J_{3,4} = J_{4,5} = J_{5,6}$ 10, $J_{1',2'}$ 3.5, $J_{2',3'}$ 11, $J_{3',4'} = J_{3',NH} = J_{4',5'} = J_{5',6'a} = J_{6'a,6'b}$ 10, and $J_{5',6'b}$ 5 Hz.

Anal. Calcd for $C_{39}H_{49}N_3O_{12}S_3 \cdot 3H_2O$: C, 51.93; H, 6.15; N, 4.66; S, 10.66. Found: C, 52.03; H. 5.85; N, 5.03; S, 10.54.

(ii) 15-Hour reaction. A mixture of **4** (438 mg) and KHF_2 (200 mg) in DMF (9 mL) was heated for 15 h at 150°. TLC of the solution as described for *i* gave spots of R_F 0.15 (**6**), 0.2 (**7**), and 0.9 (**8**). Work-up as described for *i* gave **6**, 29 mg (6.5%) **7**, 126 mg (28.2%), and **8**, 125 mg (27%).

Change of the product-ratio of **6** *and* **7** *with time in the reaction of* **4** *with* KHF_2. — A solution of **4** (10 mg) and KHF_2 (4.8 mg) in DMF (0.2 mL) was heated for a given time (10, 15, 20, 30, and 36 h) at 150° and, after cooling, $NaHCO_3$ (26 mg) and water (2 mL) were added. Thorough shaking followed by concentration gave a residue that was dissolved in $CHCl_3$ (5 mL), and the solution was washed once with aq satd $NaHCO_3$ solution (1 mL), dried (Na_2SO_4), and concentrated. The residue was dissolved in pyridine-d_5 (0.7 mL) and the ratio of intensity of the ^{19}F-signals (**6**:**7**, by ^{19}F-NMR) were measured. The ratios obtained were 0.17 (10 h), 0.33 (15 h), 0.53 (20 h), 1.9 (30 h), and 2.8 (36 h).

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