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Note

The synthesis of racemic 4-deoxyneosamine C

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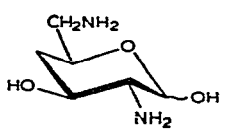
Recently, Kawaguchi *et al.*[1] described two new aminoglycoside antibiotics (coded as Bu-1975 C_1 and C_2) produced by strains of *Bacillus circulans*. It was subsequently shown[2] that these compounds are structurally related to butirosins A and B, respectively, the only difference being the replacement of neosamine C by a new aminodeoxy sugar, 2,6-diamino-2,4,6-trideoxy-D-*xylo*-hexopyranose (**1**). Bu-1975 C_1 and C_2 exhibit broader antibacterial spectra and enhanced activity against some micro-organisms than butirosins[1], which can be attributed to the presence of the new sugar unit[2]. We now report on the synthesis of racemic **1**.



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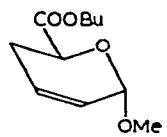

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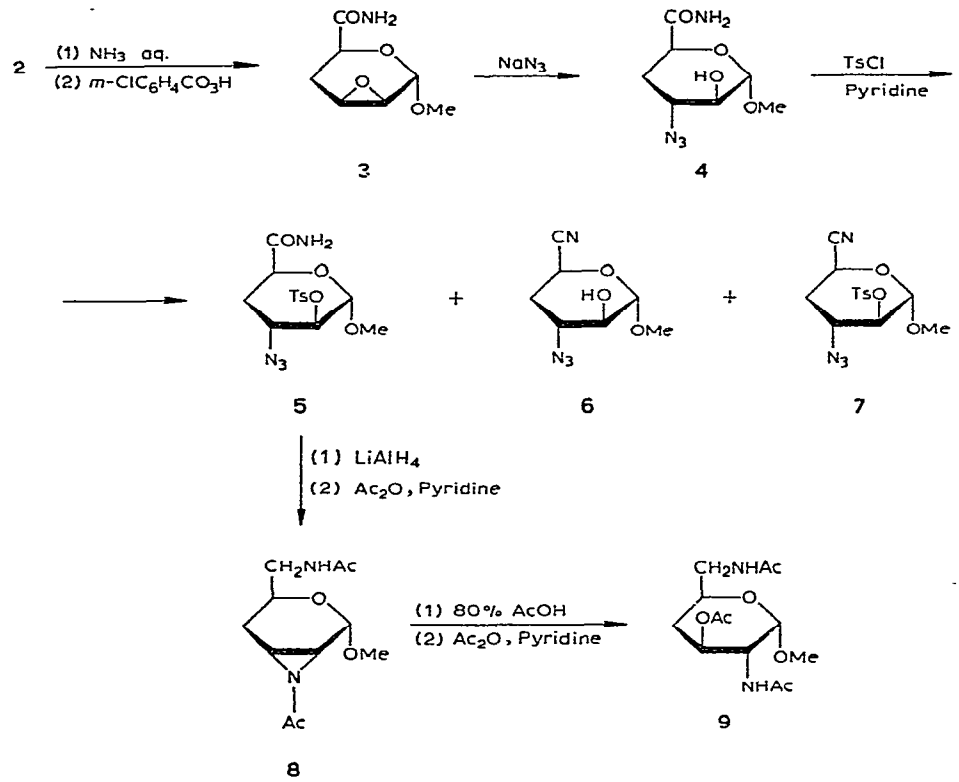
Monosaccharides containing a 4-deoxy grouping can be readily obtained by synthesis starting from the ester of 2-methoxy-5,6-dihydro-2*H*-pyran-6-carboxylic acid[3] (**2**) using the reactions in the annexed scheme (in which only D compounds are shown.

Starting with the ester **2** of *trans* configuration[3], treatment with conc. aqueous ammonia gave the amide, which was then epoxidised. The resulting mixture of racemic *ribo*- and *lyxo*-epoxides was fractionated by column chromatography. The *lyxo*-epoxide **3** was heated with sodium azide in aqueous 2-ethoxyethanol to give a single product in high yield. The location of the azide group at C-3 and the DL-*arabino* configuration were deduced from the p.m.r. spectrum. The exclusive attack of the nucleophile at C-3 in a similar system had been observed earlier[4].

An epimine ring was then generated by using the Guthrie and Liebmann method[5]. Conversion of **4** into the 2-*O*-tosyl derivative (45%) was accompanied by two additional products, namely the hydroxyazidonitrile **6** (17%) and its tosylate **7** (16%), which were identified on the basis of analytical and spectral data. The dehydration of an amide to a cyano group with tosyl chloride and pyridine is well



known[6], and it is interesting to note that **6** and **7** assume conformations having axial cyano groups (for solutions in $CDCl_3$, $J_{1,2}$ 7.0 Hz for **6**, and 4.5 Hz for **7**).

Reduction of **5** with lithium aluminium hydride gave the epimine and converted the amido into an aminomethyl group. Acetylation then gave the *N*-acetylepimine **8** in moderate yield (39%). The *ribo* configuration of **8** was indicated by the magnitude (3.7 Hz) of $J_{1,2}$ (*cf.* $J_{1,2}$ 3.5–4.5 Hz for alloepimines[7]).

The stereoselectivity of epimine-ring opening is strongly dependent[8] on the nucleophile used, conditions of the reaction, and the nature of the *N*-substituent. When **8** was heated with 80% aqueous acetic acid for 8 h and the resulting hydroxyamine was acetylated, **9** (43%) was obtained after chromatography. The p.m.r. spectrum of **9** contained a doublet for H-1 ($J_{1,2}$ 3.6 Hz) at δ 4.67, an octet for H-2 at δ 4.07 ($J_{1,3}$ 10.7, $J_{2,NH}$ 9.7 Hz), and a sextet for H-3 at δ 5.08 ($J_{3,4ax}$ 10.8, $J_{3,4eq}$ 5.0 Hz). These data indicate a 2-acetamido-3-*O*-acetyl-2-deoxy compound having the desired DL-*xylo* configuration. The reported p.m.r. and i.r. data for methyl 2,6-diacetamido-3-*O*-acetyl-2,4,6-trideoxy-α-D-*xylo*-hexopyranoside[2] agreed with those reported herein.

The synthesis described here demonstrates the simplicity and convenience of the total synthetic route to 4-deoxy sugars based on the readily available[3] Diels–Alder adduct **2**.

EXPERIMENTAL

Melting points are uncorrected. All reactions were monitored by t.l.c. on Kieselgel G (Merck). Column chromatography was performed on silica gel (100–200 mesh, Schuchardt). I.r. spectra were recorded with a Unicam SP-200 spectrophotometer. P.m.r. spectra were measured on a JEOL JNM-4H-100 instrument (100 MHz).

Compound **2** was obtained as previously reported[3]. Compound **3** was prepared in two steps by treatment of **2** with aqueous ammonia followed by *m*-chloroperoxybenzoic acid, and separation of the resulting epoxides on silica gel[9].

*Methyl 3-azido-3,4-dideoxy-α-*DL-arabino-*hexopyranosiduronamide* (**4**). — A mixture of methyl 2,3-anhydro-4-deoxy-α-DL-*lyxo*-hexopyranosiduronamide (**3**, 0.245 g, 1.4 mmol), 80% aqueous ethoxyethanol (5 ml), sodium azide (0.2 g), and ammonium chloride (0.1 g) was stirred for 5 h at 120–130°, then filtered, and concentrated to dryness. A solution of the syrupy residue in chloroform was passed through a column of silica gel to give **4** (0.27 g, 89%), m.p. 119–120° (from acetone–ether); ν_{max}^{KBr} 3460 (OH), 3350, 1680, 1665 (NHCO), and 2120 cm^{-1} (N_3). P.m.r. data ($CDCl_3$): δ 6.87 (d, $CONH_2$), 4.58 (d, $J_{1,2}$ 3.5 Hz, H-1), 4.28 (dd, $J_{5,4ax}$ 8.3, $J_{5,4eq}$ 4.3 Hz, H-5), 3.78 (m, $J_{3,4ax}$ 4.2, $J_{3,4eq}$ 6.0, $J_{2,3}$ 5.8 Hz, H-3), 3.55 (m, H-2), 3.40 (OMe), 2.90 (OH), 2.18 (m, $J_{4ax,4eq}$ 13.7 Hz, H-4a), 1.77 (m, H-4eq).

Anal. Calc. for $C_{17}H_{12}N_4O_4$: C, 38.39; H, 5.59; N, 25.92. Found: C, 39.08; H, 5.63; N, 25.83.

*The action of toluene-*p*-sulphonyl chloride in pyridine on* **4**. — To a stirred solution of **4** (0.24 g, 1.1 mmol) in dry pyridine (3 ml) at −5°, a solution of toluene-*p*-sulphonyl chloride (0.4 g, 2 mmol) in pyridine (2 ml) was added dropwise. Stirring was continued for 1 h at 0°, and then for 20 h at room temperature. T.l.c. (light petroleum–ether–methanol, 55:43:2) then showed the presence of three products. The reaction mixture was poured into ice–water, and extracted with chloroform. The extract was concentrated, and the residue was eluted from silica gel with light petroleum–ether–methanol (first 85:14.5:0.5, then 75:24.5:0.5).

The fast-moving component (38 mg, 17%), m.p. 65–67° (from acetone–ether), was methyl 3-azido-3,4,6-trideoxy-α-DL-*arabino*-hexopyranosidurononitrile (**6**); ν_{max}^{Nujol} 3500 (OH) and 2120 cm^{-1} (N_3). P.m.r. data ($CDCl_3$): δ 4.88 (dd, $J_{5,4eq}$ 2.5, $J_{5,4ax}$ 5.5 Hz, H-5), 4.54 (d, $J_{1,2}$ 7.0 Hz, H-1), 3.8 (m, $J_{3,4eq}$ 5.0, $J_{3,4ax}$ 11.2, $J_{2,3}$ 9.0 Hz, H-3), 3.57 (OMe), 3.37 (m, H-2), 3.0 (OH), 2.22 (m, H-4eq), 1.92 (m, H-4ax).

Anal. Calc. for $C_{17}H_{10}N_4O_3$: C, 42.42; H, 5.09; N, 28.27. Found: C, 42.52; H, 5.04; N, 28.48.

The second component was methyl 3-azido-3,4,6-trideoxy-2-*O*-tosyl-α-DL-*arabino*-hexopyranosidurononitrile (**7**, 62 mg, 16%), m.p. 105–106° (from ether–acetone); ν_{max}^{KBr} 2120 (N_3), 1370, and 1180 cm^{-1} (SO_2). P.m.r. data ($CDCl_3$): δ 7.84, 7.35 (2 d, aromatic protons), 4.82 (dd, $J_{5,4ax}$ 6.1, $J_{5,4eq}$ 4.5 Hz, H-5), 4.58 (d, $J_{1,2}$ 4.7 Hz, H-1), 4.30 (dd, $J_{2,3}$ 6.6 Hz, H-2), 3.86 (m, H-3), 3.32 (OMe), 2.48 (s, Me), 2.28 (m, $J_{4eq,3}$ 4.5 Hz, H-4eq), 1.92 (m, $J_{4ax,3}$ 8.0, $J_{4ax,4eq}$ 14.2 Hz, H-4ax).

Anal. Calc. for $C_{14}H_{16}N_4O_5S$: C, 43.73; H, 4.54; N, 15.91; S, 9.09. Found: C, 47.82; H, 4.66; N, 15.89; S, 8.89.

The slowest-moving component was methyl 3-azido-2-*O*-tosyl-α-DL-*arabino*-hexopyranosiduronamide (**5**, 0.18 g, 45%), m.p. 134–135° (from ether–methanol); ν_{max}^{KBr} 3480, 1700 (NHCO), 2120 (N_3), 1380, 1200, and 1180 (SO_2). P.m.r. data ($CDCl_3$): δ 7.83, 7.36 (2 d, aromatic protons), 6.45 (d, $CONH_2$), 4.70 (s, H-1), 4.3 (m, $J_{5,4ax}$ 8.5, $J_{5,4eq}$ 4.75, $J_{2,3}$ 2.2 Hz, H-2,5), 3.73 (m, $J_{3,4eq}$ 3.2, $J_{3,4ax}$ 7.5 Hz, H-3), 3.40 (OMe), 2.50 (s, Me), 2.30 (m, H-4ax,4eq).

Anal. Calc. for $C_{14}H_{18}N_4O_6S$: C, 45.41; H, 4.86; N, 15.14; S, 8.65. Found: C, 45.50; H, 4.85; N, 15.12; S, 8.54.

*Methyl 6-acetamido-2,3-*N*-acetylepimino-2,3,4,6-tetradeoxy-α-*DL-ribo-*hexopyranoside* (**8**). — A solution of **5** (0.17 g, 0.63 mmol) in tetrahydrofuran (5 ml) was added dropwise to a suspension of $LiAlH_4$ (0.5 g) in tetrahydrofuran (5 ml), and the resulting mixture was boiled under reflux for 3 h and then cooled. The excess hydride was decomposed by addition of ethanol and water, the solution was filtered and concentrated, and the residue was treated with acetic anhydride in pyridine. Elution of the crude product from silica gel with chloroform afforded syrupy **8** (74 mg, 39%); ν_{max}^{Nujol} 3350 and 1650 cm^{-1} (NHCO). P.m.r. data (Me_2CO): δ 7.18 (NH), 4.93 (d, $J_{1,2}$ 3.7 Hz, H-1), 3.74 (m, H-5), 3.45 (OMe), 3.0–3.3 (m, H-6,6'), 2.95 (m, H-2,3), 2.0, 1.9 (2 NHAc), 1.45 (m, part A of an ABMX system, $J_{4ax,4eq}$ 13.5, $J_{4ax,5}$ 11.0, $J_{4ax,3}$ 2.5 Hz, H-4ax).

Anal. Calc. for $C_{11}H_{18}N_2O_4$: C, 54.54; H, 7.43; N, 11.56. Found: C, 54.68; H, 7.70; N, 11.32.

*Methyl 2,6-diacetamido-3-*O*-acetyl-2,4,6-trideoxy-α-*DL-xylo-*hexopyranoside* (**9**). — A solution of **8** (65 mg, 0.26 mmol) in 80% aqueous acetic acid (4 ml) was kept for 8 h at 100°. Evaporation of the solvent left a syrup, which was acetylated in the usual way. Elution of the crude product from silica gel with chloroform yielded **9** (35 mg, 43%), m.p. 102° (loss of water?) and 142° (dec.); ν_{max}^{KBr} 3360, 1660, 1540 (NHCO), and 1735 cm^{-1} (OAc). P.m.r. data ($CDCl_3$): δ 5.6–6.0 (m, 2 NH), 5.08 (sextet, $J_{3,4eq}$ 5.0, $J_{3,4ax}$ 10.8, $J_{2,3}$ 10.3 Hz, H-3), 4.67 (d, $J_{1,2}$ 3.6 Hz, H-1), 4.07 (octet, J_{2NH} 9.7 Hz, H-2), 3.3–3.9 (H-5,6,6', OMe), 1.9–2.0 (3 AcO, H-4eq), 1.45 (dt, $J_{4ax,5}$ 10.5 Hz, H-4ax).

Anal. Calc. for $C_{13}H_{22}N_2O_6 \cdot 0.5H_2O$: C, 50.15; H, 7.45; N, 9.00. Found: C, 50.20; H, 7.25; N, 9.20.

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