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Note

Synthesis of methyl 2-*C*-acetamidomethyl-2-deoxy-α-D-glucopyranoside and its *manno* isomer

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Considerable effort has been devoted to the synthesis of natural products from optically active carbohydrates[1]. In connection with a project related to the synthesis of antibiotics, large quantities of methyl 2-*C*-acetamidomethyl-2-deoxy-α-D-gluco- (**11**) and -manno-hexopyranoside (**12**) were required. The replacement of the 2-amino-2-deoxy-D-glucose or 2-amino-2-deoxy-D-mannose moieties in the aminocyclitol aminoglycoside antibiotics[2], the oligosaccharide chains of glycoproteins and glycolipids[3], and the immunoadjuvant glycopeptide M.D.P.[4] by these analogues may improve the biological properties. The synthesis of carbocyclic analogues of 2-amino-2-deoxy-D-glucose has been reported[5,6].

Wittig reaction of methyl 3-*O*-benzyl-4,6-*O*-benzylidene-α-D- (**1**)[7] and -β-D-*arabino*-hexopyranosid-2-ulose (**2**)[8] with methylenetriphenylphosphorane gave the corresponding 2-*C*-methylene compounds **3** and **4** in good yield. Although, the hydroboration reaction of the α-D isomer **3** occurred only with low stereoselectivity, it furnished essentially the primary alcohols **5** and **6**. However, the β-D isomer **4**, the major constituent of the hydroboration, gave mainly an inseparable mixture of tertiary alcohols.

The *gluco* and *manno* configurations were assigned to **5** and **6**, respectively, on the basis of ^{1}H- and ^{13}C-NMR data. In the *manno* compound **6** C-4 was markedly shielded (80.2 ppm) compared to the *gluco* compound **5** (84.2 ppm). The shielding in **6** reflects[9] 1,3-type diaxial interaction of H-4 and the axial C-2–C-8 bond. Whereas in the *gluco* compound **5**, the signal for H-1 is a doublet ($J_{1,2}$ 3 Hz), that in the *manno* compound **6** is a singlet. The hydroboration products **5** and **6** were mesylated and then treated with sodium azide affording, respectively, **9** and **10**. Hydrogenolysis of the 4,6-*O*-benzylidene acetal group and reduction of the azide of **9** and **10** was performed in one step and in the presence of acetic anhydride, and gave the desired compounds **11** and **12** in reasonable overall yields.

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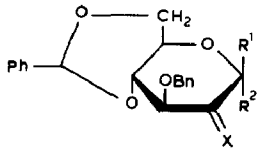
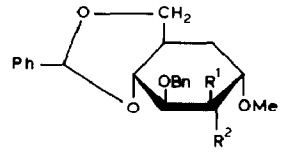
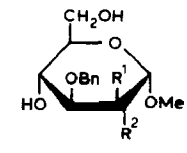


1 R^1= H, R^2= OMe, X = O
2 R^1= OMe, R^2= H, X = O
3 R^1= H, R^2= OMe, X = CH_2
4 R^1= OMe, R^2= H, X = CH_2



5 R^1= H, R^2= CH_2OH
6 R^1= CH_2OH, R^2= H
7 R^1= H, R^2= CH_2OMs
8 R^1= CH_2OMs, R^2= H
9 R^1= H, R^2= CH_2N_3
10 R^1= CH_2N_3, R^2= H



11 R^1= H, R^2= $CH_2NHCOMe$
12 R^1= $CH_2NHCOMe$, R^2= H

EXPERIMENTAL

General procedures. — A Perkin–Elmer Model 141 MC polarimeter and 1-dm tubes were used to determine specific optical rotations at 22°. NMR spectra were recorded on solutions in $CDCl_3$ (internal Me_4Si) (^1H at 200 and 400 MHz, ^{13}C at 50.31 MHz) with a Bruker WP-200 spectrometer. Microanalyses were performed by the Service Central de Microanalyse du C.N.R.S. Silica Gel 60 PF_{254} (Merck) activated at 120° was used for TLC and column chromatography. The term "standard work-up" means that the organic layer was washed with water, dried (Na_2SO_4), and filtered, and the solvent was removed at reduced pressure.

*Methyl 3-O-benzyl-4,6-O-benzylidene-2-deoxy-2-C-methylene-α-*D-arabino-*hexopyranoside* (**3**). — To a solution of methyltriphenylphosphonium bromide (4.34 g, 12.1 mmol) in tetrahydrofuran (60 mL) was added dropwise at −40° 1.6 M butyl-lithium in hexane (7.6 mL, 12.1 mmol), and the mixture was stirred for 1 h. A solution of **1**[7] (3 g, 8.1 mmol) in tetrahydrofuran (300 mL) was then added rapidly at 0° and the mixture was left to warm up to room temperature during 1 h. After the usual work-up, column chromatography (CH_2Cl_2) of the crude product gave **3** (2.02 g, 68%); mp 113–114°; $[\alpha]_D$ + 15° (*c* 2.2, $CHCl_3$). Mass spectrum (CI): *m/z* 369 (M^+ + H). NMR data: ^1H δ 7.55–7.22 (m, 10 H, 2 Ph), 5.54 (s, 1 H, H-7), 5.47 and 5.30 (2 s, 2 H, H-8a,8b), 5.00 (s, 1 H, H-1), 4.88 and 4.78 (2 d, 2 H, J_{gem} 12 Hz, PhCH_2), 4.47 (d, 1 H, $J_{3,4}$ 9 Hz, H-3), 4.30 (q, 1 H, $J_{5,6eq}$ 3, $J_{6ax,6eq}$ 12 Hz, H-6*eq*), 4.00 (m, 1 H, H-5), 3.72 (t, 1 H, $J_{5,6ax} = J_{6ax,6eq} = 12$ Hz, H-6*ax*), 3.65 (t, 1 H, $J_{3,4} = J_{4,5} = 9$ Hz, H-4), 3.37 (s, 3 H, OMe); ^{13}C, δ 142.6 (C-2), 112.9 (C-8), 103.4 (C-1), 101.3 (C-7), 84.3 (C-4), 76.8 (C-3), 73.8 (Ph*C*H_2), 69.2 (C-6), 63.9 (C-5), 54.6 (OMe).

Anal. Calcd for $C_{22}H_{24}O_5$: C, 71.73; H, 6.52. Found: C, 71.81; H, 6.49.

*Methyl 3-O-benzyl-4,6-O-benzylidene-2-deoxy-2-C-methylene-β-*D-arabino-*hexopyranoside* (**4**). — Prepared from **2**, as described above for **3**, **4** (1.07 g, 54%) had mp 166–167°; $[\alpha]_D$ − 90° (*c* 3.4, $CHCl_3$). Mass spectrum (CI): *m/z* 369 (M^+ + H).

^{13}C-NMR data: δ 141.5 (C-2), 111.1 (C-8), 101.3 (C-1, 7), 83.1 (C-4), 79.2 (C-3), 73.5 (PhCH$_2$), 69.1 (C-6), 66.6 (C-5), 57.1 (OMe).

Anal. Calcd for $C_{22}H_{24}O_5$: C, 71.73; H, 6.52. Found: C, 71.60; H, 6.49.

Methyl 3-O-benzyl-4,6-O-benzylidene-2-deoxy-2-C-hydroxymethyl-α-D-glucopyranoside (**5**) *and methyl 3-O-benzyl-4,6-O-benzylidene-2-deoxy-2-C-hydroxymethyl-α-D-mannopyranoside* (**6**). — To a solution of **3** (1.84 g, 5 mmol) in tetrahydrofuran (100 mL) at 0° was added M diborane (45 mL, 45 mmol) in tetrahydrofuran. The mixture was stirred for 48 h at room temperature; water (2.43 mL) and then aq 30% hydrogen peroxide (4.28 mL) and 3 M NaOH (4.28 mL) were added. After an additional stirring for 4 h, filtration, and the usual work-up, column chromatography (CH_2Cl_2–EtOAc, 95:5) of the product gave **5** (556 mg, 44%), **6** (641 mg, 51%), and a mixture (66 mg, 5%) of tertiary alcohols. Primary alcohol **5** had $[\alpha]_D$ + 71° (*c* 0.90, $CHCl_3$). Mass spectrum (FAB): *m/z* 387 (M^+ + H). NMR data: ^{1}H, δ 7.55–7.22 (m, 10 H, 2 Ph), 5.10 (s, 1 H, H-7), 4.98 and 4.68 (2 d, 2 H, J_{gem} 12 Hz, PhCH_2), 4.68 (d, 1 H, $J_{1,2}$ 3 Hz, H-1), 4.30 (q, 1 H, $J_{5,6eq}$ 3 Hz, $J_{6ax,6eq}$ 12 Hz, H-6*eq*), 3.97–3.40 (m, 6 H, H-3,4,5,6*ax*,8a,8b), 3.35 (s, 3 H, OMe), 2.05 (m, 1 H, H-2); ^{13}C, δ 101.7 (C-7), 101.4 (C-1), 84.2 (C-4), 75.0 and 74.9 (C-3) and Ph*C*H$_2$), 69.1 (C-6), 63.0 (C-5), 60.5 (C-8), 55.0 (OMe), 47.6 (C-2).

Anal. Calcd for $C_{22}H_{26}O_6$: C, 68.25; H, 6.73; O, 24.87. Found: C, 68.27; H, 6.81.

Compound **6** was isolated as a syrup with $[\alpha]_D$ + 29° (*c* 0.88, $CHCl_3$). Mass spectrum (FAB): *m/z* 387 (M^+ + H). NMR data: ^{1}H, δ 7.52–7.30 (m, 10 H, 2 Ph), 5.62 (s, 1 H, H-7), 4.85 and 4.68 (2 d, 2 H, J_{gem} 12 Hz, PhCH_2), 4.72 (s, 1 H, H-1), 4.30–3.70 (m, 7 H, H-3,4,5,6*ax*,6*eq*,8a,8b), 3.32 (s, 3 H, OMe), 2.52 (m, 1 H, H-2); ^{13}C, δ 101.6 (C-7), 100.9 (C-1), 80.2 (C-4), 75.6 (C-3), 73.5 (Ph*C*H$_2$), 69.1 (C-6), 63.4 (C-5), 60.7 (C-8), 54.9 (OMe), 46.6 (C-2).

Anal. Calcd for $C_{22}H_{26}O_6$: C, 68.25; H, 6.73; O, 24.87. Found: C, 68.30; H, 6.81.

The ^{1}H-NMR spectrum of the mixture of tertiary alcohols contained signals at δ 1.35 (s, 3 H, CMe) and 1.28 (s, 3 H, CMe).

Methyl 3-O-benzyl-4,6-O-benzylidene-2-deoxy-2-C-methanesulfonyloxymethyl-α-D-glucopyranoside (**7**). — To a solution of **5** (0.51 g, 1.31 mmol) in dry pyridine (20 mL) at 0° was added methanesulfonyl chloride (0.20 mL, 2.62 mmol), and the mixture was stirred overnight at room temperature. After the usual work-up, **7** (0.58 g, 95%) was isolated with mp 111°; $[\alpha]_D$ + 74° (*c* 1.5, $CHCl_3$). Mass spectrum (CI): *m/z* (465 (M^+ + H). NMR data: ^{1}H, δ 7.55–7.25 (m, 10 H, 2 Ph), 5.61 (s, 1 H, H-7), 4.92 and 4.60 (2 d, 2 H, J_{gem} 12 Hz, PhCH_2), 4.81 (d, 1 H, $J_{1,2}$ 3 Hz, H-1), 4.45–3.70 (m, 7 H, H-3,4,5,6*ax*,6*eq*,8a,8b), 3.36 (s, 3 H, OMe), 2.93 (s, 3 H, Ms), 2.35 (m, 1 H, H-2); ^{13}C, δ 101.5 (C-7), 98.4 (C-1), 84.4 (C-4), 74.5 (Ph*C*H$_2$), 73.7 (C-3), 69.1 (C-6), 68.1 (C-8), 62.7 (C-5), 55.2 (OMe), 45.7 (C-2), 37.0 (SO_2Me).

Anal. Calcd for $C_{23}H_{28}O_8S$: C, 59.48; H, 6.03; O, 27.58; S, 6.89. Found: C, 59.30; H, 6.19; S, 7.01.

Methyl 3-O-benzyl-4,6-O-benzylidene-2-deoxy-2-C-methanesulfonyloxymethyl-α-D-mannopyranoside (**8**). — Prepared from **6**, as described above for **7**, syrupy **8** (0.49 g, 93%) had $[\alpha]_D$ + 5° (*c* 1.7, $CHCl_3$). Mass spectrum (CI): *m/z* 465

($M^+ + H$). NMR data: ^1H, δ 7.55–7.25 (m, 10 H, 2 Ph), 5.60 (s, 1 H, H-7), 4.85 (s, 1 H, H-1), 4.80 and 4.65 (2 d, 2 H, J_{gem} 12 Hz, PhCH_2), 4.40–3.60 (s, 3 H, OMe), 3.02 (s, 3 H, Ms), 2.70 (m, 1 H, H-2); ^{13}C, δ 101.5 (C-7), 99.3 (C-1), 79.9 (C-4), 73.5 (C-3), 73.0 (PhCH$_2$), 68.8 (C-6), 66.7 (C-8), 63.1 (C-5), 55.0 (OMe), 44.5 (C-2), 37.0 (SO_2Me).

Anal. Calcd for $C_{23}H_{28}O_8S$: C, 59.48; H, 6.03; O, 27.58; S, 6.89. Found: C, 59.60; H, 6.08; S, 6.92.

Methyl 2-C-azidomethyl-3-O-benzyl-4,6-O-benzylidene-2-deoxy-α-D-glucopyranoside (**9**). — To a solution of **7** (0.50 g, 1.07 mmol) in dry *N,N*-dimethylformamide (20 mL) was added sodium azide (0.42 g, 6.42 mmol), and the mixture was stirred overnight under argon at 150°. After filtration and the usual work-up, syrupy **9** (0.42 g, 95%) was obtained, $[\alpha]_D$ + 77° (*c* 3.4, $CHCl_3$). Mass spectrum (CI): *m/z* 412 ($M^+ + H$). NMR data: ^1H, δ 7.55–7.28 (m, 10 H, 2 Ph), 5.60 (s, 1 H, H-7), 4.92 and 4.60 (2 d, 2 H, J_{gem} 12 Hz, PhCH_2), 4.78 (d, 1 H, $J_{1,2}$ 3 Hz, H-1), 4.30–3.30 (m, 7 H, H-3,4,5,6*ax*,6*eq*,8a,8b), 3.35 (s, 3 H, OMe), 2.10 (m, 1 H, H-2); ^{13}C δ 101.4 (C-7), 99.3 (C-1), 84.2 (C-4), 74.7 (C-3 and PhCH$_2$), 69.4 (C-6), 63.4 (C-5), 55.0 (OMe), 49.9 (C-8), 46.0 (C-2).

Anal. Calcd for $C_{22}H_{25}N_3O_5$: C, 64.23; H, 6.07; N, 10.21; O, 19.46. Found: C, 64.07; H, 5.59; N, 10.06.

Methyl 2-C-azidomethyl-3-O-benzyl-4,6-O-benzylidene-2-deoxy-α-D-mannopyranoside (**10**). — Prepared from **8**, as described above for **9**, syrupy **10** (0.36 g, 85%) had $[\alpha]_D$ − 6° (*c* 1.0, $CHCl_3$). Mass spectrum (CI): *m/z* 412 ($M^+ + H$). NMR data: ^1H, δ 7.55–7.27 (m, 10 H, 2 Ph), 5.57 (s, 1 H, H-7), 4.80 and 4.65 (2 d, 2 H, J_{gem} 12 Hz, PhCH_2), 4.78 (s, 1 H, H-1), 4.27–3.35 (m, 7 H, H-3,4,5,6*ax*,6*eq*,8a,8b), 3.35 (s, 3 H, OMe), 2.40 (m, 1 H, H-2); ^{13}C, δ 101.5 (C-7), 100.2 (C-1), 79.9 (C-4), 74.0 (C-3), 73.1 (PhCH$_2$), 69.1 (C-6), 63.4 (C-5), 55.1 (OMe), 48.3 (C-8), 44.8 (C-2).

Anal. Calcd for $C_{22}H_{25}N_3O_5$: C, 64.23; H, 6.07; N, 10.21; O, 19.46. Found: C, 64.11; H, 6.13; N, 10.03.

Methyl-2-C-acetamidomethyl-2-deoxy-α-D-glucopyranoside (**11**). — To a solution of **9** (102 mg, 0.24 mmol) in MeOH (3 mL) was added acetic anhydride (0.143 mL) and 5% Pd–C (12 mg), and the mixture was hydrogenated at atmospheric pressure for 5 days. After filtration and the usual work-up, column chromatography (CH_2Cl_2–MeOH–NH_4OH, 10:1:0.5) of the product gave syrupy **11** (69 mg, 90%), $[\alpha]_D$ + 96° (*c* 2.9, MeOH). Mass spectrum (CI): *m/z* 250 ($M^+ + H$). NMR data (CD_3OD): ^1H, δ 4.68 (d, 1 H, $J_{1,2}$ 3 Hz, H-1), 3.82–3.22 (m, 7 H, H-3,4,5,6a,6b,7a,7b), 3.34 (s, 3 H, OMe), 1.93 (s, 3 H, NAc), 1.80 (m, 1 H, H-2); ^{13}C, δ 100.8 (C-1), 74.2 (C-5), 72.7 (C-3,4), 62.7 (C-6), 55.3 (OMe), 46.7 (C-7), 42.8 (C-2), 22.6 (NAc).

Anal. Calcd for $C_{10}H_{19}NO_6$: C, 48.19; H, 7.63; N, 5.62; O, 38.55. Found: C, 48.07; H, 7.80; N, 5.77.

Methyl 2-C-acetamidomethyl-2-deoxy-α-D-mannopyranoside (**12**). — Prepared from **10**, as described above for **11**, syrupy **12** (40 mg, 77%) had $[\alpha]_D$ + 49° (*c* 1.35, MeOH). Mass spectrum (CI): *m/z* 250 ($M^+ + H$). NMR data (CD_3OD): ^1H, δ 4.63

(s, 1 H, H-1), 3.98–3.28 (m, 7 H, H-3,4,5,6a,6b,7a,7b), 3.35 (s, 3 H, OMe), 2.13 (m, 1 H, H-2), 1.93 (s, 3 H, NAc); ^{13}C, δ 101.5 (C-1), 74.3 (C-5), 71.3 and 68.9 (C-3,4), 62.7 (C-6), 55.2 (OMe), 47.0 (C-7), 37.1 (C-2), 22.6 (NAc).

Anal. Calcd for $C_{10}H_{19}NO_6$: C, 48.19; H, 7.63; N, 5.62; O, 38.55. Found: C, 48.30; H, 7.51; N, 5.83.

REFERENCES

1 S. Hanessian, *Total Synthesis of Natural Products. The Chiron Approach,* Pergamon, Oxford, 1983.
2 D.A. Cox, K. Richardson, and B.C. Ross, in P.G. Sammes (Ed.), *Topics in Antibiotic Chemistry*, Vol. I, Wiley, New York, 1977, pp. 1–90.
3 H. Paulsen, *Angew. Chem. Int. Ed. Engl.,* 21 (1982) 155–173.
4 P. Lefrancier, M. Derrien, I. Lederman, F. Nief, J. Choay, and E. Lederer, *Int. J. Peptide Protein Res.*, 11 (1978) 289–296.
5 D.H.R. Barton, S.D. Gero, S. Augy, and B. Quiclet-Sire, *J. Chem. Soc., Chem. Commun.,* (1986) 1399–1401.
6 S. Ogawa, T. Toyokuni, Y. Hattori, T. Nose, and T. Suami, *Carbohydr. Res.,* 146 (1986) 167–173.
7 T. Takamoto and R. Sudoh, *Bull. Chem. Soc. Jpn.,* 48 (1975) 3413–3414.
8 E.E. Lee, G. Keaveney, and P.S. O'Colla, *Carbohydr. Res.,* 59 (1977) 268–273.
9 J.B. Stothers, *Carbon-13 NMR Spectroscopy*, Academic Press, New York, 1972.