Carbohydrate Research, 205 (1990) 435–439
Elsevier Science Publishers B.V., Amsterdam

Note

Synthesis of phenyl 4-(*N*-benzylformamido)-4,6-dideoxy-3-*C*-methyl-2-*O*-methyl-1-thio-α-L-mannopyranoside, an *N*-formylkansosamine glycosyl donor*

István Bajza and András Lipták†
Institute of Biochemistry, L. Kossuth University, P.O. Box 55, H-4010 Debrecen (Hungary)

(Received January 4th, 1990; accepted for publication, April 18th, 1990)

Recently, 4,6-dideoxy-4-*N*-formamido-3-*C*-methyl-2-*O*-methyl-L-mannose (**1**), an *N*-substituted derivative of kansosamine, was reported[1] as the non-reducing terminus of the type-specific pentasaccharide determinant of serovariant 14 of the *Mycobacterium avium* complex. Two other naturally occurring derivatives of 4-amino-4,6-dideoxy-3-*C*-methyl-L-mannose have been reported, namely *N*-(*R*)-2-methoxypropanokansosamine {4,6-dideoxy-4-[(*R*)-2-methoxypropionamido]-3-*C*-methyl-2-*O*-methyl-L-mannopyranose} from *Mycobacterium kansasii*[2,3] and L-sibirosamine (4,6-dideoxy-3-*C*-methyl-4-methylamino-L-mannopyranose) from *Streptosporangium sibiricum*[4,5].

In connection with the synthesis of the pentasaccharide antigen of serovariant 14 of the *M. avium* complex, we now report the title compound, which is a C-1-activated derivative (**10**) of *N*-formylkansosamine.

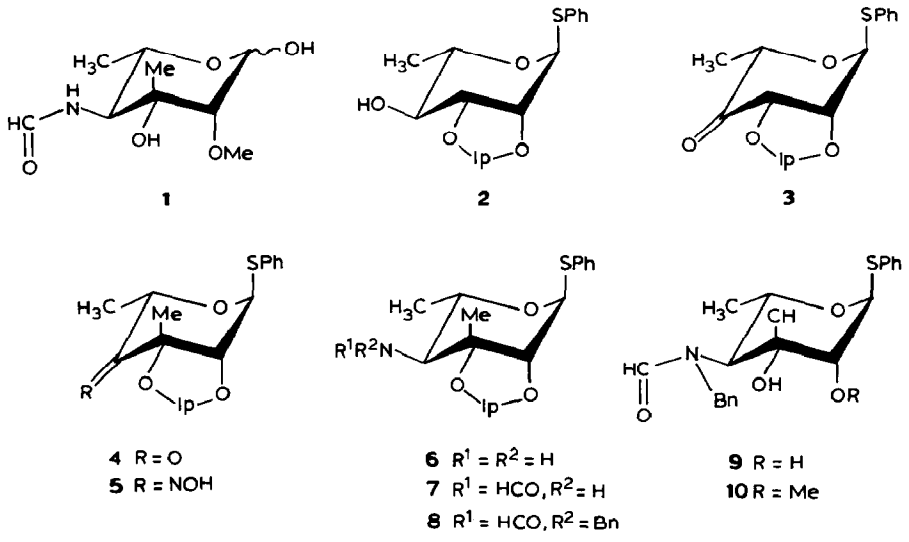
Oxidation of phenyl 6-deoxy-2,3-*O*-isopropylidene-1-thio-α-L-mannopyranoside[6] (**2**) by pyridinium chlorochromate in dichloromethane gave 70% of the ulose **3**, but no sulphoxide or sulphone. Generation of the carbanion of **3** was achieved with lithium di-isopropylamide and treatment with methyl iodide proceeded with low stereoselectivity, and only 56% of the desired axial 3-*C*-methyl derivative **4** could be isolated. Treatment of **4** with 10 equiv. of hydroxylamine hydrochloride–sodium carbonate in ethanol at 90° afforded 60% of the oxime **5**, reduction of which with 10 equiv. of lithium aluminium hydride in oxolane gave a ~1:1 mixture of the L-*manno* (**6**) and L-*talo* amines. Only **6** was isolated (30%) and was treated in dichloromethane with carbodiimide–formic acid to yield **7** (70%). The proton of the formyl group resonated at 8.04 and 8.24 p.p.m., reflecting the two environments caused by hindered rotation around the formyl C–N bond. Removal of the isopropylidene group from **7** gave a diol, attempted selective methylation of which resulted in both *O*- and *N*-methylation.

* Dedicated to Professor Leslie Hough in the year of his 65th birthday.
† Author for correspondence.

0008-6215/90/$ 03.50

Therefore, 7 was *N*-benzylated to give **8** (70%), the isopropylidene group of which was hydrolysed in aqueous 70% acetic acid at 80° to give **9** (80%). Methylation of the diol **9** then gave the title compound **10** (66%), but a di-*O*-methylated minor component could also be detected by t.l.c.

Compound **10** (after protection of the free OH group) can be activated by different thiophilic reagents (*e.g.*, benzeneselenyl triflate[7], methyl triflate[8], dimethyl (methylthio)sulfonium triflate[9]) and used as a glycosyl donor.



EXPERIMENTAL

General. — Solutions were concentrated at 40° (bath)/~15 Torr. Chromatography was performed on Kieselgel 60. Optical rotations were measured with a Perkin–Elmer 241 automatic polarimeter and i.r. spectra with a Perkin–Elmer 283B spectrophotometer. The ^{1}H-(200 MHz) and ^{13}C-n.m.r. (50.3 MHz) spectra were recorded with a Bruker WP-200 SY spectrometer for solutions in $CDCl_3$ (internal Me_4Si). Melting points are uncorrected.

*Phenyl 6-deoxy-2,3-*O*-isopropylidene-1-thio-*α*-*L*-lyxo-hexopyranosid-4-ulose* (**3**). — To a solution of phenyl 6-deoxy-2,3-*O*-isopropylidene-1-thio-α-L-mannopyranoside[6] (**2**; 4.6 g, 16 mmol) in dichloromethane (400 mL) was added pyridinium chlorochromate (16.8 g, 77 mmol). The mixture was stirred for 2 h at room temperature and worked-up conventionally. Short column chromatography (hexane–ethyl acetate, 7:3) afforded **3** as a colourless syrup (3.3 g, 72%), $[\alpha]_D$ −216° (*c* 0.2, chloroform); ν_{max} 1740 cm^{-1} (C=O). ^{1}H-N.m.r. data: δ 7.40 (m, 5 H, Ph), 5.70 (d, 1 H, $J_{1,2}$ 1.5 Hz, H-1), 4.72 (d, 1 H, $J_{5,6}$ 6.5 Hz, H-5), 4.68 (dd, 1 H, $J_{1,2}$ 1.5, $J_{2,3}$ 6 Hz, H-2), 4.50 (d, 1 H, $J_{2,3}$ 6 Hz, H-3), 1.48 and 1.40 (2 s, each 3 H, CMe_2), 1.34 (d, 3 H, $J_{5,6}$ 6.5 Hz, Me-5).

*Phenyl 6-deoxy-2,3-*O*-isopropylidene-3-*C*-methyl-1-thio-*α*-*L*-lyxo-hexopyranosid-4-ulose* (**4**). — A solution of **3** (353 mg, 1.2 mmol) in oxolane was added to a solution

of lithium di-isopropylamide (1.2 mmol) in oxolane at −76°. The mixture was stirred for 1 h at −76°, then hexamethylphosphoric triamide (333 μL) and MeI (500 μL, 8 mmol) were added. After 5 h, an aqueous 10% solution (2 mL) of NH_4Cl was added, and the mixture was diluted with dichloromethane, extracted with water (2 × 20 mL), dried ($MgSO_4$), and concentrated *in vacuo*. Chromatography (hexane–ethyl acetate, 9:1) of the residue gave **4** (209 mg, 56%) as a colourless syrup, $[\alpha]_D$ −200° (*c* 0.3, chloroform); ν_{max} 1750 cm^{-1} (C=O). ^{1}H-N.m.r. data: δ 7.40 (m, 5 H, Ph), 5.73 (d, 1 H, $J_{1,2}$ 1.5 Hz, H-1), 4.83 (d, 1 H, $J_{5,6}$ 6.7 Hz, H-5), 4.32 (d, 1 H, $J_{1,2}$ 1.5 Hz, H-2), 1.57 (s, 3 H, CMe), 1.41 (b s, 6 H, CMe and Me-3), 1.35 (d, 3 H, $J_{5,6}$ 6.7 Hz, Me-5).

*Phenyl 6-deoxy-2,3-*O*-isopropylidene-3-*C*-methyl-1-thio-α-*L*-lyxo-hexopyranosid-4-ulose oxime* (**5**). — A mixture of **4** (1.5 g, 4.9 mmol), hydroxylamine hydrochloride (1.5 g, 21 mmol), Na_2CO_3 (2.6 g, 25 mmol), and ethanol (100 mL) was boiled under reflux for 20 h, then filtered, and concentrated. Column chromatography (toluene–ethyl acetate, 97:3) of the residue gave **5** (900 mg, 64%), m.p. 112°, $[\alpha]_D$ −315° (*c* 0.4, chloroform); ν_{max} 3280 (OH), 1655 cm^{-1} (C=N). ^{1}H-N.m.r. data: δ 8.62 (s, 1 H, oxime OH), 7.40 (b m, 5 H, Ph), 5.46 (s, 1 H, H-1), 5.20 (d, 1 H, $J_{5,6}$ 6.5 Hz, H-5), 4.23 (s, 1 H, H-2), 1.62 (s, 3 H, Me-3), 1.59 (s, 3 H, CMe), 1.53 (d, 3 H, $J_{5,6}$ 6.5 Hz, Me-5), 1.51 (s, 3 H, CMe).

Anal. Calc. for $C_{17}H_{23}NO_4S$ (337.96): C, 60.4; H, 6.9; N, 4.1; S, 9.5. Found: C, 60.3; H, 6.8; N, 4.05; S, 9.45.

*Phenyl 4-amino-4,6-dideoxy-2,3-*O*-isopropylidene-3-*C*-methyl-1-thio-α-*L*-manno-pyranoside* (**6**). — To a solution of **5** (420 mg, 1.3 mmol) in oxolane (80 mL) was added $LiAlH_4$ (494 mg, 13 mmol), and the mixture was stirred at 100°. After 4 h, the excess of hydride was decomposed by the consecutive addition of ethyl acetate and aqueous KOH. The organic layer was diluted with dichloromethane, washed with water (2 × 50 mL), dried ($MgSO_4$), and concentrated *in vacuo*. Column chromatography (hexane–ethyl acetate, 9:1) of the residue afforded **6** (126 mg, 30%) as a colourless syrup, $[\alpha]_D$ −152° (*c* 0.7, chloroform). ^{1}H-N.m.r. data: δ 7.50 and 7.38 (m, 5 H, Ph), 5.73 (d, 1 H, $J_{1,2}$ 1.2 Hz, H-1), 3.95 (dd, 1 H, $J_{4,5}$ 10, $J_{5,6}$ 6.2 Hz, H-5), 4.06 (d, 1 H, $J_{1,2}$ 1.2 Hz, H-2), 2.91 (d, 1 H, $J_{4,5}$ 10 Hz, H-4), 1.52 and 1.38 (2 s, each 3 H, CMe_2), 1.44 (s, 3 H, Me-3), 1.51 (s, 2 H, NH_2) 1.24 (d, 3 H, $J_{5,6}$ 6.2 Hz, Me-5).

*Phenyl 4,6-dideoxy-4-formamido-2,3-*O*-isopropylidene-3-*C*-methyl-1-thio-α-*L*-mannopyranoside* (**7**). — To a stirred solution of **6** (236 mg, 0.76 mmol) and 1-(3-dimethylaminopropyl)-3-ethylcarbodi-imide (161 mg, 0.84 mmol) in dichloromethane (20 mL) was added formic acid (40 μL, 0.84 mmol) dropwise at room temperature. After 2 h, the mixture was diluted with dichloromethane, washed with aqueous $NaHCO_3$ (25 mL) and water (2 × 25 mL), dried ($MgSO_4$), and concentrated *in vacuo*. Chromatography (toluene–ethyl acetate, 7:3) of the product gave **7** (178 mg, 70%) as a colourless syrup, $[\alpha]_D$ −185° (*c* 0.3, chloroform). ^{1}H-N.m.r. data: δ 8.04 (d, 0.5 H, $J_{\text{formyl H,NH}}$ 10 Hz, formyl H), 8.24 (d, 0.5 H, $J_{\text{formyl H,NH}}$ 2 Hz, formyl H), 7.29–7.45 (m, 5 H, Ph), 6.20 (b d, 0.5 H, $J_{NH,4}$ 10.5 Hz, NH), 6.42 (b d, 0.5 H, $J_{\text{NH,formyl}}$ 10 Hz, NH), 5.77, 5.75 (2 s, 1 H, H-1), 4.37 (t, 0.5 H, $J_{4,5}$ 10, $J_{4,NH}$ 10 Hz, H-4), 3.37 (dd, 0.5 H, $J_{4,5}$ 10, $J_{4,NH}$ 10.5 Hz, H-4), 4.20, 3.95 (2 dd, 1 H, $J_{4,5}$ 10, $J_{5,6}$ 6.2 Hz, H-5), 4.12, 4.08 (2 s, 1 H, H-2), 1.60 −1.35 (s, 9 H, Me-3 and CMe_2), 1.23 1.21 (2 d, 3 H, $J_{5,6}$ 6.2 Hz, Me-5).

*Phenyl 4-(*N*-benzylformamido)-4,6-dideoxy-2,3-*O*-isopropylidene-3-*C*-methyl-1-thio-α-*L*-mannopyranoside* (**8**). — Compound **7** (110 mg, 0.33 mmol) was treated with NaH (20 mg, 0.66 mmol) in *N,N*-dimethylformamide for 1 h at room temperature, then benzyl bromide (78 μL, 0.66 mmol) was added. After 20 min, methanol was added to decompose the excess of the hydride, and the mixture was concentrated *in vacuo*. Column chromatography (hexane–ethyl acetate, 85:15) of the residue gave **8** (98 mg, 70%) as a colourless syrup, $[\alpha]_D$ −135° (*c* 0.5, chloroform). ^{1}H-N.m.r. data: δ 8.33 and 8.30 (2 s, formyl H), 7.30 (m, 10 H, 2 Ph), 5.50 and 5.41 (2 d, $J_{1,2}$ 2 Hz, H-1), 4.60 and 4.40 (2 H, PhCH_2), 4.45 and 3.90 (2 dd, 1 H, $J_{4,5}$ 10, $J_{5,6}$ 6 Hz, H-5), 3.80 (d, 1 H, $J_{1,2}$ 2 Hz, H-2), 3.42 and 2.90 (2 d, 1 H, $J_{4,5}$ 10 Hz, H-4), 1.50 and 1.45 (2 s, Me-3), 1.48, 1.45, 1.38, 1.35 (4 s, CMe_2), 1.20 and 1.19 (2 d, $J_{5,6}$ 6 Hz, Me-5).

*Phenyl 4-(*N*-benzylformamido)-4,6-dideoxy-3-*C*-methyl-1-thio-α-*L*-mannopyranoside* (**9**). — Compound **8** (90 mg, 0.21 mmol) was treated with aqueous 70% acetic acid (20 mL) for 7.5 h at 80°. The mixture was concentrated, and column chromatography (chloroform–methanol, 97:3) of the residue gave **9** (64 mg, 80%) as a colourless syrup, $[\alpha]_D$ −147° (*c* 0.5, chloroform). ^{1}H-N.m.r. data: δ 8.33 and 8.13 (2 s, 1 H, formyl H), 7.40 and 7.32 (b m, 10 H, Ph), 5.47 and 5.41 (2 d, 1 H, $J_{1,2}$ 2 Hz, H-1), 4.62 and 4.47 (2 d, 1 H, PhCH_2), 4.44 (dd, 1 H, $J_{4,5}$ 10, $J_{5,6}$ 6 Hz, H-5), 4.09 and 3.63 (b s, 1 H, OH), 3.84 (d, 1 H, $J_{1,2}$ 2 Hz, H-2), 3.40 (d, 1 H, $J_{4,5}$ 10 Hz, H-4), 1.51 and 1.45 (2 s, 3 H, Me-3), 0.82 (d, 3 H, $J_{5,6}$ 6 Hz, Me-5).

*Phenyl 4-(*N*-benzylformamido)-4,6-dideoxy-3-*C*-methyl-2-*O*-methyl-1-thio-α-*L*-mannopyranoside* (**10**). — Compound **9** (50 mg, 0.13 mmol) was treated with NaH (5 mg, 0.17 mmol) in *N,N*-dimethylformamide (10 mL) for 30 min at room temperature, then MeI (40 μL, 0.65 mmol) was added. After 5 min, methanol was added (5 mL) to decompose the excess of the hydride, and the mixture was concentrated *in vacuo*. A solution of the crude product in dichloromethane was washed with water (2 × 10 mL), dried ($MgSO_4$), and concentrated *in vacuo*. Column chromatography (hexane–ethyl acetate, 7:3) of the residue gave **10** (34 mg, 66%), $[\alpha]_D$ −99° (*c* 0.79, chloroform). N.m.r. data: ^{1}H, δ 8.40 (s, 0.33 H, formyl H), 8.18 (s, 0.67 H, formyl H), 7.30 and 7.45 (2 m, 10 H, 2 Ph), 5.55 (d, 0.67 H, $J_{1,2}$ 1.1 Hz, H-1), 5.51 (d, 0.33 H, $J_{1,2}$ 1.5 Hz, H-1), 4.70 and 4.52 (2 d, 2 H, PhCH_2), 4.48 (dd, 1 H, $J_{4,5}$ 10.6, $J_{5,6}$ 5.85 Hz, H-5), 4.03 (b d, 1 H, OH), 3.49 and 3.48 (2 s, 3 H, OMe), 3.42 (d, 0.67 H, $J_{1,2}$ 1.1 Hz, H-2), 3.39 (d, 0.33 H, $J_{1,2}$ 1.5 Hz, H-2), 3.26 (d, 1 H, $J_{4,5}$ 10.6 Hz, H-4), 1.55 and 1.48 (2 s, 3 H, Me-3), 0.84 (d, 3 H, $J_{5,6}$ 5.85 Hz, Me-5); ^{13}C, δ 162.43 (formyl), 136.61 and 135.04 (phenyl quaternary C), 130–127.2 (aromatic skeleton), 86.75 and 86.49 (C-1), 84.18 and 83.91 (C-2), 72.96 (C-4), 65.95 (C-3), 58.47 and 58.52 (OCH_3), 64.88 (C-5), 31.86 and 29.59 (CH_2), 21.71 and 20.57 (Me-3), 18.24 and 17.47 (Me-6).

ACKNOWLEDGMENTS

We thank Dr. J. Harangi for recording the n.m.r. spectra, and the National Research Foundation for financial support (OTKA 234 to A.L.).

REFERENCES

1 M. McNeil, H. Gaylord, and P. J. Brennan, *Carbohydr. Res.*, 177 (1988) 185–198.
2 S. W. Hunter, T. Fujiwara, R. L. Murphy, and P. J. Brennan, *J. Biol. Chem.*, 259 (1984) 9729–9734.
3 S. W. Hunter, I. Jardine, D. L. Yanagihara, and P. J. Brennan, *Biochemistry*, 24 (1985) 2798–2805.
4 A. S. Mesentsev and V. V. Kuljaeva, *Tetrahedron Lett.*, (1973) 2225–2228.
5 K. A. Parker and R. E. Babine, *J. Am. Chem. Soc.*, 104 (1982) 7330–7331.
6 A. Lipták, J. Imre, and P. Nánási, *Carbohydr. Res.*, 92 (1981) 154–165.
7 Y. Ito and T. Ogawa, *Tetrahedron Lett.*, 29 (1988) 1061–1064.
8 H. Lönn, *Carbohydr. Res.*, 139 (1985) 105–113.
9 P. Fügedi and P. J. Garegg, *Carbohydr. Res.*, 149 (1986) c9–c12.