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Note

Preparation of methyl 4,6-*O*-benzylidene-2-deoxy-2-nitro-α-D-glucopyranoside from the corresponding 2-oximino derivative

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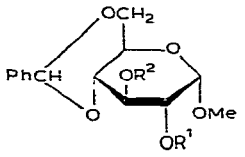
Very recently, we reported the synthesis of methyl 4,6-*O*-benzylidene-2,3-dideoxy-2-nitro-α-D-*erythro*-hex-2-enopyranoside (**12**) by the reaction of the corresponding 3-nitro alkene with sodium nitrite[1]. In this paper, we report an alternative method for the preparation of **12**.

Various types of nitro sugars were synthesized by oxidation with trifluoroperoxyacetic acid of the corresponding oximes in which all hydroxyl groups were protected by *O*-methyl, *O*-benzyl, and/or *O*-isopropylidene groups[2]. We chose the tetrahydropyranosyl ether[3] **1** as starting material, because of its facile removal after the oxidation. The crude product, prepared by oxidation of **1** with dimethyl sulfoxide and subsequent oximation, was directly oxidized with trifluoroperoxyacetic acid, giving the nitro alcohol **5** (4% yield from **1**), the oxime **4** (36%), and the sulfonyl derivative **6** (7%), instead of the desired nitro compound **8**; **6** was apparently formed from the (methylthio)methyl derivative **7**, a known by-product of oxidations with dimethyl sulfoxide. Formation of the nitro alcohol **5** suggests that prior protection of the hydroxyl group is unnecessary. In fact, a preliminary attempt at oxidation of **4** provided the nitro compound **5** in 47% yield, together with the starting material (9%). The yield of **4** *via* **2**, however, was unsatisfactory. After unsuccessful attempts at purification, the benzoate **10**, prepared by oximation of compound[4] **9**, was directly oxidized, affording only traces of nitro compound, as judged from i.r. spectroscopy. Conventional methods for debenzoylation (sodium methoxide in methanol, potassium hydroxide in ethanol, etc.) gave unsatisfactory results. However, treatment of **10** with hydroxylamine in ethanol afforded **4** in 93% yield (from **9**). When the ulose **9** was treated with hydroxylamine, both oximation and debenzoylation occurred giving **4** in 77% yield. However, similar treatment with hydroxylamine-acetic acid led only to oximation.

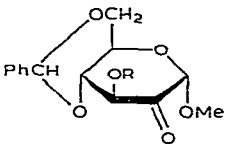
Oxidation of **4** with trifluoroperoxyacetic acid was performed under various conditions. The results showed that (*i*) both sodium hydrogencarbonate and disodium hydrogenphosphate were effective as bases, but sodium carbonate or a large excess



1 R^1 = H, R^2 =

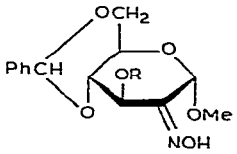
6 R^1 = CH_2SO_2Me, R^2 = H

7 R^1 = CH_2SMe, R^2 =



2 R =

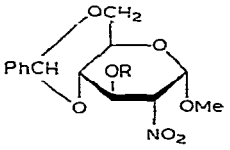
9 R = Bz



3 R =

4 R = H

10 R = Bz

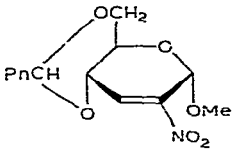


5 R = H

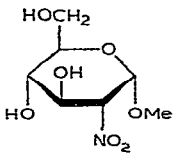
8 R =

11 R = Bz

13 R = Ac



12



14

of sodium hydrogencarbonate were not suitable; (*ii*) the oxidation was not particularly sensitive to the reaction temperature; (*iii*) when a solution in acetonitrile containing the oxidant was added to a solution of **4** in tetrahydrofuran, 1,4-dioxane, or *tert*-butanol, the yield was higher than when only acetonitrile or tetrahydrofuran were used as solvents. In dichloromethane, the yield was significantly decreased. The most satisfactory solvent-system was acetonitrile–*tert*-butanol, which improved the yield to 83.5%.

The nitro alcohol **5** was converted into the nitro alkene **12** in 94% yield by treatment with methanesulfonyl chloride–triethylamine[5]. Acetylation of **5** with pyridine–acetic anhydride in dichloromethane gave the acetate **13** in 85% yield. Deprotection of **5** with 70% aqueous acetic acid afforded **14** in 63% yield.

EXPERIMENTAL

General methods. — All melting points were determined with a Yanagimoto micro melting-point apparatus and are uncorrected. Optical rotations were measured with a JASCO DIP-4 instrument. N.m.r. spectra were recorded at 100 MHz with a JEOL spectrometer (Type JNM-4H-100) or at 60 MHz (Varian EM-360, cited),

with tetramethylsilane as the internal standard. Evaporations were performed under diminished pressure.

*Methyl 4,6-O-benzylidene-2-deoxy-2-oximino-α-*D-arabino-*hexopyranoside* (**4**). — To a solution of[4] **9** (20 g, 0.052 mol) in pyridine (100 mL) and acetic acid (100 mL) was added hydroxylamine hydrochloride (3.98 g, 0.058 mol) with stirring. After stirring for 2 h, the mixture was poured into water and extracted with dichloromethane. The extract was successively washed with diluted hydrochloric acid, water, aqueous sodium hydrogencarbonate, and water and then dried (magnesium sulfate). Evaporation of the solvent afforded a syrup which gradually crystallized. The product (**10**) was dissolved in an ethanolic solution of hydroxylamine* and kept for a week at ~24°, and then the crystals that separated were filtered off. Recrystallization from ethanol–water afforded 14.2 g (93%) of **4**; m.p. 203.5–204.5°, $[\alpha]_D^{23}$ +15° (*c* 1, acetone); ν_{max}^{KBr} 3400 cm^{-1} (OH); n.m.r. (acetone-d_6): δ 10.74 (1 H, s, NOH), 7.28–7.64 (5 H, m, Ph), 5.88 (1 H, s, PhCH), 5.64 (1 H, s, H-1), 4.55 (1 H, m, H-3), 4.32 (1 H, d, $J_{3,OH}$ 4 Hz, OH), 4.27 (1 H, m, H-6e), 3.4–4.4 (3 H, m, H-4,5,6a). and 3.45 (3 H, s, OMe).

Anal. Calc. for $C_{14}H_{17}NO_6$: C, 56.94; H, 5.80; N, 4.74. Found: C, 56.81; H, 5.76; N, 4.45.

To **9** (860 mg, 2.24 mmol) was added ethanolic hydroxylamine, prepared similarly from hydroxylamine hydrochloride (770 mg), with stirring. After stirring for 4 h, the solution was kept for a week at room temperature. Similar processing as already described afforded 512 mg (77%) of 4.

*Methyl 4,6-O-benzylidene-2-deoxy-2-nitro-α-*D-*glucopyranoside* (**5**). — (*a*) *From the tetrahydropyranyl ether* **1**. A solution of **1** (ref. 3; 2.5 g, 6.83 mmol) in dimethyl sulfoxide (30 mL)–acetic anhydride (6.0 mL) was heated for 3.5 h at 50–55°. After cooling, the mixture was poured into ice–water, and the product extracted with diethyl ether. The extract was washed well with water and aqueous sodium chloride, dried (magnesium sulfate), and evaporated. The residue was dissolved in methanol (20 mL) and hydroxylamine hydrochloride (530 mg, 7.63 mmol) and anhydrous sodium carbonate (1.20 g, 4.20 mmol) were added. The mixture was boiled under reflux with stirring for 1 h, cooled, diluted with water, and then extracted with chloroform. The extract was washed with water, dried (magnesium sulfate), and evaporated. The resulting syrup was dissolved in acetonitrile (21 mL), and disodium hydrogenphosphate (8.0 g) and urea (200 mg) were added. To the stirred solution was added, during 10 min, a solution of trifluoroperoxyacetic acid [prepared from trifluoroacetic anhydride (3.5 mL) and 90% hydrogen peroxide (0.56 mL) in acetonitrile (5.0 mL)]. The mixture was stirred for 3 h at room temperature and then boiled under reflux for 1 h. After cooling, chloroform was added and the precipitate generated was

*Hydroxylamine was prepared as follows: sodium ethoxide [from sodium metal (5.7 g) and ethanol (68 mL)] was added to 5.7 mL of an aqueous solution of hydroxylamine hydrochloride (17.4 g). The mixture was gently boiled under reflux, and the sodium chloride precipitated was filtered off and washed with ethanol (68 mL). Compound **10** was dissolved in the combined ethanolic solution.

filtered off. The filtrate was partitioned between chloroform and water and the organic layers were successively washed with aqueous sodium hydrogensulfite and water, dried (magnesium sulfate), and evaporated. The residue was chromatographed on silica gel with chloroform as eluant; the first fraction gave 92 mg of **5** (4%), the second 184 mg of **6** (7%), and the third 730 mg of **4** (36%). Compound **5** was recrystallized from ethanol; m.p. 179–180.5°, $[\alpha]_D^{23}$ +136° (*c* 1, acetone); ν_{max}^{KBr} 3350 (OH) and 1550 cm^{-1} (NO_2); n.m.r.: δ 7.20–7.80 (5 H, m, Ph), 5.54 (1 H, s, PhCH), 5.22 (1 H, d, $J_{1,2}$ 4.0 Hz, H-1), 4.74 (1 H, m, $J_{2,3} = J_{3,4}$ 10, $J_{3,OH}$ 3.0 Hz, H-3), 4.50 (1 H, q, H-2), 4.30 (1 H, q, $J_{5,6e}$ 4.0, $J_{6a,6e}$ 9.0 Hz, H-6e), 3.38–5.0 (3 H, m, H-4,5,6a), 3.38 (3 H, s, OMe), and 2.96 (1 H, d, OH).

Anal. Calc. for $C_{14}H_{17}NO_7$: C, 54.02; H, 5.51; N, 4.50. Found: C, 54.00; H, 5.49; N, 4.34.

Methyl 4,6-*O*-benzylidene-2-*O*-(methylsulfonylmethyl)-α-D-glucopyranoside (**6**) was recrystallized from methanol; m.p. 215–217°, $[\alpha]_D^{23}$ +26.4° (*c* 0.91, acetone); ν_{max}^{KBr} 3460 cm^{-1} (OH); n.m.r. (2:1 dimethyl sulfoxide-d_6–chloroform-*d*, 60 MHz): δ 7.17–7.73 (5 H, m, Ph), 5.54 (1 H, s, PhCH), 4.97 (1 H, d, $J_{1,2}$ 3.5 Hz, H-1), 4.78 (2 H, q, J_{gem} 13.5 Hz, OCH_2SO_2), 3.20–4.50 (7 H, m, H-2,3,4,5,6e,6a, and OH), 3.45 (3 H, s, OMe), 2.91 (3 H, s, SO_2Me).

Anal. Calc. for $C_{16}H_{22}O_8S$: C, 51.33; H, 5.92; S, 8.56. Found: C, 51.30; H, 5.82; S, 8.60.

(*b*) *From* **4**. Trifluoroperoxyacetic acid (prepared *in situ* by the addition of hydrogen peroxide (0.11 mL) to a solution of 0.68 mL of trifluoroacetic anhydride in 1 mL of acetonitrile) was added during 20 min to a stirred solution of **4** (1 mmol), sodium hydrogencarbonate (2.76 g), urea (20 mg), and 1,4-dioxane (2 mL) at room temperature. After stirring for 1 h, the mixture was diluted with water and extracted with dichloromethane. The extract was washed with aqueous sodium hydrogensulfite and water, dried (magnesium sulfate), and evaporated. The resulting solid was chromatographed on silica gel with chloroform as eluant to give 236 mg (76%) of **5**, which was identical (n.m.r. and i.r. spectra) with an authentic sample and pure enough for use as the starting material for the nitro alkene **12**.

Similar oxidation of **4** (10 mmol) in *tert*-butanol (30 mL) afforded **5** in 83.5% yield.

Methyl 4,6-O-benzylidene-2,3-dideoxy-2-nitro-α-D-erythro-hex-2-enopyranoside (**12**). — To an ice–water-cooled solution of **5** (933 mg, 3 mmol) and methanesulfonyl chloride (380 mg, 3.30 mmol) in dichloromethane (20 mL) was added dropwise triethylamine (667 mg, 6.60 mmol) in dichloromethane (2 mL). After 30 min, the mixture was diluted with water and extracted with dichloromethane. The extract was washed with water, dried (magnesium sulfate) for 10 min, and evaporated to give a crystalline residue. Recrystallization from benzene–hexane gave 830 mg (94%) of **12**, identical (i.r. and n.m.r. spectra) with an authentic sample[1].

Methyl 3-O-acetyl-4,6-O-benzylidene-2-deoxy-2-nitro-α-D-glucopyranoside (**13**). — To a solution of **5** (311 mg, 1 mmol) in pyridine (0.5 mL) and dichloromethane (4 mL) was added acetic anhydride (0.6 mL) at room temperature. After 8 h, the

dichloromethane was evaporated and a precipitate generated by the addition of water was filtered off and washed with water, and then recrystallized from ethanol, to give 305 mg (85%) of **13**; m.p. 196.5–198.5° (dec.), $[\alpha]_D^{23}$ +115° (*c* 1, chloroform); ν_{max}^{KBr} 1750, 1740 (ester) and 1560 cm^{-1} (NO_2); n.m.r.: δ 7.20–7.60 (5 H, m, Ph), 6.14 (1 H, t, $J_{2,3} = J_{3,4}$ 10 Hz, H-3), 5.50 (1 H, s, PhCH), 5.30 (1 H, d, $J_{1,2}$ 4.2 Hz, H-1), 4.70 (1 H, q, H-2), 4.33 (1 H, q, $J_{5,6e}$ 3.7, $J_{6a,6e}$ 9.3 Hz), ~4.00 (1 H, m, $J_{4,5}$ 8.5, $J_{5,6a}$ 9.3 Hz, H-5), 3.58 (1 H, t, H-4), 3.75 (1 H, t, H-6a), 3.40 (3 H, s, OMe), and 2.06 (3 H, s, OAc).

Anal. Calc. for $C_{16}H_{19}NO_8$: C, 54.39; H, 5.42; N, 3.96. Found: C, 54.30; H, 5.35; N, 3.80.

Methyl 2-deoxy-2-nitro-α-D-glucopyranoside (**14**). — A solution of **5** (1.0 g, 3.22 mmol) in aqueous acetic acid (70%, 50 mL) was heated for 1 h in a water bath (~90°). After cooling, the solution was evaporated, and the remaining acetic acid was removed by evaporation of water from the residue. The residue was dissolved in methanol, and the solution was decolorized with activated charcoal. Recrystallization of the product from ethanol–hexane afforded 452 mg (63%) of **14**; m.p. 151–152°, $[\alpha]_D^{23}$ +193° (*c* 1, methanol); ν_{max}^{KBr} 3520, 3480, 3360 (OH), and 1560 cm^{-1} (NO_2).

Anal. Calc. for $C_7H_{13}NO_7$: C, 37.67; H, 5.87; N, 6.28. Found: C, 37.78; H, 5.75; N, 6.23.

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