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Carbohydrate Research 340 (2005) 149–153
Carbohydrate RESEARCH

Note

Synthesis of methyl 4,6-*O*-benzylidene-2,3-dideoxy-2-*C*-formyl-α-D-*erythro*-hex-2-enopyranoside

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Received 7 September 2004; accepted 20 October 2004
Available online 21 November 2004

Abstract—The synthesis of the title compound was achieved in seven steps and 61% overall yield from methyl α-D-glucopyranoside.

Naturally occurring carbohydrates have served extensively as elements of the chiral pool in the total synthesis of a wide range of molecules.[1,2] However, the scope of carbohydrates as chiral building blocks relies on the development of convenient key intermediates that are capable of meeting appropriate stereochemical and functional requirements.[3] It is well recognized that the versatility of sugar nuclei as stereochemical templates is enhanced by the incorporation of an α,β-unsaturated carbonyl system, which appears to be an unquestionably useful synthon in organic synthesis.[4–7] There are particularly two reasons for their use: (a) they can be obtained in high enantiomeric purity, and (b) they can exert regio- and stereocontrol on different chemical processes.

In view of the increasing importance of α,β-unsaturated carbonyl systems we have already developed an efficient synthetic route starting from the methyl 2,3-anhydro-4,6-*O*-benzylidene-α-D-mannopyranoside (**1**) toward **3** and **4** (Scheme 1).

The sequence involved the regioselective oxirane ring opening of **1** with diethylaluminum cyanide (Et_2AlCN), followed by dehydration of the β-cyanohydrin **2**, as a direct approach for obtaining methyl 4,6-*O*-benzylidene-3-*C*-cyano-2,3-dideoxy-α-D-*erythro*-hex-2-enopyranoside (**3**) and subsequently its conversion into the aldehyde **4**, in high overall yield.[8]

This simple strategy was later applied to the synthesis of the methyl 4,6-*O*-benzylidene-2-*C*-cyano-2-deoxy-α-D-altropyranoside, which according to the Fürst–Platner rule[9] could be derived from the methyl 4,6-*O*-benzylidene-α-D-allopyranoside **5**. The reaction afforded a very low yield of the desired product, and a detailed study of this reaction demonstrated the influence of neighboring-group participation as the factor responsible for its failure.[10]

There are a few alternative procedures described in the literature toward the synthesis of compound **6**. Lukacs' five-step approach involves the nucleophilic oxirane ring opening of **5** with the 1,3-dithiane anion to produce a mixture of 1,2- and 2,3-unsaturated systems in variable yields.[11]

Fraser-Reid's strategy toward methyl 4,6-*O*-benzylidene-2-*C*-hydroxymethyl-α-D-*erythro*-hex-2-enopyranoside (**7**), which can be considered a good precursor for the aldehyde **6** or vice versa, implied a laborious 10-step synthetic sequence with 3.8% overall yield[12] (Scheme 2).

A third alternative, Malik's trimethylsilylcyanide approach, succeeded in the oxirane ring opening of **5**, but it reported a 47% yield for this only step to afford the methyl 4,6-*O*-benzylidene-2-*C*-cyano-2-deoxy-α-D-altropyranoside.[13]

In view of the difficulties mentioned above, we wish to report a simple and straightforward sequence that afforded the aldehyde **6** starting from **8** in high overall yield (Scheme 3).

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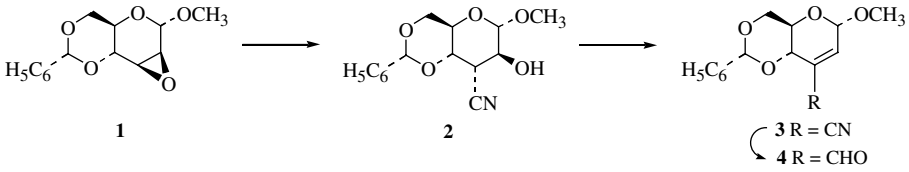
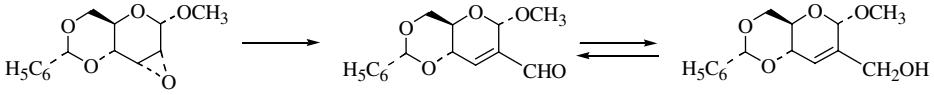
doi:10.1016/j.carres.2004.10.018



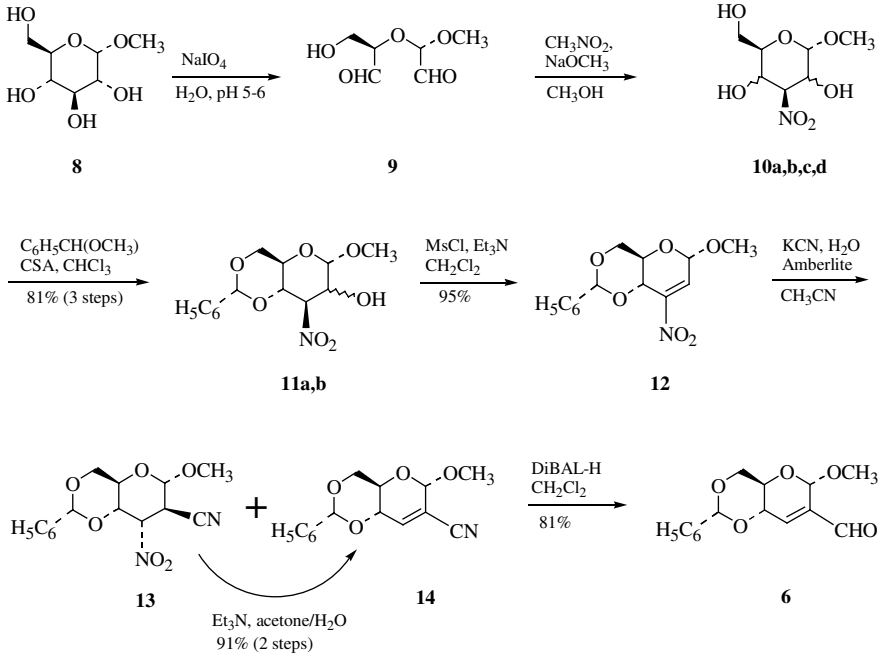
1 2

Scheme 1.



5 6 7

Scheme 2.



Scheme 3.

The synthesis involved the oxidative cleavage of the methyl α-D-glucopyranoside **8** with sodium periodate to yield the dialdehyde **9**, according to the procedure developed by Baer.[14] The crude material was treated with nitromethane and sodium methoxide to yield a mixture of four condensation products from which the gluco- and manno-isomers **10a**,**b** were the major ones. The crude mixture was treated with α,α-dimethoxytoluene to form the benzylidene acetal following a modification of a standard procedure.[15] Flash chromatographic purification of the crude reaction product afforded the combined manno- and gluco-nitro glycosides in 87% overall yield from **8**. The mixture of stereoisomers **11a**,**b** were then treated with MsCl and Et_3N in CH_2Cl_2 to afford the methyl 4,6-*O*-benzylidene-2,3-dideoxy-3-*C*-nitro-α-D-*erythro*-hex-2-enopyranoside (**12**) as a crystalline product in 95% yield. Introduction of the cyano group at C-2 was achieved according to the procedure described by Sakakibara and Sudoh[16] through a Michael-type addition of hydrogen cyanide to the α,β-unsaturated nitro system. The procedure afforded a mixture of the 1,4-adduct **13** plus product **14** derived from a direct elimination of the nitro group. Treating the crude mixture with Et_3N produced the complete conversion of **13** into **14**. This process afforded **14** in 91% overall yield from **12**. Finally, DIBAL-H reduction of nitrile derivative **14** produced the desired α,β-unsaturated aldehyde **6** in 81% yield.

This synthetic procedure allowed the preparation of **6** from glucopyranoside **8** in seven steps and 61% overall yield. It is worth mentioning that only two chromatographic purifications were necessary during the whole synthetic process.

1. Experimental

1.1. General

Melting points were taken on a Leitz Wetzlar Microscope Heating Stage, Model 350 apparatus, and are uncorrected. Optical rotations were recorded with a Jasco DIP 1000 polarimeter. Nuclear magnetic resonance spectra were recorded on a Bruker AC-200 spectrometer with Me_4Si as the internal standard and chloroform-*d* as solvent. Reactions were monitored by TLC on 0.25 mm E. Merck Silica Gel plates (60F254), using UV light and anisaldehyde–H_2SO_4–AcOH as detecting agents. Flash column chromatography, using E. Merck Silica Gel 60H, was performed by gradient elution created by mixtures of hexanes and increasing amounts of AcOEt. Reactions were performed under an argon atmosphere with dry, freshly distilled solvents under anhydrous conditions, unless otherwise noted. Yields refer to chromatographically and spectroscopically (^{1}H NMR) homogeneous materials, unless otherwise stated.

1.2. Preparation of methyl 4,6-*O*-benzylidene-3-deoxy-3-*C*-nitro-α-D-hexopyranosides (11a,b)

1.2.1. Preparation of 2-*O*-[(*S*)-formyl(methoxy)methyl]-(*R*)-glyceraldehyde (9). A magnetically stirred aqueous solution (78 mL) of $NaIO_4$ (6.6 g, 30.9 mmol) was cooled at +5 °C, and methyl α-D-glucopyranoside (3.0 g, 15.4 mmol) was added portionwise during 5 min. The solution was allowed to stand in the dark at room temperature (rt), and the formic acid formed was gradually neutralized by the addition of 1.0 M $NaHCO_3$ solution (approximately 8 mL). The reaction mixture was always maintained between pH 5 and 6. Completion of the oxidation usually took 2–3 h, and was indicated by a negative starch–potassium iodide test of an aliquot sample to which excess of $NaHCO_3$ had been added. The $NaIO_3$ was partially precipitated from the solution by the addition of EtOH. The solid was filtered under vacuum and washed with EtOH. The combined filtrate and washings were concentrated under reduced pressure. The addition of more EtOH produced the precipitation of more solid material that was removed by filtration. This procedure was repeated until no more EtOH-insoluble material was formed. Finally the solution was evaporated to obtain a syrup, which still contained a small amount of salt crystals, but these do not need to be removed.

1.2.2. Condensation of 2-*O*-[(*S*)-formyl(methoxy)methyl]-(*R*)-glyceraldehyde with nitromethane (10a–d). The crude dialdehyde obtained from 3.0 g of methyl α-D-glucopyranoside was dissolved in MeOH (19 mL). Nitromethane (0.85 mL, 15.7 mmol) was added, and the solution was cooled at 0 °C in an ice bath. NaOMe (3% w/v soln in MeOH, 11.2 mL, 14.6 mmol) was chilled and added dropwise with magnetic stirring. The reaction mixture was kept in the ice bath for 25 min, and then it was allowed to reach rt and stirred for an additional 45 min. The solution was deionized by slowly pouring the reaction mixture onto a suspension of Amberlite IR 120 (H^+) (23 g) in MeOH (31 mL) at 4 °C with vigorous stirring. This mixture was allowed to stand at 4 °C overnight, passed through an Amberlite column (23 g), and washed with cold MeOH. Concentration of the methanolic solution produced an orange syrup (5.1 g) of the crude 3-deoxy-3-nitro-α-D-hexopyranosides.

1.2.3. Preparation of methyl 4,6-*O*-benzylidene-3-deoxy-3-*C*-nitro-α-D-hexopyranosides (11a,b). The mixture of methyl 3-deoxy-3-nitro-α-D-hexopyranosides (5.1 g, 15.4 mmol) obtained from the previous procedure was dissolved in $CHCl_3$ (78 mL), and camphorsulfonic acid (160 mg, 0.64 mmol) and benzaldehyde dimethyl acetal (4.6 mL, 30.6 mmol) were added successively. The resulting mixture was stirred and refluxed in a flask fitted with a Dean–Stark trap for solvents heavier than water and loaded with 4 Å molecular sieves (8.2 g, activated at 350 °C for 3 h) overnight. K_2CO_3 (639 mg, 4.6 mmol) was added, and the reaction mixture was refluxed for an additional 30 min. The hot reaction mixture was filtered through a filter funnel with a porosity E sintered glass fritted disc with suction, and the filtrate was concentrated under reduced pressure. The resulting crude product was purified by flash chromatography to furnish the mixture of isomers **11a** and **11b** (4.2 g, 87%, three steps) and used without further purification in the next synthetic transformation. Separation of an aliquot of the mixture was performed in order to characterize both isomers. Methyl 4,6-*O*-benzylidene-3-deoxy-3-*C*-nitro-α-D-mannopyranoside (**11a**): $[\alpha]_D^{25}$ 32.9 (*c* 2.54, $CHCl_3$), reported[17] $[\alpha]_D$ 27.7 (*c* 0.8, $CHCl_3$); ^{1}H NMR ($CDCl_3$): δ 2.75 (br s, 1H, OH), 3.44 (s, 3H, OCH_3), 3.85–3.95 (m, 2H, H-5 and H-6ax), 4.34 (m, 1H, H-6eq), 4.47 (m, 1H, H-2), 4.58 (m, 1H, H-4), 4.77 (d, 1H, *J* 1.7 Hz, H-1), 4.91 (dd, 1H, $J_{3,4}$ 10.7, $J_{2,3}$ 3.2 Hz, H-3), 5.67 (s, 1H, H-7), 7.27–7.50 (m, 5H, aromatics); ^{13}C NMR ($CDCl_3$): δ 55.0 (OCH_3), 62.8 (C-5), 68.5 (C-6), 69.7 (C-2), 73.6 (C-4), 83.6 (C-3), 100.7 (C-1), 101.7 (C-7), 125.9 (2C, C*ortho*), 128.1 (2C, C*meta*), 129.1 (C*para*), 136.4 (C*ipso*). Methyl 4,6-*O*-benzylidene-3-deoxy-3-*C*-nitro-α-D-glucopyranoside (**11b**): mp 167.0–168.0 °C ($CHCl_3$–petroleum ether); $[\alpha]_D^{27}$ 91.5 (*c* 0.98, abs EtOH); reported[18] mp 167 °C, $[\alpha]_D^{27}$ 87.2 (*c* 1, EtOH); ^{1}H NMR ($CDCl_3$): δ 2.46 (d, 1H, *J* 11.50 Hz, OH), 3.49 (s, 3H, OCH_3), 3.75–3.90 (m, 2H, H-5 and H-6ax), 4.00–4.12 (m, 1H, H-4), 4.21 (ddd, 1H, $J_{2,1}$ 3.80, $J_{2,3}$ 10.10, $J_{2,OH}$ 11.60 Hz, H-2), 4.35 (m, 1H, H-6eq), 4.81 (dd, 1H, $J_{3,2} = J_{3,4}$ 10.11 Hz, H-3), 4.86 (d, 1H, $J_{1,2}$ 3.60 Hz, H-1), 5.53 (s, 1H, H-7), 7.27–7.50 (m, 5H, aromatics); ^{13}C NMR ($CDCl_3$): δ 55.8

(OCH_3), 61.9 (C-5), 68.5 (C-6), 70.3 (C-2), 77.0 (C-4), 88.3 (C-3), 98.8 (C-1), 101.3 (C-7), 125.9 (2C, C*ortho*), 128.1 (2C, C*meta*), 129.1 (C*para*), 136.0 (C*ipso*).

1.3. Preparation of methyl 4,6-*O*-benzylidene-2,3-dideoxy-3-*C*-nitro-α-D-*erythro*-hex-2-enopyranoside (12)

A mixture of manno- and gluco-nitro glycosides **11a**,**b** (629 mg, 2.0 mmol) was dissolved in dry CH_2Cl_2 (10.0 mL) and cooled at 20 °C under an argon atmosphere. MsCl (190.0 μL, 2.4 mmol) and Et_3N (1.4 mL, 10.1 mmol) were successively added to the stirred soln at −20 °C, and stirring was continued for 15 min at this temperature. The mixture was then diluted with AcOEt, washed with 5% aq $NaHCO_3$ and water, and dried (Na_2SO_4). Concentration furnished compound **12** (563.0 mg, 95%) as white needles: mp 182.0–183.0 °C ($CHCl_3$–petroleum ether); $[\alpha]_D^{29}$ −93.4 (*c* 0.93, AcOEt), reported[19] mp 183 °C, $[\alpha]_D^{23}$ −93 (*c* 0.9, AcOEt); ^{1}H NMR ($CDCl_3$): δ 3.47 (s, 3H, OCH_3), 3.89 (dd, 1H, $J_{gem} = J_{5,6}$ 10.1 Hz, H-6ax), 4.02–4.13 (m, 1H, H-5), 4.34 (dd, 1H, $J_{5,6}$ 4.1, J_{gem} 9.9 Hz, H-6eq), 4.65 (ddd, 1H, $J_{4,5}$ 8.6, $J_{2,4} = J_{1,4}$ 1.5 Hz, H-4), 5.11 (dd, 1H, $J_{1,2}$ 2.99, $J_{1,4}$ 0.75 Hz, H-1), 5.66 (s, 1H, H-7), 6.77 (dd, 1H, $J_{2,4}$ 2.1, $J_{1,2}$ 3.0 Hz, H-2), 7.30–7.50 (m, 5H, aromatics); ^{13}C NMR ($CDCl_3$): δ 56.5 (OCH_3), 64.2 (C-5), 68.4 (C-6), 72.6 (C-4), 95.2 (C-1), 101.9 (C-7), 126.0 (2C, C*ortho*), 128.1 (2C, C*meta*), 128.6 (C-2), 129.0 (C*para*), 136.4 (C-8), 149.4 (C*ipso*).

1.4. Preparation of methyl 4,6-*O*-benzylidene-2-*C*-cyano-2,3-dideoxy-α-D-*erythro*-hex-2-enopyranoside (14)

KCN (920 mg, 14.1 mmol) was dissolved in water (2.5 mL) and poured into a column of cation-exchange resin (Amberlite IR-120, H^+, 2.6 g). The column was washed successively with water (2.5 mL) and acetonitrile (14.0 mL). The eluate was added directly to a soln of the nitro-olefin (**12**) (683.6 mg, 2.3 mmol) in acetonitrile (14 mL) at 4 °C and stirred for 30 min. The mixture was diluted with AcOEt and washed with 5% aq $NaHCO_3$, water, and brine. The organic layer was dried (Na_2SO_4) and concentrated to furnish a mixture of products **13** and **14** as a yellow syrup. The crude product was dissolved in 3:2 acetone–water (15.3 mL), and Et_3N (0.35 mL, 2.5 mmol) was added with stirring at rt for 12 min. The soln was diluted with AcOEt, washed with water and brine, and dried (Na_2SO_4). Concentration and purification by flash chromatography furnished **14** (590 mg, 93%, two steps) as white needles: mp 194.5–196.0 °C ($CHCl_3$–petroleum ether); $[\alpha]_D^{24}$ 164.3 (*c* 1.01, $CHCl_3$); ^{1}H NMR ($CDCl_3$): δ 3.51 (s, 3H, OCH_3), 3.65 (dd, 1H, $J_{gem} = J_{6,5}$ 9.2 Hz, H-6ax), 3.85–4.00 (m, 1H, H-5), 4.21 (d, 1H, $J_{4,5}$ 8.5 Hz, H-4), 4.34 (dd, 1H, J_{gem} 9.1, $J_{6,5}$ 3.5 Hz, H-6eq), 4.96 (s, 1H, H-1), 5.57 (s, 1H, H-7), 6.88 (br s, 1H, H-3), 7.35–7.45 (m, 5H, aromatics); ^{13}C NMR ($CDCl_3$): δ 56.6 (OCH_3), 62.8 (C-5), 68.8 (C-6), 73.9 (C-4), 94.9 (C-1), 102.4 (C-7), 114.1 (C≡N), 115.2 (C-2), 126.1 (2C, C*ortho*), 128.2 (2C, C*meta*), 129.3 (C*para*), 136.5 (C*ipso*), 145.0 (C-3).

1.5. Preparation of methyl 4,6-*O*-benzylidene-2,3-dideoxy-2-*C*-formyl-α-D-*erythro*-hex-2-enopyranoside (6)

Methyl 4,6-*O*-benzylidene-2-*C*-cyano-2,3-dideoxy-α-D-*erythro*-hex-2-enopyranoside (**14**) (579 mg, 2.1 mmol) was azeotropically dried with dry benzene under vacuum, dissolved in anhyd CH_2Cl_2 (43 mL) and cooled at −80 °C under an argon atmosphere. Diisobutylaluminum hydride (1 M soln in hexane, 4.8 mL, 4.8 mmol) was slowly added to the magnetically stirred solution. The reaction mixture was stirred for an additional 90 min at −80 °C and then quenched with 1:1 HOAc–water soln (3.4 mL). Stirring was continued for 30 min while the temperature rose to 0 °C. The mixture was extracted with CH_2Cl_2, washed with H_2O, 5% $NaHCO_3$ soln and brine, dried (Na_2SO_4), and concentrated to furnish compound **6** (506 mg, 86%) as a white solid. Recrystallization afforded crystals as white needles: mp 195.0–196.0 °C (CH_2Cl_2–petroleum ether); $[\alpha]_D^{20}$ 131.6 (*c* 0.80, $CHCl_3$); reported[11] mp 190–192 °C; $[\alpha]_D$ 100.4 (*c* 0.25, $CHCl_3$); ^{1}H NMR ($CDCl_3$): δ 3.54 (s, 3H, OCH_3), 3.85 (dd, 1H, $J_{gem} = J_{5,6}$ 10.2 Hz, H-6ax), 4.00–4.15 (m, 1H, H-5), 4.35–4.45 (m, 2H, H-6eq and H-4), 5.21 (s, 1H, H-1), 5.63 (s, 1H, H-7), 6.97 (s, 1H, H-3), 7.30–7.55 (m, 5H, aromatics), 9.47 (s, 1H, CHO); ^{13}C NMR ($CDCl_3$): δ 56.5 (OCH_3), 63.3 (C-5), 69.3 (C-6), 75.4 (C-4), 94.6 (C-1), 102.6 (C-7), 126.1 (2C, C*ortho*), 128.3 (2C, C*meta*), 129.3 (C*para*), 136.8 (C*ipso*), 139.5 (C-2), 146.5 (C-3), 189.8 (CHO).

Acknowledgements

This research was supported by the International Foundation for Science, Stockholm, Sweden, the Organization for the Prohibition of Chemical Weapons, The Hague, The Netherlands and Agencia Nacional de Promoción Científica y Tecnológica, Argentina through the grants to A.G.S. and R.A.S. M.I.M. thanks CONICET for the award of a fellowship.

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