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Note

A general approach to the synthesis of 2,3-di-*O*-protected derivatives of D-glyceraldehyde*

JANUSZ JURCZAK, TOMASZ BAUER, AND MAREK CHMIELEWSKI
Institute of Organic Chemistry, Polish Academy of Sciences, 01-224 Warsaw (Poland)
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Although asymmetric synthesis is currently a widely used method for the stereocontrolled formation of C–C bonds in organic molecules, the application of this process still remains one of the basic problems in the total synthesis of natural products. In this connection, many monosaccharides and their readily available derivatives are versatile substrates for the synthesis of optically active target molecules[1]. 2,3-*O*-Isopropylideneglyceraldehyde is one of the most often applied compounds; it is characterized by the ready availability of both enantiomers from natural sources, and by pronounced versatility resulting from the presence of the aldehyde and protected-diol functionalities in the molecule[2].

The first effective preparation of 2,3-*O*-isopropylidene-D-glyceraldehyde was reported by Baer and Fischer[3] in 1939. D-Mannitol (**1**), a naturally occurring, inexpensive polyhydroxy compound, was used as the starting material; 1,2:5,6-di-*O*-isopropylidene-D-mannitol (**2**) was prepared in 55% yield, and then cleaved with lead tetraacetate to give the desired aldehyde in 76% yield.

In recent years, several modifications of this classical, but still most often applied method, have been reported. As concerns the first stage, namely the preparation of compound **2** from **1**, the modification of Kierstead *et al.*[4] is noteworthy. It involves the action of 2,2-dimethoxypropane on **1** in the presence of *p*-toluenesulfonic acid in dry dimethyl sulfoxide. Another improvement[5] is based on the action of 2-methoxypropene on **1** in *N,N*-dimethylformamide. Replacement of lead tetraacetate by sodium periodate has been proposed[6] for the cleavage of the *vic*-diol group in **2**.

Whereas the 2,3-*O*-isopropylidene derivative of D-glyceraldehyde is the most widely used carbohydrate synthon[2], there are reports on applications of derivatives of D-glyceraldehyde having other types of protecting groups on the diol function,

Dedicated to the memory of Prof. H. O. L. Fischer on the centenary of his birth.

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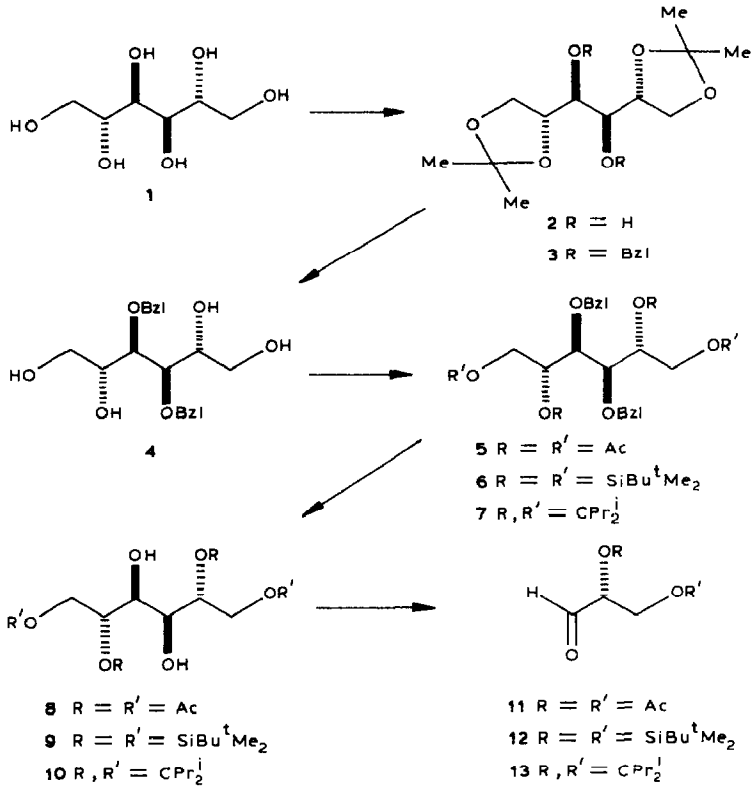
such as di-*O*-methyl[7], di-*O*-benzyl[8], carbonate[9], di-*O*-benzoyl[10], and *O*-cyclohexylidene[11]. Since further potential applications may be important, we present a general method for the synthesis of 2,3-di-*O*-protected derivatives of D-glyceraldehyde, with particular attention to three representative protective groups namely acetyl, *tert*-butyldimethylsilyl, and diisopropylmethylene.



1,2:5,6-Di-*O*-isopropylidene-D-mannitol (**2**), readily available from **1** by the original procedure of Baer and Fischer[3] or the modified one of Kierstead *et al.*[4], was benzylated under phase-transfer conditions[12] to give compound **3**, which was hydrolyzed to 3,4-di-*O*-benzyl-D-mannitol (**4**), the starting material for all further transformations. Its selection was based on its higher preparative suitability, as compared with 3,4-*O*-isopropylidene-D-mannitol, for use with highly chemoselective methods for the deprotection of positions **3** and **4**, without effect on the remaining 1,2,5,6-blocking groups.

3,4-Di-*O*-benzyl-D-mannitol (**4**) on treatment with acetic anhydride and triethylamine in the presence of 4-dimethylaminopyridine afforded compound **5**, which was hydrogenated in the presence of 10% palladium-on-charcoal to give the 3,4-dihydroxy derivative **8**. Compound **8** was cleaved with lead tetraacetate to produce 2,3-di-*O*-acetyl-D-glyceraldehyde **11** in a good yield and high purity.

Compound **4** treated with *tert*-butylchlorodimethylsilane in the presence of imidazole or reacted with diisopropyl ketone in the presence of chlorotrimethylsilane afforded the derivatives **6** and **7**, respectively. In both cases, the debenzylation reactions were carried out in good yields using sodium in liquid ammonia. The *vic*-diol grouping of compounds **9** and **10** was cleaved under standard conditions to produce 2,3-di-*O*-(*tert*-butyldimethylsilyl)-D-glyceraldehyde **12** and 2,3-*O*-diisopropylmethylene-D-glyceraldehyde **13**, respectively.

D-Glyceraldehyde derivatives **11**, **12**, and **13** can be readily and efficiently obtained even on a larger preparative scale, but they have to be used immediately due to their tendency to polymerize. However, if necessary, they can be stored in a freezer as toluene solutions; in this case distillation before use is recommended.

Summing up, it can be presumed that the general method described here for the synthesis of 2,3-di-*O*-protected derivatives of D-glyceraldehyde will be applicable to the preparation of other *O*-acylated, *O*-silylated, and acetal-type derivatives in addition to those listed below.

EXPERIMENTAL

General methods. — Melting points were determined on a Kofler hot-stage and are uncorrected. Optical rotations were measured with a Perkin–Elmer 141 automatic polarimeter. ^{1}H-N.m.r. spectra were recorded with a Varian EM-360 (60 MHz) spectrometer on solutions in $CDCl_3$ (internal Me_4Si). The progress of all reactions was monitored by t.l.c. on silica gel 60 (Merck). Flash column chromatography[13] was performed with Kieselgel 60 (230–400 mesh, Merck). 1,2:5,6-Di-*O*-isopropylidene-D-mannitol (**2**) was prepared according to Kierstead *et al.*[4] (modification of Baer and Fischer's[3] procedure).

3,4-Di-O-*benzyl-1,2:5,6-di*-O-*isopropylidene*-D-*mannitol* (**3**). — To a vigorously stirred mixture of 50% aqueous sodium hydroxide (160 mL), tetrahydrofuran (25 mL), benzyl bromide (10 mL), and tetrabutylammonium bromide (2 g, 5 mol%), 1,2:5,6-di-*O*-isopropylidene-D-mannitol (**2**; 10 g) dissolved in tetrahydrofuran (75 mL) was added. The reaction mixture was stirred at 40° for 20 h, then the phases were separated, the solvent from the organic layer was evaporated, and the residue (11.7 g, 96%) was taken to the next step without further purification. An analytical sample was purified by flash column chromatography (9:1 hexane–ethyl acetate as eluent) to give **3** as a colorless oil; $[\alpha]_D^{25}$ +36° (*c* 1.05, $CHCl_3$); ^{1}H-n.m.r. (60 MHz): δ 7.50 (broad s, 10 H, Ph-H), 4.80, (m, 4 H, CH_2Ph), 3.80–3.50 (m, 8 H, C*H*O), CH_2O), and 1.00 (s, 12 H, CCH_3).

Anal. Calc. for $C_{26}H_{34}O_6$: C, 70.6; H, 7.8. Found: C, 70.1; H, 7.8.

Removal of O-*isopropylidene groups from* **3**. — Crude compound **3**, obtained as just described, was dissolved in 70% aqueous acetic acid (200 mL) and the solution was stirred for 6 h at 45°. After evaporation of the solvent, the oily residue was crystallized from an anhydrous mixture of acetone and diethyl ether to give 9 g (74% from **2**) of 3,4-di-*O*-benzyl-D-mannitol (**4**) as highly hygroscopic, colorless

crystals. Because of its hygroscopic character, compound **4** was not analyzed.

1,2,5,6-Tetra-O-acetyl-3,4-di-O-benzyl-D-mannitol (**5**). — To a solution of **4** (0.9 g, 2.5 mmol) in dichloromethane (10 mL), acetic anhydride (1 mL), and triethylamine (1.5 mL), a few crystals of 4-dimethylaminopyridine were added, and the reaction mixture was kept for 1 h at room temperature. The solvents were evaporated *in vacuo* and the residue was purified by flash column chromatography (9:1 hexane–ethyl acetate) to afford 1.15 g (87%) of **5** as a colorless oil; $[\alpha]_D^{25}$ +41° (*c* 0.83, $CHCl_3$); ^{1}H-n.m.r. (60 MHz): δ 7.50 (broad s, 10 H, Ph-H), 5.40 (m, 2 H, C*H*OAc), 4.80 (broad s, 4 H, CH_2Ph), 4.80–4.10 (m, 4 H, CH_2OAc), 4.10–3.75 (m, 2 H, C*H*OBzl), and 2.10 (s, 12 H, CH_3CO).

Anal. Calc. for $C_{28}H_{34}O_{10}$: C, 63.4; H, 6.5. Found: C, 63.2; H, 6.8.

*3,4-Di-O-benzyl-1,2,5,6-tetra-O-(*tert*-butyldimethylsilyl)-D-mannitol* (**6**). — To a solution of **4** (0.66 g, 1.8 mmol) in anhydrous *N,N*-dimethylformamide (10 mL), *tert*-butylchlorodimethylsilane (1.2 g, 8 mmol) and imidazole (0.55 g, 8 mmol) were added under an argon atmosphere. The reaction mixture was stirred for 48 h at room temperature, then poured into water (50 mL) and extracted twice with 25 mL of hexane. The combined extracts were dried and evaporated. The residue was purified by flash column chromatography (19:1 hexane–ethyl acetate) to give 1.16 g (78%) of **6** as colorless crystals; m.p. 61–62° (from hexane), $[\alpha]_D^{25}$ +13° (*c* 0.98, $CHCl_3$); ^{1}H-n.m.r. (60 MHz): δ 7.50 (broad s, 10 H, Ph-H), 4.80 (m, 4 H, CH_2Ph), 3.80–3.60 (m, 8 H, C*H*O, CH_2O), 0.9 (s, 36 H, CCH_3), and 0.2 (s, 24 H, SiCH_3).

Anal. Calc. for $C_{44}H_{82}O_6Si_4$: C, 64.2; H, 10.0. Found: C, 64.7; H, 10.3.

3,4-Di-O-benzyl-1,2:5,6-bis-O-(diisopropylmethylene)-D-mannitol (**7**). — To a solution of **4** (1.5 g, 4.1 mmol) in anhydrous dichloromethane (10 mL) trimethylchlorosilane (5 mL, 40 mmol) and diisopropyl ketone (3 mL, 20 mmol) were added. The reaction mixture was stirred at room temperature for 48 h and then it was neutralized with saturated aqueous $NaHCO_3$. The organic layer was separated, dried, and evaporated. The residue was purified by flash column chromatography (19:1 hexane–ethyl acetate) to afford 1.26 g (56%) of **7** as colorless crystals; m.p. 79–80° (from hexane), $[\alpha]_D^{25}$ +64° (*c* 1.29, $CHCl_3$); ^{1}H-n.m.r. (60 MHz): δ 7.50 (broad s, 10 H, Ph-H), 4.80 (m, 4 H, CH_2Ph), 3.60–3.30 (m, 8 H, C*H*O, CH_2O), 2.00 (m, 4 H, C*H*Me$_2$), and 0.95 (d, 24 H, CCH_3).

Anal. Calc. for $C_{34}H_{50}O_6$: C, 73.6; H, 9.1. Found: C, 73.7; H, 9.1.

1,2,5,6-Tetra-O-acetyl-D-mannitol (**8**). — To a solution of **5** (1 g, 1.9 mmol) in a mixture of ethyl acetate and acetic acid (3:1 v/v, 20 mL) 10% palladium-on-charcoal (0.1 g) was added, and the resulting suspension was hydrogenated for 24 h (8 atm, 45°). The catalyst was then filtered off and solvents were evaporated. The residue was crystallized from diethyl ether to yield 0.5 g (75%) of **8**; m.p. 86–88°, $[\alpha]_D^{25}$ +3° (*c* 10.7, ethyl acetate); ^{1}H-n.m.r. (60 MHz): δ 5.40–5.00 (m, 2 H, C*H*OAc), 4.80–4.10 (m, 4 H, CH_2OAc), 3.90–3.60 (m, 4 H, C*H*O*H*), and 2.10 (s, 12 H, CH_3CO).

Anal. Calc. for $C_{14}H_{22}O_{10}$: C, 48.0; H, 6.3. Found: C, 47.9; H, 6.4.

*1,2,5,6-Tetra-O-(*tert*-butyldimethylsilyl)-D-mannitol* (**9**). — To liquid ammo-

nia (30 mL) a solution of **6** (1 g, 1.2 mmol) in anhydrous tetrahydrofuran (10 mL) was added. Sodium was then added portionwise until a deep blue color persisted for 15 min, whereupon solid ammonium chloride was added. The resulting mixture was left for 2 h for evaporation of the ammonia. The remaining inorganic salts were filtered off, the solvent was evaporated, and the residue was purified by flash column chromatography (9:1 hexane–ethyl acetate) to give 0.43 g (54%) of **9** as a colorless oil; $[\alpha]_D^{25}$ +16° (*c* 1.29, $CHCl_3$); ^{1}H-n.m.r. (60 MHz): δ 4.10–3.80 (m, 8 H, C*H*O, CH_2O), 3.50 (broad s, 2 H, O*H*), 1.00 (s, 36 H, CCH_3), and 0.2 (s, 24 H, SiCH_3).

Anal. Calc. for $C_{30}H_{70}O_6Si_4$: C, 56.2; H, 11.0. Found: C, 56.6; H, 10.8.

*1,2,5,6-Bis-*O*-(diisopropylmethylene)-*D*-mannitol* (**10**). — Compound **7** (0.9 g, 1.6 mmol) was treated with sodium in liquid ammonia as described for preparation of **9**, to afford 0.55 g (90%) of **10** as colorless crystals; m.p. 128–129° (from hexane–diethyl ether), $[\alpha]_D^{25}$ +27° (*c* 1.09, $CHCl_3$); ^{1}H-n.m.r. (60 MHz): δ 4.50–3.60 (m, 10 H, C*H*O, CH_2O, O*H*), 2.00 (m, 4 H, C*H*Me$_2$), and 0.95 (d, 24 H, CCH_3).

Anal. Calc. for $C_{20}H_{38}O_6$: C, 64.1; H, 10.2. Found: C, 63.8; H, 10.1.

*2,3-Di-*O*-acetyl-*D*-glyceraldehyde* (**11**) *and its 2,4-dinitrophenylhydrazone.* — Diol **8** (0.2 g, 0.57 mmol) was suspended in anhydrous toluene (10 mL), the suspension was cooled to <15°, and lead tetraacetate (0.28 g, 0.63 mmol) was added. The reaction mixture was stirred for 1 h at 15° and then it was filtered. Anhydrous potassium carbonate was added to the filtrate and the resulting suspension was stirred for 1 h at 15°. Inorganic salts were filtered off and the solvent was evaporated. Crude aldehyde **11** (0.15 g, 76%) was converted into its *2,4-dinitrophenylhydrazone* **14** using a conventional procedure; m.p. 123–124° (from ethanol), $[\alpha]_D^{25}$ +77 (*c* 0.90, acetone).

Anal. Calc. for $C_{13}H_{14}N_4O_8$: C, 44.1; H, 4.0; N, 15.8. Found: C, 43.5; H, 3.8; N, 15.8.

*2,3-Di-*O*-(*tert*-butyldimethylsilyl)-*D*-glyceraldehyde* (**12**) *and its semicarbazone.* — Diol **9** was cleaved under the same conditions as diol **8** to yield aldehyde **12** (80%), which was converted into its *semicarbazone* using a conventional procedure; m.p. 170–173°, $[\alpha]_{365}^{25}$ +20° (*c* 0.24, ethanol).

Anal. Calc. for $C_{16}H_{37}N_3O_3Si_2$: C, 51.2; H, 9.9; N, 11.2. Found: C, 50.7; H, 10.1; N, 10.8.

*2,3-O-Diisopropylmethylene-*D*-glyceraldehyde* (**13**) *and its conversion into 1-O-acetyl-2,3-O-diisopropylmethylene-*D*-glycerol.* — Diol **10** was cleaved under the same conditions as diol **8** to give aldehyde **13** (77%), which was converted (sodium borohydride reduction followed by acetylation) into 1-*O*-acetyl-2,3-*O*-diisopropylmethylene-D-glycerol, oil; $[\alpha]_D^{25}$ +7.8° (*c* 1.26, $CHCl_3$); ^{1}H-n.m.r. (60 MHz): δ 4.40–4.10 (m, 4 H, CH_2OAc, CH_2OC), 3.65 (m, 1 H, C*H*OC), 2.15 (s, 3 H, CH_3CO), 2.05 (m, 2 H, C*H*Me$_2$), and 1.05 (d, 12 H, CCH_3).

Anal. Calc. for $C_{12}H_{22}O_4$: C, 62.6; H, 9.6. Found: C, 62.6; H, 9.7.

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