Carbohydrate Research, 147 (1986) 149–154
Elsevier Science Publishers B.V., Amsterdam – Printed in The Netherlands

Note

Synthesis of 3-deoxy- and 3-deoxy-3-fluorosucrose, and α-D-allopyranosyl β-D-fructofuranoside*

THOMAS P. BINDER AND JOHN F. ROBYT†
Department of Biochemistry and Biophysics, Iowa State University, Ames, IA 50011 (U.S.A.)
(Received July 30th, 1985; accepted for publication, September 1st, 1985)

Many methods have been reported for the selective modification of sucrose[1–6], but most of these have dealt with either modification at the primary carbon atoms or modification at more than one carbon. Much less work has been done relating to selective modification at the secondary carbon atoms because of the difficulty involved. Most modifications reported have been for C-4 (refs. 7–9) and C-2 (refs. 10, 11). We were interested in modifications at C-3. Of the three modifications reported[12–14] for C-3, the first two were not suitable for preparing derivatives other than allosucrose (α-D-allopyranosyl β-D-fructofuranoside) and the third would allow ready preparation only of derivatives having the *allo* configuration. In this paper we report the synthesis of 3-deoxy- and 3-deoxy-3-fluorosucrose, and allosucrose.

Recently the preparation of 3-*O*-acetyl-1′,2:4,6-di-*O*-isopropylidenesucrose was reported[15]. With some modification of this procedure, we were able to obtain 3-*O*-benzoyl-1′,2:4,6-di-*O*-isopropylidenesucrose (**1**) in moderate yields. Compound **1** was treated with 4 equivalents of *tert*-butylchlorodimethylsilane[16] to give 3-*O*-benzoyl-3′,4′,6′-tri-*O*-*tert*-butyldimethylsilyl-1′,2:4,6-di-*O*-isopropylidenesucrose (**2**). Reductive cleavage of the ester with lithium aluminum hydride gave 3′,4′,6′-tri-*O*-*tert*-butyldimethylsilyl-1′,2:4,6-di-*O*-isopropylidenesucrose (**3**). Reaction of **3** with methanesulfonyl chloride gave 3′,4′,6′-tri-*O*-*tert*-butyldimethylsilyl-1′,2:4,6-di-*O*-isopropylidene-3-*O*-(methylsulfonyl)sucrose (**4**). Treatment of **4** with $LiAlH_4$ led to fission[17] yielding **3**, rather than reduction to the 3-deoxy compound, probably because of steric hindrance by the isopropylidene rings.

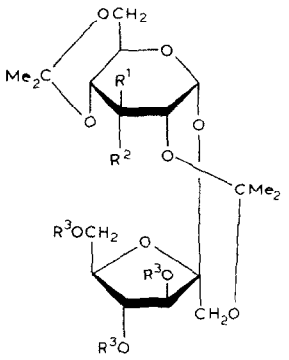
We next prepared 3′,4′,6′-tri-*O*-*tert*-butyldimethylsilyl-1′,2:4,6-*O*-isopropylidene-3-*O*-(methylthio)thiocarbonylsucrose (**5**), which was homolytically cleaved with tributyltin hydride in toluene[18] to give 3′,4′,6′-tri-*O*-*tert*-butyldimethylsilyl-3-deoxy-1′,2:4,6-di-*O*-isopropylidenesucrose (**6**). Compound **3** was oxidized by a modified chromium trioxide–pyridine complex[19] to the 3-keto com-

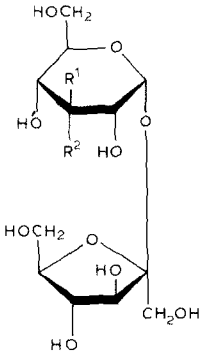
*Supported by Grant No. DE-03578 from the National Institute of Dental Research, National Institutes of Health, U.S. Public Health Service.
†To whom inquiries should be directed.

0008-6215/86/$ 03.50

pound, which was reduced with $NaBH_4$ to give 3′,4′,6′-tri-*O*-*tert*-butyldimethylsilyl-1′,2:4,6-di-*O*-isopropylideneallosucrose (**7**). Fluorination of **6** with diethylaminosulfur trifluoride[20] gave a mixture of products from which we isolated 3′,4′,6′-tri-*O*-*tert*-butyldimethylsilyl-3-deoxy-3-fluoro-1′,2:4,6-di-*O*-isopropylidenesucrose (**8**).

Removal of the protecting groups from compounds **6, 7,** and **8** gave 3-deoxysucrose (**9**), allosucrose (**10**), and 3-deoxy-3-fluorosucrose (**11**), respectively; the configuration of the fluoro derivative was confirmed by ^{19}F n.m.r. spectroscopy. Higher overall yields of the diisopropylidene acetal may be possible by using a newer isopropylidenation procedure described by Fanton *et al.*[21].





1 R^1 = OBzl, R^2 = R^3 = H
2 R^1 = OBz, R^2 = H, R^3 = TBDMS
3 R^1 = OH, R^2 = H, R^3 = TBDMS
4 R^1 = OMs, R^2 = H, R^3 = TBDMS
5 R^1 = OCS_2Me, R^2 = H, R^3 = TBDMS
6 R^1 = R^2 = H, R^3 = TBDMS
7 R^1 = H, R^2 = OH, R^3 = TBDMS
8 R^1 = F, R^2 = H, R^3 = TBDMS

9 R^1 = R^2 = H
10 R^1 = H, R^2 = OH
11 R^1 = F, R^2 = H

TBDMS = Me_3CSiMe_2—

EXPERIMENTAL

General methods. — Thin-layer chromatography (t.l.c.) of the protected sugars was conducted on Analtech HETLC-GHLF t.l.c. plates with 3:1 (v/v) hexane–ethyl acetate unless otherwise stated; sugars were detected by fluorescence quenching or acid charring. T.l.c. of the free sugars was conducted on Whatman K5F silica gel plates with two ascents with 17:3 (v/v) acetonitrile–water; sugars were detected by acid charring. Melting and decomposition points were determined with a Mel-Temp apparatus. Optical rotations were recorded with a Rudolph polarimeter and a sodium light-source. Elemental analyses were performed by Galbraith Laboratories, Knoxville, Tennessee. Nuclear magnetic resonance (n.m.r.) spectra were recorded with one of the following spectrometers: JEOL FX-90Q, Bruker WM300, or an Nicolet NT-300. ^{13}C-N.m.r. shifts (p.p.m. from Me_4Si) are

reported only for carbohydrate carbon atoms and other carbon atoms whose signals are near carbohydrate signals.

3-O-Benzoyl-1',2:4,6-di-O-isopropylidenesucrose (**1**). — Sucrose (100 g) was acetalated and benzoylated following the procedure of Binder and Robyt[4] with the following modifications: The acetalation was allowed to proceed for 90 rather than 60 min, and for the last 30 min of the benzoylation the mixture was maintained at 50°. After crystallizing and filtering off the 4,6-*O*-isopropylidenesucrose hexabenzoate from an ether–hexane mixture (yield 100 g), the filtrate was evaporated to a syrup and dissolved in 1 L of hot ethanol; this solution was kept overnight at −20°. The ethanol was decanted off, and the solid remaining was dissolved in 500 mL of dichloromethane to which was added 1.5 L of methanol and 20 g of sodium methoxide. The debenzoylation was monitored by t.l.c. with ether as the eluant. After 1.5 h, only one major, mobile u.v.-absorbing compound remained besides methyl benzoate. The deesterification was stopped by adding 21 mL of acetic acid, and the solution was evaporated under vacuum to a syrup, to which was added 1 L of dichloromethane and 1 L of water. After shaking, the two phases were allowed to separate for 3 h. The organic phase was collected, concentrated to ~200 mL, and adsorbed onto a column (8 × 68 cm) of silica gel, which was eluted with 6 L of 1:1 ethyl acetate–hexane followed by 6 L of 4:1 ethyl acetate–hexane. Compound **1** was detected by t.l.c. in the later fractions, which were combined and concentrated to 200 mL. This solution was kept for 2 h at 25°, during which time compound **2** crystallized. It was dried *in vacuo*; yield 20 g (13%); m.p. 198–200° (dec.), $[\alpha]_D$ +51.7° (*c* 2.0, acetone); ^{13}C-n.m.r. δ 77.5, 77.1, and 76.6 ($CDCl_3$, internal standard), 103.1 (C-2'), 101.4, 99.6 (isopropylidene Me), 90.9 (C-1), 82.5, 78.6, 73.2, 71.4, 71.3, 71.2, 71.0, 65.9, 63.5, and 61.7 (not specifically assigned).

3',4',6'-Tri-O-tert-butyldimethylsilyl-1',2:4,6-di-O-isopropylidenesucrose (**3**). — Compound **1** (15 g) was dissolved in 150 mL of *N,N*-dimethylformamide and 22 g of *tert*-butylchlorodimethylsilane was added, followed by 22 g of imidazole. This solution was stirred overnight at 60°. The *N,N*-dimethylformamide was removed under diminished pressure by using a rotary evaporator with a condenser cooled with Dry Ice–acetone. Ethyl acetate (250 mL) and water (250 mL) were added to the resulting syrup. The organic phase was separated and washed twice with 250 mL of water. Ethyl acetate was removed by rotary evaporation under vacuum, yielding compound **2** as a foam. Compound **2** was dissolved in 250 mL of tetrahydrofuran (THF), cooled to −30°, and 3 g of $LiAlH_4$ was added with stirring. The solution was stirred and allowed to come to 25° over a 3-h period and then filtered through a glass-fiber filter. Water (2 mL) was added dropwise to the filtrate, followed by dropwise addition of 2 mL of 15% NaOH. This mixture was filtered and the filtrate was evaporated to a syrup that was dissolved in 100 mL of methanol by heating on a steam bath. Compound **3** crystallized over a 2-day period; yield 18.8 g (86%); m.p. 206–209°, $[\alpha]_D$ +9.5° (*c* 2.0, acetone); ^{13}C-n.m.r. δ 77.5, 77.1, and 76.6 ($CDCl_3$, internal standard), 105.1 (C-2'), 101.3, 99.5 (isopropylidene Me), 91.6 (C-1), 86.3, 82.6, 80.6, 74.1, 73.3, 70.4, 67.3, 63.5, 63.2, and 62.5 (not specifically assigned).

3',4',6'-Tri-O-tert-*butyldimethylsilyl-1',2:4,6-di*-O-*isopropylidene-3*-O-*(methylsulfonyl)sucrose* (**4**). — Compound **3** (1 g) was dissolved in 6 mL of pyridine and cooled to 0°. Methanesulfonyl chloride (0.27 mL) was added with stirring. The solution was stirred for 20 h at 25° and then poured into 30 mL of saturated sodium hydrogencarbonate. This was extracted with 30 mL of dichloromethane, and the organic phase was washed twice with water. The dichloromethane solution was evaporated by rotary evaporation under diminished pressure, and the resulting syrup was dissolved in 10 mL of methanol by heating on a steam bath. On keeping overnight at 25°, compound **4** crystallized; yield 0.9 g (82%); m.p. 160–162°, $[\alpha]_D$ +10.1° (*c* 2.0, acetone); ^{13}C-n.m.r. δ 78.5, 77.1, and 75.7 ($CDCl_3$, internal standard), 105.5 (C-2'), 101.4, 99.8 (isopropylidene Me), 92.1 (C-1), 86.5, 82.7, 80.7 (2 signals superposed), 71.8, 71.6, 67.5, 63.5 (2 signals superposed), and 62.4 (not specifically assigned).

Treatment of compound **4** *with* $LiAlH_4$. — Compound **4** (0.5 g) was dissolved in 1 mL of THF. This solution was added over 10 min to 1 mL of THF containing 0.025 g of $LiAlH_4$. The solution was boiled under reflux gently for 18 h, at which time t.l.c. showed the presence of compound **3** and no other products, indicating that fission of the methanesulfonyl group was occurring instead of reduction[17].

3',4',6'-Tri-O-tert-*butyldimethylsilyl-1',2:4,6-di*-O-*isopropylidene-3-deoxy-sucrose* (**6**). — Compound **3** (8 g) was dissolved in 32 mL of THF, to which was added 1.12 g of sodium hydride (50% oil emulsion), and 13 mg of imidazole. The solution was stirred for 30 min at 25° and then 5.3 mL of carbon disulfide was added. After 1 h, 1.3 mL of methyl iodide was added and allowed to react for 1 h, giving compound **5**. The solution was poured into 200 mL of ice–water and the product extracted with 250 mL of diethyl ether. The organic phase was washed twice with water and dried over calcium sulfate. After filtration, the ether was removed by rotary evaporation and the remaining yellow syrup was dissolved in 100 mL of toluene. The flask containing this solution was purged with nitrogen, and then 4.3 mL of tributyltin hydride in 80 mL of toluene was added over a 1-h period. The solution was boiled under reflux overnight, and then cooled and washed twice with water (250 mL). The toluene was removed by rotary evaporation under diminished pressure, and the resulting syrup was dissolved in 5 mL of diethyl ether and applied to a column (3 cm × 20 cm) of silica gel, which was eluted with 3:1 hexane–diethyl ether. The fractions containing product were identified by t.l.c., and the solution was evaporated to a syrup that crystallized on being kept for several days; yield 7.0 g (93%); m.p. 89–91°, $[\alpha]_D$ +6.37° (*c* 2.0, acetone); ^{13}C-n.m.r. δ 78.5, 77.1, and 75.6 ($CDCl_3$, internal standard), 105.1 (C-2'), 100.8, 99.1 (isopropylidene Me), 91.0 (C-1), 86.2, 82.7, 80.8, 68.8, 68.2, 67.2, 65.3, 63.7, and 63.0 (not specifically assigned).

3',4',6'-Tri-O-tert-*butyldimethylsilyl-1',2:4,6-di*-O-*isopropylideneallosucrose* (**7**). — Compound **3** (9 g) was dissolved in 18 mL of dichloromethane and added with stirring to a mixture of chromium trioxide (3 g) and pyridine (4.8 mL) in 90 mL of dichloromethane. Immediately, 3 mL of acetic anhydride was added and the

solution was stirred for 20 min at 25°. The solution was then poured into 200 mL of diethyl ether and kept for 15 min. The mixture was filtered, and the filtrate was washed once with 200 mL of saturated sodium hydrogencarbonate and then twice with water. The organic phase was adsorbed onto 10 g of silica gel by rotary evaporation under diminished pressure. This was added to the top of a column (3 × 10 cm) of silica gel that was eluted with diethyl ether. The fractions containing the oxidized product were identified by t.l.c., pooled, and evaporated to a syrup that was dissolved in 60 mL of methanol. To this solution, 0.51 g of sodium borohydride was added. After 30 min at 25°, the methanol was removed by rotary evaporation, 90 mL of dichloromethane was added to the remaining syrup, and the organic phase was washed 3 times with 100 mL of water. The dichloromethane was removed by rotary evaporation to give compound **7** as a white foam; yield 8.4 g (93%); $[\alpha]_D$ +18.6° (*c* 2.0, acetone); ^{13}C-n.m.r. δ 78.4, 77.1, and 75.6 ($CDCl_3$, internal standard), 103.3 (C-2′), 99.6, 97.9 (isopropylidene Me), 90.1 (C-1), 84.6, 80.5, 74.2, 70.3, 67.6, 67.4, 65.4, 63.0, 61.2, and 57.6 (not specifically assigned).

3′,4′,6′-Tri-O-tert-*butyldimethylsilyl-3-deoxy-3-fluoro-1′,2:4,6-di*-O-*isopropylidenesucrose* (**8**). — Compound **7** (4 g) was dissolved in 20 mL of pyridine, to which was added 1.25 mL of diethylaminosulfur trifluoride at 25°. After 1 h, the solution was poured into 80 mL of saturated sodium hydrogencarbonate and the product extracted with dichloromethane. The organic phase was washed twice with water and evaporated under diminished pressure to a syrup, which was dissolved in methanol by heating on a steam bath. This solution was kept for 48 h at −20°. The resulting crystals contained three compounds, which were resolved by chromatography on a column (2.5 × 60 cm) of silica gel, using a linear gradient (2 L) of 0–10% ethyl acetate in hexane. Compound **8**, eluted last, was detected by t.l.c. and crystallized from methanol; yield 1.0 g (25%); m.p. 168–170°, $[\alpha]_D$ +8.82° (*c* 2.0, acetone); ^{13}C-n.m.r. δ 78.5, 77.1, and 75.6 ($CDCl_3$, internal standard), 105.1 (C-2′), 101.4, 99.6 (isopropylidene Me), 92.3 (C-1), 91.0 (C-3, d, $J_{C\text{-}3,F\text{-}3}$ 187 Hz), 86.4, 82.6, 80.6, 72.7, 72.0, 67.4, 63.5, 62.7, and 62.4 (not specifically assigned).

3-Deoxysucrose (**9**). — Compound **6** (5 g) was dissolved in 120 mL acetonitrile, and 0.4 g of tetrabutylammonium chloride and 5.8 g of potassium fluoride dihydrate was added[22]. The solution was kept at 70°. After 3 days, t.l.c. (acetonitrile) showed only one product. The solvent was removed by rotary evaporation to give a syrup, to which was added THF (15 mL), acetic acid (20 mL), and water (10 mL). This solution was kept for 18 h at 20°, at which time t.l.c. showed one major product moving ahead of fructose, as well as traces of faster-moving products (probably *O*-isopropylidene sugars) and fructose. The solution was evaporated under diminished pressure to a syrup by rotary evaporation with use of a condenser cooled with Dry Ice–acetone. Water (50 mL) was added and removed by rotary evaporation. The mixture of products was resolved by chromatography on a column (3 × 30 cm) of silica gel, using 500 mL of 90% acetonitrile–water followed by 500 mL of 80% acetonitrile–water. Fractions containing compound **9** were pooled, concentrated, and dissolved in 5 mL of water. The mixture was filtered and the filtrate

evaporated to a syrup, 25 mL of ethanol was added, and the solution was evaporated to a foam; yield 2 g (92%); m.p. 185° (dec.), $[\alpha]_D$ +47.0° (*c* 1.33, water); ^{13}C-n.m.r. δ 50.0 (methanol, internal standard), 104.7 (C-2'), 92.0 (C-1), 82.4 (C-5'), 77.6 (C-3'), 75.1 (C-4'), 74.2 (C-5), 67.2 and 65.0 (C-4 and C-2, not specifically assigned), 63.4 (C-6'), 61.3 (C-6), and 35.1 (C-3).

Anal. Calc. for $C_{12}H_{22}O_{10}$: C, 44.03; H, 7.08. Found: C, 43.45; H, 6.91.

Allosucrose (**10**). — Compound **7** (2 g) was deprotected as described earlier for compound **9**, except that the column of silica gel was eluted with a linear gradient (1 L) of 90 to 70% acetonitrile in water; yield 0.4 g (44%); m.p. 178° (dec.), $[\alpha]_D$ +54.4° (*c* 1.67, water); ^{13}C-n.m.r. δ 50.0 (methanol, internal standard), 105.0 (C-2'), 93.1 (C-1), 82.6 (C-5'), 77.6 (C-3'), 74.9 (C-4'), 72.2, 68.9, 67.8, 66.8 (unassigned), 63.2 (C-6'), 62.6 (C-1'), and 61.4 (C-6).

Anal. Calc. for $C_{12}H_{22}O_{11}$: C, 42.11; H, 6.43. Found: C, 41.53; H, 6.49.

3-Deoxy-3-fluorosucrose (**11**). — Compound **8** (1 g) was deprotected as described for preparing compound **9**, except that the acid-hydrolysis step was performed at 25° and the column of silica gel was eluted with a linear gradient (1 L) of 100 to 85% acetonitrile in water; yield 0.4 g (89%); m.p. 175° (dec.), $[\alpha]_D$ +58.2° (*c* 3.0, water); ^{13}C-n.m.r. δ 50.0 (methanol, internal standard), 104.9 (C-2'), 95.7 (C-3, d, $J_{C\text{-}3,F\text{-}3}$ 179 Hz), 93.5 (C-1, d, $J_{C\text{-}1,F\text{-}3}$ 10 Hz), 82.6 (C-5'), 77.5 (C-3'), 75.1 (C-4'), 73.0 (C-5, d, $J_{C\text{-}5,F\text{-}3}$ 6 Hz), 70.7 (C-2 or C-4, d, $J_{C,F\text{-}3}$ 18 Hz), 68.7 (C-2 or C-4, d, $J_{C,F\text{-}3}$ 19 Hz), 63.4 (C-6'), 62.6 (C-1'), and 60.9 (C-6); ^{19}F-n.m.r. data (p.p.m. from trichlorofluoromethane): 198.534 (dt, $J_{H\text{-}3,F\text{-}3}$ 55, $J_{H\text{-}4,F\text{-}3} = J_{H\text{-}2,F\text{-}3}$ = 12.5 Hz).

Anal. Calc. for $C_{12}H_{21}O_{10}F$: C, 41.86; H, 6.10; F, 5.52. Found: C, 40.35; H, 6.35; F, 4.66.

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