Carbohydrate Research, 162 (1987) 209–215
Elsevier Science Publishers B.V., Amsterdam – Printed in The Netherlands

BRANCHED-CHAIN SUCROSES: SYNTHESIS AND WITTIG REACTION OF THE 1′-ALDEHYDO DERIVATIVE OF SUCROSE*

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(Received August 8th, 1986; accepted for publication, November 14th, 1986)

ABSTRACT

The reaction of 2,3,4,3′,4′-penta-*O*-acetylsucrose (**1**) with 3.3 mol. equiv. of *tert*-butyldiphenylsilyl chloride in pyridine in the presence of 4-dimethylaminopyridine gave the 6,1′,6′-tris(*tert*-butyldiphenylsilyl) derivative **2** (27%) and the 6,6′-bis(*tert*-butyldiphenylsilyl) derivative (67%). Oxidation of the HO-1′ in **3** with methyl sulphoxide and trifluoroacetic anhydride gave the 1′-aldehydo derivative **5**, which reacted with the stabilised Wittig reagent ($Ph_3P{=}CHCO_2Et$) to give the 1′-ethoxycarbonylmethylene derivative **6**. Deacetylation of the hepta-acetate **7** of **6** with methanolic sodium methoxide was accompanied by a Michael addition reaction to give 2,1′-anhydro-1′-methoxycarbonylmethylsucrose.

INTRODUCTION

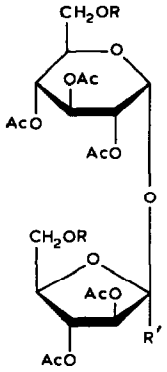
Branched-chain sugars are constituents of antibiotics[2] and nucleotides[3] and are of value in the synthesis of optically pure non-carbohydrate natural products[4]. Branched-chain derivatives of sucrose are therefore of interest, and we now describe the synthesis of the 1′-aldehydo derivative of sucrose and its reaction with a stabilised Wittig reagent to give 1′-*C*-branched-chain compounds.

RESULTS AND DISCUSSION

The reaction of 2,3,4,3′,4′-penta-*O*-acetylsucrose (**1**) with 3.3 mol. equiv. of *tert*-butyldiphenylsilyl chloride in pyridine in the presence of 4-dimethylaminopyridine at room temperature for 36 h gave, after column chromatography, the 6,1′,6′-tris(*tert*-butyldiphenylsilyl) derivative[5] **2** (27%) and the 6,6′-bis(*tert*-butyldiphenylsilyl) derivative **3** (67%). Treatment of **3** with acetic anhydride and pyridine gave the known[5] hexa-acetate **4**. Treatment of **3** in dichloromethane with methyl sulfoxide (2 mol. equiv.) and trifluoroacetic anhydride (1.5 mol. equiv.)

*Sucrochemistry, Part 39. For Part 38, see ref. 1.

0008-6215/87/$ 03.50



1 R = H, R′ = CH_2OH
2 R = $^tBuPh_2Si$, R′ = $CH_2O^tBuPh_2Si$
3 R = $^tBuPh_2Si$, R′ = CH_2OH
4 R = $^tBuPh_2Si$, R′ = CH_2OAc
5 R = $^tBuPh_2Si$, R′ = CHO
6 R = $^tBuPh_2Si$, R′ = $CH{=}CHCO_2Et$
7 R = Ac, R′ = $CH{=}CHCO_2Et$

under nitrogen at −50° followed by treatment with triethylamine gave, after column chromatography, 40% of the 1′-aldehyde **5**. The ^{1}H-n.m.r. spectrum of **5** (see Table I) contained signals for two $^tBuPh_2Si$ groups, five OAc groups, and an aldehydic proton (τ 0.59).

Treatment of **5** with ethoxycarbonylmethylenetriphenylphosphorane[6] gave 89% of the crystalline 1′-ethoxycarbonylmethylene derivative **6**. The ^{1}H-n.m.r. spectrum of **6** contained the signals for the original *tert*-butyldiphenylsilyl and acetate groups, and the coupling constants ($J_{1,2}$ 3.5, $J_{2,3} = J_{3,4}$ = 7.0 Hz) indicated the α-D-*gluco* configuration and $^4C_1$ conformation for the hexopyranosyl residue. The low-field resonances at τ 3.20 and 3.69 ($J_{1',1''}$ 15.5 Hz) were assigned to the olefinic protons H-1′ and H-1″, the splitting pattern of which was similar to that of *trans*-α,β-unsaturated esters. The characteristic quartet and a triplet at τ 5.74 and 8.68, respectively, were assigned to the ethoxy protons of the unsaturated ester group. Desilylation of **6** with tetrabutylammonium fluoride in tetrahydrofuran followed by treatment with acetic anhydride in pyridine gave the 1′-ethoxycarbonylmethylene derivative **7**. The ^{1}H-n.m.r. spectrum of **7** contained seven singlets (7.81–7.99) for acetate groups, low-field doublets at τ 3.22 and 3.70 ($J_{1',1''}$ 16.0 Hz) assigned to the *trans* olefinic protons H-1′ and H-1″, a triplet at τ 8.68 due to the ethoxycarbonyl CH_3 group, and signals due to the ethoxycarbonyl CH_2 group at τ 5.60–6.00, identified by spin-decoupling experiments.

Treatment of **7** with a catalytic amount of methanolic sodium methoxide at room temperature for 4 h gave the 2,1′-anhydro derivative **8** by way of a Michael-type addition reaction. Formation of the 2,1′-anhydro ring indicates that the α,β-unsaturated ester is in close proximity to HO-2 (**9**) which attacks at C-1′ to give the six-membered ring. Formation of 2,1′-cyclic structures in sucrose has been observed[7–11] and they require minimal displacement from the favoured geometry of the sucrose molecule[12,13].

The structure of **8** was established on the basis of the ^{1}H-n.m.r. data for the hexa-acetate **10**. The low-field doublets due to the *trans*-olefinic H-1′,1″ observed in the spectra of **6** and **7** were absent from the ^{1}H-n.m.r. spectrum of **10**. The

TABLE I

^{1}H-N.M.R. DATA[a]: FIRST-ORDER CHEMICAL SHIFTS (τ) AND COUPLING CONSTANTS (Hz) AT 250 MHz

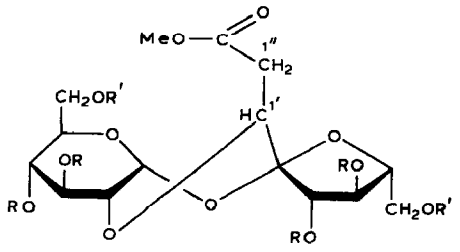
Atom	**5**	**6**	**7**	**10**	**11**
H-1	4.34 d	4.73 d	4.64 d	4.53 d	4.80 d
H-2	5.10 dd	5.10 dd	5.13 dd	6.14 dd	6.22 dd
H-3	4.70 t	4.62 t	4.57 t	4.29 t	4.32 t
H-4	4.62 t	4.61 t	4.90 t	4.97 t	4.81 t
H-5		5.91m			
H-6a		6.29 dd	5.60–6.00	5.60–5.95	6.05–6.30
H-6b	5.90–6.50	6.36 dd			
H-1'a		3.20 d	3.22 d	5.50–5.60	5.70t
H-1'b					
H-3'	4.38 d	4.86 d	4.79 d	4.80 d	4.88 d
H-4'	4.54 t	4.51 t	4.62 t	4.45 t	4.41 t
H-5'		6.20 m			5.89 qt
H-6'a	5.90–6.50	6.64 dd	5.60–6.00	5.60–5.95	6.05–6.30
H-6'b		6.74 dd			
H-1"a		3.69 d	3.70 d	7.43 d	7.45 d
H-1"b				7.42 d	
Others					
$J_{1,2}$	3.5	3.5	3.5	3.5	3.5
$J_{2,3}$	10.0	7.0	10.0	10.0	10.0
$J_{3,4}$	10.0	7.0	10.0	10.0	10.0
$J_{4,5}$	10.0	4.0	10.0	10.0	10.0
$J_{5,6a}$	—	5.5	—	—	—
$J_{5,6b}$	—	8.0	—	—	—
$J_{6a,6b}$	—	10.0	—	—	—
$J_{1',1''}$		16.0	16.0		
$J_{1',1''a}$				5.0	6.0
$J_{1',1''b}$				7.0	6.0
$J_{1''a,1''b}$				0.0	0.0
$J_{3',4'}$	5.5	3.5	5.0	7.0	6.5
$J_{4',5'}$	5.5	3.5	5.0	5.0	6.5
$J_{5',6'a}$	—	1.5	—	—	6.0
$J_{5',6'b}$	—	2.0	—	—	6.0
$J_{6'a,6'b}$	—	12.0	—	—	—
Aromatic	2.20–2.80	2.30–2.90			2.30–2.90
tert-Butyl	9.01, 9.03 (2 s)	9.0–9.01 (2 s)			8.94–8.95 (2 s)
CHO	0.59				
$-CH_2-$		5.74 qt	5.60–6.00		
$-CH_3$		8.68 t	8.68 t		
–OMe				6.31	6.31

[a]$CDCl_3$ solution.

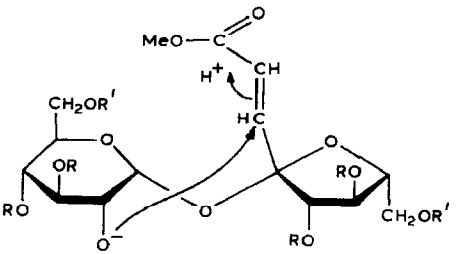
signals for H-1″,1″ in **10** appeared as doublets at τ 7.43 and 7.42 ($J_{1',1''a}$ 5.0, $J_{1',1''b}$ 7.0 Hz). The resonance due to H-1′ was identified in the region τ 5.50–5.60 by spin-decoupling experiments. The appearance of the H-2 signals at high-field suggested that position 2 was involved in the ring closure. The ^{1}H-n.m.r. spectrum of **10** also revealed the presence of MeO instead of the expected EtO, indicating that trans-esterification had occurred during the deacetylation. The rest of the spectrum agreed with positions 3,4,6,3′,4′,6′ being acetylated. The mass spectrum of **10** contained a peak at *m/z* 617 for (M^+ − OMe), but hexopyranosyl and ketofuranosyl fragments were not formed, indicating that the new ring spanned the two monosaccharide moieties. The general fragmentation pattern was similar to those of 2,1′-*O*-isopropylidene[8], 4,6:2,1′-di-*O*-isopropylidene[8], and 2,1′-anhydro[11] derivatives of sucrose.

In the ^{13}C-n.m.r. spectrum of **10**, the signals of C-2 and C-1′ appeared downfield (4.0 p.p.m.) when compared with those of sucrose octa-acetate[14], indicating involvement of C-1′ and C-2 in the 2,1′-anhydro ring. The high-field signal due to C-1″ was assigned at 38 p.p.m. and that at 51.80 p.p.m. was attributed to the methoxyl carbon, and the low-field resonance at 169.3 p.p.m. to the carbonyl carbon at C-2″.

Compound **10** was further characterised by the silylation reaction. Deacetylation of **7** and then treatment with 3 mol. equiv. of *tert*-butyldiphenylsilyl chloride in pyridine in the presence of 4-dimethylaminopyridine followed by conventional acetylation gave, after column chromatography, the bis(*tert*-butyldiphenylsilyl) tetra-acetate **11**, the ^{1}H-n.m.r. spectrum of which indicated positions 3,4,3′,4′ to be acetylated. The signals due to H-2 ($J_{1,2}$ 3.5 Hz) were identified by spin-decoupling experiments and were hidden under other signals in the region τ 6.05–6.30, where the resonances of H-5,5′ and H-6,6′ also appeared. Because of the silyl groups, the resonances due to H-6,6 and H-6′,6′ were downfield (0.4 p.p.m.), exposing a triplet at τ 5.70 which was assigned to H-1′. The high-field doublet at τ 7.45 was assigned to H-1″a and H-1″b ($J_{1',1''a} = J_{1',1''b}$ = 6.0 Hz). These assignments were confirmed by spin-decoupling experiments. A singlet at τ 6.31 was attributed to the methoxyl group. The mass spectrum of **11** showed a fragmentation pattern similar to that of **10**.



8 R = R′ = H
10 R = R′ = Ac
11 R = Ac, R′ = ^{t}BuPh$_2$Si



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EXPERIMENTAL

For general experimental details, see ref. 15.

tert-Butyldiphenylsilylation of 2,3,4,3',4'-penta-O-acetylsucrose[16] (**1**). — A solution of **1** (20 g, 36.2 mmol) in dry pyridine was treated with *tert*-butyldiphenylsilyl chloride (32.7 g, 119 mmol) and 4-dimethylaminopyridine (1 g, 8 mmol) at room temperature for 36 h. T.l.c. (ether–acetone, 4:1) then revealed two products. The mixture was poured into ice–water and extracted with ether, and the extract was dried (Na_2SO_4) and concentrated. The resulting syrup was eluted from a column of silica gel with ether–light petroleum (4:1) to give the known[5] 6,1',6'-tri-*O*-(*tert*-butyldiphenylsilyl)sucrose penta-acetate (**2**; 10 g, 27%) and 2,3,4,3',4'-penta-*O*-acetyl-6,6'-di-*O*-(*tert*-butyldiphenylsilyl)sucrose (**3**; 25 g, 67%), $[\alpha]_D$ +50° (*c* 1, chloroform).

Anal. Calc. for $C_{54}H_{66}O_{16}Si_2$: C, 63.15; H, 6.43. Found: C, 63.81; H, 6.97.

Conventional acetylation of **3** gave the known[5] 6,6'-di-*O*-(*tert*-butyldiphenylsilyl)sucrose hexa-acetate **4**.

Oxidation of **3**. — To a cooled (below −50°) mixture of dichloromethane (20 mL) and methyl sulphoxide (1.32 mL, 18.6 mmol) was added trifluoroacetic anhydride (2 mL, 14 mmol) dropwise. The reaction was exothermic. After 10 min, a solution of **3** (10 g in 100 mL of CH_2Cl_2, 9.7 mmol) was added, the mixture was stirred for 45 min at −50°, triethylamine (20 mL, 143 mmol) was then added dropwise, and, after 30 min, the mixture was allowed to attain room temperature and stirred thereat for 6–8 h. T.l.c. (ether–light petroleum, 4:1) showed the formation of a fast-moving and a slow-moving product. The mixture was diluted with dichloromethane (200 mL), washed successively with water, aqueous 10% sulphuric acid, aqueous sodium hydrogencarbonate, and water, dried (Na_2SO_4), and concentrated. The residue was eluted from a column of silica gel, using ether–light petroleum (3:2), to afford 1'-aldehydo-6,6'-di-*O*-(*tert*-butyldiphenylsilyl)sucrose penta-acetate (**5**; 4 g, 39%), $[\alpha]_D$ +52° (*c* 1, chloroform). Mass spectrum: *m/z* 527, 483.

Anal. Calc. for $C_{54}H_{64}O_{16}Si_2 \cdot H_2O$: C, 62.05; H, 6.51. Found: C, 61.72; H, 6.37.

*2,3,4,3',4'-Penta-O-acetyl-6,6'-di-O-(*tert*-butyldiphenylsilyl)-1'-deoxy-1'-ethoxycarbonylmethylenesucrose* (**6**). — A solution of **5** (4 g, 3.9 mmol) in toluene (40 mL) was treated with ethoxycarbonylmethylenetriphenylphosphorane[17] (1.2 g, 3.4 mmol) at 70° for 45 min. T.l.c. (ether–light petroleum, 4:1) then revealed one faster moving product. The mixture was cooled and concentrated, and the residue was treated with ether. The triphenylphosphine oxide which crystallised out was removed, the filtrate was concentrated, and the crude product was then eluted from a column of silica gel, using ether–light petroleum (1:1), to afford **6** (3.8 g, 89%), m.p. 100–101° (from ether–light petroleum), $[\alpha]_D$ +57° (*c* 1, chloroform). Mass spectrum [ions (a) correspond to hexopyranosyl cation and (b) to ketofuranosyl cation]: *m/z* 553 (b), 527 (a), 493 (b) 365 (a).

Anal. Calc. for $C_{58}H_{72}O_{17}Si_2$: C, 63.50; H, 6.56. Found: C, 63.48; H, 6.59.

2,3,4,6,3',4',6'-Hepta-O-acetyl-1'-deoxy-1'-ethoxycarbonylmethylenesucrose (**7**). — A solution of **6** (3.4 g, 3.1 mmol) in dry tetrahydrofuran (40 mL) was treated with M tetrabutylammonium fluoride in tetrahydrofuran (10 mL, 10 mmol). The mixture was left for 4 h at room temperature and then concentrated. The resulting syrup was treated with pyridine (10 mL) and acetic anhydride (5 mL) for 4 h at room temperature. The mixture was concentrated and the residue was eluted from a column of silica gel, using ether–light petroleum (1:1), to afford **7** (1.5 g, 83%), $[\alpha]_D$ +52° (*c* 1.1, chloroform).

Anal. Calc. for $C_{30}H_{40}O_{19}$: C, 51.15, H, 5.68. Found: C, 52.02; H, 5.89.

2,1'-Anhydro-1'-methoxycarbonylmethylsucrose (**8**). — A solution of **7** (1.4 g) in methanol (20 mL) was treated with a catalytic amount of sodium methoxide for 4 h. T.l.c. (acetone–water, 9:1) then revealed one slow-moving spot. The solution was neutralised with Amberlyst 15 (H^+) resin, filtered, and concentrated to give **8** (800 mg, 85%), $[\alpha]_D$ +16° (*c* 1, water). ^{13}C-N.m.r. data (62 MHz, D_2O): δ 176.0 (C-2″ carbonyl), 106.1 (C-2'), 95.5 (C-1), 84.5 (C-5'), 79.3 (C-3'), 76.8 (C-4'), 76.6 (C-3), 76.5 (C-5), 71.5 (C-4), 69.3 (C-2), 68.3 (C-1'), 65.2 (C-6'), 62.7 (C-6), 55.2 (CH_3O), 37.0 (C-1″).

Anal. Calc. for $C_{15}H_{24}O_{12}\cdot CH_3OH$: C, 44.85; H, 6.54. Found: C, 45.12; H, 6.75.

3,4,6,3',4',6'-Hexa-O-acetyl-2,1'-anhydro-1'-methoxycarbonylmethylsucrose (**10**). — A solution of **8** (400 mg) in pyridine (10 mL) was treated with acetic anhydride (3 mL) for 16 h at room temperature. T.l.c. (ether) then revealed one fast-moving product. The mixture was concentrated by co-distillation with toluene, and the syrupy residue was decolourised with charcoal. Compound **10** (600 mg, 93%) crystallised from ether and had m.p. 85–86°, $[\alpha]_D$ +69° (*c* 1, chloroform). Mass spectrum: *m/z* 617 (M^+ − OMe), 497, 455, 413. ^{13}C-N.m.r. data (62 MHz, $CDCl_3$): 170.5–169.3 (7 carbonyl carbons), 104.4 (C-2'), 90.0 (C-1), 79.4 (C-5'), 75.5 (C-3'), 74.8 (C-4'), 72.2 (C-3), 70.0 (C-5), 67.5 (C-4), 65.8 (C-2), 65.6 (C-1'), 63.5 (C-6'), 61.5 (C-6), 51.8 (CH_3O), 34.3 (C-1″), 20.6–20.4 (CH_3 of acetates).

Anal. Calc. for $C_{27}H_{36}O_{18}$: C, 50.00; H, 5.55. Found: C, 49.73; H, 5.78.

*3,4,3',4'-Tetra-O-acetyl-2,1'-anhydro-6,6'-di-O-(*tert*-butyldiphenylsilyl)-1'-methoxycarbonylmethylsucrose* (**11**). — A solution of **8** (400 mg, 0.6 mmol) in pyridine was treated with *tert*-butyldiphenylsilyl chloride (500 mg, 1.8 mmol) in the presence of 4-dimethylaminopyridine (100 mg, 0.8 mmol) at room temperature for 48 h. T.l.c. (ether–acetone, 4:1) then revealed one major product. Acetic anhydride (2 mL) was then added to the mixture which was kept at room temperature for 8 h and then concentrated, and the residue was eluted from a column of silica gel, using ether–light petroleum (1:1), to afford **11** (800 mg, 76%), $[\alpha]_D$ +62° (*c* 1, chloroform).

Anal. Calc. for $C_{55}H_{68}O_{16}Si_2$: C, 63.46; H, 6.53. Found: C, 64.58; H, 7.15.

ACKNOWLEDGMENT

We thank Professor R. C. Righelato (Director, Tate & Lyle Group Research and Development) for his interest and support.

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