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Carbohydrate Research 328 (2000) 419–423

CARBOHYDRATE RESEARCH

Note

Preparation of sucrose heptaesters unsubstituted at the C-1 hydroxy group of the fructose moiety via selective *O*-desilylation

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Received 3 January 2000; received in revised form 18 April 2000; accepted 18 April 2000

Abstract

Selective O-desilylation of 6,1′,6′-tri-*O*-*tert*-butyldiphenylsilyl-2,3,4,3′,4′-penta-*O*-benzoylsucrose with hydrofluoric acid in acetonitrile led to the 1′-*O*-*tert*-butyldiphenylsilyl derivative (96% yield), which was further perbenzoylated and deprotected at OH-1′ with tetrabutylammonium fluoride (86%). An analogous sequence with the corresponding O-acetylated sucrose derivative and tetrabutylammonium fluoride as desilylating agent resulted in a lower yield of the C-1′ hydroxy derivative.

Keywords: Sucrose; 1′-Hydroxy sucrose; Sucrose heptaester; Selective (de)silylation

As part of a program directed toward the valorisation of sucrose by incorporating it into polymers, its conversion to natural compounds and its possible application as a chiral auxilliary in selective asymmetric cycloaddition [1,2], we needed to obtain a derivative of sucrose, which we could functionalise easily at the primary hydroxyl at C-1 of the fructose moiety. A review of the literature revealed that heptaprotected sucrose derivatives with a free 1′-OH have been prepared [3–11]. In particular 2,3,4,6,3′,4′,6′-hepta-*O*-acetyl-sucrose has been obtained [6–11] either by partial deacylation of the octaacetylsucrose, or by multistep synthesis. Deacylation, however, was not very selective and the desired product normally had to be separated from a number of regioisomers. As a consequence, the global yields for these processes remained very low (from 11% to inseparable isomers) and unsuitable for large scale preparations. The multistep sequence reported by Li and Wu [11] is an example of the other approach. We wished to develop a short and easy route for the preparation of larger quantities of our target molecule.

We concluded that a possible route to compounds such as 2,3,4,6,3′,4′,6′-hepta-*O*-benzoyl-sucrose could involve selective silylation/desilylation of sucrose [12,13], based

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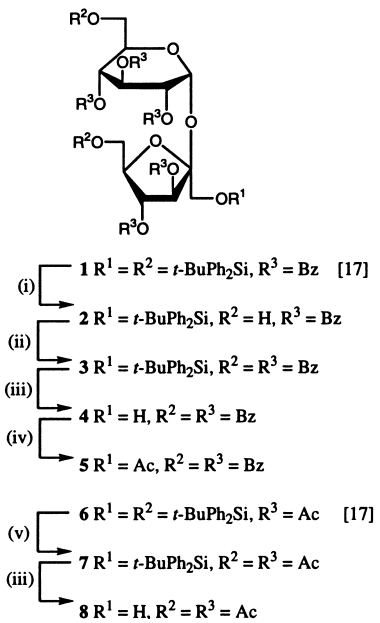
0008-6215/00/$ - see front matter
PII: S0008-6215(00)00119-1

on the fact that the primary alcohol groups are more reactive than the secondary and that between the primary hydroxyls there is a relatively well defined reactivity [14–17].

Our synthetic scheme was based upon a selective deprotection of the hydroxyl functions at the 6- and 6′-positions of the tri-*tert*-butyldiphenylsilyl derivative **1** [17] (Scheme 1). No desilylation occurred using an excess of tetrabutylammonium fluoride either in aqueous solution or under anhydrous conditions in THF. Trimethylpyridinium fluoride in THF, or heating with sodium hydroxide (5 N) were also ineffective. Use of boron trifluoride diethyl etherate for this purpose led to a mixture of products. Only 40% hydrofluoric acid in aqueous acetonitrile for a period 60 h at room temperature afforded the dihydroxysucrose derivative **2** in excellent yield (96%). In the ^{1}H NMR spectrum (300 MHz, $CDCl_3$) of **2**, we note the presence of a singlet at 1.02 ppm integrating for nine protons corresponding to the *tert*-butyl group of the silyloxy function and a broad singlet at 2.68 ppm (two hydroxylic protons), which indicated the presence of only one *tert*-butyldiphenylsilyl group. Furthermore, we have attributed (Table 1) the multiplet at 3.95–3.50 ppm — integration



Scheme 1. (i) aq HF, MeCN; (ii) BzCl/DMAP/pyridine; (iii) nBu$_4$NF, THF; (iv) Ac_2O/DMAP/pyridine; (v) (1) nBu$_4$NF, THF; (2) Ac_2O/DMAP/pyridine.

six protons — to the methylenic protons 6, 1′ and 6′. A comparison of these values with those in compound **1** showed no remarkable variations of chemical shift, which indicates the absence of migration of a benzoyl substituent to a primary hydroxy group. It was impossible at this time to be precise about the position of the silyloxy substituent (6, 1′ or 6′-position). In order to determine its position, we transformed **2** into its heptabenzoate derivative **3** by acylation with benzoyl chloride in pyridine (quantitative yield). Its ^{1}H NMR spectral data (300 MHz, $CDCl_3$) showed in particular the presence of two doublets (AB system, 3.67 and 4.06 ppm, J 10.5 Hz, one proton each) that we have attributed to the H-1′ protons. The H-6 protons (4.30 and 4.36 ppm, two doublet of doublet) and H-6′ protons (4.63 ppm, multiplet) have also been assigned. These chemical shifts were in agreement with structure **3**, which contains the ether protecting group at C-1 of the fructose moiety, and has allowed us to determine the structure of **2** as the 2,3,4,3′,4′-penta-*O*-benzoyl-1′-*O*-*tert*-butyldiphenylsilylsucrose. Compound **3** was then selectively deprotected using 2.0 equivalents of tetrabutylammonium fluoride in THF, leading to the expected compound **4** (86%) without migration. A study of its ^{1}H NMR spectral data revealed two doublets at 3.59 and 3.80 ppm (one proton each, J 12.3 Hz) attributed to H-1′ α to a hydroxyl group. As this last product was very difficult to purify and satisfactory microanalytical or mass spectrometric data could not be obtained, it has been characterised as its 1′-*O*-acetyl derivative **5**, which afforded the necessary analytical data.

A similar sequence from the 6,1′,6′-tri-*O*-silyl-2,3,4,3′,4′-penta-*O*-acetyl sucrose (**6**) [17] led to the compound **7** after selective O-desilylation using tetrabutylammonium fluoride in THF, followed by peracetylation. Unfortunately, some O-deacetylation occurred and the best yield of **7** was obtained by using 2.7 equivalents of reagent during a short period, which afforded 54% yield in two steps. A selective deprotection of the remaining *tert*-butyldiphenylsilyl group gave the expected **8** (71%), whose physical data (optical rotation and ^{1}H NMR data) were identical to those

Table 1
^{1}H NMR spectral data ($CDCl_3$, 300 MHz): chemical shifts (δ in ppm) and coupling constants (Hz) [a]

	1 [17]	**2**	**3**	**4**	**5**	**6** [17]	**7**
H-1	m 5.96 [c]	d 5.93	m 6.04	m 6.05	d 6.13	s 5.56 [c]	d 5.55
H-2	m 5.34 [c]	dd 5.23	dd 5.30	dd 5.38	dd 5.42	d 4.85 [c]	dd 4.77
H-3	m 5.96	t 6.04	m 6.04	m 6.05	t 6.20	m 5.35	t 5.28
H-4	m 5.96	t 5.46	t 5.71	t 5.75	t 5.76	m 5.35	t 4.96
H-5	m 4.25	d 4.37	m 4.63	m 4.70	m 4.67	m 3.98	m 4.24
H-6	d 3.54	m	dd 4.36	m 4.70 or d 4.45	dd 4.42	m 3.53	m 4.20
	d 3.41	3.95–3.50	dd 4.30		dd 4.32		d 4.04
H-1′	d 4.03	m 3.95–3.50	d 4.06	d 3.80	d 4.71	m 3.79	d 3.66
	d 3.65		d 3.67	d 3.59	d 4.56	m 3.53	d 3.40
H-3′	d 6.24	d 6.37	d 6.36	d 5.95	d 5.95	d 5.84 [c]	d 5.86
H-4′	m 5.96	t 6.11	m 6.04	m 6.05	t 5.89	m 5.35	t 5.38
H-5′	m 4.41	d 4.23	m 4.63	m 4.70	m 4.27	m 4.12	m 4.17
H-6′	m 3.91	m	m 4.63	m 4.70	m 4.27	m 3.79	m 4.20
		3.95–3.50		or d 4.45			
$J_{1,2}$		3.0	3.6	3.6	3.4		4.0
$J_{2,3}$		9.9	10.2	10.5	10.4	7.2	10.0
$J_{3,4}$		9.9	10.0	9.6	9.9		10.0
$J_{4,5}$		9.9	10.0	9.6	9.9		10.0
$J_{3',4'}$	7.0	7.5	7.2	5.1	5.8	4.5	7.0
$J_{4',5'}$		8.4			5.3–5.6		7.0
$J_{5,6a}$			2.7		2.5		
$J_{5,6b}$			3.0		3.2		
$J_{6,6}$	10.5		12.3	9.3 [b]	12.6		11.0
$J_{1',1'}$	10.0		10.5	12.3	12.0		11.0

[a] Key: s, singlet; d, doublet; dd, double doublet; t, triplet; m, multiplet.
[b] $J_{6,6}$ or $J_{6',6'}$.
[c] Value in agreement with the literature.

described in the literature [7,8,10], and unreacted **7** (29%). Attempts to increase the proportion of these two compounds in favour of **8** have failed because more forcing conditions result in partial removal of the acetate groups.

In summary, we have obtained the novel 1′-OH free heptabenzoyl sucrose derivative **4** via a short sequence (five steps from sucrose) with an overall yield of 66%. The flexibility of this pathway allows us to easily change the protecting groups, as has been shown by the preparation of its heptaacetate homolog **8** (overall yield 35%), and makes possible the selective preparation of several monohydroxy sucrose esters or ethers.

1. Experimental

General methods.—Melting points were determined on a Büchi 530 apparatus and are not corrected. Evaporations were performed under reduced pressure. Optical rotations were measured at 20 °C on a Perkin–Elmer 241 polarimeter (1 dm cell). Column chromatography was carried out using Silica Gel 60 H, 60 GF_{254} or 60M (230–400 mesh). Thin-layer chromatography (TLC) was performed on E. Merck 60 F_{254} plates and compounds were visualised with a soln of 30% H_2SO_4 in EtOH or a soln of phosphomolybdic acid (25 g) in EtOH (500 mL) and heating, or under UV light. Organic solvents were dried immediately before use. Anhydrous $MgSO_4$ was used to dry organic extracts. ^{1}H NMR spectra were recorded on a Bruker AMX 300 MHz. Microanalyses were performed by the Microanalytical Services of the Centre National de la Recherche Scientifique (CNRS), F-69390 Vernaison, France.

1-O-tert-*Butyldiphenylsilyl-3,4,6-tri*-O-*benzoyl-β*-D-*fructofuranosyl-2,3,4,6-tetra*-O-*benzoyl-α*-D-*glucopyranoside* (**3**).—To compound **1** [17] (300.0 mg, 0.2 mmol) dissolved in

MeCN (8 mL) was added 0.1 mL of HF (40% HF in water). After 2 days of stirring at rt, satd $NaHCO_3$ was added until neutral pH, the aq layer was extracted with CH_2Cl_2 and the combined organic layers were dried and concentrated to a yellow oil (295 mg). A purification by preparative TLC (1:2 acetone–hexane) gave 1-*O*-*tert*-butyldiphenylsilyl-3,4-di-*O*-benzoyl-β-D-fructofuranosyl-2,3,4-tri-*O*-benzoyl-α-D-glucopyranoside (**2**) (200 mg, 96%). Compound **2** (200.0 mg, 0.18 mmol) was dissolved in pyridine (1.5 mL), and DMAP (50 mg) and benzoyl chloride (84.0 μL, 4.0 equiv) were added. After one night at rt, the solution was poured into ice and $NaHCO_3$, extracted with CH_2Cl_2, and dried. Concentration of the solution gave a syrup, which was purified by preparative TLC (1:2 acetone–hexane), yielding **3** (238.0 mg, 100%): $[\alpha]_D$ +16.6° (*c* 0.5, $CHCl_3$); Anal. Calcd for $C_{77}H_{68}O_{18}Si$: C, 70.63; H, 5.23. Found: C, 70.99; H, 5.98.

1-O-*Acetyl-3,4,6-tri*-O-*benzoyl-β*-D-*fructofuranosyl-2,3,4,6-tetra*-O-*benzoyl*-α-D-*glucopyranoside* (**5**).—To compound **3** (140.0 mg, 0.11 mmol) in dry THF (1.5 mL) was added Bu_4NF (56.0 mg, 2.0 equiv) under nitrogen. After 4 h, the solvent was evaporated and the crude product was purified by silica gel chromatography (2:1 acetone–hexane), leading to the 3,4,6-tri-*O*-benzoyl-β-D-fructofuranosyl-2,3,4,6-tetra-*O*-benzoyl-α-D-glucopyranoside (**4**: 98.5 mg, 86%).

Acetylation of **4** (98.5 mg, 0.09 mmol) was achieved by dissolution in pyridine (1 mL) and addition of DMAP (20 mg) and Ac_2O (12.9 μL, 1.5 equiv). After one night of stirring, the reaction mixture was poured on ice and $NaHCO_3$ solution, extracted with CH_2Cl_2, and dried. A purification of the concentrated extracts by flash chromatography (1:3 EtOAc–hexane) afforded sirupy **5** (86.0 mg, 84%): $[\alpha]_D$ +38.3° (*c* 1, $CHCl_3$); Anal. Calcd for $C_{63}H_{52}O_{19}$: C, 67.98; H, 4.71. Found: C, 67.98; H, 4.70.

3,4,6-Tri-O-*acetyl-1*-O-tert-*butyldiphenylsilyl-β*-D-*fructofuranosyl-2,3,4,6-tetra*-O-*acetyl*-α-D-*glucopyranoside* (**7**).—To a solution of **6** (1.5 g, 1.2 mmol) in dry THF (6 mL) under nitrogen and at rt was added Bu_4NF (838.0 mg, 2.7 equiv). When highly polar products began to appear (TLC in 1:4 EtOAc–hexane), the solution was rapidly concentrated and the obtained syrup (5.1 g) was dissolved in pyridine (10 mL). DMAP (100 mg) and Ac_2O (447.0 μL, 4.0 equiv) were added. After one night at rt, the solution was poured onto ice and $NaHCO_3$, and extracted with CH_2Cl_2. Concentration of the dried solution led to a syrup, whose purification under silica gel (1:2 EtOAc–hexane) gave **7** as white crystals (560.0 mg, 54% in two steps): mp 49–50 °C; $[\alpha]_D$ +44.7° (*c* 0.6, $CHCl_3$); Anal. Calcd for $C_{42}H_{54}O_{18}Si$: C, 57.66; H, 6.22. Found: C, 57.55; H, 6.10.

3,4,6-Tri-O-*acetyl*-β-D-*fructofuranosyl-2,3,4,6-tetra*-O-*acetyl*-α-D-*glucopyranoside* (**8**).—To compound **7** (100.0 mg, 0.11 mmol) in dry THF (3 mL) and under nitrogen was added Bu_4NF (30.0 mg, 1.0 equiv.). After 30 min at rt, THF was evaporated and the crude product (244.0 mg) was purified by silica gel chromatography (2:1 EtOAc–hexane) affording unreacted **7** (29 mg, 29%) and **8** (foam, 52.0 mg, 71%): $[\alpha]_D$ +33.7° (*c* 0.5, $CHCl_3$), lit. +38.5° (*c* 1, $CHCl_3$) [7], lit. +50.2° (*c* 1.0, $CHCl_3$) [8], lit. +43° (*c* 2, $CHCl_3$) [10]; Anal. Calcd for $C_{26}H_{36}O_{18}$: C, 49.06; H, 5.70. Found: C, 49.20; H, 5.57.

Acknowledgements

This work has been supported by NATO SFS (PO-SUGARS) and the FCT (grant PRAXIS XXI/BPD/16348/98). We thank the service of NMR of the Universidade Nova de Lisboa for 2D NMR experiments. Some experiments were carried out initially by Joana Fonseca whom we thank.

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