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Note

The use of chlorodimethylthexylsilane for protecting the hydroxyl groups in cyclomaltoheptaose (β-cyclodextrin)

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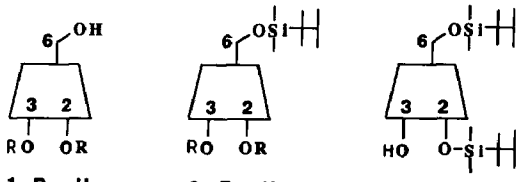
The *tert*-butyldimethylsilyl group has been used widely as a protecting group for alcohols[1], and for the protection of HO-6[2,3] and HO-2,6[3,4] of cyclomaltoheptaose (β-cyclodextrin, βCD). However, the cost and difficulty in recycling the reagent render its use for large-scale preparations unattractive. The dimethylthexylsilyl[5,6] group (thexyl = 1,1,2-trimethylpropyl) is a promising alternative with higher stability and we have investigated its use as a protecting group for βCD (**1**).

Heptakis(6-*O*-dimethylthexylsilyl)-βCD (**2**) was prepared as for the *tert*-butyldimethylsilyl analogue[3], but with a greater excess of chlorodimethylthexylsilane (molar ratio per primary hydroxyl group, 1:1.6 *versus* 1:1.1), and the reaction was monitored by t.l.c. for 36–40 h in order to ensure reaction of all of the primary hydroxyl groups. This procedure eliminated the need for column chromatography to purify **2**, which was obtained as a pure crystalline solid, and provides an economically viable large-scale synthesis of **2**, which has been used on >100 g batches of βCD.

Treatment of **2** with acetic anhydride–pyridine–4-dimethylaminopyridine[7] gave heptakis(2,3-di-*O*-acetyl-6-*O*-dimethylthexylsilyl)-βCD (**5**). The 4-dimethylaminopyridine markedly accelerated the reaction (6.5 h, *cf.* 24–30 h in the absence of catalyst) and the catalyst may be recycled with 80% efficiency.



1 R = H
5 R = Ac

2 R = H
4 R = Ac

3

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Removal of the dimethylthexylsilyl group gave higher yields than for the *tert*-butyldimethylsilyl group. Thus, treatment of **5** with boron trifluoride-etherate in alcohol-free chloroform gave heptakis(2,3-di-*O*-acetyl)-βCD (**6**, 80% after chromatography).

Protection of both HO-2 and HO-6 of βCD was acheived under conditions (95°, *N*,*N*-dimethylformamide–pyridine, 48 h) analogous to those employed by Stoddart and co-workers[8] for cyclomaltohexaose (αCD), to yield heptakis(2,6-di-*O*-dimethylthexylsilyl)-βCD (66%) and (6-*O*-dimethylthexylsilyl)hexakis(2,6-di-*O*-dimethylthexylsilyl)-βCD (32%).

EXPERIMENTAL

βCD (Roquette) was recrystallised from water and dried at 0.1 mmHg and 120° for 48 h. Pyridine and *N*,*N*-dimethylformamide were dried over, and redistilled from, CaH_2; anhydrous alcohol-free chloroform was redistilled over $CaCl_2$. Chlorodimethylthexylsilane (Fluka) and boron trifluoride-etherate (Aldrich) were used without further purification. Aqueous-washed organic solutions were dried over anhydrous Na_2SO_4. T.l.c. was performed on silica gel (F_{254}, Merck) with detection by charring with H_2SO_4, and column chromatography was performed on Silica Gel 60 (Merck, 9385). Melting points were determined with a Kofler apparatus and are uncorrected. N.m.r. spectra were recorded with a Bruker AC 200P spectrometer (200 MHz for ^1H, 50 MHz for ^{13}C) and chemical shifts (p.p.m.) are relative to those of the deuterated solvents.

Heptakis(6-O-dimethylthexylsilyl)cyclomaltoheptaose (**2**). — To a solution of anhydrous βCD (3.0 g) in dry pyridine (100 mL) at 0° was added dropwise chlorodimethylthexylsilane (6 mL). The mixture was stirred for 2 h at 0°, then allowed to warm to room temperature. The reaction was monitored by t.l.c. (butanone–1-butanol–water, 9:1:1; R_F 0.53), and the reaction was complete after 35–40 h. The pyridine was evaporated under reduced pressure, a solution of the residue in chloroform (150 mL) was washed with water and dried, and the solvent was evaporated. The residue was recrystallised from methanol–chloroform to give **2** (4.75 g, 85%), m.p. >230°. ^{13}C-N.m.r. data ($CDCl_3$): δ 101.93 (C-1), 81.64 (C-4), 73.59, 73.30, 72.50 (C-2,3,5), 61.21 (C-6), 34.14 ($Me_AMe_BCHMe_CMe_DC$), 25.03 ($Me_AMe_BCHMe_CMe_DC$), 20.33, 20.16, 18.58, 18.46 ($Me_AMe_BCHMe_CMe_DC$), −3.28 (Me_2Si).

Anal. Calc. for $C_{98}H_{196}O_{35}Si_7$: C, 55.23; H, 9.27. Found: C, 55.16; H, 9.25.

Heptakis(2,6-di-O-dimethylthexylsilyl)cyclomaltoheptaose (**3**). — To a solution of anhydrous βCD (1.0 g) in *N*,*N*-dimethylformamide (20 mL) and pyridine (5 mL) was added chlorodimethylthexylsilane (4.46 mL) dropwise at room temperature. The mixture was stirred for 48 h, the temperature was raised to 95°, water (35 mL) was added, and the mixture was extracted with heptane (2 × 100 mL). The combined extracts were washed with 2M HCl (50 mL), saturated aqueous $NaHCO_3$ (50 mL), and water (2 × 50 mL), then dried, and the solvent was evaporated under reduced pressure. Column chromatography (heptane–ethyl acetate, 95:5) of the residue (4.5 g) gave **3** (1.9 g, 66%), m.p. >230° (from ethyl acetate), R_F 0.6. ^{13}C-N.m.r. data: ($CDCl_3$): δ 102.68 (C-1), 82.08

(C-4), 74.86, 72.14, 71.70 (C-2,3,5), 61.63 (C-6), 34.14, 33.63 ($Me_AMe_BCHMe_C$-Me_DCSi-2,6), 25.49, 25.03 ($Me_AMe_BCHMe_CMe_DCSi$-2,6), 20.71, 20.24, 18.75, 18.62, 18.55, 18.29 ($Me_AMe_BCHMe_CMe_DCSi$-2,6), −1.99, −2.14 (Me_2Si-2), −3.22 (Me_2Si-6).

Anal. Calc. for $C_{154}H_{322}O_{35}Si_{14}$: C, 59.14; H, 10.38. Found: C, 59.23; H, 10.37.

(6-*O*-Dimethylthexylsilyl)hexakis(2,6-di-*O*-dimethylthexylsilyl)cyclomaltoheptaose (**4**; 0.84 g, 32%) was also obtained, m.p. >230° (from ethyl acetate), R_F 0.27. ^{1}H-N.m.r. data ($CDCl_3$): δ 5.03 (d, 1 H, H-1), 4.48 (m, 6 H, H-1), 1.71 (m, 13 H, Me_AMe_B-$CHMe_CMe_D$CSi-2,6), 0.80–0.95 (m, 156 H, $Me_AMe_BCHMe_CMe_D$CSi-2,6), 0.18 (36 H, Me_2Si-2), 0.09 (42 H, Me_2Si-6).

Heptakis(2,3-di-O-acetyl-6-O-dimethylthexylsilyl)cyclomaltoheptaose (**5**). — To a solution of **2** (1.0 g) in pyridine (20 mL) at 0° were added acetic anhydride (5.0 mL) and 4-dimethylaminopyridine (50 mg). The mixture was stirred at room temperature for 5 h, then heated to 100° for 1.5 h, and cooled. Water (5 mL) was added and the pyridine was evaporated under reduced pressure. A solution of the residue in ethyl acetate (100 mL) was washed with 2M HCl (20 mL), saturated aqueous $NaHCO_3$ (2 × 20 mL), and water (2 × 20 mL), then dried, and the solvent was evaporated under reduced pressure. Flash-column chromatography (heptane–acetone, 6:3) of the residue gave analytically pure **5** as an amorphous solid (1.36 g), R_F 0.24, m.p. 141–143°. ^{13}C-N.m.r. data ($CDCl_3$): δ 170.48, 169.29 (MeCO-2,3), 96.40 (C-1), 75.30 (C-4), 71.72, 71.34, 71.05 (C-2,3,5), 61.47 (C-6), 34.00 ($Me_AMe_BCHMe_CMe_DC$), 24.92 ($Me_AMe_BCHMe_CMe_DC$), 20.73, 20.57 (MeCO-2,3), 20.20, 19.97, 18.46, 18.26 ($Me_AMe_BCHMe_CMe_DC$), −3.33, −3.52 (Me_AMe_BSi).

Anal. Calc. for $C_{126}H_{224}O_{49}Si_7$: C, 55.64; H, 8.30. Found: C, 55.63; H, 8.40.

Heptakis(2,3-di-O-acetyl)cyclomaltoheptaose (**6**). — A solution of **5** (651 mg) and boron trifluoride-etherate (0.43 mL) in $CHCl_3$ (15 mL) was stirred overnight at room temperature, then diluted with $CHCl_3$ (50 mL), and poured into ice–water. The organic layer was separated, washed with water (15 mL), saturated aqueous $NaHCO_3$ (15 mL), and water (15 mL), dried, and concentrated. Column chromatography (ethyl acetate–methanol, 8:2) of the residue gave **6** (0.33 g, 80%). The n.m.r. data for **6** were identical to those published[2].

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