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Synthesis of Per-6-*O*-(*tert*-butyl)(diphenyl)silyl-β-cyclodextrin

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Abstract—Per-6-*O*-(*tert*-butyl)(diphenyl)silyl-β-silylcyclodextrin has been obtained regioselectively via the reaction with *tert*-butyldiphenylchlorosilane. Further treatment of the product with chlorosilanes has led to the corresponding derivatives of β-cyclodextrin with mixed silyl groups at the primary hydroxyl groups.

Keywords: silyl derivative, per-6-*O*-(*tert*-butyl)(diphenyl)silyl-β-cyclodextrin, regioselective silylation

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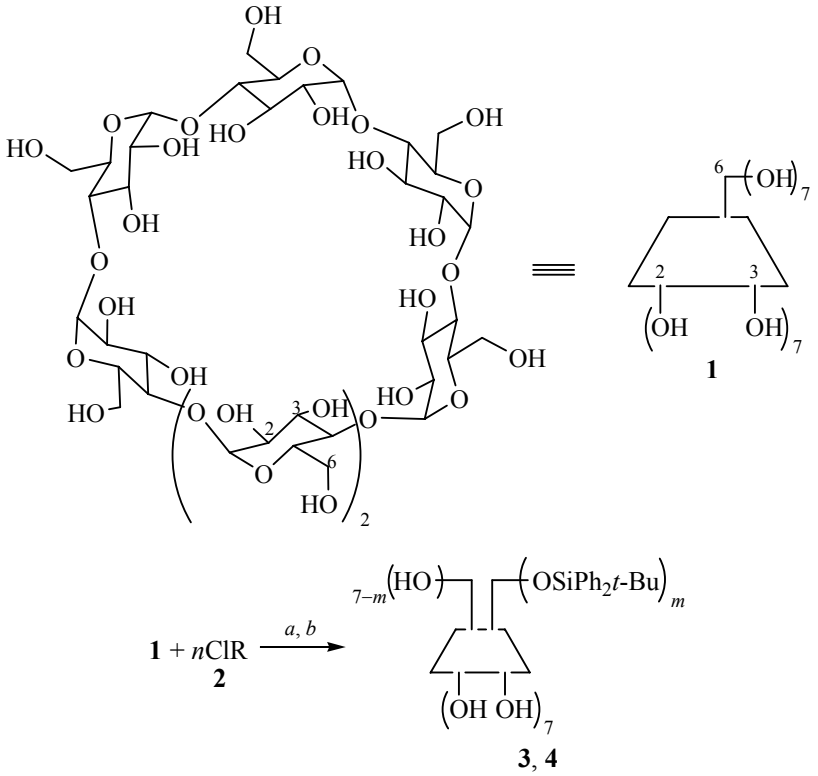
Silylated derivatives of cyclodextrins have found diverse applications in organic chemistry, for example, for the preparation of chiral stationary phases for GC [1, 2], as conjugates with β-cyclodextrin for preparation of silicon-containing nanoparticles [3], as intermediates for further transformations [4, 5], etc. Introduction of silyl groups at the cyclodextrin molecule substantially enhances the hydrophobicity of the derivatives and, most importantly, the solubility in organic solvents, thus increasing the synthetic possibilities. To do so, cyclodextrin is generally treated with the corresponding chlorosilane in the presence of a base (the hydrogen chloride acceptor). However, because of the presence of two types of hydroxyl groups in the molecule of cyclodextrin (primary groups at the C^6 positions and secondary groups at the C^2 and C^3 positions), regioselective silylation in practice is complicated. According to the literature, bulky *tert*-butyldimethylsilyl group have been widely used for selective silylation of primary hydroxy groups [6]. We have recently shown the possibility to use other chlorosilanes for this purpose: diphenylmethylchlorosilane and even trimethylchlorosilane [7], the latter having been usually considered a low-selective reagent, non-selectively silylating the primary and secondary hydroxyl groups of cyclodextrins [5, 8].

Extending the earlier study, in this work we report on the possibility of regioselective silylation of β-cyclodextrin (**1**) with the accessible *tert*-butyldichlorophenylchlorosilane (**2**). To do so, cyclodextrin **1** was treated with 8.5-fold excess of chlorosilane **2** (n = 8.5) in the pyridine solution (method *a*) or in the DMF solution in the presence of triethylamine (method *b*) (Scheme 1).

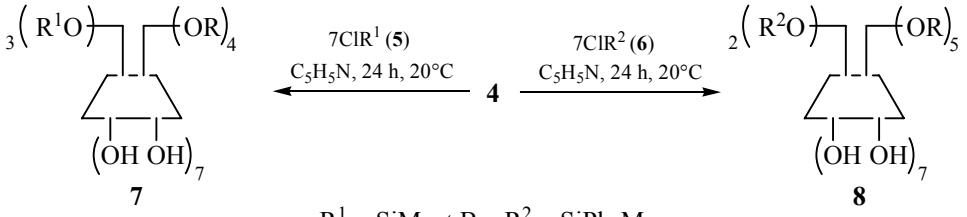
It was shown that under the conditions of silylation via method *a* (24 h, 20°C) only five silyl groups could be introduced at the primary hydroxyl groups at C^6 (the average degree of silylation m = 5, compound **3**), and under more severe conditions (n = 27, 6 h, 80°C) complete silylation could be achieved (m = 7, compound **4**). Similar results were obtained for silylation via method *b* (see Experimental). It has been earlier shown that the silylation with less bulky silylating reagents like trimethylchlorosilane or diphenylmethylchlorosilane under the above-given harsh conditions results in substitution at the secondary hydroxyl groups at C^2 and C^3 as well [7]. The number of the introduced silyl groups was evaluated by ^{1}H NMR spectroscopy and confirmed by MALDI-TOF mass spectrometry. We have earlier used the ^{29}Si NMR spectroscopy method to determine the regioselectivity of silylation, since silicon nuclei at the C^6 atom resonate in a notably stronger field than these at the C^2 and C^3 atoms [7, 9]. Compounds **3** and **4** showed the only singlet at δ^{29}_{Si} = –5.15 ppm in the spectrum, suggesting that in those compounds the silyl substi-

Scheme 1.



a, C_5H_5N, 20°C, 24 h, n = 8.5, m = 5; *b*, DMF, Et_3N, 80°C, 6 h, n = 27, m = 7.

Scheme 2.



R^1 = $SiMe_2t$-Bu, R^2 = $SiPh_2Me$.

tuents were located exclusively at the C^6 atoms. Interestingly, all trials of further silylation of compound **4** by less bulky silylating reagents *tert*-butyldimethyl- **5** or diphenylmethylchlorosilane **6** even under mild conditions (24 h, 20°C) via method *a* led to partial replacement of the silyl groups in compound **4** with less bulky ones, yielding compounds **7** and **8**, respectively, with mixed silyl groups at the C^6 atoms (as evidenced by ^1H, ^{13}C, and ^{29}Si NMR data as well as MALDI-TOF mass spectrometry results)[1]. The secondary hydroxyl groups of compounds **7** and **8** remained intact (Scheme 2).

We assumed that the described behavior was connected with supramolecular effect of the internal cavity of cyclodextrin, as it was observed earlier for some other cyclodextrin derivatives [10–12]. To verify the assumption, we treated compound **4** with chlorosilanes **5** and **6** under the conditions of method *a* in the presence of 2-fold equivalent excess of adamantane. Adamantane molecule is known to structurally fit the cavity of cyclodextrin and many of its derivatives, so that these compounds form fairly strong "host–guest" type complexes [13–15]. In the studied case, we did not observe substitution of the *tert*-butyldiphenylsilyl

[1] Compounds **3**, **7**, and **8** were mixtures of the isomers differing in the substituents location at the primary hydroxyl groups of the cyclodextrin scaffold.

groups in compound **4**, indicating the effect of the cyclodextrin cavity on the substitution of the silyl groups at C^6.

In summary, the conditions of regioselective silylation of the primary hydroxyl groups of β-cyclodextrin have been found. The trials of further silylation of the secondary hydroxyl groups with other silylating reagents have led to substantial replacement of the pre-introduced silyl groups and formation of the cyclodextrin derivatives with mixed silyl residues at the primary hydroxyl groups.

EXPERIMENTAL

All experiments were performed in anhydrous solvents purified via conventional procedures.

^{1}H and ^{13}C NMR spectra of the solutions in $CDCl_3$ were registered using a JEOL-ECX400 spectrometer with at 400 and 100.53 MHz, respectively; the chemical shifts were given relative to the solvent signals. ^{29}Si NMR spectra of the solutions in CCl_4 were registered with a Bruker DRX-500 spectrometer at 99.37 MHz relative to TMS. MALDI-TOF mass spectra were recorded with a Bruker Daltonics Ultraflex instrument in the positive ions regime taking advantage of the reflector mode; 2,5-dihydroxybenzoic acid was used as the matrix. Elemental analysis was carried out with a FlashEA 1112HT instrument. Thin-layer chromatography was performed on aluminum plates with fixed silica layer (Silufol UV-254); benzene–ethanol 3 : 1 (A) and hexane–acetone 3 : 1 (B) mixtures were used as eluents.

β-Cyclodextrin Merck (Germany) was used after additional careful dehydration.

Penta-6-*O*-(diphenyl)(*tert*-butyl)silyl-β-cyclodextrin (3). *a*. A solution of 1.03 g of chlorosilane **2** in 5 mL of pyridine was added to a stirred solution of 0.50 g of β-cyclodextrin **1** in 10 mL of pyridine at 0°C over 30 min. The mixture was stirred during 24 h at 20°C, concentrated in vacuum to 5 mL, poured into 50 mL of ice water, stirred, and incubated during 3 d; the precipitate was triturated with water (3 × 5 mL), filtered, and dried in vacuum (1 mmHg) during 5 h at 80°C. Yield 0.87 g (85%), mp 195–197°C (decomp.), R_f 0.85 (A). ^{1}H NMR spectrum, δ, ppm: 1.01 s (45H, $SiCH_3$), 3.34–3.93 m (42H, C^2H–C^5H, C^6H_2), 4.80–5.05 s (7H, C^1H), 5.20–6.52 br.s (16H, $C^{2,3,6}OH$), 7.32–7.61 m (50H, C_6H_5). ^{13}C NMR spectrum, δ_C, ppm: 18.4 [$\underline{C}(CH)_3$], 25.8 [$C(\underline{C}H)_3$], 60.46 (C^6), 70.5–73.0 (C^2, C^3, C^5), 81.2 (C^4), 101.4 (C^1), 127.2–135.8 (C_6H_5). ^{29}Si NMR spectrum, δ_{Si}: –5.15 ppm. Mass spectrum, *m/z*: 2349.333 $[M + Na]^+$ (calculated for $C_{122}H_{160}O_{35}Si_5$ 2327.01). Found, %: C 62.50; H 7.00. $C_{122}H_{160}O_{35}Si_5$. Calculated, %: C 62.97; H 6.93.

b. Similarly to method *a*, from 0.50 g of β-cyclodextrin, 0.42 g of triethylamine in 10 mL DMF, and a solution of 1.03 g of chlorosilane **2** in 3 mL DMF. Yield 0.82 g (80%), mp 195–197°C (decomp.), R_f 0.85 (A). The ^{1}H, ^{13}C, and ^{29}Si NMR spectra and MALDI-TOF mass spectra were identical to those of compound prepared via method *a*.

Per-6-*O*-(diphenyl)(*tert*-butyl)silyl-β-cyclodextrin (4). *a*. Prepared similarly to compound **3** via method *a*, from 1.00 g of β-cyclodextrin **1** in 15 mL of pyridine and a solution of 6.54 g of chlorosilane **2** in 10 mL of pyridine during 6 h at 80°C. Yield 2.09 g (85%), mp 195–210°C (decomp.), R_f 0.85 (A). ^{1}H NMR spectrum, δ, ppm: 1.01 s (63H, $SiCH_3$), 3.34–3.93 m (42H, C^2H–C^5H, C^6H_2), 4.80–5.05 s (7H, C^1H), 5.20–6.52 br.s (14H, $C^{2,3}OH$), 7.32–7.61 m (70H, C_6H_5). ^{13}C NMR spectrum, δ_C, ppm: 18.4 [$\underline{C}(CH)_3$], 25.8 [$C(\underline{C}H)_3$], 60.46 (C^6), 70.5–73.0 (C^2, C^3, C^5), 81.2 (C^4), 101.4 (C^1), 127.2–135.8 (C_6H_5). ^{29}Si NMR spectrum, δ_{Si}: –5.15 ppm. Mass spectrum, *m/z*: 2826.143 $[M + Na]^+$ (calculated for $C_{154}H_{196}O_{35}Si_7$: 2803.82). Found, %: C 65.50; H 7.00. $C_{154}H_{196}O_{35}Si_7$. Calculated, %: C 65.97; H 7.05.

b. Prepared similarly to compound **3** via method *a*, from 0.50 g of β-cyclodextrin, 1.32 g of triethylamine in 10 mL DMF, and a solution of 3.27 g of chlorosilane **2** in 5 mL DMF during 6 h at 80°C. Yield 0.98 g (79%), mp 195–210°C (decomp.), R_f 0.85 (A). ^{1}H, ^{13}C, and ^{29}Si NMR spectra and MALDI-TOF mass spectra were identical to those of compound prepared by method *a*.

Tri-6-*O*-(*tert*-butyl)(dimethyl)silyl-tetra-6-*O*-(*tert*-butyl)(diphenyl)silyl-β-cyclodextrin (7). A solution of 0.263 g of chlorosilane **5** in 5 mL of pyridine was added to a stirred solution of 0.70 g of compound **4** in 15 mL of pyridine over 30 min at 0°C. The mixture was stirred during 24 h at 20°C, concentrated to viscous residue, poured into 70 mL of ice water, and incubated during 3 days. The precipitate was filtered off, washed with water (3 × 5 mL), and dried in vacuum (1 mmHg) during 5 h at 80°C. Yield 0.303 g (50%), mp 210–215°C (decomp.), R_f 0.73 (A). ^{1}H NMR spectrum, δ, ppm: 0.01 and 0.09 s (18H, $SiCH_3$), 0.11 s [63H, $SiC(CH_3)_3$], 3.34–3.93 m (42H, C^2H–

C^5H, C^6H_2), 4.80–5.05 s (7H, C^1H), 5.20–6.52 br.s (14H, $C^{2,3}OH$), 7.32–7.61 m (40H, C_6H_5). ^{13}C NMR spectrum, δ_C, ppm: –4.57 ($SiCH_3$), 18.2 [$\underline{C}(CH_3)$], 25.8 [C($\underline{C}H_3$)], 61.6 (C^6), 70.5–73.0 (C^2, C^3, C^5), 81.2 (C^4), 101.4 (C^1), 127.2–135.8 (C_6H_5). ^{29}Si NMR spectrum, δ_{Si}: –9.02 ppm ($C^6O\underline{Si}Ph_2CH_3$), 19.90 s [$C^6O\underline{Si}(CH_3)_2C(CH_3)_3$]. Mass spectrum, *m/z*: 2453.819 [M + Na]$^+$ (calculated for $C_{124}H_{184}O_{35}Si_7$: 2431.40). Found, %: C 61.20; H 7.50. $C_{124}H_{184}O_{35}Si_7$. Calculated, %: C 61.26; H 7.63.

Di-6-*O*-(methyl)(diphenyl)silyl-penta-6-*O*-(*tert*-butyl)(diphenyl)silyl-β-cyclodextrin (8). Prepared similarly to compound **7** from 0.50 g of compound **4** in 15 mL of pyridine and a solution of 0.291 g of chlorosilane **6** in 5 mL of pyridine. Yield 0.291 g (60%), viscous oil, R_f 0.51 (B). ^1H NMR spectrum, δ, ppm: 0.56 s (6H, $SiCH_3$), 1.01 s [45H, $SiC(CH_3)_3$], 3.34–3.93 m (42H, C^2H–C^5H, C^6H_2), 4.80–5.05 s (7H, C^1H), 5.20–6.52 br.s (14H, $C^{2,3}OH$), 7.32–7.61 m (70H, C_6H_5). ^{13}C NMR spectrum, δ, ppm: –3.7 and –3.6 ($SiCH_3$), 18.4 [$\underline{C}(CH)_3$], 25.8 [C($\underline{C}H)_3$], 61.6(C^6), 70.5–73.0 (C^2, C^3, C^5), 81.2 (C^4), 101.4 (C^1), 127.2–135.8 (C_6H_5). ^{29}Si NMR spectrum, δ, ppm: –9.02 s [$C^6O\underline{Si}Ph_2CH_3$], –5.15 s [$C^6O\underline{Si}Ph_2C(CH_3)_3$]. Mass spectrum, *m/z*: 2742.825 [M + Na]$^+$ (calculated for $C_{148}H_{184}O_{35}Si_7$: 2719.66). Found, %: C 65.40; H 6.90. $C_{148}H_{184}O_{35}Si_7$. Calculated, %: C 65.36; H 6.82.

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