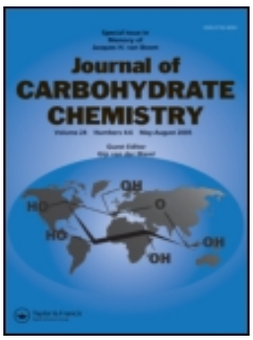

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COMMUNICATION

A CONVENIENT SYNTHESIS OF PER-*O*-METHYLATED 6-*O*-MONOSUBSTITUTED ß-CYCLODEXTRINS

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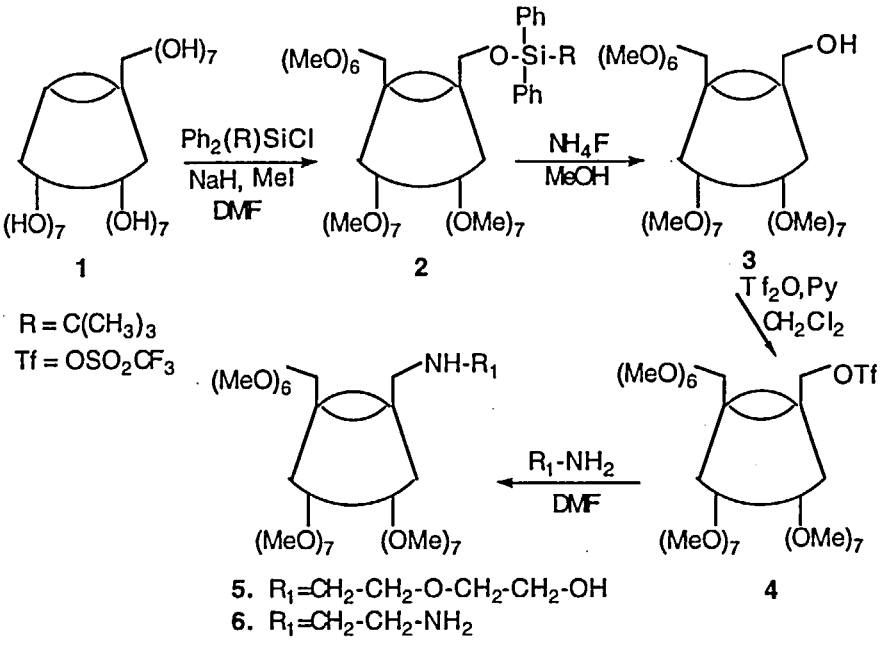
Cyclodextrins are cyclic oligosaccharides that function as chiral host molecules exhibiting enantioselectivity in reactions with racemic guests[1] and thus they represent a significant moiety of artificial enzymes.[2] The most easily obtainable and relatively inexpensive are ß-cyclodextrins (ß-CD), cyclic heptaglucosides in which glucopyranosyl residues are linked by an α(1-4) glycosidic bonds. ß-CD is surprisingly poorly soluble in water (1.8 g in 100 mL)[3] but the solubility of its derivatives is often significantly better. For instance, ß-CD with all secondary hydroxyls methylated, forms 50% aqueous solutions at room temperature,[4] and even completely methylated ß-CD is ten times more soluble in water (17 g in 100 mL)[5] than ß-CD itself. Methylation also alters the binding of the substrates to ß-CD often increasing its specificity and strength,[6] and renders the hydroxyl groups unreactive. Therefore, it is of interest to prepare derivatives of ß-CD in which the enzyme-mimicking group is bound to one hydroxyl (possibly through a tether) while the rest of the ß-CD moiety is permethylated.

To synthesize such 6-monosubstituted ß-CDs, mono 6-*O*-tosylates have been used repeatedly[7] as leaving groups for substitutions with nucleophilic reagents. However, displacement of tosylate with useful nucleophiles usually requires elevated temperatures and long reaction times, yet giving relatively low yields. For instance, it was shown recently that with amines starting from the 6-tosylate, the 6-amino derivatives are obtained in 30-50% yields after 4-8 hours at 70 °C.[7b] Consequently, we decided to explore the use of triflate group, one of the most reactive leaving groups for nucleophilic substitution,[8] to try to improve preparation of the target compounds. In fact, using the triflate of methylated ß-CD, substitution with amines occurs almost instantaneously at room temperature giving isolated yields over 75%. Therefore, even less reactive nucleophiles than previously used can be employed.

Mono 6-*O*-triflate ß-CD is prepared as depicted in Scheme 1 via a monosilyl derivative. It is well known that alkylation of cyclodextrins with sufficiently bulky agents would preferentially occur at primary hydroxyl groups. In this way mainly single trityl[9] or *t*-butyldimethylsilyl[10] derivatives can be obtained. Further methylation of all remaining 20 hydroxyl groups followed by the removal of previously introduced bulky groups yields the desired intermediate. Since the silylation with *t*-butyldimethylsilyl chloride is accompanied by a number of side products involving multiple silylation, we first tried to suppress the formation of such side products. Expecting that more sterically demanding silylating agents would show higher regiospecificity we examined thexyldimethylsilyl chloride, phenyldimethylsilyl chloride and *t*-butyldiphenylsilyl chloride in addition to *t*-butyldimethylsilyl chloride.

Thexyldimethylsilyl chloride and *t*-butyldimethylsilyl chloride gave products of comparable complexity whereas phenyldimethylsilyl chloride gave no reaction. Silylation with *t*-butyldiphenylsilyl chloride provided a cleaner desired product. Thus, silylation and exhaustive methylation of ß-CD gave **2**, which was converted to **3** upon treatment with NH_4F.[11] Triflate **4** was prepared by treatment of **3** with triflic anhydride and pyridine in dichloromethane in almost quantitative yield. ^1H NMR indicated only the presence of **3** (7-10%) and **4** (90-93%) in the reaction product. One of the most characteristic features of the NMR spectrum of **4** is the downfield shift of H-6 protons at δ 4.92 and δ 4.75 respectively, due to the electron withdrawing effect of the triflate group. ESMS was consistent with the proposed structure for **4** with *m/z* 1565 $[M+NH_4]^+$ and 1570 $[M+Na]^+$. The FTIR (nujol) of **4** shows a broad band at 1207 cm^{-1}, characteristic for an S=O stretching bond. The crude crystalline **4** (stable under argon and at -20 °C for several months) was further treated with 2-(2-aminoethoxy)ethanol and ethylenediamine giving the expected substitution products **5** and **6** in excellent yields. Products **5** and **6** thus obtained were fully characterized by ^1H and ^{13}C NMR spectroscopy and ESMS.



SCHEME 1

In conclusion, *t*-butyldiphenylsilyl chloride was found to be the silylating agent of choice yielding the single 6-silyl derivative of ß-CD with reasonable regiospecificity. After permethylation, desilylation and chromatography the overall yield of the 6-OH product **3** was 45%. The formation of crystalline triflate **4** and its substitution with bifunctional amines is essentially quantitative.

EXPERIMENTAL

General methods. Thin-Layer Chromatography (TLC) was performed on silica gel plates and visualized by spraying with 50% aq. sulfuric acid and heating at 200 °C. Silica gel (200-400 mesh, Toronto Research Chemicals) was used for flash chromatography. All starting materials were dried overnight *in vacuo* over KOH or P_2O_5 prior to use, and the solvents were distilled from appropriate drying agents. Solutions were concentrated at 1 mm Hg pressure using a rotary evaporator.

^1H and ^{13}C NMR spectra were recorded at 500 (125, ^{13}C) MHz with a Varian Unity 500 MHz spectrometer at the NMR Spectroscopy Laboratory of the Molecular Medicine Research Centre, University of Toronto. Spectra were obtained either in $CDCl_3$ containing a trace of TMS (δ=0 ppm, ^1H and ^{13}C) as the internal standard or in D_2O (99.98%, Aldrich) containing a trace of acetone (2.225 ppm relative to internal DSS, ^1H and 30.5 ppm ^{13}C) as the internal standard using δ(ppm) scale. All mass spectra were recorded with a VG Analytical ZAB-SE mass spectrometer or SCIEX API III mass spectrometer at the Mass Spectrometry Laboratory of the Molecular Medicine Research Centre, University of Toronto. The IR spectra were recorded in a nujol suspension using a Paragon 1000 PC (Perkin Elmer) FTIR spectrometer.

(2,3-Di-*O*-methyl)hexakis(2,3,6-tri-*O*-methyl)cyclomaltoheptaose (3). To a solution of dry ß-CD (2.27 g, 2 mmol) and imidazole (0.304 g, 3 mmol) in dry DMF (50 mL) was added dropwise, at 70 °C under argon, a solution of *tert*-butyldiphenylsilyl chloride (1.68 g, 6 mmol) in DMF (2 mL). After stirring for 1 h, at 70 °C, TLC using *n*-BuOH/EtOH/H_2O:5/4/3[10] indicated that starting ß-CD (R_f 0.41) and a faster migrating spot (R_f 0.61) were present in the reaction mixture. After cooling to 0 °C, NaH (60% dispersion in mineral oil, 3.2 g, 130 mmol) was added in one portion and the suspension was maintained at 0 °C for 0.5 h and at room temperature for 1 h. Then after cooling to 0 °C, MeI (39 g, 273 mmol) was added slowly over 30 min, and the reaction mixture was allowed to warm to room temperature and stirred overnight. TLC ($CHCl_3$/MeOH:10/1) showed only spots higher than permethylated ß-CD (R_f 0.68) indicating that the reaction was complete. The residual NaH was quenched with MeOH (8 mL) at 0 °C, and the resulting mixture was poured into ice water (200 mL) and extracted with $CHCl_3$ (3 x 75 mL). The chloroform extract was washed successively with $Na_2S_2O_3$ (3%, 40 mL), water (2 x 30 mL), dried (Na_2SO_4) and concentrated to dryness. The residue was dried *in vacuo* at 50 °C, dissolved in dry MeOH (100 mL) containing NH_4F (1.1 g), and refluxed for 24 h. After removal of methanol, EtOAc (100 mL) was added, the solids were filtered off using celite, and the filtrate was concentrated. The residue contained two major components R_f 0.68 (permethylated ß-CD) and R_f 0.54 (compound **3**) ($CHCl_3$/MeOH:10/1). Chromatography on a silica gel column using $CHCl_3$/MeOH:50/1 afforded permethylated ß-CD 0.68 g (23%) first, followed by pure **3** (1.27 g; 45%). The NMR and ESMS data of **3** agreed with those published earlier.[10] ^1H NMR (500 MHz, $CDCl_3$) δ 5.22 (d, 1H, J = 4.06 Hz, H-1), 5.17 (d, 1H, J = 3.85 Hz, H-1), 5.16 (d, 1H, J = 3.85 Hz, H-1), 5.1 (d, 3H, J = 3.63 Hz, H-1), 5.03 (d, 1H, J = 3.63 Hz, H-1), 3.37-3.89 (m, 95H), 3.19 (dd, 7H, J = 3.63 Hz and 9.83 Hz, H-2). ^{13}C NMR (125 MHz, $CDCl_3$) δ 99.02, 98.96, 98.78 (C-1), 82.36, 82.09, 82.02, 81.95, 81.9, 81.8, 81.72, 81.64, 81.59, 81.43, 81.11, 80.67, 80.62, 80.55, 79.96, 79.82, 78.51 (C-2, C-3, C-4), 71.7, 71.62, 71.54,

71.45, 71.33, 71.31, 71.15, 71.0, 70.82 (C-5 plus 6C-6), 61.5 (C-6(OH)), 61.61, 61.5, 61.28, 61.01 (OMe(C-2)), 59.11, 59.02, 58.95, 58.93 (OMe(C-3)), 58.69, 58.62, 58.46, 58.33, 58.24, 58.17 (OMe(C-6)). ESMS *m/z*: 1416 $[M+H]^+$, 1433 $[M+NH_4]^+$ and 1438 $[M+Na]^+$.

(2,3-Di-*O*-methyl-6-*O*-trifluoromethanesulfonyl)hexakis(2,3,6-tri-*O*-methyl) cyclomaltoheptaose (4). To a cold (-15 °C) solution of **3** (300 mg, 0.212 mmol) and pyridine (31.5 µL) in dry dichloromethane (2 mL), trifluoromethanesulfonic anhydride (90 mg, 0.319 mmol) was added dropwise. The reaction mixture was allowed to warm to room temperature and TLC ($CHCl_3$/MeOH:10/1) showed that most of the starting material was consumed and a new higher spot (R_f 0.6) was formed. The solution was cooled again (0 °C) , diluted with dichloromethane (10 mL), washed with 5% HCl (1 x 10 mL), aqueous $NaHCO_3$ (1 x 10 mL) and water (ice cold), dried over Na_2SO_4, filtered and concentrated to dryness to give a crystalline product **4** (325 mg), which was used without purification. Selected NMR data: ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.18 (d, 1H, H-1), 5.13 (m, 3H, H-1), 5.105 (d, 1H, H-1), 5.09 (d, 1H, H-1) (all having J = 3.6 Hz), 5.07 (d, 1H, J = 3.85 Hz, H-1), 4.92 (dd, 1 H, J = 1.64 Hz and 10.98 Hz, H-6(OTf)), 4.75 (dd, 1H, J = 6.6 Hz and 10.98 Hz, H-6'(OTf), 4.1 (dddd, 1H, J = 1.65 Hz and 6.6 Hz and 8.24 Hz and 10.16 Hz, H-5(OTf), 3.33-3.98 (m, 92H), 3.2 (dd, 7H, J = 3.3 Hz and 9.9 Hz, H-2). ESMS *m/z*: 1565 $[M+NH_4]^+$ and 1570 $[M+Na]^+$.

{6-Deoxy-2,3-di-*O*-methyl-6-[2(2-hydroxyethoxy)ethylamino]}hexakis(2,3,6-tri-*O*-methyl)cyclomaltoheptaose (5) and [6-Deoxy-2,3-di-*O*-methyl-6-(2-aminoethyl)amino] hexakis (2,3,6-tri-*O*-methyl)cyclomaltoheptaose (6). Dry **4** (325 mg), was dissolved in dry DMF (5 mL), cooled to 0 °C, ethylenediamine (120 mg, 2 mmol) was added, and the reaction was allowed to reach room temperature in about 45 min. TLC ($CHCl_3$/MeOH : 10/1) indicated that **4** was consumed completely and a more polar component (R_f 0.2) was formed. The volatiles were removed *in vacuo* and the residue was chromatographed on silica gel using , $CHCl_3$/MeOH:10/1 to give pure **6**, 220 mg (72% overall yield from **3**). ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.15 (d, 1H, J = 3.66 Hz, H-1), 5.13 (d, 1H, J = 3.42 Hz, H-1), 5.12 (d, 1H, J= 3.54 Hz, H-1), 5.11 (d, 1H, J = 3.54 Hz, H-1), 5.1 (d, 1H, J = 3.67 Hz, H-1), 5.08 (d, 1H, J = 3.54 Hz, H-1), 5.02 (d, 1H, J = 3.66 Hz, H-1), 3.92-3.33 (m, 96H), 3.24 (dd,1H, J = 4.5 Hz and 12.3 Hz, NH (D_2O exch)), 3.18 (brdd, 7H, J = 3.42 Hz and 9.9 Hz, H-2), 3.14 (m, 2H, CH_2), 2.8 (m, 2H, CH_2). ^{13}C NMR (125 MHz, $CDCl_3$) δ 99.76, 99.65, 98.94 (C-1), 82.1 (C-2), 81.86, 81.71, 81.44 (C-3), 80.47, 80.28, 80.17 (C-4), 71.36 (C-6), 70.94 (C-5), 61.42, 61.21 (OMe(C-2)), 59.4, 59.00, 58.85 (OMe(C-3)), 58.62, 58.49, 58,33 (OMe(C-6)). ESMS *m/z*: 1458 $[M+H]^+$.

In a similar way by using 2-(2-aminoethoxy)ethanol (3 equiv), **5** was obtained in 75% yield. ^{1}H NMR ($CDCl_3$) δ 5.15 (d,1H, J = 3.57 Hz, H-1,), 5.12 (m, 4H, H-1), 5.11 (d, 1H, J = 3.57 Hz, H-1), 5.09 (d, 1H, J = 3.57 Hz, H-1), 3.98 (dd, 1H, J = 3.66 Hz and 5.98 Hz), 3.89-3.38 (m, 100H), 3.19 (m, 7H, H-2), 3.15 (t, 2H, CH_2-N). ^{13}C NMR (125 MHz, $CDCl_3$) δ 99.35, 99.16, 98.97, 98.85, 98.74 (C-1), 82.19, 82.12, 82.03, 81.9 (C-2), 81.75, 81.68, 81.61 (C-3), 80.71, 80.46, 80.36 (C-4), 71.00, 70.96, 70.92 (C-5), 71.3 (C-6), 72.38, 61.7 (C-arm), 61.52, 61.48, 61.38, 61.33 (OMe(C-2)), 59.0 (OMe(C-3)), 58.64, 58.58, 58.52, 58.41 (OMe(C-6)). ESMS *m/z*: 1530 $[M+H]^+$ and 1525 $[M+Na]^+$.

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