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Direct and convenient access to mono 3-hydroxy per-O-methylated α-cyclodextrin

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Abstract—A direct way to reach mono 3-hydroxy per-O-methylated α-cyclodextrin by de-O-methylation with phenylthiotrimethylsilane is reported. This compound is fully characterized by NMR spectroscopy and liquid chromatography with mass spectroscopy coupling.

Cyclodextrins (CD) and their derivatives are successfully used in various chiral chromatographic techniques[1–4] for enantiomers separation: their unique structural and physical properties allow general use as chiral selectors. Moreover, coupling several hydroxyl groups' modifications lead to derivative compounds with specific physical, chemical, and/or binding properties, covering a wide range of applications.[1e,5] Nevertheless, modification of only one hydroxyl group among 21 (for β-CD for example) or modification of just one glucopyranose unit is still a difficult task[6] since the potentiality of other hydroxyl groups to react and form by-products.

Recently, a general way to access asymmetric γ-CD derivatives from the permethylated β-CD was developed in our lab.[7] This methodology inspired by Sakairi et al.[8] consists in a three-step process: ring opening of the permethylated β-CD, chain elongation with correctly modified monosaccharide derivatives and, finally, macrocyclization to obtain desired products. So, the insertion of a single glucopyranose unit differently substituted allows the lost of the pseudo eightfold axis symmetry of the asymmetric γ-CD thus obtained. These compounds are currently studied in our lab as chiral selectors for gas chromatography (GC).[9]

In order to complete this first set of asymmetric CD derivatives, this procedure has been investigated to the preparation of asymmetric β-CD derivatives. In this context, the unexpected behavior of the per-O-methylated α-CD met during the first step of the methodology quoted above, for example, the α-CD's ring opening is described.

As previously reported by Sakairi et al.,[8] 'thiolyze' is an interesting method to selectively cleave one interglucosidic bond. The reaction was performed by action of the 'Hannessian's reagent',[10] namely phenylthiotrimethylsilane (PhSTMS) (4 equiv), on the per-O-methylated CD in presence of zinc bromide (4 equiv) in 1,2-dichloroethane at room temperature during five days. This reaction was perfectly reproducible for the β-CD,[7] and purification of the mixture by chromatography on silica gel offered ring opening product as an anomeric mixture having an α:β ratio of 1:1 (determined by reverse phase high performance liquid chromatography with mass spectroscopy detection (RP-HPLC–MS) and ^{1}H NMR analysis), with a satisfactory yield of 38%.

This procedure was repeated for the thiolyze of the per-O-methylated α-CD (Scheme 1) and the reaction was monitored by TLC. After five days, TLC showed different spots with almost the same chromatographic behavior with no ultra violet (UV) absorption at 254 nm and one spot with UV absorption, which had a lower retention factor (RF) than the others. RP-HPLC-evaporated light scattered detector (ELSD) and RP-HPLC–MS analyses of the reaction mixture after washings

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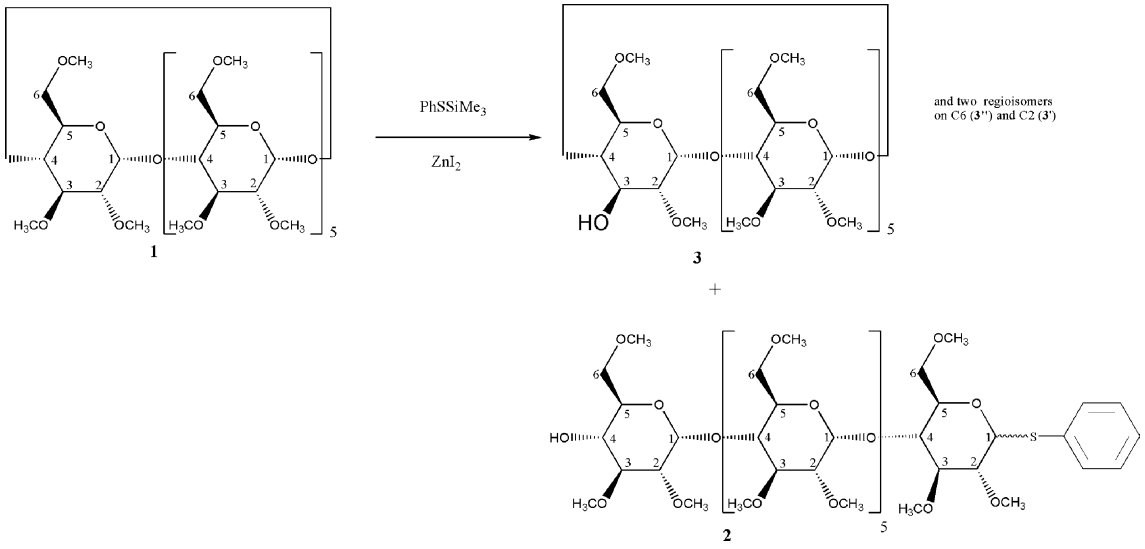

Scheme 1. de-O-Methylation of per-O-methylated α-cyclodextrin.

showed the presence of five compounds: Unchanged **1**, opening product **2**, and three isomeric mono hydroxy per-O-methylated α-CD, among them only product **3** has been isolated. Per-O-methylated α-CD **1** ($m/z = 1248.0$ [M+Na$^+$]; rt = 19.8 min; no UV $\lambda =$ 254 nm detection), mono hydroxy per-O-methylated α-CD **3″** ($m/z = 1234.0$ [M+Na$^+$]; rt = 15.52 min; no UV $\lambda = 254$ nm detection), mono hydroxy per-O-methylated α-CD **3′** ($m/z = 1234.0$ [M+Na$^+$]; rt = 14.55 min; no UV $\lambda = 254$ nm detection), mono hydroxy per-O-methylated α-CD **3** ($m/z = 1234.0$ [M+Na$^+$]; rt = 12.74 min; no UV $\lambda = 254$ nm detection), and opening product **2** ($m/z = 1358.5$ [M+Na$^+$]; rt = 6.9 min; UV $\lambda = 254$ nm detection). Purification using toluene/acetone mixture on silica gel gave compound **1** and **2** as major products, compound **3** was in smaller quantity. Using HPLC analysis comparison, compounds **3** and **3″** were respectively, identified as mono 3-hydroxy per-O-methylated α-cyclodextrin[11] and mono 6-hydroxy per-O-methylated α-cyclodextrin.[12] Compound **3′** appeared to be mono 2-hydroxy per-O-methylated α-cyclodextrin. To improve the reaction yield, other catalysts were used (ZnI_2, TfOTMS, Tf_2O) to reach about 15–25%. Yield of **3** depending of the catalyst used but classical use of molecular sieves 4 Å support formation of **2**.

Moreover, a classical de-O-methylation using iodotrimethylsilane in chloroform[13] was performed (1.3 equiv of TMS-I are added to permethylated α-cyclodextrin in chloroform ($c = 0.04$ M) with molecular sieves 4 Å under nitrogen atmosphere. The mixture is stirred during 6 h at room temp. When TLC shows two spots, the reaction mixture is stopped with 4 equiv of methanol. After diluting with diethyl ether, washing by $NaHSO_3$, $NaHCO_3$, and NaCl saturated solutions, solvents are evaporated. Purification is then performed using toluene/acetone on silica gel). The surprising result leads to mono 3-hydroxy per-O-methylated α-cyclodextrin (13%) and mono 2-hydroxy per-O-methylated α-cyclodextrin (3%, determined by HPLC). To our knowledge, de-O-methylation of cyclodextrins using iodotrimethylsilane were not described in the literature.

In order to ascertain the position of the free hydroxyl group of the compound **3**, O-methylation with $^{13}CH_3I$ was performed. So, the ^{13}C NMR spectra permits to attribute unambiguously the free hydroxyl group on the 3-O-hydroxy group position for compound **3** (Fig. 1). Furthermore, in the 57–63 ppm zoomed area of compound **3** ^{13}C NMR spectra, it appears very clearly five different signals corresponding to the five methyl groups located at the 3-O-hydroxy group positions (Fig. 1).[14] This particular behavior met during this reaction is not so surprising, since several authors[6a,15] already reported 'reactivity discriminations'. This de-O-methylation complements de-O-methylation performed with DIBAL reported by Sinaÿ and co-workers,[12] which allow access to only mono 6-hydroxy per-O-methylated α-cyclodextrin and dihydroxy per-O-methylated α-cyclodextrin.

In conclusion, the fully characterized mono 3-hydroxy per-O-methylated α-CD can be obtained in a one step synthesis with a moderate yield of 25%. This method seems to be quite an easy way versus others synthesis,[6c,11,16] which classically use the 'sledgehammer' method.

Isomeric mono hydroxy compounds are currently studied in our laboratory as chiral selector for chiral GC.

Typical procedure: Preparation of mono 3-hydroxy per-O-methylated α-cyclodextrin **3**.

Per-O-methylated α-CD was prepared following the Schurig procedure.[17]

Solvents were preliminary distilled and per-O-methylated α-CD was dry under vaccum at 90 °C.

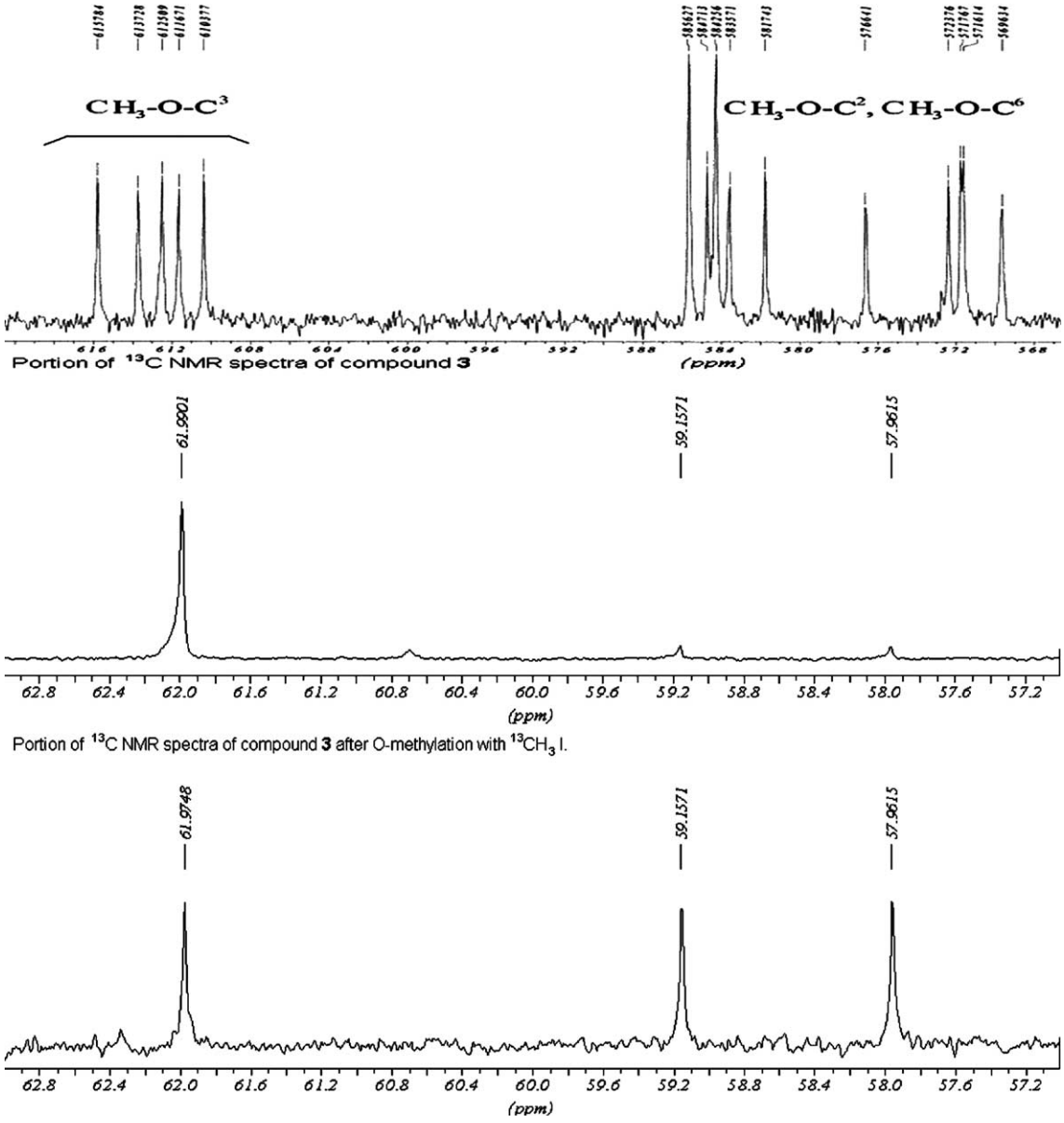

Figure 1. Portion of ^{13}C NMR spectra of per-O-methylated α-cyclodextrin.

In a round bottom flask, 3 g (2.45 mmol) of hexakis (2,3,6-tri-O-methyl)-α-cyclodextrin are dissolved in 60 mL of 1,2-dichloroethane under nitrogen atmosphere. To the stirred mixture, 3.12 g (4 equiv, 9.79 mmol) of zinc iodide and 1.86 mL (4 equiv, 9.83 mmol, 1.79 g) of phenylthiotrimethylsilane were added and the reaction was performed during five days. Reaction mixture was poured into 300 mL ice-water and extracted twice with 200 mL of 1,2-dichloroethane. To the combined extracts was then added 4:1 (v/v) methanol–triethylamine. The mixture was stirred at room temperature for 5 h and then concentrated under reduced pressure. Residue was diluted with 1,2-dichloroethane and then washed twice with a solution of $NaHCO_3$ satd, twice with brine, dried under magnesium sulfate, and evaporated to obtain a slightly yellow syrup. After chromatography using toluene/acetone (4:1) on silica gel, $2^{I–VI}$, $3^{II–VI}$, $6^{I–VI}$-heptadeca-O-methylcyclomaltohexaose was obtained (740 mg, 25%).

RP-HPLC–MS: CH_3OH/H_2O (4:1); column HYPERSIL® C18, 25 cm × 2.1 cm × 5 μm; flow = 0.25 mL/min; rt = 12.74 min; $m/z = 1234.01$ $[M+Na]^+$($[C_{53}H_{94}O_{30}+Na]^+$ requires 1233.57). $[\alpha]_D^{25}$ +117.2 (*c* 1.0 in $CHCl_3$). Anal. Calcd for $C_{53}H_{94}O_{30}$: C, 52.55; H, 7.82. Found: C, 52.54; H, 7.96.

^1H NMR: (δ ppm; 300 MHz; $CDCl_3$): 3.10 (dd, 6H, 6 × C_2–H, $^3J_{H2,H3} = 9.70$ Hz, $^3J_{H2,H1} = 3.60$ Hz), 3.32 (s, 18H, 6 × O–CH_3), 3.40–3.62 (m, –O–CH_3, Cn–H), 5.05 (m, 6H, 6 × C_1–H).

^{13}C NMR (δ ppm; 75 MHz; $CDCl_3$): 55.9, 57.1, 57.2, 57.6, 58.1, 58.3, 58.4, 58.4, 58.5, 61.0, 61.1, 61.2, 61.3,

61.5, 70.4, 70.5, 70.5, 70.6, 70.7, 71.1, 71.2, 78.9, 79.2, 80.1, 80.3, 80.3, 81.6, 81.7, 81.9, 82.0, 82.1, 82.1, 82.2, 99.1, 99.3, 99.6, 99.6, 99.7, 99.7.

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