

Short Note

2II-VII, 3I-VII, 6I-VII-Icosa-O-acetyl-2I-deoxy-cyclomaltoheptaose

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Abstract: Deoxygenation of a secondary hydroxy group on β -cyclodextrin was conducted to prepare the title compound 2II-VII, 3I-VII, 6I-VII-icosa-O-acetyl-2I-deoxy-cyclomaltoheptaose. The synthetic procedure comprised a two-step reaction—phenoxythiocarbonylation and Barton-McCombie deoxygenation. The synthesized compound was characterized by $^1\text{H-NMR}$, $^{13}\text{C-NMR}$, HRMS, and elemental analysis.

Keywords: cyclodextrin; deoxygenation; Barton-McCombie deoxygenation

1. Introduction

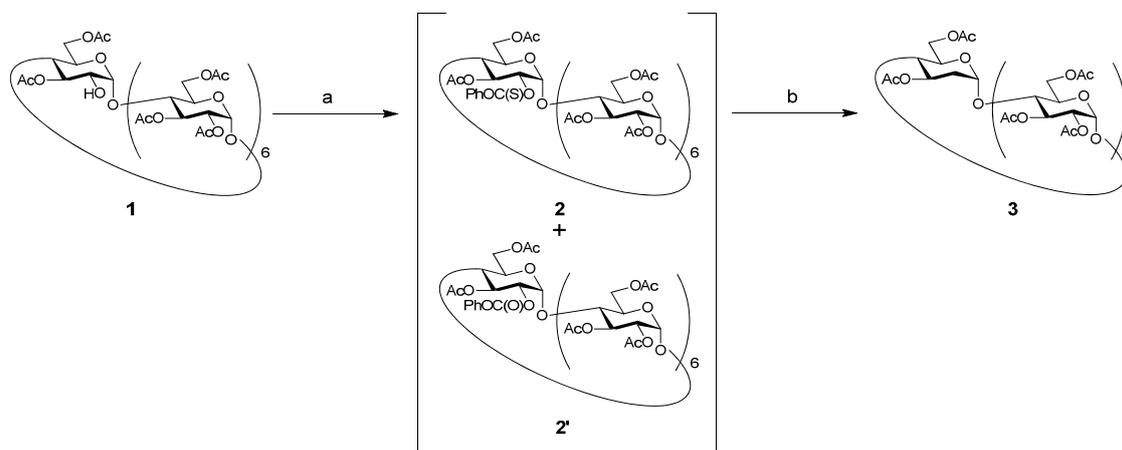
Cyclodextrins, which have a hydrophobic core and hydrophilic exterior, can form inclusion complexes with various hydrophobic compounds and thereby improve the solubility and bioavailability of such compounds. For this reason, cyclodextrins are widely used in materials science, as well as in pharmaceutical and dietary supplement applications in which hydrophobic compounds are delivered [1–5]. Regioselective modification of the hydroxyl groups of cyclodextrins has been attempted by various research groups in order to enhance the functions of the original compound [6–11]. For instance, the primary hydroxy groups at the 6-position react selectively with bulky reagents such as *tert*-butyldimethylsilyl chloride and *p*-toluenesulfonyl chloride [10,12]. Secondary hydroxy groups on cyclodextrins are able to react selectively in the presence of unprotected primary hydroxy groups by using strong bases such as sodium hydroxide and sodium hydride. Furthermore, their tosylation and alkylation have been reported, even though they required enormous efforts [6,7,9].

In this report, the hydroxy group at the 2-position of 2II-VII, 3I-VII, 6I-VII-Icosa-O-acetyl-2I-deoxy-cyclomaltoheptaose **1**—prepared by monobenylation at the 2-position, followed by acetylation [13–15]—was substituted with hydrogen via Barton-McCombie deoxygenation. The synthesis procedure and data for the synthesized compound (**3**) are reported herein.

2. Results and Discussion

The hydroxy groups are usually substituted with a thiocarbonyl group and halogen during deoxygenation. However, the substitution of a secondary hydroxy group with a halogen by using bulky reagents is often difficult; in particular, sterically hindered hydroxy groups on cyclodextrins severely restrict activation of the reagents. Therefore, thiocarbonate was selected as the leaving group for deoxygenation (Scheme 1). Compound **1** was treated with 4-dimethylaminopyridine (DMAP) and *O*-phenyl chlorothionoformate to introduce the thiocarbonyl group at the 2-position. However, even after the reaction mixture was subjected to silica gel chromatography, thiocarbonyl derivative **2** was not isolated in pure state, and a mixture including byproduct **2'** was obtained. Compound **2'**—an analogue of **2** wherein the S atom of the thiocarbonyl group is replaced by with O—was separated

after the next reaction, and its structure was confirmed by $^1\text{H-NMR}$ and mass spectroscopy (MS) data. A similar unexpected oxygen substitution was reported in a previous study [16]. Unfortunately, in our case, **2'** was produced in 51% yield. The mixture of **2** and **2'** was treated with *n*- Bu_3SnH and 2,2'-azodiisobutyronitrile (AIBN) to give the title compound (deoxy compound) **3**, albeit in a low yield of 25.3% (in two steps). The structure of **3** was elucidated by $^1\text{H-NMR}$, $^{13}\text{C-NMR}$, high-resolution mass spectroscopy (HRMS), and elemental analysis.



Scheme 1. Synthesis of deoxy compound **3**. Reagents and conditions: (a) PhOC(S)Cl , DMAP, pyridine, rt, 45 h; (b) *n*- Bu_3SnH , AIBN, toluene, $90\text{ }^\circ\text{C}$, 5 h.

3. Experimental

All reagents were purchased from commercial sources and used without further purification. AIBN was recrystallized from methanol before use. The solvents employed in the reactions were dried using molecular sieves 4 \AA activated *in vacuo* at $200\text{ }^\circ\text{C}$, and subsequently stored over molecular sieves. Thin layer chromatography (TLC) was performed on silica gel 60 F₂₅₄ 0.25 mm plates (Merck KGaA, Darmstadt, Germany). The compounds were detected under UV light and/or by treatment with $\text{EtOH}/\text{H}_2\text{O}/\text{H}_2\text{SO}_4/\text{resorcinol}$ and subsequent heating. Column chromatography was performed with silica gel 60 N, spherical neutral, particle size $40\text{--}50\text{ }\mu\text{m}$ or $63\text{--}210\text{ }\mu\text{m}$ (Kanto Chemical Co., Inc., Tokyo, Japan). The solvents for column chromatography were purchased from commercial sources and used as received. ^1H and $^{13}\text{C-NMR}$ spectra were recorded on a Bruker AVANCE 500US system (Bruker BioSpin GmbH, Rheinstetten, Germany) with a cryoprobe (500 MHz for ^1H ; 125.8 MHz for ^{13}C). Chemical shifts (in ppm) were referenced to tetramethylsilane ($\delta = 0\text{ ppm}$) in deuterated chloroform. $^{13}\text{C-NMR}$ spectra were also recorded on the same NMR spectrometers and were calibrated with the CDCl_3 peak ($\delta = 77.00\text{ ppm}$). High-resolution mass spectra were recorded on a JEOL JMS-S3000 spectrometer (JEOL Ltd., Tokyo, Japan) using 2,5-dihydroxybenzoic acid (DHBA) as the matrix. Elemental analysis was performed using Elementar Vario EL cube (Elementar Analysensysteme GmbH, Frankfurt, Germany).

2II-VII, 3I-VII, 6I-VII-Icosa-O-acetyl-2I-deoxy-cyclomaltoheptaose (**3**)

Compound **1** (920 mg, 466 μmol), which was co-evaporated thrice with dry pyridine, was dissolved in dry pyridine (23 mL). To this solution were added DMAP (300 mg, 2.46 mmol) and *O*-phenyl chlorothionoformate (1.40 mL, 10.4 mmol) dissolved in dry dichloromethane (2.0 mL). Furthermore, the mixture was stirred at room temperature for 45 h under argon atmosphere. The resulting mixture was diluted with toluene (30 mL), filtered, and concentrated. The residue was purified by silica gel chromatography using hexane–acetone (1:1 (*v/v*)) as the eluent to give a mixture of **2** and **2'**: R_f 0.63 (toluene–acetone = 4:3). The mixture was co-evaporated thrice with dry toluene and dissolved in dry toluene (30 mL). To the solution were added *n*- Bu_3SnH (1.20 mL, 4.45 mmol)

and AIBN (1.0 mg, 6.02 mmol). The mixture was stirred at 90 °C for 5 h under argon atmosphere, concentrated, diluted with acetonitrile, washed with hexane three times, and finally evaporated. The residue was purified by silica gel chromatography using toluene—acetone (7:3 (v/v)) to give the desired compound **3** (229 mg, 26.8%) along with the *O*-substitution analogue **2'** (496 mg, 51%).

R_f 0.50 (toluene—acetone = 4:3) for **3**

¹H-NMR (500 MHz, CDCl₃): δ 5.41–5.26 (m, 6H, H-3), 5.13–5.06 (m, 6H, H-1), 5.04–5.00 (m, 1H, H-3I), 4.96 (t, *J*_{1I,2I} = 3.9 Hz, 1H, H-1I), 4.84–4.72 (m, 6H H-2), 4.59–4.49 (m, 7H, H-6a), 4.34–4.22 (m, 7H, H-6b), 4.20–4.05 (m, 7H, H-5), 3.80–3.65 (m, 6H, H-4), 3.57 (dd, *J*_{3I, 4I} = 6.3 Hz, *J*_{4I,5I} = 8.9 Hz, 1H, H-4I), 2.26–2.19 (m, 1H, H-2I_{eq}), 2.18–2.03 (m, 60H, COCH₃), 1.78–1.74 (m, 1H, H-2I_{ax}).

¹³C-NMR (125 MHz, CDCl₃): δ 170.9, 170.7, 170.7, 170.7, 170.6, 170.5, 170.5, 170.4, 170.3, 170.3, 170.3, 169.7, 169.4, 169.4, 169.3, 169.3, 169.0(C=O), 99.6 (C-1I), 97.4, 96.9, 96.7, 96.7, 96.5, 96.5 (C-1), 78.1, 77.6 (C-4), 76.4, 76.0, 71.3, 71.3, 71.0, 70.9, 70.8, 70.7, 70.5, 70.5, 70.3, 70.3, 70.0, 69.9, 69.8, 69.7, 69.6, 69.5, 69.4 (C-2, 3, 5), 63.1 (C-6I), 62.5, 62.5, 62.4 (C-6), 33.7 (C-2I), 21.1, 21.0, 20.8, 20.7, 20.6.

MALDI-TOF-HRMS (*m/z*) C₈₂H₁₁₀NaO₅₄ [M + Na]⁺ calcd: 1981.5759, found: 1981.5693; C₈₂H₁₁₀KO₅₄ [M + K]⁺ calcd: 1997.5499, found: 1997.5438.

Elemental analysis C₈₂H₁₁₀O₅₄ calcd: C 50.26, H 5.66, found: C 49.99, H 5.58.

Supplementary Materials: The following are available online at <http://www.mdpi.com/1422-8599/2016/2/M900>, Figure S1: ¹H-NMR of **3**, Figure S2: ¹³C-NMR of **3**, Figure S3: MALDI-TOF-MS of **3**, Figure S4: ¹H-NMR of **2'**, Figure S5: MALDI-TOF-MS of **2'**.

Author Contributions: A.M. and H.Y. conceived and designed the experiments; K.K. and A.Y. performed the experiments; A.M. and K.K. analyzed the data; H.Y. contributed reagents/materials/analysis tools; A.M. wrote the paper.

Conflicts of Interest: The authors declare no conflict of interest.

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