Non-Natural Cyclodextrins

Synthesis of a Cycloallin Derivative from β-Cyclodextrin: Heptakis(2,3-dideoxy-2,3-epithio)-β-cycloallin**

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Macrocyclic molecules that comprise several subunits in a circular array exhibit novel functions that are otherwise not observed in the individual units. Many host molecules that consist of several identical functional subunits, such as cyclodextrins, cyclophanes, and their related natural and artificial macrocycles, have been prepared by enzymatic or synthetic methods and have developed the concept of artificial molecular recognition and catalysis.[1] Cyclodextrins, in particular, have been the leading compounds from the initial stage of this research. Despite extensive studies on the functionalization of cyclodextrins for diverse purposes such as the development of artificial receptors and enzymes, their modification has been limited mostly to their primary hydroxy groups while secondary sites have received much less attention.[2] Moreover, successful studies on complete modifications at the secondary sites are rare as the modifications on 2-OH or 3-OH do not proceed selectively and are accompanied inevitably by products of either over- or under-modification. Only per(3,6-anhydro)-[3] and per(2-*O*-tosyl)-cyclodextrins,[4] per(2,3-anhydro)-cyclomannins **1** (see Scheme 1),[4,5] cycloaltrins,[6] per(3-amino-3-deoxy)-β-cycloaltrin,[7] and per(3-deoxy)-cyclomannins[8] are available by the selective modifications of cyclodextrins at the present time. However, to the best of our knowledge, the preparation of a cycloallin family has not been studied as yet.

Here, we report the first successful one-pot preparation of a novel type of cycloallin derivative, **2**, from cyclomannin derivative **1**, which itself is obtained in three steps from β-cyclodextrin (Scheme 1). The synthesis is as simple as heating an aqueous acidic solution of **1** at 90 °C for 30 min followed by stirring at room temperature under alkaline conditions. It is quite astonishing that these simple reaction conditions not only ensure a complete conversion of the seven epoxide

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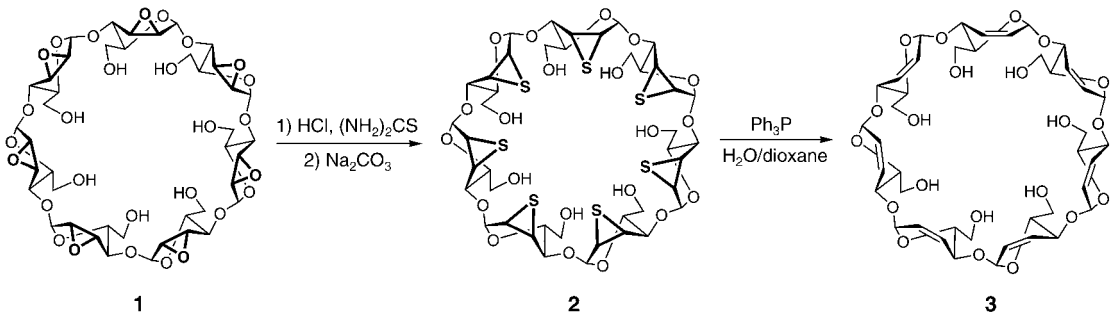


Scheme 1. Preparation of **2** from a cyclodextrin and its conversion into olefin **3**.

residues to episulfides but also guarantee the inversion of configuration at all the subunits, as revealed by the structural analysis of **2**.

The assignment of the NMR signals of **2** (Figure 1) relied on ^{1}H,^{1}H and ^{1}H,^{13}C COSY NMR spectra and indicates that **2** consists of 2,3-dideoxy-2,3-epithioallopyranose units. The

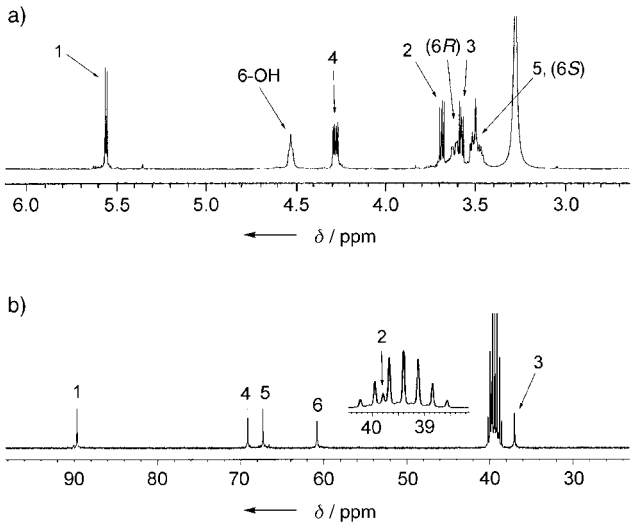
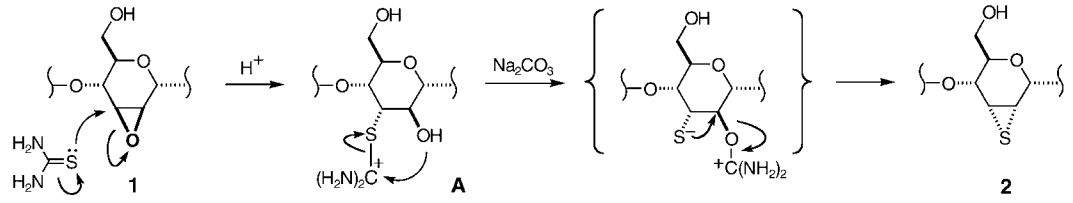


Figure 1. a) ^{1}H and b) ^{13}C NMR spectra of **2** measured in [D_6]DMSO.

remarkable upfield shifts of signals for both C-2 and C-3 ($\Delta\delta_{C2} = 8.9$ ppm and $\Delta\delta_{C3} = 16.1$ ppm relative to the corresponding signals for **1** suggest the replacement of all the oxygen atoms of the epoxide by sulfur substituents. The time-of-flight (TOF) mass spectrum of **2** showed a parent-ion peak for $[M+Na^+]$ at $m/z = 1143$, which is consistent with the molecular ion of **2** and strongly supports the above structural assignment.

The large coupling constant $J_{1,2} = 5.0$ Hz implies that the epithio groups are of allo-type rather than manno-type, after previous reports that $J_{1,2} = 4.4$ and 0 Hz for methyl 2,3-dideoxy-2,3-epithio-4,6-di-*O*-methyl-α-D-alloside or -mannoside, respectively.[9] Moreover, when the chemical shifts of C-2 and C-3 are compared with the corresponding values for mono-alloepoxy-β-cyclodextrin, the upfield shifts of $\Delta\delta_{C2} =$ 17.4 ppm and $\Delta\delta_{C3} = 16.1$ ppm are similar in magnitude. However, such similarity in the upfield shifts is not observed in comparison with mono-mannoepoxy-β-cyclodextrin, $\Delta\delta_{C2} = 10.3$ ppm and $\Delta\delta_{C3} = 17.9$ ppm, which again supports the proposed allo structure of **2**. Thus, compound **2** is assigned as per(2,3-dideoxy-2,3-epithio)-β-cycloallin. The coupling constant $J_{4,5} = 8.9$ Hz indicates that the 2,3-anhydro-2,3-epithioalloses have an $^OH_5$ conformation[10] rather than the ^5H_O conformation, and the structure of **2** is expected to be as shown in Scheme 1.

A plausible mechanism for the transformation of **1** to **2** is depicted in Scheme 2. On the basis of the known reaction behavior of mannoepoxide rings in cyclodextrins,[2] the conversion of **1** into **2** is believed to be initiated by the nucleophilic ring opening of epoxide residues with thiourea as the nucleophile. Under basic conditions, transfer of $(NH_2)_2C^+$ from 3-S to 2-O and subsequent intramolecular substitution of 2-$OC^+(NH_2)_2$ by 3-S^- take place to generate the episulfide residues. Formation of thioureidoaltropyranoside residues was confirmed by monitoring the progress of the reaction by TLC (silica gel, *n*PrOH/EtOAc/H_2O = 7:7:5 by volume). The appearance of a new spot with a retention factor $R_f \approx 0$ was noted which is much lower than the R_f values for both **1** ($R_f =$ 0.7) and the final product **2** ($R_f = 0.6$). The thioureidoaltropyranosides seem to be stable under acidic conditions until all the epoxide residues are transformed, and TOF-MS analysis of the reaction mixture clearly demonstrated a base peak at $m/z = 1540$, which is consistent with $[M-7]$ of perthioureido intermediate **A**. As soon as the reaction mixture was basified



Scheme 2. Plausible reaction mechanism for the formation of **2**.

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at room temperature, TLC analysis of the mixture revealed that the spot with $R_f = 0.6$ became more intense while that at $R_f = 0$ disappeared completely.

Molecular modeling studies were carried out to elucidate the 3D structure of **2** which is of pivotal importance in molecular design and recognition. As shown in Figure 2, all of the 2,3-epithioalloside units adopt $^{O}H_5$ conformations with Cremer–Pople ring-puckering parameters $Q = 0.504(5)$ Å, $\nu = 51.0(3)°$, and $\phi = 338(1)°$. The "straitjacket" effect of the 2,3-epithio rings enforces mean values of about 0.2° for the torsion angle about C1-C2-C3-C4 by forcing the pyranoside rings into this rigid conformation. Almost identical pyranoside geometries were also found in the solid-state structures of methyl 2,3-anhydro-4,6-bis(*O*-*p*-bromobenzyl)-α-D-mannopyranoside and its allo isomer[11] as well as per-2,3-anhydro-α-cyclomannin.[12]

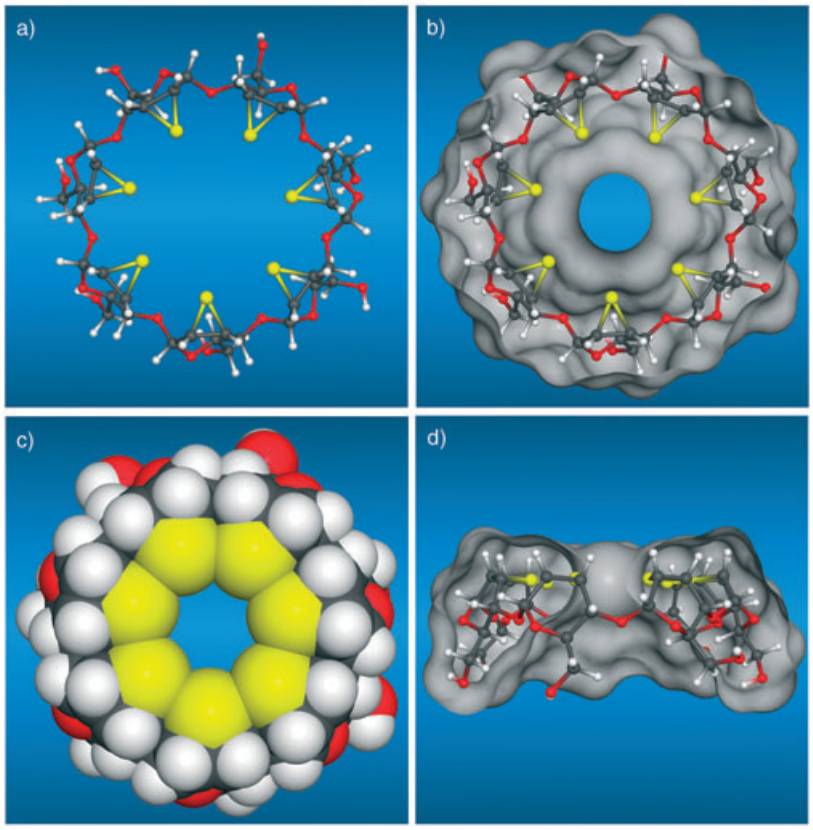

Figure 2. Molecular models of **2** displaying the arrangement of the inward pointing sulfur atoms and the reversed cavity shape of the macrocycle. (Left column (a, c): ball-and-stick and CPK-type models; right column (b, d): half-opened contact surface representations with models superimposed).

Corey–Pauling–Koltun (CPK) models and contact surface[13] representations reveal that the epithioalloside units of **2** are arranged to form a cavity whose shape is reversed from that of cyclodextrins; that is, the side on which the primary 6-OH groups reside is much wider than the other side (top side). The epithio rings are situated on the top side, parallel to the mean ring plane of the molecule, with the sulfur atoms pointing inwards and forming a circle with a radius of 3.7 Å (based on the atom positions). This arrangement of sulfur atoms substantially narrows the top side of the aperture to an inner width of about 3 Å only (diameter of the surface opening).

The unique 3D structure of **2** is of particular interest in molecular recognition. Furthermore, its seven episulfide rings make it a promising candidate for molecular recognition as well as further functionalization. As an example, thiirane **2** was converted quantitatively into the corresponding olefin species **3** simply by heating an alkaline solution of **2** in the presence of triphenylphosphine for a couple of hours. The TOF mass spectrum of **3** showed a parent-ion peak for $[M+Na^+]$ at $m/z = 919$. Seven different carbon atoms and eight different hydrogen atoms were recognized in the ^{13}C and ^{1}H NMR spectra, respectively, of **3**, consistent with C_7 symmetry. The large downfield shifts of resonances for atoms C-2 ($\delta = 127.0$ ppm), C-3 ($\delta = 130.0$ ppm), H-2 ($\delta = 5.76$ ppm), and H-3 ($\delta = 5.86$ ppm) suggest an olefinic structure.[2a]

In summary, we have reported the first successful synthesis of an epithio-β-cycloallin, which is an important intermediate in the functionalization of cyclodextrins and may equally serve as an artificial host molecule for molecular recognition.

Experimental Section

2: A solution of HCl (0.1M, 2 mL) containing **1** (29 mg, 0.029 mmol) and thiourea (720 mg, 9.3 mmol) was stirred at 90 °C for 30 min and then cooled down with a cold water bath. Sodium carbonate (28 mg, 0.26 mmol) and CH_3CN (0.9 mL) were added, and the solution was stirred at room temperature for 4 h. The solution was neutralized with HCl (1M), then diluted with 20% aq. EtOH (120 mL), and filtered through a cellulose acetate membrane (3 μm). The filtrate was purified by chromatography on a Lobar column (RP 18, size B) using initially an eluent of 20% aq. EtOH (500 mL) and then a gradient from 30% to 70% aq. EtOH (500 mL for each) to give **2** (18 mg, 56%); m.p.: 210 °C; $[\alpha]_D^{23} = +175.9$ ($c = 0.0433$ in 50% aq. ethanol); ^{1}H NMR (500 MHz, [D$_6$]DMSO, 35 °C, TMS): $\delta = 5.56$ (d, ^3J(H,H) = 5.0 Hz, 7H; H1), 4.54 (t, ^3J(H,H) = ca. 6.0 Hz, 7H; 6-OH), 4.28 (dd, ^3J(H,H) = 4.4, 8.9 Hz, 7H; H4), 3.69 (dd, ^3J(H,H) = 5.0, 6.6 Hz, 7H; H2), 3.62 (dd, ^3J(H,H) = ca. 5.5, ca. 10.5 Hz, 7H; 6R-H), 3.58 (dd, ^3J(H,H) = ca. 4.6, ca. 6.6 Hz, 7H; H3), 3.53–3.47 ppm (m, 14H; H5 and 6S-H); ^{13}C NMR (125 MHz, [D$_6$]DMSO, 35 °C, TMS): $\delta = 89.8$ (C1), 69.3 (C4), 67.4 (C5), 60.9 (C6), 39.8 (C2), 37.0 ppm (C3); TOF MS: $m/z = 1143$ $[M+Na^+]$.

3: Thiirane (**2**; 38 mg), sodium bicarbonate (8 mg), and triphenylphosphine (290 mg) were dissolved in aqueous dioxane (80% by volume, 3 mL), and the resultant solution was stirred at 95 °C for 170 min. After evaporation of the solvent, the residue was dissolved in water (70 mL), filtered through a membrane, and purified by chromatographey on a Lobar column (RP 18, size B) with a gradient elution from 40% to 80% aq. CH_3OH (500 mL for each) to give **3** (30 mg, 98%); m.p.: 188 °C; $[\alpha]_D^{25} = +105.5$ ($c = 0.133$ in 75% aq. methanol); ^{1}H NMR (500 MHz, [D$_6$]DMSO, 35 °C, TMS): $\delta = 5.86$ (dd, ^3J(H,H) = 1.4, 10.0 Hz, 7H; H3), 5.76 (ddd, ^3J(H,H) = 1.6, 3.0,

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10.0 Hz, 7H; H2), 5.12 (d, ^3J(H,H) = 3.0 Hz, 7H; H1), 4.62 (s, 7H; 6-OH), 4.15 (dd, ^3J(H,H) = 1.4, 8.9 Hz, 7H; H4), 3.80–3.71 (m, 14H; H5 and 6R-H), 3.68 ppm (dd, ^3J(H,H) = ca. 5.3, ca. 12 Hz, 7H; 6S-H); ^{13}C NMR (125 MHz, [D$_6$]DMSO, 35 °C, TMS): δ = 61.1 (C6), 69.7 (C4), 71.7 (C5), 93.3 (C1), 127.0 (C2), 130.0 ppm (C3); TOF MS: m/z = 919 [M+Na$^+$].

Molecular models and graphics were generated using the *MolArch*$^+$ program.[14]

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