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Shortcut Synthesis of β-Cyclomannin from β-Cyclodextrin

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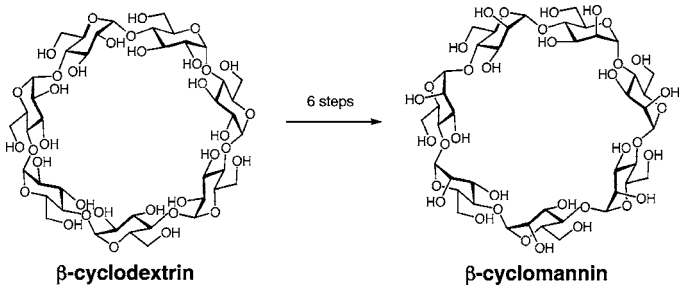
ABSTRACT



***β*-Cyclomannin, a cyclic oligosaccharide consisting of seven α-D-mannosides connected together by the (1→4) glycoside linkage, has been efficiently synthesized by the OsO_4 oxidation of heptakis(2,3-didehydroxy)-*β*-cyclodextrin which was prepared from *β*-cyclodextrin by a five-step transformation. The novel cyclooligosaccharide not only showed water solubility high enough to meet the requirement for drug formulation but also demonstrated strong binding ability toward guest molecules.**

Macrocyclic molecules have attracted much attention as molecular receptors.[1] Among them, cyclodextrins (CDs) have been in the central positions in the studies from the initial stage because of the diversity of their inclusion phenomena and enzymelike functions. Therefore many efforts have been made to prepare novel types of cyclooligosaccharides that behave better than CDs.[2]

Methodological development of chemical glycosylations enhanced chemical syntheses of non-glucose cyclooligosaccharides. α-, *β*-, and *γ*-cyclomannins consisting of six to eight α(1→4)-linked D-mannopyranosides were synthesized by cycloglycosylations of their corresponding linear precursors.[3,4] However, these syntheses not only require very long synthetic sequences in the constructions of the linear precursors but also suffer from undesirable side reactions and poor stereoselectivity in the final cycloglycosylations. Therefore, the overall yields are extremely low. Although enzymatic cycloglycosylation can be adopted as an alternative choice for the final step,[5] the target cyclooligosaccharides are not obtained in large enough amounts for further investigation of their functions and structures.

On the other hand, the discoveries of enzymes that convert natural linear oligosaccharides into cyclooligosaccharides have enabled the availability of the cyclooligosaccharides in large enough amounts for further investigation,[6] although

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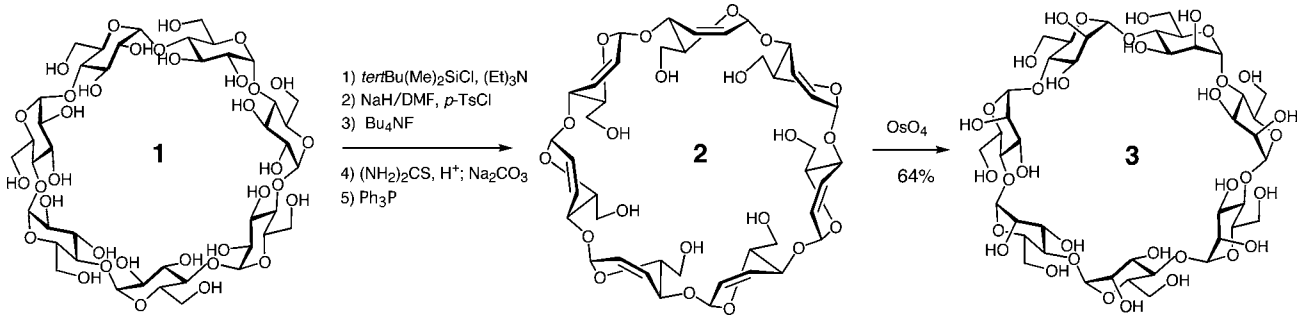
Scheme 1. Preparation of β-Cyclomannin **3** from Olefin **2** Which Is Available via Five Steps from β-CD **1**



these methodologies are obviously limited by the available sorts and amounts of enzymes and homopolysaccharides.

In this situation, CDs have been reconsidered as starting materials of cyclooligosaccharides because they are commercially available in high qualities and at low prices. Thus, effective and stereoselective transformations of all glucoside units to other sugar units gave non-glucose cyclooligosaccharides: per(3,6-anhydro)-CDs,[7] per(2,3-anhydro)-cyclomannins,[8] cycloaltrins,[9] per(3-amino-3-deoxy)-β-cycloaltrin,[10] and per(3-deoxy)-cyclomannins.[11] Recently, we added per-(2,3-dideoxy-2,3-epithio)-β-cycloallin and per(2,3-didehydroxy)-β-CD **2** as new members to this family.[12]

In this paper, we report the preparation and binding properties of β-cyclomannin **3**. The CD-based methodology for the synthesis of **3** is depicted in Scheme 1. A five-step transformation of β-CD **1** afforded the olefin **2**,[12] and the latter was treated with OsO_4/*N*-methylmorphorin-*N*-oxide in water to give cyclomannin **3** in 64% yield.[13] This synthetic process is dramatically short compared with the literature one.[3] Moreover, the literature methodology based on the cycloglycosylation of natural linear oligosaccharides is not applicable in the synthesis of **3** because $\alpha(1\rightarrow4)$-linked poly-D-mannosides are not available to the best of our knowledge.

Oxidation of the olefin **2** by OsO_4 proceeds smoothly under very mild reaction conditions (130 min at 40 °C in an aqueous solution). The complete conversion of C=C to the glycol structure is confirmed by the time-of-flight (TOF) mass spectrum of **3** which showed a parent peak for [M + Na^+] at m/z = 1157 that is consistent with the molecular ion of **3**. The NMR spectra of **3** were very simple (Figure 1), and the assignments of the signals with the aid of ^{1}H,^{1}H−

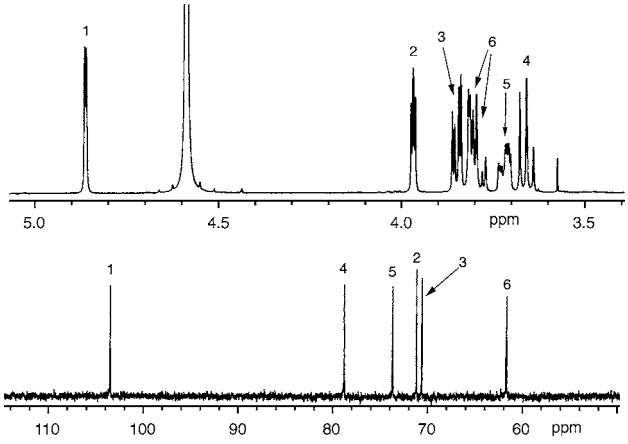


Figure 1. ^{1}H and ^{13}C NMR spectra of β-cyclomannin **3** in D_2O (CH_3CN as the internal standard). The assignments were made with the aid of ^{1}H,^{1}H− and ^{1}H,^{13}C−COSY experiments.

and ^{1}H,^{13}C−COSY spectra revealed the C_7 geometrical symmetry of **3**; that is, all seven sugar units are magnetically equivalent. Examination of the observed coupling constants ($J_{1,2}$ = 2.3, $J_{2,3}$ = 3.3, $J_{3,4}$ = 9.0, and $J_{4,5}$ = 9.0 Hz) suggested a $^4C_1$ mannopyranoside structure for the sugar units. Because

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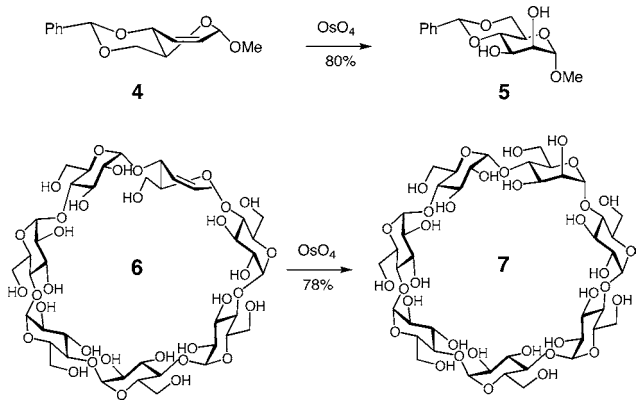
(13) To the aqueous solution (2.9 mL) containing olefin **2**[12] (41 mg) were added the solutions of aqueous 50% *N*-methylmorpholine-*N*-oxide (4.4 mL) and aqueous 4% OsO_4 (0.53 mL), and the resultant mixture was stirred at 40 °C for 130 min. After being concentrated in vacuo, the reaction solution was added dropwise to a mixture (60 mL) of acetone and methanol (4:2 v/v). The white precipitates were collected by filtration, dissolved in water (100 mL), and chromatographed on a Lobar column (Rp 18, size B) with an elution of water (150 mL) and a second gradient elution from water to 20% aqueous MeOH (500 mL for each) to give **3** (33.3 mg, 64%): mp 190 °C; $[\alpha]_D^{25}$ = +61.7 (c = 0.125 in H_2O); ^{1}H NMR (500 MHz, D_2O, 35 °C, MeCN) δ = 4.86 (d, ^3J(H,H) = 2.3 Hz, 7H, H1), 3.97 (dd, ^3J(H,H) = 2.3, 3.3 Hz, 7H, H2), 3.85 (dd, ^3J(H,H) = 3.3, 9.0 Hz, 7H, H3), 3.83 (s, dd, ^3J(H,H) = 2.3, 9.0 Hz, 7H, 6R-H), 3.79 (dd, ^3J(H,H) = 4.6, 9.0 Hz, 7H, 6S-H), 3.72 (ddd, ^3J(H,H) = 2.3, 4.6, 9.0 Hz, 7H, H5), 3.66 (t, ^3J(H,H) = 9.0, 7H, H4); ^{13}C NMR (125 MHz, D_2O, 35 °C, MeCN) δ = 103.5 (C1), 78.8 (C4), 73.7 (C5), 71.2 (C2), 70.7 (C3), 61.7 (C6); TOF MS m/z = 1157 [M + Na^+].

the absolute configurations of C-4 and C-5 are the same as those of β-CD, the large $J_{4,5}$, which is comparable to that of β-CD and reveals the trans-diaxial displacement pattern of H-5 and H-4, strongly implies that the pyranosides take a $^4C_1$ chair conformation. The similarly large $J_{3,4}$ means that the H-3 is also in axial orientation, and the O-3 is trans to the O-4. Accordingly, the mannoside structure can be deduced on the basis of the cis geometrical selectivity of OsO_4 oxidation. The small coupling constants $J_{1,2}$ and $J_{2,3}$ also support the $^4C_1$ mannopyranoside structure. Moreover, **3** was the same as that reported for β-cyclomannin[3] in ^{1}H and ^{13}C NMR spectra. Thus, compound **3** is assigned to β-cyclomannin.

The successful isolation of β-cyclomannin indicates that the oxidation is highly selective for mannopyranoside over allopyranoside, otherwise 1.5 dozens of hetero-cyclooligosaccharides with different allo-/manno- ratios would be generated from **2**, making it very difficult to separate any one product from the reaction mixture. Similar selectivity was also observed in the oxidation of methyl 4,6-*O*-benzylidene-2,3-didehydroxy-α-D-glucopyranoside **4**[14] and monoolefin **6**,[15] which gave only the corresponding mannopyranosides **5** and **7**,[16] respectively (Scheme 2). The

Scheme 2. Transformation of Olefins **4** and **6** to Mannosides **5** and **7**, Respectively



formation of mannosides was suggested by the all-axial displacements of the H-3, H-4, and H-5 protons which were elucidated by the large coupling constants $J_{3,4}$ and $J_{4,5}$ of **5** and **7**. Moreover, acid hydrolysis of **7** demonstrated that it was composed of one mannose and six glucoses.

The axial displacement of the 2-OHs of **3** prevents each 2-OH from forming an intramolecular H-bond with the 3-OH of its adjacent sugar unit. Evidence for this was collected by ^{1}H NMR measurements. The ^{1}H NMR of **3** in DMSO-d_6 showed two doublets for 2-OH and 3-OH protons that were identified by the ^{1}H,^{1}H−COSY spectrum. α-Methyl D-mannopyranoside represents the basic structure of the sugar units of **3** and was taken as a reference compound for the elucidation of a H-bonding interaction between any two adjacent pyranosides. As shown in Table 1, the chemical

Table 1. ^{1}H NMR Chemical Shifts δ [ppm],[a,b] Chemical Shift Differences $\Delta\delta$ [ppm], and Coupling Constants $^3J_{OH,CH}$ [Hz] for the Hydroxyl Protons in DMSO-d_6 at 35 °C

	2-OH			3-OH		
	δ	$\Delta\delta$	J	δ	$\Delta\delta$	J
β-cyclomannin (**3**)	4.66	0.02	4.8	4.55	0.08	6.9
α-methyl D-mannopyranoside	4.64[d]		4.6 or 5.5	4.47		6.0
β-CD (**1**)[c]	5.52	1.11	6.7	5.48	1.02	2.5
α-methyl D-glucopyranoside[c]	4.41		6.6	4.46		5.1

[a] Chemical shifts relative to TMS. [b] Chemical shifts for the H-1's of **3**, α-methyl D-mannopyranoside, β-CD, and α-methyl D-glucopyranoside are 4.72, 4.49, 4.68, and 4.32 ppm, respectively. [c] Ref 17. [d] Overlapped with the signals of 4-OH.

shifts and coupling constants ($J_{2OH,H2}$ and $J_{3OH,H3}$) of the 2-OH and 3-OH protons of **3** are quite similar to the corresponding values of α-methyl D-mannopyranoside. However, β-CD, which is well-known to have strong H-bonding between the 2-OH and 3′-OH of adjacent glucosides, displays very large downfield shifts ($\Delta\delta$ > 1 ppm) for both the 2-OH and 3-OH protons together with a half-decreased coupling constant for 3-OH in comparison with their component analogue α-methyl D-glucopyranoside in DMSO-d_6[17] as well as in D_2O.[18] These results imply that cyclomannin **3** has no intramolecular H-bonding interaction between the 3-OHs and the 2′-OHs of neighboring mannosides even in DMSO.

Because the axial 2-OH of **3** disrupts the intramolecular H-bonding, releasing itself and 3-OH for intermolecular H-bonding with bulk water, compound **3** is much more water-soluble than β-CD. A preliminary assay indicated that the water solubility of **3** is more than 30 g/10 mL at 25 °C whereas that of β-CD[19] is 0.19 g/10 mL at 27 °C.

Differently from β-CD, β-cyclomannin **3** has the 2-OHs directed to the outside of the cavity. This alternation of the

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(16) Synthesis of **5**: an olefin **4**[14] (25 mg), *N*-methylmorpholine-*N*-oxide (23.4 mg), and aqueous 0.1 M OsO_4 (40 μL) solution was added to a mixed solvent composed of water (0.5 mL) and MeCN (1 mL). The resultant mixture was stirred at room temperature for 6 days. After the addition of a saturated aqueous solution of Na_2SO_3 (2 mL), the reaction mixture was extracted three times with AcOEt. The extracts were combined, washed with 1 M HCl and then water, and dried over Na_2SO_4. Evaporation of the solvents afforded crude **5** (28.4 mg) which was purified by preparative TLC on silica gel (eluted with of AcOEt) to give pure **5** (22.7 mg, 80%): ^{1}H NMR (500 MHz, $CDCl_3$, 35 °C, TMS) δ = 7,49 and 7.37 (m, 5H, C_6H_5), 5.57 (s, 1H, benzylic H), 4.77 (s, 1H, H1), 4.29 (dd, ^3J(H,H) = 3.7, 9.2 Hz, 1H, H6), 4.08−4.05 (m, 2H, H2 and H3), 3.92 (t, ^3J(H,H) = 9.2 Hz, 1H, H4), 3.86−3.81 (m, 2H, H5 and H6), 3.40 (s, 3H, OCH_3), 2.73 and 2.71 (2H, 2- and 3-OHs); EI MS *m/z* (%) = 282 (65) [M^+], 105 (100) [$C_7H_5O^+$]. Synthesis of **7**: a procedure similar to that for the preparation of **3** was used starting with olefin **6**[15] (316 mg) to give the product **7** (253 mg, 78%): ^{1}H NMR (mannoside, 500 MHz, D_2O, 35 °C, MeCN) δ = 4.86 (d, ^3J(H,H) = 2.1 Hz, 1H, H1), 4.04 (broad t, 1H, H2), 4.00 (dd, ^3J(H,H) = 3.3, 8.6 Hz, 1H, H3), 3.69 (t, ^3J(H,H) = 8.9 Hz, 1H, H4); ^{13}C NMR (mannoside, 125 MHz, D_2O, 35 °C, MeCN) δ = 104.0 (C1), 79.8 (C4), 71.1 (C3), 70.6 (C-2); FAB MS *m/z* = 1135 [M + H^+].

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orientation of 2-OHs makes the inside of the cavity more hydrophobic and the outside more hydrophilic, as comprehensively demonstrated by the molecular lipophilicity potential profiles of α-cyclomannin and α-CD[20,21] generated by molecular modeling. Therefore, cyclomannins may exhibit interesting binding behaviors toward a hydrophobic guest.

β-Cyclomannin **3** can bind guest molecules in its cavity, as *β*-CD does. Binding of methyl orange by **3** resulted in a blue shift of the absorption around 485 nm and induced circular dichroism (ICD) absorption as well. Titration of sodium 1,8-anilinonaphthalenesulfonate (1,8-ANS) with **3** enhanced the fluorescence intensity and made the emission blue shifted. The Scatchard plots of the titration data gave good linearity, suggesting that 1:1 host−guest complexation occurred. The binding constant was estimated to be 50 M^{-1}. The degree of fluorescence enhancement of 1,8-ANS had been used as a measure for hydrophobicity of the hydrophobic pocket of host molecules including CDs.[22] The 1:1 complex of **3** and 1,8-ANS demonstrated 1.6 times stronger fluorescence intensity than the corresponding complex of *β*-CD, indicating that **3** has a more strongly hydrophobic cavity than *β*-CD. However, the binding constants of **3** for methyl orange (pH 6.86) and 1,8-ANS (pH 7.40) at 25 °C were 1850 and 50 M^{-1}, not as high as expected and even slightly smaller than the corresponding ones of *β*-CD, 3160 and 69.0 M^{-1}, respectively. These results may imply that, although the enhanced hydrophobicity of the cavity of *β*-cyclomannin favors the binding of hydrophobic guest molecules, this effect is canceled out by the countereffect of decreased rigidity due to the disruption of the intramolecular hydrogen bonding mentioned above. Similar enthalpy−entropy compensation effects are frequently observed in host−guest systems.[23] Interestingly, the complex of *β*-cyclomannin and methyl orange gave a different ICD spectrum from that of the *β*-CD complex (Figure 2),

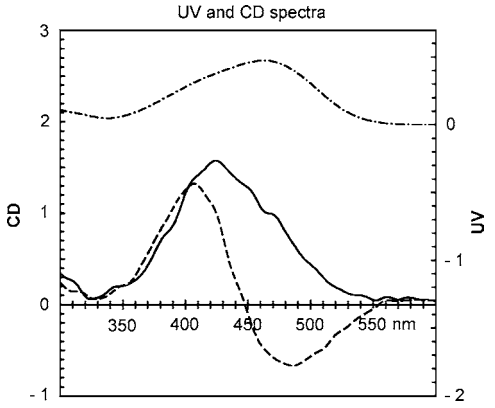

Figure 2. UV−vis spectrum of methyl orange (-·-, 2.0×10^{-5} M) and circular dichroism spectra of methyl orange (2.0×10^{-5} M) in the presence of *β*-CD (—, 1.2×10^{-3} M) and *β*-cyclomannin **3** (- -, 1.2×10^{-3} M) in pH 6.86 phosphate buffer solutions.

indicating that the change of the sugar components alters the chirality of the cavity. To the best of our knowledge, these spectral examinations of inclusion complexation are the first cases with respect to chemically synthesized cyclooligosaccharides.

We succeeded in the synthesis of *β*-cyclomannin **3** through six steps via **2** from *β*-CD. This is a dramatically shortened process compared with the reported stepwise synthesis from monosaccharides. Because **3** became easily available in a sufficient amount for investigation concerning its properties, we demonstrated for the first time its enhanced solubility in water, its ability of guest binding, and the spectra of a chromophoric guest molecule induced by complexation.

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Supporting Information Available: Full NMR spectroscopic data for compounds **3**, **5**, and **7** and the fluorescence titration data of **3** and *β*-CD. This material is available free of charge via the Internet at http://pubs.acs.org.

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