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A *Vector-Selective* Reaction Enables Efficient Construction of Specific Topology upon the Primary Side of *β*-Cyclodextrin[§]

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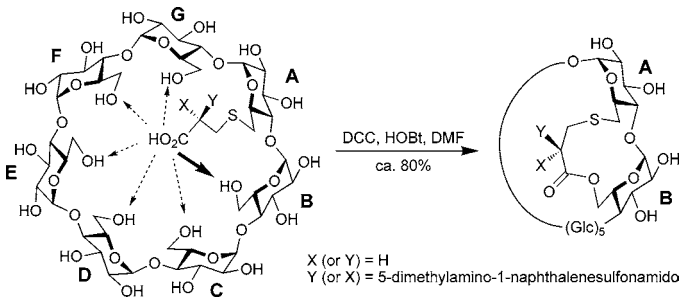
ABSTRACT



***N*-Dansylcysteines attached on the primary side of *β*-cyclodextrin reacted with the saccharide hydroxyl groups in a *vector-selective* manner, affording the corresponding lactones. The desired topology of the lactones can be efficiently constructed simply by the selection of the proper enantiomer of D/L-cysteines. In comparison with the *exo*-lactone, the *endo*-lactone displayed 4 times stronger fluorescence intensity, stronger binding affinity to sodium adamantanecarboxylate, and 15 times larger signal changes in fluorescence intensity upon binding.**

Modification of cyclodextrins (CDs)[1] is essential to the development of artificial receptors, supramolecular catalysts, drug carriers, and so forth.[2] The functionalities are usually connected to CDs by *flexible spacers*. However, such functional CDs can adopt many conformations, most of which do not favor the cooperation between the functionality and CD cavity or which even prevent the functional CDs from performing the desired selectivity. The capping technique, which uses one organic segment to link two glucose units on the same rim, has proved efficient in controlling the geometry around the cavity portals.[3,4] By reacting pyridoxamine-bearing ethanedithiol with 6^A,6^B-diiodo-*β*-CD, Breslow and colleagues synthesized two pairs of 6^A,6^B-capped CDs (*endo*- and *exo*-, with the pyridoxamino group located near A or B glucose unit) and demonstrated that they displayed different selectivity in the transamination reaction of pyruvic acids.[4] However, the difficulty in accessing the desired geometry hampered the development of research along this direction. Recently, we found that the *N*-dansyl-L-cysteine group attached on the primary side of *γ*-CD reacted with only 6^B-OH of *γ*-CD to form the lactone with

[§] Dedicated to the memory of Professor Yoshihiro Matsumura.

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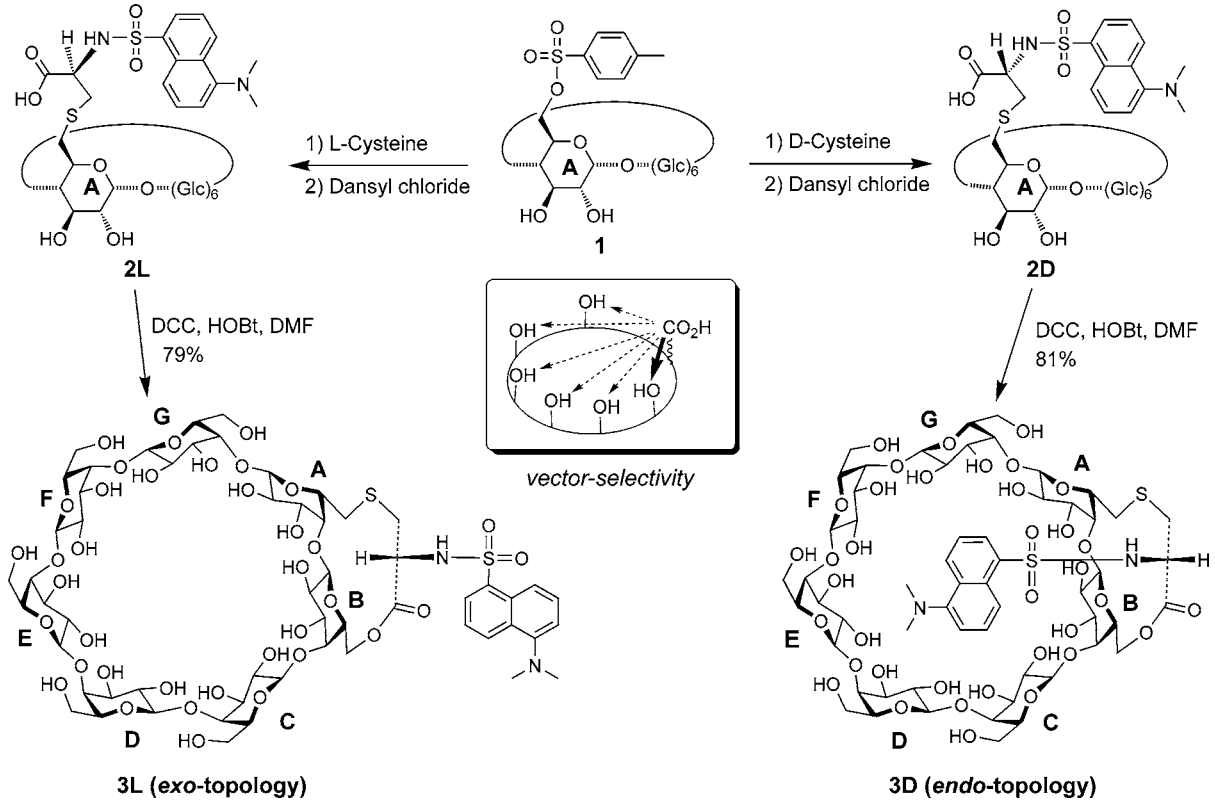
Scheme 1. Construction of *endo*- and *exo*-Topologies on the Primary Side of β-Cyclodextrin



exo-topology.[5] Herein we report that the latter reaction is *vector-selective*[6] and ensures the efficient construction of the desired topologies around the portal of the β-CD simply by selecting L- or D-cysteine as the capping segment (Scheme 1).

6-(*N*-Dansyl-L-cysteine)-β-CD (**2L**), which was obtained via tosylation of one 6-OH of β-CD (**1**), substitution with L-cysteine, and final reaction with dansyl chloride, underwent an intramolecular condensation in DMF in the presence of DCC and HOBt to give the corresponding lactone **3L**[7] exclusively. Structural determination indicated that **3L** has the 6^B-OH being acylated and thus has the *exo*-topology just as the γ-analogue[5] has. The result implies the lactone formation reaction took place both on γ- and β-CDs with similar selectivity to give the *exo*-lactones.

In order to access the *endo*-topology, we tried the reaction in aqueous solutions. If the reaction selectivity was governed by the bulky dansyl group, it would become reversed when the reaction media is switched to aqueous solutions that favor the self-inclusion of the dansyl group in the CD cavity. However, no lactones were identified although various carboxyl activating reagents including 4-(4,6-dimethoxy-1,3,5-triazin-2-yl)-4-methylmorpholinium chloride and EDC were examined.

The utilization of D-cysteine instead of L-cysteine gave an interesting result. Compound **2D** reacted smoothly in DMF in the presence of DCC and HOBt, affording lactone **3D** in 81% yield.[7] The reaction also took place at the 6^B-OH, and in this case, the product **3D** has the desired *endo*-topology.

The regiochemistry of compounds **3** was clarified by the combination of the enzymatic degradation of the macrocycles and subsequent post-source decay (PSD) TOF MS measurement (Scheme 2).[8] Compounds **3** decomposed to the corresponding trisaccharides **4** under the enzyme action of α-amylase,[7] indicating the acylation of one sugar unit adjacent to unit A. Because the α-amylase does not cleave the glucoside bond of modified glucoside residues,[9] the argument becomes whether the acylated glucoside residue is in the middle or at the nonreducing terminal of the trisaccharides. Compounds **4** were reduced to **5**,[7] and then PSD-MS measurements were applied. Both **5D** and **5L** shared the same parent molecular ions and the two major fragment peaks at *m*/*z* 689 (40%) and 669 (12%) in the PSD-MS spectra, which correspond to the cleavages at I and II, respectively (Figure 1). This result indicates that **5D** and **5L** have the same sugar sequence. The formation of the fragment ion *m*/*z* 689 (M + Na − 162) strongly suggests that the glucoside residue recovered by reduction of the lactone

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(7) For the synthetic procedure and structural data: cf. Supporting Information.

(8) Yu, H.; Makino, Y.; Fukudome, M.; Xie, R.-G.; Yuan, D.-Q.; Fujita, K. *Tetrahedron Lett.* **2007**, *48*, 3267−3271.

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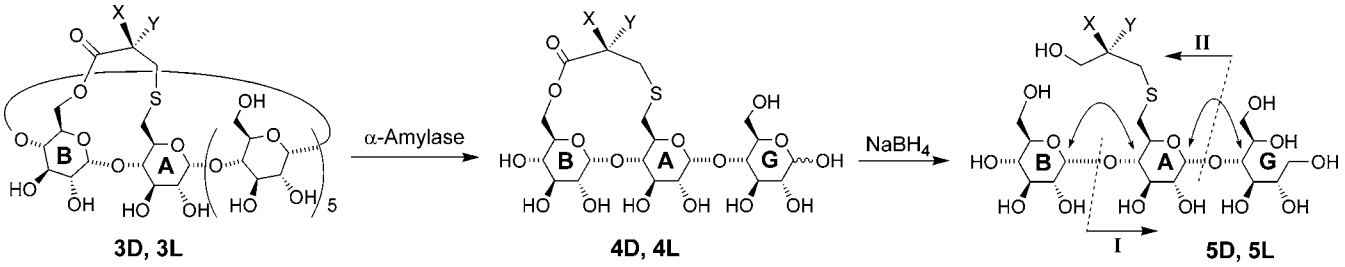
Scheme 2. Amylase-Promoted Degradation of the Lactones **3** and the Fragmentation Patterns of **5** Observed in the PSD-MS Spectra[a]



[a] L: X = 5-dimethylamino-1-naphthalenesulfonamido, Y = H; D: X = H, Y = 5-dimethylamino-1-naphthalenesulfonamido. I and II denote the fragmentation patterns observed in the PSD-MS spectra. The double-arrowed curves indicate that HMBC signals were observed between the two positions.

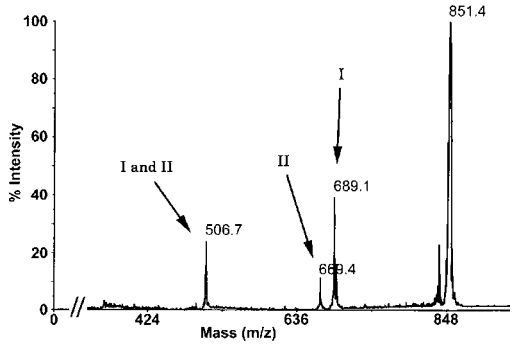


Figure 1. Post-source decay mass (PSD-MS) spectrum of **5D**.

moiety should be at the nonreducing end. The peak at *m*/*z* 507 corresponds to the two-site cleavage at both I and II.[10] Therefore, the esterified OH of both **3D** and **3L** should be 6^B-OH, the same position where *N*-dansyl-L-cysteine-γ-CD reacted.[5]

This structural assignment was further confirmed by detailed NMR analysis of compound **5D** (cf. SI). The carbon $C4^A$ (δ 82.3 ppm) of the S-bearing glucopyranoside appeared in the normal region (around δ 80 ppm) of the C4 carbons of CDs, whereas the C4 of the unmodified glucopyranoside resonated at δ 69.4 ppm, a chemical shift within the typical range of the hydroxyl-substituted secondary carbons of saccharides. This observation suggests that the unmodified glucopyranoside is at the nonreducing terminal, that is, the sugar unit B. The long-range $C4^A$−$H1^B$ and $H4^A$−$C1^B$ heteronuclei correlations, which were clearly presented in the HMBC[11] spectrum, provided solid evidence for the sugar sequence of **5D**.

It is interesting to note that both the D- and L-cysteine groups react selectively with the 6^B-OH to form the corresponding lactones with different topologies. No obvious reactions of other hydroxyl groups were detected under the experimental conditions. The orientation of the bulky dansyl group of **2** does not influence the reaction selectivity; otherwise, both the steric hindrance and the self-inclusion between the dansyl group and the CD moiety would direct the carboxylic group of the D-cysteine to the hydroxyl group on the side opposite to where the L-cysteine reacted. It is most likely that the flexible cysteine moiety differentiates the many OH groups not only by distance (*magnitude*) but also by *direction*. Therefore, the reaction is *vector-selective* (Scheme 1), and the selectivity is supposed to stem from the intrinsic structural feature of CDs[6] and the exact structural match between the CD and cysteine.

Due to the topology effects, the lactones **3D** and **3L** perform different photophysical and binding properties. As shown in Figure 2, the *endo*-lactone **3D** displayed fluorescence intensity comparable to that of **2**, while the *exo*-lactone **3L** emitted much more weakly. Because the fluorescence of the dansyl moiety is known to be environmentally sensitive, this difference implies that **3D** has a self-inclusion structure, whereas the dansyl group of **3L** is outside the cavity. The fluorescence intensity of both **3D** and **3L** increased linearly with the concentration up to 1×10^{-4} M, indicating that neither lactone forms an intermolecular complex up to this concentration. Upon addition of sodium adamantanecarboxylate (AdCA), the *endo*-lactone **3D** showed 78% quenching of the fluorescence, whereas the *exo*-lactone **3L** showed only 22% quenching (Figure 3). This observation indicates that the *endo*-lactone **3D** still has enough flexibility

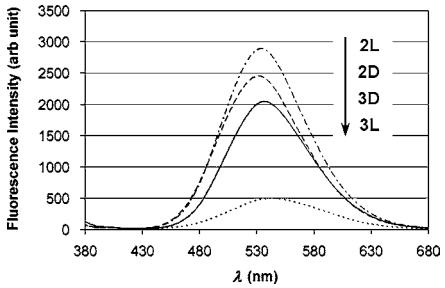


Figure 2. Fluorescence spectra of **2D** (- - -), **2L** (—·—), **3D** (—), and **3L** (···) in pH 8 phosphate buffer solutions (1.0×10^{-5} M).

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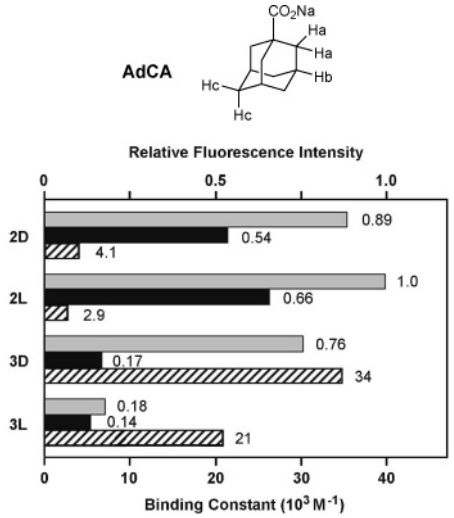

Figure 3. Relative fluorescence intensity of **2** and **3** (1.0×10^{-5} M) in the absence (gray bars) and presence (black bars) of 3.0×10^{-4} M AdCA, and the binding constants with AdCA (striped bars). All measurements were made at 25 °C in pH 8 phosphate buffer solutions.

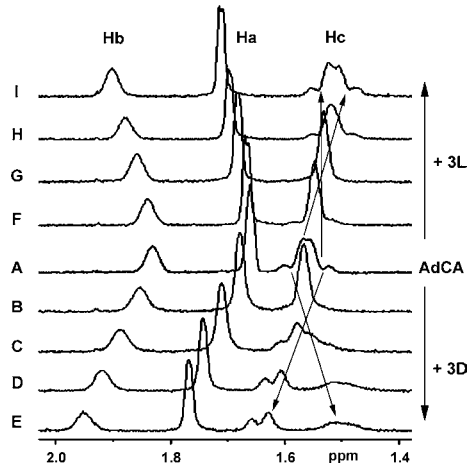

Figure 4. ^{1}H NMR spectra of AdCA in D_2O solutions in the absence of hosts (A), and in the presence of **3D** (B-E) and **3L** (F−I). AdCA/host (molar ratio): 1/0 (A), 1/0.2 (B and F), 1/0.6 (C and G), 1/1 (D and H) and 1/3 (E and I).

to ensure the inside−outside conformational iteration and AdCA can exclude the fluorophore from the CD cavity to generate a large output signal which is very important for molecular sensing.[12] Compounds **2D** and **2L** have comparable binding ability toward AdCA. The lactone formation increased the binding strength of **2D** and **2L** by ca. 8 times (Figure 3). It is interesting to note that **3D** has stronger binding ability than **3L** although the loss of hydrophobic interaction relating the exclusion of the self-included dansyl group from the CD cavity should be compensated.[13]

AdCA shows four groups of proton signals (Figure 4A) corresponding to Ha (1.63 ppm), Hb (1.81 ppm), and the two diastereotopic Hc protons (centered at 1.55 ppm). They were shifted unequally by **3D** (Figure 4B−E) and **3L** (Figure 4F−I), supporting the binding in the CD cavity. Ha and Hb showed downfield shifts toward both hosts, whereas the Hc protons were shifted differently. The *endo*-lactone **3D** shifted one Hc proton to the upfield and another to the downfield. The *exo*-lactone **3L** shifted one Hc proton to the upfield while leaving another unaffected. The different shift patterns of Hc induced by **3D** and **3L** should reasonably be a reflection of the anisotropic effect of the dansyl moiety. Therefore, AdCA is likely to bind the cavity by locating its carboxylic group near the secondary side of the CD cavity.

In summary, we found a *vector-selective* reaction to efficiently construct the desired topology on the primary side of β-CD and demonstrated that the *endo*-lactone **3D** and *exo*-lactone **3L** synthesized thereby have quite different photophysical and binding behaviors. Expanding this *vector-selective* reaction (for example, by introducing functionalities other than the dansyl group) and the photophysical measurements of the topology-controlled CD derivatives are currently in progress.

Acknowledgment. A generous gift of CDs from Japan Maize Products Co. Ltd are acknowledged.

Supporting Information Available: Synthetic procedures and full NMR spectroscopic data for compounds **2**, **3**, and **5**, and the fluorescence and NMR titration data of **3**. This material is available free of charge via the Internet at http://pubs.acs.org.

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