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Selective functionalization of β-cyclodextrin: efficient conversions of 2,3-*allo*epoxypyranosides to 2,3-*manno*epithiopyranosides

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Abstract—A two-step one-pot method was established to efficiently convert up to three 2,3-*allo*epoxypyranoside residues to the 2,3-*manno*epithiopyranosides within the β-cyclodextrin belts.

Many artificial enzymes have been made by the functionalizations of cyclodextrins (CDs) whose cavities afford substrate-binding sites.[1] Mono- to poly-functionalizations including homo and hetero ones on the primary hydroxyl sides have been extensively studied.[1,2] With respect to the secondary hydroxyl sides, there have been not so many reports on mono-functionalizations,[1–3] even less on homo-bifunctionalizations,[1–3] and none on hetero-bifunctionalizations except our recent studies.[4,5] The main problem seems to be the limited availability of versatile intermediates including 2,3-epoxy-CDs[1–3] for incorporating functionalities. The development of the thia- and aza-analogues of the 2,3-epoxy-CDs is expected to open a new way to the hereo-bifunctionalizations of CDs. Recently, we have reported the preparation of 2,3-*allo*epithio-β-CD[4] **2** from 2,3-*manno*epoxy-β-CD[4] **1** (Scheme 1), and demonstrated an example of using **2** as a potential versatile scaffold to prepare β-CDs *heterogeneously bi-functionalized* at the secondary hydroxyl sides. However, this method suffers from the formation of a considerable amount of the olefin **3** and it is not applicable in the preparation of CD derivatives with two or more epithio units. On the other hand, 2,3-*manno*epoxy-β-CD **1** has been demonstrated to react with a nucleophile to give a pair of functional CDs that are structurally complementary to that the 2,3-*allo*epoxy-β-CD **4** can afford.[3a,6]

Therefore the *manno* analogues of *allo*epithio-β-CD **2** should be of equal significance. In this Letter, we describe a two-step one-pot method for the 2,3-*manno*episulfidation which allows the efficient construction of up to three 2,3-*manno*epithio units within the CD belt.

The synthetic strategy for the 2,3-*manno*epithio-β-CDs **5**, **9**, **10** and **11** is depicted in Scheme 2. The 2,3-*allo*-epoxy-β-CDs were reacted with thiourea in acidic aqueous solutions and then treated with alkali solutions to afford the 2,3-*manno*epithio-β-CDs in moderate to good yields.

A solution of 0.2 M HCl (5 ml, 1 mmol) containing $2^A,3^A$-*allo*epoxy-β-CD **4**[7] (500 mg, 0.45 mmol) and thiourea (4.7 g, 22.4 mmol) was stirred at 70 °C for 1.5 h and then cooled down with a cold water bath. After sodium carbonate (77 mg, 0.73 mmol) was added, the solution was stirred at room temperature for 5 min. The solution was neutralized with 1 M HCl and then poured into acetone (500 ml). The precipitates were collected by membrane-filtration and dissolved in water (100 ml). Chromatography of the solution on a Lobar column (Rp-18, size C) with a gradient elution from 3% aq EtOH to 7% aq EtOH (1 l for each) gave **5** (324 mg, 64.0%).

The 2D COSY NMR spectra of **5** in D_2O enabled the assignment of most of the protons and carbons of sugar unit A (Fig. 1): δ_H 5.32 (s, H-1^A), 3.36 (d, $J_{2,3} = 6.3$ Hz, H-2^A), 3.42 (H-3^A), and 4.15 (d, $J_{4,5} = 9.3$ Hz, H-4^A); δ_C 100.3 (C-1^A), 34.3 (C-2^A), 36.4 (C-3^A), 73.3 (C-4^A), 71.3

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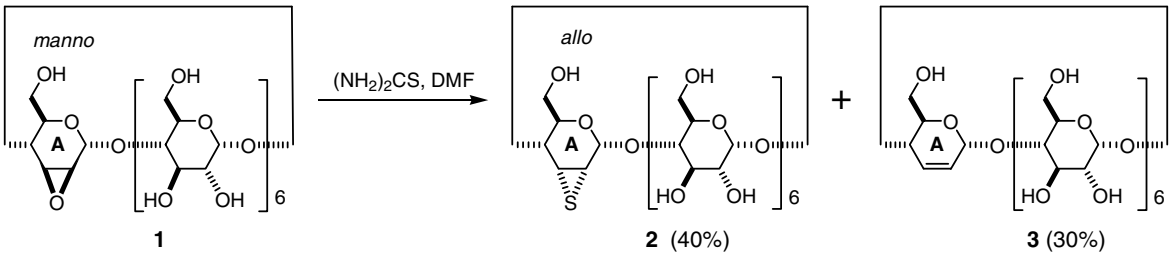
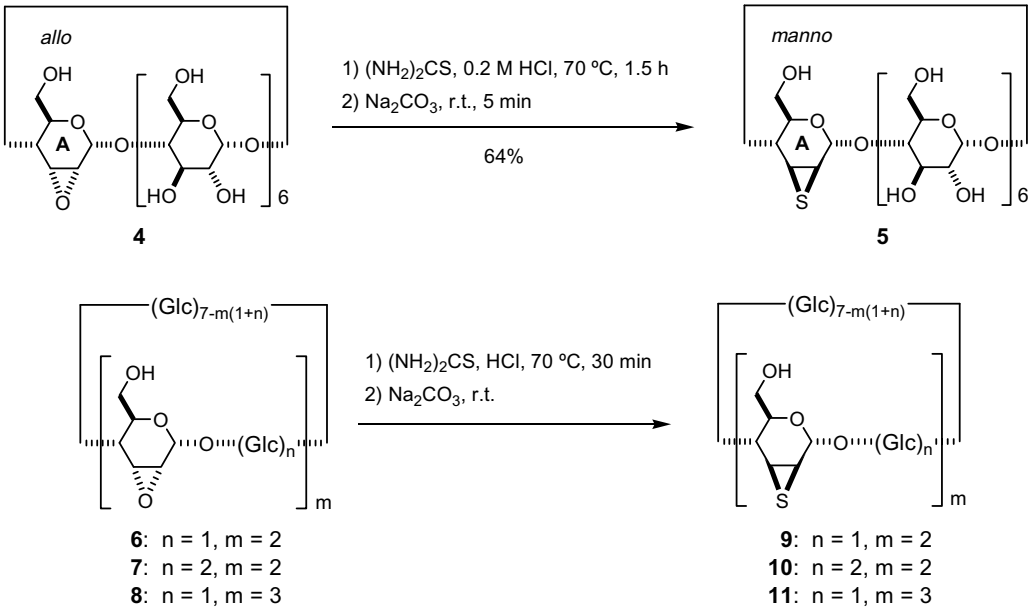


Scheme 1. Conversion of 2,3-*manno*epoxy-β-CD to 2,3-*allo*epithio-β-CD with thiourea in DMF is accompanied by the formation of the olefin species.



Scheme 2. The two-step one-pot reactions of 2,3-*allo*epoxy-β-CDs with thiourea ensure the selective syntheses of 2,3-*manno*epithio-β-CDs.

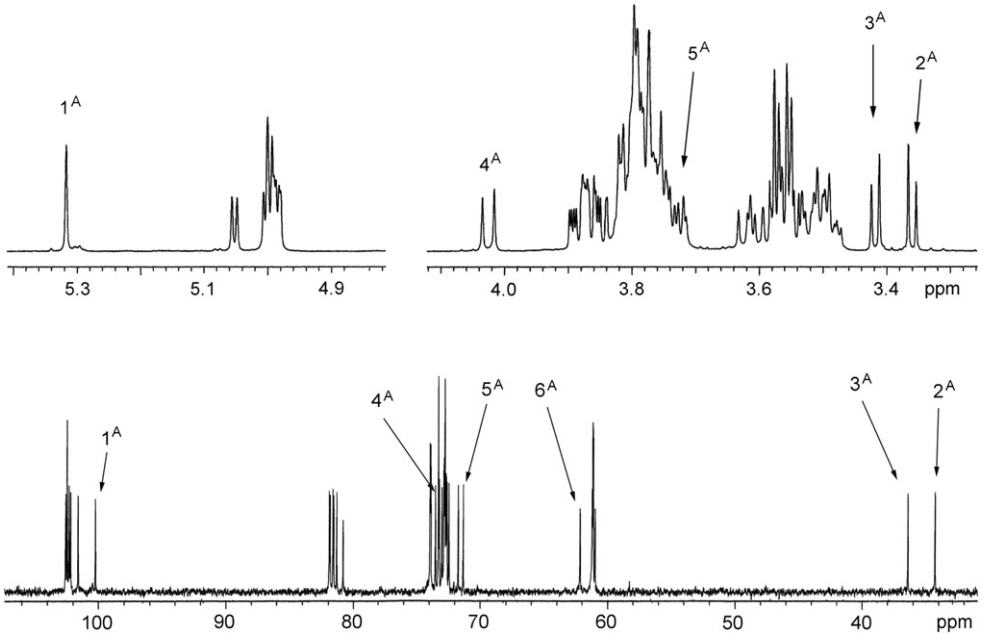


Figure 1. ^{1}H and ^{13}C NMR spectra of **5** in D_2O.

(C-5^A), and 62.2 (C-6^A). The remarkable upfield shifts of both C-2^A and C-3^A ($\Delta\delta = 22.9$ and 18.6, respectively, compared with those of 2^A,3^A-*allo*epoxy-β-CD **4**[7]) reasonably suggest the replacement of the oxygen atom of the epoxide by a sulfur-substituent. TOF-MS spectrum of **5** showed a pair of pseudo parent peaks, [M+Na$^+$] at *m*/*z* 1155 and [M+K$^+$] at *m*/*z* 1171, which are consistent with the molecular ion of the epithio species **5** and strongly support the above structural assignment. The negligibly small constant $J_{1,2}$ of the epithio sugar residue implies that the epithio group is of *manno*-type rather than *allo*-type because the $J_{1,2}$ was reported to be 4.4 Hz or 0 Hz for methyl 2,3-dideoxy-2,3-epithio-4,6-di-*O*-methyl-α-D-alloside or its mannoside analog, respectively,[8] and the large coupling constant $J_{1,2}$ (5.9 Hz) was found in the case of 2^A,3^A-*allo*epithio-2^A,3^A-dideoxy-β-CD.[4] Thus, compound **5** is assigned to 2^A,3^A-dideoxy-2^A,3^A-*manno*epithio-β-CD.

Reactions of the di*allo*epoxy-β-CDs **6**, **7**[7] and the tri-*allo*epoxy-β-CD **8**[9] with thiourea under similar conditions afforded the corresponding di*manno*epithio-β-CDs **9** and **10** and tri*manno*epithio-β-CD **11**, respectively (Table 1). The ^{1}H and ^{13}C NMR relating the *manno*epithiopyranoside residues are listed in Table 2.

A plausible mechanism for the formation of 2,3-epithio-β-CD **5** from 2,3-epoxy-β-CD **4** is depicted in Scheme 3. Based on the known reaction behaviours of *allo*epoxide rings in CDs,[3a] it can be reasonably figured out that the ring opening of the epoxide **4** by the nucleophilic attack of thiourea generates two kinds of thioureidopyranosides **12a** and **12b**.[10] Under alkaline conditions, the transfer of $(NH_2)_2C^+$ from 3-S to 2-O or from 2-S to 3-O and the subsequent intramolecular substitution of 2-O$C^+(NH_2)_2$ by 3-S$^-$ or 3-O$C^+(NH_2)_2$ by 2-S$^-$ take place to generate the same episulfide **5**. The formation of thioureidopyranosides was confirmed by monitoring the reaction progress with TLC (Silica gel, *n*-PrOH/AcOEt/H_2O = 7/3/6 by volume) which displayed the appearance of a new spot with an R_f (ca. 0) much lower than those of both **4** ($R_f = 0.4$) and the final product **5** ($R_f = 0.56$). As soon as the reaction solution was made alkaline at rt, the spot of final products appeared at $R_f = 0.56$ and the thickness increased till the spot at $R_f = 0$ disappeared completely.

The intermediates **12a** and **12b** are stable under acidic conditions and can be isolated. Both **12a** (altroside type) and **12b** (glucoside type) gave the same parent peak at *m*/*z* 1193. A purified sample of **12a** demonstrated the thioureido carbon at δ_C 171.5 ppm which correlated

Table 1. Reaction conditions and results of conversion of epoxides to episulfides

Epoxide	HCl	Thiourea (g)	Reaction time[a] (min)	Na_2CO_3 (mg)	Episulfide
4 (500 mg)	0.2 M, 5 ml	1.7	90	77	**5** (324 mg, 64.0%)
6 (300 mg)	0.4 M, 3 ml	1.0	30	92	**9** (162 mg, 52.4%)
7 (300 mg)	0.4 M, 3 ml	1.0	30	92	**10** (185 mg, 59.9%)
8 (300 mg)	0.6 M, 3 ml	1.5	20	138	**11** (98 mg, 31.3%)

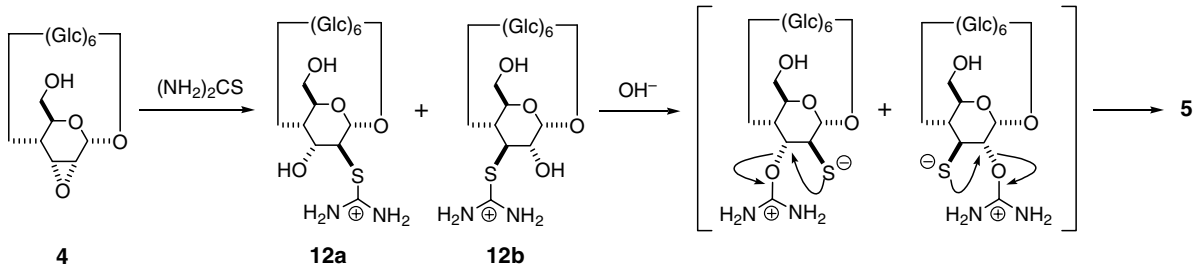
[a] The time required for the completion of the first step.

Table 2. The chemical shifts relating the 2,3-*manno*epithiopyranoside units of **5**, **9**, **10** and **11** in D_2O[a]

^{1}H, δ/ppm (coupling pattern, coupling constant ^3J/Hz, number of protons)				
Nuclei	1	2	3	4
Compound **5**	5.32 (s, 1H)	3.36 (d, 6.3, 1H)	3.42 (1H)	4.15 (d, 9.3, 1H)
Compound **9**	5.32 (s, 1H) 5.34 (s, 1H)	3.36–3.39 (m, 3H)	3.40–3.42 (m, 2H)	4.03 (d, 9.4, 1H) 4.06 (d, 8.9, 1H)
Compound **10**	5.34 (s, 1H) 5.37 (s, 1H)	3.37 (d, 6.4, 2H)	3.41 (m, 2H)	4.03 (d, 8.9, 1H) 4.04 (d, 9.5, 1H)
Compound **11**	5.34 (s, 1H) 5.34 (s, 1H) 5.37 (s, 1H)	3.36–3.39 (m, 3H)	3.40–3.42 (m, 3H)	4.05–4.07 (m, 3H)

^{13}C, δ/ppm						
Nuclei	1	2	3	4	5	6
Compound **5**	100.3	34.3	36.4	73.3	71.3	62.2
Compound **9**	99.6 100.2	34.2 34.3	36.1 36.4	72.5 72.6	71.3 71.4	62.2 62.3
Compound **10**	99.7 100.1	34.2 34.2	36.1 36.2	72.8 72.9	71.5 71.5	62.3 62.4
Compound **11**	99.5 99.6 99.7	34.2 34.2 34.3	35.9 36.1 36.2	72.4 72.4 72.5	71.3 71.5 71.5	62.2 62.3 62.4

[a] The marks s, d, and m denote singlet, doublet, and multiplet, respectively.



Scheme 3. A plausible mechanism for the formation of 2,3-*manno*episulfide **5** from 2,3-*allo*epoxide **4**.

with the $H2^A$ in the HMBC spectrum. This observation together with the high field chemical shift of $C2^A$ (δ_C 51.3 ppm) indicated that a thioureido group was attached to the $C2^A$ of **12a**. The [^{1}H,^{1}H] coupling constants, $J_{1,2}$ (7.8 Hz) and $J_{2,3}$ (11.1 Hz) of the substituted sugar unit A of **12a** are rather large, implying that the $H1^A$, $H2^A$ and $H3^A$ are axially disposed. This stereochemistry suggests that the structure of unit A is of altroside-type. On the other hand, the $C3^A$ of **12a** resonated at very high field (δ_C 53.7 ppm) and the substituted sugar unit A of **12b** showed that the $J_{1,2}$, (3.4 Hz) was rather small, consistent with the 3^A-thioureidoglucopyranoside structure.

Epithio compounds are subject to S_N2 reactions to give 2-substituted thiols or the related compounds as the ring-opening products.[11] Therefore, the preparation of compounds **5** and **9**–**11** with 1–3 *manno*epithiopyranoside residues must be of significance for the preparation of 2,3-homo- or hetero-polyfunctional β-CDs. Researches on the reactions of these epithio-β-CDs are in progress and the results will be reported in due course.

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References and notes

1. *Comprehensive Supramolecular Chemistry*; Atwood, J. L., Davis, J. E., MacNicol, D. D., Vogtle, F., Eds.; Cyclodextrins; Pergamon Elsevier: Oxford, UK, 1996; Vol. 3; Breslow, R.; Dong, S. D. *Chem. Rev.* **1998**, *98*, 1997–2011.
2. Khan, A. R.; Forgo, P.; Stine, K. J.; D'Souza, V. T. *Chem. Rev.* **1998**, *98*, 1977–1996.
3. (a) Yuan, D.-Q.; Tahara, T.; Chen, W.-H.; Okabe, Y.; Yang, C.; Yagi, Y.; Nogami, Y.; Fukudome, M.; Fujita, K. *J. Org. Chem.* **2003**, *68*, 9456–9466; (b) Yu, H.; Teramoto, A.; Fukudome, M.; Xie, R.-G.; Yuan, D.-Q.; Fujita, K. *Tetrahedron Lett.* **2006**, *47*, 8837–8840.
4. Fukudome, M.; Okabe, Y.; Sakaguchi, M.; Morikawa, H.; Fujioka, T.; Yuan, D.-Q.; Fujita, K. *Tetrahedron Lett.* **2004**, *45*, 9045–9048.
5. Fukudome, M.; Yuan, D.-Q.; Fujita, K. *Tetrahedron Lett.* **2005**, *46*, 1115–1118.
6. Yuan, D.-Q.; Ohta, K.; Fujita, K. *Chem. Commun.* **1996**, 821–822.
7. Fujita, K.; Tahara, T.; Imoto, T.; Koga, T. *J. Am. Chem. Soc.* **1986**, *108*, 2030–2034.
8. Jesudason, M. V.; Owen, L. N. *J. Chem. Soc., Perkin Trans. 1* **1974**, 2019–2024.
9. Fujita, K.; Tahara, T.; Yamamura, H.; Imoto, T.; Koga, T.; Fujioka, T.; Mihashi, K. *J. Org. Chem.* **1990**, *55*, 877–880.
10. Fukudome, M.; Shiratani, T.; Immel, S.; Nogami, Y.; Yuan, D.-Q.; Fujita, K. *Angew. Chem., Int. Ed.* **2005**, *44*, 4201–4204.
11. (a) Vasil'eva, S. A.; Kalimullina, L. Kh.; Safarov, M. G. *Chem. Heterocycl. Compd.* **2003**, *39*, 174–177; (b) Ando, W.; Choi, N.; Tokitoh, N. In *Comprehensive Heterocyclic Chemistry II*; Padwa, A., Ed.; Elsevier: Oxford, 1996; pp 173–240, 1A; (c) Chew, W.; Harpp, D. N. *Sulfur Rep.* **1993**, *15*, 1–39; (d) Luhowy, R.; Meneghini, F. *J. Org. Chem.* **1973**, *38*, 2405–2407; (e) Johnson, D. L.; Reynolds, D. D. *Mech. React. Sulfur Compd.* **1970**, *5*, 103–130; (f) Tobler, E. *Ind. Eng. Chem., Prod. Res. Develop.* **1969**, *8*, 415–420; (g) Reynolds, D. D.; Fields, D. L. In *Heterocyclic Compounds with Three- and Four-Membered Rings*; Weissberger, A., Ed.; Interscience: New York, 1964; pp 576–623, Part 1.