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SYNTHESIS OF CHIRAL AZACROWN ETHERS DERIVED FROM α-D-GLUCOSE AND THEIR CATALYTIC PROPERTIES ON THE ASYMMETRIC MICHAEL ADDITION

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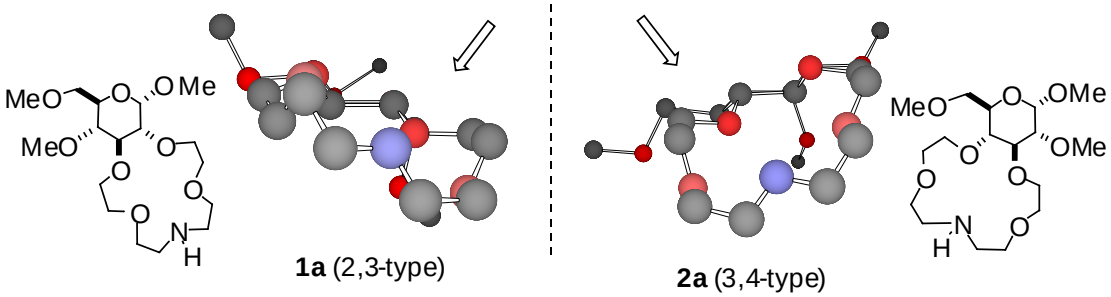
Abstract- Three types of chiral azacrown ethers have been synthesized from (+)-(4,6-*O*-benzylidene)-*O*-methyl-α-D-glucopyranoside and their catalytic properties for the asymmetric Michael addition have been investigated; enantioselectivity switching which is dependent on the azacrown ether catalysts has been achieved.

Development of a natural environmentally friendly catalyst for the asymmetric reaction is one of the current topics in recent organic synthesis; [1] several types of efficient catalysts derived from alkaloids[2] or chiral crown ethers [3] have been reported with their numerous applications.[2,3] We are attracted by chiral azacrown ethers which were derived from sugars reported by Töke and his colleagues.[4] We have previously demonstrated a simple method for resolving axially chiral biphenyldicarboxylic acids based on the kinetic controlled cyclic ester formation of racemic biphenyldicarboxylic acids with (+)-(4,6-*O*-benzylidene)-*O*-methyl-α-D-glucopyranoside.[5] In the reaction, two adjacent hydroxyl groups at the 2- and 3-positions on the glucoside had an important role in recognizing chirality.[5b,6]

Figure1. Results of MO(PM3) calculation of the optimized structure of two azacrown ethers **1a** and **2a** derived from α-D-Glucose

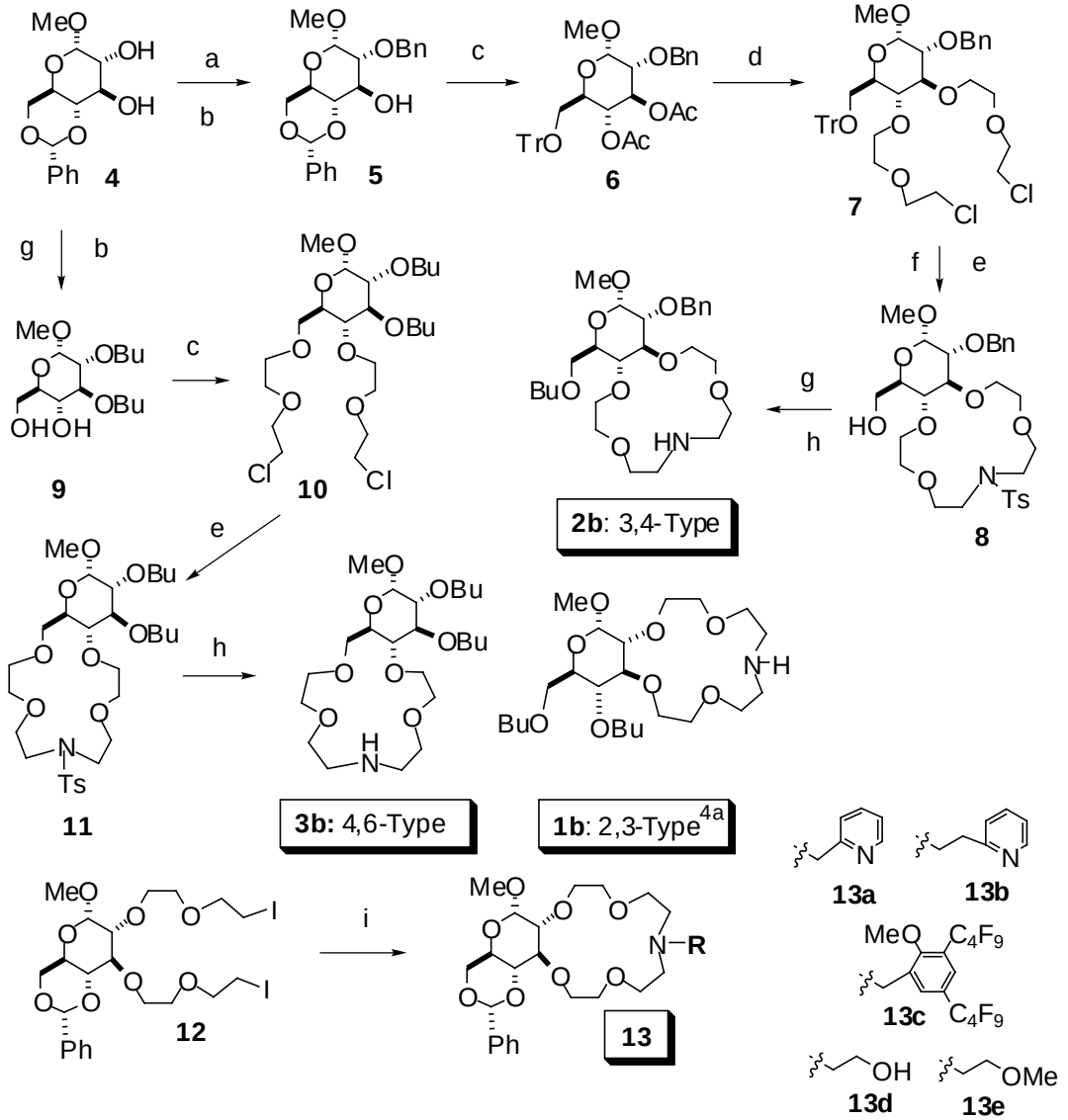


1a (2,3-type) **2a** (3,4-type)

Although no mechanistic detail for the origin of enantio-favoritism of Töke's sugar-type azacrown ether has been reported, we expected that opposite enantioselectivity could be seen between the 2,3-bridged

type of azacrown ethers (**1a**) and 3,4-bridged type azacrown ethers (**2a**), both of which are derived from the same source of α-D-glucose; the computational chemistry suggest that **2a** is a pseudo-enatiomeric form of **1a** and addition reaction of a nucleophile to a suitable acceptor would take place from the opposite side in the reactions catalyzed by azacrown ether (**1a**) or (**2a**) (Figure 1).[7]

Scheme 1. Synthesis of various types of chiral azacrown ethers derived from (4,6-O-benzylidene)-O-methyl- α-D-glucopyranoside (4)



a) Bu_2SnO, MeOH, reflux, 1 h, then BnBr, 110°C,11 h, 83%. b) 0.5 N-HCl, THF, MeOH, reflux, 4 h, 95~100%. c) TrCl, pyridine, 40°C, 8 h, then Ac_2O, rt, 2 h, >90%. d) $(ClCH_2CH_2)_2O$, 50% aq. NaOH, $NBu_4 \cdot HSO_4$, rt, 12 h, 83%. e) $TsNH_2$, K_2CO_3, DMF, 120°C, 36 h, 72%. f) TMSCl, NaI, MeCN, rt, 5 min, 97%. g) BuBr, NaH, DMF, 40°C, 10 h, >90%. h) Na·Naphthalenide, DME, -60°C, 1 h, 59%. i) RNH_2, Na_2CO_3 or Cs_2CO_3, MeCN, reflux, 36~48 h, 54~87%.

We thus decided to synthesize various types of chiral azacrown ethers systematically, and to investigate their catalytic properties on the asymmetric reaction. We synthesized two types of novel chiral azacrown ethers (**2b**) and (**3b**) from glucopyranoside (**4**) following Scheme 1. Glucoside (**4**) was converted to 2-benzyl ether through a cyclic stannyl ester to give glucoside (**5**) in 63% yield,[8] then deprotection and regioselective protection at the 6-position as trityl ether to afford **6**. Bisalkylation of **6** at 3- and 4-positions was successfully accomplished under a phase-transfer reaction condition[9] to lead to **7**; cyclization of **7** and alkylation at 6-position and final detosylation gave **2b** in good overall yield. Through the similar pathway, 4,6-bridged type azacrown ether (**3b**) was also synthesized successfully. Because a substituent at the nitrogen atom of the azacrown ether seems to affect the enantio-favoritism of the reaction by MO calculation, we also synthesized seven types of N-alkylated azacrown ethers (**13a-13e**). Using chiral azacrown ether (**1b**)[4a], we initially tested enantioselective alkylation of glycine derivative (**14**),[2h] however, only poor enantioselective reaction was observed. On the other hand, enantioselective Michael addition of an enolate derived from **14** to methyl vinyl ketone gave the addition product (**15**) in good yield with acceptable enantioselectivity (Eq. 1) and the results are summarized in Table 1.

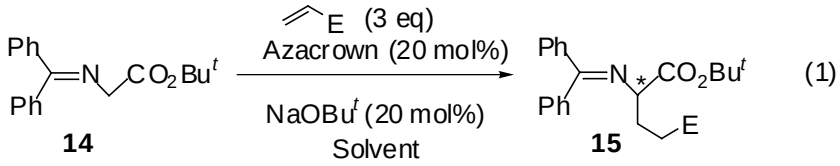


Table 1. Results of asymmetric Michael reaction mediated by chiral azacrown ethers

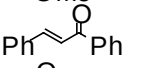
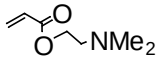
Entry	Acceptor	Crown	Solvent	Temp. (°C)	Time (h)	**15** Yield(%) [a]	**15** ee(%)[b, c]
1		**1b**	Toluene	-78	3	75	64(S)
2		**1b**	Et_2O	-78	14	77	70(S)
3		**1b**	Toluene:Et_2O=1:1	-78	7	**82**	**72 (S)**
4		**2b**	Toluene:Et_2O=1:1	-78	5.5	**79**	**60 (R)**
5		**3b**	Toluene:Et_2O=1:1	-78	39	28	2 (R)

a) Isolated yield. b) Enantiomeric excess was determined by HPLC Analysis (CHIRALCEL OD), Hexane: i-PrOH = 200:1 ~ 350:1. c) The absolute configuration was determined by comparison of specific rotation value with that of the authentic sample. [2p, y]

The optical purity of product (**15**) was strongly dependent on the solvent system, the mixed solvent system (toluene to ether = 1:1) gave a better result than that in toluene or ether. A mixture of **14**, azacrown

ether (**1b**) (20 mol%), and methyl vinyl ketone in the presence of 20 mol% of sodium *t*-butoxide at -78°C for 7 h gave the Michael adduct (**15**) in 82% yield with 72% ee (Entry 3 in Table 1). The absolute configuration of the product was found to be (*S*) by comparison of the specific rotation value of **15** with that of the authentic sample.[2p,y] As suggested by the result of MO calculation, desired "enantioselectivity switching" was realized; the Michael adduct ((*R*)-**15**) was obtained in 79% yield with 60% ee when the reaction was carried out using azacrown ether (**2b**) as catalyst (Entry 4). The reaction using 4,6-bridged type azacrown ether (**3b**) as catalyst, on the other hand, gave **15** in poor enantioselectivity (Entry 5). Because "enantioselectivity switching" was obtained for **1b** and **2b**, we assume that the most important factor determining the enantioselectivity was the difference in the torsion of the molecular flame of the azacrown ether ring; this should control the direction of the Michael acceptor attack to the enolate on the azacrown ring.

Table 2. Results of asymmetric Michael reaction mediated by chiral azacrown ethers

Entry	Acceptor	Crown	Solvent	Temp. (°C)	Time (h)	**15** Yield(%) [a]	**15** ee(%) [b]
1		**13a**	Toluene:Et_2O=1:1	-78	**0.5**	**72**	**68 (S)**
2		**13b**	Toluene:Et_2O=1:1	-78	**0.4**	**75**	**62 (S)**
3		**13c**	Toluene:Et_2O=1:1	-78	8	79	12 (S)
4		**13d**	Toluene:Et_2O=1:1	-78	5.5	61	20 (S)
5		**13e**	Toluene:Et_2O=1:1	-78	1.5	53	21 (S)
6		**1b**	Toluene:Et_2O=1:1	-50	**39**	**52**	**60 (S)**
7		**1b**	Et_2O [c]	-50	17	63	47 (S)
8		**1b**	Toluene:Et_2O=2:1	-78~25	24	0 [d]	---
9		**1b**	Toluene:Et_2O=1:1	-40	28	83	48 (S)

a) Isolated yield. b) Enantiomeric excess was determined by HPLC Analysis (CHIRALCEL OD), Hexane: i-PrOH= 200:1 ~ 350:1. c) Reaction in ether gave better result than those in the standard mixed solvent system. d) No reaction took place and the strating compound was recovered quantitatively.

Michael addition was next investigated in the presence of various types N-substituted azacrown ethers (Table 2). Remarkable acceleration was observed when the reactions were carried out in the presence of N-2-pyridylmethyl-substituted azacrown ether (**13a**) or (**13b**); only 0.4~0.5 h reaction provided (*S*)-**15** with 68% ee (Entry 1) and 62% ee (Entry 2), respectively. Significant reduction of enantioselectivity was observed when **13c** and **13d** were used as catalysts (Entries 4 and 5), though the same (*S*)-enantio-

favoritism was obtained in all reactions. Generally, results of the Michael reaction are strongly dependent on the species of Michael acceptor. The reaction with acrylonitrile (Entry 7) gave the Michael product with moderate enantioselectivity (60% ee), while poor enantioselectivity was obtained in the reactions of acrylate derivatives (Entries 8 and 10), and no Michael adduct was obtained for chalcone (Entry 9).

In conclusion, we have accomplished enantioselectivity switching of the Michael addition using three types of chiral azacrown ethers derived from the same origin of α-D-glucose. 3,4-Bridged types of azacrown ether gave (*R*)-adduct, while 2,3-bridged type of crown ether afforded (*S*)-adduct. It should be noted that the enantioselectivity can also be modified by the N-substituent group of the azacrown ether, though the major factor determining the enantioselectivity was the asymmetrical environment due to the crown ether ring. Although the enantioselectivity remained at an insufficient level, these results provide very important information for considering the transition state structure of the present azacrown ether mediated asymmetric reaction. Further investigations on optimization of the substrate using various types of N-substituted azacrown ethers are now in progress.

ACKNOWLEDGMENT

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7. MacSpartan Pro was employed for MO (PM3) calculation. Results of MO (PM3) calculation (Heat of formation): **1a**; -271.63 Kcal/mol, **2a**; -270.10 Kcal/mol.
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10. Physical constant and NMR data of **2b**: colorless syrup; Rf 0.46 ($CHCl_3$ / MeOH = 3:1); $[\alpha]_D^{23}$ +28.4° (*c*1.38, $CHCl_3$); ^{1}H NMR (200 MHz, δ, $CDCl_3$) 0.90 (3H, t, J=7.3 Hz), 1.26-1.68 (4H, m), 1.97 (1H, br s), 2.68-2.92 (4H, m), 3.33 (3H, s), 3.28-4.16 (20H, m), 4.56 (1H, d, J=3.5 Hz), 4.61 (1H, d, J=12.2 Hz), 4.73 (1H, d, J= 12.2 Hz), 7.27-7.33 (5H, m); ^{13}C NMR (50 MHz, ppm, $CDCl_3$) 13.9, 19.3, 31.7, 47.5, 47.9, 55.0, 69.1, 69.4, 69.6, 69.8, 70.0, 70.4, 71.4, 72.6, 73.1, 73.2, 80.0, 81.4, 98.1, 127.9, 128.0, 128.4, 138.1; IR (neat, cm^{-1}) 3384, 2921, 1459, and 1100.
3b: colorless solid; mp 76~78 ° C (recrystallization from $CHCl_3$); Rf 0.48 (CH_2Cl_2 / MeOH = 3:1); $[\alpha]_D^{29}$ +70.3° (*c* 0.76, $CHCl_3$); ^{1}H NMR (200 MHz, δ, $CDCl_3$) 0.91 (6H, t, J= 7.3 Hz), 1.26-1.63 (8H, m), 2.33 (1H, br s), 2.83-2.86 (4H, m), 3.12-4.10 (22H, m), 3.40 (3H, s), 4.78 (1H, d, J= 3.5 Hz); ^{13}C NMR (50 MHz, ppm, $CDCl_3$) 13.8, 13.9, 19.1, 19.3, 32.1, 32.6, 48.4, 55.0, 69.2, 69.8, 70.4, 70.8, 71.2, 71.3, 72.2, 72.3, 73.1, 78.6, 80.8, 81.6, 97.7; IR (neat, cm^{-1}) 3333, 2923, 1462, 1365, 1106, and 796.
Michael adduct (**15**): colorless syrup; Rf 0.23 (hexane / ethyl acetate = 2:1); $[\alpha]_D^{23}$ -47.9° (*c* 1.15, $CHCl_3$), 72%ee(S); ^{1}H NMR (200 MHz, δ, $CDCl_3$) 1.43 (9H, s), 2.11(3H, s), 2.15 (2H, t, J= 7.3 Hz), 2.52 (2H, dt, J= 7.3, 6.1 Hz), 3.95 (1H, t, J= 6.1 Hz), 7.13-7.64 (10H, m); ^{13}C NMR (50 MHz, ppm, $CDCl_3$) 27.7, 28.0, 29.9, 39.8, 64.7, 77.2, 81.1, 127.7, 128.0, 128.4, 128.6, 128.7, 130.3, 136.4, 139.4, 170.5, 170.9, 208.3; IR (neat, cm^{-1}) 3060, 2974, 1728, 1710, 1627, and 1154.