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Synthesis of C_2-symmetric chiral crown ethers by lipase-catalyzed reactions

Misako Nakamura, Takuya Taniguchi, Naohisa Ishida, Keishi Hayashi, Masahiro Muraoka, Yohji Nakatsuji *

Department of Applied Chemistry, Faculty of Engineering, Osaka Institute of Technology, 5-16-1 Omiya, Asahi-ku, Osaka 535-8585, Japan

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ABSTRACT

Kinetic resolution of a racemic mixture of C_2-symmetric 18-crown-6 diols (*rac*-**1a**) and 15-crown-5 diol (*rac*-**1c**) was achieved by lipase-catalyzed acetylation. The enantiomeric excess of the chiral crown diols (95% ee and 82% ee) was determined by ^{1}H NMR spectroscopy, using (*R*)-(+)-1-(1-naphthyl)ethylammonium hydrochloride as a shift reagent. The C_2-symmetric chiral 15-crown-5 diol (>95% ee) was also obtained by kinetic resolution of the racemic diacetate (*rac*-**2c**) using lipase-catalyzed solvolysis.

1. Introduction

Over the last three decades, chiral crown ethers have been well established as useful and convenient host compounds for the separation of enantiomers,[1] enantiomeric sensing[2] and enantioselective catalysis.[2a,3] Further research continues on various chiral crown ether derivatives with high complexation abilities and selectivity towards guest molecules.[1d,4] With respect to the molecular design of C-pivot lariat ethers,[5] we previously prepared a chiral crown ether containing the C-pivot methyl group, (2*R*,12*R*)-2,12-bis(hydroxymethyl)-2,12-dimethyl-18-crown-6 [(*R*,*R*)-**1b**], and determined its absolute configuration by X-ray anomalous dispersion analysis of a complex of the derivative.[6] Since (*R*,*R*)-**1b** possesses two reactive groups on the sidearms, it is possible to introduce further functionalization in pursuit of higher enantioselectivity. Recently, the introduction of aromatic sidearms into (*R*,*R*)-**1b** bearing a C-pivot methyl group was found to be a useful strategy for the design of novel chiral solvating reagents towards primary ammonium salts. The aromatic sidearm, with restricted movement due to the methyl group on the C-pivot carbon atom, should affect its enantiomeric discrimination by the combination of steric and electronic factors.[7] It is therefore of interest to provide a variety of C_2-symmetric chiral crown ethers having two reactive hydroxymethyl groups on the sidearms, such as positional isomers of (*R*,*R*)-**1b** and the corresponding 15-crown-5 ethers, for developing novel chiral recognition host molecules. From this point of view, we describe the synthesis of chiral 2,9-bis(hydroxymethyl)-2,9-dimethyl-18-crown-6 (**1a**) and 2,9-bis(hydroxymethyl)-2,9-dimethyl-15-crown-5 (**1c**) by lipase-catalyzed reactions and the determinations of their absolute configurations by comparison with the corresponding authentic samples synthesized from a chiral subunit, [(4*S*)-2,2,4-trimethyl-1,3-dioxolane-4-yl]methanol.[8]

2. Results and discussion

2.1. Synthesis of racemic mixture of 18-crown-6 derivative

The racemic mixture of 18-crown-6 derivative *rac*-**1a** was synthesized as shown in Scheme 1. Compound **5** was prepared according to the previously reported method.[9] Compound **5** was reacted with *p*-toluenesulfonyl chloride under basic conditions to give the corresponding ditosylate **6**. The K^+-template reaction of the conjugate base of ethylene glycol with **6** resulted in the formation of the crown ether **3a** in 41% yield. The *cis* and *trans* isomers of compound **3a** were separated by silica gel column chromatography using a mixture of ethyl acetate and hexane as the eluent. The trans isomer, a racemic mixture of *rac*-**3a**, was treated with potassium acetate in DMSO at 100 °C for 100 h to afford the diacetate *rac*-**2a** in 75% yield. The crown diol *rac*-**1a** was prepared by hydrolysis of *rac*-**2a** in EtOH/H_2O in the presence of sodium carbonate in 100% yield.[5d,6] All structures were determined by ^{1}H and ^{13}C NMR spectroscopy, mass spectrometry and elemental analysis.

* Corresponding author. Tel.: +81 6 6954 4275; fax: +81 6 6957 2135; e-mail address: nakatsuji@chem.oit.ac.jp (Y. Nakatsuji).

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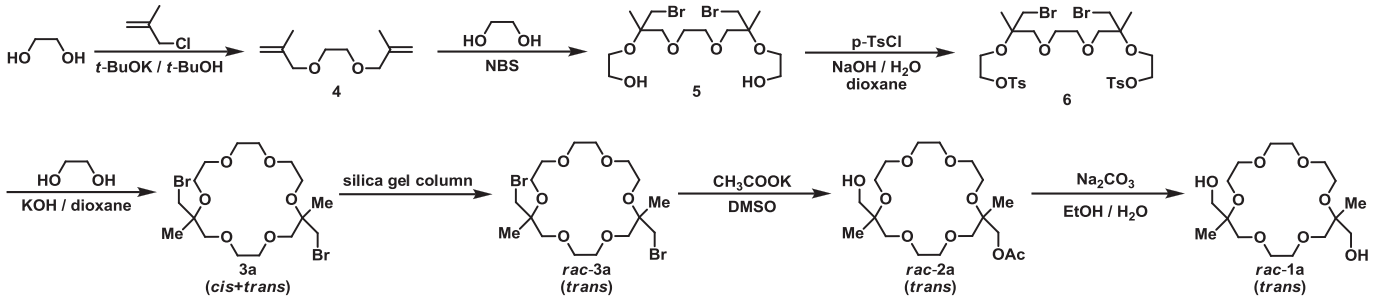
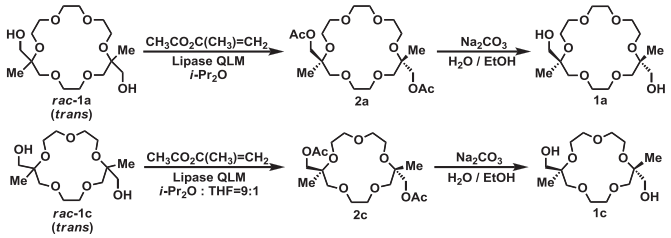


Scheme 1. Synthesis of a racemic mixture of 18-crown-6 derivative (*rac*-**1a**).

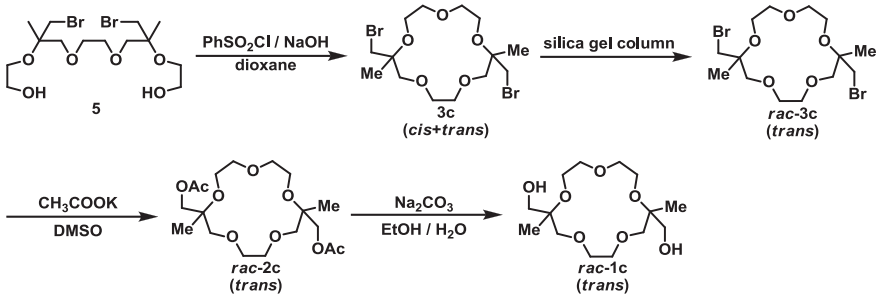
2.2. Synthesis of racemic mixture of 15-crown-5 derivative

The racemic mixtures of 15-crown-5 derivatives *rac*-**1c** and *rac*-**2c** were synthesized as shown in Scheme 2. Compound **3c** was obtained by an intramolecular cyclization reaction of the pentaethylene glycol derivative, which was prepared by a bromoalkoxylation reaction of ethylene glycol bis(2-methylallyl) ether with ethylene glycol by using benzenesulfonyl chloride under basic conditions. The *cis* and *trans* isomers of **3c** were separated by silica gel column chromatography using a mixture of ethyl acetate and hexane as eluent.[9] The trans isomer, a racemic mixture of *rac*-**3c**, was treated with potassium acetate in DMSO at 100 °C for 96 h to afford the diacetate *rac*-**2c** in 77% yield. The crown diol *rac*-**1c** was obtained by hydrolysis of *rac*-**2c** in EtOH/H_2O in the presence of sodium carbonate in 100% yield.[5d,6] All structures were determined by ^1H and ^{13}C NMR spectroscopy, mass spectrometry and elemental analysis.



Scheme 3. Lipase-catalyzed acetylation of *rac*-**1a** and *rac*-**1c**.

products were obtained after 83 h and 6 days, respectively. Thus, acetylation of the racemic diol *rac*-**1c** with isopropenyl acetate was carried out in isopropyl ether/THF=9/1 at 36 °C by using lipase QLM from *Alcaligenes* sp. as a catalyst. The reaction was stopped after 6.5 h. The diacetate **2c** was isolated by silica gel column



Scheme 2. Synthesis of a racemic mixture of 15-crown-5 derivative (*rac*-**1c**).

2.3. Optical resolution of racemic mixture of C_2-symmetric crown diol by lipase-catalyzed acetylation

Kinetic resolution of *trans*-2,9-bis(hydroxymethyl)-2,9-dimethyl-18-crown-6 (*rac*-**1a**) and *trans*-2,9-bis(hydroxymethyl)-2,9-dimethyl-15-crown-5 (*rac*-**1c**) was attempted using lipase-catalyzed acetylation. Acetylation of the racemic diol *rac*-**1a** with isopropenyl acetate was carried out in isopropyl ether at 28 °C by using lipase QLM from *Alcaligenes* sp. as a catalyst. The reaction was monitored by HPLC and was stopped when the HPLC yield of the diacetate **2a** reached 35%. The diacetate **2a** was isolated by silica gel column chromatography (hexane/ethyl acetate=70/30) in 21% yield. The diol **1a** was obtained by hydrolysis of **2a**. The enantiomeric excess (95% ee) was determined by ^1H NMR spectroscopy, using (*R*)-(+)-(1-naphthyl)ethylammonium hydrochloride[10] [(*R*)-NpEtCl] as a shift reagent (Scheme 3 and Fig. 1).

Acetylation of racemic 15-crown-5 diol *rac*-**1c** with isopropenyl acetate was successfully catalyzed by lipase QLM, in isopropyl ether containing 10 vol % tetrahydrofuran (THF). In this case, the addition of THF was necessary for dissolution of *rac*-**1c**. In a mixed solvent of isopropyl ether and THF (50/50) and THF alone, however, no

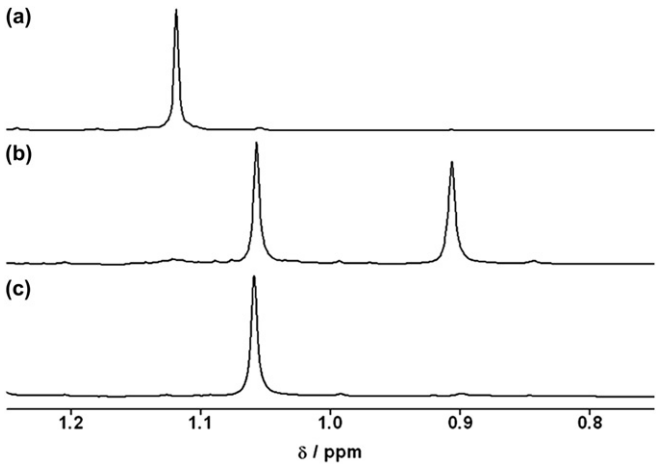


Fig. 1. Partial ^1H NMR spectra (300 MHz, $CDCl_3$, 20 °C) of (a) *rac*-**1a** (44.2 mM), (b) mixture of *rac*-**1a** (44.2 mM) and (*R*)-NpEtCl (44.2 mM) and (c) mixture of chiral diol **1a** and (*R*)-NpEtCl (44.2 mM).

chromatography (hexane/ethyl acetate=80/20) in 14% yield. The diol **1c** was obtained by hydrolysis of **2c**. As shown in Table 1 (entry 1), the enantiomeric excess (82% ee) was determined by ^{1}H NMR spectroscopy, using (*R*)-NpEtCl as a shift reagent (Scheme 3 and Fig. 2). The results of the optical resolution of 15-crown-5 diol *rac*-**1c** using various lipase catalysts are summarized in Table 1.

Table 1
Lipase-catalyzed acetylation of **1c**

Entry no.	Reaction conditions	Lipase	Reaction time/h	Isolated yield/%	Enantiomeric excess/% ee
1	*i*-Pr_2O/THF=9:1, 36 °C	QLM[a]	6.5	14	82
2	*i*-Pr_2O/THF=9:1, 36 °C	PL[a]	10.5	16	46
3	*i*-Pr_2O/THF=9:1, 36 °C	OF[b]	nr[d]	—	—
4	*i*-Pr_2O/THF=9:1, 36 °C	TL[c]	4	16	57
5	*i*-Pr_2O/THF=9:1, 25 °C	QLM[a]	22	22	77

[a] *Alcaligenes* sp.
[b] *Candida cylindracea*.
[c] *Pseudomonas stutzeri*.
[d] No reaction.

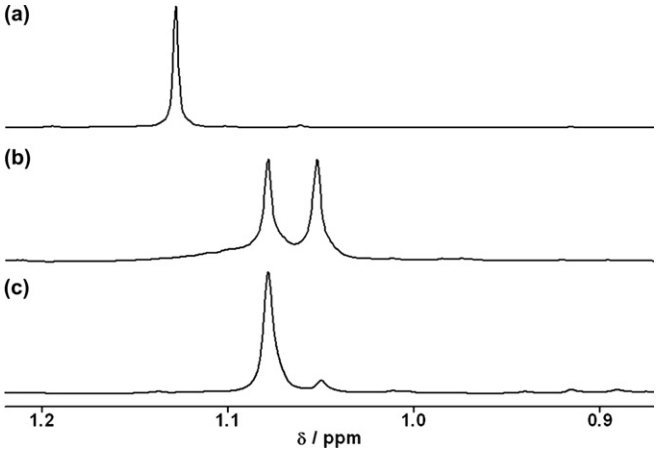


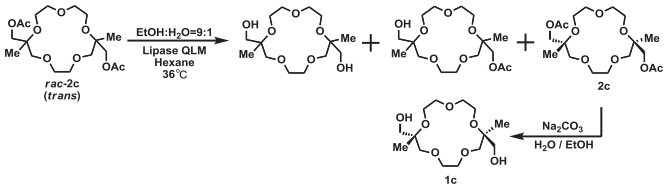
Fig. 2. Partial ^{1}H NMR spectra (300 MHz, $CDCl_3$, 20 °C) of (a) *rac*-**1c** (46.3 mM), (b) mixture of *rac*-**1c** (46.3 mM) and (*R*)-NpEtCl (46.3 mM) and (c) mixture of chiral diol **1c** (entry 1 in Table 1) and (*R*)-NpEtCl (46.3 mM).

When lipase PL was used as the catalyst, a rather low enantioselectivity was observed in comparison with the case of lipase QLM (entry 2). In the case of lipase OF, no products were obtained after 6.5 h (entry 3). The enantiomeric excess of chiral diol **1c** was 57% ee when using lipase TL (entry 4). Therefore, lipase QLM was adopted as the catalyst in the kinetic resolution of racemic crown diol *rac*-**1c**. When the reaction was carried out at 25 °C, the enantiomeric excess of **1c** was 77% ee (entry 5).

2.4. Optical resolution of racemic mixture of C_2-symmetric 15-crown-5 diacetate by lipase QLM-catalyzed solvolysis

The 82% ee of chiral diol **1c** obtained by lipase-catalyzed acetylation was considered to be insufficient for further application of this reactive crown ether to the design of new chiral host molecules. Accordingly, to improve the % ee of **1c**, lipase-catalyzed solvolysis of the corresponding diacetate *rac*-**2c** with ethanol was examined in hexane (Scheme 4). The results are summarized in Table 2.

The lipase QLM-catalyzed solvolysis reaction of *rac*-**2c** with ethanol was carried out in hexane at 45 °C for 8 days. Then compound **1c** was isolated and the enantiomeric excess (50% ee) of **1c** was determined by ^{1}H NMR spectroscopy (entry 6). Since the resulting optical purity of the diol was disappointing, we changed the target molecule from the diol to the unreacted diacetate



Scheme 4. Lipase QLM-catalyzed solvolysis of *rac*-**2c** and hydrolysis of **2c**.

Table 2
Lipase QLM-catalyzed solvolysis reaction of *rac*-**2c**

Entry no.	Reaction conditions	Reaction time/days	Isolated yield[a]/%	Enantiomeric excess/% ee
6	EtOH, 45 °C	8	28	50
7	EtOH, 45 °C	7	21	75
8	EtOH, 37 °C	11	21	75
9	EtOH/H_2O=9:1, 36 °C	6	8	>95

[a] Entry 6: diol; entries 7–9: diacetate (recovered).

recovered after reaction. The solvolysis reaction of *rac*-**2c** with ethanol was carried out in hexane at 45 °C for 5 days and then the unreacted diacetate was recovered. The enantiomeric excess was determined to be 75% ee (entry 7). When the reaction temperature was lowered from 45 °C to 37 °C, the reaction time increased, but the % ee was not improved (entries 7 and 8). On the other hand, the addition of water to the reaction system dramatically increased the % ee of **1c** (entry 9). The solvolysis of *rac*-**2c** with a mixture of ethanol and water (9:1) in hexane was performed at 36 °C for 6 days. Compound **1c** was obtained by hydrolysis of **2c** recovered after reaction and the enantiomeric excess was determined to be >95% ee (Fig. 3, entry 9 of Table 2). This result strongly suggested that water played an important role[11] in the solvolysis reaction using lipase QLM as the catalyst. The existence of the water accelerate conversion of diacetate by alcoholysis and hydrolysis. This might be the reason to get the product with very high % ee. In any case, the % ee obtained by this solvolysis reaction is acceptable for further applications.

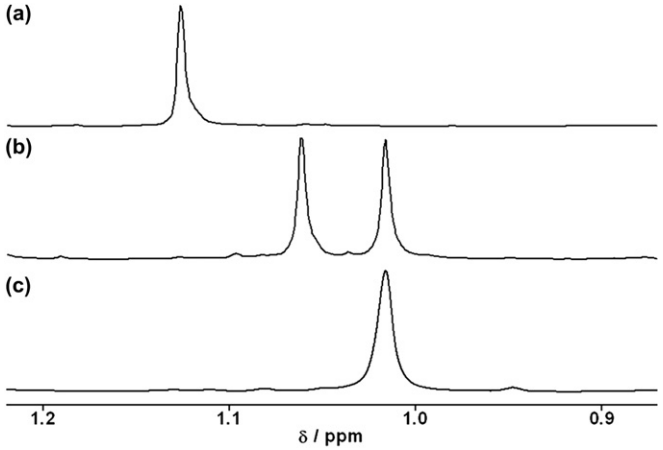


Fig. 3. Partial ^{1}H NMR spectra (300 MHz, $CDCl_3$, 20 °C) of (a) *rac*-**1c** (46.3 mM), (b) mixture of *rac*-**1c** (46.3 mM) and (*R*)-NpEtCl (46.3 mM) and (c) mixture of chiral diol **1c** (entry 9 in Table 2) and (*R*)-NpEtCl (46.3 mM).

2.5. Determination of absolute configuration using ^{1}H NMR spectroscopy

2.5.1. Absolute configuration of chiral 18-crown-6 diol. To determine the absolute configuration of chiral 18-crown-6 diol **1a** obtained in this work, an authentic sample of (*R*,*R*)-**1a** was prepared according to previously reported methods.[8] The ^{1}H NMR chemical shift of the

methyl proton signals was found to be in coincidence with that of the authentic sample, using (*R*)-NpEtCl as a shift reagent. The absolution configuration of **1a** was thus determined to be (*R*,*R*) (Fig. 4).

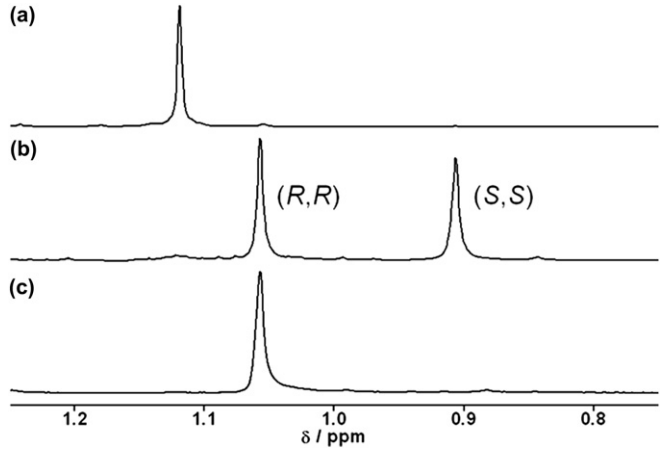


Fig. 4. Partial ^{1}H NMR spectra (300 MHz, $CDCl_3$, 20 °C) of (a) *rac*-**1a** (44.2 mM), (b) mixture of *rac*-**1a** (44.2 mM) and (*R*)-NpEtCl (44.2 mM) and (c) mixture of chiral diol (*R*,*R*)-**1a** and (*R*)-NpEtCl (44.2 mM).

2.5.2. Absolute configuration of chiral 15-crown-5 diol. In the case of 15-crown-5 diol, an authentic sample of (*R*,*R*)-**1c** was newly prepared according to Scheme 5. Compound (*R*,*R*)-**13** was prepared from a chiral subunit of (*S*)-2,2,4-trimethyl-1,3-dioxolane-4-methanol (*S*)-**7**.[8] The Na^+-template cyclization reaction of the diol (*R*,*R*)-**13** with diethylene glycol ditosylate under basic conditions afforded the crown ether (*R*,*R*)-**14** in 6% yield. (*R*,*R*)-**1c** was obtained in 72% yield by hydrogenation of (*R*,*R*)-**14**. The chemical shift of the methyl ^{1}H NMR signals of **1c** coincided with that of the (*S*,*S*) isomer, using (*R*)-NpEtCl as a shift reagent. The absolute configuration of **1c** obtained with lipase-catalyzed solvolysis was determined to be (*S*,*S*).

solvolysis reaction of the corresponding diacetate *rac*-**2c** with a mixture of ethanol and water in hexane. C_2-symmetric chiral 15-crown-5 diol **1c** (>95% ee) was obtained by hydrolysis of the unreacted diacetate recovered after reaction. The absolute configuration of **1a** was determined to be (*R*,*R*) based on agreement of the ^{1}H NMR spectrum with that of the authentic (*R*,*R*) isomer. The absolute configuration of chiral **1c** was determined to be (*S*,*S*) by comparison with the authentic (*R*,*R*) isomer newly prepared in this work.

4. Experimental section

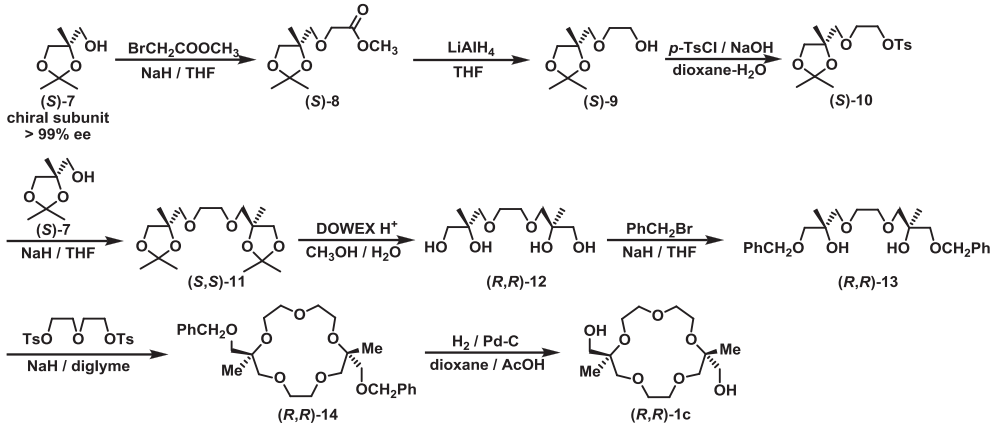
4.1. General

Lipase QLM was purchased from Meito Sangyo Co. and used without further purification. ^{1}H NMR spectra at 300 MHz and ^{13}C NMR spectra at 75 MHz were recorded with a Varian Mercury NMR spectrometer using tetramethylsilane as an internal standard. Mass spectra were measured on a JEOL JMS-DX-303 mass spectrometer. Measurements of the optical rotations were done in a DIP-370 digital polarimeter. Elemental analyses were carried out with a Yanaco CHN-Corder MT-5 analyzer.

4.2. Synthesis of racemic mixture of 18-crown-6 derivative (*rac*-1a)

The crude 4,11-bis(bromomethyl)-4,11-dimethyl-3,6,9,12-tetraoxatetradecan-1,14-diol (**5**) was prepared according to the previously reported method.[9]

*4.2.1. 4,11-Bis(bromomethyl)-4,11-dimethyl-1,14-bis(tosyloxymethyl)-3,6,9,12-tetraoxatetradecane (**6**).* To a solution of **5** (90.2 g, 0.199 mol) in dioxane (340 mL) was added NaOH aq (96% purity, 18.7 g, 0.449 mol, H_2O; 41 mL), and a solution of *p*-toluenesulfonyl chloride (78.5 g, 0.412 mol) in dioxane (235 mL) was added dropwise at room temperature. The resulting mixture was stirred at room temperature for 20 h. After water (100 mL) was added to the solu-



Scheme 5. Synthesis of the chiral crown ether (*R*,*R*)-**1c**.

3. Conclusion

In this study, we have established versatile synthetic routes for C_2-symmetric chiral crown diols. The chiral 18-crown-6 diol **1a** was obtained in 95% ee by optical resolution using lipase QLM-catalyzed acetylation of a racemic mixture of **1a**. Chiral 15-crown-5 diol **1c** was obtained in 82% ee by lipase QLM-catalyzed acetylation. To improve the % ee of chiral diol **1c**, optical resolution of a racemic mixture of **1c** was attempted by lipase-catalyzed

tion, it was then extracted with dichloromethane (400 mL×2). The combined organic layer was dried over $MgSO_4$ and the dichloromethane was evaporated off. The crude product was purified by chromatography over silica gel (toluene/dioxane=100/0 to 90/10) to give **6** as a slightly viscous liquid (55.9 g, 35%). ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.23 (s, 6H), 2.44 (s, 6H), 3.38 (d, 2H, J=9.9 Hz), 3.41 (s, 4H), 3.50 (d, 2H, J=9.8 Hz), 3.58 (s, 4H), 3.68 (t, 4H, J=5.6 Hz), 4.12 (t, 4H, J=5.3 Hz), 7.34 (d, 4H, J=8.6 Hz), 7.80 (d, 4H, J=8.4 Hz); ^{13}C NMR (75 MHz, $CDCl_3$): δ 19.8, 21.6, 36.7, 60.5, 69.4, 70.8, 74.0, 76.1, 128.0,

129.8, 132.9, 144.7; HRMS (FAB) calcd for $C_{28}H_{40}Br_2O_{10}S_2Na$: 781.0327 ($[M+Na]^+$). Found: 781.0322 ($[M+Na]^+$).

*4.2.2. 2,9-Bis(bromomethyl)-2,9-dimethyl-18-crown-6 (**3a**).* To a stirred suspension of powdered KOH (85% purity, 4.35 g, 65.9 mmol) in dioxane (100 mL) was added dropwise a mixture of **6** (9.99 g, 13.1 mmol) and ethylene glycol (1.29 g, 20.8 mmol) over a 6.5 h period at 60 °C. The mixture was stirred for 89 h at 60 °C. The insoluble matter was removed by filtration and concentrated in vacuo. Brine (150 mL) was added and the mixture was extracted with dichloromethane (150 mL×3). The combined organic layer was dried over $MgSO_4$ and the dichloromethane was evaporated off. The crude product was purified by medium pressure chromatography over silica gel (hexane/acetone=93/7) to give **3a** as a slightly yellow viscous liquid (1.91 g, 30%). ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.29 (s, 6H), 3.41–3.75 (m, 24H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 19.6 (trans isomer), 19.7 (cis isomer), 37.0 (cis isomer), 37.1 (trans isomer), 62.5, 70.6, 70.8, 71.4, 74.1 (trans isomer), 74.2 (cis isomer), 76.2. Anal. Calcd for $C_{16}H_{30}O_6Br_2$: C, 40.19; H, 6.32. Found: C, 39.79; H, 6.63.

*4.2.3. trans-2,9-Bis(bromomethyl)-2,9-dimethyl-18-crown-6 (rac-**3a**).* This product was a mixture of the *cis* and *trans* isomers of 2,9-bis(bromomethyl)-2,9-dimethyl-18-crown-6 (**3a**; 9.58 g, 20.0 mmol). The two stereo isomers were separated by medium pressure chromatography over silica gel (hexane/ethyl acetate=30/70) to give *rac*-**3a** as a slightly viscous liquid (3.44 g, 36%). The trans isomer eluted before the cis isomer. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.29 (s, 6H), 3.41–3.75 (m, 24H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 19.6, 37.1, 62.6, 70.6, 70.8, 71.4, 74.1, 76.2. Anal. Calcd for $C_{16}H_{30}O_6Br_2$: C, 40.19; H, 6.32. Found: C, 40.12; H, 6.27.

*4.2.4. trans-2,9-Bis(acetoxymethyl)-2,9-dimethyl-18-crown-6 (rac-**2a**).* To a solution of *rac*-**3a** (3.76 g, 7.86 mmol) in DMSO (10 mL) was added potassium acetate (6.20 g, 63.2 mmol) at room temperature. The resulting mixture was stirred for 100 h at 100 °C. After cooling to room temperature, the mixture was filtered and concentrated in vacuo. DMSO was removed by distillation in a Kugelrohr apparatus (45 °C, 0.64 Torr) The crude product was purified by chromatography over silica gel (ethyl acetate) to give *rac*-**2a** as a slightly yellow viscous liquid (2.58 g, 75%). ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.19 (s, 6H), 2.08 (s, 6H), 3.48–3.71 (m, 20H), 4.12 (dd, 4H, J=17.3, 11.4 Hz); ^{13}C NMR (75 MHz, $CDCl_3$): δ 18.1, 21.0, 62.4, 66.3, 70.4, 70.8, 71.4, 74.1, 76.0, 170.8. Anal. Calcd for $C_{20}H_{36}O_{10}$: C, 55.03; H, 8.31. Found: C, 54.95; H, 8.31.

*4.2.5. trans-2,9-Bis(hydroxymethyl)-2,9-dimethyl-18-crown-6 (rac-**1a**).* To a solution of *rac*-**2a** (2.01 g, 4.60 mmol) in H_2O/EtOH (2:1, 15 mL) was added sodium carbonate (0.561 g, 5.29 mmol), followed by stirring at room temperature for 17 h. The mixture was concentrated in vacuo. The residue was purified by chromatography over alumina ($CHCl_3$) to give *rac*-**1a** as a slightly viscous liquid (1.62 g, 100%). ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.12 (s, 6H), 3.09 (t, 2H, J=6.0 Hz), 3.49–3.79 (m, 24H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 17.8, 61.5, 65.1, 70.4, 70.8, 71.6, 75.4. Anal. Calcd for $C_{16}H_{32}O_8$: C, 54.53; H, 9.15. Found: C, 54.29; H, 9.24.

4.3. Synthesis of racemic mixture of 15-crown-5 derivative (*rac*-1c)

trans-2,9-Bis(bromomethyl)-2,9-dimethyl-15-crown-5 (*rac*-**3c**) was prepared according to the previously reported method.[9]

*4.3.1. trans-2,9-Bis(acetoxymethyl)-2,9-dimethyl-15-crown-5 (rac-**2c**).* The synthetic procedure was almost the same as that used for *rac*-**2a**. The crude product was purified by chromatography over silica gel (ethyl acetate) to give *rac*-**2c** as a slightly yellow viscous liquid in 77% yield.

^{1}H NMR (300 MHz, $CDCl_3$): δ 1.18 (s, 6H), 2.08 (s, 6H), 3.46–3.73 (m, 16H), 4.12 (dd, 4H, J=11.3, 6.2 Hz); ^{13}C NMR (75 MHz, $CDCl_3$): δ 18.1, 20.9, 62.4, 67.0, 70.7, 71.0, 73.5, 75.8, 170.8. Anal. Calcd for $C_{18}H_{32}O_9$: C, 55.09; H, 8.22. Found: C, 54.98; H, 8.21.

*4.3.2. trans-2,9-Bis(hydroxymethyl)-2,9-dimethyl-15-crown-5 (rac-**1c**).* The synthetic procedure was almost the same as that used for *rac*-**1a**. The residue was purified by chromatography over alumina ($CHCl_3$) to give *rac*-**1c** as a slightly viscous liquid in 100% yield. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.13 (s, 6H), 2.64 (t, 2H, J=6.2 Hz), 3.53–3.78 (m, 20H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 17.4, 61.8, 67.0, 70.5, 70.8, 75.0, 76.5. Anal. Calcd for $C_{14}H_{28}O_7$: C, 54.53; H, 9.15. Found: C, 54.53; H, 9.33.

4.4. Synthesis of chiral 15-crown-5 ether derivative [(*R*,*R*)-1c]

(2*R*,11*R*)-4,11-Dimethyl-1,14-diphenyl-2,6,9,13-tetraoxatetradecane-4,11-diol [(*R*,*R*)-**13**] was prepared according to the previously reported method.[8]

*4.4.1. (2R,9R)-2,9-bis(benzyloxymethyl)-2,9-dimethyl-15-crown-5 [(R,R)-**14**].* To a suspension of NaH (60% in oil, 423 mg, 10.5 mmol) in diglyme (10 mL) was added dropwise a solution of diethylene glycol ditosylate (1.15 g, 2.52 mmol) and (*R*,*R*)-**13** (0.880 g, 2.10 mmol) in diglyme (50 mL) and the resulting mixture was stirred for 70 h at 100 °C. After cooling to room temperature, a small portion of MeOH was added to the mixture in order to deactivate the excess NaH and the mixture was filtered and concentrated in vacuo. The residue was purified by chromatography over silica gel (toluene/ethyl acetate=95/5–1/1) to give (*R*,*R*)-**14** as a slightly yellow viscous liquid (65 mg, 6%). ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.19 (s, 6H), 3.35–3.74 (m, 20H), 4.54 (dd, 4H, J=12.3, 4.1 Hz), 7.24–7.36 (m, 10H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 18.5, 62.1, 70.6, 70.8, 73.2, 73.3, 73.5, 76.7, 127.4, 127.5, 128.2, 138.6. Anal. Calcd for $C_{28}H_{40}O_7$: C, 68.83; H, 8.25. Found: C, 68.95; H, 8.25.

*4.4.2. (2R,9R)-2,9-Bis(hydroxymethyl)-2,9-dimethyl-15-crown-5 [(R,R)-**1c**].* A suspension of (*R*,*R*)-**14** (0.117 g, 0.240 mmol) and 20% Pd/C (40 mg) in a mixed solvent of dioxane/acetic acid (1:1, 8 mL) was hydrogenated under 5 atm pressure for 220 h at room temperature. The mixture was then filtered and concentrated in vacuo. The residue was purified by chromatography over alumina ($CHCl_3$) to give (*R*,*R*)-**1c** as a slightly yellow viscous liquid (53 mg, 72%). ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.13 (s, 6H), 2.67 (br s, 2H), 3.49–3.78 (s, 20H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 17.4, 62.0, 67.2, 70.6, 71.0, 75.0, 76.5.

4.5. Optical resolution of C_2-symmetric 2,9-bis(hydroxymethyl)-2,9-dimethyl-18-crown-6 using lipase QLM-catalyzed acetylation

*4.5.1. Chiral 2,9-bis(acetoxymethyl)-2,9-dimethyl-18-crown-6 (**2a**).* To a solution of *rac*-**1a** (420 mg, 1.19 mmol) and lipase QLM (40 mg) in diisopropyl ether (20 mL) was added isopropenyl acetate (7.80 g, 77.9 mmol). The resulting mixture was stirred at 28 °C. The reaction was monitored by HPLC and stopped when the conversion to acetate reached 35%. After filtration, the diisopropyl ether was evaporated, and the residue was purified by chromatography over silica gel (hexane/ethyl acetate=70/30) to give **2a** as a slightly yellow viscous liquid (112 mg, 21%). $[\alpha]_D^{27}$ +10.2 (*c* 1.0, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.19 (s, 6H), 2.08 (s, 6H), 3.48–3.73 (m, 20H), 4.12 (dd, 4H, J=17.4, 11.4 Hz); ^{13}C NMR (75 MHz, $CDCl_3$): δ 18.1, 21.0, 62.4, 66.3,

70.7, 70.8, 71.4, 74.1, 76.0, 170.8; HRMS (FAB) calcd for $C_{20}H_{36}O_{12}$: 437.2387 ($[M+H]^+$). Found: 437.2409 ($[M+H]^+$).

*4.5.2. Chiral 2,9-bis(hydroxymethyl)-2,9-dimethyl-18-crown-6 (**1a**).* The synthesis procedure was almost the same as that used for *rac*-**1a**. The residue was purified by chromatography over alumina ($CHCl_3$) to give **1a** as a slightly viscous liquid in 100% yield. The enantiomeric excess (95% ee) was determined by ^{1}H NMR spectroscopy, using (*R*)-(+)-(1-naphthyl)ethylammonium hydrochloride [(*R*)-NpEtCl] as a shift reagent. $[\alpha]_D^{27}$ +3.67 (*c* 1.2, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.12 (s, 6H), 3.10 (t, 2H, *J*=6.0 Hz), 3.49–3.77 (m, 24H); ^{13}C NMR (300 MHz, $CDCl_3$): δ 17.8, 61.6, 65.1, 70.5, 70.8, 71.6, 75.5.

4.6. Optical resolution of C_2-symmetric 2,9-bis(hydroxymethyl)-2,9-dimethyl-15-crown-5 using lipase-catalyzed acetylation

*4.6.1. Chiral 2,9-bis(acetoxymethyl)-2,9-dimethyl-15-crown-5 (**2c**) (entry 1).* To a solution of *rac*-**1c** (288 mg, 0.936 mmol) and lipase QLM (55.9 mg) in diisopropyl ether (18 mL) and tetrahydrofuran (THF, 2 mL) was added isopropenyl acetate (6.54 mL, 60.6 mmol). The resulting mixture was stirred at 36 °C. The reaction was stopped at 6.5 h. After filtration, the diisopropyl ether and THF were evaporated, and the residue was purified by chromatography over silica gel (hexane/ethyl acetate=80/20) to give **2c** as a slightly yellow viscous liquid (52.1 mg, 14%). ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.18 (s, 6H), 2.09 (s, 6H), 3.46–3.73 (m, 16H), 4.12 (dd, 4H, *J*=11.3, 6.6 Hz); ^{13}C NMR (75 MHz, $CDCl_3$): δ 18.1, 20.9, 62.4, 66.9, 70.6, 71.0, 73.4, 75.7, 170.8. Anal. Calcd for $C_{18}H_{32}O_9$: C, 55.09; H, 8.22. Found: C, 54.77; H, 8.26.

*4.6.2. Chiral 2,9-bis(hydroxymethyl)-2,9-dimethyl-15-crown-5 (**1c**) (entry 1).* The synthetic procedure was almost the same as that used for *rac*-**1a**. The residue was purified by chromatography over alumina ($CHCl_3$) to give **1c** as a slightly viscous liquid in 79% yield. The enantiomeric excess (82% ee) was determined by ^{1}H NMR spectroscopy, using (*R*)-NpEtCl as a shift reagent. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.13 (s, 6H), 2.63 (t, 2H, *J*=6.4 Hz), 3.53–3.77 (m, 20H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 17.3, 61.8, 67.1, 70.5, 70.8, 74.8, 76.6. Anal. Calcd for $C_{14}H_{28}O_7$: C, 54.53; H, 9.15. Found: C, 54.63; H, 9.29.

*4.6.3. Chiral 2,9-bis(acetoxymethyl)-2,9-dimethyl-15-crown-5 (**2c**) (entry 2).* To a solution of *rac*-**1c** (490 mg, 1.59 mmol) and lipase PL (635 mg) in diisopropyl ether (45 mL) and THF (5 mL) was added isopropenyl acetate (4 mL, 37.1 mmol). The resulting mixture was stirred at 36 °C. The reaction was stopped at 10.5 h. After filtration, the diisopropyl ether and THF were evaporated, and the residue was purified by medium pressure chromatography over ODS (MeOH/H_2O=1/1) to give **2c** as a slightly yellow viscous liquid (94.1 mg, 16%).

*4.6.4. Chiral 2,9-bis(hydroxymethyl)-2,9-dimethyl-15-crown-5 (**1c**) (entry 2).* The synthetic procedure was almost the same as that used for *rac*-**1a**. The residue was purified by chromatography over alumina ($CHCl_3$) to give **1c** as a slightly viscous liquid in 96% yield. The enantiomeric excess (46% ee) was determined by ^{1}H NMR spectroscopy, using (*R*)-NpEtCl as a shift reagent.

*4.6.5. Chiral 2,9-bis(acetoxymethyl)-2,9-dimethyl-15-crown-5 (**2c**) (entry 3).* To a solution of *rac*-**1c** (496 mg, 1.61 mmol) and lipase OF (107 mg) in diisopropyl ether (45 mL) and THF (5 mL) was added isopropenyl acetate (4 mL, 37.1 mmol). The resulting mixture was stirred at 36 °C. The reaction did not progress and was stopped after 6.5 h.

*4.6.6. Chiral 2,9-bis(acetoxymethyl)-2,9-dimethyl-15-crown-5 (**2c**) (entry 4).* To a solution of *rac*-**1c** (522 mg, 1.69 mmol) and lipase TL (100 mg) in diisopropyl ether (54 mL) and THF (6 mL) was added isopropenyl acetate (4.5 mL, 41.8 mmol). The resulting mixture was stirred at 36 °C. The reaction was stopped at 4 h. After filtration, the diisopropyl ether and THF were evaporated, and the residue was purified by medium pressure chromatography over ODS (MeOH/H_2O=1/1) to give **2c** as a slightly yellow viscous liquid (103 mg, 16%).

*4.6.7. Chiral 2,9-bis(hydroxymethyl)-2,9-dimethyl-15-crown-5 (**1c**) (entry 4).* The synthetic procedure was almost the same as that used for *rac*-**1a**. The residue was purified by chromatography over alumina ($CHCl_3$) to give **1c** as a slightly viscous liquid in 76% yield. The enantiomeric excess (57% ee) was determined by ^{1}H NMR spectroscopy, using (*R*)-NpEtCl as a shift reagent.

*4.6.8. Chiral 2,9-bis(acetoxymethyl)-2,9-dimethyl-15-crown-5 (**2c**) (entry 5).* To a solution of *rac*-**1c** (510 mg, 1.65 mmol) and lipase QLM (114 mg) in diisopropyl ether (36 mL) and THF (4 mL) was added isopropenyl acetate (11.4 mL, 0.105 mmol). The resulting mixture was stirred at 25 °C. The reaction was stopped at 22 h. After filtration, the diisopropyl ether and THF were evaporated, and the residue was purified by medium pressure chromatography over ODS (MeOH/H_2O=1/1) to give **2c** as a slightly yellow viscous liquid (139 mg, 22%).

*4.6.9. Chiral 2,9-bis(hydroxymethyl)-2,9-dimethyl-15-crown-5 (**1c**) (entry 5).* The synthetic procedure was almost the same as that used for *rac*-**1a**. The residue was purified by chromatography over alumina ($CHCl_3$) to give **1c** as a slightly viscous liquid in 100% yield. The enantiomeric excess (77% ee) was determined by ^{1}H NMR spectroscopy, using (*R*)-NpEtCl as a shift reagent.

4.7. Optical resolution of C_2-symmetric 2,9-bis(acetoxymethyl)-2,9-dimethyl-15-crown-5 using lipase QLM-catalyzed solvolysis

*4.7.1. Chiral 2,9-bis(hydroxymethyl)2,9-dimethyl-15-crown-5 (**1c**) (entry 6).* To the solution of *rac*-**2c** (516 mg, 1.32 mmol) in EtOH (633 μL, 10.8 mmol) and hexane (25 mL) was added lipase QLM (523 mg) at 45 °C. The resulting mixture was stirred for 8 days. After filtration, EtOH and hexane were evaporated, and the residue was purified by medium pressure chromatography over ODS (MeCN/H_2O=60/40) to give **1c** as slightly viscous liquid (147 mg, 36%). The enantiomeric excess (50% ee) was determined by ^{1}H NMR spectroscopy, using (*R*)-NpEtCl as a shift reagent.

*4.7.2. Chiral 2,9-bis(acetoxymethyl)2,9-dimethyl-15-crown-5 (**2c**) (entry 7).* To the solution of *rac*-**2c** (496 mg, 1.26 mmol) in EtOH (634 μL, 10.9 mmol) and hexane (7 mL) was added lipase QLM (111 mg) at 45 °C. The resulting mixture was stirred for 7 days. After filtration, EtOH and hexane were evaporated, and the residue was purified by chromatography over silica gel (hexane/ethyl acetate=80/20) to give unreacted **2c** as a slightly yellow viscous liquid (104 mg, 21%). ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.18 (s, 6H), 2.09 (s, 6H), 3.46–3.73 (m, 16H), 4.12 (dd, 4H, *J*=11.3, 6.6 Hz); ^{13}C NMR (75 MHz, $CDCl_3$): δ 18.1, 20.9, 62.4, 66.9, 70.6, 71.0, 73.4, 75.7, 170.8. Anal. Calcd for $C_{18}H_{32}O_9$: C, 55.09; H, 8.22. Found: C, 54.75; H, 8.59.

*4.7.3. Chiral 2,9-bis(hydroxymethyl)-2,9-dimethyl-15-crown-5 (**1c**) (entry 7).* The synthetic procedure was almost the same as that used for *rac*-**1a**. The residue was purified by chromatography over alumina ($CHCl_3$) to give **1c** as a slightly viscous liquid in 100% yield. The enantiomeric excess (75% ee) was determined by ^{1}H NMR spectroscopy, using (*R*)-NpEtCl as a shift reagent. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.13 (s, 6H), 2.70 (br s, 2H), 3.77–3.73 (m, 20H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 17.4, 62.0, 67.3, 70.7, 71.0, 75.2, 76.7. Anal. Calcd for $C_{14}H_{28}O_7$: C, 54.53; H, 9.15. Found: C, 54.47; H, 9.28.

*4.7.4. Chiral 2,9-bis(acetoxymethyl)2,9-dimethyl-15-crown-5 (**2c**) (entry 8).* To the solution of *rac*-**2c** (211 mg, 0.536 mmol) in EtOH

(260 μL, 4.45 mmol) and hexane (5 mL) was added lipase QLM (41 mg) at 37 °C. The resulting mixture was stirred for 11 days. After filtration, EtOH and hexane were evaporated, and the residue was purified by chromatography over silica gel (hexane/ethyl acetate=80/20) to give unreacted **2c** as a slightly yellow viscous liquid (46 mg, 21%).

*4.7.5. Chiral 2,9-bis(hydroxymethyl)-2,9-dimethyl-15-crown-5 (**1c**) (entry 8).* The synthetic procedure was almost the same as that used for *rac*-**1a**. The residue was purified by chromatography over alumina ($CHCl_3$) to give **1c** as a slightly viscous liquid in 100% yield. The enantiomeric excess (75% ee) was determined by ^1H NMR spectroscopy, using (*R*)-NpEtCl as a shift reagent.

*4.7.6. Chiral 2,9-bis(acetoxymethyl)2,9-dimethyl-15-crown-5 (**2c**) (entry 9).* To the solution of *rac*-**2c** (404 mg, 1.03 mmol) in EtOH (456 μL, 7.81 mmol), H_2O (40 μL, 2.22 mmol) and hexane (14 mL) was added lipase QLM (82 mg) at 36 °C. The resulting mixture was stirred for 6 days. After filtration, EtOH and hexane were evaporated, and the residue was purified by chromatography over silica gel (hexane/ethyl acetate=80/20) to give unreacted **2c** as a slightly yellow viscous liquid (32 mg, 8%). $[\alpha]_D^{26}$ −6.06 (*c* 1.1, $CHCl_3$).

*4.7.7. Chiral 2,9-bis(hydroxymethyl)-2,9-dimethyl-15-crown-5 (**1c**) (entry 9).* The synthetic procedure was almost the same as that used for *rac*-**1a**. The residue was purified by chromatography over alumina ($CHCl_3$) to give **1c** as a slightly viscous liquid in 100% yield. The enantiomeric excess (>95% ee) was determined by ^1H NMR spectroscopy, using (*R*)-NpEtCl as a shift reagent. $[\alpha]_D^{26}$ +2.33 (*c* 1.0, $CHCl_3$).

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tet.2011.09.119.

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