Facile Preparation of Optically Active Bicyclo[3.3.1]nonane-2,6-diol and 3,3,7,7-Tetramethylbicyclo[3.3.1]nonane-2,6-diol by Enzyme-Catalyzed Hydrolysis, and Enantiomer Recognition Behavior of Crown Ethers and Podands Having These Diols as a Chiral Subunit[1)]

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Hydrolysis of 2,6-diacetoxybicyclo[3.3.1]nonane (**5**) using lipase from Candida *cylindracea* gave (+)-(1*S*,2*R*,5*S*,6*R*)-6-acetoxybicyclo[3.3.1]nonan-2-ol (**4**) with 81% e.e. and (−)-(1*R*,2*S*,5*R*,6*S*)-**5** with 95% e.e., and pig liver esterase-catalyzed hydrolysis of 2,6-diacetoxy-3,3,7,7-tetramethylbicyclo[3.3.1]nonane (**9**) afforded (−)-(1*S*,2*R*,5*S*,6*R*)-3,3,7,7-tetramethylbicyclo[3.3.1]nonane-2,6-diol (**7**) with 96% e.e. and (+)-(1*R*,2*S*,5*R*,6*S*)-**9** with 86% e.e. By lithium aluminum hydride reduction, (+)-**4** and (−)-**5** were converted to (+)-bicyclo[3.3.1]nonane-2,6-diol (**3**) and (−)-**3** with high optical purity, respectively, and (+)-**7** was obtained from (+)-**9**. Using these optically active diols **3** and **7** as a chiral subunit, optically active crown ethers and podands were prepared and their enantiomer recognition behavior was evaluated by the enantiomer differential transport of (±)-1,2-diphenylethylamine and methyl ester of (±)-phenylglycin hydrochloride through bulk liquid membrane.

Since Cram reported the syntheses of a variety of optically active crown ethers incorporating [1,1′-binaphthalene]-2,2′-diol with C_2-symmetry as a chiral subunit,[2)] various kind of C_2-diols have been incorporated into crown ethers as a chiral subunit.[3)] Recently, we have also reported the syntheses and chiral recognition behaviors of the chiral crown ethers having C_2-5,6,11,12-tetrahydro-6,12-methanodibenzo[*a*,*e*]cyclooctene-5,11-diol[4)] and C_2-7,8,15,16-tetrahydro-7,15-methanodinaphtho[1,2-*a*:1′,2′-*e*]cyclooctene-8,16-diol[5)] as a chiral subunit. These diols possess the bicyclo[3.3.1]nonane-2,6-diol moiety as a common structural feature. These recent results prompted us to examine the chiral recognition properties of crown ethers having the bicyclo[3.3.1]nonane derivatives containing no aromatic moiety as a chiral subunit, and we chose bicyclo[3.3.1]nonane-2,6-diol (**3**) and 3,3,7,7-tetramethylbicyclo[3.3.1]nonane-2,6-diol (**7**) as a chiral building block.

Utilization of enzymes in organic synthesis to prepare chiral compounds of synthetic value is well documented.[6)] Especially, hydrolytic enzymes useful for the preparation of optically active alcohols are attractive in this regard because they operate without requiring expensive coenzymes. We have also investigated the enantioselective reaction mediated by enzyme.[7)] Our continuing interest on biocatalysts in organic synthesis led us to resolve the C_2-diols, the chiral building block, by enzyme-catalyzed kinetic resolution. In this paper we wish to report pig liver esterase (PLE)- and lipase from Candida *cylindracea* (CCL)-catalyzed enantiomerically selective hydrolyses of racemic 2,6-diacetoxybicyclo[3.3.1]nonane (**5**) and 2,6-diacetoxy-3,3,7,7-tetramethylbicyclo[3.3.1]nonane (**9**), and to report syntheses and chiral recognition behavior of crown ethers incorporating bicyclo[3.3.1]nonane-2,6-diol (**3**) and 3,3,7,7-tetramethylbicyclo[3.3.1]nonane-2,6-diol (**7**) as a chiral subunit.

Results and Discussion

Bicyclo[3.3.1]nonane-2,6-diol (**3**) is a chiral molecule of C_2-symmetry, and an introduction of methyl groups, an additional steric barrier, into this skeleton provides 3,3,7,7-tetramethylbicyclo[3.3.1]nonane-2,6-diol (**7**) which has also C_2-symmetry.

Treatment of **1** with excess of methyl iodide and potassium *t*-butoxide in *t*-butyl alcohol gave **2** in 70% yield. Reduction of **2** with lithium aluminum hydride yielded a 95:5 mixture of diastereomers, recrystallization of which from hexane–ether provided **7**, and the minor isomer was not isolated. Treatment of **7** with acetic anhydride and pyridine gave **9**. The C_2-endo,endo-configuration of **9** was unambiguously confirmed by its ^{1}H NMR spectrum which exhibited two singlet signals at δ=0.99 and 1.04 due to the exo- and endo-methyl groups, a singlet signal at δ=2.05 due to the $-OCOCH_3$ protons, and a doublet signal at δ=4.78 (J=6.4 Hz) due to the protons on the carbon bearing the hydroxyl group.

Enzyme-Catalyzed Hydrolyses of Diacetates. PLE- and CCL-catalyzed hydrolysis of **5** and **9** were performed in 0.1 M (1 M=1 mol dm^{-3}) phosphate buffer solution at pH 8.0 and pH 7.4, respectively. In every cases, the reaction processes were monitored by GLC and the reactions were terminated at, or closs to, 50%-of-hydrolysis point. The product was extracted with chloroform and purified by column chromatography. The results are summarized in Table 1.

In the case of hydrolysis of (±)-**5**, CCL-catalyzed hydrolysis gave (+)-**4** and (−)-**5** with 81% and 95% e.e., respectively. By lithium aluminum hydride reduction, (+)-**4** and (−)-**5** were converted into (+)-**3** and (−)-**3**, respectively. Since **3** is a crystalline solid, its optical purity was further enriched by recrystallization from

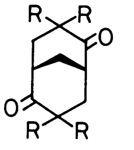
Table 1. Enantioselective Hydrolysis of Racemic Substrates

Entry	Substrate	Enzyme	Time/h	Product (% yield)	e.e./%
1	(±)-**5**	PLE	5.5	(+)-(1*S*,2*R*,5*S*,6*R*)-**4** (47)	30
				(−)-(1*R*,2*S*,5*R*,6*S*)-**5** (43)	31
2	(±)-**5**	CCL	24	(+)-(1*S*,2*R*,5*S*,6*R*)-**4** (36)	81
				(−)-(1*R*,2*S*,5*R*,6*S*)-**5** (46)	95
3	(±)-**9**	PLE	22	(−)-(1*S*,2*R*,5*S*,6*R*)-**7** (43)	96
				(+)-(1*R*,2*S*,5*R*,6*S*)-**9** (46)	86
4	(±)-**9**	CCL	71	(−)-(1*S*,2*R*,5*S*,6*R*)-**7** (5)	66
				(−)-(1*S*,2*R*,5*S*,6*R*)-**8** (40)	55
				(+)-(1*R*,2*S*,5*R*,6*S*)-**9** (40)	53

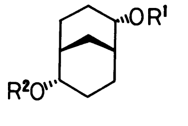
ethyl acetate and the both enantiomers of **3** with >98% e.e. were obtained. On the basis of the absolute configuration of (+)-(1*S*,2*R*,5*S*,6*R*)-**3**,[8] the chemical correlations described above revealed unambiguously the absolute configurations of the acetates **4** and **5** as illustrated in their structural formulas. The maximum rotation of (−)-**3** ($[\alpha]_{D\,max.}$ −59.8°) permitted to calculate the e.e. values of acetates **4** and **5**. PLE-catalyzed hydrolysis of (±)-**5** proceeded smoothly to give (+)-**4** and (−)-**5**, but the enantiomer selectivity of this hydrolysis is poor.

It has been described that **3** was resolved via diastereomeric camphanic acid ester,[8] but the chemical method is rather troublesome. The CCL-catalyzed kinetic resolution of **3** was more facile than the chemical method, and provided both enantiomers with high optical purity.

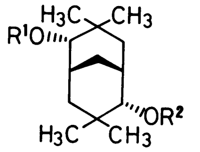
PLE-catalyzed hydrolysis of (±)-**9** gave (−)-**7** with 96% e.e. and (+)-**9** with 86% e.e. The latter was transformed to (+)-**7** by lithium aluminum hydride reduction. CCL-catalyzed hydrolysis of (±)-**9** gave (−)-**8** and (+)-**9** together with a small amount of (−)-**7**, but their optical purities were too low to be synthetically useful as a chiral building block. Reduction of (−)-**8** with lithium aluminum hydride gave (−)-**7**. The determination of absolute configurations of **2** and **7** was straightforward. Treatment of (+)-(1*S*,5*S*)-**1**[8] with methyl iodide gave (+)-(1*R*,5*R*)-**2**, which was converted into (+)-**7**. The chemical correlation assigned the 1*R*,2*S*,5*R*,6*S*-configuration to (+)-**7**. The optically active diol (−)-**7**, prepared by PLE-catalyzed hydrolysis, was converted into the optically active benzoate **10** whose e.e. value was determined to be 96%

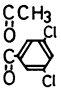


(-)-1 R = H
(-)-2 R = CH_3



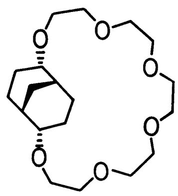
(-)-3 $R^1 = R^2 = H$
(-)-4 $R^1 = \underset{\underset{O}{\|}}{C}CH_3$ $R^2 = H$
(-)-5 $R^1 = R^2 = \underset{\underset{O}{\|}}{C}CH_3$
(-)-6 $R^1 = H$ $R^2 = CH_2Ph$



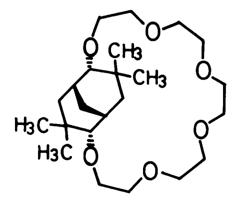
(+)-7 $R^1 = R^2 = H$
(+)-8 $R^1 = \underset{\underset{O}{\|}}{C}CH_3$ $R^2 = H$
(+)-9 $R^1 = R^2 = \underset{\underset{O}{\|}}{C}CH_3$
10 $R^1 = R^2 =$ 

by HPLC-analysis. On the basis of the e.e. value of **7**, those of the acetates **8** and **9** were confirmed. As described above, PLE-catalyzed hydrolysis of **9** provided a facile method for the preparation of the optically active both enantiomers of **7**.

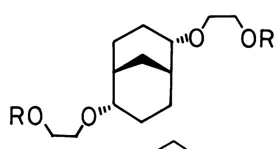
Preparation of Crown Ethers and Podands. Next our task was the preparation of crown ethers and podands using these optically active diols **3** and **7** as a chiral subunit. One of the ethylene glycol units of 18-crown-6 was replaced by the chiral diols (−)-**3** and (+)-**7** to give the crown ethers (−)-**11** and (+)-**12**,

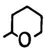


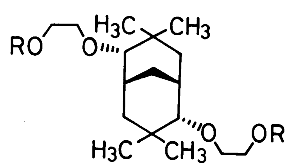
(-)-11



(+)-12

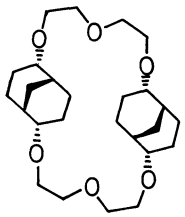


13 R = 
(-)-14 R = H
(-)-15 R = Ms
(-)-16 R = Ts
(-)-17 R = $CH_2CH_2OCH_3$

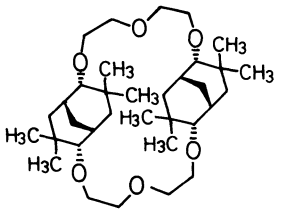


18 R = CH_2OCH_3
(+)-19 R = H
(+)-20 R = Ms
(+)-21 R = $CH_2CH_2OCH_3$

respectively. High dilution condensation of (−)-**3** with pentaethylene glycol bis(*p*-toluenesulfonate) in the presence of sodium hydride in refluxing tetrahydrofuran (THF) provided the crown ether (−)-**11** in 24% yield after chromatography and, similarly, (+)-**12** was prepared from (+)-**7** in 19% yield. The preparation of the crown ethers (−)-**22** and (+)-**23** having two chiral subunits was carried out stepwise. Treatment of (−)-**3** with the *p*-toluenesulfonate of 2-(2-tetrahydropyranyloxy)ethanol and sodium hydride in dimethyl sulfoxide (DMSO) at 40 °C gave **13**, whose protective group was removed with hydrochloric acid and methanol to yield (−)-**14** in 62% yield for two steps. The

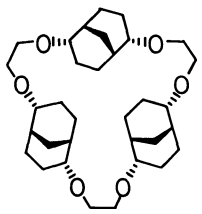


(-)-22



(+)-23

diol (−)-**14** was condensed with (−)-**15**, prepared from (−)-**14** and methanesulfonyl chloride, in the presence of sodium hydride in DMSO at 40 °C to give (−)-**22** in 14% yield. Treatment of (+)-**7** with the *p*-toluenesulfonate of 2-(methoxymethoxy)ethanol and sodium hydride gave **18**, which was transformed to (+)-**19** on treatment with hydrochloric acid and methanol. High dilution condensation of (+)-**19** with (+)-**20**, prepared from (+)-**19**, and sodium hydride in DMSO gave (+)-**23** in 14% yield.



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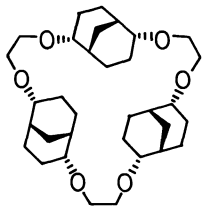

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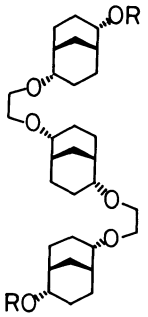
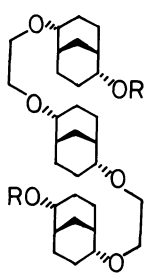
Next we attempted to prepare two diastereomeric crown ethers having three chiral subunits.[9] One of them is the crown ether, (*S,S*),(*R,R*),(*S,S*)-isomer **24**, which contains two (2*S*,6*S*)-subunits and a (2*R*,6*R*)-subunit, and the another crown ether, (*R,R*),(*R,R*),(*R,R*)-isomer **25**, contains three chiral subunits, all of which have the same configuration. The key feature of our strategy for construction of these crown ethers **24** and **25** was the preparation of the open-chain polyethers **27** and **30** with the (*S,S*),(*R,R*),(*S,S*) and the (*R,R*),(*R,R*),(*R,R*)-configuration, respectively. The diols (−)-**3** and (+)-**3** were converted into (−)-**6** and (+)-**6**, respectively, with benzyl bromide and sodium hydride in DMSO. Condensation of (+)-**16**, prepared from (+)-**14**, with 2 equiv of (−)-**6** in the presence of sodium hydride in DMSO at 40 °C yielded (−)-**26** with the (*S,S*),(*R,R*),(*S,S*)-configuration in 43% yield. Debenzylation of (−)-**26** with lithium aluminum hydride in THF gave (−)-**27** in 84% yeild, and treatment of (−)-**27** with methyl iodide and sodium hydride yielded (−)-**28** having the methoxyl groups as a terminal group in 76% yield. The another polyether (+)-**29** having three (2*R*,6*R*)-subunits was prepared in 33% yield by condensation of (+)-(2*R*,6*R*)-**16** with 2 equiv of (+)-(2*R*,6*R*)-**6**. Hydrogenolytic debenzylation of (+)-**29** with 10% Pd on carbon and *p*-toluenesulfonic acid under 1 atm of hydrogen gave (+)-**30** in 91% yield, which was also transformed to (+)-**31**. The final step



(-)-26 R = CH_2Ph
(-)-27 R = H
(-)-28 R = CH_3



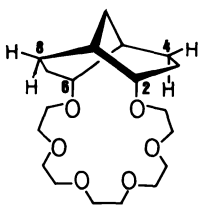
(+)-29 R = CH_2Ph
(+)-30 R = H
(+)-31 R = CH_3

of our strategy was ring closure of the open-chain polyethers (−)-**27** and (+)-**30** by condensation with ethylene glycol bis(methanesulfonate) and sodium hydride. Unfortunately, all attempts to prepare **24** and **25** were failed.

Our final synthetic task was the preparation of the chiral dipodands **17** and **21**. Reaction of (−)-**3** with the *p*-toluenesulfonate of 2-(2-methoxyethoxy)ethanol and sodium hydride in DMSO gave (−)-**17** in 78% yield, and, analogously, (+)-**21** was prepared from (+)-**7** in 90% yield.

Enantiomer Recognition Behavior of Crown Ethers and Podands. The enantiomer recognition behavior of these crown ethers and podands was evaluated by the enantiomer differential transport of (±)-1,2-diphenylethylamine and methyl ester of (±)-phenylglycin hydrochloride through bulk liquid membrane containing the optically active host molecules.[10] The results are given in Table 2.

A few conspicuous features are worth noting. The chiralities of the twisted carbon skeletons of (−)-(1*R*,2*S*,5*R*,6*S*)-subunit **3** and (+)-(1*R*,2*S*,5*R*,6*S*)-subunit **7** are opposite to each other as illustrated in the structures **32** and **33**. However, both (−)-**10** with the



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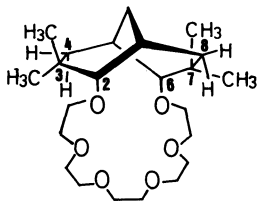

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(1*R*,2*S*,5*R*,6*S*)-subunit **3** and (+)-**11** with the (1*R*,2*S*,5*R*,6*S*)-subunit **7** transferred preferentially (*S*)-1,2-diphenylethylamine and methyl ester of (*R*)-phenylglycin. The reverse of the selectivity by introduction of the methyl groups into the chiral subunit are rationalized by assuming that, in the case of (−)-**10**, two endo-hydrogen atoms at C-4 and C-8 of the subunit act as a 'chiral steric barrier' and, in the case of (+)-**12**, two endo-methyl groups at C-3 and C-7 are more bulky

Table 2. Differential Transport of Enantiomeric Molecules through Bulk Liquid Membrane Containing Chiral Crown Ethers and Chiral Open-Chain Polyethers

Entry	Host	Guest[a)]	Time/h	Transport/%	Configuration of dominant enantiomer	Optical purity/%
1	(−)-**11**	a	2.5	10.7	*S*	21
2	(−)-**11**	b	25	9.9	*R*	20
3	(+)-**12**	a	3.0	10.8	*S*	24
4	(+)-**12**	b	26	10.1	*R*	8
5	(−)-**22**	a	4.8	10.1	*S*	24
6	(−)-**22**	b	74	10.0	*R*	13
7	(+)-**23**	a	8.0	9.9	*S*	26
8	(+)-**23**	b		0[b)]		—
9	(−)-**17**	a	5.0	10.4	*S*	26
10	(−)-**17**	b	10(days)	6.7	*R*	4
11	(+)-**21**	a	9.8	10.1	*R*	16
12	(+)-**21**	b	15(days)	4.4	*S*	4
13	(−)-**26**	a	9.4	10.0	*S*	27
14	(−)-**26**	b		0		—
15	(+)-**29**	a	6.2	10.0	*S*	15
16	(+)-**29**	b		0		—
17	(−)-**28**	a	9.8	9.9	*S*	14
18	(−)-**28**	b		0		—
19	(+)-**31**	a	7.4	10.0	*S*	7
20	(+)-**31**	b		0		—

a) a: (±)-1,2-Diphenylethylamine hydrochloride b: Methyl ester of (±)-phenylglycin hydrochloride. b) After 10 days, a significant transport of the guest molecule was not observed.

steric barrier than the endo-hydrogen atoms at C-4 and C-8 as illustrated in **32** and **33**. Introduction of the second chiral subunit into (−)-**11** and (+)-**12** produced little change in the enantiomer selectivity. The results appear to suggest that the cavities of (−)-**22** and (+)-**23**, 24-crown-6 analogue, are so large that the both chiral barriers hardly participate simultaneously in interacting on the guest molecule located in the cavity.

Recently, we examined the enantiomer recognition behavior of the chiral dipodands, and reported that, among the dipodands examined, the dipodand having the 1,4,7-trioxaoctyl groups as a side chain showed the highest enantiomer selectivity and the value was nearly equal to that of crown ether.[11] The enantiomer selectivities of dipodands (−)-**17** and (+)-**21**, both of which have two 1,4,7-trioxaoctyl groups as a side chain, were also comparable to these of crown ethers (−)-**11** and (+)-**12**. The open-chain polyethers (−)-**26** and (−)-**28** with the alternate configuration showed higher enantiomer selectivity toward 1,2-diphenylethylamine than the polyethers (+)-**29** and (+)-**31** having three subunits of the same configuration.

As described above, the parent compound, bicyclo[3.3.1]nonane-2,6-diol itself is certainly effective as a chiral subunit of a crown ether, but the enantiomer selectivity of the crown ether having this subunit is lower than those of the crown ethers containing bicyclo[3.3.1]nonane-2,6-diol derivatives with aromatic moieties as an additional bulky steric barrier.

Experimental

All melting and boiling points are uncorrected. Infrared spectral data were taken on a Hitachi 260-10 spectrophotometer, and ^{1}H NMR spectra were obtained from a JNM-MH-100. Chemical shifts are reported in parts per million (δ) down field from tetramethylsilane. Optical rotations were measured with a JASCO DIP-140 automatic polarimeter. Mass spectra were taken with a JEOL-DX-303 HF spectrometer. Elemental analyses were determined on a Yanagimoto CHN-Coder, Type II.

3,3,7,7-Tetramethylbicyclo[3.3.1]nonane-2,6-dione (2). A solution of **1**[8] (1.71 g, 11.2 mmol) was added to a solution of potassium *t*-butoxide (19.0 g, 0.170 mol) in absolute 2-methyl-2-propanol (200 mL) and then the mixture was stirred for 1.5 h at room temperature. After methyl iodide (19.2 g, 0.135 mol) was dropwise added to the reaction mixture, the resulting mixture was stirred for 1.5 h at room temperature and for an additional 14 h at reflux. The solid precipitated was removed by filtration and the filtrate was concentrated in vacuo. The residue was acidified with 5% hydrochloric acid and extracted with chloroform. The extract was washed with saturated aqueous solution of sodium hydrogencarbonate and water and dried ($MgSO_4$). After the solvent was removed in vacuo, the residue was chromatographed on alumina (hexane/benzene 2/1 v/v eluent) to give **2** (1.63 g, 70% yield) as a solid, recrystallization of which from hexane provided the sample for the analysis, mp 43—45 °C; IR (KBr) 1715, 1700 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ=1.05 (6H, s), 1.20 (6H, s), 2.01 (4H, d, J=5.2 Hz), 2.30 (2H, t, J=2.0 Hz), 2.77 (2H, m). Found: C, 74.71; H, 9.70%. Calcd for $C_{13}H_{20}O_2$: C, 74.96; H, 9.68%.

3,3,7,7-Tetramethylbicyclo[3.3.1]nonane-2,6-diol (7). A solution of **2** (1.16 g, 5.57 mmol) in dry ether (100 mL) was slowly added to a suspension of lithium aluminum hydride (600 mg, 15.8 mmol) in dry ether (100 mL) and then the mixture was heated for 13 h at reflux. After the reaction mixture was cooled in an ice bath, 10% hydrochloric acid was

added to the mixture and the resulting mixture was stirred for 1 h. The inorganic solid was removed by filtration and the solid was continuously extracted using Soxhlet-extraction apparatus. The ethereal solutions were combined and concentrated to give a solid, which was a 95:5 mixture of diastereomers (1.09 g). Recrystallization of the mixture from hexane–ether provided **7** (930 mg, 79% yield), mp 117.5—119 °C; IR (KBr) 3390, 1045 cm^{-1}; ^1H NMR ($CDCl_3$) δ=1.05 (6H, s), 1.10 (6H, s), 1.70 (2H, s), 3.65 (2H, d, J=6.4 Hz), 1.2—2.5 (8H, m). Found: C, 73.35; H, 11.10%. Calcd for $C_{13}H_{24}O_2$: C, 73.53; H, 11.39%.

2,6-Diacetoxy-3,3,7,7-tetramethylbicyclo[3.3.1]nonane (9). To a solution of **7** (15.0 g, 70.7 mmol) in dry pyridine (150 mL) was slowly added acetic anhydride (100 g, 0.980 mol) with ice cooling and then the mixture was stirred for 48 h at room temperature. After the reaction mixture was poured onto ice, the mixture was acidified with hydrochloric acid and extracted with ether. The extract was washed with saturated aqueous solution of sodium hydrogencarbonate and water and dried ($MgSO_4$). After removal of the solvent, the residue was chromatographed on alumina (hexane/benzene 4/1 v/v) to give an oily product, which was distilled to provide **9** (18.5 g, 88% yield); bp 160—165 °C (8 mmHg) (1 mmHg=133.322 Pa); IR (neat film) 1740, 1240 cm^{-1}; ^1H NMR ($CDCl_3$) δ=0.99 (6H, s), 1.04 (6H, s), 2.05 (6H, s), 4.78 (2H, d, J=7.0 Hz), 1.4—2.1 (8H, m). Found: C, 68.55; H, 9.46%. Calcd for $C_{17}H_{28}O_4$: C, 68.89; H, 9.52%.

PLE-Catalyzed Hydrolysis of 2,6-Diacetoxybicyclo[3.3.1]-nonane (5). To a solution of (±)-**5** (250 mg, 1.04 mmol) in 0.1 M phospate buffer (400 mL, pH 8.0) was added PLE (Boehringer Mannheim Gmbh Co. 104698 100 Units/mg) (460 μL), and the mixture was stirred for 5.5 h at 30 °C. The mixture was extracted with chloroform and the extract was washed with water and dried ($MgSO_4$). After removal of the solvent, the residue was chromatographed on silica gel. The fractions eluted with chloroform gave (−)-**5** (108 mg, 43% yield) as an oil and the subsequent fractions eluted with the same solvent gave (+)-**4** (97 mg, 47% yield) as an oil.

(+)-**4**; $[\alpha]_D^{23}$ +16.6° (*c* 0.802, $CHCl_3$).

(−)-**5**; $[\alpha]_D^{24}$ −23.0° (*c* 1.24, $CHCl_3$).

CCL-Catalyzed Hydrolysis of 2,6-Diacetoxybicyclo[3.3.1]-nonane (5). To a solution of (±)-**5** (500 mg, 2.08 mmol) in 0.1 M phosphate buffer (600 mL, pH 7.4) was added Lipase VII (CCL, Sigma 600—700 Units/mg) (500 mg) and the mixture was stirred for 24 h at 30 °C. The mixture was extracted with chloroform and the extract was washed with water and dried ($MgSO_4$). After removal of the solvent, the residue was chromatographed on silica gel. The fractions eluted with benzene–ether (8/2 v/v) gave (−)-**5** (230 mg, 46%) as an oil and the subsequent fractions eluted with the same solvent gave (+)-**4** (148 mg, 36% yield) as an oil.

(+)-**4**; $[\alpha]_D^{23}$ +45.2° (*c* 1.04, $CHCl_3$); IR (neat film) 3400, 1715, 1240 cm^{-1}.

(−)-**5**; $[\alpha]_D^{24}$ −70.7° (*c* 1.05, $CHCl_3$).

PLE-Catalyzed Hydrolysis of 2,6-Diacetoxy-3,3,7,7-tetramethylbicyclo[3.3.1]nonane (9). By using the same procedure described for the hydrolysis of (±)-**5**, (±)-**9** (500 mg, 1.69 mmol) was hydrolyzed with PLE (300 μL) in 0.1 M phosphate buffer (300 mL, pH 8.0). The chromatography on alumina gave (+)-**9** (230 mg, 46% yield) as an oil and (−)-**7** (155 mg, 43% yield) as a solid.

(−)-**7**; $[\alpha]_D^{24}$ −87.5° (*c* 1.26, $CHCl_3$); mp 144—145 °C.

(+)-**9**; $[\alpha]_D^{25}$ +97.0° (*c* 1.05, $CHCl_3$).

CCL-Catalyzed Hydrolysis of 2,6-Diacetoxy-3,3,7,7-tetramethylbicyclo[3.3.1]nonane (9). By using the same procedure described for the hydrolysis of (±)-**5**, (±)-**9** (250 mg, 0.843 mmol) was hydrolyzed with CCL (750 mg) in 0.1 M phosphate buffer (380 mL, pH 7.4). The chromatography on alumina gave (+)-**9** (100 mg, 40% yield) as an oil, (−)-**8** (86 mg, 40% yield) as a solid, and (−)-**7** (9 mg, 5% yield) as a solid.

(−)-**7**; $[\alpha]_D^{20}$ −60.7° (*c* 0.450, $CHCl_3$).

(−)-**8**; $[\alpha]_D^{22}$ −47.7° (*c* 1.01, $CHCl_3$); IR (KBr) 3450, 1710, 1260 cm^{-1}.

(+)-**9**; $[\alpha]_D^{20}$ +59.3° (*c* 1.91, $CHCl_3$).

(−)-(1*R*,2*S*,5*R*,6*S*)-Bicyclo[3.3.1]nonane-2,6-diol (3). To a suspension of lithium aluminum hydride (1.76 g, 46.4 mol) in dry ether (100 mL) was dropwise added a solution of (−)-**5**; $[\alpha]_D$ −70.7° (2.23 g, 9.28 mmol) in dry ether (100 mL) and then the mixture was heated for 10 h at reflux. To the reaction mixture was added a small amount of ethyl acetate and 10% hydrochloric acid with ice cooling, and the resulting mixture was stirred for 1 h at room temperature. The inorganic solid was filtered off and the solid was continuously extracted with ether using Soxhlet extraction apparatus. The etheral solutions were combined and dried ($MgSO_4$). Removal of the solvent gave **3** (1.15 g, 79% yield); $[\alpha]_D^{24}$ −56.8° (*c* 1.17, ethanol), which was recrystallized from ethyl acetate to yield the specimene; $[\alpha]_D^{25}$ −59.4° (*c* 1.02, ethanol); mp 214.5—215 °C. Found: C, 68.98; H, 10.29%. Calcd for $C_9H_{16}O_2$: C, 69.19; H, 10.32%.

(+)-(1*S*,2*R*,5*S*,6*R*)-Bicyclo[3.3.1]nonane-2,6-diol (3). By using the same procedure described above, (+)-**4**; $[\alpha]_D$ +45.2° (1.61 g, 8.13 mmol) was converted into **3** (1.08 g, 85% yield); $[\alpha]_D^{25}$ +48.5° (*c* 0.773, ethanol), which was recrystallized from ethyl acetate to yield the specimen; mp 214—215 °C; $[\alpha]_D^{26}$ +59.0° (*c* 0.770, ethanol). Found: C, 69.01; H, 10.28%. Calcd for $C_9H_{16}O_2$: C, 69.19; H, 10.32%.

Oxidation of (−)-(1*R*,2*S*,5*R*,6*S*)-Bicyclo[3.3.1]nonane-2,6-diol (3). An excess of Jones' reagent[12] was added to a chilled solution of (−)-**3**; $[\alpha]_D$ −56.4° (*c* 0.378, EtOH) (312 mg, 2.00 mmol), prepared according to Gerlach's procedure,[8] in acetone (8 mL). After stirring for 2 h with ice cooling, sodium bisulfite was added to the reaction mixture. Usual workup followed by chromatography on silica gel (ether) gave (−)-**1**; $[\alpha]_D^{25}$ −206.8° (*c* 1.01, 1,4-dioxane) (94.3% e.e.) (lit,[8] $[\alpha]_{D\,max.}$ −219.2°) (200 mg, 65% yield) as a white solid.

(+)-(1*R*,2*S*,5*R*,6*S*)-3,3,7,7-Tetramethylbicyclo[3.3.1]nonane-2,6-diol (7). By using the same procedure described for the reduction of (−)-**5**, (+)-**9**; $[\alpha]_D$ +97.0° (900 mg, 3.04 mmol) was converted into (+)-**7**; $[\alpha]_D^{25}$ +79.1° (*c* 0.953, $CHCl_3$) (610 mg, 95% yield), which was recrystallized from ether–hexane to provide the specimen; mp 143—144 °C; $[\alpha]_D^{25}$ +91.4° (*c* 1.11, $CHCl_3$). Its spectral data agreed with those of (±)-**7**.

(+)-(1*R*,5*R*)-3,3,7,7-Tetramethylbicyclo[3.3.1]nonane-2,6-dione (2). By using the same procedure described for the preparation of (±)-**2**, (+)-**1**;[8] $[\alpha]_D$ +187.0° (1.71 g, 11.2 mmol) was converted into (+)-**2** (1.25 g, 53% yield); mp 36—38 °C, $[\alpha]_D^{20}$ +100.4° (*c* 0.980, $CHCl_3$). The IR and ^1H NMR spectra are identical with those of (±)-**2**.

Lithium Aluminum Hydride Reduction of (+)-(1*R*,5*R*)-3,3,7,7-Tetramethylbicyclo[3.3.1]nonane-2,6-dione (2). By

using the same procedure described for the preparation of (±)-**7**, (+)-**2**; $[\alpha]_D$ +100.4° (1.16 g, 5.57 mmol) was converted into (+)-**7** (610 mg, 52% yield); mp 141—143 °C, $[\alpha]_D^{24}$ +70.7° (*c* 0.950, $CHCl_3$). The IR and ^1H NMR spectra are identical with those of (±)-**7**.

2,6-Bis(3,5-dichlorobenzoyloxy)-3,3,7,7-tetramethylbicyclo-[3.3.1]nonane (10). To a solution of (±)-**7** (18 mg, 0.085 mmol) in pyridine (2 mL) was added 3,5-dichlorobenzoyl chloride (540 mg, 2.58 mmol) with ice cooling and then the mixture was stirred overnight at room temperature. After addition of ice water to the reaction mixture, the mixture was acidified with 10% hydrochloric acid and then extracted with ether. The extract was washed with saturated aqueous solution of sodium hydrogencarbonate and water and dried ($MgSO_4$). After removal of the solvent, the oily residue was purified by a preparative thin layer chromatography (silica gel, benzene/ether 1/1 v/v) to yield **10** (34 mg, 72% yield) as a white solid; IR (KBr) 1720, 1580, 1270, 810, 780 cm^{-1}. Found: C, 57.76; H, 5.02; Cl, 25.29%. Calcd for $C_{27}H_{28}O_4Cl_4$: C, 58.08; H, 5.06; Cl, 25.40%.

By the same procedure descrived above, (−)-**7**; $[\alpha]_D$ −87.5° was converted into the optically active benzoate, whose e.e. value was determined to be 96% by HPLC-analysis. HPLC-analysis was carried out on Simadzu LC-6A using a chiral column (250×4.6 mm) packed with cellulose tris(3,5-dimethylphenylcarbamate) on silica gel[13] (hexane/2-propanol, 99/1 0.4 mL min^{-1}).

(−)-(1*R*,4*S*,21*S*,24*R*)-5,8,11,14,17,20-Hexaoxatricyclo[19.4.0.0^{4,24}]pentaicosane (11). A suspension of sodium hydride (177 mg, 7.38 mmol) in dry tetrahydrofuran (THF) (80 mL) was gently refluxed and to the boiling mixture a solution of (−)-**3** (327 mg, 2.10 mmol) and pentaethylene glycol bis(*p*-toluenesulfonate) (1.14 g, 2.10 mmol) in dry THF (200 mL) was added dropwise over a period of 12 h in nitrogen atmosphere. The mixture was heated for an additional 50 h at reflux. After the mixture was cooled in an ice bath, a small amount of water was added to the chilled mixture. The solvent was removed in vacuo and the residue was extracted with dichloromethane. The extract was washed with dilute hydrochloric acid, saturated aqueous solution of sodium hydrogencarbonate, and water and dried ($MgSO_4$). After removal of the solvent, the residue was chromatographed on alumina (benzene/chloroform 1/1 v/v) to give **11** (180 mg, 24% yield) as a colorless oil; $[\alpha]_D^{20}$ −33.1° (*c* 0.730, $CHCl_3$); IR (neat film) 1110 cm^{-1}; ^1H NMR ($CDCl_3$) δ=1.3—2.2 (12H, m), 3.5—3.8 (20H, m), 4.0—4.2 (2H, m); MS *m/z* 358 (M^+). Found: C, 63.11; H, 9.49%. Calcd for $C_{19}H_{34}O_6$: C, 63.66; H, 9.56%.

(+)-(1*R*,4*S*,21*S*,24*R*)-3,3,22,22-Tetramethyl-5,8,11,14,17,20-hexaoxatricyclo[19.4.0.0^{4,24}]pentaicosane (12). By using the same procedure described above, reaction of (+)-**7** (425 mg, 2.00 mmol) with pentaethylene glycol bis(*p*-toluenesulfonate) (1.08 g, 2.00 mmol) and sodium hydride (168 mg, 7.00 mmol) in dry THF. The crude product was chromatographed on alumina (benzene/chloroform 1/1 v/v) to give **12** (386 mg, 19% yield) as a colorless oil.

12; $[\alpha]_D^{22}$ +53.2° (*c* 0.470, $CHCl_3$); IR (neat film) 1100 cm^{-1}; ^1H NMR ($CDCl_3$) δ=0.97 (6H, s), 1.03 (6H, s), 1.67 (6H, s), 1.2—2.3 (8H, m), 3.14 (2H, d, *J*=6.6 Hz), 3.5—3.8 (20H, m); MS *m/z* 414 (M^+). Found: C, 63.86; H, 10.05%. Cacld for $C_{23}H_{42}O_6$: C, 66.63; H, 10.21%.

(−)-(1*R*,2*S*,5*R*,6*S*)-2,6-Bis(2-hydroxyethoxy)bicyclo[3.3.1]-nonane (14). To a suspension of sodium hydride (888 mg, 37.0 mmol) in dry dimethyl sulfoxide (DMSO) (30 mL) was added a solution of (−)-**3** (1.45 g, 9.28 mmol) in dry DMSO (30 mL) and then the mixture was heated at 35 °C for 6 h under nitrogen atmosphere. A solution of the *p*-toluenesulfonate of 2-(2-tetrahydropyranyloxy)ethanol (11.2 g, 37.3 mmol) in dry DMSO (50 mL) was added to the reaction mixture and the resulting mixture was stirred for 15 h at 35 °C. After an ice water (100 mL) was added to the reaction mixture, it was extracted with ether. The extract was washed with water, dried ($MgSO_4$), and concentrated in vacuo. The residue was chromatographed on silica gel (hexane/ether 1/1 v/v) to give **13** as a pale yellow oil, which was dissolved in methanol (50 mL). Three drops of hydrochloric acid was added to the solution and the resulting mixture was stirred for 12 h at room temperature. After sodium carbonate (1.00 g) was added to the reaction mixture, the mixture was stirred for 30 min. The solid was removed by filtration and the filtrate was concentrated in vacuo to give an oily residue, which was extracted with chloroform. The extract was washed with water and dried ($MgSO_4$). After removal of the solvent, the residue was chromatographed on silica gel (ether/methanol 96/4 v/v) to yield **14** (1.40 g, 62% yield) as a white solid; $[\alpha]_D^{23}$ −60.1° (*c* 1.03, $CHCl_3$); IR (neat film) 3420, 1100, 1090, 1060 cm^{-1}. Found: C, 63.32; H, 9.71%. Calcd for $C_{13}H_{24}O_4$: C, 63.90; H, 9.90%.

(−)-(1*R*,2*S*,5*R*,6*S*)-2,6-Bis(2-mesyloxyethoxy)bicyclo[3.3.1]-nonane (15). To a mixture of (−)-**14** (1.60 g, 6.55 mmol), triethylamine (6.63 g, 65.5 mmol) and dichloromethane (30 mL) was slowly added a solution of methanesulfonyl chloride (6.00 g, 52.4 mmol) in dichloromethane (20 mL) with ice cooling. After being stirred for 2 h at 0 °C and for an additional 1 h at room temperature, the mixture was poured onto ice and extracted with dichloromethane. The extract was washed with dilute hydrochloric acid, saturated aqueous solution of sodium hydrogencarbonate, and water and dried ($MgSO_4$). After removal of the solvent, the residue was chromatographed on silica gel (hexane/ether 1/9 v/v) to give **15** (2.22 g, 85% yield) as a pale yellow oil, which was used for the next reaction without further purification.

(−)-(1*R*,4*S*,12*S*,15*R*,17*R*,20*S*,28*S*,31*R*)-5,8,11,21,24,27-Hexaoxapentacyclo[26.4.0.0^{4,31}.0^{12,17}.0^{15,20}]dotriacontane (22). To a mixture of sodium hydride (216 mg, 9.00 mmol), potassium tetrafluoroborate (100 mg, 0.794 mmol), and dry DMSO (150 mL) was slowly added a mixture of (−)-**14** (550 mg, 2.25 mmol) and (−)-**15** (901 mg, 2.25 mmol) in dry DMSO (15 mL) over a period of 10 h at 40 °C, and then the resulting mixture was heated for an additional 60 h at this temperature under nitrogen atmosphere. After a small amount of ice water was added to the reaction mixture, the solvent was removed in vacuo and the residue was extracted with ether. The extract was washed with water and dried ($MgSO_4$). After removal of the solvent, the residue was chromatographed on silica gel (hexane/ether 4/6 v/v) to yield **22** (140 mg, 14% yield) as a white solid; mp 56—58 °C; $[\alpha]_D^{25}$ −20.0° (*c* 1.01, $CHCl_3$); IR (KBr) 1100 cm^{-1}; ^1H NMR ($CDCl_3$) δ=1.08—2.40 (24H, m), 3.16—3.76 (20H, m); MS *m/z* 452 (M^+). Found: C, 68.44; H, 9.81%. Calcd for $C_{26}H_{44}O_6$: C, 68.99; H, 9.80%.

(+)-(1*R*,2*S*,5*R*,6*S*)-2,6-Bis(2-hydroxyethoxy)-3,3,7,7-tetramethylbicyclo[3.3.1]nonane (19). By the similar procedure described for the preparation of **14**, reaction of (+)-**7** (2.07 g,

9.75 mmol) with the *p*-toluenesulfonate of 2-(methoxymethoxy)ethanol (14.0 g, 53.8 mmol) and sodium hydride (1.17 g, 48.8 mmol) in dry DMSO was carried out. The crude product was chromatographed on silica gel (hexane/ether 1/1 v/v) to give **18** (3.3 g) as an oil. Treatment of **18** (3.3 g) with methanol and hydrochloric acid followed by chromatography on silica gel gave **19** (2.21 g, 76% overall yield) as a colorless oil; $[\alpha]_D^{25}$ +99.4° (*c* 1.19, $CHCl_3$); IR (neat film) 3350, 1110 cm^{-1}; ^1H NMR ($CDCl_3$) δ=1.00 (6H, s), 1.06 (6H, s), 1.2—1.9 (6H, m), 2.15 (2H, s), 2.30 (2H, br s), 3.18 (2H, d, *J*=9.0 Hz), 3.28—3.76 (8H, m). Found: C, 67.35; H, 10.70%. Calcd for $C_{17}H_{32}O_4$: C, 67.96; H, 10.74%.

(+)-(1*R*,2*S*,5*R*,6*S*)-2,6-Bis(2-mesyloxyethoxy)-3,3,7,7-tetramethylbicyclo[3.3.1]nonane (20). By using the same procedure described for the preparation of **14**, (+)-**19** (800 mg, 2.66 mmol) was reacted with methanesulfonyl chloride (2.44 g, 21.3 mmol) and triethylamine (2.69 g, 26.6 mmol) in dichloromethane. The crude product was chromatographed on silica gel (hexane/ether 3/7 v/v) to yield **20** (1.19 g, 98% yield), which was recrystallized from hexane to give the specimen; mp 46—47 °C; $[\alpha]_D^{24}$ +71.0° (*c* 1.00, $CHCl_3$); IR (KBr) 3025, 1350, 1180 cm^{-1}; ^1H NMR ($CDCl_3$) δ=0.93 (6H, s), 1.07 (6H, s), 1.1—1.9 (8H, m), 2.32 (2H, br s), 3.03 (6H, s), 3.18 (2H, d, *J*=9.0 Hz), 3.66 (2H, m), 4.32 (4H, t, *J*=5.2 Hz). Found: C, 49.65; H, 7.73; S, 13.88%. Calcd for $C_{19}H_{36}O_8S_2$: C, 50.00; H, 7.95; S, 14.05%.

(+)-(1*R*,4*S*,12*S*,15*R*,17*R*,20*S*,28*S*,31*R*)-3,3,13,13,19,19,29,29-Octamethyl-5,8,11,21,24,27-hexaoxapentacyclo[26.4.0.0^{4,31}.0^{12,17}.0^{15,20}]dotriacontane (23). By using the same procedure described for the preparation of **22**, condensation of (+)-**19** (550 mg, 1.83 mmol) with (+)-**20** (835 mg, 1.83 mmol) and sodium hydride (180 mg, 7.50 mmol) in the presence of potassium tetrafluoroborate (100 mg, 0.794 mmol) was carried out in dry DMSO. The product was chromatographed on silica gel (hexane/ether 1/1 v/v) to give **23** (140 mg, 14% yield) as a colorless oil; $[\alpha]_D^{25}$ +104.4° (*c* 1.15, $CHCl_3$); IR (neat film) 1100 cm^{-1}; ^1H NMR ($CDCl_3$) δ=0.98 (12H, s), 1.05 (12H, s), 1.1—2.0 (12H, m), 2.28 (4H, br s), 3.14 (4H, d, *J*=9.0 Hz), 3.28—3.80 (16H, m); MS *m/z* 564 (M^+). Found: C, 67.20; H, 10.13%. Calcd for $C_{34}H_{60}O_6$: C, 72.30; H, 10.71%.

(−)-(1*R*,2*S*,5*R*,6*S*)-6-Benzyloxybicyclo[3.3.1]nonan-2-ol (6). To a suspension of sodium hydride (413 mg, 17.2 mmol) in dry DMSO (30 mL) was added a solution of (−)-**3** (1.90 g, 12.1 mmol) in dry DMSO (20 mL) and then the mixture was heated at 35 °C for 6 h. To the reaction mixture was added a solution of benzyl bromide (2.50 g, 14.6 mmol) in dry DMSO (30 mL) and the resulting mixture was stirred for 15 h at room temperature. After an ice water (50 mL) was added to the reaction mixture, the mixture was extracted with ether. The extract was washed with water, dried ($MgSO_4$), and concentrated in vacuo. The residue was chromatographed on silica gel (benzene/ether 1/1 v/v) to give **6** (1.21 g, 41% yield) as a solid; mp 59—61 °C; $[\alpha]_D^{25}$ −60.1° (*c* 1.02, $CHCl_3$); IR (KBr) 3090, 3060, 3020, 740, 700 cm^{-1}; ^1H NMR ($CDCl_3$) δ=1.2—2.2 (13H, m), 3.4—3.9 (2H, m), 4.47 (1H, d, *J*=10.8 Hz), 4.55 (1H, d, *J*=10.8 Hz), 7.2—7.4 (5H, m). Found: C, 77.55; H, 8.97%. Calcd for $C_{16}H_{22}O_2$: C, 78.01; H, 9.00%.

(+)-(1*S*,2*R*,5*S*,6*R*)-2,6-Bis(2-tosyloxyethoxy)bicyclo[3.3.1]nonane (16). To a solution of (+)-**14**; $[\alpha]_D$ +59.1° (1.05 g, 4.30 mmol), prepared from (+)-**3** by the same procedure described for the preparation of (−)-**14**, in pyridine (30 mL) was added *p*-toluenesulfonyl chloride (3.28 g, 17.2 mmol) with ice cooling and then the mixture was stirred for 2 h at the same temperature. After the reaction mixture was poured onto ice, the resulting mixture was acidified with hydrochloric acid and extracted with benzene. The extract was washed with diluted hydrochloric acid, saturated aqueous solution of sodium hydrogencarbonate, and water, and dried ($MgSO_4$). After removal of the solvent, the residue was chromatographed on silica gel (benzene/ether 9/1 v/v) to give **16** (1.58 g, 67% yield) as an oil; $[\alpha]_D^{26}$ +28.9° (*c* 0.950, $CHCl_3$); ^1H NMR ($CDCl_3$) δ=1.0—2.0 (12H, m), 2.44 (6H, s), 3.36 (2H, m), 3.58 (4H, t, *J*=4.8 Hz), 4.14 (4H, t, *J*=4.8 Hz), 7.29 (4H, d, *J*=8.0 Hz), 7.76 (4H, d, *J*=8.0 Hz). Found: C, 58.21; H, 6.50; S, 11.56%. Calcd for $C_{27}H_{36}O_8S_2$: C, 58.68; H, 6.57; S, 11.60%.

(−)-(1*S*,2*R*,5*S*,6*R*)-2,6-Bis{2-[(1*R*,2*S*,5*R*,6*S*)-6-benzyloxybicyclo[3.3.1]non-2-yloxy]ethoxy}bicyclo[3.3.1]nonane (26). To a suspension of sodium hydride (156 mg, 6.50 mmol) in dry DMSO (40 mL) was added a solution of (−)-**6** (1.00 g, 4.06 mmol) in dry DMSO (30 mL) and then the mixture was heated at 30 °C for 6 h. After the mixture was cooled in an ice bath, a solution of (+)-**16** (895 mg, 1.62 mmol) in dry DMSO (40 mL) was added to the chilled mixture. The resulting mixture was heated at 35 °C for 40 h under nitrogen atmosphere. The reaction mixture was poured into ice water and extracted with ether. The extract was washed with water, dried ($MgSO_4$), and concentrated in vacuo. The residue was chromatographed on silica gel (benzene/ether 9/1 v/v) to yield (−)-**26** (488 mg, 43% yield); mp 119—120 °C; $[\alpha]_D^{25}$ −30.3° (*c* 1.01 $CHCl_3$); IR (KBr) 3060, 3030, 1110, 740, 700 cm^{-1}; ^1H NMR ($CDCl_3$) δ=1.2—2.2 (36H, m), 3.3—3.7 (14H, m), 4.47 (2H, d, *J*=10.8 Hz), 4.55 (2H, d, *J*=10.8 Hz), 7.2—7.4 (10H, m). Found: C, 76.88; H, 9.10%. Calcd for $C_{45}H_{64}O_6$: C, 77.10; H, 9.20%.

(−)-(1*S*,2*R*,5*S*,6*R*)-2,6-Bis{2-[(1*R*,2*S*,5*R*,6*S*)-6-hydroxybicyclo[3.3.1]non-2-yloxy]ethoxy}bicyclo[3.3.1]nonane (27). To a solution of (−)-**26** (400 mg, 0.571 mmol) in dry THF (100 mL) was added lithium aluminum hydride (1.75 g, 46.1 mmol) in a small portions and then the resulting mixture was heated for 14 h at reflux. After water (10 mL) was added to the reaction mixture with ice cooling, the mixture was stirred for 2 h. The inorganic solid was removed by filtration and the solid was continuously extracted with ether using Soxhlet extraction apparatus. The organic solutions were combined, washed with water, dried ($MgSO_4$), and concentrated in vacuo. The residue was chromatographed on silica gel (ether) to yield **27** (250 mg, 84% yield) as a solid; mp 67.5—69 °C; $[\alpha]_D^{26}$ −10.8° (*c* 1.49, $CHCl_3$); IR (KBr) 3360, 2920, 2850, 1100 cm^{-1}. Found: C, 70.15; H, 9.85%. Calcd for $C_{31}H_{52}O_6$: C, 71.50; H, 10.07%.

(−)-(1*S*,2*R*,5*S*,6*R*)-2,6-Bis{2-[(1*R*,2*S*,5*R*,6*S*)-6-methoxybicyclo[3.3.1]non-2-yloxy]ethoxy}bicyclo[3.3.1]nonane (28). To a suspension of sodium hydride (55 mg, 2.3 mmol) in dry DMSO (20 mL) was added a solution of (−)-**27** (150 mg, 0.288 mmol) in dry DMSO (40 mL) and the mixture was heated at 35 °C for 4 h. After the mixture was cooled in an ice bath, a solution of methyl iodide (500 mg, 3.52 mmol) in dry DMSO (30 mL) was added to the chilled mixture. The resulting mixture was heated at 35 °C for 14 h and poured into ice water. The mixture was extracted with ether. The extract was washed with water, dried ($MgSO_4$), and concentrated in vacuo. The residue was chromatographed

on silica gel (benzene/ether 8/2 v/v) to yield (−)-**28** (120 mg, 76% yield); mp 71—73 °C; $[\alpha]_D^{20}$ −21.5° (*c* 1.08, $CHCl_3$); IR (KBr) 1110 cm^{-1}; ^1H NMR ($CDCl_3$) δ=1.2—2.1 (36H, m), 3.32 (6H, s), 3.2—3.7 (14H, m); MS *m/z* 548 (M^+).

(+)-(1*S*,2*R*,5*S*,6*R*)-2,6-Bis{2-[(1*S*,2*R*,5*S*,6*R*)-6-benzyloxybicyclo[3.3.1]non-2-yloxy]ethoxy}bicyclo[3.3.1]nonane (29). By using the same procedure described for the preparation of **26**, (+)-**29** (260 mg, 33% yield) was prepared by condensation of (+)-**6**; $[\alpha]_D$ +59.7° (700 mg, 2.84 mmol), prepared from (+)-**3**, with (+)-**16** (620 mg, 1.12 mmol) and sodium hydride (108 mg, 4.50 mmol). (+)-**29**; a colorless oil; $[\alpha]_D^{20}$ +78.7° (*c* 0.995, $CHCl_3$); IR (neat film) 1100, 740, 700 cm^{-1}; ^1H NMR ($CDCl_3$) δ=1.2—2.2 (36H, m), 3.4—3.7 (12H, m), 4.46 (2H, d, *J*=10.8 Hz), 4.54 (2H, d, *J*=10.8 Hz), 7.2—7.4 (10H, m). Found: C, 76.80; H, 9.20%. Calcd for $C_{45}H_{64}O_6$: C, 77.10; H, 9.20%.

(+)-(1*S*,2*R*,5*S*,6*R*)-2,6-Bis{2-[(1*S*,2*R*,5*S*,6*R*)-6-hydroxybicyclo[3.3.1]non-2-yloxy]ethoxy}bicyclo[3.3.1]nonane (30). A mixture of (+)-**29** (115 mg, 0.164 mmol), *p*-toluenesulfonic acid monohydrate (10 mg), 10% Pd on carbon (100 mg), and 1,4-dioxane (20 mL) was shaken at 1 atm of hydrogen at room temperature. After hydrogen uptake had ceased, the catalyst was removed by filtration. To the filtrate was added sodium carbonate (200 mg), and the resulting mixture was stirred for 1 h. The solid was removed by filtration and the filtrate was concentrated in vacuo. The residue was extracted with chloroform and the extract was washed with water, dried ($MgSO_4$), and concentrated in vacuo. The resulting oil was chromatographed on silica gel (ether) to give (+)-**30** (78 mg, 91% yield) as a colorless oil; $[\alpha]_D^{20}$ +60.6° (*c* 0.929, $CHCl_3$); IR (neat film) 3370, 1100 cm^{-1}; MS *m/z* 520 (M^+).

(+)-(1*S*,2*R*,5*S*,6*R*)-2,6-Bis{2-[(1*S*,2*R*,5*S*,6*R*)-6-methoxybicyclo[3.3.1]non-2-yloxy]ethoxy}bicyclo[3.3.1]nonane (31). By using the same procedure described for the preparation of **28**, (+)-**31** (68 mg, 86% yield) was prepared from (+)-**30** (75 mg, 0.14 mmol) with sodium hydride (28 mg, 1.2 mmol) and methyl iodide (250 mg, 1.78 mmol).

(+)-**31**; a colorless oil; $[\alpha]_D^{22}$ +70.3° (*c* 0.968, $CHCl_3$); IR (neat film) 1100 cm^{-1}; ^1H NMR ($CDCl_3$) δ=1.2—2.1 (36H, m), 3.32 (6H, s), 2.9—3.6 (14H, m); MS *m/z* 548 (M^+).

(−)-(1*R*,2*S*,5*R*,6*S*)-2,6-Bis(1,4,7-trioxaoctyl)bicyclo[3.3.1]nonane (17). To a suspension of sodium hydride (93 mg, 3.9 mmol) in dry DMSO (30 mL) was added a solution of (−)-**3** (100 mg, 0.640 mmol) in dry DMSO (20 mL), and then the resulting mixture was heated at 35 °C for 6 h. After the mixture was cooled in an ice bath, a solution of the *p*-toluenesulfonate of 2-(2-methoxyethoxy)ethanol (1.06 g, 3.87 mmol) in dry DMSO (30 mL) was added to the chilled mixture. After being heated at 35 °C for 15 h, the reaction mixture was poured into ice water and extracted with ether. The extract was washed with water, dried ($MgSO_4$), and concentrated in vacuo. The residual oil was chromatographed on silica gel (benzene/ether 1/1 v/v) to yield **17** (180 mg, 78% yield) as a colorless oil; $[\alpha]_D^{22}$ −56.7° (*c* 0.905, $CHCl_3$); IR (neat film) 1140, 1100 cm^{-1}; ^1H NMR ($CDCl_3$) δ=1.2—2.1 (12H, m), 3.36 (6H, s), 3.4—3.7 (18H, m); MS *m/z* 360 (M^+).

(+)-(1*R*,2*S*,5*R*,6*S*)-2,6-Bis(1,4,7-trioxaoctyl)-3,3,7,7-tetramethylbicyclo[3.3.1]nonane (21). By using the same procedure described for the preparation of **17**, (+)-**21** (440 mg, 90% yield) as an oil was prepared from (+)-**7** (250 mg, 1.17 mmol) and the *p*-toluenesulfonate of 2-(2-methoxyethoxy)ethanol (1.94 g, 7.13 mmol); $[\alpha]_D^{20}$ +84.4° (*c* 0.950, $CHCl_3$); IR (neat film) 1140, 1100 cm^{-1}; ^1H NMR ($CDCl_3$) δ=0.96 (6H, s), 1.04 (6H, s), 1.1—1.9 (6H, m), 2.26 (2H, br s), 3.13 (2H, d, *J*=9.0 Hz), 3.36 (6H, s), 3.4—3.7 (16H, m); MS *m/z* 416 (M^+).

Enantiomer Differential Transport. Enantiomer differential transport was carried out in an apparatus which consisted of an outer cylindrical glass vessel (24.5 mm inner diameter) and a central glass tube (15.5 mm inner diameter). The chloroform solution of the optically active host molecule (5.0×10^{-3} M) separated the inner aqueous phase (0.1 M hydrochloric acid) and the outer aqueous phase (0.08 M hydrochloric acid) containing $LiPF_6$ (0.4 M) and the racemic guest molecule (8.0×10^{-2} M). The chloroform layer was gently stirred at a constant speed (60 rpm) at 20—25 °C. Transport was monitored by ultraviolet spectrum and enantiomer excess of the guest molecule transported was monitored by circular dichroism.

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