[Chem. Pharm. Bull. 33(10)4247—4266(1985)]

Biomimetic Studies Using Artificial Systems. II.[1] Enantioselective Thiolysis of D- or L-α-Amino Acid Ester Salts by Thiol-Bearing Chiral Crown Ethers as an Enzyme Model

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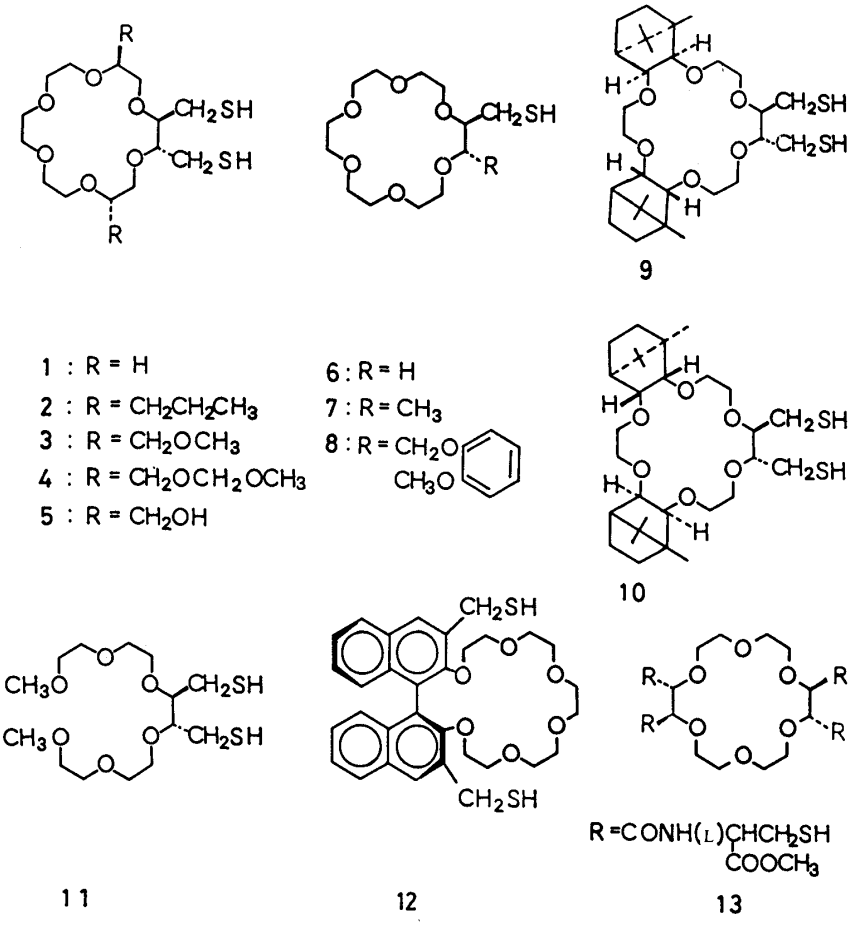
(Received February 19, 1985)

The rates of transacylation were studied between thiol-bearing chiral crown ethers (**1**—**10**) and α-amino acid *p*-nitrophenyl ester salts. Enantioselectivities, k_D/k_L ratios, of 6.5 for valine ester salt, 8.7 for phenylalanine ester salt, and 7.7 for valine ester salt were achieved by **1**, **5**, and **8**, respectively. Saturation phenomena of rate acceleration depending on crown concentration were observed and analysis of these data revealed that the chiral recognition occurs in the step of liberation of *p*-nitrophenol by intra-complex thiolysis, not in the complex-forming step. A possible mechanism for the enantioselectivity is proposed on the basis of the kinetic data.

Keywords——crown ether; transacylation; pseudo-first-order rate constant; enantioselectivity; thiolysis; intra-complex reaction; enzyme model

Extraordinary properties of enzyme-catalyzed reactions such as high reaction rates, high selectivities, and quick turnovers have fascinated organic chemists, and have led them to study enzyme models in recent years. Based on the understanding that one of the most important steps in enzyme-catalyzed reactions is the formation of non-covalent enzyme-substrate complexes prior to reactions,[2] studies have been focused on the design and synthesis of macrocyclic compounds capable of forming non-covalent complexes with various substrates.[3] Since the first report by Pedersen, crown ethers have been widely employed as artificial hosts for various cations.[3b] Cram's group initiated studies on complexes of crown ethers to mimic enzyme-catalyzed reactions, and achieved enantioselective complexation[4] and transacylation[5] between chiral crown ethers and enantiomeric primary ammonium salts. Cram's thiol-bearing chiral crown ether (**12**) showed enantioselective rate enhancement of up to 9.2 times in the thiolysis of α-amino ester salts as shown in Chart 1. A high selectivity in the similar transacylation with **13** was also reported by Lehn's group.[6] During our program aiming at constructing enzyme models based on the complexation ability of crown ethers, we found that thiol-bearing chiral crown ether (**1**)[7] exhibited enantioselectivity in the similar thiolysis of D- or L-α-amino acid ester salts. Since the chiral unit of **1** is simpler than that of Cram's (**12**)[5] and Lehn's (**13**)[6] compounds, we initiated further study on the enantioselectivity by using novel crown ethers (**2**—**10**) bearing various additional substituents. We report here the enantioselectivities achieved by these crown ethers and some mechanistic aspects of the reaction based on kinetic measurements.

Chart 1



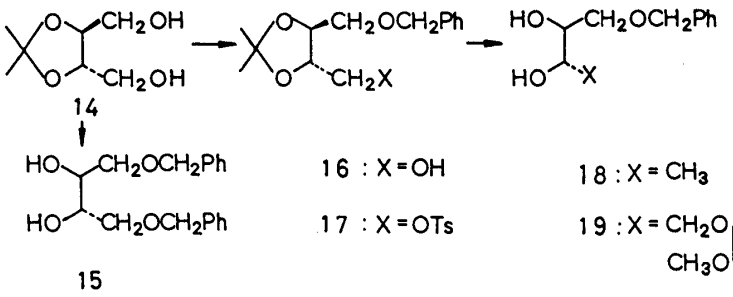
Results

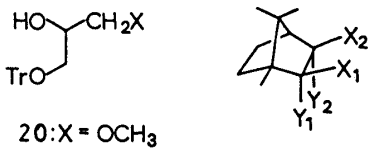
Crown Ethers

Chart 2 shows the syntheses of the crown ethers. Chiral units, **15**, **18**, **19**, **20**, **21**, **22**, **24**, and **28** were used to construct the chiral moieties of crown ethers. Formations of crown rings were carried out in *N*,*N*-dimethylformamide (DMF) by using NaH as a base. *tert*-BuOK in dimethyl sulfoxide (DMSO) was used only for the preparation of **77**. Benzyl derivatives (**39**—**42**, **55**—**57**, **67**, **77**, **81**) were converted to alcohols, tolylates (**47**—**50**, **58**—**60**, **69**, **79**, **83**), and then thiols (**1**—**11**) by the conventional methods. Since all thiol-bearing crown ethers (**1**—**11**) were stable to oxidative disulfide formation under neutral and acidic conditions, they were handled in the usual manner. Disulfides formed under drastic alkaline conditions could be easily detected by thin layer chromatography (TLC) and proton nuclear magnetic resonance (^{1}H-NMR) spectroscopy, and easily reduced to the corresponding thiols.

Kinetic Measurements

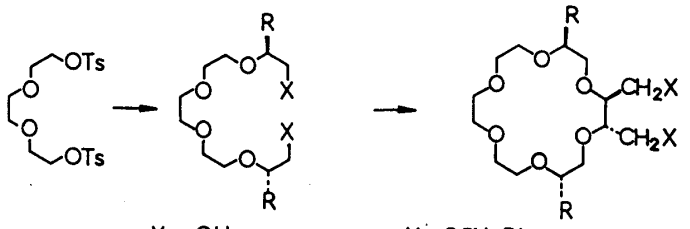
The thiolyses were carried out in 5% EtOH–CH_2Cl_2 buffered with 0.01 M AcOH and 0.02 M pyridine (pH 5.4 in H_2O) at 25.0 °C. The rates of *p*-nitrophenol liberation from α-amino acid *p*-nitrophenyl ester hydrobromides in the absence and presence (excess) of thiol-bearing compounds were followed at 320 nm. The pseudo-first-order rate constants (k) obtained by using **1**—**11** are recorded in Table I. The effects of various (excess) concentrations of **1** on the pseudo-first-order rate constant were determined. The rates approached a maximum saturation value as shown in Fig. 1. By plotting $1/k$ *vs.* 1/[Crown], a straight line was obtained as shown in Fig. 2, which has a slope of K_{diss}/k_2 and a Y intercept equal to $1/k_2$ as shown by Eq. 1.[8]





20: X = OCH_3
21: X = OCH_2Ph
22: X = CH_2CH_3

	X_1	Y_1	X_2	Y_2
23	H	OH	H	OH
24	H	OCH_2Ph	H	OH
25	H	OH	H	OCH_2Ph
26	= O		H	OCH_2Ph
27	OH	H	OH	H
28	OH	H	OCH_2Ph	H
29	OCH_2Ph	H	OH	H
30	= O		OCH_2Ph	H



X = OH
31: R = $CH_2CH_2CH_3$
32: R = CH_2OCH_3
33: R = CH_2OCH_2Ph

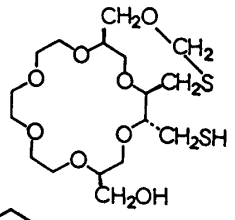
X = OTs
34: R = $CH_2CH_2CH_3$
35: R = CH_2OCH_3
36: R = CH_2OCH_2Ph
37: R = CH_2OH
38: R = $CH_2OCH_2OCH_3$

X = OCH_2Ph
39: R = H
40: R = $CH_2CH_2CH_3$
41: R = CH_2OCH_3
42: R = $CH_2OCH_2OCH_3$

X = OH
43: R = H
44: R = $CH_2CH_2CH_3$
45: R = CH_2OCH_3
46: R = $CH_2OCH_2OCH_3$

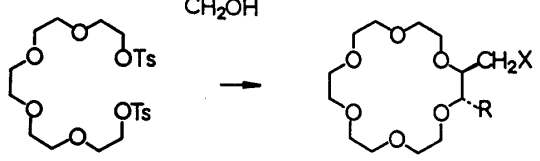
X = OTs
47: R = H
48: R = $CH_2CH_2CH_3$
49: R = CH_2OCH_3
50: R = $CH_2OCH_2OCH_3$

X = SCOPh
51: R = H
52: R = $CH_2CH_2CH_3$
53: R = CH_2OCH_3
54: R = $CH_2OCH_2OCH_3$



5i

X = SH
1: R = H
2: R = $CH_2CH_2CH_3$
3: R = CH_2OCH_3
4: R = $CH_2OCH_2OCH_3$
5: R = CH_2OH



X = OCH_2Ph
55: R = H
56: R = CH_3
57: R = CH_2O CH_3O

X = OTs
58: R = H
59: R = CH_3
60: R = CH_2O CH_3O

X = SH
6: R = H
7: R = CH_3
8: R = CH_2O CH_3O

Chart 2

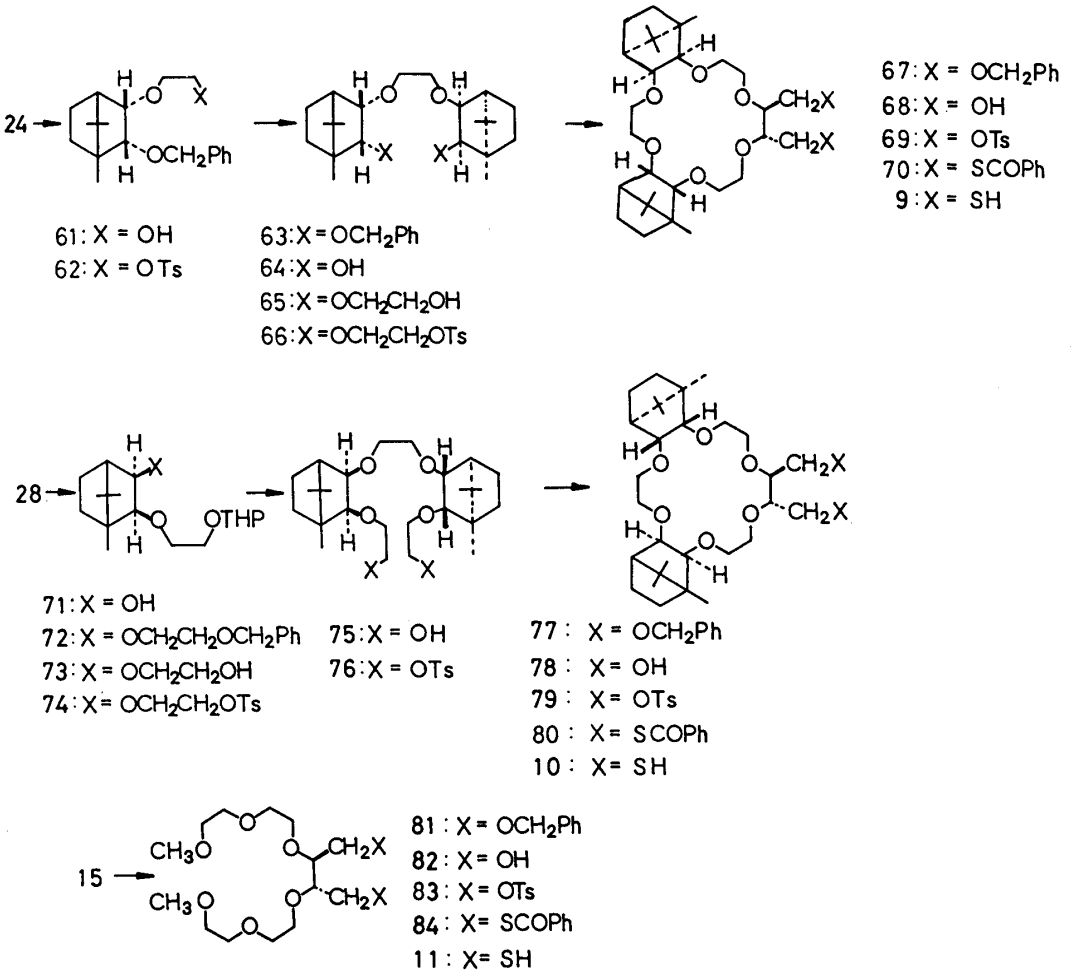


Chart 2 (continued)

$$1/k = (K_{diss}/k_2)(1/[\text{Crown}]) + 1/k_2 \quad (1)$$

The K_{diss} and k_2 values obtained from **1** and **11** by this procedure are listed in Table II. Data obtained in the same manner by using **2** and **3** are recorded in Table III.

Discussion

Rate Enhancement and Enantioselectivity

The cyclic host **1** exhibited chiral recognition by factors of 2.2, 5.1, and 6.5 for ester salts of alanine, phenylalanine, and valine, respectively, whereas the noncyclic dithiol **11** showed no chiral recognition, as shown in Table I (runs 1—7 *vs.* 8—10). The ester salts of glycine, L- and D-phenylalanine gave large $k_{\text{cyclic host}}/k_{\text{noncyclic host}}$ values of 319 (runs 1/8), 47 (runs 4/9), and 247 (runs 5/10), respectively, reflecting the effect of the crown ring. A saturation phenomenon of the pseudo-first-order rate constants was obtained by using various concentrations of **1** as shown in Fig. 1, which clearly shows the existence of a rate-determining formation of complexes.[8] Since a remarkable difference between the cyclic host **1** and the noncyclic host **11** was observed in K_{diss} values in Table II (K_{diss} values with glycine ester salt: **1**, 4.1×10^{-3} M; **11**, 13 M), the K_{diss} values obtained from the cyclic host **1** can be understood as the dissociation constants of ground-state complexes such as **85**, and the k_2 values as the rate constants of the intra-complex reactions from **85** to **87**, as depicted in Chart 3.

Values of K_{diss} and k_2 shown in Table II clearly show that the chiral recognition occurs in the intra-complex reaction (D/L ratio in k_2: 3.9) and not in complexation (D/L ratio in K_{diss}: 1).

TABLE I. Rate Constants for *p*-Nitrophenol Release from α-Amino Acid Ester Salts[a]

Run	R′CHNH$_3$Br COOAr (R′=)	Thiol (1—11)	k 10^{-3} s^{-1}	D/L ratio	Run	R′CHNH$_3$Br COOAr (R′=)	Thiol (1—11)	k 10^{-3} s^{-1}	D/L ratio
1	H	**1**	150.00		34	D-$CH_2C_6H_5$	**5**[b]	1.66	8.7
2	D-CH_3	**1**	110.00	2.2	35	L-$CH_2C_6H_5$	**5**[b]	0.19	
3	L-CH_3	**1**	50.00		36	H	**6**	7.00	
4	D-$CH_2C_6H_5$	**1**	18.00	5.1	37	D-CH_3	**6**	4.30	1.3
5	L-$CH_2C_6H_5$	**1**	3.50		38	L-CH_3	**6**	3.20	
6	D-$CH(CH_3)_2$	**1**	0.72	6.5	39	D-$CH_2C_6H_5$	**6**	0.58	2.0
7	L-$CH(CH_3)_2$	**1**	0.11		40	L-$CH_2C_6H_5$	**6**	0.29	
8	H	**11**	0.52		41	D-$CH(CH_3)_2$	**6**	0.028	1.9
9	D-$CH_2C_6H_5$	**11**	0.073	1.1	42	L-$CH(CH_3)_2$	**6**	0.015	
10	L-$CH_2C_6H_5$	**11**	0.065		43	H	**7**	45.00	
11	H	**2**	11.80		44	D-CH_3	**7**	25.00	1.9
12	D-CH_3	**2**	8.20	1.4	45	L-CH_3	**7**	13.00	
13	L-CH_3	**2**	5.80		46	D-$CH_2C_6H_5$	**7**	4.40	4.4
14	D-$CH_2C_6H_5$	**2**	1.70	2.8	47	L-$CH_2C_6H_5$	**7**	0.99	
15	L-$CH_2C_6H_5$	**2**	0.60		48	D-$CH(CH_3)_2$	**7**	0.17	4.7
16	H	**3**	15.00		49	L-$CH(CH_3)_2$	**7**	0.036	
17	D-CH_3	**3**	11.00	1:7	50	H	**8**	94.00	
18	L-CH_3	**3**	6.50		51	D-CH_3	**8**	64.00	2.1
19	D-$CH_2C_6H_5$	**3**	3.00	4.8	52	L-CH_3	**8**	30.00	
20	L-$CH_2C_6H_5$	**3**	0.63		53	D-$CH_2C_6H_5$	**8**	12.00	5.2
21	D-$CH(CH_3)_2$	**3**	0.17	4.3	54	L-$CH_2C_6H_5$	**8**	2.30	
22	L-$CH(CH_3)_2$	**3**	0.04		55	D-$CH(CH_3)_2$	**8**	0.56	7.7
23	H	**4**	21.60		56	L-$CH(CH_3)_2$	**8**	0.073	
24	D-CH_3	**4**	14.30	2.1	57	H	**9**	7.5	
25	L-CH_3	**4**	6.80		58	D-CH_3	**9**	1.20	0.6
26	D-$CH_2C_6H_5$	**4**	2.90	4.0	59	L-CH_3	**9**	2.00	
27	L-$CH_2C_6H_5$	**4**	0.71		60	D-$CH_2C_6H_5$	**9**	0.11	1.1
28	D-$CH(CH_3)_2$	**4**	0.17	4.3	61	L-$CH_2C_6H_5$	**9**	0.10	
29	L-$CH(CH_3)_2$	**4**	0.04		62	D-$CH(CH_3)_2$	**9**	0.01	1.0
30	H	**5**[b]	9.20		63	L-$CH(CH_3)_2$	**9**	0.01	
31	D-CH_3	**5**[b]	9.00	2.5	64	D-CH_3	**10**	0.27	1.9
32	L-CH_3	**5**[b]	3.10		65	L-CH_3	**10**	0.14	

a) Pseudo-first-order rate constants determined photometrically at 320 nm in 5% EtOH–CH_2Cl_2 buffered with 0.01 M AcOH and 0.02 M pyridine (pH 5.4 in water) at 25.0 °C; 10^{-4} M in α-amino ester salts, and 5×10^{-3} M in thiol-bearing compounds. *b*) Containing 40% **5i**.

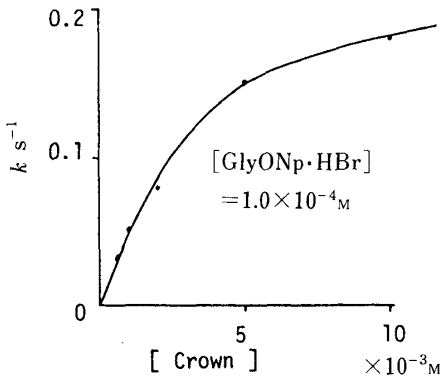


Fig. 1. The Pseudo-First-Order Rate Constant Plotted as a Function of Added Crown Ether

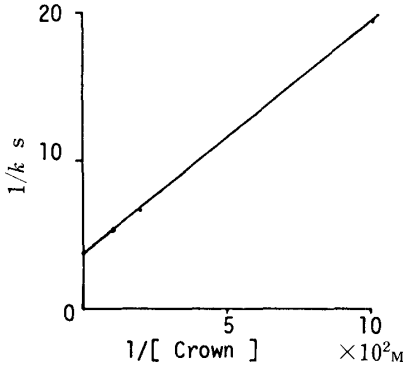


Fig. 2. $1/k$ Plotted as a Function of 1/[Crown] Data from Fig. 1.

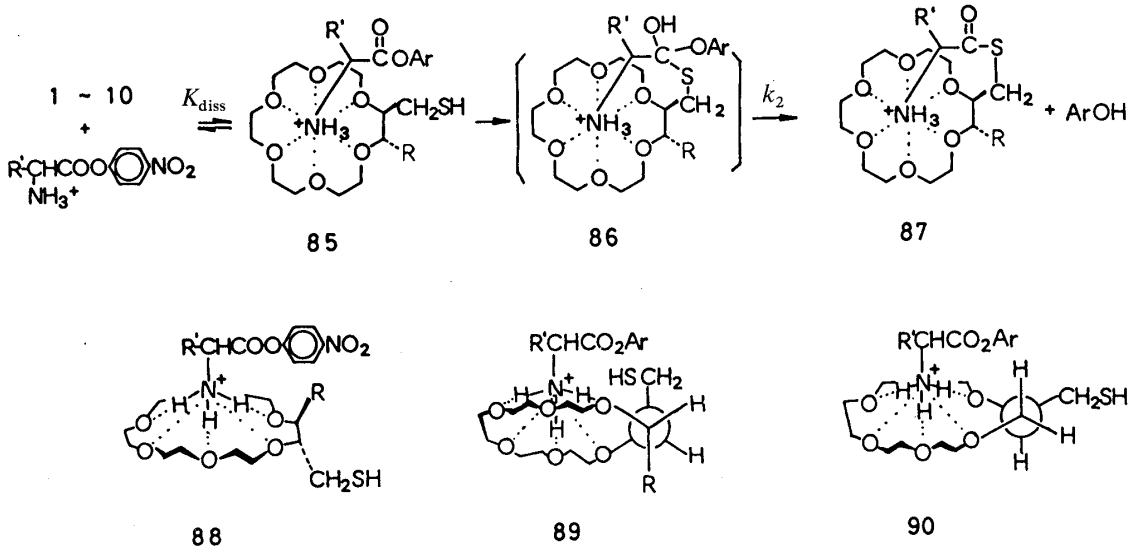


Chart 3

TABLE II. K_{diss} and k_2 Values Obtained from **1** and **11**[a)]

Run	R'CH(NH_3Br)COOAr (R'=)	Thiol	K_{diss} 10^{-3} M	k_2	
				10^{-3} s^{-1}	D/L ratio
1	H	**1**	4.1	260	
2	D-$CH_2C_6H_5$	**1**	11	54	3.9
3	L-$CH_2C_6H_5$	**1**	11	14	
4	H	**11**	13000	8	

a) Pseudo-first-order rate constants determined photometrically at 320 nm in 5% EtOH–CH_2Cl_2 buffered with 0.01 M AcOH and 0.02 M pyridine (pH 5.4 in water) at 25.0 °C; 10^{-4} M in α-amino ester salts.

TABLE III. K_{diss} and k_2 Values Obtained from **2** and **3**[a)]

Run	R'CH(NH_3Br)COOAr (R'=)	Thiol	K_{diss} 10^{-3} M	k_2	
				10^{-3} s^{-1}	D/L ratio
1	H	**2**	4.5	23	
2	D-$CH_2C_6H_5$	**2**	27	9	2.3
3	L-$CH_2C_6H_5$	**2**	27	4	
4	H	**3**	5.2	37	
5	D-$CH_2C_6H_5$	**3**	41	24	4.0
6	L-$CH_2C_6H_5$	**3**	43	6	

a) Pseudo-first-order rate constants determined photometrically at 320 nm in 5% EtOH–CH_2Cl_2 buffered with 0.01 M AcOH and 0.02 M pyridine (pH 5.4 in water) at 25.0 °C; 10^{-4} M in α-amino ester salts.

Experimental errors may be the main cause of the difference in the D/L ratios (runs 4/5 = 5.1 in Table I, runs 2/3 = 3.9 in Table II). Table I (runs 1—7) and II also show significant effects of α-alkyl substituents (R) of α-amino ester salts on complexation, rate enhancement, and enantioselectivity as follows. Both the stability of complexes and the intra-complex reaction rates with D- and L-phenylalanine ester salts are smaller than those with glycine ester salt (Table II, run 1 *vs.* 2 or 3). D/L ratios in k values (Table I, runs 2—7) depend on α-alkyl groups of α-amino ester salts (CH_3, 2.2; $CH_2C_6H_5$, 5.1; $CH(CH_3)_2$, 6.5). Chiral recognition by

the factor of 2.2 (Table I, runs 2/3) is the best ratio reported previously for alanine ester salts.[5] In order to clarify the mechanism of the enantioselectivity exhibited by the simple chirality of **1**, we further investigated the effects of substituents of the crown ether on the rates of the thiolysis.

Substituent Effects on Enantioselectivity

Crown ethers (**2**—**5**) were subjected to the same measurements as described for **1**. It was expected that $CH_2CH_2CH_3$ of **2** would work as a bulky group, CH_2OCH_3 of **3** and $CH_2OCH_2OCH_3$ of **4** as bulky groups or additional binding groups,[9] and CH_2OH of **5** as a donor for hydrogen bonding. The data listed in Table I (runs 11—35) showed the following facts. 1) Pseudo-first-order rate constants (k) were found to be decreased by any additional substituent. 2) Enantioselectivities, *i.e.* D/L ratios of psuedo-first-order rate constants, were lowered in the case of **2** ($R=CH_2CH_2CH_3$), but improved in the case of **5** ($R=CH_2OH$). Table III, recording K_{diss} and k_2 values obtained by using **2** and **3**, clearly shows that chiral recognition in k values in Table I is almost the same as that in k_2 values. The effects of substituents are significant in k_2 values but not in K_{diss} values in the case of glycine ester salt. These results show that the substituents of **2**—**5** are probably located at an important location for the thiolysis. In the case of D- or L-phenylalanine ester salts, the stabilities of the complexes of **3** (K_{diss}: 4.1, or 4.3×10^{-3} M with D- or L-, respectively) were lower than those of **2** (K_{diss}: 2.7×10^{-3} M for D- and L-), although additional ether oxygens were expected to enhance the stability of complexes of **3**.[9] Destabilization of the complex by the steric factor of the CH_2OCH_3 substituent may be greater than the stabilization effect.

Crown ethers (**6**—**8**) bearing only one reactive thiol group were designed in order to investigate the effects of substituents vicinal to the thiol group. It was expected that H of **6** would work as the least bulky group and CH_3 of **7** and $CH_2C_6H_4OCH_3$-*o* of **8** as bulkier groups. On changing the substituent from the smallest (R=H) to the bulkiest ($R=CH_2OC_6H_4OCH_3$-*o*), both rate enhancements (k values) and improved enantioselectivities (k_D/k_L ratios) were found. In paticular, the host **8** gave almost the same enhancement as **1** ($0.094\,s^{-1}$ *vs.* $0.15\,s^{-1}$ with glycine ester salt) and better enantioselectivity than **1** ($k_D/k_L=7.7$ *vs.* 6.5 with valine ester salt). Since these hosts, **6**—**8**, form complexes such as **88** which do not contribute to the intra-complex thiolysis such as in **85**, K_{diss} and k_2 values can not be obtained by the same method as used for **1**—**5**. These substituent effects showed that the bulky substituent vicinal to the reactive thiol group is essential for both rate enhancements and enantioselectivities. From an examination using CPK models, the effects on rate enhancements can be explained as follows. In the case of bulky R ($R=CH_2OC_6H_4OCH_3$-*o*), the anti conformation between CH_2SH and R should be preferred, setting the CH_2SH group perpendicular to the crown ring complexed with the substrate, as shown in **89**. Therefore, the thiol can easily attack the carbonyl of the substrate. In the complex of a crown ether having small R (R=H), a conformation such as that depicted in **90** should be preferred, in which the CH_2SH group should take the position horizontal to the crown ring. Therefore, the reaction between the thiol and the carbonyl should be retarded.

The chiral crown ethers (**9** and **10**) have been reported to exhibit enantioselectivities.[10] The pseudo-first-order rate constants are summarized in Table I (runs 57—65). Their selectivities could be explained in terms of the chiral barriers of camphor units. Since, however, the chiralities of CH_2SH groups are the same as those in the host **1**, the common preference for D-substrates should be the same. The reverse selectivity, k_L/k_D ratio of 1.7 exhibited by the host **9** (Table I, run 58 *vs.* 59), may be the result of the strong effects of the camphor units as chiral barriers.

Mechanisms of Enantioselectivity

Based on the above discussion, we may propose a speculative mechanism for the

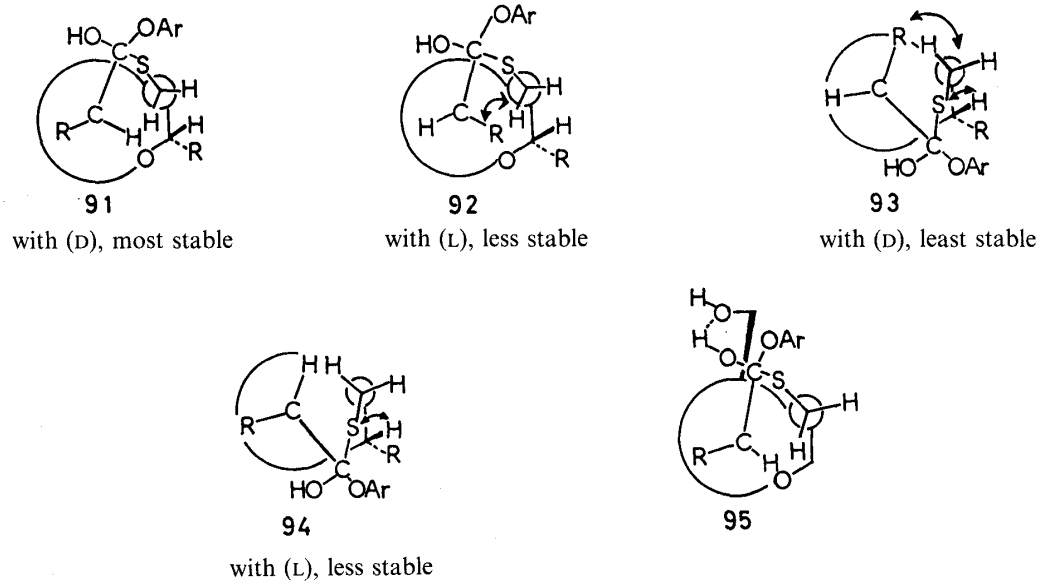


Fig. 3. Tetrahedral Intermediates

enantioselectivity in the thiolysis reaction. Since the enantioselectivities are the result of the intra-complex reaction from **85** to **87**, differences in the stability of transition state complexes, *i.e.* tetrahedral intermediates such as **86** must be taken into account. Schematic drawings of the tetrahedral intermediates are depicted in Fig. 3. The "*anti*" conformations of CH_2SH such as depicted in **89** are assumed to be preferred in the intermediates. The intermediate (**91**) formed with the D-substrate should be most stable, because no significant steric repulsion is observed. Both the intermediates (**92** and **94**) formed with the L-substrate should be less stable than **91** because of the steric repulsions depicted by the arrows. Repulsions between α-R of the substrate and the methylene of CH_2SH and between the sulfur of CH_2SH and the methine hydrogen of the crown ring are observed in **92** and **94**, respectively. The other intermediate (**93**) formed with the D-substrate should be the least stable, because both the steric repulsions seen in **92** and **94** are observed in this intermediate. The preferences of crown ethers (**1**—**9**) for the D-substrates and the larger D/L ratios exhibited with larger α-R of the substrates can be explained by the above mechanism. The effects of the substituents on the enantioselectivities can also be explained by this mechanism as follows. The intermediate with the D-substrate (**91**) is destabilized by additional steric repulsion of *n*-$CH_2CH_2CH_3$ of **2**, resulting in lower D/L ratios. CH_2OCH_3 of **3**, $CH_2OCH_2OCH_3$ of **4**, and CH_2OH of **5** stabilize the corresponding intermediates by forming hydrogen bonding such as that depicted in **95** to increase the reaction rate of the D-substrate. The host **6** bearing small R (R=H) adjacent to CH_2SH forms disordered intermediate complexes because of the preferred conformation of the CH_2SH group such as that depicted in **90**, resulting in smaller differences in the intermediates.

Conclusion

The chiral crown ethers (**1**, **3**, **4**, **5**, **7**, **8**) were shown to exhibit large rate enhancements and enantioselectivities in the thiolysis of α-amino acid *p*-nitrophenyl ester salts. The kinetic measurements revealed that the rate enhancements are attributable to the complexation between the crown ethers and the substrates, and the enantioselectivities are attributable to the subsequent intracomplex thiolysis. The fact that the hosts forming ordered complexes with the substrates are efficient in both rate enhancement and enantioselectivity clearly demonstrates the importance of the complexation between the crown ether and the α-amino ester salts.

Experimental

General——Melting points were measured on a Büchi 510 melting point apparatus, and are uncorrected. Optical rotations were recorded on a Yanaco OR-50 photodirect reading polarimeter or a JASCO DIP-181 polarimeter. Infrared (IR) spectra were recorded on a JASCO IRA-1 grating infrared spectrophotometer or JASCO DS-402G infrared spectrophotometer. Nuclear magnetic resonance (NMR) spectra were measured on a JEOL JNM-OS 100 spectrometer (^{1}H, 100 MHz), JEOL-FX100 Fourier-transform NMR spectrometer (^{1}H, 100 MHz), or Hitachi R-24 high resolution NMR spectrometer (^{1}H, 60 MHz). Chemical shifts are reported in δ values in ppm with tetramethylsilane (TMS) as an internal standard. Coupling constants (J) are reported in Hz. Abbreviations are as follows: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; br, broad. Mass spectra (MS) and high-resolution mass spectra (HRMS) were recorded on a JEOL JMS-01 SG-2 mass spectrometer or a JEOL JMS-DX300 mass spectrometer.

(−)-(2*S*,3*S*)-1-*O*-Benzyl-2,3-*O*-isopropylidene-4-*O*-tosylthreitol (17)——A mixture of **14**[11] (80 g, 0.47 mol), KOH (85% pure, 32.6 g, 0.49 mol), and benzyl chloride (56.3 ml, 0.49 mol) in benzene (500 ml) was stirred under reflux for 7 h with removal of water by a Dean-Starkapparatus. After cooling to room temperature, the reaction mixture was diluted with benzene (500 ml), washed successively with H_2O, 10% aq. HCl, satd. aq. $NaHCO_3$ and satd. aq. NaCl, and then dried over $MgSO_4$. The benzene was evaporated off to give a crude oil, which was distilled under reduced pressure to give 1-*O*-benzyl-2,3-*O*-isopropylidenethreitol (**16**) (82 g, 66% yield) as a colorless oil of bp 156—158 °C (3 mmHg). IR ν_{max}^{film} cm^{-1}: 3480, 1600, 1595, 1450, 1385, 1380, 1240, 1210, 1160, 1085, 840, 730, 690. NMR ($CDCl_3$) δ: 1.40 (6H, s, 2 × C$\underline{H}_3$), 2.32 (1H, br, O$\underline{H}$), 3.4—4.2 (6H, m, –C$\underline{H}_2$O–, –C$\underline{H}$O–), 4.56 (2H, s, –C$\underline{H}_2$Ar), 7.26 (5H, s, Ar$\underline{H}$). MS *m/e*: 252 (M^+). HRMS Calcd for $C_{14}H_{20}O_4$: 252.1360. Found: 252.1325.

A mixture of **16** (53.8 g, 0.213 mol) and TsCl (44.76 g, 0.233 mol) in pyridine (270 ml) was stirred at −20 °C for 24 h. The reaction mixture was poured into ice water (1.2 l), and extracted with AcOEt (440 ml × 2). The combined extracts were washed successively with cold 10% aq. HCl (120 ml × 3), satd. aq. $NaHCO_3$ and satd. aq. NaCl, then dried over $MgSO_4$. Removal of the solvent gave crude **17** (86.4 g, 99.5% yield) as a yellow oil. This crude oil was used for the next reaction without further purification. A sample was purified by column chromatography (silica gel, AcOEt : hexane = 1 : 3) to give pure **17** as a colorless oil. $[\alpha]_D^{20}$ −14.6° (c = 3.6, $CHCl_3$), IR ν_{max}^{film} cm^{-1}: 1600, 1500, 1455, 1370, 1190, 1180, 1095, 980, 790, 695, 660. NMR ($CDCl_3$) δ: 1.34 (3H, s, CH_3) 1.38 (3H, s, C$\underline{H}_3$), 2.44 (3H, s, ArC$\underline{H}_3$), 3.4—3.76 (2H, m, –C$\underline{H}_2$O–), 3.84—4.36 (4H, m, –C$\underline{H}_2$OTs, –C$\underline{H}$O–), 4.54 (2H, s, C$\underline{H}_2$Ar), 7.28 (5H, s, CH_2Ar$\underline{H}$), 7.25 and 7.72 (4H, ABq, J = 8 Hz, SO_2Ar$\underline{H}$). MS *m/e*: 406 (M^+). *Anal.* Calcd for $C_{21}H_{26}O_6S$: C, 62.05; H, 6.45. Found: C, 61.75; H, 6.38.

(2*S*,3*S*)-1-*O*-Benzyl-1,2,3-butanetriol (18)——A solution of **17** (41.9 g, 0.103 mol) in THF (250 ml) was added druing 1 h to a suspension of $LiAlH_4$ (7.82 g, 0.206 mol) in THF (200 ml) at 50 °C, and the whole was stirred under gentle reflux for 3 h. The reaction mixture was quenched successively with water (7.8 ml), 15% aq. NaOH (7.8 ml), and water (23.4 ml). Precipitates were filtered off and the filtrate was evaporated off to give a crude oil (24 g). This oil was dissolved in MeOH–conc. HCl (480 ml–20 ml), and the whole was stirred at 40 °C for 3 h. After neutralization with NaOH and $NaHCO_3$, the solvent was evaporated off, and the residue was extracted with AcOEt (800 ml × 3). The combined extracts were washed with satd. aq. NaCl (50 ml × 3), and then dried over $MgSO_4$. The solvent was evaporated off to give a yellow oil (20 g), which was purified by column chromatography (silica gel, AcOEt : benzene = 1 : 3) to give pure **18** (15.3 g, 82% yield) as a pale yellow oil. IR ν_{max}^{film} cm^{-1}: 3400, 1490, 1450, 1365, 1100, 730, 690. NMR ($CDCl_3$) δ: 1.18 (3H, d, J = 6 Hz, –C$\underline{H}_3$), 2.55—3.10 (2H, br, –O$\underline{H}$), 3.30—4.0 (4H, m, –C$\underline{H}_2$O–, C$\underline{H}$O–), 4.53 (2H, s, –C$\underline{H}_2$Ar), 7.28 (5H, s, Ar$\underline{H}$). MS *m/e*: 196 (M^+). HRMS Calcd for $C_{11}H_{16}O_3$: 196.1097. Found: 196.1090.

(−)-(2*S*,3*S*)-1-*O*-Benzyl-4-*O*-(2-methoxyphenyl)threitol (19)——A solution of *o*-methoxyphenol (35.3 g, 0.28 mol) in DMSO (100 ml) was added dropwise to a suspension of NaH (60% in oil, 11.3 g, 0.28 mol) in DMSO (400 ml) under Ar, and the whole was stirred at room temperature for 0.5 h. A solution of **17** (72.3 g, 0.178 mol) in DMSO (190 ml) was added dropwise to the reaction mixture, and the whole was stirred at 45—50 °C for 3.5 h. DMSO was removed *in vacuo*, and then the residue was dissolved in AcOEt (1 l). The AcOEt was washed successively with 10% aq. NaOH, satd. aq. $NaHCO_3$ and satd. aq. NaCl, then dried over $MgSO_4$. A crude oil (56.98 g) obtained by removal of the AcOEt was dissolved in MeOH–conc. HCl (550 ml–75 ml), and the whole was stirred at room temperature for 15 h. The reaction mixture was neutralized with $NaHCO_3$, and the MeOH was evaporated off. The residue was poured into ice-water, and a white powder was precipitated. The white powder was collected by filtration to give crude **19** (90 g), which was recrystallized from isopropanol (100 ml) to afford pure **19** (27.9 g, 55.1% yield) as white needles of mp 78—80 °C. $[\alpha]_D^{20}$ −8.2° (c = 2.0, $CHCl_3$). IR ν_{max}^{Nujol} cm^{-1}: 3400, 1590, 1500, 740, 690. NMR ($CDCl_3$) δ: 3.0 (2H, br, –O$\underline{H}$), 3.5—4.3 (6H, m, –C$\underline{H}_2$O–, –C$\underline{H}$O–), 3.85 (3H, s, –OC$\underline{H}_3$), 4.57 (2H, s, –C$\underline{H}_2$Ar), 6.91 (4H, s, –OAr$\underline{H}$), 7.34 (5H, s, –CH_2Ar$\underline{H}$). HRMS Calcd for $C_{18}H_{22}O_5$: 318.1468. Found: 318.1495.

(2*S*)-1-*O*-Methyl-3-*O*-tritylglycerol (20)——A solution of (2*R*)-1-*O*-methylglycerol[12] (10.3 g, 97 mmol) and TrCl (27.3 g, 98 mmol) in pyridine (75 ml) was stirred at 50 °C for 3 h. After cooling to room temperature, the whole was poured into water (100 ml) and extracted with ether (200 ml × 2). The combined extracts were washed successively with cold 15% aq. HCl, satd. aq. $NaHCO_3$ and satd. aq. NaCl, then dried over $MgSO_4$. The ether was evaporated off

to give crude **20** (37.9 g) as a yellow oil, which was purified by column chromatography (silica gel, AcOEt : hexane = 1 : 3) to give pure **20** (22.3 g, 66%) as a white powder. Recrystallization from ether–hexane afforded white prisms of mp 86—87 °C. $[\alpha]_D^{20}$ 0° (c = 0.57, $CHCl_3$). IR ν_{max}^{Nujol} cm^{-1}: 3400, 1450, 1370, 1095, 1030, 960, 750. NMR ($CDCl_3$) δ: 2.43 (1H, br, –OH), 3.43 (3H, s, $-OCH_3$), 3.18 (2H, d, J = 6 Hz, $-CH_2O-$), 3.40 (2H, d, J = 6 Hz, $-CH_2O-$) 3.6—4.1 (1H, m, –CH–), 7.1—7.4 (15H, m, ArH). *Anal.* Calcd for $C_{23}H_{24}O_3$: C, 79.28; H, 6.94. Found: C, 79.33; H, 6.95.

(−)-(2*S*)-1-*O*-Benzyl-3-*O*-tritylglycerol (21)——A solution of (2*R*)-1-*O*-benzylglycerol[13] (13.78 g, 75.6 mmol) and TrCl (22.14 g, 79.4 mmol) in pyridine (100 ml) was stirred at 50 °C for 1.5 h. The same work-up as described for the preparation of **20** afforded a crude oil, which was purified by column chromatography to give **21** (26.89 g, 84% yield) as a pink viscous oil. Recrystallization from ether–hexane afforded white needles of mp 71.5—72.5 °C. $[\alpha]_D^{20}$ −2.4° (c = 1.42, $CHCl_3$), IR ν_{max}^{film} cm^{-1}: 3400, 1600, 1460, 1360, 1180, 1100, 990. NMR ($CDCl_3$) δ: 2.39 (1H, d, J = 5 Hz, –OH), 3.19 (2H, d, J = 5 Hz, $-CH_2O-$), 3.52 (2H, d, J = 5 Hz, $-CH_2-$), 3.7—4.1 (1H, m, –CHO–), 4.51 (2H, s, CH_2Ar), 7.29 (20H, m, ArH). MS m/e: 424 (M^+). *p*-Nitrobenzoate of **23**: mp 143—144 °C (recrystallized from acetone–ethanol). $[\alpha]_D^{20}$ −13.5° (c = 2.05, $CHCl_3$). *Anal.* Calcd for $C_{36}H_{31}NO_6$: C, 75.37; H, 5.45; N, 2.44. Found: C, 75.07; H, 5.37; N, 2.73.

(+)-(2*S*)-1-*O*-Trityl-1,2-pentanediol (22)——A solution of (−)-(2*S*)-1,2-pentanediol[14] (9.6 g, 92.2 mmol) and TrCl (27 g, 96.8 mmol) in pyridine was stirred at 40 °C for 3 h and at room temperature for 12 h. Usual work-up as described for the preparation of **20** afforded crude **22**, which was purified by column chromatography (silica gel, hexane only–hexane : AcOEt = 3 : 1) to give pure **22** (28.7 g, 90% yield) as a pale yellow caramel. This product was used for the preparation of **31** without further purification. $[\alpha]_D^{20}$ +8.2° (c = 1.0, $CHCl_3$). IR ν_{max}^{film} cm^{-1}: 3400, 1595, 1485, 1440, 1070. NMR ($CDCl_3$) δ: 0.6—1.6 (7H, m, $CH_2CH_2CH_3$), 2.9—3.4 (2H, m, $-CH_2OTr$), 3.5—4.0 (1H, br, –CHO–), 7.0—7.5 (15H, m, ArH). HRMS Calcd for $C_{24}H_{26}O_2$: 346.1931. Found: 346.1931.

(+)-(1*R*,2*R*,3*S*,4*S*)-2-Benzyloxy-3-hydroxy-1,7,7-trimethylbicyclo[2.2.1]heptane (24)——A solution of (+)-(1*R*,2*R*,3*S*,4*S*)-2,3-dihydroxy-1,7,7-trimethylbicyclo[2.2.1]heptane[15] (32.5 g, 0.191 mol) in DMF (200 ml) was added dropwise to a suspension of NaH (55% in oil, 8.8 g, 0.2 mol) in DMF (300 ml) under N_2 at 0 °C, and the whole was stirred at 40 °C for 2 h, then cooled in an ice bath. Benzyl chloride (24 ml, 0.29 mol) was added to the reaction mixture, and the whole was stirred at room temperature for 3 h. The reaction mixture was diluted with benzene (1 l), and shaken with water. The aqueous phase was separated and extracted again with benzene (1 l), and the combined extracts were washed with satd. aq. NaCl, then dried over $MgSO_4$. The benzene was evaporated off to afford a crude brown oil (60 g), which was separated by column chromatography (silica gel, ether : hexane = 1 : 15) to afford **24** (17.5 g, 35% yield) as a pale yellow oil, and **25** (21.0 g, 42% yield) as a pale yellow oil. Crude **24** was distilled under reduced pressure to give pure **24** (15.92 g, 32% yield) as a colorless oil of bp 144—146 °C (0.5 mmHg). $[\alpha]_D^{20}$ +71.6° (c = 5.2, EtOH). IR ν_{max}^{film} cm^{-1}: 3550, 1600, 1455, 1390, 1370, 1090, 700. NMR ($CDCl_3$) δ: 0.85 (9H, s, $3 \times CH_3$), 1.0—2.0 (5H, m, –CH–, $-CH_2-$), 2.73 (1H, br, –OH), 3.58 (1H, dd, J = 9, 1.6 Hz, $-CHOCH_2Ar$), 4.25 (1H, br, dd after D_2O treatment, J = 9, 4 Hz, –CHOH), 4.6 (2H, ABq, J = 10 Hz, $-OCH_2Ar$), 7.3 (5H, s, ArH). MS m/e: 260 (M^+). *Anal.* Calcd for $C_{17}H_{24}O_2$: C, 78.42; H, 9.29. Found: C, 78.16; H, 9.31. Crude **25** was distilled under reduced pressure to give pure **25** (19.1 g, 38% yield) as a colorless oil of bp 148—150 °C (0.55 mmHg). $[\alpha]_D^{20}$ +43.3° (c = 5.0, EtOH). IR ν_{max}^{film} cm^{-1}: 3550, 1600. NMR ($CDCl_3$) δ: 0.83 (6H, s, $2 \times CH_3$), 0.88 (3H, s, CH_3), 1.0—2.0 (5H, m, –CH–, CH_2–), 2.67 (1H, br, OH), 3.6—4.12 (2H, m, –CHO–), 4.5 (2H, s, $-CH_2Ar$), 7.3 (5H, s, ArH). HRMS Calcd for $C_{17}H_{24}O_2$: 260.1774. Found: 260.1743.

(+)-(1*R*,2*S*,3*R*,4*S*)-2-Hydroxy-3-benzyloxy-1,7,7-trimethylbicyclo[2.2.1]heptane (28)——A solution of (−)-(1*R*,2*S*,3*R*,4*S*)-2,3-dihydroxy-1,7,7-trimethylbicyco[2.2.1]heptane[16] (12.6 g, 74.1 mmol) in DMF (100 ml) was added dropwise to a suspension of NaH (50% in oil, 3.7 g 74.4 mmol) in DMF (50 ml) under Ar at room temperature, and the whole was stirred at 50 °C for 40 min, then cooled to room temperature. Benzyl chloride (13.94 g, 81.2 mmol) was added to the reaction mixture, and the whole was stirred at room temperature for 4 h. The reaction mixture was poured into water, and extracted with ether (100 ml × 2). The combined extracts were washed with satd. aq. NaCl, and dried over $MgSO_4$. The ether was evaporated off to give a crude oil (20.29 g), which was separated by column chromatography (silica gel, ether : hexane = 1 : 9) to afford **28** (8.0 g, 41% yield) as a white powder and **29** (3.2 g, 16% yeild) as a colorless oil. **28** was recrystallized from pentane to give a white powder of mp 43—43.5 °C. $[\alpha]_D^{20}$ +0.41° (c = 4.99, EtOH). IR ν_{max}^{neat} cm^{-1}: 3540, 1600, 1580, 1495, 1480, 1450, 1385, 1280, 1130, 1065, 730, 695. NMR ($CDCl_3$) δ: 0.78 (3H, s, CH_3), 0.94 (3H, s, CH_3), 0.99 (3H, s, CH_3), 1.0—2.0 (5H, m, –CH–, $-CH_2-$), 2.9 (1H, m, –OH), 3.6 (2H, m, –CHO–), 4.58 (2H, ABq, J = 12 Hz, $-CH_2Ar$), 7.32 (5H, s, ArH). MS m/e: 260 (M^+). *Anal.* Calcd for $C_{17}H_{24}O_2$: C, 78.42; H, 9.29. Found: C, 78.35; H, 9.28. **29** was distilled under reduced pressure to afford pure **29** as a colorless oil of bp 113—114 °C (0.15 mmHg). $[\alpha]_D^{20}$ −18.2° (c = 5.02, EtOH). IR ν_{max}^{film} cm^{-1}: 3550, 1600, 1495, 1450, 1385, 1365, 1125, 1090, 1065, 730, 695. NMR ($CDCl_3$) δ: 0.79 (3H, s, $-CH_3$), 0.95 (3H, s, $-CH_3$), 1.10 (3H, s, $-CH_3$), 1.0—1.9 (5H, m, $-CH_2-$, –CH–), 2.9 (1H, d, J = 5.5 Hz, –OH), 3.40 (1H, d, J = 7 Hz, $-CHOCH_2Ar$), 3.83 (1H, dd, J = 7 Hz, 5.5 Hz, –CH–OH), 4.65 (2H, s, $-CH_2Ar$), 7.33 (5H, s, ArH). HRMS Calcd for $C_{17}H_{24}O_2$: 260.1776. Found: 260.1770.

(1*R*,3*R*,4*S*)-3-Benzyloxy-1,7,7-trimethylbicyclo[2.2.1]hept-2-one (30)——A mixture of **28** (0.6 g, 2.3 mmol), PCC (0.8 g, 3.7 mmol), and celite (1.8 g) in CH_2Cl_2 (20 ml) was stirred at room temperature for 14 h. The reaction mixture was diluted with hexane (30 ml) and filtered. The filtrate was evaporated, and the residue was purified by column

chromatography (silica gel, hexane) to afford pure **30** (0.58 g, 98% yield) as a colorless oil. IR ν_{max}^{film} cm^{-1}: 1750, 1600, 1580, 1450, 1390, 1370, 1280, 1120, 1105, 1080, 1030, 1020, 1010, 730, 690. NMR ($CDCl_3$) δ: 0.93 (6H, s, 2×C$\underline{H}_3$), 1.04 (3H, s, C$\underline{H}_3$), 0.8—2.2 (5H, m, –C$\underline{H}_2$–, C$\underline{H}$–), 3.49 (1H, s, 3-C$\underline{H}$O–), 4.77 (2H, ABq, J=12.3 Hz, C$\underline{H}_2$Ar), 7.32 (5H, s, Ar$\underline{H}$). HRMS Calcd for $C_{17}H_{22}O_2$: 258.1619. Found: 258.1619.

A solution of **30** (110 mg, 0.43 mmol) in 2 N aq. NaOH–EtOH (2 ml–2 ml) was stirred under reflux for 24 h. After cooling to room temperature, the reaction mixture was extracted with ether (50 ml), and the ether layer was separated, washed with satd. aq. NaCl and evaporated to give a crude oil (103 mg), which was distilled under reduced pressure to afford a colorless oil of bp 220 ° (2 mmHg). *Anal.* Calcd for $C_{17}H_{22}O_2$: C, 79.03; H, 8.58. Found: C, 79.00; H, 8.82. The NMR spectrum ($CDCl_3$) showed a mixture of **26** and **30** (2 : 5), based on a comparison with the NMR spectrum of authentic **26** obtained from **25**.

26 from 25——A mixture of **25** (0.16 g, 0.6 mmol) and PCC (200 mg) in CH_2Cl_2 (10 ml) was stirred at room temperature for 12 h. Usual work-up and purification as described for the preparation of **30** afforded pure **26** (0.13 g, 80% yield) as a colorless oil. IR ν_{max}^{film} cm^{-1}: 1755, 1450, 1390, 1370, 1110, 1020, 720, 690. NMR ($CDCl_3$) δ: 0.81 (3H, s, C$\underline{H}_3$), 0.89 (3H, s, C$\underline{H}_3$), 0.97 (3H, s, C$\underline{H}_3$), 0.9—2.3 (5H, m, –C$\underline{H}_2$–, –C$\underline{H}$–), 3.95 (1H, d, J=4.7 Hz, 3-C$\underline{H}$O–), 4.71 (2H, ABq, J=12 Hz, C$\underline{H}_2$Ar), 7.32 (5H, s, Ar$\underline{H}$). HRMS Calcd for $C_{17}H_{22}O_2$: 258.1619. Found: 258.1622.

(+)-(2*S*,3*S*)-2,3-Bis(benzyloxymethyl)-1,4,7,10,13,16-hexaoxacyclooctadecane (39)——A solution of (−)-1,4-di-*O*-benzylthreitol (**15**)[17] (7.17 g, 23.7 mmol) in DMF (100 ml) was added dropwise to a suspension of NaH (50% in oil, 2.5 g, 52 mmol) in DMF (100 ml) under Ar at room temperature, and the whole was stirred at 40 °C for 2 h, then cooled to room temperature. A solution of pentaethyleneglycol ditosylate[18] (12.98 g, 23.7 mmol) in DMF (300 ml) was added, and the whole was stirred at room temperature for 6 h. DMF was removed *in vacuo*, and the residue was shaken with H_2O–AcOEt (100 ml–500 ml). The aqueous layer was separated and extracted with AcOEt (250 ml × 2), and the combined extracts were washed successively with 10% aq. HCl, satd. aq. $NaHCO_3$ and satd. aq. NaCl, then dried over $MgSO_4$. The AcOEt was evaporated off to afford a brown oil (12.0 g), which was purified by column chromatography (silica gel, ether–hexane) to afford **39** (10.5 g, 88% yield) as a colorless oil. $[\alpha]_D^{20}$ +3.7 ° (c=2.5, $CHCl_3$). lit.[7] ($[\alpha]_D^{20}$ +4.0 ° (c=2.4, $CHCl_3$)). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1110. NMR ($CDCl_3$) δ: 3.6—3.9 (26H, m, –C$\underline{H}_2$O–, –C$\underline{H}$O–), 4.5 (4H, s, 2×C$\underline{H}_2$Ar), 7.3 (10H, s, 2×Ar$\underline{H}$). MS *m/e*: 504 (M^+).

(−)-(2*R*,3*R*)-2,3-Bis(mercaptomethyl)-1,4,7,10-13,17-hexaoxacyclooctadecane (1)——A mixture of **39** (9.88 g, 19.6 mmol), 5% Pd–C (1 g), and conc. HCl (3 drops) in EtOH (100 ml) was stirred under H_2 at room temperature for 3 h. The catalyst was filtered off and the filtrate was evaporated to dryness to give crude **43** (6.41 g). A solution of this crude **43** (6.4 g) and TsCl (9.8 g, 51.4 mmol) in pyridine (36 ml) was stirred at −15 °C for 3 d. Usual work-up as described for the preparation of **17** and purification by column chromatography (silica gel, $CHCl_3$: acetone : hexane = 1 : 1 : 3) afforded **47** (11.8 g, 94% yield) as a colorless caramel. $[\alpha]_D^{20}$ −4.3 ° (c=1.4, $CHCl_3$), lit.[7] $[\alpha]_D^{19.5}$ −5.8 ° (c=1.61, $CHCl_3$). IR ν_{max}^{film} cm^{-1}: 1600. NMR ($CDCl_3$) δ: 2.45 (6H, s, 2×ArC$\underline{H}_3$), 3.3—4.5 (26H, m, –C$\underline{H}$O–, –C$\underline{H}_2$O–), 7.28 and 7.7 (8H, ABq, J=8 Hz, 2×Ar$\underline{H}$). MS *m/e*: 632 (M^+). This tosylate (**47**) was used for the next reaction without further purification.

A solution of **47** (8.92 g, 14.1 mmol) in EtOH–THF (40 ml–20 ml) was added to a solution of KSCOPh (33.7 mmol) in EtOH (40 ml) under N_2, and the whole was stirred under reflux for 4 h. After removal of the solvent, the residue was shaken with ether (200 ml) and water (50 ml). The water layer was separated and extracted with AcOEt (100 ml × 2), and the combined extracts were washed successively with satd. aq. $NaHCO_3$ and satd. aq. NaCl, then dried over $MgSO_4$. The solvent was evaporated off to afford crude **51** (8.9 g) as a brown oil. A solution of this oil (2.64 g) in EtOH (5 ml, N_2 bubbled) was added to aq. 5N NaOH (3 ml, N_2 bubbled) under N_2, and the whole was stirred at room temperature for 1 h. The reaction mixture was acidified with 1 N HCl (15 ml), and then extracted with AcOEt (50 ml × 3). The combined AcOEt extracts were washed successively with satd. aq. $NaHCO_3$ and satd. aq. NaCl, then dried over $MgSO_4$. The AcOEt was evaporated off to afford crude **1**, which was purified by column chromatography (alumina, ether–hexane, and then silica gel, ether–hexane) to afford pure **1** (0.81 g, 49% yield) as a colorless oil. $[\alpha]_D^{20}$ −10.3 ° (c=3.05, $CHCl_3$). lit.[7] $[\alpha]_D^{19.5}$ −10.8 ° (c=3.4, $CHCl_3$). IR ν_{max}^{film} cm^{-1}: 2560, 1100. NMR ($CDCl_3$) δ: 1.65 (2H, dd, J=9, 8.6 Hz, 2×–S$\underline{H}$), 2.4—2.9 (4H, m, 2×–C$\underline{H}_2$S–), 3.3—3.95 (22H, m, –C$\underline{H}$O–, –C$\underline{H}$O–). MS *m/e*: 356 (M^+).

(−)-(2*S*,13*S*)-1,14-Ditosyloxy-2,13-dipropyl-3,6,9,12-tetraoxatetradecane (34)——A solution of **22** (25 g, 72.2 mmol) in DMF (100 ml) was added dropwise to a suspension of NaH (60% in oil, 3.2 g, 72.2 mmol) in DMF (100 ml) under Ar at room temperature, and the whole was stirred at 50 °C for 2 h, then cooled to 0 °C. A solution of triethyleneglycol ditosylate[19] (16.54 g, 36.1 mmol) in DMF (100 ml) was added to the reaction mixture, and the whole was stirred at 50 °C for 4 h. The DMF was evaporated and the residue was shaken with H_2O (20 ml) and ether (200 ml). The water layer was separated and extracted with ether (100 ml). The combined extracts were washed successively with 10% aq. HCl (10 ml × 2), satd. aq. $NaHCO_3$ (10 ml × 2) and satd. aq. NaCl (10 ml × 2), then dried over $MgSO_4$. The ether layer was evaporated off to give a brown oil, which was dissolved in EtOH (200 ml) containing TsOH · H_2O (2 g), and the solution was stirred at 40 °C for 2.5 h. The EtOH was evaporated off, and the residue was shaken with water (100 ml) and hexane (100 ml). The water layer was separated and extracted again with hexane (100 ml). The water layer was then saturated with K_2CO_3, and extracted with AcOEt (150 ml × 2). The combined extracts were evaporated to give a brown oil (9.5 g), which was distilled under reduced pressure to afford **31**

(7.0 g, 60% overall yield) as a pale brown oil of bp 110—150 °C (0.2—0.3 mmHg). IR ν_{max}^{film} cm^{-1}: 3440, 1460 1090. NMR ($CDCl_3$) δ: 0.7—1.7 (14H, m, 2×-C$\underline{H}_2$C$\underline{H}_2$C$\underline{H}_3$), 3.3—3.8 (20H, m, -C$\underline{H}_2$O-, C$\underline{H}$O-). MS *m/e*: 322 (M^+). This diol was used for the next reaction without further purification.

A solution of this oil (6.8 g, 21.1 mmol) and TsCl (9.6 g, 50.6 mmol) in pyridine (40 ml) was stirred at 0 °C for 14 h. Usual work-up as described for the preparation of **17**, followed by purification by column chromatography (silica gel, AcOEt : benzene = 1 : 10—1 : 5), gave pure **34** (9.46 g, 71% overall yield) as a colorless caramel. $[\alpha]_D^{20}$ −11.8° (*c* = 0.72, $CHCl_3$). IR ν_{max}^{film} cm^{-1}: 1600, 1450, 1350, 1192, 1185, 1090, 960, 810, 670. NMR ($CDCl_3$) δ: 0.6—1.6 (14H, m, 2×-C$\underline{H}_2$C$\underline{H}_2$C$\underline{H}_3$), 2.45 (6H, s, 2×ArC$\underline{H}_3$), 3.3—4.35 (18H, m, -C$\underline{H}_2$O-, -C$\underline{H}$O-), 7.33 and 7.8 (8H, ABq, *J* = 8 Hz, 2×Ar$\underline{H}$). MS *m/e*: 630 (M^+). *Anal.* Calcd for $C_{30}H_{46}O_{10}S_2$: C, 57.12; H, 7.35. Found: C, 57.35; H, 7.40.

(−)-(2*S*,3*S*,6*S*,17*S*)-2-3-Bis(tosyloxymethyl)-6,17-dipropyl-1,4,7,10,13,16-hexaoxacyclooctadecane (48)——A solution of **15**[17] (4.32 g, 14.3 mmol) in DMF (100 ml) was added dropwise to a suspension of NaH (60% in oil, 1.26 g 31.5 mmol) in DMF (100 ml) at room temperature, and the whole was stirred at 40—50 °C for 1.5 h, then cooled to room temperature. A solution of **34** (9.0 g, 14.3 mmol) in DMF (100 ml) was added to the reaction mixture, and the whole was stirred at 50—60 °C for 20 h. Usual work-up as described for the preparation of **39** gave a brown oil (8.23 g), which was purified by column chromatography (silica gel, ether : hexane = 1 : 1) to give **40** (5.66 g, 67% yield). This oil was used for the next reaction without further purification.

A mixture of **40** (5.5 g, 9.34 mmol) and 5% Pd–C (0.6 g) in EtOH–conc. HCl (60 ml–1 drop) was stirred for 3 h at room temperature under atmospheric pressure of H_2. The catalyst was filtered off, and the filtrate was evaporated to dryness to give crude **44** (3.74 g). This crude diol was used for the next reaction without futher purification. A solution of this diol (3.6 g, 9.56 mmol) and TsCl (4.7 g, 24.7 mmol) in pyridine (20 ml) was stirred at 0 °C for 14 h. Usual work-up as described for the preparation of **17** gave crude **48** (6.07 g, 89% overall yield) as a pale brown oil, which was purified by column chromatography (silica gel, hexane : AcOEt : acetone = 5 : 2 : 1) to afford **48** (5.3 g, 77% overall yield) as a white powder of mp 58—63 °C. Recrystallization from EtOH afforded a white powder of mp 66.5—67 °C. $[\alpha]_D^{20}$ −6.58° (*c* = 1.03, $CHCl_3$). IR ν_{max}^{film} cm^{-1}: 1600, 1450, 1360, 1190, 1180, 1090, 970, 810, 650. NMR ($CDCl_3$) δ: 0.65—1.6 (14H, m, 2×-C$\underline{H}_2$C$\underline{H}_2$C$\underline{H}_3$), 2.42 (6H, s, 2×ArC$\underline{H}_3$), 3.1—3.8 (20H, m, -C$\underline{H}_2$O-, -C$\underline{H}$O-), 3.8—4.6 (4H, m, 2×-C$\underline{H}_2$OTs), 7.28 and 7.77 (8H, ABq, *J* = 8 Hz, 2×Ar$\underline{H}$). MS *m/e*: 716 (M^+). *Anal.* Calcd for $C_{34}H_{52}O_{12}S_2$: C, 56.96; H, 7.31. Found: C, 56.73; H, 7.32.

(−)-(2*R*,3*R*,6*S*,17*S*)-2,3-Bis(mercaptomethyl)-6,17-dipropyl-1,4,7,10,13,16-tetraoxacyclooctadecane (2)——A solution of **48** (5.0 g, 6.97 mmol) in EtOH (10 ml) was added to a suspension of KSCOPh (7.7 mmol) in EtOH (20 ml) under Ar at room temperature, and then the whole was stirred under reflux for 4 h. Usual work-up described for the preparation of **51** gave a crude oil (5.5 g), which was purified by column chromatography (silica gel, hexane : AcOEt : acetone = 5 : 2 : 1) to afford **52** (2.47 g, 55% yield) as a red oil. IR ν_{max}^{film} cm^{-1}: 1670, 1600, 1585, 1455, 1210, 1110, 915, 775, 690. NMR ($CDCl_3$) δ: 3.40 (6H, s, 2×-OC$\underline{H}_3$), 3.4—4.0 (24H, m, -C$\underline{H}_2$O-, -C$\underline{H}$O-), 7.3—8.2 (10H, m, 2×Ar$\underline{H}$). MS *m/e*: 648 (M^+), 511. This oil was used for the next reaction without further purification.

A solution of **52** (1.9 g, 2.93 mmol) in ether (15 ml) was added dropwise to a suspension of $LiAlH_4$ (220 mg, 5.8 mmol) in ether (30 ml) at room temperature under Ar, and the whole was stirred under reflux for 3 h, then cooled to room temperature. Next, 10% aq. HCl was added to the reaction mixture and the whole was shaken. The water layer was separated and extracted with AcOEt (100 ml × 2). The combined extracts were washed successively with 10% aq. HCl, satd. aq. $NaHCO_3$ and satd. aq. NaCl, then dried over $MgSO_4$. The AcOEt was evaporated off to give a colorless oil (1.95 g), which was purified by column chromatography (silica gel, hexane : ether = 1 : 1) to afford pure **2** (0.60 g, 61% yield) as a colorless oil. $[\alpha]_D^{20}$ −12.5° (*c* = 0.62, $CHCl_3$). IR ν_{max}^{film} cm^{-1}: 2560, 1465, 1350, 1290, 1245, 1105. NMR ($CDCl_3$) δ: 0.7—1.7 (16H, m, 2×-C$\underline{H}_2$C$\underline{H}_2$C$\underline{H}_3$, 2×-S$\underline{H}$), 2.5—2.9 (4H, m, 2×-C$\underline{H}_2$SH), 3.2—4.0 (20H, m, -C$\underline{H}_2$O-, -C$\underline{H}$O-). MS *m/e*: 440 (M^+), 439, 408. *Anal.* Calcd for $C_{20}H_{40}O_6S_2 \cdot 0.5H_2O$: C, 53.42; H, 9.19. Found: C, 53.50; H, 9.01.

(−)-(2*S*,13*S*)-1,14-Bis(tosyloxy)-2,13-bis(methoxymethyl)-3,6,9,12-tetraoxatetradecane (35)——A solution of **20** (61.91 g, 0.178 mol) in DMF (100 ml) was added dropwise to a suspension of NaH (60% in oil, 7.8 g, 0.195 mol) in DMF (200 ml) at room temperature, and the whole was stirred at 50 °C for 40 min, then cooled to 0 °C. A solution of triethyleneglycol ditosylate[19] (40.72 g, 0.089 mol) in DMF (100 ml) was added to the reaction mixture, and the whole was stirred at room temperature for 4 h. Usual work-up as described for the preparation of **31** gave a brown oil (80 g). A mixture of this oil and $TsOH \cdot H_2O$ (3 g) in EtOH (200 ml) was stirred at room temperature for 1.5 h. After neutralization with K_2CO_3 (10 g), the reaction mixture was filtered, and the filtrate was evaporated. The residue was diluted with ether (300 ml), and then extracted with water (100 ml × 3). The combined watr layers were washed with ether (100 ml), saturated with K_2CO_3, and then extracted with AcOEt (250 ml × 2). The combined AcOEt extracts were dried over $MgSO_4$, and then evaporated to give crude **32** (27 g), which was tosylated without further purification.

A solution of this oil (26.3 g) and TsCl (42.6 g, 0.21 mol) in pyridine (150 ml) was stirred at 0 °C for 18 h. Usual work-up as described for the preparation of **17** gave a crude product (44.1 g), which was purified by column chromatography (silica gel, AcOEt : benzene = 1 : 1) to afford **35** (25.65 g, 56% overall yield) as a colorless oil. $[\alpha]_D^{20}$ −1.07° (*c* = 1.07, $CHCl_3$). IR ν_{max}^{film} cm^{-1}: 1600, 1450, 1355, 1180, 1100, 960, 820. NMR ($CDCl_3$) δ: 2.48 (6H, s,

ArCH$_3$), 3.3 (6H, s, 2×–OCH$_3$), 3.3—3.9 (18H, m, –CH$_2$O–, –CHO–), 3.95—4.25 (4H, m, 2×–CH$_2$OTs), 7.34 and 7.76 (8H, ABq, J=8 Hz, 2×ArH). MS *m/e*: 634 (M^+). *Anal.* Calcd for $C_{28}H_{42}O_{12}S_2$: C, 52.98; H, 6.67. Found: C, 52.70; H, 6.71.

(−)-(2*S*,3*S*,6*S*,7*S*)-2,3-Bis(tosyloxymethyl)-6,17-bis(methoxymethyl)-1,4,7,10,13,16-hexaoxacyclooctadecane (49)——A solution of **15**[17] (6.33 g, 21 mmol) in DMF (150 ml) was added dropwise to a suspension of NaH (60% in oil, 1.85 g, 46 mmol) in DMF (100 ml) at room temperature, and the whole was stirred at 40—50 °C for 1 h, then cooled to room temperature. A solution of the ditosylate (**35**) (13.29 g, 21 mmol) in DMF (150 ml) was added to the reaction mixture, and the whole was stirred at 50 °C for 17 h. Usual work-up as described for the preparation of **39** gave a brown oil (12.2 g), which was purified by column chromatography (silica gel, benzene : acetone = 10 : 1—5 : 1) to give **41** (6.32 g, 50% yield). A mixture of this oil (5.67 g, 9.58 mmol) and 5% Pd–C (0.5 g) in EtOH–conc. HCl (60 ml–1 drop) was stirred at room temperature under atmospheric pressure of H_2. The catalyst was filtered off, and the filtrate was evaporated to dryness to give the crude diol **45** (3.81 g). This crude diol was used for the next reaction without further purification. A solution of this diol (3.23 g) and TsCl (4.5 g, 23.6 mmol) in pyridine (20 ml) was stirred at 0 °C for 20 h. Usual work-up as described for the preparation of **17** gave crude **49** (4.69 g, 83% overall yield) as a white powder, which was recrystallized from ether at −20 °C to afford white needles of mp 49—50 °C. $[\alpha]_D^{20}$ −3.84° (c=1.0, $CHCl_3$). IR ν_{max}^{film} cm^{-1}: 1600, 1460, 1360, 1180, 1170, 1120, 955, 840, 740. NMR ($CDCl_3$) δ: 2.47 (6H, s, 2×ArCH$_3$), 3.35 (6H, s, 2×–OCH$_3$), 3.3—4.0 (24H, m, –CH$_2$O–, –CHO–), 4.0—4.3 (4H, m, 2×–CH$_2$OTs), 7.4 and 7.8 (8H, ABq, J=9 Hz, 2×ArH). MS *m/e*: 720 (M^+). *Anal.* Calcd for $C_{32}H_{48}O_{14}S_2$: C, 53.32; H, 6.71. Found: C, 53.07; H, 6.67.

(2*R*,3*R*,6*S*,17*S*)-2,3-Bis(benzoylthiomethyl)-6,17-bis(methoxymethyl)-1,4,7,10,13,16-hexaoxacyclooctadecane (53)——A solution of **49** (1.0 g, 1.39 mmol) in EtOH (5 ml) was added to a suspension of KSCOPh (490 mg, 2.78 mmol) in EtOH (3 ml) under Ar at room temperature, and then the whole was stirred under reflux for 3 h. Usual work-up as described for the preparation of **51** gave crude **53** (1.15 g), which was purified by column chromatography (silica gel, AcOEt) to afford **53** (0.85 g, 94% yield) as a pale brown viscous oil. IR ν_{max}^{film} cm^{-1}: 1670, 1600, 1585, 1455, 1210, 1110, 915, 775, 690. NMR ($CDCl_3$) δ: 3.40 (6H, s, 2×–OCH$_3$), 3.4—4.0 (24H, m, –CH$_2$O–, –CHO–), 7.3—8.2 (10H, m, 2×ArH). *Anal.* Calcd for $C_{32}H_{48}O_{14}S_2 \cdot 0.5H_2O$: C, 58.07; H, 6.85. Found: C, 58.14; H, 6.69.

(−)-(2*R*,3*R*,6*S*,17*S*)-2,3-Bis(mercaptomethyl)-6,17-bis(methoxymethyl)-1,4,7,10,13,16-hexaoxacyclooctadecane (3)——A solution of **53** (0.72 g, 1.1 mmol) in ether (10 ml) was added dropwise to a suspension of $LiAlH_4$ (100 mg, 2.6 mmol) in ether (10 ml) at room temperature under Ar, and then the whole was stirred under reflux for 1.5 h. Usual work-up as described for the preparation of **2** gave a colorless oil (0.78 g), which was purified by column chromatography (silica gel, ether) to afford pure **3** (0.37 g, 76% yield) as a colorless oil. $[\alpha]_D^{20}$ −4.0° (c=0.86, $CHCl_3$). IR ν_{max}^{film} cm^{-1}: 2550, 1450, 1350, 1195, 1110, 970, 840. NMR ($CDCl_3$) δ: 1.61 (2H, dd, J=9.2, 7.4 Hz, 2×–SH), 2.5—2.9 (4H, m, 2×–CH$_2$SH), 3.47 (6H, s, 2×–OCH$_3$), 3.4—4.0 (24H, m, –CH$_2$O–, –CHO–). MS *m/e*: 444 (M^+). *Anal.* Calcd for $C_{18}H_{36}O_8S_2$: C, 48.62; H, 8.16. Found: C, 48.32; H, 7.99.

(+)-(2*S*,13*S*)-1,14-Bis(tosyloxy)-2,13-bis(benzyloxymethyl)-3,6,9,12-tetraoxatetradecane (36)——A solution of **21** (64 g, 0.151 mol) in DMF (300 ml) was added dropwise to a suspension of NaH (60% in oil, 6.3 g, 0.159 mol) under Ar at room temperature, and the whole was stirred at 45—50 °C for 1 h, then cooled to 0 °C. A solution of triethyleneglycol ditosylate[19] (33.03 g, 0.072 mol) in DMF (200 ml) was added to the reaction mixture, and the whole was stirred at room temperature for 14 h. Usual work-up as described for the preparation of **31** gave a brown oil (111 g). A mixture of this oil and TsOH·H$_2$O (5 g) in EtOH (200 ml) was stirred at room temperature for 12 h. Usual work-up as described for the preparation of **31** gave a brown red oil (42.9 g), which was purified by column chromatography (silica gel, AcOEt) to afford crude **33** (18.31 g) as a colorless oil. A solution of this oil (18.31 g) and TsCl (18.97 g, 0.0995 mol) in pyridine (190 ml) was stirred at 0 °C for 14 h. Usual work-up as described for the preparation of **17** gave crude **36** (27.68 g, 52% overall yield), which was purified by column chromatography (silica gel, AcOEt : hexane = 1 : 1) to afford pure **36** as a colorless caramel, $[\alpha]_D^{20}$ +6.5° (c=2.0, $CHCl_3$). IR ν_{max}^{film} cm^{-1}: 1600, 1455, 1360, 1188, 1183, 1095, 985, 815, 650. NMR ($CDCl_3$) δ: 2.4 (6H, s, 2×ArCH$_3$), 3.66—3.93 (18H, m, –CH$_2$O–, –CHO–), 3.93—4.27 (4H, m, 2×–CH$_2$OTs), 4.40 (4H, s, 2×–CH$_2$Ar), 7.23 (10H, s, CH$_2$ArH), 7.30 and 7.77 (8H, ABq, J=8 Hz, 2×–SO$_3$ArH). MS *m/e*: 786 (M^+). *Anal.* Calcd for $C_{40}H_{50}O_{12}S_2$: C, 61.05; H, 6.40. Found: C, 60.75; H, 6.11.

(−)-(2*S*,13*S*)-1,14-Bis(tosyloxymethyl)-2,13-bis(methoxymethoxymethyl)-3,6,9,12-tetraoxatetradecane (38)——A mixture of **36** (26.68 g, 33.9 mmol) and 5% Pd–C (2 g) and conc. HCl (3 drops) in MeOH and ether (200 ml–20 ml) was stirred at room temperature under atmospheric pressure of H_2 for 2 h. The catalyst was filtered off, and the filtrate was evaporated to dryness to give **37** (21.08 g) as a colorless oil. This oil was used for the next reaction without further purification.

P_2O_5 (70 g) was added at once to a cooled solution of the above diol (11.17 g, 18.4 mmol) in $CHCl_3$–methylal (320 ml–200 ml), and then the whole was stirred vigorously with a mechanical stirrer for 1 h. The reaction mixture was poured into ice-cold 10% aq. Na_2CO_3 (200 ml). The remaining yellow gum in the flask was washed out with 10% aq. Na_2CO_3 (300 ml). The combined mixture was shaken, and then extracted with ether (300 ml × 3). The combined ether extracts were washed successively with 10% aq. Na_2CO_3 (100 ml) and satd. aq. NaCl, then dried over $MgSO_4$. The ether was evaporated off to give a pale yellow viscous oil (11.05 g), which was purified by column

chromatography (silica gel, benzene : AcOEt = 1 : 1) to afford **38** (8.05 g, 63% overall yield) as a colorless viscous oil. $[\alpha]_D^{20}$ −1.0° (c = 2.0, $CHCl_3$). IR ν_{max}^{film} cm^{-1}: 1600, 1450, 1360, 1185, 1175, 1040, 980 815, 760, 650. NMR ($CDCl_3$) δ: 2.43 (6H, s, 2×ArC<u>H</u>$_3$), 3.30 (6H, s, 2×-OC<u>H</u>$_3$), 3.30—4.0 (18H, m, -C<u>H</u>$_2$O-, -C<u>H</u>O-), 4.0—4.3 (4H, m, 2×-C<u>H</u>$_2$OTs), 4.57 (4H, s, 2×-OC<u>H</u>$_2$O-), 7.37 and 7.83 (8H, ABq, J = 8 Hz, 2×Ar<u>H</u>). *Anal.* Calcd for $C_{30}H_{46}O_{14}S_2$: C, 51.86; H, 6.67. Found: C, 51.86; H, 6.62.

(−)-(2*S*,3*S*,6*R*,17*R*)-2,3-Bis(tosyloxymethyl)-6,17-bis(methoxymethoxymethyl)-1,4,7,10,13,16-hexaoxacyclooctadecane (50)——A solution of **15**[17] (3.3 g, 10.8 mmol) in DMF (100 ml) was added dropwise to a suspension of NaH (60% in oil, 0.95 g, 23.8 mmol) in DMF (100 ml) at room temperature under Ar, and the whole was stirred at 40—50 °C for 40 min, then cooled to 0 °C. A solution of **38** (7.5 g, 10.8 mmol) in DMF (200 ml) was added to the reaction mixture, and the whole was stirred at 50 °C for 16 h. Usual work-up as described for the preparation of **39** gave a brown oil (7.07 g), which was purified by column chromatography (silica gel, benzene : AcOEt = 1 : 3) to give **42** (4.11 g, 58% yield) as a colorless oil. IR ν_{max}^{film} cm^{-1}: 1600, 1490, 1450, 1370, 1240, 1210, 1100, 1040, 915, 735, 690. NMR ($CDCl_3$) δ: 3.2 (6H, s, 2×-OC<u>H</u>$_3$), 3.4—4.1 (28H, m, -C<u>H</u>$_2$O-, -C<u>H</u>O-), 4.48 (4H, s, 2×-C<u>H</u>$_2$Ar), 4.55 (4H, s, 2×-OC<u>H</u>$_2$O-), 7.25 (10H, s, 2×Ar<u>H</u>). MS m/e: 652 (M^+), 572, 530. This oil was used for the next reaction without further purification.

A mixture of the above oil (6.8 g, 10.4 mmol) and 5% Pd–C (0.7 mg) in EtOH–conc. HCl (100 ml–1 drop) was stirred at room temperature for 12 h under atmospheric pressure of H_2. The catalyst was filtered off, and the filtrate was evaporated to dryness to give crude **46** (4.68 g). This crude diol was used for the next reaction without further purification. A solution of this diol (4.68 g) and TsCl (4.53 g, 24 mmol) in pyridine (25 ml) was stirred at −15 °C for 14 h. Usual work-up as described for the preparation of **17** and purification by column chromatography (silica gel, AcOEt : acetone : benzene = 5 : 1 : 2) gave **50** (3.9 g, 50% overall yield) as a colorless caramel. $[\alpha]_D^{20}$ −1.48° (c = 1.08, $CHCl_3$). IR ν_{max}^{film} cm^{-1}: 1600, 1450, 1360, 1190, 1170, 1100, 1040, 960, 810, 650. NMR ($CDCl_3$) δ: 2.43 (6H, s, 2×ArC<u>H</u>$_3$), 3.33 (6H, s, 2×-OC<u>H</u>$_3$), 3.31—4.4 (28H, m, -C<u>H</u>$_2$O-, -C<u>H</u>O-), 7.30 and 7.89 (8H, ABq, J = 9 Hz, Ar<u>H</u>). *Anal.* Calcd for $C_{34}H_{52}O_{16}S_2$: C, 52.29; H, 6.71. Found: C, 52.02; H, 6.62.

(−)-(2*R*,3*R*,6*R*,17*R*)-2,3-Bis(mercaptomethyl)-6,17-bis(methoxymethoxymethyl)-1,4,7,10,13,16-hexaoxacyclooctadecane (4)——A solution of **50** (3.5 g, 4.48 mmol) in EtOH (10 ml) was added to a solution of KSCOPh (4.9 mmol) in EtOH (15 ml) under N_2 at room temperature, and then the whole was stirred under reflux for 3 h. Usual work-up as described for the preparation of **51** gave crude **54**, which was purified by column chromatography (silica gel, ether) to afford **54** (1.96 g, 61% yield) as a red caramel. This thiolester was used for the next reaction without further purification.

A solution of the above caramel (1.9 g, 2.67 mmol) in ether (30 ml) was added to a suspension of $LiAlH_4$ (0.22 g, 5.8 mmol) in ether (15 ml) at room temperature under Ar, and then the whole was stirred under reflux for 1.5 h. Usual work-up as described for the preparation of **2** gave crude **4** (1.93 g), which was purified by column chromatography (silica gel, AcOEt : hexane = 1 : 1) to afford pure **4** (1.04 g, 77% overall yield) as a colorless oil. $[\alpha]_D^{20}$ −2.9° (c = 0.96, $CHCl_3$). IR ν_{max}^{film} cm^{-1}: 2560, 1460, 1350, 1300, 1250, 1210, 1100, 1040, 915. NMR ($CDCl_3$) δ: 1.65 (2H, dd, J = 9, 8.6 Hz, 2×-S<u>H</u>), 2.45—2.85 (4H, m, 2×-C<u>H</u>$_2$SH), 3.25 (6H, s, 2×-OC<u>H</u>$_3$), 3.4—3.95 (24H, m, -C<u>H</u>$_2$O-, -C<u>H</u>O-), 4.53 (4H, s, 2×-OC<u>H</u>$_2$O-). MS m/e: 504 (M^+), 503, 502, 474. *Anal.* Calcd for $C_{20}H_{40}O_{10}S_2$: C, 47.60; H, 7.99. Found: C, 47.31; H, 7.80.

(−)-(2*R*,3*R*,6*S*,17*S*)-2,3-Bis(mercaptomethyl)-6,17-bis(hydroxymethyl)-1,4,7,10,13,16-hexaoxacyclooctadecane (5)——A solution of **4** (0.75 g, 1.49 mmol) in EtOH–conc. HCl (10 ml–0.2 ml) was stirred at 40 °C for 4 h under Ar. The solvent was evaporated off to give a crude oil, which was purified by column chromatography (silica gel, AcOEt) to give crude **5** (140 mg). This oil was purified again by high performance liquid chromatography (HPLC) (Waters Radial Pack A, H_2O : MeOH : acetone = 30 : 30 : 5) to afford a mixture of **5** and **5i** (61 mg, 10% yield) as a colorless viscous oil. NMR spectra showed a 6 : 4 ratio of **5** and **5i**. $[\alpha]_D^{20}$ −27.4° (c = 0.86, $CHCl_3$). IR ν_{max}^{film} cm^{-1}: 3400, 2520, 1460, 1350, 1300, 1250, 1070, 830, 680. NMR ($CDCl_3$) δ: 1.2 (1.6H, t, J = 7 Hz, -S<u>H</u>), 2.5—2.95 (5.6H, m, 2×C<u>H</u>$_2$SH, -O<u>H</u>), 3.4—3.9 (24H, m, -C<u>H</u>$_2$O-, -C<u>H</u>O-), 4.7 (0.8H, -OC<u>H</u>$_2$O-). MS m/e: 428 (M^+ for **5i**), 416 (M^+ for **5**). HRMS Calcd for $C_{16}H_{32}O_8S_2$ for **5**: 416.1538. Found: 416.1593. Calcd for $C_{17}H_{32}O_8S_2$ for **5i**: 428.1538. Found: 428.1555.

(+)-(2*R*)-2-Tosyloxymethyl-1,4,7,10,13,16-hexaoxacyclooctadecane (58)——A solution of (*R*)-1-*O*-benzylglycerol[10] (12 g, 65.9 mmol) in DMF (100 ml) was added dropwise to a suspension of NaH (60% in oil, 6.33 g, 15.8 mmol) in DMF (300 ml) under N_2 at room temperature, and the whole was stirred at 65 °C for 1 h, then cooled to room temperature. A solution of pentaethyleneglycol ditosylate[18] (3.6 g, 65.9 mmol) in DMF (300 ml) was added, and the whole was stirred at 65 °C for 12 h. Usual work-up as described for the preparation of **39** gave crude **55** (17.6 g) as a colorless oil. This oil was used for the next reaction without further purification.

A mixture of **55** (12 g), 5% Pd–C (1.3 g), and conc. HCl (1 drop) in EtOH (300 ml) was stirred under H_2 at room temperature for 3 h. The catalyst was filtered off and the filtrate was evaporated to dryness to give the crude alcohol (8.13 g). A solution of this crude oil (8.13 g) and TsCl (21 g, 11 mmol) in pyridine (130 ml) was stirred at −15 °C for 2 d. Usual work-up as described for the preparation of **17** and purification by column chromatography (silica gel, AcOEt : hexane = 1 : 2) afforded **58** (5.72 g) as a white powder, which was recrystallized from EtOH to afford a white powder of mp 46—47.5 °C. $[\alpha]_D^{20}$ +1.3° (c = 3.0, $CHCl_3$). IR ν_{max}^{Nujol} cm^{-1}: 1600, 1460, 1375, 1170, 1105. NMR ($CDCl_3$)

δ: 2.43 (6H, s, 2 × ArC$\underline{H}_3$), 3.4—4.3 (25H, m, –C$\underline{H}$O–, –C$\underline{H}_2$O–), 7.28 and 7.7 (8H, ABq, J=8 Hz, 2 × Ar$\underline{H}$). *Anal.* Calcd for $C_{20}H_{32}O_9S$: C, 53.56; H, 7.19. Found: C, 53.79; H, 7.27.

(−)-(2*S*)-2-Mercaptomethyl-1,4,7,10,13,16-hexaoxacyclooctadecane (6)——A solution of **58** (4.61 g, 10.3 mmol) in EtOH (20 ml) was added to a solution of KSCOPh (2.17 g, 12.36 mmol) in EtOH (20 ml) under N_2, and the whole was stirred under reflux for 3 h. Usual work-up as described for the preparation of **51** gave a crude red oil (4.5 g). A solution of this oil (4.5 g) in EtOH (5 ml, N_2 bubbled) was added to aq. 5 N NaOH (6.9 ml, N_2 bubbled) under N_2, and the whole was stirred at room temperature for 8 h. The reaction mixture was acidified with 1 N HCl (15 ml), and then extracted with ether (500 ml). The ether extract was dried over $MgSO_4$, and evaporated to afford crude **6**, which was purified by column chromatography (alumina, ether, and then silica gel, AcOEt) to afford pure **6** (2.25 g, 70.4% overall yield) as a colorless oil. $[\alpha]_D^{20}$ −2.7° (c=3.0, $CHCl_3$). IR ν_{max}^{film} cm^{-1}: 2560, 1100. NMR ($CDCl_3$) δ: 1.55 (1H, t, J=8 Hz, –S$\underline{H}$), 2.5—2.9 (2H, m, –C$\underline{H}_2$S–), 3.4—4.0 (23H, m, –C$\underline{H}$O–, –C$\underline{H}$O–). HRMS Calcd for $C_{13}H_{26}O_6S$: 310.1447. Found: 310.1431.

(−)-(2*S*,3*S*)-2-Tosyloxymethyl-3-methyl-1,4,7,10,13,16-hexaoxacyclooctadecane (59)——A solution of **18** (5.7 g, 29 mmol) in DMF (200 ml) was added dropwise to a suspension of NaH (60% in oil, 2.6 g, 63.8 mmol) in DMF (200 ml) under Ar at room temperature, and the whole was stirred at 65 °C for 1.5 h, then cooled to room temperature. A solution of pentaethyleneglycol ditosylate[18] (15.96 g, 29 mmol) in DMF (300 ml) was added, and the whole was stirred at 70 °C for 19 h. Usual work-up as described for the preparation of **39** gave crude **56** (6.67 g) as a colorless oil. This oil was used for the next reaction without further purification.

A mixture of **56** (6.67 g), 5% Pd–C (0.7 g), and conc. HCl (1 drop) in EtOH (150 ml) was stirred under H_2 at room temperature for 4 h. The catalyst was filtered off and the filtrate was evaporated to dryness to give the crude diol (4.7 g). A solution of this crude oil (4.7 g) and TsCl (10 g, 52.5 mmol) in pyridine (60 ml) was stirred at −15 °C for 2 d. Usual work-up as described for the preparation of **17** and purification by column chromatography (silica gel, AcOEt : hexane = 1 : 2) afforded **59** (3.69 g, 28% overall yield) as a colorless caramel. $[\alpha]_D^{20}$ −3.8° (c=3.9, $CHCl_3$). IR ν_{max}^{film} cm^{-1}: 1600, 1450, 1350, 1290, 1245, 1190, 1185, 1100, 960, 810, 780, 660. NMR ($CDCl_3$) δ: 1.12 (3H, d, J=5 Hz, –C$\underline{H}_3$), 2.44 (3H, s, ArC$\underline{H}_3$), 3.2—4.3 (24H, m, –C$\underline{H}$O–, –C$\underline{H}_2$O–), 7.32 and 7.76 (4H, ABq, J=8 Hz, Ar$\underline{H}$). MS *m/e*: 462 (M^+), 290. *Anal.* Calcd for $C_{21}H_{34}O_9S$: C, 54.53; H, 7.41. Found: C, 54.47; H, 7.39.

(2*R*,3*S*)-2-Mercaptomethyl-3-methyl-1,4,7,10,13,16-hexaoxacyclooctadecane (7)——A solution of **59** (1.5 g, 3.24 mmol) in EtOH (6 ml) was added to a solution of KSCOPh (0.63 g, 3.56 mmol) in EtOH (6 ml) under N_2, and the whole was stirred under reflux for 2.5 h. Usual work-up as described for the preparation of **51** gave a crude oil (1.43 g), which was purified by column chromatography to give pure **50** (1.29 g) as a colorless oil. A solution of this oil (1.29 g) in EtOH (3 ml, N_2 bubbled) was added to aq. 5 N NaOH (1.94 ml, N_2 bubbled) under N_2, and the whole was stirred at room temperature for 40 min. The reaction mixture was acidified with conc. HCl (0.97 ml), and then extracted with ether (250 ml). The ether extracts was dried over $MgSO_4$, and then evaporated to afford crude **7**, which was purified by column chromatography (alumina, ether) to afford pure **7** (0.44 g, 42% overall yield) as a colorless oil. IR ν_{max}^{film} cm^{-1}: 2560, 1100. NMR ($CDCl_3$) δ: 1.23 (3H, d, J=6 Hz, –C$\underline{H}_3$), 1.65 (1H, dd, J=9, 8.6 Hz, –S$\underline{H}$), 2.4—3.0 (2H, m, –C$\underline{H}_2$S–), 3.4—3.9 (23H, m, –C$\underline{H}$O–, –C$\underline{H}$O–). MS *m/e*: 324 (M^+), 291. *Anal.* Calcd for $C_{14}H_{28}O_6S$: C, 51.83; H, 8.70. Found: C, 51.54; H, 8.60.

(−)-(2*S*,3*S*)-2-Tosyloxymethyl-3-(2-methoxyphenoxymethyl)-1,4,7,10,13,16-hexaoxacyclooctadecane (60)——A solution of **19** (17.5 g, 55 mmol) in DMF (300 ml) was added dropwise to a suspension of NaH (60% in oil, 8.8 g, 220 mmol) in DMF (1000 ml) under Ar at room temperature, and the whole was stirred at 50 °C for 1 h, then cooled to room temperature. A solution of pentaethyleneglycol ditosylate[18] (15.96 g, 29 mmol) in DMF (400 ml) was added, and the whole was stirred at 70 °C for 19 h. Usual work-up as described for the preparation of **39** gave crude **57** (7.74 g) as a colorless oil. This oil was used for the next reaction without further purification.

A mixture of **57** (7.74 g), 5% Pd–C (0.77 g) and conc. HCl (1 drop) in EtOH (180 ml) was stirred under H_2 at room temperature for 1.5 h. The catalyst was filtered off and the filtrate was evaporated to dryness to give a crude oil (6.2 g). A solution of this crude oil (6.2 g) and TsCl (3 g, 16 mmol) in pyridine (50 ml) was stirred at −15 °C for 2 d. Usual work-up as described for the preparation of **17** and purifcation by column chromatography (silica gel, AcOEt : hexane = 1 : 2) afforded **60** (7.7 g, 93% overall yield) as a colorless caramel. $[\alpha]_D^{20}$ −4.36° (c=3.0, $CHCl_3$). IR ν_{max}^{film} cm^{-1}: 1595, 1500, 1450, 1350, 1290, 1245, 1170, 1115, 1020, 940, 810, 740. NMR ($CDCl_3$) δ: 2.43 (3H, s, ArC$\underline{H}_3$), 3.4—4.6 (26H, m, –C$\underline{H}$O–, –C$\underline{H}_2$O–), 3.79 (3H, s, –OC$\underline{H}_3$), 6.85 (4H, s, OAr$\underline{H}$), 7.28 and 7.78 (4H, ABq, J= 8 Hz, –SO_3Ar$\underline{H}$). HRMS Calcd for $C_{28}H_{40}O_{11}S$: 584.2289. Found: 584.2278.

(−)-(2*R*,3*S*)-2-Mercaptomethyl-3-(2-methoxyphenoxymethyl)-1,4,7,10,13,16-hexaoxacyclooctadecane (8)——A solution of **60** (7.4 g, 13 mmol) in EtOH (6 ml) was added to a solution of KSCOPh (2.46 g, 14 mmol) in EtOH (30 ml) under N_2, and the whole was stirred under reflux for 3 h. Usual work-up as described for the preparation of **51** gave a crude oil, which was purified by column chromatography to give a colorless oil (6.52 g). A solution of this oil (6.2 g) in EtOH (25 ml, N_2 bubbled) was added to aq. 5 N NaOH (7.2 ml, N_2 bubbled) under N_2, and the whole was stirred at room temperature for 1 h. The reaction mixture was acidified with conc. HCl (0.97 ml), and then extracted with ether (250 ml). The ether extract was dried over $MgSO_4$, and then evaporated to afford crude **8**, which was purified by column chromatography (alumina, ether, and then silica gel, AcOEt–hexane) to afford pure **8** (3.0 g, 60% overall yield) as a colorless oil. $[\alpha]_D^{20}$ −5.3° (c=3.0, $CHCl_3$). IR ν_{max}^{film} cm^{-1}: 2560, 1595, 1500, 1450, 1345, 1245, 1110, 1020,

940, 740. NMR ($CDCl_3$) δ: 1.70 (1H, dd, J=9, 8.6 Hz, -SH), 2.6—3.0 (2H, m, $-CH_2S-$), 3.5—4.3 (24H, m, $-CH_2O-$, -CHO-), 6.88 (4H, s, ArH). MS *m/e*: 324 (M^+), 291. HRMS Calcd for $C_{21}H_{34}O_8S$: 446.1975. Found: 446.1996.

(+)-(1*R*,2*R*,3*S*,4*S*)-2-Benzyloxy-3-(2-hydroxyethoxy)-1,7,7-trimethylbicyclo[2.2.1]heptane (61)——A solution of **24** (9.1 g, 35 mmol) in DMF (50 ml) was added dropwise to a suspension of NaH (55% in oil, 1.61 g, 38 mmol) in DMF (30 ml) at room temperature under Ar and the whole was stirred at 40 °C for 40 min, the cooled to 0 °C. A solution of 1-tetrahydropyranyloxy-2-tosyloxyethane[20] (11.5 g, 38 mmol) in DMF (30 ml) was added to the reaction mixture, and the whole was stirred at room temperature for 2 h. The reaction mixture was diluted with benzene (300 ml), and washed with water (200 ml). The aqueous phase was separated and again extracted with benzene (300 ml). The combined benzene layers were dried over $MgSO_4$, and then evaporated to afford a brown oil (15.56 g). A solution of this oil in MeOH–conc. HCl (80 ml–8 ml) was stirred under reflux for 2 h. The MeOH was evaporated off, and the residue was extracted with AcOEt (150 ml × 2). The combined extracts were washed successively with satd. aq. $NaHCO_3$ and satd. aq. NaCl, then dried over $MgSO_4$. The AcOEt was evaporated off to give a brown oil (12.05 g), which was distilled under reduced pressure to afford pure **61** (8.55 g, 80% overall yield) as a colorless oil of bp 145—146 °C (0.2 mmHg). $[\alpha]_D^{20}$ +121.5° (c=1.14, EtOH). IR ν_{max}^{film} cm^{-1}: 3440, 1360, 1120, 1070, 730, 700. NMR ($CDCl_3$) δ: 0.88 (6H, s, 2 × $-CH_3$), 0.92 (3H, s, $-CH_3$), 0.9—2.1 (5H, m, $-CH_2-$, CH–), 2.53 (1H, br, OH), 3.2—3.75 (5H, m, $-CH_2O-$, -CHO–), 3.84 (1H, dd, J=8, 4 Hz, $-CHOCH_2-$), 4.40 and 4.66 (2H, ABq, J=12 Hz, $-CH_2Ar$), 7.18 (5H, s, ArH). MS *m/e*: 304 (M^+). *p*-Nitrobenzoate of **61**: mp 73.5—74 °C. $[\alpha]_D^{20}$ +67.3° (c=0.52, EtOH). *Anal.* Calcd for $C_{26}H_{31}N_1O_6$: C, 68.85; H, 6.89; N, 3.09. Found: C, 68.66; H, 6.85; N, 3.15.

(+)-(1*R*,2*R*,3*S*,4*S*)-2-Benzyloxy-3-(2-tosyloxyethoxy)-1,7,7-trimethylbicyclo[2.2.1]heptane (62)——A solution of **61** (7.3 g, 24 mmol) and TsCl (5.9 g, 31 mmol) in pyridine (50 ml) was stirred at 0 °C for 15 h. Usual work-up as described for the preparation of **17** gave **62** (10.41 g, 95% yield) as a white powder of mp 62—66 °C. Recrystallization from EtOH afforded a white powder of mp 69.5—70.5 °C. $[\alpha]_D^{20}$ +80.4° (c=0.5, EtOH). IR ν_{max}^{Nujol} cm^{-1}: 1595, 1450, 1350, 1170, 1130, 1010, 920, 780, 730, 650. NMR ($CDCl_3$) δ: 0.88 (6H, s, 2 × $-CH_3$), 0.92 (3H, s, $-CH_3$), 1.0—2.1 (5H, m, $-CH_2-$, -CH–), 2.37 (3H, s, $ArCH_3$), 3.3—3.67 (3H, m, $-CH_2O-$, -CHO–), 3.85 (1H, dd, J=8, 4 Hz, $-CHOCH_2-$), 4.13 (2H, t, J=5 Hz, $-CH_2OTs$), 4.37 and 4.67 (2H, ABq, J=12 Hz, $-CH_2Ar$), 7.22 (5H, s, $-CH_2ArH$), 7.20 and 7.65 (4H, ABq, J=8 Hz, $-SO_3ARH$). *Anal.* Calcd for $C_{26}H_{34}O_5S_1$: C, 68.09; H, 7.47. Found: C, 67.82; H, 7.47.

(+)-(1*R*,2*R*.3*S*,4*S*)-1,2-Bis(2-benzyloxy-1,7,7-trimethylbicyclo[2.2.1]hept-3-yloxy)ethane (63)——A solution of **24** (5.09 g, 19.6 mmol) in DMF (30 ml) was added dropwise to a suspension of NaH (55% in oil, 0.95 g, 21.5 mmol) in DMF (25 ml) at room temperature under Ar, and the whole was stirred at 40—45 °C for 40 min, then cooled to 0 °C. A solution of **62** (8.16 g, 17.8 mmol) in DMF (30 ml) was added to the reaction mixture, and the whole was stirred at room temperature for 2.5 h. Usual work-up as described for the preparation of **61** and purification by column chromatography (silica gel, ether : hexane = 1 : 3) gave **63** (8.34 g, 90% yield) as a white powder of mp 57.5—58.5 °C. Recrystallization from pentane afforded white prisms of mp 58—58.5 °C. $[\alpha]_D^{20}$ +108° (c=0.99, EtOH). IR ν_{max}^{Nujol} cm^{-1}: 1605, 1450, 1355, 1120, 1030, 730, 700. NMR ($CDCl_3$) δ: 0.78 (12H, s, 4 × $-CH_3$), 0.83 (6H, s, 2 × $-CH_3$), 0.8—2.2 (10H, m, $-CH_2-$, CH–), 3.2—3.6 (6H, m, $-CH_2O-$, -CHO–), 3.85 (2H, dd, J=8, 4 Hz, $-CHOCH_2-$), 4.26 and 4.68 (4H, ABq, J=11 Hz, 2 × $-CH_2Ar$), 7.16 (10H, s, 2 × ArH). MS *m/e*: 546 (M^+), 455. *Anal.* Calcd for $C_{36}H_{50}O_4$: C, 79.08; H, 9.22. Found: C, 78.81; H, 9.33.

(+)-(1*R*,2*R*,3*S*,4*S*)-1,2-Bis(2-hydroxy-1,7,7-trimethylbicyclo[2.2.1]hept-3-yloxy)ethane (64)——A mixture of **63** (7.8 g, 14.9 mmol) and 5% Pd–C (200 mg) in EtOH–conc. HCl (30 ml–1 drop) was stirred at room temperature for 8 h under atmospheric pressure of H_2. The catalyst was filtered off, and the filtrate was evaporated to afford a white powder (5.29 g, 97% yield) of mp 54—62 °C. Recrystallization from pentane at −20 °C afforded pure needles of mp 65.5—67 °C. $[\alpha]_D^{20}$ +50.2° (c=1.0, EtOH). IR ν_{max}^{Nujol} cm^{-1}: 3520, 3440, 1450, 1370, 1250, 1105, 1080. NMR ($CDCl_3$) δ: 0.87 (12H, s, 4 × $-CH_3$), 0.90 (6H, s, 2 × $-CH_3$), 1.0—2.0 (10H, m, $-CH_2-$, CH–), 2.76 (2H, br, 2 × -OH), 3.62 (4H, s, $-CH_2O-$), 3.82 (4H, br, -CHO–). MS *m/e*: 366 (M^+). *Anal.* Calcd for $C_{22}H_{34}O_4$: C, 72.09; H, 10.45. Found: C, 72.15; H, 10.39.

(+)-(1*R*,2*R*,3*S*,4*S*)-1,2-Bis[2-(2′-hydroxyethoxy)-1,7,7-trimethylbicyclo[2.2.1]hept-3-yloxy]ethane (65)——A solution of **64** (4.35 g, 11.9 mmol) in DMF (20 ml) was added dropwise to a suspension of NaH (55% in oil, 1.25 g, 28.4 mmol) in DMF (20 ml) at room temperature under Ar, and the whole was stirred at 40—45 °C for 40 min, then cooled to 0 °C. A solution of 1-tetrahydropyranyloxy-2-tosyloxyethane[20] (8.5 g, 28.3 mmol) in DMF (50 ml) was added to the reaction mixture, and then the whole was stirred at room temperature for 24 h. Usual work-up as described for the preparation of **61** gave a brown oil (8.26 g), which was dissolved in MeOH–conc. HCl (80 ml–10 ml). The solution was stirred at room temperature for 1.5 h, then the MeOH was evaporated off and the residue was extracted with AcOEt (100 ml × 2). The combined extracts were washed successively with satd. aq. $NaHCO_3$ and satd. aq. NaCl, then dried over $MgSO_4$. The AcOEt was evaporated off to give a brown oil (5.17 g), which was purified by column chromatography (silica gel, AcOEt : hexane = 4 : 1) to give pure **65** (2.73 g, 50% yield) as a white powder of mp 54.5—56 °C, together with the recovered diol **64** (1.77 g, 40.6% recovery yield). Recrystallization from pentane afforded a white powder of mp 55.5—56.5 °C. $[\alpha]_D^{20}$ +99.3° (c=1.0, EtOH). IR ν_{max}^{Nujol} cm^{-1}: 3520, 1450, 1360, 1295, 1180, 1115, 870, 810. NMR ($CDCl_3$) δ: 0.83 (12H, s, 4 × $-CH_3$), 0.87 (6H, s, 2 × $-CH_3$), 1.0—2.08 (10H, m, $-CH_2-$, CH–), 3.4—3.85 (16H, m, $-CH_2O-$, -CHO–, -OH), 4.0 (2H, dd, J=8, 4 Hz, $-CHOCH_2-$). MS *m/e*: 454

(M^+). *Anal.* Calcd for $C_{26}H_{46}O_6$: C, 68.68; H, 10.20. Found: C, 68.83; H, 10.48.

(+)-(1*R*,2*R*,3*S*,4*S*)-1,2-Bis[2-(2′-tosyloxyethoxy)-1,7,7-trimethylbicyclo[2.2.1]hept-3-yloxy]ethane (66)——A solution of **65** (0.95 g, 2.09 mol) and TsCl (1.1 g, 5.77 mmol) in pyridine (6 ml) was stirred at room temperature for 20 h. Usual work-up as described for the preparation of **17** and purification by column chromatography (silica gel, ether : hexane = 1 : 3) gave pure **66** (1.28 g, 80% yield) as a colorless caramel. $[\alpha]_D^{20}$ +56.0° (*c* = 0.22, EtOH). IR ν_{max}^{film} cm^{-1}: 1600, 1450, 1360, 1175, 1130, 1015, 920, 810. NMR ($CDCl_3$) δ: 0.73 (12H, s, 4 × –C<u>H</u>$_3$), 0.83 (6H, s, 2 × –C<u>H</u>$_3$), 0.8—2.0 (10H, m, –C<u>H</u>$_2$–, C<u>H</u>–), 2.42 (6H, s, 2 × ArC<u>H</u>$_3$), 3.16—4.25 (16H, m, –C<u>H</u>$_2$O–, –C<u>H</u>O–), 7.3 and 7.73 (8H, ABq, *J* = 8 Hz, 2 × Ar<u>H</u>). *Anal.* Calcd for $C_{40}H_{58}O_{10}$: C, 62.96; H, 7.66. Found: C, 63.16; H, 7.75.

(+)-(1*R*,4*S*,4a*R*,9*S*,10*S*,14a*R*,15*S*,18*R*,18a*S*,22a*S*)-Eicosahydro-4,15,23,23,24,24-hexamethyl-9,10-bis-(benzyloxymethyl)-1,4 : 15,18-dimethanodibenzo[*b*,*h*][1,4,7,10,13,16]hexaoxacyclooctadecin (67)——A folution of **15**[17] (0.93 g, 3.08 mmol) in DMF (20 ml) was added dropwise to a suspension of NaH (55% in oil, 300 mg, 6.8 mmol) in DMF (10 ml) at room temperature under Ar, and the whole was stirred at 40—50 °C for 2 h, then cooled to 0 °C. A solution of **66** (2.35 g, 3.08 mmol) in DMF (30 ml) was added to the reaction mixture, and the whole was stirred at 50 °C for 20 h. Usual work-up as described for the preparation of **39** and purification by column chromatography (silica gel, ether : hexane = 1 : 1) afforded pure **67** (1.8 g, 85% yield) as a colorless caramel. $[\alpha]_D^{20}$ +76.7° (*c* = 0.96, $CHCl_3$). IR ν_{max}^{film} cm^{-1}: 1605, 1450, 1365, 1100, 740, 700. NMR ($CDCl_3$) δ: 0.81 (18H, s, 9 × C<u>H</u>$_3$), 0.8—2.1 (10H, m, –C<u>H</u>$_2$–, –C<u>H</u>–), 3.2—4.0 (22H, m, –C<u>H</u>$_2$O–, –C<u>H</u>O–), 4.47 (4H, s, 2 × –C<u>H</u>$_2$Ar), 7.20 (10H, s, Ar<u>H</u>). MS *m/e*: 720 (M^+). *Anal.* Calcd for $C_{44}H_{64}O_8$: C, 73.30; H, 8.95. Found: C, 73.38; H, 9.12.

(+)-(1*R*,4*S*,4a*R*,9*S*,10*S*,14a*R*,15*S*,18*R*,18a*S*,22a*S*)-Eicosahydro-4,15,23,23,24,24-hexamethyl-9,10-bis-(tosyloxymethyl)-1,4 : 15,18-dimethanodibenzo[*b*,*h*][1,4,7,10,13,16]hexaoxacyclooctadecin (69)——A mixture of **67** (1.5 g, 2.17 mmol) and 5% Pd–C (0.1 g) in EtOH–conc. HCl (10 ml–1 drop) was stirred at room temperature for 12 h under atmospheric pressure of H_2. The catalyst was filtered off and the filtrate was evaporated to dryness to afford crude **68** (1.37 g). This oil was used for the next reaction without further purification.

A solution of **68** (1.37 g, 2.53 mmol) and TsCl (1.35 g, 5.2 mmol) in pyridine (6 ml) was stirred at 0 °C for 1 d. Usual work-up as described for the preparation of **17** and purification by column chromatograhy (silica gel, ether : hexane = 2 : 1) gave **69** (2.09 g, 82% overall yield) as a colorless caramel. $[\alpha]_D^{20}$ +18.6° (*c* = 2.1, $CHCl_3$). IR ν_{max}^{film} cm^{-1}: 1600, 1450, 1360, 1175, 1170, 1015, 970, 810, 720. NMR ($CDCl_3$) δ: 0.80 (18H, s, 6 × –C<u>H</u>$_3$), 0.8—2.0 (10H, m, –C<u>H</u>$_2$–, C<u>H</u>–), 2.42 (6H, s, 2 × ArC<u>H</u>$_3$), 3.2—4.4 (22H, m, –C<u>H</u>$_2$O–, –C<u>H</u>O–), 7.32 and 7.70 (8H, ABq, *J* = 8 Hz, 2 × Ar<u>H</u>). *Anal.* Calcd for $C_{40}H_{58}O_{10}$: C, 62.96; H, 7.66. Found: C, 63.16; H, 7.75.

(+)-(1*R*,4*S*,4a*R*,9*R*,10*R*,14a*R*,15*S*,18*R*,18a*S*,22a*S*)-Eicosahydro-4,15,23,23,24,24-hexamethyl-9,10-bis-(benzoylthiomethyl)-1,4 : 15,18-dimethanodibenzo[*b*,*h*][1,4,7,10,13,16]hexaoxacyclooctadecin (70)——A solution of **69** (1.96 g, 2.3 mmol) and KSCOPh (8.3 mmol) in EtOH was stirred under reflux for 4 h under Ar. Usual work-up as described for the preparation of **51** and purification by column chromatography (silica gel, ether : hexane = 1 : 3) afforded **70** (1.4 g, 78% yield) as a pale brown oil. $[\alpha]_D^{20}$ +34.3° (*c* = 1.12, $CHCl_3$). IR ν_{max}^{film} cm^{-1}: 1660, 1450, 1210, 1110, 910, 690. NMR ($CDCl_3$) δ: 0.82 (18H, s, 6 × –C<u>H</u>$_3$), 0.8—2.0 (10H, m, –C<u>H</u>$_2$–, C<u>H</u>–), 3.3—4.15 (22H, m, –C<u>H</u>$_2$O–, –C<u>H</u>O–, 2 × –C<u>H</u>$_2$S–), 7.2—8.13 (10H, m, 2 × Ar<u>H</u>). *Anal.* Calcd for $C_{44}H_{60}O_8S_2$: C, 67.66; H, 7.74. Found: C, 67.63; H, 7.82.

(+)-(1*R*,4*S*,4a*R*,9*R*,10*R*,14a*R*,15*S*,18*R*18a*S*,22a*S*)-Eicosahydro-4,15,23,23,24,24-hexamethyl-9,10-bis-(mercaptomethyl)-1,4 : 15,18-dimethanodibenzo[*b*,*h*][1,4,7,10,13,16]hexaoxacyclooctadecin (9)——A solution of **70** (0.97 g, 1.24 mmol) in ether (10 ml) was added dropwise to a suspension of $LiAlH_4$ (150 mg, 3.9 mmol) in ether (5 ml) under Ar at room temperature, and then the whole was stirred under reflux for 1 h. Usual work-up as described for the preparation of **2** and purification by column chromatography (silica gel, ether : hexane = 1 : 3) afforded **9** (560 mg, 79% yield) as a colorless oil. $[\alpha]_D^{20}$ +47.7° (*c* = 0.985, $CHCl_3$). IR ν_{max}^{film} cm^{-1}: 2540, 1470, 1360, 1110, 790. NMR ($CDCl_3$) δ: 0.89 (18H, s, 6 × –C<u>H</u>$_3$), 0.8—2.05 (10H, m, –C<u>H</u>$_2$–, C<u>H</u>–), 2.6—2.95 (4H, m, 2 × –C<u>H</u>$_2$SH), 3.4—4.15 (18H, m, –CH$_2$O–, –C<u>H</u>O–). MS *m/e*: 572 (M^+), 570, 539. *Anal.* Calcd for $C_{30}H_{52}O_6S_2$: C, 62.90; H, 9.15. Found: C, 62.96; H, 9.31.

(−)-(1*R*,2*S*,3*R*,4*S*)-2-(2-Tetrahydropyranyloxy)ethoxy-3-hydroxy-1,7,7-trimethylbicyclo[2.2.1]heptane (71)——A solution of **28** (11.87 g, 45.6 mmol) in DMF (50 ml) was added dropwise to a suspension of NaH (50% in oil, 2.62 g, 50 mmol) in DMF (15 ml) under Ar at room temperature, and the whole was stirred at 60 °C for 1.5 h, then cooled to 0 °C. A solution of 1-tetrahydropyranyloxy-2-tosyloxyethane[21] (7.9 g, 33 mmol) in DMF (60 ml) was added to the reaction mixture, and the whole was stirred at room temperature for 3 d. Usual work-up as described for the preparation of **61** and purification by column chromatography (silica gel, ether : hexane = 1 : 4) gave a pale yellow oil (15.66 g, 88% yield). This oil was used for the next reaction without further purification. A mixture of this oil (5.77 g, 14.9 mmol) and 10% Pd–C (0.3 g) in EtOH (60 ml) was stirred at room temperature for 12 h under atmospheric pressure of H_2. The catalyst was filtered off and the filtrate was evaporated to give crude **71** (4.7 g, 88% overall yield) as a colorless oil, which was purified by column chromatography (silica gel, ether : hexane = 2 : 1) to afford pure **71** as a colorless oil. $[\alpha]_D^{20}$ −32.7° (*c* = 1.05, EtOH). IR ν_{max}^{film} cm^{-1}: 3500, 1455, 1390, 1370, 1350, 1130, 1070, 1035, 985, 870, 815. NMR ($CDCl_3$) δ: 0.77 (3H, s, –C<u>H</u>$_3$), 0.92 (3H, s, –C<u>H</u>$_3$), 1.08 (3H, s, –C<u>H</u>$_3$), 0.9—2.0 (9H, m, –C<u>H</u>$_2$–, –C<u>H</u>–), 3.17—4.17 (9H, m, –C<u>H</u>$_2$O–, –C<u>H</u>O–), 4.67 (1H, br, –OC<u>H</u>O–). *Anal.* Calcd for $C_{17}H_{30}O_4$: C, 68.42; H, 10.13. Found: C, 68.59; H, 10.39.

(−)-(1*R*,2*S*,3*R*,4*S*)-2-(2-Tetrahydropyranyloxy)ethoxy-3-(2-benzyloxy)ethoxy-1,7,7-trimethylbicyclo[2.2.1]-heptane (74)——A solution of **71** (6.3 g, 21 mmol) in DMF (30 ml) was added dropwise to a suspension of NaH (50% in oil, 1.2 g, 25 mmol) in DMF (15 ml) under Ar at room temperature, and the whole was stirred at 60 °C for 1.5 h, then cooled to 0 °C. A solution of 1-benzyloxy-2-tosyloxyethane[21] (6.8 g, 22 mmol) in DMF (15 ml) was added to the reaction mixture, and the whole was stirred at room temperature for 2 d. Usual work-up as described for the preparation of **61** and purification by column chromatography (silica gel, ether : hexane = 1 : 4) gave **74** as a colorless oil (7.23 g, 79% yield). $[\alpha]_D^{20}$ −28.4° (c = 1.33, EtOH). IR ν_{max}^{film} cm^{-1}: 1450, 1390, 1370, 1350, 1200, 1120, 1070, 1035, 990, 900, 870, 815, 735, 695. NMR ($CDCl_3$) δ: 0.78 (3H, s, $-CH_3$), 0.92 (3H, s, $-CH_3$), 1.08 (3H, s, $-CH_3$), 0.9—2.0 (9H, m, $-CH_2-$, $-CH-$), 3.1—4.12 (11H, m, $-CH_2O-$, $-CHO-$), 4.57 (2H, s, $-CH_2Ar$), 4.67 (1H, br, $-OCHO-$). *Anal.* Calcd for $C_{26}H_{40}O_5$: C, 71.97; H, 9.29. Found: C, 71.70; H, 9.27.

(−)-(1*R*,2*S*,3*R*,4*S*)-2-(2-Tetrahydropyranyloxy)ethoxy-3-(2-hydroxy)ethoxy-1,7,7-trimethylbicyclo[2.2.1]-heptane (73)——A mixture of **72** (2.0 g, 4.6 mmol) and 10% Pd–C (0.3 g) in ether (20 ml) was stirred at room temperature for 15 h under atmospheric pressure of H_2. The catalyst was filtered off and the filtrate was evaporated to give crude **73** (1.69 g, quantitative) as a colorless oil, which was purified by column chromatography (silica gel, ether : hexane = 1 : 1) to afford a pure sample as a colorless oil. $[\alpha]_D^{20}$ −38.8° (c = 0.85, EtOH). IR ν_{max}^{film} cm^{-1}: 3480, 1455, 1390, 1370, 1350, 1130, 1070, 1035, 985, 870, 815. NMR ($CDCl_3$) δ: 0.78 (3H, s, $-CH_3$), 0.90 (3H, s, $-CH_3$), 1.17 (3H, s, $-CH_3$), 0.9—2.2 (11H, m, $-CH_2-$, $-CH-$), 3.0—4.0 (13H, m, $-CH_2O-$, $-CHO-$), 4.70 (1H, br, $-OCHO-$). *Anal.* Calcd for $C_{19}H_{34}O_5$: C, 66.63; H, 10.01. Found: C, 66.34; H, 9.91.

(1*R*,2*S*,3*R*,4*S*)-2-(2-Tetrahydropyranyloxy)ethoxy-3-(2-tosyloxy)ethoxy-1,7,7-trimethylbicyclo[2.2.1]heptane (74)——A solution of **73** (1.49 g, 4.33 mmol) and TsCl (1.08 g, 5.66 mmol) in pyridine (30 ml) was stirred at 0 °C for 22 h. Usual work-up as described for the preparation of **17** and purification by column chromatography (silica gel, ether : hexane = 1 : 1) afforded **74** (1.85 g, 86% yield) as a colorless oil. IR ν_{max}^{film} cm^{-1}: 1600, 1455, 1360, 1190, 1180, 1120, 1070, 1035, 985, 870, 815, 780, 660. NMR ($CDCl_3$) δ: 0.75 (3H, s, $-CH_3$), 0.90 (3H, s, $-CH_3$), 1.05 (3H, s, $-CH_3$), 1.0—2.0 (11H, m, $-CH_2-$, $-CH-$), 2.43 (3H, s, $ArCH_3$), 3.17—4.0 (10H, m, $-CH_2O-$, $-CHO-$), 4.0—4.27 (2H, m, $-CH_2OTs$), 4.63 (1H, br, $-OCHO-$), 7.27 and 7.82 (4H, ABq, J = 8 Hz, $-ArH$). *Anal.* Calcd for $C_{26}H_{40}O_7S_1$: C, 62.87; H, 8.12. Found: C, 62.59; H, 8.03.

(1*R*,2*S*,3*R*,4*S*)-1,2-Bis[2-(2′-tosyloxy)ethoxy-1,7,7-trimethylbicyclo[2.2.1]hept-3-yloxy]ethane (76)——A solution of **71** (2.8 g, 9.4 mmol) in DMF (20 ml) was added dropwise to a suspension of NaH (50% in oil, 0.59 g, 12.2 mmol) in DMF (15 ml) under Ar at room temperature, and the whole was stirred at 60 °C for 1.5 h, then cooled to 0 °C. A solution of **74** (4.67 g, 9.4 mmol) in DMF (20 ml) was added to the reaction mixture, and the whole was stirred at room temperature for 2 d. Usual work-up as described for the preparation of **61** gave a pale yellow oil (5.8 g), which was dissolved in MeOH–conc. HCl (20 ml–2 ml). The solution was stirred at 60—70 °C for 2 h. The MeOH was evaporated off and the residue was extracted with ether (300 ml). The ether layer was separated, washed successively with satd. aq. $NaHCO_3$ and satd. aq. NaCl, then dried over $MgSO_4$. The ether was evaporated off and the residue was purified by column chromatography (silica gel, ether : hexane = 5 : 1) gave **75** (3.26 g, 75% yield) as a colorless oil. IR ν_{max}^{film} cm^{-1}: 3440, 1455, 1390, 1370, 1350, 1200, 1150, 1100, 900. NMR ($CDCl_3$) δ: 0.77 (3H, s, $-CH_3$), 0.90 (3H, s, $-CH_3$), 1.10 (3H, s, $-CH_3$), 0.9—2.0 (9H, m, $-CH_2-$, $-CH-$), 3.1—4.1 (18H, m, $-CH_2O-$, $-CHO-$, $-OH$). MS m/e: 454 (M^+), 452. This diol was used for the next reaction without further purification.

A solution of **75** (3.26 g, 7.17 mmol) and TsCl (5.47 g, 28 mmol) in pyridine (100 ml) was stirred at 0 °C for 20 h. Usual work-up as described for the preparation of **16** and purification by column chromatography (silica gel, ether : hexane = 1 : 1) afforded **76** (3.80 g, 70% yield) as a colorless oil. IR ν_{max}^{film} cm^{-1}: 1600, 1460, 1370, 1195, 1180, 1160, 1100, 1035, 1020, 930, 870, 820, 780, 670. NMR ($CDCl_3$) δ: 0.70 (3H, s, $-CH_3$), 0.77 (6H, s, 2 × $-CH_3$), 0.95 (6H, s, 2 × $-CH_3$), 0.9—1.83 (10H, m, $-CH_2-$, $-CH-$), 2.43 (6H, s, 2 × $ArCH_3$), 3.07—3.88 (1H, m, $-CH_2O-$, $-CHO-$), 3.88—4.23 (4H, m, 2 × $-CH_2OTs$), 7.30 and 7.75 (8H, ABq, J = 8 Hz, 2 × $-ArH$). *Anal.* Calcd for $C_{40}H_{58}O_{10}S_2$: C, 62.96; H, 7.66. Found: C, 63.13; H, 7.63.

(−)-(1*R*,4*S*,4a*S*,9*S*,10*S*,14a*S*,15*S*,18*R*,18a*R*,22a*R*)-Eicosahydro-4,15,23,23,24,24-hexamethyl-,9,10-bis-(hydroxymethyl)-1,4 : 15,18-dimethanodibenzo[*b*,*h*][1,4,7,10,13,16]hexaoxacyclooctadecin (78)——A solution of **15**[17] (1.45 g, 4.78 mmol) in DMSO (30 ml) was added dropwise to a suspension of *tert*-BuOK (1.13 g, 10 mmol) in DMSO (50 ml) under Ar at room temperature, and the whole was stirred at 60 °C for 2 h, then cooled to 0 °C. A solution of **76** (3.65 g, 4.8 mmol) in DMF (50 ml) was added to the reaction mixture, and the whole was stirred at 60 °C for 20 h. Usual work-up as described for the preparation of **39** and purification by column chromatography (silica gel, ether : hexane = 1 : 3) gave **77** (2.29 g, 69% yield) as a colorless caramel. IR ν_{max}^{film} cm^{-1}: 1455, 1380, 1360, 1105, 730, 690. NMR ($CDCl_3$) δ: 0.70 (6H, s, 2 × $-CH_3$), 0.82 (6H, s, 2 × $-CH_3$), 1.06 (6H, s, 2 × $-CH_3$), 0.7—1.85 (10H, m, $-CH_2-$, $-CH-$), 3.05—3.9 (22H, m, $-CH_2O-$, $-CHO-$, $-OH$), 4.47 (4H, s, 2 × $-CH_2Ar$), 7.28 (10H, s, 2 × ArH). MS m/e: 720 (M^+). This product was used for the next reaction without further purification.

Small pieces of Na (0.8 g) was added to a solution of **77** (1.0 g, 1.45 mmol) in liq. NH_3–ether (30 ml–5 ml) at −70 °C, and the whole was stirred at the same temperature for 1 h. The blue color was discharged by the addition of EtOH, and then the solvent was evaporated off. The residue was extracted with AcOEt (250 ml × 2), and the combined extracts were washed successively with 10% aq. HCl, satd. aq. $NaHCO_3$ and satd. aq. NaCl, then dried over $MgSO_4$. The AcOEt was evaporated off to give a pale yellow oil (800 mg), which was crystallized from pentane to

afford **78** (460 mg, 59% yield) as a white powder of mp 79—95 °C. Recrystallization from pentane gave white needles of mp 106.5—107 °C. $[\alpha]_D^{20}$ −27.9° (c=0.54, $CHCl_3$). IR ν_{max}^{Nujol} cm^{-1}: 3500, 1460, 1390, 1375, 1355, 1130, 1105. NMR ($CDCl_3$) δ: 0.75 (6H, s, 2×-C<u>H</u>$_3$), 0.92 (6H, s, 2×-C<u>H</u>$_3$), 1.15 (6H, s, 2×-C<u>H</u>$_3$), 0.70—1.80 (10H, m, -C<u>H</u>$_2$-, -C<u>H</u>-), 3.20—4.0 (24H, m, -C<u>H</u>$_2$O-, -C<u>H</u>O-, -O<u>H</u>). MS m/e: 540 (M^+), 538, 522. *Anal.* Calcd for $C_{30}H_{52}O_8$: C, 66.63; H, 9.69. Found: C, 66.63; H, 9.97.

(−)-(1*R*,4*S*,4a*S*,9*S*,10*S*,14a*S*,15*S*,18*R*,18a*R*,22aR)-Eicosahydro-4,15,23,23,24,24-hexamethyl-9,10-bis(tosyloxymethyl)-1,4:15,18-dimethanodibenzo[*b*,*h*][1,4,7,10,13,16]hexaoxacyclooctadecin (79)——A solution of **78** (0.4 g, 0.74 mmol) and TsCl (0.6 g, 3.26 mmol) in pyridine (40 ml) was stirred at 0 °C for 3 d. Usual work-up as described for the preparation of **17** and purification by preparative TLC (silica gel, ether : hexane = 1 : 1) afforded **79** (350 mg 55% yield) as a white powder, which was recrystallized from EtOH to afford white needles of mp 124.5—126 °C. $[\alpha]_D^{20}$ −8.9° (c=0.54, $CHCl_3$). IR ν_{max}^{Nujol} cm^{-1}: 1600, 1460, 1170, 1115, 980, 810, 720. NMR ($CDCl_3$) δ: 0.75 (6H, s, 2×-C<u>H</u>$_3$), 0.83 (6H, s, 2×-C<u>H</u>$_3$), 1.00 (6H, s, 2×-C<u>H</u>$_3$), 0.80—1.80 (10H, m, -C<u>H</u>$_2$-, -C<u>H</u>-), 2.48 (4H, s, 2×ArC<u>H</u>$_3$), 3.05—4.15 (22H, m, -C<u>H</u>$_2$O-, -C<u>H</u>O-), 7.3 and 7.75 (8H, ABq, J=8 Hz, 2×Ar<u>H</u>). MS m/e: 848 (M^+). *Anal.* Calcd for $C_{44}H_{64}O_{12}S_2$: C, 62.24; H, 7.60. Found: C, 62.34; H, 7.88.

(−)-(1*R*,4*S*,4a*S*,9*R*,10*R*,14a*S*,15*S*,18*R*,18a*R*,22a*R*)-Eicosahydro-4,15,23,23,24,24-hexamethyl-9,10-bis(mercaptomethyl)-1,4:15,18-dimethanodibenzo[*b*,*h*][1,4,7,10,13,16]hexaoxacyclooctadecin (10)——A mixture of **79** (0.13 g, 0.15 mmol) and KSCOPh (0.81 g, 0.459 mmol) in EtOH (10 ml) was stirred under reflux for 8 h. Usual work-up gave **80** as a pale red oil (0.12 g), which was used for the next reaction without further purification. A solution of this crude thiolester (0.12 g) in ether (10 ml) was added dropwise to a suspension of $LiAlH_4$ (20 mg, 0.52 mmol) in ether (5 ml) under Ar at room temperature, and the whole was stirred under reflux for 2 h. Usual work-up as described for the preparation of **2** and purification by column chromatography (silica gel, ether : hexane = 1 : 4) afforded a colorless oil (40 mg, 46% overall yield). $[\alpha]_D^{20}$ −14.1° (c=0.39, $CHCl_3$). IR ν_{max}^{neat} cm^{-1}: 2560, 1470, 1450, 1380, 1360, 1340, 1310, 1280, 1230, 1100, 900, 725. NMR ($CDCl_3$) δ: 0.73 (6H, s, 2×-C<u>H</u>$_3$), 0.87 (6H, s, 2×-C<u>H</u>$_3$), 1.08 (6H, s, 2×-C<u>H</u>$_3$), 0.70—1.90 (12H, m, -C<u>H</u>$_2$-, -C<u>H</u>-, 2×S<u>H</u>), 2.47—2.9 (4H, m, 2×C<u>H</u>$_2$SH), 3.15—4.0 (18H, m, -C<u>H</u>$_2$O-, -C<u>H</u>O-), 7.3 and 7.75 (8H, ABq, J=8 Hz, 2×Ar<u>H</u>). MS m/e: 572 (M^+). HRMS Calcd for $C_{30}H_{52}O_6S_2$: 572.3202. Found: 572.3202.

(7*S*,8*S*)-1,14-Dimethoxy-7,8-bis(tosyloxymethyl)-3,6,9,12-tetraoxatetradecane (83)——A solution of **15**[17] (13 g, 0.043 mol) in DMF (200 ml) was added dropwise to a suspension of NaH (60% in oil, 5.0 g, 0.125 mol), and the whole was stirred at 40—50 °C for 2 h, then cooled to 0 °C. A solution of diethylenglycol monomethyl ether monotosylate (30 g, 0.109 mol) was added to the reaction mixture, and the whole was stirred at 40—50 °C for 4 h. Usual work-up as described for the preparation of **39** gave **81** (22 g, 100% yield) as a pale yellow oil. A mixture of **81** (20 g) and 5% Pd–C (1.1 g) in EtOH (100 ml) was stirred at room temperature for 3 h under atmospheric pressure of H_2. The catalyst was filtered off, and the filtrate was evaporated to dryness to give **82** (13 g, 100% yield) as a colorless oil. A mixture of **82** (13 g) and TsCl (20 g, 0.105 mol) in pyridine (50 ml) was stirred at −20 °C for 2 d. Usual work-up as described for the preparation of **17** and purification by column chromatography (silica gel, AcOEt : hexane = 1 : 3) gave pure **83** (20 g, 80% overall yield) as a colorless oil. $[\alpha]_D^{20}$ +0.3° (c=2.3, $CHCl_3$). IR ν_{max}^{film} cm^{-1}: 1600, 1450, 1360, 1183, 1170, 1090, 970, 810. NMR ($CDCl_3$) δ: 2.46 (6H, s, 2×Ar<u>H</u>), 3.35 (6H, s, 2×OC<u>H</u>$_3$), 3.3—4.4 (22H, m, -C<u>H</u>-, -C<u>H</u>$_2$-), 7.30 and 7.75 (8H, ABq, J=8.0 Hz, 2×Ar<u>H</u>). MS m/e: 634 (M^+). *Anal.* Calcd for $C_{28}H_{42}O_{12}S_2$: C, 52.98; H, 6.67. Found: C, 52.92; H, 6.95.

(+)-(7*S*,8*S*)-1,14-Dimethoxy-7,8-bis(mercaptomethyl)-3,6,9,12-tetraoxatetradecane (11)——A mixture of **83** (15 g, 0.024 mol) and KSCOPh (13 g, 0.074 mol) in EtOH (50 ml) was stirred under reflux for 8 h. Usual work-up as described for the preparation of **51** gave crude **84** (6.2 g) as a red oil. A solution of **84** (6.0 g) in ether (20 ml) was added to a suspension of $LiAlH_4$ (1 g) in ether (20 ml) under Ar, and the whole was stirred at room temperature for 2 h. Usual work-up as described for the preparation of **2** gave crude **11**, which was distilled under reduced pressure to afford pure **11** (5.5 g, 65% overall yield) as a colorless oil of bp 240 °C (1 mmHg). $[\alpha]_D^{20}$ +10.0° (c=3.1, $CHCl_3$). IR ν_{max}^{film} cm^{-1}: 2560, 1450, 1350, 1240, 1195, 1100. NMR ($CDCl_3$) δ: 1.75 (2H, dd, J=7.4, 10 Hz, 2×S<u>H</u>), 2.5—2.9 (4H, m, -C<u>H</u>$_2$SH), 3.37 (6H, s, 2×C<u>H</u>$_3$), 3.4—3.9 (18H, m, -C<u>H</u>$_2$-, -C<u>H</u>-). MS m/e: 356 (M^+−2), 265. *Anal.* Calcd for $C_{14}H_{30}O_6S_2$: C, 46.90; H, 8.43. Found: C, 46.93; H, 8.46.

Kinetic Measurements——Spectral- or analytical-grade solvents were used. Each run of thiolysis was initiated by adding 0.01 ml of 1×10^{-2} M α-amino acid *p*-nitrophenylester hydrobromide in EtOH to 1.0 ml of a reaction medium in a cell thermostated at 25.0 °C. The mixtures were quickly stirred and the rates of *p*-nitrophenol liberation were followed at 320 nm with a Hitachi UV spectrometer, model 323 or model 200-10. The pseudo-first-order rate constants were calculated by using Eq. 2,

$$k_{obs} = 1/t \times \ln[(A_{max} - A_0)/(A_{max} - A_t)] \quad (2)$$

in which k_{obs} is the observed psedo-first-order rate constant, A_{max} is the maximum absorbance of *p*-nitrophenol, A_0 is the absorbance at initiation, and A_t is the absorbance at time (t). Two or more kinetic measurements were made and averaged to determine k_{obs} values. Rate constants, k values listed in Table I, were calculated by using Eq. 3,

$$k = k_{obs} - k_{buffer} \quad (3)$$

in which k_{buffer} is the first-order rate constant of each substrate in the absence of thiol-bearing compound. The rates of buffer solvolysis were as follows: Gly-ONp·HBr, $3\times10^{-5}\,s^{-1}$; AlaONp·HBr, $3\times10^{-5}\,s^{-1}$; PheONp·HBr, $1\times10^{-5}\,s^{-1}$: ValONp·HBr, $1\times10^{-5}\,s^{-1}$.

In saturation experiments, pseudo-first-order rate constants were obtained in the presence of crown ethers at more than 5 different concentrations. Calculations were carried out using Lineweaver–Burk plots, in which $1/k$ is plotted against 1/[Crown]. The values of K_{diss} and k_2 were obtained as the slope (K_{diss}/k_2) and the Y intercept ($1/k_2$) of the line. The slope and the intercept were obtained by least-squares analysis.

The amino acid *p*-nitrophenyl ester hydrobromides prepared by the conventional method have the following physical properties: glycyl, mp 211—212.5 °C (dec.) (lit.[5b] 207—210 °C (dec.)); L-alanyl, mp 181—183 °C (dec.) (lit.[5b] 179—180 °C (dec.)), $[\alpha]_D^{20}$ −2.3° (*c*=2.0, EtOH) (lit.[5b] $[\alpha]_D^{20}$ −2.4°); D-alanyl, mp 181—182.5 °C (dec.) (lit.[5b] 179—181 °C (dec.)), $[\alpha]_D^{20}$ +3.1° (*c*=2.4, EtOH); L-phenyalanyl, mp 207—208 °C (dec.) (lit.[5b] 211—212 °C (dec.)), $[\alpha]_D^{20}$ +51.1° (*c*=1.1, EtOH) (lit.[5b] $[\alpha]_D^{25}$ +48.8°); D-phenylalanyl, mp 208—209 °C (dec.) (lit.[5b] 211—212 °C (dec.)), $[\alpha]_D^{20}$ −50.5° (*c*=1.0, EtOH) (lit.[5b] $[\alpha]_D^{25}$ −48°); L-valyl, mp 197—199 °C (lit.[5b] 197—199 °C (dec.)), $[\alpha]_D^{20}$ +4.5° (*c*=2.1, EtOH); D-valyl, mp 198—199 °C, $[\alpha]_D^{20}$ −4.5° (*c*=2.0, EtOH).

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