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Preparation of homochiral phenolic crown ether having chiral subunits derived from (1*R*,2*S*)-*cis*-1,2,3,4-tetrahydronaphthalene-1,2-diol: temperature-dependent enantioselectivity in complexations with neutral amines

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Abstract: Crown ether (*S*,*R*,*R*,*S*)-**1** containing chiral subunits derived from (1*R*,2*S*)-*cis*-1,2,3,4-tetrahydronaphthalene-1,2-diol and the phenol moiety bearing the intra-annular OH group and the 2,4-dinitrophenylazo group at its *para*-position have been prepared in enantiomerically pure form. The association constants for the complexes with chiral amines have been determined at various temperatures by the UV-visible spectroscopic method and thermodynamic parameters of complex formation have been calculated. © 1997 Elsevier Science Ltd

Enantiomeric recognition of chiral guests by homochiral crown ethers has received much attention. Using various kinds of natural and synthetic homochiral compounds as chiral subunits, a variety of homochiral crown ethers have been synthesized and their chiral recognition behaviours in complexation have been well documented.[1] We have also prepared homochiral crown ethers containing chiral subunits derived from synthetic homochiral compounds, examined their chiral recognition properties in complexation with amines and given an explanation for the observed enantioselectivities on the basis of CPK molecular model examination.[2] Recently, the temperature-dependent inversion of enantioselectivity in the complexation of phenolic crown ethers with 2-aminopropan-1-ol was found[3] and this demonstrated that, in order to discuss structural complementarity between a chiral host and a chiral guest on the basis of CPK molecular model examination and the observed enantioselectivity, it is important to know whether the observed enantioselectivity is governed by $-\Delta_{R,S}\Delta H$ or $-\Delta_{R,S}\Delta S$. We have now prepared homochiral azophenolic crown ether (*S*,*R*,*R*,*S*)-**1** containing the chiral subunits derived from (1*R*,2*S*)-*cis*-1,2,3,4-tetrahydronaphthalene-1,2-diol and its structural feature is that two *cis*-1,2,3,4-tetrahydronaphthalene-1,2-diol moieties limit conformational flexibility of the chiral cavity. The phenol moiety of (*S*,*R*,*R*,*S*)-**1** contains the intra-annular OH group as a binding site for neutral amines and the additional *para*-2,4-dinitrophenylazo group which serves as not only a chromophore but increasing the binding ability towards neutral amines.[4] The enantiomeric selectivity in complexation of (*S*,*R*,*R*,*S*)-**1** with chiral amines was evaluated at various temperatures by the UV-visible spectroscopic method and thermodynamic parameters in the complexation have been calculated from the observed association constants.

Results and discussion

Homochiral *cis*-1,2,3,4-tetrahydronaphthalene-1,2-diol **6** has been prepared by a variety of methods.[5] Now, (1*R*,2*S*)-**6** was derived from (*S*)-**4** which was resolved by an enzymatic method using an easily-available lipase. Oxidation of (±)-**3** with lead tetraacetate in benzene[6] gave (±)-**4**,[7] mp 73–75°C in 59% yield. After several attempts to resolve (±)-**4** by an enzymatic method, (*S*)-**4** was obtained by enantioselective alcoholysis of (±)-**4** using lipase QL from *Alcaligenes* sp. in a mixture of ethanol and hexane. The alcoholysis of (±)-**4** was terminated close to about 65% of conversion and silica

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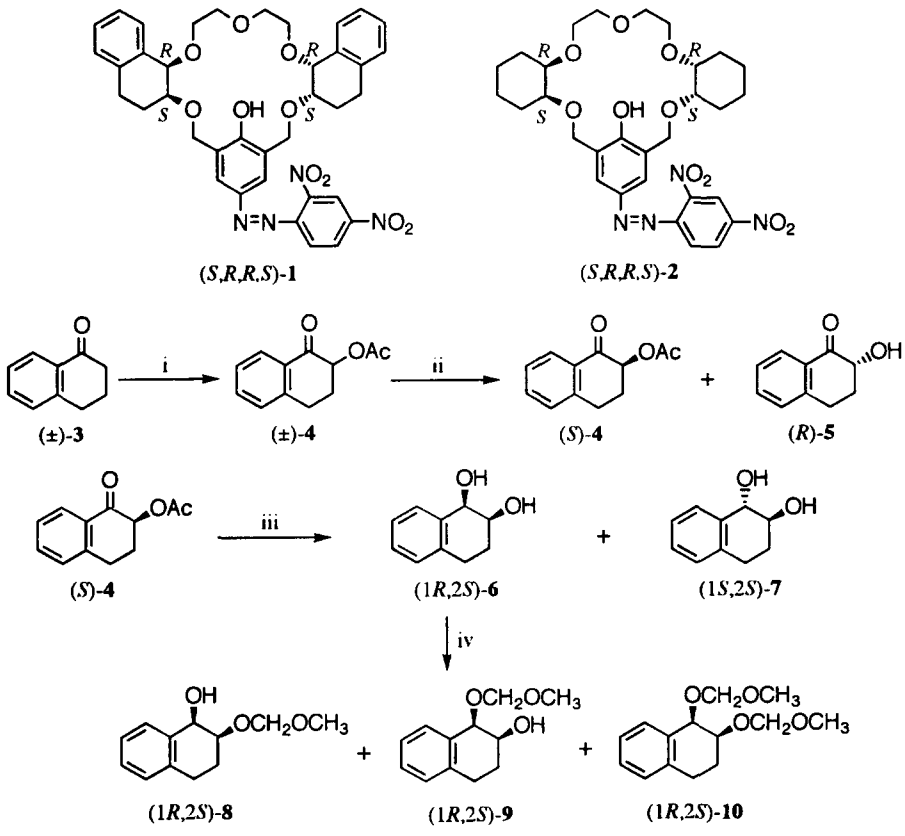
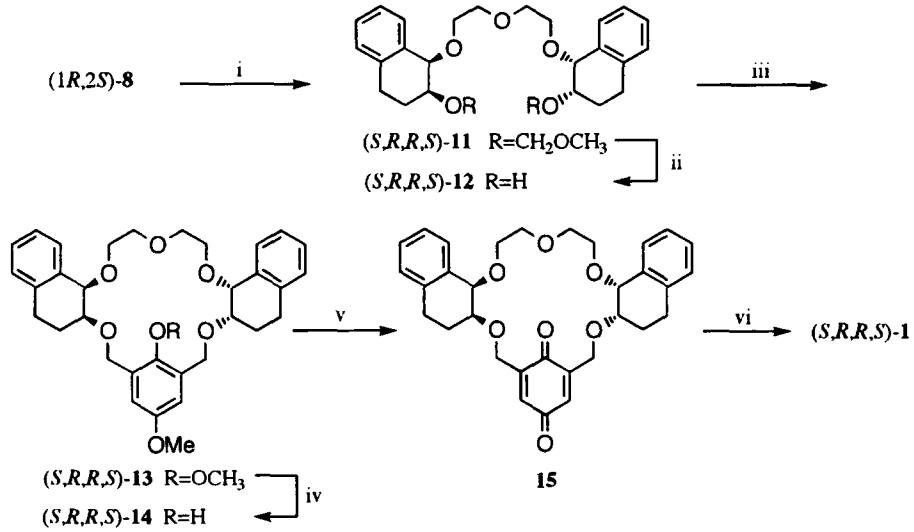
gel chromatography of the products gave (*S*)-**4** (30%), mp 71.5–73.0°C, $[\alpha]_D$ −86.8 (10^{-1} deg. cm^2 g^{-1}) ($CHCl_3$) (>98% e.e. by HPLC analysis) and (*R*)-**5** (56%), $[\alpha]_D$ +21.0 ($CHCl_3$) (49% e.e. by HPLC analysis). In the case of a practical preparation of a large quantity of the chiral subunit, (*S*)-**4** (83% e.e.) was reduced with $LiAlH_4$ at −78°C to give a 12:1 mixture of (1*R*,2*S*)-**6**[7] and (1*S*,2*S*)-**7**,[7] ^1H n.m.r. spectrum of which showed doublets at δ 4.71 due to the C1-methine proton of (1*R*,2*S*)-**6** and at δ 4.58 due to that of (1*S*,2*S*)-**7**. After chromatographic separation of the diastereoisomers, recrystallization of (1*R*,2*S*)-**6** from a mixture of hexane and benzene improved enantiomeric purity to give enantiomerically pure (1*R*,2*S*)-**6**, mp 128–129°C, $[\alpha]_D$ −27.4 ($CHCl_3$) (>99% e.e. by HPLC analysis) whose absolute configuration was determined by comparison of the sign of its specific rotation with that reported in the literature.[8]



Reagents
i $Pb(OAc)_4$ ii Lipase QL, C_2H_5OH iii $LiAlH_4$ iv CH_3OCH_2Cl, $[(CH_3)_2CH]_2NC_2H_5$

The preparation of (*S*,*R*,*R*,*S*)-**1** with the homotopic faces was carried out in a stepwise manner; two chiral subunits of the same configuration were linked with a diethylene glycol unit and then with a *m*-phenylene unit. Treatment of (1*R*,2*S*)-**6** with chloromethyl methyl ether and diisoproylethylamine gave (1*R*,2*S*)-**8** (41%), mp 61.5–62.0°C, $[\alpha]_D$ +20.6 ($CHCl_3$) together with (1*R*,2*S*)-**9** (14%), $[\alpha]_D$ −79.2 ($CHCl_3$) and (1*R*,2*S*)-**10** (15%), which were separated by chromatography on silica gel. Condensation of two mol equiv. of (1*R*,2*S*)-**8** with diethylene glycol bis(*p*-toluenesulfonate) in the presence of NaH in boiling tetrahydrofuran (THF) gave (*S*,*R*,*R*,*S*)-**11**, $[\alpha]_D$ −36.3 ($CHCl_3$) in 76% yield, which was deprotected with methanol and hydrochloric acid to give (*S*,*R*,*R*,*S*)-**12**, $[\alpha]_D$ −3.53 ($CHCl_3$) in 89% yield. Ring closure of (*S*,*R*,*R*,*S*)-**12** with 1,3-bis(bromomethyl)-2,5-dimethoxybenzene in the presence of NaH and KBF_4 in boiling THF gave (*S*,*R*,*R*,*S*)-**13**, mp 144–145°C, $[\alpha]_D$ −17.9 ($CHCl_3$) in 72% yield. For easy conversion of the dimethoxyphenyl moiety of (*S*,*R*,*R*,*S*)-13 to the benzoquinone moiety

of **15**, the inner methoxy group of (*S,R,R,S*)-**13** was selectively cleaved to give (*S,R,R,S*)-**14**, mp 168.5–169.5°C, $[\alpha]_D$ −12.0 ($CHCl_3$) in 97% yield by treatment with sodium ethanethiolate in DMF.[9] Oxidation of (*S,R,R,S*)-**14** with cerium(IV) ammonium nitrate (CAN) in acetonitrile gave **15** in 92% yield, which was directly treated with 2,4-dinitrophenylhydrazine in a mixture of ethanol, methylene dichloride and conc. H_2SO_4 to give (*S,R,R,S*)-**1**, mp 179–182°C in 72% yield as fine red needles.



Reagents
i ethylene glycol bis(*p*-toluenesulfonate), NaH, ii HCl, methanol,
iii 1,3-bis(bromomethyl)-2,5-dimethoxybenzene, NaH, KBF_4, iv C_2H_5SH, NaH, v CAN,
vi 2,4-dinitrophenylhydrazine

The association constants of the complexes of (*S,R,R,S*)-**1** with chiral amines 1-phenylethylamine **16**, 1-aminopropan-2-ol **17**, 2-aminopropan-1-ol **18** and 2-amino-3-methylbutan-1-ol **19** were determined over the temperature range 5–36°C by the Rose–Drago method[10] on the basis of the absorption maximum in the UV-visible spectrum of the complexes. An absorption maximum of (*S,R,R,S*)-**1** appeared at 405 nm in chloroform and its complexes with these amines showed an absorption maximum in the region 575–588 nm. The K_a values, the thermodynamic parameters calculated from observed K_a values and the predictive isoenantioselective temperature ($T_{iso}=\Delta_{R,S}\Delta H/\Delta_{R,S}\Delta S$) are listed in Table 1. As the *S*-selectivity of (*S,R,R,S*)-**1** towards **19** little changed during the experiment, the T_{iso} value of the complexation was not calculated.

Previously, we have prepared (*S,R,R,S*)-**2** in which the steric surroundings of the chiral cavity are similar to those of (*S,R,R,S*)-**1** and interpreted the *S*-selectivity in the complexation with **16** in terms of steric interactions between the ligand of the amine and the steric barrier of the crown ether on the basis of CPK molecular model examination.[11] From the present result of the (*S,R,R,S*)-**1**:**16** complexation, we doubted whether the *S*-selectivity of the (*S,R,R,S*)-**2**:**16** complexation observed at 25°C is governed by $-\Delta_{R,S}\Delta H$ or $-\Delta_{R,S}\Delta S$. Therefore, we now examined the temperature-dependent enantioselectivity in complexation of (*S,R,R,S*)-**2** with these amines and the results are also given in Table 1.

In Figure 1, the enthalpy changes are plotted against the entropy change demonstrating that the plot for the complex formation of (*S,R,R,S*)-**2** with the amines affords a linear relationship; so-called enthalpy–entropy compensation effect[12] and, on the other hand, that of (*S,R,R,S*)-**1** with the amines shows the characteristic feature. The ΔH-value for (*S,R,R,S*)-**1**:(*S*)-**19** interaction (○ in Figure 1) is 1.0 kJ mol^{-1} less favorable than that for (*S,R,R,S*)-**2**:(*S*)-**19** interaction (● in Figure 1), while the ΔS-value for formation of the (*S,R,R,S*)-**1**:(*S*)-**19** complex is 17 J K^{-1} mol^{-1} less unfavorable than that for formation of the (*S,R,R,S*)-**2**:(*S*)-**19** complex making the ΔG-value for the (*S,R,R,S*)-**1**:(*S*)-**19** complexation 4.0 kJ mol^{-1} (at 298 K) more favorable. The ΔH-value for (*S,R,R,S*)-**1**:(*R*)-**18** interaction

Table 1. The association constants of the complexes and thermodynamic parameters for complexation of crown ethers (*S,R,R,S*)-**1** and (*S,R,R,S*)-**2** with amines

Crown ether	Amine	*Ka* (°C) mol^{-1}				ΔH kJmol^{-1}	ΔS JK^{-1}mol^{-1}	ΔG (298K) kJmol^{-1}	*Tiso* K
1	(*R*)-**16**	174 (5)	82 (15)	38 (25)	22 (35)	-50.3	-138	-9.2	111
1	(*S*)-**16**	235 (6)	108 (16)	60 (26)	30 (35)	-49.8	-133	-10.1	
1	(*R*)-**17**	806 (5)	366 (15)	181 (25)	90 (35)	-51.6	-130	-12.8	510
1	(*S*)-**17**	1.24x10^3 (5)	628 (15)	264 (25)	131 (35)	-54.1	-135	-13.9	
1	(*R*)-**18**	865 (5)	399 (15)	189 (25)	96 (35)	-52.4	-132	-13.0	300
1	(*S*)-**18**	787 (5)	414 (15)	194 (25)	93 (35)	-51.0	-127	-13.0	
1	(*R*)-**19**	370 (5)	178 (15)	84 (25)	47 (35)	-49.2	-128	-11.0	-
1	(*S*)-**19**	474 (5)	253 (15)	111 (25)	60 (35)	-49.5	-126	-11.8	
2	(*R*)-**16**	75 (5)	30 (15)	15 (25)	7 (36)	-54.9	-162	-6.7	105
2	(*S*)-**16**	121 (5)	58 (15)	24 (25)	12 (36)	-54.2	-155	-8.0	
2	(*R*)-**17**	1.11x10^3 (6)	425 (15)	182 (25)	78 (35)	-64.5	-173	-12.9	302
2	(*S*)-**17**	1.03x10^3 (6)	430 (15)	184 (25)	79 (35)	-62.2	-166	-12.8	
2	(*R*)-**18**	1.07x10^3 (5)	486 (14)	151 (25)	68 (35)	-66.8	-182	-12.6	374
2	(*S*)-**18**	486 (5)	220 (15)	93 (25)	41 (35)	-59.9	-163	-11.2	
2	(*R*)-**19**	198 (4)	74 (15)	39 (25)	17 (35)	-55.4	-156	-8.9	384
2	(*S*)-**19**	111 (5)	41 (16)	23 (25)	12 (36)	-50.5	-143	-7.8	

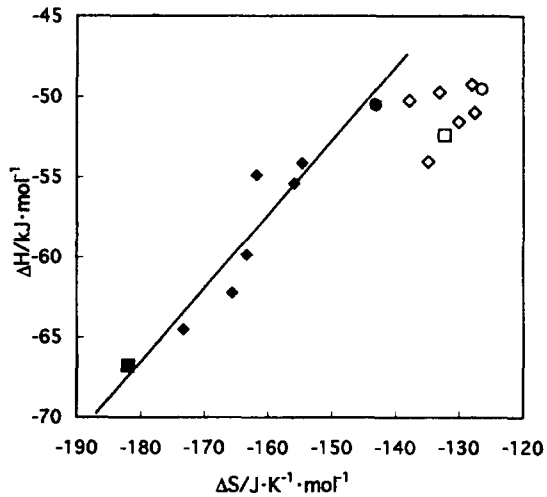


Figure 1. Enthalpy–entropy compensation plot for the complexation of (*S,R,R,S*)-**1** (◇, □ and ○) and (*S,R,R,S*)-**2** (◆, ■ and ●) with amines.

(□ in Figure 1) is 14.4 kJ mol^{-1} less negative than that for (*S,R,R,S*)-**2**:(*R*)-**18** interaction (■ in Figure 1) but the less unfavorable ΔS-value sufficiently compensates for the less favorable ΔH-value resulting in the larger negative ΔG-value for formation of the (*S,R,R,S*)-**1**:(*R*)-**18** complex than that for formation of the (*S,R,R,S*)-**2**:(*R*)-**18** complex. Since one reason for a small negative ΔS-value is a smaller conformational change, we infer that the conformation of the cavity of (*S,R,R,S*)-**1**, compared to that of (*S,R,R,S*)-**2**, is less flexible and so (*S,R,R,S*)-**1** made a much smaller conformational change during complexation with the amines than (*S,R,R,S*)-**2**.

In Figs 2 and 3, we show the temperature dependence of enantiomer selectivities ($\Delta\Delta G$=ΔG_S−ΔG_R) of formation of the (*S,R,R,S*)-**1**:amine and the (*S,R,R,S*)-**2**:amine complexes, respectively, on the basis

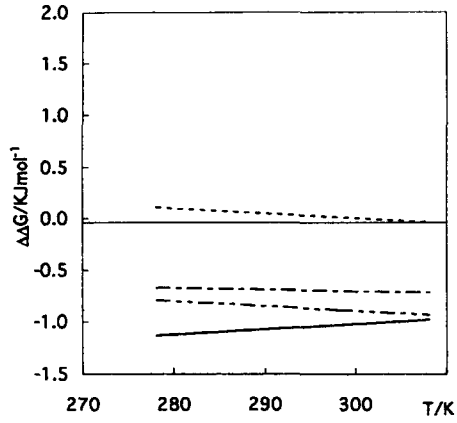
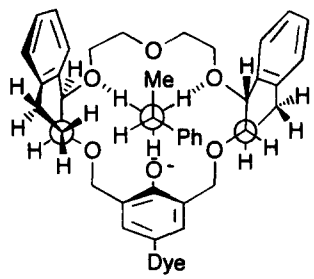


Figure 2. Temperature dependence of enantiomer selectivity for the complexation of (*S,R,R,S*)-**1** with amines; 16(– · · –), 17(—), 18(· · ·), 19(– · –).

of the K_a values observed at different temperatures. In the case of the (*S,R,R,S*)-**1**:**19** complexation, it is not clear whether the *S*-selectivity was observed above or below T_{iso}. Figures 2 and 3 show inversion of the sign of $\Delta\Delta G$-values for the (*S,R,R,S*)-**1**:**18** and the (*S,R,R,S*)-**2**:**17** complexations at the normal temperature but $\Delta\Delta G$-values observed at every temperature are too small to assure inversion at *ca.* 30°C. The present data show that T_{iso}-points of the complexation of **16** with (*S,R,R,S*)-**1** and with (*S,R,R,S*)-**2** lie below 0°C and the *S*-selectivities increased with increasing temperature over the normal temperature; the *S*-selectivity of (*S,R,R,S*)-**2** observed at 25°C is undoubtedly governed by $-\Delta_{R,S}\Delta S$.



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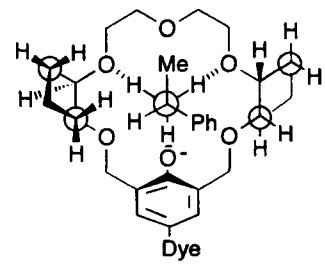

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For the predictable *R*-selectivities of (*S,R,R,S*)-**1** and of (*S,R,R,S*)-**2** towards **16** governed by $-\Delta_{R,S}\Delta H$, we propose an explanation in terms of a steric repulsion between the ligand of the amine and the crown ether. On the basis of CPK molecular model examination of the complexes using the assumption that the phenolate oxygen atom necessarily participates in binding the amine[13] and the most hindered site over the oxygen atom at the 8 o'clock position of the complexes as drawn is preferentially occupied by the hydrogen atom of the amine, the predicted geometries **20** and **21** are illustrated for the (*S,R,R,S*)-**1**:(*R*)-**16**, and the (*S,R,R,S*)-**2**:(*R*)-**16** complexes, respectively. Judging from the steric requirements of CPK molecular models of the complexes and the predictable *R*-selectivities, we infer that the area over the oxygen atom at the 4 o'clock position is less hindered than that at the 12 o'clock position and so (*R*)-**16** showed better complementarity to (*S,R,R,S*)-**1** and (*S,R,R,S*)-**2** than (*S*)-**16**. We infer that the conformation of the complexes of (*S,R,R,S*)-**1** and (*S,R,R,S*)-**2** with **16** of three point-binding mode[14] is more flexible than that of the complexes of the phenolic crown ether with 2-aminoethanol derivatives of four point-binding mode[13] and the flexible conformation of the complex leads to the small difference in a host–guest interaction between diastereomeric complexes; the (*S,R,R,S*)-**1**:**16** and the (*S,R,R,S*)-**2**:**16** interactions showed the smaller $\Delta_{R,S}\Delta H$-value than the

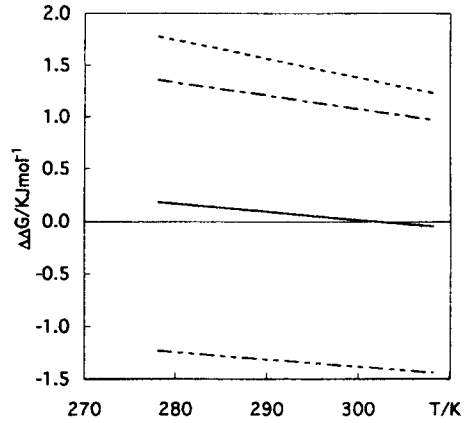

Figure 3. Temperature dependence of enantiomer selectivity for the complexation of (*S,R,R,S*)-**2** with amines; 16(– · · –), 17(—), 18(· · ·), 19(– · –).

interactions of these crown ethers with 2-aminoethanol derivatives **17** and **18**. As the $\Delta_{R,S}\Delta H$-value was small, the sign of $\Delta_{R,S}\Delta G$ of the complexations of (*S,R,R,S*)-**1** and (*S,R,R,S*)-**2** with **16** was governed by $-T\Delta_{R,S}\Delta S$ (T>*ca.* 110 K); the *S*-selectivities were found at the normal temperature.

Experimental section

General

^{1}H n.m.r. spectra were recorded at 270 MHz on a JEOL JNM-MH-270 spectrometer for solutions in $CDCl_3$ with $SiMe_4$ as internal standard and J values are given in Hz. ^{13}C n.m.r. spectra were recorded at 68.9 MHz on a JEOL JNM-MH-270 spectrometer and chloroform (δ_C 77.0) was used as chemical-shift reference. Mass spectra were recorded with 3-nitrobenzyl alcohol as a matrix on a JEOL-DX-303-HF spectrometer. HPLC analyses were carried out on a Shimadzu LC-6A chromatograph using a chiral column Opti-Pak AD (Waters), 250×4.6 mm. Elemental analyses were carried out by Yanagimoto CHN-Corder, Type 2. Melting points were measured on a Yanagimoto micro melting point apparatus and are uncorrected. IR spectra were measured on a Hitachi 260-10 spectrometer. Optical rotations were measured using a JASCO DIP-40 polarimeter at ambient temperature and $[\alpha]_D$ values are given in units of 10^{-1} deg cm^2 g^{-1}. UV and visible spectra were measured on a HITACHI 260-10 spectrometer. Lipase QL was supplied by Meito Sangyo and used without further purification. The homochiral amines (*R*)-**16**, (*S*)-**16**, (*R*)-**17**, (*S*)-**17**, (*R*)-**18**, (*S*)-**18**, (*R*)-**19** and (*S*)-**19** were purchased from the Aldrich Chemical Company, Inc. and used without further purification.

(±)-2-Acetoxy-3,4-dihydro-1(2H)-naphthalenone **4**

A mixture of 3,4-dihydro-1(2*H*)-naphthalenone **3** (106 g, 0.726 mol) and lead tetraacetate (443 g, 1.00 mol) in dry benzene (1500 cm^3) was stirred under reflux for 3 days and water was then added to the reaction mixture. The organic layer was separated and the aqueous layer was extracted with benzene. The combined benzene solutions were washed with water and concentrated under reduced pressure to give a solid, which was recrystallized from ethanol to give (±)-**4** (87.0 g, 59% yield), mp 73–75°C; IR (KBr) 2960, 2900, 1735, 1695, 1600, 1373, 1245, 1230, 1055, 942 and 760 cm^{-1}; δ_H ($CDCl_3$) 2.23 (3H, s, $COCH_3$), 2.25–2.46 (2H, m, CH_2), 3.06–3.29 (2H, m, CH_2), 5.55 (1H, dd, J 5.4 and 11.9, CH(OAc)), 7.26–7.36 (2H, m, ArH), 7.51 (1H, ddd, J 1.5, 7.5 and 7.5, ArH) and 8.06 (1H, dd, J 1.2 and 7.5, ArH); HRMS (EI) Calc'd for $C_{12}H_{12}O_3$: 205.0865. Found: 205.0827. Anal. Calc'd for $C_{12}H_{12}O_3$: C, 70.57%; H, 5.92%. Found: C, 70.51%; H, 5.76%.

Optical resolution of (±)-4

A mixture of (±)-**4** (30.0 g, 0.147 mol) and lipase QL (from *Alcaligenes* sp.) (5.0 g), ethanol (34.0 g, 0.740 mol) and hexane (2600 cm^3) was stirred for 4 days at 18–20°C. The enzyme was removed by filtration and volatile materials were evaporated under reduced pressure. Silica gel chromatography of the products gave successively (*S*)-**4** (hexane:ethyl acetate, 10:1 as eluent) (8.90 g, 30%) and (*R*)-**5** (hexane:ethyl acetate, 10:1) (13.4 g, 56%).

For (*S*)-**4**: mp 71.5–73.0°C (in a sealed capillary); $[\alpha]_D^{20}$ −86.6 (c 0.77, $CHCl_3$) (>98% e.e. by HPLC) and the spectral data were completely in accord with those of (±)-**4**. Anal. Calc'd for $C_{12}H_{12}O_3$: C, 70.57%; H, 5.92%. Found: C, 70.52%; H, 5.70%.

For (*R*)-**5**: $[\alpha]_D^{20}$ +21.4 (c 0.59, $CHCl_3$) (49% e.e. by HPLC); IR (KBr) 3100–3700, 2950, 2882, 1690, 1605, 1280, 1228, 1130, 1095, 1000, 942 and 750 cm^{-1}; δ_H ($CDCl_3$) 1.98–2.58 (2H, m, CH_2), 2.99–3.23 (2H, m, CH_2), 3.90 (1H, br s, OH), 4.39 (1H, dd, *J* 5.4 and 12.5, CH(OH)), 7.26–7.37 (2H, m, ArH), 7.52 (1H, ddd, *J* 1.4, 7.7 and 7.7, ArH) and 8.04 (1H, dd, *J* 1.4 and 7.7, ArH).

(1R,2S)-(−)-1,2-Dihydroxy-1,2,3,4-tetrahydronaphthalene ***6***

A solution of (*S*)-**4** (83% e.e. by HPLC) (10.3 g, 50.4 mmol) in dry diethyl ether (750 cm^3) was slowly added to a suspension of $LiAlH_4$ (2.68 g, 70.5 mmol) in dry diethyl ether (1000 cm^3) over a 12 h period at −78°C under a nitrogen atmosphere and the reaction mixture was then refluxed for 30 min. Acetone and aq. ammonium chloride were successively added to the reaction mixture with ice-cooling. After the deposited solid had been removed by filtration, the filtrate was washed with water and dried ($MgSO_4$). Removal of the solvent gave a 12:1 mixture of (1*R*,2*S*)-**6** and (1*S*,2*S*)-**7**, which was chromatographed on silica gel to give successively (1*R*,2*S*)-**6** (hexane:ethyl acetate, 1:1) (5.80 g) and (1*S*,2*S*)-**7** (hexane:ethyl acetate, 1:1) (450 mg). Recrystallization of (1*R*,2*S*)-**6** from a mixture of hexane and benzene gave enantiomerically and diastereomerically pure (1*R*,2*S*)-**6** (4.23 g, 51%), mp 128–129°C (in a sealed capillary); $[\alpha]_D^{28}$ −27.4 (c 1.00, $CHCl_3$) (>99% e.e. by HPLC); IR (KBr) 3650, 3253, 2950, 1360, 1250, 1200, 1120, 1078, 965, 775 and 740 cm^{-1}; δ_H ($CDCl_3$) 1.85–2.18 (2H, m, CH_2), 2.25 (2H, br s, OH), 2.73–3.03 (2H, m, CH_2), 4.03 (1H, ddd, *J* 3.6, 3.6 and 9.0, CH at C2 position), 4.71 (1H, d, *J* 3.6, CH at C1 position), 7.11–7.27 (3H, m, ArH) and 7.41–7.47 (1H, m, ArH); HRMS (EI) Calc'd for $C_{10}H_{12}O_2$: 164.0837. Found: 164.0846. Anal. Calc'd for $C_{10}H_{12}O_2$: C, 73.15%. H, 7.37%. Found: C, 73.13%. H, 7.09%.

For (1*S*,2*S*)-**7**: δ_H ($CDCl_3$) 1.79–2.20 (4H, m, CH_2 and OH), 2.90–2.93 (2H, m, CH_2), 3.83 (1H, ddd, *J* 3.5, 7.8 and 7.9, CH at C2 position), 4.58 (1H, d, *J* 7.9, CH at C1 position), 7.09–7.24 (3H, m, ArH) and 7.54–7.56 (1H, m, ArH).

(1R,2S)-(+)-1-Hydroxy-2-(methoxymethoxy)-1,2,3,4-tetrahydronaphthalene ***8***

Chloromethyl methyl ether (8.86 g, 110 mmol) was added to a solution of (1*R*,2*S*)-**6** (6.00 g, 36.6 mmol) and *N*,*N*-diisopropylethylamine (83.8 g, 650 mmol) in dry chloroform (120 cm^3) and the reaction mixture was then stirred for 12 h at room temperature. After aq. sodium hydrogencarbonate had been added to the reaction mixture, the organic layer was separated and the aqueous layer was extracted with chloroform. The combined chloroform solutions were washed with water, dried ($MgSO_4$) and evaporated under reduced pressure. Silica gel chromatography of the products gave successively (1*R*,2*S*)-**10** (hexane:ethyl acetate, 3:2) (1.34 g, 15%), (1*R*,2*S*)-**8** (hexane:ethyl acetate, 2:3) (3.11 g, 41%), (1*R*,2*S*)-**9** (hexane:ethyl acetate, 2:3) (1.10 g, 14%) and (1*R*,2*S*)-**6** (ethyl acetate) (900 mg, 15%).

For (1*S*,2*S*)-**8**: mp 61.5–62.0°C; $[\alpha]_D^{29}$ +20.6 (c 0.99, $CHCl_3$), IR (KBr) 3350, 2950, 2900, 1500, 1458, 1440, 1352, 1145, 1100, 1042, 915, 840, 750 and 720 cm^{-1}; δ_H ($CDCl_3$) 1.88–2.27 (2H, m, CH_2), 2.72–3.05 (2H, m, CH_2), 2.87 (1H, d, *J* 5.8, OH), 3.39 (3H, s, OCH_3), 4.03 (1H, ddd, *J* 3.2, 3.2 and 8.3, CH at C2 position), 4.75 (1H, dd, *J* 3.2 and 5.8, CH at C1 position), 4.77 (1H, d, *J* 6.8, OCH_2O), 4.83 (1H, d, *J* 6.8, OCH_2O), 7.09–7.25 (3H, m, ArH) and 7.47–7.51 (1H, m, ArH); MS

(FD) *m/z* (relative intensity) 509 [(M^++1) 28], 208 [(M^+) 100], 191 (8) and 176 (8). Anal. Calc'd for $C_{12}H_{16}O_3$: C, 69.21%; H, 7.74%. Found: C, 69.40%; H, 7.51%.

For (1*S*,2*S*)-**9**: $[\alpha]_D^{29}$ −79.2 (c 0.86, $CHCl_3$); IR (neat film) 3420, 3070, 3018, 2940, 2900, 2850, 1495, 1460, 1438, 1215, 1160, 1118, 1100, 1038, 920, 825, 775, 745 and 730 cm^{-1}; δ_H ($CDCl_3$) 1.89–2.20 (2H, m, CH_2), 2.74–3.08 (2H, m, CH_2), 2.92 (1H, d, *J* 7.7, OH), 3.47 (3H, s, OCH_3), 4.05 (1H, ddd, *J* 3.5, 7.3 and 11.3, CH at C2 position), 4.66 (1H, d, *J* 3.5, CH at C1 position), 4.85 (1H, d, *J* 6.8, OCH_2O), 4.88 (1H, d, *J* 6.8, OCH_2O), 7.12–7.27 (3H, m, ArH) and 7.35 (1H, dd, *J* 2.0 and 6.9, ArH).

For (1*S*,2*S*)-**10**: IR (neat film) 2940, 2890, 2838, 2820, 1495, 1458, 1210, 1150, 1100, 1040, 918, 775 and 750 cm^{-1}; δ_H ($CDCl_3$) 1.90–2.35 (2H, m, CH_2), 2.83 (1H, ddd, *J* 7.0, 9.6 and 15.1, CH_2), 3.04 (1H, ddd, *J* 4.2, 6.5 and 15.1, CH_2), 3.42 (3H, s, OCH_3), 3.43 (3H, s, OCH_3), 4.04 (1H, ddd, *J* 3.2, 3.4 and 10.1, CH at C2 positon), 4.77 (1H, d, *J* 3.4, CH at C1 position), 4.75 (1H, d, *J* 6.8, OCH_2O), 4.78 (1H, d, *J* 6.6, OCH_2O), 4.49 (1H, d, *J* 6.6, OCH_2O), 4.93 (1H, d, *J* 6.8, OCH_2O), 7.11–7.25 (3H, m, ArH) and 7.34 (1H,dd, *J* 2.0 and 6.9, ArH).

(−)-1,5-Bis[2′-(methoxymethoxy)-1′,2′,3′,4′-tetrahydronaphthoxy]-3-oxapentane ***11***

A solution of (1*R*,2*S*)-**8** (2.86 g, 13.7 mmol) in dry THF (30 cm^3) was added slowly to a suspension of NaH (1.38 g, 57.6 mmol) in dry THF (30 cm^3) and the reaction mixture was then refluxed for 1 h. After the reaction mixture had been cooled to room temperature, a solution of diethylene glycol bis(*p*-toluenesulfonate) (2.85 g, 6.88 mmol) in dry THF (30 cm^3) was added dropwise to the reaction mixture and the reaction mixture was heated at 50°C for 5 days under a nitrogen atmosphere. After a small amount of chilled water had been carefully added to the reaction mixture with ice-cooling, the solvent was removed under reduced pressure. The residue was extracted with chloroform and the combined extracts were washed with water, dried ($MgSO_4$) and evaporated under reduced pressure. The residue was chromatographed on silica gel to give (*S*,*R*,*R*,*S*)-**11** (hexane:ethyl acetate, 6:4) (2.52 g, 76%) as an oil, $[\alpha]_D^{28}$ −36.3 (c 0.93, $CHCl_3$); IR (neat film) 2930, 2890, 1460, 1152, 1105, 1040, 920, 770 and 750 cm^{-1}; δ_H ($CDCl_3$) 1.83–2.32 (4H, m, CH_2), 2.76 (2H, ddd, *J* 7.4, 7.4 and 15.7, CH_2), 3.02 (2H, ddd, *J* 6.3, 6.3 and 15.7, CH_2), 3.41 (6H, s, OCH_3), 3.67–3.93 (8H, m, OCH_2), 4.06 (2H, ddd, *J* 3.1, 3.2 and 8.9, CH at C2 position), 4.50 (2H, d, *J* 3.1, CH at C1 position), 4.76 (2H, d, *J* 6.9, OCH_2O), 4.78 (2H, d, *J* 6.9, OCH_2O), 7.02–7.22 (6H, m, ArH) and 7.37 (2H, dd, *J* 1.7 and 6.7, ArH), δ_C ($CDCl_3$) 23.7 (t), 26.7 (t), 55.4 (q), 69.2 (t), 70.9 (t), 73.6 (d), 77.9 (d), 95.1 (t), 125.6 (d), 127.7 (d), 128.4 (d), 129.3 (d), 135.2 (s) and 136.2 (s). The high-resolution mass spectrum could not be recorded because of the very weak molecular ion peak. MS (FAB) *m/z* (relative intensity) 509 [(M^++Na) 100], 487 [(M^++1) 5], 486 [(M^+) 47], 485 (12), 455 (14) and 441 (48).

(−)-1,5-Bis(2′-hydroxy-1′,2′,3′,4′-tetrahydronaphthoxy)-3-oxapentane ***12***

A solution of (*S*,*R*,*R*,*S*)-**11** (2.45 g, 5.03 mmol) in methanol (190 cm^3) containing conc. hydrochloric acid (1 cm^3) was stirred for 12 h at room temperature. After aq. sodium hydrogen carbonate had been added to the reaction mixture, the volatile materials were removed under reduced pressure. The residue was extracted with ethyl acetate and the combined extracts were washed with water, dried ($MgSO_4$) and evaporated under reduced pressure. Silica gel chromatography of the products gave (*S*,*R*,*R*,*S*)-**12** (hexane:ethyl acetate, 1:2) (1.80 g, 89%) as an oil, $[\alpha]_D^{28}$ −3.53 (c 0.91, $CHCl_3$); IR (neat film) 3400, 3060, 3020, 2950, 1462, 1110, 1088, 973, 775, 755 and 735 cm^{-1}; δ_H ($CDCl_3$) 1.86–2.24 (4H, m, CH_2), 2.75 (2H, ddd, *J* 6.6, 8.8 and 15.5, CH_2), 3.02 (2H, ddd, *J* 5.7, 5.8 and 15.5, CH_2), 3.60–3.97 (8H, m, OCH_2), 4.06–4.07 (2H, m, CH at C2 position), 4.39 (2H, d, *J* 3.5, CH at C1 position), 4.43 (2H, d, *J* 7.2, OH), 7.10–7.24 (6H, m, ArH), 7.33 (2H, dd, *J* 2.0 and 6.9, ArH). The high-resolution mass spectrum could not be recorded because of the very weak molecular ion peak. MS (FAB) *m/z* (relative intensity) 421 [(M^++Na) 100], 399 [(M^++1) 81] and 391 (63).

(4S,13R,21R,30S)-(+)-35,37-Dimethoxy-3,14,17,20,31-pentaoxahexacyclo-[31.3.1.0^{4,13}.0^{7,12}.0^{21,30}.0^{22,27}]heptatriaconta-1(37),7,9,11,22,24,26,33,35-nonaene ***13***

A solution of (*S,R,R,S*)-**12** (1.70 g, 4.27 mmol) and 1,3-bis(bromomethyl)-2,5-dimethoxybenzene (1.52 g, 4.69 mmol) in dry THF (300 cm^3) was slowly added to a suspension of NaH (307 mg, 12.8 mmol) in dry THF (150 cm^3) over a 29 h period and the reaction mixture was heated at 50°C for further 3 days under a nitrogen atmosphere. After a small amount of chilled water had been added to the reaction mixture with ice-cooling, the solvent was removed under reduced pressure. The residue was extracted with chloroform and the combined extracts were washed with water, dried ($MgSO_4$) and evaporated under reduced pressure. The products were chromatographed on silica gel to provide (*S,R,R,S*)-**13** (chloroform) (1.72 g, 72%), mp 144–145°C; $[\alpha]_D^{28}$ +17.9 (c 0.97, $CHCl_3$); IR (KBr) 2920, 1600, 1482, 1428, 1360, 1325, 1252, 1125, 1112, 1090, 1060, 1020, 758, 740 and 705 cm^{-1}; δ_H ($CDCl_3$) 1.94–2.44 (4H, m, CH_2), 2.80 (2H, ddd, *J* 7.2, 7.3 and 15.7, CH_2), 3.07 (2H, ddd, *J* 6.2, 6.3 and 15.7, CH_2), 3.45–3.66 (8H, m, OCH_2), 3.77 (3H, s, OCH_3 at C35 position), 3.95 (2H, ddd, *J* 3.0, 3.0 and 8.7, CH), 4.02 (3H, s, OCH_3 at C37 position), 4.43 (2H, d, *J* 3.0, CH), 4.53 (2H, d, *J* 10.8, benzylic CH_2), 4.79 (2H, d, *J* 10.8, benzylic CH_2), 6.89 (2H, s, $(MeO)_2ArH$), 7.10–7.22 (6H, m, ArH) and 7.31 (2H, dd, *J* 2.0 and 6.4, ArH); δ_C ($CDCl_3$) 23.2 (t), 26.7 (t), 55.5 (t), 64.0 (q), 65.9 (t), 68.9 (t), 70.2 (t), 74.4 (d), 77.5 (d), 115.9 (d), 125.6 (d), 127.6 (d), 128.5 (d), 129.1 (d), 132.7 (s), 135.2 (s), 136.4 (s), 151.8 (s) and 155.0 (s). Anal. Calc'd for $C_{34}H_{40}O_7$: C, 72.83%; H, 7.19%. Found: C, 72.66%; H, 7.17%.

(4S,13R,21R,30S)-(−)-37-Hydroxy-35-methoxy-3,14,17,20,31-pentaoxahexacyclo-[31.3.1.0^{4,13}.0^{7,12}.0^{21,30}.0^{22,27}]heptatriaconta-1(37),7,9,11,22,24,26,33,35-nonaene ***14***

To a suspension of NaH (514 mg, 21.4 mmol) in dry DMF (150 cm^3) was slowly added ethanethiol (1.46 g, 23.5 mmol) and then a solution of (*S,R,R,S*)-**13** (1.20 g, 2.14 mmol) in dry DMF (100 cm^3) was added to the resulting clear solution. The reaction mixture was stirred for 7 h at 90°C and cooled to 0–5°C. After a small amount of water had been added to the chilled reaction mixture, the volatile materials were evaporated under reduced pressure and the residue was extracted with chloroform. The combined extracts were washed with water, dried ($MgSO_4$) and evaporated under reduced pressure. Silica gel chromatography of the products gave a solid (chloroform), which was recrystallized from a mixture of hexane and methylene dichloride to give (*S,R,R,S*)-**14** (1.14 g, 94%), mp 169–170°C; $[\alpha]_D^{28}$ −12.0 (c 1.13, $CHCl_3$); IR (KBr) 3320, 2860, 1660, 1482, 1445, 1348, 1255, 1150, 1115, 1082, 1058, 840, 760, 735 and 720 cm^{-1}; δ_H ($CDCl_3$) 1.88–2.44 (4H, m, CH_2), 2.80 (2H, ddd, *J* 7.4, 7.7 and 15.8, CH_2), 3.04 (2H, ddd, *J* 6.1, 6.1 and 15.8, CH_2), 3.76 (3H, s, OCH_3), 3.71–3.82 (8H, m, OCH_2), 3.92 (2H, ddd, *J* 3.1, 3.2 and 8.9, CH), 4.64 (2H, d, *J* 3.1, CH), 4.61 (2H, d, *J* 11.4, benzylic CH_2), 4.87 (2H, d, *J* 11.4, benzylic CH_2), 6.77 (2H, s, (HO)ArH), 7.11–7.22 (6H, m, ArH), 7.35 (2H, dd, *J* 1.5 and 5.7, ArH) and 7.73 (1H, s, OH). Anal. Calc'd for $C_{33}H_{38}O_7$: C, 72.51%; H, 7.01%. Found: C, 72.33%; H, 6.96%.

(4S,13R,21R,30S)-3,14,17,20,31-pentaoxahexacyclo[31.3.1.0^{4,13}.0^{7,12}.0^{21,30}.0^{22,27}]heptatriaconta-7,9,11,22,24,26,33,36-octaene-35,37-dione ***15***

A solution of (*S,R,R,S*)-**14** (200 mg, 0.366 mmol) in acetonitrile (10 cm^3) was added to a solution of CAN (401 mg, 0.732 mmol) in acetonitrile (20 cm^3) and then the mixture was stirred for 2 h at room temperature. After the reaction mixture had been cooled to 0–5°C, water was added to the mixture. The mixture was extracted with chloroform and the combined extracts were washed with water, dried ($MgSO_4$) and evaporated under reduced pressure. The residue was chromatographed on silica gel to give **15** (hexane:ethyl acetate, 2:1) (178 mg, 92%) as a yellow solid, δ_H ($CDCl_3$) 1.88–2.39 (4H, m, CH_2), 2.77 (2H, ddd, *J* 6.4, 6.4 and 15.7, CH_2), 3.06 (2H, ddd, *J* 6.9, 6.9 and 15.7, CH_2), 3.60–3.71 (6H, m, OCH_2), 3.83–3.92 (2H, m, OCH_2), 4.07 (2H, ddd, *J* 2.8, 2.9 and 7.8, CH), 4.50 (2H, d, *J* 2.9, CH), 4.50 (2H, d, *J* 14.8, benzylic CH_2), 4.75 (2H, d, *J* 14.8, benzylic CH_2), 6.64 (2H, s, quinone

moiety CH), 7.09–7.23 (6H, m, ArH) and 7.38 (2H, dd, *J* 2.0 and 6.6, ArH). This was used for the next reaction without further purification.

Azophenolic crown ether (S,R,R,S)-1

A solution of 2,4-dinitrophenylhydrazine (280 mg, 1.41 mmol) in methylene dichloride (20 cm^3) containing conc. H_2SO_4 (1 cm^3) was added to a solution of **15** (150 mg, 0.283 mmol) in a mixture of methylene dichloride (10 cm^3) and ethanol (10 cm^3) and then the mixture was stirred for 2 h at room temperature. The mixture was diluted with water and extracted with chloroform. The combined extracts were washed with aq. sodium hydrogencarbonate and water, dried ($MgSO_4$) and evaporated under reduced pressure. The residue was chromatographed on silica gel to give a solid (chloroform), which was further purified by preparative recycling HPLC (JAIGEL 1H and 2H column, chloroform as eluent). The solid obtained was recrystallized from a mixture of hexane and methylene dichloride to give (*S,R,R,S*)-**1** (145 mg, 72%) as fine red needles, mp 179–182°C; λ_{max} ($CHCl_3$) 405 nm (ε 2.07×10^4); IR (KBr) 3300, 2900, 1605, 1542, 1470, 1438, 1355, 1300, 1138, 1125, 1105, 1075, 842 and 750 cm^{-1}; δ_H ($CDCl_3$) 1.95–2.47 (4H, m, CH_2), 2.82 (2H, ddd, *J* 7.4, 7.4 and 15.8, CH_2), 3.06 (2H, ddd, *J* 6.1, 6.1 and 15.8, CH_2), 3.72–3.90 (8H, m, OCH_2), 3.99 (2H, ddd, *J* 3.1, 3.1 and 8.7, CH), 4.67 (2H, d, *J* 3.1, CH), 4.65 (2H, d, *J* 10.9, benzylic CH_2), 4.99 (2H, d, *J* 10.9, benzylic CH_2), 7.12–7.25 (6H, m, ArH), 7.36 (2H, dd, *J* 2.0 and 6.9, ArH), 7.79 (1H, d, *J* 8.8, $(NO_2)_2ArH$), 7.84 (2H, s, (HO)ArH), 8.45 (1H, dd, *J* 2.2 and 8.8, $(NO_2)_2ArH$), 8.72 (1H, d, *J* 2.2, $(NO_2)_2ArH$) and 9.23 (1H, s, OH); δ_C ($CDCl_3$) 23.6 (t), 26.6 (t), 67.4 (t), 75.7 (d), 76.2 (d), 119.9 (d), 120.0 (d), 125.4 (s), 125.6 (d), 126.2 (d), 127.5 (d), 128.1 (d), 128.8 (d), 129.6 (d), 134.1 (s), 136.6 (s), 145.8 (s), 146.5 (s), 146.9 (s), 148.9 (s) and 161.2 (s). Anal. Calc'd for $C_{38}H_{38}N_4O_{10}$: C, 64.22%; H, 5.39%; N, 7.88%. Found: C, 63.88%; H, 5.22%; N, 7.74%.

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