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REMAEKABLE EFFECT OF SUBTLE STRUCTURAL CHANGE OF CHIRAL PSEUDO-18-CROWN-6 ON ENANTIOMER-SELECTIVITY IN COMPLEXATION WITH CHIRAL AMINO ALCOHOLS

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Abstract — Chiral receptors [(*S*,*S*)-**1**] and [(*S*,*S*,*S*,*S*)-**2**] having 1,2-dialkoxy-1-(3,5-dimethylphenyl)ethane and 1,2-dialkoxy-1-(3,5-dimethyl phenyl)cyclohexane as chiral building blocks, respectively, were prepared. Thermodynamic parameters of complexations of these and structurally related receptors [(*S*,*S*)-**3**] and [(*S*,*S*,*S*,*S*)-**4**] with 2-amino-1-propanol (**5**), 2-amino-2-phenylethanol (**6**), and 3-methylbutan-1-ol (**7**) in chloroform were determined. It was found that the host-guest systems that have same enantiomer-selectivity at 25 ºC showed opposite selectivity in the enthalpy term. For example, complexations of both (*S*,*S*)-**1** and (*S*,*S*)-**3** with **5** are *R*-selective at 25 ºC ($\Delta\Delta G$ = 2.2 and 3.8 kJ mol^{-1}, respectively), whereas in terms of the enthalpy of complexation the former is *S*-selective ($\Delta\Delta H$ = 22 kJ mol^{-1}) but the latter is *R*-selective ($\Delta\Delta H$ = 10 kJ mol^{-1}).

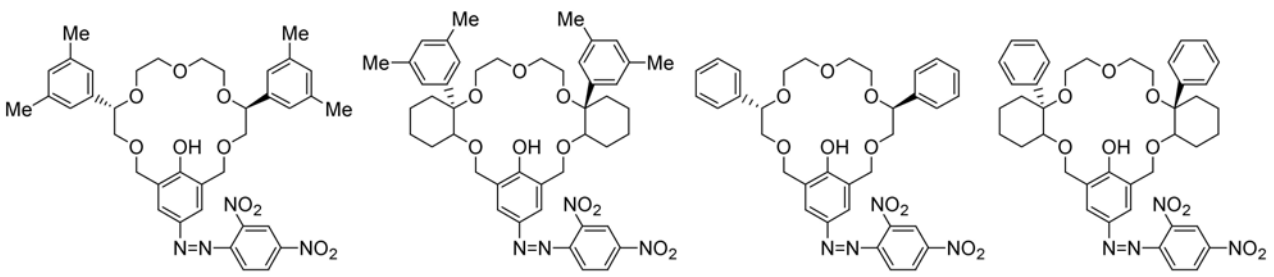
INTRODUCTION

Chiral recognition is one of the most important issues in the field of host–guest chemistry and a large number of chiral host molecules has been developed.[1] Previously, we have reported that chiral crown ethers which have a pseudo-18-crown-6 structure form complexes with chiral, primary amines, with high enantiomer-selectivity.[2] The extent of the chiral recognition abilities of chiral pseudo-18-crown-6 ethers is so high that the derivatives having a 2,4-dinitrophenylazo chromophore serve as chiral indicators.[3] As an extension of our work, we developed the chiral stationary phases (CSPs) having an optically active pseudo-18-crown-6 as a selector for chiral chromatography, one of which is now commercially available owing to its high separation property and its low cost for the preparation.[4] This CPS is one of the first

commercialized CSPs covalently bound with a chiral crown ether.[5] We have also determined the thermodynamic parameters of complexation of the pseudo-18-crown-6 derivatives and found that some of them exhibited inversion of enantiomer-selectivity as a function of temperature.[6] It is of fundamental importance to consider relationship between the enthalpy and entropy terms and the molecular structure of hosts and guests to understand the nature of the host-guest complexation. Since the current molecular design is chiefly based on the complementation between a receptor and a substrate at rt, the knowledge of the above relationship would contribute to the design of selective receptors with high precision. In this context, we planned to compare the thermodynamic parameters of structurally resembling but subtly different chiral receptors. As a result, we found that some host-guest systems which show same enantiomer-selectivity at 25 ºC exhibit opposite *R*/*S* selectivity in terms of the enthalpy term.

RESULTS AND DISCUSSION

In order to investigate the relationship between the structure of receptors and enantiomer-selectivity in complexation with chiral amines substrates, we designed the following chiral receptors [(*S*,*S*)-**1**, (*S*,*S*,*S*,*S*)-**2**, (*S*,*S*)-**3**, and (*S*,*S*,*S*,*S*)-**4**] having a common pseudo-18-crown-6 structure and different chiral moieties. Receptors [(*S*,*S*)-**1**] and [(*S*,*S*,*S*,*S*)-**2**] are structurally related to (*S*,*S*)-**3** and (*S*,*S*,*S*,*S*)-**4** having 1,2-dialkoxy-1-phenylethane and 1,2-dialkoxy-1-phenylcyclohexane as chiral building blocks, respectively, and possess additional methyl substituents on the phenyl groups. The syntheses and enantiomer selective complexations at ambient temperature of receptors [(*S*,*S*)-**3**] and [(*S*,*S*,*S*,*S*)-**4**] were reported previously.[2h,2i] In this paper, syntheses of receptors [(*S*,*S*)-**1**] and [(*S*,*S*,*S*,*S*)-**2**] and thermodynamic parameters of complexations of receptors [(*S*,*S*)-**1**, (*S*,*S*,*S*,*S*)-**2**, (*S*,*S*)-**3**, and (*S*,*S*,*S*,*S*)-**4**] with 2-amino-1-propanol (**5**), 2-amino-2-phenylethanol (**6**), and 3-methylbutan-1-ol (**7**) in chloroform are reported.

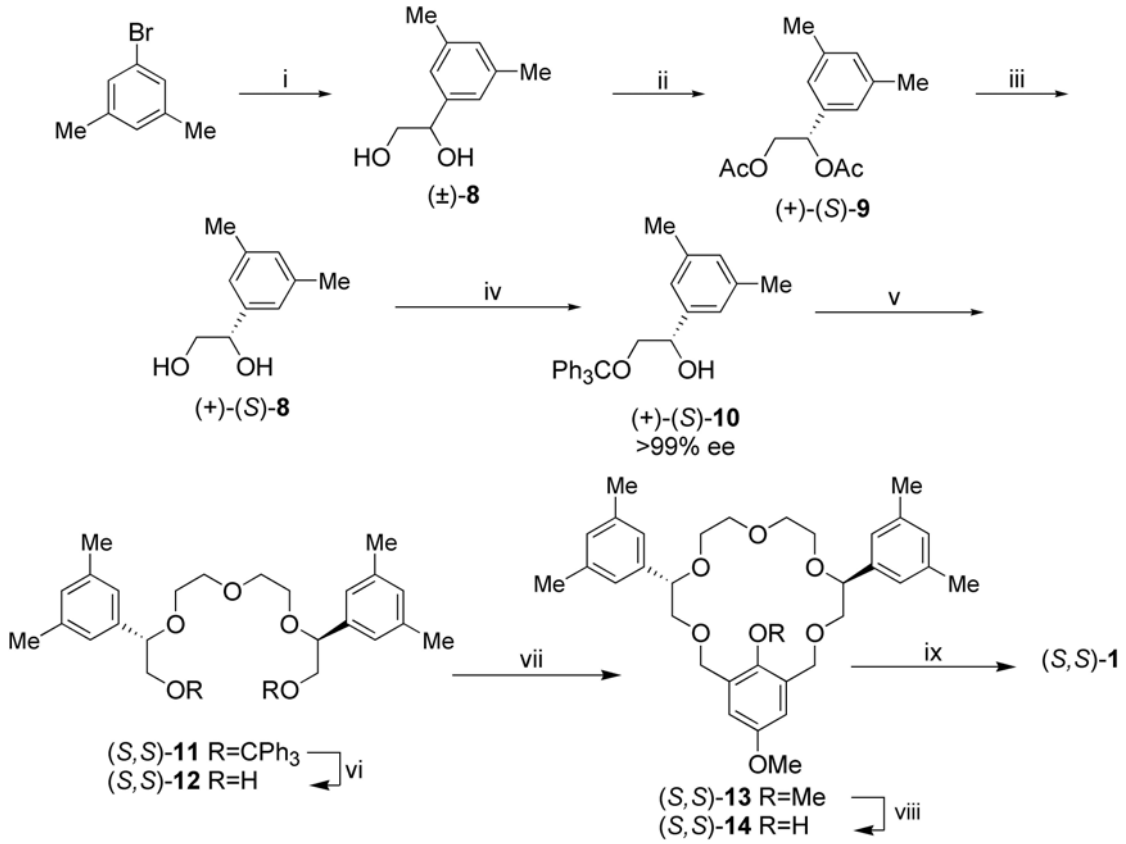


(*S*,*S*)-**1** (*S*,*S*,*S*,*S*)-**2** (*S*,*S*)-**3** (*S*,*S*,*S*,*S*)-**4**

Figure 1. List of host molecules

Synthesis of (*S*,*S*)-**1** was carried out according to Scheme 1. Coupling reaction of vinyl bromide with 3,5-dimethylphenylmagnesium bromide using a nickel catalyst followed by oxidation with osmium

tetraoxide gave diol [(±)-**8**] in 46% overall yield. Optical resolution of (±)-**8** was achieved by lipase QL (from *Alcaligenes*)-catalyzed enantioselective acylation with isopropenyl acetate as an acylating agent.[7] After 12 h stirring, the reaction was terminated by removing the lipase by filtration to give diacetate [(+)-**9**] (93% ee by HPLC) in 29% yield, which was converted to (+)-**8** in 98% yield by alkaline hydrolysis. Selective monoprotection of the primary hydroxy group with triphenylmethyl chloride gave (+)-**10** (92% ee by HPLC) in 62% yield. Recrystallization from chloroform–ethanol gave optically pure (+)-**10** (>99% ee by HPLC) in 26% yield.



Scheme 1. Synthesis of (*S,S*)-**1**: *Reagents* i. 1) Mg, Et_2O, 2) CH_2=CHBr, $NiCl_2$(dppp), 3) OsO_4, *N*-methylmorphorine-*N*-oxide, H_2O ii. Lipase QL, CH_2=C(Me)OAc, Cyclohexane iii. K_2CO_3, MeOH, H_2O iv. 1) Ph_3CCl, DMAP, Et_3N, DMF 2) Recrystallization from $CHCl_3$-EtOH v. $TsOCH_2CH_2OCH_2CH_2OTs$, NaH, THF vi. HCl, MeOH vii. 1,3-bisbromomethyl-2,5-dimethoxybenzezne, NaH, THF viii. EtSNa, DMF ix. 1) $Ce(NH_4)_2(NO_3)_6$, MeCN 2) 2,4-dinitrophenylhydrazine, H_2SO_4, EtOH.

First, the absolute configuration of (+)-**9** is assumed to be *S* on the basis of the empirical knowledge for the reactivity in kinetic resolution using lipases.[8] Accordingly, (+)-**8** and (+)-**10** are also assumed to be *S* isomers. Next, (*R*)-MTPA and (*S*)-MTPA derivatives of (+)-**10** were prepared and their chemical shift differences were investigated as shown in Figure 2. By applying the modified Mosher's method,[9] the absolute configuration of (+)-**10** was estimated to be *S*.

Finally, a single crystal X-Ray structural analysis of an (*R*)-MTPA derivative of (+)-**10** was carried out as shown in Fugure 3.[10] On the basis of the relative stereochemistry, the absolute configuration of the stereocenter was established to be *S*.

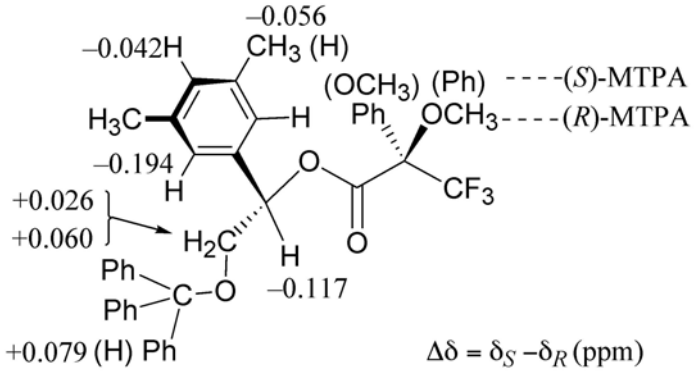


Figure 2. Chemical shift differences (ppm) between the diastereomeric (*R*)- and (*S*)-MTPA esters of (+)-**10** obtained from their ^{1}H-NMR (270MHz, 30°C, $CDCl_3$).

Condensation of two equivalents of (*S*)-(+)-**10** with diethylene glycol di(*p*-toluenesulfonate) in the presence of NaH gave (*S*,*S*)-(+)-**11** in 66% yield and deprotection of (*S*,*S*)-(+)-**11** with hydrochloric acid in methanol gave (*S*,*S*)-(+)-**12** in 84% yield. Ring closure of (*S*,*S*)-(+)-**12** with 1,3-bisbromomethyl-2,5-dimethoxybenzene was carried out in the presence of NaH under high-dilution conditions to give (*S*,*S*)-(+)-**13** in 70% yield. Demethylation of (*S*,*S*)-(+)-**13** with sodium ethanethiolate gave (*S*,*S*)-(+)-**14** in 80% yield. Oxidation of (*S*,*S*)-(+)-**14** with cerium(IV) ammonium nitrate (CAN) gave

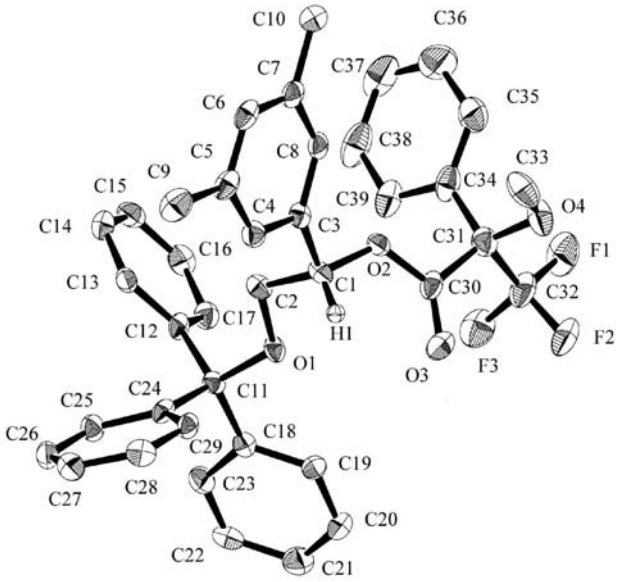
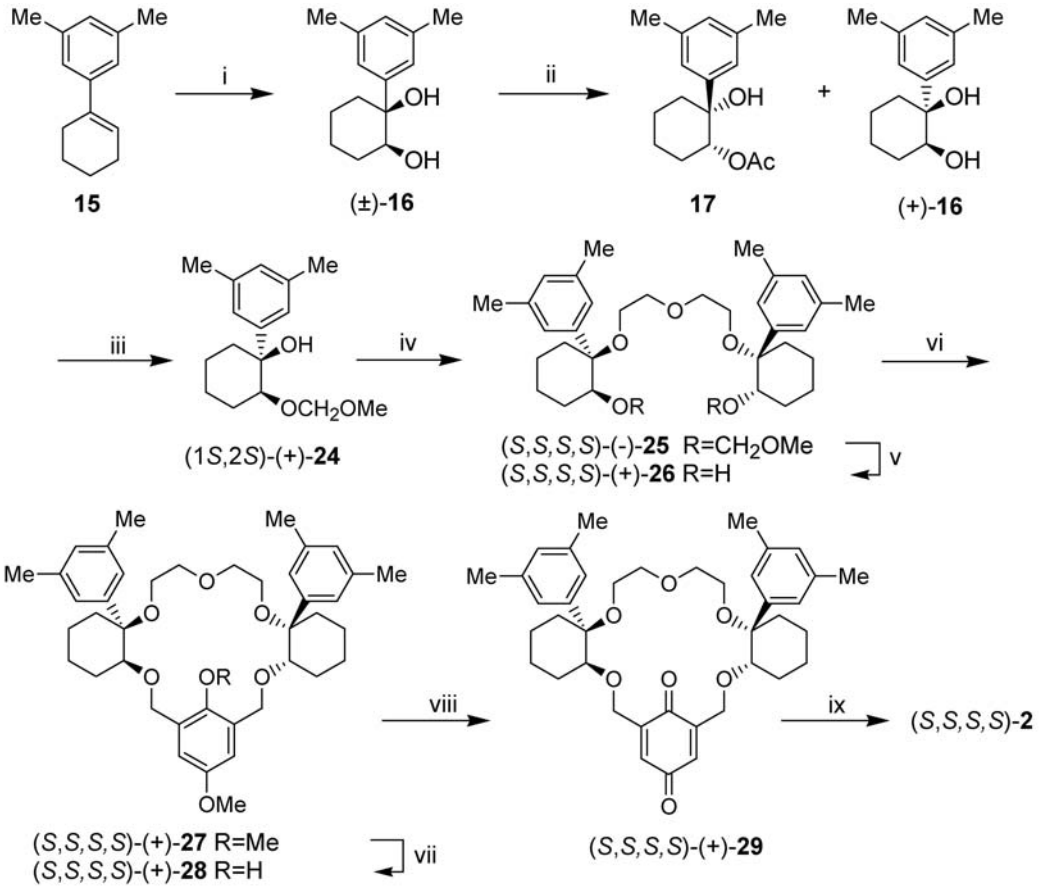


Figure 3. An ORTEP view of the (*R*)-MTPA ester of (+)-**10**. All hydrogen atoms except the one attached to the stereocenter are omitted for clarity.

the corresponding quinone, which was treated without purification with 2,4-dinitrophenylhydrazine to give (*S*,*S*)-**1** in 66% yield from (*S*,*S*)-(+)-**14** after purification by column chromatography followed by preparative recycling HPLC.

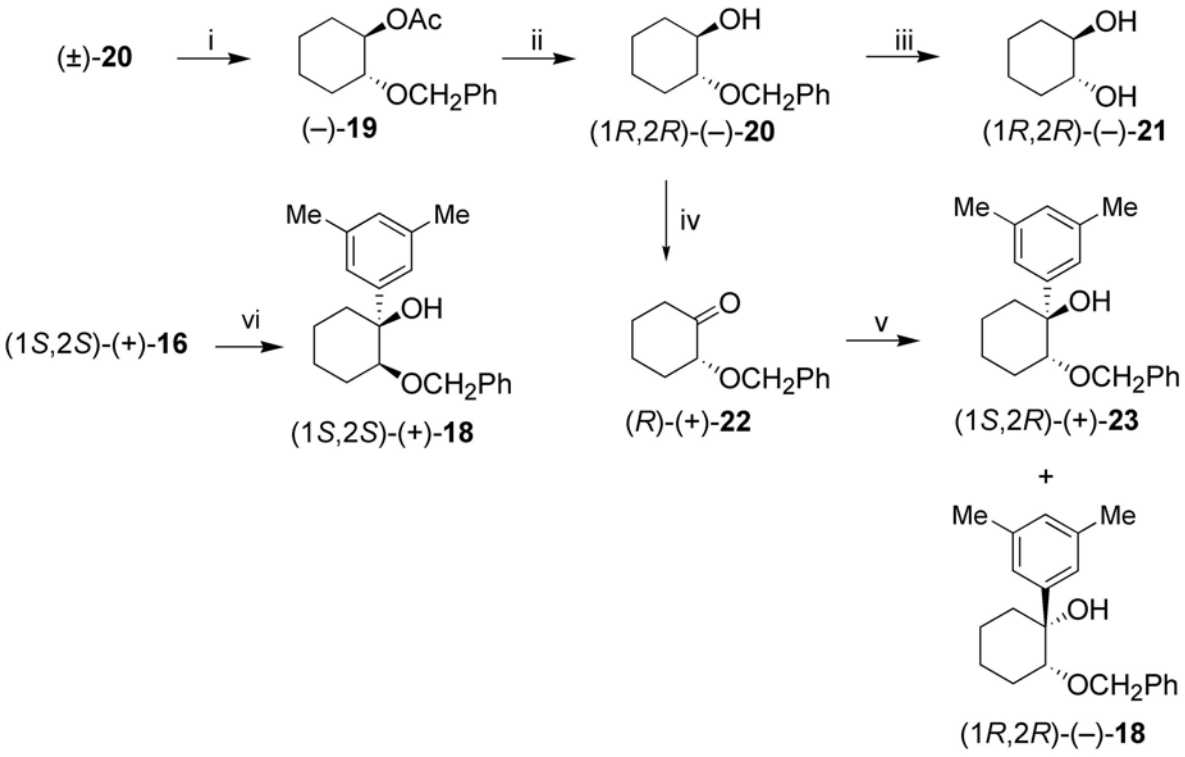
Synthesis of (*S*,*S*,*S*,*S*)-**2**: Synthesis of (*S*,*S*,*S*,*S*)-**2** was carried out as outlined in Scheme 2. Treatment of cyclohexanone with 3,5-dimethylphenylmagnesium bromide followed by dehydration gave **15** in 62% overall yield, which was converted to (±)-**16** in 66% yield by epoxidation with peroxyformic acid followed by alkaline hydrolysis. The *cis*-configuration of (±)-**16** was established on the basis of ^{1}H NMR spectral data; the signal of the methine proton appears at δ 3.99 as a doublet of doublet of doublet with coupling constants of 10.9, 3.7 and 3.7 Hz.[11] Optical resolution of (±)-**16** was achieved by lipase QL (from *Alcaligenes* sp.)-catalyzed enantioselective acylation with isopropenyl acetate as an acylating agent.[2h, 2i] The reaction was terminated at about 60% conversion to give (+)-**16** (>99% ee by HPLC) in 42% yield and **17** (94% ee by HPLC) in 52% yield after chromatographic separation.



Scheme 2. Synthesis of (*S*,*S*,*S*,*S*)-**2**: *Reagents* i. 1) HCO_3H, 2) aq. NaOH ii. Lipase QL, CH_2=C(Me)OAc, Cyclohexane iii. $CH_2(OMe)_2$ iv. $TsOCH_2CH_2OCH_2CH_2OTs$, NaH, THF v. HCl, MeOH vi. 1,3-bisbromomethyl-2,5-dimethoxybenzezne, NaH, THF vii. EtSNa, DMF viii. $Ce(NH_4)_2(NO_3)_6$, MeCN ix. 2,4-dinitrophenylhydrazine, H_2SO_4, EtOH

The absolute configuration of (+)-**16** was determined by chemical correlation to **21** of the known absolute configuration[12] as shown in Scheme 3. The preparation of the homochiral derivative of *trans*-cyclohexane-1,2-diol was advantageously performed by enzymatic resolution of the monobenzyl ether [(±)-**20**]. Lipase YS (from *Pseudomonas fluorescens*)-catalyzed enantioselective acylation[13] of (±)-**20** gave (–)-**19** (>99% ee by HPLC) in 40% yield. Alkaline hydrolysis of (–)-**19** gave (–)-**20** in 97% yield, which was transformed into (1*R*,2*R*)-(–)-**21** in 91% yield by hydrogenolysis. These results allowed an assignment of 1*R*,2*R* for (–)-**20**, from which the key compound (1*R*,2*R*)-(–)-**18** was derived as follows. Oxidation of (1*R*,2*R*)-(–)-**20** with the Jones' reagent gave (*R*)-(+)-**22** in 53% yield, treatment of which with 3,5-dimethylphenylmagnesium bromide gave (1*R*,2*R*)-(–)-**18**, $[\alpha]_D$ –27.6º (chloroform), in 34% yield together with (1*S*,2*R*)-(+)-**23** in 20% yield. On the other hand, treatment of (+)-**16** obtained by resolution of (±)-**16** (Scheme 2) with benzyl bromide gave (+)-**18**, $[\alpha]_D$ +26.2º (chloroform), in 63% yield. From comparison of the specific rotation of (+)-**18** with that of (1*R*,2*R*)-(–)-**18**, the absolute configuration of (+)-**16** was unambiguously determined as 1*S*,2*S*.

In order to prepare (*S*,*S*,*S*,*S*)-**2** having the 3,5-dimethylphenyl substituents located near the diethylene glycol bridge, the secondary hydroxy group of (1*S*,2*S*)-(+)-**16** was protected to give (1*S*,2*S*)-(+)-**24** in 84% yield by treatment with dimethoxymethane. Condensation of two equivalents of (1*S*,2*S*)-(+)-**24** with



Scheme 3. Synthetic pathway of (+/–)-**18**: *Reagents* i. Lipase YS, CH_2=C(Me)OAc, *iso*-Pr_2O ii. KOH, MeOH, H_2O iii. H_2, 10% Pd/C iv. Jones' reagent v. 3,5-dimethylphenyl magnesium bromide vi. $C_6H_5CH_2Br$, NaH, THF.

diethylene glycol di(*p*-toluenesulfonate) in the presence of NaH gave (*S*,*S*,*S*,*S*)-(–)-**25** in 77% yield and deprotection of (*S*,*S*,*S*,*S*)-(–)-**25** with hydrochloric acid in methanol gave (*S*,*S*,*S*,*S*)-(+)-**26** in 89% yield. Ring closure of (*S*,*S*,*S*,*S*)-(+)-**26** with 1,3-bis(bromomethyl)-2,5-dimethoxybenzene was carried out in the presence of NaH under high-dilution conditions to give (*S*,*S*,*S*,*S*)-(+)-**27** in 72% yield. Demethylation of (*S*,*S*,*S*,*S*)-(+)-**27** with sodium ethanethiolate gave (*S*,*S*,*S*,*S*)-(+)-**28** in 92% yield. Oxidation of (*S*,*S*,*S*,*S*)-(+)-**28** with CAN gave (*S*,*S*,*S*,*S*)-(+)-**29** which was treated with 2,4-dinitrophenylhydrazine to give (*S*,*S*,*S*,*S*)-**2** in 73% yield from (*S*,*S*,*S*,*S*)-(+)-**28**.

The association constants (K_a) of the complexes of (*S*,*S*,*S*,*S*)-**2** with chiral amines 2-aminopropan-1-ol (**5**), 2-amino-2-phenylethanol (**6**), and 2-amino-3-methylbutan-1-ol (**7**) were determined in $CDCl_3$ over the temperature range of –30–+30 ºC by the non-linear least-squares method for the ^{1}H NMR spectral data of the complexation. Those of (*S*,*S*)-**1**, (*S*,*S*)-**3**, and (*S*,*S*,*S*,*S*)-**4** were determined over the temperature range of 7–50 ºC by the Rose–Drago method on the basis of UV-VIS spectral data of the complexes in chloroform. The observed K_a values at five different temperatures and interpolated ΔG values at 25 ºC are summarized in Tables 1–4. Thermodynamic parameters for complex formations were determined by linear regression based on the van't Hoff relation[14] of the K_a values and observed temperatures shown in Tables 1–4 and are summarized in Tables 5–8.

As shown in Tables 1 and 3, (*S*,*S*)-**1** and (*S*,*S*)-**3** form complexes with *R* enantiomers of the amines at 25 ºC selectively with the $\Delta\Delta G$ values of 2–6 kJ mol^{-1}. On the other hand, in most cases, (*S*,*S*,*S*,*S*)-**2** and (*S*,*S*,*S*,*S*)-**4** do not exhibit enantiomer-selectivity at rt since the $\Delta\Delta G$ values are 0–0.4 kJ mol^{-1} except for the case of (*S*,*S*,*S*,*S*)-**4** with (*S/R*)-**6**, as shown in Tables 2 and 4. In contrast to the $\Delta\Delta G$ values at 25 ºC, with regard to the enthalpy term ($\Delta\Delta H$), the enantiomer-selectivity of (*S*,*S*)-**1** and (*S*,*S*)-**3** is different as is that of (*S*,*S*,*S*,*S*)-**2** is different from that of (*S*,*S*,*S*,*S*)-**4**. Namely, both (*S*,*S*)-**1** and (*S*,*S*,*S*,*S*)-**2** are *S*-selective towards amine **5** ($\Delta\Delta H$ = –22 and –10 kJ mol^{-1}, respectively) and non-selective towards amines (**6**) and (**7**) ($\Delta\Delta H \leq \pm$ 2 kJ mol^{-1}) in the enthalpy term (Table 5 and 6). On the other hand, both (*S*,*S*)-**3** and (*S*,*S*,*S*,*S*)-**4** are *R*-selective in the enthalpy term ($\Delta\Delta H$ = +6 – 12 kJ mol^{-1}) except for the case of (*S*,*S*,*S*,*S*)-**4**/(+/–)-**7** (Tables 7 and 8). Thus it seems that the room temperature selectivity of (*S*,*S*)-**3** and (*S*,*S*,*S*,*S*)-**4** without methyl groups is same as that in the enthalpy term, while the room temperature selectivity of (*S*,*S*)-**1** and (*S*,*S*,*S*,*S*)-**2** having methyl groups is opposite from that in the enthalpy term.

Next, the enthalpies of the complexation of (*S*,*S*)-**1** and (*S*,*S*)-**3** are compared in more detail. ΔH of the complexation of (*S*,*S*)-**1** with (*S*)-**5** (–78 kJ mol^{-1}) is similar to that of (*S*,*S*)-**3** with (*S*)-**5** (–79 kJ mol^{-1}), whereas ΔH of the complexation of (*S*,*S*)-**1** with (*R*)-**5** (–56 kJ mol^{-1}) is different from that of (*S*,*S*)-**3** with (*R*)-**5** (–89 kJ mol^{-1}). The same trend is also observed for the complexation with amines (**6**) and (**7**) (for (*S*)-**6**: –67 vs. –69 kJ mol^{-1}; for (*S*)-**7**: –66 vs. –69 kJ mol^{-1}; for (*R*)-**6**: –66 vs. –81 kJ mol^{-1}; for (*R*)-**7**: –68 vs. –81 kJ mol^{-1}).

The large difference observed in the Δ*H* term towards (*R*)-amines may be rationalized in terms of the host-guest interactions between the aromatic rings of the host and the substituents of the guest on the basis of the predicted geometries of the complexes having three NH–O and one OH–O hydrogen bonds as shown in Figure 4. Namely, the *R*-selectivity of (*S*,*S*)-**3** observed at rt towards **6** was explained in terms of attractive interactions between the phenyl substituent of the host and the phenyl substituent of

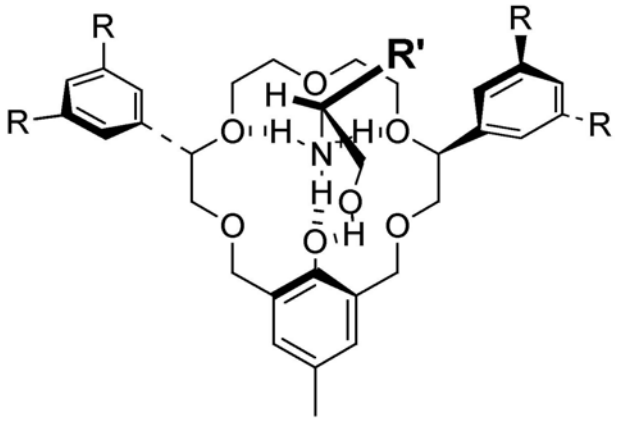


Figure 4. Predicted geometries of complexes of (*S*,*S*)-**1** (R=CH_3) and (*S*,*S*)-**3** (R=H) with (*R*)-**5**–**7** (R'=CH_3, Ph, i-Pr).

the guest, which was assumed to be more favorable in complexation with the (*R*)-amine than with the (*S*)-amine.[15] Similarly, the (*R*)-selectivities of (*S*,*S*)-**3** in the Δ*H* terms with amines (**5**) and (**7**) may be ascribed to an attractive van der Waals interaction between the phenyl group of the host and the alkyl group of the (*R*)-enantiomer of the guests, which stabilizes (*R*)-complex more than (*S*)-complex. On the other hand, because of the steric hindrance of the additional methyl groups, the complexation formation with the (*R*)-amines becomes unfavorable, making the Δ*H* values larger than the corresponding Δ*H* of (*S*,*S*)-**3** with the (*R*)-amines. A similar tendency is observed also between the pair of the hosts, [(*S*,*S*,*S*,*S*)-**2**] and [(*S*,*S*,*S*,*S*)-**4**] which possess fused cyclohexane rings as additional chiral barriers. Namely, complexation of (*S*,*S*,*S*,*S*)-**4** with (*R*)-**5** and (*R*)-**6** is more favorable than that with the corresponding (*S*)-amines in the enthalpy term because of attractive interaction, whereas almost the same Δ*H* values are observed for the complexation of (*S*,*S*,*S*,*S*)-**2** with the both amines owing to the steric repulsion arisen in the complexes with the (*R*)-amines due to the methyl groups. In general, the fact that the Δ*H* values of (*S*,*S*,*S*,*S*)-**2** and (*S*,*S*,*S*,*S*)-**4** are smaller than those of the corresponding values of (*S*,*S*)-**1** and (*S*,*S*)-**3** can be explained in terms of the steric hindrance of the cyclohexane ring. Although enantiomer-selectivites of (*S*,*S*)-**3** and (*S*,*S*,*S*,*S*)-**4** observed at 25 ºC are same as those in the enthalpy terms, i.e., *R*-selectivity, the enantiomer-selectivities of (*S*,*S*)-**1** and (*S*,*S*,*S*,*S*)-**2** at 25 ºC are opposite from those in the enthalpy term.

Table 1 The association constants for the complexes of (*S*,*S*)-**1** with chiral amines (**5**–**7**) in $CHCl_3$[a]

Amine	K_a / mL mol^{-1}					ΔG^b / kJ mol^{-1}
(*S*)-**5**	(1.90±0.07)×10^4 (19.5 ºC)	(8.92±0.85)×10^3 (26.4 ºC)	(5.32±0.36)×10^3 (31.8 ºC)	(2.27±0.08)×10^3 (39.6 ºC)	(1.63±0.04)×10^3 (44.0 ºC)	–23.0
(*R*)-**5**	(3.83±0.33)×10^4 (19.5 ºC)	(3.01±0.32)×10^4 (23.4 ºC)	(1.80±0.12)×10^4 (30.8 ºC)	(8.86±0.92)×10^3 (36.6 ºC)	(7.08±0.43)×10^3 (44.0 ºC)	–25.2
(*S*)-**6**	(4.01±0.19)×10^3 (18.9 ºC)	(2.14±0.30)×10^3 (26.6 ºC)	(1.55±0.11)×10^3 (32.1 ºC)	(8.74±0.52)×10^2 (36.6 ºC)	(4.16±0.17)×10^2 (45.0 ºC)	–19.3
(*R*)-**6**	(6.54±0.16)×10^4 (15.8 ºC)	(2.58±0.20)×10^4 (27.6 ºC)	(1.85±0.81)×10^4 (32.1 ºC)	(1.15±0.12)×10^4 (36.6 ºC)	(4.35±0.34)×10^3 (45.0 ºC)	–25.5
(*S*)-**7**	(4.22±0.20)×10^3 (19.5 ºC)	(1.89±0.10)×10^3 (26.8 ºC)	(1.25±0.15)×10^3 (31.8 ºC)	(8.28±0.23)×10^2 (36.6 ºC)	(4.21±0.22)×10^2 (44.0 ºC)	–19.1
(*R*)-**7**	(2.12±0.11)×10^4 (15.8 ºC)	(8.47±0.96)×10^3 (25.8 ºC)	(5.81±0.25)×10^3 (29.8 ºC)	(3.31±0.48)×10^3 (36.6 ºC)	(1.57±0.05)×10^3 (44.0 ºC)	–22.6

a) Temperatures of the measurements are given in parentheses. b) At 25 ºC.

Table 2 The association constants for the complexes of (*S*,*S*,*S*,*S*)-**2** with chiral amines (**5**–**7**) in $CDCl_3$ [a]

Amine	K_a / mL mol^{-1}					ΔG^b / kJ mol^{-1}
(*S*)-**5**	(8.57±0.55)×10^3 (–30.2 ºC)	(2.95±0.16)×10^3 (–15.2 ºC)	(6.70±0.40)×10^2 (0.2 ºC)	(1.76±0.12)×10^2 (14.9 ºC)	(5.78±0.49)×10 (29.9 ºC)	–11.1
(*R*)-**5**	(3.84±0.65)×10^3 (–30.2 ºC)	(1.58±0.15)×10^3 (–15.2 ºC)	(4.40±0.26)×10^2 (0.2 ºC)	(1.73±0.06)×10^2 (14.9 ºC)	(6.85±0.22)×10 (29.9 ºC)	–11.3
(*S*)-**6**	(4.16±0.36)×10^2 (–30.2 ºC)	(1.27±0.05)×10^2 (–15.2 ºC)	(3.72±0.12)×10 (0.2 ºC)	(1.18±0.06)×10 (14.9 ºC)	4.25±0.25 (29.9 ºC)	–4.5
(*R*)-**6**	(4.23±0.33)×10^2 (–30.2 ºC)	(1.19±0.04)×10^2 (–15.2 ºC)	(3.50±0.12)×10 (0.2 ºC)	(1.20±0.06)×10 (14.9 ºC)	4.58±0.25 (29.9 ºC)	–4.5
(*S*)-**7**	(8.40±0.23)×10^2 (–30.2 ºC)	(1.96±0.05)×10^2 (–15.2 ºC)	(5.42±0.11)×10 (0.2 ºC)	(1.98±0.03)×10 (14.9 ºC)	7.38±0.23 (29.9 ºC)	–5.7
(*R*)-**7**	(1.04±0.03)×10^3 (–30.2 ºC)	(2.33±0.04)×10^2 (–15.2 ºC)	(7.87±0.25)×10 (0.2 ºC)	(2.28±0.05)×10 (14.9 ºC)	8.60±0.30 (29.9 ºC)	–6.1

a) Temperatures of the measurements are given in parentheses. b) At 25 ºC.

Table 3 The association constants for the complexes of (*S*,*S*)-**3** with chiral amines (**5**–**7**) in $CHCl_3$ [a]

Amine	K_a / mL mol^{-1}					ΔG^b / kJ mol^{-1}
(*S*)-**5**	(2.84±0.25)×10^4 (13.1 ºC)	(7.77±0.64)×10^3 (25.0 ºC)	(4.03±0.30)×10^3 (30.5 ºC)	(2.44±0.23)×10^3 (33.9 ºC)	(1.12±0.10)×10^3 (44.2 ºC)	–22.1
(*R*)-**5**	(1.66±0.16)×10^5 (13.1 ºC)	(3.82±0.22)×10^4 (25.0 ºC)	(1.50±0.08)×10^4 (30.5 ºC)	(1.03±0.07)×10^4 (33.9 ºC)	(4.32±0.33)×10^3 (44.2 ºC)	–25.9
(*S*)-**6**	(3.68±0.15)×10^3 (16.5 ºC)	(1.66±0.09)×10^3 (26.3 ºC)	(1.07±0.03)×10^3 (30.2 ºC)	(6.56±0.07)×10^2 (36.0 ºC)	(3.12±0.30)×10^2 (44.0 ºC)	–18.2
(*R*)-**6**	(5.31±0.60)×10^4 (16.5 ºC)	(1.95±0.14)×10^4 (26.3 ºC)	(1.56±0.15)×10^4 (30.2 ºC)	(7.15±0.32)×10^3 (36.0 ºC)	(2.83±0.18)×10^3 (44.0 ºC)	–22.1
(*S*)-**7**	(3.32±0.33)×10^3 (16.9 ºC)	(1.69±0.35)×10^3 (25.0 ºC)	(9.84±0.34)×10^2 (30.3 ºC)	(6.12±0.29)×10^2 (35.7 ºC)	(2.85±0.24)×10^2 (44.1 ºC)	–18.5
(*R*)-**7**	(1.93±0.07)×10^4 (16.8 ºC)	(7.53±0.66)×10^3 (25.0 ºC)	(4.01±0.09)×10^3 (30.3 ºC)	(2.58±0.12)×10^3 (35.7 ºC)	(1.07±0.11)×10^3 (44.1 ºC)	–24.9

a) Temperatures of the measurements are given in parentheses. b) At 25 ºC.

Table 4 The association constants for the complexes of (*S*,*S*,*S*,*S*)-**4** with chiral amines (**5**–**7**) in $CHCl_3$[a]

Amine	K_a / mL mol^{-1}					ΔG^b / kJ mol^{-1}
(*S*)-**5**	(1.74±0.09)×10^2 (7.3 ºC)	(1.31±0.07)×10^2 (11.0 ºC)	(1.12±0.06)×10^2 (15.0 ºC)	(8.92±0.47)×10 (19.8 ºC)	(6.5±1.0)×10 (24.7 ºC)	–10.4
(*R*)-**5**	(2.07±0.15)×10^2 (7.1 ºC)	(1.57±0.05)×10^2 (11.0 ºC)	(1.20±0.06)×10^2 (15.1 ºC)	(1.01±0.05)×10^2 (19.9 ºC)	(6.46±0.56)×10 (24.7 ºC)	–10.4
(*S*)-**6**	(1.44±0.14)×10 (15.2 ºC)	(1.11±0.11)×10 (19.9 ºC)	9.4±1.2 (24.9 ºC)	6.7±1.5 (29.7 ºC)	5.4±1.1 (39.1 ºC)	–5.5
(*R*)-**6**	(6.08±0.31)×10 (15.2 ºC)	(4.54±0.28)×10 (19.8 ºC)	(3.38±0.30)×10 (24.6 ºC)	(2.56±0.21)×10 (29.3 ºC)	(1.62±0.23)×10 (38.7 ºC)	–8.7
(*S*)-**7**	(4.19±0.40)×10 (7.2 ºC)	(3.39±0.39)×10 (11.1 ºC)	(2.79±0.71)×10 (15.2 ºC)	(2.13±0.27)×10 (19.9 ºC)	(1.73±0.15)×10 (24.6 ºC)	–7.0
(*R*)-**7**	(4.49±0.18)×10 (7.2 ºC)	(3.49±0.10)×10 (11.1 ºC)	(2.95±0.11)×10 (15.2 ºC)	(2.21±0.16)×10 (19.8 ºC)	(1.80±0.16)×10 (24.6 ºC)	–7.1

a) Temperatures of the measurements are given in parentheses. b) At 25 ºC.

Table 5 Thermodynamic parameters for complexation of (*S*,*S*)-**1** with chiral amines (**5**–**7**) in $CHCl_3$

Amine	ΔH kJ mol^{-1}	ΔS J mol^{-1} K^{-1}	$\Delta\Delta H$ [a] kJ mol^{-1}	$\Delta\Delta S$ [b] J mol^{-1} K^{-1}	T_{iso} [c] ºC
(*S*)-**5**	–78±4	–186±14	–22	–84	–1.9
(*R*)-**5**	–56±8	–102±26			
(*S*)-**6**	–67±5	–161±16	–1	–24	–226
(*R*)-**6**	–66±7	–137±23			
(*S*)-**7**	–66±5	–158±15	+2	–6	–548
(*R*)-**7**	–68±2	–152±7			

a) $\Delta\Delta H = \Delta H_S - \Delta H_R$. b) $\Delta\Delta S = \Delta S_S - \Delta S_R$. c) Isoenantioselective temperature.

Table 6 Thermodynamic parameters for complexation of (*S*,*S*,*S*,*S*)-**2** with chiral amines (**5**–**7**) in $CDCl_3$

Amine	ΔH kJ mol^{-1}	ΔS J mol^{-1} K^{-1}	$\Delta\Delta H$ [a] kJ mol^{-1}	$\Delta\Delta S$ [b] J mol^{-1} K^{-1}	T_{iso} [c] ºC
(*S*)-**5**	–52±7	–137±26	–10	–35	+20
(*R*)-**5**	–42±5	–102±18			
(*S*)-**6**	–47±3	–143±11	–1	–3	+1.2
(*R*)-**6**	–46±1	–140±4			
(*S*)-**7**	–48±2	–142±8	+1	+0	+3100
(*R*)-**7**	–49±3	–142±9			

a) $\Delta\Delta H = \Delta H_S - \Delta H_R$. b) $\Delta\Delta S = \Delta S_S - \Delta S_R$. c) Isoenantioselective temperature.

Table 7 Thermodynamic parameters for complexation of (*S*,*S*)-**3** with chiral amines (**5**–**7**) in $CHCl_3$

Amine	ΔH kJ mol^{-1}	ΔS J mol^{-1} K^{-1}	$\Delta\Delta H$ [a] kJ mol^{-1}	$\Delta\Delta S$ [b] J mol^{-1} K^{-1}	T_{iso} [c] ºC
(*S*)-**5**	–79±2	–190±8	+10	+23	+194
(*R*)-**5**	–89±7	–213±23			
(*S*)-**6**	–69±7	–169±22	+12	+20	+338
(*R*)-**6**	–81±8	–189±27			
(*S*)-**7**	–69±5	–171±18	+12	+25	+182
(*R*)-**7**	–81±5	–196±17			

a) $\Delta\Delta H = \Delta H_S - \Delta H_R$. b) $\Delta\Delta S = \Delta S_S - \Delta S_R$. c) Isoenantioselective temperature.

Table 8 Thermodynamic parameters for complexation of (*S*,*S*,*S*,*S*)-**4** with chiral amines (**5**–**7**) in $CHCl_3$

Amine	ΔH kJ mol^{-1}	ΔS J mol^{-1} K^{-1}	$\Delta\Delta H$ [a] kJ mol^{-1}	$\Delta\Delta S$ [b] J mol^{-1} K^{-1}	T_{iso} [c] ºC
(*S*)-**5**	–38±6	–91±21	+6	+20	+28
(*R*)-**5**	–44±10	–111±33			
(*S*)-**6**	–32±9	–89±28	+10	+24	+160
(*R*)-**6**	–42±3	–113±9			
(*S*)-**7**	–36±2	–96±7	+0	+2	+62
(*R*)-**7**	–36±4	–98±13			

a) $\Delta\Delta H = \Delta H_S - \Delta H_R$. b) $\Delta\Delta S = \Delta S_S - \Delta S_R$. c) Isoenantioselective temperature.

In conclusion, by using pairs of structurally similar host compounds, it was found that the host-guest systems that have same enantiomer-selectivities at 25 ºC showed opposite selectivity in the enthalpy term owing to the contribution of an entropy term. This finding can thus provide an important criterion for designing host molecules. Namely, the consideration using molecular models or by computer simulation which are based on the enthalpy is not enough to predict enantiomer-selectivity at ambient temperature. Although the enthalpy-entropy compensation rule[16] is always observed, it is difficult to predict enantiomer-selectivity at the ambient temperature at the present stage, because a small deviation of a linear relationship between enthalpy and entropy causes significant difference in enantiomer-selectivity at ambient temperature; the entropy term affects to large extent on enantiomer-selectivity at ambient temperature. For example, the complexation of (*S*,*S*)-**1** with (*S*/*R*)-**6** exhibits large entropy difference ($\Delta\Delta S$= –24 J mol^{-1} K^{-1}) and small enthalpy difference ($\Delta\Delta H$= –1 kJ mol^{-1}). As a result, the enantiomer–selectivity observed at ambient temperature is substantially high ($\Delta\Delta G$= –6.2 kJ mol^{-1}).

In addition, like the previous hosts with a 2,4-dinitrophenylazo group,[3] the new hosts [(*S*,*S*)-**1**] and [(*S*,*S*,*S*,*S*)-**2**] also serve as enantiomer-selective color indicators for chiral amines. Figure 5 shows, as an example, the color and spectral changes of (*S*,*S*)-**1** upon complexation with (*R*)-**6** and (*S*)-**6**. The color of a solution of (*S*,*S*)-**1** in chloroform at 25 ºC is light yellow (Figure 5a). The absorption maximum of (*S*,*S*)-**1** appears at 402 nm as shown in UV-VIS spectrum (solid line). When (*R*)-**6** was added to the solution, the color turned to bright red (Figure 5b) by a generation of complex having λmax at 559 nm. The spectrum is shown with dotted line. In contrast, when (*S*)-**6** was added to the solution, the spectral change is small (dashed line) and the color did not changed so much (Figure 5c). Because of the high enantiomer-selectivity of (*S*,*S*)-**1** towards amine (**6**) at rt, the chirality of **6** can thus be readily identified from the color of the solution by the naked eye.

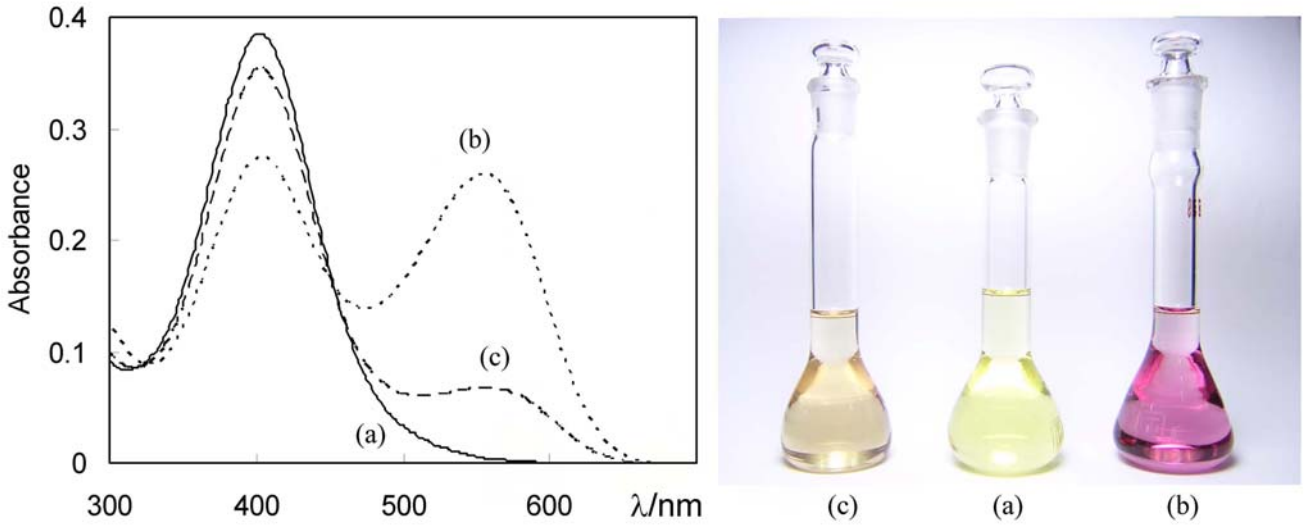


Figure 5. UV-VIS spectra and corresponding pictures: (a) A chloroform solution of (*S*,*S*)-**1** (1.85×10^{-5} M) at 25 °C (solid line); (b) The same solution as (a) containing 2 equivalent of (*R*)-**6** (dotted line); (c) The same solution as (a) containing 2 equivalent of (*S*)-**6** (dashed line).

EXPERIMENTAL

General

^{1}H NMR spectra were recorded on a JEOL GSX-270 and a JEOL AL-400 spectrometers for solutions in $CDCl_3$ with $SiMe_4$ as an internal standard and *J* values are given in Hz. ^{13}C NMR spectra were recorded at 75.5 MHz on a JEOL GSX-270 spectrometer and chloroform (δC 77.0) was used as a chemical shift reference. Multiplicities for ^{1}H NMR spectra are as follows: singlet (s), doublet (d), triplet (t), quartet (q), multiplet (m). Multiplicities for ^{13}C NMR spectra are as follows: primary (p), secondary (s), tertiary (t), quaternary (q). IR spectra were measured on a JASCO FT/IR–410 spectrophotometer. Optical rotations were measured using a JASCO DIP–40 polarimeter and [α] values are given in units of 10^{-1} deg cm^2 g^{-1}. MS spectra were recorded with 3-nitrobenzyl alcohol as a matrix on a JEOL-DX-303-HF spectrometer. X-Ray analysis was carried out on a Rigaku RAXIS-RAPID Imaging plate diffractometer, using graphite monochromated Mo Kα radiation. The intensity data were computed by teXsan Single Crystal Structure Analysis Software Version 1.11. The structure was solved by direct methods (SHELXS) and refined by full-matrix least squares techniques against Fo^2 (SHELXL-97). The hydrogen atoms were included at calculated positions with fixed thermal parameters. All non-hydrogen atoms were refined anisotropically. Elemental analyses were carried out by a PERKIN ELMER 2400 II CHNS analyzer. Melting points are uncorrected. HPLC analyses were carried out on a Shimadzu LC-6A chromatograph equipped with a UV photometric detector. GLC analyses were performed on a Shimadzu GS-8A chromatograph using SE-52 as a stationary phase in a glass column. Lipase QL (from *Alcaligenes* sp.) and lipase YS (from *Pseudomonas fluorescens*) were supplied by Meito Sangyo and by the Amano Pharmaceutical Co.,

respectively, and used as obtained. The chiral amines were purchased from Aldrich Chemical Company, Inc. Amine [(*S*)-**6**] was used after recrystallization from benzene–hexane[16] and the other amines were used as obtained.

1-(3,5-Dimethylphenyl)ethane-1,2-diol ((±)-**8**)

1,2-Dibromoethane (0.1 mL, 0.1 mol) was added to a suspension of granular magnesium (2.74 g, 113 mg atom) in dry ether (10 mL) with stirring under a nitrogen atmosphere. A solution of 1-bromo-3,5-dimethylbenzene (18.4 g, 99 mmol) in 65 mL of dry ether was added to the above suspension to furnish a Grignard reagent. The solution was added dropwise to a solution of dichloro[1,3-bis(diphenylphosphino)propane]nickel (0.052 g, 0.096 mmol) and bromoethene (37.8 g, 0.354 mol) in 65 mL of dry ether at 0 °C while cooling in an ice-salt bath. After stirring at 0 °C for 2 h, the reaction mixture was kept in a refrigerator overnight. After quenching by addition of 2N hydrochloric acid (18 mL), the mixture was extracted with ether. The extract was washed with water, saturated aqueous $NaHCO_3$, brine and dried over $MgSO_4$. The solvent was evaporated and the residual brown oil was chromatographed on SiO_2 (hexane) to afford 3,5-dimethylstyrene as a colorless oil (7.88 g, 60%). A solution of 3,5-dimethylstyrene (0.149 g, 1.13 mmol) in THF (2.3 mL) was add dropwise to a solution of *N*-methylmorphorine-*N*-oxide (0.205 g, 0.682 mmol) and osmium tetraoxide (0.012 g, 0.047 mmol) in *tert*-butanol (2.7 mL) and water (0.3 mL) over 30 min. After stirring for 3 h at rt, a 0.2 M solution of sodium bisulfate (5 mL) was added to the solution. After stirring for 15 min, the mixture was extracted 3 times with chloroform. The organic layer was washed with brine and dried over anhydrous $MgSO_4$. Evaporation of the solvent gave dark brown solid, which was chromatographed on SiO_2 (hexane:ethyl acetate=2:1) to afford (±)-**8** (0.168 g) as a colorless solid (90%). mp 49–51 °C from hexane-ethyl acetate; IR (KBr) 3334, 2917, 1608, 1460, 1354, 1101, 1079, 1031, 848, 715, 692 cm^{-1}; δ_H (400 MHz, $CDCl_3$): 2.04 (1H, br s, OH), 2.31 (6H, s, $ArCH_3$), 2.46 (1H, s, OH), 3.66 (1H, dd *J* 7.9 and 11.2, CH_2), 3.74 (1H, dd *J* 3.7 and 11.2, CH_2), 4.75 (1H, dd *J* 3.7 and 7.9, CH), 6.93 (1H, br s, ArH), 6.97 (2H, br s, ArH); MS (EI) *m/z* 166 (M^+); *Anal.* Calcd for $C_{10}H_4O_2$: C, 72.26; H, 8.49. Found: C, 72.02; H, 8.44.

Kinetic resolution of (±)-**8**

1,2-Diacetoxy-1-(3,5-dimethylphenyl)ethane ((+)-**9**)

A mixture of (±)-**8** (6.93 g, 41.7 mmol), lipase QL (4.89 g), and isopropenyl acetate (17.6 g, 176 mmol) in cyclohexane (400 mL) was stirred at 30 °C for 12 h. The reaction was terminated by filtration of the enzyme and volatile materials were removed under reduced pressure. Silica gel chromatography of the residue gave monoacetate of the primary hydroxy group **(**hexane:ethyl acetate=9:1–1:4) (5.39 g), monoacetate of the secondary hydroxy group (0.50 g), unreacted diol (0.098 g), and (+)-**9** (3.04 g, 29%). $[\alpha]_D^{26}$ +62.6° (*c* 1.03, chloroform) (93% ee by HPLC using a chiral column; Opti-pak XC, Waters,

hexane: ethanol=15:5 as an eluent, flow rate 0.2 mL/min, t_S=37.9, t_R=42.4 min); IR (neat film) 3014, 2953, 2920, 1744, 1609, 1436, 1371, 1222, 1044, 851, 703, 603 cm^{-1}; δ_H (400 MHz, $CDCl_3$): 2.06 (3H, s, $OCOCH_3$), 2.11 (3H, s, $OCOCH_3$), 2.31 (6H, s, $ArCH_3$), 4.24–4.32 (2H, m, CH_2(OAc)), 5.94 (1H, dd *J* 4.5 and 7.5, CH(OAc)), 6.96 (3H, s, ArH); MS (FAB) *m/z* 251 (M^++1).

(+)-(*S*)-1-(3,5-Dimethylphenyl)ethane-1,2-diol ((+)-(*S*)-**8**)

A mixture of (+)-(*S*)-**9** (6.71g, 26.8 mmol, 93% ee by HPLC) and K_2CO_3 (4.11 g, 29.7 mmol) in methanol (35 mL) and water (3.5 mL) was stirred at rt for 6 h. The mixture was diluted with water and extracted with ethyl acetate. The extract was washed with brine and dried over anhydrous $MgSO_4$. Evaporation of the solvent under reduced pressure gave (+)-(*S*)-**8** (4.41 g, 90% ee by HPLC; Opti-Pak XC, hexane:ethyl acetate=95:5, flow rate 0.2 mL/min, t_R = 96.5, t_S = 107.5 min). mp 46–48 °C; $[\alpha]_D^{26}$ +47.0° (*c* 1.01, chloroform) (90% ee by HPLC); IR (KBr) 3376, 2918, 1609, 1459, 1164, 1086, 1043, 871, 848, 703 cm^{-1}; δ_H (400 MHz, $CDCl_3$): 2.04 (1H, br s, OH), 2.31 (6H, s, $ArCH_3$), 2.38 (1H, br s, OH), 3.67 (1H, dd *J* 7.9 and 11.2, OCH_2), 3.75 (1H, dd *J* 3.7 and 11.2, OCH_2), 4.76 (1H, dd *J* 3.7 and 7.9, CH), 6.94 (1H, s, ArH), 6.98 (2H, s, ArH); MS (FAB) *m/z* 167 (M^++1); *Anal.* Calcd for $C_{10}H_4O_2$: C, 72.26; H, 8.49. Found: C, 72.02; H, 8.44.

(+)-(*S*)-1-(3,5-Dimethylphenyl)-2-triphenylmethoxyethanol ((+)-(*S*)-**10**)

To a solution of triethylamine (1.46 g, 14.4 mmol) in dry DMF (20 mL) was added dropwise triphenylmethyl chloride (1.79 g, 6.41 mmol), 4-dimethylaminopyridine (43 mg, 0.352 mmol), and (+)-(*S*)-**8** (0.968 g, 5.82 mmol). After stirring for 19 h, water (10 mL) was added slowly with cooling in an ice-bath. The mixture was extracted with chloroform. The combined extracts were washed with aqueous NH_4Cl and brine and dried over $MgSO_4$. The solvent was evaporated under reduced pressure. Silica gel chromatography of the residue gave (+)-(*S*)-**10** (hexane:ethyl acetate=19:1) (1.48 g, 62%). Recrystallization from chloroform–ethanol gave (+)-(*S*)-**10** (620 mg) as colorless needles (>99% ee by HPLC, Opti-Pak XC, hexane:ethanol=95:5, flow rate 0.2 mL/min, t_R = 68.0, t_S = 72.5 min). mp 167–168 °C; $[\alpha]_D^{25}$ +12.1° (*c* 1.01, chloroform) (>99% ee, by HPLC); IR (KBr) 3446, 3019, 2920, 2875, 1605, 1490, 1447, 1223, 1155, 1098, 1065, 992, 849, 771, 745, 709 cm^{-1}; δ_H (400 MHz, $CDCl_3$, 30 °C): 2.26 (6H, s, $ArCH_3$), 2.69 (1H, d *J* 2.4, OH), 3.25–3.35 (2H, m, CH_2OCPh_3), 4.69–4.72 (1H, m, CH), 6.85 (2H, br s, ArH), 6.87 (1H, br s, ArH), 7.20–7.52 (15H, m, CPh_3); MS (FAB) *m/z* 408 (M^+); *Anal.* Calcd for $C_{29}H_{28}O_2$: C, 85.26; H, 6.91. Found: C, 85.23; H, 6.98.

(+)-(2*S*,10*S*)-1,11-Bis(triphenylmethoxy)-2,10-bis(3,5-dimethylphenyl)-3,6,9-trioxaundecane ((+)-**11**)

A solution of (+)-(*S*)-**10** (1.77 g, 4.33 mmol) in dry THF (40 mL) was added to a suspension of 60% sodium hydride (0.701 g, 17.5 mmol) in dry THF (30 mL) and the mixture was then refluxed for 2 h. A

solution of diethylene glycol bis-(*p*-toluenesulfonate) (1.02 g, 2.45 mmol) in dry THF (50 mL) was slowly added to the mixture at rt. After being refluxed for 16 h, the mixture was cooled to rt. Additional sodium hydride (1.11 g, 27.8 mmol) was added to the mixture, and then the mixture was refluxed for 6 h. After cooling to rt, another sodium hydride (1.13 g, 28.2 mmol) and diethylene glycol bis(*p*-toluenesulfonate) (0.568 g, 1.37 mmol) were added to the reaction mixture and then the mixture was refluxed for further 18 h. After another addition of sodium hydride (1.02 g, 25.5 mmol) the mixture was refluxed for 4 h. After water was slowly added to the reaction mixture with ice-cooling, the mixture was concentrated under reduced pressure. The residue was extracted with chloroform and the combined extracts were washed with brine and dried over $MgSO_4$. After removal of the solvent under reduced pressure, the products were chromatographed on silica gel to give (*S,S*)-**11** (hexane:ethyl acetate=19:1) (1.27 g, 66%) as a colorless powder. mp 53–55 °C; $[\alpha]_D^{25}$ +1.10° (*c* 0.273, chloroform); IR (KBr) 3419, 3057, 3022, 2919, 2866, 2359, 2341, 1607, 1490, 1448, 1338, 1218, 1076, 1033, 850, 765, 746, 704 cm^{-1}; δ_H (400 MHz, $CDCl_3$): 2.25 (12H, s, $ArCH_3$), 3.11 (2H, dd *J* 5.1 and 9.5, CH_2OCPh_3), 3.39 (2H, dd *J* 6.8 and 9.5, CH_2OCPh_3), 3.49–3.68 (8H, m, OCH_2CH_2O), 4.31 (2H, dd *J* 5.1 and 6.8, CH), 6.84 (4H, s, ArH), 6.87 (2H, s, ArH), 7.14–7.25 (18H, m, CPh_3) and 7.35 (12H, d *J* 7.6, CPh_3); MS (FAB) *m/z* 888 (M^++1); *Anal.* Calcd for $C_{62}H_{62}O_5$: C, 83.94; H, 7.04. Found: C, 83.66; H, 7.17.

(+)-(2*S*,10*S*)-2,10-Bis(3,5-dimethylphenyl)-3,6,9-trioxaundecane-1,11-diol ((+)-**12**)

A solution of (*S,S*)-**11** (1.47 g, 1.65 mmol) in methanol (75 mL) containing *p*-toluenesulfonic acid (1.36 g, 7.12 mmol) was stirred at rt for 4 h. After being neutralized with saturated aqueous $NaHCO_3$, the mixture was concentrated under reduced pressure. The residue was extracted with chloroform and the combined extracts were washed with brine, dried over $MgSO_4$, and evaporated under reduced pressure. Silica gel chromatography of the products gave (*S,S*)-**12** (hexane:ethyl acetate=4:1) (558 mg, 84%) as a colorless oil. $[\alpha]_D^{28}$ +74.6° (*c* 0.267, chloroform); IR (neat film) 3420, 3013, 2915, 2869, 1605, 1460, 1339, 1102, 1045, 947, 849, 706 cm^{-1}; δ_H (300 MHz, $CDCl_3$): 2.32 (12H, s, CH_3), 3.59–3.76 (12H, m, CH_2), 4.21 (2H, d *J* 8.2, OH), 4.45 (2H, dd *J* 3.2 and 9.2, OCH), 6.94 (6H, s, ArH); MS (FAB) *m/z* 404 (M^++1).

(5*S*,13*S*)-(+)-19,21-Dimethoxy-5,13-bis(3,5-dimethylphenyl)-3,6,9,12,15-pentaoxabicyclo[15.3.1]-heneicosa-1(21),17,19-triene ((+)-**13**)

A solution of (+)-**12** (103 mg, 0.225 mmol) and 1,3-bis(bromomethyl)-2,5-dimethoxybenzene (82 mg, 0.259 mmol) in dry THF (35 mL) was slowly added to a suspension of 60% sodium hydride (63 mg, 1.57 mmol) in dry THF (20 mL) over a 3.5 h period and the mixture was stirred for further 4.5 h under reflux under a nitrogen atmosphere. After a small amount of water was 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 brine, dried over $MgSO_4$, and evaporated under

reduced pressure. Silica gel chromatography of the products gave (*S*,*S*)-**13** (hexane:ethyl acetate=4:1) (101 mg, 70%). mp 47–48 °C from hexane-ethyl acetate; $[\alpha]_D^{25}$ +112° (*c* 0.919, chloroform); IR (KBr) 3006, 2902, 1607, 1483, 1359, 1335, 1252, 1224, 1094, 999, 851, 799, 710 cm^{-1}; δ_H (300 MHz, $CDCl_3$): 2.32 (12H, s, $ArCH_3$), 3.43-3.75 (2H, m, CH_2), 3.81 (3H, s, OCH_3), 4.21 (3H, s, OCH_3), 4.44 (2H, m, CH), 4.45 (2H, d *J* 10.7, $ArCH_2$), 4.48 (2H, d *J* 10.7, $ArCH_2$), 6.86 (2H, s, ArH on 18, 20 positions) and 6.93 (6H, s, ArH); MS (FAB) *m/z* 565 (M^++1).

(5*S*,13*S*)-(+)-21-Hydroxy-19-methoxy-5,13-bis(3,5-dimethylphenyl)-3,6,9,12,15-pentaoxabicyclo-[15.3.1]heneicosa-1(21),17,19-triene (**14**)

Ethanethiol (550 mg, 8.85 mmol) was slowly added to a suspension of 60% sodium hydride (297 mg, 7.42 mmol) in dry DMF (4.5 mL) at 0–5 °C under a nitrogen atmosphere and then a solution of (*S*,*S*)-**13** (197 mg, 0.348 mmol) in dry DMF (7 mL) was added to the resulting clear solution. The reaction mixture was stirred for 2 h at 90 °C. After the reaction mixture was acidified (pH = *ca*. 4) with 6 M hydrochloric acid with ice-cooling, the volatile materials were evaporated under reduced pressure and the residue was extracted with ethyl acetate. The combined extracts were washed with water, dried over $MgSO_4$, and evaporated under reduced pressure. Silica gel chromatography of the products gave (*S*,*S*)-**14** (hexane:ethyl acetate=4:1) (152 mg, 80%). $[\alpha]_D^{25}$ +104° (*c* 0.163, chloroform); δ_H (300 MHz, $CDCl_3$): 2.30 (12H, s, $ArCH_3$), 3.59-3.77 (12H, m, CH_2), 3.74 (3H, s, OCH_3), 4.57 (2H, dd *J* 2.8 and 8.8, CH), 4.73 (4H, s, $ArCH_2$), 6.72 (2H, s, ArH), 6.92 (6H, s, ArH), 7.66 (1H, s, ArOH); MS (EI) *m/z* 550 (M^+).

(5*S*,13*S*)-21-Hydroxy-5,13-bis(3,5-dimethylphenyl)-19 -(2,4-dinitrophenylazo)-3,6,9,12,15-pentaoxabicyclo[15.3.1]heneicosa-1(21),17,19-triene (**1**)

A solution of (*S*,*S*)-**14** (152 mg, 0.276 mmol) in acetonitrile (10 mL) was added to a solution of cerium(IV) ammonium nitrate (CAN) (301 mg, 0.549 mmol) in acetonitrile (17 mL) and then the mixture was stirred at rt for 1.5 h. After dilution with water, the mixture was concentrated under reduced pressure and extracted with chloroform. The combined extracts were washed with water, dried over $MgSO_4$, and concentrated under reduced pressure. Silica gel chromatography of the residue gave (*S*,*S*)-(+)-5,13-Bis(3,5-dimethylpheny1)-3,6,9,12,15-pentaoxabicyclo[15.3.1]heneicosa-17,20(1)-diene-19,21-dione (hexane:ethyl acetate=4:1) (143 mg, 97%) as a yellow solid. IR (KBr) 3448, 2920, 1656, 1459, 1097, 947 cm^{-1}; δ_H (300 MHz, $CDCl_3$): 2.30 (12H, s, CH_3), 3.49–3.67 (12H, m, CH_2), 4.48 (2H, dd *J* 3.8 and 7.4, CH), 4.57(2H, d *J* 15.1, allylic CH_2), 4.68 (2H, d *J* 15.1, allylic CH_2), 6.76 (2H, s, quinone CH), 6.90 (6H, s, ArH). This material was immediately used for the next reaction.

A solution of 2,4-dinitrophenylhydrazine (155 mg, 0.782 mmol) in a mixture of ethanol (9 mL) and conc. H_2SO_4 (0.7 mL) was added to a solution of (*S*,*S*)-**15** (143 mg, 0.267 mmol) in a mixture of ethanol (7 mL) and chloroform (7 mL) and the mixture was stirred at rt for 4.5 h. After addition of water (400 mL), the

resulting mixture was extracted with chloroform. The combined extracts were washed with saturated aqueous $NaHCO_3$ and water, dried over $MgSO_4$, and concentrated under reduced pressure. Silica gel chromatography of the residue gave a solid (hexane:ethyl acetate=9:1) (166 mg), which was further purified by preparative recycling HPLC (JAIGEL 1H and 2H column, chloroform as an eluent) to give **1** (128 mg, 67%) as a reddish foam. mp 76–77 °C from $CHCl_3$. UV-VIS (chloroform): λ_{max} = 404 nm (ε 2.01×10^4); IR (KBr) 3306, 2910, 2869, 1603, 1535, 1471, 1428, 1343, 1288, 1118, 1023, 908, 849 cm^{-1}; δ_H (300 MHz, $CDCl_3$): 2.31 (12H, s, $ArCH_3$), 3.60–3.81 (12H, m, CH_2), 4.60 (2H, dd *J* 3.0 and 9.0, CH), 4.85 (4H, s, allylic CH_2), 6.94 (6H, s, ArH), 7.82 (1H, d *J* 8.8, $(NO_2)_2ArH$), 7.83 (2H, s ArH), 8.47 (1H, dd *J* 2.3 and 8.8 $(NO_2)_2ArH$), 8.74 (1H, d *J* 2.3 $(NO_2)_2ArH$), 9.17 (1H, s, OH); MS (FAB) *m/z* 715 (M^++1).

1-(3,5-Dimethylphenyl)cyclohexene (**15**)

A solution of 5-bromo-1,3-dimethylbenzene (25.0 g, 135 mmol) in dry ether (115 mL) was added slowly to granular magnesium (3.45 g, 142 mg atom) over a 20 min period and the mixture was then stirred for further 2.5 h at rt. A solution of cyclohexanone (11.0 g, 113 mmol) in dry ether (50 mL) was slowly added to the solution of 1,3-dimethylphenylmagnesium bromide with ice-cooling and then the mixture was stirred at rt for 2.5 h. After water (110 mL) was added to the reaction mixture, the mixture was acidified (pH = *ca.* 3) with 2N hydrochloric acid and extracted with a mixture of benzene, hexane, and ethyl acetate. The combined extracts were washed with saturated aqueous $NaHCO_3$ and water, dried over $MgSO_4$, and evaporated under reduced pressure. Silica gel chromatography of the products gave 1-(3,5-dimethylphenyl)cyclohexanol as a colorless oil (benzene as an eluent) (17.3 g, 76%). IR (neat film) 3428, 2933, 1603, 1447, 1179, 1035, 976, 847, 704 cm^{-1}; δ_H (270 MHz, $CDCl_3$) 1.26–1.85 (11H, m, CH_2, and OH), 2.32 (6H, s, CH_3), 6.89 (1H, br s, ArH), 7.12 (2H, br s, ArH); *m/z* (rel intensity) 204(M^+, 15) and 186 (100); HRMS (EI) *m/z* Calcd for $C_{14}H_{20}O$: 204.1514. Found: 204.1497.

A solution of 1-(3,5-dimethylphenyl)cyclohexanol (5.52 g, 27.0 mmol) and *p*-toluenesulfonic acid monohydrate (154 mg, 0.810 mmol) in benzene (200 mL) was refluxed for 1 h and the generated water was removed using a Dean-Stark trap. After being cooled to rt, the reaction mixture was washed with saturated aqueous $NaHCO_3$ and water and dried over $MgSO_4$. After removal of the solvent under reduced pressure, the products were chromatographed on silica gel to give **15** as a colorless oil (hexane as an eluent) (4.13 g, 82%); IR (neat film) 3024, 2928, 2861, 1601, 1447, 1377, 1336, 1033, 986, 919, 834 and 704 cm^{-1}; δ_H (270 MHz, $CDCl_3$) 1.60–1.81 (4H, m, CH_2), 2.16–2.28 (2H, m, CH_2), 2.29 (s, 6H, CH_3), 2.30–2.39 (2H, m, CH_2), 6.04–6.08 (1H, m, CH), 6.84 (1H, br s, ArH) and 6.97 (2H, br s, ArH); MS (EI) *m/z* 186 (M^+ 50); HRMS (EI) *m/z* Calcd for $C_{14}H_{18}$: 186.1409. Found: 186.1402.

(±)-*cis*-1-(3,5-Dimethylphenyl)cyclohexane-1,2-diol ((+)-**16**)

A 30% solution of hydrogen peroxide (7.4 mL) was slowly added to formic acid (21.0 g, 456 mmol) at 10 ºC and the mixture was then stirred at 15 ºC for 1 h. To the reaction mixture was slowly added **15** (5.00 g, 26.8 mmol) at 15–22 ºC and the resulting mixture was stirred at 22–25 ºC for 1 h and then at 35–42 ºC for 1.5 h. After a 15 % aqueous solution of sodium hydroxide (200 mL) was added to the reaction mixture at 0–5 ºC, the mixture was stirred at this temperature for 2.5 h and then extracted with ethyl acetate. The combined extracts were washed with water and dried over $MgSO_4$. After removal of the solvent under reduced pressure, the products were chromatographed on silica gel to give (±)-**16** (hexane:ethyl acetate=5:1) (3.91 g, 66%). mp 116–117 ºC after recrystallization from hexane–benzene; IR (KBr) 3365, 2936, 2857, 1605, 1445, 1374, 1334, 1297, 1179, 1095, 1078, 1030, 991, 947, 841, 822, 703 cm^{-1}; δ_H (270 MHz, $CDCl_3$) 1.38–1.88 (11H, m, CH_2, and OH), 2.33 (6H, s, CH_3), 2.51 (1H, d *J* 1.2 Hz, OH), 3.99 (1H, ddd *J* 3.7, 3.7 and 10.9 Hz, CH), 6.90 (1H, br s, ArH) and 7.11 (2H, br s, ArH); δC($CDCl_3$) 21.0 (s), 21.4 (p), 24.3 (s), 29.1 (s), 38.5 (s), 74.4 (t), 75.6 (q), 122.8 (t), 128.5 (t), 137.7 (q), 146.3 (q); MS (EI) *m/z* (rel intensity) 220 (M^+, 40) and 173 (100); *Anal.* Calcd for $C_{14}H_{20}O_2$: C, 76.33; H, 9.15. Found: C, 76.25; H, 9.32.

Optical resolution of (±)-**16**

A mixture of (±)-**16** (11.4 g, 51.7 mmol), lipase QL (11.0 g), and isopropenyl acetate (15.5 g, 155 mmol) in diisopropyl ether (700 mL) was stirred at 30 ºC for 23 h. The reaction was terminated at about 62% conversion (by GLC) by filtration of the enzyme and volatile materials were removed under reduced pressure. Silica gel chromatography of the residue gave (+)-**17 (**hexane:ethyl acetate=5:1) (6.60 g, 52%); $[\alpha]_D^{22}$ +28.9° (*c* 1.03, chloroform) (94% ee by HPLC using chiral column; CHIRALPAK AD, DAICEL, hexane:ethanol=98:2 as an eluent) and (+)-**16** (hexane:ethyl acetate=5:1) (4.82 g, 42%). mp 123–124 ºC after recrystallization from benzene–hexane; $[\alpha]_D^{22}$ +4.2° (*c* 0.936, chloroform) (>99% ee by HPLC using the same chiral column, hexane:ethanol=9:1 as an eluent). The spectral data of (+)-**16** were identical with those of (±)-**16**.

(–)-*trans*-1-2-Benzyloxycyclohexyl acetate ((+)-**19**)

A solution of (±)-**21** (1.00 g, 8.61 mmol) was slowly added to a suspension of 60% sodium hydride (1.13 g, 47.2 mmol) in dry THF (75 mL) and then the resulting mixture was stirred at rt for 2 h. To the reaction mixture was added a solution of benzyl bromide (22.0 g, 129 mmol) and the mixture was refluxed for 12 h. After a small amount of water was carefully added to the reaction mixture with ice-cooling, the solvent was evaporated under reduced pressure. The residue was diluted with water and extracted with ethyl acetate. The combined extracts were washed with water and dried over $MgSO_4$. After removal of the solvent, the residue was chromatographed on silica gel to give (±)-**20** as a colorless oil (hexane:ethyl

acetate=7:1) (5.91 g, 67%); IR (neat film) 3433, 3030, 2934, 2862, 1496, 1453, 1370, 1238, 1205, 1075, 848, 737, 698 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 1.18–1.31 (4H, m, CH_2), 1.69–1.75 (2H, m, CH_2), 2.00–2.01 (1H, m, CH_2), 2.12–2.14 (1H, m, CH_2), 2.65 (1H, s, OH), 3.14–3.23 (1H, m, CH), 3.45–3.52 (1H, m, CH), 4.48 (1H, d *J* 11.5, CH_2), 4.70 (1H, d *J* 11.5, CH_2), 7.27–7.36 (5H, m, C_6H_5); MS (EI) *m/z* (rel intensity) 206 (M^+, 10) and 115 (100).

A mixture of (±)-**20** (5.92 g, 28.7 mmol), isopropenyl acetate (7.41 g, 86.1 mmol), and lipase YS (6.2 g) in diisopropyl ether (200 mL) was stirred at 30 ºC for 8.5 h. A similar work-up as that described for the preparation of (±)-**16** followed by silica gel chromatography of the products gave (–)-**19** as a colorless oil (hexane:ethyl acetate=15:1) (2.82 g, 40%) and (+)-**20** as a colorless oil (hexane:ethyl acetate=4:1) (3.45 g, 58%); $[\alpha]_D^{24}$ +45.7° (*c* 1.39, chloroform).

For (–)-**19**; $[\alpha]_D^{23}$ –31.2° (*c* 0.765, chloroform) (>98% ee by HPLC using chiral column; Opti Pak XC, Waters, hexane:isopropanol=98:2 as an eluent); IR (neat film) 3031, 2939, 2863, 1736, 1454, 1367, 1240, 1097, 1050, 908, 738, 698, 607 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 1.19–1.46 (4H, m, CH_2), 1.62–1.73 (2H, m, CH_2), 1.99–2.10 (2H, m, CH_2), 2.03 (3H, s, CH_3), 3.35–3.41 (1H, m, CH), 4.56 (1H, d *J* 12.2, CH_2), 4.64 (1H, d *J* 12.2, CH_2), 4.80–4.86 (1H, m, CH), 7.27–7.33 (5H, m, C_6H_5).

(–)-*trans*-2-Benzyloxycyclohexanol ((–)-**20**)

A solution of (–)-**19** (4.73 g, 19.0 mmol) and potassium hydroxide (5.62 g, 0.100 mol) in a mixture of methanol (140 mL) and water (330 mL) was stirred at rt for 2 h. After the reaction mixture was neutralized with 2M hydrochloric acid, the volatile materials were removed under reduced pressure and the residue was diluted with water and extracted with ether and ethyl acetate. The combined extracts were washed with water and dried over $MgSO_4$. After removal of the solvent, chromatography of the residue on silica gel gave (–)-**20** as a colorless oil (hexane:ethyl acetate=5:1) (3.81 g, 97%); $[\alpha]_D^{26}$ –73.2° (*c* 0.945, chloroform). The spectral data were identical with those of (+)-**20**.

(–)-*trans*-Cyclohexane-1,2-diol ((–)-**21**)

A mixture of (–)-**20** (400 mg, 1.94 mmol), *p*-toluenesulfonic acid monohydrate (19 mg, 0.10 mmol) and 10% palladium on carbon (48 mg) in 1,4-dioxane (25 mL) was vigorously agitated under a 1 atm pressure of hydrogen at rt for 4.5 h. After uptake of hydrogen had ceased, the catalyst was removed by filtration and the solvent was evaporated under reduced pressure. The residue was chromatographed on silica gel to give a solid (hexane:ethyl acetate=1:2) (205 mg), which was recrystallized from benzene to give (–)-**21** (116 mg, 51%). mp 108–109 ºC from benzene; $[\alpha]_D^{21}$ –39.7° (*c* 1.02, H_2O), [lit.,[12a] $[\alpha]_D^{22}$ +41.5° (H_2O), mp 111–112 ºC or lit.,[12b] mp 113–114 ºC for (1*S*,2*S*)-(+)-**21**]. The spectral data were identical with those of an authentic sample of (±)-**21**.

(+)-2-Benzyloxycyclohexanone ((+)-**22**)

An excess Jones' reagent[13] was slowly added to a solution of (−)-**20** (505 mg, 2.45 mmol) in acetone (10 mL) with ice-cooling and then the resulting mixture was stirred at 0–5 ºC for 1.5 h. A small amount of isopropyl alcohol was added to the mixture and the resulting mixture was stirred at rt for 30 min. After the volatile materials were removed under reduced pressure, the residue was diluted with water (30 mL) and extracted with ethyl acetate. The combined extracts were washed with water and dried over $MgSO_4$. After removal of the solvent, the residue was chromatographed on silica gel to give (+)-**22** (hexane:ethyl acetate=5:1) (246 mg, 53%). mp 145–146 ºC; $[\alpha]_D^{25}$ +104.0° (*c* 1.02, chloroform); IR (neat film) 2961, 2662, 1697, 1463, 1429, 1409, 1357, 1281, 1195, 1071, 930, 736, 697cm^{-1}; δ_H (400 MHz, $CDCl_3$) 1.58–1.97 (5H, m, CH_2), 2.16–2.58 (3H, m, CH_2), 3.88 (1H, ddd *J* 1.5, 5.4 and 12.2, CH), 4.47 (1H, d *J* 12.2, OCH_2), 4.75 (1H, d *J* 12.2, OCH_2), 7.27–7.38 (5H, m, C_6H_5).

(+)-*cis*-2-Benzyloxy-1-(3,5-dimethylphenyl)cyclohexanol ((+)-**18**) from (+)-**16**

By a similar treatment as that described for the preparation of (±)-**20**, (+)-**16** (123 mg, 0.559 mmol) was reacted with benzyl bromide (286 mg, 1.67 mmol). Silica gel chromatography of the products gave (+)-**18** as a colorless oil (hexane:ethyl acetate=10:1) (109 mg, 63%). $[\alpha]_D^{23}$ +26.2° (*c* 0.870, $CHCI_3$); IR (neat film) 3556, 3454, 3029, 2935, 2860, 1604, 1496, 1453, 1355, 1300, 1263, 1205, 1178, 1075, 989, 945, 846, 741, 698 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 1.25–2.04 (8H, m, CH_2), 2.32 (6H, s, CH_3), 2.72 (l H, d *J* 2.0, OH), 3.69 (1H, dd *J* 3.1 and 7.4, CH), 4.16 (1H, d *J* 11.7, OCH_2Ph), 4.31 (1H, d *J* 11.7, OCH_2Ph), 6.89 (1H, br s, $Ar(Me)_2H$), 6.95 (2H, br s, C_6H_5), 7.05 (2H, br s, $Ar(Me)_2H$), 7.20–7.22 (3H, m, C_6H_5); δc (75.5 MHz, $CDCl_3$) 21.2 (s), 21.5 (p), 24.3 (s), 27.4 (s), 39.1 (s), 70.9 (s), 75.6 (q), 80.7 (t), 122.9 (t), 127.4 (t), 127.7 (t), 128.0 (t), 128.1 (t), 137.3 (q), 138.3 (q),147.7 (q); MS (EI) *m/z* (rel intensity) 310 (M^+, 5) and 293 (100).

(−)-*cis*-2-Benzyloxy-1-(3,5-dimethylphenyl)cyclohexanol ((−)-**18**) from (+)-**22**

A solution of (+)-**22** (138 mg, 0.676 mmol) in dry ether (5 mL) was added to a solution of 3,5-dimethylphenylmagnesium bromide which was prepared from 1-bromo-3,5-dimethylbenzene (675 mg, 3.65 mmol) and magnesium (90 mg, 3.7 mg atom) in dry ether (5 mL). The resulting mixture was stirred at rt for 1 h and then water (10 mL) was added to the reaction mixture with ice-cooling. After being acidified (pH = *ca*. 2) with 2M hydrochloric acid, the residue was diluted with water and extracted with ether and ethyl acetate. The combined extracts were washed with water and dried over $MgSO_4$. The products were purified by preparative silica gel TLC to give (−)-**18** as a colorless oil (72 mg, 34%). $[\alpha]_D^{24}$ –27.6° (*c* 0.840, chloroform), and (+)-**23** (41 mg, 20%), $[\alpha]_D^{23}$ +65.4° (*c* 0.350, chloroform). The spectral data of (−)-**18** were identical with those of (+)-**18.**

For (+)-**23**: IR (neat film) 3545, 3447, 3058, 3028, 2931, 2859, 1602, 1496, 1454, 1354, 1309, 1265, 1179, 1060, 992, 897, 846, 783, 736, 697 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 1.48–1.93 (9H, m, CH_2 and OH), 2.31 (6H, s, CH_3), 3.48 (1H, t *J* 3.0, CH), 4.01 (1H, d *J* 12.2, OCH_2Ph), 4.31 (1H, d *J* 12.2, OCH_2Ph), 6.92 (1H, br s, $Ar(Me)_2H$), 6.96 (2H, br s, C_6H_5), 7.18–7.21 (5H, m, $Ar(Me)_2H$ and C_6H_5).

(+)-*cis*-1-(3,5-Dimethylphenyl)-2-methoxymethoxycyclohexanol ((+)-**24**)

A mixture of (+)-**16 (**1.29 g, 5.86 mmol), *p*-toluenesulfonic acid monohydrate (241 mg, 1.27 mmol), lithium bromide (432 mg, 4.87 mmol), and dimethoxymethane (100 mL) was stirred at rt for 48 h. After addition of ethyl acetate (30 mL), the resulting mixture was washed with saturated aqueous $NaHCO_3$ and water and dried over $MgSO_4$. The volatile materials were evaporated under reduced pressure. Silica gel chromatography (hexane:ethyl acetate=4:1) of the residue gave (+)-**24** as a colorless oil (1.30 g, 84%); $[\alpha]_D^{27}$ +45.6° (*c* 0.700, chloroform). IR (neat film) 3483, 2937, 2850, 2817, 1604, 1446, 1356, 1300, 1152, 1135, 1101, 1032, 989, 917, 846, 708 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 1.34–1.96 (8H, m, CH_2), 2.31 (6H, s, CH_3), 2.57 (1H, s, OH), 2.91 (s, 3H, CH_3), 3.96 (1H, dd *J* 4.9 and 9.7, CH), 4.19 (1H, d *J* 7.8, CH_2), 4.48 (1H, d *J* 7.8, CH_2), 6.85 (1H, br s, ArH), 7.10 (2H, br s, ArH); MS (EI) *m/z* (rel intensity) 264 (M^+, 20) and 173 (100); HRMS (EI) *m/z* Calcd for $C_{16}H_{24}O_3$: 264.1725. Found: 264.1733.

(1'*S*,2'*S*)-(–)-1,5-Bis[1'-(3",5"-dimethylphenyl)-2'-methoxymethoxycyclohexyloxy]-3-oxapentane ((–)-**25**)

A solution of (+)-**24** (5.30 g, 20.0 mmol) in dry THF (150 mL) was added to a suspension of 60% sodium hydride (1.20 g, 50.1 mmol) in dry THF (150 mL) and the mixture was then refluxed for 2 h. A solution of diethylene glycol bis(*p*-toluenesulfonate) (4.16 g, 10.0 mmol) in dry THF (150 mL) was slowly added to the mixture at rt. After being refluxed for 4.5 h, the mixture was cooled to rt. Another 60% sodium hydride (720 mg, 30.0 mmol) and diethylene glycol bis(*p*-toluenesulfonate) (1.80 g, 4.34 mmol) were added to the reaction mixture and then the mixture was refluxed for further 5.5 h. After water (500 mL) was slowly added to the reaction mixture with ice-cooling, the mixture was concentrated under reduced pressure. The residue was extracted with a mixture of benzene, hexane, and ethyl acetate and the combined extracts were washed with water and dried over $MgSO_4$. After removal of the solvent under reduced pressure, the products were chromatographed on silica gel to give (–)-**25** (hexane:ethyl acetate=5:1) (4.60 g, 77%) as a colourless oil. $[\alpha]_D^{28}$ –11.8° (*c* 0.930, chloroform); IR (neat film) 2937, 2820, 1740, 1604, 1446, 1373, 1296, 1215, 1180, 1146, 1133, 1106, 1037, 989, 915, 846, 782, 709 cm^{-1}; δ_H (270 MHz, $CDCl_3$) 1.44–2.17 (16H, m, CH_2), 2.28 (12H, s, CH_3), 2.95 (6H, s, CH_3), 3.38–3.49 (6H, m, CH and CH_2), 3.74 (4H, t *J* 5.7, CH_2), 3.89 (2H, d *J* 7.0, CH_2), 4.36 (2H, d *J* 7.0, CH_2), 6.85 (2H, br s, ArH), 7.05 (4H, br s, ArH); MS (EI) *m/z* (rel intensity) 598 (M^+, 10) and 351 (100).

(1'*S*,2'*S*)-(+)-1,5-Bis[1'-(3",5"-dimethylphenyl)-2'-hydroxycyclohexyloxy]-3-oxapentane ((+)-**26**)

A solution of (−)-**25** (277 mg, 0.460 mmol) in methanol (30 mL) containing five drops of concentrated hydrochloric acid was stirred at rt for 26 h. After being neutralized with saturated aqueous $NaHCO_3$, the mixture was concentrated under reduced pressure. The residue was extracted with chloroform and the combined extracts were washed with water, dried over $MgSO_4$, and evaporated under reduced pressure. Silica gel chromatography of the products gave (+)-**26** (hexane:ethyl acetate=4:1) (211 mg, 89%) as a colorless oil. $[\alpha]_D^{28}$ +5.5° (*c* 0.961, chloroform); IR (neat film) 3421, 2937, 2862, 1604, 1449, 1296, 1248, 1181, 1088, 989, 845, 753, 706 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 1.43–2.16 (16H, m, CH_2), 2.33 (12H, s, CH_3), 3.23–3.28 (2H, m, CH_2), 3.34–3.40 (2H, m, CH_2), 3.51–3.56 (2H, m, CH_2), 3.68–3.74 (2H, m, CH_2), 3.90 (4H, br s, CH_2 and OH), 6.91 (2H, br s, ArH), 7.10 (4H, br s, ArH); MS (EI) *m/z* (rel intensity) 598 (M^+, 10) and 351 (100).

(4*S*,9*S*,17*S*,22*S*)-(+)-27,29-Dimethoxy-9,17-bis(3',5'-dimethylphenyl)-3,10,13,16,23-pentaoxatetracyclo-[23.3.1.$0^{4,9}$.$0^{17,22}$]nonacosa-1(29),25,27-triene ((+)-**27**)

A solution of (+)-**26** (1.12 g, 2.19 mmol) and 1,3-bis(bromomethyl)-2,5-dimethoxybenzene (782 mg, 2.41 mmol) in dry THF (250 mL) was slowly added to a suspension of 60% sodium hydride (210 mg, 8.77 mmol) in dry THF (100 mL) over a 13 h period and the mixture was stirred at 50 ºC for 14 h under a nitrogen atmosphere. After a small amount of water was carefully added to the reaction mixture with ice-cooling, the solvent was removed under reduced pressure. The residue was extracted with ethyl acetate and the combined extracts were washed with water, dried over $MgSO_4$, and evaporated under reduced pressure. Silica gel chromatography of the products gave (+)-**27** (hexane:ethyl acetate=9:1–6:1) (1.07 g, 72%). mp 83–84 ºC; $[\alpha]_D^{27}$ +108.6° (*c* 0.811, chloroform); IR (KBr) 3448, 2936, 2862, 1604, 1484, 1365, 1246, 1088, 996, 846, 707 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 1.32–2.04 (16H, m, CH_2), 2.30 (12H, s, CH_3), 3.01–3.09 (2H, m, CH_2), 3.10–3.13 (2H, m, CH_2), 3.21 (4H, t *J* 6.1, CH_2), 3.74 (3H, s, CH_3), 3.96 (3H, s, CH_3), 4.07 (2H, dd *J* 5.9 and 3.5, CH), 4.41 (2H, br s, CH_2), 4.76 (2H, d *J* 9.7, CH_2), 6.76 (2H, br s, ArH), 6.86 (2H, br s, ArH) and 7.01 (4H, br s, ArH); δC (75.5 MHz, $CDCl_3$) 21.4 (p), 21.9 (s), 22.3 (s), 26.2 (s), 55.2 (p), 61.5 (s), 62.4 (p), 66.5 (s), 70.5 (s), 79.7 (t), 80.2 (q), 115.3 (t), 125.2 (t), 128.3 (t), 133.2 (q), 134.8 (q), 141.9 (q), 151.2 (q), 154.7 (q); MS (EI) *m/z* (rel intensity) 672 (M^+, 60) and 268 (100). *Anal.* Calcd for $C_{42}H_{56}O_7$: C, 74.97; H, 8.39. Found: C, 74.80; H, 8.42.

(4*S*,9*S*,17*S*,22*S*)-(+) -29-Hydroxy-27-methoxy-9,17-bis(3',5'-dimethylphenyl)-3, 10, 13, 16, 23-pentaoxa-tetracyclo[23.3.1.$0^{4,9}$.$0^{17,22}$]nonocosa-1(29),25,27-triene ((+)-**28**)

Ethanethiol (323 mg, 5.20 mmol) was slowly added to a suspension of 60% sodium hydride (105 mg, 4.37 mmol) in dry DMF (4 mL) at 0–5 ºC under a nitrogen atmosphere and then a solution of (+)-**27** (140 mg, 0.210 mmol) in dry DMF (4 mL) was added to the resulting clear solution. The reaction mixture was heated at 90 ºC for 2 h. After the reaction mixture had been acidified (pH = *ca*. 3) with 2M hydrochloric

acid with ice-cooling, the volatile materials were evaporated under reduced pressure and the residue was extracted with ethyl acetate. The combined extracts were washed with water, dried over $MgSO_4$, and evaporated under reduced pressure. Silica gel chromatography of the products gave (+)-**28** (hexane:ethyl acetate=8:1) (126 mg, 92%). mp 86–87 ºC; $[\alpha]_D^{29}$ +68.5° (*c* 0.798, chloroform); IR (KBr) 3855, 3752, 3736, 3650, 3365, 2936, 2861, 1604, 1487, 1357, 1255, 1087, 847, 772, 706 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 1.30–2.03 (16H, m, CH_2), 2.30 (12H, s, CH_3), 3.24–3.33 (4H, m, CH_2), 3.60–3.72 (4H, m, CH_2), 3.73 (3H, s, CH_3), 3.91–3.96 (2H, m, CH), 4.45 (2H, d *J* 10.7, $ArCH_2$), 4.73 (2H, d *J* 10.7, $ArCH_2$), 6.63 (2H, br s, ArH), 6.87 (2H, br s, ArH), 7.08 (4H, br s, ArH), 8.13 (1H, s, OH); MS (EI) *m/z* (rel intensity) 658 (M+, 40) and 368 (100); HRMS (EI) *m/z* Calcd for $C_{41}H_{54}O_{7,}$: 658.3870; Found 658.3899.

(4*S*,9*S*,17*S*,22*S*)-(+)-9,17-Bis(3,5-dimethylpheny1)-3,10,13,16,23-pentaoxatetracyclo[23.3.1.$0^{4,9}$.$0^{17,22}$]-nonacosa-25, 28- diene-27,29-dione ((+)-**29**)

A solution of (+)-**28** (109 mg, 0.170 mmol) in acetonitrile (10 mL) was added to a solution of CAN (181 mg, 0.330 mmol) in acetonitrile (5 mL) and then the mixture was stirred at rt for 1.5 h. After dilution with water (100 mL), the mixture was concentrated under reduced pressure and extracted with ethyl acetate. The combined extracts were washed with water, dried over $MgSO_4$, and concentrated under reduced pressure. Silica gel chromatography of the residue gave (+)-**29** (hexane:ethyl acetate=6:1) (104 mg, 98%) as a yellow solid. mp 96–97 ºC; $[\alpha]_D^{25}$ +17.9° (*c* 0.117, chloroform); IR (KBr) 3449, 2935, 2863, 1656, 1604, 1449, 1284, 1117, 984, 918, 847, 756, 708 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 1.26–1.97 (16H, m, CH_2), 2.30 (12H, s, CH_3), 3.11–3.17 (2H, m, CH_2), 3.18–3.22 (2H, m, CH_2), 3.36 (4H, t *J* 5.5, CH_2), 3.97 (2H, br s, CH), 4.51 (2H, d *J* 13.9, allylic CH_2), 4.74 (2H, d *J* 13.9, allylic CH_2), 6.59 (2H, s, quinone CH), 6.88 (2H, br s, $(Me)_2ArH$), 7.00 (2H, br s, $(Me)_2ArH$). This material was immediately used for the next reaction.

(4*S*,9*S*,17*S*,22*S*)-29-Hydroxy-9,17-bis(3,5-dimethylphenyl)-27 -(2,4-dinitrophenylazo)-3,10,13,16,23-pentaoxatetracyclo[23.3.1.$0^{4,9}$.$0^{17,22}$]nonacosa-1(29),25,27-triene (**2**)

A solution of 2,4-dinitrophenylhydrazine (500 mg, 2.52 mmol) in a mixture of ethanol (45 mL) and conc. H_2SO_4 (2.7 mL) was added to a solution of (+)-**29** (815 mg, 1.27 mmol) in a mixture of ethanol (35 mL) and chloroform (35 mL) and the mixture was stirred at rt for 4 h. After addition of water (400 mL), the resulting mixture was extracted with chloroform. The combined extracts were washed with saturated aqueous $NaHCO_3$ and water, dried over $MgSO_4$, and concentrated under reduced pressure. Silica gel chromatography of the residue gave a solid (hexane:ethyl acetate=7:1) (895 mg), which was further purified by preparative recycling HPLC (JAIGEL 1H and 2H column, chloroform as an eluent) to give **21** (768 mg, 74%) as a red solid. mp 139–140 ºC from $CHCl_3$; IR (KBr) 3254, 2937, 2863, 1600, 1535, 1460, 1430, 1344, 1293, 1115, 1087, 907, 857, 832, 747, 706 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 1.26–2.05 (16H, m,

CH_2), 2.31 (12H, s, CH_3), 3.35–3.40 (4H, m, CH_2), 3.62–3.64 (2H, m, CH_2), 3.74–3.77 (2H, m, CH_2), 3.93 (2H, br s, CH), 4.53 (2H, d *J* 10.7, Ar CH_2), 4.74 (2H, d *J* 10.7, Ar CH_2), 6.87 (2H, br s, $(Me)_2ArH$), 7.13 (2H, br s, $(Me)_2ArH$), 7.71 (2H, br s, (HO)ArH), 7.81 (1H, d *J* 8.8, $(NO)_2ArH$), 8.47 (1H, d *J* 8.8, $(NO)_2ArH$), 8.73 (1H, br s, $(NO)_2ArH$) and 9.77 (1H, s, OH); δc (75.5 MHz, $CDCl_3$) 21.5 (p), 22.1 (s), 26.6 (s), 31.8 (s), 62.3 (s), 69.2 (s), 70.9 (s), 78.0 (q), 82.5 (t), 119.8 (t), 125.2 (t), 125.7 (t), 126.2 (t), 127.3 (t), 128.8 (t), 137.4 (q), 141.3 (q), 145.4 (q), 146.4 (q), 146.6 (q), 148.8 (q), 162.1 (q); MS (FAB) *m/z* (rel intensity) 823 (M^+, 5) and 155 (100). *Anal.* Calcd for $C_{46}H_{54}N_4O_{10}$: C, 67.14; H, 6.61; N, 6.81. Found: C, 67.36; H, 6.69; N, 6.49.

(*R*)-2-Methoxy-2-trifluoromethyl-2-phenylacetic acid 1-(3,5-dimethylphenyl)-2-triphenylmethoxyethyl ester, (*R*)-MTPA ester of **10**

(*R*)-MTPA (31.5 mg, 0.135 mmol), dicyclohexylcarbodiimide (24.8 mg, 0.128 mmol), and 4-(dimethylamino)pyridine (11.1 mg, 0.0908 mmol) were added to a solution of (+)-**10** (14.7 mg, 0.0359 mmol) in dichloromethane (1.7 mL). Then the mixture was stirred at rt for 7.5 h. The mixture was extracted 3 times with chloroform. The combined extracts were washed with water, dried over $MgSO_4$, and concentrated under reduced pressure. Silica gel chromatography (chloroform) of the residue gave a colorless solid, which was further purified by preparative recycling HPLC to give (*R*)-MTPA ester of **10** (16.2 mg, 72%) as colorless plates. mp 121–122 ºC; IR (KBr) 3440, 2945, 1753, 1606, 1535, 1492, 1448, 1283, 1173, 1076, 849, 705 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 2.24 (6H, s, CH_3), 3.21 (1H, dd *J* 3.0 and 10.7, CH_2), 3.46 (3H, s, OCH_3), 3.52 (1H, dd *J* 8.8 and 10.7, CH_2), 6.08 (1H, dd *J* 3.0 and 8.8, CH), 6.83 (2H, s, $(Me)_2ArH$), 6.91 (1H, s, $(Me)_2ArH$), 7.20-7.32 (20H, m, ArH and CPh_3); MS (EI) *m/z* 625 (M^++1).

(*S*)-2-Methoxy-2-trifluoromethyl-2-phenylacetic acid 1-(3,5-dimethylphenyl)-2-triphenylmethoxyethyl ester, (*S*)-MTPA ester of **10**

(*S*)-MTPA (35.4 mg, 0.151 mmol), dicyclohexylcarbodiimide (22.0 mg, 0.107 mmol), and 4-dimethylaminopyridine (10.6 mg, 0.0868 mmol) were added to a solution of (+)-**10** (15.6 mg, 0.0382 mmol) in dichloromethane (1.7 mL). Then the (*S*)-MTPA ester of **10** was prepared in 76% yield by a similar manner to that of the preparation (*R*)-MTPA ester as colorless needles. mp 114–116 ºC; IR (KBr) 3450, 2943, 1754, 1606, 1491, 1449, 1275, 1168, 1122, 1074, 990, 848, 707 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 2.19 (6H, s, CH_3), 3.27 (1H, dd *J* 16.4 and 10.7, CH_2), 3.55 (1H, dd *J* 16.4 and 2.7, CH_2), 3.58 (3H, s, OCH_3), 5.96 (1H, dd *J* 2.7 and 10.7, CH), 6.63 (2H, s, $(Me)_2ArH$), 6.86 (1H, s, $(Me)_2ArH$), 7.20-7.41 (20H, m, ArH and CPh_3); MS (EI) *m/z* 624 (M^+).

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