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Enantiomeric recognition and separation of chiral organic ammonium salts by chiral pyridino-18-crown-6 ligands

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Optically pure allyloxy and dimethyl-substituted pyridino-18-crown-6 (8) was attached to silica gel by the following reactions. 4-Allyloxy-2,6-pyridinedimethyl ditosylate (23) was first prepared from chelidamic acid. Ditosylate 23 was treated with (*S,S*)-dimethyl-substituted tetraethylene glycol to form 8. Ligand 8 was treated with triethoxysilane using a platinum catalyst. The resulting chiral crown-substituted triethoxysilane 32 was reacted with silica gel in toluene at 90°C to attach the crown to silica gel. Preliminary results of the separation of [α-(1-naphthyl)ethyl]ammonium perchlorate into its (*R*) and (*S*) forms using the bound chiral crown with acetone/methanol (7/3) (v/v) as the eluant are reported. The preparation of chiral dimethyl(allyloxyphenyl)pyridino-18-crown-6 (9) that could be attached to silica gel on the side opposite to the pyridine ring is also reported.

INTRODUCTION

The design, synthesis and use of macrocycles capable of selective recognition of other molecules is of great interest to workers in many fields.[1–3] Our interest is in the area of enantiomeric recognition and has focused on the interactions of chiral crown macrocycles with chiral organic ammonium cations.[4–10] We have chosen interactions of the chiral pyridino-18-crown-6 ligands because they form relatively strong complexes with the organic ammonium salts[11] and they can be prepared in the laboratory with various substituents on chiral positions on the macro-ring. We have made a systematic study of how the extent of enantiomeric recognition varies with crown substituent, guest type and solvent.[6,7,10]

Chiral pyridino-18-crown-6 ligands have been prepared with two methyl groups (compounds **1** and **2** in Fig 1),[4,12] two phenyl groups (**3** and **4**),[5,7] two *sec*-butyl groups (**5**),[6] and two *t*-butyl groups (**6** and **7**)[7] in chiral positions near the rigid pyridine portion of the macro-ring. These macrocycles were prepared by treating the relevant chiral diakyl-substituted tetraethylene glycol with dimethyl 2,6-pyridinedicarboxylate or 2,6-pyridinedimethyl ditosylate. Chiral ligand **2** was prepared by a Raney nickel reduction of the corresponding dithiono-crown where X = S.[12] A number of other chiral dialkylpyridino-18-crown-6[6] and chiral triazolo-18-crown-6 ligands[13] have been prepared but they either did not exhibit significant enantiomeric recognition or their recognition properties have not been determined.

Compounds **1**–**7** interact with [α-(1-naphthyl)-ethyl]ammonium perchlorate ($NapEtClO_4$) in a variety of solvent systems. This interaction has been studied by a temperature-dependent ^{1}H-NMR technique to give the free energy of activation ($\Delta G_c^{\ddagger}$) for the dissociation of the complex.[4–7] The log K values for the interaction of the crown ligands with $NapEtClO_4$ have been determined by a direct ^{1}H-NMR technique[8] and by a calorimetric titration method.[4,14] Log K values determined by these two methods were in good agreement.[8] Table 1 lists the enantiomeric recognition of these chiral ligands and others for the (*R*) and (*S*) forms of $NapEtClO_4$ as shown by $\Delta\Delta G_c^{\ddagger}$ and $\Delta \log K$ values. It is interesting to note that $\Delta \log K_c$ for the extraction of (*R*)- and (*S*)-$NapEtClO_4$ by **1** is 0.49[15] which is similar to the $\Delta \log K$ value determined by the direct ^{1}H-NMR technique (Table 1). The calculated $\Delta\Delta G_c^{\ddagger}$ as determined by a force-field technique is very close, in most cases, to the observed $\Delta\Delta G_c^{\ddagger}$ as determined by the temperature-dependent ^{1}H-NMR method (Table 1). It is obvious from the data in Table 1 that the best recognition was obtained when the two substituents were *t*-butyl followed by phenyl. Structures determined by X-ray crystallography[4,16] and by force-field calculations[6,7] show that the large phenyl

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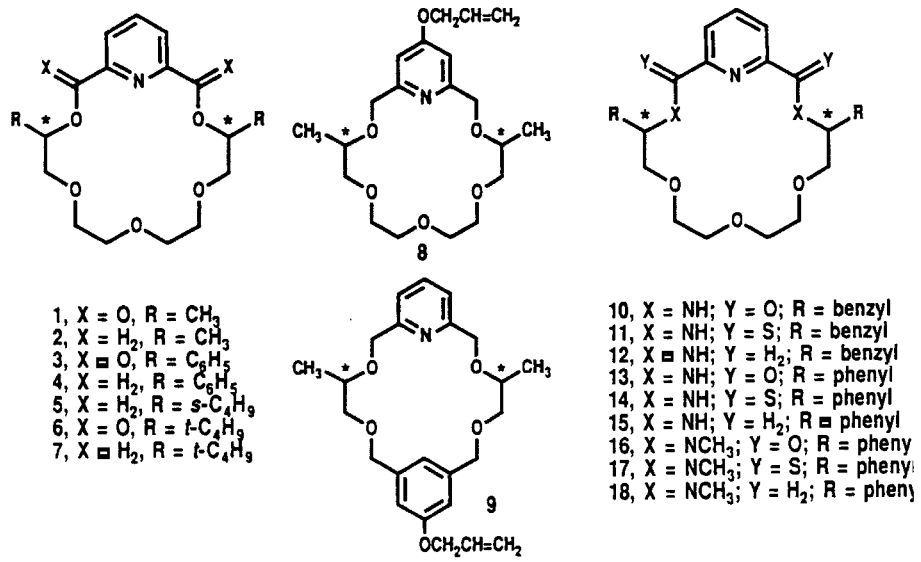


Figure 1 Chiral pyridino-18-crown-6 ligands.

Table 1 Recognition of the enantiomers of chiral [α-(1-naphthyl)-ethyl]ammonium perchlorate by various chiral pyridino-18-crown-6 ligands as measured by differences in the free energies of activation ($\Delta\Delta G_c^{\ddagger}$) (kcal/mol) or differences in log K values ($\Delta \log K$) for their interactions in CD_2Cl_2 ($\Delta\Delta G_c^{\ddagger}$ values) or in mixtures of CD_3OD (M) and $CDCl_3$ (C) ($\Delta \log K$ values)

	$\Delta\Delta G_c^{\ddagger}$ (kcal/mol)		
Ligand	*Observed*	*Calculated*	*Δ log K*
(*S,S*)-**1**	1.1[4]	0.7[6]	0.6 (5M/5C)*,[31]
(*S,S*)-**2**	1.6[4]	1.7[6]	0.54 (5M/5C)*,[24]
(*S,S*)-**3**	1.3[6]	2.5[6]	>0.85 (7M/3C)*,[7]
(*R,R*)-**4**	2.8[7]		0.28 (M)*,[7]
(*R,R*)-**5**	0.8[6]	1.7[6]	
(*S,S*)-**6**	>1.8[7]	2.5[6]	NR*,[7]
(*S,S*)-**7**	2.5[7]	2.2[6]	0.71 (1M/9C)*,[7]
(*S,S*)-**8**			0.35 (5M/5C)*,[31]
(*S,S*)-**9**			NR (5N/5C)†
(*S,S*)-**14**			0.37 (5M/5C)*,[10]
(*S,S*)-**16**	0.1[10]		
(*S,S*)-**17**	0.1[10]		0.2 (5M/5C)*,[10]
(*S,S*)-**18**	0.1[10]		0.1 (5M/5C)*,[10]

* Determined by an ^{1}H-NMR technique.[8]
† Determined by a calorimetric method.[14]
NR, no reaction.

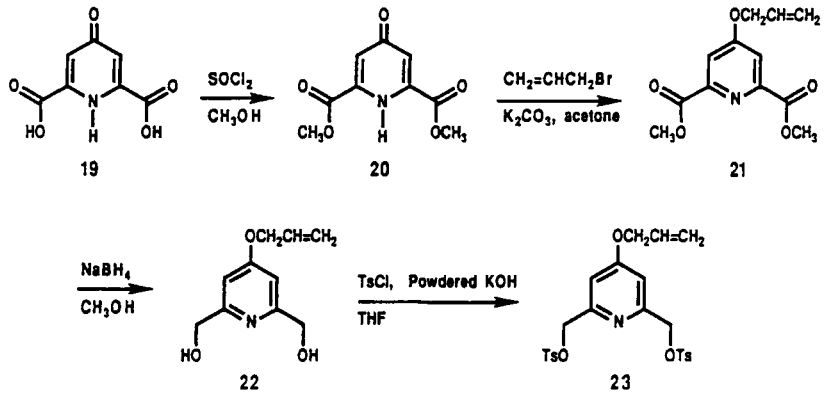
or alkyl groups on the chiral host cause a larger steric repulsion in the (*S,S*)-host–(*S*)-guest than in the other diastereomeric complex.

We have also prepared a series of chiral dibenzyl- and diphenyl-substituted diazapyridino-18-crown-6 ligands (**10**–**18**).[10] These materials were prepared by treating the relevant chiral dibenzyl- or diphenyl-substituted diamine with dimethyl 2,6-pyridinedicarboxylate, 2,6-pyridinecarbonyl dichloride, *O,O'*-dimethyl-2,6-pyridine-dicarbothioate, or 2,6-pyridine-dimethyl ditosylate. Bisthionoamido crowns **11**, **14** and **17** also were converted to the corresponding amino crowns (**12**, **15** and **18**, respectively) using Raney nickel. Some interesting structural transformations of bis-*N*-methylthionoamido crown **17**, caused by the $C(=S)N(CH_3)C^*H(C_6H_5)$ portions of the molecule, were observed.[10] With the exception of **14** and **17**, these new chiral host compounds gave no measurable recognition of the enantiomers of $NapEtClO_4$ (see Table 1).

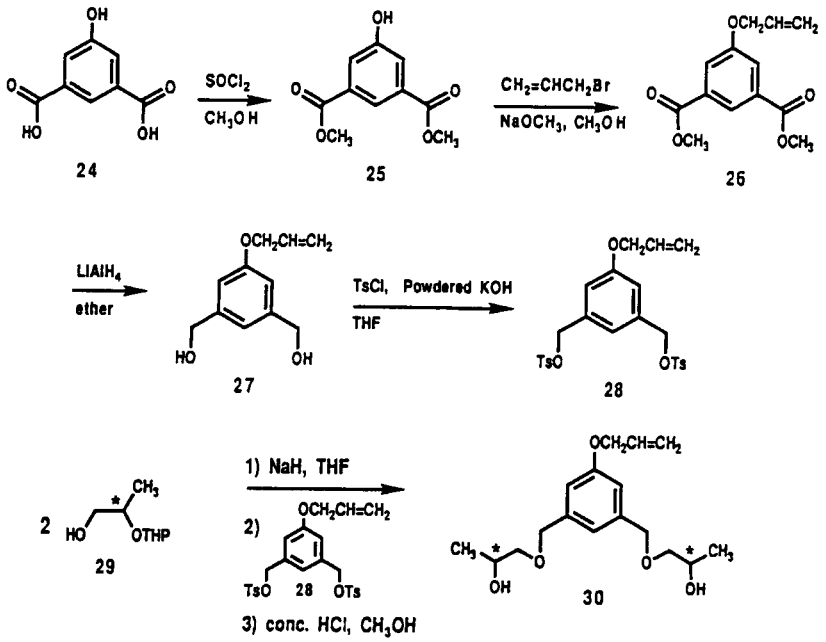
We have now covalently attached ligand **2** onto silica gel. More than a decade ago, Cram and coworkers covalently attached a different chiral crown ether to silica gel using another method, and they used this system for separation of the enantiomers of chiral organic ammonium salts.[17] Even though **2** does not exhibit the best recognition, it is the easiest chiral pyridino-18-crown-6 ligand to prepare. This paper describes the synthesis of chiral dimethyl-4-allyloxypyridino-18-crown-6 (**8**) (an analogue of **2** that can be bonded to silica gel) and its attachment to silica gel. Chiral dimethyl(ally-loxybenzo)pyridino-18-crown-6 (**9**), which could be attached to silica gel through the benzene portion of the molecule, is also reported. A preliminary study of the separtion of the (*R*) and (*S*) forms of $NapEtClO_4$ using silica gel-bound chiral crown **33** is also presented.

RESULTS AND DISCUSSION

4-Allyloxy-2,6-pyridinedimethyl ditosylate, needed for the synthesis of the chiral crown (**8**) that is capable of being attached to silica gel, was prepared as shown in



Scheme I Preparation of 4-allyloxy-2,6-pyridinedimethyl ditosylate (**23**).

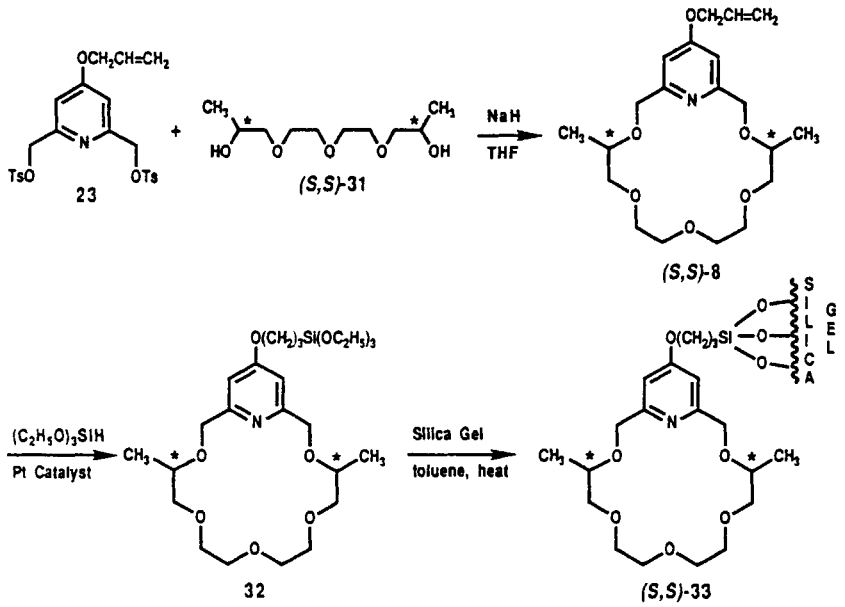


Scheme II Preparation of 5-allyloxy-1,3-benzenedimethyl ditosylate (**28**) and chiral allyloxybenzoglycol (**30**).

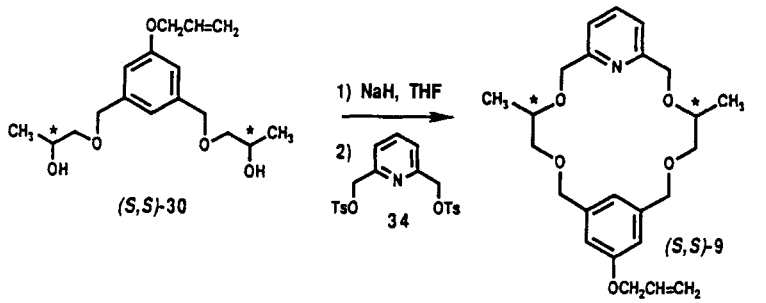
Scheme I. We have found that the use of powdered KOH in THF is a superior base-solvent system for the preparation of tosylates from alcohols and tosyl chloride.[6,7,10] The allyloxybenzo-containing chiral glycol (**30**) needed for the synthesis of chiral allyloxy-substituted crown **9** was prepared as shown in Scheme II. 5-Allyloxy-1,3-benzenedimethyl ditosylate (**28**) was prepared in much the same manner as the pyridine analogue **23** except that care was taken to insure that the unstable benzyl tosylate moieties[18] were kept at a low temperature and **28** was used immediately to form **30** without a purification step. Chiral glycol **30** is stable and can be stored for an indefinite period of time. All intermediate and starting compounds were characterized by their IR and ^{1}H-NMR spectra. No combustion analyses were carried out on these materials, however, good elemental analyses were obtained on macrocycles **8** and **9** prepared from these new starting materials.

New chiral macrocycles (*S,S*)-**8** and (*S,S*)-**9** were prepared as shown in Schemes III and IV. The synthesis of silica gel-bound chiral dimethyl-substituted pyridino-18-crown-6 [(*S,S*)-**33**] is also shown in Scheme III. Starting (*S,S*)-dimethyltetraethylene glycol [(**S,S**)-**31**] was prepared as reported.[19,20] The attachment of (*S,S*)-**8** to silica gel was accomplished by first forming the chiral crown-triethoxysilane by a simple hydrosilylation reaction and heating this material in toluene in the presence of silica gel.[21-23] The silica gel contained approximately 0.25 mmol of chiral crown per g as determined by a combustion analysis.

Before allyloxy-substituted chiral crown **8** was attached to silica gel, the log *K* for its interactions with (*R*)- and (*S*)-NapEtClO$_4$ were determined in CDCl$_3$/



Scheme III Preparation of chiral allyloxypyridino crown **8** and silica gel-bound chiral crown **33**.



Scheme IV Preparation of chiral (allyloxybenzo)pyridino crown **9**.

CD_3OD (1/1) (v/v) mixture. The log K value for the interaction of (*S,S*)-**8** with (*R*)-NapEtClO$_4$ was 3.89 and that for (*S,S*)-**8** with (*S*)-NapEtClO$_4$ was 3.54 as determined by a direct ^{1}H-NMR technique.[8,24] These values compare favorably with those for the interactions of parent chiral dimethylpyridino-18-crown-6 (**2**) with (*R*)- and (*S*)-NapEtClO$_4$ in the same solvent system. In the latter case, the log K values were 3.96 and 3.42.[24] Although the Δ log K value for chiral host–**8** interactions are not as great as for parent chiral host **2** interactions (0.35 vs. 0.54), we felt that this was good enough to attach **8** to silica gel for an enantiomeric separation study.

A preliminary study of the separation of (*R*)- and (*S*)-NapEtClO$_4$ using silica gel-bound chiral crown **33** is shown in Figure 2. Racemic NapEtClO$_4$ was placed on a column containing (*S,S*)-**33**. The elution solvent was a mixture of 70% acetone and 30% CH_3OH by volume. We used acetone because, initially, we observed a high enantiomeric selectivity in pure acetone. This selectivity proved to be an artifact of the reaction of the ammonium salt with acetone to form a Schiff-base. The relative amounds of (*R*)- and (*S*)-NapEtClO$_4$ in each sample were determined from the HPLC chromatogram of the corresponding acetamide derivatives. Each fraction was treated with base and acetic anhydride. Blank determinations using known mixtures of the (*R*) and (*S*) salts and phthalimide as internal standard showed that this technique gave quantitative values for the amounts of the chiral salts in the sample.

As can be seen in Figure 2, (*S,S*)-**33** does separate the (*R*) and (*S*) forms of NapEtClO$_4$. As expected, the (*S*) form passes through the column first although it is contaminated by some of the (*R*) form. (*S,S*)-**33** interacts more strongly with (*R*)-NapEtClO$_4$ so that the (*R*) form should come off the column last. This is a preliminary experiment. This separation and that of other chiral organic ammonium salts need to be studied in greater detail. The incomplete separation of (*S*)-NapEtClO$_4$ could be caused by overloading the column or the use of the wrong solvent system.

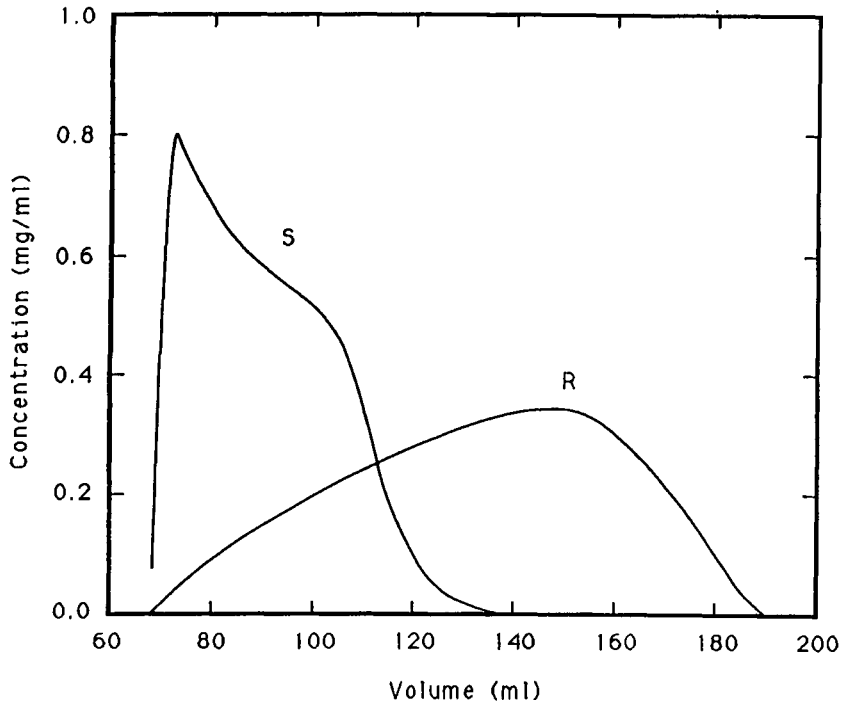


Figure 2 A smooth curve showing the separation of the enantiomers of (*R*)- and (*S*)-NapEtClO$_4$ on (*S,S*)-**33** using acetone/CH_3OH (7/3) as eluant.

It is also possible that attachment to silica gel through the pyridine ring would put the steric portion of the chiral crown too close to the solid support. This could reduce the host–guest interaction and could change the degree of enantiomeric recognition. Indeed, Schomburg and co-workers found that the chiral phase needed to be more than three atoms removed from the solid support for effective enantiomeric separation in supercritical fluid chromatography.[25] Preliminary results using (*S,S*)-**33** shown in Figure 2, indicate that there is recognition in this system. Even so, we prepared chiral (allyloxybenzo))pyridino-crown (*S,S*)-**9** so that attachment to silica gel could be in the polyether portion of the macro-ring. The X-ray structures of the solid (*R*)- and (*S*)-NapEtClO$_4$–**1** complexes clearly show that the host and guest interaction is caused by hydrogen bonds between the ammonium hydrogens and pyridine nitrogen and the symmetrically spaced ring oxygen atoms.[4,16]. Thus, the macro-ring oxygen atom opposite the pyridine ring is not involved so that a crown such as **9** with no heteroatom in that position could interact with an organic ammonium salt. Unfortunately, (*S,S*)-**9** did not interact with NapEtClO$_4$ (see Table 1) and, therefore, **9** will not be attached to silica gel. In the future, a chiral pyridino-crown similar to **32** but with a long chain spacer will be prepared, attached to silica gel, and tested.

EXPERIMENTAL

The ^{1}H-NMR spectra were obtained at 200 MHz in $CDCl_3$ with TMS as the internal standard unless otherwise indicated. Melting points are uncorrected. Starting materials were used as purchased from Aldrich Chemical Company unless otherwise noted. Dimethyl 4-allyloxy-2,6-pyridinedicarboxylate (**21**),[26] 4-allyloxy-2,6-pyridinedimethanol (**22**)[26] and chiral dimethyl-substituted tetraethylene glycol (*S,S*-**31**)[19,20] were prepared as reported. Chelidamic acid monohydrate (**19**) was made from chelidonic acid and concentrated NH_4OH as reported.[27]

Dimethyl chelidamate (20) (Scheme I)

Thionyl chloride (144 ml, 235 g, 2.0 mol) was slowly added to a stirred mixture of 71.8 g (0.36 mol) of **19** and 720 ml of CH_3OH in an ice-salt bath. The mixture was stirred in an ice-salt bath for 1 h and at room temperature (rt) for 2 days. The solvent was evaporated and the residue was mixed well with 750 ml of an 8% (w/v) $NH_4O_2CCH_3$ solution and stored in a refrigerator for 2 days. The white crystals were filtered, washed three times with 100 ml portions of cold water and dried. After recrystallization from CH_3OH, 66 g (88%) of pure **20** was obtained; m.p. 170–171°C (literature[28] m.p. 169–169.5°C).

4-Allyloxy-2,6-pyridinedimethyl ditosylate (23) (Scheme I)

To a stirred suspension of 12.6 g (0.201 mol, 87.5%) of well powdered KOH in 45 ml of THF was added 8.8 g (0.045 mol) of **22**[26] dissolved in 120 ml of THF. After 10 min of stirring at 0°C under Ar, 22.9 g (0.12 mol) of tosyl chloride dissolved in 120 ml of THF was added dropwise. After stirring the reaction mixture at 0°C for 2 h and at rt for 4 h, the solvent was evaporated under reduced pressure. The residue was dissolved in a mixture of 1200 ml of CH_2Cl_2, 200 g of ice and 400 ml of water. The phases were mixed well and separated. The organic phase was dried ($MgSO_4$), filtered and the solvent was removed under reduced pressure to give 25.6 g of crude product. The product was recyrstallized from a $ClCH_2CH_2Cl$–CH_3OH mixture to give 19.6 g (86%) of **23**; m.p. 79–81°C; IR (KBr) 1386, 1177 cm^{-1}, ^{1}H-NMR δ 2.44 (s, 6 H), 4.50–4.58 (m, 2H), 4.98 (s, 4 H), 5.29–5.48 (m, 2 H), 5.88–6.10 (m, 1 H), 6.82 (s, 2 H) 7.33 (d, 4 H, J = 10 Hz), 7.80 (d, 4 H, J = 10 Hz). Analysis calculated for $C_{24}H_{25}NO_7S_2$: C, 57.24; H, 5.00. Found: C, 57.41; H, 5.12.

Dimethyl 5-hydroxy-1,3-benzenedicarboxylate (25) (Scheme II)

To a stirred mixture of 13.0 g (71.4 mmol) of 5-hydroxyisophthalic acid and 144 ml of CH_3OH in an ice-salt bath under Ar was slowly added 29 ml (47.3 g, 398 mmol) of thionyl chloride. After addition, the reaction mixture was stirred in an ice-salt bath for 1 h, then at rt for 16 h. The reaction mixture was condensed to 40 ml and stored in a refrigerator for 1 day. The white crystals were filtered and dried in a vacuum dessicator over KOH pellets. After recrystallization from methanol, 14.3 g (95%) of pure **25** was obtained; m.p. 162–163°C (literature[29] m.p. 159–160°C); ^{1}H-NMR δ 3.88 (s, 6 H), 7.56 (s, 2 H), 7.92 (s, 1 H), 10.30 (s, 1 H, disappeared in D_2O).

Dimethyl 5-allyloxy-1,3-benzenedicarboxylate (26) (Scheme II)

To a stirred solution of 0.82 g (35.7 mmol) of sodium metal in 50 ml of dry and pure CH_3OH was added 5.0 g (23.8 mmol) of **25** in portions under Ar. The reaction mixture was stirred for 10 min and then 7.5 ml (10.5 g, 86.7 mmol) of allyl bromide was added. After stirring the reaction mixture at rt for 10 min, it was refluxed for 2 days. The solvent was evaporated under reduced pressure. The residue was dissolved in a cold mixture of 100 ml of 5% NaOH and 250 ml of CH_2Cl_2. The phases were shaken well and separated. The aqueous phase was shaken with two 100 ml portions of CH_2Cl_2. The combined organic phase was dried ($MgSO_4$), filtered, and the solvent removed under reduced pressure. The crude solid material was recrystallized from CH_3OH to give 5.24 g (88%) of pure **26**; m.p. 71–72°C; IR (KBr) 3089, 3048, 3031, 1723, 1595, 1435, 1344, 1248, 1115, 1043, 1011 cm^{-1}; ^{1}H-NMR δ 3.92 (s, 6 H), 4.58–4.68 (m, 2 H), 5.24–5.25 (m, 2 H), 5.92–6.16 (m, 1 H), 7.75 (s, 2 H), 8.25 (s, 1 H).

5-Allyloxy-1,3-benzenedimethanol (27) (Scheme II)

To a stirred suspension of 1.21 g (32 mmol) of $LiAlH_4$ in 20 ml of pure and dry ether under Ar was added dropwise at 0°C, a solution of 4.0 g (16 mmol) of **26** dissolved in 80 ml of ether. After addition of the diester, the reaction mixture was stirred at 0°C for 1 h, at rt for 18 h and at reflux temperature for 6 h. The reaction mixture was cooled to 0°C and 1.3 ml of a saturated aqueous NH_4Cl solution was slowly added. Then 2.6 ml of 5% aqueous NaOH solution was added. The resulting mixture was stirred at 0°C for 10 min, at rt for 30 min and at reflux temperature for 16 h. After the reaction mixture was cooled to rt, the white precipitate was filtered and washed three times with 50 ml portions of ether. The ethereal filtrate and washings were combined, dried ($MgSo_4$), filtered and the solvent was evaporated under reduced pressure. The resulting white solid was recrystallized from ether to give 2.64 g (85%) of **27** as white crystals; m.p. 56–58°C; IR (KBr) 3356, 3030, 1610, 1597, 1423, 1366, 1299, 1168, 1047, 989, 953, 874, 853, 708, 660 cm^{-1}; ^{1}H-NMR δ 3.35 (t, 2 H, J = 6 Hz, disappeared in D_2O), 4.40–4.48 (m, 2 H), 4.50 (t, 4 H, J = 6 Hz), 5.20–5.45 (m, 2 H), 5.9–6.13 (m), 6.72 (s, 2 H), 6.82 (s, 1 H).

5-Allyloxy-1,3-benzenedimethyl ditosylate (28) (Scheme II)

To a vigorously stirred suspension of 3.95 g (61.7 mmol, 87.6% assay) of finely powdered KOH in 20 ml of pure and dry THF at 0°C under Ar was added 2.65 g (13. 6 mmol) of **27** dissolved in 50 ml of THF. Then 6.5 g (34 mmol) of TsCl dissolved in 40 ml of THF was added dropwise. The reaction mixture was stirred at 0°C for 4 h. By that time, the TLC analysis showed the disappearance of both the starting alcohol and tosyl chloride and the appearance of a single spot at $R_f = 0.8$ [silica gel, eluant = CH_3OH/toluene (1/4)]. Isolation of **28** was done rapidly and at low temperature because the benzyl tosylates are known to be unstable at rt.[18] After the reaction was completed, the solvent was evaporated under reduced pressure and the residue was dissolved in a mixture of 200 ml of CH_2Cl_2, 50 g of ice and 40 ml of water. The phases were shaken well and separated. The aqueous phase

was shaken with 200 ml of Ch_2Cl_2. The combined organic phase was dried ($MgSO_4$), filtered and the solvent was removed under reduced pressure to give 6.63 g (97%) of an oil which was immediately used in the next step without further purification; IR (neat) 3090, 3069, 3032, 1599, 1494, 1478, 1456, 1360, 1189, 1177, 1096, 933 cm^{-1}; ^{1}H-NMR δ 2.44 (s, 6 H), 4.38–4.51 (m, 2 H), 4.94 (s, 4 H), 5.21–5.48 (m, 2 H), 5.88–6.12 (m, 1 H), 6.68 (s, 1 H), 6.72 (s, 2 H), 7.32 (d, 4 H, J = 10 Hz), 7.78 (d, 4 H, J = 10 Hz).

5-Allyloxy-1,3-bis(4-hydroxy-3*S*-(+)-methyl-2-oxabutyl)benzene (30) (Scheme II)

To a stirred suspension of 1.21 g (40.3 mmol, 80% dispersion in mineral oil) of NaH in 10 ml of dry, pure THF, was added dropwise at 0°C under Ar 4.61 g (28.8 mmol) of (*S*)-(−)-2-(tetrahydropyranyloxy)-propanol (**29**)[10] dissolved in THF. The reaction mixture was stirred at 0°C for 10 min, at rt for 10 min and at reflux temperature for 3 h. The reaction mixture was cooled to 0°C, and 6.03 g (12 mmol) of **28**, dissolved in 50 ml of THF, was added over a 3 min period. The reaction mixture was stirred at 0°C for 20 min, then at rt for 2 days and the solvent was evaporated under reduced pressure. The residue was dissolved in a mixture of 250 ml of CH_2Cl_2, 60 g of ice and 30 ml of water. The mixture was shaken well and separated. The aqueous phase was shaken twice with 100 ml portions of CH_2Cl_2. The combined organic phase was dried ($MgSO_4$), filtered and the solvent was removed under reduced pressure to give 5.7 g (99%) of THP blocked glycol. To the latter material was added a mixture of 1 ml of concentrated aqueous HCl and 100 ml of CH_3OH and the mixture was stirred at rt for 4 h. Na_2CO_3 (2.7 g) was added and the mixture was stirred overnight. The solvent was evaporated under reduced pressure and the residue was dissolved in a mixture of 200 ml of CH_2Cl_2 and 150 ml of water. The phases were mixed well and separated. The aqueous phase was shaken twice with 50 ml portions of CH_2Cl_2. The combined organic phase was dried ($MgSO_4$), filtered and the solvent was removed under reduced pressure. The crude product was purified by column chromatography on silica gel using acetone/benzene (1/4) as eluent to give 2.55 g (69%) of **30** as an oil; $[\alpha]_D^{22}$ + 16.51° (c = 2.75, $CHCl_3$); IR (neat) 3418, 3081, 1648, 1598, 1455, 1371, 1296, 1157, 1097, 1056, 1003, 930, 849 cm^{-1}; ^{1}H-NMR δ 1.12 (d, 6 H, J = 6 Hz), 2.71 (s, 2 H, broad, disappeared in D_2O), 3.22–3.46 (m, 4 H), 3.92–4.01 (m, 2 H), 4.49 (s, 4 H), 4.50–4.55 (m, 2 H), 5.23–5.43 (m, 2 H), 5.92–6.11 (m, 1 H), 6.81 (s, 2 H), 6.86 (s, 1 H); mass spectrum (low volt) m/e 310 (M^+).

19-Allyloxy-(4*S*,14*S*)-(+)-4,14-dimethyl-3,6,9,12,15-pentaoxa-21-azabicyclo[15.3.1]heneicosa-1(21),17,19-triene (8) (Scheme III)

To a well stirred suspension of 2.0 g (66 mmol) of NaH (80% dispersion in mineral oil) in 40 ml of pure, dry THF at 0°C under Ar was added dropwise 5.23 g (23.5 mmol) of (*S,S*)-**31** dissolved in 220 ml of THF. The mixture was stirred at 0°C for 10 min, at rt for 30 min and at reflux temperature for 3 h. The reaction mixture was cooled to −10°C and 12.5 g (24.8 mmol) of **23** dissolved in 260 ml of THF was added dropwise. The resulting mixture was stirred at −10°C for 20 min and then at rt for 36 h. After the reaction was complete, the solvent was evaporated under reduced pressure. The residue was dissolved in a mixture of 1000 ml of CH_2Cl_2, 100 g of ice and 200 ml of water. The resulting mixture was mixed well and separated. The aqueous phase was shaken twice with 200 ml portions of CH_2Cl_2. The combined organic phase was dried ($MgSO_4$), filtered and the solvent was removed under reduced pressure. The residue was purified on neutral alumina using toluene then C_2H_5OH/toluene (1/80) as eluents to give 5.42 g (60%) of **8** as a colourless oil; $[\alpha]_D^{22}$ + 26.88° (c = 1.50, $CHCl_3$); IR (neat) 3082, 1598, 1575, 1454, 1360, 1110, 1042 cm^{-1}; ^{1}H-NMR δ 1.12 (d, 6 H, J = 7 Hz), 3.33–3.67 (m, 12 H), 3.68–3.87 (m, 2 H), 4.51–4.61 (m, 2 H), 4.72 (s, 4 H), 5.22–5.45 (m, 2 H), 5.88–6.11 (m, 1 H), 6.76 (s, 2 H); mass spectrum (low volt), m/e 381 (M^+). Analysis calculated for $C_{20}H_{31}NO_6$: C, 62.97; H, 8.19. Found: C, 62.88; H, 7.92.

Silica gel-bound chiral crown 33 (Scheme III)

A mixture of 1.06 g (2.78 mmol) of **8** and 0.77 ml (0.685 g, 4.1 mmol) of triethoxysilane (freshly distilled under Ar) was stirred vigorously in a 5 ml one-necked flask equipped with a rubber septum. Two drops of PC072 catalyst (hüls America, Inc.) was added through the rubber septum. The hydrosilylation reaction was carried out as reported by Lewis.[30] After stirring the mixture for 6 days at rt, the ^{1}H-NMR spectra showed that the olefin protons had disappeared. The volatile compounds were removed from the reaction mixture under vacuum (0.02 mm) and the residue (1.49 g, 98%) was stirred with 6.0 g of silica gel (Davison Chemical, pore diameter 150 Å, 60–200 mesh) in 100 ml of toluene at 90°C for 2 days. After the reaction was completed, the silica gel was filtered and washed with toluene/methanol (1/1) and then with methanol. The filtrate was evaporated to give 0.47 g of unreacted organic material. This means that approximately 1.0 g (1.8 mmol) of crown was attached to the silica gel. The silica gel containing the crown was dried in a vacuum oven at 70°C for 5 h. A sample

of blank silica gel was dried the same way and it gave a combustion analysis of 0% C and 0.35% H. The combustion analysis of **33** gave C, 5.83; H, 1.16. This indicates that each gram of **33** contained 0.243 mmol (by %C) or 0.251 mmol (by %H) of the chiral crown.

10-Allyloxy-(4*S*,16*S*)-(+)-4,16-dimethyl-3,6,14,17-tetraoxa-23-aza-tricyclo[17.3.1.1^{8,12}]tetracosa-1(23),8,10,12,19,21-hexaene (*S*,*S*-9) (Scheme IV)

To a stirred suspension of 0.61 g (20 mmol, 80% dispersion in mineral oil) of NaH in 20 ml of pure, dry THF was added dropwise at 0°C and under Ar a solution of 2.23 g (7.18 mmol) of *S*,*S*-**30** dissolved in 120 ml of THF. The reaction mixture was stirred at 0°C for 10 min, at rt for 10 min and at reflux for 3 h. The mixture was cooled to 0°C and 3.55 g (7.93 mmol) of **34** dissolved in 120 ml of THF was added dropwise. After stirring the reaction mixture at 0°C for 10 min, it was stirred at rt for 2 days. When the reaction was completed, the solvent was evaporated under reduced pressure. The residue was dissolved in a mixture of 200 ml of CH_2Cl_2, 40 g of ice and 100 ml of water. The phases were shaken well and separated. The aqueous phase was shaken twice with 100 ml portions of CH_2Cl_2. The combined organic phase was dried ($MgSO_4$), filtered and the solvent was removed under reduced pressure. The residue was purified by chromatography on neutral alumina using toluene and C_2H_5OH/toluene (1/200) as eluents to give 1.37 g (46%) of **9** as a white solid; m.p. 48–49°C; $[\alpha]_D^{22}$ + 48.61° (c = 2.119, $CHCl_3$); IR (KBr) 3063, 1646, 1615, 1595, 1578, 1452, 1426, 1360, 1289, 1255, 1225, 1108, 1116, 1055, 1020, 1006, 863 cm^{-1}; ^{1}H-NMR δ 1.22 (d, 6 H, J = 6 Hz), 3.44–3.59 (m, 4 H), 3.7–3.91 (m, 2 H), 4.3–4.56 (m, 6 H), 4.65–4.81 (m, 4 H), 5.2–5.46 (m, 2 H), 5.91–6.14 (m, 1 H), 6.7 (s, 2 H), 7.0 (s, 1 H), 7.27 (d, 2 H, J = 8 Hz), 7.64 (t, 1 H, J = 8 Hz); mass spectrum (low volt) m/e 413 (M^+); Analysis calculated for $C_{24}H_{31}NO_5$: C, 69.71; H, 7.56. Found: C, 69.99; H, 7.67.

Separation of the *R*-(+) and *S*-(−) isomers of NapEtClO$_4$ using (*S*,*S*)-33

The preparation of (*R*)-(+)- and (*S*)-(−)-NapEtClO$_4$ was described earlier.[4] Pure (*R*)- and (*S*)-NapEtClO$_4$ were obtained by recrystallization from butyl acetate; (*R*)-NapEtClO$_4$; m.p. 184–185°C, $[\alpha]_{365}^{22}$ + 21.27° (c = 1, C_2H_5OH); (*S*)-NapEtClO$_4$; 183–184°C; $[\alpha]_{365}^{22}$ − 21.12° (c = 1, C_2H_5OH). (*R*)-NapEtClO$_4$ (40.0 mg) and 40.0 mg of (*S*)-NapEtClO$_4$ were dissolved in 8.0 ml of THF. $(C_2H_5)_3N$ (50 μl) was added to 2.0 ml of this solution and then 15 μl of acetic anhydride was added and the mixture was stirred at rt for 10 min. TLC analysis [silica gel with $CH_3CO_2C_2H_5$/hexane (6/4) as eluant] showed that a complete conversion of the perchlorate salt into the *N*-acetyl derivative of α-(1-naphthyl)ethylamine had occurred. After evaporation of the solvent under reduced pressure, the residue was dissolved in a mixture of 20 ml of $CH_3CO_2C_2H_5$ and 20 ml of H_2O. The mixture was shaken well and separated. The organic phase was dried ($MgSO_4$), filtered and the solvent was evaporated to give 15.7 mg (100%) of *N*-[α-(1-naphthyl)ethyl]-acetamide as white crystals; m.p. 158–159°C; ^{1}H-NMR δ 1.63 (d, 3 H, J = 6 Hz), 1.92 (s, 3 H), 5.80–6.00 (m, 2 H), 7.35–8.15 (m, 7 H); IR (KBr) 3292, 1631, 1540, 1372, 1274, 1125, 965, 780, 609 cm^{-1}. The enantiomeric ratio was determined to be 50.24% (*R*) and 49.76% (*S*) by HPLC analysis on a chiral column as mentioned below. The remainder of the above THF solution (6.0 ml) was evaporated to give 60.0 mg of racemic NapEtClO$_4$ which was dissolved in 1.0 ml of a CH_3OH/acetone (3/7) mixture and was placed onto the top of a column of 4.22 g of (*S*,*S*)-**33** and eluted with the CH_3OH/acetone (3/7 mixture). The flow rate of the eluant was 0.088 ml/min. The amount of NapEtClO$_4$ salt in each 4 ml fraction was determined using the *N*-acetyl derivitization described above. The determination was performed on Hewlett Packard HP 1090 Liquid Chromatograph (maximum pressure 300 ppsi, flow rate = 1 ml/min) using a chiracel ob chiral column (Daicel Chemical Industries, Ltd.). The internal standard was phthalimide. The HPLC solvent was 20% 2-propanol/80% n-hexane. The amount in milligrams of (*R*)(m_R)- and (*S*)-NapEtClO$_4$(m_S) in each fraction was determined from peak areas as calibrated from known samples. The calculated concentrations of (*R*)- and (*S*)-NapEtClO$_4$ were plotted versus the ml of eluant as shown in the smooth surface in Figure 2.

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