δ 207.2 (COMe), 201.3 (CHO), 170.6 (OCOMe), 66.8 (C-3), 59.4 (C-2), 51.3 (CH_2CHO), 40.5 (C-4), 33.5 (C-1), 32.5 (COMe), 27.7 (1-Me), 20.8 (OCOMe). MS: *m/z* (relative intensity) 170 (M - 42), 137 (3), 127 (6), 124 (8), 111 (5), 109 (13), 87 (99), 84 (7), 81 (9), 58 (7), 55 (4), 43 (100).

Acetate 8 (250 mg, 1.39 mmol) and *n*-Bu_4NBH_4 (308 mg, 1.25 mmol) were dissolved in 4 mL of CH_2Cl_2, and ozone was passed through the solution at -78 °C for 20 min. After the solution had been purged with N_2, the solvent was removed and a KI solution (1 M, in water) was added, which caused *n*-Bu_4NI to precipitate. The solution was filtered and extracted with Et_2O, and the Et_2O solution was dried ($MgSO_4$). TLC was run in 100% ethyl acetate. Product **10** (98.5 mg, 33%) was purified by LC with gradient elution with hexane and ethyl acetate (20–100%) then ethyl acetate and increasing amounts of MeOH.

1-[4-Acetoxy-2-(2,2-dimethoxyethyl)-2-methylcyclobutyl]ethanone (11). To a stirred solution of **10** (98.5 mg, 0.46 mmol) in methanol (0.5 mL) was added *p*-TsOH (0.36 mg, 0.002 mmol) at room temperature. After 1.5 h, saturated $NaHCO_3$ (5 mL) was added to the mixture and the product was extracted with Et_2O, dried ($MgSO_4$), and concentrated to give acetal **11** (97 mg, 82%). TLC was run in 2% methanol in CH_2Cl_2. ^1H NMR: δ 5.07 (dt, *J* = 7.8, 7.8 Hz, 3-1 H), 4.38 (dd, *J* = 7.3, 4.6 Hz, CH-$(OMe)_2$), 3.48 (dd, *J* = 7.5, 3.2 Hz, 2-1 H), 3.27 (s, OMe), 3.23 (s, OMe), 2.35 (dd, *J* = 11.4, 8.3 Hz, 4-CH_2-1 H), 2.17–2.08 (m, 4-1 H and $HCOCH_2$-1 H), 2.08 (s, COMe), 1.99 (s, OAc), 1.64 (dd, *J* = 14.2, 4.6 Hz, $HCOCH_2$-1 H), 1.26 (s, 1-Me). ^{13}C NMR: δ 206.4 (CO), 170.9 (CO), 102.3 ($CH(OMe)_2$), 66.5 (C-3), 60.1 (C-2), 53.8 (OMe), 51.5 (OMe), 39.9 (1-CH_2), 39.8 (C-4), 34.9 (C-1), 33.2 (COMe), 27.1 (1-Me), 20.8 (OCOMe). MS: *m/z* (relative intensity) 201 (M - 57, 2), 169 (3), 141 (6), 127 (5), 125 (8), 109 (19), 87 (8), 83 (7), 75 (98), 58 (14), 55 (5), 43 (100).

3,3,7-Trimethyl-2,9-dioxatricyclo[3.3.1.0^{4,7}]nonane (Lineatin, 1). To a solution of acetal **11** (15.0 mg, 0.06 mmol) in dry Et_2O (1 mL) was gradually added MeMgBr (3.0 M solution in Et_2O, 70 μL, 0.21 mmol) at 0 °C (ice bath). The mixture was stirred at room temperature for 1 h, poured into 10% HCl (1 mL, with ice added), and extracted with *n*-pentane (4 × 10 mL). The combined organic phase was washed with saturated $NaHCO_3$ (10 mL), saturated $Na_2S_2O_3$ (5 mL), and H_2O (5 mL) and then dried ($MgSO_4$) and concentrated at atmospheric pressure to give a product (9.0 mg, 92%) containing 83% of compound **1** as determined by GC. TLC was run in 40% ethyl acetate in hexane. Chromatography on silica gel using gradient elution with pentane and increasing amounts of Et_2O gave pure lineatin. ^1H NMR: δ 5.12 (d, *J* = 3.2 Hz, 1-1 H), 4.52 (dd, *J* = 4.2, 3.2 Hz, 5-1 H), 2.12 (dd, *J* = 12.6, 3.2 Hz, 8-1 Hz), 1.99 (dd, *J* = 12.6, 2.3 Hz 8-1 H), 1.93 (dd, *J* = 4.2, 1.3 Hz, 4-H), 1.76 (ddd, *J* = 10.2, 3.2, 2.3 Hz, 6-1 H), 1.68 (d, *J* = 10.2 Hz, 6-1 H), 1.27 (s, 7-Me), 1.20 (s, 3-Me), 1.19 (s, 3-Me). ^{13}C NMR: δ 92.8 (C-1), 72.5 (C-3), 71.5 (C-5), 48.1 (C-4), 43.5 (C-8), 42.1 (C-6), 37.8 (C-7), 29.0 (7-Me), 27.9 (3-Me), 26.3 (3-Me). MS: *m/z* (relative intensity) 168 (M^+, 1), 153 (5), 140 (4), 125 (34), 111 (61), 107 (51), 100 (5), 96 (65), 91 (14), 85 (100), 69 (51), 55 (96), 41 (91). The spectra are consistent with those in the literature.[21]

Acknowledgment. We thank Professor Torbjörn Norin for helpful discussions and Dr. Ulla Jacobsson for running the NOE experiments and being helpful with the NMR work in general. Fina Liotta has been very helpful in correcting the English. We also thank the Swedish Council for Planning and Coordination for Research and the Swedish Science Research Council for financial support.

Supplementary Material Available: ^1H and ^{13}C NMR spectra of intermediates **6–11** and the final product, lineatin (17 pages). Ordering information is given on any current masthead page.

(21) Some previously published ^1H NMR data on lineatin are found in refs 5b, 7d–f.

Synthesis and Complexation Properties of a Water-Soluble Optically Active Cyclophane Incorporating a 4-Naphthyl-1,2,3,4-tetrahydroisoquinoline Unit as a Chiral Spacer

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The unnatural alkaloid 6-methoxy-4-[2-(6-methoxynaphthalenyl)]-1,2,3,4-tetrahydroisoquinoline (**5**) was prepared as a chiral spacer for optically active cyclophane receptors. Optical resolution of the building block was accomplished through diastereomeric salt formation with dibenzoyltartaric acid. The *S* configuration was assigned by X-ray crystallographic methods to the hydrochloride salt of (-)-**5**. Starting from enantiomerically pure **5**, the optically active cyclophanes (*R*)- and (*S*)-**4** were prepared. These cyclophanes, in which the chiral alkaloid spacer is bridged to an achiral diphenylmethane unit, are efficient binders of naphthalene derivatives in D_2O/CD_3OD (60:40, v/v) and show a modest degree of chiral recognition in the inclusion complexation of naproxen derivatives.

In efforts to generate optically active cyclophane receptors[1] for the enantioselective complexation of naproxen derivatives, we had prepared the macrocycle (+)-**1** which incorporates the 4-phenyl-1,2,3,4-tetrahydroisoquinoline unit **2** as a chiral spacer.[2,3] In D_2O/CD_3OD (60:40, v/v), cyclophane (+)-**1** and the enantiomers of naproxen (**3a**) or its methyl ester (**3b**)[4] form diastereomeric inclusion complexes with different geometries. However, these complexes possess only moderate stability ($K_a \approx 50$–300 L mol^{-1} at 303 K), and MM2 force field calculations

(1) Recent examples of enantioselective complexation of organic guest molecules: (a) Jeong, K.-S.; Muehldorf, A. V.; Rebek, J., Jr. *J. Am. Chem. Soc.* **1990**, *112*, 6144–6145. (b) Liu, R.; Sanderson, P. E. J.; Still, W. C. *J. Am. Chem. Soc.* **1990**, *55*, 5184–5186. (c) Bradshaw, J. S.; Huszthy, P.; McDaniel, C. W.; Zhu, C. Y.; Dalley, N. K.; Izatt, R. M.; Lifson, S. *J. Org. Chem.* **1990**, *55*, 3129–3137. (d) Castro, P. P.; Georgiadis, T. M.; Diederich, F. *J. Org. Chem.* **1989**, *54*, 5835–5838. (e) Echavarren, A.; Galán, A.; Lehn, J.-M.; De Mendoza, J. *J. Am. Chem. Soc.* **1989**, *111*, 4994–4995. (f) Pirkle, W. H.; Pochapsky, T. *Chem. Rev.* **1989**, 347–362. (g) Petti, M. A.; Shepodd, T. J.; Barrans, R. E., Jr.; Dougherty, D. A. *J. Am. Chem. Soc.* **1988**, *110*, 6825–6840.

(2) Dharanipragada, R.; Ferguson, S. B.; Diederich, F. *J. Am. Chem. Soc.* **1988**, *110*, 1679–1690.

(3) There exists no correlation between the arbitrarily chosen absolute configuration in the perspective drawing of (+)-**1** and the experimentally determined sign of optical rotation. The absolute configuration of (+)-**1** is not known.

(4) Harrison, I. T.; Lewis, B.; Nelson, P.; Rooks, W.; Roszkowski, A.; Tomolonis, A.; Fried, J. H. *J. Med. Chem.* **1970**, *13*, 203–205.

0022-3263/91/1956-3362$02.50/0

pointed out that there exists a broad range of low-energy macrocycle conformations that show poor preorganization, giving a partially filled cavity. In order to prevent such unfavorable macroring conformations, we decided to construct the novel hosts (*R*)- and (*S*)-**4**, which incorporate the 4-naphthyl-1,2,3,4-tetrahydroisoquinoline unit **5** as a larger chiral spacer.[5] Whereas the O···O distances in the computed low energy conformations of the phenyl derivative **2** are 6.33 and 7.58 Å,[2] the O···O distances measured by X-ray crystallography for two conformers of the hydrochloride salt of the naphthyl spacer **5** are much larger (8.99 and 9.97 Å, respectively; see below).

This paper describes the synthesis, optical resolution, and determination of the absolute configuration of the novel tetrahydroisoquinoline alkaloid **5**. Starting from enantiomerically pure **5**, the optically active cyclophanes (*R*)- and (*S*)-**4** are prepared and their binding and chiral recognition properties in aqueous solution investigated.

Synthesis and Optical Resolution of the Chiral Spacer 5. The preparation of the tetrahydroisoquinoline **5** started with the alcohol **6**[6] obtained in 78% yield in the Grignard reaction between *m*-anisaldehyde and [2-(6-methoxynaphthyl)]magnesium bromide. Treatment of a benzene solution of **6** with gaseous HCl gave the chloride **7** in a quantitative yield. The reaction of **7** with potassium cyanide in acetonitrile in the presence of 18-crown-6 led to the nitrile **8** in 70% yield. Nitrile **8** was readily resolved on a cellulose triacetate stationary phase with ethanol as the eluant.[7] However, this resolution was not pursued on the way to the spacer **5**, since ethanol solutions of the pure enantiomers of **8** were found to completely racemize within 20 h at 20 °C.

The reduction of nitrile **8** with BH_3·tetrahydrofuran (THF) afforded the primary amine **9** which was converted with ethyl formate into the corresponding formamide **10** (80% yield starting from the nitrile). In a Bischler–Napieralski reaction,[8] the formamide was reacted with phosphorus oxychloride in dry acetonitrile to yield the crude imine **11** which was reduced with sodium borohydride to the secondary amine **5** (83% yield starting from **9**). The optical resolution of **5** was achieved through fractional crystallization (ethanol/water, 8:1) of the diastereomeric salts formed between the racemic amine and (+)- and (−)-dibenzoyltartaric acid. After three recrystallizations and removal of the resolving agent, the enantiomers (−)-**5** [$[\alpha]^{31}_{589} = -60°$ (*c* 1.04, $CHCl_3$)] and (+)-**5** [$[\alpha]^{25}_{589} = -68°$ (*c* 1.00, $CHCl_3$)] were obtained each with an optical purity ≥ 98% ee. The enantiomeric purities were determined by ^1H NMR analysis of the diastereomeric ureas that form upon addition of an excess of (*S*)-α-methylbenzyl isocyanate to $CDCl_3$ solutions of the resolved amines.[2,9] The 500-MHz ^1H NMR spectrum of the crude mixture obtained from (−)-**5** showed two doublets for benzylic protons at δ 0.97 [(α-methylbenzyl)urea diastereoisomer] and at δ 1.60 (excess isocyanate). Similarly, the spectrum of the diastereoisomer formed by (+)-**5** showed only two peaks at δ 1.60 and 1.36 [(α-methylbenzyl)urea diastereoisomer]. Expectedly, three doublets for benzylic protons at δ 1.60, 1.36, and 0.97 appear in the spectrum of the solution prepared from the racemic amine (±)-**5**. When a dichloromethane solution of (−)-**5** was washed with saturated NaCl and concentrated through slow evaporation, X-ray quality crystals of the ammonium hydrochloride salt (−)-**12** were obtained, and its absolute

Table I. Crystal and Data Collection Parameters for (−)-12

T (K)	298
formula	$C_{21}H_{21}O_2N_1$·HCl
MW	355.86
space group	$P2_1$
a (Å)	7.836 (0.9)
b (Å)	5.871 (1.1)
c (Å)	20.272 (1.8)
α (deg)	90.005 (11)
β (deg)	100.044 (8)
γ (deg)	89.976 (12)
V (calcd) (Å^3)	918.33 (22)
d (calcd) (g cm^{-3})	1.079
data collection instrument	Rigaku AFC5R
monochromator	graphite
radiation	Cu Kα
scan method	$2\theta/\omega$
crystal size	0.10 × 0.40 × 0.225 mm
total refls	1516
total refls ($I/\sigma > 3$)	1367
$2\theta_{max}$	120.0
no. of refls refined	1366
no. of parameters	210
R	0.053
R_w	0.076
GOF	2.36

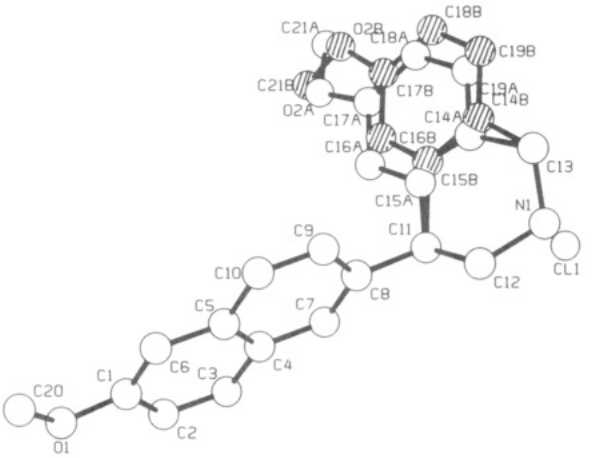

Figure 1. Molecular structure of (−)-**12** showing both conformers A and B (lined atoms) resulting from a true disorder in the tetrahydroisoquinoline ring.

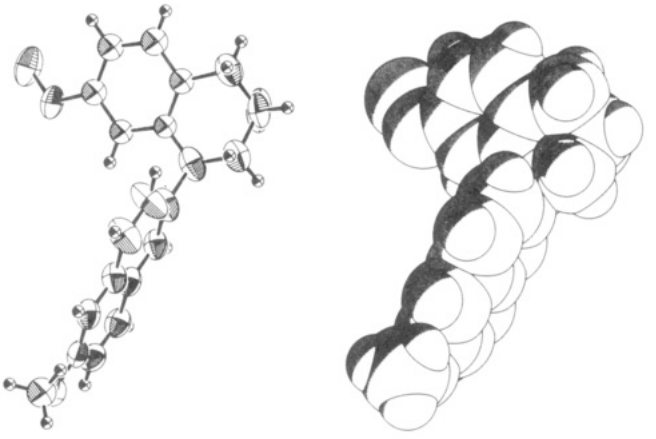

Figure 2. ORTEP and space-filling representations of conformer A of (−)-**12**.

(5) For recent syntheses of 4-phenyl-1,2,3,4-tetrahydroisoquinolines and their pharmacological properties, see: (a) Riggs, R. M.; Nichols, D. E.; Foreman, M. M.; Truex, L. L.; Glock, D.; Kohli, J. D. *J. Med. Chem.* **1987**, *30*, 1454–1458. (b) Zára-Kaczián, E.; György, L.; Deák, G.; Seregi, A.; Dőda, M. *J. Med. Chem.* **1986**, *29*, 1189–1195.

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(7) Eggersdorfer, M.; Zimmermann, H., BASF AG, Ludwigshafen, Germany, unpublished results.

(8) Bischler, A.; Napieralski, B. *Ber. Dtsch. Chem. Ges.* **1893**, *26*, 1903–1908.

(9) Rice, K. C.; Brossi, A. *J. Org. Chem.* **1980**, *45*, 592–601.

Chart I

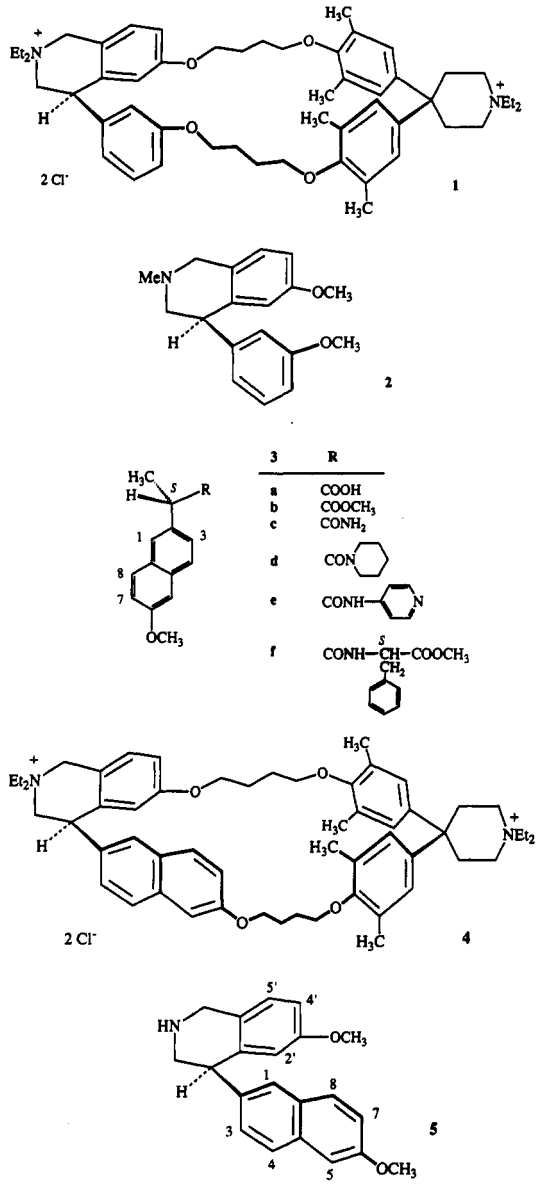
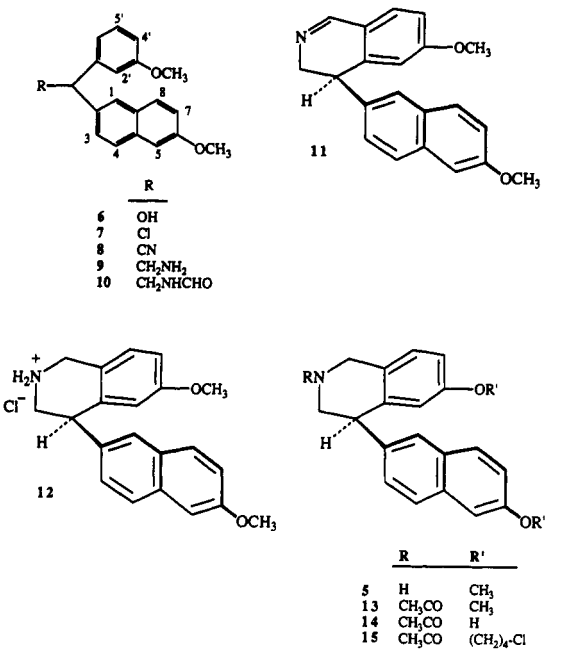


Chart II



configuration was determined using X-ray crystallographic methods.

X-ray Crystal Structure of the Hydrochloride Salt (−)-12. To determine the structural characteristics and the absolute configuration of the novel alkaloid spacer, the X-ray crystal structure of (−)-12 was solved. Table I shows the crystal and data collection parameters for (−)-12. The aromatic portion of the isoquinoline ring was found to be disordered. It is believed to be a true disorder involving two conformers (A and B in Figure 1). The O···O distance that is critical for the spacer qualities of the compound was determined as 8.99 Å in conformer A and 9.97 Å in conformer B. Figure 2 includes an ORTEP and a space-filling drawing for the A conformer of (−)-12.

Figure 3 shows that the ammonium chloride centers of the individual (−)-12 molecules in the crystal align to form an interesting channel-type array. This ion network seems to be more important than aromatic–aromatic interactions in determining the crystal packing since all intermolecular distances between naphthalene carbon atoms of the two symmetry-related molecules in the unit cell as well as between these atoms of two molecules of same orientation are larger than 3.60 Å. The only short intermolecular carbon–carbon contacts (3.51 and 3.57 Å, respectively) are

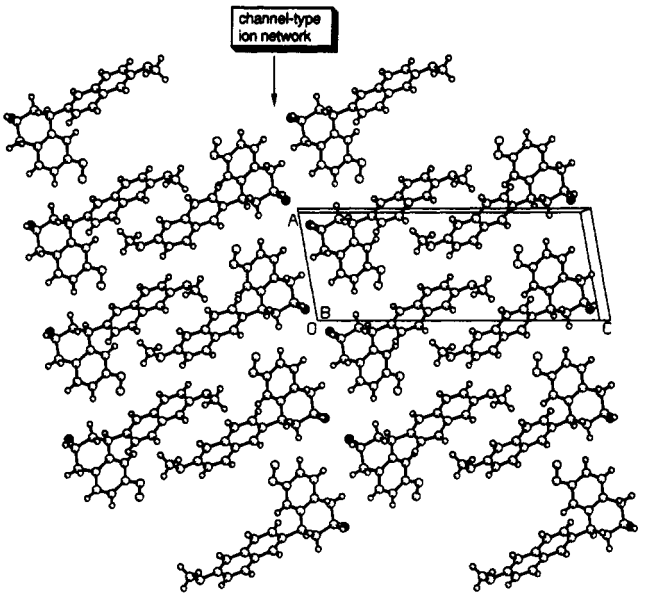


Figure 3. Crystal packing of (−)-12 showing the channel-type ion network. The dark circles represent chloride ions.

measured between the methoxy carbon atom C(20) and the naphthalene carbon atoms C(5) and C(10) of the two symmetry-related molecules in the unit cell.

The absolute configuration of (−)-12 was determined by two different methods.[10-12] The Hamilton *R* factor significance test[13-15] was done using the weighted residuals for the model and its inverse refined to convergence using the unique data. Additionally, a second data set was collected using the same crystal and instrument which included 473 Freidel pairs. The presence of a chloride ion provides a reasonable anomalous signal from which the absolute configuration can be determined. The weighted residual was compared for the model and its inverse refined

(10) Bijvoet, J. M.; Peerdeman, A. F.; Van Bommel, A. J. *Nature (London)* **1951**, *168*, 271–272.
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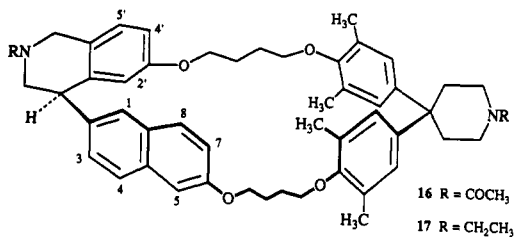
(15) Rogers, D. *Acta Crystallogr.* **1981**, *A37*, 734–741.

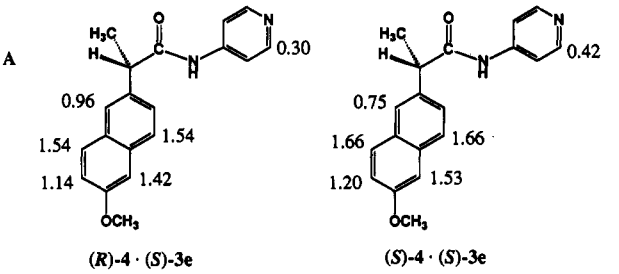
Table II. Association Constants, K_a, and Free Energies of Formation, $-\Delta G°$, of the Diastereomeric Complexes between (*R*,*S*)-4 and (*S*)-3a–f in D_2O/CD_3OD (60:40, v/v, T = 293 K)[a] (the Calculated Differences in Stability between Diastereomeric Complexes, $\Delta(\Delta G°)$, Are Shown)

	(*R*)-4		(*S*)-4		
naproxen derivative	K_a (L mol^{-1})	$-\Delta G°$ (kcal mol^{-1})	K_a (L mol^{-1})	$-\Delta G°$ (kcal mol^{-1})	$\Delta(\Delta G°)$ (kcal mol^{-1})
3a[b]	930	3.98	810	3.90	0.08
3b	1130	4.09	1070	4.06	0.03
3c	450	3.56	420	3.52	0.04
3d	730	3.84	470	3.58	0.26
3e	1210	4.13	900	3.96	0.17
3f[c]	230	3.16	200	3.08	0.08

[a] Error in $-\Delta G°$: ±0.05 kcal mol^{-1}. [b] In 0.01 M DCl/CD_3OD (60:40, v/v). [c] In D_2O/CD_3OD (50:50, v/v).

Chart III





to convergence using the Freidel pairs. The assignment of the absolute configuration was unambiguous and consistent for both tests. The structure was assigned as (*S*)-(−)-**12**.

Synthesis of the Optically Active Cyclophanes. Starting from the pure enantiomers (*R*)-(+)-**5** and (*S*)-(−)-**5**, the target cyclophanes (*R*)- and (*S*)-**4** were prepared. On the way to the *S* host, the amine (*S*)-**5** was acetylated with acetic anhydride to give the amide (*S*)-**13** ($[\alpha]^{28}_{589}$ = −20° (*c* 1.01, $CHCl_3$)) in 73% yield. Demethylation with boron tribromide afforded the diphenol (*S*)-**14**, which was dialkylated with 1,4-dichlorobutane (dimethylformamide (DMF), Cs_2CO_3) to yield the dichloride (*S*)-**15** (42% yield, $[\alpha]^{28}_{589}$ = −37° (*c* 1.10, $CHCl_3$)). Cyclization of this dichloride with 1-acetyl-4,4-bis(4-hydroxy-3,5-dimethoxyphenyl)piperidine[16] led to the macrocycle (*S*)-**16** ($[\alpha]^{28}_{589}$ = +26° (*c* 0.79, $CHCl_3$)) in 43% yield. A similar change in the sign of the optical rotation accompanying the transition from chiral cyclization component to macrocycle had previously been observed in the preparation of optically active cyclophane hosts.[1d,g,2] Reduction of the macrocyclic diamide with BH_3·THF afforded the diamine (*S*)-**17** ($[\alpha]^{27}_{589}$ = +31° (*c* 1.00, $CHCl_3$)) in 74% yield. The target compound (*S*)-**4** ($[\alpha]^{22}_{589}$ = +51° (*c* 1.02, CD_3OD)) was obtained in 80% yield by quaternization of the macrocyclic bis(tertiary amine) in pure ethyl iodide followed by ion exchange chromatography (Cl^-).

Clear evidence that the optical purity was maintained from (*R*,*S*)-**5** to the stage of the bisquaternized hosts was provided by the complexation studies described below. In addition, the two *N*-acetyl groups of the macrocyclic diamide (+)-**16** were cleaved with refluxing HCl. The crude product of the hydrolysis was mixed with (*S*)-(−)-α-methylbenzyl isocyanate in $CDCl_3$. The ^1H NMR (500 MHz) spectrum showed three doublets for benzylic methyl protons at δ = 0.95 (urea at piperidine unit), 1.45 (urea at alkaloid unit), and 1.60 (excess isocyanate). The solution of the two diastereoisomers obtained by starting with the racemic macrocyclic diamide (±)-**16** gave four signals at δ 0.95, 1.44, 1.45, and 1.60.

Complexation Studies with the Cyclophanes (*R*)- and (*S*)-4. The binding ability of the novel cyclophane

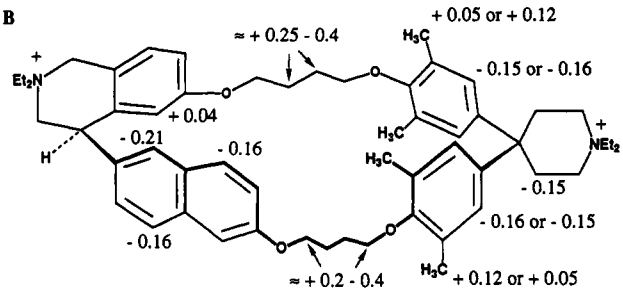


Figure 4. (A) Upfield ^1H NMR complexation shifts (ppm) calculated for saturation binding of (*S*)-**3e** by (*R*,*S*)-**4** in D_2O/CD_3OD (60:40, v/v). (b) Characteristic complexation-induced shifts of the host resonances in D_2O/CD_3OD (60:40, v/v) containing [(*R*)-**4**] = [(*S*)-**3a**] = 0.005 M (T = 293 K, + = upfield shift). Due to signal overlap, some resonances were not assigned.

system in D_2O/CD_3OD (60:40, v/v) at 293 K was analyzed in ^1H NMR binding titrations at fast exchange conditions. Host concentration ranges were chosen to reach ≈70–90% saturation binding of the guest which was taken at constant concentration. A comparative study with 6-methoxy-2-naphthonitrile as the guest showed that **4** (K_a = 2150 L mol^{-1}, $-\Delta G°$ = 4.47 kcal mol^{-1}) forms a more stable axial-type 1:1 inclusion complex than the alkaloid–macrocycle **1** (K_a = 340 L mol^{-1}, $-\Delta G°$ = 3.50 kcal mol^{-1})[2] and is as efficient as a recently reported cyclophane which incorporates the 2,2′,7,7′-tetrahydroxy-1,1′-binaphthyl unit as the chiral spacer (K_a = 1990 L mol^{-1}, $-\Delta G°$ = 4.42 kcal mol^{-1}).[1d,17] Cyclophane **4** is a better binder than **1** since the novel chiral spacer **5** generates a more open, organized binding site than the previously utilized spacer **2**.

The naproxen derivatives **3a–f** form diastereomeric 1:1 inclusion complexes of differential geometry with (*R*)- and (*S*)-**4**. Figure 4A shows the differential NMR complexation shifts of the guest resonances in the two complexes formed by (*S*)-**3e**. Figure 4B illustrates the characteristic up- and downfield shifts observed for the resonances of the complexed hosts. Table II gives the association constants, K_a, and the free energies of formation, $-\Delta G°$, for the diaste-

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reomeric complexes formed by (S)-**3a–f** and the two host enantiomers. Corresponding data are obtained in titrations with *R* guests. A significant difference in stability between the diastereomeric complexes $\Delta(\Delta G°)$ is only observed for the naproxen derivatives **3d** and **3e** with bulky amide groups. Evidently, differential steric interactions contribute to the observed enantioselectivity in binding. Table II shows that in the series of (S)-naproxen derivatives, the *R–S* complexes are more stable.

Two factors explain why only a moderate degree of enantioselection is observed in the complexation of naproxen derivatives by (*R*)- and (*S*)-**4**. (i) The binding sites of the cyclophanes are partially shaped by an achiral diphenylmethane unit. (ii) The macrorings possess considerable conformational flexibility in the unbound as well as in the complexed state. This allows the guest enantiomers to form diastereomeric complexes that are geometrically and, hence, also energetically rather similar. Consequently, improving enantiomer differentiation properties of chiral cyclophanes in future work requires a better control of macroring conformations.

Experimental Section

General. All ^{1}H NMR spectra were recorded at 500 MHz and, if not stated otherwise, at 303 K. In the characterization of new compounds below, the aromatic protons are numbered as shown in the structural drawings of Charts I–III. All coupling patterns are supported by 2D-COSY spectroscopy. EI mass spectra were obtained at 70 eV. FAB spectra were recorded in *m*-nitrobenzyl alcohol as the matrix. Melting points are uncorrected. Elemental analyses were performed at the Max-Planck-Institut für Medizinische Forschung, Heidelberg, and at Spang Microanalytical Laboratory, Eagle Harbor, MI. Analytical thin-layer chromatography (TLC) was conducted on E. Merck silica gel 60 F-254 precoated plates. Column chromatography was performed on silica gel (Kieselgel 60, 70–230 mesh) from E. Merck. The term in vacuo refers to solvent removal via a rotary evaporator at water aspirator pressure followed by evaporation at 0.5 mm for several hours. If not stated otherwise, product isolation at the end of the workup occurred by drying the combined organic phases over $MgSO_4$ followed by removal of the solvent with a rotary evaporator.

Solvents and reagents were purchased from Aldrich Chemical Co. and were used without further purification unless otherwise specified. THF was distilled from sodium benzophenone ketyl under Ar. The *R* isomer of naproxen was received as a gift from Syntex Corporation, Palo Alto, CA. The *S* isomer was provided by BASF AG. The (*S*)- and (*R*)-naproxen derivatives **3b**[2,4] and **3c**[18] were prepared according to literature procedures. In measurements of optical rotations, concentrations *c* are in grams of solute per 100 mL. The X-ray data were collected on an AFC5R Rigaku diffractometer. The TEXSAN software, distributed by Molecular Structure Corporation, was used for diffractometer and data processing in the structure determination. The chemical nomenclature used for macrocyclic compounds was determined by Chemical Abstracts Service.

^{1}H NMR Complexation Studies. All ^{1}H NMR titration data were obtained at 500 MHz in D_2O/CD_3OD (60:40, v/v) at T = 293 K, using the known position of the CH_3OD resonance against Me_4Si as an internal reference. A Sartorius 4503 microbalance and micropipettes were used for sample preparation. Usually, a stock solution of the guest in CD_3OD was added to solutions of the host in D_2O. The amount of host in each solution was individually weighted. The binding titrations were evaluated by nonlinear least-squares curve-fitting of the experimental data points. The K_a and $-\Delta G°$ values given throughout are averages of those calculated from the titration data for three or more aromatic guest protons.

Synthesis. [2-(6-Methoxynaphthalenyl)](3-methoxyphenyl)methanol (6). To 11.4 g (0.47 mol) of magnesium turnings under Ar was added 10 mL of a solution of 2-bromo-6-methoxynaphthalene (100.0 g, 0.422 mol) in 300 mL of anhydrous THF. Once the reaction had initiated, the residual solution of 2-bromo-6-methoxynaphthalene was added dropwise at a speed which maintained gentle reflux. After the addition was complete, the reaction was refluxed for 15 min, followed by the dropwise addition of 59.5 g (0.44 mol) of *m*-anisaldehyde in 200 mL of anhydrous THF. The mixture was then refluxed for 15 min and allowed to stir at 20 °C for 12 h. After evaporation of the solvent, the product was dissolved in 200 mL of CH_2Cl_2 and washed with 700 mL of 10% HCl. The aqueous layer was extracted with CH_2Cl_2 (3 × 250 mL), and the combined organic extracts were washed with water (100 mL) followed by saturated NaCl. The product **6** was obtained as a yellow oil which quickly solidified. The solid was washed with ether and collected by filtration: 97.0 g (78%) yield; mp 93–94 °C (lit.[6] mp 90–92 °C); IR ($CHCl_3$) ν (OH) 3570 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 3.78 (s, 3 H, OCH_3), 3.91 (s, 3 H, OCH_3), 5.94 (d, J = 2.4 Hz, 1 H, Ar_2CHOH), 6.8–6.85 (m, 1 H, 4′-H), 6.98 (bs, 1 H, 2′-H), 6.95–7.0 (m, 1 H, 6′-H), 7.10 (d, J = 2.4 Hz, 1 H, 5-H), 7.14 (dd, J = 8.9 and 2.4 Hz, 1 H, 7-H), 7.25–7.3 (m, 1 H, 5′-H), 7.40 (dd, J = 8.5 and 1.7 Hz, 1 H, 3-H), 7.68 (d, J = 8.5 Hz, 1 H, 4-H), 7.72 (d, J = 8.9 Hz, 1 H, 8-H), 7.79 (bs, 1 H, 1-H); EI-MS m/z (relative intensity) 294 (M^+, 100).

Chloro[2-(6-methoxynaphthalenyl)](3-methoxyphenyl)methane (7). A mixture of 100.0 g (0.34 mol) of **6** and 150 g (1.35 mol) of anhydrous calcium chloride in 400 mL of benzene was cooled under Ar to 0 °C, and a stream of HCl gas was bubbled in for 1 h. After filtration, the solvent was evaporated in vacuo, yielding 107.0 g (100%) of **7** as an oil, which was used without further purification in subsequent conversions: ^{1}H NMR ($CDCl_3$) δ 3.79 (s, 3 H, OCH_3), 3.91 (s, 3 H, OCH_3), 6.23 (s, 1 H, Ar_2CHCl), 6.82 (ddd, J = 8.3, 2.4, and 1.0 Hz, 1 H, 4′-H), 7.0–7.05 (m, 2 H, 6′-H, 2′-H), 7.10 (d, J = 2.5 Hz, 1 H, 5-H), 7.13 (dd, J = 8.9 and 2.5 Hz, 1 H, 7-H), 7.25 (t, J = 8.3 Hz, 1 H, 5′-H), 7.45 (dd, J = 8.5 and 1.5 Hz, 1 H, 3-H), 7.69 (d, J = 8.5 Hz, 2 H, 4-H, 8-H), 7.75 (d, J = 1.5 Hz, 1 H, 1-H); EI-MS m/z (relative intensity) 277 (M^+ – ^{35}Cl, 100); HRMS m/z (M^+) calcd 312.0917, obsd 312.0905. Anal. Calcd for $C_{19}H_{17}O_2Cl$ (312.5): C, 72.96; H, 5.48. Found: C, 73.37; H, 5.39.

[2-(6-Methoxynaphthalenyl)](3-methoxyphenyl)acetonitrile (8). A solution of 50.0 g (0.768 mol) of potassium cyanide, 7.2 g (0.027 mol) of 18-crown-6, and 107 g (0.34 mol) of chloride **7** in 850 mL of freshly distilled acetonitrile was stirred at 20 °C for 5 days under Ar. The solution was filtered, and the inorganic salts were collected and washed with CH_2Cl_2. The organic solutions were combined and washed with 1 L of water. The aqueous layer was extracted with CH_2Cl_2 (3 × 400 mL). Workup of the organic layers followed by recrystallization from ethyl acetate/cyclohexane yielded **8** as a white solid: 72.5 g (70% starting from alcohol **6**); mp 107–109 °C; IR ($CHCl_3$) ν (CN) 2247 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 3.76 (s, 3 H, OCH_3), 3.90 (s, 3 H, OCH_3), 5.22 (s, 1 H, Ar_2CHCN), 6.84 (ddd, J = 8.1, 2.3, and 0.7 Hz, 1 H, 4′-H), 6.89 (t, J = 2.3 Hz, 1 H, 2′-H), 6.95–7.0 (m, 1 H, 6′-H), 7.10 (d, J = 2.4 Hz, 1 H, 5-H), 7.16 (dd, J = 8.7 and 2.4 Hz, 1 H, 7-H), 7.27 (t, J = 8.1 Hz, 1 H, 5′-H), 7.31 (dd, J = 8.0 and 1.5 Hz, 1 H, 3-H), 7.70 (d, J = 8.0 Hz, 1 H, 4-H), 7.72 (d, J = 8.7 Hz, 1 H, 8-H), 7.79 (d, J = 1.5 Hz, 1 H, 1-H); EI-MS m/z (relative intensity) 303 (M^+, 100). Anal. Calcd for $C_{20}H_{17}NO_2$ (303.4): C, 79.19; H, 5.65; N, 4.62. Found: C, 79.03; H, 5.61; N, 4.51.

2-[2-(6-Methoxynaphthalenyl)]-2-(3-methoxyphenyl)ethylamine (9). A total of 445 mL (0.445 mol) of a 1 M solution of borane in THF was added dropwise at 0 °C to a solution of 30 g (0.099 mol) of nitrile **8** in 250 mL of dry THF under Ar. After being heated to reflux for 90 min, the mixture was cooled in an ice bath, and 110 mL of absolute ethanol was added dropwise at 0 °C. The amine–borane complex was destroyed by bubbling HCl gas into the solution for 75 min at 0 °C. Removal of solvents in vacuo left a white solid which was washed with 300 mL of ether. The solid was stirred with 50 mL of 2 N NaOH, and the aqueous solution was extracted with $CHCl_3$ (3 × 150 mL). The combined organic extracts were washed with water, and usual workup afforded the crude amine **9** in a quantitative yield (30.4 g) as a yellow oil which was used without further purification in the next conversion: IR ($CHCl_3$) ν (NH_2) 3520, 3378 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 2.2–2.4 (m, 2 H, NH_2), 3.37 (dd, J = 7.7 and 4.1 Hz, 2 H, Ar_2CHCH_2), 3.74 (s, 3 H, OCH_3), 3.88 (s, 3 H, OCH_3), 4.12 (t, J

(18) Bailey, D. M. U.S. Patent, US 4,169,108, 16 Aug 1973; Chem. Abstr. 1980, 92, P41647j.

= 7.7 Hz, 1 H, Ar_2CHCH_2), 7.33 (ddd, J = 8.0, 2.6, and 0.75 Hz, 1 H, 4'-H), 6.8–6.85 (m, 1 H, 2'-H), 6.85–6.9 (m, 1 H, 6'-H), 7.06 (d, J = 2.6 Hz, 1 H, 5-H), 7.11 (dd, J = 8.9 and 2.6 Hz, 1 H, 7-H), 7.21 (t, J = 8.0 Hz, 1 H, 5'-H), 7.28 (dd, J = 8.5 and 1.8 Hz, 1 H, 3-H), 7.61 (bs, 1 H, 1-H), 7.64 (d, J = 8.5 Hz, 1 H, 4-H), 7.67 (d, J = 8.9 Hz, 1 H, 8-H); EI-MS m/z (relative intensity) 307 (M^+, 10), 277 ($M^+ - CH_2NH_2$, 100); HRMS m/z (M^+, $C_{20}H_{21}NO_2$) calcd 307.1572, obsd 307.1579.

N-Formyl-2-[2-(6-methoxynaphthalenyl)]-2-(3-methoxyphenyl)ethylamine (10). A solution of 30.4 g (0.099 mol) of the crude amine **9** and a few drops of acetic acid in 650 mL (596 g, 8.0 mol) of ethyl formate was stirred at reflux under Ar for 12 h. Evaporation of the solvent afforded 32.8 g (99%) of the formamide as a brown foam. The crude product was used without further purification in the next conversion. For analytical purity, **10** was chromatographed (SiO_2, CH_2CH_2/ethyl acetate, 5:1) to give 26.5 g (80% starting from nitrile **8**) of a white foam which crystallized from ethyl acetate: mp 89–91 °C; IR ($CHCl_3$) ν (NH) 3434, (C=O) 1686 cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.75 (s, 3 H, OCH_3), 3.89 (s, 3 H, OCH_3), 3.95–4.05 (m, 2 H, Ar_2CHCH_2), 4.26 (t, J = 8.0 Hz, 1 H, Ar_2CHCH_2), 5.47 (bs, 1 H, NHCHO), 6.75–6.8 (m, 1 H, 4'-H), 6.8–6.85 (m, 1 H, 2'-H), 6.85–6.9 (m, 1 H, 6'-H), 7.08 (d, J = 2.3 Hz, 1 H, 5-H), 7.13 (dd, J = 8.9 and 2.3 Hz, 1 H, 7-H), 7.23 (t, J = 8.0 Hz, 1 H, 5'-H), 7.29 (dd, J = 8.4 and 1.6 Hz, 1 H, 3-H), 7.61 (bs, 1 H, 1-H), 7.66 (d, J = 8.4 Hz, 1 H, 4-H), 7.67 (d, J = 8.9 Hz, 1 H, 8-H), 8.09 (s, 1 H, NHCHO); EI-MS m/z (relative intensity) 335 (M^+, 23), 290 (M^+ – NHCHOH, 100). Anal. Calcd for $C_{21}H_{21}NO_3$ (335.4): C, 75.20; H, 6.31; N, 4.18. Found: C, 75.11; H, 6.22; N, 4.12.

6-Methoxy-4-[2-(6-methoxynaphthalenyl)]-3,4-dihydroisoquinoline (11). A solution of 32.8 g (0.098 mol) of crude **10** and 42 mL (69.09 g, 0.45 mol) of phosphorus oxychloride in 350 mL of dry acetonitrile was stirred at 20 °C under Ar for 12 h. The solvent was removed in vacuo to afford a yellow foam. The product was made alkaline by the addition of 10% NaOH and extracted with $CHCl_3$ (3 × 100 mL). The combined organic layers afforded **11** as a yellow foam in a quantitative yield (31.4 g). A small amount of the imine was further purified by chromatography (SiO_2, CH_2Cl_2) to yield a white solid: mp 101–103 °C; IR ($CHCl_3$) ν (C=N) 1590 cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.68 (s, 3 H, OCH_3), 3.85–3.9 (m, 1 H, Ar_2CHCH_2), 3.90 (s, 3 H, OCH_3), 4.05–4.15 (m, 1 H, Ar_2CHCH_2), 4.15–4.2 (m, 1 H, Ar_2CHCH_2), 6.4–6.45 (m, 1 H, 2'-H), 6.81 (ddd, J = 8.3, 2.6, and 0.62 Hz, 1 H, 4'-H), 7.1–7.15 (m, 2 H, 5-H, 7-H), 7.30 (dd, J = 8.5 and 1.8 Hz, 1 H, 3-H), 7.31 (d, J = 8.3 Hz, 1 H, 5'-H), 7.55 (d, J = 1.8 Hz, 1 H, 1-H), 7.66 (d, J = 8.6 Hz, 1 H, 8-H), 7.70 (d, J = 8.5 Hz, 1 H, 4-H), 8.3–8.35 (m, 1 H, $CHNCH_2$); HRMS m/z (M^+) calcd 317.1416, obsd 317.1398. Anal. Calcd for $C_{21}H_{19}NO_2$ (317.4): C, 79.47; H, 6.03; N, 4.41. Found: C, 79.23; H, 5.93; N, 4.30.

6-Methoxy-4-[2-(6-methoxynaphthalenyl)]-1,2,3,4-tetrahydroisoquinoline (5). A solution of 31.4 g (0.099 mol) of the crude imine **11** in 250 mL of absolute ethanol was stirred until it became homogeneous. The mixture was then cooled to 0 °C, and 15.0 g (0.40 mol) of $NaBH_4$ was slowly added. The reaction was stirred at 20 °C for 12 h. After removing the solvent in vacuo, 80 mL of water was added, and the aqueous solution was extracted with ethyl acetate (3 × 100 mL). The combined organic layers yielded 26.2 g (83% starting from **9**) of the amine **5** as a yellow foam which was subsequently resolved.

Optical Resolution of (±)-5. A hot solution of 11.8 g (0.03 mol) of (+)-dibenzoyl-D-tartaric acid in 45 mL of ethyl acetate was added to a hot solution of 10 g (0.03 mol) of racemic amine (±)-**5** in 10 mL of ethyl acetate. After some additional heating, the clear solution was left at 20 °C for crystallization. Three crystallizations of the collected solid from 90 mL of ethanol–water (8:1) afforded the diastereomeric salt (–)-**5**-(+)-dibenzoyl-D-tartaric acid. The salt was partitioned between 12 M NH_4OH and CH_2Cl_2. After two more extractions of the aqueous layer with CH_2Cl_2, the combined organic solutions were washed with water and saturated NaCl and then dried over sodium sulfate. Removal of the solvent in vacuo yielded 1.5 g (15%) of (*S*)-(–)-**5** in enantiomeric purity ≥98%, which eventually crystallized. To determine the optical purity (% ee), 3.0 mg (0.009 mmol) of (–)-**5** and 1.5 mg (0.01 mmol) of (*S*)-(–)-α-methylbenzyl isocyanate was dissolved in 0.7 mL of $CDCl_3$, and the integration of the 500-MHz ^1H NMR signals for the benzylic methyl protons of the two possible diastereomeric ureas was evaluated. A small amount of (–)-**5** was recrystallized from CH_2Cl_2/hexane: mp 153–154 °C, $[\alpha]^{25}_{589}$ = –60° (*c* 1.04, $CHCl_3$); IR ($CHCl_3$) ν (NH) 3331 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.90 (bs, 1 H, NH), 3.13 (dd, J = 13.2 and 6.6 Hz, 1 H, $CHCH_2NH$), 3.40 (dd, J = 13.2 and 5.3 Hz, 1 H, $CHCH_2NH$), 3.61 (s, 3 H, OCH_3), 3.89 (s, 3 H, OCH_3), 4.03 (d, J = 16.2 Hz, 1 H, $ArCH_2NH$), 4.11 (d, J = 16.2 Hz, 1 H, $ArCH_2NH$), 4.18 (t, J = 5.7 Hz, 1 H, $CHCH_2NH$), 6.44 (d, J = 2.6 Hz, 1 H, 2'-H), 6.76 (dd, J = 8.4 and 2.6 Hz, 1 H, 4'-H), 7.02 (d, J = 8.4 Hz, 1 H, 5'-H), 7.10 (bs, 1 H, 5-H), 7.1–7.15 (m, 1 H, 7-H), 7.20 (dd, J = 8.4 and 1.6 Hz, 1 H, 3-H), 7.41 (bs, 1 H, 1-H), 7.63 (d, J = 8.9 Hz, 1 H, 8-H), 7.66 (d, J = 8.4 Hz, 1 H, 4-H); EI-MS m/z (relative intensity) 319 (M^+, 44), 291 (M^+ – 28, 100), 289 (M^+ – 29, 72). Anal. Calcd for $C_{21}H_{21}NO_2$ (319.4): C, 78.97; H, 6.63; N, 4.39. Found: C, 79.06; H, 6.54; N, 4.39.

In an analogous procedure, 16.63 g (0.442 mol) of (–)-dibenzoyl-L-tartaric acid monohydrate was added to 14.1 g (0.442 mol) of (±)-**5**. After three recrystallizations and workup as described above, 1.6 g (11.4%) of (*R*)-(+)-**5** with enantiomeric purity ≥98% was obtained: $[\alpha]^{25}_{589}$ = +68° (*c* 1.00, $CHCl_3$).

(*R*)-(+)- and (*S*)-(–)-2-Acetyl-6-methoxy-4-[2-(6-methoxynaphthalenyl)]-1,2,3,4-tetrahydroisoquinoline (13). A total of 15 mL of acetic anhydride was added dropwise into an ice-cold mixture of 1.0 g (3.11 mmol) of amine **5** and 0.51 g (6.22 mmol) of sodium acetate. After the mixture was stirred at 20 °C for 48 h, the solvent was removed in vacuo, and the residue was partitioned between 10% Na_2CO_3 (40 mL) and CH_2Cl_2 (40 mL). The aqueous layer was further extracted with CH_2Cl_2 (2 × 50 mL). The combined organic layers were washed with water (30 mL), followed by saturated NaCl (30 mL), and dried over Na_2SO_4 to give a yellow foam which, upon chromatography (SiO_2 ethyl acetate/CH_2Cl_2, 1:8), gave 0.82 g (73%) of amide **13** as a white foam: IR ($CHCl_3$) ν (C=O) 1686 cm^{-1}; ^1H NMR (Me_2SO-d_6, 402 K) δ 1.81 (s, 3 H, $NCOCH_3$), 3.62 (s, 3 H, OCH_3), 3.87 (s, 3 H, OCH_3), 3.85–3.9 (m, 2 H, $CHCH_2N$), 4.3–4.35 (m, 1 H, $CHCH_2N$), 4.55 (d, J = 16.2 Hz, 1 H, $ArCH_2N$), 4.80 (d, J = 16.2 Hz, 1 H, $ArCH_2N$), 6.49 (d, J = 2.5 Hz, 1 H, 2'-H), 6.83 (dd, J = 8.5 and 2.5 Hz, 1 H, 4'-H), 7.12 (dd, J = 9.0 and 2.4 Hz, 1 H, 7-H), 7.18 (d, J = 8.5 Hz, 1 H, 5'-H), 7.21 (dd, J = 8.5 and 1.7 Hz, 1 H, 3-H), 7.24 (d, J = 2.4 Hz, 1 H, 5-H), 7.49 (bs, 1 H, 1-H), 7.68 (d, J = 9.0 Hz, 1 H, 8-H), 7.70 (d, J = 8.5 Hz, 1 H, 4-H); EI-MS m/z (relative intensity) 361 (M^+, 100); (*R*)-**13** $[\alpha]^{26}_{589}$ = +15° (*c* 1.00, $CHCl_3$); (*S*)-**13** $[\alpha]^{28}_{589}$ = –20° (*c* 1.01, $CHCl_3$). Anal. Calcd for $C_{23}H_{23}NO_3$ (361.4): C, 76.43; H, 6.41; N, 3.88. Found: C. 76.09; H, 6.32; N, 3.81.

(*R*)-(+)- and (*S*)-(–)-2-Acetyl-6-(4-chlorobutoxy)-4-[6-(4-chlorobutoxy)-2-naphthalenyl]-1,2,3,4-tetrahydroisoquinoline (15). To a solution of 81 mg (0.22 mmol) of amide **13** in 10 mL of dry CH_2Cl_2 under Ar at –78 °C was added dropwise 1 mL (1.0 mmol) of a 1 M solution of boron tribromide in CH_2Cl_2. The mixture was slowly warmed to 20 °C and stirred for 8 h. After cooling to 0 °C, 10 mL of methanol was carefully added, and the reaction mixture was stirred for an additional 24 h. The volatiles were evaporated in vacuo, and the residue was partitioned between 30 mL of water and 20 mL of ethyl acetate. After further extraction of the aqueous layer with ethyl acetate (2 × 30 mL), the combined organic layers were washed with water (10 mL), followed by saturated NaCl (10 mL), and dried over Na_2SO_4. The diol **14** was obtained as an oil, which was used in the next conversion. A small amount was further purified via preparative thin-layer chromatography using a chromatotron (SiO_2, ethyl acetate/CH_2Cl_2, 1:2) and recrystallized from methanol: mp 243–244 °C; IR (KBr) ν (OH) 3389 cm^{-1}; ^1H NMR (Me_2SO-d_6, 393 K) δ 1.84 (s, 3 H, $NCOCH_3$), 3.80 (dd, J = 13.1 and 6.6 Hz, 1 H, $CHCH_2N$), 3.91 (dd, J = 13.1 and 4.3 Hz, 1 H, $CHCH_2N$), 4.2–4.25 (m, 1 H, $CHCH_2N$), 4.55 (d, J = 16.2 Hz, 1 H, $ArCH_2N$), 4.74 (d, J = 16.2 Hz, 1 H, $ArCH_2N$), 6.36 (d, J = 2.4 Hz, 1 H, 2'-H), 6.66 (dd, J = 8.4 and 2.4 Hz, 1 H, 4'-H), 7.06 (dd, J = 8.8 and 2.5 Hz, 1 H, 7-H), 7.06 (d, J = 8.4 Hz, 1 H, 5'-H), 7.10 (bs, 1 H, 5-H), 7.16 (dd, J = 8.5 and 1.3 Hz, 1 H, 3-H), 7.47 (bs, 1 H, 1-H), 7.59 (d, J = 8.5 Hz, 1 H, 4-H), 7.63 (d, J = 8.8 Hz, 1 H, 8-H), 8.3 (s, br, 2 H, OH); EI-MS m/z (relative intensity) 333 (M^+, 100); HRMS m/z (M^+, $C_{21}H_{19}NO_3$) calcd 333.1365, obsd 333.1350.

A mixture of the crude diol **14**, 0.27 g (1.8 mmol) of cesium fluoride, and 0.76 mL (6.62 mmol) of 1,4-dichlorobutane in 70 mL of dry acetonitrile was stirred at reflux under Ar for 24 h.

After cooling, the inorganic salts were removed by filtration, and the solution was evaporated to dryness. The residual oil was chromatographed (SiO_2, CH_2Cl_2), and 48 mg (42% starting from 13) of the dichloride **15** was obtained as a yellow foam: IR ($CHCl_3$) ν (C=O) 1678 cm^{-1}; ^1H NMR (Me_2SO-d_6, T = 393 K) δ 1.7–2.0 (m, 11 H, $ClCH_2CH_2CH_2CH_2O$ and $NCOCH_3$), 3.5–3.55 (m, 2 H, CH_2Cl), 3.65–3.7 (m, 2 H, CH_2Cl), 3.8–3.9 (m, 2 H, NCH_2CH), 3.85–3.9 (m, 2 H, OCH_2), 4.1–4.2 (m, 2 H, OCH_2), 4.3–4.35 (m, 1 H, $CHCH_2N$), 4.55 (d, J = 16.4 Hz, 1 H, CCH_2N), 4.79 (d, J = 16.4 Hz, 1 H, CCH_2N), 6.48 (d, J = 2.5 Hz, 1 H, 2′-H), 6.82 (dd, J = 8.4 and 2.5 Hz, 1 H, 4′-H), 7.1–7.25 (m, 4 H, 3-H, 5-H, 5′-H, 7-H), 7.49 (bs. 1 H, 1-H), 7.68 (d, J = 8.9 Hz, 1 H, 8-H), 7.68 (d, J = 8.5 Hz, 1 H, 4-H); EI-MS m/z (relative intensity) 513 (M^+, 100); HRMS m/z (M^+, $C_{29}H_{33}NO_3Cl_2$) calcd 513.1837, obsd 513.1819; (*R*)-**15** $[\alpha]^{24}_{589}$ = +36° (c 1.00, $CHCl_3$); (*S*)-**15** $[\alpha]^{28}_{589}$ = −37° (c 1.10, $CHCl_3$).

(*R*)-(−)- and (*S*)-(+)-1,2-Diacetyl-1′,2′,3′,8′,9′,10′,11′,23′,24′,25′,26′,35′a-dodecahydro-14′,20′,38′,41′-tetramethylspiro[piperidine-4,17′-[4,6:13,16:18,21]trietheno[28,32:31,35]dimetheno[17*H*][1,6,16,21]tetraoxacyclotritriacontino[25,24-*c*]pyridine] (16). A mixture of 2.85 g (5.5 mmol) of dichloride **15**, 2.00 g (5.5 mmol) of 1-acetyl-4,4-bis(4-hydroxy-3,5-dimethoxyphenyl)piperidine, and 8.15 g (25 mmol) of cesium carbonate in 600 mL of dry DMF was stirred at 70 °C under Ar for 5 days. After cooling, the cesium salts were removed by filtration, and the solution was evaporated to dryness under reduced pressure. The crude product was chromatographed (SiO_2, ethyl acetate/CH_2Cl_2, 9:1) to yield 2.0 g (43%) of **16** as a colorless foam: IR ($CHCl_3$) ν (C=O) 1628, 1605 cm^{-1}; ^1H NMR (Me_2SO-d_6, 403 K) δ 1.7–1.9 (m, 8 H, OCH_2CH_2), 1.95 (s, 3 H, $NCOCH_3$), 1.97 (s, 3 H, $NCOCH_3$), 2.01 (s, 6 H, Ar-CH_3), 2.15 (s, 6 H, Ar-CH_3), 2.2–2.3 (m, 4 H, NCH_2CH_2), 3.35–3.5 (m, 4 H, NCH_2CH_2), 3.64 (t, J = 6.6 Hz, 2 H, OCH_2CH_2), 3.8–3.95 (m, 6 H, OCH_2CH_2, $CHCH_2N$), 4.15 (t, J = 5.8 Hz, 2 H, OCH_2CH_2), 4.31 (t, J = 7.1 Hz, 1 H, $CHCH_2N$), 4.58 (d, J = 16.5 Hz, 1 H, $ArCH_2N$), 4.80 (d, J = 16.5 Hz, 1 H, $ArCH_2N$), 6.43 (d, J = 2.7 Hz, 1 H, 2′-H), 6.77 (bs, 2 H, Ar-H), 6.82 (dd, J = 8.1 and 2.7 Hz, 1 H, 4′-H), 6.87 (bs, 2 H, Ar-H), 7.01 (dd, J = 8.8 and 2.7 Hz, 1 H, 7-H), 7.14 (d, J = 2.7 Hz, 1 H, 5-H), 7.16 (dd, J = 8.5 and 2.3 Hz, 1 H, 3-H), 7.17 (d, J = 8.1 Hz, 1 H, 5′-H), 7.48 (bs, 1 H, 1-H), 7.59 (d, J = 8.5 Hz, 1 H, 4-H), 7.60 (d, J = 8.8 Hz, 1 H, 8-H); FAB-MS m/z (relative intensity) 809 (M^+ + 1, 100); (*R*)-**16** $[\alpha]^{25}_{589}$ = −21° (c 1.00, $CHCl_3$); (*S*)-**16** $[\alpha]^{28}_{589}$ = +26° (c 0.79, $CHCl_3$). Anal. Calcd for $C_{52}H_{60}N_2O_6 \cdot 1.5H_2O$ (836.1): C, 74.70; H, 7.59; N, 3.35. Found: C, 74.77; H, 7.67; N, 3.23.

(*R*)-(−)- and (*S*)-(+)-1,2′-Diethyl-1′,2′,3′,8′,9′,10′,11′,23′,24′,25′,26′,35′a-dodecahydro-14′,20′,38′,41′-tetramethylspiro[piperidine-4,17′-[4,6:13,16:18,21]trietheno[28,32:31,35]dimetheno[17*H*][1,6,16,21]tetraoxacyclotritriacontino[25,24-*c*]pyridine] (17). A total of 20 mL (20 mmol) of a 1 M solution of borane in THF was added to a solution of 1.036 g (1.24 mmol) of diamide **16** in 50 mL of dry THF. The mixture was stirred under Ar for 24 h at 20 °C and for 2 h under reflux. After cooling in an ice bath, a total of 100 mL of absolute ethanol was carefully added dropwise, and the reaction was stirred for an additional 4 h. After bubbling HCl gas into the ice-cooled reaction for 30 min, the volatiles were removed in vacuo. The residual oil was partitioned between 50 mL of 12 M NH_4OH and 50 mL of $CHCl_3$. The organic phase was washed with 50 mL of water, followed by saturated NaCl, and dried over Na_2SO_4 to yield 0.72 g (74%) of **17** as a yellow foam: ^1H NMR ($CDCl_3$) δ 1.03 (t, J = 7.1 Hz, 3 H, NCH_2CH_3), 1.13 (t, J = 7.1 Hz, 3 H, NCH_2CH_3), 1.75–1.85 (m, 4 H, OCH_2CH_2), 1.95–2.05 (m, 4 H, OCH_2CH_2), 2.08 (s, 6 H, Ar-CH_3), 2.16 (s, 6 H, Ar-CH_3), 2.25–2.35 (m, 2 H, NCH_2CH_3), 2.3–2.5 (m, 8 H, NCH_2CH_2), 2.5–2.6 (m, 3 H, NCH_2CH_3, $CHCH_2N$), 3.13 (dd, J = 11.4 and 6.0 Hz, 1 H, $CHCH_2N$), 3.53 (d, J = 14.7 Hz, 1 H, $ArCH_2N$), 3.6–3.7 (m, 4 H, OCH_2CH_2), 3.80 (t, J = 6.4 Hz, 2 H, OCH_2CH_2), 3.82 (d, J = 14.7 Hz, 1 H, $ArCH_2N$), 4.12 (t, J = 5.6 Hz, 2 H, OCH_2CH_2), 4.32 (dd, J = 8.9 and 6.0 Hz, 1 H, $CHCH_2N$), 6.26 (d, J = 2.4 Hz, 1 H, 2′-H), 6.70 (dd, J = 8.5 and 2.4 Hz, 1 H, 4′-H), 6.71 (s, 2 H, Ar-*H*), 6.75 (s, 2 H, Ar-*H*), 6.99 (d, J = 8.5 Hz, 1 H, 5′-H), 7.03 (d, J = 2.3 Hz, 1 H, 5-H), 7.06 (dd, J = 8.8 and 2.3 Hz, 1 H, 7-H), 7.16 (dd, J = 8.5 and 1.6 Hz, 1 H, 3-H), 7.55 (d, J = 8.5 Hz, 1 H, 4-H), 7.59 (bs, 1 H, 1-H), 7.62 (d, J = 8.8 Hz, 1 H, 8-H); FAB-MS m/z (relative intensity) 781 (M^+, 100); (*R*)-**17** $[\alpha]^{23}_{589}$ = −42° (c 1.00, $CHCl_3$); (*S*)-**17** $[\alpha]^{27}_{589}$ = +31° (c 1.00, $CHCl_3$); HRMS m/z (M^+, $C_{52}H_{84}N_2O_4$) calcd 780.4866, obsd 780.4892.

(*R*)-(−)- and (*S*)-(+)-1,1,2′,2′-Tetraethyl-1′,2′,3′,8′,9′,10′,11′,23′,24′,25′,26′,35′a-dodecahydro-14′,20′,38′,41′-tetramethylspiro[piperidine-4,17′-[4,6:13,16:18,21]trietheno[28,32:31,35]dimetheno[17*H*][1,6,16,21]tetraoxacyclotritriacontino[25,24-*c*]pyridinium] Dichloride (4). A solution of 1.05 g (1.3 mmol) of diamine **17** in 20 mL of freshly distilled ethyl iodide was stirred under Ar at 20 °C for 16 h. Removal of the solvent in vacuo left the bis(quaternary ammonium) diiodide as a yellow solid, which was analyzed without further purification: mp 221–227 °C dec. Anal. Calcd for $C_{56}H_{74}N_2O_4 \cdot I_2$ (1093.0): C, 61.54; H, 6.82; N, 2.56. Found: C, 61.16; H, 6.89; N, 2.46. The diiodide was subsequently dissolved in a minimum amount of methanol (≈10 mL) and passed over a Dowex ion exchange column (Cl^-) using water/methanol (60:40) as eluent. The product was triturated with ether to afford 1.06 g (80%) of the quaternary host **4** as a yellow hygroscopic solid: mp 240–245 °C dec; ^1H NMR (CD_3OD) δ 1.27 (t, J = 7.0 Hz, 6 H, NCH_2CH_{3pip}), 1.42 (t, J = 7.1 Hz, 3 H, NCH_2CH_{3isoqu}), 1.44 (t, J = 7.1 Hz, 3 H, NCH_2CH_{3isoqu}), 1.7–1.95 (m, 8 H, OCH_2CH_2), 2.06 (s, 6 H, Ar-CH_3), 2.22 (s, 6 H, Ar-CH_3), 2.65–2.75 (m, 4 H, NCH_2CH_2), 3.35–3.6 (m, 12 H, NCH_2CH_3, NCH_2CH_2), 3.8–4.1 (m, 8 H, OCH_2CH_2), 4.6–4.9 (m, 5 H, $CH_2NEt_2CH_2CH$), 6.43 (d, J = 2.3 Hz, 1 H, 2′-H), 6.90 (s, 2 H, Ar-*H*), 6.93 (dd, J = 8.7 and 2.3 Hz, 1 H, 4′-H), 6.96 (s, 2 H, Ar-*H*), 7.04 (dd, J = 8.7 and 2.3 Hz, 1 H, 7-H), 7.13 (d, J = 2.3 Hz, 1 H, 5-H), 7.21 (dd, J = 8.4 and 1.6 Hz, 1 H, 3-H), 7.23 (d, J = 8.7 Hz, 1 H, 5′-H), 7.67 (d, J = 8.7 Hz, 1 H, 8-H), 7.68 (d, J = 8.4 Hz, 1 H, 4-H), 7.77 (bs, 1 H, 1-H); FAB-MS $C_{56}H_{74}N_2O_4 \cdot Cl_2$ m/z (relative intensity) 873.5 (M^+ − Cl, 40), 837.5 (M^+ − 2 Cl, 33), 838.5 (M^+ − 2 Cl − H, 57), 809.5 (M^+ − 2 Cl − C_2H_5, 100); (*R*)-**4** $[\alpha]^{27}_{589}$ = −57° (c 1.00, CH_3OH); (*S*)-**4** $[\alpha]^{22}_{589}$ = +51° (c 1.02, CH_3OH). Anal. Calcd $C_{56}H_{74}N_2O_4 \cdot Cl_2 \cdot 4H_2O$ (982.2): C, 68.48; H, 8.42; N, 2.85. Found: C, 68.42; H, 8.25; N, 2.88.

(*S*)-1-[2-(6-Methoxy-2-naphthyl)propionyl]piperidine (3d).[19] A solution of 0.5 g (2.17 mmol) of (*S*)-naproxen and 1.3 mL (17.8 mmol) of thionyl chloride in 25 mL of benzene was refluxed under Ar for 30 min and then stirred for 12 h at 20 °C. After evaporation in vacuo, the residue was dissolved in 5 mL of benzene which was subsequently removed in vacuo. This procedure was repeated three times. To the crude acid chloride in 20 mL of CH_2Cl_2 under Ar was added 0.7 mL (7.1 mmol) of piperidine and two drops of pyridine. After the mixture was stirred for 12 h, the solvent was removed in vacuo to produce a solid which, upon chromatography (SiO_2, CH_2Cl_2/ethyl acetate, 12:1), yielded 0.52 g (81%) of **3d** as a white powder: mp 77–78 °C; IR (KBr) ν (C=O) 1629 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.9–1.55 (m, 6 H, $NCH_2CH_2CH_2CH_2$), 1.48 (d, J = 7.2 Hz, 3 H, $COCHCH_3$), 3.25–3.75 (m, 4 H, CH_2NCH_2), 3.89 (s, 3 H, OCH_3), 3.99 (q, J = 7.2 Hz, 1 H, $COCHCH_3$), 7.09 (d, J = 2.4 Hz, 1 H, 5-H), 7.11 (dd, J = 8.8 and 2.4 Hz, 1 H, 7-H), 7.34 (dd, J = 8.4 and 1.7 Hz, 1 H, 3-H), 7.58 (bs, 1 H, 1-H), 7.66 (d, J = 8.8 Hz, 1 H, 8-H), 7.68 (d, J = 8.4 Hz, 1 H, 4-H); $[\alpha]^{23}_{589}$ = +75.7° (c 0.10, $CHCl_3$). Anal. Calcd for $C_{19}H_{23}NO_2$ (297.4): C, 76.74; H, 7.80; N, 4.71. Found: C, 76.90; H, 7.88; N, 4.82.

(*S*)-*N*-(4-Pyridyl)-2-(6-methoxy-2-naphthyl)propionamide (3e). The amide **3e** (0.67 g, 50%) was obtained as a colorless foam by addition of 4-aminopyridine to the acid chloride prepared from (*S*)-naproxen (1.01 g, 4.39 mmol) as described above in the synthesis of **3d**: IR (KBr) ν (NH) 3271, (C=O) 1680 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.64 (d, J = 6.9 Hz, 3 H, $COCHCH_3$), 3.85 (q, J = 6.9 Hz, 1 H, $COCHCH_3$), 3.91 (s, 3 H, OCH_3), 7.12 (d, J = 2.4 Hz, 1 H, 5-H), 7.12 (dd, J = 9.0 and 2.4 Hz, 1 H, 7-H), 7.26 (bs, 1 H, NH), 7.33 (dd, J = 7.6 and 2.4 Hz, 2 H, 3′-H), 7.37 (dd, J = 8.5 and 1.6 Hz, 1 H, 3-H), 7.70 (bs, 1 H, 1-H), 7.71 (d, J = 9.0 Hz, 1 H, 8-H), 7.75 (d, J = 8.5 Hz, 1 H, 4-H), 8.39 (d, J = 7.6 Hz, 2 H, 2′-H); $[\alpha]^{24}_{589}$ = +97.2° (c 0.97, $CHCl_3$).

(2*S*,α*S*)-Methyl *N*-[2-(6-Methoxy-2-naphthyl)propionyl]phenylalaninate (3f). A sample of 0.5 g (2.32 mol) of L-methyl phenylalaninate hydrochloride was shaken with 50 mL of water and 50 mL of CH_2Cl_2, and the solution was adjusted to pH 10 with aqueous NaOH. The organic phase was dried

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($MgSO_4$) and evaporated to yield L-methyl phenylalaninate in a quantitative yield. The amide **3f** (0.745 g, 91%) was obtained as colorless crystals by addition of the amino ester in 20 mL of dry CH_2Cl_2 to a solution of 0.5 g (21.7 mmol) of (*S*)-naproxen as described above for the synthesis of **3d**: mp 108–109 °C; IR (KBr) ν (NH) 3268, (C=O) 1747, 1727, 1648 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.56 (d, J = 8.6 Hz, 3 H, $COCHCH_3$), 2.95–3.05 (m, 2 H, CH_2CH), 3.63 (s, 3 H, OCH_3), 3.66 (q, J = 8.6 Hz, 1 H, $COCHCH_3$), 3.91 (s, 3 H, OCH_3), 4.75–4.8 (m, 1 H, $CHCH_2$), 5.76 (d, J = 7.3 Hz, 1 H, NH), 6.81 (d, J = 7.5 Hz, 2 H, 2′-H), 7.02 (t, J = 7.5 Hz, 2 H, 3′-H), 7.05–7.1 (m, 2 H, 4′-H, 5-H), 7.14 (dd, J = 8.8 and 2.5 Hz, 1 H, 7-H), 7.29 (dd, J = 8.4 and 1.8 Hz, 1 H, 3-H), 7.59 (bs, 1 H, 1-H), 7.67 (d, J = 8.8 Hz, 1 H, 8-H), 7.67 (d, J = 8.4 Hz, 1 H, 4-H); $[\alpha]^{24}_{589}$ = +23.2° (c 1.04, $CHCl_3$). Anal. Calcd for $C_{23}H_{25}NO_4$ (379.5): C, 72.80; H, 6.64; N, 3.69. Found: C, 73.12; H, 6.16; N, 3.67.

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Registry No. 3 (R = COCl), 51091-84-0; **3a**, 22204-53-1; **3b**, 26159-35-3; **3c**, 123675-40-1; **3d**, 123675-42-3; **3e**, 123675-41-2; **3f**, 119991-61-6; (*R*)-**4**, 133043-27-3; (*S*)-**4**, 133043-28-4; (*R*)-**4** diiodide, 133043-29-5; (*S*)-**4** diiodide, 133043-32-0; (±)-**5**, 133043-12-6; (*R*)-**5**, 133160-35-7; (*S*)-**7**, 133160-34-6; (±)-**6**, 133043-13-7; (±)-**7**, 133043-14-8; (±)-**8**, 133043-15-9; (±)-**9**, 133043-16-0; (±)-**10**, 133043-17-1; (±)-**11**, 133043-18-2; (−)-**12**, 133160-36-8; (*R*)-**13**, 133043-30-8; (*S*)-**13**, 133043-19-3; (*R*)-**14**, 133043-20-6; (*S*)-**14**, 133043-31-9; (*R*)-**15**, 133043-21-7; (*S*)-**15**, 133043-22-8; (*R*)-**16**, 133043-23-9; (*S*)-**16**, 133043-24-0; (*R*)-**17**, 133043-25-1; (*S*)-**17**, 133043-26-2; EtOCHO, 109-94-4; $Cl(CH_2)_4Cl$, 110-56-5; EtI, 75-03-6; 2-bromo-6-methoxynaphthalene, 5111-65-9; *m*-anisaldehyde, 591-31-1; 1-acetyl-4,4-bis(4-hydroxy-3,5-dimethoxyphenyl)-piperidine, 133043-11-5; 4-aminopyridine, 504-24-5; methyl L-phenylalaninate hydrochloride, 7524-50-7; methyl L-phenylalaninate, 2577-90-4.

Supplementary Material Available: Experimental details of the X-ray crystal structure analysis of (*S*)-(−)-**12**, tables of the atomic coordinates, equivalent isotropic thermal parameters, bond angles and bond lengths, intramolecular and intermolecular distances (23 pages); tables of observed and calculated structure factors (11 pages). Ordering information is given on any current masthead page.

Redox-Controlled Chemical Switching of Cation Transport in Solid-Supported Membrane Systems

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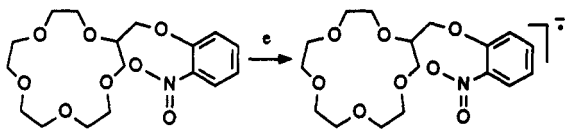
Redox-switchable anthraquinone-substituted crown ethers may be reduced by treatment with $NaBH_4$ to afford high-binding, water-stable, anion derivatives. These macrocycles, including 1-((9,10-dioxo-1-oxanthracenyl)-methyl-15-crown-5, **1**, transport Na^+ through a solid-supported, *o*-nitrophenyl octyl ether membrane with rates that depend on the charge state of the ligand and cooperation between reduction at the source phase and oxidation at the receiving phase.

The lariat ether program originated in part from our recognition that effective natural cation transport agents such as valinomycin are at once three-dimensionally enveloping and flexible.[1] This permits cation complexation and decomplexation to occur with reasonable rates while the equilibrium constant for complexation remains sufficiently high for transport. The paradox of membrane transport is that high binding strength and rapid complexation rates are required on one surface (the source phase) of the membrane while low complexation constants and rapid decomplexation rates are required at the other surface (receiving phase). The requirements make cryptands[2] ineffective as simple carriers in transport systems despite their high level of organization and three-dimensionality since their complexation and decomplexation rates, especially the latter, are relatively low.[3]

Most synthetic systems have relied upon a compromise in rates and complexation constants to achieve cation transport.[4] Our strategy from the beginning of this work was to use switching to make a weak but dynamic cation binder stronger and then to deactivate the binder after membrane transport had been accomplished.[5] The lariat ethers[6] designed for this purpose were simple crown ethers having nitrobenzene sidearms. The nitro group in nitrobenzene is a poor donor, even when appropriately placed in the ortho position. The first stage of this effort was to

Scheme I



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