A Novel Optically Active Host: Design, Computer Graphics, Synthesis, and Diastereomeric Complex Formation in Aqueous Solution

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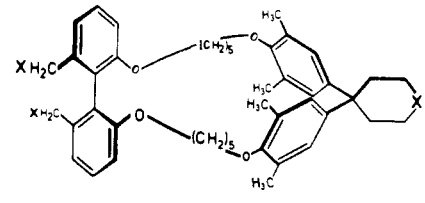
Abstract: The application of molecular mechanics (MM2) to the design of the novel optically active macrocyclic host (+)-**10** is described. The cavity binding site of host (+)-**10** is shaped by both a diphenylmethane and a 4-phenyl-1,2,3,4-tetrahydroisoquinoline unit bridged by two 1,4-dioxabutane chains. Two quaternary ammonium ions located remote of the apolar cavity binding site provide water solubility to the macrocycle. For the synthesis of (+)-**10**, the unnatural alkaloid 6-methoxy-4-(3-methoxyphenyl)-1,2,3,4-tetrahydroisoquinoline (**9**), structurally related to the natural alkaloids latifine and cherylline, was prepared in 10 steps starting from *m*-anisaldehyde and resolved through fractional crystallization of the diastereomeric salts formed with (+)-dibenzoyl-D-tartaric acid. Optically pure (−)-**9** was transformed in three steps into (−)-*N*-acetyl-6-(5-chlorobutoxy)-4-[3-(5-chlorobutoxy)phenyl]-1,2,3,4-tetrahydroisoquinoline [(−)-**24**]. Williamson ether cyclization of (−)-**24** with *N*-acetyl-4,4-bis(4-hydroxy-3,5-dimethylphenyl)piperidine afforded macrocycle (+)-**25**, which was reduced to the macrocyclic bis(tertiary amine) (+)-**26**. Quaternization followed by ion exchange afforded the target macrocycle (+)-**10**. It is shown that the optical purity was maintained in the conversion from resolved (−)-**9** to (+)-**10**. ^{1}H NMR host–guest complexation analysis in methanolic aqueous solution revealed that **26** (in acidic solution) and (+)-**10** form complexes with aromatic guests. The hosts demonstrate high specificity for 2,6-disubstituted naphthalene derivatives. Host (+)-**10** forms diastereomeric complexes with (*R,S*)-naproxen [2-(6-methoxy-2-naphthyl)propionic acid] (**28**) and with the methyl esters of naproxen (*R,S*)-**29**. The observation that the complexes of the methyl esters (*R,S*)-**29** are more stable than the complexes of naproxen (*R,S*)-**28** leads to the conclusion that ion pairing between the carboxylate of the guest and the quaternary tetrahydroisoquinolinium nitrogen of the host is not effective as a binding and discriminating interaction in the diastereomeric complexes of (*R,S*)-naproxen. Molecular mechanics (MM2) in combination with computer graphics (HYDRA) are applied to the analysis of the geometries of free host and of host–guest complexes.

Chiral recognition in diastereomeric host–guest complexes has great potential as an efficient, nondestructive method to separate optical isomers in crystallization, distribution, transport, and chromatographic experiments. Asymmetric synthesis in supramolecular complexes represents another fascinating perspective, and it is therefore not surprising that the development of optically active macrocyclic hosts has attracted increasing interest in recent years.[1] Since the first reports on chiral cyclic polyethers by Wudl[2] and Cram[3] in the eary 1970s, a large variety of designed chiral crown ligands have been prepared for the optical resolution of racemic cationic guests in organic solvents.[4] Whereas a considerable number of designed chiral hosts for cationic guests have been synthesized, only a few reports have appeared that describe the formation of diastereomeric complexes between fully synthetic, optically active ligands and neutral guests in aqueous and organic solution.[5-8] The resolution of neutral guests has almost exclusively been observed for complexes formed by free or immobilized cyclodextrins in aqueous solution.[9]

In our first entry into the field of synthetic chiral hosts for complexation in aqueous solution, we recently described macrocycle **1** with a tetrasubstituted biphenyl unit as the chiral barrier.[10,11] The quaternized, optically active macrocycle **2** was



1 X = NMe_2 X' = NMe

2 X = $NMe_3^+Cl^-$ X' = $NMe_2^+Cl^-$

designed to differentiate between the two enantiomers of arylpropionic acids, e.g., naproxen [2-(6-methoxy-2-naphthyl)propionic acid],[12,13] via a combination of three modes of interactions. Differences in apolar binding, ion pairing, and steric interactions were expected to lead to the formation of diastereomeric complexes of different stabilities. CPK molecular model examinations had indicated that macrocycles **1** and **2** could have energetically favorable conformations with the diphenylmethane unit, the aliphatic chains, and the biphenyl barrier shaping a cavity of suitable size for benzene and naphthalene derivatives. Host–guest complexation analysis in acidic aqueous solution, however, clearly showed that macrocycle **1** did not act as a host.[10] We concluded that biphenyl

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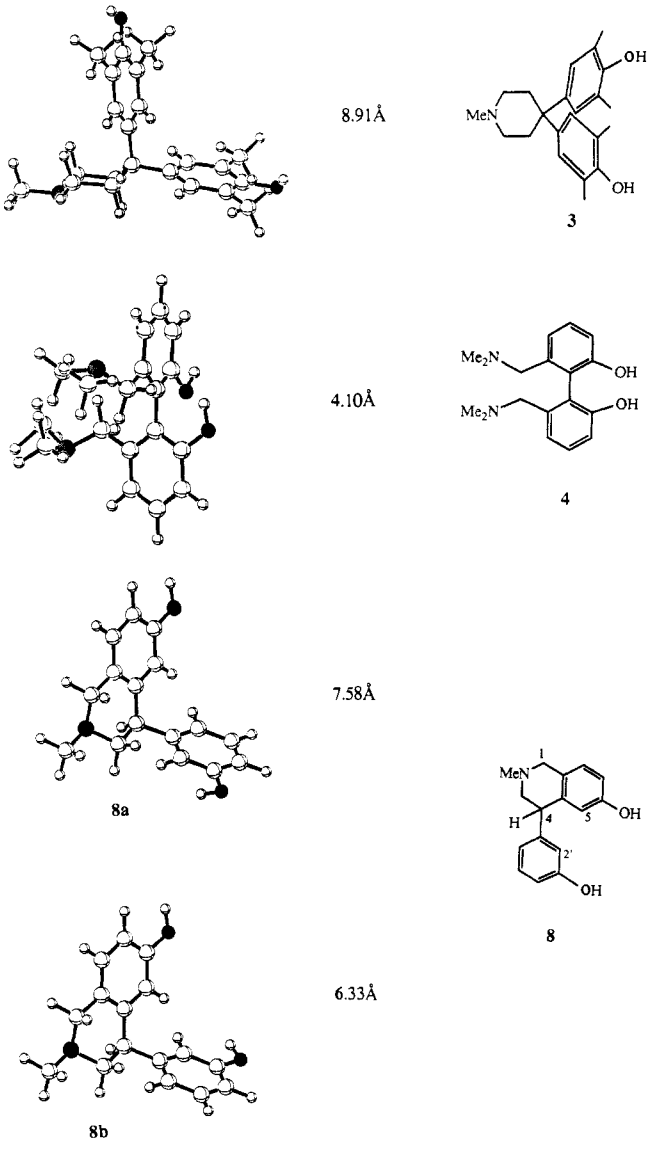

Figure 1. Minimum energy conformations of aromatic spacer units 3, 4, and 8 and O···O distances as obtained from molecular mechanics calculations (MM2).

units are not suitable spacer groups for shaping large macrocyclic cavities designed to bind flat apolar organic molecules, since these building blocks do not sufficiently widen the binding site.

In this paper, we give a full account on the design and synthesis of an optically active host incorporating an unnatural alkaloid as a chiral barrier. The formation of diastereomeric complexes in aqueous solution, as observed by ^{1}H NMR spectroscopy, will be discussed. The application of molecular mechanics in combination with computer graphics to provide a better understanding of the conformations of large macrocyclic hosts and ultimately a more rational design of such systems will be shown.[14]

Design of Chiral Building Blocks for Macrocyclic Chiral Hosts with Large Apolar Binding Sites

To avoid costly errors in design based exclusively on CPK model examinations, we started systematically applying molecular mechanics (MM2)[15] to the design of chiral building blocks. Figure 1 shows the calculated minimum energy conformations of some of the achiral and chiral cavity shaping aromatic building blocks that we considered in the calculations.[16] The calculated structure of the diphenylmethane unit **3** is in very good agreement with the structures obtained by X-ray analysis of crystalline complexes of hosts incorporating this unit.[17] The calculated distance of 8.91 Å between the oxygen atoms of the aromatic spacer **3** appears to be very favorable for the shaping of an efficient binding site for arenes and flat cycloalkanes, since we and others have observed strong inclusion complexation of such guests by hosts incorporating two diphenylmethane units.[18-22]

In agreement with our experimental findings, the biphenyl unit **4**, which we had introduced in macrocycle **1**, is *not* a suitable chiral building block. At an O···O distance of only 4.10 Å in **4**, the alkane bridges that are attached to these oxygens in hosts **1** and **2** come too close and, as shown below by the computer graphics model, do not shape an open binding cavity.

In our search for novel chiral building blocks that preorganize cavity binding sites and create an efficient asymmetric environment for complexed aromatic guests, we wanted to maintain our concept of locating water solubility providing ionic residues remote from the cavity.[19a,b] We screened tetrahydroisoquinoline alkaloids for their potential use as chiral building blocks for our hosts. CPK model examinations indicated that the benzylic linkage of the 1-benzyl-1,2,3,4-tetrahydroisoquinoline alkaloids makes derivatives of this abundant class of alkaloids, e.g., isococlaurine (**5**),[23] too

5 Isococlaurine

6 Cherylline R = H; R' = OH

7 Latifine R = OH; R' = H

flexible to be used as rigid, aromatic cavity-shaping spacer units. The far less abundant naturally occurring 4-phenyl-1,2,3,4-tetrahydroisoquinoline alkaloids seemed more promising chiral building blocks. Two of these, cherylline (**6**)[24] and latifine (**7**),[25] have received considerable attention from a synthetic standpoint. The 4-phenyltetrahydroisoquinoline alkaloids[26] are conforma-

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(16) This paper follows the correct chronological sequence of the accomplished research: MM2-assisted design of spacer units, synthesis and binding studies, and finally molecular mechanics and computer graphics of the macrocycles. For details on the MM2 calculations of **3**, **4**, and **8**, see the chapter on computer graphics.

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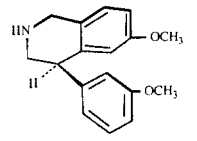
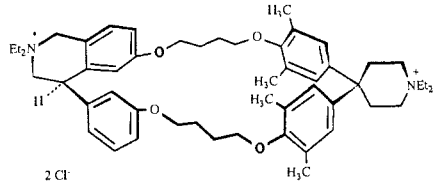
tionally more rigid than the 1-benzyltetrahydroisoquinolines, but possible unfavorable conformations of these compounds could not be excluded on the basis of CPK model examinations. The molecular mechanics calculations finally gave us the confidence to use derivatives of these alkaloids for our chiral binding sites. The unnatural derivative **8**, the *N*-methyl analogue of **9**, which we



(+)-9



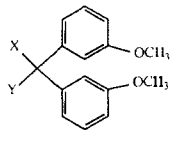
2 Cl⁻

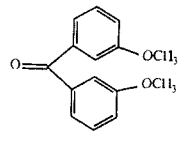
(+)-10

ultimately introduced into the novel macrocyclic host **10**, can take two energetically favorable conformations (Figure 1).[27] With O···O distances of 7.58 and 6.33 Å, this alkaloid in both conformations **8a** and **8b** should open up and preorganize macrocyclic binding sites to a greater extent than the biphenyl unit **4**. CPK model examinations of **10** suggested that the quaternary nitrogen of the isoquinolinium moiety of **10** should be accessible for ion pairing to the carboxylate of α-arylpropionic acids. We were therefore confident that host **10** would finally allow us to test our previously described concept for chiral recognition of these guests[10] based on ion pairing as a discriminating interaction in the diastereomeric complexes.

Synthesis of the Optically Active Host (+)-10

The synthesis of the chiral cavity-shaping building block 9 started with the carbinol **11** obtained in 62% in the Grignard reaction between *m*-anisylmagnesium bromide and *m*-anisaldehyde. Treatment of a benzene solution of **11** with HCl gas

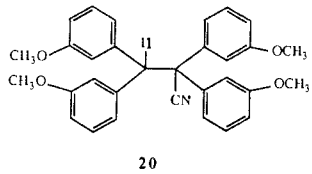




19

11	X =	OH	Y =	H
12	X =	Cl	Y =	H
13	X =	OH	Y =	CN
14	X =	Cl	Y =	CN
15	X =	CN	Y =	H
16	X =	CH_2NH_2	Y =	H
17	X =	CH_2NHBoc	Y =	H
18	X =	CH_2NBoc CH_2OH	Y =	H

(Boc = *tert*-butyloxycarbonyl)



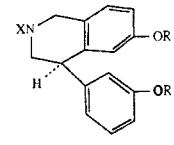
20

resulted in a smooth conversion to the chloride **12** (91%). However, attempted bimolecular displacement at 20 °C (24 h) of the chloride by potassium cyanide in dimethylformamide or under phase-transfer conditions[28] in acetonitrile afforded the tetra-*m*-anisyl derivative **20** as the only isolable product. Nitrile **15** once formed apparently reacts with unreacted starting chloride **12** either via a bimolecular displacement or possibly via radical coupling to give **20**.[29]

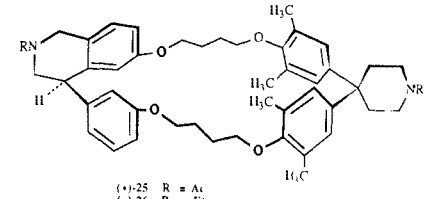
Our findings in the di-*m*-anisylmethane series are in sharp contrast to the results obtained in the di-*p*-anisylmethane series. We were able to prepare bis(4-methoxyphenyl)acetonitrile[30] in 70% yield from chlorobis(4-methoxyphenyl)methane[31] with potassium cyanide under phase-transfer conditions. The conversion of chloride **12** to the nitrile **15** following S_N1 methodology described by Reetz[32] was also not very successful. Treatment of a mixture of chloride **12** and trimethylsilyl cyanide with tin tetrachloride at 20 °C gave the desired nitrile **15** in rather poor yields, which never exceeded 15%.

To circumvent the encountered problems in the direct preparation of nitrile **15** via the chloride **12**, a lengthier route was devised. Oxidation of the carbinol **11** with pyridinium chlorochromate in dichloromethane afforded ketone **19** (90%). Reaction with trimethylsilyl cyanide in the presence of catalytic amounts of zinc iodide yielded the corresponding cyanosilyl ether,[33] which was hydrolyzed with 3N HCl in tetrahydrofuran to give the cyanohydrin **13** in 95% crude yield. Without further purification, the cyanohydrin **13** was converted with phosphorus pentachloride in benzene into the cyanochloride **14** (84%).[34] Free-radical-initiated reductive removal of the chloride in crude **14**[35] with tributyltin hydride in benzene in the presence of azobis(isobutyronitrile) gave the desired nitrile **15** as colorless solid in 77% yield. Borane–tetrahydrofuran reduction of the nitrile **15** afforded the primary amine **16** (91%), which was converted in 82% yield to the benzyloxycarbonyl derivative **17** by using di-*tert*-butyl dicarbonate in dichloromethane in the presence of triethylamine.

To carry out the ring closure leading to the tetrahydroisoquinoline, we adopted the Sánchez modification[36] of the Tscherniac–Einhorn reaction.[37] Thus, condensation of **17** with aqueous formaldehyde in dioxane in the presence of excess sodium hydroxide gave the hydroxymethylcarbamate **18** in 76% yield after chromatography on silica gel. Treatment of **18** with catalytic amounts of *p*-toluenesulfonic acid in refluxing benzene resulted in smooth cyclization (95%) to the desired 4-phenyltetrahydroisoquinoline derivative **21**. Removal of the protecting group with



21	X =	Boc	R =	CH_3
(−)-9	X =	H	R =	CH_3
(−)-22	X =	$COCH_3$	R =	CH_3
(−)-23	X =	$COCH_3$	R =	H
(−)-24	X =	$COCH_3$	R =	$(CH_2)_4Cl$



(+)-25 R = Ac
(+)-26 R = Et

trifluoroacetic acid afforded the racemic secondary amine **9** (97%), which was subsequently subjected to optical resolution.

The optical resolution of the racemic amine **9** was accomplished via fractional crystallization ($EtOH/H_2O$, 1:1) of the diastereomeric salts formed between the amine and (+)-dibenzoyl-D-tartaric acid. After three recrystallizations, the enantiomer (−)-9 [$[\alpha]_D^{23}$ −58.8° (*c* 1.27, $CHCl_3$)] subsequently used in the synthesis of

(27) There exists no correlation between the arbitrarily chosen absolute configuration at the chiral centers of compounds shown by perspective drawings and the experimentally determined sign of optical rotation. The absolute configurations of (−)-**9**, (+)-**10**, and their derivatives are not known.

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(+)-**10** was obtained in an enantiomeric purity of ≥98%. To determine the enantiomeric purity, we adopted an elegant procedure developed by Rice and Brossi for a variety of alkaloids.[38] Excess of (−)-(*S*)-α-methylbenzyl isocyanate was added to the resolved secondary amine (−)-**9** in $CDCl_3$. The 500-MHz ^1H NMR spectrum of the mixture showed two doublets for benzylic methyl protons at δ 1.22 [(α-methylbenzyl)urea diastereoisomer formed by (−)-**9**] and at δ 1.60 (excess isocyanate). Three doublets for benzylic methyl protons at δ 1.22, 140, and 1.60 appear in the spectrum of the solution of the two (α-methylbenzyl)urea diastereoisomers obtained from (*S*)-isocyanate and the racemic amine (±)-**9**.

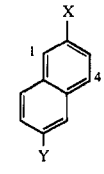
For the conversion of the resolved 4-phenyltetrahydroisoquinoline derivative (−)-**9** to the target host (+)-**10**, the amine (−)-**9** was acetylated with acetic anhydride to give the crystalline amide (−)-**22** (82%). Demethylation of (−)-**22** with boron tribromide afforded the diphenol (−)-**23** (83%), which was dialkylated with 1,4-dichlorobutane in dimethylformamide with cesium carbonate as base to yield the dichloride (−)-**24** (65%). Cyclization of the dichloride (−)-**24** with *N*-acetyl-4,4-bis(hydroxy-3,5-dimethylphenyl)piperidine[19d] in dimethylformamide in the presence of cesium carbonate as base led in 21% yield to the desired macrocycle (+)-**25**. Although it was difficult to visualize mechanisms by which any of the intermediates could have been racemized along the course of the reaction sequence leading from (−)-**9** to (+)-**25**, we applied again the simple method of Rice and Brossi[38] to ensure that we had maintained the optical purity to the stage of the macrocyclic systems. For this purpose, the two *N*-acetyl groups of the macrocycle (+)-**25** were cleaved by refluxing methanolic HCl. Upon reaction of the crude product of the hydrolysis with (*S*)-α-methylbenzyl isocyanate in $CDCl_3$, a solution of one bis[(α-methylbenzyl)urea] diastereoisomer was obtained that showed in the 500-MHz ^1H NMR spectrum three doublets for benzylic methyl protons at δ 1.15 (urea at alkaloid unit), 1.46 (urea at piperidine unit), and 1.60 (excess isocyanate). The solution of the two bis[(α-methylbenzyl)urea] diastereoisomers obtained by starting from racemic macrocycle **25** gave four CH_3 doublets at δ 1.15, 1.40 (ureas at alkaloid units), 1.46, and 1.60.

After it had been ascertained that the optical purity had been maintained to the stage of the macrocycle, the diamide (+)-**25** was reduced in 30% yield with borane in tetrahydrofuran to the macrocyclic bis(tertiary amine) (+)-**26**. Quaternization in pure ethyl iodide followed by ion-exchange chromatography (Cl^-) afforded in 71% yield the target host (+)-**10** as hygroscopic colorless solid, mp 210–215 °C. Clear evidence that the optical purity was maintained to the stage of the bisquaternized host (+)-**10** was provided by the complexation studies described below. We also prepared the racemic host **10** following the described synthetic route.

^1H NMR Complexation Studies with Hosts 26 and (+)-10 in Aqueous Solutions

From our previous binding studies, we knew that two ionic centers in hosts (+)-**10** and diprotonated **26** are not sufficient to raise the critical micelle concentration into a range that allows the use of ^1H NMR spectroscopy in the host–guest complexation analysis in pure aqueous solution. All binding studies were therefore performed in aqueous solutions containing 40% (v/v) methanol-d_4. Under these conditions we did not observe any evidence of aggregation. Previously, other researchers observed that aggregation is destroyed in aqueous solutions with an ethanol content larger than 30% (v/v).[39] It also has been reported that methanol is the best cosolvent to break the water structure and to prevent aggregation.[40]

^1H NMR complexation analysis clearly revealed that, contrary to the biphenyl derivative **1**,[10] the new macrocycles **10** and diprotonated **26** form inclusion complexes with aromatic guests in aqueous solutions. Due to fast exchange rates, the ^1H NMR signals of the guest (host) always appear at the weighted average of the chemical shifts of free guest (host) and guest (host) bound in each possible orientation. We first investigated the scope of the binding properties of the novel host system with the racemic macrocycle **26**, which is readily soluble in mixtures of weakly acidic aqueous buffers and methanol. Host **26** binds preferentially 2,6-disubstituted naphthalene guests. ^1H NMR spectra of the solutions of complexes [[**26**] = [guest] = 5×10^{-3} mol·L^{-1}, *T*, 303 K; 0.5 M KD_2PO_4/CD_3OD (60:40); CH_3OH as internal standard] indicated considerable binding of 2,6-dicyanonaphthalene (**27a**), 6-methoxy-2-naphthonitrile (**27b**), and 2,6-



27a X = Y = CN

27b X = CN, Y = OMe

27c X = Y = OMe

dimethoxynaphthalene (**27c**). As an example, the association constant of the 1:1 complex formed under the above given conditions between **26** and 6-methoxy-2-naphthonitrile (**27b**) was determined from a ^1H NMR titration as K_a = 336 L·mol^{-1}. The titration curve [[**26**] = 3×10^{-4}–3×10^{-3} mol·L^{-1}; [**27b**] = 5×10^{-4} mol·L^{-1}, $\Delta\delta_{max\ obsd}(1\text{-}H_{guest})$ = +1.25, $\Delta\delta_{sat\ calcd}(1\text{-}H_{guest})$ = +1.98; (+ = upfield shift)] was evaluated by a nonlinear-least-squares curve-fitting procedure.

For the determination of the association constant, the signal of proton 1-H adjacent to the nitrile group of guest **27b** could be monitored over a suitably large titration range, since this proton moves upfield from δ 8.33 (in free **27b**) through an open window in the NMR spectrum before being masked by the protons of the host around δ ≈7.20. A complete and accurate assignment of all aromatic signals of host and guest in solutions of complexes was not possible due to considerable overlap of the large number of resonances of the dissymmetric hosts(+)-**10** and **26** with the signals of the guests. Nevertheless, the observed complexation shifts provided good evidence for a pseudoaxial position of the complexed 2,6-disubstituted naphthalenes approximately in the plane of the cavity passing through the asymmetric carbon atom and the mean plane of the piperidine ring of host **26**. In the solutions of complexes, the protons of the guests are shifted upfield to an extent depending on their orientation to the shielding benzene rings of the host, e.g., the upfield complexation shifts of the protons 1-H, 4-H of the guests **27a–c** are more than twice as large than the shifts of 3-H. The protons of the alkane bridges of the host are shifted upfield, and the protons of the aromatic spacers exhibit weak downfield shifts as shown below in more detail for the naproxen complexes. The preferred pseudoaxial inclusion of 2,6-disubstituted naphthalenes was further supported by CPK model examinations and by docking experiments in the computer-modeling study described below. A pseudoaxial inclusion of 2,6-disubstituted naphthalenes had previously been derived by extensive ^1H NMR studies for the complexes of symmetrical hosts with two diphenylmethane units.[41,42]

Hosts **10** and **26** show nearly identical binding properties and a surprisingly high guest selectivity. Among the guests considered in this study, the 2,6-disubstituted naphthalene derivatives with neutral substituents formed by far the most stable complexes. The ^1H NMR spectra of solutions with [**26**] = [guest] = 5×10^{-3} mol·L^{-1} indicated only weak complexation of *N*-acetyltryptophan, mandelic acid, and *p*-tolunitrile with upfield shifts of the guest protons not exceeding 0.20 ppm. No complexation under the given conditions was observed with quinine, tryptophan, 1-naphth-1-

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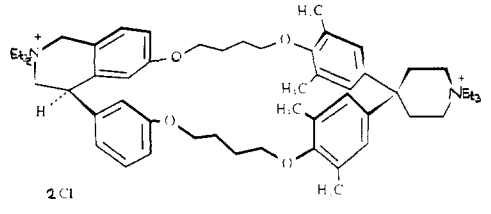
Table I. Chemical Shifts of Naproxen in the ^1H NMR Spectra of Solutions of Pure Guest and of the Diastereomeric Complexes (+)-**10**–(*R*)-**28** and (+)-**10**–(*S*)-**28**

proton	chemical shift, δ		
	pure **28**	(+)-**10**–(*R*)-**28**	(+)-**10**–(*S*)-**28**
CH_3C	1.470	1.461	1.463
CH_3O	3.930	3.866	3.872
1-H	7.726	7.596	7.627
3-H	7.488	7.456	7.459
4-H	7.760	7.610	7.639
5-H	7.299	7.140	7.167
7-H	7.160	7.053	7.057
8-H	7.800	7.626	7.653

[a] Conditions: 500 MHz, 0.5 M K_2CO_3/CD_3OD, *T* 303 K; [(+)-**10**] = 1.25×10^{-3} mol·L^{-1}, [(*R*,*S*)-**28**] = 1.00×10^{-3} mol·L^{-1}; CH_3OH as internal standard.

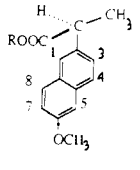
yl-1-ethylamine, dibenzoyltartaric acid, and 2,6-naphthalenedisulfonate as guests. This selectivity is considerably higher than the selectivity observed with similarly sized hosts shaped by two diphenylmethane units and must therefore result from the specific geometry of the 4-phenyltetrahydroisoquinolinium spacer unit in hosts **10** and **26**.

The optically active host (+)-**10** was designed to test a concept for chiral recognition of α-arylpropionic acids and especially of naproxen (**28**), a cyclooxygenase-inhibiting drug whose (*S*) enantiomer is 28 times more active than the (*R*) enantiomer.[12,13]



2 Cl

(*R*)-**10**



R = H (*S*)-**28**

R = CH_3 (*S*)-**29**

Macrocycle (*R*)-**10** was expected to form the more stable diastereomeric complex with (*S*)-naproxen, since additional ion pairing between the carboxylate of the pseudoaxially enclosed guest and the quaternary isoquinolinium nitrogen of the host should stabilize the complex. The complex between (*R*)-**10** and the (*R*) guest should be less stable. The bulkier methyl group of this guest enantiomer has to orient in an energetically unfavorable way toward the isoquinoline moiety if ion pairing stabilizes the complex.

The binding observed between hosts (+)-**10** and (+)-**26** and both enantiomers of naproxen (**28**) is weaker than the complexation between these hosts and 6-methoxy-2-naphthonitrile. Very similar results were obtained in the studies with (+)-**10** in 5×10^{-2} M aqueous K_2CO_3/CD_3OD (60:40) and with (+)-**26** in 0.5 M KD_2PO_4/CD_3OD (60:40; pD 4.3) (*T*, 303 K; CH_3OH as internal standard). Naproxen, unlike compounds **27a,b**, does not possess ^1H NMR signals that appear at a very downfield position (see Table I) separated from the signals of the host, which start appearing above δ ≈7.20. A considerable overlap of the downfield-moving aromatic signals of the host and the upfield-moving signals of the guest occurs at early stages of the ^1H NMR titrations, and this prevented the determination of accurate binding data. Major complexation shifts (Δδ; + = upfield) in a solution with [(+)-**26**] = [(*S*)-**28**] = 5×10^{-3} mol·L^{-1} in 0.5 M KD_2PO_4/CD_3OD (60:40) are as follows. Guest: ≈+0.3–≈+0.5 (H_{ar}, obscured by protons of (+)-**26**); +0.15 (CH_3O). Host: ≈−0.05–≈−0.1 (H_{ar}, obscured by protons of (*S*)-**28**), ≈+0.3 (OCH_2CH_2). From the Δδ values of the guest protons at given concentrations and the complexation shifts generally observed at saturation binding for protons of 2,6-disubstituted naphthalenes,[42,43] in a very crude way, the association constant of the 1:1 complex can be estimated as ≈50 ± 20 L·mol^{-1}. At low percentages of complexation, the overlap of the ^1H NMR signals is small, and under these conditions, clear evidence for the formation of diastereomeric complexes between (+)-**10** and (*R*,*S*)-naproxen in 5×10^{-2} M aqueous K_2CO_3/CD_3OD (60:40) could be obtained. Table I shows that, in the solutions of the diastereomeric complexes (+)-**10**–(*S*)-**28** and (+)-**10**–(*R*)-**28**, the aromatic signals of (*R*) and (*S*) guests are shifted to a different degree. The optical purity of (+)-**10** is demonstrated by the fact that in the solution of one diastereomeric complex the signals of the other diastereomeric complex are completely absent. In the solution of (+)-**10** and racemic naproxen, the signals assigned to the diastereomeric complexes appear side by side. Each enantiomer of naproxen can enter the cavity binding site of (+)-**10** in either of two ways, yielding complexes of different geometry. This, however, cannot be detected at fast complexation–decomplexation rates. The considerable signal overlap did not allow us to measure by independent titrations the stability of each diastereomeric complex, which would have enabled quantitative determination of the degree of chiral recognition.

Interestingly, even at higher concentrations [[host] = [guest] = 5×10^{-3} mol·L^{-1}] almost no complexation shifts and no differential shifts at all are observed for the benzylic methyl signals of both enantiomers of naproxen in the presence of (+)-**10** (Table I). We explain this finding by a geometry of complex, which locates the asymmetric carbon atom of naproxen and its substituents completely outside the binding cavity. Consequently, ion pairing between the carboxylate of the guest and the quaternary isoquinolinium nitrogen cannot be an efficient stabilizing and discriminating interaction in the diastereomeric complexes. In aqueous solution, the energy that would be gained by possible ion pairing in the confines of the binding site apparently does not compensate for the energy needed for the desolvation of the two interacting ionic centers of host and guest.

Assuming that the solvation of the carboxylate residue prevents a deeper location of the asymmetric carbon center of naproxen in the binding site, we prepared the methyl esters of naproxen (*R*,*S*)-**29**. We found, indeed, that the complexation between (+)-**10** and both enantiomers of the methyl ester **29** in D_2O/CD_3OD (60:40) is significantly stronger than the complexation between (+)-**10** and naproxen (**28**). Even at low concentrations [[(+)-**10**] = 1×10^{-3} mol·L^{-1}, [(*R*)-**29**] = 1×10^{-4} mol·L^{-1}] considerable complexation shifts are observed, e.g., protons of the guest move from δ 7.664 (1-H), 7.742 (4-H), and 7.751 (8-H), respectively, to positions above 7.35 ppm into the area of the downfield-shifting host protons. Large signal overlap prevented an accurate determination of K_a from NMR titrations. Using the crude approximation described above, we estimate the association constant for the (+)-**10**–(R)-**29** complex as K_a ≈300 ± 100 L·mol^{-1}.

In the solutions of the two diastereomeric complexes (+)-**10**–(*R*)-**29** and (+)-**10**–(*S*)-**29** the aromatic signals of (*R*) and (*S*) guests are shifted upfield to a different degree. In contrast to the findings with naproxen, however, the ^1H NMR spectra also showed small but distinct differential shifts of the weakly upfield-shifted (Δδ ≈ +0.05 ppm) benzylic methyl protons and the ester methyl protons of the ester enantiomers. At [(+)-**10**] = 1×10^{-3} mol·L^{-1} and [(*R*,*S*)-**29**] = 5×10^{-4} mol·L^{-1}, differential shifts of $\Delta\nu$ = 3.5 Hz (aryl $CHCH_3$) and of $\Delta\nu$ = 1.9 Hz ($COOCH_3$) were observed. The differential upfield shifts suggest that the asymmetric carbon center of the complexed ester and its substituents can be located inside the confines of the macrocyclic binding site and interact with the chiral barrier. The desolvation of noncharged ester residues of (*R*,*S*)-**29** is less unfavorable than

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the desolvation of the carboxylate residue of (*R,S*)-naproxen, which favors a penetration of the ester group into the apolar binding site. $\pi-\pi$ interactions between the ester residue and the aromatic ring[44] of the 4-phenyltetrahydroisoquinoline unit represent an attractive explanation for both the higher stability of the complexes formed by (*R,S*)-**29** as well as for the differential shifts observed for the protons around the asymmetric carbon atom of the guest. Again, severe signal overlap in ^{1}H NMR titrations did not allow us to analyze quantitatively the degree of chiral recognition in the complexes.

From the binding studies we draw the following conclusions for the design of chiral hosts for aqueous solutions. We have correctly recognized the importance of the O···O distance of the aromatic spacer units in our macrocyclic hosts. By introducing the chiral alkaloid building block (−)-**9**, which opens up and preorganizes an apolar binding site more than the biphenyl derivative in host **1** (Figure 1), we have prepared the novel optically active macrocycle (+)-**10**. This compound acts as a host in methanolic aqueous solution, binds selectively 2,6-disubstituted naphthalenes, and forms diastereomeric complexes with (*R,S*)-naproxen and its methyl ester. Ion pairing is not effective in the diastereomeric complexes of (*R,S*)-naproxen, presumably due to unfavorable desolvation of the ionic centers of host and guest. The complexation of the ester (*R,S*)-**29** is considerably stronger than the complexation of naproxen. Both a more favorable desolvation of the ester residue and $\pi-\pi$ interactions in the complex can explain the stronger binding and the observed differential shifts of the protons around the asymmetric carbon center of the ester enantiomers. Our results suggest the use of $\pi-\pi$ interactions rather than ion pairing as the discriminating interaction in diastereomeric complexes in aqueous solution. Our next generation of optically active hosts for chiral recognition in aqueous solution will therefore be designed to differentiate between complexed guest enantiomers via a sum of apolar, steric, and $\pi-\pi$, or in a more general sense, electron-donor–acceptor interactions.[8,43] For a systematic, quantitative ^{1}H NMR analysis of the degree of chiral recognition, chiral building blocks with C_2 symmetry are desirable. Hosts with C_2 symmetry will exhibit less signals in the NMR spectra and thus provide larger open windows in the spectra to monitor the guest protons in the course of titrations. In addition, the diastereomeric complexes formed by optically active hosts with C_2 symmetry will be better defined, since binding of guests like naproxen on both faces of the macrocycle will lead to identical complexes. Since the best possible understanding of conformations of macrocycles is needed for the design of efficient asymmetric binding sites, we have undertaken a computer modeling study, and the results are presented in the following section.

Computer Graphics in the Design of Chiral Spacer Units and Macrocyclic Hosts

The motivation behind our molecular mechanics and computer graphics studies evolved from the desire to develop a method better than building CPK models for evaluating new designs of host macrocycles and their spacer units, especially if these spacer units are not very rigid and therefore can take several conformations. Our calculations utilized Allinger's MM2 force field, which is parameterized for a wide variety of functional groups.[15] While a combination of both force field and approximate molecular orbital calculations are generally performed on compounds that have delocalized π systems,[45-47] such approaches are not feasible for compounds as large as ours due to the extensive amount of computer time that would be required. In addition, these approaches would not provide additional accuracy since they also do not take into account solvation effects. Since all the C–C bond lengths are equivalent for benzene, a particular force constant and a 1.39-Å aromatic bond length can be applied to MM2 calculations of compounds incorporating aromatic rings whose substituents do not significantly interrupt the conjugated π system.[45] By incorporating parameters of Beckhaus[48] for alkylated benzene derivatives and the MM2 vinyl ether parameters into the calculations of our aromatic spacer units and macrocycles, we were able to generate geometries very similar to crystal structures of analogous compounds.[49] The use of HYDRA software on a high-resolution graphics monitor (Silicon Graphics IRIS 3130) provided us the means to analyze and graphically display the geometries of our calculated spacer units and macrocycle models.

Using molecular mechanics methods on large molecules requires the input of reasonably low-energy starting geometries. The general scheme for the construction of good input coordinates for the macrocycles involved the initial optimization of spacer unit geometries. The spacer input coordinates were entered into the MM2 program running on a VAX 780 by using *z*-matrix internal coordinates. The output Cartesian coordinates of the geometry-optimized spacer units were used to form reasonable input geometries for calculations of the macrocycles.

Studies of the Diphenylmethane Spacer Unit 3. The crystal structure and molecular mechanics of diphenylmethane have been investigated by Mislow.[50] The diphenylmethane conformations were characterized by the dihedral angles Φ_A and Φ_B defined as the angle between the least-squares planes of the two phenyl rings, A and B, and the central plane defined by C_A–CH_2–C_B. A helical form is found in the X-ray crystal structure with Φ_A = 63.9° and Φ_B = 71.1° at −70 °C. A gable conformation with Φ_A and Φ_B equal to 90° is indicated by Raleigh scattering measurements,[51] and EHT,[52] INDO,[53] and BIGSTRN-2[50] calculations, but a wide variety of essentially isoenergetic conformations are suggested by experimental and theoretical methods.[50]

Our MM2 calculations on the diphenylmethane spacer unit **3** with no restricted motion predict a helical conformation with Φ_A = 63.1°, Φ_B = 71.9°, and an O···O distance of 8.91 Å. By restricting the two torsional angles to 90° while minimizing all other degrees of freedom[54] and then using the resultant coordinates for reminimization with the restrictions turned off, the structure minimizes to a gable conformation with Φ_A = 88.9°, Φ_B = 88.7, and an O···O distance of 9.07 Å. The calculated steric energy for the gable conformation was 0.95 kcal/mol higher than the energy of the helical form. The calculated bond lengths, valence angles, and torsional angles of **3** are in close agreement with the values derived from X-ray crystal structures of macrocycle **30**, which incorporates two diphenylmethane units as spacers.[55] For initial geometries of **3**, we used some of the torsional angles derived from these X-ray structures, but actual bond lengths and angles were only compared after we had performed the calculations. The calculated O···O distance of 8.91 Å for the diphenylmethane unit **3** was used as a calibration value against which the potential of a designed spacer unit for incorporation into a macrocycle was measured.

Studies of the Biphenyl Spacer Unit 4. Parameters for the bond joining the two benzene rings in biphenyl spacer unit **4** were chosen to reproduce the crystal structure bond length of 1.494 Å[56] and also to allow for a small rotational barrier about this bond.[57]

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(54) The torsional angle was restricted by setting the torsional parameters for the atoms C_{ar}–C_{ar}–C_{sp^3}–C_{ar} to V_1 = 0.0, V_2 = −200.0, and V_3 = 0.0.
(55) See ref 17. Important parameters of the two diphenylmethane units in the **30**–benzene complex, Φ_A = 80.7°, Φ_B = 83.7°, and O···O distance = 8.61 Å; in the **30**–*p*-xylene complex, Φ_A = 72.4°, Φ_B = 70.1°, and O···O distance = 8.84 Å.
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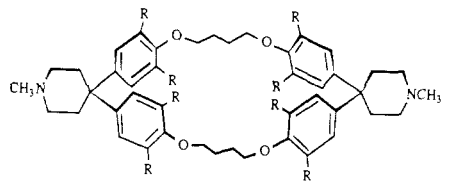
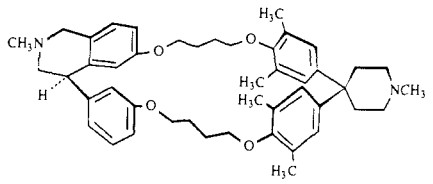


30 R = H

31 R = CH_3



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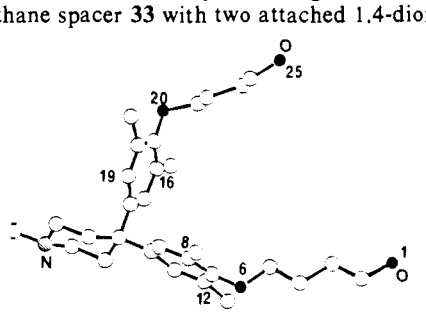
Minimization was performed on conformations with the torsional angle Φ, the angle between planes passing through the two phenyl rings, changed from 45–135° in 15° increments, corresponding to O···O distances of 2.78–4.84 Å. A torsional angle of 105° provided the lowest energy conformation with an O···O distance of 4.10 Å. This O···O distance is not large enough to open cavity binding sites of macrocycles incorporating **4** as spacer unit.[10]

Calculations on the Tetrahydroisoquinoline Spacer Unit 8. The MM2 calculations for the 4-phenyltetrahydroisoquinoline **8** suggested the incorporation of this spacer unit in a chiral macrocycle, since the calculated geometries had O···O distances significantly larger than the biphenyl spacer unit **4**. Energy-minimized geometries of conformations with the torsional angle Φ [C(6′)–C(1′)–C(4)–C(4a)] (see Figure 1 for numbering) maintained at angles of 30, 40, 50, 60, 70, and 80° had corresponding O···O distances of 8.04–6.87 Å. A torsional angle of 50° provided the lowest calculated energy conformer **8a** with an O···O distance of 7.58 Å. The other conformer **8b** formed by rotating the phenyl 180°, giving a torsional angle of −130°, was essentially isoenergetic and had an O···O distance of 6.33 Å. Our calculations yielded bond lengths and angles quite similar to values obtained from a crystal structure of the naturally occurring alkaloid latifine (**7**).[58]

Incorporating Spacer Units in Macrocycles. The next step involved the incorporation of the previously minimized spacer geometries into the macrocycles. The strategy for acquiring reasonable input geometries was worked out by forming macrocycle **31**. Since the bridging aliphatic chains of our macrocycles can take a large number of approximately isoenergetic conformations, we chose an initial geometry that provided a maximum number of antiperiplanar conformations. The input geometry for the macrocycle was constructed by combining two fragments: the diphenylmethane spacer **33** with two attached 1,4-dioxabutane



33

chains and spacer unit **3** without its phenolic hydrogens. For both fragments, the optimized diphenylmethane geometry with the dihedral angles Φ_A and Φ_B equal to 90° was used since reasonable starting geometries were simpler to describe. The distance between the terminal oxygens of **33** was varied to correspond to the O···O distance of 9.07 Å for the diphenylmethane spacer unit. Internal coordinates were used to define the initial geometry of this fragment incorporating the bond lengths, bond angles, and torsional angles of the optimized diphenylmethane spacer and maintaining a maximum number of antiperiplanar torsional angles in the bridging chains. The input geometries of the bridging chains of **33** involved setting Φ[C(5)–O(6)–C(7)–C(12)] = 90° and Φ[C(18)–C(17)–O(20)–C(21)] = 90° and all other torsional angles involving the bridging atoms, except Φ[C(17)–C(20)–O(21)–C(22)] set to 180°. The torsional angle Φ[C(17)–C(20)–O(21)–C(22)] was varied until the desired O···O distance necessary to link another spacer unit was obtained. In the X-ray structures of **30**,[55] the conformations of the bridges optimize for a maximum number of antiperiplanar torsional angles, with two synclinal angles taking varying positions in each structure. The steric constraints due to the aromatic methyl groups of **3** on the possible torsional angles around the ether oxygens, however, prevent the bridges in the macrocycles **1**, **31**, and **32** to take conformations similar to those seen in the crystal structures of **30**. For this reason, the X-ray parameters of the bridges of **30** could not be simply used in this study.

With Φ[C(17)–C(20)–O(21)–C(22)] set to 90°, the fragment **33** described by internal coordinates had an input distance between the terminal oxygens of 8.98 Å, which is close to the O···O distance of 9.07 Å in **3**. By proper orientation of their Cartesian coordinates, the two fragments **33** and **3** (without phenolic H) were joined to form the macrocycle. This macrocyclic input geometry was then fully optimized with no restrictions. The optimized structure of **31** and the corresponding space-filling model, visualized by the HYDRA color graphics software,[59] are shown in Figure 2a.

The calculated geometries of the diphenylmethane spacer units within the macrocycle are quite similar to the geometry of **3**. The input gable conformation has gone to a helical conformation with torsional angles of 103–115°. Interestingly, with values of 8.82 and 9.40 Å, the distances between the two oxygens in each spacer unit (O–Ar–CH_2–Ar–O) varies by 0.68 Å. Whether there is any physical basis for this lack of symmetry in the generated structure is uncertain, but it probably could result from the particular conformations of the bridging chains. The higher degree of symmetry in the X-ray structures could well be a consequence of molecular packing interactions.

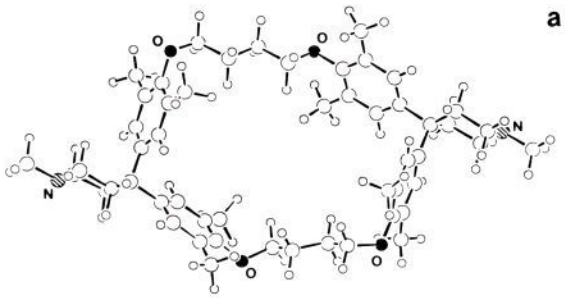
A docking procedure, which involves the minimization of van der Waals energy during complex formation, demonstrated that 2,6-disubstituted naphthalenes bind inside the macrocyclic cavity and highly prefer a near perfect pseudoaxial position. Such a favored geometry has been deduced experimentally from extensive NMR studies for complexes formed by hosts related to **31** and these guests.[42,43]

Incorporation of the Biphenyl Spacer Unit into Macrocycle 1. The biphenyl macrocycle **1** incorporating the diphenylmethane unit with two 1,5-dioxapentane chains was constructed by the method described above for **31**. The O···O distance of 4.1 Å for the biphenyl spacer requires two synclinal torsional angles in each chain to join the two fragments in the formation of the macrocycle. Figure 2b shows that the minimization leads to an extensively twisted helical geometry for **1**. This helical twist seems to be imposed on the macrocycle by the tendency of the bridging chains, which connect two spacers of significantly different O···O distances, to maximize the number of antiperiplanar torsional angles. The energy-minimized geometry shows a cavity too narrow for incorporation of a benzene or naphthalene guest, which is in agreement with our previous experimental results.[10]

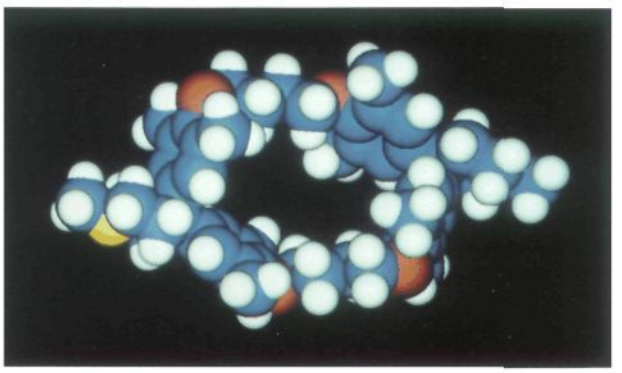
Incorporation of the 4-Phenyl-1,2,3,4-tetrahydroisoquinoline 8 into Macrocycle 32. The internal coordinates of fragment **33** were adjusted as described above to obtain terminal O···O distances close to 7.58 and 6.33 Å. These correspond to the O···O distances of the two isoenergetic conformations **8a** and **8b** of the chiral spacer

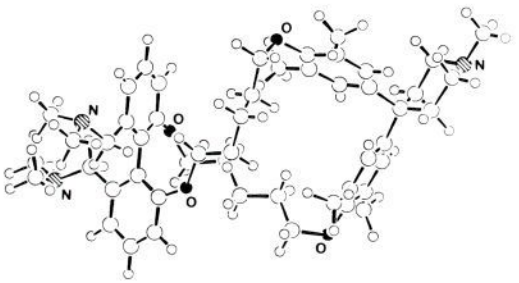
(58) Kobayashi, S.; Tokumoto, T.; Taira, Z. *J. Chem. Soc., Chem. Commun.* **1984**, 1043–1044.

(59) HYDRA 1.) Software for Silicon Graphics 3000 work station; Polygen Corp., 200 Fifth Ave, Waltham, MA 02254.

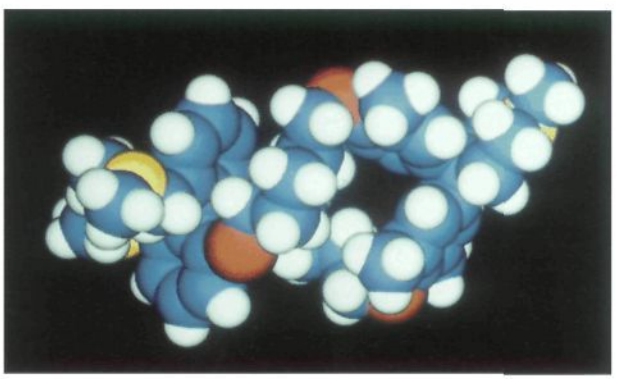


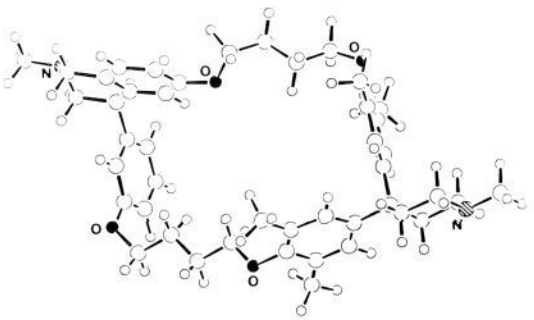
31



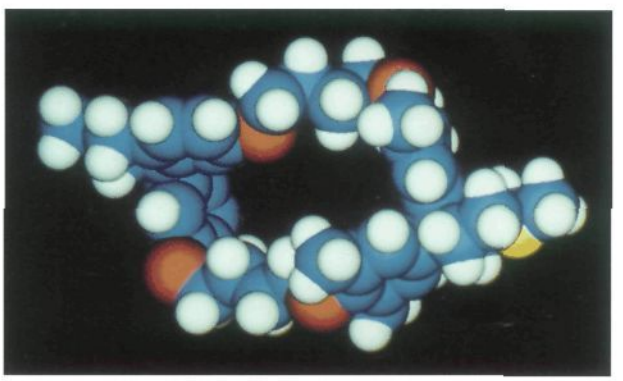


1





32d



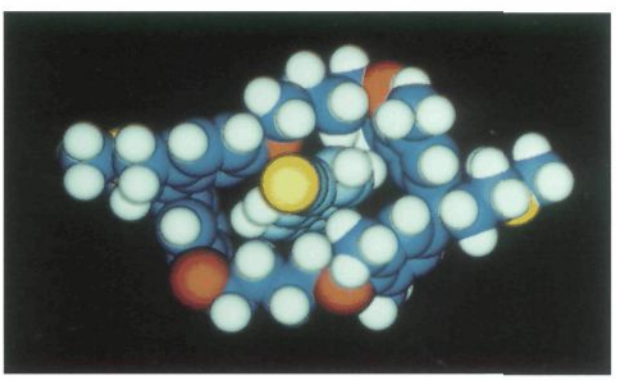


Figure 2. Optimized structures and corresponding space-filling models generated by the HYDRA color graphics software of the macrocycle **31** (Figure 2a) and macrocycle **1** (Figure 2b). Figure 2c shows the conformer **32d** of the macrocycle incorporating a 4-phenyltetrahydroisoquinoline unit. Figure 2d shows the structure of the complex formed by docking in 2,6-dicyanonaphthalene into the binding site of **32d** and by minimizing for van der Waals energy as defined by the HYDRA software.

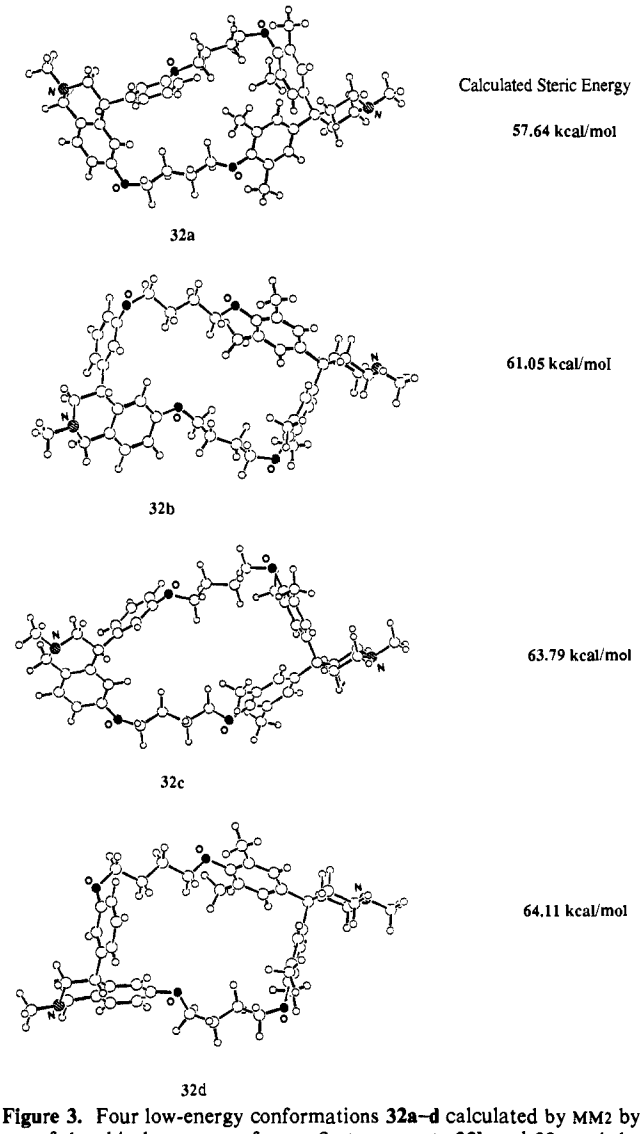


Figure 3. Four low-energy conformations **32a–d** calculated by MM2 by use of the chiral spacer conformer **8a** to generate **32b** and **32c** and the conformer **8b** to generate **32a** and **32d**.

unit. Two energy-minimized conformations of the macrocycle **32**, which is the *N*-methyl analogue of **26**, were found for each of the two rotamers. Conformations **32b** and **32c** contain spacer unit **8a**, and conformations **32a** and **32d** include the spacer unit **8b** (Figure 3). While the gas-phase steric energies calculated for these four conformations vary by about 6.0 kcal/mol, their relative energies in solution can not be analyzed and may be considerably different. Differences in torsional energies contribute almost all of the 6.0 kcal/mol.

The overall helical distorsion in all four conformations **32a–d** is considerably smaller than the distortion calculated for the biphenyl macrocycle **1** (Figure 2b). The cavities of the three conformers **32b–d** are large enough to fully incorporate 2,6-disubstituted naphthalene guests in a highly preferred pseudoaxial orientation, and indeed, our complexation studies have demonstrated that hosts **26** and **10**, closely related to **32**, are highly specific for this type of guest. Docking procedures suggest that conformation **32d** (Figure 2c) provides the most favorable binding site for complexing a guest like 2,6-dicyanonaphthalene. Figure 2d shows the complex generated by docking this guest in the energetically most favorable orientation into the binding site of conformer **32d**. The space-filling graphics shows the benzylic substituents of a complexed 2-substituted naphthalene guest, e.g., the ester residue in **29**, can be favorably oriented for $\pi-\pi$ interactions with the isoquinoline unit. It will be of interest to see in our future experimental work whether these specific interactions will be effective to discriminate between enantiomers in diastereomeric complexes of **10** and related chiral hosts. Conformation **32a** has the lowest calculated gas-phase steric energy and is more twisted than the other conformations, which makes the cavity quite small. During the docking procedure, the 2,6-dicyanonaphthalene cannot penetrate very deeply into the cavity of **32a** without van der Waals contact energies becoming extremely unfavorable. Conformations **32b** and **32c** have cavities that are of suitable size to complex naphthalenes, but the overall geometric complementarity is not as favorable as found with conformation **32d**. While we do not claim to have found the global energy minimum conformation, the calculations point out that there is a broad range of productive conformations for macrocycle **32** with complementarities to naphthalene guests ranging from excellent (**32d**) to rather poor (**32a**). Interestingly, the docking experiments show that the calculated lowest energy conformer is the poorest binder and the calculated highest energy conformer the best binder. We may have missed a very low energy geometry with excellent binding properties, and of course, solvation can alter considerably the relative energies of the host conformers in solution. Solvation could possibly have a much larger impact on the relative energies of the conformers of the ionic hosts **26** (protonated) and **10** used in the experimental study than on the stability of the conformers of the nonionic but otherwise almost identical macrocycle **32**. Our results could, however, also mean that some of the attractive binding energy has to be spent to organize the host from a less productive, lower energy conformation such as **32a** to a higher energy, productive binding conformation such as **32d**.

Conclusions. We have shown, that MM2 geometries of aromatic spacer units correspond quite well with trends seen in X-ray crystal structures, and these calculations have provided us with a tool for evaluating designed spacer units before their synthetic incorporation into macrocycles. The O···O distance of our spacers is crucial, and the diphenylmethane unit **3** can be taken as a standard with which all other units can be compared in their ability to open and shape cavity binding sites for flat aromatic and alicyclic guests.[60] After the modeling, we are now confident that hosts with productive binding sites form each time, when a chiral or achiral spacer unit with an O···O distance of $\approx\geq$6.5 Å is combined with the diphenylmethane unit **3** (O···O $\approx$9 Å). We have described a way to generate low-energy conformations of macrocyclic hosts starting from very reasonable input geometries. The experimentally observed binding capabilities of our macrocycles are very well reproduced in the computer modeling. Computer-generated space-filling color graphics visualize in a unique attractive way the calculated geometries of our macrocycles and their complexes. However, our modeling has not only generated aesthetic visualization; it also has advanced our knowledge on molecular recognition. Besides recognizing the importance of the O···O distance in the spacers, the docking experiments have provided further support for the preferred pseudoaxial inclusion of complexed 2,6-disubstituted naphthalenes, which we had deduced experimentally from extensive ^{1}H NMR binding studies. Also, the modeling has generated important insights into the conformations of aliphatic bridges connecting the spacers in our macrocycles. The severe helical distortion of macrocycle **1** as a result of connecting spacers with very different O···O distances while optimizing the aliphatic bridges for antiperiplanar torsional angles could not be deduced from CPK model examinations. With the exception of the MM2 calculations in the design of the spacer units, all computer modeling in this study has followed the experimental work. In future work, the synthetic and binding experiments will be designed to test predictions generated by computer modeling for macrocyclic hosts and their complexes.

Experimental Section

Instrumentation and Analytical Methods. ^{1}H NMR was carried out on Varian EM360, Bruker WP200, and AM500 spectrometers. All δ values in the spectra to characterize new compounds refer to Me_4Si as internal standard. If not stated otherwise, the spectra were recorded at 303 K. (For examples of parameters for the 500-MHz 2D COSY spectra

(60) Odashima, K.; Itai, A.; Iitaka, Y.; Koga, K. *J. Org. Chem.* **1985**, *50*, 4478–4484.

to determine the connectivities of spin systems, see ref 10.) Mass spectra were carried out on a AEI MS9 spectrometer and a AEI MS902 high-resolution mass spectrometer. EI mass spectra were recorded at 70 eV. Xenon FAB-mass spectra were recorded with a *m*-nitrobenzyl alcohol matrix. Melting points (uncorrected) were measured on a Büchi (Dr. Tottoli) apparatus. IR spectra were recorded on a Perkin-Elmer PE580 instrument. Elemental analysis was performed at Max-Planck-Institut für Medizinische Forschung, Heidelberg, and Spang microanalytical laboratory, Eagle Harbor, MI. Analytical thin-layer chromatography 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 Büchi rotary evaporator at water aspirator pressure followed by evaporation at 0.5 mm for several hours. Solvents and reagents were purchased from Aldrich Chemical Co. and were used without further purification unless otherwise specified. (*S*)-naproxen was purchased from Sigma Chemical Co., and (*R*)-naproxen was received as a gift from Syntex Corp., Palo Alto. Optical rotations were measured on a Perkin-Elmer 241 polarimeter in a 10-cm cell (5 mL vol) in the indicated solvent. Concentrations *c* are in grams of solute per 100 mL. (For details on ^{1}H NMR binding studies, see ref 11b, 19c, and 42.)

Synthesis. Bis(3-methoxyphenyl)methanol (11). To a suspension of 11.5 g (0.48 mol) of magnesium turnings in 25 mL of anhydrous ether was added under N_2 dropwise 10 mL of a solution of 90 g (0.48 mol) of *m*-anisyl bromide in 50 mL of anhydrous ether. The reaction was initiated by ultrasonification, and the residual solution of *m*-anisyl bromide was added over a period of 30 min. After all the magnesium had reacted, a solution of 65.4 g (0.48 mol) of *m*-anisaldehyde in 50 mL of anhydrous ether was added dropwise. The reaction mixture was stirred at room temperature for an additional 1 h and then poured into 200 mL of ice–water. After neutralization with 50 mL of saturated NH_4Cl, the organic and the aqueous layers were separated. The aqueous layer was extracted with ether (3 × 100 mL), and the combined organic extracts were washed with water (50 mL) followed by saturated NaCl. After the mixture was dried over sodium sulfate, the solvent was distilled off to leave a yellow oil, which was chromatographed on silica gel from hexane/ether (5:1) yielding 73 g (62%) of **11** as a white solid: mp 35–37 °C; IR (KBr) ν(O–H) 3480 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.77 (s, 6 H, OCH_3), 5.75 (s, 1 H, Ar_2CHOH), 6.79 (dd, J = 6, 2 Hz, 2 H, 4-H), 6.94 (s, 2 H, 2-H), 6.94 (d, J = 6 Hz, 2 H, 6-H), 7.23 (t, J = 6 Hz, 2 H, 5-H); MS, m/z 244 (M^+). Anal. Calcd for $C_{15}H_{16}O_3$ (244.3): C, 73.74; H, 6.60. Found: C, 73.82; H, 7.12.

Bis(3-methoxyphenyl) Ketone (19). To a suspension of 68 g (0.31 mol) of pyridinium chlorochromate in 300 mL of dichloromethane was added a solution of 51 g (0.21 mol) of **11** in 100 mL of dichloromethane. After the resultant mixture was stirred for 3 h at 20 °C, 300 mL of anhydrous ether was added. The precipitated solids were removed by filtration and washed once with 50 mL of ether. Evaporation of the filtrates left a yellow oil, which was chromatographed on silica gel from toluene to afford 45 g (90%) of **19** as a light yellow oil: R_f 0.56 (SiO_2, ether/hexane 1:1); IR (film) ν(C=O) 1690 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.91 (s, 6 H, OCH_3), 7.1 (m, 2 H, 4-H), 7.3–7.4 (m, 6 H, 2-H, 5-H, 6-H); MS, m/z (relative intensity) 242 (100, M^+); HRMS, m/z (M^+, $C_{15}H_{14}O_3$) calcd 242.0943, obsd 242.0929.

Cyanobis(3-methoxyphenyl)methanol (13). To a solution of 45 g (0.19 mol) of **19** in 200 mL of dichloromethane was added under N_2 23.9 g (0.24 mol) of trimethylsilyl cyanide, followed by 0.9 g (2.86 mmol) of zinc iodide. After the resultant mixture was stirred for 24 h at 20 °C, the solvents were removed in vacuo. The resulting crude bis(3-methoxyphenyl)[(trimethylsilyl)oxy]acetonitrile was dissolved in a mixture of 100 mL of tetrahydrofuran and 50 mL of 3 N HCl and refluxed for 1 h. After cooling, the reaction mixture was poured in 100 mL of water, and the organic and aqueous layers were separated. The aqueous layer was extracted with ether (3 × 50 mL), and the combined organic layers were washed with water (3 × 50 mL) and dried over magnesium sulfate. Removal of all volatile materials in vacuo gave 49 g (95%) of **13** as a light yellow oil, R_f 0.49 (SiO_2, ether/hexane 1:1), which was used without further purification in the following conversion. **13**: IR (film) ν(O–H) 3400 cm^{-1}; ^{1}H NMR (60 MHz, $CDCl_3$) δ 3.90 (s, 6 H, OCH_3), 6.8–7.4 (m, 8 H); MS, m/z 269 (M^+).

Chlorobis(3-methoxyphenyl)acetonitrile (14). To a solution of 58 g (0.21 mol) of **13** in 500 mL of dry benzene was added 90 g (0.43 mol) of phosphorus pentachloride portionwise at 0 °C. After being stirred for 12 h at 20 °C, the mixture was poured into 400 mL of water. The aqueous and organic layers were separated, and the organic layer was washed successively with water (500 mL), with cold 10% $NaHCO_3$ until the washings were neutral, with water (50 mL), and finally with concentrated NaCl (50 mL). After the organic layer was dried over sodium sulfate, the solvent was removed in vacuo to yield 51 g (84%) of **14**, which was used in the next conversion without further purification. **14**: R_f 0.75 (SiO_2, ether/hexane 1:1); ^{1}H NMR (60 MHz, $CDCl_3$) δ 3.90 (s, 6 H, OCH_3), 6.8–7.4 (m, 8 H); MS, m/z 287 (M^+).

Bis(3-methoxyphenyl)acetonitrile (15). A total of 56.5 g (0.19 mol) of tributyltin hydride was added under N_2 to a solution of 28 g (0.097 mol) of chloronitrile **14** in 500 mL of dry benzene. A catalytic amount of azobis(isobutyronitrile) (AIBN) was added to the reaction mixture, which was subsequently heated to reflux for 4 h. Removal of solvent in vacuo afforded an oil that, upon addition of 40 mL of hexane, yielded 18.9 g (77%) of **15** as a colorless solid: mp 89–91 °C (lit.[61] mp 88–89 °C); IR (KBr) ν(CN) 2180 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.78 (s, 6 H, OCH_3), 5.06 (s, 1 H, Ar_2CHCN), 6.85–6.9 (m, 4 H, 2-H, 4-H), 6.93 (d, J = 8.0 Hz, 2 H, 6-H), 7.26 (t, $J \approx$ 8 Hz, 2 H, 5-H); ^{13}C NMR (125.76 MHz, $CDCl_3$) δ 160.12, 137.16, 130.21, 119.99, 119.53, 113.65, 113.55, 55.31, 42.52; MS, m/z 253 (M^+). Anal. Calcd for $C_{16}H_{15}NO_2$ (253.3): C, 75.87; H, 5.97; N, 5.53. Found: C, 75.58; H, 6.48; N, 5.66.

1-Cyano-1,1,2,2-tetrakis(3-methoxyphenyl)ethane (20). To a solution of 4 g (16.39 mmol) of bis(3-methoxyphenyl)methanol (**11**) dissolved in 40 mL of benzene was added 4 g (36.36 mmol) of anhydrous calcium chloride. The mixture was cooled to 0 °C, and a stream of HCl gas was bubbled in for 2 h. After filtration, the solvent was evaporated in vacuo yielding 3.9 g (91%) of chlorobis(3-methoxyphenyl)methane (**12**) as pale yellow oil, which was used without further purification in subsequent conversions: R_f 0.60 (SiO_2, hexane/ethyl acetate 7:3); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 3.65 (s, 6 H, OCH_3), 5.8 (s, 1 H, Ar_2CHCl), 6.65–6.80 (m, 4 H, 2-H, 4-H), 6.90 (d, J = 8.0 Hz, 2 H, 6-H), 7.15 (t, J = 8.0 Hz, 2 H, 5-H). A total of 2.6 g (40 mmol) of potassium cyanide and 0.29 g (1.1 mmol) of 18-crown-6 was added to a solution of 3.5 g (13.35 mmol) of chloride **12** in 50 mL of acetonitrile. The mixture was stirred at 20 °C for 12 h under N_2. Since thin-layer chromatography indicated little conversion, an additional amount of 2.6 g (40 mmol) of potassium cyanide was added, and the mixture stirred for 12 h under reflux. After the mixture was cooled to 20 °C, 80 mL of water and 100 mL of chloroform were added. The layers were separated, and the organic layer was washed with 50 mL of water and 25 mL of saturated NaCl. Removal of the solvent in vacuo, followed by chromatography on silica gel from toluene, gave 0.6 g (19%) of **20**.

By using the same quantities of reagents in a reaction carried out under N_2 in dimethylformamide for 12 h at 20 °C and the same workup, a total of 2.87 g (87%) of pure **20** was obtained: mp 42–44 °C; IR (KBr) ν(CN) 2270 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.61 (s, 6 H, OCH_3), 3.66 (s, 6 H, OCH_3), 4.87 (s, 1 H, Ar_2CH), 6.67 (dd, J = 8.0, 2.2 Hz, 2 H), 6.72 (m, 4 H), 6.81 (d, J = 8.0 Hz, 2 H), 6.85 (s, br, 2 H), 6.90 (d, J = 8.0 Hz, 2 H), 7.07 (t, J = 8.0 Hz, 2 H), 7.13 (t, J = 8.0 Hz, 2 H). Anal. Calcd for $C_{31}H_{29}NO_4$ (479.6): C, 77.64; H, 6.05; N, 2.92. Found: C, 77.63; H, 6.06; N, 2.77.

2,2-Bis(3-methoxyphenyl)ethylamine (16). A total of 260 mL (0.26 mol) of a 1 M solution of borane in tetrahydrofuran was added dropwise at 20 °C under N_2 to a solution of 22 g (0.09 mol) of nitrile **15** in 200 mL of dry tetrahydrofuran. After being heated to reflux for 16 h, the mixture was cooled in an ice bath, and 100 mL of absolute alcohol was added dropwise at 0 °C. To destroy the amine–borane complex, HCl gas was bubbled into the solution for 20 min at 20 °C. Removal of solvents in vacuo left a solid, which was washed with 100 mL of ether. The solid was stirred with 50 mL of 2 N NaOH, and the aqueous solution was extracted with chloroform (3 × 100 mL). The combined chloroform extracts were washed with water (100 mL) and saturated NaCl (50 mL) and dried over sodium sulfate. Evaporation of the solvent afforded 21 g (91%) of crude amine **16** as a yellow oil, which was used without further purification in the next conversion, **16**: IR (film) ν(NH_2) 3400, 3325 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.29 (d, J = 7.9 Hz, 2 H, CH_2NH_2), 3.77 (s, 6 H, OCH_3), 3.92 (t, J = 7.9 Hz, 1 H, Ar_2CHCH_2), 6.75 (dd, J = 8.0, 2.2 Hz, 2 H, 4-H), 6.79 (t, J = 2.2 Hz, 2 H, 2-H), 6.85 (d, J = 8.0 Hz, 2 H, 6-H), 7.22 (t, J = 8.0 Hz, 2 H, 5-H); MS, m/z 257 (M^+).

***N*-(*tert*-Butyloxycarbonyl)-2,2-bis(3-methoxyphenyl)ethylamine (17).** A solution of 21 g (81.7 mmol) of amine **16** and 12.5 mL (89.9 mmol) of triethylamine in 50 mL of dichloromethane was added dropwise at 20 °C under N_2 to a solution of 20.8 g (89.9 mmol) of di-*tert*-butyl dicarbonate in 500 mL of dichloromethane. After being stirred for 3 h, the mixture was poured into 100 mL of water. The separated organic layer was washed with 1N HCl, water (50 mL) and saturated NaCl (25 mL). After the mixture was dried over magnesium sulfate, the solvent was removed in vacuo, and the resulting oil was chromatographed on silica gel from ether/hexane (1:1) to yield 24 g (82%) of **17** as a colorless oil: R_f 0.48 (SiO_2, ether/hexane 1:1); IR (film) ν(N–H) 3450 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.41 (s, 9 H, *t*-Bu), 3.74 (t, $J \approx$ 6.5 Hz, 2 H, Ar_2CHCH_2), 3.77 (s, 6 H, OCH_3), 4.10 (t, J = 7.5 Hz, 1 H,

(61) Kametami, T.; Ogasawara, K.; Terui, T.; Yamaki, K.; Fukumoto, K. *Chem. Pharm. Bull.* **1968**, *16*, 1584–1588.

Ar_2CHCH_2), 6.75–6.8 (m, 4 H, 2-H, 4-H), 6.83 (d, J = 7.8 Hz, 2 H, 6-H), 7.23 (t, J = 7.8 Hz, 2 H, 5-H); MS (16 eV) m/z 357 (M^+); HRMS m/z (M^+ – t-BuO, $C_{17}H_{18}NO_3$) calcd 284.1287, obsd 284.1281. Anal. Calcd for $C_{21}H_{27}NO_4$ (357.4): C, 70.56; H, 7.61; N, 3.92. Found: C, 71.15; H, 7.62; N, 3.88.

***N*-(*tert*-Butyloxycarbonyl)-*N*-(hydroxymethyl)-2,2-bis(3-methoxyphenyl)ethylamine (18).** To a solution of 23 g (0.064 mol) of **17** in 200 mL of dioxane were added 61 g (1.92 mol) of a 37% aqueous solution of formaldehyde and 24 mL (0.147 mol) of 2 N NaOH. The mixture was stirred at 20 °C for 72 h. At the end of the reaction, the pH was adjusted to pH ≈6 by addition of saturated NH_4Cl. The reaction mixture was extracted with chloform (2 × 100 mL), and the combined organic layers were washed with water (200 mL) and saturated NaCl (50 mL). After drying over sodium sulfate and evaporation of the solvent, a yellow oil was obtained, which was chromatographed on silica from ether/hexane (1:1) yielding 19 g (76%) of **18** as colorless oil which was used immediately for the next conversion: IR (film) ν(O–H) 3500, ν (C=O) 1710 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 1.42 (s, 9 H, t-Bu), 3.76 (s, 6 H, CH_3O), 3.90 (d, J = 7.7 Hz, 2 H, Ar_2CHCH_2), 4.27 (t, J = 7.7 Hz, 1 H, Ar_2CHCH_2), 4.61 (s, 2 H, NCH_2OH), 6.75–6.85 (m, 6 H, 2-H, 4-H, 6-H), 7.20, (t, J = 8.0 Hz, 2 H, 5-H); HRMS m/z (M^+ – CH_2O – t-BuO, $C_{17}H_{18}NO_3$) calcd 284.1287, obsd 284.1265.

***N*-(*tert*-Butyloxycarbonyl)-6-methoxy-4-(3-methoxyphenyl)-1,2,3,4-tetrahydroisoquinoline (21).** A catalytic amount of p-toluenesulfonic acid was added to a solution of 10 g (0.026 mol) of **18** in 500 mL of benzene, and the mixture was heated to reflux for 1 h. After being cooled to 20 °C, the benzene solution was washed with 10% $NaHCO_3$ (50 mL), with water (50 mL), and with saturated NaCl (50 mL). Drying over sodium sulfate followed by removal of solvent in vacuo gave a light yellow oil, which was chromatographed on silica gel from ether/hexane (1:1) to yield 9 g (95%) of **21** as colorless oil: IR (film) ν(C=O) 1690 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 1.17 and 1.26 (2 s, br, 9 H, t-Bu), 3.6–4.0 (m, br, 2 H, 3-H), 3.68 (s, 3 H, OCH_3), 3.74 (s, 3 H, OCH_3), 4.05–4.1 (s br, 1 H, 4-H), 4.4–4.9 (m, br, 2 H, 1-H), 6.49 (s, 1 H, 5-H), 6.5–6.85 (m, 4 H, 7-H, 2′-H, 4′-H, 6′-H), 7.08 (d, J = 8 Hz, 1 H, 8-H), 7.19 (t, J = 8 Hz, 1 H, 5′-H); MS (16 eV), m/z 312 (M^+ – t-Bu); HRMS m/z (M^+ – t-Bu, $C_{18}H_{18}NO_4$) calcd 312.1236, obsd 312.1233.

(–)-6-Methoxy-4-(3-methoxyphenyl)-1,2,3,4-tetrahydroisoquinoline [(–)-9]. A total of 40 mL (0.52 mol) of trifluoroacetic acid was added dropwise at 20 °C to a solution of 14 g (37.9 mmol) of **21** in 150 mL of dichloromethane. After the mixture was stirred for an additional 10 min, the volatiles were removed in vacuo. The residue was partitioned between 6 M NH_4Cl and chloroform (100 mL), and the aqueous layer was extracted two more times with chloroform (2 × 100 mL). The combined organic layers were washed with water (3 × 50 mL) and saturated NaCl and then dried over sodium sulfate. Evaporation of the solvent in vacuo left 9.78 g (97%) of racemic amine **9** as yellow oil, which was subsequently resolved.

Optical Resolution of Racemic Amine 9. A solution of 39.3 g (0.104 mol) of (+)-dibenzoyl-D-tartaric acid in 160 mL of ethyl acetate was added to a solution of 28.1 g (0.104 mol) of racemic amine **9**. Crystallization was induced by addition of a few drops of ether. After the mixture was left overnight, the solids were collected by filtration. Three recrystallizations of the collected solid from 200 mL of ethanol/water (1:1) afforded the diastereomeric salt (–)-**9**·(+)-dibenzoyl-D-tartaric acid. The salt was partitioned between 12 M NH_4OH and dichloromethane. After two more extractions of the aqueous layer with dichloromethane, the combined organic solutions were washed with water and saturated NaCl and then dried over sodium sulfate. Removal of the solvent in vacuo yielded 3.80 g (20%) of the amine (–)-**9** in enantiomeric purity (≥98%), which eventually crystallized. To determine the optical purity (percent ee), 5.126 mg (0.019 mmol) of (–)-**9** and 3.07 mg (0.020 mmol) of (–)-(*S*)-α-methylbenzyl isocyanate were dissolved in 2 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.[38] (–)-**9**: mp 58–60 °C; colorless solid; $[\alpha]^{23}_D$ –58.8° (c 1.27, $CHCl_3$); IR (KBr) ν(N–H) 3400 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 3.08 (dd, J = 13.0, 6.1 Hz, 1 H, 3-H_{ax}), 3.36 (dd, J = 13.0, 5.7, 1 H, 3-H_{eq}), 3.67 (s, 3 H, OCH_3), 3.77 (s, 3 H, OCH_3), 3.99 (m, 3 H, 1-H, 4-H), 6.45 (d, J = 2.5 Hz, 1 H, 5-H), 6.64 (t, J = 2.0 Hz, 1 H, 2′-H), 6.68 (d, J = 7.9 Hz, 1-H, 6′-H), 6.75–6.8 (m, 2 H, 7-H, 4′-H), 6.99 (d, J = 8.4 Hz, 1 H, 8-H), 7.21 (t, J = 7.9 Hz, 1 H, 5′-H); MS, m/z (relative intensity) 269 (100, M^+); HRMS m/z (M^+, $C_{17}H_{19}NO_2$) calcd 269.1417, obsd 269.1421.

Amine Hydrochloride (–)-9·HCl. Upon introduction of dry HCl gas in a solution of 0.1 g (0.37 mmol) of (–)-**9** in anhydrous ether for 5 min and removal of the volatiles in vacuo, 0.11 g (99%) of the hydrochloride salt was obtained as colorless solid: mp 182–184 °C; ^{13}C NMR (125.759 MHz, $CDCl_3$) δ 160.08, 159.16, 141.48, 136.76, 130.10, 127.72, 121.30, 119.92, 114.77, 114.23, 113.74, 113.33, 55.32, 55.23, 47.82, 44.31, 42.13. Anal. Calcd for $C_{17}H_{20}NO_2Cl$ (305.8): C, 66.77; H, 6.59; N, 4.58. Found: C, 67.08; H, 6.48; N, 4.62.

(–)-*N*-Acetyl-6-methoxy-4-(3-methoxyphenyl)-1,2,3,4-tetrahydroisoquinoline [(–)-22]. A total of 50 mL of acetic anhydride was added dropwise into an ice cold mixture of 3.7 g (13.7 mmol) of amine (–)-**9** and 2.25 g (27.4 mmol) of sodium acetate. After the mixture was stirred at 20 °C for 16 h, the solvent was removed in vacuo. The residue was partitioned between 10% Na_2CO_3 (100 mL) and dichloromethane (100 mL). The aqueous layer was further extracted with dichloromethane (2 × 100 mL), washed with water (50 mL), followed by saturated NaCl, and dried over sodium sulfate. Removal of the solvent in vacuo gave a yellow oil, which was chromatographed on silica gel from ethyl acetate to yield 3.5 g (82%) of amide (–)-**22** as colorless solid: mp 89–91 °C; $[\alpha]^{23}_D$ –12.0° (c 1.00, $CHCl_3$); IR (film) ν(C=O) 1640 cm^{-1}; ^1H NMR (500 MHz, Me_2SO-d_6, T 393 K) δ 1.79 (s, 3 H, $NCOCH_3$), 3.66 (s, 3 H, OCH_3), 3.72 (s, 3 H, OCH_3), 3.82 (m, 2 H 3-H), 4.19 (s, br, 1 H, 4-H), 4.50 (d, part of AB, J = 16 Hz, 1 H, 1-H), 4.80 (d, part of AB, J = 16 Hz, 1 H, 1-H), 6.49 (d, J = 2.4 Hz, 1 H, 5-H), 6.65–6.7 (m, 2 H, 2′-H, 6′-H), 6.8–6.85 (m, 2 H, 7-H, 4′-H), 7.1–7.2 (m, 2 H, 8-H, 5′-H); MS, m/z (relative intensity) 311 (100, M^+); HRMS m/z (M^+, $C_{19}H_{21}NO_3$) calcd 311.1522, obsd 311.1525. Anal. Calcd for $C_{19}H_{21}NO_3$·0.5H_2O (320.4): C, 71.23; H, 6.92; N, 4.37. Found: C, 70.95; H, 6.76; N, 4.14.

(–)-*N*-Acetyl-6-hydroxy-4-(3-hydroxyphenyl)-1,2,3,4-tetrahydroisoquinoline [(–)-23]. To a solution of 3.5 g (0.011 mol) of amide (–)-**22** in 60 mL of dichloromethane under N_2 at –78 °C was added dropwise 11 mL (0.11 mol) of boron tribromide. The mixture was slowly warmed to 20 °C and stirred for 24 h. After the mixture was cooled to 0 °C, 100 mL of methanol was carefully added. The volatiles were evaporated in vacuo, and the residue was partitioned between 300 mL of water and 100 mL of chloroform. After the aqueous layer was further extracted with chloroform (2 × 100 mL), the combined organic layers were washed with water (50 mL), followed by saturated NaCl (50 mL) and dried over sodium sulfate. Removal of the solvent in vacuo left an oil, which was chromatographed on silica gel from ethyl acetate to yield 2.65 g (83%) of the diphenol (–)-**23** as colorless solid: mp 153–155 °C; $[\alpha]^{23}_D$ –2.8° (c 1.00, $CHCl_3$); IR (film) ν(O–H) 3400, (C=O) 1690 cm^{-1}; ^1H NMR (500 MHz, Me_2SO-d_6, T 393 K) δ 1.83 (s, 3 H, $NCOCH_3$), 3.72 (dd, J = 9.8, 6.2 Hz, 1 H, 3-H_{ax}), 3.82 (dd, J = 9.8, 5.0 Hz, 1 H, 3-H_{eq}), 4.04 ("t", 1 H, 4-H), 4.48 (d, part of AB, J = 16 Hz, 1 H, 1-H), 4.70 (d, part of AB, J = 16 Hz, 1 H, 1-H), 6.36 (d, J = 2.5 Hz, 1 H, 5-H), 6.5 (s, br, 1 H, 2′-H), 6.57 (dd, J = 8.0, 1.1 Hz, 1 H, 6′-H), 6.6–6.65 (m, 2 H, 7-H, 4′-H), 7.02 (d, J = 8.0 Hz, 1 H, 8-H), 7.08 (t, J = 8.0 Hz, 1 H, 5′-H), 7.45 (s, br, 1 H, OH), 7.56 (s, br, 1 H, OH); MS, m/z (relative intensity) 283 (100, M^+); HRMS m/z (M^+, $C_{17}H_{17}NO_3$) calcd 283.1209, obsd 283.1205.

(–)-*N*-Acetyl-6-(4-chlorobutoxy)-4-[3-(4-chlorobutoxy)phenyl]-1,2,3,4-tetrahydroisoquinoline [(–)-24]. A mixture of 2.65 g (9.3 mmol) of diphenol (–)-**23**, 24 g (73.7 mmol) of cesium carbonate, and 47.6 g (0.374 mol) of 1,4-dichlorobutane in 50 mL of dimethylformamide dried over basic alumina was stirred at 80 °C under N_2 for 24 h. After cooling, the cesium salts were removed by filtration, and the solution was evaporated to dryness. The residual oil was chromatographed on silica gel from dichloromethane, and 2.8 g (65%) of the dichloride (–)-**24** was obtained as light yellow oil: R_f 0.55 (SiO_2, ethyl acetate/dichloromethane, 1:1); $[\alpha]^{23}_D$ –20.3° (c 1.10, $CHCl_3$); IR (film) ν(C=O) 1680 cm^{-1}; ^1H NMR (500 MHz, Me_2SO-d_6, T 393 K) δ 1.7–1.9 (m, 11 H, $ClCH_2CH_2CH_2CH_2O$ and $NCOCH_3$), 3.61 (t, J = 6.5 Hz, 2 H, CH_2Cl), 3.65 (t, J = 6.5 Hz, 2 H, CH_2Cl), 3.75–3.9 (m, 2 H, 3-H), 3.9–4.1 (m, 4 H, CH_2OAr), 4.17 (s, br, 1 H, 4-H), 4.49 (d, part of AB, J = 15 Hz, 1 H, 1-H), 4.83 (d, part of AB, J = 15 Hz, 1 H, 1-H), 6.49 (d, J = 2.5 Hz, 1 H, 5-H), 6.6–6.7 (m, 2 H, 2′-H, 6′-H), 6.75–6.85 (m, 2 H, 7-H, 4′-H), 7.16 (d, J = 8.0 Hz, 1 H, 8-H), 7.19 (t, J = 8.0 Hz, 1 H, 5′-H); MS, m/z (relative intensity) 463 (100, M^+); HRMS m/z (M^+, $C_{25}H_{31}Cl_2NO_3$) calcd 463.1683, obsd 463.1687.

(+)-1′,34-Diacetyl-32,33,34,35-tetrahydro-8,12,16,18-tetramethylspiro[1,6,20,25-tetraoxa[6.1]paracyclo[6]metacyclo[0](4,6)isoquinolinophane-13,4′-piperidine] [(+)-25].[62] A mixture of 2.75 g (5.94 mmol) of dichloride (–)-**24**, 2.18 g (5.94 mmol) of *N*-acetyl-4,4-bis(4-hydroxy-3,5-dimethylphenyl)piperidine,[19d] and 9.67 g (29.7 mmol) of cesium carbonate was stirred at 70 °C under N_2 for 6 days. After cooling, the cesium salts were removed by filtration, and the solution was evaporated to dryness under reduced pressure. Chromatography on silica gel from ethyl acetate afforded 0.945 g (21%) of the macrocycle (+)-**25**: mp 98–100 °C; $[\alpha]^{23}_D$ +2.85° (c 1.01, $CHCl_3$); IR (KBr) ν(C=O) 1672 cm^{-1}; ^1H NMR (500 MHz, Me_2SO-d_6, T 393 K) δ 1.7–1.9 (m, 11 H, $ClCH_2CH_2CH_2CH_2O$ and isoquin-$NCOCH_3$), 1.96 (s, 3 H, pip-

(62) The phane nomenclature is used; see: Vögtle, F.; Neumann, P. *Tetrahedron* **1970**, *26*, 5847–5863.

$NCOCH_3$), 2.10 (s, 6 H, Ar-CH_3), 2.16 (s, 6 H, Ar-CH_3), 2.2–2.3 (m, 4 H, 3′-H_{pip}, 5′-H_{pip}),[63] 3.4–3.5 (m, 4 H, 2′-H_{pip}, 6′-H_{pip}), 3.7–3.95 (m, 10 H, OCH_2, 3-H_{iq}),[63] 4.10 (s, br, 1 H, 4-H_{iq}), 4.41 and 4.82 (mc, br, 2 H, 1-H_{iq}), 6.43 (d, J = 2.5 Hz, 1 H, 5-H_{iq}), 6.48 (d, J = 8.0 Hz, 1 H, 6′-H_{ph}),[63] 6.67 (s, br, 1 H, 2′-H_{ph}), 6.68 (d, J = 8.0 Hz, 1 H, 4′-H_{ph}), 6.74 (dd, J = 8.0, 2.5 Hz, 1 H, 7-H_{iq}), 6.85 (s, 2 H, ar-H_{dpm}),[63] 6.88 (s, 2 H, ar-H_{dpm}), 7.06 (t, J = 8.0 Hz, 1 H, 5′-H_{ph}), 7.09 (d, J = 8.0 Hz, 1 H, 8-H_{iq}); MS, m/z (relative intensity) 758 (100, M^+). Anal. Calcd for $C_{48}H_{58}N_2O_6 \cdot H_2O$ (777.0): C, 74.19; H, 7.78; N, 3.60. Found: C, 74.27; H, 7.72; N, 3.37.

(+)-1′,34-Diethyl-32,33,34,35-tetrahydro-8,12,16,18-tetramethylspiro[1,6,20,25-tetraoxa[6.1]paracyclo[6]metacyclo[0](4,6)isoquinolinophane-13,4′-piperidine] [(+)-26]. A total of 16.6 mL (16.6 mmol) of a 1 M solution of borane in tetrahydrofuran was added to a solution 0.90 g (1.19 mmol) of macrocycle (+)-**25** in 50 mL of dry tetrahydrofuran. The mixture was stirred under N_2 for 24 h at 20 °C and for 2 h under reflux. After cooling in an ice bath, 100 mL of absolute ethanol was carefully added, followed by introduction of HCl gas for 30 min. The volatiles were removed in vacuo, and the residual oil was washed with hexane (10 mL). The oil was partitioned between 12 M NH_4OH (50 mL) and chloroform (50 mL). The organic phase was washed with water (50 mL), followed by saturated NaCl, and dried over sodium sulfate. Chromatography of the residue, left by evaporation of the solvent, on silica gel from ethyl acetate/triethylamine (19:1) gave 260 mg (30%) of (+)-**26**: mp 70–72 °C; $[\alpha]^{23}_D$ +7.0° (c, 1.0, $CHCl_3$); ^1H NMR (1D and 2D COSY, 500 MHz, $CDCl_3$) δ 0.98 (t, J = 7.2 Hz, 3 H, NCH_2CH_3), 1.04 (t, J = 7.2 Hz, 3 H, NCH_2CH_3), 1.6–1.9 (m, 8 H, $ClCH_2CH_2CH_2CH_2O$), 2.09 (s, 6 H, Ar-CH_3), 2.14 (s, 6 H, Ar-CH_3), 2.3–2.5 (m, 13 H, 2′,3′,5′,6′-H_{pip}, NCH_2CH_3, 3-$H_{iq,ax}$), 2.96 (dd, J = 8.2, 5.5 Hz, 1 H, 3-$H_{iq,eq}$), 3.44 (d, part of AB, J = 14.7 Hz, 1 H, 1-$H_{iq,ax}$), 3.7–3.9 (m, 9 H, OCH_2, 1-$H_{iq,eq}$), 4.05 ("t", ≈ 6 Hz, 1 H, 4-H_{iq}), 6.26 (d, J = 2.5 Hz, 1 H, 5-H_{iq}), 6.58 (d, J = 8.0 Hz, 1 H, 6′-H_{ph}), 6.59 (d, J = 8.0 Hz, 1 H, 4′-H_{ph}), 6.60 (dd, J = 8.0, 2.5 Hz, 1 H, 7-H_{iq}), 6.67 (s, br, 1 H, 2′-H_{ph}), 6.70 (s, 2 H, ar-H_{dpm}), 6.73 (s, 2 H, ar-H_{dpm}), 6.89 (d, J = 8.0 Hz, 1 H, 8-H_{iq}), 7.03 (t, J = 8.0 Hz, 1 H, 5′-H_{ph}); MS, m/z (relative intensity) 730 (100, M^+). Anal. Calcd for $C_{48}H_{62}N_2O_4 \cdot H_2O$ (748.5): C, 76.97; H, 8.61; N, 3.74. Found: C, 77.60; H, 8.50; N, 3.49.

(+)-1′,1′,34,34-Tetraethyl-32,33,34,35-tetrahydro-8,12,16,18-tetramethylspiro[1,6,20,25-tetraoxa[6.1]paracyclo[6]metacyclo[0](4,6)isoquinolinophanium-13,4′-piperidinium] Dichloride [(+)-10]. A solution of 80 mg (0.11 mmol) of (+)-**26** in 5 mL of freshly distilled ethyl iodide was stirred under N_2 at 20 °C for 16 h. Removal of the solvent in vacuo left a yellow solid, which was dissolved in 10 mL of methanol and passed over a Dowex ion-exchange column (Cl^-), using water/methanol (60:40) as eluant. Recrystallization from methanol/ether (1:10) afforded 67 mg (71%) of the quaternary host (+)-**10** as yellow hygrosopic solid: mp 210–215 °C dec; $[\alpha]^{23}_D$ +1.8° (c 0.42, MeOH); ^1H NMR (1D and 2D COSY, 500 MHz, MeOH-d_4) δ 1.29 (t, J = 7.2 Hz, 6 H, NCH_2CH_{3pip}), 1.37 (t, J = 7.2 Hz, 3 H, $NCH_2CH_{3iq,ax}$), 1.43 (t, J = 7.2 Hz, 3 H, $NCH_2CH_{3iq,eq}$) 1.7–1.9 (m, 8 H, $ClCH_2CH_2CH_2CH_2O$), 2.14 (s, 6 H, Ar-CH_3), 2.24 (s, 6 H, Ar-CH_3), 2.6–2.7 (m, 4 H, 3′,5′-H_{pip}), 3.4–3.5 (m, 12 H, NCH_2CH_3, 2′,6′-H_{pip}), 3.7–3.95 (m, 8 H, OCH_2,), 4.45–4.8 (m, 5 H, 1,3,4-H_{iq}; partially overlapped by large H_2O peak) 6.39 (d, J = 2.5 Hz, 1 H, 5-H_{iq}), 6.7–6.9 (m, 4 H, 7-H_{iq}, 2′,4′,6′-H_{ph}, 4′-H_{ph}) 6.94 (s, 2 H, ar-H_{dpm}), 6.99 (s, 2 H, ar-H_{dpm}), 7.19 (t, J = 8.0 Hz, 1 H, 5′-H_{ph}) 7.35 (m, 1 H, 8-H_{iq}); FAB-MS, m/z (relative intensity) 823.4 (8, $M^+ - Cl^-$), 788.5 (3, $M^+ - 2Cl^-$), 760.5 (20, $M^+ - Et - 2Cl^-$) 759.4 (100, $M^+ - H - Et - Cl^-$), 731.4 (5, $M^+ - H - 2Et - 2Cl^-$). Anal. Calcd for $C_{52}H_{72}N_2O_4Cl_2 \cdot 8H_2O$ (1004.2): C, 62.19; H, 8.83; N, 2.78. Found: C, 62.36; H, 8.79; N, 2.76.

(*S*)-(+)-Methyl 2-(6-Methoxy-2-naphthyl)propionate [(+)-29]. A total of 0.1 mL (1.42 mmol) of sulfinyl chloride was added at −5 °C to a solution of 0.3 g (1.29 mmol) of (*S*)-(+)-naproxen in 2 mL of absolute methanol.[64] The mixture was slowly warmed to 20 °C, and after 2 h, water (5 mL) and ether (10 mL) were added. The organic layer was washed with 5 mL of 10% $NaHCO_3$ and water (5 mL). Evaporation of the solvent afforded 0.13 g (41%) of (+)-**29**: mp 91 °C (lit.[65] mp 88 °C); $[\alpha]^{23}_D$ +72.2° (c 2.05, $CHCl_3$) (lit.[65] $[\alpha]^{23}_D$ +77° ($CHCl_3$)).

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Supplementary Material Available: Structure and tables listing parameters not included with the MM2 program for each compound calculated and all coordinates, bond lengths, bond angles, and torsional angles for the optimized geometries described in the paper (37 pages). Ordering information is given on any current masthead page.

(63) Dpm = diphenylmethane, iq = isoquinoline, ph = 4-phenyl, pip = piperidine.

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