shifts of an external methanol sample. The E-Z isomerization was followed by NMR integration of the (E)-**2c** *N*-*tert*-butyl signal relative to the integration of the methyl peaks of internal 1,3,5-trimethylbenzene. During the reaction the total methoxy area was invariant, and no evidence of decomposition was observed.

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Registry No. (E)-**1a**, 103202-88-6; (E)-**1b**, 55504-08-0; (E)-**1c**, 103202-89-7; (Z)-**1c**, 103202-90-0; (E)-**2a**, 103202-91-1; (-)-**2a**, 103202-96-6; (E)-**2b**, 103202-92-2; (Z)-**2b**, 103202-93-3; (Z)-**2c**, 103202-94-4; (E)-**2c**, 103202-95-5.

Chiral Recognition in Aqueous Solution. Search for Water-Soluble Chiral Hosts with Apolar Binding Sites

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Macrocycles **1a/b** with tetrasubstituted biphenyl units as chiral barriers are designed as potential hosts for the optical resolution of racemic aromatic guests with anionic residues. Synthetic attempts to prepare from a planar arene, pyrene, a chiral biphenyl barrier incorporated into a water-soluble host are presented. On the way to such a macrocycle, the 1,7,20,26-tetraoxa[8](4,5)phenanthreno[8.1]paracyclophane **7** was synthesized. Selective ozonolysis of the 9,10-bond of the phenanthrene unit of **7** to generate the chiral barrier was not successful. The phenanthrene unit, according to ^{1}H NMR, is located in the intramolecular cavity of **7** and therefore is protected from attack by ozone. On the way to **1a**, the 1,7,20,26-tetraoxa[7](2,2′)biphenylo[7.1]paracyclophane **14** with two aminomethyl groups at the 6,6′-positions of the biphenyl unit was prepared. Eschweiler–Clarke methylation of **14** afforded as major product, besides the macrocyclic tris(tertiary amine) **15**, the precursor to **1a**, a macrocycle incorporating a 6,7-dihydro-5*H*-dibenz[*c*,*e*]azepine moiety. A possible mechanism of formation of the 1,7,19,25-tetraoxa[7](1,11)-5*H*-dibenz[*c*,*e*]azepino[7.1]paracyclophane **18** is presented. The synthesis of 1′-ethyl-12,15-bis((diethylamino)methyl)-28,32,36,38-tetramethylspiro[1,7,20,26-tetraoxa[7](2,2′)biphenylo[7.1]-paracyclophane-33,4′-piperidine] (**20**) as nonquaternized precursor to **1b** is described. Binding studies in acidic aqueous solution with the triprotonated macrocyclic amines **15** and **20** below their critical micelle concentration showed that these macrocycles do not act as hosts for apolar guests.

Optically active molecular hosts and their uses in the separation of guest enantiomers through complexation in crystallization, distribution, transport, and chromatographic experiments have attracted considerable interest during the past years.[3-13] Most studies in organic solvents describe the chiral recognition of cationic guests by chiral crown ligands. In aqueous solution, cyclodextrins have almost exclusively been used to resolve racemic compounds that bind with their apolar residues to the cavity.[14-16] Only one report describes the formation of diastereomeric host–guest complexes in aqueous solution by a fully synthetic, optically active host.[17]

During the past 5 years, we have prepared water-soluble achiral hosts which form stable complexes with apolar, especially aromatic, guests in aqueous solution.[18,19] Based on the results of our complexation studies, we designed the macrocyclic host **1** for resolving racemic aromatic guests with anionic residues through complexation in aqueous solution. Guests that we had hoped to resolve are aromatic α-amino acids, aromatic carboxylic acids such as mandelic acid and atrolactic acid, and especially α-arylpropionic acids, some of which are important drugs (e.g., ibuprofen [2-(4-isobutylphenyl)propionic acid] and naproxen [2-(6-methoxy-2-naphthyl)propionic acid (**2**)]).[20] Macrocycle **1** incorporates a 2,2′,6,6′-tetrasubstituted biphenyl unit as

(1) University of California, Los Angeles.
(2) Max-Planck-Institute for medical research, Heidelberg.
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(15) For some recent examples, see: (a) Mikolajczyk, M.; Drabowicz, J. *J. Am. Chem. Soc.* **1978**, *100*, 2510-2515. (b) Yamanari, K.; Shimura, Y. *Chem. Lett.* **1982**, 1957-1958.
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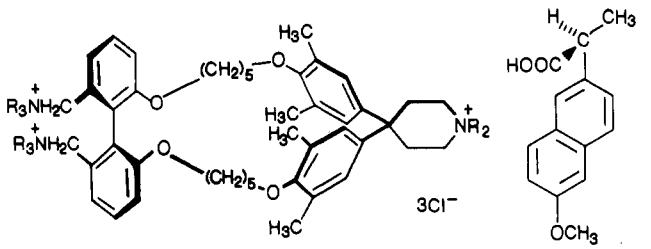
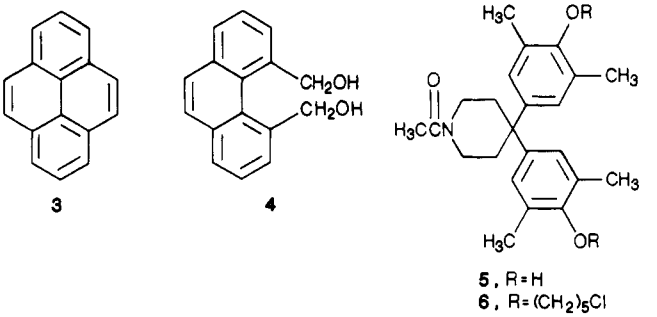
a stable[21] chiral barrier. The diastereomeric complexes which we expected to form between naproxen and the (*S*)-host 1 illustrate our concept for chiral recognition: In the complexes, naproxen will be located in the plane of the cavity of 1 which passes through the spiro carbon atom and the chirality axis. On the basis of our previous studies and according to CPK molecular models, a pseudoaxial orientation of the naphthalene part of complexed 2 in this plane could be expected. Due to the C_2 symmetry of the host, binding on both sides of the macrocycle would lead to identical complexes. Macrocycle (*S*)-1 was expected to form the more stable diastereomeric complex with (*S*)-naproxen since additional ion pairing between the carboxylate of the guest and a quaternary nitrogen of the host should stabilize the complex. The complex between (*S*)-1 and the *R* guest should be less stable. The bulkier methyl



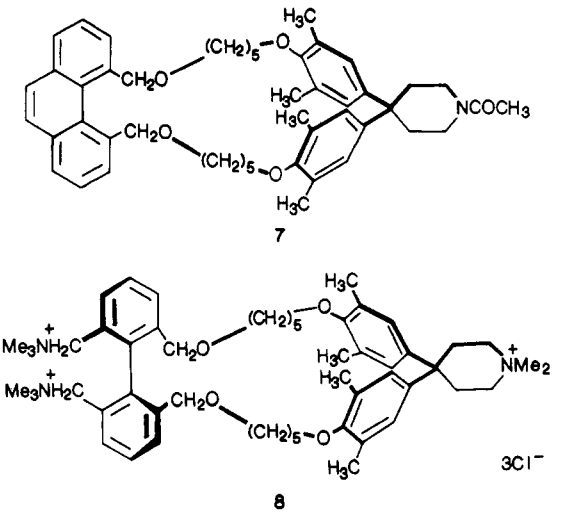
group of this guest enantiomer has to orient in an energetically unfavorable way toward the diphenyl barrier, if ion pairing stabilizes the complex. We therefore presumed that ion pairing would not be very effective in the (*S*)-1·(*R*)-2 complex. Based on our previous studies on ion pairing in complexes in aqueous solution,[18a] we expected a difference in free energy of formation of the two diastereomeric complexes of $-\Delta G \approx 1$–2 kcal·mol^{-1} which would allow optical resolution of naproxen in transport or chromatographic experiments. In this paper, we describe our first efforts toward the synthesis of water-soluble optically active hosts, and we explain why the macrocycles described in this paper did not allow us to test our concept for chiral recognition.

Results and Discussion

A Chiral Barrier from Pyrene and a Host That Acts as Its Own Guest. We found it very attractive to prepare from a planar arene, pyrene (3), a chiral biphenyl barrier incorporated into a macrocyclic host.[22] Selective monoozonation of the 4,5-bond of pyrene[23] followed by reduction leads to 4,5-phenanthrenedimethanol (4).[24] Cyclization of 4 with the dichloride 6 was expected to give the macrocycle 7. Selective ozonation of the 9,10-bond of the phenanthrene moiety of 7[25] followed by functional group transformations should yield the water-soluble macrocycle 8 with a stable chiral 2,2′,6,6′-tetrasubstituted biphenyl barrier. After optical resolution, 8 could be used



as host to test our concept for chiral recognition in complexes of aromatic guests with anionic residues.



Pyrene was monoozonized in carbon tetrachloride since the monoozonide precipitates from this solvent and is protected from further reaction. Oxidative workup gave 5-formyl-4-phenanthroic acid in 42–50% yield. Reduction with diisobutylaluminum hydride afforded 4 in 85% yield. Dichloride 6 was prepared in 62% yield from diphenol 5[18c] and 1,5-dichloropentane. Cyclization of diol 4 with dichloride 6 in tetrahydrofuran in the presence of sodium hydride and 18-crown-6 afforded the macrocycle 7 (mp 240 °C) in 12% yield. The selective ozonation of the 9,10-bond of the phenanthrene moiety of 7 was unsuccessful under all experimental conditions. Compound 7 was ozonized at different temperatures (−78 °C, 0 °C, and room temperature) in participating solvents (mixtures of methanol and dichloromethane or dimethylformamide) as well as in nonparticipating solvents[25] (dichloromethane, chloroform) until thin layer chromatography (SiO_2, CH_2Cl_2) showed the disappearance of the starting material. At −78 °C, the reaction was very slow. After reductive workup with dimethyl sulfide, thin layer chromatography indicated the formation of a large range of products in each run. A multitude of products was also obtained with a stoichiometric amount of ozone adsorbed from the O_2/O_3 stream on silica gel at −78 °C and desorbed at 0 °C in a stream of nitrogen entering the reaction flask. The failure in selective ozonation of 7 was unexpected in view of the easy selective ozonation of the 9,10-bond of phenanthrene and derivatives in yields up to 90%.[25]

A closer look at the 360-MHz ^{1}H NMR spectra (1D and 2D COSY, 303K, $CDCl_3$) of 7 provided a plausible explanation for the unsuccessful selective ozonation. Figure 1 gives the differences between the chemical shifts ($\Delta\delta$, + = upfield shift) of comparable protons of 7 and of the cyclization precursors 4/6 in $CDCl_3$. The observed $\Delta\delta$ values are striking and we had never observed cyclization shifts of this magnitude. The ^{1}H NMR data of Figure 1

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(22) Achiral biphenyl units incorporated into crown ligands have been prepared previously from pyrene, see ref 9.

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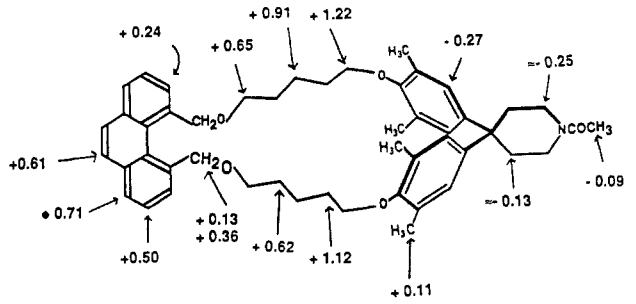
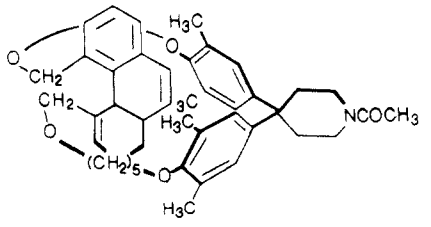


Figure 1. Differences between the chemical shifts ($\Delta\delta$, + = upfield shift) of comparable protons of 7 and of the cyclization precursors 4/6 in $CDCl_3$. Multiplet centers are used to calculate the $\Delta\delta$ values. The δ values of 4, 6, and 7, from which the $\Delta\delta$ values are calculated, are given in the Experimental Section. Similar differences in chemical shifts are calculated if protons of the aliphatic bridges and of the diphenylmethane units of 7 and of the macrocycle 13, 18, and 20 are compared.

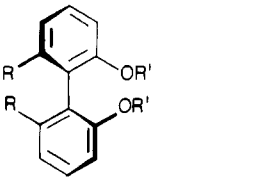
indicate that 7 largely prefers a conformation such as **7a** with the phenanthrene moiety turned into the intramolecular cavity formed by the diphenylmethane unit and the two alkane chains. In a conformation like **7a**, the reactive 9,10-bond of the phenanthrene unit is efficiently shielded from attack by ozone. Hence the attack of ozone at the electron-rich aromatic rings of the diphenylmethane unit, at other positions of the phenanthrene nucleus, and at the benzylic ether groups[26] becomes competitive which could explain the large number of products formed in the ozonation of 7. The differences between the chemical shifts of the protons of 7 and the chemical shifts of the protons of the cyclization precursors 4/6 are almost identical in different solvents ($CDCl_3$, Me_2SO-d_6) and over the temperature range of 200–400 K. In compound 7, the protons of the phenanthrene moiety are shifted upfield to an extent depending on their position to the shielding region of the diphenylmethane unit. The protons of 7 located in the plane of the phenanthrene move downfield whereas the protons which lie about perpendicular to the plane of the phenanthrene move upfield. The changes in chemical shift ($\Delta\delta$) experienced by the various groups of protons of 7 are very similar to the changes of the chemical shifts that we observed upon formation of highly structured host–guest complexes in which the aromatic guests take a location similar to the phenanthrene unit in **7a**.[18b] *We therefore see 7 as an example of a host which acts as its own guest.*



7a

Several assignments of signals of 7 that are important for a correct evaluation of the cyclization shifts shown in Figure 1 have been supported by a 2D COSY NMR spectrum. The protons 3,6-H of the phenanthrene unit appear as a doublet at δ 7.58, and the contour plot shows an orthobenzylic coupling to the benzylic methylene protons. A long range, presumably w-type coupling is visible between the protons 2,7-H of the phenanthrene moiety at δ 7.15 and the benzylic methylene protons at δ 4.85 located in the plane of the phenanthrene nucleus. The methylene protons α to the diphenylmethane–ether oxygens show a multiplet at δ 2.52. Their assignment is based on a weak coupling with the aromatic protons of the diphenylmethane unit observed in the COSY contour plot. This assignment was important for the determination of the positions of the residual methylene groups of the aliphatic C_5-bridges appearing at very unusual positions due to the shielding by the phenanthrene moiety.

Unexpected Synthesis of Macrocycle 18 with a 6,7-Dihydro-5*H*-dibenz[*c*,*e*]azepine Unit. The next target molecule that we approached was compound **1a**. We planned to form the macrocyclic carbon skeleton of **1a** in a cyclization reaction between the diphenol 11 and the dichloride 6 yielding 13. In the synthesis of 11, we started from commercially available 3-methoxy-2-nitrotoluene, which was oxidized with potassium permanganate in 50–55% yield to 3-methoxy-2-nitrobenzoic acid.[27] Catalytical hydrogenation in the presence of Raney nickel afforded 2-amino-3-methoxybenzoic acid in quantitative yield. Diazotization and aryl–aryl coupling following a procedure of Wittig and Petri[28,29] afforded 6,6′-dimethoxydiphenic acid in 70–80% yield. With sufinyl chloride the corresponding diacid dichloride formed quantitatively and reaction with ammonia gave the bis(carboxylic amide) **9** in 93% yield.[30] Reduction of **9** with borane–tetrahydrofuran followed by acetylation with acetic anhydride gave the bis(*N*-acetamide) **10** in 85% yield. Reaction of **10** with boron tribromide yielded the diphenol 11 in 94% yield. Attempts to obtain macrocycle 13 by cyclizing the diphenol 11 with the dichloride 6 in dimethylformamide in the presence of cesium carbonate as base were surprisingly unsuccessful. Thin layer chromatography indicated the formation of predominantly oligomeric material. The formation of minor amounts of 13, which we were unable to isolate by medium pressure liquid chromatography, was indicated by a very weak molecular ion of 13 (m/z 831; <1%) in the EI mass spectrum of the best chromatographic fraction. We explain the unsuccessful cyclization with the unfavorable sterical bulk of the tetrasubstituted biphenyl barrier in the final step of the ring closure. The intramolecular ring closure becomes slow and intermolecular oligomerization reactions are predominant even under high dilution.



9, R = H_2NC; R′ = CH_3
10, R = $AcNHCH_2$; R′ = CH_3
11, R = $AcNHCH_2$; R′ = H
12, R = $AcNHCH_2$; R′ = $(CH_2)_5Cl$

The failure of cyclization between 6 and 11 made it necessary to prepare 13 in a cyclization between dichloride 12 and the diphenol 5. In this cyclization, the ether bonds are formed at the sterically less congested diphenylmethane unit. In the preparation of 12, the cyclic compound 16 could be expected as a side product although the formation of 11-membered rings is not very favorable.[31]

(26) Reference 25; pp 285–295.

(27) Hall, D. M.; Turner, E. E. *J. Chem. Soc.* **1951**, 3072–3074.
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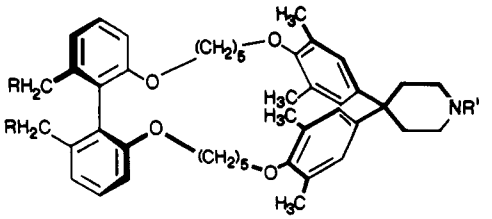
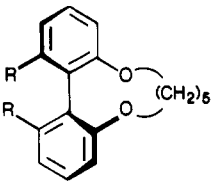
(30) Stanley, W. M.; McMahon, E.; Adams, R *J. Am. Chem. Soc.* **1933**, *55*, 706–716.



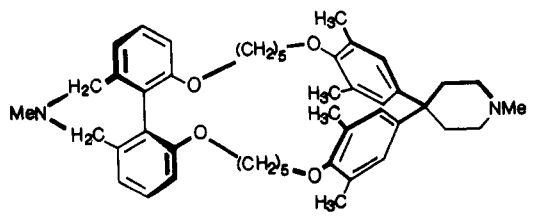
13, R=AcNH; R'=Ac
14, R=H_2N; R'=H
15, R=Me_2N; R'=Me



16, R=$AcNHCH_2$
17, R=$Et_2NC(=O)$

The reaction of 11 in 1-butanol with a large excess of 1,5-dichloropentane in the presence of sodium hydroxide led to the formation of two major products [R_f ~0.4 and ~0.05 (SiO_2/EtOAc)]. The product with the higher R_f value was isolated by chromatography and shown to be the desired dichloride 12 (50% yield). The product with the lower R_f value which we did not isolate presumably was the cyclic compound 16. This is supported by the isolation of the cyclic product 17 from a similar reaction as shown below. A change in solvent led to the almost exclusive formation of the desired dichloride 12 in very high yield. The reaction of 11 with a large excess of 1,5-dichloropentane at 80 °C in dimethylformamide with cesium, potassium, or sodium carbonate as base afforded 12 in 95% yield after chromatography and recrystallization.

The cyclization between the diphenol 5 and the dichloride 12 in dimethylformamide with cesium carbonate as base led to macrocycle 13 in the expected good yield of 28% after chromatography. The macrocyclic triamine 14 formed in 91% yield upon refluxing 10 for 36 h in a solution of potassium hydroxide in 2-methoxyethanol. We have prepared a large number of macrocyclic tertiary *N*-methylamines in yields of 70–94% using the Eschweiler–Clarke modification of the Leuckard–Wallach reaction.[18c] This reaction, when applied to the transformation 14 → 15, led to a mixture of four major products, two of which could be isolated by chromatography. Compound 15, the nonquaternized precursor to 1a, was formed in only 26% yield. The major product (42% yield) was the macrocycle 18 with a 6,7-dihydro-5*H*-dibenz[*c*,*e*]azepine unit.[32]

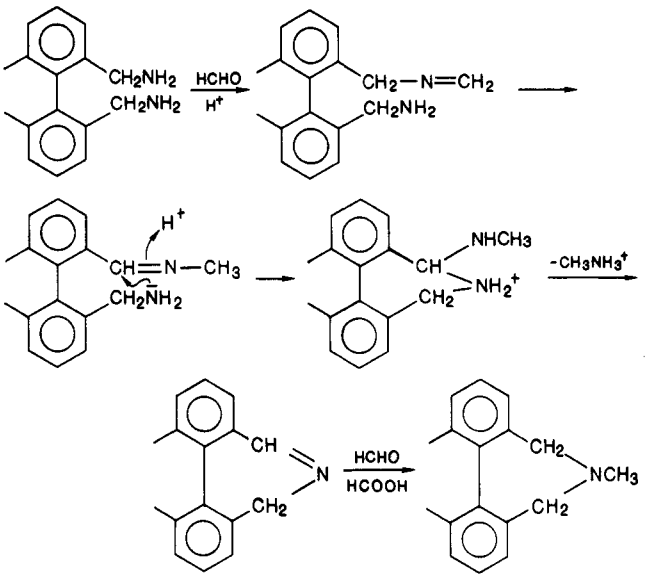


18

(31) March, J. *Advanced Organic Chemistry*, 3rd ed.; Wiley: New York, 1985; pp 134–136.

(32) For the synthesis and optical stability of 6,7-dihydro-5*H*-dibenz[*c*,*e*]acepine derivatives, see: (a) ref 21a,b. (b) Ahmed, S. R.; Hall, D. M. *J. Chem. Soc.* **1958**, 3043–3047. (c) Jeffs, P. W.; Hansen, J. F.; Brine, G. A. *J. Org. Chem.* **1975**, *20*, 2883–2890. (d) Pecherer, B.; Sunbury, R. C.; Brossi, A. *J. Med. Chem.* **1969**, *12*, 149–151.

Scheme I

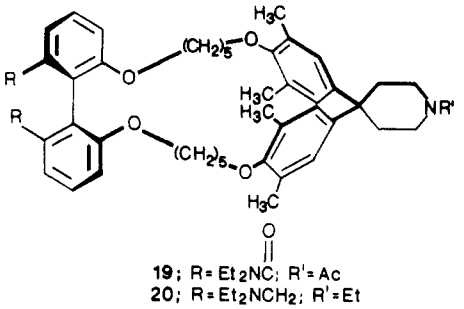


A possible mechanism for the 6,7-dihydro-5*H*-dibenz[*c*,*e*]azepine formation is suggested in Scheme I. The driving force for the postulated 1,3-hydrogen shift is the conjugation of the imine with the aromatic ring. The attack of the neighboring amino function at the electrophilic carbon of the imine under acid catalysis followed by elimination of $CH_3NH_3^+$ has its analogy in the mechanism of the Fischer indole synthesis. The cyclic imine formed by this elimination is reduced by the formic acid and the resulting secondary amino nitrogen is methylated. Compound 18 can also form after one or both of the amino residues have been monomethylated. The important side reactions in the Eschweiler–Clarke methylation leading to 18 and to two other side products, which we were unable to isolate and characterize in pure form, made it impossible to obtain larger quantities of the triamine 15. Larger quantities of 15, however, were needed for the optical resolution through fractionated crystallization of the diastereomeric salts formed between 15 and (L)-tartaric acid.[33] We therefore turned to the synthesis of 20, the nonquaternized precursor to the target molecule 1b, which does not include a reductive alkylation at the biphenyl barrier in the last steps of the preparation.

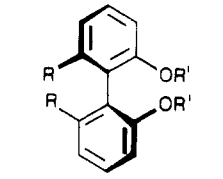
Synthesis and Study of the Biphenyl Macrocycle 20. We chose the diborane reduction of macrocycle 19 to prepare 20 as nonquaternized precursor to the chiral water-soluble host 1b. We hoped to avoid by this approach side reactions of the proximate amino acids at the biphenyl barrier encountered in the Eschweiler–Clarke methylation of 14. In a model reaction, the diborane reduction of the diamide 21, prepared in 90% yield from 6,6'-dimethoxydiphenic acid dichloride and diethylamine, gave the diamine 22 as major product (65% yield). The diamide 21 was transformed with boron tribromide in 98% yield into the diphenol 23 and reaction with 1,5-dichloropentane in the presence of base led to cyclization component 24. Again we observed a considerable difference in the ratio of dichloride 24 to cyclic ether 17, depending on the reaction conditions. With sodium hydroxide in 1-butanol, we obtained a 32% yield of dichloride 24 and an 18% yield of the cyclic ether 17 isolated as crystalline compound (mp 193–195 °C) with the lower R_f value (R_f of 24:0.4; R_f of 17:

(33) Efforts to separate the enantiomers of 15 on chiral Pirkle phases (both the ionically and covalently bound phases) or on cellulose triacetate were not successful; Dr. Eggersdorfer, BASF, private communication.

0.2; SiO_2/EtOAc). The reaction with cesium carbonate in dimethylformamide gave better yields and led to 84% of the desired dichloride **24** and to only 9% of the cyclic ether **17**.



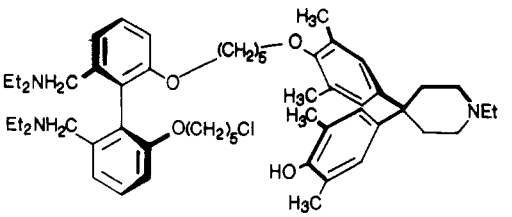
19; R = Et_2NC; R' = Ac
20; R = Et_2NCH_2; R' = Et



21, R = Et_2NC; R' = Me
22, R = Et_2NCH_2; R' = Me
23, R = Et_2NC, R' H
24, R = Et_2NC, R' = $(CH_2)_5Cl$

Cyclization of dichloride **24** with the diphenol **5** in dimethylformamide using cesium carbonate as base led to the macrocycle **19** in 31% yield. The reduction of **19** with borane–tetrahydrofuran followed by the cleavage of the amine–borane adducts with 6 N HCl under reflux[34,35] gave only a small amount of triamine **20** (<10%) together with three other major products (TLC). We had previously observed that the diborane reduction of macrocyclic and macrobicyclic amides followed by workup with refluxing 6 N HCl led to the considerable formation of undesired side products.[36] We were, however, not able to isolate them in order to learn about the mechanism of their formation. By chromatography, we could isolate the major undesired product of the reduction of **19** under the conditions described above and all analytical data are consistent with structure **25**. Compound **25** (50% yield; mp 98 °C) and presumably other side products are formed through ether cleavage by the refluxing 6 N HCl used to decompose the amine–borane adducts. The assignment of structure **25** resulting from ether cleavage at the diphenylmethane unit is based on 500-MHz ^1H NMR data. Two triplets are observed for the protons CH_2Cl and the protons CH_2O of the diphenylmethane–ether linkage. The protons-OCH_2 of the two ether linkages to the biphenyl moiety of **25**, similar to the comparable protons in **12–15**, **18–20**, and **24**, show complex multiplets indicating hindered rotation on the 500-MHz time scale.

We then tried 3% sulfuric acid in ethanol[37] to cleave the amine–borane adducts formed in the diborane reduction of **19** and obtained the macrocyclic triamine **20** (mp 47 °C) in 55% yield after chromatography and recrystallization. Interestingly, we also formed **20** in good yield (47%) by recyclizing **25** with cesium carbonate in dimethylformamide. Under the reaction conditions, the phenoxide seems to be a significantly more potent nucleophile than the tertiary piperidine nitrogen. Diphenylmethane units with *N*-alkylpiperidine rings therefore seem attractive to us as cyclization components in the synthesis of future hosts.



25

Before separating the enantiomers of **20** through diastereomeric salt formation and before quaternizing the macrocycle, we decided to study the complexation behavior of **20** in organic and acidic aqueous solution. A specific cavity effect on aromatic solvent-induced shifts (ASIS, Δ[ppm] = $\delta(CDCl_3) - \delta$(benzene-d_6)),[18c,19,38] indicating the incorporation of aromatic solvent molecules into the macrocyclic cavity of **20**, was not observed. Similar ASIS values were encountered for the protons of **22** and **20** which are best explained by particular orientations of the benzene molecules around the donor atoms (O, N) of the two solutes. We have recently observed strong binding between neutral aromatic hosts and guests in organic solvents such as alcohols, acetone and dimethyl sulfoxide.[19] We therefore looked for possible binding in dimethyl sulfoxide between **20** and the guests naproxen and *p*-toluenesulfonic acid. We expected these two guests to bind with their aromatic rings to the apolar cavity of **20**. In addition, complexes of these aromatic compounds could possibly be considerably stabilized in the dipolar aprotic solvent by ion pairing after protonation of the amino groups of the biphenyl barrier by the carboxylic or the sulfonic acid residue of the enclosed guests. By ^1H NMR, however, we could not detect any binding in dimethyl-d_6 sulfoxide.

We turned to acidic aqueous solution to study the complexation behavior of **20**. The macrocycle is easily soluble in a 0.1 M solution of KD_2PO_4 in D_2O at pD = 4.3 and by ^1H NMR we determined the critical micelle concentration (cmc) of **20** to be $\approx 3.0 \times 10^{-3}$ mol·L^{-1}.[39] Below this concentration, we studied by ^1H NMR the complexation between **20** and a variety of aromatic compounds. With $[H_0] = [G_0] = 1.0 \times 10^{-3}$ mol·L^{-1} in a 0.1 M solution of KD_2PO_4 in D_2O (sodium 2,2,3,3-tetradeuterio-3-(trimethylsilyl)-propionate (TSP) as external standard in D_2O, 303 K) we did not obtain any evidence for complexation between **20** and aromatic compounds such as (*S*)-naproxen, *p*-toluenesulfonic acid, *p*-methylbenzoic acid, L-mandelic acid, *p*-nitrotoluene, and *p*-methylbenzonitrile. No complexation was also observed with macrocycle **15** under the same conditions. Under the described conditions, we could easily observe complexation in aqueous solution between para-disubstituted benzenes and a tetraoxacyclophane with two diphenylmethane units.[18c] We therefore have to conclude that macrocycles **15** and **20** and presumably also **1a** and **1b** are not host compounds.

Macrocycles **15** and **20** are not acting as hosts in acidic aqueous solution since their cavities are not preorganized prior to complexation.[40] When designing compounds

(34) Brown, H. C.; Heim, P. *J. Org. Chem.* **1973**, *38*, 912–916.
(35) Dietrich, B.; Hosseini, M. W.; Lehn, J.-M.; Sessions, R. B. *Helv. Chim. Acta* **1983**, *66*, 1262–1278.
(36) Schürmann, G.; Lutter, D.; Diederich, F., unpublished results.
(37) Schmidtchen, F. P. *Chem. Ber.* **1980**, *113*, 864–874.
(38) Jarvi, E. T.; Whitlock, H. W., Jr. *J. Am. Chem. Soc.* **1982**, *104*, 7196–7204.
(39) For the determination of the critical micelle concentration of water-soluble macrocycles by ^1H NMR, see ref 18 a,c.

1a/b, CPK molecular model examinations indicated that these macrocycles can take energetically favorable conformations with the diphenylmethane unit, the aliphatic chains, and the biphenyl barrier shaping an apolar cavity of suitable size for benzene and naphthalene derivatives. According to our results, however, conformations of the macrocycles, where the aliphatic chains bridging the biphenyl and the diphenylmethane unit approach each other thus filling a possible cavity, seem considerably more favorable. The free energy of complexation of a guest in aqueous solution apparently does not compensate for the energy required to organize the binding cavity of **15** and **20** by bringing the aliphatic chains apart from each other.

Experimental Section

Instrumentation and Analytical Methods. ^{1}H NMR was carried out on Bruker WP80, WP200, HX360, and AM500 spectrometers. All δ values (ppm) in the spectra to characterize new compounds refer to Me_4Si as internal standard. If not stated otherwise, the spectra werre recorded at 303 K. Mass spectra were carried out on a Dupont CEC 21-492 instrument, AEI MS9 spectrometer, and AEI MS902 high resolution mass spectrometer. If not stated otherwise, EI mass spectra were recorded at 70 eV. Melting points (uncorrected) were measured on a Büchi (Dr. Tottoli) apparatus and an electrothermal melting point apparatus. IR were measured on Beckmann IR 4240 and Perkin-Elmer PE 580 spectrometers. Elemental analysis was performed on a Carlo Erba Elemental Analyzer 1106 at Max-Planck-Institut für medizinische Forschung, Heidelberg, and Spang Microanalytical Laboratory, Eagle Harbor, MI. Ozone was produced by a Fischer ozone generator. The 360-MHz and 500-MHz 2D COSY spectra were recorded to determine the connectivities of the spin systems of **7** and **20**. As an example, the spectrum of **7** at 360 MHz was obtained with a 90°-t_1-90° pulse sequence using the Bruker-2D-software, version 820601.3. The sweep width in both F1 and F2 was 1373 Hz with a matrix size of 256 × 1024 data points. The 256 incremental spectra were each recorded with 64 accumulations. The relaxation delay was 3 s. The data matrix was completed by zero-filling in F1. The FID data were processed by a sine bell window function and Fourier transformation. The matrix was symmetrized to suppress signals that cannot be correlated. The digital resolution was 5.3 Hz/point. ^{1}H NMR complexation studies in organic and aqueous solution and the ^{1}H NMR determination of critical micelle concentrations are described in full detail in references 18a–c and 19. The purification of the para-disubstituted benzene derivatives used as guests is described in ref 18c. L-Mandelic acid and (*S*)-naproxen were purchased from Sigma and used without further purification.

Syntheses. 4,5-Phenanthrenedimethanol (4). In the formation of 5-formyl-4-phenanthroic acid, the procedure in ref 23b was followed with one modification: carbon tetrachloride was used as solvent in the ozonation instead of dimethylformamide. A solution of 20.2 g (0.1 mol) of pyrene in 500 mL of carbon tetrachloride was treated at −20 °C with excess ozone until thin layer chromatography (CCl_4/SiO_2) indicated the disappearance of the starting material. The reaction flask was flushed with nitrogen to sweep out unreacted ozone. The precipitated monoozonide of pyrene was collected by filtration (*a safety shield protected the operator in this part of the preparation*), washed once with carbon tetrachloride, and dissolved in 200 mL of a 10% aqueous KOH as described in the *Organic Synthesis* procedure. Continuing the procedure afforded 10.5–12.5 g (42–50%) of 5-formyl-4-phenanthroic acid, mp 272 °C (lit.[23b] 32–38% yield, mp 272–276 °C). The diol **4**, mp 178 °C (lit.[23a] mp 171–172 °C), was obtained in 85% yield (lit.[24] 92%) by reduction of 5-formyl-4-phenanthroic acid with diisobutylaluminum hydride following a published procedure:[24] ^{1}H NMR (360 MHz, $CDCl_3$) δ 4.79 and 4.98 (AB, J = 12.5 Hz, 4 H, CH_2), 7.58 (s, 2 H, 9,10-H), 7.65 (t, $J = \simeq$ 7.5 Hz, 2 H, 2,7-H), 7.79 (d, J = 8.3 Hz, 2 H, 1,8-H), 7.82 (d, J = 7.5 Hz, 2 H, 3,6-H).

***N*-Acetyl-4,4-bis[4-(5-chloropentoxy)-3,5-dimethylphenyl]piperidine (6).** A stirred solution of 12.68 g (34.5 mmol) of diphenol **5** and 3.46 g (86.5) mmol) of sodium hydroxide in 350 mL of 1-butanol was heated to reflux under N_2. After 1 h, water was added dropwise to the boiling mixture to give a clear solution. A solution of 80.83 g (0.573 mol) of 1,5-dichloropentane in 150 mL of 1-butanol and 20 g of potassium carbonate were added and the reaction mixture was refluxed for 2 days. The solvents were removed in vacuo and the residue was partitioned between dichloromethane and water. The organic phase was extracted three times with 2 N KOH, washed three times with water, and dried over magnesium sulfate, and the solvent was removed. Chromatography on silica gel from ethyl acetate followed by recrystallization from ether/hexane yielded 12.3 g (62%) of **6**: mp 116 °C; IR (KBr) ν(C=O) 1640 cm^{-1}; ^{1}H NMR (360 MHz, $CDCl_3$) δ 1.65 (quint, $J \approx$ 6.5 Hz, 4 H, $OCH_2CH_2CH_2$), 1.80 (quint, $J \approx$ 6.5 Hz, 4 H, CH_2CH_2Cl), 1.86 (quint, $J \approx$ 6.5 Hz, 4 Hz, CH_2CH_2O), 2.06 (s, 3 H, CH_3CO), 2.1–2.3 (m, 4 H, NCH_2CH_2C), 2.21 (s, 12 H, aryl-CH_3), 3.4–3.6 (m, 4 H, NCH_2CH_2C), 3.56 (t, $J \approx$ 6.5 Hz, 4 H, CH_2Cl), 3.74 (t, $J \approx$ 6.5 Hz, 4 H, OCH_2), 6.82 (s, aryl-H); MS, m/z (relative intensity) 575 (100, M^+). Anal. Calcd for $C_{33}H_{47}Cl_2NO_3$ (576.6): C, 68.61; H, 8.20; N, 2.42; Cl, 12.27. Found: C, 68.78; H, 8.23; N, 2.38; Cl, 12.28.

1′-Acetyl-28,32,36,38-tetramethylspiro[1,7,20,26-tetraoxa[8](4,5)phenanthreno[8.1]paracyclophane-33,4′-piperidine] (7).[41] A mixture of 4.8 g (0.1 mol) of a 50% dispersion of sodium hydride in mineral oil and 2.5 g of 18-crown-6 in 1500 mL of dry tetrahydrofuran was heated to reflux under Ar. To the refluxing mixture were added solutions of 14.4 g (25 mmol) of **6** and 5.95 g (25 mmol) of **4** in dry tetrahydrofuran dropwise and simultaneously over a period of 8 h. After heating for 6 days, 10 mL of methanol was added and the mixture was evaporated to dryness under reduced pressure. The residue was partitioned between water and chloroform. The organic phase was washed once with water and dried over magnesium sulfate, and the solvent was removed in vacuo. Chromatography on silica gel from dichloromethane/ethyl acetate (1:1) followed by recyrstallization from ether and drying at 100 °C/10^{-3} torr afforded 2.21 g (12%) of **7**: mp 240 °C; IR (KBr) ν(C–H_{Ar}) 3040, ν(C=O) 1635, δ (C–H_{Ar}) 830, 725 cm^{-1}; ^{1}H NMR (360 MHz, 1D and 2D COSY, $CDCl_3$) δ 0.55–0.95 (m, mc[42] $\simeq$ 0.74, 8 H, $CH_2CH_2CH_2O$-aryl), 1.05–1.35 (m, mc $\simeq$ 1.18, 4 H, $CH_2OCH_2CH_2$), 2.10 (s, 12 H, aryl-CH_3), 2.15 (s, 3 H, CH_3CO), 2.4–2.65 (m, 4 H, NCH_2CH_2C), 2.4–2.65 (m, mc $\simeq$ 2.52, 4 H, CH_2O-aryl), 2.8–3.05 (m, mc $\simeq$ 2.91, 4 H, $CH_2OCH_2CH_2$), 3.55–3.8 (m, 4 H, NCH_2CH_2C), 4.43 and 4.85 (AB, J_{AB} = 12.1 Hz, 4 H, Phen-CH_2O),[43] 6.97 (s, 2 H, Phen-9,10-H), 7.08 (d, J = 7.5 Hz, 2 H, Phen-1,8-H), 7.09 (s, 4 H, aryl-H_{DPM}),[43] 7.15 (t, $J \simeq$ 7.5 Hz, 2 H Phen-2,7-H), 7.58 (d, J = 7.0 Hz, 2 H, Phen-3,6-H); MS, m/z 741 (M^+). Anal. Calcd for $C_{49}H_{59}NO_5$ (742.0): C, 79.32; H, 8.01; N, 1.89. Found: C, 79.32; H, 8.17; N, 2.15.

6,6′-Dimethoxy-2,2′-biphenyldicarboxamide (9). A solution of 35.1 g (0.116 mol) of 6,6′-dimethoxydiphenic acid and 140 mL of sulfinyl chloride was heated to reflux for 3 h. After removal in vacuo of the excess of sulfinyl chloride, dry toluene was added twice and removed each time in vacuo. The residual crude diacid dichloride was suspended in 300 mL of dry toluene and a saturated solution of dry ammonia in dry toluene was added rapidly at 0 °C to the vigorously stirred suspension. After addition, stirring was continued for 1 h. The precipitated colorless dicarboxamide was collected by filtration, washed once with ether and dried at 100 °C/20 torr. Washing the product twice with 300 mL of water removed traces of ammonium chloride and drying at 100 °C/20 torr yielded 32.4 g (93%) of analytically pure **9**: mp 273 °C (lit.[30] mp 273–274 °C); ^{1}H NMR (80 MHz, Me_2SO-d_6) δ

(40) According to X-ray analysis, the cavities of macrocycles with *two* diphenylmethane units are highly preorganized prior to complexation. The empty cavity of 1′,1″-dimethyldispiro[1,7,21,27-tetraoxa[7.1.7.1]-paracyclophane-14,4′:34,4″-bispiperidine] is very similar in size and shape (Krieger, C.; Diederich, F., unpublished results) to the cavity of the host complexed to a benzene molecule. In this complex, the benzene ring is perfectly located in the intramolecular cavity of the host (Krieger, C.; Diederich, F. *Chem. Ber.* **1985**, *118*, 3620–3631).

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

(42) The multiplet centers (mc) are used to calculate the cyclization shifts shown in Figure 1.

(43) Phen = phenanthrene; DPM = diphenylmethane; Bp = biphenyl; DBA = dibenzodiazepine.

3.57 (s, 6 H, CH_3O), 6.95–7.5 (m, 6 H, aryl-H), 7.80 (s, br, 4 H, NH_2).

2,2′-Bis(acetamidomethyl)-6,6′-dimethoxybiphenyl (10). A total of 488 mL (0.488 mol) of a 1 M solution of borane in tetrahydrofuran was added under Ar to 15.65 g (52 mmol) of **9** in 680 mL of tetrahydrofuran and the mixture was heated to reflux for 12 h. After being cooled in an ice bath, the reaction mixture was carefully hydrolized with water; 500 mL of 6 N HCl was added and the solution was heated to reflux for 1 h. The hydrochloric acid was removed under reduced pressure after which 150 mL of acetic anhydride and 50 g of sodium acetate were added to the residue. After standing for 3 h, the excess of acetic anhydride was removed in vacuo. The residue was partitioned between 1 N Na_2CO_3 and dichloromethane. The aqueous phase was extracted two times with dichloromethane and the combined organic phases were dried over magnesium sulfate. After evaporation of the solvent, chromatography of the crude product on silica gel from ethyl acetate/chloroform/methanol (5:4:1) afforded **10** which was recrystallized from toluene: 15.84 g (85%): mp 118 °C; IR (KBr) ν(N—H) 3280, ν(C=O) 1640 cm^{-1}; ^1H NMR (80 MHz, $CDCl_3$) δ 1.86 (s, 6 H, CH_3CON), 3.67 (s, 6 H, CH_3O-aryl), 4.00 (d, J = 6.3 Hz, 4 H, CH_2), 6.31 (s, br, 2 H, NH), 6.89 (dd, J = 8.0 + 1.5 Hz, 2 H, 5.5″-H), 7.03 (dd, J = 8.0 + 1.5 Hz, 2 H, 3,3′-H), 7.34 (t, $J \simeq$ 8 Hz, 2 H, 4.4′-H); MS, m/z (relative intensity) 356 (40, M^+), 238 (100). Anal. Calcd for $C_{20}H_{24}N_2O_4$ (356.4): C, 67.40; H, 6.79; N, 7.86. Found: C, 67.42; H, 6.61; N, 8.07.

2,2′-Bis(acetamidomethyl)-6,6′-dihydroxybiphenyl (11). A total of 14.5 mL (38.28g, 153 mmol) of boron tribromide was added at −78 °C to a stirred solution of 10.87 g (30.5 mmol) of **10** in 220 mL of dry dichloromethane. After being stirred at −78 °C for 1 h, the reaction mixture was stored at 0–5 °C in the refrigerator for 5 h. After careful hydrolysis with methanol under cooling with an ice bath, the solvent was evaporated. Upon addition of water to the residue, **11** crystallized and was collected by filtration. Washing three times with water and drying at 80°C/1 torr afforded 9.43 g (94%) of analytically pure **11**: mp 287–288 °C dec; IR (KBr) ν(N—H and O—H) 3390, br and vs, ν(C=O) 1640 cm^{-1}; ^1H NMR (80 MHz, Me_2SO-d_6) δ 1.81 (s, 6 H, CH_3CO), 3.94 (m, 4 H, CH_2), 6.7–7.2 (m, 6 H, aryl-H), 7.99 (t, $J \simeq$ 6.2 Hz, 2 H, NH), 9.02 (s, 2 H, OH); MS, m/z (relative intensity) 328 (64, M^+), 226 (70), 210 (100). Anal. Calcd for $C_{18}H_{20}N_2O_4$ (328.4): C, 65.84; H, 6.14; N, 8.53. Found: C, 65.92; H, 6.16; N, 8.39.

2,2′-Bis(acetamidomethyl)-6,6′-bis(5-chloropentoxy)biphenyl (12). (a) By Williamson Ether Synthesis with Sodium Hydroxide as Base in 1-Butanol. Following the procedure described above for the synthesis of **6**, 5.93 g (18.0 mmol) of **11** and 94.96 g (0.673 mol) of 1,5-dichloropentane afforded a crude product containing two major components with $R_f \approx 0.4$ and $R_f \approx 0.05$ (SiO_2/EtOAc). Chromatography on silica gel from ethyl acetate and recrystallization from ether/hexane gave 4.87 g (50%) of dichloride **12** with the higher R_f value: mp 133 °C dec; IR (KBr) ν(N—H) 3260, ν(C=O) 1640 cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$) δ 1.28 (q, $J \simeq$ 7.5 Hz, 4 H, $OCH_2CH_2CH_2$), 1.5–1.65 (m, 8 H, $OCH_2CH_2CH_2CH_2$), 1.91 (s, 6 H, CH_3CO), 3.37 (t, $J \simeq$ 6.5 Hz, 4 H, CH_2Cl), 3.75–3.95 (m, 4 H, OCH_2), 4.02 and 4.11 (AB part of ABX, J = 15.0 and 5.4 Hz, 4 H, aryl-CH_2NH), 6.65 (s, br, X-part of ABX, 2 H, CH_2NH), 6.85 (d, J = 8.2 Hz, 2 H, 5.5′-H), 7.04 (d, J = 7.6 Hz, 2 H, 3,3′-H), 7.29 (t, $J \simeq$ 8 Hz, 2 H, 4.4′-H); MS, m/z 536 (M^+). Anal. Calcd for $C_{28}H_{38}N_2O_4Cl_2$ (537.5): C, 62.56; H, 7.13; N, 5.21; Cl, 13.12. Found: C, 62.51; H, 7.32; N, 5.01; Cl 13.27.

(b) By Williamson Ether Synthesis with Cesium Carbonate in Dimethylformamide. A mixture of 19.0 g (0.058 mol) of **11**, 123 g (0.87 mol) of 1,5-dichloropentane, and 37.8 g (0.116 mol) of cesium carbonate in 400 mL of dimethylformamide dried over basic alumina was stirred at 80 °C under N_2 for 16 h. After cooling, the cesium salts were removed by filtration and the solution was evaporated to dryness. TLC (SiO_2/EtOAc) showed that the residue contained dichloride **12** as the only major product with $R_f \approx 0.4$. Filtration over silica gel with ethyl acetate and recrystallization from ether gave 29.6 g (95%) of **12**, which was shown by IR, NMR, and mp to be identical with the product isolated from the reaction with sodium hydroxide in 1-butanol. Yields of **12** around 95% are also obtained, if cesium carbonate as base is replaced by sodium or potassium carbonate.

1′-Acetyl-12,15-bis(acetamidomethyl)-28,32,36,38-tetramethylspiro[1,7,20,26-tetraoxa[7](2,2′)biphenylo[7.1]paracyclophane-33,4′-piperidine] (13). A mixture of 10.8 g (20.0 mmol) of dichloride **12**, 7.35 g (20 mmol) of diphenol **5**, and 19.5 g (60 mmol) of cesium carbonate in 1.5 L of dry dimethylformamide was stirred at 80 °C under N_2 for 3 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 4.69 g (28%) of analytically pure macrocycle **13** as colorless glass: IR (KBr) ν(N—H) 3300, ν(C=O) 1625 cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$) δ 1.2–1.3 (m, 4 H, $OCH_2CH_2CH_2$), 1.45–1.6 (m, 8 H, $OCH_2CH_2CH_2CH_2$), 1.97 (s, 6 H, CH_3CONH), 2.11 [s, 3 H, $CH_3CON(CH_2)_2$], 2.14 (s, 12 H, aryl-CH_3), 2.25–2.45 (m, 4 H, NCH_2CH_2C), 3.55–3.75 (m, 4 H, NCH_2CH_2C), 3.65–3.85 (m, 8 H, $OCH_2CH_2CH_2CH_2CH_2O$), 3.93 and 4.10 (AB part of ABX, J = 14.8 and 5.1 Hz, 4 H, aryl-CH_2NH), 6.55 (d, J = 8.2 Hz, 2 H, Bp-3,3′-H),[43] 6.79 (s, 4 H, aryl-H_{DPM}), 6.94 (d, J = 7.6 Hz, 2 H, Bp-5,5′-H), 7.01 (s, br, X-part of ABX, 2 H, NH), 7.06 (t, $J \simeq$ 7.9 Hz, 2 H, Bp-4,4′-H); MS, m/z 831 (M^+). Anal. Calcd for $C_{51}H_{65}N_3O_7$ (832.1): C, 73.62; H, 7.81; N, 5.05. Found: C, 73.63; H, 7.70; N, 5.04.

12,15-Bis(aminomethyl)-28,32,36,38-tetramethylspiro[1,7,20,26-tetraoxa[7](2,2′)biphenylo[7.1]paracyclophane-33,4′-piperidine] (14). A solution of 2.89 g (3.47 mmol) of **13** and 8 g (0.12 mol) of potassium hydroxide (85%) in 100 mL of 2-methoxyethanol was heated to reflux for 36 h. After evaporation of 70 mL of the solvent in vacuo, 200 mL of water were added. The aqueous phase was extracted five times with chloroform, dried over sodium sulfate, and evaporated in vacuo to give 2.24 g (91%) of **14** as an NMR-pure colorless oil which was used for the Eschweiler–Clarke methylation without further purification: IR (neat) ν(N—H) 3400 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 1.1–1.25 (m, 4 H, $OCH_2CH_2CH_2$), 1.4–1.6 (m, 8 H, $OCH_2CH_2CH_2CH_2$), 2.07 (s, br, 5 H, NH, NH_2), 2.15 (s, 12 H, aryl-CH_3), 2.2–2.4 (m, 4 H, NCH_2CH_2C), 2.85–3.05 (m, 4 H, NCH_2CH_2C), 3.38 (s, 4 H, N-CH_2-aryl), 3.6–3.75 (m, 8 H, $OCH_2CH_2CH_2CH_2CH_2O$), 6.51 (d, J = 8.2 Hz, 2 H, Bp-3,3′-H), 6.83 (s, 4 H, aryl-H_{DPM}), 6.97 (d, J = 7.6 Hz, 2 H, Bp-5,5′-H), 7.11 (t, $J \simeq$ 7.9 Hz, 2 H, Bp-4,4′-H); MS, m/z (relative intensity) 705 (100, M^+).

12,15-Bis((dimethylamino)methyl)-1′,28,32,36,38-pentamethylspiro[1,7,20,26-tetraoxa[7](2,2′)biphenylo[7.1]paracyclophane-33,4′-piperidine] (15) and 13,14-Dihydro-1′,13,27,31,35,37-hexamethylspiro[1,7,19,25-tetraoxa[7](1,11)-5*H*-dibenz[*c*,*e*]azepino[7.1]paracyclophane-32,4′-piperidine] (18). A stirred mixture of 1.1 g (1.56 mmol) of **14**, 1.38 g (30 mmol) of formic acid, and 1.08 g (12.6 mmol) of a 35% aqueous solution of formaldehyde in a 10-mL flask was heated slowly until the evolution of CO_2 started (at ~60 °C). Stirring was continued without further heating until the end of the evaluation of gas; then the mixture was heated to 100 °C for 12 h. After cooling, the reaction mixture was added to 50 mL of 2 N NaOH and the aqueous solution was extracted three times with chloroform. The combined organic phases were washed with water and dried over sodium sulfate, and the solvent was evaporated in vacuo. Chromatography of the residue on silica gel from ethyl acetate/hexane/triethylamine (50:50:5) gave 315 mg (26%) of **15**, R_f ~0.3, and 470 mg (42%) of **18**, R_f ~0.1.

15: mp 77 °C (ether); ^1H NMR (500 MHz, $CDCl_3$) δ 1.1–1.2 (m, 4 H, $OCH_2CH_2CH_2$), 1.35–1.6 (m, 8 H, $OCH_2CH_2CH_2CH_2$), 2.07 (s, 12 H, $(CH_3)_2NCH_2$), 2.14 (s, 12 H, aryl-CH_3), 2.24 (s, 3 H, NCH_3), 2.2–2.4 (m, 4 H, NCH_2CH_2C), 2.4–2.6 (m, 4 H, NCH_2CH_2C), 2.93 and 2.95 (AB, J = 14.5 Hz, 4 H, N-CH_2-aryl), 3.55–3.75 (m, 8 H, $OCH_2CH_2CH_2CH_2CH_2O$), 6.47 (d, J = 8.0 Hz, 2 H, Bp-3,3′-H), 6.82 (s, 4 H, aryl-H_{DPM}), 7.1–7.15 (m, 4 H, Bp-4,4′,5,5′-H); MS, m/z (70 eV) (relative intensity) 775 (14, M^+), 70 (100); m/z (16 eV) 775 (100). Anal. Calcd for $C_{50}H_{69}N_3O_4$ (776.1): C, 77.38; H, 8.96; N, 5.41. Found: C, 77.51; H, 9.04; N, 5.31.

18: mp 209 °C (EtOH); ^1H NMR (500 MHz, $CDCl_3$) δ 1.1–1.2 (m, 4 H, $OCH_2CH_2CH_2$), 1.4–1.6 (m, 8 H, $OCH_2CH_2CH_2CH_2$), 2.17 (s, 12 H, aryl-CH_3), 2.24 (s, 3 H, NCH_3), 2.30 (s, 3 H, NCH_3), 2.3–2.6 (m, 8 H, NCH_2CH_2C), 3.02 and 3.36 (AX, J = 12.2 Hz, 4 H, MeN-CH_2-Aryl), 3.55-3.8 (m, 8 H, $OCH_2CH_2CH_2CH_2CH_2O$), 6.46 (d, J = 8.2 Hz, 2 H, DBA-2,10-H),[43] 6.85 (d, J = 7.3 Hz, 2 H, DBA-4,8-H), 6.90 (s, 4 H, aryl-H_{DPM}), 7.09 (t, $J \simeq$ 7.8 Hz, 2 H, DBA-3,9-H); MS, m/z (relative intensity) 716 (100, M^+), 358 (16, M^{2+}). Anal. Calcd for $C_{47}H_{60}N_2O_4$ (717.0): C, 78.73; H, 8.44; N, 3.91. Found: C, 78.79; H, 8.45; N, 3.81.

N,N,N',N'-Tetraethyl-6,6'-dimethoxy-2,2-biphenyldicarboxamide (21). A solution of 40.9 g (0.135 mol) of 6,6'-dimethoxydiphenic acid in 100 mL of sulfinyl chloride was heated to reflux for 3 h. The excess of sulfinyl chloride was removed in vacuo. Dry toluene was added twice and removed each time in vacuo. The residue was suspended in 200 mL of dry toluene and a solution of 102.4 g (1.4 mol) of diethylamine in 100 mL of dry toluene was added under vigorous stirring at 0 °C. Stirring was continued for 1 h after which the solvent and the excess of diethylamine were removed in vacuo. The residue was dissolved in chloroform and the organic solution was washed successively with water, with 1 N HCl, with water, with 2 N Na_2CO_3, and again with water. After drying the organic phase over magnesium sulfate, the solvent was removed in vacuo. Recrystallization of the residue from chloroform/ether afforded 50.23 g (90%) of **21**: mp 144–145 °C; IR (KBr) ν(C=O) 1630 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 0.78 (t, J = 6.8 Hz, 6 H, CH_3CH_2N), 0.95 (t, J = 6.8 Hz, 6 H, CH_3CH_2N), 3.0–3.4 (m, br, 8 H, CH_3CH_2N), 3.61 (s, 6 H, CH_3O), 6.82 (d, J = 7.6 Hz, 2 H, 3,3'-H), 6.98 (d, J = 8.2 Hz, 2 H, 5,5'-H), 7.30 (t, $J \simeq$ 8Hz, 2 H, 4,4'-H); MS, m/z (relative intensity) 412 (30, M^+), 72 (100). Anal. Calcd for $C_{24}H_{32}N_2O_4$ (412.6): C, 69.87; H, 7.82; N, 6.79. Found: C, 69.75; H, 7.79; N, 6.72.

2,2'-Bis((diethylamino)methyl)-6,6'-dimethoxybiphenyl (22). A total of 32 mL (32 mmol) of a 1 M solution of borane in tetrahydrofuran was added to a solution of 2.67 g (6.5 mmol) of **21** in dry tetrahydrofuran. After being stirred for 12 h at 20 °C, the reaction mixture was heated to reflux for 1 h. The mixture was cooled in an ice bath and carefully hydrolized with water, and the solvent was removed in vacuo. Then 50 mL of 6 N HCl was added and the resulting solution was heated to reflux for 2 h. Evaporation to dryness under reduced pressure left a residue which was partitioned between 2 N NaOH and dichloromethane. The aqueous phase was extracted three more times with dichloromethane and the combined organic phases were dried over sodium sulfate. Chromoatography on silica gel from ethyl acetate/hexane/triethylamine (5:5:0.5) afforded 1.62 g (65%) of **22**: mp 63–64 °C; ^1H NMR (200 MHz, $CDCl_3$) δ 0.88 (t, J = 7.3 Hz, 12 H, CH_3CH_2N), 2.2–2.5 (m, 8 H, CH_3CH_2N), 3.08 and 3.13 (AB, J = 14.6 Hz, 4 H, NCH_2-aryl) 3.67 (s, 6 H, CH_3O), 6.84 (d, J = 8.2 Hz, 2 H, 5,5'-H), 7.25–7.35 (m, 4 H, 3,3',4,4'-H); MS, m/z 384 (M^+). Anal. Calcd for $C_{24}H_{36}N_2O_2$ (384.6): C, 74.96; 9.44; N, 7.28. Found: C, 74.78; H, 9.29; N, 7.26.

N,N,N',N'-Tetraethyl-6,6'-dihydroxy-2,2-biphenyldicarboxamide (23). A total of 213 g (0.85 mol) of boron tribromide was added at −78 °C to a solution of 70.6 g (0.17 mol) of **22** in 1 L of dichloromethane. The reaction mixture was warmed to 20 °C and stirred for 12 h. The mixture was carefully hydrolyzed with methanol under cooling in an ice bath and the solvent was evaporated under reduced pressure. The product crystallized upon addition of water and was collected by filtration: 64.5 g (98%) of **23**: mp >360 °C; IR (KBr) ν(O—H) 3600–2700, ν(C=O) 1580 (br) cm^{-1}; ^1H NMR (200 MHz, methanol-d_4) δ 0.91 (t, J = 7.1 Hz, 6 H, CH_3CH_2N), 1.27 (t, J = 7.1 Hz, 6 H, CH_3CH_2N), 3.2–3.8 (m, 8 H, CH_3CH_2N), 6.99 (d, J = 7.2 Hz, 2 H, 3,3'-H), 7.10 (d, J = 8.3 Hz, 2 H, 5,5'-H), 7.42 (t, $J \simeq$ 7.8 Hz, 2 H, 3,3'-H); HRMS, m/z (M^+, $C_{22}H_{28}N_2O_4$) calcd 384.2050, obsd 383.2040.

N,N,N',N'-Tetraethyl-6,6'-bis(5-chloropentoxy)-2,2-biphenyldicarboxamide (24). A mixture of 32.5 g (0.085 mol) of **23**, 179.1 g (1.27 mol) of 1,5-dichloropentane, and 55.2 g (0.17 mol) of cesium carbonate in 800 mL of dimethylformamide dried over basic alumina (activity 1) was stirred at 80 °C under N_2 for 16 h. After cooling, the cesium sallts were removed by filtration and the solution was evaporated to dryness. The residue was chromatographed on silica gel from ethyl acetate to yield 42.18 g (84%) of **24** as viscous oil, R_f ~0.4, and 3.46 g (9%) of compound **17** (R_f ~0.2) which is described below: IR (KBr) ν(C=O) 1640 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 0.89 (t, J = 6.5 Hz, 6 H, CH_3CH_2N), 1.01 (t, J = 6.5 Hz, 6 H, CH_3CH_2N), 1.2–1.4 (m, 4 H, $OCH_2CH_2CH_2$), 1.45–1.75 (m, 8 H, $OCH_2CH_2CH_2CH_2$), 3.0–3.3 (m, 8 H, CH_3CH_2N), 3.40 (t, $J \simeq$ 6.4 Hz, 4 H, CH_2Cl), 3.8–4.0 (m, 4 H, OCH_2), 6.86 (d, $J \simeq$ 8.2 Hz, 4 H, 3,3',5,5'-H), 7.25 (t, $J \simeq$ 7.9 Hz, 2 H, 4,4'-H); MS, m/z 592 (M^+).

12,15-Bis(diethylcarbamoyl)-1,7-dioxa[7](2,2')biphenylophane (17). Following the procedure described above for the Williamson ether synthesis of **6** with sodium hydroxide as base in 1-butanol, 19.2 g (0.05 mol) of **23** and 211.5 g (1.5 mol) of 1,5-dichloropentane afforded a crude product containing two major components with R_f ~0.4 (**24**) and R_f ~0.2 (**17**). Chromoatography on silica gel from ethyl acetate yielded 9.5 g (32%) of pure **24** followed by 4.2 g (18%) of pure **17**: mp 193–195 °C; IR (KBr) ν(C=O) 1630 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 0.8–1.2 (m, 12 H, CH_3CH_2N), 1.5–1.6 (m, 2 H, $OCH_2CH_2CH_2$), 1.6–1.8 (m, 4 H, $OCH_2CH_2CH_2$), 2.9–3.6 (m, 8 H, CH_3CH_2N), 3.95–4.45 (m, 4 H, OCH_2), 6.88 (d, J = 7.5 Hz, 2 H, Bp-5,5'-H), 6.95 (d, J = 8.2 Hz, Bp-3,3'-H), 7.26 (t, $J \simeq$ 7.7 Hz, 2 H, Bp-4,4'-H); MS, m/z 452 (M^+). Anal. Calcd for $C_{27}H_{36}N_2O_4$ (452.7): C, 71.65; H, 8.02; N, 6.19. Found: C, 71.77; H, 8.05; N, 6.12.

1'-Acetyl-12,15-bis(diethylcarbamoyl)-28,32,36,38-tetramethylspiro[1,7,20,26-tetraoxa[7](2,2')biphenylo[7.1]paracyclophane-33,4'-piperidine] (19). A mixture of 5.16 g (8.69 mmol) of dichloride **24**, 3.19 g (8.69 mmol) of diphenol **5**, and 9.3 g (28.5 mmol) of cesium carbonate in 2 L of dimethylformamide was stirred under N_2 for 48 h at 80 °C. After evaporation of the solvent, the residue was partitioned between water and chloroform. The aqueous layer was extracted three more times with chloroform and the combined organic phases were dried over magnesium sulfate. The solvent was removed in vacuo and chromatography of the residue on silica gel from ethyl acetate yielded 2.39 g (31%) of **19** as colorless glass: IR (KBr) ν(C=O) 1640 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 0.8–0.95 (m, 6 H, CH_3CH_2N), 0.95–1.1 (m, 6 H, CH_3CH_2N), 1.1–1.3 (m, 4 H, $OCH_2CH_2CH_2$), 1.4–1.7 (m, 8 H, $OCH_2CH_2CH_2CH_2$), 2.09 (s, 3 H, CH_3CON), 2.17 (s, 12 H, aryl-CH_3), 2.2–2.4 (m, 4 H, NCH_2CH_2C), 2.9–3.3 (m, 8 H, CH_3CH_2N), 3.45–3.7 (m, 4 H, NCH_2CH_2C), 3.6–3.85 (m, 8 H, $OCH_2CH_2CH_2CH_2CH_2O$), 6.64 (d, J = 8.2 Hz, 2 H, Bp-3,3'-H), 6.80 (s, 4 H, aryl-H_{DPM}), 6.85 (d, J = 7.6 Hz, 2 H, Bp-5,5'-H), 7.14 (t, $J \simeq$ 7.9 Hz, 2 H, Bp-4,4'-H); MS, m/z (relative intensity) 887 (100, M^+). Anal. Calcd for $C_{55}H_{73}N_3O_7$ (888.3): C, 74.37; H, 8.28; N, 4.73. Found: C, 74.01; H, 8.09; N, 4.54.

1'-Ethyl-12,15-bis((diethylamino)methyl)-28,32,36,38-tetramethylspiro[1,7,20,26-tetraoxa[7](2,2')biphenylo[7.1]paracyclophane-33,4'-piperidine] (20). A total of 23.7 mL (23.7 mmol) of a 1 M solution of borane in tetrahydrofuran was dropped under N_2 into a solution fo 1.056 g (1.19 mmol) of **19** in 25 mL of dry tetrahydrofuran. The mixture was stirred at 20 °C for 20 h, then heated to reflux for 2 h. After cooling, the solution was carefully hydrolized by addition of water and the solvent was distilled off. The residue in a 3% solution of sulfuric acid in ethanol was heated to reflux for 30 min. After neutralization with sodium carbonate, the solvent was removed in vacuo, leaving the crude product which was partitioned between chloroform and 2 N NaOH. The aqueous phase was extracted three more times with chloroform and the combined organic phases were dried over sodium sulfate. The solvent was distilled off and chromatography of the residue on silica gel from ethyl acetate/*n*-hexane/triethylamine (25:70:5) afforded 554 mg (55%) of **19**: R_f ~0.4; mp 46–47 °C; ^1H NMR (500 MHz, 1D and 2D COSY, $CDCl_3$) δ 0.81 (t, J = 7.0 Hz, 12 H, CH_3CH_2N), 1.01 [t, J = 7.2 Hz, 3 H, $CH_3CH_2N(CH_2)_2$], 1.0–1.2 (m, 4 H, $OCH_2CH_2CH_2$), 1.3–1.55 (m, 8 H, $OCH_2CH_2CH_2CH_2$), 2.09 (s, 12 H, aryl-CH_3), 2.2–2.35 [m, 10 H, CH_3CH_2N and $CH_3CH_2N(CH_2)_2$], 2.35–2.55 (m, 8 H, NCH_2CH_2C), 3.00 (s, 4 H, N-CH_2-aryl; gives AB in Me_2SO-d_6 and benzene-d_6), 3.5–3.7 (m, 8 H, $OCH_2CH_2CH_2CH_2CH_2O$), 6.45 (d, J = 8.1 Hz, 2 H, Bp-3,3'-H), 6.82 (s, 4 H, aryl-H_{DPM}), 7.08 (t, $J \simeq$ 7.9 Hz, 2 H, Bp-4,4'-H), 7.20 (d, J = 7.8 Hz, 2 H, Bp-5,5'-H); MS, m/z 845 (M^+). Anal. Calcd for $C_{55}H_{79}N_3O_4$ (846.24): C, 78.06; H, 9.41; N, 4.96. Found: C, 78.18; H, 9.34; N, 4.93. Reduction of 1.00 g (1.12 mmol) of **19** with 22.5 mL (22.5 mmol) of a 1 M solution of borane in tetrahydrofuran as described above followed by 2 h reflux with 6 N HCl to destroy the amine–borane adducts gave less than 10% yield of **20**. Three major products were detected at the end of the workup by thin layer chromoatography and 495 mg (50%) of the ether-cleavage product **25** with R_f ~0.6 was isolated by chromatography on silica gel from ethyl acetate. **25**: mp 98 °C (*n*-hexane); IR (KBr) ν(O-H) 3450 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 0.85 (t, J = 7.1 Hz, 6 H, CH_3CH_2N), 0.86 (t, J = 7.1 Hz, 6 H, CH_3CH_2N), 1.00 [t, J = 7.2 Hz, 3 H, $CH_3CH_2N(CH_2)_2$], 1.2–1.4 (m, 4 H, $OCH_2CH_2CH_2$), 1.4–1.7 (m, 8 H, $OCH_2CH_2CH_2CH_2$), 2.16 (s, 6 H, aryl-CH_3), 2.18 (s, 6 H, aryl-CH_3), 2.2–2.6 [m, 18 H, CH_3CH_2N, $CH_3CH_2(CH_2)_2$, and NCH_2CH_2C], 3.07 and 3.14 (AB, J = 14.8 Hz, 2 H, N-CH_2-aryl),

3.07 and 3.15 (AB, J = 14.8 Hz, 2 H, N-CH_2-aryl), 3.36 (t, J = 6.7 Hz, 2 H, CH_2Cl), 3.58 (t, J = 6.6 Hz, 2 H, DPM-OCH_2CH_2), 3.7–3.9 (m, 4 H, Bp-OCH_2CH_2), 6.73 (dd, J = 7.7 and 1.3 Hz, 1 H, Bp-3 or 3′-H), 6.78 (m, 1 H, Bp-3 or 3′-H), 6.85 (s, 2 H, aryl-H_{DPM}), 6.87 (s, 2 H, aryl-H_{DPM}), 7.15–7.25 (m, 4 H, Bp-4,4′,5,5′-H); MS, m/z (relative intensity) 882 (62, M^+), 809 (100). Anal. Calcd for $C_{55}H_{80}N_3O_4Cl$ (882.8): C, 74.84; H, 9.14; N, 4.76; Cl, 4.02. Found: C, 74.68; H, 9.33; N, 4.53; Cl, 4.13.

A mixture of 663 mg (0.75 mmol) of **25** and 975 mg (3 mmol) of cesium carbonate in 30 mL of dry dimethylformamide was stirred under N_2 for 16 h at 80 °C. The cesium salts were removed by filtration and the solution was evaporated to dryness. Chromatography on silica gel from ethyl acetate/n-hexane/triethylamine (25:70:5) afforded 299 mg (47%) of **20**, which was shown by TLC, IR, NMR, and mp to be identical with **20** obtained from the diborane reduction as described above.

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Addition Compounds of Alkali Metal Hydrides. 29. Preparation and Properties of Chiral Dialkylmonoalkoxyborohydrides. A New Class of Asymmetric Reducing Agents

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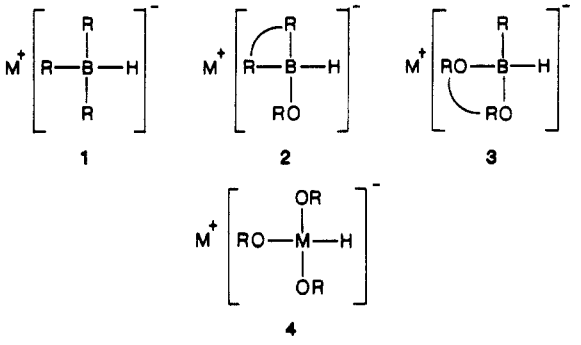
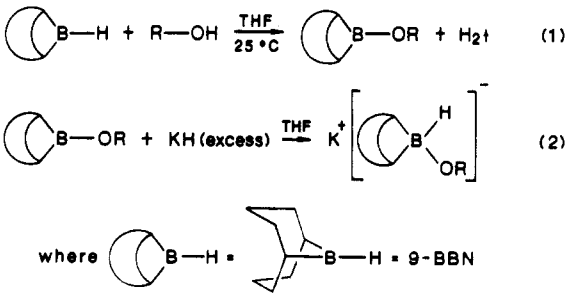
A series of chiral 9-alkoxy-9-borabicyclo[3.3.1]nonane derivatives were synthesized by the reaction of 9-borabicyclo[3.3.1]nonane (9-BBN) with several readily available chiral alcohols, such as (−)-isopinocampheol, (+)-menthol, (−)-4-isocaranol, (+)-*trans*-2-methylcyclopentanol, and (−)-1,2:5,6-di-*O*-isopropylidene-α-D-glucofuranose. A chiral borinic ester possessing a cyclic chiral dialkylboryl moiety, (+)-2-(cyclohexyloxy)-4,8-dimethyl-2-borabicyclo[3.3.1]nonane, was also synthesized. With one exception, all of these chiral borinic esters were readily converted into the corresponding chiral dialkylmonoalkoxyborohydrides by treatment with excess potassium hydride in THF at 25 °C. The addition of potassium hydride to (+)-9-(menthyloxy)-9-borabicyclo[3.3.1]nonane (9-*O*-Men-9-BBN) was very slow, requiring 15 days at 65 °C (refluxing THF). The chiral dialkylmonoalkoxyborohydrides thus formed are all stable at 25 °C and can be stored for several months. They were tested against acetophenone and 3-methyl-2-butanone as representative prochiral ketones. These reagents reduce acetophenone with up to 78% ee and 3-methyl-2-butanone with up to 61% ee at −78 °C.

The syntheses of trisubstituted borohydrides containing a single substituent, such as trialkylborohydrides[2] **1** and trialkoxyborohydrides[3] **4**, were well established some time ago. However, the general syntheses of "mixed" trisubstituted borohydrides became possible only recently by using cyclic moieties, such as 9-BBN in dialkylmonoalkoxyborohydrides[4,5] **2** and glycols in dialkoxymonoalkylborohydrides[6] **3**, to stabilize the products toward disproportionation.



1 **2** **3** **4**

Among these mixed trisubstituted borohydrides, the potassium 9-alkoxy-9-boratabicyclo[3.3.1]nonane (K 9-OR-9-BBNH) derivatives have achieved the most favorable stereoselectivities,[4,5] approaching those obtained by the trialkylborohydrides **1**. The syntheses of these dialkylmonoalkoxyborohydrides involve the reaction of 9-BBN with alcohols (eq 1), followed by conversion of the resulting borinic esters into the corresponding potassium dialkylmonoalkoxyborohydrides by treatment with excess potassium hydride (eq 2).



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