2.20 (s, 3 H), 3.75 (s, 2 H); ^{13}C NMR (75.48 MHz, $CDCl_3$) (*Z* isomer) δ 190.86, 170.16, 146.97, 143.59, 140.86, 135.51, 135.23, 121.67, 117.36, 113.70, 102.33, 102.28, 61.20, 31.57, 20.31; (*E* isomer) δ 192.73, 173.82, 147.38, 144.70, 141.01, 138.20, 130.87, 117.78, 115.60, 111.82, 102.67, 62.15, 29.09, 20.08; MS (low-resolution EI) *m/e* (relative intensity) 260 (M^+,9), 218 (48), 200 (100), 172 (30), 121 (26), 115 (38), 101 (22), 89 (11), 77 (20), 62 (18). Anal. Calcd for $C_{14}H_{12}O_5$: C, 64.61; H, 4.65. Found: C, 64.54; H, 4.65.

5-(2-Acetoxyethylidene)-2-cyclopenten-1-one (6i/7i) (0.18 mmol): IR (CH_2Cl_2) 2880–2980, 1745, 1705, 1670, 1660, 1380, 1240 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) (*Z* isomer) δ 7.58 (m, 1 H), 6.38 (M, 1 H), 6.08 (t, *J* = 5.5 Hz, 1 H), 5.33 (d, *J* = 5.6 Hz, 2 H), 3.25 (s, 2 H), 2.10 (s, 3 H); (*E* isomer) δ 7.62 (m, 1 H), 6.54 (t, *J* = 5.6 Hz, 1 H), 6.38 (m, 1 H), 4.80 (d, *J* = 5.6 Hz, 2 H), 3.32 (s, 2 H), 1.22 (s, 3 H); ^{13}C NMR ($CDCl_3$, 75.48 MHz) (*Z* isomer) δ 196.64, 171.62, 163.26, 139.06, 134.34, 132.82, 61.67, 38.75, 21.56; ^{13}C assignments for the *E* isomer were not determined due to a limited amount of material. Anal. Calcd for $C_9H_{10}O_3$: C, 65.05; H, 6.07. Found: C, 64.95; H, 6.10.

Acknowledgment. This investigation was supported by Grant No. CA44404 awarded by the National Cancer Institute, DHHS. We acknowledge the use of a VG 70-S mass spectrometer purchased through funding from the National Institutes of Health (Grant No. S10-RR-02478) and a 300-MHz NMR and 360-MHz NMR purchased through funding from the National Science Foundation (Grant Nos. NSF CHE-85-16614 and NSF CHE-8206103, respectively). We thank Dr. J. Stuart McCallum for sharing his results on the transformation of compound **10** into **11** and **12**.

Registry No. **1a**, 83897-48-7; **1b**, 127230-91-5; **1c**, 127230-92-6; **1d**, 38425-48-8; **1e**, 127230-93-7; **1e** (4,4-dichloro derivative), 85973-82-6; **1f**, 4683-54-9; **1g**, 3469-06-5; **1h**, 118112-19-9; **2a**, 127230-99-3; **2b**, 127231-00-9; **2c**, 127231-01-0; **2d**, 127231-02-1; **2e**, 127231-03-2; **2f**, 127231-04-3; **2g**, 127231-05-4; **2h**, 127231-06-5; **4a**, 127231-07-6; **4b**, 127231-08-7; **4c**, 127231-09-8; **4d**, 127231-10-1; **4e**, 127231-11-2; **4f**, 127231-12-3; **4g**, 127231-13-4; **4h**, 127231-14-5; **5a**, 127231-16-7; **5b**, 127231-17-8; **5c**, 127231-18-9; **5d**, 127231-19-0; **5e**, 127231-20-3; **5g**, 127231-21-4; **5h**, 127231-22-5; **5i**, 127231-23-6; **6a**, 127231-24-7; **6b**, 127231-25-8; **6c**, 127231-26-9; **6d**, 127231-27-0; **6e**, 127231-28-1; **6g**, 127231-29-2; **6h**, 127231-30-5; **6i**, 127231-31-6; **7a**, 127231-32-7; **7b**, 127231-33-8; **7c**, 127231-34-9; **7d**, 127231-35-0; **7e**, 127231-36-1; **7g**, 127231-37-2; **7h**, 127231-38-3; **7i**, 127231-39-4; **10**, 127230-94-8; **11**, 127230-95-9; **12**, 127230-96-0; **13**, 127230-97-1; **14**, 127230-98-2; **15**, 71721-73-8; $MeOCH{=}C{=}CH_2$, 13169-00-1; $H_3CC{\equiv}CCH_3$, 503-17-3; $ClC(O)CHCl_2$, 79-36-7; $HC{\equiv}CCH_3$, 6443-91-0; cyclobutane-1,3-dione, 15506-53-3; 3-ethoxycyclobutan-1-one, 30830-26-3; 3-ethoxy-1-(1-methoxypropadienyl)-cyclobutan-1-ol, 127231-15-6.

Supplementary Material Available: ^1H and/or ^{13}C NMR spectra for compounds **2a–2f**, **10**, **11**, and **14** (12 pages). See any current masthead page for ordering information.

Host–Guest Complexation. 53. Functional Groups Preorganized in Hemispherands for Binding Alkali Metal and Ammonium Cations[1]

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Received December 20, 1989

The synthesis and free energies are reported for 10 new hemispherands (**1**, **2**, **4**, **6**, **7–9**, **11–13**) binding alkali metal and ammonium picrate salts at 25 °C in $CDCl_3$ saturated with D_2O. These hemispherands possess the general structure I, in which two 4-substituted anisole units flank and preorganize for binding the heteroatoms of substituted aromatic or heterocyclic systems. These macrocycles, like three previously reported (**3**, **5**, **10**), contain 18-membered rings with common $(CH_2OCH_2)_3$ and two $ArOCH_3$ units but differing central A units (I). Most of the 13 hemispherands compared show the highest binding for Na^+ and the exceptions, for K^+. Arrangement of the 13 systems in decreasing order of their contributions to their systems binding Na^+ is as follows, with the $-\Delta G°$ values (kcal mol^{-1}) appearing in parentheses: **1**, 4-$CH_3C_6H_2CON(CH_3)_2$ (15.1); **2**, 4-$CH_3C_6H_2CO_2CH_3$ (12.4); **3**, 4-$CH_3C_6H_2OCH_3$ (12.2); **4**, pyridine oxide (12.2); **5**, $(CH_2)_3N_2C{=}O$ (12.0); **12**, 4-$CH_3C_6H_2SOCH_3$ (11.4); **6**, 4-$CH_3C_6H_2NO_2$ (11.0); **7**, pyridine (10.8); **11**, 4-$CH_3C_6H_2SCH_3$ (10.8); **13**, 4-$CH_3C_6H_2SO_2CH_3$ (9.5); **8**, 4-$CH_3C_6H_2NH_2$ (9.3); **9**, furan (8.9); **10**, 4-$CH_3C_6H_2OH$ (7.9). The largest specificities for hosts binding Na^+ over hosts binding K^+ involved **12**, with A = $CH_3C_6H_2SOCH_3$ [$-\Delta(\Delta G°) = 3.8$] and **13** with A = $CH_3C_6H_2SO_2CH_3$ [$-\Delta(\Delta G°) = 3.2$ kcal mol^{-1}]. The corresponding specificites for these two systems binding Na^+ over Li^+ were $-\Delta(\Delta G°) = 3.7$ and 2.8 kcal mol^{-1}, respectively. The crystal structures of **1**, **2**, **2**·$NaSbF_6$, **4**, **6**, and **6**·$NaSbF_6$ are reported.

A central objective in this series of papers is to correlate the structures of hosts and guests with their binding free energies in the applications of the principles of complementarity and preorganization to host design.[2] There is vast literature on the binding of the alkali metal ions by corands containing aliphatic ether oxygen, amine nitrogen, or sulfide sulfur, reflecting the fact that these functional groups are readily introduced as ring members into macrocycles and macrobicycles to provide systems partially preorganized for binding by their respective macroring systems.[3] Crystal structures of hemispherands established that three or four anisole units attached to one another at their 2- and 6-positions and incorporated into respective 18- and 20-membered macrorings[4] provide a means of preorganizing methoxyaryl oxygens for binding alkali metal

(1) We thank the Division of Basic Sciences of the Department of Energy for support of the research involving binding of the alkali-metal ions and the U.S. Public Health Services for Grant 12640 for that involving the ammonium and alkylammonium ions and the crystal structures.

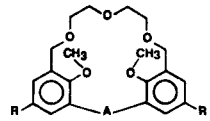
(2) (a) Cram, D. J. *Angew. Chem., Int. Ed. Engl.* **1986**, *25*, 1039–1057. (b) Cram, D. J. *Science* **1988**, *240*, 760–767.

(3) For example: (a) Izatt, R. M., Christensen, J. J., Eds. *Synthetic Multidentate Macrocyclic Compounds*; Academic Press: New York, 1978. (b) Weber, E.; Vögtle, F. Crown-Type Compounds - An Introductory Overview. In *Host Guest Complex Chemistry I*; Boschke, F. L., Ed.; Springer-Verlag: Berlin, 1981; pp 1–42.

(4) Cram, D. J. *Chemtracts* **1988**, *1*, 89–101.

0022-3263/90/1955-4622$02.50/0

ions as in **3**.[5] The fact that these hemispherand-complexing agents were more strongly and specifically binding than were their oxygen corand counterparts[5,6] suggests that compounds of general structure I with A groups containing



I, A is 2,6-disubstituted

1, R = CH_3, A = 4-$CH_3C_6H_2CON(CH_3)_2$

2, R = CH_3, A = 4-$CH_3C_6H_2CO_2CH_3$

3, R = CH_3, A = 4-$CH_3C_6H_2OCH_3$

4, R = CH_3, A = 

5, R = CH_3, A = 

6, R = CH_3, A = 4-$CH_3C_6H_2NO_2$

7, R = CH_3, A = 

8, R = CH_3, A = 4-$CH_3C_6H_2NH_2$

9, R = CH_3, A =

10, R = CH_3, A = 4-$CH_3C_6H_2OH$

11, R = $(CH_3)_3C$, A = 4-$CH_3C_6H_2SCH_3$

12, R = $(CH_3)_3C$, A = 4-$CH_3C_6H_2SOCH_3$

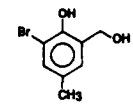
13, R = $(CH_3)_3C$, A = 4-$CH_3C_6H_2SO_2CH_3$

other functionalities might be preorganized enough to show high and selective binding toward complementary cations. Amido, ester, sulfoxide, sulfone, nitro, hydroxyl, and primary amino are groups that are particularly difficult to preorganize without their attachment to an aryl that itself is part of the A group of I. Units such as pyridine, pyridine oxides, 2,5-disubstituted furan, and cyclic urea are capable of being directly incorporated into macrocycles as A groups in I.

This paper reports the synthesis and binding properties at 25 °C in $CDCl_3$ (saturated with D_2O) of new hemispherands **1**, **2**, **4**, **6–9**, and **11–13** toward the picrate salts of Li^+, Na^+, K^+, Rb^+, Cs^+, NH_4^+, $CH_3NH_3^+$, and $(CH_3)_3CNH_3^+$. Included are the crystal structures of free hosts **1**, **2**, **4**, and **6**, as well as complexes **2**·$NaSbF_6$ and **6**·$NaSbF_6$. The first section describes the syntheses of the new hosts. The second provides views and discussions of crystal structures. The third reports the hosts binding free energies and compares them to those of **3**,[5] **5**,[7] and **10**[8] published previously. Correlations between structure and binding are discussed in the fourth part.

Results and Discussion

Syntheses. The key reaction in many of the syntheses was the Suzuki unsymmetrical coupling between appropriate aryl bromides or iodides and an arylboronic acid, catalyzed by $Pd(PPh_3)_4$.[9] The reaction is first illustrated in the syntheses of **1**, **2**, **6**, and **8**. Hydroxymethylation of 2-bromo-4-methylphenol to give **14** was reported previously.[10] This compound was doubly alkylated with $(CH_3)_2SO_4$–NaH to provide **15** (93%). The aryllithium derivative of **15** was generated at −78 °C in THF with *n*-BuLi and was cannulated into a solution of $(CH_3O)_3B$–THF to give after hydrolytic isolation the arylboronic acid **16** (83%), which could be stored for months without decomposition. Diazotization of **17** and treatment of the diazonium salt produced with $CuSO_4$–KCN gave nitrile **18**.[11] Hydrolysis of **18** gave the corresponding amide **19**, which was further hydrolyzed (via diazotization)[12] to the acid **20**[13] isolated as its methyl ester **21**, which has been reported.[13] The coupling of ester dibromide **21** with 2 mol of boronic acid **16** was conducted in a two-phase refluxing mixture of the reactants in benzene–aqueous 2 M Na_2CO_3–$Pd(Ph_3)_4$ to produce terphenyl derivative **24**, the precursor to macrocycle **2**.



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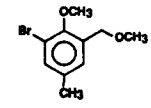

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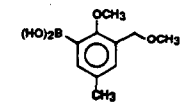

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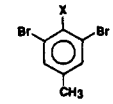
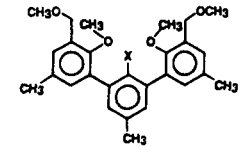
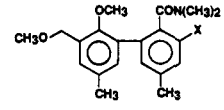




17, X = NH_2; 18, X = CN; 19, X = $CONH_2$; 20, X = CO_2H; 21, X = CO_2CH_3; 22, X = $CON(CH_3)_2$; 23, X = NO_2

24, X = CO_2CH_3; 25, X = $CON(CH_3)_2$; 26, X = NO_2; 27, X = NH_2

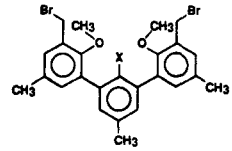
The terphenyl precursors **25–27** to respective hemispherands **1**, **6**, and **8** were similarly synthesized. Dibromo acid **20** was converted via its acid chloride with $(CH_3)_2NH$ to amide **22** (97%), which when submitted to a 2-fold Suzuki coupling with boronic acid **16** gave **25** (18%) in addition to greater amounts of monocoupled products **28** and **29**. In the synthesis of nitro compound **26**, amine **17**



28, X = H; 29, X = Br

was diazotized ($NaNO_2$–AcOH–H_2SO_4), and the diazonium salt was mixed with $CuSO_4$ and $NaNO_2$ to produce nitro compound **23** (25%). This substance underwent the 2-fold Suzuki coupling reaction with boronic acid **16** to provide **26** (61%). Amine **27** was similarly prepared (36%) by the 2-fold Suzuki coupling of **16** with 2,6-diiodo-4-methylaniline.[14]

Terphenyl derivatives **24–26** were converted to their respective dibromides **30–32** in essentially quantitative yields by treatment with HBr–$CHCl_3$. Under the same



30, X = CO_2CH_3; 31, X = $CON(CH_3)_2$; 32, X = NO_2

conditions, terphenylamine **27** gave an unstable product. Accordingly, **27** was subjected to BCl_3–CH_2Cl_2 to give **34** (94%), which when treated with base gave the free amine **33**.

Terphenyl dihalides **30–32** and **34** were submitted to macroring closure with diethylene glycol under high-dilu-

(5) Koenig, K. E.; Lein, G. M.; Stückler, P.; Kaneda, T.; Cram, D. J. *J. Am. Chem. Soc.* **1979**, *101*, 3553–3566.
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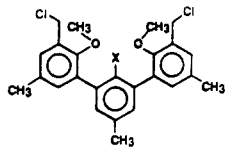
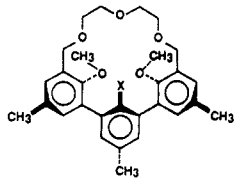


33, X = NH_2; 34, X = NH_3Cl

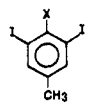
tion conditions in NaH–THF to give **2**, **1**, **6**, and **8**, re-



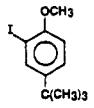
1, X = $CON(CH_3)_2$; 2, X = CO_2CH_3;
6, X = NO_2; 8, X = NH_2

spectively, in yields of 20%, 31%, 11%, and 7%. The hosts were easily isolated by reversed-phase flash chromatography[15] with NaBr–H_2O–$(CH_3)_2CO$ as the mobile phase. Aminohemispherand **8** was also produced (46%) by reduction of nitrohemispherand **6** with $NaBH_4$–10% Pd–C.[16]

The macrocyclic sulfide **11**, sulfoxide **12**, and sulfone **13** also involved a 2-fold Suzuki unsymmetrical aryl–aryl coupling reaction[9] as the critical step in their syntheses. Treatment of *p*-toluidine with ICl–AcOH gave **35** (80%),[14]



35, X = NH_2
36, X = CH_3S



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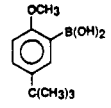

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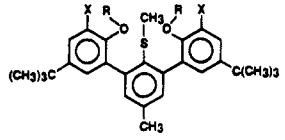
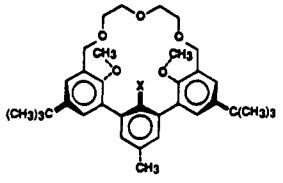
which was diazotized with isoamyl nitrite, and the corresponding diazonium compound was methiolated[17] with dimethyl disulfide to provide **36** (70%). Treatment of this diiodide with 2 mol of 2-methoxy-5-*tert*-butylbenzeneboronic acid (**38**) (prepared from **37**)[18] and $Pd(PPh_3)_4$ gave terphenyl sulfide **39** (80%). Demethylation of the two



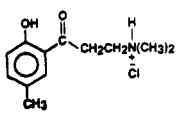
39, X = H, R = CH_3; 40, X = R = H;
41, X = CH_2OH, R = H; 42, X = CH_2OH, R = CH_3



11, X = SCH_3; 12, X = $SOCH_3$;
13, X = SO_2CH_3

methoxyl groups of **39** with BBr_3–CH_2Cl_2 gave the corresponding diphenol **40** (90%). This material was bishydroxymethylated (CH_2O, NaOH, $(CH_3)_2CHOH$) to give tetrol **41** (50%), whose two phenolic hydroxyl groups were selectively remethylated (CH_3I, NaH, THF) to provide the desired diol **42** (60%). When submitted to macroring closure with $TsO(CH_2CH_2O)_2Ts$–NaH–THF under high-dilution conditions, **42** yielded hemispherand **11** (40%). Oxidation of **11** with 1 mol of 3-$ClC_6H_4CO_3H$ in $CHCl_3$ gave sulfoxide **12** (60%), whereas with 2 mol **11** gave sulfone **13** (70%).

Hemispherands **7** and **4** containing the respective pyridine and pyridine oxide units were synthesized as follows. 2-Acetyl-4-methylphenol was submitted to the Mannich reaction ($(CH_3)_2NH_2Cl$, CH_2O, $(CH_3)_2CHOH$) to give salt **43**. Treatment of 2-(2-chloroacetyl)-4-methylphenol[19] with



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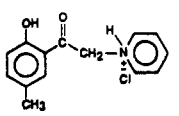

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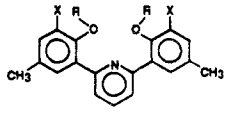
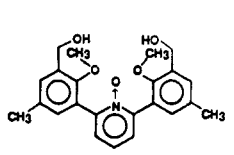
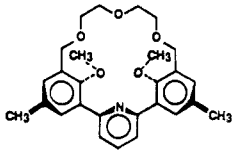


45, X = R = H; 46, X = CH_2OH, R = H;
47, X = CH_2OH, R = CH_3

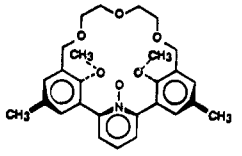
pyridine provided the second salt, **44**. These two salts together when heated with NH_4OAc–HOAc underwent the Kröhnke pyridine synthesis[20] to yield pyridine–diphenol **45** (60%). Twofold hydroxymethylation of **45** with CH_2O–KOH–$(CH_3)_2CHOH$ gave tetrol **46**, selective methylation of which with $(CH_3)_2SO_4$–K_2CO_3–$(CH_3)_2CO$ provided diol **47** (60%). When submitted to high-dilution macroring closure with $TsO(CH_2CH_2O)_2Ts$–NaH–THF, **47** gave hemispherand **7** (40%). Oxidation of **47** with 3-$ClC_6H_4CO_3H$–$CHCl_3$ provided pyridine oxide **48** (93%), macroring closure of which with $TsO(CH_2CH_2O)_2Ts$–NaH–THF gave hemispherand **4** (21%).



48

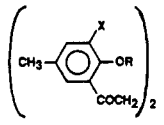


7

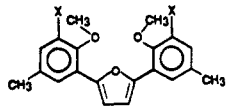


4

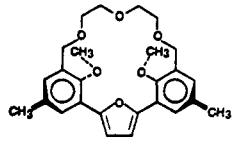
The hemispherand containing the furan unit (**9**) was prepared by a route that involved a double Fries rearrangement. The known bis(4-methylphenyl) succinate[21] (64% from succinic acid, *p*-cresol, and $POCl_3$) when heated neat with $AlCl_3$ gave diketone **49** (49%) which was bro-



49, X = R = H;
50, X = Br, R = H



51, X = Br; 52, X = CO_2Et;
53, X = CH_2OH; 54, X = CH_2Br

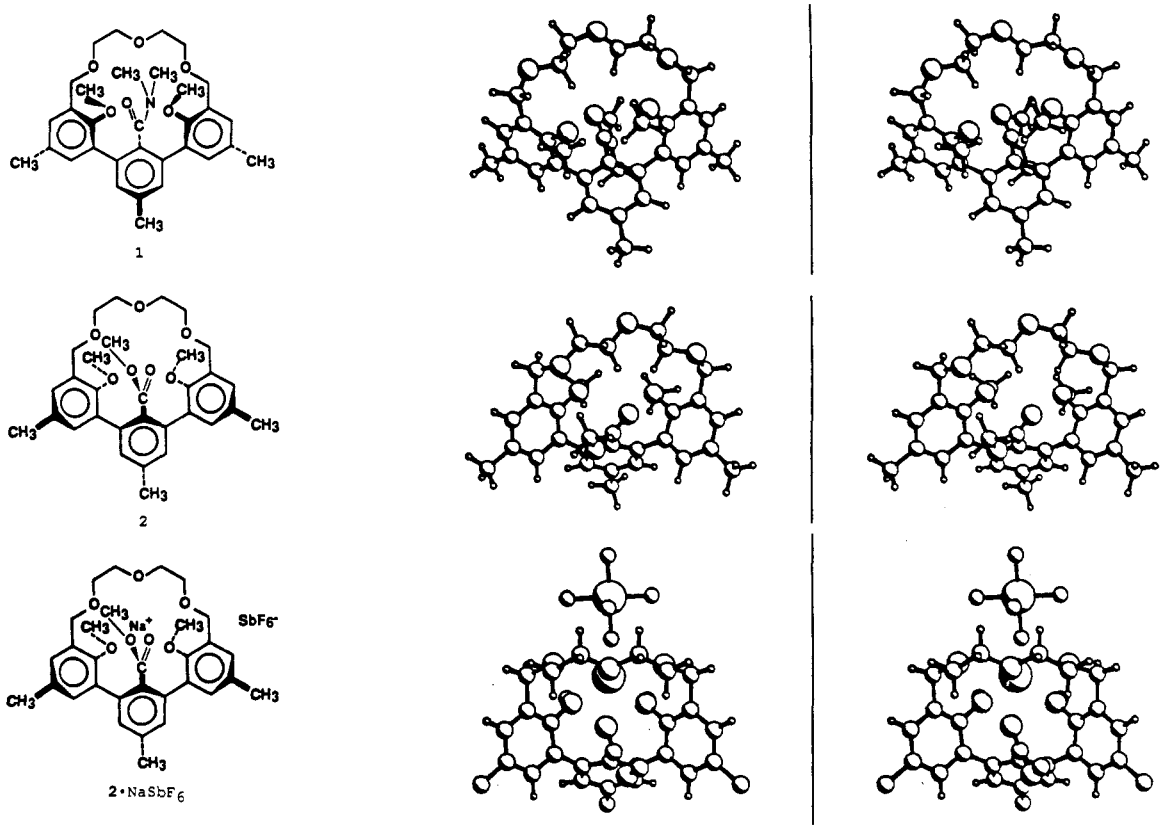


9

minated with 2,4,4,6-tetrabromocyclohexa-2,5-dienone[22]

(15) Kühler, T.; Lindsten, G. R. *J. Org. Chem.* **1983**, *48*, 3589–3591.
(16) Neilson, T.; Wood, H. C. S.; Wylie, A. G. *J. Chem. Soc.* **1962**, 371–372.
(17) Giam, C. S.; Kikukawa, K. *J. Chem. Soc., Chem. Commun.* **1980**, *756*–757.
(18) Rosenwald, R. H. *J. Am. Chem. Soc.* **1952**, *74*, 4602–4605.
(19) (a) Cullinane, N. M.; Edwards, B. F. R. *J. Appl. Chem.* **1959**, *9*,, 133–136. (b) Fries, K.; Finck, G. *Chem. Ber.* **1908**, *41*, 4271–4284.
(20) Kröhnke, F. *Synthesis* **1976**, 1–24.
(21) Thomas, F. D.; Shamma, M.; Fernelius, W. C. *J. Am. Chem. Soc.* **1958**, *80*, 5864–5867.
(22) Calo, V.; Ciminale, F.; Lopez, L.; Todesco, P. E. *J. Chem. Soc. C* **1971**, 3652–3653.

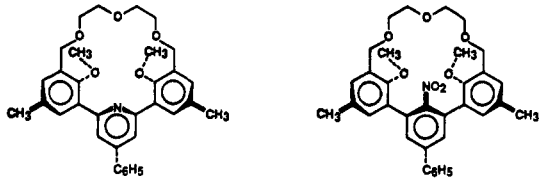
Chart I. Crystal Structure Stereoviews of Hemispherands and Hemispheraplexes



to provide dibromide–diketone **50** (88%). When treated with polyphosphoric acid in Ac_2O,[23] the furan ring was formed and the hydroxyl groups were acetylated. Without isolation, this diacetate was hydrolyzed ($NaOH–H_2O$) and the bisphenol produced (**50**) was methylated ($((CH_3)_2SO_4–NaOH$) to provide **51** (72% overall). This material was metalated with *n*-BuLi–THF, and the bisorganometallic formed was quenched with EtO_2CCl to give diester **52** (70%). Reduction of **52** with $LiAlH_4$ gave diol **53** (99%), which when mixed with $C_6H_6–PBr_3$ gave the bis(benzyl bromide) **54** (82%). This compound was cyclized by treatment under high-dilution conditions with $HO(CH_2CH_2O)_2H–NaH–THF$ to provide hemispherand **9** (32%).

Most cycles were purified by reversed-phase flash chromatography[15] with mixtures of $(CH_3)_2CO–H_2O–NaBr$ as the mobile phase. This method of purification has greatly simplified the isolation of our host compounds. The NaBr complexes usually crystallized out of the reversed-phase eluent upon evaporation of the acetone. The hemispheraplexes were easily decomplexed by washing of their CH_2Cl_2 solutions several times with distilled water. The easy decomplexation procedure reflects a large decomplexation rate.

While our work was in progress, Reinhoudt et al.[24] reported a resynthesis of **3** and a crystal structure for its larger analogue with a $CH_2O(CH_2CH_2O)_2CH_2$ bridge. They also describe hemispherand **7** containing the central pyridine group, the related hemispherand **55** and its crystal structure, and the new hemispherand **56**, closely related to our **6** containing the central arylnitro group. These authors report syntheses for **3**, **7**, **55**, and **56** with entirely different construction routes for assembling the terphenyl units than those reported here.[24]



Crystal Structures. The crystal structures of cyclic urea host **5** and **5**·$(CH_3)_3CHNH_3ClO_4$ were previously reported,[7] as were the crystal structures of **3**[25] and **3**·$(CH_3)_3CNH_3Cl_4$.[26] In the structures of both **5** and **3**, the three oxygens attached to three six-membered rings possess down–up–down arrangements and the methyl groups attached to the anisoles diverge from the cavity, which is occupied by inward-turned CH_2 groups of the $OCH_2CH_2OCH_2CH_2O$ bridge. Thus, only the conformations of the bridge require reorganization for complexation to occur. These structures differ from those of Reinhoudt et al. for the higher analogue of **3** and for **55** both of which have one OCH_3 methyl turned inward partially filling the cavity,[24] although the three heteroatoms attached to the aromatic rings possess the down–up–down arrangement.

Chart I records stereoviews of the crystal structures of amide **1**, of ester **2**, and of complex **2**·$NaSbF_6$, and Chart II, of pyridine oxide **4**, of nitro compound **6**, and of complex **6**·$NaSbF_6$. In all of the structures, the two methoxyl oxygens and the central functional group possess down–up–down conformations whose carbonyl oxygens, when present, converge on the cavity. In all six structures except that of **4**, the methyls of the anisyl oxygens diverge from

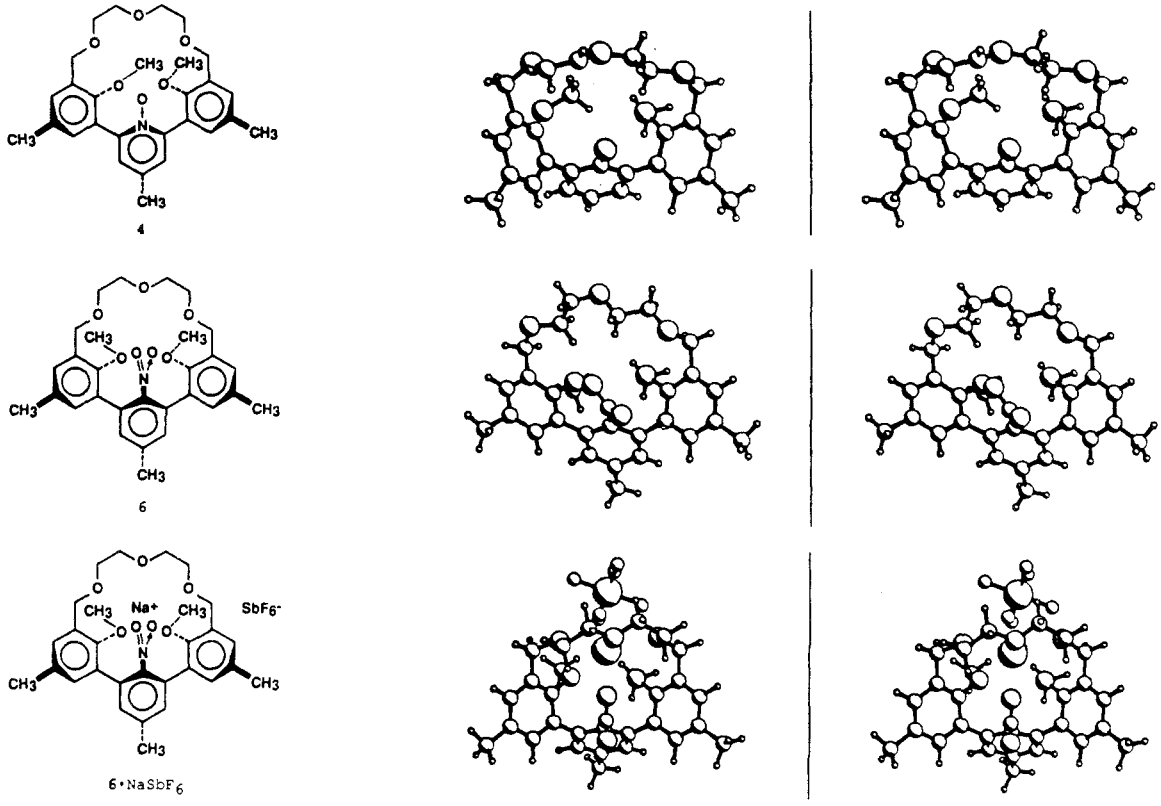
(23) Bailey, P. S.; White, H. M.; Colomb, H. O. *J. Org. Chem.* **1965**, *30*, 487–491.

(24) Dijkstra, P. J.; den Hertog, H. J., Jr.; van Steen, B. J.; Zijlstra, S.; Skowronska-Ptasinska, M.; Reinhoudt, D. N.; van Eerden, J.; Harkema, S. *J. Org. Chem.* **1987**, *52*, 2433–2442.

(25) Goldberg, I. *Acta Crystallogr.* **1980**, *B36*, 2104–2108.

(26) Cram, D. J.; Trueblood, K. N. *Top. Curr. Chem.* **1981**, *98*, 43–106.

Chart II

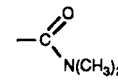
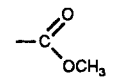
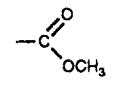
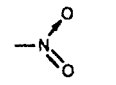
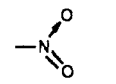


the cavity, as does the $(CH_3)_2N$ group of **1** and the CH_3O of the ester in **2** and **2**·$NaSbF_6$. The cavities of these free hemispherands are partially filled by inward-turned methylene groups of the $O(CH_2CH_2O)_2$ bridges, each of which contains two anti conformations. In the pyridine oxide system **4**, the methyl of one anisyl methoxyl is oriented inward, partially filling the cavity. The bridge of this system possesses only one anti conformation, one of whose methylenes is partially oriented inward.

In Table I are recorded the dihedral angles between the planes of the functional groups for the amide, esters, and nitro compounds and the planes of the aryls to which these functional groups are attached. Not surprisingly, the greater spacial requirement of the $(CH_3)_2N$ in **1** imposes a larger dihedral angle (71.2°) on the amide as compared to that of the CH_3O in ester **2** (44.9°). However, the intermediate dihedral angle of 49.8° is observed for the NO_2 group of **6**, whose diverging oxygen is the least space occupying. Possibly the full negative charge distributed between the two oxygens of the NO_2 provides enough repulsion for the unshared electron pairs of the flanking CH_3O groups to increase this bond angle over that for the CO_2CH_3 group, whose single carbonyl oxygen bears only a partial negative charge.

As expected, when **2** becomes complexed to form **2**·$NaSbF_6$, this dihedral angle increases by ~19° to 63.8° for the complex. A much more striking increase of ~51° to give 90° is observed when nitro compound **6** becomes complexed to form **6**·$NaSbF_6$. Two surveys of the Cambridge Crystallographic Data File have appeared and correlate the directionality of hydrogen bonds to sp^3- and sp^2-hybridized oxygen atoms.[27a,b] Ketones and esters show a strong preference for hydrogen bond formation in the direction of the orbitals of the sp^2 unshared electron pairs. Crystal structures of amides coordinated to alkaline-earth and transition-metal cations also show a preference for binding closer to the direction of an sp^2 orbital occupied by an unshared electron pair on oxygen rather than to either an sp^3 orbital or the delocalized p orbital on oxygen.

Table I. Dihedral Angles between Planes of Functional Groups and Planes of Aryls to Which They Are Attached

compd		angle, deg
1		71.2
2		44.9
2·$NaSbF_6$		63.8
6		49.8
6·$NaSbF_6$		90.0

In Table II are listed the $O\cdots Na^+$ binding distances and $C{-}O\cdots Na^+$, $C{=}O\cdots Na^+$, and $N{\rightarrow}O\cdots Na^+$ binding angles in 2·$NaSbF_6$ and **6**·$NaSbF_6$. The $C{=}O\cdots Na^+$ binding angle in 2·$NaSbF_6$ is 133°, whereas the ester–benzene dihedral angle is 63.8°. The C=O bond distance in 2·$NaSbF_6$ is 1.197 (5) Å, which is close to a recently measured distance of 1.21 Å for esters.[27c] These facts are consistent with the ligation occurring roughly in the direction of sp^2 orbitals of unshared electron pairs on oxygen, adjusted somewhat to the constraints of the ring systems.

The $N{\rightarrow}O\cdots Na^+$ binding angle in **6**·$NaSbF_6$ is 140°, whereas the dihedral angle between the planes of the nitro

(27) (a) Taylor, R.; Kennard, O.; Versichel, W. *J. Am. Chem. Soc.* **1983**, *105*, 5761–5766. (b) Murray-Rust, P.; Glusker, J. P. *Ibid.* **1984**, *106*, 1018–1025. (c) In recently determined structures of $C_6H_5CO_2CH_3$ and $C_6H_5CO_2C_2H_5$, the C=O distances are 1.217 (8) and 1.207 (5) Å.

Table II. Sodium Ion to Ligating Oxygen Distances and Binding Angles

	ligating oxygen			
complex	clock posn[a]	ligand type	dist to Na^+, Å	angle L–O···Na^+, deg
2·$NaSbF_6$	12	$(CH_2CH_2)_2O$	2.40	115, 116
	2	$ArCH_2(CH_2)O$	2.55	122, 109
	4	$Ar(CH_3)O$	2.54	118, 127
	6	$Ar(CH_3O)C{=}O$	2.34	133
	8	$Ar(CH_3)O$	2.46	117, 128
	10	$ArCH_2(CH_2)O$	2.58	107, 121
6·$NaSbF_6$	12	$(CH_2CH_2)_2O$	2.38	119, 114
	2	$ArCH_2(CH_2)O$	2.54	111, 122
	4	$Ar(CH_3)O$	2.46	116, 129
	6	$ArNO_2$	2.43	140
	8	$Ar(CH_3)O$	2.43	124, 121
	10	$ArCH_2(CH_2)O$	2.62	124, 106

[a] See drawings of Chart I.

and its attached benzene is 90°. The N=O distance for the nonligating oxygen is 1.218 (7) Å, nearly the same as the N→O distance for the ligating oxygen of 1.204 (7) Å in 6·$NaSbF_6$. The N→O distances in the free host (6) are 1.207 (9) and 1.223 (9) Å, not far from one another. These facts are consistent with the Na^+ in 6·$NaSbF_6$ ligating with an sp^3 electron pair on oxygen carrying more than half of a formal negative charge.

The van der Waals radius of oxygen is 1.40 Å, and the ionic radius of Na^+ is 1.02 Å[28], the sum being 2.42 Å. Most of the O···Na^+ distances in Table II are close to, or greater than, this value except for the C=O···Na^+ value of 2.34 Å in 2·$NaSbF_6$. This shortened distance implies this carbonyl provides a stronger binding site and greater s character in the coordinating sp^2-hydridized orbitals on oxygen of the carbonyl group. The N→O···Na^+ distance in 6·$NaSbF_6$ is 2.43 Å, which correlates with the higher p character of the sp^3-hydridized orbitals on this coordinating oxygen. The distances for the R_2O···Na^+ vary between a low of 2.38 to a high of 2.62 Å, while those for $Ar(CH_3)O$···Na^+ vary from 2.43 to 2.54, the averages for the two types of ether coordination being 2.51 and 2.47 Å, respectively. Although these values are close together, the aryl ether coordinating orbital electrons at oxygen may be slightly richer in s character than the aliphatic ether coordinating electrons. The ether oxygen binding angles (L-O···Na^+) of Table II range from 106° to 124°, to provide an average of 116°. The four ArO···Na^+ binding angles vary only from 116° to 124° in the two complexes, and the CH_3O···Na^+ binding angles are also similar to one another, ranging only from 121° to 129°.

Association Constants and Binding Free Energies. The association constants (K_a, M^{-1}) and binding free energies ($-\Delta G°$, kcal mol^{-1}) were determined at 25 °C by distributing Li^+, Na^+, K^+, Rb^+, Cs^+, NH_4^+, $CH_3NH_3^+$, and $(CH_3)_3CNH_3^+$ picrate salts between D_2O and $CDCl_3$ solutions of the hosts.[5,29,30] The results are recorded in Table III, which include those reported earlier for 3,[5] 5,[7a] and 10.[8] The values recorded are the averages of two determinations.

Correlations between Structure and Binding. Hosts 1–13 range in their $-\Delta G°$ values from <6 to 15.1 kcal mol^{-1} in binding the eight cations. Three hosts, pyridine 7, furan 9, and phenol 10, gave peak binding with K^+, but the other 10 gave their highest $-\Delta G°$ values with Na^+. The 18-membered macroring and two anisyl units common to all 13 hosts seem generally responsible for their complementarity to Na^+. Even for 7, 9, and 10, the $-\Delta G°$ values for K^+ and Na^+ are within experimental error of one another.

The character of the central A functional group strongly affects the binding power of the hemispherand toward most of the guests. The most strongly binding host contains the 4-$CH_3C_6H_2CON(CH_3)_2$ group providing $-\Delta G°$ values that range from 15.1 kcal mol^{-1} for Na^+ to 8.6 for $CH_3NH_3^+$. The hosts containing the 4-$CH_3C_6H_2CO_2CH_3$, 4-$CH_3C_6H_2OCH_3$, pyridine oxide, and cyclic urea groups show comparable binding toward Li^+, Na^+, and K^+, but the $-\Delta G°$ values for the ester binding the larger ions drop off much more sharply than do the others, presumably because the carbonyl group of the ester penetrates more deeply into the cavity than do the oxygens of the other three groups. The intrinsically powerful binding power of the $CON(CH_3)_2$ group toward all cations appears to compensate for its even greater steric requirements than that of the CO_2CH_3. The carbonyl oxygen of an amide possesses higher electron density than that of an ester. Thus, the dipole moment of methyl benzoate is 1.85 D,[31] whereas that of benzamide is 3.6 D.[32]

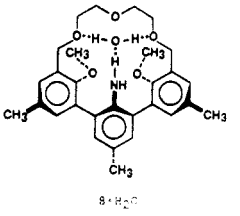
Host 6 containing the $CH_3C_6H_2NO_2$ group is a moderately strong but not very discriminating binding system, with $-\Delta G°$ values that range from 11.0 (for Na^+) to <6 kcal mol^{-1} for $(CH_3)_3CNH_3^+$. The $-\Delta G°$ values for 6 closely resemble those observed by Reinhoudt for 56,[24] whose structure differs from 6 only by the substitution of a C_6H_5 in 56 for the CH_3 of 6 in the position para to the nitro group. The profiles of $-\Delta G°$ values for 6 and 3 (A = $CH_3C_6H_2OCH_3$) binding the eight cations are quite similar, except that those of 3 exceed those of 6 by about 1 kcal mol^{-1}.

The hemispherand containing the pyridyl (7) and furan groups (9) potentially have the largest cavities. These hosts exhibit a low spread in $-\Delta G°$ values with changes in guests, while 7 is the much better general binder by several kilocalories per mole for all ions. Pyridyl system 7 is the strongest binding host among the 13 systems for the largest cations, Rb^+, Cs^+, NH_4^+, $CH_3NH_3^+$, and $(CH_3)_3CNH_3^+$, providing $-\Delta G°$ values that range from 9.7 to 11.7 kcal mol^{-1}. The low binding power of 9 ($-\Delta G°$ value range, 9.2–<6 kcal mol^{-1}) correlates with that for the furan-containing corands examined previously.[33] The fact that the $-\Delta G°$ values reported by Reinhoudt[24] for pyridyl system 7 binding Li^+, Na^+, K^+, Rb^+, and Cs^+ picrates at 25 °C saturated with water differ from ours by an average of only 0.16 kcal mol^{-1} is gratifying (those for 7 binding NH_4^+, $CH_3NH_3^+$, and $(CH_3)_3CNH_3^+$ were not reported).[24]

Hemispherands 8 containing the 4-$CH_3C_6H_2NH_2$ and 10 the 4-$CH_3C_6H_2OH$ groups are the weakest binders among the 13 hosts, with a total range of $-\Delta G°$ values of 9.3–<6 kcal mol^{-1}. The amino and hydroxyl groups in these hosts are both good donating and accepting groups for the hydrogen bonds of the water present in the assays. The aniline-containing host 8 held onto water tenaciously in the solid state, as shown by carbon and hydrogen elemental analysis data. Most of the hosts reported here were obtained free of water by heating the samples to 80–100 °C under high vacuum. When dried under high vacuum 8 at

(28) Waser, J.; Trueblood, K. N.; Knobler, C. M. *Chem One*; McGraw-Hill: New York, 1976; p 283.
(29) Helgeson, R. C.; Weisman, G. R.; Toner, J. L.; Tarnowski, T. L.; Chao, Y.; Mayer, J. M.; Cram, D. J. *J. Am. Chem. Soc.* **1979**, *101*, 4928–4941.
(30) Ericson, J. Ph.D. Dissertation, Department of Chemistry and Biochemistry, University of California, Los Angeles, 1988.
(31) Gordon, A. J.; Ford, R. A. *The Chemist's Companion*; Wiley: New York, 1972; p 127.
(32) *CRC*, 64th ed.; Weast, R. C., Ed.; CRC Press: Boca Raton, FL, 1983.
(33) Timko, J. M.; Moore, S. S.; Walba, D. M.; Hiberty, P. C.; Cram, D. J. *J. Am. Chem. Soc.* **1977**, *99*, 4207–4219.

25 and 110 °C retained 0.5 mol of water, which decreased to 0.25 mol of water at 150 °C and to 0 only at 180 °C. In CPK models, 1 mol of water is beautifully complementary to the cavity of **8**, as is pictured in **8**·H_2O. The low binding power of **8** and **10** is probably associated with the increased energy cost of displacing water associated with the hydrogen bond donating ability of the respective NH_2 and OH groups.



Sulfide **11** with the central 4-$CH_3C_6H_2SCH_3$ group shows a binding profile toward the eight cations very similar to that of **3** with the central 4-$CH_3C_6H_2OCH_3$ unit except that the latter is the stronger binder by an average of ~1.4 kcal mol^{-1} in $-\Delta G°$ value. Since the cavities of **11** and **3** have similar shapes and sizes, shape and size appear associated with the patterns of specificity, while the one softer sulfur-ligating atom of **11** binds the relatively hard alkali metal and hydrogen binding RNH_3^+ guests less well than the hard oxygen atom of **3**.

The hosts containing the central sulfoxide $CH_3C_6H_2S$-OCH_3 (**12**) and sulfone 4-$CH_3C_6H_2SO_2CH_3$ units (**13**) provide the highest specificity for Na^+ of any of the systems treated here. Thus, sulfoxide **12** binds Na^+ with 11.4 kcal mol^{-1}, Li^+ with 7.7 kcal mol^{-1}, K^+ with only 7.6 kcal mol^{-1}, and the other cations with even lower $-\Delta G°$ values. These values translate into $K_a^{Na^+}/K_a^{Li^+}$ = 500 and $K_a^{Na^+}/K_a^{K^+}$ = 650 for **12**. Sulfone **13** binds Na^+ with 9.5 kcal mol^{-1}, Li^+ with 6.7 kcal mol^{-1}, K^+ with 6.3 kcal mol^{-1}, Rb^+ with 6.6 kcal mol^{-1}, and the rest of the ions with 6 kcal mol^{-1}. Thus, **13** gives $K_a^{Na^+}/K_a^{Li^+}$ = 110 and $K_a^{Na^+}/K_a^{K^+}$ = 220. Unlike the sulfoxide unit,[34] the sulfone is a notoriously weak ligand for hydrogen bonds and metal cations. The poor intrinsic binding power coupled with the large steric requirements of the SO_2CH_3 group are responsible for **13** ranking fourth from the bottom in $-\Delta G°$ values among the 13 hosts of Table III. The rapid equilibrations of free hemispherand with hemispheraplexes coupled with the high specificity of sulfoxide **12** and sulfone **13** for Na^+ over Li^+, K^+, and NH_4^+ might make them and their analogues useful in sodium assays of body fluids.

Experimental Section

General Procedures. All air-sensitive reactions were performed under a N_2 atmosphere in glassware oven-dried for at least 6 h at 150 °C. For cyclizations, the oven-dried glassware was assembled under a flow of N_2 and flame-dried. All compounds were dried according to the procedure providing a correct C and H analysis prior to any further synthetic manipulations and before determining association constants. Tetrahydrofuran (THF) and Et_2O were freshly distilled from benzophenone ketyl. Benzene was dried over 3-Å sieves. Gravity column chromatography was performed on E. Merck silica gel 60 (70–230 mesh). Silica thin-layer chromatography was done on E. Merck plastic or aluminum-backed plates (silica gel 60, F_{254}, 0.2 mm). Reversed-phase chromatography was performed on the support described by Kühler and Lindsten.[15] Reversed-phase thin-layer chromatography was done on Whatman 0.2-mm $KC_{18}F$ octadecylsilane-bonded coated glass plates. Gel permeation chromatography was performed on a 20 ft × 0.375 in. (outer diameter) column packed with 200 g of 100-Å Styragel (Waters Associates) with CH_2Cl_2 as the mobile phase with flow rates of 3.5–4.0 mL/min. All melting points are uncorrected. FAB mass spectra were determined with *m*-nitrobenzyl alcohol (NOBA) as the matrix.

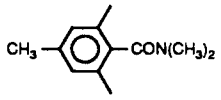
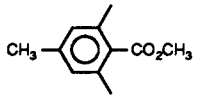
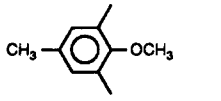
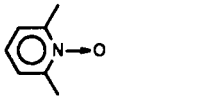
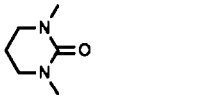
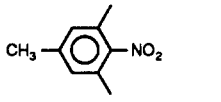
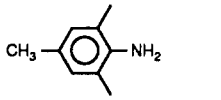
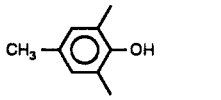
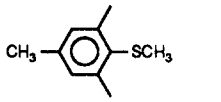
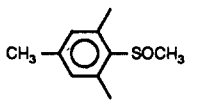
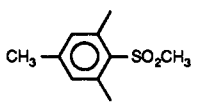
2-Bromo-6-(methoxymethyl)-4-methylanisole (15). A solution of 2-bromo-6-(hydroxymethyl)-4-methylphenol[10] (**14**; 6.4 g, 29 mmol) in 125 mL of THF was stirred. Sodium hydride (3 g, 50% oil dispersion) was washed with pentane several times in a fritted glass funnel and added to the above solution. After H_2 gas evolution subsided, 11.4 mL (120 mmol) of $(CH_3)_2SO_4$ was added. The mixture was stirred overnight, and ammonium hydroxide was added. (*Caution*: gas evolution!) The THF was evaporated under reduced pressure, and the residue was extracted with ether and water. The organic layer was washed with brine, dried ($MgSO_4$), and evaporated to give 6.9 g (93%) of **15** as a pale yellow liquid: R_f (silica gel, CH_2Cl_2) 0.7; ^1H NMR (200 MHz, $CDCl_3$) δ 2.29 (s, 3 H, $ArCH_3$), 3.42 (s, 3 H, OCH_3), 3.82 (s, 3 H, OCH_3), 4.48 (s, 2 H, CH_2OMe), 7.14 (s, 1 H, ArH), 7.31 (s, 1 H, ArH); MS (EI, 70 eV), Br isotope pattern at *m/e* 244 (93%, M^+), 246 (93%, M^+). Anal. (dried at 25 °C, 10^{-5} Torr, 5 h) Calcd for $C_{10}H_{13}BrO_2$: C, 49.00, H, 5.35. Found: C, 49.04; H, 5.43.

1,1′:3′,1″-Terphenyl-2′-carboxylic Acid, 2,2″-Dimethoxy-3,3″-bis(methoxymethyl)-5,5′,5″-trimethyl-, Methyl Ester (24). The aryl bromide **15** (9.8 g, 40 mmol) was dissolved in 250 mL of dry benzene that was distilled to remove water. After the mixture was cooled to 25 °C, 250 mL of THF was added. The flask was cooled to −78 °C, and 19.1 mL (44 mmol) of a 2.3 M solution of *n*-butyllithium in *n*-hexane was added. In a separate flask, 20 mL (180 mmol) of $(CH_3O)_3B$ was added to 100 mL of THF and the mixture was cooled to −78 °C. After the mixture was stirred 10 min, the lithiate was cannulated into the $(CH_3O)_3B$ solution and the resulting mixture was slowly warmed to 25 °C. Water was carefully added to destroy excess *n*-butyllithium. The THF was evaporated under reduced pressure and the residue shaken with Et_2O and water. The aqueous layer was extracted twice with Et_2O. The organic layers were combined and washed three times with aqueous 3 M NaOH. The basic layer was acidified and extracted twice with Et_2O. This organic layer was washed with brine, dried ($MgSO_4$), and evaporated to give 7.3 g (86%) of the boronic acid **16** as a waxy solid: ^1H NMR (200 MHz, $(CD_3)_2SO$ and ca. 10% D_2O) δ 2.27 (s, 3 H, $ArCH_3$), 3.33 (s, 3 H, OCH_3), 3.71 (s, 3 H, OCH_3), 4.41 (s, 2 H, $ArCH_2OMe$), 7.21 (s, 1 H, ArH), 7.29 (s, 1 H, ArH). Dibromo acid **20** was prepared as before[13] and converted to its known ester **21** whose physical properties matched those already reported.[13] Dibromo ester **21** (2.1 g, 7 mmol) was dissolved in 50 mL of benzene, and 25 mL of 2 M aqueous Na_2CO_3 was added. Boronic acid **16** (3.7 g, 18 mmol) was dissolved in a minimum amount of 95% EtOH and the mixture added to the benzene–water mixture. The catalyst, $Pd(PPh_3)_4$ (30 mg), was added, and the mixture was refluxed with vigorous stirring for 36 h. After cooling, the layers were separated and the organic layer was dried ($MgSO_4$), concentrated, and chromatographed on 250 mL of silica gel. The polarity of the mobile phase was increased from CH_2Cl_2 to 2.5% EtOAc and finally to 5% EtOAc. The fractions corresponding to the product were combined, and the solvent was evaporated to give 2.5 g (71%) of **24** isolated as an oil: R_f (silica gel, CH_2Cl_2) 0.2; ^1H NMR (500 MHz, $CDCl_3$) δ 2.30 (s, 6 H, $ArCH_3$), 2.41 (s, 3 H, $ArCH_3$), 3.31 (s, 3 H, $ArCO_2CH_3$), 3.43–3.44 (overlapping s, 12 H, $ArOCH_3$, $ArCH_2OCH_3$) 4.51 (br s, 4 H, $ArCH_2OMe$), 6.97 (s, 2 H, ArH), 7.18 (s, 2 H, ArH), 7.23 (s, 2 H, ArH); IR ($CDCl_3$) 1745 cm^{-1}; MS (EI, 70 eV) *m/e* 478 (68%, M^+). Anal. (dried at 110 °C, 10^{-5} Torr, 3 h) Calcd for $C_{29}H_{34}O_6$: C, 72.78; H, 7.16. Found: C, 72.61; H, 7.00.

1,1′:3′,1″-Terphenyl-2′-carboxylic Acid, 3,3′-Bis(bromomethyl)-2,2″-dimethoxy-5,5,5″-trimethyl-, Methyl Ester (30). Compound **24** (1.0 g, 2.1 mmol) was dissolved in 100 mL of $CHCl_3$, and HBr was bubbled through the solution for 15 min. Water was added, and the layers were separated. The organic layer was dried ($MgSO_4$), filtered, and evaporated to give **30**: 1.25 g (>90%) as a foam; R_f (silica gel, CH_2Cl_2) 0.5; ^1H NMR (200 MHz, $CDCl_3$) δ 2.30 (s, 6 H, $ArCH_3$), 2.43 (s, 3 H, $ArCH_3$), 3.35 (s, 3 H, $ArCO_2CH_3$), 3.51 (s, 6 H, $ArOCH_3$), 4.58 (s, 4 H, $ArCH_2Br$), 6.99 (s, 2 H, ArH), 7.17 (s, 2 H, ArH), 7.25 (s, integration obscured by residual protons in $CDCl_3$, ArH); MS (EI, 70 eV) Br_2 isotope pattern centered at *m/e* 576 (33%, M^+). Anal. (dried at 110 °C,

(34) Joesten, M. D.; Schaad, L. J. *Hydrogen Bonding*; Marcel Dekker: New York, 1974; pp 309–335.

Table III. Association Constants (K_a, M^{-1}) and Binding Free Energies ($-\Delta G°$, kcal mol^{-1}) of Hosts for Picrate Salt Guests at 25 °C in $CDCl_3$ Saturated with D_2O

host			guest cation							
no.	central A group[a]		Li^+	Na^+	K^+	Rb^+	Cs^+	NH_4^+	$MeNH_3^+$	t-$BuNH_3^+$
1		$-\Delta G°$	11.7[b]	15.1[b]	12.9[b]	10.8[b]	9.1	9.8	8.6	8.9
		K_a	4.0×10^8	1.2×10^{11}	2.7×10^9	7.8×10^7	5.4×10^6	1.6×10^7	2.1×10^6	4.0×10^6
2		$-\Delta G°$	7.2	12.4[b]	10.9[b]	8.4	6.9	7.8	6.4	<6
		K_a	1.9×10^5	1.1×10^9	9.8×10^7	1.4×10^6	1.1×10^5	5.3×10^5	5.5×10^4	$<2 \times 10^4$
3		$-\Delta G°$	7.0	12.2	11.8	10.5	9.0	9.9	8.2	7.7
		K_a	1.3×10^5	9.2×10^8	4.6×10^8	4.6×10^7	3.7×10^6	1.5×10^7	9.9×10^5	4.2×10^5
4		$-\Delta G°$	6.8	12.2	11.9	10.1	8.8	9.5	9.1	9.9
		K_a	9.5×10^4	8.3×10^8	4.9×10^8	2.3×10^7	2.7×10^6	8.7×10^6	4.3×10^6	1.8×10^7
5		$-\Delta G°$	6.7	12.0	11.3	9.9	8.7	9.3	9.1	9.5
		K_a	8.1×10^4	6.1×10^8	1.9×10^8	1.8×10^7	2.4×10^6	6.5×10^6	4.6×10^6	9.1×10^6
6		$-\Delta G°$	7.1	11.0	10.6[b]	9.1	7.8	8.3	7.0	<6
		K_a	1.6×10^5	1.1×10^8	7.0×10^7	3.6×10^6	5.8×10^5	1.2×10^6	1.5×10^5	$<2 \times 10^4$
7		$-\Delta G°$	7.2	10.8	10.9	10.1	9.7	10.8	11.1	11.7[b]
		K_a	1.7×10^5	8.8×10^7	9.0×10^7	2.3×10^7	1.2×10^7	8.2×10^7	1.3×10^8	3.9×10^8
8		$-\Delta G°$	6.9	9.3	9.0	7.8	7.2	7.4	6.6	
		K_a	1.9×10^5	6.4×10^6	4.0×10^6	6.0×10^5	2.2×10^5	2.6×10^5	6.9×10^4	
9		$-\Delta G°$	<6	8.9	9.2	8.2	7.4	7.5	6.8	6.8
		K_a	$<2 \times 10^4$	3.3×10^6	5.5×10^6	1.0×10^6	2.6×10^5	3.1×10^5	9.5×10^4	9.5×10^4
10		$-\Delta G°$	6.8	7.9	8.0	6.7	6.7	6.4	<6	<6
		K_a	6.0×10^4	6.3×10^5	7.2×10^5	9.8×10^4	6.2×10^4	4.9×10^4	$<2 \times 10^4$	$<2 \times 10^4$
11		$-\Delta G°$	<6	10.8	10.5	8.8	7.8	8.3	7.3	6.0
		K_a	$<2 \times 10^4$	8.1×10^7	3.0×10^7	2.8×10^6	5.2×10^5	1.2×10^6	2.2×10^5	2.5×10^4
12		$-\Delta G°$	7.7	11.4	7.6	7.1	<6	6.6	<6	<6
		K_a	4.4×10^5	2.2×10^8	3.4×10^5	1.6×10^5	$<2 \times 10^4$	6.8×10^4	$<2 \times 10^4$	$<2 \times 10^4$
13		$-\Delta G°$	6.7	9.5	6.3	6.6	<6	<6	<6	<6
		K_a	8.1×10^4	9.1×10^6	4.1×10^4	6.8×10^4	$<2 \times 10^4$	$<2 \times 10^4$	$<2 \times 10^4$	$<2 \times 10^4$

[a] In compound family I. [b] Determined at 10^{-3} M concentration scale for both host and guest. All other determinations were made at 10^{-2} M concentrations.

10^{-5} Torr, 3 h) Calcd for $C_{27}H_{28}Br_2O_4$: C, 56.27; H, 4.90. Found: C, 56.37; H, 4.82.

13,16,19-Trioxatetracyclo[19.3.1.1^{2,6}.1^{7,11}]heptacosa-1(25),2,4,6(27),7,9,11(26),21,23-nonaene-27-carboxylic Acid, 25,26-Dimethoxy-4,9,23-trimethyl-, Methyl Ester (2). Bis(benzyl bromide) **30** (1.14 g, 2 mmol) and dry diethylene glycol (0.18 mL, 1.9 mmol) were dissolved in 70 mL of THF, and the mixture was stirred vigorously. Sodium hydride (0.6 g, 50% oil dispersion, 12 mmol) was added, and the mixture was refluxed for 5 h. After the mixture was cooled to 25 °C, water was added. The THF was evaporated, and the mixture was extracted with CH_2Cl_2 and water. The organic layer was concentrated, preabsorbed on 15 mL of reversed-phase silica gel, and flash chromatographed through an additional 70 mL of this support with 3% (w/v) NaBr in 3:2 acetone–water as the mobile phase. Fractions corresponding to the product were combined, and the volume was reduced. Methylene chloride was added, and the layers were separated. The CH_2Cl_2 layer was washed four times with distilled water. Crystallization from acetone–water afforded 0.10 g (10%) of cycle **2** from the first crop. The second crop, which yielded crystals suitable for X-ray analysis, was ca. 10%: mp 168–170 °C; R_f (reversed-phase silica gel, 1% wt/v NaBr in 7:3 acetone–water) 0.7; ^1H NMR (500 MHz, $CDCl_3$) δ 2.32 (s, 6 H, $ArCH_3$), 2.50 (s, 3 H, $ArCH_3$), 2.97 (s, 3 H, $ArCO_2CH_3$), 3.30 (s, 6 H, $ArOCH_3$), 3.60–3.69 (m, 6 H, $-CH_2O-$), 3.81–3.84 (m, 2 H, $-CH_2O-$), 4.39 (d, 2 H, $ArCH_2O-$, J = 11.5 Hz), 4.61 (d, 2 H, $ArCH_2O-$, J = 11.5 Hz), 7.01 (s, 2 H, ArH), 7.09 (s, 2 H, ArH), 7.29 (s, 2 H, ArH); MS (FABS, NOBA) m/e 543 (100%, M + Na^+),

520 (14%, M^+). Anal. (dried at 110 °C, 10^{-5} Torr, 3 h) Calcd for $C_{31}H_{36}O_7$: C, 71.52; H, 6.97. Found: C, 71.21; H, 7.35.

2,6-Dibromo-*N*,*N*,4-trimethylbenzamide (22). The acid chloride of 2,6-dibromo-4-methylbenzoic acid (**20**)[13] was prepared by the standard thionyl chloride method. This material (2.7 g, 9.2 mmol) was dissolved in 50 mL of THF, and 9 mL of dimethylamine was added. The solvent was evaporated and the residue extracted with ether and water. The organic layer was washed with 3 M NaOH and brine and dried ($MgSO_4$). The volume was reduced in vacuo to give 2.9 g (97%) of amide (**22**) as a brown oil: IR ($CDCl_3$) 1680 cm^{-1}; R_f (silica gel, 17:3 CH_2CH_2–EtOAc) 0.5; ^1H NMR (200 MHz, $CDCl_3$) δ 2.32 (s, 3 H, $ArCH_3$), 2.86 (s, 3 H, $CON(CH_3)_2$, 3.15 (s, 3 H, $CON(CH_3)_2$, 7.35 (s, 2 H, ArH); MS (EI, 70 eV) 1:2:1 Br_2 isotope pattern centered at m/e 321 (18%, M^+), 277 (100%, $M^+ - NMe_2$). Anal. (dried at 80 °C, 10^{-5} Torr, 3 h) Calcd for $C_{10}H_{11}Br_2NO$: C, 37.42; H, 3.45. Found: C, 37.46; H, 3.43%.

1,1′:3′,1″-Terphenyl-2′-carboxamide, 2,2″-Dimethoxy-3,3″-bis(methoxymethyl)-*N*,*N*,5,5′,5″-pentamethyl- (25). The 2,6-dibromo amide **22** (2.8 g, 8.8 mmol) was dissolved in 60 mL of benzene, and 25 mL of 2 M Na_2CO_3 was added with vigorous stirring. The boronic acid **16** (5.5 g, 26 mmol) was dissolved in 95% EtOH and the resultant mixture added to the above mixture along with 10 mg of $Pd(PPh_3)_4$. The reaction was refluxed for 24 h, during which time more boronic acid and catalyst were added. The layers were separated, and the organic layer was evaporated in vacuo. To obtain analytically pure material, the residue was submitted to reversed-phase silica gel flash chromatography, with 1% (w/v) NaBr in 4:1 methanol–water as the mobile phase, followed by silica gel chromatography (15–20% EtOAc in CH_2Cl_2) to yield **25** as a foam. The bulk of the material was chromatographed on silica gel (1–5% methanol in CH_2Cl_2), and this impure material was used directly in the next step. The pure sample of **25** gave the following: R_f (silica gel, 4:1 CH_2Cl_2–EtOAc) 0.2; ^1H NMR (200 MHz, $CDCl_3$) δ 2.28 (s, 6 H, $ArCH_3$), 2.41 (s, 3 H, $ArCH_3$), 2.57 (s, 3 H, $CON(CH_3)_2$, 2.63 (s, 3 H, $CON(CH_3)_2$), 3.44 (s, 6 H, OCH_3), 3.55 (s, 6 H, OCH_3), 4.51 (s, 4 H, $ArCH_2OMe$), 6.98 (s, 2 H, ArH), 7.17 (s, 2 H, ArH) (one aryl proton is obscured by the residual proton of the solvent); MS (EI, 70 eV) m/e 491 (80%, M^+), 460 (70%, $M^+ - OMe$). Anal. (dried at 80 °C, 10^{-5} Torr, 3 h) Calcd for $C_{30}H_{37}NO_5$: C, 73.29; H, 7.59. Found: C, 73.18; H, 7.66.

1,1′:3′,1″-Terphenyl-2′-carboxamide, 3,3″-Bis(bromomethyl)-2,2″-dimethoxy-*N*,*N*,5,5′,5″-pentamethyl- (31). The impure **25** described above was dissolved in $CHCl_3$, and HBr was bubbled through for 20 min. Water was added, and the layers were separated. The organic layer was dried ($MgSO_4$), concentrated, and flash chromatographed (medium pressure) on silica gel (10% EtOAc in CH_2Cl_2). The bis(benzyl bromide) **31** was isolated as a foam: 0.140 g (16% overall); R_f (silica gel, 4:1 CH_2Cl_2–EtOAc) 0.6; ^1H NMR (200 MHz, $CDCl_3$) δ 2.27 (s, 6 H, $ArCH_3$), 2.43 (s, 3 H, $ArCH_3$), 2.59 (s, 3 H, $CON(CH_3)_2$), 2.61 (s, 3 H, $CON(CH_3)_2$), 3.61 (s, 6 H, $ArOCH_3$), 4.54, 4.60 (q, 4 H, $ArCH_2Br$), 7.00 (br s, 2 H, ArH), 7.16 (s, 2 H, ArH), 7.29 (s, 2 H, ArH); MS (FABS, NOBA) 1:2:1 Br_2 isotope pattern centered at m/e 590 (100% $M + H^+$). Anal. (dried at 110 °C, 10^{-5} Torr, 3 h) Calcd for $C_{28}H_{31}Br_2NO_3$: C, 57.06; H, 5.30. Found: C, 56.96; H, 5.26.

13,16,19-Trioxatetracyclo[19.3.1.1^{2,6}.1^{7,11}]heptacosa-1(25),2,4,6(27),7,9,11(26),21,23-nonaene-27-carboxamide, 25,26-Dimethoxy-*N*,*N*,4,9,23-pentamethyl- (1). A suspension of NaH (130 mg, 60% oil dispersion) in 300 mL of THF was refluxed. The bis(benzyl bromide) **31** (0.28 g, 0.47 mmol) and dry diethylene glycol (45 mL, 0.47 mmol) were dissolved in 50 mL of THF, and the resultant mixture was added to the sodium glycoxide solution over 10 h from a constant-rate addition funnel. After the mixture was refluxed for an additional 5 h, water was added and the THF was removed in vacuo. The residue was extracted with CH_2Cl_2. The organic layer was concentrated, preabsorbed on 10 mL of reversed-phase silica gel, and flash chromatographed through an additional 50 mL of this support, with 1% (w/v) NaBr in 1:1 acetone–water as the mobile phase. The fractions corresponding to the product were combined, and the acetone was evaporated. Methylene chloride was added, and the layers were separated. The organic layer was washed five times with distilled water. Evaporation of the CH_2Cl_2 gave 77 mg (31%) of cycle **1** isolated as a solid: mp 153–155 °C; R_f (reversed-phase silica gel, 1% w/v NaBr in 3:2 acetone–water) 0.3; ^1H NMR (200 MHz, $CDCl_3$) δ 2.21 (s, 3 H, $ArCH_3$), 2.27 (s, 6 H, $ArCH_3$), 2.45 (s, 3 H, $CON(CH_3)_2$), 2.51 (s, 3 H, $CON(CH_3)_2$), 3.36 (s, 6 H, $ArOCH_3$), 3.35–3.70 (m, 8 H, $-OCH_2CH_2O-$), 4.25 (d, 2 H, $ArCH_2O-$, J = 11.8 Hz), 4.70 (d, 2 H, $ArCH_2O-$, J = 11.8 Hz), 6.94 (s, 2 H, ArH), 6.99 (s, 2 H, ArH), 7.28 (s, 2 H, ArH); MS (FABS, NOBA) m/e 556 (100%, $M + Na^+$), 534 (81%, $M + H^+$). Anal. (dried at 80 °C, 10^{-5} Torr, 6 h) Calcd for $C_{32}H_{39}NO_6$: C, 72.02; H, 7.37. Found: C, 72.26; H, 7.61.

2,6-Dibromo-4-methylnitrobenzene (23). The following is a modification of a literature procedure.[35] A suspension of 2,6-dibromo-4-methylaniline (**17**) (50 g, 190 mmol) in 360 mL of glacial AcOH was added to a solution of 36 g $NaNO_2$ (522 mmol) in 180 mL of concentrated H_2SO_4 in a wet ice bath. The mixture was mechanically stirred for 30 min, and 2 L of Et_2O was added. While the reaction mixture stirred an additional 2 h, the following mixture was prepared: Copper sulfate (175 g) in 500 mL of water was mixed with Na_2SO_3 (175 g) in 500 mL of water. A greenish brown solid formed that was filtered and washed with water. This solid along with 350 g of $NaNO_2$ was added to 1500 mL of water. The diazonium salt generated initially was filtered, washed twice with Et_2O and four times with 95% EtOH, mixed with 500 mL of ice water, and slowly added to the copper salt solution. The resulting mixture was stirred 12 h. Ether (500 ml) was added, and the suspension was filtered. The filtrate layers were separated, and the organic layer was washed three times with aqueous 3 M NaOH and once with brine. The organic layer was dried ($MgSO_4$) and concentrated. The solid residue was dissolved in CH_2Cl_2 and filtered through a pad of silica gel (300 mL) on a coarse fritted funnel, with additional CH_2Cl_2 as a mobile phase. The resulting product was recrystallized from CH_2Cl_2–cyclohexane to give 20.4 g of **23** (36%): mp 80–81.5 °C; R_f (silica gel, CH_2Cl_2) 0.8; ^1H NMR (200 MHz, $CDCl_3$) δ 2.39 (s, 3 H, $ArCH_3$), 7.43 (s, 2 H, ArH); MS (EI, 70 eV) m/e 295 (98%, M^+). Anal. Calcd for $C_7H_5Br_2NO_2$: C, 28.51; H, 1.71. Found: C, 28.60; H, 1.66.

1,1′:3′,1″-Terphenyl, 2,2″-Dimethoxy-3,3″-bis(methoxymethyl)-5,5′,5″-trimethyl-2′-nitro- (26). Dibromide **23** (5.9 g, 20 mmol) was dissolved in 100 mL of benzene, and 50 mL of 2 M Na_2CO_3 and $Pd(PPh_3)_4$ (50 mg) were added. Boronic acid **16** (11.2 g, 54 mmol) was dissolved in a minimum amount of 95% EtOH and the resultant solution added to the mixture that was stirred vigorously at reflux for 3 days, during which time more catalyst was added. After cooling, the layers were separated and the benzene layer was extracted with aqueous 3 M NaOH. The organic layer was dried ($MgSO_4$), filtered, and concentrated. Chromatography of the residue on 700 mL of silica gel (CH_2Cl_2) afforded 5.7 g (61%) of **26** isolated as an oil: R_f (silica gel, CH_2Cl_2) 0.2; ^1H NMR (500 MHz, $CDCl_3$) δ 2.31 (s, 6 H, $ArCH_3$), 2.44 (s, 3 H, $ArCH_3$), 3.44 (s, 6 H, OCH_3), 3.49 (s, 6 H, OCH_3), 4.49 (br s, 4 H, $ArCH_2OMe$), 6.98 (s, 2 H, ArH), 7.23 (s, 2 H, ArH), 7.27 (s, integration obscured by residual protons of solvent, ArH); MS (EI, 16 eV) m/e 465 (100%, M^+). Anal. (dried at 78 °C, 10^{-3} Torr, 6 h) Calcd for $C_{27}H_{31}NO_6$: C, 69.66; H, 6.71. Found: C, 69.46; H, 6.75.

1,1′:3′,1″-Terphenyl, 3,3″-Bis(bromomethyl)-2,2″-dimethoxy-5,5′,5″-trimethyl-2′-nitro- (32). Compound **26** (0.91 g, 2 mmol) was dissolved in 100 mL of $CHCl_3$, and HBr was bubbled through the solution for 40 min. Water was added, and the layers were separated. The organic layer was dried ($MgSO_4$), filtered, and evaporated to yield 1.0 g (92%) of **32** as a foam: R_f (silica gel, CH_2Cl_2) 0.7; ^1H NMR (500 MHz, $CDCl_3$) δ 2.30 (s, 6 H, $ArCH_3$), 2.47 (s, 3 H, $ArCH_3$), 3.57 (s, 6 H, $ArOCH_3$), 4.58 (br s, 4 H, $ArCH_2Br$), 6.99 (s, 2 H, ArH), 7.22 (s, 2 H, ArH), 7.29 (s, 2 H, ArH); MS (FABS, NOBA) Br_2 isotope pattern centered at m/e 563 (17%, $M + H^+$). Anal. (dried at 100 °C, 10^{-5} Torr, 3 h) Calcd for $C_{25}H_{25}Br_2NO_4$: C, 53.31, H, 4.47. Found: C, 53.50; H, 4.71.

13,16,19-Trioxatetracyclo[19.3.1.1^{2,6}.1^{7,11}]heptacosa-1(25),2,4,6(27),7,9,11(26),21,23-nonaene, 25,26-Dimethoxy-4,9,23-trimethyl-27-nitro- (6). A suspension of 400 mg of NaH (60% oil dispersion) in 400 mL of THF was stirred at reflux. A solution of bis(benzyl bromide) **32** (1.35 g, 2.4 mmol) and dry diethylene glycol (0.245 mL, 2.6 mmol) in 200 mL of THF was

(35) Hodgson, H. H.; Mahadevan, A. P.; Ward, E. R. *Organic Syntheses*; Wiley: New York, 1955; Collect. Vol. III, pp 341–343.

added over 15 h from a constant-rate addition funnel. After the reaction mixture was cooled, water was added and the THF was evaporated. The residue was extracted with CH_2Cl_2–H_2O. The organic layer was concentrated, preabsorbed on 15 mL of reversed-phase silica gel, and flash chromatographed through an additional 70 mL of this support with 1% (w/v) NaBr in 1:1 acetone–water as the mobile phase. The fractions corresponding to the product were combined, and the acetone was removed in vacuo. Methylene chloride was added, and the layers were separated. The CH_2Cl_2 layer was washed four times with distilled water. Evaporation of solvent yielded 65 mg of **6** (11%) as a solid: mp 211–215 °C; R_f (reversed-phase silica gel, 1% w/v NaBr in 1:1 acetone–water) 0.2; ^{1}H NMR (200 MHz, $CDCl_3$) δ 2.30 (s, 6 H, $ArCH_3$), 2.54 (s, 3 H, $ArCH_3$), 3.38 (s, 6 H, $ArOCH_3$), 3.57–3.67 (m, 8 H, $-OCH_2CH_2O-$), 4.34 (d, 2 H, $ArCH_2O-$, J = 12 Hz), 4.69 (d, 2 H, $ArCH_2O-$, J = 12 Hz), 7.07 (br s, 4 H, ArH), 7.34 (s, 2 H, ArH); MS (FABS, NOBA) m/e 530 (100%, M + Na^+), 507 (7%, M + H^+). Anal. (dried at 110 °C, 10^{-5} Torr, 3 h) Calcd for $C_{29}H_{33}NO_7$: C, 68.62; H, 6.55. Found: C, 68.54; H, 6.51.

1,1′:3′,1″-Terphenyl-2′-amine, 2,2″-Dimethoxy-3,3″-bis(methoxymethyl)-5,5′,5″-trimethyl- (27). A solution of 2,6-diiodo-4-methylaniline (**35**)[14] (7.0 g, 20 mmol) in 200 mL of benzene was vigorously stirred with 100 mL of aqueous 2 M Na_2CO_3. Boronic acid **16** (10.7 g, 51 mmol) was dissolved in 95% EtOH and the solution added to the above mixture, along with $Pd(PPh_3)_4$ (10 mg). The mixture was refluxed for 24 h. The layers were separated, and the organic layer was washed with aqueous 3 M NaOH, dried ($MgSO_4$), and concentrated. The residue was chromatographed on 400 mL of silica gel with 5% EtOAc in CH_2Cl_2 as the mobile phase. The polarity of that phase was incrementally increased from 5 to 10% EtOAc. The chromatography yielded 2.8 g (36%) of **27** as a foam: R_f (silica gel, 9:1 CH_2Cl_2–EtOAc) 0.3; ^{1}H NMR (200 MHz, $CDCl_3$) δ 2.30 (s, 3 H, $ArCH_3$), 2.34 (s, 6 H, $ArCH_3$), 3.46 (s, 6 H, OCH_3), 3.48 (s, 6 H, OCH_3), 4.53 (d, 4 H, $ArCH_2OMe$), 6.98 (s, 2 H, ArH), 7.07 (s, 2 H, ArH), 7.21 (s, 2 H, ArH); MS (EI, 70 eV) m/e 435 (43%, M^+). Anal. (dried at 78 °C, 10^{-5} Torr) Calcd for $C_{27}H_{33}NO_4$: C, 74.45; H, 7.64. Found: C, 74.27; H, 7.55.

1,1′:3′,1″-Terphenyl-2′-amine, 3,3″-Bis(chloromethyl)-2,2″-dimethoxy-5,5′,5″-trimethyl-, Hydrochloride (34). Compound **27** (2 g, 4.5 mmol) was dissolved in 100 mL of CH_2Cl_2, and 13.5 mL (13.5 mmol) of BCl_3 (1 M in CH_2Cl_2) was added. After 10 min, methanol was added and the solvents were evaporated. The bis(benzyl chloride) **34** (1.92 g) was isolated as a foam (94%): R_f (alumina, 11:9 CH_2Cl_2–$(CH_2)_6$) 0.7; ^{1}H NMR (200 MHz, $CDCl_3$) δ 2.39 (s, 6 H, $ArCH_3$), 2.48 (s, 3 H, $ArCH_3$), 3.61 (s, 6 H, $ArOCH_3$), 4.53 (d, 2 H, $ArCH_2Cl$, J = 11.4 Hz), 4.85 (d, 2 H, $ArCH_2Cl$, J = 11.4 Hz), 7.24 (s, 2 H, ArH), 7.30 (s, 2 H, ArH), 7.34 (s, 2 H, ArH); IR ($CDCl_3$ solution) broad NH stretch at 3400–2300 cm^{-1} (the free aniline **34** gives a doublet at 3370 and 3440 cm^{-1}; MS (FABS, NOBA) m/e 444 (100%, M^+). Anal. (dried at 80 °C, 10^{-5} Torr, 3 h) Calcd for $C_{25}H_{28}Cl_3NO_2$: C, 62.45; H, 5.87; Cl, 22.12. Found: C, 62.45; H, 5.82; Cl, 22.15.

13,16,19-Trioxatetracyclo[19.3.1.1^{2,6}.1^{7,11}]heptacosa-1(25),2,4,6(27),7,9,11(26),21,23-nonaene-27-amine, 25,26-Dimethoxy-4,9,23-trimethyl- (8). Method A. A solution of bis(benzyl chloride) **34** (0.101 g, 0.23 mmol) in 20 mL of THF was added to 50 mL of THF. Dry diethylene glycol (21 μL, 0.23 mmol), LiBr (2 mg), and NaH (30 mg, 60% oil dispersion) were added, and the mixture was refluxed for 42 h. Water was added, and the THF was removed in vacuo. The residue was extracted with CH_2Cl_2. The organic layer was concentrated, preabsorbed on 10 mL of reversed-phase silica gel, and flash chromatographed through an additional 50 mL of this support with 1% (w/v) NaBr in 13:7 acetone–water as the mobile phase. The fractions corresponding to the product were combined, and the acetone was removed in vacuo. Methylene chloride was added, and the layers were separated. The organic layer was washed four times with distilled water. Evaporation of the organic layer yielded 7 mg (7%) of cycle 8.

Method B. Nitrohemispherand **6** (0.12 g, 0.23 mmol) was dissolved in absolute EtOH with heating and the solution added to a mixture of 10% Pd/C (<10 mg) and $NaBH_4$ (100 mg) in water.[16] After being stirred for 1.5 h, the reaction mixture was carefully quenched with HCl. The mixture was washed with aqueous 3 M NaOH and extracted with CH_2Cl_2 twice. The organic layers were combined, concentrated, and chromatographed as in method A except the mobile phase was 1% (w/v) NaBr in 1:1 acetone–water. The isolation was the same as above to give 50 mg (46%) of cycle 8: mp 162–164 °C; IR ($CDCl_3$) doublet at 3420 and 3360 cm^{-1}; R_f (reversed-phase silica gel, 1% NaBr (w/v) in 13:7 acetone–water) 0.4; ^{1}H NMR (200 MHz, $CDCl_3$) δ 2.30 (s, 6 H, $ArCH_3$), 2.39 (s, 3 H, $ArCH_3$), 3.35–3.62 (m, 14 H, $-OCH_2CH_2O-$, $ArOCH_3$), 4.27 (d, 2 H, $ArCH_2-$, J = 11.2 Hz), 4.91 (d, 2 H, $ArCH_2O-$, J = 11.2 Hz), 7.00 (s, 2 H, ArH), 7.07 (s, 2 H, ArH), 7.16 (s, 2 H, ArH); MS (FABS, NOBA) m/e 500 (30%, M + Na^+), 478 (39%, M + H^+). Anal. (dried at 180 °C, 10^{-5} Torr, 3 h) Calcd for $C_{29}H_{35}NO_5$: C, 72.93; H, 7.39. Found: C, 72.68; H, 7.27.

2,6-Diiodo-4-(methylthio)anisole (36). The method of Giam and Kikukawa was used.[17] To a solution of 50 g (0.14 mol) of 2,6-diiodo-4-methylaniline[14] in 220 mL of CH_3SSCH_3 at 75 °C was added 50 mL (0.37 mol) of isoamyl nitrite. The mixture was heated 1.5 h at 90 °C, cooled to 25 °C, and evaporated under reduced pressure. The residue was dissolved in 40 mL of CH_2Cl_2–$(CH_2)_6$ (1:2) and the resultant solution added to a silica gel column (600 g) made up in hexane. Elution of the column with hexane gave 30.4 g (56%) of **36**: mp 49–50 °C; MS (70 eV, 90 °C) m/e 390 (M^+, 100); ^{1}H NMR (200 MHz, $CDCl_3$) δ 2.17 (s, $ArCH_3$, 3 H), 2.23 (s, SCH_3, 3 H), 7.76 (s, ArH, 2 H). Anal. Calcd for $C_8H_8I_2S$: C, 24.64; H, 2.07. Found: C, 24.65; H, 2.13.

2-Methoxy-5-*tert*-butylbenzeneboronic Acid (38). To a solution of 110 g (0.48 mol) of 2-bromo-4-*tert*-butylanisole[18] in 500 mL of THF under argon at −78 °C was added 240 mL of 2.2 M *n*-butyllithium (hexane). After being stirred 5 min, the organometallic solution was cannulated (45 min) into 180 g (1.7 mol) of $(CH_3O)_3B$ in 500 mL of Et_2O at −50 °C. The mixture was stirred 30 min at −50 °C, slowly warmed to 25 °C, diluted with 600 mL of 2 N hydrochloric acid, and stirred for 12 h at 25 °C. The layers were separated, and the ether layer was extracted with six 250-mL portions of 3 N aqueous NaOH solution. The basic extracts were cooled to 5 °C and acidified to pH 1 with concentrated hydrochloric acid. Extraction of the aqueous suspension with two 400-mL portions of Et_2O and evaporation of the ether extracts (no drying) at 25 °C (30 mm) gave 78 g (77%) of **38** as a waxy solid that was stored at 5 °C and used without further purification: ^{1}H NMR (200 MHz, $(CD_3)_2SO$) δ 1.25 (s, CCH_3, 9 H), 3.78 (s, OCH_3, 3 H), 6.89–7.60 (m, ArH, 3 H). A sample was recrystallized from water; mp 104–106 °C. Anal. Calcd for $C_{11}H_{17}BO_3$: C, 63.50; H, 8.24. Found: C, 63.59; H, 8.36.

5,5″-Di-*tert*-butyl-5′-methyl-2′-(methylthio)-1,1′:3′,1″-terphenyl-2,2″-diol (40). To a mixture of 25 g (64 mmol) of **36** in 320 mL of benzene and 160 mL of 2 M aqueous Na_2CO_3 at 25 °C under N_2 were added 0.5 g (0.4 mmol) of $Pd(PPh_3)_4$ and a solution of 40 g (0.19 mol) of boronic acid **38** in 80 mL of ethanol. This vigorously stirred two-phase mixture was refluxed for 22 h and cooled to 25 °C, and the layers were separated. The benzene layer was dried, concentrated to 50 mL, and added to an Al_2O_3 column (300 g) made up in 3:1 cyclohexane–benzene. Elution of the column with 3-L portions of cyclohexane–benzene (3:1 and 1:1) gave ~26 g (88%) of **39** as an oil. Compound **39** was characterized by its ^{1}H NMR spectrum and was converted to **40** without further purification. The ^{1}H NMR spectrum (200 MHz, $CDCl_3$) of **39** gave absorptions at δ 1.33 (s, CCH_3, 18 H), 1.69 (s, SCH_3, 3 H), 2.38 (s, $ArCH_3$, 3 H), 3.78 (s, OCH_3, 6 H), and 6.80–7.45 (m, ArH, 8 H). To a solution of 26 g (56 mmol) of **39** in 1 L of CH_2Cl_2 at 0 °C under N_2 was added 63 g (0.25 mol) of BBr_3. After being stirred at 0 °C (1 h) and 25 °C (6 h), the mixture was cooled to 0 °C and H_2O was slowly added to decompose excess BBr_3. The layers were separated, and the CH_2Cl_2 solution was dried ($MgSO_4$) and evaporated. The residue was dissolved in 40 mL of benzene and the solution added to a silica gel column (400 g) made up in benzene. Elution of the column with Et_2O–C_6H_6 (1:99 and 1:49) gave 22.4 g (81% based on **36**) of **40**: mp 128–130 °C after recrystallization from hexane–cyclohexane; MS (70 eV, 160 °C) m/e 434 (M^+, 100); ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.33 (s, CCH_3, 18 H), 1.80 (s, SCH_3, 3 H), 2.39 (s, $ArCH_3$, 3 H), 6.78–7.34 (m, ArH, 8 H). Anal. Calcd for $C_{28}H_{34}O_2S$: C, 77.39; H, 7.89. Found: C, 77.44; H, 7.69.

5,5″-Di-*tert*-butyl-2,2″-dimethoxy-5′-methyl-2′-(methylthio)-1,1′:3′,1″-terphenyl-3,3″-dimethanol (42). This two-step conversion was accomplished by dissolving 7.2 g (16.6 mmol) of

40 in 480 mL of isopropyl alcohol and then adding 100 mL of H_2O, 17 g (0.3 mol) of KOH, and 36 g (1.2 mol) of paraformaldehyde at 25 °C under N_2. After being stirred for 9 days at 25 °C, the solution was diluted with saturated aqueous $NaHCO_3$ (to pH 8) and then 500 mL of $CHCl_3$. The layers were separated, and the $CHCl_3$ layer was dried and evaporated under reduced pressure. The residue was dissolved in 40 mL of CH_2Cl_2 and the resultant solution added to a silica gel column made up in CH_2Cl_2. Elution of the column with 1:19 Et_2O–CH_2Cl_2 gave ~4 g (49%) of diphenol **41** as a yellow foam that was used to prepare **42** without further purification. The ^1H NMR spectrum (200 MHz, $CDCl_3$) of **41** gave absorptions at δ 1.32 (s, CCH_3, 18 H), 1.72 (s, SCH_3, 3 H), 2.40 (s, $ArCH_3$, 3 H), 4.84 (s, $ArCH_2$, 4 H), and 7.17–7.26 (m, ArH, 6 H). A mixture of 4 g (8.1 mmol) of **41**, 14 g (0.1 mol) of K_2CO_3, and 15 mL (0.25 mol) of CH_3I in 300 mL of acetone was refluxed for 72 h under N_2. The acetone was evaporated and the residue partitioned between $CHCl_3$ and H_2O (500 mL of each). The $CHCl_3$ layer was dried, concentrated to 30 mL, and added to a silica gel column (200 g) made up in CH_2Cl_2. Elution of the column with 1:19 Et_2O–CH_2Cl_2 gave 3.7 g (43% based on **40**) of **42**: mp 190–192 °C; MS (70 eV, 150 °C) *m/e* 522 (M^+, 11), 491 (M – OCH_3, 100); ^1H NMR (200 MHz, $CDCl_3$) δ 1.34 (s, CCH_3, 18 H), 1.74 (s, SCH_3, 3 H), 2.41 (s, $ArCH_3$, 3 H), 3.47 (s, OCH_3, 6 H), 4.77 (s, $ArCH_2$, 4 H), 7.21–7.38 (m, ArH, 6 H). Anal. Calcd for $C_{32}H_{42}O_4S$: C, 73.53; H, 8.10. Found: C, 73.59; H, 8.20.

9,23-Di-*tert*-butyl-25,26-dimethoxy-4-methyl-27-(methylthio)-13,16,19-trioxatetracyclo[19.3.1.1^{2,6}.1^{7,11}]heptacosa-1(25),2,4,6(27),7,9,11(26),21,23-nonaene (11). To a solution of 1.25 g (2.4 mmol) of **42** and 1.1 g (2.6 mmol) of dry diethylene glycol ditosylate in 600 mL of THF was added 1.5 g (31 mmol) of NaH (50% mineral oil dispersion). The mixture was refluxed for 72 h, cooled to 25 °C, diluted with 5 mL of H_2O, and evaporated under reduced pressure. The residue was partitioned between $CHCl_3$ and H_2O (300 mL of each). The organic layer was dried, concentrated to 30 mL, and added to an Al_2O_3 column (150 g) made up in $CHCl_3$. Elution of the column with $CHCl_3$ and recrystallization of the product from CH_2Cl_2–heptane gave 0.55 g (39%) of **11**: mp 210–212 °C; MS (16 eV, 270 °C) *m/e* 561 (M – OCH_3, 100); ^1H NMR (200 MHz, $CDCl_3$) δ 1.33 (s, CCH_3, 18 H), 1.57 (s, SCH_3, 3 H), 2.50 (s, $ArCH_3$, 3 H), 3.30 (s, OCH_3, 6 H), 3.65–3.82 (m, OCH_2CH_2, 8 H), 4.45 (d, *J* = 11.7 Hz, $ArCH_2$, 2 H), 4.74 (d, *J* = 11.7 Hz, $ArCH_2$, 2 H), 7.24–7.34 (m, ArH, 6 H). Anal. Calcd for $C_{36}H_{40}O_5S$: C, 72.94; H, 8.16. Found: C, 73.09; H, 8.16.

9,23-Di-*tert*-butyl-25,26-dimethoxy-4-methyl-27-(methylsulfinyl)-13,16,19-trioxatetracyclo[19.3.1.1^{2,6}.1^{7,11}]heptacosa-1(25),2,4,6(27),7,9,11(26),21,23-nonaene (12). To a solution of 118 mg (0.2 mmol) of **11** in 65 mL of CH_2Cl_2 at −78 °C was added a solution of 41 mg (0.2 mmol) of 85% *m*-chloroperoxybenzoic acid. The mixture was kept at −78 °C for 7 h and then warmed to 25 °C and stirred for 16 h. The colorless solution was extracted with 10% aqueous $NaHCO_3$ (three 100-mL portions) and deionized H_2O (2 × 200 mL). The CH_2Cl_2 solution was concentrated to 15 mL, and adventitious H_2O was removed by azeotropic distillation with two 100-mL portions of benzene. The residue was crystallized from CH_2Cl_2–heptane to give 79 mg (65%) of **12**: mp 226–228 °C; ^1H NMR (200 MHz, $CDCl_3$) δ 1.33 (s, CCH_3, 9 H), 1.34 (s, CCH_3, 9 H), 2.29 (s, SCH_3, 3 H), 2.50 (s, $ArCH_3$, 3 H), 3.26 (s, OCH_3, 3 H), 3.38 (s, OCH_3, 3 H), 3.53–3.84 (m, OCH_2CH_2, 8 H), 4.38–4.62 (m, ArH, 4 H), 7.20–7.58 (m, ArH, 6 H). Anal. Calcd for $C_{36}H_{42}O_6S$: C, 71.73; H, 7.02. Found: C, 71.68; H, 7.18.

9,23-Di-*tert*-butyl-25,26-dimethoxy-4-methyl-27-(methylsulfonyl)-13,16,19-trioxatetracyclo[19.3.1.1^{2,6}.1^{7,11}]heptacosa-1(25),2,4,6(27),7,9,11(26),21,23-nonaene (13). To a solution of 118 mg (0.2 mmol) of **11** in 60 mL of CH_2Cl_2 at 0 °C was added a solution of 140 mg of 85% *m*-chloroperoxybenzoic acid in 15 mL of CH_2Cl_2. The mixture was warmed to 25 °C over 1 h, stirred 7 h at 25 °C, and extracted with 10% aqueous $NaHCO_3$ (two 150-mL portions), 100 mL of aqueous 1 N NaOH, and deionized H_2O (200 mL). The CH_2Cl_2 solution was dried ($MgSO_4$) and evaporated. The residue was crystallized from cyclohexane–heptane to give 90 mg (73%) of **13**: mp 242–244 °C; ^1H NMR (200 MHz, $CDCl_3$) δ 1.34 (s, CCH_3, 18 H), 2.51 (s, $ArCH_3$, 3 H), 3.00 (s, SCH_3, 3 H), 3.31 (s, OCH_3, 6 H), 3.43–3.79 (m, OCH_2CH_2, 8 H), 4.35 (d, *J* = 10.3 Hz, $ArCH_2$, 2 H), 4.60 (d, *J* = 10.3 Hz, $ArCH_2$, 2 H), 7.21–7.48 (m, ArH, 6 H). Anal. Calcd for $C_{36}H_{40}O_7S$: C, 68.11; H, 6.67. Found: C, 68.24; H, 6.80.

(2-Hydroxy-5-methylphenacyl)pyridinium Chloride (44). The method of Cullinane and Edwards was used to prepare 2-hydroxy-5-methylphenacyl chloride.[19a] A mixture of 23 g (0.125 mol) of this compound and 20 g (0.25 mol) of pyridine in 600 mL of benzene was refluxed for 20 h, cooled to 25 °C, stirred 12 h, and filtered to give 26 g (79%) of **44**: mp 234–235 °C; ^1H NMR ($(CD_3)_2SO$, 200 Hz) δ 2.27 (s, $ArCH_3$, 3 H), 6.26 (s, CH_2, 2 H), 7.09 (d, ArH, 1 H), 7.39 (d, ArH, 1 H), 7.62 (s, ArH, 1 H), 8.23 (m, PyrH, 2 H), 8.70 (m, PyrH, 1 H), 9.02 (m, PyrH, 2 H). Anal. Calcd for $C_{14}H_{14}ClNO_2$: C, 63.76; H, 5.35. Found: C, 63.56; H, 5.24.

3-(Dimethylamino)-1-(2-hydroxy-5-methylphenyl)-1-propanone Hydrochloride (43). A mixture of 84 g (0.56 mol) of 2-hydroxy-5-methylacetophenone, 43.2 g (1.44 mol) of paraformaldehyde, 100 g (1.23 mol) of dimethylamine hydrochloride, 4 mL of 12 N hydrochloric acid, and 250 mL of isopropyl alcohol was refluxed for 2 h, cooled to 25 °C, and allowed to stand for 96 h. The precipitate was filtered, washed with isopropyl alcohol (100 mL), and dried at 25 °C (0.01 mm) to give 108.4 g (79%) of **43**: mp 192–193 °C; ^1H NMR (200 MHz, $(CD_3)_2SO$) δ 2.29 (s, $ArCH_3$, 3 H), 2.83 (s, NCH_3, 6 H), 3.24–3.61 (m, CH_2, 4 H), 6.92 (d, ArH, 1 H), 7.36 (d, ArH, 1 H), 7.70 (s, ArH, 1 H). Anal. Calcd for $C_{12}H_{18}ClNO_2$: C, 59.14; H, 7.44. Found: C, 58.97; H, 7.24.

2,6-Bis(2-hydroxy-5-methylphenyl)pyridine (45). A suspension of 26.3 g (0.1 mol) of **44**, 24.3 g (0.1 mol) of **43**, 100 g of NH_4OAc, and 160 mL of HOAc under N_2 was refluxed for 6 h, cooled to 25 °C, diluted with 300 mL of H_2O, and stirred 12 h.[20] The solid was collected and dissolved in 300 mL of $CHCl_3$ and the solution extracted with 400 mL of H_2O. The organic layer was dried, concentrated to 50 mL, and added to a silica gel column made up in CH_2Cl_2. Elution of the column with 5 L of CH_2Cl_2 gave 17.5 g (60%) of **45**: mp 170–171 °C; MS (70 eV, 120 °C) *m/e* 291 (M^+, 100); ^1H NMR (200 MHz, $CDCl_3$) δ 2.35 (s, CH_3, 6 H), 6.93 (d, ArH, 2 H), 7.13 (m, ArH, 2 H), 7.46 (d, ArH, 2 H), 7.67 (d, PyrH, 2 H), 7.95 (t, PyrH, 1 H). Anal. Calcd for $C_{19}H_{17}NO_2$: C, 78.33; H, 5.88. Found: C, 78.37; H, 5.83.

2,6-Bis[2-hydroxy-3-(hydroxymethyl)-5-methylphenyl]-pyridine (46). To a suspension of 5.0 g (17.2 mmol) of **45** in 250 mL of isopropyl alcohol was added a solution of 13 g (0.23 mol) of KOH in 80 mL of 37% formaldehyde solution. The homogeneous solution was stirred 14 days under N_2 at 25 °C. The mixture was diluted with saturated aqueous $NaHCO_3$ (to pH 8), stirred 10 h, and extracted with two 400-mL portions of $CHCl_3$. The organic extracts were dried, evaporated, dissolved in 100 mL of CH_2Cl_2, and added to a silica gel column (150 g) made up in CH_2Cl_2. Elution of the column with CH_2Cl_2 (1 L) and CH_2Cl_2–$(CH_3)_2CO$ (99:1 and 19:1, 3 L of each) gave 0.6 g (12%) of **45**. Further elution with 9:1 and 4:1 CH_2Cl_2–$(CH_3)_2CO$ (4 L of each) gave 3.0 g (50%) of **46** as an amorphous solid. Recrystallization from CH_2Cl_2 gave clear yellow needles of **46**: mp 143–144 °C; MS (70 eV, 150 °C) *m/e* 351 (M^+, 100); ^1H NMR (200 MHz, $CDCl_3$) δ 2.34 (s, $ArCH_3$, 6 H), 4.80 (s, CH_2, 4 H), 7.09 (bs, ArH, 2 H), 7.46 (br s, ArH, 2 H), 7.72–7.97 (AB_2, *J* = 7.7 Hz, PyrH, 3 H). Anal. Calcd for $C_{21}H_{21}NO_4$: C, 71.78; H, 6.02. Found: C, 71.87; H, 5.98.

2,6-Bis[3-(hydroxymethyl)-2-methoxy-5-methylphenyl]-pyridine (47). A mixture of 15 g (43 mmol) of **46**, 16.1 g (128 mmol) of $(CH_3)_2SO_4$, and 30 g (0.22 mol) of K_2CO_3 in 600 mL of acetone under N_2 was refluxed 25 h, cooled to 25 °C, concentrated to 50 mL, and stirred 1 h with 400 mL of 10% NH_4OH. The mixture was extracted with 400 mL of $CHCl_3$, and the organic layer was dried, concentrated to 50 mL, and added to a silica gel column (350 g) made up in CH_2Cl_2. Elution of the column with CH_2Cl_2–$(CH_3)_2CO$ mixtures from 99:1 to 19:1 gave traces of unidentified material. Further elution with 9:1 CH_2Cl_2–$(CH_3)_2CO$ (5 L) gave 7.5 g (41%) of **47** after recrystallization from CH_2Cl_2–heptane: mp 126–127 °C; MS (16 eV, 180 °C) *m/e* 379 (M^+, 49), 364 (M – CH_3, 100); ^1H NMR (200 MHz, $CDCl_3$) δ 2.38 (s, $ArCH_3$, 6 H), 3.53 (s, OCH_3, 6 H), 4.72 (s, CH_2, 4 H), 7.20 (br s, ArH, 2 H), 7.59 (bs, ArH, 2 H), 7.79 (bs, PyrH, 3 H). Anal. Calcd for $C_{23}H_{25}NO_4$: C, 72.80; H, 6.64. Found: C, 72.70; H, 6.64.

2,6-Bis[3-(hydroxymethyl)-2-methoxy-5-methylphenyl]-pyridine *N*-Oxide (48). To a solution of 3.6 g (9.5 mmol) of **47** in 110 mL of $CHCl_3$ at 25 °C was added 9 g (44 mmol) of 85% *m*-chloroperoxybenzoic acid. The mixture was stirred 23 h and filtered to remove *m*-chlorobenzoic acid, and the filtrate was

extracted with two 250-mL portions of 1 M aqueous NaOH. The $CHCl_3$ layer was dried, concentrated to 90 mL, and diluted with 90 mL of cyclohexane. Spontaneous crystallization occurred to give 3.5 g (93%) of **48**: mp 205–206 °C; MS (70 eV, 180 °C) *m/e* 395 (M^+, 1) 364 (M – OCH_3, 100); ^1H NMR (200 MHz, $CDCl_3$) δ 2.33 (s, $ArCH_3$, 6 H), 3.58 (s, OCH_3, 6 H), 4.71 (s, $ArCH_2$, 4 H), 7.26–7.46 (m, Ar*H* and Pyr*H*, 7 H). Anal. Calcd for $C_{23}H_{25}N_5O_5$: C, 69.86; H, 6.37. Found: C, 69.68; H, 6.36.

25,26-Dimethoxy-9,23-dimethyl-13,16,19-trioxa-27-azatetracyclo[19.3.1.1^{2,6}.1^{7,11}]heptacosa-1(25),2,4,6(27),7,9,11-(26),21,23-nonaene (7). To a solution of 2 g (5.3 mmol) of **47** and 2.5 g (6.0 mmol) of diethylene glycol ditosylate in 700 mL of THF at 25 °C under N_2 was added 2 g (42 mmol) of NaH (50% oil dispersion). The mixture was refluxed 96 h, cooled to 25 °C, diluted with 5 mL of CH_3OH to decompose the excess NaH, and evaporated. The residue was partitioned between $CHCl_3$ and 4 M aqueous NaCl (400 mL of each). The organic layer was dried, concentrated to 25 mL, and added to an Al_2O_3 column (150 g) made up in $CHCl_3$. Elution of the column with 3 L of $CHCl_3$ gave crude **7**, which was further purified by gel permeation chromatography (R_v = 157 mL) to give 0.95 g (40%) of **7**: mp 148–149 °C after recrystallization from CH_2Cl_2–heptane; MS (16 eV, 180 °C) *m/e* 449 (M^+, 50); ^1H NMR (200 MHz, $CDCl_3$) δ 2.31 (s, $ArCH_3$, 6 H), 3.48 (s, OCH_3, 6 H), 3.50–3.54 (m, OCH_2CH_2, 8 H), 4.56 (s, $ArCH_2$, 4 H), 7.04–7.13 (m, Ar*H*, 4 H), 7.44 and 7.87 (A_2B, *J* = 7.7 Hz, Pyr*H*, 3 H). Anal. Calcd for $C_{27}H_{31}NO_5$: C, 72.14; H, 6.95. Found: C, 72.11; H, 7.01.

25,26-Dimethoxy-9,23-dimethyl-13,16,19-trioxa-27-azatetracyclo[19.3.1.1^{2,6}.1^{7,11}]heptacosa-1(25),2,4,6(27),7,9,11-(26),21,23-nonaene 27-Oxide (4). To a solution of 1.8 g (4.6 mmol) of **48** and 2.4 g (5.8 mmol) of diethylene glycol ditosylate in 600 mL of THF was added 1 g (21 mmol) of NaH (50% oil dispersion) at 25 °C under N_2. The mixture was refluxed for 72 h, cooled to 25 °C, diluted with 10 mL of H_2O, and evaporated. The residue was partitioned between $CHCl_3$ and 4 M aqueous NaCl (400 mL of each). The organic layer was dried, filtered, and evaporated. The residue was dissolved in CH_2Cl_2 and subjected to gel permeation chromatography to give 1.6 g of crude **4**·NaCl (R_v = 158 mL). Crystallization of **4**·NaCl from $CHCl_3$ (30 mL) and toluene (175 mL) gave 650 mg (27%) of **4**·NaCl, which was characterized by its ^1H NMR spectrum (200 MHz, $CDCl_3$): δ 2.34 (s, $ArCH_3$, 6 H), 3.35–3.90 (m, OCH_2CH_2, 8 H), 3.82 (s, OCH_3, 6 H), 4.04 (d, *J* = 10.4 Hz, $ArCH_2$, 2 H), 5.16 (d, *J* = 10.4 Hz, $ArCH_2$, 2 H), 7.08–7.66 (m, Ar*H* and Pyr*H*, 7 H). Decomplexation of **4**·NaCl was accomplished by extracting a $CHCl_3$ solution of the complex with five portions of deionized H_2O to give 450 mg (21%) of **4**: mp 170–180 °C; MS (16 eV, 190 °C) *m/e* 465 (M^+, 1) 434 (M – OCH_3, 100); ^1H NMR (200 MHz, $CDCl_3$) δ 2.29 (s, $ArCH_3$, 6 H), 3.31–3.70 (m, OCH_2CH_2, 8 H), 3.60 (s, OCH_3, 6 H), 4.33 (d, *J* = 12 Hz, $ArCH_2$, 2 H), 4.86 (d, *J* = 12 Hz, $ArCH_2$, 2 H), 6.98–7.53 (m, Ar*H* and Pyr*H*, 7 H). Anal. Calcd for $C_{27}H_{31}NO_6$: C, 69.66; H, 6.71. Found: C, 69.75; H, 6.66.

1,4-Bis(3-bromo-2-hydroxy-5-methylphenyl)-1,4-butanedione (50). Known compound 1,4-bis(2-hydroxy-5-methylphenyl)-1,4-butanedione (**49**)[21] was prepared as follows: To 66.40 g (0.2226 mol) of bis(4-methylphenyl)butanedioate[21] were added 67.05 g (0.5028 mol) of $AlCl_3$ and 200 mL of CS_2. The mixture was stirred well and the CS_2 subsequently removed under reduced pressure. The solid, yellowish residue was heated at 180–185 °C for 12.5 h, cooled, and stirred in ice–concentrated aqueous HCl for 1 h. After filtering, the collected solid was triturated with hot ethanol, filtered, and dried. Chromatography of this material through a short, wide silica gel column with $CHCl_3$ as the mobile phase afforded a solid that was again triturated with hot ethanol. The product was filtered and dried in vacuo to give diketone **49** (32.70 g, 0.1096 mol, 49%) as a light, off-white solid pure enough for direct use: mp 180–189 °C (lit.[21] mp 184–186 °C); ^1H NMR (200 MHz, $CDCl_3$) δ 2.34 (s, 3 H, $ArCH_3$), 3.48 (s, 2 H, CH_2), 6.90 (H_B of ABX, 1 H, ArH, J_{AB} = 8.5 Hz), 7.30 (H_A of ABX, 1 H, ArH, J_{AB} = 8.5 Hz, J_{AX} = 2.0 Hz), 7.67 (H_X of ABX, 1 H, ArH, J_{AX} = 2.0 Hz). To a solution of 19.11 g (64.05 mmol) of diketone **49** in 1 L of CH_2Cl_2 at 0 °C was added 55.58 g (135.66 mmol) of 2,4,4,6-tetrabromocyclohex-2,5-dienone.[22] The reaction mixture was stirred at 0 °C and allowed to warm slowly to 25 °C over 13 h, concentrated under reduced pressure, and triturated with hot ethanol (~400 mL). The crude product was filtered, washed with cold $CHCl_3$ followed by pentane, and dried under vacuum to yield **50** as a slightly yellow solid in sufficient purity to use in subsequent reactions (25.63 g, 56.19 mmol, 88%). An analytical sample twice recrystallized from EtOH–$CHCl_3$ gave canary yellow needles: mp 238–240 °C; ^1H NMR (200 MHz, $CDCl_3$) δ 2.34 (s, 3 H, $ArCH_3$), 3.50 (s, 2 H, CH_2), 7.61 (d, 1 H, ArH, *J* = 1.2 Hz), 7.65 (d, 1 H, ArH, *J* = 1.2 Hz); MS (16 (eV, 190 °C) *m/e* M^+ (^{79}Br) 454 (9). Anal. Calcd for $C_{18}H_{16}Br_2O_4$: C, 47.40; H, 3.54; Br, 35.03. Found: C, 47.51; H, 3.49; Br, 35.06.

2,5-Bis(3-bromo-2-methoxy-5-methylphenyl)furan (51). A mixture of 17.90 g (39.24 mmol) of diketone **50**, 250 mL of Ac_2O, and 2 g of polyphosphoric acid[23] was refluxed for 30 min, poured onto ice, stirred, and filtered. The collected solid was dried and added to a solution of 31.31 g (7.83 mmol) of aqueous NaOH, 500 mL of water, and 100 mL of ethanol. This mixture was refluxed for 18 h, cooled, and then poured into ice. After careful acidification to pH 1 with aqueous HCl (concentrated), the solid material was filtered, dried, and added to a mixture of 500 mL of THF, 50 mL of water, and 25.5 g (638 mmol) of aqueous NaOH. After the mixture was stirred for 5 min, 25 mL (264 mmol) of $(CH_3)_2SO_4$ was added and the resulting mixture was then refluxed for 13 h. The mixture was then cooled and quenched with aqueous NH_4OH (concentrated), and the products were partitioned between 100 mL of Et_2O and 100 mL of water. The aqueous layer was extracted with 250 mL of Et_2O, and the combined organic layers were dried ($MgSO_4$) and concentrated in vacuo. The residue was flash chromatographed (SiO_2, 7 × 28 cm, 10% CH_2Cl_2–hexane) to give furan **51** as a solid that was recrystallized from CH_2Cl_2–EtOH to afford white needles: 13.12 g, 28.14 mmol, 72%; mp 129–131.5 °C. An analytical sample prepared by recrystallization from CH_2Cl_2–EtOH gave fine, white needles: mp 133.5–135 °C; ^1H NMR (200 MHz, $CDCl_3$) δ 2.38 (s, 3 H, $ArCH_3$), 3.83 (s, 3 H, OCH_3), 7.10 (s, 1 H, furan H), 7.30 (d, 1 H, ArH, *J* = 1.5 Hz), 7.64 (d, 1 H, ArH, *J* = 1.5 Hz); MS (16 eV, 190 °C) *m/e* M^+ (^{79}Br) 464 (50). Anal. Calcd for $C_{20}H_{18}Br_2O_3$: C, 51.53; H, 3.89; Br, 34.28. Found: C, 51.44; H, 3.84; Br, 34.31.

Diethyl 3,3′-(2,5-Furandiyl)bis[2-methoxy-5-methylbenzoate] (52). To a solution of 8.35 g (17.91 mmol) of dibromide **51** in 180 mL of dry THF at −78 °C was added 38.2 mmol of *n*-butyllithium in hexane. The mixture was stirred for 3 min at −78 °C, and 100 mL (1.046 mol) of EtO_2CCl was added in one portion. The cloudy dilithiate suspension was quickly converted to a clear, yellow solution that was allowed to stir 1 h at −78 °C, followed by 7 h at 25 °C. The reaction mixture was then concentrated under reduced pressure and partitioned between 300 mL of CH_2Cl_2 and 100 mL of 1:1 (v/v) water–$NaHCO_3$ solution (saturated). The organic phase was dried ($MgSO_4$) and evaporated in vacuo. The residue was chromatographed (medium-pressure silica gel, 7:3 $CHCl_3$–hexane) to give **52** as a white solid (5.71 g, 12.62 mmol, 70%). An analytical sample was recrystallized from CH_2Cl_2–cyclohexane to give white needles: mp 127–128 °C; ^1H NMR (200 MHz, $CDCl_3$) δ 1.43 (t, 3 H, OCH_2CH_3, *J* = 7.1 Hz), 2.43 (s, 3 H, $ArCH_3$), 3.84 (s, 3 H, OCH_3), 4.42 (q, 2 H, OCH_2CH_3, *J* = 7.1 Hz), 7.12 (s, 1 H, furan H), 7.52 (d, 1 H, ArH, *J* = 1.3 Hz), 7.87 (d, 1 H, ArH, *J* = 1.3 Hz); MS (70 eV, 190 °C) *m/e* M + 452 (100). Anal. Calcd for $C_{26}H_{28}O_7$: C, 69.01; H, 6.24. Found: C, 68.93; H, 6.24.

3,3′-(2,5-Furandiyl)bis(2-methoxy-5-methylbenzenemethanol) (53). A solution of 7.60 g (16.80 mmol) of diester **52** in 100 mL of THF was added dropwise over 20 min to a suspension of 1.55 g (40.84 mmol) of $LiAlH_4$ in 150 mL of THF at −78 °C. The reaction mixture was maintained at −78 °C for 2 h and then stirred for 1 h at 25 °C. After being quenched with 10% aqueous NaOH, the mixture was filtered through $MgSO_4$ and the filter cake was washed liberally with Et_2O. Removal of the solvent from the filtrate gave the diol **53** as a white solid after drying (6.12 g, 16.61 mmol, 99%). An analytical sample prepared by recrystallization from $CHCl_3$–heptane produced colorless crystals: mp 167.5–169 °C; ^1H NMR (200 MHz, $CDCl_3$) δ 2.39 (s, 3 H, $ArCH_3$), 3.77 (s, 3 H, OCH_3), 4.75 (s, 2 H, CH_2), 7.02 (s, 1 H, furan H), 7.11 (d, 1 H, ArH, *J* = 1.6 Hz), 7.66 (d, 1 H, ArH, *J* = 1.6 Hz); MS (70 eV, 190 °C) *m/e* M^+ 368 (100). Anal. Calcd for $C_{22}H_{24}O_5$: C, 71.72; H, 6.57. Found: C, 71.67; H, 6.56.

3,3′-(2,5-Furandiyl)bis[1-(bromomethyl)-2-methoxy-5-methylbenzene] (54). To 6.12 g (16.61 mmol) of diol **53** in 250 mL of dry benzene was added 2.5 mL (26.60 mmol) of PBr_3. The

suspension was stirred at 25 °C for 46 h during which it slowly dissolved. The reaction mixture was partitioned between 250 mL of Et_2O and 200 mL of 1:1 (v/v) water–$NaHCO_3$ (saturated). The aqueous phase was extracted with 200 mL of Et_2O, and the combined organic phases were dried ($MgSO_4$) and concentrated under reduced pressure to yield **54** as a white solid (6.70 g, 13.56 mmol, 82%). An analytical sample was recrystallized from CH_2Cl_2–heptane to give white warts: mp 154–155.5 °C; ^1H NMR (200 MHz, $CDCl_3$) δ 2.38 (s, 3 H, $ArCH_3$), 3.85 (s, 3 H, OCH_3), 4.60 (s, 2 H, CH_2), 7.04 (s, 1 H, furan H), 7.15 (d, 1 H, ArH, J = 2.2 Hz), 7.65 (d, 1 H, ArH, J = 2.2 Hz); MS (70 eV, 190 °C) m/e M^+ (^{79}Br) 492 (22). Anal. Calcd for $C_{22}H_{22}Br_2O_3$: C, 53.47; H, 4.49. Found: C, 53.54; H, 4.48.

24,25-Dimethoxy-8,22-dimethyl-12,15,18,26-tetraoxatetracyclo[18.3.1.1^{2,5}.1^{6,10}]hexacosa-1(24),2,4,6,8,10(25),20,22-octaene (9). To a refluxing suspension of 974 mg (w/oil) of NaH (20.30 mmol) in 250 mL of dry THF was added dropwise under high dilution over 30 h a solution of 2.342 g (4.74 mmol) of dibromide **54** and 517 mg (4.87 mmol) of dry diethylene glycol in 215 mL of THF. Reflux was maintained an additional 41 h. The reaction mixture was cooled, the excess NaH was quenched with water, and the products were partitioned between 100 mL of Et_2O and 100 mL of water. The aqueous layer was extracted with 250 mL of Et_2O, and the combined organic phases were washed with 200 mL of ion-free water, dried ($MgSO_4$), and evaporated in vacuo. The residue was taken up in CH_2Cl_2 and chromatographed on silica gel. Concentration of the eluate with a retention volume between 146 and 173 mL provided a solid that was washed with pentane and dried in vacuo. The cycle, thus obtained, was a fine, white solid pure by ^1H NMR (661 mg, 1.51 mmol, 32%). An analytical sample was purified by recrystallization from CH_2Cl_2–heptane to give fine, fluffy, white needles: mp 147–148 °C; ^1H NMR (200 MHz, $CDCl_3$) δ 2.30 (s, 3 H, $ArCH_3$), 3.50 (s, 3 H, OCH_3), 3.55–3.72 (m, 4 H, OCH_2), 4.55 (s, 2 H, $ArCH_2O$), 6.56 (s, 1 H, furan H), 7.00 (d, 1 H, ArH, J = 2.0 Hz), 7.16 (d, 1 H, ArH, J = 2.0 Hz); MS (70 eV, 190 °C) m/e M^+ 438 (100). Anal. Calcd for $C_{26}H_{30}O_6$: C, 71.21; H, 6.90. Found: C, 71.25; H, 6.86.

Crystal Structure Data. Compound **1** crystallized from CH_2Cl_2–CH_3OH–C_2H_5OH as colorless platelets in the monoclinic system $P2_1/c$. Unit cell dimensions are as follows: a = 13.936 (2) Å, b = 23.699 (3) Å, c = 18.599 (2) Å, β = 104.618 (4)°, V = 5944 Å^3, Z = 4. The crystal was examined on a modified Syntex P$\bar{1}$ diffractometer with Cu Kα radiation at 25 °C. The structure was determined by direct methods. Refinement of 208 parameters (4340 reflections with $I > 3\sigma(I)$) has an agreement value R currently at 0.097. Compound **2** crystallized from acetone–H_2O as very thin colorless platelets in the triclinic system P$\bar{1}$. Unit cell dimensions are as follows: a = 7.672 (1) Å, b = 9.243 (1) Å, c = 20.329 (3) Å, α = 100.151 (6)°, β = 94.383 (6)°, γ = 97.725 (6)°, V = 1403 Å^3, Z = 2. The crystal was examined on a modified Picker FACS-1 diffractometer with Mo Kα radiation at 25 °C. The structure was determined by direct methods. Refinement of 206 parameters (1905 reflections with $I > 3\sigma(I)$) has an agreement value currently at 0.075.

Compound **2**·$NaSbF_6$·CCl_4 crystallized from CCl_4–acetone as colorless multifaceted crystals in the monoclinic system $P2_1/n$. Unit cell dimensions are as follows: a = 13.5025 (6) Å, b = 15.1959 (7) Å, c = 18.9251 (8) Å, β = 92.411 (1)°, V = 3880 Å^3, Z = 4. The crystal was examined on a modified Picker FACS-1 diffractometer with Mo Kα radiation at 25 °C. The structure was determined by direct methods. Refinement of 318 parameters (4743 reflections with $I > 3\sigma(I)$) has an agreement value currently at 0.04.

Compound **4** crystallized from $CHCl_3$–C_2H_5OH as colorless parallelepipeds in the triclinic system P$\bar{1}$. Unit cell dimensions are as follows: a = 11.172 (4) Å, b = 11.895 (3) Å, c = 10.358 (3) Å, α = 111.71 (2)°, β = 93.08 (3)°, γ = 102.24 (3)°, V = 1236 Å^3, Z = 2. The crystal was examined on a Syntex P$\bar{1}$ diffractometer with Mo Kα radiation at 25 °C. The structure was determined by direct methods. Refinement of 343 parameters (3268 reflections with $I > 3\sigma(I)$) has an agreement value currently at 0.092.

Compound **6** crystallized from acetone–methanol as colorless needles in the monoclinic system $P2_1/a$. Unit cell dimensions are as follows: a = 7.304 (1) Å, b = 33.050 (5) Å, c = 11.068 (2) Å, β = 95.874 (5)°, V = 2658 Å^3, Z = 4. The crystal was examined on a modified Picker diffractometer with Mo Kα radiation at 25 °C. The structure was determined by direct methods. Refinement of 219 parameters (1925 reflections with $I > 2\sigma(I)$) has an agreement value currently at 0.11.

Compound **6**·$NaSbF_6$ crystallized from CH_2Cl_2–benzene as colorless parallelepipeds in the monoclinic system $P2_1/c$. Unit cell dimensions are as follows: a = 17.737 (2) Å, b = 11.366 (1) Å, c = 18.290 (2) Å, β = 117.208 (3)°, V = 3266 Å^3, Z = 4. The crystal was examined on a modified Picker FACS-1 diffractometer, with Mo Kα radiation at 25 °C. The structure was determined by direct methods. Refinement of 276 parameters (3120 reflections with $I > 3\sigma(I)$) has an agreement value currently at 0.05.

Further crystallographic details will be published elsewhere.

Acetylsilane *O*-Silylcyanohydrins as Precursors to α-Silyl Ketones and β-Siloxy-*N*,*N*-bissilylenamines

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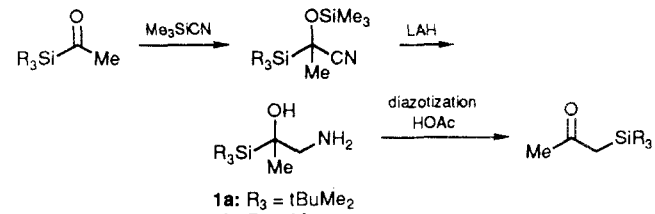
Reduction of acetylsilane *O*-silylcyanohydrins gave β-amino-α-hydroxysilanes, which were diazotized to give α-silyl ketones. The addition of organolithium reagents to the cyanohydrins was accompanied by sequential C → N and O → N silyl group migrations. Silylation of the resulting lithium enolates afforded β-siloxy-*N*,*N*-bissilylenamines.

Introduction

We have previously shown[1] that certain α,β-dihydroxysilanes undergo a proton-induced silapinacol rearrangement to afford α-(*tert*-butyldimethylsilyl) aldehydes and ketones, species that are synthetically useful as vinyl cation equivalents.[2] The less-hindered, but much more economical trimethylsilyl analogues, however, are unstable to the acidic conditions necessary for their formation,[1,3] and alternative approaches to these species were sought.

Scheme I



1a: R_3 = $tBuMe_2$
1b: R_3 = Me_3

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