= 15.5, 8.0 Hz), 5.63 (dd, 1 H, J = 15.5, 6.0 Hz); mass spectrum, m/e 269 (M + 1), 268, 250, 179, 151, 133, 119, 99, 71, 43 (base).

77: R_f 0.25 (100% ethyl acetate); IR ($CDCl_3$) 975, 1100, 1200, 1770, 3240–3560, 3620 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.88 (t, 3 H, J = 6.7 Hz), 1.24–1.55 (m, 8 H), 1.97 (ddd, 1 H, J = 14.8, 7.0, 2.9 Hz), 2.33 (q, 1 H, J = 7.8 Hz), 2.47 (dd, 1 H, J = 17.9, 1.7 Hz), 2.45–2.66 (m, 2 H), 2.75 (dd, 1 H, J = 17.9, 9.7 Hz), 3.99 (q, 1 H, J = 7.0 Hz), 4.11 (q, 1 H, J = 6.1 Hz), 4.91 (td, 1 H, J = 7.0, 2.9 Hz), 5.49 (ddd, 1 H, J = 15.5, 8.1, 0.9 Hz), 5.64 (dd, 1 H, J = 15.5, 5.9 Hz). Anal. Calcd for $C_{15}H_{24}O_4$: C, 67.14; H, 9.01. Found: C, 67.12; H, 8.98.

Acknowledgment. This research was supported in part by a grant from the National Institutes of Health (CA 22237). We also acknowledge the NSF for providing departmental funds for the purchase of JEOL-FX90Q, Brüker WM-360, and Brüker AM-300 NMR spectrometers.

Preorganized Macrocyclic Ligands: A Novel Approach to Functionalized Hemispherands via Aromatization

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Received February 23, 1987

Reaction of the 1,3-diaryl-2-propanone moiety in the flexible 18-membered macrocycle **2b** with nitromalonodialdehyde to yield the hemispherand **1f** represents a novel method for the synthesis of partly preorganized macrocyclic ligands. The O–O repulsion in the macrocyclic cavity is compensated for by the energetically favorable formation of an aromatic ring. The macrocycle **2b** was synthesized in five steps from **3a**. The carbonyl group of **3a** was protected via ketalization. Subsequent lithiation, reaction with dimethylformamide, reduction, and cyclization with diethylene glycol ditosylate gave the macrocycle **2a** in a yield of 68%. The X-ray crystal structure of **2a** shows that the methoxy groups are located at opposite faces of the macroring and the macrocyclic cavity is filled by the methoxy methyl groups. The binding free energies ($\Delta G°$) of **2a** and **2b**, determined by the picrate extraction method showed that they are poor ligands for alkali cations with the highest values measured for K^+ [8.5 (**2a**) and 7.6 (**2b**) kcal·mol^{-1}]. An alternative synthesis of functionalized hemispherands **1b–e** involved the synthesis of 5′-functionalized *m*-teranisyls and the subsequent introduction of the polyethyleneoxy bridge via the corresponding 3,3″-bis(hydroxymethyl) derivatives. Compound **3c** was synthesized in three steps from **8a** and converted into **4c** by reaction with nitromalonodialdehyde. The terphenyl **4c** was converted into *m*-teranisyls with different functional groups at the 5′-position. Depending on the functional group present at the 5′-position, an aldehyde group at the 3- and 3″-positions was introduced by either bromo to lithium exchange and reaction with dimethylformamide (**7a,e**) or by reaction of the 3,3″-unsubstituted *m*-teranisyls **4d** and **9b** with hexamethylenetetramine in trifluoroacetic acid. The hemispherands **1b–e** were obtained after reduction of the dialdehydes and macrocyclization of the bis(hydroxymethyl) derivatives with diethylene glycol ditosylate in 35–40% yields.

Introduction

The selective complexation of metal and organic cations has been studied mainly with flexible macrocyclic polyether hosts.[1] Complexation of a guest cation by a host molecule can be optimized by variation of the geometrical relationship between host and guest, and with polyfunctional cations such as guanidinium[2] or uronium[3] this approach has been proven successful.

An alternative way to increase the stability of a host–guest complex was introduced by Cram et al.[4] who demonstrated that preorganization of binding sites in a rigid molecular framework may lead to very stable complexes. This principle was experimentally demonstrated with the synthesis of the spherands and their complexes with Li^+ and Na^+ cations.[5] The very high negative values for the free energy of complexation can be attributed to three factors. First, because of the rigid molecular framework the host hardly undergoes the conformational changes upon complexation that generally lower the stability of complexes with flexible macrocyclic hosts. Second, as a consequence of the preorganization of the rigid host, repulsive forces between electronegative binding sites cannot be minimized by conformational changes in the uncomplexed host. Upon complexation of an electron-deficient guest, these repulsive forces are converted into attractive forces between host and guest. Third, the methoxy groups prevent solvent molecules from entering the cavity. Therefore the binding sites do not have to be desolvated during complexation.

In addition to the spherands, Cram et al. have synthesized compounds in which at least half of the binding

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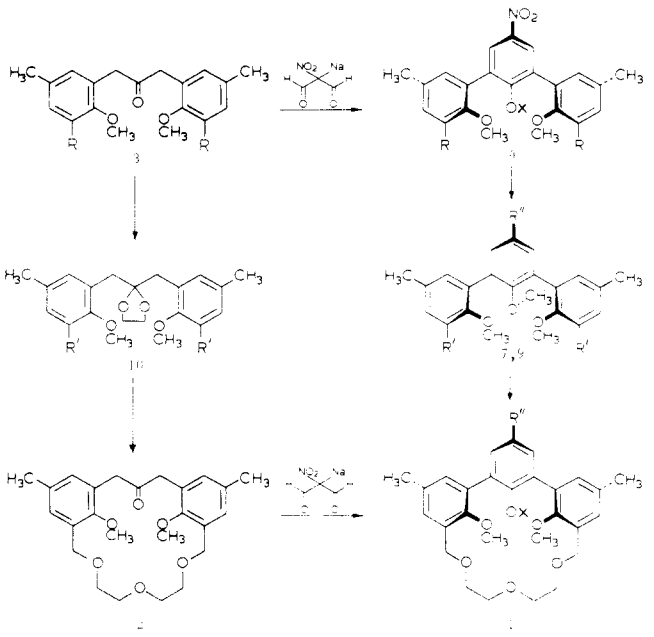
(5) (a) Cram, D. J.; Kaneda, T.; Helgeson, R. C.; Bruce Brown, R.; Knobler, C. B.; Maverick, E.; Trueblood, K. N. *J. Am. Chem. Soc.* **1985**, *107*, 3645. (b) Cram, D. J.; Lein, G. M. *J. Am. Chem. Soc.* **1985**, *107*, 3657.

0022-3263/87/1952-4913$01.50/0

Scheme I[a]



[a] Synthetic routes to functionalized hemispherands: R = H, Br; R′ = H, Br, CHO, CH_2OH, CH_2Br; R″ (see 1, 4, 7, 9); X = H, CH_3.

sites are preorganized, the (crypta)hemispherands. They have established that for the complexation of complementary alkali cations the free energy of binding decreases in the order spherands > cryptahemispherands > cryptands > hemispherands > chorands.[6]

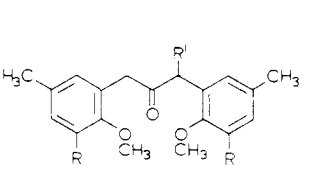
Hemispherands are of interest in our own work for two reasons. First, preorganization of ligating sites in macrocyclic hosts possibly increases the stability of complexes with *neutral* guest species such as urea,[7] nitromethane,[8] or malononitrile.[9] We have recently shown that in the complexation of neutral molecules by flexible macrocyclic hosts there is a large negative contribution of $T\Delta S°$ to the overall free energy of complexation that is small compared with the free energy of complexation of cations.[9] Since the molecular cavity of spherands and cryptahemispherands is only accessible for small cations, these hosts can be eliminated as potential hosts for neutral organic guests, leaving the hemispherands as an alternative.[10] Second, we have recently developed microsensors on the basis of ion-sensitive field-effect transistors (ISFET) modified by synthetic ionophores.[11,12] For stable microsensors based on this principle the covalent attachment of the ionophore to the oxide surface of the ISFET is a prerequisite. Moreover, we have found a highly selective response toward potassium cations in the presence of a large excess of sodium ions ($K_{K^+/Na^+} > 10^3$) using an ISFET modified with a membrane containing a certain hemispherand.[12b] Hemispherands with functional groups at the outer sphere will be required for covalent binding to the ISFET surface.

A fundamental problem in the synthesis of preorganized macrocycles with a high "ground-state" energy due to repulsion between the electron-rich binding sites is that this repulsion will also render the macrocyclization unfavorable. Although this may be partly compensated for by using a template electrophilic cation, yields of such preorganized molecules are generally low.

In this paper we describe the synthesis of hemispherands with modified outer spheres via the "classical" macrocyclization method together with a novel approach to these molecules (Scheme I). The strategy chosen was to synthesize a relatively flexible macrocyclic molecule that was subsequently converted into a rigid hemispherand by the introduction of the third aromatic ring via a condensation reaction of an incorporated dibenzyl ketone moiety with nitromalonodialdehyde. Tautomerization of the resulting 2,6-disubstituted 4-nitrocyclohexa-2,5-dien-1-one provides the aromatization energy, which compensates for the increased O···O repulsion in the resulting hemispherand.

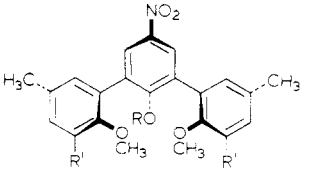
Results and Discussion

In a previous paper,[13] the synthesis of spherands with functional groups at the outer sphere according to Cram's method[5] was described. We anticipated that the synthesis of functionalized hemispherands, composed of the rigid *m*-teranisyl moiety and a flexible polyethyleneoxy bridge might be possible through the same intermediates (e.g., **7a**). The key step in the synthesis of *m*-teranisyls was the reaction of the 1,3-diarylpropanone **3a** and nitromalonodialdehyde to give **4a** in high yield. Methylation of the



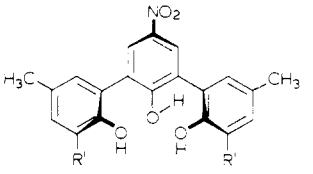
3

a, R = Br , R′ = H
b, R = H , R′ = $COOCH_2CH_3$
c, R = H , R′ = H



4

a, R = H , R′ = Br
b, R = CH_3 , R′ = Br
c, R = H , R′ = H
d, R = CH_3 , R′ = H



5

a, R = H
b, R = Br

2′-hydroxy group of **4a** to give **4b** and subsequent conversion of the 5′-nitro group provided a versatile method to synthesize a number of 5′-functionalized *m*-teranisyls. Alternatively, intermediate **4b** could be prepared from **4c**

(6) (a) Cram, D. J.; Ho, S. P. *J. Am. Chem. Soc.* **1986**, *108*, 2998. (b) Cram, D. J.; Ho, S. P.; Knobler, C. B.; Maverick, E.; Trueblood, K. N. *J. Am. Chem. Soc.* **1986**, *108*, 2989. (c) Lein, G. M.; Cram, D. J. *J. Am. Chem. Soc.* **1985**, *107*, 448.

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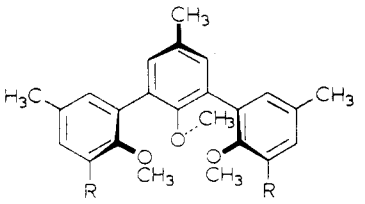
(vide infra). Selective direct bromination of **4c** with bromine in chloroform could not be achieved, and consequently **4c** was first demethylated with BBr_3 in CH_2Cl_2 to give **5a** in 79% yield. Bromination with Br_2 in $CHCl_3$ and methylation afforded **5b** and **4b** in 98% and 80% yields, respectively.

We have investigated several possibilities for the introduction of hydroxymethyl groups at the 3- and 3″-positions of the *m*-teranisyl moiety. In the literature, a method is described involving bromo or hydrogen to lithium exchange and reaction of the resulting 3,3″-dilithio-*m*-teranisyl with the electrophiles CO_2 or $ClCO_2Et$[14] to yield a dicarboxylic acid or diester, respectively, followed by reduction. Alternatively, a synthesis of **1a** has been described in which the 3- and 3″-hydroxymethyl groups were introduced ortho to the phenolic groups by reaction with formaldehyde and KOH.[6c]

We have investigated the introduction of formyl groups at the 3′ and 3″-positions of *m*-teranisyls because these can be easily reduced with sodium borohydride to the hydroxymethyl groups. It was important that this method is compatible with substituents at the 5′-position reactive toward reduction (e.g., **9c**). Two different methods have been tested with readily available *m*-teranisyls **6a**[5a] and **6b**.[14]

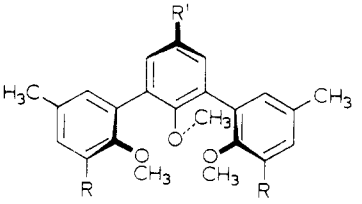


6

a, R = Br
b, R = H
c, R = CHO
d, R = CH_2OH

Lithiation of **6a** with *n*- or *tert*-butyllithium in diethyl ether gave the corresponding 3,3″-dilithio derivative, which was subsequently reacted with dimethylformamide. The yields of **6c** varied from 65 to 70%, and reduction of **6c** with sodium borohydride in methanol gave **6d** in high yield (>98%). In the second method **6b** was reacted with hexamethylenetetramine in trifluoroacetic acid (Duff reaction).[15] This method was an equally good way to synthesize **6c**. Contrary to the nonselective bromination of the *m*-teranisyl **4c** (vide supra), only the ortho-substituted product **6c** was obtained. The two methods used are to some extent complementary. The second method can be applied to 5′-functionalized *m*-teranisyls when the functional group present is reactive toward butyllithium reagents, but it cannot be applied for *m*-teranisyls unsubstituted at the 5′-position, because a formyl group will also be introduced there.

The first formylation method mentioned, via lithiation, has been applied to compounds **7a**[13] and **7e**. A hemispherand derived from **7a** would have a single activated site para to the central methoxy group, and a hemispherand derived from **7e** already contains an acyl substituent that can be further modified. The *m*-teranisyl **7a** was

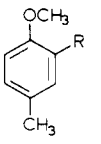


7

a, R = Br , R′ = H
b, R = CHO , R′ = H
c, R = CH_2OH , R′ = H
d, R = Br , R′ = $COCH_3$
e, R = Br , R′ =
f, R = CHO , R′ = ″
g, R = CH_2OH , R′ = ″

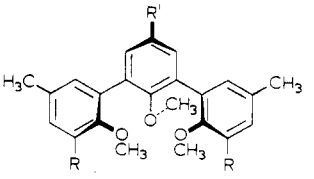
acylated with acetic acid P_2O_5 in methanesulfonic acid to give **7d** in 86% yield. The carbonyl group was protected through the cyclic ethylene ketal by reaction of **7d** and ethylene glycol to give **7e** in 80% yield. Reaction of **7a** or **7e** with *n*- or *tert*-butyllithium and subsequently DMF afforded **7b** and **7f**, respectively. These compounds were reduced with sodium borohydride in methanol to afford **7c** and **7g** in 55% overall yield based on **7a** and **7e**, respectively.

To investigate the scope of the Duff methodology mentioned we prepared two other 5′-functionalized *m*-teranisyls **4d** (R′ = NO_2) and **9b** (R′ = Br), which are unsubstituted at the 3- and 3″-positions. The intermediate **4c** was synthesized as described for **4b**,[13] starting from a 1,3-diarylpropanone and subsequent conversion into a 1,1′:3′,1″-terphenyl by reaction with nitromalonodialdehyde. Starting from 4-methylanisole, **8a** was prepared by reaction with formaldehyde and hydrochloric acid in 64% yield.[16] The benzyl chloride **8a** was converted into

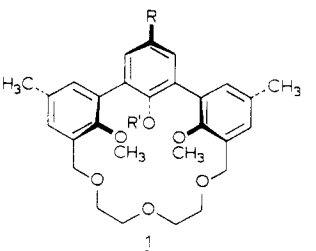


8

a, R = CH_2Cl
b, R = CH_2CN
c, R = $CH_2COOCH_2CH_3$
d, R = CH_2COOH



9



1

a, R = H , R′ = NH_2
b, R = H , R′ = Br
c, R = CHO , R′ = NO_2
d, R = CHO , R′ = Br
e, R = CH_2OH , R′ = NO_2
f, R = CH_2OH , R′ = Br
g, R = CH_2Br , R′ = NO_2

a, R = CH_3 , R′ = CH_3
b, R = H , R′ = CH_3
c, R = $COCH_3$, R′ = CH_3
d, R = Br , R′ = CH_3
e, R = NO_2 , R′ = CH_3
f, R = NO_2 , R′ = H
g, R = CH_3 , R′ = H

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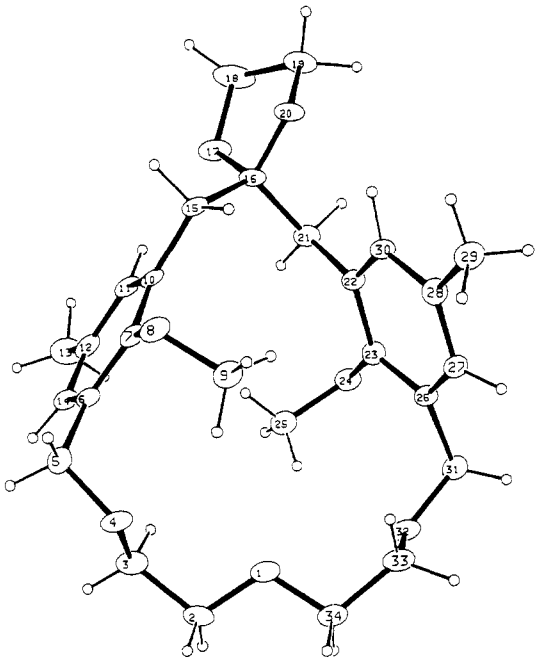


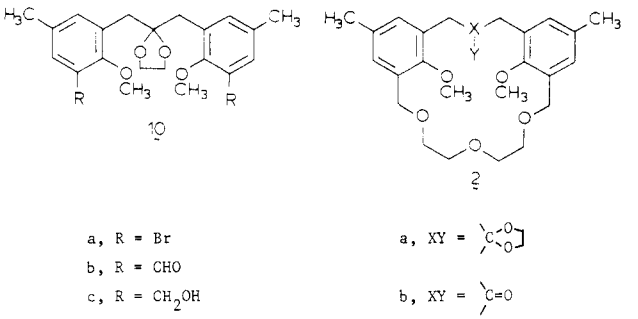
Figure 1. View of the structure of **2a** showing atom numbering.

the corresponding benzyl cyanide **8b** upon reaction with sodium cyanide and a catalytic amount of sodium iodide in dichloromethane in 93% yield as an oil. By a modification of the Pinner synthesis,[17] **8b** in a mixture of ethanol and 60% sulfuric acid was converted to the ethyl arylacetate **8c** in 89% yield together with 5–10% of the corresponding arylacetic acid **8d**. The Claisen condensation of **8c** with isopropylmagnesium bromide was performed as described for **3a**[13] to give the β-keto ester **3b**, which was directly converted into **3c**. The overall yield of these two reactions was 56%. Reaction of **3c** with nitromalonodialdehyde sodium salt and sodium hydroxide in water/ethanol afforded **4c** in 50% yield. Methylation of the 2′-hydroxy group with methyl iodide in dry acetone and K_2CO_3 afforded **4d** in 95% yield. The 5′-bromo-substituted 1,1′:3′,1″-terphenyl **9b** was synthesized by reduction of the 5′-nitro group in **4d** with tin(II) chloride in ethanol[18] to give **9a** in 70% yield followed by a Sandmeyer reaction to afford **9b** in 42% yield.

Upon reaction with hexamethylenetetramine in trifluoroacetic acid, **4d** and **9b** were converted into the 3,3″-formyl-substituted compounds **9c** and **9d**, respectively, in 53–60% yield. The ^1H NMR spectra of **9c** and **9d** showed doublets (J = 1.5 Hz) for the formyl-substituted aromatic rings. This coupling constant is characteristic for a meta coupling and shows that substitution ortho to the methyl substituents does not occur. Reduction of the formyl substituents in **9c** and **9d** with sodium borohydride in methanol gave the bis(hydroxymethyl) derivatives **9e** and **9f** in almost quantitative yields.

Macrocyclization of the bis(hydroxymethyl) derivatives **7c**, **7g**, and **9f** to the corresponding hemispherands was achieved by reaction with diethylene glycol ditosylate and sodium hydride as a base in tetrahydrofuran (THF) under high-dilution conditions. The hemispherands **1b** and **1d** were obtained in 38% and 40% yields, respectively, whereas **1c** was obtained in 38% yield after subsequent acid hydrolysis of the reaction mixture and isolation. The bis(hydroxymethyl) derivative **9e** was first converted into the bis(bromomethyl) derivative **9g** by reaction with PBr_3 in benzene in 75% yield. Reaction of **9g** with diethylene glycol and sodium hydride in THF afforded the hemispherand **1e** in 34% yield.

Generally, the disadvantage in the synthesis of hemispherands is the modest yield in the macrocyclization reaction when the rigid *m*-teranisyl unit is incorporated in the starting compound. An alternative way would be the synthesis of a rather flexible macrocycle, which generally proceeds in better yield, and the subsequent introduction of the rigid moiety. The synthesis of *m*-teranisyls, as described above for the reaction of nitromalondialdehyde with 1,3-diarylpropanones **3a** and **3c**, would provide a novel route to macrocycles with preorganized cavities when this reaction could be applied to a macrocycle incorporating the flexible 1,3-diarylpropanone moiety. To investigate this method, we started from **3a**, the carbonyl group of which was protected via ketalization to give **10a** in almost quantitative yield. This protecting group is



10

a, R = Br
b, R = CHO
c, R = CH_2OH

2

a, XY =
b, XY =

resistant to alkyllithium reagents under the subsequent reaction conditions.[19] Bromo to lithium exchange with *tert*-butyllithium in diethyl ether at −78 °C and subsequent reaction with DMF gave **10b** as an oil after chromatographic purification. Subsequent sodium borohydride reduction of the formyl groups of **10b** afforded **10c** in 49% yield based on **10a**. The new macrocycle **2a** was obtained from **10c** and diethylene glycol ditosylate and sodium hydride in THF in 65–70% yield. Our predictions of higher flexibility and higher yield for this macrocycle appeared to be correct, as was confirmed by the X-ray crystal structure of **2a**. The ORTEP view (Figure 1) shows that the methoxy groups are situated at different faces of the macroring and their methyl groups are directed toward the center of the cavity. This converging of the oxygen methyl groups appears to be characteristic for flexible macrocycles containing anisyl units and has been found in expanded hemispherands[14b] and hemispherands containing a central pyridine ring.[10] The cyclic ketal function is positioned outwardly, and the conformation of the ethyleneoxy bridge is all-gauche. Extensive conformational changes are necessary to provide a cavity that places the methoxy groups on the same face of the macroring.

The ^1H NMR spectrum ($CDCl_3$) of **2a** shows the aryl hydrogen atoms at δ 7.67 and 6.89. The methoxy hydrogen atoms are found at δ 3.02 and the hydrogen atoms of the cyclic ketal at δ 4.14. The $ArCH_2O$ protons appear as a singlet at δ 4.41. This is different from the AB system found for the $ArCH_2O$ protons in **1a**, resulting from slow ring inversion on the ^1H NMR time scale. Upon complexation of **2a** with potassium picrate, all signals except the $ArCH_3$ signal become broad in the temperature range of −70 to +25 °C. Therefore, we conclude that in the

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complex several slowly interconverting conformations exist.

The association constants (K_a) and binding free energies ($-\Delta G°$) of complexation of **2a** and alkali picrates were measured in deuteriochloroform according to the method described by Cram and co-workers.[14] The K_a (M^{-1}) and $-\Delta G°$ (kcal·mol^{-1}) values obtained were for Na^+, 1.9×10^5 (7.2); for K^+, 1.8×10^6 (8.5); for Rb^+, 4.1×10^5 (7.6); and for Cs^+, 8.0×10^4 (6.7), respectively, whereas the value for lithium picrate was too low to be measured.

Deprotecting **2a** in a methanol/hydrochloric acid mixture afforded **2b** in 98% yield. The ^1H NMR spectrum of **2b** showed a singlet for the $ArCH_2O$ protons at δ 4.36. As in the case of **2a**, upon complexation of **2b** with potassium picrate only broad signals were observed in the ^1H NMR spectrum. The K_a and $-\Delta G°$ values (vide supra) measured were for Na^+, 9.0×10^4 (6.7); for K^+, 4.0×10^5 (7.6); for Rb^+, 2.1×10^5 (7.2); and for Cs^+, 8.1×10^4 (6.6), whereas the values for lithium picrate were too low to be measured.

Reaction of **2b** with the sodium salt of nitromalonodialdehyde and sodium hydroxide in an ethanol/water mixture afforded the hemispherand **1f**. The reaction could be forced to completion when a large excess of nitromalonodialdehyde was used, giving **1f** in 89% yield. The ^1H NMR spectrum ($CDCl_3$) showed the symmetry of the product, a singlet for the 4′,6′-hydrogen atoms at δ 8.41 and singlets for methoxy and methyl hydrogen atoms at δ 3.54 and 2.35, respectively. As expected, the benzylic hydrogen atoms appear as an AB system (J_{AB} = 11.5 Hz) due to the slow ring inversion on the ^1H NMR time scale. The K_a and $-\Delta G°$ values obtained as described above were for Li^+, 1.3×10^5 (6.9); for Na^+, 5.3×10^5 (7.9); for K^+ 4.7×10^5 (7.7); for Rb^+, 1.8×10^5 (7.1); and for Cs^+, 8.0×10^4 (6.6). The values correspond well with those reported by Cram et al. for **1g**.[6c] Methylation of the hydroxyl group in **1f** with methyl iodide and K_2CO_3 afforded **1e** in 95% yield. The K_a and $-\Delta G°$ values of alkali picrate complexation (as described above) determined for **1e** and other functionalized hemispherands are nearly the same as reported for **1a**,[6c] substituent effects were within the accuracy of the method ($-\Delta G° \sim 0.3$ kcal·mol^{-1}). This result confirms our picture with regard to the synthesis of hemispherands. A flexible macrocycle **2a** or **2b** was synthesized in good yields, and the aromatization of the 2,6-disubstituted 4-nitrocyclohexa-2,5-dien-1-one to the 2,6-disubstituted 4-nitrophenol is energetically favorable and can be used for the introduction of the rigid moiety in a macrocyclic ketone of type **2b**.

Experimental Section

Melting points were determined with a Reichert melting point apparatus and are uncorrected. ^1H NMR spectra were recorded with a Bruker WP-80 spectrometer, and ^{13}C NMR spectra were recorded with a Nicolet MT 200 spectrometer in $CDCl_3$ unless otherwise indicated (Me_4Si as an internal standard). Mass spectra were obtained with a Varian MAT 311A spectrometer and IR spectra with a Perkin-Elmer 257 spectrophotometer. Absorbance readings in the UV for association constants were taken on a Zeiss M4QIII spectrophotometer. Elemental analyses were carried out by A. M. Christenhusz of the Laboratory of Chemical Analysis, University of Twente.

Tetrahydrofuran (THF) was freshly distilled from sodium benzophenone ketyl, whereas *N*,*N*-dimethylformamide (DMF) and diethyl ether were dried over 4-Å molecular sieves. All reactions in which dry solvents were used were carried out in a nitrogen atmosphere. Chromatographic separations mentioned were performed on silica gel 60 (SiO_2) (E. Merck, particle size 0.040–0.063 mm, 230–240 mesh) or aluminum oxide (Al_2O_3) (E. Merck, neutral grade, particle size 0.063–0.300 mm, 70–230-mesh ASTM). Nitromalonodialdehyde sodium salt was prepared from mucobromic acid.[20] All mass spectra were calculated for ^{79}Br.

2-Methoxy-5-methylbenzeneacetonitrile (8b). A mixture of **8a**[16] (85.0 g, 0.5 mol), sodium cyanide (38.0 g, 0.77 mol), and sodium iodide (3.9 g, 0.026 mol) in 250 mL of acetone was heated under reflux for 15 h. After filtration, the solvent was evaporated under reduced pressure. The resulting oil was distilled to give **8b** as a pale yellow oil: yield 93%; bp 108 °C (2 mmHg); ^1H NMR δ 7.60–7.20 (m, 3 H, Ar H), 3.75 (s, 3 H, OCH_3), 3.55 (s, 2 H, CH_2), 2.25 (s, 3 H, CH_3); IR (NaCl) 2240 (C≡N) cm^{-1}.

Ethyl 2-Methoxy-5-methylbenzeneacetate (8c). A solution of **8b** (29.0 g, 0.18 mol) in 50 mL of ethanol and 50 mL of H_2SO_4 was refluxed for 18 h. Upon cooling to room temperature, the mixture was poured into 100 mL of water. The resulting mixture was extracted with diethyl ether (3 × 50 mL). The combined organic phases were washed first with water and then a 10% aqueous $NaHCO_3$ solution and dried with $MgSO_4$. The solvent was removed under reduced pressure to give **8c** as an oil, which was distilled under reduced pressure: yield 89%; bp 112 °C (0.1 mmHg); mass spectrum, *m/e* 208.110 (M^+) (calcd 208.110); ^1H NMR δ 7.04–6.68 (m, 3 H, Ar H), 4.15 (q, 2 H, CH_2), 3.76 (s, 3 H, OCH_3), 3.54 (s, 2 H, Ar CH_2), 2.23 (s, 3 H, Ar CH_3), 1.24 (t, 3 H, CH_3); IR (NaCl) 1733 (C=O) cm^{-1}.

1,3-Bis(2-methoxy-5-methylphenyl)-2-propanone (3c). An ice-cold filtered through glass wool solution of isopropylmagnesium bromide (66.3 g, 0.45 mol) in 225 mL of dry diethyl ether was added slowly to a solution of **8c** (45.0 g, 0.22 mol) in 225 mL of dry diethyl ether at 0 °C. The reaction mixture was stirred for 18 h at room temperature and poured on 800 g of ice. The resulting mixture was acidified to pH 4 with concentrated sulfuric acid, and the layers were separated. The aqueous layer was extracted with two more portions of diethyl ether. The combined organic phases were dried ($MgSO_4$), and the solvent was removed under reduced pressure to give a pale yellow oil. To this oil were added 700 mL of dioxane and 900 mL of 4 N HCl, and the resulting mixture was stirred under reflux for 18 h. The reaction mixture was poured into 1 L of water and extracted with diethyl ether (3 × 300 mL). The combined organic phases were washed with water, dried ($MgSO_4$), and filtered, and the solvent was removed under reduced pressure. The resulting oil crystallized slowly from ligroin (bp 60–80 °C) at −20 °C to afford **3c**, as white crystals: yield 56%; mp 51–52 °C; mass spectrum, *m/e* 298.159 (M^+) (calcd 298.157); ^1H NMR δ 7.08–6.70 (m, 6 H, Ar H), 3.75 (s, 6 H, OCH_3), 3.66 (s, 4 H, CH_2), 2.25 (s, 6 H, CH_3). Anal. Calcd for $C_{19}H_{22}O_3$: C, 76.49; H, 7.43. Found: C, 76.71; H, 7.65.

2,2″-Dimethoxy-5,5″-dimethyl-5′-nitro-1,1′:3′,1″-terphenyl-2′-ol (4c). A solution of **3c** (0.24 g, 0.81 mmol) in 3 mL of ethanol was added to a solution of nitromalonodialdehyde sodium salt in 0.6 mL of water. A solution of NaOH (0.13 g, 3.25 mmol) in 0.3 mL of water was added dropwise (20 min), and the reaction mixture was stirred for 18 h at 35 °C. The reaction mixture was concentrated under reduced pressure and acidified with 4 N HCl to pH 2–3. The reaction products were extracted with diethyl ether (3 × 25 mL), and the combined organic phases were dried with $MgSO_4$. After filtration the solvent was removed under reduced pressure to give a residue that upon crystallization from ethanol gave pale yellow crystals of **4c**: yield 50%; mp 152–153 °C; mass spectrum, *m/e* 379.144 (M^+) (calcd for 379.142); ^1H NMR δ 8.19 (s, 2 H, 4′,6′-H), 7.17–6.87 (m, 6 H, Ar H), 3.81 (s, 6 H, OCH_3), 2.36 (s, 6 H, CH_3). Anal. Calcd for $C_{22}H_{21}NO_5$: C, 69.64; H, 5.58; N, 3.69. Found: C, 69.64; H, 5.81; N, 3.40.

2,2′,2″-Trimethoxy-5,5″-dimethyl-5′-nitro-1,1′:3′,1″-terphenyl (4d). A mixture of **4c** (20.0 g, 53 mmol), K_2CO_3 (9.9 g, 72 mmol), and methyl iodide (16.9 g, 120 mmol) in 200 mL of dry acetone was heated under reflux for 16 h. The reaction mixture was cooled to 10 °C and filtered, and the filtrate was concentrated under reduced pressure. The residue obtained was recrystallized from ethanol to give **4d**: yield 95%; mp 118–119 °C; mass spectrum *m/e* 393.156 (M^+) (calcd 393.158); ^1H NMR δ 8.13 (s, 2 H, 4′,6′-H), 7.22–7.12 (m, 6 H, Ar H), 3.78 (s, 6 H, OCH_3), 3.28 (s, 3 H, 2′-OCH_3), 2.32 (s, 6 H, Ar CH_3). Anal. Calcd for $C_{23}H_{23}NO_5$: C, 70.21; H, 5.89; N, 3.56. Found: C, 70.19; H, 6.13; N, 3.45.

5,5″-Dimethyl-5′-nitro-1,1′:3′,1″-terphenyl-2,2′,2″-triol (5a). BBr_3 (4.4 mL, 46 mmol) was slowly added to a solution of **4c** (12.1

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g, 32 mmol) in 250 mL of CH_2Cl_2 at −78 °C. The reaction mixture was warmed to room temperature, stirred for 16 h, and poured into water. The reaction products were extracted with another 200 mL of CH_2Cl_2. The combined organic layers were dried ($MgSO_4$), and the solvent was removed under reduced pressure to give a residue, which was recrystallized from ethanol to give pure **5a**: yield 79%; mp 270–271 °C; mass spectrum, *m/e* 351.107 (M^+) (calcd 351.111); ^1H NMR (acetone-d_6), δ 8.15 (s, 2 H, 4′,6′-H), 7.17–6.86 (m, 6 H, Ar H), 2.31 (s, 6 H, CH_3). Anal. Calcd for $C_{20}H_{17}NO_5$: C, 68.37; H, 4.88; N, 3.99. Found: C, 68.17; H, 4.77; N, 3.88.

3,3″-Dibromo-5,5″-dimethyl-5′-nitro-1,1′:3′,1″-terphenyl-2,2′,2″-triol (5b). To a mixture of **5a** (5.06 g, 14.4 mmol) and 180 mL of $CHCl_3$ was added a solution of Br_2 (1.6 mL, 28.8 mmol) in 15 mL of $CHCl_3$ dropwise at 0 °C. The reaction mixture was stirred for 20 h at room temperature. To the resulting mixture was added 100 mL of a 5% $NaHSO_3$ solution, and the reaction products were extracted with $CHCl_3$. The combined organic layers were washed once with 100 mL of water, and the solvent was evaporated to give a yellow residue, which was recrystallized from acetone to give pale yellow crystals of pure **5b**: yield 98%; mp >300 °C; mass spectrum, *m/e* 506.933 (M^+) (calcd 506.932); ^1H NMR (acetone-d_6), δ 8.13 (s, 2 H, 4′,6′-H), 7.42 and 7.15 (d, 4 H, Ar H), 2.77 (br s, 3 H, OH), 2.32 (s, 6 H, Ar CH_3). Anal. Calcd for $C_{20}H_{15}Br_2NO_5 \cdot H_2O$: C, 45.56; H, 3.25; N, 2.66. Found: C, 45.81; H, 3.13; N, 2.43.

3,3″-Dibromo-2,2′,2″-trimethoxy-5,5″-dimethyl-5′-nitro-1,1′:3′,1″-terphenyl (4b). To a solution of **5b** (5.72 g, 11.2 mmol) in 200 mL of THF was added a solution of KOH (7.2 g, 0.13 mol) in 8.5 mL of water. Dimethyl sulfate (13.6 g, 0.11 mol) was added over a 5-min period, and the resulting mixture was heated under reflux for 16 h. The organic solvent was evaporated under reduced pressure, and the residue was shaken with 100 mL of diethyl ether and 100 mL of water. The organic phase was washed with 100 mL of water and dried ($MgSO_4$), and the solvent was evaporated under reduced pressure to give a residue, which was crystallized from ethanol to give pure **4b**, yield 80%. The product was identical with the previously described **4b**.[13]

3,3″-Dibromo-2,2′,2″-trimethoxy-5,5″-dimethyl-1,1′:3′,1″-terphenyl-5′-ethanone (7d). A mixture of P_2O_5 (2.1 g, 15 mmol) in 15 mL of methanesulfonic acid was stirred for 1 h at 60 °C. Then 0.6 mL of glacial acetic acid and **7a**[13a] (1.51 g, 3.0 mmol) were added. The resulting mixture was stirred for 20 h at room temperature, poured into 40 mL of water, and extracted with chloroform (2 × 50 mL). The combined organic phases were washed with water, 10% $NaHCO_3$, and water again and dried ($MgSO_4$). The solvent was evaporated under reduced pressure, and the product was purified by chromatography (SiO_2, $CHCl_3$) and recrystallization from ethanol to give pure **7d** as white crystals: yield 86%; mp 84–85 °C; mass spectrum, *m/e* 546.000 (M^+) (calcd 546.004); ^1H NMR δ 7.94 (s, 2 H, 4′,6′-H), 7.42 and 7.12 (d, 4 H, Ar H), 3.56 (s, 6 H, OCH_3), 3.31 (s, 3 H, 2′-OCH_3), 2.60 (s, 3 H, $COCH_3$), 2.34 (s, 6 H, Ar CH_3). Anal. Calcd for $C_{25}H_{24}Br_2O_4$: C, 54.77; H, 4.41. Found: C, 54.83; H, 4.67.

3,3″-Dibromo-2,2′,2″-trimethoxy-5,5″-dimethyl-1,1′:3′,1″-terphenyl-5′-ethanone Ethylene Acetal (7e). In a round-bottomed flask fitted with a Soxhlet extractor (containing 4-Å molecular sieves) was heated under reflux for 48 h a mixture of **7d** (0.8 g, 1.5 mmol), ethylene glycol (1.0 g, 16 mmol), and *p*-toluenesulfonic acid monohydrate (0.02 g) in 100 mL of dry benzene. The solvent was evaporated under reduced pressure, and 50 mL of water and 25 mL of chloroform was added. The aqueous phase was extracted with another 25 mL of chloroform, and the combined organic phases were washed with water and brine and dried ($MgSO_4$), and the solvent was evaporated under reduced pressure. The product was purified by chromatography (SiO_2, $CHCl_3$) and crystallized from ethanol to give **7e**: yield 80%; mp 120–121 °C; mass spectrum, *m/e* 590.035 (M^+) (calcd, 590.030); ^1H NMR δ 7.45 (s, 2 H, 4′,6′-H), 7.38 (d, 2 H, Ar H), 7.14 (d, 2 H, Ar H), 4.04–3.82 (m, 4 H, OCH_2), 3.54 (s, 6 H, OCH_3), 3.24 (s, 3 H, 2′-OCH_3), 2.32 (s, 6 H, Ar CH_3), 1.69 (s, 3 H, CH_3). Anal. Calcd for $C_{27}H_{28}Br_2O_5$: C, 54.56; H, 5.09. Found: C, 54.89; H, 5.02.

2,2′,2″-Trimethoxy-5,5″-dimethyl-1,1′:3,1″-terphenyl-5′-amine (9a). A mixture of **4d** (1.0 g, 2.54 mmol) and $SnCl_2$ (5.17 g, 22.9 mmol) in 10 mL of ethanol was refluxed for 16 h. The reaction mixture was poured into 50 mL of water and extracted with $CHCl_3$ (3 × 25 mL). The combined organic phases were washed with water and dried with $MgSO_4$, and the solvent was evaporated under reduced pressure. The white solid obtained was recrystallized from ethanol to give **9a**: yield 70%; mp 155–156 °C; mass spectrum, *m/e* 363.182 (M^+) (calcd 363.183); ^1H NMR δ 7.30–6.80 (m, 6 H, Ar H), 6.60 (s, 2 H, 4′,6′-H), 3.76 (s, 6 H, OCH_3), 3.48 (br s, 2 H, NH_2), 3.12 (s, 3 H, 2′-OCH_3), 2.30 (s, 6 H, Ar CH_3). Anal. Calcd for $C_{23}H_{25}NO_3$: C, 76.01; H, 6.93; N, 3.85. Found: C, 76.02; H, 6.98; N, 3.66.

5′-Bromo-2,2′,2″-trimethoxy-5,5″-dimethyl-1,1′:3′,1″-terphenyl (9b). A mixture of **9a** (2.0 g, 5.5 mmol), 20 mL of glacial acetic acid, 4 mL of sulfuric acid, and 5 mL of water was heated to give a clear solution and cooled to room temperature. To the resulting suspension was added a solution of $NaNO_2$ (0.57 g, 8.2 mmol) in 5 mL of water at 0–5 °C, and the resultant mixture was stirred for 0.5 h. The excess $NaNO_2$ was destroyed by the addition of sulfamic acid until evolution of N_2 ceased. The cooled reaction mixture was added to a solution of CuBr (0.87 g, 6.1 mmol) in 4 mL of 47% HBr at 5 °C. The resulting mixture was slowly heated to 45 °C where gas evolution occurs and heated for 0.5 h at 90 °C. After cooling, the mixture was extracted with chloroform (3 × 25 mL), and the combined organic phases were washed with water, a 10% aqueous $NaHCO_3$ solution, and water and dried ($MgSO_4$), whereupon the organic solvent was evaporated under reduced pressure. The residue was submitted to chromatography (SiO_2, CH_2Cl_2/ligroin (bp 40–60 °C), 1/2, v/v) to give **9b**, which was recrystallized from ethanol: yield 42%; mp 143–144 °C; mass spectrum, *m/e* 426.082 (M^+) (calcd 426.083); ^1H NMR δ 7.35–6.79 (m, 8 H, Ar H), 3.76 (s, 6 H, OCH_3), 3.18 (s, 3 H, 2′-OCH_3), 2.30 (s, 6 H, Ar CH_3). Anal. Calcd for $C_{23}H_{23}BrO_3$: C, 64.64; H, 5.42. Found: C, 64.56; H, 5.50.

2,2′,2″-Trimethoxy-5,5′,5″-trimethyl-1,1:3′,1″-terphenyl-3,3″-dicarboxaldehyde (6c). Procedure A. To a solution of **6a**[5a] (0.52 g, 1 mmol) in 20 mL of dry diethyl ether was added *tert*-butyllithium (3.0 mL, 2.0 mmol) at −78 °C. The mixture was stirred for 10 min, and dimethylformamide (0.31 mL, 4 mmol) was added. The reaction mixture was slowly warmed up to room temperature, and 20 mL of 2 M HCl was added. The reaction products were extracted with chloroform (3 × 25 mL). The combined organic layers were washed with water and dried ($MgSO_4$), and the solvent was evaporated under reduced pressure. The product was purified by chromatography (SiO_2, $CHCl_3$). A small sample was crystallized from diisopropyl ether to give pure **6c** as white crystals: yield 66%; mp 134–135 °C; mass spectrum, *m/e* 418.780 (M^+) (calcd 418.780); ^1H NMR δ 10.43 (s, 2 H, CHO), 7.69 (d, 2 H, Ar H), 7.43 (d, 2 H, Ar H), 7.20 (s, 2 H, Ar H), 3.63 (s, 6 H, OCH_3), 3.18 (s, 3 H, 2′-OCH_3), 2.39 (s, 9 H, CH_3). Anal. Calcd for $C_{26}H_{26}O_5$: C, 74.62; H, 6.26. Found: C, 74.58; H, 6.51.

Procedure B. A mixture of **6b**[14] (3.54 g, 9.7 mmol), hexamethylenetetraamine (4.2 g, 30 mmol), and 45 mL of trifluoroacetic acid was stirred at 80–90 °C for 4 days. The reaction mixture was poured into 300 mL of water, stirred for 11 h, and extracted with chloroform (3 × 75 mL). The combined organic layers were washed with 4 M HCl, water, 10% $NaHCO_3$ and brine and dried over $MgSO_4$. After evaporation of the solvent under reduced pressure, the crude product was purified as described in procedure A to give **6c**, yield 67%.

2,2′,2″-Trimethoxy-5,5″-trimethyl-1,1′:3′,1″-terphenyl-3,3″-dicarboxaldehyde (7b). Procedure A was applied to **7a**.[13a] The product obtained after chromatography was submitted to the next reaction without full characterization: yield 62%; mp 121–122 °C; mass spectrum, *m/e* 404.165 (M^+) (calcd for $C_{25}H_{24}O_5$ 404.162); ^1H NMR δ 10.45 (s, 2 H, CHO), 7.69–7.26 (m, 7 H, Ar H), 3.61 (s, 6 H, OCH_3), 3.21 (s, 3 H, 2′-OCH_3), 2.40 (s, 6 H, CH_3); ^{13}C NMR δ 190.3 (d, CHO).

2,2′,2″-Trimethoxy-5,5″-dimethyl-5′-[1-(ethylenedioxy)ethyl]-1,1′:3,1″-terphenyl-3,3″-dicarboxaldehyde (7f). Procedure A was applied to **7e**. The reaction product obtained was purified by chromatography (SiO_2, ethyl acetate/25% ligroin, 40/60) and submitted to the next reaction: yield 50%; ^1H NMR δ 10.42 (s, 2 H, CHO), 7.62 (d, 2 H, Ar H), 7.48 (s, 2 H, Ar H), 7.40 (d, 2 H, Ar H), 4.20–3.80 (m, 4 H, OCH_2), 3.60 (s, 6 H, OCH_3), 3.19 (s, 3 H, 2′-OCH_3), 2.40 (s, 6 H, Ar CH_3), 1.70 (s, 3 H, CH_3).

2,2′,2″-Trimethoxy-5,5″-dimethyl-5′-nitro-1,1′:3,1″-terphenyl-3,3″-dicarboxaldehyde (9c). Procedure B was applied to **4d** to give **9c** as pale yellow crystals: yield 53%; mass spectrum, *m/e* 449.150 (M^+) (calcd 449.147); ^1H NMR δ 10.42 (s, 2 H, CHO), 8.31 (s, 2 H, 4′,6′-H), 7.76 (d, 2 H, Ar H), 7.45 (d, 2 H, Ar H), 3.65 (s, 6 H, OCH_3), 3.31 (s, 3 H, 2′-OCH_3), 2.42 (s, 6 H, Ar CH,3). Anal. Calcd for $C_{25}H_{23}NO_7$: C, 66.81; H, 5.16; N, 3.12. Found: C, 66.89; H, 5.45; N, 3.30.

5′-Bromo-2,2′,2″-trimethoxy-5,5″-dimethyl-1,1′:3′,1″-terphenyl-3,3″-dicarboxaldehyde (9d). Procedure B was applied to **9b** to give pure **9d** as white crystals: yield 60%; mp 150–152 °C; mass spectrum *m/e* 482.071 (M^+) (calcd 482.073); ^1H NMR δ 10.43 (s, 2 H, CHO), 7.70 (d, 2 H, Ar H), 7.55 (s, 2 H, 4′,6′-H), 7.43 (d, 2 H, Ar H), 3.65 (s, 6 H, OCH_3), 3.20 (s, 3 H, 2′-OCH_3), 2.40 (s, 6 H, Ar CH_3). Anal. Calcd for $C_{25}H_{23}Br_2O_5$: C, 62.12; H, 4.80. Found: C, 62.81; H, 5.13.

3,3′-[2-(Ethylenedioxy)-1,3-propanediyl]bis(2-methoxy-5-methylbenzaldehyde) (10b). Procedure A was applied to **10a** to give a pale yellow oil. The oil was chromatographed (Al_2O_3, toluene/chloroform, 2/1) to give **10b** as a colorless oil: yield 66%; mas spectrum *m/e* 398.175 (M^+) (calcd for $C_{23}H_{26}O_6$ 398.173); ^1H NMR δ 10.34 (s, 2 H, CHO), 7.52 (m, 4 H, Ar H), 3.85 (s, 6 H, OCH_3), 3.54 (s, 4 H, OCH_2), 3.07 (s, 4 H, Ar CH_2), 2.33 (s, 6 H, Ar CH_3); ^{13}C NMR δ 190.3 (d, CHO), 160.4 (s, $COCH_3$), 139.6 (d, Ar CH), 111.0 (s, OCO).

General Procedure for the Sodium Borohydride Reduction of the Dialdehydes. To a suspension of the dialdehyde (1 mmol) in 30 mL of methanol was added sodium borohydride (1 mmol) at 0 °C. The mixture was stirred for 30 min at 0 °C and 30 min at room temperature. To the reaction mixture were added 50 mL of water and 25 mL of $CHCl_3$. The layers were separated, and the aqueous phase was extracted with another 25 mL of $CHCl_3$. The combined organic layers were washed three times with water and dried with $MgSO_4$, and the solvent was evaporated under reduced pressure. The product was purified by chromatography (SiO_2, $CHCl_3$) or crystallization.

2,2′,2″-Trimethoxy-5,5″-dimethyl-1,1′:3,1″-terphenyl-3,3″-dimethanol (7c) was obtained from **7b** as a white solid: yield 87%; mp 171–172 °C; mass spectrum, *m/e* 408.192 (M^+) (calcd 408.194); ^1H NMR δ 7.32–7.16 (m, 7 H, Ar H), 4.74 (s, 4 H, Ar CH_2), 3.48 (s, 6 H, OCH_3), 3.24 (s, 3 H, 2′-OCH_3), 2.34 (s, 6 H, Ar, CH_3).

3,3″-Bis(hydroxymethyl)-2,2′,2″-trimethoxy-5,5″-dimethyl-1,1′:3′,1″-terphenyl-5′-ethanone ethylene acetal (7g) was obtained from **7f** as a white foam: yield 98%; mass spectrum, *m/e* 494.236 (M^+) (calcd 494.230); ^1H NMR δ 7.48 (s, 2 H, 4′,6′-H), 7.16 (d, 4 H, Ar H), 4.74 (s, 4 H, Ar CH_2), 4.06–3.82 (m, 4 H, OCH_2), 3.47 (s, 6 H, OCH_3), 3.23 (s, 3 H, 2′-OCH_3), 2.34 (s, 6 H, Ar CH_3), 2.30 (br s, 2 H, OH), 1.70 (s, 3 H, CH_3). Anal. Calcd for $C_{29}H_{34}O_7$: C, 70.43; H, 6.92. Found: C, 70.22; H, 7.27.

2,2′,2″-Trimethoxy-5,5″-dimethyl-5′-nitro-1,1′:3′,1″-terphenyl-3,3″-dimethanol (9e) was obtained from **9c** as a pale yellow foam: yield 93%; mass spectrum, *m/e* 453.180 (M^+) (calcd 453.179); ^1H NMR δ 8.26 (s, 2 H, 4′,6′-H), 7.26 (s, 2 H, Ar H), 7.13 (s, 2 H, Ar H), 4.76 (s, 4 H, Ar CH_2), 3.51 (s, 6 H, OCH_3), 3.32 (s, 3 H, 2′-OCH_3), 2.37 (s, 6 H, Ar CH_3), 2.20 (br s, 2 H, OH); IR (KBr) 3400 (OH) cm^{-1}.

5′-Bromo-2,2′,2″-trimethoxy-5,5″-dimethyl-1,1′:3′,1″-terphenyl-3,3″-dimethanol (9f) was obtained from **9d** as a white foam: yield 98%; mass spectrum, *m/e* 486.102 (M^+) (calcd for $C_{25}H_{27}BrO_5$ 486.104); ^1H NMR δ 7.50 (s, 2 H, Ar H), 7.20 (d, 2 H, Ar H), 7.10 (d, 2 H, Ar H), 4.74 (s, 4 H, CH_2) 3.51 (s, 6 H, OCH_3), 3.20 (s, 3 H, OCH_3), 2.34 (s, 6 H, Ar CH_3); ^{13}C NMR δ 133.4 (d, ArH), 131.4 (d, Ar CH), 129.6 (d, Ar CH), 61.6 (t, CH_2), 61.0 (q, OCH_3), 60.6 (q, OCH_3), 20.8 (q, CH_3); IR (KBr) 3520 (OH) cm^{-1}.

1,3-Bis[3-(hydroxymethyl)-2-methoxy-5-methylphenyl]-2-propanone ethylene acetal (10c) was obtained from **10b** as white crystals from benzene: yield 98%; mp 126–127 °C; mass spectrum, *m/e* 402.207 (M^+) (calcd 402.204); ^1H NMR δ 7.35 (s, 2 H, Ar H), 7.20 (s, 2 H, Ar H), 4.67 (s, 4 H, CH_2OH), 3.72 (s, 6 H, OCH_3), 3.55 (s, 4 H, OCH_2), 3.01 (s, 4 H, Ar CH_2), 2.27 (s, 8 H, Ar CH_3, OH). Anal. Calcd for $C_{23}H_{30}O_6$: C, 68.64; H, 7.51. Found: C, 68.58; H, 7.54.

3,3″-Bis(bromomethyl)-2,2′,2″-trimethoxy-5,5″-dimethyl-5′-nitro-1,1′:3′,1″-terphenyl (9g). To a solution of **9e** (1.3 g, 2.9 mmol) in 50 mL of benzene was added PBr_3 (1.3 g, 4.8 mmol). The reaction mixture was stirred for 16 h and poured into 20 mL of water. The layers were separated, and the aqueous phase was extracted with another 50 mL of benzene. The combined organic phases were washed with water, 10% $NaHCO_3$ and water and dried ($MgSO_4$). The solvent was evaporated under reduced pressure to give a white foam: yield 75%; mass spectrum, *m/e* 577.013 (M^+) (calcd 577.010); ^1H NMR δ 8.27 (s, 2 H, 4′,6′-H), 7.27 (d, 2 H, Ar H), 7.13 (d, 2 H, Ar H), 4.61 (s, 4 H, Ar CH_2), 3.57 (s, 6 H, OCH_3), 3.32 (s, 3 H, 2′-OCH_3), 2.36 (s, 6 H, Ar CH_3). Anal. Calcd for $C_{25}H_{25}Br_2NO_5$: C, 51.83; H, 4.35; N, 2.42. Found: C, 51.85; H, 4.37; N, 2.25.

1,3-Bis(3-bromo-2-methoxy-5-methylphenyl)-2-propanone Ethylene Acetal (10a). In a round-bottomed flask fitted with a Soxhlet (containing 4-Å molecular sieves) was heated for 4 days a mixture of **3a**[13a] (5.0 g, 11 mmol), ethylene glyol (4.2 g, 66 mmol), and *p*-toluenesulfonic acid (0.05 g) in 100 mL of dry benzene. The reaction mixture was cooled to room temperature and washed with 10% $NaHCO_3$ and water. The organic phase was dried ($MgSO_4$), and the solvent was evaporated under reduced pressure to give a colorless oil, which was crystallized from *n*-pentane at −20 °C to give pure **10a** as white crystals: yield 99%; mp 64–66 °C; mass spectrum, *m/e* 453.983 (M^+) (calcd 453.978); ^1H NMR δ 7.80 (d, 2 H, Ar H), 7.48 (d, 2 H, Ar H), 3.85 (s, 6 H, OCH_3), 3.59 (s, 4 H, OCH_2), 3.05 (s, 4 H, Ar CH_2), 2.34 (s, 6 H, Ar CH_3). Anal. Calcd for $C_{21}H_{24}Br_2O_4$: C, 50.42; H, 4.84. Found: C, 50.70; H, 4.86.

General Procedure for the Preparation of the Hemispherands 1b–d and Macrocycle 2a. A solution of the bis(hydroxymethyl) derivative (2 mmol) and diethylene glycol ditosylate (0.91 g, 2.2 mmol) in 50 mL of dry THF was added over a 10-h period to a suspension of sodium hydride (0.12 g, 4 mmol) in 150 mL of dry THF under reflux. The reaction mixture was heated under reflux for another 8 h and cooled to room temperature, and a small volume of water was added. The solvent was evaporated under reduced pressure, and the residue was partitioned between 50 mL of chloroform and 50 mL of water. The water layer was extracted with another two portions of chloroform, whereupon the combined organic layers were washed with 50 mL of water and dried with $MgSO_4$, and the solvent was removed under reduced pressure. The residue was submitted to column chromatography (Al_2O_3, CH_2Cl_2/THF, 95/5).

25,26,27-Trimethoxy-9,23-dimethyl-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 (1b) was obtained from **7c** as white crystals: yield 38%; mp 192–193 °C; mass spectrum, *m/e* 478.235 (M^+) (calcd 478.236); ^1H NMR δ 7.44 (A_2B, 1 H, 4-H), 7.27 (A_2B, J = 7.7 Hz, 2 H, 3,5-H), 7.08 (br s, 4 H, Ar H), 4.80 and 4.38 (ABq, J = 11.6 Hz, 2 H, Ar CH_2), 3.61 (s, 8 H, OCH_2), 3.38 (s, 6 H, OCH_3), 2.60 (s, 3 H, center OCH_3), 2.32 (s, 6 H, Ar CH_3). Anal. Calcd for $C_{29}H_{34}O_6$: C, 72.78; H, 7.16. Found: C, 72.44; H, 7.12.

25,26,27-Trimethoxy-9,23-dimethyl-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-4-ethanone (1c) was obtained from **7g** as white crystals: yield 48%; mp 150–152 °C; mass spectrum, *m/e* 520.250 (M^+) (calcd 520.246); ^1H NMR δ 8.10 (s, 2 H, Ar H), 7.11 (s, 4 H, Ar H), 4.80 (ABq, J = 11.7 Hz, 2 H, Ar CH_2), 4.39 (ABq, J = 11.7 Hz, 2 H, Ar CH_2), 3.61 (s, 8 H, OCH_2), 3.45 (s, 6 H, OCH_3), 2.68 (s, 6 H, center OCH_3, $COCH_3$), 2.34 (s, 6 H, Ar CH_3). Anal. Calcd for $C_{31}H_{36}O_7$: C, 71.52; H, 6.97. Found: C, 71.45; H, 7.02.

4-Bromo-25,26,27-trimethoxy-9,23-dimethyl-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 (1d) was obtained from **9f** as white crystals: yield 38%; mp 238–240 °C; mass spectrum, *m/e* 556.246 (M^+) (calcd 556.246); ^1H NMR δ 7.58 (s, 2 H, Ar H), 7.08 (s, 4 H, Ar H), 4.80 (ABq, J = 11.7 Hz, 2 H, Ar CH_2), 4.38 (ABq, J = 11.7 Hz, 2 H, Ar CH_2), 3.59 (s, 8 H, OCH_2), 3.42 (s, 6 H, OCH_3), 2.57 (s, 3 H, center OCH_3), 2.32 (s, 6 H, Ar CH_3). Anal. Calcd for $C_{29}H_{33}BrO_6$: C, 62.48; H, 5.97. Found: C, 62.00; H, 6.06.

25,26,27-Trimethoxy-9,23-dimethyl-4-nitro-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 (1e) was prepared from **9g**, and diethylene glycol with sodium hydride as a base in THF as described for the synthesis of the hemispherands **1b–d**: yield 31%; mass spectrum, *m/e* 523.219 (M^+) (calcd 523.221); ^1H NMR δ 8.37 (s, 2 H, Ar H), 7.13 (s, 4 H, Ar H), 4.80 (ABq, J = 11.7 Hz, 2 H, Ar CH_2), 4.39 (ABq, J = 11.7 Hz, 2 H, Ar CH_2), 3.59 (s, 8 H, OCH_2), 3.40 (s,

Table I. Fractional Atomic Coordinates (Non-Hydrogen Atoms) of 2a

atom	x	y	z
O1	−0.0515 (3)	0.4664 (3)	0.8205 (2)
C2	−0.1258 (5)	0.5505 (4)	0.7498 (3)
C3	0.0049 (5)	0.5480 (4)	0.6636 (3)
O4	0.1244 (3)	0.5962 (2)	0.6985 (2)
C5	0.2677 (5)	0.5839 (3)	0.6259 (3)
C6	0.3760 (4)	0.4512 (3)	0.6024 (3)
C7	0.4960 (4)	0.3895 (3)	0.6623 (3)
O8	0.5156 (3)	0.4499 (2)	0.7465 (2)
C9	0.4025 (5)	0.4408 (4)	0.8327 (3)
C10	0.6031 (4)	0.2696 (3)	0.6360 (3)
C11	0.5830 (4)	0.2139 (3)	0.5494 (3)
C12	0.4614 (5)	0.2715 (4)	0.4895 (3)
C13	0.4404 (5)	0.2060 (4)	0.3975 (4)
C14	0.3608 (4)	0.3930 (4)	0.5162 (3)
C15	0.7448 (4)	0.2071 (3)	0.6960 (3)
C16	0.7820 (4)	0.0681 (3)	0.7099 (3)
O17	0.8521 (3)	0.0008 (3)	0.6161 (2)
C18	1.0105 (5)	−0.0831 (4)	0.6268 (4)
C19	1.0177 (5)	−0.0904 (3)	0.7361 (3)
O20	0.9108 (3)	0.0303 (2)	0.7721 (2)
C21	0.6311 (4)	0.0276 (3)	0.7485 (3)
C22	0.5257 (4)	0.0897 (3)	0.8435 (3)
C23	0.3545 (4)	0.1032 (3)	0.8548 (3)
O24	0.2869 (3)	0.0635 (2)	0.7783 (2)
C25	0.2149 (5)	0.1638 (4)	0.7146 (3)
C26	0.2542 (4)	0.1458 (3)	0.9456 (3)
C27	0.3259 (5)	0.1817 (3)	1.0217 (3)
C28	0.4951 (5)	0.1748 (3)	1.0118 (3)
C29	0.5694 (5)	0.2153 (4)	1.0954 (3)
C30	0.5925 (4)	0.1270 (3)	0.9216 (3)
C31	0.0771 (5)	0.1410 (3)	0.9626 (3)
O32	−0.0400 (3)	0.2416 (2)	0.9190 (2)
C33	−0.0700 (5)	0.3585 (3)	0.9679 (3)
C34	−0.1647 (5)	0.4567 (3)	0.9036 (3)

6 H, OCH_3), 2.72 (s, 3 H, center OCH_3), 2.35 (s, 6 H, Ar CH_3). Anal. Calcd for $C_{29}H_{33}NO_8$: C, 66.53; H, 6.35; N, 2.68. Found: C, 66.20; H, 6.03; N, 1.76.

Preparation of 1e from 1f. A mixture of **1f** (0.051 g, 0.1 mmol), methyl iodide (0.043 g, 0.3 mmol), and K_2CO_3 (0.028 g, 0.2 mmol) in 2 mL of dry acetone (K_2CO_3) was stirred for 2 h at 30 °C. The reaction mixture was cooled to 0 °C and filtered, and the filtrate was concentrated under reduced pressure. Recrystallization from ethanol afforded pure **1e**, yield 95%.

23,24-Dimethoxy-7,21-dimethyl-11,14,17-trioxatricyclo-[17.3.1.1^{5,9}]tetracosa-1(23),5,7,9(24),19,21-hexaen-3-one ethylene acetal (2a) was obtained from **10c** and recrystallized from methanol to give **2a** as white crystals: yield 53%; mp 115–116 °C; mass spectrum, *m/e* 472.245 (M^+) (calcd 472.246); ^1H NMR δ 7.67 (d, 2 H, Ar H), 6.88 (d, 2 H, Ar H), 4.36 (s, 4 H, Ar CH_2O), 4.14 (s, 4 H, $COCH_2CH_2O$), 3.53 (s, 8 H, OCH_2CH_2O), 3.03 (s, 10 H, OCH_3, Ar CH_2C), 2.30 (s, 6 H, Ar CH_3). Anal. Calcd for $C_{27}H_{36}O_7$: C, 68.62; H, 7.68. Found: C, 68.36; H, 7.68.

23,24-Dimethoxy-7,21-dimethyl-11,14,17-trioxatricyclo-[17.3.1.1^{5,9}]tetracosa-1(23),5,7,9(24),19,21-hexaen-3-one (2b). A suspension of **2a** (0.53 g, mmol) in 6 mL of 4 M HCl and 6 mL of methanol was stirred for 16 h at room temperature. The product was filtrated and recrystallized from methanol to give pure **2b** as white crystals: yield 98%; mp 121–122 °C; mass spectrum, *m/e* 428.220 (M^+) (calcd 428.220); ^1H NMR δ 6.96–6.92 (m, 4 H, Ar H), 4.41 (s, 4 H, Ar CH_2O), 3.71 (s, 4 H, Ar CH_2), 3.58 (s, 8 H, OCH_2CH_2O), 3.29 (s, 6 H, OCH_3), 2.24 (s, 6 H, CH_3). Anal. Calcd for $C_{25}H_{32}O_6$: C, 70.07; H, 7.53. Found: C, 69.97; H, 7.60.

25,26-Dimethoxy-9,23-dimethyl-4-nitro-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-nonaen-27-ol (1f). To a solution of **2b** (0.105 g, 0.24 mmol) in 20 mL of ethanol was added a solution of nitromalonodialdehyde sodium salt (0.55 g, 4.0 mmol) in 1 mL of water and a solution of sodium hydroxide (0.037 g, 0.92 mmol) in 0.5 mL of water. The reaction mixture was warmed to 46 °C and stirred for 16 h. After being cooled to room temperature, the reaction mixture was acidified with 2 N hydrochloric acid and extracted with chloroform (3 × 10 mL). The combined organic layers were washed with water and dried with $MgSO_4$, and the solvent was evaporated under reduced pressure to give a yellow solid. Recrystallization from acetic acid afforded pure **1f**: yield 89%; mp 240–242 °C; mass spectrum, *m/e* 509.207 (M^+) (calcd 509.205); ^1H NMR δ 8.41 (s, 2 H, Ar H), 7.12 (m, 4 H, Ar H), 4.90 (d, J = 11.5 Hz, 2 H, Ar CH_2), 4.37 (d, J = 11.5 Hz, 2 H, Ar CH_2), 3.55 (s, 6 H, OCH_3), 3.55–3.40 (m, 8 H, OCH_2CH_2O), 2.35 (s, 6 H, Ar CH_3). Anal. Calcd for $C_{28}H_{31}NO_8$: C, 66.00; H, 6.13; N, 2.75. Found: C, 65.59; H, 6.32; N, 2.67.

X-ray Diffraction. The crystal structure of **2a** was determined. Intensities were measured at T = 100 K on a CAD4 diffractometer (Mo Kα radiation, graphite monochromator). Cell dimensions were obtained by least squares from 22 centered refections ($4° < \theta < 10°$).

Crystal data: $C_{27}H_{36}O_7$; triclinic; space group $P\bar{1}$; a = 8.477 (2) Å, b = 11.325 (4) Å, c = 13.535 (2) Å; α = 89.71 (2)°, β = 83.04 (2)°, γ = 71.92 (2)°; V = 1225 (1) Å^3; Z = 2; fw = 472.58; D_{calcd} = 1.28 g cm^{-3}; $F(000)$ = 508; μ = 0.9 cm^{-1}.

A total of 4252 reflections were measured in the $\omega/2\theta$ scan mode (scan width 1.3 + 0.34 tan θ; variable scan speed 2–7° min^{-1}). The intensities were corrected for the decay of three standard reflections and for Lorentz polarization. The structure was solved by direct methods and refined with full-matrix least squares. A total of 2973 reflections having $F_o^2 > 3\sigma(F_o^2)$ were included in the refinement. The weight for each reflection was calculated as $w = 4F_o^2/\sigma^2(F_o^2)$, $\sigma^2(F_o^2) = \sigma^2(I) + (0.02F_o^2)^2$, $\sigma(I)$ based on counting statistics. All hydrogen atoms were located on a difference Fourier map and included in the refinement. The number of parameters refined was 452: scale factor, isotropic extinction parameter (final value 9 × 10^{-7}), positional and anisotropic thermal parameters for the non-hydrogen atoms, positional and isotropic thermal parameters for the hydrogen atoms. Refinement converged at R = 5.9%, R_w = 8.0%. The largest shift/error ratio in the last cycle was 0.18. The largest peak on the final difference Fourier map was 0.4 e Å^{-3}. All calculations were done with SDP.[21] The atomic positional parameters are given in Table I. A view of the structure, with atom numbering, is in Figure 1. From this view it can be seen that the macrocyclic cavity is filled by the anisole methyl groups (nonbonded distances: C9···O1 = 3.79 Å, C9···O4 = 3.22 Å, C25···O1 = 3.66 Å, C25···O32 = 3.24 Å, C9···C25 = 4.32 Å). The ketal group is pointing away from the cavity, which means that the seven oxygen atoms of **2a** do not converge onto a central cavity to define a potential cation receptor site. The geometry of the five-membered ketal group is definitely nonplanar: the four atoms C16, O17, C18 and O20 are within 0.03 Å of their mean plane, from which C19 is displaced by 0.48 Å.

The geometry of the anisole groups is slightly distorted:[4] the methoxy oxygens are displaced out of the mean planes of their attached aryls by 0.03 Å (O8) and 0.02 Å (O24). The angles C7–O8–C9 (113°) and C23–O24–C25 (112°) are smaller than the normal value of 118°.

Association Constants. The association constants K_a (M^{-1}) and binding free energies $-\Delta G°$ (kcal·mol^{-1}) of the novel hemispherands were determined with the picrate extraction method.[14]

1c: [K_a ($-\Delta G°$)] Li^+, 1.2 × 10^5 (6.9); Na^+, 9.2 × 10^8 (12.1); K^+, 3.7 × 10^8 (11.6); Rb^+, 5.0 × 10^7 (10.4); Cs^+, 4.2 × 10^6 (8.9).

1d: [K_a ($-\Delta G°$)] Li^+, 1.1 × 10^5 (6.9); Na^+, 1.1 × 10^9 (12.2); K^+, 7.9 × 10^8 (12.0); Rb^+, 3.4 × 10^7 (10.2); Cs^+, 3.9 × 10^6 (8.9).

1e: [K_a ($-\Delta G°$)] Li^+, 1.3 × 10^5 (7.0); Na^+, 1.1 × 10^9 (12.2); K^+, 7.9 × 10^8 (12.0); Rb^+, 6.5 × 10^7 (10.5); Cs^+, 4.5 × 10^6 (9.0).

Acknowledgment. We thank The Dutch Kidney Foundation Fund and The Netherlands Foundation for Technical Research (STW), Future Technical Science Branch/Division of The Netherlands Organization for the Advancement of Pure Research (ZWO), for support of these investigations.

Registry No. **1b**, 110355-10-7; **1c**, 110355-11-8; **1d**, 110355-12-9; **1e**, 110355-13-0; **1f**, 110355-14-1; **1g**, 93645-01-3; **2a**, 110355-15-2; **2b**, 110355-16-3; **3a**, 96608-69-4; **3c**, 110355-17-4; **4b**, 96625-86-4; **4c**, 110355-18-5; **4d**, 110355-19-6; **5a**, 110355-20-9; **5b**, 110355-21-0; **6a**, 95839-30-8; **6b**, 71128-90-0; **6c**, 110355-22-1; **6d**, 71128-92-2; **7a**, 96625-88-6; **7b**, 110355-23-2; **7c**, 110355-24-3; **7d**, 110355-25-4;

(21) *Structure Determination Package*; B. A. Frenz and Associates: College Station, TX 1983; Enraf Nonius: Delft, 1983.

7e, 110355-26-5; **7f**, 110355-27-6; **7g**, 110355-28-7; **8a**, 7048-41-1; **8b**, 7048-42-2; **8c**, 58506-25-5; **8d**, 58506-24-4; **9a**, 110355-29-8; **9b**, 110355-30-1; **9c**, 110355-31-2; **9d**, 110355-32-3; **9e**, 110355-33-4; **9f**, 110355-34-5; **9g**, 110355-35-6; **10a**, 110355-36-7; **10b**, 110355-37-8; **10c**, 110355-38-9; nitromalonodialdehyde sodium salt, 34461-00-2; diethylene glycol ditosylate, 7460-82-4.

Supplementary Material Available: Tables of the anisotropic thermal parameters for the non-hydrogen atoms, positional and isotropic thermal parameters for hydrogen atoms, and bond distances, angles, and torsion angles (6 pages); tables of observed and calculated structure factors (11 pages). Ordering information is given on any current masthead page.

An O → N Acyl Transfer. An Important Activation Step for a Formal Nucleophilic Substitution in a Cyclopropane Derivative

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Received April 23, 1987

Acylated (piperidinocyclopropyl)dimedone **8** proved to be a suitable starting material for smooth generation of a highly reactive cyclopropylidenedimedone species (**9**). The latter can be trapped in a [2 + 4] cycloaddition with enol ethers **14** leading to **15** or with methylene dihydrofuran derivatives **10** and **16** producing **11** and **17**. These latter adducts (**11** and **17**) isomerize to more stable furans **13** and **18**. Without a trapping reagent **9** is transformed to **10**; thus, compounds **11** or **13** can be prepared by simple heating of **8**. Derivatives **11**, **13**, **15**, **17**, and **18** can formally be regarded as the products of two consecutive nucleophilic substitutions starting from a cyclopropanone *N,O*-acetal **1**. In bicyclic compound **19**, steric reasons prohibited analogous reactions.

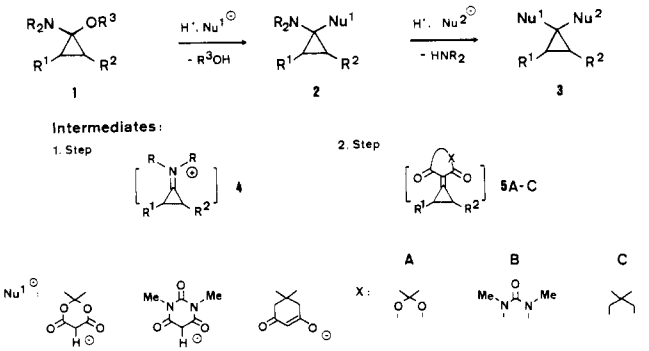
Introduction

Nucleophilic substitutions on cyclopropanes generally are characterized to be "notoriously difficult".[1] However, this is not correct for compounds of type **1**, in which the amino moiety promotes the nucleophilic substitution of the R^3O group by stabilizing the intermediate cyclopropyl cation **4**.[2,3] We could demonstrate (Scheme I) that with suitable nucleophiles Nu^1 **1** even acts as a starting material for a twofold nucleophilic substitution;[4] Meldrum's acid or barbituric acid as HNu^1 gave compounds **2**, in which the amino moiety may be displaced by further nucleophiles. Thus, nucleophiles Nu^2 as $^-CRR'$,[5-8] CN^-,[9] H^-,[9] RO^-,[9] or HO^-[10] reacted with **2**, forming cyclopropanes **3**. This second nucleophilic substitution is to be described as an elimination–addition sequence involving intermediates **5A** and **5B**.

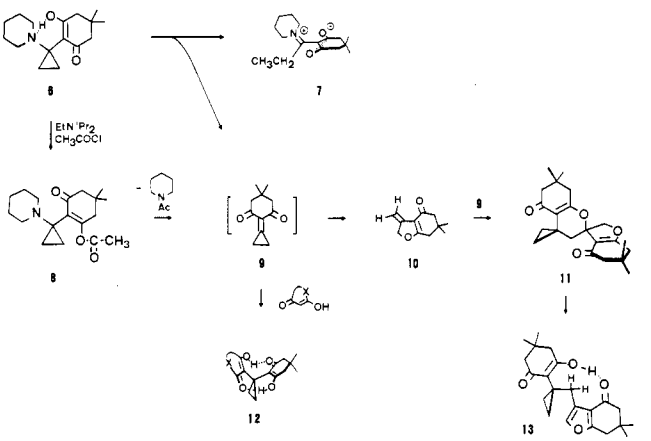
Nucleophiles Nu^1 derived from less strong CH acids (e.g., dimedone) so far allowed a twofold nucleophilic substitution in some exceptional cases only.[6,7] Whereas **6** could be synthesized from **1** ($R^1 = R^2 = H$, $R^3 = SiMe_3$[11]) and dimedone (step 1, Scheme I) without any problem,[6] a homoenamine ring opening[3] of **6** generating **7** interfered strongly with the nucleophilic substitution of the piperidino group in **6** to give **12** (step 2).[6] Thermolysis of **6** without added nucleophiles exclusively gave **7** as the product of a homoenamine ring opening.[6]

Ketene or isocyanates caused an acylation and a removal of the tertiary amino moiety in dialkylhydroxycyclopropylamines **1** ($R^3 = H$).[12] Cyclopropanone, which decomposed very quickly, was thereby formed in addition to the amide. We found that acylation of **6**, a vinylogous hydroxycyclopropylamine, also allows the removal of the amino moiety under smooth conditions, forming unexpected products of a nucleophilic substitution. An inter-

Scheme I



Scheme II



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