Use of Pyrylium Synthons in the Synthesis of Hemispherands with Modified Cavities. X-ray Structures of the 21-Hemispherand and a Pyrido Hemispherand

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The effect of variation of the rigid part of the parent Cram hemispherand **1a** on the preorganization of the macrocyclic cavity has been studied. Four novel 18-membered hemispherands (**3**, **4a–c**) have been synthesized via a novel multistep route using 2,6-di- and 2,4,6-triarylpyrylium building blocks. Host **3** contains a nitroaryl and host **4a–c** a pyridine moiety, flanked by anisyl units. For comparison the 21-membered hemispherand **1b** was synthesized and structures of **1b** and **4a** have been determined by single-crystal X-ray analysis. The effect of incorporation of a nitro group in the terphenyl moiety on the complexation, studied by ^{1}H NMR spectroscopy and two-phase picrate extraction, is a decrease of 1.7 kcal mol^{-1} in free energy of binding for all alkali cations except Li^+, when compared with **1a**. The pyrido hemispherands **4a–c** exhibit lower $-\Delta G°$ values, particularly for the complexation with the smaller alkali cations. This reflects the increased flexibility of the macrocyclic cavity in pyrido hemispherands. However, this conformational flexibility can be reduced by the introduction of alkyl groups in the 3- and 5-positions of the pyridinium moiety. The 21-membered hemispherand **1b** shows a selectivity for the larger alkali cations K^+, Rb^+, and Cs^+. The X-ray structures of **1b** and **4a** revealed that an OCH_3 methyl group partly fills the macrocyclic cavity.

In 1979 Cram and co-workers[1] reported the synthesis and the complexation with alkali and alkylammonium salts of a new class of host molecules, viz., the hemispherands. In the parent molecule, the molecular cavity is composed of a rigid *m*-teranisyl moiety in which the oxygen binding sites are conformationally organized prior to complexation, and a flexible polyether chain. Later the synthesis and binding properties of several hemispherands composed of three[2a] or four[3] anisyl units or anisyl and cyclic urea units[4,5] were reported. Maximum binding for different cations has been achieved by variation of the cavity size from 18 to 23 ring atoms through enlarging of the conformationally "mobile" part of the hemispherands.[3] A very elegant and more recent example is the cryptahemispherands.[2b] The concept of preorganization of ligating sites has found its extreme application in the synthesis of spherand hosts with the highest thermodynamic stabilities of complexes with the smaller alkali cations (Li^+ and Na^+) presently known.[6]

Our interest in alkali cation carriers that can be applied in biological systems has led us to synthesize spherands with protected functional groups at the outer sphere[7] so that they can be covalently linked to biologically active species. However, this means that only the smaller alkali cations Li^+ and Na^+ can be strongly complexed. For the strong and irreversible complexation of the larger alkali cations (K^+, Rb^+, and Cs^+), it would be desirable to design and synthesize other spherand-type molecules. Such a preference for the complexation of the larger alkali cations might be effected by enlarging the flexible part of the host. However, this will result in the reduction of preorganization of the ligating sites and inevitably will lead to weaker complexes. This leaves the variation of ligating sites in the rigid part of the spherands[8,9] or hemispherands as the alternative.

In this paper we describe a new strategy for the synthesis of hemispherands, which are modified in their inner sphere by substitution of the central anisyl unit in the prototype hemispherand **1a** by a 2,6-nitrophenyl (**3**) or a 2,6-pyridyl (**4**) moiety. The K_a values of the complexes of these new hosts with alkali picrate salts have been determined, the ^{1}H NMR spectra have been studied, and the relation to structural parameters is discussed. Finally, the X-ray structures of two hemispherands have been determined.

Results and Discussion

In a previous paper we have reported a novel methodology for the construction of the central aromatic ring of 1,1′:3′,1″-terphenyls and the application in the synthesis of spherands. Reaction of the three-carbon building block nitromalondialdehyde with a substituted dibenzyl ketone gives a 1,1′:3′,1″-terphenyl that was used for the synthesis of spherands functionalized at the outer sphere.[10]

Our new concept for constructing the central aromatic ring of terphenyl moieties in hemispherands comprises the conversion of pyrylium salts into aromatic or heterocyclic rings. Via this approach, reactions of 2,6-diarylpyrylium salts provide a way to modify the central aryl ring of a "terphenyl" moiety present in the prototype hemispherand **1a**. Consequently, suitably functionalized pyrylium salts were our first target molecules for the synthesis of hemispherands with modified inner spheres.

The synthesis and reactivity of pyrylium salts have been discussed extensively in the literature.[11,12] According to

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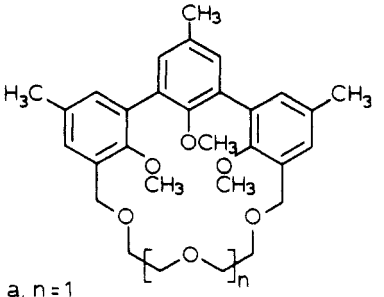

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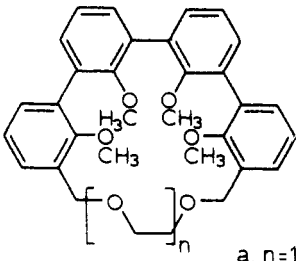
b, n = 2

1



2

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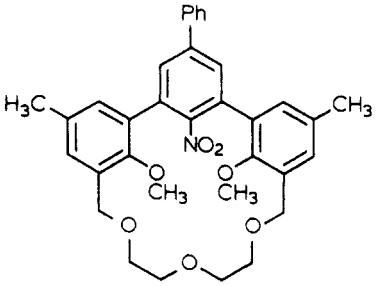

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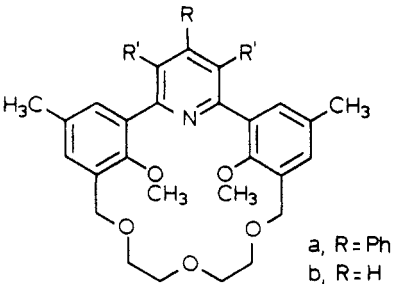

4

a, R = Ph R' = H
b, R = H R' = H
c, R = H R' = CH_3

Table I. Selected Chemical Shifts in ^1H and ^{13}C NMR Spectra (CD_3CN) of Pyrylium Salts

	^1H NMR, δ				^{13}C NMR, δ					
no.	pyrylium H	2,6-Ar H	OCH_3	CH_3	pyrylium 2,6-C	3,5-C	4-C	Ar 4-C	OCH_3	CH_3
8a	8.62 (s)	7.81–7.11 (m)	4.00	2.34	169.7	119.2	165.1	138.1	57.3	20.5
8b	8.93 (s)	7.92, 7.90 (d)	3.90	2.46	170.3	120.9	167.8	141.5	63.1	20.7
11	8.89 (s), δ_A 8.92	7.83, 7.51 (d)	3.80	2.45	171.3	120.0	167.1	139.4	63.4	20.9
12a	δ_B 8.70 (AB_2), J_{AB} = 8.5 Hz	7.83, 7.52 (d)	3.78	2.44	172.7	124.3	158.5	140.1	63.7	21.3
12b	8.87 (s)	7.40, 7.33 (d)	3.48	2.49	172.6	136.0	163.0	137.8	64.2	21.1

Katritzky,[12] these salts are important in organic synthesis because of their simple preparation and facile isolation and purification, as well as the high reactivity toward nucleophiles.

Since hemispherands like **1a** have a symmetrical structure, the synthesis of the corresponding 2,6-diaryl-substituted pyrylium salts requires only simple starting materials. The synthesis involves the reaction of 2 equiv of an appropriately functionalized acetophenone and 1 equiv of an aldehyde or a synthetic equivalent, in acidic media. We have synthesized both 2,6-diaryl- and 2,4,6-triaryl-substituted pyrylium salts. Whereas 2,6-diaryl-pyrylium salts react with nucleophiles either at the more reactive 2- and 6-positions or at the less hindered 4-position,[13] the 2,4,6-triarylpyrylium salts undergo mainly reactions at the 2- and 6-positions.

Synthesis. The starting acetophenones **5** were synthesized from 4-methylanisole. Reaction with acetyl chloride and $AlCl_3$ in dichloromethane gave the acylated and demethylated compound **5a**[14] in 87% yield. When the $AlCl_3$ was deactivated by the addition of a small amount of water prior to the acylation, **5b** was obtained in a yield of 90%. Reaction of 2 equiv of **5b** with 1 equiv of benzaldehyde and 2 equiv of boron trifluoride etherate afforded the pyrylium salt **8a**, which crystallized from the reaction mixture as orange crystals in 20% yield. This pyrylium salt was characterized by its spectroscopic data (Table I) and converted without further purification into 2,2″-dimethoxy-5,5″-dimethyl-2′-nitro-5′-phenyl-1,1′:3′,1″-terphenyl (**9a**) by reaction with nitromethane and potassium *tert*-butoxide in *tert*-butyl alcohol. The yield of pure **9a** calculated on the crude pyrylium salt was 90%. The ^1H NMR spectrum of **9a** ($CDCl_3$) showed the 4′- and 6′-hydrogen atoms at δ 7.58 and singlets for OCH_3 and CH_3 at δ 3.65 and 2.34, respectively. Functionalization at the 3- and 3″-positions for the further introduction of a polyethyleneoxy bridge was performed through formylation by reaction with hexamethylenetetramine in trifluoroacetic acid[15] to give **9b** (56%). The formyl groups were reduced with sodium borohydride in methanol to afford **9c** in 78% yield, and reaction of **9c** with phosphorous tribromide in benzene gave the corresponding bis(bromomethyl) derivative **9d** in 80% yield. Finally, the hemispherand **3** was synthesized in 23% yield from **9d** and diethylene glycol with sodium hydride as a base in tetrahydrofuran (THF) under high dilution conditions. The ^1H NMR spectrum of the new hemispherand **3** in $CDCl_3$ showed singlets for the OCH_3 and CH_3 hydrogen atoms at δ 3.43 and 2.33, respectively. The benzylic hydrogen atoms appear as an AB quartet at δ 4.52 (J_{AB} = 12.0 Hz), showing that ring inversion has become slow on the ^1H NMR time scale.

For the synthesis of the appropriate precursor for hemispherands containing a central pyridine unit, the pyrylium salt **8a** was converted into **10a** in a yield of 90% by reaction of **8a** with ammonium acetate in glacial acetic acid. Selective formylation of **10a** as applied in the synthesis of

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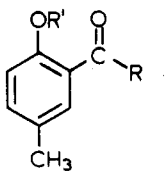
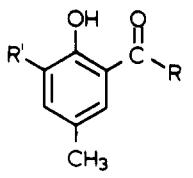


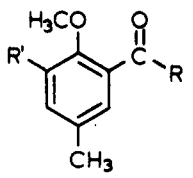
5

a, R = CH_3, R' = H
b, R = CH_3, R' = CH_3
c, R = CH_2CH_3, R' = H
d, R = CH_3, R' = $CH_2CH{=}CH_2$
e, R = CH_2CH_3, R' = $CH_2CH{=}CH_2$



6

a, R = CH_3, R' = Br
b, R = CH_3, R' = $CH_2CH{=}CH_2$
c, R = CH_2CH_3, R' = $CH_2CH{=}CH_2$



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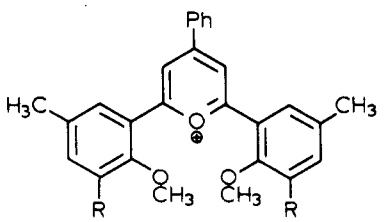
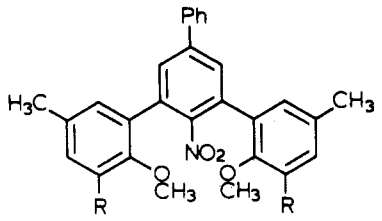


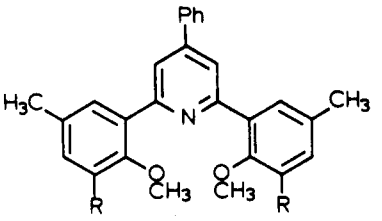
8

a, R = H
b, R = Br
c, R = $CH_2CH{=}CH_2$



9

a, R = H
b, R = CHO
c, R = CH_2OH
d, R = CH_2Br



10

a, R = H
b, R = Br

9b was not successful. Therefore, we investigated the possibility of dilithiation ortho to the methoxy substituents of **10a**. To facilitate the formation of the dilithio species by bromo to lithium exchange (which can be performed at much lower temperatures than direct lithiation of **10a**), we synthesized **10b** by starting from **5a**. The 3-position of **5a** was selectively brominated by reaction with *N*-bromosuccinimide in dimethylformamide (DMF) to give **6a** in 96% yield. Methylation of **6a** with methyl iodide and K_2CO_3 as a base afforded **7a** in 90% yield. The pyrylium tetrafluoroborate **8b** was obtained in 34% yield from **7a** and benzaldehyde as described for **8a** and was subsequently converted into the 2,6-diarylpyridine **10b** (82%) by reaction of **8b** with ammonium acetate in glacial acetic acid. Bromo to lithium exchange upon reaction with either *n*-, *sec*-, or *tert*-butyllithium in THF or in diethyl ether and reaction of the dilithiated compound with DMF or with CO_2 afforded mixtures of products. The dialdehyde **13c** could be obtained only in low yield (<5%). As an alternative to this metalation reaction, we have introduced aldehyde groups by oxidation of 1-propenyl substituents. This approach, which we have successfully used in earlier work,[16] is based on the Claisen rearrangement of allyl aryl ethers to *o*-allylphenols. The phenol obtained from this reaction can be alkylated, and the allyl substituent can be converted to a reactive substituent. Although it is unknown, we assumed that an allyl substituent in the acetophenone would be inert under the acidic conditions required for the synthesis of the pyrylium salt. Therefore, acetophenone **7b** was the required starting material for the pyrylium salt **8c**. Allylation of the 2-hydroxyacetophenone **5a** with allyl bromide and potassium hydroxide as a base afforded **5d** in 81% yield. The Claisen rearrangement is often performed in *N*,*N*-diethylaniline, but this has the disadvantage of an extended workup procedure. We found that this reaction could more easily be performed by heating neat **5d** to a controlled temperature of 190 °C. Distillation from the reaction flask after the reaction was completed gave the rearranged acetophenone **6b** in 95% yield. Methylation with dimethyl sulfate and potassium hydroxide as a base afforded **7b** in 90% yield after distillation. The synthesis of the corresponding pyrylium salt from **7b** and benzaldehyde with boron trifluoride etherate gave **8c** after repeated recrystallization from acetone/diethyl ether in 18% yield. The 2,6-diarylpyrylium salt **11a** was synthesized by reaction of **7b** with triethyl orthoformate and perchloric acid. The yield of this pyrylium salt, 27%, was somewhat higher than that found for **8c**, which was mainly due to a more simple purification by recrystallization from THF. The pyrylium salts **8c** and **11a** were converted into the pyridines **12a** and **13a** by reaction with ammonium acetate in glacial acetic acid. Without full characterization of the sticky oils obtained, these compounds were subjected to reaction with potassium *tert*-butoxide in THF, under which conditions the 2-propenyl group isomerizes to a 1-propenyl group. The overall yields of **12b** and **13b** from **8c** and **11a**, respectively, were 66% and 69%. We have investigated the oxidation of the 1-propenyl double bond both by reaction with osmium tetraoxide and sodium periodate in water and by ozonolysis in methanol. It appeared that the latter procedure gave somewhat better yields. The dialdehyde **13c** was obtained in 80% yield, and reduction of the formyl groups with sodium borohydride in methanol afforded **13d** in almost quantitative yield. Reaction of **13d** with phos-

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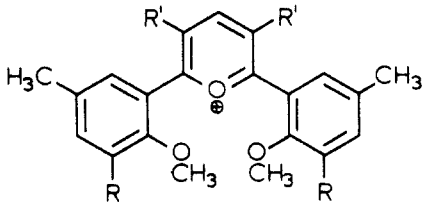
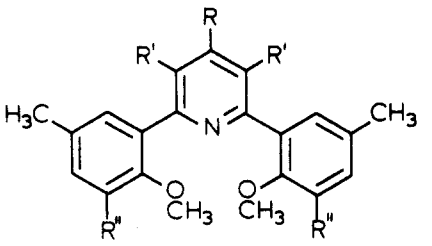


11

a, R = $CH_2CH=CH_2$, R' = H

b, R = $CH_2CH=CH_2$, R' = CH_3



12

12, R = Ph , R' = H

13, R = H , R' = H

14, R = H , R' = CH_3

12, 13, 14; a, R" = $CH_2CH=CH_2$

b, R" = $CH=CHCH_3$

c, R" = CHO

d, R" = CH_2OH

e, R" = CH_2Br

phorous tribromide in benzene gave **13e** in 80% yield. The analogous reactions applied to **12b** gave compounds **12c**, **12d**, and **12e**, of which **12c** and **12d** could only be characterized spectroscopically. The overall yield of pure **12e** based on pure **12b** was 67%.

Hosts **4a** and **4b** were obtained from **12e** and **13e**, in 60% and 54% yields, respectively, by reaction with diethylene glycol and sodium hydride as a base in THF under high dilution conditions. The ^1H NMR spectra ($CDCl_3$) of hosts **4a** and **4b** show singlets for OCH_3 hydrogen atoms at δ 3.54 and 3.48, respectively. As expected, **4a** gave a singlet and **4b** an A_2B system (J_{AB} = 7.89 Hz) for the pyridine hydrogen atoms. In contrast to the hemispherands **1a** and **3**, which showed an AB quartet for the benzylic hydrogen atoms, both **4a** and **4b** gave a singlet for these hydrogen atoms at δ 4.58 and 4.55, respectively. This indicates that ring inversion is fast on the ^1H NMR time scale (vide infra). Obviously, the replacement of the central anisyl unit in **1a** by a pyridine unit reduces the degree of preorganization of the cavity of the hemispherands **4a** and **4b**.

From CPK molecular models it is clear that the rigidity of the 2,6-diarylpyridine moiety in **4a** and **4b** is enhanced by the introduction of "bulky" substituents in the 3- and 5-positions of the pyridine ring and this might enhance the preorganization of the cavity. Therefore, the more rigid host **4c**, bearing methyl groups in the 3- and 5-positions of the pyridine ring, was prepared by starting from the propiophenone **5c**.[17] Compound **7c** was synthesized according to a sequence of reactions as described for **7b**, in 57% overall yield. Reaction of **7c**, triethyl orthoformate, and perchloric acid gave in 25% yield the pyrylium perchlorate **11b**. This pyrylium salt showed characteristic differences in the ^1H and ^{13}C NMR spectra[18] in comparison with **8c** and **11a** (Table I). Due to hindered rotation around the pyrylium phenyl bonds, caused by the methyl groups at the 3- and 5-positions of the pyrylium ring and the *o*-aryl protons in **11b**, these are shifted upfield to δ 7.40 when compared with **8c** (δ 7.83) and with **11a** (δ 7.83). In the ^{13}C NMR spectrum of **11b**, the C-4 atom is shifted upfield to δ 137.8 whereas for **8c** and **11a** these absorptions are found at δ 140.1 and 139.4, respectively. The pyrylium salt **11b** was converted into host **4c** in 34% overall yield as described above for the conversions of **8c** into **4a** and of **11a** into **4b**. However, the ^1H NMR spectrum ($CDCl_3$) of **4c** showed singlets for the OCH_3 and the CH_3 hydrogen atoms and also a singlet for the benzylic hydrogen atoms at δ 4.55, indicating that the ring inversion at room temperature is still fast on the ^1H NMR time scale.

Table II. Distances (Å) and Angles (°) in Crystal Structures 1a,b and 4a

	1a[2a]	1b	4a
Distances between O's			
OCH_2CH_2O	3.61	2.81–3.64	2.89
$OArCH_2O$ (av)	3.58	3.40	3.09
outer–outer CH_3O's	3.56	4.49	4.98
N to CH_3O's			2.92
outer–inner CH_3O's	2.84	2.94–3.63	
Angles			
aryl fold around O–Ar–CH_3 axis	2.5	0.3–6.1	3.0, 7.4
Ar–Ar dihedral angles	58	82, 60	54, 47

To compare the binding properties of the new hosts **4a–c**, which contain modified and more conformationally mobile 18-membered rings, with those of the hemispherands containing meta-coupled anisyl units, we have also prepared host **1b**. As was found for the hemispherand with four meta-coupled anisyl units in a 21-membered ring,[3] host **1b** was expected to be conformationally more mobile compared to the hemispherand **1a**. Reaction of 3,3″-bis(bromomethyl)-2,2′,2″-trimethoxy-5,5′,5″-trimethyl-1,1′:3′,1″-terphenyl[1] and triethylene glycol with sodium hydride as a base in THF under high dilution conditions afforded **1b** in 31% yield.

Crystal Structures of Hosts 1b and 4a. The structures of the free hosts **1b** and **4a** were determined by X-ray crystallography. ORTEP[19] views of these structures are given

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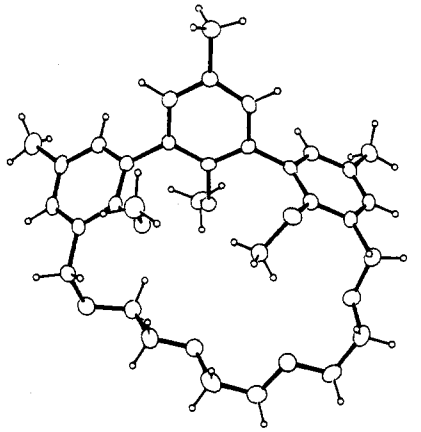
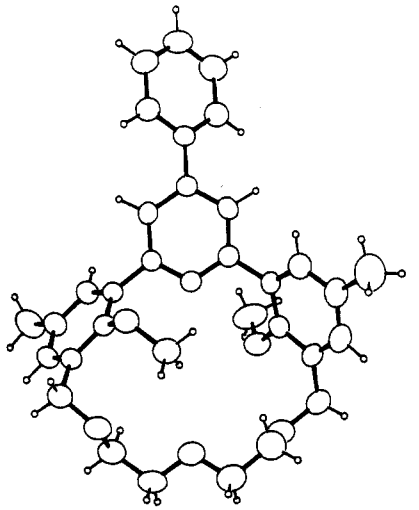


(a)



(b)

Figure 1. Crystal structures of the free hosts **1b** (a) and **4a** (b).

in Figure 1. In Table II selected distances and angles of the structures **1b** and **4a** are presented together with those reported by Lein and Cram for **1a**.[2a]

As shown in Figure 1, the extension of the ethyleneoxy bridge in **1b** by one OCH_2CH_2 unit, compared to **1a**, allows a methoxy group of an outer anisyl unit to occupy partly the cavity. As a consequence, the unshared electron pairs of this methoxy group diverge from the cavity and the distance between the oxygen atoms of the outer methoxy groups increases from 3.56 Å in **1a** to 4.49 Å in **1b**. The oxygen to oxygen distances in the ethyleneoxy bridge are 2.81 Å and 3.64 Å because an anti conformation in **1a** is gauche in **1b**. Whereas in **1a** the ring is too small to orient an outer methoxy group into the cavity, host **1b** is more conformationally mobile and the preorganization of the *m*-teranisyl moiety has been distorted. For complexation with alkali metal cations to occur, **1b** has to be reorganized by a 180° rotation of the inward-pointing methoxy group and the anti to gauche conformational change of the ethyleneoxy bridge. CPK molecular models reveal for **1b** a cavity of 3–4 Å, which is complementary to the larger alkali cations (K^+, Rb^+, and Cs^+).

In the crystal structure of host **4a**, the methoxy groups of the anisyl units are situated at opposite sides of the macroring and one methoxy group is oriented into the cavity. Due to the all-gauche conformations in the ethyleneoxy bridge, distances between all nearby oxygen and nitrogen atoms vary only from 2.89 to 3.15 Å. For complexation with alkali cations, a 180° rotation of the inward-pointing methoxy group must occur in order to converge the unshared electron pairs to form a cavity. This reorganization gives a cavity with a diameter of ~2–3 Å and is complementary to Na^+ and K^+. In CPK molecular models, rotation of a methoxy group through the cavity is possible without breaking bonds. In this way a conformation is obtained that resembles the structure of **1a** with a cavity of ~2–3 Å, complementary to Na^+ and K^+.

The crystal structures of **1b** and **4a** resemble each other. Compared with **1a**, they both show a decrease in preorganization, which allows a methoxy group to fill partly the cavity. Upon complexation, both hosts **1b** and **4a** have to be reorganized. Whereas in **1b** a 180° rotation of the inward-pointing methyl group restores the up–down–up arrangement of the *m*-teranisyl moiety, host **4a** can be reorganized in different ways. From molecular mechanics calculations (MM2),[20,21] we found that conformations that have the methoxy groups at the same or at opposite sides of the macroring are almost equal in their steric energy, with a somewhat lower energy for the former. This conformation resembles the structure of **1a** and may have a large contribution to the overall complexation.

Complexation. From the crystal structure of **1a** and the corresponding *tert*-butylammonium complex, it has been shown that the teranisyl moiety is preorganized for the complexation and only a minor conformational reorganization of this part of the molecule occurs during complexation. The ethyleneoxy bridge is conformationally much more mobile and does reorganize during complexation. These differences between the solid-state structures of the free ligand and of the *tert*-butylammonium complex are consistent with the spectral changes observed in solution.[2a] The benzylic hydrogen atoms in **1a** appear as an AB quartet due to the slow ring inversion on the ^1H NMR time scale. Upon complexation of **1a** with alkali picrates, the reported chemical-shift differences are analogous to those found for the *tert*-butylammonium complex. The 18-membered hemispherands (e.g., **2a**) with four meta-coupled anisyl units generally bind Na^+ more strongly in comparison with **1a**, and they also exhibit a higher selectivity of Na^+ complexation.

Enlarging of the macroring from 18 to 23 atoms generally causes an increased complexation with the larger alkali cations (K^+, Rb^+, and Cs^+). These ligands have a higher conformational mobility, as is obvious not only from their CPK models but also from the crystal structures of these expanded hemispherands.[22] The outer methoxy groups in these expanded hemispherands are turned toward the cavity in the free ligand in a way similar to that observed in the crystal structures of **1b** and **4a**.

In order to compare the new hosts **1b**, **3**, and **4a–c** with the known hemispherand **1a** and **2a–b**, we have studied the ^1H NMR spectra of the corresponding picrate complexes and we have also determined the association constants (K_a) and binding free energies ($-\Delta G°$) with the picrate extraction method as described by Cram and co-

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Table III. Association Constants (K_a) and Binding Free Energies ($-\Delta G°$) of Complexes of Hosts with Alkali Picrates in $CDCl_3$ Saturated with H_2O at 22 °C[a]

	K_a, M^{-1}					$-\Delta G°$, kcal mol^{-1}				
no.	Li^+	Na^+	K^+	Rb^+	Cs^+	Li^+	Na^+	K^+	Rb^+	Cs^+
1a	1.4×10^5	1.1×10^9	1.1×10^9	4.6×10^7	3.1×10^6	7.0	12.3	12.1	10.4	8.9
1b	8.5×10^4	2.8×10^5	9.3×10^7	1.6×10^8	8.5×10^7	6.7	7.4	10.9	11.2	10.8
3	1.6×10^5	7.3×10^7	2.7×10^7	2.5×10^6	6.9×10^5	7.0	10.6	10.0	8.6	7.9
4a	3.6×10^5	1.8×10^8	1.2×10^8	3.8×10^7	1.1×10^7	7.5	11.1	10.9	10.2	9.5
4b	2.7×10^5	2.0×10^8	1.2×10^8	2.5×10^7	1.1×10^7	7.3	11.2	10.9	10.0	9.5
4c	4.3×10^5	5.0×10^8	1.6×10^8	3.9×10^7	1.6×10^7	7.6	11.7	11.1	10.2	9.7

[a] The association constants were determined as described by Cram et al.[2a]

Table IV. ^1H NMR Data of the Complexation of Alkali Picrates with 4b and 4c in $CDCl_3$ at 22 °C

		δ ($ArCH_2O$)		
host	% extr[a]	T = 18 °C	T = −50 °C	T_c, °C
4b	*b*	4.55 (s)	4.63 (s) 5.15; 4.01 (AB)[c]	<−60
4c	*b*	4.55 (s)	4.98; 4.26 (AB)[c]	−2
4b·NaPic	40	5.23; 4.02 (AB)[c]	5.28; 4.12 (AB)[c]	>60
4c·NaPic	49	5.16; 4.04 (AB)[c]	5.20; 4.12 (AB)[c]	>60
4b·KPic	47	4.8–4.1 (AB, br)	4.78; 4.17 (AB)[c]	~38
4c·KPic	48	4.88; 4.03 (AB)[c]	4.94; 4.08 (AB)[c]	~58

[a] Experiments with alkali picrates were carried out by dissolving the salt in a solution of **4b** or **4c** in $CDCl_3$. [b] Free ligand. [c] J = 9.5 Hz.

workers.[2a] Aqueous solutions containing either 0.0150 M Li^+, Na^+, or K^+ picrate or 0.0100 M Rb^+ or Cs^+ picrate in H_2O were equilibrated with $CDCl_3$ in the presence and absence of hosts at 22 °C. The K_a and $-\Delta G°$ values determined are the averages of at least three measurements, and the results are given in Table III.

The novel hemispherand **3** possessing a central nitro group as ligating site is expected to have a more preorganized terphenyl moiety than **1a** because ring inversion due to rotations around the aryl–aryl bonds will depend on the size of the groups (nitro vs. methoxy).[23] As expected, the ^1H NMR spectrum of **3** at room temperature showed the benzylic hydrogen atoms as an AB quartet (vide supra). Upon complexation of **3** with sodium picrate in different molar ratios, the ^1H NMR spectrum ($CDCl_3$) showed two AB quartets, viz., the free and the complexed host.

Obviously the decomplexation rate becomes slow on the 80-MHz ^1H NMR time scale. The association constants determined show a decrease of ~1.7 kcal mol^{-1} in binding free energies for all alkali cations except Li^+ as compared to **1a**. Although no complexation data on crown ethers with a nitroaryl group are available, the earlier findings in the lariat ethers have revealed that the side-armed nitroaryl group is not a good ligating site whereas the analogous methoxyaryl side arm gave an increase in alkali cation binding.[24] Another negative effect on the ability to complex alkali cations might be due to increased strain in the terphenyl unit, especially upon complexation.

The novel host molecules **4a–c** all possess an 18-membered ring, but they differ in their preorganization when compared with **1a** because one methoxy group is replaced by a pyridine nitrogen atom. Compounds **4a** and **4b** differ only in their outer-sphere functionalization and will resemble each other in their complexation abilities. In the ^1H NMR spectra ($CDCl_3$) of **4a** and **4b** at 18 °C, the Ar CH_2 hydrogen atoms are present as singlets, indicating a fast ring inversion on the ^1H NMR time scale (vide supra). However, upon complexation of **4a** and **4b** with sodium or potassium picrate, these protons exhibit an AB quartet at different temperatures (Table IV), indicating slow ring inversion on the ^1H NMR time scale. These spectral data are consistent with the corresponding binding free energies, which are ~1.0 kcal mol^{-1} lower compared with **1a**. Although the pyridine nitrogen atom is a much better ligating site than the methoxy oxygen atom, the conformational flexibility of the hosts **4a** and **4b** is reflected in the reduced free energies of complexation when compared with that of **1a**. Whereas the Li^+ ion is too small, as reflected in a low $-\Delta G°$ value, the binding free energies for the larger alkali cations Rb^+ and Cs^+ have decreased by only 0.7 and 1.4 kcal mol^{-1} in comparison with that for the corresponding K^+ complex. This diminished discrimination between the larger alkali cations may be attributed to the higher conformational mobility of the 2,6-diarylpyridine unit of the molecules, which allows the dihedral angles between the anisyl and pyridine units to increase without introducing too much strain upon complexation.

The conformational mobility of **4a** and **4b** can be partly reduced by the introduction of substituents in the 3- and 5-positions of the pyridine moiety. Introducing methyl groups in these positions might increase the steric interaction between the ortho hydrogen atoms of the adjacent anisyl groups and the 3,5-methyl groups, as is obvious from the CPK molecular model of **4c**. The ^1H NMR spectrum of **4c** ($CDCl_3$) showed a singlet for the Ar CH_2 protons at 18 °C (vide supra). However, upon lowering the temperature, these protons coalesced at 0 °C, and at −55 °C two conformations are frozen out, as was shown by the appearance of two AB quartets and by two different singlets for the pyridine 4-proton. This indicates that rotation around the pyridine aryl bonds becomes slow on the ^1H NMR time scale. Complexation with either sodium or potassium picrate gave a ^1H NMR spectrum ($CDCl_3$) in which the Ar CH_2 protons are present as an AB quartet. For **4c**·K^+Pic^- a coalescence temperature of 58 °C was found. This proves that the introduction of the methyl groups in the pyridine ring rigidifies the molecule, which is reflected in an increase in the binding power toward the alkali cations, especially Na^+.

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The 21-membered host **1b** shows a selectivity for the larger alkali cations K^+, Rb^+, and Cs^+. Although by Cram's definition this host is not a hemispherand because less than half of the molecule is preorganized, it gives free energies of binding for the larger alkali cations almost equal to that of **2b** and in addition an enhanced discrimination of K^+ over Na^+. CPK molecular models show both hosts **1b** and **2b** to be conformationally mobile. Obviously the loss of preorganization in **1b** compared to **2b** is compensated for by the better ligating site, ethylene oxygen vs. anisyl oxygen.

When we summarize the binding properties of the novel macrocyclic ligands, we can conclude that replacement of the central methoxy group in the parent 18-hemispherand by a pyridine nitrogen atom causes the same binding pattern as found for **1a** and a small decrease in the free energy of complexation with Na^+, K^+, and Rb^+. However, with Li^+ and Cs^+ more stable complexes are formed. The effect of the enhanced rigidity of the 2,6-diarylpyridine moiety in **4c** supports the principle of preorganization.

The synthesis of appropriate pyrylium building blocks for the construction of hemispherands has been shown to be an appropriate methodology to obtain inner-sphere-modified hemispherands that differ in their degree of preorganization, their ligating sites, and as a consequence their behavior toward alkali metal complexation. Subsequent functionalization of the outer sphere is possible by substituting benzaldehyde in the synthesis of **4a** for an appropriately substituted benzaldehyde.

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 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. Elemental analyses were carried out by E. Hoogendam of the Laboratory of Chemical Analysis of the Twente University of Technology.

Tetrahydrofuran (THF) was freshly distilled from sodium benzophenone ketyl. Chromatographic separations mentioned were performed on silica gel (SiO_2) 60 (E. Merck, particle size 0.040–0.063 mm, 230–400 mesh) or aluminum oxide (Al_2O_3) (E. Merck, neutral grade, particle size 0.063–0.300 mm, 70–230 mesh ASTM). All reactions in which dry solvents were used were carried out in a nitrogen atmosphere. All mass spectra were calculated for ^{79}Br.

1-[5-Methyl-2-(2-propenyloxy)phenyl]-1-ethanone (5d). A mixture of **5a** (120.0 g, 0.8 mol), K_2CO_3 (110.4 g, 0.8 mol), and 1-bromo-2-propene (150 g, 1.24 mol) in 450 mL of dry acetone (K_2CO_3) was stirred under reflux for 72 h. The solvent and excess 1-bromo-2-propene were removed under reduced pressure. To the residue was added 500 mL of water, and the resulting mixture was extracted with diethyl ether (3 × 150 mL). The combined organic layers were washed with water and 2 M HCl and dried with $MgSO_4$, and the solvent was removed under reduced pressure. The resulting oil was distilled to give **5d**, which crystallized upon cooling: yield 81%; bp 90–92 °C (0.06 mmHg); mp 30–32 °C; mass spectrum, *m/e* 190.102 (M^+, calcd 190.099); ^1H NMR δ 7.54–6.78 (m, 3 H, Ar H), 6.26–5.86 (m, 1 H, =CH), 5.54–5.21 (m, 2 H, $=CH_2$), 4.65–4.55 (m, 2 H, OCH_2), 2.63 (s, 3 H, CH_3), 2.29 (s, 3 H, Ar CH_3).

Anal. Calcd for $C_{12}H_{14}O_2$: C, 75.76; H, 7.42. Found: C, 75.89; H, 7.80.

1-[5-Methyl-2-(2-propenyloxy)phenyl]-1-propanone (5e) was prepared from **5c** similarly to **5d**. The product obtained after workup was recrystallized from pentane to give **5e** as white crystals: yield 74%; mp 39–40 °C; mass spectrum, *m/e* 204.114 (M^+, calcd 204.115); ^1H NMR δ 7.46–6.76 (m, 3 H, Ar H), 6.30–5.80 (m, 1 H, =CH), 5.48–5.20 (m, 2 H, $=CH_2$), 4.62–4.52 (m, 2 H, OCH_2), 3.00 (q, 2 H, CH_2), 2.28 (s, 3 H, Ar CH_3), 1.15 (t, 3 H, CH_3).

Anal. Calcd for $C_{13}H_{16}O_2$: C, 76.44; H, 7.90. Found: C, 76.46; H, 8.10.

1-(3-Bromo-2-hydroxy-5-methylphenyl)-1-ethanone (6a). *N*-Bromosuccinimide (67.8 g, 0.38 mol) in 200 mL of DMF was dropwise added to a solution of **5a** (57.1 g, 0.38 mol) in 200 mL of DMF at 0 °C. The reaction mixture was stirred for 16 h at room temperature. The solvent was removed under reduced pressure, and to the residue was added 1 L of water. Stirring for 2 h afforded a crystalline product, which was filtered off and recrystallized from ethanol to give pure **6a**: yield 96%; mp 88–89 °C; mass spectrum, *m/e* 227.980 (M^+, calcd 227.979); ^1H NMR δ 12.72 (s, 1 H, OH), 7.57 (s, 1 H, Ar H), 7.49 (s, 1 H, Ar H), 2.63 (s, 3 H, CH_3), 2.31 (s, 3 H, Ar CH_3).

Anal. Calcd for $C_9H_9BrO_2$: C, 47.19; H, 3.96. Found: C, 47.29; H, 4.01.

1-[2-Hydroxy-5-methyl-3-(2-propenyl)phenyl]-1-ethanone (6b). In an argon atmosphere, **5d** (100 g, 0.53 mol) was stirred and heated at 190 °C for 20 h. Distillation under reduced pressure gave **6b** as a yellow oil: yield 95%; bp 94–96 °C (0.15 mmHg); mass spectrum, *m/e* 190.101 (M^+, calcd for $C_{12}H_{14}O_2$ 190.099); ^1H NMR δ 12.42 (s, 1 H, OH), 7.37 (d, 1 H, Ar H), 7.17 (d, 1 H, Ar H), 6.25–5.75 (m, 1 H, =CH), 5.21–4.93 (m, 2 H, $=CH_2$), 3.38 (d, 2 H, Ar CH_2), 2.58 (s, 3 H, CH_3), 2.28 (s, 3 H, Ar CH_3); ^{13}C NMR δ 204.4 (s, C=O), 158.2 (s, COH), 136.2 (d, =CH), 115.8 (t, $=CH_2$); IR (NaCl) 1660 (C=O) cm^{-1}.

1-[2-Hydroxy-5-methyl-3-(2-propenyl)phenyl]-1-propanone (6c) was prepared from **5e** as described for **6b**. The reaction product was crystallized by the addition of a small volume of ethanol to give **6c** as white crystals: yield 80%; mp 40–41 °C; mass spectrum, *m/e* 204.115 (M^+, calcd 204.115); ^1H NMR δ 12.51 (s, 1 H, OH), 7.42 (d, 1 H, Ar H), 7.17 (d, 1 H, Ar H), 6.19–5.77 (m, 1 H, =CH), 5.22–4.96 (m, 2 H, $=CH_2$), 3.40 (d, 2 H, Ar CH_2), 3.02 (q, 2 H, CH_2), 2.29 (s, 3 H, Ar CH_3), 1.23 (t, 3 H, CH_3).

Anal. Calcd for $C_{13}H_{16}O_2$: C, 76.44; H, 7.90. Found: C, 76.62; H, 8.16.

1-(3-Bromo-2-methoxy-5-methylphenyl)-1-ethanone (7a). A mixture of **6a** (20.0 g, 87 mmol), K_2CO_3 (14.5 g, 200 mmol), and methyl iodide (32.6 g, 230 mmol) in 150 mL of dry acetone (K_2CO_3) was stirred for 20 h at room temperature. The solvent and excess methyl iodide were removed under reduced pressure. The residue was partitioned between 100 mL of 1 M HCl and 100 mL of diethyl ether. The aqueous phase was extracted with diethyl ether (2 × 100 mL), and the combined organic phases were dried ($MgSO_4$) and concentrated under reduced pressure. The resulting oil was distilled to give **7a** as a yellow oil: yield 94%; bp 90 °C (4 mmHg); mass spectrum, *m/e* 241.995 (M^+, calcd for $C_9H_9BrO_2$ 241.994); ^1H NMR δ 7.50 (d, 1 H, Ar H), 7.34 (d, 1 H, Ar H), 3.85 (s, 3 H, OCH_3), 2.63 (s, 3 H, CH_3), 2.32 (s, 3 H, Ar CH_3); ^{13}C NMR δ 199.2 (s, C=O); IR (KBr) 1700 (C=O) cm^{-1}.

1-[2-Methoxy-5-methyl-3-(2-propenyl)phenyl]-1-ethanone (7b). A solution of KOH (160 g, 2.85 mol) in 160 mL of water was dropwise added to a mixture of **6b** (109 g, 0.57 mol) and dimethyl sulfate (134 g, 1.06 mol) in 400 mL of THF. After the addition, the reaction mixture was heated under reflux for 3 h. The THF was removed under reduced pressure, and 250 mL of diethyl ether was added. The aqueous phase was extracted with another 250 mL of diethyl ether, and the combined organic phases were washed with water (2 × 250 mL), dried ($MgSO_4$), and concentrated in vacuo. The resulting oil was distilled to give **7b** as a colorless oil: yield 90%; bp 87–88 °C (0.07 mmHg); mass spectrum, *m/e* 204.115 (M^+, calcd for $C_{13}H_{16}O_2$ 204.115); ^1H NMR δ 7.27 (d, 1 H, Ar H), 7.13 (d, 1 H, Ar H), 6.15–5.74 (m, 1 H, =CH), 5.18–4.93 (m, 2 H, $=CH_2$), 3.72 (s, 3 H, OCH_3), 3.41 (d, 2 H, Ar CH_2), 2.61 (s, 3 H, CH_3), 2.29 (s, 3 H, Ar CH_3); ^{13}C NMR δ 204.0 (s, C=O), 155.3 (s, $COCH_3$), 136.8 (d, =CH), 116.1 (t, $=CH_2$); IR (NaCl) 1700 (C=O) cm^{-1}.

1-[2-Methoxy-5-methyl-3-(2-propenyl)phenyl]-1-propanone (7c) was prepared from **6c** similarly to **7b**. Distillation afforded **7c** as a colorless oil: yield 96%; bp 88–90 °C (0.10 mmHg); mass spectrum, *m/e* 218.133 (M^+, calcd for $C_{14}H_{18}O_2$ 218.131); ^1H NMR δ 7.16 (d, 1 H, Ar H), 7.11 (d, 1 H, Ar H), 6.07–5.86 (m, 1 H, =CH), 5.12–5.02 (m, 2 H, $=CH_2$), 3.70 (s, 3 H, OCH_3), 3.41 (d, 2 H, Ar CH_2), 2.97 (q, 2 H, CH_2), 2.29 (s, 3 H, Ar CH_3), 1.17 (t, 3 H, CH_3); ^{13}C NMR δ 204.8 (s, C=O), 154.4 (s, $COCH_3$), 136.8 (d, =CH), 116.1 (t, $=CH_2$).

General Procedure for the Preparation of the Pyrylium Tetrafluoroborates 8a–c. To a mixture of the ethanone **5b** (**7a**, **7b**) (0.20 mol) and freshly distilled benzaldehyde (10.6 g, 0.10 mol) was added boron trifluoride etherate (38.6 g, 0.20 mol) at 70 °C. The reaction mixture was heated for 2 h at 70 °C meanwhile allowing diethyl ether to evaporate from the reaction mixture. After cooling to room temperature, the pyrylium salt was filtered off or was crystallized by addition of diethyl ether (250 mL) to the reaction mixture. After the crystals were washed with diethyl ether, the product was recrystallized (solvent). Characteristic ^1H and ^{13}C NMR data are given in Table I.

2,6-Bis(2-methoxy-5-methylphenyl)-4-phenylpyrylium tetrafluoroborate (8a) was obtained from **5b** as orange crystals (acetic acid): yield 20%; mp 225–230 °C; mass spectrum, *m/e* 397.180 (M^+, calcd for $C_{27}H_{25}O_3$ 397.182).

2,6-Bis(3-bromo-2-methoxy-5-methylphenyl)-4-phenylpyrylium tetrafluoroborate (8b) was obtained from **7a** as yellow crystals (acetic acid): yield 48%; mp 189–191 °C; mass spectrum, *m/e* 553.002 (M^+, calcd for $C_{27}H_{23}Br_2O_3$ 553.003).

2,6-Bis[2-methoxy-5-methyl-3-(2-propenyl)phenyl]-4-phenylpyrylium tetrafluoroborate (8c) was obtained from **7c** as orange crystals (acetone/diethyl ether, 1/1 v/v): yield 16%; mp 160–167 °C; mass spectrum, *m/e* 478.252 ($M^+ - H$, calcd for $C_{33}H_{34}O_3$ 478.251).

2,2″-Dimethoxy-5,5″-dimethyl-2′-nitro-5′-phenyl-1,1′:3′,1″-terphenyl (9a). To a solution of **8a** (2.2 g, 4.5 mmol) in 11 mL of nitromethane was added a hot solution of potassium *tert*-butoxide (1.0 g, 8.9 mmol) in 18 mL of *tert*-butyl alcohol. The reaction mixture was heated under reflux for 45 min, cooled to room temperature, and filtrated. Addition of 100 mL of water to the remaining solution gave a crystalline product, which was filtered off and recrystallized from acetic acid to give pure **9a**: yield 90%; mp 182–184 °C; mass spectrum, *m/e* 439.175 (M^+, calcd 439.178); ^1H NMR δ 7.58 (s, 2 H, 3′,5′-H), 7.71–6.74 (m, 11 H, Ar H), 3.66 (s, 6 H, OCH_3), 2.35 (s, 6 H, CH_3).

Anal. Calcd for $C_{28}H_{25}NO_4$: C, 76.53; H, 5.70; N, 3.18. Found: C, 76.24; H, 5.86; N, 3.06.

2,2″-Dimethoxy-5,5″-dimethyl-2′-nitro-5′-phenyl-[1,1′:3′,1″-terphenyl]-3,3″-dicarboxaldehyde (9b). A mixture of **9a** (4.4 g, 10 mmol), hexamethylenetetramine (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 1 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 by chromatography (SiO_2, ethyl acetate/chloroform, 1/9 v/v) to give white crystals: yield 56%; mp 107–109 °C; mass spectrum, *m/e* 495.170 (M^+, calcd 495.165); ^1H NMR δ 10.40 (s, 2 H, CHO), 7.76 (s, 2 H, Ar H), 7.8–7.35 (m, 9 H, Ar H), 3.68 (s, 6 H, OCH_3), 2.39 (s, 6 H, CH_3); IR (KBr) 1690 (C=O) cm^{-1}.

Anal. Calcd for $C_{30}H_{25}NO_6$: C, 72.72; H, 5.08; N, 2.83. Found: C, 72.54; H, 5.14; N, 2.81.

2,2″-Dimethoxy-5,5″-dimethyl-2′-nitro-5′-phenyl-[1,1′:3′,1″-terphenyl]-3,3″-dimethanol (9c) was obtained by sodium borohydride reduction of **9b** similarly to **12d**. This gave **9c** after chromatographic purification (SiO_2, ethanol/chloroform, 2/98 w/w) and recrystallization from toluene as white crystals. This product was not further purified and was submitted to the next reaction: yield 78%; mp 135–136 °C; mass spectrum, *m/e* 499.207 (M^+, calcd 499.200); ^1H NMR δ 7.72 (s, 2 H, Ar H), 7.7–7.0 (m, 9 H, Ar H), 4.74 (br s, 4 H, CH_2), 3.56 (s, 6 H, OCH_3), 2.33 (s, 6 H, CH_3).

3,3″-Bis(bromomethyl)-2,2″-dimethoxy-5,5″-dimethyl-2′-nitro-5′-phenyl-1,1′:3′,1″-terphenyl (9d) was prepared from **9c** and PBr_3 as described for **12e** to afford **9d** as a white foam after chromatographic purification (SiO_2, $CHCl_3$): yield 80%; mass spectrum, *m/e* 623.028 (M^+, calcd 623.031); ^1H NMR δ 7.73 (s, 2 H, Ar H), 7.7–7.0 (m, 9 H, Ar H), 4.58 (s, 4 H, CH_2), 3.61 (s, 6 H, OCH_3), 2.32 (s, 6 H, CH_3).

Anal. Calcd for $C_{30}H_{27}Br_2NO_4$: C, 57.62; H, 4.35; N, 2.24. Found: C, 57.49; H, 4.50; N, 2.13.

General Procedure for the Preparation of the Pyrylium Perchlorates 11a,b. To a mixture of the ethanone **7b** or the propanone **7c** (100 mmol) and triethyl orthoformate (230 mmol) heated to 70 °C was added 70% perchloric acid (50 mmol) at a rate that maintained reflux. The reaction mixture was heated with an oil bath of 70 °C for another 2 h. After cooling to room temperature, the pyrylium salt could be filtered off or was crystallized by the addition of diethyl ether (250 mL). The product was washed with diethyl ether and recrystallized (solvent). Characteristic ^1H and ^{13}C NMR data are summarized in Table I.

2,6-Bis[2-methoxy-5-methyl-3-(2-propenyl)phenyl]pyrylium perchlorate (11a) was obtained from **7c** as orange crystals (THF): yield 27%; mp 155–156 °C; mass spectrum, *m/e* 402.224 ($M^+ + H$, calcd for $C_{27}H_{30}O_3$ 402.220).

2,6-Bis[2-methoxy-5-methyl-3-(2-propenyl)phenyl]-3,5-dimethylpyrylium perchlorate (11b) was obtained from **7d** as yellow crystals (acetic acid): yield 25%; mp 143–145 °C; mass spectrum, *m/e* 429.242 (M^+, calcd for $C_{29}H_{33}O_3$ 429.243).

General Procedure for the Preparation of the Pyridines 10a,b, 12a, 13a, and 14a. A solution of the pyrylium salt (10 mmol) and ammonium acetate (100 mmol) in 100 mL of glacial acetic acid was refluxed for 3 h. After cooling to room temperature, the reaction mixture was poured into ice water (200 mL). The resulting mixture was extracted with chloroform (3 × 100 mL), and the combined organic phases were washed with water, 10% $NaHCO_3$, and water. The organic phase was dried with $MgSO_4$, and the solvent was removed under reduced pressure.

2,6-Bis(2-methoxy-5-methylphenyl)-4-phenylpyridine (10a) was obtained from **8a** as colorless crystals by recrystallization from ethanol: yield 90%; mp 124–125 °C; mass spectrum, *m/e* 395.189 (M^+, calcd 395.189); ^1H NMR (CD_3CN) δ 8.32 (s, 2 H, pyridine H), 8.08–7.15 (m, 11 H, Ar H), 4.02 (s, 6 H, OCH_3), 2.40 (s, 6 H, CH_3).

Anal. Calcd for $C_{27}H_{25}NO_2$: C, 82.00; H, 6.37; N, 3.54. Found: C, 81.70; H, 6.47; N, 3.47.

2,6-Bis(3-bromo-2-methoxy-5-methylphenyl)-4-phenylpyridine (10b) was obtained from **8b** as yellow crystals by crystallization from benzene: yield 82%; mp 184–185 °C; mass spectrum, *m/e* 551.007 (M^+, calcd 551.010); ^1H NMR δ 8.12 (s, 2 H, pyridine 3,5-H), 7.77–7.43 (m, 9 H, Ar H), 3.63 (s, 6 H, OCH_3), 2.38 (s, 6 H, CH_3).

Anal. Calcd for $C_{27}H_{23}Br_2NO_2$: C, 58.62; H, 4.19; N, 2.53. Found: C, 59.03; H, 4.06; N, 2.37.

2,6-Bis[2-methoxy-5-methyl-3-(2-propenyl)phenyl]-4-phenylpyridine (12a) was obtained from **8c** as a yellow viscous oil after chromatography (SiO_2, $CHCl_3$); yield 80%; mass spectrum, *m/e* 475.259 (M^+, calcd for $C_{33}H_{33}NO_2$ 475.251); ^1H NMR δ 8.06 (s, 2 H, pyridine H), 7.85–7.05 (m, 9 H, Ar H), 6.2–5.81 (m, 2 H, =CH), 5.22–4.96 (m, 4 H, $=CH_2$), 3.51 (s, 6 H, OCH_3), 3.48 (d, 4 H, CH_2), 2.37 (s, 6 H, Ar CH_3); ^{13}C NMR δ 153.9 (s, pyridine 2,6-C), 148.4 (s, pyridine 4-C), 120.6 (d, pyridine CH).

2,6-Bis[2-methoxy-5-methyl-3-(2-propenyl)phenyl]pyridine (13a) was obtained from **11a** as a yellow viscous oil after chromatography (SiO_2, $CHCl_3$): yield 78%; mass spectrum, *m/e* 399.217 (M^+, calcd for $C_{27}H_{29}NO_2$ 399.220); ^1H NMR δ 7.76 (s, 3 H, pyridine H), 7.51 (d, 2 H, Ar H), 7.05 (d, 2 H, Ar H), 6.29–5.80 (m, 2 H, =CH), 5.23–4.95 (m, 4 H, $=CH_2$), 3.45 (s, 6 H, OCH_3), 3.46 (d, 4 H, CH_2), 2.35 (s, 6 H, CH_3); ^{13}C NMR δ 153.9 (s, pyridine 2,6-C), 136.0 (d, pyridine 4-C), 122.6 (d, pyridine 3,5-C).

2,6-Bis[2-methoxy-5-methyl-3-(2-propenyl)phenyl]-3,5-dimethylpyridine (14a) was obtained from **11b** as white crystals by recrystallization from ethanol: yield 89%; mp 84–85 °C; mass spectrum, *m/e* 427.252 (M^+, calcd 427.251); ^1H NMR (CD_3CN) δ 8.89 (s, 1 H, pyridine H), 7.41 (s, 2 H, Ar H), 7.35 (s, 2 H, Ar H) 6.29–5.79 (m, 2 H, =CH), 5.22–4.98 (m, 4 H, $=CH_2$), 3.49 (s, 6 H, OCH_3), 3.45 (m, 4 H, Ar CH_2), 2.50 (s, 6 H, CH_3), 2.37 (s, 6 H, CH_3).

Anal. Calcd for $C_{29}H_{33}NO_2$: C, 81.46; H, 7.78; N, 3.27. Found: C, 81.67; H, 7.88; N, 2.91.

2,6-Bis[2-methoxy-5-methyl-3-(1-propenyl)phenyl]-4-phenylpyridine (12b). A mixture of **12a** (6.0 g, 12.6 mmol), potassium *tert*-butoxide (4.8 g, 42.8 mmol), and 0.5 mL of *tert*-butyl alcohol in 150 mL of dry THF was heated under reflux for 18 h. After cooling to room temperature, the reaction mixture was diluted with water and extracted with diethyl ether (3 × 100

mL). The combined organic layers were washed with water and dried ($MgSO_4$), and the solvent was removed in vacuo to give a yellow oil. Addition of *n*-pentane gave a crystalline product, which was filtered off and recrystallized from ethanol to give **12b** as pale yellow crystals: yield 83%; mp 141–142 °C; mass spectrum, *m/e* 475.252 (M^+, calcd 475.251); ^1H NMR δ 8.07 (s, 2 H, pyridine H), 7.83–7.31 (m, 9 H, Ar H), 6.88–6.14 (m, 4 H, =CH), 3.54 (s, 6 H, OCH_3), 2.38 (s, 6 H, Ar CH_3), 1.94 (d, 6 H, CH_3).

Anal. Calcd for $C_{33}H_{33}NO_2$: C, 83.33; H, 6.99; N, 2.94. Found: C, 83.03; H, 7.09; N, 2.78.

2,6-Bis[2-methoxy-5-methyl-3-(1-propenyl)phenyl]pyridine (13b) was obtained from **13a** as described for **12b**. Recrystallization from ethanol afforded **13b** as pale yellow crystals: yield 88%; mp 107–108 °C; mass spectrum, *m/e* 399.221 (M^+, calcd 399.220); ^1H NMR δ 7.79 (t, 3 H, pyridine H), 7.50 (d, 2 H, Ar H), 7.30 (d, 2 H, Ar H), 6.86–6.12 (m, 4 H, =CH), 3.49 (s, 6 H, OCH_3), 2.36 (s, 6 H, Ar CH_3), 1.93 (d, 6 H, CH_3).

Anal. Calcd for $C_{27}H_{29}NO_2$: C, 81.17; H, 7.32; N, 3.51. Found: C, 81.19; H, 7.35; N, 3.51.

2,6-Bis[2-methoxy-5-methyl-3-(1-propenyl)phenyl]-3,5-dimethylpyridine (14b) was obtained from **14a** as described for **12b**. The product was recrystallized from ethanol to give **14b** as white crystals. The product could not be further purified and was submitted to the next reaction: yield 92%; mp 162–163 °C; mass spectrum, *m/e* 427.25 (M^+, calcd 427.251); ^1H NMR δ 7.42 (s, 1 H, pyridine H), 7.25 (s, 2 H, Ar H), 6.97 (s, 2 H, Ar H), 6.81–6.09 (m, 4 H, =CH), 3.39 (s, 6 H, OCH_3), 2.30 (s, 6 H, pyridine CH_3), 2.20 (s, 6 H, Ar CH_3), 1.90 (d, 6 H, CH_3).

3,3′-(4-Phenyl-2,6-pyridinediyl)bis(2-methoxy-5-methylbenzaldehyde) (12c). A suspension of **12b** (0.75 g, 1.58 mmol) in 30 mL of methanol was cooled to −30 °C. Ozone was passed through at a flow rate of 0.15 mmol min^{-1} for 3 h, whereupon a white emulsion was formed. To the mixture was added a solution of I_2 (1.5 g, 5.91 mmol) in 10 mL of glacial acetic acid, and the mixture was stirred for 10 min at room temperature. Sodium thiosulfate (1 M) was added until the solution remained decolorized. The mixture was extracted with chloroform (3 × 30 mL), and the combined organic layers were washed with water and 10% $NaHCO_3$ and dried with $MgSO_4$. Evaporation of the solvent under reduced pressure afforded a residue, which was crystallized from diisopropyl ether. Recrystallization from diethyl ether gave **12c**: yield 82%; mp 176–178 °C; mass spectrum, *m/e* 451.181 (M^+, calcd 451.178); ^1H NMR δ 10.48 (s, 2 H, CHO), 8.14 (s, 2 H, pyridine H), 7.98–7.51 (m, 9 H, Ar H), 3.71 (s, 6 H, OCH_3), 2.46 (s, 6 H, Ar CH_3); ^{13}C NMR δ 189.9 (s, CHO).

3,3′-(2,6-Pyridinediyl)bis(2-methoxy-5-methylbenzaldehyde) (13c) was obtained from **13b** as described for **12c**. Recrystallization from diethyl ether afforded white crystals: yield 80%; mp 137–138 °C; mass spectrum, *m/e* 375.148 (M^+, calcd 375.147); ^1H NMR δ 10.47 (s, 2 H, CHO), 7.94 (d, 2 H, Ar H), 7.89 (s, 3 H, pyridine H), 7.73 (d, 2 H, Ar H), 3.67 (s, 6 H, OCH_3), 2.44 (s, 6 H, CH_3); ^{13}C NMR δ 190.0 (s, CHO).

Anal. Calcd for $C_{23}H_{21}NO_4$: C, 73.58; H, 5.64; N, 3.73. Found: C, 73.03; H, 5.65; N, 3.53.

3,3′-(3,5-Dimethyl-2,6-pyridinediyl)bis(2-methoxy-5-methylbenzaldehyde) (14c) was obtained from **14b** as described for **12c**. The product was recrystallized from diethyl ether to afford **14c** as white crystals: yield 64%; mp 148–151 °C; mass spectrum, *m/e* 403.178 (M^+, calcd 403.178); ^1H NMR δ 10.42 (s, 2 H, CHO), 7.71 (d, 2 H, Ar H), 7.59 (s, 1 H, pyridine H), 7.42 (d, 2 H, Ar H), 3.56 (s, 6 H, OCH_3), 2.39 (s, 6 H, pyridine CH_3), 2.27 (s, 6 H, Ar CH_3).

Anal. Calcd for $C_{25}H_{25}NO_4$: C, 74.42; H, 6.24; N, 3.47. Found: C, 74.37; H, 6.49; N, 3.15.

3,3′-(4-Phenyl-2,6-pyridinediyl)bis(2-methoxy-5-methylbenzenemethanol) (12d). To a suspension of **12c** (2.0 g, 4.4 mmol) in 20 mL of methanol was added sodium borohydride (1.0 g, 26.4 mmol) at 0 °C. After the mixture was stirred for 20 min, the resulting solution was warmed to room temperature and stirring was continued for 30 min. To the reaction mixture was added 50 mL of water, and the resulting mixture was extracted with chloroform (3 × 50 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 white foam, which was crystallized by the addition of diethyl ether. Recrystallization from diethyl ether afforded **12d** as white crystals: yield 95%; mp 128–129 °C; mass spectrum, *m/e* 455.210 (M^+, calcd 455.211); ^1H NMR δ 8.06 (s, 2 H, pyridine H), 7.73–7.22 (m, 9 H, Ar H), 4.77 (s, 4 H, CH_2), 3.57 (s, 6 H, OCH_3), 2.39 (s, 6 H, CH_3), 2.35 (br s, 2 H, OH).

3,3′-(2,6-Pyridinediyl)bis(2-methoxy-5-methylbenzenemethanol) (13d) was obtained from **13c** as described for **12d**. The product was recrystallized from ethanol to give **13d** as white crystals: yield 94%; mp 128–129 °C; mass spectrum, *m/e* 379.180 (M^+, calcd 379.178); ^1H NMR δ 7.77 (s, 3 H, pyridine H), 7.58 (d, 2 H, Ar H), 7.21 (d, 2 H, Ar H), 4.74 (s, 4 H, CH_2), 3.52 (s, 6 H, OCH_3), 2.41 (br s, 2 H, OH), 2.38 (s, 6 H, CH_3).

Anal. Calcd for $C_{23}H_{25}NO_4$: C, 72.80; H, 6.64; N, 3.69. Found: C, 72.59; H, 6.67; N, 3.46.

3,3′-(3,5-Dimethyl-2,6-pyridinediyl)bis(2-methoxy-5-methylbenzenemethanol) (14d) was prepared from **14c** similarly to **12d**, yield 94%. A small sample of the product was recrystallized from diethyl ether for analysis: mp 161–162 °C; mass spectrum, *m/e* 407.209 (M^+, calcd 407.210); ^1H NMR δ 7.45 (s, 1 H, pyridine H), 7.14 (s, 2 H, Ar H), 7.07 (s, 2 H, Ar H), 4.69 (s, 4 H, CH_2), 3.42 (s, 6 H, OCH_3), 2.32 (s, 6 H, Ar CH_3), 2.21 (s, 6 H, pyridine CH_3).

Anal. Calcd for $C_{25}H_{29}NO_4 \cdot 0.5H_2O$: C, 72.09; H, 7.26; N, 3.36. Found: C, 72.49; H, 7.41; N, 3.11.

2,6-Bis[3-(bromomethyl)-2-methoxy-5-methylphenyl]-4-phenylpyridine (12e). To a solution of **12d** (2.0 g, 4.4 mmol) in 20 mL of benzene was slowly added phosphorous tribromide (0.45 mL, 4.8 mmol) at 5 °C, whereupon the reaction mixture was stirred for 16 h at room temperature. After the addition of 50 mL of water, the mixture was neutralized with 10% $NaHCO_3$. After the layers were separated, the aqueous phase was extracted with chloroform (2 × 50 mL). The combined organic phases were dried ($MgSO_4$), and the solvent was evaporated in vacuo to give **12e** as a white foam: yield 82%; mass spectrum, *m/e* 579.035 (M^+, calcd 579.041); ^1H NMR δ 8.06 (s, 2 H, pyridine H), 7.73–7.26 (m, 9 H, Ar H), 4.64 (s, 4 H, CH_2), 3.63 (s, 6 H, OCH_3), 2.39 (s, 6 H, CH_3).

Anal. Calcd for $C_{29}H_{27}Br_2NO_2$: C, 59.91; H, 4.68; N, 2.41. Found: C, 59.88; H, 4.74; N, 2.20.

2,6-Bis[3-(bromomethyl)-2-methoxy-5-methylphenyl]-pyridine (13e) was obtained from **13d** as described for **12e**. The product was recrystallized from diethyl ether to give colorless crystals: yield 82%; mp 105–106 °C; mass spectrum, *m/e* 503.007 (M^+, calcd 503.010); ^1H NMR δ 7.79 (s, 3 H, pyridine H), 7.60 (d, 2 H, Ar H), 7.24 (d, 2 H, Ar H), 4.62 (s, 4 H, CH_2), 3.58 (s, 6 H, OCH_3), 2.37 (s, 6 H, CH_3).

Anal. Calcd for $C_{23}H_{23}Br_2NO_2$: C, 54.68; H, 4.59; N, 2.77. Found: C, 54.85; H, 4.70; N, 2.57.

2,6-Bis[3-(bromomethyl)-2-methoxy-5-methylphenyl]-3,5-dimethylpyridine (14e) was obtained from **14d** as described for **12e**. The product was recrystallized from diethyl ether to give white crystals: yield 76%; mp 197–199 °C; mass spectrum, *m/e* 531.035 (M^+, calcd 531.041); ^1H NMR δ 7.61 (s, 1 H, pyridine H), 7.20 (d, 2 H, Ar H), 7.05 (d, 2 H, Ar H), 4.66 (s, 4 H, CH_2), 3.44 (s, 6 H, OCH_3), 2.32 (s, 6 H, Ar CH_3), 2.25 (s, 6 H, pyridine 3,5-CH_3).

Anal. Calcd for $C_{25}H_{27}Br_2NO_2$: C, 56.30; H, 5.10; N, 2.63. Found: C, 56.38; H, 5.23; N, 2.43.

General Procedure for the Preparation of the Hemispherands 3 and 4a–c. A solution of **12e** (**13e**, **14e**) (2 mmol) and diethylene glycol (0.23 g, 2.2 mmol) in 50 mL of dry THF was added over a 10-h period to a suspension of sodium hydride (0.11 g, 4.4 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 removed 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 water and dried with $MgSO_4$ and the solvent was removed under reduced pressure. The residue was submitted to column chromatography (Al_2O_3, dichloromethane/THF, 9/1) and was recrystallized (solvent).

25,26-Dimethoxy-9,23-dimethyl-27-nitro-4-phenyl-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 (3) was prepared from **9d** and was recrystallized from ethanol/benzene to afford pale

Table V. Crystal Data of 1b and 4a

	1b	4a
formula	$C_{32}H_{40}O_7$	$C_{35}H_{40}NO_{5.5}$
lattice type	tetragonal	monoclinic
space group	$P\bar{4}2_1c$	$C2/c$
temperature, K	100	293
cell dimensions		
a, Å	20.493 (10)	26.613 (12)
b, Å		15.862 (6)
c, Å	13.679 (5)	16.607 (6)
β, deg		115.38 (4)
V, Å^3	5745 (8)	6334 (12)
Z	8	8
D_{calcd}, g cm^{-3}	1.24	1.18
μ (Mo Kα), cm^{-1}	0.8	0.7
θ range, deg	3-25	3-25
no. of unique reflections		
measured	2796	5562
observed ($F_o^2 > 3\sigma(F_o^2)$)	2025	2604
final no. of variables	392	422
R, %	2.5	3.6
R_w, %	3.1	5.1

yellow crystals: yield 23%; mp 194-195 °C; mass spectrum, m/e 569.246 (M^+, calcd 569.241); ^1H NMR δ 7.78 (s, 2 H, Ar H), 7.7-7.1 (m, 9 H, Ar H), 3.64 (s, 8 H, OCH_2), 4.52 (AB q, J_{AB} = 12.0 Hz, 4 H, Ar CH_2), 3.43 (s, 6 H, OCH_3), 2.33 (s, 6 H, CH_3).

Anal. Calcd for $C_{34}H_{35}NO_7$: C, 71.69; H, 6.19; N, 2.46. Found: C, 71.74; H, 6.24; N, 2.11.

25,26-Dimethoxy-9,23-dimethyl-4-phenyl-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 (4a) was obtained from **12e**. Recrystallization of the product from diethyl ether afforded pure **4a** as white crystals: yield 60%; mp 104-115 °C; mass spectrum, m/e 525.257 (M^+, calcd 525.252); ^1H NMR δ 7.75-7.46 (m, 5 H, Ar H), 7.70 (s, 2 H, pyridine H), 7.21 (d, 2 H, Ar H), 7.06 (d, 2 H, Ar H), 4.58 (s, 4 H, Ar CH_2), 3.54 (s, 14 H, OCH_3 and OCH_2), 2.32 (s, 6 H, Ar CH_3).

Anal. Calcd for $C_{33}H_{35}NO_5 \cdot 0.5C_4H_{10}O$: C, 74.77; H, 7.17; N, 2.49. Found: C, 74.59; H, 7.28; N, 2.25.

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 (4b) was obtained from **13e**. Recrystallization of the product from diethyl ether yielded **4b** as white crystals: yield 54%; mp 134-135 °C; mass spectrum, m/e 449.218 (M^+, calcd 449.220); ^1H NMR δ 7.85 and 7.45 (A_2B, J = 7.89 Hz, 3 H, pyridine H), 7.10 (s, 2 H, Ar H), 7.05 (s, 2 H, Ar H), 4.55 (s, 4 H, Ar CH_2), 3.53 (s, 8 H, OCH_2), 3.48 (s, 6 H, OCH_3), 2.31 (s, 6 H, Ar CH_3).

Anal. Calcd for $C_{27}H_{31}NO_5$: C, 72.14; H, 6.95; N, 3.12. Found: C, 71.74; H, 6.94; N, 2.95.

25,26-Dimethoxy-3,5,9,23-tetramethyl-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 (4c) was obtained from **14e**. Recrystallization of the product from acetone afforded **4c** as colorless crystals: yield 54%; mp 197-199 °C; mass spectrum, m/e 477.255 (M^+, calcd 477.252); ^1H NMR δ 7.51 (s, 1 H, pyridine H), 6.99 (s, 4 H, Ar H), 4.55 (s, 4 H, Ar CH_2), 3.47 (s, 6 H, OCH_3), 3.44 (m, 8 H, OCH_2), 2.39 (s, 6 H, pyridine CH_3), 2.27 (s, 6 H, Ar CH_3).

Anal. Calcd for $C_{29}H_{35}NO_5$: C, 72.93; H, 7.39; N, 2.93. Found: C, 73.22; H, 7.47; N, 2.82.

28,29,30-Trimethoxy-4,9,26-trimethyl-13,16,19,22-tetraoxatetracyclo[22.3.1.1^{2,6}.1^{7,11}]triaconta-1(28),2,4,6(30),7,9,11(29),24,26-nonaene (1b) was prepared from 3,3″-bis(bromomethyl)-2,2′,2″-trimethoxy-5,5′,5″-trimethyl-1,1′:3′,1″-terphenyl[1] (2.0 g, 3.6 mmol) and triethyleneglycol (0.54 g, 3.6 mmol) as described for **3** and **4a-c**. The product was recrystallized from ethanol to give pure **1b**: yield 31%; mp 157-158 °C; mass spectrum, m/e 536.277 (M^+, calcd 536.278); ^1H NMR δ 7.13-7.08 (m, 6 H, Ar H), 4.83 (AB q, J_{AB} = 10.5 Hz, 2 H, Ar CH_2), 4.22 (AB q, J_{AB} = 10.5 Hz, 2 H, Ar CH_2), 3.74-3.20 (m, 12 H, OCH_2), 3.56 (s, 6 H, outer OCH_3), 2.88 (s, 3 H, inner OCH_3), 2.39 (s, 3 H, inner CH_3), 2.33 (s, 6 H, outer CH_3).

Anal. Calcd for $C_{32}H_{40}O_7$: C, 71.62; H, 7.51. Found: C, 71.43; H, 7.56.

X-ray Crystallography. Measurements were performed on a CAD-4 single-crystal diffractometer (Mo Kα radiation, graphite monochromator). Crystal data are shown in Table V. Intensities were measured by using the $\omega/2\theta$ scan mode (correction for Lorentz polarization and intensity variations of three control reflections; no absorption correction). The structures were solved by direct methods.[25] Refinement (on F, weight $w = 4F_o^2/\sigma^2(F_o^2)$) was performed by full-matrix least-squares. Hydrogens were located on difference Fourier maps. The methoxy hydrogens were included in the refinement; all other hydrogens were put in calculated positions (C-H distance 0.96 Å) and treated as riding on their parent C atoms. Both structures show some disorder: all aryl methyl hydrogens are rotationally disordered, and the crystal structure of **4b** contains half a solvent molecule of diethyl ether; it was found to be disordered around the twofold axis. All calculations were done by using SDP.[26] Full details will be published elsewhere.

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Supplementary Material Available: Tables of atomic positional and thermal parameters and bond distances and angles of **1b** and **4a** (12 pages). Ordering information is given on any current masthead page.

Preparation and Chemistry of the Diels-Alder Adducts of Levopimaric Acid and Activated Thiocarbonyl Dienophiles

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The reactions of levopimaric acid (1) with the activated dienophiles methyl cyanodithioformate (2) and *N*-benzoyl-*N*-phenylcyanothioformamide (3) are reported. The resulting Diels-Alder adducts were then subjected to various reaction conditions, including acid and/or base hydrolysis, permanganate oxidation, and catalytic hydrogenation, where applicable.

After reinvestigating the fundamental chemistry of the model formaldehyde-levopimaric acid adduct,[1] I became especially interested in a group of analogous heteroatomic dienophiles, the activated thiocarbonyls. First of all, these

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