Novel Spherand-Type Calixarenes — Synthesis, Conformational Studies, and Isomer Separation

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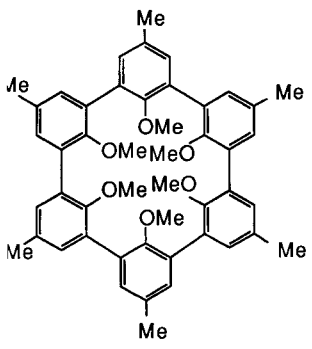
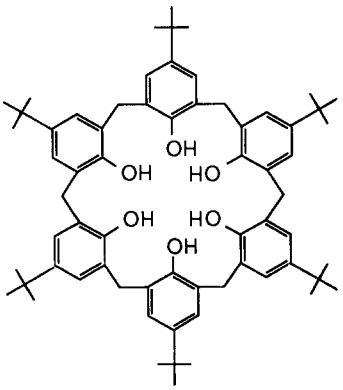
The novel macrocyclic compounds hexahydroxy[1.0.1.0.1.0]-**6b** and octahydroxy[1.0.1.0.1.0.1.0]metacyclophane **6c** have been prepared in 50–70% yield by base-catalyzed condensation of 5,5′-di-*tert*-butyl-2,2′-dihydroxybiphenyl (**5**) with formaldehyde in xylene. The conformations of trimer **6b** and tetramer **6c** have been evaluated from their dynamic ^{1}H-NMR spectra. Methylation of the hydroxyl groups of **6b** and **6c** with MeI gives the corresponding methoxy[1$_n$]metabiphenylophanes **7b** and **7c** in good yields. The metacyclophane **7b** has been found to consist of two isomers, out of which one was separated pure. The structural characterization of these products is discussed.

Due to their importance in supramolecular chemistry[1] a large variety of macrocyclic compounds such as crown ethers[2], cryptates[3], cyclophanes[4], and spherands[5] have been synthesized and their properties investigated. Our present work is directly related to the studies of Cram and his co-workers[5] in designing spherands possessing 1,1′-biarene units (e.g. **1**) which contain enforced, spherical cavities lined with electron pairs of heteroatoms so that upon complexation with metal ions no conformational rearrangement is possible.

Closely related to the spherands are the "calixarenes", [1$_n$]metacyclophanes (example **2a**), prepared by base-catalyzed condensation of *p*-substituted phenols with formaldehyde[6a]. These are attractive building blocks, their phenolic hydroxyl groups being ordered in well-shaped cyclic arrays[6] which can be functionalized[7] to give novel guest inclusion blocks.



1

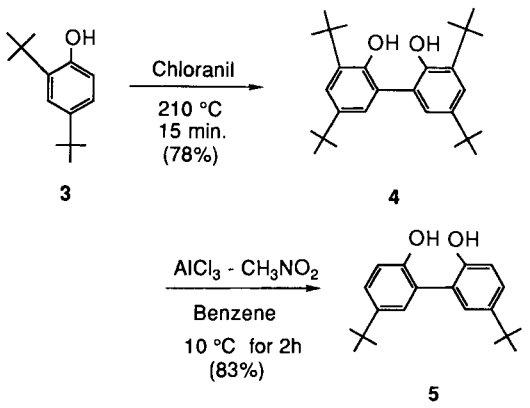


2a

The combination of structural elements of both spherands and calixarenes is expected to lead to novel macrocyclic compounds, which may be highly stimulating for future work in the field of host-guest chemistry.

Recently, we have demonstrated a convenient synthesis of the propane-bridged calixareneanalogs of metacyclophanes such as tetrahydroxy [3.1.3.1]metacyclophanes involving base-catalyzed condensation of 1,3-bis(5-*tert*-butyl-2-hydroxyphenyl)propane with formaldehyde under xylene reflux and reported their unique properties[8]. This strategy is also suitable for the preparation of hydroxy[1$_n$]metabiphenylophanes.

Scheme 1



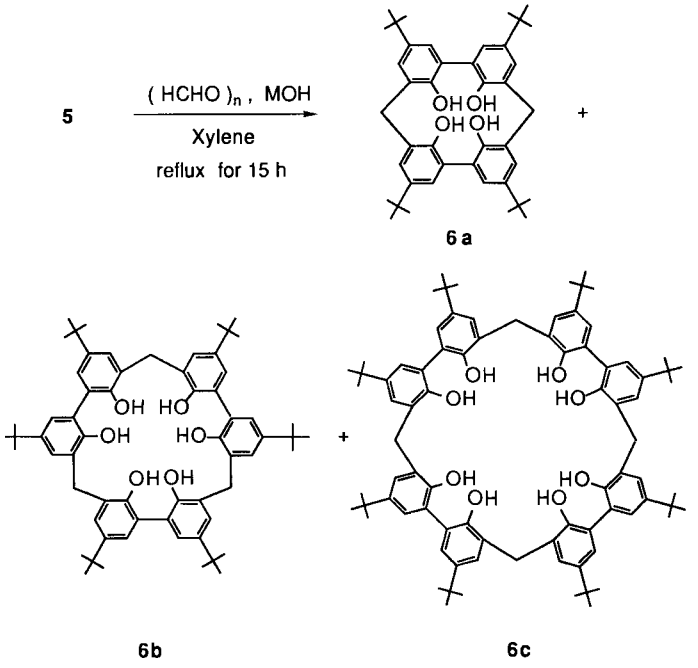
We describe in this paper the first example of the synthesis of a series of hydroxy[1$_n$]metabiphenylophanes with three and four biarene units, **6**, and their methoxy derivatives **7**, derived from 5,5′-di-*tert*-butyl-2,2′-dihydroxybiphenyl (**5**). These compounds are expected to have combined properties of both the spherands and the calixarenes.

The starting compound **5**[9] was prepared in two steps from 2,4-di-*tert*-butylphenol (**3**) by using the *tert*-butyl group as a positional protective group on the aromatic ring[9–13].

When **5** was treated with paraformaldehyde in refluxing xylene under basic conditions[14], the expected products 4,10,17,23,30,36-hexa-*tert*-butyl-7,13,20,26,33,39-hexahydroxy-

[1.0.1.0.1.0]- (**6b**) and -4,10,17,23,30,36,43,49-octa-*tert*-butyl-7,13,20,26,33,39,46,52-octahydroxy[1.0.1.0.1.0.1.0]metacyclophane (**6c**) were obtained. These compounds were easily separated from the crude reaction mixture by column chromatography. However, under these conditions the formation of the dimer, 4,10,17,23-tetra-*tert*-butyl-7,13,20,26-tetrahydroxy[1.0.1.0]metacyclophane (**6a**) has not been observed. This finding seems to support the strained nature of **6a** compared to **6b** and **6c** having larger rings. The structures of **6b** and **6c** were elucidated based on their elemental analyses and spectral data. Especially, the mass spectral data for **6b** and **6c** (M^+ = 931 and 1241) strongly support the cyclic trimeric and tetrameric structures, respectively.

Scheme 2



The calixarenes show concentration-independent OH stretching bands in the 3200-cm^{-1} region of the infrared spectrum and the signal at δ = 8 – 10 in the ^{1}H-NMR spectrum, indicative of very strong intramolecular hydrogen bonding and the cyclic nature of calixarenes[6a]. IR and ^{1}H-NMR spectral data for cyclo-oligomers **6b** and **6c** together with those of calix[*n*]arenes are summarized in Table 1.

The IR (KBr) spectra of **6b** and **6c** show the OH stretching absorption around 3297 and 3245 cm^{-1}, respectively. The ^{1}H-NMR spectra (in $CDCl_3$) exhibit the signals for hydroxy groups around δ = 8.48 and 8.34, respectively.

Table 1. Selected ^{1}H-NMR and IR spectral data for calix[6]arene **2a**, calix[8]arene **2b**, and hydroxy[1_n]metabiphenylophanes **6b**, **6c**

Compound	IR [KBr] υ (OH)	^{1}H NMR δ [$CDCl_3$] OH
2a	3150-3160	10.5
2b	3230	9.6
6b	3297	8.5
6c	3245	8.3

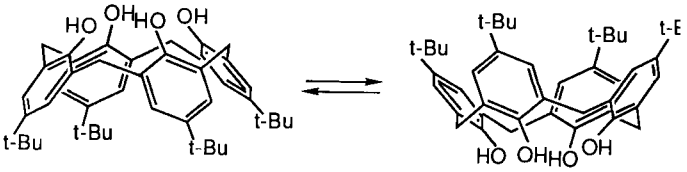
Table 2. Condensation of **5** with paraformaldehyde in the presence of alkali metal hydroxides. The reaction was carried out under xylene reflux

Alkali hydroxide	Cation diameter (Å)	Product yield [%] **6b**	**6c**
NaOH	1.94	52	trace
KOH	2.66	32	29
CsOH	3.34	4	66

The ratio of the products **6b** and **6c** is governed by the nature of alkali metal hydroxide used as a catalyst as revealed by the results listed in Table 2. Thus, when sodium hydroxide is used in this reaction, trimer **6b** is obtained as a major product in 52% yield. On the other hand, when cesium hydroxide is employed, tetramer **6c** is formed in 66% yield besides 4% yield of trimer **6b**. However, in the case of potassium hydroxide the above selectivity is not observed. The smaller alkaline metal Na^+ obviously gives rise to the formation of a smaller macrocyclic compound **6b**, while the action of the larger Cs^+ leads to larger macrocycle **6c**. These results seem to indicate that the template effect of an alkaline metal cation plays an important role in this condensation reaction as previously observed in the preparation of calixarenes[14].

The ^{1}H-NMR spectrum of the macrocyclic trimer **6b** exhibits single peaks for *tert*-butyls (δ = 1.35), methylenes (4.02), aromatics (7.20 and 7.39), and phenolic OH (8.48) at room temperature due to a rapid conformational flipping. However, at −50°C in $CDCl_3$ the signal of the methylene protons of $ArCH_2Ar$ splits into two broad singlets at δ = 3.79 and 4.21 (Figure 1). This behavior is rationalized by the conformational inversion of macrocycle **6b** in the same way as Gutsche's hydroxy[1_n]metacyclophanes (calix[*n*]arenes)[15,16] (Scheme 3).

Scheme 3



The coalescence temperature for this process was found to be −42°C (Figure 1), and the free energy of activation for inversion is estimated as 10.6 kcal/mol (T_c = −42°C, $\Delta\nu$ = 215.44 Hz). We have also obtained even a lower-temperature (−100°C) spectrum in $CDCl_3/CS_2$ (1:3), however, the exact conformation of **6b** could not be deduced because of its complicated pattern.

On the other hand, in the case of tetramer **6c** at 0°C the corresponding methylene signal (δ = 4.02) splits into four sets of doublets at δ = 3.63, 4.15 (AB system, J_{AB} 14.2 Hz) and 3.88, 4.70 (AB system, J_{AB} 13.7 Hz), indicating that the rate of conformational ring flipping of macrocycle **6c** is faster than the NMR time scale at room temperature (Figure 2).

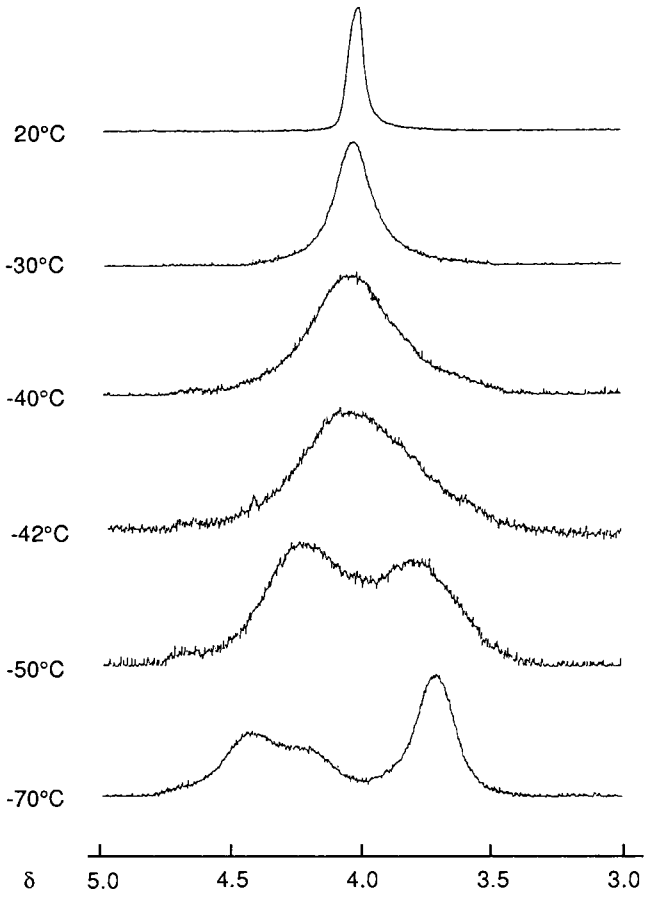


Figure 1. Dynamic ^{1}H-NMR spectrum of **6b** at 270 MHz ($CDCl_3$)

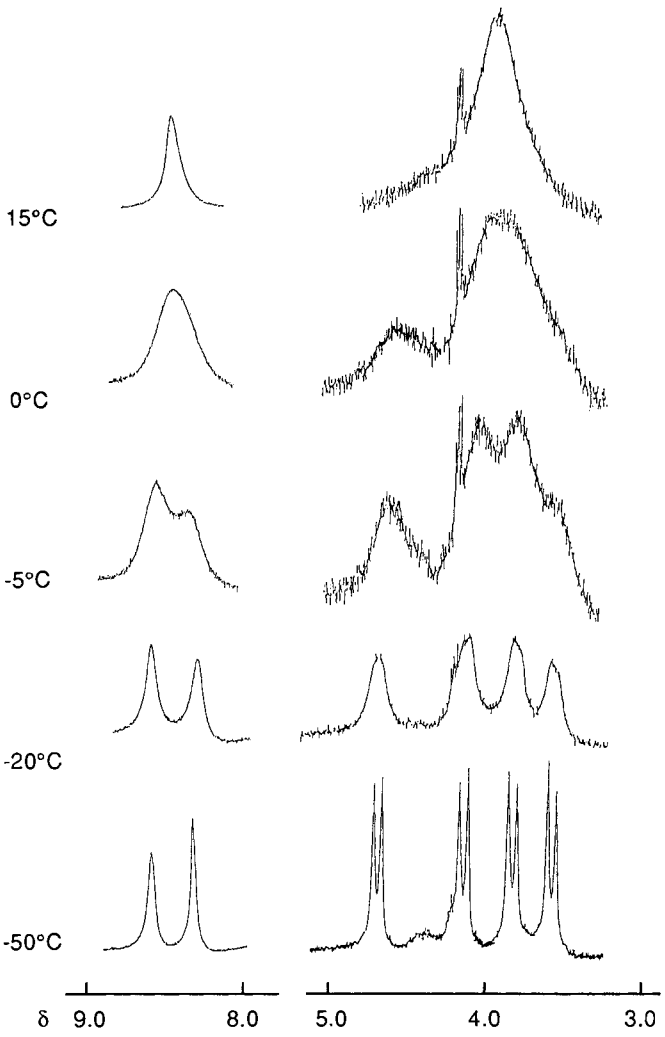


Figure 2. Dynamic ^{1}H-NMR spectrum of **6c** at 270 MHz ($CDCl_3$)

The coalescence temperature for the methylene protons is 15°C, and the free energy of activation for inversion is estimated as 13.5 kcal/mol (T_c = 15°C, $\Delta\nu$ = 168.51 Hz). The value of the free energy of activation for inversion is smaller than that of calix[8]arene (15.7 kcal/mol)[16]. Consideration of the structures of **6b** and **6c** based on Corey-Pauling-Koltun (CPK) models suggests that the intramolecular hydrogen bonding among the OH groups should occur between diarylmethane units rather than the biarene units. This result seems to indicate that the tetramer **6c** is fixed to form a "cone-like" conformation like the calix[8]arenes due to the much stronger intramolecular hydrogen bonding among the OH groups than in the trimer **6b**.

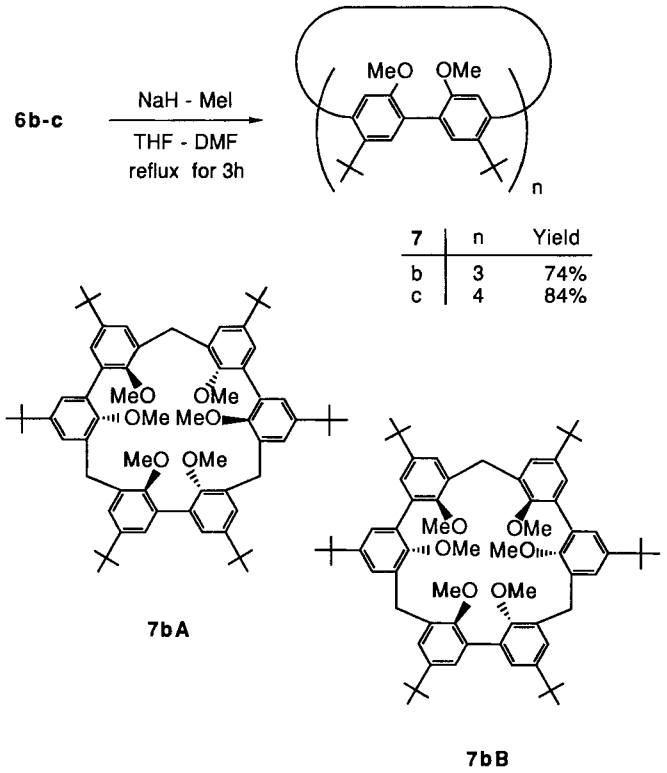
It has also been found that below 0°C the singlet signal of the phenolic OH at δ = 8.34 begins to decoalesce and at −50°C is completely split into a pair of singlets at δ = 8.34 and 8.60. The two doublet signals of aromatic protons at δ = 7.08 and 7.43 (J = 2.44 Hz) also split into four sets of doublets at δ = 7.05, 7.12, 7.43, and 7.54 (J = 2.44 Hz), respectively. This phenomenon seems to be attributed to the formation of two sets of non-equivalent phenolic OH and four sets of non-equivalent aromatic protons because the conformational ring inversion is frozen at this temperature.

From the dynamic ^{1}H-NMR studies and consideration of a CPK model of tetramer **6c**, it is concluded that below 15°C the conformation of **6c** should be expected to be a "flattened 1,3-alternate" conformation with respect to the diarylmethane units due to the intramolecular hydrogen bonding among the OH groups.

On the other hand, the spectra of the hexamethoxy derivative **7b**, which has been prepared by methylation of trimer **6b** with MeI (Scheme 4), shows four kinds of methoxy protons, each as a singlet. By column chromatography on silica gel using benzene as eluent, a mixture of two conformers **7bA** and **7bB** was obtained in a ratio of 1:6. Recrystallization from hexane gives only conformer **7bB**. In spite of the fact that the isolation of a pure sample of **7bA** was not successful, it has been found that **7bA** and **7bB** are thermally stable and not interconvertible at 150°C in [D_6]DMSO.

The ^{1}H-NMR spectrum of conformer **7bA** shows resonances for methoxy protons at δ = 2.45, for methylene protons at δ = 4.02, and for aromatic protons at δ = 7.25, 7.30, indicating a symmetrical structure. On the other hand, the ^{1}H-NMR spectrum of the other conformer **7bB** reveals methoxy proton signals at δ = 2.45, 3.02 and 3.30 (relative intensity 1:1:1). The methylene protons appear as two sets of doublets (δ = 3.35 and 4.60, J_{AB} = 14.0 Hz) and a singlet

Scheme 4



(δ = 3.98) (relative intensity 1:1:1). These signals correspond to an asymmetric structure. From these data it is deduced that **7bA** adopts a symmetric conformation (C_3 symmetry) and **7bB** an unsymmetric conformation (C_1 symmetry). In conformer **7bA** the six methoxy groups are all affected by the ring current of the benzene ring resulting in an upfield shift. Thus, the structure of **7bA** is concluded to be folded into the π cavity formed by two benzene rings. In contrast, in conformer **7bB** the same effect is observed only for the two methoxy groups, and therefore it is assumed to adopt a conformation as shown in the formulas **7bA** and **7bB**.

Although the octamethoxy derivative **7c** has been prepared by methylation of tetramer **6c** in 74% yield, attempts to separate and characterize the conformers, however, failed.

In conclusion, the presently prepared calixarene- and spherand-analogous metacyclophanes **6** and **7** are useful sources of new host compounds, especially since these compounds are easily available in reasonable quantities. We are presently testing their behavior as host compounds.

Experimental

All melting and boiling points are uncorrected. – IR (KBr or NaCl): Nippon Denshi JIR-AQ2OM. – ^{1}H NMR: Nippon Denshi Jeol FT-270 in $CDCl_3$, TMS as reference. – MS: Nippon Denshi JMS-01SA-2. – Elemental analysis: Yanaco MT-5.

3,3',5,5'-Tetra-tert-butyl-2,2'-dihydroxybiphenyl (**4**): A mixture of 2,4-di-*tert*-butylphenol (**3**) (60 g, 0.29 mol) and chloranil (17 g, 0.07 mol) was heated at 210°C for 15 min while stirring. After the reaction mixture was cooled to room temp., methanol (60 ml) was added and stirring was continued for 30 min. The precipitate was filtered and recrystallized from methanol to give 46.4 g (0.113 mol, 78%) of **4** as colorless prisms, m.p. 200.5–202°C (ref.[9] 196–198°C).

5,5'-Tetra-tert-butyl-2,2'-dihydroxybiphenyl (**5**): To a solution of **4** (15 g, 37 mmol) in benzene (280 ml) was added gradually a solution of $AlCl_3$ (9.0 g, 67.5 mmol) in a mixture of nitromethane (70 ml) and benzene (70 ml) at 10°C. After the reaction mixture was stirred for 2 h at 10°C, ice/water was added and the mixture extracted with CH_2Cl_2. The extract was washed with water, dried (Na_2SO_4), and the solvent was evaporated under reduced pressure. Recrystallization from tetrachloromethane gave 9.12 g of **5** (30.6 mmol, yield 83%) as colorless prisms, m.p. 174–177°C (ref.[9] 204–205°C). – IR (KBr): $\tilde{\nu}$ [cm^{-1}] = 3276 (OH). – ^{1}H NMR ($CDCl_3$): δ = 1.33 (18H, s), 5.25 (2H, s), 6.99 (2H, d, *J* = 8.06 Hz), 7.26 (2H, d, *J* = 2.19 Hz), 7.35 (2H, dd, *J* = 2.19/8.06 Hz). – MS (70 eV), *m/z*: 298 [M^+].

$C_{20}H_{26}O_2$ (298.4) Calcd. C 80.50 H 8.78
Found C 80.90 H 8.60

Condensatiuon of **5** *with Paraformaldehyde in the Presence of Sodium Hydroxide:* To a mixture of **5** (5.0 g, 16.75 mmol) and paraformaldehyde (1.1 g, 35.75 mmol) in xylene (85 ml) was added aqueous 5 N NaOH (1.5 ml) under nitrogen with vigorous stirring. After the reaction mixture had been refluxed for 16 h, it was cooled to room temp., acidified with 1 N HCl (50 ml), and extracted with CH_2Cl_2. The extract was washed with water, dried (Na_2SO_4), and the solvent was evaporated under reduced pressure. The residue was chromatographed on SiO_2 using hexane and benzene as eluents to give 3.20 g of crude **6b** and a trace amount of **6c**, respectively. Recrystallization from hexane gave 2.72 g of **6b** (2.93 mmol, yield 52%), colorless prisms (hexane), m.p. 253–256°C. – IR (KBr): $\tilde{\nu}$ [cm^{-1}] = 3297 (OH). – ^{1}H NMR ($CDCl_3$, 20°C): δ = 1.35 (54H, s), 4.02 (6H, s), 7.20 (6H, d, *J* = 2.44 Hz), 7.39 (6H, d, *J* = 2.44 Hz), 8.48 (6H, broad s). – ^{1}H NMR (–50°C): δ = 1.35 (54H, s), 3.79 (3H, broad s), 4.21 (3H, broad s), 7.21 (6H, d, *J* = 2.44 Hz), 7.44 (6H, d, *J* = 2.44 Hz), 8.48 (6H, broad s). – MS (70 eV), *m/z*: 931 [M^+].

$C_{63}H_{78}O_6$ (931.3) Calcd. C 81.25 H 8.44
Found C 80.90 H 8.60

Condensation of **5** *with Paraformaldehyde in the Presence of Cesium Hydroxide:* To a mixture of **5** (5.0 g, 16.75 mmol) and paraformaldehyde (1.1 g, 35.75 mmol) in xylene (85 ml) was added aqueous 5 N CsOH (1.5 ml) under nitrogen with vigorous stirring. After the reaction mixture had been refluxed for 16 h, it was cooled to room temp., acidified with 1 N HCl (50 ml), and extracted with CH_2Cl_2. The extract was washed with water, dried (Na_2SO_4), and the solvent was evaporated under reduced pressure. The residue was chromatographed on SiO_2 using hexane and benzene as eluents to give 204 mg of **6b** (0.22 mmol, yield 4%) and 3.80 g of **6c**, respectively. Recrystallization from benzene gave 3.44 g of **6c** (2.77 mmol, yield 66%), colorless prisms (benzene), m.p. >300°C. – IR (KBr): $\tilde{\nu}$ [cm^{-1}] = 3245 (OH). – ^{1}H NMR ($CDCl_3$, 20°C): δ = 1.30 (72H, s), 4.02 (8H, broad s), 7.08 (8H, d, *J* = 2.44 Hz), 7.43 (8H, d, *J* = 2.44 Hz), 8.34 (8H, broad s). – ^{1}H NMR (–50°C): δ = 1.29 (36H, s), 1.32 (36H, s), 3.63 (2H, d, *J* = 14.2 Hz), 3.88 (2H, d, *J* = 13.7 Hz), 4.15 (2H, d, *J* = 14.2 Hz), 4.70 (2H, d, *J* = 14.2 Hz), 7.05 (4H, d, *J* = 2.44 Hz), 7.12 (4H, d, *J* = 2.44 Hz), 7.43 (4H, d, *J* = 2.44 Hz), 7.54 (4H, d, *J* = 2.44 Hz), 8.34 (4H, broad s), 8.60 (4H, broad s). – MS (70 eV), *m/z*: 1241 [M^+].

$C_{84}H_{104}O_8$ (1241.8) Calcd. C 81.25 H 8.44
Found C 81.05 H 8.40

Methylation of **6b**: To a suspension of NaH (300 mg, 12.5 mmol) in THF (5 ml) was added a solution of **6b** (500 mg, 0.54 mmol) in

a mixture of DMF (5 ml) and THF (15 ml) under nitrogen, and the reaction mixture was stirred at room temp. for 1 h. Then MeI (3.25 ml, 43 mmol) was added and the mixture heated at reflux for 3 h. After cooling of the reaction mixture to room temp., water was added and the mixture extracted with CH_2Cl_2. The extract was washed with water, dried (Na_2SO_4), and the solvent was evaporated under reduced pressure. The residue was chromatographed on SiO_2 by using benzene as eluent. Recrystallization from hexane furnished 394.6 mg (0.389 mmol, yield 72%) of **7bB**.

7bA: ^{1}H NMR: δ = 1.30 (54H, s), 2.47 (18H, s), 4.08 (6H, s), 7.25 (6H, d, *J* = 2.44 Hz), 7.30 (6H, d, *J* = 2.44 Hz).

7bB: Colorless prisms ($CHCl_3$/MeOH), m.p. 252–254°C. – ^{1}H NMR: δ = 1.24 (18H, s), 1.30 (36H, s), 2.45 (6H, s), 3.04 (6H, s), 3.29 (6H, s), 3.34 (2H, d, *J* = 13.4 Hz), 3.95 (2H, s), 4.56 (2H, d, *J* = 13.4 Hz), 7.05 (2H, d, *J* = 2.44 Hz), 7.15 (4H, d, *J* = 2.44 Hz), 7.18 (2H, d, *J* = 2.44 Hz), 7.24 (2H, d, *J* = 2.44 Hz), 7.28 (2H, d, *J* = 2.44 Hz). – MS (70 eV), *m/z*: 1014 [M^+].

$C_{69}H_{90}O_6$ (1015.5) Calcd. C 81.61 H 8.93
Found C 81.89 H 9.35

Compound **7c** was prepared in the same manner as described above in 74% yield. Colorless prisms ($CHCl_3$/MeOH), m.p. >300°C. – MS (70 eV), *m/z*: 1353 [M^+].

$C_{92}H_{120}O_8$ (1354.0) Calcd. C 81.61 H 8.93
Found C 81.74 H 8.99

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