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Proximally Functionalized Cavitands and Synthesis of a Flexible Hemicarcerand*

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Abstract. A general study on the synthesis of partly bridged octols **3a–d** and **4c–d** is described. Tri-bridged diol **3c** can be prepared in 54% yield in DMSO at 70°C with excess CH_2BrCl or in 52% yield in DMF at 70°C with only 4 equiv. of CH_2BrCl. 1,3-Di-bridged tetrol **4a**, one of the two possible di-bridged isomers formed in preference to the other, was obtained in 30% yield. Tri-bridged diols **3c** and **d** can be selectively debrominated in one step by treatment with 5 equiv. of *n*-BuLi in THF to afford the corresponding dibromo derivatives **8a** and **b** in 77% and 76% yields, respectively. After incorporation of the fourth bridge, the remaining two bromines can be replaced by C(O)OMe to give **9c** (60%), by OH to give **9d** (62%) or by CN to give **9f** (> 95%). When the lithiated derivatives of **3c** and **d** are quenched with electrophiles other than H^+, a selectively functionalized tri-bridged diol with hydroxyl (**8c**, 47%) and selectively functionalized cavitands with thiomethyl (**9g**, 25%) or iodo (**9h**, 20%) groups can be synthesized. Two molecules of **9d** were coupled with CH_2BrCl in DMSO/THF under high dilution conditions to give the flexible hemicarcerand **10** in 71% yield.

Key words: Partly bridged octols, selective functionalization, hemicarcerand.

Supplementary Data. A list of observed and calculated structure factors have been deposited with the British Document Supply Centre as Supplementary Publication No. SUP 82170 (50 pages)

1. Introduction

After calixarenes were rediscovered and their structures were elucidated by Gutsche [1, 2], the molecules have been studied in great detail thanks to their vase-like shape and their ability to complex guest molecules. At first, most efforts dealt with the synthesis of tetrafunctionalized calix[4]arenes [3–7], but more recently attention has increasingly been focused on the introduction of functional groups at *specific* positions in the molecule. This has resulted in a number of convenient syntheses for selectively functionalized calix[4]arenes [8], viz. mono- [9, 10], 1,2-di- [10–12], 1,3-di [13–15] and trifunctionalized [10, 16, 17] calix[4]arenes, making these molecules valuable building blocks in supramolecular chemistry.

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In contrast to the parent calix[4]arenes, selective functionalization of the resorcinol-based calix[4]arenes [18] has hardly been studied. Partly functionalized cavitands have only been isolated as side products in the synthesis of tetrafunctionalized cavitands [19, 20]. Although such dissymmetric cavitands have been used in the synthesis of chiral cavitands [21] and hemicarcerands [20] with promising applications [22], their synthesis was never studied in detail. While our work was in progress [23], Sorrell and Richards showed that cavitands can be selectively functionalized at the upper rim by means of a Claisen rearrangement [24]. In this paper we describe the synthesis of partly bridged octols [25] together with a novel route to functionalize these cavitands selectively in a proximal way.

2. Experimental

General

Melting points were determined with a Reichert melting point apparatus and are uncorrected. ^{1}H-NMR and ^{13}C-NMR spectra were recorded with a Bruker AC 250 spectrometer with Me_4Si as internal standard. Mass spectra were recorded with a Finnigan MAT 90 spectrometer using *m*-NBA as a matrix. IR spectra were obtained using a Nicolet 5SXC FT-IR spectrophotometer. All reagents were distilled before use. THF was distilled from Na/benzophenone, PE 60-80, CH_2Cl_2 and ethyl acetate from K_2CO_3, DMSO from CaH_2. DMF and acetonitrile were dried over molecular sieves for at least 3 days. *N*-Bromosuccinimide was recrystallized from H_2O and dried over $CaCl_2$. *n*-BuLi was used as a 1.5 M solution in hexane. Prior to lithiation, the starting compound was first dissolved in THF and evaporated to dryness. This process was repeated until no other guest molecule than THF was present. Flash column chromatography was performed using silica 60 (0.040–0.063 mm, 230–400 mesh) or when necessary silica 60H (0.005–0.040 mm). Compounds **1a** [19], **1b** [26], **1c** [27] and **1d** [28] were prepared according to literature procedures.

5,11,17,23-Tetrabromo-2,8,14,20-tetraundecylpentacyclo[19.3.1.1^{3,7}.1^{9,13}.1^{15,19}]-octacosa-1(25),3,5,7(28),9,11,13(27),15,17,19(26),21,23-dodecaen-4,6,10,12,16,18,22,24-octol (**1e**). To a solution of octol **1d** (32.6 g, 29.5 mmol) in DMF (500 mL) was added *N*-bromosuccinimide (21.3 g, 120 mmol) and the mixture was stirred for 24 h at room temperature with protection from light. The reaction mixture was poured out into water (1.15 L), the precipitate was filtered off and washed several times with water. After drying the solid for 20 h at 15 mm Hg, it was dissolved in acetone (2.3 L), the hot solution was filtered and the volume was reduced to 115 mL. The precipitate formed after standing for 18 h at -20°C was filtered off, washed with acetone and dried. Yield 82%, mp 288–290°C (acetone). Mass spectrum (FAB, NBA): m/z 1265.5 [(M—$C_{11}H_{23}$)$^+$, *calc.* 1265.3]. ^{1}H-NMR (acetone-d_6): δ 8.33 (s, 8H, OH), 7.63 (s, 4H, ArH), 4.45 [t, 4H, J = 7.7 Hz, C*H*$(CH_2)_{10}CH_3$], 2.4–2.2 [m, 8H, CHC*H*$_2(CH_2)_9CH_3$], 1.5–1.2 [m, 72H, $CHCH_2(CH_2)_9CH_3$], 0.88 [t, 12H, J = 6.8 Hz, $CH(CH_2)_{10}CH_3$]. ^{13}C-NMR (DMSO-d_6): δ 149.7 (s, ArC—OH), 126.0

(s, ArCCH), 124.1 (d, ArCH), 102.0 (s, ArCBr). *Anal. Found*: C, 60.78; H, 7.94. *Calc.* for $C_{72}H_{108}Br_4O_8$: C, 60.84; H, 7.66.

General Procedures for the Preparation of Compounds **2d**, **3a–d** *and* **4c–d**. A solution of octol **1** (5.0 mmol), K_2CO_3 (1.73 g, 12.5 mmol) and CH_2BrCl in *degassed* DMF or DMSO (250 mL) was stirred; experimental details are given in Table IV.

Work-up Procedure A. The solvent was removed *in vacuo*, the residue was poured into demineralized water and the precipitate was filtered off through Celite. After drying the filtered solid at 100°C under vacuo for 6 h, a Soxhlet extraction was performed for several days using $CHCl_3$ as the solvent, having 5 g of silica per gram **1** used in the collecting flask. The $CHCl_3$ solution was evaporated to dryness and the product, absorbed on silica, was further purified by flash column chromatography.

Work-up Procedure B. The solvent was removed *in vacuo*, the residue was dissolved in $CHCl_3$ and washed with H_2O (3×), brine and subsequently dried over $MgSO_4$. After removal of the solvent, the product was further purified by flash column chromatography.

*7,11,15,28-Tetrabromo-1,21,23,25-tetraundecyl-2,20:3,19-dimetheno-1*H,*21*H,*23*H,*25*H-*bis[1,3]dioxocino[5,4*-i:*5′,4′*-i′*]benzo[1,2*-d:*5,4*-d′*]bis[1,3]benzodioxocin* (**2d**) was isolated after flash column chromatography (SiO_2, CH_2Cl_2) as a black viscous oil. It was further purified by dissolving it in a 1 : 1 (v/v) mixture of CH_2Cl_2/hexane and filtering it over silica, to give **2d** as a colorless oil. Mass spectrum (FAB, NBA, high resolution): m/z 1468.494 (M^+, *calc.* 1468.474). ^{1}H-NMR ($CDCl_3$): δ 7.02 (s, 4H, ArH), 5.95 (d, 4H, J = 7.4 Hz, outer OCH_2O), 4.84 [t, 4H, J = 4.0 Hz, $CH(CH_2)_{10}CH_3$], 4.38 (d, 4H, J = 7.4 Hz, inner OCH_2O), 2.3–2.2 [m, 8H, $CHCH_2(CH_2)_9CH_3$], 1.5–1.2 [m, 72H, $CHCH_2(CH_2)_9CH_3$], 0.88 (t, 12H, J = 6.5 Hz, CH_3). ^{13}C-NMR ($CDCl_3$): δ 152.1 (s, Ar*C*OCH_2O), 139.3 (s, Ar*C*CH), 119.1 (d, ArCH), 113.5 (s, ArCBr), 98.5 (t, OCH_2O), 37.6 (d, ArCHAr).

*4,8,12,16-Tetrabromo-20,22,24,25-tetraphenyl-2,18-methano-20*H,*22*H,*24*H-*dibenzo[*d,d′*][1,3]dioxocino[5,4*-i:*7,8*-i*]bis[1,3]benzodioxocin-3,17-diol* (**3b**) was isolated after flash column chromatography (SiO_2, EtOAc/CH_2Cl_2, 0 : 100–10 : 90) as a white solid. mp > 290°C (CH_2Cl_2/MeOH). Mass spectrum (FAB, NBA): m/z 1144.9 [$(M+H)^+$, *calc.* 1144.9]. ^{1}H-NMR ($CDCl_3$): δ 7.4–7.1 (m, 20H, C_6H_5), 6.91 (s, 2H, ArH meta to OCH_2O), 6.83 (s, 2H, ArH meta to OH), 6.52, 6.42, 6.10 [3s (1 : 2 : 1), 4H, CHPh], 6.07, 6.05 (2d, 3H, J = 7.3 Hz, outer OCH_2O), 4.57, 4.49 (2d, 3H, J = 7.3 Hz, inner OCH_2O). ^{13}C-NMR ($CDCl_3$): δ 152.9–152.3 (s, Ar*C*OCH_2O), 150.9 (s, ArCOH), 126.3, 126.2 (d, ArCH), 113.1, 107.6 (s, ArCBr), 98.4 (t, OCH_2O), 42.5, 42.3, 41.0 (d, ArCHAr). *Anal. Found*: C, 57.40; H, 3.55. *Calc.* for $C_{55}H_{36}Br_4O_8$: C, 57.72; H, 3.17.

*4,8,12,16–Tetrabromo-20,22,24,25-tetrakis(2-phenylethyl)-2,18-methano-20*H,22H,*24*H-*dibenzo*[d,d′][*1,3*]*dioxocino*[*5,4*-i:*7,8*-i]*bis*[*1,3*]*benzodioxocin-3,17-diol* (**3c**) was isolated after flash column chromatography (SiO_2, EtOAc/CH_2Cl_2, 0 : 100–5 : 95) as a white solid. mp > 290°C (CH_2Cl_2/MeOH). Mass spectrum (FAB, NBA): m/z 1256.3 (M^+, *calc.* 1256.0). ^{1}H-NMR ($CDCl_3$): δ 7.3–7.0 (m, 24H, C_6H_5 + ArH), 5.92, 5.89 (2d, 3H, J = 7.4 Hz, outer OCH_2O), 4.89, 4.84, 4.40 [3t, 4H (2 : 1 : 1), J = 8.0, 7.6 and 7.6 Hz, C*H*$(CH_2)_2C_6H_5$], 4.36, 4.28 (2d, 3H, J = 7.4 Hz, inner OCH_2O), 2.8–2.4 [m, 16H, CH(C*H*$_2)_2C_6H_5$]. ^{13}C-NMR ($CDCl_3$): δ 152.5–152.0 (s, Ar*C*OCH_2O), 148.4 (s, ArCOH), 121.1, 118.5 (d, ArCH), 114.0, 107.2 (s, ArCBr), 98.6 (t, OCH_2O), 37.5, 35.6 (d, ArCHAr). *Anal. Found*: C, 60.35; H, 4.42. *Calc.* for $C_{63}H_{52}Br_4O_8$: C, 60.21; H, 4.17.

*4,8,12,16-Tetrabromo-20,22,24,25-tetraundecyl-2,18-methano-20*H,*22*H,*24*H-*dibenzo*[d,d′][*1,3*]*dioxocino*[*5,4*-i:*7,8*-i]*bis*[*1,3*]*benzodioxocin-3,17-diol* (**3d**) was isolated after flash column chromatography (SiO_2, CH_2Cl_2) as a light-brown solid which could not be recrystallized. mp 80–82°C. Mass spectrum (FAB, NBA): m/z 1456.4 (M^+, *calc.* 1456.5). ^{1}H-NMR ($CDCl_3$): δ 7.01 (s, 4H, ArH + OH), 6.95 (s, 2H, ArH), 5.90, 5.87 (2d, 3H, J = 7.4 Hz, outer OCH_2O), 4.78, 4.68, 4.32 [3t, 4H (2 : 1 : 1), J = 8.0 Hz, C*H*$(CH_2)_{10}CH_3$], 4.34, 4.25 (2d, 3H, J = 7.4 Hz, inner OCH_2O), 2.3–2.0 [m, 8H, CHC*H*$_2(CH_2)_9CH_3$], 1.5–1.2 [m, 72H, $CHCH_2(CH_2)_9CH_3$], 0.81 [t, 12H, J = 6.8Hz, $CH(CH_2)_{10}CH_3$]. ^{13}C-NMR ($CDCl_3$): δ 152.1–151.6 (s, Ar*C*OCH_2O), 148.0 (s, ArCOH), 121.1, 118.5 (d, ArCH), 113.5, 106.7 (s, ArCBr), 98.4 (t, OCH_2O), 37.4–35.7 (d, ArCHAr). *Anal. Found*: C, 61.99; H, 7.44. *Calc.* for $C_{75}H_{108}Br_4O_8$: C, 61.82; H, 7.47.

5,11,17,23-Tetrabromo-2,14,27,32-tetrakis(2-phenylethyl)-7,9,19,21-tetraoxaheptacyclo[13.9.5.5^{3,13}*.0*^{6,33}*.0*^{10,31}*.0*^{18,28}*.0*$^{22.26}$*]tetratriaconta-3,5,10,12,15,17,22,24,25,28,30,33-dodecaene-4,12,16,24-tetrol* (**4c**) was isolated after flash column chromatography (SiO_2, EtOAc/CH_2Cl_2, 5 : 95) as a white solid, mp 187–188°C ($CHCl_3$). Mass spectrum (FAB, NBA): m/z 1244.0 (M^+, *calc.* 1244.1). ^{1}H-NMR ($CDCl_3$): δ 7.3–7.1 [m, 24H, $CH(CH_2)_2C_6H_5$ + ArH], 6.95 (s, 4H, OH), 5.98 (d, 2H, J = 7.4 Hz, outer OCH_2O), 4.89, 4.47 [2t, 4H, J = 7.9 Hz, C*H*$(CH_2)C_6H_5$], 4.36 (d, 2H, J = 7.4 Hz, inner OCH_2O), 2.8–2.4 [m, 16H, CH(C*H*$_2)_2C_6H_5$]. ^{13}C-NMR ($CDCl_3$): δ 152.2 (s, Ar*C*OCH_2O), 148.4 (s, ArCOH), 120.6 (d, ArCH), 107.1 (s, ArCBr), 98.7 (t, OCH_2O), 37.2–36.1 (d, ArCHAr). *Anal. Found*: C, 53.68; H, 3.77. *Calc.* for $C_{62}H_{52}Br_4O_8 \cdot 1.5CHCl_3$: C, 53.57; H, 3.79.

5,11,17,23-Tetrabromo-2,14,27,32-tetraundecyl-7,9,19,21-tetraoxaheptacyclo[13.9.5.5^{3,13}*.0*^{6,33}*.0*^{10,31}*.0*^{18,28}*.0*$^{22.26}$*]tetratriaconta-3,5,10,12,15,17,22,24,25,28,30,33-dodecaene-4,12,16,24-tetrol* (**4d**) was isolated after flash column chromatography (SiO_2, EtOAc/CH_2Cl_2, 5 : 95) as an off-white solid which could not be recrystallized. mp 117–120°C. Mass spectrum (FAB, NBA, negative mode): m/z 1443.2 [$(M—H)^-$, *calc.* 1443.5]. ^{1}H-NMR ($CDCl_3$): δ 7.06 (s, 4H, ArH), 6.76 (s, 4H,

OH), 5.90 (d, 2H, J = 7.4 Hz, outer OCH_2O), 4.75, 4.32 [2t, 4H, J = 7.9 Hz, $CH(CH_2)_{10}CH_3$], 4.34 (d, 2H, J = 7.4 Hz, inner OCH_2O), 2.3–2.0 [m, 8H, $CHCH_2(CH_2))_9CH_3$], 1.4–1.1 [m, 72H, $CHCH_2(CH_2)_9CH_3$], 0.81 [t, 12H, J = 6.4 Hz, $CHCH_2(CH_2)_9CH_3$]. ^{13}C-NMR ($CDCl_3$): δ 151.9 (s, ArCOCH_2O), 148.1 (s, ArCOH), 120.6 (d, ArCH), 106.8 (s, ArCBr), 98.7 (t, OCH_2O), 37.2–36.1 (d, ArCHAr). *Anal. Found*: C, 61.85; H, 8.00. *Calc.* for $C_{74}H_{108}Br_4O_8$: C, 61.49; H, 7.53.

2,2′,2″,2‴[[5,11,17,23-Tetrabromo-2,14,27,32-tetramethyl-7,9,19,21-tetraoxaheptacyclo[13.9.5.5^{3,13}.0^{6,33}.0^{10,31}.0^{18,28}.0^{22,26}]tetratriaconta-3,5,10,12,15,17,22,24,25,28,30,33-dodecaene-4,12,16,24-tetryl]tetrakis(oxy)]tetraacetic acid, tetramethyl ester (**6a**). The reaction mixture was worked up according to procedure A, with the exception that the Soxhlet extraction was carried out without silica in the collecting flask. The $CHCl_3$ solution was evaporated to dryness and the residue was suspended in CH_3CN (200 mL). To this suspension was added K_2CO_3 (8.04 g, 58.2 mmol) and methyl bromoacetate (3.11 mL, 31.7 mmol) and the mixture was refluxed for 18 h. The solvent was evaporated, the residue was dissolved in CH_2Cl_2 (250 mL), successively washed with sat. NH_4Cl (50 mL), with H_2O (2 × 50 mL) and brine (50 mL), and dried over $MgSO_4$. After removal of the solvent, the crude product was separated by flash column chromatography (SiO_2 60H, CH_2Cl_2/hexane, 98 : 2) to give pure **6a** as a white solid. mp 291–293°C (CH_2Cl_2/pentane). Mass spectrum (FAB, NBA): m/z 1173.0 ([(M+H)$^+$, *calc.* 1173.4). ^{1}H-NMR ($CDCl_3$): δ 7.59 (s, 4H, ArH), 6.00 (d, 2H, J = 7.4 Hz, outer OCH_2O), 5.38, 5.07 (2q, 4H, J = 7.4 Hz, —CHCH$_3$), 4.68 and 4.39 [ABq, 8H, J = 15.1 Hz, OCH_2C(O)OCH_3], 4.36 (d, 2H, J = 7.4 Hz, inner OCH_2O), 3.81 [s, 12H, $OCH_2C(O)OCH_3$], 1.87, 1.59 (2d, 12H, J = 7.4 Hz, CHCH_3). ^{13}C-NMR ($CDCl_3$): δ 168.8 (s, C=O), 152.6, 151.2 [s, ArCOCH_2O + ArCOCH_2C(O)OCH_3], 122.2 (d, ArCH), 113.1 (s, ArCBr), 98.9 (t, OCH_2O), 70.1 [t, OCH_2C(O)OCH_3], 52.1 (q, OCH_3), 32.2, 28.4 (d, ArCHAr), 24.4, 16.6 (q, CHCH$_3$). *Anal. Found*: C, 47.58; H, 3.86. *Calc.* for $C_{46}H_{44}Br_4O_{16}$: C, 47.12; H, 3.78.

*2,2′,2″,2‴[[4,8,12,24-Tetrabromo-16,18,19,26-tetramethyl-2,14-(methano[1,3]benzenomethano)-16*H,*18*H*-benzo[1,2-d:5,4-d′]bis[1,3]benzodioxocin-3,13,23,25-tetryl]tetrakis(oxy)tetraacetic acid, tetramethyl ester* (**7a**) was isolated as a minor product in the synthesis of **6a**. mp 214–216°C (CH_2Cl_2/hexane). Mass spectrum (FAB, NBA): m/z 1173.3 [(M+H)$^+$, *calc.* 1173.4). ^{1}H-NMR ($CDCl_3$): δ 7.35, 7.24, 6.70 [3s, 4H (2 : 1 : 1), ArH], 5.96 (d, 2H, J = 7.3 Hz, outer OCH_2O), 5.3–5.1 (m, 4H, CHCH$_3$), 4.84, 4.67 and 4.44, 4.32 [2ABq, 8H, J = 15.1 Hz, OCH_2C(O)OCH_3], 4.44 (d, 2H, J = 7.4 Hz, inner OCH_2O), 3.81, 3.77 [2s, 12H, $OCH_2(O)OCH_3$], 1.79, 1.51 (2d, 12H, J = 7.4 Hz, CHCH_3). ^{13}C-NMR ($CDCl_3$): δ 168.8, 168.7 (s, C=O), 152.1–151.5 [s, ArCOCH_2O + ArCOCH_2C(O)OCH_3], 125.2, 120.9, 118.5 (d, ArCH), 112.8, 122.2 (s, ArCBr), 98.3 (t, OCH_2O), 70.1, 69.0 [t, OCH_2C(O)OCH_3], 52.1, 52.0 (q, OCH_3), 32.1, 30.3 (d, ArCHAr), 23.9,

15.6 (q, $CHCH_3$). *Anal. Found*: C, 47.34; H, 3.92. *Calc.* for $C_{46}H_{44}Br_4O_{16}$: C, 47.12; H, 3.78.

*4,16-Dibromo-20,22,24,25-tetrakis(2-phenylethyl)-2,18-methano-20*H,*22*H,*24*H-*dibenzo[*d,d′*][1,3]dioxocino[5,4-*i*:7,8-*i*]bis[1,3]benzodioxocin-3,17-diol* (**8a**). To a solution of diol **3c** (0.40 g, 0.32 mmol) in THF (15 mL) was quickly added *n*-BuLi (0.73 mL, 0.95 mmol) at -70°C. After 15 sec the reaction mixture was quenched with excess water. The solution was allowed to warm to room temperature and the solvent was removed *in vacuo*. The residue was taken up in CH_2Cl_2 (25 mL) and successively washed with 1 N HCl (10 mL), H_2O (3 × 10 mL), brine (10 mL) and dried over $MgSO_4$. The crude product was purified by flash column chromatography (SiO_2, CH_2Cl_2) to give **8a** as a white solid in 77% yield. mp > 290°C ($CHCl_3/CH_3CN$). Mass spectrum (FAB, NBA): m/z 1098.9 $[(M+H)^+$, *calc.* 1099.2]. ^{1}H-NMR ($CDCl_3$): δ 7.3–7.1 (m, 24H, $CH(CH_2)_2C_6H_5$ + ArH), 6.57 (s, 2H, ArH), 5.89, 5.74 (2d, 3H, J = 7.3 Hz, outer OCH_2O), 4.90, 4.79, 4.46 (3t, 4H, (2 : 1 : 1), J = 7.7, 7.8 and 7.8 Hz, $CH(CH_2)_2C_6H_5$], 4.44, 4.39 (2d, 3H, J = 7.3 Hz, inner OCH_2O), 2.8–2.4 (m, 16H, $CH(CH_2)_2C_6H_5$]. ^{13}C-NMR ($CDCl_3$): δ 155.4–152.6 (s, $ArCOCH_2O$), 148.2 (s, ArCOH), 121.1, 120.1, 117.1 (d, ArCH), 106.9 (s, ArCBr), 99.2 (t, OCH_2O), 37.0–36.3 (d, ArCHAr). *Anal. Found*: C, 68.87; H, 5.04. *Calc.* for $C_{63}H_{54}Br_2O_8$: C, 68.86; H, 4.95.

*4,16-Dibromo-20,22,24,25-tetraundecyl-2,18-methano-20*H,*22*H,*24*H-*dibenzo[*d, d′*][1,3]dioxocino[5,4-*i*:7,8-*i*]bis[1,3]benzodioxocin-3,17-diol* (**8b**). The reaction was carried out following the procedure for **8a**, using **3d** (1.0 g, 0.69 mmol), *n*-BuLi (2.1 mL, 3.15 mmol) and THF (150 mL) to give pure **8b** after column chromatography (SiO_2, CH_2Cl_2) in 76% yield. The compound could not be recrystallized. mp 154–156°C. Mass spectrum (FAB, NBA): m/z 1298.1 $[(M—H)^+$, *calc.* 1297.7]. ^{1}H-NMR ($CDCl_3$): δ 7.07, 6.98 (2s, 4H, ArH), 6.43 (s, 2H, ArH), 5.79, 5.64 (2d, 3H, J = 7.3 Hz, outer OCH_2O), 4.71, 4.60, 4.32 [3t, 4H, (2 : 1 : 1), J = 8.0 Hz, $CH(CH_2)_{10}CH_3$], 4.34, 4.29 (2d, 3H, J = 7.3 Hz, inner OCH_2O), 2.3–2.0 [m, 8H, $CHCH_2(CH_2)_9CH_3$], 1.5–1.1 [m, 72H, $CHCH_2(CH_2)_9CH_3$], 0.81 [t, 12H, J = 6.8 Hz, $CH(CH_2)_{10}CH_3$]. ^{13}C-NMR ($CDCl_3$): δ 154.9–152.2 (s, $ArCOCH_2O$), 147.6 (s, ArCOH), 121.1, 120.1, 116.5 (d, ArCH), 106.4 (s, ArCBr), 99.0 (t, OCH_2O), 36.5–36.1 (d, ArCHAr). *Anal. Found*: C, 69.13; H, 8.60. *Calc.* for $C_{75}H_{110}Br_2O_8$: C, 69.32; H, 8.53.

*4,16-Dibromo-20,22,24,25-tetraundecyl-2,18-methano-20*H,*22*H,*24*H-*dibenzo[*d, d′*][1,3]dioxocino[5,4-*i*:7,8-*i*]bis[1,3]benzodioxocin-3,8,12,17-tetrol* (**8c**). To a solution of diol **3d** (2.05 g, 1.41 mmol) in THF (150 mL) was added excess NaH (0.17 g, 5.6 mmol) and the solution was stirred at room temperature until the evolution of hydrogen stopped. The reaction mixture was cooled down to -70°C and *n*-BuLi (4.7 mL, 7.0 mmol) was quickly added. After 15 sec, the reaction mixture was quenched with $B(OMe)_3$ (1.6 mL, 14 mmol). The solution was warmed

to room temperature and stirred for 1 h. After cooling the reaction mixture again to -70°C, a 15% solution of H_2O_2 in 1.5 M NaOH (14 mL, 70 mmol) was added and the mixture was stirred overnight. Excess H_2O_2 was destroyed by adding $Na_2S_2O_5$ (13 g, 70 mmol) to the solution. The solvent was removed *in vacuo*, H_2O (100 mL) was added and the precipitated solid was filtered off and washed with H_2O (3 × 50 mL). After drying the solid at 80°C under vacuum for 3 h, it was dissolved in THF (100 mL), silica (4 g) was added and the solution was evaporated to dryness. The crude product, absorbed on silica, was purified by flash column chromatography (SiO_2, EtOAc/CH_2Cl_2, 20 : 80) to give pure **8c** in 47% yield. The compound could not be recrystallized. mp 72–75°C. Mass spectrum (FAB, NBA): *m/z* 1330.8 (M^+, *calc.* 1330.7). ^{1}H-NMR ($CDCl_3$): δ 7.04 (s, 2H, ArH para to Br), 6.67 (s, 2H, ArH para to OH), 5.95, 5.92 (2d, 3H, J = 7.3 Hz, outer OCH_2O), 5.6 (bs, 2H, OH), 4.77, 4.63, 4.40 [3t, 4H (2 : 1 : 1), J = 8.0 Hz, $CH(CH_2)_{10}CH_3$], 4.42, 4.38 (2d, 3H, J = 7.2 and 6.8 Hz, inner OCH_2O), 2.3–2.1 [m, 8H, $CHCH_2(CH_2)_9CH_3$], 1.5–1.2 [m, 72H, $CHCH_2(CH_2)_9CH_3$], 0.87 [t, 12H, J = 6.5 Hz, $CH(CH_2)_{10}CH_3$]. ^{13}C-NMR ($CDCl_3$): δ 152.3 (s, Ar$COCH_2O$), 148.0 (s, ArCOH ortho to Br), 142.3 (s, ArCOH), 121.5 (d, ArCH para to Br), 109.5 (d, ArCH para to OH), 106.6 (s, ArCBr), 99.2 (t, OCH_2O), 37.0–35.9 (t, ArCHAr). *Anal. Found*: C, 67.60; H, 8.73. *Calc.* for $C_{75}H_{110}Br_2O_{10}$: C, 67.65; H, 8.33.

*7,11-Dibromo-1,21,23,25-tetrakis(2-phenylethyl)-2,20:3,19-dimetheno-1*H,*21*H,*23*H,*25*H-*bis[1,3]dioxocino[5,4*-i:*5′,4′*-i′*]benzo[1,2*-d:*5,4*-d′*]bis[1,3]benzodioxocin* (**9a**). To a suspension of **8a** (0.92 g, 0.84 mmol) and K_2CO_3 (1.2 g, 8.4 mmol) in CH_3CN (100 mL) was added CH_2BrCl (2.2 mL, 33 mmol) and the mixture was refluxed for 24 h. The solvent was removed and the residue was taken up in CH_2Cl_2 (50 mL). The solution was successively washed with 1 N HCl (20 mL), H_2O (3 × 10 mL), brine (10 mL), dried over $MgSO_4$, whereupon the solvent was removed under vacuum. The crude product was dissolved in a 1/9 (v/v) hexane/CH_2Cl_2 mixture and filtered over silica. After removal of the solvent, pure **9a** was obtained as a white solid in 92% yield. mp 270–272°C (CH_2Cl_2/CH_3CN). Mass spectrum (FAB, NBA): *m/z* 1110.2 (M^+, *calc.* 1110.3). ^{1}H-NMR ($CDCl_3$): δ 7.3–7.1 [m, 24H, $CH(CH_2)_2C_6H_5$ + ArH], 6.57 (s, 2H, ArH), 5.98, 5.88, 5.77 [3d, 4H, (1 : 2 : 1), J = 7.3 Hz, outer OCH_2O], 5.0–4.8 [m, 4H, $CH(CH_2)_2C_6H_5$], 4.48, 4.43, 4.40 [3d, 4H (1 : 2 : 1), J = 7.3 Hz, inner OCH_2O], 2.8–2.4 [m, 16H, $CH(CH_2)_2C_6H_5$]. ^{13}C-NMR ($CDCl_3$): δ 155.2–152.1 (s, Ar$COCH_2O$), 120.5, 118.9, 117.1 (d, ArCH), 113.6 (s, ArCBr), 99.5–98.6 (t, OCH_2O), 37.8–36.5 (d, ArCHAr). *Anal. Found*: C, 68.84; H, 4.89. *Calc.* for $C_{64}H_{54}Br_2O_8$: C, 69.19; H, 4.90.

*7,11-Dibromo-1,21,23,25-tetraundecyl-2,20:3,19-dimetheno-1*H,*21*H,*23*H,*25*H-*bis[1,3]dioxocino[5,4*-i:*5′,4′*-i′*]benzo[1,2*-d:*5,4*-d′*]bis[1,3]benzodioxocin* (**9b**). The reaction was carried out following the procedure for **9a**, using **8b** (0.25 g, 0.19 mmol), K_2CO_3 (0.31 g, 2.3 mmol), CH_2BrCl (0.65 mL, 10 mmol) and CH_3CN (55 mL). Pure **9b** was obtained as a glass in 99% yield. mp 65–67°C. Mass spec-

trum (FAB, NBA): m/z 1310.9 (M^+, *calc.* 1310.7). ^{1}H-NMR ($CDCl_3$): δ 7.01, 6.99 (2s, 4H, ArH), 6.44 (s, 2H, ArH), 5.88, 5.78, 5.68 [3d, 4H (1 : 2 : 1), J = 7.3 Hz, outer OCH_2O], 4.78, 4.71, 4.65 [3t, 4H (1 : 2 : 1), J = 8.0 Hz, $CH(CH_2)_{10}CH_3$], 4.38, 4.33, 4.30 [3d, 4H (1 : 2 : 1), J = 7.3 Hz, inner OCH_2O], 2.3–2.0 [m, 8H, $CHCH_2(CH_2)_9CH_3$], 1.5–1.1 [m, 72H, $CHCH_2(CH_2)_9CH_3$], 0.81 [t, 12H, J = 6.8 Hz, $CH(CH_2)_{10}CH_3$]. ^{13}C-NMR ($CDCl_3$): δ 155.0–151.8 (s, $ArCOCH_2O$), 120.6, 119.1, 116.7 (d, ArCH), 113.2 (s, ArCBr), 99.0, 98.6 (t, OCH_2O), 37.7–36.3 (d, ArCHAr). *Anal. Found*: C, 68.97; H, 8.63. *Calc.* for $C_{76}H_{110}Br_2O_8 \cdot 0.25H_2O$: C, 69.36; H, 8.46. Karl-Fischer found: 0.42; calc. for $0.25H_2O$: 0.34.

*1,21,23,25-Tetraundecyl-2,20:3,19-dimetheno-1*H,*21*H,*23*H,*25*H-*bis[1,3]dioxocino[5,4-*i*:*5′,4′*-*i′*]*benzo[1,2-*d*:*5,4-*d′*]bis[1,3]benzodioxocin-7,11-dicarboxylic acid, dimethyl ester* (**9c**). To a solution of **9b** (0.21 g, 0.16 mmol) in THF (50 mL) was added *n*-BuLi (1.2 mL, 1.8 mmol) at -100°C (using $EtOH/N_2$). After stirring for 15 min at this temperature, the reaction was quenched with ClC(O)OMe (0.45 mL, 5.8 mmol). The mixture was allowed to warm to room temperature, the solvent was removed *in vacuo* and the residue was dissolved in CH_2Cl_2 (25 mL). The solution was successively washed with 1 N HCl (10 mL), H_2O (3 × 10 mL), brine (10 mL), dried over $MgSO_4$ and evaporated to dryness. The crude product was purified with flash column chromatography (SiO_2, CH_2Cl_2) to give pure **9c** in 65% yield. The compound could not be recrystallized. mp 175°C. Mass spectrum (FAB, NBA): m/z 1269.7 [$(M+H)^+$, *calc.* 1269.9]. ^{1}H-NMR ($CDCl_3$): δ 7.10, 7.00 (2s, 4H, ArH), 6.46 (s, 2H, ArH), 5.66, 5.61, 5.58 [3d, 4H (1 : 2 : 1), J = 7.4 Hz, outer OCH_2O], 4.7–4.6 [m, 4H, $CH(CH_2)_{10}CH_3$], 4.52, 4.41, 4.33 [3d, 4H (1 : 2 : 1), J = 7.4 Hz, inner OCH_2O], 3.78 [s, 6H, $C(O)OCH_3$], 2.2–2.0 [m, 8H, $CHCH_2(CH_2)_9CH_3$], 1.4–1.1 [m, 72H, $CHCH_2(CH_2)_9CH_3$], 0.81 [t, 12H, J = 6.4 Hz, $CH(CH_2)_{10}CH_3$]. ^{13}C–NMR ($CDCl_3$): δ 166.2 [s, $C(O)OCH_3$], 155.1–150.9 (s, $ArCOCH_2O$), 123.4 [s, $ArCC(O)OCH_3$], 121.7, 120.3, 116.9 (d, ArCH), 99.5 (t, OCH_2O), 52.7 [q, $C(O)OCH_3$], 36.3 (d, ArCHAr). *Anal. Found*: C, 75.53; H, 9.61. *Calc.* for $C_{80}H_{116}O_{12}$: C, 75.67; H, 9.21.

*1,21,23,25-Tetraundecyl-2,20:3,19-dimetheno-1*H,*21*H,*23*H,*25*H-*bis[1,3]dioxocino[5,4-*i*:*5′,4′*-*i′*]*benzo[1,2-*d*:*5,4-*d′*]bis[1,3]benzodioxocin-7,11-diol* (**9d**). To a solution of **9b** (0.21 g, 0.16 mmol) in THF (50 mL) was quickly added *n*-BuLi (0.50 mL, 0.75 mmol) at -70°C. After 30 sec, the reaction mixture was quenched with $B(OMe)_3$ (0.27 mL, 2.4 mmol). The solution was warmed to room temperature and stirred for 1 h. After cooling the reaction mixture again to -70°C, a 15% solution of H_2O_2 in 1.5 M NaOH (4.2 mL, 20 mmol) was added and the mixture allowed to warm to room temperature and was stirred overnight. Excess H_2O_2 was destroyed by adding $Na_2S_2O_5$ (3.8 g, 20 mmol) to the solution. The THF was removed *in vacuo*, the residue was dissolved in CH_2Cl_2 (50 mL) and the solution was washed with H_2O (3 × 10 mL), with brine (10 mL), dried over $MgSO_4$ and evaporated to dryness. The crude product was purified with preparative TLC

(SiO_2, EtOAc/CH_2Cl_2, 30 : 70) to give pure **9d** in 62% yield. mp 150–152°C (CH_2Cl_2/EtOH). Mass spectrum (FAB, NBA): m/z 1184.6 (M^+, *calc.* 1184.8). ^{1}H-NMR ($CDCl_3$): δ 7.10 (s, 2H, ArH para to H), 6.64 (s, 2H, ArH para to OH), 6.50 (s, 2H, ArH ortho to OCH_2O), 5.94, 5.84, 5.75 [3d, 4H (1 : 2 : 1), J = 6.9, 7.0 and 7.2 Hz, outer OCH_2O], 5.65 (s, 2H, OH), 4.8–4.6 [m, 4H, $CH(CH_2)_{10}CH_3$], 4.5–4.4 (m, 4H, inner OCH_2O), 2.3–2.1 [m, 8H, $CHCH_2(CH_2)_9CH_3$], 1.5–1.2 [m, 72H, $CHCH_2(CH_2)_9CH_3$], 0.88 [t, 12H, J = 6.5 Hz, $CH(CH_2)_{10}CH_3$]. ^{13}C-NMR ($CDCl_3$): δ 154.9–154.8 (s, Ar*C*OCH_2O), 140.9 (s, ArCOH), 120.9, 116.5, 109.8 (d, ArCH), 99.7 (t, OCH_2O), 36.8–36.3 (d, ArCHAr). *Anal. Found*: C, 76.32; H, 9.50. *Calc.* for $C_{76}H_{112}O_{10}\cdot 0.5H_2O$: C, 76.41; H, 9.53. Karl-Fischer found: 0.71; calc. for $0.5H_2O$: 0.75.

*1,21,23,25-Tetraundecyl-2,20:3,19-dimetheno-1*H,*21*H*23*H,*25*H*-bis[1,3]dioxocino[5,4*-i:*5′,4′*-i′*]benzo[1,2*-d:*5,4*-d′*]bis[1,3]benzodioxocin-7,11-dicarbonitrile* (**9f**). A solution of **9b** (0.82 g, 0.63 mmol), CuCN (0.44 g, 4.9 mmol) in *N*-methylpyrrolidone (5 mL) was refluxed for 21 h. After cooling the reaction mixture to room temperature, $FeCl_3\cdot 6H_2O$ (1.0 g) and 1 N HCl (2 mL) were added and the mixture was stirred at 75°C for 30 min. After cooling the reaction mixture to room temperature, H_2O (25 mL) was added and the mixture was extracted twice with $CHCl_3$ (2 × 50 mL). The combined organic layers were washed with sat. NH_4Cl (4×10 mL), with H_2O (3×10 mL), with brine (10 mL) and dried over $MgSO_4$. After removal of the solvent the crude product was recrystallized from CH_2Cl_2/MeOH to give pure **9f** in 99% yield. mp 112–114°C (CH_2Cl_2/MeOH). Mass spectrum (FAB, NBA): m/z 1203.8 [$(M+H)^+$, *calc.* 1203.9]. ^{1}H-NMR ($CDCl_3$): δ 7.23, 7.00 (2s, 4H, ArH), 6.47 (s, 2H, ArH), 5.99, 5.84, 5.69 [3d, 4H (1 : 2 : 1), J = 7.2, 7.3 and 7.4 Hz, outer OCH_2O], 4.8–4.6 [m, 4H, $CH(CH_2)_{10}CH_3$], 4.55, 4.44, 4.30 [3d, 4H (1 : 2 : 1), J = 7.4, 7.3 and 7.2 Hz, inner OCH_2O], 2.3–2.0 [m, 8H, $CHCH_2(CH_2)_9CH_3$], 1.5–1.1 [m, 72H, $CHCH_2(CH_2)_9CH_3$], 0.80 [t, 12H, J = 6.5 Hz, $CH(CH_2)_{10}CH_3$]. ^{13}C-NMR ($CDCl_3$): δ 156.7–154.6 (s, Ar*C*OCH_2O), 125.0, 120.3, 116.8 (d, ArCH), 112.7 (s, Ar*C*CN), 103.9 (s, ArC*C*N), 99.6–98.7 (t, OCH_2O), 36.3 (d, ArCHAr). *Anal. Found*: C, 77.65; N, 1.96; H, 9.57. *Calc.* for $C_{78}H_{110}N_2O_8$: C, 77.83; N, 2.33; H, 9.21.

*7,11-Dibromo-1,21,23,25-tetrakis(2-phenylethyl)-15,28-bis(thiomethyl)-2,20:3,19-dimetheno-1*H,*21*H,*23*H,*25*H-bis[1,3]dioxocino[5,4*-i:*5′,4′*-i′*]benzo[1,2*-d:*5,4*-d′*]bis[1,3]benzodioxocin* (**9g**). To a solution of diol **3c** (0.50g, 0.40 mmol) in THF (25 mL) was added excess NaH (1.6 mmol) and the solution was stirred at room temperature until the evolution of hydrogen stopped. The reaction mixture was cooled to -70°C and *n*-BuLi (1.3 mL, 20 mmol) was quickly added. After 15 sec the reaction mixture was quenched with excess CH_3SSCH_3 (0.36 mL, 4.0 mmol). The mixture was allowed to warm to room temperature and the solvent was removed *in vacuo*. The residue was taken up in CH_2Cl_2 (25 mL) and the solution was successively washed with 1 N HCl (10 mL), H_2O (3 × 10 mL), brine (10 mL), dried

over $MgSO_4$ and evaporated to dryness. To a suspension of the crude product in CH_3CN (25 mL) were added K_2CO_3 (0.55 g, 4.0 mmol) and CH_2BrCl (1.0 mL, 16 mmol) whereupon the mixture was refluxed for 24 h. The solvent was removed and the residue was taken up in CH_2Cl_2 (25 mL). The solution was successively washed with 1 N HCl (10 mL), H_2O (3 × 10 mL), and brine (10 mL), dried over $MgSO_4$, and the solvent was removed under vacuum. The crude product was purified with flash column chromatography (SiO_2 60H, CH_2Cl_2/hexane, 55 : 45) to give pure **9g** as a white solid in 25% yield: mp 178–180°C (CH_2Cl_2/hexane). Mass spectrum (FAB, NBA): m/z 1203.5 [$(M+H)^+$, *calc.* 1203.2]. ^{1}H-NMR ($CDCl_3$): δ 7.3–7.0 [m, 24H, $CH(CH_2)_2C_6H_5$ + ArH], 5.97 (d, 4H, J = 7.3 Hz, outer OCH_2O), 5.0–4.8 [m, 4H, $CH(CH_2)_2C_6H_5$], 4.41, 4.38, 4.35 [3d, 4H (1 : 2 : 1), J = 7.4 Hz, inner OCH_2O], 2.8–2.4 [m, 16H, $CH(CH_2)_2C_6H_5$], 2.43 (s, 6H, $ArSCH_3$). ^{13}C-NMR ($CDCl_3$): δ 155.9–152.2 (s, $ArCOCH_2O$), 124.9 (s, $ArCSCH_3$), 119.7, 118.9 (d, ArCH), 113.9 (s, ArCBr), 98.9 (t, OCH_2O), 37.8–37.6 (d, ArCHAr), 17.9 (q, SCH_3). *Anal. Found*: C, 66.22; H, 4.78. *Calc.* for $C_{66}H_{58}Br_2O_8S_2$: C, 65.89; H, 4.86.

*7,11-Dibromo-15,28-diiodo-1,21,23,25-tetrakis(2-phenylethyl)-2,20:3,19-dimetheno-1*H,*21*H,*23*H,*25*H-*bis[1,3]dioxocino[5,4*-i:*5′,4′*-i′*]benzo[1,2*-d:*5,4*-d′*]bis[1,3]benzodioxocin* (**9h**) was synthesized according to the procedure for **9g**, with the exception that the lithiation reaction was quenched with I_2 instead of CH_3SSCH_3. The reaction was carried out using **3c** (0.56 g, 0.45 mmol), *n*-BuLi (1.5 mL, 2.2 mmol), THF (25 mL), I_2 (1.15 g, 4.5 mmol), K_2CO_3 (1.23 g, 8.9 mmol), CH_2BrCl (0.58 mL, 8.9 mmol) and CH_3CN (25 mL) to give pure **9h** after flash column chromatography (SiO_2 60H, CH_2Cl_2/hexane, 40 : 60) in 20% yield. mp 198–201°C (CH_2Cl_2). Mass spectrum (FAB, NBA): m/z 1361.9 (M^+, *calc.* 1362.1). ^{1}H-NMR ($CDCl_3$): δ 7.2–7.0 [m, 24H, $CH(CH_2)_2C_6H_5$ + ArH], 5.92, 5.91, 5.90 [3d, 4H (1 : 2 : 1), J = 7.4, 7.4 and 7.3 Hz, outer OCH_2O], 4.89 [t, 4H, J = 7.7 Hz, $CH(CH_2)_2C_6H_5$], 4.33, 4.31, 4.27 [3d, 4H (1 : 2 : 1), J = 7.4, 7.4 and 7.5 Hz, inner OCH_2O], 2.7–2.3 [m, 16H, $CH(CH_2)_2C_6H_5$]. ^{13}C-NMR ($CDCl_3$): δ 155.2, 152.3 (s, $ArCOCH_2O$), 120.5, 118.9 (d, ArCH), 113.9 (s, ArCBr), 98.7–98.5 (t, OCH_2O), 93.5 (s, ArCI), 38.1–37.8 (d, ArCHAr). *Anal. Found*: C, 53.47; H, 3.74. *Calc.* for $C_{64}H_{52}Br_2I_2O_8 \cdot CH_2Cl_2$: C, 53.10; H, 3.76.

*1,19,21,29,47,49,57,62-Octaundecyl-23,27:51,55-dimethano-2,46:3,45:17,31:18,30-tetrametheno-1*H,*19*H,*21*H,*29*H,*47*H,*49*H-*bis[1,3]benzodioxocino[9,8*-d:*9′,8′*-d″*][1,3,6,8,11,13,16,18]octaoxacycloeicosino[4,5*-j:*10,9*-j′:*14,15*-j″:*20,19*-j‴*]tetrakis[1,3]benzodioxocin (C-isomer)* (**10**). A solution of diol **9d** (75 mg, 0.063 mmol) and CH_2BrCl (10 μL, 0.14 mmol) in a mixture of DMSO (5 mL) and THF (1 mL) was added to a solution of Cs_2CO_3 (0.21 g, 0.63 mmol) in DMSO (25 mL) at 60°C over a 4 h period. After 17 h, another portion of CH_2BrCl (15 μL, 0.23 mmol) was added and the temperature was raised to 100°C. The addition of CH_2BrCl (15 μL, 0.23 mmol) was repeated every 24 h. After a total reaction

TABLE I. Crystallographic data.

Experimental	
Crystal data	
$C_{46}H_{44}Br_2O_{16}\cdot 2C_5H_{10}$	$D_c = 1.61$ Mg m^{-3}
$M_r = 1172.4$	MoK_α radiation
triclinic	$P\bar{1}$
$a = 9.777(3)$ Å	$\alpha = 105.46(2)°$
$b = 13.601(4)$ Å	$\beta = 106.65(2)°$
$c = 22.271(8)$ Å	$\gamma = 105.47(2)°$
$V = 2686.1(7)$ Å^3	$T = 173(1)$ K
$Z = 2$	
Refinement	
Final $R = 0.065$	$wR = 0.091$
3872 reflections	325 parameters

time of 72 h, the solvent was removed *in vacuo*. The residue was dissolved in CH_2Cl_2 (50 mL), washed with H_2O (2 × 10 mL), with brine (10 mL) and dried over $MgSO_4$. The solution was evaporated to dryness and the product was purified by flash column chromatography (SiO_2, CH_2Cl_2/hexane, 50 : 50) to give pure **10** as a white solid in 71% yield. mp 178–182°C (CH_2Cl_2/MeOH). Mass spectrum (FAB, NBA): m/z 2395.0 (M^+, *calc.* 2394.7). ^{1}H-NMR ($CDCl_2CDCl_2$, 90°C): δ 7.12 (s, 4H, ArH para to H), 6.86 (s, 4H, ArH para to OCH_2O), 6.52 (s, 4H, ArH ortho to OCH_2O), 5.95 (d, 2H, $J = 6.4$ Hz, outer OCH_2O), 5.89 (d, 2H, $J = 7.4$ Hz, outer OCH_2O), 5.4, 5.2 [2bs, 3H (2 : 1), OCH_2O connecting the two parts], 5.2–4.9 [m, 9H, outer OCH_2O (4H) + OCH_2O connecting the two parts (1H) + inner OCH_2O (2H) + $CH(CH_2)_{10}CH_3$ (2H)], 4.92 [t, 2H, $J = 7.9$ Hz, $CH(CH_2)_{10}CH_3$], 4.73 (d, 2H, $J = 7.4$ Hz, inner OCH_2O), 4.46 [t, 4H, $J = 7.9$ Hz, $CH(CH_2)_{10}CH_3$], 3.51 (d, 4H, $J = 7.4$ Hz, inner OCH_2O), 2.4–2.2 [m, 8H, $CHCH_2(CH_2)_9CH_3$], 2.2–2.0 [m, 8H, $CHCH_2(CH_2)_9CH_3$], 1.6–1.4 [m, 16H, $CHCH_2CH_2(CH_2)_8CH_3$], 1.4–1.2 [m, 128H, $CH(CH_2)_2(CH_2)_8CH_3$], 0.88 [t, 24H, $J = 6.5$ Hz, $CH(CH_2)_{10}CH_3$]. *Anal. Found*: C, 77.37; H, 10.29. *Calc.* for $C_{154}H_{224}O_{20}$: C, 77.21; H, 9.43.

X-Ray Structure Determination

A small sample of **6a** was recrystallized from CH_2Cl_2/pentane and its crystal structure was determined by X-ray diffraction. The most important crystallographic data are collected in Table I.

Data were collected in the $\omega/2\theta$ scan mode (scan width (ω): $1.10 + 0.34 \tan\theta$), using graphite monochromated MoK_α radiation. The intensity data were corrected for Lorentz and polarization effects and for long-time-scale variation. No absorption correction was applied. The structure was solved with MULTAN [29] and refined by

TABLE II. Fractional atomic coordinates and equivalent isotropic thermal parameters for non-H atoms, with e.s.ds in parentheses. $B_{eq} = (8\pi^2/3)\Sigma_i\Sigma_j U_{ij} a_i^* a_j^* a_i \cdot a_j$.

Atom	x	y	z	B_{eq}
Br(1)	0.7932(1)	0.30815(9)	0.02473(6)	2.20(3)
Br(2)	0.0286(1)	-0.18739(9)	0.40527(6)	2.34(3)
Br(3)	0.1860(1)	0.44472(9)	0.52321(6)	2.31(3)
Br(4)	0.0158(1)	-0.03727(9)	0.13681(6)	2.54(3)
O(7)	0.9078(7)	0.5433(5)	0.1112(3)	1.5(1)
O(10)	0.6583(8)	0.5993(6)	0.0379(4)	2.4(2)
O(12)	0.8203(8)	0.7362(6)	0.1142(4)	2.9(2)
O(27)	1.0138(7)	0.7533(5)	0.2611(3)	1.5(1)
O(30)	0.8128(8)	0.8384(6)	0.2583(4)	2.1(2)
O(32)	0.6337(8)	0.6811(6)	0.2164(4)	2.2(2)
O(33)	1.2974(7)	0.7735(5)	0.4582(4)	1.9(2)
O(35)	1.3559(8)	0.6478(5)	0.5009(4)	2.0(2)
O(47)	1.2523(8)	0.2668(6)	0.4282(4)	2.1(2)
O(50)	0.8930(8)	0.0973(6)	0.4018(4)	2.8(2)
O(52)	1.0928(8)	0.1144(6)	0.4712(4)	2.7(2)
O(67)	1.1824(8)	0.0757(6)	0.2735(4)	2.1(2)
O(70)	1.450(1)	-0.0232(8)	0.3246(5)	5.1(2)
O(71)	1.2961(8)	0.0338(6)	0.3777(4)	2.7(2)
O(73)	1.1376(8)	0.1152(5)	0.0663(4)	1.9(2)
O(75)	1.0608(7)	0.2378(5)	0.0252(4)	1.8(2)
C(1)	0.985(1)	0.3877(8)	0.0724(5)	1.3(2)
C(2)	1.019(1)	0.4939(8)	0.1104(5)	1.5(2)
C(3)	1.158(1)	0.5498(8)	0.1474(2)	1.6(2)
C(4)	1.260(1)	0.4952(8)	0.1472(5)	1.3(2)
C(5)	1.228(1)	0.3904(8)	0.1088(5)	1.3(2)
C(6)	1.092(1)	0.3389(8)	0.0714(5)	1.5(2)
C(8)	0.895(1)	0.5864(8)	0.0592(6)	1.8(2)
C(9)	0.788(1)	0.6500(8)	0.0741(6)	1.8(2)
C(11)	0.545(1)	0.652(1)	0.0494(7)	3.3(3)
C(13)	1.195(1)	0.6700(8)	0.1868(5)	1.5(2)
C(14)	1.329(1)	0.7372(8)	0.1689(6)	1.9(2)
C(21)	1.152(1)	0.7555(8)	0.3591(5)	1.4(2)
C(22)	1.126(1)	0.7293(8)	0.2934(5)	1.5(2)
C(23)	1.220(1)	0.6880(8)	0.2583(5)	1.3(2)
C(24)	1.341(1)	0.6732(8)	0.2942(5)	1.3(2)
C(25)	1.367(1)	0.6971(8)	0.3599(5)	1.2(2)
C(26)	1.272(1)	0.7395(8)	0.3924(5)	1.4(2)
C(28)	0.869(1)	0.6775(8)	0.2502(5)	1.4(2)
C(29)	0.761(1)	0.7327(8)	0.2386(6)	1.9(2)
C(31)	0.704(1)	0.896(1)	0.2455(7)	3.1(3)
C(34)	1.246(1)	0.6943(8)	0.4869(6)	1.9(2)

TABLE II. *(continued)*

Atom	x	y	z	B_{eq}
C(36)	1.492(1)	0.6799(8)	0.3988(6)	1.8(2)
C(37)	1.630(1)	0.6929(8)	0.3700(6)	1.9(2)
C(41)	1.297(1)	0.4559(8)	0.4609(5)	1.4(2)
C(42)	1.360(1)	0.5577(8)	0.4550(5)	1.5(2)
C(43)	1.436(1)	0.5679(8)	0.4071(5)	1.3(2)
C(44)	1.451(1)	0.4750(8)	0.3671(5)	1.3(2)
C(45)	1.390(1)	0.3727(8)	0.3720(5)	1.5(2)
C(46)	1.311(1)	0.3648(8)	0.4190(5)	1.2(2)
C(48)	1.104(1)	0.2164(9)	0.3967(6)	2.1(3)
C(49)	1.036(1)	0.1380(8)	0.4296(6)	1.8(2)
C(51)	0.805(1)	0.014(1)	0.4249(7)	3.0(3)
C(53)	1.415(1)	0.2713(8)	0.3300(5)	1.5(2)
C(54)	1.579(1)	0.2907(9)	0.3336(6)	2.2(3)
C(61)	1.160(1)	0.0981(8)	0.1703(5)	1.5(2)
C(62)	1.227(1)	0.1368(8)	0.2346(5)	1.5(2)
C(63)	1.334(1)	0.2366(8)	0.2616(5)	1.4(2)
C(64)	1.370(1)	0.2981(8)	0.2203(5)	1.5(2)
C(65)	1.305(1)	0.2617(8)	0.1550(5)	1.5(2)
C(66)	1.200(1)	0.1589(8)	0.1311(5)	1.3(2)
C(68)	1.230(1)	-0.020(1)	0.2643(6)	3.0(3)
C(69)	1.339(1)	-0.0035(9)	0.3248(6)	2.4(3)
C(72)	1.394(1)	0.054(1)	0.4382(7)	3.6(3)
C(74)	1.013(1)	0.1435(9)	0.0432(6)	2.2(3)
C(76)	1.340(1)	0.3281(8)	0.1099(6)	1.9(2)
C(77)	1.499(1)	0.4015(8)	0.1277(6)	1.9(2)
C(80)	0.403(2)	-0.036(1)	0.0919(8)	4.5(4)
C(81)	0.516(2)	0.051(1)	0.1447(9)	5.9(4)
C(82)	0.652(2)	0.062(1)	0.1126(8)	5.6(4)
C(83)	0.625(2)	-0.056(1)	0.0683(8)	5.2(4)
C(84)	0.476(1)	-0.1063(8)	0.0589(5)	1.5(2)
C(90)	0.167(1)	0.5597(8)	0.7260(5)	1.1(2)
C(91)	0.055(2)	0.544(1)	0.6781(8)	5.0(4)
C(92)	0.051(2)	0.412(1)	0.292(1)	7.1(5)
C(93)	0.961(2)	0.321(1)	0.2341(9)	6.0(4)
C(94)	0.172(2)	0.641(1)	0.7788(8)	5.5(4)

full-matrix least-squares methods. Weights for each reflection in the refinement (on F) were $w = 4F_0^2/\sigma(F_0^2)$, $\sigma(F_0^2) = \sigma^2(I) + (pF_0^2)^2$; the value of the instability factor p was determined to be 0.04. All calculations were done with SDP [30]. Atomic scattering factors were taken from the *International Tables for X-Ray Crystallography* [31]. Atomic parameters are given in Table II. Bond distances and angles are given in Table III. The atom numbering and structure determined

TABLE III. Bond distances (Å) and angles (°) for the heavy atoms with e.s.ds in parentheses

Atom 1	Atom 2	Distance	Atom 1	Atom 2	Distance
Br(1)	C(1)	1.900(9)	C(13)	C(14)	1.55(2)
Br(2)	C(21)	1.88(1)	C(13)	C(23)	1.52(2)
Br(3)	C(41)	1.88(1)	C(21)	C(22)	1.38(2)
Br(4)	C(61)	1.884(9)	C(21)	C(26)	1.40(2)
O(7)	C(2)	1.43(1)	C(22)	C(23)	1.42(2)
O(7)	C(8)	1.44(2)	C(23)	C(24)	1.43(2)
O(10)	C(9)	1.31(1)	C(24)	C(25)	1.38(2)
O(10)	C(11)	1.49(2)	C(25)	C(26)	1.41(2)
O(12)	C(9)	1.20(1)	C(25)	C(36)	1.52(2)
O(27)	C(22)	1.40(1)	C(28)	C(29)	1.49(2)
O(27)	C(28)	1.46(1)	C(36)	C(37)	1.55(2)
O(30)	C(29)	1.32(1)	C(36)	C(43)	1.55(2)
O(30)	C(31)	1.51(2)	C(41)	C(42)	1.41(2)
O(32)	C(29)	1.22(1)	C(41)	C(46)	1.39(1)
O(33)	C(26)	1.38(1)	C(42)	C(43)	1.39(2)
O(33)	C(34)	1.41(2)	C(43)	C(44)	1.39(1)
O(35)	C(34)	1.43(2)	C(44)	C(45)	1.40(2)
O(35)	C(42)	1.38(1)	C(45)	C(46)	1.39(2)
O(47)	C(46)	1.39(1)	C(45)	C(53)	1.54(2)
O(47)	C(48)	1.42(1)	C(48)	C(49)	1.51(2)
O(50)	C(49)	1.35(1)	C(53)	C(54)	1.54(2)
O(50)	C(51)	1.48(2)	C(53)	C(63)	1.51(2)
O(52)	C(49)	1.18(2)	C(61)	C(62)	1.39(2)
O(67)	C(62)	1.39(2)	C(61)	C(66)	1.38(2)
O(67)	C(68)	1.47(2)	C(62)	C(63)	1.39(1)
O(70)	C(69)	1.18(2)	C(63)	C(64)	1.42(2)
O(71)	C(69)	1.32(2)	C(64)	C(65)	1.40(2)
O(71)	C(72)	1.46(2)	C(65)	C(66)	1.42(1)
O(73)	C(66)	1.39(1)	C(65)	C(76)	1.53(2)
O(73)	C(74)	1.44(2)	C(68)	C(69)	1.53(2)
O(75)	C(6)	1.41(1)	C(76)	C(77)	1.54(1)
O(75)	C(74)	1.42(1)	C(80)	C(81)	1.50(2)
C(1)	C(2)	1.39(1)	C(80)	C(84)	1.45(3)
C(1)	C(6)	1.38(2)	C(81)	C(82)	1.57(3)
C(2)	C(3)	1.39(1)	C(82)	C(83)	1.58(3)
C(3)	C(4)	1.40(2)	C(83)	C(84)	1.40(2)
C(3)	C(13)	1.55(1)	C(90)	C(91)	1.35(2)
C(4)	C(5)	1.38(1)	C(90)	C(94)	1.37(2)
C(5)	C(6)	1.36(1)	C(91)	C(92)	1.48(3)
C(5)	C(76)	1.55(2)	C(92)	C(93)	1.50(3)
C(8)	C(9)	1.54(2)	C(93)	C(94)	1.54(3)

TABLE III. *(continued)*

Atom 1	Atom 2	Atom 3	Angle	Atom 1	Atom 2	Atom 3	Angle
C(2)	O(7)	C(8)	111.5(9)	O(33)	C(26)	C(25)	121(1)
C(9)	O(10)	C(11)	116.8(8)	C(21)	C(26)	C(25)	121(2)
C(22)	O(27)	C(28)	115.4(8)	O(27)	C(28)	C(29)	108.2(9)
C(29)	O(30)	C(31)	115.3(8)	O(30)	C(29)	C(32)	125(1)
C(26)	O(33)	C(34)	116.4(7)	O(30)	C(29)	C(28)	114.6(8)
C(34)	O(35)	C(42)	117.8(8)	O(32)	C(29)	C(28)	120(1)
C(46)	O(47)	C(48)	113(1)	O(33)	C(34)	O(35)	110.3(9)
C(49)	O(50)	C(51)	117(1)	C(25)	C(36)	C(37)	114(2)
C(62)	O(67)	C(68)	114.4(9)	C(25)	C(36)	C(43)	107.3(8)
C(69)	O(71)	C(72)	117(2)	C(37)	C(36)	C(43)	112(1)
C(66)	O(73)	C(74)	117.3(9)	Br(3)	C(41)	C(42)	118.9(8)
C(6)	O(75)	C(74)	119.0(9)	Br(3)	C(41)	C(46)	121.0(8)
Br(1)	C(1)	C(2)	120.9(9)	C(42)	C(41)	C(46)	120(2)
Br(1)	C(1)	C(6)	120.0(7)	O(35)	C(42)	C(41)	119(2)
C(2)	C(1)	C(6)	119.1(9)	O(35)	C(42)	C(43)	120.6(9)
O(7)	C(2)	C(1)	118.7(9)	C(41)	C(42)	C(43)	120(1)
O(7)	C(2)	C(3)	120.8(9)	C(36)	C(43)	C(42)	118.7(9)
C(1)	C(2)	C(3)	120(2)	C(36)	C(43)	C(44)	123(2)
C(2)	C(3)	C(4)	118.2(9)	C(42)	C(43)	C(44)	119(2)
C(2)	C(3)	C(13)	120(2)	C(43)	C(44)	C(45)	123(1)
C(4)	C(3)	C(13)	122.3(8)	C(44)	C(45)	C(46)	118(1)
C(3)	C(4)	C(5)	121.6(9)	C(44)	C(45)	C(53)	123(2)
C(4)	C(5)	C(6)	119(2)	C(46)	C(45)	C(53)	120(1)
C(4)	C(5)	C(76)	121.8(8)	O(47)	C(46)	C(41)	118(2)
C(6)	C(5)	C(76)	119.4(9)	O(47)	C(46)	C(45)	121.0(9)
O(75)	C(6)	C(1)	117.4(9)	C(41)	C(46)	C(45)	121(1)
O(75)	C(6)	C(5)	120(2)	O(47)	C(48)	C(49)	108(1)
C(1)	C(6)	C(5)	122(1)	O(50)	C(49)	O(52)	125(2)
O(7)	C(8)	C(9)	103(1)	O(50)	C(49)	C(48)	107(2)
O(10)	C(9)	O(12)	124(1)	O(52)	C(49)	C(48)	128.3(9)
O(10)	C(9)	C(8)	112.1(8)	C(45)	C(53)	C(54)	109.8(7)
O(12)	C(9)	C(8)	124.2(9)	C(45)	C(53)	C(63)	113(1)
C(3)	C(13)	C(14)	109.2(9)	C(54)	C(53)	C(63)	110(1)
C(3)	C(13)	C(23)	112(1)	Br(4)	C(61)	C(62)	120.0(9)
O(14)	C(13)	C(23)	111.3(8)	Br(4)	C(61)	C(66)	120.2(7)
Br(2)	C(21)	C(22)	120.8(9)	C(62)	C(61)	C(66)	119.8(8)
Br(2)	C(21)	C(26)	118.8(9)	O(67)	C(62)	C(61)	118.8(8)
C(22)	C(21)	C(26)	120(2)	O(67)	C(62)	C(63)	120(1)
O(27)	C(22)	C(21)	120(2)	C(61)	C(62)	C(63)	122(1)
O(27)	C(22)	C(23)	119(1)	C(53)	C(63)	C(62)	121(2)
C(21)	C(22)	C(23)	121(2)	C(53)	C(63)	C(64)	122.5(8)
C(13)	C(23)	C(22)	119(2)	C(62)	C(63)	C(64)	117(1)
C(13)	C(23)	C(24)	124(2)	C(63)	C(64)	C(65)	122.8(8)

TABLE III. *(continued)*

Atom 1	Atom 2	Atom 3	Angle	Atom 1	Atom 2	Atom 3	Angle
C(22)	C(23)	C(24)	117(2)	C(64)	C(65)	C(66)	118(2)
C(23)	C(24)	C(25)	123(2)	C(64)	C(65)	C(76)	123.7(8)
C(24)	C(25)	C(26)	118(2)	C(66)	C(65)	C(76)	119.4(9)
C(24)	C(25)	C(36)	124(2)	O(73)	C(66)	C(61)	118.5(8)
C(26)	C(25)	C(36)	118(1)	O(73)	C(66)	C(65)	120(2)
O(33)	C(26)	C(21)	118(2)	C(61)	C(66)	C(65)	122(1)
O(67)	C(68)	C(69)	108.1(9)	C(80)	C(81)	C(82)	100(1)
O(70)	C(69)	O(71)	123(1)	C(81)	C(82)	C(83)	103(1)
O(70)	C(69)	C(68)	124(1)	C(82)	C(83)	C(84)	105(1)
O(71)	C(69)	C(68)	113(2)	C(80)	C(84)	C(83)	113(1)
O(73)	C(74)	O(75)	109.7(8)	C(91)	C(90)	C(94)	111(1)
C(5)	C(76)	C(65)	107(1)	C(90)	C(91)	C(92)	107(1)
C(5)	C(76)	C(77)	113.4(9)	C(91)	C(92)	C(93)	105(1)
C(65)	C(76)	C(77)	113(1)	C(92)	C(93)	C(94)	100(1)
C(81)	C(80)	C(84)	106(1)	C(90)	C(94)	C(93)	109(1)

are shown in Figure 1. The bromine atoms were refined anisotropically. Hydrogen atoms were not resolved.

3. Results and Discussion

Cavitands containing an enforced cavity [32] are generally prepared via a four-fold bridging reaction of an octol (**1**) with a dihalide to give compounds of general structure **2** (Scheme 1) [19, 20, 33, 34]. Several years ago, tri-bridged diol **3a** was isolated in a yield of 27% as a side product in the synthesis of cavitand **2a** [19]. Such tri-bridged diols, in which three out of four pairs of hydroxyl groups are connected via a methylene spacer, are interesting molecules with respect to selective functionalization. They have a lower degree of symmetry than tetra-bridged cavitands, which means that the reactivity of the aromatic rings bearing the hydroxyl groups will be different from the others.

First, we optimized the synthesis of tri-bridged diol **3** by variation of the reaction conditions, temperature (and the reaction time), solvent, and amount of CH_2BrCl. These reactions were carried out with octols with different side chains (R_1). The results are summarized in Table IV.

One of the first things that becomes clear from the data in Table IV is that reactions run at 70°C (entries 2, 6, 7, 10, 12 and 14–16) generally give higher overall yields than the corresponding reactions at room temperature (entries 1, 5, 8, 9, 11 and 13). With respect to the formation of tri-bridged diol **3** there is a marked difference between the solvents DMF (entries 4, 11, 12, 15 and 16) and DMSO (entries 1–3, 5–10, 13 and 14).

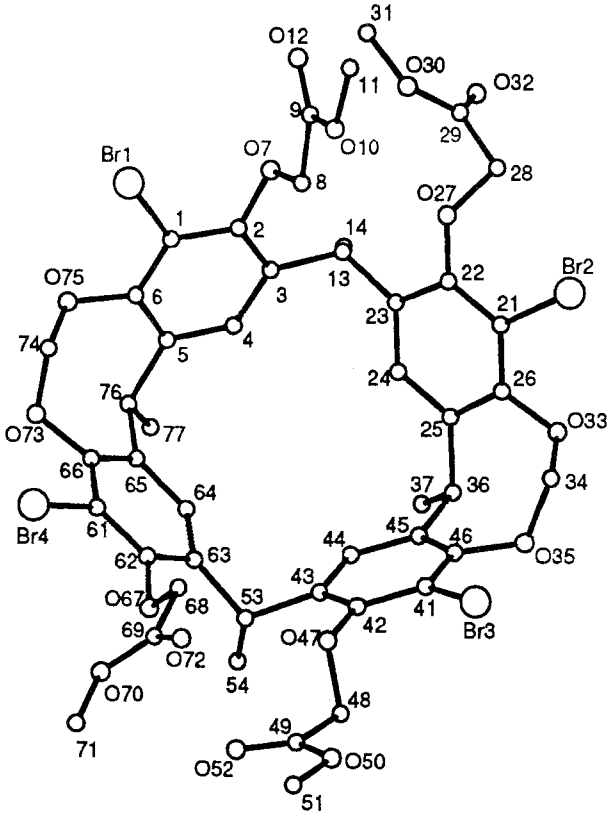
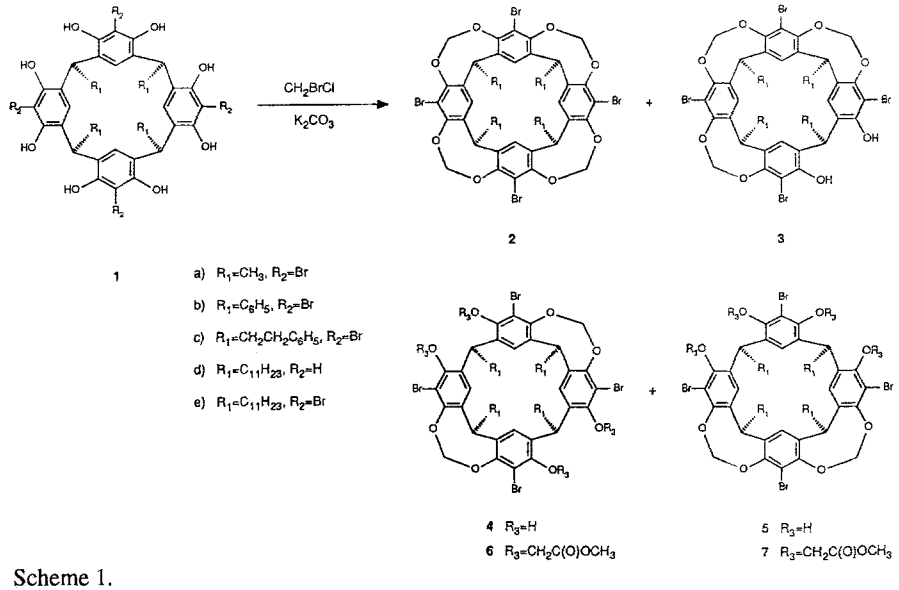


Fig. 1. View of the X-ray crystal structure of tetramethyl ester **6a** (the cyclopentane molecules are not located in the cavity of **6a** and have therefore been omitted for clarity) made using PLUTO [39].

In DMF the reaction at room temperature (entry 11) gives mainly diol **3** and only a small amount of cavitand **2** is formed. At this temperature the introduction of the fourth methylene bridge is considerably slower than the formation of the other three bridges. The reason for this decreased reactivity has been attributed to the fact that cavitands become progressively more rigid when more bridges are introduced and they are therefore less adaptable to the linear transition state required for bridging [35]. If the temperature is raised to 70°C (entry 15), the fourth bridge can be easily introduced when excess CH_2BrCl is present, leading to high yields of **2**. In order to facilitate the isolation of reasonable amounts of **3**, the amount of CH_2BrCl was lowered to 4 equiv. (entries 12 and 16).

In DMSO the reaction temperature has hardly any influence. Both at room temperature and at 70°C the tri-bridged diol **3** is formed as the main product, regardless of the amount of excess CH_2BrCl used. The introduction of the fourth bridge took place, to some extent, only in the case of octol **1a** (entry 2). This result is quite surprising, because DMSO is one of the best solvents for S_N2 reactions [36].



Scheme 1.

However, sulfoxides are also good nucleophiles that can be alkylated by methyl halides to form the corresponding sulfoxonium salts [37]. This reaction normally takes place at room temperature with methyl iodide, but apparently requires a higher temperature when a less reactive halide like CH_2BrCl is involved.

These results show that the optimum reaction conditions for the formation of tri-bridged diols **3** are: (a) reaction at 70°C for 3 days in DMSO with excess CH_2BrCl; or (b) in DMF with 4 equiv. of CH_2BrCl; comparable results can be obtained by reaction at room temperature in DMF of DMSO with excess CH_2BrCl for 8 days.

From the reactions of **1c** in DMSO at room temperature (entries 8 and 9), in addition to the compounds **2** and **3** we isolated considerable amounts of a di-bridged tetrol. According to the ^{1}H-NMR spectrum, this product appears to be the more symmetrical A,C-bridged isomer **4c** (*vide infra*). No A,B-bridged isomer could be isolated in these reactions. In an attempt to optimize the reaction conditions for the formation of **4a** (entries 3 and 4), using only 2 equiv. of CH_2BrCl, we observed that, in addition to the A,C-di-bridged tetrol **4a**, a substantial amount of A,B-di-bridged tetrol **5a** was formed. Since these products could not be isolated in a pure state, due to their low solubility, they were first converted to the corresponding tetramethyl esters **6a** and **7a**, respectively, by reaction with 4 equiv. of methyl bromoacetate [38]. The structure of **6a**·$2C_5H_{10}$ was unambiguously proven by solving the X-ray crystal structure (Figure 1). The structure of this molecule is rather rigid because all four aromatic rings are fixed to a neighbouring ring via a methylene bridge. The molecule therefore possesses a crown-like conformation. Compound **7a** is much more flexible, because only three aromatic rings are bridged and one ring is free in

TABLE IV. Synthesis of cavitands **2–5** under different reaction conditions.

Entry	R_1	Solvent	Temperature (°C)	Reaction time (days)	Equiv. CH_2BrCl	Yield (%)	Product distribution (%) **2**	**3**	**4**	**5**
1	CH_3	DMSO	25	8	3.3 + 7(5d)	47[b]	<2	45	–[c]	–[c]
2	"	"	70	3	8	60[a]	40	20	0	0
3	"	"	70	1	2	48[a]	0	0	30[d]	18[d]
4	"	DMF	70	2	2	45[a]	0	9[d]	24[d,e]	9[d]
5	C_6H_5	DMSO	25	8	4 + 8(5d)	13[a]	<1	12	–[c]	–[c]
6	"	"	70 70–85 95	2.5 1 0.5	8 4(3.5d) –	65[a]	22	43	0	0
7	"	"	70	3.5	8	49[b]	7	42	0	0
8	$(CH_2)_2Ph$	"	25	8	4 + 4(5d)	59[a]	1	41	17	0
9	"	"	25	8	4 + 4(5d)	80[b]	2	49	29	0
10	"	"	70	3	8	65[b]	11	54	0	0
11	"	DMF	25	18	8 + 8(6d)	53[b]	11	42	0	0
12	"	"	70	4	4	62[b]	16	46	0	0
13	$C_{11}H_{23}$	DMSO	25	8	8 + 8(5d)	43[a]	6	34	4	0
14	"	"	70	3	8	61[a]	22	39	–[c]	–[c]
15	"	DMF	70	3	8	80[a]	73	7	0	0
16	"	"	70	3	4	82[a]	30	52	–[c]	–[c]

[a] Work-up according to procedure A.

[b] Work-up according to procedure B.

[c] Compounds **4** and **5** were not isolated.

[d] Isolated as the tetramethyl esters **6** and **7**.

[e] An additional 3% of the corresponding tribromo derivative was also isolated.

this molecule. This ring is considerably tilted with respect to the others according to the marked upfield shift of the only Ar—H proton in this aryl ring (from 7.3 to 6.7 ppm) in the ^{1}H-NMR spectrum, compared to the same protons in the other aryl rings.

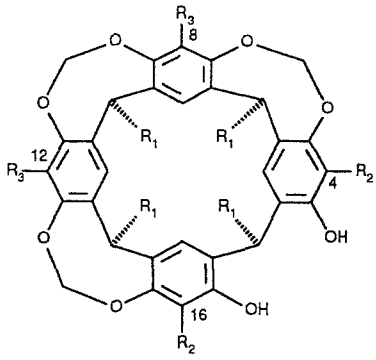
The formation of the tetrols **4** and **5** is generally believed to occur via the introduction of a methylene bridge at the distal position C (formation of A,C-di-bridged tetrol **4**) or at the proximal position B (formation of A,B-di-bridged tetrol **5**) of a mono-bridged hexol. The formation of an A,B-di-bridged tetrol without bromo atoms has been reported by Cram *et al.* [35]. In this case, no A,C-di-bridged tetrol could be detected. This selectivity can be attributed to the different acidities of the different phenolic moieties in the mono-bridged hexol. Due to the presence of the methylenedioxy bridge, the acidity of the phenolic hydroxyl group meta to this bridge increases, because the electron-releasing effect of a methyleneoxy substituent is generally smaller than that of a hydroxyl group [40].

When bromo substituents are present at the ortho positions of the phenolic hydroxyl groups, the selectivity is reversed. In this case the nucleophilic attack at the distal phenolic groups seems to be more favorable and the A,C-di-bridged tetrol **4a** is preferably formed. We believe that this change in selectivity can be attributed both to an inductive and a steric effect of the bulky bromo substituents. It is known that the pK_a of 2-bromophenol is 1.5 pK_a units lower than that of phenol [41]. Therefore the much smaller increase of the acidity due to the introduction of a methyleneoxy substituent is simply overruled. The bulky bromo substituents will also shield the hydroxyl groups and therefore hinder the attack of the incoming nucleophile. The flexibility of the different aromatic rings will now play an important role in determining which phenolic group will be alkylated first. Considering the mono-bridged hexol, which is the precursor of the tetrols, we believe that the *decreased* flexibility of the two aromatic rings connected via the methylenedioxy spacer mainly governs the selectivity of the reaction, i.e. that nucleophilic attack takes place preferentially at the distal phenolic groups.

TRANSFER OF FUNCTIONALITY

As was stated earlier (*vide supra*), **3** is an interesting compound in regard to selective functionalization of the upper rim, because of its lower degree of symmetry. Several strategies can be used to exploit the different chemical reactivity of the aromatic rings involved, one of which was recently used by Sorrell and Richard [24]. We have developed a very simple and straightforward procedure for the one-step synthesis of proximally functionalized cavitands **8** and **9** (Charts 1 and 2), in which a variety of functional groups can be easily introduced.

In an attempt to fully debrominate **3a** by treatment with excess *n*-BuLi in THF at -78°C, we observed that bromo-lithium exchange is not equally fast at all four positions. The same reaction with diol **3c** using only 5 equiv. of *n*-BuLi and quenching the reaction mixture with excess H_2O after a reaction time of only



8a $R_1 = CH_2CH_2C_6H_5$, R_2 = Br, R_3 = H

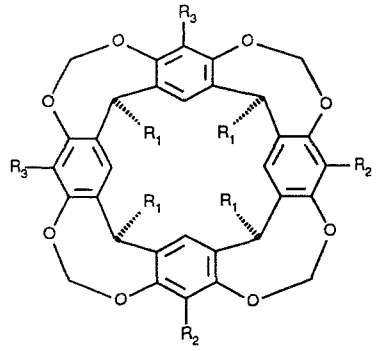
8b $R_1 = CH_2(CH_2)_9CH_3$, R_2 = Br, R_3 = H

8c $R_1 = CH_2(CH_2)_9CH_3$, R_2 = Br, R_3 = OH

8d $R_1 = CH_2CH_2C_6H_5$, R_2 = Br, $R_3 = SCH_3$

8e $R_1 = CH_2CH_2C_6H_5$, R_2 = Br, R_3 = I

Chart 1.



9a $R_1=CH_2CH_2C_6H_5$, R_2 = Br, R_3=H

9b $R_1=CH_2(CH_2)_9CH_3$, R_2 = Br, R_3=H

9c $R_1=CH_2(CH_2)_9CH_3$, R_2 = C(O)OMe, R_3=H

9d $R_1=CH_2(CH_2)_9CH_3$, R_2 = OH, R_3=H

9e $R_1=CH_2CH_2C_6H_5$, R_2 = OH, R_3=H

9f $R_1=CH_2(CH_2)_9CH_3$, R_2 = CN, R_3=H

9g $R_1=CH_2CH_2C_6H_5$, R_2 = Br, $R_3=SCH_3$

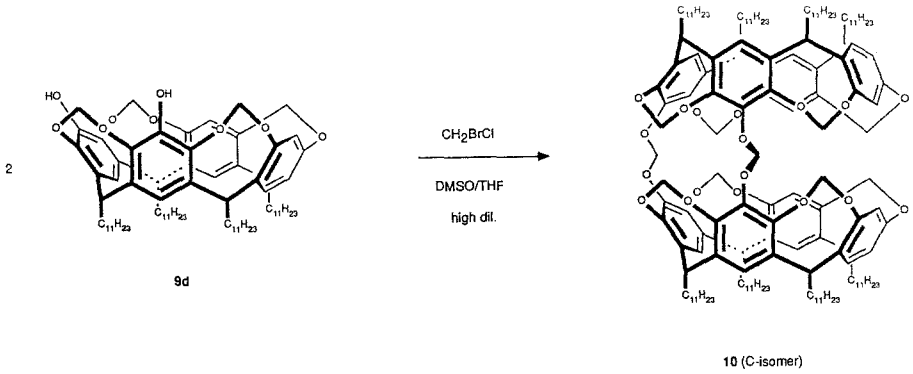
9h $R_1=CH_2CH_2C_6H_5$, R_2 = Br, R_3=I

Chart 2.

15 sec yielded the selectivity debrominated diol **8a** in 77% yield. In a similar way **8b** could be obtained in 76% yield from **3b**.

The ^{1}H-NMR spectra of **8a** and **8b** exhibit a characteristic singlet at about 6.5 ppm for the protons that are introduced. Definite proof for the regioselectivity was given by a single-crystal X-ray analysis of **8a** [23], which clearly showed that the remaining bromo substituents are adjacent to the free hydroxyl groups. The inhibition of bromo-lithium exchange at these two aromatic rings is due to the presence of the hydroxyl groups. Upon addition of *n*-BuLi, the hydroxyl groups are deprotonated first and this increases the electron density on the aromatic ring to such an extent, that bromo-lithium exchange is strongly disfavored. A similar lack of reactivity in bromo-lithium exchange reactions has previously been observed in the case of bromoanilines and cyanomethylphenyl bromides [42].

The tri-bridged diols **8a** and **8b** were converted quantitatively into the cavitands **9a** and **9b** with excess of CH_2BrCl and K_2CO_3 in refluxing CH_3CN for 24 h. Subsequently, the two remaining bromines could be easily substituted for a variety of functional groups, leaving the 8- and 12-positions unaffected. Treatment of **9b** with *n*-BuLi in THF at -100°C for 15 min followed by quenching with ClC(O)OMe gave diester **9c** in 60% yield. Quenching the lithiated product at -78°C with $B(OMe)_3$



Scheme 2.

followed by oxidation with basic H_2O_2 afforded diol **9d** in 62% yield. In this way diol **9e**, which was reported previously by Cram *et al.* [20] in an overall yield of 0.7% starting from the corresponding tetrabromooctol **1c**, could be prepared in an overall yield of 19%. Heating **9b** with CuCN in refluxing *N*-methylpyrrolidone for several hours gave the dicyano cavitand **9f** in almost quantitative (> 95%) yield.

Attempts to substitute **9a** at the 15- and 28-positions by direct iodination [43] or nitration failed and only starting material was recovered. This clearly demonstrates that the debrominated aromatic rings are not able to undergo electrophilic aromatic substitutions, although they are expected to be activated for this type of reaction. It is possible that the non-planar intermediate formed in electrophilic aromatic substitution reactions is energetically too unfavorable in the case of a fully bridged cavitand. Even bromination with NBS, a reaction which is generally believed to occur via a radical mechanism, did not give any reaction on these rings. Apparently, these positions have lost their reactivity upon bridging the *o*-hydroxyl groups with methylene bridges.

Another way to introduce functional groups at the debrominated rings is to quench the lithiated products, obtained by reaction of **3** with *n*-BuLi (*vide supra*), with electrophiles other than H^+. In order to carry out these reactions successfully, it turned out to be necessary to treat diol **3** with NaH, prior to lithiation, since considerable amounts of hydrogen were otherwise incorporated at the 8- and 12-positions. According to ^{1}H-NMR spectroscopy of the crude reaction mixtures, pretreatment of diol **3** with NaH decreased the amount of hydrogen incorporated to roughly half the original amount. This strongly suggests that the hydroxyl groups protonate the lithiated positions before reaction with another electrophile can take place. Such *in situ* protonation of the lithiated species formed has been described by Beak *et al.* [44].

When the lithiated product, obtained by reaction of **3d** with *n*-BuLi, was quenched with $B(OMe)_3$, we were able to isolate tri-bridged diol **8c** functionalized at the 8- and 12-positions with hydroxyl groups in 47% yield. In the same way, starting from **3c**, two thiomethyl (**8d**) or iodo (**8e**) groups could be intro-

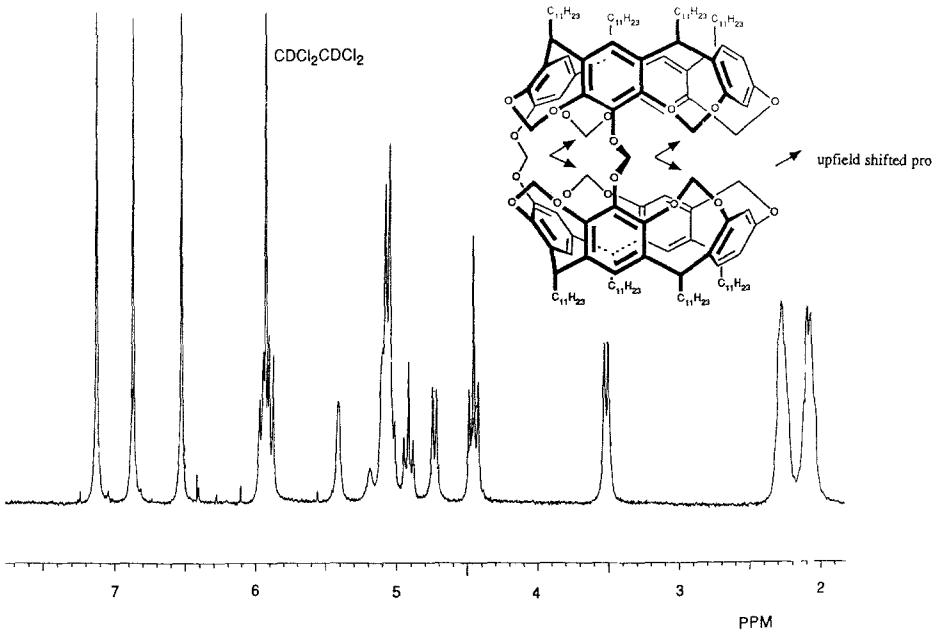


Fig. 2. ^{1}H-NMR spectrum of hemicarcerand **10** (isomer *C*) in $CDCl_2CDCl_2$ at 90°C.

duced. Because of serious problems in the purification of these compounds they were converted to the corresponding selectively functionalized cavitands **9g** and **9h** in overall yields of 25% and 20%, respectively. In these cases the yields were considerably lower than in the reaction starting from **3d** (47%). We cannot explain this decrease in yield, but we cannot rule out that, in addition to bromo-lithium exchange, reaction takes place at the CH_2CH_2Ph chains.

To illustrate the utility of selectively functionalized cavitands, we subjected diol **9d** to a coupling reaction with CH_2BrCl in order to synthesize for the first time a hemicarcerand which is only coupled by two proximal bridges (Scheme 2). The reaction was performed under Cram's high dilution conditions [20] in DMSO/THF. After a reaction time of 4 days, a colorless compound was obtained in 71% yield. This was identified by MS-FAB as the expected coupled product (M^+ = 2395). Although two diastereomers (denoted *C* and *Z*, analogously to recently published related hemicarcerands [35]) can be formed, ^{1}H-NMR spectroscopy strongly suggests that only one isomer is actually present. The spectrum is broad in $CDCl_3$ at room temperature, but sharpens up when measured in $CDCl_2CDCl_2$ at 90°C (Figure 2). This indicates that the molecule is flexible to a certain extent, something which was not seen for the hemicarcerands with three spacers prepared by Cram [20]. The most significant changes in the spectrum are the upfield shift for half of the inner and outer protons of the methylene bridges, shifting from 4.4 to 3.5 ppm and from 5.8 to 5.1 ppm, respectively. We believe that these marked upfield shifts can only be present in **10** (isomer *C*), because only in this isomer are

the methylene bridges able to enter into the molecular cavity of the opposite octol fragment, causing the upfield shift. This also implies that the hemicarcerand does not contain an enforced molecular cavity in which a guest molecule is complexed. This is in accordance with the ^{1}H-NMR and MS FAB spectra, in which no guest molecule could be detected.

The present work shows that in the bridging reaction of octols of type **1** with CH_2BrCl, the introduction of the fourth bridge is generally slower than the other three, and that the rate of the reaction is solvent dependent. This provides the synthetic methodology to prepare tri-bridged diols **3**. Reduction of the amount of CH_2BrCl to 2 equiv. yields considerable amounts of doubly bridged cavitands, preferentially the 1,3-bridged product **4**.

The different aromatic rings in the tri-bridged diols (**3**) exhibit different reactivities. Bromo-lithium exchange of two bromo substituents with *n*-BuLi provides an easy way to selectively functionalized cavitands of type **8**. After incorporation of the fourth bridge, the remaining two bromines can be substituted for a variety of functional groups, leading to selectively functionalized cavitands **9c–h**.

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