results obtained with the T-60 were also compared with the 300-MHz and the results agree closely. For example, the T-60 analysis of the benzaldehyde aldol products from diethyl ketone showed 21% syn, 79% anti (Table V), as compared to the values of 21% syn, 79% anti and 20% syn, 80% anti obtained in two analyses with the 300-MHz instrument. In the case of ethyl isopropyl ketone, the T-60 analysis showed no peak corresponding to the minor isomer (syn) but a careful analysis with 300-MHz instrument showed 98% for anti and 2% for the syn aldol. In a number of cases, the enolization produced essentially one of a pair of isomeric enolates. Since it is difficult to see very small amounts of the minor component against the background with T-60 instrument, we have indicated the products to be <3% for the minor isomer and >97% for the major isomer, although the spectrum itself shows only the major isomer.

At this stage of our studies, our aim was to explore the generation of enol borinates and not to explore their applications to aldol reactions. However, the quantitative aldolization of chiral ketones with various aldehydes such as aliphatic, α,β-unsaturated, and aromatic aldehydes with this reagent has already been demonstrated by isolating the products.[19] In the present study, the aldolization with benzaldehyde was used only as a tool to determine the enolate geometry. The ^{1}H NMR spectra of the benzaldehyde aldol product mixture give the syn/anti ratio which essentially corresponds to the Z/E ratio of the enol borinates. The syn/anti ratio of the isolated aldol products might be different from that of the crude product mixture since some of the aldol products might be lost during the separation process, and so no attempt was made to determine this ratio by purification.

Acknowledgment. We gratefully acknowledge financial support from the United States Office of Naval Research, which made this research possible.

Supplementary Material Available: ^{1}H NMR spectra of the enol borinates (**2, 7, 8, 13, 18, 22, 23, 29, 33, 34, 35, 37, 38**) and those of the corresponding benzaldehyde aldol products of the enol borinates (**8, 9, 12**) selected as representatives from each table (15 pages). Ordering information is given on any current masthead page.

Oxacyclophanes Based on a *m*-Terphenyl Framework

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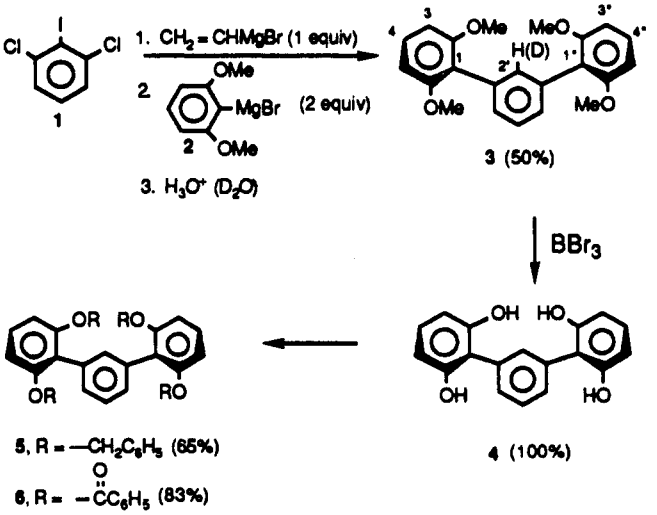
m-Terphenyl tetraphenol **4** (Scheme I) and tetrabenzyl alcohol **19** (Scheme IV) were efficiently synthesized from 2,6-dichloroiodobenzene and an appropriate aryl Grignard, using tandem aryne technology. Each tetrol was used to construct bicyclic oxacyclophanes by linking the 3,3″ and 5,5″ substituents with bis-alkylating or acylating agents. Examples are **7, 14, 15,** and **20–24**. Only the meta isomer of xylylene dichloride formed a bicyclic oxacyclophane with **4**; the ortho and para isomers gave polymers. However all three isomers gave oxacyclophanes (i.e., **10–12**) with the diphenol **9** (only one link across the *m*-terphenyl framework) and bicyclic oxacyclophanes with **19** (i.e., **20–22**), where each link contains two additional atoms. Para-linked **12** and **21** show restricted rotation of the *p*-xylylene rings. Two noninterconvertible conformers were obtained when the *m*-xylylene linking group contained a vicinal methoxy substituent (i.e., **15uu** and **15ud**).

m-Terphenyls appropriately substituted in the "outer" rings form an excellent base for the construction of novel cyclophanes (cuppedophanes[1a–c] or cappedophanes[1a,b,d]). The required *m*-terphenyls can be assembled in just a few steps, the first one being the tandem aryne addition of an aryl Grignard reagent to a 1,2,3-trihalobenzene.[2] In examples described to date, cyclophanes were prepared in which the links between the "outer" *m*-terphenyl rings contained sulfur[1a,b] or nitrogen[1c] atoms. We describe here the first examples of oxacyclophanes with this design.[3]

Results and Discussion

The first template to be used as the framework for oxacyclophane construction was tetraphenol **4**. It was synthesized (Scheme I) in two steps from 2,6-dichloroiodobenzene (**1**).[4] Treatment of **1** with 1 equiv of vinylmagnesium bromide at −22 °C gave (2,6-dichlorophenyl)magnesium bromide which, when added to a refluxing THF solution of (2,6-dimethoxyphenyl)magnesium bromide, underwent tandem aryne elimination–nucleophilic addition to give, after aqueous quench, 2,2″,6,6″-tetramethoxy-*m*-terphenyl (**3**) in 50% yield. ^{1}H and ^{13}C NMR spectra confirmed the molecule's C_{2v} symmetry. The proton spectrum showed a singlet for the four methoxyls and a mutually coupled doublet and triplet for the $H_{3,3'',5,5''}$

Scheme I



(1) (a) Vinod, T. K.; Hart, H. *J. Am. Chem. Soc.* **1988**, *110*, 6574–6575. (b) Vinod, T. K.; Hart, H. *J. Org. Chem.* **1990**, *55*, 881–890. (c) Vinod, T. K.; Hart, H. *Ibid.* **1990**, *55*, 5461–5466. (d) Vinod, T. K.; Hart, H. *Ibid.* **1991**, *56*, 5630–5640.

(2) (a) Du, C.-J. F.; Hart, H.; Ng, K.-K. D. *J. Org. Chem.* **1986**, *51*, 3162–3165. (b) Du, C.-J. F.; Hart, H. *Ibid.* **1987**, *52*, 4311–4314.

(3) For a preliminary account, see: Grewal, R. S.; Hart, H. *Tetrahedron Lett.* **1990**, *31*, 4271–4274.

(4) Bolton, R.; Sandall, J. P. B. *J. Chem. Soc., Perkin Trans. 2* **1977**, 278–280.

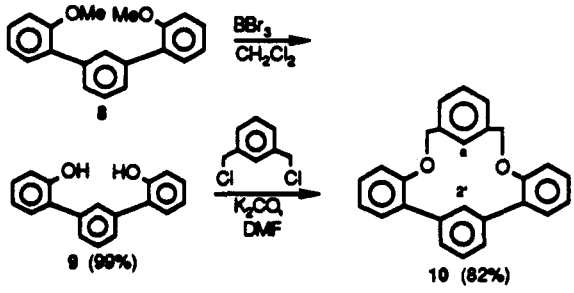
0022-3263/92/1957-2721$03.00/0

Table I. ^{1}H NMR Spectra of 7, 14, 20, and 21

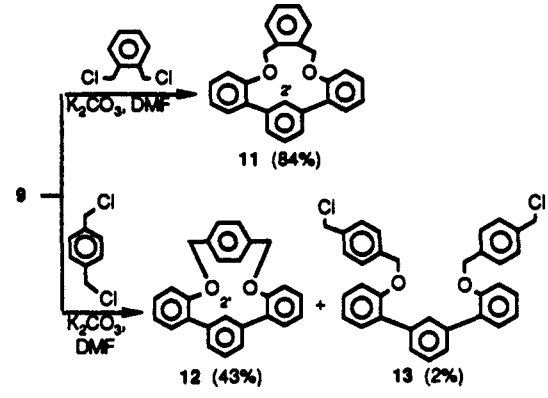
compd	CH_2	$H_{2'}$	$H_{3,3'',5,5''}$	H_b	H_c	$H_{4',6'}$	$H_{4,4''}$	$H_{5'}$	H_a
7	5.02, 5.09 (AB q, 12.3)	6.60 (t, 1.7)	6.80 (d, 8.3)	6.95 (dd, 7.7, 1.1)	7.10 (t, 7.7)	7.19 (dd, 7.4, 1.7)	7.32 (t, 8.3)	7.41 (t, 7.4)	7.43 (br s)
14		7.00 (t, 1.6)	7.83 (d, 8.5)	8.16 (dd, 7.8, 1.8)	7.56 (t, 7.8)	7.02–7.14 (m)	7.55 (t, 8.5)	7.85 (m)	8.26 (t, 1.8)
20	3.98 (s, 8 H); 4.50, 4.59 (AB q, 12.5)	6.71 (t, 1.7)	*a*	7.58 (d, 7.7)	7.45 (t, 7.7)	6.86 (dd, 7.5, 1.7)	*a*	7.13 (t, 7.6)	6.95 (s)
21	3.33, 3.46 (AB q, 11.6); 4.60, 4.62 (AB q, 11.7)	6.21 (t, 1.5)	7.50 (d, 7.1)	*b*	*b*	7.02 (dd, 7.6, 1.5)	7.40 (t, 7.1)	7.36 (t, 7.6)	*b*

[a] Multiplet at 7.21–7.34. [b] The *p*-xylylene ring protons appeared as two 4-proton doublets at δ 7.06 and 7.14, $J \approx 1$ Hz.

Scheme II



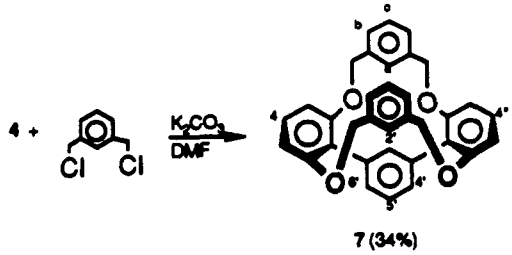
Scheme III



and $H_{4,4''}$ protons, respectively. The aromatic protons of the central ring appeared as a four-proton multiplet. The ^{13}C NMR spectrum showed only 9 unique carbons for this C_{22} compound. Quenching with D_2O gave the 2′-*d* analogue whose spectra were identical except that the central ring multiplet integrated for only three protons.

Cleavage of the methoxyl groups with BBr_3 was quantitative to give **4**, mp 213–215 °C. The O*H* protons appeared as a broad singlet at δ 9.00 and the ^{13}C NMR spectrum showed only eight signals as required for C_{2v} symmetry. As models for the oxacyclophanes described below, **4** was converted in conventional ways to its tetrabenzyl derivative **5**, mp 161–162 °C, and its tetrabenzoyl derivative **6**, mp 223–225 °C.

The first oxacyclophane **7** was obtained in 34% yield by treatment of **4** with *m*-xylylene dichloride and K_2CO_3 in DMF. Each magnetically unique proton was easily discerned in its ^{1}H NMR spectrum (see Table I). The highest field aromatic proton was $H_{2'}$ (δ 6.60, triplet, weakly coupled with $H_{4',6'}$) shielded by the *m*-xylylene aryl rings, whereas the lowest field aromatic protons were H_a (δ 7.43, br s) in the deshielding region of the central ring. The ^{13}C NMR spectrum showed 13 signals for the 34 carbons, consistent with C_{2v} symmetry.



For comparison with **7**, we prepared the corresponding dioxacyclophane **10** from the known dimethoxyterphenyl **8**[2a] (Scheme II). Coupling of *m*-xylylene dichloride with diphenol **9** proceeded in much higher yield than with tetraphenol **4** (82% vis-a-vis 34%), an indication that introduction of the second link in **7** requires a constrained geometry and perhaps some strain. The more flexible nature of **10** cf. **7** was also evident from its ^{1}H NMR spectrum. The methylene products in **10** appeared as a sharp singlet (δ 5.14), indicating that the central *m*-terphenyl ring and/or the bridging aryl ring are not conformationally rigid. Although it was not possible to uniquely assign $H_{2'}$ and H_a, they appeared as a triplet and a slightly broadened singlet at rather high field (δ 7.71 and 7.88, not necessarily respectively), unlike the corresponding protons in **7**. All of the remaining aryl protons in **10** were multiplets, unlike the easily assigned unique aryl signals in **7**. Thus **10** is clearly a much more flexible molecule than **7**.

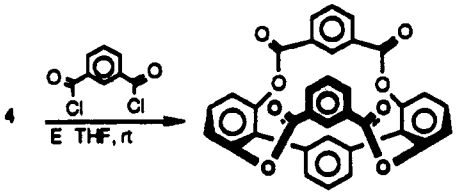
Another indication of the strain in **7** is that it was not possible to prepare the corresponding *o*- or *p*-xylylene analogues. Attempted coupling of tetraphenol **4** with *o*- or *p*-xylylene dichlorides gave only polymeric products. On the other hand, coupling of these dihalides with diphenol **9** readily gave the corresponding dioxacyclophanes **11** and **12** (Scheme III). The yield of the ortho cyclophane **11** was nearly twice that of the para cyclophane **12**, indicative of the greater strain in the latter. Also, **12** was accompanied by a small amount of the uncyclized bis-ether **13**.

The ^{1}H NMR spectra of **11** and **12** show some interesting features. In each, the methylene protons appear as a sharp singlet (**11**, δ 5.14; **12**, δ 4.84). In **11**, $H_{2'}$ is the lowest field aromatic proton (δ 8.17), presumably deshielded by the oxygens, whereas in **12** that proton occurs at highest field (δ 6.39), possibly shielded by the *p*-xylylene ring. The protons of that ring appeared as a sharp singlet (δ 6.67), indicating that there is a mechanism whereby the aryl protons on each "side" of the *p*-xylylene ring equilibrate.[1c]

These results indicate that the introduction of the second bridge linking the "outer" *m*-terphenyl rings in **7** is accompanied by some conformational constraints and strain that is exacerbated when the link is too short (*o*-

xylylene) or too long (p-xylylene).

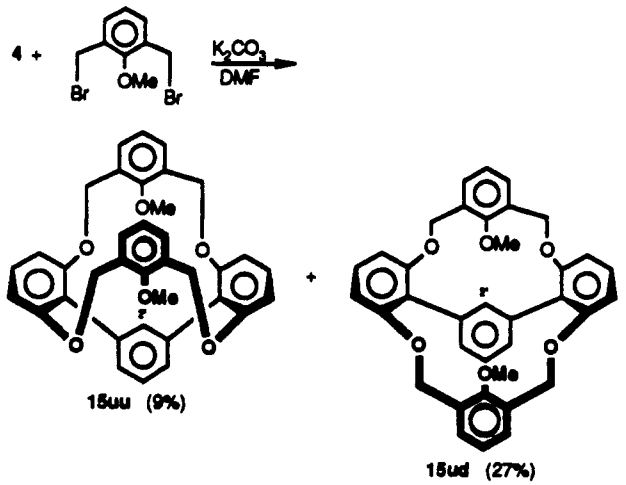
It seemed interesting to see the effect of changing from alkylation (S_N2) to acylation (nucleophilic addition–elimination). Treatment of 4 with isophthaloyl chloride (THF, Et_3N) gave a modest yield of 14, mp 325–327 °C. As with



14 (33%)

7, 14 has a rather rigid structure that permits each type of aryl proton to be rigorously assigned. The ^1H NMR spectra of 7 and 14 are compared in Table I. Although there is a general downfield shift in the spectrum on replacing the CH_2 groups of 7 by the C=O groups of 14, certain peaks retain their same relative positions. Thus $H_{2'}$ is the most shielded and H_a is the most deshielded aryl proton in both spectra, presumably for the reasons given above in the case of 7.

Replacement of H_a by Methoxyl Groups in 7. Formation of an Oxacyclophane with Noninterconvertible Conformers. As described above, it seems that tetraoxacyclophane 7 is conformationally quite rigid and has a fairly crowded structure. It was of interest to increase the crowding in 7 by replacing the hydrogens H_a with larger groups. Accordingly, tetraphenol 4 was coupled with 2,6-bis(bromomethyl)anisole.[5] Two products were isolated, assigned for reasons outlined below the structures **15uu** (9%, mp 257–259 °C) and **15ud** (27%, mp 294–296 °C). These two products, which differ only in conformation, were not interconverted in DMSO-d_6 at temperatures up to 130 °C (VT NMR studies).

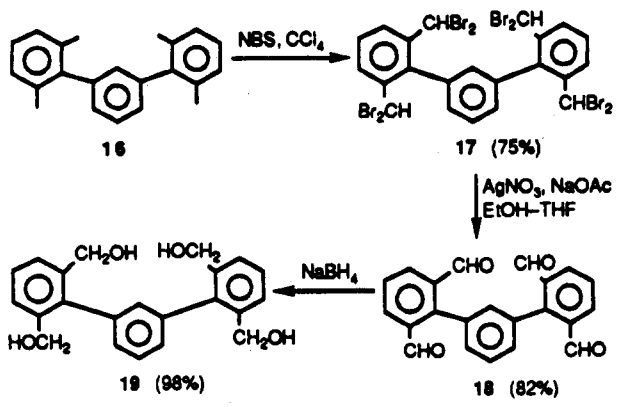


15uu (9%) 15ud (27%)

The product (**15uu**) assigned the "up-up" conformation (these descriptors refer to the orientation of the anisyl rings relative to the m-terphenyl moiety) showed only one 6-proton singlet for the OCH_3 protons (δ 3.14), whereas the "up-down" conformer (**15ud**) showed two 3-proton methoxyl singlets (δ 3.24, 3.56). That the second product must be up-down is clear, but the first product could have the up-up or down-down arrangement of the methoxyls (both of which have C_{2v} symmetry); indirect evidence favoring the up-up arrangement is given below.

The methylene signals corroborate the molecular symmetry conclusions based on the methoxyl signals. In **15uu**,

Scheme IV



these protons appeared as two geminally coupled 4-proton doublets (δ 4.77 and 5.46, J = 11.5 Hz), whereas in **15ud** these protons appeared as two sets of 2-proton doublets (at δ 4.70 and 5.48, J = 11.5 Hz, and at δ 4.73 and 5.10, J = 9.5 Hz).

An unambiguous assignment of all the aromatic protons in each conformer is not possible without extensive labeling experiments, but one important feature stands out. $H_{2'}$ in **15uu** appears at exceptionally high field for an aromatic proton (δ 3.84, t, J = 1.8 Hz), highly shielded as a consequence of its location between the two anisyl rings. The same proton in **15ud** is also shielded, but considerably less so (δ 5.70, t, J = 1.7 Hz). The identity of these protons was unequivocally established by deuterium labeling (using **4–2′d** as the starting precursor).

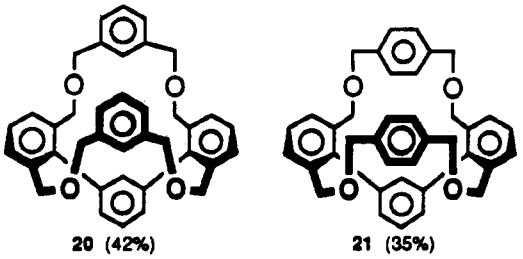
NOE experiments helped to indirectly favor the **uu** vis-a-vis **dd** arrangement for the C_{2v} conformer. Irradiation[6] of the methoxyl singlet at δ 3.56 in **15ud** resulted in a 5% enhancement of the signal at δ 5.70 due to $H_{2'}$; there was no effect on $H_{2'}$ when the methoxyl singlet at δ 3.24 was irradiated. Models show that the methoxyl group is much closer to $H_{2'}$ in the "down" link than in the "up" link. Thus we assign the peak at δ 3.56 to the methoxyl on the down link. The chemical shift similarity of the methoxyl protons in the C_{2v} isomer (δ 3.14) to that of the up branch in **15ud** (δ 3.24) and the fact that no NOE of $H_{2'}$ (δ 3.84) was observed when the methoxyls (δ 3.14) in the C_{2v} conformer were irradiated all support the up-up arrangement for that conformer. The complete absence of the down-down conformer is probably a consequence of steric strain.

Oxacyclophanes Based on Tetrabenzyl Alcohol 19. As an alternative m-terphenyl base to tetraphenol 4, we prepared its homologous tetrabenzyl alcohol **19** as shown in Scheme IV. The synthesis is similar to that previously described[1b] for the corresponding 2′-bromo analogues. Tetramethylterphenyl **16** was converted with excess NBS to the tetrakis(dibromomethyl)terphenyl **17**, which was hydrolyzed with the aid of silver nitrate to tetraaldehyde **18**, mp 208 °C. Sodium borohydride reduction to tetrabenzyl alcohol **19**, mp 192 °C, was essentially quantitative.

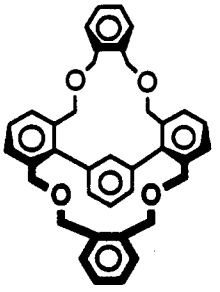
In contrast with tetraphenol 4, it was possible to obtain oxacyclophanes **20–22** from the reaction of all three xylylene dichlorides with **19**. As with **4**, all of the aromatic protons in **20** could be readily assigned (Table I). Again $H_{2'}$ was at highest field (δ 6.71), comparable to the same proton in 4 (δ 6.60), shielded by the m-xylylene rings. Not surprisingly, this proton was even more shielded (δ 6.21) in the para isomer **21**. In the ortho isomer **22**, however, $H_{2'}$ appeared in the mid-range of aryl chemical shifts, between two multiplets for the remaining aryl protons. It

(5) Vögtle, F.; Neumann, P. *Tetrahedron* **1970**, *26*, 5299–5318.

(6) 1D NOE difference spectrum at 300 MHz and 25 °C.



20 (42%) 21 (35%)

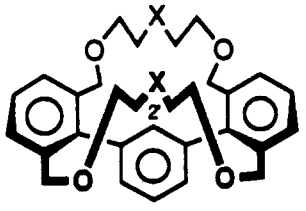


22 (20%)

seems that **22** has a much more flexible structure than its regioisomers and that the *o*-xylylene rings are oriented out rather than face-to-face. A similar situation has been observed with the sulfur analogues of **20–22**.[1b]

The ^1H NMR and ^{13}C NMR spectra of the para isomer **21** show other interesting features. The *p*-xylylene protons appeared as two sets of 4-proton signals, at δ 7.06 and 7.14, with a weak meta coupling (~1 Hz) between them. Clearly the *p*-xylylene rings are rigid and not freely rotating. Consistent with this conclusion, the ^{13}C spectrum of **21** showed 13 peaks rather than the 12 that would have been expected had there been some mechanism for equilibrating the "top" and "bottom" carbons of the *p*-xylylene rings.

Finally, for comparison with the aryl-bridged oxacyclophanes described above, we prepared the aliphatically linked oxacyclophanes **23** and **24** from **19** and the corresponding ditosylates. The yields were low (15–16%). $H_{2'}$



23 (X = CH_2)
24 (X = O)

appeared at slightly higher field in **24** (δ 7.05) than in **23** (δ 7.19), possibly due to some shielding by the central oxygen, but as expected, this proton appeared at lower field than in the aryl-bridged analogues.[7]

In summary, we have described a number of oxacyclophanes based on a *m*-terphenyl framework in which the two outer rings are approximately orthogonal to the central ring. Synthesis of the necessary starting materials **4** and **19** is fairly short, and a variety of linking groups can be used. Whether or not these materials will be useful as hosts or as complexing agents remains to be seen.

Experimental Section

General Procedures. Melting points are uncorrected. Silica gel for chromatography was 100–200 mesh. ^1H and ^{13}C NMR spectra were recorded at 300 MHz and 75 MHz, respectively, in $CDCl_3$ unless otherwise specified. Mass spectra were obtained at the Michigan State University mass spectrometry facility, supported in part by a grant (DRR-00480) from the Biotechnology Resources Branch of the National Institutes of Health.

2,2″,6,6″-Tetramethoxy-1,1′:3′,1″-terphenyl (3). Vinylmagnesium bromide (24.5 mL of a 1.0 M solution in THF) was added (Ar, –22 °C) to a stirred solution of 2,6-dichloroiodobenzene[4] (7.0 g, 25.7 mmol) in dry THF (70 mL). After 2 h, the mixture was added via a cannula to a refluxing solution of (2,6-dimethoxyphenyl)magnesium bromide [prepared from 2,6-dimethoxybromobenzene[8] (11.7 g, 53.9 mmol) and Mg turnings (1.31 g, 53.9 mg-atom) in dry THF (140 mL)]. After 3 h of additional reflux the mixture was cooled and quenched with dilute HCl, and the THF was removed (Rotavap). Water was added and the mixture was extracted with CH_2Cl_2 (3×). Combined organic extracts were dried ($MgSO_4$) and concentrated, and the residue was chromatographed on silica gel using 1:3 CH_2Cl_2/hexanes as eluent to give 4.47 g (50%) of **3**, mp 172–174 °C (recrystallized from CH_2Cl_2/hexanes): ^1H NMR δ 3.75 (s, 12 H, OCH_3), 6.67 (d, J = 8.3 Hz, 4 H, $H_{3,3'',5,5''}$), 7.28 (t, J = 8.3 Hz, 2 H, $H_{4,4''}$), 7.31–7.48 (m, 4 H, central arom ring); ^{13}C NMR δ 55.8, 104.4, 120.0, 126.9, 128.5, 129.6, 133.1, 133.9, 158.1; MS (FAB, *m*-nitrobenzyl alcohol matrix)[9] 351 (MH^+). Anal. Calcd for $C_{22}H_{22}O_4$: C, 75.41; H, 6.33. Found: C, 75.43; H, 6.26. For **3-2′*d***, the same procedure was followed except that the reaction was quenched with D_2O (5 mL). The ^1H NMR spectrum was the same as for **3** except that the multiplet at δ 7.31–7.48 integrated for 3 H; MS (FAB) 352 (MH^+).

1,1′:3′,1″-Terphenyl-2,2″,6,6″-tetrol (4). BBr_3 (15.0 mL of 1.0 M solution in CH_2Cl_2) was added (Ar, rt) to a solution of tetraether **3** (2.41 g, 6.88 mmol) in dry CH_2Cl_2 (70 mL). The mixture was heated at reflux for 1 h, quenched with concentrated HCl, and evaporated to dryness (Rotavap). The residue was dissolved in ethyl acetate, passed through a short silica gel column, and evaporated, and the resulting solid was washed with CH_2Cl_2 to give 2.02 g (100%) of **4**, mp 213–215 °C: ^1H NMR (DMSO-d_6) δ 6.38 (d, J = 8.1 Hz, 4 H, $H_{3,3'',5,5''}$), 6.88 (t, J = 8.1 Hz, 2 H, $H_{4,4''}$), 7.13–7.39 (m, 4 H, central arom ring), 9.00 (br s, 4 H, OH); ^{13}C NMR (DMSO-d_6) δ 107.0, 116.3, 126.5, 128.2, 129.2, 133.8, 134.0, 156.0; MS (FAB) 295 (MH^+); HRMS calcd for $C_{18}H_{15}O_4$ (MH^+) 295.0971, found 295.0964. The deuterio analogue **4-2′*d***, similarly prepared from **3-2′*d***, had an identical ^1H NMR spectrum except for the multiplet at δ 7.13–7.39, which integrated for 3 H; MS (FAB) 296 (MH^+).

2,2″,6,6″-Tetrakis(benzyloxy)-1,1′:3′,1″-terphenyl (5). A solution of tetrol **4** (150 mg, 0.51 mmol) in dry DMF (30 mL) was added dropwise (Ar, 1 h) to a stirred suspension of K_2CO_3 (4.0 g) and benzyl bromide (523 mg, 3.06 mmol) in dry DMF (30 mL). The mixture was stirred at rt for 15 h and then evaporated to dryness. The residue was dissolved in CH_2Cl_2 and filtered to remove inorganic salts, and the filtrate was concentrated. The residue was chromatographed (silica gel, 1:1 CH_2Cl_2/hexanes) to give 217 mg (65%) of **5**, mp 161–162 °C (recrystallized from CH_2Cl_2/hexanes): ^1H NMR δ 4.92 (s, 8 H, CH_2), 6.68 (d, J = 8.3 Hz, 4 H, $H_{3,3'',5,5''}$), 7.08–7.22 (m, 23 H), 7.45 (m, 2 H), 7.60 (m, 1 H); ^{13}C NMR δ 70.6, 107.3, 122.0, 126.6, 127.2, 128.1, 128.3, 129.5, 133.2, 133.8, 137.4, 157.0 (one signal overlapped); MS (FAB) 655 (MH^+); HRMS calcd for $C_{46}H_{39}O_4$ (MH^+) 655.2849, found 655.2887. Anal. Calcd for $C_{46}H_{38}O_4$: C, 84.38; H, 5.85. Found: C, 84.25; H, 5.94.

2,2″,6,6″-Tetrakis(benzoyloxy)-1,1′:3′,1″-terphenyl (6). A solution of tetrol **4** (100 mg, 0.34 mmol) in dry THF (30 mL) was added dropwise (Ar, 1 h) to a stirred solution of benzoyl chloride (382 mg, 2.72 mmol) and triethylamine (0.42 mL, 3.0 mmol) in dry THF (30 mL). The mixture was stirred at rt for 15 h and then evaporated. The residue was dissolved in CH_2Cl_2 and washed with aqueous Na_2CO_3, and the aqueous layer was re-extracted with CH_2Cl_2 (2×). The combined organic extracts were dried ($MgSO_4$) and concentrated. The residue was chromatographed (silica gel, 1:1 CH_2Cl_2/hexanes) to give 200 mg (83%) of **6**, mp 223–225 °C (recrystallized from CH_2Cl_2/hexanes): ^1H NMR δ 7.06 (t, J = 7.6 Hz, 1 H, $H_{5'}$), 7.15–7.25 (m, 10 H), 7.30 (d, J =

(7) Except for **22**, where this proton may actually be in the deshielding region of the *o*-xylylene rings.

(8) Eade, R. A.; McDonald, F. J.; Pham, H.-P. *Aust. J. Chem.* **1978**, *31*, 2699–2706.

(9) All FAB MS were determined using this matrix.

8.0 Hz, 4 H, $H_{3,3'',5,5''}$), 7.44 (t, J = 7.4 Hz, 4 H, para hydrogens of the benzoyl groups), 7.51 (t, J = 8.2 Hz, 2 H, $H_{4,4''}$), 7.55–7.64 (m, 8 H), 7.68 (m, 1 H); ^{13}C NMR δ 120.5, 128.0, 128.35, 128.39, 128.7, 128.9, 129.4, 130.0, 131.5, 132.0, 133.4, 149.3, 164.9; MS (FAB) 711 (MH^+). Anal. Calcd for $C_{46}H_{30}O_8$: C, 77.74; H, 4.25. Found: C, 77.80; H, 4.25.

Coupling of Tetraphenol 4 with m-Xylylene Dichloride. Tetraoxacyclophane 7. To a solution of tetrol 4 (300 mg, 1.02 mmol) in dry DMF (50 mL) was added 357 mg (2.04 mmol) of 1,3-bis(chloromethyl)benzene, and the resulting mixture was added dropwise over 10–12 h (Ar, rt) to a stirred suspension of anhydrous K_2CO_3 (5.0 g) in dry DMF (50 mL). Two hours after addition was complete, the mixture was evaporated to dryness. The residue was taken up in CH_2Cl_2 and filtered to remove inorganic salts. The filtrate was concentrated and the residue was recrystallized from hexanes/CH_2Cl_2 to give 172 mg (34%) of 7, mp 270–272 °C: ^1H NMR, see Table I; ^{13}C NMR δ 72.1, 108.6, 125.2, 126.0, 127.4, 127.7, 127.8, 128.9, 129.0, 132.2, 134.8, 138.0, 157.9; MS (FAB) 499 (MH^+); HRMS calcd for $C_{34}H_{27}O_4$ (MH^+) 499.1910, found 499.1878. Anal. Calcd for $C_{34}H_{26}O_4$: C, 81.91; H, 5.26. Found: C, 81.96; H, 5.30.

Two Conformers of Dimethoxytetraoxacyclophane 15. The coupling of tetrol 4 with 2,6-bis(bromomethyl)anisole[5] was carried out on a 1.0-mmol scale as described for 7. The crude product was chromatographed on silica gel using 15% ethyl acetate in hexanes as eluent. The product to elute first was **15uu** (50 mg, 9%), mp 257–259 °C (recrystallized from hexanes/CH_2Cl_2): ^1H NMR δ 3.14 (s, 6 H, OCH_3), 3.84 (t, J = 1.8 Hz, 1 H, $H_{2'}$), 4.77 (d, J = 11.5 Hz, 4 H, CH_2), 5.46 (d, J = 11.5 Hz, 4 H, CH_2), 6.65–6.79 (m, 8 H), 6.98 (t, J = 7.8 Hz, 1 H, $H_{5'}$), 7.02 (d, J = 8.2 Hz, 4 H), 7.42 (t, J = 8.2 Hz, 2 H); ^{13}C NMR δ 63.2, 71.5, 114.5, 122.2, 126.4, 128.1, 129.0, 129.5, 130.2, 130.3, 131.3, 136.0, 157.9, 158.6; MS (FAB) 559 (MH^+). Anal. Calcd for $C_{36}H_{30}O_6$: C, 77.40; H, 5.41. Found: C, 77.41; H, 5.50.

The second product to elute was **15ud** (152 mg, 27%), mp 294–296 °C (recrystallized from hexanes/CH_2Cl_2): ^1H NMR δ 3.24 (s, 3 H, OCH_3), 3.56 (s, 3 H, OCH_3), 4.70 (d, J = 11.5 Hz, 2 H, CH_2), 4.73 (d, J = 9.5 Hz, 2 H, CH_2), 5.10 (d, J = 9.5 Hz, 2 H, CH_2), 5.48 (d, J = 11.5 Hz, 2 H, CH_2), 5.70 (t, J = 1.7 Hz, 1 H, $H_{2'}$), 6.60–6.82 (m, 7 H), 6.86 (t, J = 7.4 Hz, 1 H, $H_{5'}$), 6.95–7.05 (m, 3 H), 7.15 (d, J = 7.4 Hz, 2 H, $H_{4',6'}$), 7.39 (t, J = 8.2 Hz, 2 H); ^{13}C NMR δ 59.7, 63.1, 69.4, 71.9, 107.2, 113.7, 121.8, 122.0, 126.2, 127.3, 128.8, 128.9, 129.6, 130.7, 131.2, 131.5, 132.0, 134.3, 157.2, 158.8, 158.9, 160.7; MS (FAB) 559 (MH^+). Anal. Calcd for $C_{36}H_{30}O_6$: C, 77.40; H, 5.41. Found: C, 77.54; H, 5.53.

The 2'-deuterio analogues of **15uu** and **15ud** were similarly prepared from tetrol **4-2'd**. Their ^1H NMR spectra were as above except that the triplets at δ 3.84 and 5.70, respectively, were absent; MS (FAB) 560 MH^+ for each conformer.

2,2''-Dimethoxy-1,1':3',1''-terphenyl (8). The procedure was analogous to that for 3 except that the aryl Grignard reagent was (2-methoxyphenyl)magnesium bromide [prepared from 2-methoxybromobenzene (10.1 g, 53.9 mmol) and Mg turnings (1.35 g, 55.5 mg-atom) in dry THF (140 mL)]. The crude product was recrystallized from hexanes/CH_2Cl_2 to give 6.3 g (85%) of 8, mp 97–98 °C (lit.[2a] mp 97–98.5 °C); ^1H NMR δ 3.83 (s, 6 H, OCH_3), 6.98–7.10 (m, 4 H), 7.30–7.57 (m, 7 H), 7.70 (t, J = 1.8 Hz, 1 H, $H_{2'}$); ^{13}C NMR δ 55.5, 111.2, 120.8, 127.5, 128.2, 128.5, 130.7, 130.8, 131.0, 138.1, 156.5.

1,1':3',1''-Terphenyl-2,2''-diol (9). BBr_3 (10.3 mL of a 1.0 M solution in CH_2Cl_2) wad added (Ar, rt), to a solution of 8 (3.0 g, 10.3 mmol) in dry CH_2Cl_2 (100 mL), and the mixture was heated at reflux for 2 h. The reaction was quenched with concentrated HCl and the mixture was evaporated to dryness (Rotavap). The residue was taken up in ethyl acetate and passed through a short silica gel column. The effluent was concentrated and the residue was triturated with CH_2Cl_2/hexanes to give 2.68 g (99%) of 9, mp 119–121 °C: ^1H NMR δ 5.20 (br s, 2 H, OH), 6.95–7.06 (m, 4 H), 7.24–7.34 (m, 4 H), 7.49–7.68 (m, 4 H); ^{13}C NMR δ 116.0, 121.0, 127.8, 128.2, 129.2, 129.7, 129.9, 130.3, 137.90, 152.3; MS (FAB) 262 (M^+). Anal. Calcd for $C_{18}H_{14}O_2$: C, 82.42; H, 5.38. Found: C, 82.44; H, 5.30.

Coupling of Diol 9 with m-Xylylene Dichloride. Dioxacyclophane 10. To a solution of diol 9 (300 mg, 1.14 mmol) in dry DMF (50 mL) was added 200 mg (1.14 mmol) of 1,3-bis(chloromethyl)benzene, and the resulting solution was added (Ar, rt) dropwise over 10–12 h to a stirred mixture of anhydrous K_2CO_3 (5.0 g) in dry DMF (50 mL). Two hours after addition was complete, the mixture was evaporated to dryness (Rotavap). The residue was taken up in CH_2Cl_2 and filtered, and the filtrate was concentrated. The residue was chromatographed on silica gel using 1:1 CH_2Cl_2/hexanes as eluent to give 343 mg (82%) of 10, mp 170–171 °C (recrystallized from hexanes/CH_2Cl_2): ^1H NMR δ 5.14 (s, 4 H, CH_2), 7.01–7.13 (m, 6 H), 7.18–7.25 (m, 1 H), 7.30–7.40 (m, 6 H), 7.48–7.55 (m, 1 H), 7.71 (t, J = 1.7 Hz, 1 H), 7.88 (s, 1 H); ^{13}C NMR δ 69.4, 113.3, 121.3, 124.8, 126.1, 127.6, 128.3, 128.4, 128.8, 131.1, 132.1, 132.9, 138.1, 138.6, 155.9; MS (FAB) 364 (M^+). Anal. Calcd for $C_{26}H_{20}O_2$: C 85.69; H, 5.53. Found: C, 85.70; H, 5.69.

o-Dioxacyclophane 11. The procedure was the same as for 10 except that the dichloride was 1,2-bis(chloromethyl)benzene; yield 352 mg (84%), mp 258–260 °C: ^1H NMR δ 5.14 (s, 4 H, CH_2), 7.12–7.20 (m, 2 H), 7.32–7.53 (m, 13 H), 8.17 (t, J = 1.8 Hz, 1 H, $H_{2'}$); ^{13}C NMR δ 71.4, 118.1, 123.0, 126.7, 128.8, 129.2, 129.3, 130.6, 132.5, 132.8, 133.6, 136.1, 137.2, 156.5; MS (FAB) 364 (M^+). Anal. Calcd for $C_{26}H_{20}O_2$: C, 85.69; H, 5.53. Found: C, 85.79; H, 5.65.

p-Dioxacyclophane 12. The procedure was the same as for 10 except that the dichloride was 1,4-bis(chloromethyl)benzene; yield 180 mg (43%), mp 197–199 °C: ^1H NMR δ 4.84 (s, 4 H, CH_2), 6.39 (t, J = 1.8 Hz, 1 H, $H_{2'}$), 6.67 (s, 4 H, p-xylylene ring), 7.10–7.40 (m, 11 H); ^{13}C NMR δ 79.2, 123.7, 124.4, 126.1, 128.5, 129.1, 129.3, 131.0, 131.6, 136.0, 137.2, 139.0, 157.1; MS (FAB) 364 (M^+). Anal. Calcd for $C_{26}H_{20}O_2$: C, 85.69; H, 5.53. Found: C, 85.74; H, 5.59.

Continued elution gave a small amount (11 mg, 2%) of a second product, the bis-ether 13, mp 102–104 °C: ^1H NMR δ 4.54 (s, 4 H, $ClCH_2$), 5.06 (s, 4 H, OCH_2), 7.01–7.09 (m, 4 H), 7.24–7.39 (m, 12 H), 7.42–7.49 (m, 1 H), 7.54–7.59 (m, 2 H), 7.81 (t, J = 1.7 Hz, 1 H, $H_{2'}$): ^{13}C NMR δ 45.8, 70.1, 113.5, 121.7, 127.5, 127.7, 128.4, 128.7, 128.8, 131.2, 131.3, 131.7, 136.9, 137.7, 138.2, 155.9; MS (FAB) 538 (M^+), 540 [$(M + 2)^+$]; HRMS calcd for $C_{34}H_{28}O_2Cl_2$ 538.1467, found 538.1475.

Coupling of Tetrol 4 with Isophthaloyl Chloride. Tetraester Cyclophane 14. To a stirred solution of triethylamine (0.11 mL) in dry THF (100 mL) was added (Ar, rt) simultaneously over 6–8 h solutions of tetrol 4 (100 mg, 0.34 mmol) and isophthaloyl chloride (146 mg, 0.72 mmol), each in 100 mL of dry THF. After an additional 2 h of stirring, the mixture was evaporated to dryness. The residue was taken up in CH_2Cl_2 and washed with aqueous Na_2CO_3. The aqueous layer was re-extracted with CH_2Cl_2 (2×) and the combined organic extracts were dried ($MgSO_4$) and concentrated. The residue was chromatographed on silica gel using 1:1 CH_2Cl_2/hexanes as eluent to give 63 mg (33%) of 14, mp 325–327 °C (recrystallized from hexanes/CH_2Cl_2): ^1H NMR, see Table I; ^{13}C NMR δ 117.5, 127.0, 129.3, 129.5, 129.69, 129.74, 130.7, 131.0, 133.8, 134.4, 134.7, 150.8, 163.2; MS (FAB) 555 (MH^+). Anal. Calcd for $C_{34}H_{18}O_8$: C, 73.65; H. 3.27. Found: C, 73.71; H, 3.26.

2,2'',6,6''-Tetrakis(dibromomethyl)-1,1':3',1''-terphenyl (17). A solution of tetramethylterphenyl 16[1b] (11.5 g, 40.2 mmol) in CCl_4 (600 mL) was heated at reflux and NBS (100 g, 0.56 mol) was added in 6 equal portions 8–10 h apart during 48 h. Each addition of NBS was followed by a catalytic amount of benzoyl peroxide. After addition was complete, the mixture was heated for an additional 2 d and then cooled to rt. The resulting solid was collected by filtration, suspended in acetone (600 mL), and triturated overnight. Filtration and air drying afforded 27.7 g (75%) of 17 as an off-white solid, mp > 280 °C dec: ^1H NMR δ 6.28 (s, 4 H, $CHBr_2$) 7.23 (t, J = 1.8 Hz, 1 H, $H_{2'}$), 7.49 (dd, J = 7.5, 1.8 Hz, 2 H, $H_{4',6'}$), 7.61 (t, J = 8.1 Hz, 2 H, $H_{4,4''}$), 7.75 (t, J = 7.5 Hz, 1 H, $H_{5'}$), 8.06 (d, J = 8.1 Hz, 4 H, $H_{3,3'',5,5''}$).

2,2'',6,6''-Tetraformyl-1,1':3',1''-terphenyl (18). A mixture of octabromide 17 (23.9 g, 26.0 mmol), anhydrous sodium acetate (20.32 g, 24.8 mmol), silver nitrate (36.49 g, 21.5 mmol), and 800 mL of THF/H_2O (3:1) was heated at reflux for 48 h. The cooled mixture was filtered, the precipitate was washed with THF, and the combined organic layers were concentrated (Rotavap). The residue was taken up in $CHCl_3$ and washed successively with saturated Na_2CO_3 and water. The combined aqueous layers were re-extracted with $CHCl_3$ (2×). Combined $CHCl_3$ layers were dried ($MgSO_4$) and evaporated to dryness, and the product was triturated with a little ether to give 7.3 g (82%) of 18, mp 208 °C: ^1H

NMR δ 7.27-7.75 (m, 6 H), 8.26 (d, J = 7.7 Hz, 4 H, $H_{3,3'',5,5''}$), 9.92 (s, 4 H, C*H*O); ^{13}C NMR δ 128.7, 129.0, 131.0, 132.2, 133.4, 133.5, 134.7, 146.0, 190.1. Anal. Calcd for $C_{22}H_{14}O_4$: C, 77.18; H, 4.12. Found: C, 77.06; H, 4.24.

2,2'',6,6''-Tetrakis(hydroxymethyl)-1,1':3',1''-terphenyl (19). To a solution of tetraldehyde 18 (7.08 g, 20.7 mmol) in 400 mL of THF/MeOH (3:1) was added at rt 1.56 g (41.2 mmol) of $NaBH_4$, and the mixture was stirred at rt for 16 h. The reaction was quenched with concentrated HCl until slightly acidic. The solvent was removed (Rotavap) and the crude product was extracted (soxhlet) with MeOH/$CHCl_3$ (2:3) for 3 d to yield 7.10 g (98%) of **19**, mp 192 °C: ^1H NMR (DMSO) δ 4.20 (d, J = 5.5 Hz, 8 H, C*H*$_2$), 5.11 (t, J = 5.5 Hz, 4 H, O*H*), 6.89 (t, J = 1.5 Hz, 1 H, $H_{2'}$), 7.15 (dd, J = 7.5, 1.5 Hz, 2 H, $H_{4',6'}$), 7.35-7.53 (m, 7 H); ^{13}C NMR δ 60.9, 125.0, 127.2, 127.8, 128.4, 129.5, 137.4, 138.0, 139.6. Anal. Calcd for $C_{22}H_{22}O_4 \cdot B_2O_3$: C, 62.90; H, 5.28. Found: C, 63.04; H, 5.42.

Coupling of Tetrol 19 with *m*-Xylylene Dichloride. *m*-Tetraoxacyclophane 20. To a solution of tetrol 19 (300 mg, 0.86 mmol) in dry DMF (30 mL) was added 282 mg (1.61 mmol) of 1,3-bis(chloromethyl)benzene, and the resulting mixture was added dropwise over 8-10 h to a stirred suspension of NaH (210 mg 80% in oil, 7.0 mmol) in dry DMF (30 mL) under Ar at 65-70 °C. After addition was complete, the cooled mixture was cautiously quenched with water to destroy the excess NaH. The mixture was evaporated to dryness, the residue was taken up in CH_2Cl_2 and filtered, and the filtrate was concentrated. The residue was chromatographed on silica gel using 1:1 ethyl acetate/hexanes as eluent to give 200 mg (42%) of **20**, mp 267-269 °C (recrystallized from hexanes/CH_2Cl_2): ^1H NMR, see Table I; ^{13}C NMR δ 67.7, 72.7, 126.2, 127.8, 127.9, 128.2, 128.3, 128.9, 129.1, 130.0, 136.1, 136.9, 137.8, 138.3; MS (FAB) 553 (MH^+ - 2 H). Anal. Calcd for $C_{38}H_{34}O_4$: C, 82.28; H, 6.18. Found: C, 82.25; H, 6.06.

***p*-Tetraoxacyclophane 21.** The procedure was the same as for the meta isomer, except that 1,4-bis(chloromethyl)benzene was used; yield 167 mg (35%), mp 247-249 °C: ^1H NMR, see Table I; ^{13}C NMR δ 66.8, 72.4, 127.2, 127.4, 127.6, 127.8, 129.3, 129.5, 129.7, 136.2, 137.1, 137.6, 138.9; MS (FAB) 553 (MH^+ - 2 H). Anal. Calcd for $C_{38}H_{34}O_4$: C, 82.28; H, 6.18. Found: C, 81.93; H, 6.15.

***o*-Tetraoxacyclophane 22.** The procedure was the same as for the meta isomer, except that 1,2-bis(chloromethyl)benzene was used; yield 95 mg (20%), mp 215-217 °C: ^1H NMR δ 4.30, 4.33 (AB q, J = 10.7 Hz, 8 H, C*H*$_2$), 4.40, 4.44 (AB q, J = 10.7 Hz, 8 H, C*H*$_2$), 7.17-7.30 (m, 10 H), 7.19 (t, J = 1.6 Hz, 1 H, $H_{2'}$), 7.40-7.57 (m, 7 H); ^{13}C NMR δ 70.4, 71.1, 127.6, 128.1, 128.2, 128.5, 129.8, 130.1, 132.5, 136.0, 136.8, 138.6, 141.9; MS (FAB) 555 (MH^+); HRMS calcd for $C_{38}H_{34}O_4$ (M^+), 554.2457, found 554.2469. Anal. Calcd for $C_{38}H_{34}O_4$: C, 82.28; H, 6.18. Found: C, 82.33; H, 6.13.

Bis(*n*-pentyl)tetraoxacyclophane 23. To a solution of tetrol 19 (250 mg, 0.71 mmol) in dry DMF (30 mL) was added 588 mg (1.43 mmol) of 1,5-pentanediol ditosylate,[10] and the resulting solution was added dropwise over 8-10 h under Ar to a stirred suspension of NaH (180 mg 80% in oil, 7.0 mmol) in dry DMF (30 mL) at 65-70 °C. After addition was complete, the cooled mixture was quenched with water to destroy the excess NaH and evaporated to dryness. The residue was taken up in CH_2Cl_2 and filtered. The filtrate was concentrated and the residue was chromatographed on silica gel using 1:1 ethyl acetate/hexane as eluent to afford 52 mg (15%) of **23**, mp 157-159 °C (recrystallized from hexanes/CH_2Cl_2): ^1H NMR δ 1.20-1.40 (m, 4 H, central C*H*$_2$), 1.41-1.57 (m, 8 H, methylenes adjacent to central CH_2), 3.38-3.57 (m, 8 H, C*H*$_2$ adjacent to O), 4.23, 4.36 (AB q, J = 11.8 Hz, 8 H, benzylic C*H*$_2$), 7.11 (dd, J = 7.5, 1.6 Hz, $H_{4',6'}$), 7.19 (t, J = 1.6 Hz, 1 H, $H_{2'}$), 7.36-7.50 (m, 7 H); ^{13}C NMR δ 22.1, 27.9, 69.6, 70.0, 127.7, 127.8, 128.0, 128.6, 129.8, 136.6, 138.4, 140.2; MS (FAB) 487 (MH^+); HRMS calcd for $C_{32}H_{39}O_4$ (MH^+) 487.2849, found 487.2844. Anal. Calcd for $C_{32}H_{38}O_4$: C, 78.98; H, 7.87. Found: C, 79.08; H, 7.73.

Hexaoxacyclophane 24. The procedure was the same as for **23** except that diethylene glycol ditosylate (591 mg, 1.43 mmol) was used; yield 56 mg (16%), mp 146-148 °C (recrystallized from hexanes/CH_2Cl_2): ^1H NMR δ 3.44-3.73 (m, 16 H, C*H*$_2$ adjacent to O), 4.27, 4.66 (AB q, J = 12.8 Hz, 8 H, benzylic), 7.05 (t, J = 1.6 Hz, 1 H, $H_{2'}$), 7.12 (dd, J = 7.6, 1.6 Hz, 2 H, $H_{4',6'}$), 7.35-7.49 (m, 7 H); ^{13}C NMR δ 69.9, 71.5, 72.3, 126.5, 127.6, 128.2, 130.2, 136.7, 138.3, 139.4 (one overlapped); MS (FAB) 491 (MH^+); HRMS calcd for $C_{30}H_{35}O_6$ (MH^+) 491.2434, found 491.2439. Anal. Calcd for $C_{30}H_{34}O_6$: C, 73.45; H, 6.99. Found: C. 73.65; H, 6.83.

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Supplementary Material Available: ^1H and ^{13}C NMR spectra of 19 (8 pages). Ordering information is given on any current masthead page.

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Asymmetric Synthesis of Oxygen- and Nitrogen-Substituted Difluoromethylene Products

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1,1-Difluoroalkyl sulfinylmethyl ketones **3** are synthesized in enantiomerically pure form through acylation of (+)-(*R*)-methyl *p*-tolyl sulfoxide (**1**) with α,α-difluorocarboxylates **2**. These ketones have been reduced with complete diastereoselection to give the corresponding alcohols. Removal of the auxiliary sulfinyl group and further elaborations afforded enantiomerically pure 2-(benzyloxy)-3,3-difluoro alcohols, esters, oximes, hydroxylamines, and nitriles.

The selective introduction of a fluorine atom or a perfluorinated residue into a chiral organic compound imparts specific and often useful properties with respect to those of the parent, unfluorinated product.[1]

For these reasons, various chemical and enzymatic approaches have been recently reported for the asymmetric synthesis of monofluoro[2] or trifluoromethyl[3] substituted compounds, while very few methods are available for the

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