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The synthesis of spirophanes from a pentaerythrityl core

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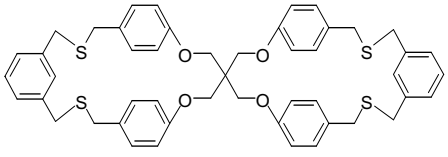
Abstract—Various thia- and oxa-spirobicyclic cyclophanes were synthesized from a pentaerythrityl building block and appropriate dithiols/bisphenols.

The pentaerythrityl core acts as a versatile building block in supramolecular chemistry and has been employed for the syntheses of various spiro crown ethers,[1] spiro-macrocyclic ligands,[2] spiro-bicyclic peptides,[3] spiro-catenanes[4] and dendrimers.[5] However, to the best of our knowledge, no pentaerythritol-based spirobicyclic cyclophanes incorporating rigid aromatic spacers have been reported. These cyclophanes would function as potential bi-site receptors and hence two guest molecules could be accommodated in a single cyclophane molecule despite the electrostatic repulsion between the guest molecules.[1b] Since the two macrocyclic units in these cyclophanes are oriented orthogonally to each other, the resulting complexes are poised to be in different planes and this phenomenon could be used for the construction of novel magnetic[6] and electronic materials.[7] Herein we report the synthesis of various spiro-bicyclic cyclophanes viz., thiaspirophane **1**, intraannularly functionalized thiaspirophanes **2a**–**c**, oxaspirophane **3** and chiral oxaspirophane **4** from a pentaerythritol-derived aromatic tetrabromide **7**.

This extended tetrabromide **7** has two advantages over the starting pentaerythrityl tetrabromide: (i) it possesses



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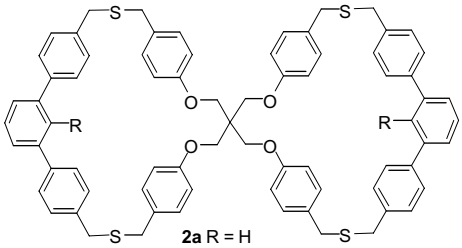
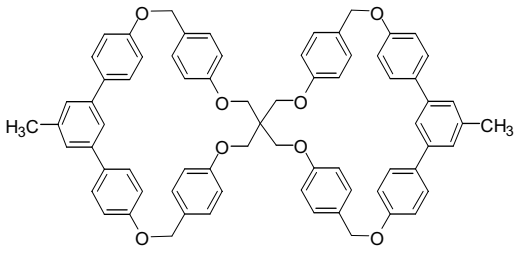


2a R = H
2b R = Br
2c R = CO_2Me



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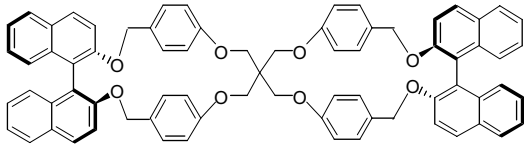

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Keywords: Spirophanes; Pentaerythrityl; *m*-Terphenyl; Chiral cyclophane.
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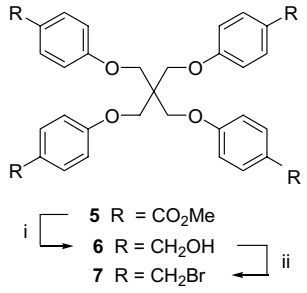
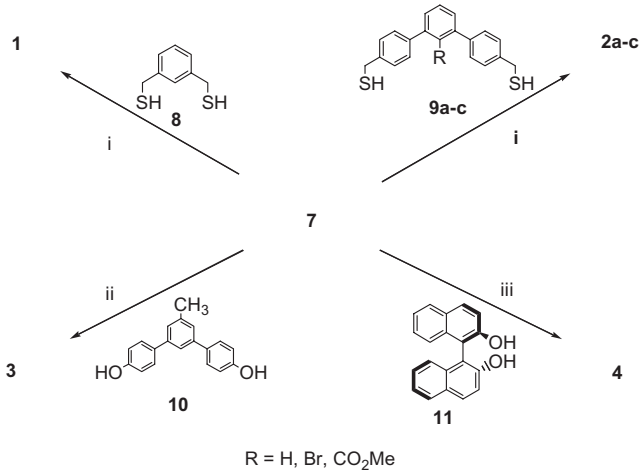


Scheme 1. Reagents and conditions: (i) $LiAlH_4$, THF, reflux, 12 h, 72%; (ii) MsCl, Et_3N, THF, 0 °C, 3 h; then LiBr, acetone, rt, 12 h, 69%.

the more reactive benzylic bromide functionality and (ii) the presence of aromatic spacers would avoid steric congestion during cyclization. The tetrabromide **7** was synthesized as outlined in Scheme 1. The tetraester **5**, obtained by the fourfold *O*-alkylation of pentaerythrityl tetrabromide with methyl-4-hydroxybenzoate,[8] was reduced with $LiAlH_4$ in refluxing THF to afford the tetra-alcohol **6** in a 72% yield. Conversion of the tetra-alcohol **6** to the corresponding tetrabromide **7** was attempted with various brominating agents such as PBr_3 in CH_2Cl_2, CBr_4/PPh_3 in THF and Br_2/PPh_3 in CH_3CN but the results were not satisfactory. Thus, tetraalcohol **6** was treated with MsCl in the presence of Et_3N in THF to give a tetramesylated compound, which was then converted into the tetrabromide **7** in 69% yield by an exchange reaction with LiBr in acetone.

In order to test the utility of the tetrabromide **7** for the synthesis of spirobicyclic cyclophanes, 1 equiv of **7** was reacted with 2 equiv of *m*-xylene dithiol (**8**) in the presence of KOH in a C_6H_6–EtOH (1:9, v/v) mixture under high dilution conditions. The spirobicyclic cyclophane **1** was thus obtained in 40% yield after column chromatographic purification (Scheme 2). The structure of the cyclophane **1** was confirmed by spectroscopic and analytical data[9] and XRD studies.[10] It is interesting to note that in the ^1H NMR spectrum of **1**, the intra-annular *m*-xylenyl proton was highly shielded and appeared at δ 6.09. The ORTEP plot of the crystal structure of **1**



Scheme 2. Reagents and conditions: (i) KOH, C_6H_6/EtOH (1:9, v/v), 12 h; afforded **1** (40%) and **2a** (25%) **2b** (18%) and **2c** (23%); (ii) K_2CO_3, CH_3CN, 60 °C, 16 h, 15%; (iii) K_2CO_3, acetone, rt, 10 d, 12%.

(Fig. 1) indicates that the two macrocyclic units are perpendicular to each other.

Incorporation of *m*-terphenyl building blocks into these kinds of cyclophanes would make the cyclophanes have large noncollapsible rigid cavities with intra-annular functionality.[11] With this idea in mind, the tetrabromide **7** was coupled with each of the *m*-terphenyl dithiols **9a**–**c**[12] under high dilution conditions to afford the spirobicyclic cyclophanes **2a**,[13] **2b** and **2c** in 25%, 18% and 23% yields, respectively (Scheme 2).

Having succeeded in establishing a method for the synthesis of thia-spirobicyclic cyclophanes, we focussed our attention on the synthesis of similar oxacyclophanes. Thus stirring 1 equiv of **7** with 2 equiv of the bisphenol **10** (obtained by cleaving the corresponding dimethoxy compound[14] with HBr in AcOH) in the presence of K_2CO_3 in CH_3CN at 60 °C for 16 h afforded the spirobicyclic oxacyclophane **3**[15] in 15% yield (Scheme 2).

To extend the utility of the tetrabromide **7** for the synthesis of chiral spirophanes, **7** was stirred with 2 equiv

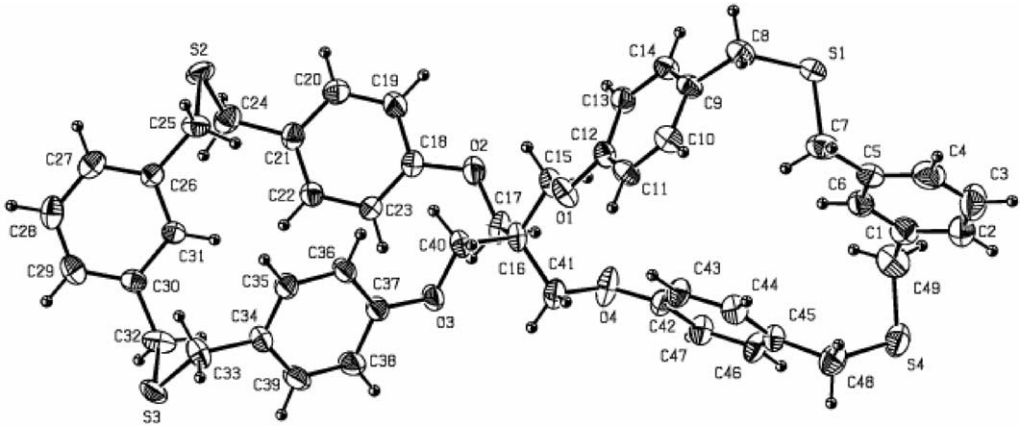


Figure 1. ORTEP plot of the crystal structure of **1**.

of (*S*)-BINOL (**11**) in the presence of K_2CO_3 in acetone at room temperature for 10 days to give cyclophane **4**[16] in 12% yield (Scheme 2). This chiral cyclophane having a spiro backbone may be useful for chiral molecular recognition and asymmetric catalysis.[17] In the ^1H NMR spectrum of cyclophane **4**, the CH_2 protons attached to the BINOL unit as well as those attached to the spiro carbon appear as two doublets due to the atropisomerism of the (*S*)-BINOL unit.[18]

In conclusion, we have synthesized various thia- and oxa-spirobicyclic cyclophanes from a pentaerythritol-derived aromatic tetrabromide. The utility of this potential precursor for the synthesis of other similar cyclophanes and detailed complexation studies with these cyclophanes are under investigation.

Acknowledgements

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9. Cyclophane **1**: yield 40%; mp 208 °C; ^1H NMR (500 MHz, $CDCl_3$): δ 3.34 (s, 8H); 3.41 (s, 8H); 4.38 (s, 8H); 6.09 (s, 2H); 6.84 (d, 8H, $J = 8.6$ Hz); 7.10 (d, 8H, $J = 8.6$ Hz); 7.25–7.33 (m, 6H); ^{13}C NMR (125 MHz, $CDCl_3$); δ 33.5, 33.8, 47.0, 66.2, 114.7, 127.6, 129.5, 130.0, 130.3, 131.3, 137.4, 158.0; *m/z* (FAB-MS) 828 (M^+). Elemental anal. calcd for $C_{49}H_{48}O_4S_4$: C, 70.98; H, 5.83. Found: C, 70.86; H, 5.71.
10. This work has been carried out as a collaborative work with Prof. D. Velmurugan, Department of Crystallography and Biophysics, University of Madras, Guindy Campus, Chennai 600 025 and will appear as a separate communication.
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13. Cyclophane **2a**: yield 25%; mp 185 °C; ^1H NMR (400 MHz, $CDCl_3$): δ 3.68 (s, 8H); 3.76 (s, 8H); 3.98 (s, 8H); 6.61 (d, 8H, $J = 7.5$ Hz); 6.88 (d, 8H, $J = 7.2$ Hz); 7.06 (d, 8H, $J = 7.1$ Hz); 7.24-7.67 (m, 16H); ^{13}C NMR (100 MHz, $CDCl_3$); δ 36.5, 36.8, 67.5, 114.6, 125.1, 125.7, 126.9, 129.4, 129.9, 131.4, 138.6, 138.7, 139.3, 141.5, 157.8; *m/z* (FAB-MS) 1132 (M^+). Elemental anal. calcd for $C_{73}H_{64}O_4S_4$: C, 77.35; H, 5.69. Found: C, 77.27; H, 5.62.
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15. Cyclophane **3**: yield 15%; mp 155 °C; ^1H NMR (400 MHz, $CDCl_3$): δ 2.42 (s, 6H); 4.20 (s, 8H); 5.25 (s, 8H); 6.74–6.76 (m, 10H); 6.79 (d, 8H, $J = 8.6$ Hz); 7.15 (d, 8H, $J = 8.6$ Hz); 7.19–7.20 (m, 12H); ^{13}C NMR (100 MHz, $CDCl_3$); δ 23.4, 46.5, 64.8, 69.6, 107.3, 114.4, 116.7, 124.9, 128.5, 129.6, 133.8, 134.5, 138.1, 157.8; *m/z* (FAB-MS) 1040 (M^+). Elemental anal. calcd for $C_{71}H_{60}O_8$: C, 81.90; H, 5.81. Found: C, 81.79; H, 5.73.
16. Cyclophane **4**: Yield 12%; $[\alpha]_D^{25} = -125.0$; mp 139 °C; ^1H NMR (500 MHz, $CDCl_3$): δ 4.03 (d, 4H, $J = 10.3$ Hz); 4.26 (d, 4H, $J = 10.3$ Hz); 4.71 (d, 4H, $J = 11.5$ Hz); 4.95 (d, 4H, $J = 11.5$ Hz); 6.31 (d, 8H, $J = 8.6$ Hz); 6.61 (d, 8H, $J = 8.8$ Hz); 7.12-7.32 (m, 12H); 7.53 (d, 4H, $J = 9.2$ Hz); 7.87 (d, 4H, $J = 8.6$ Hz); 7.96 (d, 4H, $J = 9.2$ Hz); ^{13}C NMR (125 MHz, $CDCl_3$); δ 47.9, 67.1, 70.9, 115.1, 116.8, 121.4, 123.8, 125.4, 126.4, 128.0, 128.1, 129.4, 129.7, 154.0, 159.2; *m/z* (FAB-MS) 1060 (M^+). Elemental anal. calcd for $C_{73}H_{56}O_8$: C, 82.62; H, 5.32. Found: C, 82.52; H, 5.24.
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