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# Synthesis of an annularly linked bicyclic chiral cyclophane by pre-organization of a dibromide

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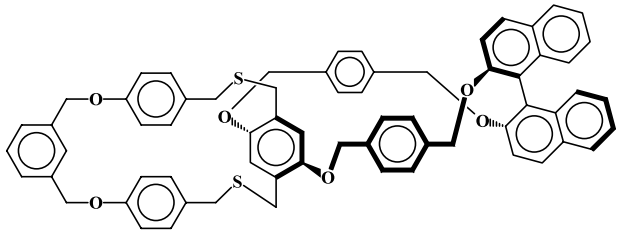
**Abstract**—An annularly linked bicyclic chiral cyclophane was synthesized from a suitable pre-organized chiral dibromide. © 2003 Published by Elsevier Science Ltd.

Pre-organization[1] of macrocycles plays a vital role in many biochemical mechanisms such as enzyme/substrate activity,[2] protein folding,[3] antisense applications,[4] molecular recognition,[5] etc. Stoddart[6] has reported the synthesis of an annularly linked macro bicyclic cyclophane with a bipyridyl building unit. Such bicyclic cyclophanes show self-assembly and other novel properties. Chiral cyclophanes based on BINOL have recently been reported from our laboratory.[7] Herein, we wish to report the synthesis of a new class of annularly linked chiral cyclophanes **1** through coupling a pre-organized chiral dibromide.



**1**

Initially, we proposed to synthesize annularly linked chiral bicyclic cyclophanes of type **1** by coupling the chiral cyclophane **7** with various dibromides. The cyclophane **7** was obtained from cyclophane **6** by CAN oxidation[8] followed by reduction using sodium dithionate. Cyclophane **6** was synthesized from the dichloride **2**.[9] However, the cyclophane **6** gave only uncharacterizeable polymeric material after reduction (Scheme 1). Moreover, the yield of the cyclophane **6** from the coupling of bromide **5** with (*S*)-BINOL was low (8%) and hence further chemical transformations could not be achieved.

Hence, the scheme was modified by oxidizing the dichloride **2** with CAN and the resulting 2,6-bis-(chloromethyl)benzoquinone was then used for coupling with a suitable dithiol. Cyclophane **14** can function as a suitable precursor for the synthesis of annularly linked bicyclic chiral cyclophanes.

Treatment of *m*-xylenyl dibromide **8** with *p*-hydroxybenzaldehyde in the presence of $K_2CO_3$ in DMF gave dialdehyde **9**, which was reduced to diol **10** by $NaBH_4$ in methanol. Diol **10** was then converted into dibromide **11** by treating with $PBr_3$ in $CH_2Cl_2$. Dibromide **11** was treated with thiourea in THF to give the thiouronium salt, which was hydrolyzed using KOH in THF to give dithiol **12**. Coupling dithiol **12** with 2,6-bis-(chloromethyl) benzoquinone in EtOH–benzene under high dilution conditions[10] gave thiacyclophane **13** in good yield.[11] Reduction of the cyclophane **13** into cyclophane **14**[12] was carried out smoothly with sodium dithionate in ethyl acetate at 0°C without affecting the C–S bonds.

Treatment of the cyclophane **14** with the chiral dibromide **15** in the presence of $K_2CO_3$ in acetone at rt for 120 h afforded the annularly linked bicyclic chiral cyclophane **1**[13] in 10% yield (Scheme 2). Though two isomers might be expected for the final coupling reaction, only one isomer of **1** was formed. This may be attributed to the pre-organization of the dibromide **15**, which exclusively reacts with one rotameric form of the diol **14**.

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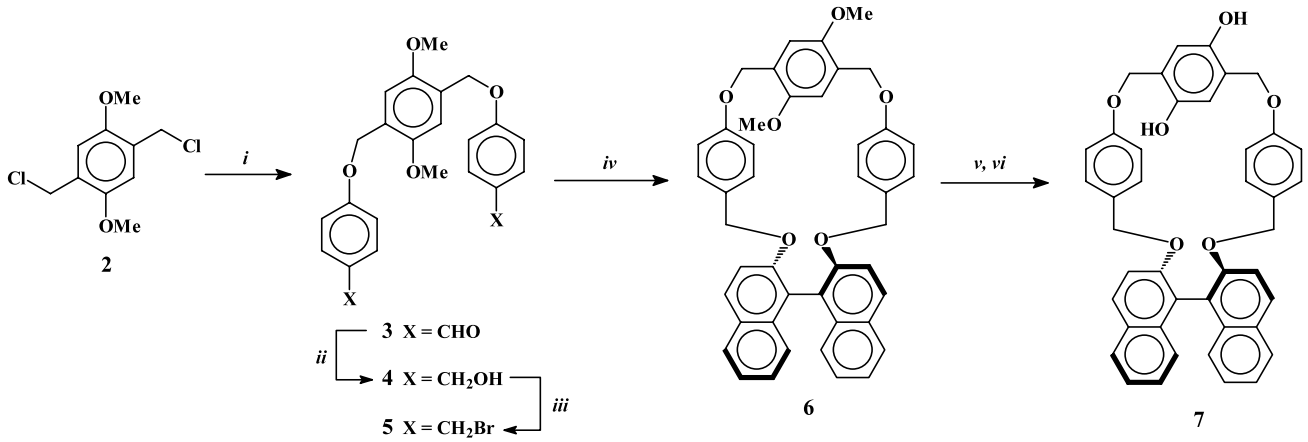
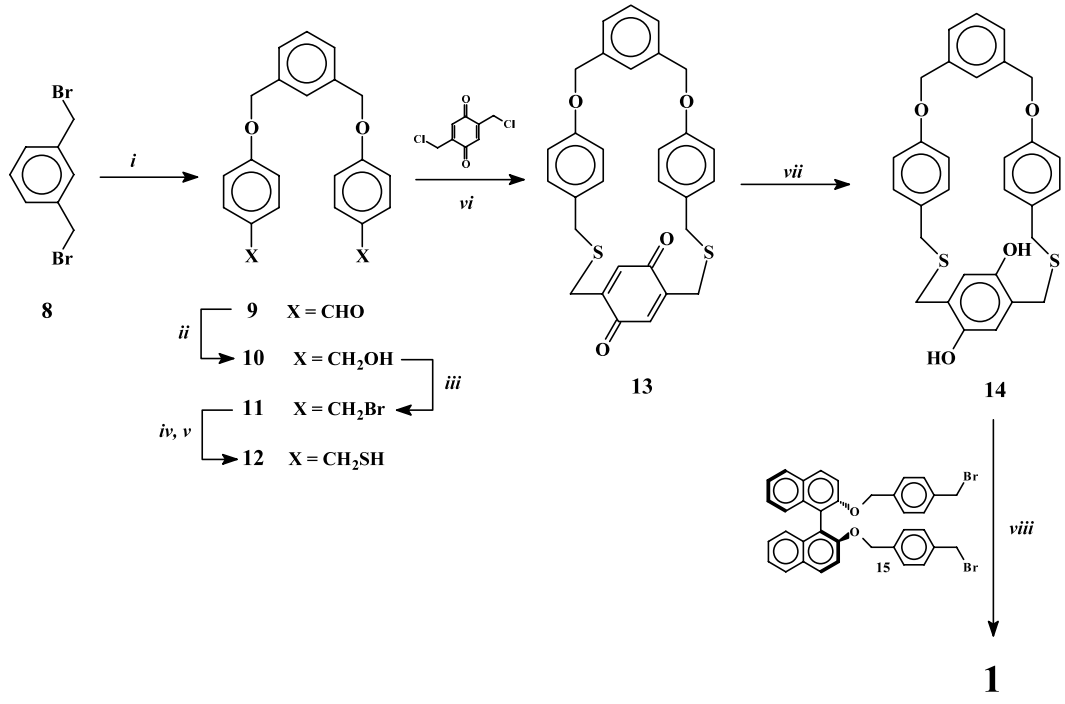



**Scheme 1.** *Reagents and conditions*: (i) *p*-Hydroxybenzaldehyde, $K_2CO_3$, DMF, 60°C, 48 h, 82%; (ii) $NaBH_4$, MeOH, 0°C, 4 h, 94%; (iii) $PBr_3$, $CH_2Cl_2$, 0°C, 6 h, 73%; (iv) BINOL, $K_2CO_3$, acetone, rt, 120 h, 8%; (v) CAN, $CH_3CN$, 0°C, 2 h, 43%; (vi) $Na_2S_2O_4$, EtOAc, 0°C, 22%.




**Scheme 2.** *Reagents and conditions*: (i) *p*-Hydroxybenzaldehyde, $K_2CO_3$, DMF, 60°C, 48 h, 86%; (ii) $NaBH_4$, MeOH, 0°C, 4 h, 95%; (iii) $PBr_3$, $CH_2Cl_2$, 0°C, 6 h, 87%; (iv) thiourea, THF, 60°C, 6 h, 97%; (v) KOH, THF, 60°C, 6 h, 62%; (vi) KOH, EtOH/benzene, rt, 24 h, 55%; (vii) $Na_2S_2O_4$, EtOAc, 0°C, 3 h, 37%; (viii) $K_2CO_3$, acetone, rt, 120 h, 10%.

The $^1$H NMR of the bicyclic cyclophane **1** showed the -S-$CH_2$- methylene protons as singlets, whereas the methylene protons attached to the *m*-xylyl moiety appeared as two doublets; one doublet appearing at $\delta$ 4.84 ($J=9.3$ Hz) while the other doublet merged with the multiplet of the *p*-xylyl moiety. Due to the anisotropic effect of the BINOL group, the methylene protons of the *p*-xylyl moiety appeared as multiplets. The protons of the central benzene ring appeared in the upfield region at $\delta$ 6.70 as a singlet along with other aromatic protons in the region $\delta$ 6.76 to 7.88 as multiplets.

The $^{13}$C NMR of the chiral cyclophane **1** showed five distinct signals for methylene carbons in the aliphatic region in addition to 26 carbons in the aromatic region. The FAB-MS of the chiral cyclophane **1** showed a molecular ion peak at 1006, which further supported the structure of **1**.

Semi empirical calculations based on MOPAC (AM1) have also been carried out for the bicyclic chiral cyclophane **1** (Fig. 1), which show that both the rings are perpendicular to each other. It also reveals that the central benzene ring through which both the rings are

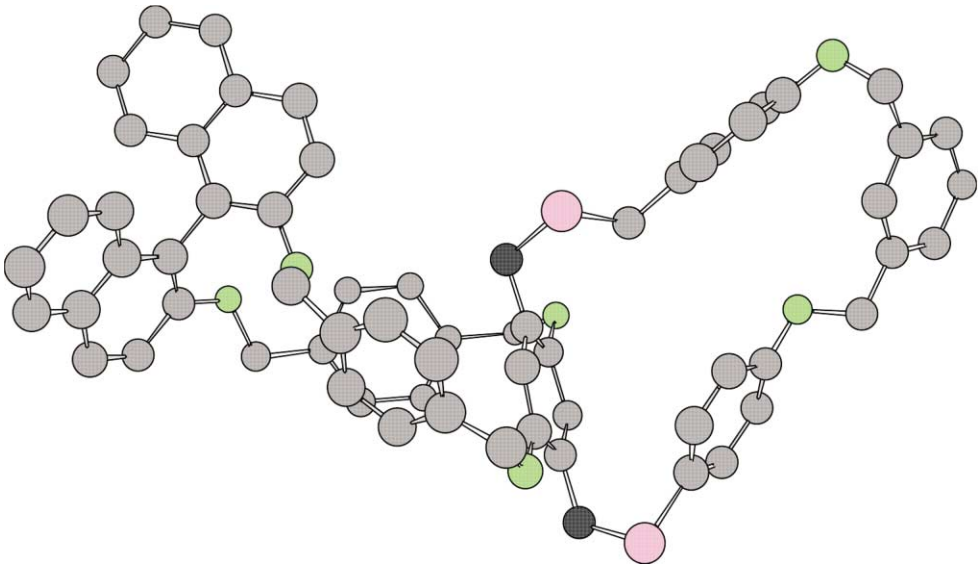


**Figure 1.** Energy minimized structure of bicyclic chiral cyclophane **1**.

connected lies perpendicular to both the cyclophane units. Synthetic studies on other similar annularly linked bicyclic chiral cyclophanes are under further investigation.

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11. Yield 55%; mp 142°C; IR (KBr, $cm^{-1}$) 1740 (C=O); $^1H$ NMR (400 MHz, $CDCl_3$) $\delta$ 3.67 (s, 4H); 3.80 (s, 4H); 5.10 (s, 4H); 6.92 (s, 2H); 7.23–7.78 (m, 12H). Anal. calcd for $C_{30}H_{26}O_4S_2$: C, 70.01; H, 5.09. Found: C, 69.93; H, 4.81.
12. Yield 37%; mp 110°C; IR (KBr, $cm^{-1}$) 3340 (OH); $^1H$ NMR (400 MHz, $CDCl_3$) $\delta$ 3.60 (s, 4H); 3.69 (s, 4H); 5.06 (s, 4H); 6.81 (bs, 2H, exchangeable with $D_2O$); 7.13–7.89 (m, 14H). Anal. calcd for $C_{30}H_{28}O_4S_2$: C, 69.74; H, 5.46; Found: C, 69.68; H, 5.42.
13. Yield 10%; mp 142°C; $[\alpha]_D^{25} = -90.0$ (*c* 0.2, $CHCl_3$); $^1H$ NMR (400 MHz, $CDCl_3$) $\delta$ 3.19 (s, 4H); 3.29 (s, 4H); 4.84 (d, 2H, $J = 9.3$ Hz); 4.98–5.06 (m, 6H); 5.56–5.59 (m, 4H); 6.70–6.76 (m, 12H); 7.12–7.38 (m, 14H); 7.75–7.88 (m, 8H); $^{13}C$ NMR (100.4 MHz, $CDCl_3$) $\delta$ 31.6, 34.2, 70.3, 70.5, 70.6, 115.6, 115.7, 115.8, 115.9, 120.7, 123.6, 125.2, 125.8, 126.2, 126.3, 126.5, 126.6, 126.7, 126.8, 126.9, 127.0, 127.1, 127.8, 127.9, 129.1, 129.2, 129.3, 134.2, 136.3, 142.4, 153.9; *m/z* (FAB-MS) 1006 ($M^+$). Anal. calcd for $C_{66}H_{54}O_6S_2$: C, 78.70; H, 5.40. Found: C, 78.69; H, 5.09.