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Synthesis of chiral cyclophanes based on *meta*-terphenyl and pyridyl blocks

Perumal Rajakumar* and Muthialu Srisailas

Department of Organic Chemistry, University of Madras, Guindy Campus, Chennai Tamil Nadu 600 025, India

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Abstract—Coupling of *m*-terphenyl dibromide with binol afforded the corresponding optically active cyclophane. Chiral cyclophanes were also obtained by the coupling of *p*-nitrophenol or 4,4″-bis(bromomethyl)-1,3-dibenzylbenzene with binol.

Extensive studies on the use of chiral binaphthol based crown ethers as hosts for molecular recognition have been carried out as early as 1970.[1] Though the first binaphthyl crown ether was reported in 1973,[2] the *m*-terphenyl and pyridyl based cyclophanes are not known so far. Cyclophanes based on *m*-terphenyl building blocks possess a large non-collapsible rigid cavity.[3] Hence, bisbinaphthyl cyclophanes based on *m*-terphenyls would have a macrocyclic cavity and they could find application in chiral resolution and asymmetric induction. Further, when *m*-terphenyl and pyridyl units are employed, the binol cyclophanes could function as excellent receptors for chiral molecules. Herein, we report the preparation of such cyclophanes by a simple route and by using conventional reagents.

Hart reaction[4] affords a simple route for the synthesis of various 2′-substituted *m*-terphenyls in good yield. In order to test whether *m*-terphenyl dibromides could be used for coupling with binapthol, reaction of 2 equiv. of (*S*)-binaphthol with 1 equiv. of *m*-terphenyl dibromide **1a** was carried out in acetone in the acetone in the presence of K_2CO_3 at room temperature for 48 h. The bisalkylated product **2a** was obtained in 65% yield after usual work up. ^{1}H NMR of **2a** showed OCH_2 protons at δ 5.12 as singlet in addition to the aromatic protons and the IR showed the OH stretching at 3340 cm^{-1}. Further coupling of one more equivalent of *m*-terphenyl dibromide under high dilution conditions afforded the cyclophane **3a** in 40% yield. By a similar sequence the bisalkylated product **2b** was obtained in 57% yield from the *m*-terphenyl ester dibromide **1b** and binol. The bisalkylated product **2b** has been converted into cyclophane **3b** by its further reaction with one more equivalent of **1b**. Unsymmetrical cyclophane **3c** was obtained in 32% yield by the reaction of the bisalkylated product **2b** with one equivalent of the *m*-terphenyl ester dibromide **1a**. Similarly, the tetrabromide ethylene glycol ester **1c** on reaction with 2 equiv. of binaphthol gave the intra-annularly linked bisbinaphthyl cycolphane **3d** in 40% yield. All the chiral cyclophanes displayed two doublets with the same coupling constant for the OCH_2 protons attached with the binol unit. The reactions are summarised in Scheme 1 and the optical rotations are given in Table 1.

In order to explore the synthesis of cyclophanes based on binol unit, the chiral cyclophane **5a** and **5b** were derived from *m*-xylenyl dibromide and *p*-nitrophenol, respectively as given in Scheme 2. The *m*-xylenyl dibromide was bisalkylated using methyl *p*-hydroxybenzoate to give diester, which was converted into the corresponding diol using LAH. The dibromide **4a**,[5] obtained by treating the diol with PBr_3 in CH_2Cl_2, was coupled with 1 equiv. of the binol in presence of K_2CO_3 in acetone for 120 h to give the cyclophane **5a** in 45% yield. Same strategy was followed for the synthesis of dibromide **4b** from 1,3-bis-(bromomethyl),2-acetoxy,5-nitrobenzene,[6] with a slight modification. Bisalkylation has been carried out using *p*-hydroxybenzaldehyde and the resulting dialdehyde was reduced with $NaBH_4$ (Table 2).

Binol based optically active pyridinophane **7** is derived from 2,6-bisbromomethyl pyridine as shown in Scheme 3. The dibromide **6** obtained by the reduction of respective dialdehyde was treated with 1 equiv. of the binol in presence of K_2CO_3 in acetone for 120 h to furnish the pyridinophane **8** in 42% yield as shown in Scheme 3.

Another optically active novel binol cyclophane **9** was obtained from dibromide **8**. The dibromide **8**, which has not been so far used for the synthesis of cyclophanes, was prepared from isophthaloyl chloride and toluene in presence

Keywords: chiral cyclophanes; *meta*-terphenyl; pyridyl.

* Corresponding author. Tel.: +91-44-2351265, ext. 213; fax: +91-44-2352494; e-mail: perumalrajakumar@hotmail.com

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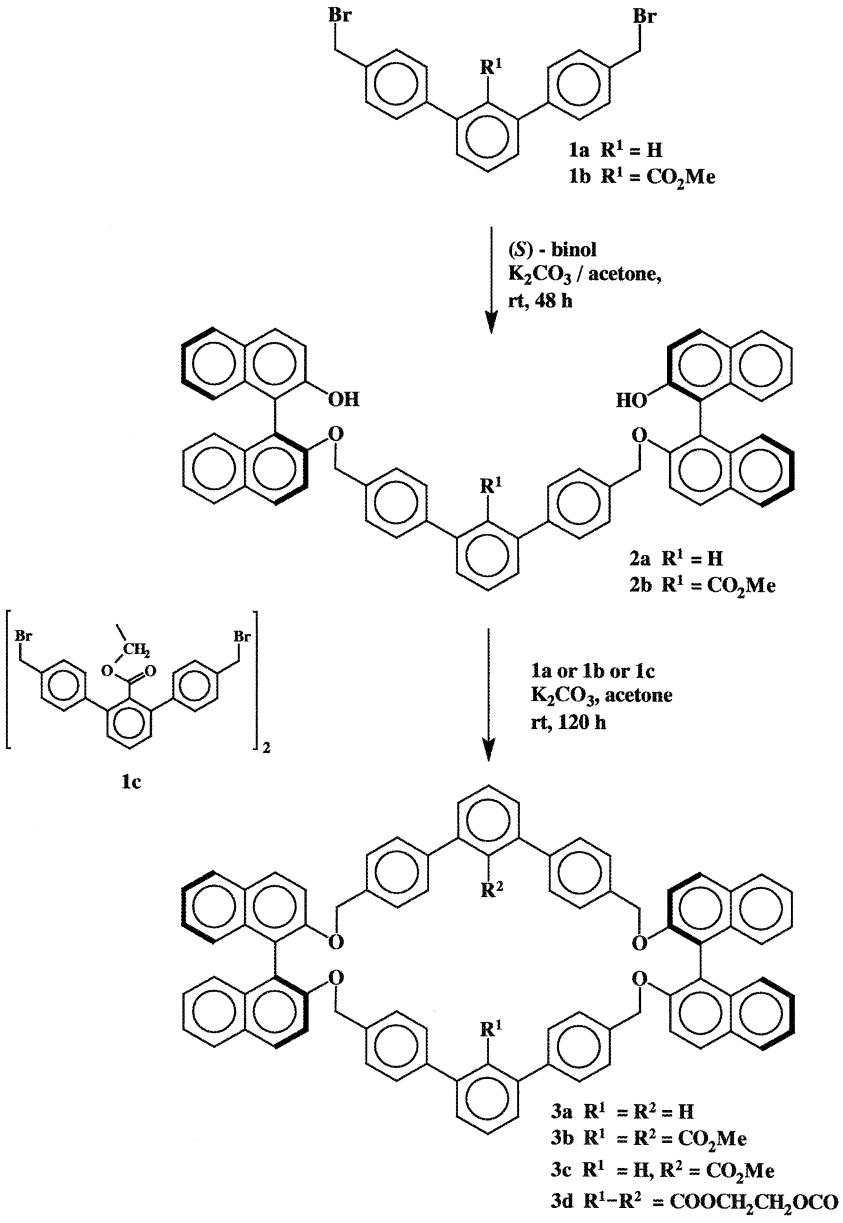


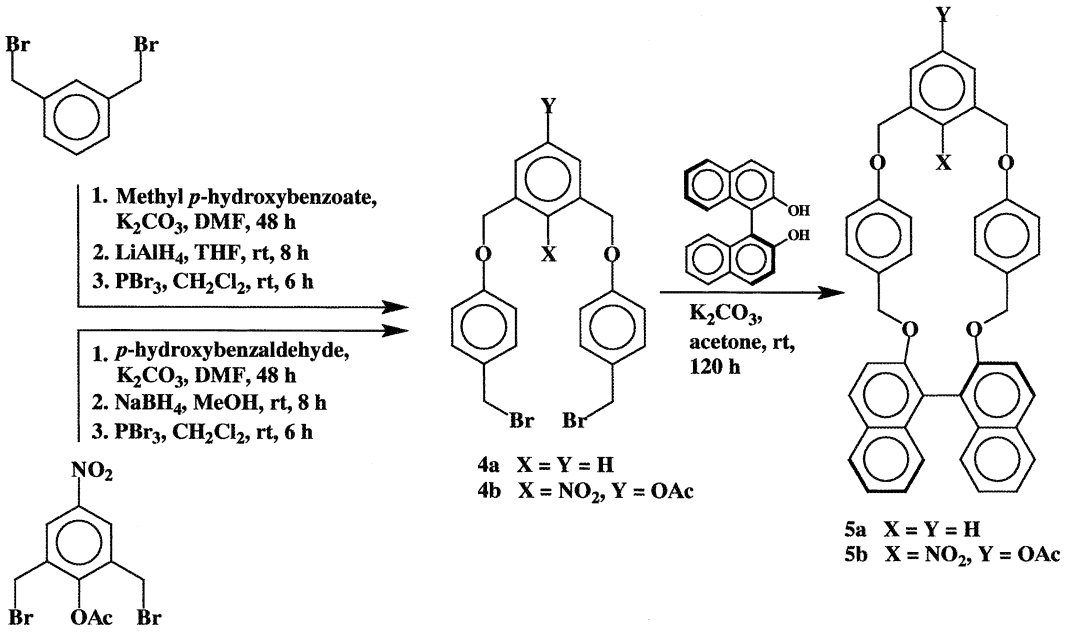
Scheme 1.

Table 1.

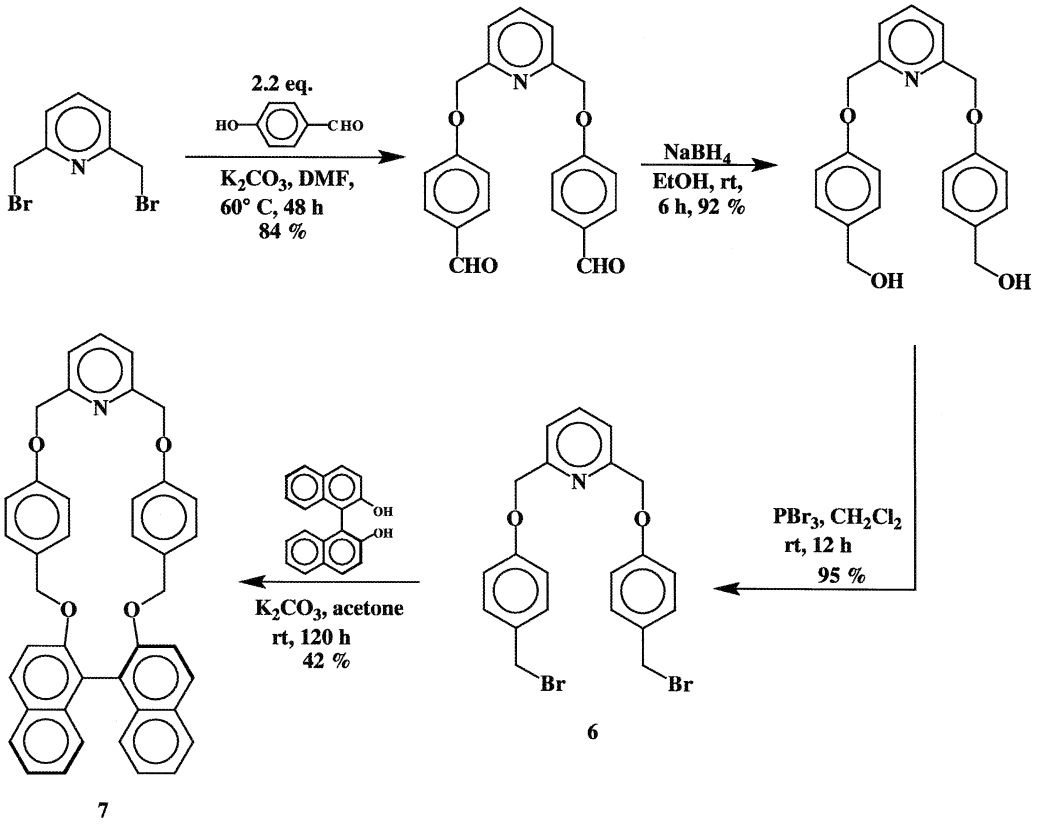
Compound	Yield (%)	Mp (°C)	$[\alpha]_D^{25}$ (*c* 0.1 $CHCl_3$)
3a	40	210	−140.0
3b	32	208	−152.4
3c	28	206	−146.7
3d	40	215	−171.3

Table 2.

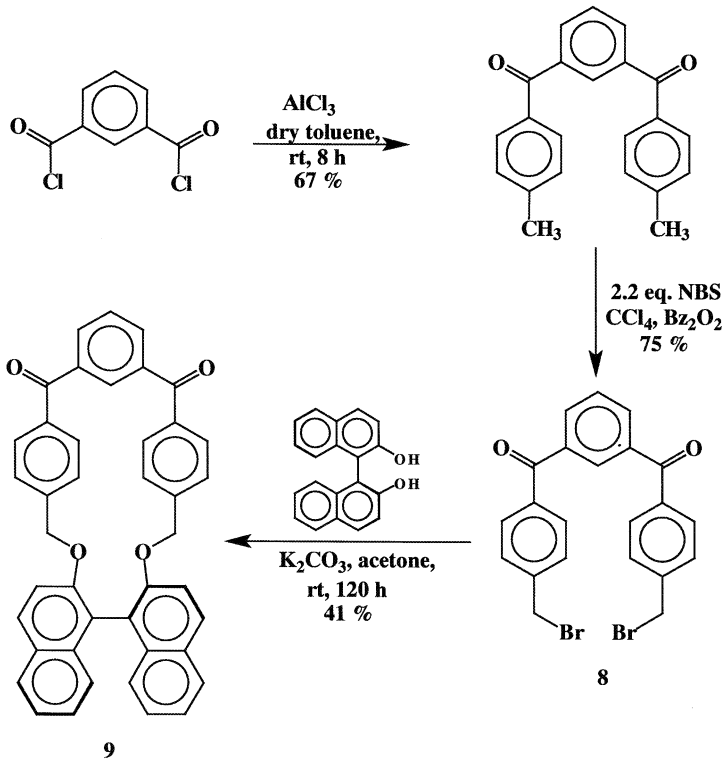
Compound	X	Y	Yield (%)	Mp (°C)	$[\alpha]_D^{25}$ ($CHCl_3$)
5a	H	H	45	208	−212.5 (*c* 0.12)
5b	NO_2	OAc	42	235	−210.0 (*c* 0.10)



Scheme 2.



Scheme 3.



Scheme 4.

of $AlCl_3$ to give diketone, followed by NBS bromination in CCl_4 in presence of benzoyl peroxide. Coupling of the dibromide **8** with the binol in presence of K_2CO_3 in acetone for 120 h at room temperature afforded the cyclophane **9** as shown in Scheme 4.

Reduction of the cyclophane **9** could result in the formation of optically active diol. Synthesis of other binol based chiral cyclophanes and other applications are under investigation.

1. Experimental

1.1. General

All the melting points are uncorrected. The IR spectra were recorded using Shimadzu FT-IR 8300 instrument. The ^1H and ^{13}C NMR spectra of all compounds in $CDCl_3$ were recorded using Jeol GSX 400 (400 MHz) NMR spectrometer. The mass spectra were recorded using Jeol (EI, 70 eV and FAB-MS). The rotations were recorded using Autopol II (Automatic Polarimeter) at 25°C. The column chromatography was performed using silica gel (100–200 mesh).

1.2. General procedure for the preparation of precyclophanes

Dibromide (1 mmol) and (*S*)-binaphthol (2 mmol) were stirred with K_2CO_3 in acetone at room temperature for 48 h after which the reaction mixture was acidified and evaporated to dryness. The residue obtained was extracted with CH_2Cl_2 (3×100 mL), washed with water (3×100 mL) and dried ($MgSO_4$). Evaporation of the organic layer gave a residue, which was chromatographed over SiO_2 using $CHCl_3$ afforded the corresponding precyclophane.

1.2.1. Precyclophane 2a. Yield 65%; mp 172°C; $[\alpha]_D^{25}=-14.68$, (*c* 2.3, $CHCl_3$); IR (cm^{-1}) 3340 (b, OH); ^1H NMR δ 5.13 (s, 4H), 6.82 (bs, 2H, exchangeable with D_2O), 7.08 (m, 6H), 7.25–7.54 (m, 22H), 7.86–8.02 (m, 8H), ^{13}C NMR 71.4, 115.8, 120.6, 122.6, 123.4, 124.9, 125.2, 125.7, 125.9, 126.4, 127.2, 127.4, 128.1, 129.5, 130.8, 134.2, 136.6, 139.9, 141.2; Anal. Calcd for $C_{60}H_{42}O_4$: C, 87.14, H, 5.12; Found: C, 87.02; H, 5.01.

1.2.2. Precyclophane 2b. Yield 57%, mp 165°C; $[\alpha]_D^{25}=-17.2$, (*c* 2, $CHCl_3$); IR (cm^{-1}) 3340 (b, OH), 1722 (CO); ^1H NMR ($CDCl_3$) δ 3.46 (s, 3H), 5.12 (s, 4H), 6.50 (bs, 2H, exchangeable with D_2O); 7.12–7.18 (m, 6H), 7.28–7.54 (m, 21 H); 7.88–8.04 (m, 8H); ^{13}C NMR δ 30.4, 71.4, 115.9, 120.2, 123.7, 125.5, 125.7, 126.6, 126.8, 127.1, 127.9, 128.8, 129.6, 129.8, 134.2, 136.6, 139.9, 142.4, 138.4, 143.2; Anal. Calcd for $C_{62}H_{44}O_6$: C, 84.14; H 5.01; Found: C, 84.07, H, 4.89.

1.3. General procedure for the preparation of cyclophanes

Precyclophane (0.5 mmol) and dibromide (0.5 mmol) were stirred with K_2CO_3 in acetone at room temperature for 120 h after which the reaction mixture was acidified and evaporated to dryness. The residue obtained was extracted with CH_2Cl_2 (3×100 mL), washed with 10% NaOH (2×50 mL); with water (3×100 mL) and dried ($MgSO_4$). Evaporation of the organic layer gave a residue which was chromatographed over SiO_2 using $CHCl_3$/hexane (1:1) afforded the corresponding cyclophane.

1.3.1. Cyclophane 3a. Yield 40%, mp 210°C; $[\alpha]_D^{25}=-140.0$, (*c* 0.1, $CHCl_3$); IR (cm^{-1}), 2964, 1590, 1263, 1118, 806, 748; ^1H NMR ($CDCl_3$) δ 5.03 (d, 4H, *J*=12.7 Hz), 5.19 (d, 4H, *J*=12.7 Hz), 6.97 (d, 4H, *J*=8 Hz), 7.03 (d, 4H, *J*=8 Hz), 7.06–7.35 (m, 30H), 7.47 (d, 2H, *J*=9.3 Hz), 7.89 (d, 4H, *J*=8.3 Hz), 7.97 (d, 4H, *J*=8.8 Hz); ^{13}C NMR 70.2, 115.5, 120.5, 123.5, 124.8, 125.4, 125.5, 126.4, 126.7, 127.2, 127.9, 128.6, 129.2, 129.3, 132.3, 134.3, 136.3, 139.8, 140.5, 148.3, 153.8; *m/z* (FAB-MS) 1080 (M^+); Anal. Calcd for $C_{80}H_{56}O_4$: C, 88.86; H, 5.22; Found: C, 88.81, H, 5.12.

1.3.2. Cyclophane 3b. Yield 32%, mp 208°C; $[\alpha]_D^{25}=-152.4$, (*c* 0.1, $CHCl_3$); IR (cm^{-1}) 1722 (CO); ^1H NMR ($CDCl_3$) 3.96 (s, 6H), 5.06 (d, 8H, *J*=12.7 Hz), 5.16 (d, 8H, *J*=12.7 Hz), 6.96–7.36 (m, 30H), 7.82–8.00 (m, 8H); ^{13}C NMR 29.7, 70.6, 115.8, 120.6, 123.7, 125.5, 125.7, 126.4, 126.8, 127.0, 127.9, 128.9, 129.3, 129.4, 134.2, 136.6, 139.9, 140.9, 165.2; *m/z* (FAB-MS) 1096 (M^+); Anal. Calcd for $C_{84}H_{60}O_8$: C, 84.26; H, 5.05; Found: C, 84.11, H, 4.94.

1.3.3. Cyclophane 3c. Yield 28%, mp 206°C; $[\alpha]_D^{25}=-146.7$, (*c* 0.1, $CHCl_3$); IR (cm^{-1}) 1724 (CO); ^1H NMR 3.84 (s, 3H), 5.08 (d, 8H, *J*=12.7 Hz), 5.17 (d, 8H, *J*=12.7 Hz), 6.96–7.34 (m, 29H), 7.86–8.14 (m, 8H); ^{13}C NMR 29.5, 70.4, 115.8, 121.6, 123.7, 124.8, 124.9, 125.1, 125.3, 125.5, 125.9,126.1, 126.2, 127.0, 127.9, 128.7, 129.5, 129.4, 134.4, 136.8, 139.4, 140.1, 167.5; Anal. Calcd for $C_{82}H_{58}O_6$:C, 86.44, 5.13; Found: C, 86.31, H, 5.09.

1.3.4. Cyclophane 3d. Yield 40%, mp 215°C; $[\alpha]_D^{25}=-171.3$, (*c* 0.1, $CHCl_3$); IR 1722 (CO); ^1H NMR 3.97 (s, 4H), 5.06 (d, 8H, *J*=12.7 Hz), 5.18 (d, 8H, *J*=12.7 Hz), 7.02–7.42 (m, 30H), 7.82–8.00 (m, 8H); ^{13}C NMR 31.3, 71.6, 115.9, 121.6, 123.4, 124.5, 125.2, 125.4, 125.8, 126.4, 127.5, 128.9, 129.3, 129.4, 134.8, 137.6, 139.9, 141.5, 168.8; *m/z* (FAB-MS) 1194 (M^+); Anal. Calcd for $C_{84}H_{58}O_8$: C, 84.40; H, 4.89; Found: C, 84.31, H, 4.75.

1.3.5. Cyclophane 5a. Dibromide **4a** (0.5 mmol) and (*S*)-binaphthol (0.5 mmol); Yield 38%, mp 208°C; $[\alpha]_D^{25}=-212.5$, (*c* 0.12, $CHCl_3$); ^1H NMR ($CDCl_3$) 4.84 (d, 2H, *J*=12.7 Hz), 4.97 (d, 2H, *J*=12.7 Hz), 5.05 (d, 2H, *J*=14.7 Hz), 5.12 (d, 4H, *J*=14.7 Hz), 6.42 (d, 4H, *J*=8.8 Hz), 6.75 (d, 4H, *J*=8.8 Hz), 7.16–7.36 (m, 12H), 7.82–7.85 (m, 4H); ^{13}C NMR 69.5, 70.7, 115.4, 116.4, 120.8, 123.6, 125.3, 125.5, 125.7, 126.3, 127.8, 127.9, 128.9, 129.0, 129.4, 129.6, 134.1, 137.8, 153.9, 157.0; *m/z* (EI, 70 eV) 600 (M^+); Anal. Calcd for $C_{42}H_{32}O_4$: C, 83.98; H, 5.37; Found: C, 83.91, H, 5.25.

1.3.6. Cyclophane 5b. Dibromide **4b** (0.5 mmol) and (*S*)-binaphthol (0.5 mmol); Yield 29%, mp 208°C; $[\alpha]_D^{25}=-210$, (*c* 0.1, $CHCl_3$); ^1H NMR ($CDCl_3$) 1.77 (s, 3H); 4.85 (d, 2H, *J*=12.7 Hz), 4.99 (d, 2H, *J*=12.7 Hz), 5.12 (d, 2H, *J*=14.7 Hz), 5.21 (d, 2H, *J*=14.7 Hz), 6.46 (d, 4H, *J*=8.8 Hz), 6.82 (d, 4H, *J*=8.8 Hz), 7.20–7.32 (m, 12H), 7.93 (s, 2H); ^{13}C NMR 30.5, 69.8, 70.9, 115.7, 116.2, 120.8, 123.6, 125.5, 125.6, 126.3, 126.7, 127.8, 127.9, 128.9, 129.4, 129.6, 129.9, 134.1, 136.8, 153.0, 157.0, 170.4; *m/z* (EI, 70 eV) 703 (M^+); Anal. Calcd for $C_{44}H_{33}NO_8$: C, 75.10; H, 4.73, N, 1.99; Found: C, 74.97; H, 54.69, N, 1.91.

1.3.7. Cyclophane 7. Dibromide **6** (0.5 mmol) and (*S*)-binaphthol (0.5 mmol); Yield 42%, mp 213°C; $[\alpha]_D^{25}=-75.47$, (*c* 0.31, $CHCl_3$); ^1H NMR ($CDCl_3$) 4.83 (d, 2H, *J*=12.7 Hz), 4.96 (d, 2H, *J*=12.7 Hz), 5.18 (d, 2H, *J*=14.2 Hz), 5.21 (d, 2H, *J*=14.2 Hz), 6.57 (d, 4H, *J*=8.8 Hz), 6.82 (d, 4H, *J*=8.8 Hz), 7.14–7.36 (m, 10H), 7.57 (t, 1H, *J*=7.8 Hz), 7.82 (t, 4H, *J*=6.8 Hz); ^{13}C NMR 70.7, 70.9, 115.2, 116.6, 120.8, 121.2, 123.6, 125.3, 126.2, 127.8, 128.0, 128.9, 129.4, 129.6, 134.1, 137.7, 153.9, 156.9, 157.1; *m/z* (EI, 70 eV) 601 (M^+); Anal. Calcd for $C_{41}H_{31}NO_4$: C, 81.84; H, 5.19; N, 2.33; Found: C, 81.81, H, 5.15, N, 2.28.

1.3.8. Cyclophane 9. Dibromide **8** (1 mmol) and (*S*)-binaphthol (1 mmol); yield 41%, mp 213°C; $[\alpha]_D^{25}=-47.7$, (*c* 0.5, $CHCl_3$); IR (cm^{-1})1660 (CO); ^1H NMR 4.85 (d, 2H, *J*=12.7 Hz), 5.19 (d, 2H, *J*=12.7 Hz), 7.14 (d, 4H, *J*=7.8 Hz), 7.24 (d, 2H, *J*=8.3 Hz), 7.33 (s, 2H), 7.35 (s, 2H), 7.38 (d, 2H, *J*=8.3 Hz), 7.55 (d, 4H, *J*7.8 Hz), 7.63 (s, 1H), 7.71 (t, 1H, *J*=7.8 Hz), 7.88 (t, 4H, *J*=9.3 Hz), 8.25 (d, 2H, *J*=7.8 Hz); ^{13}C NMR 70.7, 115.6, 120.5,123.8, 125.3, 126.5, 127.3, 127.9, 129.3, 129.4, 129.7, 132.9, 134.2, 135.8, 136.4, 136.8, 142.2, 153.8, 195.1; *m/z* (EI, 70 eV) 596 (M^+); Anal. Calcd for $C_{42}H_{28}O_4$: C, 84.54; H, 4.73; Found: C, 84.51, H, 4.68.

1.3.9. Synthesis of dibromide 8. Isophthaloyl chloride (2.03 g, 10 mmol) in toluene (100 mL) was added anhydrous $AlCl_3$ (13.34 g, 0.1 m) at 0°C) in portions over a period of 30 min after which the reaction mixture was stirred at room temperature for 8 h. The reaction mixture was then acidified with 4N HCl and extracted with CH_2Cl_2, washed with water, dried ($MgSO_4$). Evaporation of the solvent afforded the diketone in 67% yield. The diketone (3.144 g, 10 mmol) and NBS (3.916 g, 22 mmol was refluxed in CCl_4 with benzoyl peroxide for 24 h, after which the reaction mixture was filtered and evaporated to dryness. The residue obtained was purified by column chromatography over SiO_2 using $CHCl_3$/hexane (1:1) to furnish the dibromide **8**. Yield 75%, mp 176°C; IR 1660 (CO); ^1H NMR 4.56 (s, 4H), 6.96 and 7.21 (d, 8H, *J*=8.8 Hz), 7.14 (s, 1H), 7.34 (t, 1H, *J*=4 Hz), 7.56 (d, 2H, *J*=4 Hz); Anal. Calcd for $C_{22}H_{16}Br_2O_2$: C, 55.96, H, 3.42; Found: C, 55.72; H, 3.30.

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