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Diversity-oriented approach to cyclophanes via Claisen rearrangement and ring-closing metathesis as key steps

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Abstract

Among numerous reactions to prepare cyclophane derivatives, Claisen rearrangement reaction is very useful. We have prepared cyclophanes containing ethylelene oxy bridge by double Claisen rearrangement reaction and ring-closing metathesis reaction as key steps.

Keywords

Cyclophanes / Claisen rearrangement / Metathesis / Hydrogenation / Macrocycle

Cyclophanes[1-10] play an important role in designing host—guest molecules, molecular self-assembly, charge-transfer agents, transistors, and sensors. Also, cyclophanes containing heterocyclic unit are known to exhibit biological activities such as antimicrobial,[11] anti-inflammatory,[12] and antifungal.[13, 14] Recently, novel approaches to design intricate cyclophanes are actively pursued.[15-19] To this end, various name reactions have been employed in assembling cyclophane derivatives. Claisen rearrangement[20-25] has been used to create cyclophane derivatives. Among several variations of Claisen rearrangement (CR), aromatic Claisen rearrangement was used to create polyaromatic compounds,[26, 27] calixarenes,[28] crownophanes,[29, 30] and rotaxanes.[31, 32] In continuation of our efforts[33-35] to design various macrocycles, we conceived double Claisen rearrangement (DCR)[36, 37] and ring-closing metathesis[38-42] (RCM) as key steps to assemble a library of cyclophane derivatives. The strategy used here consists of double Claisen rearrangement followed by ring-closing metathesis to generate cyclophane molecules.

Our previous approaches to synthesize cyclophane molecules resulted in uncyclized product.[43] We thought of increasing the chain length between two aromatic moieties and in this regard ethylene oxy linkage was considered as a viable option. Based on this concept, we devised a simple strategy for the synthesis of cyclophanes by double Claisen rearrangement (DCR) and RCM as key steps (Figure 1).

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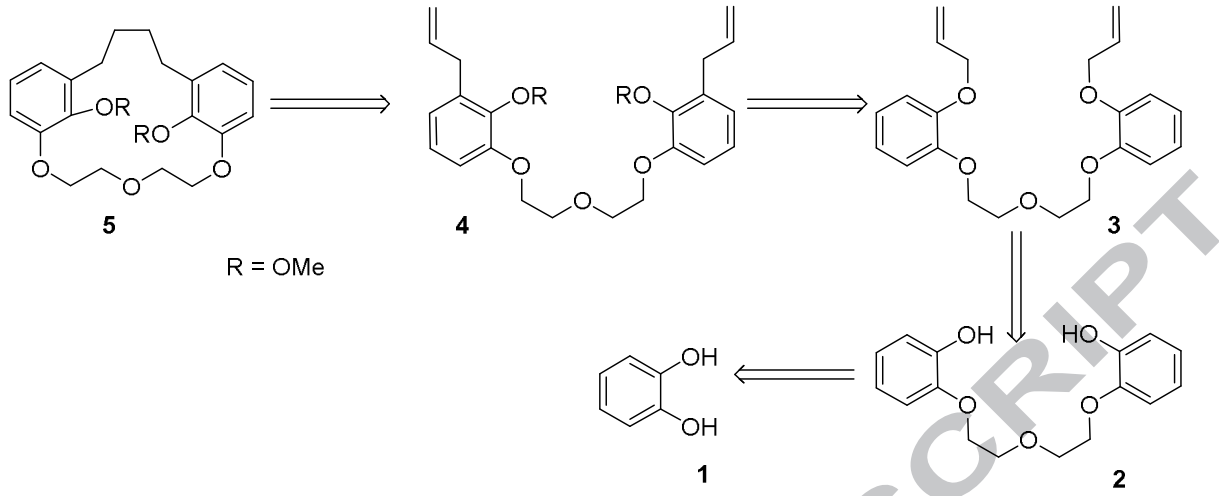
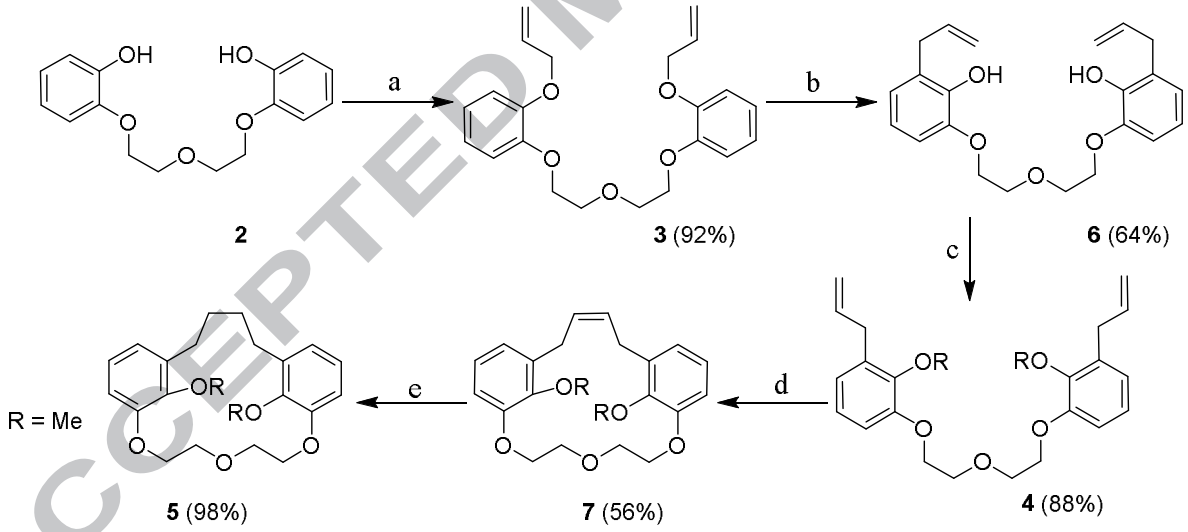


Figure 1. Retrosynthetic analysis to *meta*-cyclophane derivative **5**.

To realize the strategy shown in Figure 1, bisphenol derivative **2** was prepared according to the literature procedure[44] and it was treated with 3-bromoprop-1-ene to give o-allylated compound **3** in 92% yield. DCR of **3** was carried out in 1,2-dichlorobenzene at reflux temperature to generate the rearranged product **6** in 64% yield.



Reagents and conditions: (a) 3-bromoprop-1-ene, acetone, 12 h, reflux; (b) dichlorobenzene, 24 h, reflux; (c) MeI, K_2CO_3, acetone, 6 h, reflux; (d) G-I or G-II, toluene, 12 h, reflux; (e) H_2, Pd/C, ethyl acetate, 12 h, rt.

Scheme 1. Preparation of cyclophane **5** by using DCR and RCM strategy.

Compound **6** was subjected to RCM in presence of Grubb's first generation catalyst (G-I) and Grubb's second generation catalyst (G-II) to deliver a low yield of cyclized product. A literature report indicates that the free –OH group present in the phenol moiety inhibits the RCM process.[45] Therefore, -

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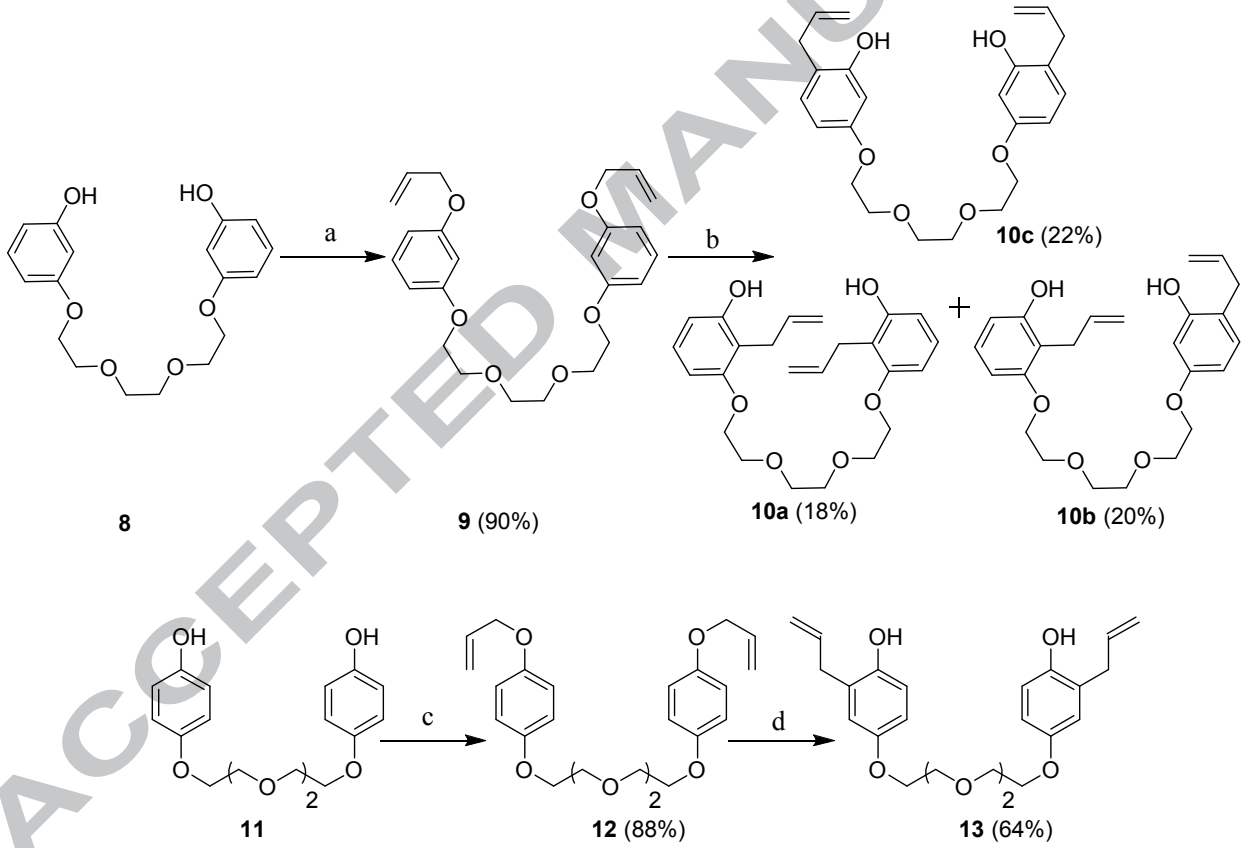
OH groups were protected as methyl ether groups to generate **4** (88% yield). Later, the dimethoxy derivative **4** was subjected to RCM protocol in the presence of G-I or G-II to deliver **7** in 56% yield which was further hydrogenated in the presence of Pd/C under 1 atm pressure of H_2 to give cyclophane derivative **5** in 98% yield (Scheme 1).

To generalize this strategy to other cyclophane derivatives, precursors **8** and **11** were synthesized by using readily available starting materials such as resorcinol and hydroquinone moieties respectively.[46] To generate a library of cyclophane derivatives, the ethylene oxy chain length was varied. Bisphenol **8** was subjected to alkylation with 3-bromoprop-1-ene to generate **9** in 90% yield. DCR of **9** gave three regio-isomeric products **10a-c** which were separated by column chromatography. These three isomers **10a**, **10b**, and **10c** were separately methylated by using methyl iodide to generate the corresponding dimethoxy derivatives **14a-c** (Scheme 2).



Reagents and conditions: (a) 3-bromoprop-1-ene, K_2CO_3, acetone, 12 h, reflux; (b) dichlorobenzene, 24 h, reflux; (c) 3-bromoprop-1-ene, K_2CO_3, acetone, 12 h, reflux; (d) dichlorobenzene, 24 h, reflux.

Scheme 2. Preparation of substrates **10a-c** and **13** by DCR reaction.

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Compounds **14a-c** were subjected to RCM with G-I catalyst to give the respective cyclized products **15a-c**. Further, hydrogenation of unsaturated cyclophane derivatives **15a-c** was carried out under 1 atm. pressure of H_2 to deliver saturated derivatives **16a-c**. Interestingly, **14c** on RCM reaction gives inseparable mixture of two isomeric products, in which one isomer having both methoxy groups are *cis* to each other while other isomer having methoxy group on opposite side. The difference in chemical shift of olefinic protons of these two isomers is 0.3 ppm. This type of atropisomerism in cyclophanes is rare in literature.[47] Hydrogenation of the corresponding mixture gave single product **16c**, and its structure is supported by ^{1}H NMR and ^{13}C NMR spectral data.

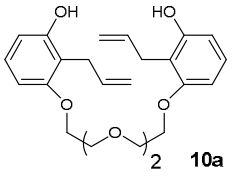
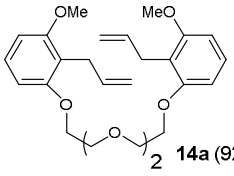
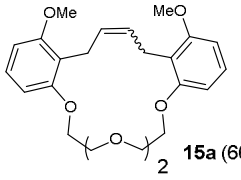
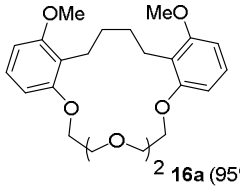
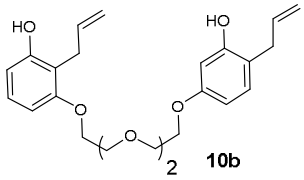
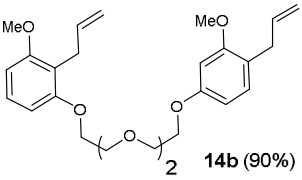
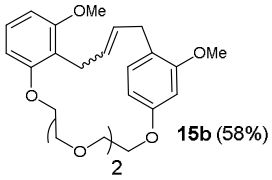
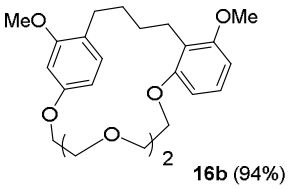
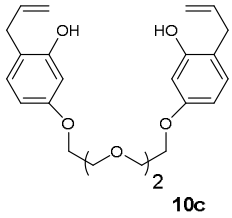
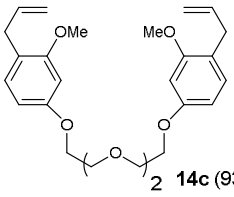
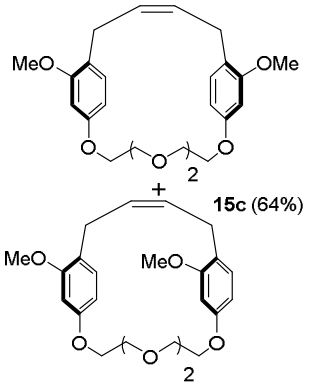
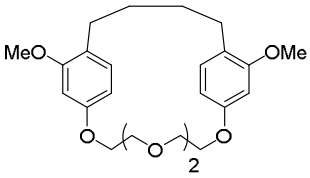
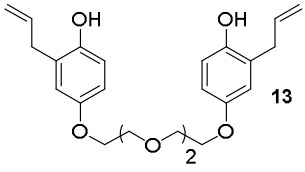
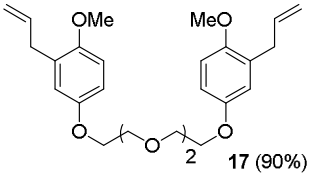
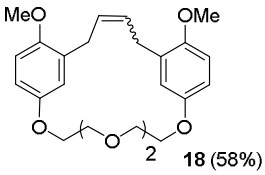
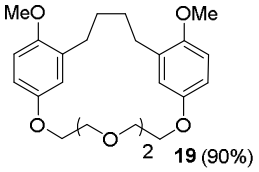
Claisen product	Methylation product	RCM product	Hydrogenated product
 **10a**	 **14a** (92%)	 **15a** (66%)	 **16a** (95%)
 **10b**	 **14b** (90%)	 **15b** (58%)	 **16b** (94%)
 **10c**	 **14c** (93%)	 **15c** (64%)	 **16c** (94%)
 **13**	 **17** (90%)	 **18** (58%)	 **19** (90%)

Table 1 List of cyclophane derivatives prepared by DCR and RCM strategy.

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Along similar lines, *O*-allyl precursor **12** was prepared which underwent DCR in dichlorobenzene to give **13** (64% yield). Compound **13** was methylated to provide compound **17** which was further reacted with G-I to deliver RCM product **18** (58% yield). Hydrogenation of **36** with Pd/C in presence of H_2 gave cyclophane **19** in 90% yield.

We have designed interesting strategies towards the synthesis of cyclophane derivatives by DCR and RCM as key steps. Diverse cyclophane derivatives were successfully assembled when ethylene oxy tether was employed for connecting the two phenolic moieties. Later, double Claisen rearrangement and RCM protocols were found to be useful to design various cyclophane derivatives.

Acknowledgments

The authors thank the Council of Scientific and Industrial Research (CSIR), New Delhi and the Department of Science and Technology (DST), New Delhi for financial support. Sophisticated Analytical Instrument Facility (SAIF), Mumbai is thanked for providing the spectroscopic data. G. T. W thanks CSIR for the award of a research fellowship. S. K thanks DST for the award of a J. C. Bose fellowship. We thank the reviewers for the useful suggestions.

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General procedure for *O*-allylation

To a stirred solution of bisphenol (**2**, **8**, or **11**) (1 mmol) in acetone (15 mL) was added K_2CO_3 (5 mmol) and the resultant suspension was stirred for 30 min. Then, allyl bromide (3 mmol) was added dropwise into the reaction mixture over a period of 10 minutes. Further, reaction mixture was stirred for 12 h at reflux. At the conclusion of reaction (TLC monitoring), the crude mixture was filtered through Celite pad (washed with CH_2Cl_2) and concentrated under reduced pressure. The crude product was purified by column chromatography (silica-gel, 5% EtOAc-petroleum ether)

3: (yellow oil); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.95-3.98 (m, 4H), 4.18-4.21 (m, 4H), 4.56-4.58 (td, J_1 = 1.6 Hz, J_2 = 5.8 Hz, 4H), 5.24 (ddd, J_1 = 1.8 Hz, J_2 = 3.1 Hz, J_3 = 7.0 Hz, 2H), 5.38 (ddd, J_1 = 1.8 Hz, J_2 = 3.0 Hz, J_3 = 7.1 Hz, 2H), 6.01-6.10 (m, 2H), 6.87-6.95 (m, 8H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 69.04, 70.12 (2), 114.66, 114.90, 117.57, 121.55, 121.68, 133.74, 148.90, 149.01: HRMS (Q-Tof) m/z: $[M+Na]^+$ calcd. for $C_{22}H_{26}O_5Na$ 393.1675, found 393.1672; IR (neat): υ_{max}: 745, 1128, 1266, 1508, 1591, 2926, 2982 cm^{-1}.

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9: (yellow oil); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.74 (s, 4H), 3.85 (t, *J* = 4.4 Hz, 4H), 4.10 (t, *J* = 4.4 Hz, 4H), 4.49 (d, *J* = 5.2 Hz, 4H), 5.25-5.41 (m, 4H), 5.99-6.08 (m, 2H), 6.47-6.54 (m, 6H), 7.14 (t, *J* = 8 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 67.54, 68.95, 69.93, 71.02, 102.03, 107.14, 107.40, 117.82, 129.98, 133.40, 159.93, 160.13; HRMS (Q-Tof) m/z: $[M+Na]^+$ calcd. for $C_{24}H_{30}O_6K$ 453.1671, found 453.1674;IR (neat): υ_{max}: 740, 1265, 1453, 1598, 2873, 3054 cm^{-1}.

12: (yellow oil); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.70 (s, 4H), 3.83 (t, *J* = 5.3 Hz, 4H), 4.07 (t, *J* = 5.3 Hz, 4H), 4.46 (td, J_1 = 1.1 Hz, J_2 = 5.3 Hz, 4H), 5.24-5.41 (m, 4H), 5.99-6.08 (m, 2H), 6.83 (s, 8H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 68.21, 69.61, 70.06, 71.00, 115.74, 115.79, 117.65, 133.74, 153.06, 153.22; HRMS (Q-Tof) m/z: $[M+Na]^+$ calcd. for $C_{24}H_{30}O_6Na$ 437.1943, found 437.1935; IR (neat): υ_{max}: 743, 1112, 1229, 1265, 1456, 1506, 2987, 3054 cm^{-1}.

General procedure for Claisen rearrangement

Product obtained by allylation (**3**, **9**, or **12**) (1 mmol) was dissolved in dichlorobenzene (10 mL) and reaction mixture was heated at reflux for a period of 24 h After completion of the reaction (TLC monitoring), reaction mixture was cooled. Crude reaction mixture was directly subjected to column chromatography. Dichlorobenzene was removed by elution with petroleum ether. Further elution of compound was done by using petroleum ether/ethyl acetate mixture.

6: (colourless oil); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.43 (d, *J* = 6.7 Hz, 4H), 3.82-3.84 (m, 4H), 4.17-4.19 (m, 4H), 5.02-5.10 (m, 4H), 5.97-6.07 (m, 2H), 6.74-7.24 (m, 6H), 7.28 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 34.16, 69.64, 69.83, 113.51, 115.54, 119.51, 124.00, 127.53, 136.96, 145.37, 145.71; HRMS (Q-Tof) m/z: $[M+Na]^+$ calcd. for $C_{22}H_{26}O_5Na$ 393.1674, found 393.1672; IR (neat): υ_{max}: 736, 1265, 1455, 1586, 2935, 2984, 3690 cm^{-1}.

10a: (colourless oil); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.45 (d, *J* = 6.2 Hz, 4H), 3.74 (s, 4H), 3.85 (t, *J* = 4.7 Hz, 4H), 4.10 (t, *J* = 4.7 Hz, 4H), 5.91-6.00 (m, 2H), 6.41-6.50 (m, 4H), 6.46 (dd, J_1 = 2.9 Hz, J_2 = 8.3 Hz, 4H), 7.02 (t, *J* = 8.0 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 27.73, 68.34, 70.05, 71.13, 104.74, 109.20, 114.33, 115.58, 127.66, 136.60, 155.38, 157.56; HRMS (Q-Tof) m/z: $[M+Na]^+$ calcd. for $C_{24}H_{30}O_6Na$ 437.1935, found 437.1931; IR (neat): υ_{max}: 728, 1268, 1422, 1596, 2927, 2986, 3584 cm^{-1}.

13: (colourless oil); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.33 (d, *J* = 6.0 Hz, 4H), 3.72 (s, 4H), 3.82 (t, *J* = 6.0 Hz, 4H), 4.03 (t, *J* = 6.0 Hz, 4H), 5.01 (bs, 2H), 5.09-5.14 (m, 4H), 5.90-6.01 (m, 2H), 6.61-6.72 (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 35.30, 68.10, 70.09, 70.95, 113.55, 116.52, 116.61, 117.02, 126.70, 136.39, 148.34, 152.94; HRMS (Q-Tof) m/z: $[M+Na]^+$ calcd. for $C_{24}H_{30}O_6Na$ 437.1935, found 437.1943; IR (neat): υ_{max}: 749, 1262, 1422, 1506, 2987, 3055, 3689 cm^{-1}.

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General procedure for methylation of phenol derivatives

To a stirred solution of Claisen rearrangement product (**6**, **10a**, or **13**) (1 mmol) dissolved in acetone (15 mL), K_2CO_3 (5 mmol) was added and the resultant suspension was stirred for 30 min. Then MeI (10 mmol) was added and reaction mixture was further stirred for 6 h. At the conclusion of reaction (TLC monitoring), the crude mixture was filtered through Celite pad (washed with CH_2Cl_2) and concentrated under reduced pressure. The crude product was purified by column chromatography (silica-gel, 5% EtOAc-petroleum ether) to afford **4**, **14a**, or **17**.

4: (colourless oil); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.40 (d, *J* = 6.6 Hz, 4H), 3.82 (s, 6H), 3.95 (t, *J* = 4.6 Hz, 4H), 4.17 (t, *J* = 4.6 Hz, 4H), 5.02-5.07 (m, 4H), 5.91-6.01 (m, 2H), 6.77-7.81 (m, 4H), 6.96 (t, *J* = 7.9 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 34.29, 60.78, 68.52, 70.18, 112.52, 115.66, 122.67, 123.92, 134.27, 137.50, 147.69, 152.09; HRMS (Q-Tof) m/z: $[M+Na]^+$ calcd. for $C_{24}H_{30}O_5Na$ 421.1985, found 421.1985; IR (neat): υ_{max}: 740, 1265, 1422, 1965, 2986, 3555 cm^{-1}.

14a: (colourless oil); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.42 (d, *J* = 6.3 Hz, 4H), 3.74 (s, 4H), 3.80 (s, 6H), 3.86 (t, *J* = 5.2 Hz, 4H), 4.03 (t, *J* = 5.2 Hz, 4H), 4.89-5.01 (m, 4H), 5.99-6.01 (m, 2H), 6.53 (dd, J_1 = 5.8 Hz, J_2 = 8.3 Hz, 4H), 7.11 (t, *J* = 8.3 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 27.59, 56.01, 68.39, 70.12, 71.20, 104.26, 105.30, 114.23, 117.27, 127.25, 137.15, 157.61, 158.49; HRMS (Q-Tof) m/z: $[M+Na]^+$ calcd. for $C_{26}H_{34}O_6Na$ 465.2248, found 465.2248; IR (neat): υ_{max}: 745, 1266, 1421, 1595, 2986, 3054 cm^{-1}.

17: (colourless oil); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.34 (d, *J* = 6.6 Hz, 4H), 3.74 (s, 4H), 3.77 (s, 6H), 3.83 (t, *J* = 4.7 Hz, 4H), 4.07 (t, *J* = 4.7 Hz, 4H), 5.01-5.07 (m, 4H), 5.91-6.01 (m, 2H), 6.70-6.76 (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 34.41, 56.17, 68.11, 70.09, 70.99, 111.42, 112.37, 115.80, 117.23, 129.93, 136.88, 151.85, 152.86; HRMS (Q-Tof) m/z: $[M+Na]^+$ calcd. for $C_{26}H_{34}O_6Na$ 465.2248, found 465.2247; IR (neat): υ_{max}: 745, 896, 1266, 1274, 1464, 1495, 1638, 2911, 2986, 3054 cm^{-1}.

General procedure for RCM

Product obtained by methylation (**4**, **14a**, or **17**) was dissolved in dry toluene (10 mL) and degassed with nitrogen for 15 min. Then, Grubbs first generation catalyst (5 mol %) was added and reaction mixture was refluxed overnight. At the conclusion of reaction (TLC monitoring), the crude mixture was filtered through Celite pad (washed with CH_2Cl_2) and concentrated under reduced pressure. The crude product was purified by column chromatography (silica-gel/ EtOAc-petroleum ether) to afford cyclophane derivatives **7**, **15a**, or **18** respectively.

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7: (colourless oil); ^{1}H NMR (500 MHz, $CDCl_3$): δ = 3.32 (d, *J* = 6.0 Hz, 4H), 3.81 (s, 6H), 3.88 (t, *J* = 5.1 Hz, 4H), 4.09 (t, *J* = 5.1 Hz, 4H), 4.71-4.80 (m, 2H), 6.60 (dd, J_1 = 2.1 Hz, J_2 = 8.3 Hz, 4H), 7.10 (t, *J* = 8.3 Hz, 2H); ^{13}C NMR (125.75 MHz, $CDCl_3$): δ = 34.55, 59.69, 68.56, 69.42, 112.57, 112.89, 122.80, 123.13, 130.04, 135.47, 151.40; HRMS (Q-Tof) m/z: $[M+Na]^+$ calcd. for $C_{22}H_{26}O_5Na$ 393.1672, found 393.1679; IR (neat): υ_{max}: 742, 1265, 1456, 1598, 2883, 3054 cm^{-1}.

15a: (colourless oil); (cis/trans isomer ratio = 1:5): ^{1}H NMR (500 MHz, $CDCl_3$): δ = 3.41 (d, *J* = 6.1 Hz, 4H), 3.74 (s, 4H), 3.81 (s, 6H), 3.88-3.90 (m, 4H), 4.09-4.11 (m, 4H), 5.69 (td, J_1 = 1.8 Hz, J_2 = 3.9 Hz, 2H), 6.47-6.54 (m, 4H), 7.08 (t, *J* = 8.3 Hz, 2H); ^{13}C NMR (125.75 MHz, $CDCl_3$): δ = 26.89, 56.08, 68.27, 69.97, 71.26, 104.25, 104.47, 118.17, 126.82, 128.52, 157.45, 158.36; HRMS (Q-Tof) m/z: $[M+Na]^+$ calcd. for $C_{24}H_{30}O_6Na$ 437.1935, found 437.1933; IR (neat): υ_{max}: 748, 1266, 1454, 1472, 1594, 2987, 3054 cm^{-1}.

18: (colourless oil); (cis/trans isomer ratio = 1:5): ^{1}H NMR (500 MHz, $CDCl_3$): δ = 3.41 (d, *J* = 6.1 Hz, 4H), 3.74 (s, 4H), 3.79 (s, 6H), 3.82 (t, *J* = 5.3 Hz, 4H), 4.03 (t, *J* = 5.3 Hz, 4H), 5.68 (t, *J* = 2.5 Hz, 2H), 6.66-6.89 (m, 6H); ^{13}C NMR (125.75 MHz, $CDCl_3$): δ = 26.91, 32.18, 56.12, 56.20, 67.99, 68.03, 69.94, 69.98, 70.83, 70.91, 111.10, 111.16, 111.54, 116.59, 116.70, 128.72, 130.29, 130.51, 130.80, 151.51, 151.69, 153.05, 153.09; HRMS (Q-Tof) m/z: $[M+Na]^+$ calcd. for $C_{24}H_{30}O_6Na$ 437.1935, found 437.1943; IR (neat): υ_{max}: 745, 1104, 1258, 1472, 1594, 2932 cm^{-1}.

General procedure for hydrogenation

RCM product obtained (**7**, **15a**, or **18**) (0.5 mmol) was dissolved in ethyl acetate (10 mL) and 5% Pd/C was added. Further, reaction mixture was stirred at rt under hydrogen atmosphere (1 atm) for 12 h. After the completion of the reaction (TLC monitoring), the crude mixture was filtered through Celite pad and the solvent was evaporated under reduced pressure. The crude product was purified by silica gel column chromatography. Elution of the column with 10% (ethyl acetate/ petroleum ether) gave the hydrogenated products **5**, **16a**, or **19** respectively.

5: (colourless oil); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.60 (bs, 4H), 2.70 (bs, 4H), 3.80 (s, 6H), 3.83 (t, *J* = 5.4 Hz, 4H), 4.08 (t, *J* = 5.4 Hz, 4H), 6.55 (dd, J_1 = 2.2 Hz, J_2 = 8.3 Hz, 4H), 7.08 (t, *J* = 8.3 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 23.76, 30.46, 55.8, 69.89, 70.88, 104.04, 104.44, 120.20, 126.47, 155.60, 158.55; HRMS (Q-Tof) m/z: $[M+Na]^+$ calcd. for $C_{22}H_{28}O_5Na$ 395.1829, found 395.1826; IR (neat): υ_{max}: 747, 1266, 1453, 1506, 2925, 3402 cm^{-1}.

16a: (colourless oil); ^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.57 (bs, 4H), 2.66 (bs, 4H), 3.82 (s, 6H), 3.82 (s, 4H), 3.89 (t, *J* = 3.8 Hz, 4H), 4.10 (t, *J* = 3.8 Hz, 4H), 6.50 (dd, J_1 = 2.2 Hz, J_2 = 8.3 Hz, 4H), 7.08 (t, *J* =

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3.8 Hz, 2H); ^{13}C NMR (125.75 MHz, $CDCl_3$): δ = 23.78, 30.46, 55.95, 68.62, 69.90, 70.88, 104.07, 104.44, 120.20, 126.47, 157.60, 158.51; HRMS (Q-Tof) m/z: $[M+Na]^+$ calcd. for $C_{24}H_{32}O_6Na$ 439.2091, found 439.2091; IR (neat): υ_{max}: 747, 1266, 1453, 1506, 2925, 3402 cm^{-1}.

19: (colourless oil); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.60 (bs, 4H), 2.62 (bs, 4H), 3.73 (s, 6H), 3.76 (s, 4H), 3.83 (bs, 4H), 4.07 (bs, 4H), 6.65-6.67 (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 27.91, 29.08, 56.12, 68.33, 69.85, 70.88, 111.22, 111.76, 117.80, 132.09, 152.04, 152.70; HRMS (Q-Tof) m/z: $[M+Na]^+$ calcd. for $C_{24}H_{32}O_6Na$ 439.2091, found 439.2090; IR (neat): υ_{max}: 747, 1266, 1453, 1506, 2925, 3402 cm^{-1}.

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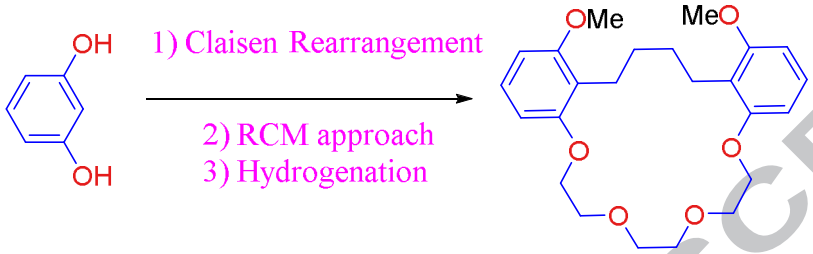
Graphical Abstract



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