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Diversity Oriented Approach to Crownophanes by Enyne Metathesis and Diels–Alder Reaction as Key Steps

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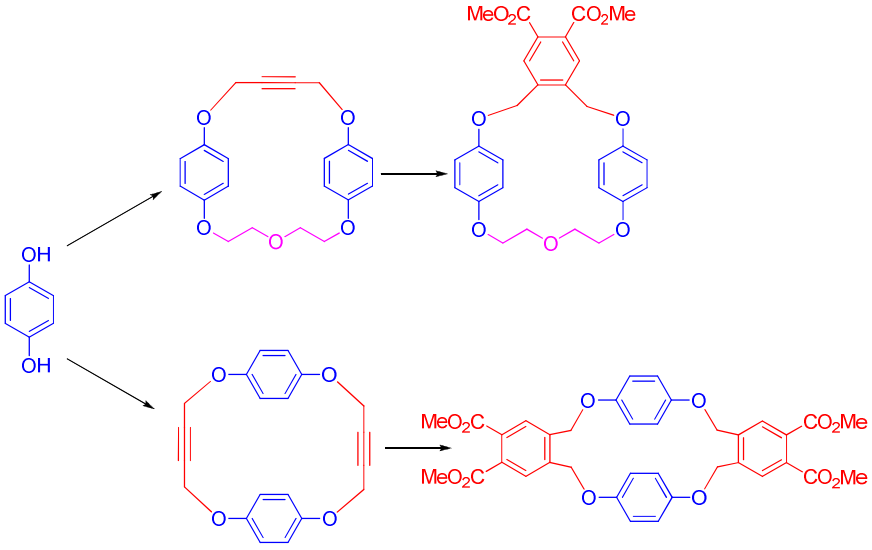
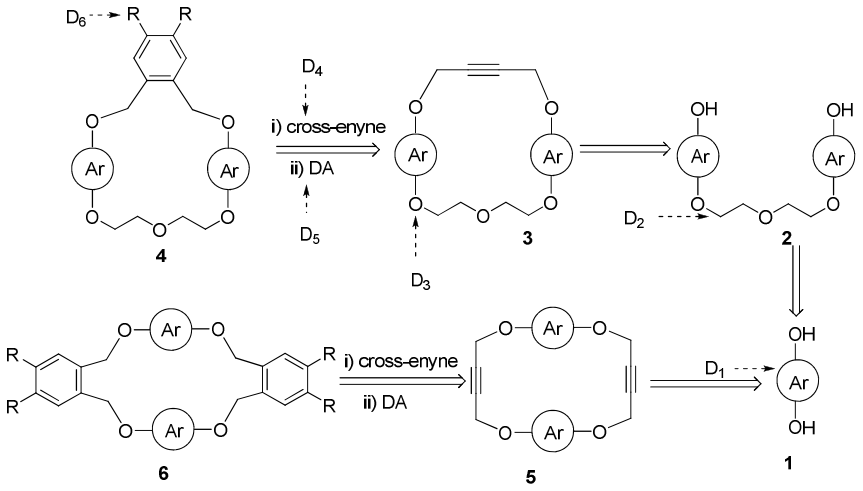


Various crownophanes are assembled starting with simple phenol derivatives such as catechol, resorcinol and hydroquinone. Here, cross enyne metathesis (CEM) and Diels–Alder (DA) reaction have been used as key steps. This strategy has embedded six diversity points.

The pioneering studies of Pederson, Lehn and Cram was the beginning of molecular recognition.[1,2] Structural rigidity in macrocycles draws a special attention in supramolecular chemistry[3] due to the binding properties, and their extended use in material science. Crownophanes exhibit hybrid properties of crown ethers[4] and cyclophanes[5,6] in structural aspect. They are also useful building blocks in supramolecular chemistry. Ethylene oxy linkage present in crown ether moiety provides flexibility and the phenyl rings impart rigidity to the macrocyclic system. Moreover, hard oxygen atoms can act as redox active components. Crownophanes are also used as hosts for cation, anion, and neutral molecules. Haptoselectivity[7] (binding of more than one metal atoms in the molecule) in crownophanes is an interesting aspect in macrocycles.

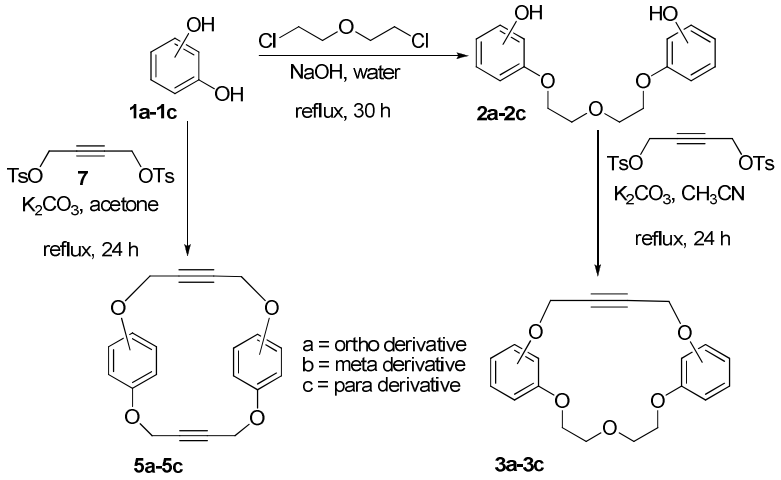
Enzymes and biomembranes contain a variety of ions and their functions are understood on the basis of molecular recognition principles. Macrocycles like crownophanes can play crucial role in similar processes. A variety of olefination reactions are utilized during the formation of cyclophanes. For example, McMurry reaction, Ramberg-Backlund reaction, ring-closing metathesis (RCM), and Wittig reaction.[8] Cross enyne metathesis (CEM)[9] is a useful tool to create diene moieties in the macrocyclic system. CEM involving ethylene as a coupling partner is an atom economy reaction.[10] Although, crownophanes are prepared by different routes,[11] assembly of crownophanes by a simple and general strategy is worthy of systematic investigation. Our strategy to crownophanes hinges on double cross enyne metathesis and Diels–Alder (DA) reaction as key steps. By adopting the same strategy we are able to prepare both symmetrical as well as unsymmetrical crownophanes. Symmetrical crownophane synthesis involves two direction synthesis.[12] There are six diversity points (D_1-D_6, Scheme 1) in our strategy. Utilization of double cross enyne metathesis to design polycyclics is rare, and here we report our results to assemble crownophanes via enyne metathesis, and DA reaction as key steps. These two strategies are powerful tools to install C–C bonds, and a strategic combination of these two reactions can be used to create diverse polycyclic aromatic compounds to achieve ‘‘step economy”.[13a-f] At each stage of diversity point, by judicious selection of proper functional groups, one can generate a library of cyclophane derivatives containing crown ether moieties. In our theme, one can visualize involvement of a variety of tactics to generate diversity. For example, choice of various resorcinol derivatives (D_1) (e. g. -*m*, -*o*, -*p* derivatives and the other corresponding heteroaromatics) ethylene oxy linkage can be extended (D_2), or oxygen atom can be replaced by other heteroatoms (D_3). CEM provides an opportunity to introduce various ethylene derivatives (D_4). During the DA sequence a variety of dienophiles (D_5) can be

incorporated in cyclophane moiety. Electron withdrawing groups such as ester functionality can easily be introduced during the DA sequence. The ester group can be further synthetically manipulated to generate additional diversity (D_6) in the target macrocyclic system.



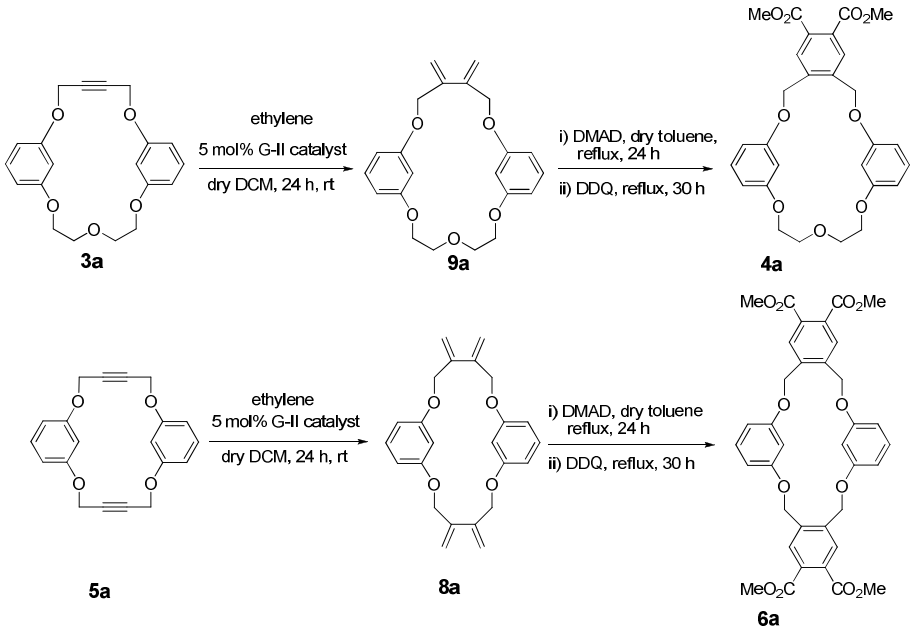
Scheme 1. diversity strategy to crownophanes involving various points

The First step in our journey towards crownophane synthesis involves generation of enyne metathesis precursor such as **3a** (Scheme 2). In this regard, commercially available resorcinol (**1a**) was treated with bis(2-chloroethyl) ether with aqueous NaOH as a base under reflux conditions to generate bisphenol **2a** (37% yield).[14] Similar procedure was employed to generate bisphenols **2b** and **2c**.[15] Although the crown compound **3a** can be prepared by using but-2-yne 1, 4-dibromide[16] we found improved yield of **3a** (97%) by using but-2-yne 1, 4-ditosylate **7**. It is interesting to note that the ditosylate **7** is a better coupling partner in connection with the preparation of **3** (or **5**) rather than the corresponding dibromide [*i.e.,* but-2-yne 1,4-dibromide]. Compound **3a** undergoes CEM in presence of Grubbs second generation catalyst to give the corresponding diene **8a**. ^{1}H NMR spectral data of the diene **8a** indicates the presence of olefin moieties at δ 5.27, and 5.33, which was further supported by ^{13}C NMR spectral data. Various dienes (**8a-8c** and **9a-9c**) prepared here seems to be stable at room temperature and they decompose around 190 °C.



Scheme 2. Preparation of enyne building blocks **3a-3c** and **5a-5c**

Later, the diene **9a** was subjected to DA reaction with DMAD (dimethyl acetylenedicarboxylate) under toluene reflux conditions. The DA product was contaminated with partially aromatized product. Therefore, isolation and identification of the DA adduct was not attempted and the crude product was directly reacted with DDQ (2,3-dichloro-5,6-dicyano-1,4-benzoquinone) to give the aromatized product **4a** in 83% yield after column chromatography (Scheme 3).



Scheme 3. Synthesis of crownophanes via CEM and DA reaction as key steps

To generalize this strategy, we prepared various crownophane derivatives starting with catechol and hydroquinone.

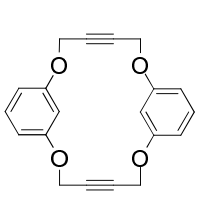
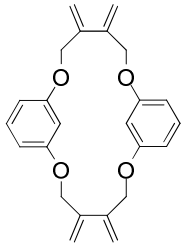
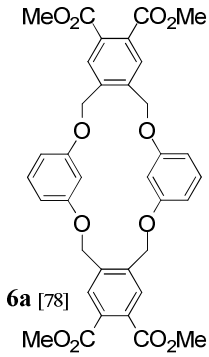
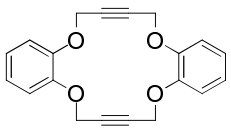
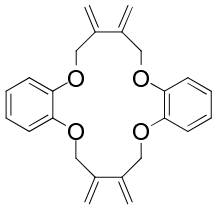
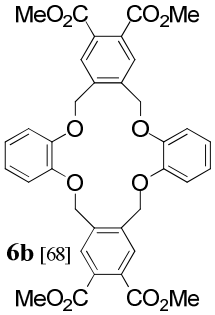
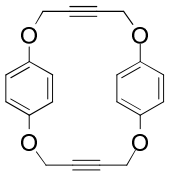
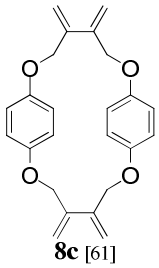
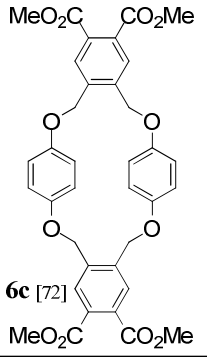
Entry	Starting material	Diene / [Yield %]	Two step yield %
1	 **5a**	 **8a** [78]	 **6a** [78]
2	 **5b**	 **8b** [62]	 **6b** [68]
3	 **5c**	 **8c** [61]	 **6c** [72]

Table 1. Preparation of crownophanes **6a-6c** via CEM and DA reaction as key steps

Along similar lines, compounds **5a-5c** were prepared[17] and subjected to CEM, DA reaction and aromatization sequences to deliver the crownophanes **6a-6c** involving the corresponding diene intermediates **8a-8c** (Table 1).

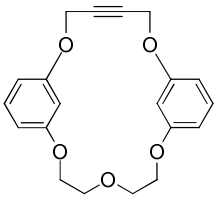
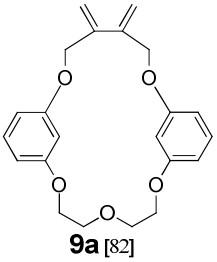
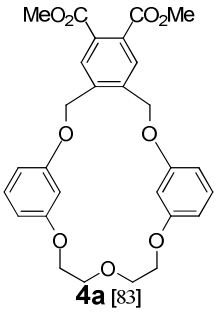
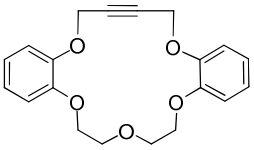
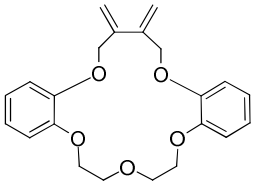
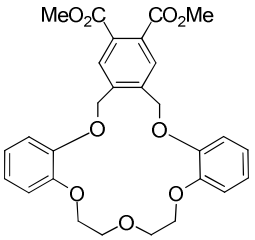
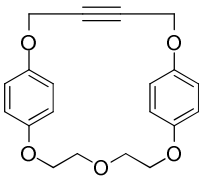
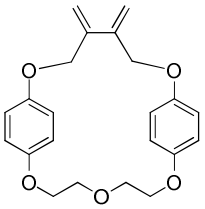
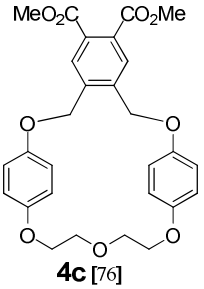
Entry	Starting material	Diene / [Yield %]	Two step yield %
1	 **3a**	 **9a** [82]	 **4a** [83]
2	 **3b**	 **9b** [93]	 **4b** [63]
3	 **3c**	 **9c** [69]	 **4c** [76]

Table 2. Preparation of crownophanes **4a-4c** via CEM and DA reaction as key steps

Various other enyne building blocks that has undergone CEM, DA reaction, and aromatization sequences are shown in Table 2. All the new products obtained in this sequence are well characterized by ^{1}H NMR and ^{13}C NMR spectral data and further supported by HRMS data. Further, dienes **8b** and **9b** were treated with tetracyanoethylene to get crownphanes **10** and **11** with good yield as shown in Table 3.

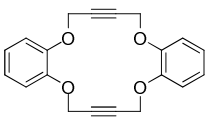
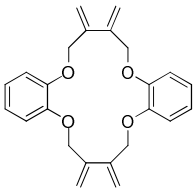
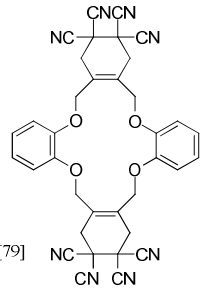
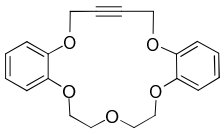
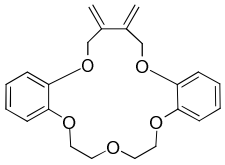
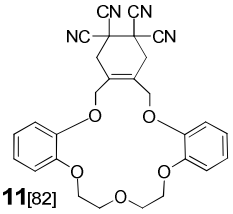
Entry	Starting material	Diene	DA adduct yield
1	 **5b**	 **8b** [62]	 **10**[79]
2	 **3b**	 **9b** [93]	 **11**[82]

Table 3. Preparation of crownophanes **10-11** using tetracyanoethylene as a dienophile

In conclusion, we have demonstrated a new and simple methodology for the synthesis of crownophanes via CEM and DA reaction as key steps, and our strategy has embedded six diversity points which can generate a library of crown compounds. It is interesting to note that our strategy involve creation of eight new C-C bonds during CEM and DA sequence achieving step economy and atom economy. By adopting two directional synthesis the brevity of the synthetic strategy has increased substantially.

Experimental Section

General procedure for cyclization of bisphenol with 7

To a well stirred solution of bisphenol **2a-2c** (500 mg, 1.72 mmol) in dry acetonitrile (20 mL) was added K_2CO_3 (1.18 g, 8.60 mmol) and the reaction mixture was further refluxed for 0.5 h. A solution of but-2-yne 1, 4-ditosylate (681 mg, 1.72 mmol) **7** in acetonitrile was added and refluxed for 24 h. At the conclusion of the reaction (TLC monitoring), the reaction mixture was cooled and filtered through celite. The filtrate was concentrated under reduced pressure to give the crude product, which was further purified by silica gel column chromatography using

appropriate mixture of ethyl acetate/ petroleum ether, which affords pure cyclized product **3a-3c** as a white solid.

3a: 480 mg, yield: 82%; mp: 116-118 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.91 (t, *J* = 4.36 Hz, 4H), 4.11 (t, *J* = 4.35 Hz, 4H), 4.72 (s, 4H), 6.50 (d, *J* = 7.5 Hz, 4H), 6.63 (t, *J* = 1.9 Hz, 2H), 7.11 (t, *J* = 8.3 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 55.8, 67.5, 70.0, 82.6, 102.0, 106.9, 109.3, 129.8, 158.6, 160.1; HRMS (Q-Tof) m/z: $[M+H]^+$ calcd. for $C_{20}H_{21}O_5$ 341.1389, found 341.1393. IR (neat): υ_{max} 1599, 1159, 1351, 2718, 2809 cm^{-1}.

3b: 556 mg, yield: 95%; mp 141-143 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 4.05 (t, *J* = 5.1 Hz, 4H), 4.19 (t, *J* = 5.1 Hz, 4H), 4.71 (s, 4H), 6.88-7.00 (m, 8H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 59.4, 69.3, 70.2, 82.3, 114.9, 117.7, 121.7, 123.4, 148.1, 150.3; HRMS (Q-Tof): m/z = $[M+H]^+$ calcd. for $C_{20}H_{21}O_5$ 341.1389, found 341.1381. IR (neat): υ_{max} 1017, 1124, 1266, 1500, 3034 cm^{-1}.

3c: 463 mg, yield: 79%; mp 150-152 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.84-3.86 (m, 4H), 4.12-4.14 (m, 4H), 4.65 (s, 4H), 6.69 (d, *J* = 2.8 Hz, 4H); 6.70 (d, *J* = 2.8 Hz, 4H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 56.4, 69.1, 70.0, 83.5, 116.3, 116.4, 151.3, 153.5; HRMS (Q-Tof) m/z: $[M+H]^+$ calcd. for $C_{20}H_{21}O_5$ 341.1389, found 341.1393. IR (neat): υ_{max} 739, 896, 1129, 1200, 1509, 1653, 3054 cm^{-1}.

General procedure for the preparation of dienes

Cyclized product **3a-c** or **5a-c** [(100 mg, 0.294 mmol), or (100 mg, 0.313 mmol)] was dissolved in dry DCM (10-20 mL) and it was degassed by N_2 for 5 min., then Grubbs second generation catalyst (5 mol %) was added. Further the reaction mixture was degassed with ethylene, and stirred at rt under ethylene for 24 h. After the completion of the reaction (TLC monitoring), the solvent was removed on a rotavapour. The crude product was purified by silica gel column

chromatography. Elution of the column with appropriate mixture of ethyl acetate/petroleum ether gave the pure diene **9a-c** and **8a-c** as a white solid.

9a: 89.00 mg, yield: 82%; mp 76-78 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.88-3.90 (m, 4H), 4.12-4.13 (m, 4H), 4.76 (s, 4H), 5.27 (s, 2H), 5.33(s, 2H), 6.55 (t, J = 2 Hz, 2H), 6.46-6.49 (ddd, J_1 =1 Hz, J_2 =2 Hz, J_3 = 8 Hz, 2H), 6.57-6.60 (ddd, J_1 = 1 Hz, J_2 = 2 Hz, J_3 = 8 Hz, 2H), 7.15 (t, J = 8Hz, 2H)**;** ^{13}C NMR (100 MHz, $CDCl_3$): δ = 68.0, 69.2, 69.9, 103.2, 106.8, 108.9, 114.5, 129.8, 140.9, 159.6, 160.3; HRMS (Q-Tof) m/z: $[M+H]^+$ calcd. for $C_{22}H_{25}O_5$ 369.1702, found 369.1695. IR (neat): υ_{max} 1155, 1181, 1489, 1603, 2933 cm^{-1}.

9b: 100.00 mg, yield: 93%; mp 78-80 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.97 (t, J = 4.36 Hz, 4H), 4.13 (t, J = 4.36 Hz, 4H), 4.77 (s, 4H), 5.35 (s, 2H), 5.40 (s, 2H), 6.91-7.01 (m, 8H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 69.9, 70.4, 72.1, 115.6, 115.8, 117.0, 121.9, 122.4, 142.2, 149.5, 150.0; HRMS (Q-Tof) m/z: $[M+H]^+$ calcd. for $C_{22}H_{25}O_5$ 369.1702, found 369.1698. IR (neat): υ_{max} 1017, 1124, 1266, 1500, 3034 cm^{-1}.

9c: 75.00 mg, yield: 69%; mp 130-132 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.77-3.79 (m, 4H), 4.12-4.14 (m, 4H), 4.73 (s, 4H), 5.53 (s, 4H), 6.47 (s, 4H), 6.48 (d, J = 9.1 Hz, 4H), 6.66 (d, J = 9.1 Hz, 4H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 69.4, 70.2, 70.5, 116.4, 116.4, 116.8, 141.3, 152.4, 153.0; HRMS (Q-Tof) m/z: $[M+H]^+$ calcd. for $C_{22}H_{25}O_5$ 369.1702, found 369.1699. IR (neat): υ_{max} 896, 1042, 1127, 1266, 1507, 2855 cm^{-1}.

8a: 91.60 mg, yield: 78%; mp 140-142 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 4.71 (s, 8H), 5.20 (s, 4H), 5.29 (s, 4H), 6.54 (dd, J = 8.5 Hz, J = 2 Hz, 4H), 6.62 (t, J = 2 Hz, 2H), 7.16 (t, J = 8.5 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 69.3, 102.6, 107.4, 114.5, 129.7, 141.5, 159.6; HRMS (Q-Tof) m/z: $[M+H]^+$ calcd. for $C_{24}H_{25}O_4$ 377.1753, found 377.1743. IR (neat): υ_{max} 1048, 1248, 1737, 3019 cm^{-1}.

8b: 72.85 mg, yield: 62%; mp 128-130 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 4.68 (s, 8H), 5.29 (s, 4H), 5.38 (s, 4H), 6.94-7.02 (m, 8H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 72.4, 115.3, 117.4, 122.6, 142.4, 150.2; HRMS (Q-Tof) m/z: $[M+H]^+$ calcd. for $C_{24}H_{25}O_4$ 377.1753, found 377.1758. IR (neat): υ_{max} 896, 1046, 1134, 1266, 1498 cm^{-1}.

8c: 71.60 mg, yield: 61%; mp 128-130 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 4.68 (s, 8H), 5.29 (s, 4H), 5.38 (s, 4H), 6.94-7.02 (m, 8H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 71.4, 115.3, 117.4, 120.6, 143.4, 150.3; HRMS (Q-Tof) m/z: $[M+H]^+$ calcd. for $C_{24}H_{25}O_4$ 377.1753, found 377.1758. IR (neat): υ_{max} 1013, 1499, 1597, 2918, 3097 cm^{-1}.

General procedure for Diels−Alder reaction with DMAD

To a stirred solution of the diene [**9a-9c** (50 mg, 0.136 mmol) or **8a-8c** (50 mg, 0.133 mmol)] in toluene (15 mL) was added DMAD [(23.19 mg, 0.272 mmol) for **9a-9c** and (46.38 mg, 0.327 mmol) for **8a-8c**] under N_2 and the reaction mixture was refluxed for 30 h. Crude reaction contains DA adduct and partially aromatized product. Later, DDQ was added, and the reaction mixture was further refluxed for 24 h. At the conclusion of the reaction (TLC monitoring), the solvent was removed on a rotavapour. The crude reaction mixture was diluted with ethyl acetate and then washed with aq. KOH solution and then with brine. The combined organic layer was concentrated under reduced pressure and the crude product was purified by column chromatography by eluting with appropriate mixture of ethyl acetate/petroleum ether mixture.

4a: 57.20 mg, yield: 83%; mp 186-188 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.88-3.95 (m, 4H), 3.92 (s, 6H), 4.12-4.15 (m, 4H), 5.17 (s, 4H), 6.51-6.66 (m, 4H), 7.19 (t, *J* = 8 Hz, 2H), 7.89 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 52.9, 67.8, 68.1, 69.9, 103.1, 107.4, 108.2, 129.0, 130.2, 131.8, 138.7, 159.6, 160.2, 167.8; HRMS (Q-Tof) m/z: $[M+H]^+$ calcd. for $C_{28}H_{29}O_9$ 509.1812, found 509.1823. IR (neat): υ_{max} 1030, 1177, 765, 1350, 1727, 1489, 1602, 2931 cm^{-1}.

4b: 43.50 mg, yield: 63%; mp 112-114 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.84 (t, *J* = 1.82 Hz, 4H), 4.13 (m, 4H), 3.92 (s, 6H), 5.25 (s, 4H), 6.85-7.06 (m, 8H), 8.04 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 52.8, 67.9, 69.7, 70.3, 113.1, 119.8, 121.2, 123.8, 123.4, 131.1, 139.5, 147.9, 150.9, 168.2; HRMS (Q-Tof) m/z: $[M+H]^+$ calcd. for $C_{28}H_{29}O_9$ 509.1812, found 509.1823. IR (neat): υ_{max} 1046, 1117, 1351, 1598, 1727, 2922 cm^{-1}.

4c: 52.50 mg, yield: 76%; mp 186-188 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.77-3.78 (m, 4H), 3.92 (s, 6H), 4.12-4.14 (m, 4H), 5.07 (s, 4H), 6.52-6.53 (d, *J* = 7 Hz, 4H), 6.63-6.64 (d, *J* = 2 Hz, 4H), 7.80 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 52.9, 69.0, 69.4, 69.6, 116.1, 116.3, 130.5, 132.0, 139.5, 153.0, 153.0, 167.3; HRMS (Q-Tof) m/z: $[M+H]^+$ calcd. for $C_{28}H_{29}O_9$ 509.1812, found 509.1813 IR (neat): υ_{max} 1045, 1134, 1265, 1421, 1735 cm^{-1}.

6a: 68.00 mg, yield: 78%; mp 210-212 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.90 (s, 12H), 5.15 (s, 8H), 6.68 (dd, *J* = 8.2 Hz, *J* = 2 Hz, 4H), 6.85 (t, *J* = 2 Hz, 2H), 7.26 (t, *J* = 8.2 Hz, 2H), 7.88 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 52.9, 67.9, 102.1, 108.2, 129.1, 130.5, 132.0, 138.5, 159.7, 167.7; HRMS (Q-Tof) m/z: $[M+H]^+$ calcd. for $C_{36}H_{33}O_{12}$ 657.1972, found 657.1973. IR (neat): υ_{max} 896, 1422, 1603, 1730, 2986 cm^{-1}.

6b: 59.30 mg, yield: 68%; mp 208-210 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.89 (s, 12H), 5.10 (s, 8H), 6.99-7.05 (m, 8H), 7.90 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 52.8, 69.4, 116.5, 123.0, 129.9, 131.9, 138.6, 149.2, 167.8; HRMS (Q-Tof) m/z: $[M+H]^+$ calcd. for $C_{36}H_{33}O_{12}$ 657.1972, found 657.1973. IR (neat): υ_{max} 1045, 1132, 1384, 1595, 1768, 2924 cm^{-1}.

6c: 62.70 mg, yield: 72%; mp 208-210 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.94 (s, 12H), 5.10 (s, 8H), 6.54 (s, 8H), 7.81 (s, 4H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 53.0, 70.1, 116.1, 131.1, 132.2, 139.7, 154.0, 167.6; HRMS (Q-Tof) m/z: $[M+H]^+$ calcd. for $C_{36}H_{33}O_{12}$ 657.1972, found 657.1973. IR (neat): υ_{max} 1046, 1133, 1255, 1498, 1728 cm^{-1}.

General procedure for Diels–Alder reaction with Tetracyanoethylene

To a stirred solution of the diene [**9b** (50 mg, 0.136 mmol) or **8b** (50 mg, 0.133 mmol)] in toluene (15 mL) was added tetracyanoethelyne [(20.88 mg, 0.163 mmol) for **9b** and (41.78 mg, 0.326 mmol) for **8b**] under N_2 and the reaction mixture was refluxed for 20 h. At the conclusion of the reaction (TLC monitoring), the solvent was removed on a rotavapour. The crude reaction mixture was diluted with ethyl acetate washed with brine. The combined organic layer was concentrated under reduced pressure and the crude product was purified by column chromatography by eluting with appropriate mixture of ethyl acetate/petroleum ether mixture.

10: 66.38 mg, yield: 79%; mp 180-182 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.41 (s, 8H), 4.57 (s, 8H), 6.89-6.99 (m, 8H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 34.9, 37.8, 67.3, 110.4, 117.4, 123.9, 128.1, 148.2; HRMS (Q-Tof) m/z: $[M+Na]^+$ calcd. for $C_{38}H_{24}N_8O_4$ Na 655.1818, found 655.1818 IR (neat): υ_{max} 1046, 1133, 1255, 1498, 2250 cm^{-1}.

11: 65.95 mg, yield: 82%; mp 172-174 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.39 (s, 4H), 3.90-3.92 (m, 4H), 4.17-4.19 (m, 4H), 4.76 (s, 4H), 6.87-7.07 (m, 8H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 34.1, 37.9, 66.74, 67.7, 69.6, 110.8, 113.7, 121.7, 122.0, 125.0, 127.2, 146.9, 151.1; HRMS (Q-Tof) m/z: $[M+H]^+$ calcd. for $C_{28}H_{25}N_4O_5$ 497.1821, found 497.1825 IR (neat): υ_{max} 1046, 1133, 1255, 1498, 2250 cm^{-1}.

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Supporting Information

The ^{1}H and ^{13}C NMR spectra of all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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