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

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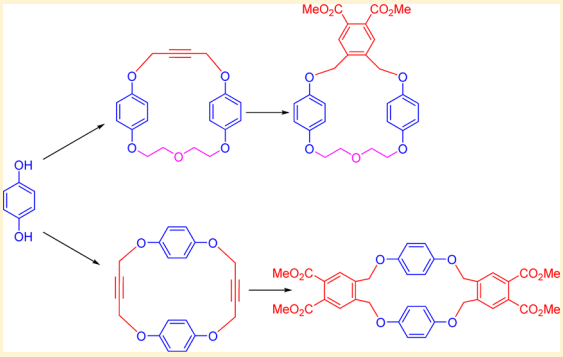
Supporting Information

ABSTRACT: 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 were the beginning of molecular recognition.[1,2] The structural rigidity of macrocycles draws special attention in supramolecular chemistry[3] because of its binding properties and extended use in material science. Crownophanes exhibit the structural hybrid properties of crown ethers[4] and cyclophanes.[5,6] They are also useful building blocks in supramolecular chemistry. The ethyleneoxy 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 atom 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 a crucial role in similar processes. A variety of olefination reactions are utilized during the formation of cyclophanes, for example, the McMurry reaction, Ramberg–Backlund reaction, ring-closing metathesis (RCM), and Wittig reaction.[8] Cross-enyne metathesis (CEM)[9] is a useful tool for creating 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 a 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 the 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.

The first step in our journey toward crownophane synthesis involves generation of an 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).[15] A similar procedure was employed to generate bisphenols **2b** and **2c**.[14] Although the crown compound **3b** can be prepared by using but-2-yne 1,4-dibromide,[16] we found improved yield of **3b** (95%) by using but-2-yne 1,4-ditosylate **7**. It is interesting to note that the ditosylate **7** is a

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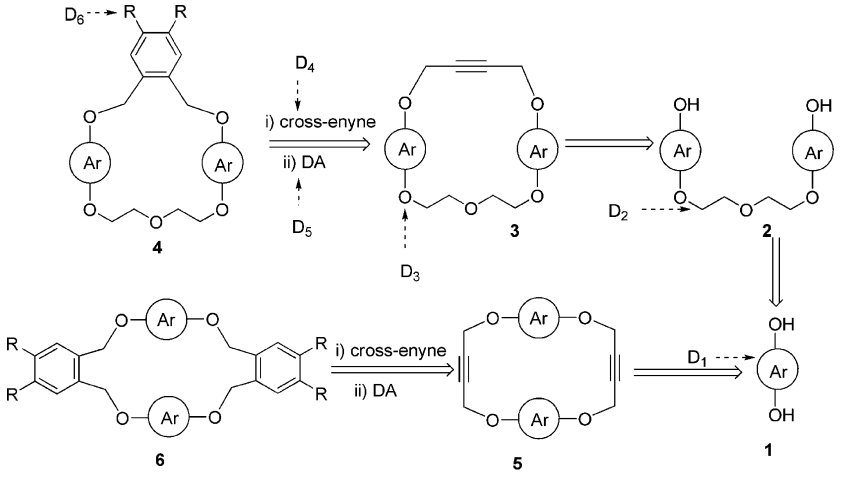
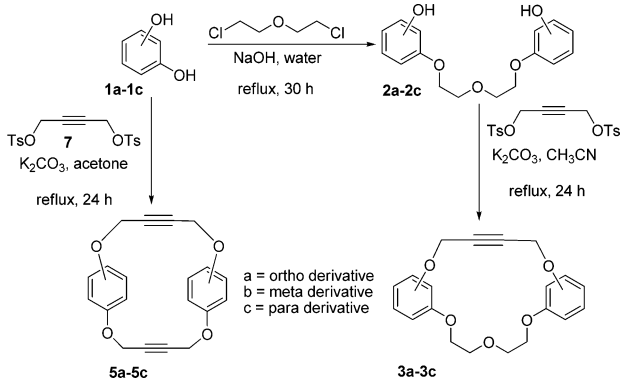
Scheme 1. Diversity Strategy to Crownophanes Involving Various Points



Scheme 2. Preparation of Enyne Building Blocks 3a–c and 5a–c



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 **9a**. ^{1}H NMR spectral data of the diene **9a** 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–c** and **9a–c**) prepared here seem to be stable at room temperature, and they decompose around 190 °C.

Later, the diene **9a** was subjected to a DA reaction with dimethyl acetylenedicarboxylate (DMAD) 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).

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

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).

Various other enyne building blocks that has undergone CEM, DA reaction, and aromatization sequences are shown in Table 2. All of the new products obtained in this sequence are well characterized by ^{1}H NMR and ^{13}C NMR spectral data and

Scheme 3. Synthesis of Crownophanes via CEM and DA Reaction as Key Steps

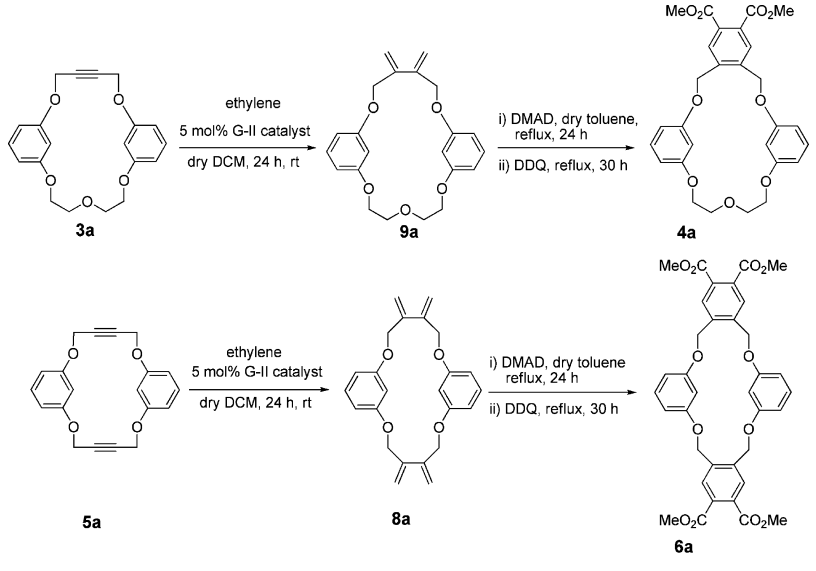


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Table 1. Preparation of Crownophanes 6a−c via CEM and DA Reaction as Key Steps

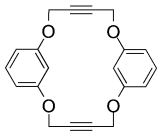
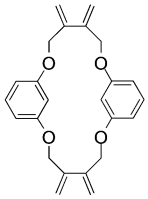
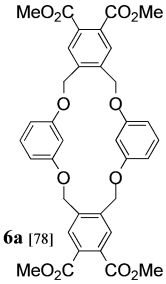
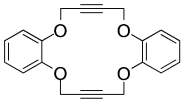
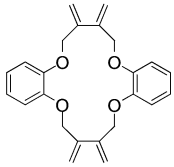
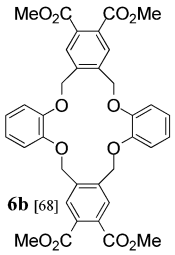
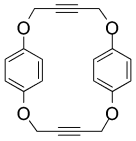
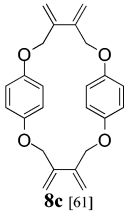
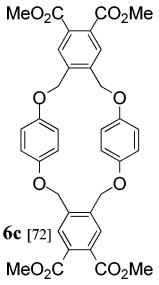
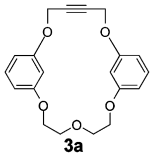
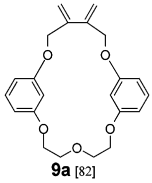
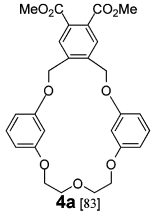
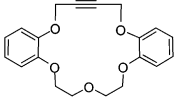
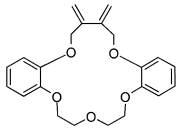
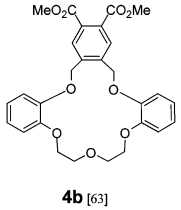
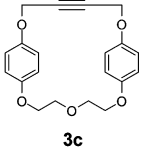
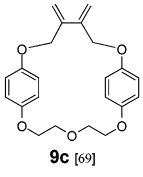
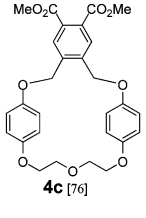
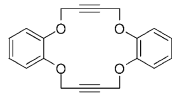
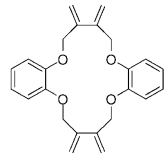
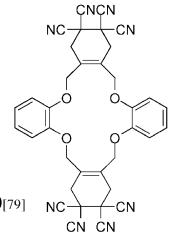
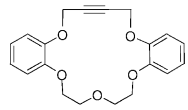
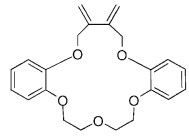
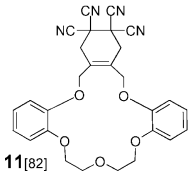
Entry	Starting material	Diene / [Yield %]	Two step yield %
1	 **5a**	 **8a** [78]	 **6a** [78]
2	 **5b**	 **8b** [62]	 **6b** [68]
3	 **5c**	 **8c** [61]	 **6c** [72]

Table 2. Preparation of Crownophanes 4a−c via CEM and DA Reactions as Key Steps

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]

further supported by HRMS data. Further, dienes **8b** and **9b** were treated with tetracyanoethylene to get crownophanes **10** and **11** with good yield as shown in Table 3.

Table 3. Preparation of Crownophanes 10 and 11 Using Tetracyanoethylene as a Dienophile

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

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 involves creation of eight new C−C bonds during the 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−c** (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 **7** (681 mg, 1.72 mmol) 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 an appropriate mixture of ethyl acetate/petroleum ether, which affords pure cyclized product **3a−c** 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) ν_{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) ν_{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) ν_{max} 739, 896, 1129, 1200, 1509, 1653, 3054 cm^{-1}.

General Procedure for the Preparation of Dienes. Cyclized product **3a−c** (100 mg, 0.294 mmol) or **5a−c** (100 mg, 0.313 mmol)

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was dissolved in dry DCM (10−20 mL) and degassed by N_2 for 5 min, and 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 completion of the reaction (TLC monitoring), the solvent was removed on a rotavapor. 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 = 8 Hz, 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) ν_{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) ν_{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, 2H), 6.47 (s, 2H), 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) ν_{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) ν_{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) ν_{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) ν_{max} 1013, 1499, 1597, 2918, 3097 cm^{-1}.

General Procedure for Diels−Alder Reaction with DMAD. To a stirred solution of the diene [**9a−c** (50 mg, 0.136 mmol) or **8a−c** (50 mg, 0.133 mmol)] in toluene (15 mL) was added DMAD [(23.19 mg, 0.272 mmol) for **9a−c** and (46.38 mg, 0.327 mmol) for **8a−c**] under N_2, and the reaction mixture was refluxed for 30 h. The crude reaction mixture 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 rotavapor. The crude reaction mixture was diluted with ethyl acetate and then washed with aq KOH solution and brine. The combined organic layer was concentrated under reduced pressure, and the crude product was purified by column chromatography by eluting with the 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, 6H), 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) ν_{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) ν_{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) ν_{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, 4H); ^{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) ν_{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, 4H); ^{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) ν_{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) ν_{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 tetracyanoethylene [(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 rotavapor. 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) ν_{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) ν_{max} 1046, 1133, 1255, 1498, 2250 cm^{-1}.

■ ASSOCIATED CONTENT

Ⓢ 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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Notes

The authors declare no competing financial interest.

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■ DEDICATION

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