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# Diversity-Oriented Approach to Macrocyclic Cyclophane Derivatives by Suzuki–Miyaura Cross-Coupling and Olefin Metathesis as Key Steps‡

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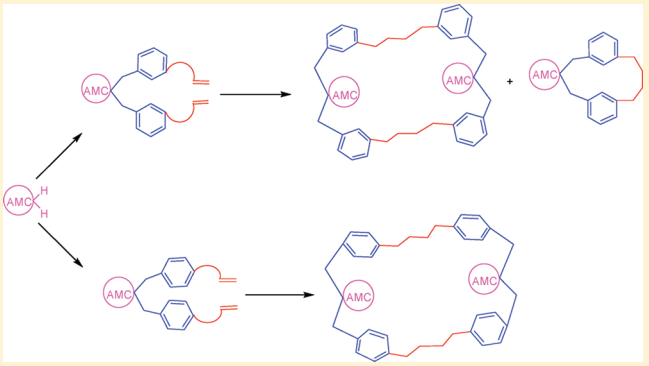
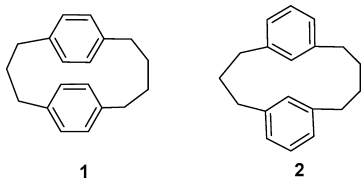
Supporting Information

**ABSTRACT:** Palladium-catalyzed Suzuki–Miyaura (SM) cross-coupling reaction with allylboronic acid pinacol ester and titanium assisted cross-metathesis (CM)/ring-closing metathesis (RCM) cascade has been used to synthesize macrocyclic cyclophane derivatives.




## INTRODUCTION

Suzuki–Miyaura (SM) cross-coupling reaction[1] has attracted a great deal of attention in organic synthesis in recent times. Ring-closing metathesis (RCM)[2] has also widely been used for macrocyclic synthesis,[3] which is commonly found in many natural products, pharmaceuticals, materials science, catalysis, and supramolecular chemistry.[4a−d,e−k,l] These two themes are individually used in combination with other C−C bond forming reactions to synthesize a variety of polycyclic compounds.[4m] Among polycycles, cyclophanes[5] play an important role in host–guest chemistry. Therefore, there is a continuous need to develop new methods for the synthesis of cyclophanes by efficient and simple routes. Several methods are available to synthesize various cyclophane derivatives, including pyrolysis of sulfones[6a] and polymerization of *p*-xylene,[6b] acyloin condensation,[6c,f] carbene insertion,[6d,e] Wurtz coupling,[6f] and Ni-catalyzed Grignard coupling.[6g] However, syntheses of cyclophanes using RCM,[7] SM cross-coupling,[8] or a combination of these two methods are limited.[9] Kwochka and co-workers have reported various cyclophane derivatives by SM cross-coupling reaction of *bis*-9-BBN adduct of various dienes with aryl bromides.[8b] Kotha and co-workers synthesized the [1.1.6]metacyclophane derivatives by SM cross-coupling and RCM as key steps.[9a] Guan's group has synthesized the *m*-terphenyl-based cyclophanes by utilizing the SM cross-coupling and RCM strategy.[9b] In continuation with our interest in cyclophane synthesis,[10] here we conceived a short synthetic route to [3.4]cyclophane derivatives with SM cross-coupling and RCM as key steps. A strategy based on these two key reactions is expected to be unique and concise because of the inherent nature of the efficiency in C−C bond formation and also because of the catalytic nature of these reactions. Recently, Hopf's group reported a simple synthetic route to [3.4]-paracyclophane (**1**) via extrusion of sulfur dioxide under flash vacuum pyrolysis (FVP) conditions.[6a] Earlier, Cram and Allinger have also synthesized [3.4]paracyclophane with acyloin condensation as a key step.[6c] In 1982, Lehner and Krois reported the synthesis of [3.4]metacyclophane (**2**) with a carbene insertion reaction as a key step (Figure 1).[6e]



1 2

**Figure 1.** [3.4]Meta/paracyclophane.

Our strategy begins with dialkylation of active methylene compound (AMC) with a suitably functionalized benzyl bromide derivative, followed by the introduction of allyl group or alkenyl group with the aid of SM cross-coupling reaction. Finally, RCM and hydrogenation sequence can lead to the required cyclophane derivatives (Figure 2). The diversity-oriented approach conceived here is capable of producing a variety of cyclophane derivatives. Here, several diversity points are available at our disposal. The first one is related to the selection of active methylene moiety and the second point of diversity involves the variation of the aromatic unit related to benzyl bromide component. For example, introduction of

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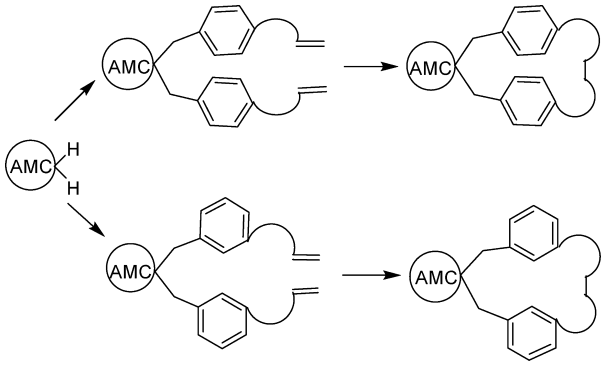



**Figure 2.** Our strategy to cyclophane derivatives.

heteroaryl derivatives such as furan- or thiophene-based molecules will open up additional opportunities for further synthetic manipulation. The third variation involves utilization of various commercially available unsaturated boronic acid components during the cross-coupling reaction, which will deliver cyclophanes of varying ring size. The double bond left at the end of RCM sequence would provide an additional handle for further synthetic maneuver.

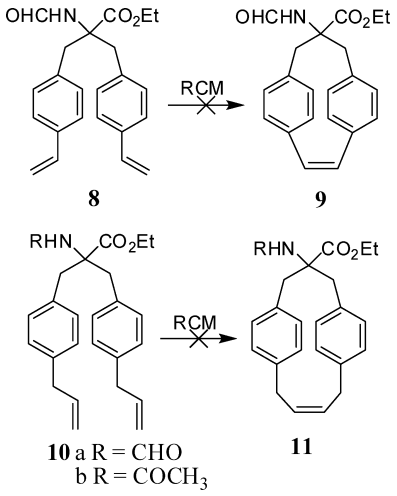
## RESULTS AND DISCUSSION

In connection with a major program aimed at designing various polycyclic compounds using SM cross-coupling and RCM as key steps,[11] we conceived a short and alternative route to cyclophanes by utilizing SM cross-coupling and RCM sequence.

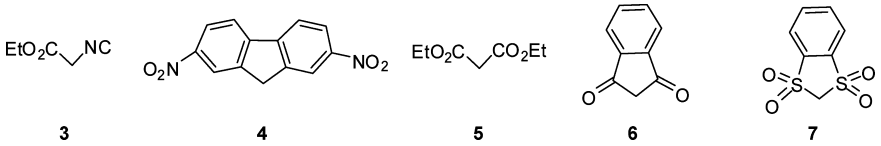
Among various active methylene compounds **3**−**7** (Figure 3), we have chosen ethyl isocycanoacetate (**3**) to prepare *p*-vinyl derivative **8** using 4-vinyl benzyl chloride[10a,b] and subjected to RCM.[12] Unfortunately, the reaction did not lead to the expected ring-closing product **9** (Scheme 1).Therefore, we thought that the substrate containing a vinyl appendage may not be long enough to undergo the RCM reaction, and therefore, the replacement of vinyl group with allyl moiety may increase the chances for cyclization reaction. The required diallyl derivatives **10a** and **10b** were obtained by SM cross-coupling reaction of the corresponding dibromo derivatives[13] with allylboronic acid pinacol ester as coupling partner.[14] Later, the diallylated compounds **10a** and **10b** were subjected to RCM reaction under various reaction conditions; unfortunately, the RCM reaction failed to deliver the required cyclophane derivatives **11a**−**b**. Later, we tried the RCM protocol under Lewis acid catalysis conditions involving titanium isopropoxide [Ti(*i*OPr)$_4$]. However, these conditions are also not useful to realize RCM. X-ray crystal structure of similar derivatives indicated unfavorable disposition of the double bonds, which is responsible for the unsuccessful RCM sequence.[15]

By increasing the steric bulk of active methylene compound, one may be able to design a precursor with a favorable conformation suitable for RCM. Therefore, we intend to alter the active methylene component, and in this regard, the 2,7-dinitrofluorene (**4**) was chosen as an active methylene partner. To this end, fluorene-based precursor 9,9-bis(*p*-bromobenzyl)-2,7-dinitrofluorene (**12**) was prepared by the C-9 dibenzylation of 2,7-dinitrofluorene (**4**) with 2 equiv of *p*-bromobenzyl bromide in presence of $K_2CO_3$ in dry acetonitrile under phase-transfer catalysis (PTC) conditions. Because of the poor solubility of 2,7-dinitrofluorene (**4**), low yield of the product **12** was observed. Next, we subjected the dibromo derivative **12** to Pd-catalyzed SM cross-coupling reaction with excess of allylboronic acid pinacol ester to obtain the diallyl product **13** in 45% yield. Then, we attempted the RCM of diallyl compound **13** with Grubbs first- as well as second-generation catalysts, but unfortunately diallyl substrate **13** did not deliver the required cyclophane derivative **14** by RCM sequence (Scheme 2).

**Scheme 1. Attempts to Synthesize Cyclophane Derivative by RCM**




At this junction, we considered an alternate active methylene precursor that may overcome the solubility problem associated with the compound **4**. Therefore, we choose the diethyl malonate (DEM) (**5**) as active methylene partner, and it was successfully dibenzylated in the presence of $K_2CO_3$ under acetonitrile reflux conditions or 4 N NaOH under PTC conditions using benzyl triethylammonium chloride (BTEACl) to give compounds **15a**−**b**.[16] We have also attempted the dibenzylation reaction under KF-Celite conditions in acetonitrile. Unfortunately, monobenzylated product was obtained as major product. These dibenzylated derivatives **15a**−**b** were allylated by SM cross-coupling reaction with excess of allylboronic acid pinacol ester with the aid of Pd(0) catalyst.[14] Having prepared the diallyl compounds **16a**−**b**, our attention was focused on the RCM step. Initially, treatment of the diallyl compound **16a** with Grubbs first-generation catalyst gave low yield of the RCM product. Later, the reaction was carried out with Grubbs first- as well as second-generation catalysts under different reaction conditions (such as G-II, DCM at 40 °C; G-I,




3 4 5 6 7

**Figure 3.** Active methylene components.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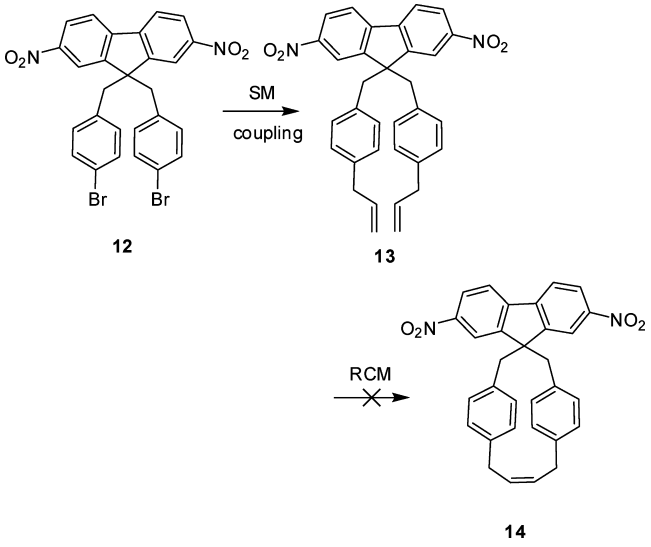
**Scheme 2. Another Attempt to Synthesize [3.4]Paracyclophane Derivative by RCM**




toluene/rt; and G-II, toluene/80 °C) gave no RCM product; i.e., [3.4]cyclophane derivative was not formed in good yield. Finally, we found that Lewis acid such as titanium(IV) isopropoxide aids the metathesis process with Grubbs first generation catalyst in dry DCM at 40 °C to deliver the macrocyclic product **17a** in moderate yield.[17] In the case of *m*-allyl derivative **16a**, metathesis reaction gave the [3.4]-cyclophane derivative **19** by RCM along with the dimeric product **17a** by CM-RCM sequence, but in the case of *p*-allyl derivative **16b**, we isolated only macrocyclic dimer **17b**. The formation of dimeric cyclophane derivatives **17a–b** and monomer **19** was further confirmed by single crystal X-ray crystallographic data (Figures 4 and 5),[18] which clearly shows that the double bonds are in trans arrangement. The dimeric cyclophane derivatives **17a–b** were crystallized in triclinic crystal system with space group *P*-1, and monomeric cyclophane derivative **19** was crystallized in orthorhombic crystal system with space group *Fdd*2. In the case of **17a**, some disorder with one ester group and one benzene ring has been observed. Hydrogenation of unsaturated cyclophane derivatives **17a–b** and **19** using 5% Pd/C in the presence of hydrogen in dry ethyl acetate furnished the saturated cyclophanes[19] **18a–b** and **20**, respectively. The aromatic proton (C–CH*–C) of [3.4]metacyclophane derivative **20** is more shielded (6.02 ppm) as compared to macrocyclic cyclophane derivative **18a** (6.84 ppm) (C–CH*–C) (Scheme 3).

Later, we considered 1,3-indanedione[20] (**6**) as the active methylene component. The dialkylation process with benzyl

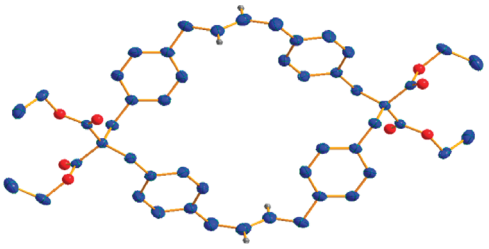
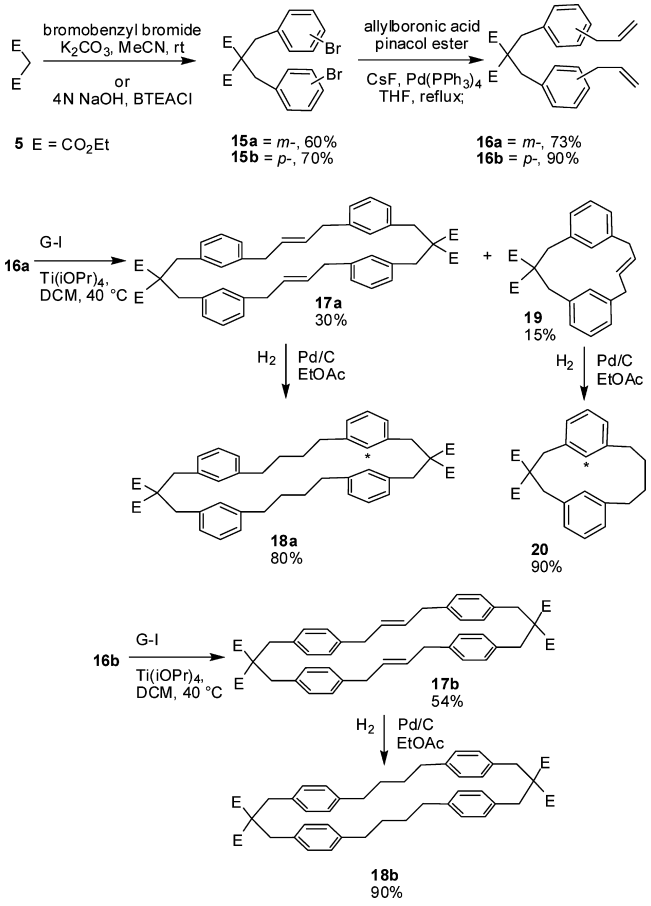


**Figure 5.** The molecular crystal structure of **17b** with 50% probability.

**Scheme 3. Synthesis of Macrocyclic Cyclophane Derivatives 18a–b and 20**




bromide derivatives involving 1,3-diketone seems to be a nontrivial task. Various attempts to dibenzylate 1,3-indanedione (**6**) were unsuccessful under NaH/THF conditions. On the basis of our earlier experience,[21] 1,3-indanedione (**6**) was successfully dialkylated using freshly prepared KF-Celite in one

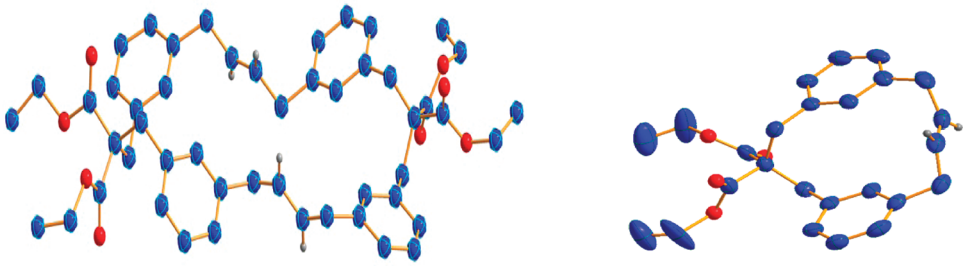


**Figure 4.** The molecular crystal structure of **17a** with 50% probability and **19** with 30% probability.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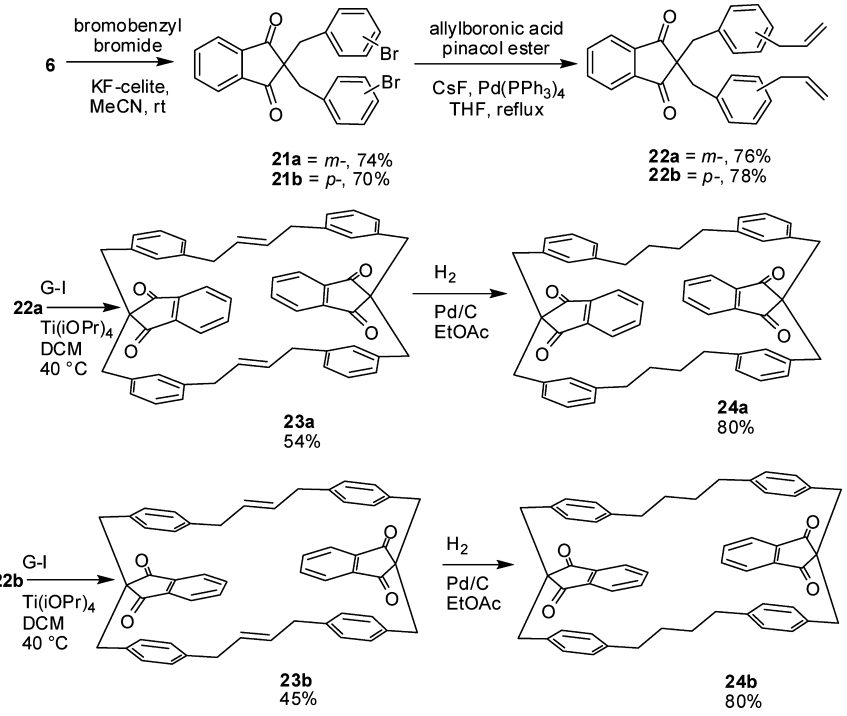
**Scheme 4. Synthesis of Macrocyclic Cyclophane Derivatives 24a–b**



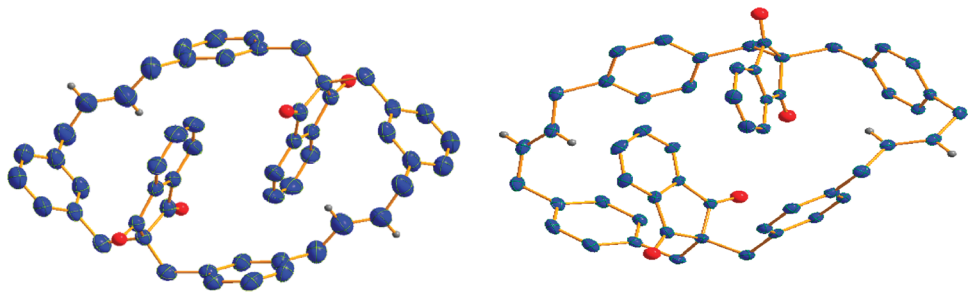



**Figure 6.** The molecular crystal structure of **23a** and **23b** with 30% probability.

step.[22,23] Thus, the 1,3-indanedione (**6**) was treated with 2.2 equiv of bromobenzyl bromide in dry acetonitrile under KF-Celite conditions to generate the required dibenzylated products **21a–b** in good yields. Along similar lines, allylation was achieved by SM cross-coupling reaction with excess of allylboronic acid pinacol ester under CsF and $Pd(PPh_3)_4$ in dry THF reflux conditions to deliver the required diallyl derivatives **22a–b** in good yield. Then, these diallylated compounds **22a–b** were subjected to metathesis reaction with G-I in the presence of $Ti(iOPr)_4$ to deliver macrocyclic cyclophane derivatives **23a–b**. The formation of macrocyclic products **23a–b** was further confirmed by single crystal X-ray crystallographic studies (Figure 6),[24] which clearly show that the double bonds are in trans arrangement. The macrocyclic cyclophane derivatives **23a–b** were crystallized in monoclinic crystal system with space group *P*21/*c*. Later, the macrocyclic products **23a–b** were hydrogenated using catalytic amount of 5% Pd/C or $PtO_2$ in the presence of hydrogen in dry ethyl acetate to deliver the saturated macrocyclic cyclophane derivatives **24a–b** (Scheme 4). The aromatic protons attached to the benzene ring of indanedione experience a greater shielding effect in the $^1H$ NMR ($\delta$ 5.50 ppm) spectrum of **24b**.

## CONCLUSION

Herein, we have demonstrated a short and efficient synthetic route to macrocyclic cyclophane derivatives by utilizing SM cross-coupling reaction and CM/RCM cascade. The present methodology opens up a new and short synthetic sequence to several macrocyclic cyclophane derivatives without the involvement of protecting groups. Various diversity points involved in this strategy provide ample opportunities to generate a library of cyclophane derivatives.

## EXPERIMENTAL SECTION

**General Remarks.** All the reactions were monitored by employing TLC technique using appropriate solvent system for development. Reactions involving oxygen-sensitive reagents or catalysts were performed in degassed solvents. Dry tetrahydrofuran (THF) was obtained by distillation over sodium benzophenone ketyl freshly prior to use. Dichloromethane was distilled over $P_2O_5$ and acetonitrile over $CaH_2$. Magnesium sulfate/sodium sulfate was dried in an oven at 130 °C for one day. All the solvent extracts were washed successively with water and brine (saturated sodium chloride solution), dried over anhydrous magnesium sulfate/sodium sulfate, and concentrated at the reduced pressure on a rotary evaporator. Yields refer to the chromatographically isolated yield. All the commercial grade reagents were used without further purification. NMR samples were generally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made in chloroform-*d* solvent, and chemical shifts were reported in $\delta$ scale using tetramethylsilane (TMS) as an internal standard. The standard abbreviation s, d, t, q and m, refer to singlet, doublet, triplet, quartet, and multiplet, respectively. Coupling constants (*J*) are reported in Hertz.

**Dibenzylation of Diethyl Malonate.** *Method A.* To an aqueous solution of 4 N NaOH (2 mL), benzyltriethyl ammonium chloride (142 mg, 0.62 mmol) was added, and the mixture was stirred for 5 min. Then, diethyl malonate (100 mg, 0.625 mmol) and bromo benzylbromide (344 mg, 1.37 mmol) were added, and the mixture was stirred at room temperature for 3 h. After the completion of the reaction, the reaction mixture was diluted with water and extracted with ethyl acetate (3 × 20 mL). The combined organic layer was washed with brine, dried over $Na_2SO_4$, and concentrated under reduced pressure. The product was purified by silica gel column chromatography. Elution of the column with 2% of ethyl acetate/petroleum ether gave the pure 2,2-dibenzylated diethyl malonates in good yield.

*Method B.* To a solution of diethyl malonate (100 mg, 0.62 mmol) in dry acetonitrile (15 mL), 10 equiv of $K_2CO_3$ (862.5 mg, 6.25 mmol), tetrabutylammonium hydrogen sulfate (212 mg, 0.62 mmol), and 2.2 equiv of bromo benzylbromide (344 mg, 1.37 mmol) were added, and the mixture was refluxed for 36 h. After the completion of the reaction, the reaction mixture was filtered over short pad of Celite through a sintered funnel and washed with ethyl acetate (20 mL). The combined organic layer was concentrated under reduced pressure, and the product was purified by silica gel column chromatography. Elution of the column with 2% ethyl acetate/petroleum ether gave the required 2,2-dibenzylated diethyl malonates in good yield.

**Diethyl 2,2-*bis*(*m*-Bromobenzyl) Malonate (15a).** Spectral data: yield ~60%; $R_f$ = 0.5 (silica gel, 10% EtOAc/petroleum ether); mp 62−64 °C; $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 7.38 (dq, $J_1$ = 7.8 Hz, $J_2$ = 1.4 Hz, 2H), 7.30 (t, *J* = 1.7 Hz, 2H), 7.15 (t, *J* = 7.6 Hz, 2H), 7.10 (dt, $J_1$ = 7.8 Hz, $J_2$ = 1.4 Hz, 2H), 4.13 (q, *J* = 7.2 Hz, 4H), 3.16 (s, 4H), 1.18 (t, *J* = 7.2 Hz, 6H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 170.5, 138.6, 133.3, 130.3, 129.9, 128.9, 122.4, 61.7, 60.2, 39.3, 14.0; IR (KBr, $cm^{-1}$) 2960, 2811, 1715, 1594, 1384, 1351, 1257; HRMS (Q-Tof) *m*/*z* $[M + H]^+$ calcd for $C_{21}H_{23}O_4Br_2$ 496.9963, found 496.9981.

**Diethyl 2,2-*bis*(*p*-Bromobenzyl) Malonate (15b).** Spectral data: yield ~70%; $R_f$ = 0.5 (silica gel, 10% EtOAc/petroleum ether); mp 106−110 °C; $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 7.39 (d, *J* = 8.4 Hz, 4H), 7.02 (d, *J* = 8.8 Hz, 4H), 4.11 (q, *J* = 7.2 Hz, 4H), 3.14 (s, 4H), 1.16 (t, *J* = 7.2 Hz, 6H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 170.7, 135.3, 131.9, 131.5, 121.2, 61.6, 61.0, 39.1, 14.0; IR (KBr, $cm^{-1}$) 2964, 2811, 2111, 1731, 1594, 1351, 1199; HRMS (Q-Tof) *m*/*z* $[M + H]^+$ calcd for $C_{21}H_{23}O_4Br_2$ 496.9963, found 496.9962.

**Synthesis of Compounds 16a and 16b.** A solution of diethyl 2,2-*bis*(bromobenzyl) malonate **15a−b** (100 mg, 0.20 mmol), cesium fluoride (122 mg, 0.80 mmol), and $Pd(PPh_3)_4$ (11.6 mg, 5 mol %) in dry THF (20 mL) was stirred at rt for 10 min, and then, allylboronic acid pinacol ester (135 mg, 0.80 mmol) was added dropwise and stirred at 80 °C for 24 h. Again, cesium fluoride (61 mg, 0.40 mmol), $Pd(PPh_3)_4$ (11.6 mg, 5 mol %), and allylboronic acid pinacol ester (68 mg, 0.40 mmol) were added, and the mixture was stirred for another 24 h. After the completion of the reaction, the reaction mixture was diluted with ether and washed with water (3 × 20 mL). The organic layer was dried over $Na_2SO_4$ and concentrated under reduced pressure. The crude product was purified by silica gel column chromatography. Elution of the column with 2% ethyl acetate/petroleum ether gave the diallyl products **16a−b**.

**Diethyl 2,2-*bis*(*m*-Allylbenzyl) Malonate (16a).** Spectral data: yield 73%; $R_f$ = 0.55 (silica gel, 10% EtOAc/petroleum ether); $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 7.19 (t, *J* = 7.6 Hz, 2H), 7.06 (d, *J* = 7.9 Hz, 2H), 7.02 (d, *J* = 7.6 Hz, 2H), 6.99 (s, 2H), 5.95 (m, 2H), 5.07 (m, 4H), 4.11 (q, *J* = 7.2 Hz, 4H), 3.35 (d, *J* = 6.7 Hz, 4H), 3.19 (s, 4H), 1.17 (t, *J* = 7.2 Hz, 6H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 171.1, 140.0, 137.6, 136.7, 130.7, 128.4, 128.1, 127.3, 116.0, 61.4, 60.3, 40.3, 39.0, 14.1; IR (neat, $cm^{-1}$) 2979, 1733, 1445, 1196, 1095, 915; HRMS (Q-Tof) *m*/*z* $[M + H]^+$ calcd for $C_{27}H_{33}O_4$ 421.2379, found 421.2363.

**Diethyl 2,2-*bis*(*p*-Allylbenzyl) Malonate (16b).** Spectral data: yield 90%; $R_f$ = 0.55 (silica gel, 10% EtOAc/petroleum ether); $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 7.09 (s, 8H), 5.94 (m, 2H), 5.07 (m, 4H), 4.10 (q, *J* = 7.2 Hz, 4H), 3.35 (dt, $J_1$ = 6.7 Hz, $J_2$ = 1.4 Hz, 4H), 3.18 (s, 4H), 1.16 (t, *J* = 7.2 Hz, 6H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 171.2, 138.8, 137.6, 134.2, 130.4, 128.6, 115.9, 61.3, 60.4, 40.0, 38.7, 14.1; IR (neat, $cm^{-1}$) 2979, 1733, 1513, 1444, 1267, 1179; HRMS (Q-Tof) *m*/*z* $[M + H]^+$ calcd for $C_{27}H_{33}O_4$ 421.2379, found 421.2365.

**Synthesis of Compounds 17a−b and 19.** A solution of diallyl compound **16a−b** (65 mg, 0.15 mmol) in dry DCM (25 mL) was degassed with $N_2$ gas for 5 min, then 20 mol % of $Ti(iOPr)_4$ (8.8 mg, 0.03 mmol) and 10 mol % of Grubbs first generation catalyst (12.7 mg) were added, and the reaction mixture was stirred at 40 °C for 7 h. After the completion of the reaction, the solvent was removed under reduced pressure, and the product was purified by silica gel column chromatography. Elution of the column with 10% ethyl acetate/petroleum ether gave the RCM products. In the case of starting material **16a**, we have isolated the two products **17a** and **19**.

**Compound 17a.** Spectral data: yield 30%; $R_f$ = 0.27 (silica gel, 10% EtOAc/petroleum ether); mp 168−170 °C; $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 7.15−7.01 (m, 12H), 6.87 (m, 4H), 5.67 (m, 4H), 4.16 (q, *J* = 7.2 Hz, 8H), 3.35 (d, *J* = 4.9 Hz, 8H), 3.12 (s, 8H), 1.23 (t, *J* = 7.2 Hz, 12H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 171.2, 140.5, 136.5, 131.1, 130.7, 128.6, 127.3, 127.3, 61.4, 60.0, 39.2, 37.6, 14.1; IR (KBr, $cm^{-1}$) 2850, 1730, 1598, 1384, 1351, 1198, 1042; HRMS (Q-Tof) *m*/*z* $[M + H]^+$ calcd for $C_{50}H_{57}O_8$ 785.4053, found 785.4060.

**Compound 19.** Spectral data: yield 15%; $R_f$ = 0.62 (silica gel, 10% EtOAc/petroleum ether); mp 134−136 °C; $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 7.16 (t, *J* = 7.6 Hz, 2H), 7.03 (d, *J* = 7.5 Hz, 2H), 6.71 (d, *J* = 7.8 Hz, 2H), 6.63 (s, 2H), 5.65 (m, 2H), 4.37 (q, *J* = 7.2 Hz, 4H), 3.24 (d, *J* = 6.2 Hz, 4H), 3.04 (bs, 4H), 1.36 (t, *J* = 7.2 Hz, 6H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 171.6, 139.8, 135.8, 135.1, 130.7, 128.6, 127.1, 125.6, 61.8, 58.9, 38.6, 37.5, 14.3; IR (KBr, $cm^{-1}$) 2812, 1729, 1598, 1384, 1351, 1202; HRMS (Q-Tof) *m*/*z* $[M + H]^+$ calcd for $C_{25}H_{29}O_4$ 393.2066, found 393.2072.

**Compound 17b.** Spectral data: yield 54%; $R_f$ = 0.27 (silica gel, 10% EtOAc/petroleum ether); mp 186−188 °C; $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 7.14−7.07 (m, 16H), 5.66 (m, 4H), 4.21 (q, *J* = 7.2 Hz, 8H), 3.35 (d, *J* = 5.2 Hz, 8H), 3.16 (s, 8H), 1.25 (t, *J* = 7.2 Hz, 12H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 171.3, 139.5, 133.9, 130.8, 130.3, 128.6, 61.5, 59.9, 38.6, 37.0, 14.2; IR (KBr, $cm^{-1}$) 2811, 1733, 1598, 1384, 1351, 1191; HRMS (Q-Tof) *m*/*z* $[M + H]^+$ calcd for $C_{50}H_{57}O_8$ 785.4053, found 785.4060.

**Synthesis of Compounds 18a−b and 20.** To a solution of olefinic compound **17a−b** or **19** (10 mg) in dry ethyl acetate (10 mL), 20 mol % of 5% Pd/C was added, and the mixture was stirred at room temperature under hydrogen atmosphere (1 atm) for 6 h. After the completion of the reaction, the solvent was evaporated under reduced pressure, and the product was purified by silica gel column chromatography. Elution of the column with 7.5% ethyl acetate/petroleum ether gave the hydrogenated products in good yield.

**Compound 18a.** Spectral data: yield 80%; $R_f$ = 0.36 (silica gel, 10% EtOAc/petroleum ether); mp 154−158 °C; $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 7.14 (t, *J* = 7.5 Hz, 4H), 7.05 (d, *J* = 7.8 Hz, 4H), 7.01 (s, 4H), 6.84 (d, *J* = 7.5 Hz, 4H), 4.21 (q, *J* = 7.2 Hz, 8H), 3.15 (s, 8H), 2.65 (m, 8H), 1.72 (m, 8H), 1.25 (t, *J* = 7.2 Hz, 12H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 171.4, 142.4, 136.4, 131.2, 128.5, 127.2, 126.7, 61.5, 59.8, 37.5, 36.1, 31.7, 14.2; IR (KBr, $cm^{-1}$) 2931, 2811, 1733, 1598, 1384, 1351, 1197; HRMS (Q-Tof) *m*/*z* $[M + H]^+$ calcd for $C_{50}H_{61}O_8$ 789.4366, found 789.4389.

**Compound 18b.** Spectral data: yield 90%; $R_f$ = 0.36 (silica gel, 10% EtOAc/petroleum ether); mp 166−168 °C; $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 6.95 (ABq, $J_1$ = 8.4 Hz, $J_2$ = 2.6 Hz, 16H), 4.17 (q, *J* = 7.2 Hz, 8H), 3.13 (s, 8H), 2.57 (m, 8H), 1.52 (m, 8H), 1.20 (t, *J* = 7.2 Hz, 12H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 171.5, 140.8, 133.5, 130.3, 128.5, 61.4, 59.6, 38.1, 34.9, 29.8, 14.1; IR (KBr, $cm^{-1}$) 2933, 2813, 1727, 1598, 1384, 1351, 1208; HRMS (Q-Tof) *m*/*z* $[M + H]^+$ calcd for $C_{50}H_{61}O_8$ 789.4366, found 789.4377.

**Compound 20.** Spectral data: yield 90%; $R_f$ = 0.67 (silica gel, 10% EtOAc/petroleum ether); mp 78−82 °C; $^1$H NMR (400 MHz,


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$CDCl_3$) $\delta$ 7.15 (t, $J$ = 7.6 Hz, 2H), 6.96 (d, $J$ = 7.5 Hz, 2H), 6.77 (d, $J$ = 7.8 Hz, 2H), 6.02 (s, 2H), 4.38 (q, $J$ = 7.2 Hz, 4H), 3.16 (s, 4H), 2.48 (m, 4H), 1.50 (m, 4H), 1.36 (t, $J$ = 7.2 Hz, 6H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 172.3, 140.7, 135.5, 132.1, 128.9, 128.0, 125.1, 62.0, 57.0, 37.8, 34.1, 25.3, 14.3; IR (KBr, cm$^{-1}$) 2931, 2854, 1732, 1447, 1265, 1207; HRMS (Q-Tof) $m/z$ [M + H]$^+$ calcd for $C_{25}H_{31}O_4$ 395.2222, found 395.2218.

**Synthesis of 2,2-*bis*(Bromobenzyl) 1,3-Indanedione (21a and 21b).** To a solution of 1,3-indanedione (**6**) (1 g, 6.85 mmol) and bromobenzyl bromide (3.77 g, 15.07 mmol) in dry acetonitrile (40 mL), freshly prepared KF-Celite (7 g) was added, and the reaction mixture was stirred at rt for 24 h. Again, 3 g of KF-Celite was added, and the stirring was continued for another 24 h. After the completion of the reaction, the reaction mixture was filtered through sintered funnel, and solvent was removed under reduced pressure. The crude product was purified by silica gel column chromatography. Elution of the column with 5% ethyl acetate/petroleum ether gave the 2,2-*bis*(bromobenzyl) 1,3-indanedione **21a–b** as a white crystalline compound.

**2,2-*Bis*(*m*-Bromobenzyl) 1,3-Indanedione (21a).** Spectral data: yield 74%; $R_f$ = 0.63 (silica gel, 10% EtOAc/petroleum ether); mp 184–186 °C; $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 7.68 (dd, $J_1$ = 5.6 Hz, $J_2$ = 2.8 Hz, 2H), 7.58 (dd, $J_1$ = 5.6 Hz, $J_2$ = 2.8 Hz, 2H), 7.12 (m, 4H), 6.91 (m, 4H), 3.18 (s, 4H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 202.7, 142.6, 137.5, 135.7, 132.9, 130.1, 129.7, 128.7, 122.7, 122.2, 61.6, 40.8; IR (KBr, cm$^{-1}$) 2923, 1736, 1702, 1593, 1352, 1249, 782; HRMS (Q-Tof) $m/z$ [M + H]$^+$ calcd for $C_{23}H_{17}O_2Br_2$ 482.9595, found 482.9599.

**2,2-*Bis*(*p*-Bromobenzyl) 1,3-Indanedione (21b).** Spectral data: yield 70%; $R_f$ = 0.63 (silica gel, 10% EtOAc/petroleum ether); mp 162–164 °C; $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 7.64 (dd, $J_1$ = 5.6 Hz, $J_2$ = 2.8 Hz, 2H), 7.59 (dd, $J_1$ = 5.6 Hz, $J_2$ = 2.8 Hz, 2H), 7.14 (d, $J$ = 8.4 Hz, 4H), 6.85 (d, $J$ = 8.4 Hz, 4H), 3.18 (s, 4H); $^{13}$C NMR (75 MHz, $CDCl_3$) $\delta$ 203.1, 142.6, 135.8, 134.2, 131.6, 131.3, 122.7, 121.0, 61.7, 40.7; IR (KBr, cm$^{-1}$) 2923, 1741, 1705, 1593, 1490, 1353, 1251, 1075, 1016, 808, 792; HRMS (Q-Tof) $m/z$ [M + H]$^+$ calcd for $C_{23}H_{17}O_2Br_2$ 482.9595, found 482.9590.

**Synthesis of 2,2-*bis*(Allylbenzyl) 1,3-Indanedione (22a and 22b).** A solution of 2,2-*bis*(bromobenzyl) 1,3-indanedione **21a–b** (1 g, 2.07 mmol), cesium fluoride (1.26 g, 8.26 mmol), and $Pd(PPh_3)_4$ (119 mg, 5 mol %) in dry THF (50 mL) was stirred at rt for 10 min, then allylboronic acid pinacol ester (1.34 g, 8.26 mmol) was added dropwise, and the mixture was stirred at 80 °C for 24 h. Again, cesium fluoride (630 mg, 4.13 mmol), $Pd(PPh_3)_4$ (60 mg, 2.5 mol %), and allylboronic acid pinacol ester (700 mg, 4.32 mmol) were added, and the mixture was stirred at 80 °C for another 24 h. After the completion of the reaction, the reaction mixture was diluted with ether and washed with water (3 × 20 mL). The organic layer was dried over $Na_2SO_4$ and concentrated under reduced pressure. The crude product was purified by silica gel column chromatography. Elution of the column with 2% ethyl acetate/petroleum ether gave the diallylated products **22a–b** as a white crystalline solid.

**2,2-*Bis*(*m*-Allylbenzyl) 1,3-Indanedione (22a).** Spectral data: yield 76%; $R_f$ = 0.67 (silica gel, 10% EtOAc/petroleum ether); mp 84–86 °C; $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 7.59 (dd, $J_1$ = 5.6 Hz, $J_2$ = 3.2 Hz, 2H), 7.49 (dd, $J_1$ = 5.6 Hz, $J_2$ = 3.2 Hz, 2H), 6.94 (t, $J$ = 7.2 Hz, 2H), 6.80 (m, 6H), 5.75–5.69 (m, 2H), 4.93 (dq, $J_1$ = 8.4 Hz, $J_2$ = 1.6 Hz, 2H), 4.79 (dq, $J_1$ = 17.2 Hz, $J_2$ = 1.6 Hz, 2H), 3.24 (s, 4H), 3.15 (d, $J$ = 7.2 Hz, 4H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 203.6, 143.0, 139.7, 137.3, 135.6, 135.1, 130.3, 128.2, 127.8, 127.2, 122.4, 115.6, 62.3, 41.6, 39.9; IR (KBr, cm$^{-1}$) 3077, 2924, 1730, 1705, 1597, 1439, 1362, 1253, 994, 913; HRMS (Q-Tof) $m/z$ [M + H]$^+$ calcd for $C_{29}H_{27}O_2$ 407.2011, found 407.2011.

**2,2-*Bis*(*p*-Allylbenzyl) 1,3-Indanedione (22b).** Spectral data: yield 78%; $R_f$ = 0.67 (silica gel, 10% EtOAc/petroleum ether); mp 124–126 °C; $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 7.62 (dd, $J_1$ = 5.6 Hz, $J_2$ = 3.0 Hz, 2H), 7.50 (dd, $J_1$ = 5.6 Hz, $J_2$ = 3.2 Hz, 2H), 6.91 (d, $J$ = 8.4 Hz, 4H), 6.81 (d, $J$ = 8.4 Hz, 4H), 5.80–5.74 (m, 2H), 4.91 (dq, $J_1$ = 10.0 Hz, $J_2$ = 1.6 Hz, 2H), 4.78 (dq, $J_1$ = 16.8 Hz, $J_2$ = 1.6 Hz, 2H), 3.22 (s, 4H), 3.14 (d, $J$ = 6.4 Hz, 4H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 203.8, 143.0, 138.4, 137.5, 135.2, 133.3, 130.1, 128.5, 122.6, 115.7, 62.4, 41.3, 39.7; IR (KBr, cm$^{-1}$) 3075, 2918, 1739, 1702, 1595, 1358, 1250, 914; HRMS (Q-Tof) $m/z$ [M + H]$^+$ calcd for $C_{29}H_{27}O_2$ 407.2011, found 407.2001.

**Synthesis of Compound 23a and 23b.** A solution of diallyl compound **22a–b** (50 mg, 0.12 mmol) in dry DCM (25 mL) was degassed with $N_2$ for 5 min, then Ti(*i*OPr)$_4$ (7 mg, 20 mol %) and 10 mol % of Grubbs first generation catalyst (10 mg) were added, and the reaction mixture was stirred at 40 °C for 7 h. After the completion of the reaction, the solvent was removed under reduced pressure, and the product was purified by silica gel column chromatography. Elution of the column with 10% ethyl acetate/petroleum ether mixture gave the metathesis products **23a–b** as white solids.

**Compound 23a.** Spectral data: yield 54%; $R_f$ = 0.34 (silica gel, 10% EtOAc/petroleum ether); mp decomposed at 250 °C; $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 7.05 (dd, $J_1$ = 5.6 Hz, $J_2$ = 3.0 Hz, 4H), 6.94 (s, 4H), 6.89 (t, $J$ = 7.6 Hz, 4H), 6.79 (d, $J$ = 7.8 Hz, 4H), 6.72 (d, $J$ = 7.6 Hz, 4H), 6.61 (dd, $J_1$ = 5.6 Hz, $J_2$ = 3.0 Hz, 4H), 5.31 (m, 4H), 3.27 (s, 8H), 3.21 (d, $J$ = 4.0 Hz, 8H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 203.3, 142.5, 140.4, 135.8, 134.8, 131.1, 129.8, 128.2, 127.7, 127.1, 122.3, 62.4, 41.5, 38.3; IR (KBr, cm$^{-1}$) 2921, 2814, 1738, 1702, 1590, 1486, 1443, 1383, 1351, 1253; HRMS (Q-Tof) $m/z$ [M + H]$^+$ calcd for $C_{54}H_{45}O_4$ 757.3318, found 757.3333.

**Compound 23b.** Spectral data: yield 45%; $R_f$ = 0.34 (silica gel, 10% EtOAc/petroleum ether); mp decomposed at 230 °C; $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 6.87 (m, 12H), 6.71 (d, $J$ = 8.0 Hz, 8H), 6.04 (dd, $J_1$ = 5.6 Hz, $J_2$ = 3.0 Hz, 4H), 4.97 (m, 4H), 3.19 (s, 8H), 3.06 (d, $J$ = 4.0 Hz, 8H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 203.4, 142.3, 139.1, 134.4, 133.5, 130.4, 130.1, 128.5, 122.2, 62.9, 40.8, 37.9. IR (KBr, cm$^{-1}$) 2922, 2812, 1740, 1705, 1598, 1439, 1384, 1352, 1249; HRMS (Q-Tof) $m/z$ [M + H]$^+$ calcd for $C_{54}H_{45}O_4$ 757.3318, found 757.3308.

**Synthesis of Compounds 24a and 24b.** To a solution of olefinic compound **23a–b** (10 mg, 0.02 mmol) in dry ethyl acetate (10 mL), 5% Pd/C or 20 mol % of $PtO_2$ was added, and the mixture was stirred at rt under hydrogen atmosphere (1 atm) for 2 h. After the completion of the reaction, the solvent was evaporated under reduced pressure, and the product was purified by silica gel column chromatography. Elution of the column with 10% ethyl acetate/petroleum ether gave the hydrogenated products **24a–b** in good yield.

**Compound 24a.** Spectral data: yield 80%; $R_f$ = 0.54 (silica gel, 20% EtOAc/petroleum ether); mp decomposed at 250 °C; $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 6.88 (m, 12H), 6.77 (d, $J$ = 7.6 Hz, 4H), 6.70 (d, $J$ = 7.6 Hz, 4H), 6.14 (dd, $J_1$ = 5.6 Hz, $J_2$ = 3.2 Hz, 4H), 3.22 (s, 8H), 2.45 (m, 8H), 1.29 (m, 8H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 203.4, 142.3, 142.1, 135.7, 134.6, 130.7, 128.0, 127.3, 126.8, 122.2, 62.4, 41.6, 35.5, 29.1; IR (KBr, cm$^{-1}$) 2925, 2856, 1738, 1703, 1591, 1384, 1352, 1111; HRMS (Q-Tof) $m/z$ [M + H]$^+$ calcd for $C_{54}H_{49}O_4$ 761.3631, found 761.3594.

**Compound 24b.** Spectral data: yield 80%; $R_f$ = 0.54 (silica gel, 20% EtOAc/petroleum ether); mp decomposed at 230 °C; $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 6.82 (d, $J$ = 8.0 Hz, 8H), 6.70 (d, $J$ = 8.4 Hz, 8H), 6.59 (dd, $J_1$ = 5.6 Hz, $J_2$ = 3.2 Hz, 4H), 5.50 (dd, $J_1$ = 5.6 Hz, $J_2$ = 3.2 Hz, 4H), 3.17 (s, 8H), 2.31 (m, 8H), 0.96 (m, 8H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 203.5, 142.2, 140.8, 134.5, 133.3, 130.2, 128.1, 121.5, 63.4, 40.9, 35.1, 29.4; IR (KBr, cm$^{-1}$) 2925, 2850, 1740, 1703, 1595, 1383, 1351, 1249; HRMS (Q-Tof) $m/z$ [M + H]$^+$ calcd for $C_{54}H_{49}O_4$ 761.3631, found 761.3626.

## ■ ASSOCIATED CONTENT

### Supporting Information

The $^1$H and $^{13}$C NMR spectra of all new compounds, X-ray crystallographic data and refinement parameters for **17a**, **17b**, **19**, **23a**, and **23b**, and a ZIP file containing CIF files giving crystallographic data for **17a**, **17b**, **19**, **23a**, and **23b**. This material is available free of charge via the Internet at http://pubs.acs.org.


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## DEDICATION

‡Dedicated to Dr. Christian Bruneau on occassion of his 60th birthday.

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