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NHC-Mediated Synthesis of Tricyclic Spirocarbocycles via an Intramolecular Stetter Reaction of Cyclic Enal-Enones

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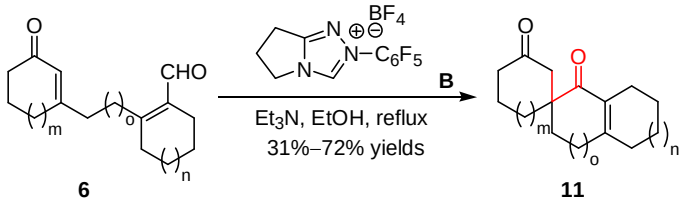


Abstract: A general and efficient method for the synthesis of tricyclic spirocarbocycles is described. Various cyclic enal-enones were reacted with an N-heterocyclic carbene and an intramolecular Stetter reaction proceeded smoothly to give various tricyclic spiro-1,4-diketones in 31–72% yields. The ring size of the spiro compounds can be easily controlled using different cyclic enals and enones, or by altering the length of the carbon tether.

Over the past two decades, the broad application of N-heterocyclic carbenes (NHCs) in organic synthesis has become an important synthetic tool.[1] Among these, the nucleophilic carbene can transform an aldehyde into an acyl anion equivalent via polarity reversal, which enables the aldehyde to react with several different electrophiles.[2] In particular, the conjugate addition of the acyl anion derived from an aldehyde to an electron-deficient alkene is called the Stetter reaction, which is one of the highly explored reactions in the field of NHC-organocatalysis, and provides efficient access to unique 1,4-dicarbonyl

compounds.[3] 1,4-Dicarbonyl compounds are important synthons for the synthesis of natural products[4] and the Stetter reaction offers a practical route to the synthesis of this class of compounds.

Recently, our research work has focused on the development of a general and efficient method to prepare spiro compounds because there are many natural products that contain spiro structures, which exhibit a wide range of biological activities.[5,6] Due to their importance in nature, the synthesis of spiro compounds has become a major focal point in synthetic chemistry. For this reason, there has been a great deal of research interest in developing a multitude of methods for their synthesis.[7] We have reported an efficient synthesis of spiro tricyclic 1,4-diketones via a NHC-catalyzed intramolecular Stetter reaction of various aromatic aldehydes tethered to a cyclic enone (Scheme 1).[8] In our ongoing interest in this research field, we planned to apply a similar synthetic strategy on other substrates. A literature review revealed that only a few examples have been reported to date based on the intramolecular Stetter reaction of aliphatic aldehydes in the construction of the spiro skeletons.[9] This prompted our group to develop a general intramolecular Stetter reaction of α,β-unsaturated aldehydes tethered to a cyclic enone to obtain various tricyclic spirocarbocycles. α,β-Unsaturated aldehydes were used as substrates rather than their corresponding saturated aldehyde derivatives because their cyclized products, tricyclic spirocarbocycles, contain at least one functional group in each ring, which can be used for further functional group transformations or carbon side-chain elongation reactions. In addition, natural products przewalskin B[10a] and holophyllin A[10b] possess a tricyclic carbon framework and exhibit some interesting biological properties (Figure 1).[10] Thus, this methodology is of potential synthetic use for the syntheses of przewalskin B, holophyllin A, and other related natural products.

Scheme 1. Synthetic strategies used to construct spiro skeletons

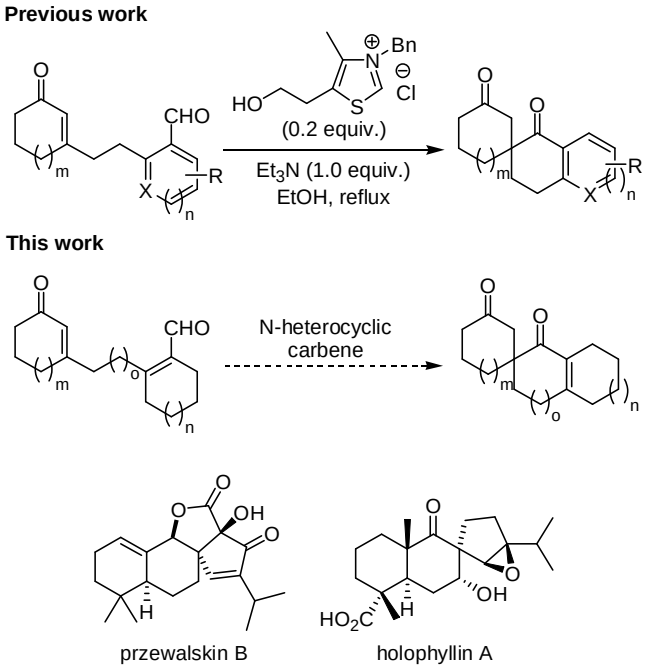
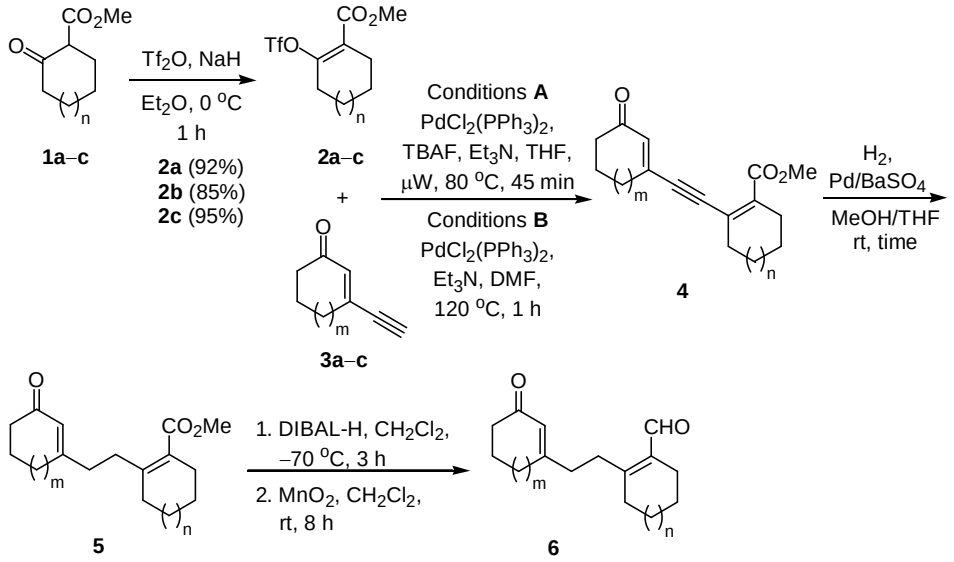


Figure 1. Examples of natural products containing a tricyclic spirocarbocycle

The precursors, cyclic enal-enones **6**, were prepared from commercially available α-carbomethoxycycloalkanones **1**. Conversion of the ketone moiety into the vinyl triflate using sodium hydride and triflic anhydride gave **2** in good to excellent yields (Table 1).[11] The coupling reaction of **2** and **3**[8] was performed using two different reaction conditions. For enynones **3a**–**b**, the coupling reaction was carried out using triethylamine and tetrabutylammonium fluoride (TBAF) in the presence of bis(triphenylphosphine)palladium(II) dichloride in THF at 80 °C under microwave irradiation.[12] However, using the same reactions conditions for enynone **3c** did not give the desired coupling product. Thus, the coupling reaction of enynone **3c** was carried out using triethylamine and the same palladium catalyst, $PdCl_2(PPh_3)_2$, in dimethylformamide (DMF) at 120 °C for 1 h.[13] The desired coupling products **4** were obtained in good yield. The next step was the selective hydrogenation of the triple bond using 5% $Pd/BaSO_4$ in MeOH/THF at room temperature to furnish the corresponding α,β-unsaturated ester-enones **5**, with the exception of **4aa**, which was performed at 0 °C (entry 1).[14] Careful control of the reaction time and the solvent system used for the selective reduction of the triple bond were essential to prevent further reduction of the conjugated double bond. The next stage was the conversion of the ester group into the requisite aldehyde. This was achieved upon treating **5** with DIBAL-H followed by

oxidation of the resulting allylic alcohol with MnO_2 to give the desired cyclic enal-enone **6** in good overall yields.

Table 1. Preparation of the aliphatic spiro precursors **6**



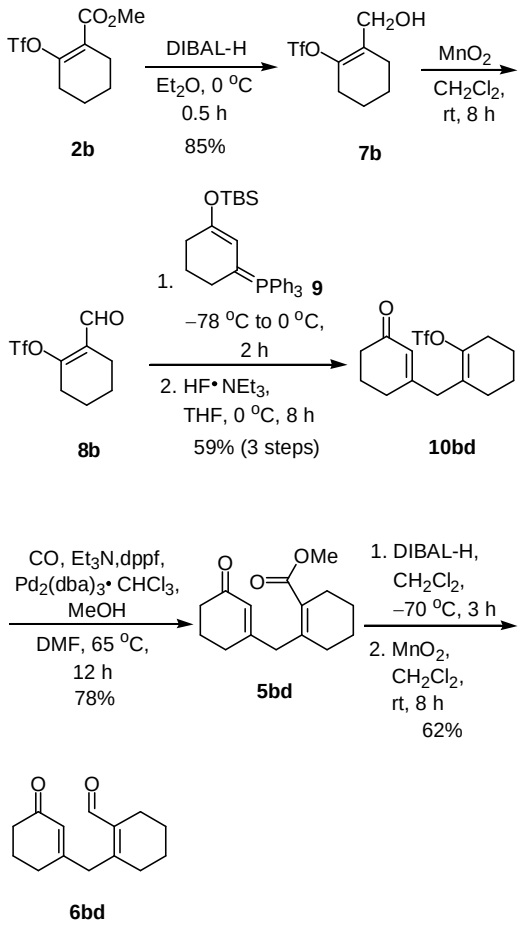
Entry	Triflate	Enynone	Sonogashira reaction / Product **4** (yield)	Hydrogenation MeOH:THF / time	Product **5** (yield)	Product **6** (yield)
1	**2a**: n = 0	**3a**: m = 0	**A** / **4aa** (70%)	1:2 / 1.5 h[a]	**5aa** (70%)	**6aa** (64%)
2	**2a**: n = 0	**3b**: m = 1	**A** / **4ab** (78%)	1:2 / 45 min	**5ab** (71%)	**6ab** (60%)
3	**2a**: n = 0	**3c**: m = 2	**B** / **4ac** (72%)	1:5 / 2 h	**5ac** (67%)	**6ac** (55%)
4	**2b**: n = 1	**3a**: m = 0	**A** / **4ba** (71%)	1:2 / 1 h	**5ba** (78%)	**6ba** (58%)
5	**2b**: n = 1	**3b**: m = 1	**A** / **4bb** (75%)	1:15 / 1 h	**5bb** (80%)	**6bb** (60%)
6	**2b**: n = 1	**3c**: m = 2	**B** / **4bc** (73%)	1:5 / 2.5 h	**5bc** (60%)	**6bc** (65%)
7	**2c**: n = 2	**3a**: m = 0	**A** / **4ca** (70%)	1:2 / 1.5 h	**5ca** (70%)	**6ca** (60%)

[a]Reaction was carried out at 0 °C.

In order to extend the scope of the intramolecular Stetter reaction, a cyclic enal-enone containing a one-carbon tether (**6bd)** was also prepared from triflate **2b**. This was accomplished by the reduction of the ester group using DIBAL-H followed by oxidation of the resulting alcohol with MnO_2 to obtain aldehyde **8b** (Scheme 2). A Wittig reaction of **8b** with phosphorus ylide **9** followed by treatment with HF afforded cyclohexenone **10bd**.[15] Conversion of the triflate to the methyl ester was performed using CO and methanol in the presence of tris(dibenzylideneacetone)dipalladium–chloroform ($Pd_2(dba)_3 \bullet CHCl_3$)[16] to give **5bd** in 78% yield. Using other palladium catalysts in the carbonylation

reaction (e.g., $Pd(OAc)_2$,[17] $Pd(PPh_3)_4$[18]) gave the desired product, but in low yields. Finally, the ester and ketone moieties in **5bd** were reduced by using excess DIBAL-H and the resultant allyl alcohol groups were oxidized to conjugate aldehyde and ketone, respectively, by MnO_2.

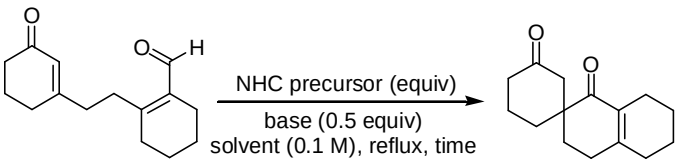
Scheme 2. Preparation of the spiro precursor **6bd** containing a one-carbon tether



With the precursors in hand, we first used **4bb** to examine the Stetter reaction conditions. Compound **4bb** was treated with thiazolium salt **A** (0.5 equiv) and triethylamine (1.0 equiv) in refluxing ethanol (0.1 M). However, these reaction conditions gave a complicated mixture of products containing trace amounts of the desired product (**11bb)** after 48 h of reaction (Table 2, entry 1). Increasing the amount of thiazolium salt **A** from 0.5 equiv to 1.0 and 2.0 equiv under the same conditions led to the same results (entries 2–3). We then turned to use triazolium salt **B** (0.5 equiv) instead of thiazolium salt **A** in refluxing ethanol. Gratifyingly, the intramolecular Stetter reaction proceeded smoothly under these reaction conditions and gave the desired product **11bb** in 30% yield along with the recovered starting

material in 35% yield (entry 4). Increasing the amount of triazolium salt **B** from 0.5 equiv to 1.0 equiv under the same reaction conditions led to the formation of spiro compound **11bb** in 65% yield (entry 5). When the reaction was carried out using 2.0 equiv of triazolium salt **B**, the reaction was completed in 14 h and the product formed in 78% yield (entry 6). Increasing the amount of triethylamine from 0.5 equiv to 1.0 equiv decreased the product yield (entry 7). When other alcoholic solvents such as MeOH, *i*-PrOH, and *t*-BuOH were employed, lower yields of the product were observed (entries 8–10). Changing the base from triethylamine to Cs_2CO_3 in refluxing ethanol or DMF at 90 °C resulted in the recovery of the starting material (entries 11–12), whereas the use of KHMDS in toluene at 90 °C gave a complicated mixture of products (entry 13). Although the best yield was observed using 2.0 equiv of triazolium salt **B** and 0.5 equiv of triethylamine in ethanol at reflux (entry 6), the amount of triazolium salt **B** used was considerable. Thus, in the subsequent reactions of other enal-enone substrates, we used 1.0 equiv of triazolium salt **B** and 0.5 equiv of triethylamine in refluxing ethanol for 48 h (entry 5). In contrast to our previous study on aromatic aldehydes, aliphatic aldehydes require a stoichiometric amount of NHC to carry out the intramolecular Stetter reaction.[19] This is probably due to aliphatic aldehydes being more reactive towards a nucleophile or base, which will cause some undesired reactions. As a consequence, a large amount of the NHC was needed to perform the Stetter reaction in order to diminish these side reactions.

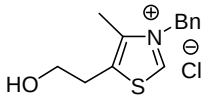
Table 2. Reaction conditions for the attempted intramolecular Stetter reaction



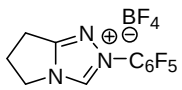
6bb **11bb**

entry	NHC precursor	base	solvent	temp	time	yield
1	**A** (0.5)	Et_3N	EtOH	reflux	48 h	trace[a]
2	**A** (1.0)	Et_3N	EtOH	reflux	48 h	trace[a]
3	**A** (2.0)	Et_3N	EtOH	reflux	48 h	trace[a]
4	**B** (0.5)	Et_3N	EtOH	reflux	48 h	30%[b]
5	**B** (1.0)	Et_3N	EtOH	reflux	48 h	65%
6	**B** (2.0)	Et_3N	EtOH	reflux	14 h	78%
7	**B** (1.0)	Et_3N[c]	EtOH	reflux	48 h	26%
8	**B** (1.0)	Et_3N	MeOH	reflux	48 h	27%
9	**B** (1.0)	Et_3N	*i*-PrOH	reflux	48 h	40%
10	**B** (1.0)	Et_3N	*t*-BuOH	reflux	48 h	10%[d]
11	**B** (1.0)	Cs_2CO_3	EtOH	reflux	48 h	–[e]
12	**B** (1.0)	Cs_2CO_3	DMF	90 °C	48 h	–[e]
13	**B** (0.5)	KHMDS	PhMe	90 °C	48 h	–[a]

[a]Complicated mixture. [b]**4bb** was recovered in 35% yield. [c]1.0 equiv of Et_3N was used. [d]**4bb** was recovered in 20% yield. [e]No reaction.



A

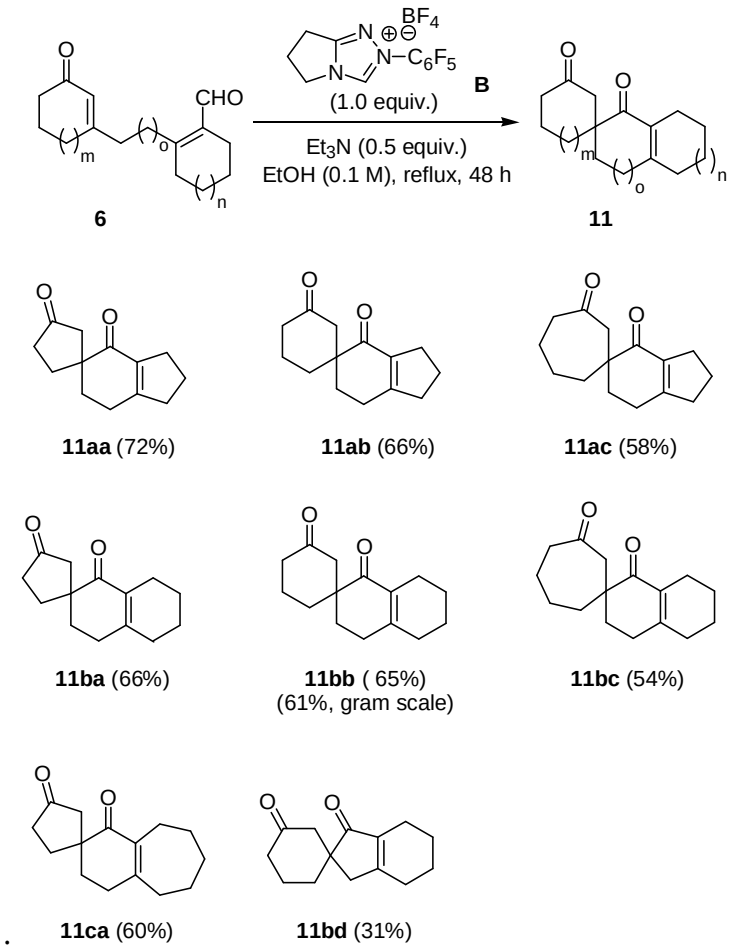


B

With the optimized conditions in hand, we next used other enal-enones in the reaction. The desired tricyclic spirocycles were produced in moderate to good yields (Scheme 3). The reactions of enal-enones with a two-carbon tether proceeded smoothly (**11aa**–**ca**). The reaction also proceeded well on a gram scale (**11bb**) without any significant influence on the product yield (61%). The reaction of the enal-enones with a one-carbon tether (**6bd)** gave product **11bd** in low yield (31%). This was presumably because **6bd** is an active hydrogen compound, which contains two electron-withdrawing groups at the

connected carbon atom leading to an increase in the acidity of the hydrogen atom, which can easily undergo deprotonation under the Stetter reaction conditions to cause some undesired side reactions.

Scheme 3. The intramolecular Stetter reaction



The structures of tricyclic spirocarbocycles **11** were characterized using IR spectroscopy, ^{1}H and ^{13}C NMR, and low- and high-resolution mass spectrometry. The ^{13}C NMR spectra of these compounds showed two ketone carbonyl and a spirocarbon signals at around 200–220 and 50 ppm, respectively. It is noteworthy mentioning that tricyclic spiro-1,4-diketone **11ba** contains the same tricyclic carbon framework as przewalskin B and holophyllin A. Therefore, compound **11ba** could be used toward the syntheses of przewalskin B and holophyllin A.

Conclusions

We have developed a general and efficient method for the preparation of tricyclic spirocarbocycles. A variety of α,β-unsaturated aldehydes underwent an intramolecular Stetter reaction under NHC-mediated conditions to form five- and six-membered rings. The ring size of the spiro compounds can be easily controlled by either using different cyclic enals or enones, or by altering the length of the carbon tether. Although a stoichiometric amount of NHC was used in the Stetter reaction, this methodology provides a way to readily access various ring sizes of tricyclic spiro-1,4-diketones. Efforts to use this methodology toward the total syntheses of przewalskin B, holophyllin A, and other related natural products are now in progress.

Experimental Section

General Information. Unless stated otherwise, reagents were obtained from commercial sources and used without further purification. All reactions were performed under an argon or nitrogen atmosphere in anhydrous solvents, which were dried prior to use following standard procedures. Reactions were monitored by thin-layer chromatography on 0.25 mm E. Merck silica gel plates (60F-254) using 7% ethanolic phosphomolybdic acid as developing agent. Merck silica gel 60 (particle size 0.040–0.063 mm, 230–400 mesh) was employed for flash chromatography. IR spectra were recorded as films on KBr plates. ^{1}H NMR spectra were obtained in $CDCl_3$ at 400 MHz or 500 MHz. ^{13}C NMR spectra were obtained at 100 MHz or 125 MHz. Chemical shifts were reported in δ (ppm) using solvent resonance as the internal reference. High resolution mass spectra (HRMS) were obtained on a TOF MS instrument with an EI source.

General Procedure for Preparation of Enol Triflates 2. A suspension of NaH (50.0 mmol, 60% dispersion in mineral oil, 5.0 equiv) in Et_2O (40 mL) was cooled to 0 °C and added a solution of **1** (10.0 mmol, 1.0 equiv) in Et_2O (30 mL). The mixture was stirred at 0 ^{o}C for 40 min and then added trifluoromethanesulfonic anhydride (20.0 mmol, 2.0 equiv). After stirred at 0 ^{o}C for 1 h, the mixture was quenched carefully with saturated aqueous NH_4Cl at 0 ^{o}C and extracted with Et_2O. The combined

extracts were washed with brine, dried over $MgSO_4$, filtered, and concentrated. The crude product was purified by column chromatography on silica gel (EtOAc/hexanes) to afford **2**.

Methyl 2-(trifluoromethylsulfonyloxy)cyclopent-1-enecarboxylate (2a).[11] Chromatography (EtOAc/hexanes = 1:15); colorless oil; 2.52 g; yield 92%; IR (neat) ν 2957, 1729, 1669, 1428, 1355, 1212, 1142, 1032, 1010, 928, 846, 767 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 3.78 (s, 3H), 2.77–2.66 (m, 4H), 2.05–1.99 (m, 2H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 162.7, 154.0, 122.9, 118.3 (q, J = 318 Hz), 51.8, 32.7, 29.1, 18.8; MS (EI) *m/z* (% base peak) 274 (M^+, 34), 243 (49), 179 (41), 141 (30), 109 (100), 85 (49), 69 (84), 59 (45); HRMS (EI-TOF) *m/z*: $[M]^+$ Calcd for $C_8H_9F_3O_5S$ 274.0123; Found 274.0124.

Methyl 2-(trifluoromethylsulfonyloxy)cyclohex-1-enecarboxylate (2b).[11] Chromatography (EtOAc/hexanes = 1:20); colorless oil; 2.45 g; yield 85%; IR (neat) ν 2954, 2870, 1730, 1670, 1422, 1361, 1289, 1245, 1210, 1140, 1093, 1043, 897, 819 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 3.75 (s, 3H), 2.48–2.42 (m, 2H), 2.40–2.35 (m, 2H), 1.79–1.72 (m, 2H), 1.66–1.61 (m, 2H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 165.0, 151.7, 122.7, 118.2 (q, J = 318 Hz), 51.9, 28.5, 26.0, 22.1, 20.9; MS (EI) *m/z* (% base peak) 288 (M^+, 10), 257 (67), 219 (8), 193 (3), 168 (6), 155 (47), 139 (13), 123 (100), 95 (34), 79 (36), 67 (34), 59 (32); HRMS (EI-TOF) *m/z*: $[M]^+$ Calcd for $C_9H_{11}F_3O_5S$ 288.0279; Found 288.0279.

Methyl 2-(trifluoromethylsulfonyloxy)cyclohept-1-enecarboxylate (2c).[11] Chromatography (EtOAc/hexanes = 1:15); colorless oil; 2.87 g; yield 95%; IR (neat) ν 2925, 2854, 1728, 1652, 1614, 1423, 1353, 1284, 1209, 1140, 1096, 1004, 866, 760 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 3.78 (s, 3H), 2.58 (t, J = 5.5 Hz, 2H), 2.52 (t, J = 5.4 Hz, 2H), 1.80–1.61 (m, 6H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 166.1, 155.0, 127.8, 118.3 (q, J = 317 Hz), 52.2, 33.9, 30.6, 27.9, 25.2, 23.7; MS (EI) *m/z* (% base peak) 302 (M^+, 10), 271 (53), 233 (6), 169 (27), 153 (68), 137 (100), 109 (54), 81 (80); HRMS (EI-TOF) *m/z*: $[M]^+$ Calcd for $C_{10}H_{13}F_3O_5S$ 302.0436; Found 302.0435.

General Procedure for Sonogashira Cross-Coupling. (i) Conditions A. A mixture of **2a**–**c** (3.50 mmol, 1.0 equiv), **3a**–**b** (4.20 mmol, 1.2 equiv), bis(triphenylphosphine)palladium(II) dichloride ($Pd(PPh_3)_2Cl_2$) (246 mg, 0.35 mmol, 0.1 equiv), TBAF (915 mg, 3.50 mmol, 1.0 equiv), and triethylamine (1.46 mL, 10.50 mmol, 3.0 equiv) in THF (5 mL) in a sealed reaction vessel was irradiated

with microwave (110 W) maintained at 80 ^{o}C for 45 min, the temperature was monitored with an internal probe. The contents were cooled to room temperature, quenched with saturated aqueous NH_4Cl, and extracted with EtOAc. The combined organic extracts were washed with brine, dried over $MgSO_4$, filtered and concentrated under reduced pressure. The crude product was purified by column chromatography on silica gel (EtOAc/hexanes) to afford **4aa**–**4ab**, **4ba**–**4bb**, **4ca**.

(ii) Conditions B. To a stirred solution of **2a**–**b** (2.00 mmol, 1.0 equiv), bis(triphenylphosphine)palladium(II) dichloride ($Pd(PPh_3)_2Cl_2$) (140 mg, 0.20 mmol, 0.1 equiv), and **3c** (2.40 mmol, 1.2 equiv) in DMF (20 mL, 0.10 M) was added triethylamine (0.84 mL, 6.00 mmol, 3.0 equiv) under Ar atmosphere at room temperature. The reaction mixture was then heated in an oil bath to 120 ^{o}C for 1 h. The contents were cooled to room temperature and the solvent was evaporated in vacuo to give a residue. The crude product was purified by column chromatography on silica gel (EtOAc/hexanes) to afford **4ac**, **4bc**.

Methyl 2-((3-oxocyclopent-1-en-1-yl)ethynyl)cyclopent-1-enecarboxylate (4aa). Conditions A; chromatography (EtOAc/hexanes = 1:3); yellow oil; 564 mg; yield 70%; IR (neat) ν 2951, 2852, 2189, 1705, 1614, 1572, 1435, 1252, 1170, 862, 762 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.37 (t, *J* = 1.8 Hz, 1H), 3.81 (s, 3H), 2.87–2.73 (m, 6H), 2.51–2.48 (m, 2H), 2.06–1.98 (m, 2H); $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$): δ 209.2, 164.4, 156.3, 141.1, 136.6, 132.9, 99.8, 93.7, 51.7, 38.6, 34.8, 33.5, 32.4, 22.4; MS (EI) *m/z* (% base peak) 230 (M^+, 100), 215 (67), 199 (48), 187 (92), 171 (31), 159 (18), 141 (19), 128 (33), 115 (45), 87 (18); HRMS (EI-TOF) *m/z*: $[M]^+$ Calcd for $C_{14}H_{14}O_3$ 230.0943; Found 230.0946.

Methyl 2-((3-oxocyclohex-1-en-1-yl)ethynyl)cyclopent-1-enecarboxylate (4ab). Conditions A; chromatography (EtOAc/hexanes = 1:3); yellow oil; 667 mg; yield 78%; IR (neat) ν 2950, 2185, 1705, 1673, 1613, 1579, 1435, 1238, 1188, 1133, 963, 888, 765 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.28 (brs, 1H), 3.80 (s, 3H), 2.80–2.70 (m, 4H), 2.57–2.52 (m, 2H), 2.47–2.43 (m, 2H), 2.11–1.95 (m, 4H); $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$): δ 198.6, 164.5, 142.9, 140.5, 133.2, 132.8, 97.4, 95.1, 51.5, 38.7, 37.3, 33.5, 30.2, 22.5, 22.2; MS (EI) *m/z* (% base peak) 244 (M^+, 100), 229 (20), 215 (32), 201 (81), 183 (16), 173

(32), 157 (20), 128 (36), 115 (25), 91 (13); HRMS (EI-TOF) *m/z*: $[M]^+$ Calcd for $C_{15}H_{16}O_3$ 244.1099 ; Found 244.1096.

Methyl 2-((3-oxocyclohept-1-en-1-yl)ethynyl)cyclopent-1-enecarboxylate (4ac). Conditions B; chromatography (EtOAc/hexanes = 1:5); yellow oil; 372 mg; yield 72%; IR (neat) ν 2944, 2864, 2187, 1704, 1660, 1609, 1580, 1437, 1245, 1133, 878 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 6.35 (brs, 1H), 3.77 (s, 3H), 2.76–2.61 (m, 8H), 2.01–1.80 (m, 6H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 202.9, 164.6, 139.9, 139.8, 137.0, 133.7, 100.4, 92.0, 51.6, 42.5, 38.8, 33.9, 33.4, 25.2, 22.3, 21.1; MS (EI) *m/z* (% base peak) 258 (M^+, 3), 218 (61), 190 (8), 176 (26), 175 (20), 149 (70), 108 (100), 91 (20), 79 (45); HRMS (EI-TOF) *m/z*: $[M]^+$ Calcd for $C_{16}H_{18}O_3$ 258.1256; Found 258.1259.

Methyl 2-((3-oxocyclopent-1-en-1-yl)ethynyl)cyclohex-1-enecarboxylate (4ba). Conditions A; chromatography (EtOAc/hexanes = 1:3); yellow oil; 607 mg; yield 71%; IR (neat) ν 2940, 2862, 2187, 1707, 1612, 1576, 1435, 1275, 1235, 1170, 1061, 860, 759 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 6.24 (brs, 1H), 3.73 (s, 3H), 2.78–2.72 (m, 2H), 2.43–2.30 (m, 6H), 1.66–1.60 (m, 4H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 209.2, 166.9, 156.8, 136.8, 135.8, 127.3, 104.1, 90.8, 51.6, 34.6, 32.4, 31.6, 26.3, 21.4, 21.3; MS (EI) *m/z* (% base peak) 244 (M^+, 51), 229 (36), 213 (16), 201 (100), 185 (14), 173 (9), 155 (5), 141 (10), 128 (27), 115 (18), 91 (11), 71 (12); HRMS (EI-TOF) *m/z*: $[M]^+$ Calcd for $C_{15}H_{16}O_3$ 244.1099; Found 244.1101.

Methyl 2-((3-oxocyclohex-1-en-1-yl)ethynyl)cyclohex-1-ene-1-carboxylate (4bb). Conditions A; chromatography (EtOAc/hexanes = 1:5); yellow oil; 678 mg; yield 75%; IR (neat) ν 2944, 2864, 2187, 1718, 1671, 1610, 1582, 1432, 1300, 1231, 1187, 1137, 963, 887, 760 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 6.21 (t, J = 1.5 Hz, 1H), 3.77 (s, 3H), 2.51–2.48 (m, 2H), 2.42–2.35 (m, 4H), 2.35–2.34 (m, 2H), 2.07–2.01 (m, 2H), 1.67–1.64 (m, 4H); $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$): δ 198.7, 167.2, 143.4, 136.5, 132.4, 127.6, 99.4, 94.5, 51.7, 37.3, 31.8, 30.3, 26.4, 22.5, 21.5, 21.4; MS (EI) *m/z* (% base peak) 258 (M^+, 97), 243 (41), 227 (29), 215 (100), 187 (30), 171 (20), 142 (73), 128 (44), 115 (43), 91 (32), 77 (37); HRMS (EI-TOF) *m/z*: $[M]^+$ Calcd for $C_{16}H_{18}O_3$ 258.1256; Found 258.1257.

Methyl 2-((3-oxocyclohept-1-en-1-yl)ethynyl)cyclohex-1-enecarboxylate (4bc). Conditions B; chromatography (EtOAc/hexanes = 1:5); yellow oil; 398 mg; yield 73%; IR (neat) ν 2939, 2864, 2182, 1708, 1657, 1582, 1432, 1231, 1054, 878, 753 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 6.31 (brs, 1H), 3.77 (s, 3H), 2.67–2.60 (m, 4H), 2.43–2.33 (m, 4H), 1.91–1.78 (m, 4H), 1.67–1.60 (m, 4H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 203.0, 167.3, 140.4, 136.5, 135.9, 127.9, 97.3, 96.3, 51.7, 42.5, 34.0, 31.9, 26.4, 25.3, 21.6, 21.5, 21.2; MS (EI) *m/z* (% base peak) 272 (M^+, 20), 257 (11), 244 (8), 229 (32), 218 (26), 201 (18), 190 (100), 163 (20), 149 (17), 129 (25), 122 (68), 101 (46), 91 (36), 79 (85), 59 (74), 55 (58); HRMS (EI-TOF) *m/z*: $[M]^+$ Calcd for $C_{17}H_{20}O_3$ 272.1412; Found 272.1410.

Methyl 2-((3-oxocyclopent-1-en-1-yl)ethynyl)cyclohept-1-enecarboxylate (4ca). Conditions A; chromatography (EtOAc/hexanes = 1:3); yellow oil; 633 mg; yield 70%; IR (neat) ν 2941, 2861, 2185, 1712, 1660, 1439, 1248, 1126, 911, 881 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 6.27 (brs, 1H), 3.77 (s, 3H), 2.80–2.76 (m, 2H), 2.63–2.55 (m, 4H), 2.45–2.42 (m, 2H), 1.84–1.78 (m, 2H), 1.60–1.53 (m, 4H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 209.2, 167.9, 156.9, 143.4, 135.9, 132.3, 105.5, 91.7, 51.9, 36.4, 34.7, 32.4, 32.0, 30.0, 25.7, 25.3; MS (EI) *m/z* (% base peak) 258 (M^+, 5), 244 (53), 230 (82), 215 (71), 199 (42), 187 (100), 171 (27), 159 (28), 145 (19), 128 (35), 115 (53), 91 (27), 77 (24); HRMS (EI-TOF) *m/z*: $[M]^+$ Calcd for $C_{16}H_{18}O_3$ 258.1256; Found 258.1253.

General Procedure for Regioselective Hydrogenation. To a mixture of **4** (2.00 mmol, 1 equiv) and 5% $Pd/BaSO_4$ (1.00 g, 0.50 mmol, 0.25 equiv) in flask was added solvent (0.05 M) (see Table **1** for the solvent used). The reaction mixture was then stirred under a hydrogen balloon at room temperature for a period of time (see Table **1** for the duration of hydrogenation). Filtration and concentration in vacuo gave a residue, which was purified by column chromatography on silica gel (EtOAc/hexanes) to afford **5**.

Methyl 2-(2-(3-oxocyclopent-1-en-1-yl)ethyl)cyclopent-1-enecarboxylate (5aa). Chromatography (EtOAc/hexanes = 1:3); yellowish oil; 328 mg; yield 70%; IR (neat) ν 2948, 2861, 1708, 1616, 1436, 1188, 1115, 841, 768 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 5.97 (t, J = 1.3 Hz, 1H), 3.71 (s, 3H), 2.89 (t, J = 7.7 Hz, 2H), 2.65–2.55 (m, 6H), 2.50 (t, J = 7.7 Hz, 2H), 2.42–2.39 (m, 2H), 1.87–1.79 (m, 2H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 210.1, 181.9, 166.3, 157.7, 129.7, 128.4, 51.1, 37.8, 35.4, 33.5,

31.6, 31.4, 27.4, 21.4; MS (EI) *m/z* (% base peak) 234 (M^+, 10), 219 (12), 203 (18), 192 (25), 174 (39), 146 (18), 131 (26), 109 (100), 96 (50), 79 (46), 69 (36); HRMS (EI-TOF) *m/z*: $[M]^+$ Calcd for $C_{14}H_{18}O_3$ 234.1256; Found 234.1253.

Methyl 2-(2-(3-oxocyclohex-1-en-1-yl)ethyl)cyclopent-1-enecarboxylate (5ab). Chromatography (EtOAc/hexanes = 1:3); yellowish oil; 353 mg; yield 71%; IR (neat) ν 2950, 2868, 1709, 1670, 1433, 1256, 1192, 1115, 1041, 966, 887, 770 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 5.85 (brs, 1H), 3.70 (s, 3H), 2.79 (t, *J* = 7.9 Hz, 2H), 2.63–2.56 (m, 2H), 2.50–2.45 (m, 2H), 2.37–2.32 (m, 6H), 2.00–1.94 (m, 2H), 1.85–1.77 (m, 2H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 200.0, 166.3, 165.7, 158.0, 128.1, 125.8, 51.0, 38.0, 37.3, 36.1, 33.4, 29.4, 27.4, 22.6, 21.4; MS (EI) *m/z* (% base peak) 248 (M^+, 8), 216 (21), 188 (35), 160 (40), 123 (100), 110 (86), 91 (37), 79 (57), 77 (37); HRMS (EI-TOF) *m/z*: $[M]^+$ Calcd for $C_{15}H_{20}O_3$ 248.1412; Found 248.1409.

Methyl 2-(2-(3-oxocyclohept-1-en-1-yl)ethyl)cyclopent-1-enecarboxylate (5ac). Chromatography (EtOAc/hexanes = 1:3); yellowish oil; 352 mg; yield 67%; IR (neat) ν 2932, 2854, 1729, 1708, 1656, 1435, 1347, 1258, 1194, 1113, 1038, 848 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 5.91 (brs, 1H), 3.71 (s, 3H), 2.78 (t, *J* = 7.7 Hz, 2H), 2.65–2.55 (m, 4H), 2.51–2.45 (m, 4H), 2.33 (t, *J* = 7.7 Hz, 2H), 1.87–1.76 (m, 6H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 204.0, 166.3, 161.4, 158.3, 129.5, 128.0, 51.0, 42.2, 39.2, 38.1, 33.5, 32.5, 28.2, 25.2, 21.5, 21.3; MS (EI) *m/z* (% base peak) 262 (M^+, 3), 230 (24), 202 (29), 173 (26), 147 (29), 137 (57), 124 (100), 109 (43), 108 (31), 91 (30), 79 (73), 67 (42), 55 (38); HRMS (EI-TOF) *m/z*: $[M]^+$ Calcd for $C_{16}H_{22}O_3$ 262.1569; Found 262.1567.

Methyl 2-(2-(3-oxocyclopent-1-en-1-yl)ethyl)cyclohex-1-enecarboxylate (5ba). Chromatography (EtOAc/hexanes = 1:3); yellowish oil; 387 mg; yield 78%; IR (neat) ν 2932, 2859, 1708, 1616, 1435, 1279, 1232, 1180, 1075, 1049, 841, 766 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 5.97 (brs, 1H), 3.71 (s, 3H), 2.70–2.55 (m, 6H), 2.45–2.42 (m, 2H), 2.34–2.29 (m, 2H), 2.21–2.15 (m, 2H), 1.70–1.59 (m, 4H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 209.9, 182.4, 168.5, 148.2, 129.2, 125.3, 51.0, 35.1, 32.9, 32.1, 31.4, 31.2, 26.2, 21.98, 21.97; MS (EI) *m/z* (% base peak) 248 (M^+, 4), 217 (21), 206 (28), 189 (19), 165

(13), 152 (56), 121 (12), 109 (100), 96 (52), 93 (40), 58 (56); HRMS (EI-TOF) *m/z*: $[M]^+$ Calcd for $C_{15}H_{20}O_3$ 248.1412; Found 248.1411.

Methyl 2-(2-(3-oxocyclohex-1-en-1-yl)ethyl)cyclohex-1-enecarboxylate (5bb). Chromatography (EtOAc/hexanes = 1:3); yellowish oil; 420 mg; yield 80%; IR (neat) ν 2934, 2859, 1711, 1670, 1624, 1450, 1432, 1279, 1232, 1076, 966, 887, 760 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 5.88 (brs, 1H), 3.70 (s, 3H), 2.56–2.51 (m, 2H), 2.38–2.25 (m, 6H), 2.20–2.10 (m, 2H), 1.99–1.96 (m, 2H), 1.80–1.58 (m, 6H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 199.9, 168.9, 166.1, 148.6, 125.6, 125.4, 51.2, 37.3, 36.9, 33.3, 31.5, 29.7, 26.4, 22.7, 22.3, 22.2; MS (EI) *m/z* (% base peak) 262 (M^+, 2), 230 (10), 202 (13), 174 (13), 152 (48), 123 (48), 110 (100), 93 (37), 79 (26); HRMS (EI-TOF) *m/z*: $[M]^+$ Calcd for $C_{16}H_{22}O_3$ 262.1569; Found 262.1567.

Methyl 2-(2-(3-oxocyclohept-1-en-1-yl)ethyl)cyclohex-1-enecarboxylate (5bc). Chromatography (EtOAc/hexanes = 1:5); yellowish oil; 332 mg; yield 60%; IR (neat) ν 2930, 2861, 1709, 1658, 1440, 1231, 1075, 1049, 850 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 5.92 (brs, 1H), 3.71 (s, 3H), 2.60–2.55 (m, 2H), 2.54–2.45 (m, 4H), 2.34–2.25 (m, 4H), 2.16–2.12 (m, 2H), 1.82– 1.77 (m, 4H), 1.62–1.58 (m, 4H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 204.2, 168.9, 162.1, 148.7, 129.2, 125.2, 51.3, 42.3, 39.9, 34.1, 32.7, 31.6, 26.4, 25.2, 22.23, 22.20, 21.3; MS (EI) *m/z* (% base peak) 276 (M^+, 4), 258 (8), 244 (13), 231 (7), 216 (14), 201 (9), 187 (12), 165 (14), 152 (34), 137 (69), 124 (100), 109 (54), 93 (38), 81 (46), 79 (44), 55 (50); HRMS (EI-TOF) *m/z*: $[M]^+$ Calcd for $C_{17}H_{24}O_3$ 276.1725; Found 276.1722.

Methyl 2-(2-(3-oxocyclopent-1-en-1-yl)ethyl)cyclohept-1-enecarboxylate (5ca). Chromatography (EtOAc/hexanes = 1:5); yellowish oil; 367 mg; yield 70%; IR (neat) ν 2924, 2852, 1709, 1678, 1616, 1436, 1287, 1258, 1201, 1107, 1038, 840 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 5.96 (brs, 1H), 3.70 (s, 3H), 2.65–2.57 (m, 4H), 2.47–2.39 (m, 4H), 2.34–2.29 (m, 2H), 1.82–1.75 (m, 2H), 1.70–1.48 (m, 6H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 209.9, 182.1, 169.9, 152.7, 131.8, 129.4, 51.3, 35.4, 35.3, 34.6, 32.2, 31.8, 31.5, 29.9, 26.2, 25.5; MS (EI) *m/z* (% base peak) 262 (M^+, 7), 231 (13), 220 (24), 203 (32), 179 (11), 166 (82), 159 (18), 135 (13), 109 (100), 96 (74), 79 (38), 67 (22), 55 (16); HRMS (EI-TOF) *m/z*: $[M]^+$ Calcd for $C_{16}H_{22}O_3$ 262.1569; Found 262.1572.

General Procedure for Preparation of Enol-Enones 6. To a stirred solution of **5** (2.00 mmol, 1.0 equiv) in CH_2Cl_2 (10 mL) at –70 ^oC under Ar atmosphere was added diisobutylaluminum hydride (6.00 mL, 6.00 mmol, 1.0 M solution in hexanes, 3.0 equiv). After stirred at –70 ^oC for 3 h, the mixture was then stirred at 0 ^oC for 10 min. The reaction mixture was quenched with water and extracted with CH_2Cl_2. The combined organic extracts were washed with brine, dried over $MgSO_4$, filtered and concentrated under reduced pressure to give a residue. A mixture of the resulting crude product (2.00 mmol, 1.0 equiv) and MnO_2 (40.0 mmol, 20.0 equiv) in CH_2Cl_2 (10 mL) was stirred at room temperature for 8 h. The mixture was filtered through a pad of Celite. The filtrate was concentrated in vacuo to give a residue, which was purified by column chromatography on silica gel (EtOAc/hexanes) to afford **6**.

2-(2-(3-Oxocyclopent-1-en-1-yl)ethyl)cyclopent-1-ene-1-carbaldehyde (6aa). Chromatography (EtOAc/hexanes = 1:2); yellowish oil; 261 mg; yield 64%; IR (neat) ν 2954, 2923, 2856, 1707, 1670, 1612, 1436, 1260, 1184, 1024, 799, 722 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 10.02 (s, 1H), 6.00 (brs, 1H), 2.90 (t, *J* = 7.9 Hz, 2H), 2.66–2.56 (m, 8H), 2.45–2.40 (m, 2H), 1.92–1.84 (m, 2H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 209.4, 187.4, 180.1, 163.1, 139.3, 130.0, 38.1, 35.2, 32.0, 31.5, 30.4, 26.0, 21.3; MS (EI) *m/z* (% base peak) 204 (M^+, 4), 190 (2), 176 (5), 162 (5), 147 (7), 133 (10), 109 (100), 96 (70), 81 (29), 67 (27); HRMS (EI-TOF) *m/z*: $[M]^+$ Calcd for $C_{13}H_{16}O_2$ 204.1150; Found 204.1148.

2-(2-(3-Oxocyclohex-1-en-1-yl)ethyl)cyclopent-1-ene-1-carbaldehyde (6ab). Chromatography (EtOAc/hexanes = 1:3); yellowish oil; 262 mg; yield 60%; IR (neat) ν 2929, 2856, 1661, 1427, 1249, 1190, 796, 752 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 9.98 (s, 1H), 5.88 (brs, 1H), 2.80 (t, *J* = 7.7 Hz, 2H), 2.64–2.55 (m, 4 H), 2.43 (t, *J* = 7.7 Hz, 2H), 2.36 (t, *J* = 6.7 Hz, 2H), 2.31 (t, *J* = 5.8 Hz, 2H), 2.04–1.96 (m, 2H), 1.90–1.83 (m, 2H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 199.4, 187.5, 163.8, 163.6, 139.2, 126.3, 38.2, 37.2, 36.3, 30.3, 29.5, 25.9, 22.6, 21.3; MS (EI) *m/z* (% base peak) 218 (M^+, 6), 200 (4), 190 (6), 161 (7), 147 (9), 131 (14), 121 (10), 110 (100), 108 (66), 95 (8), 79 (26), 58 (40); HRMS (EI-TOF) *m/z*: $[M]^+$ Calcd for $C_{14}H_{18}O_2$ 218.1307; Found 218.1305.

2-(2-(3-Oxocyclohept-1-en-1-yl)ethyl)cyclopent-1-ene-1-carbaldehyde (6ac). Chromatography (EtOAc/hexanes = 1:3); yellowish oil; 256 mg; yield 55%; IR (neat) ν 2926, 2859, 1660, 1447, 1354, 1256, 1194, 1030 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 10.00 (s, 1H), 5.92 (brs, 1H), 2.80 (t, *J* = 7.7 Hz, 2H), 2.63–2.55 (m, 6H), 2.46–2.40 (m, 4H), 1.92–1.75 (m, 6H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 203.6, 187.5, 163.9, 159.4, 139.1, 129.9, 42.2, 39.3, 38.2, 32.7, 30.3, 26.7, 25.2, 21.3, 21.2; MS (EI) *m/z* (% base peak) 232 (M^+, 11), 218 (12), 203 (4), 174 (11), 161 (11), 149 (31), 137 (45), 124 (43), 108 (100), 98 (72), 79 (62), 67 (58), 55 (52); HRMS (EI-TOF) *m/z*: $[M]^+$ Calcd for $C_{15}H_{20}O_2$ 232.1463; Found 232.1465.

2-(2-(3-Oxocyclopent-1-en-1-yl)ethyl)cyclohex-1-ene-1-carbaldehyde (6ba). Chromatography (EtOAc/hexanes = 1:2); yellowish oil; 253 mg; yield 58%; IR (neat) ν 2932, 2861, 1702, 1665, 1616, 1436, 1235, 1183, 843 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 10.10 (s, 1H), 5.99 (brs, 1H), 2.81 (t, *J* = 8.1 Hz, 2H), 2.63–2.58 (m, 4 H), 2.44–2.41 (m, 2H), 2.30–2.18 (m, 4H), 1.68–1.57 (m, 4H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 209.5, 190.2, 180.4, 157.4, 134.6, 129.9, 35.3, 33.5, 32.0, 31.6, 29.7, 22.4, 22.0, 21.5; MS (EI) *m/z* (% base peak) 218 (M^+, 13), 206 (5), 190 (35), 161 (17), 147 (13), 122 (100), 109 (36), 96 (55), 79 (52), 58 (38); HRMS (EI-TOF) *m/z*: $[M]^+$ Calcd for $C_{14}H_{18}O_2$ 218.1307; Found 218.1305.

2-(2-(3-Oxocyclohex-1-en-1-yl)ethyl)cyclohex-1-ene-1-carbaldehyde (6bb). Chromatography (EtOAc/hexanes = 1:3); yellowish oil; 279 mg; yield 60%; IR (neat) ν 2933, 2861, 1665, 1626, 1423, 1371, 1250, 1233, 1191, 964, 887 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 10.07 (s, 1H), 5.87 (brs, 1H), 2.72 (t, *J* = 8.0 Hz, 2H), 2.45–2.17 (m, 10 H), 2.04–1.95 (m, 2H), 1.70–1.55 (m, 4H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 199.5, 190.2, 164.0, 157.7, 134.5, 126.2, 37.8, 37.2, 32.0, 29.71, 29.68, 22.6, 22.4, 22.0, 21.5; MS (EI) *m/z* (% base peak) 232 (M^+, 7), 214 (3), 204 (5), 189 (4), 175 (4), 163 (12), 135 (11), 122 (73), 110 (100), 91 (23), 79 (41), 58 (38), 55 (10); HRMS (EI-TOF) *m/z*: $[M]^+$ Calcd for $C_{15}H_{20}O_2$ 232.1463; Found 232.1465.

2-(2-(3-Oxocyclohept-1-en-1-yl)ethyl)cyclohex-1-ene-1-carbaldehyde (6bc). Chromatography (EtOAc/hexanes = 1:3); yellowish oil; 320 mg; yield 65%; IR (neat) ν 2933, 2864, 1704, 1661, 1447,

1382, 1211, 1068, 802 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 10.09 (s, 1H), 5.91 (brs, 1H), 2.70 (t, *J* = 8.0 Hz, 2H), 2.58 (t, *J* = 6.0 Hz, 2H), 2.45–2.36 (m, 4H), 2.29–2.17 (m, 4H), 1.84–1.77 (m, 4H), 1.70–1.55 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 203.7, 190.3, 159.6, 158.0, 134.5, 129.9, 42.2, 40.9, 33.0, 32.1, 30.5, 25.2, 22.3, 22.0, 21.6, 21.2; MS (EI) *m/z* (% base peak) 246 (M^+, 5), 228 (5), 218 (5), 189 (6), 175 (4), 163 (21), 135 (7), 124 (100), 122 (46), 109 (15), 95 (20), 79 (25), 67 (16); HRMS (EI-TOF) *m/z*: $[M]^+$ Calcd for $C_{16}H_{22}O_2$ 246.1620; Found 246.1621.

2-(2-(3-Oxocyclopent-1-en-1-yl)ethyl)cyclopent-1-ene-1-carbaldehyde (6ca). Chromatography (EtOAc/hexanes = 1:2); yellowish oil; 279 mg; yield 60%; IR (neat) ν 2924, 2849, 1755, 1705, 1663, 1613, 1447, 1280, 1185, 966, 887, 845 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 10.02 (s, 1H), 6.00 (brs, 1H), 2.87 (t, *J* = 8.1 Hz, 2H), 2.64–2.57 (m, 4 H), 2.50–2.41 (m, 6H), 1.83–1.76 (m, 2H), 1.70–1.56 (m, 2H), 1.45–1.38 (m, 2H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 209.5, 189.5, 180.3, 163.7, 140.5, 130.0, 36.9, 35.3, 32.4, 32.3, 31.6, 30.7, 26.0, 25.9, 24.5; MS (EI) *m/z* (% base peak) 232 (M^+, 1), 204 (2), 181 (3), 169 (4), 149 (13), 136 (10), 125 (10), 109 (37), 96 (58), 81 (55), 69 (79), 55 (100); HRMS (EI-TOF) *m/z*: $[M]^+$ Calcd for $C_{15}H_{20}O_2$ 232.1463; Found 232.1463.

2-(Hydroxymethyl)cyclohex-1-en-1-yl trifluoromethanesulfonate (7b).[17] To a stirred solution of **2b** (880 mg, 3.05 mmol) in Et_2O (7.6 mL) at 0 °C under Ar atmosphere was added diisobutylaluminum hydride (9.10 mL, 9.10 mmol, 1.0 M solution in hexanes). After stirred at 0 °C for 0.5 h, the mixture was quenched with EtOAc and 1 M HCl. The solution was extracted with Et_2O. The combined organic extracts were washed with brine, dried over $MgSO_4$, filtered and concentrated under reduced pressure. The crude product was purified by column chromatography on silica gel (EtOAc/hexanes = 1/8) to afford **7b** (675 mg, 85%) as a yellow oil. ^1H NMR (400 MHz, $CDCl_3$) δ 4.20 (s, 2H), 2.37–2.30 (m, 4H), 1.81–1.63 (m, 4H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 144.1, 129.9, 118.3 (q, *J* = 317 Hz), 59.7, 27.6, 26.4, 22.9, 21.4.

2-Formylcyclohex-1-en-yl trifluoromethanesulfonate (8b, 80b). A mixture of **7b** (880 mg, 3.41 mmol) and MnO_2 (5.93 g, 68.2 mmol) in CH_2Cl_2 (5 mL) was stirred at room temperature for 8 h. The mixture

was filtered through a pad of Celite. The filtrate was concentrated in vacuo to give a crude product **8b**, which was immediately used in the next step without further purification.

2-((3-Oxocyclohex-1-en-1-yl)methyl)cyclohex-1-en-1-yl trifluoromethanesulfonate (10bd). A mixture of cyclohexanone (471 mg, 4.91 mmol), trimethylsilyl trifluoromethanesulfonate (1.09 g, 4.91 mmol), and PPh_3 (1.29 g, 4.91 mmol) in THF (8.2 mL) was stirred at room temperature for 1.5 h and then cooled to –78 ^oC. *n*-BuLi (1.80 mL, 4.41 mmol, 2.5 M solution in hexanes) was added dropwise to the reaction mixture and stirred for another 1 h. Crude **8b** (3.41 mmol) was then added to the mixture and it was stirred at room temperature for 2 h. The reaction mixture was quenched with water and the solvent was evaporated. The residue was then dissolved in EtOAc and washed successively with water, brine and dried over $MgSO_4$, filtered and concentrated under reduced pressure. The crude product was dissolved in THF (8.2 mL) and added $Et_3N{\bullet}3HF$ (2.4 mL, 14.73 mmol) at 0 ^oC. The mixture was stirred at 0 ^oC for 8 h and extracted with EtOAc. The combined organic extracts were washed with brine, dried over $MgSO_4$, filtered and concentrated under reduced pressure. The crude product was purified by column chromatography on silica gel (EtOAc/hexanes = 1/5) to afford **10bd** (669 mg, 59% over 3 steps) as a yellow oil. IR (neat) ν 2943, 2866, 1675, 1629, 1409, 1211, 1140, 1022, 887, 817 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 5.84 (s, 1H), 3.06 (s, 2H), 2.40–2.35 (m, 4H), 2.26 (t, *J* = 6.0 Hz, 2H), 2.09–1.90 (m, 4H), 1.82–1.75 (m, 2H), 1.67–1.60 (m, 2H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 199.5, 161.4, 145.5, 127.1, 125.9, 118.2 (q, *J* = 317 Hz), 38.8, 37.2, 29.3, 28.7, 27.5, 23.0, 22.5, 21.6; MS (EI) *m/z* (% base peak) 339 (M^+ + H, 0.3), 257 (6), 172 (58), 107 (31), 91 (76), 83 (22), 69 (100), 65 (37), 58 (21); HRMS (EI-TOF) *m/z*: $[M]^+$ Calcd for $C_{14}H_{17}F_3O_4S$ 338.0800; Found 338.0797.

Methyl 2-((3-oxocyclohex-1-en-1-yl)methyl)cyclohex-1-enecarboxylate (5bd). To a stirred solution of **10bd** (500 mg, 1.48 mmol) in MeOH (13.1 mL) and DMF (4.6 mL) was saturated with CO (**Caution:** Carbon monoxide is an extremely flammable and toxic gas. All manipulations with carbon monoxide must be performed in a well-ventilated fume hood. Keep shield and/or hood sash between reaction vessel and laboratory worker.).[20] A solution of tris(dibenzylideneacetone)dipalladium(0)-chloroform adduct (155 mg, 0.15 mmol) and 1,1'-bis(diphenylphosphino)ferrocene (164 mg, 0.30 mmol) in DMF

(4.6 mL) and triethylamine (0.41 mL, 2.94 mmol) were added to the reaction mixture. The mixture was heated in an oil bath to 65 ^{o}C for 12 h. The contents were cooled to room temperature and then added saturated aqueous NH_4Cl. The aqueous layer was extracted with Et_2O. The combined organic extracts were washed with brine, dried over $MgSO_4$, filtered and concentrated under reduced pressure. The crude product was purified by column chromatography on silica gel (EtOAc/hexanes = 1/10) to afford **5bd** (285 mg, 78%) as a yellow oil. IR (neat) ν 2932, 2856, 1709, 1670, 1429, 1232, 1187, 1069, 1045, 966, 888, 759 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.78 (brs, 1H), 3.69 (s, 3H), 3.36 (s, 2H), 2.38–2.29 (m, 6H), 2.10–2.01 (m, 2H), 1.99–1.90 (m, 2H), 1.62–1.55 (m, 4H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 200.0, 168.6, 164.6, 144.6, 127.7, 125.7, 51.4, 43.1, 37.4, 31.8, 29.8, 26.5, 22.6, 22.1, 22.0; MS (EI) *m/z* (% base peak) 248 (M^+, 46), 217 (39), 188 (90), 171 (26), 160 (100), 145 (27), 131 (21), 117 (22), 105 (18), 91 (43), 79 (24), 77 (22), 55 (15); HRMS (EI-TOF) *m/z*: $[M]^+$ Calcd for $C_{15}H_{20}O_3$ 248.1412; Found 248.1409.

2-((3-Oxocyclohex-1-en-1-yl)methyl)cyclohex-1-ene-1-carbaldehyde (6bd). To a stirred solution of **5bd** (286 mg, 1.15 mmol) in CH_2Cl_2 (5.8 mL) at –70 ^{o}C under Ar atmosphere was added diisobutylaluminum hydride (3.45 mL, 3.45 mmol, 1.0 M solution in hexanes). After stirred at –70 ^{o}C for 3 h, the mixture was then stirred at 0 ^{o}C for 10 min. The reaction mixture was quenched with water and extracted with CH_2Cl_2. The combined organic extracts were washed with brine, dried over $MgSO_4$, filtered and concentrated under reduced pressure to give a residue. A mixture of the crude product and MnO_2 (2.00 g, 23.0 mmol) in CH_2Cl_2 (5.8 mL) was stirred at room temperature for 8 h. The mixture was filtered through a pad of Celite. The filtrate was concentrated in vacuo to give a residue, which was purified by column chromatography on silica gel (EtOAc/hexanes = 1/3) to afford **6bd** (156 mg, 62% over 2 steps) as a yellowish oil. IR (neat) ν 2934, 2859, 1712, 1667, 1626, 1447, 1238, 1190, 1137, 967, 888, 736 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.02 (s, 1H), 5.85 (brs, 1H), 3.44 (s, 2H), 2.38 (t, *J* = 6.7 Hz, 2H), 2.32–2.24 (m, 4H), 2.20–2.16 (m, 2H), 2.07–2.01 (m, 2H), 1.67–1.62 (m, 4H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 199.3, 190.4, 162.3, 153.2, 136.4, 127.1, 40.0, 37.2, 32.3, 29.8, 22.6, 22.5, 21.9, 21.5; MS (EI) *m/z* (% base peak) 218 (M^+, 12), 205 (25), 188 (19), 177 (19), 161 (30), 149 (100), 136

(49), 129 (32), 109 (55), 97 (83), 85 (83), 71 (91), 57 (96), 55 (74); HRMS (EI-TOF) *m/z*: $[M]^+$ Calcd for $C_{14}H_{18}O_2$ 218.1307; Found 218.1310.

General Procedure for Intramolecular Stetter Reaction. A suspension of triazolium salt **B** (182 mg, 0.50 mmol, 1.0 equiv) in absolute ethanol (2.5 mL) was added triethylamine (0.035 mL, 0.25 mmol, 0.5 equiv) under Ar atmosphere at room temperature. After stirred at room temperature for 10 min, a solution of **6** (0.50 mmol, 1.0 equiv) in absolute ethanol (2.5 mL) was added. The reaction mixture was then heated in an oil bath to reflux for 48 h. The contents were cooled to room temperature and then added saturated aqueous NH_4Cl. The aqueous layer was extracted with EtOAc. The combined organic extracts were washed with brine, dried over $MgSO_4$, filtered and concentrated under reduced pressure. The crude product was purified by column chromatography on silica gel (EtOAc/hexanes) to afford **11**.

2',3',6',7'-Tetrahydrospiro[cyclopentane-1,5'-indene]-3,4'(1'*H*)-dione (11aa). Chromatography (EtOAc/hexanes = 1:3); yellow oil; 74 mg; yield 72%; IR (neat) ν 2957, 2924, 2854, 1743, 1704, 1654, 1456, 1394, 1259, 1167, 887 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 2.73 (d, *J* = 18.2 Hz, 1H), 2.65–2.20 (m, 9H), 2.17–1.83 (m, 6H); $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$): δ 217.3, 199.3, 164.4, 136.1, 49.4, 46.9, 37.7, 36.3, 34.5, 30.4, 29.4, 24.0, 21.8; MS (EI) *m/z* (% base peak) 204 (M^+, 61), 176 (100), 149 (42), 148 (26), 133 (12), 108 (100), 91 (30), 79 (58), 77 (26); HRMS (EI-TOF) *m/z*: $[M]^+$ Calcd for $C_{13}H_{16}O_2$ 204.1150; Found 204.1150.

2',3',6',7'-Tetrahydrospiro[cyclohexane-1,5'-indene]-3,4'(1'*H*)-dione (11ab). Chromatography (EtOAc/hexanes = 1:4); yellow oil; 72 mg; yield 66%; IR (neat) ν 2936, 2855, 1712, 1656, 1515, 1391, 1228, 940, 887 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 2.71 (d, *J* = 14.6 Hz, 1H), 2.58–2.22 (m, 8H), 2.03 (d, *J* = 14.6 Hz, 1H), 2.03–1.83 (m, 7H), 1.68–1.60 (m, 1H); $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$): δ 210.4, 199.2, 164.0, 135.9, 48.9, 48.2, 40.5, 37.6, 33.3, 30.1, 29.3, 23.4, 21.8, 21.7; MS (EI) *m/z* (% base peak) 218 (M^+, 77), 190 (7), 176 (27), 175 (21), 149 (80), 147 (12), 108 (100), 91 (17), 79 (43), 75 (25), 58 (22); HRMS (EI-TOF) *m/z*: $[M]^+$ Calcd for $C_{14}H_{18}O_2$ 218.1307; Found 218.1304.

2',3',6',7'-Tetrahydrospiro[cycloheptane-1,5'-indene]-3,4'(1'*H*)-dione (11ac). Chromatography (EtOAc/hexanes = 1:3); yellow oil; 67 mg; yield 58%; IR (neat) ν 2926, 2854, 1742, 1698, 1661, 1515,

1456, 1388, 1260, 1195, 1028, 803 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 3.00 (d, *J* = 12.9 Hz, 1H), 2.66–2.30 (m, 9H), 2.07–2.00 (m, 1H), 1.96–1.76 (m, 7H), 1.66–1.56 (m, 2H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 213.2, 199.7, 163.7, 135.4, 50.0, 45.9, 43.8, 37.6, 36.5, 33.3, 29.5, 24.6, 23.9, 23.4, 21.8; MS (EI) *m/z* (% base peak) 232 (M^+, 10), 214 (3), 197 (2), 177 (13), 149 (79), 127 (7), 108 (100), 99 (13), 85 (36), 71 (38), 57 (20); HRMS (EI-TOF) *m/z*: $[M]^+$ Calcd for $C_{15}H_{20}O_2$ 232.1463; Found 232.1460.

3',4',5',6',7',8'-Hexahydro-1'*H*-spiro[cyclopentane-1,2'-naphthalene]-1',3-dione (11ba). Chromatography (EtOAc/hexanes = 1:4); yellow oil; 72 mg; yield 66%; IR (neat) ν 2923, 2859, 1742, 1657, 1459, 1379, 1224, 1168, 1075, 967, 845, 799 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 2.70 (d, *J* = 18.0 Hz, 1H), 2.44–2.36 (m, 2H), 2.29–2.12 (m, 7H), 2.07–1.99 (m, 1H), 1.98 (d, *J* = 18.0 Hz, 1H), 1.94–1.86 (m, 2H), 1.68–1.63 (m, 2H), 1.59–1.54 (m, 2H); $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$): δ 217.4, 200.9, 156.0, 130.4, 48.8, 47.5, 36.2, 33.2, 31.6, 30.7, 28.2, 22.3, 22.0, 21.9; MS (EI) *m/z* (% base peak) 218 (M^+, 19), 190 (100), 163 (12), 147 (4), 122 (62), 105 (4), 91 (12), 79 (28), 77 (9), 58 (17); HRMS (EI-TOF) *m/z*: $[M]^+$ Calcd for $C_{14}H_{18}O_2$ 218.1307; Found 218.1306.

3′,4′,5′,6′,7′,8′-Hexahydro-1′*H*-spiro[cyclohexane-1,2′-naphthalene]-1′,3-dione (11bb). Chromatography (EtOAc/hexanes = 1:3); yellow oil; 76 mg; yield 65%; IR (neat) ν 2930, 2856, 1712, 1654, 1634, 1445, 1385, 1217, 1178, 940, 844 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 2.68 (d, *J* = 14.5 Hz, 1H), 2.45–2.00 (m, 9H), 2.01 (d, *J* = 14.5 Hz, 1H), 1.92–1.80 (m, 4H), 1.70–1.50 (m, 5H); $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$): δ 210.4, 200.6, 155.4, 130.4, 48.9, 48.3, 40.5, 32.1, 31.5, 30.2, 27.6, 22.3, 22.1, 21.9, 21.6; MS (EI) *m/z* (% base peak) 232 (M^+, 67), 190 (39), 189 (24), 163 (94), 122 (100), 110 (7), 91 (22), 79 (53), 58 (52); HRMS (EI-TOF) *m/z*: $[M]^+$ Calcd for $C_{15}H_{20}O_2$ 232.1463; Found 232.1466.

3',4',5',6',7',8'-Hexahydro-1'*H*-spiro[cycloheptane-1,2'-naphthalene]-1',3-dione (11bc). Chromatography (EtOAc/hexanes = 1:3); yellow oil; 67 mg; yield 54%; IR (neat) ν 2958, 2927, 2851, 1735, 1716, 1518, 1459, 1378, 1260, 1083, 1020, 967, 802, cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 2.97 (d, *J* = 13.0 Hz, 1H), 2.67–2.55 (m, 1H), 2.41–2.32 (m, 1H), 2.34 (d, *J* = 13.0 Hz, 1H), 2.30–1.98 (m, 7H), 1.90–1.45 (m, 11H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 213.3, 201.0, 155.2, 129.9, 50.5, 45.2, 43.8,

36.7, 31.7, 31.5, 27.6, 24.5, 23.9, 22.5, 22.2, 21.9; MS (EI) *m/z* (% base peak) 246 (M^+, 6), 211 (3), 197 (4), 177 (15), 163 (15), 149 (63), 141 (10), 127 (16), 122 (26), 113 (23), 99 (28), 85 (75), 71 (100), 57 (78); HRMS (EI-TOF) *m/z*: $[M]^+$ Calcd for $C_{16}H_{22}O_2$ 246.1620; Found 246.1620.

3′,4′,6′,7′,8′,9′-Hexahydrospiro[benzo[7]annulene-2,1'-cyclopentane]-1,3'(5*H*)-dione (11ca). Chromatography (EtOAc/hexanes = 1:3); yellow oil; 70 mg; yield 60%; IR (neat) ν 2920, 2848, 1742, 1651, 1514, 1449, 1375, 1249, 1153, 964, 834 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 2.69 (d, *J* = 18.2 Hz, 1H), 2.62–2.18 (m, 9H), 2.07–1.75 (m, 6H), 1.57–1.50 (m, 2H), 1.42–1.35 (m, 2H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 217.4, 200.2, 161.9, 136.2, 48.0, 47.5, 36.6, 36.3, 33.2, 32.2, 30.7, 30.0, 26.2, 25.4, 24.3; MS (EI) *m/z* (% base peak) 232 (M^+, 0.5), 219 (2), 204 (1), 181 (5), 169 (7), 149 (15), 131 (14), 119 (17), 109 (42), 96 (82), 83 (59), 69 (100), 55 (99); HRMS (EI-TOF) *m/z*: $[M]^+$ Calcd for $C_{15}H_{20}O_2$ 232.1463; Found 232.1460.

4',5',6',7'-Tetrahydrospiro[cyclohexane-1,2'-indene]-1',3(3'*H*)-dione (11bd). Chromatography (EtOAc/hexanes = 1:3); yellow oil; 34 mg; yield 31%; IR (neat) ν 2929, 2854, 1699, 1643, 1430, 1398, 1276, 1226, 1073, 905, 755 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 2.65 (d, *J* = 13.7 Hz, 1H), 2.48–2.10 (m, 7H), 2.05–1.93 (m, 2H), 1.85–1.40 (m, 8H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 211.0, 208.9, 171.0, 136.1, 51.5, 48.7, 42.7, 40.9, 32.2, 28.3, 24.0, 22.0, 21.5, 20.0; MS (EI) *m/z* (% base peak) 218 (M^+, 29), 190 (6), 175 (10), 161 (10), 149 (100), 147 (9), 136 (6), 105 (5), 91 (13), 79 (9), 58 (72); HRMS (EI-TOF) *m/z*: $[M]^+$ Calcd for $C_{14}H_{18}O_2$ 218.1307; Found 218.1310.

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Supporting Information Available: Copies of ^1H and ^{13}C NMR for compounds **2**, **4**–**6**, **7b**, **10bd**, and **11**.

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