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Article

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Construction of Spiro-Fused Tricyclic Frameworks by NHC-Catalyzed Intramolecular Stetter Reaction of Benzaldehyde Tether with a Cyclic Enone

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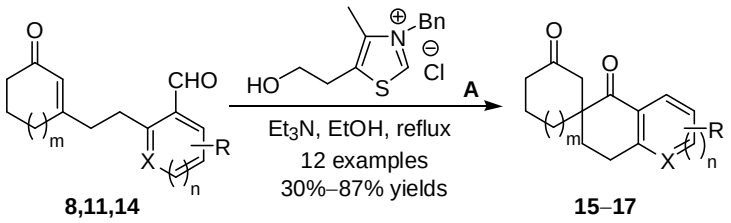
Keywords: Spiro compounds, enone-benzaldehydes, N-heterocyclic carbene, Stetter, cyclization



8,11,14 **15**–**17**

Abstract: Various benzaldehyde tethers with a cyclic enone were prepared from commercially available 2-hydroxybenzaldehydes via a three-step sequence involving triflate formation, Sonogashira cross-coupling and regioselective hydrogenation. These substrates were then exposed to an N-heterocyclic carbene, whereupon intramolecular Stetter reaction proceeded smoothly to give various spiro-fused tricyclic 1,4-diketones in 30%-87% yields. Furaldehyde and nicotinaldehyde derivatives also participated in the reaction under the Stetter conditions.

Introduction

Recently, spiro compounds have received much attention in organic and medicinal chemistry because of their interesting conformational features and structural implications in biological systems.[1] The asymmetric nature of the molecules, which is attributable to the chiral spiro carbon, is one of the important criteria for biological activity. Spiro core systems are also found in a variety of natural products with wide-ranging biological activities (Figure 1).[2] Moreover, the unique structural features of spiro compounds have been exploited for the synthesis of new catalysts and ligands with excellent results.[3] Consequently, the development of new and efficient strategies for constructing the spiro core has become a major focal point for synthetic chemistry.[4] Recently, we developed intramolecular cyclizations of enone-aldehydes via samarium diiodide-mediated reductive cyclization[5] and thiol-mediated acyl radical cyclization[6] to prepare spirocyclic γ-hydroxyketones and 1,4-diketones, respectively (Scheme 1). As a continuation of our work, we report here the intramolecular Stetter reaction of benzaldehyde tethers with a cyclic enone to construct various spiro-fused tricyclic 1,4-diketones. The challenge in this strategy is the 1,4-addition of a Breslow intermediate[7] to the β-disubstituted enone, which is less reactive toward nucleophiles than are the corresponding β-mono-substituted and unsubstituted enones due to steric hindrance.

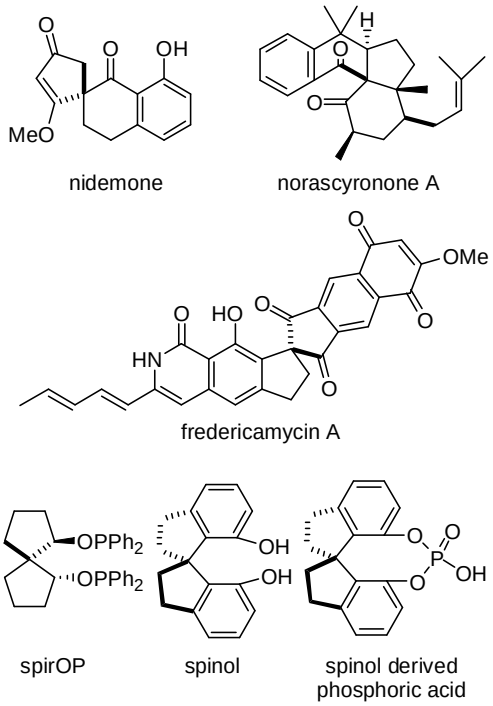
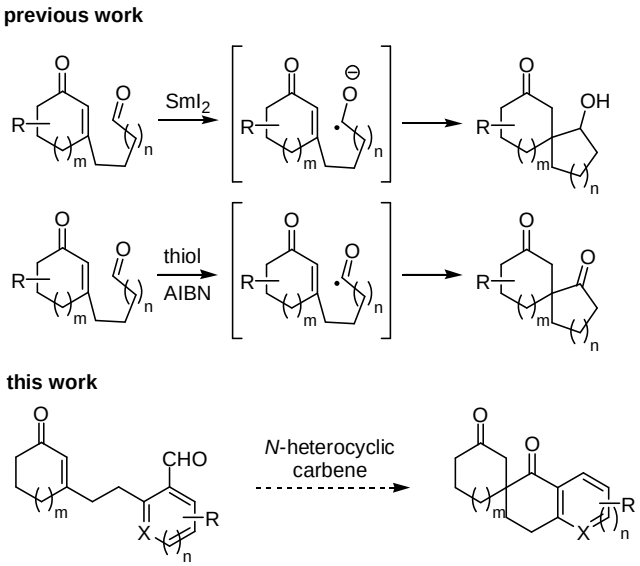


Figure 1. Examples of natural products and chiral ligands containing a carbocyclic spiro skeleton

Scheme 1. Strategies for constructing spiro skeletons

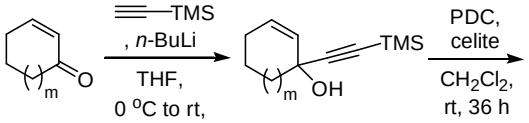


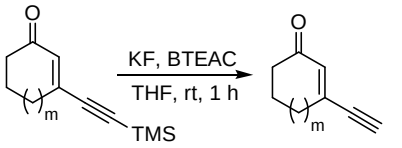
The Stetter reaction, which was discovered in 1976,[8a,b] involves the conjugate addition of an aldehyde to an electron-deficient alkene to form a 1,4-dicarbonyl system in the presence of a catalytic amount of N-heterocyclic carbene (NHC).[8] This reaction can be performed in an asymmetric fashion by utilizing a chiral NHC.[9] NHCs used to prepare spirocyclic structures are well known;[4i] however, only a few examples based on the Stetter reaction have been reported to date. A literature survey revealed that Gravel and coworkers used domino intermolecular Stetter reaction–intramolecular Michael or aldol reactions to construct the spiro bis-indane framework with a spiro[4.4]nonane core.[10] Ye and coworker employed NHC-catalyzed [4+1] annulation of phthalaldehyde and *N*-phenylmaleimide to form a spirocyclic hydroxyindanone with a heterocyclic spiro[4.4]nonane structure via a tandem process involving an intermolecular Stetter reaction, proton shift, and aldol reaction.[11] Rovis and coworker reported an intramolecular Stetter reaction to construct a heterocyclic spiro[4.4]nonane skeleton and applied it to the total synthesis of (–)-cephalimysin A.[12] Later, Zanardi and coworkers adopted an intramolecular 1,6-Stetter reaction to prepare spiro[4.5]decanone derivatives.[13] It is noteworthy that these intramolecular Stetter reactions led to the formation of a five-membered ring in the spirocyclic structures. In contrast to the literature procedures, our method results in the creation of a six-membered ring in the spirocyclic skeletons.

Results and Discussion

(a) Preparation of Sonogashira Cross-coupling Substrates. Our synthesis strategy toward spiro precursors **8** involved the combination of enynones **4** and triflates **6**, followed by selective reduction of the triple bond. Therefore, the necessary enynones **4** were prepared from cyclic enones **1**, as outlined in Scheme 2. 1,2-Addition of the lithium acetylide, which was generated from trimethylsilylacetylene and *n*-BuLi,[14] to the ketone afforded tertiary allylic alcohols **2**. Oxidation of **2** with PDC[15] afforded enynones **3**, and subsequent removal of the silyl group[16] furnished the desired conjugated enynones **4**.

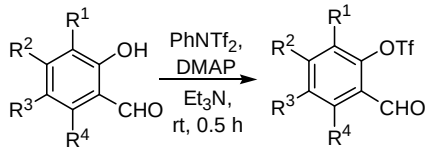
Scheme 2. Preparation of conjugated cyclic enynones **4**





On the other hand, triflates **6** were obtained from commercially available 2-hydroxybenzaldehydes **5** in excellent yields by using phenylbis(trifluoromethanesulfonimide) as a triflating reagent (Scheme 3).[17a]

Scheme 3. Preparation of triflates **6**

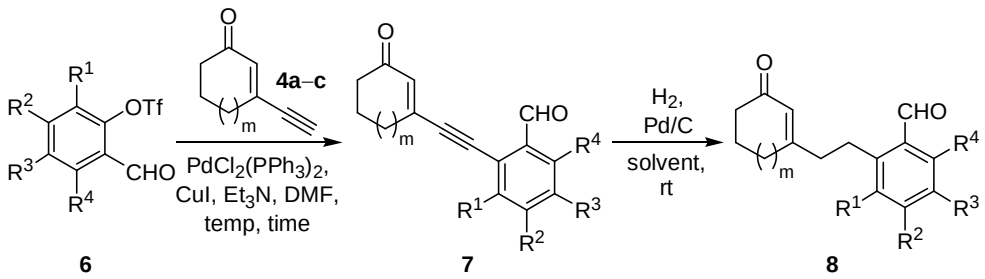


5a: $R^1 = R^2 = R^3 = R^4 = H$ **6a** (91%)
5b: $R^1 = OMe$, $R^2 = R^3 = R^4 = H$ **6b** (98%)
5c: $R^1 = H$, $R^2 = OMe$, $R^3 = R^4 = H$ **6c** (99%)
5d: $R^1 = R^2 = H$, $R^3 = OMe$, $R^4 = H$ **6d** (99%)
5e: $R^1 = R^2 = R^3 = H$, $R^4 = OMe$, **6e** (98%)
5f: $R^1 = R^2 = H$, $R^3 = Me$, $R^4 = H$ **6f** (97%)
5g: $R^1 = R^2 = H$, $R^3 = CO_2Me$, $R^4 = H$ **6g** (87%)

(b) Preparation of Cyclic Enone-benzaldehydes. Coupling reactions of **4** and **6** were carried out with triethylamine in the presence of bis(triphenylphosphine)palladium(II) dichloride and copper(I)

iodide in DMF at 120 ^{o}C.[18] As an exception, the reaction of the triflate with an ester moiety reaction occurred at room temperature (Table 1, entry 9). The desired coupling products **7** were obtained in moderate to good yields. The coupling reaction of triflate **6e** and enynone **4a** gave the product in only 50% yield, probably because **4a** was thermal unstable and easily decomposed under heat (entry 2). The next step was selective hydrogenation at the triple bond.[19] After screening multiple solvents for this reaction, we found that is difficult to identify a common solvent system for the regioselective hydrogenation. In all the solvents tested, either the reduction did not proceed or the double bond was also reduced along with the triple bond. Therefore, selective reduction of the alkyne moiety with hydrogen in the presence of 10% Pd/C was carried out in a suitable solvent, as indicated in Table 1 (0.1 M), at room temperature to furnish enone-benzaldehydes **8**. Careful control of the reaction time for the selective reduction of the triple bond is essential to prevent overreduction.

Table 1. Preparation of aromatic spiro precursors **8**



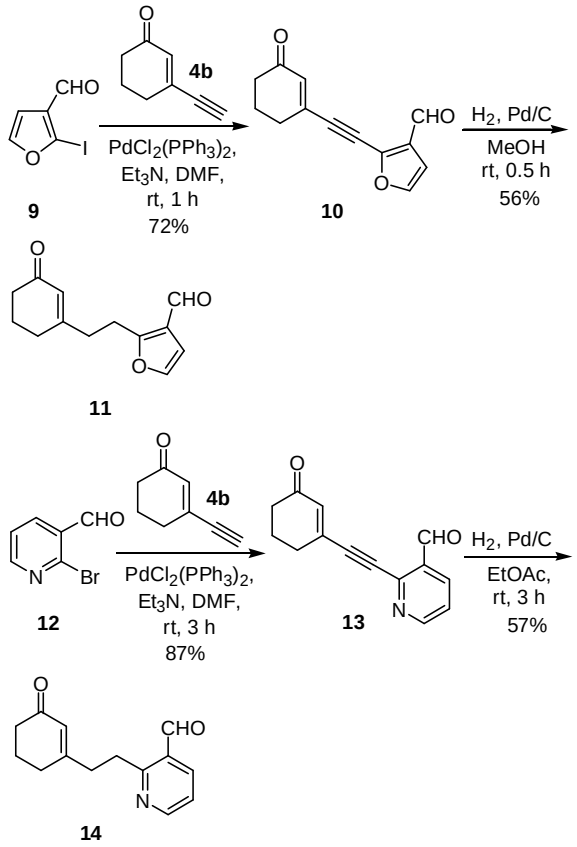
6 **7** **8**

a: $R^1 = R^2 = R^3 = R^4 = H$
b: $R^1 = OMe$, $R^2 = R^3 = R^4 = H$
c: $R^1 = H$, $R^2 = OMe$, $R^3 = R^4 = H$
d: $R^1 = R^2 = H$, $R^3 = OMe$, $R^4 = H$
e: $R^1 = R^2 = R^3 = H$, $R^4 = OMe$,
f: $R^1 = R^2 = H$, $R^3 = OMe$, $R^4 = H$
g: $R^1 = R^2 = H$, $R^3 = CO_2Me$, $R^4 = H$

Entry	Triflate	Enynone	Sonogashira temp / time	Product **7** (yield)	Hydrogenation solvent / time	Product **8** (yield)
1	**6a**	**4a**: m = 0	120 °C / 10 min	**7aa** (65%)	*i*-PrOH : EtOAc (1:1) / 1 h	**8aa** (74%)
2	**6e**	**4a**: m = 0	120 °C / 60 min	**7ea** (50%)	*i*-PrOH : EtOAc (1:1) / 1 h	**8ea** (70%)
3	**6a**	**4b**: m = 1	120 °C / 15 min	**7ab** (92%)	EtOAc / 1 h	**8ab** (91%)
4	**6b**	**4b**: m = 1	120 °C / 20 min	**7bb** (77%)	*i*-PrOH : EtOAc (1:1) / 1 h	**8bb** (83%)
5	**6c**	**4b**: m = 1	120 °C / 20 min	**7cb** (78%)	MeOH : THF (1:1) / 1 h	**8cb** (90%)
6	**6d**	**4b**: m = 1	120 °C / 40 min	**7db** (81%)	MeOH : THF (1:1) / 2.5 h	**8db** (64%)
7	**6e**	**4b**: m = 1	120 °C / 15 min	**7eb** (81%)	EtOAc / 2.5 h	**8eb** (62%)
8	**6f**	**4b**: m = 1	120 °C / 40 min	**7fb** (72%)	MeOH : THF (1:1) / 0.5 h	**8fb** (82%)
9	**6g**	**4b**: m = 1	rt / 30 min	**7gb** (76%)	MeOH : THF (1:1) / 1.5 h	**8gb** (86%)
10	**6a**	**4c**: m = 2	120 °C / 30 min	**7ac** (77%)	*i*-PrOH : EtOAc (1:1) / 1 h	**8ac** (64%)

In order to expand the substrate scope of the intramolecular Stetter reaction, heteroaromatic aldehydes **11** and **14** were also prepared from the corresponding aryl iodide **9**[20] and bromide **12**,[21] respectively, in good overall yields by using the same procedure, i.e., Sonogashira cross-coupling and selective hydrogenation (Scheme 4).

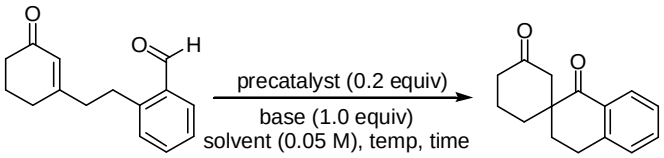
Scheme 4. Preparation of heteroaromatic spiro precursors **11** and **14**



(c) Intramolecular Stetter Reaction. With these spiro precursors in hand, we first used **8ab** to optimize the reaction conditions. Compound **8ab** was first treated with thiazolium salt **A** (0.2 equiv)[22] and triethylamine (1.0 equiv) in ethanol (0.05 M) at room temperature. However, the reaction did not proceed at this temperature even after 168 h, and the starting material was recovered (Table 2, entry 1). Upon increasing the reaction temperature to 80 ^{o}C, the intramolecular Stetter reaction proceeded smoothly to give the desired product **15ab** in 47% yield, along with the starting material, after 24 h (entry 2). In refluxing ethanol, the reaction proceeded to completion within 24 h to afford **15ab** in 85% yield (entry 3). Decreasing the amount of thiazolium salt **A** from 0.2 equiv to 0.1 equiv under the same conditions led to the formation of spiro compound **15ab** in 49% yield over a longer reaction time (entry 4). Increasing the amount of triethylamine from 1.0 equiv to 2.0 equiv decreased the product yield (entry 5). Dilution of the reaction medium (0.01 M) also caused a decrease in the yield (entry 6). When other alcoholic solvents such as *i*-PrOH and *t*-BuOH were employed, the reaction took a longer time to complete and lower yields of the product were observed (entries 7–8). Moreover, the reaction did not proceed in aprotic solvents (PhMe and THF) under the same conditions (entries 9–10). This was

presumably due to the intermolecular hydrogen bonding between the carbonyl group of the enone and the alcohol, which may increase the electrophilicity of the enone (Figure 2).[23] In the absence of hydrogen bonding, the enone moiety would not be sufficiently electrophilic to induce cyclization for the formation of a six-membered ring under Stetter conditions. Next, we used another thiazolium salt **B** and triazolium salt **C**, but the yields did not improve and a longer time was required for completion of the reaction (entries 11–12). We also attempted to use a chiral tetracyclic triazolium salt **D** for the asymmetry Stetter reaction. Unfortunately, when the reaction was carried out under the same conditions, a complicated mixture of the products was observed (entry 13). The Stetter reaction did not proceed in this case, probably due to the bulky Breslow intermediate, which does not readily undergo 1,4-addition to the β-disubstituted enone. Changing the base from triethylamine to 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) also gave a complicated mixture of products (entry 14), whereas the use of diisopropylethylamine and Cs_2CO_3 resulted in decreased yields (entries 15–16). Therefore, the best yield for this reaction was obtained with 0.2 equiv of thiazolium salt **A** and 1.0 equiv of triethylamine in refluxing ethanol for 24 h.

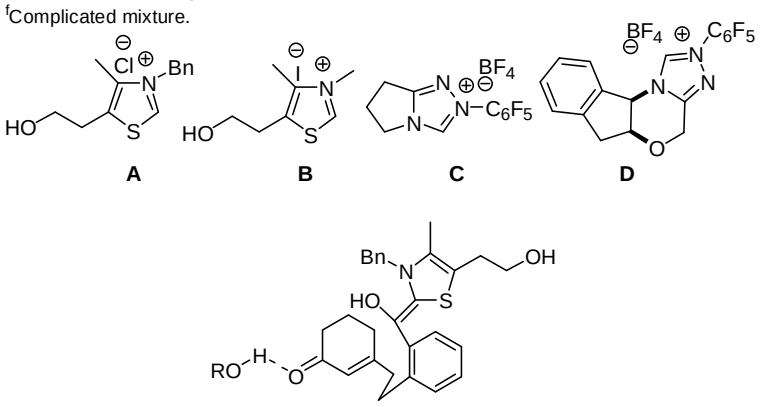
Table 2. Conditions for attempted intramolecular Stetter reaction



8ab **15ab**

entry	precatalyst	base	solvent	temp	time	yield
1	**A**	Et_3N	EtOH	rt	168 h	–[a]
2	**A**	Et_3N	EtOH	80 °C	24 h	47%[b]
3	**A**	Et_3N	EtOH	reflux	24 h	85%
4	**A**[c]	Et_3N	EtOH	reflux	48 h	49%
5	**A**	Et_3N[d]	EtOH	reflux	24 h	55%
6	**A**	Et_3N	EtOH[e]	reflux	36 h	60%
7	**A**	Et_3N	*i*-PrOH	reflux	48 h	53%
8	**A**	Et_3N	*t*-BuOH	reflux	168 h	24%[b]
9	**A**	Et_3N	PhMe	80 °C	24 h	–[a]
10	**A**	Et_3N	THF	reflux	48 h	–[a]
11	**B**	Et_3N	EtOH	reflux	72 h	60%
12	**C**	Et_3N	EtOH	reflux	36 h	81%
13	**D**	Et_3N	EtOH	reflux	24 h	–[f]
14	**A**	DBU	EtOH	reflux	24 h	–[f]
15	**A**	DIPEA	EtOH	reflux	48 h	62%
16	**A**	Cs_2CO_3	EtOH	reflux	24 h	17%

[a]No reaction. [b]Reaction was not completed. [c]Used 0.1 equiv of precatalyst A.
[d]Used 2.0 equiv of Et_3N. [e]Reaction was carried In 0.01 M of EtOH.
[f]Complicated mixture.

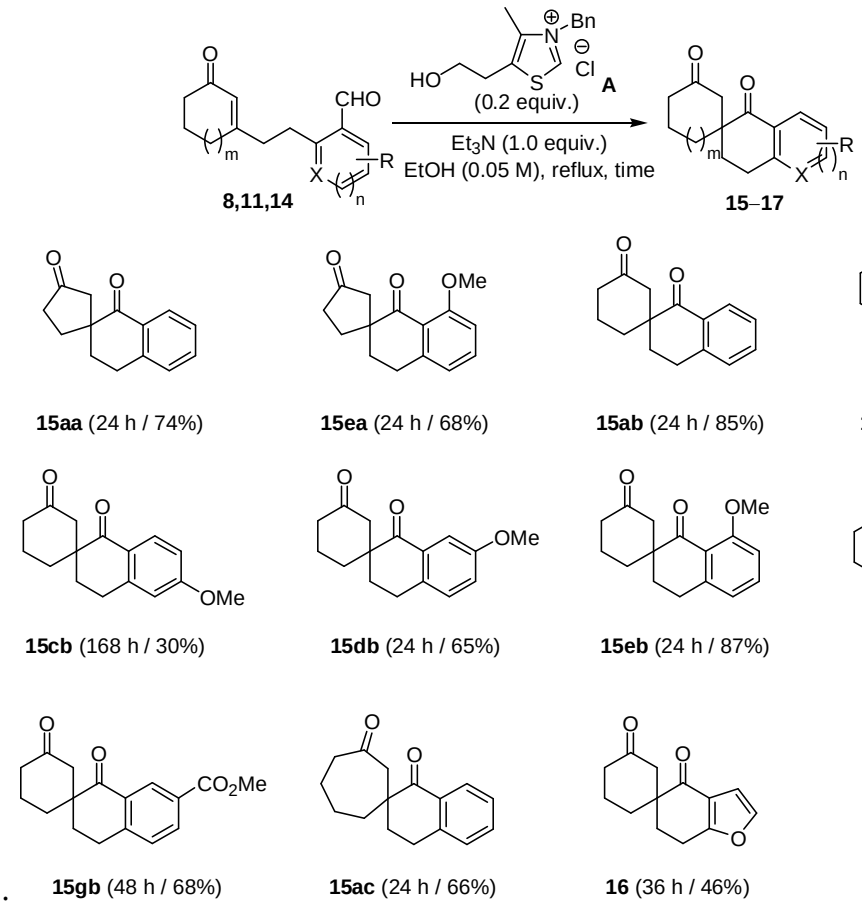


A **B** **C** **D**

Figure 2. Intermolecular hydrogen bonding assists Stetter reaction

With the optimized conditions in hand, we next used other enone-aldehydes in the reaction. Most of these reactions were completed within 48 h and the desired spirocyclic products were produced in moderate to good yields (Scheme 5). Reactions of benzaldehyde tethers with a five-, six-, and seven-membered ring of the enone proceeded smoothly (**15aa**–**15ac**). Both electron-donating and electron-withdrawing substituents at different positions on the phenyl ring were well tolerated under the optimized conditions (**15ea**, **15bb**–**15gb**). The reaction of substrate **8cb** bearing a methoxy group at the *para*-position of benzaldehyde was very sluggish (168 h) and a low yield (30%) of product **15cb** was obtained. This was presumably because the electron-donating group at the 4-position of the benzene ring decreased the reactivity of benzaldehyde toward the NHC. Heterocyclic moieties such as furaldehyde and nicotinaldehyde were compatible with these reaction conditions and gave the corresponding cyclized products, albeit in slightly low yields (**16**, **17**).

Scheme 5. Intramolecular Stetter reaction



The structures of **15**–**17** were characterized by IR spectroscopy, ^{1}H and ^{13}C NMR, and low- and high-resolution mass spectrometry. The ^{13}C NMR spectra of these compounds showed spiroatom absorptions at around 50 ppm in the ^{13}C NMR spectra. Note that spiro compound **15ea** has been used in the total synthesis of the proposed structure of nidemone (Figure 3).[24a]

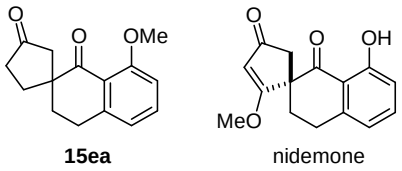


Figure 3. Application of **15ea** to the total synthesis of nidemone

Conclusion

In summary, we have developed an efficient and general method for the preparation of spiro-fused tricyclic 1,4-diketones. A variety of aromatic aldehydes underwent the intramolecular Stetter reaction under NHC-catalyzed conditions. Intramolecular Stetter reactions for constructing a six-

membered ring are known.[9f] However, to the best of our knowledge; this is the first example of the use of the intramolecular Stetter reaction to construct a six-membered ring in spirocyclic structures. Our methodology was also successfully applied to the total synthesis of nidemone.[24] Efforts to develop an asymmetric version of this reaction using chiral catalysts 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. Melting points are uncorrected. IR spectra were recorded as films on KBr plates. ^{1}H NMR spectra were obtained in $CDCl_3$ at 400 MHz. ^{13}C NMR spectra were obtained at 100 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 Propargylic alcohols 2. To a stirred solution of trimethylsilylacetylene (8.5 mL, 60.0 mmol) in THF (70 mL) under Ar atmosphere at 0 ^{o}C was added *n*-BuLi (2.5 M in hexanes, 24.0 mL, 60.0 mmol). The mixture was stirred at room temperature for 0.5 h and then cooled to 0 ^{o}C. Cyclic enone **1** (50.0 mmol) was added to the reaction mixture and stirred at room temperature for 3 h. The mixture was quenched with saturated aqueous NaCl solution and extracted with Et_2O. The combined extracts were washed with brine, dried over $MgSO_4$, filtered and concentrated. The residue was used in the next step without further purification. Analytically pure **2** was purified by silica-gel chromatography.

1-(Trimethylsilylethynyl)-2-cyclopenten-1-ol (2a). Chromatography (EtOAc/hexanes = 1:5); colorless oil; 8.02 g; yield 89%; IR (neat) ν 3403, 3058, 2960, 2163, 1733, 1250, 1047, 860, 843 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 6.01–5.98 (m, 1H), 5.82–5.79 (m, 1H) , 2.58–2.49 (m, 1H), 2.46–2.38 (m, 2H), 2.18–2.12 (m, 1H), 2.05 (brs, 1H), 0.17 (s, 9H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 135.3, 134.7, 108.0, 88.6, 78.1, 41.0, 31.0, –0.1; MS (EI) *m/z* (% base peak) 180 (M^+, 2), 165 (100), 163 (19), 147 (17), 145 (12), 105 (13), 99 (40), 75 (37), 73(25); HRMS (EI-TOF) *m/z*: $[M]^+$ Calcd for $C_{10}H_{16}OSi$ 180.0970; Found 180.0973.

1-(Trimethylsilylethynyl)-2-cyclohexen-1-ol (2b).[14] Chromatography (EtOAc/hexanes = 1:5); white solid; 8.94 g; yield 92%; mp 39–40 ^oC; IR (neat) ν 3358, 3031, 2954, 2158, 1250, 843 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 5.84–5.80 (m, 1H), 5.75–5.71 (m, 1H), 2.08–1.98 (m, 4H), 1.92–1.86 (m, 1H), 1.79–1.71 (m, 2H), 0.16 (s, 9H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 130.3, 129.9, 109.2, 87.7, 65.4, 37.8, 24.6, 19.0, –0.1; MS (EI) *m/z* (% base peak) 194 (M^+, 3), 177 (100), 166 (36), 151 (35), 135 (8), 133 (8), 105 (7), 97 (21), 75 (42), 73 (34); HRMS (EI-TOF) *m/z*: $[M]^+$ Calcd for $C_{11}H_{18}OSi$ 194.1127; Found 194.1124.

1-(Trimethylsilylethynyl)-2-cyclohepten-1-ol (2c). Chromatography (EtOAc/hexanes = 1:10); white solid; 9.69 g; yield 93%; mp 54–55 ^oC; IR (neat) ν 3380, 3026, 2930, 2856, 2163, 1446, 1250, 1025, 843, 759 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 5.80–5.70 (m, 2H), 2.27–2.12 (m, 2H), 2.06 (brs, 1H), 1.97–1.82 (m, 4H), 1.79–1.70 (m, 1H), 1.49–1.40 (m, 1H), 0.17 (s, 9H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 137.4, 131.4, 107.5, 89.0, 71.4, 41.0, 27.4, 26.7, 25.6, –0.1; MS (EI) *m/z* (% base peak) 208 (M^+, 5), 191 (100), 175 (3), 163 (3), 147 (2), 135 (5), 117 (10), 111 (7), 97 (7), 73 (29); HRMS (EI-TOF) *m/z*: $[M]^+$ Calcd for $C_{12}H_{20}OSi$ 208.1283; Found 208.1280.

General Procedure for Preparation of Trimethylsilylenynones 3. A mixture of PDC (43.3 g, 115.0 mmol) and Celite (43.3 g) was added **2** (50.0 mmol) and CH_2Cl_2 (250 mL, 0.2 M) at room temperature. The mixture was stirred at room temperature for 36 h. The mixture was then filtered through a pad of Celite and washed with Et_2O. The solvent was evaporated to give a crude product which was used in the next step without further purification. Analytically pure **3** was purified by silica-gel chromatography.

3-(Trimethylsilylethynyl)-2-cyclopenten-1-one (3a).[24b] Chromatography (EtOAc/hexanes = 1:10); yellowish oil; 8.20 g; yield 92%; IR (neat) ν 2961, 2150, 1709, 1582, 1267, 1171, 848 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 6.28 (t, *J* = 1.9 Hz, 1H), 2.75–2.71 (m, 2H), 2.44–2.40 (m, 2H), 0.24 (s, 9H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 208.6, 156.1, 136.3, 111.0, 99.4, 34.2, 32.0, –0.9; MS (EI) *m/z* (% base peak) 178 (M^+, 22), 163 (100), 133 (1), 119 (1), 107 (8), 97 (2), 83 (4), 77 (3), 75 (3); HRMS (EI-TOF) *m/z*: $[M]^+$ Calcd for $C_{10}H_{14}OSi$ 178.0814; Found 178.0815.

3-(Trimethylsilylethynyl)-2-cyclohexen-1-one (3b).[25] Chromatography (EtOAc/hexanes = 1:10); yellowish oil; 8.94 g; yield 93%; IR (neat) ν 2956, 2147, 1677, 1585, 1249, 845 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 6.21 (t, *J* = 1.4 Hz, 1H), 2.46–2.37 (m, 4H) , 2.05–1.98 (m, 2H), 0.21 (s, 9H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 198.6, 142.9, 133.0, 105.9, 103.4, 37.2, 30.2, 22.5, –0.5; MS (EI) *m/z* (% base peak) 192(M^+, 56), 177 (100), 164 (37), 149 (52), 121 (11), 107 (8), 97 (12), 73 (14); HRMS (EI-TOF) *m/z*: $[M]^+$ Calcd for $C_{11}H_{16}OSi$ 192.0970; Found 192.0973.

3-(Trimethylsilylethynyl)-2-cyclohepten-1-one (3c). Chromatography (EtOAc/hexanes = 1:10); yellow oil; 9.29 g; yield 90%; IR (neat) ν 2956, 2138, 1664, 1590, 1252, 845 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 6.31 (s, 1H), 2.62–2.57 (m, 4H) , 1.87–1.78 (m, 4H), 0.21 (s, 9H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 203.1, 139.8, 137.1, 106.3, 102.2, 42.5, 34.0, 25.2, 21.1, –0.3; MS (EI) *m/z* (% base peak) 206 (M^+, 20), 191 (100), 178 (22), 163 (42), 149 (9), 135 (7), 107 (7), 97 (8), 75 (11), 73 (16); HRMS (EI-TOF) *m/z*: $[M]^+$ Calcd for $C_{12}H_{18}OSi$ 206.1127; Found 206.1128.

General Procedure for Preparation of Enynones 4. A mixture of **3** (50.0 mmol) and benzyltriethylammonium chloride (BTEAC, 1.14 g, 5.00 mmol) in THF (100 mL, 0.5 M) at room temperature was added 2 M KF (32.5 mL, 65.0 mmol). The reaction mixture was stirred at room temperature for 1 h 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 to afford **4**.

3-Ethynyl-2-cyclopenten-1-one (4a). Chromatography (Et_2O/hexanes = 1:5); white solid; 4.56 g; yield 86%; mp 55–56 ^oC;[24b] IR (neat) ν 3194, 2926, 2854, 2095, 1701, 1664, 1578, 1435, 1285, 1177, 872,

729 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 6.32 (t, *J* = 1.7 Hz, 1H), 3.85 (s, 1H) , 2.75–2.71 (m, 2H), 2.42–2.39 (m, 2H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 209.1, 155.7, 137.7, 92.2, 78.9, 34.6, 32.2; MS (EI) *m/z* (% base peak) 106 (M^+, 100), 105 (12), 78 (47), 77 (20), 52 (15), 51 (13); HRMS (EI-TOF) *m/z*: $[M]^+$ Calcd for C_7H_6O 106.0419; Found 106.0420.

3-Ethynyl-2-cyclohexen-1-one (4b).[16] Chromatography (Et_2O/hexanes = 1:5); yellow oil; 5.53 g; yield 92%; IR (neat) ν 3295, 2913, 2089, 1694, 1610, 855, 726 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 6.21 (s, 1H), 3.53 (s, 1H) , 2.44–2.36 (m, 4H), 2.03–1.97 (m, 2H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 198.5, 142.2, 134.0, 87.1, 82.4, 37.3, 30.1, 22.4; MS (EI) *m/z* (% base peak) 120 (M^+, 63), 92 (100), 91 (33), 64 (35), 63 (20), 58 (12), 51 (4); HRMS (EI-TOF) *m/z*: $[M]^+$ Calcd for C_8H_8O 120.0575; Found 120.0578.

3-Ethynyl-2-cyclohepten-1-one (4c). Chromatography (Et_2O/hexanes = 1:5); yellow oil; 5.64 g; yield 84%; IR (neat) ν 3250, 2940, 2086, 1658, 1593, 1259, 884 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 6.34 (s, 1H), 3.35 (s, 1H) , 2.62–2.58 (m, 4H), 1.89–1.72 (m, 4H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 202.9, 138.7, 137.9, 85.1, 83.7, 42.6, 34.0, 25.3, 21.1; MS (EI) *m/z* (% base peak) 134 (M^+, 19), 125 (31), 105 (42), 91 (71), 75 (100), 73 (44), 63 (19), 51 (14); HRMS (EI-TOF) *m/z*: $[M]^+$ Calcd for $C_9H_{10}O$ 134.0732; Found 134.0731.

General Procedure for Preparation of Trifluoromethanesulfonate 6. A mixture of **5** (5.00 mmol), *N*-phenylbis(trifluoromethanesulfonimide) (1.97 g, 5.50 mmol), and 4-dimethylaminopyridine (DMAP) (61 mg, 0.50 mmol) in CH_2Cl_2 (10 mL, 0.5 M) was added triethylamine (1.4 mL, 10.0 mmol) at 0 ^oC. The reaction mixture was stirred at room temperature for 0.5 h. Then the solvent was removed in vacuo gave a residue, which was purified by silica-gel column chromatography on silica gel to afford **6**.

2-Formylphenyl trifluoromethanesulfonate (6a).[17a] Chromatography (EtOAc/hexanes = 1:10); colorless oil; 1.16 g; yield 91%; IR (neat) ν 1699, 1607, 1490, 1423, 1204, 1136, 1076, 899, 772 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 10.27 (s, 1H), 8.01 (dd, *J* = 7.6, 2.0 Hz, 1H) , 7.73 (ddd, *J* = 8.2, 7.6, 2.0 Hz, 1H), 7.56 (dd, *J* = 7.6, 7.6 Hz, 1H), 7.41 (d, *J* = 8.2 Hz, 1H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 186.5, 149.8, 135.9, 130.9, 128.9, 128.5, 122.4, 118.6 (q, *J* = 319 Hz); MS (EI) *m/z* (% base peak) 254

(M^+, 11), 253 (10), 189 (59), 185 (11), 162 (11), 120 (100), 104 (17), 92 (44), 81 (15), 69 (55), 65 (54); HRMS (EI-TOF) *m/z*: $[M]^+$ Calcd for $C_8H_5F_3O_4S$ 253.9861; Found 253.9859.

2-Formyl-6-methoxyphenyl trifluoromethanesulfonate (6b).[17b] Chromatography (EtOAc/hexanes = 1:3); white solid; 1.39 g; yield 98%; mp 36–37 ^oC; IR (neat) ν 1707, 1580, 1480, 1423, 1289, 1208, 1137, 882, 785, 758 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 10.25 (s, 1H), 7.53 (dd, *J* = 8.0, 1.6 Hz, 1H), 7.47 (dd, *J* = 8.0, 8.0 Hz, 1H), 7.31 (dd, *J* = 8.0, 1.6 Hz, 1H), 3.97 (s, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 186.7, 151.6, 139.1, 129.5, 129.1, 121.2, 118.6, 118.6 (q, *J* = 319 Hz), 56.5; MS (EI) *m/z* (% base peak) 284 (M^+, 37), 225 (22), 151 (100), 136 (14), 108 (29), 92 (44), 65 (29); HRMS (EI-TOF) *m/z*: $[M]^+$ Calcd for $C_9H_7F_3O_5S$ 283.9966; Found 283.9969.

2-Formyl-5-methoxyphenyl trifluoromethanesulfonate (6c).[17c] Chromatography (EtOAc/hexanes = 1:3); colorless oil; 1.41 g; yield 99%; IR (neat) ν 1699, 1612, 1505, 1428, 1249, 1212, 1139, 1075, 955, 831 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 10.13 (s, 1H), 7.95 (d, *J* = 8.7 Hz, 1H) , 7.03 (dd, *J* = 8.7, 2.4 Hz, 1H), 6.87 (d, *J* = 2.4 Hz, 1H), 3.93 (s, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 185.4, 165.3, 151.3, 132.2, 121.8, 118.6 (q, *J* = 319 Hz), 114.2, 108.2, 56.2; MS (EI) *m/z* (% base peak) 284 (M^+, 100), 283 (20), 219 (25), 151 (80), 150 (45), 134 (17), 108 (21), 95 (32), 69 (31); HRMS (EI-TOF) *m/z*: $[M]^+$ Calcd for $C_9H_7F_3O_5S$ 283.9966; Found 283.9965.

2-Formyl-4-methoxyphenyl trifluoromethanesulfonate (6d).[17a] Chromatography (EtOAc/hexanes = 1:3); colorless oil; 1.41 g; yield 99%; IR (neat) ν 1701, 1589, 1490, 1426, 1212, 1140, 1031, 870 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 10.23 (s, 1H), 7.43 (d, *J* = 3.4 Hz, 1H) , 7.32 (d, *J* = 9.2 Hz, 1H), 7.20 (dd, *J* = 9.2, 3.4 Hz, 1H), 3.88 (s, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 186.3, 159.3, 143.6, 129.3, 123.7, 122.2, 118.6 (q, *J* = 319 Hz), 113.0, 56.0; MS (EI) *m/z* (% base peak) 284 (M^+, 35), 225 (7), 151 (100), 123 (23), 108 (19), 95 (25), 92 (16), 69 (18); HRMS (EI-TOF) *m/z*: $[M]^+$ Calcd for $C_9H_7F_3O_5S$ 283.9966; Found 283.9965.

2-Formyl-3-methoxyphenyl trifluoromethanesulfonate (6e).[17d] Chromatography (EtOAc/hexanes = 1:3); white solid; 1.39 g; yield 98%; mp 70–71 ^oC; IR (neat) ν 3105, 2925, 2782, 1692, 1610, 1476, 1426, 1276, 1202, 1139, 1064, 955, 833 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 10.46 (s, 1H), 7.59 (dd, *J*

= 8.4, 8.0 Hz, 1H) , 7.06 (d, *J* = 8.4 Hz, 1H), 6.90 (d, *J* = 8.0 Hz, 1H), 3.98 (s, 3H); $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$): δ 187.0, 162.9, 148.0, 135.7, 118.6 (q, *J* = 319 Hz), 117.9, 114.5, 111.9, 56.6; MS (EI) *m/z* (% base peak) 284 (M^+, 60), 151 (100), 123 (22), 108 (25), 95 (27), 69 (28), 65 (17), 63 (8), 52 (8); HRMS (EI-TOF) *m/z*: $[M]^+$ Calcd for $C_9H_7F_3O_5S$ 283.9966; Found 283.9965.

2-Formyl-4-methylphenyl trifluoromethanesulfonate (6f).[17e] Chromatography (EtOAc/hexanes = 1:10); white solid; 1.30 g; yield 97%; mp 139–140 ^{o}C; IR (neat) ν 2868, 2764, 1705, 1606, 1488, 1428, 1214, 1140, 872, 615 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.23 (s, 1H), 7.78 (d, *J* = 2.1 Hz, 1H) , 7.50 (dd, *J* = 8.4, 2.1 Hz, 1H), 7.28 (d, *J* = 8.4 Hz, 1H), 2.45 (s, 3H); $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$): δ 186.7, 147.9, 139.4, 136.4, 131.0, 128.1, 122.2, 118.6 (q, *J* = 319 Hz), 20.8; MS (EI) *m/z* (% base peak) 268 (M^+, 67), 203 (41), 175 (16), 151 (18), 135 (100), 134 (48), 107 (52), 91 (15), 77 (99), 69 (62); HRMS (EI-TOF) *m/z*: $[M]^+$ Calcd for $C_9H_7F_3O_4S$ 268.0017; Found 268.0020.

Methyl 3-formyl-4-trifluoromethylsulfonyloxybenzoate (6g).[17f] Chromatography (EtOAc/hexanes = 1:10); yellowish oil; 1.36 g; yield 87%; IR (neat) ν 3111, 2960, 1732, 1606, 1432, 1300, 1245, 1217, 1137, 1112, 919, 867, 609 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.29 (s, 1H), 8.65 (d, *J* = 2.2 Hz, 1H) , 8.37 (dd, *J* = 8.6, 2.2 Hz, 1H), 7.51 (d, *J* = 8.6 Hz, 1H), 3.98 (s, 3H); $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$): δ 185.7, 164.4, 152.1, 136.6, 132.4, 131.0, 128.4, 122.7, 118.5 (q, *J* = 319 Hz), 52.8; MS (EI) *m/z* (% base peak) 312 (M^+, 15), 281 (44), 217 (85), 189 (40), 178 (100), 162 (31), 136 (28), 120 (31), 119 (25), 92 (98), 69 (63), 58 (80); HRMS (EI-TOF) *m/z*: $[M]^+$ Calcd for $C_{10}H_7F_3O_6S$ 311.9915; Found 311.9917.

General Procedure for Sonogashira Cross-coupling. To a stirred solution of **6, 9, 12** (2.00 mmol), bis(triphenylphosphine)palladium(II) dichloride ($Pd(PPh_3)_2Cl_2$) (70 mg, 0.10 mmol), CuI (38 mg, 0.20 mmol), and **4** (4.00 mmol) in DMF (13 mL, 0.15 M) was added triethylamine (1.25 mL, 9.00 mmol) under Ar atmosphere at room temperature. The reaction mixture was then stirred at room temperature or heated in an oil bath to 120 ^{o}C for a period of time (see Table **1** and Scheme **4** for the duration of heating and temperature). 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 to afford **7, 10, 13**.

2-[(3-Oxocyclopent-1-en-1-yl)ethynyl]benzaldehyde (7aa). Chromatography (EtOAc/hexanes = 1:3); yellowish solid; 273 mg; yield 65%; mp 72–73 ^{o}C; IR (neat) ν 3073, 2924, 2852, 2198, 1704, 1674, 1580, 1175, 758 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.50 (s, 1H), 7.98 (d, *J* = 7.6 Hz, 1H) , 7.66–7.62 (m, 2H), 7.58–7.53 (m, 1H), 6.44 (t, *J* = 2.2 Hz, 1H), 2.91–2.87 (m, 2H), 2.54–2.50 (m, 2H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 208.9, 190.7, 155.5, 137.1, 136.0, 133.9, 133.6, 130.2, 128.0, 124.6, 99.4, 90.8, 34.8, 32.4; MS (EI) *m/z* (% base peak) 210 (M^+, 30), 182 (100), 181 (84), 153 (86), 152 (40), 126 (41), 101 (10), 76 (17), 58 (16); HRMS (EI-TOF) *m/z*: $[M]^+$ Calcd for $C_{14}H_{10}O_2$ 210.0681; Found 210.0680.

2-Methoxy-6-[(3-oxocyclopent-1-en-1-yl)ethynyl]benzaldehyde (7ea).[24a] Chromatography (EtOAc/hexanes = 1:2); orange-red solid; 240 mg; yield 50%; mp 127–128 ^{o}C; IR (neat) ν 2932, 2839, 1708, 1586, 1488, 1270, 1177, 753 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.58 (s, 1H), 7.52 (dd, *J* = 8.4, 7.6 Hz, 1H), 7.20 (d, *J* = 7.6 Hz, 1H), 7.06 (d, *J* = 8.4 Hz, 1H), 6.40 (t, *J* = 1.6 Hz, 1H), 3.95 (s, 3H), 2.90–2.87 (m, 2H), 2.50–2.47 (m, 2H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 209.4, 189.2, 161.5, 156.5, 136.6, 134.5, 126.4, 125.0, 123.3, 113.1, 102.2, 89.4, 56.1, 34.8, 32.4; MS (EI) *m/z* (% base peak) 240 (M^+, 16), 230 (8), 202 (10), 189 (11), 161 (12), 148 (100), 115 (7), 105 (8), 91 (22); HRMS (EI-TOF) *m/z*: $[M]^+$ Calcd for $C_{15}H_{12}O_3$ 240.0786; Found 240.0784.

2-[(3-Oxocyclohex-1-en-1-yl)ethynyl]benzaldehyde (7ab). Chromatography (EtOAc/hexanes = 1:5); yellow solid; 413 mg; yield 92%; mp 59–60 ^{o}C; IR (neat) ν 3065, 2948, 2743, 2202, 1697, 1671, 1590, 1190, 765 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.41 (s, 1H), 7.87 (d, *J* = 7.8 Hz, 1H) , 7.56–7.52 (m, 2H), 7.48–7.43 (m, 1H), 6.27 (t, *J* = 1.6 Hz, 1H), 2.53 (dt, *J* = 6.1, 1.6 Hz, 2H), 2.41 (t, *J* = 6.8 Hz, 2H), 2.07–2.01 (m, 2H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 198.4, 190.9, 142.1, 136.0, 133.9, 133.5, 133.3, 129.8, 127.8, 125.0, 94.6, 94.5, 37.3, 30.2, 22.6; MS (EI) *m/z* (% base peak) 224 (M^+, 67), 206 (11), 196 (28), 181 (21), 168 (100), 167 (31), 139 (71), 126 (9), 89 (5); HRMS (EI-TOF) *m/z*: $[M]^+$ Calcd for $C_{15}H_{12}O_2$ 224.0837; Found 224.0834.

3-Methoxy-2-[(3-oxocyclohex-1-en-1-yl)ethynyl]benzaldehyde (7bb). Chromatography (EtOAc/hexanes = 1:3); yellow solid; 392 mg; yield 77%; mp 114–115 ^{o}C; IR (neat) ν 2943, 2841, 2195,

1663, 1585, 1474, 1273, 1242, 1187, 756 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 10.48 (s, 1H), 7.55 (d, *J* = 7.9 Hz, 1H), 7.47 (dd, *J* = 7.9, 7.9 Hz, 1H), 7.15 (d, *J* = 7.0 Hz, 1H), 6.37 (t, *J* = 1.6 Hz, 1H), 3.95 (s, 3H), 2.61 (dt, *J* = 6.3, 1.6 Hz, 2H), 2.47 (t, *J* = 6.7 Hz, 2H), 2.14–2.07 (m, 2H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 198.5, 191.1, 160.8, 142.6, 137.1, 132.9, 130.7, 119.5, 115.7, 114.4, 98.9, 91.1, 56.3, 37.3, 30.3, 22.6; MS (EI) *m/z* (% base peak) 254 (M^+, 19), 253 (12), 212 (9), 198 (13), 183 (13), 155 (8), 111 (13), 97 (18), 83 (16), 71 (19), 58 (100); HRMS (EI-TOF) *m/z*: $[M]^+$ Calcd for $C_{16}H_{14}O_3$ 254.0943; Found 254.0946.

4-Methoxy-2-[(3-oxocyclohex-1-en-1-yl)ethynyl]benzaldehyde (7cb). Chromatography (EtOAc/hexanes = 1:3); yellow solid; 397 mg; yield 78%; mp 96–97 °C; IR (neat) ν 2946, 2838, 2753, 1684, 1592, 1297, 1225, 1025 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 10.25 (s, 1H), 7.83 (dd, *J* = 8.6, 2.8 Hz, 1H), 6.98–6.92 (m, 2H), 6.26 (t, *J* = 1.6 Hz, 1H), 3.84 (s, 3H), 2.52 (t, *J* = 5.9 Hz, 2H), 2.40 (dt, *J* = 7.5, 1.6 Hz, 2H), 2.09–2.02 (m, 2H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 198.1, 189.3, 163.6, 142.0, 133.1, 129.8, 129.5, 126.8, 117.3, 116.3, 94.4, 94.0, 55.6, 37.1, 30.0, 22.4; MS (EI) *m/z* (% base peak) 254 (M^+, 10), 222 (6), 198 (6), 155 (3), 85 (65), 83 (100), 58 (83); HRMS (EI-TOF) *m/z*: $[M]^+$ Calcd for $C_{16}H_{14}O_3$ 254.0943; Found 254.0943.

5-Methoxy-2-[(3-oxocyclohex-1-en-1-yl)ethynyl]benzaldehyde (7db). Chromatography (EtOAc/hexanes = 1:3); yellow solid; 412 mg; yield 81%; mp 91–92 °C; IR (neat) ν 2943, 2736, 1704, 1667, 1609, 1500, 1260, 1037 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 10.41 (s, 1H), 7.50 (d, *J* = 8.7 Hz, 1H), 7.39 (d, *J* = 2.6 Hz, 1H), 7.12 (dd, *J* = 8.7, 2.6 Hz, 1H), 6.28 (brs, 1H), 3.86 (s, 3H), 2.55 (dt, *J* = 6.0, 1.5 Hz, 2H), 2.44 (t, *J* = 6.7 Hz, 2H), 2.11–2.04 (m, 2H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 198.4, 190.7, 160.7, 142.5, 137.5, 135.0, 132.6, 121.5, 117.6, 110.5, 95.0, 93.5, 55.7, 37.3, 30.3, 22.6; MS (EI) *m/z* (% base peak) 254 (M^+, 34), 226 (12), 211 (8), 198 (21), 183 (18), 155 (16), 127 (12), 113 (4), 58 (100); HRMS (EI-TOF) *m/z*: $[M]^+$ Calcd for $C_{16}H_{14}O_3$ 254.0943; Found 254.0940.

2-Methoxy-6-[(3-oxocyclohex-1-en-1-yl)ethynyl]benzaldehyde (7eb). Chromatography (EtOAc/hexanes = 1:2); orange-yellow solid; 412 mg; yield 81%; mp 114–116 °C; IR (neat) ν 2945, 2874, 2195, 1688, 1664, 1572, 1470, 1295, 1258, 1188, 1136, 1062, 966, 793 cm^{-1}; ^1H NMR (400 MHz,

$CDCl_3$) δ 10.56 (s, 1H), 7.49 (dd, *J* = 8.4, 7.7 Hz, 1H), 7.16 (d, *J* = 7.7 Hz, 1H), 7.02 (d, *J* = 8.4 Hz, 1H), 6.32 (t, *J* = 1.4 Hz, 1H), 3.93 (s, 3H), 2.59 (dt, *J* = 6.1, 1.4 Hz, 2H), 2.44 (t, *J* = 6.7 Hz, 2H), 2.11–2.04 (m, 2H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 198.6, 189.2, 161.5, 143.0, 134.4, 132.9, 126.4, 125.1, 123.7, 112.8, 97.3, 93.1, 56.0, 37.4, 30.2, 22.6; MS (EI) *m/z* (% base peak) 254 (M^+, 100), 239 (16), 225 (18), 211 (23), 198 (47), 165 (15), 155 (21), 139 (21), 127 (10); HRMS (EI-TOF) *m/z*: $[M]^+$ Calcd for $C_{16}H_{14}O_3$ 254.0943; Found 254.0943.

5-Methyl-2-[(3-oxocyclohex-1-en-1-yl)ethynyl]benzaldehyde (7fb). Chromatography (EtOAc/hexanes = 1:5); yellow solid; 343 mg; yield 72%; mp 63–64 ^oC; IR (neat) ν 2946, 2842, 2195, 1692, 1670, 1585, 1493, 1277, 1226 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 10.41 (s, 1H), 7.72 (brs, 1H), 7.47 (d, *J* = 7.9 Hz, 1H), 7.39 (d, *J* = 7.9 Hz, 1H), 6.29 (t, *J* = 1.4 Hz, 1H), 2.55 (dt, *J* = 6.0, 1.4 Hz, 2H), 2.44 (t, *J* = 6.7 Hz, 2H), 2.41 (s, 3H), 2.10–2.04 (m, 2H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 198.5, 191.1, 142.2, 140.6, 135.8, 134.8, 133.5, 133.0, 128.2, 122.3, 95.0, 93.9, 37.3, 30.3, 22.6, 21.5; MS (EI) *m/z* (% base peak) 238 (M^+, 93), 223 (10), 210 (27), 195 (24), 182 (100), 153 (46), 139 (30), 115 (12), 84 (35), 85 (51); HRMS (EI-TOF) *m/z*: $[M]^+$ Calcd for $C_{16}H_{14}O_2$ 238.0994; Found 238.0995.

Methyl 3-formyl-4-[(3-oxocyclohex-1-en-1-yl)ethynyl]benzoate (7gb). Chromatography (EtOAc/hexanes = 1:3); yellow solid; 429 mg; yield 76%; mp 101–102 ^oC; IR (neat) ν 2953, 2855, 1726, 1695, 1674, 1602, 1435, 1300, 1235, 1178, 1119, 766 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 10.45 (s, 1H), 8.55 (d, *J* = 1.7 Hz, 1H), 8.22 (d, *J* = 8.1 Hz, 1H), 7.66 (d, *J* = 8.1 Hz, 1H), 6.35 (t, *J* = 1.2 Hz, 1H), 3.94 (s, 3H), 2.58 (dt, *J* = 6.1, 1.2 Hz, 2H), 2.46 (t, *J* = 6.8 Hz, 2H), 2.14–2.07 (m, 2H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 198.2, 189.9, 165.4, 141.5, 136.0, 134.2, 133.9, 133.7, 131.3, 129.2, 128.7, 96.8, 93.6, 52.7, 37.3, 30.1, 22.5; MS (EI) *m/z* (% base peak) 282 (M^+, 29), 225 (49), 195 (20), 167 (18), 139 (20), 92 (100), 65 (45), 57 (23); HRMS (EI-TOF) *m/z*: $[M]^+$ Calcd for $C_{17}H_{14}O_4$, 282.0892; Found 282.0892.

2-[(3-Oxocyclohept-1-en-1-yl)ethynyl]benzaldehyde (7ac). Chromatography (EtOAc/hexanes = 1:3); yellowish oil; 367 mg; yield 77%; IR (neat) ν 2924, 2852, 1699, 1592, 1464, 1260, 1190, 759 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 10.49 (s, 1H), 7.94 (d, *J* = 7.4 Hz, 1H) , 7.62–7.56 (m, 2H), 7.52–7.47 (m, 1H), 6.44 (brs, 1H), 2.74 (t, *J* = 5.9 Hz, 2H), 2.67 (t, *J* = 6.3 Hz, 2H), 1.97–1.83 (m, 4H); $^{13}C\{^1H\}$ NMR

(100 MHz, $CDCl_3$): δ 202.8, 191.0, 138.9, 137.3, 136.0, 133.8, 133.4, 129.5, 127.7, 125.5, 97.3, 91.4, 42.6, 34.0, 25.3, 21.1; MS (EI) *m/z* (% base peak) 238 (M^+, 100), 210 (48), 195 (37), 181 (99), 167 (40), 152 (57), 139 (47), 126 (29), 115 (28), 85 (28), 71 (28), 58 (57); HRMS (EI-TOF) *m/z*: $[M]^+$ Calcd for $C_{16}H_{14}O_2$ 238.0994; Found 238.0996.

2-[(3-Oxocyclohex-1-en-1-yl)ethynyl]-3-furaldehyde (10). Chromatography (EtOAc/hexanes = 1:3); orange-yellow solid; 308 mg; yield 72%; mp 58–59 ^oC; IR (neat) ν 3128, 2951, 2188, 1677, 1426, 1243, 1134, 755 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 9.98 (s, 1H), 7.45 (d, *J* = 2.0 Hz, 1H) , 6.78 (d, *J* = 2.0 Hz, 1H), 6.33 (brs, 1H), 2.54 (t, *J* = 6.1 Hz, 2H), 2.43 (t, *J* = 6.7 Hz, 2H), 2.11–2.04 (m, 2H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 197.9, 184.0, 145.8, 143.1, 140.3, 134.1, 130.8, 108.5, 97.0, 85.3, 37.3, 29.6, 22.5; MS (EI) *m/z* (% base peak) 214 (M^+, 100), 186 (43), 185 (36), 158 (52), 157 (21), 129 (22), 128 (11), 102 (29), 58 (90); HRMS (EI-TOF) *m/z*: $[M]^+$ Calcd for $C_{13}H_{10}O_3$ 214.0630; Found 214.0628.

2-[(3-Oxocyclohex-1-en-1-yl)ethynyl]nicotinaldehyde (13). Chromatography (EtOAc/hexanes = 1:10); yellow solid; 392 mg; yield 87%; mp 88–89 ^oC; IR (neat) ν 3056, 2948, 2868, 1791, 1698, 1673, 1578, 1428, 1243, 966 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 10.49 (s, 1H), 8.82 (dd, *J* = 4.8, 1.8 Hz, 1H), 8.21 (dd, *J* = 7.9, 1.8 Hz, 1H), 7.45 (dd, *J* = 7.9, 4.8 Hz, 1H), 6.41 (t, *J* = 1.6 Hz, 1H), 2.60 (dt, *J* = 6.0, 1.6 Hz, 2H), 2.47 (t, *J* = 6.7 Hz, 2H), 2.14–2.07 (m, 2H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 198.0, 189.8, 154.5, 144.6, 140.9, 135.1, 134.6, 132.2, 124.1, 93.4, 93.1, 37.3, 29.9, 22.5; MS (EI) *m/z* (% base peak) 225 (M^+, 69), 196 (37), 182 (18), 169 (100), 168 (46), 141 (36), 140 (24), 114 (15); HRMS (EI-TOF) *m/z*: $[M]^+$ Calcd for $C_{14}H_{11}NO_2$ 225.0790; Found 225.0789.

General Procedure for Regioselective Hydrogenation. To a mixture of **7, 10, 13** (100 mg) and 10% Pd/C (20 mg) in flask was added solvent (0.1 M) (see Table **1** and Scheme **4** 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** and Scheme **4** for the duration of hydrogenation). Filtration and concentration in vacuo gave a residue, which was purified by column chromatography on silica gel to afford **8, 11, 14**.

2-[(3-Oxocyclopent-1-en-1-yl)ethyl]benzaldehyde (8aa). Chromatography (EtOAc/hexanes = 1:2); colorless solid; 75 mg; yield 74%; mp 54–55 ^oC; IR (neat) ν 3075, 2961, 2926, 2743, 1698, 1603, 1191,

800, 756 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 10.17 (s, 1H), 7.82 (dd, *J* = 7.8, 1.0 Hz, 1H), 7.54 (ddd, *J* = 7.8, 7.5, 1.3 Hz, 1H), 7.46 (ddd, *J* = 7.5, 7.5, 1.0 Hz, 1H), 7.29 (d, *J* = 7.5 Hz, 1H), 6.00 (t, *J* = 1.2 Hz, 1H), 3.32 (t, *J* = 8.0 Hz, 2H), 2.70 (t, *J* = 8.0 Hz, 2H), 2.66–2.63 (m, 2H), 2.44–2.41 (m, 2H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 210.0, 193.1, 181.5, 142.9, 134.7, 133.9, 133.7, 131.0, 129.9, 127.2, 35.3, 35.0, 31.6, 30.9; MS (EI) *m/z* (% base peak) 214 (M^+, 5), 186 (100), 159 (14), 130 (19), 118 (21), 90 (16), 58 (15); HRMS (EI-TOF) *m/z*: $[M]^+$ Calcd for $C_{14}H_{14}O_2$ 214.0994; Found 214.0997.

2-Methoxy-6-(2-(3-oxocyclopent-1-en-1-yl)ethyl)benzaldehyde (8ea).[24a] Chromatography (EtOAc/hexanes = 1:2); white solid; 71 mg; yield 70%; mp 89–90 °C; IR (neat) ν 2926, 2851, 1706, 1682, 1596, 1473, 1269, 1181, 1075, 792 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 10.62 (s, 1H), 7.43 (dd, *J* = 8.4, 7.6 Hz, 1H), 6.88 (d, *J* = 8.4 Hz, 1H), 6.80 (d, *J* = 7.6 Hz, 1H), 5.97 (s, 1H), 3.91 (s, 3H), 3.19 (t, *J* = 8.0 Hz, 2H), 2.68–2.63 (m, 4H), 2.41–2.38 (m, 2H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 210.1, 192.1, 182.3, 163.6, 144.3, 134.9, 129.6, 123.2, 122.8, 109.9, 55.8, 35.3, 34.8, 31.8, 31.6; MS (EI) *m/z* (% base peak) 244 (M^+, 60), 216 (8), 187 (11), 163 (10), 148 (100), 109 (10), 96 (11), 83 (22), 58 (25); HRMS (EI-TOF) *m/z*: $[M]^+$ Calcd for $C_{15}H_{16}O_3$ 244.1099; Found 244.1100.

2-[(3-Oxocyclohex-1-en-1-yl)ethyl]benzaldehyde (8ab). Chromatography (EtOAc/hexanes = 1:5); yellowish solid; 93 mg; yield 91%; mp 38–39 °C; IR (neat) ν 3028, 2939, 2868, 2741, 1695, 1667, 1599, 1453, 1252, 1193, 887, 756 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 10.14 (s, 1H), 7.79 (d, *J* = 7.5 Hz, 1H) , 7.51 (dd, *J* = 7.8, 7.4 Hz, 1H), 7.41 (dd, *J* = 7.5, 7.4 Hz, 1H), 7.25 (d, *J* = 7.8 Hz, 1H), 5.87 (brs, 1H), 3.22 (t, *J* = 8.0 Hz, 2H), 2.47 (t, *J* = 8.0 Hz, 2H), 2.37–2.32 (m, 4H), 2.02–1.94 (m, 2H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 199.8, 192.9, 165.2, 143.1, 134.3, 133.8, 133.6, 131.1, 127.0, 126.0, 39.5, 37.2, 30.8, 29.6, 22.6; MS (EI) *m/z* (% base peak) 228 (M^+, 28), 210 (15), 185 (32), 172 (29), 159 (39), 157 (36), 129 (41), 118 (86), 115 (19), 91 (85), 90 (19), 58 (100); HRMS (EI-TOF) *m/z*: $[M]^+$ Calcd for $C_{15}H_{16}O_2$ 228.1150; Found 228.1151.

3-Methoxy-2-[(3-oxocyclohex-1-en-1-yl)ethyl]benzaldehyde (8bb). Chromatography (EtOAc/hexanes = 1:3); yellow solid; 84 mg; yield 83%; mp 68–69 °C; IR (neat) ν 2943, 2730, 1695, 1665, 1585, 1466, 1263, 790 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 10.17 (s, 1H), 7.42–7.34 (m, 2H),

7.10 (dd, *J* = 7.5, 1.2 Hz, 1H), 5.86 (brs, 1H), 3.86 (s, 3H), 3.26 (t, *J* = 8.0 Hz, 2H), 2.42–2.33 (m, 6H), 2.03–1.96 (m, 2H); $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$): δ 200.0, 192.8, 166.0, 157.8, 134.7, 131.8, 127.5, 125.8, 125.2, 115.6, 55.9, 38.2, 37.3, 29.6, 22.7, 22.5; MS (EI) *m/z* (% base peak) 258 (M^+, 43), 215 (6), 189 (9), 161 (11), 149 (100), 148 (21), 115 (4), 91 (43), 84 (9), 58 (26); HRMS (EI-TOF) *m/z*: $[M]^+$ Calcd for $C_{16}H_{18}O_3$ 258.1256; Found 258.1253.

4-Methoxy-2-[(3-oxocyclohex-1-en-1-yl)ethyl]benzaldehyde (8cb). Chromatography (EtOAc/hexanes = 1:3); yellowish solid; 91 mg; yield 90%; mp 47–48 ^{o}C; IR (neat) ν 2940, 2868, 2736, 1682, 1600, 1566, 1250, 1106, 811 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.00 (s, 1H), 7.75 (d, *J* = 8.6 Hz, 1H), 6.90 (dd, *J* = 8.6, 2.4 Hz, 1H), 6.74 (d, *J* = 2.4 Hz, 1H), 5.89 (brs, 1H), 3.88 (s, 3H), 3.21 (t, *J* = 8.0 Hz, 2H), 2.49 (t, *J* = 8.0 Hz, 2H) 2.39–2.34 (m, 4H), 2.03–1.96 (m, 2H); $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$): δ 199.9, 191.3, 165.3, 163.7, 145.8, 137.4, 127.3, 126.1, 116.9, 111.6, 55.5, 39.4, 37.3, 31.2, 29.7, 22.7; MS (EI) *m/z* (% base peak) 258 (M^+, 18), 215 (9), 202 (8), 189 (19), 176 (9), 148 (78), 121 (7), 91 (7), 58 (100); HRMS (EI-TOF) *m/z*: $[M]^+$ Calcd for $C_{16}H_{18}O_3$ 258.1256; Found 258.1255.

5-Methoxy-2-[(3-oxocyclohex-1-en-1-yl)ethyl]benzaldehyde (8db). Chromatography (EtOAc/hexanes = 1:3); yellow solid; 65 mg; yield 64%; mp 55–56 ^{o}C; IR (neat) ν 2944, 2837, 2737, 1705, 1667, 1609, 1500, 1260, 1037, 885 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.12 (s, 1H), 7.29 (d, *J* = 2.6 Hz, 1H), 7.14 (d, *J* = 8.5 Hz, 1H), 7.04 (dd, *J* = 8.5, 2.6 Hz, 1H), 5.84 (brs, 1H), 3.82 (s, 3H), 3.13 (t, *J* = 8.0 Hz, 2H), 2.43 (t, *J* = 8.0 Hz, 2H), 2.35–2.30 (m, 4H), 1.99–1.92 (m, 2H); $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$): δ 199.8, 192.1, 165.1, 158.5, 135.4, 134.4, 132.2, 126.1, 120.3, 117.1, 55.5, 40.1, 37.3, 29.73, 29.72, 22.6; MS (EI) *m/z* (% base peak) 258 (M^+, 22), 230 (9), 215 (16), 202 (12), 189 (25), 176 (23), 148 (100), 121 (10), 91 (10), 83 (13), 58 (74); HRMS (EI-TOF) *m/z*: $[M]^+$ Calcd for $C_{16}H_{18}O_3$ 258.1256; Found 258.1256.

2-Methoxy-6-[(3-oxocyclohex-1-en-1-yl)ethyl]benzaldehyde (8eb). Chromatography (EtOAc/hexanes = 1:2); colorless solid; 63 mg; yield 62%; mp 96–97 ^{o}C; IR (neat) ν 2930, 2856, 1728, 1682, 1667, 1595, 1473, 1267, 1076, 796 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.62 (s, 1H), 7.42 (dd, *J* = 8.4, 7.6 Hz, 1H), 6.87 (d, *J* = 8.4 Hz, 1H), 6.78 (d, *J* = 7.6 Hz, 1H), 5.87 (brs, 1H), 3.90 (s, 3H), 3.14–3.09 (m, 2H), 2.45

(t, *J* = 7.9 Hz, 2H), 2.40–2.33 (m, 4H), 2.02–1.95 (m, 2H); $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$): δ 200.0, 192.1, 165.9, 163.5, 144.6, 134.9, 125.9, 123.3, 122.8, 109.8, 55.8, 39.4, 37.4, 32.0, 29.6, 22.7; MS (EI) *m/z* (% base peak) 258 (M^+, 19), 215 (11), 189 (19), 176 (15), 148 (100), 121 (8), 91 (11), 58 (42); HRMS (EI-TOF) *m/z*: $[M]^+$ Calcd for $C_{16}H_{18}O_3$ 258.1256; Found 258.1256.

5-Methyl-2-[(3-oxocyclohex-1-en-1-yl)ethyl]benzaldehyde (8fb). Chromatography (EtOAc/hexanes = 1:3); yellowish oil; 83 mg; yield 82%; IR (neat) ν 2926, 2867, 2733, 1687, 1668, 1625, 1568, 1242, 1156, 885, 831 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.12 (s, 1H), 7.59 (d, *J* = 1.0 Hz, 1H), 7.31 (dd, *J* = 7.7, 1.0 Hz, 1H), 7.14 (d, *J* = 7.7 Hz, 1H), 5.86 (brs, 1H), 3.18 (t, *J* = 8.0 Hz, 2H), 2.46 (t, *J* = 8.0 Hz, 2H), 2.40 (s, 3H), 2.37–2.33 (m, 4H), 2.02–1.95 (m, 2H); $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$): δ 199.7, 193.0, 165.2, 140.2, 136.8, 134.7, 134.6, 133.5, 131.1, 126.1, 39.7, 37.3, 30.4, 29.7, 22.7, 20.7; MS (EI) *m/z* (% base peak) 242 (M^+, 40), 199 (23), 186 (17), 173 (30), 171 (30), 133 (100), 132 (94), 105 (88), 83 (64), 77 (38), 58 (42); HRMS (EI-TOF) *m/z*: $[M]^+$ Calcd for $C_{16}H_{18}O_2$ 242.1307; Found 242.1306.

Methyl 3-formyl-4-[(3-oxocyclohex-1-en-1-yl)ethyl]benzoate (8gb). Chromatography (EtOAc/hexanes = 1:1); yellow solid; 87 mg; yield 86%; mp 106–108 ^{o}C; IR (neat) ν 2950, 2866, 1723, 1665, 1610, 1436, 1293, 1195, 1113, 762 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.19 (s, 1H), 8.47 (d, *J* = 1.6 Hz, 1H), 8.16 (dd, *J* = 8.0, 1.6 Hz, 1H), 7.36 (d, *J* = 8.0 Hz, 1H), 5.88 (brs, 1H), 3.96 (s, 3H), 3.29 (t, *J* = 8.0 Hz, 2H), 2.49 (t, *J* = 8.0 Hz, 2H), 2.39–2.35 (m, 4H), 2.04–1.97 (m, 2H); $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$): δ 199.7, 192.3, 165.8, 164.5, 148.0, 135.8, 134.4, 133.8, 131.5, 129.3, 126.2, 52.4, 39.1, 37.3, 31.1, 29.7, 22.6; MS (EI) *m/z* (% base peak) 286 (M^+, 59), 255 (21), 243 (46), 230 (25), 217 (62), 215 (31), 176 (100), 171 (28), 143 (18), 133 (24), 110 (25); HRMS (EI-TOF) *m/z*: $[M]^+$ Calcd for $C_{17}H_{18}O_4$, 286.1205; Found 286.1203.

2-[(3-Oxocyclohept-1-en-1-yl)ethyl]benzaldehyde (8ac). Chromatography (EtOAc/hexanes = 1:2); yellowish oil; 65 mg; yield 64%; IR (neat) ν 2933, 2864, 2739, 1695, 1656, 1452, 1268, 1191, 756 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.18 (s, 1H), 7.81 (dd, *J* = 7.4, 1.2 Hz, 1H) , 7.52 (ddd, *J* = 7.4, 7.4, 1.4 Hz, 1H), 7.43 (ddd, *J* = 7.4, 6.9, 1.2 Hz, 1H), 7.27 (d, *J* = 6.9 Hz, 1H), 5.93 (brs, 1H), 3.22 (t, *J* = 8.0 Hz, 2H), 2.58 (t, *J* = 6.0 Hz, 2H), 2.52 (t, *J* = 6.0 Hz, 2H), 2.46 (t, *J* = 8.0 Hz, 2H), 1.86–1.75 (m, 4H);

$^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$): δ 204.0, 192.9, 160.9, 143.4, 134.2, 133.9, 133.7, 131.2, 129.7, 127.0, 42.8, 42.3, 32.8, 31.7, 25.2, 21.3; MS (EI) *m/z* (% base peak) 242 (M^+, 20), 224 (54), 214 (21), 185 (22), 159 (100), 129 (30), 118 (55), 109 (54), 91 (70); HRMS (EI-TOF) *m/z*: $[M]^+$ Calcd for $C_{16}H_{18}O_2$ 242.1307; Found 242.1306.

2-[(3-Oxocyclohex-1-en-1-yl)ethyl]-3-furaldehyde (11). Chromatography (EtOAc/hexanes = 1:2); yellow oil; 57 mg; yield 56%; IR (neat) ν 3126, 2924, 2851, 1674, 1425, 1253, 1124, 892, 755 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.92 (s, 1H), 7.32 (d, *J* = 2.0 Hz, 1H) , 6.68 (d, *J* = 2.0 Hz, 1H), 5.83 (brs, 1H), 3.19 (t, *J* = 7.6 Hz, 2H), 2.62 (t, *J* = 7.6 Hz, 2H), 2.36–2.28 (m, 4H), 2.02–1.94 (m, 2H); $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$): δ 199.3, 184.7, 163.1, 162.6, 142.4, 126.5, 122.5, 108.8, 37.2, 35.9, 29.5, 24.9, 22.6; MS (EI) *m/z* (% base peak) 218 (M^+, 17), 200 (11), 190 (9), 162 (13), 133 (7), 109 (100), 108 (26), 81 (18), 58 (17); HRMS (EI-TOF) *m/z*: $[M]^+$ Calcd for $C_{13}H_{14}O_3$ 218.0943; Found 218.0946.

2-[(3-Oxocyclohex-1-en-1-yl)ethyl]nicotinaldehyde (14). Chromatography (EtOAc/hexanes = 2:1); yellow oil; 58 mg; yield 57%; IR (neat) ν 3058, 2927, 2866, 1663, 1582, 1440, 1256, 1030, 755 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.24 (s, 1H), 8.70 (dd, *J* = 4.8, 1.6 Hz, 1H) , 8.10 (dd, *J* = 7.7, 1.6 Hz, 1H), 7.37 (dd, *J* = 7.7, 4.8 Hz, 1H), 5.84 (brs, 1H), 3.43 (t, *J* = 7.9 Hz, 2H), 2.66 (t, *J* = 7.9 Hz, 2H), 2.40 (t, *J* = 5.9 Hz, 2H), 2.35 (t, *J* = 6.7 Hz, 2H), 2.03–1.96 (m, 2H); $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$): δ 199.8, 191.3, 164.9, 162.0, 153.2, 139.9, 129.2, 126.0, 122.1, 37.3, 37.2, 32.6, 29.7, 22.6; MS (EI) *m/z* (% base peak) 229 (M^+, 24), 201 (89), 200 (37), 173 (100), 172 (48), 144 (33), 130 (16), 117 (8), 93 (13), 77 (10); HRMS (EI-TOF) *m/z*: $[M]^+$ Calcd for $C_{14}H_{15}NO_2$ 229.1103; Found 229.1106.

General Procedure for Intramolecular Stetter Reaction. To a stirred solution of **8, 11, 14** (0.13 mmol) and thiazolium salt **A** (7 mg, 0.026 mmol) in absolute ethanol (2.6 mL, 0.05 M) was added triethylamine (0.018 mL, 0.13 mmol) under Ar atmosphere at room temperature. The reaction mixture was then heated in an oil bath for a period of time (see Scheme **5** for the duration of heating). The contents were cooled to room temperature and the solvent was evaporated. The residue was purified by column chromatography on silica gel to afford **15**–**17**.

3',4'-Dihydro-1'*H*-spiro[cyclopentane-1,2'-naphthalene]-1',3-dione (15aa). Chromatography (EtOAc/CH_2Cl_2 = 1:100); yellowish solid; 20.6 mg; yield 74%; mp 50–51 ^oC; IR (neat) ν 3066, 2927, 1743, 1675, 1600, 1229, 1160, 746 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.03 (dd, *J* = 8.0, 1.0 Hz, 1H), 7.49 (ddd, *J* = 8.0, 7.5, 1.0 Hz, 1H), 7.32 (dd, *J* = 8.0, 7.5 Hz, 1H), 7.25 (d, *J* = 8.0 Hz, 1H), 3.20–3.12 (m, 1H), 2.95 (ddd, *J* = 17.2, 5.0, 5.0 Hz, 1H), 2.80 (d, *J* = 17.8 Hz, 1H), 2.48–2.23 (m, 4H), 2.16–2.09 (m, 1H), 2.09 (d, *J* = 17.8 Hz, 1H), 2.03–1.94 (m, 1H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 216.6, 200.2, 143.2, 133.6, 130.7, 128.7, 128.0, 126.9, 49.9, 47.3, 36.1, 34.2, 30.5, 25.8; MS (EI) *m/z* (% base peak) 214 (M^+, 94), 196 (10), 185 (29), 171 (23), 157 (39), 142 (19), 129 (21), 119 (53), 118 (51), 91 (100), 58 (37); HRMS (EI-TOF) *m/z*: $[M]^+$ Calcd for $C_{14}H_{14}O_2$, 214.0994; Found 214.0995.

8'-Methoxy-3',4'-dihydro-1'*H*-spiro[cyclopentane-1,2'-naphthalene]-1',3-dione (15ea).[24a] Chromatography (EtOAc/hexanes = 1:1); white solid; 21.6 mg; yield 68%; mp 72–73 ^oC; IR (neat) ν 2926, 2849, 1742, 1671, 1591, 1467, 1270, 1208, 1076, 962 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.41 (dd, *J* = 8.4, 7.7 Hz, 1H), 6.85 (d, *J* = 8.4 Hz, 1H), 6.82 (d, *J* = 7.7 Hz, 1H), 3.90 (s, 3H), 3.16–3.07 (m, 1H), 2.93 (ddd, *J* = 17.1, 5.3, 5.3 Hz, 1H), 2.83 (d, *J* = 18.0 Hz, 1H), 2.54–2.42 (m, 2H), 2.34–2.16 (m, 2H), 2.10–2.03 (m, 2H), 1.97–1.89 (m, 1H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 217.0, 199.6, 161.3, 146.0, 134.4, 120.7, 120.2, 110.1, 55.9, 51.4, 47.9, 36.3, 34.1, 31.2, 26.8; MS (EI) *m/z* (% base peak) 244 (M^+, 18), 216 (100), 189 (40), 173 (11), 148 (92), 115 (7), 90 (18); HRMS (EI-TOF) *m/z*: $[M]^+$ Calcd for $C_{15}H_{16}O_3$ 244.1099; Found 244.1097.

3',4'-Dihydro-1'*H*-spiro[cyclohexane-1,2'-naphthalene]-1',3-dione (15ab). Chromatography (EtOAc/CH_2Cl_2 = 1:100); yellowish oil; 25.2 mg; yield 85%; IR (neat) ν 3065, 2932, 1712, 1678, 1599, 1453, 1226, 741 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.02 (dd, *J* = 8.0, 1.0 Hz, 1H), 7.48 (ddd, *J* = 7.7, 7.5, 1.0 Hz, 1H) , 7.31 (dd, *J* = 8.0, 7.5 Hz, 1H), 7.22 (d, *J* = 7.7 Hz, 1H), 3.16–3.07 (m, 1H), 2.92 (ddd, *J* = 17.5, 4.5, 4.5 Hz, 1H), 2.81 (d, *J* = 14.4 Hz, 1H), 2.47–2.41 (m, 1H), 2.35–2.28 (m, 1H), 2.15–2.00 (m, 4H), 1.92–1.85 (m, 2H), 1.83–1.73 (m, 1H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 209.8, 200.0, 142.9, 133.6, 130.8, 128.7, 128.1, 126.9, 49.3, 48.7, 40.4, 33.0, 29.6, 24.9, 21.4; MS (EI) *m/z* (% base

peak) 228 (M^+, 100), 185 (56), 159 (98), 129 (27), 118 (78), 115 (17), 83 (56); HRMS (EI-TOF) *m/z*: $[M]^+$ Calcd for $C_{15}H_{16}O_2$ 228.1150; Found 228.1148.

5'-Methoxy-3',4'-dihydro-1'*H*-spiro[cyclohexane-1,2'-naphthalene]-1',3-dione (15bb). Chromatography (EtOAc/hexanes = 1:2); yellowish oil; 21.8 mg; yield 65%; IR (neat) ν 2924, 2851, 1714, 1680, 1583, 1470, 1262, 1062, 753 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.63 (d, *J* = 8.0 Hz, 1H), 7.27 (dd, *J* = 8.0, 8.0 Hz, 1H), 7.02 (d, *J* = 8.0 Hz, 1H), 3.86 (s, 3H), 3.00 (ddd, *J* = 18.3, 4.5, 4.5 Hz, 1H), 2.86–2.76 (m, 2H), 2.46–2.27 (m, 2H), 2.11 (d, *J* = 14.6 Hz, 1H), 2.09–2.00 (m, 2H), 1.89–1.74 (m, 4H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 209.8, 200.3, 156.7, 131.9, 131.7, 127.1, 119.6, 114.2, 55.6, 48.9, 48.6, 40.5, 32.2, 29.5, 21.4, 18.8; MS (EI) *m/z* (% base peak) 258 (M^+, 100), 215 (40), 189 (89), 161 (16), 148 (34), 120 (19), 90 (13), 58 (26); HRMS (EI-TOF) *m/z*: $[M]^+$ Calcd for $C_{16}H_{18}O_3$ 258.1256; Found 258.1253.

6'-Methoxy-3',4'-dihydro-1'*H*-spiro[cyclohexane-1,2'-naphthalene]-1',3-dione (15cb). Chromatography (Et_2O/hexanes = 1:2); colorless solid; 10.1 mg; yield 30%; mp 106–107 ^oC; IR (neat) ν 2933, 2852, 1712, 1668, 1599, 1256 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.00 (d, *J* = 8.8 Hz, 1H), 6.84 (dd, *J* = 8.8, 2.4 Hz, 1H), 6.67 (d, *J* = 2.4 Hz, 1H), 3.85 (s, 3H), 3.13–3.03 (m, 1H), 2.87 (ddd, *J* = 17.4, 4.5, 4.5 Hz, 1H), 2.81 (d, *J* = 14.6 Hz, 1H), 2.49–2.41 (m, 1H), 2.34–2.26 (m, 1H), 2.12 (d, *J* = 14.6 Hz, 1H), 2.13–1.98 (m, 3H), 1.93–1.86 (m, 2H), 1.80–1.75 (m, 1H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 210.0, 198.7, 163.8, 145.4, 130.7, 124.5, 113.6, 112.4, 55.5, 49.1, 48.8, 40.5, 33.1, 29.8, 25.3, 21.5; MS (EI) *m/z* (% base peak) 258 (M^+, 78), 215 (27), 189 (100), 148 (70), 120 (11), 83 (18), 58 (35); HRMS (EI-TOF) *m/z*: $[M]^+$ Calcd for $C_{16}H_{18}O_3$ 258.1256; Found 258.1258.

7'-Methoxy-3',4'-dihydro-1'*H*-spiro[cyclohexane-1,2'-naphthalene]-1',3-dione (15db). Chromatography (EtOAc/CH_2Cl_2 = 1:100); yellowish solid; 21.8 mg; yield 65%; mp 79–80 ^oC; IR (neat) ν 2937, 1714, 1677, 1608, 1496, 1419, 1275, 1244, 1028, 824 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.50 (d, *J* = 2.6 Hz, 1H), 7.14 (d, *J* = 8.4 Hz, 1H), 7.07 (dd, *J* = 8.4, 2.6 Hz, 1H), 3.82 (s, 3H), 3.09–3.00 (m, 1H), 2.85 (ddd, *J* = 17.3, 4.4, 4.4 Hz, 1H), 2.80 (d, *J* = 14.6 Hz, 1H), 2.49–2.27 (m, 2H), 2.13 (d, *J* = 14.6 Hz, 1H), 2.13–1.99 (m, 3H), 1.92–1.85 (m, 2H), 1.82–1.75 (m, 1H); $^{13}C\{^1H\}$ NMR (100 MHz,

$CDCl_3$): δ 209.8, 200.0, 158.5, 135.4, 131.6, 130.0, 122.2, 109.8, 55.5, 49.2, 48.7, 40.5, 33.3, 29.6, 24.1, 21.5; MS (EI) *m/z* (% base peak) 258 (M^+, 100), 215 (44), 189 (79), 161 (17), 148 (24), 120 (51), 91 (9); HRMS (EI-TOF) *m/z*: $[M]^+$ Calcd for $C_{16}H_{18}O_3$ 258.1256; Found 258.1254.

8'-Methoxy-3',4'-dihydro-1'*H*-spiro[cyclohexane-1,2'-naphthalene]-1',3-dione (15eb). Chromatography ($EtOAc/CH_2Cl_2$ = 1:15); yellow solid; 29.2 mg; yield 87%; mp 99–100 °C; IR (neat) ν 2939, 1709, 1675, 1593, 1469, 1270, 1210, 1085, 963, 800 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.39 (dd, *J* = 8.4, 7.2 Hz, 1H), 6.83 (d, *J* = 8.4 Hz, 1H), 6.79 (d, *J* = 7.2 Hz, 1H), 3.88 (s, 3H), 3.08–2.99 (m, 1H), 2.89 (ddd, *J* = 17.4, 5.1, 5.1 Hz, 1H), 2.84 (d, *J* = 14.6 Hz, 1H), 2.47–2.27 (m, 2H), 2.13 (d, *J* = 14.6 Hz, 1H), 2.13–1.75 (m, 6H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 210.3, 199.1, 161.2, 145.5, 134.2, 120.6, 120.5, 110.0, 55.9, 50.6, 48.7, 40.5, 32.2, 30.4, 25.7, 21.6; MS (EI) *m/z* (% base peak) 258 (M^+, 62), 215 (14), 191 (49), 189 (77), 148 (100), 113 (16), 85 (27); HRMS (EI-TOF) *m/z*: $[M]^+$ Calcd for $C_{16}H_{18}O_3$ 258.1256; Found 258.1256.

7'-Methyl-3',4'-dihydro-1'*H*-spiro[cyclohexane-1,2'-naphthalene]-1',3-dione (15fb). Chromatography (Et_2O/hexanes = 1:2); yellow oil; 21.7 mg; yield 69%; IR (neat) ν 3026, 2932, 2854, 1714, 1677, 1610, 1497, 1238, 1170, 821 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.84 (brs, 1H), 7.30 (dd, *J* = 7.7, 1.5 Hz, 1H), 7.13 (d, *J* = 7.7 Hz, 1H), 3.11–3.02 (m, 1H), 2.88 (ddd, *J* = 17.4, 4.5, 4.5 Hz, 1H), 2.82 (d, *J* = 14.2 Hz, 1H), 2.49–2.41 (m, 1H), 2.35 (s, 3H), 2.35–2.28 (m, 1H), 2.13 (d, *J* = 14.2 Hz, 1H), 2.12–2.01 (m, 3H), 1.92–1.85 (m, 2H), 1.82–1.76 (m, 1H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 209.9, 200.2, 140.0, 136.6, 134.6, 130.6, 128.7, 128.2, 49.3, 48.7, 40.5, 33.0, 29.6, 24.5, 21.5, 20.9; MS (EI) *m/z* (% base peak) 242 (M^+, 100), 199 (46), 173 (96), 171 (15), 145 (18), 132 (63), 128 (14), 104 (34), 77 (8); HRMS (EI-TOF) *m/z*: $[M]^+$ Calcd for $C_{16}H_{18}O_2$ 242.1307; Found 242.1307.

Methyl 1',3-dioxo-3',4'-dihydro-1'*H*-spiro[cyclohexane-1,2'-naphthalene]-7'-carboxylate (15gb). Chromatography (EtOAc/hexanes = 1:3); yellow oil; 25.3 mg; yield 68%; IR (neat) ν 2956, 2924, 2851, 1722, 1685, 1609, 1436, 1297, 1210, 1120, 759 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.66 (brs, 1H), 8.12 (dd, *J* = 8.0, 1.3 Hz, 1H), 7.32 (d, *J* = 8.0 Hz, 1H), 3.91 (s, 3H), 3.17–3.10 (m, 1H), 2.98 (ddd, *J* = 18.0, 4.5, 4.5 Hz, 1H), 2.82 (d, *J* = 14.6 Hz, 1H), 2.47–2.41 (m, 1H), 2.35–2.29 (m, 1H), 2.14 (d, *J* =

14.6 Hz, 1H), 2.10–2.04 (m, 3H), 1.92–1.77 (m, 3H); $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$): δ 209.4, 199.1, 166.2, 147.5, 134.0, 131.0, 129.7, 129.3, 129.2, 52.3, 49.2, 48.8, 40.5, 32.4, 29.5, 25.1, 21.4; MS (EI) *m/z* (% base peak) 286 (M^+, 81), 255 (16), 243 (53), 217 (100), 189 (12), 176 (55), 148 (11), 128 (13), 117 (11), 85 (9), 58 (13); HRMS (EI-TOF) *m/z*: $[M]^+$ Calcd for $C_{17}H_{18}O_4$ 286.1205; Found 286.1204.

3',4'-Dihydro-1'*H*-spiro[cycloheptane-1,2'-naphthalene]-1',3-dione (15ac). Chromatography ($EtOAc/CH_2Cl_2$ = 1:100); yellowish oil; 20.8 mg; yield 66%; IR (neat) ν 3065, 2929, 2858, 1681, 1600, 1455, 1286, 1221, 915, 745 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.03 (d, *J* = 8.0 Hz, 1H), 7.47 (ddd, *J* = 7.7, 7.4, 1.0 Hz, 1H), 7.31 (dd, *J* = 8.0, 7.4 Hz, 1H), 7.22 (d, *J* = 7.7 Hz, 1H), 3.12 (d, *J* = 13.0 Hz, 1H), 3.02–2.98 (m, 2H), 2.66 (ddd, *J* = 18.4, 5.7, 5.7 Hz, 1H), 2.46 (d, *J* = 13.0 Hz, 1H), 2.46–2.39 (m, 1H), 2.14–2.04 (m, 2H), 1.95 (ddd, *J* = 14.0, 5.2, 5.2 Hz, 1H), 1.89–1.75 (m, 5H); $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$): δ 212.8, 200.3, 142.9, 133.4, 130.8, 128.7, 128.3, 126.8, 50.0, 46.2, 43.9, 36.0, 32.4, 24.8, 24.4, 23.9; MS (EI) *m/z* (% base peak) 242 (M^+, 100), 224 (20), 198 (14), 185 (39), 159 (98), 129 (27), 118 (66), 90 (37); HRMS (EI-TOF) *m/z*: $[M]^+$ Calcd for $C_{16}H_{18}O_2$, 242.1307; Found 242.1305.

6,7-Dihydro-4*H*-spiro[benzofuran-5,1'-cyclohexane]-3',4-dione (16). Chromatography ($EtOAc/CH_2Cl_2$ = 1:100); colorless oil; 13.1 mg; yield 46%; IR (neat) ν 3124, 2943, 1712, 1673, 1597, 1436, 1232, 1122, 955, 742 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.33 (d, *J* = 1.9 Hz, 1H), 6.65 (d, *J* = 1.9 Hz, 1H), 2.98–2.84 (m, 2H), 2.80 (d, *J* = 14.6 Hz, 1H), 2.47–2.39 (m, 1H), 2.32–2.27 (m, 1H), 2.13–2.03 (m, 3H), 1.95–1.84 (m, 2H), 1.76–1.69 (m, 2H); $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$): δ 209.7, 196.1, 165.1, 143.3, 119.2, 107.2, 49.6, 47.9, 40.4, 32.6, 30.1, 21.8, 20.3; MS (EI) *m/z* (% base peak) 218 (M^+, 100), 190 (19), 176 (20), 149 (55), 121 (7), 108 (73), 80 (23); HRMS (EI-TOF) *m/z*: $[M]^+$ Calcd for $C_{13}H_{14}O_3$, 218.0943; Found 218.0942.

7',8'-Dihydro-5'*H*-spiro[cyclohexane-1,6'-quinoline]-3,5'-dione (17). Chromatography (EtOAc/hexanes = 1:1); yellowish oil; 17.9 mg; yield 60%; IR (neat) ν 3065, 2941, 1712, 1684, 1582, 1457, 1226, 762 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.70 (dd, *J* = 4.8, 1.9 Hz, 1H), 8.29 (dd, *J* = 7.8, 1.9 Hz, 1H), 7.30 (dd, *J* = 7.8, 4.8 Hz, 1H), 3.32–3.22 (m, 1H), 3.14(ddd, *J* = 18.3, 4.6, 4.6 Hz, 1H), 2.81 (d, *J* = 14.6 Hz, 1H), 2.50–2.42 (m, 1H), 2.37–2.29 (m, 1H), 2.16 (d, *J* = 14.6 Hz, 1H), 2.14–2.06

(m, 3H), 1.98–1.79 (m, 3H); $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$): δ 209.1, 199.7, 162.1, 153.9, 136.1, 126.5, 122.5, 49.1, 48.4, 40.4, 31.9, 29.6, 28.1, 21.4; MS (EI) *m/z* (% base peak) 229 (M^+, 76), 201 (100), 186 (53), 173 (26), 160 (91), 145 (69), 130 (66), 119 (40), 91 (29); HRMS (EI-TOF) *m/z*: $[M]^+$ Calcd for $C_{14}H_{15}NO_2$, 229.1103; Found 229.1103.

Supporting Information Available: Copies of ^{1}H and ^{13}C NMR for compounds **2**–**4**, **6**–**8**, **10**–**11**, and **13**–**17**.

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