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Sequential Allylic Substitution/Pauson–Khand Reaction: A Strategy to Bicyclic Fused Cyclopentenones from MBH-Acetates of Acetylenic Aldehydes

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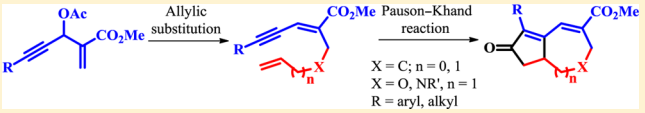
Supporting Information

ABSTRACT: An efficient approach for the construction of novel bicyclic fused cyclopentenones starting from Morita–Baylis–Hillman (MBH) acetates of acetylenic aldehydes with flexible scaffold diversity has been achieved using a two-step reaction sequence involving allylic substitution and the Pauson–Khand reaction. This strategy provided a facile access to various bicyclic cyclopentenones fused with either a carbocyclic or a heterocyclic ring system in good yield.



INTRODUCTION

The Morita–Baylis–Hillman (MBH) reaction, the α-hydroxyalkylation of activated olefins, is one of the most useful carbon–carbon bond-forming reactions that offers densely functionalized new chemical entities.[1] MBH-adducts and their acetate derivatives have received considerable attention as flexible precursors for the formation of useful structural motifs including heterocycles and carbocycles through various transformations.[2] Nevertheless, novel developments in the MBH-adduct efficacy to generate complex molecular structures are continuously significant and of interest. One such case is the use of Morita–Baylis–Hillman adducts of acetylenic aldehydes, which remains less investigated despite being a potentially valuable addition to the MBH-adducts group.[3] In addition to the common allylic alcohol and conjugated ester functionalities, MBH-adducts of acetylenic aldehydes have an additional alkyne functionality to provide a new dimension of applications in the modern organic synthesis. In the recent past, we have initiated a research program on the use of MBH-acetates of acetylenic aldehydes and demonstrated the synthesis of functionalized pyrroles, thiophenes, furans, and cyclopentenes using allylic substitution, followed by cyclization.[4] We envisioned that new bicyclic fused cyclpentenone frameworks could also be easily obtained from MBH-acetates of acetylenic aldehydes via allylic substitution with the appropriate olefin, followed by intramolecular Pauson–Khand reaction.

The bicyclic fused cyclopentenones are key structural scaffolds embedded in numerous biologically active compounds.[5−7] Among these, bicyclo[5.3.0]decane,[5] bicyclo[4.3.0]-nonane,[6] and bicyclo[3.3.0]octane[7] frameworks are frequently found in bioactive natural products. For example, sootepdienone,[5a] guanacastepene,[5b] (−)-cyclocolorenone,[8c] alisol-L,[6a] cucumins-B,[7d] and (+)-connatusin[7f] are some of the representative natural products bearing 5,7-bicyclic, 5,6-bicyclic, and 5,5-bicyclic cyclopentenone motifs in their structures (Figure 1). In addition, bicyclic fused cyclopentenone

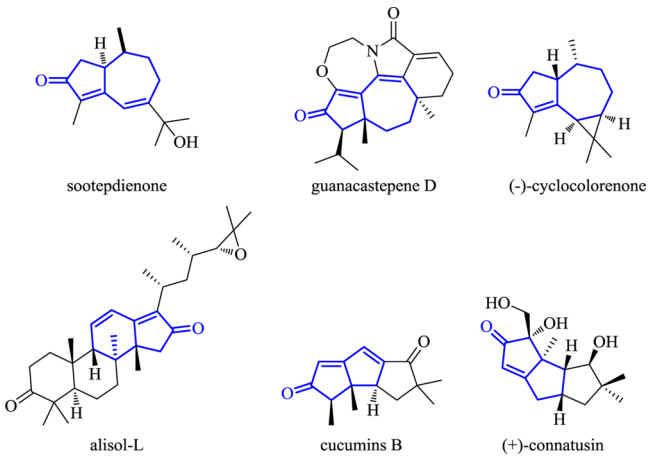


Figure 1. Denoted natural products having a bicyclic fused cyclopentenone system.

derivatives also serve as valuable building blocks in the synthesis of various natural products.[8] Consequently, these skeletons have attracted much attention from synthetic organic chemists, and several approaches have been developed.[9,10] The Pauson–Khand reaction, a [2 + 2 + 1]-carbonylative cyclization reaction, is one of the widely used methods to construct bicyclic fused cyclopentenones.[10] However, the intramolecular Pauson–Khand reaction toward the synthesis of bicyclic cyclopentenones fused with a heterocyclic ring system has not been explored enough.[11] Herein, we disclose the results of our strategy for the synthesis of novel bicyclic fused cyclpentenones from easily accessible MBH-acetates of acetylenic aldehydes. The unique feature of this method is the formation of bicyclic fused cyclopentenones having a

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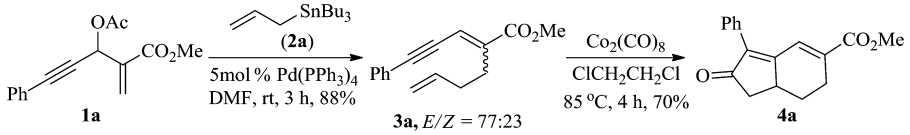
Scheme 1. Synthesis of 5,6-Bicyclic Fused Cyclopentenone 4a from MBH-Acetate 1a



conjugated dienone functionality, which are commonly found in several natural products.[7a] To the best of our knowledge, these kinds of bicyclic ring systems have not been explored yet using the Pauson–Khand reaction.

RESULTS AND DISCUSSION

We began our investigation with the preparation of the desired ene-yne intermediate **3a**, which was obtained by the treatment of MBH-acetate **1a** with allyl tri-*n*-butyltin (**2a**) in the presence of 5 mol % $Pd(PPh_3)_4$ (Scheme 1).[12] It is noteworthy to mention that product **3a** obtained (88% yield) as an inseparable mixture of *E*/*Z* isomers in a 77:23 ratio was directly used for the next reaction. Thus, the ene-yne **3a** was subjected to Pauson–Khand reaction using Co_2CO_8 (1.1 equiv) in 1,2-dichloroethane at 85 °C for 4 h, and to our delight, the reaction progressed smoothly to provide 5,6-bicyclic cyclopentenone **4a**, in 70% yield. At this stage also, we were unable to isolate the unreacted *Z*-isomer of **3a** in pure form due to its nonpolar nature, which eluted along with the other unidentified byproducts. The screening of a few other solvents, such as THF, CH_2Cl_2, and toluene, for the Pauson–Khand reaction of **3a** revealed that 1,2-dichloroethane was the best choice in terms of yield and reaction profile (Scheme 1).

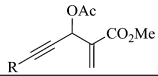
Under the optimized conditions, the scope of the two-step reaction sequence was evaluated using MBH-acetates of acetylenic aldehydes having either an alkyl group (**1b**) or a *tert*-butylsilyl group (**1c**) on the alkyne functionality. Accordingly, **1b** and **1c** were independently subjected to the allylic substitution with **2a** to obtain **3b** (79%, *E*/*Z* = 77:23) and **3c** (82%, *E*/*Z* = 50:50), respectively. Subsequently, the treatment of **3b** and **3c** under $Co_2(CO)_8$/$ClCH_2CH_2Cl$/85 °C conditions provided the corresponding 5,6-bicyclic cyclopentenones **4b** and **4c** (entries 2 and 3, Table 1). The Pauson–Khand reaction of **3c** gave the product **4c** having the TBS group intact in 45% yield, as the *E*/*Z* ratio was 1:1 during the allylic substitution.

With the success in obtaining a 5/6-ring system, we were prompted to explore the formation of a 5/7-ring skeleton, bicyclo[5.3.0]decane,[5] an important and challenging framework in organic synthesis. Thus, 2-allylcyclohexane-1,3-dione **2b** was used as the alkene partner for allylic substitution with MBH-acetate **1a** under K_2CO_3/DMF/rt conditions to afford **3d** (*E*/*Z* = 80:20) in 65% yield. The treatment of **3d** under Pauson–Khand reaction conditions furnished the required cyclopentenone with a 5/7-ring system **4d** in 72% yield (entry 4, Table 1). In the same way, compound **2b** also participated in allylic substitution with MBH-acetate **1b** to provide **3e** (*E*/*Z* = 92:8, 61% yield), which subsequently underwent Pauson–Khand cyclization to give a spiro-cyclic cyclopentenone **4e** in 75% yield (entry 5, Table 1). Further, we planned to expand the scope of the present reaction toward the synthesis of 3,3′-cycloheptyl-spirooxindoles, which are also important structural motifs in a variety of bioactive natural products.[13] We were pleased to find that 3-allyloxindole **2c** could react with MBH-acetate **1a** under K_2CO_3/DMF/rt conditions to give **3f** (*E*/*Z* = 85:15) in 74% yield, which successfully participated in the following Pauson–Khand cyclization to provide a novel spiro-oxindole having a bicyclic fused cyclopentene, 3,3′-cycloheptyl-spirooxindole **4f**, as diastereometic mixture (8:2 ratio) in 71% yield (entry 6, Table 1). This two-step reaction sequence is tolerant of alkyl substitution on the alkyne functionality of MBH-acetate **1b**, allowing access to the corresponding 3,3′-spirocyclic oxindole **4g** (67%, diastereomeric ratio 9:1) via intermediate **3g** (entry 7, Table 1).

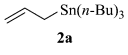
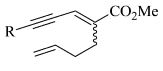
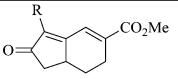
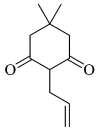
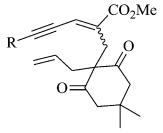
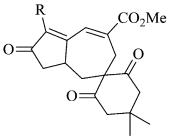
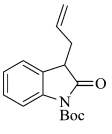
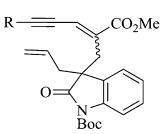
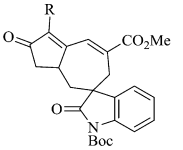
Later, we were encouraged to prepare a 5,5-bicyclic ring, for which MBH-acetate **1a** was treated with *trans*-2-phenylvenylboronic acid (**2d**) under 5 mol % $Pd(OAc)_2$/Na_2CO_3/MeOH conditions[14] to yield the corresponding ene-yne intermediate **3h** (*E*/*Z* = 97:3) in 93% yield. Subsequently, compound **3h** was subjected to Pauson–Khand reaction conditions to obtain the 5,5-bicyclic cyclopentenone **4h** as a diastereomeric mixture (7:3) in 85% yield. Similarly, MBH-acetate **1b** also well participated in the current two-step reaction strategy with **2d**, to give the cyclopentenone **4i** (70%, d.r. = 9:1) via ene-yne **3i** (Scheme 2).

The relative stereochemistry of compound **4h** at C7 and C8 was determined by using detailed NMR experiments. The scalar coupling constant between H7–H8 ($^3J_{H7-H8}$ = 5.6 Hz), in

Table 1. Synthesis of Bicyclic Fused Cyclopentenones[a,b,c,d]



R = Ph, **1a**
R = *n*-C_3H_7, **1b**
R = TBS, **1c**

entry	alkene partner (**2**)	reaction time/yield[b] ene-yne (**3**)[c]	fused cyclopentenone (**4**)
1	**2a** 	 R = Ph, **3a**, 3 h, 88%, *E*/*Z* = 77:23	 R = Ph, **4a**, 3 h, 70%
2	**2a**	R = *n*-C_3H_7, **3b**, 2 h, 79%, *E*/*Z* = 77:23	R = *n*-C_3H_7, **4b**, 2 h, 63%
3	**2a**	R = TBS, **3c**, 2 h, 82%, *E*/*Z* = 50:50	R = TBS, **4c**, 3 h, 45%
4	**2b** 	 R = Ph, **3d**, 10 h, 65%, *E*/*Z* = 80:20	 R = Ph, **4d**, 3 h, 72%
5	**2b**	R = *n*-C_3H_7, **3e**, 8 h, 61%, *E*/*Z* = 92:8	R = *n*-C_3H_7, **4e**, 2 h, 75%
6[d]	**2c** 	 R = Ph, **3f**, 7 h, 74%, *E*/*Z* = 85:15	 R = Ph, **4f**, 3 h, 71%, d.r. = 8:2
7[d]	**2c**	R = *n*-C_3H_7, **3g**, 5 h, 71%, *E*/*Z* = 90:10	R = *n*-C_3H_7, **4g**, 2 h, 67%, d.r. = 9:1

[a]Reaction conditions: (i) for **3a** to **3c**: 5 mol % $Pd(PPh_3)_4$, DMF, rt; (ii) for **3d** to **3g**: K_2CO_3, DMF, rt; (iii) for **4a** to **4g**: $Co(CO)_8$, $ClCH_2CH_2Cl$, rt to 85 °C. [b]Isolated yields. [c]*E*/*Z* ratios were determined from ^{1}HNMR. [d]Diastereomeric ratio shown by integration of well separated signals of ^{1}H NMR spectra.

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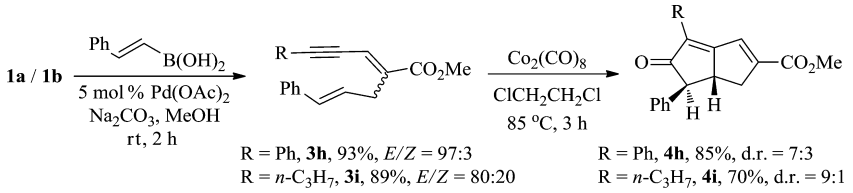
Scheme 2. Synthesis of 5,5-Bicyclic Fused Cyclopentenones 4h and 4i



addition to the appearance of nOe cross-peaks between H8−H6′ and H7−H9, indicates that H7 and H8 are in a *trans* orientation, as represented in Figure 2.

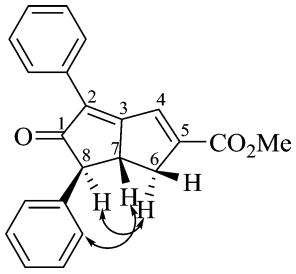
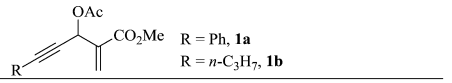


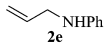
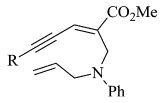
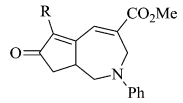
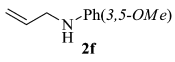
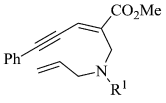
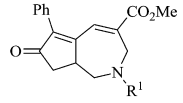
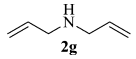
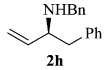
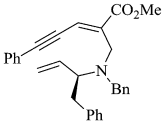
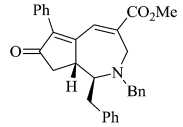
Figure 2. nOe observations in compound **4h**.

Encouraged by these results, we diverted our attention to the synthesis of heterocyclic fused cyclopentenones from MBH-acetates of acetylenic aldehydes through the similar two-step reaction approach with appropriate alkenes. We were delighted to see that the allylic substitution reaction of **1a** with *N*-allyl aniline (**2e**), in the presence of 10 mol % $Pd(PPh_3)_4$ in CH_3CN at room temperature, afforded the ene-yne (**3j**) tethered with the *N*-allyl group in 95% yield (the allylic substitution reaction of **1a** with *N*-allyl aniline was not successful under K_2CO_3/DMF conditions). Subsequent Pauson−Khand reaction of **3j** was also fruitful to provide the corresponding cyclopentenone fused with azepine (seven-membered azacycle) **4j** in 74% yield under standard conditions (entry 1, Table 2). The developed sequential substitution/Pauson−Khand reactions were equally effective for MBH-acetate **1b** having *n*-propyl substitution on the alkyne functionality to provide **4k** in 69% yield via ene-yne **3k** (entry 2, Table 2). Other *N*-substituted allyl amines, **2f** and **2g**, were also found to be suitable partners in reaction with **1a** for the formation of ene-ynes **3l** and **3m**, respectively, which subsequently underwent Pauson−Khand reaction to provide the corresponding bicyclo[5.3.0]decanes **4l** and **4m** in good yield (entries 3 and 4, Table 2). The chiral amine **2h**, obtained from phenyl alanine,[15] was tested for the present strategy by reacting with MBH-acetate **1a**. Gratifyingly, the reaction provided the expected 5/7-bycyclic compound **4n** in 72% yield with >99% diastereoselectivity through the ene-yne intermediate **3n** (entry 5, Table 2).

The relative absolute stereochemistry of the compound **4n** was determined by using detailed 1D and 2D NMR experiments. The large three bond scalar coupling constant between H8−H9 ($^3J_{H8-H9}$ = 9.0 Hz), along with the appearance of nOe cross-peaks between H9/H11, H9/H11′, H8/H10′, indicates that H8 and H9 protons are in a *trans* orientation. The azepine ring was elucidated as a half-chair conformation based on the appearance of nOe cross-correlations between H8/H10′, H6/H9, H6/H11, H6/H11′, which yield C3−C4−C5−C6−C9 in plane, where N7−C8 is below the plane of the ring (Figure 3).

Table 2. Synthesis of Cyclopentenones Fused with Azepine[a,b,c]



entry	alkene partner (**2**)	reaction time/yield[b] ene-yne (**3**)[c]	fused cyclopentenone (**4**)
1	 **2e**	 R = Ph, **3j**, 8 h, 95%	 R = Ph, **4j**, 3 h, 74%
2	**2e**	R = *n*-C_3H_7, **3k**, 5 h, 90%	R = *n*-C_3H_7, **4k**, 2 h, 69%
3	 **2f**	 R^1 = Ph(*3,5-OMe*), **3l**, 4 h, 96%	 R^1 = Ph(*3,5-OMe*), **4l**, 3 h, 70%
4	 **2g**	R^1 = allyl, **3m**, 2 h, 91%	R^1 = allyl, **4m**, 3 h, 65%
5	 **2h**	 **3n**, 4 h, 89%	 **4n**, 4 h, 72%

[a]Reaction conditions: (i) for **3j** to **3n**: 10 mol % $Pd(PPh_3)_4$, CH_3CN, rt; (ii) for **4j** to **4n**: $Co(CO)_8$, $ClCH_2CH_2Cl$, rt to 85 °C. [b]Isolated yields. [c]No traces of *E*-isomer found.

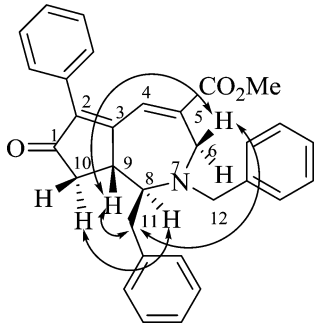


Figure 3. nOe observations in compound **4n**.

To further expand the scope of the present methodology, we undertook the synthesis of cyclopentenones fused with oxepine. The allylic substitution reaction of MBH-acetate **1a** with allyl alcohol (**2i**) was tested independently using K_2CO_3 in DMF and 10 mol % $Pd(PPh_3)_4$ in CH_3CN conditions. Unfortunately, both of these reactions failed to promote the substitution reaction to give ene-yne **3o**, presumably due to the less nucleophilic nature of the hydroxyl group. Therefore, we adopted an alternative sequence of reactions, wherein the MBH-acetate **1a** was first converted to a bromide intermediate and that was used as an alkylating agent for the alkylation of

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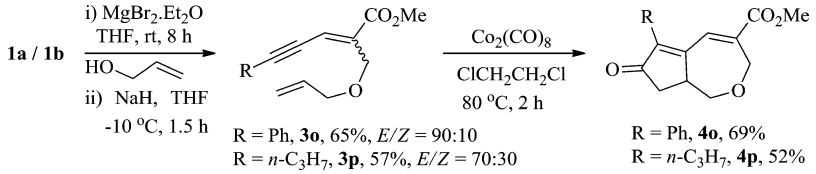
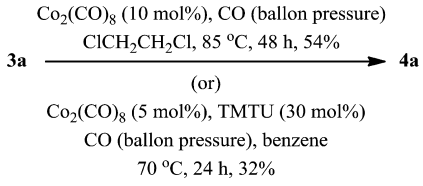
Scheme 3. Synthesis of Oxacyclic Fused Cyclopentenones



allyl alcohol (**2i**) in the presence of NaH in THF.[16] To our delight, the desired *O*-allyl ene-yne **3o** was obtained in 65% yield (*E*/*Z* = 90:10), which subsequently participated in Pauson–Khand cycloaddition reaction to provide the oxepine-fused cyclopentenone **4o** in 69% yield. Likewise, employment of MBH-acetate **1b** in the above strategy furnished the corresponding cyclopentenone **4p** via ene-yne **3p** in good yield (Scheme 3).

In order to test the feasibility of the Pauson–Khand reaction under catalytic conditions, compound **3a** was treated with $Co_2(CO)_8$ (10 mol %)/carbon monoxide (balloon pressure) in 1,2-dichloroethane at 85 °C,[17] which gave the desired product **4a** in 54% yield. Independently, the same reaction has also been carried out in benzene at 100 °C by adding tetramethylthiourea (TMTU)[18] as a ligand to obtain **4a** in 32% yield (Scheme 4).

Scheme 4. Conversion of 3a to 4a under Catalytic Methods



In summary, we have developed an efficient strategy for the synthesis of functionalized bicyclic fused cyclopentenones from readily accessible MBH-acetates of acetylenic aldehydes, via the sequential allylic substitution/Pauson–Khand reactions. This approach with simple experimental conditions provided an access to novel bicyclic frameworks having diverse functionalities/substitutions. The reaction was found to be compatible with three different tethers, such as carbon, nitrogen, and oxygen. We believe that the developed reaction strategy will find the applications on relevant substrates to the synthesis of bioactive compounds.

EXPERIMENTAL SECTION

All the reagents and solvents were used, unless otherwise specified, as they were received. The progress of the reactions was monitored by thin-layer chromatography using silica gel coated aluminum sheets; the spots were visualized under UV light after being dipped in alkaline $KMnO_4$ solution. The products were purified by eluting through a 60–120 mesh silica gel column by variable ratios of EtOAc/hexanes at room temperature. The eluted fractions with desired product were concentrated under reduced pressure at 45 °C. All the compounds were characterized by ^{1}H NMR and ^{13}C NMR taken on either 300 or 500 MHz, FT-IR, and HRMS (FTMS). ^{1}H and ^{13}C NMR values given are for the major isomer, whenever an *E*/*Z*-isomeric/diastereomeric mixture was obtained. FT-IR were recorded as neat or KBr matrix. Mass spectra were obtained on a VG 70–70H or LC/MSD trapSL spectrometer operating at 70 eV using a direct inlet system. Specific rotation of chiral compounds was taken on a digital Polarimeter.

Morita–Baylis–Hillman acetates **1a**–**1c**,[4f] 3-allyl-*N*-Boc-oxindole (**2c**),[19] and the chiral amine **2h**[15] have been prepared using the literature procedures. Analytical data of all of these compounds were correlated with the corresponding reported data.

Procedure for the Synthesis of Ene-ynes 3a–3c. To a solution of MBH-acetate **1a**/**b**/**c** (1.0 mmol) and allyltributyl stannane (**2a**) (1.0 mmol) in DMF (15 mL) was added $Pd(PPh_3)_4$ (0.05 mmol), and the mixture was stirred at rt for 3 h. Then, it was filtered through a short pad of Celite and concentrated under reduced pressure. The crude was suspended in cold water and extracted with ethyl acetate (2 × 50 mL); organic fractions were mixed and concentrated under reduced pressure. This was purified by column chromatography to get the desired ene-yne compound **3a**/**b**/**c**.

*(E)-Methyl-2-(3-phenylprop-2-yn-1-ylidene)hex-5-enoate (**3a**).* Colorless liquid, R_f = 0.75 (EtOAc/hexanes = 1:19), 178 mg, 88% yield; *E*/*Z* = 77:23, ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.53–7.43(m, 2H), 7.41–7.30 (m, 3H), 6.87 (s, 1H), 5.97–5.73 (m, 1H), 5.12–4.59 (m, 2H), 3.79 (s, 3H), 2.71 (t, *J* = 7.5 Hz, 2H), 2.36–2.23 (m, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 167.1, 142.3, 137.7, 131.7, 129.0, 128.4, 120.2, 117.5, 115.0, 101.5, 85.9, 52.0, 32.9, 29.1; IR (KBr): ν_{max} = 3078, 2928, 2196, 1714, 1438, 1250, 914, 756, 689 cm^{-1}; MS (ESI): *m*/*z* 263 (M + Na)$^+$; HRMS (ESI): *m*/*z* calcd for $C_{16}H_{16}NaO_2$ (M + Na)$^+$: 263.1043, found: 263.1056.

*(E)-Methyl-2-(but-3-en-1-yl)oct-2-en-4-ynoate (**3b**).* Colorless liquid, R_f = 0.83 (EtOAc/hexanes = 1:19), 174 mg, 79%, *E*/*Z* = 77:23; ^{1}H NMR ($CDCl_3$, 300 MHz): δ 6.65 (s, 1H), 5.98–5.69 (m, 1H), 5.12–4.91 (m, 2H), 3.76 (s, 3H), 2.59 (t, *J* = 7.9 Hz, 2H), 2.40 (td, *J* = 7.9, 2.2 Hz, 2H), 2.23 (q, *J* = 7.1 Hz, 2H), 1.71–1.50 (m, 2H), 1.02 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 167.4, 141.3, 137.9, 121.1, 114.8, 103.7, 78.03, 51.8, 32.89, 28.83, 21.99, 21.91, 13.45; (KBr): ν_{max} = 2958, 2927, 2213, 1714, 439, 1259, 1207, 762 cm^{-1}; Anal. Calcd for $C_{13}H_{18}O_2$: C, 75.6; H: 8.8; O: 15.5, found: C, 75.8, H, 8.6.

*(E)-Methyl 2-(3-(tert-Butyldimethylsilyl)prop-2-yn-1-ylidene)hex-5-enoate (**3c**).* Pale yellow liquid, R_f = 0.87 (EtOAc/hexanes = 1:19), 227 mg, 82%, *E*/*Z* = 50:50; ^{1}H NMR ($CDCl_3$, 300 MHz): δ 6.64 (s, 1H), 5.87–5.73 (m, 1H), 5.06–4.94 (m, 2H), 3.76 (s, 3H), 2.63 (t, *J* = 7.4 Hz, 1H), 2.43 (dt, *J* = 7.3, 1.2 Hz, 1H), 2.27–2.18 (m, 2H), 0.96 (s, 9H), 0.16 (s, 3H), 0.14 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 167.1, 143.6, 137.5, 120.0, 115.0, 106.5, 101.5, 52.0, 32.8, 29.6, 26.0, 16.6, −4.7; IR (KBr): ν_{max} = 3078, 2953, 2929, 2857, 2135, 1717, 1438, 1253, 1209, 830, 776 cm^{-1}; MS (ESI): *m*/*z* 301 (M + Na)$^+$; HRMS (ESI): *m*/*z* calcd for $C_{16}H_{27}O_2Si$ (M + H)$^+$: 279.1781, found: 279.1780.

Procedure for the Synthesis of Ene-ynes 3d–3g. To a solution of MBH-acetate **1** (1.0 mmol) and alkene nucleophile **2b** or **2c** (1.2 mmol) in DMF (15 mL) at room temperature was added K_2CO_3 (3 mmol) under a N_2 atmosphere, and the mixture was stirred at rt for 10 h. Then, it was diluted with ethyl acetate and sequentially washed with water (2 × 50 mL) and brine (1 × 30 mL). The ethyl acetate layer was dried over Na_2SO_4 and concentrated under reduced pressure to get the crude product, which was purified by silica gel column chromatography.

*(E)-Methyl-2-((1-allyl-4,4-dimethyl-2,6-dioxocyclohexyl)methyl)-5-phenylpent-2-en-4-yno-ate (**3d**).* Colorless syrup, R_f = 0.4 (EtOAc/hexanes = 1:9), 245 mg, 65%, *E*/*Z* = 80:20; ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.56–7.52 (m, 2H), 7.41–7.36 (m, 3H), 7.01 (s, 1H), 5.57–5.49 (m, 1H), 5.14–4.94 (m, 2H), 3.75 (s, 3H), 3.06 (s, 2H), 2.93 (d, 14.6, 2H), 2.75 (d, *J* = 7. 5 Hz, 2H), 2.42 (d, *J* = 14.6 Hz, 2H), 1.13(s, 3H), 0.84 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 209.0, 166.6, 136.4, 133.6, 131.9, 129.4, 128.5, 124.1, 119.4, 103.2, 85.8, 67.8, 52.1, 51.9, 37.5, 34.4, 30.7, 30.5, 26.7; IR (KBr): ν_{max} = 2954, 2195, 1715, 1695, 1640, 1436, 1253, 1213, 758, 690 cm^{-1}; MS (ESI): *m*/*z* 401 (M +

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Na)$^+$; HRMS (ESI): m/z calcd for $C_{24}H_{26}NaO_4$ (M + Na)$^+$: 401.1723, found: 401.1734.

*(E)-Methyl-2-((1-allyl-4,4-dimethyl-2,6-dioxocyclohexyl)methyl)-oct-2-en-4-ynoate (**3e**).* Colorless syrup, R_f = 0.5 (EtOAc/hexanes = 1:9), 209 mg, 61% yield, E/Z = 92:8; ^{1}H NMR ($CDCl_3$, 300 MHz): δ 6.80 (t, J = 2.2 Hz, 1H), 5.51 (dt, J = 10.0, 7.3 Hz, 1H), 5.07 (td, J = 17.0, 1.0 Hz, 1H), 4.96 (dd, J = 10.2, 2.2, Hz, 1H), 3.71 (s, 3H), 2.94 (s, 4H), 2.66 (d, J = 7.3 Hz, 2H), 2.50−2.34 (m, 4H), 1.63 (q, J = 7.1 Hz, 2H), 1.13 (s, 3H), 1.03 (t, J = 7.1 Hz, 3H), 0.82 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 209.0, 166.9, 148.2, 133.7, 125.2, 119.2, 105.9, 77.4, 67.9, 52.1, 52.0, 37.2, 34.2, 30.7, 26.6, 21.9, 13.5; IR (KBr): ν_{max} = 2959, 2873, 2211, 1717, 1697, 1435, 1263, 1170, 921, 766 cm^{-1}; MS (ESI): m/z 367 (M + Na)$^+$; HRMS (ESI): m/z calcd for $C_{21}H_{28}O_4Na$ (M + Na)$^+$: 367.1879, found: 367.1880.

*(E)-tert-Butyl-3-allyl-3-(2-(methoxycarbonyl)-5-phenylpent-2-en-4-yn-1-yl)-2-oxoindoline-1-carboxylate (**3f**).* Colorless syrup, R_f = 0.7 (EtOAc/hexanes = 2:8), 348 mg, 74%, E/Z = 85:15; ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.79 (d, J = 8.0 Hz, 1H), 7.54−7.49 (m, 2H), 7.41−7.36 (m, 3H), 7.23 (d, J = 8.0 Hz, 1H), 7.18 (d, J = 7.6 Hz, 1H), 7.10 (d, J = 7.6 Hz, 1H), 6.83 (s, 1H), 5.46−5.36 (m, 1H), 5.01 (dd, J = 16.9, 1.6 Hz, 1H), 4.92 (dd, J = 10.2, 1.6 Hz, 1H), 3.57 (s, 3H), 3.27 (d, J = 13.7 Hz, 1H), 3.20 (d, J = 13.7 Hz, 1H), 2.81 (dd, J = 13.7, 7.6 Hz, 1H), 2.66 (dd, J = 13.7, 7.6 Hz, 1H), 1.58 (s, 9H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 177.1, 166.8, 149.2, 139.3, 137.8, 131.8, 131.7, 129.2, 128.4, 128.1, 124.1, 123.7, 122.7, 119.5, 114.7, 102.2, 85.8, 83.9, 60.3, 52.9, 51.8, 42.0, 36.9, 27.9; IR (KBr): ν_{max} = 2980, 2195, 1723, 1614, 1350, 1284, 1154, 762, 453 cm^{-1}; MS (ESI): m/z 494 (M + Na)$^+$; HRMS (ESI): m/z calcd for $C_{29}H_{29}O_5NNa$: 494.1937, found: 494.1933.

*(E)-tert-Butyl-3-allyl-3-(2-(methoxycarbonyl)oct-2-en-4-yn-1-yl)-2-oxoindoline-1-carboxy-late (**3g**).* Colorless syrup, R_f = 0.8 (EtOAc/hexanes = 2:8), 303 mg, 71%, E/Z = 90:10; ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.77 (d, J = 8.0 Hz, 1H), 7.26−7.22 (m, 1H), 7.16−7.06 (m, 2H), 6.63 (t, J = 2.2 Hz, 1H), 5.42−5.32 (m, 1H), 4.99 (dd, J = 17.0, 1.6 Hz, 1H), 4.91 (d, J = 10.0 Hz, 1H), 3.53 (s, 3H), 3.16 (d, J = 13.7 Hz, 1H), 3.07 (d, J = 13.7 Hz, 1H), 2.76 (dd, J = 13.5, 7.6 Hz, 1H), 2.60 (dd, J = 13.6, 6.8 Hz, 1H), 2.41 (dt, J = 7.3, 2.2 Hz, 2H), 1.68−1.58 (m, 11 H) 1.04 (t, J = 7.3 Hz, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 177.2, 167.0, 149.2, 139.2, 131.8, 129.3, 128.0, 124.0, 123.8, 123.6, 119.4, 114.6, 104.7, 83.8, 52.8, 51.6, 42.1, 40.6, 36.5, 28.0, 21.8, 13.5; IR (KBr): ν_{max} = 2926, 2855, 1726, 1615, 1468, 1250, 1155, 1034, 759 cm^{-1}; MS (ESI): m/z 460 (M + Na)$^+$; HRMS (ESI): m/z calcd for $C_{26}H_{31}O_5NNa$ (M + Na): 460.2094, found: 460.2102.

Procedure for the Synthesis of Een-ynes 3h and 3i. To a solution of MBH-acetate **1** (1.0 mmol) and alkenyl boronic acid **2d** (1.2 mmol) in methanol (25 mL) were added $Pd(OAc)_2$ (0.05 mmol) and Na_2CO_3 (1.5 mmol), and the mixture was stirred at rt for 2 h. After completion of the reaction, the reaction mixture was concentrated under reduced pressure to remove methanol, and the residue was suspended in ethyl acetate (50 mL) and washed with water (2 × 30 mL). The organic fraction was dried over Na_2SO_4 and concentrated under reduced pressure and purified by flash column.

*(E)-Methyl-2-cinnamyl-5-phenylpent-2-en-4-ynoate (**3h**).* Yellow semisolid, R_f = 0.7 (EtOAc/hexanes = 1:9), 280 mg, 93%, E/Z = 97:3; ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.54−7.46 (m, 2H), 7.41−7.25 (m, 7H), 7.21−7.16 (m, 1H), 6.93 (s, 1H), 6.53 (d, J = 15.7 Hz, 1H), 6.27 (td, J = 15.7, 6.8 Hz, 1H), 3.80 (s, 3H), 3.51 (d, J = 6.8 Hz, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 166.8, 140.4, 137.3, 131.8, 131.6, 129.1, 128.4, 127.1, 126.1, 120.4, 101.9, 85.7, 52.1, 32.9; IR (KBr): ν_{max} = 3025, 2951, 2192, 1712, 1438, 1245, 1097, 1034, 967, 751, 690 cm^{-1}; MS (ESI): m/z 303 (M + H)$^+$; HRMS (ESI): m/z calcd for $C_{21}H_{19}O_2$ (M + H)$^+$: 303.1379, found: 303.1384.

*(E)-Methyl-2-cinnamyloct-2-en-4-ynoate (**3i**).* Colorless liquid, R_f = 0.8 (EtOAc/hexanes = 1:9), 238 mg, 89%; *E:Z*=80:20; ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.42−7.15 (m, 5H), 6.71 (t, J = 2.2 Hz, 1H), 6.46 (d, J = 15.6 Hz, 1H), 6.29−6.11 (m, 1H), 3.76 (s, 3H), 3.40 (d, J = 6.6 Hz, 2H), 2.43 (dt, J = 6.9, 2.2 Hz, 2H), 1.70−1.54 (m, 2H), 1.03 (t, J = 7.7 Hz, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 167.1, 139.4, 137.4, 131.2, 128.3, 127.0, 126.4, 126.0, 121.4, 104.2, 77.4, 52.0, 32.6, 21.9, 13.5; IR (KBr): ν_{max} = 2953, 2196, 1720, 1612, 1438, 1243, 1152, 1028, 758 cm^{-1}; MS (ESI): m/z 301 (M + Na)$^+$; HRMS (ESI): m/z calcd for $C_{18}H_{21}O_2$ (M + H)$^+$: 269.1497, found: 269.1541.

General Procedure for the Synthesis of Ene-ynes (3j−3n) from BMH-Acetate 1 and Allylamines 2e−2h. To a solution of MBH-acetate **1** (1.0 mmol) and *N*-allyl aniline **2** (1.1 mmol) in CH_3CN (15 mL) was added $Pd(PPh_3)_4$ (0.1 mmol) at rt under a N_2 atmosphere, and the mixture was stirred at rt for 8 h. The reaction mixture was filtered through a Celite pad and concentrated under reduced pressure; the obtained crude was purified by silica gel column chromatography to get the desired ene-yne **3**.

*(Z)-Methyl-2-((allyl(phenyl)amino)methyl)-5-phenylpent-2-en-4-ynoate (**3j**).* Yellow liquid, R_f = 0.4 (EtOAc/hexanes = 1:19), 215 mg, 95%; ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.41−7.27 (m, 5H), 7.21 (t, J = 7.1 Hz, 2H), 6.99 (s, 1H), 6.88 (d, J = 8.1, 2H), 6.70 (t, J = 7.1 Hz, 1H), 5.93−5.77 (m, 1H), 5.21−5.07 (m, 2H), 4.44 (s, 2H), 4.01 (d, J = 4.7 Hz, 2H), 3.76 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 166.9, 148.5, 139.5, 133.6, 131.7, 129.1, 128.9, 128.3, 121.5, 116.6, 116.1, 113.0, 85.2, 52.4, 52.0, 49.1; IR (KBr): ν_{max} = 2923, 2853, 2194, 1715, 1598, 1503, 1436, 1246, 1105, 752, 690 cm^{-1}; MS (ESI): m/z 354 (M + Na)$^+$; HRMS (ESI): m/z calcd for $C_{22}H_{22}NO_2$ (M + H)$^+$: 332.1645, found: 332.1677.

*(Z)-Methyl-2-((allyl(phenyl)amino)methyl)oct-2-en-4-ynoate (**3k**).* Pale yellow liquid, R_f = 0.6 (EtOAc/hexanes = 1:19), 267 mg, 90%; ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.21−7.17 (m, 2H), 6.85 (d, J = 8.0 Hz, 2H), 6.75 (t, J = 2.4 Hz, 1H), 6.63 (d, J = 7.6 Hz, 1H), 5.88−5.77 (m, 1H), 5.15−5.09 (m, 2H), 4.34 (s, 2H), 3.99 (td, J = 4.8, 1.9 Hz, 2H), 3.72 (s, 3H), 2.37 (dt, J = 7.0, 2.4 Hz, 2H), 1.61−1.53 (m, 2H), 0.99 (t, J = 7.4 Hz, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 167.2, 148.5, 138.9, 133.9, 128.8, 129.1, 122.7, 115.8, 113.0, 117.4, 116.4, 105.5, 76.8, 51.9, 48.8, 52.4, 29.6, 21.8, 13.5; IR (KBr): ν_{max} = 2925, 2855, 2211, 1717, 1503, 1383, 1248, 1103, 751 cm^{-1}; MS (ESI): m/z 298 (M + H)$^+$; HRMS (ESI): m/z calcd for $C_{19}H_{24}O_2N$ (M + H)$^+$: 298.1801, found: 298.1797.

*(Z)-Methyl-2-((allyl(3,5-dimethoxyphenyl)amino)methyl)-5-phenylpent-2-en-4-ynoate (**3l**).* Pale yellow liquid, R_f = 0.6 (EtOAc/hexanes = 1:19), 375 mg, 96%; ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.43−7.39 (m, 2H), 7.38−7.28 (m, 3H), 6.98 (s, 1H), 6.06 (d, J = 1.9 Hz, 2H), 5.96−5.81 (m, 2H), 5.19−5.12 (m, 2H), 4.42 (s, 2H), 4.01 (d, J = 4.1 Hz, 2H), 3.74 (s, 3H), 3.73 (s, 6H), ; ^{13}C NMR ($CDCl_3$, 125 MHz): δ 166.8, 161.4, 150.5, 139.7, 135.2, 133.7, 131.8, 129.2, 128.3, 121.4, 116.1, 92.2, 89.2, 85.1, 55.1, 53.1, 52.1, 49.4, 46.5; IR (Neat): ν_{max} = 2926, 2851, 2194, 1715, 1611, 1201, 1152, 1069, 808, 758 cm^{-1}; MS (ESI): m/z 392 (M + H)$^+$; HRMS (ESI): m/z calcd for $C_{24}H_{26}NO_4$ (M + H)$^+$: 392.1861, found: 392.1872.

*(Z)-Methyl-2-((diallylamino)methyl)-5-phenylpent-2-en-4-ynoate (**3m**).* Pale yellow liquid, R_f = 0.7 (EtOAc/hexanes = 1:19), 241 mg, 91%; ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.51−7.46 (m, 2H), 7.39−7.33 (m, 3H), 6.90 (s, 1H), 5.96−5.87 (m, 2H), 5.19 (ddt, J = 17.2, 3.3, 1.5 Hz, 2H), 5.12 (ddt, J = 10.2, 1.9, 1.0 Hz, 2H), 3.80 (s, 3H), 3.55 (s, 2H), 3.15 (td, J = 6.4, 1.2 Hz, 4H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 167.2, 146.9, 135.6, 131.6, 129.0, 128.5, 127.7, 126.5, 117.3, 85.6, 77.1, 56.8, 52.0, 50.8; IR (KBr): ν 3078, 2927, 2214, 1707, 1639, 1440, 1215, 1100, 1001, 769, 701 cm^{-1}; MS (ESI): m/z 296 (M + H)$^+$; HRMS (ESI): m/z calcd for $C_{19}H_{22}NO_2$ (M + H)$^+$: 296.1645, found: 296.1666.

*(S,Z)-Methyl-4-(benzyl(1-phenylbut-3-en-2-yl)amino)-2-(phenylethynyl)but-2-enoate (**3n**).* Red liquid, R_f = 0.5 (EtOAc/hexanes = 1:19), 387 mg, 89%, [α]: +0.86° (c1, CH_3Cl, 20 °C); ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.49−7.45 (m, 2H), 7.41−7.30 (m, 3H), 7.25−7.06 (m, 10H), 6.80 (s, 1H), 5.90 (ddd, J = 10.3, 2.4, 1.0 Hz, 1H), 5.19 (dd, J = 10.3, 1.0 Hz, 1H), 5.04 (dd, J = 17.2, 1.0 Hz, 1H), 3.88 (d, J = 14.1 Hz, 1H), 3.71 (d, J = 12.9 Hz, 1H), 3.66−3.61 (m, 4H), 3.52 (d, J = 14.1 Hz, 1H), 3.43 (q, J = 7.9 Hz, 1H), 3.05 (dd, J = 13.2, 6.2 Hz, 1H), 2.83 (dd, J = 13.7, 8.2 Hz, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 167.4, 141.2, 140.0, 139.7, 135.6, 131.6, 129.3, 128.7, 128.4, 127.8, 126.6, 125.6, 121.1, 118.1, 101.0, 85.6, 63.5, 54.1, 51.7, 48.4, 38.2, 29.6; IR (KBr): ν_{max} = 3062, 3026, 2924, 2845, 2194, 1717, 1441, 1238, 1122, 921, 765, 694 cm^{-1}; MS (ESI): m/z 436 (M + H)$^+$; HRMS (ESI): m/z calcd for $C_{30}H_{30}NO_2$ (M + H)$^+$: 436.2271, found: 436.2280.

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Procedure for the Synthesis of Ene-ynes 3o and 3p. To a solution of MBH-acetate **1** (1.0 mmol) in THF (15 mL) was added $MgBr_2{\cdot}Et_2O$ (3.0 mmol) at room temperature; then, it was stirred at rt for 8 h. After completion of **1** (monitored by TLC), the crude reaction mixture was filtered through Celite and concentrated under reduced pressure to get the bromo compound, which was used for the next step without further purification.

To a solution of NaH (1.2 mmol) in dry THF (10 mL) at −10 °C under a N_2 atmosphere was added a solution of allyl alcohol **2i** (1.1 mmol) in dry THF (5 mL), and the mixture was stirred at the same temperature for 1 h. Then, a solution of the above bromo compound in dry THF (5 mL) was added slowly and stirred for 30 min at −10 °C. It was quenched with ice and extracted with ethyl acetate (2 × 30 mL), and the combined organic layer was dried over Na_2SO_4 and concentrated under reduced pressure. The obtained crude was purified by silica gel column chromatography to get pure ene-yne **3o** or **3p**.

*(E)-Methyl-2-((allyloxy)methyl)-5-phenylpent-2-en-4-ynoate (**3o**).* Colorless liquid, R_f = 0.5 (EtOAc/hexanes = 1:19), 166 mg, 65%, *E*/*Z* = 90:10; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.55−7.45 (m, 2H), 7.43−7.30 (m, 3H), 7.05 (s, 1H), 6.03−5.88 (m, 1H), 5.32 (d, *J* = 19.3 Hz, 1H), 5.18 (d, *J* = 19.3 Hz, 1H), 4.48 (s, 2H), 4.08 (d, *J* = 5.6 Hz, 2H), 3.82 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 166.5, 138.1, 134.6, 131.8, 129.3, 128.4, 123.9, 122.1, 117.3, 102.5, 85.0, 71.4, 65.2, 52.2; IR Neat): ν_{max} = 2925, 2195, 1717, 1614, 1438, 1237, 1076, 758 cm^{-1}; MS (ESI): *m*/*z* 279 (M + Na)$^+$; HRMS (ESI): *m*/*z* calcd for $C_{16}H_{16}NaO_3$ (M + Na)$^+$: 279.0992, found: 279.0996.

*(E)-Methyl-2-((allyloxy)methyl)oct-2-en-4-ynoate (**3p**).* Colorless liquid, R_f = 0.6 (EtOAc/hexanes = 1:19), 120 mg, 57%, *E*/*Z* = 72:28; ^{1}H NMR ($CDCl_3$, 500 MHz): δ 6.83 (t, *J* = 2.2 Hz, 1H), 5.99−5.88 (m, 1H), 5.37−5.15 (m, 2H), 4.38 (s, 2H), 4.04−4.01 (m, 2H), 3.79 (s, 3H), 2.41 (dt, *J* = 7.0, 2.2 Hz, 2H), 1.64−1.56 (m, 2H), 1.02 (t, *J* = 7.3 Hz, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 166.8, 134.7, 132.0, 125.0, 117.0, 105.1, 76.8, 71.4, 65.1, 52.0, 21.9, 21.8, 13.4.; IR (KBr): ν_{max} = 2959, 2927, 2865, 2213, 1719, 1616, 1439, 1238, 1119, 925, 764 cm^{-1}; MS (ESI): *m*/*z* 245 (M + Na)$^+$; HRMS (ESI): *m*/*z* calcd for $C_{13}H_{18}O_3Na$ (M + Na)$^+$: 245.1148, found: 245.1154.

General Experimental Procedure for Pauson−Khand Reaction. To a solution of compound **3** (0.5 mmol) in 1,2-dichloroethane (10 mL) at room temperature was added $Co_2(CO)_8$ (0.55 mmol) under a N_2 atmosphere, and the mixture was stirred at room temperature until the complete formation of the $Co_2(CO)_8$-ene-yne complex (monitored by TLC, ∼2 h). Then, it was heated to 85 °C for 2 h (monitored by TLC). The reaction mixture was filtered through a Celite pad and concentrated under reduced pressure to get the crude material, which was purified by silica gel column chromatography to obtain the corresponding cyclopentenone **4**.

*Methyl-2-oxo-3-phenyl-2,6,7,7a-tetrahydro-1H-indene-5-carboxylate (**4a**).* Pale yellow solid, R_f = 0.5 (EtOAc/hexanes = 2:8), 94 mg, 70%, mp 89−91 °C; ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.70 (d, *J* = 2.6 Hz, 1H), 7.51−7.33(m, 5H), 3.8 (s, 3H), 2.98−2.80 (m, 3H), 2.63−2.46 (m, 1H), 2.39−2.16 (m, 2H), 1.60−1.47 (m, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 205.8, 166.8, 163.4, 139.4, 138.9, 130.5, 129.5, 129.1, 128.4, 128.3, 52.1, 42.01, 36.3, 28.2, 26.0; IR (KBr): ν_{max} = 2862, 1699, 1605, 1256, 1081, 964, 766, 700, 599 cm^{-1}; MS (ESI): *m*/*z* 269 (M + H)$^+$; HRMS (ESI): *m*/*z* calcd for $C_{17}H_{16}NaO_3$ (M + Na)$^+$: 291.0992, found: 291.0993.

*Methyl-2-oxo-3-propyl-2,6,7,7a-tetrahydro-1H-indene-5-carboxylate (**4b**).* Yellow syrup, R_f = 0.6 (EtOAc/hexanes = 2:8), 74 mg, 63%; ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.60 (d, *J* = 2.6 Hz, 1H), 3.83 (s, 3H), 2.85−2.65 (m, 3H), 2.55−2.40 (m, 1H), 2.33−2.16 (m, 3H), 2.1−1.99 (m, 1H), 1.55−1.22 (m, 3H), 0.90 (t, *J* = 7.3 Hz, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 207.9, 166.9, 163.0, 141.6, 137.1, 128.8, 52.1, 41.5, 36.3, 28.4, 25.9, 24.8, 22.0, 13.9; IR (KBr): ν_{max} = 2958, 2871, 1700, 1629, 1437, 1260, 11 95, 1089, 765 cm^{-1}; MS (ESI): *m*/*z* 235 (M + H)$^+$; HRMS (ESI): *m*/*z* calcd for $C_{14}H_{18}NaO_3$ (M + Na)$^+$: 257.1148, found: 257.1134.

*Methyl-3-(tert-butyldimethylsilyl)-2-oxo-2,6,7,7a-tetrahydro-1H-indene-5-carboxylate (**4c**).* Pale yellow liquid, R_f = 0.6 (EtOAc/hexanes = 2:8), 68 mg, 45%; ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.71 (s, 1H), 3.82 (s, 3H), 2.87−2.72 (m, 2H), 2.66 (dd, *J* = 7.4, 18.0 Hz, 1H), 2.55−2.41 (m, 1H), 2.31−2.17 (m, 1H), 2.12−1.99 (m, 1H), 1.52−1.39 (m, 1H), 0.88 (s, 9H), 0.29 (s, 6H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 211.8, 178.2, 167.0, 141.2, 138.0, 131.6, 52.2, 42.7, 39.5, 29.6, 28.6, 26.6, 25.7, −4.1, −4.5; IR (KBr): ν_{max} = 2951, 2928, 2855, 1717, 1691, 1549, 1254, 1188, 1082, 832, 766 cm^{-1}; MS (ESI): *m*/*z* 329 (M + Na)$^+$; HRMS (ESI): *m*/*z* calcd for $C_{17}H_{26}NaO_3Si$ (M + Na)$^+$: 329.1543, found: 329.1548.

*Methyl-4′,4′-dimethyl-2,2′,6′-trioxo-1-phenyl-3,3a,4,6-tetrahydro-2H-spiro[azulene-5,1′-cyclohexane]-7-carboxylate (**4d**).* Pale yellow solid, R_f = 0.4 (EtOAc/hexanes = 3:7), 146 mg, 72%; mp 168−170 °C; ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.57 (s, 1H), 7.49−7.37 (m, 3H), 7.34−7.27 (m, 2H), 3.75 (s, 3H), 3.51 (bs, 1H), 13.42 (d, *J* = 13.9 Hz, 1H), 3.10 (d, *J* = 14.6 Hz, 1H), 3.06−2.92 (m, 2H), 2.88 (d, *J* = 14.6 Hz, 1H), 2.60 (d, *J* = 13.9 Hz, 1H), 2.49 (d, *J* = 13.9 Hz, 1H), 2.39−2.20 (m, 3H), 1.12 (s, 3H), 0.90 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 208.5, 206.8, 205.3, 167.3, 165.9, 143.9, 134.2, 134.5, 130.2, 129.8, 128.8, 128.4, 67.8, 52.7, 50.9, 43.5, 36.5, 32.6, 31.5, 30.6, 29.6, 29.3, 27.4, 30.1; IR (KBr): ν_{max} = 2955, 2925, 2854, 1696, 1440, 1243, 1196, 1142, 969, 700 cm^{-1}; MS (ESI): *m*/*z* 407 (M + H)$^+$; HRMS (ESI): *m*/*z* calcd for $C_{25}H_{26}NaO_5$ (M + Na)$^+$: 429.1672, found: 429.1668.

*Methyl-4′,4′-dimethyl-2,2′,6′-trioxo-1-propyl-3,3a,4,6-tetrahydro-2H-spiro[azulene-5,1′-cyclohexane]-7-carboxylate (**4e**).* Pale yellow solid, R_f = 0.4 (EtOAc/hexanes = 3:7), 137 mg, 75%, mp 103−105 °C; ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.59 (bs, 1H), 3.84 (s, 3H), 3.35 (d, *J* = 14.7 Hz, 2H), 3.04 (d, *J* = 15.1 Hz, 1H), 2.98−2.74 (m, 3H), 2.64 (d, *J* = 15.1 Hz, 1H), 2.49 (d, *J* = 14.3 Hz, 1H), 2.36−2.00 (m, 5H), 1.57−1.33 (m, 2H), 1.09 (s, 3H), 1.01−0.76 (m, 6H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 208.5, 207.2, 206.9, 167.4, 165.2, 145.8, 133.3, 132.7, 67.8, 52.7, 50.8, 42.5, 36.3, 33.1, 30.5, 30.9, 29.6, 29.1, 27.6, 25.1, 22.1, 13.9; IR (KBr): ν_{max} = 2959, 2932, 2871, 1718, 1689, 1621, 1256, 1204, 1090, 773 cm^{-1}; MS (ESI): *m*/*z* 395 (M + Na)$^+$; HRMS (ESI): *m*/*z* calcd for $C_{22}H_{28}O_5Na$ (M + Na)$^+$: 395.1829, found: 395.1828.

*1′-tert-Butyl-7-methyl-2,2′-dioxo-1-phenyl-3,3a,4,6-tetrahydro-2H-spiro[azulene-5,3′-indoline]-1′,7-dicarboxylate (**4f**):).* Yellow syrup, R_f = 0.6 (EtOAc/hexanes = 2:8), 141 mg, 71%; d.r. = 8:2; ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.88−7.83 (m, 2H), 7.53−7.41 (m, 3H), 7.40−7.35 (m, 2H), 7.30 (dt, *J* = 8.6, 1.2 Hz, 1H), 7.08 (t, *J* = 7.5 Hz, 1H), 7.04−6.95 (m, 1H), 4.17−4.09 (m, 1H), 3.67 (s, 3H), 3.48 (t, *J* = 15.2 Hz, 1H), 3.06 (dd, *J* = 18.8, 6.9 Hz, 1H), 3.00 (d, *J* = 14.7 Hz, 1H), 2.31 (d, *J* = 14.7 Hz, 1H), 2.24 (td, *J* = 18.8, 3.7 Hz, 1H), 2.12−2.00 (m, 1H), 1.67 (s, 9H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 205.2, 178.5, 166.9, 166.2, 149.1, 144.3, 138.1, 135.4, 135.1, 132.3, 129.9, 128.5, 124.6, 122.5, 115.2, 84.8, 52.6, 50.1, 43.4, 40.0, 36.2, 33.4, 28.1; IR (KBr): ν_{max} = 3261, 2953, 1703, 1618, 1469, 1245, 1146, 753, 699 cm^{-1}; MS (ESI): *m*/*z* 522 (M + Na)$^+$; HRMS (ESI): *m*/*z* calcd for $C_{30}H_{29}O_6NNa$ (M + Na)$^+$: 522.1887, found: 522.1892.

*1′-tert-Butyl-7-methyl-2,2′-dioxo-1-propyl-3,3a,4,6-tetrahydro-2H-spiro[azulene-5,3′-indol-ine]-1′,7-dicarboxylate (**4g**).* Pale yellow syrup, R_f = 0.7 (EtOAc/hexanes = 2:8), 155 mg, 67%; d.r. = 9:1; ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.87 (bs, 1H), 7.84 (d, *J* = 8.2 Hz, 1H), 7.29 (dt, *J* = 7.6, 1.3 Hz, 1H), 7.09 (dt, *J* = 7.6, 1.0 Hz, 1H), 7.03 (dd, *J* = 7.6, 1.0 Hz, 1H), 3.94 (m, 1H), 3.73 (s, 3H), 3.40 (d, *J* = 14.8 Hz, 1H), 2.95 (d, *J* = 14.8 Hz, 1H), 2.87 (dd, *J* = 18.9, 6.8 Hz, 2H), 2.36 (t, *J* = 7.6 Hz, 2H), 2.01 (dd, *J* = 18.9, 3.3 Hz, 1H), 1.87 (dd, *J* = 14.8, 12.0 Hz, 1H), 1.66 (s, 9H), 1.56−1.48 (m, 2H), 0.96 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 207.2, 178.6, 167.2, 165.6, 149.1, 146.2, 138.1, 134.1, 133.6, 132.6, 128.5, 124.6, 122.5, 115.2, 84.7, 60.3, 52.7, 50.1, 42.4, 40.4, 36.2, 33.2, 29.6, 28.0, 25.3, 22.3, 14.0; IR (KBr): ν_{max} = 2960, 2928, 1718, 1469, 1249, 1152, 757 cm^{-1}; MS (ESI): *m*/*z* 488 (M + Na)$^+$; HRMS (ESI): *m*/*z* calcd for $C_{27}H_{31}NNaO_6$ (M + Na)$^+$: 488.2049, found: 488.2055.

*Methyl-5-oxo-4,6-diphenyl-1,5,6,6a-tetrahydropentalene-2-carboxylate (**4h**).* Pale yellow solid, R_f = 0.7 (EtOAc/hexanes = 2:8), 140 mg, 85%, mp 102−104 °C; d.r. = 7:3 (determined by ^{1}H NMR); ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.73−7.65 (m, 3H), 7.46−7.26 (m, 8H), 3.84 (s, 3H), 3.80−3.76 (m, 1H), 3.74−3.68 (m, 1H), 3.13 (ddd, *J* = 17.3, 7.3, 1.5 Hz, 1H), 2.72 (ddd, *J* = 17.3, 5.2, 2.4 Hz, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 205.4, 174.5, 148.8, 137.5, 134.6, 128.3, 128.2,

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128.0, 127.8, 126.8, 128.7, 127.8, 60.6, 52.6, 51.8, 35.7; IR (KBr): ν_{max} = 2952, 1709, 1441, 1263, 1117, 769, 698 cm^{-1}; MS (ESI): m/z 331 $(M + Na)^+$; HRMS (ESI): m/z calcd for $C_{22}H_{19}O_3$ $(M + H)^+$: 331.1328, found: 331.1340.

*Methyl-5-oxo-6-phenyl-4-propyl-1,5,6,6a-tetrahydropentalene-2-carboxylate (**4i**).* Colorless syrup, R_f = 0.7 (EtOAc/hexanes = 2:8), 103 mg, 70%; d.r. = 9:1; ^1H NMR ($CDCl_3$, 500 MHz): δ 7.34 (t, J = 7.0 Hz, 2H), 7.29−7.26 (m, 2H), 7.13 (d, J = 7.0 Hz, 2H), 3.84 (s, 3H), 3.29 (d, J = 4.4 Hz, 1H), 2.95−2.89 (m, 1H), 2.66 (dd, J = 14.0, 7.9 Hz, 1H), 2.42−2.28 (m, 2H), 2.14 (dd, J = 22.7, 8.8 Hz, 1H), 1.61 (quintet, J = 7.3 Hz, 2H), 0.97 (t, J = 7.3 Hz, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 207.8, 169.4, 168.0, 139.3, 138.0, 133.6, 130.1, 128.7, 128.1, 127.2, 66.1, 52.9, 44.9, 31.8, 26.2, 21.5, 14.0; IR (KBr): ν_{max} = 2960, 1715, 1443, 1256, 767, 701 cm^{-1}; MS (ESI): m/z 319 $(M + Na)^+$; HRMS (ESI): m/z calcd for $C_{19}H_{21}O_3$ $(M + H)^+$: 297.1485, found: 297.1490.

*Methyl-7-oxo-2,6-diphenyl-1,2,3,7,8,8a-hexahydrocyclopenta[c]-azepine-4-carboxylate (**4j**).* Pale brown solid, R_f = 0.5 (EtOAc/hexanes = 3:7), 132 mg, 74%, mp 165−167 °C; ^1H NMR ($CDCl_3$, 300 MHz): δ 7.63 (s, 1H), 7.47−7.34 (m, 3H), 7.33−7.20 (m, 4H), 6.77 (d, J = 8.6 Hz, 3H), 4.66 (d, J = 18.2 Hz, 2H), 4.52 (d, J = 18.2 Hz, 1H), 4.16 (dd, J = 12.2, 5.2 Hz, 1H), 3.84 (s, 3H), 3.72−3.57 (m, 1H), 2.91 (dd, J = 18.8, 6.7, Hz, 1H), 2.38 (dd, J = 18.8, 2.4 Hz, 1H), ; ^{13}C NMR ($CDCl_3$, 125 MHz): δ 205.1, 166.6, 164.3, 147.8, 144.1, 140.6, 135.7, 130.2, 129.7, 129.4, 128.9, 128.3, 117.7, 112.6, 55.1, 52.6, 47.1, 40.0, 38.9; IR (KBr): ν_{max} = 2919, 2851, 1698, 1596, 1502, 1272, 1235, 1144, 1076, 741 cm^{-1}; MS (ESI): m/z 382 $(M + Na)^+$; HRMS (ESI): m/z calcd for $C_{23}H_{22}NO_3$ $(M + H)^+$: 360.1594, found: 360.1599.

*Methyl-7-oxo-2-phenyl-6-propyl-1,2,3,7,8,8a-hexahydrocyclo-penta[c]azepine-4-carboxylate (**4k**).* Pale brown liquid, R_f = 0.5 (EtOAc/hexanes = 3:7), 112 mg, 69%; ^1H NMR ($CDCl_3$, 300 MHz): δ 7.69 (s, 1H), 7.28−7.17 (m, 2H), 6.80−6.67 (m, 3H), 4.67 (d, J = 18.1, 1H), 4.38 (d, J = 18.1, 1H), 4.18−4.03 (m, 2H), 3.91 (s, 3H), 3.58−3.45 (m, 1H), 3.14 (t, J = 12.8 Hz, 1H), 2.72 (dd, J = 18.8, 6.0 Hz, 1H), 2.33−2.11 (m, 2H), 1.49−1.31 (m, 2H), 0.87 (t, J = 7.5 Hz, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 207.0, 166.7, 163.8, 147.5, 146.7, 139.3, 134.4, 129.4, 117.4, 112.3, 54.9, 52.6, 46.5, 38.6, 29.6, 25.4, 21.9, 13.9; IR (KBr): ν_{max} = 2957, 2925, 2870, 1697, 1596, 1500, 1437, 1359, 1232, 1080, 752 cm^{-1}; MS (ESI): m/z 348 $(M + Na)^+$; HRMS (ESI): m/z calcd for $C_{20}H_{24}NO_3$ $(M + H)^+$: 326.1751, found: 326.1773.

*Methyl-2-(3,5-dimethoxyphenyl)-7-oxo-6-phenyl-1,2,3,7,8,8a-hexahydrocyclopenta[c]azepine-4-carboxylate (**4l**).* Pale brown solid, R_f = 0.6 (EtOAc/hexanes = 3:7), 146 mg, 70%, mp 156−158 °C; ^1H NMR ($CDCl_3$, 300 MHz): δ 7.62 (s, 1H), 7.45−7.37 (m, 3H), 7.31−7.25 (m, 2H), 6.03−5.96 (m, 2H), 5.94 (bs, 1H), 4.66 (d, J = 18.1 Hz, 1H), 4.46 (d, J = 18.1 Hz, 1H), 4.12 (q, J = 7.3 Hz, 1H), 3.82 (s, 3H), 3.76 (s, 6H), 3.69−3.60 (m, 1H), 3.32 (q, J = 12.5 Hz, 1H), 2.91 (dd, J = 18.9, 7.1 Hz, 1H), 2.35 (dd, J = 18.9, 2.4 Hz, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 205.0, 164.2, 161.7, 149.6, 144.2, 140.4, 135.8, 130.2, 129.7, 128.9, 128.3, 91.8, 89.8, 55.3, 52.6, 47.0, 39.9, 38.7; IR (neat): ν_{max} = 2928, 2846, 2194, 1715, 1610, 1459, 1202, 1152, 1067, 810 cm^{-1}; MS (ESI): m/z 420 $(M + H)^+$; HRMS (ESI): m/z calcd for $C_{25}H_{26}O_5N$ $(M + H)^+$: 420.1805, found: 420.1815.

*Methyl-2-allyl-7-oxo-6-phenyl-1,2,3,7,8,8a-hexahydrocyclo-penta[c]azepine-4-carboxylate (**4m**).* Red liquid, R_f = 0.6 (EtOAc/hexanes = 3:7), 104 mg, 65%; ^1H NMR ($CDCl_3$, 500 MHz): δ 7.64 (s, 1H), 7.47−7.37 (m, 5H), 5.91−5.82 (m, 1H), 5.25−5.16 (m, 2H), 3.89 (d, J = 17.5 Hz, 1H), 3.78−3.71 (m, 4H), 3.39−3.19 (m, 4H), 2.83 (dd, J = 18.6, 7.0 Hz, 1H), 2.66 (t, J = 11.4 Hz, 1H), 2.25 (dd, J = 18.7, 2.8 Hz, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 205.1, 166.6, 147.7, 144.0, 140.6, 136.5, 135.6, 130.2, 129.4, 128.4, 128.3, 117.6, 55.0, 52.5, 51.5, 47.1, 38.8, 29.6; IR (KBr): ν_{max} = 2923, 1703, 1605, 1437, 1255, 1141, 1075, 997, 699 cm^{-1}; MS (ESI): m/z 324 $(M + H)^+$; HRMS (ESI): m/z calcd for $C_{20}H_{22}NO_3$ $(M + H)^+$: 324.1594, found: 324.1599.

*(1S)-Methyl-1,2-dibenzyl-7-oxo-6-phenyl-1,2,3,7,8,8a-hexahydro-cyclopenta[c]azepine-4-carboxylate (**4n**).* Yellow syrup, R_f = 0.3 (EtOAc/hexanes = 3:7), 166 mg, 72%; $[\alpha]$: +3.25° (c1, CH_3Cl, 20 °C); ^1H NMR ($CDCl_3$, 300 MHz): δ 7.69 (d, J = 1.7 Hz, 1H), 7.57−7.40 (m, 5H), 7.35−7.21 (m, 4H), 7.14 (t, J = 7.3 Hz, 4H), 6.85 (dd, J = 7.5, 2.2 Hz, 2H), 4.00−3.83 (m, 2H), 3.73−3.62 (m, 4H), 3.50 (d, J = 13.0 Hz, 1H), 3.28−3.16 (m, 1H), 2.90−2.70 (m, 4H), 2.30 (d, J = 18.8 Hz, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 205.6, 167.0, 164.2, 142.9, 139.8, 138.9, 138.1, 134.7, 129.7, 129.6, 128.9, 128.5, 128.2, 128.0, 127.0, 126.2, 130.6, 71.0, 59.4, 52.1, 47.9, 45.6, 42.7, 40.7; IR (KBr): ν_{max} = 3026, 2921, 2850, 1698, 1493, 1436, 1252, 1143, 1066, 745, 698 cm^{-1}; MS (ESI): m/z 464 $(M + H)^+$; HRMS (ESI): m/z calcd for $C_{31}H_{30}NO_3$ $(M + H)^+$: 464.2220, found: 464.2222.

*Methyl-7-oxo-6-phenyl-3,7,8,8a-tetrahydro-1H-cyclopenta[c]-oxepine-4-carboxylate (**4o**).* Colorless syrup, R_f = 0.3 (EtOAc/hexanes = 3:7), 45 mg, 69%; ^1H NMR ($CDCl_3$, 300 MHz): δ 7.68 (s, 1H), 7.50−7.31 (m, 5H), 4.81 (d, J = 16.9 Hz, 1H), 4.64 (d, J = 16.9 Hz, 1H), 4.33 (q, J = 4.8 Hz, 1H), 3.77 (s, 3H), 3.62−3.45 (m, 2H), 2.88 (dd, J = 4.5, 18.5 Hz, 1H), 2.22 (d, J = 18.5 Hz, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 204.9, 166.1, 163.5, 143.7, 140.0, 134.4, 130.2, 129.7, 128.9, 128.3, 74.3, 67.9, 52.3, 41.6, 38.4; IR (KBr): ν_{max} = 3057, 2952, 2922, 2848, 1690, 1704, 1436, 1244, 1062, 697 cm^{-1}; MS (ESI): m/z 307 $(M + Na)^+$; HRMS (ESI): m/z calcd for $C_{17}H_{16}NaO_4$ $(M + Na)^+$ 307.0974, found: 307.0933.

*Methyl-7-oxo-6-propyl-3,7,8,8a-tetrahydro-1H-cyclopenta[c]-oxepine-4-carboxylate (**4p**).* Pale gray solid, R_f = 0.4 (EtOAc/hexanes = 3:7), 61 mg, 52%; mp 102−104; ^1H NMR ($CDCl_3$, 600 MHz): δ 7.73 (s, 1H), 4.83 (d, J = 17.6 Hz, 1H), 4.49 (d, J = 17.6 Hz, 1H), 4.25 (bs, 1H), 3.83 (s, 3H), 3.42−3.28 (m, 2H), 2.61 (dd, J = 4.8, 19.2 Hz, 1H), 2.40−2.23 (m, 2H), 2.01 (d, J = 18.4 Hz, 1H), 1.48 (t, J = 7.1 Hz, 2H), 0.91 (t, J = 7.1 Hz, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 205.6, 153.8, 146.6, 139.2, 133.0, 114.0, 74.3, 68.3, 52.5, 42.0, 37.6, 25.4, 22.0, 14.1; IR (KBr): ν_{max} = 2959, 1704, 1439, 1256, 1069, 763 cm^{-1}; MS (ESI): m/z 251 $(M + H)^+$; Anal. Calcd for $C_{14}H_{18}O_4$: C, 67.1; H: 7.2, found: C, 67.8, H, 7.0.

■ ASSOCIATED CONTENT

Supporting Information

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

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Notes

The authors declare no competing financial interest.

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