JOC The Journal of Organic Chemistry

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Access to Fused Tricyclic γ-Butyrolactones, A Natural Product-like Scaffold

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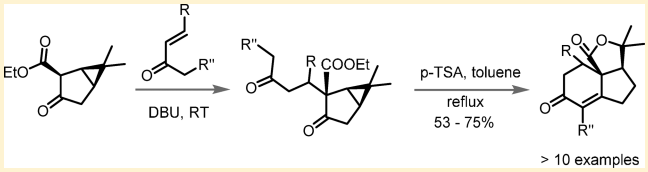
Supporting Information

ABSTRACT: Serendipitous findings of an acid mediated skeletal rearrangement of bicyclo-β-ketoester having cyclopropyl ring to access fused tricyclic γ-butyrolactones has been described. This novel transformation has been optimized to 30 mol% *p*-toluenesulfonic acid (*p*-TSA) in toluene using Dean–Stark apparatus, where the aldol condensation, cyclopropyl ring opening followed by cyclization took place in a single-pot operation. The resulting tricyclic compounds are interesting chemotype with natural product resemblance and may find useful applications in the future.



Greater than 10% of structurally elucidated natural products have a γ-butyrolactone core and it is also a common structural constituent of many organic compounds.[1] Monocyclic γ-butyrolactones having mono-, di-, and tri-substitution are well-known.[2] More complex scaffolds, such as bicyclic and tricyclic ring systems, are also found in the literature[3] (Figure 1). They show a broad range of interesting

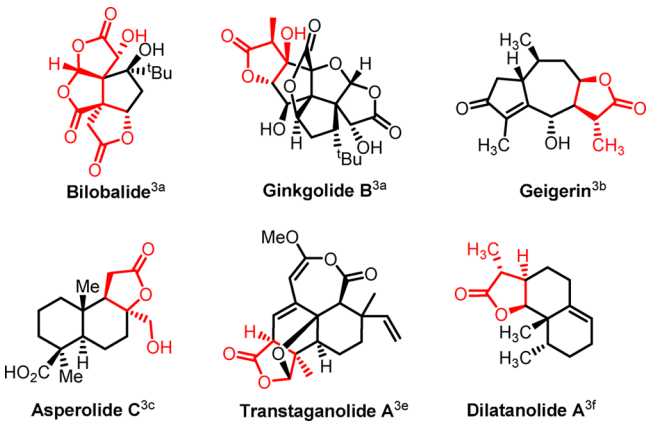


Figure 1. Selected natural products with γ-butyrolactone unit.

biological activities, such as antibiotic,[4] antihelmintic,[5] antifungal,[6] antitumor,[7] antiviral,[8] antiinflammatory,[9] and cytostatic properties.[10] Due to their diverse biological activities, γ-butyrolactones are interesting lead structures for developing new drugs. As a consequence many studies have been directed at increasing synthetic access to this class of compounds.[11] Along these lines, here we report a new method to access tricyclic γ-butyrolactones using skeletal rearrangements of fused cyclopropane systems. Cyclopropane derivatives are valuable starting points, when the strained three-membered ring is appropriately substituted for the rapid generation of molecular complexity. When compared to their corresponding acyclic counterparts or larger ring systems, cyclopropanes are synthetically more useful due to their high π character, characteristic angle, and torsional strain.[12]

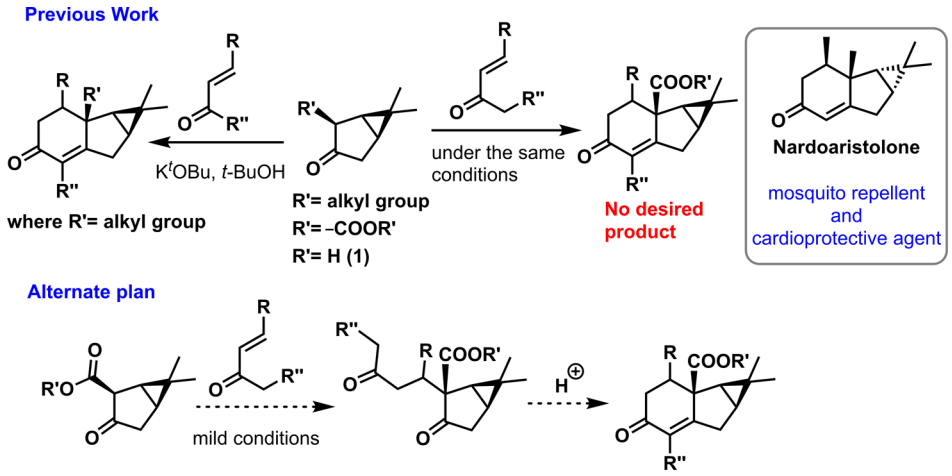
As part of our research groups interest, we have been working on generation of library of molecules around nardoaristolone,[13] a natural product with impressive insect repellent and cardio-protective activities. We have prepared several compounds starting from bicyclic ketone[14] derivatives obtained from 3-carene using Robinson annulation method (Scheme 1).[15] However, access to nardoaristolone analogues with angular carboxylic ester moiety using the same method proved to be difficult. This led us to plan a two-step protocol which involves base-mediated Michael adduct formation followed by acid-mediated aldol condensation to have desired bicyclic products.

As per the plan, starting from symmetric ketone (**1**), a bicyclo-β-ketoester (**2**) was synthesized by using reported procedures.[16] Then we found that DBU in ethanol solvent at room temperature is optimal condition for Michael addition with methyl vinyl ketone (**3a**) to furnish the 1,4-addition product (**4a**) in 80% yield (Table 1).[17] Then, we used the protocol developed by Sodeoka et al.[18] for intramolecular aldol condensation of **4a** with an equimolar concentration of pyrrolidine in acetic acid. However, the reaction was not successful and only staring material was recovered. Also we attempted the same reaction using *p*-toluenesulfonic acid in toluene at room temperature, still no significant change in reaction profile was observed. However, at varying reaction temperature (50 to 100 °C), formation of fused tricyclic compound (**5a**) was observed instead of nardoaristolone

Received: April 5, 2017
Published: June 21, 2017

DOI: 10.1021/acs.joc.7b00794
J. Org. Chem. 2017, 82, 7614–7620

Scheme 1. Background



analogue. The optimal condition for this product formation is Michael adduct (**4a**) in the presence of 30 mol% of *p*-toluenesulfonic acid in toluene at reflux temperature using Dean–Stark apparatus (Table 1). All the spectral data of compound **5a** are in agreement with the assigned structure. Although construction of desired nardoaristolone scaffold was not observed, the serendipitous formation of tricyclic compound **5a** is a pleasing outcome because a natural product-like structure was obtained through skeletal rearrangements.

The *cis* orientation between the ethyl ester group and cyclopropane unit of Michael adduct (**4a**) was confirmed by the NOE experiment (Table 1), which eventually supports the formation of fused tricyclic skeleton (**5a**). Then we looked at the literature and found that there are reports in literature[19a−g] where cyclopropane derivatives were used for natural product synthesis. Paquette described that the silyl-substituted cyclopropanes are the versatile intermediates in organic synthesis.[19h] However, formation of fused tricyclic γ-butyrolactones were not documented in the literature except for some similarity with the Corey's report where they have synthesized bicyclic bis-lactone by the skeletal rearrangement of cyclopropanes.[19i] The reaction was carried out by using Dean–Stark apparatus to remove the water and ethanol from the reaction mixture and to shift the equilibrium toward product formation. Having this protocol in hand, we became interested in testing the scope of the method and the results are compiled in Table 1.

Bicyclo-β-ketoester (**2**) on Michael addition with ethyl vinyl ketone using optimized reaction conditions gave compound **4b** in good yield (85%). The benzyl vinyl ketone underwent 1,4-addition reaction with **2** to afford the adduct **4c** in moderate yield (62%). The reactions of aryl vinyl ketones, such as 4-chloro, 4-methoxy, 4-methyl, and 2-bromo- compounds, also react with compound **2** and produce corresponding products (**4d–g**) in moderate yields (52–62%). Additionally, the substrate scope was extended to disubstituted Michael acceptor, such as (*E*)-3-pentene-2-one, 3-hexene-2-one and bicyclo-β-ketoester (**2**), to afford the corresponding Michael adducts (**4h** and **4ia**, **4ib**) in moderate to good yields (60–74%). Subsequently all the Michael adducts prepared were subjected to acid-mediated rearrangements using the optimized conditions for preparation of compound **5a**. The diketoester **4b** on treatment with *p*-TSA undergoes the aldol condensation-skeletal rearrangement to afford compound **5b** in 69% yield. To our delight, other Michael adducts (**4c–g**) smoothly undergo same transformation to give the corresponding tricyclic products (**5c–g**) in moderate yields (57–65%).

Encouraged by these results in hand, we extended the scope of the reaction to remaining Michael adducts (**4h**, **4ia**, and **4ib**) and found that all of them resulted in the formation of corresponding desired compounds (**5h**, **5ia**, and **5ib**) with tricyclic skeleton in 53–60% yields. Although, we are sure about the assigned structures to tricyclic compounds (**5a** to **5ib**), we wanted to establish the structural confirmation including stereochemistry without any ambiguity through a crystal structure analysis. For this purpose, compound **5h** was recrystallized using mixture of solvent (pet ether/ethyl acetate/dichloromethane) and **5ia** was recrystallized using ethanol to obtain suitable crystals for diffraction. The structure and relative stereochemistry of tricyclic skeleton in compound **5h** and **5ia** were confirmed through single crystal X-ray analysis (see Figure S1 and S2 of Supporting Information for the ORTEP diagram).

To understand more about the skeletal rearrangement, control experiments were performed to support the reaction mechanism which were described in Scheme S1 of Supporting Information. Based on control experiments (see Supporting Information, Scheme S1) plausible mechanistic pathways of the reaction are proposed in Scheme 2. First, an acid mediated aldol condensation of Michael adduct (**4a**) is expected under standard manner to give bicyclo enone (**12**). The cyclopropane ring opening in **12** to create carbocation followed by trapping with oxygen atom of ester moiety in a stepwise manner to afford fused tricyclic skeleton (**5a**). Alternatively, the formation of product (**5a**) can also be proposed in cascade process as described in Scheme 2.

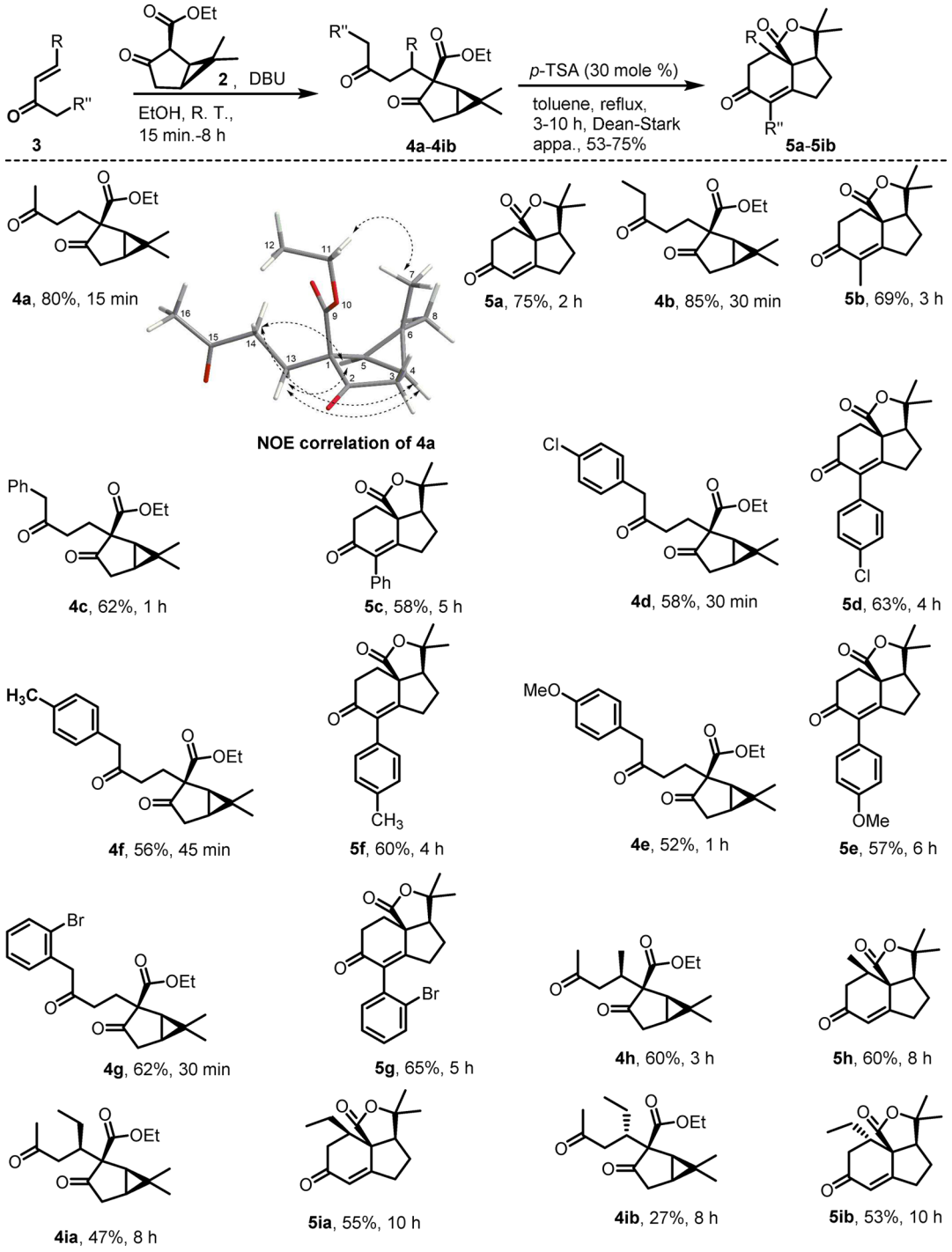
In summary, we have developed an interesting method for the synthesis of fused tricyclic skeleton having γ-butyrolactone core present in it. The scope of the developed method was tested with a variety of substrates. The final compounds from this method are interesting structural frameworks which resemble natural products and may be useful for the construction more complex molecules. Ultimately, all these compounds may find use in the field of medicinal chemistry.

EXPERIMENTAL SECTION

General Information. All reactions were carried out in oven-dried glassware under a positive pressure of argon or nitrogen unless otherwise mentioned with magnetic stirring. Air sensitive reagents and

DOI: 10.1021/acs.joc.7b00794
J. Org. Chem. 2017, 82, 7614−7620

Table 1. Scope of the Method



solutions were transferred via syringe or cannula and were introduced to the apparatus via rubber septa. All reagents, starting materials and solvents were obtained from commercial suppliers and used as such without further purification. Reactions were monitored by thin layer chromatography (TLC) with 0.25 mm precoated silica gel plates (60 F254). Visualization was accomplished with either UV light, or by immersion in ethanolic solution of phosphomolybdic acid (PMA), *para*-anisaldehyde, 2,4-DNP, $KMnO_4$ solution or iodine adsorbed on silica gel followed by heating with a heat gun for ~15 s. Column chromatography was performed on silica gel (100−200 or 230−400 mesh size). Melting points (mp) were determined using a Bruker capillary melting point apparatus and are uncorrected. *S**/*R** nomenclature has used to show the relative stereochemistry of product. Deuterated solvents for NMR spectroscopic analyses were used as received. All ^{1}H NMR and ^{13}C NMR spectra were obtained using a 400 or 500 MHz spectrometer. Coupling constants were measured in Hertz. Chemical shifts were quoted in ppm, relative to TMS, using the residual solvent peak as a reference standard. The following abbreviations were used to explain the multiplicities: s = singlet, d = doublet, dd = doublet of doublets, ddd = doublet of doublet of doublets, dddd = doublet of doublet of doublet of doublets, dt = doublet of triplets, t = triplet, td = triplet of doublets, q = quartet, m = multiplet. HRMS (ESI) were recorded on ORBITRAP mass analyzer (Thermo Scientific, QExactive). Infrared (IR) spectra were recorded on a FT-IR spectrometer as a thin film. Chemical nomenclature was generated using Chem Bio Draw Ultra 14.0.

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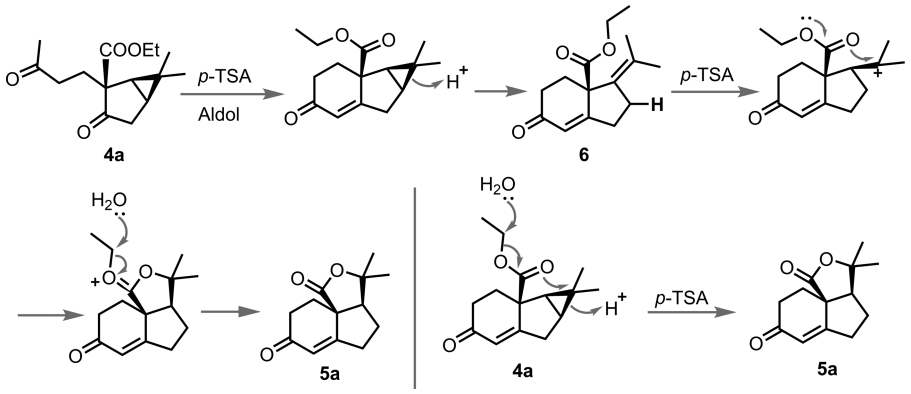
Scheme 2. Proposed Reaction Mechanism



Ethyl (1S,2S*,5S*)-6,6-Dimethyl-3-oxobicyclo[3.1.0]hexane-2-carboxylate (**2**).* A 100 mL flask was charged with diethyl carbonate (2.44 mL, 20.13 mmol) and 30 mL dry THF and NaH (57% suspension in mineral oil, 1.13 g, 27 mmol) was added to the mixture under stirring. The mixture was heated to reflux for 1 h, and then, a solution of symmetrical ketone **1** (1.0 g, 8.05 mmol) in anhydrous THF (10 mL) was added dropwise to the mixture for a period of 0.5 h. The mixture was refluxed for an additional 1.5 h. After complete consumption of starting material (monitored by TLC), the mixture was cooled to room temperature and hydrolyzed by 3N hydrochloric acid, then poured into water, extracted by CH_2Cl_2 (40 mL × 3). The combined organic layer was dried and evaporated to give the crude product which was purified by column chromatography using silica gel (petroleum ether/ethyl acetate, 95:5, v/v as a eluent) to afford the desired product **2** as a colorless liquid (1.26 g, 80%). IRυ_{max}(film): 2985, 1754, 1716, 1280, 762 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 4.19 (q, J = 7.1 Hz, 2H), 3.06 (s, 1H), 2.70 (dd, J = 20.0, 6.6 Hz, 1H), 2.27 (d, J = 19.9 Hz, 1H), 1.57 (d, J = 7.8 Hz, 1H), 1.45 (t, J = 7.2 Hz, 1H), 1.27 (t, J = 7.1 Hz, 3H), 1.11 (s, 3H), 0.87 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 213.2, 168.8, 61.7, 54.9, 38.6, 27.8, 26.9, 23.4, 20.1, 14.5, 14.3; HRMS (ESI) m/z calcd for $C_{11}H_{17}O_3$ $[M+H]^+$: 197.1178, found: 197.1179.

*General Experimental Procedure for Michael Addition Reaction of Bicyclo-β-ketoester (**2**) and Enones (**3**).* 1,8-Diazabicyclo[5.4.0]-undec-7-ene (DBU, 0.12 M) was added dropwise to a mixture of bicyclo-β-ketoester (**2**, 0.48 M) and Michael acceptor (**3**, 0.57 M) in 8 mL of absolute ethanol at room temperature and the resultant yellow mixture was allowed to stir under an argon atmosphere until the disappearance of starting material (15 min−8 h) in TLC was observed. After removal of the solvent under reduced pressure, the resulting crude product was purified by silica gel column chromatography (petroleum ether/ethyl acetate, 93:7, v/v as a eluent) to afford the desired Michael adduct **4** in moderate to good yields (52−85%).

Ethyl (1R,2S*,5S*)-6,6-Dimethyl-3-oxo-2-(3-oxobutyl)bicyclo-[3.1.0]hexane-2-carboxylate (**4a**).* Yield 80% (780 mg); yellowish oily liquid; IRυ_{max}(film): 3023, 1755, 1717, 1238, 759 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 4.23−4.11 (m, 2H), 2.70−2.55 (m, 2H), 2.47 (ddd, J = 18.1, 9.4, 5.9 Hz, 1H), 2.28 (d, J = 11.9 Hz, 1H), 2.11 (s, 3H), 2.09−2.01 (m, 2H), 1.35 (d, J = 7.6 Hz, 1H), 1.27 (dt, J = 10.6, 6.9 Hz, 4H), 1.07 (s, 3H), 0.86 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 212.4, 207.4, 170.7, 61.2, 58.9, 38.4, 37.8, 33.8, 31.5, 30.1, 27.3, 20.9, 20.2, 15.8, 14.3; HRMS (ESI) m/z calcd for $C_{15}H_{23}O_4$ $[M+H]^+$: 267.1597, found: 267.1598.

Ethyl (1R,2S*,5S*)-6,6-Dimethyl-3-oxo-2-(3-oxopentyl)bicyclo-[3.1.0]hexane-2-carboxylate (**4b**).* Yield 85% (395 mg); yellowish oily liquid; IRυ_{max}(film): 2978, 1758, 1718, 1278, 756 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 4.24−4.11 (m, 2H), 2.67 (dd, J = 19.9, 6.4 Hz, 1H), 2.61−2.52 (m, 1H), 2.47 (dd, J = 9.2, 6.3 Hz, 1H), 2.40 (q, J = 7.3 Hz, 2H), 2.30 (d, J = 19.9 Hz, 1H), 2.15−2.03 (m, 2H), 1.36 (d, J = 7.6 Hz, 1H), 1.31−1.25 (m, 4H), 1.08 (s, 3H), 1.02 (t, J = 7.3 Hz, 3H), 0.87 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 212.3, 210.1, 170.7, 61.1, 59.1, 37.8, 37.1, 36.1, 33.8, 31.6, 27.3, 20.9, 20.2, 15.8, 14.3, 7.9; HRMS (ESI) m/z calcd for $C_{16}H_{25}O_4$ $[M+H]^+$: 281.1747, found: 281.1746.

Ethyl (1R,2S*,5S*)-6,6-Dimethyl-3-oxo-2-(3-oxo-4-phenylbutyl)-bicyclo[3.1.0]hexane-2-carboxylate (**4c**).* Yield 62% (185 mg); yellowish oily liquid; IRυ_{max}(film): 3021, 2955, 1756, 1720, 1216, 761 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.33 (dd, J = 14.9, 7.7 Hz, 2H), 7.26 (dd, J = 9.4, 4.4 Hz, 1H), 7.19 (d, J = 7.4 Hz, 2H), 4.20−4.11 (m, 2H), 3.68 (s, 2H), 2.68−2.60 (m, 2H), 2.57−2.48 (m, 1H), 2.29 (d, J = 19.9 Hz, 1H), 2.11−2.06 (m, 2H), 1.32 (d, J = 7.6 Hz, 1H), 1.27 (t, J = 5.2 Hz, 1H), 1.24 (t, J = 7.2 Hz, 3H), 1.07 (s, 3H), 0.87 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 212.3, 206.9, 170.6, 134.1, 129.6 (2C), 128.8 (2C), 127.2, 61.1, 59.0, 50.2, 37.8, 36.9, 33.7, 31.6, 27.3, 20.9, 20.2, 15.8, 14.2; HRMS (ESI) m/z calcd for $C_{21}H_{27}O_4$ $[M+H]^+$: 343.1904, found: 343.1902.

Ethyl (1R,2S*,5S*)-2-(4-(4-Chlorophenyl)-3-oxobutyl)-6,6-dimethyl-3-oxobicyclo[3.1.0]hexane-2-carboxylate (**4d**).* Yield 58% (170 mg); yellowish oily liquid; IRυ_{max}(film): 3019, 2957, 1754, 1722, 1211, 759 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.30 (d, J = 8.1 Hz, 2H), 7.12 (d, J = 8.0 Hz, 2H), 4.23−4.10 (m, 2H), 3.67 (s, 2H), 2.70−2.62 (m, 2H), 2.58−2.49 (m, 1H), 2.31 (d, J = 19.9 Hz, 1H), 2.10 (dd, J = 14.1, 6.4 Hz, 2H), 1.33 (t, J = 7.4 Hz, 1H), 1.26 (q, J = 7.5 Hz, 4H), 1.09 (s, 3H), 0.88 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 212.3, 206.4, 170.6, 133.1, 132.5, 130.9 (2C), 128.9 (2C), 61.2, 58.9, 49.2, 37.8, 37.1, 33.8, 31.5, 27.2, 20.9, 20.2, 15.8, 14.2; HRMS (ESI) m/z calcd for $C_{21}H_{26}ClO_4$ $[M+H]^+$: 377.1514, found: 377.1514.

Ethyl (1R,2S*,5S*)-2-(4-(4-Methoxyphenyl)-3-oxobutyl)-6,6-dimethyl-3-oxobicyclo[3.1.0]hexane-2-carboxylate (**4e**).* Yield 52% (110 mg); off white solid; mp 64−66 °C; IRυ_{max}(film): 3024, 2959, 1752, 1718, 1324, 1218, 763 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.08 (d, J = 8.1 Hz, 2H), 6.84 (d, J = 8.1 Hz, 2H), 4.15−4.12 (m, 2H), 3.77 (s, 3H), 3.60 (s, 2H), 2.61 (dt, J = 12.4, 6.9 Hz, 2H), 2.53−2.45 (m, 1H), 2.27 (d, J = 19.9 Hz, 1H), 2.06 (d, J = 5.6 Hz, 2H), 1.31−1.26 (m, 2H), 1.24−1.20 (m, 3H), 1.05 (s, 3H), 0.85 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 212.3, 207.4, 170.6, 158.8, 130.5 (2C), 126.1, 114.2 (2C), 61.1, 59.0, 55.3, 49.2, 37.8, 36.7, 33.6, 31.6, 27.2, 20.9, 20.2, 15.8, 14.2; HRMS (ESI) m/z calcd for $C_{22}H_{29}O_5$ $[M+H]^+$: 373.2010, found: 373.2008.

Ethyl (1R,2S*,5S*)-6,6-Dimethyl-3-oxo-2-(3-oxo-4-(p-tolyl)-butyl)bicyclo[3.1.0]hexane-2-carboxylate (**4f**).* Yield 56% (200 mg); yellowish oily liquid; IRυ_{max}(film): 3024, 2958, 1759, 1723, 1219, 764 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.14 (d, J = 7.9 Hz, 2H), 7.08 (d, J = 7.9 Hz, 2H), 4.25−4.11 (m, 2H), 3.65 (s, 2H), 2.69−2.60 (m, 2H), 2.57−2.49 (m, 1H), 2.36−2.33 (m, 4H), 2.09 (ddd, J = 8.9, 6.6, 2.4 Hz, 2H), 1.35−1.28 (m, 2H), 1.25 (t, J = 7.1 Hz, 3H), 1.09 (s, 3H), 0.89 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 212.3, 207.2, 170.6, 136.8, 131.0, 129.5 (2C), 129.4 (2C), 61.1, 59.0, 49.8, 37.8, 36.8, 33.6, 31.6, 27.2, 21.2, 20.9, 20.2, 15.8, 14.2; HRMS (ESI) m/z calcd for $C_{22}H_{29}O_4$ $[M+H]^+$: 357.2060, found: 357.2058.

Ethyl (1R,2S*,5S*)-2-(4-(2-Bromophenyl)-3-oxobutyl)-6,6-dimethyl-3-oxobicyclo[3.1.0]hexane-2-carboxylate (**4g**).* Yield 62% (245 mg); yellowish oily liquid; IRυ_{max}(film): 3022, 2956, 1757, 1721, 1217, 1208, 762 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.55 (d, J = 7.9 Hz, 1H), 7.27 (t, J = 7.4 Hz, 1H), 7.21 (d, J = 7.5 Hz, 1H), 7.13

DOI: 10.1021/acs.joc.7b00794
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(t, J = 7.6 Hz, 1H), 4.23−4.12 (m, 2H), 3.89−3.81 (m, 2H), 2.73−2.64 (m, 2H), 2.61−2.54 (m, 1H), 2.30 (d, J = 19.9 Hz, 1H), 2.18−2.09 (m, 2H), 1.35 (d, J = 7.6 Hz, 1H), 1.27 (dt, J = 14.1, 7.0 Hz, 4H), 1.08 (s, 3H), 0.87 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 212.2, 205.5, 170.6, 134.6, 132.8, 131.9, 128.9, 127.7, 125.0, 61.1, 58.9, 50.1, 37.8, 37.4, 33.6, 31.5, 27.2, 20.9, 20.2, 15.8, 14.2; HRMS (ESI) m/z calcd for $C_{21}H_{26}BrO_4[M+H]^+$: 421.1009, found: 421.1008.

Ethyl (1R,2S*,5S*)-6,6-Dimethyl-3-oxo-2-((R)-4-oxopentan-2-yl)bicyclo[3.1.0]hexane-2-carboxylate (**4h**).* Yield 60% (370 mg); yellowish oily liquid; IRυ_{max}(film): 2980, 1755, 1720, 1279, 761 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.23−4.09 (m, 2H), 2.94 (dd, J = 17.5, 3.9 Hz, 1H), 2.73−2.65 (m, 1H), 2.60 (dd, J = 19.9, 6.6 Hz, 1H), 2.30 (d, J = 20.0 Hz, 1H), 2.27−2.20 (m, 1H), 2.12 (s, 3H), 1.42 (d, J = 7.4 Hz, 1H), 1.27 (dd, J = 13.7, 6.7 Hz, 4H), 1.11 (s, 3H), 0.98 (d, J = 6.8 Hz, 3H), 0.81 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 212.5, 207.3, 170.1, 63.1, 61.0, 46.1, 39.4, 36.5, 32.0, 30.5, 27.4, 20.5, 20.5, 16.4, 15.9, 14.3; HRMS (ESI) m/z calcd for $C_{16}H_{25}O_4$ $[M+H]^+$: 281.1747, found: 281.1747.

Ethyl (1R,2S*,5S*)-6,6-Dimethyl-3-oxo-2-((R)-5-oxohexan-3-yl)-bicyclo[3.1.0]hexane-2-carboxylate (**4ia**).* Yield 47% (105 mg); yellowish oily liquid; IRυ_{max}(film): 2983, 1757, 1723, 1274, 764 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.19−4.06 (m, 2H), 3.24 (dd, J = 18.8, 6.5 Hz, 1H), 2.69 (dd, J = 19.7, 6.6 Hz, 1H), 2.55−2.49 (m, 1H), 2.24 (d, J = 19.8 Hz, 2H), 2.12 (s, 3H), 1.73−1.63 (m, 2H), 1.46 (d, J = 7.6 Hz, 1H), 1.26 (t, J = 7.2 Hz, 4H), 1.10 (s, 3H), 0.85 (t, J = 7.3 Hz, 3H), 0.77 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 212.5, 207.9, 169.8, 63.1, 60.9, 43.4, 42.4, 39.1, 32.5, 30.2, 27.4, 24.2, 20.5, 20.1, 15.9, 14.3, 12.5; HRMS (ESI) m/z calcd for $C_{17}H_{27}O_4$ $[M+H]^+$: 295.1904, found: 295.1903.

Ethyl (1R,2S*,5S*)-6,6-Dimethyl-3-oxo-2-((S)-5-oxohexan-3-yl)-bicyclo[3.1.0]hexane-2-carboxylate (**4ib**).* Yield 27% (60 mg); yellowish oily liquid; IRυ_{max}(film): 2985, 1758, 1721, 1272, 766 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.15−3.99 (m, 2H), 3.06 (dd, J = 18.7, 5.3 Hz, 1H), 2.63−2.58 (m, 1H), 2.46 (dd, J = 20.2, 6.6 Hz, 1H), 2.32−2.22 (m, 2H), 2.12 (d, J = 4.2 Hz, 3H), 1.97−1.90 (m, 1H), 1.42 (d, J = 7.5 Hz, 1H), 1.30 (dd, J = 13.4, 6.3 Hz, 1H), 1.26 (t, J = 7.1 Hz, 3H), 1.10 (s, 3H), 0.98−0.89 (m, 1H), 0.84 (t, J = 7.2 Hz, 3H), 0.80 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 213.4, 207.4, 170.8, 61.9, 61.1, 43.7, 43.2, 40.4, 34.1, 30.2, 27.3, 23.8, 21.2, 20.7, 15.6, 14.2, 12.5; HRMS (ESI) m/z calcd for $C_{17}H_{27}O_4$ $[M+H]^+$: 295.1904, found: 295.1904.

General Experimental Procedure for Aldol Condensation Followed by Skeletal Rearrangement of Cyclopropyl Ring. To a stirred solution of Michael adduct (**4a**, 0.32 M) in toluene (8 mL) was added *p*-toluenesulfonic acid (0.096 M) at room temperature. The reaction mixture was heated at 125−130 °C for a period of 2−10 h. Dean−Stark apparatus was used to remove the water and ethanol formed in the reaction mixture. The progress of reaction was monitored by TLC, after complete consumption of starting material the reaction mass was concentrated under reduced pressure to afford the crude product. It was purified by silica gel column chromatography (petroleum ether/ethyl acetate, 80:20, v/v as a eluent) to afford the desired fused tricyclic skeleton (**5a**) in good yield (75%). The same procedure has been followed for the other Michael adducts (**4b**−**ib**) to afford the desired fused tricyclic skeleton (**5b**−**ib**) in moderate to good yields (53−69%).

(3aS,9aS*)-3,3-Dimethyl-3,3a,4,5,8,9-hexahydro-1H,7H-indeno-[1,7a-c]furan-1,7-dione (**5a**).* Yield 75% (40 mg); colorless solid; mp 114−116 °C; IRυ_{max}(film): 2975, 1753, 1666, 1269, 772 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.99 (s, 1H), 3.14 (ddd, J = 17.6, 14.3, 5.6 Hz, 1H), 2.55 (ddd, J = 13.3, 5.6, 1.8 Hz, 1H), 2.51−2.45 (m, 3H), 2.36 (ddd, J = 17.6, 5.0, 1.5 Hz, 1H), 2.23−2.14 (m, 1H), 2.10 (ddd, J = 14.9, 7.7, 4.0 Hz, 1H), 1.90 (dddd, J = 14.0, 10.3, 9.6, 8.3 Hz, 1H), 1.53 (s, 3H), 1.47 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 198.3, 175.2, 166.1, 123.8, 84.6, 56.1, 54.8, 33.3, 33.1, 32.4, 31.5, 26.2, 24.7; HRMS (ESI) m/z calcd for $C_{13}H_{17}O_3$ $[M+H]^+$: 221.1178, found: 221.1179.

(3aS,9aS*)-3,3,6-Trimethyl-3,3a,4,5,8,9-hexahydro-1H,7H-indeno[1,7a-c]furan-1,7-dione (**5b**).* Yield 69% (60 mg); white crystalline solid; mp 108−110 °C; IRυ_{max}(film): 2978, 1751, 1664, 1267, 769 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.09 (ddd, J = 17.9, 14.4, 5.6 Hz, 1H), 2.63−2.55 (m, 1H), 2.53−2.44 (m, 2H), 2.42−2.34 (m, 2H), 2.17 (td, J = 13.7, 5.2 Hz, 1H), 2.06−1.89 (m, 2H), 1.78 (s, 3H), 1.52 (s, 3H), 1.45 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 197.8, 175.7, 159.6, 130.4, 84.2, 56.8, 55.5, 33.2, 32.9, 30.8, 30.4, 26.4, 24.9, 12.24; HRMS (ESI) m/z calcd for $C_{14}H_{19}O_3$ $[M+H]^+$: 235.1329, found: 235.1329.

(3aS,9aS*)-3,3-Dimethyl-6-phenyl-3,3a,4,5,8,9-hexahydro-1H,7H-indeno[1,7a-c]furan-1,7-dione (**5c**).* Yield 58% (40 mg); off white solid; mp 176−178 °C; IRυ_{max}(film): 2978, 1750, 1675, 1465, 1266, 755 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.39−7.28 (m, 3H), 7.15 (d, J = 6.9 Hz, 2H), 3.33 (ddd, J = 17.8, 14.4, 5.6 Hz, 1H), 2.61 (ddd, J = 16.5, 9.1, 6.0 Hz, 2H), 2.54 (d, J = 2.3 Hz, 1H), 2.48−2.40 (m, 2H), 2.39−2.32 (m, 1H), 2.10−2.03 (m, 1H), 1.85 (ddd, J = 18.9, 13.9, 9.5 Hz, 1H), 1.58 (s, 3H), 1.50 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 196.4, 175.5, 161.4, 135.5, 134.7, 129.9, 128.0 (2C), 127.8 (2C), 84.5, 56.6, 55.0, 33.4, 32.8, 31.8, 31.6, 26.5, 24.7; HRMS (ESI) m/z calcd for $C_{19}H_{21}O_3$ $[M+H]^+$: 297.1485, found: 297.1485.

(3aS,9aS*)-6-(4-Chlorophenyl)-3,3-dimethyl-3,3a,4,5,8,9-hexahydro-1H,7H-indeno[1,7a-c]furan-1,7-dione (**5d**).* Yield 63% (25 mg); yellowish solid; mp 186−188 °C; IRυ_{max}(film): 2967, 1753, 1678, 1472, 1269, 759 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.32 (d, J = 8.1 Hz, 2H), 7.07 (d, J = 8.1 Hz, 2H), 3.34−3.25 (m, 1H), 2.63−2.54 (m, 2H), 2.52 (d, J = 3.3 Hz, 1H), 2.42 (dd, J = 8.8, 5.9 Hz, 2H), 2.33 (td, J = 13.8, 5.1 Hz, 1H), 2.05 (dd, J = 9.3, 3.8 Hz, 1H), 1.89−1.79 (m, 1H), 1.56 (s, 3H), 1.48 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 196.1, 175.3, 161.9, 134.5, 133.8, 133.0, 131.4 (2C), 128.3 (2C), 84.6, 56.7, 54.9, 33.3, 32.7, 31.8, 31.6, 26.5, 24.7; HRMS (ESI) m/z calcd for $C_{19}H_{20}ClO_3$ $[M+H]^+$: 331.1095, found: 331.1096.

(3aS,9aS*)-6-(4-Methoxyphenyl)-3,3-dimethyl-3,3a,4,5,8,9-hexahydro-1H,7H-indeno[1,7a-c]furan-1,7-dione (**5e**).* Yield 57% (65 mg); yellowish solid; mp 172−174 °C; IRυ_{max}(film): 2978, 1749, 1672, 1461, 1263, 751 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.05 (d, J = 7.8 Hz, 2H), 6.88 (d, J = 7.9 Hz, 2H), 3.80 (s, 3H), 3.33−3.24 (m, 1H), 2.61−2.40 (m, 5H), 2.36−2.28 (m, 1H), 2.03 (d, J = 4.1 Hz, 1H), 1.87−1.76 (m, 1H), 1.55 (s, 3H), 1.47 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 196.6, 175.6, 160.9, 159.01, 134.9, 131.2 (2C), 126.8, 113.5 (2C), 84.5, 56.6, 55.3, 54.9, 33.4, 32.7, 31.8, 31.6, 26.5, 24.7. HRMS (ESI) m/z calcd for $C_{20}H_{23}O_4$ $[M+H]^+$: 327.1591, found: 327.1591.

(3aS,9aS*)-3,3-Dimethyl-6-(p-tolyl)-3,3a,4,5,8,9-hexahydro-1H,7H-indeno[1,7a-c]furan-1,7-dione (**5f**).* Yield 60% (75 mg); yellowish solid; mp 176−178 °C; IRυ_{max}(film): 2969, 1756, 1676, 1474, 1270, 753 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.16 (d, J = 7.7 Hz, 2H), 7.02 (d, J = 7.7 Hz, 2H), 3.34−3.25 (m, 1H), 2.62−2.50 (m, 3H), 2.48−2.42 (m, 2H), 2.37−2.29 (m, 4H), 2.06−2.01 (m, 1H), 1.82 (ddd, J = 19.3, 13.8, 9.6 Hz, 1H), 1.55 (s, 3H), 1.47 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 196.5, 175.6, 161.1, 137.5, 135.4, 131.6, 129.8 (2C), 128.7 (2C), 84.5, 56.6, 54.9, 33.3, 32.7, 31.8, 31.6, 26.4, 24.7, 21.3; HRMS (ESI) m/z calcd for $C_{20}H_{23}O_3$ $[M+H]^+$: 311.1642, found: 311.1643.

(3aS,9aS*)-6-(2-Bromophenyl)-3,3-dimethyl-3,3a,4,5,8,9-hexahydro-1H,7H-indeno[1,7a-c]furan-1,7-dione (**5g**).* Yield 65% (85 mg); yellowish solid; mp 126−128 °C; IRυ_{max}(film): 2978, 2933, 1751, 1676, 1468, 1267, 1028, 963, 753 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.60−7.54 (m, 1H), 7.31 (dd, J = 13.1, 5.8 Hz, 1H), 7.20−6.99 (m, 2H), 3.42−3.19 (m, 1H), 2.65−2.49 (m, 3H), 2.45−2.35 (m, 1H), 2.34−2.22 (m, 2H), 2.08−1.86 (m, 2H), 1.57 (s, 3H), 1.46 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 195.3, 175.2, 162.5, 136.3, 133.0, 132.4, 131.8, 129.6, 127.6, 123.0, 84.5, 56.7, 55.4, 33.1, 32.7, 31.4, 31.3, 26.3, 24.7; HRMS (ESI) m/z calcd for $C_{19}H_{20}BrO_3$ $[M+H]^+$: 377.0570, found: 377.0564.

(3aS,9R*,9aS*)-3,3,9-Trimethyl-3,3a,4,5,8,9-hexahydro-1H,7H-indeno[1,7a-c]furan-1,7-dione (**5h**).* Yield 60% (40 mg); off white solid; mp 136−138 °C; IRυ_{max}(film): 2977, 1753, 1662, 1264, 762 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.99 (s, 1H), 3.11 (dd, J = 18.4, 14.3 Hz, 1H), 2.64 (d, J = 8.6 Hz, 1H), 2.57−2.41 (m, 2H), 2.31−2.26 (m, 2H), 2.16 (dd, J = 13.5, 6.9 Hz, 1H), 1.81−1.71 (m, 1H), 1.55 (s, 3H), 1.47 (s, 3H), 1.21 (d, J = 6.4 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 198.9, 174.2, 166.2, 123.5, 84.6, 60.9, 51.9, 40.8, 38.5, 33.8,

DOI: 10.1021/acs.joc.7b00794
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31.3, 27.2, 24.6, 18.5; HRMS (ESI) m/z calcd for $C_{14}H_{19}O_3$ $[M+H]^+$: 235.1329, found: 235.1329.

(3aS,9R*,9aS*)-9-Ethyl-3,3-dimethyl-3,3a,4,5,8,9-hexahydro-1H,7H-indeno[1,7a-c]furan-1,7-dione (**5ia**).* Yield 55% (25 mg); yellowish solid; mp 126−128 °C; IRυ_{max}(film): 2981, 1756, 1665, 1267, 768 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 6.00 (s, 1H), 2.99−2.93 (m, 1H), 2.68 (d, J = 5.7 Hz, 1H), 2.52−2.47 (m, 3H), 2.16−2.02 (m, 2H), 1.82−1.76 (m, 2H), 1.59 (s, 3H), 1.46 (s, 3H), 1.39 (s, 1H), 0.98 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 199.1, 166.4, 123.5 (2C), 84.6, 60.9, 51.8, 44.9, 37.0, 33.9, 31.3, 27.3, 25.3, 24.6, 11.3; HRMS (ESI) m/z calcd for $C_{15}H_{21}O_3$ $[M+H]^+$: 249.1485, found: 249.1486.

(3aS,9S*,9aS*)-9-Ethyl-3,3-dimethyl-3,3a,4,5,8,9-hexahydro-1H,7H-indeno[1,7a-c]furan-1,7-dione (**5ib**).* Yield 53% (15 mg); yellowish solid; mp 92−94 °C; IRυ_{max}(film): 2983, 1754, 1668, 1265, 762 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 6.00 (s, 1H), 3.36 (dd, J = 17.6, 4.9 Hz, 1H), 2.80 (dd, J = 8.7, 5.2 Hz, 1H), 2.57−2.41 (m, 4H), 2.09−1.98 (m, 2H), 1.93−1.82 (m, 1H), 1.51 (s, 3H), 1.47 (s, 3H), 1.21 (d, J = 7.8 Hz, 1H), 0.95 (t, J = 7.4 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 197.9, 175.2, 163.9, 124.1, 83.8, 61.7, 50.9, 42.3, 36.0, 32.2, 30.7, 26.9, 24.7, 22.5, 11.9. HRMS (ESI) m/z calcd for $C_{15}H_{21}O_3$ $[M+H]^+$: 249.1485, found: 249.1486.

*Ethyl 6-oxo-3-(Propan-2-ylidene)-1,2,3,4,5,6-hexahydro-3aH-indene-3a-carboxylate (**6**).* Yield 15% (35 mg); yellowish oily liquid; IRυ_{max}(film): 2980, 1747, 1662, 942, 768 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 5.88 (s, 1H), 4.12 (d, J = 5.9 Hz, 2H), 3.06−2.92 (m, 2H), 2.73−2.50 (m, 3H), 2.36 (d, J = 16.4 Hz, 2H), 1.82 (d, J = 10.0 Hz, 1H), 1.75 (s, 3H), 1.66 (s, 3H), 1.22 (t, J = 6.4 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 199.4, 171.2, 171.1, 134.8, 129.2, 122.5, 61.4, 54.7, 34.7, 33.3, 31.9, 29.6, 22.9, 20.2, 14.1. HRMS (ESI) m/z calcd for $C_{15}H_{20}O_3Na$ $[M+Na]^+$: 271.1305, found: 271.1302.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.7b00794.

^1H and ^{13}C NMR spectra of all compounds, COSY and NOESY spectrum of compound **4a** (PDF)

X-ray crystallographic data for **5h** (CIF)

X-ray crystallographic data for **5ia** (CIF)

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Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

We acknowledge the Council of Scientific and Industrial Research (CSIR), New Delhi, for the financial support through NCL-IGIB Joint Research Program (BSC-0124) and ORIGIN (CSC-0108). Dr. Rajesh Gonnade, Mr. Samir Shaikh, and Mis. Ekta Sangtani of the Center for Materials Characterization (CSIR-NCL, Pune) for the single crystal X-ray analysis. We thank Prof. Santosh Gharpure of IIT Bombay, Mumbai for useful discussions. H.P.K. thanks SERB for the award of National Postdoctoral Fellowship (N-PDF) and K.L.H. thanks CSIR, New Delhi, for the award of senior research fellowship.

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