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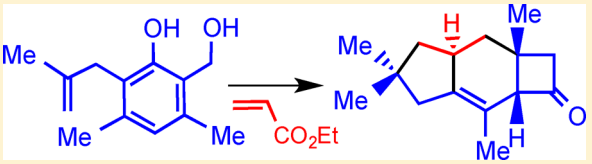
Cycloaddition of Spiroepoxycyclohexa-2,4-dienones, Radical Cyclization and 1,3-Acyl Shift in Excited State: Aromatics to Sterpuren-4-one

Raghaba Sahu and Vishwakarma Singh*

Department of Chemistry, Indian Institute of Technology Bombay, Mumbai 400076, India

Supporting Information

ABSTRACT: A stereoselective route to sterpuren-4-one from a simple aromatic precursor is presented. Oxidative dearomatization, π^4s + π^2s cycloaddition of 6,6-spiroepoxycyclohexa-2,4-dienones with ethyl acrylate, radical cyclization and 1,3-acyl shift in excited state are the important aspects of our approach. An interesting effect of a remote substituent on radical cyclization has also been presented.



INTRODUCTION

Sterpuranes are a unique class of sesquiterpenoids whose molecular architecture features a tricyclic network comprising a linearly fused four-, six-, and five- membered carbocyclic rings. Most of the sterpurenes have been isolated from *Stereum purpureum* and are responsible for the silver leaf disease in plants.[1,2] Sterpuric acid **1a** (Figure 1) and its derivative was first

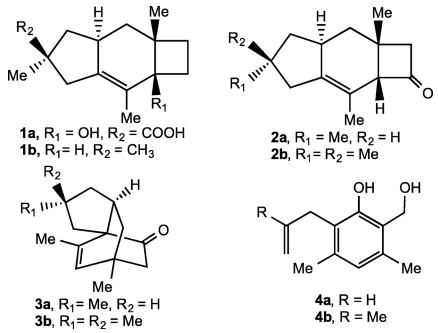


Figure 1. Structure of sterpurenes and precursors.

isolated by Ayer and co-workers from *Stereum purpureum.*[1a] Subsequently, the parent hydrocarbon sterepurene **1b** was isolated along with other hydroxylated members of the family by Ayer and co-workers from the same fungus.[1b] Some hydroxylated sterpurenes were isolated from the fungus *Merulius tremellosus* by Steglich and co-workers.[1e] Recently, new sterpurenes were isolated from the extract of the fungus *P. uda.*[2f−h] Biosynthetically, sterpurenes are derived from farnesyl pyrophosphate through humulene cyclization cascade.[3]

There has been considerable interest in synthesis of sterpuranes due to their highly unusual structures comprising a linearly fused 4/6/5 ring system containing a double bond at the 5/6 ring junction, substitution pattern and functionality. A number of approaches have been designed for the synthesis of sterpuranes involving π^2s + π^2s cycloaddition,[4a,b] Diels−Alder reaction/π^2s + π^2s photoaddition,[4c] and cycloaddition involving allenes.[4d,e] Other methods include insertion reactions,[4f] [4 + 3]-cycloaddition/Favorskii ring contraction,[4g] rearrangement[4h] and photochemical 1,3-acyl shift.[5] Recently, Banwell and co-workers reported[5a] enantioselective synthesis of 4,12-dihydroxysterpurene via intramolecular cycloaddition of enzymatically derived dihydrocatechol and suggested revision of the previously assigned[2a] structure.

Oxidative dearomatization of phenols and the chemistry of resulting species such as masked *o*-quinones, *α*-acetoxycyclohexa-2,4-dienones and congeners have proved to be a powerful methodology for the creation of molecular complexity.[6−8] We have been engaged in developing methods involving oxidative dearomatization of *o*-hydroxymethyl phenols, cycloaddition of the resulting spiroepoxycyclohexa-2,4-dienones and sigmatropic shifts in excited states.[8] Some time ago, we described our exploratory studies toward synthesis of tricyclic core of sterpuranes by 1,3-acyl shift in annulated bicyclo[2.2.2]-octenones that were prepared via intramolecular[5b] and intermolecular[5c] Diels−Alder reaction of cyclohexadienones.

In continuation of our studies in this area, we conceptualized that a photochemical 1,3-acyl shift in the compound **3b** endowed with methyl groups at appropriate centers would directly furnish sterpuren-4-one **2b** (Figure 1). However, the tricyclic compound **3b** is not readily accessible. Hence, we considered devising a new route to the key tricyclic chromophoric system **3b** (and its simpler analogue **3a**) from simple aromatics **4a,b** and examine their photochemical transformation toward sterpuranes. We wish to report our results herein.

Our generalized strategy is outlined in Scheme 1. Recognition of the molecular attributes of sterpurenes with the tricyclic systems of type **3** is pivotal to our plan. As mentioned earlier, we envisaged that sterpurenones **2a,b** would

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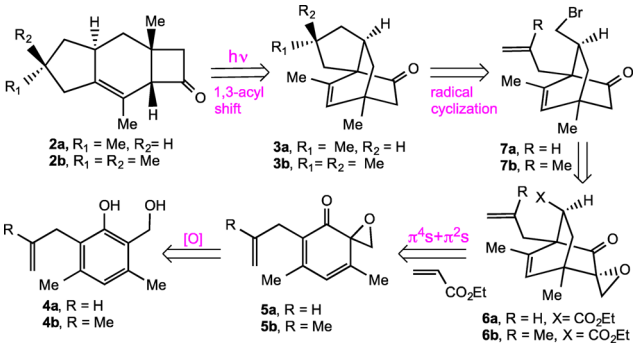
Scheme 1. Retrosynthetic Strategy



be readily accessible from the tricyclic precursors **3a,b** respectively, via a photochemical 1,3-acyl shift. The key intermediates **3a,b** would be made from the bicyclic precursor **7a,b** by a radical induced *exo*-trig cyclization.[9] The precursors **7a,b** containing a suitable olefinic tether would be obtained from the keto-epoxides **6a,b** by manipulation of the carboethoxy group. The keto-epoxides in turn would be prepared from the *o*-hydroxymethyl phenols **4a,b** via oxidative dearomatization to cyclohexa-2,4-dienones **5a,b** followed by π^4s + π^2s cycloaddition with ethyl acrylate (Scheme 1).

Some important aspects of the above plan are as follows. It is interesting to note that structural and functional elements including quaternary methyl groups of sterpurenone are inherently present in the tricyclic enone **3b** and that the sterpurene structure having correct relative stereochemical disposition is generated in a single step. Further, all the 15 carbons of sterpurene framework are derived from the aromatic precursor **4b** and ethyl acrylate that are easily combined to form the keto-epoxide **6b** containing compatible functionalities including a β,γ-enone chromophore for further manipulation in the ground and excited states.

RESULTS AND DISCUSSION

In principle, the compounds of type **3** may be accessible by the π^4s + π^2s cycloaddition of either the annulated diene **I** (Figure 2) with a ketene equivalent or cycloaddition of the dienone **II**

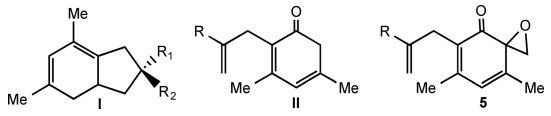


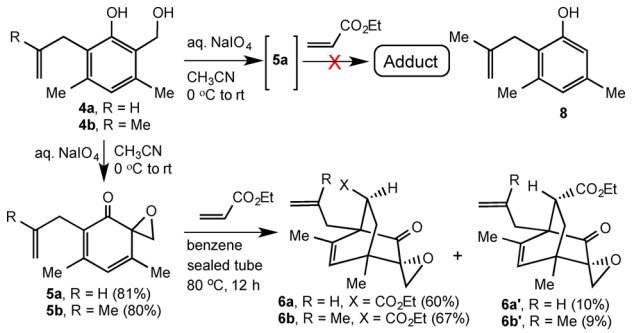
Figure 2. Potential precursors.

with ethyl acrylate and subsequent transformation of the adducts. However, neither the cyclohexadienone **II** that is a keto-tautomer of the corresponding phenol, nor the annulated diene **I** appeared easily accessible. Hence, the spiroepoxycyclohexa-2,4-dienone of type **5** was employed as an equivalent of the cyclohexadienone **II**.

In order to test the feasibility of our plan, we first considered exploring synthesis of the keto-epoxide **6a**, its transformation into the bicyclic precursor **7a** and radical cyclization of **7a** to tricyclic compound **3a** (a simpler analogue of **3b**) (Scheme 1). Therefore, oxidative dearomatization of the readily available *o*-hydroxymethyl phenol[5b] **4a** to generate 6,6-spiroepoxycyclohexa-2,4-dienone **5a** and its interception with ethyl acrylate was attempted.

In view of the above, a solution of *o*-hydroxymethyl phenol **4a** and ethyl acrylate in acetonitrile was oxidized with aq. sodium metaperiodate[10] according to reported procedure.[11] However, the desired adduct **6a** was not obtained instead the known[5b] cyclohexadienone **5a** was isolated (Scheme 2). Apparently, the activation energy necessary for the reaction between the cyclohexa-2,4-dienone **5a** and ethyl acrylate was not available under mild reaction conditions.

Scheme 2. Oxidative Dearomatization and Cycloaddition



Hence, a solution of the spiroepoxycyclohexa-2,4-dienone **5a** and ethyl acrylate in benzene was heated in a sealed tube which furnished *endo*-adduct **6a** as a major product and the *exo*-isomer **6a′** as a result of a highly regio- and stereoselective cycloaddition (Scheme 2).

The structure of adducts was determined from their spectroscopic features. Thus, the IR spectrum of the adduct **6a** showed absorption band at 1733 cm^{-1} due to carbonyl groups. The ^{1}H NMR (400 MHz, $CDCl_3$) spectrum of **6a** exhibited signals at δ 5.98−5.85 (m, 2H) and 5.09−5.01 (m, 2H) for four olefinic protons. The protons of oxirane moiety showed highly characteristic signals as parts of AB system at δ 3.15 (J_{AB} = 5.8 Hz, 1H) and 2.94 (J_{AB} = 5.8 Hz, 1H). The carboethoxy group exhibited characteristic resonances at δ 4.18−4.05 (complex m, 2H) and 1.24 (t, J = 7.1 Hz, 3H) due to oxymethylene and methyl group, respectively. In addition to the signals due to other methine and methylene protons, signals were shown at δ 1.91(d, J = 1.5 Hz, 3H) and 1.02 (s, 3H) due to olefinic methyl and the methyl group at the bridgehead, respectively.

The presence of four olefinic protons, characteristic AB system for the oxymethylene protons of the oxirane ring and signals due to carboethoxy group indicated that the cycloaddition had occurred. The $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) spectrum also supported the above formulation as it displayed characteristic signals at δ 203.8 and 173.1 due to carbonyl group present in the ethano bridge and carboethoxy group, respectively. Further, signals were shown at δ 139.2, 134.3, 133.8, 118.4 for four olefinic carbons, in addition to the resonances due to other carbons. The high resolution mass spectrum showed molecular ion peak at (m/z) 313.1414 $(M + Na)^+$ for $C_{17}H_{22}O_4Na$. The above spectroscopic characteristics suggested the structure of adduct. The stereochemical orientation of oxirane moiety and ester group in the *endo*-adduct **6a** was further confirmed with the help of a single crystal X-ray structure determination (see the Supporting Information).

Subsequently, the aromatic precursor **4b** was prepared by the hydroxymethylation of the readily available[12] phenol **8** and subjected to oxidative dearomatization which also gave the

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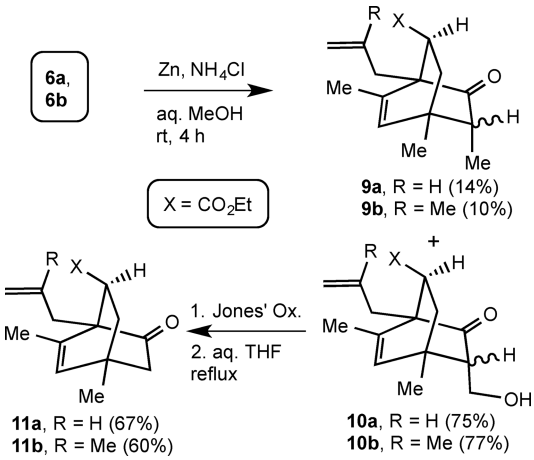
corresponding spiroepoxycyclohexa-2,4-dienone **5b** in excellent yield. Heating the cyclohexadienone **5b** with ethyl acrylate furnished the *endo*-adduct **6b** along with the *exo*-isomer **6b′** as a minor product (Scheme 2).

The structure of adducts **6b** and **6b′** was also deduced from their spectroscopic features and also by comparing with that of **6a** and **6a′**. The *endo*-stereochemistry of carboethoxy group in **6b** was further deduced via its derivative whose structure was confirmed by a single crystal X-ray diffraction (vide infra).

The presence of a carbonyl group adjacent to the oxirane moiety in adducts provided a unique opportunity for further manipulation. Thus, the *endo*-adducts **6a,b** were treated with Zn-NH_4Cl in aq. methanol at room temperature to give the *β*-hydroxy ketones **10a,b** as major products along with minor products **9a,b**. Treatment of the *β*-hydroxy ketones **10a,b** with Jones' reagent and subsequent decarboxylation of the resulting *β*-keto-acid readily furnished the keto-esters **11a,b** respectively (Scheme 3).

Scheme 3. Manipulation of the Adducts

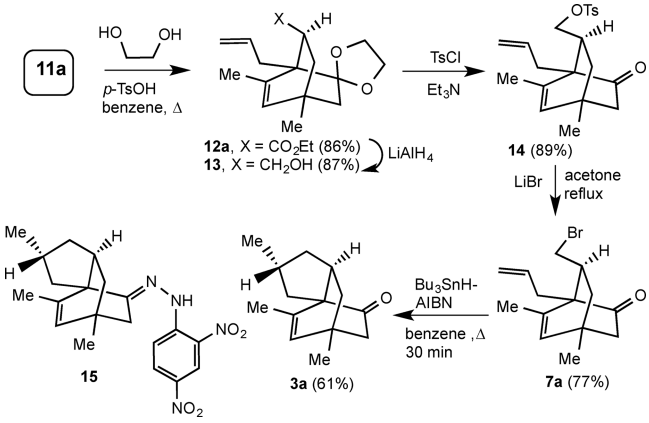


At this juncture, we first considered exploring the transformation of the keto-ester **11a** into the bromoketone **7a** and its radical cyclization. Thus, the carbonyl group in **11a** was protected as ethylene ketal to give **12a** that upon reaction with lithium aluminum hydride gave the ketal-alcohol **13**. Interestingly, the treatment of **13** with TsCl-Et_3N followed by workup directly gave the keto-tosylate **14** as a result of tosylation as well as removal of the ketal moiety (Scheme 4). Treatment of tosylate **14** with LiBr in refluxing acetone easily furnished the desired bromoketone **7a**, the precursor for radical cyclization in excellent yield.

Interestingly, the treatment of **7a** with Bu_3SnH-AIBN in refluxing benzene ensued a fast and smooth reaction leading to the desired tricyclic compound **3a** in reasonably good yield (Scheme 4). The structure of cyclized product **3a,** especially the stereochemistry of the newly generated stereogenic center in the five membered ring, was fully ascertained from crystal structure of its 2,4-DNP derivative **15** (see the Supporting Information).

After having checked the feasibility of our approach for the synthesis of tricyclic chromophoric systems of type **3a**, we then embarked on the transformation of the keto-ester **11b** into the radical precursor **7b** and its cyclization. Thus, the keto-ester **11b** was treated with ethylene glycol in the presence of *p*-TsOH so as to protect the ketone moiety. However, the desired

Scheme 4. Transformation of Keto-Ester 11a into Tricyclic Compound 3a



ketal **12b** was not obtained and it gave a complex mixture of products (Scheme 5). This result was indeed unusual and disappointing especially since its congener **11a** had undergone a smooth reaction to give the corresponding ketal **12a** (vide supra). Attempts to protect the carbonyl group with other reagents/conditions including thio-ketalization were futile. Apparently, methyl group in the olefinic tether in **11b** is responsible for the unusual behavior under the reaction conditions. Such a profound effect of a methyl group is worth noting.

Therefore, an alternate route was devised for the synthesis of the precursor **7b** (Scheme 5). Thus, the keto-ester **11b** was treated with $LiAlH_4$ to give the diol **16** as result of reduction of both the ketone and ester groups. Regioselective tosylation of **16** furnished the hydroxytosylate **17** whose structure was thoroughly established through single-crystal X-ray structure determination (see the Supporting Information). Thus, the structure of other precursors such as the diol **16** and the stereochemistry of the carboethoxy group in **11b** and the adduct **6b** were also confirmed. Oxidation of **17** with TPAP (tetrapropyl ammonium perruthenate)-NMO (4-methylmorpholin-*N*-oxide) gave the keto-tosylate **18** that upon reaction with LiBr in refluxing acetone afforded the desired bromoketone **7b** (Scheme 5) required for radical cyclization.

Having prepared the precursor **7b**, its radical cyclization was attempted. Thus, the compound **7b** was treated with Bu_3SnH-AIBN in refluxing benzene that led to a fast and efficient reaction. Chromatography of the product mixture, however, did not give the desired cyclized product **3b** the compound **19** was obtained instead (Scheme 6).

It was rather unfortunate to note that the bromo-ketone **7b** did not undergo the desired radical cyclization instead fragmentation of the bridged structure occurred to give the cyclohexenone derivative **19**.

A mechanistic rationale for the formation of **19** is outlined in Scheme 7. It appears that the initially formed radical **III** induced selective scission of *α*-C−C bond to form the stabilized radical **IV** that upon allylic rearrangement gives the radical **V**. Subsequently, the radical **V** abstracts a hydrogen radical to furnish the compound **19**. It seems that the *exo*-attack of radical **III** to olefinic carbon of the tether (red arrows), is not favorable as compared to the fragmentation (blue arrows) and hence the radical prefers to follow the latter pathway.

It was remarkable to note the difference in the reactivity of substrates **7a** and **7b** toward radical cyclization. Whereas the

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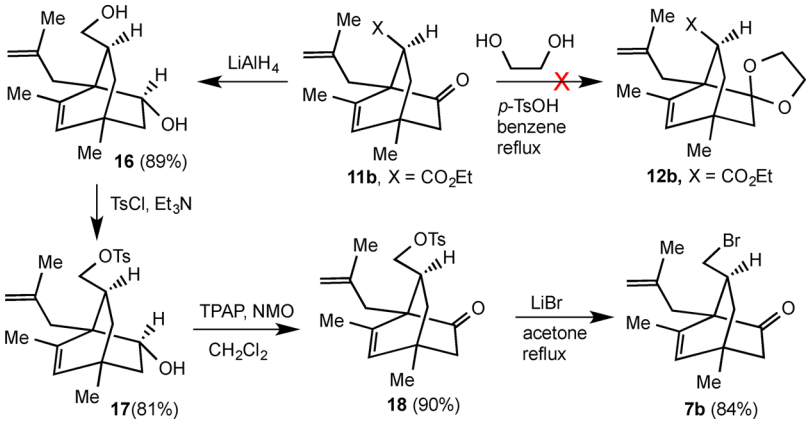
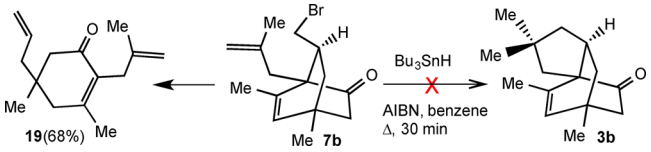
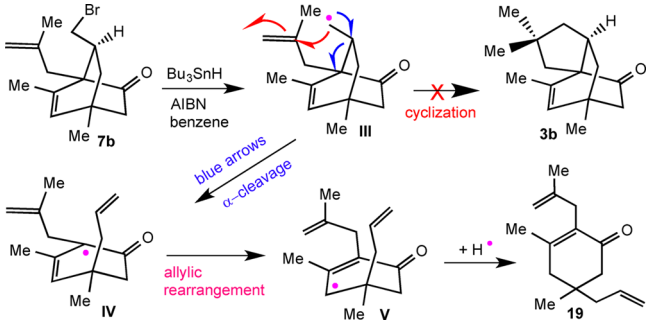
Scheme 5. Transformation of 11b into Precursor 7b for Radical Cyclization



Scheme 6. Attempted Redical Cyclization of 7b



Scheme 7. Mechanism for the Formation of 19



bromoketone **7a** undergoes a smooth cyclization (vide supra), the compound **7b** having just one additional methyl group in the tether, does not follow cyclization pathway and leads to fragmentation. We surmised that the steric hindrance during the cyclization (in the radical **III**) and formation of the stabilized radicals **IV** and **V** after fragmentation are responsible for the aforementioned reaction.

Therefore, we considered preparing the bromo-alcohol **20** and then attempt radical cyclization with a hope that the radical generated from **20** would be less prone toward fragmentation. Hence, the hydroxy-tosylate **17** was converted into the bromo-alcohol **20** and subjected to radical cyclization (Scheme 8).

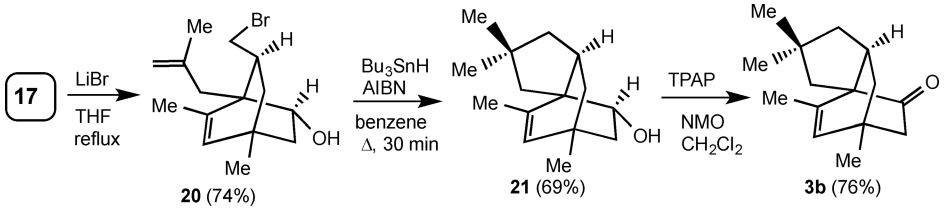
It was indeed gratifying to note that the treatment of the bromo-alcohol **20** with Bu_3SnH-AIBN in refluxing benzene led to the desired radical cyclization and furnished the tricyclic alcohol **21** in good yield (Scheme 8).

The structural identity of the tricyclic alcohol **21** was established from the following spectroscopic features. The IR spectrum of **21** showed an absorption band at 3433 cm^{-1} due to hydroxyl group. The ^1H NMR (400 MHz, $CDCl_3$) spectrum of product **21** exhibited only one signal for olefinic proton of the bicyclo[2.2.2]octane moiety at δ 5.87 (s, 1H). Further the cyclized product exhibited three characteristic resonances for quaternary methyl groups at δ 1.10 (s, 3H), 1.08 (s, 3H) and 1.05 (s, 3H). The presence of only one olefinic proton and signals for three methyl groups clearly indicated that the desired cyclization had occurred. The signal for olefinic methyl group was overlapped with a multiplet due to other protons and appeared at δ 1.90−1.81 (m, total 5H). Moreover, resonances were shown at δ 3.70 (d, J = 7.5 Hz, 1H), 2.17 (d, J = 14.0 Hz, 1H), 1.47−1.34 (m, 3H), 0.91−0.82 (m, 2H) and 0.81−0.75 (m, 1H) due to other methine and methylene protons. The $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) spectrum also suggested its structure as it showed signals at δ 137.5, 134.1 for two olefinic carbons, besides the other signals. The high resolution mass spectrum showed the molecular ion peak at (m/z) 243.1713 for molecular formula $C_{15}H_{24}ONa$.

Subsequently, the cyclized product **21** was oxidized with TPAP in the presence of NMO to give the desired tricyclic compound **3b** having a β,γ-enone chromophore (Scheme 8).

After having developed synthesis of the key tricyclic compounds **3a,b** endowed with a β,γ-enone chromophore, their photochemical reaction was examined. Photoreactions of β,γ-enones have generated interest for a long time[13] that has further enhanced due to their synthetic potential.[14−17] Rigid β,γ-enones generally undergo a 1,2-acyl shift or oxa-di-π-methane rearrangement upon sensitized irradiation (triplet excited state) whereas direct irradiation (singlet excited state) results in a 1,3-acyl shift. While, a large number of examples of

Scheme 8. Synthesis of Tricyclic Chromophoric System 3b



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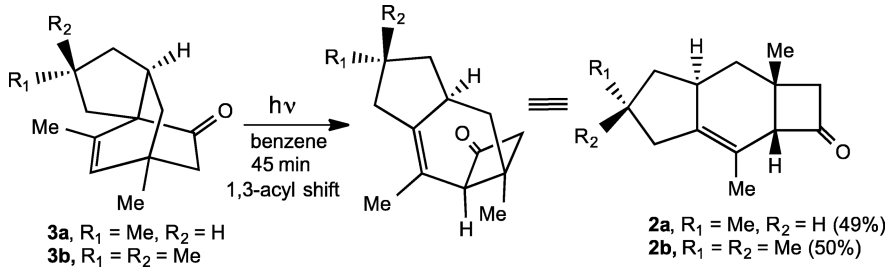
Scheme 9. Synthesis of Sterpurenones



1,2-acyl shift or oxa-di-π-methane reactions have been reported, studies on 1,3-acyl shift are limited. Though reactions of β,γ-enones are representative of their excited states, structure of the substrate often indirectly controls the photoreaction and products resulting from α-cleavage and decarbonylation are some times observed during direct irradiation.

Keeping above in mind, a solution of the ketone **3a** in benzene was irradiated by a mercury vapor lamp (125 W, Phillips) in a Pyrex immersion well for 45 min. Solvent was removed and the product was chromatographed to give the cyclobutyl ketone **2a** in good yield (Scheme 9). Similar irradiation of the tricyclic compound **3b** furnished sterpurenone **2b**.

The photochemical reactions occurred with moderate efficiency to give the 1,3-acyl shift products. In addition to the desired photoproducts, unreacted starting materials were also recovered in each case (~20%). Irradiation for longer duration did not improve the yield of the desired photoproducts and led to decomposition.

The structure of the photoproducts was determined from their spectroscopic features. Thus, IR spectrum of the compound **2b** showed a highly characteristic absorption band at 1777 cm^{-1} due to the cyclobutanone ring. The ^1H NMR (400 MHz, $CDCl_3$) spectrum of the photoproduct **2b** did not show any signal in the olefinic region and exhibited signals at δ 3.08−3.06 (br m, 1H), 2.89 (d of part of an AB system, J_{AB} = 17.5 Hz, J_2 = 2.7 Hz, 1H), 2.58 (d of part of an AB system, J_{AB} = 17.5 Hz, J_2 = 5.3 Hz, 1H) for the methine and methylene protons of the cyclobutanone ring. In addition to resonances due to other protons, characteristic signals were shown at δ 1.64 (s, 3H), 1.32 (s, 3H), 1.09 (s, 3H) and 1.02 (s, 3H) for four methyl groups. The $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$) spectrum displayed a signal at δ 208.1 for the carbonyl carbon. In addition to the signals due to other carbons, characteristic resonances were shown at δ 140.7 and 118.8 for the olefinic carbons. The compound **2a** also exhibited similar spectral features.

CONCLUSION

Synthesis of sterpurenone from a simple aromatic precursor is delineated. Oxidative dearomatization of *o*-hydroxymethyl phenols led to relatively stable spiroepoxycyclohexa-2,4-dienone that upon Diels−Alder reaction with ethyl acrylate furnished appropriately functionalized and appended bicyclo[2.2.2]octenones. Manipulation of adducts led to precursors that underwent radical induced cyclization and gave the requisite tricyclic chromophoric systems. Photochemical 1,3-acyl shift in chromophoric systems furnished sterpuranes. In addition, interesting effect of remote substituent on the ketalization of the carbonyl group and radical cyclization has also been described.

EXPERIMENTAL SECTION

General Experimental Details. IR spectra were recorded on FT-IR instrument. ^1H NMR and ^{13}C NMR spectra were recorded in $CDCl_3$ on 400 and 500 MHz spectrometers using TMS as an internal standard. Chemical shifts are reported in parts per million (ppm) and coupling constants are reported in Hertz (Hz). High resolution mass spectra were recorded on a Q-TOF mass spectrometer using electrospray ionization in the positive ion mode. Melting points are uncorrected. Thin layer chromatography (TLC) was done on glass plates coated with silica gel and spots were visualized using iodine vapor. Compounds were purified by column chromatography on silica gel (60−120 or 100−200 mesh).

2-Allyl-3,5-dimethyl-6-spiroepoxy-cyclohexa-2,4-dienone (5a). To a solution of phenol **4a** (5.4 g, 28.12 mmol) in acetonitrile (30 mL), was added a solution of sodium *meta*-periodate (18.05 g, 84.37 mmol in ~100 mL of water) dropwise at 0 °C. The reaction mixture was stirred for 3 h at room temperature. The reaction mixture was filtered through a Celite bed to remove inorganic salts. The organic layer was separated from the filtrate and the aqueous layer was extracted with diethyl ether (4 × 25 mL). The organic extracts were combined and washed with brine (30 mL) and dried over sodium sulfate. The solvent was removed under vacuum and crude product was chromatographed on silica gel. Elution with petroleum ether/ethyl acetate (94:6) afforded the cyclohexadienone **5a** (4.32 g, 81%) as a yellow liquid [R_f = 0.6 petroleum ether/ethyl acetate (92:8)]. IR (film) ν_{max} 2926, 1655 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 6.19 (s, 1H), 5.80−5.70 (m, 1H), 5.00−4.91 (m, 2H), 3.20−3.10 (AB system overlapped with a multiplet, total 4H), 2.10 (s, 3H), 1.78 (s, 3H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 194.2, 150.2, 143.7, 134.8, 129.7, 129.5, 115.1, 58.4, 57.9, 29.4, 20.6, 16.1. HRMS (ESI-QTOF) m/z [M + K]$^+$ calcd for $C_{12}H_{14}O_2K$ 229.0625; Found 229.0622. The above spectral features are in agreement with those reported earlier.[5b]

Ethyl-4-allyl-1,5-dimethyl-3-oxospiro[bicyclo[2.2.2]oct[5]-ene-2,2′-oxirane]-8-carboxylate (6a and 6a′). A mixture of cyclohexadienone **5a** (1.1 g, 5.78 mmol) and ethyl acrylate (2.0 mL, excess) in benzene (2.0 mL) was heated in sealed tube at 80 °C for 12 h. After which the reaction mixture was charged on a column of silica gel. Elution with petroleum ether/ethyl acetate (98:2) gave the residual ethyl acrylate. Continued elution with petroleum ether/ethyl acetate (96:4) gave the *endo*-adduct **6a** (1.0 g, 60%) as a colorless solid, mp 67−69 °C [R_f = 0.6 petroleum ether/ethyl acetate (95:5)]. IR (film) ν_{max} 2977, 1733 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 5.98−5.85 (m, 2H), 5.09−5.01 (m, 2H), 4.18−4.05 (m, 2H), 3.15 (part of an AB system, J_{AB} = 5.8 Hz, 1H), 2.99 (dd, J_1 = 10.8 Hz, J_2 = 5.9 Hz, 1H), 2.94 (part of an AB system, J_{AB} = 5.8 Hz, 1H), 2.86−2.78 (m, 1H), 2.60 (dd, J_1 = 13.8 Hz, J_2 = 9.7 Hz, 1H), 2.34 (dd, J_1 = 12.6 Hz, J_2 = 10.8 Hz, 1H), 1.91 (d, J = 1.5 Hz, 3H), 1.49 (dd, J_1 = 12.6 Hz, J_2 = 5.9 Hz, 1H), 1.24 (t, J = 7.1 Hz, 3H), 1.02 (s, 3H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 203.8, 173.1, 139.2, 134.3, 133.8, 118.4, 60.7, 59.6, 55.7, 49.9, 42.8, 36.9, 36.8, 31.9, 18.6, 17.4, 14.3. HRMS (ESI-QTOF) m/z (M + Na)$^+$ calcd for $C_{17}H_{22}O_4Na$ 313.1410; Found 313.1414.

Further elution with petroleum ether/ethyl acetate (96:4) gave the *exo*-adduct **6a′** as a colorless liquid (0.16 g, 10%) [R_f = 0.5 petroleum ether/ethyl acetate (95:5)]. IR (film) ν_{max} 2977, 1733 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 5.98−5.83 (m, 2H), 5.14−5.03 (m, 2H), 4.17−

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4.05 (m, 2H), 3.09 (part of an AB system J_{AB} = 5.8 Hz, 1H), 2.97 (part of an AB system, J_{AB} = 5.8 Hz, 1H) 2.93 (dd, J_1 = 10.0 Hz, J_2 = 6.2 Hz, 1H), 2.77−2.71 (m, 1H), 2.38 (dd, J_1 = 14.0 Hz, J_2 = 8.2 Hz, 1H), 2.12 (dd, J_1 = 14.0 Hz, J_2 = 10.0 Hz, 1H), 1.88−1.81 (m, overlapped with d, J = 1.5 Hz, total 4H), 1.23 (t, J = 7.1 Hz, 3H) 1.03 (s, 3H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 205.1, 174.4, 140.0, 134.3, 132.3, 118.4, 60.8, 60.3, 54.0, 50.3, 45.5, 40.6, 34.8, 33.9, 17.9, 15.4, 14.3. HRMS (ESI-QTOF) m/z $[M + Na]^+$ Calcd for $C_{17}H_{22}O_4Na$ 313.1410; Found 313.1414.

2-(Hydroxymethyl)-3,5-dimethyl-6-(2-methylallyl)-phenol (4b). Sodium-ethoxide was prepared by addition of freshly cut sodium (1.72 g, 74.98 mmol) to dry ethanol (50 mL) at 0 °C and stirred for 1 h at ambient temperature. To this solution, 3,5-dimethyl-2-(2-methylallyl)-phenol **8** (10.0 g, 74.84 mmol) and paraformaldehyde (6.5 g, 83.2 mmol) were added slowly and stirring was continued for 10 h. The reaction mixture was neutralized with saturated solution of NH_4Cl and ethanol was removed. The resulting aqueous mixture was extracted with diethyl ether (3 × 30 mL). The combined organic layer was washed with brine solution (30 mL) and dried over Na_2SO_4. The solvent was removed and the residue was chromatographed on silica gel. Elution with petroleum ether/ethyl acetate (90:10) gave the compound **4b** (4.8 g, 40%) as a colorless solid, mp 80−82 °C [R_f = 0.5 petroleum ether/ethyl acetate (90:10)]. IR (film) ν_{max} 3561, 2944, 1638 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 7.41 (s, 1H), 6.56 (s, 1H), 4.86 (d, J = 5.5 Hz, 2H), 4.77 (s, 1H), 4.52 (s, 1H), 3.32 (s, 2H), 2.33 (t, J = 5.5 Hz, 1H), 2.22 (s, 3H), 2.20 (s, 3H), 1.80 (s, 3H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 154.8, 144.3, 137.8, 133.5, 124.0, 123.0, 120.0, 110.3, 60.4, 34.3, 23.0, 19.5, 19.1. HRMS (ESI-QTOF) m/z $[M + Na]^+$ calcd for $C_{13}H_{18}O_2Na$ 229.1199; Found 229.1201.

6,8-Dimethyl-5-(2-methylallyl)-1-oxaspiro[2.5]octa-5,7-dien-4-one (5b). To a solution of phenol **4b** (3.25 g, 15.77 mmol) in acetonitrile (10 mL) was added a solution sodium *meta*-periodate (10.2 g, 47 mmol in ∼100 mL water) dropwise at 0 °C. The reaction mixture was stirred for 3 h at room temperature, filtered and extracted with diethyl ether (4 × 25 mL). The combined organic layer was washed with brine solution (20 mL) and then dried over sodium sulfate. The solvent was removed under reduced pressure at ambient temperature and the residue was purified by column chromatography. Elution with petroleum ether/ethyl acetate (94:6) gave the compound **5b** as a yellow liquid (2.57 g, 80%) [R_f = 0.6 petroleum ether/ethyl acetate (94:6)]. IR (film) ν_{max} 2975, 1651 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 6.19 (d, J = 1.5 Hz, 1H), 4.67 (s, 1H), 4.50 (s, 1H), 3.18 (part of an AB system, J_{AB} = 8.2 Hz, 1H), 3.11 (part of an AB system, J_{AB} = 8.2 Hz, 1H), 3.09−2.99 (m, 2H), 2.04 (s, 3H), 1.78 (d, J = 1.5 Hz, 3H), 1.69 (s, 3H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 194.3, 150.8, 143.7, 142.7, 129.9, 129.4, 110.2, 58.3, 57.9, 32.8, 22.9, 20.8, 16.1. HRMS (ESI-QTOF) m/z $[M + Na]^+$ calcd for $C_{13}H_{16}O_2Na$: 227.1043; Found 227.1044.

Ethyl-4-(2-methylallyl)-1,5-dimethyl-3-oxospiro[bicyclo-[2.2.2]oct[5]ene-2,2′-oxirane]-8-carboxylate (6b and 6b′). A solution of cyclohexadienone **5b** (1.1 g, 5.39 mmol) and ethyl acrylate (2 mL, excess) in benzene (2 mL) was heated in a sealed tube at 80 °C for 12 h. After which reaction mixture was charged on a column of silica gel. Elution with petroleum ether/ethyl acetate (98:2) gave the residual ethyl acrylate. Continued elution with petroleum ether/ethyl acetate (96:4) gave the adduct **6b** (1.1 g, 67%) as a colorless solid, mp 61−63 °C [R_f = 0.5 petroleum ether/ethyl acetate (95:5)]. IR (film) ν_{max} 2969, 1734 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 5.90 (s, 1H), 4.80 (s, 1H), 4.60 (s, 1H), 4.06 (q, J = 7.1 Hz, 2H), 3.16 (part of an AB system, J_{AB} = 5.8 Hz, 1H), 2.96 (dd, overlapped with another signal, J_1 = 12.1 Hz, J_2 = 5.6 Hz, 1H), 2.91 (part of an AB system, J_{AB} = 5.8 Hz, 1H), 2.83 (part of AB system, J_{AB} = 13.9 Hz, 1H), 2.72 (part of an AB system, J_{AB} = 13.9 Hz, 1H), 2.36 (overlapped dd, J_1 = J_2 = 12.1 Hz, 1H), 1.91 (s, 3H), 1.66 (s, 3H), 1.44 (dd, J_1 = 12.1, J_2 = 5.6 Hz, 1H), 1.22 (t, J = 7.1 Hz, 3H), 0.90 (s, 3H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 203.1, 173.5, 142.2, 140.5, 133.9, 116.0, 60.7, 59.6, 55.9, 49.7, 42.3, 37.0, 36.7, 33.9, 24.4, 18.9, 17.5, 14.2. HRMS (ESI-QTOF) m/z $[M + Na]^+$ calcd for $C_{18}H_{24}O_4Na$: 327.1567; Found 327.1568.

Further elution with petroleum ether/ethyl acetate (95:5) gave the *exo*-adduct **6b′** as a colorless liquid (0.15 g, 9%). IR (film) ν_{max} 2973, 1733 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 5.85 (s, 1H), 4.89 (s, 1H), 4.72 (s, 1H), 4.20−4.05 (m, 2H), 3.13 (part of an AB system, J_{AB} = 5.7 Hz, 1H), 2.97 (part of an AB system overlapped with another signal, J_{AB} = 5.7 Hz, total 2H), 2.76 (part of an AB system, J_{AB} = 14.9 Hz, 1H), 2.40 (part of an AB system, J_{AB} = 14.9 Hz, 1H), 2.12 (d of part of an AB system, J_{AB} = 13.5 Hz, J_2 = 10.0 Hz, 1H), 1.96 (d of part of an AB system, J_{AB} = 13.5 Hz, J_2 = 6.0 Hz, 1H), 1.86 (d, J = 1.3 Hz, 3H), 1.75 (s, 3H), 1.25 (t, J = 7.1 Hz, 3H), 1.04 (s, 3H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 204.4, 174.4, 141.9, 140.4, 132.6, 115.2, 60.8, 60.3, 54.2, 50.1, 45.6, 40.6, 36.0, 34.1, 25.0, 18.1, 15.6, 14.4. HRMS (ESI-QTOF) m/z $[M + Na]^+$ calcd for $C_{18}H_{24}O_4Na$: 327.1567; Found 327.1564.

Ethyl-1-allyl-4,6,8-trimethyl-7-oxobicyclo[2.2.2]oct-5-ene-2 carboxylate (9a) and Ethyl-1-allyl-8-(hydroxymethyl)-4,6-dimethyl-7-oxobicyclo[2.2.2]oct-5-ene-2-carboxylate (10a). To a stirred solution of keto-epoxide **6a** (3.0 g, 10.35 mmol) in MeOH−H_2O (6:1, 140 mL) were added activated zinc (21.0 g, excess) and NH_4Cl (2.75 g, 51.75 mmol). The reaction mixture was stirred for 4 h at room temperature, after which it was filtered through a Celite bed to remove zinc and washed with ethyl acetate (3 × 30 mL). The filtrate was concentrated in vacuum, so as to remove most of the solvent and the residue was diluted with water (20 mL) and extracted with ethyl acetate (3 × 30 mL). The combined organic layer was washed with brine (20 mL) and dried over anhydrous sodium sulfate. The solvent was removed under vacuum, product was chromatographed on silica gel. Elution with petroleum ether/ethyl acetate (97:3) first gave the minor compound **9a** as a colorless thick liquid (0.40 g, 14%, mixture of *syn:anti* isomers) [R_f = 0.7 petroleum ether/ethyl acetate (90:10)]. IR (film) ν_{max} 2966, 1731 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 5.94 and 5.77 (s, total 1H), 5.92−5.81 (m, 1H), 5.04−4.95 (m, 2H), 4.08 (q, J = 7.1 Hz, 2H), 2.88−2.78 (m, 1H), 2.70 (dd, J_1 = 10.4 Hz, J_2 = 6.7 Hz, 1H), 2.48 (dd, J_1 = 13.8 Hz, J_2 = 9.7 Hz, 1H), 2.15 and 2.02 (dd, J_1 = 12.8 Hz, J_2 = 10.4 Hz, total 1H), 1.90−1.76 (m, overlapped with s, total 4H), 1.48 and 1.27 (dd, J_1 = 12.4 Hz, J_2 = 6.7 Hz, total 1H), 1.22 (t, J = 7.1 Hz, 3H), 1.15 and 1.13 (s, total 3H), 1.02 (d, J = 7.1 Hz, 3H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 213.1, 173.3, 137.7, 137.0, 134.7, 118.0, 60.6, 60.5, 56.1, 53.9, 43.0, 37.5, 36.0, 31.7, 22.0, 18.3, 14.2. HRMS (ESI-QTOF) m/z $[M + Na]^+$ calcd for $C_{17}H_{24}O_3Na$ 299.1618; Found 299.1616.

Further elution with petroleum ether/ethyl acetate (85:15) gave the keto alcohol **10a** (2.10 g, 75%, mixture of *syn:anti* isomers) as a colorless liquid [R_f = 0.4 petroleum ether/ethyl acetate (90:10)]. IR (film) ν_{max} 3445, 2923, 1720 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 5.95 and 5.82 (s, total 1H), 5.91−5.76 (m, 1H), 5.08−4.98 (m, 2H), 4.10−4.02 (m, 2H), 3.82 (br s, 1H), 3.62 and 3.48 (dd, J_1 = 11.0 Hz, J_2 = 7.4 Hz, total 1H), 2.91−2.76 (m, 2H), 2.57−2.48 (m, 1H), 2.14 and 2.08 (m, 1H), 2.02−1.95 (m,1H), 1.85 and 1.81 (d, J = 1.5 Hz, total 3H), 1.48−1.40 and 1.32−1.26 (m, total 1H), 1.25−1.19 (triplet overlapped with singlet, total 6H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 213.2, 173.4, 173.3, 137.8, 137.1, 135.9, 134.7, 134.6, 134.3, 118.4, 118.1, 63.1, 60.7, 60.6, 60.1, 53.9, 53.6, 43.0, 41.6, 41.2, 37.5, 37.4, 36.0, 31.7, 31.4, 22.1, 21.5, 18.4, 17.9, 14.3. HRMS (ESI-QTOF) m/z $[M + Na]^+$ calcd for $C_{17}H_{24}O_4Na$ 315.1567; Found 315.1578.

Ethyl-1-allyl-4,6-dimethyl-7-oxobicyclo[2.2.2]oct-5-ene-2-carboxylate (11a). To a solution of keto-alcohol **10a** (2.0 g, 6.85 mmol) in acetone (80 mL) was added a freshly prepared Jones' reagent dropwise at ∼5 °C. After completion of reaction (TLC, 1 h), 2-propanol (10 mL) was added slowly to quench excess Jones' reagent. Solvent was removed under vacuum and the residue was diluted with water and extracted with ethyl acetate (3 × 30 mL). The combined organic layer was washed with brine (20 mL) and dried over anhydrous sodium sulfate. Removal of solvent gave a β-keto acid which was directly subjected to decarboxylation as follows.

The β-keto acid was taken up in aqueous THF (70 mL, 1:1) and refluxed for 18 h. After which THF was removed under vacuum and the aqueous layer was extracted with ethyl acetate (3 × 20 mL). Combined organic layer was washed with brine (20 mL) and dried over anhydrous sodium sulfate. Removal of solvent followed by chromatography on silica gel [petroleum ether/ethyl acetate (90:10)] gave the compound **11a** (1.2 g, 67%) as a colorless solid, mp 50−52

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°C [R_f = 0.6 petroleum ether/ethyl acetate (92:8)]. IR (film) ν_{max} 2928, 1726 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 5.93−5.80 (s, overlapped with m, total 2H), 5.09−4.92 (m, 2H), 4.08 (q, J = 7.1 Hz, 2H), 2.92−2.78 (m, 2H), 2.50 (dd, J_1 = 13.8 Hz, J_2 = 9.8 Hz, 1H), 2.00 (dd, partly overlapped with s, J_1 = 12.2 Hz, J_2 = 10.8 Hz, total 3H), 1.82 (d, J = 1.5 Hz, 3H), 1.50−1.40 (m, 1H), 1.21 (t, overlapped with s, J = 7.1 Hz, total 6H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 209.6, 173.5, 137.5, 135.5, 134.8, 118.0, 60.6, 56.1, 46.5, 42.3, 40.4, 35.7, 31.6, 24.1, 18.2, 14.3. HRMS (ESI-QTOF) m/z [M + Na]$^+$ calcd for $C_{16}H_{22}O_3Na$ 285.1461; Found 285.1467.

Ethyl-4,6,8-trimethyl-1-(2-methylallyl)-7-oxobicyclo[2.2.2]-oct-5-ene-2-carboxylate (9b) and Ethyl 8-(hydroxymethyl)-4,6-dimethyl-1-(2-methylallyl)-7-oxobicyclo[2.2.2]oct-5-ene-2-carboxylate (10b). To a solution of the adduct **6b** (2.2 g, 7.22 mmol) in MeOH-H_2O (6:1, 140 mL) were added activated zinc (14.0 g, excess) and NH_4Cl (1.91 g, 36.18 mmol). The reaction mixture was stirred at ambient temperature (~30 °C). After completion of reaction (TLC, 4 h) the reaction mixture was filtered through Celite pad and washed with ethyl acetate (3 × 25 mL). The filtrate was concentrate under vacuum, the residue was diluted with water (15 mL) and extracted with ethyl acetate (4 × 25 mL). The combined extract was washed with brine and dried over sodium sulfate. The solvent was evaporated under reduced pressure and the residue was purified by column chromatography. Elution with petroleum ether/ethyl acetate (97:3) gave the minor compound **9b** as a colorless liquid (0.20 g, yield 10%, as a mixture of syn:anti isomers) [R_f = 0.7 petroleum ether/ethyl acetate (95:5)]. IR (film) ν_{max} 2967, 1724 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 5.89 and 5.74 (s, total 1H), 4.82 and 4.75 (s, total 1H), 4.59 and 4.54 (s, total 1H), 4.04 (q, J = 7.1 Hz, 2H), 2.86 (part of an AB system, J_{AB} = 13.9 Hz, 1H), 2.73 (dd, J_1 = 10.5 Hz, J_2 = 6.5 Hz, 1H), 2.60 (part of an AB system, J_{AB} = 13.9 Hz, 1H), 2.19 (overlapped dd, J_1 = J_2 = 13.4 Hz, 1H), 1.92 (dd, J_1 = 13.4 Hz, J_2 = 7.4 Hz, 1H), 1.82 (d, J = 1.5 Hz, 3H), 1.63 (s, 3H), 1.25 (dd, J_1 = 6.5 Hz, J_2 = 1.8 Hz, 1H), 1.22 (t, J = 7.1 Hz, 3H), 1.14 and 1.12 (s, total 3H), 1.02 (d, J = 7.5 Hz, 3H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 211.2, 173.8, 142.7, 138.1, 137.6, 115.3, 60.4, 55.8, 47.1, 41.9, 37.9, 34.7, 33.6, 24.4, 21.9, 18.4, 14.2, 12.2. HRMS (ESI-QTOF) m/z [M + Na]$^+$ calcd for $C_{18}H_{26}O_3Na$: 313.1774; Found 313.1778.

Continued elution with petroleum ether/ethyl acetate (85:15) gave the β-keto alcohol **10b** as a colorless thick liquid (1.7 g, 77%, as a mixture of *syn:anti* isomers) [R_f = 0.2 petroleum ether/ethyl acetate (95:5)]. IR (film) ν_{max} 3496, 2961, 1719 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 5.95 and 5.80 (s, total 1H), 4.80 (s, 1H), 4.62 and 4.56 (s, total 1H), 4.10−4.02 (m, 2H), 3.93−3.84 (m, 1H), 3.71−3.64 and 3.54−3.47 (m, total 1H), 3.16−3.10 and 3.00−2.94 (m, total 1H), 2.94−2.82 and 2.69−2.61(m, total 3H), 2.25−2.15 (m, 1H), 2.09−2.02 (m, 1H), 1.88 and 1.85 (d, J = 1.5 Hz, total 3H), 1.70 and 1.64 (s, total 3H), 1.43 and 1.29 (dd, J_1 = 11.6 Hz, J_2 = 6.5 Hz, total 1H), 1.25−1.20 (singlets merged with triplets, total 6H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 212.2, 211.5, 173.7, 173.6, 142.5, 142.3, 138.1, 137.8, 137.1, 134.6, 115.9, 115.4, 63.1, 60.64, 60.61, 60.5, 60.4, 56.4, 56.2, 54.1, 53.2, 42.9, 42.1, 40.5, 37.4, 37.3, 36.1, 33.7, 33.3, 29.8, 24.5, 24.3, 22.1, 21.5, 18.6, 18.1, 14.2. HRMS (ESI-QTOF) m/z [M + Na]$^+$ calcd for $C_{18}H_{26}O_4Na$: 329.1723; Found 329.1724.

Ethyl-4,6-dimethyl-1-(2-methylallyl)-7-oxobicyclo[2.2.2]oct-5-ene-2-carboxylate (11b). To a solution of the β-keto alcohol **10b** (2.36 g, 8.36 mmol) in acetone (80 mL) was added a freshly prepared Jones' reagent dropwise at ~5 °C. After the reaction was complete (TLC, 1 h), 2-propanol (10 mL) was added slowly to quenched excess Jones' reagent. Solvent was removed under vacuum, residue was diluted with water and extracted with ethyl acetate (3 × 30 mL). The combined organic layer was washed with brine (20 mL) and dried over anhydrous sodium sulfate. Removal of the solvent gave a β-keto acid which was directly subjected to decarboxylation as follows.

The β-keto acid thus obtained was taken up in THF−H_2O mixture (80 mL, 1:1) and the reaction mixture was refluxed for 15 h. THF was removed in vacuum, the aqueous layer was extracted with ethyl acetate and dried over anhydrous sodium sulfate. The solvent was removed and the residue was chromatographed on silica gel. Elution with petroleum ether/ethyl acetate (95:5) gave the compound **11b** as a colorless solid (1.2 g, 60%), mp 44−46 °C [R_f = 0.5 petroleum ether/ethyl acetate (95:5)]. IR (film) ν_{max} 2962, 1725 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 5.88 (s, 1H), 4.78 (s, 1H), 4.60 (s, 1H), 4.07 (q, J = 7.1 Hz, 2H), 2.93 (part of an AB system, J_{AB} = 13.8 Hz, 1H), 2.88 (dd, J_1 = 10.9 Hz, J_2 = 6.1 Hz, 1H) 2.66 (part of an AB system, J_{AB} = 13.8 Hz, 1H), 2.10 (overlapped dd, J_1 = J_2 = 12.1 Hz, 1H), 2.02 (s, 2H), 1.86 (s, 3H), 1.67 (s, 3H), 1.45 (dd, J_1 = 12.1 Hz, J_2 = 6.1 Hz, 1H), 1.23 (s, overlapped with t, J = 7.1 Hz, total 6H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 208.9, 173.9, 142.7, 138.7, 135.4, 115.6, 60.5, 56.3, 46.5, 41.6, 40.8, 35.6, 33.5, 24.4, 24.1, 18.4, 14.2. HRMS (ESI-QTOF) m/z [M + Na]$^+$ calcd for $C_{17}H_{24}O_3Na$ 299.1618; Found 299.1615.

Ethyl-1-allyl-4,6-dimethylspiro[bicyclo[2.2.2]oct-[5]-ene-2,2′-[1,3-dioxolane]-7-carboxylate (12a). To a mixture of ethylene glycol (4 mL), *p*-toluene sulfonic acid (0.05 g, catalytic) and benzene (75 mL) dried in a Dean−Stark apparatus was added a solution of compound **11a** (1.0 g, 3.86 mmol) in dry benzene (30 mL) under nitrogen atmosphere. The reaction mixture was refluxed for 4 h. After which it was cooled and poured into a saturated solution of sodium bicarbonate (25 mL) and stirred vigorously. The benzene layer was separated and the aqueous layer was extracted with diethyl ether (3 × 20 mL). The combined organic extract was washed with brine (10 mL) and dried over anhydrous sodium sulfate. Removal of solvent followed by chromatography on silica gel [petroleum ether/ethyl acetate (95:5)] gave the compound **12a** as a colorless liquid (1.0 g, 86%). [R_f = 0.6 petroleum ether/ethyl acetate (95:05)]. IR (film) ν_{max} 2952, 1734 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 6.15−6.01 (m, 1H), 5.73 (s, 1H), 4.96−4.85 (m, 2H), 4.10−3.99 (m, 2H), 3.94−3.78 (m, 4H), 3.15 (dd, J_1 = 10.4 Hz, J_2 = 5.8 Hz, 1H), 2.70−2.54 (m, 2H), 1.90−1.83 (multiplet overlapped with d, J = 1.5 Hz, total 4H), 1.52 (s, 2H), 1.29−1.23 (m, 1H), 1.20 (t, J = 7.1 Hz, 3H), 1.09 (s, 3H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 175.1, 140.9, 137.2, 132.2, 115.4, 115.1, 64.3, 64.1, 60.1, 49.5, 48.6, 42.8, 40.4, 34.3, 32.5, 24.7, 19.7, 14.3. HRMS (ESI-QTOF) m/z [M + Na]$^+$ calcd for $C_{18}H_{26}O_4Na$ 329.1723; Found 329.1725.

(1-Allyl-4,6-dimethylspiro[bicyclo[2.2.2]oct[5]ene-2,2′-[1,3]-dioxolane]-7 yl)methanol (13). A solution of ketal-ester **12a** (1.0 g, 3.33 mmol) in dry THF (25 mL) was slowly added to a stirred suspension of lithium aluminum hydride (0.38 g, 9.99 mmol) in THF (40 mL) at ~5 °C under nitrogen atmosphere. After completion of reaction (TLC, 6 h), the reaction mixture was cooled in ice bath and it was quenched by dropwise addition of cold water. The reaction mixture was filtered through a Celite bed and washed with ethyl acetate (2 × 20 mL). Solvent was removed under vacuum, the residue was diluted with water (10 mL) and extracted with ethyl acetate (3 × 20 mL). The combined organic extract was washed with brine (20 mL) and dried over anhydrous sodium sulfate. Removal of solvent followed by chromatography on silica gel [petroleum ether/ethyl acetate (80:20)] furnished the alcohol **13** as a colorless liquid (0.75 g, 87%) [R_f = 0.3 petroleum ether/ethyl acetate (85:15)]. IR (film) ν_{max} 3420, 2946 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 6.23−6.13 (m, 1H), 5.72 (s, 1H), 5.02 (d with structure, J = 17.2 Hz, 1H), 4.96 (d with structure, J = 11.5 Hz, 1H), 3.89−3.80 (m, 4H), 3.74 (dd, J_1 = 10.2 Hz, J_2 = 4.1 Hz, 1H), 3.21 (dd, J_1 = 9.7 Hz, J_2 = 8.9 Hz, 1H), 2.73 (d of part of an AB system, J_{AB} = 15.6 Hz, J_2 = 6.1 Hz, 1H), 2.52−2.45 (m, 1H), 2.40 (d of part of an AB system, J_{AB} = 15.6 Hz, J_2 = 7.5 Hz, 1H), 1.76 (d, J = 1.5 Hz, 3H), 1.68 (dd, J_1 = 12.5 Hz, J_2 = 9.4 Hz, 1H), 1.52−1.49 (s, 2H), 1.26 (br s, 1H), 1.18−1.13 (m, 1H) 1.08 (s, 3H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 140.2, 137.3, 133.5, 115.6, 114.9, 64.9, 64.2, 63.8, 50.2, 48.6, 38.6, 38.5, 34.2, 32.1, 25.0, 19.6. HRMS (ESI-QTOF) m/z [M + Na]$^+$ calcd for $C_{16}H_{24}O_3Na$ 287.1618; Found 287.1616.

(1-Allyl-4,6-dimethyl-7-oxobicyclo[2.2.2]oct-5-en-2-yl)-methyl-4-methylbenzenesulfonate (14). To a solution of alcohol **13** (0.90 g, 3.40 mmol) in dichloromethane (40 mL) was added freshly distilled triethylamine (2.4 mL, 17.0 mmol) under nitrogen atmosphere at 0 °C. After stirring for 10 min, tosyl chloride (1.94 g, 10.2 mmol) was added and the reaction mixture was further stirred for 6 h (TLC) at room temperature. After which saturated aqueous sodium hydrogen carbonate solution (10 mL) was added to the reaction mixture and extracted with dichloromethane (3 × 20 mL).

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The combined organic extract was washed with brine (10 mL) and dried over anhydrous sodium sulfate. The solvent was removed under vacuum and the product was chromatographed on silica gel. Elution with petroleum ether/ethyl acetate (85:15) gave the tosylate **14** (1.13 g, 89%) [R_f = 0.5 petroleum ether/ethyl acetate (85:15)] as a colorless thick liquid. IR (film) ν_{max} 2922, 1718 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 7.73 (d, J = 8.1 Hz, 2H), 7.34 (d, J = 8.1 Hz, 2H), 5.83 (d, J = 1.5 Hz, 1H), 5.82−5.70 (m, 1H), 4.90 (d with structure, J = 10.1 Hz, 1H), 4.85 (d with structure, J = 17.1 Hz, 1H), 4.03 (dd, J_1 = 9.1 Hz, J_2 = 3.9 Hz, 1H), 3.68 (overlapped dd, J_1 = J_2 = 9.1 Hz, 1H), 2.85−2.75 (m, 1H), 2.44 (s, 3H), 2.29−2.20 (m, 1H), 2.04 (dd, J_1 = 14.4 Hz, J_2 = 9.5 Hz, 1H), 1.91 (br s, 2H), 1.73 (dd, J_1 = 12.1 Hz, J_2 = 9.5 Hz, 1H), 1.62 (d, J = 1.5 Hz, 3H), 1.30−1.23 (m, 1H), 1.17 (s, 3H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 210.3, 145.0, 136.8, 135.6, 134.2, 132.9, 129.9, 128.0, 117.9, 71.3, 55.5, 46.5, 38.5, 35.7, 35.1, 31.2, 24.1, 21.7, 18.0. HRMS (ESI-QTOF) m/z $[M + Na]^+$ calcd for $C_{21}H_{26}O_4SNa$ 397.1444; Found 397.1447.

1-Allyl-7-(bromomethyl)-4,6-dimethylbicyclo[2.2.2]oct-5-en-2-one (7a). To a solution of tosylate **14** (0.38 g, 1.01 mmol) in acetone (25 mL) was added lithium bromide (2.0 g, excess) and the reaction mixture was refluxed for 12 h. After completion of reaction (TLC), reaction mixture was cooled to room temperature. Acetone was evaporated under reduced pressure and the residue was diluted with water (10 mL). Aqueous layer was extracted with diethyl ether (3 × 25 mL) and combined organic extract was washed with brine (10 mL), dried over sodium sulfate. The solvent was removed and the residue was chromatographed on silica gel. Elution with petroleum ether/ethyl acetate (95:5) gave the bromide **7a** (0.22 g, 77%) [R_f = 0.7 petroleum ether/ethyl acetate (90:10)] as a colorless liquid. IR (film) ν_{max} 2931, 1722, 1451 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 5.98−5.84 (m, 2H), 5.22−5.10 (m, 2H), 3.63 (dd, J_1 = 9.1 Hz, J_2 = 3.3 Hz, 1H), 2.95−2.84 (overlapped m, 2H), 2.46−2.37 (m, 1H), 2.26 (dd, J_1 = 14.4 Hz, J_2 = 9.5 Hz, 1H), 1.96 (d, J = 1.9 Hz, 2H), 1.87 (dd, J_1 = 12.9 Hz, J_2 = 9.5 Hz, 1H), 1.71 (d, J = 1.5 Hz, 3H), 1.40−1.33 (m, 1H), 1.23 (s, 3H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 210.7, 137.0, 135.4, 134.4, 118.0, 58.2, 46.5, 41.4, 39.2, 36.9, 35.2, 31.3, 24.3, 18.5. HRMS (ESI-QTOF) m/z $[M + Na]^+$ calcd for $C_{14}H_{19}BrONa$ 305.0511; Found 305.0512.

2,4,6-Trimethyl-1,2,3,6,7,7a-hexahydro-3a,6-ethanoinden-9-one (3a). To a stirred solution of AIBN (0.098 g, 0.60 mmol) and the bromide **7a** (0.16 g, 0.60 mmol) in dry benzene (40 mL) was added tributyltin hydride (0.32 mL, 1.20 mmol) under nitrogen atmosphere. The reaction mixture was refluxed for 30 min. The reaction mixture was cooled to room temperature, the solvent was evaporated under vacuum and the residue was purified by column chromatography. Elution with petroleum ether first gave the tin impurities. Further elution with petroleum ether/ethyl acetate (96:4) gave the compound **3a** (0.07 g, 61%) as a colorless liquid [R_f = 0.5 petroleum ether/ethyl acetate (95:5)]. IR (film) ν_{max} 2929, 1724 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 5.90 (s, 1H), 2.26−2.12 (m, 3H), 1.95 (part of an AB system, J_{AB} = 18.0 Hz, 1H), 1.83 (d part of an AB system, J_{AB} = 18.0 Hz, J_2 = 2.5 Hz, 1H), 1.76−1.70 (s, overlapped with multiplet, total 4H), 1.52 (partially overlapped dd, J_1 = 13.2 Hz, J_2 = 7.3 Hz, 1H), 1.47−1.43 (m, 1H), 1.35−1.28 (m, 1H), 1.20 (s, 3H), 1.10−1.06 (m, 1H), 1.02 (d, J = 6.7 Hz, 3H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 212.1, 136.2, 134.8, 65.5, 46.3, 42.1, 39.8, 39.3, 38.2, 32.1, 31.7, 24.2, 23.7, 18.6. HRMS (ESI-QTOF) m/z $[M + Na]^+$ calcd for $C_{14}H_{20}ONa$ 227.1406; Found 227.1410.

1-(2,4-Dinitrophenyl)-2-(2,4,6-trimethyl-1,2,3,6,7,7a-hexahydro-3a,6-ethanoinden-9-ylidene) hydrazine (15). A freshly prepared 2,4-dinitrophenylhydrazine reagent (3 drops) was added to a solution of ketone **3a** (0.020 g) in methanol (2 mL). The contents were heated in a water bath. The color of the reaction changed from colorless to orange-yellow and the precipitate formed was filtered and recrystallized with methanol to give the hydrazone derivative **15** as a yellow crystalline solid, mp 145−147 °C. IR (film) ν_{max} 2957, 2922, 1617 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 10.76 (s, 1H), 9.11 (d, J = 2.6 Hz, 1H), 8.28 (dd with structure, J_1 = 9.6 Hz, J_2 = 2.5 Hz, 1H), 7.95 (d, J = 9.6 Hz, 1H), 5.85 (s, 1H), 2.37−2.28 (m, 2H), 2.18−2.01 (m, 3H), 1.78 (d, J = 1.5 Hz, 3H), 1.74−1.68 (m, 2H), 1.47 (ddd, J_1 = 12.5 Hz, J_2 = 7.5 Hz, J_3 = 2.1 Hz, 1H), 1.34−1.28 (s, overlapped with a multiplet, total 4H), 1.14−1.11 (m, 1H), 1.08 (d, J = 7.5 Hz, 3H), $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$) δ 166.0, 145.6, 137.9, 137.5, 135.1, 130.0, 129.0, 123.7, 116.6, 57.9, 43.6, 40.0, 39.6, 38.2, 37.8, 34.5, 31.9, 24.7, 24.0, 18.3. HRMS (ESI-QTOF) m/z $[M + Na]^+$ calcd for $C_{20}H_{24}N_4O_4Na$ 407.1690; Found 407.1680.

7-(Hydroxymethyl)-4,6-dimethyl-1-(2methylallyl)bicyclo-[2.2.2]oct-5-en-2-ol (16). A solution of β-keto-ester **11b** (0.95 g, 3.44 mmol) in dry THF (25 mL) was slowly added to a stirred suspension of lithium aluminum hydride (0.52 g, 13.76 mmol) in THF (40 mL) at ∼5 °C under nitrogen atmosphere. After completion of reaction (4 h), the reaction mixture was cooled in ice bath and it was quenched by dropwise addition of cold water. The reaction mixture was filtered through a Celite bed and washed with ethyl acetate (3 × 20 mL). Solvent was removed under vacuum, residue was diluted with water (10 mL) and extracted with ethyl acetate (3 × 20 mL). The combined organic layer was washed with brine (20 mL) and dried over anhydrous sodium sulfate. Removal of solvent followed by chromatography on silica gel [petroleum ether/ethyl acetate (70:30)] furnished the alcohol **16** (0.73 g, 89%) as a colorless solid, mp 98−100 °C [R_f = 0.4 petroleum ether/ethyl acetate (75:25)]. IR (film) ν_{max} 3390, 2923 cm^{-1}. ^1H NMR (400 MHz, C_6D_6) δ 5.53 (s, 1H), 5.06−5.03 (m, 2H), 3.81 (d, J = 7.4 Hz, 1H), 3.69 (dd, J_1 = 10.0 Hz, J_2 = 3.6 Hz, 1H), 2.98 (t, J = 9.5 Hz, 1H), 2.81 (part of an AB system, J_{AB} = 13.1 Hz, 1H), 2.30 (part of an AB system, J_{AB} = 13.1 Hz, 1H), 1.90 (s, 3H), 1.78−1.72 (m, 1H), 1.61 (dd partially overlapped with another d, J_1 = 13.1 Hz, J_2 = 8.5 Hz, 1H), 1.51 (partially overlapped d, J = 1.5 Hz, 3H), 1.21 (dd, J_1 = 13.1 Hz, J_2 = 8.5 Hz, 1H), 0.96−0.90 (s overlapped with a multiplet, total 4H), 0.79−0.72 (m, 1H). $^{13}C\{^1H\}$ NMR (125 MHz, C_6D_6) δ 143.3, 139.3, 133.3, 116.2, 71.7, 65.3, 48.2, 47.6, 40.0, 39.6, 35.1, 33.6, 26.3, 25.6, 20.4. HRMS (ESI-QTOF) m/z $[M + Na]^+$ calcd for $C_{15}H_{24}O_2Na$ 259.1669; Found 259.1657.

(7-Hydroxy-4,6-dimethyl-1-(2-methylallyl)bicyclo[2.2.2]oct-5-en-2-yl) methyl, 4-methylbenzenesulfonate (17). To a stirred solution of diol **16** (0.60 g, 2.54 mmol) and triethylamine (1.4 mL, 10.16 mmol) in dry dichloromethane (15 mL) was added p-toluene sulfonyl chloride (2.42 g, 12.7 mmol) at ∼10 °C and the reaction mixture was stirred for 14 h at ambient temperature. A solution of saturated $NaHCO_3$ solution was added to the reaction mixture and extracted with dichloromethane (4 × 20 mL). The combined organic phase was dried over Na_2SO_4. Removal of solvent under reduced pressure followed by chromatography [petroleum ether/ethyl acetate (75:25)] of the residue gave the tosylate **17** (0.80 g, 81%) as a colorless solid, mp 94−96 °C [R_f = 0.6 petroleum ether/ethyl acetate (70:30)]. IR (film) ν_{max} 3471, 2924 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$) δ 7.75 (d, J = 8.1 Hz, 2H), 7.34 (d, J = 8.1 Hz, 2H), 5.76 (s, 1H), 4.88 (s, 1H), 4.68 (s, 1H), 4.22 (dd, J_1 = 8.9 Hz, J_2 = 3.9 Hz, 1H), 3.90−3.82 (br s, 1H), 3.55 (overlapped dd, J_1 = J_2 = 9.1 Hz, 1H), 2.73 (part of an AB system, J_{AB} = 14.0 Hz, 1H), 2.45 (s, 3H), 2.18 (part of an AB system, J_{AB} = 14.0 Hz, 1H), 2.08−1.99 (m, 1H), 1.81 (dd, J_1 = 13.4 Hz, J_2 = 8.3 Hz, 1H), 1.75 (s, 3H), 1.66 (d, J = 1.5 Hz, 3H), 1.34 (dd, J_1 = 12.7 Hz, J_2 = 8.3 Hz, 1H), 1.19−1.14 (br m, 1H), 1.04 (s, 3H), 0.93 (dt, J_1 = 13.4 Hz, J_2 = 3.5 Hz, 1H), 0.87 (dt, J_1 = 12.7 Hz, J_2 = 4.0 Hz, 1H). $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$) δ 144.9, 142.0, 137.7, 133.9, 133.1, 129.9, 128.0, 116.1, 73.5, 71.4, 47.3, 46.6, 38.7, 36.8, 34.9, 33.2, 25.5, 24.8, 21.7, 20.0. HRMS (ESI-QTOF) m/z $[M + Na]^+$ calcd for $C_{22}H_{30}O_4SNa$ 413.1757; Found 413.1754.

(4,6-Dimethyl-1-(2-methylallyl)-7-oxobicyclo[2.2.2]oct-5-en-2-yl)methyl, 4-methylbenzenesulfonate (18). To a stirred solution of alcohol **17** (0.50 g, 1.28 mmol) in dry dichloromethane (50 mL) were added molecular sieves (∼1.0 g), NMO (0.225 g, 1.92 mmol) and TPAP (0.02 g, 5 mol %). The reaction mixture was stirred at room temperature for 6 h. The reaction mixture was filtered through Celite bed, washed with dichloromethane (3 × 20 mL). The combined filtrate was concentrated under vacuum and residue was purified by column chromatography on silica gel. Elution with petroleum ether ethyl acetate (85:15) provided the keto-tosylate **18** (0.45 g, 90%) as a colorless liquid. [R_f = 0.6 petroleum ether/ethyl acetate (80:20)]. IR (film) ν_{max} 2926, 1715 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 7.68 (d, J

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= 8.1 Hz, 2H), 7.24 (d, J = 8.1 Hz, 2H), 5.75 (br m, 1H), 4.63 (br m, 1H), 4.31 (s, 1H), 4.02 (dd, J_1 = 9.0 Hz, J_2 = 3.9 Hz, 1H), 3.63 (overlapped dd, J_1 = J_2 = 9.0 Hz, 1H), 2.81 (d, J = 15.4 Hz, 1H), 2.39 (s, 3H), 2.33−2.29 (m, 1H), 2.06 (d, J = 15.4 Hz, 1H), 1.90 (d, J = 1.9 Hz, 2H), 1.71 (dd, J_1 = 12.8 Hz, J_2 = 9.4 Hz, 1H), 1.58 (d, J = 1.5 Hz, 3H), 1.53 (s, 3H), 1.25−1.18 (m, 1H), 1.11 (s, 3H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 209.4, 145.0, 141.6, 136.9, 136.6, 133.0, 129.9, 128.0, 114.8, 72.4, 56.1, 46.8, 38.8, 36.0, 35.2, 33.5, 24.8, 24.2, 21.7, 18.3. HRMS (ESI-QTOF) m/z $[M + Na]^+$ calcd for $C_{22}H_{28}O_4SNa$ 411.1601; Found 411.1603.

7-(Bromomethyl)-4,6-dimethyl-1-(2-methylallyl)bicyclo-[2.2.2]oct-5-en-2-one (7b). To a solution of the β-keto-tosylate **18** (0.45 g, 1.15 mmol) in acetone (40 mL) was added lithium bromide (0.50 g, excess). The reaction mixture was refluxed for 10 h. It was cooled to room temperature. Solvent was removed under reduced pressure and the residue was diluted with water and extracted with diethyl ether (3 × 25 mL). The combined ethereal extracts were dried over sodium sulfate. Removal of the solvent under reduced pressure followed by purification over column chromatography gave the compound **7b** (0.29 g, 84%) as a colorless liquid [R_f = 0.7 petroleum ether/ethyl acetate (90:10)]. IR (film) ν_{max} 2926, 1723, 1659 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 5.90 (s, 1H), 4.92 (s, 1H), 4.69 (s, 1H), 3.68 (dd, J_1 = 9.1 Hz, J_2 = 3.1 Hz, 1H), 2.98−2.87 (m, 2H), 2.54−2.44 (m, 1H), 2.33 (d, J = 14.0 Hz, 1H), 2.00 (s, 2H), 1.89 (dd, J_1 = 14.0 Hz, J_2 = 9.0 Hz, 1H), 1.73 (s, 3H), 1.71 (d, J = 1.5 Hz, 3H), 1.39−1.33 (m, 1H), 1.23 (s, 3H). $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$) δ 209.9, 142.0, 136.9, 136.4, 115.0, 58.8, 46.9, 41.7, 39.9, 38.2, 35.3, 33.7, 25.0, 24.4, 18.7. HRMS (ESI-QTOF) m/z $[M + Na]^+$ calcd for $C_{15}H_{21}BrONa$ 319.0668; Found 319.0673.

5-Allyl-3,5-dimethyl-2-(2-methylallyl)cyclohex-2-enone (19). To a stirred solution of AIBN (28 mg, 0.17 mmol) and the bromide **7b** (50 mg, 0.17 mmol) in dry benzene (25 mL) was added tributyltin hydride (0.14 mL, 0.34 mmol). The reaction mixture was refluxed for 30 min under nitrogen atmosphere. The solvent was evaporated under vacuum and ethyl acetate was added and washed with saturated solution of potassium fluoride. Organic layer was separated and the aqueous layer was extracted with ethyl acetate (3 × 20 mL). The combined organic extract was dried over sodium sulfate, concentrated under reduced pressure and the residue was purified by column chromatography. Elution with petroleum ether first gave tin impurities. Further elution with petroleum ether/ethyl acetate (94:6) furnished the compound **19** (0.025 g, 68%) as a colorless liquid [R_f = 0.4 petroleum ether/ethyl acetate (95:05)]. IR (film) ν_{max} 2960, 1654 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$) δ 5.84−5.73 (m, 1H), 5.10 (d with structure J = 10.1 Hz, 1H), 5.03 (d with structure J = 17.0 Hz, 1H), 4.69 (s, 1H), 4.50 (s, 1H), 3.02 (br s, 2H), 2.38 (part of an AB system, J_{AB} = 18.1 Hz, 1H), 2.33 (part of an AB system, J_{AB} = 15.8 Hz, 1H), 2.24 (part of an AB system, J_{AB} = 15.8 Hz, 1H), 2.16 (part of an AB system, J_{AB} = 18.1 Hz, 1H), 2.08 (d, J = 7.4 Hz, 2H), 1.88 (s, 3H), 1.72 (s, 3H), 1.00 (s, 3H). $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$) δ 198.4, 154.3, 143.7, 134.0, 132.5, 118.5, 109.8, 49.5, 45.7, 44.9, 35.7, 32.6, 25.3, 23.1, 21.7. HRMS (ESI-QTOF) m/z $[M + Na]^+$ calcd for $C_{15}H_{22}ONa$ 241.1563; Found 241.1566.

7-(Bromomethyl)-4,6-dimethyl-1-(2-methylallyl)bicyclo-[2.2.2]oct-5-en-2-ol (20). To a solution of hydroxy tosylate **17** (0.1 g, 0.256 mmol) in dry THF (25 mL) was added LiBr (0.217 g, 2.5 mmol) and the reaction mixture was refluxed for 12 h (TLC). A saturated aqueous solution of $NaHCO_3$ (20 mL) and brine was added into the reaction mixture and the THF layer was separated. The aqueous layer was extracted with ethyl acetate (3 × 20 mL). The combined organic extract was dried over sodium sulfate and concentrated in vacuum. Purification of the residue by column chromatography (silica gel, Petroleum Ether/EtOAc 95:5) afforded bromide **20** (0.06 g, 74%) [R_f = 0.6 petroleum ether/ethyl acetate (95:5)]. IR (film) ν_{max} 3452, 2929 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 5.85 (s, 1H), 5.04 (br m, 1H), 4.90 (br s, 1H), 3.91 (dd, J_1 = 8.2 Hz, J_2 = 2.5 Hz, 1H), 3.81 (dd, J_1 = 9.3 Hz, J_2 = 2.5 Hz, 1H), 2.85−2.77 (m, 2H), 2.38 (d, J = 13.9 Hz, 1H), 2.19−2.10 (m, 1H), 1.92 (s, 3H), 1.87 (dd, J_1 = 13.0 Hz, J_2 = 8.3 Hz, 1H), 1.73 (d, J = 1.5 Hz, 3H), 1.50 (dd, J_1 = 12.3 Hz, J_2 = 8.3 Hz, 1H), 1.10 (s, 3H), 0.99−0.90 (m, 2H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 142.0, 137.6, 133.9, 116.3, 71.5, 50.0, 46.8, 41.6, 40.6, 39.7, 34.7, 33.6, 25.7, 25.0, 20.3. HRMS (ESI-QTOF) m/z $[M + Na]^+$ calcd for $C_{15}H_{23}BrONa$ 321.0824; Found 321.0832.

2,2,4,6-Tetramethyl-1,2,3,6,7,7a-hexahydro-3a,6-ethanoinden-9-ol (21). To a stirred solution of AIBN (0.11 g, 0.67 mmol) and hydroxy bromide **20** (0.20 g, 0.67 mmol) in dry benzene (25 mL) was added tributyltin hydride (0.35 mL, 1.33 mmol). The reaction mixture was refluxed for 30 min under nitrogen atmosphere. The solvent was removed under vacuum and the product was dissolved in ethyl acetate and washed with saturated solution of potassium fluoride. Organic layer was separated and the aqueous layer was extracted with ethyl acetate (3 × 20 mL). The combined organic extract was dried over sodium sulfate, concentrated under reduced pressure and the residue was purified by column chromatography. Elution with petroleum ether first gave tin impurities. Further elution with petroleum ether/ethyl acetate (96:4) furnished the compound **21** (0.10 g, 69%) as a colorless liquid. [R_f = 0.5 petroleum ether/ethyl acetate (95:5)]. IR (film) ν_{max} 3433, 2950 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 5.87 (s, 1H), 3.70 (d, J = 7.5 Hz, 1H), 2.17 (d, J = 14.0 Hz, 1H), 1.90−1.81 (m, 5H), 1.47−1.34 (m, 3H), 1.10 (s, 3H), 1.08 (s, 3H), 1.05 (s, 3H), 0.91−0.82 (m, 2H), 0.81−0.75 (m, 1H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 137.5, 134.1, 80.0, 56.2, 47.8, 45.9, 44.4, 41.6, 39.8, 38.5, 36.0, 33.1, 30.7, 24.9, 22.7. HRMS (ESI-QTOF) m/z $[M + Na]^+$ calcd for $C_{15}H_{24}ONa$ 243.1719; Found 243.1713.

2,2,4,6-Tetramethyl-1,2,3,6,7,7a-hexahydro-3a,6-ethanoinden-9-one (3b). To a stirred solution of alcohol **21** (0.10 g, 0.45 mmol) in dry dichloromethane (25 mL were added molecular sieves (~1.0 g), NMO (0.08 g, 0.68 mmol) and TPAP (0.01 g, 5 mol %). The reaction mixture was stirred at room temperature for 6 h. After which it was filtered through Celite pad, washed with dichloromethane (3 × 15 mL). The combined filtrate was concentrated under vacuum and the product was charged on silica gel for column chromatography. Elution with petroleum ether/ethyl acetate (96:4) provided the compound **3b** (0.075 g, 76%) as a colorless liquid [R_f = 0.6 petroleum ether/ethyl acetate (96:4)]. IR (film) ν_{max} 2953, 1724 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 5.92 (s, 1H), 2.33−2.24 (m, 1H), 2.00 (s, 1H), 1.96 (d, J = 4.9 Hz, 1H), 1.85−1.65 (s, overlapped with a multiplet, total 6H), 1.53 (dd, J_1 = 11.8 Hz, J_2 = 5.7 Hz, 1H), 1.20 (s, 3H), 1.12 (s, 3H), 1.09−1.01 (s, overlapped with a multiplet, total 4H), 1.00−0.60 (m, 1H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 211.1, 136.7, 134.9, 65.4, 47.1, 45.6, 42.7, 38.7, 38.5, 37.6, 36.4, 32.4, 30.8, 24.2, 20.4. HRMS (ESI-QTOF) m/z $[M + Na]^+$ calcd for $C_{15}H_{22}ONa$ 241.1563; Found 241.1568.

2a,5,7-Trimethyl-2,2a,3,3a,4,5,6,7a-octahydro-1*H*-cyclobuta-[*f*]inden-1-one (2a). A solution of compound **3a** (0.1 g, 0.52 mmol) in degassed benzene (100 mL) was irradiated with a mercury vapor lamp (125 W) in a Pyrex immersion well for 45 min under nitrogen atmosphere. Benzene was removed under vacuum and the residue was chromatographed. Elution with petroleum ether/ethyl acetate (98:2) gave the 1,3-acyl shift product **2a** (0.049 g, 49%) as a colorless liquid [R_f = 0.5 petroleum ether/ethyl acetate (98:2)]. IR (film) ν_{max} 2924, 1776 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 3.09−3.04 (br m, 1H), 2.89 (d of part of an AB system, J_{AB} = 17.5 Hz, J_2 = 2.8 Hz, 1H), 2.58 (d of part of an AB system, J_{AB} = 17.5 Hz, J_2 = 5.2 Hz, 1H), 2.55−2.48 (overlapped m, 1H), 2.45−2.32 (br m, 1H), 2.26−2.15 (m, 1H), 1.97−1.89 (m, 2H), 1.75−1.65 (m, overlapped with s, total 4H), 1.48−1.39 (m, 1H), 1.32 (s, 3H), 0.99 (d, J = 7.0 Hz, 3H), 0.88 (overlapped dd, J_1 = J_2 = 11.8 Hz, 1H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 208.1, 140.6, 118.5, 70.2, 54.0, 40.8, 37.9, 36.7, 35.6, 31.2, 30.1, 28.9, 21.9, 19.3. HRMS (ESI-QTOF) m/z $[M + Na]^+$ calcd for $C_{14}H_{20}ONa$ 227.1406; Found 227.1405.

Continued elution with the same solvent gave unreacted starting material **3a** (0.022 g, 22%).

2a,5,5,7-Tetramethyl-2,2a,3,3a,4,5,6,7a-octahydro-1*H*-cyclobuta[*f*]inden-1-one (2b). A stirred solution of ketone **3b** (100 mg, 0.45 mmol) in dry degassed benzene (100 mL) was irradiated with a mercury vapor lamp (125 W) in a Pyrex immersion well for 45 min. The solvent was removed under reduced pressure and the product was chromatographed on silica gel. Elution with petroleum

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ether/ethyl acetate (97:3) gave the 1,3-acyl shift product **2b** (0.05 g, 50%) as a colorless liquid. [R_f = 0.6 petroleum ether/ethyl acetate (96:4)]. IR (film) ν_{max} 2952, 1777 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.08−3.06 (br m, 1H), 2.89 (d of part of an AB system, J_{AB} = 17.5 Hz, J_2 = 2.7 Hz, 1H), 2.58 (d of part of an AB system, J_{AB} = 17.5 Hz, J_2 = 5.3 Hz, 1H), 2.50−2.42 (br s, 1H), 2.14 (s, 2H), 1.92 (dd, J_1 = 12.3 Hz, J_2 = 5.4 Hz, 1H), 1.76 (dd, J_1 = 12.3 Hz, J_2 = 7.1 Hz, 1H), 1.64 (s, 3H), 1.32 (s, 3H), 1.18 (overlapped dd, J_1 = J_2 = 11.4 Hz, 1H), 1.09 (s, 3H), 1.02 (s, 3H), 0.91 (overlapped dd, J_1 = J_2 = 11.4 Hz, 1H). ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$) δ 208.1, 140.7, 118.8, 70.2, 54.0, 48.1, 44.8, 37.29, 37.27, 36.7, 30.3, 30.1, 29.1, 28.9, 19.3. HRMS (ESI-QTOF) m/z [M + Na]$^+$ calcd for $C_{15}H_{22}ONa$ 241.1563; Found 241.1555.

Further elution with the same solvent gave unreacted starting material **3b** (0.020 g, 20%).

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.7b00867.

^{1}H, ^{13}C NMR spectra of all compounds and crystal structure and data of compounds **6a** (CCDC No. 1495717), **15** (CCDC No. 1525988) and **17** (CCDC No. 1539250) (PDF)

Crystal data for compound **6a** (CIF)

Crystal data for compound **15** (CIF)

Crystal data for compound **17** (CIF)

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: vks@chem.iitb.ac.in.

ORCID

Vishwakarma Singh: 0000-0002-4258-9832

Notes

The authors declare no competing financial interest.

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■ REFERENCES

(1) (a) Ayer, W. A.; Saeedi-Ghomi, M. H.; van Engen, D.; Tagle, B.; Clardy, J. *Tetrahedron* **1981**, *37* (Supplement No. 1), 379. (b) Ayer, W. A.; Saeedi-Ghomi, M. H. *Can. J. Chem.* **1981**, *59*, 2536. (c) Abell, C.; Leech, A. P. *Tetrahedron Lett.* **1988**, *29*, 1985. (d) Cimino, G.; De Giulio, A.; De Rosa, S.; De Stefano, S. *Tetrahedron* **1989**, *45*, 6479. (e) Sterner, O.; Anke, T.; Sheldrick, W. S.; Steglich, W. *Tetrahedron* **1990**, *46*, 2389.

(2) (a) Xie, J.-L.; Li, L.-P.; Dai, Z.-Q. *J. Org. Chem.* **1992**, *57*, 2313. (b) Jonassohn, M.; Anke, H.; Sterner, O.; Svensson, C. *Tetrahedron Lett.* **1994**, *35*, 1593. (c) Arnone, A.; De Gregorio, C.; Nasini, G.; De Pava, O. V. *J. Chem. Soc., Perkin Trans. 1* **1997**, 1523. (d) Arnone, A.; De Gregorio, C.; Mele, A.; Nasini, G.; De Pava, O. V. *J. Chem. Soc., Perkin Trans. 1* **2000**, 745. (e) Rasser, F.; Anke, T.; Sterner, O. *Phytochemistry* **2000**, *54*, 511. (f) Fraga, B. M. *Nat. Prod. Rep.* **2013**, *30*, 1226. (g) Wang, Y.; Bao, L.; Yang, X.; Li, L.; Li, S.; Gao, H.; Yao, X.-S.; Wen, H.; Liu, H.-W. *Food Chem.* **2012**, *132*, 1346. (h) Schüffler, A.; Wollinsky, B.; Anke, T.; Liermann, J. C.; Opatz, T. *J. Nat. Prod.* **2012**, *75*, 1405.

(3) Ayer, W. A.; Nakashima, T. T.; Saeedi-Ghomi, M. H. *Can. J. Chem.* **1984**, *62*, 531.

(4) (a) Zhao, S.-K.; Helquist, P. *J. Org. Chem.* **1990**, *55*, 5820. (b) Mehta, G.; Sreenivas, K. *Tetrahedron Lett.* **2002**, *43*, 703 and references therein. (c) Strunz, G. M.; Bethell, R.; Dumas, M. T.; Boyonoski, N. *Can. J. Chem.* **1997**, *75*, 742 and references therein. (d) Krause, N. *Liebigs Ann. Chem.* **1993**, *1993*, 521. (e) Ovaska, T. V.; Kyne, R. E. *Tetrahedron Lett.* **2008**, *49*, 376 and references therein. (f) Ishii, S.; Zhao, S.; Mehta, G.; Knors, C. J.; Helquist, P. *J. Org. Chem.* **2001**, *66*, 3449. (g) Harmata, M.; Bohnert, G. J. *Org. Lett.* **2003**, *5*, 59. (h) El-Hachach, N.; Gerke, R.; Noltemeyer, M.; Fitjer, L. *Tetrahedron* **2009**, *65*, 1040 and references therein.

(5) (a) Lan, P.; Banwell, M. G.; Willis, A. C. *Org. Lett.* **2015**, *17*, 166. (b) Singh, V.; Praveena, G. D.; Karki, K.; Mobin, S. M. *J. Org. Chem.* **2007**, *72*, 2058. (c) Singh, V.; Alam, S. Q. *Chem. Commun.* **1999**, 2519.

(6) (a) Magdziak, D.; Meek, S. J.; Pettus, T. R. R. *Chem. Rev.* **2004**, *104*, 1383. (b) Liao, C. C. *Pure Appl. Chem.* **2005**, *77*, 1211. (c) Pouysegu, L.; Deffieux, D.; Quideau, S. *Tetrahedron* **2010**, *66*, 2235. (d) Hardin Narayan, A. R.; Simmons, E. M.; Sarpong, R. *Eur. J. Org. Chem.* **2010**, 3553. (e) Roche, S. P.; Porco, J. A., Jr. *Angew. Chem., Int. Ed.* **2011**, *50*, 4068. (f) Yang, Q.; Njardarson, J. T.; Draghici, C.; Li, F. *Angew. Chem., Int. Ed.* **2013**, *52*, 8648. (g) Kou, K. G. M.; Li, B. X.; Lee, J. C.; Gallego, G. M.; Lebold, T. P.; Dipasquale, A. G.; Sarpong, R. *J. Am. Chem. Soc.* **2016**, *138*, 10830.

(7) (a) Wood, J. L.; Graeber, J. K.; Njardarson, J. T. *Tetrahedron* **2003**, *59*, 8855. (b) Mehta, G.; Maity, P. *Tetrahedron Lett.* **2008**, *49*, 318. (c) Morton, J. G. M.; Draghici, C.; Kwon, L. D.; Njardarson, J. T. *Org. Lett.* **2009**, *11*, 4492. (d) Krawczuk, P. J.; Schone, N.; Baran, P. S. *Org. Lett.* **2009**, *11*, 4774. (e) Gong, J.; Lin, J.; Sun, W.; Li, C. C.; Yang, Z. *J. Am. Chem. Soc.* **2010**, *132*, 16745. (f) Constantin, M. A.; Conrad, J.; Merisor, E.; Koschorreck, K.; Urlacher, V. B.; Beifuss, U. *J. Org. Chem.* **2012**, *77*, 4528. (g) Tong, G.; Liu, Z.; Li, P. *Org. Lett.* **2014**, *16*, 2288.

(8) (a) Singh, V. *Acc. Chem. Res.* **1999**, *32*, 324. (b) Singh, V.; Pal, S.; Mobin, S. M. *J. Org. Chem.* **2006**, *71*, 3014. (c) Singh, V.; Sahu, P. K.; Sahu, B. C.; Mobin, S. M. *J. Org. Chem.* **2009**, *74*, 6092. (d) Singh, V. *Synlett* **2013**, *24*, 2641.

(9) Giese, B.; Kopping, B.; Gobel, T.; Dickhaut, J.; Thoma, G.; Kulicke, K. J.; Trach, F. *Radical Cyclization Reactions*; John Wiley & Sons, Inc. 2004.

(10) (a) Adler, E.; Brasen, S.; Miyake, H. *Acta Chem. Scand.* **1971**, *25*, 2055. (b) Adler, E.; Holmberg, K. *Acta Chem. Scand., Sect. B* **1974**, *28*, 465.

(11) Singh, V.; Porinchu, M.; Vedantham, P.; Sahu, P. K. *Org. Synth.* **2005**, *81*, 171.

(12) (a) Habich, A.; Barner, R.; von Philpsborn, W.; Schmid, H. *Helv. Chim. Acta* **1965**, *48*, 1297. (b) Watanabe, A.; Noguchi, N.; Fujisawa, A.; Kodama, T.; Tamura, K.; Cynashi, O.; Niki, E. *J. Am. Chem. Soc.* **2000**, *122*, 5438 While there are no experimental details for the preparation of phenol **8** in ref 12b, the procedure described in ref 12a is rather complex. Therefore, we prepared the compound **8** following a methodology described in the reference 5b..

(13) (a) Schuster, D. I. In *Rearrangement in Ground and Excited States*; de Mayo, P., Ed.; Academic: New York, NY, 1980; Vol. *3*, p 167. (b) Engel, P. S.; Schexnayder, M. A. *J. Am. Chem. Soc.* **1975**, *97*, 145. (c) Coffin, R. L.; Givens, R. S.; Carlson, R. G. *J. Am. Chem. Soc.* **1974**, *96*, 7554.

(14) (a) Demuth, M.; Hinsken, W. *Angew. Chem., Int. Ed. Engl.* **1985**, *24*, 973. (b) Padwa, A.; Zhi, L.; Fryxel, Z. E. *J. Org. Chem.* **1991**, *56*, 1077. (c) Zimmerman, H. E.; Armesto, D. *Chem. Rev.* **1996**, *96*, 3065.

(15) (a) Armesto, D.; Ortiz, M. J.; Romano, S.; Agarrabeitia, A. R.; Gallega, M. G.; Ramos, A. In *CRC Handbook of Organic Photochemistry and Photobiology*; Horspool, W. M., Lenci, F., Eds.; CRC Press: Boca Raton, FL, 2004; Ch. 95. (b) Singh, V. In *CRC Handbook Organic Photochemistry and Photobiology*; Horspool, W. M., Lenci, F., Eds.; CRC: Boca Raton, FL, 2004; Chapters 78 and 79. (c) Banwell, M. G.; Bon David, J.-Y. D. In *Molecular Rearrangements in Organic Synthesis*; Rojas, C. M., Ed.; John Wiley & Sons, 2016; Chapter 9.

DOI: 10.1021/acs.joc.7b00867
J. Org. Chem. 2017, 82, 6268−6278

(16) (a) Maiti, B. C.; Lahiri, S. *Tetrahedron* **1997**, *53*, 13053. (b) Maiti, B. C.; Singh, R.; Lahiri, S. *J. Photochem. Photobiol., A* **1995**, *91*, 27. (c) McClure, C. K.; Kiessling, A.; Link, J. S. *Org. Lett.* **2003**, *5*, 3811.
(17) (a) Bon, D. J. Y.; Banwell, M. G.; Cade, I. A.; Willis, A. C. *Tetrahedron* **2011**, *67*, 8348. (b) Goodell, J. R.; Poole, J. L.; Beeler, A. B.; Aube, J.; Porco, J. A., Jr. *J. Org. Chem.* **2011**, *76*, 9792. (c) Bach, T.; Hehn, J. P. *Angew. Chem., Int. Ed.* **2011**, *50*, 1000.

DOI: 10.1021/acs.joc.7b00867
J. Org. Chem. 2017, 82, 6268−6278