# Formal Total Synthesis of (±)-Silphinene via Radical Cyclization[1]

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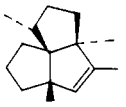
Synthesis of (±)-silphinene from readily available 3,5,5-trimethylcyclohexenone (isophorone) is reported. The cornerstone of the synthesis involves the highly stereoselective intramolecular radical cyclization of **30** to give **5**, an advanced intermediate in the synthesis of silphinene reported by Crimmins. The strategy reported indicates the feasibility of adopting a similar approach for the synthesis of laurenene as well.

The widespread occurrence and interesting biological properties of the tricyclopentanoid skeleta have made them popular targets for synthesis during the last decade. Among the tricyclopentanoids, research directed toward the preparation of the angular triquinane class has progressed rapidly over the past few years. This class of compounds is represented by the hydrocarbons isocomene (**1**) and silphinene (**2**). The tricyclo[6.3.0.0$^{1,5}$]undecane ring system, which forms an integral part of these compounds, is also embedded in more complex natural products that include laurenene (**3**) and crinipellin A (**4**).



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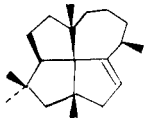

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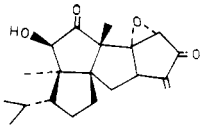

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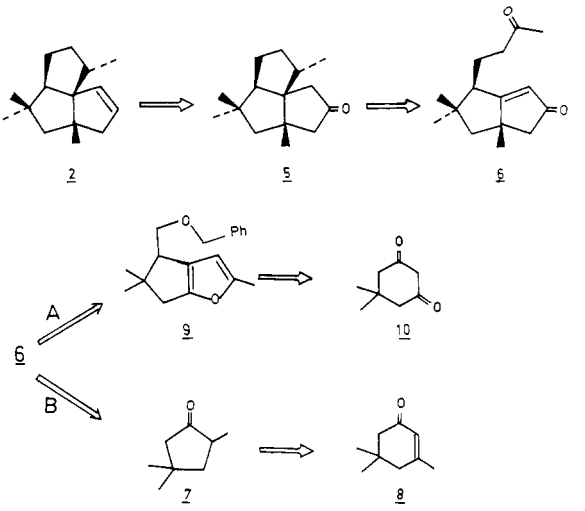
As part of a program directed toward the synthesis of some of these angularly fused polyquinanes, we were interested in employing free-radical reactions for the generation of such ring systems. Silphinene was chosen as a prototype to test our strategy because of both its unique structural features as well as its resemblance to three of the four rings that form part of laurenene (**3**), the only fenestrane occurring in nature.

Silphinene was isolated from the roots of *Silphium perfoliatum* by Bohlmann and Jakupovic.[2] The strategically placed methyl substituents as well as the double bond make silphinene a unique molecule among the angular triquinanes. At present, six groups,[3] including ours,[1] have achieved its synthesis. In this paper we describe the different strategies adopted for the synthesis of silphinene, including the one that was successful.

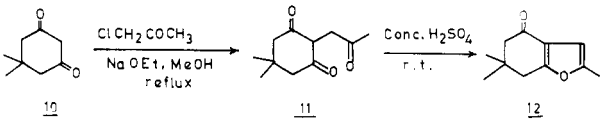
A retrosynthetic analysis for the synthesis of silphinene is shown in Scheme I.

It is evident from the retrosynthetic analysis that the synthesis of silphinene would proceed *via* a bicyclo[3.3.0]octane skeleton such as **6** with the third five-membered ring being generated through the 4-carbon side chain. It is also evident that both the starting materials, namely dimedone **10** and isophorone (**8**), have a *gem*-dimethyl group which would ultimately become the *gem*-dimethyl group of the bicyclo[3.3.0]octane skeleton, thereby obviating the need for the introduction of such a group at a later stage.

**Scheme I**




**Scheme II**




## Results and Discussion

As the synthesis of silphinene proceeds via a bicyclo[3.3.0]octane skeleton, attempts were initially directed toward achieving this goal. Although a variety of methods are available to build this basic skeleton,[4] we set out to construct the bicyclic nucleus from a furan ring, functioning as an equivalent of 1,4-diketone (path A, Scheme I).

Our initial objective was to obtain an intermediate like **9** (path A, Scheme I). Hydrolysis of the furan ring in **9** to a 1,4-diketone followed by an intramolecular aldol reaction should then lead to the bicyclo[3.3.0]octane skeleton. Dimedone (**10**) was alkylated with chloroacetone, and the product obtained was dehydrated to give 2,6,6-trimethyl-4-oxo-4,5,6,7-tetrahydrobenzofuran (**12**)[5] (Scheme II).

In order to effect the ring contraction of the cyclohexanone moiety so as to deliver a substituted cyclopentane annelated to the furan ring, the Wolff rear-

(1) Taken in part from the Ph.D. Thesis of Y.K.R., University of Hyderabad, 1988. For a preliminary communication, see: Koteswar Rao, Y.; Nagarajan, M. *Tetrahedron Lett.* **1988**, *29*, 107.

(2) Bohlmann, F.; Jakupovic, J. *Phytochemistry* **1980**, *19*, 259.

(3) (a) Tsunoda, T.; Kodama, M.; Ito, S. *Tetrahedron Lett.* **1983**, *24*, 83. (b) Paquette, L. A.; Leone-Bay, A. *J. Am. Chem. Soc.* **1983**, *105*, 7352. (c) Wender, P. A.; Ternansky, R. J. *Tetrahedron Lett.* **1985**, *26*, 2625. (d) Sternbach, D. D.; Hughes, J. W.; Burdi, D. F.; Banks, B. A. *J. Am. Chem. Soc.* **1985**, *107*, 2149. (e) Crimmins, M. T.; Mascarella, S. W. *J. Am. Chem. Soc.* **1986**, *108*, 3435.

(4) Paquette, L. A. *Top. Curr. Chem.* **1984**, *119*.

(5) Schaeffer, H. J.; Vince, R. *J. Org. Chem.* **1962**, *27*, 4502.

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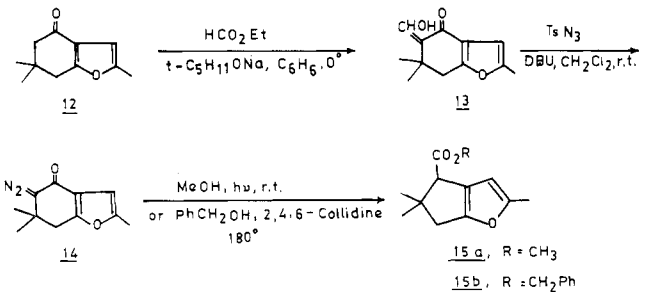
**Scheme III**




rangement was chosen, and accordingly, the substrate required for the Wolff rearrangement was prepared (Scheme III).

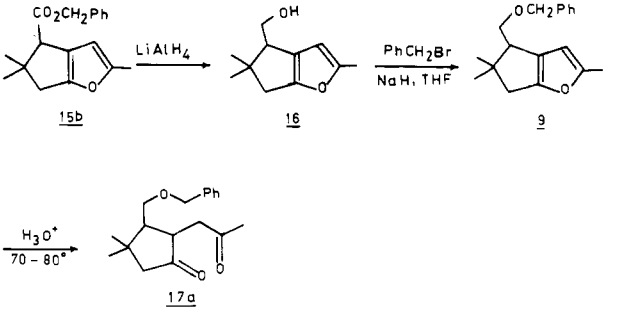
Attempted formylation of **12** using a variety of bases including NaOMe/MeOH, NaOEt/EtOH, NaH/THF, KO*t*Bu/*t*BuOH, and LDA/THF were uniformly unsuccessful, and only the starting material was recovered in each case. Finally, the much needed formylation was found to proceed with sodium *tert*-amyloxide in benzene, and after considerable experimentation, 6,7-dihydro-5-formyl-2,6,6-trimethyl-4(5*H*)-benzofuranone (**13**) was obtained in 94% yield. Reaction of **13** under the usual Regitz conditions[6] with *p*-toluenesulfonyl azide and triethylamine to effect diazo transfer was unsuccessful. As **13** is a sterically hindered ketone, modifications of the Regitz reaction employing bases like potassium ethanolate[7] and phase transfer catalyzed method,[8] which are known to be useful in such instances, were attempted. However, they too were found to be unsuccessful. Therefore, a systematic investigation of the reaction of **13** with *p*-toluenesulfonyl azide and various bases was undertaken. While bases like diisopropylethylamine and 4-(dimethylamino)pyridine (DMAP) were not useful, the reaction of **13** proceeded moderately well in the presence of 1,4-diazabicyclo-[2.2.2]octane (DABCO) to give the required 5-diazo-6,7-dihydro-2,6,6-trimethyl-4(5*H*)-benzofuranone (**14**) in 56% yield. Encouraged by this result, 1,8-diazabicyclo[5.4.0]-undec-7-ene (DBU) was used, and a dramatic improvement in yield (95%) and reduction in reaction time (15 min) was observed.[9]

The stage was now set for the crucial Wolff rearrangement. When **14** was photolyzed in degassed methanol with a Hanovia 450-W medium-pressure mercury lamp using a Pyrex filter, the rearranged product, methyl 2,5,5-trimethyl-5,6-dihydro-4*H*-cyclopenta[*b*]furan-4-carboxylate (**15a**) was obtained in 67% yield. As this reaction could not be performed on a large scale due to experimental limitations, the Wolff rearrangement was performed under thermolytic conditions employing benzyl alcohol as the medium, and the desired rearranged benzyl ester (**15b**) was obtained in almost quantitative yield.

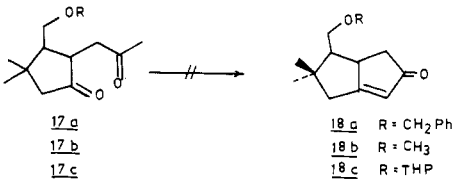
With a serviceable route to **15b** in hand, attention was then turned toward building the bicyclo[3.3.0]octane skeleton. Accordingly, the benzyl ester was reduced with $LiAlH_4$ in THF to the alcohol **16**. When **16** was treated with NaH in THF employing benzyl bromide as the alkylating agent, the corresponding benzyl ether was obtained in 88% yield.

The spectral data (IR and $^1H$ NMR) of **16** and **9** are consistent with the proposed structures. Now it only remained to transform the furan ring in **9** to a cyclo-

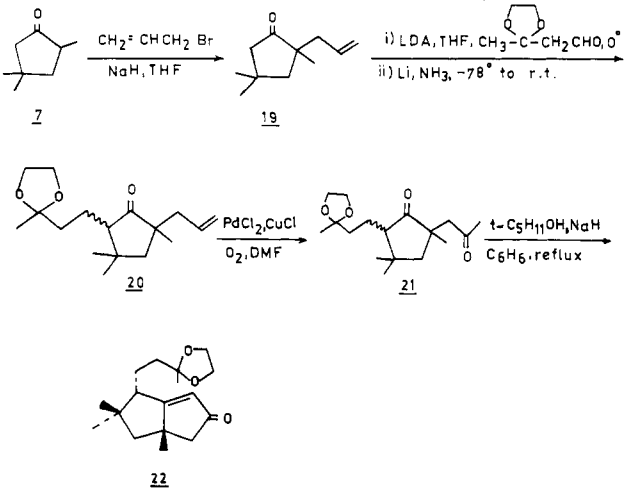
**Scheme IV**




**Scheme V**




**Scheme VI**



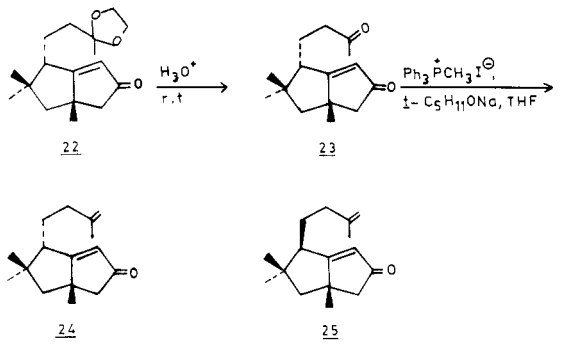

pentenone. Hydrolysis of **9** with aqueous acetic acid–sulfuric acid at 70–80 °C gave the corresponding 1,4-diketone **17a** (Scheme IV) in 82% yield. The structure of **17a** is supported by its IR and NMR spectra. The $^{13}C$ NMR spectrum of **20a** clearly showed two resonances at 217.3 and 205.8 ppm, characteristic of cyclopentanone and acetonyl carbonyls.

A variety of bases (NaOMe, KOH, KO*t*Bu, and KH among others) were tried to effect the aldol reaction on **17a**, but all the attempts were futile. Analogues of **17a**, with methyl and 2-tetrahydropyranyl as protecting groups of the alcohol, were prepared and subjected to the aldol reaction conditions. These were also unsuccessful (Scheme V).

As all the attempts at constructing the required bicyclo[3.3.0]octane skeleton were unsuccesful, we were forced to have a fresh look at the synthesis of silphinene, and accordingly, the route described in path B, Scheme I, was undertaken. 2,4,4-Trimethylcyclopentanone (**7**), was identified as a suitable starting material in view of its ready availability from 3,5,5-trimethyl-2-cyclohexenone (isophorone).[10] Secondly, it has three methyl groups which correspond to the four methyl groups present in silphinene.

(6) Regitz, M. *Angew Chem., Int. Ed. Engl.* **1967**, *6*, 733.
(7) Regitz, M.; Heck, G. *Chem. Ber.* **1967**, *97*, 1482.
(8) Ledon, H. *Synthesis* **1974**, 347.
(9) Koteswar Rao, Y.; Nagarajan, M. *Ind. J. Chem.* **1986**, *25B*, 735.
(10) House, H. O.; Ryerson, G. D.; Wasson, R. L. *Organic Syntheses*; Wiley: New York, 1963; Collect. Vol. IV, p 957.

**Scheme VII**




In this instance as well, the *gem*-dimethyl group is located in the correct position.

Cyclopentanone **7** was alkylated regiospecifically at the 2-position with allyl bromide under thermodynamically controlled conditions with NaH as the base and THF as the solvent. This particular combination of base and solvent was found to be the most suitable among a variety of base–solvent combinations tried (NaH/DME, NaH/DMF, KO*t*Bu/*t*BuOH, THF). This one-step preparation of 2-allyl-2,4,4-trimethylcyclopentanone (**19**) (Scheme VI) was found to be far superior to a four-step preparation of the same compound reported in the literature,[11] both in terms of overall yield and the number of steps involved. The identity of **19** was established by comparison of its spectral data (IR, $^1$H NMR, $^{13}$C NMR) with those reported earlier.

The next step was to introduce a suitable 4-carbon side chain at the 5-position of **19**. For this purpose, alkylation of **19** with 1-iodo-3,3-ethylenedioxybutane using lithium diisopropylamide (LDA) as base was attempted without success. However, this problem was overcome by performing an aldol reaction between **19** and 2-(2-methyl-1,3-dioxolan-2-yl)acetaldehyde using LDA as base in THF. As a result, the enone as mixture of *E* and *Z* isomers in the ratio of 60:40 was obtained. The aldol was not isolated. The structure of the enone was evident from its spectral data. The enone was then reduced by lithium in ammonia at −78 °C to furnish cyclopentanone **20**, which was also obtained as a mixture of isomers. The terminal olefin in **20** was oxidized to a methyl ketone (**21**), employing Tsuji's conditions[12] in a 54% yield.

When **21** was subjected to intramolecular aldol reaction using NaH in benzene with a catalytic amount of *tert*-amyl alcohol, enone **22** was obtained as a colorless solid after purification by column chromatography. The presence of a doublet at $\delta$ 5.64 in the $^1$H NMR spectrum and bands at 1710 and 1640 cm$^{-1}$ in the IR spectrum indicated the presence of an enone moiety in **25**. As the stereochemistry of the side chain in **22** has to be established beyond doubt, the ketal in **22** was hydrolyzed to enedione **23**. This was followed by reaction of **23** and methylenetriphenylphosphorane to give **24** (Scheme VII).

Comparison of **24** with **25**, a similar compound reported by Crimmins,[13] indicated that the side chain in **24** was opposite in stereochemistry to that in **25**. The $^1$H NMR spectrum clearly establishes that **24** and **25** are different compounds. As the side chain in **25** is known to be cis to the quaternary methyl group, it is apparent that in **24** the two substituents are trans. This was further confirmed by a single-crystal X-ray analysis of **22**, which unequivocally established the trans stereochemistry of the side chain.[14] It is obvious that such a disposition is not desired for the synthesis of silphinene. Attempted epimerization of the side chain in **22** with bases like NaOMe/MeOH, DBU/$C_6H_6$, KO*t*Bu/*t*BuOH, and KO*t*Bu/THF was of little help. In order to obtain an idea of the energy difference between the two epimers, MM2 calculations were performed on **23** and **6**, which indicated that **23** was more stable than **6** by about 2.5 kcal/mol.[15]

In view of these results, we were forced to take a fresh look at the synthesis of silphinene. With the information gained from the above operations, it was felt that instead of performing the aldol reaction on **21**, which involves rather drastic conditions, an intramolecular Wittig–Horner reaction under milder conditions would be preferable. The substrate would now be a $\beta$-ketophosphonate instead of the acetonyl group as in **24**. Epimerization of the side chain to the more favorable and less desirable *endo*-face could be avoided (unlike the earlier case), due to the milder reaction conditions. Consequently, the possibility of isolating the correct isomer would now be enhanced.

Toward this end, the terminal olefin in **20** was oxidatively cleaved to an acid with $RuCl_3$/$NaIO_4$,[16] which was esterified with diazomethane to give the corresponding ester, **26** (Scheme VIII).

Ketalization of **26** using triethyl orthoformate/ethylene glycol/*p*-toluenesulfonic acid gave **27**. Conversion of the ester to the $\beta$-ketophosphonate **28** was achieved by reacting **27** with the lithium salt of dimethyl methylphosphonate[17] followed by hydrolysis of the ketals with aqueous hydrochloric acid. The crude material obtained was directly subjected to the intramolecular Wittig–Horner reaction employing the recently reported conditions of Heathcock,[18] which utilize phase transfer catalysis (PTC) conditions involving tetrabutylammonium hydroxide as the base. As expected, the corresponding enone **6** with the side chain in the desired stereochemistry was obtained. That the side chain in **6** indeed had the correct stereochemistry was confirmed by converting **6** into **25** by a simple Wittig olefination and then comparing the spectral data (IR and $^1$H NMR) with those reported for the same compound by Crimmins.[13]

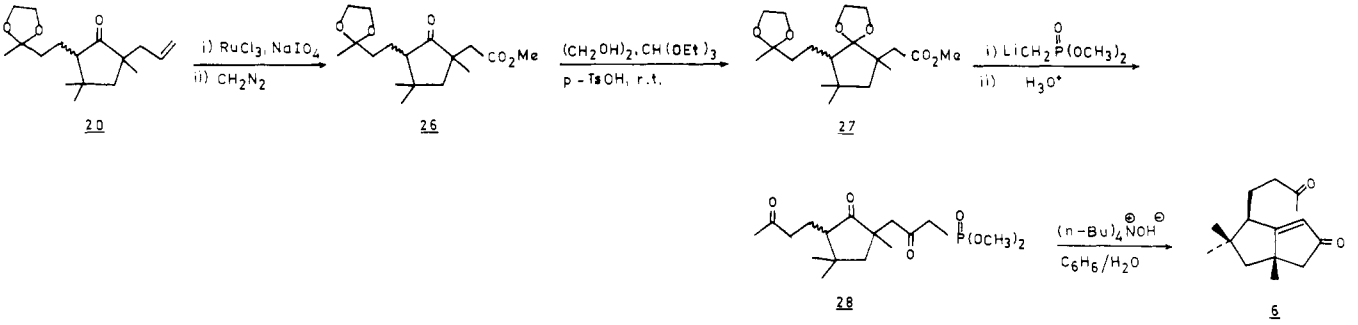
At this stage, conversion of **6** into silphinene proved to be quite simple. The saturated ketone in the side chain of **6** was selectively reduced with sodium borohydride in methanol, and the resulting alcohol **29** was converted into the *p*-tolylthionocarbonate derivative **30**. Treatment of **30** with tributyltin hydride generated a radical, which added in a stereospecific fashion to the double bond of the enone, giving the angular triquinane **5**, exclusively (Scheme IX).

The structure of **5** was confirmed by comparison of its spectra (IR and $^1$H NMR) with those provided by Crimmins for the same compound.[3e]

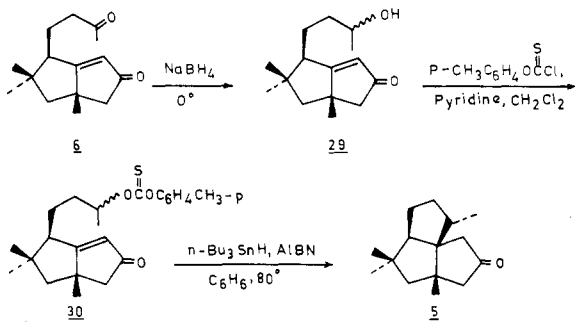
As **5** has already been converted to silphinene by Crimmins in two steps,[3e] the work described above constitutes a formal total synthesis of silphinene. This work, involving an intramolecular radical cyclization, is among the first few approaches toward the tricyclo[6.3.0.0$^{1,5}$]undecane skeleton

(11) Eaton, P. J.; Jogia, M. K.; O'Connor, A. W.; Weavers, R. T. *Aust. J. Chem.* **1983**, *36*, 1399.
(12) Takahashi, T.; Kasuga, K.; Takahashi, M.; Tsuji, J. *J. Am. Chem. Soc.* **1979**, *101*, 5072.
(13) Crimmins, M. T.; Mascarella, S. W.; Bredon, L. D. *Tetrahedron Lett.* **1985**, *26*, 997.
(14) Nalini, V.; Desiraju, G. R. *Acta. Crystallogr., Sect. C: Cryst. Struct. Commun.* **1988**, *C44*, 510.
(15) Jemmis, E. D. Personal communication.
(16) Carlson, P. H. J.; Katsuki, T.; Martin, V. S.; Sharpless, K. B. *J. Org. Chem.* **1981**, *46*, 3936.
(17) Clark, R. D.; Kazar, L. G.; Heathcock, C. H. *Synth. Commun.* **1975**, *5*, 1.
(18) Davidsen, S. K.; Heathcock, C. H. *Synthesis* **1986**, 842.

**Scheme VIII**




**Scheme IX**




using such a method. The only other work is that of Curran,[19] who has utilized such a radical cyclization approach in establishing a tricyclo[6.3.0.0$^{1,5}$]undecane skeleton and has implemented it successfully in synthesizing silphiperforl-6-ene.

In conclusion, we have described different strategies toward silphinene starting from cheap and abundantly available starting materials. As the intermediates are obtained in simple and straightforward operations, this work can also be extended to the synthesis of laurenene with minor modifications. Efforts are under way in that direction at present.

## Experimental Section

Melting points are uncorrected. $^1$H NMR and $^{13}$C NMR spectra were recorded at 100 and 25 MHz, respectively. Mass measurements were carried out in the electron-impact mode.

Column chromatography was performed using Acme's silica gel (100–200 mesh) and usually eluted with 20–30% ethyl acetate–hexane, unless otherwise mentioned. All moisture-sensitive reactions were carried out under dry nitrogen, and all solvents were distilled from appropriate drying agents just before use. Petroleum ether refers to the fraction boiling between 60 and 80 °C.

**6,7-Dihydro-5-formyl-2,6,6-trimethyl-4(5*H*)-benzofuranone (13).** To a solution of **12** (10.0 g, 0.056 mol) in 25 mL of toluene was slowly added sodium *tert*-amyloxide (7.4 g, 0.067 mol) in 15 mL of benzene, and the mixture was stirred for 1 h at room temperature. The mixture was then cooled in an ice bath, and ethyl formate (12.4 g, 0.168 mol) was added dropwise. After the addition was complete, the mixture was allowed to come to room temperature and stirred overnight. Water (20 mL) was added to the mixture, and it was extracted with dichloromethane. The organic layer was removed; the aqueous layer was made acidic with concentrated HCl and was extracted with dichloromethane (3 × 25 mL). The combined organic layers were dried ($MgSO_4$) and evaporated. The crude material obtained was recrystallized from hexane: yield 10.8 g (94%); mp 64–65 °C; IR (KBr, cm$^{-1}$) 3350, 1680, 1600, 1440, 1220; $^1$H NMR (100 MHz, $CDCl_3$) δ 7.32–7.24 (d, 1 H, olefinic), 6.24 (br s, 1 H, furan proton), 2.68 (2, 2 H), 2.28 (s, 3 H, furan methyl), 1.24 (s, 6 H, *gem*-dimethyl); mass 206 (M$^+$), 178, 163, 135, 94. Anal. Calcd for $C_{12}H_{14}O_3$: C, 69.88; H, 6.84. Found: C, 69.95; H, 7.19.

**5-Diazo-6,7-dihydro-2,6,6-trimethyl-4(5*H*)-benzofuranone (14).** To a solution of **13** (4.0 g, 19.4 mmol) in 25 mL of dichloromethane cooled to 5–10 °C was added dropsise DBU (4.40 g, 29 mmol), followed by the addition of *p*-toluenesulfonyl azide (3.82 g, 19.4 mmol). The mixture was stirred for 15 min and then washed with water (thrice). The organic layer was dried ($MgSO_4$) and evaporated. The crude material obtained was recrystallized from hexane: yield 3.76 g (95%); mp 102–103 °C; IR (KBr, cm$^{-1}$) 3000, 2100, 1620, 1420, 1300, 900, 640; $^1$H NMR (100 MHz, $CDCl_3$) δ 6.27 (s, 1 H, furan proton), 2.82 (s, 2 H), 2.30 (s, 3 H, furan methyl), 1.38 (s, 6 H, *gem*-dimethyl); mass 204 (M$^+$), 176 (M − 28), 161, 148, 133, 105, 79, 43. Anal. Calcd for $C_{11}H_{12}N_2O_2$: C, 64.69; H, 5.92. Found: C, 65.22; H, 6.36.

**Methyl 2,5,5-Trimethyl-5,6-dihydro-4*H*-cyclopenta[*b*]-furan-4-carboxylate (15a).** Compound **14** (0.204 g, 1 mmol) was dissolved in 150 mL of degassed methanol and photolyzed for 1 h with a Hanovia 450-W medium-pressure mercury lamp using a Pyrex filter. At the end of this period, the solvent was evaporated and the crude material was purified by column chromatography, eluting with 5% ethyl acetate–hexane: yield 0.140 g (67%); IR (neat, cm$^{-1}$) 2900, 1720, 1460, 1180; $^1$H NMR (100 MHz, $CDCl_3$) δ 5.83 (br s, 1 H, furan proton), 3.64 (s, 3 H, carbomethoxy), 3.37 (br s, 1 H, methine proton), 2.54 (s, 2 H, methylene protons adjacent to *gem*-dimethyls), 2.23 (s, 3 H, furan methyl), 1.33 (s, 3 H, methyl), 1.09 (s, 3 H, methyl). Anal. Calcd for $C_{12}H_{16}O_3$: C, 69.10; H, 7.54.

**Benzyl 2,5,5-Trimethyl-5,6-dihydro-4*H*-cyclopenta[*b*]-furan-4-carboxylate (15b).** A solution of **14** (4.08 g, 20 mmol), benzyl alcohol (6.48 g, 60 mmol), and 2,4,6-collidine (2.42 g, 20 mmol) was heated to 180–190 °C for 15 min. During the course of the reaction, vigorous evolution of nitrogen gas was observed. After the reaction was over, the mixture was cooled to room temperature and extracted with dichloromethane. The organic layer was washed with 10% HCl and water, dried, and evaporated. The crude material was then purified by fractional distillation: yield 5.60 g (98%); bp 170–180 °C (0.1 mm); IR (neat, cm$^{-1}$) 2900, 1730, 1470, 1150, 800; $^1$H NMR (100 MHz, $CDCl_3$) δ 7.24 (s, 5 H, aromatic), 5.84 (s, 1 H, furan proton), 5.08 (s, 2 H, benzyl protons), 3.40 (s, 1 H, methine proton), 2.48 (s, 2 H, methylene protons adjacent to *gem*-dimethyls), 2.20 (s, 3 H, furan methyl), 1.28 (s, 3 H, methyl), 1.08 (s, 3 H, methyl); $^{13}$C NMR (25.0 MHz, $CDCl_3$) 172.3, 155.6, 154.9, 135.6, 128.0, 127.8, 127.6, 122.3, 102.8, 65.5, 53.7, 48.5, 40.2, 29.9, 25.0, 13.1 ppm. Anal. Calcd for $C_{18}H_{20}O_3$: C, 76.03; H, 7.08. Found: C, 75.88; H, 7.03.

**5,6-Dihydro-4-(hydroxymethyl)-2,5,5-trimethyl-4*H*-cyclopenta[*b*]furan (16).** To a suspension of LAH (0.380 g, 10 mmol) in 20 mL THF was added a solution of **15b** (2.84 g, 10 mmol) in 10 mL of THF, and the mixture was stirred at room temperature overnight. The next day, the mixture was quenched with a saturated solution of aqueous sodium sulfate (10 mL). The mixture was filtered, and the filtrate was extracted with dichloromethane. The combined layers were washed with water, dried ($MgSO_4$), and evaporated, and the product was distilled: yield 1.54 g (86%); bp 100–105 °C (0.1 mm); IR (neat, cm$^{-1}$) 3350, 2950, 1460, 1400, 1020; $^1$H NMR (100 MHz, $CDCl_3$) δ 6.12 (s, 1 H, furan proton), 3.80–3.68 (m, 2 H, methylene protons adjacent to hydroxy group), 2.76–2.68 (t, 1 H, methine proton), 2.60 (s, 3 H, methylene protons adjacent to *gem*-dimethyls), 2.36 (s, 3 H, furan methyl), 1.28 (s, 3 H, methyl), 1.20 (s, 3 H, methyl). Anal. Calcd for $C_{11}H_{16}O_2$: C, 73.29; H, 8.94. Found: C, 73.55; H, 8.80.

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**4-[(Benzyloxy)methyl]-5,6-dihydro-2,5,5-trimethyl-4-cyclopenta[*b*]furan (9).** Furan **16** (0.540 g, 3 mmol) in 2 mL of THF was added to sodium hydride (0.2 g, 4.0 mmol of 50% washed with pentane to remove mineral oil) to 5 mL of THF followed by a catalytic amount (30 mg) of tetra-*n*-butylammonium iodide. The mixture was stirred for 30 min, and benzyl bromide (0.684 g, 4 mmol) was added. The mixture was stirred for 14 h at room temperature and then quenched with 10% HCl (2 mL) and extracted with dichloromethane. After drying and evaporation of the solvent, the crude material was purified by column chromatography using 10% ethyl acetate–hexane as eluant: yield 0.710 g (88%); bp 170–180 °C (0.3 mm); IR (neat, $cm^{-1}$) 2950, 1620, 1070, 890; $^1H$ NMR (100 MHz, $CDCl_3$) $\delta$ 7.20 (s, 5 H, aromatic), 5.72 (s, 1 H, furan proton), 4.44 (s, 2 H, benzyl protons), 3.48–3.40 (d, 2 H, $CH_2OCH_2Ph$), 2.76–2.60 (t, 1 H, methine proton), 2.40 (s, 2 H, methylene protons adjacent to *gem*-dimethyls), 2.20 (s, 3 H, furan methyl), 2.04 (s, 3 H, methyl), 1.12 (s, 3 H, methyl). Anal. Calcd for $C_{18}H_{22}O_2$: C, 79.96; H, 8.20. Found: C, 79.66; H, 8.41.

**2-(2-Oxopropyl)-3-[(benzyloxy)methyl]-4,4-dimethylcyclopentanone (17a).** Compound **9** (0.270 g, 1 mmol) was dissolved in 5 mL of 80% aqueous acetic acid, and a drop of concentrated $H_2SO_4$ was added to it. The mixture was heated to 70–80 °C for 1 h. The mixture was cooled, taken into dichloromethane, washed with saturated aqueous $NaHCO_3$ and water, dried, and evaporated. The crude material was then subjected to distillation: yield 0.240 g (82%); bp 200–210 °C (0.3 mm); IR (neat, $cm^{-1}$) 2900, 1730, 1360, 1080, 720; $^1H$ NMR (100 MHz, $CDCl_3$) $\delta$ 7.24 (s, 5 H, aromatic), 4.60 (s, 2 H, benzyl protons), 3.92–3.48 (m, 2 H, $CH_2OCH_2Ph$), 3.0–2.88 (t), 2.72–2.56 (band) (together integrating for 3 H), 2.36–2.32 (d, 2 H), 2.04 (br s, 4 H), 1.28 (s, 3 H, methyl), 1.0 (s, 3 H, methyl); $^{13}C$ NMR (25.0 MHz, $CDCl_3$) 217.3, 205.8, 137.8, 127.9, 127.1, 72.7, 70.3, 53.6, 49.7, 47.4, 42.4, 35.5, 29.4, 28.1, 22.2 ppm. Anal. Calcd for $C_{18}H_{24}O_3$: C, 74.96; H, 8.38. Found: C, 74.89; H, 8.41.

**2-Allyl-2,4,4-trimethylcyclopentanone (19).**[11] Compound **7** (7.0 g, 0.056 mol) in 5 mL of THF was added to a suspension of NaH (2.88 g, 0.120 mol of 50%) in 10 mL of THF, and the mixture was stirred at 55–60 °C for 5 h. Then it was cooled to room temperature, and allyl bromide (4.8 mL, 0.056 mol) was added dropwise. After the addition was complete, the reaction mixture was maintained at 55–60 °C overnight. The reaction mixture was quenched with dilute HCl, extracted with dichloromethane, dried ($MgSO_4$), and evaporated. The crude mixture was then distilled: yield 8.1 g (88%); bp 100 °C (0.8 mm); IR (neat, $cm^{-1}$) 3080, 1730, 1645, 1000, 920; $^1H$ NMR (100 MHz, $CDCl_3$) $\delta$ 5.72 (m, 1 H), 5.03 (m, 2 H), 1.13 (s, 3 H), 1.11 (s, 6 H); $^{13}C$ NMR (25.0 MHz, $CDCl_3$) 221.7, 133.8, 118.2, 53.0, 49.0, 48.7, 44.1, 33.0, 30.4, 30.1, 25.0 ppm.

**2-Allyl-5-[3,3-(ethylenedioxy)butyl]-2,4,4-trimethylcyclopentanone (20).** *n*-BuLi (16.6 mL of 1.2 M, 20 mmol) was added dropwise over a period of 30 min to a solution of diisopropylamine (2.525 g, 25 mmol) in 5 mL of THF cooled in an ice bath. After the mixture was allowed to stir for 30 min, compound **19** (3.32 g, 20 mmol) in 2 mL of THF was added slowly, and after the addition was over, the mixture was stirred at 5–10 °C for 2 h. Then a solution of 2-(2-methyl-1,3-dioxolan-2-yl)acetaldehyde (3.2 g, 24.6 mmol) in 2 mL of THF was added, and the mixture was stirred for 15 h at room temperature. At the end of this period, water (20 mL) was added, and the mixture was extracted with dichloromethane. The organic layer was dried over anhydrous $Na_2SO_4$ and evaporated. The crude mixture was purified by column chromatography using 20% ethyl acetate in hexane as the eluent: yield 3.04 g (100% based on **19** recovered); IR (neat, $cm^{-1}$) 3000, 1710, 1640, 1200, 1060; $^1H$ NMR (100 MHz, $CDCl_3$) $\delta$ 6.68–6.52 (t, olefin proton from enone in *Z* isomer), 6.0–5.84 (t, olefin proton from enone in *E* isomer) (together integrating for 1 H), 5.72–5.44 (m, 1 H, olefinic), 5.08–4.92 (m, 2 H, olefinic), 3.92 (s, 4 H, ketal protons), 3.04–2.96 (d, proton coupled to olefin proton of enone in *Z* isomer), 2.64–2.56 (d, proton coupled to olefin proton of the enone in *E* isomer) (together integrating for 2 H), 2.16–2.08 (d, 2 H), 1.96–1.44 (dd, 2 H, methylene protons of cyclopentanone), 1.32 (br s, 6 H, 2 methyls), 1.20 (s, 3 H, methyl), 1.08 (s, 3 H, methyl).

The enone obtained from the above operation (3.05 g, 11 mmol) in 5 mL of THF was added dropwise to a suspension of lithium (0.460 g, 66 mmol) in about 250 mL of liquid ammonia at −78 °C. After the addition was over, the reaction mixture was stirred at −78 °C for 1 h and then quenched with ammonium chloride (1.06 g, 20 mmol). After the evaporation of ammonia, the crude mixture was extracted with ether, washed once with water, dried ($Na_2SO_4$), evaporated, and purified by column chromatography (eluent: 20% ethyl acetate in hexane) to give a colorless liquid: yield 1.84 g (60%); IR (neat, $cm^{-1}$) 3000, 1740, 1660, 1480, 1400, 1060; $^1H$ NMR (100 MHz, $CDCl_3$) $\delta$ 5.92–5.44 (m, 1 H, olefinic), 5.08–4.92 (m, 2 H, olefinic), 3.92 (s, 4 H, ketal protons), 2.12–1.44 (band, 8 H), 1.32 (s, 3 H, methyl), 1.16 (s, 3 H, methyl), 1.08 (s, 3 H, methyl), 0.84 (s, 3 H, methyl). Anal. Calcd for $C_{17}H_{28}O_3$: C, 72.81; H, 10.06. Found: C, 72.56; H, 9.98.

**2-(2-Oxopropyl)-5-[3,3-(ethylenedioxy)butyl]-2,4,4-trimethylcyclopentanone (21).** Ketone **20** (0.50 g, 1.8 mmol) in 1 mL of DMF was added to a suspension of palladium chloride (0.106 g, 0.6 mmol) and cuprous chloride (0.360 g, 3.6 mmol) in 2 mL of DMF, and the reaction mixture was stirred at room temperature with oxygen bubbling through the reaction mixture for 20 h. The mixture was diluted with dichloromethane and filtered, and the filtrate was repeatedly (4–5 times) washed with water. After drying and evaporation, the crude material was purified by column chromatography (eluent: 30% ethyl acetate in hexane) to afford pure **21** as a viscous liquid: yield 0.285 g (54%); IR (neat, $cm^{-1}$) 3000, 1720, 1400, 1220, 1060; $^1H$ NMR (100 MHz, $CDCl_3$) $\delta$ 3.80 (s, 4 H, ketal protons), 2.52 (s, 2 H), 2.0 (s, 3 H, $COCH_3$), 1.80–1.40 (band, 6 H), 1.20 (s, 3 H, methyl), 1.08 (s, 3 H, methyl), 1.0 (s, 3 H, methyl), 0.80 (s, 3 H, methyl). Anal. Calcd for $C_{17}H_{28}O_4$: C, 68.88; H, 9.52. Found: C, 68.85; H, 9.50.

**(4*SR*,6a*RS*)-4-[3,3-(ethylenedioxy)butyl]-4,5,6,6a-tetrahydro-5,5,6a-trimethyl-2(1*H*)-pentalenone (22).** *tert*-Amyl alcohol (one drop) was added to a suspension of NaH (0.20 g, 4 mmol of 50%) in 5 mL of benzene, and the mixture was stirred at 60–70 °C for 15 min. Then **21** (0.56 g, 1.9 mmol) in 2 mL of benzene was added, and the reaction mixture was allowed to stir at 60–70 °C for 6 h. The mixture was cooled to room temperature, quenched with water, and extracted with dichloromethane. The organic layer was washed with water, dried, and evaporated. The crude material was subjected to purification by column chromatography and then crystallized from petroleum ether 40–60 °C: yield 0.315 g (60%); mp 73–74 °C; IR (neat, $cm^{-1}$) 3000, 1710, 1640, 1400, 1060; $^1H$ NMR (100 MHz, $CDCl_3$) $\delta$ 5.68–5.64 (d, 1 H, olefin proton from enone), 3.80 (s, 4 H, ketal protons), 2.48–2.40 (m, 1 H, allyl proton), 2.26 (AB, 2 H, methylene proton adjacent to cyclopentanone), 1.68–1.28 (band, 6 H), 1.20 (s, 3 H, methyl), 1.12 (s, 6 H, methyls), 1.06 (s, 3 H, methyl); $^{13}C$ NMR (25.0 MHz, $CDCl_3$) 210.3, 196.7, 121.7, 109.6, 64.5, 53.5, 52.7, 50.0, 46.1, 42.7, 38.7, 30.3, 30.0, 25.1, 23.5, 20.1 ppm. Anal. Calcd for $C_{17}H_{26}O_3$: C, 73.34; H, 9.41. Found: C, 73.60; H, 9.44.

**4-(3-Oxobutyl)-4,5,6,6a-tetrahydro-5,5,6-trimethyl-2-(1*H*)-pentalenone (23).** Compound **22** (0.275 g, 1 mmol) was dissolved in 6 mL of 80% aqueous acetic acid and stirred for 3 h at room temperature. The mixture was diluted with dichloromethane, the organic layer was washed with saturated aqueous $NaHCO_3$ and water, dried ($MgSO_4$), and evaporated. The crude material was purified by column chromatography, eluting with 10% ethyl acetate in hexane: yield 0.210 g (90%); IR (neat, $cm^{-1}$) 3000, 1710, 1640, 1460, 1400, 860, 840; $^1H$ NMR (100 MHz, $CDCl_3$) $\delta$ 5.68–5.64 (d, 1 H, olefin proton from enone), 2.64–2.44 (m, 3 H), 2.28–2.24 (AB, 2 H, methylene proton adjacent to *gem*-dimethyl), 2.12 (s, 3 H, $COCH_3$), 1.80–1.44 (band, 4 H), 1.20 (s, 6 H, methyls), 0.72 (s, 3 H, methyl). Anal. Calcd for $C_{15}H_{22}O_2$: C, 76.88; H, 9.46. Found: C, 76.80; H, 9.40.

**4-(3-Methyl-3-butenyl)-4,5,6,6a-tetrahydro-5,5,6a-trimethyl-2(1*H*)-pentalenone (24).** Sodium *tert*-amyl oxide (0.047 g, 0.427 mmol) in 1 mL of THF was added to a suspension of methyltriphenylphosphonium iodide (0.215 g, 0.535 mmol) in 2 mL of THF and stirred for 15 min. Compound **23** (0.050 g, 0.213 mmol) in 1 mL of THF was added to the deep red solution obtained, and the mixture was stirred at room temperature for 15 min. At the end of this period, the mixture was quenched with water (2 mL), diluted with ether, dried ($MgSO_4$), and evaporated. The product was purified by column chromatography (eluent: 10% ethyl acetate in hexane) to give **24** as a clear liquid: yield 0.024 g (50%); IR (neat, $cm^{-1}$) 2900, 1710, 1460, 800, 840; $^1H$ NMR (100 MHz, $CDCl_3$) $\delta$ 5.72–5.70 (d, 1 H, olefin from enone), 4.72–4.64 (band, 2 H, olefin protons in the side chain), 2.60–2.44 (m, 1 H,

allyl proton), 2.28–2.24 (AB, 2 H), 2.20–1.40 (m, 6 H), 1.72 (br s, 3 H, methyl), 1.20 (br s, 6 H, methyls), 0.72 (s, 3 H, methyl).

**Methyl 5-[3,3-(Ethylenedioxy)butyl]-2,4,4-trimethylcyclopentanone-2-acetate (26).** Sodium periodate (1.070 g, 5 mmol) and ruthenium(III) chloride (10 mg, catalytic) were added to a solution of **20** (0.560 g, 2.0 mmol) in 3 mL of carbon tetrachloride, 3 mL of acetonitrile, and 5 mL of water, and the reaction mixture was stirred at room temperature for 3 h. The mixture was diluted with dichloromethane, washed repeatedly with water (3–4 times), dried ($MgSO_4$), and evaporated.

The material obtained from the above procedure (0.580 g) was esterified with diazomethane, obtained as an ethereal solution from 1.05 g of *N*-nitróso-*N*-methylurea (10 mmol), and the resulting product was purified by column chromatography, using 20% ethyl acetate in hexane as the eluent: yield 0.60 g (100%); IR (neat, $cm^{-1}$) 3000, 1740, 1460, 1400, 1080; $^1H$ NMR (100 MHz, $CDCl_3$) $\delta$ 3.88 (s, 4 H, ketal protons), 3.60 (s, 3 H, carbomethoxy), 2.08 (s, 2 H, $CH_2CO_2Me$), 1.84–1.40 (m, 7 H), 1.28 (s, 3 H, methyl), 1.12 (s, 6 H, methyls), 0.84 (s, 3 H, methyl). Anal. Calcd for $C_{17}H_{28}O_5$: C, 65.36; H, 9.03. Found: C, 65.23; H, 8.94.

**Methyl 2,2-(Ethylenedioxy)-3-[3,3-(ethylenedioxy)butyl]-1,4,4-trimethylcyclopentaneacetate (27).** Triethyl orthoformate (2.22 g, 15 mmol) and *p*-toluenesulfonic acid (10 mg, catalytic) were added to a solution of **26** (0.930 g, 3 mmol) in ethylene glycol (1.86 g, 30 mmol), and the mixture was stirred at room temperature for 30 h. The mixture was then taken into dichloromethane and washed in succession with saturated aqueous $NaHCO_3$ and water, dried ($MgSO_4$), and evaporated. Purification of the compound was effected by column chromatography (eluent: 20% ethyl acetate–hexane). The title compound was obtained as a colorless liquid: yield 0.630 g (60%); IR (neat, $cm^{-1}$) 2950, 1720, 1460, 1380, 1060; $^1H$ NMR (100 MHz, $CDCl_3$) $\delta$ 3.92 (s, 8 H, protons from two ketals), 3.60 (s, 3 H, carbomethoxy), 2.40–1.44 (band, 9 H), 1.30 (s, 3 H, methyl), 1.16 (s, 6 H methyls), 0.88 (s, 3 H, methyl). Anal. Calcd for $C_{19}H_{32}O_6$: C, 64.02; H, 9.05. Found: C, 63.95; H, 9.03.

**Dimethyl 2-Oxo-3-[1,4,4-trimethyl-3-(oxobutyl)-2-oxocyclopentyl]propylphosphonate (28).** *n*-Butyllithium (3.16 mL of 1 M solution, 3.16 mmol) was added dropwise to a solution of dimethyl methylphosphonate (0.390 g, 3.16 mmol) in 2 mL of THF maintained at −78 °C, and after the addition was complete, the mixture stirred at −78 °C for 30 min. Compound **27** (0.450 g, 1.26 mmol) in 2 mL of THF was added to the solution at −78 °C over a period of 15 min, and after the addition, the reaction mixture was stirred at −78 °C for 5 h. The mixture was slowly allowed to come to room temperature, and then 3 N HCl (4 mL) was slowly added and the contents washed once with water, dried ($MgSO_4$), and evaporated to give crude **28**, which was used directly in the next step: yield 0.450 g (100%); IR (neat, $cm^{-1}$) 2950, 1720, 1740, 1040.

**4-(3-Oxobutyl)-4,5,6,6a-tetrahydro-5,5,6a-trimethyl-2(1*H*)-pentalenone (6).** Tetra-*n*-butylammonium hydroxide (40 wt % in water, 0.9 mL, 1.25 mmol) was added to a solution of **28** (0.450 g, 1.25 mmol) in 15 mL of benzene and 15 mL of water, and the mixture was stirred at room temperature for 30 min. The organic layer was removed, and the aqueous layer was added to the benzene solution, dried ($MgSO_4$), and evaporated. The material obtained was purified by column chromatography, eluting with 20% ethyl acetate in hexane: yield 0.20 g (70%); IR (neat, $cm^{-1}$) 2950, 1710, 1640, 1460, 1380, 860, 820; $^1H$ NMR (100 MHz, $CDCl_3$) $\delta$ 5.80 (s, 1 H, olefin proton from enone), 2.52–2.36 (m, 5 H), 2.16 (s, 3 H, $COCH_3$), 2.0–1.52 (m, 4 H), 1.32 (s, 3 H, methyl), 1.20 (s, 3 H, methyl), 1.0 (s, 3 H, methyl). Anal. Calcd for $C_{15}H_{22}O_2$: C, 76.88; H, 9.46. Found: C, 77.10; H, 9.48.

**4-(3-Hydroxybutyl)-4,5,6,6a-tetrahydro-5,5,6a-trimethyl-2(1*H*)-pentalenone (29).** Sodium borohydride (12 mg, 0.315 mmol) in 0.5 mL of methanol was added to a solution of **6** (55 mg, 0.235 mmol) in 1.5 mL of methanol at 0–5 °C, and the reaction mixture was stirred for 5 min. The reaction mixture was then quenched with acetone (1 mL) and stirred for another 5 min. The solvent was removed under vacuum, and the material obtained was purified by column chromatography (eluent: 20% ethyl acetate in hexane): yield 0.040 g (72%); IR (neat, $cm^{-1}$) 3300, 2950, 1710, 1640, 1060; $^1H$ NMR (100 MHz, $CDCl_3$) $\delta$ 5.80 (s, 1 H, olefin from enone), 2.40–2.20 (m, 5 H), 1.60–1.40 (m, 4 H), 1.32–1.24 (d, 3 H, methyl), 1.20 (s, 3 H, methyl), 1.04 (s, 3 H, methyl), 1.0 (s, 3 H, methyl). Anal. Calcd for $C_{15}H_{24}O_2$: C, 76.22; H, 10.23. Found: C, 76.10; H, 10.22.

**4-(*p*-Tolylthionocarbonato)-4,5,6,6a-tetrahydro-5,5,6a-trimethyl-2(1*H*)-pentalenone (30).** Pyridine (50 mg, 0.627 mmol) and *O*-*p*-tolyl chlorothioformate (37 mg, 0.627 mmol) were added to a solution of **29** (25 mg, 0.169 mmol) in 5 mL of dichloromethane, and the mixture was stirred for 1.5 h at room temperature. The solvents were removed under vacuum, and the product was purified by column chromatography (eluent: 20% ethyl acetate in hexane) and used as such in the next step: yield 0.040 g (70%); IR (neat, $cm^{-1}$) 3000, 1710, 1630, 1500, 1440, 1300, 1200, 840, 800; $^1H$ NMR (100 MHz, $CDCl_3$) $\delta$ 7.20–6.88 (AA'BB', 4 H, aromatic), 5.80 (s, 1 H, olefin proton from enone), 2.32 (s, 3 H), 1.80–1.48 (m, 9 H), 1.44–1.36 (d, 3 H, methyl), 1.28 (s, 3 H, methyl), 1.16 (s, 3 H, methyl), 0.96 (s, 3 H, methyl).

**2,2,4,9-Tetramethyltricyclo[6.3.0.0$^{1,5}$]undecan-6-one (5).** Compound **30** (35 mg, 0.090 mmol), 2.3 mg of AIBN, and tributyltin hydride (31 mg, 0.138 mmol) were added to 60 mL of thoroughly degassed toluene, and the mixture was heated to 80–90 °C for 3.5 h. The mixture was then cooled to room temperature, washed with 10% potassium fluoride, dired, and evaporated: yield 0.016 g (75%); IR (neat, $cm^{-1}$) 3000, 1740, 1460, 1400, 1200; $^1H$ NMR (270 MHz, $CDCl_3$) $\delta$ 2.30 (AB, 2 H), 2.18–1.90 (band, 3 H), 1.78 (s, 1 H), 1.75–1.15 (band, 2 H), 1.27 (s, 3 H, methyl), 1.11 (s, 3 H, methyl), 1.05 (s, 3 H, methyl), 1.0 (d, 3 H, methyl); $^{13}C$ NMR (25.0 MHz, $CDCl_3$) 219.1, 96.3, 64.4, 55.3, 53.4, 47.6, 44.5, 38.7, 36.3, 34.0, 29.3, 24.8, 24.0, 17.1 ppm; high-resolution mass expected for $C_{15}H_{24}O$ 220.1827, found 220.1822.

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