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Synthesis of heliannuols A and K, allelochemicals from cultivar sunflowers and the marine metabolite helianane, unusual sesquiterpenes containing a benzoxocane ring system

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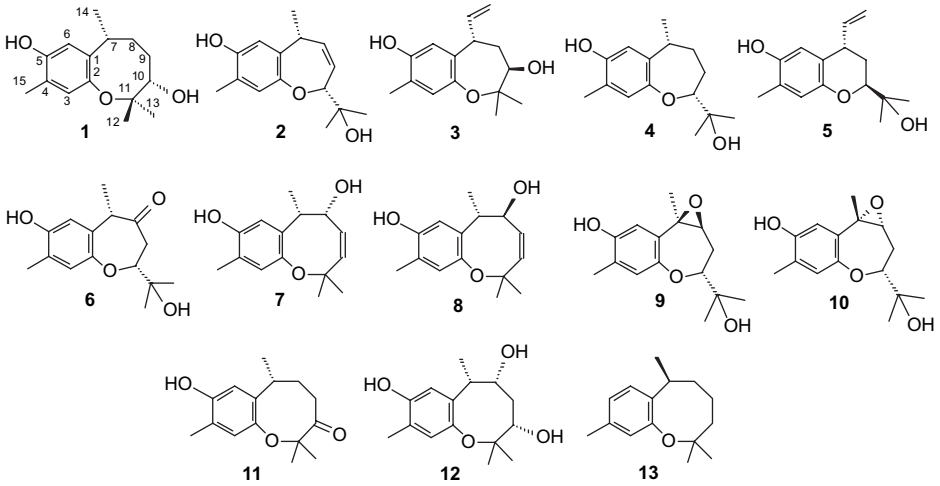
Abstract—Synthesis of the allelochemicals heliannuols A and K, and the sesquiterpene helianane is described. A regioselective cleavage of a benzo-fused oxabicyclo(5.1.0)octane system under hydrogenation as well as radical induced condition was developed to generate the basic benzoxocane ring system of these unusual sesquiterpenes.

1. Introduction

The development of a variety of chemicals as herbicides constitutes an important aspect of agricultural research. However, the exceedingly high cost of such chemical control agents, and the increasing awareness on their potential environment hazards have persuaded a fresh look at devising alternate ways of weed control. Sunflowers are cultivated in many parts of the world for production of oil. The plant (*Helianthus annus*) is also a rich source of a variety of natural products like sesquiterpenes and other plant metabolites displaying a wide spectrum of biological activity including allelopathic activity. Heliannuol A **1**[1] was the first member in a new group of phenolic sesquiterpenes isolated from the cultivar sunflowers and is distinctive in that it possesses a hitherto unknown benzoxocane ring system. The structure and relative stereochemistry was established from extensive spectral and single crystal X-ray diffraction analyses. This, together with its siblings heliannuols B–E **2**–**5**,[2] provides an interesting complement of benzo-fused six-, seven- and eight-membered cyclic ether skeletons and is believed to be involved in the allelopathic activity displayed by these flowers. Heliannuols F–L **6**–**12**, the oxidised variants of some of these main compounds, have also been isolated from these flowers subsequently.[3] Allelopathy, which is concerned with biochemical plant–plant and plant–microorganism interactions, including positive and negative effects, has been proposed as a possible alternate weed management policy.[4] The ongoing concern on the natural ecological balance and the risk posed by the indiscriminate use of synthetic



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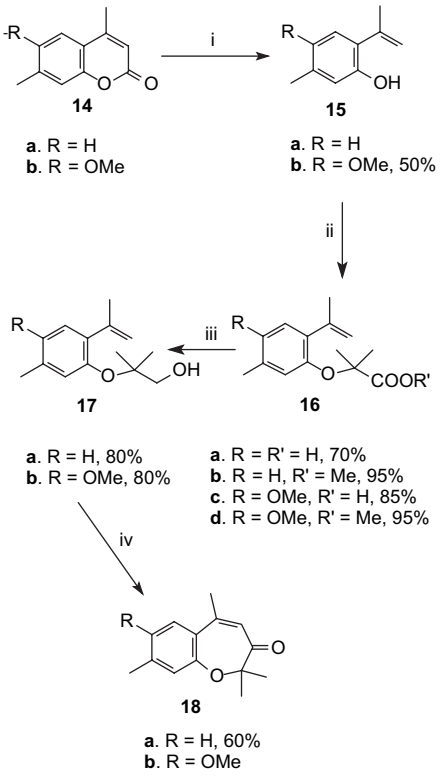
pesticides has provided a new impetus for the exploration of allelochemicals and their analogues as useful pest control agents obviating the hazardous side effects. In this context heliannuols, possessing significant allelopathic activity as natural herbicide models, have been very attractive targets for synthetic investigations from many laboratories.[5] Helianane **13**,[6] the C-5, C-10 deoxygenated ally of **1**, interestingly has been isolated from a marine sponge and differs from **1** in the configuration of the stereogenic centre bearing the secondary methyl group. This would suggest an interesting biogenesis of these two compounds and it has been suggested that while implicating bisabolene as the biogenetic precursor an interesting situation develops during the formation of the initial chirality, with the chiral centre emerging along two antipodal directions, one in plants as 5*R* and another in marine sponges as 5*S*.[6] We have initiated a comprehensive programme directed to the synthesis of the above compounds and have reported the synthesis of heliannuols A **1**,[7] C **3**[8] and D **4**[9] and helianane **13**.[10] In this paper we provide the full details of our synthesis of heliannuols A **1** and K **11** and the successful transformation of a model compound to helianane **13**.

2. Results and discussion

The crucial points to be taken care of in any effort to the synthesis of **1** are the incorporation of the *gem*-dimethyl group on C-11 and the stereochemistry at the two chiral centres. In formulating a synthetic approach to **1**, we proposed the initial development of a synthetic protocol for 5-deoxyheliannuol A **23a** with a two-fold objective. Primarily, if a methodology is developed for **23a**, it can then be applied to a suitable 5-hydroxy substituted starting material (or a protected variant) for transformation to **1**. Furthermore, it was envisaged that removal of the secondary hydroxy group in **23a** would also lead to a synthesis of helianane **13**. We describe herein the successful materialisation of this proposal.

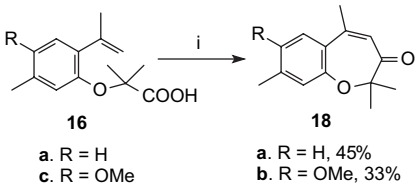
The synthesis began with the known styrenol **15a**, which had previously been employed by us in a synthesis of some marine sesquiterpenes.[11] This was subjected to a Bargellini reaction,[12] which provides a ready methodology for the incorporation of a geminal dialkyl group through alkylation onto alcohols, which had also been capitalised by other workers. In the event, reaction of **15a** with chloroform and acetone in presence of powdered sodium hydroxide furnished the *gem*-dimethyl incorporated carboxylic acid **16a** in 70% yield as a semisolid and was characterised as the corresponding methyl ester **16b**, obtained quantitatively on treatment with diazomethane. This ester was then reduced with lithium aluminium hydride to furnish the carbinol **17a** in excellent yield. In the next step of the synthesis, the carbinol **17a** was subjected to treatment with PCC in methylene chloride to obtain the corresponding aldehyde. However, the only product isolated in moderate yield was the benzoxepinenone **18a**, arising from the intermediate aldehyde undergoing an intramolecular aldo–ene reaction followed by reoxidation (Scheme 1). The structural assignment followed readily from the spectral data. In the IR the carbonyl absorption was seen at 1648 cm^{-1}. In the ^1H NMR, the vinylic methyl and the olefinic hydrogens appeared at δ 2.32 and 6.27, respectively. PCC induced intramolecular



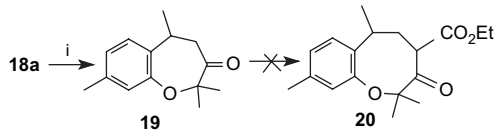
Scheme 1. Reagents and conditions: (i) KOH, ethylene glycol, reflux, 2 h; (ii) (a) $CHCl_3$, NaOH, acetone, reflux, 5 h; (b) CH_2N_2, ether; (iii) $LiAlH_4$, ether, reflux, 4 h; (iv) PCC, CH_2Cl_2, rt, 24 h.

carbonyl–ene cyclisations to lead to common rings has precedent,[13] but the present case appeared to be the first instance of such cyclisation to lead to a seven-membered ring. This benzoxepinenone **18a** could also be obtained in a moderate yield directly from the acid **16a** following our previous intramolecular acylation procedure involving treatment with thionyl chloride (Scheme 2).[14]

The ready availability of the unsaturated ketone **18a** in a single step from the alcohol **17a** (or the acid **16a**) encouraged us to proceed further with the synthesis involving transformation of this seven-membered ring compound to the benzoxocane ring system enshrined in **1** and **13**. This required a regioselective one-carbon ring expansion with retention of the carbonyl group in the same carbon atom. Catalytic hydrogenation of **18a** in presence of palladium carbon furnished the benzoxepanone **19** in quantitative yield. In keeping with our previous experience,[11] this ketone was subjected to a ring expansion with ethyl diazoacetate in presence of borontrifluoride etherate, anticipating a regioselective homologation involving migration of the less sterically encumbered primary bond adjacent to the keto-group to lead to the β-keto ester **20** (Scheme 3). However, under various

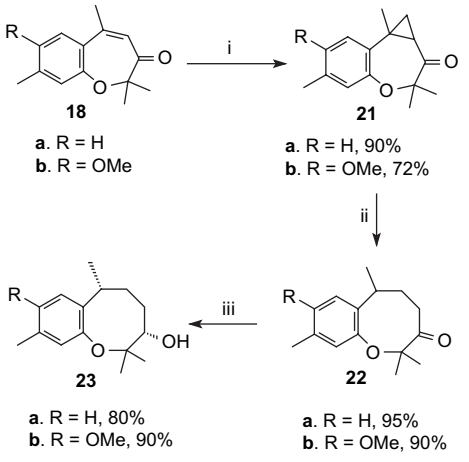


Scheme 2. Reagents and conditions: (i) $SOCl_2$, benzene, reflux, 3 h.



Scheme 3. Reagents and conditions: (i) H_2, Pd–C (10%), EtOH.

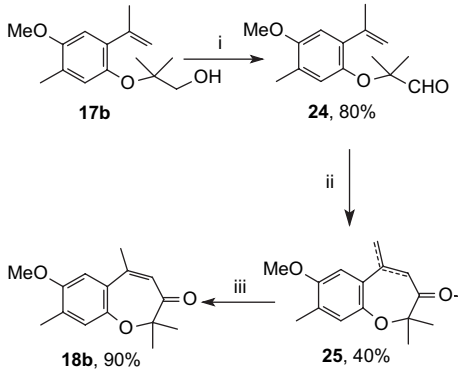
conditions tried, the benzoxepanone **19** remained obdurately unchanged. Change of catalyst to triethyloxonium fluoroborate also did not yield any desired result. Searching for alternative methods for effecting the crucial ring expansion, we reverted to the unsaturated ketone **18a**. It was proposed to convert this to the cyclopropyl ketone **21a**, anticipating that under reduction conditions, a selective cleavage of the more labile internal bond will ensue leading to the desired benzoxocanone **22a**. With this in view the benzoxopinenone **18a** was treated with diazomethane in presence of a catalytic amount of palladium acetate affording the cyclopropyl ketone **21a** in very good yield. This cyclopropyl ketone, when subjected to catalytic hydrogenation underwent the expected selective bond fission delivering the benzoxocanone **22a** exclusively in excellent yield. The presence of a single secondary methyl group in the ^{1}H NMR spectrum established the structural identity of the compound since in the event of any other bond cleavage it would have resulted in a seven-membered ring compound containing an additional secondary methyl group or a *gem*-dimethyl group. Thus, the development of a novel process for the generation of an eight-membered ring system through the selective cleavage of the central bond in a cyclopropane annulated cycloheptane ring has provided a ready access to the benzoxocane ring system of **1** and **13**. It is expected that this methodology, with its implied potential, will find future applications in synthesis. Reduction of the ketone **22a** with sodium borohydride in methanol furnished 5-deoxyheliannuol A **23a** in a stereocontrolled manner (Scheme 4). Although conformational flexibility is associated with the oxocane ring system, the secondary methyl group at C-7 would seem to direct the incoming hydride from the opposite side leading to the observed stereocontrol. This assignment has also an analogy in a previous synthesis of **1**.[5a] The assigned stereochemistry was further confirmed from NOE experiments between the C-7 and C-10 hydrogens.



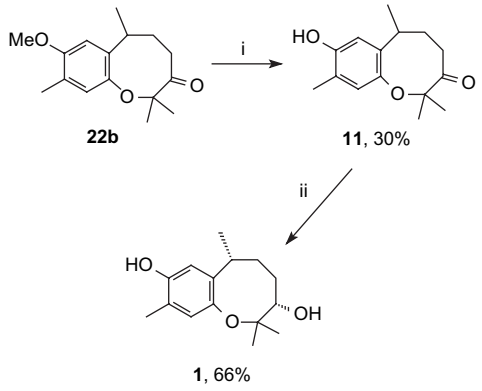
Scheme 4. Reagents and conditions: (i) CH_2N_2, $Pd(OAc)_2$ (cat.), ether, 0 °C, 4 h; (ii) H_2, Pd–C (10%), EtOH; (iii) $NaBH_4$, MeOH, rt, 4 h.

Encouraged by the successful development of the above procedure for a synthesis of 5-deoxyheliannuol A, efforts were then taken to apply the sequence of transformations to a suitably C-4 substituted derivative of the styrenol **15a**. Our focus fell on methoxy group as the appropriate substituent, since this functionality was unlikely to be affected under the reaction conditions employed in the synthesis of **23a** and furthermore, the demethylation of 5-*O*-methylheliannuol A to **1** had been reported earlier.[5a] 4,7-Dimethyl-6-hydroxycoumarin was methylated to **14b** under standard conditions involving reaction with methyl iodide in refluxing acetone in presence of potassium carbonate. This coumarin **14b** was then subjected to a decarboxylative hydrolysis by refluxing an ethylene glycol solution with added potassium hydroxide and afforded the required methoxy protected styrenol **15b**. Bargellini condensation of this styrenol with chloroform and acetone in presence of sodium hydroxide proceeded smoothly furnishing the *gem*-dimethyl substituted carboxylic acid **16c** in 85% yield as a very viscous liquid and was characterised as the methyl ester **16d**, obtained from reaction with diazomethane. Reduction of the ester **16d** with lithium aluminium hydride generated the carbinol **17b** (80%) for carrying out the next step of PCC oxidation, as for **17a**, to obtain the methoxy benzoxopinenone **18b** (Scheme 1). However, in this particular case the oxidation resulted in only a complex mixture of products and no benzoxopinenone derivative could be identified. Since the further continuation of the synthesis entirely hinged on the preparation of the methoxy benzoxopinenone **18b**, a modification in the oxidation step was deemed in order. To this end, the carbinol **17b** was subjected to an oxidation under Swern condition employing oxalyl chloride and dimethyl sulfoxide furnishing the aldehyde **24**, in good yield (80%). When this aldehyde was treated with PCC, it underwent the expected aldo–ene cyclisation and reoxidation to deliver the methoxy benzoxopinenone **25**, in a moderate yield as a mixture of exocyclic and endocyclic isomers. Brief treatment of this mixture in THF with a catalytic amount of sulfuric acid resulted in the isomerisation of the *exo*-isomer to the more stable *endo*-isomer and the desired benzoxopinenone **18b** was obtained in an overall yield of 40% (Scheme 5). Application of the single-step procedure to the acid **16c** involving reaction with thionyl chloride also resulted in an intramolecular cyclisation to furnish the same unsaturated ketone **18b** in a moderate yield (Scheme 2). This unsaturated ketone was transformed to the 5-methoxy benzoxocanone **22b**, following the previously established sequence of reactions (Scheme 4). Thus, reaction of **18b** with diazomethane in presence of palladium acetate furnished the cyclopropyl ketone **21b**, which on catalytic hydrogenation delivered the benzoxocanone **22b** (*O*-methyl heliannuol K) in good overall yield. Reduction of **22b** with sodium borohydride proceeded in a stereocontrolled manner as before to afford *O*-methyl heliannuol A **23b** whose spectral data matched with reported values.[5a] Demethylation of **23b** to heliannuol A **1** has already been reported,[5a] thus concluding a formal synthesis of this allelochemical. The synthesis of heliannuol K **11** was completed by demethylation of **22b** employing in situ generated iodotrimethyl silane[15] furnishing **11** in 30% yield (Scheme 6). The ^{1}H NMR spectral features of synthetic **11** matched with those reported[3a] for the natural compound establishing the identity. Additionally, reduction of **11** with sodium borohydride in methanol afforded

heliannuol A **1** in 66% yield, whose spectral characteristics were also in agreement with the reported values.[5f]

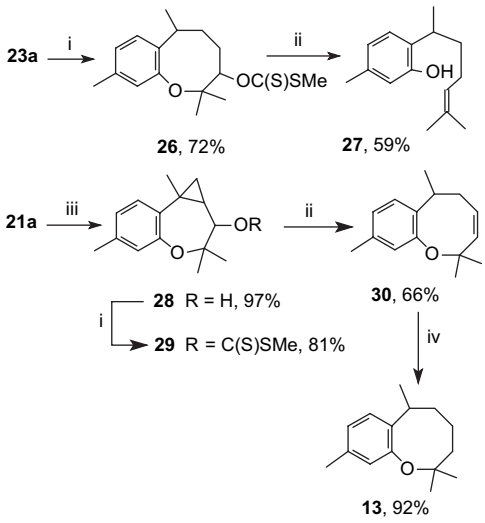


Scheme 5. Reagents and conditions: (i) $(COCl)_2$, DMSO, CH_2Cl_2, −68 °C, 45 min; (ii) PCC, CH_2Cl_2, rt, 24 h; (iii) H_2SO_4 (cat.), THF, 24 h.



Scheme 6. Reagents and conditions: (i) $(CH_3)_3SiCl$, NaI, CH_3CN, reflux, 48 h; (ii) $NaBH_4$, MeOH, rt, 4 h.

It will be recalled that the synthesis of 5-deoxyheliannuol A **23a** was undertaken with the additional objective of transforming this to helianane **13**, through a deoxygenation. For this we proposed to employ the well established Barton–McCombie radical induced deoxygenation of the corresponding *S*-methyl thionocarbonate.[16] Towards this, **23a** was converted to the thionocarbonate **26** by interaction with carbon disulfide and methyl iodide in presence of sodium hydride. When this derivative was subjected to a radical reaction with tri-*n*-butyltin hydride, the only product isolated in moderate yield was curcuphenol **27**[17] arising from a fragmentation induced by the generated radical (Scheme 7). Seemingly, the stability of the phenoxy radical resulting from a cleavage took precedence to reduction. In view of this turn of events, it was decided to harness the cyclopropyl ketone **21a** for achieving the desired result. Reduction of this ketone with sodium borohydride furnished the carbinol **28** in excellent yield as a single isomer. No effort was made to establish the stereochemistry of this alcohol since it was not considered relevant to subsequent steps. We argued that if this carbinol is subjected to the same radical deoxygenation, a cleavage of the cyclopropyl ring will take place in preference to fragmentation to a phenol. Furthermore, it was also anticipated that the selectivity in the cleavage of the cyclopropane ring will follow the same pattern encountered in the hydrogenation of **21a**. Following this argument, when the carbinol **28** was converted to the thionocarbonate **29** and subjected to reaction with tri-*n*-butyltin hydride, it underwent the expected selective cleavage of the cyclopropane central bond affording the ring-enlarged alkene **30** in good overall yield (Scheme 7). The presence of two olefinic hydrogens in the ^{1}H NMR spectrum in combination with the appropriate features for the other hydrogens matching with the values reported previously,[18] attested to the formation of this alkene. Catalytic hydrogenation of this alkene in presence of palladium carbon furnished helianane **13**, spectroscopically identical with the sample previously synthesised in this laboratory.[10]



Scheme 7. Reagents and conditions: (i) NaH, CS_2, MeI, THF, rt, 18 h; (ii) ^{n}Bu_3SnH, AIBN, toluene, reflux, 4 h; (iii) $NaBH_4$, MeOH, rt, 4 h; (iv) H_2, Pd–C (10%), EtOH.

In summary, a novel construction of the benzoxocane ring system enshrined in the sesquiterpenes heliannuol A, K and helianane has been developed in which an intramolecular aldo–ene cyclisation to generate a benzoxepane ring system and a ring enlargement involving a selective central bond cleavage in a cyclopropane annulated cycloheptane ring are the key steps. It is anticipated that these methodologies will have wider implications in the generation of complex ring systems of sesquiterpenes and related natural products.

3. Experimental

3.1. General

Melting points are uncorrected. Purity of products was routinely monitored by TLC. Preparative TLC was performed with silica gel 60 HF_{254} plates of 1 mm thickness. The petroleum ether used is that fraction of bp 60–80 °C. Na_2SO_4 was used to dry organic extracts. The IR spectra are of $CHCl_3$ solutions. ^{1}H NMR spectra of $CDCl_3$ solutions were recorded at 300 MHz and ^{13}C NMR spectra at 75 MHz.

3.1.1. Methyl-2-methyl-2-(2′-isopropenyl-5′-methyl) phenoxy-propionate (16b). Powdered NaOH (14 g, 350 mmol) was added in small portions with stirring to a solution of 2-isopropenyl-5-methyl phenol **15a** (5.52 g, 37.3 mmol) in acetone (50 mL). The mixture became warm and was cooled to about 35 °C. To this stirred solution chloroform (15 mL)

was added within 10 min. The reaction mixture was then refluxed for 5 h, cooled, concentrated to one-third of its volume and diluted with water (20 mL). It was acidified with 6 M HCl and extracted thoroughly with ether (50 mL×3). The combined ethereal extract was further extracted with saturated aqueous $NaHCO_3$ (50 mL×3). The alkaline aqueous part was neutralised with cold 6 M HCl, extracted with ether (30 mL×3), washed with brine (20 mL×2) and dried. The solvent was removed to afford the phenoxy propionic acid **16a** (5.07 g, 70%) as a semisolid residue. This acid was esterified with diazomethane to furnish the methyl ester **16b**, which was purified by column chromatography over silica gel eluting with petroleum ether–ethyl acetate (20:1) to give the ester **16b** as a colourless liquid (5.10 g, 95%). IR 1750 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 7.07 (d, 1H, J=7 Hz), 6.76 (d, 1H, J=7.6 Hz), 6.49 (s, 1H), 5.07 (br s, 1H), 5.01 (br s, 1H), 3.78 (s, 3H), 2.26 (s, 3H), 2.11 (s, 3H), 1.50 (s, 6H). δ_C (75 MHz, $CDCl_3$) 175.6, 152.8, 144.9, 138.1, 133.7, 129.9, 123.2, 118.8, 115.3, 79.8, 52.8, 25.6, 25.6, 23.6, 20.7. Anal. Calcd for $C_{15}H_{20}O_3$: C, 72.55; H, 8.12. Found: C, 72.52; H, 7.95.

3.1.2. 2-Methyl-2-(2′-isopropenyl-5′-methyl phenoxy) propan-1-ol (17a). To a magnetically stirred slurry of $LiAlH_4$ (2.14 g, 45 mmol) in dry ether (100 mL) was added dropwise a solution of the ester **16b** (7 g, 30 mmol) in dry ether (50 mL). The reaction mixture was refluxed for 4 h, cooled and then decomposed with cold saturated aqueous Na_2SO_4 solution. The ether layer was separated and the aqueous layer was extracted with ether (30 mL×2). The combined ether extracts were washed with brine, dried and concentrated to afford an oil, which was purified by column chromatography over silica gel eluting with petroleum ether–ethyl acetate (9:1) to furnish the alcohol **17a** as a colourless liquid (5.27 g, 80%). IR 3440 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 7.07 (d, 1H, J=8.1 Hz), 6.85 (m, 2H), 5.18 (br s, 1H), 5.04 (br s, 1H), 3.52 (s, 2H), 2.31 (s, 3H), 2.10 (s, 3H), 1.27 (s, 6H). δ_C (75 MHz, $CDCl_3$) 151.8, 144.8, 137.7, 135.4, 129.0, 124.0, 123.7, 115.4, 81.8, 70.5, 23.7, 23.4, 23.4, 21.2. Anal. Calcd for $C_{14}H_{20}O_2$: C, 76.32; H, 9.15. Found: C, 76.12; H, 9.07.

3.1.3. 2,3-Dihydro-2,2,5,8-tetramethyl-1-benzoxepin-4-en-3-one (18a). To a magnetically stirred suspension of PCC (1 g, 4.7 mmol) in DCM (10 mL) was added the styrenol **17a** (520 mg, 2.3 mmol) in DCM (10 mL) in one portion. After stirring overnight, dry ether (50 mL) was added and the supernatant liquid was decanted from the black gum. The insoluble residue was washed thoroughly with ether (25 mL). The combined organic extract was concentrated and the residual oil was purified by column chromatography over silica gel using petroleum ether–ethyl acetate (19:1) as the eluent to afford the benzoxepinenone **18a** (353 mg, 60%) as a colourless liquid. IR 1648 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 7.34 (d, 1H, J=8.1 Hz), 7.01 (d, 1H, J=8.1 Hz), 6.94 (s, 1H), 6.27 (br s, 1H), 2.36 (s, 3H), 2.32 (s, 3H), 1.34 (s, 6H). δ_C (75 MHz, $CDCl_3$) 203.0, 153.9, 146.6, 141.8, 128.1, 125.1, 124.5, 113.5, 86.7, 25.3, 24.2, 24.2, 23.0, 21.2. Anal. Calcd for $C_{14}H_{16}O_2$: C, 77.7; H, 7.46. Found: C, 77.7; H, 7.40.

3.1.4. Direct preparation of 18a from acid 16a. To a solution of the phenoxy propionic acid **16a** (200 mg, 0.855 mmol) in dry benzene (15 mL) was added freshly distilled thionyl chloride (234 mg, 1.97 mmol). The reaction mixture was heated under reflux for 3 h. It was then cooled and excess thionyl chloride was removed by azeotropic distillation under vacuum with fresh addition of benzene (5 mL×3). The residue was extracted with ether (20 mL×3), washed with brine and water, dried and concentrated. The crude residue was subjected to column chromatography over silica gel. Elution with petroleum ether–ethyl acetate (19:1) afforded the benzoxepinenone **18a** (83 mg, 45%) as a colourless liquid spectroscopically identical with the sample above.

3.1.5. 2,2,5,8-Tetramethyl-1-benzoxepan-3-one (19). The unsaturated ketone **18a** (200 mg, 0.869 mmol) in double distilled ethanol was subjected to hydrogenation in the presence of 10% Pd–C (50 mg) as catalyst at atmospheric pressure. After 1.5 h it was filtered and concentrated. The residual oil was purified by column chromatography over silica gel. Elution with petroleum ether–ethyl acetate (20:1) furnished the benzoxepanone **19** (180 mg, 90%) as colourless oil. IR 1710 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 7.02 (d, 1H, J=7.5 Hz), 6.89 (d, 1H, J=7.5 Hz), 6.76 (s, 1H), 3.19–3.09 (m, 2H), 2.91–2.86 (m, 1H), 2.27 (s, 3H), 1.42 (s, 3H), 1.32 (d, 3H, J=6.6 Hz), 1.28 (s, 3H). δ_C (75 MHz, $CDCl_3$) 214.7, 153.6, 137.6, 132.9, 130.0, 125.9, 125.3, 88.2, 45.1, 33.7, 25.4, 24.6, 23.5, 21.1. Anal. Calcd for $C_{14}H_{18}O_2$: C, 77.03; H, 8.31. Found: C, 77.13; H, 8.26.

3.1.6. 2,6,6,10-Tetramethyl-7-oxa-tricyclo[6.4.0^{1,8}.0^{2,4}]-dodec-1,9,11-trien-5-one (21a). To a stirred solution of the unsaturated ketone **18a** (1 g, 4 mmol) and $Pd(OAc)_2$ (10 mg) in dry ether (15 mL), a large excess of ethereal diazomethane solution was added dropwise at 0 °C and the resulting mixture was stirred continuously at room temperature for 12 h. The oil, after removal of ether, was purified by column chromatography over silica gel and eluted with petroleum ether–ethyl acetate (49:1) to furnish the cyclopropyl ketone **21a** (600 mg, 60%) as a colourless oil. The yield was 90% based on the recovered starting material (200 mg). IR 1675 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 7.23 (d, 1H, J=7.9 Hz), 6.92 (d, 1H, J=7.9 Hz), 6.71 (s, 1H), 3.09–3.06 (m, 1H), 2.28 (s, 3H), 2.13–2.08 (m, 2H), 1.52 (s, 6H), 1.24 (s, 3H). δ_C (75 MHz, $CDCl_3$) 211.1, 152.8, 137.5, 132.6, 128.5, 125.9, 125.8, 88.3, 39.1, 27.8, 27.7, 26.2, 23.4, 21.8, 21.1. Anal. Calcd for $C_{15}H_{18}O_2$: C, 78.23; H, 7.88. Found: C, 78.55; H, 7.72.

3.1.7. 2,2,6,9-Tetramethyl-1-benzoxocan-3-one (22a). The cyclopropyl ketone **21a** (200 mg, 0.8 mmol) in double distilled ethanol (3 mL) was hydrogenated using 10% Pd–C (50 mg) as catalyst at atmospheric pressure. After 2 h it was filtered and the solvent was removed under reduced pressure. The residual oil was purified by column chromatography over silica gel and eluted with petroleum ether–ethyl acetate (49:1) to afford the cyclic ketone **22a** (180 mg, 95%) as a colourless oil. IR 1710 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 7.05 (d, 1H, J=7.8 Hz). 6.91 (d, 1H, J=7.8 Hz), 6.76 (s, 1H), 3.15–3.10 (m, 1H), 2.50–2.44 (m, 2H), 2.28 (s, 3H), 2.02–1.97 (m, 1H), 1.62–1.58 (m, 1H), 1.51 (s, 3H), 1.45 (s, 3H), 1.31 (d, 3H, J=6.9 Hz). δ_C (75 MHz, $CDCl_3$) 212.0, 152.8, 136.1, 127.2, 126.1, 125.9, 125.9, 86.1, 35.9, 34.6, 33.7, 24.4, 23.3, 20.8, 20.3. Anal. Calcd for $C_{15}H_{20}O_2$: C, 77.55; H, 8.68. Found: C, 77.46; H, 8.65.

3.1.8. 2,2,6,9-Tetramethyl-1-benzoxocan-3-ol, 5-deoxyheliannuol A (23a). The above ketone **22a** (50 mg, 0.2 mmol) in methanol (1 mL) was cooled to 0 °C (ice bath) and $NaBH_4$ (20 mg, 0.4 mmol) was added portionwise with stirring and left overnight. Next day it was diluted with twice its volume of water and extracted with ether (10 mL×2). The combined ethereal extract was washed with water, dried and concentrated. The residual oil was purified by thin layer chromatography. Elution with petroleum ether–ethyl acetate (19:1) afforded the alcohol **23a** (41 mg, 80%) as a colourless liquid. IR 3440 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 7.06 (d, 1H, J=9 Hz), 6.90 (d, 1H, J=9 Hz), 6.79 (s, 1H), 3.40 (d, 1H, J=9 Hz), 3.20–3.15 (m, 1H), 2.29 (s, 3H), 2.0–1.96 (m, 4H), 1.66–1.54 (br, 1H), 1.45 (s, 3H), 1.40 (s, 3H), 1.26 (d, 3H, J=9 Hz). δ_C (75 MHz, $CDCl_3$) 153.0, 138.2, 136.0, 126.1, 126.0, 125.9, 125.5, 83.4, 36.5, 32.9, 32.2, 26.1, 23.5, 21.3, 21.3. Anal. Calcd for $C_{15}H_{22}O_2$: C, 76.88; H, 9.46. Found: C, 76.82; H, 9.40.

3.1.9. 2-Isopropenyl-4-methoxy-5-methyl phenol (15b). 4,7-Dimethyl-6-methoxy coumarin **14b** (13 g, 74.7 mmol) was added portionwise to a solution of KOH (18 g, 321 mmol) in water (8 mL) and ethylene glycol (120 mL) and the reaction mixture was refluxed for 2 h. It was cooled and poured into crushed ice and extracted with ether (50 mL×3). The organic layer was washed with brine and dried. The residue after removal of solvent was distilled to afford the styrenol **15b** (5.7 g, 50%), bp 108–110 °C/1 mm Hg. δ_H (300 MHz, $CDCl_3$) 6.50 (s, 1H), 6.38 (s, 1H), 5.13 (br s, 1H), 5.13 (br s, 1H), 4.90 (s, 1H), 3.54 (s, 3H), 1.96 (s, 3H), 1.89 (s, 3H). δ_C (75 MHz, $CDCl_3$) 151.7, 145.8, 142.8, 127.7, 126.6, 118.3, 115.8, 110.2, 56.4, 24.5, 16.3. Anal. Calcd for $C_{11}H_{14}O_2$: C, 74.16; H, 7.86. Found: C, 74.11; H, 7.85.

3.1.10. Methyl-2-methyl-2-(2′-isopropenyl-4′-methoxy-5′-methyl) phenoxy-propionate (16d). The styrenol **15b** was converted to the phenoxy propionic acid **16c** in 70% yield as a semisolid product following conditions as for **16a** and was esterified with diazomethane to furnish the ester **16d** in 95% yield as a colourless liquid. IR 1751 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 6.64 (s, 1H), 6.59 (s, 1H), 5.09 (br s, 1H), 5.03 (br s, 1H), 3.79 (s, 3H), 3.78 (s, 3H), 2.14 (s, 3H), 2.13 (s, 3H), 1.49 (s, 6H). δ_C (75 MHz, $CDCl_3$) 175.3, 153.0, 145.5, 145.1, 135.1, 125.8, 122.2, 115.0, 111.2, 80.1, 55.6, 52.3, 25.3, 25.0, 23.3, 16.1. Anal. Calcd for $C_{16}H_{22}O_4$: C, 69.06; H, 7.91. Found: C, 68.20; H, 7.84.

3.1.11. 2-Methyl-2-(2′-isopropenyl-4′-methoxy-5′-methyl phenoxy) propan-1-ol (17b). The ester **16b** was reduced with $LiAlH_4$ as for **17a** to afford the alcohol **17b** in 80% yield as a colourless oil. δ_H (300 MHz, $CDCl_3$) 6.79 (s, 1H), 6.63 (s, 1H), 5.19 (br s, 1H), 5.07 (br s, 1H), 3.79 (s, 3H), 3.51 (s, 2H), 2.17 (s, 3H), 2.13 (s, 3H), 1.23 (s, 6H). δ_C (75 MHz, $CDCl_3$) 153.4, 145.2, 144.6, 136.2, 136.2, 125.9, 125.7, 115.4, 110.5, 81.4, 70.1, 55.4, 23.5, 23.3, 15.9. Anal. Calcd for $C_{15}H_{22}O_3$: C, 72.0; H, 8.80. Found: C, 71.76; H, 8.75.

3.1.12. 2,3-Dihydro-2,2,5,8-tetramethyl-7-methoxy-1-benzoxepin-4-en-3-one (18b). To a solution of oxalyl chloride (3.35 g, 26 mmol) in DCM (30 mL), dimethyl sulfoxide (4.12 g, 530 mmol) in DCM (4 mL) was added dropwise at −68 °C. After 6 min a solution of the alcohol **17b** (3.3 mg, 132 mmol) in DCM (12 mL) was added to the complex. After 25 min, NEt_3 (6.58 g, 66 mmol) was added. After 15 min the cooling bath was removed and the reaction was quenched with water (50 mL). The reaction mixture was partitioned between water and DCM. The organic layer was washed with water and brine and then dried. Removal of solvent afforded the aldehyde **24** as a colourless oil (2.6 g, 80%). IR 1735 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 9.76 (s, 1H), 6.56 (s, 1H), 6.49 (s, 1H), 5.05 (d, 1H, J=1.6 Hz), 4.97 (d, 1H, J=1.23 Hz), 3.70 (s, 3H), 2.05 (s, 3H), 2.03 (s, 3H), 1.25 (s, 6H). δ_C (75 MHz, $CDCl_3$) 203.9, 153.8, 145.4, 145.2, 135.7, 126.5, 123.6, 115.9, 111.6, 84.5, 56.0, 23.8, 22.2, 22.1, 16.3. This was directly used in the next step without further purification.

To a magnetically stirred suspension of PCC (4.5 g, 20.9 mmol) in DCM (70 mL) was added the styrene aldehyde **24** (2.55 g, 10.3 mmol) in DCM (20 mL) in one portion. After stirring for 24 h, dry ether (100 mL) was added and the supernatant liquid was decanted from the black gum. The insoluble residue was washed thoroughly with ether (50 mL). The combined organic extract was concentrated and the residual oil contained a mixture of exocyclic and endocyclic isomers (^1H NMR). Brief treatment of this isomeric mixture in THF with a few drops of dilute H_2SO_4 resulted in isomerisation to the desired endocyclic isomer as yellow coloured viscous oil. It was purified by column chromatography over silica gel. Elution with petroleum ether–ethyl acetate (49:1) afforded the benzoxepinenone **18b** (1.02 g, 40%) as a colourless solid, which was crystallised from petroleum ether, mp 117–118 °C. IR 1647 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 6.90 (s, 1H), 6.80 (s, 1H), 6.28 (s, 1H), 3.84 (s, 3H), 2.33 (s, 3H), 2.23 (s, 3H), 1.32 (s, 6H). δ_C (75 MHz, $CDCl_3$) 203.4, 154.2, 147.4, 146.5, 130.5, 128.6, 128.5, 125.9, 108.7, 86.9, 55.7, 25.2, 24.1, 24.1, 16.1. Anal. Calcd for $C_{15}H_{18}O_3$: C, 73.17; H, 7.32. Found: C, 73.31; H, 7.38. This was also prepared in 33% yield directly from the acid **16c** employing the thionyl chloride procedure.

3.1.13. 2,6,6,10-Tetramethyl-11-methoxy-7-oxa-tricyclo[6.4.0^{1,8}.0^{2,4}]dodec-1,9,11-trien-5-one (21b). This was prepared from the unsaturated ketone **18b** following procedure for **18a** and obtained as a colourless solid in 72% yield. Crystallised from ether–petroleum ether, mp 78–79 °C. IR 1678 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 6.79 (s, 1H), 6.68 (s, 1H), 3.80 (s, 3H), 2.93 (t, 1H, J=5.1 Hz), 2.13 (s, 3H), 2.10 (m, 1H), 1.53 (s, 3H), 1.48 (s, 3H), 1.26 (s, 3H), 1.22 (m, 1H). δ_C (75 MHz, $CDCl_3$) 210.7, 154.6, 145.8, 133.0, 126.7, 125.2, 110.2, 87.7, 55.7, 38.1, 27.1, 26.7, 25.8, 23.1, 21.1, 15.6. Anal. Calcd for $C_{16}H_{20}O_3$: C, 73.85; H, 7.69. Found: C, 73.68; H, 7.93.

3.1.14. 2,2,6,9-Tetramethyl-8-methoxy-1-benzoxocan-3-one (22b). The cyclopropyl ketone **21b** was hydrogenated following conditions as for **21a** and afforded the cyclic ketone **22b** as a colourless oil in 90% yield. IR 1712 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 6.73 (s, 1H), 6.57 (s, 1H), 3.77 (s, 3H), 3.15–3.09 (m, 1H), 2.55–2.44 (m, 2H), 2.14 (s, 3H), 2.0–1.94 (m, 1H), 1.73–1.68 (m, 1H), 1.48 (s, 3H), 1.44 (s, 3H), 1.35 (d, 3H, J=5.1 Hz). δ_C (75 MHz, $CDCl_3$) 212.9, 154.8, 145.9, 136.9, 127.4, 124.3, 108.7, 85.9, 55.4, 36.0, 34.6, 34.4, 24.3, 23.4, 20.4, 15.7. Anal. Calcd for $C_{16}H_{22}O_3$: C, 73.25; H, 8.45. Found: C, 72.96; H, 8.43.

3.1.15. 2,2,6,9-Tetramethyl-8-methoxy-1-benzoxocan-3-ol, *O*-methyl heliannuol A (23b). Reduction of the ketone **22b** with $NaBH_4$ as for **22a** furnished *O*-methyl heliannuol A **23b** in 90% yield as a colourless oil. IR 3446 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 6.66 (s, 1H), 6.53 (s, 1H), 3.72 (s, 3H), 3.31 (d, 1H, *J*=8.9 Hz), 3.11 (m, 1H), 2.07 (s, 3H), 2.03–1.94 (m, 2H), 1.92–1.85 (m, 2H), 1.70 (br s, 1H), 1.34 (s, 3H), 1.28 (s, 3H), 1.19 (d, 3H, *J*=7 Hz). δ_C (75 MHz, $CDCl_3$) 154.8, 146.0, 138.9, 127.3, 124.1, 107.8, 83.0, 76.0, 55.9, 36.4, 33.2, 32.3, 26.0, 23.4, 21.4, 16.2. Anal. Calcd for $C_{16}H_{24}O_3$: C, 72.69; H, 9.15. Found: C, 72.53; H, 9.50.

3.1.16. 2,2,6,9-Tetramethyl-8-hydroxy-1-benzoxocan-3-one, heliannuol K (11). To a solution of the ketone **22b** (150 mg, 0.573 mmol) and sodium iodide (103 mg, 0.687 mmol) in acetonitrile (3 mL), chlorotrimethylsilane (0.07 mg, 0.69 mmol) was added slowly and the reaction mixture was refluxed for 48 h. Then it was cooled, water (5 mL) was added and extracted with ether (10 mL×3). The combined organic extract was washed with saturated aqueous sodium thiosulfate and water and dried. The solvent was removed and the residue subjected to thin layer chromatography with petroleum ether–ethyl acetate (12:1) to furnish heliannuol K **11** (30 mg, 30%) as colourless oil. IR 3404.1, 1708.8 cm^{-1}; δ_H (300 MHz, $CDCl_3$): 6.70 (s, 1H), 6.55 (s, 1H), 3.06 (m, 1H), 2.47 (m, 2H), 2.17 (s, 3H), 1.95 (m, 2H), 1.49 (s, 3H), 1.43 (s, 3H), 1.27 (d, 3H, *J*=7.08 Hz). δ_C (75 MHz, $CDCl_3$): 213.2, 151.2, 146.3, 137.9, 127.6, 121.7, 113.6, 86.0, 36.2, 34.7, 34.0, 24.6, 23.4, 20.5, 15.6. HRMS (*m/z*) [M+Na] calcd for $C_{15}H_{20}O_3$: 271.1309, found: 271.1287.

3.1.17. 2,2,6,9-Tetramethyl-8-hydroxy-1-benzoxocan-3-ol, heliannuol A (1). To an ice cold solution of heliannuol K **11**, obtained above, (22 mg, 0.089 mmol) in dry methanol (2 mL) was added $NaBH_4$ (6.6 mg, 0.18 mmol) and the reaction mixture was stirred at room temperature for 2 h. Then it was diluted with water (3 mL) and extracted with ether (5 mL×3). The combined ether extract was washed with water (5 ml×2) and dried. The residue after removal of the solvent was purified by thin layer chromatography and eluted with petroleum ether–ethyl acetate (9:1) to furnish heliannuol A **1** (20 mg, 66%) as a colourless solid, mp 79–80 °C. HRMS (*m/z*) [M+Na] calcd for $C_{15}H_{22}O_3$: 273.1466, found: 273.1467. The spectral data matched with those reported previously.[5f]

3.1.18. Attempted deoxygenation of 5-deoxyheliannuol A 23a. To a stirred suspension of NaH (60 mg, 1.2 mmol, 50% dispersion in oil) in dry THF (3 mL) was added a solution of 5-deoxyheliannuol A **23a** (100 mg, 0.4 mmol) in dry THF (3 mL) and the mixture was stirred at room temperature for 2 h. Carbon disulfide (0.6 mL, 9.95 mmol) and methyl iodide (0.2 mL, 3.21 mmol) were added consecutively and the mixture was stirred for 18 h. It was cooled in ice and saturated aqueous ammonium chloride solution was added dropwise followed by ether and the mixture was stirred for 15 min. The ether layer was separated and the aqueous layer extracted with ether (10 mL×3). The combined organic extract was washed with brine, dried and concentrated to afford a yellow liquid. It was then subjected to column chromatography over silica gel. Elution with petroleum ether–ethyl acetate (49:1) furnished the *S*-methyl thionocarbonate **26** (100 mg, 72%) as a yellow oil. δ_H (300 MHz, $CDCl_3$) 7.08 (d, 1H, *J*=9 Hz), 6.94 (d, 1H, *J*=9 Hz), 6.78 (s, 1H), 5.32 (d, 1H, *J*=9 Hz), 3.15–3.10 (m, 1H), 2.54 (s, 3H), 2.27 (s, 3H), 2.25–2.15 (m, 2H), 1.85–1.75 (m, 2H), 1.51 (s, 3H), 1.36 (s, 3H), 1.30 (d, 3H, *J*=6 Hz).

A solution of the above *S*-methyl thionocarbonate **26** (100 mg, 0.3 mmol) in dry toluene (3 mL) was heated to 80 °C and 2,2-azobis (2-methyl) propionitrile (5 mg) was added followed by tri-*n*-butyltin hydride (140 mg, 0.45 mmol) and then heated under reflux under a nitrogen atmosphere for 4 h. Toluene was removed under vacuum and to the residue saturated aqueous potassium fluoride (3 mL) was added and stirred at room temperature for 5 h. The product was extracted with ether (20 mL×3) and the combined organic layer was washed with brine, dried and concentrated to afford a pale yellow oily residue, which was subjected to preparative thin layer chromatography. Elution with petroleum ether–ethyl acetate (10:1) furnished curcuphenol **27** (40 mg, 59%) as a colourless oil. IR 3406 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 7.02 (d, 1H, *J*=6 Hz), 6.74 (d, 1H, *J*=6 Hz), 6.58 (s, 1H), 5.12 (t, 1H, *J*=6 Hz), 3.0–2.93 (m, 1H), 2.27 (s, 3H), 1.70 (s, 3H), 1.97–1.90 (m, 2H), 1.68–1.54 (m, 2H), 1.51 (s, 3H), 1.22 (d, 3H, *J*=6 Hz). δ_C (75 MHz, $CDCl_3$) 152.9, 136.5, 132.0, 129.9, 126.8, 124.6, 121.7, 116.1, 37.3, 31.4, 26.1, 25.7, 21.1, 20.9, 17.6. Anal. Calcd for $C_{15}H_{22}O$: C, 82.56; H, 10.09. Found: C, 82.51; H, 9.89.

3.1.19. 2,6,6,10-Tetramethyl-7-oxa-tricyclo[6.4.0^{1,8}.0^{2,4}]-dodec-1,9,11-trien-5-ol (28). The cyclopropyl ketone **21a** (240 mg, 1.043 mmol) in methanol (8 mL) was cooled to 0 °C (ice bath) and $NaBH_4$ (77.6 mg, 2.09 mmol) was added portionwise and stirring continued for 4 h. Then it was diluted with twice its volume of water and extracted with ether (20 mL×3). The combined ethereal extract was washed with water, dried and concentrated. The residual oil was purified by thin layer chromatography. Elution with petroleum ether–ethyl acetate (9:1) afforded the alcohol **28** (235 mg, 97%) as a colourless liquid. IR 3479 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 7.23 (d, 1H, *J*=7.6 Hz), 6.89 (d, 1H, *J*=7.6 Hz), 6.74 (s, 1H), 3.86 (d, 1H, *J*=4.6 Hz), 2.32 (s, 3H), 1.53 (s, 3H), 1.39 (s, 3H), 1.36 (s, 3H), 0.91 (t, 2H, *J*=4.7 Hz), 0.83 (dd, 1H, *J*=8.7, 4.7 Hz). δ_C (75 MHz, $CDCl_3$) 154.7, 138.1, 135.4, 130.3, 125.6, 123.9, 83.6, 74.3, 28.1, 26.9, 24.3, 23.3, 21.4, 18.6, 15.3. Anal. Calcd for $C_{15}H_{20}O_2$: C, 77.58; H, 8.62. Found: C, 77.49; H, 8.55.

3.1.20. 2,2,6,9-Tetramethyl-5,6-dihydro-2*H*-benzo[*b*]-oxocine (30). To a stirred suspension of NaH (77.6 mg, 1.6 mmol, 50% dispersion in oil) in dry THF (3 mL) was added a solution of the alcohol **28** (250 mg, 1.07 mmol) in dry THF (3 mL) and the mixture was stirred at room temperature for 2 h. Carbon disulfide (1.62 mL, 26.9 mmol) and methyl iodide (0.2 mL, 3.21 mmol) were added consecutively and the mixture was stirred for 18 h. The mixture was cooled, and saturated ammonium chloride solution was added dropwise, then ether was added and the mixture was stirred for 15 min. The aqueous layer was extracted thoroughly with ether. The combined organic extract was washed with brine, dried and concentrated to afford a yellow liquid. It was then subjected to column chromatography over silica gel. Elution with petroleum ether–ethyl acetate (49:1) furnished the *S*-methyl thionocarbonate **29** (280 mg,

81%) as a yellow oily liquid. IR 1500 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 7.22 (d, 1H, J=7.6 Hz), 6.88 (d, 1H, J=7.6 Hz), 6.74 (s, 1H), 6.11 (d, 1H, J=4.7 Hz), 2.30 (s, 3H), 1.71 (s, 3H), 1.64 (s, 3H), 1.38 (s, 3H), 1.26 (s, 3H), 0.89 (m, 1H), 0.45 (t, 2H, J=4.9 Hz). δ_C (75 MHz, $CDCl_3$) 213.8, 154.4, 137.6, 135.9, 130.5, 126.3, 124.0, 89.1, 83.9, 82.2, 28.1, 26.9, 23.6, 21.6, 21.5, 19.4, 16.7. Anal. Calcd for $C_{17}H_{22}O_2S_2$: C, 63.35; H, 6.83. Found: C, 63.30; H, 6.78.

A solution of the above *S*-methyl thionocarbonate **29** (120 mg, 0.37 mmol) in dry toluene (3 mL) was heated to 80 °C and to it was added 2,2-azobis (2-methyl) propionitrile (5 mg) and tri-*n*-butyltin hydride (0.2 mL, 0.74 mmol) and then heated under reflux under nitrogen atmosphere for 4 h. Toluene was removed under vacuum and to the residue saturated aqueous potassium fluoride was added and stirred at room temperature for 5 h. The resulting solution was extracted with ether and the combined organic layer was washed with brine, dried and concentrated to afford a pale yellow oily residue, which was subjected to preparative thin layer chromatography with petroleum ether furnishing the alkene **30** (53 mg, 66%) as a colourless oil. δ_H (300 MHz, $CDCl_3$) 6.98 (d, 1H, J=7.7 Hz), 6.89 (d, 1H, J=7.8 Hz), 6.75 (s, 1H), 5.69 (ddd, 1H, J=12.7, 10.3, 2.5 Hz), 5.27 (d, 1H, J=10.9 Hz), 2.95 (m, 1H), 2.29 (s, 3H), 2.14 (m, 2H), 1.62 (s, 3H), 1.41 (s, 3H), 1.26 (d, 3H, J=6.9 Hz). δ_C (75 MHz, $CDCl_3$) 152.9, 137.4, 136.0, 135.7, 130.8, 128.7, 125.7, 125.7, 81.6, 34.5, 29.8, 29.7, 28.9, 25.5, 21.3. Anal. Calcd for $C_{15}H_{20}O$: C, 83.33; H, 9.25. Found: C, 83.12; H, 9.03.

3.1.21. 2,2,6,9-Tetramethyl-3,4,5,6-tetrahydro-2*H*-benzo-[*b*]oxocine, helianane (13). The above alkene **30** (53 mg, 0.25 mmol) in methanol (10 mL) was hydrogenated using 10% Pd–C (10 mg) and the product upon preparative thin layer chromatography using petroleum ether as eluent furnished helianane **13** (49 mg, 92%) as a viscous oil. δ_H (300 MHz, $CDCl_3$) 6.99 (d, 1H, J=7.8 Hz), 6.83 (d, 1H, J=7.8 Hz), 6.64 (s, 1H), 3.11 (m, 1H), 2.21 (s, 3H), 1.68 (m, 2H), 1.52 (m, 2H), 1.35 (s, 3H), 1.30 (m, 2H), 1.22 (s, 3H), 1.18 (d, 3H, J=7.2 Hz). δ_C (75 MHz, $CDCl_3$) 153.0, 138.9, 135.3, 125.8, 124.9, 124.9, 81.0, 38.2, 29.8, 29.7, 26.7, 26.6, 21.9, 21.9, 20.9. Anal. Calcd for $C_{15}H_{22}O$: C, 83.33; H, 9.25. Found: C, 83.12; H, 9.03.

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