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Synthesis of *O*-methyl *epi*-heliannuol E

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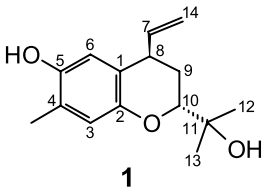
Abstract—A synthesis of the methyl ether of an epimer of the alleochemical heliannuol E is described. The route involves indium mediated allylation of a benzopyranone carboxylate and subsequent one carbon degradation to a vinyl group.

1. Introduction

Heliannuol E **1**,[1] isolated recently from the extracts of *Helianthus annus*, represents a new structural type among the family of heliannuol sesquiterpenes obtained from cultiver sun flowers. These compounds have been found to display significant allelopathic activity,[2] a new branch of applied science involving biochemical plant–plant and plant–microorganism interactions. Increasing awareness into the need to restore the natural ecological balance and efforts to reduce the use of artificial weed control agents in agriculture have provided a new impetus to find natural herbicide models. In this, allelochemicals, isolated from plants and microbes, have assumed prime importance during the last two decades as biocommunicators[3] and as a potential source of new structural types of herbicides with new modes of action without harmful effects of synthetic pesticides. The cultiver sun flowers are a rich source of useful allelochemicals and continued investigations have led to the isolation of a new group of sesquiterpenes termed heliannuols. Heliannuol E **1**, along with the other reported heliannuols A–D **2**–**5**,[4] comprise an interesting complement of benzofused 6, 7 and 8 membered cyclic ether skeleta. The gross structure and relative stereochemistry of **1** was established by Macias[1] and the absolute stereochemistry was assigned as 8*R*,10*S* by Shishido following a synthesis.[5]



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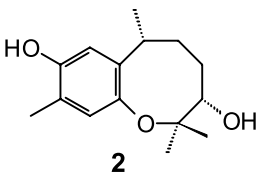

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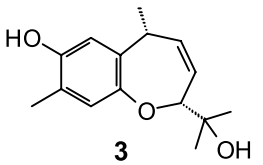

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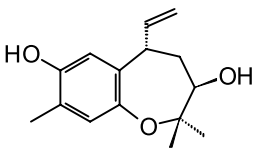

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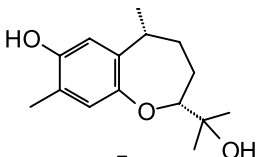

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The irregular terpenoid structure of **1** and the associated significant biological activity are expected to prompt further reports on its synthesis.[6] We have initiated a comprehensive programme into the synthesis of these structurally intriguing new terpenoid compounds and have recently reported a synthesis of heliannuol A and D.[7] We now report a synthesis of the methyl ether of an epimer of heliannuol E.

2. Results and discussion

We envisaged that a properly substituted benzopyranone carboxylate **10**,[8] embodying the central benzoxacyclic core of **1**, could serve as a suitable intermediate for transformation into the natural compound. The presence of the ester

Keywords: allelochemical; heliannuol E; methyl ether of epimer; transfer hydrogenation of chromone; indium mediated allylation.
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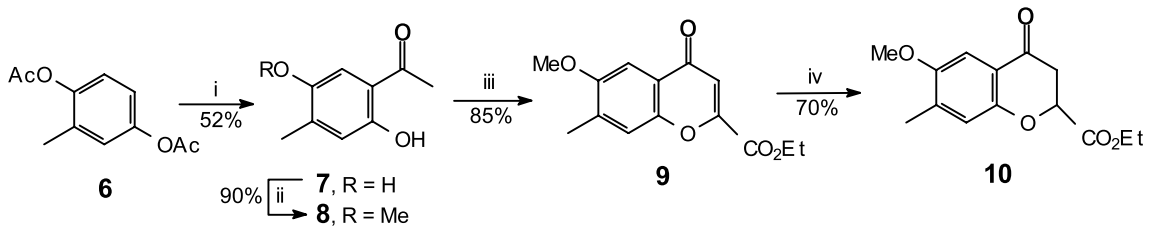
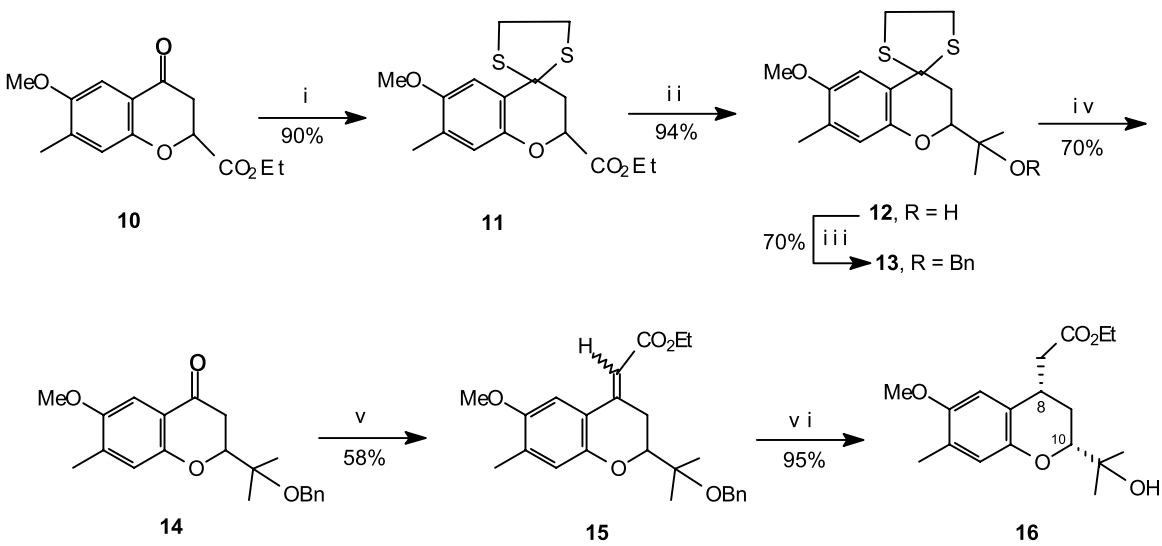


Scheme 1. *Reagents and conditions*: (i) anhyd. $AlCl_3$, 160–165°C; (ii) MeI, K_2CO_3, acetone, reflux; (iii) diethyl oxalate, NaH, THF, then PTSA, benzene, reflux; (iv) $HCOONH_4$, C_2H_5OH, Pd–C (10%), reflux, or H_2, Pd–C (10%), C_2H_5OH, then Jones oxidation.

function may facilitate a preferred nucleophilic attack on the carbonyl group from the opposite face to provide the required *trans* geometry of the resulting 1,3 substitutions. The ester function is also amenable for conversion into the isopropanol moiety. With this in mind, synthesis of the benzopyranone carboxylate **10** was undertaken.

2-Methylhydroquinone diacetate **6**, on Fries rearrangement followed by monomethylation afforded the acetophenone **8** in an overall yield of 56%. We have found this procedure to be more convenient with better overall yield compared to a reported method.[9] Base induced condensation of this acetophenone with diethyl oxalate[10] followed by treatment of the resulting product with toluene-*p*-sulfonic acid in boiling benzene afforded the chromone carboxylate **9** in 85% yield. Reduction of the double bond in **9** was fraught with problems. However, application of a transfer hydrogenation procedure[11] involving refluxing an ethanolic solution of **9** with ammonium formate in presence of Pd–C led to facile reduction to furnish the desired benzopyranone carboxylate **10** in good yield (Scheme 1). We have recently generalised this as a useful protocol for the reduction of chromones to chromanones.[12] Subsequently it was also found that carefully controlled (monitored by TLC) catalytic hydrogenation of **9** in the presence of Pd–C (10%) results in smooth reduction of the double bond and also the ketone to produce the corresponding chromanol, which could be efficiently oxidised by Jones reagent to the benzopyranone carboxylate **10** in good overall yield.

The C-8 carbonyl group in **10** proved impervious to a variety of conditions to introduce an aldehyde or a methylene group through a Wittig reaction for further transformation into a vinyl side chain as in **1**. The sulfonium or sulfoxonium methylide procedure also did not yield any useful results. Attempted direct introduction of a vinyl residue through reaction of **10** with vinyl magnesium bromide resulted in a primary attack on the ester function. Hence, it was decided to transform the ester function first into the desired isopropanol moiety and then direct efforts for incorporation of the vinyl group at the site of the carbonyl function. This required the initial protection of the carbonyl group. Attempted ketalisation through condensation with ethylene glycol catalysed by toluene-*p*-sulfonic acid in refluxing benzene did not afford any reasonable yield of the corresponding ketal even after long hours of reaction. However, condensation with ethane dithiol in the presence of boron trifluoride etherate proceeded smoothly to furnish the thioketal **11** in excellent yield. Reaction of this thioketal with excess methyl magnesium iodide afforded the isopropanol **12**, also in high yield. The hydroxy group in **12** was protected as the benzyl ether through reaction with benzyl bromide in the presence of sodium hydride and furnished the benzylated thioketal **13** as a crystalline solid which on treatment with mercuric chloride and calcium carbonate in aqueous acetonitrile resulted in the deprotection of the thioketal moiety to reveal benzylated benzopyranone **14**. The keto group in this benzopyranone also failed to respond to various attempts at a one carbon homologation to incorporate an aldehyde function.



Scheme 2. *Reagents and conditions*: (i) $HSCH_2CH_2SH$, $BF_3.(C_2H_5)_2O$, $(C_2H_5)_2O$, rt, 8 h; (ii) MeMgI, $(C_2H_5)_2O$, reflux; (iii) BnBr, NaH, THF, rt, 10 h; (iv) $HgCl_2$, $CaCO_3$, CH_3CN, H_2O, rt, 14 h; (v) $[(C_2H_5)O]_2P(O)CH_2CO_2C_2H_5$, NaH, THF, 20 h, rt; (vi) Pd–C (10%), C_2H_5OH,6 h.

However, a Wittig–Horner condensation with triethyl phosphonoacetate in the presence of sodium hydride gave the unsaturated ester **15**, as a single unknown isomer in reasonable yield. The stereochemical outcome was not deemed relevant since the next step involved hydrogenation. Thus, catalytic hydrogenation of the unsaturated ester **15** in the presence of Pd–C resulted in the reduction of the double bond and concomitant cleavage of the benzyl protecting group to afford the saturated ester **16** (Scheme 2). However, this proved to be the undesired *cis* isomer. The stereochemistry was arrived at from the NOE effect observed between the hydrogens at C-8 and C-10.

In view of the failure to achieve the desired *trans* orientation of the substituents for a subsequent transformation into heliannuol E, it was decided to once again explore the possibility of addition of appropriate nucleophiles to the carbonyl group in the benzopyranone carboxylate **10**. The ester group may be usefully utilised for any required epimerisation. Success was finally achieved in allylation through indium metal[13] promoted reaction of **10** with allyl bromide and afforded the allylated carboxylates **17** in 74% yield as a 2:1 mixture of diasteromers. Separation of the isomers proved difficult at this stage and hence the mixture was taken to the next sequence of steps for conversion of the allyl side chain into a vinyl residue. Treatment of **17** with osmium tetroxide followed by cleavage of the resulting diol furnished the aldehydes **18**. Borohydride reduction to the diols **19** followed by hydrogenolysis of the benzylic hydroxy group produced the 1,3-disubstituted carboxylate **20**, encouragingly as a single isomer. This also proved to be the undesired *cis* isomer as evidenced from the NOE effect observed between the C-8 and C-10 hydrogens. It was, however, decided to proceed further and transform the ethanolic side chain at C-8 into a vinyl group as in the natural product and explore the possibility of any epimerisation to the desired *trans* isomer.

Dehydration of the primary hydroxy group to the vinyl side chain was smoothly achieved through application of Grieco's protocol.[14] Thus, the alcohol was converted into the *o*-nitrophenyl selenide **21** by reaction with *o*-nitrophenyl selenocyanate in the presence of tri *n*-butyl phosphine. Treatment of this selenide with hydrogen peroxide resulted in oxidative elimination to afford the vinylated carboxylate **22**. Efforts at base catalysed epimerisation of this vinylated carboxylate for even minor conversion to the *trans* isomer were infructuous. Interaction of **22** with excess methyl magnesium iodide furnished the methyl ether **23** of *epi*-heliannuol E (Scheme 3). This showed no NOE effects between H-7 and H-10 as reported for the natural compound further attesting to the stereochemical assignment.

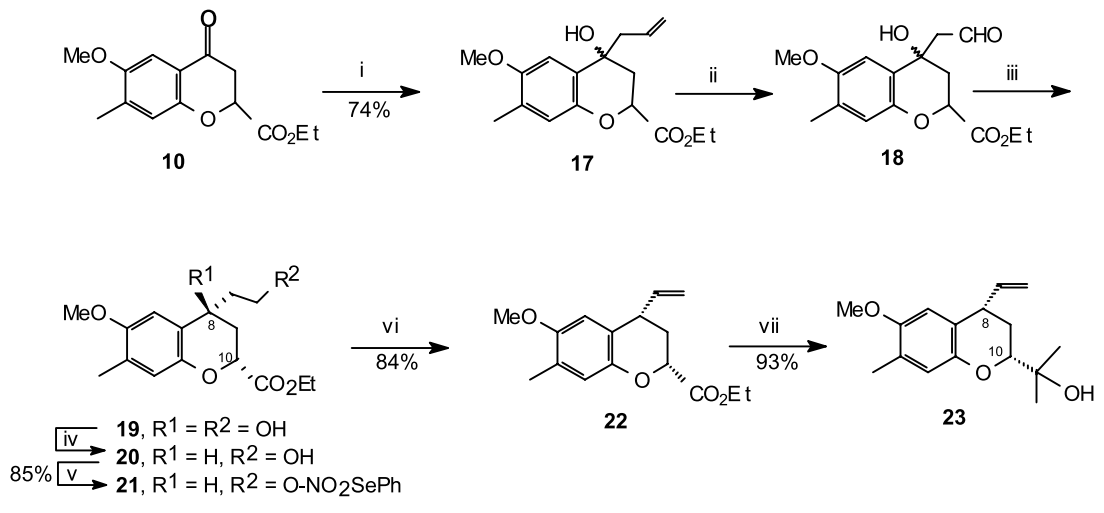
In summary we have described a short approach to the development of the basic structural features as found in the allelochemical heliannuol E, resulting in a synthesis of the methyl ether of its epimer. Further studies are under way and are expected to provide useful analogs for exploration of structure activity relationships.

3. Experimental

3.1. General

Melting points are uncorrected. Purity of the products was routinely monitored by TLC. Preparative TLC was performed with silica gel 60 HF_{254} plates of 1-mm thickness. The petroleum ether that was 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. ^1H NMR spectra of $CDCl_3$ solutions were recorded at 300 MHz and ^{13}C NMR spectra at 75 MHz.

3.1.1. 2,5-Dihydroxy-4-methyl acetophenone (7). A finely powdered mixture of 2-methyl hydroquinone diacetate **6** (20 g, 96 mmol) and anhydrous aluminium chloride (43 g, 321 mmol) was heated slowly in an oil bath to 110–120°C and kept at this temperature for 30 min. Then it was raised to 160–165°C and kept at this temperature for 3 h. The reaction mixture was cooled and decomposed with crushed ice (150 g) and conc.hydrochloric acid (15 mL). The resulting solid was filtered and washed with cold water (3×30 mL). It was crystallised from ethanol to furnish the



Scheme 3. *Reagents and conditions*: (i) In, $BrCH_2CH{:}CH_2$,THF, rt; (ii) OsO_4, $NaIO_4$, $(C_2H_5)_2O$, H_2O; (iii) $NaBH_4$, C_2H_5OH, 0°C; (iv) H_2, Pd–C (10%), C_2H_5OH, AcOH, $HClO_4$, 60% overall for three steps; (v) *o*-$NO_2C_6H_4SeCN$, $^nBu_3P$, THF, rt; (vi) 30% H_2O_2, THF, rt; (vii) MeMgI, $(C_2H_5)_2O$, reflux.

dihydroxy acetophenone **7** (8.3 g, 52%), mp 139–141°C; IR 1665 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 2.26 (s,3H),2.54 (s, 3H), 4.95 (bs, OH),6.76 (s,1H), 7.09 (s,1H), 11.86 (s, OH); δ_C (75 MHz, $CDCl_3$) 15.6, 25.5, 113.8, 116.5, 118.9, 134.9, 145.1, 155.6, 202.5. Anal. calcd for $C_9H_{10}O_3$: C,65.06; H,6.02. Found: C, 64.66; H, 5.70.

3.1.2. 2-Hydroxy-5-methoxy-4-methyl acetophenone (8). A solution of dihydroxy acetophenone **7** (5 g, 30 mmol), anydrous potassium carbonate (4.5 g, 32.6 mmol) and methyl iodide (6.4 g, 45 mmol) in acetone (60 mL) was refluxed for 6 h. The reaction mixture was cooled and most of the acetone was distilled off. The residue was poured into water (40 mL) and extracted with dichloromethane (20 mL×3). The organic extract was washed with water (10 mL×3), dried and concentrated to afford a yellow solid which was subjected to chromatography over silica gel. Elution with ethyl acetate–petroleum ether (1:5) furnished the monomethylated acetophenone **8** as a pale yellow solid, (4.9 g, 90%); crystallised from ether–petroleum ether, mp 107–108°C (lit.,[9] mp 108–109°C); IR 1660 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 2.19 (s, 3H), 2.55 (s, 3H), 3.78 (s, 3H), 6.72 (s, 1H), 6.94 (s,1H), 11.99 (s, OH); δ_C (75 MHz, $CDCl_3$) 17.2, 26.9, 56.1, 109.9, 117.3, 120.4, 138.7, 150.6, 157.3, 203.7. Anal. calcd for $C_{10}H_{12}O_3$: C, 66.67; H, 6.67. Found: C, 66.36; H,6.43.

3.1.3. Ethyl-6-methoxy-7-methyl chromone-2-carboxylate (9). To a cooled (ice-bath), stirred slurry of sodium hydride, freed from oil (3 g, 62.5 mmol, 50% dispersion in oil) in anhydrous ether (15 mL) under nitrogen, a mixture of 2-hydroxy-4-methyl-5-methoxy acetophenone **8** (5.8 g, 32.2 mmol) and diethyloxalate (9.4 g, 64.4 mmol) in THF (20 mL) was added slowly and the reaction mixture was left overnight at rt. It was then poured into ice-water (70 mL) and acidified with cold dilute hydrochloric acid (6N, 25 mL) and extracted with ether (40 mL×3). The ether extract was washed with water (20 mL×2), dried and concentrated. The solid residue was dissolved in benzene (120 mL) and toluene-*p*-sulfonic acid (80 mg) was added and refluxed for 8 h, using a Dean–Stark water separator. It was then cooled, washed with saturated aqueous sodium bicarbonate solution, water, dried and solvent removed to get a yellowish solid. This was subject to chromatography over silica gel. Elution with ethyl acetate–petroleum ether (1:3) furnished the chromone carboxylate **9** as a colourless solid, (7 g, 85%); crystallised from ether–petroleum ether, mp 132–134°C; IR 1643, 1739 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 1.43 (t, J=7.2 Hz, 3H), 2.34 (s, 3H), 3.92 (s, 3H), 4.45 (q, J=7.2 Hz, 2H), 7.08 (s, 1H), 7.40 (s, 1H), 7.43 (s, 1H); δ_C (75 MHz, $CDCl_3$) 13.9, 16.9, 55.8, 62.7, 102.5, 113.7, 120.0, 123.1, 136.8, 150.5, 151.5, 156.0, 160.5, 178.0. Anal. calcd for $C_{14}H_{14}O_5$: C, 64.12; H, 5.34. Found: C, 64.09; H, 5.32.

3.1.4. Ethyl-6-methoxy-7-methyl-2*H*-1-benzopyran-4-one-2-carboxylate (10). A solution of the chromone **9** (260 mg, 1 mmol) and ammonium formate (190 mg, 3 mmol) in ethanol (5 mL) containing palladium charcoal (10%, 80 mg) was refluxed for 6 h. The catalyst was filtered and the residue after removal of ethanol was extracted with ether (20 mL×3). The ether extract was washed with brine solution and dried. Removal of solvent followed by column chromatography of the residue and elution with ethyl acetate–petroleum ether (1:4) furnished benzopyranone carboxylate **10** as a colourless solid (200 mg, 75%), crystallised from ether–petroleum ether, mp 99–101°C; IR 1678, 1759 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 1.29 (t, J=7.2 Hz, 3H), 2.23 (s, 3H), 3.0 (d, J=6.5 Hz, 2H), 3.81 (s, 3H), 4.26 (J=7.2 Hz, 2H), 5.01 (t, J=6.5 Hz, 1H), 6.90 (s, 1H), 7.19 (s, 1H); δ_C (75 MHz, $CDCl_3$) 14.1, 17.0, 39.3, 55.7, 62.0, 75.2, 105.0, 118.7, 119.9, 138.1, 153.1, 154.6, 168.9, 189.5. Anal. calcd for $C_{14}H_{16}O_5$: C, 63.64; H, 6.06. Found: C, 63.62; H, 6.01.

A solution of the chromone **9** (260 mg, 1 mmol) in ethanol (5 mL) containing Pd–C (10%, 40 mg) was subjected to hydrogenation. Immediately after the disapperance of the starting material (TLC) the catalyst was filtered off and ethanol was removed. The colourless solid residue (240 mg) obtained corresponded to the 4-chromanol (IR 3410, 1760 cm^{-1}). The above crude chromanol was taken in acetone and oxidised with Jones reagent. Usual work-up followed by chromatographic purification [ethyl acetate–petroleum ether (1:4)] afforded the benzopyranone carboxylate **10** as a colourless solid (180 mg, 70%). The mp and spectra (IR and ^1H NMR) were identical with material obtained from transfer hydrogenation.

3.1.5. Ethyl-6-methoxy-7-methyl-4,4-dithioethane-2*H*-1-benzopyran-2-carboxylate (11). To a mixture of the benzopyranone carboxylate **10** (530 mg, 2 mmol) and ethane dithiol (750 mg, 8 mmol) in ether (5 mL) boron trifluoride etherate (0.4 mL) was added in ice-cold condition. The mixture was left at rt for 10 h, then diluted with water (30 mL) and extracted with ether (25 mL×3). The ethereal extract was washed with water (15 mL×3), dried, and concentrated. The viscous residue was chromatographed over neutral alumina. Fraction eluted by ethyl acetate–petroleum ether (1:9) furnished the thioketal **11** as a solid (610 mg, 90%); Crystallised from ether–petroleum ether, mp 52–54°C; IR 1755 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 1.26 (t, J=7.2 Hz, 3H), 2.07 (s, 3H), 2.51–2.77 (m, 2H), 3.31–3.65 (m, 4H), 3.73 (s, 3H), 4.23 (q, J=7.2 Hz, 2H), 4.73 (dd, J=2.7, 10.5 Hz, 1H), 6.63 (s, 1H), 7.14 (s, 1H). δ_C (75 MHz, $CDCl_3$) 14.6, 16.4, 40.6, 41.3, 45.0, 56.1, 62.0, 64.5, 74.0, 110.6, 119.5, 119.9, 129.8, 147.3, 152.8, 170.2. Anal. calcd for $C_{16}H_{20}O_4S_2$: C, 56.47; H, 5.88. Found: C, 56.32; H, 5.72.

3.1.6. 2-(1-Hydroxy-1-methyl)-ethyl-4,4-dithioethane-6-methoxy-7-methyl-2*H*-1-benzopyran (12). To a magnetically stirred solution of MeMgI [prepared from Mg (120 mg, 5 mmol), MeI (850 mg, 6 mmol)] in ether (5 mL) at 0°C was added a solution of the thioketal **11** (680 mg, 2 mmol) in ether (4 mL). The mixture was brought to rt and stirred for 30 min. Then it was refluxed for 4 h. The reaction mixture was cooled to 0°C and was decomposed by adding saturated aqueous NH_4Cl solution (2 mL). The organic layer was separated. The aqueous layer was extracted with ether (10 mL×2). The combined organic layer was washed with water (5 mL×2), dried and concentrated. The residue after column chromatography over neutral alumina using ethyl acetate–petroleum ether (1:6) afforded the alcohol **12** (610 mg, 94%), as a highly viscous oil. IR 3445 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 1.21 (s,

3H), 1.26 (s, 3H), 2.07 (s, 3H), 2.29–2.43 (m, 2H), 3.26–3.63 (m, 4H), 3.73 (s, 3H), 3.92 (dd, J=2.49, 10.5 Hz, 1H), 6.52 (s, 1H), 7.15 (s, 1H); δ_C (75 MHz, $CDCl_3$) 16.3, 25.3, 25.9, 40.4, 41.2, 43.0, 56.1, 65.4, 71.8, 81.6, 110.9, 119.0, 120.8, 129.3, 148.3, 152.2. Anal. calcd for $C_{16}H_{22}O_3S_2$: C, 58.89; H, 6.74. Found: C, 58.78; H, 6.63.

3.1.7. 2-(1-Benzyloxy-1-methyl)-ethyl-4,4-dithioethane-6-methoxy-7-methyl-2*H*-1-benzopyran (13). To a magnetically stirred suspension of NaH [(70 mg, 1.5 mmol, 50% dispersion in oil)] in THF (2 mL) was added dropwise a solution of the tertiary alcohol **12** (330 mg, 1 mmol) in THF (3 mL). The mixture was stirred at rt for 2 h and then cooled in a ice-bath. HMPA (0.3 mL) was added followed by benzyl bromide (340 mg, 2 mmol). After stirring for 30 min. at rt it was refluxed for 6 h, cooled to rt and quenched by adding cold water (3 mL). It was extracted with ether (15 mL×2). Concentration of the ether extract followed by column chromatography of the residue using ethyl acetate–petroleum ether (1:19) as eluent furnished the benzyl ether **13** (290 mg, 70%) as a colourless solid, crystallised from ether–petroleum ether; mp 103–105°C; δ_H (300 MHz, $CDCl_3$) 1.27 (s, 3H), 1.35 (s, 3H), 2.07 (s, 3H), 2.30–2.60 (m, 2H), 3.22–3.63 (m, 4H), 3.73 (s, 3H), 4.13 (dd, J=1.4, 11.4 Hz, 1H), 4.51 (s, 2H), 6.53 (s, 1H), 7.17 (s, 1H), 7.22–7.27 (m, 5H); δ_C (75 MHz, $CDCl_3$) 16.1, 21.5, 23.3, 40.0, 40.9, 42.5, 55.9, 64.3, 65.6, 76.1, 80.0, 110.7, 119.0, 120.5, 127.2, 127.3, 128.3, 129.0, 139.6, 148.6, 152.0. Anal. calcd for $C_{23}H_{28}O_3S_2$: C, 66.34; H, 6.73. Found: C, 65.94; H, 6.32.

3.1.8. 2-(1-Benzyloxy-1-methyl)-ethyl-6-methoxy-7-methyl-2*H*-1-benzopyran-4-one (14). To a solution of the thioketal **13** (420 mg, 1 mmol) in CH_3CN:H_2O (4:1) (15 mL) was added $HgCl_2$ (600 mg, 2.2 mmol) followed by $CaCO_3$ (230 mg, 2.3 mmol) at rt and stirred for 10 h. Then the reaction mixture was filtered and the filtrate extracted with ether (15 mL×2). The ethereal extract was washed with brine, dried and concentrated to afford a yellow mass. Purification was carried out by column chromatography over silica gel using ethyl acetate–petroleum ether (1:4) to furnish **14** as a colourless solid (240 mg, 70%); crystallised from ether–petroleum ether, mp 88–89°C; IR 1682 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 1.34 (s, 6H), 2.16 (s, 3H), 2.73–2.77 (m, 2H), 3.74 (s, 3H), 4.23 (m, 1H), 4.47 (d, J=11.4 Hz, 1H), 4.52 (d, J=11.4 Hz, 1H), 6.75 (s, 1H), 7.14 (s, 1H), 7.16–7.25 (m, 5H). δ_C (75 MHz, $CDCl_3$) 15.9, 19.6, 22.0, 36.8, 54.6, 63.2, 74.9, 82.2, 104.0, 117.7, 118.7, 126.0, 126.2, 127.2, 136.3, 138.1, 151.5, 155.0, 192.0. Anal. calcd for $C_{21}H_{24}O_4$: C, 74.11; H, 7.05. Found: C, 73.75; H, 6.75.

3.1.9. 2-(1-Benzyloxy-1-methyl)-ethyl-4-carbethoxymethylene-6-methoxy-7-methyl-2*H*-1-benzopyran (15). To a magnetically stirred suspension of NaH (50 mg, 1 mmol, 50% dispersion in oil) in dry THF (1 mL), triethylphosphonoacetate (280 mg, 1.25 mmol) was added at rt and stirring was continued untill a clear solution was obtained. This clear solution was stirred at rt for another 40 min. Then the benzyl ether **14** (170 mg, 0.5 mmol) in THF (2 mL) was added dropwise and allowed to stir for additional 20 h. The reaction mixture was poured into cold water (7 mL) and extracted with ether (10 mL×3). The ethereal extract was dried, concentrated and the residue subjected to column chromatography over silica gel. Elution with ethyl acetate–petroleum ether (3:17) furnished the product **15** as a gummy oil (120 mg, 58%). IR 1708 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 1.22 (t, J=7.1 Hz, 3H), 1.33 (s, 3H), 1.34 (s, 3H), 2.12 (s, 3H), 2.50–2.60 (m, 2H), 3.74 (s, 3H), 3.86 (dd, J=2.2, 13.1 Hz, 1H), 4.14 (q, J=7.1 Hz, 2H), 4.49 (d, J=11.5 Hz, 1H), 4.54 (d, J=11.5 Hz, 1H), 6.18 (bs 1H), 6.67 (s, 1H), 6.86 (s, 1H), 7.15–7.31 (m, 5H); δ_C (75 MHz, $CDCl_3$) 12.3, 14.4, 19.2, 21.2, 24.9, 53.7, 57.8, 62.3, 74.4, 79.0, 102.1, 106.9, 118.1, 125.15, 125.2, 126.2, 126.3, 130.6, 137.6, 147.2, 149.1, 150.3, 164.9. Anal. calcd for $C_{25}H_{30}O_5$: C, 73.17; H, 7.31. Found: C, 72.90; H, 7.12.

3.1.10. 2-(1-Hydroxy-1-methyl)-ethyl-4-carbethoxymethyl-6-methoxy-7-methyl-2*H*-1-benzopyran (16). An ethanolic solution of **15** (50 mg, 0.121 mmol) containing Pd–C (10%, 20 mg) was stirred over a hydrogen atmosphere till hydrogen uptake was complete. The catalyst was filtered, the solvent removed and the residue was purified by preparative TLC ((ethyl acetate–petroleum ether (1:4)(to furnish the saturated hydroxy ester **16** as a colourless liquid (35 mg, 91%). IR 1732, 3446 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 1.18 (s, 3H), 1.20 (t, J=7.2 Hz, 3H), 1.23 (s, 3H), 1.41–1.53 (m, 1H), 1.61 (–OH), 2.08 (s, 3H), 2.29–2.37 (m, 2H), 2.86 (dd, J=4.7, 15.6 Hz, 1H), 3.28–3.38 (m, 1H), 3.60–3.75 (m, 1H), 3.68 (s, 3H), 4.12 (q, J=7.2 Hz, 2H), 6.51 (s, 1H), 6.59 (s, 1H). δ_C (75 MHz, $CDCl_3$) 13.2, 14.7, 23.3, 24.8, 28.5, 30.6, 39.4, 54.9, 59.6, 70.7, 80.6, 107.2, 118.0, 120.6, 125.6, 147.2, 150.9, 171.4. Anal. calcd for $C_{18}H_{25}O_5$: C, 67.28; H 7.78. Found: C, 66.89; H, 7.62.

3.1.11. Ethyl-4-hydroxy-4-(prop-2-enyl)-6-methoxy-7-methyl-2*H*-1-benzopyran-2-carboxylate(s) (17). To a stirred mixture of indium metal (170 mg, 1.5 mmol, small pieces) in THF (2 mL), allyl bromide (300 mg, 2 mmol) was added dropwise and stirring was continued at rt untill all the metal dissolved. To this solution the benzopyran carboxylate **10** (260 mg, 1 mmol) in THF (3 mL) was added slowly. The reaction was carried out at rt over a period of another 2 h. and then quenched by aqueous NH_4Cl solution (0.5 mL), extracted with ether (10 mL×3) and concentrated. The residue was subjected to column chromatography using silica gel. Elution with ethyl acetate–petroleum ether (1:4) afforded the allylated product **17** as a viscous liquid (220 mg, 71%); IR 1739 cm^{-1}; For two isomers δ_H (300 MHz, $CDCl_3$) 1.20 (t, J=7.1 Hz, 3H), 2.09 (s, 3H), 2.11 (s, 3H), 2.36 (dd, J=4.3, 14.0 Hz, 1H), 2.42–2.76 (m, 2H), 2.84–3.09 (m, 2H), 3.71 (s, 3H), 3.74 (s, 3H), 4.15 (m, 2H), 4.62 (dd, J=4.2, 7.0 Hz, 1H), 4.68 (dd, J=4.2, 7.0 Hz, 1H), 5.06–5.10 (m, 3H), 5.31 (dd, J=1.7, 16.4 Hz), 5.52–5.90 (m, 1H). δ_C (75 MHz, $CDCl_3$) (13.0, 13.1), (15.0, 15.1), (27.2, 31.1), (34.6, 35.8), (44.8, 45.4), (54.7, 54.8), (60.3, 60.4), (72.3, 72.6), (104.8, 105.8), (116.3, 117.1), (118.3, 118.5), (127.6, 128.3), (132.0, 132.1), (133.8), (144.9, 146.2), (151.4, 151.5), (169.3, 170.4). Anal. calcd for $C_{17}H_{22}O_5$: C, 66.66; H, 7.18. Found: C, 66.24; H, 7.02.

3.1.12. Ethyl-4-(2-hydroxyethyl)-6-methoxy-7-methyl-2*H*-1-benzopyran-2-carboxylate (20). To a stirred suspension of $NaIO_4$ (1.28 g, 6 mmol) in water (5 mL), the alkenol(s) **17** (310 mg, 1 mmol) in diethyl ether (10 mL) was added. After stirring for 15 min, a catalytic amount of

OsO_4 was added and stirred at rt till the starting alkenol disappeared completely (TLC). The organic layer was separated, washed with aqueous saturated $NaHCO_3$ solution (3 mL×2), water (5 mL×2), dried and concentrated to furnish a coloured viscous material (210 mg). IR 1734, 1754 cm^{-1}.

$NaBH_4$ (30 mg, 0.789 mmol) was added with stirring in small portions to a solution of the above crude aldehyde (210 mg) in ethanol (2 mL) at ice-cold temperature. Stirring was continued at that temperature for additional 2 h. Ethanol was removed and the residue diluted with water (2 mL) and extracted with ether (10 mL×2). The ethereal extract was washed with water (3 mL×2) and concentrated to furnish the corresponding crude diol which without further purification was subject to hydrogenolysis. An ethanolic solution of the dihydroxy compound containing Pd–C (10%), (20 mg), $HClO_4$ (2 drops), AcOH (3 drops) was hydrogenated as for **16**. The crude material was purified by preparative TLC to furnish the hydroxy ester **20** (180 mg, 60% overall for three steps) as a crystalline colourless solid, mp 42–44°C; IR 1754, 3400 cm^{-1}. δ_H (300 MHz, $CDCl_3$) 1.24 (t, J=7.1 Hz, 3H), 1.51–1.63 (m, 1H), 1.71–1.83 (m, 1H), 1.86 (bs, OH), 2.06 (s, 3H), 2.12–2.23 (m, 1H), 2.36 (ddd, J=2.6, 6.3, 13.4 Hz, 1H), 3.06–3.10 (m, 1H), 3.68 (s, 3H), 3.70–3.76 (m, 2H), 4.17 (q, J=7.1 Hz, 2H), 4.44 (dd, J=2.6, 10.3 Hz, 1H), 6.56 (s, 1H), 6.68 (s, 1H). δ_C (75 MHz, $CDCl_3$) 14.5, 16.2, 31.4, 31.6, 38.1, 56.2, 60.5, 61.8, 74.1, 109.1, 119.7, 122.9, 126.8, 147.8, 152.7, 171.5. Anal. calcd for $C_{16}H_{22}O_5$: C, 65.30; H, 7.48. Found: C, 64.96; H, 7.42.

3.1.13. Ethyl-4-(2-nitrophenylselenoethyl)-6-methoxy-7-methyl-2*H*-1-benzopyran-2-carboxylate (21). To a solution of the alcohol **20** (30 mg, 0.102 mmol) in THF (0.5 mL) containing *o*-nitrophenyl selenocyanate (50 mg, 0.22 mmol) was added tri-*n*-butylphosphine (40 mg, 0.198 mmol) dropwise, resulting in a brick red solution that slowly turned bright yellow over 4 h stirring at rt. The solvent was removed in vacuum and the residue purified by column chromatography. Elution with ethyl acetate–petroleum ether (1:6) afforded the seleno derivative as a solid product (40 mg, 82%), crystallised from ether petroleum ether, mp 122–124°C; IR 1752 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 1.33 (t, J=7.1 Hz, 3H), 1.92–2.08 (m, 2H), 2.15 (s, 3H), 2.27–2.34 (m, 1H), 2.42–2.50 (ddd, J=2.64, 6.48, 10.77 Hz, 1H), 2.84–3.03 (m, 2H), 3.21–3.24 (m, 1H), 3.74 (s, 3H), 4.30 (*q*, J=7.1 Hz, 2H), 4.55 (dd, J=2.5, 10.4 Hz, 1H), 6.56 (s, 1H), 6.78 (s, 1H), 7.30–7.36 (m, 1H), 7.45–7.55 (m, 2H), 8.29 (dd, J=1.1, 8.1 Hz, 1H). δ_C (75 MHz, $CDCl_3$) 14.6, 16.2, 22.8, 31.1, 33.5, 34.6, 56.3, 61.9, 74.0, 108.8, 120.0, 121.5, 125.9, 126.9, 127.3, 129.3, 129.4, 133.5, 134.0, 147.6, 152.9, 171.2. Anal. calcd for $C_{22}H_{25}O_6NSe$: C, 55.22; H, 5.23. Found: C, 54.92; H, 5.18.

3.1.14. Ethyl-4-ethenyl-6-methoxy-7-methyl-2*H*-1-benzopyran-2-carboxylate (22). A stirred solution of the selenoether **21** (40 mg, 0.083 mmol) in THF (2 mL) was treated dropwise with 30% H_2O_2 (80 mg, 2.352 mmol) at rt and stirring was continued for 3 h. The reaction mixture was extracted with ether (10 mL×3), washed with brine (2 mL×2), dried and concentrated. The residual oil on purification by column chromatography [ethyl acetate–petroleum ether (1:9)] furnished the alkene **22** (20 mg, 86%) as a colourless liquid. IR 1750 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 1.24 (t, J=7.1 Hz, 2H), 1.84–1.95 (m, 1H), 2.08 (s, 3H), 2.29 (ddd, J=2.4, 6.1, 7.2 Hz, 1H), 3.48–3.59 (m, 1H), 3.67 (s, 3H), 4.19 (q, J=7.1 Hz, 3H), 4.52 (dd, J=2.4, 10.7 Hz, 1H), 5.11–5.20 (m, 2H), 5.57–5.69 (m, 1H), 6.46 (s, 1H), 6.69 (s, 1H). δ_C (75 MHz, $CDCl_3$) 14.5, 16.2, 32.7, 40.7, 56.2, 61.7, 73.9, 110.5, 117.5, 119.6, 120.8, 127.4, 140.6, 147.0, 152.6, 171.0. Anal. calcd for $C_{16}H_{20}O_4$: C, 69.56; H, 7.24. Found: C, 69.31; H, 7.02.

3.1.15. 4-Ethenyl-2-(1-hydroxy-1-methyl)-ethyl-6-methoxy-7-methyl-2*H*-1-benzopyran (23). To a magnetically stirred solution of MeMgI [prepared from Mg (5 mg, 0.208 mmol), MeI (200 mg, 0.140 mmol)] in ether (2 mL), at 0°C was added a solution of the ester **22** (15 mg, 0.54 mmol) in ether (2 mL). The mixture was brought to rt and stirred for 30 min. Then it was refluxed for 2 h. The reaction mixture was cooled to 0°C and was decomposed by adding saturated aqueous NH_4Cl solution (0.5 mL) and was extracted with ether (5 mL×3). The ether solvent was dried and concentrated. The residue was purified by preparative TLC, ethyl acetate–petroleum ether (1:9) to afford the alcohol **23** (13.5 mg, 95%) as a colourless liquid. IR 3438, 1637 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 1.19 (s, 3H), 1.24 (s, 3H), 1.52–1.65 (m, 1H), 1.96 (ddd, J=1.5, 5.7, 13.2 Hz, 1H), 2.03 (s, 3H), 3.39–3.44 (m, 1H), 3.67 (s, 3H), 3.72 (dd, J=1.5, 11.4 Hz, 1H), 5.13 (dd, J=1.5, 9.9 Hz, 1H), 5.19 (dd, J=1.5, 7.1 Hz, 1H), 5.58–5.70 (m, 1H), 6.5 (s, 1H), 6.59 (s, 1H). δ_C (75 MHz, $CDCl_3$) 14.9, 23.3, 24.8, 28.7, 40.3, 54.9, 70.8, 80.5, 109.3, 115.6, 117.7, 120.2, 125.7, 140.0, 146.8, 150.8. Anal. calcd for $C_{16}H_{22}O_3$: C, 73.28; H, 8.39. Found: C, 73.19; H, 8.32.

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