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Radical induced fragmentation in a benzoxocane ring system: application to the synthesis of elvirol and a formal synthesis of 7,8-dihydroxycalamenene

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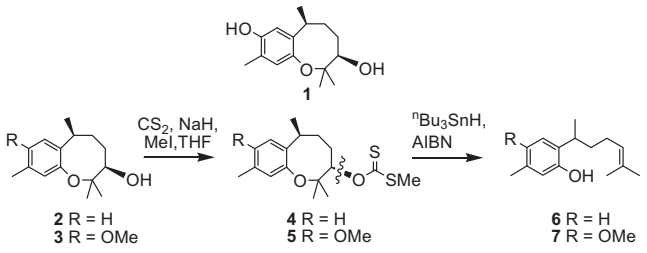
ABSTRACT

A novel radical induced fragmentation in a benzoxocane ring system has been employed for a synthesis of elvirol **8** and an advanced intermediate in the synthesis of 7,8-dihydroxycalamenene **20**. The coumarins **9**, **22** were taken through a sequence of reactions to the benzoxocanols **16**, **30**, which when subjected to Barton's deoxygenation conditions involving conversion to the corresponding thionocarbonates **17**, **31** followed by exposure to tri-*n*-butyltin hydride, underwent a radical induced fragmentation to furnish elvirol **8** and the curcuphenol derivative **32**, which was converted to the dimethoxy compound **33**. This had served as an advanced intermediate in a previous synthesis of dihydroxycalamenene.

1. Introduction

During the last three decades, radical induced carbon–carbon bond formation processes have revolutionised preparative organic synthesis.[1] This has resulted in the development of novel methodologies with vast potential in the synthesis of complex natural products. An important but still somewhat less well-exploited area of radical chemistry is the radical induced bond cleavage processes in cyclic systems. Such cleavages have been encountered in carbocyclic systems and their utility demonstrated by application to generate complex carbocyclic frameworks towards natural product synthesis.[2] There have been only limited examples of similar fragmentations extending to heterocyclic systems and these have been only in the cases of epoxides.[3]

In connection with our synthesis of heliannuol A **1** the primary constituent of allelochemicals from cultiver sun flowers, we had disclosed the first case of a radical induced fragmentation in a benzoxocane system.[4] This arose out of our efforts to carry out a deoxygenation of an alcohol employing the celebrated Barton–McCombie reaction.[5] Thus, the heliannuol derivatives **2** and **3** on conversion to the corresponding thionocarbonates **4** and **5** followed by exposure to radical formation conditions resulted in the heterocyclic ring cleavage to furnish the curcuphenols **6** and **7**, respectively. Formation of curcuphenols represented a novel radical induced fragmentation in a strategically placed oxygenated ring system where the generated radical undergoes fragmentation resulting in a phenoxy radical (Scheme 1).



Scheme 1. Radical induced fragmentation.

To demonstrate further the utility of this fragmentation process, we have applied the sequence of reactions to a synthesis of elvirol **8** and a formal synthesis of 7,8-dihydroxycalamenene **20** and the details are presented below.

2. Results and discussion

2.1. Synthesis of elvirol

Elvirol **8** is a bisabolene sesquiterpene metabolite, isolated from *Elvira biflora*.[6] Although **8** has been assigned a terpenoid basis, it is

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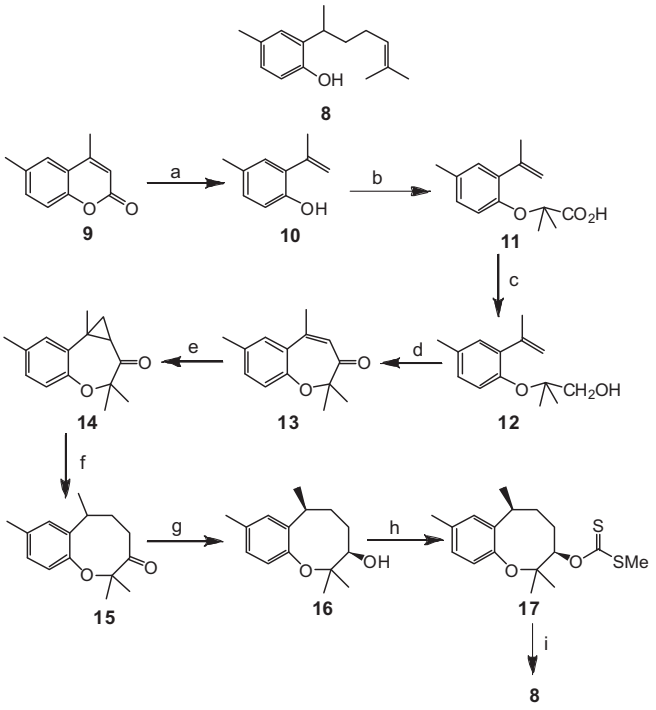
unique in that it does not conform to the isoprene rule that goes to make up all the terpene constituents. Enantiomeric nature of elvirol has not been referred to in its isolation and as such no information is available on its possible biological activity. Interestingly, its better known structural sibling curcuphenol displays interesting biological activities of both its enantiomers.[7,8] Synthesis of elvirol both as racemate as well as enantiomers has also been disclosed.[9]

In view of our interest to illustrate the utility of the new fragmentation process as above encountered by us, we decided to employ the methodology for a synthesis of this curcuphenol congener. The synthesis began with 4,6-dimethyl coumarin **9** and essentially followed the same schematic pathway as applied for the synthesis of curcuphenol.[4] This coumarin was transformed to the styrenol **10** following the reported method.[10] The styrenol **10** was subjected to a Bargellini reaction[11] involving interaction with chloroform in presence of powdered sodium hydroxide in refluxing acetone and furnished the *gem*-dimethyl carboxylic acid **11** in 61% yield. This acid could be smoothly reduced in very good yield to the corresponding alcohol **12** with lithium aluminium hydride. Taking cue from our previous experience,[4] when this alcohol was subjected to oxidation with PCC, it afforded the benzoxopinenone **13** in a moderate yield following a two-step procedure involving an intramolecular aldo-ene cyclisation and reoxidation.

The benzoxopinenone **13** was subjected to ring expansion to the eight-membered benzoxocane **15** following previous procedure.[4] Thus, treatment of **13** with diazomethane in the presence of catalytic amount of palladium acetate furnished the cyclopropyl ketone **14** in very good yield (85%). Catalytic hydrogenation of this cyclopropyl ketone **14** resulted in the expected regioselective cleavage of the central bond revealing the benzoxocanone **15** in excellent yield. Reduction of this ketone **15** with sodium borohydride proceeded in a stereocontrolled fashion yielding the alcohol **16** although the resultant stereochemistry was not quite relevant. This alcohol was transformed to the thionocarbonate **17** through interaction with carbon disulfide and methyl iodide in presence of sodium hydride. Treatment of this thionocarbonate with tri-*n*-butyltin hydride[5] in toluene under reflux effected the anticipated fragmentation of the eight-membered ring and furnished elvirol **8** in an overall yield of 52% from the alcohol **16** (Scheme 2). The spectroscopic data [^{1}H NMR and ^{13}C NMR] of our synthetic **8** were fully consistent with the reported values.[7,8]



Scheme 2. Reagents and conditions: (a) KOH, ethylene glycol, 2 h, reflux, 60%; (b) (i) $CHCl_3$, NaOH, acetone, 5 h, reflux, 61%; (ii) CH_2N_2, ether, 61%; (c) $LiAlH_4$, ether, 4 h, reflux, 86%; (d) PCC, DCM, 24 h, 40%; (e) CH_2N_2, diethyl ether, $Pd(OAc)_2$ (cat), 4 h, 0 °C, 85%; (f) H_2/Pd/C, 6 h, 94%; (g) $NaBH_4$, MeOH, 4 h, rt, 90%; (h) NaH, THF, CS_2, MeI, NH_4Cl, 20 h, 70%; (i) Tri-*n*-butyltin hydride, AIBN, toluene, 4 h, reflux, 74%.

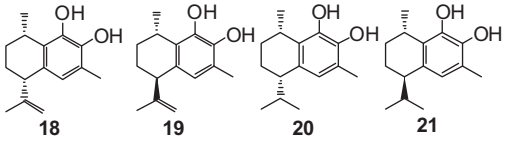


Fig. 1. Calamenenes.

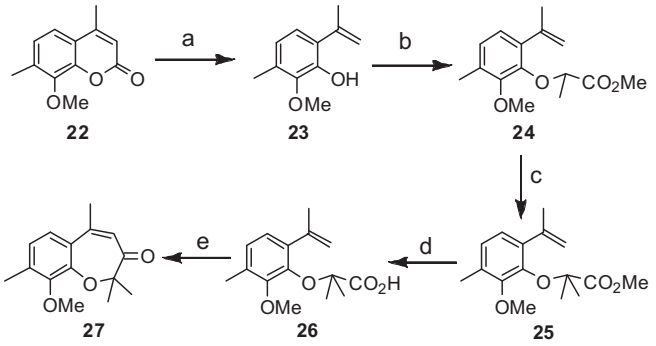
2.2. Synthesis of 7,8-dihydroxycalamenene

Hoffmann et al. isolated two *o*-catechol derivatives, along with other components from *Guardia platyphylla*. These two catechols were isolated as a mixture and identified as (1*S*,4*S*)-7,8-dihydroxy-11,12-dehydro calamenene **18** and (1*S*,4*R*)-7,8-dihydroxy-11,12-dehydro calamenene **19** (Fig. 1).[12] These were found to be antiinfective and inhibited the in vitro growth of *Staphylococcus aureusUA 9-29*, *Bacillus subtilis UA 2-27*, *Klebsiella pneuoniea UA 3-9* and *Candida albicans UA 97*. These were highly unstable and subsequently it was found that the corresponding dihydro derivatives **20** and **21** also showed the same activity (Fig. 1).[12] However, the activity was dependent on the type of hydroxyl protection function. Thus, the corresponding acetates and dimethyl ethers were devoid of any activity and the mono-methyl derivatives showed loss of gram negative activity. In view of the reported instability of these catechols and the similar activity profile of the dihydro derivatives, synthetic efforts have been directed to the latter compounds.[13,14]

Concurrent to the synthesis of elvirol **17**, it was of interest to extend the sequence of reactions to a formal synthesis of dihydroxycalamenene **20**. This emanated from the synthesis by Kraus et al., where the curcuphenol analogue **33**, had served as an advanced intermediate.[14] Hence, a synthesis of this curcuphenol should constitute a formal synthesis of **20**.

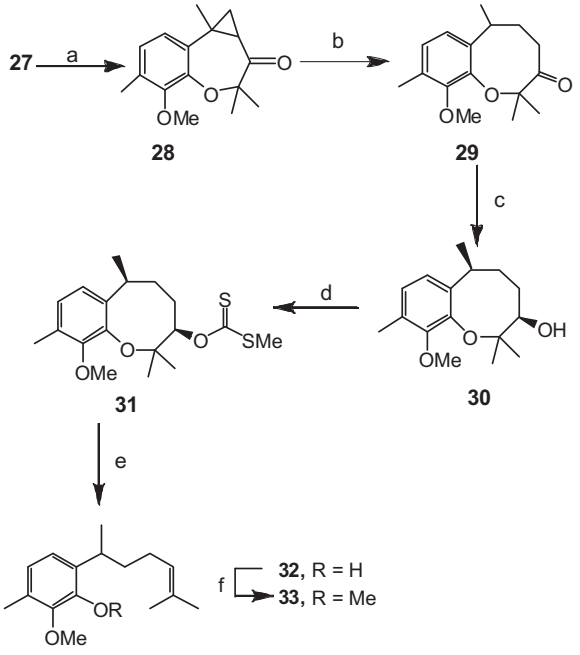
The synthesis relied essentially on some of the key sequences as for the synthesis of elvirol. The properly anointed 4,7-dimethyl-8-methoxy coumarin **22**[15] was employed as the starting material. This was subjected to decarboxylative hydrolysis by refluxing in ethylene glycol in presence of added potassium hydroxide and furnished the styrenol **23**, in 50% yield. Alkylation of this with methyl α-bromopropionate in presence of potassium carbonate afforded the styrenecarboxylate **24** in a yield of 87%. Reaction of this ester with LDA followed by treatment of the resultant enolate with methyl iodide provided the *gem*-dimethyl incorporated ester **25** in excellent yield. Alkaline hydrolysis of the ester delivered the carboxylic acid **26**. Intramolecular acylation of this acid was carried out by refluxing a benzene solution with added thionyl chloride and furnished the benzoxepinenone **27** in a satisfactory yield (Scheme 3).

This was converted to the cyclopropyl ketone **28** by exposing to diazomethane in presence of palladium acetate. As in previous cases,[4] catalytic hydrogenation proved to be highly regioselective leading to the eight-membered ketone **29** in excellent yield. Reduction of this ketone with sodium borohydride furnished a single alcohol **30** and based on previous analogy[4] could be assigned the cis configuration, although the stereochemical outcome of this reduction was not material to the next course of reactions. This alcohol was converted to the thionocarbonate **31** by sequential treatment with carbon disulfide and methyl iodide in presence of sodium hydride. Exposure of this to tri-*n*-butyltin hydride as per earlier conditions for radical formation resulted in the expected fragmentation



Scheme 3. Reagents and conditions: (a) KOH, ethylene glycol, reflux, 2 h, 50%; (b) K_2CO_3, $CH_3CH(Br)COOMe$, acetone, reflux, 5 h, 87%; (c) LDA, THF, MeI, −20 °C to rt, 2 h, 90%; (d) 10% NaOH, MeOH, 50 °C, 1 h, 94%; (e) $SOCl_2$, benzene, reflux, 3 h, 68%.

to finally deliver the curcuphenol derivative **32** in very good yield. Brief treatment of this styrenol with methyl iodide in presence of sodium hydride furnished the desired dimethoxy compound **33** (Scheme 4), the advanced intermediate in the synthesis of **20** by Kraus et al.[14] The spectral features were fully consistent with those reported for the same. Since this has been transformed to the dihydroxycalamenene **20** in two further steps, the present study concluded a formal synthesis of this bioactive catechol derivative.



Scheme 4. Reagents and conditions: (a) $Pd(OAc)_2$, CH_2N_2, ether, 0 °C, 3 h, 72%; (b) H_2, Pd/C, EtOH, 2 h, 90%; (c) $NaBH_4$, MeOH, 0 °C, 95%; (d) NaH, CS_2, MeI, 0 °C to rt, 8 h, 92%; (e) TBTH, AIBN, toluene, reflux, 3 h, 90%; (f) MeI, K_2CO_3, acetone, reflux, 4 h, 97%.

In summary, we have demonstrated the utility of the novel radical induced fragmentation in an eight-membered oxygenated ring system by application to the synthesis of a curcuphenol analogue elvirol and a formal synthesis of an antiinfective compound 7,8-dihydroxycalamenene. It is expected that this observation will find more such applications in organic synthesis.

3. Experimental

3.1. General

All non aqueous reactions were carried out under an inert atmosphere (argon). Melting points were taken in open capillary tubes in a sulfuric acid bath and are uncorrected. Dry solvents and reagents were prepared from reagent grade materials by conventional methods. Petroleum ether refers to the fraction of bp 60–80 °C. The purity of the products was routinely monitored by TLC. Drying of organic layers was done with sodium sulfate. ^{1}H NMR spectra were recorded at 60 or 300 MHz in CCl_4 (for 60 MHz) or $CDCl_3$ solutions. ^{13}C NMR spectra were recorded in $CDCl_3$ solutions at 75 MHz. Peak positions are indicated in parts per million downfield from internal TMS standard. IR spectra of liquid products were recorded in thin films or in $CHCl_3$ solution. IR spectra of solids were recorded as KBr pellets. Elemental analyses were recorded in Perkin–Elmer (CHN Analyzer) 2400 series-2. High-resolution mass spectra (HRMS) were measured in QTOF I (quadrupole-hexapole-TOF) mass spectrometer with an orthogonal Z-spray-electrospray interface on Micro (YA-263) mass spectrometer.

3.2. 2-(2-Isopropenyl-4-methyl-phenoxy)-2-methyl-propionic acid (11)

Isopropenyl cresol **10** (3.2 g, 21.6 mmol) in acetone (30 mL) was taken in a three-necked flask with a dropping funnel and a condenser. Powdered sodium hydroxide (5.3 g, 132.5 mmol) was added in small portions with stirring. The warm mixture was cooled to room temperature and chloroform (2.4 mL) was added within 15 min. Then the mixture was refluxed for 5 h, cooled and diluted with water, acidified with cold HCl (6 N) and thoroughly extracted with ether. The combined organic extract was washed with brine, dried and concentrated to afford the *gem*-di-methyl incorporated carboxylic acid **11** (3.1 g, 61%) as a semi solid residue. ^{1}H NMR (60 MHz, CCl_4): δ 6.94–6.96 (m, 3H), 5.15 (br s, 1H), 5.05 (br s, 1H), 3.51 (s, 1H), 2.35 (s, 3H), 2.21 (s, 3H), 1.25 (s, 6H).

3.3. 2-Methyl-2-(4-methyl-2-vinyl-phenoxy)-propan-1-ol (12)

To a magnetically stirred slurry of lithium aluminium hydride (1 g, 240 mmol) in dry ether (120 mL) was added dropwise to a solution of the acid **11** (3 g, 13 mmol) in dry ether (40 mL). After the addition was complete, the mixture was refluxed for 4 h, cooled and decomposed with cold saturated aqueous Na_2SO_4 solution. The ether layer was separated and the aqueous layer was extracted with ether. The combined ether extract was washed with brine, dried and concentrated to furnish the alcohol **12** as a colourless liquid. It was subjected to column chromatography over silica gel. Elution with ethyl acetate (1:9) furnished the pure alcohol (2.5 g, 86%). ν_{max}/cm^{-1} (thin film) 3440. ^{1}H NMR (60 MHz, CCl_4): δ 7.07 (d, J=8.1 Hz, 1H), 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). Found C, 76.14; H, 9.12%. $C_{14}H_{20}O_2$ requires C, 76.32; H, 9.15%.

3.4. (*Z*)-2,2,5,7-Tetramethylbenzo[*b*]oxepin-3(2*H*)-one (13)

To a magnetically stirred suspension of pyridinium chlorochromate (3.67 g, 17 mmol) in dichloromethane (100 mL) was added the styrene alcohol **12** (2.5 g, 11.4 mmol) in dichloromethane (50 mL) in one portion. After stirring for 24 h, dry ether (50 mL) was added and the supernatant liquid was decanted from the black gummy residue. This residue was washed thoroughly with ether (20 mL) for at least 3–4 times. The combined ether extract was concentrated and the residual oil was purified by column chromatography over silica gel. Elution with ethyl acetate (1:49) afforded benzoxepinenone **13** (980 mg, 40%) as a colourless liquid. ν_{max}/cm^{-1} 1649. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.16 (br s, 1H), 7.05 (d, J=8.1 Hz, 1H), 6.91 (d, J=8.1 Hz, 1H), 6.2 (s, 1H), 2.27 (s, 3H), 2.24 (s, 3H), 1.24 (s, 6H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 203.93, 152.06, 146.94, 134.10, 131.95, 130.99, 129.97, 128.97, 124.24, 87.56, 25.57, 24.65,

21.34. Found: C, 77.81; H, 7.35%. $C_{14}H_{16}O_2$ requires C, 77.75; H, 7.46%.

3.5. 3,3,7,8b-Tetramethyl-1a,8b-dihydro-1*H*-4-oxa-benzo[*a*] cyclopropa[*c*]cyclohepten-2-one (14)

To a stirred solution of the above unsaturated ketone **13** (670 mg, 3.1 mmol) in dry ether (6 mL) in presence of $Pd(OAc)_2$ (8 mg), a large excess of ethereal diazomethane solution was added dropwise at 0 °C and the resulting mixture was stirred continuously at room temperature for 4 h. Then it was filtered through a short column of silica gel to afford a yellow coloured liquid, which was subjected to column chromatography over silica gel. Elution with ethyl acetate in petroleum ether (1:49) furnished pure cyclopropyl ketone **14** (610 mg, 85%) as a colourless oil. ν_{max}/cm^{-1} 1680. ^1H NMR (300 MHz, $CDCl_3$): δ 7.07 (br s, 1H), 6.84 (d, J=8 Hz, 1H), 6.69 (d, J=7.9 Hz, 1H), 2.99 (t, J=5.2 Hz, 1H), 2.22 (s, 3H), 2.03 (m, 1H), 1.43 (s, 3H), 1.42 (s, 3H), 1.15 (s, 3H), 1.12 (m, 1H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 211.00, 150.82, 135.43, 134.67, 129.60, 127.96, 124.97, 88.28, 39.18, 27.91, 27.62, 26.30, 23.37, 21.82, 21.44. Found C, 78.19; H, 7.81%. $C_{15}H_{18}O_2$ requires C, 78.23; H, 7.88%.

3.6. 10-Methoxy-2,2,6,9-tetramethyl-5,6-dihydro-4*H*-benzo [*b*]oxocin-3-one (15)

The cyclopropyl ketone **14** (610 mg, 2.6 mmol) in double distilled ethanol (6 mL) was hydrogenated by using Pd/C (10%, 100 mg) as a catalyst at room temperature and atmospheric pressure. After complete consumption of hydrogen gas the solution was filtered. The solvent was removed and the residual oil was purified by column chromatography using silica gel. Elution with ethyl acetate in petroleum ether (1:99) afforded the cyclic ketone **15** (610 mg, 94%) as a colourless oil. ν_{max}/cm^{-1} 1712. ^1H NMR (300 MHz, $CDCl_3$): δ 6.89 (s, 1H), 6.85 (d, J=8.8 Hz, 1H), 6.75 (d, J=8 Hz, 1H), 3.02–3.09 (m, 1H), 2.14–2.43 (m, 2H), 2.21 (s, 3H), 1.92 (m, 1H), 1.50–1.62 (m, 1H), 1.42 (s, 3H), 1.37 (s, 3H), 1.25 (d, J=7 Hz, 3H). ^{13}C NMR ($CDCl_3$, 75 Hz): δ 213.25, 151.18, 139.40, 135.07, 128.58, 127.57, 86.50, 36.43, 35.07, 34.54, 24.90, 23.81, 21.82, 21.44. Found: C, 77.59; H, 8.62%. $C_{15}H_{20}O_2$ requires C, 77.55; H, 8.68%.

3.7. 2,2,6,8-Tetramethyl-3,4,5,6-tetrahydro-2*H*-benzo[*b*] oxocin-3-ol (16)

The above ketone **15** (610 mg, 2.5 mmol) in methanol (20 mL) was cooled at 0 °C and sodium borohydride (185 mg, 5 mmol) was added portion wise to the cold mixture with stirring for 4 h. The methanol was evaporated, excess sodium borohydride was quenched with cold water and extracted with ether (3×15 mL). The combined ether extract was washed with water, dried and concentrated to afford a light yellow coloured liquid. This was purified by column chromatography (petroleum ether/EtOAc 19:1) to furnish the alcohol **16** as a colourless dense liquid (550 mg, 90%). ν_{max}/cm^{-1} 3458. ^1H NMR (300 MHz, $CDCl_3$): δ 7.00 (br s, 1H), 6.96–6.81(m, 2H), 3.64 (s, 1H), 3.36 (d, J=9 Hz, 1H), 3.21–3.23 (m, 1H), 2.33 (s, 3H), 1.45 (s, 3H), 1.39 (s, 3H), 1.29 (d, J=7 Hz, 3H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 150.74, 141.06, 134.11, 127.03, 126.86, 124.91, 83.37, 75.86, 36.68, 32.66, 26.11, 23.32, 21.51, 21.41. Found C, 77.12; H, 9.45%. $C_{15}H_{22}O_2$ requires C, 76.88; H, 9.46%.

3.8. 2-(1,5-Dimethyl-hex-4-enyl)-1-methoxy-4-methyl-benzene, elvirol (8)

*Preparation of the S-methylthionocarbonate (**17**).* To a stirred suspension of sodium hydride (0.43 g, 9 mmol, 50% dispersion in oil) in dry THF (10 mL) was added a solution of the alcohol **16** (700 mg, 3 mmol) in dry THF (7 mL) and the mixture was stirred at room temperature for 2 h. Carbon disulfide (4.5 mL, 75 mmol) and methyl iodide (0.55 mL, 9 mmol) were added consecutively and the mixture was stirred for 20 h. Next day saturated aqueous solution of NH_4Cl was added to decompose. Ether of 10 mL was added and stirred for 15 min, the ether layer was separated and the aqueous layer was extracted exhaustively with ether. The combined ether layer was washed with brine, dried and concentrated to afford a yellow oil, which was purified by column chromatography over silica gel. Elution with ethyl acetate in petroleum ether (1:99) furnished the *S*-methylthionocarbonate **17** (670 mg, 70%). ^1H NMR (300 MHz, $CDCl_3$): δ 6.9 (s, 1H), 6.84 (d, J=8.4 Hz, 1H), 6.75 (d, J=8.1 Hz, 1H), 5.25 (d, J=9 Hz, 1H), 3.227–3.29 (m, 2H), 2.45 (s, 3H), 2.19 (s, 3H), 2.08–2.14 (m, 2H), 1.68–1.75 (m, 2H), 1.42 (s, 3H), 1.26 (s, 3H), 1.19 (d, J=6 Hz, 3H).

A solution of above *S*-methylthionocarbonate **17** (670 mg, 2 mmol) in dry toluene (20 mL) was heated under reflux with tri-*n*-butyltin hydride (0.892 mL, 3.1 mmol) and 2,2-azobisbutyronitrile (AIBN) (5 mg) for 4 h. Toluene was removed under pressure and saturated aqueous solution of potassium fluoride (2 mL) was added and stirred at room temperature for 5 h. The precipitated solid was filtered off and the filtrate was extracted with ether. The ethereal extract was washed with brine, dried and solvent was removed to afford a deep yellow coloured liquid. This was subjected to column chromatography using silica gel. Elution with ethyl acetate in petroleum ether (1:19) furnished elvirol **8** as a colourless oil (340 mg, 74%). ν_{max}/cm^{-1} 3372. ^1H NMR (300 MHz, $CDCl_3$): δ 6.86 (s, 1H), 6.78 (d, J=8.1 Hz, 1H), 6.58 (d, J=8.1 Hz, 1H), 5.07 (t, J=6.9 Hz, 1H), 4.56 (s, 1H), 2.84–2.94 (m, 1H), 2.19 (s, 3H), 1.83–1.91 (m, 2H), 1.59 (s, 3H), 1.56–1.58 (m, 2H), 1.46 (s, 3H), 1.16 (d, J=6 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 149.74, 131.78, 131.02, 128.95, 126.56, 126.00, 123.57, 114.25, 36.23, 30.60, 25.06, 24.70, 19.97, 19.70, 16.64. Found: C, 82.32; H, 10.31%. $C_{15}H_{22}O$ requires C, 82.51; H, 10.16%.

3.9. 6-Isopropenyl-2-methoxy-3-methyl-phenol (23)

4,7-Dimethyl-8-methoxy coumarin **22** (13 g, 74.7 mmol) was added portion wise to a solution of KOH (18 g, 321 mmol) in water (8 mL) and ethylene glycol (120 mL). The reaction mixture was refluxed for 2 h. It was cooled and poured into crushed ice and extracted with ether. The organic layer was washed with saturated brine and dried. The residue after removal of solvent was distilled to afford the styrenol **23** (5.72 g, 50%). This styrenol **23** displayed a tendency to rapidly polymerise and hence only ^1H NMR was recorded and taken to the next step. ^1H NMR (300 MHz, $CDCl_3$): δ 6.88 (d, J=7.8 Hz, 1H), 6.66 (d, J=7.8 Hz, 1H), 5.98 (br s, 1H), 5.23 (s, 2H), 3.83 (s, 3H), 2.22 (s, 3H), 2.14 (s, 3H).

3.10. 2-(6-Isopropenyl-2-methoxy-3-methyl-phenoxy)-propionic acid methyl ester (24)

A mixture of the styrenol **23** (2 g, 13.5 mmol), methyl α-bromopropionate (2.44 g, 13.5 mmol), anhydrous K_2CO_3 (3.73 g, 27 mmol) and KI (20 mg) in dry acetone (60 mL) was heated under reflux with stirring for 5 h. It was then concentrated to one-third of the volume, diluted with water and extracted with ether (3×40 mL). The combined organic layer was washed with cold 5% NaOH solution and water. Then it was dried and concentrated. The residual oil was passed through a short column of alumina and eluted with petroleum ether to afford the alkylated product **24** (2.6 g, 87%). ^1H NMR (300 MHz, $CDCl_3$): δ 6.89 (s, 2H), 5.11 (s, 1H), 5.05 (s, 1H), 4.66 (q, J=6.7 Hz, 1H), 3.79 (s, 3H), 3.75 (s, 3H), 2.25 (s, 3H), 2.15 (s, 3H), 1.47 (d, J=6.8 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 172.7, 151.5, 148.3, 144.0, 136.7, 131.6, 126.0, 124.2, 115.5, 77.7, 60.5, 52.0, 23.7, 18.6, 15.9; HRMS (ES+ve) calcd for $C_{15}H_{20}O_4Na$ $[M+Na]^+$ 287.1259, found 287.1253.

3.11. 2-(6-Isopropenyl-2-methoxy-3-methyl-phenoxy)-2-methyl-propionic acid methyl ester (25)

To a well stirred solution of LDA [prepared from *n*-butyllithium (1.4 mL of 1.6 M solution in hexane, 2.24 mmol) and diisopropylamine (0.32 mL, 2.3 mmol)] in THF at −20 °C, a solution of the ester **24** (530 mg, 2.00 mmol) in THF (2 mL) was added dropwise under cold condition (−40 °C). After 30 min, methyl iodide (0.15 mL, 2.4 mmol) was added and stirred for another 2 h at −20 °C and then allowed to attain room temperature and stirred at this temperature for 30 min. The reaction mixture was then quenched with saturated solution of ammonium chloride in water and extracted with ether. The combined ethereal extract was washed with water, brine, dried and the solvent was removed under reduced pressure. The residual oil was purified by column chromatography over silica gel and eluted with ethyl acetate in petroleum ether (1:20) to furnish the methylated ester **25** (510 mg, 90%). ^{1}H NMR (300 MHz, $CDCl_3$): δ 6.87 (d, J=7.8 Hz, 1H), 6.82 (d, J=7.8 Hz, 1H), 5.09 (s, 1H), 4.97 (s, 1H), 3.80 (s, 3H), 3.68 (s, 3H), 2.25 (s, 3H), 2.12 (s, 3H), 1.41 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 174.27, 152.9, 145.9, 145.0, 138.81, 130.98, 126.4, 124.06, 115.44, 81.23, 60.23, 52.19, 25.03, 23.64, 15.9; HRMS (ES+ve) calcd for $C_{16}H_{22}O_4Na$ $[M+Na]^+$ 301.1416, found 301.1411.

3.12. 2-(6-Isopropenyl-2-methoxy-3-methyl-phenoxy)-2-methyl-propionic acid (26)

To a stirred solution of the ester **25** (510 mg, 1.8 mmol) in methanol (0.3 mL) 10% NaOH solution (in water) was added. The reaction mixture was heated at 50 °C for 1 h. After cooling the reaction mixture was acidified by cold dil HCl (6 N) and extracted with ether (3×20 mL). The combined ether layer was washed with a saturated aqueous $NaHCO_3$ solution. The alkali part was then acidified with cold dil HCl and extracted with ether (3×20 mL). The combined ether layer was washed with water, brine, dried and concentrated over vacuum to afford the pure acid **26** as colourless gummy liquid (470 mg, 94%). ^{1}H NMR (300 MHz, $CDCl_3$): δ 10.5 (br s, 1H), 6.82 (d, J=7.8 Hz, 1H), 6.76 (d, J=7.8 Hz, 1H), 5.07 (s, 1H), 4.94 (s 1H), 3.70 (s, 3H), 2.20 (s, 3H), 2.03 (s, 3H), 1.38 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 176.7, 151.2, 143.87, 143.77, 137.6, 129.7, 125.9, 123.5, 115.1, 81.7, 59.7, 23.6, 22.5, 14.9.

3.13. (*Z*)-9- Methoxy-2,2,5,8-tetramethylbenzo[*b*]oxepin-3(2*H*)-one (27)

To a stirred solution of acid **26** (200 mg, 1.70 mmol) in dry benzene (10 mL) was added freshly distilled $SOCl_2$ (0.28 mL, 3.9 mmol). The reaction mixture was heated under reflux for 3 h. It was then cooled and excess $SOCl_2$ was removed by azeotropic distillation under vacuum with fresh addition of dry benzene (3×5 mL). The residual mass was decomposed by crushed ice and extracted with ether (3×15 mL). The combined ether layer was then washed with saturated aqueous $NaHCO_3$ solution, water, brine and then dried. Elution with ethyl acetate/petroleum ether (1.5%) furnished the ketone **27** as colourless oil (120 mg, 68%). ν_{max}/cm^{-1} 1648. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.02 (d, J=8.1 Hz, 1H), 6.9 (d, J=8.1 Hz, 1H), 6.19 (s, 1H), 3.78 (s, 3H), 2.23 (s, 3H), 2.22 (s, 3H), 1.3 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 203.4, 152.0, 147.4, 146.7, 134.4, 130.5, 128.1, 125.9, 122.5, 87.6, 60.5, 25.3, 23.6, 16.3; HRMS (ES+ve) calcd for $C_{15}H_{18}O_3Na$ $[M+Na]^+$ 269.1154, found 269.1156.

3.14. 5-Methoxy-3,3,6,8b-tetramethyl-1a,8b-dihydro-1*H*-4-oxa-benzo[*a*]cyclopropa[*c*]cyclohepten-2-one (28)

To a stirred solution of the above unsaturated ketone **27** (1 g, 4.06 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 3 h. The oil after removal of ether was purified by column chromatography over silica gel (petroleum ether/ethyl acetate 49:1) to furnish the cyclopropyl ketone **28** as a colourless solid (760 mg, 72%). It was crystallized from ether/petroleum ether; mp 60–62 °C. ν_{max}/cm^{-1} (thin film) 1678. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.00 (d, J=8.1 Hz, 1H), 6.90 (d, J=8.1 Hz, 1H), 3.84 (s, 3H), 3.09 (t, J=4.5 Hz, 1H), 2.15 (s, 3H), 2.08 (dd, J=8.7, 5.9 Hz, 1H), 1.56 (s, 3H), 1.51 (s, 3H), 1.32–139(m, 1H), 1.25 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 211.28, 152.6, 146.17, 134.7, 130.4, 126.3, 122.9, 89.0, 60.4, 39.0, 27.8, 27.3, 26.2, 22.29, 21.6, 15.98; HRMS (ES+ve) calcd for $C_{16}H_{20}O_3Na$ $[M+Na]^+$ 283.1310, found 283.1314.

3.15. 10-Methoxy-2,2,6,9-tetramethyl-5,6-dihydro-4*H*-benzo-[*b*]oxocin-3-one (29)

The cyclopropyl ketone **28** (200 mg, 0.77 mmol) in distilled ethanol (3 mL) was hydrogenated using Pd/C (10%, 50 mg) as catalyst at room temperature and atmospheric pressure. After 2 h the mixture was filtered and the solvent was removed under reduced pressure to furnish a colourless oil, which was purified by column chromatography over silica gel (petroleum ether/ethyl acetate 49:1) to afford the cyclic ketone **29** (180 mg, 90%) as a colourless oil. ν_{max}/cm^{-1} (thin film) 1715. ^{1}H NMR (300 MHz, $CDCl_3$): δ 6.95 (d, J=3.9 Hz, 1H), 6.85 (d, J=3.9 Hz, 1H), 3.85–3.88 (m, 1H), 3.79 (s, 3H), 3.07 (m, 1H), 2.42 (td, J=11.8, 4.2 Hz, 1H), 2.25 (s, 3H), 2.02–2.16 (m, 2H), 1.55 (s, 3H), 1.44 (s, 3H), 1.27 (d, J=6.9 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 211.89, 152.58, , 146.47, 139.11, 129.94, 127.04, 121, 87.76, 59.54, 35.40, 34.83, 31.78, 24.12, 22.1, 20.09, 16.06; HRMS (ES+ve) calcd for $C_{16}H_{22}O_3Na$ $[M+Na]^+$ 285.1466, found 285.1469.

3.16. 10-Methoxy-2,2,6,9-tetramethyl-3,4,5,6-tetrahydro-2*H*-benzo[*b*]oxocin-3-ol (30)

The ketone **29** (550 mg, 2.1 mmol) in methanol (10 mL) was cooled to 0 °C (ice bath) and $NaBH_4$ (220 mg, 4.2 mmol) was added portion wise with stirring for 2 h. The methanol was evaporated, excess sodium borohydride was quenched with cold water and extracted with ether (3×15 mL). The combined ethereal extract was washed with water, dried and concentrated. The residual oil was purified by column chromatography (petroleum ether/ethyl acetate 19:1) to afford the alcohol **30** (526 mg, 95%) as a colourless oil. ν_{max}/cm^{-1} (thin film) 3432. ^{1}H NMR (300 MHz, $CDCl_3$): δ 6.91 (d, J=7.8 Hz, 1H), 6.82 (d, J=7.8 Hz, 1H), 3.77 (s, 3H), 3.49 (m, 1H), 3.26 (m, 1H), 2.23 (s, 3H), 2.11 (m, 2H), 1.82 (m, 2H), 1.29 (s, 6H), 1.25 (d, J=6.9 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 152.7, 147.08, 140.1, 129.25, 126.21, 120.74, 116.29, 85.5, 76.73–76.89, 59.47, 35.18, 31.76, 27.07, 25.74, 23.0, 21.05, 16.0; HRMS (ES+ve) calcd for $C_{16}H_{24}O_3Na$ $[M+Na]^+$ 287.1623, found 287.1625.

3.17. *S*-Methylthionocarbonate (31)

To a stirred suspension of sodium hydride (0.25 g, 1.04 mmol, 50% dispersion in oil) in dry THF (10 mL) was added a solution of the alcohol **30** (260 mg, 0.9 mmol) in dry THF (4 mL) and the mixture was stirred at room temperature for 2 h. Carbon disulfide (1.5 mL, 24.6 mmol) and methyl iodide (0.2 mL, 3 mmol) were added consecutively and the mixture was stirred for 8 h. The reaction mixture was quenched by saturated solution of NH_4Cl. Ether of 10 mL was added and stirred for 15 min. The ether layer was separated and the aqueous layer was extracted exhaustively with ether. The combined ether layer was washed with brine, dried and concentrated to afford yellow oil, which as then purified by column chromatography over silica gel. Elution with petroleum ether in pentane (50:50) furnished the *S*-methylthionocarbonate **31**

(310 mg, 92%). ν_{max}/cm^{-1} (thin film): 1730. ^1H NMR (300 MHz, $CDCl_3$): δ 6.94 (d, J=7.8 Hz, 1H), 6.84 (d, J=7.8 Hz, 1H), 5.4 (d, J=9.7 Hz, 1H), 3.79 (s, 3H), 3.48 (m, 1H), 2.63 (s, 3H), 2.24 (s, 3H), 2.07–2.15(m, 2H), 1.70–1.76 (m, 2H), 1.36 (s, 3H), 1.25 (d, J=6.9 Hz, 3H); ^{13}C NMR (75 MHz, CD Cl_3): δ 215.7, 152.5, 146.8, 140.3, 129.3, 126.6, 120.5, 88.1, 83.7, 59.5, 35.4, 26.6, 23.3, 22.6, 20.5, 20.3, 19.0, 16.1; HRMS (ES+ve) calcd for $C_{18}H_{26}O_3S_2Na$ $[M+Na]^+$ 377.1221, found 377.1224.

3.18. 6-(1,5-Dimethyl-hex-4-enyl)-2-methoxy-3-methyl-phenol (32)

A solution of above *S*-methylthionocarbonate **31** (90 mg, 0.25 mmol) in dry toluene (5 mL) was heated under reflux with tri-*n*-butyltin hydride (0.087 mL, 0.31 mmol) and 2,2-azobisbutyronitrile (AIBN) (0.5 mg) for 4 h. Toluene was removed under reduced pressure and saturated aqueous solution of potassium fluoride (2 mL) was added and stirred at room temperature for 6 h. The precipitated solid was filtered off and the filtrate was extracted with ether. The ethereal extract was washed with brine, dried and solvent was removed to afford a deep yellow coloured liquid. This was then subjected to column chromatography using silica gel. Elution with petroleum ether in pentane (1:1) furnished the cleaved product **32** as a colourless oil (50 mg, 90%). ^1H NMR (300 MHz, $CDCl_3$): δ 6.81 (d, J=7.9 Hz, 1H), 6.65 (d, J=7.9 Hz, 1H), 5.73 (s, 1H), 5.12 (t, J=6 Hz, 1H), 3.79 (s, 3H), 3.09 (m, 1H), 2.27 (s, 3H), 1.93 (m, 3H), 1.67 (s, 3H), 1.54 (s, 3H), 1.21 (d, J=6.9 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 146.52, 145.22, 131.78, 131.36, 127.47, 124.90, 122.36, 121.75, 60.72, 37.14, 32.36, 26.39, 25.87, 21.03, 17.76, 15.82; HRMS (ES+ve) calcd for $C_{16}H_{24}O_2Na$ $[M+Na]^+$ 271.1674, found 271.1671.

3.19. 1-(1,5-Dimethyl-hex-4-enyl)-2,3-dimethoxy-4-methyl-benzene (33)

A mixture of styrenol **32** (50 mg, 0.2 mmol), MeI (40 mg, 0.2 mmol), anhydrous K_2CO_3 (125 mg, 1 mmol) and KI (5 mg) in dry acetone (3 mL) was heated under reflux with stirring for 5 h. It was then concentrated to one-third of the volume, diluted with water and extracted with ether (3×10 mL). The combined organic layer was washed with cold 5% aqueous NaOH solution and water. Then it was dried and concentrated to afford the dimethyl ether **33** (49.6 mg, 94%). ^1H NMR (300 MHz, $CDCl_3$): δ 6.8 (d, J=7.9 Hz, 1H), 6.75 (d, J=7.9 Hz, 1H), 5.04 (t, J=6 Hz, 1H), 3.76 (s, 3H), 3.75 (s, 3H), 3.05 (m, 1H), 2.16 (s, 3H), 1.76–1.95 (m, 3H), 1.59 (s, 3H), 1.46 (s, 3H), 1.11 (d, J=6.9 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 151.41, 150.93, 139.47, 131.46, 129.47, 125.75, 124.80, 121.61, 60.78, 60.05, 37.94, 31.83, 26.55, 25.85, 22.13, 17.78, 15.81; HRMS (ES+ve) calcd for $C_{17}H_{26}O_2Na$ $[M+Na]^+$ 285.1830, found 285.1831.

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