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Synthesis of Phenolic Sesquiterpenes via Oxidative Cleavage of Benzocycloalkenols

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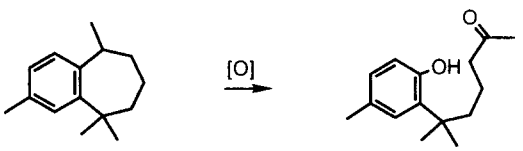
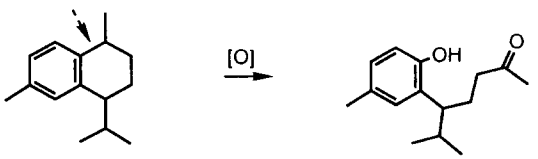
Abstract. Phenolic sesquiterpenes including sesquichamaenol, 6-(2-hydroxy-4-methylphenyl)-2-methyl-3-heptanone, and curcuphenol methyl ether have been obtained from oxidative cleavage of bicyclic precursors by treatment with acidic hydrogen peroxide in a process which probably parallels a biogenetic step A ketone intermediate for curcudiol has also been acquired in the same manner.

Introduction

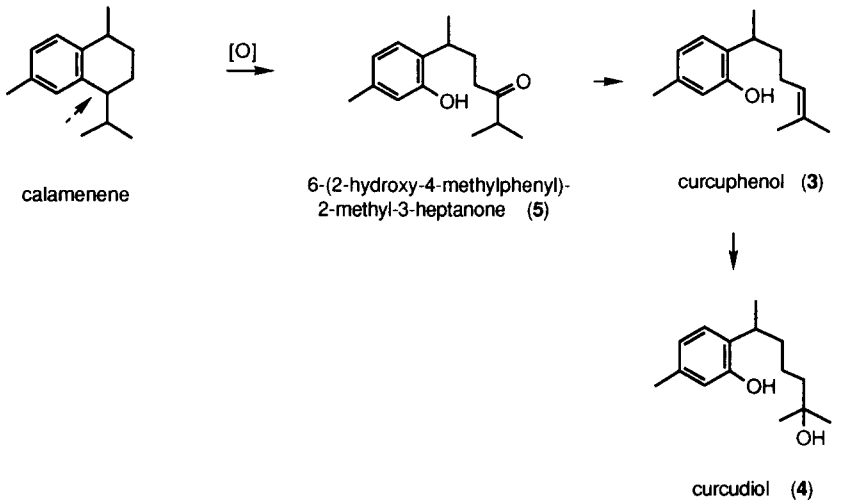
The biogenetic origin of phenolic sesquiterpenes is most intriguing. *A priori*, these substances can arise from oxidation of the hydrocarbon congeners, or by aromatization of cyclic ketone precursors. A third possibility features oxidative cleavage of bicyclic entities. Structural comparison of certain monocyclic phenolic sesquiterpenes with bicyclic compounds, for example, himasecolone (**1**)[1] with *ar*-himachalene; sesquichamaenol (**2**),[2] curcuphenol (**3**)[3] and curcudiol (**4**)[4] with calamenene leads to the conclusion that the oxidative cleavage process is not only logical but also quite commonly employed by Nature in biosynthesis (Eq. 1-3). According to this conjecture himasecolone and sesquichamaenol are the direct ring cleavage products, but in the generation of curcuphenol and curcudiol further modification of the sidechain must be involved. A possible precursor of curcuphenol is 6-(2-hydroxy-4-methylphenyl)-2-methyl-3-heptanone (**5**) which has been



ar-himachalene himasecolone (**1**) (1)



calamenene sesquichamaenol (**2**) (2)



calamenene

6-(2-hydroxy-4-methylphenyl)-2-methyl-3-heptanone (**5**)

curcuphenol (**3**)

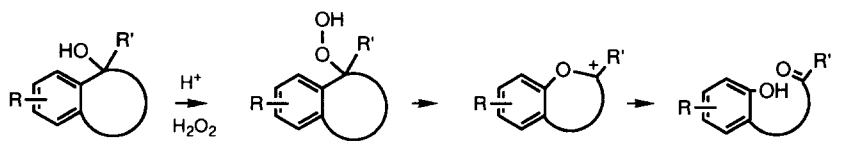
(3)

curcudiol (**4**)

isolated[5] from *Juniperus chinensis* L. var. kaizuka Hort. Interestingly, this last compound occurs in a higher plant whereas curcuphenol and curcudiol are produced by coral and sponge. Note that the skeletons of sesquichamaenol and himasecolone cannot be dissected into contiguous "isoprene units", curcuphenol and curcudiol belong to the normal bisabolane/curcumane-type substances.

The above-mentioned phenolic sesquiterpenes are relatively simple and many of them have been synthesized.[3,6] Except for a synthesis of curcuphenol acetate[7] which embodied extension of citronellal to a dienoic acid and subsequent cyclization to construct the aromatic ring *de novo*, all other work started from phenolic compounds to elaborate the proper sidechains. We were fascinated by the biogenetic hypothesis of oxidative cleavage and investigated a biomimetic approach to several of the phenolic sesquiterpenes. We considered the creation of bicyclic benzylic hydroperoxides that would undergo rearrangement *in situ* to release a ketonic sidechain while accompanying generation of the phenolic group. The proper substrates would be the corresponding benzylic alcohols (Scheme 1).

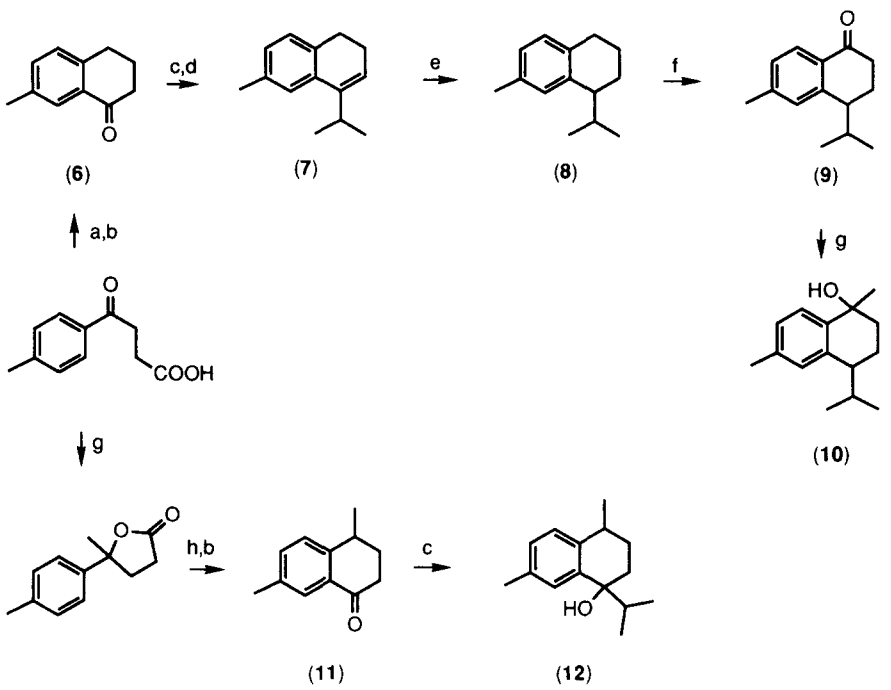
Scheme 1



Results and Discussion

Isomeric hydroxycalamenenes and therefore two different α-tetralones were required in our routes to sesquichamaenol and curcuphenol (Scheme 2). The starting material for both series of compounds was 4-(4-methylphenyl)-4-oxobutanoic acid, the Friedel-Crafts reaction product of toluene and succinic anhydride. For

Scheme 2



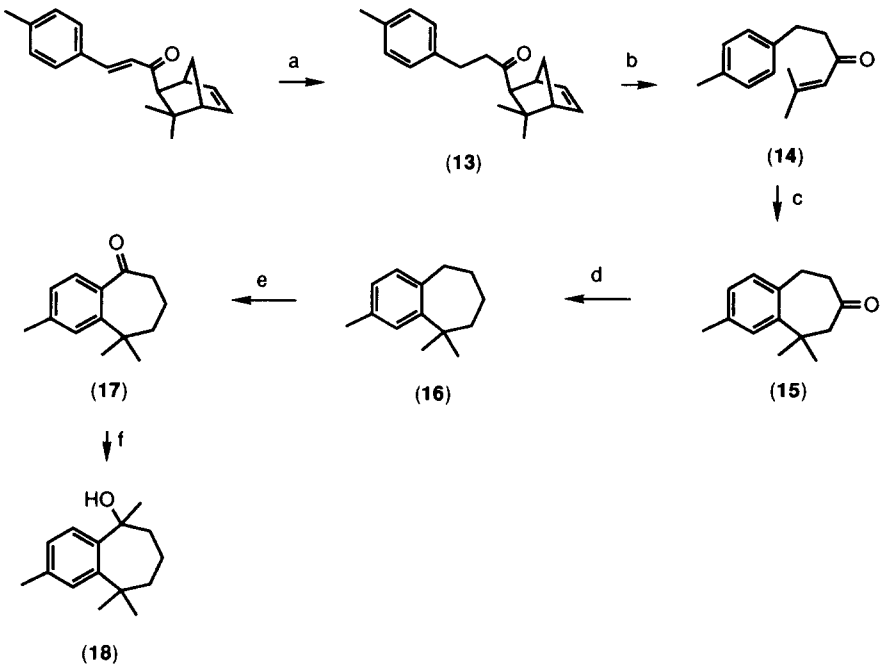
(a) Zn-Hg, HCl; (b) P_2O_5, MsOH; (c) iPrMgBr; (d) TsOH, PhH, Δ; (e) H_2, Pd/C; (f) Jones; (g) MeMgI; (h) H_2, ($HClO_4$), Pd-C

the access to sesquichamaenol the keto acid was subjected to Clemmensen reduction, cycloacylation to afford 7-methyl-α-tetralone (**6**).[8] Grignard reaction with isopropylmagnesium bromide and dehydration led to (**7**). The tetralin (**8**) obtained by hydrogenation underwent benzylic oxidation with Jones' reagent to give 4-isopropyl-6-methyl-α-tetralone (**9**)[9], which was reacted with methylmagnesium iodide to afford (**10**).

Alternatively, the keto acid was reacted with methylmagnesium iodide to give a γ-lactone. Hydrogenolysis and cycloacylation led to 4,7-dimethyl-α-tetralone (**11**)[10]. The substrate (**12**) for the oxidative ring cleavage was acquired by another Grignard reaction with isopropylmagnesium bromide.

For our projected synthesis of himasecolone, a trimethylbenzosuberone was prepared in the following manner (Scheme 3). *exo*-5-(4-Methylcinnamoyl)-6,6-dimethylbicyclo[2.2.1]hept-2-ene, which was readily obtained from an aldol condensation of 5-acetyl-6,6-dimethylbicyclo[2.2.1]hept-2-ene with 4-methylbenzaldehyde,[11] was reduced with zinc dust in acetic acid, and the Retro-Diels-Alder reaction of the resulting dihydro compound (**13**) furnished 2-methyl-6-(4-methylphenyl)-2-hexen-4-one (**14**). On treatment of the enone with aluminum chloride in refluxing carbon disulfide[12] or cyclohexane cyclization occurred (79% and 53% yield of (**15**), respectively). Remarkably, more polar solvents such as dichloromethane and nitromethane were totally unsuitable, as no cyclization product could be detected. The reaction temperature should not be a major factor in

Scheme 3



(a) Zn, HOAc; (b) Δ; (c) $AlCl_3$, CS_2; (d) Zn-Hg, HCl; (e) CrO_3, HOAc; (f) MeMgI

determining this reaction (b.p. of CH_2Cl_2 40°C; CS_2 46°C; C_6H_{12} 81°C; CH_3NO_2 102°C), the conformation of the complex must be responsible for the dramatic difference. In our opinion, nonpolar solvents favor a tight Lewis acid complex in which the enone moiety assumes an *s-trans* geometry.[13] A smaller solvent pocket to surround a more compact complex is energetically sound and this compact form is that which the conjugated double bond bends back towards the aromatic ring. Thus the bulk solvent entropy compensates the entropy of the Lewis acid complex which adopts a conformation very similar to the transition state of the cyclization. On the other hand, the more polar solvents may cause ion-pair separation and also stabilize the more extended conformation of the complex, thereby rendering it inactive for cyclization.

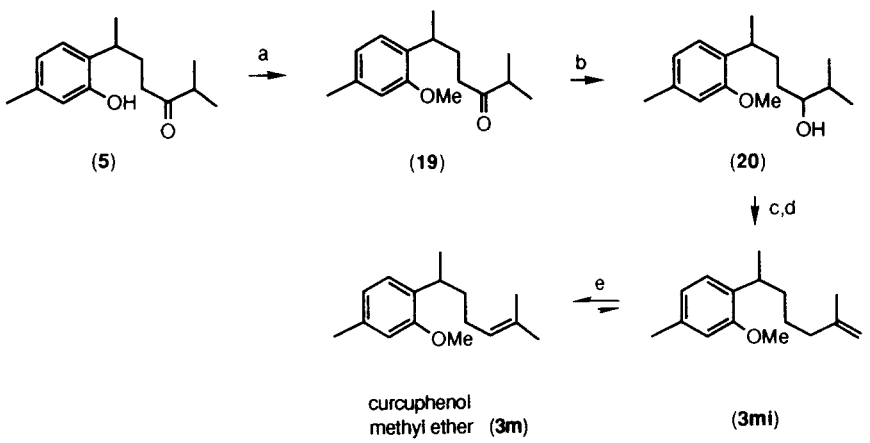
The ketone group of the benzosuberone (**15**) was removed by Clemmensen reduction and another one was reintroduced in the benzylic position by oxidation of (**16**) with chromic oxide in acetic acid. Reaction of the benzosuberone (**17**) with methylmagnesium iodide completed the preparation of the potential substrate (**18**) of himasecolone.

We are not aware of any literature precedence for the biomimetic step of oxidative cleavage, although it is well known that cumene hydroperoxide gives phenol and acetone on exposure to aqueous acid. α,α–Dimethylbenzyl alcohol undergoes the same transformation on reaction with acidic hydrogen peroxide or *t*-butyl hydroperoxide.[14] We decided to simulate the latter process in our work.

To effect the transformation the tertiary benzylic alcohols (**10**), (**12**), and (**18**) were dissolved in tetrahydrofuran, treated with excess 35% hydrogen peroxide and catalytic amount of sulfuric acid at room temperature, and the reaction was monitored by tlc. In this manner sesquichamaenol (**2**) and 6-(2-hydroxy-4-methylphenyl)-2-methyl-3-heptanone (**5**) were obtained in 76% and 82% yield, respectively. It was rather unfortunate that we were not able to isolate himasecolone from an analogous reaction of (**18**). Examination of the reaction product mixture indicated deep-seated rearrangement of the aliphatic moiety had occurred. However, the initial oxidative cleavage did occur as judged by the absorption pattern of aromatic protons in its NMR spectrum.

6-(2-Hydroxy-4-methylphenyl)-2-methyl-3-heptanone (**5**) thus obtained was converted into curcuphenol methyl ether (**3m**) by a five-step reaction sequence (Scheme 4). Methylation of the phenol with dimethyl sulfate which furnished ether (**19**) followed by reduction with sodium borohydride led to the secondary alcohol (**20**). The latter compound was reacted with phosphorus tribromide, but the resulting bromide was found to be rather labile, as on standing it isomerized largely into the tertiary bromide (NMR evidence: six-proton singlet) which could be dehydrobrominated with a base (e.g. *t*-BuOK). Interestingly, a mixture of two olefins was also readily produced upon storage of an ethereal solution of the secondary bromide over anhydrous sodium sulfate. The mixture enriched in the disubstituted olefin (10:1 ratio) was equilibrated by *p*-toluenesulfonic acid in refluxing benzene, resulting in curcuphenol methyl ether contaminated with the disubstituted olefin isomer (**3mi**) which could not be separated.

Scheme 4



(**5**) (**19**) (**20**)

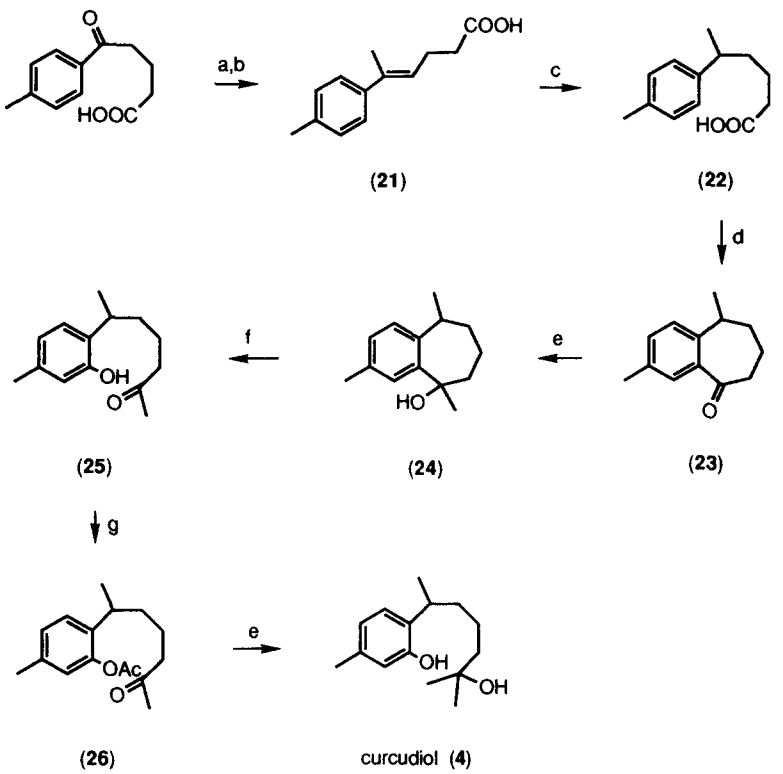
curcuphenol methyl ether (**3m**) (**3mi**)

(a) Me_2SO_4, K_2CO_3; (b) $NaBH_4$; (c) PBr_3; (d) Na_2SO_4; (e) TsOH, PhH, Δ

We sought another approach to the curcuphenol. Since curcudiol has been dehydrated to give curcuphenol, an access to curcudiol constitutes a formal synthesis of our original target compound. Actually we wished to test the oxidative cleavage reaction in terms of applicability to other benzosuberols than the designated precursor of himasecolone. Accordingly, 1,5,8-trimethylbenzocycloheptenol (**24**) was prepared via (**21**)-(**23**) as shown in Scheme 5. The phenolic ketone (**25**) was produced. For purification and characterization purposes

the product was isolated as the acetate in 37% yield. Reaction with methyllithium completed a synthesis of curcudiol.

Scheme 5



(a) MeMgI; (b) TsOH, PhH, Δ; (c) H_2, ($HClO_4$), Pd-C; (d) P_2O_5, MsOH; (e) MeLi; (f) H_2O_2, H_2SO_4; (g) Ac_2O, py.

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Experimental

Ir spectra were measured neat. NMR spectra were run in $CDCl_3$ solutions: proton spectra at 300 MHz and carbon-13 spectra at 75MHz. Workup extracts of reactions were dried over anhydrous sodium sulfate and column chromatography was over silica gel.

3,4-Dihydro-1-(1-methylethyl)-7-methylnaphthalene (**7**): 7-Methyl-α–tetralone (5.0 g, 31.3 mmol) dissolved in anhydrous ether (10 mL) was added from a dropping funnel to a Grignard reagent prepared from magnesium turnings (0.91 g, 37.4 g.atom.) and 2-bromopropane (4.6 g, 37.4 mmol) in ether (30 mL). After stirring at room temperature for 48 hrs and at reflux for another 24 hrs, the reaction mixture was poured into aqueous ammonium chloride and extracted with ether (3x50 mL). The combined extracts were dried, evaporated, and the residue was redissolved in benzene (100 mL), treated with *p*-toluenesulfonic acid (0.2 g) and refluxed under a Dean-Stark trap for 6 hrs. The cooled solution was washed with saturated sodium bicarbonate solution, dried, and evaporated under reduced pressure. The product was chromatographed using hexane as eluent to afford the dihydronaphthalene (**7**) (3.0 g, 53% yield). M^+ calcd. for $C_{14}H_{18}$ 186.1409; found 186.1407. δ_H 1.14 (6H, d, J=6.9 Hz), 2.19 (2H, m), 2.33 (3H, s), 2.62 (2H, t, J=7.8 Hz), 2.9-3.0 (1H, m), 5.86 (1H, m), 6.95 (1H, d, J=7.2 Hz), 7.02 (1H, d, J=7.2 Hz), 7.12 (1H, s). δ_C 21.44, 22.34, 23.21, 28.14, 121.40, 123.24, 126.77, 127.44, 134.05, 134.87, 135.45, 142.62.

1,2,3,4-Tetrahydro-1-(1-methylethyl)-7-methylnaphthalene (**8**): A suspension of 10% Pd/C catalyst (0.1 g) in ethyl acetate (30 mL) was presaturated with hydrogen and used in the hydrogenation of the dihydronaphthalene (**7**) (2.0 g, 10.7 mmol) at room temperature and slightly higher than atmospheric pressure (balloon technique). The filtered solution was evaporated to give the tetralin (**8**) (1.95 g, 97% yield). M^+ calcd. for $C_{14}H_{20}$ 188.1565; found 188.1573. δ_H 0.77 (3H, d, J=6.9 Hz), 1.04 (3H, d, J=6.9 Hz), 1.56-1.72 (2H, m), 1.78-2.02 (2H, m), 2.2-2.36 (1H, m), 2.34 (3H, s), 2.66-2.78 (3H, m), 6.92 (1H, d, J=7.8 Hz), 6.98 (1H, d, J=7.8 Hz), 7.06 (1H, s). δ_C 17.39, 21.20, 21.32, 21.61, 23.27, 29.60, 31.49, 43.44, 126.01, 128.78, 134.52, 135.01, 140.14.

3,4-Dihydro-6-methyl-4-(1-methylethyl)-1(2*H*)-naphthalenone (**9**): A solution of the tetralin (**8**) (2.5 g, 13.3 mmol) in acetone (50 mL) was cooled in an ice bath and treated with Jones reagent (35 mL). The reaction was allowed to proceed for 6 hrs, quenched with isopropanol, diluted with water (200 mL) and extracted with ether (3x50 mL). The ether extracts were combined, washed with water, dried, and evaporated. The residue was chromatographed using 49:1 hexane-ethyl acetate as eluent to afford the tetralone (**9**) (1.0 g, 37% yield). M^+ calcd. for $C_{14}H_{18}O$ 202.1358; found 202.1357. ν 1682 cm^{-1}. δ_H 0.93 (3H, d, J=9.3 Hz), 0.94 (3H, d, J=9.3 Hz), 1.96-2.18 (3H, m), 2.37 (3H, s), 2.45-2.58 (2H, m), 2.65-2.79 (1H, m), 7.04 (1H, s), 7.08 (1H, d, J=8.1 Hz), 7.88 (1H, d, J=7.8 Hz). δ_C 19.69, 21.44, 21.70, 24.12, 29.97, 35.04, 44.69, 127.35, 127.41, 129.18, 129.91, 143.32, 147.31, 198.18.

1,2,3,4-Tetrahydro-1,6-dimethyl-4-(1-methylethyl)naphthalen-1-ol (**10**): Addition of an ethereal methyllithium solution (1.8 mL, 1.2M, 2.2 mmol) to the ketone (**9**) (0.4 g, 1.98 mmol) in anhydrous ether was followed by stirring at room temperature for 24 h, and at reflux for 24 h. The cooled reaction mixture was quenched with saturated ammonium chloride solution, twice extracted with ether. The dried ether extracts were evaporated, and the crude product was purified by column chromatography using 19:1 hexane-ethyl acetate as eluent to afford the benzylic alcohol (**10**) (0.37 g, 87% yield). M^+ calcd. for $C_{15}H_{22}O$ 218.1671; found 218.1673. ν 3356 cm^{-1}. δ_H 0.73 (3H, d, J=6.9 Hz), 1.02 (3H, d, J=6.9 Hz), 1.52 (3H, s), 1.7-1.84 (4H, m), 1.92-2.4 (1H, m), 2.28-2.40 (1H, m), 2.30 (3H, s), 2.54-2.64 (1H, m), 7.00 (1H, d, J=7.8 Hz), 7.05 (1H, s), 7.45 (1H, d, J=7.8 Hz).

Sesquichamaenol (**2**): To a solution of the alcohol (**10**) (0.2 g, 0.92 mmol) in THF (5 mL) was added 35% hydrogen peroxide (1.8 g, 1.85 mmol) and a drop of conc. sulfuric acid. The mixture was stirred at room temperature for 12 h. Product isolation involved dilution with water (20 mL) and extraction with ether, and purification by column chromatography using 9:1 hexane-ethyl acetate as eluent. Sesquichamaenol was obtained (0.16 g, 76% yield). M^+ calcd. for $C_{15}H_{22}O_2$ 234.1620; found 234.1626. ν 3386, 1704, 1611 cm^{-1}. δ_H (300MHz, $CDCl_3$) 0.70 (3H, d, J=6.3 Hz), 0.98 (3H, d, J=6.3 Hz), 1.6-1.9 (3H, m), 2.03 (3H, s), 2.23 (3H, s), 2.60 (1H, m), 6.69 (1H, d, J=7.8 Hz), 6.82 (1H, s), 6.83 (1H, d, J=7.8 Hz). δ_C (75MHz, $CDCl_3$) 20.69, 20.82, 21.23, 26.60, 30.03, 32.93, 41.83, 115.57, 127.22, 128.52, 129.76, 129.79, 151.95, 210.88.

6-(2-Hydroxy-4-methylphenyl)-2-methyl-3-heptanone (**5**): A solution of 4,7-dimethyl-α-tetralone (**11**)[10] (5.0 g) in ether (8 mL) was added slowly to an ice-cooled, stirred Grignard reagent prepared from magnesium (0.77 g, 31.7 mga) and 2-bromopropane (3.9 g, 31.7 mmol). After stirring at room temperature for 2 days and under reflux for 1 day, the reaction mixture was quenched with aq. ammonium chloride. Ether extraction led to the isolation of unreacted tetralone and the desired product (**12**) (5.47 g) in 1:1 ratio according to NMR. Because of the alcohol was susceptible to dehydration part of the mixture (3.68 g) was dissolved in THF (30 mL) and treated with 35% hydrogen peroxide (1.78 g) and 8 drops of sulfuric acid for 12 hrs. Workup in the same manner as above and chromatography (9:1 hexane-ethyl acetate) of the product furnished the unreacted tetralone (1.6 g) and the hydroxy ketone (**5**) (1.8 g, 82% yield based on consumed tetralone). M^+ calcd. for $C_{15}H_{22}O_2$ 234.1620; found 234.1621. ν 3404, 1698 cm^{-1}. δ_H 1.08 (3H, d, J=6.6 Hz), 1.08 (3H, d, J=6.6 Hz), 1.23 (3H, d, J=6.6 Hz), 1.58 (1H, unsym. sext, J=6 Hz), 1.82-1.93 (1H, m), 2.26 (3H, s), 2.40-2.65 (3H, m), 2.91 (1H, sext, J=6.6 Hz), 6.68 (1H, d, J=7.8 Hz), 6.70 (1H, s), 7.00 (1H, d, J=7.8 Hz). δ_C 18.23, 19.25, 20.87, 30.60, 31.64, 37.64, 40.88, 116.80, 120.97, 125.85, 128.84, 136.95, 153.94, 217.42.

6-(2-Methoxy-4-methylphenyl)-2-methyl-3-heptanone (**19**): A stirred mixture of the hydroxy ketone (**5**) (1.6 g, 6.84 mmol), anhydrous potassium carbonate (1.23 g, 8.9 mmol) and dimethyl sulfate (1.12 g, 8.9 mmol) in acetone (40 mL) was refluxed for 12 hrs. Acetone was removed from the cooled filtrate to leave an oil which was distributed between water and ether. The organic solution provided the ketone (**19**) (1.54 g, 91% yield) after purification by column chromatography (19:1 hexane-ethyl acetate as eluent). M^+ Calcd. for $C_{16}H_{24}O_2$ 248.1776; found 248.1787. ν 3400-2500, 1711 cm^{-1}. δ_H 0.99 (3H, d, J=6.6 Hz), 1.00 (3H, d, J=6.6 Hz), 1.16 (3H, d, J=6.9 Hz), 1.76-1.88 (2H, m), 2.2-2.4 (1H, m), 2.31 (3H,s), 2.44-2.56 (1H, m), 3.10 (1H, sext, J=7.2 Hz), 3.77 (3H, s), 6.65 (1H, s), 6.72 (1H, d, J=7.2 Hz), 7.01 (1H, d, J=7.2 Hz). δ_C 18.17, 21.26, 21.38, 30.79, 31.26, 38.66, 40.67, 55.26, 111.44, 121.20, 126.62, 131.63, 136.56, 156.56, 156.92, 215.14.

6-(2-Methoxy-4-methylphenyl)-2-methyl-3-heptanol (**20**): Sodium borohydride (230 mg, 6.1 mmol) was added to a solution of the ketone (**19**) (1.5 g, 6 mmol) in dry ethanol (10 mL). After 6 hrs, the reaction mixture was stirred into satd. ammonium chloride solution (20 mL), extracted with ether. The product was chromatographed (19:1 hexane-ethyl acetate) to give the alcohol (**20**) (1.39 g, 92% yield) as a diastereomeric mixture. M^+ Calcd. for $C_{16}H_{26}O_2$ 250.1933; found 250.1932. ν 3392 cm^{-1}. This compound was used in the next step without firther purification.

Curcuphenol methyl ether (**3m**): While cooling in an ice bath the alcohol (**20**) (1.4 g, 5.6 mmol) was treated with phosphorus tribromide (1.5 g, 5.6 mmol). The reaction was allowed to proceed at room temperature and after 24 hrs it was quenched with ice water, and extracted with ether. When the extracts were stored with anhydrous sodium sulfate for 24 hrs, a mixture of olefins resulted. Evaporation of the filtered solution gave 0.7 g of material (10:1 disubt.:trisubst.olefins as shown by NMR) which was isomerized by refluxing with *p*-toluenesulfonic acid monohydrate (30 mg) in benzene for 12 hrs. The final product was purified by column chromatography using hexane as eluent to provide a product enriched in curcuphenol methyl ether (**3m**) (admixture with the inseparable disubstituted olefin isomer (**3mi**) in a 6:1 ratio) M^+ 232.1836. δ_H 1.18 (3H, d, J=7 Hz), 1.54 (3H, s), 1.68 (3H, s), 2.34 (3H, s), 3.14 (1H, sext. J=7.5 Hz), 3.80 (3H, s), 5.13 (1H, t, J= Hz), 6.68 (1H, s), 6.74 (1H, d, J=7.8 Hz), 7.05 (1H, d, J=7.8 Hz).

(E)-5-(4-Methylphenyl)-4-hexenoic Acid (**21**): 5-(4-Methylphenyl)-5-oxopentanoic acid (7.0 g, 34 mmol) was dissolved in THF (30 mL) and the solution was slowly added to a Grignard reagent made from magnesium turnings (2.0 g) and iodomethane (11.68 g, 82.3 mmol) in dry ether (60 mL). After stirring at room temperature for 24 hrs, and refluxing for 2 hrs, the mixture was poured into ice water, and acidified with 3% hydrochloric acid. The crude product obtained from ether extraction was redissolved in benzene (100mL) and refluxed with *p*-toluenesulfonic acid (0.4 g) for 6 hrs under a Dean-Stark trap. The cooled solution was washed with saturated bicarbonate solution to romove acidic material. On acidification of the aqueous layer the unsaturated acid (**21**) was obtained (2.0 g, 29% yield; mp. 80-82°C). M^+ Calcd. for $C_{13}H_{16}O_2$ 204.1150; found 204.1146. ν 3400-2500, 1707 cm^{-1}. δ_H 1.92 (3H, s), 2.21 (3H, s), 2.35-2.45 (4H, m), 5.54-5.66 (1H, m), 6.93 (2H, d, J=7.8 Hz), 7.13 (2H, d, J=7.8 Hz). δ_C 15.81, 20.97, 23.92, 33.97, 124.71, 125.51, 128.82, 136.27, 136.43, 140.57, 179.32.

5-(4-Methylphenyl)hexanoic acid (**22**): The unsaturated acid (**21**) (1.5 g, 7.35 mmol) was hydrogenated in the presence of 10% Pd/C (0.1 g) in ethyl acetate (20 mL) to give, after removal of the catalyst by filtration and evaopration, the saturated acid (**22**) (1.47 g, 97% yield). M^+ Calcd. for $C_{13}H_{18}O_2$ 206.1307; found 206.1306. ν 3500-2500, 1709 cm^{-1}. δ_H 1.21 (3H, d, J=6.9 Hz), 1.4-1.64 (4H, m), 2.24-2.34 (2H, m), 2.31 (3H, s), 2.58-2.72 (1H, m), 7.04-7.11 (4H, m). δ_C 20.94, 22.37, 22.81, 34.06, 37.58, 39.24, 126.77, 129.04, 135.36, 143.96, 180.26.

6,7,8,9-Tetrahydro-3,9-dimethyl-5*H*-benzocyclohepten-5-one (**23**): Acid (**22**) (0.9 g, 4.37 mmol) was stirred with a phosphorus pentoxide (3.0 g) and methanesulfonic acid (30 g) at room temperature for 24 hrs. The reaction mixture was poured into water (100 mL), extracted with ether (3x30 mL), and the combined extracts were washed with aq. sodium bicarbonate, dried, and evaporated with a rotary evaporator. Chromatography (19:1 hexane-ethyl acetate as eluent) afforded the benzosuberone (**23**) (0.54 g, 66% yield). M^+ Calcd. for $C_{13}H_{16}O$ 188.1201; found 188.1199. ν 1680 cm^{-1}. δ_H 1.32 (3H, d, J=6.6 Hz), 1.4-1.17 (2H, m), 1.78-2.0 (2H, m), 2.31 (3H, s), 2.5-2.78 (2H, m), 2.97-3.1 (1H, m), 7.11 (1H, d, J=7.8 Hz), 7.23 (1H, dd, J=7.8, 1.5 Hz), 7.32 (1H, d, J=1.5 Hz). δ_C 19.28, 20.33, 20.65, 33.88, 34.17, 41.10, 125.22, 128.28, 132.59, 136.00, 139.21, 140.29, 208.70.

6,7,8,9-Tetrahydro-2,5,9-trimethyl-5*H*-benzocyclohepten-9-ol (**24**): A solution of the benzosuberone (**23**)

(0.39 g, 2.07 mmol) in anhydrous ether (4 mL) was treated with methyllithium (2 mL, 1.2 M in ether, 2.4 mmol) and left at room temperature for 24 hrs. The reaction was quenched with aq. ammonium chloride, extracted with ether, dried, and evaporated. Column chromatographic isolation with silica gel which was pretreated with a small amount of triethylamine gave the alcohol (**24**) (0.35 g, 83% yield) M^+ Calcd. for $C_{14}H_{20}O$ 204.1514; found 204.1508. ν 3405 cm^{-1}. δ_H 1.33 (3H, d, J=7.5 Hz), 1.56 (3H, s), 1.6-1.7 (1H, m), 1.7-1.93 (4H, m), 2.0-2.1 (1H, m), 2.33 (3H, s), 3.0-3.1 (1H, m), 7.01 (1H, dd, J=7.8, 1.5 Hz), 7.10 (1H, d, J=7.8 Hz), 7.06 (1H, d, 1.5 Hz). δ_C 20.77, 21.09, 23.30, 29.60, 34.61, 36.09, 42.47, 76.39, 125.37, 126.53, 127.28, 135.54, 138.54, 146.75. (Note the NMR spectra were taken with material of a chromatographic fraction which was apparently one of the diastereomers).

6-(2-Acetoxy-4-methylphenyl)-2-heptanone (**26**): The alcohol (**24**) (0.1 g, 0.49 mmol) was dissolved in THF (4 mL), 35% hydrogen peroxide (0.95 g, 9.8 mmol) and a drop of conc. sulfuric acid were added. The mixture was stirred at room temperature for 12 hrs, diluted with water (30 mL), and extracted into ether. The crude product (**25**) obtained from the extracts was treated with acetic anhydride (1 mL) and pyridine (3 mL) for 6 hrs. Aqueous quenching, ether extraction removed the product which was freed from residual reagents by washing with 5% hydrochloric acid and 2N sodium carbonate, and purified by column chromatography (eluent: 19:1 hexane-ethyl acetate). There was obtained the keto acetate (**26**) (0.47 g, 37% yield). M^+ Calcd. for $C_{16}H_{22}O_3$ 262.1569; found 262.1568. ν 1763, 1715 cm^{-1}. δ_H 1.14 (3H, d, J=6.7 Hz), 1.34-1.6 (4H, m), 2.06 (3H, s), 2.29 (6H, s), 2.34 (2H, t, J=6 Hz), 2.7-2.84 (1H, m) 6.78 (1H, m), 6.98 (1H, d, J=7.8 Hz), 7.10 (1H, d, J=7.8 Hz). δ_C 20.80, 20.94, 21.29, 21.93, 29.77, 32.33, 36.76, 43.61, 122.80, 126.88, 127.20, 135.42, 136.67, 148.18, 169.71, 209.02.

Curcudiol (**4**): The keto acetate (**26**) (0.04 g, 0.153 mmol) was dissolved in anhydrous ether (2 mL) and treated with ethereal methyllithium (0.8 mL, 1.2M, 0.96 mmol) under a nitrogen atmosphere. After stirring at room temperature for 24 hrs, and under reflux for another 24 hrs, the reaction mixture was poured into aqueous ammonium chloride. The aqueous solution with extracted with ether and the extracts dried, evaporated to give curcudiol (30 mg, 83% yield). M^+ Calcd. for $C_{15}H_{24}O_2$ 236.1776; found 236.1776. ν_{OH} 3355, 3338 cm^{-1}. δ_H 1.15 (3H, s), 1.17 (3H, s), 1.19 (3H, d, J=6.9 Hz), 1.25-1.38 (2H, m), 1.4-1.55 (4H, m), 1.58-1.7 (2H, m), 2.24 (3H, s), 3.05 (1H, sext, J=7.2 Hz), 6.56 (1H, s), 6.68 (1H, d, J=7.8 Hz), 7.00 (1H, d, J=7.8 Hz). δ_C 20.88, 22.13, 28.89, 29.56, 31.37, 37.62, 43.31, 71.30, 116.27, 121.63, 126.79, 130.40, 136.40, 152.85.

exo-5-[3-(4-Methylphenyl)propanoyl]-6,6-dimethylbicyclo[2.2.1]hept-2-ene (**13**): *exo*-5-(4-Methylcinnamoyl)-6,6-dimethylbicyclo[2.2.1]hept-2-ene (10.0 g, 37.6 mmol) was dissolved in acetic acid (80 mL). After addition of water (20 mL) and zinc dust (20 g) with stirring for 1 hr, solids were filtered, the filtrate was diluted with water (100 mL), and extracted several times with ether. The ethereal extracts were evaporated and the residue chromatographed (19:1 hexane: ethyl acetate) to give ketone (**13**) (8.8 g, 87% yield). M^+ Calcd. for $C_{19}H_{24}O$ 268.1827; found 268.1826. ν 1707 cm^{-1}. δ_H 0.96 (3H, s), 1.04 (3H, s), 1.38 (1H, dd, J=9.0, 2.1 Hz), 1.95 (1H, d, J=8.7 Hz), 2.02 (1H, d, J=2.1 Hz), 2.28 (1H, d, J=2.4 Hz), 2.25 (1H, br.), 2.64 (3H, s), 2.64-2.94 (4H, m), 6.1-6.2 (2H, m), 7.07 (4H, s). δ_C 20.97, 26.23, 29.25, 29.45, 43.04, 46.20, 47.14, 47.48, 54.41, 60.57, 128.23, 129.11, 135.50, 136.61, 137.85, 138.18, 213.07.

2-Methyl-6-(4-methylphenyl)-2-hexen-4-one (**14**): Ketone (**13**) (8.0 g, 30 mmol) was placed in a flask and connected to a rotary evaporator. Under water aspirator vacuum the flask was heated with a burner for 5 min. The cooled residue was chromatographed (19:1 hexane: ethyl acetate) to give enone (**14**) (3.48 g, 57.4% yield). M^+ Calcd. for $C_{14}H_{18}O$ 202.1358; found 202.1350. ν 1689 cm^{-1}. δ_H 1.87 (3H, s), 2.13 (3H, s), 2.29 (3H, s), 2.64 (2H, m), 2.81 (2H, m), 6.01 (1H, m), 7.03 (4H, s). δ_C 20.69, 20.89, 27.59, 29.57, 45.86, 123.57, 128.11, 129.02, 135.28, 138.25, 155.27, 199.91.

5,6,8,9-Tetrahydro-2,9,9-trimethyl-7*H*-benzocyclohepten-7-one (**15**): To a stirred suspension of aluminum chloride (4.58 g, 34.4 mmol) in carbon disulfide (40 mL) was added a solution of enone (**14**) (3.5 g, 17.3 mmol) in the same solvent (40 mL). The whole mixture was brought to reflux and maintained for 30 hrs. The cooled contents of the flask were poured into 10% hydrochloric acid, extracted with dichloromethane. The crude product was chromatographed (19:1 hexane: ethyl acetate) to furnish the bicyclic ketone (**15**) (2.75 g, 79% yield). M^+ Calcd. for $C_{14}H_{18}O$ 202.1358; found 202.1350. ν 1707 cm^{-1}. δ_H 1.39 (6H, s), 2.31 (3H, s), 2.56-2.60 (2H, m), 2.84 (2H, s), 3.06-3.10 (2H, m), 6.91 (1H, dd, J=7.5, 1.2 Hz), 6.98 (1H, d, J=7.5 Hz), 7.19 (1H, br.s). δ_C 21.15, 31.49, 32.36, 38.83, 43.78, 55.76, 127.14, 128.78, 131.37, 135.19, 136.50, 145.73, 212.17.

6,7,8,9-Tetrahydro-2,9,9-trimethyl-5*H*-benzocycloheptene (**16**): Ketone (**15**) (2.25 g, 11.1 mmol) was refluxed with almagamated mossy zinc (5.6 g) in toluene (5 mL), water (5 mL), and conc. hydrochloric acid (12 mL), with additional portions (2 mL) of conc. HCl introduced to the flask at every 6 hr. interval during a 30 hr. period. The cooled mixture was diluted with water, extracted with ether. The crude product was purified by chromatography using hexane as eluent to give the hydrocarbon (**16**) (1.7 g, 81% yield). M^+ Calcd. for $C_{14}H_{20}$ 188.1565; found 188.1564. δ_H 1.36 (6H, s), 1.65 (4H, br.), 1.84 (2H, br.), 2.32 (3H, s), 2.89 (2H, br.), 6.88 (1H, d, J=7.5 Hz), 6.95 (1H, d, J=7.5 Hz), 7.18 (1H, s). δ_C 21.26, 26.59, 28.34, 30.15, 36.97, 39.15, 41.72, 126.36, 127.26, 131.25, 135.13, 139.12, 148.35.

6,7,8,9-Tetrahydro-2,9,9-trimethyl-5*H*-benzocyclohepten-5-one (**17**): To a stirred solution of the hydrocarbon (**16**) (2.0 g, 10.6 mmol) in glacial acetic acid (250 mL) was added in portions a 10% solution of chromic oxide in HOAc (120 mL). After 7 hrs, the reaction mixture was poured into water (1 L), and the product was extracted into ether, which in turn was washed in succession with water, bicarbonate solution, and brine. The dried solutions were evaporated and the residue was chromatographed (19:1 hexane: ethyl acetate) to give the benzosuberone (**17**) (0.67 g, 31% yield). M^+ Calcd. for $C_{14}H_{18}O$ 202.1358; found 202.1351. ν 1684 cm^{-1}. δ_H 1.31 (6H, s), 1,78-1.98 (4H, m), 2.34 (3H, s), 2.67 (2H, t, J=7.5 Hz), 7.01 (1H, d, J=7.5 Hz), 7.19 (1H, s), 7.26 (1H, d, J=7.5 Hz). δ_C 21.17, 21.26, 31.72, 38.74, 40.23, 42.71, 126.82, 127.00, 128.31, 138.16, 140.89, 147.10, 208.81.

6,7,8,9-Tetrahydro-2,5,9,9-tetramethyl-5*H*-benzocyclohepten-9-ol (**18**): Benzosuberone (**17**) (0.3 g, 1.5 mmol) was dissolved in anhydrous ether (3 mL) and treated with methyllithium (1.5 mL, 1.2 M, 1.8 mmol) for 24 hrs. at room temperature and 12 hrs. at reflux. The cooled mixture was quenched with aq. ammonium chloride, extracted with ether, and the crude product chromatographed (19:1 hexane: ethyl acetate) on silica gel column pretreated with triethylamine to give the alcohol (**18**) (0.25 g, 76% yield). M^+ Calcd. for $C_{15}H_{22}O$

218.1671; found 218.1680. ν 3396 cm^{-1}. δ_H 1.36 (3H, s), 1.42 (3H, s), 1.64 (3H, s), 1.64-2.22 (6H, m), 2.32 (3H, s), 6.99 (1H, dd, J=7.8, 1.5 Hz), 7.24 (1H, d, J=1.5 Hz), 7.70 (1H, d, J=7.8 Hz). δ_C 20.30, 20.94, 30.03, 35.31, 38.86, 39.53, 41.08, 75.54, 126.39, 128.14, 128.98, 135.80, 144.80.

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