

PROCESS

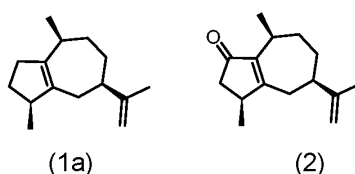
The present invention relates to a method of producing the α,β -unsaturated ketone Rotundone by allylic oxidation of α -Guaiane using catalytic amounts of an unsubstituted iron(II)phthalocyanine complex.

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BACKGROUND

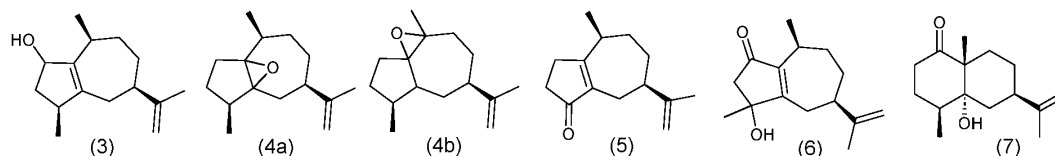
There is a need for a simple, sustainable synthesis route to Rotundone ((3*S*,5*R*,8*S*)-3,8-dimethyl-5-(prop-1-en-2-yl)-3,4,5,6,7,8-hexahydroazulen-1(2*H*)-one) (2) from α -Guaiane ((1*S*,4*S*,7*R*)-1,2,3,4,5,6,7,8-octahydro-1,4-dimethyl-7-(1-methylethenyl)azulene; CAS 3691-12-1) (1a) with a competitive selectivity and yield.

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Unsaturated terpenes such as α -Guaiane are important substrates in the flavor and fragrance industry, giving after allylic oxidation, valuable flavor and fragrance ingredients such as Rotundone. Oxidative transformations of this substrate is especially challenging because the substrate has multiple sites which are sensitive to oxidation and can give various oxidation products arising from competing epoxidation, ene oxidation or unselective allylic oxidation side reactions.

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Potential side products include Rotundol (3), epoxy-Guaiane (4a), epoxy-Bulnesene (4b), ketone (5), hydroxy-Rotundone (6), and Corymbolon (7).

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The isolation and oxidation of Guaiane sesquiterpenes from Agarwood was reported by Ishihara et al., *Phytochemistry* 30, 3343 (1991). A crude mixture of isolated Guaienes was subjected to oxidation in a stirred suspension of pyridinium chlorochromate and Celite in dichloromethane to yield Rotundone.

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WO2011/106166 relates to allylic oxidation catalysts. An exemplary method comprises the step of catalyzing oxidation of an allylic compound using an allylic oxidation catalyst

comprising palladium, gold, and titanium. Example 4 describes the oxidation of Guaiene to form Rotundone using the catalyst (2.5% Au + 2.5% Pd/TiO₂) in an autoclave charged with oxygen at 30 bar. No yield results were reported.

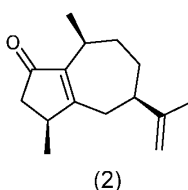
- 5 More recently, WO 2019/110493 describes a process of preparing the α,β -unsaturated ketone Rotundone by allylic oxidation of α -Guaiene using catalytic amounts of iron(III)porphyrin complexes in the presence of molecular oxygen and in a sustainable solvent.

10 SUMMARY OF INVENTION

- At its most general, the present invention provides a method (or process) for producing Rotundone from allylic oxidation of α -Guaiene in the presence of a catalytic amount of iron (II) phthalocyanine (FePc). The present invention also provides use of iron (II) phthalocyanine (FePc) in the allylic oxidation of α -Guaiene to produce Rotundone. The
15 invention further provides Rotundone obtained by the method described herein.

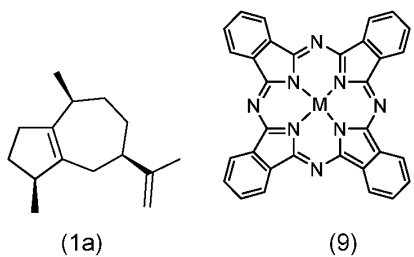
- As described above, α -Guaiene has multiple sites which are sensitive to oxidation and can give various oxidation products arising from competing epoxidation, eneoxidation or unselective allylic oxidation side reactions. This makes oxidative transformations especially
20 challenging. The present inventors have found that using iron (II) phthalocyanine (FePc) as a catalyst in this reaction provides good yields of Rotundone while minimizing side product formation. This is considered surprising as the iron metal in the catalyst is in a different oxidation state to some previously used iron catalysts. In addition, the use of iron phthalocyanine in allylic oxidation have been inefficient and non-selective and have
25 preferentially produced other oxidations products such as epoxides and alcohols, rather than ketones. As such, prior art has focused on substituted iron phthalocyanines with electron withdrawing substituents. The relatively low cost of iron (II) phthalocyanine (FePc) also makes the process commercially attractive.

- 30 In a first aspect, the present invention provides a method of producing a compound of formula (2) by allylic oxidation,



the method comprising the steps of:

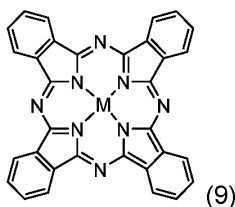
- a) forming a mixture of a compound of formula (1a) and a catalytic amount of compound of formula (9) wherein M is selected from the group consisting of Fe, Co, and Mn ;



and

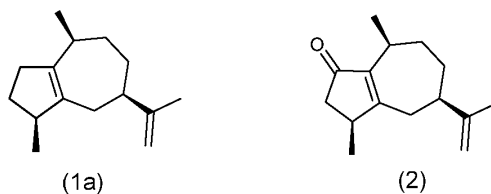
- b) oxidizing the compound of formula (1a) to produce the compound of formula (2).

In a second aspect, the present invention provides use of a compound of formula (9)

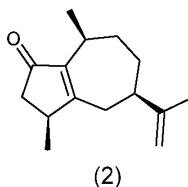


wherein M is selected from the group consisting of Fe, Mn and Co,

- in the allylic oxidation of a compound of formula (1a) to produce a compound of formula (2)

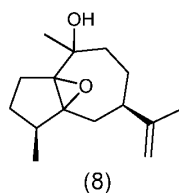


In a third aspect, the present invention provides a compound of formula (2)



- obtained by the method disclosed herein.

In a fourth aspect, the present invention provides a mixture comprising a compound of formula (2) and a compound of formula (8)



and the use in fragrance.

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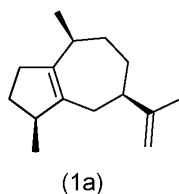
DETAILED DESCRIPTION

Method of the present invention

The method (or process) of the present invention involves oxidizing compound 1a with a catalytic amount of compound of formula (9) in a solvent.

10 Reactants in the mixture

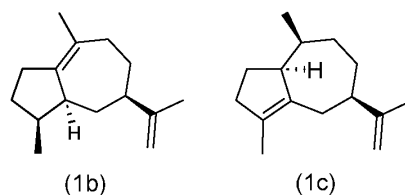
The compound of formula (1a) is known as α -Guaiene or (1*S*,4*S*,7*R*)-1,2,3,4,5,6,7,8-octahydro-1,4-dimethyl-7-(1-methylethenyl)azulene) and has the following structure:



- 15 Guaienes are natural chemical compounds that have been isolated from a variety of plant sources. The guaienes are sesquiterpenes with the molecular formula $C_{15}H_{24}$. α -Guaiene was first isolated from guaiac wood oil. As another natural source of α -Guaiene one may mention patchouli oil or light fractions thereof. α -Guaiene obtained by biotechnological production, e.g. by fermentation of sugars, may also be used. The biotechnological
- 20 production is described, for example, in WO 2011/141855 A1 and in Plant Physiol 2010, 154, 1998-2007.

- Mixtures comprising α -Guaiene used for the process described herein, preferably contain at least 15 weight % (which includes 20 wt%, 30 wt%, 40 wt%, 50 wt %, 60 wt %, 70 wt%, 75
- 25 wt%, 80 wt%, 85 wt %, 90 wt% or more) α -Guaiene based on the total weight of Guaienes.

The mixture of the compound of formula (1a), the compound of formula (9) and the solvent may further include one or both of the compounds of formula (1b) and formula (1c)



Compound (1b) is known as Bulnesene or (3*S*,3*aS*,5*R*)-3,8-dimethyl-5-prop-1-en-2-yl-1,2,3,3*a*,4,5,6,7-octahydroazulene. Compound (1c) is known as Aciphyllene or (5*R*,8*S*,8*aS*)-3,8-dimethyl-5-(prop-1-en-2-yl)-1,2,4,5,6,7,8,8*a*-octahydroazulene.

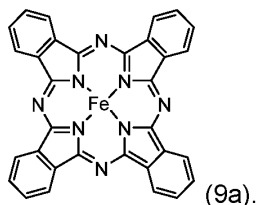
When the mixture includes one or both of the compounds of formula (1b) and formula (1c), the compound of formula (1a) amounts to at least 10 %, but preferentially to at least 50 % by weight or 50% by mole based on the total weight or moles of compounds of formula (1a), formula (1b) and/or formula (1c). In a particular embodiment, the mixture includes both of the compounds of formula (1b) and formula (1c).

In further particular embodiments, the mixture includes the compound of formula (1b). In these embodiments, the mixture may further include the compound of formula (1c). Alternatively, the mixture may be substantially free of the compound of formula (1c). In other words, the mixture may include compounds of formula (1a) and formula (1b) and be substantially free of the compound of formula (1c).

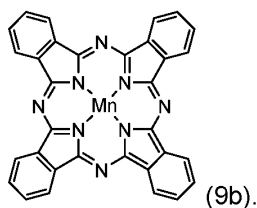
The compound of formula (1a) may be included in the mixture as a purified compound. Alternatively, the compound of formula (1a) is included in the mixture as a naturally derived product containing the compound of formula (1a). Naturally-derived products are products derived from natural sources. As such, the products contain a complex mixture of components (e.g. compounds). The naturally derived product may be an essential oil. For example, the mixture may include Patchouli oil.

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The compound of formula (9) wherein M is Fe is known as iron (II) phthalocyanine (FePc) and has the following structure:

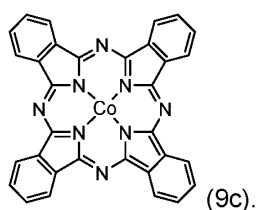


The compound of formula (9) wherein M is Mn is known as manganese (II) phthalocyanine (MnPc) and has the following structure:



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The compound of formula (9) wherein M is Co is known as cobalt (II) phthalocyanine (CoPc) and has the following structure:



- 10 The phthalocyanine ligand is an unsubstituted phthalocyanine. The metal (Fe, Mn, Co) is in a +2 oxidation state (in other words Fe(II), Mn(II) and Co(II)).

The compound of formula (9) is present in a catalytic amount. The molar ratio of compound of formula (9) (which encompasses the compound of formula (9a), (9b) and (9c)) to compound of formula (1a) present in the mixture may be 1:5 or lower. In some embodiments, the molar ratio of compound of formula (9) to compound of formula (1a) present in the mixture may be 1:10 or lower, 1:20 or lower, 1:50 or lower. In particular embodiments, molar ratio of compound of formula (9) to compound of formula (1a) present in the mixture may be 1:100 or lower. In the above molar ratios, a lower molar ratio has a higher molar amount of the compound of formula (1a) than stated in the molar ratio given. For example, a molar ratio compound of formula (9) to compound of formula (1a) of 1:50 is a lower molar ratio than a molar ratio compound of formula (9) to compound of formula (1a) of 1:10.

25 In one embodiment, the compounds of formula (1a) and (9) can be combined with a solvent to form a mixture.

The solvent may be selected from the group consisting of water, alcohol, acetone, ethyl acetate, isopropyl acetate, methyl ethyl ketone, and mixtures thereof.

As used in relation to solvent unless otherwise indicated "alcohol" refers to ROH wherein R is alkyl (e.g., C₁ – C₆) optionally comprising one further -OH group and/or one –O– group. Non-limiting examples are ethanol, methanol, propanol (e.g. isopropanol), butanol (e.g. 1-butanol, t-butanol). Especially alcohols with a higher flash point than ethanol are useful for the

5 oxidation reaction. Non-limiting examples of such alcohols are isopropanol, n-propanol, ethyleneglycol, 1,2-propanediol, ethyleneglycolmonobutylether and dipropyleneglycol.

Alternatively, the solvent may be selected from the group consisting of cyclohexane, heptane, toluene, methylcyclohexane, methyl t-butyl ether, isooctane, acetonitrile, xylenes,

10 dimethyl sulfoxide, acetic acid and mixtures thereof.

In particular embodiments, the solvent includes an alcohol-water mixture, for example a mixture of water and ethanol and/or butanol.

15 The mixture typically includes an oxidant for the oxidation reaction. The oxidant may be molecular oxygen, such as molecular oxygen in air. The oxidant may be also pure molecular oxygen. The method may include introducing molecular oxygen into the mixture prior to and/or during the oxidizing reaction. In some embodiments, the method includes bubbling air through the mixture prior to and/or during the oxidation reaction. Alternatively, molecular

20 oxygen may be introduced into the mixture by reacting in an oxygen atmosphere with strong stirring. Molecular oxygen may be introduced into the mixture by processing the reaction in a flow reactor.

The mixture may further include a base coordination compound, for example, an amine, such

25 as triethylamine or an inorganic base, such as NaOH or K₂CO₃. The base coordination compound is preferably a N-heterocycle (a N-containing heterocycle), such as pyridine, imidazole or N-methylimidazole, or NaOH, further preferably imidazole or NaOH.

Oxidizing the compound of formula (1a)

30 Oxidation of the compound of formula (1a) may start when the compound of formula (1a) is combined with the compound of formula (9) (which encompasses the compound of formula (9a), (9b) and (9c)). The reaction may proceed at ambient temperature, the mixture may be heated, or the mixture may be cooled. In some embodiments, the step of oxidizing the compound of formula (1a) may be carried out at a temperature in the range of 10 to 65 °C.

35 In some embodiments, the step of oxidising compound (1a) is performed at a temperature in the range of 10 to 40 °C, such as 15 to 30 °C. The step of oxidising compound (1a) may be

performed in a range of 20 to 30 °C, or about 25 °C. In alternative embodiments, step of oxidising compound (1a) is performed at a temperature in the range of more than 40 to 65 °C, such as 40 to 50 °C, or about 45 °C.

- 5 Although not required, the subject process may include exposing the mixture to electromagnetic radiation, preferably UV and visible light radiation. The wavelength range of the light used to expose the mixture may be in the range of about 200 nm to about 800 nm. Alternatively, the process may be carried out in the dark, or under ambient light conditions.
- 10 In a further embodiment there is provided an allylic oxidation method as herein described, characterized in that compound of formula (2) is produced with a GC-purity of 5% or higher (e.g. 7, 10, 12, 15, 17, 20, 25, 27, 30, 35, 40, 45, 50, or higher) measured in % relative peak area based on the oxidative products obtained by the allylic oxidation. The GC methods used for the calculation of the GC-purity are described herein below.

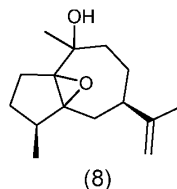
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Optional further steps

- In the subject process, as herein described, peroxides might be formed. Since peroxides tend to behave explosively in high concentrations and at high temperatures, they should preferably be deactivated by means known to the person skilled in the art before
- 20 concentration and distillation of the oxidation product. Suitable reagents for the destruction of peroxide are, for example, aqueous base, triphenylphosphine (PPh₃), dimethyl sulfide, sodium sulfite (Na₂SO₃), hydrogen in the presence of transition metal catalysts such as palladium on charcoal, activated alumina, zeolites, ferrous sulfate (FeSO₄) in sulfuric acid.
- 25 Depending on reagent, solvent and conditions used, applicants observed a certain isomerisation of Rotundone 2 to 3-epi-Rotundone ((3*R*,5*R*,8*S*)-3,8-dimethyl-5-(prop-1-en-2-yl)-3,4,5,6,7,8-hexahydroazulen-1(2H)-one). In order to obtain the highest possible yield of Rotundone 2, the use of NaOH, in particular at higher temperature and a solvent such as ethanol, should be thus avoided. Almost no isomerisation was observed when NaOH is used
- 30 around room temperature. When using, for example, triphenylphosphine, or sodium sulfite (Na₂SO₃), no isomerisation was observed, and these reagents thus should preferably be used for the deactivation of peroxide.

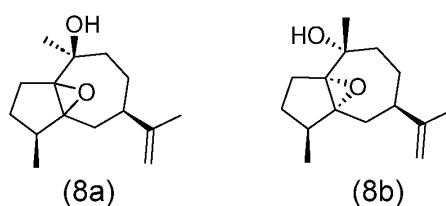
- In the subject process, the produced α,β -unsaturated ketone, Rotundone, obtained in a
- 35 mixture may be further purified by means known to the person skilled in the art. For example, the crude mixture may be purified by bulb-to-bulb distillation, e.g. at about 150 -230°C at 0.04-0.1 mbar, optionally followed by flash chromatography.

Applicant surprisingly found that by using the method of producing a compound of formula (2) as described hereinabove, a novel compound of formula (8) is also obtained



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The epoxy-alcohol of formula (8) does exist in the form of the relative isomers of formula (8a) and the isomer of formula (8b), as depicted below:



10 Accordingly, there is provided in a fourth aspect a mixture comprising a compound of formula (2) and a compound of formula (8) (which encompasses the compound of formula (8a) and formula (8b)). In one embodiment the mixture may comprise the compound of formula (8) and the compound of formula (2) in a ratio of 1 : 5 to 1 : 500, for example 1 : 10 to 1 : 100.

15 Use of the second aspect and compound of the third aspect

The optional and preferred features described above in relation to the method apply equally to use of the compound of formula (9) (encompassing the compound of formula (9a), (9b) and (9c)) of the second aspect and the compound obtained by the methods described herein of the third aspect.

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The disclosure is now further described with reference to the following non-limiting examples. These examples are for the purpose of illustration only and it is understood that variations and modifications can be made by one skilled in the art.

25

EXAMPLES

Analytical Procedures Employed

Polar GCMS: 35 °C / 2 min, 10 °C / min to 50 °C, 2.5 °C / min to 240 °C, 240 °C / 5 min.

30 Thermo Scientific TSQ8000evo + Trace 1310 system. Polar column: Varian VF WAX (polar,

PEG phase). Column dimensions: 30 m length, 0.25 mm ID, 0.25 μ m film thickness. Injector: splitless. Flow: 1.2 ml/min. Carrier gas: Helium. Injection volume: 1 μ l. Injector temperature: 230 °C. Transfer line: 250 °C. MS-quadrupol: 160 °C. MS-source: 230 °C. Ionization mode: Electron Impact (EI) at 70 eV. By this method GC-conversion and product distribution was measured and relative peak areas of the main components 1 to 8 are given in %.

Nonpolar GC: 100 °C / 2 min, 15 °C / min to 240 °C, 240 °C / 5 min. Thermo Focus GC. Nonpolar column: Agilent Technologies J&W Scientific DB-5 (nonpolar, 5% Phenylmethylpolysiloxane). Column dimensions: 30 m length, 0.32 mm ID, 0.25 μ m film thickness. Injector: Split. Injector temperature: 240 °C. Detector: FID. Detector temperature: 270 °C. Injection volume: 1 μ l. Carrier gas: Hydrogen. Split ratio: 1 / 42.3. Pressure: 70 kPa. Integrator: Hewlett Packard. By this method the GC-purity of Rotundone after distillation was measured in % rpa (relative peak area).

Polar GC: 125 °C / 75 min, 20 °C / min to 220 °C, 220 °C / 3 min. Thermo Trace GC Ultra. Chiral column: BGB-178 (30% 2,6-diethyl-6-tert-butyldimethylsilyl-beta-cyclodextrin dissolved in BGB-15 (15% phenyl-, 85% methylpolysiloxane)). Column dimensions: 30 m length, 0.25 mm ID, 0.25 μ m film thickness. Injector: Split. Injector temperature: 250 °C. Detector: FID. Detector temperature: 250 °C. Injection volume: 1 μ l. Carrier gas: Hydrogen. Split ratio: 1 / 33.3. Column flow: 1.5 ml/min. Integration Software: Chromeleon 7. By this method, Rotundone (t_R : 48.5 min) and 3-*epi*-Rotundone (t_R : 49.5 min) are baseline-separated, thus allowing the determination of the epimeric ratio.

α -Guaiene 91% was isolated from Guaiac wood oil by a modified literature procedure (D.K.Taylor et al. Agric & Food Chem. 63, 1932, 2015). The purity of α -Guaiene 91% was determined by $^1\text{H-NMR}$ with the internal standard anisaldehyde. NMR spectra were measured in CDCl_3 at 400 MHz.

Example 1. Preparation of Rotundone from a mixture of α -Guaiene and Bulnesene under Fe(II)-phthalocyanine catalysis

Air was bubbled into a mixture of iron phthalocyanine (2.8 mg, 4.9 μ mol), imidazole (6.7 mg, 0.1 mmol) and α -guaiene / bulnesene 60:33 (1 g, 4.5 mmol) in 1:1 ethanol / water (20 ml) under stirring at 45 °C. After 22 hours, GC analysis indicated a conversion > 93% to a mixture comprising Rotundone 2 (22%), rotundol 3 (2%), epoxy-guaiene 4a (2%), epoxy-bulnesene 4b (6%), ketone 5 (3%), hydroxy-rotundone 6 (8%), corymbolon 7 (0.5%) and epoxy-alcohol 8 (1%). NaOH (100 mg, 2.5 mmol) was added to the reaction mixture which was heated to reflux for 6 h while bubbling nitrogen through the reaction mixture. After evaporation of ethanol under

reduced pressure (45 °C, 70 mbar), sat. aq. NaCl was added and the aq. phase was extracted with *tert*-butyl methyl ether (2 x 30 ml). The combined organic layers were washed with water (30 ml) and sat. aq. NaCl, dried over MgSO₄, filtered and evaporated giving 0.9 g of an oil, which was purified by bulb-to-bulb distillation at 50 - 180 °C / 0.05 mbar yielding 0.65 g of Rotundone 2 with 29% GC-purity (nonpolar GC) and 0.19 g of a residue.

Example 2. Preparation of Rotundone from α -Guaiene under Fe(II)-phthalocyanine catalysis

Air was bubbled into a mixture of iron phthalocyanine (16.7 mg, 29.4 μ mol, 0.3%), imidazole (13.3 mg, 0.2 mmol) and α -guaiene 91% (2 g, 9.6 mmol) in 1:1 ethanol / water (40 ml) under stirring at 45 °C. After 30 hours, GC analysis indicated a conversion > 99% to a mixture comprising Rotundone 2 (32%), rotundol 3 (0.5%), epoxy-guaiene 4a (3%), ketone 5 (7%), hydroxy-rotundone 6 (12%), corymbolon 7 (1%) and epoxy-alcohol 8 (0.5%). NaOH (200 mg, 5 mmol) was added to the reaction mixture which was heated to reflux for 6 h while bubbling nitrogen through the reaction mixture. After evaporation of ethanol under reduced pressure (45 °C, 70 mbar), sat. aq. NaCl was added and the aq. phase extracted with *tert*-butyl methyl ether (2 x 30 ml). The combined organic layers were washed with water (30 ml) and sat. aq. NaCl, dried over MgSO₄, filtered and evaporated giving 1.8 g of an oil, which was purified by bulb-to-bulb distillation at 50 - 180 °C / 0.02 mbar yielding 1.08 g of Rotundone 2 with 42% GC-purity (nonpolar GC) and 0.57 g of a residue.

Example 3. Preparation of Rotundone from α -Guaiene under Fe(II)-phthalocyanine catalysis in the dark

The experiment described in example 2 was repeated in a flask wrapped in aluminum foil to exclude light. After 52 h GC analysis indicated 97% conversion of the starting material to a mixture comprising Rotundone 2 (35%), rotundol 3 (3%), epoxy-guaiene 4a (4%), ketone 5 (5%), hydroxy-rotundone 6 (16%), corymbolon 7 (0.5%) and epoxy-alcohol 8 (2%). Isolation and purification as described in example 2 gave 0.82 g of rotundone with 41% GC-purity (nonpolar GC) and 0.7 g of a residue.

Example 4. Preparation of Rotundone from α -Guaiene under Fe(II)-phthalocyanine catalysis and light irradiation

The experiment described in example 2 was repeated under irradiation of an Osram 300 W Vitalux lamp. After 48 h GC analysis indicated 99% conversion of the starting material to a mixture comprising Rotundone 2 (32%), rotundol 3 (0.2%), epoxy-guaiene 4a (4%), ketone 5 (7%), hydroxy-rotundone 6 (18%), corymbolon 7 (0.5%) and epoxy-alcohol 8 (2%). Isolation and purification as described in example 2 gave 1 g of rotundone with 44% GC-purity (nonpolar GC) and 0.6 g of a residue.

Example 5. Preparation of Rotundone from Patchouli oil containing α -Guaiene under Fe(II)-phthalocyanine catalysis

Air was bubbled into a mixture of iron phthalocyanine (16.7 mg, 29.4 μ mol, 0.3%), imidazole (13.3 mg, 0.2 mmol) and a fraction of distilled patchouli oil containing 34% α -guaiene (2 g, 3.3 mmol) in 1:1 ethanol / water (40 ml) under stirring at 45 °C. After 21 hours, GC analysis indicated a quantitative conversion of α -Guaiene to a mixture comprising Rotundone 2 (11%), rotundol 3 (0.5%), epoxy-guaiene 4a (1%), epoxy-bulnesene 4b (1%), ketone 5 (4%), hydroxy-rotundone 6 (4%), and epoxy-alcohol 8 (1%). NaOH (200 mg, 5 mmol) was added to the reaction mixture which was heated to reflux for 6 h while bubbling nitrogen through the reaction mixture. After evaporation of the ethanol under reduced pressure (45 °C, 70 mbar), sat. aq. NaCl was added and the residue extracted with tert-butyl methyl ether (2 x 30 ml). The combined organic layers were washed with water (30 ml) and sat. aq. NaCl, dried over MgSO₄, filtered and evaporated giving 1.55 g of an oil, which was purified by bulb-to-bulb distillation at 50 - 180 °C / 0.03 mbar yielding 1.08 g of a mixture containing Rotundone 2 with 14% GC-purity (nonpolar GC) and 0.44 g of a residue.

Example 6. Preparation of Rotundone from α -Guaiene under Mn(II)Pc catalysis

The experiment described in example 2 was repeated with manganese(II)phthalocyanine (16.7 mg, 29 μ mol) instead of the FePc catalyst. After 69 h GC indicated a 98% conversion to a mixture comprising rotundone 2 (29%), rotundol 3 (2%), epoxy-guaiene 4a (4%), ketone 5 (4%), hydroxy-rotundone 6 (12%), corymbolon 7 (1%) and epoxy-alcohol 8 (2%). Standard work-up and bulb-to-bulb distillation as in example 2 gave 1.1 g of rotundone with 32% GC-purity (nonpolar GC; 17% corr. yield) and 0.5 g of a residue.

Example 7. Preparation of Rotundone 2 from α -Guaiene 1a under Co(II)Pc catalysis

The experiment described in example 2 was repeated with cobalt(II)phthalocyanine (16.8 mg, 29 μ mol) instead of the FePc catalyst. After 47 h GC indicated a 99% conversion to a mixture comprising rotundone 2 (26%), rotundol 3 (2%), epoxy-guaiene 4a (3%), ketone 5 (1%), hydroxy-rotundone 6 (9%), corymbolon 7 (1%) and epoxy-alcohol 8 (1%). Standard work-up and bulb-to-bulb distillation as in example 2 gave 1.06 g of rotundone with 34% GC-purity (nonpolar GC; 18% corr. yield) and 0.6 g of a residue.

Example 8. Preparation of Rotundone from a mixture of α -Guaiene, Bulnesene, and Aciphyllene

Air was bubbled into a mixture of iron phthalocyanine (0.4 g, 0.73 mmol, 0.3%), imidazole (0.3, 5 mmol) and a mixture containing α -guaiene 61%, bulnesene 13% and aciphyllene 18% (50 g,

149 mmol) in 1:1 ethanol / water (250 ml) under stirring at 45 °C. After 47 hours, GC analysis indicated a conversion > 94% to a mixture comprising Rotundone 2 (21%), rotundol 3 (1%), epoxy-guaiene 4a (1%), ketone 5 (3%), hydroxy-rotundone 6 (5%) and epoxy-alcohol 8 (1%). NaOH (5 g, 122 mmol) was added to the reaction mixture which was heated to reflux for 6 h while bubbling nitrogen through the reaction mixture. After evaporation of ethanol under reduced pressure (45 °C, 70 mbar) the aq. phase was extracted with *tert*-butyl methyl ether (2 x 150 ml). The combined organic layers were washed with sat. aq. NaCl (150 ml), dried over MgSO₄, filtered and evaporated giving 42.5 g of an oil which was mixed with paraffine oil (8.3 g) and subjected to short-path distillation at 70 - 130 °C / 0.02 mbar yielding 28.1 g of a mixture containing Rotundone in 7 fractions and 11.4 g of a residue. Pooling of the olfactorily good fractions yielded 27.5 g of a material (53% weight yield) containing α -Guaiene 1a (0.5%), bulnesene 1b (1%), rotundone 2 (23%), rotundol 3 (1.5%), epoxy-guaiene 4a (1%), epoxy-bulnesene 4b (2%), ketone 5 (3%) hydroxy-rotundone 6 (6%) and epoxy-alcohol 8 (0.5%)

15 Example 9. Preparation of Rotundone from a mixture of α -Guaiene, Bulnesene and Aciphyllene at 20 °C

The experiment described in example 8 was repeated at 20 °C (instead of at 45 °C). After 47 h GC analysis indicated a conversion > 96% to a mixture comprising Rotundone 2 (21%), rotundol 3 (2%), epoxy-guaiene 4a (1%), epoxy-bulnesene 4b (2%), ketone 5 (2%), hydroxy-rotundone 6 (6%) and epoxy-alcohol 8 (0.5%). Isolation and purification as described in example 8 gave 32 g of a mixture containing Rotundone in 7 fractions and 10.5 g of a residue. Pooling of the olfactorily good fractions yielded 31.4 g of a material (58% weight yield) containing α -Guaiene 1a (0.5%), Rotundone 2 (22%), rotundol 3 (1.5%), epoxy-guaiene 4a (1%), epoxy-bulnesene 4b (2%), ketone 5 (2%), hydroxy-rotundone 6 (6%) and epoxy-alcohol 8 (0.5%).

25 Example 10. Preparation of Rotundone from α -Guaiene with NaOH instead of imidazol

The experiment described in example 2 was repeated with α -guaiene 61%, bulnesene 13% and aciphyllene 18% (2 g, 6 mmol) at 20 °C (instead 45 °C) and with NaOH (8 mg, 0.2 mmol) instead of imidazol. After 28 h GC analysis indicated a quantitative conversion to a mixture comprising Rotundone 2 (19%), rotundol 3 (1%), epoxy-guaiene 4a (1%), epoxy-bulnesene 4b (3%), epoxyketone 5 (5%), hydroxy-rotundone 6 (10%) and epoxy-alcohol 8 (0.5%). Isolation and purification as described in example 2 gave 1.19 g of Rotundone with 26% GC-purity (nonpolar GC) and 0.5 g of a residue.

Example 11. Preparation of Rotundone from α -Guaiene without base

The experiment described in example 10 was repeated without any base during air oxidation. After 30 h GC analysis indicated a quantitative conversion to a mixture comprising Rotundone 2 (19%), rotundol 3 (0.5%), epoxy-guaiene 4a (1%), epoxyketone 5 (4%), hydroxy-rotundone 6 (9%), corymbolon 7 (1%) and epoxy-alcohol 8 (0.5%). Isolation and purification as described in

Example 12. Preparation of Rotundone with analysis of the Rotundone isomerization during NaOH treatment

Air was bubbled into a mixture of iron phthalocyanine (8.3 mg, 14.7 μ mol, 0.3%), imidazole (6.7 mg, 0.1 mmol) and a mixture of α -guaiene 61% (1a), bulnesene 15% (1b) and aciphyllene 15% (1c) (1 g, 4.9 mmol) in 1:1 alcohol / water (20 ml) under stirring at 20 °C. Polar GC-analysis indicated 23% Rotundone 2. No *epi*-Rotundone was detected.

NaOH (100 mg, 2.5 mmol) was added to the reaction mixture which was heated to reflux for 70 h while bubbling nitrogen through the reaction mixture. Over time, samples were taken and analyzed by polar GC (see table below).

Time [h]	0	1	2	4	6	24	28	47
Rotundone 2 [% ratio]	100	92	81	69	63	54	55	54
3- <i>epi</i> -Rotundone [% ratio]	0	8	19	31	37	46	45	46

a) % ratio = % Rotundone or % *epi*-Rotundone / (% Rotundone + % *epi*-Rotundone) x 100. Percentages from polar GC.

The reaction progress table above shows that Rotundone 2 is epimerizing in the presence of NaOH at reflux. In about 24h the epimerization reached is maximum with a ratio of Rotundone 2 / *epi*-Rotundone of about 55 / about 45. No further epimerization occurs after 24 hours.

Example 13. Preparation of Rotundone with analysis of the Rotundone isomerization using alternative peroxide destruction methods

The experiment described in example 12 was repeated until complete conversion of the Guaiene / Bulnesene / Aciphyllene 61:15:15 mixture to 23% Rotundone 2.

The reaction mixture was than treated with peroxide destruction reagents as indicated in the table below:

run	peroxide destruction reagent	mol-eq / substrate	T [°C]	time [h]	Rotundone 2 [% ratio]	3-epi-Rotundone [% ratio]
1	NaOH	0.5	100	23	54	46
2	NaOH	0.5	25	45	95	5
3 ^a	PPh ₃	0.6	100	17	95	5
4 ^b	PPh ₃	0.25	25	24	100	0
5	Na ₂ SO ₃	1.5	25	24	100	0

a) PPh₃/Ph₃PO 53:13; b) PPh₃/Ph₃PO 8:28 (ratios observed at the end of the peroxide destruction treatment which indicate that the peroxides are completely destroyed because not further conversion of the PPh₃ takes place).

The table above shows that the isomerization of Rotundone 2 to 3-epi-Rotundone during a subsequent peroxide destruction treatment can be avoided under certain conditions.

The efficacy of triphenylphosphine for the decomposition of potentially presence of peroxide can be easily measured by the analysis of the ratio of PPh₃ to Ph₃PO.

Example 14. Isolation and characterization of epoxy-alcohol isomers 8

Under nitrogen and stirring chromium trioxide (18.75 g, 118 mmol) was added in six portions to 3,5-dimethylpyrazol (36 g, 374 mmol) in dichloromethane at -30 °C. After 30 min α -Bulnesene (32 g, 157 mmol) in dichloromethane was added dropwise at -20 °C over 1 h. After 5 h at -10 °C and another 22 h at room temperature a 15% conversion to a few oxidation products was determined by GC. The reaction mixture was poured onto 8M aq. NaOH (400 ml). After the addition of *tert*-butyl methyl ether (600 ml) the organic layer was separated and the aq. layer extracted with *tert*-butyl methyl ether (300 ml). The combined organic layers were washed with 2M HCl (2 x 200 ml), water (2 x 200 ml) and aq. sat. NaCl (200 ml), dried over MgSO₄, filtered and evaporated under reduced pressure giving 34.3 g of a residue, which was bulb-to-bulb-distilled at 90 – 100 °C / 0.1 mbar giving 25 g of fractions containing mainly α -Bulnesene with 58 – 89% purity. This material was subjected to column chromatography (SiO₂, hexane / *tert*-butylether) giving the epoxyalcohol isomers 8a and 8b.

Analytical data of 8a:

¹H-NMR (400 MHz, C₆D₆): δ (ppm) = 4.865 (d, 1H), 4.795 (d, 1H), 1.8 – 2.2 (5H), 2.9 (br, 1 H), 1.71 (s, 3 H), 1.4 – 1.6 (5H), 1.32 (s, 3 H), 1.0-1.2 (2H), 1.05 (s, 3 H).

¹³C-NMR (100 MHz, C₆D₆): δ (ppm) = 150.8 (s), 108.6 (t), 73.8 (s), 72.0 (s), 68.5 (s), 44.7 (d), 37.6 (t), 36.4 (d), 33.5 (t), 30.3 (t), 28.5 (q), 28.0 (t), 27.2 (t), 19.9 (q), 13.5 (q) ppm.

(EI⁺-MS): m/z = 236 [M]⁺ (0.2 %), 221 [M-CH₃]⁺ (5 %), 203 (14 %), 175 (29%), 165 (14%), 161 (15%), 151 (10%), 149 (14%), 147 (17%), 137 (19%), 135 (20%), 133 (27%), 119 (24%), 111 (63%), 109 (38%), 107 (39%), 105 (26%), 97 (30 %), 95 (32%), 93 (48 %), 91 (31%), 83 (26%), 81 (38%), 79 (32%), 77 (22%), 71 (23%), 69 (50 %), 67 (47%), 65 (12%), 57 (16%), 55 (51%),
 5 53 (23 %), 43 (100%), 41 (41 %).

Analytical data of 8b:

¹H-NMR (400 MHz, C₆D₆): δ (ppm) = 4.83 (d, 1H), 4.81 (d, 1H), 1.1 – 2.3 (12H), 1.73 (s, 3 H), 1.3 (s, 3 H), 0.75 (s, 3 H).

10 ¹³C-NMR (100 MHz, C₆D₆): δ (ppm) = 150.8 (s), 108.8 (t), 74.9 (s), 71.5 (s), 70.8 (s), 42.5 (d), 39.8 (t), 39.6 (d), 32.7 (t), 30.2 (t), 26.1 (t), 25.9 (t), 24.3 (q), 20.6 (q), 16.6 (q) ppm.

(EI⁺-MS): m/z = 221 [M-CH₃]⁺ (2 %), 218 [M-H₂O]⁺ (3 %) 203 (16 %), 185 (10%), 175 (25%), 163 (10%), 161 (13%), 149 (10%), 147 (13%), 145 (16%), 135 (17%), 134 (15%), 133 (28%), 125 (12%), 123 (17%), 121 (29%), 119 (27%), 111 (53%), 109 (29%), 107 (39%), 105 (29%),
 15 97 (41 %), 95 (31%), 93 (49%), 91 (33%), 83 (29%), 81 (32%), 79 (33%), 77 (24%), 71 (19%), 69 (48%), 67 (45%), 65 (12%), 57 (13%), 55 (54%), 53 (26 %), 43 (100%), 41 (47 %).

Example 15. Preparation of Rotundone in various alcohol / water mixtures

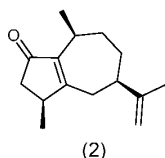
Air was bubbled into a mixture of iron phthalocyanine (8.3 mg, 14.7 μmol, 0.3%), imidazole (6.7
 20 mg, 0.1 mmol) and a mixture of α-guaiene 61% (1a), bulnesene 13% (1b) and aciphyllene 18% (1c) (1 g, 4.9 mmol) in 1:1 alcohol / water (20 ml) under stirring at 20 °C. After 45 hours, GC analysis indicated an extensive conversion to Rotundone 2, rotundol 3, epoxy-guaiene 4a, epoxy-bulnesene 4b, ketone 5, hydroxy-rotundone 6, corymbolon 7 and epoxy-alcohol 8. Standard work-up as described in example 2 gave an oil, which was purified by bulb-to-bulb
 25 distillation yielding Rotundone 2 as indicated in the table below.

run	alcohol	Guaiene in crude ^a [% GC ^c]	Rotundone in crude ^a [% GC ^c]	Rotundone yield (corr, dist) ^b [%]
1	ethanol	0	20	20
2	isopropanol	0.5	25	24
3	ethylenglycol	1	23	24
4	Ethylenglycol monobutylether	5	21	27
5	dipropylenglycol	0	23	28
6	propandiol	0	28	21

a) crude = crude oil after extraction and before bulb-to-bulb distillation. b) Yield corrected by the purity of Guaiene in the substrate and the purity of Rotundone in the product. c) nonpolar GC.

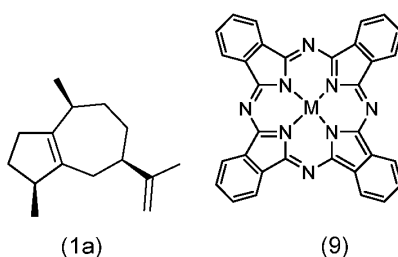
Claims

1. A method of producing a compound of formula (2) by allylic oxidation,



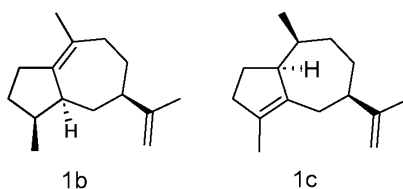
the method comprising the steps of:

- a) forming a mixture of a compound of formula (1a) and a catalytic amount of compound of formula (9)



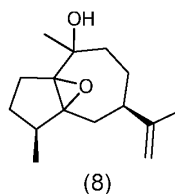
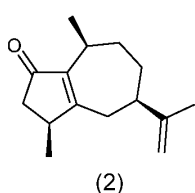
wherein M is Fe, Mn or Co;

- b) oxidizing the compound of formula (1a) to produce the compound of formula (2).
2. The method according to claim 1 wherein the method includes introducing molecular oxygen into the mixture of the compound of formula (1a) and the compound of formula (9) prior to and/or during the step of oxidizing the compound of formula (1a).
3. The method according to claim 2 wherein the method includes introducing air into the mixture prior to and/or during the step of oxidizing the compound of formula (1a).
4. The method according to any one of claims 1 to 3 wherein the mixture of the compound of formula (1a) and the compound of formula (9) further includes one or both of the compounds of formula (1b) and formula (1c)

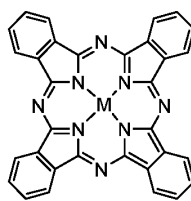


5. The method according to claim 4 wherein the mixture includes the compound of formula (1b) and optionally further includes the compound of formula (1c).

6. The method according to any one of claims 1 to 5 wherein the mixture of the compound of formula (1a) and the compound of formula (9) further includes a base coordination compound.
7. The method according to claim 6 where the base coordination compound is an amine, such as trimethylamine, or an inorganic base, such as NaOH or K₂CO₃.
8. The method according to any one of the claims 1 to 7 wherein step a) takes place in the present of a solvent.
9. The method according to claim 8 wherein the solvent is selected from the group consisting of water, alcohol, acetone, ethyl acetate, isopropyl acetate, methyl ethyl ketone, cyclohexane, heptane, toluene, methylcyclohexane, methyl t-butyl ether, isooctane, acetonitrile, xylenes, dimethyl sulfoxide, acetic acid, ethylene glycol and mixtures thereof.
10. The method according to claim 9 wherein the solvent is a water/alcohol mixture.
11. The method according to claim 9 or claim 10 wherein the alcohol is selected from the group consisting of ethanol, methanol, propanol, butanol, isopropanol, n-propanol, ethyleneglycol, 1,2-propanediol, ethyleneglycolmonobutylether, dipropyleneglycol and mixtures thereof.
12. The method according to any one of the claims 1 to 11 producing a compound of formula (2) and a compound of formula (8)

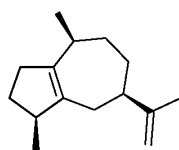


13. Use of a compound of formula (9) wherein M is Fe, Mn, or Co

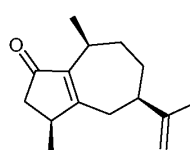


(9)

in the allylic oxidation of a compound of formula (1a) to produce a compound of formula (2)

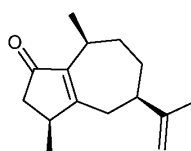


1a

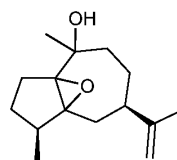


2

14. A composition comprising a compound of formula (2) and a compound of formula (8)



(2)



(8)