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Ultrasound assisted reductive cleavage of eudesmane and guaiane γ-enonelactones. Synthesis of 1α,7α,10α*H*-guaian-4,11-dien-3-one and hydrocolorenone from santonin

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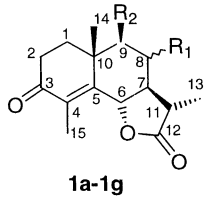
Abstract—Ultrasound enhances the rate of reductive cleavage of the C_6–oxygen bond of sesquiterpene enonelactones. *trans*-Eudesmanolides **1c**–**1g**, *cis*-eudesmanolides **2a**–**2c**, and *trans*-guaianolides **4a**–**4d** react with Zn in acetic acid–H_2O under sonochemical conditions to afford the corresponding sesquiterpene acids **3a**–**3g** and **5a**–**5d**, respectively in good yields. Starting from **5d** two natural guaianes 1α,7α,10α*H*-guaian-4,11-dien-3-one (**6**) and hydrocolorenone (**7**) have been prepared in good yields through a straightforward sequence.

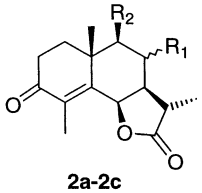
1. Introduction

Sesquiterpene lactones constitute a very interesting group of natural compounds[1,2] on account of their wide spectrum of biological activities. The corresponding sesquiterpene acids are also interesting natural products not only because of their biological activity but also because of their utility as synthetic intermediates.[1–4]

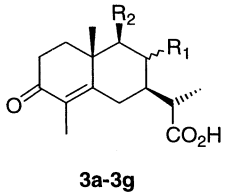
Usually, sesquiterpene acids like **3** are prepared from the most commonly occurring *trans*-lactones in a two step process involving C_6-epimerization to the *cis*-lactone and subsequent reduction with Zn dust in acetic acid–methanol at reflux. This procedure has been applied to the transformation of the eudesmanolides santonin (**1a**), artemisin (**1b**) and its derivatives **1d** and **1e** into the sesquiterpene acids **3a**,[5] **3b**,[6] **3d**[7] and **3e**,[8] respectively, which have been used as



1a-1g

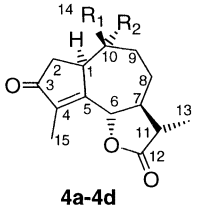


2a-2c

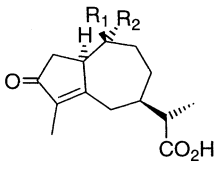


3a-3g

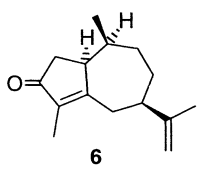
a: $R_1 = R_2 =$ H, 1,2-dehydro; **b:** R_1 = α-OH, R_2 = H, 1,2-dehydro; **c:** $R_1 = R_2 =$ H; **d:** R_1 = α-OH, R_2 = H; **e:** R_1 = H, R_2 = OH; **f:** R_1 = β-OH, R_2 = H; **g:** R_1 = β-OAc, R_2 = H



4a-4d



5a-5d



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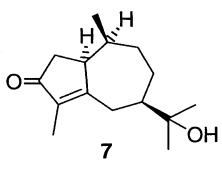

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a: R_1 = Me, R_2 = OAc; **b:** R_1 = Me, R_2 = OH; **c:** $R_1,R_2 = CH_2$=; **d:** R_1 = Me, R_2 = H

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intermediates in the synthesis of several natural sesquiterpenes[3,5,8] and sesquiterpene lactones.[3,6–8]

A different procedure has been used by Loewenthal et al. in their synthesis of 1-epicyclocolerenone.[9] These authors carried out the hydrogenolysis of three guaianolides with chromous chloride in acetic acid with variable yields. From guaianolide **4d** these authors obtained the corresponding acid **5d** in 50% yield. More recently Suarez et al. have developed an organosulfur or organoselenium mediated method for this transformation which has been applied to eudesmanolides **1a**, **1c** and **2a**, and to guaianolide **4a**.[10] This method gives in most cases better results but requires special experimental conditions.

As part of our current synthetic programme related to natural sesquiterpenes with biological activity,[4] we have described in a previous communication an easy ultrasound assisted reductive cleavage of several sesquiterpene γ-enonelactones.[11] In this paper we wish to report in full, our investigation on the ultrasound assisted cleavage of eudesmanolides **1a**–**1g** and **2a**–**2c** and specially the extension to guaianolides **4a**–**4d** to prepare the corresponding sesquiterpene acids **3a**–**3g** and **5a**–**5d**, respectively. We also wish to report the synthesis of 1α,7α,10α*H*-guaian-4,11-dien-3-one (**6**) and hydrocolorenone (**7**) from **5d** as an example of the utility of these sesquiterpene acids as synthetic intermediates. Structure **6** has been assigned to a compound isolated from *Baccharis boliviensis*[12] and hydrocolorenone (**7**) was first isolated from *Euryops pedunculatus* by Bohlmann's group[13] and recently from the indonesian soft coral *Nephthea chabrolii*.[14] Compound **7** exhibits insecticidal activity towards neonate larvae of the polyphagous pest insect *Spodoptera littoralis*.[14]

2. Results and discussion

The use of ultrasound to enhance the chemical reactivity of metal powder in heterogeneous solid–liquid systems is well established and it has been the subject of several reviews.[15] In the present work various reductive systems that have been used for the ultrasound assisted reduction of different functional groups were tried in order to carry out the reductive cleavage of the lactone ring. The use of aluminium–nickel chloride/THF[16] and zinc–nickel chloride/2-methoxyethanol–water[17] resulted unsucessful. Thus no reaction was observed and the starting material was recovered unaltered with the first system while complex reaction mixtures were obtained with the second one. However, zinc/acetic acid–water[18] gave good yields of the hydrogenolysis product in all the samples where a γ-enonelactone moiety was present.

Table 1 displays the results obtained with several eudesmane and guaiane γ-enonelactones. As expected, the reaction proceeded extremely quickly and with good yields with eudesmane *cis*-lactones **2a**–**2c** (entries 1–3) as the axial disposition of the C_6–oxygen fulfils the stereoelectronic requirements for an effective electron transfer from the carbonyl group to the leaving group, and allows a minimum expenditure of energy for the elimination.[19] More interestingly, the reaction also took place with the most usually occurring *trans*-lactones **1c**–**1g** where the C_6–oxygen bond is equatorial (entries 4–8) overriding the stereoelectronic requirements for the reductive elimination. The method is compatible with hydroxyl or acetate groups in the B ring, although in one case (entry 7) the hydroxy acid **3f** obtained suffered partial lactonization to give the 8,12-eudesmanolide **3h**. Unfortunately, when a dienone system was present (compounds **1a** and **1b**), complex reaction mixtures were obtained due to the decomposition of the dienone system.

Table 1 also displays the results for four guaiane *trans*-γ-enonelactones obtained from santonin (**1a**) (Scheme 1). Irradiation of **4a**–**4d** in the same conditions (entries 9–12) gave in all cases good results of the corresponding guaiane acids **5a**–**5d**. The method is compatible with the presence of tertiary acetate or hydroxyl groups in the B ring as well as with an exomethylene double bond. Neither enone reduction products nor epimerization at the C-1 position were observed in any case.

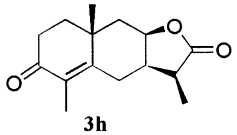
Compound **5d** has one of the two epimeric structures proposed for 11,13-dihydropechuloic acid, a natural guaiane acid isolated from *Decachaeta scabrella*.[20] However comparison of the natural product reported data[20] with those of our synthetic compound showed significant differences in their ^{1}H NMR data for H-6α, H-6β and H-7 (δ 2.63, 2.47 and 2.56, respectively, for the natural compound; δ 2.70, 2.40 and 2.15, respectively, for **5d**), and in the ^{13}C NMR data for C-2, C-6, C-8 and C-9 (δ 41.0, 36.5, 27.9 and 36.3, respectively, for the natural compound;δ 40.7, 29.4, 27.6 and 38.4, respectively, for **5d**). On the basis of these differences the structure of compound **5d** should be discarded for the natural product.

With compound **5d** in our hands[21,22] we undertook the

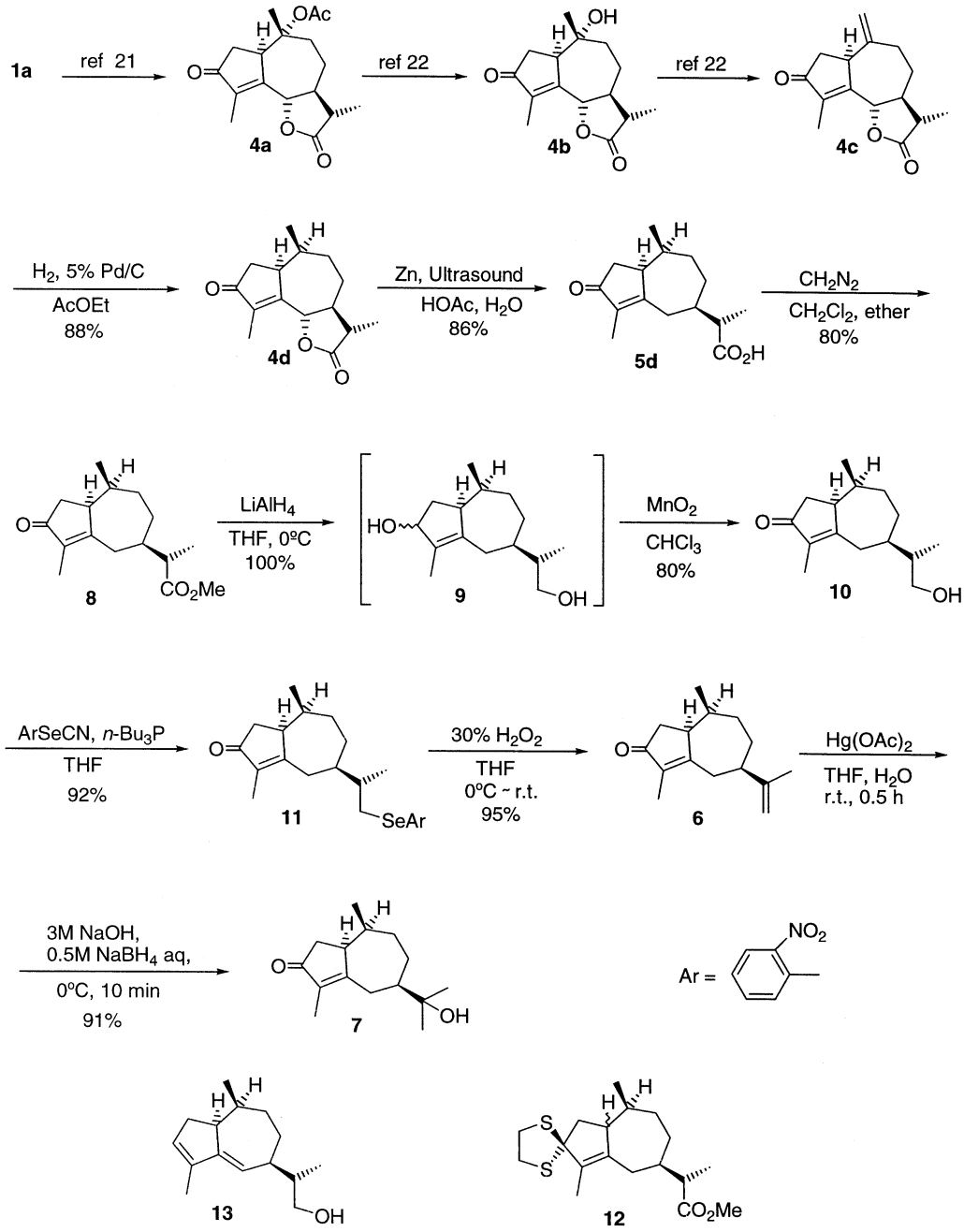
Table 1. Ultrasound assisted reductive cleavage of sesquiteerpene γ-enonelactones

Entry	Substrate	Time (min)	Product[a]	Yield (%)[b,c]
1	**2a**	2	**3a**	75
2	**2b**	2	**3b**	73
3	**2c**	2	**3c**	86
4	**1c**	60	**3c**	80(85)
5	**1d**	120	**3d**	71(75)
6	**1e**	120	**3e**	68(71)
7	**1f**	120	**3f**	66(70)[d]
8	**1g**	120	**3g**	65(70)
9	**4a**	60	**5a**	85
10	**4b**	120	**5b**	78
11	**4c**	120	**5c**	70
12	**4d**	120	**5d**	70

[a] As methyl ester after methylation with excess of ethereal diazomethane.
[b] Yields refer to isolated and chromatographically pure compounds. Yields in brackets refer to consumed starting material.
[c] In entries 4–8 some reduction product (3–5%) of the unsaturated ketone was observed.
[d] Part of the 8,12-lactonization product **3h** appeared during hydrogenolysis. This yield refers to the 8,12-lactone **3h** isolated after treatment of the crude mixture with *p*-TsOH acid in benzene at reflux.



3h



Scheme 1.

modification of the C_7 side chain in order to obtain compounds **6** and **7** (Scheme 1). In a first approach we decided to protect the oxo group as a thioketal, which was carried out by reaction of the methyl ester **8** with ethanedithiol in acetic acid–boron trifluoride for 48 h at reflux. Unexpectedly this treatment caused epimerization at C-1 yielding (76%) an epimeric mixture of thioketals **12** (H-1β/H-1α in a ratio 3:1). Since the major reaction product was the undesired C_1 epimer, we decided not to protect the ketone group and to reduce both carbonyl groups with excess $LiAlH_4$ to obtain the corresponding diol **9** as a C_3 epimeric mixture, which could be selectively reoxidized at C_3 with MnO_2 in $CHCl_3$ at room temperature to afford the desired compound **10** (80% yield for the two steps). It is important to remark that oxidation of diol **9** must be performed immediately after reduction of compound **8** since it was observed that diol **9** is unstable and rapidly dehydrate to diene **13** [^{1}H NMR (200 MHz) δ 5.62 and 5.36 (two br. s, 1H each, H-3 and H-6); ^{13}C NMR (200 MHz) δ 150.7, 140.2 (C, C-4, C-5), 131.9, 121.2 (CH, C-3, C-6)].

The elimination of the C-12 hydroxyl group was achieved in two steps following the procedure described by Grieco et al.[23] The sequence involves transformation of the hydroxyl group into *o*-nitrophenyl selenide **11** by treatment with *o*-nitrophenyl selenocyanate and tri-*n*-butylphosphine (92%), followed by spontaneous elimination of the corresponding selenoxide upon treatment with hydrogen peroxide to give compound **6** in 95% yield. The physical

and spectral data of compound **6** were in complete agreement with those reported for the natural 11α,7α, 10α*H*-guaia-4,11-dien-3-one isolated from *Baccharis boliviensis*.[12] Finally, hydromercuration–demercuration[24] of compound **6** afforded hydrocolorenone (**7**) (91%) which showed the same spectral features and optical rotation sign than the natural compound isolated from *E. pedunculatus*[13] and *N. chabrolii*.[14]

In summary, an ultrasound assisted procedure for the reductive cleavage of γ-enonelactones has been developed. This method constitutes a simple alternative to the literature procedures and it is very much simpler and safer from the experimental point of view. With regard to the classical method[5–8] the yields are higher, reaction times shorter and for the most usually occurring eudesmane *trans*-lactones there is no need for epimerization at the C_6 carbon of the lactone moiety. The procedure can also be applied to *trans*-guaianolides with good results and it compares favourably with the chromous chloride method.[9] It is also safer than the organosulfur or organoselenium mediated method[10] which requires a heavy wall tube with a high vacuum valve, heating at high temperatures, and the recommended use of a protective shield. The synthesis of guaiane acid **5d** obtained by this method allows us to discard this structure for the natural 11,13-dihydropechuloic acid isolated from *D. scabrella*.[20] We have also showed that compound **5d** is a good starting material for the synthesis of natural guaianes **6** and **7** which were obtained in 56 and 50% overall yield, respectively. The structure and absolute stereochemistry of both compounds have been confirmed.

3. Experimental

3.1. General methods

All melting points are uncorrected. Column chromatography was performed on silica gel (SDS, silica gel 40–60 μm). Commercial reagents and solvents were analytical grade or were purified by standard procedures prior to use.[25] All reactions involving air or moisture sensitive materials were carried out under argon atmosphere. Specific rotations were measured in $CHCl_3$. IR spectra were recorded as liquid film in NaCl for oils and as KBr discs for solids. NMR spectra were run in $CDCl_3$ (except stated otherwise) at 200.1, 299.95, or 399.95 MHz for ^1H and at 50.3 or 75.4 MHz for ^{13}C NMR, and referenced to the solvent as internal standard (δ_H=7.24 ppm). The carbon type was determined by DEPT experiments. Mass spectra were run by electron impact at 70 eV or chemical ionisation using methane as ionising gas. A J.P. Selecta S.A ultrasound bath (100 W, 40 KHz, ref 03000683) was used for sonication.

3.2. General procedure for the ultrasound assisted cleavage of γ-enonelactones

Starting material (0.2 mmol) was dissolved in a mixture of acetic acid–water (1:1) (4 mL). Zinc dust (8 mmol) was added and the reaction mixture irradiated with an ultrasound bath at room temperature (ice addition) for 2 min or 1 h (see Table 1). For longer reaction times one portion of Zn (1.6 mmol) was added and the reaction mixture was sonicated for one additional hour. Then, the reaction mixture was filtered through Celite, extracted with ethyl acetate and the combined organic layers were washed with brine and dried over Na_2SO_4. Solvent removal afforded the acid which was esterified with an excess of ethereal diazomethane to give the corresponding methyl ester for characterization.

3.2.1. Compound 3a. 75%; yellow oil; $[\alpha]_D^{24}=-78.7$ (*c* 1.60) [lit.[5] $[\alpha]_D^{23}=-99$ (*c* 0.8, MeOH)]; IR (NaCl) ν_{max} 1730, 1660, 1630, 1610 cm^{-1}; ^1H NMR (200 MHz) δ 6.72 (d, *J*=9.8 Hz, 1H, H-1), 6.20 (d, *J*=9.8 Hz, 1H, H-2), 3.70 (s, 3H, –OMe), 2.71 (dt, *J*=2.8, 12.8 Hz, 1H, H-6α), 2.44 (quint, *J*=6.9 Hz, 1H, H-11), 2.01 (t, *J*=12.8 Hz, 1H, H-6β), 1.86 (s, 3H, 3H-15), 1.81 (dd, *J*=2.9, 12.4 Hz, 1H, H-9β), 1.75–1.40 (m, 3H, H-7, H-8α, H-9α), 1.32 (td, *J*=3.4, 12.4 Hz, 1H, H-8β), 1.19 (d, *J*=7.2 Hz, 3H, 3H-13), 1.18 (s, 3H, 3H-14); ^{13}C NMR (50.3 MHz) δ 186.3, 175.9, 158.9 (C, C-3, C-12, C-5), 156.4 (CH, C-1), 129.3 (C, C-4), 126.1 (CH, C-2), 51.5 (CH_3, $-OCH_3$), 44.8, 42.0 (CH, C-7, C-11), 40.1 (C, C-10), 37.5, 31.8, 24.0 (CH_2, C-8, C-9, C-6), 23.2, 14.2, 10.3 (CH_3, C-14, C-13, C-15).

3.2.2. Compound 3b. 73%; mp 93–94°C (hexane–EtOAc); $[\alpha]_D^{24}=-24.4$ (*c* 1.47) [lit.[6] $[\alpha]_D^{25}=-14$ (*c* 0.1−0.3)]; IR (KBr) ν_{max}, 3450, 1725, 1660, 1630, 1610 cm^{-1}; ^1H NMR (200 MHz) δ 6.65 (d, *J*=9.8 Hz, 1H, H-1), 6.14 (d, *J*=9.8 Hz, 1H, H-2), 3.99 (td, *J*=4.5, 10.8 Hz, 1H, H-8), 3.66 (s, 3H, $-OCH_3$), 2.92 (dq, *J*=2.3, 7.0 Hz, 1H, H-11), 2.76 (dd, *J*=3.8, 14.0 Hz, 1H, H-6α), 2.13 (t, *J*=14.0 Hz, 1H, H-6β), 2.04 (dd, *J*=4.5, 12.5 Hz, 1H, H-9β), 1.85 (s, 3H, 3H-15), 1.80–1.60 (m, 1H, H-7), 1.21 (d, *J*=7.0 Hz, 3H, 3H-13), 1.17 (s, 3H, 3H-14); ^{13}C NMR (50.3 MHz) δ 186.1, 176.0, 157.5 (C, C-3, C-12, C-5), 155.4 (CH, C-1), 129.6 (C, C-4), 125.8 (CH, C-2), 66.4 (CH, C-8), 51.6 (CH_3, $-OCH_3$), 48.4 (CH, C-7), 45.2 (CH_2, C-9), 40.2 (C, C-10), 39.3 (CH, C-11), 28.2 (CH_2, C-6), 24.4, 13.3, 10.4 (CH_3, C-14, C-13, C-15).

3.2.3. Compound 3c. 80% from **1c**, 86% from **2c**; oil; $[\alpha]_D^{24}=+120$ (*c* 1.60) [lit.[5] $[\alpha]_D^{23}=+115$ (*c* 0.2, MeOH)]; IR (NaCl) ν_{max}, 1735, 1665, 1610 cm^{-1}; ^1H NMR (200 MHz) δ 3.68 (s, 3H, $-OCH_3$), 2.60 (dt, *J*=2.2, 12.6 Hz, 1H, H-6α), 2.49–2.31 (m, 3H, 2H-2, H-11), 1.88 (td, *J*=1.3, 12.6 Hz, 1H, H-6β), 1.78–1.58 (m, 5H, 2H-1, H-7, H-8, H-9), 1.72 (d, *J*=1.2 Hz, 3H, 3H-15), 1.46–1.35 (m, 2H, H-8′, H-9′), 1.17 (d, *J*=6.6 Hz, 3H, 3H-13), 1.16 (s, 3H, 3H-14); ^{13}C NMR (50.3 MHz) δ 199.0, 176.1, 161.3, 128.8 (C, C-3, C-12, C-5, C-4), 51.5 (CH_3, $-OCH_3$), 45.0, 41.3 (CH, C-7, C-11), 41.5, 33.7, 32.0, 37.3 (CH_2, C-2, C-8, C-9, C-1), 35.8 (C, C-10), 24.6 (CH_2, C-6), 22.3, 13.9, 10.7 (CH_3, C-14, C-13, C-15).

3.2.4. Compound 3d. 71%; mp 119–121°C (ether) [lit.[6] mp 120–121°C (ether)]; $[\alpha]_D^{24}=+98.5$ (*c* 0.97) [lit.[6] $[\alpha]_D^{25}=+58$ (*c* 0.1–0.3)]; IR (KBr) ν_{max}, 3300, 1730, 1650, 1610 cm^{-1}; ^1H NMR (200 MHz) δ 3.92 (ddd, *J*=4.2, 10.5, 11.5 Hz, 1H, H-8), 3.70 (s, 3H, $-OCH_3$), 2.88 (qd, *J*=2.7, 7.2 Hz, 1H, H-11), 2.69 (dd, *J*=3.6, 14.5 Hz, 1H, H-6α), 2.60–2.30 (m, 2H, 2H-2), 2.02 (br. t, *J*=14.5 Hz, 1H, H-6β), 1.92 (dd, *J*=4.2, 12.7 Hz, H-9β), 1.89–1.69 (m, 3H, 2H-1, H-7), 1.76 (d, *J*=1.3 Hz, 3H, 3H-15), 1.36 (dd, *J*=11.1, 12.7 Hz, 1H, H-9α), 1.24 (d, *J*=7.2 Hz, 3H,

3H-13), 1.19 (s, 3H, 3H-14); ^{13}C NMR (50.3 MHz) δ 198.6, 176.3, 159.4, 129.3 (C, C-3, C-12, C-5, C-4), 66.9 (CH, C-8), 51.8 (CH_3, $-OCH_3$), 50.1 (CH_2, C-9), 47.8, 39.7 (CH, C-7, C-11), 37.2 (CH_2, C-1), 37.0 (C, C-10), 33.2, 29.1 (CH_2, C-2, C-6), 23.2, 12.9, 11.0 (CH_3, C-14, C-13, C-15).

3.2.5. Compound 3e. 68%; oil; $[\alpha]_D^{22}=+96.0$ (*c* 1.80) [lit.[8] $[\alpha]_D^{23}=+98.0$ (*c* 1.90)]; IR (NaCl) ν_{max}, 3450, 1730, 1660, 1610 cm^{-1}; ^{1}H NMR (200 MHz) δ 3.70 (s, 3H, $-OCH_3$), 3.44 (dt, *J*=4.4, 11.2 Hz, 1H, H-9α), 2.59 (ddd, *J*=2.0, 3.6, 14.0 Hz, 1H, H-6α), 2.43 (dd, *J*=4.4, 9.6 Hz, 2H, 2H-2), 2.43 (dq, *J*=6.8, 7.6 Hz, 1H, H-11), 2.11 (dt, *J*=4.4, 13.6 Hz, 1H, H-1), 1.90 (br. dt, *J*=1.6, 14.0 Hz, 1H, H-6β), 1.88 (dddd, *J*=2.0, 3.6, 4.4, 12.0 Hz, H-8α), 1.78 (dt, *J*=9.6, 13.6 Hz, 1H, H-1′), 1.82–1.70 (m, 2H, H-7, OH), 1.75 (d, *J*=0.8 Hz, 3H, 3H-15), 1.47 (q, *J*=12.0 Hz, 1H, H-8β), 1.19 (d, *J*=6.8 Hz, 3H, 3H-13), 1.14 (s, 3H, 3H-14); ^{13}C NMR (50.3 MHz) δ 198.9, 175.8, 159.1, 130.4 (C, C-3, C-12, C-5, C-4), 77.6 (CH, C-9), 51.6 (CH_3, $-OCH_3$), 44.5, 37.2 (CH, C-7, C-11), 41.4 (C, C-10), 33.3, 33.3, 33.0, 31.4 (CH_2, C-1, C-2, C-6, C-8), 15.6, 13.9, 11.2 (CH_3, C-14, C-13, C-15).

3.2.6. Compound 3h. 66%, after treatment of the reaction mixture with a catalytic amount of *p*-TsOH in benzene (3.8 mL) at reflux for 1 h, mp 104–105°C (hexane–CH_2Cl_2) [lit.[6] mp 103–104°C (hexane–CH_2Cl_2)]; $[\alpha]_D^{24}=+91.6$ (*c* 0.83) [lit.[6] $[\alpha]_D^{25}=+92$ (*c* 0.1–0.3, Cl_3CH)]; IR (KBr) ν_{max}, 1764, 1660, 1620 cm^{-1}; ^{1}H NMR (200 MHz) δ 4.51–4.45 (m, 1H, H-8), 2.88 (quint, *J*=7.0 Hz, 1H, H-11), 2.65 (dd, *J*=5.8, 13.9 Hz, 1H, H-6α), 2.53–2.38 (m, 3H, 2H-2, H-7), 2.28 (dd, *J*=2.5, 15.5 Hz, 1H, H-9β), 1.94 (br. t, *J*=1.3, 13.9 Hz, 1H, H-6β), 1.90–1.60 (m, 2H, 2H-1), 1.80 (s, 3H, 3H-15), 1.70 (dd, *J*=4.4, 15.5 Hz, 1H, H-9α), 1.28 (s, 3H, 3H-14), 1.26 (d, *J*=7.0 Hz, 3H, 3H-13); ^{13}C NMR (50.3 MHz) δ 198.3, 178.6, 157.5, 130.3 (C, C-3, C-12, C-5, C-4), 76.6 (CH, C-8), 41.9 (CH_2, C-9), 41.7, 40.8 (CH, C-7, C-11), 37.3 (CH_2, C-1), 34.9 (C, C-10), 33.3 (CH_2, C-2), 24.8 (CH_3, C-14), 24.4 (CH_2, C-6), 11.2, 9.6 (CH_3, C-15, C-13).

3.2.7. Compound 3g. 65%; oil; $[\alpha]_D^{24}=+68.5$ (*c* 1.25); HRMS (CI) *m*/*z* 322.1780 (M^+, 5, $C_{18}H_{26}O_5$ required 322.1780), 262 (100), 249 (20), 202 (62); IR (NaCl) ν_{max}, 1730, 1655, 1600, 1240 cm^{-1}; ^{1}H NMR (200 MHz) δ 5.25–5.15 (m, 1H, H-8), 3.70 (s, 3H, $-OCH_3$), 2.54–2.36 (m, 4H, 2H-2, H-6α, H-11), 2.30 (t, *J*=14.0 Hz, 1H, H-6β), 2.10 (s, 3H, CH_3CO_2-), 2.14–2.03 (m, 1H, H-9β), 1.95–1.85 (m, 1H, H-7), 1.73 (d, *J*=1.1 Hz, 3H, 3H-15), 1.75–1.69 (m, 2H, 2H-1), 1.50 (dd, *J*=2.9, 15.5 Hz, 1H, H-9α), 1.26 (s, 3H, 3H-14), 1.13 (d, *J*=6.9 Hz, 3H, 3H-13); ^{13}C NMR (50.3 MHz) δ 198.5, 176.1, 170.3, 159.7, 129.4 (C, C-3, C-12, CH_3CO_2-, C-5, C-4), 68.6 (CH, C-8), 51.8 (CH_3, $-OCH_3$), 44.9 (CH_2, C-9), 43.2, 41.8 (CH, C-7, C-11), 37.3 (CH_2, C-1), 35.3 (C, C-10), 33.2, 27.7 (CH_2, C-2, C-6), 24.1, 21.2, 15.5, 10.7 (CH_3, C-14, CH_3CO_2-, C-13, C-15).

3.2.8. Compound 5a. 85%; mp 50–51°C (hexane–EtOAc) [lit.[10] mp 50–52°C]; $[\alpha]_D^{22}=0$ (*c* 1.16); IR (KBr) ν_{max} 1730, 1700, 1630 cm^{-1}; ^{1}H NMR (200 MHz) δ 4.06–4.02 (m, 1H, H-1), 3.66 (s, 3H, –OMe), 2.67 (br. d, *J*=19 Hz, 1H, H-6), 2.50–2,40 (m, 2H, H-9, H-11), 2.35 (d, *J*=4.3 Hz, 2H, 2H-2), 2.32–2.25 (m, 1H, H-6′), 2.21–2.08 (m, 2H, H-7, H-8), 1.94 (s, 3H, CH_3CO_2-), 1.79 (ddd, *J*=3.7, 4.5, 15.0 Hz, 1H, H-9′), 1.63 (s, 3H, 3H-15), 1.25–1.15 (m, 1H, H-8′), 1.14 (d, *J*=7.0 Hz, 3H, 3H-13), 1.00 (s, 3H, 3H-14); ^{13}C NMR (75.4 MHz) δ 207.3, 175.6, 170.9, 170.3, 138.6, 86.2 (C, C-3, C-12, C-5, CH_3CO-, C-4, C-10), 51.7 (CH_3, $-OCH_3$), 48.4, 45.3, 38.3 (CH, C-1, C-7, C-11), 38.9, 37.2, 35.8, 28.6 (CH_2, C-2, C-6, C-9, C-8), 22.4, 19.3, 12.8, 8.2 (CH_3, CH_3CO-, C-14, C-13, C-15).

3.2.9. Compound 5b. 78%; oil; $[\alpha]_D^{19}=+58.1$ (*c* 1.48); HRMS (CI) *m*/*z* 309.2059 ($M^+ + C_2H_5$, 76, $C_{18}H_{29}O_4$ required 309.2065), 281 ($M^+ + 1$, 100), 280 (M^+, 88), 263 (92), 249 (42), 231 (48), 209 (63), 193 (82); IR (NaCl) ν_{max} 3445, 1730, 1684, 1618 cm^{-1}; ^{1}H NMR (200 MHz) δ 3.64 (s, 3H, –OMe), 3.15–3.09 (m, 1H, H-1), 2.63 (br. d, *J*=18.6 Hz, 1H, H-6), 2.46–2.23 (m, 3H, H-6′, H-9, H-11), 2.39 (d, *J*=4.8 Hz, 2H, 2H-2, overlapped with H-6′, H-9, H-11), 2.15–2.05 (m, 1H, H-7), 1.93 (dt, *J*=2.9, 8.9 Hz, 1H, H-9′), 1.58 (s, 3H, 3H-15), 1.12 (d, *J*=7.1 Hz, 3H, 3H-13), 0.82 (s, 3H, 3H-14); ^{13}C NMR (50.3 MHz) δ 208.4, 175.7, 171.9, 138.1, 74.3 (C, C-3, C-12, C-5, C-4, C-10), 51.7 (CH, C-1), 51.6 (CH_3, $-OCH_3$), 45.2, 38.5 (CH, C-7, C-11), 46.0, 37.5, 36.0, 28.8 (CH_2, C-2, C-6, C-9, C-8), 20.5, 12.7, 8.0 (CH_3, C-14, C-13, C-15).

3.2.10. Compound 5c. 70%; oil; $[\alpha]_D^{18}=+51.5$ (*c* 1.78); HRMS (CI) *m*/*z* 263 ($M^+ + 1$, 100), 262.1566 (M^+, 45, $C_{16}H_{22}O_3$ required 262.1568), 261 (7), 247 (7), 231 (9), 175 (41); IR (NaCl) ν_{max} 1730, 1707, 1631 cm^{-1}; ^{1}H NMR (300 MHz) δ 4,84 (s, 1H, H-14), 4.77 (s, 1H, H-14′), 3.66 (s, 3H, –OMe), 3.57–3.53 (m, 1H, H-1), 2.65 (ddd, *J*=0.6, 6.6, 18.6 Hz, 1H, H-9), 2.55 (br. d, *J*=18.6 Hz, 1H, H-6), 2.47 (br. dd, *J*=3.3, 13.8 Hz, 1H, H-2), 2.42 (dq, *J*=6.9, 7.2 Hz, 1H, H-11), 2.32–2.27 (m, 1H, H-7), 2.29 (dd, *J*=2.7, 18.6 Hz, 1H, H-6′), 2.23–2.09 (m, 2H, H-2′, H-9′), 1.61 (s, 3H, 3H-15), 1.13 (d, *J*=6.9 Hz, 3H, 3H-13); ^{13}C NMR (75.4 MHz) 208.3, 175.9, 173.5, 149.7, 135.6 (C, C-3, C-12, C-4, C-5, C-10), 111.0 (CH_2, C-14), 51.6 (CH_3, $-OCH_3$), 46.7, 44.5 (CH, C-1, C-7), 42.0 (CH_2, C-2), 36.9 (CH, C-11), 35.1, 34.3, 32.5 (CH_2, C-6, C-8, C-9), 13.8, 8.0 (CH_3, C-13, C-15).

3.2.11. 3-Oxo-1,7,10α*H*,6,11β*H*-guai-4-en-6,12-olide (4d). A mixture of compound **4c** (600 mg, 2.43 mmol), EtOAc (21 mL) and 5% Pd/C (167 mg) was vigorously stirred under H_2 (1 atm) for 2 h. The catalyst was removed by filtration on silica gel (EtOAc), the filtrate concentrated under vacuum and the residue chromatographed with 6:4–4:6 hexane–EtOAc mixtures to separate 30 mg (5%) of **4c** and 530 mg (88%) of compound **4d**: oil; $[\alpha]_D^{22}=+185.0$ (*c* 0.70) [lit.[9] $[\alpha]_D=+200$]; MS (CI) *m*/*z* 249 ($M^+ + 1$, 100), 248 (M^+, 20), 220 (6), 175 (5); IR (NaCl) ν_{max} 1778, 1700, 1305 cm^{-1}; ^{1}H NMR (200 MHz) δ 4.82 (br. d, *J*=10.6 Hz, 1H, H-6), 3.20–3.10 (m, 1H, H-1), 2.65 (dd, *J*=6.6, 19.1 Hz, 1H, H-2), 2.29 (dq, *J*=6.9, 11.5 Hz, 1H, H-11), 2.25–1.92 (m, 3H, H-2′, H-7, H-10), 1.86 (s, 3H, 3H-15), 1.24 (d, *J*=6.9 Hz, 3H, 3H-13), 0.66 (d, *J*=7.2 Hz, 3H, 3H-14); ^{13}C NMR (50.3 MHz) δ 207.7, 177.5, 164.0, 142.2 (C, C-3, C-12, C-5, C-4), 81.7, 48.8, 44.3, 41.3 (CH, C-6, C-7, C-1, C-11), 40.7, 35.1 (CH_2, C-2, C-9), 34.9 (CH, C-10), 24.8 (CH_2, C-8), 12.2, 12.2, 9.0 (CH_3, C-13, C-14, C-15).

3.2.12. (11*S*)-3-Oxo-1,7,10α*H*-guai-4-en-12-oic acid (5d). By the same general procedure used in the synthesis of **3a**–**3g** and **5a**–**5c**, compound **4d** (380 mg, 1.53 mmol) gave 330 mg (86%) of acid **5d**: mp 124–125°C (hexane–EtOAc) [lit.[9] mp 136–136.5°C (hexane–isopropyl ether)]; $[\alpha]_D^{17}=+141.1$ (*c* 1.80); HRMS (CI) *m/z* 250.1567 (M^+, 44, $C_{15}H_{22}O_3$ required 250.1570), 248 (6), 177 (100), 176 (13); IR (KBr) ν_{max} 3200–2600, 1736, 1689, 1616 cm^{-1}; ^1H NMR (400 MHz) δ 3.14–3.08 (m, 1H, H-1), 2.70 (br. d, *J*=19.2 Hz, 1H, H-6), 2.57 (dd, *J*=6.4, 18.8 Hz, 1H, H-2), 2.52 (dq, *J*=4.8, 7.2 Hz, 1H, H-11), 2.40 (dd, *J*=12.0, 19.2 Hz, 1H, H-6′), 2.15–2.08 (m, 2H, H-7, H-10), 2.04 (br. d, *J*=18.8 Hz, 1H, H-2′), 1.81 (br. ddd, *J*=4.0, 6.8, 14.0 Hz, 1H, H-9), 1.72–1.66 (m, 2H, H-8, H-9′), 1.64 (s, 3H, 3H-15), 1.39 (ddt, *J*=3.2, 10.8, 14.0 Hz, 1H, H-8′), 1.19 (d, *J*=7.2 Hz, 3H, 3H-13), 0.60 (d, *J*=6.8, 3H, 3H-14); ^{13}C NMR (50.3 MHz) δ 208.8, 180.5, 175.4, 137.1 (C, C-3, C-12, C-5, C-4), 45.8, 45.3 (CH, C-1, C-11), 41.0 (CH_2, C-2), 38.6 (CH, C-7), 36.5, 36.3 (CH_2, C-6, C-9), 35.1 (CH, C-10), 27.9 (CH_2, C-8), 12.2, 11.9, 7.9 (CH_3, C-13, C-14, C-15).

3.2.13. Methyl (11*S*)-3-oxo-1,7,10α*H*-guai-4-en-12-oate (8). To a solution of compound **5d** (330 mg, 1.32 mmol) in CH_2Cl_2 was added ethereal diazomethane in excess and the reaction mixture was stirred for 1 h. After solvent removal, the residue was chromatographed (8:2 hexane–EtOAc) to yield 279 mg (80%) of methyl ester **8** as a colourless oil with the following features: $[\alpha]_D^{18}=+175.5$ (*c* 0.77); HRMS (CI) *m/z* 265 (M^++1, 27), 264.1725 (M^+, 95, $C_{16}H_{24}O_3$ required 264.1725), 232 (36), 178 (60), 176 (100); IR (NaCl) ν_{max} 1730, 1690, 1630 cm^{-1}; ^1H NMR (400 MHz) δ 3.68 (s, 3H, $-OCH_3$), 3.12–3.06 (m, 1H, H-1), 2.64 (br. d, *J*=19.6 Hz, 1H, H-6), 2.54 (dd, *J*=6.4, 19.2 Hz, 1H, H-2), 2.47 (dq, *J*=5.2, 7.2 Hz, 1H, H-11), 2.34 (br. dd, *J*=12.8, 19.6 Hz, 1H, H-6′), 2.11–2.04 (m, 2H, H-7, H-10), 2.01 (d, *J*=19.2 Hz, 1H, H-2′), 1.79 (ddd, *J*=4.0, 7.6, 14.0 Hz, 1H, H-9), 1.71–1.65 (m, 2H, H-8, H-9′), 1.63 (br. s, 3H, 3H-15), 1.38–1.28 (m, 1H, H-8′), 1.16 (d, *J*=7.2 Hz, 3H, 3H-13), 0.59 (d, *J*=7.2 Hz, 3H, 3H-14); ^{13}C NMR (50.3 MHz) δ 208.0, 175.7, 174.4, 137.6 (C, C-3, C-12, C-5, C-4), 51.5 (CH_3, $-OCH_3$), 45.6, 45.3 (CH, C-1, C-11), 41.1 (CH_2, C-2), 38.9 (CH, C-7), 36.3 (CH_2, C-6, C-9), 35.1 (CH, C-10), 28.0 (CH_2, C-8), 12.6, 11.9, 7.8 (CH_3, C-13, C-14, C-15).

3.2.14. (11*S*)-3-Oxo-1,7,10α*H*-guai-4-en-12-ol (10). To a suspension of $LiAlH_4$ (150 mg, 3.97 mmol) in dry 35 mL of THF cooled at 0°C under argon was added via syringe a solution of compound **8** (175 mg, 0.66 mmol) in 4 mL of THF. The reaction mixture was stirred for 15 min and quenched at 0°C with saturated aqueous NH_4Cl. The mixture was extracted with ether and dried on anhydrous Na_2SO_4 and the solvent removed under vacuum to afford a mixture of epimeric diols **9** [^1H NMR (200 MHz) δ 4.65–4.40 (two m, H-3), 3.70–3.35 (two m, 2H-12)] as an oil which was used in the following step without purification.

To a solution of diols **9** in $CHCl_3$ (8.7 mL, filtered through basic alumina) was added MnO_2 (745 mg, 7.94 mmol) and the mixture was stirred at rt. After 6 h an additional portion of MnO_2 (745 mg, 7.94 mmol) was added and vigorous stirring continued for 18 h. The solid was filtered off through silica gel (EtOAc), the solvent removed under vacuum and the residue chromatographed with 7:3–5:5 mixtures of hexane–EtOAc to give 125 mg (80%) of compound **10**: oil; $[\alpha]_D^{19}=+142.0$ (*c* 1.0); HRMS (CI) *m/z* 237 (M^++1, 100), 236.1782 (M^+, 56, $C_{15}H_{24}O_2$ required 236.1776), 218 (48), 176 (20); IR (NaCl) ν_{max} 3500–3300, 1692, 1627, 1043 cm^{-1}; ^1H NMR (400 MHz) δ 3.58 (dd, *J*=7.6, 10.8 Hz, 1H, H-12), 3.52 (dd, *J*=6.4, 10.8 Hz, 1H, H-12′), 3.14–3.08 (m, 1H, H-1), 2.62 (br. d, *J*=19.6 Hz, 1H, H-6), 2.54 (ddd, *J*=1.2, 6.8, 18.8 Hz, 1H, H-2), 2.40 (dd, *J*=12.4, 19.6 Hz, 1H, H-6′), 2.11–2.06 (m, 1H, H-10), 2.01 (dd, *J*=2.0, 18.8 Hz, 1H, H-2′), 1.91 (dddd, *J*=2.8, 3.2, 10.8, 12.4 Hz, 1H, H-7), 1.84–1.78 (m, 1H, H-9), 1.76–1.60 (m, 3H, H-8, H-9′, H-11), 1.64 (d, *J*=1.2 Hz, 3H, 3H-15), 1.27 (dddd, *J*=3.6, 10.8, 13.6, 14.0 Hz, 1H, H-8′), 0.88 (d, *J*=6.8 Hz, 3H, 3H-13), 0.60 (d, *J*=7.2 Hz, 3H, 3H-14); ^{13}C NMR (50.3 MHz) δ 208.5, 176.1, 137.4 (C, C-3, C-5, C-4), 65.8 (CH_2, C-12), 45.8, 42.1 (CH, C-1, C-11), 41.3, 37.3 (CH_2, C-2, C-9), 37.1 (CH, C-7), 36.7 (CH_2, C-6), 35.4 (CH, C-10), 26.5 (CH_2, C-8), 12.1, 11.9, 7.9 (CH_3, C-13, C-14, C-15).

3.2.15. (11*S*)-12-*o*-Nitrophenylselenyl-1,7,10α*H*-guai-4-en-3-one (11). To a suspension of compound **10** (52 mg, 0.22 mmol) and *o*-nitrophenylselenocyanate (122 mg, 0.53 mmol) in THF (2.7 mL) at rt and under argon, was added via syringe *n*-Bu_3P (175 μL, 0.682 mmol). After 1 h, the resulting solution was separated from a yellow precipitate which was washed with ether. The organic solvents were removed under reduced pressure and the residue was chromatographed on silica gel (7:3 hexane–EtOAc) to give 85 mg (92%) of compound **11** as a yellow oil, IR (NaCl) ν_{max} 1685, 1625, 1585, 1560, 1505, 1330 cm^{-1}; ^1H NMR (200 MHz) δ 8.25 (d, *J*=8.4 Hz, 1H, Ar-H), 7.50–7.48 (m, 2H, 2Ar-H), 7.32–7.28 (m,1 H, Ar-H), 3.10–3.00 (m, 1H, H-1), 2.96 (dd, *J*=6.6, 11.7 Hz, 1H, H-12), 2.81 (td, *J*=7.3, 11.7 Hz, 1H, H-12′), 2.61 (br. d, *J*=19.7 Hz, 1H, H-6), 2.51 (dd, *J*=6.4, 18.3 Hz, 1H, H-2), 2.39 (dd, *J*=11.7, 19.5 Hz, 1H, H-6′), 1.62 (br. s, 3H, 3H-15), 1.00 (d, *J*=6.6 Hz, 3H, 3H-13), 0.59 (d, *J*=6.6 Hz, 3H, 3H-14); ^{13}C NMR (50.3 MHz) δ 208.1, 174.8, 137.6, 146.9 (C, C-3, C-5, C-4, Ar), 133.5 (CH, Ar), 133.2 (C, Ar), 129.0, 126.4, 125.3 (CH, Ar), 45.7 (CH, C-1), 41.2 (CH_2, C-2), 40.6, 38.7 (CH, C-11, C-7), 37.0, 36.0 (CH_2, C-6, C-9), 35.2 (CH, C-10), 31.6, 26.4 (CH_2, C-12, C-8), 15.9, 12.0, 8.0 (CH_3, C-13, C-14, C-15).

3.2.16. 1,7,10α*H*-Guai-4,11-dien-3-one (6). A solution of compound **11** (39 mg, 0.09 mmol) in THF (2.4 mL) at 0°C was treated with 30% H_2O_2 (230 μL) and after removal of the ice bath the temperature was allowed to rise to rt. The reaction mixture was stirred for 4.5 h, diluted with EtOAc and extracted in the usual way. Chromatography of the residue with 8:2 hexane–EtOAc eluted 19 mg (95%) of compound **6** as an oil which presented the following features: $[\alpha]_D^{23}=+157.1$ (*c* 0.84) [lit.[12] $[\alpha]_D^{24}=+63$ (*c* 0.23)]; HRMS (CI) *m/z* 219 (M^++1, 100), 218.1620 (M^+, 15, $C_{15}H_{22}O$ required 218.1670), 163 (5), 161 (3), 109 (3); IR (NaCl) ν_{max} 1693, 1630 cm^{-1}; ^1H NMR (400 MHz) δ 4.73 (br. s, 1H, H-12), 4.68 (br. s, 1H, H-12′), 3.14–3.08 (m, 1H, H-1), 2.75 (br. d, *J*=19.2 Hz, 1H, H-6), 2.57 (dd, *J*=6.4,

18.8 Hz, 1H, H-2), 2.47 (br. dd, J=12.0, 19.2 Hz, 1H, H-6′), 2.31 (br. dd, J=10.8, 12.0 Hz, 1H, H-7), 2.12–2.07 (m, 1H, H-10), 2.03 (d, J=18.8 Hz, 1H, H-2′), 1.85–1.80 (m, 1H, H-9), 1.75 (br. s, 3H, 3H-15), 1.77–1.68 (m, 2H, H-8, H-9′), 1.64 (br. s, 3H, 3H-13), 1.64–1.50 (m, 1H, H-8′), 0.63 (d, J=7.2 Hz, 3H, 3H-14); ^{13}C NMR (50.3 MHz) δ 208.1, 175.2, 150.8, 137.5 (C, C-3, C-5, C-11, C-4), 108.8 (CH_2, C-12), 45.9, 44.4 (CH, C-1, C-7), 41.2, 37.9, 36.6 (CH_2, C-2, C-6, C-9), 35.3 (CH, C-10), 31.2 (CH_2, C-8), 20.0, 12.0, 7.9 (CH_3, C-13, C-14, C-15).

3.2.17. 3-Oxo-1,7,10α*H*-guai-4-en-11-ol (hydrocolorenone) (7). To a solution of compound **6** (19 mg, 0.087 mmol) in 0.54 mL of 1:1 THF–H_2O mixture were added 29 mg (0.09 mmol) of $Hg(OAc)_2$ and the mixture was stirred at rt for 30 min. To quench the reaction it was first diluted with ether (0.27 mL), cooled to 0°C and it was added dropwise 3 M NaOH (0.1 mL) and 0.5 M aqueous $NaBH_4$ (0.1 mg) and 69 mg of NaCl. The resulting mixture was vigorously stirred at 0°C for 10 min diluted with ether and water and extracted in the usual way. Chromatography with 1:1 hexane–EtOAc as eluent afforded 19 mg (91%) of compound **7** as an oil with the following features: $[\alpha]_D^{21}$=+103.8 (c 0.79) [lit.[13] $[\alpha]_D$=+58.6 (c 0.46); lit.[14] $[\alpha]_D^{24}$=+18 (c 0.2)]; HRMS (CI) m/z 237.1857 (M^++1, 88, $C_{15}H_{25}O_2$ required 237.1885), 219 (100), 218 (35), 177 (11), 163 (23); IR (KBr) ν_{max} 3500–3300, 1681, 1625 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.12–3.06 (m, 1H, H-1), 3.07 (br. d, J=19.6 Hz, 1H, H-6), 2.54 (ddd, J=1.2, 6.4, 18.4 Hz, 1H, H-2), 2.18 (br. dd, J=12.4, 19.6 Hz, 1H, H-6′), 2.12–2.09 (m, 1H, H-10), 2.03 (br. d, J=18.4 Hz, 1H, H-2′), 1.93–1.87 (m, 1H, H-8), 1.86–1.81 (m, 1H, H-9), 1.71–1.64 (m, 2H, H-7, H-9′), 1.66 (d, J=1.2 Hz, 3H, 3H-15), 1.28–1.23 (m, 1H, H-8′), 1.26 (s, 3H, 3H-12), 1.21 (s, 3H, 3H-13), 0.61 (d, J=7.2 Hz, 3H, 3H-14); ^{1}H NMR (400 MHz, CD_3COCD_3) δ 3.16–3.12 (m, 1H, H-1), 3.14 (br. d, J=19.5 Hz, 1H, H-6), 2.46 (ddd, J=1.2, 6.6, 18.3 Hz, 1H, H-2), 2.24 (br. dd, J=11.6, 19.5 Hz, 1H, H-6′), 2.15–2.07 (m, 1H, H-10), 1.96–1.89 (m, 1H, H-8), 1.92 (ddd, J=1.2, 1.8, 18.6 Hz, 1H, H-2′), 1.83 (dddd, J=3.0, 3.6, 4.5, 13.7 Hz, 1H, H-9), 1.73 (dddd, J=3.0, 3.6, 10.2, 13.6 Hz, 1H, H-9′), 1.72–1.64 (m, 1H, H-7), 1.50 (q, J=1.5 Hz, 3H, 3H-15), 1.34–1.25 (m, 1H, H-8′), 1.21 (s, 3H, 3H-12), 1.17 (s, 3H, 3H-13), 0.62 (d, J=6.9 Hz, 3H, 3H-14); ^{13}C NMR (50.3 MHz, $CDCl_3$) δ 208.4, 175.4, 137.8, 73.1 (C, C-3, C-5, C-4, C-11), 48.0, 45.7 (CH, C-7, C-1), 41.3, 36.8 (CH_2, C-2, C-9), 35.3 (CH, C-10), 33.7, 27.1 (CH_2, C-6, C-8), 27.4, 26.0, 12.2, 8.0 (CH_3, C-12, C-13, C-14, C-15); ^{13}C NMR (75.4 MHz, CD_3COCD_3) δ 206.3, 175.0, 137.1, 71.8 (C, C-3, C-5, C-4, C-11), 48.3, 45.4 (CH, C-7, C-1), 41.1, 37.0 (CH_2, C-2, C-9), 35.8 (CH, C-10), 33.7, 27.1 (CH_2, C-6, C-8), 26.8, 25.7, 11.8, 7.3 (CH_3, C-12, C-13, C-14, C-15).

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