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Synthesis of (+)-pechueloic acid and (+)-aciphyllene. Revision of the structure of (+)-aciphyllene

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Abstract—1α*H*,7α*H*,10α*H*-Guaia-4,11-dien-3-one and its 1β*H*,10β*H* diastereomer, easily obtained from (+)-dihydrocarvone, are good starting materials for the synthesis of natural guaiane derivatives. Allylic oxidation of the 1α*H*,10α*H* isomer gave as main product its 13-hydroxy derivative and a small amount of (+)-7β-hydroxy-1α*H*,10α*H*-guaia-4,11-dien-3-one, whereas the 1β*H*,10β*H* diastereomer afforded selectively the (−)-7α-hydroxy-1β*H*,10β*H* enantiomer in excellent yield. From the 13-hydroxy derivative (+)-pechueloic acid and (+)-methyl pechueloate were synthesized. Deoxygenation at C_3 of the 1β*H*,10β*H* guaiadienone afforded a guaiadiene with the reported structure for aciphyllene but its spectral data did not agree with those reported for the natural diene. The structure of natural (+)-aciphyllene has been corrected to 1α*H*,7α*H*,10α*H*-guaia-4,11-diene obtained by deoxygenation of the 1α*H*,10α*H* guaiadienone.

1. Introduction

The guaianes constitute a large group of naturally occurring compounds with a wide spectrum of biological activities.[1,2] The need of an exact knowledge of their structures as well as their low availability from natural sources has aroused a great interest in their synthesis.[2,3] Some guaianes are characterized by the presence of 1*H*,7*H*,10*H* hydrogen atoms in their structures and a common problem in the structural determination is the assignment of the configuration at C_1, C_7 and C_{10}. However, the synthesis of the hydroazulene framework with the desired functionalization and stereochemistry presents many difficulties and only a few syntheses of 1*H*,7*H*,10*H*-guaiane derivatives can be found in the literature.[3–6] Recently we have reported a straightforward synthesis of natural guaia-4,11-dien-3-ones **1** and **2** (Fig. 1), as well as their 1*H*,10*H*-*trans* diastereomers **3** and **4**, starting from (+)-dihydrocarvone (**5**).[7] Compounds **1** and **2** have also been synthesized from santonin by Loewenthal and colleagues[4] (compound **2**) and by our group (compound **1**).[5]

Several compounds related to guaiadienones **1** and **2** have also been reported from natural sources (Fig. 1). Methyl pechueloate (**6**) was first reported in *Pechuel-Loeschea leibnitziae*,[8] and later isolated from *Decachaeta scabrella* together with the parent acid **7** (pechueloic acid) and its 11,12-dihydro derivative **8**.[9] 13-Functionalized derivatives of **2** have also been reported, such as compound **9** in *Jungia stuebelii*,[10] and esters **10** and **11** in *Moscharia pinnatifida*.[11,12] Structure **12** was assigned by Yu and colleagues to rupestonic acid isolated from *Artemisia rupestris*,[13] but

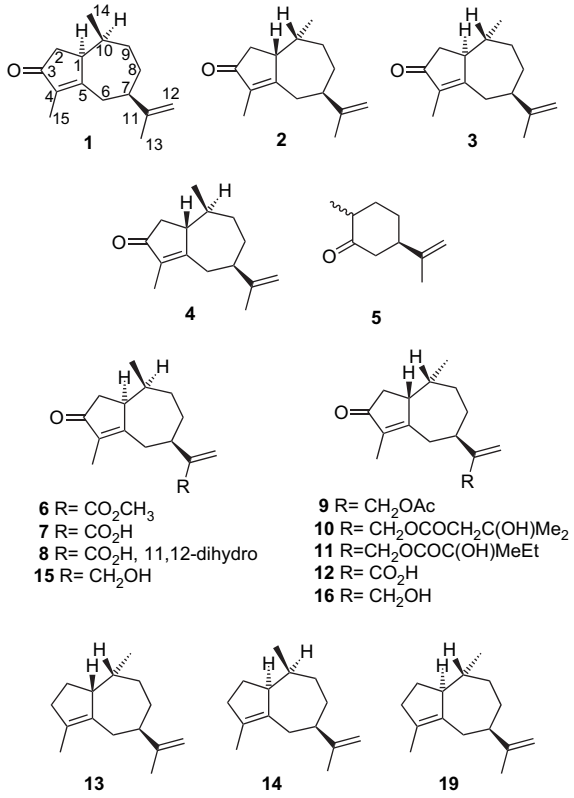

Figure 1. Guaia-4,11-dien-3-ones and their natural and synthetic derivatives.

Keywords: Sesquiterpene synthesis; Guaiadienones; Pechueloic acid; Aciphyllene.
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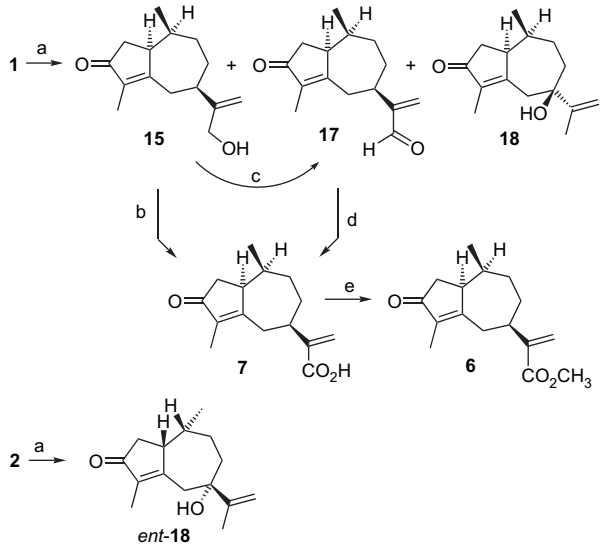
recently, in a review Wu draws for this acid the antipode structure of pechueloic acid (**7**).[14] On the other hand, structure **13**, the 3-deoxy derivative of guaiadienone **2**, has been assigned to (+)-aciphyllene, a guaiadiene isolated for the first time from the essential oil of the roots of *Lindera glauca*.[15] This diene has also been reported as a component of the essential oil of the liverwort *Dumortiera hirsuta* [(+)-enantiomer],[16] and of several medicinally valuable sources (*Shorea robusta*,[17] *Toona sinensis*,[18] *Pogostemon cablin*[19,20]). It is also a component of the volatile blends let out by *Ficus* trees to attract their specific pollinating wasps.[21]

As a continuation of our research programme on the synthesis of biologically active sesquiterpenoids, we now want to report the synthesis of pechueloic acid (**7**) and methyl pechueloate (**6**) from guaiadienone **1** and the reported structure for aciphyllene (**13**) from compound **2**. As the spectral data of the synthetic diene did not agree with those reported for the natural product isolated from *D. hirsuta*,[16] the structure of natural aciphyllene has been revised to 1α*H*,7α*H*,10α*H*-guaia-4,11-diene (**14**) which has been obtained by deoxygenation of the 1α*H*,10α*H* guaiadienone **1**.

2. Results and discussion

From compounds **1** and **2** the synthesis of several 1*H*,10*H*-guaiane derivatives was possible. First we carried out a comparative study of the allylic oxidation at C_{13} of both guaiadienones (Scheme 1). The allylic alcohols resulting from the C-13 oxidation, **15** and **16**, respectively (Fig. 1), could be good intermediates for the synthesis of other C-13 functionalized natural guaianes, such as **6** and **7** starting from **15** and **9**–**12** starting from **16**. The system SeO_2–*t*-BuOOH in CH_2Cl_2[22] was chosen to carry out the allylic oxidation as it afforded us good results in a similar transformation.[23] However, with this reagent compound **1** showed low reactivity at two reactive points at C-13 and C-7 giving variable amounts of the desired primary alcohol **15**, the corresponding aldehyde **17** and the tertiary alcohol **18**. The best results on allylic alcohol **15** (28% yield, 56% yield on consumed **1**) were obtained with the addition of SeO_2 (1 equiv) and *t*-BuOOH (7.5 equiv) in two portions at 16 h interval and 40 h total reaction time. In these conditions a significant amount of compound **1** (50%) was recovered unchanged but no aldehyde **17** or 7-hydroxy derivative **18** was isolated in significant yield.[24] The configuration at C_7 of tertiary alcohol **18** was established by NOE experiments, and the positive NOE effect between H_1 and H_{12} indicates an α disposition of the isopropenyl side chain (Fig. 2).



Scheme 1. Reagents and conditions: (a) SeO_2, *t*-BuOOH, CH_2Cl_2, 0 °C; (b) Jones reagent, acetone, −20 °C; (c) CrO_3–3,5-DMP, CH_2Cl_2, rt; (d) $NaClO_2$, NaH_2PO_4, 2-methyl-2-butene, *t*-BuOH–H_2O, rt; (e) CH_2N_2, ether, rt.

On the other hand, the behaviour of compound **2** in the allylic oxidation was quite different from that of its diastereomer **1**, and afforded after 8 h 7-hydroxy derivative *ent*-**18** in high yield (94%) (Scheme 1). This compound presented the same spectral features as those of **18** obtained by oxidation of guaiadienone **1**. The opposite values of their optical rotation signs, $[\alpha]_D^{24}$ −141 for **18** and $[\alpha]_D^{24}$ +144 for the new compound *ent*-**18**, indicated the enantiomer relationship between **18** and *ent*-**18**. The complete regioselectivity in the allylic oxidation of **2** agrees with the order proposed by Bhalerao and Rapoport for the oxidation of disubstituted olefins ($CH>CH_2>CH_3$),[25] although the isolation of the tertiary alcohol as the only reaction product is not frequent. More interesting is the different stereoselectivity in the formation of the tertiary alcohols **18** and *ent*-**18**. Scheme 2 shows the proposed pathways for the hydroxylation reactions.[26] In the ene addition, from compound **2** only allyl seleninic ester $\mathbf{a_1}$ is favoured, but for compound **1** the formation of two esters $\mathbf{a_2}$ and $\mathbf{a_3}$ should result from their relative stability and the steric bias of the molecule. The α or β disposition of the C_7-OH in **18** and *ent*-**18** results from the preferred spatial disposition of the seleninic ester group in the 2,3-sigmatropic rearrangement, from the α face for $\mathbf{a_1}$ and from the β face for $\mathbf{a_3}$, to afford $\mathbf{b_1}$ and $\mathbf{b_3}$ which are hydrolyzed by *t*-BuOOH to *ent*-**18** and **18**, respectively.

The undesired results in the allylic oxidation of compound **2** drove us to direct our efforts only to the synthesis of the 1α*H*,10α*H* derivatives **6** and **7** from allylic alcohol **15**. The oxidation of **15** with Jones reagent at −20 °C afforded in a short time (10 min) aldehyde **17** (TLC) and after 3 h a mixture of two α,β-unsaturated acids, one of them being the minor product and probably epimer of the main product.

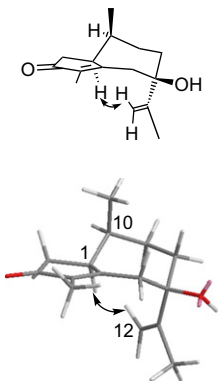
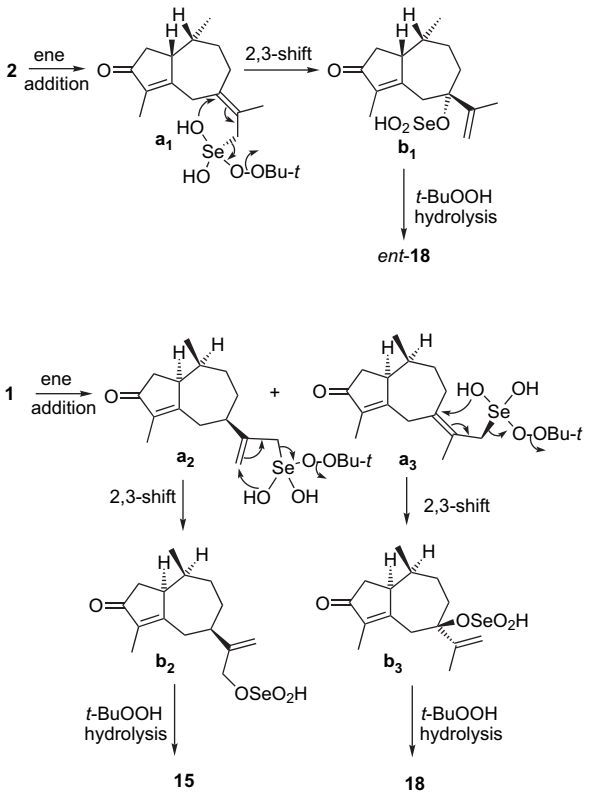


Figure 2. Conformational depiction of compound **18** and observed H_1–H_{12} NOE.



Scheme 2. Proposed pathways for the hydroxylation of guaiadienones **1** and **2**.

By column chromatography a small amount of aldehyde **17** (5%) and α,β-unsaturated acid **7** (30% yield) were separated. These results were improved by a two-step oxidation sequence. Treatment of **15** with CrO_3–3,5-dimethylpyrazole[27] at 0 °C gave aldehyde **17** (75%) and further oxidation with $NaClO_2$ in presence of a small amount of 2-methyl-2-butene[28] afforded the α,β-unsaturated acid **7** in 56% yield (42% for the two steps). The physical and spectral features of compound **7** agree with those reported for pechueloic acid isolated from *D. scabrella*.[9] Esterification of **7** with an ethereal solution of diazomethane gave in quantitative yield ester **6** with the same physical and spectral features as those of methyl pechueloate isolated by Bohlmann and colleague from *P.-L. leibnitiziae*.[8]

On the other hand, for the synthesis of guaiadiene **13** a straightforward approach was possible by direct deoxygenation at C_3 of guaiadienone **2**. So, treatment of **2** at −20 °C with $LiAlH_4$–$AlCl_3$[29] afforded in 50% yield a compound whose spectral features agreed with structure **13**. Nevertheless its ^1H and ^{13}C NMR spectral data differed from those reported for aciphyllene isolated from *D. hirsuta*,[16] specially in the NMR values for H_1, H_{10} and H_{14}, and C_{14} (Table 1). A possible C_1 epimerization under the reaction conditions was discarded as we disposed off the 1α*H*,10β*H* diastereomer **3**,[7] whose deoxygenation in the same reaction conditions afforded a new guaiadiene **19** (52%) (Fig. 1). The spectral features of compound **19** also differed from those of the natural aciphyllene (Table 1),[16] and a revision of its structure was needed.

From a comparison of the spectral features of the natural aciphyllene with those of **13** and **19** and the patterns observed in the ^1H and ^{13}C NMR features of diastereomers **1**–**4** (Table 1) a 1α*H*,10α*H* disposition for natural aciphyllene could be proposed, guaiadienone **1** being its parent compound. So, deoxygenation of **1** with $LiAlH_4$–$AlCl_3$ afforded in 78% yield compound **14** with the same spectral features and optical rotation sign as (+)-aciphyllene isolated from *D. hirsuta*.[16]

3. Conclusion

In conclusion, 1α*H*,7α*H*,10α*H*-guaia-4,11-dien-3-one (**1**) and its 1β*H*,10β*H* diastereomer **2**, easily obtained from (+)-dihydrocarvone (**5**), are good starting materials for the synthesis of other guaiane derivatives. Allylic oxidation of the 1α*H*,10α*H* isomer **1** gave the 13-hydroxy derivative **15** as the main product besides a small amount of (+)-7β-hydroxy-1α*H*,10α*H*-guaia-4,11-dien-3-one (**18**). Natural (+)-pechueloic acid (**7**) and (+)-methyl pechueloate (**6**) have been synthesized from 13-hydroxy derivative **15** and their structures as well as their absolute configuration have been confirmed. Selective allylic oxidation was observed for the 1β*H*,10β*H* guaiadienone diastereomer **2** to afford the (−)-7α-hydroxy-1β*H*,10β*H*-guaia-4,11-dien-3-one (*ent*-**18**) in excellent yield. On the other hand, deoxygenation at C_3 of the 1β*H*,10β*H* guaiadienone **2** afforded a diene with the reported structure for aciphyllene but its spectral data did not agree with those reported for the natural diene. The structure of natural (+)-aciphyllene has been corrected to 1α*H*,7α*H*,10α*H*-guaia-4,11-diene (**14**) obtained by deoxygenation of the 1α*H*,7α*H*,10α*H* guaiadienone **1**.

Table 1. Selected ^1H and ^{13}C NMR data for guaiadienones **1**–**4**,[7] guaiadienes **13**, **14** and **19**, and natural aciphyllene[16]

Compound	^1H NMR [δ_H, m, *J* (Hz) in parentheses][a]			^{13}C NMR (δ_C)[a]		
	H_1	H_{10}	H_{14}	C_1	C_{10}	C_{14}
1 (1α*H*,10α*H*)	3.15–3.10, m	2.15–2.07, m	0.65, d (7.2)	45.9	35.3	12.0
2 (1β*H*,10β*H*)	3.02–2.96, m	2.14, br dq (6.8, 8.0)	0.95, d (6.8)	46.8	34.2	19.8
3 (1α*H*,10β*H*)	2.63–2.57, m	1.45–1.32, m	1.03, d (6.0)	48.7	40.0	22.6
4 (1β*H*,10α*H*)	2.40–2.25, m	1.31–1.20, m	1.04, d (6.6)	50.3	40.9	22.8
13 (1β*H*,10β*H*)	2.77–2.68, m	2.00–1.90, m	0.89, d (7.2)	52.9	36.1	20.1
19 (1α*H*,10β*H*)	2.36–2.28, m	1.46–1.18, m	0.89, d (6.4)	55.7	39.2	21.6
14 (1α*H*,10α*H*)	2.99–2.92, m	1.90–1.80, m	0.76, d (7.1)	53.2	36.9	12.9
Aciphyllene[16]	2.95	1.80–1.90	0.75, d (7.0)	53.2	36.3	12.9

[a] At 400 MHz in $CDCl_3$ on the basis of DEPT, ^1H–^{13}C HSQC and ^1H–^1H decoupling experiments.

4. Experimental

4.1. General

All reagents are commercially available in analytical grade or were purified by standard procedures prior to use. All operations involving air or moisture sensitive materials were performed under an argon atmosphere using syringes, oven-dried glassware, and freshly distilled and dried solvents. Melting points were determined on a Büchi B-545 digital melting point apparatus and are uncorrected. Specific optical rotations were measured using a Perkin–Elmer 243 apparatus in $CHCl_3$ using sodium light (D line 589 nm). Reactions were monitored by TLC analysis using Merck silica gel 60 F_{254} thin layer plates. Column chromatography refers to flash chromatography and it was performed on Merck silica gel 60, 230–400 mesh. IR spectra were recorded as thin films on NaCl plates for oils and as KBr discs for solids. NMR spectra were run in $CDCl_3$ at 300 or 400 MHz for ^1H and at 75 or 100 MHz for ^{13}C, and referenced to the solvent as internal standard. For compounds **13**, **14** and **19** the solvent was filtered through basic alumina prior to use. Carbon substitution degrees were established by DEPT pulse sequences. A combination of HSQC, ^1H–^1H decoupling and NOE experiments was used in selected cases to aid assignment when necessary. Low and high resolution mass spectra were recorded on an Autospec GC 8000 apparatus by electron impact (EI) at 70 eV.

4.1.1. SeO_2–*t*-BuOOH allylic oxidation of compounds 1 and 2.

4.1.1.1. (+)-13-Hydroxy-1α*H*,7α*H*,10α*H*-guaia-4,11-dien-3-one (15). The reagent was prepared by reaction of SeO_2 (12 mg, 0.108 mmol) and *t*-BuOOH (78 μL, 0.80 mmol) in CH_2Cl_2 (1 mL) under argon at 0 °C for 30 min. To the resulting suspension was added a solution of compound **1** (47 mg, 0.215 mmol) in CH_2Cl_2 (1.3 mL) and the mixture was stirred at 0–6 °C for 16 h. After this time, additional portion of SeO_2 (12 mg, 0.108 mmol) and *t*-BuOOH (78 μL, 0.80 mmol) were added and stirring resumed for additional 24 h. The reaction was quenched with saturated aqueous $NaHCO_3$ and the mixture extracted with CH_2Cl_2, the combined organic layers were washed with brine, dried ($MgSO_4$) and the solvent removed at reduced pressure. Column chromatography with mixtures hexane–EtOAc (98:2 to 6:4) separated 24 mg (50%) of starting material **1** and 14 mg (28%) of hydroxy derivative **15**: colourless oil; $[\alpha]_D^{24}$ +139.6 (*c* 0.60); IR (NaCl) ν_{max} 3600–3200, 3090, 1690, 1626 cm^{-1}; MS (EI) *m/z* 234 (M^+, 52), 219 (5), 216 (100), 201 (37), 174 (46), 159 (58); HRMS (EI) *m/z* calcd for $C_{15}H_{22}O_2$: 234.1620. Found: 234.1630; ^1H NMR (400 MHz) δ 5.07 (1H, s), 4.98 (1H, s), 4.14 (2H, s), 3.16–3.10 (1H, m), 2.84 (1H, br d, *J*=18.8 Hz), 2.58 (1H, ddd, *J*=1.2, 6.6, 18.6 Hz), 2.497 (1H, br dd, *J*=11.2, 18.3 Hz), 2.38 (1H, br t, *J*=11.2 Hz), 2.16–2.08 (1H, m), 2.04 (1H, br d, *J*=18.8 Hz), 1.88–1.70 (2H, m), 1.70–1.56 (2H, m), 1.65 (3H, d, *J*=1.2 Hz), 0.66 (3H, d, *J*=7.2 Hz); ^{13}C NMR (75 MHz) δ 208.2 (s), 174.8 (s), 154.5 (s), 137.7 (s), 108.6 (t), 65.1 (t), 45.9 (d), 41.3 (t), 39.9 (d), 38.5 (t), 36.8 (t), 35.3 (d), 31.9 (t), 12.1 (q), 8.0 (q).

4.1.1.2. (−)-7β-Hydroxy-1β*H*,10β*H*-guaia-4,11-dien-3-one (*ent*-18). To a suspension of SeO_2 (4 mg, 0.034 mmol) and *t*-BuOOH (21 μL, 0.214 mmol) in CH_2Cl_2 (0.2 mL) prepared as previously reported, was added compound **2** (6 mg, 0.027 mmol) in CH_2Cl_2 (0.2 mL) and the mixture was stirred at 0 °C. After 5 h, additional portion of SeO_2 (4 mg, 0.034 mmol) and *t*-BuOOH (21 μL, 0.214 mmol) were added and stirring resumed to a total reaction time of 8 h. The reaction was quenched and extracted as previously reported and the solvent removed at reduced pressure to afford 6 mg (94%) of compound *ent*-**18** as a solid, which was characterized without further purification: white crystals, mp 103–105 °C (hexane–EtOAc); $[\alpha]_D^{24}$ −140.9 (*c* 0.53); IR (KBr) ν_{max} 3600–3200, 1685, 1638 cm^{-1}; MS (EI) *m/z* 234 (M^+, 17), 219 (3), 150 (43), 137 (45), 110 (100); HRMS (EI) *m/z* calcd for $C_{15}H_{22}O_2$: 234.1620. Found: 234.1626; ^1H NMR (400 MHz) δ 5.00 (1H, s), 4.91 (1H, s), 2.99–3.06 (1H, m), 2.87 (1H, d, *J*=14.8 Hz), 2.81 (1H, d, *J*=14.8 Hz), 2.44 (1H, dd, *J*=6.3, 18.2 Hz), 2.12–2.04 (1H, m), 2.05 (1H, dd, *J*=3.6, 18.2 Hz), 1.92 (1H, dddd, *J*=0.8, 3.2, 9.6, 14.6 Hz), 1.87 (3H, s), 1.82–1.74 (1H, m), 1.74 (3H, d, *J*=2.0 Hz), 1.43 (1H, dddd, *J*=2.4, 7.6, 10.0, 14.8 Hz), 1.37–1.28 (1H, m), 0.91 (3H, d, *J*=7.2 Hz); ^{13}C NMR (75 MHz) δ 208.5 (s), 171.3 (s), 150.1 (s), 140.0 (s), 111.1 (t), 76.4 (s), 46.6 (d), 40.5 (t), 39.8 (t), 38.5 (t), 34.5 (d), 27.8 (t), 19.0 (q), 17.5 (q), 8.6 (q).

4.1.2. (+)-Pechueloic acid and (+)-methyl pechueloate.

4.1.2.1. Jones reagent oxidation of compound 15: (+)-3-oxo-1α*H*,7α*H*,10α*H*-guaia-4,11-dien-12-oic acid [(+)-pechueloic acid] (7). To a solution of compound **15** (7.9 mg, 0.034 mmol) in acetone (0.9 mL) under argon at −20 °C was added dropwise 44 μL (0.119 mmol) of previously prepared 2.7 M Jones reagent. After 2 h an additional amount of reagent (0.119 mmol) was added to the mixture and stirring resumed for 1 h. The reaction was quenched with aqueous saturated $Na_2S_2O_3$, the acetone removed at reduced pressure and the mixture extracted with EtOAc. The combined organic layers were washed with water and brine and dried ($MgSO_4$). Removal of the solvent followed by column chromatography (hexane–EtOAc 8:2 to 4:6) separated 0.4 mg (5%) of aldehyde **17** and 2.6 mg (31%) of an oil which was identified as (+)-pechueloic acid **7**: colourless oil; $[\alpha]_D^{24}$ +67.6 (*c* 0.25); IR (NaCl) ν_{max} 3300–2800, 1716, 1691, 1621 cm^{-1}; MS (EI) *m/z* 248 (M^+, 100), 230 (36), 202 (24), 145 (19), 109 (39); HRMS (EI) *m/z* calcd for $C_{15}H_{20}O_3$: 248.1412. Found: 248.1422; ^1H NMR (400 MHz) δ 6.38 (1H, s, H_{12}), 5.76 (1H, s, $H_{12'}$), 3.22–3.16 (1H, m, H_1), 2.92 (1H, br t, *J*=10.4 Hz, H_7), 2.87 (1H, br d, *J*=19.6 Hz, H_6), 2.61 (1H, dd, *J*=6.8, 18.8 Hz, H_2), 2.47 (1H, dd, *J*=13.2, 18.8 Hz, $H_{6'}$), 2.18–2.10 (1H, m, H_{10}), 2.06 (1H, br d, *J*=19.2 Hz, $H_{2'}$), 1.88–1.76 (3H, m, H_8, $2H_9$), 1.74–1.60 (1H, m, $H_{8'}$), 1.65 (3H, br s, $3H_{15}$), 0.67 (3H, d, *J*=7.2 Hz, $3H_{14}$); ^{13}C NMR (100 MHz) δ 209.6 (s, C_3), 174.1, 170.6, 145.4, 137.9 (s, C_5, C_{13}, C_{11}, C_4), 125.6 (t, C_{12}), 45.9 (d, C_1), 41.3 (t, C_2), 38.3 (t, C_6), 37.7 (d, C_7), 36.6 (t, C_9), 35.3 (d, C_{10}), 31.6 (t, C_8), 12.1 (q, C_{14}), 8.0 (q, C_{15}).

4.1.2.2. Two-step oxidation of compound 15. (a) (+)-3-Oxo-1α*H*,7α*H*,10α*H*-guaia-4,11-dien-12-al (**17**). The reagent was prepared by stirring under argon a mixture of CrO_3 (21 mg, 0.212 mmol) and 3,5-DMP (20 mg, 0.212 mmol) in CH_2Cl_2 (0.3 mL) at −20 °C. After 30 min the temperature was raised to 0 °C and a solution of compound **15** (9 mg, 0.038 mmol) in CH_2Cl_2 (0.2 mL) was

added and the mixture stirred for 40 min at 0 °C. Filtration through silica gel topped with a Celite™ bed with ether as eluent afforded 6.7 mg (75%) of compound **17**: colourless oil; $[\alpha]_D^{24}$ +122.3 (*c* 0.34); IR (NaCl) ν_{max} 2810, 2720, 1692, 1632 cm^{-1}; MS (EI) *m/z* 232 (M^+, 100), 217 (15), 204 (18), 161 (26), 105 (27); HRMS (EI) *m/z* calcd for $C_{15}H_{20}O_2$: 232.1463. Found: 232.1468; ^1H NMR (400 MHz) δ 9.53 (1H, s), 6.35 (1H, s), 6.04 (1H, s), 3.23–3.17 (1H, m), 2.93 (1H, br dd, *J*=10.0, 12.0 Hz), 2.75 (1H, br d, *J*=19.2 Hz), 2.60 (1H, ddd, *J*=1.2, 6.4, 18.8 Hz), 2.43 (1H, br dd, *J*=12.0, 19.2 Hz), 2.19–2.12 (1H, m), 2.05 (1H, ddd, *J*=1.2, 1.6, 18.8 Hz), 1.86–1.79 (2H, m), 1.75–1.65 (2H, m), 1.63 (3H, q, *J*=1.6 Hz), 0.67 (3H, d, *J*=7.2 Hz); ^{13}C NMR ^{13}C (75 MHz) δ 208.1 (s), 194.0 (d), 173.9 (s), 155.6 (s), 137.9 (s), 133.2 (t), 45.8 (d), 41.3 (t), 37.7 (t), 36.5 (t), 35.3 (d), 34.6 (d), 31.1 (t), 12.1 (q), 8.0 (q).

(b) Oxidation of aldehyde **17**. To a solution of compound **17** (6.2 mg, 0.027 mmol) in 0.56 mL of *t*-BuOH at room temperature was added 2-methyl-2-butene (0.133 mL, 1.255 mmol) and after stirring for 5 min a solution of $NaClO_2$ (22 mg, 0.244 mmol) and NaH_2PO_4 (22 mg, 0.185 mmol) in 222 μL of H_2O was added to the mixture. After stirring for 50 min the excess of 2-methyl-2-butene was removed at reduced pressure, and the mixture was diluted with water and acidified with 1 M HCl to pH=4. Extraction with ether as usual followed by column chromatography over silica gel (hexane–EtOAc 8:2 to 4:6) gave 3.7 mg (56%) of compound **7** with identical spectral features to (+)-pechueloic acid obtained by oxidation of compound **15** with Jones reagent.

4.1.2.3. (+)-Methyl 3-oxo-1α*H*,7α*H*,10α*H*-guaia-4,11-dien-12-oate [(+)-methyl pechueloate] (6). A solution of compound **7** (2.6 mg, 0.010 mmol) in 0.2 mL of ether was treated with ethereal diazomethane till permanence of the yellow colour. The mixture was stirred at room temperature for 2 h and the solvent removed under vacuum to afford 2.7 mg (100%) of compound **6** as a colourless oil: $[\alpha]_D^{24}$ +35.5 (*c* 0.05)[lit.[8] $[\alpha]_D^{24}$ +24 (*c* 0.40)]; IR (NaCl) ν_{max} 1717, 1695, 1629 cm^{-1}; MS (EI) *m/z* 262 (M^+, 100), 247 (11), 230 (85), 202 (35), 176 (37); HRMS (EI) *m/z* calcd for $C_{16}H_{22}O_3$: 262.1569. Found: 262.1559; ^1H NMR (400 MHz) δ 6.22 (1H, s, H_{12}), 5.63 (1H, s, $H_{12'}$), 3.78 (3H, s, CH_3O), 3.22–3.17 (1H, m, H_1), 2.92 (1H, br t, *J*=11.2 Hz, H_7), 2.83 (1H, br d, *J*=19.4 Hz, H_6), 2.60 (1H, ddd, *J*=1.2, 6.6, 18.8 Hz, H_2), 2.45 (1H, dd, *J*=12.2, 18.4 Hz, $H_{6'}$), 2.18–2.12 (1H, m, H_{10}), 2.05 (1H, br d, *J*=18.8 Hz, $H_{2'}$), 1.86–1.79 (2H, m, $2H_9$), 1.79–1.75 (1H, m, H_8), 1.69–1.62 (1H, m, $H_{8'}$), 1.64 (3H, d, *J*=1.5 Hz, $3H_{15}$), 0.67 (3H, d, *J*=7.2 Hz, $3H_{14}$); ^{13}C NMR (75 MHz) δ 208.0 (s, C_3), 174.1 (s, C_5), 167.3 (s, COO), 146.3 (s, C_{11}), 137.5 (s, C_4), 123.2 (t, C_{12}), 52.0 (q, CH_3O), 45.9 (d, C_1), 41.4 (t, C_2), 38.3 (t, C_6), 38.1 (d, C_7), 36.6 (t, C_9), 35.4 (d, C_{10}), 31.7 (t, C_8), 12.1 (q, C_{14}), 8.0 (q, C_{15}).

4.1.3. Synthesis of guaia-4,11-dienes 13, 14 and 19.

4.1.3.1. (−)-1β*H*,7α*H*,10β*H*-Guaia-4,11-diene (13). A solution of $AlCl_3$ (249 mg, 1.863 mmol) in ether (1 mL) at 0 °C was added to a suspension of $LiAlH_4$ (15.7 mg, 0.414 mmol) in ether (0.3 mL) at 0 °C and stirred till bubbling stopped (5 min). The mixture was cooled at −20 °C and a solution of compound **2** (15 mg, 0.069 mmol) in ether (0.3 mL) was added via syringe. After 9 min the reaction was quenched with ice and extracted with ether. Careful removal of solvent at reduced pressure followed by column chromatography on silica gel with pentane as eluent afforded 7 mg (50%) of compound **13** as an unstable colourless oil: $[\alpha]_D^{24}$ −13.2 (*c* 0.35); IR (NaCl) ν_{max} 3070, 1641 cm^{-1}; MS (EI) *m/z* 204 (M^+, 61), 189 (43), 161 (39), 119 (59), 95 (100); HRMS (EI) *m/z* calcd for $C_{15}H_{24}$: 204.1878. Found: 204.1883; ^1H NMR (400 MHz) δ 4.68 (1H, s), 4.65 (1H, br s), 2.77–2.68 (1H, m), 2.41 (1H, br d, *J*=11.3 Hz), 2.26–2.14 (1H, m), 2.09 (1H, br dd, *J*=9.2, 14.8 Hz), 2.00–1.90 (1H, m), 1.90–1.66 (4H, m), 1.73 (3H, br s), 1.63 (3H, br s), 1.41–1.22 (3H, m), 0.89 (3H, d, *J*=7.2 Hz); ^{13}C NMR (75 MHz) δ 151.7, 139.2, 132.6 (s), 108.0 (t), 52.9 (d), 50.2 (d), 36.7 (t), 36.2 (t), 36.1 (d), 31.7 (t), 30.0 (t), 25.3 (t), 20.6 (q), 20.1 (q), 13.8 (q).

4.1.3.2. (−)-1α*H*,7α*H*,10β*H*-Guaia-4,11-diene (19). By the same procedure used in the synthesis of compound **13**, from compound **3** (15.8 mg, 0.072 mmol) was obtained compound **19** (7.5 mg, 52%): colourless oil; $[\alpha]_D^{24}$ −22.1 (*c* 0.41); IR (NaCl) ν_{max} 1635, 893 cm^{-1}; MS (EI) *m/z* 204 (M^+, 100), 189 (73), 161 (50), 147 (60), 95 (99); HRMS (EI) *m/z* calcd for $C_{15}H_{24}$: 204.1878. Found: 204.1888; ^1H NMR (400 MHz) δ 4.66 (1H, br s), 4.60 (1H, br s), 2.47 (1H, br d, *J*=14.3 Hz), 2.36–2.28 (1H, m), 2.22–2.02 (4H, m), 1.96–1.87 (1H, m), 1.86–1.75 (2H, m), 1.73 (3H, s), 1.59 (3H, s), 1.46–1.18 (4H, m), 0.89 (3H, d, *J*=6.4 Hz); ^{13}C NMR (75 MHz) δ 152.5, 138.0, 132.1 (s), 107.6 (t), 55.7 (d), 45.2 (d), 39.8 (t), 39.2 (d), 36.3 (t), 36.1 (t), 34.5 (t), 30.1 (t), 21.6 (q), 20.3 (q), 14.5 (q).

4.1.3.3. (+)-1α*H*,7α*H*,10α*H*-Guaia-4,11-diene (14) [(+)-aciphyllene]. By the procedure used in the synthesis of compound **13**, from compound **1** (15.1 mg, 0.069 mmol) was obtained compound **14** (11.2 mg, 78%): colourless oil; $[\alpha]_D^{24}$ +52.2 (*c* 0.53); IR (NaCl) ν_{max} 3080, 1640, 887 cm^{-1}; MS (EI) *m/z* 204 (M^+, 60), 189 (67), 161 (41), 147 (58), 95 (71); HRMS (EI) *m/z* calcd for $C_{15}H_{24}$: 204.1878. Found: 204.1883; ^1H NMR (400 MHz) δ 4.67 (1H, br s, H_{12}), 4.60 (1H, br s, $H_{12'}$), 2.99–2.92 (1H, m, H_1), 2.42 (1H, br d, *J*=17.6 Hz, H_6), 2.28–2.14 (2H, m, $2H_3$), 2.14–2.07 (2H, m, $H_{6'}$, H_7), 1.95 (1H, ddt, *J*=5.2, 8.8, 12 Hz, H_2), 1.90–1.80 (1H, m, H_{10}), 1.80–1.50 (4H, m, $2H_8$, $2H_9$), 1.72 (3H, br s, $3H_{13}$), 1.58 (3H, s, $3H_{15}$), 1.45 (1H, ddt, *J*=12.8, 9.4, 6.6 Hz, $H_{2'}$), 0.76 (3H, d, *J*=7.1 Hz, $3H_{14}$); ^{13}C NMR (100 MHz) δ 152.8, 135.1, 132.5 (s, C_5, C_4, C_{11}), 107.5 (t, C_{12}), 53.2 (d, C_1), 45.7 (d, C_7), 37.4 (t, C_3), 37.1 (t, C_8 or C_9), 36.9 (d, C_{10}), 35.1 (t, C_6), 31.9 (t, C_8 or C_9), 28.5 (t, C_2), 20.2 (q, C_{13}), 14.1 (q, C_{15}), 12.9 (q, C_{14}).

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24. Treatment of compound **15** with SeO_2 (0.5 equiv), *t*-BuOOH (3.75 equiv) at 0 °C for 28 h, followed by addition of *t*-BuOOH (1.85 equiv) and further stirring for 3 h afforded a mixture of **1** (54%), **17** (22%) and hydroxy derivative **18** (10%). Compound **18**, $[\alpha]_D^{24}$ −141, presented spectral features identical to those reported for *ent*-**18**.
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