Muurolane Sesquiterpenes from *Illicium tsangii*

Koon-Sin Ngo, Wing-Tak Wong, and Geoffrey D. Brown*

Chemistry Department, The University of Hong Kong, Pokfulam Rd., Hong Kong

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A dichloromethane extract of *Illicium tsangii* has yielded five novel muurolane sesquiterpenes (**1**, **2**, **6**, **7**, **9**) and three new menthane monoterpenes (**10**−**12**) in addition to several known compounds. Biogenetic relationships among the sesquiterpenes are discussed.

Illicium tsangii A. C. Sm. (Illiciaceae) is a poisonous shrub from southern China used in traditional medicine for treating pain.[1] No previous phytochemical investigations of *I. tsangii* have been reported.

Results and Discussion

Extraction of the aerial parts of *I. tsangii* with dichloromethane has yielded nine muurolane-derived sesquiterpenes (**1**−**9**) and three menthane monoterpenes (**10**−**12**). Structures of most of these compounds were established by spectroscopic techniques, in particular 2D NMR, and absolute stereochemistry of two compounds was deduced by X-ray crystallography.

High-resolution mass spectroscopy of compound **1** demonstrated the molecular formula $C_{15}H_{26}O_2$. Neither 1D NMR (^{1}H and ^{13}C) nor IR spectra showed any evidence for the presence of multiple bonds consistent with a tricyclic sesquiterpene. More detailed analysis of the ^{1}H NMR spectrum showed a single proton (δ 3.41) associated with an oxygen-bearing carbon, while the ^{13}C NMR/DEPT spectra revealed three oxygen-bearing carbons (δ 77.8, 72.8, and 72.3). After a D_2O shake experiment, only one of these carbon atoms (δ 77.8) underwent a significant upfield shift ($\Delta\delta$ = 0.15 ppm), which required that the other two quaternary oxygenated carbons be involved in an ether linkage (carbon atoms attached to OH are expected to undergo secondary isotope effects when converted to −OD).[2] All three of these oxygenated carbons were located within the overall carbon framework of **1** by means of 2D NMR experiments such as HSQC (Tables 1 and 2), HMBC (Figure 1) and ^{1}H−^{1}H COSY (Figure 1), which established the planar structure as that of 4,10-epoxy-muuralan-5-ol and also provided rigorous assignments for all ^{13}C and ^{1}H resonances. Knowledge of the ^{1}H resonances was then useful in determining the relative stereochemistry for the six chiral centers in **1** from correlations observed in NOESY spectra (Figure 2). Two closely related sesquiterpenes, 4,-10-epoxymuurolane[3] and 4,7-epoxy-5-muurolanol,[4] have been previously reported as natural products.

Compound **2** had the same molecular formula as **1** from the results of HREIMS, but was significantly more polar. In addition, 1D NMR spectroscopy showed the presence of a terminal double bond (δ 147.8, 110.6; δ 4.83), which replaced one of the quaternary oxygenated carbons and one of the methyl groups in **1**. 2D NMR showed that **2** incorporated an allylic secondary hydroxyl group and conclusively demonstrated the planar structure of **2** as 5,-10-dihydroxy-muurol-4(15)-ene. NOESY correlations were also broadly similar to **1** and confirmed the cis stereochemistry of the decalin ring and α-orientation of the allylic hydroxide group. The absolute stereochemistry of **2** was established by X-ray crystallography (Figure 3).

Table 1. ^{13}C NMR Data (δ) for Compounds **1**, **2**, **4**, **6**, **7**, and **9**

assignment	**1**	**2**	**4**	**6**	**7**	**9**
1	32.1	41.4	38.6	79.3	78.8	199.0
2	21.2	23.0	25.3	21.8	25.0	35.3
3	25.5	29.2	26.5	30.0	24.8	37.1
4	72.3	147.8	135.9	75.2	78.2	68.8
5	77.8	72.7	119.5	126.3	70.2	149.7
6	46.3	43.4	36.0	148.4	130.2	139.5
7	45.4	36.6	45.0	39.4	145.7	42.0
8	20.3	21.4	27.2	19.3	21.6	24.8
9	34.4	34.7	123.9	26.7	27.5	42.0
10	72.8	72.4	133.7	30.6	33.8	209.0
11	25.8	25.5	28.8	27.5	29.7	31.9
12	22.1[a]	21.6[a]	20.8[a]	21.4[a]	21.4[a]	20.5[a]
13	21.2[a]	14.7[a]	21.5[a]	16.9[a]	20.4[a]	20.2[a]
14	27.8	27.7	20.6	15.4	15.0	29.9
15	24.5	110.6	24.1	22.0	21.2	27.7

[a] Assignments interchangeable within column.

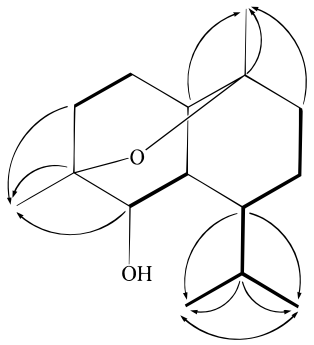

Figure 1. HMBC correlations for compound **1** indicated by arrow from ^{13}C to ^{1}H; ^{1}H-^{1}H COSY correlations for compound **1** indicated by bold lines in structure.

Compounds **1** and **2** are proposed to be biogenetically derived from the 10-hydroxy muurolane (**3**) (Scheme 1), which was present in large amounts in the extract (as previously, the planar structure and relative stereochemistry of **3** was established by 2D NMR). There are 16 possible diastereoisomers of compound **3**. A review of the literature gave excellent agreement for both ^{1}H and ^{13}C spectra of **3** from *I. tsangii* with those of racemic torreyol obtained synthetically[5] (^{13}C NMR assignments reported for C-2/C-9 in the literature should be reversed). However, there is considerable confusion in the literature concerning the physical properties (including NMR) and stereochemical constitution of this series of isomeric natural products, which comprises torreyol[6] (previously erroneously assigned and referred to as δ-cadinol[7]), T-cadinol[8−10] (1α-H, 6β-H,

* To whom correspondence should be addressed. Tel: 852-2859 7915. Fax: 852-2857 1586. E-mail: GDBROWN@HKUCC.HKU.HK.

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Table 2. ^{1}H NMR Data[a] (δ) for Compounds **1**, **2**, **4**, **6**, **7**, and **9**

assignment	1	2	4	6	7	9
1	1.45	2.16	2.32			
2	1.38 (α)	1.88 (α)	1.99	1.34 (α)	2.07	2.64 (dt 16.0, 6.9)
	1.99 (β)	1.53 (β)	1.63	2.15 (β)	1.71	2.44
3	1.87 (α)	2.42 (α)	2.00	1.49 (α)	2.17	2.10
	1.50 (β)	2.20 (β)	1.82	1.99 (β)	1.89	1.06
5	3.41 (br)	4.33 (d 2.7)	5.17 (s)	5.99 (d 2.4)	4.40 (s)	6.40 (s)
6	1.73	1.86	2.62			
7	1.14	1.36	1.13	2.45		2.44
8	1.51 (α)	1.12 (α)	1.99	1.23 (α)	2.03	1.89
	1.79 (β)	1.58 (β)	1.54	1.70 (β)	2.03	1.61
9	1.33	1.60 (α)	5.40 (d 5.7)	1.29 (α)	1.69	2.44
	1.23	1.48 (β)		1.79 (β)	1.31	2.27
10				2.02	1.66	
11	1.69	1.89	1.61	2.07	3.01 (quin 6.8)	1.66
12	0.94 (3H d 6.5)[b]	0.87 (3H d 6.9)[b]	0.90 (3H d 6.6)[b]	0.98 (3H d 6.8)[b]	1.06 (3H d 6.8)[b]	0.77 (3H d 6.7)[b]
13	0.93 (3H d 6.5)[b]	0.79 (3H d 6.9)[b]	0.93 (3H d 6.6)[b]	0.79 (3H d 6.8)[b]	1.02 (3H d 6.8)[a]	0.86 (3H d 6.7)[b]
14	1.20 (3H s)	1.32 (3H s)	1.63 (3H s)	0.96 (3H d 6.9)	0.91 (3H d 6.9)	2.09 (3H s)
15	1.18 (3H s)	4.83 (2H br)	1.62 (3H s)	1.37 (3H s)	1.22 (3H s)	1.46 (3H s)

[a] Integral (when not [1H]), multiplicity, and coupling constant(s) in Hz when clearly resolved in 1D ^{1}H NMR are indicated in parentheses. [b] Assignments within each column are interchangeable.

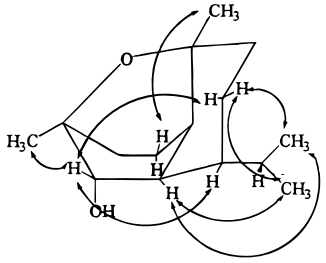


Figure 2. Critical NOESY correlations used in establishing relative stereochemistry of compound **1** indicated by double headed arrows from ^{1}H to ^{1}H.

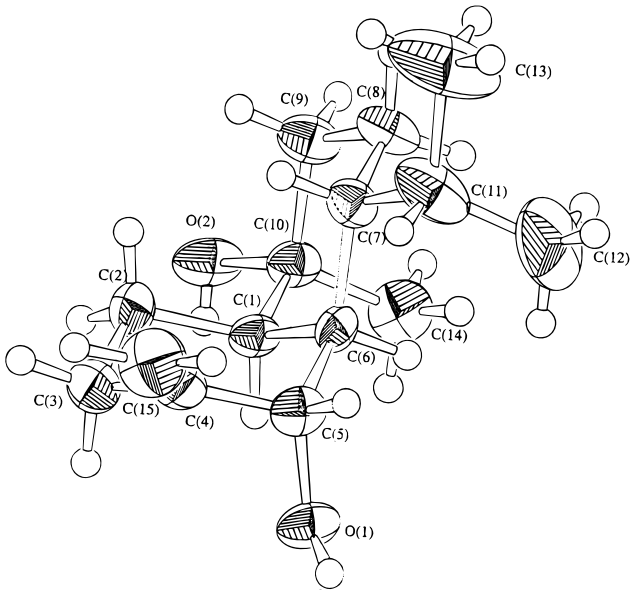


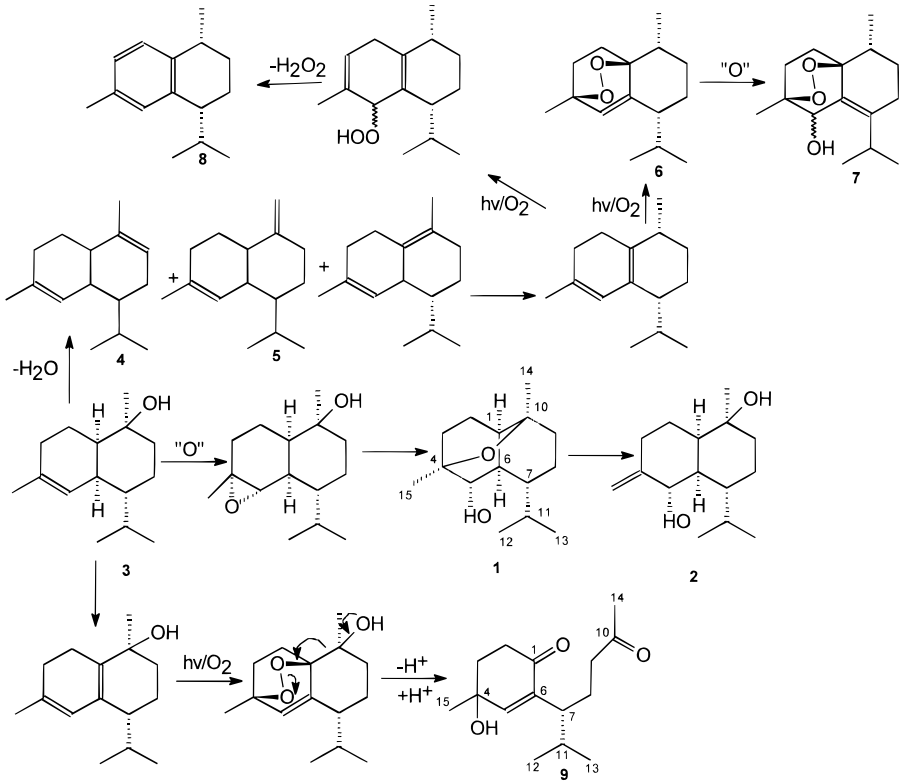
Figure 3. ORTEP diagram for X-ray crystal structure of compound **2**.

7β-^{i}Pr, 10α-Me), T-muurolol[8,10,11] (1β-H, 6β-H, 7β-^{i}Pr, 10α-Me), and α-cadinol[8,10,12,13] (1α-H, 6β-H, 7β-^{i}Pr, 10β-Me) sesquiterpenes. Thus, the more limited ^{1}H NMR data published for racemic synthetic torreyol as prepared by Taber and Gunn[14] was slightly different from that of Rodriguez−Avial Franke et al.,[5] while ^{1}H NMR data for (−)-torreyol, isolated as a natural product from *Pinus sylvestris*,[8] was even more at variance with that from **3** in this study (although data for torreyol from this source did give a better match with **3** than for the other three diastereoisomeric sesquiterpenes, α-cadinol, T-muurolol, and T-cadinol, which are also described in this paper).

The sesquiterpene hydrocarbons **4** and **5** were isolated as an inseparable mixture of isomers. Fortunately, NMR resonances for the two compounds were sufficiently different to allow elucidation of their planar structures even though they were present as a mixture. Eight possible diastereoisomers exist for each of compounds **4** and **5**: biogenetic considerations have led us to propose that **4** and **5** should share the same stereochemistry at the 1-, 6-, and 7-positions as that already established for compounds **1**−**3** (i.e., **4** and **5** are dehydration products of **3**, see Scheme 1). However, it proved impossible to confirm the proposed stereochemistry for either **4** or **5** by comparison with the literature (α-muurolene,[15] α-cadinene,[16] or α-amorphene[17,18] and γ-muurolene,[19] γ-cadinene,[20] γ-amorphene,[19] or γ-bulgarene,[21,22] respectively). Unfortunately, NOESY correlations were also inconclusive in establishing the relative stereochemistry of **4** and **5** as a result of overlapping resonances in the mixture, and in consequence, the muurolane sterochemistry ascribed to **4** and **5** must remain tentative due to lack of direct evidence.

The structures of compounds **6** and **7** were established as muurolane endoperoxides by CIMS, HREIMS, and 2D NMR (Figure 5; only structure **7** shown), and the relative stereochemistry at the 1-, 4-, 7-, and 10-positions for **6** was determined by NOESY experiments and the absolute stereochemistry confirmed by X-ray crystallography (Figure 4). The location of the double bond at the 5-position in compound **6**, and the observation that the new endoperoxide functional group is trans to the existing 7-isopropyl group, is suggestive of endoperoxide formation by a [4 + 2] "Diels−Alder"-type cycloaddition reaction of singlet molecular oxygen with a conjugated muurola-1(6),4-diene system. This putative diene (which is a known compound)[23] might itself be an alternative dehydration product of **3** (cf. proposed biogenesis of **4** and **5**, Scheme 1). This interpretation was supported by the presence in the extract of calamenene (**8**), which can be regarded as the product of an alternative "ene-type" reaction of singlet molecular oxygen with this same diene, forming a hydroperoxide intermediate, followed by elimination of hydrogen peroxide to generate the aromatically stabilized product **8**. NMR data for **8** gave good agreement with that reported in the literature for (7*R*,10*R*)-calamanene[24] (as opposed to other isomers of calamanene)[11,24−28] as would be expected if

Scheme 1. Possible Biogenetic Relationships between Muurolane Sesquiterpenes from *I. tsangii*



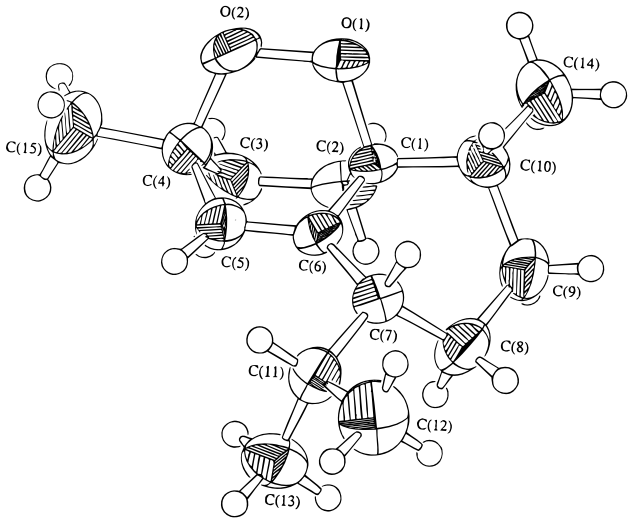


Figure 4. ORTEP diagram for X-ray crystal structure of compound **6**.

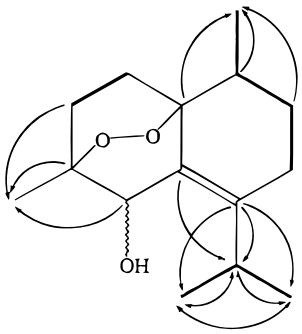


Figure 5. HMBC correlations for compound **7** indicated by arrows from ^{13}C to ^{1}H; $^{1}H-^{1}H$ COSY correlations indicated by bold lines in structure.

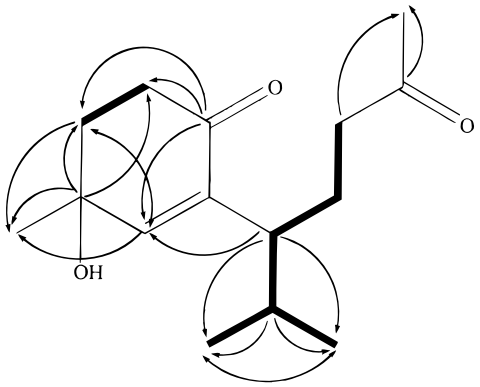


Figure 6. HMBC correlations for compound **9** indicated by arrows from ^{13}C to ^{1}H; $^{1}H-^{1}H$ COSY correlations indicated by bold lines in structure.

compound **8** were biogenetically related to compound **3** (Scheme 1). ^{13}C NMR assignments reported for C-10/C-11 in the literature[24] should be reversed, while assignments reported as interchangeable are in fact correct as given.

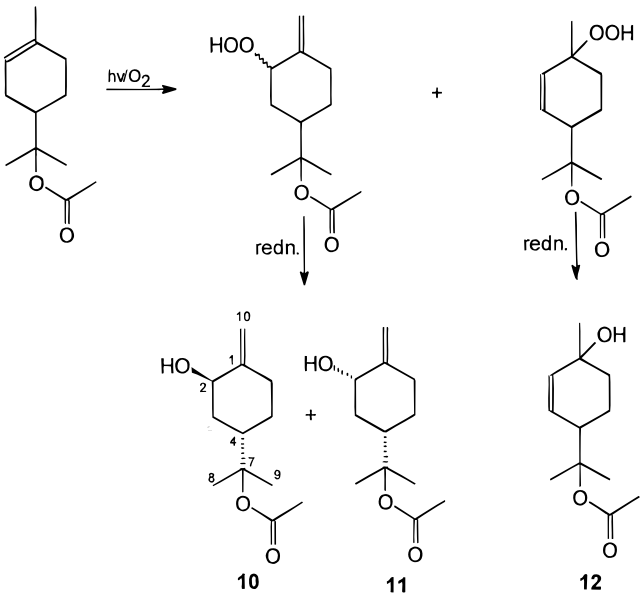
HREIMS of compound **9** demonstrated the molecular formula $C_{15}H_{24}O_3$, and 2D NMR (Tables 1 and 2; Figure 6) established the structure of **9** as that of a 1,10-*seco*-muurolane. Although several *seco*-sesquiterpenes are known which have undergone carbon−carbon cleavage at various positions around the decalin ring, to the best of our knowledge, sesquichamaenol from *Chamaecyparis formosensis* is the only other representative of such a 1,10-scission product.[29] Significantly, both the 1- and 10-positions at which bond cleavage is presumed to have occurred in **9** and in sesquichamenol are at the highest possible oxidation level (e.g., both ketones for **9**); this is a common observation for many *seco*-sesquiterpenes. A proposal for the biogenesis of **9**, which is consistent with the oxidation chemistry suggested for the other muurolane sesquiterpenes encountered in the extract, is given in Scheme 1.

Table 3. ^{13}C and ^{1}H NMR[a] Data for Compounds **10**−**12**

	δ_C			δ_H		
assignment	**10**	**11**	**12**	**10**	**11**	**12**
1	149.6	151.2	67.0			
2	72.3	72.1	134.6	4.38 (br)	4.08 (ddd 11.4, 2.5, 2.5)	5.74 (s)
3	34.6	37.9	129.7	2.00	2.14	5.74 (s)
				1.40	1.12	
4	39.8	44.7	44.4	2.40	2.25	2.75 (dd 9.9,4.8)
5	28.1	28.2	20.2	1.88	1.78	1.68
				1.18	1.11	1.51
6	29.7	33.3	37.0	2.45	2.45	1.88
				2.21	2.00	1.52
7	84.3	84.2	84.3			
8	23.5[b]	23.4[b]	23.7[b]	1.44 (3H s)[b]	1.43 (3H s)[b]	1.46 (3H s)[b]
9	23.2[b]	23.7[b]	23.1[b]	1.42 (3H s)[b]	1.41 (3H s)[b]	1.40 (3H s)[b]
10	110.1	103.8	29.7	4.85 (d 1.6)	4.93 (d 1.6)	1.29 (3H s)
				4.76 (t 2.0)	4.78 (d 1.7)	
CH_3CO	170.2	170.2	170.5			
CH_3CO	23.1	22.5	22.5	1.97 (3H s)	1.98 (3H s)	1.99 (3H s)

[a] Integral (when not [1H]), multiplicity, and coupling constant(s) in Hz when clearly resolved in 1D ^{1}H NMR are indicated in parentheses. [b] Assignments within each column are interchangeable.

Scheme 2. Possible Biogenetic Relationships between Menthane Monoterpenes from *I. tsangii*



In addition to the foregoing sesquiterpenes, three novel menthane monoterpenes were also isolated from the extract (Table 3). Compounds **10** and **11** are secondary allylic hydroxides that are diastereoisomeric at the 2-position, while compound **12** is a tertiary allylic hydroxide. *p*-Menth-1(10)-ene-2,7-diol, which is the de-acetylated analogue of **10**/**11** has been reported previously as a product from a chemical reaction.[30] Relative stereochemistry only is indicated for these menthane monoterpenes. The structures of allylic alcohols **10**−**12** are highly suggestive of formation via ene reaction of molecular oxygen with a Δ^1-*p*-menthene monoterpene. The initial product of this reaction would be the secondary and tertiary hydroperoxide analogues of **10**−**12**, which could then be readily converted to the alcohols, isolated as natural products, by reduction (Scheme 2). The extract also contained significant quantities of sitosterol, caryophyllene oxide, matairesinol,[31,32] and 4-hydroxyphenylethanol.

Experimental Section

General Experimental Procedures. Chemical shifts are expressed in parts per million (δ) relative to TMS as internal standard. All NMR experiments were run on a Bruker DRX 500 instrument. HSQC and HMBC spectra were recorded with 1024 data points in F_2 and 256 data points in F_1. HRMS were recorded in EI mode at 70 eV on a Finnigan-MAT 95 MS spectrometer. IR spectra were recorded in $CHCl_3$ on a Shimadzu FT-IR-8201 PC instrument. Column chromatography was performed using Si gel 60−200 μm (Merck). HPLC separations were performed using a Varian chromatograph equipped with RI star 9040 and UV 9050 detectors and an Intersil PREP−SIL 20 mm × 25 cm column, flow rate 8 mL/min. X-ray analysis was performed with a Rigaku AFC7R diffractometer with graphite monochromated Mo Kα radiation and a 12 kW rotating anode generator.

Plant Material. *I. tsangii* was collected from Conghua County, Guangdong Province, China. Voucher specimens (Q. Lin and G. Hao 939) are held at the University of Hong Kong herbarium and the IBSC herbarium.

Extraction and Isolation. The sample (750 g) was ground to a fine powder under liquid N_2 and then extracted with CH_2Cl_2 over several days. The organic extract was then dried and evaporated under reduced pressure to yield a pale yellow gum (16.6 g; 2.2% w/w). Compounds **1**−**14** were isolated by gradient column chromatography using hexane and EtOAc (TLC plates used to monitor the column were visualized using *p*-anisaldehyde). In most cases, further purification was required by HPLC, using EtOAc−hexane. Compound **1** (11 mg) (t_R 20.7 min in 22% EtOAc−hexane); **2** (10 mg) (t_R 23.2 min in 50% EtOAc−hexane−1% HOAc); **3** (120 mg) (t_R 21.5 min in 16% EtOAc−hexane); **4** and **5** (206 mg) (R_f 0.7 in hexane); **6** (122 mg) (t_R 27.8 min in 2% EtOAc−hexane); **7** (11 mg) (t_R 19.2 min in 20% EtOAc−hexane); **8** (7 mg) (t_R 9.6 min in 0.7% EtOAc−hexane); **9** (9 mg) (t_R 38.7 min in 50% EtOAc−hexane−1% HOAc); **10** (25 mg) (t_R 29.5 min in 23% EtOAc−hexane); **11** (8 mg) (t_R 34.3 min in 23% EtOAc−hexane); **12** (8 mg) (t_R 30.6 min in 23% EtOAc−hexane); **13** (2 mg) (t_R 18.3 min in 50% EtOAc−hexane−1% HOAc).

***4β,10β*-Epoxy-muuralan-5α-ol (1)**: oil; $[\alpha]_D$ −16.6° (*c* 0.2, $CHCl_3$); IR ($CHCl_3$) ν_{max} 3414 (br), 2960, 2931, 2874, 1456, 1375, cm^{-1}; ^{1}H and ^{13}C NMR, see Tables 1 and 2; HREIMS *m*/*z* 238.1929 [M^+, 238.1933 calcd for $C_{15}H_{26}O_2$] (74), 220 (16), 195 (51), 194 (59), 177 (46), 151 (67), 137 (97), 107 (72), 93 (84), 81 (100).

5α,10*β*-Dihydroxy-muurol-4(15)-ene (2): crystal, mp 200−201 °C; $[\alpha]_D$ +25.8° (*c* 0.3, $CHCl_3$); IR ($CHCl_3$) ν_{max} 3429 (br), 2964, 2872, 1460, 1385 cm^{-1}; ^{1}H and ^{13}C NMR, see Tables 1 and 2; HREIMS *m*/*z* 238.1935 [M^+, 238.1933 calcd for $C_{15}H_{26}O_2$] (1), 220 (30), 205 (9), 177 (100), 150 (43), 135 (27), 123 (23), 107 (30), 95 (27), 93 (25).

X-ray Crystallographic Analysis of 2.[33] The compound crystallizes in the space group $P2_1$ (#4) a = 7.014 (3), b = 7.937 (4), c = 13.147 (3) Å, β = 97.07 (2)°, V = 726.3 (4) Å^3, Z = 2 and with a calculated density of 1.09 g/cm^3. The structure was

solved by direct methods and expanded using Fourier techniques. The nonhydrogen atoms were refined anisotropically. Hydrogen atoms were included but not refined. The final cycle of full-matrix least-squares refinement was based on 716 observed reflections [$I > 1.50\,\sigma(I)$] and 153 variable parameters and converged (largest parameter shift was 0.01 times its esd) with unweighted and weighted agreement factors of $R = 0.039$ and $R_w = 0.033$. The standard deviation of observation of unit weight was 1.96. The weighting scheme was based on counting statistics and included a factor ($p = 0.002$) to downweight the intense reflections.

4-Muurolen-10-ol (torreyol) (3): Physical data as are given by Rodriguez-Avial Franke et al.[5]

1,4-Peroxy-muurol-5-ene (6): crystal; mp 70.5−71.5 °C; $[\alpha]_D$ +2.3° (*c* 3.6, $CHCl_3$); IR ($CHCl_3$) ν_{max} 2963, 2934, 2864, 1458, 1377 $cm^{-1;}$ ^1H and ^{13}C NMR, see Tables 1 and 2; HREIMS *m*/*z* 204.1887 [$M^+ - O_2$, 204.1878 calcd for $C_{15}H_{24}$] (100), 189 (20), 161 (75), 134 (15), 105 (10); CIMS *m*/*z* 237 [M + 1] (12), 220 (21), 203 (100), 177 (6).

X-ray Crystallographic Analysis of 6.[33] The compound crystallizes in the space group $P2_12_12_1$ (#19) $a = 14.898$ (3), $b = 16.617$ (3), $c = 5.625$ (4) Å, $V = 1392.5$ (7) $Å^3$, $Z = 4$ and with a calculated density of 1.13 g/cm^3. The structure was solved by direct methods and expanded using Fourier techniques. The nonhydrogen atoms were refined anisotropically. Hydrogen atoms were included but not refined. The final cycle of full-matrix least-squares refinement was based on 773 observed reflections [$I > 1.50\,\sigma(I)$] and 154 variable parameters and converged (largest parameter shift was 0.01 times its esd) with unweighted and weighted agreement factors of $R = 0.044$ and $R_w = 0.034$. The standard deviation of observation of unit weight was 1.74. The weighting scheme was based on counting statistics and included a factor ($p = 0.006$) to downweight the intense reflections.

1,4-Peroxy-5-hydroxy-muurol-6-ene (7): oil; $[\alpha]_D$ −10.7° (*c* 0.1, $CHCl_3$); IR ($CHCl_3$) ν_{max} 3392 (br), 2934, 2864, 1458, 1379 $cm^{-1;}$ ^1H and ^{13}C NMR, see Tables 1 and 2; HREIMS *m*/*z* 252.1736 [M^+, 252.1725 calcd for $C_{15}H_{24}O_3$] (11), 234 (8), 201 (28), 191 (95), 181 (100), 152 (50), 149 (50), 121 (47), 93 (51).

(7*R*,10*R*)-Calamenene (8): Physical data are given by Bunko et al.

1,10-*seco*-4ξ-Hydroxy-muurol-5-ene-1,10-diketone (9): oil; IR ($CHCl_3$) ν_{max} 3393 (br), 3024, 2961, 1717, 1697, 1456, 1373 cm^{-1}; ^1H and ^{13}C NMR, see Tables 1 and 2; HREIMS *m*/*z* 252.1732 [M^+, 252.1725 calcd for $C_{15}H_{24}O_3$] (3), 234 (26), 208 (25), 193 (27), 176 (42), 149 (53), 121 (52), 109 (100).

***p*-Menth-1(10)-ene-2,7-diol, 7-acetate (*trans*) (10)**: oil; IR ($CHCl_3$) ν_{max} 3385 (br), 2932, 1717, 1458, 1373, 1269 $cm^{-1;}$ ^1H and ^{13}C NMR, see Table 3.

***p*-Menth-1(10)-ene-2,7-diol, 7-acetate (*cis*) (11)**: oil; $[\alpha]_D$ −5.8° (*c* 0.25, $CHCl_3$); IR ($CHCl_3$) ν_{max} 3422 (br), 2934, 2874, 1720, 1458, 1371, 1265, 1124 $cm^{-1;}$ ^1H and ^{13}C NMR, see Table 3.

***p*-Menth-2-ene-1,7-diol, 7-acetate (12)**: oil; $[\alpha]_D$ +1.2° (*c* 0.26, $CHCl_3$); IR ($CHCl_3$) ν_{max} 3429 (br), 3010, 2933, 1720, 1458, 1371, 1265, 1132 $cm^{-1;}$ ^1H and ^{13}C NMR, see Table 3.

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