Sesquiterpenes and Monoterpenes from the Bark of *Inula macrophylla*

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Eleven new sesquiterpenes (**1**−**11**) and two thymol derivatives (**12**, **13**), along with 12 known sesquiterpenes and monoterpenes, were isolated from the bark of *Inula macrophylla*. Their structures were determined on the basis of spectral evidence (especially by HREIMS and 2D NMR) as well as chemical transformations. The structure of macrophyllic acid A (**1**) was confirmed by X-ray analysis, and the absolute configuration of **1** was determined on the basis of the appropriate chemical conversions and the application of a modified Mosher's method.

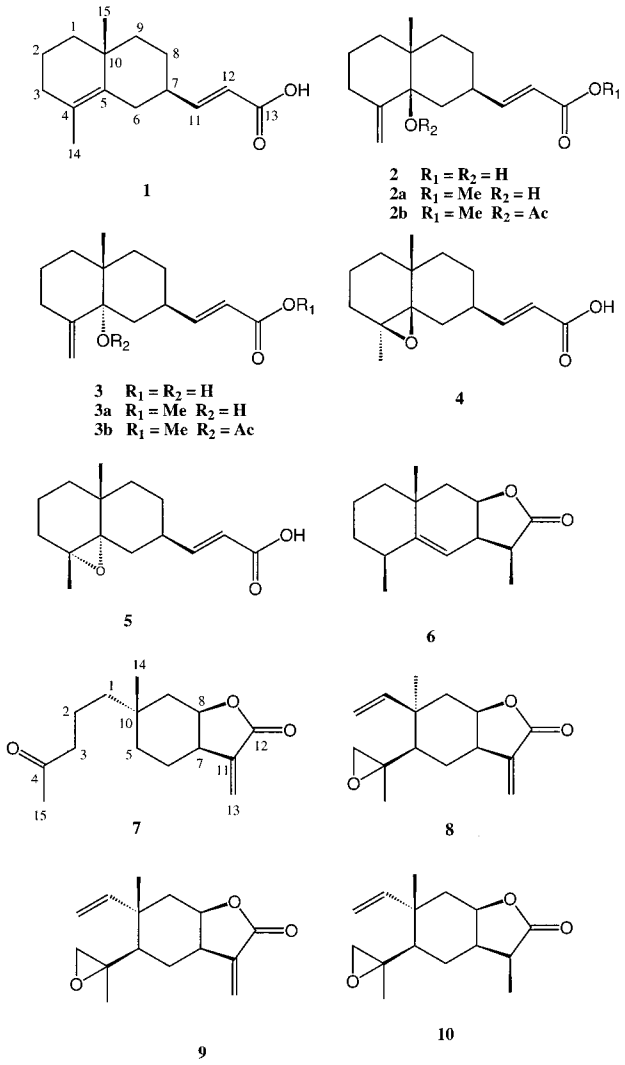
A traditional Uzbekistan herb, *Inula macrophylla* Kar. et Kir. (Compositae), has been used to treat intestinal ulcers, bronchitis, lung diseases, and diabetes. In previous papers,[1,2] we reported the structures of two unusual mono- and sesquiterpene dimers, macrophyllols A and B, and two novel sesquiterpene dimers, macrophyllidimers A and B, from the bark of *I. macrophylla*. We report here the isolation and structural elucidation of 13 additional new terpenoid compounds: macrophyllic acids A−E (**1**−**5**), six other new sesquiterpenes (**6**−**11**), and two thymol derivatives (**12**, **13**). The possible biosynthetic pathway for macrophyllic acids A−E (**1**−**5**) is also discussed.

Results and Discussion

The ^{1}H NMR spectrum of macrophyllic acid A (**1**) showed signals of two methyl groups (δ_H 1.60 and 1.04), a trans double bond which should be conjugated with a carbonyl group based on their chemical shifts and coupling constants (δ_H 7.08 and 5.82), other methylenes, and a methine. Its ^{13}C NMR spectrum (Table 1) showed signals of four quaternary carbons, three methines, six methylenes, and two methyls. The chemical shifts of C-11 and C-12 further indicated that the double bond was conjugated with the carbonyl group (δ_C 172.6). Its IR spectrum indicated the presence of an α,β-unsaturated carboxy group (1696 cm^{-1}). HREIMS (*m*/*z* 234.1608) of **1** gave a molecular formula of $C_{15}H_{22}O_2$, in agreement with the above NMR spectral data.

The ^{1}H−^{1}H COSY correlations of H-12 to H-11, H-11 to H-7, H-7 to H-6 and H-8, H-8 to H-9, H-1 to H-2, and H-2 to H-3 suggested the structure of **1** as shown. This structure was confirmed by the observed correlations of H-11 to C-12, C-13, C-7, C-6, and C-8, H-12 to C-13, C-11, and C-7, H-15 to C-5, C-10, C-1, and C-9, H-14 to C-3, C-4, and C-5, and H-6 to C-7, C-8, C-11, C-4, C-5, and C-10 in its HMBC spectrum. The structure of **1** was finally verified by an X-ray analysis (Figure 1).

To determine the absolute configuration of macrophyllic acid A, **1** was treated with $KMnO_4$ and HIO_4 to give **14** (Figure 2). The (*S*)- and (*R*)-PGME (phenylglycine methyl ester) amides were obtained after **14** was treated with (*R*)- and (*S*)-PGME, respectively. Thus, the absolute configurations of 7*R* and 10*R* for **1** can be assigned according to the $\Delta\delta$ values ($\Delta\delta = \delta S - \delta R$) (Figure 2).[3]



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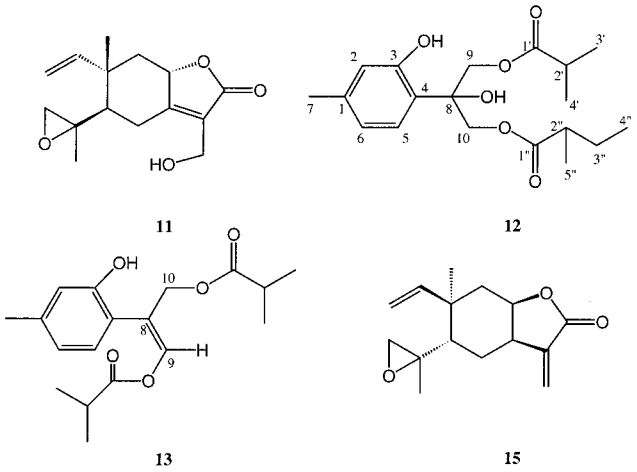

Table 1. ^{13}C NMR and DEPT Spectral Data of Macrophyllic Acids A−E (**1**−**5**) (100 MHz, δ, ppm, $CDCl_3$)[a]

no.	1	2	3	4	5
1	40.2 t	34.6 t	35.0 t	35.5 t	34.0 t
2	19.0 t	22.5 t	22.2 t	16.7 t	16.0 t
3	33.2 t	32.1 t	31.7 t	31.2 t	28.9 t
4	125.8 s	148.2 s	151.4 s	64.2 s	63.6 s
5	133.2 s	86.5 s	75.3 s	67.9 s	68.9 s
6	30.5 t	29.2 t	35.6 t	31.5 t	30.8 t
7	42.3 d	35.5 d	35.9 d	40.4 d	38.5 d
8	27.6 t	25.9 t	25.9 t	27.1 t	26.6 t
9	41.5 t	33.8 t	33.6 t	35.5 t	36.8 t
10	34.4 s	38.7 s	38.0 s	33.7 s	33.3 s
11	156.8 d	156.2 d	156.9 d	154.8 d	155.9 d
12	118.6 d	118.8 d	118.6 d	119.0 d	118.9 d
13	172.6 s	170.9 s	171.9 s	171.4 s	171.8 s
14	19.4 q	111.7 t	108.2 t	21.4 q	20.7 q
15	24.5 q	21.1 q	20.0 q	23.0 q	20.8 q

[a] The assignments were based on $^1H-^1H$ COSY, HSQC, and HMBC spectra.

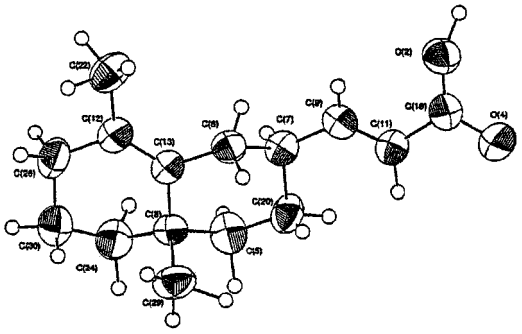

Figure 1. ORTEP drawing of compound **1**.

The ^1H NMR data of macrophyllic acid B (**2**) were similar to those of **1** except for the characteristic exomethylene signals at δ_H 5.05 and 4.74 in **2** instead of the methyl signal at δ_H 0.91 in **1**. The ^{13}C NMR spectral data (Table 1) of **2** indicated an oxygenated quaternary carbon at δ_C 86.5 (C-5). In the HMBC spectrum, the proton signals at δ_H 4.74 (H-14) and 5.05 (H-15) showed long-range correlation with carbon signals at δ_C 86.5 (C-5). These NMR data suggested the exocyclic double bond was located between C-4 and C-14 and a hydroxyl group was attached to C-5 in **2**. HIEIMS (*m*/*z* 250.1587) gave a molecular formula of $C_{15}H_{22}O_3$. The observed HMBC correlations of H-14 to C-3, C-4, and C-5, H-6 to C-4, C-5, C-7, C-8, C-10, and C-11, and H-15 to C-1, C-9, C-5, and C-10 confirmed its structure.

HREIMS of macrophyllic acid C (**3**) also gave a molecular formula of $C_{15}H_{22}O_3$. An evident difference between **2** and **3** was in the chemical shift of C-5. The same $^1H-^1H$ COSY and HMBC correlations as in **2** were observed for **3**, suggesting that **2** and **3** were stereoisomers. The hydroxyl groups should adopt an equatorial orientation and an axial orientation in **2** and **3**, since a hydroxyl group with an axial orientation has a stronger shielding effect. To confirm the determined structures, **2** and **3** were treated with MeOH and DCC in a CH_2Cl_2 solution at room temperature for 2 h, and **2a** and **3a** were obtained. Both **2a** and **3a** were further acetylated using acetic anhydride and pyridine in the presence of a catalytic amount of 4-(dimethylamino)-pyridine at room temperature, overnight, to give **2b** and **3b**. NOESY correlation between H-15 and acetylmethyl was observed for compound **2b**.

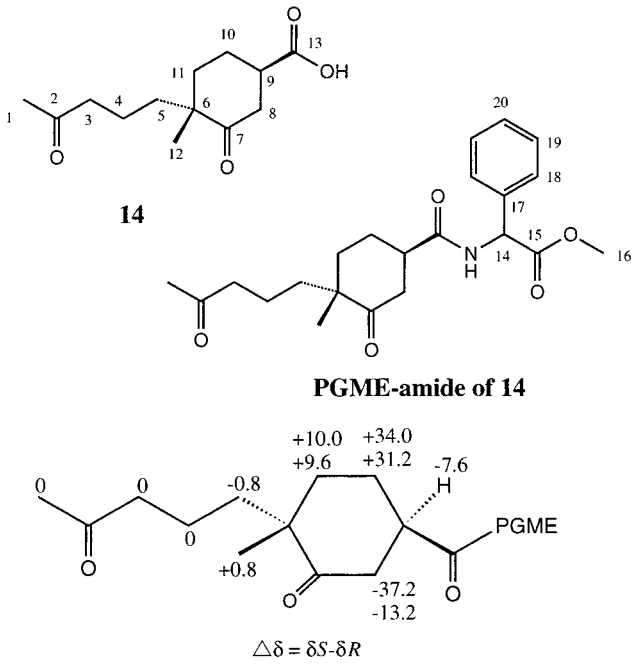

Figure 2. Structures of **14** and (*S*)-and (*R*)-PGME amides of **14** and their $\Delta\delta$ values.

HREIMS of macrophyllic acid D (**4**) and macrophyllic acid E (**5**) gave the same molecular formula of $C_{15}H_{22}O_3$, which, combined with their similar NMR data, suggested that they were another pair of stereoisomers. The chemical shifts of C-4 (**4**, δ_C 64.2, s; **5**, δ_C 63.6, s) and C-5 (**4**, δ_C 67.9, s; **5**, δ_C 68.9, s) suggested the existence of epoxy groups in **4** and **5**, which also had identical molecular formulas. HMBC correlations of H-14 to C-3, C-4, and C-5 and H-15 to C-1, C-5, C-9, and C-10 were observed for both **4** and **5**; these correlations verified that their epoxy groups were between C-4 and C-5. In the NOESY spectrum of **5**, H-14 correlated to H-15, suggesting that the two methyls were in a *cis* relationship in **5**. The signal of H-14 of **4** (δ_H 1.33) showed a downfield shift relative to that of **5** (δ_H 1.26), and a NOESY correlation between H-14 and H-15 was not observed for **4**.

Aristophyllides A−D, the derivatives of rearranged *ent*-elemane sesquiterpenes with a new carbon skeleton, have recently been reported.[4] 11(13)-Eudesmen-12-oic acid is a common type of natural product, and several sesquiterpenes of this type have been isolated from various plant materials.[5−10] However, macrophyllic acids A−E (**1**−**5**) possess a new rearranged carbon skeleton, and this is the first report of a sesquiterpene acid of this type. A possible biosynthetic pathway of macrophyllic acid A (**1**) from the related 11(13)-eudesmen-12-oic acid is shown in the Supporting Information.

Table 2. ^{13}C NMR and DEPT Data of Compounds **6**−**11** and **16** (100 MHz, δ, ppm, $CDCl_3$)[a]

no.	6	7	8	9	16[b]	10	11
1	42.4 t	34.3 t	146.2 d	147.3 d	148.0 d	149.1 d	145.3 d
2	17.0 t	23.4 t	111.9 t	112.2 t	111.8 t	111.1 t	112.9 t
3	33.1 t	43.7 t	56.5 t	56.2 t	52.2 t	52.5 t	56.1 t
4	38.7 d	208.5 s	57.0 s	57.5 s	57.6 s	57.8 s	56.8 s
5	150.8 s	17.3 t	47.3 d	50.4 d	47.1 d	45.5 d	54.1 d
6	115.7 d	30.8 t	22.9 t	27.3 t	25.7 t	23.3 t	25.1 t
7	38.9 d	37.8 d	38.7 d	40.0 d	39.4 d	35.4 d	163.5 s
8	77.1 d	75.7 d	75.5 d	76.0 d	75.5 d	77.1 d	78.2 d
9	43.1 t	37.4 t	44.1 t	44.1 t	41.9 t	39.6 t	46.8 t
10	33.2 s	23.0 s	39.2 s	37.9 sd	38.5 s	38.0 s	40.2 s
11	40.5 d	139.1 s	136.7 s	141.2 s	140.3 s	39.2 d	123.4 s
12	179.2 s	170.4 s	170.4 s	170.4 s	170.4 s	179.4 s	173.7 s
13	10.8 q	122.7 t	121.0 t	121.2 t	121.9 t	10.4 q	54.9 q
14	28.8 q	18.3 q	17.0 q	19.4 q	20.2 q	20.6 q	18.0 q
15	23.1 q	30.2 q	19.3 q	19.5 q	23.1 q	24.0 q	19.5 q

[a] The assignments were based on $^1H-^1H$ COSY, HSQC, and HMBC spectra. [b] **16**: 5α-epoxyalantolactone.

The ^1H and ^{13}C NMR (Table 2) data of **6** ($C_{15}H_{22}O_2$) were similar to those of alantolactone, and this was identified by comparison of its NMR data with those in the literature.[11] However, the characteristic doublets of exocyclic methylene were not observed for **6**. Combined with the chemical shift of C-12 (δ_C 179.2), this suggested that the five-memberd lactone ring in **6** was saturated. This was confirmed by the observed $^1H-^1H$ COSY correlations of H-7 to H-11, H-6, and H-8, and H-13 to H-11, and the HMBC correlations of H-13 to C-11, C-7, and C-12, and H-7 to C-11, C-12, C-13, C-5, C-6, and C-9. In the NOESY spectrum of **6**, H-7 correlated to H-11 and H-8. The coupling constant ($J_{7,11}$ = 7.9 Hz) between H-7 and H-11 was also consistent with a *cis* orientation. Thus, **6** was determined to be 11α,13-dihydroalantolactone.

The ^1H and ^{13}C NMR (Table 2) spectral data of **7** ($C_{15}H_{22}O_3$) indicated the existence of an α-methylene-γ-lactone moiety at δ_H 6.25 (1H, d, J = 2.8 Hz, H-13a) and 5.56 (1H, d, J = 2.8 Hz, H-13b) and δ_C 139.1 (s, C-11), 122.7 (t, C-13) and 170.4 (s, C-12). The NMR data also showed a methyl ketone at δ_H 2.17 (3H, s, H-15) and δ_C 30.2 (q, C-15) and 208.5 (s, C-4). The fragment ion peak at m/z 206 [M − CH_3CO − H]$^+$ in EIMS and the undisturbed α-methylene (δ_H 2.53, H-3; δ_C 43.7, C-3) of a ketone also suggested this group. The NMR signals of the methyl ketone side chain of **7** were very similar to those of **14**, the oxidation product of **1**. All of the above findings prompted us to consider that **7** was a *seco*-eudesmanolide sesquiterpene. In the $^1H-^1H$ COSY spectrum of **7**, H-8 correlated to H-7 and H-9, H-7 to H-6, and H-2 to H-3 and H-1. In the HMBC spectrum, H-15 correlated to C-3 and C-4, H-3 to C-4, C-15, C-2, and C-1, H-14 to C-1, C-5, C-9, and C-10, and H-8 to C-9, C-10, C-6, C-7, and C-11. The 14-methyl of **7** was *cis* to H-8 on the basis of the observed NOESY correlations of H-8 to H-7 and H-14. Accordingly, **7** was determined to be 4,5-*seco*-11(13)-eudesmen-12,8-olid-4-one. Other *seco* sesquiterpenes similar to **7** have been reported.[12−15]

The ^1H and ^{13}C NMR (Table 2) data of **8**, **9**, and **15** were very similar to each other, and their HREIMS spectra indicated the same molecular formula ($C_{15}H_{20}O_3$). The characteristic signals of H-1, H-2, C-1, and C-2 suggested that these three compounds were elemane-type sesquiterpene derivatives. The presence of epoxides was likely based on the chemical shifts of H-3, C-3, and C-4. Furthermore, their EIMS spectra all gave strong fragment ion peaks at m/z 233 [M − CH_3]$^+$, due to the loss of 15-CH_3. These three compounds had the same gross structure, which was determined on the basis of correlations in their $^1H-^1H$ COSY, HSQC, and HMBC spectra. In their NOESY spectra, strong correlations between H-7 and H-8 were observed, suggesting that H-7 and H-8 were in a *cis* relationships. Consequently, any differences in relative configuration among them must be in C-3, C-4, C-5, and C-10. Their structures were established as shown by analyzing correlations in their NOESY spectra, and the relative configurations of the 3,4-epoxy groups are still unknown. The structure of **15** has been reported in previously.[16]

HREIMS of **10** indicated a molecular formula of $C_{15}H_{22}O_3$, 2 amu more than those of **8**, **9**, and **15**. Its ^1H and ^{13}C NMR (Table 2) data were similar to those of **8**, **9**, and 5α-epoxyalantolactone,[19,26] and the characteristic signals of H-1, H-2, C-1, and C-2 suggested that this compound was an elemane-type sesquiterpene derivative. However, exocyclic methylene doublets were not observed for **10**, and the methyl at δ_H 1.22 (3H, d, J = 7.4 Hz, H-13) was seen instead. The chemical shift of the ester carbonyl group at δ_C 179.4 (C-12) suggested that the five-memberd lactone ring of **10** was saturated, like that of **6**. The relative stereochemistry of **10** was established as shown based on the observed NOESY correlations of H-7 to H-11, H-8, and H-5, and H-5 to H-1 and H-2. All of the NMR data were assigned on the basis of the correlations of $^1H-^1H$ COSY, HSQC, and HMBC. Accordingly, **10** was determined to be 3,4-epoxy-11α,13-dihydroelemen-12, 8-olide.

The NMR data of **11** ($C_{15}H_{22}O_4$) also showed the characteristic signals of H-1, H-2, C-1, and C-2 of elemane-type sesquiterpenes and the presence of a 3,4-epoxy group. The ^{13}C NMR and DEPT spectra of **11** showed two quaternary double bond carbons (C-7 and C-11) other than C-1 and C-2. This double bond should be conjugated with the carbonyl group on the basis of their chemical shifts (C-12, δ_C 173.7; C-7, δ_C 163.5; C-11, δ_C 123.4). The signals at δ_C 54.9 (t, C-13) and δ_H 4.42 (2H, br s, H-13) seemed to belong to a hydroxymethyl attached to a quaternary carbon. In the HMBC spectrum of **11**, H-13 correlated to C-7, C-11, and C-12, H-8 to C-6, C-7, C-11, C-12, C-9, and C-10, and H-6 to C-4, C-5, C-10, C-7, C-8, and C-11. In its NOESY spectrum, correlations of H-8 to H-9β (δ_H 2.17, dd, J = 12.0, 6.2 Hz), H-14 to H-9b, and H-1 to H-9α (δ_H 1.36, dd, J = 12.0, 11.8 Hz) and H-5 were observed. Thus, **11** was determined to be 3,4-epoxy-7,11-dehydro-13-hydroxymethylelemen-12,8-olide.

The NMR data of **12** ($C_{15}H_{28}O_4$) were close to those of a known compound, 8-hydroxy-9,10-isobutyryloxythymol,[17,18] and its structure was determined on the basis of NMR studies as well as by comparison with the published data. However, there were two isobutyloxyl groups in 8-hydroxy-9,10-isobutyryloxythymol, while there was one isobutyloxyl group and one 2-methylbutyryl group in **12**. In the HMBC spectrum of **12**, the overlapping signals of H-9 and H-10 (δ_H 4.41−4.50, 4H, m) correlated to both C-1′ (the carbonyl carbon of the isobutyloxyl group) and C-1″ (the carbonyl carbon of the 2-methylbutyryl group). Thus, **12** was determined to be 8-hydroxy-9-isobutyryloxy-10(2)-methylbutyrylthymol.

The NMR spectra of **13** ($C_{18}H_{24}O_5$) showed that it was also a thymol derivative that possessed two isobutyloxyl groups. Both ^1H and ^{13}C NMR spectra showed a double bond and an oxygenated methylene in addition to the signals of a 1,3,4-trisbustituted aromatic ring, an aromatic methyl, and two isobutyloxyl groups. The double bond and oxygenated methylene should be C-8, C-9, and C-10 of the thymol skeleton. In the HMBC spectrum of **13**, H-9 correlated to C-4, C-8, C-10, and C-1′, and H-10 to C-4, C-8, C-9, and C-1″, suggesting the structure shown. The *cis*

relationship between H-9 and H-10 was established on the basis of their correlation in the NOESY spectrum.

The known compounds telekin,[17,19−21] 5-epitelekin,[17] 8β-H-secoeudesmanolide,[22] 8α-H-secoeudesmanolide,[22] 1β-hydroxy-11-epicolartin,[23,24] 1β-hydroxyarbusculin A,[23,24] costunolide,[25] 5α-epoxyalantolactone,[19,26] and 8,9-epoxy-3,10-isobutyryloxythymol[27−30] were determined on the basis of NMR studies, and the structures of all of these compounds and 3,4-epoxyelemasteriractinolide, alantolactone, and 8-hydroxy-9,10-isobutyryloxythymol were further confirmed by 2D NMR (^{1}H−^{1}H COSY, HSQC, NOESY, and HMBC). An X-ray structure for 5α-epoxyalantolactone also was measured, but the same result for this compound had already been recently reported.[26]

Experimental Section

General Experimental Procedures. For the X-ray structure of **1**: All diagrams and calculations were performed using maXus (MacScience, Japan); data collections (DIP image plate); data reductions (maXus); programs used to solve structure (maXus SIR92); programs used to refine structures (maXus); molecular graphics (maXus). NMR (400 MHz for ^{1}H NMR, 100 MHz for ^{13}C NMR, both use TMS as internal standard) were measured on a Bruker AM 400 spectrometer and MS spectra on a JEOLJMSD-300 instrument; CC, silica gel 60 (Merck); HPLC, GPC (General Permeation Chromatography, shodex H-2001, 2002, $CHCl_3$), Si gel (Si 60, Hibar RT 250-25). IR spectra were recorded on a Jasco Fourier transform infrared spectrometer (FT/IR-420), and UV spectra on a UV2100 UV−vis recording spectrometer (Shimadzu). Optical rotations were measured with a Jasco DIP-370 digital polarimeter.

Plant Material. The bark of *Inula macrophylla* (1.6 kg, dried weight) was purchased from a medicinal market in Uzbekistan, in August 1997, and identified by Dr. Olimjon K. Kodzhimatov. A voucher specimen (ESM4141) is preserved at the Herbarium of Institute of Botany, Academy of Sciences, Uzbekistan.

Extraction and Isolation. The powdered air-dried bark (1.6 kg) of *I. macrophylla* was extracted with MeOH (3 × 8 L) at 60 °C, each for 6 h. After concentration of the combined extracts under reduced pressure, the residue (228 g) was suspended in H_2O and then extracted with $CHCl_3$ and *n*-butanol, respectively. The $CHCl_3$ extract (115 g) was chromatographed over a Si gel column (10 × 65 cm, Merck Si gel 60, 1.4 kg) and eluted with *n*-hexanes−EtOAc (10:1 to 1:1, then with pure EtOAc); 11 fractions were obtained. A part of fraction 1 (200 mg) was purified by GPC ($CHCl_3$), giving 8,9-epoxy-3,10-isobutyloxythymol (54 mg) and another fraction (fraction 1.02). 8β-H-Secoeudesmanolide (50 mg) was obtained after further purification of fraction 1.02 by HPLC (silica, *n*-hexane−EtOAc, 4:1). Fraction 2 (0.7 g) was purified by HPLC (silica, *n*-hexane−EtOAc, 4:1), giving 8β-H-secoeudesmanolide (19 mg), **6** (6 mg), coustunolide (21 mg), and fraction 2.03. Fraction 2.03 was further purified by HPLC (silica, *n*-hexane−EtOAc, 10:1), giving compounds alatolactone (14 mg), 8α-H-secoeudesmanolide (15 mg), and fraction 2.03.03. Fraction 2.03.03 was further purified by GPC ($CHCl_3$), giving compounds **2** (4 mg) and **5** (6 mg). Fraction 5 (250 mg) was separated by HPLC (silica, *n*-hexane−EtOAc, 4:1), giving **1** (95 mg), **12** (38 mg), **13** (14 mg), and 5α-epoxyalantolactone (24 mg). Fraction 6 (0.7 g) was purified by HPLC (silica, *n*-hexane−EtOAc, 4:1), yielding 12 fractions (fractions 6.01−6.12). Compounds **1** (570 mg), 8-hydroxy-9,10-isobutyryloxythymol (28 mg), and **8** (20 mg) were obtained after the purifications of fractions 6.03, 6.05, and 6.12 by GPC ($CHCl_3$), respectively. Fraction 7 (10.2 g) was chromatographed over a Si gel column (5 × 70 cm, Merck Si gel 60, 200 g) eluted with *n*-hexane−acetone (6:1 to 1:1) and gave six fractions (fractions 7.01−7.06). Fraction 7.01 (120 mg) was purified by HPLC (silica, *n*-hexane−EtOAc, 7:2) to give **15** (4 mg) and **9** (6 mg). Fraction 7.01 was further purified by GPC ($CHCl_3$) to give **3** (14 mg) and **4** (10 mg). Fraction 7.03 (0.5 g) was separated by HPLC (silica, *n*-hexane−EtOAc, 2:1), and 15 fractions were obtained (fractions 7.03.01−7.03.15). Fractions 7.03.08 and 7.03.14 were purified by GPC ($CHCl_3$), giving telekin (5 mg) and 5-epitelekin (6 mg), respectively. Compounds **7** (1.5 mg) and **10** (1.5 mg) were obtained after the purification of fraction 7.03.15 by GPC ($CHCl_3$). Fraction 9 (200 mg) was separated by HPLC (silica, *n*-hexane−EtOAc, 1:3), giving three fractions (fractions 9.01−9.03). Fractions 9.01, 9.02, and 9.03 were purified by GPC ($CHCl_3$), giving **11** (5 mg), 1β-hydroxy-11-epicolartin (4 mg), and 1β-hydroxyarbusculin A (8 mg), respectively.

Macrophyllic acid A (1): $[\alpha]_D^{24}$ +8.0° (*c* 0.85, $CHCl_3$); UV (MeOH) λ_{max} (log ϵ) 207.4 (br, 3.89) nm; IR ($CHCl_3$) ν_{max} 3680, 3520, 2928, 2679, 1696, 1647, 1421, 1374, 1292, 1217, 981 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.08 (1H, dd, J = 15.7, 7.0 Hz, H-11), 5.82 (1H, dd, J = 15.7, 0.7 Hz, H-12), 2.58 (1H, dd, J = 13.7, 1.4 Hz, H-6a), 2.12 (1H, m, H-7), 1.83−2.04 (2H, m, H-3), 1.77 (1H, dd, J = 13.7, 12.6 Hz, H-6b), 1.63 (2H, m, H_2-8), 1.60 (3H, s, H_3-14), 1.58 (1H, m, H-9a), 1.57 (2H, m, H_2-2), 1.55 (1H, m, H-1a), 1.30 (1H, m, H-1b), 1.27 (1H, m, H-9b), 1.04 (3H, s, H_3-15); ^{13}C NMR, see Table 1; EIMS *m*/*z* 234 $[M]^+$ (96.2), 219 (100), 201 (8.8), 173 (32.1), 163 (14.4), 159 (31.9), 149 (10.9), 147 (28.1), 145 (23.2), 131 (23.3), 123 (42.6), 117 (20.0), 107 (47.8), 105 (49.4), 95 (31.4), 91 (68.1), 81 (49.4), 79 (54.7), 77 (37.3), 55 (44.7), 41 (56.0); HREIMS *m*/*z* 234.1608 (calcd for $C_{15}H_{22}O_2$, 234.1620).

X-ray Crystallographic Analysis Data of Macrophyllic Acid A (1). A colorless triclinic crystal was obtained from *n*-hexane−EtOAc (4:1). Crystal size = 0.35 × 0.20 × 0.15 mm; cell parameters, a = 7.621000(0) Å, b = 8.402000(0) Å, c = 12.184000(0) Å, V = 687.200012 Å^3, space group $P1$ (Z = 2). Data collection was performed on a DIP image plate, the structure was solved by direct methods (maXus SIR92), and the final R and R_w values were 0.075 and 0.099, respectively, for 1866 observed reflections.[31]

Preparation of 14 from 1. Compound **1** (30 mg, 0.136 mmol) was dissolved in 1.5 mL of *t*-BuOH, and an H_2O solution (3 mL) of $KMnO_4$ (3 mg, 0.019 mmol) and $NaIO_4$ (232 mg, 1.084 mmol) was added. K_2CO_3 (48 mg) was added to adjust the pH value (pH 9). The reaction mixture was stirred for 3 h at room temperature, then diluted with CH_2Cl_2, and washed with 5% HCl and brine. The organic layer was extracted with saturated $NaHCO_3$ solution, followed by acidification. Then, the aqueous layer was extracted with ether and washed with brine; 22 mg of **14** was obtained as a yellowish oil: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.792 (1H, dd, J = 14.4, 10.8 Hz, H-8), 2.671 (1H, sept, J = 4.0 Hz, H-9), 2.421 (2H, m, H_2-3), 2.412 (1H, dd, J = 14.4, 4. 0 Hz, H-8), 2.210 (3H, s, H_3-1), 2.124 (1H, m, H-10), 2.021 (1H, m, H-10), 1.787 (1H, ddd, J = 13.6, 11.2, 4.0 Hz, H-11), 1.659 (1H, dt, J = 4.0, 13.6 Hz, H-11), 1.470 (2H, m, H_2-4), 1.459 (2H, m, H_2-5), 1.126 (3H, s, H_3-12).

Conversion of 14 to the Corresponding PGME Amides. Conversion procedures to the corresponding (*R*)-PGME amide are as follows: 6 mg of **14** and (*R*)-phenylglycine methyl ester (PGME) (8 mg, 0.0375 mmol) were dissolved in 1 mL of DMF. pyBOP (20 mg, 0.0375 mmol), HOBt (5 mg, 0.0375 mmol), and 0.05 mL of triethylamine were added to the solution, and the mixture was stirred for 5 h at room temperature. After stirring, the reaction mixture was diluted with ethyl acetate and washed with 5% HCl solution, saturated $NaHCO_3$ solution, and brine, respectively. The obtained crude product was purified using PTLC (*n*-hexane−ethyl acetate, 1:2), affording 6 mg (yield 59.5%) of (*R*)-PGME amide **14-*R*** [7 mg, yield 69.4%, (*S*)-PGME amide **14-*S***]. **14**-[(*R*)-PGME amide]: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.319−7.377 (5H, m, H-18, H-19, H-20), 6.451 (1H, br d, J = 7.2 Hz, NH), 5.529 (1H, d, J = 7.2 Hz, H-14), 3.719 (3H, s, H_3-16), 2.779 (1H, dd, J = 14.4, 10.8 Hz, H-8), 2.607 (1H, sept, J = 4.0 Hz, H-9), 2.445 (1H, dd, J = 14.4, 4.0 Hz, H-8), 2.425 (2H, m, H_2-3), 2.120 (3H, s, H_3-1), 1.965 (1H, m, H-10), 1.896 (1H, m, H-10), 1.762 (1H, ddd, J = 13.6, 11.3, 4.0 Hz, H-11), 1.640 (1H, ddd, J = 13.6, 11.2, 4.0 Hz, H-11), 1.473 (2H, m, H_2-4), 1.457 (2H, m, H_2-5), 1.129 (3H, s, H_3-12); ^{13}C NMR data ($CDCl_3$, 100 MHz) δ 18.0 (t, C-4), 22.8 (q, C-12), 24.5 (t, C-10), 29.8 (q, C-1), 35.7 (t, C-11), 37.0 (t,

C-5), 40.2 (t, C-8), 44.0 (t, C-3), 45.1 (d, C-9), 47.4 (s, C-6), 52.8 (q, C-16), 56.3 (d, C-14), 127.1 (d, C-20), 128.6 (d, C-19), 129.0 (d, C-18), 136.3 (s, C-17), 171.2 (s, C-15), 172.4 (s, C-13), 208.7 (s, C-2), 213.5 (s, C-7). **14**-[(*S*)-PGME amide]: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.306−7.368 (5H, m, H-18, 19, 20), 6.426 (1H, br d, J = 7.2 Hz, NH), 5.541 (1H, d, J = 7.2 Hz, H-14), 3.727 (3H, s, H_3-16), 2.746 (1H, dd, J = 14.4, 10.8 Hz, H-8), 2.607 (1H, sept, J = 4.0 Hz, H-9), 2.425 (2H, m, H_2-3), 2.352 (1H, dd, J = 14.4, 4.0 Hz, H-8), 2.210 (3H, s, H_3-1), 2.050 (1H, m, H-10), 1.974 (^{1}H, m, H-10), 1.787 (1H, ddd, J = 13.6, 11.3, 4.0 Hz, H-11), 1.659 (1H, td, J = 13.6, 4.0 Hz, H-11), 1.472 (2H, m, H_2-4), 1.455 (2H, m, H_2-5), 1.131 (3H, s, H_3-12); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 18.0 (t, C-4), 22.8 (q, C-12), 24.4 (t, C-10), 29.6 (q, C-1), 35.7 (t, C-11), 37.0 (t, C-5), 40.3 (t, C-8), 44.0 (t, C-3), 45.1 (d, C-9), 47.4 (s, C-6), 52.8 (q, C-16), 56.3 (d, C-14), 127.0 (d, C-20), 128.6 (d, C-19), 129.0 (d, C-18), 136.1 (s, C-17), 171.2 (s, C-15), 172.4 (s, C-13), 208.7 (s, C-2), 213.5 (s, C-7).

Macrophyllic acid B (2): $[\alpha]_D^{24}$ +125.4° (*c* 0.86, $CHCl_3$); UV (MeOH) λ_{max} (log ϵ) 210 (br, 4.12) nm; IR ($CHCl_3$) ν_{max} 3521, 3939, 2865, 1698, 1649, 1417, 1291, 1217, 1042, 985, 911 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.07 (1H, dd, J = 15.8, 6.6 Hz, H-11), 5.85 (1H, dd, J = 15.8, 1.2 Hz, H-12), 5.05 (1H, s, H-14), 4.74 (1H, s, H-14), 2.73 (1H, m, H-7), 2.49 (1H, m, H-3a), 2.18 (1H, br d, J = 13.2 Hz, H-3b), 2.15 (1H, dd, J = 12.6, 2.4 Hz, H-6a), 1.81 (1H, m, H-1a), 1.78 (1H, m, H-9a), 1.61−1.68 (3H, m, H_2-2 and H-8a), 1.49 (1H, dddd, J = 13.2, 12.7, 12.7, 3.8 Hz, H-8b), 1.46 (1H, dd, J = 13.2, 12.6 Hz, H-6b), 1.18 (1H, ddd, J = 13.2, 4.0, 2.4 Hz, H-9b), 1.03 (1H, br d, J = 14.0 Hz, H-1b), 0.91 (3H, s, H_3-15); ^{13}C NMR, see Table 1; EIMS *m*/*z* 250 [M]$^+$ (85.5), 235 (91), 215 (94), 213 (47.5), 203 (58.7), 188 (100), 185 (92.4), 173 (96.9), 171 (91.4), 159 (81.6), 151 (92.4), 138 (61.4), 123 (82.4), 117 (90.6), 106 (70.8), 97 (90.4), 83 (83.3), 68 (93.5), 65 (99), 40 (73.4); HREIMS *m*/*z* 250.1587 (calcd for $C_{15}H_{22}O_3$, 250.1569).

Methyl ester of macrophyllic acid B (2a): ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.02 (1H, dd, J = 15.8, 6.6 Hz, H-11), 5.87 (1H, dd, J = 15.8, 1.2 Hz, H-12), 5.08 (1H, s, H-14), 4.77 (1H, s, H-14), 3.75 (3H, s, OMe), 2.73 (1H, m, H-7), 2.47 (1H, m, H-3a), 2.19 (1H, br d, J = 13.3 Hz, H-3b), 2.17 (1H, dd, J = 12.5, 2.4 Hz, H-6a), 1.82 (1H, m, H-1a), 1.79 (1H, m, H-9a), 1.61−1.70 (3H, m, H_2-2 and H-8a), 1.49 (1H, dddd, J = 13.2, 12.7, 12.7, 3.8 Hz, H-8a), 1.47 (1H, dd, J = 13.2, 12.5 Hz, H-6b), 1.19 (1H, ddd, J = 13.2, 4.0, 2.4 Hz, H-9b), 1.04 (1H, br d, J = 14.0 Hz, H-1b), 0.93 (3H, s, H_3-15).

Acetate of 2a (2b): ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.00 (1H, dd, J = 15.8, 6.6 Hz, H-11), 5.85 (1H, dd, J = 15.8, 1.2 Hz, H-12), 5.05 (1H, s, H-14), 4.82 (1H, s, H-14), 3.73 (3H, s, OMe), 2.80 (1H, m, H-7), 2.65 (1H, dd, J = 12.5, 2.4 Hz, H-6a), 2.60 (1H, m, H-3a), 2.32 (3H, s, OAc), 1.82 (1H, dd, J = 13.2, 12.5 Hz, H-6b), 0.90 (3H, s, H_3-15).

Macrophyllic acid C (3): $[\alpha]_D^{24}$ +49.3° (*c* 0.92, $CHCl_3$); UV (MeOH) λ_{max} (log ϵ) 211.4 (br, 4.10) nm; IR ($CHCl_3$) ν_{max} 3680, 3592, 2937, 2864, 1697, 1647, 1417, 1288, 1238, 1151, 1046, 987, 909, 871 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.09 (1H, dd, J = 15.7, 6.7 Hz, H-11), 5.85 (1H, dd, J = 15.7, 1.3 Hz, H-12), 4.84 (1H, s, H-14), 4.69 (1H, s, H-14), 2.83 (1H, m, H-7), 2.59 (1H, ddd, J = 15.8, 13.5, 6.7 Hz, H-3a), 2.14 (1H, dd, J = 13.2, 2.0 Hz, H-3b), 1.87 (1H, m, H-1a), 1.85 (1H, m, H-9a), 1.73 (1H, dd, J = 13.2, 12.7 Hz, H-6a), 1.67 (1H, dd, J = 13.2, 2.8 Hz, H-6b), 1.63 (3H, m, H_2-2 and H-8a), 1.51 (1H, dddd, J = 13.2, 12.7, 12.7, 3.6 Hz, H-8b), 1.23 (1H, ddd, J = 13.2, 4.1, 2.3 Hz, H-9b), 1.09 (1H, br d, J = 15.3 Hz, H-1b), 0.88 (3H, s, H_3-15); ^{13}C NMR, see Table 1; EIMS *m*/*z* 250 [M]$^+$ (55.3), 233 (58.2), 217 (36.4), 205 (20.5), 204 (47.9), 192 (29.8), 189 (44.4), 162 (82.8), 147 (47.4), 138 (52.0), 124 (66.0), 121 (66.6), 108 (93.6), 94 (81.0), 79 (96.0), 77 (78.0), 67 (100), 53 (99.0), 39 (53.0); HREIMS *m*/*z* 250.1561 (calcd for $C_{15}H_{22}O_3$, 250.1569).

Methyl ester of macrophyllic acid C (3a): ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.00 (1H, dd, J = 15.7, 6.6 Hz, H-11), 5.83 (1H, dd, J = 15.7, 1.2 Hz, H-12), 4.83 (1H, s, H-14), 4.67 (1H, s, H-14), 3.74 (3H, s, OMe), 2.79 (1H, m, H-7), 2.59 (1H, ddd, J = 15.8, 13.5, 6.7 Hz, H-3a), 2.15 (1H, dd, J = 13.2, 2.2 Hz, H-3b), 1.87 (1H, m, H-1a), 1.85 (1H, m, H-9a), 1.71 (1H, dd, J = 13.2, 12.6 Hz, H-6a), 1.67 (1H, dd, J = 13.2, 2.8 Hz, H-6b), 1.63 (3H, m, H2−2 and H-8a), 1.50 (1H, dddd, J = 13.2, 12.7, 12.7, 3.6 Hz, H-8b), 1.21 (1H, ddd, J = 13.2, 4.1, 2.3 Hz, H-9b), 1.08 (1H, br d, J = 14.7 Hz, H-1b), 0.87 (3H, s, H_3-15).

Acetate of 3a (3b): ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.01 (1H, dd, J = 15.7, 6.6 Hz, H-11), 5.85 (1H, dd, J = 15.7, 1.2 Hz, H-12), 4.83 (1H, s, H-14), 4.67 (1H, s, H-14), 3.74 (3H, s, OMe), 2.80 (1H, m, H-7), 2.60 (1H, m, H-3a), 2.19 (3H, s, OAc), 2.16 (1H, dd, J = 12.6, 2.2 Hz, H-6a), 1.80 (1H, dd, J = 13.2, 12.6 Hz, H-6b), 0.87 (3H, s, H_3-15).

Macrophyllic acid D (4): $[\alpha]_D^{24}$ −18.1° (*c* 0.74, $CHCl_3$); UV (MeOH) λ_{max} (log ϵ) 209.2 (br, 4.01) nm; IR ($CHCl_3$) ν_{max} 3679, 3518, 2935, 1697, 1648, 1422, 1376, 1287, 1227, 1109, 983, 911, 872 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.04 (1H, dd, J = 15.7, 6.8 Hz, H-11), 5.81 (1H, dd, J = 15.7, 1.2 Hz, H-12), 2.29 (1H, m, H-7), 1.86 (1H, m, H-9a), 1.83 (1H, dd, J = 13.8, 12.5 Hz, H-6a), 1.80 (2H, m, H_2-3), 1.76 (1H, m, H-8a), 1.56 (1H, dd, J = 13.8, 3.2 Hz, H-6b), 1.53 (1H, m, H-8b), 1.47 (3H, m, H-1a, H-9b and H-2a), 1.41 (1H, m, H-2b), 1.33 (3H, s, H_3-14), 1.06 (3H, s, H_3-15), 1.05 (1H, m, part overlapped with H-15, H-1b); ^{13}C NMR, see Table 1; EIMS *m*/*z* 250 [M]$^+$ (26.9), 233 (35.7), 217 (18.1), 214 (38.5), 207 (36.6), 180 (36.0), 177 (29.8), 175 (62.2), 164 (88.5), 161 (33.5), 146 (33.3), 135 (43.5), 131 (36.5), 119 (98.4), 105 (92.1), 109 (75.0), 93 (100), 81 (83.2), 67 (56.0), 53 (71.6), 39 (73.5); HREIMS *m*/*z* 250.1580 (calcd for $C_{15}H_{22}O_3$, 250.1569).

Macrophyllic acid E (5): $[\alpha]_D^{24}$ +21.3° (*c* 0.95, $CHCl_3$); UV (MeOH) λ_{max} (log ϵ) 210.1 (br, 4.08) nm; IR ($CHCl_3$) ν_{max} 3681, 3516, 2936, 1698, 1649, 1460, 1417, 1290, 1217, 982, 875 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.04 (1H, dd, J = 15.7, 6.7 Hz, H-11), 5.81 (1H, dd, J = 15.7, 1.2 Hz, H-12), 2.54 (1H, m, H-7), 1.91 (1H, m, H-3a), 1.79 (1H, m, H-3b), 1.77 (1H, dd, J = 14.0, 12.8 Hz, H-6a), 1.72 (1H, m, H-8a), 1.53−1.60 (4H, m, H-8b, H-9a, H-2a and H-1a), 1.48 (1H, dd, J = 14.0, 3.7 Hz, H-6b), 1.39 (2H, m, H-9b and H-2b), 1.26 (3H, s, H3−14), 1.07 (3H, s, H_3-15), 0.95 (1H, m, H-1b); ^{13}C NMR, see Table 1; EIMS *m*/*z* 250 [M]$^+$ (19.1), 233 (22.5), 232 (94.7), 207 (26.1), 192 (95.1), 180 (84.0), 174 (89.2), 164 (70.6), 147 (96.1), 137 (39.2), 133 (32.3), 119 (68.7), 109 (75.1), 94 (99.7), 81 (64.4), 79 (97.7), 71 (100), 67 (49.9), 55 (77.7), 41 (84.3), 39 (31.3); HREIMS *m*/*z* 250.1556 calcd for $C_{15}H_{22}O_3$, 250.1569).

11α, 13-Dihydroalantolactone (6): $[\alpha]_D^{24}$ −35.0° (*c* 0.20, $CHCl_3$); UV (MeOH) λ_{max} (log ϵ) 204.3 (br, 3.86) nm; IR ($CHCl_3$) ν_{max} 2928, 1760, 1459, 1371, 1331, 1217, 1182, 1039, 978, 916 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 5.18 (1H, d, J = 3.1 Hz, H-6), 4.73 (1H, m, H-8), 3.04 (1H, m, H-7), 2.88 (1H, dq, J = 7.9, 7.6 Hz, H-11), 2.50 (1H, m, H-4), 2.12 (1H, dd, J = 14.7, 3.1 Hz, H-9a), 1.83 (1H, m, H-2a), 1.55−1.62 (3H, m, H-1a and H_2-3), 1.51 (1H, dd, J = 14.7, 2.4 Hz, H-9b), 1.44 (1H, m, H-2b), 1.24 (3H, s, H_3-14), 1.22 (3H, d, J = 7.6 Hz, H_3-13), 1.14 (3H, d, J = 7.6 Hz, H_3-15), 1.13 (1H, m, H-1b); ^{13}C NMR, see Table 2; EIMS *m*/*z* 234 [M]$^+$ (56.4), 219 (53.5), 179 (19.8), 178 (45.1), 163 (16.3), 161 (19.2), 145 (100), 133 (15.3), 131 (12.0), 121 (15.0), 119 (19.5), 105 (38.1), 93 (17.3), 91 (30.9), 77 (17.4), 67 (10.6), 55 (163.9), 41 (24.2), 39 (10.8); HREIMS *m*/*z* 234.1618 (calcd for $C_{15}H_{22}O_2$, 234.1620).

4,5-Seco-11(13)-eudesmen-12,8-olide-4-one (7): $[\alpha]_D^{24}$ +41° (*c* 0.20, $CHCl_3$); UV (MeOH) λ_{max} (log ϵ) 211.0 (br, 3.94) nm; IR ($CHCl_3$) ν_{max} 2944, 1755, 1710, 1352, 1267, 1217, 1152, 993, 782, 749 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 6.25 (1H, d, J = 2.8 Hz, H-13a), 5.56 (1H, d, J = 2.8 Hz, H-13b), 4.97 (1H, m, H-8), 3.15 (1H, m, H-7), 2.53 (2H, t, J = 7.5 Hz, H_2-3), 2.30−2.45 (2H, m, H-6a and H-9a), 2.17 (3H, s, H_3-15), 1.51−1.65 (4H, m, H_2-1, H-2a and H-5a), 1.09 (3H, s, H_3-14), 0.87−0.99 (2H, m, H-6b and H-9b), 0.46 (1H, m, H-2b), 0.38 (1H, m, H-5b); ^{13}C NMR, see Table 2; EIMS *m*/*z* 250 [M]$^+$ (16.2), 215 (17.5), 207 (15.5), 206 (29.1), 191 (25.3), 175 (25.5), 162 (19.8), 145 (62.2), 133 (31.4), 131 (36.7), 118 (37.4), 109 (48.3), 105 (57.9), 95 (56.5), 91 (76.8), 84 (84.0), 81 (63.9), 41 (100); HREIMS *m*/*z* 250.1543 (calcd for $C_{15}H_{22}O_3$, 250.1569).

3,4-Epoxy-5-epi-elemasteriractinolide (8): $[\alpha]_D^{24}$ +18.2° (*c* 0.45, $CHCl_3$); UV (MeOH) λ_{max} (log ϵ) 211.5 (br, 3.90) nm; IR ($CHCl_3$) ν_{max} 2977, 2938, 1761, 1454, 1384, 1313, 1238, 1212, 1109, 992 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 6.32 (1H, d, J = 3.1 Hz, H-13a) 5.73 (1H, dd, J = 17.5, 10.8 Hz, H-1), 5.61 (1H, d, J = 3.1 Hz, 13b), 5.02 (1H, d, J = 17.5 Hz, H-2a), 5.00 (1H, d, J = 10.8 Hz, H-2b), 4.78 (1H, m, H-8), 3.31 (1H, m, H-7),

2.60 (2H, brs, H_2-3), 2.31 (2H, m, H_2-6), 1.96 (1H, dd, J = 13.2, 13.2 Hz, H-9a), 1.86 (1H, dd, J = 13.2, 5.8 Hz, H-9b), 1.25 (3H, s, H_3-15), 1.15 (3H, s, H_3-14), 1.07 (1H, dd, J = 12.4, 4.1 Hz, H-5); ^{13}C NMR, see Table 2; EIMS *m/z* 248 $[M]^+$ (15.0), 233 (100), 219 (43.3), 205 (56.2), 193 (49.3), 191 (66.1), 175 (51.9), 163 (48.1), 159 (66.9), 149 (69.6), 145 (90.9), 137 (84.1), 133 (71.7), 123 (68.1), 119 (82.2), 109 (85.9), 107 (100), 93 (98.0), 82 (99.7), 79 (99.0), 67 (80.2), 53 (97.8), 39 (65.7); HREIMS *m/z* 248.1388 (calcd for $C_{15}H_{20}O_3$, 248.1412).

3,4-Epoxy-5,10-epi-elemasteriractinolide (9): $[\alpha]_D^{24}$ +23° (*c* 0.40, $CHCl_3$); UV (MeOH) λ_{max} (log ϵ) 211.2 (br, 4.02) nm; IR ($CHCl_3$) ν_{max} 2938, 1760, 1661, 1266, 1217, 1166, 976, 915 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 6.20 (1H, d, J = 0.9 Hz, H-13a), 5.76 (1H, dd, J = 17.5, 10.8 Hz, H-1), 5.63 (1H, d, J = 0.7 Hz, H-13b), 5.08 (1H, d, J = 10.8 Hz, H-2a), 5.06 (1H, d, J = 17.5 Hz, H-2b), 4.53 (1H, m, H-8), 3.02 (1H, m, H-7), 2.69 (1H, d, J = 4.5 Hz, H-3a), 2.63 (1H, d, J = 4.5 Hz, H-3b), 2.00 (1H, ddd, J = 13.6, 7.5, 2.6 Hz, H-6a), 1.95 (1H, dd, J = 15.2, 3.6 Hz, H-9a), 1.62−1.72 (2H, m, H-6b and H-9a), 1.22 (3H, s, H_3-15), 1.20 (3H, s, H_3-14), 1.14 (1H, dd, J = 13.2, 2.6 Hz, H-5); ^{13}C NMR, see Table 2; EIMS *m/z* 248 $[M]^+$ (3.5), 233 (49.2), 205 (29.2), 193 (56.1), 191 (68.3), 177 (28.3), 175 (42.5), 161 (44.4), 151 (47.9), 145 (60.7), 137 (67.8), 133 (65.3), 125 (65.2), 123 (99.6), 119 (97.6), 111 (98.5), 109 (98.6), 107 (98.3), 105 (96.5), 93 (96.3), 82 (100), 79 (98.8), 67 (99.7), 53 (99.9), 39 (87.5); HREIMS *m/z* 248.1427 (calcd for $C_{15}H_{20}O_3$, 248.1412).

3,4-Epoxy-11α,13-dihydroelemen-12,8-olide (10): $[\alpha]_D^{24}$ +42.6° (*c* 0.23, $CHCl_3$); UV (MeOH) λ_{max} (log ϵ) 204.2 (br, 4.02) nm; IR ($CHCl_3$) ν_{max} 2936, 1763, 1606, 1465, 1375, 1101 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 6.04 (1H, dd, J = 17.5, 10.8 Hz, H-1), 5.02 (1H, d, J = 17.5 Hz, H-2a), 4.98 (1H, d, J = 10.8 Hz, H-2b), 4.64 (1H, m, H-8), 2.78 (1H, dq, J = 7.4, 7.4 Hz, H-11), 2.62 (1H, m, H-7), 2.60 (1H, d, J = 4.5 Hz, H-3a), 2.53 (1H, d, J = 4.5 Hz, H-3b), 2.03 (1H, dd, J = 15.3, 4.4 Hz, H-9a), 1.77 (1H, dd, v15.3, 14.1 Hz, H-9b), 1.65 (1H, m, H-6a), 1.42−1.19 (2H, m, H-5 and H-6b), 1.36 (3H, s, H_3-15), 1.22 (3H, d, J = 7.4 Hz, H_3-13), 1.17 (3H, s, H_3-14); ^{13}C NMR, see Table 2; EIMS *m/z* 250 $[M]^+$ (20.1), 235 (33.8), 207 (54.0), 193 (48.0), 177 (71.7), 150 (60.4), 147 (57.8), 145 (45.2), 139 (37.0), 137 (71.5), 132 (74.4), 123 (59.0), 109 (79.4), 93 (83.7), 81 (84.0), 79 (100), 74 (58.6), 67 (80.5), 53 (74.5), 39 (46.8); HREIMS *m/z* 250.1552 (calcd for $C_{15}H_{22}O_3$, 250.1569).

3,4-Epoxy-7,11-dehydro-13-hydroxymethylelemen-12,8-olide (11): $[\alpha]_D^{24}$ −38.4° (*c* 0.25, $CHCl_3$); UV (MeOH) λ_{max} (log ϵ) 216.4 (br, 4.16) nm; IR ($CHCl_3$) ν_{max} 3683, 3594, 2997, 1745, 1687, 1337, 1238, 1071, 1015, 917 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 5.76 (1H, dd, J = 17.5, 10.8 Hz, H-1), 5.10 (1H, d, J = 10.8 Hz, H-2a), 5.08 (1H, d, J = 17.5 Hz, H-2b), 4.89 (1H, dd, J = 11.8, 6.2 Hz, H-8), 4.42 (2H, brs, H_2-13), 3.11 (1H, dd, J = 13.6, 3.8 Hz, H-6a), 2.67 (1H, d, J = 4.4 Hz, H-3a), 2.65 (1H, d, J = 4.4 Hz, H-3b), 2.58 (1H, dd, J = 13.6, 13.2 Hz, H-6b), 2.17 (1H, dd, J = 12.0, 6.2 Hz, H-9a), 1.36 (1H, dd, J = 12.0, 11.8 Hz, H-9b), 1.31 (3H × 2, s, H3−14 and H_3-15), 1.22 (1H, dd, J = 13.2, 3.8 Hz, H-5); ^{13}C NMR, see Table 2; EIMS *m/z* 249 $[M - CH_3]^+$ (53.7), 189 (88.1), 175 (54.8), 165 (64.7), 161 (71.1), 149 (93.0), 137 (99.8), 133 (70.6), 123 (99.8), 119 (99.7), 109 (99.8), 91 (98.8), 77 (99.6), 53 (100), 39 (99.9); HREIMS *m/z* 264.1326 (calcd for $C_{15}H_{20}O_4$, 264.1362).

8-Hydroxy-9-isobutyryloxy-10(2)-methylbutyrylthymol (12): $[\alpha]_D^{24}$ +8.6° (*c* 0.95, $CHCl_3$); UV (MeOH) λ_{max} (log ϵ) 275.5 (br, 3.45), 218.2 (br, 3.94), 206.1 (sh, 4.18) nm; IR ($CHCl_3$) ν_{max} 3568, 3357, 2973, 2877, 1732, 1626, 1575, 1511, 1461, 1384, 1254, 1152, 1009, 953 cm^{-1}; ^{1}H NMR($CDCl_3$, 400 MHz) δ 6.91 (1H, d, J = 8.0 Hz, H-5), 6.68 (1H, br s, H-2), 6.64 (1H, br d, J = 8.0 Hz, H-6), 4.41−4.45 (4H, m, H_2-9 and H_2-10), 2.55 (1H, m, H-2′), 2.39 (1H, m, H-2″), 2.26 (3H, s, H_3-7), 1.18 (6H, d, J = 7.0 Hz, H_3-3′ and H_3-4′), 1.60 (1H, m, H-3″a), 1.42 (1H, m, H-3″b), 1.10 (3H, d, J = 6.8 Hz, H_3-5″), 0.83 (3H, t, J = 6.9 Hz, H_3-4″); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 177.5 (s, C-1′), 177.2 (s, C-1″), 156.5 (s, C-3), 140.1 (s, C-1), 126.6 (d, C-5), 120.5 (d, C-6), 119.2 (s, C-4), 118.5 (d, C-2), 78.5 (s, C-8), 67.31 and 67.25 (t, C-9 and C-10, maybe exchangeable), 41.0 (d, C-2″), 34.0 (d, C-2′), 26.6 (t, C-3″), 21.0 (q, C-7), 18.9 (q, C-3′ and C-4′), 16.5 (q, C-5″), 11.5 (q, C-4″); EIMS *m/z* 352 $[M]^+$ (50.7), 333 (98.4), 252 (100), 238 (93.5), 233 (23.9), 219 (53.0), 168 (49.8), 150 (94.0), 146 (60.3), 133 (60.6), 129 (69.8), 105 (52.0), 91 (79.0), 86 (97.6), 77 (89.9), 72 (84.1), 58 (80.6), 55 (70.6), 44 (44.8), 39 (44.9); HREIMS *m/z* 352.1918 (calcd for $C_{19}H_{28}O_6$, 352.1886).

8,9-Dehydro-9,10-isobutyryloxythymol (13): UV (MeOH) λ_{max} (log ϵ) 283.7 (br, 3.42), 247.2 (br, 3.52), 205.2 (br, 4.12) nm; IR ($CHCl_3$) ν_{max} 3685, 3590, 2978, 1742, 1609, 1508, 1463, 1346, 1240, 1213, 1142, 997 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.36 (1H, s, H-9), 6.99 (1H, d, J = 8.0 Hz, H-5), 6.72 (1H, br s, H-2), 6.70 (1H, br d, J = 8.0 Hz, H-6), 5.00 (2H, s, H_2-10), 2.72 (1H, m, H-2′), 2.52 (1H, m, H-2″), 2.31 (3H, s, H_3-7), 1.28 (6H, d, J = 7.0 Hz, H_3-3′ and H_3-4′), 1.10 (6H, d, J = 7.0 Hz, H_3-3″ and H_3-4″); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 177.2 (s, C-1″), 173.5 (s, C-1′), 154.2 (s, C-3), 140.1 (s, C-1), 137.6 (d, C-9), 130.5 (d, C-5), 121.3 (d, C-6), 119.4 (s, C-4), 117.8 (s, C-8), 116.8 (d, C-2), 61.1 (t, C-10), 34.0 (d, C-2″ and C-2′), 21.2 (q, C-7), 18.9 (q, C-3″ and C-4″), 18.8 (q, C-3′ and C-4′); EIMS *m/z* 320 $[M]^+$ (25.0), 235 (10.1), 233 (52.2), 232 (77.9), 194 (22.4), 164 (20.,1), 163 (82.2), 145 (100), 133 (97.5), 124 (24.6), 105 (99.2), 91 (23.5), 77 (30.2), 41 (51.3); HREIMS *m/z* 320.1658 (calcd for $C_{18}H_{24}O_5$, 320.1624).

Supporting Information Available: Possible biosynthetic pathway to **1**. This material is available free of charge via the Internet at http://pubs.acs.org.

References and Notes

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(31) Crystallographic data for the structure reported in this paper have been deposited with the Cambridge Crystallographic Data Center.

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