PERGAMON

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Triterpenoid and xanthone constituents of *Cratoxylum cochinchinense*

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Abstract

Two new compounds, the triterpenoid (13*E*,17*E*)-polypoda-7,13,17,21-tetraen-3β-ol and the xanthone *E*-7-geranyloxy-1,3,7-trihydroxyxanthone have been isolated from the bark of Vietnamese *Cratoxylum cochinchinense*. The known compounds lupeol, β-mangostin, 2-geranyl-1,3,7-trihydroxy-4-(3-methylbut-2-enyl)xanthone and 1,3,7-trihydroxy-2,4-di(3-methylbut-2-enyl)xanthone were also obtained.

Keywords: *Cratoxylum cochinchinense*; Guttiferae; (13*E*,17*E*)-Polypoda-7,13,17,21-tetraen-3β-ol; *E*-7-Geranyloxy-1,3-dihydroxyxanthone; 2-Geranyl-1,3,7-trihydroxy-4-isoprenylxanthone; 1,3,7-Trihydroxy-2,4-diisoprenylxanthone; -MANGOSTIN

1. Introduction

Cratoxylum is a small genus belonging to the Guttiferae family and is found mainly in Southeast Asia (Robson, 1974). *Cratoxylum* species have been used in traditional medicine (Usher, 1984) and four chemical investigations have been reported. The bark of *C. sumatranum* ssp. *sumatranum* (syn. *C. celebicum*) contained 3,4,8-trihydroxy-2-methoxy-1-(3-methylbut-2-enyl)-xanthone (celebixanthone) (Stout, Stout, & Welsh, 1963) while quercetin, hyperoside, 1,3,6,7-tetrahydroxyxanthone, mangiferin and isomangiferin were isolated from the leaves and stems of *C. formosum* ssp. *pruniflorum* (syn. *C. pruniflorum*) (Van, Kitanov, & Assenov, 1987; Kitanov, Van, & Assenov, 1988). The constituents of the bark of *C. cochinchinense* (Lour.) Bl. were previously identified as a bicyclic triterpenoid (**1**), friedelin, three tocotrienols, seven xanthones, a xanthonolignoid and a bisxanthone (Bennett, Harrison, Sia, & Sim, 1993; Sia, Bennett, Harrison, & Sim, 1995). Nine xanthones and two flavonoids have recently been isolated from the roots of *C. formosum* (Jack) Dyer (Iinuma, Tosa, Ito, Tanaka, & Madulid, 1996).

2. Results and discussion

The bark, root and leaves of *C. cochinchinense* are used in folk medicines to treat fevers, coughs, diarrhoea, itches, ulcers and abdominal complaints (Vo, 1997). We have now studied the hexane extract of the bark collected in Vietnam. Extensive chromatographic separation of the extract gave the known compounds lupeol, β-mangostin, 1,3,7-trihydroxy-2,4-di(3-methylbut-2-enyl)xanthone (**2**) and 2-geranyl-1,3,7-trihydroxy-4-(3-methylbut-2-enyl)xanthone (**3**) as well as two novel compounds.

The major component (0.5% of the dried plant material) was obtained as a colourless oil (**4**), $C_{30}H_{50}O$ (m/z 426.3877), $[\alpha]_D$ +3.8. Its IR spectrum showed a characteristic hydroxyl absorption band (3420 cm^{-1}) whilst its ^1H and ^{13}C NMR spectra contained signals characteristic of four trisubstituted double bonds [δ_H 5.38 (1H, br s), 5.12 (3H, m), H-7, H-13, H-17 and H-21; δ_C 121.9, 124.6, 124.4 and 124.1 (each d, C-7, C-13, C-17 and C-21) and 140.0, 134.7, 134.6 and 130.7 (each s, C-8, C-14, C-18 and C-22)], a secondary alcohol [δ_H 3.23 (1H, dd, J = 5.0 and 10.8 Hz, H-3); δ_C 78.7 (d, C-3)], five vinyl methyls [δ_H 1.71 (3H, br s), 1.68 (3H, br s) and 1.60 (9H, br s), H_3-26, H_3-27, H_3-28, H_3 29, H_3-30; δ_C 25.6 (q, C-30), 21.9 (q, C-26), 17.5 (C-29), 16.0 (q, C-27) and 15.9 (q, C-28)] and three tertiary methyls [δ_H 0.97, 0.85, 0.74 (each 3H, br

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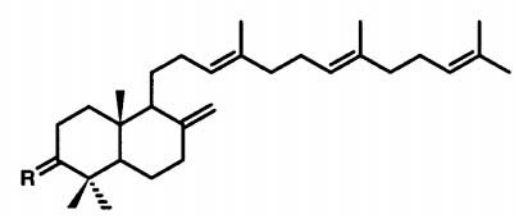
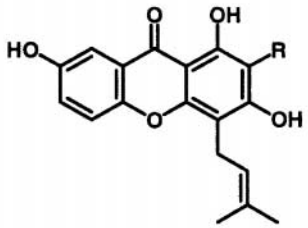


(1) R = α-H, β-OH
(8) R = H_2



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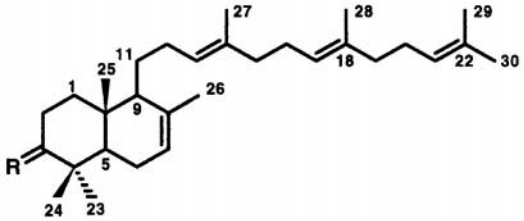
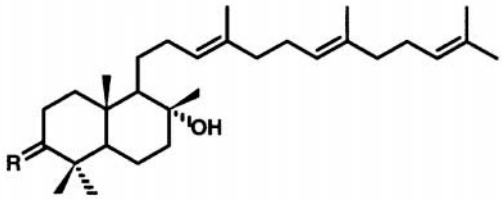
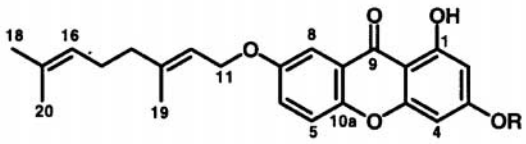


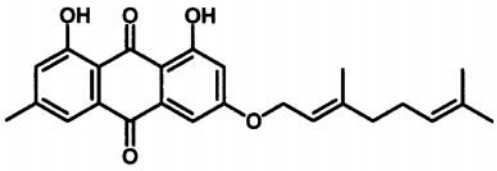
(4) R = α-H, β-OH
(5) R = H_2
(6) R = α-H, β-OAc
(7) R = O



(9) R = H_2
(10) R = α-H, β-OH
(11) R = O



(12) R = H
(13) R = Me



(14)

s, H_3-23, H_3-24 and H_3-25); δ_C 27.9, 15.1 and 13.4 (each q, C-23, C-24, C-25)] as well as nine methylenes, two methines and two fully substituted carbons. The molecule is therefore a bicarbocyclic triterpenoid. Bicarbocyclic triterpenoids are quite rare and comparison of the ^1H and ^{13}C NMR spectra of **4** with those of (13*E*,17*E*)-polypoda-8(26),13,17,21-tetraen-3β-ol (**1**) previously isolated from *C. cochinchinense* (Bennett et al., 1993) and of γ-polypoda-7,13,17,21-tetraene (**5**) from *Polystichum* ferns (Shiojima, Arai, Masuda, Kamada, & Ageta, 1983) clearly indicated that **2** was (13*E*,17*E*)-polypoda-7,13,17,21-tetraen-3β-ol (Table 1). The MS fragmentations (Fig. 1) were in good agreement with the presence of a farnesyl chain.

Acetylation of **4** with acetic anhydride in pyridine afforded the monoacetate (**6**) [ν_{max} 1725 cm^{-1}; δ_H 2.05 (3H, s, CH_3CO); δ_C 170.9 (s, CH_3**C = O**) and 21.2 (q, **CH_3**CO)] which showed the expected deshielding of H-3 in the ^1H NMR spectrum [δ_H 4.50 (1H, dd, J = 10.8 and 5.0 Hz, H-3)]. Jones oxidation of **4** gave the ketone (**7**) [ν_{max} 1719 cm^{-1} (C=O); δ_C 216.8 (s, C-3)]. The absolute configuration of **4** has not been determined but it is assumed that the compound belongs to the normal series.

Table 1
^{13}C NMR chemical shifts for polypodanes **1**, **4**, **6**, **7** and **5**

C	**1** Bennett et al., 1993	**4**	**6**	**7**	**5** Shiojima et al., 1983
1	38.2	37.3	36.8	37.9	39.3
2	28.0	27.3	23.8	34.5	18.9
3	78.9	78.7	81.0	216.8	42.4
4	39.3[a]	36.4	36.3	47.3	33.0
5	55.9[b]	54.0	53.9	53.1	54.4
6	24.0	23.4	23.2	23.9	23.9
7	37.1	121.9	121.5	121.6	122.1
8	148.1	140.0	135.4[c]	135.5[c]	135.6
9	54.7[b]	49.5	49.6	51.2	50.3
10	39.1[a]	38.5	37.4	36.4	36.8
11	23.9	27.3	27.2	27.3	27.3
12	26.7	30.1	30.1	29.8	30.3
13	124.9[d]	124.6[a]	124.4[a]	124.3[a]	124.9
14	134.9[c]	134.7[c]	135.1[c]	135.4[c]	134.9
15	39.8	39.6	39.6	39.6	39.8
16	26.8	26.7[b]	26.7[b]	26.7[b]	26.9
17	124.4[d]	124.4[a]	124.3[a]	124.2[a]	124.3
18	135.1[c]	134.6[c]	134.9[c]	134.9[c]	134.9
19	39.8	39.6	39.6	39.6	39.8
20	26.8	26.5[b]	26.5[b]	26.5[b]	26.8
21	124.3[d]	124.1[a]	124.1[a]	124.0[a]	124.5
22	131.2	130.7[c]	131.1[c]	131.1[c]	131.1
23	28.3	27.9	27.7	25.6	33.2
24	15.4	15.1	16.1	21.9[d]	21.9
25	14.5	13.4	13.4	13.1	13.6
26	106.6	21.9	21.9	22.0[d]	22.2
27	15.4	16.0	16.0	16.1	16.2
28	16.0	15.9	15.9	15.9	16.0
29	17.7	17.5	17.6	17.6	17.7
30	25.7	25.6	25.6	24.9	25.7
$CH_3\underline{CO}$			170.9		
$CH_3\underline{CO}$			21.2		

[a,b,c,d]Identically marked assignments within a column are interchangeable.

Table 2
^{1}H (300 MHz) and ^{13}C (75 MHz) NMR data and HMBC correlations for **12** in $CDCl_3$ (J in Hz in parentheses).

Position	δ_H	Correlations ^{3}J	^{3}J	δ_C
1				163.2
2	6.28d	C-1, C-3	C-4, C-9a	98.2
3				163.6
4	6.38 d (1.9)	C-3, C-4a	C-2, C-9a	94.0
4a				157.9
5	7.36 d (9.0)	C-7	C-10a	118.8
6	7.31 dd (2.7,	23.4	23.2	23.9
7				150.6
8	7.62 d (2.7)	C-7	C-6, C-9 (9.0)	106.1[c]
8a				120.7
9				181.5
9a				103.5
10a				155.2
11	4.63 d (6.3)	C-12	C-13	27.3
12	5.51 br t (6.3)			118.7
13				142.0
14	2.11 m	C-13, C-15	135.1[c]	39.5
15	2.11 m	C-16		26.6
16	5.09 br t (6.3)			123.6
17				131.8
18	1.67 br s	C-17	C-16, C-20	25.6
19	1.77 br s	C-13	C-12, C-14	16.6
20	1.60 br s	C-17	C-16, C-18	17.6[b]
1-OH	12.96 s	C-1	C-2, C-9a	

[a,b,c,d]Identically marked assignments within a column are interchangeable.

Polypodanes are rarely encountered in nature and only six examples have been reported so far. α-Polypodatetraene (**8**), γ-polypodatetraene (**5**) and polypoda-13,17,21-trien-8α-ol (**9**) were isolated from polypodiaceous ferns (Shiojima et al., 1983; Arai, Hirohara, Ageta, & Hsu, 1992; Arai et al., 1996). Polypoda-13,17,21-trien-3β,8α-diol (**10**) and 8α-hydroxypolypoda-13,17,21-trien-3-one (**11**) were found in pistacia resins (Boar, Couchman, Jaques, & Perkins, 1984; Marner, Freyer, & Lex, 1991) while polypoda-8(26)-13,17,21-tetraen-3β-ol (**1**) was obtained from the bark of *Cratoxylum cochinchinense* (Bennett et al., 1993).

The hexane extract also yielded 7-geranyloxy-1,3-dihydroxyxanthone (**12**) as yellow needles. HR-MS showed the molecular formula to be $C_{23}H_{24}O_5$. The compound gave a positive reaction with alcoholic ferric chloride, indicating its phenolic nature. Its UV spectrum exhibited four maxima at 236, 260, 316 and 364 nm which were characteristic of a hydroxylated xanthone as were the IR absorptions at ν_{max} 3162 (br, OH), 1652 (chelated C=O) and 1608 cm^{-1} (aromatic ring).

The ^{1}H and ^{13}C NMR spectra (Table 2) of **12** revealed the presence of a chelated hydroxyl group [δ_H 12.96 (1H, s, exchangeable with D_2O, 1-OH)] and the corresponding chelated xanthone carbonyl [δ_C 180.5 (s, C-9)], a 1,2,4-trisubstituted benzene ring [δ_H 7.62 (1H, d, J = 2.8 Hz, H-8)], 7.36 (1H, d, J = 9.1 Hz, H-5) and 7.31 (1H, dd, J = 2.8 and 9.1 Hz, H-6); δ_C 125.5 (C-6), 118.8 (C-5) and 106.1 (C-8)], two *meta*-coupled protons [δ_H 6.38 (1H, d, J = 1.9 Hz, H-4) and 6.28 (1H, d, J = 1.9 Hz, H-2); δ_C 98.2 (C-2) and 94.0 (C-4)], two trisubstituted double bonds [δ_H 5.51 (1H, br t, J = 5.9 Hz, H-12) and 5.09 (1H, br t, J = 5.9 Hz, H-16); δ_c 118.7 (t, C-12), 142.0 (s, C-13), 123.6 (t, C-16), 131.8 (s, C-17)], three methylenes [δ_H 4.63 (2H, d, J = 6.5 Hz, H_2-11) and 2.11 (4H, m, H_2-14 and H_2-15); δ_C 65.6 (t, C-11), 39.5 (t, C-14) and 26.2 (t, C-15)] and three vinyl methyls [δ_H 1.77 (3H, br s, H_3-19), 1.67 (3H, br s, H_3-18) and 1.60 (3H, br s, H_3-20); δ_C 16.7 (d, C-19), 25.6 (q, C-18) and 17.6 (q, C-20)] as well as seven substituted aromatic carbons, five of which were oxygenated. Treatment of **12** with diazomethane afforded a monomethyl ether (**13**) [δ_H 3.85 (3H, s, OMe); δ_C 55.7 (q, OMe)] which still retained

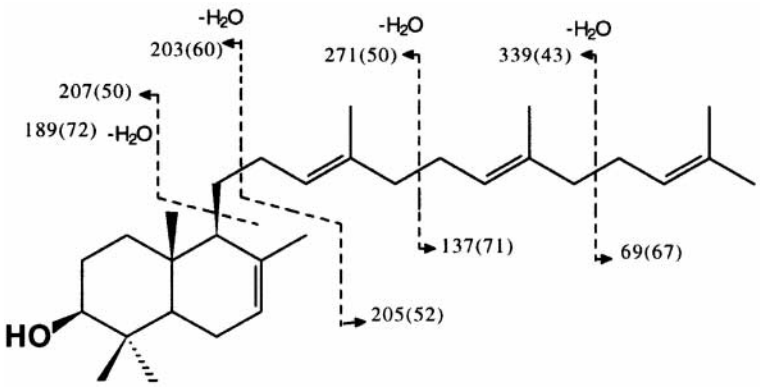


Fig. 1.

the chelated hydroxyl [δ_H 12.90 (1H, s, OH)]. The natural product was therefore a dihydroxyxanthone derivative. The third substituent was identified as a geranyloxy group since its ^{1}H and ^{13}C chemical shifts were in good agreement with the corresponding values for 3-geranyloxy-6-methyl-1,8-dihydroxyanthraquinone (**14**) which was isolated from *Psorospermum febrifugum* (Guttiferae) Botta, Delle Monache, Delle Monache, Marini Bettolo & Oguakwa, 1981. Based on the coupling patterns, the xanthone must be either 1,3,6- or 1,3,7-trioxygenated. The latter was preferred since the ^{1}H chemical shift of the most deshielded aromatic proton [δ_H 7.62 (H-8)] indicated that it must be placed *peri* to the carbonyl. HMQC and HMBC spectroscopy (Table 2) confirmed the above structural assignments and enabled the complete assignment of the ^{13}C NMR signals. The question of the position of attachment of the geranyloxy group could not be solved using HMBC spectroscopy due to the absence of correlations between the protons of the oxygenated methylene (H_2-11) and the xanthone nucleus. This was established by recourse to difference NOE spectroscopy when irradiation of the most deshielded methylene protons (H_2-11) caused enhancement of both the H-6 (3.0%) and H-8 (21.6%) resonances. The natural product was therefore 7-geranyloxy-1,3-dihydroxyxanthone (**12**) and the monomethyl ether was 7-geranyloxy-1-hydroxy-3-methoxyxanthone (**13**). Although a number of *C*-geranylated xanthone derivatives have been reported (Bennett et al., 1993; Asai et al., 1995; Minami, Takahashi, Kodama, & Fukuyama, 1996), this is the first example of a xanthone bearing a geranyloxy group.

3. Experimental

M.p.'s: uncorr.; $[\alpha]_D$: $CHCl_3$. IR: $CHCl_3$ soln unless otherwise specified; UV: EtOH; CC: silica gel (Baker, 40 μm), DIOL (Lichrosorb 40–63 μm), C_{18} (Bakerbond, 40 μm); GPC: Sephadex LH-20 ($CHCl_3$–MeOH 1:1 as eluant); EIMS: 70 eV; NMR: 300 (^{1}H) and 75 MHz (^{13}C) in $CDCl_3$ relative to TMS at $\delta = 0.0$. Difference NOE spectra were run using the NOEMULT programme. The relaxation delay was 2.5 s and the total irradiation time was 3–4 s. Proton-detected HMQC experiments were optimized for a $^1J_{CH}$ value of 140 Hz. The relaxation delay was 2.5 s. 512 increments, each of 32 or 64 scans, were used in t_1 and zero filled to 1K prior to Fourier transformation. In t_2, 2K points were used prior to Fourier transformation. Sine multiplication was used in both dimensions to improve the signal to noise ratio and suppress truncation errors. Proton-detected HMBC experiments were performed under the same conditions as in the HMQC experiment except for modulation tuning which was optimized for $^nJ_{CH} = 10$ Hz and a composite pulse which was used to eliminate $^1J_{CH}$.

The stem bark of *Cratoxylum cochinchinense* (Lour.) Bl. was collected in south Vietnam and identified by Professor Le Cong Kiet and Nguyen Thien Tich, Department of Botany, National University of HoChiMinh City. A reference sample (VCC-1) is kept in the Department of Chemistry, National University of Singapore. The ground plant material (1 kg) was continuously extracted by percolation with hot hexane. CC of the crude extract (36 g) (silica gel, EtOAc–hexane step gradient) gave ten fractions. ^{1}H NMR indicated that frs 1–3 contained lipids and they were not further investigated. Fr. 4 (5.5 g) was further purified using GPC followed by CC (C_{18}, Me_2CO–MeCN gradient) to afford polypoda-7,13,17,21-tetraen-3β-ol (**4**) (5 g) and lupeol (15.8 mg). Separation of the major fr. 9 (12.2 g) (silica gel, 60–80% $CHCl_3$–hexane gradient) gave two fractions, 9A and 9B. Fr. 9A was identified as β-mangostin (1.4 g) by comparison with an authentic sample. Fr. 9B (10.8 g) was subjected to CC (C_{18}, 80% Me_2CO–water) to afford 3 frs. Fr. B1 (230 mg) was not further investigated whilst fr. B2 was identified as **2** (4.6 g), by comparison of its spectroscopic data with literature values (Iinuma, Tosa, Tanaka, & Riswan, 1996). Fr. B3 was subjected to repeated CC

(silica gel and DIOL, EtOAc–CH_2Cl_2 8:1) to give **3** (632 mg) and **14** (96 mg). Compound **3** was identical (TLC, MS, ^{1}H NMR) to an authentic sample (Bennett et al., 1993).

3.1. (13E,17E)-Polypoda-7,13,17,21-tetraen-3β-ol (**4**)

Oil, HRMS: *m/z* 426.3877 ($C_{30}H_{50}O$ requires *m/z* 426.3862); $[\alpha]_D$ +3.8 (*c* 1.4); IR ν_{max} cm^{-1}: 3420, 2922, 2851. EIMS *m/z* (rel. int.): 426 $[M]^+$ (48), 408 $[M–H_2O]^+$ (59), 393 (42), 339 (43), 271 (50), 219 (60), 207 (50), 205 (52), 203 (60), 189 (72), 187 (76), 161 (64), 137(71), 135 (69), 123 (72), 81 (78), 69 (67), 57 (74), 43 (100); ^{1}H NMR: see Section 2. ^{13}C NMR: Table 1.

3.2. (13E,17E)-3β-Acetoxypolypoda-7,13,17,21-tetraene (**6**)

Compound **4** (50 mg) was acetylated in the usual manner with Ac_2O–pyridine to give the oily acetate **6** (46 mg), HRMS: *m/z* 468.3974 ($C_{32}H_{52}O_2$ requires *m/z* 468.3967); $[\alpha]_D$ +33.8 (*c* 1.4); IR ν_{max} cm^{-1}: 1725; EIMS: *m/z* (rel. int.): 468 $[M]^+$ (18), 408 $[M–C_2H_4O_2]^+$ (36), 339 (24), 171 (41), 203 (42), 189 (56), 187 (61), 137 (44), 81 (65), 69 (70), 43 (100); ^{1}H NMR: δ 5.37 (1H, br s), 5.11 (3H, m), (H-7, H-13, H-17 and H-21), 4.50 (1H, dd, *J* = 5.0 and 10.8 Hz, H-3), 2.05 (3H, s, CH_3CO), 1.70 and 1.67 (each 3H, br s, vinyl Me), 1.60 (9H, br s, 3×vinyl Me), 0.92, 0.85 and 0.76 (each 3H, s, Me); ^{13}C NMR: Table 2.

3.3. (13E,17E)-Polypoda-7,13,17,21-tetraen-3-one (**7**)

Jones reagent was added dropwise to a stirred soln of **4** (150 mg) in Me_2CO. After 20 min, the reaction was worked up in the usual manner. CC of the crude product (silica gel, 1% EtOAc–hexane) gave the ketone **7** (110 mg), oil, HRMS: *m/z* 424.3696 ($C_{30}H_{48}O$ requires *m/z* 424.3705); $[\alpha]_D$ +0.17 (*c* 1.2); IR ν_{max} cm^{-1}: 1719. EIMS *m/z* (rel. int.): 424 $[M]^+$ (29), 287 (18), 231 (40), 203 (58), 136 (66), 95 (75), 81 (89), 69 (100), 43 (99); ^{1}H NMR: δ 5.42 (1H, br s), 5.11 (3H, m), (H-7, H-13, H-17 and H-21), 2.68 (1H, td, *J* = 14.4 and 5.1 Hz, H-2ax), 2.24 (1H, dt, *J* = 14.4 and 3.8 Hz, H-2eq), 1.73 (3H, br s, vinyl Me), 1.67 (3H, br s, vinyl Me), 1.59 (9H, br s, 3×vinyl Me), 1.09, 1.04 and 0.97 (each 3H, s, Me); ^{13}C NMR: Table 1.

3.4. 7-Geranyloxy-1,3-dihydroxyxanthone (**12**)

M.p. 138–140° (yellow needles from CH_2Cl_2–hexane); HRMS: *m/z* 380.1604 ($C_{23}H_{24}O_5$ requires *m/z* 380.1623); UV λ_{max} nm (log ε): 206 (4.25), 236 (4.48), 260 (4.39), 316 (3.89), 364 (3.94). IR ν_{max} cm^{-1} (KBr): 3162, 1652, 1608, 1590; EIMS *m/z* (rel. int.): 380 $[M^+]$ (3), 244 (80), 215 (38), 187 (28), 137 (22), 91 (49), 81 (51), 69 (100), 41 (57); ^{1}H and ^{13}C NMR: Table 1.

3.5. 7-Geranyloxy-1-hydroxy-3-methoxyxanthone (**13**)

Compound **12** (6 mg) was treated with ethereal CH_2N_2. CC of the crude product (silica gel, 5% EtOAc–hexane) afforded 7-geranyloxy-1-hydroxy-3-methoxyxanthone (**13**) (4.8 mg) as pale yellow needles from hexane, m.p. 67–69°, HRMS: *m/z* 394.1774 ($C_{24}H_{26}O_5$ requires *m/z* 394.1780); UV λ_{max} nm (log ε): 204 (4.3), 238 (4.3), 260 (4.4), 306 (2.9), 370 (3.4); IR ν_{max} cm^{-1} (KBr): 3447, 2924, 2852, 1652, 1605, 1584. EIMS *m/z* (rel. int.): 394 $[M]^+$ (1.8), 258 (100), 229 (71), 200 (23), 94 (63), 69 (98), 41 (71); ^{1}H NMR: δ 12.90 (1H, s, 1-OH), 7.62 (1H, d, *J* = 2.9 Hz, H-8), 7.36 (1H, d, *J* = 9.1, H-5), 7.31 (1H, dd, *J* = 9.1, 2.9, H-6), 6.42 (1H, d, *J* = 2.3, H-4), 6.35 (1H, d, *J* = 2.3, H-2), 5.51 (1H, br t, *J* = 6.5, H-12), 5.10 (1H, br t, *J* = 6.5, H-16), 4.63 (2H, d, *J* = 6.5, H_2-11), 3.89 (3H, s, OMe), 2.12 (4H, m, H_2-14 and H_2-15), 1.77 (3H, br s, H_3-19), 1.67 (3H, br s, H_3-18), 1.60 (3H, br s, H_3-20); ^{13}C NMR: δ 180.6 (s, C-9), 166.5 (s, C-1), 157.7 (s, C-4a), 155.2 (s, C-10a), 150.7 (s, C-7), 142.0 (s, C-13), 131.8 (s, C-17), 125.3 (d, C-6), 123.0 (d, C-16), 120.7 (s, C-8a), 118.8 (d, C-5), 118.7 (d, C-12), 106.1 (d, C-8), 103.6 (s, C-9a), 96.9 (d, C-2), 92.4 (d, C-4), 65.5 (t, C-11), 55.7 (q, 3-OMe), 39.5 (t, C-14), 26.2 (t, C-15), 25.5 (q, C-18), 17.6 (q, C-20), 16.6 (q, C-19).

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