Full Papers

Guaianolides from *Tanacetum argenteum* Subsp. *canum* var. *canum*

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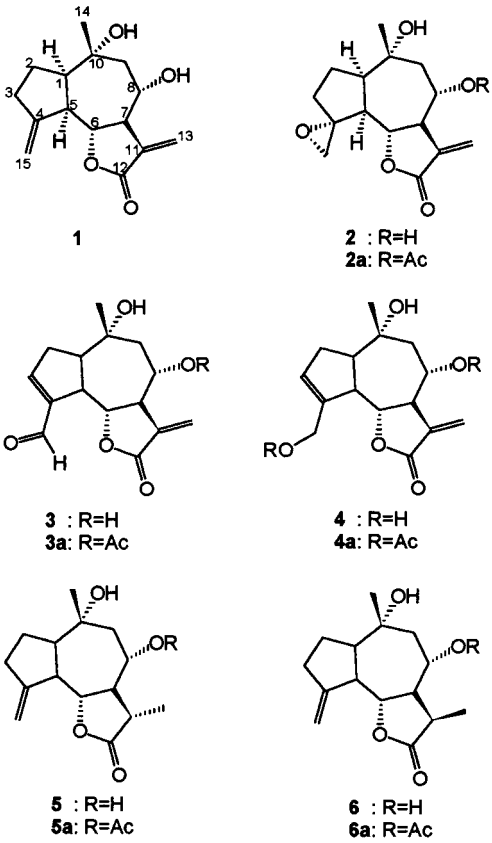
The aerial parts of *Tanacetum argenteum* subsp. *canum* var. *canum* (Compositae) afforded six guaianolides, five of them (**2**−**6**) being new: flabellin (**1**), epoxyflabellin (**2**), $\Delta^{3(4)}$-15-oxo-flabellin (**3**), $\Delta^{3(4)}$-15-hydroxydihydroflabellin (**4**), 11α-dihydroflabellin (**5**), and 11β-dihydroflabellin (**6**). The structures of the compounds were elucidated by spectral methods including NMR (^{1}H NMR, COSY, APT, HETCOR, NOE) and X-ray diffraction, as well as by some chemical reactions.

The genus *Tanacetum* is of interest because of its bioactive sesquiterpene lactones, which are the main secondary metabolites. In the course of our studies on Turkish *Tanacetum* species, we investigated *Tanacetum argenteum*, which is divided into three subspecies: subsp. *argenteum*, subsp. *flabellifolium*, subsp. *canum*. *Tanacetum argenteum* subsp. *canum* is further divided into two varities: var. *canum* and var. *pumilum*.[1] Like other *Tanacetum* species, *Tanacetum argenteum* subsp. *canum* var. *canum*, which grows on the limestone slopes and rocks in the southern part of Turkey, afforded a variety of sesquiterpene lactones consisting primarily of germacranolides, eudesmanolides,[2] and guaianolides. In addition to flabellin (**1**), first isolated from *Tanacetum argenteum* subsp. *flabellifolium*,[3] *Tanacetum argenteum* subsp. *canum* var. *canum* yielded five new guaianolides which are derivatives of flabellin. In this paper, we report the isolation and the structure elucidation of the new guaianolides **2**−**6**.



Results and Discussion

The guaianolides **1**−**6** were isolated from the aerial parts of *T. argenteum* subsp. *canum* var. *canum* by standard methods (see Experimental Section). The IR spectrum of **2** showed lactone and hydroxyl group absorptions at 1740 and 3450 cm^{-1}. The HRMS spectrum of **2** displayed a quasi molecular ion peak corresponding to $C_{15}H_{21}O_5$ $[M + 1]^+$ at *m/z* 281.1397. The ^{1}H NMR spectrum of **2** suggested a guaianolide with an α-methylene-γ-lactone group. A pair of broadened doublets was observed at δ 6.20 (br d, J = 3.5 Hz, H-13) and 6.02 (br d, J = 3 Hz, H-13′) indicating a vicinal α-hydroxyl group.[4] The ^{1}H NMR spectrum of compound **2** was very similar to that of flabellin (**1**), which was first isolated from *Tanacetum argenteum* subsp. *flabellifolium* in a previous work[3]. The main difference between compounds **1** and **2** was the presence of the epoxy group at C-4 in **2**, which appeared at δ 3.23 (d, J = 4.5 Hz, H-15) and 2.93 (d, J = 4.5 Hz, H-15′), instead of the exocyclic methylene group at that position in compound **1** (Table 1). The stereoposition of the epoxy group was determined by X-ray analysis. The secondary alcohol group at δ 3.90 (m, H-8) partially overlapped with the lactone proton (H-6) at δ 4.00 (t, J = 10.5 Hz) and the OH at δ 3.56 (br d, J = 10.5 Hz, exchangeable with D_2O) as in flabellin. H-7 appeared as a four-fold doublet at δ 3.37 (dddd, J = 10.5, 9, 3.5, 3 Hz). The quaternary methyl group appeared at δ 1.33 (3H, s, H-14). Relative to flabellin, H-5 was shifted upfield to

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Table 1. 1D and 2D ^{1}H NMR Spectra of **1**−**6** (200 MHz)

H	**1**	**2**[a]	**2**[b]	**3**[a]	**3a**[a]	**4**[a]	**4a**[a]	**5**[a]	**5**[c]	**5a**[a]	**6**[a]	**6**[c]	**6a**[a]
1	2.23 m	2.58 m	2.03 m	2.55 m	2.53 m	2.55 m			2.37 m	2.45 m		2.37 m	2.30 m
2	1.80 m	1.61 m	1.30−1.50 m	2.55 m		2.35 m	2.63 m	1.55 m	1.90 m			1.85 m	1.73 m
2′	1.53 m	1.48 m	0.82 ddd	2.30 m		2.20 m						1.34 m	
3	2.44 m	2.58 m	1.90−2.10 m	6.94 br s	6.93 br s	5.81 br s	5.83 br s	2.36 m	2.45 m	2.40 m	2.44 m	2.35 m	2.40 m
3′	2.30 m	2.35 m	1.90−2.10 m										
5	2.91 br dd	2.04 dd	1.70 dd	3.47 m	3.47 m	2.99 dd	3.00 dd	2.81 dd	2.78 dd	2.85 dd	2.83 dd	2.78 m	2.83 dd
6	3.88 t	4.00 t	3.02 t	3.87 t	3.90 m	3.95 t	4.00 t	3.88 t	4.13 t	3.99 t	4.00 t	4.30 t	4.11 t
7	3.45 dddd	3.37 dddd	2.98 m	3.47 m	3.90 m	3.49 dddd	3.90 dddd	2.45 m	2.37 m	2.77 q	2.95 m	2.78 m	3.20 q
8	3.88 m	3.90 m	3.50 m	3.90 m	5.18 br dd	3.90 m	5.18 ddd	3.78 m	3.80 m	5.11 ddd	3.95 m	3.90 ddd	5.11 ddd
9	2.16 dd	2.17 dd	1.30−1.50 m	2.21 dd	2.32 dd	2.18 dd	2.32 dd	2.45 m	2.23 dd	2.28 dd		2.23 dd	2.25 dd
9′	1.89 br d	1.89 br d	1.30−1.50 m	1.99 br d	1.91 br d	1.94 dd	1.86 br d	1.87 br d	1.79 m	1.70 dd		1.79 m	1.77 dd
11								2.45 m	2.55 m	2.45 m	2.92 m	2.78 m	2.78 dq
13	6.17 dd	6.20 br d	6.29 br d	6.22 br d	6.20 d	6.21 dd	6.20 d	1.41 d	1.30 d	1.27 d	1.25 d	1.27 d	1.17 d
13′	6.00 dd	6.02 br d	5.98 br d	6.02 br d	5.62 d	6.05 dd	5.51 d						
14	1.33 s	1.33 s	0.77 s	1.38 s	1.29 s	1.34 s	1.26 s	1.30 s	1.17 s	1.24 s	1.25 s	1.14 s	1.26 s
15	5.16 br s	3.23 d	3.17 d	9.74 s	9.74 s	4.34 s	4.90 d	5.17 br s	5.04 t	5.17 br s	5.18 br s	5.05 t	5.18 br s
15′	5.02 br s	2.93 d	2.71 d			4.34 s	4.76 d	4.99 br s	4.89 t	5.00 br s	5.01 br s	4.89 t	5.01 br s
OH	3.62 br d	3.56 br d		3.20 br d		3.28 br d							
OAc					2.18 s		2.18 s			2.12 s			2.09 s
OAc							2.08 s						

[a] $CDCl_3$. [b] C_6D_6. [c] Me_2CO-d_6 *J* (Hz) **1**: 1,5=6.5; 5,6=6,7=7,8=11; 8,9=5.5; 9,9′=16; 13,13′=1.5; 7,13=3.5; 7,13′=3; **2**: 1,5=6.5; 5,6=6,7=8,OH=10.5; 8,9=5.5; 9,9′=16; 7,8=9; 7,13=3.5; 7,13′=3; 15,15′=4.5; **3**: 5,6=6,7=10; 8,9=6; 9,9′=16; 7,13=3.5; 7,13′=3; 8,OH=10.5; 7,8=8; **4**, **4a**: 1,5=7; 5,6=6,7=7,8=10; 7,13=3.5; 7,13′=3; 8,9=6; 9,9′=16; 8,OH=10.5; 15,15′=14; **5, 6**: 1,5=7; 5,6=6,7=7,8=7,11=10; 8,9=5.5; 8,9′=4, 9,9′=16; 11,13=7.

Table 2. ^{13}C NMR Spectra of **1**−**6** (50.32 MHz, $CDCl_3$)[a]

C	**1** (APT)	**2** (APT)a	**3** (APT)	**4** (APT)	**5a** (APT)	**6** (APT)
1	54.0 (−)	54.2 (−)	55.2 (−)	55.4 (−)	51.8 (−)	57.1 (−)
2	26.7 (+)	25.3 (+)	34.5 (+)	33.7 (+)	26.2 (+)	26.7 (+)
3	29.5 (+)	28.9 (+)	147.5 (−)	126.6 (−)	30.0 (+)	29.7 (+)
4	149.0 (+)	66.1 (+)	147.6 (+)	147.4 (+)	149.9 (+)	149.7 (+)
5	53.0 (−)	52.8 (−)	51.3 (−)	51.9 (−)	51.3 (−)	53.3 (−)
6	76.6 (−)	75.8 (−)	78.7 (−)	80.3 (−)	77.4 (−)	77.3 (−)
7	52.2 (−)	52.4 (−)	48.5 (−)	51.5 (−)	52.5 (−)	51.2 (−)
8	71.4 (−)	71.5 (−)	72.0 (−)	71.8 (−)	73.9 (−)	66.5 (−)
9	40.5 (+)	39.7 (+)	40.2 (+)	40.1 (+)	42.7 (+)	41.3 (+)
10	75.4 (+)	75.8 (+)	75.2 (+)	75.5 (+)	73.5 (+)	75.5 (+)
11	140.2 (+)	139.4 (+)	139.6 (+)	139.5(+)	42.4 (−)	38.3 (−)
12	170.2 (+)	169.8 (+)	[b]	[b]	170.2 (+)	179.6 (+)
13	121.0 (+)	121.7 (+)	121.6 (+)	121.7 (+)	15.2 (−)	12.0 (−)
14	33.4 (−)	33.2 (−)	33.5 (−)	33.6 (−)	31.2 (−)	32.9 (−)
15	111.5 (+)	50.4 (+)	188.1 (+)	62.0 (−)	110.4 (+)	111.2 (+)
OAc					21.3 (−)	

[a] All protonated carbons correlated with their bound protons in the HETCOR experiments. [b] Not observed.

δ 2.04, between H-9 and H-9′ located at δ 2.17 and 1.89, while ^{13}C NMR resonances of C-5 and C-9 had almost the same frequency at δ 52.8 (d, C-5) and δ 39.7 (t, C-9) as in flabellin. The spin decoupling and ^{1}H−^{1}H COSY experiments allowed all resonances to be assigned. The ^{13}C NMR, which consists of 15 carbons, exhibited resonances at 139.4 (s, C-11), 169.8 (s, C-12), and 121.7 (t, C-13), indicating an α-methylene-γ-lactone group. The signals at δ 50.4 (t, C-15) and 66.1 (s, C-4) confirmed the presence of the epoxy group. The other ^{13}C NMR resonances were observed at δ 75.8 (d) for C-6, 52.4 (d) for C-7, and at δ 71.5 (d) for C-8. Although the resonances of C-6 and C-10 overlapped at δ 75.8, the APT spectrum allowed to distinguish these two signals giving a positive signal for the quaternary C-10 and a negative signal for the C-6 methine carbon (Table 2). The compound was also obtained by epoxidation of flabellin with *m*-CPBA. Acetylation gave the monoacetyl derivative **2a**. In the ^{1}H NMR spectrum of **2a** in $CDCl_3$, H-8 was shifted downfield from δ 3.90 to 5.17 and an acetyl resonance appeared at δ 2.18. The proton-bearing carbon signals were assigned by HETCOR experiments. The relative configuration of **2** was determined by X-ray measurements, and a thermal ellipsoid drawing is shown in Figure 1.

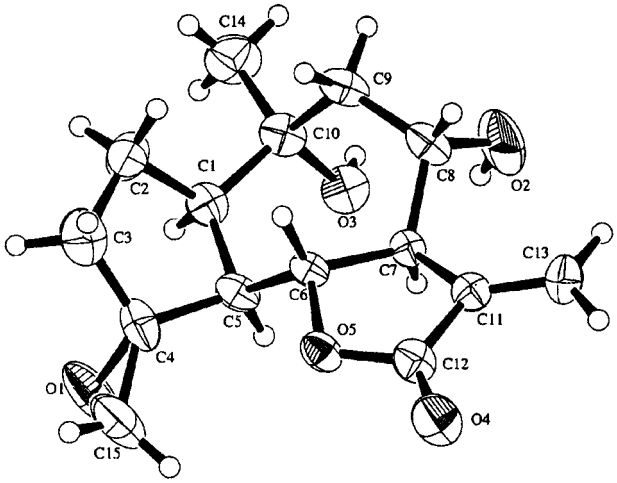

Figure 1. Molecular structure of **2**.

Compounds **3** and **4** are derivatives of flabellin having a double bond between C-3 and C-4. Compound **3** has an aldehyde group at C-4, while compound **4** has a hydroxymethylene group at that position. This was clearly seen from their mass spectra. The HRMS of **3** exhibited a peak at *m*/*z* 248.1050 corresponding to $C_{14}H_{16}O_4$ $[M-CHOH]^+$, whereas the HRMS of **4** afforded a peak at *m*/*z* 280.1305 corresponding to $C_{15}H_{20}O_5$ $[M]^+$. In the ^{1}H NMR of **3** a singlet at δ 9.74 indicated the presence of an aldehyde group, due to this group the olefinic proton signal was shifted downfield to δ 6.94 (br s, H-3). The rest of the spectrum of **3** was quite similar to that of flabellin (Table 1). The ^{1}H NMR of **4** displayed the olefinic proton at δ 5.81 (br s, H-3) and a broadened singlet at δ 4.34 (2H, H_2-15), indicating the presence of a hydroxymethylene group at C-4, showing that the downfield shift of the olefinic proton in compound **3** was caused by the effect of the aldehyde group (Table 1). The other signals of compound **4** were similar to that of flabellin. Spin decoupling, APT, and HETCOR experiments were used to assign the resonances of the two compounds. Acetylation of the compounds afforded a monoacetyl derivative for **3** (**3a**) and a diacetyl derivative for **4** (**4a**) (Table 1). In the ^{1}H NMR spectrum

of **3a,** H-8 shifted downfield from δ 3.90 to 5.18 and an acetyl signal was observed at δ 2.18. In the ^{1}H NMR spectrum of **4a**, H-8 shifted downfield from δ 3.90 to 5.18, while H_2-15 shifted from δ 4.34 (2H) to 4.90 (1H, d, J = 14 Hz, H-15) and 4.76 (1H, d, J = 14 Hz, H-15′) and two acetyl signals were observed at δ 2.18 and 2.08. The HRMS spectrum of **3a** gave a peak at *m/z* 321.1334 corresponding to $C_{17}H_{21}O_6$ $[M + 1]^+$.

The *Rf* values of compounds **5** and **6** were quite different from each other, Rf_5: 0.10 and Rf_6: 0.21 in ether. The IR spectra showed lactone absorption at 1780 cm^{-1} and 1750 cm^{-1}, respectively. There were few differences, however, in the ^{1}H NMR spectra of **5** and **6**, although they were very similar to the spectrum of flabellin. In the ^{1}H NMR of compound **5**, a secondary methyl resonance was observed at δ 1.41 (d, J = 7 Hz, H-13) rather than the exocyclic γ-lactone methylene protons in **1,** in addition to a methyl singlet attached to a hydroxyl group at δ 1.30 (s, H-14). The exocyclic methylene protons (H_2-15) appeared at δ 5.17 (br s) and 4.99 (br s) in the spectrum of **5**. The compound gave a better dispersion in Me_2CO-d_6 for the resonances of hydrogens 1 through 9. In the ^{1}H NMR of **6** the secondary methyl doublet appeared at δ 1.25 (d, J = 7 Hz, H-13) and the tertiary methyl singlet at δ 1.25 (s, H-14). The exocyclic methylene signals were observed at δ 5.18 (br s, H-15) and 5.01 (br s, H-15′). As seen in the Table 1, the chemical shifts of the other signals were also slightly different from each other in each spectrum. Compound **6** also gave a better dispersion in Me_2CO-d_6 and the overlapped methyl signals appeared at δ 1.27 (d, J = 7 Hz, H-13) and δ 1.14 (s, H-14). Thus, compounds **5** and **6** seemed to be C-11 epimers. Acetylation of compounds **5** and **6** yielded the monoacetyl derivatives **5a** and **6a**. NOE experiments were carried out on **5a**. Irradiation of H-11 at δ 2.45 (m, overlapped with H-1) showed NOE with the β-oriented protons at δ 3.99 (H-6) and δ 5.11 (H-8) indicating the α-orientation of the methyl group at the lactone ring. It also showed NOE with H-14 at δ 1.24 due to the overlapping H-1 signal. In addition, a NOE was observed between the neighboring protons, H-11 and H-13. The ^{13}C NMR spectrum of **5a** supported the proposed structure giving 16 carbon resonances, two of them being methyl carbons at δ 15.2 (C-13) and 31.2 (C-14), an olefinic methylene carbon at δ 110.4 (C-15), an olefinic quaternary carbon at δ 149.9 (C-4), and the other signals of the skeleton (Table 2). The ^{13}C NMR spectrum of **6** supported the proposed structure giving 15 carbon signals (Table 2). The proton-bearing carbons were assigned by HETCOR experiments. HRMS of **5a** gave a peak at *m/z* 308.1630 corresponding to $C_{17}H_{24}O_5$ $[M]^+$, while **6** gave a peak at *m/z* 266.1642 corresponding to $C_{15}H_{22}O_4$ $[M]^+$.

Experimental Section

General Experimental Procedures. Column chromatography was carried out on Kieselgel 60 (0.063−0.200 mm, Merck) and Sephadex LH-20 (Pharmacia); TLC was performed on precoated Si gel 60 F_{254}, 0.2-mm plates (Merck); spots were detected under UV and spraying acidified ceric sulfate followed by heating. Melting point was determined on a Dupont 910 DSC instrument. IR spectra were run on a Perkin−Elmer 983 instrument. ^{1}H NMR, COSY, APT, HETCOR spectra were recorded in $CDCl_3$, C_6D_6, and Me_2CO-d_6 on a Bruker AC-200L (^{1}H NMR 200 MHz, ^{13}C NMR 50.37 MHz). TMS was used as internal reference in the NMR spectra. NOE spectrum was performed on a Varian instrument (200 MHz). EIMS, CIMS, and HRMS were recorded on a VG ZabSpec instrument (70 eV). X-ray data were collected on a Rigaku AFC6S. Optical rotations were performed on Opt. Act. Ltd. AA-5 polarimeter.

Plant Material. *T. argenteum* (Lam.) Wild., subsp. *canum* (C. Koch) Grierson var. *canum* was collected from southeast Taurus Mountains (Gülek Tepe-Adana) and identified by Prof. Dr. N. Özhatay. A voucher specimen (ISTE 64366) is deposited in the Herbarium of the Faculty of Pharmacy, University of Istanbul, Turkey.

Extraction and isolation. Dried and powdered aerial parts (1 kg) were extracted successively with petroleum ether (40−60°), EtOAc, and MeOH. The EtOAc and MeOH extracts (60 g) were combined, evaporated to dryness *in vacuo* and the residue dissolved in MeOH by heating in a H_2O bath up to 70 °C, and placed in a refrigerator (4 °C) for several hours. The precipitate was removed by filtration, and the filtrate was concentrated *in vacuo* to dryness. The residue was applied to a Si gel column and eluted with petroleum ether with 10%, 15%, 25%, 50%, 100% CH_2Cl_2, followed by 10%, 15%, 25%, 50%, 100% EtOAc, then 10%, 15%, 25%, 50%, 100% Me_2CO, and finally 10%, 15%, 25%, 50%, 100% MeOH; 24 fractions were obtained from the column. The fractions from column chromatography were monitored by TLC, and the similar fractions were combined and further separated by Si gel and/or Sephadex LH-20 columns and preparative TLC. The guaianolides were obtained from the most polar fractions. The compounds **1**−**4** were isolated from the fractions 13−17 and compounds **5** and **6** from the fractions 18−24. Thus, 630 mg of **1**, 6 mg of **2**, 34 mg of **3**, 22 mg of **4**, 35 mg of **5**, and 23 mg of **6** were obtained.

Epoxyflabellin (2): $[\alpha]^{20}_D \pm 0°$ (*c* 0.1, $CHCl_3$), mp 184 °C; IR ν_{max} ($CHCl_3$) 3500, 1740, 1640, 1200, 910 cm^{-1}; ^{1}H NMR, see Table 1; ^{13}C NMR, see Table 2; EIMS *m/z* (rel int) 281 $[M + 1]^+$ (3), 262 $[M - H_2O]^+$ (10), 244 $[262 - H_2O]^+$ (28), 219 $[262 - CH_3CO]^+$ (37), 216 $[244 - CO]^+$ (30), 201 $[219 - H_2O]^+$ (66), 189 (48), 173 (53), 166 (56), 161 (38), 145 (44), 137 (52), 131 (54), 123 (79), 107 (71), 97 (90), 91 (84), 87 (77), 79 (88), 69 (100); HRMS *m/z* 281.1397 ($C_{15}H_{21}O_5$) $[M + 1]^+$.

Acetylation of 2. Compound **2** (6 mg) was dissolved in pyridine (1 mL) and treated with $(Ac)_2O$ (1 mL) overnight. After evaporation it was separated by preparative TLC, yielding **2a** (4.5 mg).

8α-Acetylepoxyflabellin (2a): ^{1}H NMR, see Table 1.

$\Delta^{3(4)}$-15-Oxoflabellin (3): $[\alpha]^{20}_D$ −33.3° (*c* 0.6, $CHCl_3$); IR ν_{max} ($CHCl_3$) 3430, 1750, 1660 cm^{-1}; ^{1}H NMR, see Table 1; ^{13}C NMR, see Table 2; HRMS *m/z* 248.1050 ($C_{14}H_{16}O_4$) $[M - CHOH]^+$; EIMS *m/z* (rel int) 279 $[M + 1]^+$ (8), 249 $[279 - CHOH]^+$ (100), 231 $[249 - H_2O]^+$ (96), 213 $[231 - H_2O]^+$ (18), 205 (15), 185 (10), 159 (8), 117 (15), 80 (80).

Acetylation of 3. Compound **3** (8 mg) was dissolved in pyridine (1 mL) and added $(Ac)_2O$ (1 mL) overnight. After evaporation it was separated by preparative TLC, yielding **3a** (5 mg).

$\Delta^{3(4)}$-8α-*O*-acetyl-15-oxoflabellin (3a): ^{1}H NMR, see Table 1; EIMS *m/z* (rel int) 321 $[M + 1]^+$ (17), 307 $[M - CH_2]^+$ (10), 278 $[307 - CHO]^+$ (19), 260 $[278 - H_2O]^+$ (55), 242 $[260 - H_2O]^+$ (48), 231 (22), 214 $[242 - CO]^+$ (34), 199 $[214 - CH_3]^+$ (40), 171 (40), 165 (57), 147 (53), 135 (58), 122 (84), 95 (100), 69 (91), 57 (53). HRMS *m/z* 321.1334 $(C_{17}H_{21}O_6)[M + 1]^+$.

$\Delta^{3(4)}$-15-Hydroxydihydroflabellin (4): $[\alpha]^{20}_D$ +48.6° (*c* 1.5, $CHCl_3$); IR ν_{max} ($CHCl_3$) 3400, 1760, 1660 cm^{-1}; ^{1}H NMR, see Table 1; ^{13}C NMR, see Table 2; EIMS *m/z* (rel int) 280 $[M]^+$(8), 262 $[M - H_2O]^+$ (12), 244 $[262 - H_2O]^+$ (40), 226 $[244 - H_2O]^+$ (24), 215 (29), 201 $[244 - CH_3CO]^+$ (42), 186 $[201 - CH_3]$ (29), 176 (40), 165 (24), 159 (35), 149 (48), 131 (58), 123 (93), 107 (81), 95 (98), 79 (95), 69 (100); HRMS *m/z* 280.1305 $(C_{15}H_{20}O_5)$ $[M]^+$.

Acetylation of 4. Compound **4** (6 mg) was dissolved in pyridine (1 mL) and added $(Ac)_2O$ (1 mL) overnight. After evaporation it was separated by preparative TLC, yielding **4a** (5 mg).

$\Delta^{3(4)}$-8α-*O*-Acetyl-15-acetoxydihydroflabellin (4a): ^{1}H NMR, see Table 1; EIMS *m/z* (rel int) 364 $[M]^+$ $(C_{19}H_{24}O_7)$ (28), 321 $[M - COCH_3]^+$ (100), 279 $[321 - CH_2CO]^+$ (17), 262 $[321 - CH_3COO]^+$ (39), 244 $[262 - H_2O]^+$ (69), 226 $[244 - H_2O]^+$ (61), 201 (71), 186 (60), 173 (39), 165 (43), 155 (51), 137 (40), 131 (53), 123 (67), 105 (58), 91 (61), 79 (86), 67 (43).

11α-Dihydroflabellin (5): IR ν_{max} ($CHCl_3$) 3430, 1780, 1660, 1470, 1385, 1170, 905, 760 cm^{-1}; ^{1}H NMR, see Table 1; EIMS *m/z* (rel int) 266 $[M]^+$ (7), 248 $[M - H_2O]^+$ (15), 230 $[248 - H_2O]^+$ (8), 215 $[230 - CH_3]^+$ (5), 205 (21), 180 (60), 132 (54), 121 (67), 108 (100), 91 (58), 81 (85), 69 (78), 57 (38).

Acetylation of 5. Compound **5** (23 mg) was dissolved in pyridine (2 mL) and added $(Ac)_2O$ (2 mL) overnight. After evaporation it was separated by preparative TLC, yielding **5a** (18 mg).

8α-*O*−Acetyl-11α-dihydroflabellin (5a): $[\alpha]^{20}_D$ +16.9° (*c* 0.6, $CHCl_3$); ^{1}H NMR, see Table 1; ^{13}C NMR, see Table 2; EIMS *m/z* (rel int) 308 $[M]^+$ (22), 293 $[M - CH_3]^+$ (36), 290 $[M - H_2O]^+$ (24), 248 $[M - CH_3COOH]^+$ (58), 230 $[248 - H_2O]^+$ (48), 215 $[230 - CH_3]^+$ (16), 205 (39), 190 (53), 174 (42), 167 (100), 159 (33), 149 (40), 132 (74), 125 (57), 107 (60), 95 (47), 81 (75), 69 $[C_5H_9]^+$ (55), 57 (30); HRMS *m/z* 308.1630 $(C_{17}H_{24}O_5)[M]^+$.

11β-Dihydroflabellin (6): $[\alpha]^{20}_D$ −44.3° (*c* 0.32, $CHCl_3$); IR ν_{max} ($CHCl_3$) 3430, 1750, 1660 cm^{-1}; ^{1}H NMR see Table 1; ^{13}C NMR, see Table 2; EIMS *m/z* (rel int) 267 $[M + 1]^+$ (57), 249 $[M - H_2O]^+$ (82), 231 $[249 - H_2O]^+$ (76), 203 $[231\text{-}CO]^+$(60), 185(52), 153(36), 135(32), 83(54), 69(10), 59(100). HRMS *m/z* 266.1642 $(C_{15}H_{22}O_4)[M]^+$.

Acetylation of 6. Compound **6** (9 mg) was dissolved in pyridine (1 mL) and added $(Ac)_2O$ (1 mL) overnight. After evaporation it was separated by preparative TLC, yielding **6a** (7) mg.

8α-*O*−Acetyl-11β-dihydroflabellin (6a): ^{1}H NMR, see Table 1; EIMS *m/z* (rel int) 308 $[M]^+$ (21), 293 $[M - CH_3]^+$ (35), 290 $[M - H_2O]^+$ (23), 248 $[M - CH_3COOH]^+$ (57), 230 (48), 205 (38), 190 (53), 174 (42), 167 (100), 132 (73), 125 (56), 107 (60), 95 (47), 81 (74), 69 (55), 57 (30).

X-ray Analysis. **X-ray Diffraction Studies.** All data were collected on a Rikagu AFC6S diffractometer with graphite monochromated Cu Kα radiation (λ = 1.54178 Å) and a constant speed ω-2θ scan technique ($2\theta_{max}$ = 158.0°) with weak reflections rescanned a maximum of four times. The unit cell was orthorhombic with space group $P2_12_12_1$. Unit cell parameters were obtained from a least-squares refinement of 25 centered reflections in the 2θ range 58.7−77.4° giving a = 8.952(2), b = 24.271(2), and c = 6.549(2) Å with V = 1423.1(5) Å^3, Z = 4, D_{calc} = 1.308 g cm^{-3}, and μ = 7.70 cm^{-1}. Lorenz-polarization, a Ψ-scan empirical absorption correction and an extinction correction were applied. The structure was solved by direct methods[6] and refined and analyzed by teXsan[7] and PLATON[8] giving R = 0.072 and R_w = 0.071, $(\Delta/\sigma)_{max}$ = 0.20 and ρ_{diff} = −0.46, +0.50 e$^-$/Å^3. The coordinates, distances and angles have been deposited with Cambridge Crystallographic Data Centre.

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