(8*Z*,13*Z*,20*Z*)-Strobilinin and (7*Z*,13*Z*,20*Z*)-Felixinin: New Furanosesterterpene Tetronic Acids from Marine Sponges of the Genus *Ircinia*

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Methanolic extracts of the marine sponges *Ircinia felix*, *I. strobilina* and *I. campana* occurring in the Colombian Caribbean afforded similar complex mixtures of antimicrobial furanosesterterpene tetronic acids. Each mixture was acetylated and then fractionated by HPLC. GC, GC-MS and NMR analyses of the HPLC fractions revealed the novel (8*Z*,13*Z*,20*Z*)-strobilinin and (7*Z*,13*Z*,20*Z*)-felixinin, together with the known (8*E*,13*Z*,20*Z*)-strobilinin, (7*E*,13*Z*,20*Z*)-felixinin and (7*E*,12*E*,18*R*,20*Z*)-variabilin.

Key words strobilinin; felixinin; variabilin; furanosesterterpene; *Ircinia*; marine sponge

Marine sponges of the genus *Ircinia* are a source of bioactive furanosesterterpene tetronic acids.[1] We have recently reported on the occurrence of (18*R*)-variabilin and variabilin 11-methyloctadecanoate in *Ircinia felix*.[2,3] As a continuation of our studies on *Ircinia* marine sponges occurring in the Colombian Caribbean, we reisolated the furanosesterterpene mixture from *I. felix* and obtained the corresponding mixtures from *I. strobilina* and *I. campana* also. These mixtures were acetylated and subjected to HPLC separation to give three fractions, designated as fractions I—III, for each sponge species, as shown in Fig 1.

GC and GC-MS analyses of fraction I isolated from *I. felix* revealed that it is composed of a 1 : 1 mixture of the acetylated furanosesterterpene tetronic acids **1** and **2** (Fig. 2). The molecular weights of **1** and **2** (*m/z* 440) were identical to that of variabilin acetate, suggesting that they are geometric or double-bond positional isomers of variabilin. The fragment ions at *m/z* 81 (C-5/C-6 cleavage), 95 (C-6/C-7 cleavage) and 163 (C-11/C-12 cleavage) in the mass spectrum of **1** arose due to the characteristic allylic bond cleavage, indicating the presence of double bonds at the C-8 and C-13 positions, while in the case of **2**, the allylic bond cleavage produced ions at *m/z* 81, 95, 149 (C-10/C-11 cleavage) and 163, indicating the presence of double bonds at the C-7 and C-13 positions. These fragmentation patterns are apparently different from that of the C-7- and C-12-olefinic compound, variabilin acetate.

The ^{1}H- and ^{13}C-NMR spectra of fraction I showed the characteristic signals of acetylated furanosesterterpene tetronic acids. The most significant feature in the ^{13}C-NMR spectrum was the appearance of two sets of some signals in *ca.* 1 : 1 ratio, confirming the presence of two furanosesterterpene isomers. The chemical shifts of olefinic methyl protons (δ_H 1.68 and 1.66), and carbon signals for olefinic methyls (δ 23.34, four overlapped signals) and

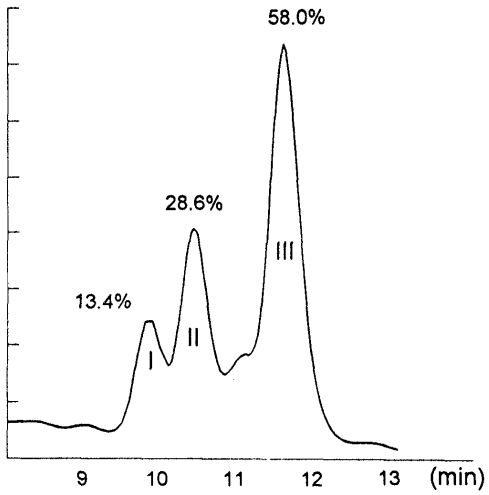

Fig. 1. HPLC Profile of the Acetylated Furanosesterterpene Tetronic Acid Mixture Isolated from *Ircinia felix*

Similar profiles were obtained for the acetylated mixtures isolated from *I. strobilina* and *I. campana*.

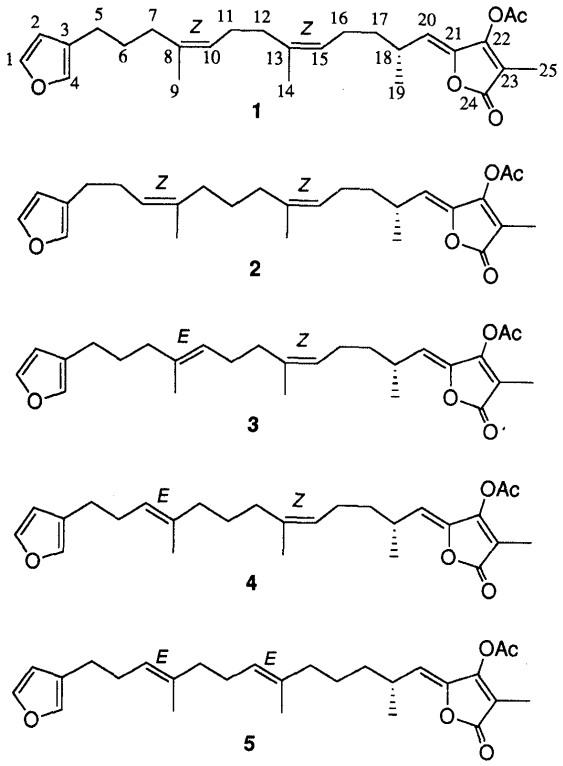

Fig. 2. Structures of the Furanosesterterpene Tetronic Acids Identified as Their Acetate Forms in the Marine Sponges, *Ircinia felix*, *I. strobilina* and *I. campana*

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Table 1. ^{13}C-NMR Data (125 MHz, $CDCl_3$)[a] for Compounds **1**—**4**

Carbon	1	2	3	4
1	142.62	142.51	142.54	142.47
2	110.89	111.03	110.99	111.03
3	125.02	124.88	125.10	124.93
4	138.70	138.76	138.72	138.72
5	24.61	25.21	24.22	24.99
6	28.28	28.28	28.12	28.37
7	31.32	124.37	39.13	123.65
8	134.99	135.98	134.79	135.78[b]
9	23.34	23.34	15.79	15.90
10	125.15	31.61[c]	124.37	39.49
11	26.27	26.27	26.42	26.25
12	32.07	31.66[c]	31.81	31.34
13	135.45	135.69	135.56	135.83[b]
14	23.34	23.34	23.36	23.36
15	124.59	124.48	124.55	124.37
16	25.72	25.68	25.74	25.68
17	37.37	37.37	37.39	37.39
18	30.86	30.86	30.88	30.88
19	20.47	20.47	20.49	20.49
20	116.47	116.47	116.48	116.48
21	142.36	142.36	142.36	142.36
22	154.25	154.25	154.27	154.27
23	114.67	114.67	114.66	114.66
24	168.62	168.62	168.62	168.62
25	8.37	8.37	8.35	8.35
$CH_3\underline{C}O$	165.37	165.37	165.35	165.35
$\underline{C}H_3CO$	20.42	20.42	20.42	20.42

a) Chemical shifts, δ, are expressed in parts per million and are referenced to the $CDCl_3$ signal (δ 77.0). *b, c*) Assignments may be interchanged.

allylic methylenes (δ 31.32, 31.61, 31.66 and 32.07 were characteristic of *Z*-trisubstituted double bond geometry,[4] indicating that compounds **1** and **2** have two such double bonds. The 20*Z* geometry for **1** and **2** was assigned on the basis of the chemical shifts of C-20 (δ 116.47).[5] Although our efforts to separate compounds **1** and **2** were unsuccessful, further structure analysis was undertaken using NMR spectroscopy, including two dimensional (2D)-NMR, of fraction I isolated from *I. strobilina* and *I. campana* (4:1 and 7:3 mixtures of **1** and **2**, respectively). These studies made it possible to distinguish and assign all the NMR signals for each compound, and to establish the structures of **1** and **2**.

The H–H correlation spectroscopy (COSY) spectrum revealed the connectivity of H-5 (δ 2.39, t)—H-6 (δ 1.64, m)—H-7 (δ 2.05, t) for the major component **1**. The chemical shift and coupling pattern of H-7 confirmed that **1** has the *Z*-double bond at C-8, not C-7. Another connectivity found in the spectrum was

H-20 (δ 5.05, d)
H-19 (δ 1.06, d) > H-18 (δ 2.83, m)—H-17 (δ 1.40, m)—H-16 (δ 1.95, m)—H-15 (δ 5.09, t).

The connectivity of H-17—H-16—H-15 was somewhat ambiguous due to the overlap of proton resonances at δ *ca.* 1.95, but seems highly likely based on the chemical shifts of H-17 and H-16. The carbon resonance at δ 37.37, linked to H-17, is characteristic of C-17 for C-13-olefinic compounds (δ *ca.* 37.4 for C-17 of C-13-olefinic compounds[5,6]; δ *ca.* 36.7 for C-17 of C-12-olefinic compounds).[7] On the basis of these data, compound **1** was established to be a novel (8*Z*,13*Z*)-compound and was named (8*Z*,13*Z*,20*Z*)-strobilinin.

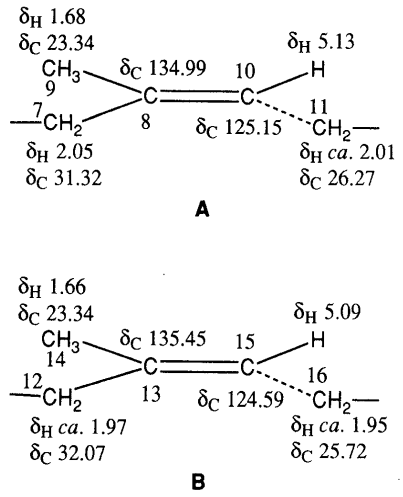

Fig. 3. Partial Structures of **1**

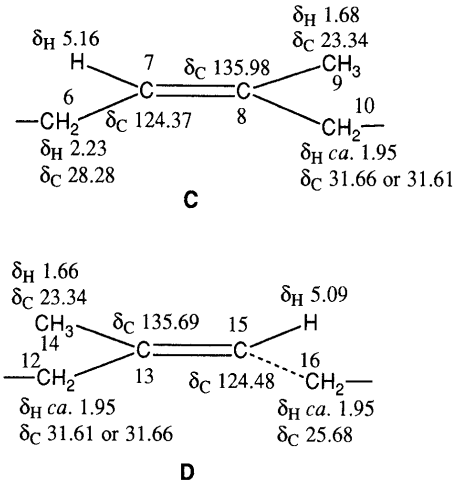

Fig. 4. Partial Structures of **2**

The ^{13}C assignments of **1** (Table 1) were made as follows. The correlations obtained from the C–H long-range COSY spectrum plus the C–H COSY spectrum, allowed us to build two partial structures, A and B, for **1** (Fig. 3). The assignment of A, C-7 to C-10, was based on the H–H correlation between H-6 and H-7 (*vide supra*). The partial structure B was, therefore, assigned to C-12 to C-15, although the connectivity between H-16 and H-15 was not conclusive again, due to the overlap of signals in the methylene region. Finally, the remaining methylene carbon resonance at δ 26.27, coupled to the proton at δ 2.01, was assigned to C-11.

The elucidation of the structure of **2** was performed in the same manner as described for **1**. The H–H COSY spectrum showed clear correlations for H-5 (δ 2.43, t)—H-6 (δ 2.23, q-like)—H-7 (δ 5.16, t) connectivity for the minor component **2**, confirming the presence of the C-7 double-bond. Proton resonances assignable to H-15 to H-19 were superimposed on the corresponding signals of **1**. Furthermore, the C-17 signal appeared at δ 37.37 (overlapped with that of **1**). These results are entirely consistent with the C-7- and C-13-olefinic structure. The C–H and C–H long-range COSY spectra gave information

on the connectivity for the trisubstituted olefinic moieties of the minor component (C and D). The H–H COSY correlation between H-6 and H-7 allowed us to assign the partial structure C to C-6 to C-10, and thus D to C-12 to C-15. The very similar chemical shifts of C-6 and C-12 prevented their assignment. The remaining methylene carbon at δ 26.27, coupled to the proton at δ 1.40, was assigned to C-11. Complete ^{13}C-NMR assignments for **2** are listed in Table 1. On the basis of the spectral data discussed above, compound **2** was determined to be a novel (7*Z*,13*Z*)-compound and was named (7*Z*,13*Z*,20*Z*)-felixinin.[8]

The 1 : 1 mixture of the acetylated furanosesterterpene tetronic acids **1** and **2** exhibited antimicrobial activity against Gram-positive bacteria (*Staphylococcus aureus*) with a minimum inhibitory concentration (MIC) value of 2—3μg.

Fraction II from *I. felix* showed a single peak in HPLC and GC analyses. The molecular weight was determined to be *m/z* 440 from the GC-MS studies. However, the ^{1}H- and ^{13}C-NMR spectra indicated the presence of two acetylated furanosesterterpene tetronic acids **3** and **4** in a 1 : 1 ratio. For example, in the ^{1}H-NMR spectrum four singlets (δ 1.57, 1.59, 1.66 and 1.68) were observed for olefinic methyls and two doublets for H_3-19 (δ 1.05 and 1.06). In the ^{13}C-NMR spectrum four signals (δ 15.79, 15.90, 23.36 and 23.36 (overlap of two signals)) appeared due to olefinic methyls, and four signals (δ 31.34, 31.81, 39.13 and 39.49) due to allylic methylenes. The chemical shifts of these carbon resonances indicated the presence of two *E*- and two *Z*-trisubstituted double bonds in the mixture of **3** and **4**.[4] At this time, there remained two possibilities concerning the geometry of the trisubstituted double bonds: either one of **3** and **4** has two *Z*-double bonds and the other has two *E*-double bonds or *vice versa* and, or both **3** and **4** have one *Z*- and one *E*-trisubstituted double bonds. Although HPLC separation of **3** and **4** was not successful, the latter turned out to be the case, based on NMR analysis of fraction II obtained from *I. strobilina*, which is composed of **3** and **4** in 1 : 3 ratio. Fraction II from *I. campana* was a 1 : 1 mixture of **3** and **4**.

The ^{1}H- and ^{13}C-NMR data of the more intense signals (due to compound **4**) in the NMR spectra of fraction II from *I. strobilina* showed the following features. The H–H COSY spectrum showed the connectivity of H-5 (δ 2.45, t)—H-6 (δ 2.24, q-like)—H-7 (δ 5.16, t), indicating the presence of a trisubstituted double bond at C-7. The signal due to C-17 resonated at δ 37.39, confirming the C-13 double bond. The C–H long-range COSY spectrum allowed us to connect H-9 (δ 1.57, a typical value of an *E*-trisubstituted olefin moiety) to C-7 (δ 39.49), which in turn showed connnectivity to H-7 in the C–H COSY. It was apparent that the other trisubstituted olefin moiety has *Z*-geometry (δ 1.66 for H-14 and δ 23.36 for C-14). Compound **4** was thus determined to be the known (7*E*,13*Z*)-compound and was named (7*E*,13*Z*,20*Z*)-felixinin acetate.[8] The ^{13}C-NMR data (Table 1) were in excellent agreement with those published for the 7*E*,13*Z*,20*Z*-compound except for the reversed assignments of C-11 and C-16.[5] The assignments of C-11 and C-16 are based on the fact that clear correlation peaks were observed between C-11 (δ 26.25) and H-11 (δ 1.44, m) and between C-16 (δ 25.68) and H-16 (δ 1.95, m, allylic methylene).

Table 2. $[\alpha]_D$ Values of Furanosesterterpene Tetronic Acids and Configuration at C-18

Compound	$[\alpha]_D$ value	C-18[a]
Variabilin (acetate)[b]	+33.3	*R*
Variabilin (acetate)[c]	−28.9	*S*
Variabilin[c,d]	−39.9	*S*
A 1 : 1 mixture of **1** and **2** (acetate)[e]	+34.8	(*R*)
A 1 : 1 mixture of **3** and **4** (acetate)[e]	+45.6	(*R*)
A mixture of **3** and (8*Z*,13*E*,20*Z*)-strobilinin (acetate)[f]	+30.0	(*R*)
Ircinin-1[g]	−34.1	(*S*)
Ircinin-2[g]	−40.2	(*S*)

a) The configuration in parenthesis is suggested by the sign of $[\alpha]_D$. *b*) Ref. 2. *c*) Ref. 9. *d*) Ref. 10. *e*) Present work. *f*) Ref. 6. *g*) Ref. 11.

The structure of the other component of fraction II, **3**, was analyzed similarly. The connectivity of H-5 (δ 2.38, t)—H-6 (δ 1.64, m)—H-7 (δ 2.00, t) and the chemical shift of C-17 (δ 37.39) indicated an 8,13-diene system, in which one of the trisubstituted olefins has *E*-(δ_C 15.79, 39.13) and the other has *Z*-geometry (δ_C 23.36, 31.81). Due to the overlap of signals in the ^{1}H-NMR spectrum (H-7 and H-12 at δ 2.00 and H-15 and H-10 at δ 5.09) it was not possible to assign the geometry of the double bonds unambiguously using the NMR data. Therefore, (8*E*,13*Z*)-geometry was assigned to **3** by analogy with the 13*Z*-geometric compounds **1**, **2** and **4**, and the very close similarity in chemical shifts, *e.g.*, C-13 to C-18, of **3** and **1**. Thus, compound **3** was characterized as (8*E*,13*Z*,20*Z*)-strobilinin acetate with the revised ^{13}C-NMR assignment. Isolation of this compound as an inseparable mixture with (8*Z*,13*E*,20*Z*)-strobilinin acetate has been reported recently.[6]

Fraction III isolated from *I. felix* was composed of a single acetylated furanosesterterpene tetronic acid and its structure, (7*E*,12*E*,18*R*,20*Z*)-variabilin acetate **5**, has been established.[2] Fractions III from *I. strobilina* and *I. campana* were also composed of pure (7*E*,12*E*,18*R*,20*Z*)-variabilin acetate.

The $[\alpha]_D$ values of furanosesterterpene tetronic acids having a C-18 stereogenic center are listed in Table 2. It would appear that the sign and the magnitude of $[\alpha]_D$ values are relatively insensitive to structure modifications. Although the C-18 configurations of **1**—**4** remain to be definitively established, they are most likely to be 18*R*, the same as that established for variabilin isolated from the same species.

Variabilin is the major furanosesterterpene tetronic acid (between 58.0 and 59.8%) in the three Caribbean *Ircinia* sp. examined, followed by (8*E*,13*Z*,20*Z*)-strobilinin plus (7*E*,13*Z*,20*Z*)-felixinin (28.6, 27.1 and 27.5%, in *I. felix*, *I. strobilina* and *I. campana*, respectively), with lesser amounts of (8*Z*,13*Z*,20*Z*)-strobilinin plus (7*Z*,13*Z*,20*Z*)-felixinin (13.4, 13.1 and 13.9%, in *I. felix*, *I. strobilina* and *I. campana*, respectively).

The occurrence of (7*E*,12*E*,20*Z*)-variabilin in *Ircinia* species is quite common.[12] Furthermore, its presence seems to be a chemical characteristic of this genus, while (8*E*,13*Z*,

20*Z*)-strobilinin has only been reported in *I. strobilina*[13] and in an Australian *Ircinia*,[6] and (7*E*,13*Z*,20*Z*)-felixinin has only been found in a sponge of the genus Sarcotragus.[5] (8*Z*,13*Z*,20*Z*)-Strobilinin and (7*Z*,13*Z*,20*Z*)-felixinin are novel compounds. It would be interesting to search for these new compounds in *Ircinia* sponges collected at latitudes other than the tropics.

Experimental

General Methods GC was carried out on a Hewlett Packard 5890 series II gas chromatograph equipped with FID and with an HP OV-101 fused silica capillary column (30 m × 0.25 mm i.d.; film thickness, 0.25 μm). The column was operated isothermally at 240 °C. Injector and detector temperatures were kept at 320 °C. GC-MS was performed on a JEOL JMS-DX303 mass spectrometer coupled to a Shimadzu GC-14A gas chromatograph equipped with a methyl silicon coated fused capillary column (25 m × 0.32 mm i.d.; film thickness, 0.17 μm). The same column conditions as mentioned above for GC were used. Other conditions were as follows: carrier gas (He) flow rate, 1.1 ml/min; temperature of ion source and all connecting parts, 305 °C; electron energy, 70 eV. Preparative HPLC was performed on a Shimadzu STR PREP-ODS column (250 × 20 mm i.d.) using a Shimadzu LC-6A liquid chromatograph and a Shimadzu SPD-6A UV detector, with methanol–water (15 : 1) as the mobile phase (flow rate, 5 ml/min), monitoring at 270 nm. The ^{1}H- and ^{13}C-NMR spectra were recorded in $CDCl_3$ solution on a JEOL JNM GSX-500 instrument. UV spectra were taken on a Beckman 25 instrument in methanol solution. Optical rotations were determined with a JASCO DIP-360 polarimeter. Column chromatography was carried out with Merck Kieselgel 60.

Extraction and Isolation of Furanosesterterpene Tetronic Acid Mixtures *I. felix*, *I. strobilina* and *I. campana* specimens were collected at Santa Marta Bay on the Caribbean coast of Colombia at a depth of 15—20 m. Voucher specimens have been deposited in the reference collection of the Institute de Investigaciones Marinas de Punta Betín, Colombia. Local populations have been described in ref. 14. A sample of thawed *I. felix* (1.8 kg) was soaked in methanol (2 l) for 24 h and filtered. After concentration of the extract, it was partitioned between AcOEt and H_2O. The organic layer was dried and the solvent was removed, giving a brown residue (19.4 g). Part of the residue (15 g) was acetylated using 50 ml of acetic anhydride–pyridine (1 : 1) and further purified by column chromatography on silica gel to give 1.1 g of crude acetylated furanosesterterpene tetronic acid mixture. A similar procedure was followed for the extraction of this mixture from *I. strobilina* and *I. campana*. Preparative HPLC separation of the acetylated furanosesterterpene tetronic acids gave three fractions per sponge species, containing five variabilin-type isomers.

Fraction I Colorless oil (68 mg) from *I. felix*, $[\alpha]_D^{25}$ +34.8° (c = 0.42, MeOH). Capillary GC analysis of the fraction showed two peaks (t_R: 24.7 and 24.1 min) which corresponded to **1** and **2**, respectively. (8*Z*,13*Z*,18*R*,20*Z*)-Strobilinin acetate (**1**): UV λ_{max} nm: 273. EI-MS m/z (rel. int. %): 440 (M^+, 15), 425 (3), 398 (5), 235 (8), 217 (10), 213 (14), 195 (5), 163 (55), 153 (22), 149 (10), 135 (63), 121 (19), 109 (37), 95 (39), 81 (100), 69 (26), 55 (25). ^{1}H-NMR (500 MHz) δ: 1.06 (3H, d, J = 6.8 Hz, H_3-19), 1.40 (2H, m, H_2-17), 1.64 (2H, m, H_2-6), 1.66 (3H, s, H_3-14), 1.68 (3H, s, H_3-9), 1.82 (3H, s, H_3-25), 1.95-2.01 (6H, m, H_2-11, H_2-12, H_2-16), 2.05 (2H, t, J = 6.8 Hz, H_2-7), 2.35 (3H, s, AcO), 2.39 (2H, t, J = 6.8 Hz, H_2-5), 2.82 (1H, m, H-18), 5.05 (1H, d, J = 9.8 Hz, H-20), 5.09 (1H, t, J = 6.8 Hz, H-15), 5.13 (1H, t, J = 6.8 Hz, H-10), 6.27 (1H, s, H-2), 7.21 (1H, s, H-4), 7.34 (1H, s, H-1). ^{13}C-NMR, see Table 1.

(7*Z*,13*Z*,18*R*,20*Z*)-Felixinin acetate (**2**): UV λ_{max} nm: 273. EI-MS m/z (rel. int. %): 440 (M^+, 13), 425 (8), 398 (5), 380 (3), 235 (5), 217 (10), 213 (35), 195 (8), 163 (21), 153 (48), 149 (18), 135 (63), 122 (25), 121 (20), 109 (30), 95 (38), 81 (100), 69 (35), 55 (19). ^{1}H-NMR (500 MHz) δ: 1.06 (3H, d, J = 6.8 Hz, H_3-19), 1.40 (4H, m, H_2-11 and H_2-17), 1.66 (3H, s, H_3-9), 1.68 (3H, s, H_3-14), 1.82 (3H, s, H_3-25), *ca.* 1.95 (6H, m, H_2-10, H_2-12, H_2-16), 2.23 (2H, q, J = 6.8 Hz, H_2-6), 2.37 (3H, s, AcO), 2.43 (2H, t, J = 6.8 Hz, H_2-5), 2.82 (1H, m, H-18), 5.05 (1H, d, J = 9.8 Hz, H-20), 5.09 (1H, t, J = 6.8 Hz, H-15), 5.16 (1H, t, J = 6.8 Hz, H-7), 6.27 (1H, s, H-2), 7.21 (1H, s, H-4), 7.35 (1H, s, H-1). ^{13}C-NMR, see Table 1.

Fraction II Colorless oil (135 mg) from *I. felix*, $[\alpha]_D^{25}$ +45.6° (c = 0.17, MeOH). Capillary GC analysis of the fraction showed a single peak at 24.7 min. (8*E*,13*Z*,18*R*,20*Z*)-Strobilinin acetate (**3**): UV λ_{max} nm: 273. EI-MS for the mixture of compounds **3**+**4**, m/z (rel. int. %): 440 (M^+, 15), 425 (3), 398 (4), 236 (6), 235 (5), 218 (10), 217 (6), 203 (17), 195 (8), 163 (40), 153 (27), 149 (12), 135 (68), 121 (20), 109 (27), 95 (40), 81 (100), 69 (40), 55 (27). ^{1}H-NMR (500 MHz) δ: 1.05 (3H, d, J = 6.8 Hz, H_3-19), 1.42 (2H, m, H_2-17), 1.59 (3H, s, H_3-9), 1.64 (2H, m, H_2-6), 1.68 (3H, s, H_3-14), 1.82 (3H, s, H_3-25), 1.95 (2H, m, H_2-16), 2.00 (4H, m, H_2-7, H_2-12), 2.04 (2H, t, J = 6.8 Hz, H_2-11), 2.35 (3H, s, AcO), 2.38 (2H, t, J = 6.8 Hz, H_2-5), 2.83 (1H, septet, J = 6.8 Hz, H-18), 5.05 (1H, d, J = 10.7 Hz, H-20), 5.09 (2H, m, H-10 and H-15), 6.27 (1H, s, H-2), 7.21 (1H, s, H-4), 7.33 (1H, s, H-1). ^{13}C-NMR, see Table 1.

(7*E*,13*Z*,18*R*,20*Z*)-Felixinin acetate (**4**): UV λ_{max} nm: 273. ^{1}H-NMR (500 MHz) δ: 1.06 (3H, d, J = 6.8 Hz, H_3-19), 1.42 (2H, m, H_2-17), 1.44 (2H, m, H_2-11), 1.57 (3H, s, H_3-9), 1.66 (3H, s, H_3-14), 1.82 (3H, s, H_3-25), *ca.* 1.95 (6H, m, H_2-10, H_2-12, H_2-16), 2.24 (2H, q, J = 6.8 Hz, H_2-6), 2.35 (3H, s, AcO), 2.45 (2H, t, J = 6.8 Hz, H_2-5), 2.83 (1H, septet, J = 6.8 Hz, H-18), 5.06 (1H, d, J = 10.7 Hz, H-20), 5.09 (1H, t, J = 6.8 Hz, H-15), 5.16 (1H, t, J = 6.8 Hz, H-7), 6.28 (1H, s, H-2), 7.21 (1H, s, H-4), 7.33 (1H, s, H-1). ^{13}C-NMR, see Table 1.

Fraction III (7*E*,12*E*,18*R*,20*Z*)-Variabilin acetate (**5**): 290 mg from *I. felix* as a colorless oil, $[\alpha]_D^{25}$ +33.3° (c = 0.18, MeOH). UV, MS, ^{1}H- and ^{13}C-NMR and optical rotation data are in good agreement with values previously published by our group.[2]

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References and Notes

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