

ON THE STEREOCHEMISTRY AND BIOGENESIS OF C₂₁ LINEAR FURANOTERPENES IN *IRCINIA* SP.

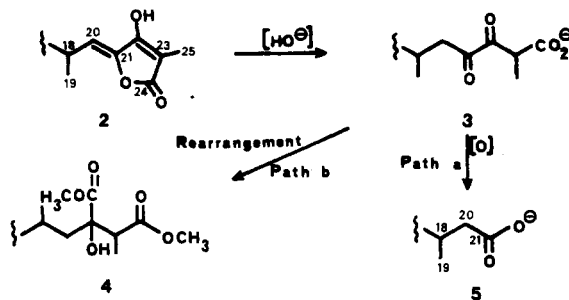
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ABSTRACT.—Two linear furanosesterterpenes (**6a**) and (**8a**) were isolated from *Ircinia dendroides*. Their stereochemistry, and that of the previously described variabilin (**1a**) (1), at the trisubstituted isoprenoid double bonds was established on the basis of their ¹H-nmr and ¹³C-nmr data. Each sesterterpene was shown to co-occur with a structurally and stereochemically related C₂₁ furanoterpene, **7a** and **9a**. A biogenetic-type degradation of the sesterterpenes to the related C₂₁ furanoterpenes was carried out.

Sponges of the *Ircinia* genus have been shown to be a source of linear furanoterpenes belonging to two main groups: tetric acid sesterterpenes and furanoterpenes with a twenty-one carbon skeleton (1).

The biogenetic origin of C₂₁ compounds is, at present, a matter of speculation. Radiolabelling experiments (1) have suggested that sponges are unable to synthesize terpenoids *de novo*. In view of this fact and of the co-occurrence in some animals of furanosesterterpenes and C₂₁ furanoterpenes with very closely related structures, Minale *et al.* have preferred the idea that the C₂₁ compounds are derived by degradation of a related sesterterpenoid to the idea of the possibility of their biosynthesis by addition of a C₁ unit to a diterpenoid precursor. Faulkner (2) considers a biogenetic scheme in which the loss of the four-carbon fragment goes through an oxidative rupture of the α -diketone (**3**) arising from hydrolysis of tetric acid (2) (Path a in scheme 1).

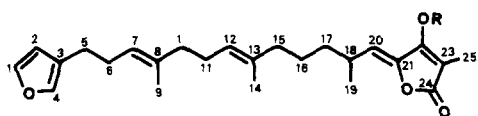


Scheme 1

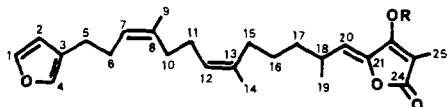
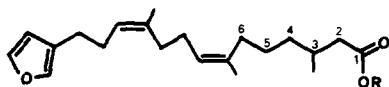
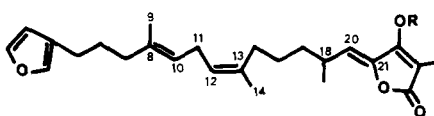
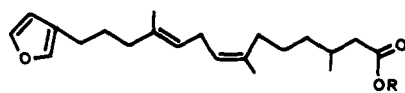
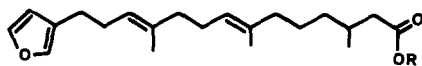
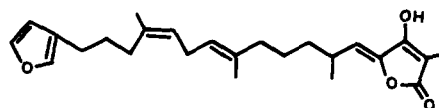
An additional and related question, not yet conclusively answered, is the assignment of the stereochemistry at the trisubstituted isoprenoid double bonds (1). Those compounds are usually oils (3), and the assignments have to be made on the basis of spectroscopic grounds. In this paper we report the structure elucidation of compounds **6a**, **7a**, **8a** and **9a**, isolated from *I. dendroides* (4). We also assign the stereochemistry of the trisubstituted isoprenoid double bonds for all described compounds. In addition we report the chemical transformation of acetates **6b** and **8b** into compounds **7b** and **9b**, respectively, through a reaction which mimics the above-mentioned biogenetic scheme.

From the ether soluble portion of the acetone extract of fresh tissues of *I. dendroides*, we isolated a mixture of compounds which gave a positive Ehrlich test. After acetylation we resolved the natural mixture in two parts. The acetylatable portion was also a mixture of two compounds, as was shown by glc (SE—30, 2.5%) of their methyl ethers **6c** and **8c**.

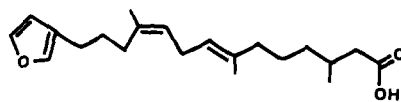
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1 a R = H b R = Ac

6 a R = H; b R = Ac; c R = CH₃7 a R = H; b R = CH₃8 a R = H; b R = Ac; c R = CH₃9 a R = H; b R = CH₃10 a R = H; b R = CH₃

11



12

The isolation of acetates **6b** and **8b** as pure compounds was achieved by short column chromatography (5) over silica gel-AgNO₃ (10%).

The molecular formula (C₂₇H₃₆O₅) of **6b** is supported by the mass spectrum (M⁺ *m/e* 440, base peak 81). The ¹H-nmr spectrum resembles that of **1a**, the most striking difference being the chemical shifts of the vinyl methyl groups, δ 1.55 and 1.58 ppm for **1a**² and δ 1.65 and 1.68 ppm for **6b**. Moreover, ozonolysis proved that the location of double bonds is identical in **1a** and **6a**, so the compounds should differ in their stereochemistry at isoprenoid double bonds.

It is known (6) that ¹H-nmr chemical shifts of methyl groups on trisubstituted double bonds in isoprenoid chains appear more upfield in E double bonds than in Z double bonds. This suggests an E,E stereochemistry for the variabilin Δ^{7,8} and Δ^{12,13} double bonds and a Z,Z stereochemistry for the equivalent bonds in **6a**. This was confirmed by ¹³C-nmr spectroscopy, table 1. The vinyl methyl of variabilin appears at 15.6 and 15.8 ppm as expected for E double bonds (7). For **6b** no resonances appear around 15.7 ppm; instead, the ¹³C-nmr spectrum shows two overlapping quartets at 23.3 ppm. Moreover, the signals at 39.4 and 39.5 ppm assigned to the C-10 and C-15 methylenes in variabilin are shifted upfield (8) to 32.3 and 31.5 ppm in **6b**. All the above, together with the fact that no additional significant differences exist between the ¹³C-nmr spectra of **1a** and **6b** is consistent with a change in the stereochemistry of the trisubstituted isoprenoid double bonds from the E,E stereochemistry in **1** to Z,Z in **6**.

The structure of **8b** was established on the basis of spectral similarities to **6b**. The mass spectrum (M⁺ *m/e* 440, base peak 135) supports the molecular formula C₂₇H₃₆O₅. Its ¹H-nmr spectrum presents few but significant differences to that of **6b**. Thus, the multiplet at 5.10 ppm assigned to the olefinic protons C-7 and C-12 in **6b** is replaced by a triplet centered at 5.08 ppm (2H, *J* = 7 Hz) in **8b**. Moreover, a triplet at 2.65 ppm (2H, *J* = 7 Hz) for this last compound is not present for **6b**. Double irradiation ¹H-nmr experiments showed that both

²The authors thank Dr. D. J. Faulkner (Scripps Institution of Oceanography) who kindly provided the ¹H-nmr and ¹³C-nmr spectra of variabilin.

TABLE 1. ^{13}C -NMR chemical shifts of sesterterpenes **1a**, **6b** and **8b**.

Carbon	1a	6b	8b
1.....	142.3	142.5	142.5
2.....	110.9	111.1	111.0
3.....	124.8	125.1	124.6
4.....	138.6	138.8	138.8
5.....	28.2	28.3	28.2
6.....	24.8	25.3 ^d	24.3 ^d
7.....	123.5	123.9 ^f	39.1
8.....	135.5	135.8 ^e	134.9 ^e
9.....	15.6	23.3 ^h	15.9
10.....	39.5	32.3	123.6 ^a
11.....	26.3	26.3 ^d	26.8 ^a
12.....	124.2	124.7 ^f	124.1 ^a
13.....	134.6	135.2 ^e	134.5 ^e
14.....	15.8	23.3 ^h	23.3
15.....	39.4	31.5	31.5
16.....	25.5	25.7 ^d	25.6 ^d
17.....	36.4	36.8	36.8
18.....	30.7	31.1	31.1
19.....	20.4	20.6	20.4
20.....	116.1	116.4	116.3
21.....	142.9	142.6	142.5
22.....	162.7	168.6 ^b	168.6 ^b
23.....	98.7	114.8	114.7
24.....	172.6	154.4 ^b	154.4 ^b
25.....	5.9	8.3	8.3
26.....		165.4 ^b	165.4 ^b
27.....		20.7	20.6

a-g: assignments interchangeable
h: overlapping signals

triplets are mutually coupled. All the above agrees with the presence in the molecule of an A_2X_2 system of the $-\text{C}=\text{CH}-\text{CH}_2-\text{CH}=\text{C}-$ type. The location of double bonds was confirmed by ozonolysis. The ^{13}C -nmr spectrum of **8b** supported the proposed structure and allowed us to assign the stereochemistry of the isoprenoid double bonds. The quartets at 15.9 ppm and 23.3 ppm correspond to vinyl methyls in double bonds with E and Z stereochemistry, respectively. The triplets at 39.1 and 31.5 ppm attributable to the C-7 and C-15 methylenes give additional support.

The mild alkaline treatment of acetates **6b** and **8b** yields the natural compounds **6a** and **8a**. The most significant difference between the ^1H -nmr spectra of the naturally occurring alcohols, as compared with those of the acetates, is the slightly downfield displacement in the former of the resonances corresponding to the C-25 methyls and the protons on C-20, together with the expected absence of the singlets at δ 2.30 ppm assigned in **6b** and **8b** to the methyls of the acetates.

The mass spectra of **7b** and **9b**, (M^+ m/e 346, base peak S1) suggest a molecular formula of $\text{C}_{22}\text{H}_{34}\text{O}_3$ for both compounds. The ^1H -nmr spectra were conclusive in the structure assignment as they closely resemble that of **6b** and **8b**, respectively, if the resonances of the tetronic acid moiety are not taken into account. Moreover, the signals of the A_2X_2 system in **9b** are clearer than in **8b** because the resonances of the protons on C-18 and C-20, which in **8b** partially overlapped the triplets at δ 2.65 ppm and 5.08 ppm have moved in **9b** to a different field due to the absence of the tetronic acid moiety. The location of the double bonds of both **7b** and **9b** was confirmed by ozonolysis.

As for the stereochemistry at the trisubstituted double bonds in **7b**, the vinyl methyl resonances at δ 1.65 and δ 1.67 ppm indicate a Z,Z stereochemistry, identical with that of **6b**. This was confirmed by a biogenetic-type degradation. It has been reported (9) that drastic alkaline treatment of tetronic acid furano-

sesterterpenes affords new C₂₅ compounds through a benzylic rearrangement (Path b in scheme 1). It was thought that if an oxidant such as H₂O₂ were present (10), an oxidative degradation to the C₂₁ furanoterpenes (Path b in scheme 1) could compete with the rearrangement. Initial experiments in this sense proved, however, disappointing; but, when the alkali was substituted by basic Al₂O₃, a compound was isolated in 30% yield after methylation from the degradation mixture, the chromatographic and spectroscopical behaviour of which is identical with that of **7b**. Although the chemical shift of the vinyl methyls in the ¹H-nmr spectrum of **9b**, δ 1.60 and 1.67 ppm, indicate the same (E,Z) stereochemistry as **8b**, the attempt to carry out the conversion of **8b** to **9b** under the above experimental conditions failed. We think this was a consequence of the reactivity of C-11 methylene towards peroxides since when we repeated the degradation sequence with a sample of acetate of variabilin **1b** previously isolated as an alcohol from a different *Ircinia* sp. we obtained compound **10b**.

The ms of **10b** supports the molecular formula C₂₂H₃₄O₃. The ¹H-nmr spectrum closely resembles that of **7b**, again the most striking difference being the chemical shift of the vinyl methyl signal, δ 1.57 ppm (6H) for **10b** versus δ 1.65 and 1.67 ppm for **7b**. In the ¹³C-nmr spectrum, table 2, the quartets at 15.9 ppm and the

TABLE 2. ¹³C-NMR shifts of furanoterpene **10b**

Carbon	
1.....	142.5
2.....	111.1
3.....	125.0
4.....	138.8
5.....	28.4
6.....	25.1 ^c
7.....	123.8
8.....	135.8 ^b
9.....	15.9 ^d
10.....	39.7 ^e
11.....	26.5
12.....	124.3 ^a
13.....	135.1 ^b
14.....	15.9 ^d
15.....	39.7 ^e
16.....	25.2 ^c
17.....	36.4
18.....	30.3
19.....	19.4
20.....	41.6
21.....	173.8
22.....	51.4

a-c: assignments interchangeable
d,e: overlapping signals

triplets at 39.7 ppm are in accordance with an E,E stereochemistry for the $\Delta^{7,8}$ and $\Delta^{12,13}$ double bonds of **10b**, identical with the equivalent bonds in variabilin.

We are presently investigating the occurrence of **10a** as a natural product. The stereochemistry at $\Delta^{20,21}$ double bonds in the sesterterpenes is also under investigation.

It is clear that, although the above ¹³C-nmr data do not allow us to exclude the alternative structures **11** and **12** instead of **8a** and **9a**, a useful and unambiguous relationship can be set between the ¹³C-nmr chemical shift of alpha groups (methyl and methylene) to the quaternary carbons of isoprenoid double bonds and their stereochemistry in the same line that the ¹H-nmr-based correlations were set some years ago (6). Moreover, the described degradation gives "chemical sense" to the Minale-Faulkner biogenetic scheme.

EXPERIMENTAL³

EXTRACTION OF I. DENDROIDES.—Fresh material (1.600 g) (weighed dry after extraction) collected at Mogan, Grand Canary, was extracted with acetone (4 liters) for two days at rt. This operation was repeated three times. The combined solutions were concentrated under reduced pressure and extracted with ether. The ethereal solution was taken to dryness and the oily residue (52 g) chromatographed over silica gel. In this way, a complex mixture of Ehrlich active compounds was isolated.

ISOLATION OF SESTERTERPENE ACETATES AND C-21 FURANOTERPENE MIXTURES.—All attempts to isolate single natural compounds from the natural Ehrlich active mixture by chromatography over silica gel were unsuccessful, and the mixture was acetylated with pyridine and acetic anhydride at rt overnight. A tlc of the acetylation products showed the split of the initial mixture into two parts, both Ehrlich active, the more polar one having the same R_f as the starting unacetylated material. After chromatography over silica gel, we isolated the less polar material as a mixture of sesterterpene acetates and the more polar one as a C₂₁ furanoterpene mixture.

ISOLATION OF COMPOUNDS (6b) AND (8b).—In order to investigate the complexity of the sesterterpene acetate mixture, 50 mg were hydrolyzed with 5 ml of 5% NaOH for 15 minutes at rt. After this time the solution was neutralized with 5% HCl and extracted with ether. The dry ethereal solution was methylated with CH₂N₂ at -50°. The methyl ether mixture was analyzed by glc (SE-30, 2.5%, 25°), showing two components of very close retention time. The by-products resulting from the well-known behaviour of tetric acid towards diazomethane (9) are of longer retention time and were not investigated.

The isolation of **6b** and **8b** as pure compounds was achieved by short column chromatography over silica gel-AgNO₃ (10%) monitored by tlc (silica gel-AgNO₃, 10%) and glc (the same conditions as above).

GENERAL PROCEDURE FOR OZONOLYSIS.—The sample dissolved in ethyl acetate was ozonized at -50° following the procedure described by Minale *et al.* (9).

Authentic samples of methyl 5-ketohexanoate and methyl 2-methyl-6-oxo-heptanoate were obtained by ozonolysis and oxidative work-up followed by methylation of methyl cyclopentene and 1,3-dimethylcyclohexene, respectively.

COMPOUND 6b.—Compound **6b** was isolated as a pale yellow oil, 190 mg, had the following spectroscopic properties: ir (film), 1760, 1650, 1490, 1175, 1060, 1020, 875 and 755 cm⁻¹; ¹H-nmr, (90 MHz, CCl₄, δ): 7.29 (1H, t, 0.5 Hz), 7.18 (1H, s), 6.20 (1H, s), 5.12 (2H, m), 4.88 (1H, d, $J=10$ Hz), 2.86 (1H, m), 2.30 (3H, singlet overlapping a broad signal), 1.79 (3H, s), 1.68 (3H, s), 1.65 (3H, s), 1.05 (3H, d, $J=6$ Hz); ms, (m/e , %), M⁺ 440 (7), 249 (11), 231 (12), 203 (12), 175 (19), 153 (40), 149 (20), 136 (20), 135 (38), 123 (45), 121 (10), 109 (26), 107 (10), 95 (28), 93 (10), 83 (32), 81 (100), 69 (45), 67 (12), 55 (35); ¹³C-nmr spectrum, see table 1.

COMPOUND 6a.—Compound **6b** (50 mg) was hydrolyzed with 5% NaOH for 15 minutes at rt, the resulting oil having the following properties: ir (film), 3500, 2960, 1715, 1620, 1440, 1370, 1300, 1235, 1185, 1160, 1060, 1025, 945, 870, 775, 760 cm⁻¹; ¹H-nmr (90 MHz, CCl₄, δ), 7.29 (1H, t, $J=0.5$ Hz), 7.17 (1H, s), 6.19 (1H, s), 5.41 (1H, d, $J=11$ Hz), 5.10 (2H, m), 2.35 (2H, m), 1.83 (3H, s), 1.68 (6H, bs), 1.09 (3H, d, $J=6$ Hz); ms, (m/e , %), M⁺ 398 (10), 203 (15), 175 (35), 154 (10), 153 (50), 149 (35), 136 (37), 135 (65), 123 (45), 109 (19), 105 (10), 95 (35), 91 (10), 81 (100), 69 (60), 67 (23), 41 (40).

OZONOLYSIS OF 6b.—Compound **6b** (30 mg) was ozonized according to the general procedure. After solvent removal the degradation mixture was analyzed by glc (SE-30, 2.5%, 160°), and shown to comprise methyl succinate, methyl levulinate and methyl 2-methyl-6-oxo-heptanoate by comparison with authentic samples.

COMPOUND (8b).—Compound **8b** (500 mg) exhibited the following spectral data: ir (film), 1760, 1640, 1510, 1165, 1065, 1020, 875 and 775 cm⁻¹; ¹H-nmr (90 MHz, CCl₄, δ), 7.29 (1H, t, $J=0.5$ Hz), 7.18 (1H, s), 6.20 (1H, s), 5.08 (2H, t, $J=7$ Hz), 4.95 (1H, d, $J=10$ Hz), 2.85 (1H, m), 2.65 (2H, t, $J=7$ Hz), 2.30 (3H, singlet overlapping a broad signal), 1.79 (3H, s), 1.66 (3H, s), 1.61 (3H, s), 1.07 (3H, d, $J=6$ Hz); ms (m/e , %), M⁺ 440 (7), 203 (10), 175 (12), 167 (10), 166 (10), 161 (10), 153 (27), 149 (34), 137 (12), 136 (30), 135 (100), 127 (12), 122 (10), 121 (29), 119 (10), 107 (21), 105 (12), 95 (33), 94 (13), 93 (28), 90 (14), 83 (30), 82 (20), 81 (55), 78 (18), 69 (36), 67 (20), 55 (35), 53 (10). ¹³C-nmr, see table 1.

COMPOUND 8a.—Compound **8b** (50 mg) was hydrolyzed with 5% NaOH for 15 minutes at rt. The resulting oil had the following properties: ir (film), 3500, 2960, 1730, 1640, 1440, 1410, 1370, 1300, 1160, 1060, 1025, 945, 876, 775, 760 cm⁻¹; ¹H-nmr (90 MHz, CCl₄, δ), 7.29 (1H, t, $J=0.5$ Hz), 7.17 (1H, s), 6.20 (1H, s), 5.40 (1H, d, $J=11$ Hz), 5.68 (2H, t, $J=7$ Hz), 2.65 (2H, t, $J=7$ Hz), 2.36 (2H, t, $J=7$ Hz), 1.86 (3H, s), 1.65 (3H, s), 1.60 (3H, s), 1.07 (3H, d, $J=6$ Hz);

³Ir spectra were obtained with Perkin-Elmer 257 and PYE UNICAM-SP-1100 instruments. ¹H-nmr spectra were recorded on Perkin-Elmer R-12 (60 MHz) and R-32 (90 MHz) instruments, with tetramethylsilane as the internal reference. ¹³C-nmr spectra were recorded in Bruker HX-90-E and Varian CFT-20 instruments. Ms spectra were obtained with a Micromass ZAB-2F apparatus. For glc, we used Perkin-Elmer 900 and Hewlett-Packard 5710 A instruments.

ms, (*m/e*, %), M⁺ 398 (10), 219 (10), 203 (12), 175 (12), 167 (15), 153 (35), 149 (35), 135 (100), 121 (25), 109 (20), 95 (35), 91 (30), 81 (70), 69 (75), 55 (45), 43 (65), 41 (55).

OZONOLYSIS OF 8b.—Compound **8b** (60 mg) was ozonized according to the general procedure. The degradation mixture, analyzed by glc (SE-30, 2.5%, 160°), was shown to comprise dimethyl malonate, methyl 5-ketohexanoate and methyl-2-methyl-6-oxo-heptanoate, by comparison with authentic samples.

ISOLATION OF 7b AND 9b.—Methylation of the C₂₁ furanoterpene mixture and analysis by glc (SE-30, 5%, 230°), showed the presence of two components. The isolation of **7b** and **9b** as pure compounds was achieved by short column chromatography over silica gel-AgNO₃ (10%).

COMPOUND 7b.—Compound **7b** was isolated as a pale yellow oil, 40 mg. It gave the following spectral data: ir (film), 1730, 1460, 1360, 1150, 1025, 875 and 780 cm⁻¹; ¹H-nmr (90 MHz, CCl₄, δ), 7.28 (1H, t, *J*=0.5 Hz), 7.18 (1H, s), 6.20 (1H, s), 5.15 (2H, m), 3.60 (3H, s), 1.64 (3H, s), 1.66 (3H, s), 0.91 (3H, d, *J*=8 Hz); ms, (*m/e*, %), M⁺ 346 (10), 175 (26), 165 (14), 149 (12), 147 (11), 137 (10), 135 (23), 127 (12), 123 (72), 121 (18), 109 (15), 95 (35), 83 (32), 82 (16), 81 (100), 69 (31), 67 (16), 55 (40). Compound **7b** (25 mg) was ozonized according to the general procedure. Dimethyl succinate and methyl levulinate were identified from the degradation mixture by comparative glc (SE-30, 2.5%, 160°) with authentic samples and methyl 3-methyl-7-oxo-octanoate by glc-ms.

OXIDATIVE DEGRADATION OF 6b.—Compound **6b** (66 mg, 0.15 mmol) was dissolved in dioxane (5 ml). Tlc aluminium oxide H basic (type 60/E), Merck, (1.5 g) and H₂O₂ (0.5 ml, 30% volume) were added to the solution. The reaction mixture was kept at reflux temperature for 12 h. Every hour the presence of peroxides was checked by the potassium iodide test.⁴ When no peroxides were present, an additional 0.5 ml of the H₂O₂ was added. The reaction mixture was filtered and the aluminium oxide washed with 5 x 2 ml of methanol. The combined organic solution was taken to dryness; the residue was re-dissolved in ethyl ether and methylated with CH₃N₂. By chromatography over silica gel, we isolated 15 mg of a compound identical with (**7b**).

COMPOUND 9b.—Compound **9b** was isolated as a pale yellow oil, 50 mg. It gave the following spectral data: ir (film), 1730, 1450, 1165, 1025, 870 cm⁻¹; ¹H-nmr (90 MHz, CDCl₃, δ), 7.34 (1H, t, *J*=0.5 Hz), 7.20 (1H, s), 6.28 (1H, s), 5.11 (2H, t, *J*=8 Hz), 3.65 (3H, s), 2.68 (2H, t, *J*=8 Hz), 1.68 (3H, s), 1.60 (3H, s), 0.93 (3H, d, *J*=8 Hz); ms (*m/e*), M⁺ 346, 331, 217, 203, 175, 163, 149, 147, 135, 121, 109, 96, 95, 81, 69, 67. Compound **9b** (30 mg) was treated with ozone according to the general procedure. The degradation mixture was shown to comprise dimethyl malonate and methyl 5-keto-oxo-hexanoate by comparative glc with authentic samples and methyl 3-methyl-7-oxo-octanoate by glc-ms.

COMPOUND 10b.—Variabilin **1a** was isolated as the main furanosesterterpene component of an *Ircinia* sp.,⁵ collected at Güimar, Tenerife. The sponge was extracted as described for *I. dendroides*. Variabilin was isolated as an acetate which was then saponified and identified by comparison of its ¹³C-nmr and ¹H-nmr spectra with those of **1a** and by ozonolysis.

Acetate **1b** was submitted to oxidative degradation as described for **6b**. After methylation and chromatography over silica gel, 29 mg of compound **10b** was obtained. It exhibited the following spectral data: ir (film), 1735, 1500, 1435, 1385, 1250, 1150, 1025, 875, 780 cm⁻¹; ¹H-nmr (90 MHz, CCl₄, δ), 7.28 (1H, t, *J*=0.5 Hz), 7.15 (1H, s), 6.20 (1H, m), 5.10 (2H, m), 3.59 (3H, s), 1.57 (6H, s), 0.91 (3H, d, *J*=8 Hz); ms (*m/e*, %), M⁺ 346 (5), 331 (4), 264 (5), 251 (6), 203 (7), 175 (20), 165 (18), 149 (7), 147 (7), 135 (11), 129 (9), 123 (55), 109 (9), 95 (20), 83 (20), 81 (100), 69 (22), 55 (35); ¹³C-nmr spectrum, see table 2.

Compound **10b** (25 mg) was ozonized according to the general procedure. From the degradation mixture, dimethyl succinate and methyl levulinate were identified by comparison (glc) with authentic samples and methyl 3-methyl-7-oxo-octanoate by glc-ms.

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