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KETO-ENOLIC TAUTOMERISM AND SPECTRAL DATA OF PRENYLATED ANTHRANOIDS FROM *VISMIA* GENUS

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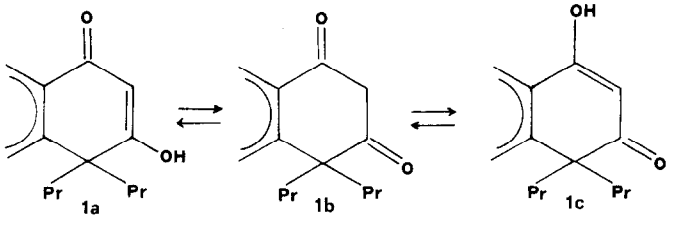
Abstract—A keto-enolic tautomerism is present in ring C of ferruginins, as demonstrated by chemical and physico-chemical methods. In particular, spectroscopic data of ferruginins, vismiones and their derivatives are reported and discussed. This study constitutes the first report on the application of ^{13}C NMR spectroscopy to this type of structure.

During the past years a number of prenylated anthranoids, i.e. ferruginin A, **1**, and B, **2**, harunganin, **3**, vismin, **4**, γ-hydroxyferruginin A, **5**, γ,γ'-dihydroxyferruginin A, **6** vismione A, **7**, deacetylvismione A, **8**, and visimone B, **9**, have been isolated from the berries of eight *Vismia* spp (Guttiferae)[1–4] and from the leaves of one.[5] The structure determination of these products indicated that they are all derived from an anthracene moiety with one non-aromatic ring. They should have a common biogenetic pathway, as previously indicated[6] and may be divided in two groups: ferruginins, **1–6** (non-aromatic C ring) and vismiones, **7–9** (non-aromatic A ring), both substituted with prenyl chains in the aromatic rings but only the former also in the non-aromatic ring.

Their structures are rather uncommon among the secondary metabolites of plants. Examples in the literature of the former group (non-aromatic C ring) are harunganin, **3**, previously found in *Harungana madagascariensis* (Guttiferae)[7] and germichrysone, isolated from the seedlings of *Cassia torosa* (Guttiferae),[8] whereas examples of the latter group (non-aromatic A ring) are torosachrysone and the corresponding atropoisomeric-dimers from the same plant,[9] and the dimeric toxins isolated from *Karwinskia humboldtiana* (Rhamnaceae).[10]

Keto-enolic tautomerism. Ring C in ferruginin A, **1**, and related structures could exist in the keto-enolic tautomeric forms **1a**, **1b** and **1c**, as already noted in other natural products.[11,12] A form **1a** and **1b** vs **1c** should be more stable considering the very strong intramolecular hydrogen bonding interaction, as indicated by the low field chemical shift value of the C(13)-OH. In fact, whereas in the ^1H NMR spectrum of ferruginin A in acetone-d_6 (Fig. 1), pyridine-d_5 and dioxane-d_6 only the keto-enolic form **1a** is evident, the ^1H NMR spectrum in $CDCl_3$ (Fig. 2) clearly indicated the co-existence of two tautomeric forms (**1a** and **1b**). This follows from the splitting of the two lowest field signals, due to the chelated hydroxyl groups, from the reduced intensity of the H-2 signal (δ 5.90) and from the appearance of a singlet at δ 3.60, attributable to the C(2)-methylene of the diketonic form **1b**. A predominance of the diketonic form **1b** vs **1a** for 53% at 30°, for 58% at 45° and for 70% at 63° was roughly calculated by integrating the above signals in the ^1H NMR spectra (100 MHz). Furthermore, exchange with D_2O (in acetone-d_6) determined the disappearance *not only* of the signals at δ 17.75 and 10.35 (C(13)-OH and C(11)-OH, respectively), *but also* of the signal at δ 5.75, due to the labile H-2. No immediate evidence of the third tautomeric form, **1c**, was obtained from the ^1H NMR spectra. Therefore, we attempted to fix the three tautomeric forms **1a–c** by methylation under various conditions.

Methylation with dimethylsulphate gave only the monomethylether **10** and the dimethylethers **11** and **12**. In all these compounds, the tautomer **1a** is frozen as a consequence of the methylation of C(3)-OH. The structures were easily determined by UV (Table 1), ^1H NMR (Table 2) and MS spectra (See Experimental). In particular, the ^1H NMR spectra indicated which and how many hydroxyl groups were substituted, whereas the UV



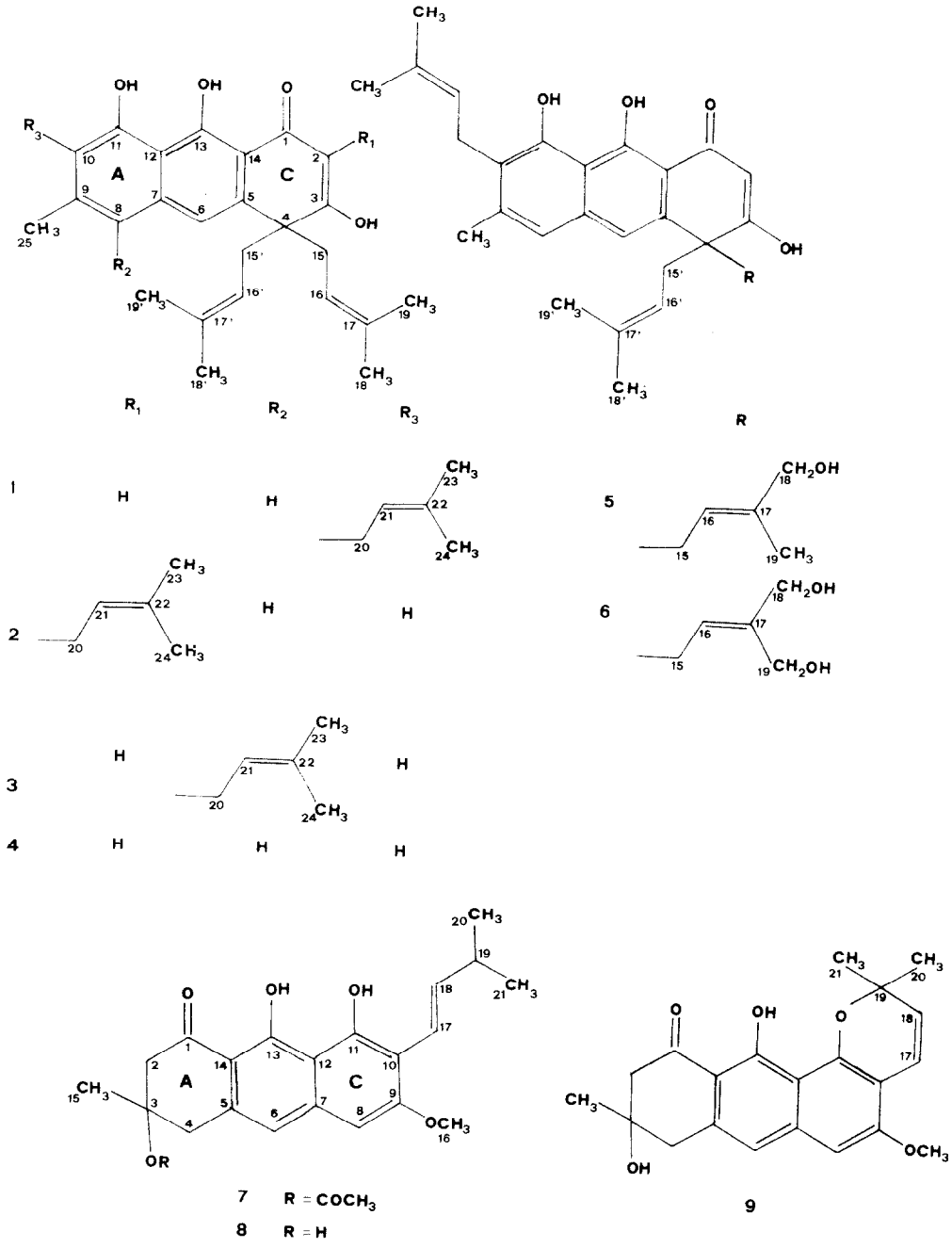
and MS spectra (the expected ions being regularly shifted by 14 and 28 m.u. in comparison with those of **1**[2]) showed that the skeleton was substantially unalterated.

Methylation with diazomethane led to the formation of the above compounds, **10–12** (derived from **1a**) and of 1,13-di-*O*-methyl derivative **13**, of the keto-enolic form **1c**. The structure of the last compound was shown by the ^{1}H NMR spectrum and from the UV and MS spectral data, which indicated a changed chromophore. ^{13}C NMR spectrum provides further confirmation of its structure (*vide infra*).

Finally, methylation with CH_3I-K_2CO_3, in addition to **10–12**, gave three other compounds, **14–16**, derived from C- and/or O-methylation of the diketonic form **1b**, frozen by the C(2) *gem*-dimethyl group. Also the structures **14–16** were deduced from the spectral data. In particular, in the ^{1}H NMR spectrum the H-2 signal is substituted by a 6H singlet (δ 1.25) and in the MS spectra the characteristic losses,[2] due to the prenyl chains, are present together with the losses of the *gem*-dimethyls.

^{13}C NMR analysis. In order to acquire new spectral data of this class of compounds, which can be useful for the structure elucidation of new members, we have measured the ^{13}C NMR spectra of vismiones, **7–9**, and ferruginins, **1–6**, as well as of the methyl derivatives, **11**, **12** and **13** (Table 3).

Starting the analysis from compound **8**, the signal at lowest field belongs to the carbon atom C(1) of the carbonyl group. The second highest value is assigned to C(13), which is more shielded than C(11) owing to the *peri* position with a carbonyl and a hydroxyl group; furthermore its value is very similar to the corresponding



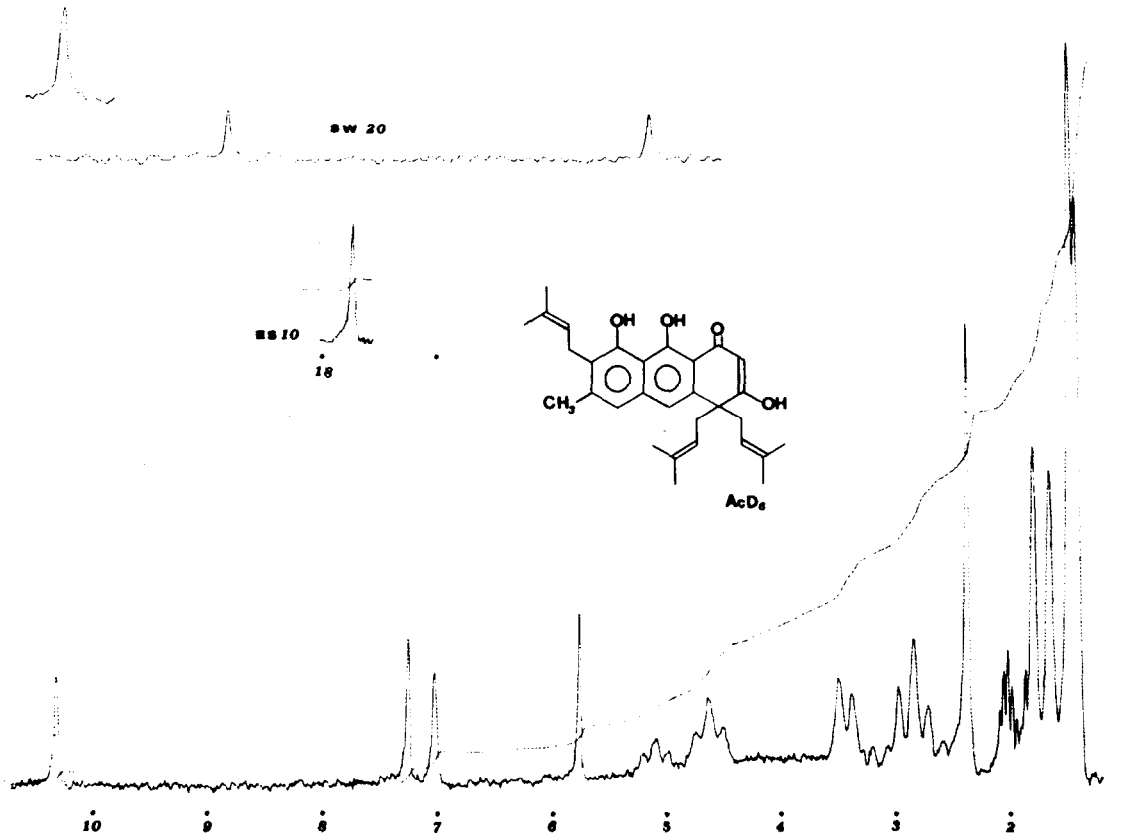


Fig. 1.

Table 1. UV-visible spectra of ferruginin A and its methyl derivatives

	λ_{max} (EtOH), nm	λ_{max} (EtOH+$AlCl_3$), nm*
1	246, 323, 340(sh), 412	456
10	244, 262, 292, 422	467
11	243, 260(sh), 294(sh), 394	444
12	238, 270, 320(sh), 392	392
13	242, 306(sh), 382(sh)	382(sh)
14	236, 278, 315(sh), 424	463
15	234, 276, 309(sh), 396	400
16	235, 273, 320(sh), 382	377

* Also hyperchromic shift was observed for the compounds with C(13)-OH

value in 2-hydroxyacetophenone (161.2 ppm).[13] As a first approximation, for the assignments of the other carbon atoms, the naphthalene system may be chosen as a model; in the literature complete studies can be found of substitution effects in naphthalene derivatives,[14–16] however differences can be expected for positions *peri* and *ortho* polysubstituted and for the presence of hydrogen bonding. Values calculated for compound **8** are reported in parentheses in Table 3 and they are, in general, in agreement with assignments; for the side-chain the effect of an ethyl group was taken approximately. Anyway, assignments of C(5) vs C(7) is confirmed by the constancy of C(4a) in naphthalene and several hydroxy, acetoxy, methoxy, etc. derivatives.[14–16] As for assignments of other quaternary aromatic carbon atoms, they are more shielded than the former ones being in *ortho* positions to carbon atoms which are oxygen-substituted, acetylation of **8** changes in **7** only the value of C(14), whereas cyclization of the side-chain (**8**→**9**) changes only C(10); C(2) and C(4) methylenes absorb at different values owing to the differing influence of adjacent groups. The esterification effects on C(3) (+9.8 ppm) and on C(4) (−1.6 ppm) and C(2) (−2.4 ppm) in **7** ($CDCl_3$) vs **8** are in accordance with those

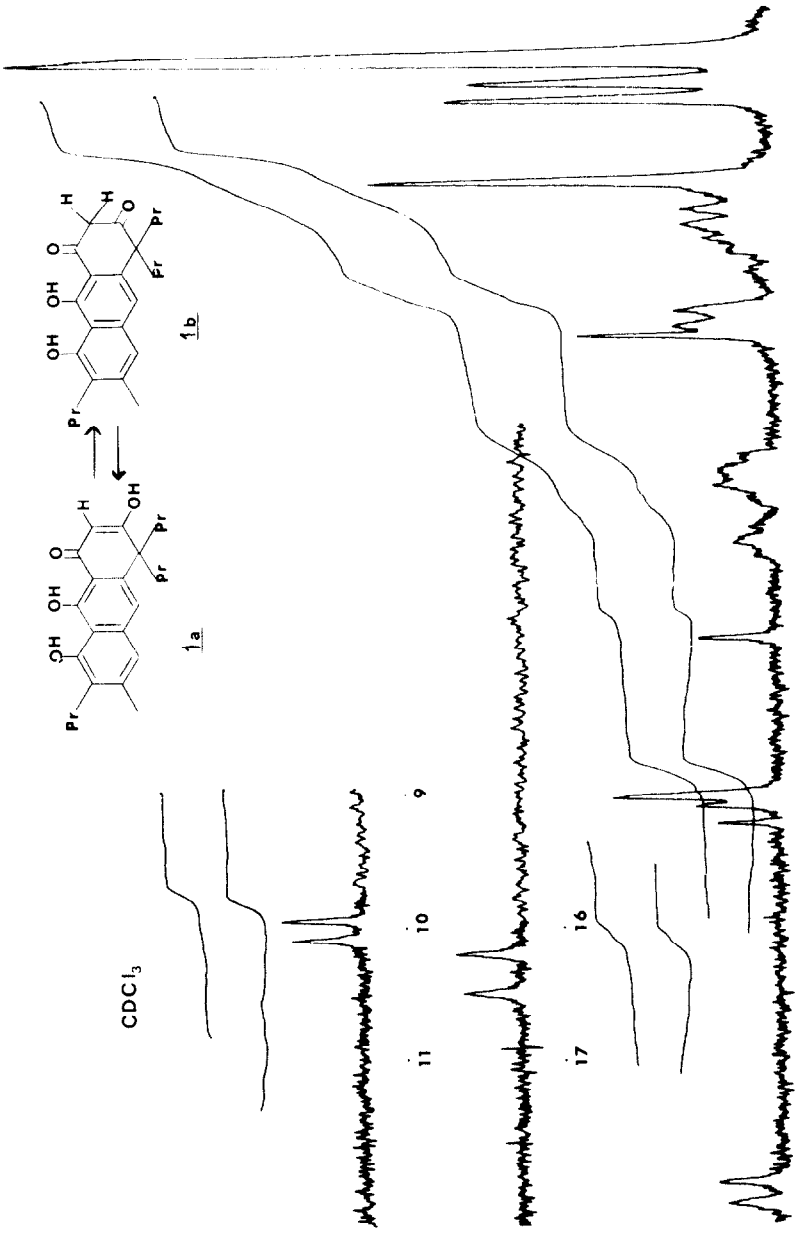


Fig. 2.

Table 2. ^{1}H NMR data ($CDCl_3$) of methyl derivatives of ferruginin A*

	C(1)-OCH_3	C(2)-R	C(3)-OCH_3	C(8)-H	C(11)-OR	C(13)-OR	C(6)-H
10	-	5.67 (1H)	3.74	6.94	10.10 (1H)	16.85 (1H)	7.01
11	-	5.70 (1H)	3.72	7.23	3.88 (3H)	15.48 (1H)	7.09
12	-	5.75 (1H)	3.73	7.06	10.23 (1H)	4.00 (3H)	7.50
13	3.90	5.72 (1H)	-	7.06	10.02 (1H)	3.94 (3H)	7.43
14	-	1.28 (6H)	-	7.08	9.96 (1H)	16.28 (1H)	7.15
15	-	1.26 (6H)	-	7.30	3.90 (3H)	14.68 (1H)	7.14
16	-	1.20 (6H)	-	7.20	9.94 (1H)	4.10 (3H)	7.52

*The resonances of the aromatic methyl groups and of the prenyl chains are not reported. All the signals are sharp singlets, except C(8)-H showing long chain coupling with C(9)-CH_3.

Table 3. ^{13}C NMR data of vismiones

	7°*	7+#	8#	9#
C(1)	202.0	200.3	200.2	201.1
C(2)	50.1	49.1	50.7	52.0
C(3)	82.0	80.6	70.8	70.7
C(4)	40.8	39.6	43.0	43.8
C(5)	140.1	138.7	138.3 (140.9)	140.4
C(6)	118.3	117.2[a]	117.8[a] (116.7)	117.0
C(7)	136.1	134.0	134.6 (133.0)	135.7
C(8)	99.4	98.0	97.8 (97.0)	98.1
C(9)	157.9	156.5	156.5 (158.6)	157.0
C(10)	109.6[a]	108.2	107.9 (115.6)	102.2
C(11)	162.6	161.4	161.4	178.2
C(12)	109.1[a]	111.5	111.1 (115.4)	112.0
C(13)	167.0	165.8	165.8	167.6
C(14)	112.5	113.9	109.6 (109.3)	109.2
C(15)	25.4	24.4	29.0	28.6
C(16)	56.7	55.6	55.5	55.5
C(17)	118.3	116.4[a]	117.2[a]	117.0
C(18)	143.8	143.0	143.7	127.8
C(19)	34.9	33.2	33.2	78.4
C(20)	24.1	22.7	22.9	27.7[a]
C(21)	24.1	22.7	22.9	27.4[a]

°In dioxane-d_8. *The acetyl C=O and CH_3 chemical shifts are 171.1 and 22.6 ppm, respectively.

In $CDCl_3$. +The acetyl C=O and CH_3 chemical shifts are 170.2 and 22.0, respectively.

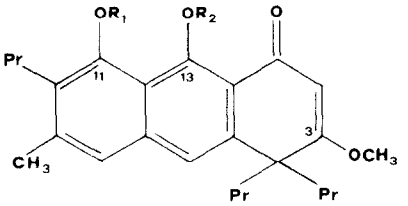
[a] Within the same column assignments may be reversed.

reported in acetylation of tertiary cyclic alcohols,[17,18] whereas the shielding of C(15) (−3.6 ppm) can be attributed to the influence of the carbonyl group, by a mechanism already observed in acetyl derivatives of carbinols.[19] Particularly good confirmation of previous assignments is the comparison with reported values of 8-*O*-β-D-glucopyranosyltorachrysone.[20]

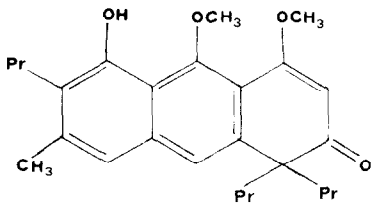
Previous trends can be used to confirm structures in compounds **1–6** and their derivatives **11**, **12** and **13**, whose assignments are reported in Table 4. The spectra of **1–6** were measured in dioxane-d_8, where only one form of the aforementioned keto-enolic tautomerim of ring C is present. The tautomerism is absent in the derivatives which have been frozen by O-methylation. For a better comparison, values of compound **7** in dioxane-d_8 are reported in Table 3. In **1–6** the conjugated carbonyl

carbon C(1) resonates at the same value, which is higher than those of similar conjugated ketones,[21] under the deshielding influence of the *peri* hydroxy group, as observed in other structures, i.e. flavones and xanthones.[22,23] C(2) and C(3) can be assigned by analogy with the corresponding values reported in 3-methoxy-2-cyclohexenone (102.3 and 178.5 ppm, respectively)[24] and 5,5'-dimethyl-3-ethoxycyclohexenone (101.2 and 175.2 ppm).[25] As a confirmation, the C(3) value changes only in **2**, as a consequence of the introduction of the prenyl group at C(2) and in **11** and **12** shows the shielding due to the O-methylation. Regarding C(11) and C(13), the latter must be located at lower field, as a consequence of the influence of the groups in the *peri* position. As independent confirmation, C(13) practically remains constant in **1–6**, whereas C(11) is subjected to the effects of ring A substitution. Concerning the other carbon atoms forming rings A and B, C(6), C(8) and C(10) can be distinguished considering their positions and different substitutions in each compound. In **1–6**, the signals belonging to quaternary carbon atoms resonating at highest field must be attributed to C(12) and C(14); the lower value was assigned to C(12) in consideration of its constancy, whereas C(14) changes in **2**, in consequence of substitution at C(2). Fully coupled spectra (gate decoupled) were used to confirm assignments; in fact, although an exact measurement of long-range coupling constants was not always possible owing to the complexity of the patterns arising from the tricyclic substituted aromatic system, differences in the "fingerprint" of each signal were compared.[26] In this way, C(17), C(17') and C(22) isopropylic carbon atoms can be distinguished by their characteristic multiplets. C(7) is confirmed not only by its chemical shift, similar to that one in **7–9**, but also by its form as a singlet in **4** and related compounds, whereas in **3** it resembles a triplet; similarly, C(5) shows a triplet which is further split and C(9) a quartet, changing form in the differently substituted compounds. Methyl groups of prenyl chains are usually coincident; higher field values were assigned to methyl groups in *cis* positions.[27] In compound **5**, the stereochemistry of the oxygenated prenyl chain, previously undetermined,[4] is now assigned by comparison with reported data for monoterpenes[28] and for angelic and tiglic acids.[29] Values of **6** confirm the presence of two hydroxyl groups in the same prenyl chain.[29]

Chemical shift values of compounds **11**, **12** and **13** give confirmation of previously assigned structures. Locations of methoxy groups in **11** and **12** are assigned by C(1), C(3) and C(13) chemical shifts. In particular, loss of intramolecular hydrogen bonding in **12** generates an upfield shift of *ca* 5 ppm for C(1), the same value already observed in other O-methylation and O-allylation.[22,23] Furthermore, methylation of disubstituted *ortho*, *ortho'* hydroxyl groups results in steric inhibition to resonance and consequent deshielding of *ortho* carbon atoms.[30,31] In this way, in **11**, in comparison with **4**, C(10) and C(12) are deshielded, but not C(14) and in **12** only C(12) and C(14) change their values similarly. Comparison of **13** with **11** and **12** confirms its structure: the different con-



	R_1	R_2
10	H	H
11	CH_3	H
12	H	CH_3



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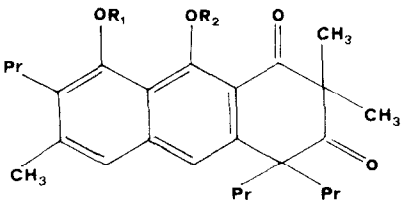

	R_1	R_2
14	H	H
15	CH_3	H
16	H	CH_3

Table 4. ^{13}C NMR data of ferruginins and their derivatives*

	1	2	3	4	5	6	11	12	13
C(1)	192.6	192.5	192.6	192.6	192.6	192.6	189.9	184.4	169.7
C(2)	105.9	117.0	106.0	105.9	105.8	105.9	103.7	105.6	104.5
C(3)	180.8	182.2	180.5	180.9	181.1	181.2	177.3	174.3	200.5
C(4)	51.3	50.7	51.3	51.3	51.1	51.1	50.0	49.3	57.6
C(5)	142.6	142.9	141.1	141.7	142.0	142.0	144.5	141.9	142.5
C(6)	116.2	115.9	114.3	116.3	116.1	116.0	124.1	122.3	124.4
C(7)	137.9	139.8	138.8	135.3	137.9	137.9	137.5	135.3	136.2
C(8)	124.5	123.5	134.6	126.4	124.4	124.4	123.0	120.5	123.9
C(9)	140.8	141.5	140.9	140.0	140.7	140.7	140.4	139.7	140.8
C(10)	123.5	113.0	113.5	113.1	123.7	123.7	131.1	122.0	124.2
C(11)	155.8	159.0	157.3	159.0	155.8	155.9	155.8	151.7	153.1
C(12)	109,7	109.9	110.3	109.9	109.7	109.7	114.5[a]	114.2	116.2[a]
C(13)	164.9	164.6	165.1	164.6	165.0	165.1	161.9	157.4	157.1
C(14)	112.7	117.7	113.2	112.6	112.7	112.2	114.4[a]	118.6	117.1[a]
C(15)	41.9	43.1	42.0	42.2	42.4	41.9	40.8	39.6	42.5
C(15')	41.9	43.1	42.0	42.2	41.4	40.2	40.8	39.6	42.5
C(16)	120.2	120.3	120.2	120.4	120.1	123.4	118.5	118.2	120.1
C(16')	120.2	120.3	120.2	120.4	120.1	120.1	118.5	118.2	120.1
C(17)	135.2	135.2	135.3	135.3	139.5	143.0	134.0	133.5	134.6
C(17')	135.2	135.2	135.3	135.3	135.5	135.7	134.0	133.5	134.6
C(18)	26.6	26.6	26.5	26.5	68.4	66.1	25.7	25.3	26.8
C(18')	26.6	26.6	26.5	26.5	26.7	26.6[a]	25.7	25.3	26.8
C(19)	21.6	21.9	21.7	22.9	14.9	59.8	17.9[b]	17.3	21.6
C(19')	21.6	21.9	21.7	22.9	21.6	21.6	17.9[b]	17.3	21.6
C(20)	26.3	26.8	28.8		26.3	26.4	29.8	24.8	26.8
C(21)	119.9	118.9	120.2		119.9	120.1	119.1	118.0	120.1
C(22)	132.0	134.1	131.6		132.1	132.2	131.1	130.8	132.1
C(23)	26.6	26.6	26.5		26.7	26.8[a]	25.7	25.3	26.8
C(24)	21.6	22.9	21.7		21.6	21.6	18.0[b]	17.3	21.6
C(25)	19.1	19.1	19.1		19.1	19.1	20.5	20.1	19.1
C(3)-OCH_3							55.8	55.1	
C(11)-OCH_3							62.6		
C(13)-OCH_3								63.6	64.9
C(1)-OCH_3									56.8

*In dioxane-d_8, except 11 and 12 (in $CDCl_3$).

[a,b]Within the same column assignments may be reversed.

stitution of ring C is reflected in changes in C(1), C(3), C(4) and methoxy groups values. In fact, it must be noted that C(4) shows in **13** vs **11** and **12** a shift (*ca* +7.5 ppm) very similar to that observed for C(5') in griseofulvin vs isogriseofulvin, where a similar conversion is involved.[25] The similarity of **13** to **12**, in particular in C(8) and C(10) chemical shifts, attests the presence of the methoxy group at C(13). Finally, methoxy groups in **11**, **12** and **13** were assigned in consideration that methoxy carbon atoms *ortho*, *ortho'* disubstituted resonate at lower field than 60 ppm, whereas ordinary OMe groups are usually found between 55–57 ppm.[32,33]

EXPERIMENTAL

UV spectra were recorded on a Beckmann Acta III, IR spectra on a Perkin–Elmer 247, mass spectra on an AEI 12 and ^1H NMR spectra on a Varian EM 360 spectrometer, except those at variable temperature (Varian XL 100), values in δ and TMS as internal standard. Natural abundance ^{13}C NMR spectra were recorded at 32° using a Varian XL 100 Fourier Transform spectrometer operating at 25.2 MHz, in 0.4–0.8*M* solutions and using TMS as internal reference. Usual measurement techniques (PND, SFORD and gate decoupled spectra) were used for exact determination of ^{13}C chemical shifts and differentiation of carbon atoms. SiO_2 MN Kieselgel was used for column chromatography and Kieselgel 60 F_{254} for tlc. M.ps are uncorrected.

Methylation of ferruginin A

(a) *With dimethylsulphate.* Ferruginin A (250 mg), K_2CO_3 (500 mg) and dimethylsulphate (1.7 ml) were refluxed for 4 h. Standard work-up and chromatographic separation (SiO_2; CH_2Cl_2) gave 3-*O*-methylferruginin A, **10**, (80 mg), 3,11-di-*O*-methylferruginin A, **11** (40 mg), and 3,13-di-*O*-methylferruginin A, **12** (80 mg), successively.

(b) *With diazomethane.* Diazomethane in Et_2O was added to ferruginin A (250 mg) in $CHCl_3$ and the soln left overnight.

Standard work-up and chromatographic separation (SiO_2, CH_2Cl_2) gave **10** (15 mg), **11** (40 mg), 1,13-di-*O*-methylisoferruginin A, **13** (56 mg) and **12** (80 mg), successively.

(c) *With methyliodide.* Ferruginin A (250 mg) in acetone (20 ml), K_2CO_3 (250 mg) and CH_3I (2 ml) were refluxed for 3 h. After evaporation, the raw product was separated on a SiO_2 column. Elution with CH_2Cl_2: *n*-hexane 1:1 gave 2,2-dimethyl-diketoferruginin A, **14**, (32 mg), **10** (38 mg), 11-*O*-methyl-2,2-dimethyl-diketoferruginin A, **15**, (13 mg), and 13-*O*-methyl-2,2-dimethyl-diketoferruginin A, **16**, (50 mg), successively. Elution with CH_2Cl_2 gave **11** (32 mg) and **12** (62 mg).

3-O-*methylferruginin A*, **10**. Dark yellow crystals from *n*-heptane, m.p. 81–82°. UV in Table 1. IR ($CHCl_3$), ν_{max} 3360, 1367, 1620, 1600 and 1580 cm^{-1}. ^1H NMR in Table 2. MS, *m/e* (%): 474 (M^+, 14), 419 ($[M-C_4H_7]^+$, 5), 406 ($[M-C_5H_8]^+$, 34), 405 ($[M-C_5H_9)^+$, 100), 375 (6), 363 (18), 362 (15), 350 (12), 349 (9), 342 (13), 337 (13), 326 (16), 319 (15), 307 (50), 301 (10), 298 (16), 295 (28), 294 (9).

3,11-*di*-O-*methylferruginin A*, **11**. Dark yellow crystals from *n*-heptane, m.p. 91–92°. UV in Table 1. IR ($CHCl_3$), ν_{max} 3400, 1632, 1625 and 1595 cm^{-1}. ^1H NMR in Table 2 and ^{13}C NMR in Table 4. MS, *m/e* (%): 488 (M^+, 50), 433 ($[M-C_4H_7]^+$, 6), 420 ($[M-C_5H_8]^+$, 100), 419 ($[M-C_5H_9]^+$, 96), 405 (16), 389 (9), 377 (9), 376 (6), 364 (52), 363 (100), 359 (18), 333 (18), 331 (28), 321 (15).

3,13-*di*-O-*methylferruginin A*, **12**. Orange crystals from petrol ether, m.p. 93–95°. UV in Table 1. ^1H NMR in Table 2 and ^{13}C NMR in Table 4. MS, *m/e* (%): 488 (M^+, 10), 433 ($[M-C_4H_7]^+$, 62), 420 ($[M-C_5H_8)^+$, 45), 419 ($[M-C_5H_9]^+$, 68), 405 (28), 403 (38), 393 (46), 377 (90), 375 (43), 365 (90), 363 (52), 351 (48), 333 (60), 321 (100), 309 (76), 295 (46).

1,13-*di*-O-*methylisoferruginin A*, **13**. Yellow crystals from *n*-heptane, m.p. 79–80°. UV in Table 1. ^1H NMR in Table 2 and ^{13}C NMR in Table 4. MS, *m/e* (%): 488 (M^+, 56), 420 ($[M-C_5H_8]^+$, 100), 419 ($[M-C_5H_9]^+$, 70), 405 (12), 391 (18), 365 (25), 363 (13), 341 (16), 321 (23), 301 (34), 287 (64).

2,2-*dimethyl-diketoferruginin A*, **14**. Orange needles from MeOH, m.p. 71–72°. UV in Table 1. IR ($CHCl_3$), ν_{max} 1710 and 1630 cm^{-1}. ^1H NMR in Table 2. MS, *m/e* (%): 488 (M^+, 70), 420 ($[M-C_5H_8]^+$, 64), 419 ($[M-C_5H_9]^+$, 100), 405 (419 − CH_3, 6), 365 (5), 364 (27), 363 (36), 349 (364 − CH_3, 22), 321 (12), 293 (85).

2,2-*dimethyl*-11-O-*methyl-diketoferruginin A*, **15**. Amorphous solid. UV in Table 1. IR ($CHCl_3$), ν_{max} 1720 and 1620 cm^{-1}. ^1H NMR in Table 2. MS, *m/e* (%): 502 (M^+, 91), 434 ($[M-C_5H_8]^+$, 93), 433 ($[M-C_5H_9]^-$, 100), 419 (16), 379 (45), 378 (41), 377 (69), 363 (74), 335 (20), 307 (83).

2,2-*dimethyl*-13-O-*methyl-diketoferruginin A*, **16**. Yellow crystals from MeOH, m.p. 84–86°. UV in Table 1. IR ($CHCl_3$), ν_{max} 1720 and 1685 cm^{-1}. ^1H NMR in Table 2. MS, *m/e* (%): 502 (M^+, 97), 434 ($[M-C_5H_8]^+$, 97), 433 ($[M-C_5H_9]^+$, 77), 419 (9), 379 (12), 378 (26), 377 (13), 363 (81), 335 (10), 307 (100).

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