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INDOLE ALKALOIDS AND TERPENOIDS FROM *TABERNAEMONTANA MARKGRAFIANA*

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Key Word Index—*Tabernaemontana markgrafiana*; Apocynaceae; bark; triterpenes; indole alkaloids.

Abstract—The bark of *Tabernaemontana markgrafiana* yielded five acetylated pentacyclic triterpenes and 24 monoterpene indole alkaloids. The major triterpene was baurenyl acetate, which constituted *ca* 6% of the crude petrol extract. An X-ray study of *iso*-ursenyl acetate was carried out for the first time. The indole alkaloids were primarily of the iboga-type and constituted *ca* 3% of the dried bark and 20% of the total extracts. The major alkaloids were coronaridine, (19*S*)-heyneanine, voacangine and ibogamine. Among the minor components, four new alkaloids were identified: 5,6-dehydro-coronaridine, 3*R*-methoxy-coronaridine, 3*R*-methoxyvoacangine and the 10,11-demethoxy chippiine.

INTRODUCTION

Tabernaemontana markgrafiana, syn. *Bonafousia longituba* is a tree, growing sparsely in South America, giving a white latex. It is widely used in traditional medicine as a febrifuge and disinfectant in Brazil [1], as a contraceptive and against toothache in Peru, and as a fungicide, against toothache and insect bites in Ecuador [1, Ghia, unpublished results].

The genus *Tabernaemontana* has *ca* 120 species distributed in the tropical region and is characterized by its content of monoterpene indole alkaloids [2]. The genus is under revision by Leeuwenberg and has a large number of synonyms [1, 3]. The title species has not previously been investigated chemically. Extracts from the powdered bark showed a strong alkaloidal reaction with the Hager, Mayer, Dragendorff, Wanger and silicotungsten reagents.

RESULTS AND DISCUSSION

Since the alkaloid content in the bark was unusually high, the work was focused on this class of compounds; *ca* 3% of the dried bark and 20% of the total extracts consisted of alkaloids. ^{1}H NMR spectra of the crude alkaloidal fractions indicated the presence of indole alkaloids, which frequently occur in the genus *Tabernaemontana*. The plant material was successively extracted with petrol, dichloromethane and methanol. It was later established that the same alkaloids were present in both the dichloromethane and methanol fractions, and also to some extent in the petrol fraction. Therefore, the work-up procedure could be simplified by just carrying out a petrol and a methanol extraction. Alkaloids were separated by extraction with 1% hydrochloric acid and basification with sodium hydrogen carbonate. The neutral petrol extract contained long-chain hydrocarbons (polyprenes), fatty acids, stigmasterol, α-amyrin acetate, β-amyrin acetate, baurenyl acetate **1a**, *iso*-ursenyl acetate **2** and 20(30)-taraxasten-3β-yl acetate **3a**. The terpenes were identified by mp, $[\alpha]_D$, mass spectrometry, NMR, and by comparison with authentic samples. The last mentioned triterpene **3a** had mp and $[\alpha]_D$ in closer agreement with 20(30)-ursen-3-yl acetate, **4** [4–6]. Hydrolysis of **3a** gave the corresponding alcohol **3b**, which by spectral comparison with an authentic sample was shown to be 20(30)-taraxasten-3-ol (taraxasterol), **3b** [7] (Fig. 1).

Baurenyl acetate, **1a**, precipitated as crystals during evaporation of the petrol extract. Its identity was confirmed by X-ray analysis. An X-ray determination of the structure has been carried out previously [8]. Basic hydrolysis yielded baurenol **1b**. Baurenyl acetate was the major triterpene and constituted *ca* 6% of the crude petrol extract. A minor amount of another triterpene co-occurred with β-amyrin acetate. It could be purified by fractional recrystallization and an X-ray investigation proved it to be iso-ursenyl acetate **2** (Fig. 2). No new neutral compounds were isolated from the dichloromethane extract, which consisted mainly of alkaloids.

The alkaloids (Fig. 3) were represented primarily by iboga alkaloids, accounting for more than 90% of the isolated alkaloids (IA). A few per cent of the isolated alkaloids consisted of the aspidospermine-type alkaloids, *O*-acetylvallesamine **20** and vallesamine **21**, and of the

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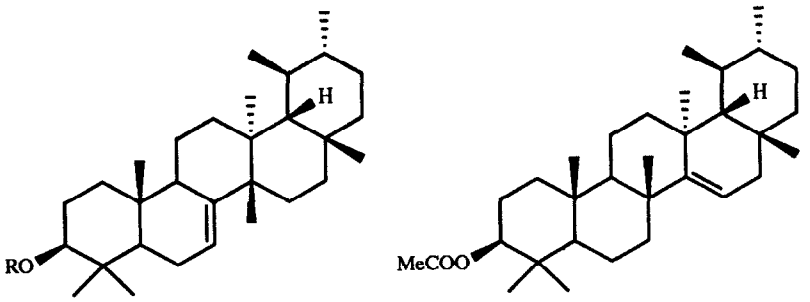
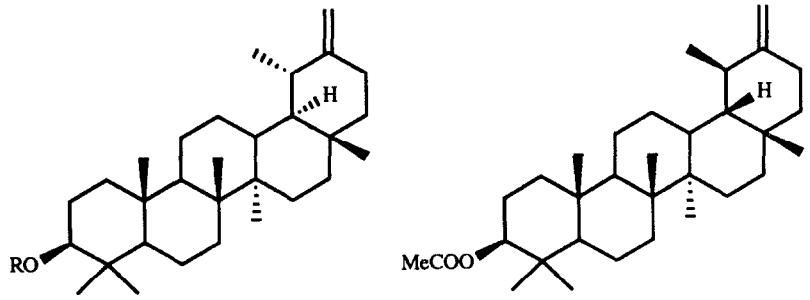


	R
1a	MeCO
1b	H

2



	R
3a	MeCO
3b	H

4

Fig. 1. Isolated triterpenoids (**1**–**4**).

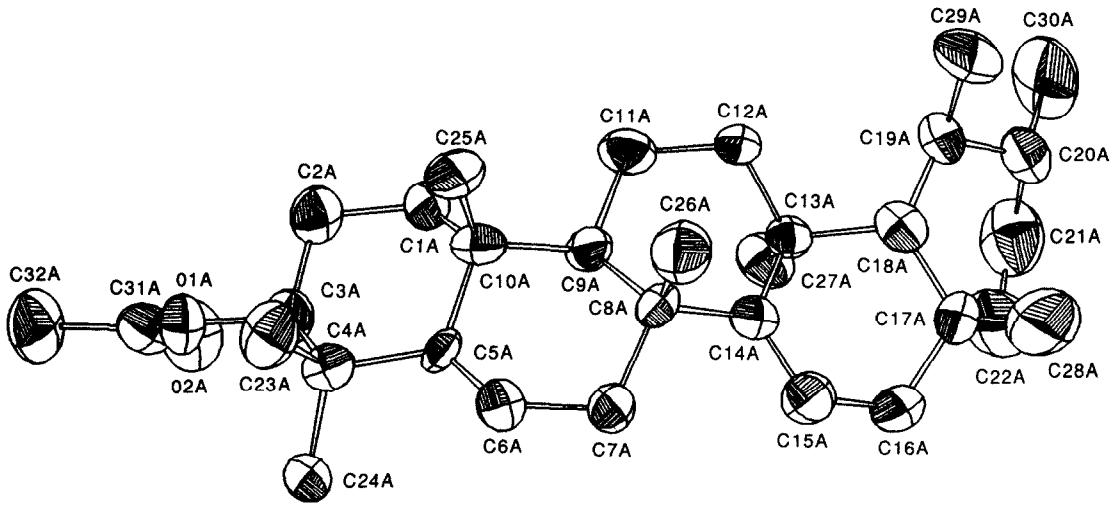
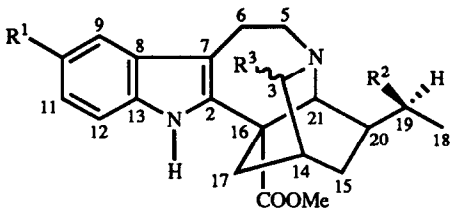


Fig. 2. Perspective drawing of *iso*-ursenyl acetate (**2**), showing the atomic numbering.

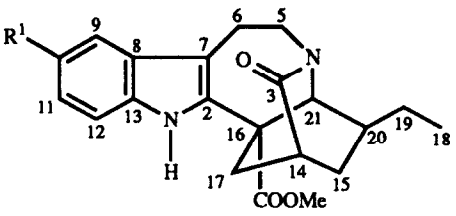
corynantheine-type alkaloids, akuammidine **22** and 19*E*-16*R*-isositsirikine **23**.

Coronaridine **5** (39% of IA), (19*S*)-heyneanine **7** (22%), voacangine **6** (9%), occurring in all extracts, and ibogamine **14** (8%) occurring in the dichloromethane and methanol extracts were the main alkaloids. The related alkaloids (19*S*)-voacristine **8** and ibogaine **15** isolated from the dichloromethane and methanol extracts constituted 4–5% of the alkaloid fraction. All the known alkaloids had physical data that agreed with those cited in the literature (see Experimental).

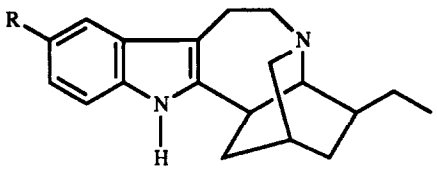
From the non-polar fraction of the dichloromethane extract a new unstable alkaloid was isolated, M_r 336, i.e. 2 mu less than coronaridine 5. The ^{1}HNMR showed a *cis*-substituted double bond, but for the rest, most of the ^{1}H and ^{13}CNMR characteristics of **5**. Compound **10**, i.e.



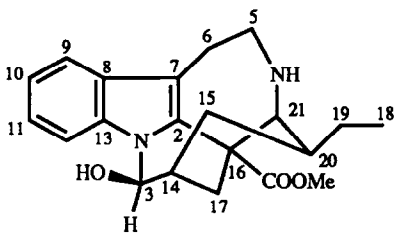
	R^1	R^2	R^3
5	H	H	H
6	OMe	H	H
7	H	OH	H
8	OMe	OH	H
10	H	H	H, $\Delta_{5,6}$
11	H	H	OH (3*R*/*S*)
12	H	H	OMe (3*R*)
13	H	OMe	OMe (3*R*)



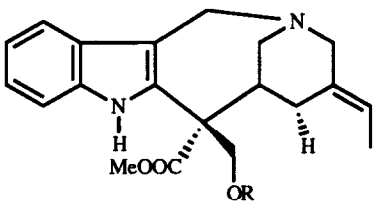
	R
9a	H
9b	OMe



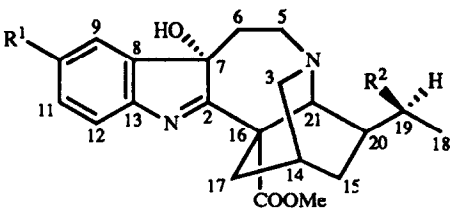
	R
14	H
15	OMe



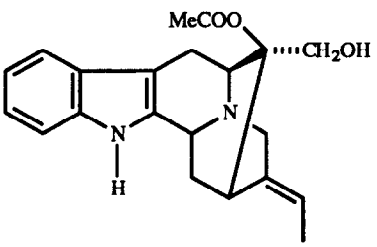
19



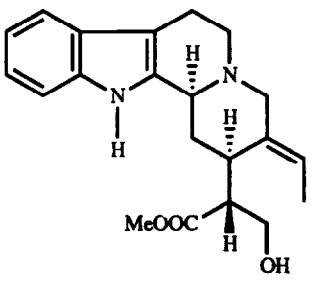
	R
20	COMe
21	H



	R^1	R^2
16	H	H
17	OMe	H
18	H	OH



22



23

Fig. 3. Isolated alkaloids (**5**–**23**).

5,6-dehydro-coronaridine is therefore proposed for this alkaloid (0.3%).

The formation of the skeleton of the new alkaloid **19** (2%), is explained by hydrolysis of the (C-3)–(N-4) bond in **11** and recyclization involving the formation of the (N-1)–(C-3) bond. One alkaloid, chippiine, with the same structural features has been reported previously [9]. Chippiine, is the 10,11-dimethoxyderivative of **19**. The 15-α-H of **19** is located above the pyrrole ring, which explains its unusually low chemical shift of δ 0.32. The observed

chemical shift for H-3, δ5.46, indicated a pseudo-axial orientation as shown in **19**. The ^{1}H NMR spectrum of **19** is in close agreement with that of chippiine [9].

Secondary oxidations at C-3 and C-7 occur frequently in the iboga alkaloid series. The known compounds 3-oxocoronaridine **9a** (0.6%), 3-oxovoacangine **9b** (0.1%), 3*R*/*S*-hydroxycoronaridine, i.e. eglandine **11** (0.1%), and three 7-hydroxyindolenines **16**, **17** and **18**, 1.6, 1.5 and 0.1% of IA, were identified. From our 2D NMR measurements and Damak's data on **7** and **18** [10, 11], we have assigned the spectra of coronaridine hydroxyindolenine **16** and voacangine hydroxyindolenine **17** (see Experimental).

A minor alkaloid was isolated from the polar fractions. It contained two methyl groups, one at δ3.7 (carbomethoxy), the other at δ3.21 indicating an OMe-group of an N,O-acetal. The carbon atom at δ96.4, correlating with a proton at δ4.01, further confirmed the N,O-acetal structure at C-3 in an iboga alkaloid. Comparing the NMR spectra with data of **11** [12], and of 3*R*/*S*-ethoxycoronaridine [13], it became evident that the isolated compound was 3*R*-methoxycoronaridine **12**. This alkaloid has not previously been described. It is not an artifact, since the petrol extract, in which it also occurred, had not been in contact with methanol. It was reported that 3-ethoxycoronaridine was isolated from *T. eglandulosa* and the authors stress that only solvents free from ethanol were used [13]. The 3*R*-configuration in **12** is proposed on the basis that the H-3*R* in the 3-hydroxy series is located at δ4.1, while the H-3*S* is located at δ4.4. The corresponding ^{13}C NMR shifts are δ95 (C-3*R*) and δ86 (C-3*S*) [9].

A small amount of 3*R*-methoxyvoacangine **13**, occurring in the methanol extract, was also isolated and structurally determined by analogy to **12**.

The four minor alkaloids, *O*-acetylvallesamine **20** (0.7%), vallesamine **21** (0.5%), 19(*E*)-akuammidine **22** (1.8%) and 19(*E*)-16*R*-isositsirikine **23** (0.8%), were isolated from the methanol extract and identified by comparing their spectral data with those cited in the literature. Moreover, the structure of **22** was confirmed by an X-ray study (Fig. 4).

EXPERIMENTAL

General. ^{1}H and ^{13}C NMR were recorded at 200 and 50 MHz, respectively, with TMS as int. standard. Units for chemical shifts are in ppm. For CC, Kieselgel 60, 63–200 μm, was used. Prep. TLC was carried out on glass plates 20 × 20 × 0.18 cm, on Kieselgel 60, $Pf_{254+366}$ Merck. Mp are uncorr. Optical rotations were measured at 22–25°. Mass spectra were recorded at 70 eV, direct inlet.

Plant material. Bark of *T. markgrafiana* was collected in the Plantacion Forestal, Endesa, near the village of Pedro Vincente de Maldonado, Provincia de Pichincha, Ecuador at an altitude of 750 m. Voucher specimens, FG 475, are deposited at the Escuela Polytécnica Nacional, Quito. The bark was dried in a ventilated hood at *ca* 45° in the dark.

Extraction. Dried and ground bark (1.24 kg) was extracted at 25° in the dark with petrol (3 × 4 l), CH_2Cl_2 (3 × 4 l) and MeOH (3 × 4 l). Extracts were evapd *in vacuo* to give 48, 39 and 97 g, respectively.

The petrol extract yielded a ppt., which by recrystallization in CH_2Cl_2, gave crystals of *baurenyl acetate* (**1a**), 3 g. Glistening plates (CH_2Cl_2). Mp 294–298° (lit. 292–294° [14], 282–284° [15]). $[\alpha]_D$ −2.3° ($CHCl_3$; *c* 1.02) (lit. −2.5° [15]). IR ν_{max}^{KBr} cm^{-1}: 1735, 1255, 821. EIMS *m/z*: 468 $[M]^+$, 408, 393, 229. ^{13}C NMR ($CDCl_3$): δ12.8, 15.6, 16.6, 21.2, 22.4, 22.5, 23.5, 23.8, 24.0, 25.5, 27.3, 28.7, 29.0, 31.4, 31.9 (2 × C), 32.2, 34.9, 35.2, 36.4, 37.55, 37.59 (2 × C), 37.9, 41.1, 48.0, 50.5, 54.8, 81.1, 116.3, 145.6, 171.3. Basic hydrolysis of **1a** afforded baurenol (**1b**) as needles (EtOH). Mp 203–209° (lit. 208–210° [15]). $[\alpha]_D$ −22.3° ($CHCl_3$; *c* 0.89), (lit. −18° [15]). IR ν_{max}^{KBr} cm^{-1}: 3430, 821. EIMS *m/z*: 426 $[M]^+$, 408, 229. ^{13}C NMR ($CDCl_3$): δ12.8, 14.5, 16.6, 22.4, 22.5, 23.5, 24.0, 25.5, 27.4, 27.5, 28.7, 29.0, 31.3,

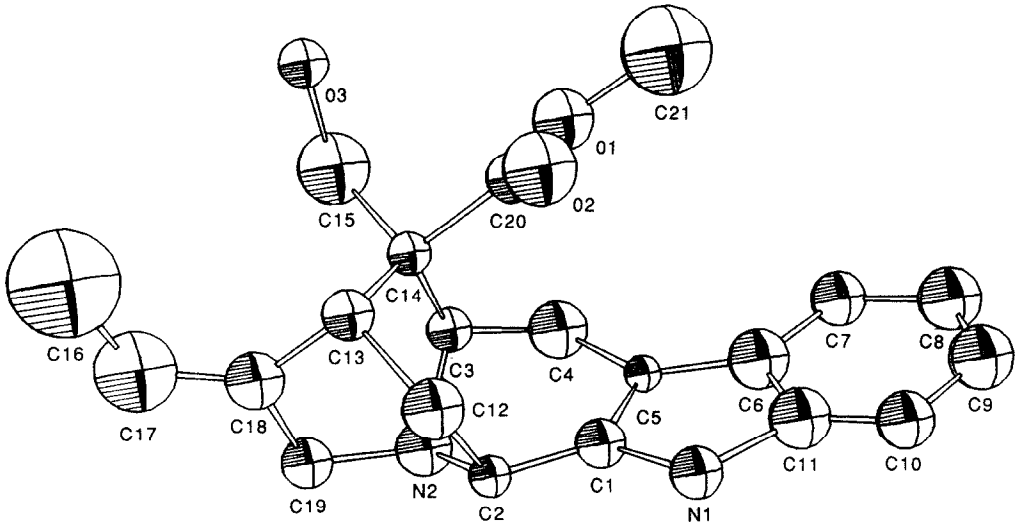


Fig. 4. Perspective drawing of 19(*E*)-akuammidine (**22**), showing the atomic numbering.

31.9 (2 × C), 32.2, 35.0, 35.2, 36.7, 37.5, 37.9, 38.7, 41.1, 48.1, 50.3, 54.8, 58.3, 79.2, 116.5, 145.5.

The petrol filtrate was extracted with 1% HCl to give a neutral fr. (39 g) and an alkaloid fr. (2.4 g). The neutral fr. was chromatographed on silica gel with petrol containing increasing amounts of EtOAc as eluent. The non-polar frs contained satd hydrocarbons and polyisoprenes. By TLC of the terpenoid frs, fractional recrystallization, comparison with authentic samples and lit. NMR data, α- and β-amyrin acetate, stigmasterol, *iso*-ursenyl acetate **2** (X-ray analysis, Fig. 1) and 20(30)-taraxasten-3-yl acetate **3a** [16] were identified. Basic hydrolysis of **3a** afforded taraxasterol **3b** [7, 18, 19] as thin needles. The more polar frs contained fatty acids.

iso-*Ursenyl acetate* (**2**). Transparent needles (EtOAc). Mp 196–200° (lit. 214–216° [16], 213° [17]). ^{1}H NMR ($CDCl_3$): δ0.85 (3H, *s*), 0.93 (6H, *s*), 0.93 (6H, *s*), 0.99 (3H, *s*), 1.06 (3H, *s*), 4.46 (1H, *m*), 5.49 (1H, *dd*, *J* = 3 and 8 Hz). ^{13}C NMR ($CDCl_3$): δ15.1, 16.4, 17.3, 18.6, 19.2, 22.3, 23.4, 26.2, 27.3, 27.8, 28.3, 32.0, 33.7, 35.3, 36.4, 37.0, 37.2, 37.5, 37.7, 38.3, 38.8, 39.9, 40.5, 41.7, 49.0, 55.4, 60.4, 81.0, 116.5, 159.6, 171.3.

The alkaloids of the petrol fr. were chromatographed on a silica gel column with petrol containing increasing amounts of EtOAc to give **5** [2, 11] (1.3 g), **6** [11, 21] (0.14 g), **16** [20] (0.01 g), **17** [20, 22] (0.06 g), **9a** [12, 23] (0.04 g), **12** (0.02 g) and **7** [2, 10, 11, 20, 21] (0.07 g), eluted in order of increasing polarity of the mobile phase. Purification of frs was carried out by TLC with petrol–Et_2O and $CHCl_3$–MeOH as solvent systems.

The alkaloid content of the CH_2Cl_2 extract was *ca* 50%. Despite repeated extraction with 1% HCl, it was not possible to completely remove all alkaloids. The 'neutral fr.' contained similar compounds to those found in the neutral petrol fr. No new compounds were detected. Crude alkaloids (8.6 g) from the CH_2Cl_2 extract (total 17 g) were sepd on a silica gel column starting with petrol–CH_2Cl_2 (1:1) and increasing amounts of CH_2Cl_2, followed by CH_2Cl_2–MeOH mixts. 5,6-Dehydrocoronaridine **10** (33 mg) occurred in the early frs. It was followed by **5** (2.32 g), **6** (0.37 g), **7** (0.4 g), **16** (0.03 g), **17** (0.03 g) and **18** [10] (0.01 g). The major part of the alkaloids (5 g) was eluted as a narrow band with CH_2Cl_2–MeOH (20:1). From a fr. at the end of the band, a small amount of *O*-acetyl-vallesamine **20** [24, 25] (0.05 g) was isolated. The last frs, which were eluted with CH_2Cl_2–MeOH (5:1), contained several minor polar alkaloids which were not studied further. The major fr. (5 g) was rechromatographed on silica gel with a petrol–EtOAc–MeOH system and the frs obtained were further purified by TLC on silica gel to give **6** (66 mg), **7** (790 mg), **8** [21, 26, 27] (135 mg), **12** (70 mg), **14** [2, 11, 20] (324 mg), **15** [11, 20] (219 mg) and small amounts of **16** and **17**.

The MeOH extract (97 g) was extracted × 2 with EtOAc (250 ml) for 1 day with stirring at 25°, to give 7.1 g of soluble material, which was partitioned into a neutral fr. (1.5 g) and an alkaloid fr. (3.4 g). The ^{1}H NMR spectrum of these crude alkaloids was identical to the spectrum of the crude alkaloids obtained from the CH_2Cl_2 extract. Therefore, the work was concd on the basic constituents of the solid residue (85 g), poorly soluble in EtOAc. It was finely divided in a mortar and 36 g of the pulverized extract was extracted with HCl (8 × 100 ml), with stirring at 25°. Filtration left a solid residue of 9 g, which was discarded. The filtrate was basified with $NaHCO_3$ and extracted with EtOAc. The emulsion was filtered, the organic phase sepd and evapd to give 4.8 g alkaloids. The EtOAc–insoluble ppt. (*ca* 1 g) also showed a strong alkaloid reaction, but was not further investigated. The alkaloid fr. (4.8 g) was chromatographed on a silica gel column with $CHCl_3$–MeOH (97:3) and increasing amounts of MeOH. The combined frs were rechromatographed on another column by gradient elution with petrol–Et_2O–MeOH. Further purification was carried out by TLC using $CHCl_3$–MeOH, Et_2O–MeOH–NH_3, toluene–EtOAc–NH_3 and toluene–EtOH–NH_3. An NH_3 atm. was obtained by placing a flask containing NH_3 (aq.) in the chamber. The TLC plates were satd 20 min prior to development. The following alkaloids were isolated with increasing polarity of the mobile phase: **5** (360 mg), **6** (156 mg), **11** [12] (5 mg), **16** (16 mg), **17** (9 mg), **7** (433 mg), **14** (192 mg), **12** (75 mg), **13** (24 mg), **9a** (40 mg), **9b** [22] (11 mg), **8** (159 mg), **15** (143 mg), **20** (28 mg), **19** (60 mg), **21** [24, 25, 28] (19 mg), **22** (47 mg) [26, 28–30] and **23** [31, 32] (16 mg). Additionally a vallesamine isomer was isolated (18 mg), the absolute configuration of which was not elucidated.

5,6-*Dehydrocoronaridine* (**10**). Amorphous reddish-white material which decomposed in $CHCl_3$. EIMS *m/z*: 336 $[M]^+$. ^{1}H NMR ($CDCl_3$–CCl_4, 3:2): δ0.86 (3H, *t*, *J* = 7 Hz, H-18), 1.15 (1H, *dm*, *J* = 12 Hz, H-15), 1.2–1.85 (6H, *m*), 2.62 (1H, *br d*, *J* = 9 Hz, H-3), 3.00 (1H, *d*, *J* < 0.5 Hz, H-21), 3.01 (1H, *dm*, *J* = 12 Hz, H-17), 3.36 (1H, *br d*, *J* = 9 Hz, H-3), 3.70 (3H, *s*, COOMe) 6.12 (1H, *d*, *J* = 7.5 Hz, H-6), 6.27 (1H, *d*, *J* = 7.5 Hz, H-5), 7.03–7.18 (2H, *m*), 7.22 (1H, *br d*, *J* ~ 7.5 Hz), 7.62 (1H, *br d*, *J* ~ 7.5 Hz), 7.87 (1H, *br s*, NH). ^{13}C NMR ($CDCl_3$–CCl_4, 3:2): δ12.2, 22.6, 28.8, 30.3, 36.1, 37.2, 52.7, 53.5, 54.5 (2 × C), 106.3, 110.2, 110.8, 118.9, 120.1, 122.6, 127.8, 135.6, 137.1, 137.4, 175.0.

(−)-3R-*Methoxycoronaridine* (**12**). Amorphous light yellow solid. $[\alpha]_D$ −44° ($CHCl_3$; *c* 0.3). IR ν_{max}^{film} cm^{-1}: 3360, 3260, 1720, 1660, 1455. EIMS *m/z* (rel. int.): 368 $[M]^+$ (3), 367 (2, $[M-1]^+$), 366 (4, $[M-2]^+$), 353 (5, $[M-15]^+$), 352 (18, $[M-16]^+$), 338 (54), 336 (66), 323 (15), 307 (12), 278 (11), 277 (27). ^{1}H NMR ($CDCl_3$): δ0.92 (3H, *t*, *J* = 7 Hz, H-18), 1.32 (1H, *m*, H-20), 1.45–1.65 (5H, *m*, H-5,5′,15,19,19′), 1.93 (1H, *dd*, *J* = 13.5 and 4 Hz), 2.05 (1H, *br m*, H-14), 2.79 (1H, *dd*, *J* = 13.5 and 2 Hz, H-17′), 3.11 (2H, *m*, H-6,6′), 3.21 (3H, *s*, OMe), 3.70 (3H, *s*, COOMe), 4.01 (1H, *d*, *J* = 2 Hz, H-3), 7.10 (1H, *br dd*, *J* = 7 Hz, H-10), 7.17 (1H, *br dd*, *J* = 7 Hz, H-11), 7.28 (1H, *br d*, *J* = 7 Hz, H-12), 7.51 (1H, *br d*, *J* = 7 Hz, H-9), 7.9 (1H, *br s*, NH). ^{13}C NMR($CDCl_3$): δ12.2 (*q*, C-18), 22.3 (*t*, C-6), 25.5 (*t*, C-15), 27.1 (*t*, C-19), 30.5 (*d*, C-14), 35.9 (*t*, C-17), 38.3 (*d*, C-20), 53.1 (*t*, C-5), 53.2 (*q*, COOMe), 54.5 (*q*, OMe), 54.8 (*s*, C-16), 56.0 (*d*, C-21), 96.4 (*d*, C-3), 110.6 (*s*, C-7), 111.0 (*d*, C-12), 118.8 (*d*, C-9), 119.8 (*d*, C-10), 122.4 (*d*, C-11), 128.7 (*s*, C-8), 136.0 (*s*, C-13), 136.9 (*s*, C-2), 175.4 (*s*, COOMe).

(−)-3R-*Methoxyvoacangine* (**13**). Amorphous light green solid. $[\alpha]_D$ −39° ($CHCl_3$; *c* 0.4). EIMS *m/z* (rel. int.): 398 $[M]^+$ (2.3), 382 (12), 369 (8), 368 (34), 367 (34), 366 (100), 365 (16), 351 (17), 337 (21), 308 (21), 307 (33), 283 (16), 279 (20), 268 (26), 267 (12), 258 (17), 244 (18), 225 (22), 184 (17), 153 (13), 136 (33), 135 (22), 124 (18), 122 (24). ^{1}H NMR ($CDCl_3$): δ0.91 (3H, *t*, *J* = 7.4 Hz, H-18), 1.35 (1H, *m*, H-20), 1.5–1.6 (5H, *m*, H-5,5′,15,19,19′), 1.90 (1H, *dd*, *J* = 13.5 and 3.5 Hz, H-17), 2.04 (1H, *br s*, H-14), 2.79 (1H, *dd*, *J* = 13.5 and 2.3 Hz, H-17′), 3.07 (2H, *m*, H-6,6′), 3.21 (3H, *s*, OMe), 3.70 (3H, *s*, COOMe), 3.86 (3H, *s*, ArOMe), 4.02 (1H, *d*, *J* = 2.4 Hz, H-3*S*), 6.82 (1H, *dd*, *J* = 8.6 and 3.4 Hz, H-11), 6.95 (1H, *d*, *J* = 3.4 Hz, H-9), 7.16 (1H, *d*, *J* = 8.6 Hz, H-12), 7.77 (1H, (1H, *br s*, NH). ^{13}C NMR($CDCl_3$): δ12.2 (C-18), 22.4 (C-6), 25.4 (C-15), 27.1 (C-19), 30.4 (C-14), 35.8 (C-17), 38.3 (C-20), 53.0 (C-5), 53.2 (COOMe), 54.5 (OCMe), 54.9 (C-16), 56.0 (C-21), 56.5 (ArOMe), 96.4 (C-3), 101.0 (C-9), 110.4 (C-7), 111.7 (C-12), 112.4 (C-11), 128.1 (C-8), 131.1 (C-13), 137.9 (C-2), 154.6 (C-10), 175.4 (COOMe).

Coronaridine hydroxyindolenine (**16**). Amorphous light brown solid. $[\alpha]_D$ − 8° ($CHCl_3$; *c* 1.04). ^{1}H NMR ($CDCl_3$): δ0.86 (3H, *t*, *J* = 7.5 Hz, H-18), 1.14 (1H, *br dd*, *J* = 12 and 5 Hz, H-15), 1.36 (1H, *m*, H-20), 1.44 (2H, *m*, H-19, 19′), 1.73 (1H, *m*, H-15′), 1.86 (1H, *m*, H-6), 1.90 (1H, *m*, H-14), 1.97 (1H, *m*, H-6′), 2.46 (1H, *ddd*, *J* = 14, 4 and 3 Hz, H-17), 2.67 (1H, *m*, H-17′), 2.71 (2H, *m*, H-3), 2.96 (1H, *ddd*, *J* = 15, 4 and 2 Hz, H-5), 3.47 (1H, *ddd*, *J* = 15, 12 and 4 Hz, H-5′), 3.68 (3H, *s*, COOMe), 3.79 (1H, *br s*, H-21), 7.17–7.38 (3H, *m*, H-9,11,12), 7.44 (1H, *br d*, *J* = 7 Hz, H-10). ^{13}C NMR ($CDCl_3$): δ12.1 (*q*, C-18), 27.0 (*t*, C-19), 27.5 (*d*, C-14), 32.5 (*t*, C-15), 34.3 (*t*, C-6), 35.3 (*t*, C-17), 38.0 (*d*, C-20), 49.2 (*t*, C-3), 49.6 (*t*, C-5), 53.7 (*q*, COOMe), 58.9 (*d*, C-21), 59.0 (*s*, C-16), 88.8 (*s*, C-7), 121.3 (*d*, C-10), 121.7 (*d*, C-12), 127.3 (*d*, C-9), 129.9 (*d*, C-11), 143.1 (*s*, C-8), 151.8 (*s*, C-13), 189.7 (*s*, C-2).

Voacangine hydroxyindolenine (**17**). Amorphous yellow-green solid. $[\alpha]_D$ − 26° ($CHCl_3$; *c* 1.1) (lit. $[\alpha]_D$ − 23.1° [33], − 18°[20]). EIMS *m/z*: 384 $[M]^+$, 383, 367, 355, 325, 260, 218, 190, 176, 162, 160. ^{1}H NMR ($CDCl_3$): δ0.87 (3H, *t*, *J* = 7 Hz, H-18), 1.10 (1H, *br dd*, *J* = 12 and 5 Hz, H-15), 1.35–1.48 (3H, *m*, H-19, 20), 1.63 (1H, *br s*, OH), 1.7–1.95 (4H, *m*, H-6,14,15), 2.47 (1H, *ddd*, *J* = 14, 5 and 2 Hz, H-17), 2.71 (1H, *dm*, *J* = 14 Hz, H-17′), 2.74 (2H, *m*, H-3), 2.97 (1H, *ddd*, *J* = 15, 4 and 2 Hz, H-5), 3.5 (1H, *ddd*, *J* = 15, 11 and 4 Hz, H-5′), 3.61 (1H, *d*, *J* = 1.8 Hz), 3.71 (3H, *s*, COOMe), 3.77 (1H, *s*, H-21), 3.83 (3H, *s*, ArOMe), 6.81 (1H, *dd*, *J* = 8.5 and 2.5 Hz, H-11), 6.92 (1H, *d*, *J* = 2.5 Hz, H-9), 7.37 (1H, *d*, *J* = 8.5 Hz, H-12). ^{13}C NMR ($CDCl_3$): δ11.7 (*q*, C-18), 26.7 (*t*, C-19), 27.2 (*d*, C-14), 32.3 (*t*, C-15), 34.4 (*t*, C-6), 34.7 (*t*, C-17), 37.8 (*d*, C-20), 48.9 (*t*, C-3), 49.4 (*t*, C-5), 53.5 (*q*, COOMe), 56.0 (*q*, ArOMe), 58.8 (*d*, C-21), 58.9 (*s*, C-16), 88.7 (*s*, C-7), 108.4 (*d*, C-9), 114.2 (*d*, C-11), 121.8 (*d*, C-11), 121.8 (*d*, C-12), 145.0* (*s*, C-8), 145.4* (*s*, C-13), 159.7 (*s*, C-10), 187.5 (*s*, C-2).

Alkaloid (**19**). Brown oil. $[\alpha]_D$ − 26° ($CHCl_3$; *c* 0.02). IR ν_{max}^{film} cm^{-1}: 3370, 1725, 1470. EIMS *m/z* (rel. int.): 355 (5), 354 $[M]^+$ (21), 338 (9), 337 (10), 336 $[M-H_2O]^+$ (24), 238 (8), 180 (7), 169 (8), 168 (6), 167 (8), 154 (9), 143 (7), 136 (5), 135 (5), 86 (70), 84 (100). ^{1}H NMR (300 MHz, $CDCl_3$): δ0.32 (1H, *ddd*, *J* = 14.2, 14.1 and 7.1 Hz, H-15α), 0.91 (3H, *t*, *J* = 7 Hz, H-18), 1.00 (1H, *dqd*, *J* = 12.9, 6.9 and 7.1 Hz, H-19), 1.39 (1H, *dqd*, *J* = 12.9, 6.9 and 7.1 Hz, H-19′), 1.62 (1H, *ddd*, *J* = 14.2, 10.5 and 3.4 Hz, H-15β), 1.84 (1H, *ddddd*, *J* = 14.0, 6.9, 6.9, 6.9 and 3.4 Hz, H-20), 2.02 (1H, *dd*, *J* = 13.4 and 5 Hz, H-17β), 2.34 (1H, *dd*, *J* = 13.4 and 1 Hz, H-17α), 2.49 (1H, *m*, H-14), 2.67 (2H, *m*, H-6,6′), 2.95 (1H, *m*, H-5β), 3.19 (1H, *m*, H-5α), 3.70 (3H, *s*, COOMe), 3.93 (1H, *d*, *J* = 6.9 Hz, H-21), 5.46 (1H, *d*, *J* = 2.2 Hz, H-3), 7.16 (1H, *ddd*, *J* = 7.1, 7.1 and 1.1 Hz, H-10), 7.22 (1H, *ddd*, *J* = 7.1, 7.1 and 1.1 Hz, H-11), 7.47 (1H, *dd*, *J* = 7.1 and 1.1 Hz, H-12), 7.50 (1H, *dd*, *J* = 7.1 and 1.1 Hz, H-9). ^{13}C NMR (50 MHz, $CDCl_3$): δ12.9 (*q*, C-18), 23.5 (*t*, C-15), 24.4 (*t*, C-17), 24.5 (*t*, C-6), 24.7 (*t*, C-19), 34.9 (*d*, C-14), 36.4 (*d*, C-20), 40.9 (*t*, C-5), 49.7 (*s*, C-16), 53.2 (*q*, OMe), 58.8 (*d*, C-21), 80.0 (*d*, C-3), 109.9 (*d*, C-12), 110.1 (*s*, C-7), 118.8 (*d*, C-9), 120.9 (*d*, C-10), 122.2 (*d*, C-11), 129.5 (*s*, C-8), 132.0 (*s*, C-8), 132.0 (*s*, C-13), 137.7 (*s*, C-2), 176.7 (*s*, C =O).

19E-16R-*Isositsirikine* (**23**). Brown oil. ^{13}C NMR ($CDCl_3$): δ13.9, 18.1, 30.1, 33.0, 49.9, 51.3, 52.8, 53.2, 61.0, 62.4, 107.9, 111.9 118.5, 120.1, 122.2, 125.4, 127.8, 133.0, 133.2, 136.8, 175.7.

Vallesamine isomer. $[\alpha]_D$ + 80° (MeOH; *c* 0.8) (lit. 19(*E*)-val.: $[\alpha]_D$ + 165° ($CHCl_3$) [25, 28], 19(*Z*)-val.: $[\alpha]_D$ + 182° ($CHCl_3$) [28]. EIMS *m/z* (rel. int.): 354 (19), 340 (14, $[M]^+$), 339 (17, $[M-1]^+$), 310 (32, $[M-30]^+$), 309 ($[M-31]^+$), 215 (25), 208 (18), 202 (19), 201 (15), 194 (17), 124 (24), 123 (28), 122 (100). ^{1}H NMR ($CDCl_3$): δ1.73 (3H, *d*, *J* = 7 Hz, H-18), 2.16 (1H, *m*, H-14), 2.22 (1H, *m*, H-14′), 3.00–3.30 (2H, *m*, H-3, 3′), 3.60 (2H, *m*, H-21, 21′), 3.66 (1H, *m*, H-15), 3.75 (3H, *s*, COOMe), 3.85 (1H, *d*, *J* = 10.5 Hz, H-17), 4.08 (1H, *d*, *J* = 16.2 Hz, H-6), 4.22 (1H, *d*, *J* = 10.5 Hz, H-17′), 5.09 (1H, *d*, *J* = 16.2 Hz, H-6′), 5.58 (1H, *q*, *J* = 7 Hz, H-19), 7.10 (1H, *t*, *J* = 7 Hz, H-11), 7.20 (1H, *t*, *J* = 7 Hz, H-10), 7.34 (1H, *br d*, *J* = 7.7 Hz, H-12), 7.49 (1H, *br d*, *J* = 7.8 Hz, H-9), 10.34 (1H, *br s*, NH). ^{13}C NMR ($CDCl_3$): δ14.8 (C-18), 21.2 (C-14), 35.2 (C-15), 47.9 (C-3), 49.1 (C-6), 52.3 (OMe), 53.8 (C-21), 58.9 (C-16), 70.5 (C-17), 102.4 (C-7), 111.7 (C-12), 120.6 (C-10), 123.6 (C-11), 125.7 (C-19), 127.8 (C-8), 130.5 (C-20), 135.3 and 135.3 (C-2 and C-13), 173.8 (C =O).

X-ray data for **1a**, **2** *and* **22**. Crystals were mounted on a Huber diffractometer. Unit cell dimensions were determined from the setting angles of reflections measured at ±θ and at high and low χ with graphite monochromated Mo K_α (λ = 0.71073 Å) radiation.

Crystal data. Compound **1a**, $C_{32}H_{49}O_2$, M_r = 465.74, orthorhombic space group $P2_12_12_1$, *a* = 11.084(9), *b* = 8.294(5), *c* = 30.040(17) Å; *V* = 2764(3) Å^3 from 80 reflections; *Z* = 4, D_c = 1.119 g cm^{-3}; μ(Mo) = 0.63 cm^{-1}; *T* = 294 K. Compound **2**, $C_{32}H_{52}O_2$, M_r = 468.77, monoclinic space group $P2_1$, *a* = 14.713(2), *b* = 7.381 (2), *c* = 26.079(5) Å, β = 96.048(8)° from 100 reflections; *V* = 2816.4(9) Å^3; *Z* = 4, D_c = 1.105 g cm^{-3}; μ(Mo) = 0.62 cm^{-1}; *T* = 294 K. Compound **22**, $C_{21}H_{24}N_2O_3 \cdot CHCl_3$, M_r = 471.83, orthorhombic space group $P2_12_12_1$, *a* = 6.311(3), *b* = 13.450(9), *c* = 28.501(17) Å; *V* = 2419(2) Å^3 from 120 reflections; *z*

$= 4$, $D_c = 1.295\ g\,cm^{-3}$; $\mu(Mo) = 4.03\ cm^{-1}$; $T = 294$ K. Data were collected with the $\omega - 2\theta$ scan technique, $2.0 \leqslant 2\theta \leqslant 48.0°$, reflections were corrected for background, Lorentz and polarization effects, and for absorption. For **1a**, 2582 unique reflections, 1181 with $I > 3\sigma(I)$, were measured from a crystal of dimensions $0.70 \times 0.70 \times 0.14$ mm. For **2**, 4815 unique reflections 1851 with $I > 3\sigma(I)$, were measured from a crystal of dimensions $0.16 \times 0.45 \times 0.20$ mm. For **22**, 2491 unique reflections, 1371 with $I > 3\sigma(I)$, were measured from a crystal of dimensions $0.55 \times 0.25 \times 0.04$ mm. During data collection $CHCl_3$ was lost and intensities fell off by nearly 50%. The first small data set of 1345 reflections with $2\theta \leqslant 40.0°$, of which 819 with $I > \sigma(I)$ were used in the final refinements.

Structures were solved by direct methods using SHELX-86 on a VAX 6210 computer and refined by the least-squares minimization of $\Sigma\, w(|F_o| - |F_c|)^2$. Hydrogen atoms were located on a difference map, but were included at calcd positions (C–H = 0.95 Å), the methyl groups were disordered in **2**. The final *R*-values were $RF = 0.050$ and $wR(F) = 0.058$ for **1a**, $R(F) = 0.050$ and $wRF = 0.057$ for **2**, and $R(F) = 0.164$ and $wRF = 0.158$ for **22**. In **2**, there are two almost identical molecules in the asymmetric unit. The crystals of **22** contained solvent, but the molecular structure found is similar to that in ref. [34].

Fractional coordinates, thermal parameters, bond distances and angles have been deposited at the Cambridge Crystallographic Data Centre.

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