Pergamon

PII: S0031-9422(98)00245-3

*Phytochemistry* Vol. 49, No. 8, pp. 2539–2543, 1998

Printed in Great Britain
0031-9422/98/$ - see front matter

# ALKALOIDS FROM *CRINUM DELAGOENSE*§

JERALD J. NAIR, WILLIAM E. CAMPBELL, DAVID W. GAMMON, CARL F. ALBRECHT,†
FRANCESC VILADOMAT,‡ CARLES CODINA‡ and JAUME BASTIDA‡,*

Department of Chemistry, University of Cape Town, Rondebosch 7700, South Africa; †Department of Pharmacology, University of Stellenbosch, Tygerberg 7505, South Africa; ‡Departament de Productes Naturals, Facultat de Farmàcia, Universitat de Barcelona, 08028 Barcelona, Spain

(*Received* 18 *December* 1997)

**Key Word Index**—*Crinum delagoense*; Amaryllidaceae; bulbs; alkaloids; lycorine; hamayne; 6-hydroxycrinamine; criwelline; delagoensine; delagoenine.

**Abstract**—Six alkaloids have been isolated from fresh bulbs of *Crinum delagoense*. The alkaloids, delagoensine and delagoenine, are reported here for the first time. The structure and stereochemistry of the new alkaloids have been determined by physical and spectroscopic methods. $^{1}H$ and $^{13}C$ NMR spectra were completely assigned by means of 2D NMR techniques. 

## INTRODUCTION

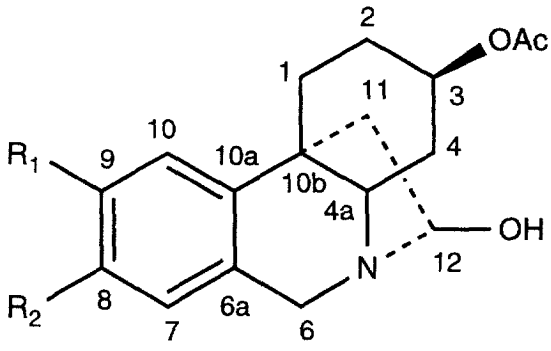
Plants of the Amaryllidaceae, belonging almost exclusively to the tribes Amaryllideae and Haemantheae [2], have for sometime been used in the medicinal preparations of several of the indigenous peoples of South Africa [3,4]. In this regard, *Crinum delagoense*, which is distributed throughout the Gauteng and KwaZulu-Natal Provinces of South Africa, is used in Zulu and Xhosa traditional medicine, the Zulus in particular employ aqueous extracts to treat urinary tract infections and swelling of the body [3]. However, substantiated reports [5] of the cure of a human cancer by the oral intake of a hot water extract of five species, including *C. delagoense*, led us to select this species as a viable candidate for phytochemical analysis. This investigation forms part of our ongoing research of the Amaryllidaceae endemic to southern Africa (for a revision, see ref. [6]). Inititially, a preparative HPLC investigation of a hot water extract of bulbs of the plant yielded five major components, one of which was active against BL6 mouse melanoma cells. Subsequently, an ethanolic extract of fresh bulbs was investigated and after repeated column chromatography (see Experimental) six alkaloids were isolated, four of which are known, while the remaining two, delagoensine (**1**) and delagoenine (**2**), are novel compounds. Lycorine, which is widely distributed in this genus and is known to exhibit several biological and pharmacological activities [7], was found to be the principal constituent. All six compounds were examined for cytotoxicity but only lycorine and 6-hydroxycrinamine (the water-soluble component), were active against BL6 mouse melanoma cells. The isolation of criwelline and 6-hydroxycrinamine from the same plant is of biosynthetic significance [8]. Compounds **1** and **2** are the first crinane-type alkaloids with an hydroxyl group in the C-12 position, as opposed to the usual 11-substitution.

## RESULTS AND DISCUSSION

The absolute configuration of alkaloids with a 5,10b-ethano bridge (hamayne, 6-hydroxycrinamine, **1** and **2**) were determined from circular dichroism (CD) curves, which were qualitatively similar to those of the α-5,10b-ethanophenanthridine alkaloids with a maximum around 290 nm and a minimum around 250 nm [9–11].

Compound **1**, $C_{18}H_{21}NO_5$, as well as the related compound **2**, $C_{19}H_{25}NO_5$, were isolated for the first time from a natural source. The IR spectrum of both exhibited carbonyl and the hydroxyl bands. Compound **1** exhibited, additionally, a band corresponding to a methylenedioxyl group. Their EI mass spectra displayed a similar fragmentation pattern, with an intense $[M]^+$ at *m/z* 331 and 347, respectively, and important fragments at *m/z* $[M-44]^+$, $[M-101]^+$, $[M-103]^+$, $[M-104]^+$,

*Author to whom correspondence should be addressed.
§Part 6 in the series "Alkaloids from South African Amaryllidaceae". For part 5 see ref. [1].




**1**: $R_1 + R_2 = OCH_2O$
**2**: $R_1 = R_2 = OMe$

$[M-105]^+$, $[M-130]^+$, $[M-131]^+$, $[M-146]^+$ and 115. The base peaks at *m/z* 226 and 243, respectively, were associated with the loss of the acetoxyl group from the $[M-44]^+$ fragment.

The signals in the $^1H$ NMR spectrum of **1** (Table 1) were similar to those of maritinamine [12]; however, due to the presence of the hydroxyl group at the 12*exo* position, supported by the NOE effect (Table 2) between H-12*endo* ($\delta$ 5.04) and H-6$\alpha$ ($\delta$ 3.90), a pronounced deshielding effect ($\Delta\delta \sim 2.2$ ppm) on H-12*endo*, with respect to the maritinamine data was observed. A less pronounced deshielding effect ($\Delta\delta \sim 1.05$ ppm), due to the presence of the acetoxyl group, was observed for the H-3 ($\delta$ 5.20) resonance. The magnitude of the coupling constant between H-2ax ($\delta$ 1.82) and H-3, and between H-3 and H-4ax ($\delta$ 2.24), was small

Table 1. $^1H$ NMR, HMQC and HMBC data for compound **1**

| H | $\delta$ | Correlated C-atom HMQC | HMBC |
|---|---|---|---|
| 1ax | 1.88 *ddd* (13.5, 13.0, 4.0) | 23.2 *t* | C-3, C4a, C-10a, C-11 |
| 1eq | 2.16 *dddd* (13.5, 3.5, 2.6, 1.0) | 23.2 *t* | C-3, C-4a |
| 2ax | 1.82 *dddd* (13.0, 12.5, 2.6, 2.5) | 24.8 *t* | C-4, C-10b |
| 2eq | 1.98 *ddddd* (12.5, 4.0, 3.5, 3.5, 1.0) | 24.8 *t* | C-4, C-10b |
| 3eq | 5.20 *ddddd* (4.0, 3.5, 2.5, 2.5, 1.0) | 69.4 *d* | COMe |
| 4ax | 2.24 *ddd* (13.0, 12.2, 2.5) | 31.0 *t* | C-2, C-10b |
| 4eq | 2.05 *dddd* (13.0, 5.5, 4.0, 1.0) | 31.0 *t* | C-2, C-10b |
| 4a | 3.22 *ddd* (12.2, 5.5, 1.0) | 62.2 *d* | C-12 |
| 6$\alpha$ | 3.90 *d* (16.7) | 58.4 *t* | C-7, C-10a |
| 6$\beta$ | 4.36 *d* (16.7) | 58.4 *t* | C-4a, C-7, C-10a, C-12 |
| | | 124.1 *s* (C-6a) | |
| 7 | 6.46 *s* | 105.9 *d* | C-6, C-9, C-10a |
| | | 146.5 *s* (C-8) | |
| | | 146.0 *s* (C-9) | |
| 10 | 6.73 *s* | 103.5 *d* | C-6a, C-8, C-10b |
| | | 141.3 *s* (C-10a) | |
| | | 44.6 *s* (C-10b) | |
| 11*exo* | 2.30 *dd* (13.5, 5.0) | 47.1 *t* | C-1, C-4a |
| 11*endo* | 2.27 *ddd* (13.5, 6.5, 1.0) | 47.1 *t* | C-1, C-4a, C-10a |
| 12*endo* | 5.04 *dd* (6.5, 5.0) | 93.0 *d* | |
| $OCH_2O$ | 5.90 *d*-5.92 *d* (1.5) | 100.8 *t* | C-8, C-9 |
| COMe | 1.97 *s* | 21.2 *q* | |
| | | 170.2 *s* (COMe) | |

Table 2. Scalar and spatial correlation of the protons of compound **1**

| H | COSY | NOESY |
|---|---|---|
| 1ax | H-1eq, H-2ax, H-2eq | H-1eq, H-2eq, H-10 |
| 1eq | H-1ax, H-2ax, H-2eq, H-3eq | H-1ax, H-2ax, H-2eq, H-10 |
| 2ax | H-1ax, H-1eq, H-2eq, H-3eq | H-1eq, H-2eq, H-3eq, H-4ax, H-11*exo* |
| 2eq | H-1ax, H-1eq, H-2ax, H-3eq, H-4eq | H-1ax, H-1eq, H-2ax, H-3eq |
| 3eq | H-1eq, H-2ax, H-2eq, H-4ax, H-4eq | H-2ax, H-2eq, H-4ax, H-4eq |
| 4ax | H-3eq, H-4eq, H-4a | H-2ax, H-3eq, H-4eq, H-11*exo* |
| 4eq | H-2eq, H-3eq, H-4ax, H-4a | H-3eq, H-4ax, H-4a |
| 4a | H-4ax, H-4eq, H-11*endo* | H-4eq, H-6$\beta$ |
| 6$\alpha$ | H-6$\beta$ | H-6$\beta$, H-7, H-12*endo* |
| 6$\beta$ | H-6$\alpha$ | H-4a, H-6$\alpha$, H-7 |
| 7 | | H-6$\alpha$, H-6$\beta$ |
| 10 | | H-1ax, H-1eq |
| 11*exo* | H-11*endo*, H-12*endo* | H-2ax, H-4ax, H-11*endo* |
| 11*endo* | H-4a, H-11*exo*, H-12*endo* | H-11*exo*, H-12*endo* |
| 12*endo* | H-11*exo*, H-11*endo* | H-6$\alpha$, H-11*endo* |
| $OCH_2O$ | | |
| COMe | | |

Table 3. $^1$H NMR, HMQC and HMBC data for compound **2**

| H | $\delta$ | Correlated C-atom HMQC | HMBC |
|---|---|---|---|
| 1ax | 1.97 *ddd* (13.4, 13.0, 4.5) | 23.3 *t* | C-3, C4a, C-10a, C-11 |
| 1eq | 2.27 *dddd* (13.4, 3.7, 2.8, 1.0) | 23.3 *t* | C-3, C-4a |
| 2ax | 1.86 *dddd* (13.0, 12.5, 2.8, 2.5) | 24.7 *t* | C-4, C-10b |
| 2eq | 2.05 *ddddd* (12.5, 4.5, 3.7, 3.5, 1.0) | 24.7 *t* | C-10b |
| 3eq | 5.23 *ddddd* (4.0, 3.5, 2.5, 2.5, 1.0) | 68.9 *d* | COMe |
| 4ax | 2.34 *ddd* (12.5, 12.2, 2.5) | 30.3 *t* | C-2, C-10b |
| 4eq | 2.20 *dddd* (12.5, 5.8, 4.0, 1.0) | 30.3 *t* | C-2, C-10b |
| 4a | 3.38 *ddd* (12.2, 5.8, 1.0) | 62.5 *d* | C-12 |
| 6$\alpha$ | 4.10 *d* (16.5) | 56.9 *t* | C-4a, C-10a |
| 6$\beta$ | 4.42 *d* (16.5) | 56.9 *t* | C-4a, C-7, C-10a, C-12 |
| | | 121.4 *s* (C-6a) | |
| 7 | 6.52 *s* | 108.9 *d* | C-6, C-9, C-10a |
| | | 148.2 *s* (C-8) | |
| | | 148.1 *s* (C-9) | |
| 10 | 6.73 *s* | 106.2 *d* | C-6a, C-8, C-10b |
| | | 139.0 *s* (C-10a) | |
| | | 44.3 *s* (C-10b) | |
| 11*exo* | 2.37 *dd* (13.5, 5.0) | 46.2 *t* | C-1, C-4a |
| 11*endo* | 2.34 *ddd* (13.5, 6.2, 1.0) | 46.2 *t* | C-1, C-4a, C-10a |
| 12*endo* | 5.20 *dd* (6.2, 5.0) | 93.8 *d* | |
| 8-OMe | 3.85 *s* | 56.0 *q* | C-8 |
| 9-OMe | 3.88 *s* | 56.0 *q* | C-9 |
| COMe | 2.01 *s* | 21.2 *q* | |
| | | 170.2 *s* (COMe) | |

(2.5 Hz), denoting in both a dihedral angle of *ca* 60°, which led us to assign the equatorial disposition for H-3 and a *trans*-relationship between the C-3 acetoxyl substituent ($\delta$ 1.97) and the 5,10b-ethano bridge. Additionally, a significant feature of the $^1$H NMR spectrum, confirmed by a COSY experiment, was the long-range W coupling between H-1eq ($\delta$ 2.16) and H-3, indicating that they were in the same plane. The same feature was observed between H-2eq ($\delta$ 1.98) and H-4eq ($\delta$ 2.05). The assignment of the H-6 protons was supported by the NOE effect between H-12*endo* and H-6$\alpha$, as well as between H-6$\beta$ ($\delta$ 4.36) and H-4a; additionally, H-6$\beta$ was assigned at lower field due to its *cis*-relation with the nitrogen lone pair [13]. The aromatic singlet resonance at $\delta$ 6.73 was assigned to H-10, because of the three-bond correlation with C-6a, as well as with C-10b and C-8 (HMBC experiment [14]), and this was corroborated by the spatial proximity between H-10 and H-1eq (ROESY experiment [15]).

The $^1$H NMR spectrum (Table 3) of compound **2** was similar to that of **1**, only the substitution of the methylenedioxyl group by two methoxyl groups was significant. The exact location of the aromatic methoxyl groups was deduced from NOE measurements (Table 4), which interrelated 9-OMe ($\delta$ 3.88), H-10 ($\delta$ 6.73) and H-1eq ($\delta$ 2.27), while the assignment of 8-OMe ($\delta$ 3.85) was supported by a NOE with H-7, and by a three-bond connectivity with C-8.

The $^{13}$C NMR spectra of **1** and **2** were similar and the assignment of the carbon signals were confirmed taking into account the HMQC [16] and HMBC connectivities (Tables 1 and 3). For com-

Table 4. Scalar and spatial correlation of the protons of compound **2**

| H | COSY | NOESY |
|---|---|---|
| 1ax | H-1eq, H-2ax, H-2eq | H-1eq, H-2eq, H-10 |
| 1eq | H-1ax, H-2ax, H-2eq, H-3eq | H-1ax, H-2ax, H-2eq, H-10 |
| 2ax | H-1ax, H-1eq, H-2eq, H-3eq | H-1eq, H-2eq, H-3eq, H-4ax, H-11*exo* |
| 2eq | H-1ax, H-1eq, H-2ax, H-3eq, H-4eq | H-1ax, H-1eq, H-2ax, H-3eq |
| 3eq | H-1eq, H-2ax, H-2eq, H-4ax, H-4eq | H-2ax, H-2eq, H-4ax, H-4eq |
| 4ax | H-3eq, H-4eq, H-4a | H-2ax, H-3eq, H-4eq, H-11*exo* |
| 4eq | H-2eq, H-3eq, H-4ax, H-4a | H-3eq, H-4ax, H-4a |
| 4a | H-4ax, H-4eq, H-11*endo* | H-4eq, H-6$\beta$ |
| 6$\alpha$ | H-6$\beta$ | H-6$\beta$, H-7, H-12*endo* |
| 6$\beta$ | H-6$\alpha$ | H-4a, H-6$\alpha$, H-7 |
| 7 | | H-6$\alpha$, H-6$\beta$, 8-OMe |
| 10 | | H-1ax, H-1eq, 9-OMe |
| 11*exo* | H-11*endo*, H-12*endo* | H-2ax, H-4ax, H-11*endo* |
| 11*endo* | H-4a, H-11*exo*, H-12*endo* | H-11*exo*, H-12*endo* |
| 12*endo* | H-11*exo*, H-11*endo* | H-6$\alpha$, H-11*endo* |
| 8-OMe | | H-7 |
| 9-OMe | | H-10 |
| COMe | | |

pound **1**, at lower field, five carbon singlets for the acetoxyl carbonyl group and the quaternary carbons of the aromatic ring were observed. The assignation of the acetoxyl carbonyl group ($\delta$ 170.2) at the C-3 position was confirmed by the three-bond connectivity with H-3. Three-bond correlations to either H-10 or H-7 allowed the assignment of C-8 ($\delta$ 146.5), C-6a ($\delta$ 124.1), C-9 ($\delta$ 146.0) and C-10a ($\delta$ 141.3). Finally, the singlet at $\delta$ 44.6 showed correlations with H-2, H-4 and H-10, and was assigned to C-10b. The C-12 resonance (*d*, $\delta$ 93.0) was significantly deshielded from that observed in other 5,10b-ethanophenanthridine alkaloids [7], in which this signal occurs at *ca* $\delta$ 50. This is consistent with the presence of the hydroxyl group at the 12*exo*-position. A similar pattern was observed in the $^{13}C$ NMR spectrum of compound **2**.

## EXPERIMENTAL

### *General*

Mps are uncorr. IR spectra were measured in dry films. EIMS at 70 eV. $^1H$, $^{13}C$ NMR, DEPT, $^1H$ COSY, HMQC, HMBC and ROESY spectra were recorded on a Varian VXR 500, using the solvent specified with TMS as int. standard. Chemical shifts are reported in $\delta$ units and coupling constants (*J*) in Hz. Silica gel Merck (70–230 mesh) and silica gel SDS chromagel 60 A CC (230–400 mesh) were used for CC and flash CC, respectively. Sephadex LH-20 (Pharmacia) was used for gel filtration, and silica gel 60 $F_{254}$ (Merck) for analytical (0.25 mm) and prep. (1 mm) TLC. Spots on chromatograms were detected under UV light (254 nm) and by spraying with Dragendorff's reagent.

### *Plant material*

Bulbs of *C. delagoense* Verdoorn were collected in February, 1993, during the flowering period, in the Natal province (South Africa). The material was authenticated by both Dr Anne Hutchings of the University of Zululand and Prof. Karl Pegel of the University of Natal. A voucher specimen is deposited in the Compton Herbarium of the National Botanic Institute, Kirstenbosch, South Africa.

### *Extraction and isolation of alkaloids*

Fr. bulbs (1.5 kg) were crushed and macerated with EtOH for 48 hr. The extract was evapd under red. pres., the residue dissolved in $H_2O$ and acidified to pH 4. After removing neutral material with $Et_2O$, the acidic soln was extracted with $CHCl_3$ to provide extract A. Basifying the soln to pH 8–9 and extracting with $CHCl_3$ gave extract C. Finally, $CHCl_3$–MeOH (3:2) extraction of the basic soln gave extract D. Extracts A, C and D were combined (5.9 g) and subjected to flash CC on silica gel, eluting with $CHCl_3$–MeOH (19:1) and increasing the gradient for the last steps until (4:1), to yield 5 frs. Lycorine crystallized directly from from fr. 1; recrystallization from MeOH afforded 120 mg. Fr. 2 was rechromatographed by CC using a $CHCl_3$–MeOH step gradient; criwelline and more lycorine (22 mg) were isolated. Criwelline crystallized directly and recrystallization from EtOH afforded 20 mg. After a similar chromatographic processing to that described for fr. 2, fr. 3 afforded 6-hydroxycrinamine (19 mg) and criwelline (10 mg), and, fr. 4, hamayne (30 mg) and 6-hydroxycrinamine (9 mg). Fr. 5 was additionally purified by prep. TLC using EtOAc–MeOH (9:1) and, after final purification on Sephadex LH-20, afforded **1** (25 mg) and **2** (16 mg), respectively.

*Delagoensine* (**1**). Found: C, 64.32; H, 6.55; N, 4.05. $C_{18}H_{21}NO_5$ requires: C, 65.24; H, 6.39; N, 4.23%. Mp 132–134°. $[\alpha]_D^{20}$ +28.2° (MeOH; *c* 0.475). CD $[\Theta]_{246}$ − 2029, $[\Theta]_{297}$ + 4652. IR $\upsilon_{max}$ $cm^{-1}$: 3131 (–OH), 2925, 2860, 1732 (>C = O), 1502, 1483, 1373, 1325, 1235, 1099, 1041, 935 (–$OCH_2O$–), 847, 755. EIMS 70 eV, *m/z* (rel. int.): 331 $[M]^+$ (80), 287 (27), 286 (16), 230 (24), 228 (56), 227 (93), 226 (100), 216 (17), 211 (17), 201 (41), 200 (51), 199 (18), 188 (17), 187 (19), 185 (26), 115 (25). $^1H$ NMR (500 MHz, $CDCl_3$) and $^{13}C$ NMR (50 MHz, $CDCl_3$), see Table 1.

*Delagoenine* (**2**). Found: C, 64.52; H, 7.30; N, 3.89. $C_{19}H_{25}NO_5$ requires: C, 65.69; H, 7.25; N, 4.03%. Mp 120–122°. $[\alpha]_D^{20}$ +34.2° (MeOH; *c* 0.48). CD $[\Theta]_{242}$ − 1962, $[\Theta]_{282}$ + 3844. IR $\upsilon_{max}$ $cm^{-1}$: 3166 (–OH), 2928, 2856, 1732 (>C=O), 1509, 1464, 1373, 1310, 1252, 1139, 1108, 1068, 1023, 990, 846, 755. EIMS 70 eV, *m/z* (rel. int.): 347 $[M]^+$ (79), 303 (31), 302 (22), 246 (23), 244 (71), 243 (100), 242 (99), 232 (17), 228 (27), 227 (28), 217 (32), 216 (30), 215 (18), 211 (22), 203 (18), 202 (28), 201 (26), 115 (20), 91 (16), 57 (17), 55 (20). $^1H$ NMR (500 MHz, $CDCl_3$) and $^{13}C$ NMR (50 MHz, $CDCl_3$), see Table 3.

*Lycorine* [17], *hamayne* [18], *6-hydroxycrinamine* [19] and *criwelline* [20] were identified by a comparison of their chromatographic and spectroscopic properties (TLC, $[\alpha]_D$, CD, IR, MS, $^1H$ and $^{13}C$ NMR) with those of authentic samples obtained from other plant sources.

*Acknowledgements*—Part of this work was supported financially by CIRIT-CICYT project (QFN95-4711) and the Comissionat per a Universitats i Recerca, Generalitat de Catalunya. W.E.C. and J.J.N. thank the University of Cape Town for financial support. J.J.N. also thanks the Ministerio de Educación y Cultura for a postdoctoral fellowship. The authors are very much indebted to Dr Anne Hutchings and Prof. Karl Pegel for authentification of plant material.

## REFERENCES


1. Campbell, W. E., Nair, J. J., Gammon, D. W., Bastida, J., Codina, C., Viladomat, F., Smith, P. J. and Albrecht, C. F., *Planta Medica*, 1998, **64,** 91.
2. Snijman, D. A. and Linder, H. P., *Ann. Missouri Botanical Garden*, 1996, **83,** 362.
3. Watt, J. M. and Breyer-Brandwijk, M. G., *The Medicinal and Poisonous Plants of Southern and Eastern Africa*. E. and S. Livingston, Ltd., Edinburgh-London, 1962.
4. Hutchings, A., Scott, A. H., Lewis, G. and Cunningham, A. B., *Zulu Medicinal Plants. An Inventory*. University of Natal Press, Pietermaritzburg, 1996.
5. Fortmann, J. H. L., Personal communication.
6. Viladomat, F., Bastida, J., Codina, C., Nair, J. J. and Campbell, W. E., in *Recent Research and Developments in Phytochemistry*, ed. S. G. Paridalai. Research Signpost Publisher, Trivandrum, 1997, **1**, 131.
7. Bastida, J., Viladomat, F. and Codina, C., in *Studies in Natural Product Chemistry*, ed. Atta-ur-Rahman. Elsevier Science Publishers, Amsterdam, 1997, **20**, 323.
8. Murphy, C. F. and Wildman, W. C., *Tetrahedron Letters*, 1964, **51,** 3863.
9. De Angelis, G. G. and Wildman, W. C., *Tetrahedron*, 1969, **25,** 5099.
10. Ali, A. A., Ramadan, M. A. and Frahm, A. W., *Planta Medica*, 1984, **50,** 424.
11. Wagner, J., Pham, H. L. and Döpke, W., *Tetrahedron*, 1996, **52,** 6591.
12. Pabuççuoglu, V., Richomme, P., Gözler, T., Kivçak, B., Freyer, A. J. and Shamma, M., *Journal of Natural Products*, 1989, **52,** 785.
13. Moyenehan, T. M., Schoffield, K., Jones, R. A. Y. and Katritzky, R. A., *Journal of the Chemical Society*, 1962, 2637.
14. Bax, A. and Summers, M. F., *Journal of the American Chemical Society*, 1986, **108,** 2093.
15. Bax, A. and Davis, D. G., *Journal of Magnetic Resonance*, 1985, **63,** 207.
16. Bax, A. and Subramanian, S., *Journal of Magnetic Resonance*, 1986, **67,** 565.
17. Likhitwitayawuid, K., Angerhofer, C. K., Chai, H., Pezzuto, J. M., Cordell, G. A. and Ruangrungsi, N., *Journal of Natural Products*, 1993, **56,** 1331.
18. Viladomat, F., Bastida, J., Codina, C., Campbell, W. E. and Mathee, S., *Phytochemistry*, 1994, **35,** 809.
19. Viladomat, F., Almanza, G. R., Codina, C., Bastida, J., Campbell, W. E. and Mathee, S., *Phytochemistry*, 1994, **34,** 1379.
20. Razafimbelo, J., Andriantsiferana, M., Baudouin, G. and Tillequin, F., *Phytochemistry*, 1996, **41,** 323.