Phytochemistry, Vol. 22, No. 3, pp. 763–766, 1983.
Printed in Great Britain.

0031-9422/83/030763-04$03.00/0

FOUR PHENOLIC NEOLIGNANS FROM *MAGNOLIA LILIFLORA*

TOSHIYUKI IIDA and KAZUO ITO

Faculty of Pharmacy, Meijo University, Yagoto, Tempaku, Nagoya 468, Japan

(*Received* 22 *June* 1982)

Key Word Index—*Magnolia liliflora*; Magnoliaceae; neolignans; liliflol A; liliflol B; liliflone; piperenone; liliflodione; denudatone; maglifloenone.

Abstract—A chloroform extract of fresh leaves of *Magnolia liliflora* contained the four new phenolic neolignans, liliflodione [a bicyclo(3,2,1)octanoid], liliflol A and B (dihydrobenzofuranoids) and liliflone (a hexahydrobenzofuranoid), along with seven known neolignans. The absolute structures of the new compounds were elucidated by means of chemical and spectral studies.

INTRODUCTION

In the preceding paper, we investigated burchellin type and spirocyclohexadienone type neolignans from *Magnolia denudata* (Japanese name, Hakumokuren) [1]. Recently, a new neolignan designated (−)-maglifloenone was isolated from *M. liliflora* [2]. This compound, however, is identical with denudatone (**11**) which we had isolated from *M. denudata*.

As a result of further investigation of *M. liliflora* Desr. (Japanese name, Shimokuren), we isolated the dihydrobenzofuranoid neolignans **3** and **4**, the hexahydrobenzofuranoid neolignan **6** and the bicyclo(3,2,1)octanoid neolignan **9** [3–6]. In addition to these four new compounds, seven other known compounds were isolated: the tetrahydrobenzofuranoid neolignans, denudatin A (**1**), denudatin B (**2**) and burchellin (**5**); the hexahydrobenzofuranoid neolignan, piperenone (**7**) [7]; the 2,5-diaryltetrahydrofuranoid neolignan, (+)-veraguensin (**8**); the spirocyclohexadienone neolignan, futoenone (**10**) and denudatone (maglifloenone) (**11**).

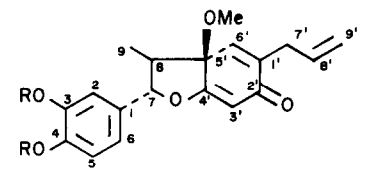
This paper deals with the isolation and stereostructure of the four new phenolic neolignans which we have named liliflol A (**3**), liliflol B (**4**), liliflone (**6**) and liliflodione (**9**).

RESULTS AND DISCUSSION

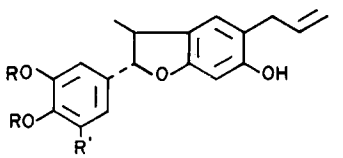
Dihydrobenzofuranoid neolignans [liliflol A (3) and liliflol B (4)]

Liliflol A (**3**), $C_{19}H_{18}O_4$ (M^+, 310) was isolated as a colourless oil. It gave a green colouration with ethanolic ferric chloride and its IR spectrum showed a hydroxyl absorption at 3600–3200 cm^{-1} but no carbonyl band.

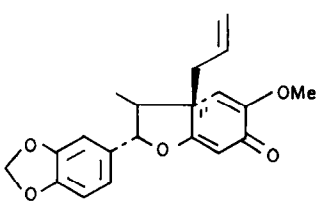
The ^1H NMR spectrum revealed the presence of Me–CH–CH–Ar (Ar, piperonyl portion; ■, carbon carrying no hydrogen) with the Ar and Me groups in a *trans*-relationship ($J_{7H,8H}$ = 8 Hz), $-CH_2-CH=CH_2$ and five aromatic protons. The ^1H NMR spectrum was superimposable on that of **4a** previously synthesized from mirandin A except for the presence of a tri-*O*-



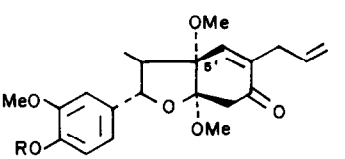
1 R + R = CH_2
2 R = Me



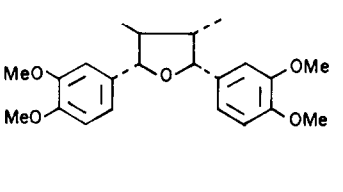
3 R + R = CH_2, R' = H
4 R = Me, R' = H
4a R = Me, R' = OMe



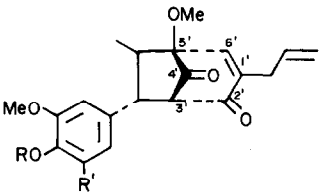
5



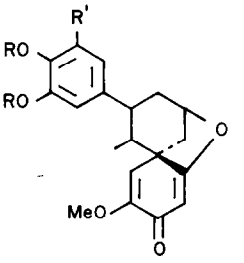
6 R = H
7 R = Me



8



9 R = R' = H
9a R = Me, R' = H
9b R = Me, R' = OMe



10 R + R = CH_2, R' = H
11 R = Me, R' = OMe

methylpyrogallyl function (Table 1) [8, 9]. From this physical data and the mass spectrum, liliflol A was assigned structure **3**.

The proposed structure was confirmed by formation of **3** by both pyrolysis ($Et_2N\phi$/220°) and photolysis (hν/MeOH) of denudatin A (**1**) with known stereochemistry (7*S*,8*R*) [8, 9].

Instead of a piperonyl group as in liliflol A, liliflol B (**4**) bears a veratryl substituent (*m/z* 178, 100%) (^{1}H NMR and MS).

Hexahydrobenzofuranoid neolignan [*liliflone* (**6**)]

Liliflone (**6**), $C_{21}H_{26}O_6$ (M^+, 374) in its IR spectrum showed the presence of a phenolic group (3600–3200 cm^{-1}) and an α,β-unsaturated carbonyl group (strong band at 1680 cm^{-1}). The ^{1}H NMR and mass spectra (*m/z* 164, 100%) indicated the presence of a 3-methoxy-4-hydroxyphenyl function and, as in liliflol A of a moiety Me–CH–CH–Ar with Ar and Me groups in a *trans*-relationship (δ 4.08, *d*, $J_{7H,8H}$ = 10 Hz, H-7).

Table 1. ^{1}H NMR data for liliflol A (**3**), liliflol B (**4**) and **4a** (100 MHz, $CDCl_3$)

	3	4	4a
H-7	4.96 *d* (9)*	5.02 *d* (8)	4.95–5.43†
H-8	3.19–3.40 *m*	3.20–3.48 *m*	3.25–3.88 *m*
H-9	1.33 *d* (7)	1.36 *d* (7)	1.38 *d* (7)
H-3'	6.32 *s*	6.35 *s*	6.40 *s*
H-6'	6.80 *s*	6.81 *s*	6.83 *s*
OH	5.0 *s*	5.06 *s*	5.0 *s*
$-OCH_2O-$	5.9 *s*	—	—
Ar-OMe	—	3.86 *s* × 2	3.85 *s* × 3

*Figures in parentheses are coupling constants in Hz.
†Signal partially obscured.

The additional C_6–C_3 unit must be represented by a cyclohexenone having two methoxyl groups (δ 3.38 and 3.5) linked to the fully substituted sp^3-carbons and an allyl group (δ 3.12, *br d*, J = 7 Hz, H-7') linked to the sp^2-carbon.

These physical data were completely identical with those of piperenone from *Piper futokadzura* [7]. In fact, methylation of **6** with diazomethane gave piperenone (**7**).

Bicyclo(3,2,1)*octanoid neolignan* [*liliflodione* (**9**)]

The third type of lignan, liliflodione (**9**), was obtained as a colourless oil, $C_{20}H_{22}O_5$ (M^+, 342), $[\alpha]_D$ + 254.4°, which contained in its IR spectrum absorption bands due to a hydroxyl group (3550 cm^{-1}), a cyclopentanone group (1765 cm^{-1}) and an α,β-unsaturated ketone group (1670 and 1640 cm^{-1}).

As in the case of **6**, a prominent mass spectral fragment ion at *m/z* 164 and the aromatic proton signal pattern of the ^{1}H NMR spectrum revealed that **9** contained a C_6–C_3 moiety possessing a 3-methoxy-4-hydroxyphenyl function. The ^{13}C NMR spectrum showed that the C_6–C_3 unit with a β-diketone group (δ 194.4 and 201.1) was a cyclohexenedione having a methoxyl group linked to the fully substituted sp^3-carbon (δ 87.0, *s*) and an allyl group linked to the sp^2-carbon (δ 141.0, *s*).

From the NMR spectral data and decoupling experiments (at H-7, H-8 and H-3'), liliflodione (**9**) was shown to be 1'-allyl-5'-methoxy-8-methyl-7-(3-methoxy-4-hydroxy) phenyl-$\Delta^{6'}$-2',4'-dioxobicyclo(3,2,1)octane [10].

The absolute stereochemistry of **9** was confirmed by the following chemical transformation. A rearrangement product (**9a**) was obtained by acid-catalysed (*p*-TsOH–MeOH) reaction of denudatin B (**2**) with the known stereochemistry (7*S*,8*R*) [11, 12]. Both liliflodione (**9**) and the rearrangement product (**9a**) have superimposable CD curves (positive Cotton effect) and UV spectra and **9** should, therefore, possess the stereochemistry 7*S*,8*R*,3'*S*,5'*S* (Table 2) [10]. In fact, the *O*-methylated (diazomethane) product of **9** was identical with the rearrangement product (**9a**). Therefore, it was clarified

Table 2. ^{1}H NMR data for liliflodione (**9**), **9a** and **9b** (100 MHz, $CDCl_3$)

	9	**9a**	**9b** [10]
H-7	3.16 *dd* (5, 7.5)*	3.20 *dd* (5, 7.5)	2.60 *d* (8)
H-8	2.44–2.8 *m*	2.48–2.8 *m*	2.45 *dq* (6.5, 8)
H-9	1.15 *d* (7)	1.18 *d* (7)	1.12 *d* (7)
H-3′	3.74 *d* (7.5)	3.76 *d* (7.5)	3.05 *s*
H-6′	7.32 *br s*	7.32 *br s*	6.75 *br s*
OMe-5′	3.66 *s*	3.66 *s*	3.58 *s*
Ar-OMe	3.84 *s*	3.84 *s* × 2	3.81 *s*, 3.84 *s* × 2
OH	5.56 *s*		

*Coupling constants in Hz.

that, the reaction proceeds by opening of the benzylic O-7 bond, followed by Michael type recyclization (C_3–C_7) in spite of sterically crowded all-*cisoid* substituents (Me-8, OMe-5′ and –C=O–4′) in the transition state of this rearrangement) [12].

EXPERIMENTAL

Mps are uncorr. ^{1}H NMR (100 MHz) and ^{13}C NMR (25 MHz) spectra were determined in $CDCl_3$. MS (70 eV) direct insertion. IR: $CHCl_3$. $[\alpha]_D$ and UV: MeOH. Spots were detected by UV light (254 nm) and spraying the plates with 10% H_2SO_4 and heating. Si gel 60 (70–230 mesh) was used for CC and Si gel 60 F-254 and Si gel 60 F-254 impregnated with $AgNO_3$ (5%) for TLC (0.25 mm) and prep. TLC (0.5 mm).

Extraction and separation of compounds. The MeOH extract of fresh leaves (11 kg) of *M. liliflora* collected in Oct. 1981 at Anpachi, Gifu Prefecture, was divided into *n*-hexane and $CHCl_3$ soluble fractions. The $CHCl_3$ fraction was extracted repeatedly by 2% HCl, and the base was taken-up. Evaporation of the solvent from the dried extract afforded a gummy residue (34 g), which was chromatographed on a column of Si gel (300 g) using C_6H_6 with gradually increasing proportions of EtOAc as an eluent. The following five fractions were collected and further purified on prep. TLC:1 (C_6H_6–EtOAc, 40:1), denudatin A (**1**, 520 mg), denudatin B (**2**, 590 mg), liliflol A (**3**, 25 mg), liliflol B (**4**, 12 mg) and liliflodione (**9**, 100 mg); 2 (20:1), (+)-veraguensin (**8**, 320 mg); 3 (5:1), piperenone (**7**, 43 mg) and liliflone (**6**, 16 mg); 4 (1:1), burchellin (**5**, 60 mg) and futoenone (**10**, 630 mg); 5 (EtOAc), denudatone (**11**, 25 mg). The known compounds were characterized by spectroscopic methods (IR, ^{1}H NMR and MS).

Liliflol A [(7S,8R)-1′-*allyl*-2′-*hydroxy*-8-*methyl*-7-*piperonyl*-7,8-*dihydrobenzofuran*] (**3**). Viscous oil. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3600–3200, 1620, 1500, 1485; MS *m/z*: 310 [M]$^+$ (100), 295 (21), 254 (25), 175 (54); ^{1}H NMR: δ 1.33 (3H, *d*, *J* = 7 Hz, Me-8), 3.19–3.40 (1H, *m*, H-8), 3.3 (2H, *d*, *J* = 7 Hz, H-7′), 4.96 (1H, *d*, *J* = 9Hz, H-7), 5.0 (1H, *s*, OH-2′), 5.02–5.24 (2H, *m*, H-9′), 5.76–6.20 (1H, *m*, H-8′), 5.9 (2H, *s*, OC$\underline{H}_2$O), 6.32 (1H, *s*, H-3′), 6.80 (1H, *s*, H-6′), 6.68–6.88 (3H, *m*, Ar-H).

Photolysis of denudatin A (**1**). A soln of **1** (18 mg) in MeOH (5 ml) under N_2 was irradiated by a 100 W high pres. Hg lamp (without Pyrex filter) for 2 hr. The soln was evaporated and the residue was purified by prep. TLC. The compound (3 mg) was identical in all respects with liliflol A.

Pyrolysis of denudatin A (**1**). A soln of **1** (57 mg) in $Et_2N\phi$ (5 ml) under N_2 was maintained at 220° for 1.5 hr. The cooled reaction soln was treated in the usual manner. The residue was fractionated by prep. TLC to give liliflol A (13 mg) and starting material (39 mg).

Liliflol B [(7S,8R)-1′-*allyl*-2′-*hydroxy*-8-*methyl*-7-*veratryl*-7,8-*dihydrobenzofuran*] (**4**). Viscous oil. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3625–3200, 1620, 1600, 1515, 1485, 1465; MS *m/z*: 326 [M]$^+$ (100), 311 (23), 175 (23); ^{1}H NMR: δ 1.36 (3H, *d*, *J* = 7 Hz, Me-8), 3.2–3.48 (1H, *m*, H-8), 3.34 (2H, *br d*, *J* = 6 Hz, H-7′), 3.86 (6H, *s*, Ar-OMe), 5.02 (1H, *d*, *J* = 8Hz, H-7), 5.06 (1H, *s*, OH-2′), 5.06–5.28 (2H, *m*, H-9′), 5.76–6.2 (1H, *m*, H-8′), 6.35 (1H, *s*, H-3′), 6.81 (1H, s, H-6′), 6.72–7.0 (3H, *m*, Ar-H).

Liliflone [(7S,8R,4′R,5′S)-1′-*allyl*-4′,5′-*dimethoxy*-8-*methyl*-2′-*oxo*-7-(3-*methoxy*-4-*hydroxy*)*phenyl*-7,8,2′,3′,4′,5′-*hexahydrobenzofuran*] (**6**). Viscous oil. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3600–3200, 1625, 1605, 1595, 1510, 1460. MS *m/z*: 374 [M]$^+$ (4), 164 (100); ^{1}H NMR: δ 0.98 (3H, *d*, *J* = 7 Hz, Me-8), 2.58 (1H, *d*, *J* = 16 Hz, H-3′), 2.86 (1H, *dd*, *J* = 7, 10 Hz, H-8), 3.12 (2H, *br d*, *J* = 7 Hz, H-7′), 3.26 (1H, *d*, *J* = 16 Hz, H-3′), 3.38 (3H, *s*, OMe-5′), 3.5 (3H, *s*, OMe-4′), 3.86 (3H, *s*, Ar-OMe), 4.08 (1H, *d*, *J* = 10 Hz, H-7), 5.0–5.26 (2H, *m*, H-9′), 5.66–6.1 (1H, *m*, H-8′), 6.46 (1H, *br s*, H-6′), 6.54 (1H, *d*, *J* = 8 Hz, H-5), 6.76–6.96 (2H, *m*, Ar-H), 8.12 (1H, *s*, OH-4).

Methylation of **6**. A soln of **6** (9 mg) in ethereal CH_2N_2 (2 ml) was kept at 0–5° for 2 days, and then concd. The residue was purified by prep. TLC ($CHCl_3$–Me_2CO, 10:1) to afford piperenone (**7**) as a viscous oil (4 mg).

Piperenone [(7S,8R,4′R,5′S)-1′-*allyl*-4′,5′-*dimethoxy*-8-*methyl*-2′-*oxo*-7-*veratryl*-7,8,2′,3′,4′,5′-*hexahydrobenzofuran*] (**7**). Mp 80–83°. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1680, 1640, 1605, 1590, 1510, 1460; UV λ_{max}^{MeOH} nm (ε): 222 (20 594), 266 (11 416). $[\alpha]_D$ −109° (MeOH; c 1.67); MS *m/z*: 388 [M]$^+$ (5), 287 (29), 246 (11), 210 (36), 178 (100), 151 (86); CD (MeOH; *c* 0.017): $[\theta]_{275}$ 0, $[\theta]_{300}$ −14 774, $[\theta]_{340}$ 0, $[\theta]_{350}$ + 448, $[\theta]_{380}$ 0; ^{1}H NMR: δ 1.02 (3H, *d*, *J* = 7 Hz, Me-8), 2.62 (1H, *d*, *J* = 16 Hz, H-3′), 2.9 (1H, *dd*, *J* = 7, 10 Hz, H-8), 3.16 (2H, *br d*, *J* = 7 Hz, H-7′), 3.3 (1H, *d*, *J* = 16 Hz, H-3′), 3.42 (3H, *s*, OMe-5′), 3.56 (3H,*s*, OMe-4′), 3.92 (6H, *s*, Ar-OMe), 4.14 (1H, *d*, *J* = 10 Hz, H-7), 5.04–5.3 (2H, *m*, H-9′), 5.7–6.1 (1H, *m*, H-8′), 6.48 (1H, *br s*, H-6′), 6.82–6.94 (3H, *m*, Ar-H).

Liliflodione [(7R,8R,3′S,5′S)-1′-*allyl*-5′-*methoxy*-8-*methyl*-7-(3-*methoxy*-4-*hydroxy*)*phenyl*-$\Delta^{6'}$-2′,4′-*dioxobicyclo*(3,2,1)*octane*] (**9**). Viscous oil. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3550, 1765, 1670, 1640, 1610, 1510; UV λ_{max}^{MeOH} nm (ε): 208 (13 484), 226 (10 983), 276 (3907); $[\alpha]_D$ + 254.4° (MeOH; *c* 1.07); MS *m/z*: 342 [M]$^+$ (100), 327 (9), 314 (10), 283 (14), 273 (15), 177 (60), 164 (70); CD (MeOH; *c* 0.0169): $[\theta]_{245}$ 0, $[\theta]_{271}$ + 35 687, $[\theta]_{336}$ + 6083, $[\theta]_{385}$ 0; ^{1}H NMR: δ 1.15 (3H, *d*, *J* = 7 Hz, Me-8), 2.44–2.8 (1H, *m*, H-8), 2.88 (2H, *br d*, *J* = 6 Hz, H-7′), 3.16 (1H, *dd*, *J* = 5, 7.5 Hz, H-7), 3.66 (3H, *s*, OMe-5′), 3.74 (1H, *d*, *J* = 7.5 Hz, H-3′), 3.84 (3H, *s*, Ar-OMe), 4.92–5.2 (2H, *m*, H-9′), 5.56 (1H, *s*, OH-4), 5.5–6.0 (1H, *m*, H-8′), 6.48 (1H, *dd*, *J* = 2, 8 Hz, H-6), 6.52 (1H, *br s*, H-2), 6.8 (1H, *d*, *J* = 8 Hz, H-5), 7.32 (1H, *br s*, H-6′); ^{13}C NMR: δ 129.5 (*s*, C-1), 111.2 (*d*, C-2), 146.6 (*s*, C-3), 145.1 (*s*, C-4), 114.4 (*d*, C-5), 120.5 (*d*, C-6), 43.0 (*d*, C-7), 48.1 (*d*, C-8), 16.9 (*q*, C-9), 141.0 (*s*, C-1′), 194.4 (*s*, C-2′), 69.0 (*d*, C-3′), 201.1 (*s*, C-4′), 87.0 (*s*, C-5′), 149.1

(*d*, C-6'), 32.6 (*t*, C-7'), 133.7 (*d*, C-8'), 118.0 (*t*, C-9'), 54.6 (*q*, OMe-5'), 55.9 (*q*, OMe-3).

Methylation of **9**. Liliflodione (**9**) (10 mg) was methylated with CH_2N_2 in the usual way. The methylation product was purified by prep. TLC using $CHCl_3$–Me_2CO (20:1) to afford a viscous oil of **9a** (5 mg).

Rearrangement of denudatin B (**2**). A mixture of **2** (20 mg) and *p*-TsOH (3 mg) in dry MeCN (5 ml) was maintained at 70° for 15 hr. The cooled soln was neutralized with $NaHCO_3$ and evaporated. The residue was separated by prep. TLC ($CHCl_3$–Me_2CO, 20:1) into **9a** (14 mg). Viscous oil. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3525, 1765, 1670, 1640, 1620, 1590, 1510; UV λ_{max}^{MeOH} nm (ε): 209 (15419), 229 (12660), 278 (4202); CD (MeOH; *c* 0.0157): $[\theta]_{244}$ 0, $[\theta]_{271}$ +40815, $[\theta]_{300}$ +19047, $[\theta]_{336}$ +5896, $[\theta]_{385}$0; MS *m/z*: 356 $[M]^+$ (50), 341 (5), 191 (91), 178 (100); ^1H NMR: δ 1.18 (3H, *d*, *J* = 7 Hz, Me-8), 2.48–2.8 (1H, *m*, H-8), 2.9 (2H, *br d*, *J* = 6 Hz, H-7'), 3.2 (1H, *dd*, *J* = 5, 7.5 Hz, H-7), 3.66 (3H, *s*, OMe-5'), 3.76 (1H, *d*, *J* = 7.5 Hz, H-3'), 3.84 (6H, *s*, Ar-OMe), 4.96–5.28 (2H, *m*, H-9'), 5.54–6.0 (1H, *m*, H-8'), 6.5–6.64 (2H, *m*, H-2, H-6), 6.78 (1H, *d*, *J* = 8Hz, H-5), 7.32 (1H, *br s*, H-6').

Acknowledgements—We are very grateful to Dr. T. Tanaka, Gifu College of Pharmacy for his supply of the plant material and Dr. M. Haruna of our University for ^{13}C NMR measurements. We are also indebted to Mr. T. Kondo, a student of our laboratory, for his help in our experiments.

REFERENCES

1. Iida, T., Ichino, K. and Ito, K. (1982) *Phytochemistry* **21**, 2939.
2. Talapatra, B., Chadhuri, P. K. and Talapatra, S. K. (1982) *Phytochemistry* **21**, 747.
3. Iida, T. and Ito, K. (1982) *Phytochemistry* **21**, 701.
4. Iida, T., Nakano, M. and Ito, K. (1982) *Phytochemistry* **21**, 673.
5. Iida, T., Noro, Y. and Ito, K. (1983) *Phytochemistry* **21**, 211.
6. Ito, K., Iida, T., Ichino, K., Tsunezuka, M., Hattori, M. and Namba, T. (1982) *Chem. Pharm. Bull.* **30**, 3347.
7. Matsui, K. and Munakata, K. (1975) *Tetrahedron Letters* 1905.
8. Aiba, C. J., Fernandes, J. B., Gottleib, O. R. and Maia, J. G. S. (1975) *Phytochemistry* **14**, 1597.
9. Aiba, C. J., Gottlieb, O. R., Pagliosa, F. M., Yoshida, M. and Magalhães, M. T. (1977) *Phytochemistry* **16**, 745.
10. Filho, R. B., Figliuolo, R. and Gottlieb, O.R. (1980) *Phytochemistry* **19**, 659.
11. Alvarenga, M. A. de, Castro, O. C., Giesbrecht, A. M. and Gottlieb, O. R. (1977) *Phytochemistry* **16**, 1801.
12. Alvarenga, M. A. de, Brocksom, U., Gottlieb, O. R. and Yoshida, M. (1978) *Chem. Commun.* 831.