Tetrahedron Vol. 47, No.20/21, pp. 3463-3470, 1991
Printed in Great Britain

0040-4020/91 $3.00+.00

TWO *NEO*-CLERODANE DITERPENOIDS CONTAINING AN UNUSUAL 2,6-DIOXABICYCLO[2.2.1]HEPTANE STRUCTURAL MOIETY

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(*Received in UK 3 December* 1990)

Abstract.- Two new diterpenoids, teucrolivins G and H, have been isolated from the aerial parts of *Teucrium oliverianum* (Labiatae). The structures of teucrolivin G [6α,19-diacetoxy-4α,18;15,16-diepoxy-3-oxo-*neo*-cleroda-13(16), 14-dien-12,8β,10β-acetal, **1**] and teucrolivin H [19-acetoxy-4α,18;15,16-diepoxy-6α-hydroxy-3-oxo-*neo*-cleroda-13(16),14-dien-12,8β,10β-acetal, **2**] were established mainly by spectroscopic means, including an X-ray diffraction analysis of the former (**1**). Compounds **1** and **2** possess an unusual 2,6-dioxabicyclo [2.2.1] heptane structural moiety which, to the best of our knowledge, has now been found for the first time in natural products.

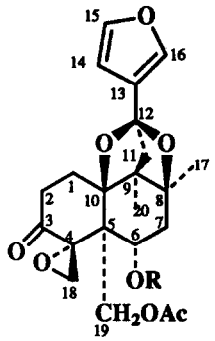
The *Teucrium* genus (family Labiatae) is so far the most abundant natural source of *neo*-clerodane and 19-nor-*neo*-clerodane diterpenoids[1]. These compounds have attracted interest in the last few years due to their biological activities, specially as insect antifeedants and as antifungal, antitumour, antimicrobial and molluscicidal agents[2]. In our continued search for new insect antifeedants from natural sources[3], we have studied *Teucrium oliverianum* collected in Saudi Arabia, where it is used in folk medicine against diabetes[4]. We wish to report herein the isolation and structure determination of two new *neo*-clerodane diterpenoids, teucrolivins G (**1**) and H (**2**), possessing a very unusual structural feature, namely a 2,6-dioxabicyclo[2.2.1]heptane moiety.

RESULTS AND DISCUSSION

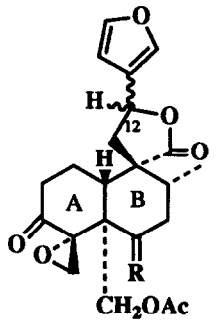
Repeated column chromatography of the acetone extract of the aerial parts of *Teucrium oliverianum* (see Experimental Section) led to the isolation of compounds **1** and **2** (teucrolivins G and H, respectively).

Combustion analysis and low-resolution mass spectrometry indicated the molecular formula $C_{24}H_{28}O_9$ for teucrolivin G (**1**) and its IR spectrum showed furan (3140, 3115, 1505, 875 cm^{-1}), acetate (1760, 1740, 1245 cm^{-1}) and saturated ketone (1720 cm^{-1}) absorptions. The ^1H and ^{13}C NMR spectra of compound **1** were

in good accordance with a clerodane diterpenic skeleton, showing signals (see Tables I and II) attributable to a β-substituted furan [δ_H 7.51, 1H, m (H-16), 7.41, 1H, t (H-15) and 6.43, 1H, dd (H-14); δ_C 121.26 s (C-13), 108.75 d (C-14), 143.12 d (C-15) and 140.44 d (C-16)], a 4α,18-oxirane [C-18 protons at δ 2.55 and 3.29 as an AB system, J_{gem}=5.2 Hz; δ_C 63.35 s (C-4) and 52.75 t (C-18)], an acetoxymethylene group at C-19 [δ_H 4.43, 1H, br d and 4.79, 1H, d (C-19 protons, J_{gem}=12.1 Hz), and δ 2.02, 3H, s (OAc); $\delta_{C\text{-}19}$ 61.85 t] and two tertiary methyl groups [δ_H 1.28, 3H, s and 1.34, 3H, s; δ_C 24.70 q and 12.57 q, Me-17 and Me-20, respectively (vide infra)], identical with those observed in other *neo*-clerodane diterpenoids isolated from *Teucrium* species[5-8]. Compound **1** also possessed a ketone function (υ_{CO} 1720 cm^{-1}, δ_C 204.54 s), which must be undoubtedly placed at the C-3 position[9], because the signal of the H_B-18 proton (δ 3.29) appeared as a doublet, without the long-range H_B-18, H-3α coupling characteristic of 4α,18-epoxyclerodanes having a C-3 methylene group[5-8]. Furthermore, the ^1H NMR spectrum of teucrolivin G (**1**, Table I) showed a one-proton signal at δ 5.67, broad dd, corresponding to the H-6β axial proton[8], geminal to the other acetoxyl group of this diterpenoid and coupled with the H_A-19 proton (long-range coupling, J<0.3 Hz, see Table I) and its vicinal C-7 methylene protons[6-9], which appeared at δ 1.71 (H-7α) and 1.97 (H-7β) as double doublets (J_{gem}=14.0 Hz, $J_{6\beta,7\alpha}$=11.8 Hz, $J_{6\beta,7\beta}$=5.0 Hz), thus establishing that C-8 was a fully substituted carbon atom.



1 R=Ac
2 R=H



3 R=αH,βOH; (12*S*)
4 R=αOAc,βH;(12*R*)

The ^{13}C NMR spectrum of teucrolivin G (**1**, Table II) showed a one-carbon signal at δ 103.02 s, characteristic of an acetal function[5,6] that must be placed at the C-12 position, because the ^1H NMR spectrum of compound **1** exhibited two one-proton signals forming an AB system without vicinal couplings (δ 2.26 and 2.34, J_{gem}=10.6 Hz), which were assigned to the C-11 methylene protons. An alternative structural hypothesis with the acetal group at the C-11 position was discarded, taking into account the observed ^{13}C NMR chemical shifts of the furanic and methylene carbons and the δ values of the isolated methylene protons of compound **1** as compared with the data reported for furoclerodane derivatives with[5-9] and without[10] oxygen substituents at C-12. This acetal group must also involve the C-8 and C-10 carbons, both appearing as singlets at δ 86.39 and 82.59 in the ^{13}C NMR spectrum of teucrolivin G.

Table I. ^{1}H NMR data of compounds **1** and **2**[a]

	1	2	J(Hz)	1	2
H-1α	2.38 td	2.35 td	1α,1β	13.2	13.3
H-1β	2.11 ddd	~2.07[d]	1α,2α	5.3	5.4
H-2α	2.57 ddd	2.60 ddd	1α,2β	13.2	13.3
H-2β	2.73 ddd	2.73 ddd	1β,2α	1.7	2.0
H-6β	5.67 br dd	4.49 br dd	1β,2β	6.6	6.6
H-7α	1.71 dd	1.59 dd	2α,2β	16.4	16.4
H-7β	1.97 dd	~2.04[d]	6β,7α	11.8	11.7
H_A-11[c]	2.26 d	2.25 d	6β,7β	5.0	4.6
H_B-11[c]	2.34 d	2.30 d	6β,19A	<0.3	<0.3
H-14	6.43 dd	6.40 dd	7α,7β	14.0	14.2
H-15	7.41 t	7.41 t	11A,11B	10.6	10.5
H-16	7.51 m	7.49 m	14,15	1.7	1.8
Me-17	1.28 s	1.29 s	14,16	0.7	0.7
H_A-18[c]	2.55 d	2.80 d	15,16	1.7	1.8
H_B-18[c]	3.29 d	3.49 d	18A,18B	5.2	4.7
H_A-19	4.43 br d	4.38 br d	19A,19B	12.1	12.3
H_B-19	4.79 d	4.85 d			
Me-20	1.34 s	1.33 s			
OAc	2.02(6H) s	2.02(3H) s			
6-OH[e]	----	2.65 s			

[a]At 300 MHz in $CDCl_3$ solution, with TMS as internal standard; chemical shifts are in ppm(δ).
[b]Spectral parameters were obtained by first order approximation. All these assignments were confirmed by double resonance experiments.
[c]Protons H_A-11 (pro-*R*), H_B-11 (pro-*S*), H_A-18 (*exo* with respect to ring B) and H_B-18 (*endo*) were distinguished by NOE experiments (see Table III).
[d]Overlapped signal.
[e]Disappeared after addition of D_2O.

The relative configuration of all the asymmetric centres of this diterpenoid (**1**) was established by NOE experiments. The data collected in Table III clearly showed that H-6β and the C-18 methylene protons are on the same side of the plane defined by the substituted decalin moiety, because irradiation at δ 5.67 (H-6β) caused a NOE enhancement in the signal of H_B-18 (*endo* proton with respect to ring B) and a small negative effect in H_A-18 (*exo* hydrogen). Irradiation under NOE conditions of the protons of the two C-Me groups allowed the unequivocal assignment of them and established that the A/B ring junction of the decalin part of teucrolivin G was *trans*. In fact, irradiation of the methyl singlet signal at δ 1.34 (Me-20) caused NOE enhancements in the signals of H-1α, H-7α and C-19 methylene protons, only compatible with a *trans*-decalin in which the C-20 methyl group and the H-1α, H-7α and C-19 methylene protons are in a *cis* 1,3-diaxial relationship. Consequently, the acetalic oxygen atom attached to C-10 and the C-11 substituent must be in a β configuration, thus establishing that the 2,6-dioxabicyclo[2.2.1]heptane moiety of compound **1** involved the C-8β position. Moreover, irradiation of the methyl singlet signal at δ 1.28 (Me-17, in an equatorial C-8α configuration) produced NOE enhancement

in the signal of the C-20 methyl group (δ 1.34), whereas no effect was observed in the signal of H-6β and the C-19 protons. These NOE experiments also allowed an unambiguous assignment of each one of the methylene protons at C-11, because irradiation at δ 1.34 (C-20 methyl group) caused an identical NOE enhancement in the two signals of the C-11 methylene group, whereas on irradiation at δ 1.28 (Me-17) only the signal at δ 2.34 showed a positive NOE. Obviously, this proton and the Me-17 group are on the same side of the plane defined by the C-8, C-9, C-11, C-12 substituted tetrahydrofuran ring, and it is the pro-*S* hydrogen of the C-11 methylene grouping.

Table II. ^{13}C NMR data of teucrolivin G (1)[a]

C	δ	C	δ	C	δ
1	29.74 t	9	52.20 s	17	24.70 q
2	35.19 t[b]	10	82.59 s[c]	18	52.75 t
3	204.54 s	11	46.04 t	19	61.85 t
4	63.35 s	12	103.02 s	20	12.57 q
5	48.74 s	13	121.26 s	OAc	169.89 s
6	66.33 d	14	108.75 d		169.48 s
7	34.95 t[b]	15	143.12 d		21.12 q
8	86.39 s[c]	16	140.44 d		20.58 q

[a]Chemical shifts are reported in parts per million downfield from internal TMS, $CDCl_3$ solution, 50.3.MHz. Multiplicities were determined by DEPT pulse sequences.
[b,c]Assignments bearing the same sign may be interchanged, but those given here are considered to be the most likely.

From all the above data it was evident that teucrolivin G possessed the structure and relative stereochemistry depicted in **1**. The *neo*-clerodane absolute configuration[11] of this substance was established from its CD curve, which showed a positive Cotton effect ($\Delta\varepsilon_{278}$ + 1.98) due to the C-3 ketone chromophore identical with those observed in compounds **3** and **4**, two diterpenoid derivatives whose *neo*-clerodane absolute configuration is well known[12].

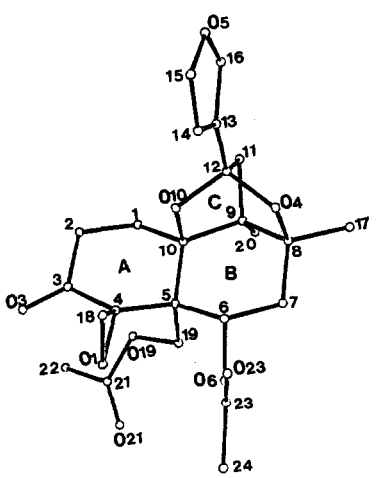


Figure 1. A perspective view of the molecular structure of teucrolivin G (1), showing the atomic-numbering scheme.

The other diterpenoid isolated from *Teucrium oliverianum*, teucrolivin H (**2**, $C_{22}H_{26}O_8$), was the 6-*O*-deacetyl derivative of compound **1**. The structural difference between compounds **1** and **2** was evidenced by their molecular formulae, the hydroxyl absorption of **2** in its IR spectrum (3510 cm^{-1}) and their ^1H NMR spectra, which were almost identical (Table I) except for the upfield resonance of the H-6β proton in compound **2** (δ 4.94 br dd, $J_{6\beta,7\alpha}$=11.7 Hz, $J_{6\beta,7\beta}$=4.6 Hz, $J_{6\beta,19A}$<0.3 Hz) and the presence of only one acetoxyl group in **2** (δ 2.02, 3H, s) instead of the two acetates (δ 2.02, 6H, s) of compound **1**. Moreover, acetic anhydride-pyridine treatment of teucrolivin H (**2**) yielded compound **1**.

In order to confirm all the above conclusions, a single-crystal X-ray determination of teucrolivin G (**1**) was undertaken. Figure 1 shows the X-ray molecular model of compound **1**, supporting the preceding deductions on its structure and relative stereochemistry. The absolute configuration of this diterpenoid was not established from the X-ray data (see Experimental). As revealed by the torsion angles, rings A and B of compound **1** are *trans*-fused and they exhibit some distorted chair conformation, ring A being slightly flattened in the region C-3, C-4, whereas ring C (C-8, C-9, C-10, O-10, C-12, O-4) presents a boat conformation. The angle between rings A and B of the decalin moiety is 170° and the angle between rings B and C is 84°. In the crystal, there are no shorter contacts between adjacent molecules than the sums of van der Waals radii.

Table III. NOE experiments on compound **1**

Irradiation at δ (proton)	5.67 (H-6β)	4.43 (H_A-19)	1.34 (Me-20)	1.28 (Me-17)
Observed NOE enhancement[a]				
H-1α	0	*b*	(+)	0
H-7α	0	(+)	(+)	(++)
H-7β	*b*	0	0	(++)
H_A-11[c]	0	0	(+)	0
H_B-11[c]	0	0	(+)	(+)
Me-17	0	0	*b*	--
H_A-18[d]	(-)	0	0	0
H_B-18[e]	(++)	0	0	0
H_A-19	0	--	(+)	0
H_B-19	0	(+++)	(+)	0
Me-20	0	(++)	--	(++)

[a](+), (++) and (+++) mean weak, medium and strong enhancements, respectively; (-) means weak negative NOE.
[b]Not measured.
[c]The H_A-11 and H_B-11 protons are the pro-*R* and pro-*S* hydrogens, respectively (see irradiation on the Me-17 protons).
[d]*Exo* hydrogen with respect to ring B (see irradiation on the H-6β proton).
[e]*Endo* hydrogen with respect to ring B.

The 2,6-dioxabicyclo[2.2.1]heptane structural feature, which involves the C-8, C-9, C-10, C-11 and C-12 carbons in the *neo*-clerodane skeleton of teucrolivins G (**1**) and H (**2**), is very rare in organic compounds

and, as far as we know, not previously found in natural products. From a biogenetic point of view, it is interesting to note that compounds **1** and **2** are the first *neo*-clerodane diterpenoids simultaneously oxidized at the C-8 and C-10 positions found in *Teucrium*, although several A/B *cis* 8β,10β-dihydroxy-*neo*-clerodane derivatives have recently been isolated[13] from some *Pteronia* species (Compositae).

EXPERIMENTAL

Melting points were determined on a Kofler apparatus and are uncorrected. Optical rotations were measured with a Perkin-Elmer 241 MC polarimeter, with a 1 dm cell. IR spectra were obtained on a Perkin-Elmer 681 spectrophotometer. ^1H and ^{13}C NMR spectra were recorded at 300 and 50.3 MHz, respectively, with a Varian XL-300 and a Bruker AM-200 spectrometers. The proton NOE measurements were made at 300 MHz, by the FT difference method, with the decoupler operating in the gated mode. Elemental analyses were carried out with the help of a Horaeus CHN-O Rapid analyzer. Low-resolution mass spectra were obtained on a VG 12-250 spectrometer (mode EI, 70 eV, solid probe).

Extraction and isolation of the diterpenoids. Dried and powdered *Teucrium oliverianum* (Ging. *ex* Benth.) R. Br. aerial parts (800 g)[14] were extracted with Me_2CO (5 l) at room temperature for a week. The acetone extract (30 g) was dissolved in 96% EtOH (1 l) and then 400 ml of water were slowly added with vigorous stirring, giving an insoluble resinous material which was discarded. The hydroalcoholic solution was subsequently extracted with *n*-hexane and $CHCl_3$ (3x700 ml). The chloroform extract (18 g) was chromatographed on a silica gel column (Merck, No. 7734, deactivated with 10% H_2O, 450 g) eluted with *n*-hexane and *n*-hexane-EtOAc mixtures.The fraction eluted with *n*-hexane-EtOAc 3:2 yielded a residue (4.8 g) which in turn, was rechromatographed (silica gel, $CHCl_3$-MeOH 19:1 as eluent) yielding, among other diterpenoids, teucrolivin G (**1**, 40 mg, less polar constituent) and teucrolivin H (**2**, 14 mg).

Teucrolivin G (**1**). Mp 199-201°C (EtOAc-*n*-hexane or MeOH); $[\alpha]_D^{24}$ +35.2° ($CHCl_3$; *c* 0.213); CD nm (Δε): 321 (0), 278 (+1.98), 214 (0) (MeOH; *c* 0.0566); IR (KBr) υ_{max} cm^{-1}: 3140, 3115, 1505, 875 (furan), 3070 (oxirane), 1760, 1740, 1245, 1215 (OAc), 1720 (ketone), 2970, 1480, 1370, 1170, 1115, 1040, 1030, 950, 925, 870, 795; ^1H NMR: see Table I; ^{13}C NMR: see Table II; MS, *m/z* (relative intensity): 460 $[M]^+$(1.3), 432 (3.5), 417 (19), 373 (5), 297 (2), 203 (5), 175 (11), 162 (59), 95 (100, base peak), 43 (32). Anal. Calcd. for $C_{24}H_{28}O_9$: C, 62.60; H, 6.13. Found: C, 62.87; H, 6.11.

Teucrolivin H (**2**). Mp 176-177°C (EtOAc-*n*-hexane); $[\alpha]_D^{24}$ +56.6° ($CHCl_3$; *c* 0.122); IR (KBr) $\upsilon_{max}cm^{-1}$: 3510 (OH), 3170, 3130, 1508, 878 (furan), 3080 (oxirane), 1750, 1220 (OAc), 1730 (ketone), 2980, 1480, 1383, 1160, 1145, 1125, 1050, 1035, 950, 920, 793; ^1H NMR: see Table I; MS, *m/z* (relative intensity): 418$[M]^+$ (7), 400 (5), 390 (6), 375 (11), 327 (33), 309 (15), 203 (11), 177 (15), 175 (19), 162 (72), 95 (100, base peak), 43 (55). Anal. Calcd. for $C_{22}H_{26}O_8$: C, 63.15; H, 6.26. Found: C, 62.93; H, 6.40.

Acetylation of teucrolivin H (**2**) ***to give teucrolivin G*** (**1**). Compound **2** (6 mg) was treated with Ac_2O-pyridine (1:1, 2ml) for 48 hours at room temperature. Work-up in the usual manner yielded a

compound (5 mg) identical in all respects (mp, mixed mp, $[\alpha]_D$, ^{1}H NMR, MS, TLC) with natural teucrolivin G (**1**).

***X-Ray structure determination of teucrolivin G* (1).** Compound **1** crystallized from MeOH as colourless very well formed prisms. A crystal of dimensions 0.4x0.2x0.2 mm was selected for data collection. The cell dimensions were determined by least-squares from setting 36 reflections with $10°<\theta<45°$: a=16.939(1), b=14.098(1) and c=9.4209(4) Å. The crystal of compound **1**, $C_{24}H_{28}O_9$, M_r 460.480 g.mol^{-1}, is orthorhombic, space group $P\ 2_12_12_1$ (determined from systematic absences: $h00$, h odd; $0k0$, k odd; $00l$, l odd), Z=4, V=2249.7(8) Å^3, D_c=1.3595 g.cm^{-3}. The data were collected on a Philips PW 1100 four-circle diffractometer, with graphite monochromated CuKα radiation (1.5418 Å). Two reference reflections were checked every 90 reflections and they showed no intensity variation. The intensity measurement was performed up θ=65°, $\omega/2\theta$ scan technique, scan speed 0.055 s^{-1}. A total of 2168 independent reflections were measured, 2114 of which were considered as observed with the $I>2\sigma(I)$ criterion and were used for structure solution and refinement. The data were corrected for geometrical factors, but not for absorption (μ=8.133 cm^{-1}). The structure was solved by direct methods (*DIRDIF*[15]) and Fourier synthesis, and it was refined by full-matrix least-squares with anisotropic thermal parameters. All the hydrogen atoms were located from difference synthesis and included in the structure factor calculations, but their positional and isotropic parameters were not refined. An empirical weighting scheme was applied so as to give no trends in $\langle w\Delta^2F\rangle$ vs. $\langle F_O\rangle$ and $\langle\sin\theta/\lambda\rangle$. The final R and R_w values are 3.8% and 4.6%.

The absolute configuration was tried to determine by the Bijvoet pairs, but the results were very poor, and it was not possible to determine the correct enantiomer. The η refinements for the oxygen dispersors[16] were done starting at: ($+x$, $+y$, $+z$; $\Delta f''$=+0.032), ($+x$, $+y$, $+z$; $\Delta f''$=0) and ($+x$, $+y$, $+z$; $\Delta f''$=-0.032) (the $\Delta f''$ values were taken from ref.[17]). The refinements converged to η values of +0.5(2), +0.5(2) and -0.5(2), respectively, all with R values of R=0.039 and R_w=0.046, thus confirming the proposed chirality, but denoting the structure somehow centric at just the oxygen atoms.

The final difference synthesis shows the residual electron density no greater than ±0.35 eÅ^{-3}, the final shit error is 0.011; number of variables 298, degrees of freedom 1816 and the ratio of freedom is 7.1.

Scattering factors were taken from the literature[17]. All calculations were performed on a VAX 750/11 computer using the *X-Ray 76 System*[18] and several local programs. Lists of atomic coordinates, thermal parameters and structure factors corresponding to compound **1** have been deposited at the Cambridge Crystallographic Data Centre.

Acknowledgements. This work was subsidized by the Spanish "Dirección General de Investigación Científica y Técnica" (Grant PB87-0418), "Scientific Research Funds" from the Italian Ministry of Education, and "Programa Conjunto No. 3.3 CSIC-CNR".

REFERENCES AND NOTE

1. Piozzi, F.; Rodríguez, B.; Savona, G. *Heterocycles* **1987**, *25*, 807.
2. Martinez-Ripoll, M.; Fayos, J.; Rodríguez, B.; García-Alvarez, M.C.; Savona, G.; Piozzi, F.; Paternostro, M.; Hanson, J.R. *J. Chem. Soc. Perkin Trans. I*, **1981**, 1186. Miyase, T.; Kawasaki, H.; Noro, T.; Ueno, A.; Fukushima, S.; Tekemoto, T. *Chem. Pharm. Bull.* **1981**, *29*, 3561. Hanson, J.R.; Rivett, D.E.A.; Ley, S.V.; Williams, D.J. *J.Chem. Soc. Perkin Trans. I*, **1982**, 1005. Camps, F.; Coll, J.; Dargallo, O.; Rius, J.; Miravitlles, C. *Phytochemistry* **1987**, *26*, 1475. Belles, X.; Camps, F.; Coll, J.; Piulachs, M.D. *J. Chem. Ecol.* **1985**, *11*, 1439. Blaney, W.M.; Simmonds, M.S.J.; Ley, S.V.; Jones, P.S. *Entomol. Exp. Appl.* **1988**, *46*, 267. Habtemariam, S.; Gray, A.I.; Halbert, G.W.; Waterman, P.G. *Planta Med.* **1990**, *56*, 187. Nakajima, M.; Okazaki, T.; Iwado, S.; Kinoshita, T.; Haneishi, T. *J. Antibiotics* **1989**, *42*, 1741.
3. Simmonds, M.S.J.; Blaney, W.M.; Ley, S.V.; Savona, G.; Bruno, M.; Rodríguez, B. *Phytochemistry*, **1989**, *28*, 1069.
4. Ajabnoor, M.A.; Al-Yahya, M.A.; Tariq, M.; Jayyab, A.A. *Fitoterapia* **1984**, *55*, 227.
5. Carreiras, M.C.; Rodríguez, B.; Piozzi, F.; Savona, G.; Torres, M.R.; Perales, A. *Phytochemistry* **1989**, *28*, 1453.
6. de la Torre, M. C.; Rodríguez, B.; Piozzi, F.; Savona, G,; Bruno, M.; Carreiras, M.C. *Phytochemistry* **1990**, *29*, 579.
7. Savona, G.; Bruno, M.; Piozzi, F.; Servettaz, O.; Rodríguez, B. *Phytochemistry* **1984**, *23*, 849.
8. Fayos, J.; Fernández-Gadea, F.; Pascual, C.; Perales, A.; Piozzi, F.; Rico, M.; Rodríguez, B.; Savona, G. *J. Org. Chem.* **1984**, *49*, 1789.
9. de la Torre, M.C.; Rodríguez, B.; Bruno, M.; Savona, G.; Piozzi, F.; Perales, A.; Torres, M.R.; Servettaz, O. *Phytochemistry* **1990**, 29, 2229.
10. Savona, G.; Passannanti, S.; Paternostro, M.; Piozzi, F.; Hanson, J.R.; Hitchcock, P.B.; Siverns, M. *J. Chem. Soc. Perkin Trans. I* , **1978**, 356.
11. Rogers, D.; Unal, G.G.; Williams, D.J.; Ley, S.V.; Sim, G.A.; Joshi, B.S.; Ravindranath, K.R. *J. Chem. Soc. Chem. Commun.* **1979**, 97.
12. Savona, G.; Piozzi, F.; Servettaz, O.; Rodríguez, B.; Fernández-Gadea, F.; Martín-Lomas, M. *Phytochemistry* **1984**, *23*, 843. García-Alvarez, M.C.; Marco, J.L.; Rodríguez, B.; Savona, G.; Piozzi, F. *Phytochemistry* **1982**, *21*, 2559. Pascual, C.; Fernández, P.; García-Alvarez, M.C.; Marco, J.L.; Fernández-Gadea, F.; de la Torre, M.C.; Hueso-Rodríguez, J.A.; Rodríguez, B.; Bruno, M.; Paternostro, M.; Piozzi, F.; Savona, G. *Phytochemistry* **1986**, *25*, 715.
13. Zdero, C.; Jakupovic, J.; Bohlmann, F. *Phytochemistry* **1990**, *29*, 1231.
14. Plant materials were collected in April 1987 at the Gassim province, Saudi Arabia, and a voucher specimen (No. 25) was deposited in the Herbarium of the Faculty of Agriculture at Gassim, King Saud University, Buriedah, Saudi Arabia.
15. Beurskens, P.T.; Bosman, W.P.; Doesburg, H.M.; Gould, R.O.; van der Hark, T.E.M.; Prick, P.A.J.; Noordik, J.H.; Beurskens, G.; Parthasarathi, V.; Bruins, S.H.J.; Haltivanger, R.C.; Smits, J.M.M. *DIRDIF System*; Crystallography Laboratory, Toernooiveld, Nijmegen: The Netherlands, 1984.
16. Rogers, D. *Acta Cryst.* **1981**, *A37*, 734.
17. "International Tables for X-Ray Crystallography"; Kynock Press: Birmingham, 1974; Vol. IV.
18. Stewart, J.M.; Machin, P.A.; Dickinson, C.W.; Ammon, H.L.; Heck, H.; Flack, H. *The X-Ray 76 System*; Computer Science Center, University of Maryland, College Park: MD, 1976.