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Synthesis and Crystal Structure of *trans*-3-(4-Acetoxy-3-methoxyphenyl)-8-acetyloxy-2-methyl-2,3-dihydro-1,4-benzodioxine

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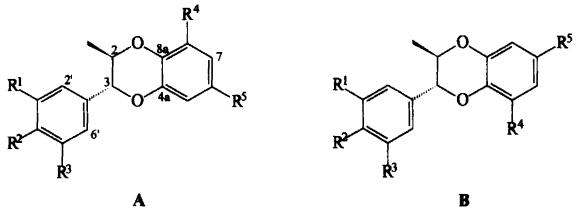
A synthesis of the neolignan model compound 3-(4-hydroxy-3-methoxyphenyl)-8-hydroxy-2-methyl-2,3-dihydro-1,4-benzodioxine (**3A**) was achieved with high stereo- and regio-selectivity by oxidative coupling of phenols in the presence of Ag_2O. The regiochemical assignments at C-8 were derived from a crystal structure determination by single-crystal X-ray diffraction analysis of diacetate **5A**, which could not be established unambiguously by NMR spectroscopy. Compound **5A** crystallizes as colourless prisms in the monoclinic space group $P2_1/a$ with $a=11.524(2)$, $b=11.959(2)$, $c=14.284(1)$ Å, $\alpha=90°$, $\beta=109.14(1)$, $\gamma=90°$, $V=1860.3(5)$ Å^3 and $Z=4$. A final R-value of 0.059 was obtained.

The 1,4-benzodioxane ring system is of considerable interest owing to its remarkable diversity of biological activity. In particular, the 3-aryl-1,4-benzodioxane skeleton constitutes the framework of several natural neolignans, coumarino-, xantho-, and flavanolignoids[1] with cytotoxic,[2] neurotrophic[3] and hepatoprotective[4] activities.

The benzodioxane-type neolignans, named eusiderins have been isolated from *Eusideroxylon*,[5] *Aniba* and *Licaria*[6] (Lauraceae), as well as *Virola*[7] (Myristicaceae) species. Their structural elements seem to occur only rarely in lignins.[8] Despite the simplicity of the structures, the localization of the substituents on the aromatic part of the benzodioxane units has been a delicate problem in the structure elucidations of the compounds. The stereochemistry assignments of the *trans* vs. *cis* series are distinguished by ^{1}H and ^{13}C NMR data.[6,9] However, the distinction between the regioisomeric possibilities **A** or **B** (Fig. 1) is difficult even on the basis of NMR spectra.[10] This problem has been solved by the Lanthanide Induced Shift NMR technique for representative eusiderins,[11,12] and an X-ray crystallographic analysis for eusiderin A (**1A**).[13] In recent years, Merlini *et al.*[10,14,15] reported the efficient synthesis of natural neolignans including **1A** by oxidative coupling of phenols in the presence of Ag_2O.

A free-radical coupling mechanism has been suggested[16,17] (Scheme 1), where the first step is the intermolecular *O*-β coupling of two phenoxyl radicals (**I** and **II**), followed by a nucleophilic attack of the hydroxyl group on the quinonemethide system of the intermediate (**III**) to furnish 2,3-*trans*-fused ring systems. However, Antus *et al.*[18,19] using the self-coupling of caffeic acid ethyl ester under Merlini's conditions obtained a benzofuran derivative with complete regioselectivity as a major product,



1 $R^1=R^2=R^3=R^4=OMe$, $R^5=$ Allyl

2 $R^1=R^2=OH$, $R^3=R^4=OMe$, $R^5=$ Allyl

3 $R^1=OMe$, $R^2=R^4=OH$, $R^3=R^5=H$

4 $R^1=R^2=R^4=OMe$, $R^3=R^5=H$

5 $R^1=OMe$, $R^2=R^4=OAc$, $R^3=R^5=H$

Fig. 1. Benzodioxane-type neolignans and related compounds.

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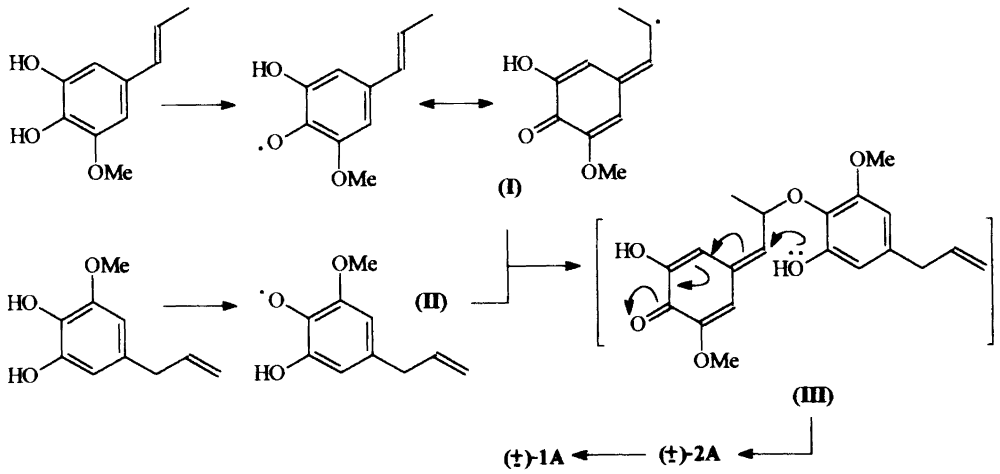


Scheme 1. Free-radical coupling mechanism for benzodioxane neolignans.

instead of the expected *trans*-1,4-benzodioxane. To obtain an independent basis for the assignment of regio- and stereo-isomers of compounds related to eusiderins we have prepared the diastereoisomers of 3-(4-hydroxy-3-methoxyphenyl)-8-hydroxy-2-methyl-2,3-dihydro-1,4-benzodioxine by Merlini's procedure using pyrogallol and isoeugenol. Primarily on the basis of ^{1}H NMR spectral comparisons with eusiderins, it was suggested that the synthesized compound was the *trans* isomer (**3A**) as major product. The *trans* form of the diacetate derivative (**5A**) could be obtained in a pure state by fractional crystallization. The crystal structure of **5A** confirms the *trans* stereochemistry and enables conclusions to be drawn about the coupling pathway.

Results and discussion

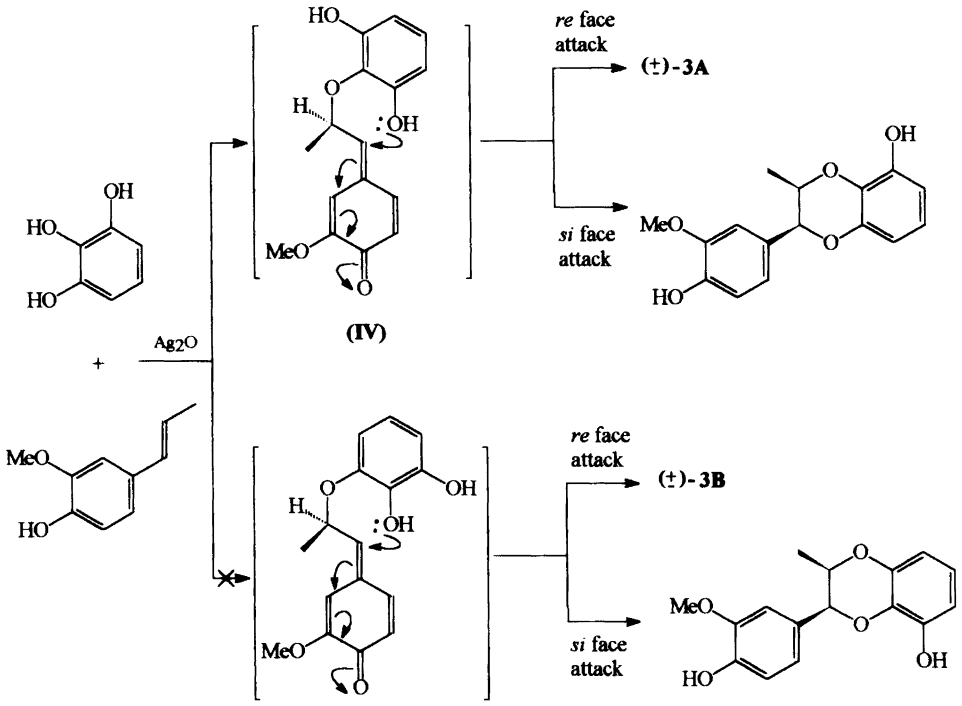
The oxidative reaction between pyrogallol and isoeugenol, using silver oxide, took place with nearly complete conversion of isoeugenol. The ^{1}H NMR spectrum of the crude product showed an essentially pure diastereoisomer **3A** with a *trans/cis* ratio of approximately 21:1. Methylation of this mixture afforded the tri-*O*-methylate derivative **4A** (a different, but related synthesis of the latter compound has recently been published by Marques and Yoshida).[20] The relative stereochemistry[6] was easily verified by analysis of the chemical shift of the methyl and H-3 protons, and the H-2/H-3 coupling constant (*trans*: δ_{Me} 1.20; $\delta_{H\text{-}3}$ 4.12, J 8 Hz; *cis*: δ_{Me} 1.12; $\delta_{H\text{-}3}$ 5.13, J 2.5 Hz). The *trans* form of the diacetate **5A** could be obtained in a pure state by fractional crystallization. Its X-ray analysis (see below) allowed the identification of one C-8 substituent as an acetyloxy group, thus confirming the identity of the regioisomer and of the coupling pathway (Scheme 2). The electron-donating effect of the hydroxy groups should make the oxidation of the di-*ortho* hydroxy easier and therefore induce high regioselectively. The preferential nucleophilic attack of the hydroxy group on the *re* face of the quinonemethide intermediate **IV** determines the stereochemical outcome of the reaction to furnish the majority of the 2,3-*trans*-fused benzodioxane skeleton. Complimentary proton–proton shift correlation (^{1}H–^{1}H COSY), carbon-13–proton shift correlation (^{13}C–^{1}H HETCOR) and long-range COLOC spectra on the **4A** enabled us to assign all the proton and carbon signals (Table 1).

Crystal structure of trans-*3-(4-acetyloxy-3-methoxyphenyl)-8-acetyloxy-2-methyl-2,3-dihydro-1,4-benzodioxine* (**5A**). A summary of the crystal data and data-collection for **5A** is given in Table 2. Fractional atomic coordinates and equivalent isotropic thermal parameters are given in Table 3. Fig. 2 shows the molecule and the atomic labelling. The crystals of the *trans* form of **5A** consist of four molecules held together by Van der Waals forces. Within the limits of experimental error, the ring carbon atoms are situated in the aromatic ring planes, mean deviations being close to 0.002 and 0.006 Å. The oxygen atoms of the benzodioxane linkage are slightly twisted [O(4), −0.019(3) and O(5), −0.029(4) Å] out of the benzene ring plane as has also been found in neolignan-related compounds.[21,22] The deviations of C(10), C(11) and O(6) from the 1,4-benzodioxane unit are 0.395(5), 0.340(5) and −0.093(4) Å, respectively. The two benzene ring planes form an angle of 125.0(2)° with each other.

Experimental

General. Melting points were determined on a Kofler hot-stage apparatus and are uncorrected. ^{1}H and ^{13}C NMR spectra were recorded at 300 MHz and 75.5 MHz, respectively, with a Varian Gemini 300 instrument in $CDCl_3$, using TMS as an internal reference. EI mass spectra were measured at 70 eV with a Varian 311A spectrometer.

Synthesis of trans-*3-(4-hydroxy-3-methoxyphenyl)-8-hydroxy-2-methyl-2,3-dihydro-1,4-benzodioxine* (**3A**). A mixture of pyrogallol (1,2,3-trihydroxybenzene,



Scheme 2. Mechanism proposed for the free-radical coupling of the isoeugenol and pyrogallol.

Table 1. ^{13}C NMR spectral data of compounds **3A** and **4A** (75.5 MHz, $CDCl_3$, δ-values).

C	3A	4A
1′	128.8	129.7
2′	109.5	110.3
3′	147.1	149.8
4′	146.6	149.6
5′	114.7	111.3
6′	121.2	120.4
Me-2	17.3	17.3
2	74.5	74.3
3	81.1	80.8
4a	144.6	145.0
5	107.8	104.3
6	121.0	120.3
7	108.9	110.1
8	145.3	149.6
8a	131.4	133.4
OMe	56.1	56.1
OMe	—	56.0

124.8 mg, 0.99 mmol) and isoeugenol (2-methoxy-4-propenylphenol, 160.7 mg, 0.98 mmol) in dry benzene was treated with Ag_2O (Fischer: 792532-S-184, 502 mg, 2.17 mmol), and stirred under an N_2 atmosphere with the exclusion of light for 12 h at 45 °C. The suspension was filtered, the filtrate evaporated and the product **3A** recovered as a ca. 21 : 1 mixture with the *cis* stereoisomer by flash chromatography on silica gel with hexane–ethyl acetate (4:1); yield 231.8 mg (82%), m.p. 149–150 °C. ^1H NMR: δ 1.21 (d, *J* 6.4 Hz, Me-2), 3.91 (s, OMe), 4.14 (dq, *J* 6.4 and 8.0 Hz, H-2), 4.59 (d, *J* 8.0 Hz, H-3), 5.60 (s, 2 × OH), 6.53 (dd, *J* 1.4 and 8.2 Hz, H-5), 6.57

Table 2. Crystal and experimental data for *trans*-2-methyl-3-(4-acetoxy-3-methoxyphenyl)-8-acetoxy-2,3-dihydro-1,4-benzodioxine, **5A**, $C_{20}H_{20}O_7$.

M_r	372
Crystal system	Monoclinic
Space group	$P2_1/a$ (No. 14)
Unit cell dimensions/Å or °	$a = 11.524(2)$
	$b = 11.959(2)$
	$c = 14.284(1)$
	$\beta = 109.14(1)$
	$V = 1860.3(5)$
Z	4
D_c/g cm^{-1}	1.33
M.p./°C	230
μ(Mo Kα)/mm^{-1}	0.52
Crystal size/mm	0.50 × 0.20 × 0.25
Reflections for cell determination	22
(No./θ range/°)	0–25
Scan mode	ω–2θ
2θ range/°	0–50
Total No. of independent reflections measured	2729
No. of observed independent reflections [$I > 3\sigma(I)$]	1637
Method used to solve structure	Direct methods; electron density difference map
No. of parameters refined	245
Weights calculated according to	$[\sigma^2(\lvert F_o\rvert) + 0.0003\lvert F_o\rvert^2]^{-1}$
R	0.059
Maximum residual electron density/e Å^{-3}	0.25

Table 3. Atomic fractional coordinates and B_{eq} (B_{iso} for H) for *trans*-2-methyl-3-(4-acetoxy-3-methoxyphenyl)-8-acetoxy-2,3-dihydro-1,4-benzodioxine, **5A**, $C_{20}H_{20}O_7$. Space group $P2_1/a$. $B_{eq} = {}^4/_3 \Sigma_i \Sigma_j B_{ij}\, a_i a_j$.

Atom	*x*	*y*	*z*	B_{eq}
C(1)	0.0295(5)	0.9520(5)	0.6447(3)	5.2(2)
C(2)	0.0650(5)	1.0350(5)	0.7260(3)	4.2(2)
C(3)	0.1066(4)	1.0588(4)	0.8960(3)	3.2(1)
C(4)	0.2242(4)	1.0714(4)	0.9587(3)	3.7(2)
C(5)	0.2502(4)	1.1426(4)	1.0400(3)	3.6(1)
C(6)	0.1562(4)	1.2024(3)	1.0570(3)	3.0(1)
C(7)	0.0355(4)	1.1878(4)	0.9936(3)	3.1(1)
C(8)	0.0107(4)	1.1163(4)	0.9133(3)	3.1(1)
C(9)	−0.2025(5)	1.1569(5)	0.8625(4)	4.8(2)
C(10)	0.1814(4)	1.2808(4)	1.1435(3)	3.2(1)
C(11)	0.1685(4)	1.2253(4)	1.2351(3)	3.5(1)
C(12)	0.2578(5)	1.1306(4)	1.2754(4)	5.1(2)
C(13)	0.1389(4)	1.4081(4)	1.2874(3)	3.1(1)
C(14)	0.0912(4)	1.4402(3)	1.1895(3)	2.9(1)
C(15)	0.0368(4)	1.5453(4)	1.1659(3)	3.6(1)
C(16)	0.0323(4)	1.6163(4)	1.2406(4)	4.2(2)
C(17)	0.0802(5)	1.5841(4)	1.3382(4)	4.4(2)
C(18)	0.1330(4)	1.4795(4)	1.3604(3)	3.8(2)
C(19)	0.1332(6)	1.3674(5)	1.4948(4)	5.1(2)
C(20)	0.2092(6)	1.3308(6)	1.5941(4)	7.1(2)
O(1)	0.0786(4)	1.1333(3)	0.7180(3)	6.5(2)
O(2)	0.0820(3)	0.9865(3)	0.8154(2)	3.7(1)
O(3)	−0.1020(3)	1.0978(3)	0.8471(2)	4.3(1)
O(4)	0.1944(3)	1.3060(3)	1.3144(2)	4.0(1)
O(5)	0.0967(3)	1.3725(2)	1.1134(2)	3.4(9)
O(6)	0.1900(3)	1.4481(3)	1.4596(2)	4.6(1)
O(7)	0.0348(4)	1.3321(4)	1.4497(3)	7.9(2)
H1(C1)	0.0183	0.9881	0.5826	
H2(C1)	0.0914	0.8962	0.6546	
H3(C1)	−0.0459	0.9165	0.6419	
H(C4)	0.2900	1.0298	0.9472	
H(C5)	0.3344	1.5116	1.0830	
H(C7)	0.0295	1.2269	1.0072	
H1(C9)	−0.2780	1.1367	0.8125	
H2(C9)	−0.2098	1.1356	0.9259	
H3(C9)	−0.1910	1.2344	0.8620	
H(C10)	0.2656	1.3069	1.1601	
H(C11)	0.0845	1.1970	1.2159	
H1(C12)	0.2475	1.0975	1.3327	
H2(C12)	0.2512	1.0748	1.2268	
H3(C12)	0.3414	1.1602	1.2949	
H(C15)	0.0009	1.5676	1.0978	
H(C16)	−0.0048	1.6882	1.2241	
H(C17)	0.0749	1.6334	1.3898	
H1(C20)	0.2856	1.3722	1.6146	
H2(C20)	0.1689	1.3435	1.6413	
H3(C20)	0.2285	1.2536	1.5934	

(dd, *J* 1.4 and 4.1 Hz, H-7), 6.75 (dd, *J* 8.1 and 8.2 Hz, H-6), 6.85 (d, *J* 1.8 Hz, H-2′), 6.87 (dd, *J* 1.8 and 7.9 Hz, H-6′), 6.95 (d, *J* 7.9 Hz, H-5′). ^{13}C NMR spectrum, see Table 1. EIMS [*m/z* (% rel. int.)]: 288 (52, M^+), 245 (11), 165 (12), 164 (100), 151 (22), 137 (37).

trans-*3-(3,4-Dimethoxyphenyl)-8-methoxy-2-methyl-2,3-dihydro-1,4-benzodioxine* (**4A**). **3A** (30 mg, 0.1 mmol), dimethyl sulphate (0.04 ml, 0.4 mmol), and anhydrous K_2CO_3 (0.1 g) was stirred in boiling acetone for 2 h. The reaction mixture was poured into 10 ml of water and

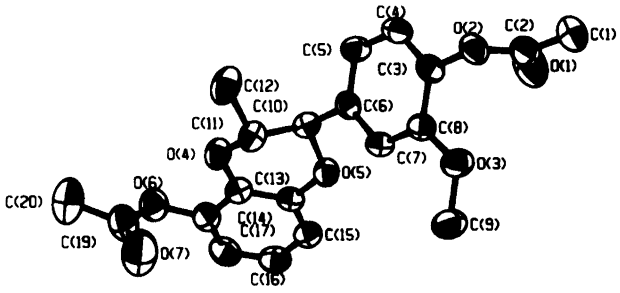


Fig. 2. The *trans*-2-methyl-3-(4-acetoxy-3-methoxyphenyl)-8-acetoxy-2,3-dihydro-1,4-benzodioxine (**5A**) molecule showing the atomic numbering.

extracted with EtOAc. Crystallization from methanol yield **4A** as colourless needles (31 mg, 94 %), m.p. 105–107 °C. ^{1}H NMR: δ 1.25 (d, *J* 6.4 Hz, Me-2), 3.90 (s, 2 × OMe), 3.91 (s, OMe), 4.13 (dq, *J* 6.4 and 7.9 Hz, H-2), 4.60 (d, *J* 7.9 Hz, H-3), 6.53 (dd, *J* 1.4 and 8.2 Hz, H-5), 6.62 (dd, *J* 1.4 and 8.3 Hz, H-7), 6.80 (dd, *J* 8.2 and 8.3 Hz, H-6), 6.87 (d, *J* 1.8 Hz, H-2′), 6.89 (d, *J* 7.9 Hz, H-5′), 6.94 (dd, *J* 1.8 and 7.9 Hz, H-6′). ^{13}C NMR spectrum, see Table 1. EIMS [*m/z* (% rel. int.)]: 316 (10, M^+), 274 (5), 179 (15), 178 (100), 165 (23), 163 (23), 151 (48).

trans-*3-(4-Acetoxy-3-methoxyphenyl)-8-acetoxy-2-methyl-2,3-dihydro-1,4-benzodioxine* (**5A**). Acetylation of **3A** was carried out in a mixture of dry pyridine and acetic anhydride (1:1) at room temp. For work-up the solution was evaporated under vacuum. Crystallization of the residue in hexane–EtOAc yielded colourless prisms, m.p. 230 °C. ^{1}H NMR (80 MHz): δ 1.18 (d, *J* 6.5 Hz, Me-2), 2.30 (s, 2 × CH_3CO), 3.83 (s, OMe), 4.13 (dq, *J* 6.5 and 8.1 Hz, H-2), 4.63 (d, *J* 8.1 Hz, H-3), 6.58–7.10 (m, Ar-H). EIMS [*m/z* (% rel. int.)]: 372 (30, M^+), 332 (10), 331 (48), 288 (34), 245 (11), 165 (12), 164 (100), 151 (16), 137 (37).

Structure determination. The diffraction experiments were performed on an Enraf-Nonius CAD-4 X-ray diffractometer, using graphite-monochromated Mo Kα radiation. The unit cell dimensions were determined from diffractometer setting angles for 22 reflections. The diffracted intensities were corrected for Lorentz and polarization effects. The atomic coordinates of all non-hydrogen atoms were determined by direct methods[23] and by electron density calculations. Hydrogen atoms were located geometrically, all with a common isotropic temperature factor of 0.08 Å. Intensity statistics indicated a centric structure, and a plausible solution was obtained within the space group $P2_1/a$. Full-matrix least-squares refinement of positional and anisotropic thermal parameters gave $R = 0.059$.

Further details concerning the refinement of the structure are given in Table 2. Atomic scattering factors were taken from *International Tables for X-Ray Crystallography.*[24] Most of the calculations were per-

formed on a VAX-6000 computer using the SHELXS-86 crystallographic software package.[23] Lists of *U*-values and structure factors tables are available from one of the authors (C.L.) on request.

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References

1. Whiting, D. A. *Nat. Prod. Rep. 7* (1990) 349.
2. Sharma, D. K. and Hall, I. H. *J. Nat. Prod. 54* (1991) 1298.
3. Fukuyama, Y., Hasegawa, T., Toda, M., Kodama, M. and Okazaki, H. *Chem. Pharm. Bull. 40* (1992) 252.
4. Hikino, H., Kiso, Y., Wagner, H. and Fiebig, M. *Planta Med. 50* (1984) 248.
5. Hobbs, J. J. and King, F. E. *J. Chem. Soc.* (1960) 4732.
6. Silva, M. S., Barbosa-Filho, J. M., Yoshida, M. and Gottlieb, O. R. *Phytochemistry 28* (1989) 3477.
7. Ferri, P. H. and Barata, L. E. S. *Phytochemistry 31* (1992) 1375.
8. Hwang, B. H. and Sakakibara, A. *Holzforschung 35* (1981) 297.
9. Arnoldi, A. and Merlini, L. *J. Chem. Soc., Perkin Trans. 1* (1985) 2555.
10. Merlini, L. and Zanarotti, A. *Tetrahedron Lett. 42* (1975) 3621.
11. Braz-Filho, R., Mourão, J. C., Gottlieb, O. R. and Maia, J. G. S. *Tetrahedron Lett. 43* (1976) 3621.
12. Fernandes, J. B., Ribeiro, M. N. S., Gottlieb, O. R. and Gottlieb, H. E. *Phytochemistry 19* (1980) 1523.
13. Rodrigues, M. M., Fernandes, J. B., Braz-Filho, R., Yoshida, M. and Gottlieb, O. R. *Phytochemistry 23* (1984) 667.
14. Merlini, L., Zanarotti, A., Pelter, A., Rochefort, M. P. and Hansel, R. *J. Chem. Soc., Perkin Trans. 1* (1980) 775.
15. Arnoldi, A., Arnone, A. and Merlini, L. *Heterocycles 22* (1984) 1537.
16. Erdtman, H. *Recent Advances in Phytochemistry*, Appleton-Century-Crofts, New York 1968, Vol. 1, p. 29.
17. Gottlieb, O. R. *Phytochemistry 11* (1972) 1537.
18. Antus, S., Baitz-Gács, E., Bauer, R., Gottsegen, Á, Seligmann, O. and Wagner, H. *Liebigs Ann. Chem.* (1989) 1147.
19. Antus, S., Gottsegen, Á, Kolonits, P. and Wagner, H. *Liebigs Ann. Chem.* (1989) 593.
20. Marques, M. O. M. and Yoshida, M. *Quím. Nova 13* (1990) 245.
21. Johansson, A., Lundquist, K. and Stomberg, R. *Acta Chem. Scand. 46* (1992) 901.
22. Stomberg, A. and Lundquist, K. *Acta Chem. Scand., Ser. B 41* (1987) 304.
23. Sheldrick, G.M. SHELXS 86. *Crystal Structure Solution Computer Program*, University of Göttingen, Göttingen 1986.
24. *International Tables for X-Ray Crystallography*, Kynoch Press, Birmingham 1974, Vol. IV.

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