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TWO NEW COMPOUNDS FROM *ARTEMISIA ANNUA*

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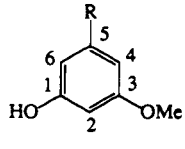
ABSTRACT.—Two novel compounds, 5-nonadecylresorcinol 3-*O*-methyl ether (phenol-3-methoxy-5-nonadecyl) [**1**] and dihydro-epideoxyarteannuin B [**4**], were isolated from the aerial parts of *Artemisia annua* (Compositae). Several long chain 5-alkyl resorcinols have been described previously, but this is the first report of a monomethylated 5-alkyl resorcinol. A number of known compounds not previously reported for *A. annua* are also described.

Artemisia annua L. (Compositae) has received much attention from natural products chemists over the past decade, following the discovery of qinghaosu (artemisinin) (1), a sesquiterpene lactone with pronounced antimalarial activity (2). Previous chemical investigations have concentrated largely on terpenoids (3) and flavonoids (4), which traditionally are the characteristic chemotaxonomic markers in the Compositae and are produced in great profusion by *A. annua*. This report describes two new components isolated from *A. annua*.

RESULTS AND DISCUSSION

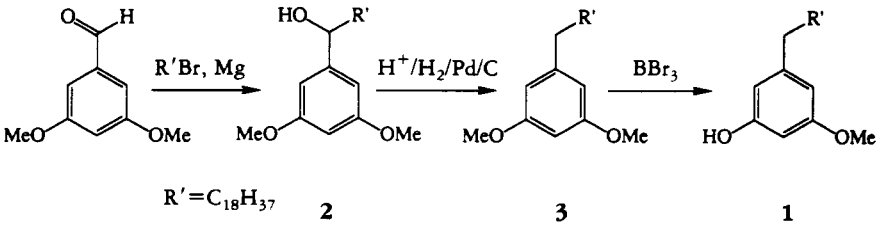
Cc followed by hplc of an Et_2O extract of the aerial parts yielded the new compound 5-nonadecylresorcinol-3-*O*-methyl ether [**1**]. The structure of **1** was deduced largely from nmr spectroscopy. The ^{1}H-nmr spectrum showed 3 distinct aromatic signals at δ 6.32, 6.26, 6.23, each appearing as a singlet broadened by small poorly resolved meta-couplings, and thereby defining a 1,3,5 substitution pattern for the benzene ring. One of these substituents was an OH group as evidenced by the exchangeable proton at δ 4.70 in the ^{1}H nmr and a sharp peak at 3612 cm^{-1} in the ir. The MeO group required by the singlet at δ 3.76 gave an nOe enhancement with the protons at δ 6.23 (H-2) and δ 6.32 (H-4). The triplet at δ 2.50 ($J = 7.0$ Hz) is characteristic of the methylene group of an alkyl chain attached to a benzene ring; as expected, nOe irradiation of this group enhanced the two aromatic protons at δ 6.26 (H-6) and δ 6.32 (H-4). ^{1}H-COSY showed this methylene group to be coupled to its neighboring methylenic group in the alkyl chain at δ 1.52. Subsequent methylenic groups coalesced into a broad peak at δ 1.26, and the alkyl chain terminated with an Me triplet at δ 0.88. The nmr spectrum precluded the occurrence of branching or unsaturation in the alkyl chain, and integration of the methylene envelope at δ 1.26 suggested a C_{19} chain length. This was supported by the ^{13}C spectrum where aromatic and MeO signals were clearly resolved and the number of carbon atoms in the alkyl side chain was approximately 19. Eims showed the required peak for 5-nonadecylresorcinol at *m/z* 390 daltons, but also gave two other peaks at *m/z* 418 and 446. It was thought that these peaks represented molecular ions corresponding to C_{21} and C_{23} homologues (25 and 9% molecular ion intensities, respectively, relative to the C_{19} compound), but, since these presumed homologues could not be chromatographically separated from the principal C_{19} component, it was neces-



1 R=$C_{19}H_{39}$
(also $C_{21}H_{43}$ and $C_{23}H_{47}$)

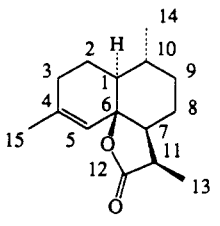
sary to embark upon a synthesis of the 5-nonadecylresorcinol-3-*O*-methyl ether to prove the identity of the natural product.

Synthesis of **1** was by way of Grignard condensation of stearyl bromide with 3,5-dimethoxybenzaldehyde to yield the secondary alcohol **2**. This alcohol was then reduced to the corresponding saturated hydrocarbon **3** by simultaneous acid-catalyzed dehydration and hydrogenation (5). 5-Nonadecylresorcinol dimethyl ether was finally deprotected using boron tribromide to give low yields of the monomethyl ether **1** (complete demethylation to the resorcinol was the preferred reaction) which was identical with the natural product in all respects (Scheme 1).



SCHEME 1

Several samples of the natural product **1** were contaminated by the new sesquiterpene dihydro-epideoxyarteannuin B [**4**]. Compounds **1** and **4** could be separated only by hplc. Hreims of **4** gave a composition of $C_{15}H_{22}O_2$, and further structural elucidation rested upon comparison of ^1H and ^{13}C spectra with the known epideoxyarteannuin B [**5**] (running just prior to **4** in hplc). The presence of a double bond substituted by an Me group was established in the ^1H nmr by a 3-proton resonance at δ 1.75 (s) and a broad low-field singlet at δ 5.63; other ^{13}C and ^1H values closely matched those of epideoxyarteannuin B [**5**] (6). The only significant difference between **4** and **5** was the absence of resonances at δ 6.17 and δ 5.56 corresponding to the α-methylene unit of the butyrolactone ring [the associated allylic proton at δ 2.71 (t, $J = 6.6$ Hz) was also absent]. Instead, **4** demonstrated a doublet of quartets at δ 3.15 ($J = 7.2$ Hz) and a three-proton doublet at δ 1.15 ($J = 7.2$ Hz), suggesting that a saturated Me-CH linkage had replaced the α-methylene linkage of **5** (i.e., **4** is the dihydro derivative of **5**). The stereochemistry of dihydro-epideoxyarteannuin B was assumed to be as that of **5** (its presumed biogenetic precursor) with the additional point that the new Me group be β (this must be the case since $J_{7,11} = 7$ Hz, hence requiring that H-7 and H-11 are cis to one another). This β configuration of the 11-methyl group is also found in all other dihydrocadinanolides from *A. annua* (e.g., artemisinin, which is also presumably derived by reduction of the α-methylene lactone group of artemistene). The structure of **4** was confirmed by reduction of **5** with $NaBH_4$, which gave a single product identical in all respects with the natural product **4**.



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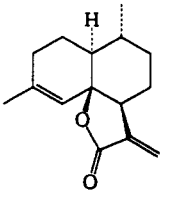

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In addition to these two new compounds, several known aromatic compounds were isolated that had not previously been reported from *A. annua*. Among these were 2-hydroxy-4,6-dimethoxyacetophenone, 2,4-dihydroxy-6-methoxyacetophenone, *trans*-phytol, and coumaric acid. Coumarin (7), scopoletin (7), and the flavonoids chrysosplenetin (8), casticin (8), artemetin (7), and 5-hydroxy-3,6,7,4′-methoxyflavone (7) were also isolated and have all been previously described from *A. annua*.

This is the first report of a 5-alkylresorcinol monomethyl ether as a natural product [there has been one recently reported preparation of a monomethylated 5-alkylresorcinol, for which spectroscopic data was not recorded (9)]. Long chain 5-alkylresorcinols (non-methylated) have previously been reported from a handful of sources, such as the bacteria *Azotobacter vinelandii* (10) and *Pseudomonas carboxydoflava* (11), the cereal crops rye, wheat, and barley (12), *Grevillea robusta* (Proteaceae) (13), *Lysimachia japonica* (Primulaceae) (14), and, most interestingly, from two other members of the Compositae, *Conzya podocephala* (15) and *Baccharis quitensis* (16).

Because of the unusual structure of these compounds, consisting of a hydrophilic headgroup attached to a long hydrophobic tail, it has been suggested that long chain 5-alkylresorcinols may exhibit their biological activity by interacting with membranes (17). It has been shown that such resorcinols are able to induce a decrease in membrane fluidity (18) by hydrogen bonding between the aromatic OH groups and the phosphate headgroups of the lipid bilayer (9). The observed biological activity of 5-*n*-alkylresorcinols has been credited to this ability to incorporate into unit membranes, and such incorporation may result in the stimulation of thromboxane production from blood platelets (19) and inhibition of Na^+-K^+-ATPase (20). It is interesting to speculate, therefore, whether the MeO analogue of this class might have analogous biological activity.

Of the other new compounds from *A. annua*, dihydro-epideoxyarteannuin B belongs to the cadinanolide class of sesquiterpene lactones, which are only found in *A. annua*. 2-Hydroxy-4,6-dimethoxyacetophenone is of quite widespread occurrence in the plant kingdom and is especially prevalent in the genus *Artemisia* (21–26). 2,4-Dihydroxy-6-methoxyacetophenone has only been reported three times as a natural product, once from the genus *Artemisia* (27). *trans*-Phytol and coumaric acid are both of widespread occurrence.

EXPERIMENTAL

GENERAL EXPERIMENTAL PROCEDURES.—^{1}H- and ^{13}C-nmr spectra were taken on Bruker 250 and 400 MHz spectrometers, ms was recorded on a Varian spectrograph, and ir spectra were from a Perkin Elmer 1600 series FTIR. Mp's were taken on a hot-stage microscope.

PLANT MATERIAL.—*A. annua* plants were grown from seed under greenhouse conditions. Seeds were kindly supplied and taxonomically verified by Dr. J. Twibell of the NCCPG collection, Cambridge. The aerial parts were harvested when the plants had reached 2 m in height in late May and just before they came into flower. Voucher specimens are held by Dr. J. Twibell at Avenue Farm Cottage, 31 Smith St., Elsworth, Cambridge.

EXTRACTION AND ISOLATION.—Fresh stem and leaf material (1 kg) was ground to a fine powder under liquid N_2, then extracted in a Soxhlet apparatus (8 h) with Et_2O. The Et_2O extract was dried and the solvent removed in vacuo to yield a green pleasant-smelling gum (9.0 g). This residue was chromatographed on Si gel using an increasingly polar solvent mix [hexane→hexane-Et_2O (9:1)→hexane-Et_2O (4:1)→Et_2O→15% EtOAc/Et_2O→30% EtOAc/Et_2O). Fractions were monitored by tlc, and on this basis 20 pooled crude fractions were generated. Each fraction was then separated into its components by preparative hplc (YMC SIL-15 column, 20 × 250 mm; flow rate 8.0 ml/min).

Compound **1** (36 mg) was obtained pure by cc in hexane-Et_2O (4:1) followed by hplc in 10% EtOAc/hexane (Rt = 16.1 min). 2-Hydroxy-4,6-dimethoxyacetophenone (8 mg) eluted just after **1** [hexane-Et_2O (4:1)] and was subsequently purified by hplc (10% EtOAc/hexane; Rt = 18.4 min). 2,4-Dihydroxy-6-

methoxyacetophenone (17 mg) eluted with Et_2O, was further purified by preparative hplc (30% EtOAc/hexane; Rt = 16.5 min) and finally recrystallized form $CHCl_3$. Compound **4** (4 mg) could only be separated from **1** by hplc (10% EtOAc/hexane; Rt = 14.6 min), and epideoxyarteannuin B (18 mg) had a slightly shorter retention time (14.1 min) on hplc under the same conditions.

Also characterized were *trans*-phytol (9 mg), coumaric acid (20 mg), coumarin (50 mg), scopoletin (43 mg), chrysosplenetin (33 mg), casticin (10 mg), artemetin (10 mg), and 5-hydroxy-3,6,7,4′-methoxyflavone (11 mg).

5-Nonadecylresorcinol,3-O-methyl ether [**1**].—White solid: mp 62–64°; ^{1}H nmr ($CDCl_3$) δ 6.32 (1H, s, H-4); 6.26 (1H, s, H-6); 6.23 (1H, s, H-2); 4.70 (1H, br s, exch. D_2O, 1-OH), 3.76 (3H, s, 3-OMe); 2.50 (2H, t, J = 7.0 Hz, H-1′); 1.56 (2H, m, H-2′); 1.26 (32H, br s, H-3′–H-18′); 0.88 (3H, t, J = 6.8 Hz, H-19′). NOe irradiation at δ 3.76 led to an 8.8% enhancement at δ 6.23 and 5.8% enhancement at δ 6.32. Irradiation at δ 2.50 gave 3.5% enhancement at δ 6.26 and 3.6% at δ 6.32. ^{13}C nmr 160.1 C (C-3), 156.6 C (C-1), 145.9 C (C-5), 108.0 CH (C-6), 106.8 CH (C-4), 98.7 CH (C-2), 55.3 Me (3-OMe), 36.2 CH_2 (C-1′), 32.0 CH_2 (C-2′), 31.3 CH_2 (C-3′), 29.8–29.4 CH_2 (×14) (C-4′–C-17′), 22.8 CH_2 (C-18′), 14.2 Me (C-19′); ir (CCl_4) cm^{-1} 3612, 2927, 2855, 1599; eims *m/z* (rel. int.) $[M]^+$ 390 (30), 138 (65), 137 (14), 57 (96), 55 (83).

Dihydro-epideoxyartannuin B [**4**].—Colorless oil: ^{1}H nmr ($CDCl_3$) δ 5.63 (1H, s, H-5); 3.15 (1H, dq, J = 7.2, 7.0 Hz, H-11), 1.75 (3H, s, H-15), 1.15 (3H, d, J = 7.2 Hz, H-13), 0.93 (3H, d, J = 6.6 Hz, H-14); ^{13}C nmr 179.5 C (C-12), 142.5 C (C-4), 121.8 CH (C-5), 83.4 C (C-6), 46.6 CH, 42.9 CH, 39.7 CH, 32.7 CH, 32.4 CH_2, 30.8 CH_2, 23.8 CH_2, 23.5 Me (C-15), 21.0 CH_2 (C-8), 19.6 Me (C-14), 9.4 Me (C-13); ir (CCl_4) cm^{-1} 2938, 1770; eims *m/z* (rel. int.) $[M]^+$ 234 (11), 188 (18), 186 (7), 173 (18), 161 (40), 105 (44), 81 (65).

Epideoxyartannuin B [**5**].—Colorless oil: ^{1}H nmr ($CDCl_3$) δ 6.17 (1H, s, H_a-13), 5.56 (1H, s, H_b-13), 5.28 (1H, s, H-5), 2.71 (1H, t, J = 6.6 Hz, H-7), 2.11–1.73 (m), 1.67 (3H, s, H-15), 0.97 (3H, d, J = 6.6 Hz, H-14); ^{13}C nmr 170.5 C (C-12), 142.9 C (C-11), 141.3 C (C-4), 123.8 CH_2 (C-13), 120.6 CH (C-5), 83.2 C (C-6), 45.0 CH, 44.3 CH, 31.0 CH_2, 29.9 CH_2, 28.5 CH_2, 28.4 CH (C-10), 23.2 Me (C-15), 21.7 CH_2 (C-8), 20.0 Me (C-14); ir (CCl_4) cm^{-1} 2932, 2871, 2829, 1763, 1672; eims *m/z* (rel. int.) $[M]^+$ ($C_{15}H_{20}O_2$) 232 (28), $[M-Me]^+$ 217 (9), $[M-CO_2]^+$ 188 (17), $[M-CO_2-Me]^+$ 173 (18), 151 (29), 109 (28), 85 (52).

2-Hydroxy-4,6-dimethoxyacetophenone.—White crystals: mp 76–77°; ^{1}H nmr ($CDCl_3$) δ 6.51 (1H, s, exch. D_2O, 2-OH); 6.07 (1H, d, J = 2.4 Hz, H-3), 5.92 (1H, d, J = 2.4 Hz, H-5), 3.86 (3H, s, 6-OMe), 3.82 (3H, s, 4-OMe), 2.61 (3H, s, MeCO); ^{13}C nmr 203.2 C (C=O), 167.6 C (C-4), 166.1 C (C-6), 162.9 C (C-2), 105.0 C (C-1), 93.6 CH (C-3), 90.8 CH (C-5), 55.6 Me (×2) (4-OMe and 6-OMe), 32.8 Me (MeCO); eims *m/z* (rel. int.) $[M]^+$ 196 (34), 181 (100), 166 (9), 151 (5).

2,4-Dihydroxy-6-methoxyacetophenone.—White crystals: mp 195–198°; ^{1}H nmr ($CDCl_3$) δ 5.99 (1H, d, J = 2.4 Hz, H-5), 5.91 (1H, d, J = 2.4 Hz, H-3), 3.87 (3H, s, 6-OMe), 2.61 (3H, s, MeCO); ^{13}C nmr 204.2 C (C=O), 168.2 C (C-4), 166.7 C (C-6), 165.2 C (C-2), 106.2 C (C-1), 96.8 CH (C-3), 92.0 CH (C-5), 56.1 Me (6-OMe); 33.0 Me (Ac); eims *m/z* (rel. int.) $[M]^+$ 182 (38), 167 (100), 152 (10), 124 (5).

SYNTHESIS.—*5-(1′-Hydroxynonadecyl)-resorcinol dimethyl ether* [**2**].—A few drops of a solution of stearyl bromide (7.0 g) in dry Et_2O (20 ml) were added to Mg turnings (0.6 g) covered with Et_2O (10 ml), and the reaction was initiated by a crystal of I_2 and two drops of ethylene dibromide. The remainder of the stearyl bromide solution was added over 30 min with heating and stirring, and formation of the Grignard reagent was complete after a further 2 h at reflux. After cooling, a solution of 3,5-dimethoxybenzaldehyde (2.0 g) in Et_2O (10 ml) was added over 30 min with stirring and then refluxed for a further 2 h. The mixture was worked up by addition of ice-H_2O (50 ml), washed with 2 N H_2SO_4 (2 × 30 ml), Na_2CO_3 (30 ml), and H_2O (50 ml), dried ($MgSO_4$), and evaporated under reduced pressure to give a white solid **2**, mp 66–68° (3.6 g, 71%). Compound **2** was purified by cc (30% EtOAc/hexane, R_f 0.39): ^{1}H nmr ($CDCl_3$) δ 6.51 (2H, d, J = 2.3 Hz, H-4 and H-6), 6.38 (1H, t, J = 2.3 Hz, H-2), 4.61 (1H, t, J = 6.1 Hz, H-1′), 3.80 (6H, s, 1-OMe and 3-OMe), 1.26 (34H, br s, H-2′–H-18′), 0.88 (3H, t, J = 7.5 Hz, H-19′); ^{13}C nmr 160.8 C (×2) (C-1 and C-3), 147.8 C (C-5), 103.8 CH (×2) (C-4 and C-6), 99.3 CH (C-2), 74.7 CH (C-1′), 55.3 Me (×2) (1-OMe and 3-OMe), 39.1 CH_2 (C-2′), 32.8 CH_2 (C-3′), 32.0 CH_2 (C-4′), 29.8–29.5 CH_2 (×13) (C-5′–C-17′), 22.7 CH_2 (C-18′), 14.2 Me (C-19′).

5-Nonadecylresorcinol dimethyl ether [**3**].—The alcohol **2** (900 mg) in EtOAc (25 ml) containing concentrated H_2SO_4 (2 drops) was hydrogenated at room temperature and pressure over 10% palladium on activated carbon (100 mg). After 4 h with stirring the mixture was filtered through celite, and the solvent was removed in vacuo to give a white solid **3**: mp 54–56° (720 mg 84%); ^{1}H nmr ($CDCl_3$) δ 6.35 (2H, br s, H-4 and H-6), 6.31 (1H, br s, H-2), 3.78 (6H, s, H-1 and H-3), 2.54 (2H, t, J = 6.6 Hz, H-1′), 1.59 (2H, m, H-2′), 1.26 (32H, br s, H-3′–H-18′), 0.88 (3H, t, J = 7.5 Hz, H-19′); ^{13}C nmr 160.7 C (×2)

(C-1 and C-3), 145.4 C (C-5), 106.5 CH (×2) (C-4 and C-6), 97.6 CH (C-2), 55.2 Me (×2) (1-OMe and 3-OMe), 36.4 CH_2 (C-1′), 32.0 CH_2 (C-2′), 31.4 CH_2 (C-3′), 29.8–29.4 CH_2 (×14) (C-4′–C-17′), 22.8 CH_2 (C-18′), 14.2 Me (C-19′).

5-Nonadecylresorcinol 3-O-methyl ether [**1**].—A solution of **3** (300 mg) in CH_2Cl_2 (20 ml) was slowly added to a solution of BBr_3 in CH_2Cl_2 (1 M, 0.75 ml) at −78°. The mixture was kept at this temperature with stirring for 5 h and then quenched by addition of H_2O (60 ml) and Et_2O (40 ml) to redissolve the precipitate. The organic layer was washed with $NaHCO_3$ (50 ml) and H_2O (50 ml), then dried and solvent removed in vacuo. The monomethyl ether (90 mg, 31%) was purified from starting material and 5-nonadecylresorcinol by cc (20% EtOAc/hexane, R_f 0.37).

All spectral and chromatographic details were identical to those of the natural product **1**, except that in the ms a molecular ion at 390 only was observed.

REDUCTION OF EPIDEOXYARTEANNUIN B TO **4**.—To epideoxyateannuin B [**5**] (10 mg) in EtOH (5 ml) on ice was added a solution of $NaBH_4$ (2.0 mg/5 ml) over 15 min with stirring. The mixture was kept at 0–5° (2 h), then allowed to warm to room temperature (2 h). The reaction was taken up in H_2O (40 ml) and extracted with Et_2O (3 × 40 ml); the combined organic phases were dried ($MgSO_4$) and the solvent removed to yield a colorless oil (8 mg, 80%) which had spectral characteristics identical to those of the natural product **4** (28).

ACKNOWLEDGMENTS

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LITERATURE CITED

1. Qinghaosu Research Group, *Sci. Sin.*, **23**, 380 (1980).
2. J.-B. Jiang, G.-Q. Li, X.-B. Guo, Y.C. Kong, and K. Arnold, *Lancet*, 285 (1982).
3. Y.-Y. Tu, M.-Y. Ni, Y.-R. Zhong, L.-N. Li, S.-L. Cui, M.-Q. Zhang, X.-Z. Wang, Z. Ji, and X.-T. Liang, *Planta Med.*, **44**, 143 (1982).
4. Y. Shilin, M.F. Roberts, and J.D. Philipson, *Phytochemistry*, **28**, 1509 (1989).
5. K.A. Cirigottis, L. Cleaver, J.E.T. Corrie, R.G. Grasby, G.H. Green, J. Mock, S. Nimigarawath, R.W. Reed, E. Ritchie, W.C. Taylor, A. Vadasz, and W.R.G. Webb, *Aust. J. Chem.*, **27**, 345 (1974).
6. R.J. Roth and N. Acton, *Planta Med.*, **53**, 576 (1987).
7. Y.-Y. Tu, J.-P. Yin, L. Ji, M.-M. Huang, and X.-I. Liang, *Zhongcaoyao*, **16**, 200 (1985).
8. D. Jeremic, M. Stefanovic, D. Dokovic, and S. Milosavljevic, *Glas. Hem. Drus. Beograd.*, **44**, 615 (1979).
9. V.V. Bitkov, V.A. Nenashev, Z.H.-M. Hashaev, N.N. Pridachina, and S.G. Batrakov, *Biol. Membr.*, **7**, 135 (1990).
10. R.N. Reusch and H.L. Sadoff, *Nature*, **302**, 268 (1983).
11. G.A. Osipov, G.I. El-reqistan, V.A. Svetlichnyi, A.N. Kozlava, V.I. Duda, A.S. Karpelyants, and V.V. Pamaznov., *Mikrobiologiya*, **54**, 186 (1985).
12. M. Salek and A. Brudzynski, *Acta Aliment. Pol.*, **7**, 119 (1981).
13. D.D. Ridley, E. Ritchie, and W.C. Taylor, *Aust. J. Chem.*, **21**, 2979 (1968).
14. M. Arisawa, K. Ohmura, A. Kobayashi, and N. Morita, *Chem. Pharm. Bull.*, **37**, 2431 (1989).
15. F. Bohlmann and P. Wegner, *Phytochemistry*, **21**, 1693 (1982).
16. F. Bohlmann, W. Kramp, M. Grenz, H. Robinson, and R.M. King, *Phytochemistry*, **20**, 1907 (1981).
17. A. Kozubek, *Acta Biochim. Pol.*, **34**, 387 (1987).
18. A. Kozubek, A. Jezierski, and A.F. Sikorski, *Biochim. Biophys. Acta*, **944**, 465 (1988).
19. P. Hengtrakul, M. Mathias, and K. Lorenz, *J. Nutr. Biochem.*, **2**, 20 (1991).
20. S. Noburu, U. Akemi, and T. Tsunematsu, *J. Nat. Prod.*, **47**, 350 (1984).
21. I. Feuerstein, D. Müller, K. Hobert, A. Danin, and R. Segal, *Phytochemistry*, **25**, 2343 (1986).
22. A. Rustaiyan, H. Sigari, J. Jakupovic, and M. Grenz, *Phytochemistry*, **28**, 2723 (1989).
23. T. Sacco, C. Frattini, and C. Bicchi, *Planta Med.*, **48**, 178 (1983).
24. B. Akyev, M.I. Yusopov, Sh.Z. Kasymov, and G.P. Sidyakin, *Khim. Prir. Soedin.*, **9**, 422 (1973).
25. P. Weyerstahl, V.K. Kaul, M. Weirauch, and H. Marschall-Weyerstahl, *Planta Med.*, **53**, 66 (1987).
26. A. Rustaiyan, K. Zare, M.T. Ganji, and H.A. Sadri, *Phytochemistry*, **28**, 1535 (1989).
27. J.F. Sanz, A. Rustaiyan, and J.A. Marco, *Phytochemistry*, **29**, 2919 (1990).
28. S.B. Kadin, *J. Org. Chem.*, **31**, 620 (1966).

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