Tetrahedron Vol. 47, No. 47, pp. 9751-9758, 1991
Printed in Great Britain

0040-4020/91 $3.00+.00

Three New Bioactive Styryllactones from *Goniothalamus giganteus* (Annonaceae)

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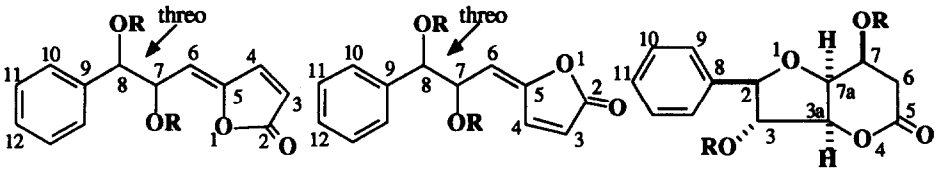
(*Received in USA* 20 *August* 1991)

Key Words: *Goniothalamus giganteus*; Goniobutenolide A and B; Goniofupyrone; Brine Shrimp Lethality; Cytotoxicity.

Abstract:. *Three new styryllactones, goniobutenolides A (1) and B (3) and goniofupyrone (5), have been isolated from the bark of Goniothalamus giganteus (Annonaceae). The structures were elucidated by ir, ms, ^1H nmr, ^{13}C nmr, ^1H-^1H COSY, nOe difference, and NOESY spectra. These compounds are marginally cytotoxic to human tumor cells in culture.*

INTRODUCTION

The ethanolic extract of the stem bark of *Goniothalamus giganteus* Hook. f. & Thomas (Annonaceae) from Thailand showed significant murine toxicity in the 3PS lymphocytic leukemia system.[1] Two major classes of bioactive compounds have been found from this plant material in our previous bioactivity-directed studies, including the Annonaceous acetogenins, goniothalamicin, annonacin,[2] gigantecin,[3] gigantetrocin, gigantriocin,[4] giganenin, and 4-deoxygigantecin,[5] and the styryllactones, altholactone (syn: goniothalenol), goniothalamin,[6] goniotriol,[7] goniofufurone, goniopypyrone, 8-acetylgoniotriol,[8] 9-deoxygoniopypyrone, 7-epigoniofufurone, and goniodiol.[9] In our continuing investigation of this plant as a source of bioactive compounds, three new styryllactones, goniobutenolides A (**1**) and B (**3**) and goniofupyrone (**5**), have been isolated by brine shrimp lethality-directed fractionation of the ethanolic extract of the stem bark. The structures were elucidated by ir, ms, ^1H nmr, ^{13}C nmr, ^1H-^1H COSY, nOe difference and NOESY spectra as well as chemical derivatization. These compounds are marginally cytotoxic against human tumor cell lines[10] (Table 1).



1 R = H **3** R = H **5** R = H
2 R = Ac **4** R = Ac **6** R = Ac

Table 1. Bioactivities of Compounds **1**, **3**, and **5**

Compound	BST[a] LC_{50}(μg/ml)	A-549[b] ED_{50}(μg/ml)	MCF-7[c] ED_{50}(μg/ml)	HT-29[d] ED_{50}(μg/ml)
1	52.79	3.73	7.76	3.41
3	60.11	9.05×10^{-1}	19.85	2.67
5	> 500	56.36	> 100	38.02
Adriamycin[e]	8×10^{-2}	8.21×10^{-4}	3.27×10^{-1}	1.75×10^{-3}

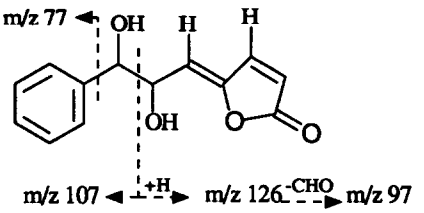
a) Brine shrimp lethality test. b) Human lung carcinoma. c) Human breast carcinoma. d) Human colon adenocarcinoma.
e) Positive control standard; adriamycin in aqueous solution was added directly to the brine in the BST.

RESULTS AND DISCUSSION

Compound **1** was isolated as a yellowish oil. The molecular weight of **1** was indicated by peaks at m/z 233 (MH^+) or 250 (MNH_4^+) in the isobutane and ammonia cims, respectively. The high resolution chemical ionization (isobutane) mass measurement (hrcims) gave m/z 233.0812 (calcd. 233.0814) for the MH^+, corresponding to the molecular formula, $C_{13}H_{12}O_4$. The presence of two hydroxyl moieties was suggested by two successive losses of water (m/z 18) from the MNH_4^+ in the ammonia cims. In addition , the ir spectrum contained a broad absorption band at 3405 cm^{-1}, consistent with the presence of hydroxyl groups. The molecular weight and the presence of two hydroxyl groups were also confirmed by the preparation of a diacetate derivative (**2**) which gave peaks at m/z 317 (MH^+), 257 (MH^+ - AcOH), and 197 (MH^+ - 2AcOH) in the cims and two peaks at δ 2.10 (3H, Ac) and 2.00 (3H, Ac) in the ^1H nmr spectrum. The presence of a monosubstituted phenyl moiety was indicated by the proton resonances at δ 7.36 - 7.30 (5H) and carbon resonances at δ 138.91 (C-9), 128.37 (C-11,13), 128.11 (C-12), and 126.36 (C-10,14) (Tables 2 and 3).

A prominant ir carbonyl absorption at 1756 cm^{-1}, uv λ_{max} at 275 nm (log ε 3.50) and 202 nm (log ε 3.53), and a carbon peak at δ 168.94 suggested the existence of the highly conjugated unsaturated lactone system. The assignments of the ^1H and ^{13}C nmr spectra suggested the presence of a 5-methylene-2(5H)-furanone and a diol fragment. The proton resonances at δ 7.27 (d, H-4), 6.16 (d, H-3) and 5.29 (d, H-6), and carbon peaks at δ 150.52 (C-5), 143.45 (C-4), 120.52 (C-3) and 112.68 (C-6) indicated the two conjugated double bonds in the 5-methylene-2(5H)-furanone. The proton resonances at δ 4.98 (H-7) and 4.94 (H-8) coupling with each other and carbon peaks at δ 75.97 (C-8) and 70.71 (C-7) indicated the diol fragment which was further confirmed by preparation of the diacetate derivative (**2**). The structure was proposed as 5-(2,3-

dihydroxyl-3-phenylpropylidene)-2(5H)-furanone and supported by comparison of the ^1H and ^{13}C nmr spectra with those of acetylmelodorinol (**7**) whose structure was proven by X-ray crystallography.[11]



Scheme 1. Eims Fragments of Goniobutenolide A (**1**)

The Z-configuration of the C_5-C_6 double bond was suggested by comparison of the ^1H and ^{13}C nmr data of **1** and **3** (discussed in the structural elucidation of **3**), and further proven by the nOe difference ^1H nmr spectrum (Fig. 1), in which the H-6 was enhanced by irradiating the H-4, and, visa versa, the H-4 was also enhanced by irradiating the H-6 due to the closer distance between these two protons in the Z-configuration. The relative stereochemistry of the diol moeity was proposed to be the threo configuration based on the observed $J_{7,8}$ = 4.32 Hz, which indicated that the H-7 and H-8 should be in the gauche and not the anti ($J_{7,8,anti}$ = 6 - 8 Hz) conformation; thus , the bulky groups [phenyl and 5-methylene-2(5H)-furanone] could be in the more stable anti conformation. The assignment of the threo-configuration was supported by comparing the coupling constants of two adjacent diol protons for several similar compounds.[7,12,13] A possible ms fragmentation pattern of **1** was proposed (Scheme 1), and the structure was concluded to be threo-(Z)-5-(2,3-dihydroxyl-3-phenylpropylidene)-2(5H)-furanone; this is a new natural compound to which the trivial name, goniobutenolide A, has been given.

Table 2. ^1H Nmr Data [δ(J/Hz), 500 MHz, $CDCl_3$)] of Compounds **1-6**

Proton	1	2	3	4	Proton	5	6
H-3	6.16 d (5.45)	6.20 d (5.50)	6.12 dd (5.56,1.78)	6.18 dd (5.65,1.80)	H-2	4.69 d (6.34)	4.92 d (4.0)
H-4	7.27 d (5.45)	7.29 d (5.50)	7.49 dd (5.56,0.70)	7.43 dd (5.65, 0.72)	H-3	4.27 dd (6.34,2.52)	5.31 dd (4.0,1.0)
H-6	5.29 d (8.36)	5.21 d (8.0)	5.78 ddd (7.88, 1.78,0.70)	5.65 ddd(9.92, 1.80,0.72)	H-3a	4.95 dd (5.15,2.52)	4.94 dd (3.5,1.0)
H-7	4.98 dd (8.36,4.32)	6.06 dd (8.0,5.0)	4.63 dd (7.88,4.53)	5.78 dd (9.92,4.31)	H-7a	4.32 br t (5.15,3.90)	4.34 br t (3.5)
H-8	4.94 d (4.23)	6.08 d (5.0)	4.87 d (4.53)	6.02 d (4.31)	H-7	4.43 ddd(5.62, 3.90,3.63)	5.47 q (4.2,3.8,3.5)
OH	2.53 br s	-----	2.39 br s	-----	H-6a	2.89 dd (16.88,3.63)	3.10 dd (17.5,4.2)
OH	2.53 br s	-----	2.32 br s	-----	H-6b	2.67 dd (16.88,5.62)	2.73 dd (17.5,3.8)
OAc	-----	2.10 s(3H)	-----	2.13 s(3H)	3-OH	2.95 br s	-----
OAc	-----	2.00 s(3H)	-----	2.03 s(3H)	7-OH	2.46 br s	-----
Ph	7.36-7.30 m	7.33-7.27 m	7.39-7.27 m	7.34-7.27 m	OAc	-----	2.13 s(3H)
					OAc	-----	2.11 s(3H)
					Ph	7.36-7.27 m	7.35-7.28

Compound **3** was also isolated as a yellowish oil. The molecular weight of **3** was indicated by peaks at m/z 233 (MH^+) and 250 (MNH_4^+) in the isobutane and ammonia cims, respectively. The hrcims gave m/z 233.0810 (calcd. 233.0814) for the MH^+, corresponding to the molecular formula, $C_{13}H_{12}O_4$. As with **1**, the presence of a phenyl moiety, a conjugated α,β and γ,δ-unsaturated γ-lactone system and a diol fragment was indicated by ir, uv, ms, nmr data (Tables 2 and 3), and preparation of a diacetate derivative (**4**). The assignment and comparison of the ^1H and ^{13}C nmr spectra of **3** with those of **1** suggested that these two compounds had the same structural skeleton but with a different conjugated double bond configuration. The observed $J_{3,6}$ value was less than 0.5 Hz in **1** and 1.78 Hz in **3**, suggesting a (Z)- C_5-C_6 double bond for **1** and an (E)- for **3**, because the proton coupling constant of the H-3 and H-6 in the E-configuration was relatively larger than that in the Z-configuration.[14,15] Also, the chemical shift of H-6 in the E-configuration should be more downfield than that in the Z-configuration due to the deshielding effect of O-1. The observed chemical shifts of H-6 in **1** (δ 5.29) and **3** (δ 5.78) supported these proposed configurations for compounds **1** and **3**. Furthermore, the E-configuration of **3** was confirmed by the nOe difference spectrum (Fig. 1), in which no nOe effect was observed when irradiating either H-4 or H-6, due to the longer distance between H-4 and H-6 in the E-configuration. The observed coupling constant (4.53 Hz) of H-7 and H-8 of **3** was similar to that of **1**. Thus, the relative configuration of the diol fragment was again proposed to be threo. This assignment was further supported by **3** having almost the same chemical shifts for H-7 and H-8 as those of similar protons in threo-7,8-dihydro-7,8-dihydroxypiperolide.[13,16] **3** showed the same mass fragmentation (Scheme 1) as that of **1** in both the cims and eims. Thus, the structure of **3** was determined as threo-(E)-5-(2,3-dihydroxyl-3-phenylpropylidene)-2(5H)-furanone; this new compound was named goniobutenolide B.

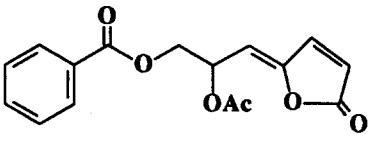
Table 3. ^{13}C Nmr Data (δ, 125 MHz, $CDCl_3$) of Compounds **1**, **3**, and **5**

Carbon	1	3	Carbon	5
2	168.94	168.05	2	85.68
3	120.52	121.20	3	83.68
4	143.45	140.57	3a	86.67
5	150.52	151.75	5	169.18
6	112.68	112.16	6	35.07
7	70.71*	72.28*	7	65.85
8	75.97*	77.20*	7a	76.43
9	138.91	138.88	8	137.90
10,14	126.36	126.54	9,13	126.04
11,13	128.37	128.67	10,12	128.77
12	128.11	128.51	11	128.52

* Signals may be interchangeable.

Compound **5** was obtained as a colorless oil. The molecular weight of **5** was indicated by peaks at m/z 250 (M^+) in the eims and 251 (MH^+) in the isobutane cims. The ^1H and ^{13}C nmr spectra of **5** showed 14 protons and 13 carbons at 11 different frequencies. The hrcims (isobutane) gave m/z 251.0917 (calcd. 251.0919) for the MH^+, corresponding to the molecular formula $C_{13}H_{14}O_5$. The existence of two hydroxyl moieties was indicated by two successive losses of water (m/z 18) from the MH^+ and M^+ in the cims and eims, respectively, and a broad ir absorption band at 3407 cm^{-1}. The molecular weight and presence of two hydroxyl moieties were further proven by the preparation of the diacetate derivative (**6**) of **5** which gave peaks at m/z 335

(MH^+), 275 (MH^+ - AcOH) and 215 (MH^+ - 2 AcOH) in the cims and two proton resonances at δ 2.13 (AcO) and 2.11 (AcO). A saturated δ-lactone was indicated by a strong ir carbonyl absortion at 1726 cm^{-1} and a carbon peak at δ 169.18. A phenyl moiety was again suggested by the ^1H and ^{13}C nmr data (Tables 2 and 3).



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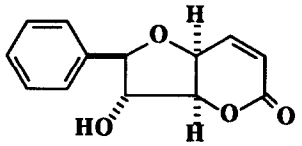

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The comparison of the ^1H and ^{13}C nmr data of **5** with those of natural or synthetic altholactone (**8**),[6,17] its stereocongeners,[18] and other styryllactones[8,9] suggested that compound **5** was a 7-hydroxyl-6-hydro-altholactone. The ^1H nmr signals of **5** were assigned based on its ^1H -^1H COSY spectrum. The furan ring of **5** showed very similar chemical shifts and coupling constants of the H-2/H-3, H-3/H-3a and H-3a/H-7a, as well as the carbon frequencies as those of the furan ring in altholactone (**8**), suggesting that both have the same relative configuration about their furan rings. A molecular model, which was based on molecular graphic energy minimization caculations, showed that the pyranone ring of **5** prefers a pseudo-boat conformation to keep both bulky groups on the C-3a and C-7a (fused furan ring) equatorial and the H-3a and H-7a axial. Thus, the cis H-7 would be in the equatorial and the trans H-7 in the axial conformations. Consequently, the cis H-7 would show a relatively smaller $J_{7,7a}$ value (< 6 Hz) and the trans H-7 a larger $J_{7,7a}$ value (6 - 8 Hz). The cis relative configuration of the H-7 and H-7a was proposed because of the relatively smaller $J_{7,7a}$ (3.90 Hz). The cis H-7/H-7a configuration was proven by the presence of a cross peak between the 7-hydroxyl proton and a phenyl proton in the NOESY spectrum (Fig. 2), indicating an axial 7-OH close to the phenyl ring. The observed coupling correlation between the 7-OH and the phenyl proton was possibly due to the formation of inter- or intra-hydrogen bonding which may enhance the 7-OH proton signal in the ^1H nmr. The other proposed relative configuration of **5** was partially confirmed by the NOESY spectrum (Fig. 2). Thus, the structure of compound **5** was determined as (2R*, 3R*, 3aS*, 7S*, 7aS*)-3-hydroxy-2-phenyl-(2H,3aH)-furano[3,2-b]-6,7,7a,3a-tetrahydropyran-5-one. This new compound was named goniofupyrone.

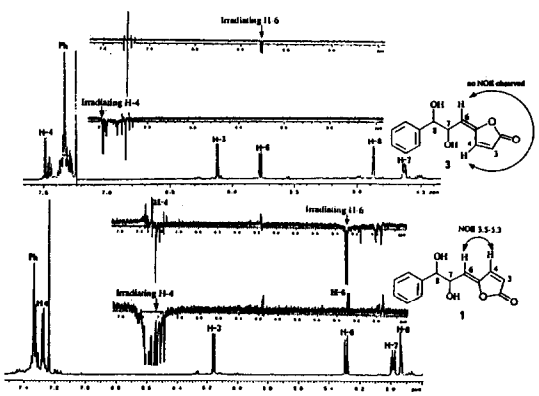

Fig. 1. NOe Difference Spectra of **1** and **3**

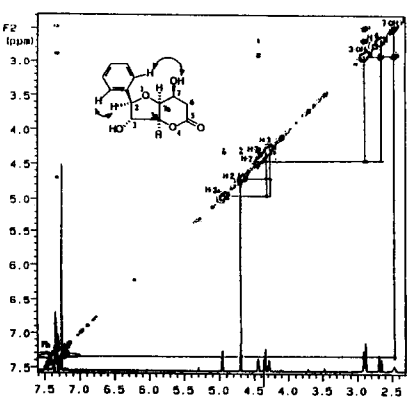

Fig. 2. NOESY Spectrum of **5**

EXPERIMENTAL

General experimental procedures. Mps were determined on a Mettler FP5 hot-stage apparatus and are uncorrected. The optical rotations were determined on a Perkin-Elmer 241 polarimeter. Uv spectra were taken in EtOH on a Beckman DU-7 spectrophotometer. Ir spectra were obtained in KBr pellets on a Perkin-Elmer 1600 FTIR spectrophotometer. Low resolution ms were recorded on a Finnigan 400 mass spectometer. The exact masses were determined on a Kratos 50 ms spectrometer through peak matching. ^1H and ^{13}C Nmr spectra were recorded on a Varian VXR-500S spectrometer.

Plant material. The stem bark of *G. giganteus* (B-826538, PR-50604) was collected in Thailand in Sept. 1978 under the auspices of Dr. Robert E. Perdue, Medicinal Plant Laboratory, U.S.D.A., Beltsville, Maryland, where voucher specimens are maintained.

Bioassays. Brine shrimp lethality (BST) [19] was tested in our laboratory. The cytotoxicity tests against A-549 (human lung carcinoma), MCF-7 human breast carcinoma), and HT-29 (human colon adenocarcinoma)[10] cells were performed in the Purdue Cell Culture Laboratory, Purdue Cancer Center, using standard protocols with adriamycin as a positive standard control.

Extraction and isolation. The residue of the crude EtOH extract of 4 kg of the stem bark was partitioned between H_2O and $CHCl_3$ to give a H_2O layer and a $CHCl_3$ layer, the residue of the $CHCl_3$ layer was partitioned between hexane and 10% H_2O in MeOH to give a MeOH layer, ca. 100 g dry residue, and a hexane layer. The MeOH residue was repeatedly chromatographed over silica gel columns and chromatotron separations directed by BST activity, using gradients of C_6H_6-EtOAc-MeOH, hexane-EtOAc, and $CDCl_3$-MeOH, and gave three oils of **1** (5 mg), **3** (3 mg), and **5** (4 mg).

Goniobutenolide A (1). Yellowish oil, $[\alpha]^{25}_D$ + 82.0 (c 0.25 in $CHCl_3$); uv λ_{max} (MeOH): 275 nm (log ε 3.50), 202 nm (log ε 3.53); ir ν_{max} (film) cm^{-1}: 3405 (s), 2923, 1781, 1756 (s), 1723, 1660, 1585, 1124, 1038, 917, 821, and 705; cims (ammonia) m/z (%): 250 (MNH_4^+, 100), 232 (MNH_4^+ - H_2O, 44), 215 (232 - OH, 36), 199 (10), 144 (10), and 127 (12); cims (isobutane) m/z (%): 233 (MH^+, 9), 215 (MH^+ - H_2O, 25), 199 (1), 127 (100), 107 (41), and 79 (25); hrcims (isobutane) m/z: 233.0812 for $C_{13}H_{13}O_4$ (MH^+, calcd. 233.0814); eims m/z (%): 126 (100), 107 (52), 97 (25), 91 (7), 79 (73), 77 (60), 71 (27), 69 (23), and 57 (33); ^1H nmr (see Table 2); ^{13}C nmr (see Table 3); ^1H nOe difference nmr (500 MHz, $CDCl_3$) showed 5.3% enhancement of the H-4 signal when irradiating the H-6 and 3.2% enhancement of the H-6 signal when irradiating the H-4 (see Fig. 1).

Goniobutenolide A diacetate (2). **1** (1.5 mg) was acetylated (Ac_2O-pyridine; 24 h; room temp.), and the mixture was partitioned between water and $CHCl_3$. The $CHCl_3$ extract on concentration and silica gel micro-column chromatography afforded **2**, ca. 1 mg oil. Cims (isobutane) m/z (%): 317 (MH^+, 0.2), 275 (MH^+ - 42, 4), 257 (MH^+ - AcOH, 100), 215 (49), 197 (MH^+ - 2 AcOH, 18), and 168 (6); ^1H nmr (see Table 2).

Goniobutenolide B (3). Yellowish oil, $[\alpha]^{25}_D$ - 36.5 (c 0.2 in $CHCl_3$); uv λ_{max} (MeOH): 276 nm (log ε 3.28), 202 nm (log ε 3.31); ir ν_{max} (film) cm^{-1}: 3416 (s), 2925, 1777 (s), 1754 (s), 1720, 1677, 1583, 1114, 1058, 1025, 939, 816, 755, and 703; cims (ammonia) m/z (%): 250 (MNH_4^+, 82), 233 (MH^+, 100), 215 (233 - H_2O, 46), 199 (11), 144 (12), and 127 (14); cims (isobutane) m/z (%): 233 (MH^+, 10), 215 (MH^+ - H_2O, 30), 127 (100), and 107 (35); hrcims (isobutane) m/z: 233.0810 for $C_{13}H_{13}O_4$ (MH^+, calcd. 233.0814); eims m/z (%): 126 (100), 107 (45), 97 (21), 91 (4), 79 (68), and 77 (53); ^1H nmr (see Table 2); ^{13}C nmr (see

Table 3); ^{1}H nOe difference nmr (500 MHz, $CDCl_3$) did not show an nOe effect between the H-4 and H-6 (see Fig. 1).

Goniobutenolide B diacetate (4). Acetylation of **3** (1 mg) by the same procedure as with **1** gave **4**, ca. 1 mg oil. Cims (isobutane) m/z (%): 257 (MH^+ - AcOH, 100), 215 (44), 197 (MH^+ - 2 AcOH), and 168 (6); ^{1}H nmr (see Table 2).

Goniofupyrone (5). Colorless oil, $[\alpha]^{25}_D$ - 5.0 (c 0.1 in $CHCl_3$); uv λ_{max} (MeOH): 206 nm (log ε 4.66); ir ν_{max} (film) cm^{-1}: 3407 (s), 2925, 1726 (s), 1663, 1384, 1237, 1048, 916, 887, 759, and 703; cims (isobutane) m/z (%): 251 (MH^+, 100), 233 (MH^+ - H_2O, 58), 215 (MH^+ - 2 H_2O, 33), 187 (7), 173 (6), 163 (10), 145 (10), 137 (11), 133 (10), 131 (18), 119 (18), 115 (30), 107 (12), and 91 (46); hrcims (isobutane) m/z: 251.0917 for $C_{13}H_{15}O_5$ (MH^+, calcd. 251.0919); eims m/z (%): 250 (M^+, 6), 232 (M^+ - H_2O, 3), 215 (232 - OH, 3), 175 (3), 160 (9), 149 (6), 144 (18), 133 (21), 131 (19), 125 (24), 120 (36), 117 (18), 107 (88), 91 (100), 77 (72), 55 (42), and 51 (61); ^{1}H nmr (see Table 2); ^{13}C nmr (see Table 3); ^{1}H-^{1}H COSY (500 MHz, $CDCl_3$); NOESY (500 MHz, $CDCl_3$, mixture time 0.4 sec) (see Fig. 2).

Goniofupyrone diacetate (6). Acetylation of **5** (1.5 mg) by the same procedure as with **1** gave **6**, ca. 1 mg oil. Cims (isobutane) m/z (%): 335 (MH^+, 16), 292 (MH^+ - 43, 6), 275 (MH^+ - AcOH, 100), 215 (MH^+ - 2 AcOH, 15), 163 (12), 144 (8), and 105 (3); ^{1}H nmr (see Table 2).

ACKNOWLEDGMENTS

This investigation was supported by R01 grant no. CA30909 from the National Cancer Institute, National Institutes of Health. Thanks are due to the Purdue Cell Culture Laboratory, Purdue Cancer Center, for cytotoxicity testing, and to Dr. John M. Cassady for help in obtaining the plant material.

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