Tetrahedron Vol. 36, pp. 1167 to 1172
Pergamon Press Ltd., 1980. Printed in Great Britain

NEW CYTOTOXIC DITERPENES FROM *RONDELETIA PANAMENSIS* (RUBIACEAE)[a]

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(*Received in U.S.A.* 11 *June* 1979)

Abstract—From the wood stem and stem bark of the Panamanian plant *Rondeletia panamensis* (Rubiaceae), three novel diterpenes have been isolated. The structure of oxidopanamensin (2) was determined by single crystal X-ray crystallography of the diacetate derivative. Panamensin (4) was correlated with oxidopanamensin (2) by epoxidation under alkali conditions and with rondeletin (6) by hydrogenation to 14,15-dihydrorondeletin (8). Of the three isolates, panamensin (4) and oxidopanamensin (2) were cytotoxic in the KB test system but rondeletin was inactive.

In our continuing search for novel plant anticancer agents it was found that ethanol extracts of the Panamanian plant *Rondeletia panamensis* DC. (Rubiaceae) exhibited cytotoxic activity.[2] No previous phytochemical or folkloric reports on this genus could be found in the literature.

Partition of a methanol extract of the wood stem and stem bark of *R. panamensis* indicated that cytotoxicity remained in the chloroform phase. Through extensive chromatography with concommitant bioassay two cytotoxic compounds, oxidopanamensin and panamensin, were obtained together with a third, closely related but inactive compound, rondeletin.

The similarity of the main features of the proton NMR and UV spectral data of the three isolates suggested that a determination of one of the structures might permit deduction of the remaining structures. Interpretation of the spectral data did not prove fruitful in terms of a unique skeleton and consequently X-ray analysis was carried out. The parent compounds were unsuitable for analysis but crystals of the diacetate of oxidopanamensin were found to be appropriate, and it was this compound which was therefore analyzed.

Oxidopanamensin diacetate crystallized from methanol in the orthorohombic space group $P2_12_12_1$ with the cell dimensions $a = 12.430$, $b = 10.969$, $c = 16.320$.

Final values of the cell dimensions were determined by least-squares treatment of angular measurements on a four-circle diffractometer. For the intensity measurements, reflections were surveyed in the range $\theta \leq 30°$ and 1910 independent reflections with $I > 3\sigma$ (I) were obtained.

The crystal structure was elucidated by direct phasing procedures, using the program MULTAN-76. The approximate atomic coordinates were adjusted by the least-squares program CRYLSQ from the XRAY-72 suite of programs. Four rounds of calculations, with isotropic thermal parameters for the C and O atoms, reduced R to 0.13. After this, a difference synthesis revealed 27 out of the 32 H atoms in the molecule. These atoms were then incorporated in the refinement procedure with isotropic thermal parameters while the C and O atoms were assigned anisotropic parameters. Eight successive rounds of calculations converged at $R = 0.058$.

The atomic co-ordinates for the C and O atoms are listed in Table 1 and the bond lengths, bond angles, and torsion angles are in Tables 2–4. The molecular structure is shown in Fig. 1.

The analysis establishes that the compound has constitution and relative stereochemistry 1.

Ring A has an envelope-like conformation, with atom C (5) at the flap. Ring B has a distorted chair conformation with torsion angles ranging from 41 to 61°; the maximum puckering of the ring is at C_8 and the minimum at C_5. In ring C the departure from ideal chair geometry

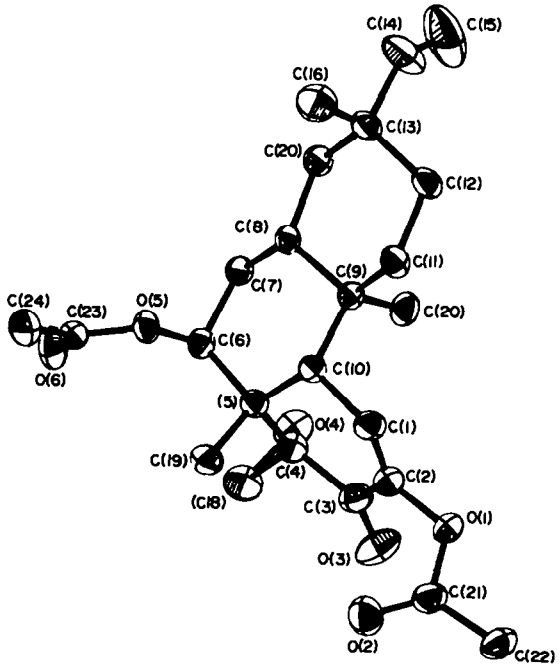


Fig. 1. Molecular structure of oxidopanamensin diacetate

[a]Paper XII in the series "Potential Anticancer Agents", for paper XI see Ref. 1.

Table 1. Atomic co-ordinates (× 10^4), with standard deviations in parentheses

Atom	x	Y	z
O(1)	3418(3)	2397(4)	6745(2)
O(2)	1686(3)	1911(5)	6919(2)
O(3)	3119(4)	0859(3)	5436(3)
O(4)	2204(3)	1576(3)	3983(2)
O(5)	1570(3)	5234(3)	3515(2)
O(6)	0710(3)	4345(4)	2466(2)
C(1)	3185(4)	4052(5)	5837(3)
C(2)	3188(4)	2864(5)	5961(3)
C(3)	3029(4)	1955(5)	5320(3)
C(4)	2792(4)	2452(4)	4465(3)
C(5)	2383(4)	3766(4)	4437(3)
C(6)	2360(4)	4254(4)	3540(3)
C(7)	3430(4)	4773(4)	3230(2)
C(8)	3916(3)	5704(4)	3828(2)
C(9)	4153(3)	5098(4)	4660(2)
C(10)	3046(3)	4620(4)	5006(2)
C(11)	4588(4)	6097(5)	5233(3)
C(12)	5600(4)	6730(5)	4893(3)
C(13)	5422(4)	7285(6)	4030(3)
C(14)	6495(6)	7704(9)	3675(4)
C(15)	7294(6)	7343(15)	3545(6)
C(16)	4706(6)	8406(6)	4057(5)
C(17)	4920(4)	6306(5)	3459(3)
C(18)	3327(5)	1779(5)	3793(3)
C(19)	1209(4)	3701(5)	4750(3)
C(20)	4988(4)	4057(5)	4602(3)
C(21)	2589(5)	1860(5)	7165(3)
C(22)	2989(5)	1283(7)	7939(3)
C(23)	0754(4)	5126(5)	2970(3)
C(24)	-0076(5)	6090(6)	3097(4)

is much less pronounced, the range of torsion angles being 51–58°, and here the smallest pucker is at C_{13}.

In the epoxide group, the C–C bond (1.480 Å) is slightly longer than the C–O bonds (1.440, 1.446 Å) and the C–O–C angle (61.7°) is slightly larger than the O–C–C angles (59.0, 59.4°). Moreover, the C–C(epoxide)–C(epoxide) angles (114.4 and 126.6°) are larger than the corresponding C–C(epoxide)–O(epoxide) angles (111.1 and 116.3°), and the C–C(epoxide)–O(epoxide)–C(epoxide) torsion angles (106.6 and 118.8°) are larger than the

Table 2. Bond lengths (Å), with standard deviations in parentheses

O (1)–C (2)	1.409 (6)	C (5)–C (19)	1.548 (7)
O (1)–C (21)	1.370 (7)	C (6)–C (7)	1.534 (7)
O (2)–C (21)	1.193 (7)	C (7)–C (8)	1.537 (6)
O (3)–C (3)	1.222 (6)	C (8)–C (9)	1.541 (6)
O (4)–C (4)	1.440 (6)	C (8)–C (17)	1.536 (6)
O (4)–C (18)	1.446 (8)	C (9)–C (10)	1.576 (6)
O (5)–C (6)	1.457 (6)	C (9)–C (11)	1.538 (6)
O (5)–C (23)	1.354 (5)	C (9)–C (19)	1.546 (7)
O (6)–C (23)	1.188 (6)	C (11)–C (12)	1.541 (7)
C (1)–C (2)	1.319 (8)	C (12)–C (13)	1.541 (6)
C (1)–C (10)	1.502 (6)	C (13)–C (14)	1.524 (9)
C (2)–C (3)	1.458 (7)	C (13)–C (16)	1.518 (9)
C (3)–C (4)	1.526 (7)	C (13)–C (17)	1.553 (7)
C (4)–C (5)	1.546 (7)	C (14)–C (15)	1.090 (12)
C (4)–C (18)	1.480 (7)	C (21)–C (22)	1.497 (8)
C (5)–C (6)	1.558 (6)	C (23)–C (24)	1.494 (8)
C (5)–C (10)	1.556 (6)		

Table 3. Bond angles (deg.), with standard deviations in parentheses

C (2)-O (1)-C (21)	117.2 (4)	C (9)-C (8)-C (17)	112.1 (3)
C (4)-O (4)-C (18)	61.7 (3)	C (8)-C (9)-C (10)	107.0 (3)
C (6)-O (5)-C (23)	117.3 (4)	C (8)-C (9)-C (11)	107.2 (4)
C (2)-C (1)-C (10)	123.2 (4)	C (8)-C (9)-C (20)	113.1 (3)
C (1)-C (2)-O (1)	119.9 (5)	C (10)-C (9)-C (11)	109.0 (3)
C (3)-C (2)-O (1)	115.5 (5)	C (10)-C (9)-C (20)	111.3 (4)
C (1)-C (2)-C (3)	124.5 (5)	C (11)-C (9)-C (20)	109.1 (4)
C (2)-C (3)-O (3)	123.3 (5)	C (1)-C (10)-C (5)	110.5 (4)
C (4)-C (3)-O (3)	120.7 (5)	C (1)-C (10)-C (9)	111.2 (3)
C (4)-C (3)-C (2)	115.9 (4)	C (5)-C (10)-C (9)	116.7 (3)
C (3)-C (4)-C (5)	115.4 (4)	C (9)-C (11)-C (12)	112.9 (4)
C (3)-C (4)-O (4)	111.1 (4)	C (11)-C (12)-C (13)	112.8 (4)
C (5)-C (4)-O (4)	116.3 (4)	C (12)-C (13)-C (14)	109.8 (4)
O (4)-C (4)-C (18)	59.4 (4)	C (12)-C (13)-C (16)	112.1 (5)
C (3)-C (4)-C (18)	114.4 (4)	C (12)-C (13)-C (17)	109.3 (5)
C (5)-C (4)-C (18)	126.6 (4)	C (14)-C (13)-C (16)	106.3 (6)
C (4)-C (5)-C (6)	110.0 (4)	C (14)-C (13)-C (17)	109.4 (5)
C (4)-C (5)-C (10)	111.9 (4)	C (16)-C (13)-C (17)	109.5 (5)
C (4)-C (5)-C (19)	105.1 (4)	C (13)-C (15)-C (15)	139.6 (12)
C (6)-C (5)-C (10)	111.3 (4)	O (4)-C (18)-C(4)	59.0 (3)
C (6)-C (5)-C (19)	108.0 (4)	C (8)-C (17)-C(13)	112.8 (4)
C (19)-C (5)-C (10)	109.2 (4)	O (1)-C (21)-O (2)	121.3 (5)
C (5)-C (6)-O (5)	107.1 (3)	O (1)-C (21)-C (22)	115.5 (5)
C (7)-C (6)-O (5)	107.5 (4)	O (2)-C (21)-C (22)	128.0 (5)
C (5)-C (6)-C (7)	114.9 (4)	O (5)-C (23)-O (6)	123.5 (5)
C (6)-C (7)-C (8)	112.2 (3)	O (5)-C (23)-C (24)	111.4 (4)
C (7)-C (8)-C (9)	110.4 (4)	O (6)-C (23)-C (24)	125.1 (5)
C (7)-C (8)-C (17)	110.8 (3)		

C–C(epoxide)–C(epoxide)–O(epoxide) torsion angles (100.9 and 101.6°). This pattern of results is a feature of other terpenoid epoxides.[3,4]

With the structure of oxidopanamensin diacetate determined attention refocused on an interpretation of the spectral data of oxidopanamensin (2) and comparison with the data for the other two isolates.

The molecular formula of oxidopanamensin, $C_{20}H_{28}O_4$, had previously suggested a tricyclic diterpene which, from the IR spectrum contained OH (ν_{max} 3480 cm^{-1}) and α,β-unsaturated CO (1680 cm^{-1}) functionalities. In the UV spectrum a maximum was observed at 288 nm which was shifted bathochromically in alkali to 335 nm and hypsochromically on acetylation to 253 nm. Such data are typical for an α-hydroxy-α,β-unsaturated alicylic ketone.

Table 4. Torsion angles (deg.), standard deviations are *ca.* 0.5°

Ring A		Ring C	
C (10)-C (1)-C (2)-C (3)	-1.8	C (17)-C (8)-C (11)	58.3
C (1)-C (2)-C (3)-C (4)	-3.0	C (8)-C (9)-C (11)-C (12)	-57.7
C (2)-C (3)-C (4)-C (5)	-19.7	C (9)-C (11)-C (12)-C (13)	56.2
C (3)-C (4)-C (5)-C (10)	45.0	C (11)-C (12)-C(13)-C (17)	50.6
C (4)-C (5)-C (10)-C (1)	-47.5	C (12)-C (13)-C (17)-C (8)	51.7
C (2)-C (1)-C (10)-C (5)	27.6	C (9) -C (8) -C (17)-C (13)	-57.9

Ring B		Epoxide	
C (10)-C (5)-C (6)-C (7)	40.8	C (3)-C (4)-O (4)-C (17)	-106.6
C (5)-C (6)-C (7)-C (8)	-50.4	C (3)-C (4)-C (18)-O (4)	100.9
C (6)-C (7)-C (8)-C (9)	61.2	C (5)-C (4)-O (4)-C (17)	118.8
C (7)-C (8)-C (9)-C (10)	-60.7	C (5)-C (4)-C (18)-O (4)	-101.6
C (8)-C (9)-C (10)-C (5)	54.3		
C (6)-C (5)-C (10)-C (9)	-44.2		

The NMR spectrum indicated the presence of three quaternary methyl groups (singlets at 0.72, 1.09 and 1.32 ppm) and an alcoholic methine proton at 3.43 ppm shifting in the diacetate derivative, to 4.65 ppm. Three protons showing a characteristic ABX pattern at 4.86, 4.91 and 5.83 ppm could be assigned to vinyl protons at the C-15 and C-16 positions, similar to other diterpenes such as methyl isopimarate (3)[5]. A pair of doublets ($J = 7$ Hz) at 2.52 and 6.31 were attributed to the C_{10} and C_1 protons respectively. A two proton singlet at 3.12 ppm was ascribed to the geminal protons on the epoxide group. These data are in complete agreement with the structure 2 deduced for oxidopanamensin, and permit a comparison to be made with panamensin and rondeletin.

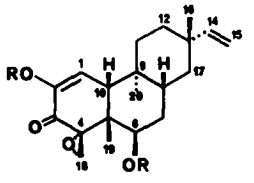
Panamensin (4) was obtained as a pale yellow oil and from the molecular formula ($C_{20}H_{28}O_3$ by high-resolution mass spectrometry) differed from oxidopanamensin (2) by one less oxygen atom. Like 2, panamensin showed both OH (ν_{max} 3450 cm^{-1}) and α,β-unsaturated carbonyl (1660 cm^{-1}) groupings from the IR spectrum, and formed a diacetate 5. Similarly, the UV spectrum showed an α-hydroxy-α,β-unsaturated ketone to be present having λ_{max} 303 nm shifting in alkali to 360 nm and on acetylation to 255 nm. Fundamentally the NMR spectrum of panamensin was quite similar to that of oxidopanamensin, with three methyl singlets at 0.62, 1.09 and 1.23 ppm, an ABX system at 4.84, 4.89 and 5.34 ppm for a vinyl group and a hydroxy methine proton at 4.20 ppm (5.45 ppm in the diacetate 5). Absent from the spectrum was a two proton signal around 3.2 ppm, replaced by two slightly broadened one proton singlets at 5.34 and 6.27 ppm. These data suggested that the epoxide group of 2 was not present in panamensin and that the two downfield singlets could be assigned to the *cis* and *trans* protons respectively on C_{18}.

The small differences in UV λ_{max}, IR (CO ν_{max}) and NMR (δ of C-6 H) could now be explained, in the first and second instances, by an extended chromophoric system, and in the third instance by the C-6 α proton lying in a deshielding area of the C_4–C_8 double bond. Although an AB system ($J = 7$ Hz) was still observed for the C_1 and C_{10} protons at 6.21 and 2.41 ppm respectively suggesting that the A/B ring junction stereochemistry was the same as that in 2, the remaining stereochemical assignments were less sure.

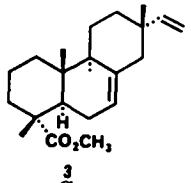
Support for the stereochemistry of panamensin shown in 4 was obtained by treatment of panamensin with alkaline hydrogen peroxide at room temperature to afford oxidopanamensin (2) in approximately 80% isolated yield. The partially synthetic material was identical with the natural material in every respect. Panamensin therefore has the complete structure shown in 4.

Rondeletin (6) was also obtained as a pale yellow oil and the molecular formula was determined to be $C_{20}H_{30}O_3$, an addition of two hydrogens compared with 4. Like 4, rondeletin contained a highly unsaturated carbonyl system (ν_{max} 1660 cm^{-1}) together with a hydroxyl group (absorption at 3420 cm^{-1}). The UV spectrum indicated an α-hydroxy-α,β-unsaturated ketone grouping, but now the λ_{max} at 285 nm (shifting in alkali to 333 nm) was more similar to that of oxidopanamensin (2).

Rondeletin, like 2 and 4 formed a diacetate derivative 7 (λ_{max} 253 nm), thereby accounting for all the O atoms in the molecule. In the NMR spectrum, rondeletin showed three singlet methyl groups at 0.61, 1.36 ppm, an oxymethine proton at 4.11 ppm and a vinyl group (ABX system at 4.88, 4.83 and 5.81 ppm). These data supported the assignment of a skeleton to rondeletin similar to that in panamensin where ring A had been reduced by the addition of two hydrogens with isomerization of the ketoenol system. On this basis structure 6 was proposed for rondeletin, in which the signals at 2.74 and 2.00 ppm could be assigned to the C_1 and C_{10} protons respectively. In addition the small, equal coupling constant of H_{10} with H_1-α and H_1-β indicated this proton to be equatorially disposed to ring A.



1 R = $COCH_3$
2 R = H



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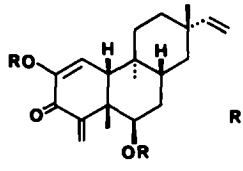
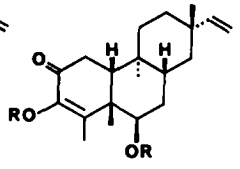
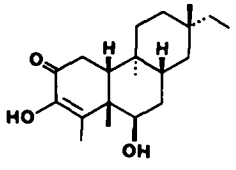


4 R = H
5 R = $COCH_3$



6 R = H
7 R = $COCH_3$



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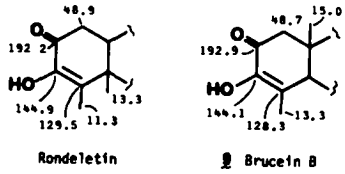
Confirmation of this structure assignment came when panamensin was reduced catalytically. The product was 14,15-dihydrorondeletin (8), identical with a product obtained by reduction of rondeletin under similar conditions. During the reduction of ring A, therefore, isomerization to the fully substituted enolone system occurs.

The assignment of a 3,4-enol-2-one skeleton to ring A of rondeletin is supported by the ^{13}C NMR spectrum which compares well with the corresponding data of brucein B (9) (Fig. 2)[6]. Signals for the vinyl group were

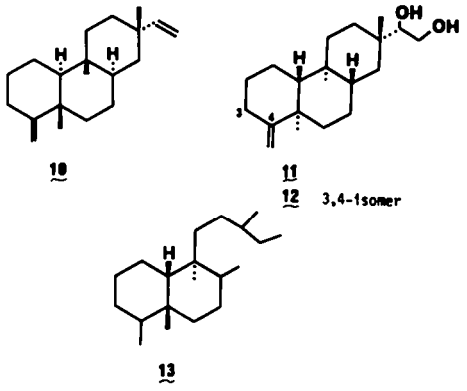


Rondeletin 9 Brucein B

observed at 150.8 ppm (C_{15}) and 108.9 ppm (C_{16}) and for C_6 at 71.0 ppm. Although several other assignments could be made tentatively, lack of data for the other diterpenes and the absence of data on appropriate model compounds preclude discussion in more definitive terms.

Panamensin (4), oxidopanamensin (2) and rondeletin

(6) are the most highly oxygenated members of diterpenoids in the dolabradiene (10)[7] series of which erythroxydiol Y (11) and erythroxydiol Z (12) are two further representatives.[8]



None of these diterpenes, however, has an A/B *cis* ring junction. Several compounds in the *cis*-clerodane (13) series are known,[9,10] but by definition these lack the 13,14 σ-bond. The isolates described in this paper may therefore be regarded as a new group of diterpenes, and are numbered based on a biogenesis from the clerodane nucleus.

Cytotoxic evaluation. Each of the isolates was evaluated for cytotoxicity in the Eagle's carcinoma of the nasopharynx (KB) test system according to established protocols.[2] Rondoletin (6) was inactive but panamensin (NSC-282703) (4) and oxidopanamensin (NSC-282704) (2) were cytotoxic at 2.6 and 1.9 μg/ml respectively.

What is fascinating about these structures is the similarity of the A ring to the A ring of certain compounds in the quassinoid series which display cytotoxicity and in some instances antitumor activity.[11-14]

EXPERIMENTAL

M.ps were obtained by means of the Kofler hot plate apparatus and are uncorrected. UV spectra were obtained in MeOH solution with a Beckmann Model DB-G, grating spectrophotometer. IR spectra were determined with a Beckmann Model IR 18-A, spectrophotometer. Proton NMR spectra were recorded in $CDCl_3$ soln with a Varian model T-60A instrument, operating at 60 MHz with a Nicolet Model TT-7 Fourier Transform attachment. TMS was used as an internal standard and chemical shifts are reported in δ (ppm) values. Low resolution mass spectra were obtained with a Hitachi Perkin Elmer, Model RMU-6D, single focusing spectrometer operating at 270 ev. High resolution mass spectra were obtained by Dr. F. I. Carroll, Research Triangle Institute, North Carolina, using an AEI MS 902 double focusing instrument. TLC data are for Si gel plates (Merck) eluting with $CHCl_3$:MeOH (20:1).

Plant collection. The wood stem and stem bark of *Rondeletia panamensis* DC. (Rubiaceae) were collected in Panama in July of 1975 and authenticated by botanists, at the Medicinal Plant Resources Laboratory of the United States Department of Agriculture, Beltsville, Md. An herbarium specimen is deposited at the Herbarium of the National Arboretum, Agricultural Research Service, U.S.D.A.; Washington, D.C.

Extraction and isolation. The air-dried and milled stem bark material (9 kg) was exhaustively extracted with MeOH and the MeOH extract evaporated *in vacuo* to a dark brown gum (330 g). To the residue dissolved in MeOH (500 ml) was added water (3 l) and the mixture extracted successively with $CHCl_3$ (5 l) and EtOAc (5 l). The combined organic phases were dried (Na_2SO_4), filtered and evaporated *in vacuo* to afford 67 g of residue. Cytotoxicity in the KB test system was observed in this extract (ED_{50} 3.0 μg/ml) but not in the lyophilized aqueous phase.

The total organic extract was chromatographed on silica gel (Merck PF-254, 800 g) eluting initially with C_6H_6 and successively by gradient elution with $CHCl_3$ and finally MeOH. Panamensin (4) and rondeletin (6), were eluted as a mixture with C_6H_6:MeOH (40:1) and were isolated by chromatography on Florisil, eluting with mixtures of petroleum ether-ether. Oxidopanamensin (2) was eluted with C_6H_6:MeOH (30:1) and was purified on Florisil eluting with $CHCl_3$. Only fractions containing panamensin (4) and oxidopanamensin (2) were active in the KB test system.

Oxidopanamensin (2). The diterpene was obtained as fine microcrystals from petroleum ether-ether (yield 50 mg 0.0005%) having the following physical data; m.p. 210–211°; ν_{max} (KBr) 3480, 2920 and 1680 cm^{-1}; λ_{max} (MeOH) 288 nm (ϵ 15,000), λ_{max} (MeOH + NaOH) 335 nm; δ ($CDCl_3$) 0.72 (s, 3 H, 20-CH_3), 1.09 (s, 3 H, 16-CH_3), 1.28 (s, 3 H, 19-CH_3), 2.52 (d, J = 7.0 Hz, 1 H, C_{10}–H), 3.12 (s, 2 H, C_{18}–H_2), 3.43 (m, 1 H, C_6–H), 4.86 (dd, J = 10.1, 1.6 Hz, 1 H, C_{15}–H), 4.91 (dd, J = 17.5, 1.6 Hz, 1 H, C_{15}–H), 5.83 (dd, J = 10.1, 17.5 Hz, 1 H, C_{14}–H), 6.31 (d, J = 7.0 Hz, 1 H, C_1–H); MS *m/e* 332 (M^+, 3%, Found 332.1981; calcd. for $C_{20}H_{28}O_4$, 332.1980), 314 (M^+-18, 1), 179 (13), 161 (40) and 136 (100); R_f 0.40.

Oxidopanamensin-2,6-diacetate (1). Oxidopanamensin (2, 30 mg) was acetylated with acetic anhydride:pyridine (1 ml, 1:1) at room temp. over night. Work up in the standard manner afforded an acetate (1, 28 mg) as prisms from MeOH having the following physical properties: m.p. 184–186°; $[\alpha]_D^{26}$ + 79 (c 1.0, $CHCl_3$); ν_{max} (KBr) 2930, 1770, 1740 and 1700 cm^{-1}; λ_{max} (MeOH) 253 nm; δ ($CDCl_3$) 0.86 (s, 3 H, 20-CH_3), 1.10 (s, 3 H, 16-CH_3), 1.28 (s, 3 H, 19-CH_3), 2.09 (s, 3 H, 6-$OCOCH_3$), 2.24 (s, 3 H, 2-$OCOCH_3$), 2.59 (d, J = 7.0 Hz, 1 H, C_{10}–H), 3.12 (s, 2 H, C_{18}–H_2), 4.65 (m, 1 H, C_6–H), 4.85 (dd, J = 10.1, 1.6 Hz, 1 H, C_{15}–H), 4.90 (dd, J = 17.5, 1.6 Hz, 1 H, C_{15}–H), 5.81 (dd, J = 10.1, 17.5 Hz, 1 H, C_{14}–H), 6.71 (d, J = 7.0 Hz, 1 H, C_1–H); MS *m/e* 416 (M^+, 2%), 374 (M^+-42, 4), 356 (M^+-60, 7), 326 (9), 314 (M^+-60-42, 7), 296 (M^+-60-60, 8), 284 (8), 196 (17), 179 (7), 161 (9) and 136 (100).

Crystal data of 1. $C_{24}H_{32}O_6$, M = 416.5. Orthorhombic, a = 12.430 (2), b = 10.969 (2), c = 16.320(2) Å, U = 2225 Å,[3] Z = 4, D_m = 1.25, D_c = 1.243 g cm^{-3}, $F(000)$ = 896, space group $P2_12_12_1$ (D_2^4). Mo-K_α radiation, λ = 0.7107 Å, μ(Mo-K_α) = 0.95 cm^{-1}.

Panamensin (4). The compound was obtained as a yellow oil (50 mg, 0.0005%) having the following physical data: ν_{max} (thin film) 3450, 2930, 1660, 1600 and 755 cm^{-1}; λ_{max} (MeOH) 303 nm (ϵ 9200), λ_{max} (MeOH + NaOH) 360 nm; δ ($CDCl_3$) 0.62 (s, 3 H, 20-CH_3), 1.09 (s, 3 H, 16-CH_3), 1.23 (s, 3 H, 19-CH_3), 2.41 (d, J = 7.0 Hz, 1 H, C_{10}–H), 4.20 (m, 1 H, C_6–H), 4.84 (dd, J = 10.1, 1.6 Hz, 1 H, C_{15}–H), 4.89 (dd, J = 17.5, 1.6 Hz, 1 H, C_{15}–H), 5.34 (s, 1 H, C_{18}–H), 5.82 (dd, J = 10.1, 17.5 Hz, 1 H, C_{14}–H), 6.21 (d, J = 7.0 Hz, 1 H, C_1–H), 6.27 (s, 1 H, C_{18}–H); MS *m/e* 316 (M^+, 9%, Found 316.2031; calcd. for $C_{20}H_{28}O_3$, 316.2037), 298 (11), 180 (17), 162 (27) and 139 (100); R_f 0.58.

Panamensin-2,6-diacetate (5). Panamensin (4, 20 mg) was treated with acetic anhydride:pyridine (1 ml, 1:1) at room temperature overnight. Work-up in the usual way[12] afforded an acetate (5, 16 mg) as prisms from MeOH having the following physical properties: m.p. 141–143°; $[\alpha]_D^{26}$ + 61.1 (c 0.9, $CHCl_3$); ν_{max} (KBr) 2930, 1765, 1740, 1685 and 1610 cm^{-1}; λ_{max} (MeOH) 255 nm; δ 0.74 (s, 3 H, 20-CH_3), 1.09 (s, 3 H, 16-CH_3), 1.20 (s, 3 H, 19-CH_3), 2.13 (s, 3 H, $OCOCH_3$), 2.26 (s, 3 H, $OCOCH_3$), 2.47 (d, J = 7.0 Hz, 1 H, C_{10}–H), 4.85 (dd, J = 10.1, 1.6 Hz, 1 H, C_{15}–H), 4.88 (dd, J = 17.5, 1.6 Hz, 1 Hz, 1 H, C_{15}–H), 5.45 (m, 1 H, C_6–H), 5.45 (s, 1 H, C_{18}–H), 5.81 (dd, J = 10.1, 17.5 Hz, 1 H, C_{14}–H), 6.29 (s, 1 H, C_{18}–H), 6.60 (d, J = 7.0 Hz, 1 H, C_1–H); MS *m/e* 400 (M^+, 7%), 368 (M^+-42, 7), 340 (M^+-60, 14), 298 (M^+-60-42, 26), 280 (M^+-60-60, 6), 180 (100), 161 (44), 150 (24) and 137 (57).

Partial synthesis of oxidopanamensin (2). Panamensin (4, 5 mg) was dissolved in EtOH (0.2 ml) and 0.5 N NaOH (0.5 ml) and H_2O_2 (1 ml) were added. The mixture was stirred at room temp for 1.5 hr and then extracted with $CHCl_3$ (2 ml × 3). The $CHCl_3$ extract afforded oxidopanamensin (2, 4 mg) after purification by preparative tlc on silica gel preparative layers. The product was identical (m.p., IR, UV, NMR, MS and tlc) with natural 2.

Rondeletin (6). The material was obtained as a yellow oil (100 mg, 0.001%) having the following physical properties: $[\alpha]_D^{26}+45.4$ (*c* 1.6, $CHCl_3$); ν_{max} (thin film) 3420, 2930, 1660 and 1635 cm^{-1}; λ_{max} (MeOH) 285 nm (ϵ 7000), λ_{max} (MeOH + NaOH) 333 nm; δ ($CDCl_3$) 0.61 (s, 3 H, 20-CH_3), 1.06 (s, 3 H, 16-CH_3), 1.36 (s, 3 H, 19-CH_3), 1.87 (s, 3 H, 18-CH_3), 2.00 (t, J = 3.8 Hz, 1 H, C_{10}–H), 2.74 (d, J = 3.8 Hz, 2 H, C_1–H_2), 4.11 (m, 1 H, C_6–H), 4.83 (dd, J = 10.1, 1.6 Hz, 1 H, C_{15}–H), 4.88 (dd, J = 17.7, 1.6 Hz, 1 H, C_{15}–H), 5.81 (dd, J = 10.1, 17.7 Hz, 1 H, C_{14}–H); MS *m/e* 318 (M^+, 16%, Found 318.2192; Calcd. for $C_{20}H_{30}O_3$, 318.2187), 303 (M^+-15, 4), 300 (M^+-18, 3), 285 (M^+-15-18, 2), 260 (3), 164 (4), 139 (100) and 138 (73); R_f 0.53.

Rondeletin-3,6-diacetate (7). Rondeletin (6, 20 mg) was treated with acetic anhydriede:pyridine (1 ml, 1:1) at room temp overnight. Work-up in the usual way[12] afforded 7 (18 mg) as prisms from MeOH having the following physical data: m.p. 175–177°, ν_{max} (KBr) 2920, 1755, 1730, 1670 and 1620 cm^{-1}, λ_{max} (MeOH) 253 nm; δ ($CDCl_3$) 0.75 (s, 3 H, 20-CH_3), 1.05 (s, 3 H, 16-CH_3), 1.33 (s, 3 H, 19-CH_3), 1.90 (s, 3 H, 18-CH_3), 2.13 (s, 3 H, $OCOCH_3$), 2.24 (s, 3 H, $OCOCH_3$), 2.76 (d, J = 3.9 Hz, 2 H, C_1–H_2), 4.85 (dd, J = 10.1, 1.6 Hz, 1 H, C_{15}–H), 4.88 (dd, J = 17.8, 1.6 Hz, 1 H, C_{15}–H), 5.39 (m, 1 H, C_6–H), 5.81 (dd, J = 10.1, 17.8 Hz, 1 H, C_{14}–H); MS *m/e* 402 (M^+, 10%), 360 (M^+-42, 100), 318 (M^+-42-42, 18), 300 (M^+-42-60, 35), 285 (M^+-42-60-15, 28), 201 (21), 149 (55), 139 (43) and 138 (41).

Hydrogenation of panamensin (4). Panamensin (4, 5 mg) was hydrogenated with PtO_2 (1 mg) in MeOH (0.5 ml) for 2 hr at 1 atm pressure of H_2. Evaporation, filtration of the organic soluble material through celite and purification by preparative tlc on silica gel afforded a tetrahydro derivative as an oil identified as 8 (3 mg) having the following physical properties: $[\alpha]_D^{26}+35.3$ (*c* 1.3, $CHCl_3$); ν_{max} (thin film) 3440, 2920, 1665 and 1635 cm^{-1}; λ_{max} (MeOH) 285 nm; δ ($CDCl_3$) 0.59 (s, 3 H, 20-CH_3), 0.90 (s, 3 H, 16-CH_3), 1.35 (s, 3 H, 19-CH_3), 1.86 (s, 3 H, 18-CH_3), 1.86 (s, 3 H, 18-CH_3), 1.96 (t, J = 4.0 Hz, 1 H, C_{10}–H), 2.74 (d, J = 4.0 Hz, 2 H, 2 H, C_1–H_2), 4.10 (m, 1 H, C_6–H); MS *m/e* 320 (M^+, 13%), 305 (M^+-15, 5), 302 (M^+-18, 3), 181 (4), 164 (8), 139 (100) and 138 (89).

Reduction of rondeletin (6). Rondeletin (6, 10 mg) was hydrogenated with PtO_2 (3 mg) in MeOH (1 ml) for 2 hr under 1 atm pressure of H_2. Work-up in the usual way and purification by preparative tlc on silica gel afforded a dihydro derivative identified as 8 (7 mg) as an oil. The product was identical in all respects (IR, UV, NMR, MS and tlc) with the product from the reduction of 4.

Acknowledgements—The authors would like to thank the staff of the Medicinal Plant Resources Laboratory, Agricultural Research Service, U.S.D.A., Beltsville, Md., which is funded by the National Cancer Institute, for the provision of plant material and Dr. F. I. Carroll, Research Triangle Institute, North Carolina, for the provision of high resolution mass spectral data. The work at the University of Illinois was carried out under contract NCI CM-67090 with the Natural Products Branch, Developmental Therapeutics Program, National Cancer Institute.

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