Journal of Natural Products
Vol. 52, No. 4, pp. 822-828, Jul-Aug 1989

4-HYDROXY-25-DESOXYNEOROLLINICIN, A NEW BISTETRAHYDROFURANOID ACETOGENIN FROM *ROLLINIA PAPILIONELLA*

MILTON J. ABREO and ALBERT T. SNEDEN*

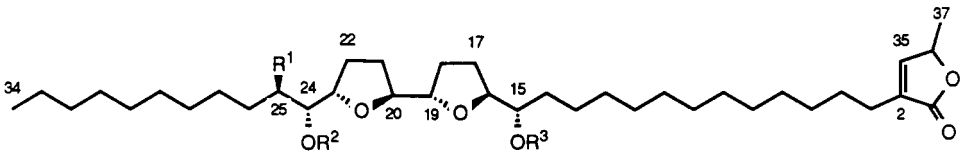
Department of Chemistry, Virginia Commonwealth University, Richmond, Virginia 23284-2006

ABSTRACT.—4-Hydroxy-25-desoxyneorollinicin [**2**], a new linear bistetrahydrofuranoid acetogenin, has been isolated from *Rollinia papilionella*. The structure was elucidated from high resolution mass spectral and nmr data. The relative stereochemistry of six of the eight stereogenic centers was established by analysis of the ^{1}H-nmr spectra of the triacetate of **2**. In addition, the relative stereochemistry of seven of the eight stereogenic centers of rollinicin [**1**], a previously reported bistetrahydrofuranoid acetogenin, was established by analysis of the ^{1}H nmr spectra of the triacetate of **1** and the mass spectra of the tristrimethylsilyl ether of **1**.

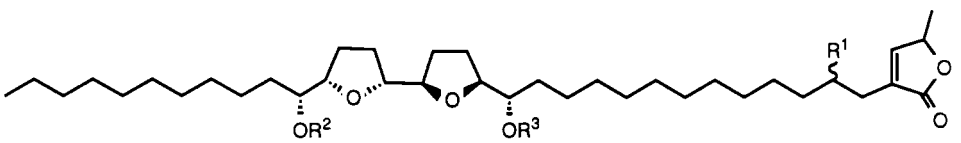
Over the past few years, investigations of several genera of the Annonaceae have resulted in the characterization of twelve novel linear acetogenins containing one or two tetrahydrofuran rings, a terminal γ-lactone, and several hydroxyl moieties (1–10). Of the acetogenins reported to date, those with two adjacent tetrahydrofuran rings contain 34 carbon atoms in the main chain (1–7, 9), while those with only one tetrahydrofuran ring have 32 carbon atoms in the main chain (8, 10). With two exceptions, cherimoline and dihydrocherimoline (4), the tetrahydrofuran rings are located between C-16 or C-14 and subsequent carbons and are flanked by oxygenated carbons. All—except 14-hydroxy-25-desoxyrollinicin, which was evidently not tested (7)—demonstrate significant biological activity against a variety of bioassay systems.

Previous activity-guided fractionation of EtOH extracts of the roots of *Rollinia papilionella* Diels. led to the isolation of rollinicin [**1**], isorollinicin, and rollinone (2,3). However, the isolation procedure was tedious and only small quantities of the active principles were obtained. In an effort to obtain additional amounts of these acetogenins for additional biological testing, a new isolation procedure was developed. The EtOH extract of *R. papilionella* was concentrated and subjected to a relatively common partitioning sequence between $CHCl_3$ and H_2O, petroleum ether and 90% MeOH, and CH_2Cl_2 and 70% MeOH. The CH_2Cl_2 layer was washed with 1 N HCl to remove oxoaporphine alkaloids (11) that had interfered with previous separations of the acetogenins. The CH_2Cl_2 layer was concentrated and applied in 500-mg aliquots to a low pressure liquid chromatographic column of Sephadex LH-20. The column was eluted with CH_2Cl_2 and, as expected in this size exclusion chromatographic separation, the acetogenins were concentrated in the first two fractions. Final separation and purification of the acetogenins from the first fraction was achieved by three cc separations and one trituration step; no preparative tlc was required. In particular, this procedure gave additional quantities of rollinicin [**1**] as well as a new acetogenin **2**.

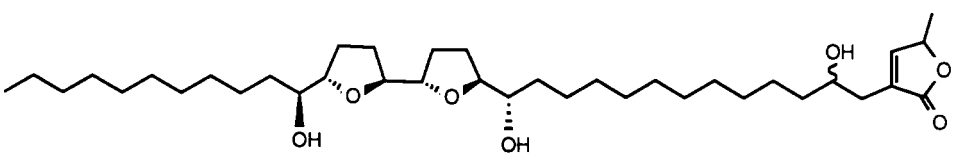
The new acetogenin appeared to have many of the same characteristics as rollinicin [**1**] (2). A white, waxy solid, the new acetogenin melted at approximately 25°. The ir spectrum established the presence of hydroxyl moieties (3478 cm^{-1}) and a lactone (1763 cm^{-1}) as well as a high degree of aliphatic character. The fab hrms established the molecular formula as $C_{37}H_{66}O_7$ (*m/z* 629.4965 $[M + Li]^+$), identical to that of rollinicin (1). Ions at *m/z* 517 (loss of the lactone + C-3), *m/z* 345 (loss of C-24–C-34 from *m/z* 517), *m/z* 317 (loss of C-4–C-15 from *m/z* 517), and *m/z* 147 (C-16–C-23 + Li) indicated that a bistetrahydrofuran moiety was located between C-16 and C-23 and that two hydroxyl groups were located between C-3 and C-15. Acetylation of the new acetogenin gave a triacetate **3**, indicating the presence of three hydroxyl groups.



	R^1	R^2	R^3
1	OH	H	H
6	H	Ac	H
7	OAc	Ac	Ac
8	H	Ac	Ac
9	OTMS	TMS	TMS



	R^1	R^2	R^3
2	OH	H	H
3	OAc	Ac	Ac
5	OH	H	H



4

The ^{1}H- and ^{13}C-nmr spectra of the new acetogenin were very similar to those of rollinicin [**1**] and served to establish the carbon backbone and placement of functional groups. In the ^{1}H-nmr spectrum of **2**, the α,β-unsaturated-γ-lactone was clearly evident from resonances at δ 7.2 (d, H-35), δ 5.06 (br q, H-36), and δ 1.43 (d, H_3-37). A distorted triplet at δ 0.88 (H_3-34) and a broad resonance at δ 1.25 indicated the long alkyl chain present in this class of acetogenins. The protons on carbons bearing oxygens were seen as broad resonances at δ 3.41 (1H, H-15) and δ 3.8–3.9 (6H). This was different from the spectrum of rollinicin [**1**], which exhibited an additional broad one-proton resonance at δ 3.6 (H-25) and only five protons under the δ 3.8–3.9 envelope.

One other major difference was noted between the ^{1}H-nmr spectra of the new acetogenin **2** and rollinicin [**1**]. In the spectrum of rollinicin [**1**], the H_2-3 resonance appeared as a broad triplet at δ 2.0; in the spectrum of the new acetogenin, the two C-3 protons appeared as two distinct, slightly broadened doublets of doublets at δ 2.40 and δ 2.53. This indicated that the two protons were not in chemically equivalent environments and suggested the presence of a substituent at C-4. The most likely substituent was a hydroxyl group at C-4 as found in asimicin [**4**] (6) and rolliniastatin I [**5**] (9). This was confirmed by analysis of the COSY spectra of the new acetogenin **2** and its triacetate **3**. In these spectra, the C-3 protons were seen to exhibit allylic coupling to the C-35 proton, confirming their assignment. In the spectrum of the new acetogenin, the C-3 protons were also found to couple to a proton buried in the δ 3.8–3.9 envelope, i.e., to a proton on an oxygen-bearing carbon. In the spectrum of the triacetate **3**, the relationship between H_2-3 and H-4 was more clear. Resonances for the protons on acetoxy-bearing carbons shifted downfield, two as a multiplet at δ 4.91 and one as a multiplet at δ 5.10. The latter resonance was coupled to the H_2-3 multiplet (the two distinct dou-

TABLE 1. ^{1}H-nmr Chemical Shifts in δ for Compounds **2**, **3**, and **7**. Coupling constants are in parentheses.

Proton	Compound		
	2	**3**	**7**
H-3a	2.40 dd (8, 15)	2.54 m	2.26 br t (7)
H-3b	2.53 ddd (3, 15, 1.5)	2.54 m	2.26 br t (7)
H-4	3.88 m	5.10 ddt (7, 7.5, 2)	1.5 m
H-5	1.5 m	1.5 m	1.25 m
H-6–13	1.25 m	1.25 m	1.25 m
H-14	1.5 m	1.5 m	1.5 m
H-15	3.41 m	4.91 m	4.70–5.0 m
H-16	3.80–3.92 m	3.95 m	3.98 m
H-17,18	1.7–2.0 m	1.7–2.0 m	1.7–2.0 m
H-19,20	3.80–3.92 m	3.86 m	3.89 m
H-21,22	1.7–2.0 m	1.7–2.0 m	1.7–2.0 m
H-23	3.80–3.92 m	3.95 m	3.98 m
H-24	3.80–3.92 m	4.91 m	4.70–5.0 m
H-25	1.5 m	1.5 m	4.70–5.0 m
H-26	1.25 m	1.25 m	1.5 m
H-27–33	1.25 m	1.25 m	1.25 m
H-34	0.88 t (6.8)	0.88 t (6.8)	0.88 t (6.8)
H-35	7.20 br s	7.08 br s	6.99 d (1.5)
H-36	5.06 q (6.8)	5.01 dq (6.8, 1.2)	5.01 dq (6.8, 1.5)
H-37	1.43 d (6.8)	1.40 d (6.8)	1.40 d (6.8)
OAc	—	2.026	2.033
OAc	—	2.050	2.052
OAc	—	2.073	2.080

blets of doublets collapsed to a multiplet in the spectrum of **3**) at δ 2.54, confirming the presence of a hydroxyl group on C-4 in **2**.

The COSY spectrum of **3** also served to locate the remaining two hydroxyl groups at C-15 and C-24. The two-proton multiplet at δ 4.91 was coupled to a two-proton multiplet due to the C-16 and C-23 protons at δ 3.95, which was coupled in turn to a multiplet at δ 1.7–2.0 (C-17, C-18, C-21, and C-22 protons). This defined the position of the remaining two hydroxyl groups as adjacent to the bistetrahydrofuran moiety as seen in all the previous acetogenins of this class. The multiplet at δ 1.7–2.0 was also coupled to a two-proton multiplet at δ 3.86 due to the C-19 and C-20 protons.

These data served to establish the backbone and functional groups of the new acetogenin as **2**, analogous to the structures of both asimicin [**4**] and rolliniastatin I [**5**]. Asimicin [**4**] and rolliniastatin I [**5**] have previously been shown to be diastereomers by comparison of their nmr data (9). Comparison of the ^{1}H- and ^{13}C-nmr data for **2** with the reported data for **4** (6) clearly established that they were also diastereomers. In the ^{1}H-nmr spectrum of **4**, the resonances for H-15 and H-24 appeared as a single, broad resonance at δ 3.37. In the spectrum of **2** only H-15 appeared at δ 3.39; H-24 appeared at δ 3.80–3.92. In the ^{13}C-nmr spectrum of **4**, the six oxygen-bearing carbons, C-15, C-16, C-19, C-20, C-23, and C-24, were represented by only three resonances at 74.0, 81.8, and 83.1 ppm, suggesting a highly symmetrical structure. In the spectrum of **2**, these six carbons appeared as six distinct resonances at 71.88, 73.95, 80.95, 81.08, 82.89, and 83.0 ppm, suggesting a stereochemically unsymmetrical structure. Thus, **4** and **2** must be diastereomers.

The relationship between **2** and rolliniastatin I [**5**] was less distinct, but also diastereomeric. Comparison of the ^{1}H-nmr data of **2** with that of **5** (9) showed very small

TABLE 2. ^{13}C-nmr Chemical Shifts (ppm) for Compound **2**.[a]

Carbon	ppm	Carbon	ppm
C-1	174.4 s	C-21	28.4 t[d]
C-2	131.3 s	C-22	28.7 t[d]
C-3	33.3 t	C-23	82.89 d[c]
C-4	69.9 d	C-24	71.88 d
C-5	37.4 t	C-25	34.19 t[b]
C-14	32.8 t[b]	C-32	31.84 t
C-15	73.95 d	C-33	22.61 t
C-16	83.0 d[c]	C-34	14.04 q
C-17	23.72 t[d]	C-35	151.65 d
C-18	27.86 t[d]	C-36	77.87 d
C-190	81.08 d[e]	C-37	19.05 q
C-20	80.95 d[e]	C-6–13, 26–31	25.5,25.7,26.96, 29.3,29.5,29.55, 29.6,29.6 all t

[a]Multiplicities were determined by APT and off-resonance decoupling experiments, and assignments were made from a HETCOR experiment.

[b–e]Values with the same superscript may be interchanged.

differences in the chemical shifts of several protons; these could be attributed to experimental differences. However, comparison of the ^{13}C-nmr spectra clearly established a difference between the two compounds. As noted above, **2** showed six distinct resonances for the oxygenated carbons of the bistetrahydrofuran and adjacent hydroxyl groups, whereas only five resonances were reported for **5** (9). In addition, a resonance at 23.7 ppm in the spectrum of **2** is not found in either the spectrum of **5** or the spectrum of asimicin [**4**]. This resonance was assigned to one of the methylene carbons of a tetrahydrofuran ring via a HETCOR experiment. Thus, there were sufficient differences between the spectra of **2** and **5** to establish their diastereomeric relationship. Finally, comparison of **2** and **5** by tlc and mixed tlc showed them to be different compounds after several developments.

Unfortunately, none of the derivatives prepared from **2** gave a crystalline derivative. Therefore, to establish the relative stereochemistry of the bistetrahydrofuran moiety and adjacent hydroxyl groups in **2**, the ^{1}H nmr correlation method of Hoye and Suhadolnik (12) was used. This method examines the chemical shifts of selected protons in the high field ^{1}H-nmr spectra of the peracetate derivatives of these acetogenins and was used to establish the relative configuration of the stereogenic centers other than C-36 in uvaricin [**6**] (12), the first member of this class of acetogenins (1). In this analysis, an acetate singlet at δ 2.051 $\pm$ 0.007 ppm defines the C-15–C-16 or C-23–C-24 stereochemical relationship as erythro. An acetate singlet at δ 2.07 $\pm$ 0.006 defines this relationship as threo. The acetate singlets considered for this analysis must be clearly assignable to acetates on C-15 and C-24.

In addition, if the two tetrahydrofuran rings have opposite stereochemistry, i.e., if one ring is trans and the other is cis (relative to the main chain), then H-16 and H-23 will have widely different chemical shifts. If both rings have the same stereochemistry, i.e., both are cis or both are trans, then H-16 and H-23 will have virtually identical chemical shifts. Once these relationships are determined, comparison of the chemical shifts for the protons on C-15, C-16, C-19, C-20, C-23, and C-24 with the data for the analogous protons of the twelve diastereomeric model compounds reported by Hoye and Suhadolnik (12) allows establishment of the relative stereochemistry of these stereogenic centers with a great deal of confidence. As this manuscript was being prepared, Hoye and Zhuang (13) extended this analysis to asimicin [**4**] and rolliniastatin I

[**5**], and the analysis was particularly verified by their obtaining the same relative stereochemistry for **5** as defined from the X-ray diffraction study.

This analysis was applied to the 300 MHz ^{1}H-nmr spectra of **3**. Proton assignments and relationships were determined by examination of the COSY spectra. The presence of two distinct acetate singlets, at δ 2.05 and δ 2.073, indicated that there was one erythro and one threo relationship between a tetrahydrofuran ring and its adjacent acetate-bearing carbon. The identical chemical shift, δ 3.95, for H-16 and H-23 established that the two tetrahydrofuran rings were either both cis or both trans. Comparison of the chemical shifts for the protons in question with the data for the twelve model diastereomers in Hoye and Suhadolnik (12) indicated the best match was with those diastereomers having the cis-threo-cis relationship between the two tetrahydrofuran rings. This was the same relationship found in rolliniastatin I [**5**], where the relative stereochemistry was determined by a crystal structure (9). This determination combined with the close similarity of the ^{13}C-nmr chemical shifts for the oxygenated carbons in **2** and **5** led to the assignment of the relative stereochemistry as shown in **2**, i.e., erythro-cis-threo-cis-threo moving from C-24 to C-15. [It should be emphasized that this nmr experiment cannot distinguish between the erythro-cis-threo-cis-threo relative stereochemistry and the threo-cis-threo-cis-erythro relative stereochemistry (moving from C-24 to C-15). This particular assignment was made based upon the strong similarities between the ^{1}H- and ^{13}C-nmr spectra of **2** and **5**. The relative stereochemistry of **5** was determined through a crystal structure, and the relative stereochemistry of **2** was tentatively assigned as identical to that of **5**.] This is diastereomeric with the relative stereochemistry of rollinicin [**1**], as will be shown below, and **2** has been given the name 4-hydroxy-25-desoxyneorollinicin to emphasize this difference. The difference between **2** and **5** must therefore be found in the stereochemistry at C-4 or C-36. The relative stereochemistry of these two sites has not yet been established for **2**.

The same analysis was applied to the ^{1}H-nmr spectra of rollinicin triacetate [**7**] (2). Again, assignments were confirmed through analysis of the COSY spectra. Two separate acetate singlets, at δ 2.052 and δ 2.08, established one erythro and one threo relationship as in **2**. The H-16 and H-23 protons both resonated at the same chemical shift, δ 3.98, indicating that both tetrahydrofuran rings had the same stereochemistry. Comparison of the data for the six stereogenic centers in question with the analogous data in Hoye and Suhadolnik (12) indicated that the best match was a trans-threo-trans relationship between the two tetrahydrofuran rings. This relationship is the same as found in uvaricin [**6**], and the similarity of the ^{1}H-nmr data between the critical resonances for **7** and uvaricin acetate [**8**] (12) led to a tentative assignment of the relative stereochemistry as erythro-trans-threo-trans-threo for **1** from C-24 through C-15. (It is recognized that this assignment is based strictly upon nmr comparisons to **8** and could instead be threo-trans-threo-trans-erythro.)

The relationship between C-24 and C-25 in rollinicin [**1**] was determined to be erythro by analysis of the ci mass spectrum of the tristrimethylsilyl ether **9** of rollinicin prepared as in Dabrah and Sneden (2). In 1978, Murata *et al.* (14) established that the position and stereochemistry of double bonds in unsaturated fatty acids could be determined by analysis of the cims of the pertrimethylsilyl ethers of diols or tetraols prepared by stereospecific oxidation of the double bonds. In particular, if the MH − 90 − 72 $[MH - Me_3SiOH - Me_3Si]^+$ ion were much more intense than the MH − 90 − 90 $[MH - Me_3SiOH - Me_3SiOH]^+$ ion in the spectrum of a bistrimethylsilyl ether derivative of the fatty acid, the relationship of the diol was erythro. In the cims of the tristrimethylsilyl ether **9** of rollinicin, the MH − 90 − 72 ion (*m/z* 677) was twice as intense as the MH − 90 − 90 ion (*m/z* 659). In addition, the ions resulting after loss of the

third trimethylsilyl ether, MH − 180 − 72 (*m/z* 587) and MH − 180 − 90 (*m/z* 569), showed this same relationship. Thus, the conclusion from these data was that the C-24–C-25 relationship in rollinicin [**1**] is indeed erythro, and the overall relative stereochemistry of **1**, except for C-36, is erythro-erythro-trans-threo-trans-threo or erythro-threo-trans-threo-trans-erythro.

The isolation from the same plant of two related acetogenins with a diastereomeric relationship between the bistetrahydrofuran moieties is not surprising if these compounds are biogenetically derived from triepoxidation of a triene intermediate followed by a zipper-like epoxide ring opening and closure to the subsequent epoxide to form the bistetrahydrofuran and adjacent hydroxyl groups. Interestingly, a retrosynthetic analysis of both rollinicin [**1**] and 4-hydroxy-25-desoxyneorollinicin [**2**] with the proposed stereochemistries shows that both could be derived from a common triene, i.e., a derivative of tetratriaconta-(15*Z*),(19*Z*),(23*E*)-trienoic acid. If this intermediate is visualized in a standard staggered conformation, then epoxidation of all three double bonds from the same face followed by ring opening and closure would give the compounds with the relative stereochemistry proposed for **2**. If the (19*Z*) double bond was epoxidized from the face opposite to the face from which the (15*Z*) and (23*E*) double bonds were epoxidized, then the relative stereochemistry postulated for rollinicin [**1**] would result from the zipper reaction. One question remains to be answered: Will all the bistetrahydrofuranoid acetogenins from *R. papilionella* have stereochemistry that could derive from a common triene or will other compounds have different precursors? Obviously those from other plants, e.g., asimicin [**4**], can have different precursors.

Rollinicin [**1**] was shown previously to be cytotoxic against the P388 lymphocytic leukemia in vitro ($ED_{50} = 2.9 \times 10^{-8}$ μg/ml) (2). 4-Hydroxy-25-desoxyneorollinicin [**2**] was found to be cytotoxic (in vitro) against the A-549 human lung carcinoma ($ED_{50} < 10^{-3}$ μg/ml), the MCF-7 human breast carcinoma ($ED_{50} < 10^{-3}$ μg/ml), and the HT-29 human colon adenocarcinoma ($ED_{50} = 1.26$ μg/ml). With the isolation and characterization of additional homologues, screening of diastereomers in the same systems will help to answer the important question about the relationship of the biological activity to the stereochemistry of the bistetrahydrofuran system.

EXPERIMENTAL

GENERAL EXPERIMENTAL PROCEDURES.—Melting points were determined on a Fisher-Johns apparatus and are uncorrected. Ir spectra were measured on a Perkin-Elmer Model 1600 FTIR. Nmr spectra were recorded on a General Electric QE-300 spectrometer at 300 MHz (^{1}H) or 75 MHz (^{13}C) in $CDCl_3$ with TMS as an internal standard. Fab ms were obtained at the Midwest Center for Mass Spectrometry at the University of Nebraska. Low resolution cims were obtained at the University of Pennsylvania Mass Spectrometry Center. Cytotoxicity assays were carried out at the Cell Culture Laboratory, Purdue Cancer Center, in the Department of Medicinal Chemistry and Pharmacognosy at Purdue University.

PLANT MATERIAL.—Roots of *R. papilionella* (B806512, PR-45518) were collected in Peru in October 1975, and were supplied by the Medicinal Plant Resources Laboratory, USDA, Beltsville, Maryland, where voucher specimens are preserved.

ISOLATION OF 4-HYDROXY-25-DESOXYNEOROLLINICIN [**2**].—Dried, ground roots of *R. papilionella* (10.08 kg) were percolated in a Soxhlet extractor with 80 liters of 95% EtOH for 24 h. The resulting extract was concentrated in vacuo to give a dark, viscous solid (250 g). The solid material was partitioned between $CHCl_3$ (500 ml) and H_2O (2 × 500 ml), and the combined $CHCl_3$ layers were concentrated in vacuo. The resulting solid was partitioned between petroleum ether (2 × 500 ml)/90% MeOH (500 ml) and CH_2Cl_2 (500 ml)/70% MeOH (2 × 500 ml). The CH_2Cl_2 layer was washed with 1 N HCl (4 × 1000 ml) and concentrated in vacuo to a dark brown solid (35.1 g). This solid material was subjected to size exclusion chromatography over Sephadex LH-20 in 500-mg portions. The column was eluted with CH_2Cl_2, and 50-ml fractions were collected. The first two fractions from each column contained the acetogenins.

The combined fraction 1 (9.3 g) was subjected to cc over Si gel, eluting with CH_2Cl_2 followed by increasing amounts of MeOH in CH_2Cl_2. The fraction eluting with 1.5% MeOH/CH_2Cl_2 was concentrated

in vacuo to give 1.8 g of solid material. This material was triturated with petroleum ether to give 1.0 g of material enriched in the acetogenins. This material was subjected to isocratic cc over Si gel, eluting with MeOH-EtOH-iPrOH-CH_2Cl_2 (2:2:1:95). One hundred fractions (10 ml each) were collected and combined according to tlc to give six fractions. Fraction 4 (0.53 g) was dissolved in CH_2Cl_2 and precipitated with hexane. The supernatant was removed and concentrated in vacuo to give 175 mg of amorphous material. This was subjected to cc over Si gel, eluting with EtOAc-CH_2Cl_2 (30:70), EtOAc-CH_2Cl_2 (50:50), and EtOAc. Concentration of the EtOAc fraction in vacuo gave **2** (56 mg).

4-HYDROXY-25-DESOXYNEOROLLINICIN [**2**].—Compound **2**: mp 25°; ir (CCl_4) 3478, 2928, 2856, 1763, 1465, 1318, 1074 cm^{-1}; ^1H nmr see Table 1; ^{13}C nmr see Table 2; hr fab ms *m/z* 629.4965 (calcd for $C_{37}H_{66}O_7$ + Li, 629.4968); fab ms *m/z* $[M + Li]^+$ 629, 517, 345, 317, 147.

ACETYLATION OF **2**.—4-Hydroxy-25-desoxyneorollinicin [**2**] (18.6 mg) was treated with 2 ml Ac_2O-pyridine (1:1) under N_2 at room temperature for 30 h. The mixture was dissolved in CH_2Cl_2 (5 ml) and washed with 1 N HCl (2 × 3 ml) and H_2O (2 × 3 ml). The CH_2Cl_2 layer was dried over anhydrous Na_2SO_4 and evaporated in vacuo to give 12.6 mg of **3** as a clear oil: ir (CCl_4) 2928, 2856, 1766, 1738 cm^{-1}; ^1H nmr see Table 1.

ACKNOWLEDGMENTS

The support of the VCU Faculty Grant-in-Aid program and the Biomedical Grant-in-Aid program of the College of Humanities and Sciences at VCU is gratefully acknowledged. MJA acknowledges fellowship support from the Mary E. Kapp Endowment of the Department of Chemistry. We also thank Dr. G.R. Pettit for generously supplying an authentic sample of rolliniastatin I. We are especially grateful to Dr. Jerry L. McLaughlin for arranging for the cytotoxicity assays.

LITERATURE CITED

1. S.D. Jolad, J.J. Hoffmann, K.H. Schram, J.R. Cole, M.S. Tempesta, G.R. Kriek, and R.B. Bates, *J. Org. Chem.*, **47**, 3151 (1982).
2. T.T. Dabrah and A.T. Sneden, *Phytochemistry*, **23**, 2013 (1984).
3. T.T. Dabrah and A.T. Sneden, *J. Nat. Prod.*, **47**, 652 (1984).
4. D. Cortes, J.L. Rios, A. Villar, and S. Valverde, *Tetrahedron Lett.*, **25**, 3199 (1984).
5. S.D. Jolad, J.J. Hoffmann, J.R. Cole, C.E. Barry II, R.B. Bates, G.S. Linz, and W.A. Konig, *J. Nat. Prod.*, **48**, 644 (1985).
6. J.K Rupprecht, C.-J. Chang, J.M. Cassady, J.L. McLaughlin, K.L. Mikolajczak, and D. Weisleder, *Heterocycles*, **24**, 1197 (1986).
7. J.T. Etse and P.G. Waterman, *J. Nat. Prod.*, **49**, 684 (1986).
8. T.G. McCloud, D.L. Smith, C.-J. Chang, and J.M. Cassady, *Experientia*, **43**, 947 (1987).
9. G.R. Pettit, G.M. Cragg, J. Polonsky, D.L. Herald, A. Goswami, C.R. Smith, C. Moretti, J.M. Schmidt, and D. Weisleder, *Can. J. Chem.*, **65**, 1433 (1987).
10. A. Alkofahi, J.K. Rupprecht, D.L. Smith, C.-J. Chang, and J.L. McLaughlin, *Experientia*, **44**, 83 (1988).
11. T.T. Dabrah and A.T. Sneden, *J. Nat. Prod.*, **46**, 436 (1983).
12. T.R. Hoye and J.C. Suhadolnik, *J. Am. Chem. Soc.*, **109**, 4402 (1987).
13. T.R. Hoye and Z. Zhuang, *J. Org. Chem.*, **53**, 5578 (1988).
14. T. Murata, T. Ariga, and E. Araki, *J. Lipid Res.*, **19**, 172 (1978).

Received 7 March 1989