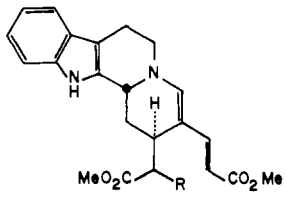
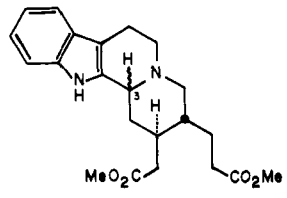


a, R = CO_2Me
b, R = H

3

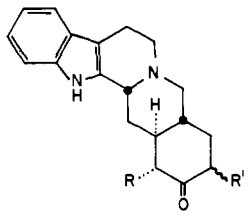


a, H(3β)
b, H(3α)

4

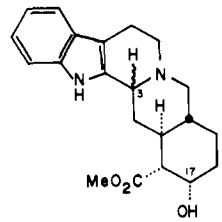
NMR ($CDCl_3$) δ 3.58, 3.67 (each s, 3), 3.91 (br s, 1), 6.9–7.5 (m, 4)).

Treatment of **4a** with sodium hydride in tetrahydrofuran (50 °C, 1.5 h) gave (44 and 36%, respectively) keto esters **5a**[2] (mp 227–228.5 °C; IR ($CHCl_3$) 3460, 1735, 1710 cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.87 (s, 3), 4.53 (br s, 1), 6.9–7.5 (m, 4)) and **5b**[2] (mp 223–225 °C; IR ($CHCl_3$) 3465, 1720, 1655, 1615



a, R = CO_2Me, R' = H
b, R = H, R' = CO_2Me
c, R = R' = H

5



a, H(3β)
b, H(3α)

6

cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.67 (s, 3), 4.60 (br s, 1), 6.9–7.6 (m, 4)). Alkaline hydrolysis and acid-induced decarboxylation of the latter afforded (±)-pseudoyohimbone (**5c**), mp 247–250 °C (lit.[1] mp 249–251 °C) (spectra identical with those of authentic sample), confirming the stereochemistry of all precursors. Hydrogenation of **5a** (platinum, 1:1 methanol–acetic acid, 1 drop of 36% hydrochloric acid, atmospheric pressure, room temperature, 48 h) yielded (72%) (±)-pseudoyohimbine (**6a**),[2,4,5] mp 249–251 °C dec (lit. mp[4] 252–256 °C, charring at 250 °C; mp[5] 248–251 °C) (spectra identical with those of an authentic specimen).

Hydrolysis of diester **4a** in refluxing 2:1 18% hydrochloric–acetic acids (24 h), followed by esterification with methanolic hydrogen chloride, led to the recovery (27%) of starting ester and the formation (41%) of isomer **4b:** mp 153–155 °C (lit.[6] mp 152–154 °C); IR (KBr) 3375, 1735, 1718 cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.67, 3.71 (each s, 3), 7.0–7.8 (m, 4). In view of the previous conversion of the latter into (+)-yohimbine (**6b**)[6] and (−)-β-yohimbine (17-*iso*-**6b**),[6] this constitutes a formal total synthesis of these alkaloids also.[5]

Acknowledgment. The authors are indebted to the U.S. Public Health Service for support of this work.

References and Notes

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(8) NATO fellowship holder during 1975–1976.

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Structure of Mildiomycin, a New Antifungal Nucleoside Antibiotic

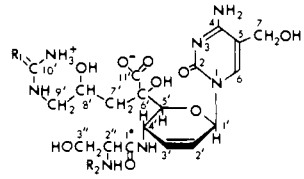
Sir:

A new nucleoside antibiotic, mildiomycin, was isolated from the culture filtrate of *Streptoverticillium rimofaciens* B-98891 in our laboratories.[1] It shows strong activity against powdery mildews on various plants[1a] and remarkably low toxicity in mammals and fishes.[1b] This paper deals with the structural elucidation of mildiomycin carried out on the basis of chemical degradations and spectral evidence as shown in Chart I.

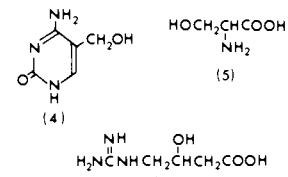
Mildiomycin (**1**)[1b] is a water-soluble, basic antibiotic: $C_{19}H_{30}N_8O_9 \cdot H_2O$; mp >300 °C dec; $[\alpha]^{23}_D$ +100°;[2] pK_a' = 2.8 (-COO^-), 4.2 (3-NH^+=), 7.2 (2″-NH_3^+), and >12 (guanidine); ν 1650 (-CONH-) and 1000–1150 (-C-O-) cm^{-1};[3] λ (pH 7) 271 nm (ε 8720) and λ (0.1 N HCl) 280 nm (ε 13 100); positive with Sakaguchi, Greig-Leaback and ninhydrin reactions. Because **1** is noncrystallizable, hygroscopic and nonvolatile, determination of the molecular formula of **1** was based on two crystalline derivatives, 2″-*N*-monobenzoate **2** ($C_{19}H_{30}N_8O_9 \cdot C_7H_4O \cdot 2H_2O$ (benzoyl chloride/5% $NaHCO_3$), mp >300 °C, $[\alpha]^{27}_D$ +92.5° (AcOH-H_2O (2:8)) and 2′,3′-dihydromildiomycin (**3**, $C_{19}H_{32}N_8O_9 \cdot H_2O$ (PtO_2/water), mp >300 °C, $[\alpha]^{22}_D$ ±0°). The ^{13}C NMR spectra of **1** and **3** also support the molecular formula as shown in Table I.

On acidic hydrolysis (2 N HCl, reflux, 2 h), **1** gave 5-hydroxymethylcytosine (**4**) and L-serine (**5**), which were identified with the authentic samples. The ^{13}C NMR signals of **1**

Chart I



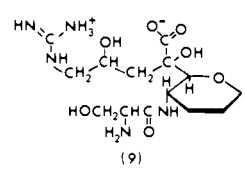
(1): R_1=NH, R_2=H (Mildiomycin)
(2): R_1=NH, R_2=Bz
(3): 2′,3′-Dihydro derivative of (1)
(6): R_1=O, R_2=H, Not ionized
(7): Formic acid salt of (1)



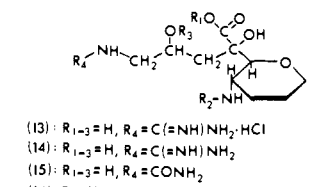
(4)

(5)

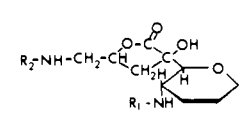
(8)



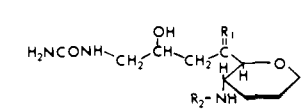
(9)



(13): R_{1-3}=H, R_4=C(=NH)NH_2·HCl
(14): R_{1-3}=H, R_4=C(=NH)NH_2
(15): R_{1-3}=H, R_4=$CONH_2$
(16): R_1=H, R_{2-3}=Ac, R_4=CONHAc
(17): R_1=CH_3, R_{2-3}=Ac, R_4=CONHAc



(10): R_1=COCH(NHBz)CH_2OH, R_2=$CONH_2$
(11): R_1=COCH(NHBz)CH_2OAc, R_2=CONHAc
(12): R_1=H·HCl, R_2=C(=NH)NH_2·HCl



(18): R_1=O, R_2=H
(19): R_1=H,OH, R_2=Ac

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which correspond to those of **4** and **5** have been assigned without any ambiguity.

The presence of a guanidyl group in **1** was established as follows. **1** was hydrolyzed (0.2 N NaOH, reflux, 2 h) to give ammonia and an ureido compound (**6**, $[\alpha]^{22}_D$ +83.0°, negative Sakaguchi and positive *p*-dimethylaminobenzaldehyde reactions). On an alternate hydrolysis (saturated $Ba(OH)_2$, reflux, 2 h), **1** afforded urea (mp 134 °C), **4**, **5**, **6**, and ammonia. A singlet signal at 158.0 ppm in the ^{13}C NMR spectrum of **1** can be reasonably assigned to the guanidyl carbon.

The aliphatic moiety was unveiled by proton spin-decoupling studies of mildiomycin formic acid salt (**7**, $[\alpha]^{22}_D$ +86.7°). On irradiation of a methine proton at 3.92 ppm (m, $H_{8'}$), two methylene signals at 1.95 (dq, $H_{7'}$) and 3.35 ppm (dq, $H_{9'}$) were collapsed into two sets of AB quartet signals; only the 8′-proton signal was decoupled when each of the methylene protons was irradiated. In the ^{13}C NMR spectrum of **1**, the signals at 48.1 and 39.2 ppm should be assigned to the $C_{9'}$ and $C_{7'}$ methylenes. These spectral data evidence that **1** has the following moiety: $>NCH_2CHCH_2C\lessgtr$. Furthermore, this partial structure was elucidated from a decomposition product. **1** was subjected to periodate oxidation (6% HIO_4–2 N HCl, reflux, 2 h) to afford optically active γ-guanidino-β-hydroxybutyric acid (**8**, mp 250 °C dec, $[\alpha]^{27}_D$ −19.5°(AcOH–0.05 N HCl–MeOH (3:7:10)) which was identified with an authentic sample of the racemic compound synthesized.[4] The chemical shifts for the $C_{7'}$ to $C_{10'}$ signals in the ^{13}C NMR spectrum of **1** also receive support from the corresponding signals of **8**.

The presence of pyran-3-ene moiety in **1** was suggested by ^1H and ^{13}C NMR spectra of **1**, **3** and **7**. In the ^1H NMR spectrum of **1** an anomeric and two olefinic proton signals were observed at 6.43 (s like, $H_{1'}$), 6.05 (d like, J = 10 Hz (cis coupling), $H_{2'}$), and 5.88 ppm (d like, J = 10 Hz, $H_{3'}$), while, in the ^1H NMR spectrum of **3**, the anomeric proton shifted to 5.66 (q, J = 10 and 2 Hz, $H_{1'}$) and newly occurring methylene signals were observed at 1.8 and 1.9–2.2 ppm (2 H × 2, m, $H_{2'}$ and $H_{3'}$). The presence of two olefinic carbons at $C_{2'}$ and $C_{3'}$ was also supported by the ^{13}C NMR spectra of **1** and **3**. When the olefinic proton at 5.88 ppm ($H_{3'}$) in **7** was irradiated, the methine proton at 4.95 ppm (d like, $H_{4'}$) was sharpened. On irradiation of this methine proton, the doublet signal at 4.24 ppm (J = 10 Hz, $H_{5'}$) collapsed into a singlet, while irradiation of the 5′ proton led to collapse of the 4′ proton into a singlet-like signal. The presence of pyran-3-ene moiety is further supported by ^1H and ^{13}C NMR data in the sugar moiety of blasticidin S.[5,6]

Valuable information came from a compound (**9**, $C_{14}H_{27}N_5O_7$, $[\alpha]^{23}_D$ −21.8°, pK_a' = 3.45 (-COO^-), 7.2 (2″-NH_3^+), and >12 (guanidine), ν 1650 cm^{-1} (-CONH-)) which was obtained along with **3** and **4** by hydrogenation of **1** (PtO_2/water). In the ^1H NMR spectrum of **9**, the signals indicated that **9** lacked the pyrimidine skeleton, that the anomeric proton was lost, and that a methylene signal had newly appeared at 3.85 ppm (m, $H_{1'}$), which corresponded to the signal at 3.95 ppm (m) in the hydrogenolysis product of blasticidin S.[5] The chemical shifts and off-resonance data of pyran ring of **9** in ^{13}C NMR spectrum were in good accord with those of the product.[6] These clearly demonstrated that the pyrimidine moiety should be bound to the anomeric carbon in **1**.

Alkaline hydrolysis of **9** (0.2 N NaOH, reflux, 2 h) gave a ureido compound which was benzoylated to yield 2″-*N*-benzoate **10** ($[\alpha]^{23}_D$ +22.8°, λ 228 nm (ε 11 600), ν 1770 cm^{-1} (lactone)). On acetylation (Ac_2O/pyridine) **10** afforded 10′-*N*-3″-*O*-diacetate **11** ($[\alpha]^{23}_D$ +29.8°, ν 1780 (lactone), 1740 (OAc), and 1700 (NAc) cm^{-1}). In the ^1H NMR spectrum of **11** in Me_2SO-d_6 the signals were observed at 10.31 (s, AcHN $C_{10'}$), 8.50 (t, J = 5 Hz, -NH $C_{9'}$), 8.48 (d, J = 8 Hz, NH $C_{2''}$), 7.96 (d, J = 8 Hz, -NH $C_{4'}$), 4.34 (m, $H_{3''}$), 2.03 (s,

Table I. ^{13}C NMR Spectra of Mildiomycin and Related Compounds

compd	carbon number																			
	C-2	C-4	C-5	C-6	C-7	C-1′	C-2′	C-3′	C-4′	C-5′	C-6′	C-7′	C-8′	C-9′	C-10′	C-11′	C-1″	C-2″	C-3″
1	157.9 (s)	165.9 (s)	107.9 (s)	142.2 (d)	58.4 (t)	81.0 (d)	126.8 (d)	133.8 (d)	44.1 (d)	80.8 (d)	79.5 (s)	39.2 (t)	67.9 (d)	48.1 (t)	158.1 (s)	178.7 (s)	175.1 (s)	57.1 (d)	64.5 (t)
3	157.4 (s)	165.6 (s)	107.3 (s)	141.7 (d)	58.5 (t)	83.9 (d)	30.1 (t)	30.3 (t)	45.9 (d)	83.4 (d)	80.0 (s)	39.7 (t)	68.2 (d)	48.0 (t)	158.0 (s)	178.9 (s)	174.9 (s)	57.2 (d)	64.4 (t)
9						68.5 (t)	25.2 (t)	31.6 (t)	47.0 (d)	83.4 (d)	80.0 (s)	39.9 (t)	68.2 (d)	48.0 (t)	158.0 (s)	179.4 (s)	173.6 (s)	57.0 (d)	63.9 (t)
12						69.2 (t)	24.8 (t)	28.9 (t)	47.9 (d)	79.3 (d)	78.3 (s)	37.3 (t)	77.5 (d)	45.1 (t)	157.9 (s)	177.8 (s)			
14						67.9 (t)	25.6 (t)	33.3 (t)	49.4 (d)	86.1 (d)	80.4 (s)	40.7 (t)	68.9 (d)	48.3 (t)	158.1 (s)	179.8 (s)			
18						68.6 (t)	23.8 (t)	27.5 (t)	48.1 (d)	80.9 (d)	210.9 (s)	43.8 (t)	66.9 (d)	45.8 (t)	162.2 (s)				
	5-hydroxymethyl cytosine[a] (**4**)					sugar moiety of blasticidin S[b]					γ-guanidino-β-hydroxybutyric acid (**8**)						L-serine (**5**)		
	149.6 (s)	160.0 (s)	105.7 (s)	145.9 (d)	57.3 (t)	80.6 (d)	126.9 (d)	133.7 (d)	47.5 (d)	78.5 (d)	175.6 (s)	39.6 (t)	67.4 (d)	47.2 (t)	158.2 (s)		173.1 (s)	57.2 (d)	61.0 (t)

[a] In CF_3COOD. [b] Determined by subtracting signals of blastidic acid[5,6] and cytosine from those of blasticidin S.

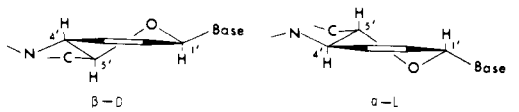
-Ac), and 1.98 ppm (s, -Ac). These data suggested that the serine moiety is bound to the 4′-amino function forming an amide bond.

Vigorous acid hydrolysis of **9** (3 N HCl, reflux, 15 h) gave a lactone dihydrochloride (**12**, $C_{11}H_{20}N_4O_4 \cdot 2HCl$, $[\alpha]^{23}_D$ ±0°) and **5**. **12** gave a monohydrochloride (**13**, $[\alpha]^{23}_D \pm 0°$) upon treatment with NH_4OH or IR-45, while a free base (**14**, $[\alpha]^{23}_D$ −7.9°, pK_a' = 2.8 (-COO^-), 8.6 (new 4′-NH_3^+), and >12 (guanidine)) was obtained by treatment with IRA-410. In the ^{13}C NMR spectrum of **14** the signals at $C_{3'}$ and $C_{5'}$ showed downfield shifts,[7] 4.4 and 6.8 ppm, when compared with those of **12**; therefore, the new primary amine should be located at 4′. The IR spectrum of **12** showed a strong absorption at 1770 cm^{-1} attributable to a five-membered lactone which disappeared in the spectra of **13** and **14**. The ^{13}C NMR signal of $C_{8'}$ shifted to 77.5 ppm in **12** from 68.9 ppm in **14**. In the ^1H NMR spectrum of **14** the signals at 3.75 (m, $H_{8'}$) and 1.95 ppm (m, $H_{7'}$) showed downfield shifts to 4.95 and 2.62 ppm (d like) in **12**, respectively. These data provided evidence for the structure of the lactone **12** as well as for the location of the carboxyl group in question.

Another ureido compound (**15**) was a key compound for establishing the location of the α-hydroxyl carboxylic acid. **14** was hydrolyzed (0.2 N NaOH, reflux, 2 h) to give ammonia and an ureido compound (**15**, mp 248 °C dec, $[\alpha]^{23}_D$ +5.9°, pK_a' = 7.75 (4′-NH_3^+) and 2.9 (-COO^-), δ 3.8 (d, $H_{5'}$) and 2.02 (m, $H_{7'}$)). On acetylation (Ac_2O/pyridine), **15** gave a triacetate (**16**, $[\alpha]^{25}_D$ +14.6°, pK_a' = 2.8 (-COO^-), ν 1700–1740 cm^{-1}, δ (Me_2SO-d_6) 1.98 (3 H, s) and 2.02 (3 H × 2, s)). On methylation (CH_2N_2/MeOH-Et_2O), **16** afforded a methyl ester (**17**, $[\alpha^{23}]_D$ +14.1°, ν 1740 cm^{-1}, δ ($CDCl_3$) 3.80 (s, -$COOCH_3$)).

Oxidation of **15** ($Pb(OAc)_4$/AcOH-water) yielded CO_2 and a ketone (**18**, $[\alpha]^{23}_D$ −1.2°, ν 1720 cm^{-1} (-CO-), δ 3.97 (d, $H_{5'}$) and 2.54 (m, $H_{7'}$)). In the ^{13}C NMR spectrum of **18** the signal of an isolated carbonyl group newly appeared at 210.9 ppm (s, $C_{6'}$) instead of the signal at 80.4 (s, $C_{6'}$) and 179.8 ppm (s, $C_{11'}$) in **14**. The 4′-*N*-acetate of **18** was reduced with $NaBH_4$/MeOH to give a diol (**19**, $[\alpha]^{27}_D$ +59.0°). Proton spin-decoupling studies of **19** confirmed the structure: when the 7′-methylene proton at 2.20 ppm (m) was irradiated, the methine signals at 4.25 (m, $H_{6'}$) and 4.03 ppm (m, $H_{8'}$) collapsed into a doublet (J = 7 Hz) and a double doublet, respectively. On irradiation of the methine proton at 3.78 ppm (q, $H_{5'}$) of **19**, the $H_{6'}$ methine signal at 4.25 ppm collapsed into a doublet (J = 4 Hz). From these data the presence of α-hydroxycarboxyl structure was established.

As for the absolute configuration of pyran-3-ene ring, the stereochemistry of $H_{4'}$ and $H_{5'}$ should be diaxial on the basis of the coupling constant of $J_{4',5'}$ = 10 Hz in **7**. Also the stereochemistry of $H_{1'}$ was assigned axial from $J_{1',2'}$ = 10 and 2 Hz in **3**. Thus, three bulky groups in the pyran-3-ene ring should reasonably be all equatorial. Only two sterically stable stereostructures of β-D or α-L could be permitted among all the possible isomers of pyran-3-ene as shown. Since these formula are mirror images, the Cotton effect of the CD spectrum in the B_{2u} band should be of opposite sign to each other.



β-D α-L

The CD spectra of the model and mildiomycin compounds follow: blasticidin S, $[\theta]_{270}$ −12 900; **1**, $[\theta]_{273}$ −8700; cytosinine, $[\theta]_{271}$ −9500; deseryl derivative of **1** (**20**, $[\alpha]^{24}_D$ +26.9°)), $[\theta]_{273}$ −9300; gougerotin, $[\theta]_{280}$ − 2700; **3**, $[\theta]_{285}$ −1800. The absolute configuration of blasticidin S and gougerotin has been determined as β-D.[8,9] These mildiomycin compounds showed negative Cotton effects quite similar to those of the model compounds, indicating that the pyranene ring should be β-D. The absolute configuration of **1** was thus assigned 1′*R*,4′*S*,5′*S*,2″*S*.

One of the interesting structural features of **1** is that the carboxyguanidino butyl group is bound to the unsaturated pyranoside with C-C bond. The aspects of the biosynthesis of this antibiotic provide another interesting problem—whether the quaternary carbon originates from an amino acid or sugar as a precursor.

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References and Notes

(1) (a) T. Iwasa, T. Kusaka, and K. Suetomi, *J. Antibiot.*, in press; (b) S. Harada and T. Kishi, *ibid.*, in press.
(2) Satisfactory elemental analyses were obtained for all compounds herein as containing some molecules of water of crystallization; adhesion was measured by thermogravimetric analysis. The melting points were measured by FT-5 (Mettler) at 3 °C/min. The specific rotations were also measured at the concentration of 0.5–1.0 in water unless otherwise stated.
(3) The IR spectra were measured in KBr pellet. The δ values in the ^1H and ^{13}C NMR spectra using XL-100 (Varian) were recorded in parts per million downfield from Me_4Si. All spectra herein were measured at the concentration of 20 mg/0.4 mL (^1H) and 200–300 mg/3 mL (^{13}C) in D_2O unless otherwise stated. In the ^{13}C NMR spectra dioxane was the internal standard (67.4 ppm).
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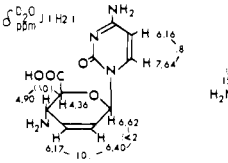
(6) Blasticidin S and its related compounds described herein were prepared by us and their spectral data were measured under the same conditions as those of our samples for comparison studies. The ^1H NMR of cytosinine and the ^{13}C NMR of hydrogenolysis product of blasticidin S follow.



Cytosinine Hydrogenolysis product of blasticidin S

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^{13}C-Enriched *S*-Methylmethionyl Residues as a Probe of Protein Conformation[1]

Sir:

Specific ^{13}C labeling of proteins has enhanced the usefulness of ^{13}C NMR spectroscopy as a tool for the study of these macromolecules. One highly selective method for ^{13}C enrichment of proteins which permits their observation in an essentially native form is the methyl exchange reaction at methionyl residues.[2] This method has now been applied in our laboratories to the basic pancreatic trypsin inhibitor (BPTI).[3] In the course of this work we have had occasion to make spectroscopic observations on the ^{13}C labeled protein intermediate, which possesses an enriched *S*-methylmethionyl residue at position 52 ([ε-^{13}C-SMM-52]-BPTI). Detailed NMR spectroscopic studies of *S*-methylmethionine-containing

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