lution in MeOH) was added to the filtrate followed by ether (50 mL). The precipitate was collected by centrifugation and decantation and reprecipitated from MeOH with ether to afford 20 mg (40%) of **2**: IR 3.00 (OH, NH), 5.83 (C=O), 6.20, 6.35 μm (H-bonded quinone); UV-vis (MeOH) λ_{max} (ϵ) 252 (25 391), 287 (9716), 478 (12 063), 492 (12 091), 531 (6913); NMR (Me_2SO-d_6) δ 1.18 (d, 3 H, 6′-H_3), 1.80 (m, 2 H, 2′-H_2), 2.12 (m, 2 H, 8-H_2), 2.78 (d, 1 H, J = 19 Hz, 10β-H), 3.04 (d, 1 H, J = 19 Hz, 10 α-H), 3.61 (m, 2 H, 3′- and 4′-H's), 3.92 (s, 3 H, OMe), 4.17 (m, 1 H, 5′-H), 4.61 (s, 2 H, 14-H_2), 4.87 (br s, 1 H, 7-H), 5.28 (br s, 1 H, 1′-H), 5.47 (br s, 1 H, 9-OH), 7.57 (m, 1 H, 3-H), 7.80 (m, 2 H, 1- and 2-H's), 13.11 (s, 1 H, phenolic OH), 13.93 (s, 1 H, phenolic OH).

Anal. Calcd for $C_{27}H_{29}NO_{11}\cdot HCl\cdot 0.75H_2O$: C, 54.64; H, 5.35; N, 2.36. Found: C, 54.34; H, 5.03; N, 2.02.

Acknowledgments. This work was supported by contract NO1-CM-33742 from the Division of Cancer Treatment, National Cancer Institute, National Institutes of Health, Department of Health, Education, and Welfare. The authors are grateful to Professor A. S. Kende (University of Rochester) and Dr. E. M. Action (SRI) for valuable discussions during the course of this work, and to Ms. Mary Tan Fong (SRI) for technical assistance in the adriamycin coupling experiments.

Registry No.—**1**, 20830-81-3; **1** HCl, 23541-50-6; **2**, 23214-92-8; **2** HCl, 25316-40-9; **3**, 32384-98-8; **4**, 40940-87-2; **5**, 59325-97-2; **6a**, 530-93-8; **6b**, 37464-90-7; **7**, 63625-93-4; **8a**, 63625-94-5; **8b**, 63625,95-6; **8c**, 63625-96-7; **9a**, 63625-97-8; **9a** PNB, 63625-98-9; **9b**, 63625-99-0; **9b** PNB, 63626-00-6; **11**, 63626-01-7; **11** PNB, 63626-02-8; **14**, 63626-03-9; **15**, 63626-04-0; **16**, 63626-05-1; **17**, 33628-85-2; **18**, 59325-99-4; **19**, 59326-00-0; **20**, 59367-18-9; **21**, 63626-06-2; **22**, 38554-25-5; **26**, 21794-55-8; **27**, 59325-98-3; **29**, 24385-10-2; **30**, 59326-04-4; **32** HCl, 19196-51-1; **33**, 52471-40-6; **34**, 63700-24-3; **36**, 63700-25-4; **39**, 52583-24-1; triethyl phosphonoacetate, 867-13-0; diethyl cyanomethylphosphonate, 2537-48-6; sodium triethylphosphonoacetate, 22822-85-1; vinyl chloride, 75-01-4; dihydropyran, 110-87-2; methyl iodide, 74-88-4; p-anisylchlorodiphenylmethane, 14470-28-1; S-ethyl trifluorothioacetate, 383-64-2; p-nitrobenzoyl chloride, 122-04-3; pyrrolidone hydrotribromide, 52215-12-0.

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(22) A recent report in the patent literature (F. Arcamone, L. Berdardi, B. Patelli, and S. Penco, Belgian Patent 842 930, 1976) indicates that **37** may be coupled with complete stereospecificity in the presence of $AgSO_3CF_3$.

Macrocyclic Spermidine Alkaloids from *Maytenus serrata* and *Tripterygium wilfordii*[1a]

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Four new spermidine alkaloids, celacinnine (1), celallocinnine (2), celafurine (3), and celabenzine (4), have been isolated in studies of *Maytenus serrata* (Hochst., ex A. Rich.) R. Wilczek and *Tripterygium wilfordii* Hook. The 13-membered macrocyclic structures of the alkaloids were elucidated by chemical degradation and by a study of the spectral properties of the alkaloids and their derivatives.

The twigs of *Maytenus serrata* (Hochst., ex A. Rich.) R. Wilczek (Celastraceae) have yielded two novel spermidine alkaloids, celacinnine (**1**) and celallocinnine (**2**), as the principal basic components.[2] Celacinnine (**1**) has also been isolated from the roots of *Tripterygium wilfordii* Hook (Celastraceae), together with the related alkaloids celafurine (**3**) and celabenzine (**4**).[2] We report herein our detailed studies on the isolation and structural elucidation of these four alkaloids.

Studies of the fruit of *M. serrata* in these laboratories have yielded the nicotinoyl sesquiterpene alkaloids maytoline, maytine, and maytolidine,[3] and the highly active tumor-inhibitory ansa-macrolide maytansine,[4] but these compounds could not be detected in the twigs and no spermidine alkaloids were detected in the fruit. A series of complex nicotinoyl sesquiterpene alkaloids has been previously reported from the roots of *T. wilfordii*.[5]

Table I. NMR Spectra of Spermidine Alkaloids and Derivatives from *M. serrata* and *T. wilfordii*[a]

Compd	Registry no.	C-7 (2 H)	C-8 (1 H)	CH_2	Aryl-H	Acyl groups
1	53938-05-9	7.50 d (7.0)	6.00 t (7.0)	6.2–7.0 br m (9 H) 7.2–8.6 br m (7 H)	2.5–2.8 m (10 H)	2.23 d (1 H), 3.12 d (1 H) (15.5) (15.5)
2	53990-48-0	7.55 d (7.0)	6.10 t (7.0)	5.9–7.0 br m (9 H) 7.4–8.8 br m (7 H)	2.5–2.8 m (10 H)	3.40 d (1 H), 3.96 d (1 H) (13) (13)
3	53938-09-3	7.58 d (7.0)	6.13 t (7.0)	6.2–8.9 br m (16 H)	2.75–2.95 m (5 H)	2.40 d (1 H), 2.69 t (1 H), 3.54 d (1 H) (1.5) (1.5) (1.5)
4	53938-08-2	7.58 d (7.0)	6.12 t (7.0)	6.2–8.9 br m (16 H)	2.6–2.9 m (10 H)	
5	53938-06-0	7.55 d (7.0)	6.03 t (7.0)	br m	2.7–2.8 m (10 H)	
7[b]	63301-66-6	7.60 m	6.00 br d (12)	6.4–8.8 m	2.5–3.0 m (10 H)	2.40 d (1 H), 3.32 d (1 H) (15) (15)
8[c]	53938-07-1	7.10 m	4.32 br d (12)	6.0–8.5 m	2.5–3.0 m (10 H)	2.26 d (1 H), 3.16 d (1 H) (15) (15)

[a] Spectra are of $CDCl_3$ solutions. Chemical shifts are given in τ units. Coupling constants in hertz are given in parenthesis; d, doublet; t, triplet; s, singlet; br m, broad multiplet; br d, broad doublet. [b] Peak at τ 7.98 s (3 H) *N*-methyl. [c] Peak at τ 7.53 s (3 H) CH_3CON–.

In the present study the ground dried twigs of *M. serrata*[6] were extracted with aqueous ethanol and the extract was partitioned between ethyl acetate and water. The ethyl acetate soluble material was chromatographed on SilicAR CC-7 and then on neutral alumina to give a crystalline alkaloid fraction. Recrystallization gave the major alkaloid, celacinnine (**1**, $C_{25}H_{31}N_3O_2$). TLC of the mother liquors yielded additional **1** and an isomeric alkaloid, celallocinnine (**2**). Both alkaloids gave strong positive reactions with either Dragendorff's reagent or iodoplatinic acid.

The ground dried roots of *T. wilfordii*[6] were extracted with 95% ethanol and the extract was partitioned between ethyl acetate and water. The ethyl acetate soluble material was extracted with aqueous citric acid solution, which was then treated with base and extracted with ethyl acetate to yield a basic fraction. Successive chromatography of the basic fraction on neutral alumina and silica gel, TLC purification on alumina and silica gel, and crystallization yielded **1**, celafurine (**3**, $C_{21}H_{27}N_3O_3$), and celabenzine (**4**, $C_{23}H_{29}N_3O_2$).

Similarity among the spectra of the four alkaloids suggested that **1–4** differed only in the acyl side chain. In each case the infrared spectrum contained two amide carbonyl bands at 6.02–6.06 and 6.19–6.25 μm and the mass spectrum contained prominent ions with *m/e* 274 ($C_{16}H_{24}N_3O$), 160 ($C_{11}H_{14}N$), 146 (C_9H_8NO), and 131 (C_9H_7O).[7] The NMR spectra (see Table I) showed few distinctive signals, but all four alkaloids appeared to contain 16 aliphatic protons (τ 5.9–8.9), at least five aryl protons, and a spin-coupled CH_2–CH system [τ 7.5 (2 H) and 6.1 (1 H), J = 7 Hz].

The NMR spectrum of **1** also contained an AB quartet (J = 15.5 Hz) at τ 2.23 and 3.12, and signals for a second monosubstituted aromatic ring. These signals, together with the ultraviolet absorption band at λ_{max} 277 nm (ϵ 23 000), suggested the presence of a *trans*-cinnamoyl group [cf., *N,N*-dimethyl-*trans*-cinnamide: UV λ_{max} 278 nm (ϵ 22 400);[8] NMR τ 2.17 and 3.54 (J = 15.5 Hz)[9]]. The NMR spectrum of the isomeric alkaloid **2** contained an AB quartet (J = 13 Hz) at τ 3.40 and 3.96, and the UV spectrum contained absorption bands at λ_{max} 255 and 264 (infl) nm (ϵ 11 800, 9500), suggesting a *cis*-cinnamoyl group [cf., *cis*-cinnamide, UV λ_{max} 254 nm (ϵ 10 600);[10] and methyl *cis*-cinnamate, NMR τ 3.1 and 4.1 (J = 12.4 Hz)[11]]. Hydrogenation of both **1** and **2** yielded dihydrocelacinnine (**5**), which lacked the strong ultraviolet absorption and contained no olefinic proton signals in the NMR spectrum. Although the mass spectra of **1** and **2** both contained peaks at *m/e* 131 (C_9H_7O) characteristic of a cinnamoyl group, this peak was also present in the spectrum of the other alkaloids, including **5** and its dideuterio isomer **6**, and can therefore result from a double fragmentation (vide infra).

The NMR spectrum of **3** contained intercoupled one-proton signals at τ 2.40 (d), 2.69 (t), and 3.54 (d), and the base peak in the mass spectrum of **3** appeared at *m/e* 95 ($C_5H_3O_2$), consistent with the presence of a β-furoyl group.[12,13] β-Furoic acid and its derivatives occur rarely in nature; they have been isolated primarily from the Celastraceae[14] and include two of the nicotinoyl sesquiterpene alkaloids, wilforgine and wilfortrine, from *T. wilfordii*.[5]

The NMR spectrum of alkaloid **4** contained ten aromatic but no olefinic proton signals, and the mass spectrum contained an intense peak at *m/e* 105 (C_7H_5O). These data suggested that a benzoyl group was present.

The unsaturated acyl groups appeared to be attached by an amide linkage to a common $C_{16}H_{24}N_3O$ nucleus, which contained both an aromatic ring and a saturated amide group. The relationship of the nitrogen functions was established by chemical degradation; vigorous acidic hydrolysis of **1** followed by acetylation of the reaction mixture yielded triacetylspermidine (**9**). A similar cleavage of a benzylic secondary amine has been reported in the acid hydrolysis of tetrahydro-*seco*-chaenorhine.[15] Hydrogenation of **1** gave **5**, so the single remaining unidentified unsaturation represented by the molecular formula could be attributed to the presence of a cyclic structure. The residue left after subtracting the acyl and spermidine units from the empirical formulas of the alkaloids corresponded in each case to a phenylpropionyl group. The NMR chemical shifts (Table I) of the CH_2–CH group protons were nearly identical with analogous peaks in *N*-methyl-β-phenyl-β-alanine methyl ester [τ 6.03 (CH), 7.50 (CH_2)], indicating that a β-amino-β-phenylpropionamido group was present in the alkaloids.

Acetylation of the basic nitrogen in **1** with acetic anhydride in pyridine gave *N*-acetylcelacinnine (**8**), whose NMR spectrum contained signals at τ 4.38 and 7.08 (J = 7 Hz). Comparison with the spectra of *N*-acetyl-β-phenyl-β-alanine methyl ester, τ 4.52 and 7.14 (J = 7 Hz), and *N*-acetyl-β-phenyl-α-alanine methyl ester, τ 5.12 and 6.91 (J = 7 Hz), confirmed that the basic amino group was in the β position of the phenylpropionamide and that in the original alkaloid it was not the site of the unsaturated acyl group. A similar shift of the CH signal upon acetylation, from τ 6.16 to 4.47 (dd, J = 10, 6 Hz), has been reported for a model β-phenyl-β-alanine derivative studied during the elucidation of the structure of the spermine alkaloid chaenorhine.[15] From the optical rotation of **1–4**, no assignment of the stereochemistry at C-8 could be made.

At this point, data for the structure of **1** were also consistent

Scheme I. Mass Spectral Fragmentation of Celaccinnine and Its Derivatives

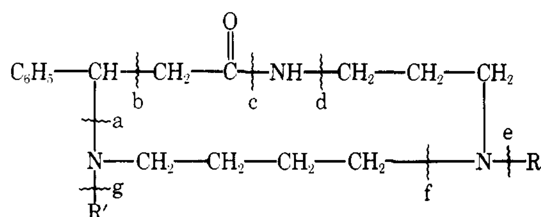


Table II. Mass Spectra of Spermidine Alkaloids and Derivatives from *M. serrata* and *T. wilfordii*[a]

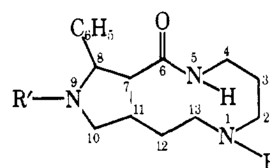
	m/e							
Compd	M^+	i	ii	iii	iv	v	vi	vii
1[b,c]	405	333	274	260	160	159	146	131[d]
	(23)	(1)	(100)	(17)	(21)	(16)	(29)	(90)
3[e]	369	297	274	224	160	159	146	131
	(47)	(18)	(29)	(52)	(30)	(20)	(38)	(14)
4[f]	379	307	274	234	160	159	146	131
	(24)	(4)	(57)	(4)	(25)		(25)	(12)
5[c]	407	335	274	262	160	159	146	131
	(100)	(10)	(65)	(23)	(41)	(51)	(67)	(16)
6[c,g]	409	337	274	264	160	159	146	131
	(100)	(9)	(81)	(22)	(44)	(71)	(82)	(22)
7	419		288		160	159	146	131
	(28)		(97)		(98)	(1)	(8)	(100)
8	447		316					131
	(38)		(80)					(100)

[a] Relative abundances are given in parentheses. Fragmentations refer to Scheme I: i = $M^+ - C_3H_6NO$; ii = M^+ − e; iii = M^+ − vi; iv, v = b + g + f; vi = a + d; vii = a + c. [b] Spectrum of 2 was quantitatively identical with 1 with minor variations in relative abundances. [c] All assignments confirmed by HRMS. [d] Note that for 1 the peak at m/e 131 is not characteristic of the acyl group. [e] Base peak m/e 95 assigned to $C_5H_3O_3$ (furoyl). [f] Base peak m/e 105 assigned to C_7H_5O (benzoyl). [g] Registry no.: 63301-67-7.

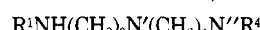
with structures **14, 15,** and **16.** Previous workers have reported that mass spectral fragmentation of triacetylspermidine (**9**) involves preferential fission of the three-carbon chain, with little involvement of the four-carbon chain.[16] Mild acid hydrolysis of **1,** followed by esterification and acetylation, yielded the triacyl spermidine **17,** resulting from hydrolysis of the saturated amido group. The mass spectrum of **17** contained peaks at m/e 345, 333, and 319 corresponding to ions **18, 19,** and **20,** respectively, resulting from cleavage of the three-carbon chain. The ester derived from **15** would be expected to have the same fragments. However, fission of the three-carbon chain in esters derived from alternative structures **14** and **16** should give rise to a much different fragmentation pattern.

N-Methylation of **1** gave **7,** whose methiodide was converted by Hofmann degradation to **10.** Alternatively, **10** was synthesized by partial cinnamoylation of spermidine,[17] separation of N,N'-dicinnamide **11,** and methylation. Both derived and synthetic **10** gave identical spectra. Mass spectral peaks at m/e 155, 143, and 129 corresponded to preferential fragmentation to give **21, 22,** and **23,** respectively. Although conversion of **1** to **10** confirmed the orientation of the spermidine unit, this transformation did not exclude **15** as a possible structure for the starting material.

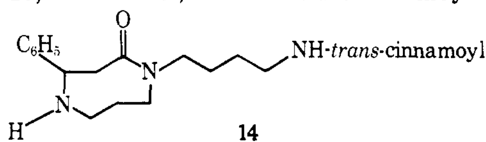
Macrocyclic structure **1** was ultimately assigned to celaccinnine on the basis of high-resolution mass spectral data. Principal fragmentations of the alkaloids and their derivatives are shown in Scheme I and Table II. The peaks at m/e 131 (vii, C_9H_7O) and 146 (vi, C_9H_8NO) were present in all four alkaloids as well as in the dihydro and dideuterio derivatives. The



1, R = *trans*-PhCH=CHCO; R' = H
2, R = *cis*-PhCH=CHCO; R' = H
3, R = —CO; R' = H
4, R = PhCO; R' = H
5, R = $PhCH_2CH_2CO$; R' = H
6, R = PhCHDCHDCO; R' = H
7, R = *trans*-PhCH=CHCO; R' = CH_3
8, R = *trans*-PhCH=CHCO; R' = CH_3CO



9, $R^1 = R^2 = R^3$ = Ac; R^4 = H
10, $R^1 = R^2$ = *trans*-cinnamoyl; $R^3 = R^4$ = Me
11, $R^1 = R^2$ = *trans*-cinnamoyl; $R^3 = R^4$ = H
12, $R^1 = R^3$ = *trans*-cinnamoyl; $R^2 = R^4$ = H
13, $R^1 = R^4$ = H; $R^2 = R^3$ = *trans*-cinnamoyl



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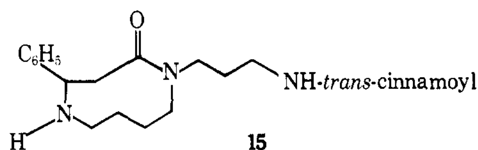

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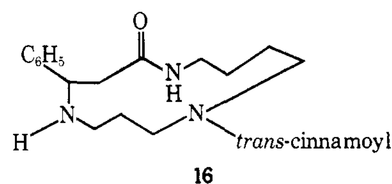
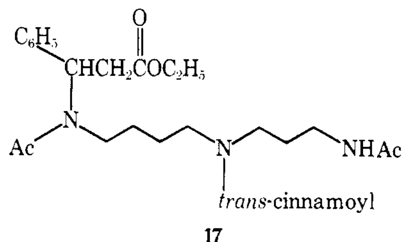
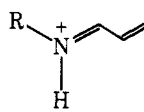


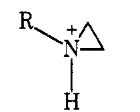
16



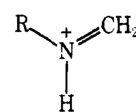
17



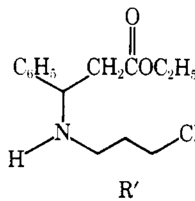
18, R = R'
21, R = R''



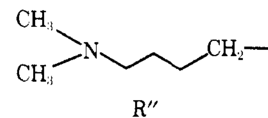
19, R = R'
22, R = R''



20, R = R'
23, R = R''



R'



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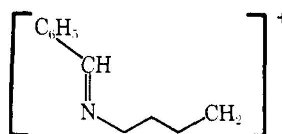

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presence of the m/e 146 peak in compounds **3–6**, which do not contain a cinnamide moiety, and the absence of a peak at m/e 148 ($C_9H_{10}NO$) for **5** and m/e 150 ($C_9H_8D_2NO$) for **6** suggest that the m/e 146 peak arises from elimination of the β-amino amide to yield a dicinnamoyl spermidine, which then undergoes cleavage at the C-4–N-5 bond. Although a triple cleavage might generate a similar m/e 146 peak for **15**, the $M^+ - C_9H_8NO$ peak (iii) observed in **1**, **5**, and **6** would not be possible for **15** and its derivatives.

Peaks at $M^+ - C_3H_6NO$ (i), attributed to a double cleavage in which the ring amide and either the C-7 or C-4 methylene groups are lost, provide additional support for assignment of structure 1 to celacinnine. No reasonable rationalization for loss of this fragment was possible for alternative structure **15**, and high-resolution mass spectroscopy clearly established that the m/e 333 peak did not result from loss of $C_4H_{10}N$, an alternative fragment which might arise from either **1** or **15**.

Loss of the acyl side chain (cleavage e) gave a peak (ii) at m/e 274, which changed to m/e 288 and 316 in the corresponding N-methyl (**7**) and N-acetyl (**8**) derivatives. Prominent peaks in all the spectra at m/e 160 (iv, $C_{11}H_{14}N$) and 159 (v, $C_{11}H_{13}N$) can be derived by cleavage b with loss of the substituent on N (cleavage g), followed by fragmentation f to give ion **24**.

A number of closely related spermidine alkaloids have been reported, including periphylline[18] and maytenine (**12**),[19,20] from Celastraceae species, and the *Lunaria* alkaloids.[20] A second series of alkaloids based on spermine, including homaline[20] and chaenorhine,[15] has many similarities. Most such alkaloids appear to originate from dicinnamic acid amides of the tri- or tetraamine, but in a few cases other acyl groups have been incorporated. Unlike many other alkaloids, these compounds do not seem to be associated with a particular plant family.

Experimental Section

Melting points were determined on a Hoover Uni-Melt melting point apparatus and are uncorrected. Values of $[\alpha]_D$ were obtained on a Perkin-Elmer 141 polarimeter. CD spectra were measured on a modified JELCO instrument.[21] UV spectra were determined on a Beckman DK-2A ratio recording spectrophotometer or a Coleman Hitachi EPS-3T spectrometer, IR spectra on a Perkin-Elmer 257 spectrophotometer, and NMR spectra on a Varian HA-100 spectrometer. MS were obtained on a Hitachi Perkin-Elmer RMU-6E spectrometer and high-resolution mass spectra (HRMS) on an AEI MS-902 mass spectrometer. Microanalyses were carried out by Spang Microanalytical Laboratory, Ann Arbor, Mich.

Celacinnine (1) and Celallocinnine (2) from *M. serrata*. The ground dried twigs of *Maytenus serrata* (1.5 kg) were extracted with cold aqueous EtOH (1:1) for 3 days. Evaporation yielded an extract (178 g), which was partitioned between EtOAc and H_2O. The EtOAc-soluble fraction (20 g) was chromatographed on SilicAR CC-7 (Mallinckrodt, 500 g); elution with $CHCl_3$ followed by 5% MeOH/$CHCl_3$ yielded the alkaloid fraction (1.7 g). The alkaloid fraction was chromatographed on neutral alumina (activity I, Woelm, 20 g) and eluted with C_6H_6 followed by $CHCl_3/C_6H_6$ (1:1). The resulting crystalline fractions (310 mg) were rechromatographed on alumina and repeatedly crystallized from hexane/$CHCl_3$ to give fine needles of celacinnine (**1**, 31 mg): mp 203–204 °C; $[\alpha]^{25}_D$ −19° (c 0.16, $CHCl_3$); CD max (MeOH) 230, 275 nm ($\Delta\epsilon$ −2.0, 1.7); UV (MeOH) λ_{max} 223 (infl), 277 nm (ϵ 16 000, 23 000); IR ($CHCl_3$) 2.89, 3.00, 6.06, 6.25, 6.45, 6.67 μm; IR (KBr) 3.0 (br), 6.02, 6.24, 6.46, 6.67, 13.0, 14.3 μm; MS m/e 405.2423 (M^+ calcd for $C_{25}H_{31}N_3O_2$, 405.2416).

Anal. Calcd for $C_{25}H_{31}N_3O_2$: C, 74.04; H, 7.71; N, 10.36. Found: C, 73.71; H, 7.66; N, 10.19.

The combined mother liquors (300 mg) from a number of isolations were separated by TLC on silica gel (10% MeOH/EtOAc) to give two basic fractions having R_f 0.60 and 0.55, respectively. The higher R_f fraction on crystallization from $Et_2O/CHCl_3$ yielded **1** (117 mg). The lower R_f fraction (46 mg) was recrystallized from EtOAc/Et_2O/hexane to give needles of celallocinnine (**2**, 13 mg): mp 172–173 °C; $[\alpha]^{25}_D$ −24° (c 0.23, $CHCl_3$); CD max (MeOH) 225, 255, 275 nm ($\Delta\epsilon$ −1.0, 0.3, −0.16); UV (MeOH) λ_{max} 255, 264 (infl) nm (ϵ 11 800, 9500); IR ($CHCl_3$) 2.76 2.90, 6.02, 6.20 μm; MS m/e 405 (M^+).

Anal. Calcd for $C_{25}H_{31}N_3O_2$: C, 74.04; H, 7.71. Found: C, 74.09; H, 7.76.

Celacinnine (1), Celafurine (3), and Celabenzine (4) from *T. wilfordii*. The ground dried roots of *Tripterygium wilfordii* (21 kg) were extracted with refluxing 95% EtOH for 2 days. Evaporation yielded an extract (2 kg), which was partitioned between EtOAc and H_2O. The EtOAc-soluble fraction (722 g) was extracted with 0.5 M citric acid, which was then made basic by addition of NH_4OH. Extraction of the basic solution with EtOAc and subsequent concentration at reduced pressure yielded a crude mixture of alkaloids (14.8 g), a portion (12.4 g) of which was separated by TLC on alumina (10% MeOH/EtOAc). The major component, R_f 0.5–0.7, was recovered to yield an enriched alkaloid fraction (6.5 g), and a portion (4.7 g) of the enriched fraction was chromatographed on a silica gel column (Merck, 70–325 mesh, 500 g). Slow elution with EtOAc yielded a mixture of the alkaloids (1.27 g) from which TLC on alumina (EM, Type T, 10% MeOH/EtOAc) gave two fractions, R_f 0.45 and 0.50. The lower band (300 mg) was recovered and crystallized from EtOAc to yield celafurine (**3**, 250 mg): mp 154–155 °C; $[\alpha]^{25}_D$ −11° (c 0.11, $CHCl_3$); UV (95% EtOH) λ_{max} 222 (infl), 232 (infl), 285 nm (ϵ 10 000, 6960, 1230); IR ($CHCl_3$) 2.91, 3.00, 6.04, 6.19, 6.65, 6.99, 8.35 μm; MS m/e 369.2063 (M^+ calcd for $C_{21}H_{27}N_3O_3$, 369.2052).

Anal. Calcd for $C_{21}H_{27}N_3O_3$: C, 68.35; H, 7.32; N, 11.38. Found: C, 68.09; H, 7.40; N, 11.19.

TLC of the higher band on silica (ChromAR 7GF, Mallinckrodt) with 10% MeOH/EtOAc gave two closely spaced bands having R_f 0.45 and 0.50, respectively. The higher R_f fraction (140 mg) was crystallized from EtOAc to yield celacinnine (**1**, 120 mg). The lower R_f fraction crystallized from EtOAc to yield celabenzine (**4**, 28 mg): mp 156–158 °C; $[\alpha]^{25}_D$ 0° (c 0.14, $CHCl_3$); UV (95% EtOH) λ_{max} 258 (infl), 264 (infl), 268 (infl) nm (ϵ 1390, 935, 685); IR ($CHCl_3$) 2.90, 3.00, 6.04, 6.20, 6.48, 6.99, 7.60, 8.95 μm; MS m/e 379.2202 (M^+ calcd for $C_{23}H_{29}N_3O_2$, 379.2260).

Anal. Calcd for $C_{23}H_{29}N_3O_2$: C, 72.82; H, 7.65; N, 11.08. Found: C, 72.79; H, 7.64; N, 11.07.

Dihydrocelacinnine (5). A. From Celacinnine (1). A solution of celacinnine (37 mg) in EtOAc (10 mL) was hydrogenated over 10% Pd/C for 4 h. The product was crystallized from EtOAc/Et_2O/hexane to give dihydrocelacinnine (**5**, 12.5 mg): mp 172–173 °C; UV (MeOH) λ_{max} 253, 260, 265, 269 nm (ϵ 520, 600, 520, 380); IR ($CHCl_3$) 2.78, 6.03, 6.14 μm; MS m/e 407.2574 (M^+ calcd for $C_{25}H_{33}N_3O_2$, 407.2573).

Anal. Calcd for $C_{25}H_{33}N_3O_2$: C, 73.67; H, 8.16; N, 10.31. Found: C, 73.91; H, 7.92; N, 10.20.

B. From Celallocinnine (2). A solution of celallocinnine (12 mg) in EtOAc (5 mL) was hydrogenated over 5% Pd/C for 4 h. The product was crystallized twice from EtOAc/Et_2O/hexane to give dihydrocelacinnine (**5**, 3.3 mg), identical with material from A on comparison by TLC, UV, IR, NMR, and MS.

Dideuteriocelacinnine (6). A solution of celacinnine (16 mg) in EtOAc (5 mL) was hydrogenated using deuterium over 10% Pd/C for 5 h (uptake 0.95 mol). The product was crystallized from EtOAc/Et_2O/hexane to give dideuteriocelacinnine (**6**, 9.6 mg): mp 174–175 °C; UV (MeOH) λ_{max} 254, 260, 265, 269 nm (ϵ 630, 680, 630, 580); IR ($CHCl_3$) 2.90, 6.02, 6.13, 10.9 μm; isotopic purity by MS, 95% (M^+:$M^+ - 2$) MS m/e 409.2713 (100%; M^+ calcd for $C_{25}H_{31}D_2N_3O_2$, 409.2698).

Vigorous Hydrolysis of Celacinnine. A solution of celacinnine (**1**, 58 mg) in 2 N HCl (3 mL) in a sealed tube was heated to 150 °C. After 17 h the solution was cooled and extracted with EtOAc (two 10-mL portions). The aqueous solution was neutralized ($NaHCO_3$), then washed with $CHCl_3$ (three 10-mL portions) and evaporated to dryness under vacuum. The residue was dissolved in dry MeOH and saturated with HCl gas. After evaporation the residue was dissolved in pyridine (2 mL) and acetic anhydride (0.5 mL) and kept at room temperature overnight. The solution was worked up to yield an oil, which was separated by TLC on silica gel (25% MeOH/EtOAc). The major component, R_f 0.2, was triacetylspermidine (**9**, 2.0 mg), identical with an authentic sample by TLC (silica gel, 25% MeOH/EtOAc and 5% HOAc/acetone) and by MS.

Mild Hydrolysis of Celacinnine. A solution of celacinnine (15 mg) in 6 N HCl (6 mL) was heated to 100 °C in a sealed tube for 2 h. The cooled solution was neutralized ($NaHCO_3$) and freeze-dried, and the residue dissolved in dry EtOH saturated with HCl gas and stirred. After evaporation, the product was dissolved in pyridine (1 mL) and acetic anhydride (0.2 mL) and allowed to stand at room temperature for 12 h. Evaporation of the pyridine followed by TLC of the residue on silica gel (EtOH/EtOAc) yielded degradation product **17**, R_f 0.7, as a pale yellow oil: IR 5.78, 6.00, 6.18, 7.25, 8.38 μm; NMR τ 2.25 (d, 1 H, J = 15.5 Hz), 2.6–2.9 (m, 10 H), 3.15 (d, 1 H, J = 15.5 Hz), 4.30 (dd, 1 H, J = 3, 12 Hz), 6.00 (q, 2 H, J = 7 Hz), 6.0–8.5 (m, 17 H), 7.56

(s, 3 H), 7.85 (s, 3 H), 8.82 (t, 3 H, J = 7 Hz); MS m/e 535.3044 (M^+ calcd for $C_{31}H_{41}N_3O_5$, 535.3036).

N-Acetylcelacinnine (8). Celacinnine (20 mg) was dissolved in pyridine (2 mL) and acetic anhydride (0.5 mL) was added. The mixture was stirred at room temperature (24 h), $CHCl_3$ (25 mL) was added, and the solution was washed with H_2O (three 10-mL portions). The $CHCl_3$ fraction was dried (Na_2SO_4) and the solvent evaporated. Chromatography of the residue on alumina (10% MeOH/EtOAc) yielded N-acetylcelacinnine (**8**, 14 mg) as a white amorphous powder: IR 6.00, 6.10, 6.18, 6.33 μm; MS m/e 447.2476 (M^+ calcd for $C_{27}H_{33}N_3O_3$, 447.2514).

N-Methylcelacinnine (7). Celacinnine (**1**, 18 mg) was dissolved in EtOH (1 mL) and methyl iodide (0.5 mL) was added. The mixture was heated at 65 °C for 20 h. After removal of solvent, chromatography of the residue on silica gel (10% MeOH/EtOAc) yielded N-methylcelacinnine (**7**, 13 mg): UV (MeOH) λ_{max} 224 (infl), 279 nm (ϵ 14 200, 22 100).

Hofmann Degradation of N-Methylcelacinnine. A solution of **7** (9 mg) and methyl iodide (1.5 mL) in acetone (1 mL) was heated at 65 °C for 24 h. After evaporation of the solvent, distilled water (1 mL) and silver oxide (10 mg, freshly prepared) were added to the residue and the mixture was stirred at room temperature for 20 h. The solution was filtered and the filtrate was concentrated to dryness. The residue was heated at 140 °C for 20 h and then separated by TLC on silica gel (10% MeOH/EtOAc) to yield the degradation product (**10**, 1 mg): MS m/e (rel intensity) 433 (3), 334 (27), 302 (13), 257 (33), 243 (98), 188 (85), 187 (100), 155 (10), 143 (12), 131 (100), 129 (21).

Synthesis of Degradation Product 10. Spermidine (5 g) was added to a suspension of barium hvdroxide (6 g) in EtOH (200 mL), and cinnamoyl chloride (8.5 g) was added in small portions with stirring and cooling over 1 h. The mixture was then stirred at room temperature overnight. The solution was filtered and the filtrate was concentrated to dryness. Chromatography on alumina (Woelm, neutral, 200 g) using CH_2Cl_2 as eluent gave tricinnamoylspermidine (4.7 g), and elution with CH_2Cl_2/MeOH (1:1) gave a mixture of three products. Rechromatography of the mixture on alumina (15% MeOH/CH_2Cl_2) yielded N,N'-dicinnamoylspermidine (**11**, 248 mg): mp 127 °C; UV (MeOH) λ_{max} 223, 276 nm (ϵ 29 600, 41 000); IR (KBr) 2.90, 3.03, 6.06, 6.22, 6.45 μm; MS m/e (rel intensity) 405 (M^+, 5), 336 (7), 335 (6), 314 (5), 274 (9), 245 (13), 205 (36), 188 (30), 131 (100), 127 (29), 115 (4), 103 (98), 101 (4). Additionally, bands were obtained for maytenine (**12**, 2.3 g)[17] and for N',N''-dicinnamoylspermidine (**13**, 9 mg): mp 107 °C; UV (MeOH) λ_{max} 223, 278 nm (ϵ 27 300, 40 500); IR (KBr) 2.90, 3.08, 5.97, 6.15, 6.45; MS$m/e$ (rel intensity) 405 (M^+, 4), 387 (4), 335 (8), 300 (8), 274 (10), 257 (10), 245 (14), 231 (10), 205 (36), 188 (34), 159 (56), 153 (16), 131 (100), 127 (26), 115 (6), 103 (98), 101 (5).

A solution of the dicinnamoylspermidine **11** (20 mg) and methyl iodide (0.6 mL) in EtOH (1 mL) was kept at room temperature for 3 days and then heated at 100 °C for 3 days. The product was chromatographed on alumina (15% MeOH/CH_2Cl_2) to yield **10** (6 mg), identical by MS with material from the Hofmann degradation of N-methylcelacinnine.

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References and Notes

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W-7783, a Unique Antifungal Antibiotic

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W-7783, $C_{28}H_{42}O_6$, an antifungal antibiotic with a unique structure, is produced by a myxobacteriale *Polyangium cellulosum* var. *fulvum.* The structure was deduced from chemical and spectral evidence including single-crystal x-ray analysis.

The structure of W-7783 (5,6-dihydroxypolyangioic acid),[2] an antifungal antibiotic produced by growth under appropriate conditions from a soil inhabiting myxobacteriale *Polyangium cellulosum* var. *fulvum*,[3a] has been deduced from chemical and spectral data including single-crystal x-ray analysis. W-7783 shows in vitro[3a] and in vivo activity[3b] against a variety of pathogenic fungi including *Histoplasma capsulatum* and *Coccidioides immitis. Histoplasmois* and *coccidioidomycosis* are treated at the present time with the highly toxic agent amphotericin B requiring iv administration and prolonged hospitalization. W-7783 (**1**, see Scheme I) represents a completely novel type of antibiotic. It is an orally active