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Novel Cage Indoles from a Malaysian *Kopsia*

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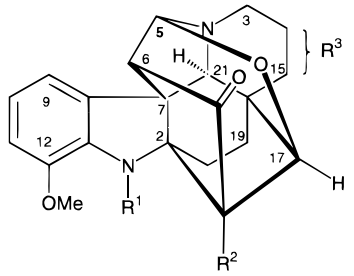
The EtOH extract of the leaves of *Kopsia teoi* yielded the octacyclic alkaloids kopsinitarines A−D (**1**−**4**) and mersingines A and B (**5** and **6**), all possessing a novel cage carbon skeleton. The structures of the alkaloids were established by spectral methods and, in the case of kopsinitarine D (**4**), confirmed by X-ray analysis.

The genus *Kopsia* (Apocynaceae) comprises some 30 species of shrubs and trees distributed mainly over Southeast Asia, India and China.[1,2] There are about 12 species distributed over the lowland forest of Peninsular Malaysia and another six in North Borneo.[1,2] Some medicinal uses have been reported for the cultivated species *K. officinalis*, which is used in China for the treatment of rheumatoid arthritis, dropsy, and tonsilitis,[2] and in Malaysia the roots of several *Kopsia* species are used for poulticing ulcerated noses in tertiary syphilis.[3] The genus has yielded a prodigious array of new natural products with novel carbon skeletons as well as useful bioactivities.[4−14] We have previously reported in preliminary form the occurrence of caged indoles from the leaf extract of *Kopsia teoi* L. Allorge[5,6] and would like now to furnish full details as well as the further isolation of a new member of this class of alkaloids, *viz.*, kopsinitarine D for which we have also carried out X-ray analysis.

Results and Discussion

The cage alkaloids, kopsinitarines A−D, (**1**−**4**), are found in minute amounts (with the exception of kopsinitarine D, **4**) only from the leaf extract, while the stem extract provided kopsingine as well as several other aspidofractinine-type alkaloids.[7] Two successive extractions of the alkaloids were carried out. In the first study, kopsinitarines A, B, and C (**1**−**3**) and mersingines A and B (**5**, **6**) were isolated. In contrast, in the second investigation, involving a different collection of plant material, kopsinitarines A (**1**), B (**2**), and D (**4**) and mersingine A (**5**) were isolated. The structures of kopsinitarines A−C have been discussed previously, whereas kopsinitarine D (**4**) represents a new addition to this group of indole alkaloids. We have previously proposed[5] that the kopsinitarines possess an unprecedented cage structure in which an oxygen bridge connects carbons 5 and 17 of the aspidofractinine-like unit, whereas carbons 6 and 16 are joined by a ketonic carbonyl reminiscent of that in kopsin. These structural features give rise to a novel skeletal framework in which



1 $R^1 = CO_2Me$, $R^2 = OH$, $R^3 = \Delta^{14,15}$

2 $R^1 = H$, $R^2 = OH$, $R^3 = \Delta^{14,15}$

3 $R^1 = H$, $R^2 = OH$, $R^3 = 15\text{-}\alpha\text{-}OH$

4 $R^1 = CO_2Me$, $R^2 = OH$, $R^3 = 15\text{-}\alpha\text{-}OH$

5 $R^1 = H$, $R^2 = NH_2$, $R^3 = \Delta^{14,15}$

6 $R^1 = H$, $R^2 = NH_2$, $R^3 = 15\text{-}\alpha\text{-}OH$

7 $R^1 = H$, $R^2 = NHCOMe$, $R^3 = \Delta^{14,15}$

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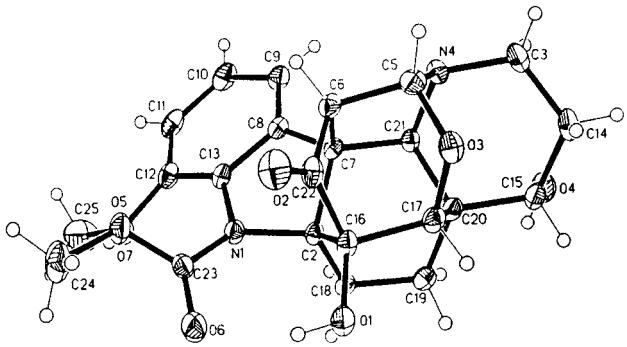
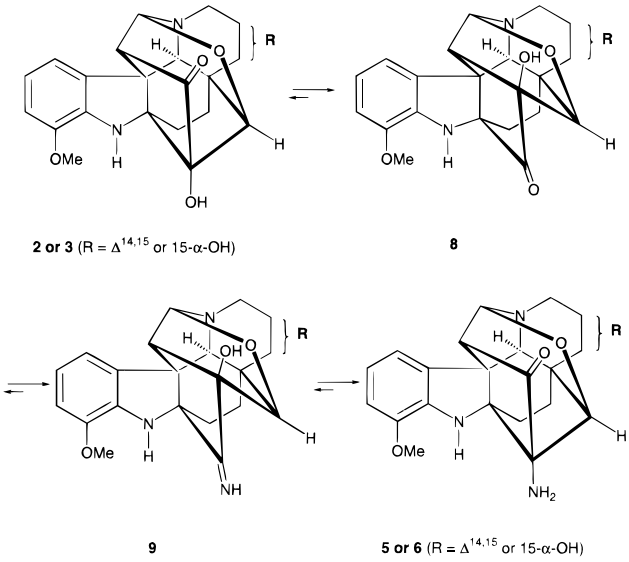


Figure 1. Perspective diagram of kopsinitarine D (**4**).

Scheme 1



a central cage unit is formed that is circumscribed by two five-membered rings and three six-membered rings. The isolation of **4** in sufficient quantities has now enabled us to revise some of our previous assignments of the ^{13}C NMR spectra of these compounds (Table 2) and also allowed us to confirm our earlier proposal of the structure by carrying out X-ray analysis.

The EIMS of (**4**) showed a molecular ion at *m*/*z* 440 ($C_{23}H_{24}N_2O_7$) with mass spectral fragmentation similar to those of compounds **1**−**3**. The UV spectrum showed absorptions at 217, 246, and 288 nm, typical of a dihydroindole chromophore. The ^1H and ^{13}C NMR spectral data of **4** showed signals due to a 12-methoxy-substituted dihydroindole, a 16-carbomethoxy group, a 16-OH function, a urethane group on *N*-1, a ketonic carbonyl (C-22), and three oxymethines (C-5, C-17 and C-15). In common with the other kopsinitarines, the ^1H spectrum displayed the characteristic pair of AX doublets at δ 5.25 and 2.79 (J = 4.9 Hz) due to H-5 and H-6, respectively, as well as the presence of an OH group on C-15. The spectral data thus show that **4** has the same cagelike carbon framework as compounds **1**, **2** and **3**, with a carbamate substituent on the indole nitrogen and a hydroxyl group on C-15. The stereochemistry of the 15-OH could not be readily established from NMR since the H-15 and 17 resonances are overlapped in **4** and in close proximity in **3**,[5] precluding NOE experiments. The matter is now resolved unequivocally by an X-ray analysis on **4**, allowing confirmation of the structure of the kopsinitarines as well as establishment of the configuration at carbon-15 in the case of **4**.

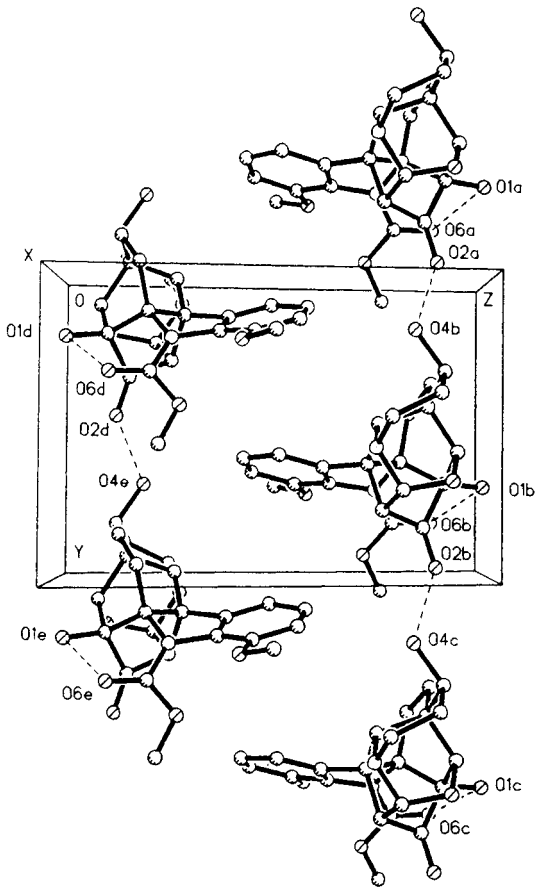


Figure 2. Packing diagram of **4** viewed down the *a*-axis showing intra- and intermolecular hydrogen bonding.

The crystals of **4** are monoclinic belonging to the space group $P2_1$, with a = 8.981(2) Å, b = 8.724(2) Å, c = 13.008(1) Å, $\alpha = \gamma = 90°$, β = 100.67(1)°, V = 1001.6(3) Å^3; D_x = 1.460 Mg m^{-3}, and Z = 2. The structure was solved by the direct method SHELXS86[15] and refined by full-matrix least-squares methods. The final *R*-factor was 0.0702. Both intra- and intermolecular hydrogen bonding were observed, in the former case between O6 (carbamate carbonyl) and 16-OH with the O6 to H distance at 1.963 Å and the O6 to O1 distance at 2.686 Å. The intermolecular hydrogen bond is from O2 (ketonic carbonyl) of one molecule to 15-OH of another at 2.171 Å with the O2 to O4 distance at 2.914 Å. The perspective diagram (Figure 1) confirms the structure deduced from spectral data.

In addition to the cage kopsinitarines, we have also isolated trace amounts of compounds **5** and **6**. These compounds had NMR spectral data that indicated their structural affinity to the kopsinitarines. In addition, they were shown by HREIMS to possess an additional nitrogen atom. Compounds **5** and **6** gave positive tests with ninhydrin indicating the presence of a primary amino group.[16] Furthermore, **5** was readily acetylated (Ac_2O/pyridine) to the amide derivative **7**. In the case of compound **6**, the stereochemistry of the 15-OH could be readily determined, since unlike kopsinitarine C (**3**), the H-15 and -17 resonances were sufficiently separated. Thus, irradiation of the H-15 signal resulted in NOE enhancement of H-17, indicating that the 15-OH is α.

We believe that compounds **5** and **6** are probably artifacts derived from further reaction of the kopsinitarines in the basic media under which extraction of alkaloids was carried out. One possible genesis of these

Table 1. ^{1}H NMR Spectral Data for Compounds **1**−**6** (270 MHz, $CDCl_3$)[a]

H	1	2	3	4	5	6
3	3.67 m	3.68 m	3.25 dd (14, 6.4)	3.25 dd (14, 6.4)	3.68 m	3.25 dd (14, 6.4)
	3.76 m	3.78 m	3.52 td (14, 4.9)	3.50 td (14, 4.9)	3.77 m	3.51 td (14, 4.9)
5	5.20 d (4.9)	5.16 d (4.9)	5.20 d (4.9)	5.25 d (4.9)	5.14 d (4.9)	5.18 d (4.9)
6	2.78 d (4.9)	2.73 d (4.9)	2.73 d (4.9)	2.79 d (4.9)	2.67 d (4.9)	2.68 d (4.9)
9	6.90 dd *(7.3, 1)*	6.87 dd (7.3, 1)	6.87 dd (7.3, 1)	6.92 dd (7.3, 1)	6.87 dd (7.3, 1)	6.87 dd (7.3, 1)
10	7.12 dd (7.8, 7.3)	6.79 dd (7.8, 7.3)	6.78 dd (7.8, 7.3)	7.11 dd (7.8, 7.3)	6.79 dd (7.8, 7.3)	6.78 dd (7.8, 7.3)
11	6.86 dd (7.8, 1)	6.71 dd (7.8, 1)	6.68 dd (7.8 1)	6.85 dd (7.8, 1)	6.69 dd (7.8, 1)	6.68 dd (7.8, 1)
14	6.07 dt (10, 2.5)	6.05 dt (10, 2.5)	1.57 m	1.57 m	6.07 dt (10, 2.5)	1.56 m
			2.71 m	2.70 m		2.71 m
15	5.60 dt (10, 2)	5.66 dt (10, 2)	3.91 m	3.93 m	5.59 dt (10, 2)	3.87 m
17	3.40 d (2)	3.75 m	3.87 d (2)	3.93 m	3.46 d (2)	3.63 d (2)
18	1.61 m	1.63 m	1.68 m	1.64 ddd (14, 11, 8.5)	1.67 m	1.69 m
	2.23 m	1.78 m	2.09 m	2.18 ddd (14, 11, 2)	1.73 m	2.08 m
19	1.53 m	1.63 m	1.08 m	1.19 ddd (14, 11, 8.5)	1.52 m	1.03 m
	1.66 m	1.63 m	1.68 m	2.04 ddd (14, 11, 2)	1.63 m	1.69 m
21	3.65 d (2)	3.53 d (2)	4.04 d (2)	3.93 m	3.54 d (2)	4.05 d (2)
16-OH	6.70 s			6.67 s		
ArOMe	3.83 *s*	3.80 s	3.79 s	3.82 s	3.79 s	3.78 s
NCO_2Me	3.77 s			3.78 s		

[a] Assignments based on COSY and COSYLR.

compounds derives from initial formation of an isokopsin-like precursor **8** formed under basic conditions *via* a reversible acyloin rearrangement[17] of the kopsinitarine precursor (**2** or **3**). This could be followed by a reversible condensation with ammonia resulting in the unstable imine **9**, which could then subsequently rearrange back to the original kopsin-like alkaloid (**5** or **6**), which now incorporates a 16-α-amino function as shown in Scheme 1. Unfortunately, we could not verify this proposal due to paucity of material in the case of compounds **2** and **3**, and in the case of kopsinitarine D (**4**), attempted reaction failed to yield the corresponding 16-α-amino derivative. One possible explanation for this is that in the case of **4** (as well as in **1**) where a carbamate function is present, the 16-OH is unreactive due to H-bonding involving the promimate carbamate carbonyl function. This proposal is supported by the observation that only mersingines (*e.g.*, **5** and **6**) derived from kopsinitarine partners in which the indole nitrogen does not carry a urethane substituent (*e.g.*, **2** and **3**) were isolated, whereas the corresponding artifacts derived from kopsinitarines A and D (**1** and **4**) were notably absent. This explanation is also supported by the observation of such intramolecular H-bonding even in the solid state (Figure 2).

Experimental Section

General Experimental Procedures. All melting points were uncorrected. UV spectra were recorded on a Shimadzu UV-160A spectrophotometer. Optical rotations were determined on a JASCO DIP-370 digital polarimeter. Mass spectra were obtained on a VG ProSpec spectrometer. ^{1}H and ^{13}C NMR spectra were recorded in $CDCl_3$ using TMS as internal standard on a JEOL JNM-GSX 270 spectrometer at 270 and 67.8 MHz, respectively.

Plant Material. Plant material was collected in Johore, Malaysia. Voucher specimens (3976) are deposited at the Herbarium, Department of Chemistry, University of Malaya.

Extraction and Isolation. Extraction of the ground leaves was carried out in the usual manner by partitioning the concentrated EtOH extract with dilute acid as has been described in detail elsewhere.[7,10] The alkaloids were isolated by initial column chromatography on Si gel using $CHCl_3$ with increasing proportions of MeOH followed by rechromatography of appropriate partially resolved fractions using centrifugal TLC.

Table 2. ^{13}C NMR Spectral Data for Compounds **1**−**6** (67.8 MHz, $CDCl_3$)[a]

C	1	2	3	4	5	6
2	72.2	68.1	68.3	72.2	68.8	69.0
3	47.4	47.5	42.2	42.1	47.4	42.1
5	95.8	95.9	95.2	95.1	95.9	95.3
6	56.2	56.6	58.3	57.5	57.4	59.0
7	59.4	59.7	60.0	59.5	60.0	60.3
8	136.6	131.0	131.3	136.6	131.6	131.8
9	113.2	115.2	115.4	113.0	115.3	115.4
10	126.8	120.6	120.6	126.8	120.6	120.7
11	115.0	110.5	110.6	115.1	110.4	110.4
12	149.7	145.9	145.9	149.5	145.9	146.6
13	131.0	139.8	139.3	130.3	139.8	139.7
14	131.0	130.8	32.6	32.4	130.7	32.6
15	128.6	129.1	70.8	70.3	129.1	70.9
16	87.5	86.3	87.1	88.1	72.0	72.6
17	87.8	87.9	88.7	88.3	87.7	88.5
18	18.6	19.4	19.4	18.5	20.0	20.1
19	25.6	26.2	23.2	22.2	26.1	23.1
20	31.1	32.3	35.9	34.5	32.0	35.6
21	62.2	62.1	60.3	60.2	62.3	60.5
ArOMe	56.1	55.3	55.4	56.0	55.3	55.3
NCO_2Me	53.5			53.5		
NCO_2Me	156.2			156.1		
CO	205.6	207.0	206.9	205.9	209.0	208.9

[a] Assignments based on HMQC and HMBC.

Solvent systems used for centrifugal TLC were Et_2O, Et_2O−EtOAc (3:1), Et_2O−EtOAc (8:1), and Et_2O−hexane (2:1). The yields (g kg^{-1}) of the alkaloids **1**−**6** are as follows:

Extraction 1: **1** (0.004), **2** (0.003), **3** (0.003), **5** (0.007), **6** (0.003).

Extraction 2: **1** (0.002), **2** (0.001), **4** (0.019), **5** (0.002).

Kopsinitarine A (**1**): $[\alpha]_D = +23°$ ($CHCl_3$, *c* 0.093), UV (EtOH) λ_{max} (log ϵ) 215 (4.41), 245 (3.85), 289 (3.06); EIMS *m*/*z* (rel int) 422 [M^+] (100), 394 (31), 393 (63), 363 (14), 362 (15), 335 (22) 307 (5.5); HREIMS, M^+ found 422.145, calcd for $C_{23}H_{22}N_2O_6$ 422.147; ^{1}H NMR and ^{13}C NMR, see Tables 1 and 2.

Kopsinitarine B (**2**): $[\alpha]_D = +188°$ ($CHCl_3$, *c* 0.051); UV (EtOH) λ_{max} (log ϵ) 212 (4.60), 246 (3.90), 290 (3.33); EIMS *m*/*z* (rel int) 364 [M^+] (100), 335 (52), 307 (7); HREIMS M^+ found 364.1433, calcd for $C_{21}H_{20}N_2O_4$ 364.1423 ^{1}H NMR and ^{13}C NMR, see Tables 1 and 2.

Kopsinitarine C (**3**): $[\alpha]_D = -96°$ ($CHCl_3$, *c* 0.026); UV (EtOH) λ_{max} (log ϵ) 213 (4.49), 246 (3.80), 290 (3.15); EIMS *m*/*z* (rel int) 382 [M^+] (90), 354 (52), 353 (55), 337 (15), 309 (12); HREIMS M^+ found 382.1529, calcd for $C_{21}H_{22}N_2O_5$ 382.1529; ^{1}H NMR and ^{13}C NMR, see Tables 1 and 2.

Table 3. Atomic Coordinates ($\times 10^4$) and Equivalent Isotropic Displacement Parameters ($A^2 \times 10^3$) for **4**[a]

atom	x	y	z	*U* (eq)
O(1)	−4004(3)	−3039(4)	−194(2)	43(1)
O(2)	−3000(4)	−435(4)	−1315(3)	52(1)
O(3)	−696(3)	−3289(3)	−1043(2)	36(1)
O(4)	−965(4)	−8115(3)	−1886(2)	44(1)
O(5)	−6948(3)	−713(4)	2874(2)	42(1)
O(6)	−6556(4)	−1812(4)	−1287(2)	50(1)
O(7)	−8405(3)	−2786(4)	−4266(2)	50(1)
N(1)	−5736(3)	−2953(4)	−2650(2)	30(1)
N(4)	−747(3)	−4355(4)	−2750(2)	31(1)
C(2)	−4461(4)	−3888(4)	−2087(3)	24(1)
C(3)	607(4)	−5319(6)	−2437(3)	41(1)
C(5)	−790(4)	−3003(5)	−2142(3)	35(1)
C(6)	−2380(4)	−2329(4)	−2557(3)	31(1)
C(7)	−3347(4)	−3826(4)	−2877(3)	24(1)
C(8)	−4400(4)	−3715(4)	−3909(3)	27(1)
C(9)	−4208(5)	−4130(5)	−4899(3)	35(1)
C(10)	−5453(6)	−4009(5)	−5714(3)	42(1)
C(11)	−6848(5)	−3551(5)	−5537(3)	41(1)
C(12)	−7059(4)	−3145(5)	−4539(3)	34(1)
C(13)	−5786(4)	−3185(4)	−3738(3)	28(1)
C(14)	728(5)	−6075(6)	−1368(3)	42(1)
C(15)	−762(5)	−6774(5)	−1231(3)	35(1)
C(16)	−3441(4)	−3176(5)	−1117(3)	29(1)
C(17)	−1959(4)	−4210(5)	−880(3)	30(1)
C(18)	−4975(4)	−5503(4)	−1885(3)	32(1)
C(19)	−3600(5)	−6460(4)	−1417(3)	34(1)
C(20)	−2118(4)	−5678(4)	−1544(3)	26(1)
C(21)	−2181(4)	−5128(4)	−2667(3)	25(1)
C(22)	−2947(4)	−1744(5)	−1611(3)	33(1)
C(23)	−6434(4)	−1813(5)	−2201(3)	31(1)
C(24)	−7672(7)	552(6)	−2441(4)	62(2)
C(25)	−9728(5)	−3042(11)	−5014(5)	81(2)

[a] *U*(eq) is defined as one third of the trace of the orthogonalized $\mathbf{U}_{ij}$ tensor.

Kopsinitarine D (**4**)**:** colorless crystals (CH_2Cl_2−ether); mp 258−260 °C; $[\alpha]_D = -46°$ ($CHCl_3$, *c* 0.079); UV (EtOH) λ_{max} (log ϵ) 217 (4.43), 246 (3.86), 288 (3.03); EIMS *m*/*z* (rel int) 440 [M^+] (100), 422 (65), 412 (20), 411 (70), 394 (10), 393 (50), 380 (18), 363 (5), 353 (15), 335 (15), 123 (5), and 109 (5); ^{1}H NMR and ^{13}C NMR see Tables 1 and 2.

Mersingine A (**5**): $[\alpha]_D = +88°$ ($CHCl_3$, *c* 0.058); UV (EtOH) λ_{max} (log e) 213 (4.54), 247 (3.85), 290 (3.28); EIMS *m*/*z* (rel int) 363 [M^+] (90), 335 (50), 334 (100), 307 (15); HREIMS, M^+ found 363.1578, calcd for $C_{21}H_{21}N_3O_3$ 363.1583; ^{1}H NMR and ^{13}C NMR, see Tables 1 and 2.

Mersingine B (**6**): $[\alpha]_D = -82°$ ($CHCl_3$, *c* 0.022); UV (EtOH) λ_{max} (log e) 213 (4.72), 246 (4.05), 290 (3.52); EIMS *m*/*z* (rel int) 381 [M^+] (100), 353 (94), 352 (95), 336 (24), 335 (24), 334 (34); HREIMS M^+ found 381.1685, calcd for $C_{21}H_{23}N_3O_4$ 381.1688; ^{1}H NMR and ^{13}C NMR, see Tables 1 and 2.

Acetylation of 5 to 7. Ac_2O (0.02 mmol) was added to a stirred solution of (**5**) (0.04 mmol) in pyridine (1.5 mL) at 27 °C. After *ca*. 2.5 h, saturated Na_2CO_3 (5 mL) was added, and the mixture was extracted with $CHCl_3$ (2 × 10 mL). The extract was then dried (Na_2SO_4) and the solvent evaporated. Flash chromatograpthy over SiO_2 (1% MeOH−$CHCl_3$) afforded 4.8 mg (81%) of (**7**): EIMS *m*/*z* (rel int):405 [M^+] (100), 376 (48), 364 (15), 335 (16), 334 (15), 305 (25); HREIMS M^+ found 405.1686, calcd for $C_{23}H_{23}N_3O_4$ 405.1688; UV (EtOH) λ_{max} (log e) 213 (4.51), 247 (3.86), 289 (3.28); ^{1}H NMR ($CDCl_3$, 270 MHz) δ 1.45 (ddd, J = 13.3, 11.3, 2.3 Hz, H-19), 1.77 (ddd, J = 13.3, 11.3, 7.3 Hz, H-18), 1.88 (ddd, J = 13.3, 11.3, 2.3 Hz, H-18), 2.10 (*s*, NHCO*Me*), 2.40 (ddd, J = 13.3, 11.3, 7.3 Hz, H-19), 2,79 (d, J = 4.9 Hz, H-6), 3.50 (d, 2 Hz, H-21), 3.70−3.84 (*m*, 2 × H-3), 3.79 (s, 12-OMe), 4.45 (d, J = 2 Hz, H-17), 5.19 (d, J = 4.9 Hz, H-5), 5.71 (dt, J = 10, 2 Hz, H-15), 6.06 (dt, J = 10, 2.5 Hz, H-14), 6.71 (dd, J = 7.8, 1 Hz, H-11), 6.80 (dd, J = 7.8, 7.3 Hz, H-10), 6.88 (dd, J = 7.3, 1 Hz, H-9); ^{13}C NMR ($CDCl_3$, 67.8 MHz) δ 21.9 (C-19), 24.2 (NHCO*Me*) 26.4 (C-18), 32.9 (C-20), 47.4 (C-3), 55.4 (12-OMe), 57.4 (C-6), 61.0 (C-7), 63.2 (C-21), 70.7 (C-2), 72.5 (C-16), 83.1 (C-17), 96.5 (C-5), 110.4 (C-11), 115.4 (C-9), 120.9 (C-10), 129.5 (C-15), 130.5 (C-14), 131.3 (C-8), 139.5 (C-13), 146.1 (C-12), 170.3 (NH*C*OMe), 204.2 (C-22).

X-ray Diffraction Analysis. A total of 3762 reflections were collected up to θ_{max} of 25° on a CAD4 diffractometer at 27 °C using Mo K_α (λ = 0.710 73 Å). The data were collected by the $\omega-2\theta$ method, 3523 observed reflections with $I > 2\sigma(I)$, and were corrected for Lorentz-polarization effect but not for absorption. The structure was solved by using the direct method SHELXS86.[15] All non-hydrogen atoms were refined anisotropically by full-matrix least-squares refinement on an IBM 486 PC to $R = 0.0702$, $wR = 0.1719$ for the observed reflections, $w = [\sigma^2(F_o^2) + (0.1293P)^2 + 0.2044P]^{-1}$ where $P = (F_o^2 + 2F_c^2)/3$. Hydrogen atoms were generated geometrically at C−H 0.95 Å and were allowed to ride on their respective parent atoms with B fixed at 1.3 times that of the parent atom. The atomic coordinates for the non-hydrogen atoms and their equivalent isotropic displacement parameters are given in Table 3. Calculated coordinates for the hydrogen atoms, anisotropic displacement parameters for the non-hydrogen atoms, a full list of bond distances and angles, and the structure factor table have been deposited at the Cambridge Crystallographic Data Center.[18]

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References and Notes

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(18) The coordinates can be obtained, upon request, from Dr. Olga Kennard, University Chemical Laboratory, 12 Union Road, Cambridge CB2 1EZ, U.K.

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