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Tenuisines A - C and Tenuiphylline, Novel Bisindoles from *Kopsia Tenuis*

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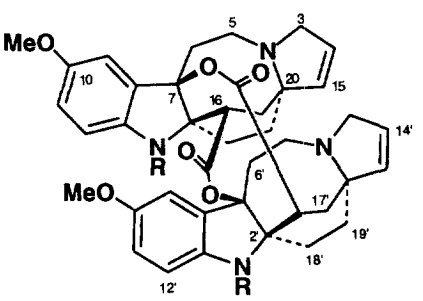
Abstract : The EtOH extract of the leaves of *Kopsia tenuis* yielded the novel bisindole alkaloids, tenuisines A - C and tenuiphylline. The structures of the alkaloids were established by spectral methods. © 1997 Published by Elsevier Science Ltd.

Kopsia tenuis Leenh. & Steenis is one of about 17 *Kopsia* species that occur in Malaysia and is endemic to Sarawak, in North Borneo.[1,2] Plants of this genus have yielded a number of novel alkaloids including some with useful bioactivities.[2-11] We have previously reported in preliminary form the structure of the novel bisindole tenuisine A **1**, from the leaf extract of this plant[7] and would like now to furnish full details as well as the structures of two new members of this class of alkaloids, *viz.*, tenuisines B and C (**2** and **3**) as well as a fourth dimeric indole of a novel structure type, tenuiphylline **4**.

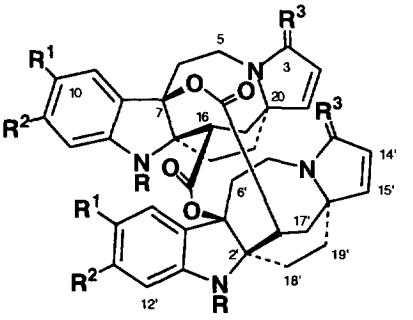
The dimeric indoles tenuisines A - C (**1** - **3**) and tenuiphylline **4** were obtained only from the leaf extract of *Kopsia tenuis*. We have previously proposed that tenuisine A **1** is a bisindole constituted from two identical monomeric units which are connected *via* carboxyl linkages from C-16 of one half to C-7 of the other as shown in **1**.[7] This structure results in the presence of a C_2 axis passing through the two halves, irrespective of the conformation adopted due to free rotation of the carboxyl linkages. The C_2 axis passes in between the two monomers and is orthogonal to the approximate plane defined by the central 10-membered ring. This structure is also in accord with the 23 degrees of unsaturation deduced from the molecular formula and is also consistent with the homotropic behaviour shown by the NMR spectra. In addition to tenuisine A **1**, the related compounds tenuisines B **2** and C **3**, and a novel dimer tenuiphylline **4** were also obtained.

Tenuisine B **2**, was obtained in amorphous form, $[\alpha]_D$ 51° ($CHCl_3$, *c* 0.09). The EIMS of **2** showed the highest mass fragment at *m/z* 426 ($C_{23}H_{26}N_2O_5$) which was also the base peak. However, as in the case

of tenuisine A **1**, the FABMS of **2** clearly showed a MH^+ peak at *m/z* 853 with a significant fragment at *m/z* 427 corresponding to cleavage of the parent ion resulting in two equal halves. HRFABMS measurements gave the exact mass of the MH^+ ion as 853.3666 corresponding to the molecular formula $C_{46}H_{52}N_4O_{12}$ (calcd. MH^+, 853.3660). The UV spectrum showed absorption maxima at 214, 252 and 300 nm (log ε 4.47, 4.08 and 3.70 respectively) which was similar to that of **1** and indicated the presence of a dihydroindole chromophore. The ^1H and ^{13}C NMR spectral data (Tables 1 and 2) were generally similar to that of **1** except for changes in the aromatic resonances as well as the presence of an additional methoxy peak (δ_H 3.89; δ_C 56.1). The two aromatic methoxy groups are deduced to be at C-10 and C-11 from the aromatic H resonances which appear as two singlets (δ_H 6.88, 7.74). Aside from these differences, the NMR spectra are similar to that of **1** showing the presence of a CO_2Me function at N_1 (δ_C 152.2), a low field quaternary carbon attributable to oxygenation at C-7 (δ_C 91.7), a lactone carbonyl (δ_C 177.1, IR 1754 cm^{-1}) and a 14,15-double bond which is part of a five membered ring (δ_H 5.72, 5.51; $J_{14\text{-}15}$ = 6 Hz; δ_C 127.1, 135.7). As in the case of **1**, the ^1H and ^{13}C NMR spectra are also complicated by the existence of equilibrating rotamers due to the carbomethoxy substituent on the indole nitrogen (Tables 1 and 2) which has been addressed previously in the case of tenuisine A **1**[7] and well documented in other similar compounds.[12, 13] In the case of **2**, two pairs of identical signals, each pair integrating for one hydrogen each, are seen for H-12 (δ_H 7.74, 7.19) and H-16 (δ_H 3.41, 3.31). In both cases the ratio of the major *versus* the minor conformer was also constant at 1.7 : 1. The same is also true for H-18 although the signals are not sufficiently well resolved for determination of the relative proportions. Increasing temperature led to a gradual broadening of these signals. The same behaviour was



1 R = CO_2Me



2 R = CO_2Me, $R^1 = R^2$ = OMe, $R^3 = H_2$

3 R = CO_2Me, R^1 = OMe, R^2 = H, R^3 = O

observed in the carbon spectrum where splitting of signals occurred for 13 of the carbon resonances (Table 2). As with **1**, the NMR data of **2** also shows simplification of the spectra due to homotropic behaviour of the two halves (Tables 1 and 2), indicating presence of a C_2 axis in tenuisine B and confirming the structure as shown in **2**.

Table 1. ^{1}H NMR Spectral Data for compounds **1** - **3**[a]

H	1	2	3
3a, 3a'	3.13 br d (16)	3.16 br d (16)	-
3b, 3b'	3.80 m	3.80 m	-
5a, 5a'	2.87 m	2.86 m	3.21 dd (16, 12)
5b, 5b'	3.20 dd (13, 8)	3.20 dd (13, 8)	2.2 ddd (16, 7, 2)
6a, 6a'	2.08 m	2.10 m	2.28 m
6b, 6b'	2.67 dd (16, 9)	2.68 dd (16, 9)	2.90 dd (16, 7)
9, 9'	6.90 br s	6.88 br s	6.97 br s
11, 11'	6.88 br d (8)	-	6.96 m
12, 12'	7.46 br d (8)	7.74 br s	7.52 br d (8)
	7.92 br d (8)	7.19 br s	
14, 14'	5.70 d (6)	5.72 m	6.11 d (6)
15, 15'	5.50 m	5.51 d (6)	6.85 d (6)
16, 16'	3.39 m	3.41 m	3.97 br d (12)
	3.27 m	3.31 m	
17a, 17a'	2.02 br d (14)	1.99 br d (14)	2.06 br d (15)
17b, 17b'	2.20 m	2.20 m	2.67 dd (15, 12)
18a, 18a'	1.64 m	1.65 m	1.88 m
18b, 18b'	2.60 m	2.60 m	2.44 m
	1.68 m	1.69 m	
	2.40 m	2.41 m	
19a, 19a'	2.02 m	2.01 m	1.65 m
19b, 19b'	2.06 m	2.07 m	2.21 m
10-OMe, 10-OMe'	3.77 s	3.87 s	3.83 s
11-OMe, 11-OMe'	-	3.89 s	-
NCO_2Me, NCO_2Me'	3.85 s	3.87 s	3.92 s

[a] $CDCl_3$, 270 MHz; assignments based on COSY, TOCSY and HMQC and NOESY.

Tenuisine C **3** was obtained in minute amounts. The EIMS of **3** showed the highest mass fragment at *m/z* 410 which was also the base peak. The molecular ion was detected by LCMS which gave a MH^+ peak at *m/z* 821 corresponding to the formula $C_{44}H_{44}N_4O_{12}$. The NMR spectral data displayed the same general features as that of **1** and **2** (Tables 1 and 2) showing similar homotropic behaviour, except that in tenuisine C **3**, possibly due to paucity of material, the spectrum did not show the presence of the minor conformer. The NMR data also indicated the presence of a lactam function (δ_C 171.4, IR 1682 cm^{-1}) which is deduced to be at C-3 from the substantial downfield shift of the H-15 olefinic resonance to δ 6.85, which is characteristic of a β-proton of an α,β-unsaturated carbonyl moiety. This assignment is also supported by the observed deshielding experienced by H-5β suggesting anisotropy due to a proximate carbonyl function and consistent with location of the lactam function at position 3. The structure of tenuisine C is therefore as shown in **3**.

Tenuisine A **1** was obtained in slightly greater amount compared to tenuisines B **2** and C **3**, but was somewhat unstable and decomposed on storage. Attempted hydrolysis of tenuisine A **1** with refluxing HCl/

Table 2. ^{13}C NMR Spectral Data for compounds **1** - **3**[a]

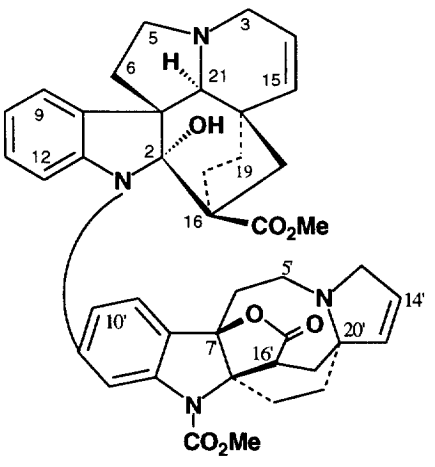
Position	1	2	3
2, 2'	74.1	74.0	72.8
	73.7	74.4	
3, 3'	61.5	61.6	171.4
5, 5'	47.2	47.4	34.7
6, 6'	29.8	30.2	29.2
7, 7'	90.2	91.7	91.3
	90.8	91.9	
8, 8'	130.8	119.1	128.8
	129.4	120.0	
9, 9'	109.8	107.1	109.6
	107.4	107.4	
10, 10'	155.9	151.4	156.3
		151.3	
11, 11'	116.3	145.7	116.6
12, 12'	116.3	100.0	117.2
	116.5	100.3	
13, 13'	134.4	136.5	134.9
		135.0	
14, 14'	126.6	127.1	124.7
	126.8	126.8	
15, 15'	135.8	135.7	154.9
	135.6	136.0	
16, 16'	44.7	45.8	39.5
	45.7	44.9	
17, 17'	38.5	38.8	31.3
18, 18'	21.5	23.0	21.2
	22.8	21.7	
19, 19'	24.8	25.0	28.7
20, 20'	67.1	67.2	64.1
CO (urethane)	152.5	152.2	152.9
	151.9	152.4	
CO (lactone)	177.3	177.1	178.0
	176.9	177.5	
10-OMe, 10-OMe'	55.6	56.1	55.8
11-OMe, 11-OMe'	-	56.4	-
NCO_2Me, NCO_2Me'	52.5	52.7	52.7

[a] $CDCl_3$, 270 MHz; assignments based on COSY, TOCSY and HMQC and NOESY.

MeOH as well as refluxing OH^-/MeOH resulted essentially in recovery of starting material suggesting that the dimer is inert to hydrolysis. A possible reason for the observed lack of reactivity is that the tenuisines are resistant to nucleophilic attack due to steric reasons. Examination of models reveal that the lactone carbonyls are 'buried' in an inaccessible region occupied by the central 10 membered ring which bridge the two large monomeric entities thus effectively shielding the carbonyls from nucleophilic attack.

The tenuisines represent dimeric indoles of a novel structure type linked by carboxyl bridges and possessing a C_2 axis of symmetry giving rise to homotropic behaviour of the NMR spectra.

Tenuiphylline **4**, was obtained in minute amounts and in amorphous form, $[\alpha]_D$ -22° ($CHCl_3$, *c* 0.05). The FABMS of **4** showed a MH^+ peak at *m/z* 717. HRFABMS measurements gave the exact mass of the MH^+ ion as 717.3331 corresponding to the molecular formula $C_{42}H_{44}N_4O_7$ (calcd. MH^+, 717.3288). The UV spectrum showed absorption maxima at 202, 212, 249, 301 and 318 nm (log ε 4.44, 4.33, 3.99, 3.54, and 3.50 respectively) indicating presence of dihydroindole chromophores. The IR spectrum showed bands due to hydroxyl (3641, 3347 cm^{-1}), urethane (1699 cm^{-1}), ester and lactone (1750 cm^{-1}, δ_C 177.6) functions. The 270 MHz ^1H NMR spectrum showed extensive overlap and proved unsuitable for definitive structure elucidation. In common with the tenuisines, the ^1H NMR spectrum is also complicated to some extent by the existence of equilibrating conformers due to the carbomethoxy substituent on the dihydro indole nitrogen.[7] An improved spectrum was obtained at 600 MHz which resolved most of the signals. The NMR spectral data (Table 3) showed the presence of two methoxy groups at δ 3.87 and 3.13 which are associated with carbamate (δ_C 152.9, broad H-12' singlet at δ 7.67) and ester (δ_C 177.6) functions respectively. The aromatic region integrated for a total of 7 hydrogens and since no other aromatic substituents are indicated, the dimer can be deduced to be branched from an aromatic carbon of one monomeric unit. The other site of attachment can be inferred to be on a dihydro indole nitrogen of the other monomer unit since only one urethane function is present and there is no evidence of an NH function. The ^1H NMR spectrum also shows the presence of 4 olefinic hydrogens. Two of these (δ_H 5.72, 5.42; $J_{14\text{-}15}$ = 10 Hz; δ_C 125.5, 131.8) are associated with a 6-membered ring while the other two (δ_H 5.71, 5.51; $J_{14'\text{-}15'}$ = 5 Hz; δ_C 127.4, 135.9) are part of a 5-membered



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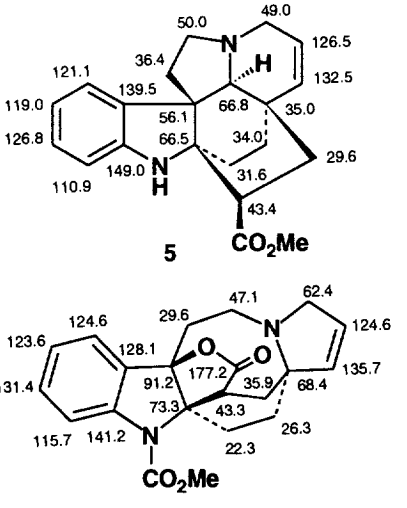

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ring as deduced from the value of their respective coupling constants.[2] Analysis of the ^{1}H and ^{13}C NMR spectra using COSY, HMQC, HMBC and NOESY allowed full assignments of the spectral data and revealed the two monomeric moieties as shown in **4**. One of these possesses the hexacyclic indole system incorporating a five membered lactone ring (lapidilectine B **6**) found recently in another *Kopsia* species.[8, 14] This is evident from the fragments deduced from COSY and HMQC as well as from the excellent correlation of the ^{13}C shifts, in particular the non-aromatic carbon shifts, with those of **6**. The other monomeric unit can be considered as having a novel, previously unencountered carbon framework, or a rearranged venalstonine. The ^{13}C shifts of this second unit generally resemble that of venalstonine **5** except for changes involving carbons 2, 12, 16, 17, 18, 20 and 21.[15] The COSY spectrum indicated the presence of the same fragments as in venalstonine **5** and the downfield shifts observed for C-20 (45.4) and C-21 (74.4) are reminiscent of those of vindolinine derivatives (*e.g.*, *N*-methyl vindolinine, C-20, 45.6; C-21, 77.0),[15] suggesting a change in the connectivity involving the C18-C19 fragment. The presence of the hydroxyl group at position 2 is supported by the presence of an oxygenated quaternary carbon at δ_C 99.8, its downfield shift due to its being α to both an oxygen and nitrogen. This is supported by HMBC which showed correlations (^{3}J) from C-2 to H-6 and H-21. The presence of the OH function on C-2 requires that C-18 be now linked to C-16, which is consistent with the observed C-16 shift of 59.1, involving a significant downfield shift when compared to venalstonine **5**. This conclusion is also supported by the observed ^{3}J correlations in the HMBC spectrum from both C-18 and C-19 to H-17. The aromatic portion associated with this monomeric unit is shown to be unsubstituted from the COSY spectrum which identified the uninterrupted 4-H aromatic network and from the NOE interaction observed between H-9 and H-21 as well as the observed ^{3}J interaction between C-13 and H-9 in HMBC. The upfield shift of the aromatic C-12 when compared with venalstonine is consistent with the change from NH in venalstonine to N-C11' in tenuiphylline.[15] The point of branching is therefore from N_1 of this venalstonine-like monomer to the aromatic ring of the other lactone containing monomer. The attachment can be at either C-10' or C-11' from the observed coupling pattern of the aromatic hydrogens. The NOE interaction observed between the aromatic doublet at δ 7.33 and H-6'β allowed the assignment of this signal to H-9'. This rules out position 10' as the site of substitution and the attachment to the aromatic ring must therefore be at C-11', which is also consistent with the observed HMBC correlation from C-7' to H-9' (^{3}J). The dimer is therefore linked from N_1 of one unit to C-11' of the other. Examination of models reveals that there should be restricted rotation about the N_1-C11' bond due to steric congestion, which would preclude the molecule adopting a conformation in which the two dihydro indole portions are coplanar. The most favourable conformation is likely to be one in which the approximately planar dihydro indole portions of the two monomers are nearly mutually orthogonal to each other. This proposal is supported by the observed NOE interaction between H12-H10' and H9'/H10'-Me (ester). An additional observation in support of this is the unusual upfield shift of the ester methyl group to δ 3.13 (the usual value being about δ 3.8[16, 17]), which is most

probably due to the anisotropic effect from the other aromatic ring, this being the case due to placement of the ester function above the other aromatic ring as a result of the preferred conformation adopted. The stereochemistry of the 2-OH is deduced to be α based on several factors. Firstly, had the hydroxyl been β, it

Table 3. ^{1}H and ^{13}C NMR Spectral Data for tenuiphylline **4**[a]

Position	δ_C	δ_H	Position	δ_C	δ_H
2	99.8	-	2'	72.8	-
3	53.6	2.84 *dt* (16, 2)	3'	61.6	3.16 *br d* (16)
		3.57 *m*			3.80 *ddd* (16, 2.5, 1.5)
5	54.1	2.38 *m*	5'	47.4	2.88 *m*
		3.30 *t* (8)			3.22 *dd* (13, 8)
6	35.4	1.38 *m*	6'	30.6	2.14 *m*
		3.59 *m*		-	2.72 *dd* (16, 8)
7	55.8	-	7'	90.1	-
8	136.7	-	8'	126.8	-
9	121.5	7.14 *dd* (7.7, 1.5)	9'	124.5	7.33 *br d* (8)
10	118.1	6.66 *t* (7.7)	10'	121.5	7.13 *m*
11	126.5	6.95 *td* (7.7, 1.5)	11'	141.8	-
12	105.1	6.40 *d* (7.7)	12'	116.9	7.67 *br* s
13	147.7	-	13'	141.6	-
14	125.5	5.72 *ddd* (10, 5, 2)	14'	127.4	5.71 *dd* (5, 2)
15	131.8	5.42 *dt* (10, 2)	15'	135.9	5.51 *m*
16	59.1	-	16'	44.8	3.40 *m*
17	43.0	1.32 *br d* (13)	17'	38.7	1.99 *br d* (14)
		2.40 *dt* (13, 2)			2.20 *m*
18	25.6	1.86 *m*	18'	21.9	1.65 *m*
	-	2.37 *m*		-	2.63 *m*
19	35.5	1.50 *m*	19'	25.0	2.02 *m*
		1.57 *m*			2.09 *m*
20	45.4	-	20'	67.3	-
21	74.4	2.63 *br s*	21'	-	-
NCO_2Me	-	-	NCO_2Me'	52.9	3.87 *s*
$N\underline{C}O_2Me$	-	-	$N\underline{C}O_2Me'$	152.9	-
CO_2Me	52.5	3.13 *s*	CO_2Me'	-	-
$\underline{C}O_2Me$	177.6	-	$\underline{C}O_2Me'$	-	-
			$\underline{C}O'$	177.6	-

[a] $CDCl_3$, 600 MHz; assignments based on COSY, HMQC, HMBC and NOESY.

would be expected to be intramolecularly H-bonded with the proximate ester function, giving rise to a clear NMR signal in the relatively lower field region (δ 6 to 7) as is seen in many aspidofractinine-type compounds where such H-bonding exists.[16, 17] Secondly, had the OH been β, the ester function would then be too far removed, not only to experience NOE interaction with H-9' and H-10' but also to experience the observed anisotropy from the other aromatic ring. Based on the above considerations, the structure of this novel dimeric indole is as shown in **4**.

In preliminary screening for cytotoxic activities of these dimeric alkaloids, tenuisine B **2** showed strong activity against mouse leukemia P388 and adriamycin resistant P388 cells at a concentration of 25 μg ml^{-1}, but was inactive against human leukemia HL-60 cells at the same concentration, whereas tenuiphylline **4** showed moderate activity against HL-60 but was inactive against P388 cells at the same concentration.

Experimental Section

General Experimental Procedures. All mp's were uncorrected. UV spectra were recorded on Shimadzu UV-3101PC spectrophotometer. IR spectra were recorded on a Perkin-Elmer 1600 Series FT-IR spectrophotometer. Optical rotations were determined on a JASCO DIP-370 digital polarimeter. Mass spectra were obtained on a VG ProSpec spectrometer. ^1H 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 and in some cases on a Jeol Lambda-600 spectrometer at 600 MHz.

Collection, Extraction and Isolation. Plant material was collected in Sarawak, Malaysia. Herbarium voucher specimens (S 61803) are deposited at the Herbarium of the Sarawak Forest Department, Kuching, Sarawak, Malaysia. 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.[18, 19] 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. Solvent systems used for centrifugal TLC were 0.5 % MeOH-$CHCl_3$, 4 % MeOH-$CHCl_3$ and Et_2O - EtOAc (1 : 1). The yields (g kg^{-1}) of the alkaloids (**1** - **4**) are as follows: **1** (0.45), **2** (0.045), **3** (0.0026) and **4** (0.04).

Tenuisine A 1, $[\alpha]_D$ = 77° ($CHCl_3$, *c* 0.76); IR (dry film) υ max 1750 cm^{-1} (C=O, lactone), 1700 cm^{-1} (C=O, carbamate); UV (EtOH), λ_{max} (log ε) 206 (4.46), 247 (3.99) and 304 (3.64). EIMS, *m/z* (rel. int.): 396 (100), 366 (10), 352 (25), 325 (60), 293 (15), 246 (50), 104 (40) and 94 (45). FABMS, *m/z* (rel. int): 793 (60), 397 (100) and 353 (50). HRFABMS, MH^+ found 793.3447, calcd. for $C_{44}H_{48}N_4O_{10}$+H, 793.3449. ^1H NMR and ^{13}C NMR : see Tables 1 and 2.

Tenuisine B 2, $[\alpha]_D$ = 51° ($CHCl_3$, *c* 0.09); IR (dry film) υ max 1754 cm^{-1}, 1704; UV (EtOH), λ_{max} (log ε) 214 (4.48), 252 (4.08) and 300 (3.70). EIMS, *m/z* (rel. int.): 426 (100), 382 (15), 367 (10), 355 (25), 276 (22), 262 (5), 106 (5) and 94 (10). FABMS, *m/z* (rel. int): 853 (50), 427 (100) and 383 (50).

HRFABMS, MH^+ found 853.3663, calcd. for $C_{46}H_{52}N_4O_{12}$+H, 853.3660. ^1H NMR and ^{13}C NMR: see Tables 1 and 2.

Tenuisine C 3, $[\alpha]_D$ = 87° ($CHCl_3$, *c* 0.06); IR (dry film) υ max 1770 cm^{-1} (C=O, lactone), 1694 cm^{-1} (C=O, carbamate) and 1682 cm^{-1} (C=O, lactam); UV (EtOH), λ_{max} (log ε) 203 (4.41), 247 (4.10) and 304 (3.55). EIMS, *m/z* (rel. int.): 410 (100), 366 (40), 352 (10), 338 (20), 308 (10), 244 (25) and 122 (15). LCMS, *m/z* (rel. int): 821 (MH^+, $C_{44}H_{44}N_4O_{12}$, 65), 411 (100) and 367 (50). ^1H NMR and ^{13}C NMR: see Tables 1 and 2.

Tenuiphylline 4, $[\alpha]_D$ = -22° ($CHCl_3$, *c* 0.05); IR (dry film) υ max 3641, 3347 cm^{-1} (OH), 1750 cm^{-1} (C=O, lactone) and 1699 cm^{-1} (C=O, carbamate); UV (EtOH), λ_{max} (log ε) 202 (4.44), 212 (4.33) 249 (3.99) 301 (3.54) and 318 (3.50). HRFABMS, MH^+ found 717.3331, calcd. for $C_{42}H_{44}N_4O_7$+H, 717.3288. ^1H NMR and ^{13}C NMR: see Table 3.

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