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Synthesis of vinca alkaloids and related compounds XXXVIII[1]. Formation of dimers under Polonovski reaction conditions

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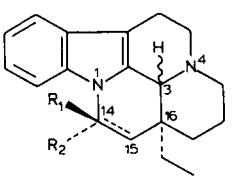
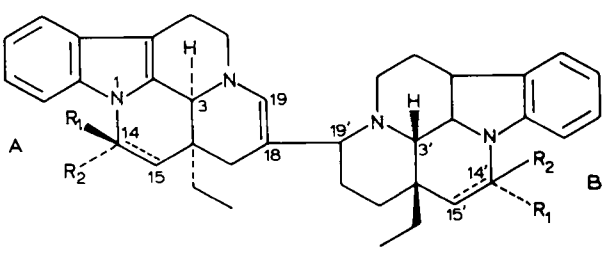
Abstract. The dimeric products (**1a-c**) have been prepared by treatment of *N*-oxides derived from some indole alkaloids. Their structures have been elucidated by detailed NMR investigations and the structure of **1c** determined by X-ray analysis. The importance of the E_2-type *trans*-axial elimination of the *N*-acyloxy intermediate in the dimer formation has also been established. The iminium salts **4a-b** and the derived pseudocyanide **6** have been prepared.

In a preliminary communication[2] we have described the formation of dimeric products **1a-c** by treatment of *N*-oxides derived from vincamone (**2a**), vincamine (**2b**) and apovincaminic acid ethyl ester (**2c**) with acetic anhydride.
On water elimination and transesterification, **1b** can be transformed into **1c**.
It was shown that the most likely pathway for this dimer formation involves the interaction of intermediate enamine (*e.g.* **3**) with the corresponding iminium salt (*e.g.* **5**). Similar dimerizations with related molecules under different conditions have been previously observed[3].
In order to support the presumed reaction mechanism, enamine **3** was prepared as described in the literature[4] using a photochemical method, but in poor yield. It was found, however, that treatment of vincamone *N*-oxide (**2f**) with $K_2Cr_2O_7$[5] afforded the desired enamine in 45% yield[6]. In the first step, probably an E_2-type elimination occurs from the chromic ester and thus stereoelectronic factors favour the formation of kinetic iminium ion **5** instead of the thermodynamically more stable **4a**. The basification of **5** yields **3**, which gives rise to **1a** with acetic acid.
Iminium salt **5** was characterized through the formation of pseudocyanide **6** in 33.5% yield. The nitrile group in **6** is axial, which indicates a kinetically controlled attack of the nucleophile on the carbon–nitrogen double bond.
Treatment of the *N*-oxide **2h** with $K_2Cr_2O_7$ did not give the easily separable crystalline enamine as did the same treatment of **2f**, and subsequent chromatography afforded dimer **1c**, formed presumably in the course of chromatography[6].
To investigate the scope and limitations of the dimer formation under *Polonovski*-type reaction conditions, the modi-



2a-j

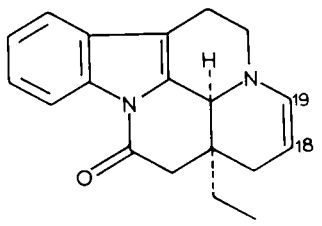
Compound	R-1(+ R-2)	H-3	C-14⊖C-15	N-4-oxide
a	O	α	single bond	f
b	OH + $COOCH_3$	α	single bond	g
c	$COOC_2H_5$	α	double bond	h
d	O	β	single bond	i
e	$COOCH_3$	β	double bond	j



1a-c

Compound	R^1 (+ R^2)	C-14 ⊖ C-15
a	O	single bond
b	OH + $COOCH_3$	single bond
c	$COOC_2H_5$	double bond
d	$COOCH_3$	double bond

Scheme 1. Structure of dimeric products **1a-c**.



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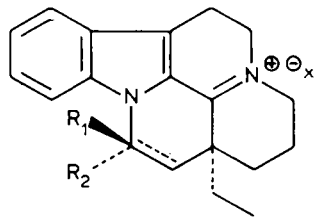


4a-b

Compound	R-1 (+ R-2)	C-14⊖C-15
a	O	single band
b	$COOCH_3$	double band

fied version[7], using trifluoracetic anhydride, was first investigated. In contrast to the statement of a Belgian patent[8], no iminium salts (**4**) were found, and only the dimers **1** were isolated in rather poor yield.

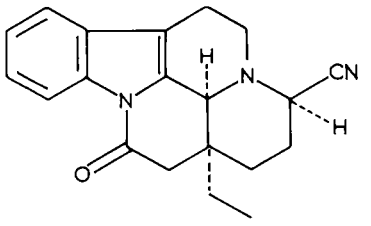
A dramatic change was observed, however, when the reaction was carried out with the *trans* series instead of the natural *cis* compounds.

When the *N*-oxide of *trans*-vincamone (**2i**) or *trans*-apovincamine (**2j**) was treated with trifluoroacetic anhydride, iminium salts **4a** and **4b** were obtained, respectively, as main products. Not a trace of dimer could be isolated.

The difference in the behaviour of the two (*cis* and *trans*) types of compounds can be rationalized by consideration of stereoelectronic factors.

In the *cis*-series (see Scheme 2), only the H_{ax}-19 of the *N*-acyloxy intermediate can be attacked by the acylate anion in an E_2-type *trans*-axial elimination reaction. On the other hand, in the *trans* series (Scheme 3), in addition to the above bond, the H_{ax}-5 and H-3 bonds are also in the appropriate stereoposition and, since the elimination of the latter leads to the thermodynamically most stable iminium salt, presumably the transition state energy requirement is the lowest for this particular reaction.

Our findings support the importance of E_2-type stereoelectronic requirements in the key-step of the Polonovski reaction.



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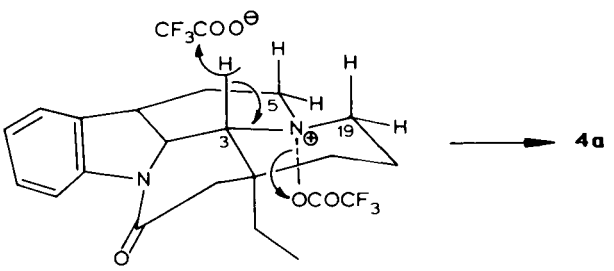
Structure determinations

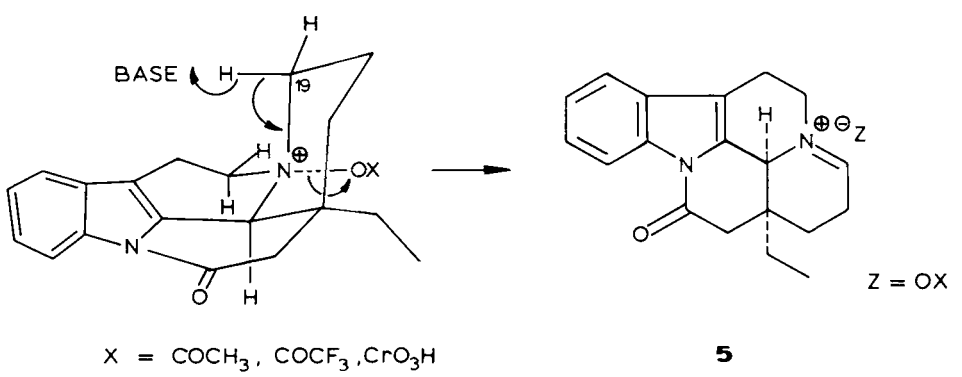
1. *NMR spectroscopy*

The structures of the dimeric compounds were first deduced from detailed ^1H and ^{13}C NMR studies of compound **1a**. The presence of the characteristic H-3 singlets (δ 4.13 and 3.82), the sharp vinylic proton signal at δ 5.82 and the three CH carbon signals between δ 55–59 ppm etc. all pointed to the suggested dimeric structure (Scheme 1). (This type of structure was later confirmed by X-ray analysis of compound **1c**; *vide infra.*)

In order to eliminate some of the uncertainties in the ^1H assignments (400 MHz) owing to the presence of the two similar units in the molecule, two-dimensional proton–proton correlation maps were also recorded: a COXY-45[9] spectrum at 360 MHz and one at 250 MHz, the latter optimized in order to reveal the presence of weak long-range coupling interactions. These correlations gave excellent starting points for tracing the homonuclear scalar connectivities in the various sub-spin systems. For example, the vinylic proton H-19 in unit A (δ 5.82) shows allylic couplings to the $H_{a,e}$-17 protons (δ 1.85 and 1.67), a "W" coupling with H-3 (δ 4.13) (the other characteristic H-3'* singlet (δ 3.82) is thus also assigned) and a further allylic coupling to H-19' of unit B, buried among other overlapping multiplets (δ 2.60–2.76). The respective coupling correlations of the above-mentioned signals (see Table II) readily led to the assignments given in Table I.



Scheme 3. Formation of the thermodynamically most stable iminium salt **4a**.



X = $COCH_3$, $COCF_3$, CrO_3H

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Scheme 2. Kinetically controlled formation of iminium salt **5**.

* Accent (') indicates unit B.

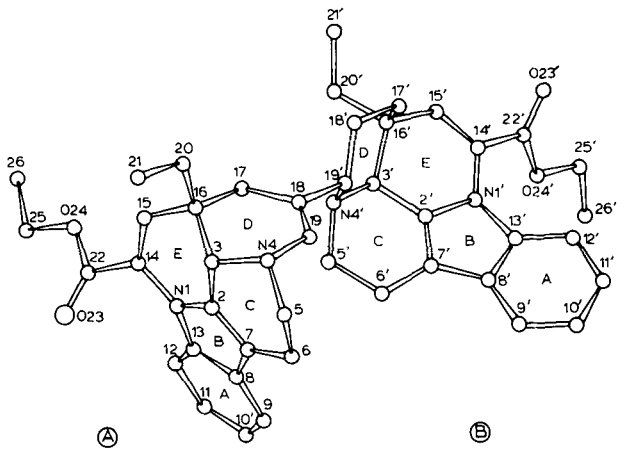

Fig. 1. A perspective view of dimer **1c** *showing the atomic labelling. The numbers are for carbon atoms, unless indicated otherwise. The H atoms are deliberately omitted. (The configuration presented is chosen in accordance with that of the natural vincamine skeleton.)*

Most of the ^{13}C assignments for **1a** were clarified by 2D C,H correlation measurements[10] (62.5/250 MHz) which also allowed the secure assignments of some very closely spaced signals (*e.g.* C-17, C-17′ and C-18′); see Table III. Monomeric indole derivatives **2a** and **3** were used as reference compounds. Assignments of the ^1H NMR spectra (400 MHz) were straightforward (see Tables I and II). (The ^1H chemical shifts for **2a** are consistent with those reported elsewhere[11].) ^{13}C signals were assigned (Table III) by using

Table I ^1H *chemical shifts for compounds* **1a**, **2a** *and* **3** *(400 MHz, $CDCl_3$, δ_{TMS} 0.00 ppm).*

Proton	**1a**		**3**	**2a**[a]
	unit A	unit B		
H_a-3	4.13	3.82	4.14	3.97
H_e-5	3.57	2.36–2.58	3.59	3.32
H_a-5	3.30	2.36–2.58	3.32	3.23
H_e-6	2.60–2.76	2.13	2.58	2.47
H_a-6	2.60–2.76	2.36–2.58	2.73	2.90
H-9	7.42	7.42	7.39	7.31
H-10	7.25–7.35	7.25–7.35	7.27	7.26
H-11	7.25–7.35	7.25–7.35	7.30	7.30
H-12	8.35	8.35	8.35	8.36
H_e-15	2.84	2.55	2.77	2.67
H_a-15	2.69	2.55	2.62	2.57
H_e-17	1.85	1.48	1.58–1.78	1.48
H_a-17	1.67	1.10 1.18 (eq.)	1.58–1.78	1.04 1.38 (eq.)
H-18	–	~1.63 (ax.) –	4.45	1.76 (ax.) 2.58 (eq.)
H-19	5.82	2.60–2.76 (ax.)	5.84	2.41 (ax.)
H_x-20	1.60	2.02	1.58–1.78	2.04
H_y-20	1.60	1.48	1.58–1.78	1.66
H_3-21	0.99	0.87	0.98	0.93

[a] See also ref. 12.

Table II Selected coupling constants (Hz) for compounds **1a**, **2a** *and* **3** *(400 MHz).*

^xJ(H-*y*-H-*z*)	**1a**		**3**	**2a**
	unit A	unit B		
^2J 5–5	13.9	[b]	14.0	13.9
6–6	[b]	15.8	16.1	16.9
15–15	17.0	[b]	17.0	16.6
17–17	[b]	14.0	17.0	13.4
18–18	–	[b]	–	13.4
19–19	–	[b]	–	10.7
20–20	[b]	14.3	[b]	14.4
^3J 5a–6a	10.7	[b]	11.5	10.6
5a–6e	5.5	[b]	4.7	5.7
5e–6a	5.0	[b]	6.0	6.6
5e–6e	<1	[b]	<1	<1
18–17e (α)	–	–	5.6	–
18–17a (β)	–	–	2.8	–
18–19	–	–	7.8	–
17a–18a	–	~14.0	–	13.4
17a–18e	–	[b]	–	3.9
17e–18a	–	[b]	–	3.4
17e–18e	–	[b]	–	3.1
18a–19a	–	[b]	–	12.5
18a–19e	–	–	–	3.2
18e–19a	–	[b]	–	2.9
18e–19e	–	–	–	3.2
^4J 3–17e	[a]	[a]	~2.4	1.6
19–17a	~2.0	–	2.4	–
19–17e	[a]	–	[b]	–
3–19	[a]	–	[b]	–
3–19e	–	–	–	~1
17e–19e	–	–	–	1.6
19–19′a	[a]	–	–	–
^5J 3–6a	[a]	[a]	3.2	2.9
3–6e	[a]	[a]	2.2	2.6

[a] Small coupling which is either not clearly resolved, or concealed by overlapping. The corresponding long-range correlations are detected in the COSY spectra. [b] Unreliably measured, mainly because of overlapping.

2D C,H correlation maps (measured at 25/100 MHz for **3** and at 100/400 MHz for **2a**).

A comparison of the ^1H and ^{13}C NMR shifts of **1a** with those of **2a** and **3** supports the deduced dimeric structure. Note, that the $H_{a,e}$-5′ signals (unit B) are shifted *ca.* 0.8 ppm upfield from their values in **2a**. This might be attributed to the shielding effect of the indolic part of unit A, which passes "above" these protons during rotation around the C-18–C-19′ bond.

The coupling constants of the H-19′ signal in unit B are difficult to measure because of serious overlap. In the 2D heterocorrelated contour plot, however, the corresponding C-19′–H-19′ crosspeak clearly reveals the presence of a large $J(H_a\text{-}19'\text{-}H_a\text{-}18')$ coupling in the ^1H dimension, which evidently points to the axial (β) position of H-19′. This is also supported by the fact that no long-range coupling interaction is detected between H-3′ and H-19′ (*cf.* $^4J(H\text{-}3\text{-}H_e\text{-}19) \sim 1$ Hz, arising from the "W" pathway in **2a** – Table II).

Note that in unit A, as well as in **3**, δ(C-6) is shifted downfield relative to its δ *ca.* 16 ppm value, characteristic of the eburnane skeleton possessing *cis* D/E (and consequently *cis* C/D) ring fusions[12]. This downfield shift can be explained by the loss of the γ-gauche interaction between C-19 and C-6, owing to the "enamine" character of N-4. Nevertheless, the *cis* D/E ring fusion of unit A and **3** is reflected by the

Table III ^{13}C *chemical shifts for compounds* **1–4** *and* **6** *(25 MHz,* $CDCl_3$, δ_{TMS} *0.0 ppm).*

	1a		**1b**		**1c**		**2a**	**2b**[q]	**2c**	**2d**	**2e**	**2f**	**2g**	**2h**	**2i**[p]	**2j**	**3**	**4a**	**4b**	**6**
	A	B	A	B	A	B														
C-2	133.5[a]	132.6[a]	133.0[a]	132.2[a]	132.4[a]	131.5[a]	132.1	131.5	130.8	133.3	133.0	127.9[a]	127.2	128.2[a]	129.0	128.4[a]	133.5	125.2	125.1[a]	130.9
C-3	55.2	58.4	57.7[b]	60.0	53.7	57.7[b]	57.4	59.2	55.4	65.7	64.2	69.8	72.0	69.2	71.0	69.2	55.1	168.5	167.5	55.6
C-5	49.4	46.6	49.8	47.1	50.6	47.6	50.6	51.0	51.2	52.1	52.2	68.8	69.3	69.9	64.6	66.5	49.5	52.1	50.8	50.2
C-6	20.3	16.5	20.5	16.9	20.4	16.5	16.5	16.9	16.1	21.5[a]	21.4[a]	19.6	20.1	19.8	18.3[a]	18.3	20.7	19.8	19.8	18.5
C-7	113.1[c]	112.9[c]	106.9[c]	106.7[c]	109.6	109.6	112.3	105.9	108.4	112.9	109.0	112.6	105.1	107.9	111.6	107.6	113.2	128.6	125.2[a]	115.2
C-8	130.0[d]	129.7[d]	129.5	129.5	129.1[d]	129.9[d]	130.1	129.5	128.8	129.9	128.9[b]	128.7[a]	127.2	127.9[a]	126.9	126.8[a]	130.1	126.7	126.0[b]	129.9
C-9	118.0	118.0	118.4	118.4	118.2	118.2	117.9	118.5	118.0	118.1	118.1	118.3	118.6	118.4	118.8	118.7	118.2	122.4	122.4	118.6
C-10	123.8[e]	123.9[e]	120.2	120.2	120.2[e]	120.4[e]	123.7	120.3	120.0	123.8	120.1	124.3	120.7	120.9	124.3	120.7	123.9	126.7	123.6	124.1
C-11	124.3[f]	124.5[f]	121.6[f]	121.5[f]	121.7[f]	122.0[f]	124.1	121.7	121.5	124.0	121.4	125.6	122.9	123.1	124.8	122.0	124.4	132.1	130.4	124.8
C-12	116.3	116.3	110.3[g]	111.0[g]	112.6	112.6	116.1	110.3	112.3	116.2	112.4	116.3	111.6	112.8	115.8	113.2	116.4	116.9	115.2	116.0
C-13	134.5[h]	134.1[h]	134.5[h]	134.0[h]	135.0[h]	134.0[h]	134.2	134.1	133.8	135.0	135.1	134.8	135.5	134.8	134.9	134.4	134.5	138.2	139.3	134.3
C-14	167.7[i]	167.5[i]	82.4[i]	81.9[i]	129.1[d]	128.3[d]	167.5	82.0	128.2	167.6	128.1[b]	166.6	82.0	127.2[a]	165.8	127.6[a]	167.8	163.9	127.8[b]	166.5
C-15	43.3	44.1	43.9[k]	44.5[k]	128.6[j]	127.6[j]	44.2	44.6[a]	127.7	44.1	131.7	43.3	43.6	128.2	44.7	129.1	43.6	42.3	123.9	43.9
C-16	37.6	38.2	34.8[l]	35.1[l]	37.5[l]	37.9[l]	38.3	35.2	37.4	39.3	38.6	40.0	37.1	39.3	40.7	39.5	37.7	41.7	40.9	37.5
C-17	26.2	26.0	25.4	23.9	26.2	26.0	27.0	25.2	27.1	31.7	30.0	26.9	25.2	28.5	31.0	29.7	26.7	25.0	24.7	23.7
C-18	113.1	26.8	114.0	26.5	114.0	27.8	20.7	20.9	20.2	21.2[a]	22.9[a]	16.4	16.8	15.9	17.9[a]	18.3	99.4	17.5	17.1	25.4
C-19	130.0	57.3	129.5	56.7[b]	130.2	56.9[b]	44.3	44.5[a]	44.7	55.3	54.9	57.8	57.9	58.4	66.9	67.4	132.2	52.6	52.6	47.4
C-20	29.1	28.0	29.9	28.7	28.5	28.0	28.2	29.0	28.5	20.7[a]	21.4[a]	30.3	30.9	29.9	21.9	24.0	29.5	29.7	33.2	29.0
C-21	8.0	7.6	8.0	7.6	8.9	8.5	7.7	7.6	8.6	7.4	8.2	8.3	8.4	9.4	8.0	9.2	8.0	7.4	7.8	7.6
other			174.6[n]	174.2[n]	163.3[m]	163.4[m]		174.6[n]	163.2[m]		163.4[n]		173.8[n]	162.4[m]		162.7[n]			161.6[n]	
			54.3	54.3	61.7	61.7		54.3	61.5		52.1		53.8	61.9		52.5			53.1	
					14.3	14.3			14.0					14.0						

[a-l] Tentative assignment. [m] COOEt. [n] COOMe. [q] See also ref. 11. [p] $CDCl_3$ + few drops of CD_3OD.

relatively high chemical shift of C-20[13] (δ 29.1 and 29.5 ppm, respectively).

As a consequence of the γ-gauche interaction with C-18, the C-5′ signal in unit B is shifted *ca.* 4 ppm upfield relative to its value in **2a**. With C-17′, however, no upfield shift is found, which also confirms the indicated relative configuration of C-19′.

For **1b** and **1c**, ^{13}C assignments were based on the data given for **1a**. To allow comparisons, ^{13}C data for monomeric compounds **2b**[12] and **2c** are also included in Table III, together with those of the corresponding *N*-oxide derivatives **2f-h**. As to the ^{13}C assignments of the latter compounds, the definite identification of the C-18 and C-6 signals was the only problem, which was readily solved by a 2D C,H correlation measurement for **2f**. (^1H chemical shifts are given in the Experimental). Note, that while the C-18 signals show proper γ-gauche upfield shifts (~ −4 ppm) in **2f-h** due to the interaction with the N−O oxygen, interestingly, more than +3 ppm downfield shifts are found on the C-6 signals owing to the corresponding γ-*anti* effect.

In the case of *trans* isomers **2d** and **2e**, ^{13}C assignments were based on data reported earlier[13]. Assignment of *N*-oxides **2i**

Table IV Oxygen β(SCS) values (ppm) for compounds **2f-j**.

Carbon atom	2f	2g	2h	2i	2j
C-3	12.4	12.8	13.8	5.3	5.0
C-5	18.2	18.3	18.7	12.5	14.3
C-19	13.5	13.4	13.7	11.6	12.5

Table V Positional parameters of **1c**.

Atom	x/a	y/b	z/c	Atom	x/a	y/b	z/c
O(23,)	−0.0249(4)	0.4201(2)	1.5916(2)	H(3)	0.911	0.470	0.902
O(23)	0.4163(4)	0.4097(2)	0.6489(2)	H(3,)	0.132	0.428	1.210
O(24,)	−0.1532(3)	0.5107(2)	1.4962(2)	H(5b)	0.993	0.595	0.964
O(24)	0.3883(4)	0.3061(1)	0.7412(2)	H(5a)	0.968	0.616	1.075
N(1)	0.5373(4)	0.4820(2)	0.8374(2)	H(5a,)	0.213	0.508	1.081
N(1,)	0.1485(4)	0.5212(2)	1.3896(2)	H(5b,)	0.408	0.514	1.058
N(4)	0.8845(4)	0.5133(2)	1.0384(2)	H(6a)	0.692	0.652	1.040
N(4,)	0.3698(4)	0.4469(2)	1.1732(2)	H(6b)	0.781	0.681	0.947
C(2)	0.6700(5)	0.5165(2)	0.8976(3)	H(6a,)	0.464	0.603	1.176
C(2,)	0.2173(5)	0.5147(2)	1.2983(3)	H(6b,)	0.283	0.627	1.125
C(3,)	0.2380(5)	0.4409(2)	1.2474(3)	H(9)	0.390	0.711	0.892
C(3)	0.8194(5)	0.4733(2)	0.9462(3)	H(9,)	0.302	0.742	1.298
C(5,)	0.3295(5)	0.5132(3)	1.1099(3)	H(10)	0.114	0.701	0.809
C(5)	0.9156(6)	0.5929(3)	1.0161(4)	H(10,)	0.239	0.801	1.448
C(6,)	0.3448(5)	0.5893(2)	1.1651(3)	H(11)	0.016	0.588	0.739
C(6)	0.7499(6)	0.6373(2)	0.9823(4)	H(11,)	0.140	0.732	1.580
C(7,)	0.2679(5)	0.5823(2)	1.2646(3)	H(12)	0.196	0.482	0.741
C(7)	0.6316(6)	0.5890(2)	0.9149(3)	H(12,)	0.080	0.604	1.564
C(8)	0.4616(6)	0.6026(2)	0.8651(3)	H(15)	0.678	0.312	0.854
C(8,)	0.2313(5)	0.6354(2)	1.3409(3)	H(15,)	0.111	0.345	1.443
C(9)	0.3524(7)	0.6649(3)	0.8614(4)	H(17a)	0.649	0.342	1.083
C(9,)	0.2587(6)	0.7137(2)	1.3515(4)	H(17b)	0.523	0.396	1.022
C(10)	0.1887(7)	0.6586(3)	0.8130(4)	H(17a,)	0.483	0.337	1.411
C(10,)	0.2218(6)	0.7483(2)	1.4403(4)	H(17b,)	0.477	0.424	1.409
C(11)	0.1314(6)	0.5910(3)	0.7700(4)	H(18a,)	0.702	0.382	1.319
C(11,)	0.1596(7)	0.7075(3)	1.5191(4)	H(18b,)	0.572	0.335	1.250
C(12)	0.2363(6)	0.5282(3)	0.7712(3)	H(19,)	0.582	0.490	1.259
C(12,)	0.1252(6)	0.6311(2)	1.5102(3)	H(20b)	0.981	0.361	1.057
C(13,)	0.1599(5)	0.5961(2)	1.4200(3)	H(20a)	0.886	0.293	1.005
C(13)	0.4038(6)	0.5351(2)	0.8189(3)	H(20a,)	0.283	0.302	1.209
C(14)	0.5480(5)	0.4048(2)	0.8167(3)	H(20b,)	0.102	0.301	1.253
C(14,)	0.0976(5)	0.4551(2)	1.4396(3)	H(21a)	1.155	0.308	0.942
C(15)	0.6619(5)	0.3622(2)	0.8734(3)	H(21c)	1.009	0.321	0.856
C(15,)	0.1503(6)	0.3883(2)	1.4090(3)	H(21b)	1.104	0.389	0.908
C(16)	0.7651(5)	0.3918(2)	0.9670(3)	H(21a,)	0.242	0.189	1.286
C(16,)	0.2673(5)	0.3763(2)	1.3249(3)	H(21b,)	0.215	0.229	1.387
C(17,)	0.4604(5)	0.3794(2)	1.3695(3)	H(21c,)	0.396	0.230	1.343
C(17)	0.6386(6)	0.3896(2)	1.0516(3)	H(25a)	0.185	0.300	0.639
C(18,)	0.5862(6)	0.3798(2)	1.2884(3)	H(25b)	0.353	0.266	0.601
C(18)	0.6693(5)	0.4481(2)	1.1308(3)	H(25a,)	−0.338	0.470	1.578
C(19,)	0.5550(5)	0.4471(2)	1,2180(3)	H(25b,)	−0.236	0.536	1.631
C(19)	0.7817(5)	0.5046(2)	1.1222(3)	H(26a)	0.166	0.171	0.640
C(20)	0.9257(6)	0.3425(3)	0.9951(4)	H(26b)	0.166	0.201	0.749
C(20,)	0.2241(6)	0.3019(2)	1.2694(3)	H(26c)	0.335	0.167	0.711
C(21,)	0.2740(7)	0.2308(3)	1.3264(4)	H(26a,)	−0.510	0.576	1.571
C(21)	1.0609(8)	0.3401(4)	0.9179(5)	H(26b,)	−0.472	0.552	1.463
C(22,)	−0.0274(5)	0.4600(2)	1.5185(3)	H(26c,)	−0.370	0.618	1.515
C(22)	0.4439(6)	0.3751(2)	0.7253(3)				
C(25)	0.2855(7)	0.2706(3)	0.6576(4)				
C(25,)	−0.2867(6)	0.5172(3)	1.5682(4)				
C(26)	0.2337(7)	0.1953(3)	0.6924(4)				
C(26,)	−0.4217(7)	0.5706(3)	1.5255(5)				

and **2j** was straightforward. The C-6 and C-18 signals are shifted *ca.* 3 ppm upfield owing to the γ-gauche interactions with the N–O oxygen. The β(SCS) (substituent-induced chemical shift) values of the N–O oxygen in compounds **2i-j** show characteristic differences (Table IV), depending on the axial (Δδ 11.6–14.3 ppm) or equatorial (Δδ 18.2–18.7 ppm) position of the oxygen in the corresponding ring. In compounds **2i** and **2j**, however, the deshielding effect on C-3 is strikingly smaller (Δδ 5.0–5.3 ppm).

Both structure elucidations and ^{13}C assignments for iminium salts **4a** and **4b** were based on recently reported data[14]. In the case of **4b**, an unambiguous differentiation of the not readily assignable C-20–C-17; C-18–C-6 and C-10–C-15 signal pairs was also achieved by recording a C,H correlation map (25/100 MHz) and by considering the corresponding ^1H chemical shift relations (see Experimental).

For compound **6**, the ^{13}C and ^1H data justify the C-19 position of the CN group in a self-explanatory manner. Assignment of the H-19 signal was unambiguously confirmed by a 2D hetero-correlation measurement (see Experimental). The small couplings of H-19 [$J(H_e\text{-}19\text{–}H_a\text{-}18)$ 4.9 Hz, $J(H_e\text{-}19\text{–}H_e\text{-}18)$ 2.3 Hz] establish the axial (β) position of the CN group. This conclusion is supported by the ~0.6 ppm downfield shift of the H_a-17 and H_a-6 signals (*cf.* **2a**), owing to the anisotropic effect of the axial CN group, and also by the γ-gauche effect found on the C-17 carbon signal (–3.3 ppm).

2. *X-ray structure determination of* **1c**

Crystals of **1c** are monoclinic (M_w = 695.89) space group $P2_1$, a = 7.686(1), b = 17.828(5), c = 13.287(2) Å, β = 94.37(1)°, V = 1815.3(10) Å^3, Z = 2, d_c = 1.273 g/cm^3, $F(000)$ = 742. Intensities were measured from a crystal of 0.15 × 0.18 × 0.30 mm^3 dimensions with an Enraf-Nonius CAD-4 diffractometer at room temperature (295 ± 1 °K) using graphite monochromated CuK_α radiation (λ = 1.54184 Å) θ/2θ mode, 1.5 < θ < 75.0°, scan width (θ): (0.60 + 0.14tgθ).

The solution of the phase problems (MULTAN)[15] and full-matrix refinement of the atomic parameters were based on 3087 reflections with $I > 1.5\sigma(I)$ (from counting statistics). In the course of isotropic refinement of the positional parameters of non-hydrogen atoms, an empirical absorption correction (μ = 6.1 cm^{-1}) was calculated with the programme DIFABS[16]; minimum and maximum absorption corrections 0.546 and 1.616. Refinement of scale factor, positional and anisotropic thermal parameters of non-hydrogen atoms resulted in R = 0.055, R_w = 0.058, R_{tot} = 0.066, S = 3.76. The largest parameters shift/error in the last cycle of refinement was 0.57; maximum and minimum peak heights in final Δρ map 0.27 e/Å^3. Positions of H atoms were generated from assumed geometries; their positions were taken into account without refinement in the structure factor calculations with isotropic temperature factors ($B_{iH} = B_{iC}$ + 1 Å^2). Positional parameters are given in Table V. A drawing of the structure of **1c** showing atomic numbering (whilst the hydrogens are deliberately omitted for clarity) substantiates a dimeric structure (indicated as unit A and B) via a C-18–C-19′ single bond of 1.507(6) Å, which, as expected, assumes an α-equatorial position [C-18–C-19′–C-18′–C-17′ 176.2(8)°] to the D ring of unit B. The saturated D ring in unit B possesses chair conformation while in unit A it retains a transitional form between a half-chair ($^3H_{16}$) and envelope (^3E) in accordance with the double bond between C-18 and C-19 [1.336(6) Å]. The puckering of the C and E rings is unaffected by the change in that of ring D. In both A and B units, ring C has an ^4E envelope shape while ring E assumes a skew (1,3-diplanar) conformation.

Experimental

Reagents and solvents were used as obtained from the supplier. In preparative column and TLC chromatography, MERCK Kieselgel 60 was used. The optical rotations were recorded in chloroform at 25 ± 2°C. IR spectra were recorded on a Specord IR 75 spectrometer using KBr pellets or film. The UV absorption spectra were recorded on a UV Specortd UV-VIS spectrometer; the spectra were measured in ethanol.

All the NMR spectra were recorded in the PFT mode, with internal deuterium lock at ambient temperature (298 K), on Bruker WH-400/DS, Bruker WM-250, Bruker WH-360, Varian XL-400 and Jeol FX-100 spectrometers. The ^1H chemical shifts and coupling constants were calculated as first-order spectra at 400 MHz. Two-dimensional experiments were recorded by using the standard spectrometer software packages. Mass spectra were recorded on an AEI-MS-902 (70 eV, direct insertion) mass spectrometer. M.p. s are uncorrected.

Preparation of N-*oxides* (**2f-j**)

(–)-Vincamone N-*oxide* (**2f**). To a solution of (–)-Vincamone **2a** (29.4 g, 0.1 mol) in chloroform (700 ml), a solution of *m*-chloroperbenzoic acid (*m*-CPBA) (Fluka, 25.8 g, 0.15 mol) in chloroform (100 ml) was added and the mixture stirred at room temp. for 1 h. The reaction mixture was shaken with 120 ml 10% NaOH solution. The aqueous solution was extracted with chloroform (2 × 50 ml) and the combined organic layers were washed with water (2 × 50 ml) and dried (Na_2SO_4). The filtrate was evaporated *in vacuo* and the residue (29.6 g) was crystallized from ether (50 ml) to yield 28.3 g of **2f** (91.3%); m.p. 220–222°C; $[\alpha]_D$ –61.9 (*c* 0.2, $CHCl_3$). Anal. $C_{19}H_{22}O_2N_2$ (310.38) calcd.: C 73.52, H 7.14, N 9.03; found: C 73.49, H 7.22, N 8.97%. UV (EtOH) λ_{max}/nm (lgε): 202 (4.44), 239 (4.33), 263 (4.09), 291 (4.87), 298 (4.87). IR (KBr): 1720, 1630, 1140 cm^{-1}. MS *m/e* (%): 310 (M$^+$, 57), 294 (M – 16,100), 293 (96), 291 (11), 265 (28), 263 (10), 251 (8), 237 (22), 236 (14), 224 (61), 222 (11), 209 (7), 196 (7), 194 (8), 180 (20), 167 (20). ^1H NMR (100 MHz, $CDCl_3$) δ: 1.00 (t, 3H, $-CH_2C\underline{H}_3$), 2.39 (q, 2H, $-C\underline{H}_2CH_3$), 2.82 (d, 1H, 15-H), 2.50 (d, 1H, 15-H), 0.9–1.7 (m, 3H, 17-H_2 + 18-H_e), 2.2–3.4 (m, 5H, 19-H_2 + 6-H_2 + 18-H_a), 3.6–4.2 (m, 2H, 5-H_2), 4.48 (s, 1H, 3-H), 7.20–7.35 (m, 3H, 9-H, 10-H, 11-H), 8.35 (m, 1H, 12-H).

2g-j were prepared according to the above procedure.

(–)-Vincamine N-*oxide* (**2g**). Yield 84.8%; m.p. 275–276°C (from ethyl acetate) (lit.[17] 280°C); $[\alpha]_D$ –8.9 (*c* 1, $CHCl_3$) (lit.[17] –2 ± 5). Anal. $C_{21}H_{26}O_4N_2$ (370.43) calcd.: C 68.09, H 7.07, N 7.56; found: C 67.95, H 7.13, N 7.49. IR (KBr): 1750, 3450, 960 cm^{-1}. MS *m/e* (%): 370 (M$^+$, 24), 354 (38), 353 (28), 337 (2). ^1H NMR (100 MHz, $CDCl_3$) δ: 1.00 (t, 3H, $-CH_2C\underline{H}_3$), 4.34 (s, 1H, 3-H), 2.27 (s, 2H, 15-H), 3.78 (s, 3H, $-COOC\underline{H}_3$), 7.44 (m, 1H, 9-H), 7.00–7.30 (m, 3H, 10-H, 11-H, 12-H), 1.15 (m, 14H, skeletal + $-C\underline{H}_2CH_3$).

(+)-Apovincaminic acid N-*oxide ethyl ester* (**2h**). Yield 96.1%; m.p. 98–99°C (from a mixture of ethyl acetate/petroleum ether 3/7); $[\alpha]_D$ +111.6 (*c* 0.2, $CHCl_3$). Anal. $C_{22}H_{26}O_3N_2$ (366.44) calcd.: C 72.10, H 7.15, N 7.65; found: 72.18, H 7.04, N 7.66%. UV (EtOH) λ_{max}/nm (lgε): 204 (4.39), 225 (4.46), 269 (4.09), 313 (3.94). IR (KBr): 1700, 1610 cm^{-1}. ^1H NMR (100 MHz, $CDCl_3$) δ: 1.10 (t, 3H, $-CH_2C\underline{H}_3$), 2.30 (q, 2H, $-C\underline{H}_2CH_3$), 4.65 (s, 1H, 3-H), 6.05 (s, 1H, 15-H), 7.45 (m, 1H, 9-H), 7.10–7.30 (m, 3H, 9-H, 10-H, 11-H), 1.20–4.20 (m, 10H, skeletal).

(±)-3-Epieburnamenin-14(15H)-one N-*oxide* (**2i**). Yield 80%; m.p. 127–131°C (from ethyl acetate). Anal. $C_{19}H_{22}O_2N_2$ (310.38) calcd.: C 73.52, H 7.14, N 9.03; found: C 73.60, H 7.28, N 8.99%. IR (KBr): 1700, 1650, 1640 cm^{-1}. ^1H NMR (100 MHz, $CDCl_3$) δ: 0.70 (t, 3H, $-CH_2C\underline{H}_3$), 2.39 (d, 1H, 15-H), 2.95 (d, 1H, 15-H), 4.61 (s, 1H, 3-H), 1.2–4.8 (m, 12H, skeletal + $-C\underline{H}_2CH_3$). 7.2–7.5 (m, 3H, 9-H, 10-H, 11-H), 8.30 (m, 1H, 12-H).

(–)-14-(Methoxycarbonyl)-(3β,16α)-eburnamenine N-*oxide* (**2j**). Yield 74%; m.p. 125–128°C (from ether). $[\alpha]_D$ –141.2 (*c* 0.2, $CHCl_3$).

Anal. $C_{21}H_{24}O_3N_2$ (352.42) calcd.: C 71.57, H 6.86, N 7.95; found: C 71.34, H 6.95, N 8.01. UV (EtOH) λ_{max}/nm (lgε): 205 (4.39), 227 (4.33), 270 (3.97), 312 (3.82). IR (KBr): 1720, 1650, 1600 cm^{-1}. ^1H NMR (100 MHz, $CDCl_3$) δ: 0.70 (t, 3H, $-CH_2C\underline{H}_3$), 3.90 (s, 3H, $-COOC\underline{H}_3$), 4.02 (s, 1H, 3-H), 6.17 (s, 1H, 15-H), 7.05–7.5 (m, 4H, 9-H, 10-H, 11-H, 12-H), 1.3–3.9 (m, 12H, skeletal + $-C\underline{H}_2CH_3$).

Preparation of dimers **1a-c**

Route A: reaction of N*-oxides with acetic anhydride*

1a. **2f** (12.41 g, 40 mmol) was dissolved in acetic anhydride (50 ml. 0.53 mol) and the mixture stirred at room temp. for 24 h. The precipitated crystals were filtered off, washed with ether (2 × 10 ml) and dried to give **1a** (6.14 g, 52.5%). For physical data see ref. 2.

1b. **2g** (52 g, 0.14 mol) was dissolved in acetic anhydride (500 ml, 5.3 mol) and the mixture stirred at room temp. for 24 h. The reaction mixture was poured into 400 g of broken ice and 3 l of ethyl acetate were added. The mixture was alkalized to pH 8 by adding concentrated aqueous amonium hydroxide solution (0.9 l) while stirring. The organic layer was separated and washed with water (7 × 100 ml), dried (Na_2SO_4), filtered and evaporated under reduced pressure. The residue (46.5 g) was crystallized rom methanol (120 ml) to give 22 g of **1b** (44.4%). For physical data see ref. 2.

1c. **2h** (3 g, 8.2 mmol) was dissolved in acetic anhydride (10 ml, 0.105 mol) and the mixture stirred at room temp. for 24 h. The reaction mixture was poured into 60 g of broken ice and 200 ml of ethyl acetate was added. The mixture was alkalized to pH 8 by adding concentrated aqueous ammonium hydroxide solution (16 ml) while stirring. The organic layer was separated and washed with water (4 × 20 ml), dried (Na_2SO_4), filtered and evaporated under reduced pressure. The residue (2.4 g) was chromatographed on silica (eluent: cyclohexane/ethyl acetate 7/3). The collected eluates were evaporated *in vacuo* and the residue (1.02 g) was crystallized from ethanol (15 ml) to afford **1c** (0.8 g, 28%). For physical data see: ref. 2.

Route B: water elimination and transesterification of **1b**

1d. A mixture containing **1b** (14.03 g, 20 mmol) and *p*-toluenesulphonic acid monohydrate (20.12 g, 0.105 mol) in benzene (1000 ml) was refluxed using a water-separating device for 4 h and then cooled. After adding 200 ml of water, the pH was adjusted to 8 by using concentrated aqueous ammonium hydroxide solution (30 ml). After extraction, the benzene phase was washed with water (3 × 100 ml), dried (Na_2SO_4), filtered and the filtrate evaporated to dryness under reduced pressure. The residue was crystallized from methanol (100 ml) to give a crude product (11.1 g, 80.6%), which was dissolved in chloroform (400 ml), cleared with silica (50 g), filtered and the filtrate evaporated under reduced pressure. The residue was crystallized from methanol (50 ml) to afford **1d** (6.8 g, 49.4%); m.p. 178–190°C; $[\alpha]_D$ −224.3 (*c* 0.2, $CHCl_3$). Anal. $C_{42}H_{44}O_4N_4$ (668.80) calcd.: C 75.42, H 6.63, N 8.38; found: C 75.39, H 6.65, N 8.29%. MS *m/e* (%): 668 (M^+, 17), 640 (1.5), 639 (1.2), 637 (1), 610 (1.4), 609 (1.3), 373 (47), 360 (3.8), 343 (4.7), 335 (49), 334 (M/2, 14), 280 (10), 266 (100), 251 (11), 135 (3.1), 71 (7.6), 57 (7.1), 50 (16), 44 (9). ^1H NMR (100 MHz, $CDCl_3$) δ: 0.94 (t, 3H, $-CH_2C\underline{H}_3$), 1.07 (t, 3H, $-CH_2C\underline{H}_3$), 4.28 (s, 1H, 3-H), 3.9 (s, 1H, 3-H, overlap), 3.95 (s, 3H, $-COOC\underline{H}_3$), 3.90 (s, 1H, $-COOC\underline{H}_3$), 6.40 (s, 1H, 15-H), 6.12 (s, 1H, 15-H), 5.84 (d, *J* 1.5 Hz, 1H, 19-H in part A), 7.00–7.30 (m, 6H, 10-H, 11-H, 12-H), 7.44 (m, 2H, 9-H), 1.20–3.80 (m, 20H, skeletal + $-C\underline{H}_2CH_3$).

1.37 g (2 mmol) of this substance and potassium *tert*-butoxide (0.01 g) in anhydrous ethanol (100 ml) was refluxed for 3 h. After cooling the solution to room temp., the precipitated crystals were filtered off and washed with ethanol (2 × 10 ml) to yield **1c** (1.2 g, 79.5%).

Route C: reaction of N*-oxide* **2h** *with* $K_2Cr_2O_7$

1c. **2h** (1.46 g, 4 mmol) was dissolved in water (100 ml) at 75–80°C. A solution of $K_2Cr_2O_7$ (1.2 g, 4 mmol) in water (5 ml) was added and the mixture stirred for 5 min. After cooling to room temp., 30 ml saturated $NaHCO_3$ solution was added under stirring and the mixture was extracted with ethyl acetate (5 × 50 ml). The combined organic phase was washed with water (3 × 10 ml), dried (Na_2SO_4), filtered and evaporated under reduced pressure. The residue (1.3 g) was chromatographed on silica (eluent: cyclohexane/ethyl acetate 99/1, 200 ml; 9/1, 100 ml; 7/3, 100 ml). The solvent was evaporated under reduced pressure and the residue was crystallized from ethanol (10 ml) to give **1c** (0.62 g, 44.9%).

Route D: reaction of N*-oxide* **2h** *with trifluoracetic anhydride*

1c. **2h** (0.36 g, 1 mmol) was dissolved in dry methylene chloride (5 ml), cooled to −20°C and trifluoracetic anhydride (Aldrich, 0.3 ml, 2.1 mmol) was added dropwise over a period of 3 min. Stirring was continued at −20°C for 1 h and the same amount of trifluoroacetic anhydride was then added. The mixture was evaporated under reduced pressures and the residue dissolved in a mixture of hot water (5 ml) and ethanol (2 ml). The solvent was then alkalized to pH 8 by adding a concentrated aqueous ammonium hydroxide solution. The precipitated crystals were filtered, washed with water and dried to give a crude product (190 mg) which was chromatographed by preparative TLC on silica (20 × 20 cm, 1.5 mm thick layer, using a 9/1 mixtureof cyclohexane and ethyl acetate) to afford **1c** (90 mg, 23%).

Route E: reaction of enamine **3** *with acetic acid*

3 (292 mg, 1 mmol) was dissolved in glacial acetic acid (10 ml) and stirred at 80°C for 1½ h. After removal of the acetic acid *in vacuo*, the residue was dissolved in a mixture of ethyl acetate/saturated $NaHCO_3$ solution (50/20 ml). The organic layer was separated and washed with water (2 × 25 ml), dried (Na_2SO_4) and filtered. The solution was then concentrated under reduced pressure to 5 ml ands allowed to crystallize to afford **1a** (148 mg, 50.7%).

Preparation of enamine **3**

(−)-18,19-Dehydro-(3α,16α)-eburnamenin-14(15H)-one (**3**). **2f** (1.24 g, 4 mol) was dissolved in water (35 ml) at 65–70°C. A solution of $K_2Cr_2O_7$ (1.2 g, 4 mmol) in water (5 ml) was then added and the mixture stirred for 5 min at 75–80°C. After cooling to room temp., 30 ml saturated $NaHCO_3$ solution was added under stirring and the mixture was extracted with ethyl acetate (5 × 10 ml). The combined organic layer was washed with water (3 × 10 ml), dried (Na_2SO_4), filtered and evaporated *in vacuo*. The residue (0.9 g) was crystallized from methanol (20 ml) to give **3** (44.8%); m.p. 153–154°C (lit.[4] 153°C). $[\alpha]_D$ −102.8 (*c* 0.2, $CHCl_3$). $C_{19}H_{20}ON_2$ (292.37) calcd.: C 78.05, H 6.90, N 9.58; found: C 78.12, H 6.73, N 9.32%. MS *m/e* (%): 292 (M^+, 78), 291 (31), 277 (2.4), 264 (9), 263 (22), 261 (5.3), 235 (5.4), 224 (M-68, 100), 196 (4.8), 180 (9.6), 168 (14), 167 (18). ^1H and ^{13}C NMR data see Tables I–III.

Preparation of iminium salts **4a-b**

(±)-3,4-Dehydroeburnamenin-14(15H)-one (**4a**). **2i** (0.31 g, 1 mmol) was dissolved in dry methylene chloride (15 ml), cooled below 0°C and trifluoroacetic anhydride (0.6 ml, 4.2 mmol) was added dropwise. Stirring was continued at 0°C for 1 h and at room temp. for 24 h. After evaporation of the solvent under reduced pressure (bath temp. 20°C), the oily iminium compound **4a** was obtained in quantitative yield. ^1H NMR (100 MHz, $CDCl_3$) δ: 0.97 (t, 3H, $-CH_2C\underline{H}_3$), 1.4–2.3 (m, 6H, $-C\underline{H}_2CH_3$ + 17-H_2 + 18-H_2), 3.01 (d, 1H, 15-H), 3.22 (d, 1H, 15-H), 3.2–3.5 (m, 2H, 6-H_2), 3.8–4.6 (m, 4H, 5-H_2 + 19-H_2), 7.1–7.9 (m, 3H, 9-H, 10-H, 11-H), 8.36 (dd, 1H, 12-H).

Following the above procedure compound **4b** was prepared from **2j**.

(−)-3,4-Dehydro-14-(methoxycarbonyl)-(16α)-eburnamenine **4b**. $[\alpha]_D$ −398.9 (*c* 0.2, $CHCl_3$). UV (EtOH) λ_{max}/nm (lgε): 210 (4.53), 238 (4.27), 260 (4.09), 358 (4.20). IR (film): 1800, 1740, 1660, 1590 cm^{-1}. ^1H NMR (100 MHz, $CDCl_3$) δ: 0.83 (t, 3H, $-CH_2C\underline{H}_3$), 1.90 (q, 2H, $-C\underline{H}_2CH_3$), 1.9–2.5 (m, 4H, 17-H_2 + 18-H_2), 3.35 (m, 2H, 6-H_2), 3.99 (s, 3H, $-COOC\underline{H}_3$), 3.55–4.35 (m, 4H, 5-H_2 + 19-H_2), 6.32 (s, 1H, 15-H), 7.30 (t, 1H, 10-H), 7.66 (d, 1H, 9-H), 7.40–7.56 (m, 2H, 11-H, 12-H).

Cyanide trapping of iminium salt **5**

(+)-19-Cyano-(3α,16α,19β)-eburnamenine-14(15H)-one (**6**). To a solution of **2f** (0.44 g, 1.5 mmol) in dry methylene chloride (15 ml) at 0°C, trifluoroacetic anhydride (1 ml, 7 mmol) was added and the reaction mixture was stirred at room temp. for 24 h. Solvent

and excess reagent were removed by rotatory evaporation without heating and methylene chloride (20 ml) added, followed, at 0 °C, by potassium cyanide (0.5 g, 7.6 mmol) in water (1 ml). The pH was immediately adjusted to 4 by trifluoroacetic acid addition and the mixture stirred at room temp. for 1 h. Saturated $NaHCO_3$ solution was added to pH 8 and the layers separated. The organic layer was washed with water (2 x 25 ml), dried (Na_2SO_4), filtered and evaporated to give a brown oil, which was crystallized from methanol (10 ml) to yield **6** (0.16 g, 33.5%); m.p. 194–198 °C; $[\alpha]_D$ + 56.9 (*c* 0.2, $CHCl_3$). $C_{20}H_{21}ON_3$ (319.39) calcd.: C 75.21, H 6.63, H 13.16; found: C 75.09, H 6.57, N 12.09%. IR (KBr): 1690, 1610, 1420, 1430 cm^{-1}. MS *m/e* (%): 319 (M^+, 100), 318 (23), 292 (26), 291 (26), 290 (47), 263 (15), 262 (16), 224 (57), 209 (8.1), 180 (12), 168 (13), 167 (15), 159.5 (6.5). ^1H NMR (250 MHz, $CDCl_3$) δ: 0.95 (t, 3H, 21-H_3), 1.4–1.7 (m, 3H, 20-H_x + 17-H_a + 17-H_e), 1.78 (dq, 1H, 18-H_e, J_{gem} 14.0 Hz, $J_{18e,17e} \sim J_{18e,19e}$ 2.3 Hz, $J_{18e,17a}$ 3.2 Hz), 2.05 (dq, 1H, 20-H_y), 2.15 (m, 1H, 18-H_a), 2.59 (dm, 1H, 6-H_e), 2.7 (s, 2H, 15-H_2), 3.35–3.6 (m, 3H, 6-H_a, 5-H_a, 5-H_e), 3.97 (dd, 1H, 19-H_e, $J_{19e,18a}$ 4.9 Hz, $J_{19e,18e}$ 2.3 Hz), 4.07 (t, 1H, 3-H, *J* ~1.7 Hz), 7.28 (td, 1H, 10-H), 7.35 (td, 1H, 11-H), 7.44 (dd, 1H, 9-H), 8.35 (dd, 1H, 12-H).

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