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SYNTHESIS OF VINCA ALKALOIDS AND RELATED COMPOUNDS XLII[1] TRANSFORMATION OF VINCAMONE INTO VINCAMINES VIA DIAZOMETHANE ASSISTED HOMOLOGIZATION. APPLICATION OF ^{1}H-NOE MEASUREMENTS FOR THE CONFIGURATIONAL ASSIGNMENT OF THE SPIRO-OXIRANE RING[2]

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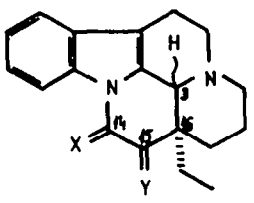
Abstract - The α-oxo-acids 4 and 5 derived from vincamone (1) were transformed into vincamines 2,9,10, respectively by methylene insertion with diazomethane. Homologization of 3 and 6 dioxo compounds led to oxirane derivatives 8,16,11,13, 18, respectively. Configuration of the oxiranes was determined by ^{1}H-NOE measurements.

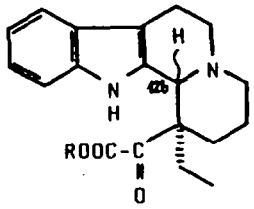
Vincamone (1) and vincamine (2) the two pharmacologically important representatives of *Hunteria* alkaloids have been objective of a number of total and partial syntheses[3]. Up till now several transformations of vincamine (2) into vincamone (1) have been known[4] but for the inverse approach (1→2) so far only one patent[5] has been published.

As we reported earlier[6] the (-)-cis-α-oxo-lactam 3 prepared from (-)-vincamone (1) underwent a ring opening followed by epimerization-racemization reaction with alkali to give a mixture of cis- (4) and trans-α-oxo-acids (5)[7]. To determine the composition of the resulting α-oxo-acid mixture as a function of the reaction conditions of the alkaline treatment, in addition to $POCl_3$ assisted cyclization[6], the esterification with diazomethane was also used. The mixture of 4,5 was treated with a small excess of diazomethane in dichloromethane resulting in cis- 3 and trans-α-oxo-lactams 6 via the corresponding esters (7,12). Ring closure of the latters was so rapid that only 3 and 6 were isolated, in accord with the observations of Bartlett and Taylor[8]. The isolation of vincamine (2) as minor compound (1-2 %) revealed a possible methylene insertion by diazomethane[9] as side reaction.

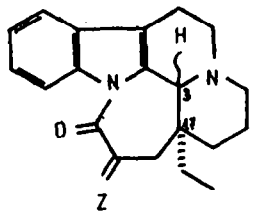
In order to favour the homologization reaction (-)-cis-α-oxo-acid 4 was treated with a large excess (10-12 eq.) of diazomethane in dichloromethane at room temperature for 4 h affording (+)-vincamine (2) (yield 32 %), proved to be identical in all respects with the natural product. From the mother liquor the 15-oxirano derivative (-)-8 (yield 27 %) was isolated by thin layer chromatography.



	X	Y	3-H
1	O	H_2	α
2	αCO_2CH_3 β OH	H_2	α
3	O	O	α
6	O	O	β
8	O	$-OCH_2-$	α
9	α OH βCO_2CH_3	H_2	β
10	αCO_2CH_3 β OH	H_2	β
11	O	$-OCH_2-$	β
13	O	$-OCH_2-$	β
14	O	H_2	β



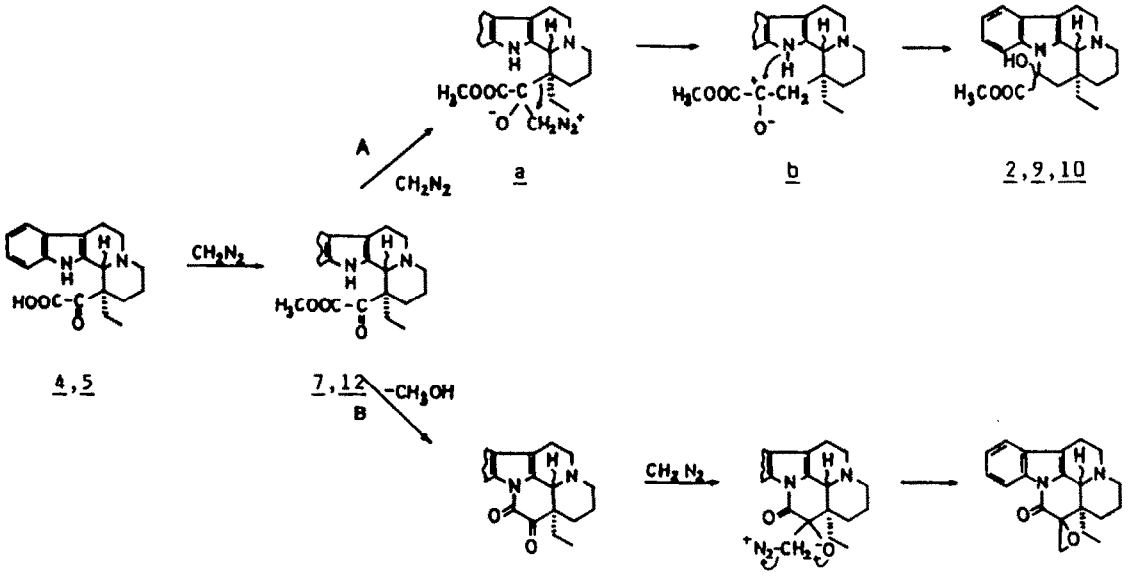
	R	12b-H
4	H	α
5	H	β
7	CH_3	α
12	CH_3	β



	Z	3-H
15	H_2	α
16	$-OCH_2-$	α
17	H_2	β
18	$-OCH_2-$	β

Under the same conditions (±)-trans-α-oxo-acid 5 led mainly to (±)-3-epi-14--epivincamine (9) (yield 41 %), to the more stable epimer in the C/D-trans series[10]. As minor products (±)-3-epivincamine (10)[10] (yield 4 %) and (±)11 trans-oxirane derivative (yield 17 %) were also isolated and characterized. Influence of Lewis acids ($Al(i\text{-}PrO)_3$, BF_3) on the homologization was also studied. In the cis-series no change was observed in the product ratio, but (±)-5 trans-α-oxo-acid gave with CH_2N_2 in the presence of catalytic amount of $Al(i\text{-}PrO)_3$, beside 9,10 and 11 a new trans-oxirane derivative (13) (yield 5 %), too.

According to the generally accepted mechanism[9] diazomethane addition on the ketone carbonyl leads to a diazonium betain(a). Subsequent C_1-C_1, bond migration and loss of nitrogen would give homo-esters(b) which close immediately[11] to the pentacyclic vincamine derivatives (Scheme 1., step A). Isolation of oxiranes may be explained by the sterically favoured ring closure reaction following the diazomethane addition (step B).



Scheme 1

In order to substantiate the supposed mechanism (step B) cis-α-oxo-lactam (-)-3 was allowed to react with a large excess of diazomethane in dichloromethane and methanol affording (-)-8 oxirane (yield 59 %) as expected. From the mother liquor (-)-16 E-homo-oxirane (yield 10 %) was isolated. Trans-α-oxo-lactam (±)-6 under similar conditions gave (±)-11 trans-oxirane (yield 58 %) and its E-homo derivative (±)-18 (yield 2 %).

The structure elucidation of the new compounds was accomplished by nuclear magnetic resonance methods.

The ^1H and ^{13}C NMR data of epoxy derivatives - together with those of the corresponding 14-oxo-eburnanes (1 and 14) and 14-oxo-homoeburnanes (15 and 17) - are included in Tables 1-3.

The complete assignment of all proton resonances for molecules 1, 8, 11 and 13 - 18 was achieved either by homonuclear decoupling or by COSY[12] experiments. Connectivities between identified protons and all protonated carbons were obtained by means of HETCOR[13] experiments.

The ring C/D stereochemistry of the new compounds was derived from the chemical shift values of H-3 protons and C-6 carbons[14] (4.0-4.36 ppm and 16.5 - - 17.58 ppm for cis-fused, and 3.0 -3.42 ppm and 21.2 - 21.92 ppm for trans-fused

system, respectively). The site of epoxy substitution on the six- and seven-membered ring E is evident from the proton and carbon chemical shift values. Of these the 3.5 - 5 ppm upfield shift of C-14 resonances is noteworthy, which can be ascribed to the β effect of the oxirane ring.

Significant (6-7 ppm) chemical shift differences can be observed for the C-15′ epoxide carbons. In the six-membered ring E derivatives this carbon undergoes an upfield shift due to the γ-gauche interaction with C-20 in the cis-fused C/D ring system (8) and with C-17 in the trans-fused C/D ring systems (11 and 13). In molecules 16 and 18 having seven-membered ring E, no such interaction exists.

The configurational assignment of the epoxy group on ring E was obtained by one- and two-dimensional (1-D and 2-D) ^{1}H NOE experiments[15,16]

Inspection of the Dreiding models of the six-membered ring E derivatives revealed, that spatial proximity of the H-15′$_B$ oxirane proton with the protons of ring D or the ethyl group is dependent on both the stereo-chemistry of the C/D ring junction and the configuration of the oxirane ring. Thus in the trans-C/D-ring-fused molecules (11 and 13) H-15′$_B$ approaches the H-17$_{eq}$ proton in case the oxirane ring is in β position (oxygen β), while it comes close to the H-17$_{ax}$ proton if the oxirane ring is α (oxygen α). Saturation of the doublet at 2.93 ppm (H-15′$_B$) in 11 produced an NOE enhancement for H-17$_{eq}$ (1.49 ppm) which points to β oxirane stereochemistry (Fig.1). In this geometry the H-15′$_A$ proton is considerably deshielded (3.76 ppm) as it lies in the plane of the carbonyl group in the vicinity of the carbonyl oxygen atom.

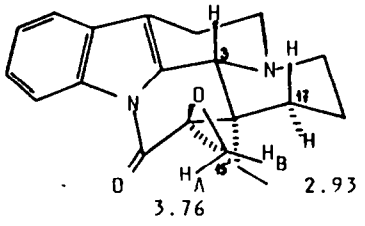


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Figure 1

Contrary to this, Dreiding model of the α-oxirane derivative (13) indicates that the H-15′$_A$ proton is above the plane of the carbonyl group (Fig. 2). Accordingly, the oxirane protons of 13 are less deshielded (2.85 and 3.08 ppm) than those of 11. The two-dimensional NOE experiment helped us to assign the doublet at 3.08 ppm to H-15′$_B$, since this proton had a cross peak with H-17$_{ax}$, whereas no NOEs were observed from the proton at 2.85 ppm to the protons other than H-15′$_B$. This was confirmed by a conventional (1-D) NOE difference experiment.

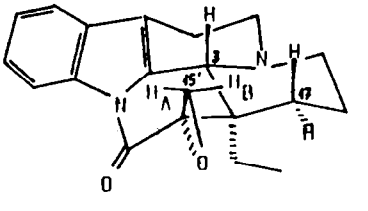

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Figure 2

In the cis-C/D-ring-fused molecule (8) irradiation of the doublet at 3.04 ppm (the higher field oxiranic proton) gave enhancements of both H-20 protons. Dreiding models of the molecule indicate that these interactions are likely for both configurations of the oxirane ring. The chemical shift value of H-15′$_A$ (3.70 ppm) helped to distinguish between the two possible stereoisomers; α configuration of the oxirane ring places H-15′$_A$ in the plane of the carbonyl group (Fig.3), whereas in the case of β configuration this proton is situated above the carbonyl group, where intense shielding would be expected.

In contrast to the 14-oxo-eburnane derivatives, which have rigid six-membered rings E, chemical shifts and steric interactions of the oxiranic protons in the 14-oxo-E-homoeburnane derivatives are considerably influenced by the conformational flexibility of the seven-membered ring E. In order to clarify the conformational properties of these molecules, and to gain information on the configuration of the oxirane ring, we had to differentiate between H-16$_\alpha$ and H-16$_\beta$ protons, which was also accomplished by NOE measurements.

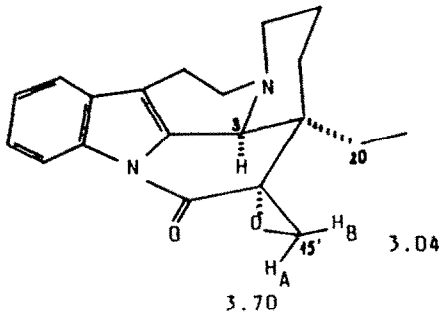

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Figure 3

In the case of 18 a significant ($\Delta\delta$ = 0.6 ppm) downfield shift of the H-3 proton signal was found, related to that of compound 17. The increased chemical shift value can only be interpreted by β configuration of the oxirane ring where H-3 approaches the oxygen atom[17]. This steric arrangement confines the E ring conformation as chair-like (Fig. 4). In close agreement with this stereostructure, irradiation of the H-16$_\beta$ (1.38 ppm) gave enhancements on H-18$_{eq}$ and H-15'$_B$ protons, while saturation of the H-16$_\alpha$ proton (2.51 ppm) produced NOE enhancements on H-21$_A$ and C-22-H$_3$ protons. The observed selective NOEs on one of the ethyl protons and also the four-bond "W" couplings of H-21$_A$ with H-18$_{ax}$ and H-21$_B$ with H-16$_\beta$ may be explained in terms of a strongly preferred orientation of the ethyl group.

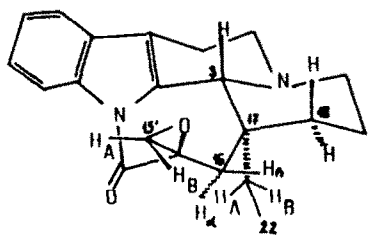

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Figure 4

The H-3 proton in 16 is deshielded by 0.3 ppm with respect to its value in 15. This difference is too small to be associated with an α configuration of the oxirane ring and a twist-boat conformation of ring E. On the other hand, the result of NOE measurements contradicts both chair-like conformation and β epoxy orientation. Presaturation of the H-3 proton resulted in a NOE of H-16$_\alpha$. Upon irradiation of the H-15'$_B$ proton (2.81 ppm) both H-16 protons, while none of the ring D protons exhibit NOE. These findings indicate that the conformation of ring E is best represented by sofa arrangement where C-3, C-2, N, C-14, C-15, C-15' and C-16 are nearly coplanar, with C-17 above the plane (Fig.5). This distortion of the twist-boat conformation towards the sofa structure places the α oriented oxirane oxygen atom far from the H-3 proton, which explains the low deshielding effect.

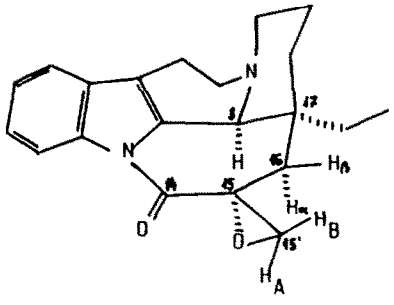

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Figure 5

Table 1. ^{1}H 400 MHz NMR Parameters[a,b]

	1	8	11	13	14
H-3	4.00 (2.9;2.4;1.2)	4.17 (3.0;2.5;1.2)	3.36 (3.2;2.2)	3.23 (3.1;2.4)	3.00 (3.2;2.2)
H-5$_{ax}$	3.26 (13.9;11.0;5.7)	3.27 (13.9;11.0;5.8)	2.58 (11.5;11.0;4.5)	2.57 (11.5;11.2;4.5)	2.50 (11.5;11.5;4.5)
H-5$_{eq}$	3.34 (13.9;6.6;1.0)	3.33 (13.9;7.0;1.0)	3.11 (11.5;6.0;1.0)	3.13 (11.5;6.0;1.1)	3.09 (11.5;6.0;1.0)
H-6$_{ax}$	2.91 (16.8;11.0;6.6;2.9)	2.93 (16.9;11.0;7.0;3.0)	2.88 (15.8;11.0;6.0;3.2)	2.91 (16.0;11.2;6.0;3.1)	2.88 (16.0;11.5;6.0;3.2)
H-6$_{eq}$	2.51 (16.8;5.7;1.0;2.4)	2.52 (16.9;5.8;1.0;2.5)	2.67 (15.8;4.5;1.0;2.2)	2.69 (16.0;4.5;1.1;2.4)	2.64 (16.0;4.5;1.0;2.2)
H-15$_{\alpha}$	2.59 (16.9)	-	-	-	2.79 (16.5)
H-15$_{\beta}$	2.67 (16.9)	-	-	-	2.35 (16.5 + 2.0)
H-17$_{ax}$	1.04 (13.7;13.4;3.9)	1.17 (13.5;13.4;3.9)	1.38 (13.5;13.5;4.5;1.5)	1.13 (13.3;13.0;4.5;1.5)	1.18 (13.5;13.5;3.2;1.5)
H-17$_{eq}$	1.50 (13.7;3.6;3.0;1.2;1.1)	1.53 (13.5;3.5;3.0;1.2;1.2)	1.49 (13.5;4.5;2.5)	1.79 (13.3;4.3;2.4)	1.9 (overlapped), 1.40[c] (13.5;4.0;2.5)[c]
H-18$_{ax}$	1.78 (13.6;13.4;12.2;4.0;3.6)	1.77 (13.4;12.5;13.4;4.6;3.5)	1.88 (14.0;12.5;13.5;4.5;4.5)	1.89 (14.0;12.5;13.0;4.3;4.5)	1.89 (overlapped), 1.55[c] (13.8;12.5;13.0;4.0;5.0)[c]
H-18$_{eq}$	1.39 (13.6;3.9;3.2;3.0;2.5)	1.47 (13.4;3.9;3.2;3.0;2.4)	1.66 (14.0;4.5;3.5;2.5;2.2)	1.67 (14.0;4.5;2.4;3.5;2.1)	1.62 (13.8;3.5;3.2;2.5;2.5)
H-19$_{ax}$	2.43 (11.4;12.2;3.2)	2.48 (11.5;12.5;3.2)	2.28 (11.0;12.5;3.5)	2.29 (11.0;12.5;3.5)	2.29 (11.0;12.5;3.5)
H-19$_{eq}$	2.61 (11.4;4.0;2.5;1.1)	2.60 (11.5;4.6;2.4;1.2)	3.01 (11.0;4.5;2.2)	3.07 (11.0;4.5;2.1)	3.05 (11.0;4.5;2.5)
H-20$_{A}$	1.67 (15.2;7.5)	1.75, 1.58[c] (15.3;7.5)[c]	1.18 (15.5;7.5;1.5)	1.23 (15.5;7.5;1.5)	0.84 (15.5;7.5;1.5)
H-20$_{B}$	2.06 (15.2;7.5)	1.76, 1.66[c] (15.3;7.5)[c]	2.05 (15.5;7.5)	2.06 (15.5;7.5)	1.9 (overlapped), 1.79[c] (15.5;7.5;2.0)[c]
H-21	0.95 (7.5)	0.97 (7.5)	0.79 (7.5)	0.90 (7.5)	0.78 (7.5)
H-15'$_{A}$[d]	-	3.70 (5.3)	3.76 (5.5)	2.85 (5.9)	-
H-15'$_{B}$[e]	-	3.04 (5.3)	2.93 (5.5)	3.08 (5.9)	-
H-9 - H-12	7.42;7.27;7.30;8.34	7.45;7.31;7.34;8.32	7.42;7.28;7.31;8.29	7.43;7.31;7.34;8.34	7.40;7.26;7.29;8.31

[a] In $CDCl_3$, δ ppm from TMS. [b] First-order coupling constants (Hz) in parenthesis. [c] In C_6D_6. [d] Directed towards C14. [e] Directed towards ring D.

Table 2. ^{1}H 400 MHz NMR parameters[a,b]

	15	16	17	18
H-3	4.03 (3.1;2.1;1.4)	4.36 (3.0;2.1;1.3)	3.42 (3.0;2.0)	4.02 (3.0;1.8)
$H\text{-}5_{ax}$	2.93 (13.0;12.0;4.3)	3.12 (13.0;12.0;4.5)	2.56 (11.0;11.0;3.5)	2.67 (11.0;11.0;3.7)
$H\text{-}5_{eq}$	3.26 (13.0;5.7;0.8)	3.29 (13.0;5.9;0.5)	3.01 (11.0;5.9;1.5)	2.99 (11.0;5.5;1.0)
$H\text{-}6_{ax}$	3.05 (15.8;12.0;5.7;3.1)	3.04 (16.0;12.0;5.9;3.0)	2.88 (15.8;11.0;5.9;3.0)	2.88 (15.8;11.0;5.5;3.0)
$H\text{-}6_{eq}$	2.40 (15.8;4.3;0.8;2.1)	2.51 (16.0;4.5;0.5;2.1)	2.60 (15.8;3.5;1.5;2.0)	2.60 (15.8;3.7;1.0;1.8)
$H\text{-}15_{\alpha}$	2.64 (overlapped), 2.20[c] (15.5;11.9;1.6;1.3)[c]	-	3.05 (15.5;14.0;2.5)	-
$H\text{-}15_{\beta}$	2.69 (overlapped), 2.41[c] (15.5;8.2;1.5)[c]	-	2.72 (15.5;6.5;2.5)	-
$H\text{-}16_{\beta}$	1.50 (overlapped), 1.14[c] (15.2;11.9;1.5;1.4)[c]	1.89 (15.2)	1.97 (15.1;14.0;2.5)	1.38 (15.6;0.8)
$H\text{-}16_{\alpha}$	2.05 (15.2;8.2;1.6)	2.14 (15.2 + 0.8)	1.63 (15.1;6.5;2.5)	2.51 (15.6;0.5)
$H\text{-}18_{ax}$	0.99 (13.8;13.5;3.8)	1.27 (13.5;13.5;4.0)	1.35 (13.8;13.5;4.0;1.1)	1.43 (13.5;13.2;4.0;1.0)
$H\text{-}18_{eq}$	1.48 (13.8;3.0;3.0;2.0;1.4;1.3)	1.47 (13.5;3.2;2.5;1.5;1.3)	1.84 (13.8;4.0;2.5;2.0)	1.84 (13.5;4.0;2.5;2.0)
$H\text{-}19_{ax}$	1.65 (13.0;12.5;13.5;4.3;3.0)	1.78 (13.0;12.5;13.5;4.5;3.2)	1.78 (13.0;12.0;13.5;4.0;4.5)	1.74 (13.0;13.2;12.0;4.0;4.0)
$H\text{-}19_{eq}$	1.37 (13.0;3.8;3.5;3.0;2.5)	1.40 (13.0;2.5;3.5;4.0;2.5)	1.53 (13.0;4.0;3.5;2.5;2.5)	1.50 (13.0;4.0;3.2;2.5;2.5)
$H\text{-}20_{ax}$	2.74 (11.5;12.5;3.5)	2.74 (11.5;12.5;3.5)	2.44 (11.5;12.0;3.5)	2.52 (11.5;12.0;3.2)
$H\text{-}20_{eq}$	2.61 (11.5;4.3;2.5;2.0)	2.62 (11.5;4.5;2.5;1.5)	3.04 (11.5;4.5;2.5;2.0)	3.00 (11.5;4.0;2.5;2.0)
$H\text{-}21_{A}$	1.54 (15.0;7.5)	1.69 (14.9;7.5)	0.94 (15.0;7.5;1.1)	1.08 (15.0;7.5;1.0)
$H\text{-}21_{B}$	2.08 (15.0;7.5;1.4)	2.23 (14.9;7.5)	2.06 (15.0;7.5)	2.11 (15.0;7.5;0.8)
H-22	0.85 (7.5)	0.87 (7.5)	0.70 (7.5)	0.73 (7.5)
$H\text{-}15'_{A}$[d]	-	3.32 (5.9;0.8)	-	3.45 (5.5)
$H\text{-}15'_{B}$[e]	-	2.81 (5.8)	-	2.76 (5.5;0.5)
H-9 - H-12	7.42;7.26;7.32;8.14	7.38;7.26;7.28;8.45	7.41;7.26;7.30;8.48	7.41;7.27;7.30;8.39

[a] In $CDCl_3$, δ ppm from TMS. [b] First-order coupling constants (Hz) in parenthesis. [c] In C_6D_6. [d] Directed towards C15. [e] Directed towards ring D.

Table 3. ^{13}C NMR data (δ ppm, $CDCl_3$ solution)

Carbon	1	8	11	13	14	Carbon	15	16	17	18
C2	132.18	130.85	132.26	131.95	133.10	C2	133.06	133.07	133.15	134.10
C3	57.62	55.35	62.32	64.02	65.77	C3	62.42	63.44	67.63	66.74
C5	50.64	50.63	52.15	52.11	52.11	C5	51.50	51.02	52.21	52.74
C6	16.54	16.67	21.13	21.22	21.08	C6	17.31	17.58	21.92	22.48
C7	112.35	113.62	114.32	114.12	112.80	C7	117.60	118.89	118.39	120.13
C8	130.19	130.23	129.99	129.80	129.71	C8	130.06	130.26	129.37	130.32
C9	118.05	118.22	118.32	118.32	117.95	C9	117.53	117.68	117.47	118.16
C10	123.82	124.34	124.35	124.29	123.62	C10	123.53	124.18	123.51	124.63
C11	124.28	124.51	124.42	124.57	123.90	C11	124.58	125.06	124.35	125.19
C12	116.25	116.24	116.18	116.31	116.01	C12	117.45	117.77	117.06	117.52
C13	134.27	134.26	134.96	134.72	134.87	C13	136.11	136.61	136.18	136.78
C14	167.36	163.94	164.09	166.02	167.50	C14	173.21	168.02	172.74	167.57
C15	44.28	61.49	60.81	62.61	44.08	C15	32.45	57.64	33.66	59.61
C16	38.41	39.12	40.05	40.43	39.23	C16	31.83	38.79	33.15	40.73
C17	26.99	25.94	22.74	25.17	31.62	C17	37.54	38.46	37.56	39.69
C18	20.66	20.86	20.75	20.94	21.37	C18	31.86	29.87	35.44	37.25
C19	44.37	43.96	54.71	55.01	55.24	C19	21.15	20.87	22.17	22.83
C20	28.35	20.46	20.82	22.23	20.55	C20	46.06	44.97	56.39	56.61
C21	7.64	9.80	7.78	8.16	7.24	C21	28.33	29.62	25.63	25.37
C15'	-	47.53	46.32	47.07	-	C22	7.56	7.21	6.72	7.46
						C15'	-	53.75	-	53.19

EXPERIMENTAL

M.p.s. are uncorrected. IR spectra were recorded on Spectromom 2000 Infrared Spectrometer. NMR spectra and NOE measurements were obtained on Varian XL-100-15 and on Varian XL-400 instruments in $CDCl_3$ with TMS as internal standard. Mass spectra were measured on an AEI-MS-902 (70eV, direct insertion) mass spectrometer. General work up: the excess of CH_2N_2 was destroyed with AcOH, a solution of $NaHCO_3$ was added and the organic layer was separated. The aqueous phase was extracted with CH_2Cl_2, the combined organic layers were dried ($MgSO_4$), the solvent was evaporated to dryness. The purification by chromatography were made on silicagel (KG-60 $PF_{254+366}$).

Reaction of (-)-cis-α-oxo-acid 4 with diazomethane

A suspension of (-)-4 (300 mg, 0.92 mmoles) in methanol (5 ml) was allowed to react with diazomethane in CH_2Cl_2 prepared from 1.20 g (11.6 mmoles) of N-nitroso-N-methyl-urea at 0 °C for 4 h. After the general work up the residue was crystallized from methanol (10 ml) to afford (+)-vincamine (2) (85 mg, 26 %) identical in all respects with the natural product. From the mother liquor beside further 20 mg (6 %, total yield: 32 %) of (+)-vincamine a faster running fraction (120 mg) was isolated by preparative thin layer chromatography (CH_2Cl_2:MeOH, 200:12) which was identified as (-)-14-oxo-15α-oxirano-eburnane (8) (82 mg, 27 %), M.p. 100-101 °C (ether), $[\alpha]_D^{25}$-113, $[\alpha]_{546}^{25}$ -147 (C.1, CH_2Cl_2). Calc. for $C_{20}H_{22}N_2O_2$ (322.4): C, 74.50; H, 6.88; N, 8.69. Found: C, 74.41; H, 6.99; N, 8.92. IR (KBr) 1700 cm^{-1} (lactam CO). MS m/z (%) 322 (M^+, 100), 321 (43), 294 (12), 293 (49), 277 (4), 275 (4), 265 (6), 263 (6), 250 (4), 237 (4), 236 (4), 222 (3), 209 (3).

Reaction of (±)-trans-α-oxo-acid 5 with diazomethane

A. A suspension of (±)-5 (300 mg, 0.92 mmoles) in methanol (5 ml) was reacted with diazomethane in CH_2Cl_2 prepared from 1.40 g (13.6 mmoles) of N-nitroso-N-methylurea at 0 °C for 4 h. Work up usual followed by thin layer chromatography (hexane:acetone 5:1) yielded (±)-3-epi-14-epivincamine (9) (134 mg, 41 %), (±)-3-epivincamine (10) (15 mg, 4 %) identical in all respects with the described products[10]. From the faster running fraction (±)-14-oxo-15β--oxirano-3-epieburnane (11) (52 mg, 17 %) was crystallized with methanol. M.p. 148-149.5 °C (methanol). Calc. for $C_{20}H_{22}N_2O_2$ (322.4): C, 74.50; H, 6.88; N, 8.69. Found: C, 74.22; H, 7.05; N, 8.91. IR (KBr) 2850-2765 cm^{-1} (Bohlmann-bands), 1705 cm^{-1} (CO). MS m/z (%) 323(22), 322 (M^+, 100), 321(72), 307 (1), 293 (26), 275 (6), 263 (7), 237 (2).

B. The above described in the presence of 15 mg (0.07 mmoles) of aluminium isopropoxide after the usual work up and thin layer chromatography afforded (±)-9 (130 mg, 40 %), (±)-10 (7 mg, 2 %), (±)-11 (53 mg, 18 %) and (±)-14-oxo--15α-oxirano-3-epieburnane (13) (15 mg, 5 %). M.p. 187-190 °C (methanol). IR (KBr) 2820-2740 cm^{-1} (Bohlmann-bands), 1700 cm^{-1} (CO). MS m/z (%) 322 (M^+, 100), 321(99) 293 (62), 292 (24), 291(8), 277 (8), 275 (20), 265 (10), 264 (12), 263 (18).

Homologization of (-)-14,15-dioxo-eburnane (3)

A solution of (-)-3 (3.00 g, 9.74 mmoles) in CH_2Cl_2 (45 ml) was allowed to react with diazomethane in CH_2Cl_2 prepared from 8.40 g (81.5 mmoles) of N-nitroso-N-methylurea at room temp. for 12 h. After the usual work up the residue

was chromatographed (hexane:acetone 5:1) to yield (-)-8 (1.86 g, 59 %) and (-)-14-oxo-15α-oxirano-E-homoeburnane (16)(0.35 g, 10 %), M.p. 144-147 °C (methanol).$[\alpha]_D^{25}$-10, $[\alpha]_{546}^{25}$ -15 (C.1, CH_2Cl_2). Calc. for $C_{21}H_{24}N_2O_2$ (336.42): C, 74.97; H, 7.19; N, 8.33. Found: C, 75.18; H, 7.33; N, 8.18. IR (KBr) 1700 cm^{-1} (lactam CO). MS m/z (%) 336 (M^+, 100), 335 (50), 321 (4), 319 (4), 307 (22), 293 (3), 291 (3), 280 (7), 279 (57).

Homologization of (±)-14,15-dioxo-3-epieburnane (6)

A solution of (±)-6 (1.00 g, 3.25 mmoles) in CH_2Cl_2 (15 ml) was reacted with diazomethane in CH_2Cl_2 made from 4.2 g (40.7 mmoles) of N-nitroso-N-methylurea at room temp. for 2 days. After the usual work up the residue was crystallized from methanol to afford (±)-11 (560 mg, 51 %). From the mother liquor further (±)-11 (80 mg, 7 %, total yield: 58 %) and a new product (±)-14-oxo-15β-oxirano--3-epi-E-homoeburnane (18) (25 mg, 2 %) were isolated by chromatography (hexane: acetone 5:1). M.p. 119-121 °C (ether). Calc. for $C_{21}H_{24}N_2O_2$ (336.42); C, 74.97; H, 7.19; N, 8.33. Found: C, 75.09; H, 7.40; N, 8.11. IR (KBr) 1690 cm^{-1} (lactam CO). MS m/z (%) 337 (22), 336 (M^+, 100), 335 (47), 321 (2), 319 (5), 307 (18), 293 (3), 291 (2), 279 (16).

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