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Synthesis of Vinca Alkaloids and Related Compounds, XXXIV[1]

Synthesis of (3*S*,14*S*,16*S*)-Bromovincamines and Bromoapovincamines by Regioselective Bromination

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By bromination of the iminium salt **2a** (X–Cl), the 9-bromo derivative **2c** (X=ClO_4) is obtained in isomer-free state. Bromination of the lactam **8d** leads to a ca. 7.5:1 mixture of 11-bromo **(8c)** and 9-bromo **(8a)** lactams. These precursors have been used to synthesize 9-, 10- and 11-bromovincamines **(11a–c)**, and 9-, 10- and 11-bromoapovincamines **(12a–c)**.

Über die Synthese von Vinca-Alkaloiden und verwandten Verbindungen. 34. Mitt.: Synthese von (3S, 14S, 16S)-Bromvincamin und Bromapovincamin durch regioselektive Bromierung entsprechender Zwischenprodukte

Das 9-Bromderivat **2c** (X=ClO_4) wurde in isomerfreiem Zustand durch die Bromierung des Immoniumsalzes **2a** (X=Cl) hergestellt. Die Bromierung von Laktam **8d** führte zu einer Mischung ca. 7.5:1 von 11-Brom- **(8c)** und 9-Bromlaktam **8a**. Aus diesen Intermedieren wurden die 9-, 10- und 11-Bromvinkamine **(11a–c)**, weiterhin die 9-, 10- und 11-Bromapovinkamine **(12a–c)** synthetisiert.

(+)-Vincamine **(11d)** and its semisynthetic derivative, the ethyl ester of (+)-apovincaminic acid (CAVINTON®), are known to possess significant cerebral vasodilator effect[2]. Similarly valuable therepeutic effects, namely vigilance increasing and psychostimulant effects, are displayed by vincamine derivatives having a halogen atom in the aromatic ring, such as (+)-10-bromovincamine **(11b)**[3a,b] obtained by the rearrangement of (–)-15-bromo-vincadifformine or (+)-11-bromovincamine**(11c)**[4] obtained by the direct bromination of (+)-vincamine **(11d)** furthermore the semisynthetic vincamine derivatives[5] bearing bromine in various positions.

Since the regioselectivity of the above methods is not satisfactory, new synthetic approaches have been studied in order to introduce the bromine atom into the appropriate positions of the benzene nucleus more selectively.

Buzás et al.[6] have found that bromination of the enamine **1a**, prepared by Wenkert[7], in THF at –70° leads to the 1-bromo-indolo [2,3-a] quinolizin-5-ium bromide (**2b**; X=Br). In order to decrease the electron density on rings C and D, or to decrease their nucleophilic character, thereby assisting the bromination of the aromatic A ring, the iminium salt **2a** was chosen as starting material. When **2a** (X=Cl) was reacted with Br_2 at room temp. in glacial acetic acid, the 9-bromo derivative **2c** (X=ClO_4) was ob-

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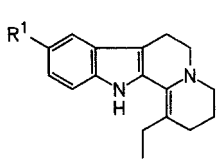

	R^1	R^2
a	H	H
b	H	Br
c	Br	H
d	Br	$-(CH_2)_2-CO_2CH_3$

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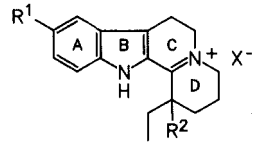

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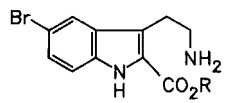
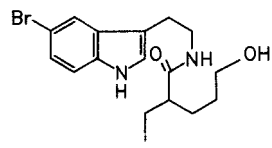


	R
3	C_2H_5
4	H



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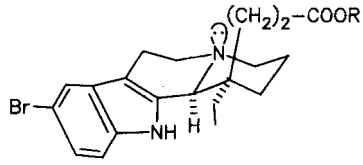
tained in a yield of ca. 86 %, free of isomers, which was suitable for the further steps of the synthesis.

The position of bromine, which has been supported fully by physical investigations carried out on further derivatives, was proved by independent synthesis. Applying the basic principle of our tryptamine synthesis[8], from the semi-acid obtained by the partial hydrolysis of diethyl 3-chloropropyl malonate and from 4-bromobenzene-diazonium cloride 5-bromotryptamine-2-carboxylic acid **(4)** was prepared, the acidic decarboxylation of which yielded 5-bromotryptamine. This latter was reacted with 2-ethyl-5-pentanolide[9], and the resulting hydroxy-acid amide **5** was converted into the 9-bromo derivative **1c** with $POCl_3$ and by subsequent alkaline treatment. The perchlorate of the latter **(2c)** is identical in all chemical and physical properties with the product obtained by bromination of **2a**.



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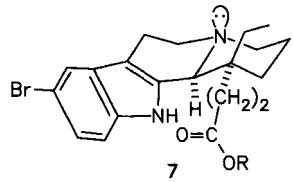
	R
a	CH_3
b	H



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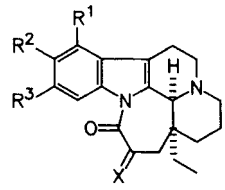


	R^1	R^2	R^3	X
8a	Br	H	H	
b	H	Br	H	H_2
c	H	H	Br	
d	H	H	H	
9a	Br	H	H	
b	H	Br	H	N–OH
c	H	H	Br	
10a	Br	H	H	
b	H	Br	H	O
c	H	H	Br	

The enamine **1c** obtained from **2c** (X=ClO_4) with aqueous NaOH solution reacted with methyl acrylate, to the iminium perchlorate **2d** in a yield of 75 %. Catalytic hydrogenation of indoloquinolizinium salts of related structure under appropriate conditions yields, as main product, the *cis*-derivative considering 12b-H and the C-1-ethyl group[10]. In our case, because of the risk of reductive dehalogenation, only chemical reducing agents could be used. We have found that a reduction of the perchlorate **2d** with $NaBH_4$ at 0° yields a ca. 2:1 mixture of the saturated esters **6a** and **7a**, which were separated by prep. TLC. **6a** and **7a** could also be separated chemically. In the *trans* isomer **7a** the equatorial propionic ester group is sterically very close to the indole NH group, which as a neighbour group[11] accelerates the hydrolysis of the ester group: When the mixture of the two esters was boiled in aqueous EtOH with 0.5 equivalent NaOH, the *trans* derivative **7a** was converted to the carboxylic acid **7b**, which could be separated easily from the unreacted *cis* ester **6a** because of its good solubility in alkaline medium.

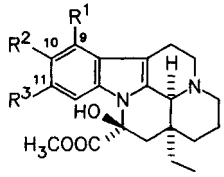
The racemic *cis* ester **6a** obtained in a yield of 54 % was resolved with D-dibenzoyl tartaric acid. Base catalysed ring closure of (−)-**6a** ester, obtained in a yield of 35 %, or $POCl_3$-treatment of the carboxylic acid (−)-**6b**, obtained from the latter by alkaline hydrolysis, led to the lactam (+)-**8b**.

For the preparation of 9- and 11-bromovincamines lactam (+)-**8d**[10] was chosen as precursor. By brominating this lactam in $CHCl_3$ in the presence of $FeCl_3 \times 6\,H_2O$, the 11-bromo-lactam (+)-**8c** was obtained regioselectively (42.5 %) beside the 9-bromo-lactam (+)-**8a**, which could be isolated in 5.6 %. The isomers were separated by crystallization and by prep. TLC, respectively.

For the determination of the position of bromine, the ^{1}H-NMR investigation of the bromolactams (+)-**8a–c** seemed to be appropriate, since the determination of the coupling constants of the protons in the aromatic ring is facilitated by the fact in these derivatives the signal of H-12 appears at higher δ-values, separated from the other signals, due to the deshielding effect of the 14-carbonyl group (Table 1). Moreover, it was of great help that the structure of **8b** had been proved by independent synthesis.

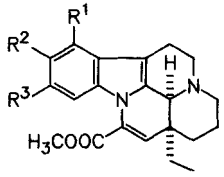
Next, the bromolactams (+)-**8a–c** were α-isonitrosated with t-butylnitrite. Oximes **9a–c** obtained in yields of 55–70 % were isolated as their hydrochlorides (Table 2).

For the preparation of bromovincamines and bromoapovincamines the reactions decribed by us[10] were used.



11

11-12	R^1	R^2	R^3
a	Br	H	H
b	H	Br	H
c	H	H	Br
d	H	H	H



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Oximes **9a–c**, when heated with paraformaldehyde in glacial acetic acid in the presence of p-TsOH, and the raw reaction mixture treated with $NaOCH_3$ in CH_3OH, were transformed into the corresponding (+)-**11a–c** bromovincamines in 33–35 % yields. In this reaction the dioxo derivatives **10a–c** are formed first, which are subsequently transformed into the corresponding bromovincamines by base catalysed me-

Tab. 1: ^{1}H-NMR-spectral data of **8a–c**, **11a–c** and **12a–c** (100 MHz, TMS as internal standard)[a)]

Compound	C9–H	C10–H	C11–H	C12–H	C3–H	C21–H_3	C15–H	$COOCH_3$	C14–OH
8a[f)]		7.35	7.09	8.43	4.04	0.86	–	–	–
		(7.5 + 1.5)	(8.0 + 7.5)	(8.0 + 1.5)					
$\Delta\delta$[g)]		+0.10	−0.11	0					
8b[f)]	7.55	–	7.33	8.27	4.13	0.87	–	–	–
	(2.0 + 0.3)		(8.5 + 2.0)	(8.5 + 0.3)					
$\Delta\delta$[g)]	+0.18		+0.13	−0.16					
8c[f)]	7.30	7.35	–	8.55	4.09	0.87	–	–	–
	d	d		(1.8 + 0.3)					
$\Delta\delta$[g)]	−0.07	+0.10		+0.12					
11a[b)]		7.25	6.94	7.03	3.86	0.91	–	3.80	4.48
		(7.1 + 1.6)	(8.2 + 7.1)	(8.2 + 1.6)					
$\Delta\delta$[c)]		+0.15	−0.16	−0.07					
11b[b)]	7.58	–	7.21	6.95	3.88	0.90	–	3.80	4.52
	(1.6 + 0.3)		(8.6 + 1.6)	(8.6 + 0.3)					
$\Delta\delta$[c)]	+0.10		+0.11	−0.15					
11c[b)]	7.34	7.25	–	7.30	3.86	0.90	–	3.83	4.50
	d	(8.5 + 1.5)		d					
$\Delta\delta$[c)]	−0.14	+0.15		+0.20					
12a[b)]		7.25	6.94	7.14	4.13	1.01	6.18	3.91	–
		(7.3 + 1.4)	(8.4 + 7.3)	(8.4 + 1.4)					
$\Delta\delta$[e)]		+0.15	−0.16	−0.06					
12b[b)]	7.57	–	7.24	7.12	4.10	1.00	6.18	3.90	–
	(1.8 + 0.4)		(8.6 + 1.8)	(8.6 + 0.4)					
$\Delta\delta$[e)]	+0.13		+0.14	−0.08					
12c[b)]	7.30	7.22	–	7.42	4.08	1.00	6.19	3.94	–
	(8.5 + 0.3)	(8.5 + 1.5)		(1.5 + 0.3)					
$\Delta\delta$[e)]	−0.14	+0.12		+0.22					

a) Chemical shifts are in ppm. Values in parentheses are coupling constants, J (Hz). b) In $CDCl_3$ solution.
c) ppm, relative to vincamine **11d**; positive values indicate downfield shifts. d) Overlapped signals; coupling constants have not been observed.
e) ppm, relative to apovincamine (**12d**). f) In $CDCl_3$–DMSO-d_6 solution. g) ppm, relative to the unsubstituted lactam (**8d**).

Tab. 2: Characteristic physical data of **9a–c**, and **12a–c**

Products	Mp. [°C] (Solvent)	Molecular formula[a] (Mw)	IR (KBr), [cm^{-1}] CO	C=N	C=C	Yields [%]	MS [m/z. (%)][c]	$[\alpha]_D^{23}$ [o] (c, solvent)
9a[b]	264 (MeOH)	$C_{20}H_{23}N_3O_2BrCl$ (452.8)	1770	1620		64.2	415(M^+·, 50), 398(30). 385(100), 370(60).	−12 (1.00, DMF)
9b[b]	243–245 (MeOH)	– " –	1720	1630		47	415(M^+·, 50), 398(30). 385(100), 370(30).	−23 (0.50, CH_2Cl_2/MeOH 3:1)
9c[b]	235 (MeOH)	– " –	1710	1622		56	415(M^+·, 62), 398(29). 385(100), 370(60).	+ 45.6 (1.14, DMF)
11a[b]	225 (MeOH)	$C_{21}H_{26}N_2O_3BrCl$ (469.8)	1738			32	432(M^+·, 100), 431(43), 417(8). 403(4), 386(4), 385(9), 376(4), 373(19), 372(7), 371(5), 362(9).	+ 29.9 (1.06, $CHCl_3$/MeOH 1:1)
11b	207 (MeOH)	$C_{21}H_{25}N_2O_3Br$ (433.3)	1738			40.8	432(M^+·, 100), 431(48), 417(8), 385(24), 373(56), 372(52), 371(31), 362(13), 345(86), 344(31).	+ 32.7 (0.90, $CHCl_3$)[3), 13)]
11c	210 (MeOH)	– " –	1742			39	432(M^+·, 95), 431(34), 417(9), 385(17), 373(34), 372(19), 371(14), 362(10), 345(48), 344(19).	+ 19[4)] (1.00, pyridine)
12a[b]	225–227 (MeOH)	$C_{21}H_{24}N_2O_2BrCl$ (451.8)	1710		1620	71	414(M^+·, 17), 413(25), 385(100), 371(7), 356(15), 344(55), 325(40), 305(75), 262(40).	+ 123 (1.00, CH_2Cl_2)
12b[b]	199–201 (MeOH)	– " –	1720		1639	64.6	414(M^+·, 31), 385(100), 344(95.5).	+ 73 (1.04, CH_2Cl_2)[13)]
12c[b]	228 (MeOH)	– " –	1718		1622	58.7	414(M^+·, 41), 385(100), 344(93).	+ 37.6 (0.34, CH_2Cl_2)
10c	154–156 (ether)	$C_{20}H_{21}N_2O_2Br$ (401.3)	1710 1690			46	400(M^+·, 24), 399(29), 383(2.7), 371(100), 343(80).	+ 44 (1.00, CH_2Cl_2)

a) Satisfactory microanalyses obtained C ± 0.30, H ± 0.30, N ± 0.30. b) Isolated as hydrochloride. c) The heavy isotope peaks are neglected.

thanolysis and subsequent epimerization[12]. To prove this reaction path, the (+)-**10c** dioxo derivative was isolated and identified (Table 2).

The resulting bromo derivatives, in addition to their pharmacological value, could also be used for the preparation of the corresponding alkoxy derivatives, such as vincine and isovincine. These results will be described in our next paper.

Experimental

IR spectra: Spectromom 2000 spectrophotometer. – NMR spectra: Varian XL-100-15 (Fourier transform) instrument. – Mass spectra: AEI-MS-902 (70 eV, direct insertion). – Mps are uncorrected.

Ethyl 5-bromotryptamine-2-carboxylate hydrochloride **(3)**

3-hydrochloride was prepared from diethyl 3-chloropropyl-malonate (23.70 g, 0.10 mole) and 4-bromoaniline (17.20 g, 0.11 mole) by the procedure described[8] in a yield of 36 %. M.p. 248–249° (EtOH). – IR (KBr): 3340 (NH), 1705 cm^{-1} (ester CO). – $C_{13}H_{16}N_2O_2ClBr$ (347.6) Calc. C 44.9 H 4.63 N 8.0 Found C 44.7 H 4.70 N 7.8. – ^{1}H-NMR ($CDCl_3$): δ (ppm) = 7.82 (1H, H-4), 7.45–7.10 (2H, m, H-6 and H-7), 4.40 (2H, q, J = 7.0 Hz, $C\underline{H}_2CH_3$), 1.40 (3H, t, J = 7.0 Hz, $CH_2C\underline{H}_3$).

5-Bromotryptamine-2-carboxylic acid **(4)**

3-hydrochloride (1.00 g, 2.87 mole) was refluxed in a mixture of EtOH (10 ml) and 4N NaOH (10 ml) for 2 h. The solution was poured into ice water, the pH value was adjusted with acetic acid to 6, the crystalline product was filtered and washed with water to yield 0.75 g (91 %) of **4**. M.p. 248–249°. – IR (KBr): 3320 (NH), 1585 cm^{-1} (COOH). – $C_{11}H_{11}BrN_2O_2$ (283.1) Calc. C 46.6 H 3.91 N 9.8 Found C 46.5 H 3.85 N 9.9.

5-Bromotryptamine

The carboxylic acid **4** (1.00 g, 3.53 mmole) was refluxed in 10 % aqueous H_2SO_4 for 30 h. The solution was basified with conc. NH_4OH to pH 9, and extracted with $CHCl_3$ (4 × 20 ml). The org. layer was washed with 5 % aqueous NaOH and water, dried on $MgSO_4$, filtered and the solvent was evaporated *in vacuo* to give 5-bromotryptamine (0.58 g, 58 %). Hydrochloride: m.p. 292° (water); lit.[13] m.p. 290° (water). Formate: m.p. 175–176° (EtOH). $C_{11}H_{12}BrN_2O_2$ (284.1) Calc. N 9.8 Found N 9.71.

9-Bromo-1-ethyl-1,2,3,4,6,7-hexahydro-12H-indolo[2,3-a]quinolizin-5-ium perchlorate **(2c)**

A. 5-Bromotryptamine (0.48 g, 2.0 mmole) and 2-ethylpentanolide[9] was refluxed in xylene (5 ml) for 4 h. The solvent was evaporated *in vacuo* and the residue was washed with petroleum ether (2 × 3 ml) to give 0.59 g (80 %) of **5**; IR (KBr): 3320 (NH, OH), 1640 cm^{-1} (amide CO). Crude **5** was refluxed in $POCl_3$ (5 ml) for 6 h. The solution was evaporated to dryness *in vacuo*, the residue was dissolved in CH_2Cl_2 (5 ml), and stirred with 4N NaOH for 15 min. The org. layer was separated and the water phase extracted with CH_2Cl_2 (3 × 3 ml). After drying ($MgSO_4$) the solvent was removed *in vacuo*. The residual oil (0.65 g) was dissolved in MeOH (3 ml), and acidified with 70 % $HClO_4$ to pH 5 to give **2c**-perchlorate (0.40 g, 46 % calc. for 5-bromotryptamine). M.p. 233–234° (MeOH). – IR (KBr): 3250 (indole NH), 1622, 1545 cm^{-1} (C=N). $C_{17}H_{20}BrN_2 \cdot ClO_4$ (431.7) Calc. C 47.2 H 4.67 N 6.49 Found C 47.1 H 4.55 N 6.36.

B. The suspension of **2a** perchlorate (60.00 g, 0.17 mole) in CH_2Cl_2 (600 ml) was stirred with 2 % aqueous NaOH (475 ml) for 10 min. The org. layer was separated, dried ($MgSO_4$), and evaporated to dryness *in vacuo*. The residue was dissolved in MeOH (100 ml), and acidified with HCl/CH_3OH to pH 4.

The solvent was removed *in vacuo*, and the residual hydrochloride was dissolved in glacial acetic acid (350 ml) and MeOH (25 ml). Thereafter bromine (11 ml, 0.22 mole) in glacial acetic acid (150 ml) was added dropwise at room temp. under stirring. The solvent was evaporated *in vacuo*, and the residual oil was dissolved in boiling MeOH (150 ml), 70 % $HClO_4$ (14.64 ml) was added, the crystalline perchlorate was filtered off and washed with MeOH to give **2c** perchlorate (63.30 g, 86 %), which was in all respects identical with that prepared according to A.

9-Bromo-1-ethyl-1-methoxycarbonylethyl-1,2,3,4,6,7-hexahydro-indolo[2,3-a]quinolizin-5-ium perchlorate **(2d)**

The suspension of perchlorate **2c** (7.00 g, 16.2 mmole) in CH_2Cl_2 (160 ml) was stirred with 2 % NaOH solution (140 ml) for 10 min. The org. layer was dried (K_2CO_3), to the filtrate methyl acrylate (8.9 g, 0.10 mole) was added, and the mixture was allowed to stand at room temp. for 2 d. The solvent was removed *in vacuo*, the residual oil was dissolved in MeOH (50 ml), acidified with 70 % $HClO_4$ to pH 4, the crystalline product filtered off and washed with MeOH to yield perchlorate **2d** (5.90 g, 70 %). M.p. 221–222° (MeOH). – IR (KBr): 3300 (indole NH), 1718 (ester CO), 1620 and 1538 cm^{-1} (C=N). $C_{21}H_{26}BrN_2O_2 \cdot ClO_4$ (517.8). Calc. C 48.7 H 5.06 N 5.4 Found C 48.6 H 5.12 N 5.2.

Methyl 3-(9-bromo-1a-ethyl-1,2,3,4,6,7,12,12ba-octahydro-indolo[2,3-a]quinolizin-1β-yl)-propionate **(6a)**, *and methyl 3-(9-bromo-1β-ethyl-1,2,3,4,6,7,12,12ba-octahydro-indolo[2,3-a]quinolizin-1a-yl)propionate* **(7a)**

To a stirred suspension of perchlorate **2d** (7.45 g, 14.4 mmole) in MeOH (40 ml) and CH_2Cl_2 (40 ml) $NaBH_4$ (0.55 g) was added in portions at –20°. After the addition, stirring was continued for 30 min. Thereafter the mixture was acidified with acetic acid to pH 6, and evaporated *in vacuo*. The residue was treated with 5 % Na_2CO_3 and extracted with CH_2Cl_2. The org. layer was dried ($MgSO_4$), filtered and evaporated to dryness. The residual oil was separated by prep. TLC (silica gel, benzene-MeOH 14:3, elution with CH_2Cl_2/CH_3OH 10:2, R_f: **7a** > **6a**) to yield **6a** (2.70 g, 44.5 %). M.p. 167–168° (MeOH). – IR (KBr): 3380 (indole NH), 2750 (*Bohlmann* band), 1720 cm^{-1} (ester CO). – $C_{21}H_{27}BrN_2O_2$ (419.3) Calc. C 60.1 H 6.49 N 6.6. Found C 60.3 H 6.53 N 6.4. – MS m/z (%): 418 ($M^{+\cdot}$, 81), 403 (8.1), 387 (5.4), 345 (100), 315 (2.6), 275 (30.7), 248 (31.6). – ^{1}H-NMR (DMSO-d_6, $CDCl_3$): δ (ppm) = 7.62–7.12 (3H, m, aromatic), 3.58 (3H, s, CO_2CH_3), 3.50 (1H, s, 12b-H), 1.11 (3H, t, J = 7.0 Hz, $CH_2\underline{CH}_3$), and the compound **7a** (2.02 g, 33.3 %). M.p. 140–142° (MeOH). IR (KBr): 3300 (indole NH), 2750 (*Bohlmann* band), 1710 cm^{-1} (ester CO). – $C_{21}H_{27}BrN_2O_2$ (419.3) Calc. C 60.1 H 6.49 N 6.6 Found C 59.9 H 6.64 N 6.5. – MS m/z (%): 418 ($M^{+\cdot}$, 100), 403 (12), 387 (10), 345 (90.8), 315 (7.4), 275 (27.4), 248 (27.1). – ^{1}H-NMR($CDCl_3$): δ (ppm) = 9.00 (1H, s, indole NH), 7.62–7.10 (3H, m, aromatic), 3.80 (3H, s, CO_2CH_3), 3.33 (1H, s, 12b-H), 0.68 (3H, t, J = 7.0 Hz, $CH_2\underline{CH}_3$).

Separation of epimers **6a** *and* **7a** *by selective hydrolysis*

A mixture of **6a** and **7a** (23.0 g, 54.9 mmole) was refluxed with NaOH (1.25 g, 28.7 mmole) in MeOH (250 ml) and water (10 ml) under stirring for 1.5 h. The solvent was evaporated *in vacuo*, the residue was treated with 2 % NaOH (100 ml). The crystalline product was filtered off, washed with water, dissolved in CH_2Cl_2 (100 ml) and extracted with 2 % NaOH. The org. layer was separated, dried ($MgSO_4$), filtered, evaporated and the residue recrystallized from MeOH to give the *cis* ester **6a** (12.60 g, 54 %).
The basic filtrate was extracted with CH_2Cl_2, acidified with acetic acid to pH 6, and the crystals were filtered off, washed with water to yield *trans* acid **7b** (8.90 g, 40 %). M.p. 180°.

*(–)-1(S),12b(S)-***6a**

To the solution of (rac.)-**6a** ester (7.63 g, 18.20 mmole) in CH_2Cl_2 (40 ml) a solution of D-dibenzoyltartaric acid (6.52 g, 18.20 mmole) in CH_2Cl_2 (60 ml) was added, and allowed to stand at room temp. for 1 d.

The precipitated crystals were filtered off, washed with CH_2Cl_2 to yield D-dibenzoyltartaric acid salt of (–)-**6a** (4.95 g, 35 %). M.p. 150°; $[\alpha]_D^{25} = -100°$ (DMF, c = 1.00). The suspension of this salt in CH_2Cl_2 (50 ml) was extracted with 5 % aqueous Na_2CO_3 (3 × 50 ml). The org. layer was dried ($MgSO_4$), filtered and evaporated to give (–)-**6a** as a colourless oil (2.67 g, 35 %). $[\alpha]_D^{25} = -106.5°$ ($CHCl_3$, c = 1.01). (–)-**6a**-HCl melted at 258° (MeOH).

3(S),17(S)-10-Bromo-14-oxo-E-homo-eburnane [(+)-**8b**]

A. To (–)-**6a** (0.18 g, 0.43 mmole) in dry toluene (6 ml) t-BuONa (0.12 g) was added and the solution was stirred under N_2 at room temp. for 4 h. NH_4Cl (0.20 g) in water (6 ml) was added and stirring was continued for 10 min. The org. layer was separated and the aqueous phase was extracted with CH_2Cl_2 (4 × 2 ml). The org. extracts were dried ($MgSO_4$), filtered, evaporated and (+)-**8b** was crystallized from MeOH (0.12 g, 71 %). M.p. 121–122°. – IR (KBr): 1710 cm^{-1} (lactam CO). – $C_{20}H_{23}BrN_2O$ (387.3) Calc. C 62.0 H 5.98 N 7.2 Found C 62.2 H 5.82 N 7.4. – MS m/z (%): 386 ($M^{+\cdot}$, 100), 385 (51), 358 (6.4), 357 (9.5), 343 (4.1) 329 (10), 315 (5.5). – $[\alpha]_D^{25} = +34°$ (CH_2Cl_2, c = 1.00).

B. (–)-**6a** (2.05 g, 4.9 mmole) in EtOH (20 ml) and water (1 ml) was refluxed with NaOH (1.0 g) for 1.5 h. The solvent was removed *in vacuo*, the residue was dissolved in water (15 ml), acidified with acetic acid to pH 6, the crystalline product was filtered off and washed with water to give the acid (–)-**6b** (1.65 g, 83.5 %). M.p. 172° (ether). – $[\alpha]_D^{26} = -87°$ (DMF, c = 1.00).
The solution of (–)-**6b** (1.45 g, 3.67 mmole) in $POCl_3$ (16 ml) was stirred at room temp. for 1 d. Benzene (16 ml) was added to the solution which was evaporated *in vacuo* to dryness. The residue was dissolved in CH_2Cl_2 (10 ml), ice-water (5 ml) was added to the solution, which was basified with conc. NH_4OH to pH 9 and extracted with CH_2Cl_2 (3 × 11 ml). The org. extracts were dried ($MgSO_4$), filtered, evaporated to dryness, and the residue was recrystallized from MeOH to give (+)-**8b** (1.00 g, 70 %), identical with that prepared according to A.

*(+)-3(S),17(S)-11-Bromo-(+)-***8c** *and (+)-3(S),17(S)-9-bromo-14-oxo-E-homo-eburnane* [(+)-**8a**]

To (+)-**8d** (1.00 g, 3.24 mmole)[10] and $FeCl_3 \cdot 6H_2O$ (1.00 g, 3.68 mmole) in $CHCl_3$ (5 ml) Br_2 (0.95 g, 5.93 mmole) in $CHCl_3$ (5 ml) was added dropwise at 0° under stirring. Stirring was continued at 0° for 24 h. Thereafter 15 % aqueous NH_4OH was added to the reaction mixture, and the precipitate was filtered off and washed with $CHCl_3$. The org. layer was separated, the aqueous phase extracted with $CHCl_3$. The org. extracts were dried ($MgSO_4$), filtered, evaporated and the residue was separated by preparative TLC (silica gel, CH_2Cl_2/CH_3OH 20:1, elution with CH_2Cl_2/CH_3OH 20:4, R_f: (+)-**8d** > (+)-**8a** = (+)-**8c**) to give (+)-**8d** (0.10 g, 10 %) and mixture of (+)-**8a** and (+)-**8c** (0.75 g), which was separated by preparative TLC (silica gel, benzene-MeOH 14:3, elution with CH_2Cl_2/CH_3OH 20:4, R_f: (+)-**8a** > (+)-**8c**) to yield (+)-**8c** and (+)-**8a**. (+)-**8c**: (0.53 g, 42.5 %) m.p. 122–123° (CH_3CN). – IR (KBr): 1706 cm^{-1} (lactam CO). – $C_{20}H_{23}BrN_2O$ (387.3) Calc. C 62.0 H 5.98 N 7.23 Found C 62.1 H 5.82 N 7.4. MS m/z (%): 386 ($M^{+\cdot}$, 100), 385 (56), 357 (8.9), 343 (3.4), 329 (8.1), 315 (4.8), 261 (4.8), 248 (4.4). – $[\alpha]_D^{20} = +13.1°$ (DMF, c = 2.06).
(+)-**8a** (71 mg, 5.6 %). M.p. 154–156° (CH_3CN). IR (KBr): 1712 cm^{-1} (lactam CO). – $C_{20}H_{23}BrN_2O$ (387.3) Calc. C 62.0 H 5.98 N 7.23 Found C 61.9 H 5.72 N 7.0. – MS m/z (%): 386 ($M^{+\cdot}$, 100), 385 (72), 357 (15), 343 (7.5), 329 (20), 315 (11), 261 (9.3), 248 (11). – $[\alpha]_D^{20} = +31.5°$ (DMF, c = 2.26). ^{1}H-NMR data see Table 1.

*General method for the preparation of 3(S),17(S)-9-bromo-(–)-***9a**, *3(S),17(S)-10-bromo-(–)-***9b** *and 3(S),17(S)-11-bromo-14-oxo-15-hydroxyimino-E-homo-eburnane* [(+)-**9c**]

To the suspension of the bromolactams **8a–c** (0.52 g, 1.34 mmole) in dry toluene (5.5 ml) tert.-butyl nitrit (1.2 ml) and tert.-BuOK (0.40 g) were added. The reaction mixture was stirred under N_2 at room temp. for 25 min. Thereafter NH_4Cl (1.7 g) in water (26 ml) was added, and stirring was continued for 5 min.

The org. layer was separated, and the water phase was extracted with CH_2Cl_2 (2 × 10 ml). The org. extracts were dried ($MgSO_4$), filtered and evaporated to dryness *in vacuo*. The residue was dissolved in MeOH (2 ml), acidified with HCl/CH_3OH to pH 4, and the crystalline hydrochlorides filtered off, washed with MeOH and dried (Table 2).

*General method for the preparation of (+)-(3S,14S,16S)-9-bromo-(+)-***11a**, *(+)-(3S,14S,16S)-10-bromo-(+)-***11b** *and (+)-(3S,14S,16S)-11-bromo-vincamine* [(+)-**11c**]

A solution of the bromoxime hydrochlorides **9a–c** (0.39 g, 0.86 mmole) in glacial acetic acid (6 ml) was heated at 110–15° with p-TsOH (0.80 g) and paraformaldehyde (1.20 g) for 3 h. The cold solution was poured into ice-water (15 ml), basified with conc. NH_4OH to pH 9 and the precipitate was filtered off, washed with water, dissolved in CH_2Cl_2 (10 ml), dried ($MgSO_4$), filtered and evaporated to dryness. The residue was dissolved in MeOH (1.2 ml) containing tert.-BuOK (30 mg) and the reaction mixture was allowed to stand at room temp. for 2 h. The crystalline bromovincamines were filtered off and washed with cold MeOH. The mother liquor was separated by prep. TLC (silica gel, benzene-MeOH 14:3, elution with acetone) (Table 1 and 2).

*General method for the preparation of (+)-(3S,16S)-9-bromo-(+)-***12a**, *(+)-(3S,16S)-10-bromo-(+)-***12b** *and (+)-(3S,16S)-11-bromo-apovincamine hydrochloride* [(+)-**12c**]

The oxime hydrochlorides **9a–c** (1.00 g, 2.21 mmole) were heated in a mixture of MeOH (22 ml) and conc. H_2SO_4 (8 ml) at 120° for 6 h. The cold solution was poured into ice-water (120 ml), basified with conc. NH_4OH to pH 9, and extracted with CH_2Cl_2 (3 × 20 ml). The extracts were dried ($MgSO_4$), filtered and evaporated to dryness. The residual oils were converted into their hydrochlorides with HCl/CH_3OH (Table 1 and 2).

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