SYNTHESIS OF VINCA ALKALOIDS AND RELATED COMPOUNDS XXX[1]. TOTAL SYNTHESIS OF (±)-TACAMINE, (±)-APOTACAMINE AND THEIR 20-EPIMERS

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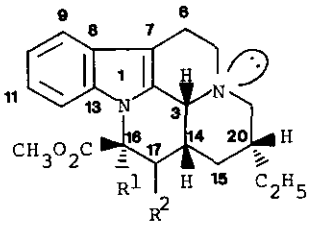
Abstract - Starting from iminium salt 3 two different methods have been elaborated for the synthesis of (±)-tacamine 1, (±)-apotacamine 2 and their 20-epimers.

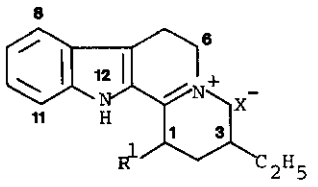
Van Beek et al. reported recently the isolation of two new alkaloids, tacamine 1[2] and apotacamine 2[3] from the leaves of Tabernaemontana eglandulosa.



	R^1	R^2
1	OH	H
2	$\Delta^{16,17}$	

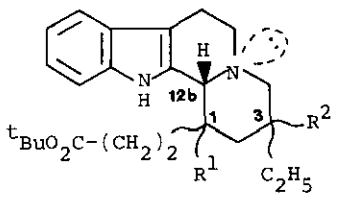
The semisynthesis of the enantiomers of these alkaloids, named pseudovincamine and pseudoapovincamine, using (-)-tabersonine as a starting material has already been published by Le Men et al.[4]

The iminium salt 3 described by Massiot et al.[5] proved to be a suitable educt in our hands for the total synthesis of racemic 1 and 2. In order to minimize the possibility of dialkylation, 3 (X = ClO_4) was reacted with the bulky tert-butyl acrylate in methylene chloride in the presence of triethylamine affording the perchlorate 4[6] in a yield of 79 %.



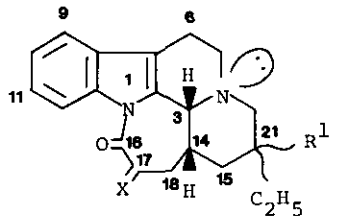
	R^1
3	H
4	$-(CH_2)_2CO_2Bu^t$
5	$-CH_2-C(NOH)-CO_2C_2H_5$

The base, prepared from 4 by aqueous NaOH was reduced with $NaBH_4$ giving rise to three stereoisomers: 6 (yield 37.5 %)[7], 7 (yield 10 %)[8] and 8 (yield 30 %)[9] after TLC separation. Their indicated configuration is substantiated by ^1H and ^{13}C NMR data. It is worth to mention that very recently Lounasmaa et al. described the methyl ester of the fourth possible isomer as the only product arising from their method[10].



	R^1	R^2
6	β-H	α-H
7	α-H	α-H
8	β-H	β-H

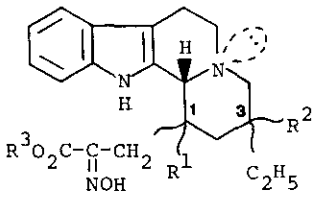
On boiling 6 or 8 in chloroform with $POCl_3$, lactam 9 (yield 86 %)[11] or 10 (yield 80 %)[12] was obtained. Both lactams were transformed to the corresponding isonitroso derivatives (11 and 12) on treatment with tert-butyl nitrite in toluene in the presence of $KOBu^t$. The seven membered oximes 11 (yield 49 %)[13] and 12 (yield 53 %)[14] are mixtures of Z and E isomers.



	R^1	X
9	α-H	H_2
10	β-H	H
11	α-H	=NOH
12	β-H	=NOH

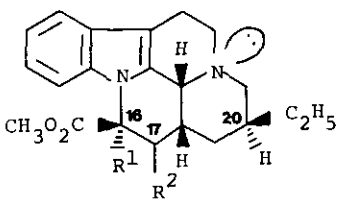
Using the method described earlier by us[15] oxime 12 was boiled in methanol with concentrated sulphuric acid affording (±)-apotacamine (2, yield 42 %)[16]. Compound 11 was transformed by the same treatment to (±)-20-epi-apotacamine (18, yield 53.5 %)[17]. All the spectroscopic data of 2 were identical with those described in the literature[2].

It was found that the above reaction sequence can be improved by boiling 11 or 12 in $CH_3OH/NaOCH_3$. As a result the oxime esters 13 (yield 60.8 %)[18] and 14 (yield 54.8 %)[19] were formed respectively being again mixtures of Z and E isomers.



	R^1	R^2	R^3
13	β-H	α-H	CH_3
14	β-H	β-H	CH_3
15	β-H	α-H	C_2H_5
16	β-H	β-H	C_2H_5

When 13 was boiled in diluted acetic acid in the presence of sulphuric acid and sodium pyrosulphite (±)-20-epi-tacamine 17 was formed in 37 % yield[20]. Under similar conditions 14 could be transformed to (±)-tacamine (1, yield 28 %)[21], which proved to be identical, except optical rotation, with the natural product[22].



	R^1	R^2
17	OH	H
18	$\Delta^{16,17}$	

(±)-Apotacamine 2 can also be obtained by boiling oxime 14 in methanol/H_2SO_4, in 47 % yield.

Utilizing the reaction sequence successfully used for another model by us[23] a simple and efficient approach to 13 and 14 was found. The enamine obtained from the iminium perchlorate 3 was reacted with ethyl bromopyruvate oxime[24] giving rise to the iminium bromide 5 in 55.5 % yield[25]. The latter salt was reduced by $NaBH_4$ in ethanol affording ester 15 (yield 80.8 %)[26] which transformed to the corresponding methyl ester 13 (yield 86.6 %) on boiling in methanol in the presence

of base.

When the iminium salt 5 was kept in ethanol in the presence of sodium ethoxide at ambient temperature for half an hour, and reduced by $NaBH_4$ afterwards, the stereoisomer oxime esters 15 (yield 31.6 %) and 16 (yield 28.2 %)[27] were isolated. Ethyl ester 16 was transformed to the corresponding methyl ester 14, using the above described method, in 81.6 % yield[28].

ACKNOWLEDGEMENTS

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5. G. Massiot, F. Sousa Oliveira and J. Lévy, Bull. Soc. Chim. France, II, 185 (1982).
6. Compound 4 (X = ClO_4): mp 199-200 °C (methanol); IR (KBr) 3220 cm^{-1} (indole NH), 1720 cm^{-1} (ester CO), 1625 cm^{-1} (C=N).
7. Compound 6: mp 137-138 °C (ether); MS m/z (%) 382 (M^+, 89.8), 353 (12.7), 326 (55.7), 325 (100.0), 309 (27.6), 267 (31.4), 225 (33.1), 170 (40.8); IR (KBr) 3400 cm^{-1} (indole NH), 1712 cm^{-1} (ester CO); ^1H NMR[29] ($CDCl_3$) δ (ppm) 0.91 (3H, t, $-CH_2-CH_3$), 1.44 (9H, s, $-C(CH_3)_3$), 3.30 (1H, m, H-12b), 6.9-7.5 (4H, m, aromatic), 8.9 (1H, s, indole NH); ^{13}C NMR ($CDCl_3$) δ (ppm) 11.4 ($-CH_2-CH_3$), 21.5 ($-CH_2-CH_2-COOC(CH_3)_3$), 21.9 (C_7), 27.4 ($-CH_2-CH_3$), 28.1 ($-C(CH_3)_3$), 32.0 ($-CH_2-CH_2-COOC(CH_3)_3$), 32.6 (C_3), 33.2 (C_2), 34.3 (C_1), 54.3 (C_6), 62.6 (C_4), 64.6 (C_{12b}), 80.6 ($-C(CH_3)_3$), 109.5 (C_{7a}), 111.2 (C_{11}), 117.8 (C_8), 119.0 (C_9), 119.9 (C_{10}), 127.6 (C_{7b}), 134.7 (C_{12a}), 136.8 (C_{11a}), 174.1 ($-CH_2-CH_2-COOC(CH_3)_3$).

8. Compound 7: mp 108-109 °C (ether); MS m/z (%) 382 (M^+, 95.4), 353 (16.4), 326 (68.6), 325 (100.0), 309 (34.3), 267 (39.2), 225 (42.3), 170 (49.7); IR (KBr) 3460 cm^{-1} (indole NH), 1700 cm^{-1} (ester CO); ^1H NMR ($CDCl_3$) δ (ppm) 0.91 (3H, t, $-CH_2-CH_3$), 1.45 (9H, s, $-C(CH_3)_3$), 3.10 (1H, m, H-12b), 6.90-7.40 (4H, m, aromatic), 9.56 (1H, s, indole NH); ^{13}C NMR ($CDCl_3$) δ (ppm) 11.4 ($-CH_2-CH_3$), 22.0 (C_7), 27.2 ($-CH_2-CH_3$), 28.1 ($-C(CH_3)_3$), 29.4 ($-CH_2-CH_2-COOC(CH_3)_3$), 32.0 ($-CH_2-CH_2-COOC(CH_3)_3$), 35.5 (C_3), 37.4 (C_1), 38.2 (C_2), 52.4 (C_6), 61.2 (C_4), 63.2 (C_{12b}), 81.4 ($-C(CH_3)_3$), 109.6 (C_{7a}), 111.1 (C_{11}), 117.8 (C_8), 118.9 (C_9), 121.1 (C_{10}), 126.9 (C_{7b}), 135.1 (C_{12a}), 136.4 (C_{11a}), 174.6 ($-CH_2-CH_2-COOC(CH_3)_3$).
9. Compound 8: Oil; MS m/z (%) 382 (M^+, 95.3), 381 (35.1), 353 (16.7), 326 (53.0), 325 (100.0), 309 (31.9), 267 (35.1), 253 (15.8), 225 (34.3), 170 (43.1); IR (KBr) 3310 cm^{-1} (indole NH), 1710 cm^{-1} (ester CO); ^1H NMR ($CDCl_3$) δ (ppm) 0.85 (3H, t, $-CH_2-CH_3$), 1.45 (9H, s, $-C(CH_3)_3$), 4.05 (1H, m, H-12b), 6.90-7.50 (4H, m, aromatic), 8.32 (1H, s, indole NH); ^{13}C NMR ($CDCl_3$) δ (ppm) 11.8 ($-CH_2-CH_3$), 18.0 (C_6), 27.3 ($-CH_2-CH_3$), 28.1 ($-C(CH_3)_3$), 28.1 ($-CH_2-CH_2-COOC(CH_3)_3$), 31.8 ($-CH_2-CH_2-COOC(CH_3)_3$), 33.6 (C_2), 37.8 (C_3), 39.4 (C_1), 53.2 (C_4), 59.9 (C_{12b}), 80.8 ($-C(CH_3)_3$), 107.1 (C_{7b}), 109.2 (C_{7a}), 111.1 (C_{11}), 117.7 (C_8), 119.2 (C_9), 121.3 (C_{10}), 132.4 (C_{12a}), 136.0 (C_{11a}), 173.6 ($-CH_2-CH_2-COOC(CH_3)_3$).
10. R. Jokela, S. Schüller, and M. Lounasmaa, Heterocycles, 23, 1751 (1985).
11. Compound 9 (HCl salt): mp 283-284 °C (methanol); MS m/z (%) 308 (M^+, 100.0), 307 (92.0), 280 (22.7), 279 (17.2), 252 (15.8), 251 (11.1), 224 (11.1), 223 (20.4), 169 (11.6), 167 (13.3); IR (KBr) 1690 cm^{-1} (lactam CO); ^1H NMR ($CDCl_3$, base) δ (ppm) 0.92 (3H, t, $-CH_2-CH_3$), 4.55 (1H, m, H-3), 7.20-7.50 (3H, m, H-9, H-10, H-11), 8.45 (1H, m, H-12); ^{13}C NMR ($CDCl_3$, base) δ (ppm) 12.6 ($-CH_2-CH_3$), 17.1 (C_6), 23.7 ($-CH_2-CH_3$), 27.3 (C_{18}), 30.2 (C_{21}), 32.5 (C_{15}), 34.8 (C_{14}), 34.9 (C_{17}), 48.4 (C_{22}), 51.2 (C_5), 58.5 (C_3), 117.0 (C_{12}), 117.3 (C_7), 117.6 (C_9), 123.7 (C_{11}), 124.9 (C_{10}), 129.5 (C_8), 131.5 (C_2), 136.2 (C_{13}), 173.0 (C_{16}).
12. Compound 10 (HCl salt): mp 244-245 °C (methanol); MS m/z (%) 308 (M^+, 100.0), 307 (81.6), 280 (23.3), 279 (19.4), 252 (14.4), 251 (9.4), 224 (11.6), 223 (19.4), 169 (10.0), 167 (13.8); IR (KBr) 1695 cm^{-1} (lactam CO); ^1H NMR ($CDCl_3$, base) δ (ppm) 1.35 (3H, t, $-CH_2-CH_3$), 4.52 (1H, m, H-3), 7.20-7.50 (3H, m, H-9, H-10, H-11), 8.45 (1H, m, H-12); ^{13}C NMR ($CDCl_3$, base) δ (ppm) 11.4

($-CH_2-\underline{C}H_3$), 17.1 (C_6), 27.0 (C_{18}), 27.3 ($-\underline{C}H_2-CH_3$), 35.2 (C_{15}), 35.5 (C_{17}), 36.3 (C_{21}), 38.3 (C_{14}), 50.9 (C_{22}), 51.5 (C_5), 58.1 (C_3), 117.0 (C_{12}), 117.4 (C_7), 117.6 (C_9), 123.6 (C_{11}), 124.8 (C_{10}), 129.7 (C_8), 132.4 (C_2), 136.2 (C_{13}), 173.1 (C_{16}).

13. Compound 11: mp 227-230 °C (methanol); MS m/z (%) 337 (M^+, 72.3), 336 (49.3), 320 (49.5), 318 (3.9), 309 (22.5), 308 (27.2), 307 (49.7), 293 (27.2), 292 (100.0), 251 (15.3), 237 (5.5), 223 (20.2), 169 (18.8), 168 (17.2), 167 (16.9); IR (KBr) 3350 cm^{-1} (OH), 1700 cm^{-1} (lactam CO), 1600 cm^{-1} (C=N); ^1H NMR ($CDCl_3$) δ (ppm) 1.02 (3H, t, $-CH_2-\underline{C}H_3$), 4.2 (1H, d, J=6.8 Hz, H-3), 7.10-7.50 (3H, m, H-9, H-10, H-11), 8.35 (1H, m, H-12), 12.0 (1H, broad s, oxime =NOH); ^{13}C NMR ($CDCl_3$) δ (ppm) 12.5 ($-CH_2-\underline{C}H_3$), 17.3 (C_6), 23.5 ($-\underline{C}H_2-CH_3$), 29.1 (C_{21}), 29.9 (C_{18}), 32.4 (C_{15}), 34.6 (C_{14}), 49.8 (C_{22}), 51.1 (C_5), 57.6 (C_3), 117.5 (C_{12}), 118.0 (C_9), 119.0 (C_7), 124.3 (C_{10}), 125.1 (C_{11}), 130.5 (C_8), 131.8 (C_2), 136.4 (C_{13}), 152.7 (C_{17}), 164.4 (C_{16}).
14. Compound 12: mp 225-231 °C (ether); MS m/z (%) 337 (M^+, 82.2), 336 (58.4), 321 (26.2), 320 (57.1), 308 (23.1), 307 (38.1), 294 (37.7), 293 (100.0), 223 (17.1), 170 (16.3), 169 (18.2); IR (KBr) 3320 cm^{-1} (OH), 1688 cm^{-1} (lactam CO), 1590 cm^{-1} (C=N); ^1H NMR (DMSO-d_6) δ (ppm) 0.80 (3H, t, $-CH_2-\underline{C}H_3$), 4.30 (1H, m, H-3), 7.15-7.55 (3H, m, H-9, H-10, H-11), 8.30 (1H, m, H-12), 11.27 (1H, broad s, oxime =NOH); ^{13}C NMR (DMSO-d_6) δ (ppm) 11.0 ($-CH_2-\underline{C}H_3$), 16.4 (C_6), 26.3 ($-\underline{C}H_2-CH_3$), 32.8 (C_{18}), 34.8 (C_{15}), 36.4 (C_{21}), 37.7 (C_{14}), 49.9 (C_{22}), 50.7 (C_5), 57.4 (C_3), 115.7 (C_{12}), 118.1 (C_7), 118.2 (C_9), 124.0 (C_{10}), 124.7 (C_{11}), 129.8 (C_8), 132.1 (C_2), 134.7 (C_{13}), 149.3 (C_{17}), 162.5 (C_{16}).
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16. Compound 2 (HCl salt): mp 204-205 °C (methanol); MS m/z (%) 336 (M^+, 68.1), 335 (37.0), 292 (100.0), 276 (19.7), 252 (7.6), 238 (51.3), 168 (6.6); IR (KBr) 1725 cm^{-1} (ester CO), 1642 cm^{-1} (C=C); ^1H NMR ($CDCl_3$, base) δ (ppm) 0.46 (1H, ddd, J=12.5 Hz, J=12.5 Hz, J=12.5 Hz, H-15$_\alpha$), 0.85 (3H, t, $-CH_2\underline{C}H_3$), 1.08 (2H, m, $-\underline{C}H_2-CH_3$), 1.45 (1H, m, H-20), 1.72 (1H, ddd, J=12.5 Hz, J=2.5 Hz, J=2.5 Hz, H-15$_\beta$), 2.20 (1H, dd, J=11.0 Hz, J=11.0 Hz, H-21$_\alpha$), 2.35-3.20 (4H, m, H-14, H-21$_\beta$, H-6), 3.35 (2H, m, H-5), 4.42 (1H, broad d, J=7.0 Hz, H-3), 6.38 (1H, d, J=7.3 Hz, H-17), 7.05-7.30 and 7.45 (4H, m, aromatic); ^{13}C NMR ($CDCl_3$, base) δ (ppm) 11.3 ($-CH_2-\underline{C}H_3$), 16.3 (C_6), 26.9

($-\underline{C}H_2-CH_3$), 31.6 (C_{15}), 33.4 (C_{20}), 37.2 (C_{14}), 51.1 (C_{21}), 51.1 (C_5), 52.1 (C_3), 52.5 ($-COO\underline{C}H_3$), 108.8 (C_7), 112.4 (C_{12}), 118.3 (C_9), 120.2 (C_{10}), 122.0 (C_{11}), 123.6 (C_{17}), 129.0 (C_{16}), 129.1 (C_2), 130.4 (C_8), 134.3 (C_{13}), 163.7 ($-\underline{C}OOCH_3$).

17. Compound 18 (HCl salt): mp 212-214 °C (methanol); MS m/z (%) 336 (M^+, 65.8), 335 (31.7), 293 (41.8), 292 (100.0), 277 (7.7), 276 (17.3), 239 (10.9), 238 (60.7), 168 (7.1); IR (KBr) 1723 cm^{-1} (ester CO), 1639 cm^{-1} (C=C); ^1H NMR ($CDCl_3$, base) δ (ppm) 0.92 (3H, t, $-CH_2\underline{C}H_3$), 3.90 (3H, s, $-O\underline{C}H_3$), 4.38 (1H, d, J=7.1 Hz, H-3), 6.33 (1H, d, J=7.1 Hz, H-17), 7.00~7.55 (4H, m, aromatic); ^{13}C NMR ($CDCl_3$, base) δ (ppm) 12.3 ($-CH_2-\underline{C}H_3$), 16.2 (C_6), 22.6 ($-\underline{C}H_2-CH_3$), 28.2 (C_{20}), 28.7 (C_{15}), 34.5 (C_{14}), 47.4 (C_{21}), 51.3 (C_5), 52.1 (C_3), 52.1 ($-COO\underline{C}H_3$), 108.8 (C_7), 112.3 (C_{12}), 118.1 (C_9), 120.1 (C_{10}), 121.8 (C_{11}), 124.0 (C_{17}), 129.0 (C_{16}), 129.3 (C_8), 130.0 (C_2), 163.6 ($-\underline{C}OOCH_3$).

18. Compound 13: mp 251-253 °C (methanol); MS m/z (%) 369 (M^+, 94.0), 368 (61.0), 353 (31.0), 352 (100.0), 340 (7.1), 310 (10.0), 293 (22.1), 292 (36.0) 276 (11.0), 267 (9.0), 253 (28.0); IR (KBr) 3320 cm^{-1} (indole NH, OH), 1715 cm^{-1} (ester CO).

19. Compound 14 (HCl salt): mp 194-196 °C (methanol); MS m/z (%) 369 (M^+, 19.0), 368 (22.0), 353 (28.1), 352 (100.0), 335 (7.0), 310 (3.0), 293 (14.0), 292 (31.0), 276 (15.0), 267 (6.0), 253 (13.0); IR (KBr) 3400 cm^{-1} (indole NH,OH), 1712 cm^{-1} (ester CO); ^1H NMR (DMSO-d_6, base) δ (ppm) 0.90 (3H, t, $-CH_2-\underline{C}H_3$), 3.65 (1H, m, H-3), 3.75 (3H, s, $-O\underline{C}H_3$), 6.90-7.15 (2H, m, H-10, H-11), 7.20-7.45 (2H, m, H-9, H-12), 10.4 (1H, broad s, indole NH), 11.1 (1H, broad s, oxime =NOH); ^{13}C NMR (DMSO-d_6, base) δ (ppm) 13.0 ($-CH_2-\underline{C}H_3$), 20.6 (C_7), 27.8 ($-\underline{C}H_2-CH_3$), 30.1 ($-\underline{C}H_2-C(NOH)-COOCH_3$), 31.7 ($C_2$), 34.2 ($C_3$), 36.0 ($C_1$), 51.8 ($-CH_2-C(NOH)-COO\underline{C}H_3$), 52.8 ($C_6$), 57.9 ($C_4$), 62.7 ($C_{12b}$), 108.4 ($C_{7a}$), 111.2 ($C_{11}$), 117.4 ($C_8$), 118.3 ($C_9$), 120.5 ($C_{10}$), 127.1 ($C_{7b}$), 130.7 ($C_{12a}$), 136.5 ($C_{11a}$), 150.3 ($-CH_2-\underline{C}(NOH)-COOCH_3$), 163.9 ($-CH_2-C(NOH)-\underline{C}OOCH_3$).

20. Compound 17: mp 180-181 °C (methanol); MS m/z (%) 354 (M^+, 100.0), 353 (79.0), 339 (25.3), 336 (3.6), 295 (23.0), 294 (8.6), 293 (36.6), 292 (40.6), 268 (42.3), 252 (63.0), 238 (7.3), 223 (42.3), 196 (29.0); IR (KBr) 3360 cm^{-1} (OH), 1722 cm^{-1} (ester CO); ^1H NMR ($CDCl_3$) δ (ppm) 0.94 (3H, t, $-CH_2-\underline{C}H_3$), 3.82 (3H, s, $-O\underline{C}H_3$), 4.30 (1H, m, H-3), 4.60 (1H, s, OH), 7.00-7.20 and 7.45 (4H, m, aromatic); ^{13}C NMR ($CDCl_3$) δ (ppm) 12.6 ($-CH_2-\underline{C}H_3$), 17.0 (C_6), 22.9 ($-\underline{C}H_2-CH_3$), 26.9 (C_{20}), 27.8 (C_{15}), 35.2 (C_{14}), 40.2 (C_{17}), 47.3 (C_{21}),

50.9 (C_5), 54.3 (-COO<u>C</u>H_3), 54.5 (C_3), 81.8 (C_{16}), 106.4 (C_7), 110.5 (C_{12}), 118.5 (C_9), 120.3 (C_{10}), 121.7 (C_{11}), 129.0 (C_8), 130.7 (C_2), 134.5 (C_{13}), 174.5 (-<u>C</u>OOCH_3).

21. Compound <u>1</u>: mp 193-195 °C (methanol); MS m/z (%) 354 (M^+, 100.0), 353 (85.0), 339 (28.2), 336 (8.5), 295 (33.2), 294 (52.1), 293 (79.1), 292 (48.6), 252 (48.0), 238 (12.6), 223 (34.1), 196 (23.4); IR (KBr) 3350 cm^{-1} (OH), 1718 cm^{-1} (ester CO); ^1H NMR ($CDCl_3$) δ (ppm) 0.83 (3H, t, -CH_2-C<u>H</u>$_3$), 3.79 (3H, s, -OC<u>H</u>$_3$), 4.34 (1H, m, H-3), 7.0-7.30 and 7.48 (4H, m, aromatic); ^{13}C NMR ($CDCl_3$) δ (ppm) 11.5 (-CH_2-<u>C</u>H_3), 17.0 (C_6), 26.9 (-<u>C</u>H_2-CH_3), 31.1 (C_{15}), 32.1 (C_{14}), 38.3 (C_{20}), 40.1 (C_{17}), 50.5 (C_{21}), 50.7 (C_5), 54.2 (-COO<u>C</u>H_3), 54.2 (C_3), 81.8 (C_{16}), 106.2 (C_7), 110.4 (C_{12}), 118.4 (C_9), 120.2 (C_{11}), 121.7 (C_{10}), 128.8 (C_8), 130.8 (C_2), 134.5 (C_{13}), 174.3 (-<u>C</u>OOCH_3).

22. We are indebted to Dr. T.A. van Beek for the authentic tacamine sample and the MS and NMR spectra.

23. J. Sápi, L. Szabó, Gy. Kalaus and Cs. Szántay, unpublished results.

24. T.L. Gilchrist, D.A. Lingham and T.G. Roberts, <u>J. Chem. Soc. Chem. Commun.,</u> 1089 (1979).

25. Compound <u>5</u> (X=Br): mp 152-154 °C (ethanol); IR (KBr) 3465 cm^{-1}, 3350 cm^{-1} (indole NH, OH), 1702 cm^{-1} (ester CO), 1625 cm^{-1} (C=N).

26. Compound <u>15</u>: mp 256-258 °C (water); MS m/z (%) 383 (M^+, 90.8), 382 (52.1), 367 (25.4), 366 (100.0), 354 (7.5), 310 (13.2), 294 (14.8), 293 (32.4), 253 (36.0), 225 (23.4), 223 (17.7), 184 (41.2), 170 (72.2), 169 (58.2); IR (KBr) 3290 cm^{-1} (indole NH, OH), 2780 cm^{-1} (Bohlmann band), 1695 cm^{-1} (ester CO), 1610 cm^{-1} (C=N); ^1H NMR (DMSO-d_6) δ (ppm) 1.17 (3H, t, -CH_2-C(NOH)-COOCH_2C<u>H</u>$_3$), 0.85 (3H, t, -CH_2-C<u>H</u>$_3$), 3.52 (1H, s, H-3), 4.0 (2H, q, -CH_2-C(NOH)-COOC<u>H</u>$_2$CH$_3$), 6.80-7.10 (2H, m, H-10, H-11), 7.20-7.45 (2H, m, H-9, H-12), 10.51 (1H, s, indole NH), 12.08 (1H, s, oxime =NOH); ^{13}C NMR (DMSO-d_6) δ (ppm) 11.4 (-CH_2-<u>C</u>H_3), 14.1 (-CH_2-C(NOH)-COOCH_2<u>C</u>H_3), 21.8 (C_7), 23.5 (-<u>C</u>H_2-C(NOH)-COOCH_2CH$_3$), 27.0 (-<u>C</u>H_2-CH_3), 32.6 (C_3), 34.2 (C_1), 34.4 (C_2), 53.1 (C_6), 60.8 (-CH_2-C(NOH)-COO<u>C</u>H_2-CH_3), 62.3 (C_4), 63.7 (C_{12b}), 108.2 (C_{7a}), 111.2 (C_{11}), 117.5 (C_8), 118.3 (C_9), 120.4 (C_{10}), 126.8 (C_{7b}), 134.5 (C_{12a}), 136.4 (C_{11a}), 151.7 (-CH_2-<u>C</u>(NOH)-COOCH_2CH$_3$), 164.1 (-CH_2-C(NOH)-<u>C</u>OOCH_2CH$_3$).

27. Compound <u>16</u>: mp 190-192 °C (ethanol); MS m/z (%) 383 (M^+, 71.5), 382 (44.4), 366 (100.0), 310 (11.1), 292 (33.2), 253 (25.4), 225 (17.9), 223 (17.6),

184 (33.8), 170 (56.9), 169 (50.1); IR (KBr) 3300 cm^{-1} (indole NH, OH), 1703 cm^{-1} (ester CO), 1610 cm^{-1} (C=N), ^{1}H NMR ($CDCl_3$) δ (ppm) 0.87 (3H, t, $-CH_2-C\underline{H}_3$), 1.30 (3H, t, $-CH_2-C(NOH)-COOCH_2C\underline{H}_3$), 4.23 (1H, s, H-12b), 4.24 (2H, q, $-CH_2-C(NOH)-COOC\underline{H}_2CH_3$), 7.00-7.30 (3H, m, H-10, H-11, H-12), 7.45 (1H, broad s, indole NH), 7.35-7.55 (1H, m, H-9), 9.32 (1H, broad s, oxime =NOH); ^{13}C NMR ($CDCl_3$) δ (ppm) 11.4 ($-CH_2-\underline{C}H_3$), 14.0 ($-CH_2-C(NOH)-COOCH_2\underline{C}H_3$), 16.9 ($C_7$), 27.1 ($-\underline{C}H_2-CH_3$), 30.1 ($-\underline{C}H_2-C(NOH)-COOCH_2CH_3$), 32.8 ($C_2$), 36.1 ($C_3$), 37.6 ($C_1$), 50.5 ($C_4$), 51.2 ($C_6$), 57.2 ($C_{12b}$), 62.1 ($-CH_2-C(NOH)-COO\underline{C}H_2-CH_3$), 108.7 ($C_{7a}$), 111.5 ($C_{11}$), 117.8 ($C_8$), 119.4 ($C_9$), 121.6 ($C_{10}$), 127.0 ($C_{7b}$), 131.1 ($C_{12a}$), 136.5 ($C_{11a}$), 148.1 ($-CH_2-\underline{C}(NOH)-COOCH_2CH_3$), 166.5 ($-CH_2-C(NOH)-\underline{C}OOCH_2CH_3$).

28. All products gave satisfactory elemental analysis.

29. All NMR measurements were performed on a Jeol FX-100 instrument. A detailed discussion of the NMR data will be published later on.

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